Scalable tests for ergodicity analysis of large-scale interconnected stochastic reaction networks

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Introduction to stochastic reaction networks

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Framework

Stochastic reaction network

- d molecular species $\boldsymbol{X_1}, \ldots, \boldsymbol{X_d}$
- K reaction channels $R_1, \ldots, R_K$
- $\lambda_k(\cdot)$: propensity function of the k-th reaction
- ζ_k: stoichiometry vector of the k-th reaction: $x \xrightarrow{R_i} x + \zeta_i$
- Under the homogeneous mixing assumption[1] $(X(t))_{t\geq 0}$ is a Markov process

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1 D. Anderson and T. G. Kurtz. Continuous time Markov chain models for chemical reaction networks, H. Koeppl, D. Densmore, G. Setti, and M. di Bernardo, editors, *Design and analysis of biomolecular circuits - Engineering Approaches to Systems and Synthetic Biology*

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Type	Reaction	$\lambda(x)$ (deterministic)	$\lambda(x)$ (stochastic)
Unimolecular	$\emptyset \longrightarrow \boldsymbol{X_i}$	k	$k\Omega$
	$\boldsymbol{X_i} \longrightarrow \cdot$	kx_i	kx_i
Bimolecular	$\boldsymbol{X_i} + \boldsymbol{X_i} \longrightarrow \cdot$	kx_i^2	$\frac{k}{\Omega}x_i(x_i - 1)$
	$\boldsymbol{X_i} + \boldsymbol{X_j} \xrightarrow{k} \cdot$	kx_ix_j	$\frac{k}{\Omega}x_ix_j$

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Example - SIR model

Network

$$\mathbf{S}+\mathbf{I} \xrightarrow{k_{si}} 2\mathbf{I}, \qquad \mathbf{I} \xrightarrow{k_{ir}} \mathbf{R}, \qquad \mathbf{R} \xrightarrow{k_{rs}} \mathbf{S}$$

We have $x = (S, I, R)$, $d = 3$ and $K = 3$.

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Reaction	Propensity function	Stoichiometric vector
R_1	$\lambda_1(x) = k_{si}SI$	$\zeta_1 = (-1, 1, 0)$
R_2	$\lambda_2(x) = k_{ir}S$	$\zeta_2 = (0, -1, 1)$
R_3	$\lambda_3(x) = k_{rs}R$	$\zeta_3 = (1, 0, -1)$

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Deterministic model

$$\dot{x}(t)=\sum_{i=1}^{3}\zeta_i\lambda_i(x)=\left\{\begin{array}{l} -k_{si}S(t)I(t)+k_{rs}R(t)\\ k_{si}S(t)I(t)-k_{ir}I(t)\\ k_{ir}I(t)-k_{rs}R(t)\end{array}\right.$$

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Random time-change representation[2]

$$X(t)=\sum_{i=1}^{3}\zeta_i Y_i\left(\int_0^t \lambda_i(X(s))ds\right)$$

where the Y_i's are independent unit-rate Poisson processes.

2 S. N. Ethier and T. G. Kurtz. *Markov Processes: Characterization and Convergence*. Wiley, 1986

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Chemical master equation

Chemical master equation

- Let us denote the state-space of the Markov process by $\mathcal{S} \subset \mathbb{N}_0^d$ and let $p(\cdot, t)$ be a probability measure on $\mathcal{S}$
- Then the CME is given by

$$\dot{p}_{x_0}(x,t) = \sum_{k=1}^{K} \left(p_{x_0}(x-\zeta_k,t)\lambda_k(x-\zeta_k) - p_{x_0}(x,t)\lambda_k(x)\right) \tag{1}$$

where $p_{x_0}(x,t)$ is the probability to be in state $x \in \mathcal{S}$ at time t provided that $p(x_0, 0) = 1$.

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Remarks

- When $\mathcal{S}$ is infinite $\rightarrow$ infinite set of linear equations
- Exactly solvable in very particular cases only
- Can be approximately solved using numerical schemes

Analysis of reaction networks

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Ergodicity analysis

Theorem ([3])

Assume that the state-space $\mathcal{S}$ of the reaction network is irreducible and that there exist $v \in \mathbb{R}^d_{>0}$ and positive scalars $c_1, \ldots, c_4$ such that the conditions

$$\sum_{k=1}^{K} \lambda_k(x)\langle v, \zeta_k\rangle \le c_1 - c_2\langle v, x\rangle \quad \text{and} \quad \sum_{k=1}^{K} \lambda_k(x)\langle v, \zeta_k\rangle^2 \le c_3 + c_4\langle v, x\rangle$$

hold for all $x \in \mathcal{S}$.

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[3] A. Gupta, C. Briat, and M. Khammash. A scalable computational framework for establishing long-term behavior of stochastic reaction networks, *PLOS Computational Biology*, 2014

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hold for all $x \in \mathcal{S}$.

Then, the Markov process is exponentially ergodic and all the moments are bounded and converging.

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Consequences

- Ergodicity ensures that for all $x_0 \in \mathcal{S}$, we have that $p_{x_0}(x,t) \to \pi$ as $t \to \infty$ where π is the unique stationary distribution of the process.
- We also have for any polynomial function f the following property

$$\frac{1}{t}\int_0^t f(X(s))ds \overset{t\to\infty}{\longrightarrow} \sum_{x\in\mathcal{S}} \pi(x) f(x) \quad \text{a.s.} \tag{2}$$

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Unimolecular reaction networks

Proposition (Ergodicity of unimolecular networks[4])

Let us consider a general unimolecular reaction network and assume that the state-space $\mathbb{N}_0^d$ is irreducible. Let the matrices $A \in \mathbb{R}^{d\times d}$ and $b \in \mathbb{R}^d_{\geq 0}$ be further defined as

$$\sum_{n=1}^{K} \lambda_n(x)\langle v, \zeta_n\rangle = x^T A v + b^T v. \tag{3}$$

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Then, the following statements are equivalent:

(a) *The matrix A is Hurwitz, i.e. all its eigenvalues lie in the open left half-plane.*

(b) *There exists a vector $v \in \mathbb{R}_{>0}^d$ such that $Av < 0$.*

Moreover, when one of the above statements holds, then the Markov process describing the reaction network is exponentially ergodic and all its moments are bounded and converging.

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Moreover, when one of the above statements holds, then the Markov process describing the reaction network is exponentially ergodic and all its moments are bounded and converging.

Remarks

- Identical to the stability conditions of linear positive systems (A is Metzler here)
- Linear conditions $\rightarrow$ computationally tractable

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Let us consider a general bimolecular reaction network and assume that the state-space $\mathbb{N}_0^d$ is irreducible. Let the matrices $M(v) \in \mathbb{S}^d$, $A \in \mathbb{R}^{d\times d}$ and $b \in \mathbb{R}_{\ge 0}^d$ be further defined as

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Assume that there exists $v \in \mathbb{R}^d_{>0}$ such that the conditions

$$Av < 0 \text{ and } v^T S_b = 0 \tag{5}$$

hold where S_b is the stoichiometric matrix associated with the bimolecular reactions.

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Remarks

- *The term $v^T S_b = 0$ implies that $M(v) = 0$ and ensures that $\langle v, \zeta\rangle = 0$ for every stoichiometric vector associated with a bimolecular reaction.*
- *Conditions are linear (LP problem)*

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Analysis of interconnections of reaction networks

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State localization problem

Nonlocalized state

- The state may be nonlocal, i.e. the same state can be shared by multiple subnetworks

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State localization problem

Nonlocalized state

- The state may be nonlocal, i.e. the same state can be shared by multiple subnetworks
- For instance

$$\begin{array}{rcl} \mathcal{N}_1 & : & \emptyset \xrightarrow{\quad k \quad} \boldsymbol{X_1} \\ \mathcal{N}_2 & : & \boldsymbol{X_1} \xrightarrow{\quad \gamma \quad} \emptyset \end{array} \tag{6}$$

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- What dynamical model for this interconnection?
- The problem comes from the mass transfer between the two networks

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Localized state

$$\begin{array}{lcl} \mathcal{N}_1 & : & \emptyset \xrightarrow{k_1} \boldsymbol{X_1} \xrightarrow{\gamma_1} \emptyset \\ \mathcal{N}_2 & : & \emptyset \xrightarrow{k_2 X_1} \boldsymbol{X_2} \xrightarrow{\gamma_2} \emptyset \end{array} \tag{7}$$

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- In this case, there is no mass transfer, just information transfer, so the state is localized
- X_1 for the first network and X_2 for the second.

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Let us consider a general interconnection of unimolecular reaction networks and assume that the state-space $\mathbb{N}_0^d$ *is irreducible. Let the matrices* $A_i \in \mathbb{R}^{d_i \times d_i}$, $b_i \in \mathbb{R}_{\geq 0}^{d_i}$ *and* $B_{ij} \in \mathbb{R}_{\geq 0}^{d_i \times d_{ij}}$ *be further defined as*

$$\mathbb{A}_i V_i(x_i) \quad = \quad x_i^T A_i v_i + \sum_{j \neq i} B_{ij} z_{ij} + b_i^T v_i \tag{8}$$

with $z_{ij} = C_{ij} x_j$ *and* $z_i = \mathrm{col}_{j \neq i}\, z_{ij}$.

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$$v_i^T A_i + \sum_{j \neq i}^{N} \ell_{ji}^T C_{ji} \quad < \quad 0 \quad \text{and} \quad v_i^T B_{ij} - \ell_{ij}^T \quad < \quad 0 \tag{9}$$

hold for all $i, j = 1, \ldots, N$, $j \neq i$.

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hold for all $i, j = 1, \ldots, N$, $j \neq i$ *where* S_b^i *is the stoichiometric matrix associated with the bimolecular reactions of subnetwork* i.

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with $z_{ij} = C_{ij} x_j$ and $z_i = \mathrm{col}_{j\neq i}\, z_{ij}$. Assume that there exist vectors $v_i \in \mathbb{R}^{d_i}_{>0}$, $\ell_{ij} \in \mathbb{R}^{d_{ij}}$ such that the conditions

$$v_i^T A_i + \sum_{j\neq i}^{N} \ell_{ji}^T C_{ji} < 0, \quad v_i^T B_{ij} - \ell_{ij}^T < 0 \quad \text{and} \quad v_i^T S_b^i = 0 \tag{11}$$

hold for all $i, j = 1, \ldots, N$, $j \neq i$ where S_b^i is the stoichiometric matrix associated with the bimolecular reactions of subnetwork i.

Then, the network interconnection is exponentially ergodic and has all its moment bounded and converging.

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Conclusion and future works

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Conclusion and future works

Conclusions

- Conditions for checking the ergodicity of reaction networks
- Conditions for checking the ergodicity of interconnections of reaction networks when the state is localized
- Conditions can be checked using optimization techniques (LP)
- Conditions can be also solved in a distributed way

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Future works

- Robust analysis
- Address the case of nonlocal states
- Network decomposition/interface detection
- Control of networks

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Thank you for your attention