

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

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# Introduction to stochastic reaction networks



## Stochastic reaction network

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

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D. Anderson and T. G. Kurtz. Continuous time Markov chain models for chemical reaction networks, H. Koepl, 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	$\emptyset \longrightarrow X_i$	$k$	$k\Omega$
	$X_i \longrightarrow \cdot$	$kx_i$	$kx_i$
Bimolecular	$X_i + X_i \longrightarrow \cdot$	$kx_i^2$	$\frac{k}{\Omega} x_i(x_i - 1)$
	$X_i + X_j \xrightarrow{k} \cdot$	$kx_i x_j$	$\frac{k}{\Omega} x_i x_j$

<sup>1</sup>

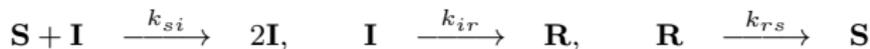


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## Example - SIR model

### Network

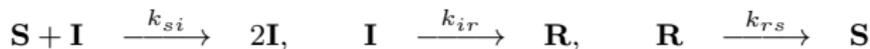


We have  $x = (S, I, R)$ ,  $d = 3$  and  $K = 3$ .



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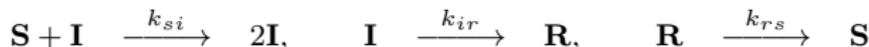
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Reaction	Propensity function	Stoichiometric vector
$R_1$	$\lambda_1(x) = k_{si}SI$	$\zeta_1 = (-1, 1, 0)$
$R_2$	$\lambda_2(x) = k_{ir}S$	$\zeta_2 = (0, -1, 1)$
$R_3$	$\lambda_3(x) = k_{rs}R$	$\zeta_3 = (1, 0, -1)$



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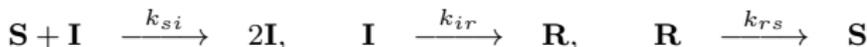
### Deterministic model

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



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### Random time-change representation<sup>2</sup>

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

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





# 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

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

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



## Theorem (3)

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

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

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





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hold for all  $x \in S$ .

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## Consequences

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

$$\frac{1}{t} \int_0^t f(X(s)) ds \xrightarrow{t \rightarrow \infty} \sum_{x \in S} \pi(x) f(x) \quad \text{a.s.} \quad (2)$$





## Unimolecular reaction networks

### Proposition (Ergodicity of unimolecular networks<sup>4</sup>)

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  $b \in \mathbb{R}_{\geq 0}^d$  be further defined as

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

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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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### 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  $b \in \mathbb{R}_{\geq 0}^d$  be further defined as

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

$$A v < 0 \text{ and } v^T S_b = 0 \quad (5)$$

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



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



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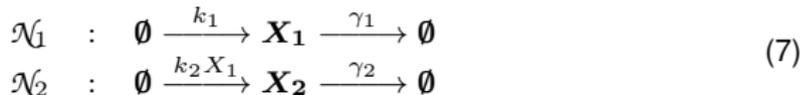
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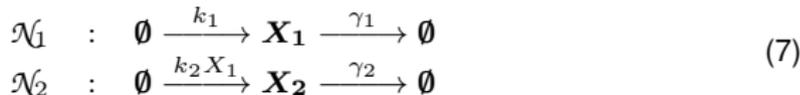
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### Localized state



- 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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### Theorem (Unimolecular networks)

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

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



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



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



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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