21st International Symposium on
Mathematical Theory of Networks and Systems
July 7-11, 2014. Groningen, The Netherlands

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

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***Index Terms*— Stochastic reaction networks; Markov processes; reaction network theory; ergodicity; systems biology**

I. Introduction

A wide variety of processes arising in chemistry, biochemistry, ecology, epidemiology and social sciences can be represented as reaction networks [1]–[3]. The core idea is to represent a given system in terms of the evolution of a population of different agents. The time-evolution of the respective populations is described by a set of reactions, which, when they take place, change the populations in a fixed and given manner. Deterministic reaction networks, represented in terms of ordinary, functional or partial differential equations, have been historically considered first. Famous examples are the Lotka-Volterra equations in ecology and SIR-models in epidemiology; see e.g. [4]. A deterministic representation of networks remains valid as long as the populations of the agents are large. However, when populations are small, random effects become dominant and cannot be neglected anymore. Under a well-mixed assumption, it has been shown that the evolution of the populations can be described by a Markov process [5]. The case of low-copy numbers arises quite frequently in biochemistry of the cell [6] where randomness can lead to important discrepancies in the behavior of identical organisms. More surprisingly, certain biological circuits have been shown to exploit randomness in order to achieve their function in an efficient way; see e.g. [7]–[9].

The behavior of deterministic models can be analyzed using the rich underlying mathematical theory of deterministic dynamical systems and differential equations. Stability properties can be, for example, studied using Lyapunov theory. When it comes to stochastic reaction networks, the analysis becomes much more complicated due to the random nature of the system. Fewer tools moreover available for stochastic reaction networks; see e.g. [10]–[12].

The goal of this paper/talk, is to provide an efficient way for analyzing the long-term behavior of stochastic reaction networks. We first recall some conditions for establishing (structural) ergodicity and moments boundedness/convergence of a given reaction network that have been developed in [12]. Ergodicity, for stochastic processes, is analogous to having a globally asymptotically stable equilibrium point for deterministic dynamics [13]. It thus provides a suitable stability notion in our context since it guarantees that the stochastic reaction network has a unique attractive stationary distribution. We then extend these results to address the problem of establishing ergodicity of interconnected reaction networks, that is, ergodicity of a network of networks. We show that ergodicity of interconnected networks can be expressed through local (to each network) ergodicity criteria taking the form of linear programs that involve additional parameters. It is emphasized that the scalability of the approach can be enhanced by relying on a distributed implementation of the dual optimization problem. Several examples are given for illustration.

Notations: The set of whole numbers is denoted by $\mathbb{N}_0$, the set of positive real numbers by $\mathbb{R}_{>0}$ and the set of integers by $\mathbb{Z}$. For $x, y \in \mathbb{R}^n$, $\langle x, y\rangle$ is the standard inner-product on $\mathbb{R}^n$. The set of symmetric matrices of dimension n is denoted by $\mathbb{S}^n$. The vector column made of the terms $x_1, \ldots, x_n$ is denoted by $\mathrm{col}_i(x_i)$.

II. Stochastic reaction networks

Let us consider a reaction network with d species $\mathbf{S_1}, \ldots, \mathbf{S_d}$ and K reactions $R_1, \ldots, R_K$. For each reaction R_k, we associate the stoichiometric vector $\zeta_k \in \mathbb{Z}^d$ which describes how the populations change when the reaction R_k fires. That is, if the state is x and the reaction R_k fires, then the state immediately after the reaction is given by $x+\zeta_k$. The propensity function of reaction R_k is denoted by $\lambda_k(x) \geq 0$ (see Table I) which means that, when the state is equal to x, the reaction R_k fires after a random time that is exponentially distributed with rate $\lambda_k(x)$.

TABLE I
List of the considered reactions and their propensity function

Type	Reaction	Propensity $\lambda(x)$
1	$\emptyset \xrightarrow{k} \mathbf{S_1}$	k
2	$\mathbf{S_i} \xrightarrow{k} \cdot$	kx_i
3	$\mathbf{S_i}+\mathbf{S_i} \xrightarrow{k} \cdot$	$\frac{k}{2}x_i(x_i-1)$
4	$\mathbf{S_i}+\mathbf{S_j} \xrightarrow{k} \cdot$	kx_ix_j

The evolution of the system is represented as a Markov process $(X_{x_0}(t))_{t\geq 0}$ where x_0 is the initial state. The popula-

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tion of the species $\mathbf{S_i}$ is simply given by the i-th component of $X_{x_0}(t)$, which we denote by $X_i(t)$ where we drop the dependence on x_0 for simplicity. Since in stochastic models the current count of species is tracked, then we have that $X_{x_0}(t) \in \mathbb{N}_0^d$ provided that $x_0 \in \mathbb{N}_0^d$. The state-space $\mathcal{S}$ of the reaction network can then be defined as the smallest non-empty set of $\mathbb{N}_0^d$ verifying the property: if $x \in \mathcal{S}$ and $\lambda_k(x) > 0$ for some $k = 1, \ldots, K$, then $x + \zeta_k \in \mathcal{S}$. So, if $x_0 \in \mathcal{S}$, then $X_{x_0}(t) \in \mathcal{S}$ for all $t \geq 0$.

The state of the Markov process evolves according to [5]

$$X_{x_0}(t) = \sum_{k=1}^{K} \zeta_k Y_k \left(\int_0^t \lambda_k(X_{x_0}(s))\mathrm{d}s \right), \ X(0) = x_0 \quad (1)$$

where the Y_k's are independent unit rate Poisson processes.

Alternatively, the Markov process can be described by the Chemical Master Equation (or forward Kolmogorov equation) given by

$$\dot{p}_{x_0}(x,t) = \sum_{k=1}^{K} \left(p_{x_0}(x - \zeta_k, t)\lambda_k(x - \zeta_k) - p_{x_0}(x,t)\lambda_k(x) \right) \quad (2)$$

where $p_{x_0}(x,t)$ is the probability to be in state $x \in \mathcal{S}$ at time t provided that $p(x_0, 0) = 1$ and where $p(\cdot, t)$ is a probability measure on $\mathcal{S}$. For more details, see e.g. [5], [14].

III. Ergodicity analysis of stochastic reaction networks

We recall in this section several theoretical results for establishing ergodicity and moments convergence of stochastic reaction networks that have been developed in [12].

A. General theoretical results

The following result is a less general version of the one in [12]:

Theorem 1 ([12]): Assume there exist $v \in \mathbb{R}_{>0}^d$ and positive scalars $c_1, \ldots, c_4$ such that the conditions

$$\sum_{k=1}^{K} \lambda_k(x)\langle v, \zeta_k \rangle \leq c_1 - c_2\langle v, x \rangle \text{ and} \quad (3a)$$

$$\sum_{k=1}^{K} \lambda_k(x)\langle v, \zeta_k \rangle^2 \leq c_3 + c_4\langle v, x \rangle \quad (3b)$$

hold for all $x \in \mathbb{N}_0^d$.

Then, all the moments are bounded and converging. Moreover, if the state-space $\mathcal{S}$ is irreducible, then the Markov process is exponentially ergodic. △

B. Theoretical results for affine and quadratic reaction networks

We recall here our results specialized to the case of affine and quadratic reaction networks that are defined in the following way:

Definition 2 (Affine/quadratic reaction networks): A reaction network is said to be

- *affine* if it involves only reactions of types 1 and 2 in Table I.
- *quadratic* if it involves at least one reaction of type 3 or 4 in Table I.

Based on the results of the last section, we can state the following propositions:

Proposition 3 (Ergodicity of affine networks, [12]): Let us consider a general affine reaction network and assume that the state-space $\mathcal{S}$ of the underlying Markov process is irreducible. Let the matrices $A \in \mathbb{R}^{d \times d}$ and $b \in \mathbb{R}_{\geq 0}^d$ be further defined as

$$\sum_{n=1}^{K} \lambda_n(x)\langle v, \zeta_n \rangle = x^{\mathsf{T}} A v + b^{\mathsf{T}} v. \quad (4)$$

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 $Av < 0$.
c) The stochastic reaction network has all its moments bounded and converging.

Moreover, when one of the above statements holds, the Markov process describing the reaction network is exponentially ergodic. △

Proposition 4 (Ergodicity of quadratic networks, [12]): Let us consider a general quadratic reaction network and assume that the state-space $\mathcal{S}$ of the underlying Markov process 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

$$\sum_{n=1}^{K} \lambda_n(x)\langle v, \zeta_n \rangle = x^{\mathsf{T}} M(v) x + x^{\mathsf{T}} A v + b^{\mathsf{T}} v. \quad (5)$$

Then, the underlying Markov process is exponentially ergodic and has all its moments bounded and converging if there exists $v \in \mathbb{R}_{>0}^d$ such that

$$Av < 0 \text{ and } M(v) = 0. \ \triangle \quad (6)$$

IV. Ergodicity analysis of interconnected stochastic reaction networks

A. Preliminaries

Let us consider now interconnections of networks. By interconnection, it is meant here that propensity functions of reactions involved in a subnetwork may depend on the state of another subnetwork. We do not consider here the case where different networks involve the same species. Let $x \in \mathbb{N}_0^d$ be the state of the overall network and let $x_i \in \mathbb{N}_0^{d_i}$ be the state of the subnetwork i where $d = \sum_{i=1}^{N} d_i$, N being the number of subnetworks. We assume that, w.l.o.g., we have that $x = \mathrm{col}_i(x_i)$. Note that this is consistent with the fact that every species is local to a subnetwork. Let K_i be the number of reactions involved in subnetwork i, ζ_k^i be the stoichiometry vector of reaction k in subnetwork i and $\lambda_k^i(x_i, z_i)$ is the propensity of reaction k in subnetwork i. The propensity functions depend on the state of the other subnetworks through the variables $z_i = \mathrm{col}_{j \neq i}(z_{ij})$, $z_{ij} = C_{ij} x_j$, $z_{ij} \in \mathbb{N}_0^{d_{ij}}$.

The generator of the Markov process describing the subnetwork i is acting on a function $f(x_i)$ in the domain of $\mathbb{A}_i$ as

$$\mathbb{A}_i f(x_i) = \sum_{k=1}^{K_i} \lambda_k^i(x_i, z_i) \left[f(x_i + \zeta_k^i) - f(x_i)\right]. \quad (7)$$

We can now state the following general result

Theorem 5: The following statements are equivalent

a) For $V(x) = v^\intercal x$, there exist $v \in \mathbb{R}_{>0}^d$ and $c_1, c_2 > 0$ such that
$$\mathbb{A}V(x) \le c_1 - c_2 V(x) \quad (8)$$
holds for all $x \in \mathbb{N}_0^d$ where $\mathbb{A}$ is the generator of the interconnected network.

b) For $V_i(x_i) = v_i^\intercal x_i$, there exist $v_i \in \mathbb{R}_{>0}^{d_i}$, $i = 1, \ldots, N$, and $\theta_1, \theta_2 > 0$ such that
$$\mathbb{A}_i V_i(x_i) \le \theta_1 - \theta_2 V_i(x_i) \quad (9)$$
for all $x_i \in \mathbb{N}_0^{d_i}$ and all $i = 1, \ldots, N$.

B. Affine and quadratic networks

We now specialize the above result to the case of affine and quadratic networks interconnections.

Theorem 6 (Affine networks): Let us consider a general interconnection of affine reaction networks and assume that the state-space $\mathcal{S}$ of the overall Markov process is irreducible. Let the matrices $A_i \in \mathbb{R}^{d_i \times d_i}$, $b_i \in \mathbb{R}_{\ge 0}^{d_i}$ and $B_{ij} \in \mathbb{R}_{\ge 0}^{d_i \times d_{ij}}$ be further defined as

$$\begin{array}{rcl} \mathbb{A}_i V_i(x_i) & = & \sum_{n=1}^{K_i} \lambda_n^i(x_i, z_i)\langle v_i, \zeta_n^i\rangle \\ & = & x_i^\intercal A_i v_i + \sum_{j\neq i} B_{ij} z_{ij} + b_i^\intercal v_i. \end{array} \quad (10)$$

Assume that there exist vectors $v_i \in \mathbb{R}_{>0}^{d_i}$, $\ell_{ij} \in \mathbb{R}_{>0}^{d_{ij}}$ such that the inequalities

$$\begin{array}{rcl} v_i^\intercal A_i + \sum_{j\neq i}^N \ell_{ji}^\intercal C_{ji} & < & 0 \\ v_i^\intercal B_{ij} - \ell_{ij}^\intercal & < & 0 \end{array} \quad (11)$$

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

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

Theorem 7 (Quadratic networks): Let us consider a general interconnection of affine reaction networks and assume that the state-space $\mathcal{S}$ of the overall Markov process is irreducible. Let the matrices $M_i(v) \in \mathbb{S}^{d_i + \sum_{j\neq i} d_{ij}}$, $A_i \in \mathbb{R}^{d_i \times d_i}$, $b_i \in \mathbb{R}_{\ge 0}^{d_i}$ and $B_{ij} \in \mathbb{R}_{\ge 0}^{d_i \times d_{ij}}$ be further defined as

$$\begin{array}{rcl} \mathbb{A}_i V_i(x_i) & = & \sum_{n=1}^{K_i} \lambda_n^i(x_i, z_i)\langle v_i, \zeta_n^i\rangle \\ & = & \begin{bmatrix} x_i \\ z_i \end{bmatrix}^\intercal M_i(v_i) \begin{bmatrix} x_i \\ z_i \end{bmatrix} + v_i^\intercal A_i x_i \\ & & + \sum_{j\neq i} B_{ij} z_{ij}. \end{array} \quad (12)$$

Assume that there exist vectors $v_i \in \mathbb{R}_{>0}^{d_i}$, $\ell_{ij} \in \mathbb{R}_{>0}^{d_{ij}}$ such that the conditions

$$\begin{array}{rcl} v_i^\intercal A_i + \sum_{j\neq i}^N \ell_{ji}^\intercal C_{ji} & < & 0 \\ v_i^\intercal B_{ij} - \ell_{ij}^\intercal & < & 0 \\ M_i(v_i) & = & 0 \end{array} \quad (13)$$

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

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

C. Distributed implementation

Interestingly, the decomposed conditions stated in the section above can be solved in a distributed way by relying on the dual formulation of the corresponding linear programs. This leads us to the following distributed formulation of the problem:

Proposition 8: The following optimization routine allows us to determine in a distributed way whether there exist $v_i \in \mathbb{R}_{>0}^{d_i}$ and $\ell_{ij} \in \mathbb{R}_{>0}^{n_{ij}}$, $i, j = 1, \ldots, N$, $j \neq i$, such that (11) in Theorem 6 holds. Below, every LP (indexed by i) is solved in a separate process (i.e. in parallel). In the last step, the different tasks share information and solve again the problem until it converges to a common solution.

a) Initialize $\kappa_{ij}(0)$

b) Repeat until the desired tolerance is achieved.

  a) For each i at each step k let:

$$\begin{array}{rcl} \digamma_i(k) & := & \operatorname{argmin} \quad L_i(v_i, \ell_i, \mu_i, \delta_i, \vartheta_i, \kappa_{ij}(k)) \\ & & \text{s.t.} \quad \vartheta_{Ai}, \vartheta_{vi}\vartheta_{\delta i}, \vartheta_{\mu i}, \overline{\vartheta}_{ij}^i, \vartheta_{ij}^i \ge 0 \end{array}$$

  where $\digamma_i(k) = [v_i(k), \ell_i(k), \mu_i(k), \delta_i(k), \vartheta_i(k)]$, $L_i(\cdot)$ is the Lagrangian of the problem and the variables besides the v_i's and ℓ_{ij}'s are Lagrange multipliers.

  b) Set $\kappa_{ij}(k+1) = \kappa_{ij}(k) + \alpha(\ell_{ij}^i(k) - \ell_{ij}^j(k))$ for an appropriate step size $\alpha > 0$.

V. Examples

A. Birth-death process

Let us consider first a simple birth-death process described by the reactions

$$\phi \xrightarrow{\alpha + Xf(X)} \mathbf{S}, \qquad \mathbf{S} \xrightarrow{\gamma} \phi \quad (14)$$

where $f(X)$ is an arbitrary positive function of the population count X of the species $\mathbf{S}$ and $\alpha, \gamma > 0$. Note that the state-space of the corresponding Markov process is irreducible.

Result 9: The reaction network is exponentially ergodic and has all its moments bounded if the condition $\sup_{x\in\mathbb{N}_0} f(x) < \gamma$ holds for all $x \in \mathbb{N}_0$. △

B. Open SIR-model

Let us consider now the following SIR-model

$$\begin{array}{rclrcl} \phi & \xrightarrow{k_1} & \mathbf{S_1}, & \phi & \xrightarrow{k_2} & \mathbf{S_2}, \\ \phi & \xrightarrow{k_3} & \mathbf{S_3}, & \mathbf{S_1} & \xrightarrow{\gamma_1} & \phi, \\ \mathbf{S_2} & \xrightarrow{\gamma_2} & \phi, & \mathbf{S_3} & \xrightarrow{\gamma_3} & \phi, \\ \mathbf{S_2} & \xrightarrow{k_{23}} & \mathbf{S_3}, & \mathbf{S_3} & \xrightarrow{k_{31}} & \mathbf{S_1}, \\ \mathbf{S_1} + \mathbf{S_2} & \xrightarrow{k_{12}} & 2\mathbf{S_2}. & & & \end{array} \quad (15)$$

where $\mathbf{S_1}$, $\mathbf{S_2}$ and $\mathbf{S_3}$ represent susceptible, infectious and recovered people. The first three reactions represent people entering the process whereas the next three ones model how people leave the system. The two following ones describe how people pass from the infectious to the recovered state, and from the recovered to the susceptible state, respectively.

The last one, finally, is the contamination reaction transforming one susceptible person into an infectious one. It can be shown that the state-space of the underlying Markov process is irreducible since any state can be reached from any other state using a sequence of reactions having positive propensities.

Result 10: For any positive values of the rate of the parameters, the above SIR-model is exponentially ergodic and has all its moment bounded and converging.

C. SIR-decomposition

The network (15) can be decomposed as

$$\begin{array}{ccccc} \phi & \xrightarrow{k_1+k_{31}X_3} & \mathbf{S_1} & \xrightarrow{\gamma_1} & \phi, \\ \phi & \xrightarrow{k_2} & \mathbf{S_2} & \xrightarrow{\gamma_2+k_{23}} & \phi, \\ \mathbf{S_1}+\mathbf{S_2} & \xrightarrow{k_{12}} & 2\mathbf{S_2} & & \\ \hline \phi & \xrightarrow{k_3+k_{23}X_2} & \mathbf{S_3} & \xrightarrow{\gamma_3+k_{31}} & \phi. \end{array} \tag{16}$$

Note first that the above network is *not equivalent* to (15) since, the stationary distribution, and thus the moments, will differ. This comes from the break down of several reactions. However, in the current setup, ergodicity of the networks is equivalent since we are relying on *linear Foster-Lyapunov functions*. The ergodicity conditions of these networks are, in this case, identical.

This network can then be decomposed as the interconnection of two networks. The first subnetwork contains susceptible and infectious people whereas recovered people are located in the second one. In such a case, the first network is quadratic and the second one is affine. Therefore, we have that $M_1(v_1) = 0$ iff $v_1 = \theta_1 \begin{bmatrix} 1 & 1 \end{bmatrix}^\mathsf{T}$ for some $\theta_1 > 0$ and $M_2(v_2)$ is automatically 0 since the network is affine. Note that if the network was decomposed in three subnetworks, then the same species $\mathbf{S_1}$ and $\mathbf{S_2}$ would be involved in multiple networks, which is not allowed by the current framework.

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