

Stochastic Robust Simulation and Stability Properties of Chemical Reaction Networks

*Original*

Stochastic Robust Simulation and Stability Properties of Chemical Reaction Networks / Possieri, Corrado; Teel, Andrew R.. - In: IEEE TRANSACTIONS ON CONTROL OF NETWORK SYSTEMS. - ISSN 2325-5870. - (2019), pp. 2-12. [10.1109/TCNS.2018.2789724]

*Availability:*

This version is available at: 11583/2724550 since: 2021-04-12T20:00:39Z

*Publisher:*

Institute of Electrical and Electronics Engineers Inc.

*Published*

DOI:10.1109/TCNS.2018.2789724

*Terms of use:*

This article is made available under terms and conditions as specified in the corresponding bibliographic description in the repository

*Publisher copyright*

IEEE postprint/Author's Accepted Manuscript

©2019 IEEE. Personal use of this material is permitted. Permission from IEEE must be obtained for all other uses, in any current or future media, including reprinting/republishing this material for advertising or promotional purposes, creating new collecting works, for resale or lists, or reuse of any copyrighted component of this work in other works.

(Article begins on next page)

# Stochastic Robust Simulation and Stability Properties of Chemical Reaction Networks

Corrado Possieri and Andrew R. Teel

**Abstract**—In this paper, a novel algorithm to perform robust stochastic simulations of chemical reaction networks is proposed. Such a procedure relies on the definition of a stochastic difference inclusion, whose trajectories match those of the chemical reaction network. By taking advantage of the correspondence between chemical reaction networks and stochastic difference inclusions, mathematical tools available for the latter discrete-time systems are used to characterize stability properties of chemical reaction networks. Namely, Lyapunov conditions are given to guarantee asymptotic stability in probability, global strong recurrence, and global weak reachability of a given set for the reaction network. Practical examples of application of the given algorithm and of the Lyapunov approach are reported.

## I. INTRODUCTION

In spatially homogeneous systems of chemical reactions, the time evolution of the concentrations of the involved molecules are usually computed by solving a large set of coupled Ordinary Differential Equations [1], [2], [3], [4]. This framework is widely adopted to represent a large setting of chemical reactions (see, for instance, [5], where a detailed differential model for the lac operon was developed to study diauxic growth on glucose and lactose). Such an approach is based on the so called “deterministic formulation” of chemical reactions [6], in which the concentrations of the involved species are considered as continuous function of time and reactions are viewed as rates of consumption or generation whose evolution is governed by a wholly predictable process. Even if such a deterministic approach is adequate in many cases of practical interest, some other interesting models for such reaction networks are receiving a growing interest as: Bayesian networks [7], cluster analysis [8], information-theoretic approaches [9], Boolean Networks [10], [11], [12].

One of the main limitations of the deterministic approach is that it does not take into account the stochastic nature of many chemical reactions. As a matter of fact, experimental evidences [13], [14] highlighted the fact that, when some species involved in the chemical reaction are present in very few numbers, the stochastic effects have a crucial role in the evolution of the reaction network. By this reasoning, stochastic models for chemical networks have received an increasing interest (see, e.g., [15], [16], [17], [18]). In such a stochastic approach, the chemical species concentrations evolve according to a sort of random-walk process, governed by a single Partial Differential Equation (the so called *Chemical Master Equation* [19]). This stochastic approach has a basis that relies on the actual physics of the system, but the Chemical Master Equation is often mathematically

intractable. By this reasoning, in [20], a procedure (namely, the Stochastic Simulation Algorithm) has been proposed to carry out exact numerical simulations of the given chemical network. Several methods have been proposed to execute such a procedure (see [21], [22] for a comparison of the different formulations of Gillespie’s algorithm), including specific toolkits (e.g., the software *StochKit* presented in [23]). Such algorithms received increasing interest since they provide a deeper understanding of the dynamics of complex reaction networks [24], [25], allowing to quantify the dependence of the system behavior on the reaction parameters [26].

The Stochastic Simulation Algorithm is considered exact because it does not approximate infinitesimal time increments by finite time steps and because it is based on the same physical principles of the Chemical Master Equation. It is worth stressing that, in the literature, also inexact stochastic simulation algorithm have been proposed (see, e.g., [27], [28]), but in this paper we focus just on exact methods.

The Stochastic Simulation Algorithm is a Monte Carlo type method and it can be easily employed to generate trajectories of the chemical reaction system and hence to compute statistics of the values of the variables. The main limitation of such a method is that it requires the exact knowledge of the *propensity functions*, i.e., those functions relating the current concentration of chemical species with the propensity that a certain reaction occurs. One of the main objectives of this paper is to propose an algorithm to perform stochastic simulation of chemical reaction networks without an exact knowledge of the propensity functions. Namely, by employing the modern theory about stochastic difference inclusions (see [29] and references therein), an algorithm is proposed to perform simulations of the chemical network when the reaction kinetics are not known exactly and are, possibly, time-varying. Practical examples of application of the proposed algorithm to models taken from the literature are given.

By taking advantage of this correspondence between chemical reaction networks with partially known kinetic constants and stochastic difference inclusions, the mathematical tools specifically developed for the latter class of systems can be employed to characterize stability properties of the chemical network. Namely, by employing Lyapunov arguments, conditions are given for asymptotic stability in probability, global strong recurrence, and global weak reachability of the chemical reaction network (for the formal definitions of these stability properties, see Section V). These properties are particularly interesting for biochemical reaction networks, since the presence of a certain chemical species above or below a given threshold may determine cell life or death [30], [31].

The remainder of the paper is organized as follows. The

notation employed in the paper is summarized in Section II. In Section III, stochastic methods used to model spatially homogeneous chemical reaction networks are reviewed. In Section IV, an algorithm to perform Robust Stochastic simulations of chemical reaction networks is given. In Section V, stability properties of the chemical reaction network are studied. Finally, conclusions are formulated in Section VI.

## II. NOTATION

We adopt the same notation used in [29].  $\mathbb{R}_{\geq 0}$  and  $\mathbb{Z}_{\geq 0}$  denote the set of real and integer numbers that are greater than or equal to zero, respectively. Given  $k \in \mathbb{Z}_{\geq 0}$ , the symbol  $\mathbb{Z}_{< k}$  is used to denote the set  $\{1, 2, \dots, k\}$ . Given a closed set  $\mathcal{A} \subset \mathbb{R}^\ell$  and  $x \in \mathbb{R}^\ell$ ,  $|x|_{\mathcal{A}} = \inf_{y \in \mathcal{A}} |x - y|$  denotes the Euclidean distance to  $\mathcal{A}$ . The symbols  $\mathbb{B}$  and  $\mathbb{B}^o$  represent the closed and open unit ball of appropriate dimensions, respectively. The symbol  $\mathbb{I}_{\mathcal{A}}(x)$  denotes the *indicator function* of  $\mathcal{A}$ , i.e.,  $\mathbb{I}_{\mathcal{A}}(x) = 1$ , if  $x \in \mathcal{A}$ , or  $\mathbb{I}_{\mathcal{A}}(x) = 0$ , otherwise. A function  $\alpha : \mathbb{R}_{\geq 0} \rightarrow \mathbb{R}_{\geq 0}$  is of class  $\mathcal{K}$ , denoted  $\alpha \in \mathcal{K}$ , if it is continuous, strictly increasing and  $\alpha(0) = 0$ . A function  $\alpha : \mathbb{R}_{\geq 0} \rightarrow \mathbb{R}_{\geq 0}$  is of class  $\mathcal{K}_\infty$ , denoted  $\alpha \in \mathcal{K}_\infty$ , if  $\alpha \in \mathcal{K}$  and it is unbounded. A function  $\phi : \mathbb{R}^\ell \rightarrow \mathbb{R}^s$  is *upper semicontinuous* if for each sequence  $x_i$  converging to  $x$ ,  $\limsup_{i \rightarrow \infty} \phi(x_i) \leq \phi(x)$ . A function  $\phi : \mathbb{R}^\ell \rightarrow \mathbb{R}^s$  is *lower semicontinuous* if  $-\phi$  is upper semicontinuous. A set-valued mapping  $G : \mathbb{R}^\ell \rightrightarrows \mathbb{R}^s$  is a relation assigning to each point  $x$  in  $\mathbb{R}^\ell$  a set  $G(x)$  in  $\mathbb{R}^s$ . A set-valued mapping  $G : \mathbb{R}^\ell \rightrightarrows \mathbb{R}^s$  is *outer semicontinuous* at  $\bar{x} \in \mathbb{R}^\ell$  if  $\limsup_{x \rightarrow \bar{x}} G(x) \subset G(\bar{x})$ , where  $\limsup_{x \rightarrow \bar{x}} G(x) := \{y \in \mathbb{R}^s : \exists x^\nu \rightarrow \bar{x}, \exists y^\nu \rightarrow y, \text{ with } y^\nu \in G(x^\nu)\}$ . A mapping  $G : \mathbb{R}^\ell \rightrightarrows \mathbb{R}^s$  is locally bounded if, for each bounded set  $S \subset \mathbb{R}^\ell$ ,  $G(S) := \bigcup_{x \in S} G(x)$  is bounded. A mapping  $G : \mathbb{R}^\ell \rightrightarrows \mathbb{R}^s$  is measurable if, for every open set  $\mathcal{O} \subset \mathbb{R}^s$ , the set  $G^{-1}(\mathcal{O}) := \{y \in \mathbb{R}^\ell : S(y) \cap \mathcal{O} \neq \emptyset\}$  is measurable.

## III. STOCHASTIC MODELING OF CHEMICAL REACTIONS

In this section, we review stochastic methods for modeling (spatially homogeneous) systems of chemical reactions following the exposition given in [20], [6], [32], [33].

The problem considered in this paper is the following: ‘Consider a fixed volume  $V$  that contains a spatially uniform distribution of  $n$  molecules which can interact through  $m$  chemical reactions. Given the numbers of molecules of each species present at some initial time, what will these molecular population levels be at any later time?’ Before turning to a quantitative solution to such problem, we need to introduce some terminology related to the chemical reaction network, that is usually characterized by the following two properties:

- *Stoichiometry*: specifies the species that participate in a chemical reaction, together with the molar ratio in which they are produced or consumed.
- *Reaction kinetics*: describe the dynamics of the reaction based on its mechanism and the enzyme properties.

In structural analysis of biochemical network, since metabolic reactions are usually characterized by fast kinetic, the dynamics of the reactions are usually neglected [34]. This

led to the following formal description of the structure and stoichiometry of a reaction network:

- $n$ : number of (internal) chemical species;
- $m$ : number of chemical reactions;
- $S$ : a matrix in  $\mathbb{Z}^{m \times n}$ , whose  $(i, j)$ -th entry  $s_{i,j}$  represents the stoichiometric coefficient of specie  $j$  in reaction  $i$ , with the following convention:  $s_{i,j} > 0$ , if  $i$  produces  $j$ ,  $s_{i,j} < 0$ , if  $i$  consumes  $j$ .

Note that, in such a framework, a reversible reaction can be modeled as two separate reactions proceeding in opposite directions and that the structure of any reaction network can be modeled through such a formalism. Furthermore, simple linear algebra techniques can be employed to efficiently perform Stoichiometric Network Analysis (briefly, SNA). In fact, *conservation relations* (i.e., weighted sums of reagent concentrations which remain constant in the system) can be computed as row vectors  $y \in \mathbb{Z}^{1 \times m}$  lying in the left null-space of the stoichiometric matrix  $S$ . Moreover, by applying the *quasi steady state assumption* [35], the right null-space of the matrix  $S$  provides the set of all flux distributions such that the production (sum of positive fluxes) and the consumption (sum of negative fluxes) of a reagent are equal.

The analysis tools reported so far can be efficiently employed to perform analysis of biochemical networks where the concentration of biomolecules is sufficiently high to guarantee that the network dynamics behave deterministically. However, many biological processes are triggered by random collisions of molecules. Especially when the concentration of biomolecules is low (and hence a particular reaction happens infrequently), these random collisions could lead to substantial fluctuations, which may affect other reactions and hence propagate through the network. This aspect led to the necessity of developing a tool able to deal with such randomness.

In [20], Gillespie proposed a simple digital computer algorithm which uses a rigorously derived Monte Carlo procedure to numerically simulate the time evolution of the given chemical system. Namely, let  $n$  be the number of chemical species involved,  $m$  be the number of chemical reactions, and  $S$  be the *stoichiometric matrix* corresponding to the reaction network. Define the vector  $x = [x_1 \ \dots \ x_n]^\top \in \mathbb{Z}_{\geq 0}^n$ , whose  $j$ -th entry  $x_j$  denotes the number of molecules of specie  $j$ . The rate of occurrence of reaction  $i$  is characterized by the  $i$ -th *propensity function*  $r_i : \mathbb{Z}_{\geq 0}^n \rightarrow \mathbb{R}_{\geq 0}$ , which depends only on the current state of the system. In fact, letting  $\theta_i$  be the kinetic coefficient of the  $i$ -th reaction and letting

$$\mathcal{N}_i := \{j \in \{1, \dots, n\} : \ell_{i,j} \neq 0\},$$

where  $\ell_{i,j}$  denotes the molar ratio in which the  $j$ -th specie is consumed by the  $i$ -th reaction, the  $i$ -th propensity function is

$$r_i(x) = \begin{cases} \theta_i \prod_{j \in \mathcal{N}_i} \binom{x_j}{\ell_{i,j}}, & \text{if } \mathcal{N}_i \neq \emptyset, \\ \theta_i, & \text{if } \mathcal{N}_i = \emptyset. \end{cases} \quad (1)$$

It is worth remarking that the stoichiometric matrix  $S$  encodes also the change of the number of molecules due to the  $i$ -th reaction. Namely, reaction  $i$  changes component  $j$

from  $x_j$  to  $x_j + s_{i,j}$ ,  $i = 1, \dots, m$ ,  $j = 1, \dots, n$ . Thus, the probability that some reaction occurs can be characterized by

$$r_0(x) = \sum_{i=1}^m r_i(x).$$

By employing these observations, Gillespie defined a simple algorithm (formalized through Algorithm 1) for generating individual paths of the random process [36].

---

**Algorithm 1** Stochastic Simulation Algorithm.

---

**Input:** Functions  $r_1(x), \dots, r_m(x)$ , stoichiometric matrix  $S$ , initial time  $t_0$ , final time  $t_f$ , initial condition  $x_0 \in \mathbb{Z}_{\geq 0}^n$  of the reaction network, and a sufficiently small  $\varepsilon > 0$ .

**Output:** A stochastic simulation of the reaction network.

- 1: Define the sequences  $\mathbf{t} := \{t_0\}$  and  $\mathbf{x} := \{x_0\}$ .
- 2: **while**  $t \leq t_f$  **do**
- 3: Let  $x = [x_1 \ \dots \ x_n]^\top$  be the last element of the sequence  $\mathbf{x}$ , and let  $\bar{r}_i = r_i(x)$ ,  $i = 1, \dots, m$ .
- 4: Compute  $\bar{r}_0 := \sum_{i=1}^m \bar{r}_i$ .
- 5: Pick a random number  $v_1$  from Uniform(0, 1).
- 6: Pick a random number  $v_2$  from Uniform( $\varepsilon$ , 1).
- 7: Compute  $\tau = \frac{1}{\bar{r}_0} \ln(\frac{1}{v_2})$ .
- 8: Find  $\mu \in \{1, \dots, m\}$  such that

$$\sum_{i=1}^{\mu-1} r_i(x) < v_1 r_0 \leq \sum_{i=1}^{\mu} r_i(x).$$

- 9: Let  $t$  be the last element of  $\mathbf{t}$  and append  $t + \tau$  to  $\mathbf{t}$ .
  - 10: Append  $[x_1 + s_{\mu,1} \ \dots \ x_n + s_{\mu,n}]^\top$  to  $\mathbf{x}$ .
  - 11: **end while**
  - 12: **return** The sequences  $\mathbf{t}$  and  $\mathbf{x}$ .
- 

The output of Algorithm 1 is two sequences  $\mathbf{t}$  and  $\mathbf{x}$  representing the times  $\mathbf{t}_k$  in which a chemical reaction has occurred and the state  $\mathbf{x}_k(t)$  of the biological reaction network for all times  $t \in [\mathbf{t}_k, \mathbf{t}_{k+1})$ .

#### IV. ROBUST STOCHASTIC SIMULATION

In this section, the results reviewed in Section III are extended to cope with uncertainties in the kinetic parameters  $\theta_i$ ,  $i = 1, \dots, m$ . Namely, one limitation of the Stochastic Simulation Algorithm 1 is that the  $\theta_i$ 's, employed in (1) to compute the propensity functions  $r_i$ 's, have to be time-invariant and exactly known. One of the main objectives of this paper, achieved in this section, is to formalize a robust stochastic simulation algorithm where such a requirement may not be satisfied. This goal is attained by exploiting a class of stochastic difference inclusions, taken from [29], [37], that appears particularly suitable for such a scope.

Let  $\xi = [x^\top \ \theta^\top \ t]^\top \in \mathbb{R}^{n+m+1}$ , where  $x = [x_1 \ \dots \ x_n]^\top$  denotes the concentration of the molecules of each specie involved in the chemical reaction,  $\theta$  denotes the current parameter that is employed to carry out the simulation and  $t$  is the reaction time. Let  $\varepsilon > 0$  be a sufficiently small parameter related to the maximum dwell time between two chemical reactions. Let  $v = [v_1 \ v_2]^\top$  be the input and

assume that the only available knowledge about  $\theta_i$  is that  $\theta_i \in [\underline{\theta}_i, \bar{\theta}_i] \subset \mathbb{R}_{>0}$ ,  $i = 1, \dots, m$ . Hence, define the set

$$\Theta = [\underline{\theta}_1, \bar{\theta}_1] \times [\underline{\theta}_2, \bar{\theta}_2] \times \dots \times [\underline{\theta}_m, \bar{\theta}_m] \subset \mathbb{R}_{>0}^m. \quad (2)$$

**Remark 1.** In order to define the set  $\Theta$  in (2), upper and lower bounds on the kinetic coefficients  $\theta_1, \dots, \theta_m$  have to be determined. Several computational methods are available in the literature to determine such constants [38], [39]. As an example, by using the Bennett–Chandler procedure [40], [41], define the *correlation function*  $F_i$  of the  $i$ -th reaction,

$$F_i(t) := \frac{\langle \mathbb{I}_{A_i}(0) \mathbb{I}_{B_i}(t) \rangle}{\langle \mathbb{I}_{A_i} \rangle},$$

where  $A_i$  are the reactants,  $B_i$  are the products,  $\mathbb{I}_{A_i}(t)$  (respectively,  $\mathbb{I}_{B_i}(t)$ ) equals 1 if the system at time  $t$  is in state  $A_i$  (respectively,  $B_i$ ) or 0 if it is not, and  $\langle \cdot \rangle$  denotes equilibrium averages (for further details, see [42]). Then, the rate of the reaction from  $A_i$  to  $B_i$  is given by

$$\theta_i = \dot{F}_i, \quad i = 1, \dots, m.$$

Since  $F_i(t)$  need not be constant during the reaction, the upper and lower bounds in (2) can be defined as

$$\underline{\theta}_i = \inf_{t \geq 0} \dot{F}_i(t), \quad \bar{\theta}_i = \sup_{t \geq 0} \dot{F}_i(t).$$

Letting  $s_{i,j}$ ,  $\ell_{i,j}$ , and  $\mathcal{N}_i$  be defined as in Section III, let  $\tilde{r}_i : \mathbb{Z}_{\geq 0}^n \times \Theta \rightarrow \mathbb{R}_{\geq 0}$ ,  $i = 0, \dots, m$ ,

$$\tilde{r}_i(x, \theta) = \begin{cases} \theta_i \prod_{j \in \mathcal{N}_i} (\ell_{i,j}^{x_j}), & \text{if } \mathcal{N}_i \neq \emptyset, \\ \theta_i, & \text{if } \mathcal{N}_i = \emptyset, \end{cases} \quad (3a)$$

$$\tilde{r}_0(x, \theta) = \sum_{i=1}^m \tilde{r}_i(x, \theta), \quad (3b)$$

and define  $s : \mathbb{Z}_{\geq 0}^n \times \Theta \times [0, 1] \rightrightarrows \mathbb{Z}_{\geq 0}^n$  as

$$\begin{cases} \{S_{\mu-1}^\top, S_\mu^\top\}, & \text{if } \sum_{i=1}^{\mu-1} \tilde{r}_i(x, \theta) = v \tilde{r}_0(x, \theta) = \sum_{i=1}^{\mu} \tilde{r}_i(x, \theta), \\ S_\mu^\top & \text{if } \sum_{i=1}^{\mu-1} \tilde{r}_i(x, \theta) < v \tilde{r}_0(x, \theta) \leq \sum_{i=1}^{\mu} \tilde{r}_i(x, \theta), \end{cases}$$

where  $S_\mu = [s_{\mu,1} \ \dots \ s_{\mu,n}]^\top$ . Hence, define the set-valued mapping  $G : \mathbb{R}^{n+m+3} \rightrightarrows \mathbb{R}^{n+m+1}$  as follows:

- (a) if  $x \in \mathbb{R}^n \setminus \mathbb{Z}_{\geq 0}^n$ , or  $\theta \in \mathbb{R}^m \setminus \Theta$ , or  $t \notin \mathbb{R}_{\geq 0}$ , or  $v_1 \notin [0, 1]$ , or  $v_2 \notin [\varepsilon, 1]$ , then

$$G(x, \theta, t, v) = \emptyset; \quad (4a)$$

- (b) if  $(x, \theta) \in \mathbb{Z}_{\geq 0}^n \times \Theta$  is such that  $\tilde{r}_0(x, \theta) = 0$ , then

$$G(x, \theta, t, v) = \emptyset, \quad (4b)$$

for each  $v \in \mathbb{R}^2$ ;

- (c) if both items (a) and (b) do not hold, then

$$G(x, \theta, t, v) = \begin{bmatrix} x + s(x, \theta, v_1) \\ \Theta \\ t + \frac{1}{\tilde{r}_0(x, \theta)} \ln(\frac{1}{v_2}) \end{bmatrix}. \quad (4c)$$

Thus, consider the stochastic difference inclusion with state  $\xi \in \mathbb{R}^{n+m+1}$  and random input  $v \in \mathbb{R}^2$

$$\xi^+ \in G(\xi, v), \quad (5)$$

where the first three arguments of the set-valued mapping  $G$  have been lumped together in the vector  $\xi$ . In order to define random solutions, we add a probability structure to (5). Let  $(\Omega, \mathcal{F}, \mathbb{P})$  be a probability space and let  $\mathbf{v} = \{\mathbf{v}_k\}_{k=0}^\infty$  be a sequence of independent, identically distributed (i.i.d.) input random variables defined on  $(\Omega, \mathcal{F}, \mathbb{P})$ . Namely, letting  $\mathbf{v}_k : \Omega \rightarrow \mathbb{R}^2$ ,  $k \in \mathbb{Z}_{\geq 0}$ , denote the elements of such a sequence,  $\mathbb{P}(\{\omega \in \Omega : \mathbf{v}_k(\omega) \in A\})$  is well defined and independent of  $k$  for each  $A$  in the Borel  $\sigma$ -field over  $\mathbb{R}^2$ , denoted  $\mathbf{B}(\mathbb{R}^2)$ . Therefore, the distribution function  $\mu : \mathbf{B}(\mathbb{R}^2) \rightarrow [0, 1]$ , is defined as  $\mu(A) := \mathbb{P}(\{\omega \in \Omega : \mathbf{v}_k(\omega) \in A\})$ . We use  $\mathcal{F}_k$  to denote the collection of sets  $\{\omega \in \Omega : (\mathbf{v}_0(\omega), \dots, \mathbf{v}_k(\omega)) \in A\}$ ,  $A \in \mathbf{B}((\mathbb{R}^2)^k)$ , which are the sub- $\sigma$ -fields of  $\mathcal{F}$  that form the minimal filtration of  $\mathbf{v}$  [43].

The *graph* of a sequence  $\{\phi_k\}_{k=0}^{K-1}$  is defined as  $\text{grp}(\phi) := \bigcup_{k=0}^{K-1} \{k\} \times \{\phi_k\}$ . A sequence  $\{(\xi_k, \mathbf{u}_k)\}_{k=0}^{K-1}$  with  $(\xi_k, \mathbf{u}_k) \in \mathbb{R}^{n+m+1} \times \mathbb{R}^2$  is a *regular solution* to (5) starting at  $\xi$  if  $\xi_0 = \xi$  and  $\xi_{k+1} \in G(\xi_k, \mathbf{u}_k)$  for all  $k \in \{0, \dots, K-2\}$ . A map  $\xi$  from  $\Omega$  to sequences in  $\mathbb{R}^{n+m+1}$  is a *random solution* to (5) starting at  $\xi$  if the following two conditions hold:

- for each  $\omega \in \Omega$ , the sequence  $\{(\xi_k(\omega), \mathbf{u}_k(\omega))\}_{k=0}^{\mathbf{K}_\xi(\omega)-1}$  is a regular solution to (5) starting at  $\xi$ , where  $\mathbf{K}_\xi : \Omega \rightarrow \mathbb{Z}_{\geq 0} \cup \{\infty\}$  denotes the length of the sequence  $\xi$ ;
- for all  $k \in \mathbb{Z}_{\geq 0}$ , the map  $\omega \mapsto \xi_{k+1}(\omega)$  is  $\mathcal{F}_i$ -measurable, where  $(\mathcal{F}_0, \mathcal{F}_1, \dots)$  is the minimal filtration of  $\mathbf{v}$ .

The first condition guarantees that for each outcome of the random sequence  $\mathbf{v}$ ,  $\{(\xi_k(\omega), \mathbf{v}_k(\omega))\}_{k=0}^{\mathbf{K}_\xi(\omega)-1}$  is a regular solution to the difference inclusion (5), while the second condition prevents the  $k$ -th value of the state sequence from anticipating the values of the random input at future times.

A random solution  $\mathbf{x}$  is *maximal*, denoted  $\mathbf{x} \in \mathcal{S}_r(x)$ , if there does not exist another random solution  $\mathbf{y}$  to (5) starting at  $x$  such that  $\text{dom } \mathbf{x}_k \subset \text{dom } \mathbf{y}_k$ , for all  $k \in \mathbb{Z}_{\geq 0}$ ,  $\mathbf{y}_k(\omega) = \mathbf{x}_k(\omega)$  for all  $\omega \in \text{dom } \mathbf{x}_k$  and all  $k \in \mathbb{Z}_{\geq 0}$ , and  $\text{dom } \mathbf{x}_k \neq \text{dom } \mathbf{y}_k$ , for some  $k \in \mathbb{Z}_{\geq 0}$ .

It is worth noticing that fixing  $\omega \in \Omega$  corresponds to selecting a sequence of inputs  $\mathbf{v}$ . With such fixed inputs, system (5) can be viewed as a time-varying, deterministic difference inclusion that can be studied through classical tools [44]. On the other hand, the main objective of this paper is to study the properties of the network induced by the given probability structure.

In order to define a stochastic simulation algorithm through the stochastic difference inclusion (5), in the remainder of this paper we will assume the following distribution of the entries of the input:  $v_1 \sim \text{Uniform}(0, 1)$  and  $v_2 \sim \text{Uniform}(\varepsilon, 1)$ . As a matter of fact, with such a choice for the random input, if the parameters  $\theta_i$ 's of the chemical reaction are known exactly, i.e.,  $\underline{\theta}_i = \bar{\theta}_i = \theta_i$ ,  $i = 1, \dots, m$ , then  $\Theta = \{\theta_1\} \times \{\theta_2\} \times \dots \times \{\theta_m\}$  and hence  $\xi(\omega) \in \mathcal{S}_r([x^\top \ \theta_1 \ \dots \ \theta_m \ 0]^\top)$  corresponds to the output of the Stochastic Simulation Algorithm 1 with initial condition  $x_0 = x$ , provided that solutions exist. Moreover, thanks to its structure, the stochastic system (5) allows to cope with partially known and time-varying kinetic coefficients.

The following theorem allows to guarantee the existence of random solutions to the stochastic difference inclusion (5).

**Theorem 1.** *The set valued mapping  $G : \mathbb{R}^{n+m+3} \rightrightarrows \mathbb{R}^{n+m+1}$  is locally bounded and the mapping  $v \mapsto \text{grp}(G(\cdot, v)) := \{(\xi, y) \in \mathbb{R}^{n+m+3} \times \mathbb{R}^{n+m+1} : y \in G(x, v)\}$  is measurable with closed values.*

*Proof.* For each  $(\bar{\xi}, \bar{v}) \in \mathbb{R}^{n+m+1} \times \mathbb{R}^2$  such that  $G(\bar{\xi}, \bar{v}) \neq \emptyset$ , there exists a neighborhood  $\mathcal{U}$  of  $(\bar{\xi}, \bar{v})$  and  $\delta \in \mathbb{R}_{>0}$  such that  $G(\xi, v) \subset \delta \mathbb{B}$ , for all  $(\xi, v) \in \mathcal{U}$ . Hence, the set valued mapping  $G$  is locally bounded. Furthermore, for each  $(x, \theta, t, v)$  such that both items (a) and (b) do not hold, the mapping  $(x, \theta, v) \mapsto s(x, \theta, v)$  is outer semicontinuous and hence the map  $v \mapsto \text{grp}(G(\cdot, v))$  has closed values. The measurability of the mapping  $v \mapsto \text{grp}(G(\cdot, v))$  follows from the measurability of the mappings  $v_1 \mapsto \text{grp}(s(\cdot, \cdot, v_1))$ ,  $v_2 \mapsto \text{grp}(\frac{1}{\bar{r}_0(\cdot, \cdot)} \ln(\frac{1}{v_2}))$  and the same arguments employed in the proofs of [37, Prop. 3] and [45, Ex. 1].  $\square$

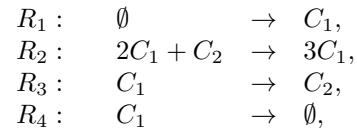
Theorem 1 guarantees that the stochastic difference inclusion (5) satisfies Standing Assumption 1 of [29], [46] and hence that, for each  $(\xi, v) \in \mathbb{R}^{n+m+1} \times \mathbb{R}^2$   $G(\xi, v)$  is a compact (possibly, empty) set and that random solutions to (5) exist. Taking advantage of the latter result, in the following proposition we provide a characterization of maximal solution to the stochastic difference inclusion (5).

**Proposition 1.** *Let  $\xi \in \mathbb{Z}_{\geq 0}^n \times \Theta \times \mathbb{R}_{\geq 0}$  be given and let  $\xi \in \mathcal{S}_r(\xi)$ . Then, the length  $\mathbf{K}_\xi$  of  $\xi$  is bounded if and only if  $\xi_{\mathbf{K}_\xi(\omega)}(\omega)$  is such that no chemical reaction can occur.*

*Proof.* By Theorem 1 and [37, Prop. 15], maximal random solutions to (5) exist. Then, by the definition of the set-valued mapping  $G : \mathbb{R}^{n+m+3} \rightrightarrows \mathbb{R}^{n+m+1}$ , if  $\xi \in \mathbb{Z}_{\geq 0}^n \times \Theta \times \mathbb{R}_{\geq 0}$  then item (a) does not hold for any  $k \in \mathbb{Z}_{\geq 0}$  because  $G(\xi \in \mathbb{Z}_{\geq 0}^n \times \Theta \times \mathbb{R}_{\geq 0} \times [0, 1] \times [\varepsilon, 1]) \subset \mathbb{Z}_{\geq 0}^n \times \Theta \times \mathbb{R}_{\geq 0}$ . Hence, since (b) holds if and only if no chemical reaction can occur, then the length  $\mathbf{K}_\xi(\omega)$  is bounded for some  $\omega \in \Omega$  if and only if  $\xi_{\mathbf{K}_\xi(\omega)}(\omega)$  is such that no chemical reaction can occur.  $\square$

The following two examples show how to compute a random solution  $\mathbf{x}(\omega)$  for some  $\omega \in \Omega$  to the system (5).

**Example 1.** Consider a simple auto-catalytic system consisting of two homogeneously distributed chemical species  $C_1$ ,  $C_2$ , and four reactions:



where  $\emptyset$  denotes arbitrary external sources and sinks for the reactions. Define the state  $x = [x_1 \ x_2]^\top \in \mathbb{Z}_{\geq 0}^2$ , where  $x_j$  counts the number of copies of the  $j$ -th specie  $C_j$ . In such a reaction network the propensity functions are given by

$$\begin{aligned} \tilde{r}_1(\theta, x) &= \theta_1, \\ \tilde{r}_2(\theta, x) &= \theta_2 \frac{x_1(x_1-1)}{2} x_2, \\ \tilde{r}_3(\theta, x) &= \theta_3 x_1, \\ \tilde{r}_4(\theta, x) &= \theta_4 x_1. \end{aligned}$$

Let  $\theta_i$  be the kinetic parameter corresponding to reaction  $R_i$ ,  $i = 1, \dots, 4$ , and define the stoichiometric matrix

$$S := \begin{bmatrix} 1 & 1 & -1 & -1 \\ 0 & -1 & 1 & 0 \end{bmatrix}^\top.$$

Assume that the kinetic parameters are known with uncertainty, i.e.,  $\Theta = [9.8, 10.1] \times [0.9, 1.01] \times [49, 50] \times [0.8, 1.2]$ . The following Algorithm 2 allows to compute a random sample from solutions belonging to  $S_r(\xi)$ .

---

**Algorithm 2** Robust Stochastic Simulation Algorithm.

---

**Input:** stoichiometric matrix  $S$ , number of steps  $K$ , initial condition  $\xi_0 \in \mathbb{Z}_{\geq 0}^n \times \Theta \times \{0\}$  and  $\varepsilon > 0$ .

**Output:** A stochastic simulation of system (5).

- 1: Define the sequence  $\xi := \{\xi_0\}$  and let  $k = 0$ .
  - 2: **while**  $k \leq K$  **do**
  - 3:   Let  $\xi_k = [x^\top \ \theta^\top \ t]^\top$  be the last element of  $\xi$ .
  - 4:   Use (3) to compute  $r_i(x, \theta)$  for  $i = 0, \dots, m$ .
  - 5:   Pick a random number  $v_1$  from Uniform(0, 1).
  - 6:   Pick a random number  $v_2$  from Uniform( $\varepsilon$ , 1).
  - 7:   Use (5) to compute  $\xi_{k+1}$ .
  - 8:   **if**  $\xi_{k+1} = \emptyset$  **then**
  - 9:     **return** The algorithm has been interrupted because no reaction will occur.
  - 10:   **end if**
  - 11:   Append  $\xi_{k+1}$  to  $\xi$  and set  $k = k + 1$ .
  - 12: **end while**
  - 13: **return** The sequence  $\xi$ .
- 

It is worth remarking that the output of Algorithm 2 is not a random solution to system (5), which is a function mapping  $\omega \in \Omega$  to sequences in  $\mathbb{R}^{n+m+1}$ . In fact, such an output is the value of a random solution  $\xi(\omega)$  computed for some  $\omega \in \Omega$  (namely, one of the  $\omega$ 's corresponding to the values of the random inputs picked at Steps 5 and 6 for all  $k \in \{0, \dots, K\}$ ). However, since a closed-form expression for random solutions to system (5) cannot be easily determined, Algorithm 2 is a powerful tool to analyze the behavior of the chemical reaction network. In fact, as Algorithm 1, by repeating such a procedure until a sufficient amount of data is gathered, statistically correct estimates of the system behavior can be obtained.

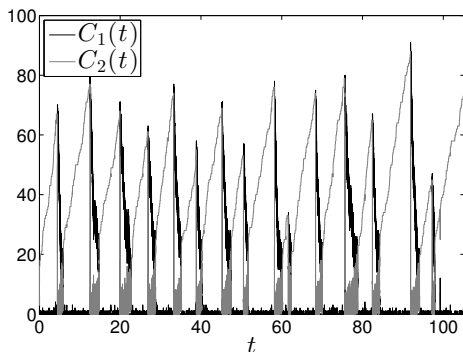


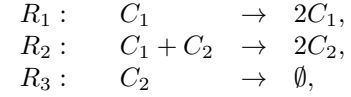
Fig. 1: Simulation corresponding to the output of Algorithm 2 in the first example.

Figure 1 depicts a simulation of the chemical reaction network obtained through Algorithm 2 with input  $S$ ,  $K = 10^5$ ,  $\xi_0 = [x_0^\top \ \theta_0^\top \ 0]^\top$ ,  $x_0 = [10 \ 5]^\top$ ,  $\theta_0 = [10 \ 1 \ 50 \ 1]^\top$ ,  $\varepsilon = 10^{-12}$ , and the next value of  $\theta$  is chosen uniformly randomly in  $\Theta$ .  $\triangle$

In order to carry out Step 7 of Algorithm 2, a vector in  $G(\xi_k, v)$  (that generically is not a singleton) has to be selected. In Example 1, such a selection has been made by choosing the next value of  $\theta$  uniformly randomly in  $\Theta$ , but, in principle, any other selection can be made.

The following example illustrates the possible interruption of Algorithm 2 due to the fact that no reaction can occur and highlights its similarities with Algorithm 1 in the case of perfectly known reaction coefficients.

**Example 2.** Consider the following predator–prey model, consisting of two species  $C_1$  and  $C_2$  and three reactions:



Define the state vector  $x = [x_1 \ x_2]^\top \in \mathbb{Z}_{\geq 0}^2$  and define the stoichiometric matrix

$$S := \begin{bmatrix} 1 & -1 & 0 \\ 0 & 1 & -1 \end{bmatrix}^\top.$$

For this reaction network, the propensity functions are

$$\begin{aligned} \tilde{r}_1(\theta, x) &= \theta_1 x_1, \\ \tilde{r}_2(\theta, x) &= \theta_2 x_1 x_2, \\ \tilde{r}_3(\theta, x) &= \theta_3 x_1. \end{aligned}$$

Let  $\Theta = \{0.2\} \times \{0.1\} \times \{0.2\}$  (i.e., the kinetic parameters for such a reaction are known exactly). Algorithm 2 has been employed with input  $S$ ,  $K = 200$ ,  $\xi_0 = [5 \ 2 \ 0.2 \ 0.1 \ 0.2 \ 0]^\top$ ,  $\varepsilon = 10^{-12}$  to simulate the behavior of the reaction network. Note that, since the set  $\Theta$  is a singleton,  $\Theta = \{\bar{\theta}\}$ , for almost all  $x \in \mathbb{R}^n$ ,  $t \in \mathbb{R}_{\geq 0}$ ,  $v_1 \in [0, 1]$ , and  $v_2 \in [\varepsilon, 1]$ , the set  $G([x^\top \ \bar{\theta}^\top \ t]^\top, [v_1 \ v_2]^\top)$  is a singleton. Therefore, for almost all the initial conditions  $\xi_0$  of the reaction network, the Robust Stochastic Simulation Algorithm 2 reduces to Algorithm 1 since the steps that have to be carried out in the two procedures are, in this case, the same.

Figure 2 depicts two simulations of the behavior of the chemical reaction network obtained through Algorithm 2.

In the first simulation, depicted in Figure 2(a), Algorithm 2 has not been interrupted since, for the selected  $\omega$ , there does not exist  $k \in \{0, \dots, K\}$  such that  $\xi_k(\omega)$  is such that no reaction can occur. On the other hand, in the second simulation, depicted in Figure 2(b), Algorithm 2 has been interrupted at  $k = 85$  because, for the selected  $\omega$ ,  $\xi_{85}(\omega)$  is such that no reaction can occur. In fact, in such a latter simulation,  $\xi_{85}(\omega) = [0 \ 0 \ 0.2 \ 0.1 \ 0.2 \ 0]^\top$  and hence, since

$$\tilde{r}_0(x, \theta) = 0,$$

no reaction will occur for all future times.  $\triangle$

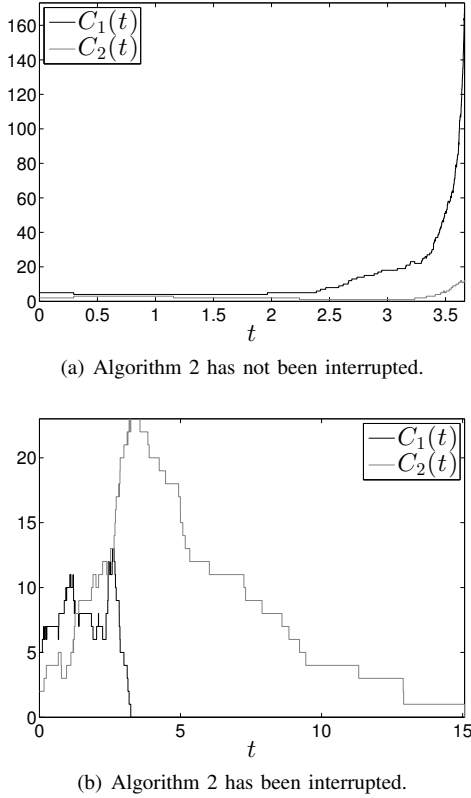
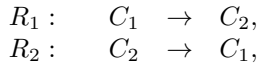


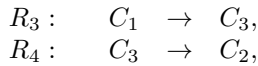
Fig. 2: Simulations corresponding to the output of Algorithm 2 in the second example.

Note that the set-valued nature of system (5) can be exploited to deal with reactions with unknown mechanisms and intermediate species, as shown in the following example.

**Example 3.** Consider the reaction network consisting of two species  $C_1$  and  $C_2$  and two reactions:



where there is a possible intermediate species  $C_3$  in  $R_1$ . To cope with such intermediate species, define the additional reactions



that substitute  $R_1$  if the intermediate species is present. Thus, define the (extended) state vector  $x_e = [x_1 \ x_2 \ x_3]^\top \in \mathbb{Z}_{\geq 0}^3$ , the stoichiometric matrix  $S_1$  involving  $R_1$  and  $R_2$ ,

$$S_1 = \begin{bmatrix} -1 & 1 & 0 \\ 1 & -1 & 0 \end{bmatrix},$$

and the stoichiometric matrix  $S_2$  involving  $R_3$ ,  $R_4$  and  $R_2$ ,

$$S_2 = \begin{bmatrix} -1 & 0 & 1 \\ 0 & 1 & -1 \\ 1 & -1 & 0 \end{bmatrix}.$$

Let  $\theta_e \in \mathbb{R}_{>0}^4$  be the extended vector of reaction rates, let  $\Theta_e \subset \mathbb{R}_{>0}^4$ , let  $\xi_e = [x_e^\top \ \theta_e^\top \ t]^\top \in \mathbb{R}^8$  and define the set valued mapping  $G_i : \mathbb{R}^{10} \rightrightarrows \mathbb{R}^8$  by using (3) and (4)

with  $S$  substituted by  $S_i$ ,  $i = 1, 2$ . Thus, consider the set-valued mapping  $G(\xi_e, u) = G_1(\xi_e, u) \cup G_2(\xi_e, u)$ . Clearly,  $G$  is locally bounded and by [43, Prop. 14.11(b)] the mapping  $v \mapsto \text{grp}(G(\cdot, v))$  is measurable with closed values, thus ensuring existence of random solutions to

$$\xi_e^+ \in G(\xi_e, u). \quad (6)$$

Note that the stochastic difference inclusion (6) encodes both the networks composed by  $R_1, R_2$  and by  $R_3, R_4, R_2$ , thus accounting for the possibility of an intermediate specie.

Assuming that the kinetic parameters are known,

$$\Theta_e = \{1\} \times \{0.3\} \times \{0.2\} \times \{0.8\},$$

Algorithm 2 has been used to simulate the behavior of the reaction network with  $K = 98$   $\xi_0 = [x_0^\top \ \theta_e^\top \ 0]^\top$ ,  $x_0 = [20 \ 10 \ 0]^\top$ , and  $\varepsilon = 10^{-12}$ . Note that, even if the kinetic parameters are known, in this case, Algorithm 2 does not reduce to Algorithm 1 because  $G$  need not be a singleton. Figure 3 depicts the results of such a simulation.  $\triangle$

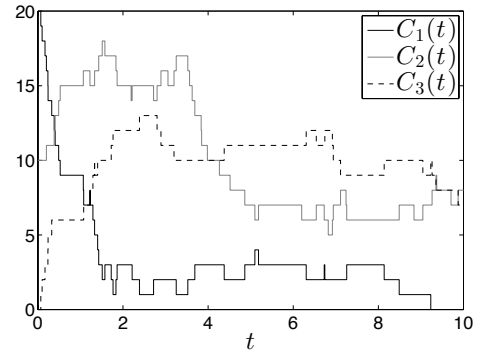


Fig. 3: Simulation obtained through Algorithm 2 for an uncertain reaction network.

The following example illustrates the application of Algorithm 2 to a real reaction network.

**Example 4.** Consider the reaction network for the combustion of propane presented in [47]. The network consists of 83 reactions and 29 chemical species, including  $C_3H_8$ ,  $CO$ ,  $HO_2$ ,  $H_2O_2$ , and a catalyst  $M$ . By [47], the kinetic coefficients of the reaction can be expressed as a function  $\psi : \mathbb{R}_{>0} \rightarrow \mathbb{R}_{>0}^{83}$  of the temperature  $T$  of the combustion process, which is in the range 1150–2600K. Therefore, letting  $\Theta := \psi([1150, 2600]) = \bigcup_{T \in [1150, 2600]} \psi(T)$ , Algorithm 2 can be used to simulate the behavior of such a chemical reaction network.

Figure 4 depicts the average of the outcomes of 1000 simulations of the combustion reaction performed with Algorithm 2, assuming that, at the initial time, 500, 600, and 200 molecules of  $C_3H_8$ ,  $O_2$ , and  $H_2O$  are present, respectively, whereas all the other chemical species are absent.

Figure 5 depicts the average of the outcomes of 1000 simulations of the same chemical reaction network, with the same initial conditions, apart from the number of molecules of the catalyst  $M$  that are assumed to be 300 (in the previous simulation they were assumed to be absent).

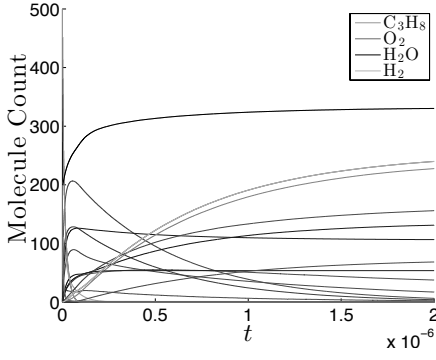


Fig. 4: Simulation of the combustion without catalyst.

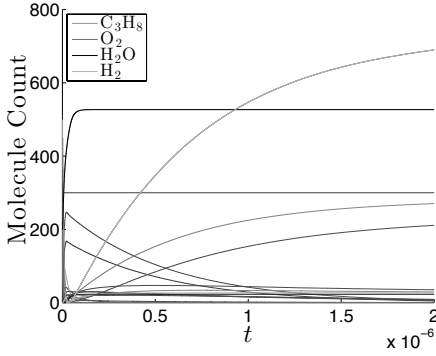


Fig. 5: Simulation of the combustion with catalyst.

These two simulations suggest that the presence of the catalyst  $M$  increases the final concentration of  $H_2$  and  $H_2O$  in the combustion of propane, thus highlighting how Algorithm 2 can be used to analyze the behavior of real reactions.  $\triangle$

## V. STABILITY, RECURRENCE AND REACHABILITY FOR CHEMICAL REACTIONS NETWORK

In Section IV, a stochastic difference inclusion able to reproduce the behavior of a chemical reaction network with partially known and time-varying kinetic parameters network has been given. In this section, we exploit such a difference inclusion to characterize stability properties of the chemical network by exploiting the results given in [37], [45], [46].

In order to perform stability analysis of a given chemical reaction network, consider the stochastic difference inclusion

$$\chi^+ \in \tilde{G}(\chi, u), \quad (7)$$

where  $\chi = [x^\top \ \theta^\top]^\top$ ,  $u \sim \text{Uniform}(0, 1)$ , and  $\tilde{G} : \mathbb{R}^{n+m+1} \rightrightarrows \mathbb{R}^{n+m}$  is such that  $\tilde{G}(\chi, u)$  equals the projection onto  $\mathbb{R}^{n+m}$  of the set-valued mapping  $G([\chi^\top \ 0]^\top, [u \ 1]^\top)$ , for all  $(\chi, u) \in \mathbb{R}^{n+m+1} \times \mathbb{R}$ .

The following theorem guarantees that the set-valued mapping  $\tilde{G}$  satisfies the basic assumptions stated in [37].

**Lemma 1.** *The set valued mapping  $\tilde{G} : \mathbb{R}^{n+m+1} \rightrightarrows \mathbb{R}^{n+m}$  is locally bounded and the mapping  $u \mapsto \text{grp}(\tilde{G}(\cdot, u))$  is measurable with closed values.*

*Proof.* Since  $\tilde{G}$  is the projection onto  $\mathbb{R}^{n+m}$  of the mapping  $G([\chi^\top \ 0]^\top, [u \ 1]^\top)$ , it is trivially locally

bounded. Furthermore, since  $\text{grp}(\tilde{G}(\cdot, u))$  is the projection of  $\text{grp}(G(\cdot, v))$ , [48, Thm. 14.11(a)] guarantees that the mapping  $u \mapsto \text{grp}(\tilde{G}(\cdot, u))$  is measurable with closed values.  $\square$

Lemma 1 guarantees that the stochastic difference inclusion (7) is well posed and hence the existence of maximal random solution. Furthermore, since the stochastic difference inclusion (7) is essentially the projection of the system (5) onto  $\mathbb{R}^{n+m}$ , then the result stated in Proposition 1 applies also to such a system. Namely, letting  $\chi \in \mathbb{Z}_{\geq 0}^n \times \Theta$  be given and letting  $\chi \in \mathcal{S}_r(\chi)$ , the length  $K_\chi$  of  $\chi$  is bounded if and only if  $\chi_{K_\chi(\omega)}(\omega)$  is such that no chemical reaction can occur.

Taking advantage of Lemma 1 and of the results given in [46], [37], [45], in the remainder of this section, we provide tools to establish stability properties for system (7).

Before introducing the stability properties that will be characterized in the remainder of this section, consider the following technical lemma.

**Lemma 2.** *Every bounded set  $\mathcal{A} \subset \mathbb{Z}_{\geq 0}^n \times \Theta$  is compact.*

*Proof.* Every bounded  $\mathcal{A} \subset \mathbb{Z}_{\geq 0}^n \times \Theta$  is given by a finite union of sets of the form  $\{x_\nu\} \times \Theta$ , with  $x_\nu \in \mathbb{Z}_{\geq 0}^n$ . Since such sets are compact and the union of a finite sequence of compact sets is compact [49],  $\mathcal{A}$  is compact.  $\square$

A bounded set  $\mathcal{A} \subset \mathbb{Z}_{\geq 0}^n \times \Theta$  is *stable in probability* for the stochastic difference inclusion (7) if for each  $\epsilon > 0$  and  $\eta > 0$  there exists  $\delta > 0$  such that

$$\chi \in \mathcal{A} + \delta \mathbb{B}, \chi \in \mathcal{S}_r(\chi) \implies \mathbb{P}(\text{grp}(\chi) \subset (\mathbb{Z}_{\geq 0} \times (A + \epsilon \mathbb{B}^o))) \geq 1 - \eta. \quad (8)$$

On the other hand, a bounded set  $\mathcal{A} \subset \mathbb{Z}_{\geq 0}^n \times \Theta$  is *strongly globally recurrent* for (7) if

$$\begin{aligned} \chi \in \mathbb{R}^{n+m}, \epsilon > 0, \chi \in \mathcal{S}_r(\chi) \implies \\ \lim_{k \rightarrow \infty} \mathbb{P}((\text{grp}(\chi) \subset \mathbb{Z}_{\leq k} \times \mathbb{R}^{n+m}) \\ \vee (\text{grp}(\chi) \cap (\mathbb{Z}_{\leq k} \times (\mathcal{A} + \epsilon \mathbb{B}^o)) \neq \emptyset)) = 1, \end{aligned} \quad (9)$$

where  $\vee$  denotes the logical OR operator.

A bounded set  $\mathcal{A} \subset \mathbb{Z}_{\geq 0}^n \times \Theta$  is *globally asymptotically stable in probability* for (7) if it is stable in probability for (7) and it is strongly globally recurrent for (7). Finally, a bounded set  $\mathcal{A} \subset \mathbb{Z}_{\geq 0}^n \times \Theta$  is *globally weakly reachable* for (7) if for each  $\chi \in \mathbb{Z}_{\geq 0}^n \times \Theta$  there exists  $\chi \in \mathcal{S}_r(\chi)$  such that

$$\lim_{k \rightarrow \infty} \mathbb{P}((\text{grp}(\chi) \cap (\mathbb{Z}_{\leq k} \times \mathcal{A}) \neq \emptyset)) = 1. \quad (10)$$

Informally speaking, a compact set  $\mathcal{A}$  is stable in probability for (7) if the probability that solutions starting close to  $\mathcal{A}$  stay close to  $\mathcal{A}$  for all  $k$  is close to 1; a compact set  $\mathcal{A}$  is strongly globally recurrent for (7) if the probability that all maximal solutions eventually reach the set  $\mathcal{A}$  as time goes to infinity is 1; finally, a compact set  $\mathcal{A}$  is globally weakly reachable for (7) if for each  $\chi \in \mathbb{Z}_{\geq 0}^n \times \Theta$  the probability that there exists at least a random solution to (7) starting at  $\chi$  that eventually reaches the set  $\mathcal{A}$  as time goes to infinity is 1.



An upper semicontinuous function  $V : \mathbb{Z}_{\geq 0}^n \times \Theta \rightarrow \mathbb{R}_{\geq 0}$  is a *Lyapunov function* relative to the bounded set  $\mathcal{A} \subset \mathbb{Z}_{\geq 0}^n \times \Theta$  for (7) if there exists  $\alpha_1, \alpha_2 \in \mathcal{K}_\infty$  and  $\varrho \in \mathcal{PD}(\mathcal{A})$  such that

$$\alpha_1(|\chi|_{\mathcal{A}}) \leq V(\chi) \leq \alpha_2(|\chi|_{\mathcal{A}}), \quad (11a)$$

$$\int_0^1 \max_{g \in \tilde{G}(\chi, v)} V(g) dv \leq V(\chi) - \varrho(\chi), \quad (11b)$$

for all  $\chi \in \mathbb{Z}_{\geq 0}^n \times \Theta$ . The following proposition states that the existence of a Lyapunov function relative to  $\mathcal{A}$  for (7) is a necessary and sufficient condition for global asymptotic stability in probability of  $\mathcal{A}$  for (7). Such a proposition relies on the results for stochastic difference inclusions given in [29], [37], where it is established that the existence of a Lyapunov function is a necessary and sufficient condition for global asymptotic stability in probability of a compact set.

**Proposition 2.** *The bounded set  $\mathcal{A} \subset \mathbb{Z}_{\geq 0}^n \times \Theta$  is globally asymptotically stable in probability for (7) if and only if there exists a Lyapunov function relative to  $\mathcal{A}$  for (7) that is smooth on  $(\mathbb{Z}_{\geq 0}^n \times \Theta) \setminus \mathcal{A}$ .*

*Proof.* By Lemma 1, the set-valued mapping  $\tilde{G} : \mathbb{R}^{n+m+1} \rightrightarrows \mathbb{R}^{n+m}$  satisfies [29, Stand. Ass. 1]. Therefore, since, by Lemma 2,  $\mathcal{A}$  is compact, by [29, Thm. 1 and 2], if there exists an upper semicontinuous function  $V$  such that (11) holds, then the compact set  $\mathcal{A}$  is globally asymptotically stable for (7). Moreover, always by Lemma 1, the mapping  $\tilde{G}$  satisfies [37, Stand. Ass. 1] and hence, by [37, Thm. 1], if  $\mathcal{A}$  is globally asymptotically stable in probability for (7) then there exists a Lyapunov function relative to  $\mathcal{A}$  for (7) that is smooth on  $(\mathbb{Z}_{\geq 0}^n \times \Theta) \setminus \mathcal{A}$ .  $\square$

Let a compact set  $\mathcal{A} \subset \mathbb{Z}_{\geq 0}^n \times \Theta$  be given. An upper semicontinuous function  $V : \mathbb{Z}_{\geq 0}^n \times \Theta \rightarrow \mathbb{R}_{\geq 0}$  is a *recurrence-Lyapunov function* relative to  $\mathcal{A}$  for (7) if it is radially unbounded and there exists a continuous function  $\varrho : \mathbb{Z}_{\geq 0}^n \times \Theta \rightarrow \mathbb{R}_{> 0}$  such that, for all  $\chi \in \mathbb{Z}_{\geq 0}^n \times \Theta$ ,

$$\int_0^1 \max_{g \in \tilde{G}(\chi, v)} V(g) dv \leq V(\chi) - \varrho(\chi) + \mathbb{I}_{\mathcal{A}}(\chi). \quad (12)$$

The following proposition states that the existence of a recurrence-Lyapunov function is a necessary and sufficient condition for strong global recurrence of the set  $\mathcal{A}$ . Such a proposition relies on [46], where it is established that the existence of a recurrence-Lyapunov function is a necessary and sufficient condition for global strong recurrence.

**Proposition 3.** *The bounded set  $\mathcal{A} \subset \mathbb{Z}_{\geq 0}^n \times \Theta$  is globally strongly recurrent for (7) if and only if there exists a recurrence-Lyapunov function relative to  $\mathcal{A}$  for (7) that is smooth on  $(\mathbb{Z}_{\geq 0}^n \times \Theta) \setminus \mathcal{A}$ .*

*Proof.* By Lemma 1, the set-valued mapping  $\tilde{G} : \mathbb{R}^{n+m+1} \rightrightarrows \mathbb{R}^{n+m}$  satisfies [29, Stand. Ass. 1]. Therefore, since, by Lemma 2,  $\mathcal{A}$  is compact, by [46, Thm. 1 and 2], the set  $\mathcal{A}$  is strongly globally recurrent if and only if there exists a recurrence-Lyapunov function  $V$  relative to  $\mathcal{A}$  for (7) and by [37, Prop. 5],  $V$  can be made smooth on  $(\mathbb{Z}_{\geq 0}^n \times \Theta) \setminus \mathcal{A}$ .  $\square$

We conclude this section by studying a sufficient condition for global weak reachability. Let a compact set  $\mathcal{A} \subset \mathbb{Z}_{\geq 0}^n \times \Theta$  be given. A lower semicontinuous function  $V : \mathbb{Z}_{\geq 0}^n \times \Theta \rightarrow \mathbb{R}_{\geq 0}$  is a *reachability-Lyapunov function* relative to  $\mathcal{A}$  for (7) if it is radially unbounded and there exists a continuous function  $\varrho : \mathbb{Z}_{\geq 0}^n \times \Theta \rightarrow \mathbb{R}_{> 0}$  such that, for all  $\chi \in (\mathbb{Z}_{\geq 0}^n \times \Theta) \setminus \mathcal{A}$ ,

$$\int_0^1 \max_{g \in \tilde{G}(\chi, v)} V(g) dv \leq V(\chi) - \varrho(\chi), \quad (13)$$

and, for all  $\chi \in \mathbb{Z}_{\geq 0}^n \times \Theta$ ,

$$\int_0^1 \max_{g \in \tilde{G}(\chi, v)} V(g) dv < \infty. \quad (14)$$

The following proposition, whose proof follows directly from [45, Prop. 1], provides a necessary condition that allows the existence of a set  $\mathcal{A}$  that is globally weakly reachable.

**Proposition 4.** *If there exists an interval  $\mathcal{Q} \subset [0, 1]$  such that  $\int_{\mathcal{Q}} 1 dv \neq 0$  and  $\tilde{G}(x, \theta, u) = \emptyset$  for some  $(x, \theta) \in \mathbb{Z}_{\geq 0}^n \times \Theta$  and for all  $u \in \mathcal{Q}$ , then there does not exist a compact set  $\mathcal{A} \subset \mathbb{Z}_{\geq 0}^n \times \Theta$  that is globally weakly reachable.*

Note that if there exists  $\mathcal{Q} \subset [0, 1]$  such that the assumptions of Proposition 4 hold, then there exists  $(x, \theta) \in \mathbb{Z}_{\geq 0}^n \times \Theta$  such that, letting  $\chi = [x^\top \ \theta^\top]^\top$ , each random solution in  $\chi \in S_r(\chi)$  consists of only its initial condition  $\chi$ , with positive probability, thus ruling out the existence of a set  $\mathcal{A}$  that is globally weakly reachable.

The statement of Proposition 4 clearly does not apply for strong global recurrence. As a matter of fact the latter condition is just about maximal solutions that are also complete (e.g., if all the maximal solutions of a given reaction network are defined on a bounded time domain, then any set is strongly globally recurrent). The conditions considered for global weak reachability require, instead, that there exists a solution that actually visits the set  $\mathcal{A}$  from any initial condition, and hence one has to require that maximal solutions are also complete.

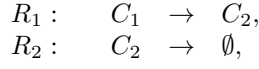
The following proposition provides a sufficient condition to ensure global weak reachability of a bounded set  $\mathcal{A}$ . Such a statement relies on the results given in [45], where it is shown that the existence of a reachability-Lyapunov function is a sufficient condition for global weak reachability of the set  $\mathcal{A}$ .

**Proposition 5.** *If there here exists a reachability-Lyapunov function relative to the bounded set  $\mathcal{A} \subset \mathbb{Z}_{\geq 0}^n \times \Theta$  for (7), then the set  $\mathcal{A}$  is globally weakly reachable for (7).*

*Proof.* By Lemma 1, the set-valued mapping  $\tilde{G} : \mathbb{R}^{n+m+1} \rightrightarrows \mathbb{R}^{n+m}$  satisfies [45, Stand. Ass. 1]. Therefore, by [45, Thm. 1], if the assumptions of Proposition 4 do not hold and there exists a reachability-Lyapunov function relative to the bounded set  $\mathcal{A} \subset \mathbb{Z}_{\geq 0}^n \times \Theta$  for (7), then the set  $\mathcal{A}$  is globally weakly reachable for (7).  $\square$

The following example shows how the techniques proposed in this section can be employed to characterize stability properties of a chemical reaction network.

**Example 5.** Consider the following reaction network composed by two species  $C_1$  and  $C_2$  and two reactions:



Define the state vector  $x = [x_1 \ x_2]^\top \in \mathbb{Z}_{\geq 0}^2$  and define the stoichiometric matrix

$$S := \begin{bmatrix} -1 & 0 \\ 1 & -1 \end{bmatrix}^\top.$$

For this reaction network, the propensity functions are

$$\begin{aligned} \tilde{r}_1(\theta, x) &= \theta_1 x_1, \\ \tilde{r}_2(\theta, x) &= \theta_2 x_2. \end{aligned}$$

Let  $\Theta$  be any compact subset of  $\mathbb{R}_{>0}^2$ . The set  $\mathcal{A} = \{0\} \times \Theta$  is globally asymptotically stable in probability for (7). In fact, letting  $r_0(\theta, x) = \theta_1 x_1 + \theta_2 x_2$ , consider the set-valued mapping  $\tilde{G} : \mathbb{Z}_{\geq 0}^n \times \Theta \times [0, 1] \rightarrow \mathbb{Z}_{\geq 0}^n \times \Theta$  given by

$$\tilde{G} = \begin{cases} \emptyset, & \text{if } r_0(\theta, x) = 0, \\ \begin{bmatrix} x_1 - 1 \\ x_2 + 1 \\ \Theta \end{bmatrix}, & \text{if } r_0(\theta, x) \neq 0 \wedge ur_0(\theta, x) \leq \theta_1 x_1, \\ \begin{bmatrix} x_1 \\ x_2 - 1 \\ \Theta \end{bmatrix}, & \text{if } r_0(\theta, x) \neq 0 \wedge ur_0(\theta, x) \geq \theta_1 x_1. \end{cases}$$

Hence, the function  $V : \mathbb{Z}_{\geq 0}^n \times \Theta \rightarrow \mathbb{R}_{\geq 0}$ ,

$$V(x, \theta) = x_1 + \frac{1}{2}x_2$$

is such that (11a) holds and

$$\begin{aligned} \int_0^1 \max_{g \in \tilde{G}(x, v)} V(g) dv &= \frac{\theta_1 x_1}{\theta_1 x_1 + \theta_2 x_2} ((x_1 - 1) + \frac{1}{2}(x_2 + 1)) \\ &\quad + (1 - \frac{\theta_1 x_1}{\theta_1 x_1 + \theta_2 x_2}) (x_1 + \frac{1}{2}(x_2 - 1)), \end{aligned}$$

and hence (11b) holds with  $\varrho(x, \theta) = \frac{1}{2}$ .

We tested global asymptotic stability of the set  $\mathcal{A}$  through numerical simulations. Namely, Algorithm 2 has been used to carry out  $10^5$  simulations of the behavior of the chemical network assuming  $\Theta = \{1\} \times \{1\}$ ,  $x_0 = [10 \ 10]^\top$  and  $\varepsilon = 10^{-12}$ . Figure 6 depicts the results of such a simulation.

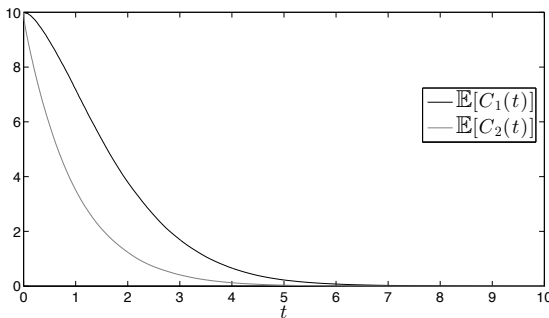


Fig. 6: Simulation for the third example.

As such a simulation confirms,  $\mathcal{A}$  is globally asymptotically stable in probability for (7), because both (8) and (9) hold.

It is worth stressing that, despite the existence of a set  $\mathcal{A}$  that is globally asymptotically stable for the stochastic difference

inclusion (7), there does not exist a set  $\mathcal{A}$  that is globally weakly reachable for (7). As a matter of fact each maximal solution starting from  $x_0 = [0 \ 0]^\top$  has a bounded time domain and hence (10) is not satisfied.  $\triangle$

## VI. CONCLUSIONS

In this paper, an algorithm is proposed to perform robust stochastic simulations of chemical reaction networks with kinetic parameters that are not known exactly. Such a goal is achieved by defining a set-valued mapping such that the trajectories of the corresponding stochastic difference inclusion match those of the chemical reaction network. Since such a set-valued mapping satisfies some regularity assumptions (namely, [29, Stand. Ass. 1]), the Lyapunov theory developed for stochastic difference inclusion allows us to obtain conditions guaranteeing stability of the chemical reaction network. In fact, asymptotic stability in probability, strong recurrence and weak reachability are framed in terms of the existence of monotonically decreasing functions.

The complexity of the proposed algorithm is comparable with the direct formulation of the stochastic simulation algorithm, which has been proved to be more efficient than the next reaction method [22]. In fact, if Step 7 of Algorithm 2 is performed efficiently (e.g., through the extremum-seeking technique given in [50]), such a procedure requires the generation of just a single additional random number.

Examples of application of the given technique and of the theoretical results have been reported all through the paper.

## REFERENCES

- [1] J. Verwer, "An evaluation of explicit pseudo-steady-state approximation schemes for stiff ODE systems from chemical kinetics," *J. Comput. Phys.*, vol. 113, no. 2, pp. 347–352, 1994.
- [2] V. Alexandrov, A. Sameh, Y. Siddique, and Z. Zlatev, "Numerical integration of chemical ODE problems arising in air pollution models," *Environ. Model. Assess.*, vol. 2, no. 4, pp. 365–377, 1997.
- [3] M. Bansal, G. Della Gatta, and D. Di Bernardo, "Inference of gene regulatory networks and compound mode of action from time course gene expression profiles," *BMC Bioinf.*, vol. 22, no. 7, pp. 815–822, 2006.
- [4] S. H. Strogatz, *Nonlinear dynamics and chaos: with applications to physics, biology, chemistry, and engineering*. Westview press, 2014.
- [5] P. Wong, S. Gladney, and J. D. Keasling, "Mathematical model of the lac operon: inducer exclusion, catabolite repression, and diauxic growth on glucose and lactose," *Biotechnol. Progr.*, vol. 13, no. 2, pp. 132–143, 1997.
- [6] Y. Cao, L. R. Petzold, M. Rathinam, and D. T. Gillespie, "The numerical stability of leaping methods for stochastic simulation of chemically reacting systems," *J. Chem. Phys.*, vol. 121, no. 24, pp. 12169–12178, 2004.
- [7] J. Yu, V. A. Smith, P. P. Wang, A. J. Hartemink, and E. D. Jarvis, "Advances to Bayesian network inference for generating causal networks from observational biological data," *BMC Bioinf.*, vol. 20, no. 18, pp. 3594–3603, 2004.
- [8] M. B. Eisen, P. T. Spellman, P. O. Brown, and D. Botstein, "Cluster analysis and display of genome-wide expression patterns," *Proc. Natl. Acad. Sci.*, vol. 95, no. 25, pp. 14863–14868, 1998.
- [9] A. A. Margolin, I. Nemenman, K. Basso, C. Wiggins, G. Stolovitzky, R. D. Fava, and A. Califano, "ARACNE: an algorithm for the reconstruction of gene regulatory networks in a mammalian cellular context," *BMC Bioinf.*, vol. 7, no. 1, pp. 1–15, 2006.
- [10] A. G. Busetto and J. Lygeros, "Experimental design for system identification of boolean control networks in biology," in *53rd Conf. Decision Control*, pp. 5704–5709, IEEE, 2014.
- [11] C. Possieri and A. R. Teel, "Weak reachability and strong recurrence for stochastic directed graphs in terms of auxiliary functions," in *55th Conf. Decision Control*, pp. 3714–3719, IEEE, 2016.

- [12] C. Possieri and A. R. Teel, "Asymptotic stability in probability for stochastic boolean networks," *Automatica*, vol. 83, pp. 1–9, 2017.
- [13] A. Arkin, J. Ross, and H. H. McAdams, "Stochastic kinetic analysis of developmental pathway bifurcation in phage  $\lambda$ -infected *Escherichia coli* cells," *Genetics*, vol. 149, no. 4, pp. 1633–1648, 1998.
- [14] M. B. Elowitz, A. J. Levine, E. D. Siggia, and P. S. Swain, "Stochastic gene expression in a single cell," *Science*, vol. 297, no. 5584, pp. 1183–1186, 2002.
- [15] C. Gadgil, C. H. Lee, and H. G. Othmer, "A stochastic analysis of first-order reaction networks," *Bull. Math. Biol.*, vol. 67, no. 5, pp. 901–946, 2005.
- [16] J. Sun and L. Wan, "Convergence dynamics of stochastic reaction–diffusion recurrent neural networks with delays," *Int. J. Bifurcation Chaos*, vol. 15, no. 07, pp. 2131–2144, 2005.
- [17] H.-W. Kang, T. G. Kurtz, *et al.*, "Separation of time–scales and model reduction for stochastic reaction networks," *Ann. Appl. Prob.*, vol. 23, no. 2, pp. 529–583, 2013.
- [18] L. Marchetti, C. Priami, and V. H. Thanh, "HRSSA—efficient hybrid stochastic simulation for spatially homogeneous biochemical reaction networks," *J. Comp. Phys.*, vol. 317, pp. 301–317, 2016.
- [19] N. G. Van Kampen, *Stochastic processes in physics and chemistry*, vol. 1. Elsevier, 1992.
- [20] D. T. Gillespie, "Exact stochastic simulation of coupled chemical reactions," *J. Chem. Phys.*, vol. 81, no. 25, pp. 2340–2361, 1977.
- [21] M. A. Gibson and J. Bruck, "Efficient exact stochastic simulation of chemical systems with many species and many channels," *J. Phys. Chem. A*, vol. 104, no. 9, pp. 1876–1889, 2000.
- [22] Y. Cao, H. Li, and L. Petzold, "Efficient formulation of the stochastic simulation algorithm for chemically reacting systems," *J. Chem. Phys.*, vol. 121, no. 9, pp. 4059–4067, 2004.
- [23] H. Li, Y. Cao, L. R. Petzold, and D. T. Gillespie, "Algorithms and software for stochastic simulation of biochemical reacting systems," *Biotechnol. Progr.*, vol. 24, no. 1, pp. 56–61, 2008.
- [24] H. De Jong, "Modeling and simulation of genetic regulatory systems: a literature review," *J. Comput. Bio.*, vol. 9, no. 1, pp. 67–103, 2002.
- [25] S. Asmussen and P. W. Glynn, *Stochastic simulation: algorithms and analysis*. Springer Sci. Bus. Media, 2007.
- [26] R. Gunawan, Y. Cao, L. Petzold, and F. J. Doyle, "Sensitivity analysis of discrete stochastic systems," *Biophys. J.*, vol. 88, no. 4, pp. 2530 – 2540, 2005.
- [27] C. J. Morton-Firth and D. Bray, "Predicting temporal fluctuations in an intracellular signalling pathway," *J. Theor. Biol.*, vol. 192, no. 1, pp. 117–128, 1998.
- [28] D. T. Gillespie, "Approximate accelerated stochastic simulation of chemically reacting systems," *J. Chem. Phys.*, vol. 115, no. 4, pp. 1716–1733, 2001.
- [29] A. Teel, "A Matrosov theorem for adversarial Markov decision processes," *IEEE Trans. Autom. Control*, vol. 58, no. 8, pp. 2142–2148, 2013.
- [30] M. Chaves, "Methods for qualitative analysis of genetic networks," in *Eur. Control Conf.*, pp. 671–676, IEEE, 2009.
- [31] T. Eissing, M. Chaves, and F. Allgöwer, "Live and let die—a systems biology view on cell death," *Comput. Chem. Eng.*, vol. 33, no. 3, pp. 583–589, 2009.
- [32] J. Paulsson and J. Elf, "Stochastic modeling of intracellular kinetics," in *System Modeling in Cellular Biology: From Concepts to Nuts and Bolts* (Z. Szallasi, J. Stelling, and V. Periwal, eds.), ch. 8, pp. 149–175, Cambridge, MA: MIT Press, 2006.
- [33] R. Erban, J. Chapman, and P. Maini, "A practical guide to stochastic simulations of reaction–diffusion processes," *arXiv:0704.1908*, 2007.
- [34] S. Klamt and J. Stelling, "Stoichiometric and constraint–based modeling," in *System Modeling in Cellular Biology: From Concepts to Nuts and Bolts*, ch. 5, pp. 73–96, Cambridge, MA: MIT Press, 2006.
- [35] R. Heinrich and S. Schuster, "Metabolic control analysis," in *The Regulation of Cellular Systems*, ch. 5, pp. 138–291, US: Springer, 1996.
- [36] D. T. Gillespie and L. Petzold, "Numerical simulation for biochemical kinetics," in *System Modeling in Cellular Biology: From Concepts to Nuts and Bolts*, ch. 16, pp. 331–354, Cambridge, MA: MIT Press, 2006.
- [37] A. R. Teel, J. P. Hespanha, and A. Subbaraman, "A converse Lyapunov theorem and robustness for asymptotic stability in probability," *IEEE Trans. Autom. Control*, vol. 59, no. 9, pp. 2426–2441, 2014.
- [38] R. J. Allen, P. B. Warren, and P. R. Ten Wolde, "Sampling rare switching events in biochemical networks," *Phys. Rev. Lett.*, vol. 94, no. 1, p. 018104, 2005.
- [39] A. Fernández-Ramos, J. A. Miller, S. J. Klippenstein, and D. G. Truhlar, "Modeling the kinetics of bimolecular reactions," *Chem. Rev.*, vol. 106, no. 11, pp. 4518–4584, 2006.
- [40] C. H. Bennett, "Molecular dynamics and transition state theory: The simulation of infrequent events," in *Algorithms for Chemical Computations* (R. E. Christoffersen, ed.), Am. Chem. Soc., 1977.
- [41] D. Chandler, "Statistical mechanics of isomerization dynamics in liquids and the transition state approximation," *J. Chem. Phys.*, vol. 68, no. 6, pp. 2959–2970, 1978.
- [42] G. Menzl, A. Singraber, and C. Dellago, "S-shooting: a Bennett–Chandler-like method for the computation of rate constants from committor trajectories," *Faraday Discussions*, vol. 195, pp. 345–364, 2017.
- [43] B. E. Fristedt and L. F. Gray, *A modern approach to probability theory*. Springer Sci. Bus. Media, 2013.
- [44] C. M. Kellett and A. R. Teel, "Smooth Lyapunov functions and robustness of stability for difference inclusions," *Syst. Control Lett.*, vol. 52, no. 5, pp. 395–405, 2004.
- [45] C. Possieri and A. R. Teel, "A Lyapunov theorem certifying global weak reachability for stochastic difference inclusions with random inputs," *Syst. Control Lett.*, vol. 109, pp. 37–42, 2017.
- [46] A. Subbaraman and A. R. Teel, "A converse Lyapunov theorem for strong global recurrence," *Automatica*, vol. 49, no. 10, pp. 2963–2974, 2013.
- [47] C. J. Jachimowski, "Chemical kinetic reaction mechanism for the combustion of propane," *Combustion Flame*, vol. 55, no. 2, pp. 213–224, 1984.
- [48] R. T. Rockafellar and R. J.-B. Wets, *Variational analysis*. Springer Sci. Bus. Media, 2009.
- [49] N. Bourbaki, *General Topology*. Springer Sci. Bus. Media, 1998.
- [50] M. Sassano, D. Carnevale, and A. Astolfi, "Extremum seeking-like observer for nonlinear systems," *IFAC Proc. Vol.*, vol. 44, no. 1, pp. 1849–1854, 2011.

**Corrado Possieri** received his bachelor's and master's degrees in Medical engineering and his Ph.D. degree in Computer Science, Control and Geoinformation from the University of Roma Tor Vergata, Italy, in 2011, 2013, and 2016, respectively. From September 2015 to June 2016, he visited the University of California, Santa Barbara (UCSB). His current research interests include stability and control of hybrid systems, the application of computational algebraic geometry techniques to control problems, and stochastic systems.

**Andrew R. Teel** received his A.B. degree in Engineering Sciences from Dartmouth College in Hanover, New Hampshire, in 1987, and his M.S. and Ph.D. degrees in Electrical Engineering from the University of California, Berkeley, in 1989 and 1992, respectively. After receiving his Ph.D., he was a postdoctoral fellow at the Ecole des Mines de Paris in Fontainebleau, France. In 1992 he joined the faculty of the Electrical Engineering Department at the University of Minnesota, where he was an assistant professor until 1997. Subsequently, he joined the faculty of the Electrical and Computer Engineering Department at the University of California, Santa Barbara, where he is currently a Distinguished Professor and director of the Center for Control, Dynamical systems, and Computation. His research interests are in nonlinear and hybrid dynamical systems, with a focus on stability analysis and control design. He has received NSF Research Initiation and CAREER Awards, the 1998 IEEE Leon K. Kirchmayer Prize Paper Award, the 1998 George S. Axelby Outstanding Paper Award, and was the recipient of the first SIAM Control and Systems Theory Prize in 1998. He was the recipient of the 1999 Donald P. Eckman Award and the 2001 O. Hugo Schuck Best Paper Award, both given by the American Automatic Control Council, and also received the 2010 IEEE Control Systems Magazine Outstanding Paper Award. In 2016, he received the Certificate of Excellent Achievements from the IFAC Technical Committee on Nonlinear Control Systems. He is Editor-in-Chief for *Automatica*, and a Fellow of the IEEE and of IFAC.