Analysis of stochastic reaction networks with Markov reward models

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ABSTRACT

This paper considers Markov chains describing stochastic reaction networks. These Markov chains often have a huge state space which make their analysis unfeasible. We show that there exist cases when the original Markov chain can be transformed into a Markov reward model with a smaller state space and whose analysis gives information on the moments of the quantity of the involved species. We derive the necessary mathematics and provide numerical examples to illustrate the approach.

Keywords: systems biology; stochastic reaction networks; Markov reward models.

ACM Computing Classification: G.3. Markov processes.

1. INTRODUCTION

The analysis of the continuous time Markov chain (CTMC) introduced by Gillespie in [9] to model stochastic reaction networks is still an open problem. The main reason is that the state space blows up exponentially with the number of reagents.

Several approximation techniques have been proposed to tackle the problem of the huge state space. One among them is the mean-field technique which uses a differential equation-based description of the system [14, 15] and provides a deterministic approximation of the system behaviour. Other techniques obtain approximations by operating directly on the state space of the model. As the state space can be infinite, it is natural to bound the set of states that are considered [6]. Since the calculations can be slow even on the reduced state space, recently, faster approximate uniformisation methods have been proposed [17, 28]. Another possibility is to apply aggregation: nearby states are aggregated in [27, 4] and a more intricate aggregation can be obtained by applying flow equivalence [3, 5]. An important body of works uses simulation to the analysis. Because of the huge state space and the fact that a large amount of reactions can occur in a short time interval, even simulation is not straightforward. Starting from [9], several papers have proposed approaches to increase the efficiency of simulation of reaction systems [8, 22, 2].

In this paper we propose a novel analysis approach. The motivation behind this approach is that there exist particular, but not rare, cases when the system contains species whose quantity can only grow and their quantity does not affect the intensity of the reactions. A trivial example of these models is the system of reactions described in [10] in which a single unit of Dna is switched on/off by polymerase binding/unbinding. The polymerase bound (i.e., switched-on) Dna is able to produce $mRna$. Figure 1 depicts the graph representing the states of the system, showing how the binding/unbinding cycle is replicated for each possible level of $mRna$ quantity. It is clear that the complexity of the problem can be drastically reduced if the $mRna$ production is not described explicitly in the state space. Thus, our goal is to consider the stochastic process which describes only the state of the Dna (the states in the dashed box in Figure 1) and build another stochastic process which depends on the first and describes the production of $mRna$.

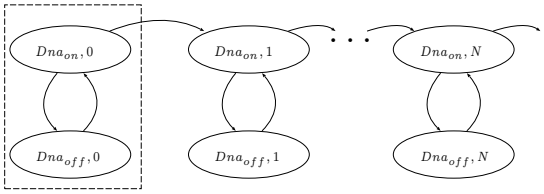

Figure 1: Gene transcription model: state space

This goal can be achieved by using *stochastic reward models* which were introduced in the '80s for the performance analysis of communication systems and a large number of numerical methods were developed to make effective use of them. In general, a reward model can be classified through four criteria: (1) the stochastic behaviour of the underlying process, (2) the type of the reward accumulation, (3) the possibility and the type of the loss that the reward can suffer, (4) and the evaluated measure (for a more detailed description, see [19, 20, 12]).

In this paper, we consider the case in which (1) the underlying process is a CTMC, (2) the reward accumulation is through instantaneous impulses of pre-fixed "gains", (3) no reward loss is possible and (4) the considered measure is the moments of the accumulated reward. Accordingly, the context is most akin to the one considered in [26, 1].

In [26] it has been shown that the moments of the accumulated reward can be computed efficiently even for reward models with large underlying CTMCs. Moreover, as it was described in [21, 12, 25], the moments can be then used to obtain bounds of the distribution of the accumulated reward.

The method we propose, when applicable, is an alternative to the widely used simulation based approaches [8, 22, 2] initiated by Gillespie in [9]. As mentioned earlier, simulation is not straightforward and hence development of alternative methods is important. Moreover, the estimation of the probability of rare events by simulation can be unfeasible because it requires the generation of enormous amount of simulation traces. The study of these events can be important to describe anomalous behaviours of the system under study. Our approach provides probability estimates of rare events with lower computational cost than required by simulation. We further comment on this in Section 5.

The paper is organised as follows. In Section 2 we briefly describe the original CTMC representing stochastic reaction networks. In Section 3, after defining the considered class of reward models, we show how to construct (if possible) a reward model with smaller state space from the original CTMC and derive the formulae to characterise the accumulated reward in time and transform domain. In Section 4 we provide an efficient method for the computation of the moments of the accumulated reward. The main contribution of the paper is in Section 3 and 4 and the crucial difference between our work and those proposed previously is that in our context we have to consider multiple reward variables. In Section 5 we illustrate the approach on numerical examples. Conclusions are given in Section 6.

2. ORIGINAL MARKOVIAN CHAIN

The classical approach of stochastic modeling of a biochemical system was introduced by Gillespie in [9]. It considers a fixed volume containing a well-stirred mixture of M biochemical species, $L_1, \ldots, L_M$, interacting by means of R reactions

$$\sum_{m=1}^{M} a_{n,m} L_m \xrightarrow{\mu_n} \sum_{m=1}^{M} b_{n,m} L_m, \quad 1 \leq n \leq R$$

where $a_{n,m}$ ($b_{n,m}$) is the integer number of units of species L_m consumed (produced) by the nth reaction and μ_n gives its propensity. By introducing the vectors $a_n = (a_{n,1}, \ldots, a_{n,M})$ and $b_n = (b_{n,1}, \ldots, b_{n,M})$, the overall effect of the nth reaction can be described by the vectors $e_n = b_n - a_n$, $1 \leq n \leq R$. As explained in [18, 9], the stochastic approach considers the state of the system as a vector of integers providing the quantity of each species. Reaction n can occur in the state $x = (x_1, \ldots, x_M)$ if $x \geq a_n$, i.e., if $x_m \geq a_{n,m}$, for all $i \leq m \leq M$. If a reaction n is possible in state x than its intensity $s_n(x)$ is given by

$$s_n(x) = \mu_n \prod_{m=1}^{M} \binom{x_m}{a_{n,m}} \tag{1}$$

In this paper the only form of intensity we consider is the one in (1) but the extension to a more general case is straightforward. Given an initial state, the system evolves in time by means of reaction occurrences in such a way that if reaction n occurs in state x then the next state is $x' = x + e_n$. In [9], Gillespie showed that the sojourn times in the states of the process follow the exponential distribution with intensity given in (1) and, as a consequence, the underlying process is a continuous time Markov chain. This CTMC is completely described by its infinitesimal generator matrix $\mathbf{Q} = [q_{i,j}]_{i,j \in \mathcal{S}}$ defined as

$$q_{i,j} = \begin{cases} \sum_{\forall n: j = i + e_n} s_n(i) & i \neq j \\ -\sum_{\forall j \neq i} q_{i,j} & i = j \\ 0 & otherwise \end{cases} \tag{2}$$

where $\mathcal{S}$ represents the set of the reachable states. Given the matrix $\mathbf{Q}$ and the initial distribution $\pi(0)$, it is well-known that the state probability vector at time t can be computed as $\pi(t) = \pi(0) e^{\mathbf{Q}t}$.

Considering the system introduced in Section 1 and using the notation provided above, the reactions are

$$Dna_{off} \xrightarrow{\mu_1} Dna_{on}, Dna_{on} \xrightarrow{\mu_2} Dna_{off},$$
$$Dna_{on} \xrightarrow{\mu_3} mRna + Dna_{on}.$$

The state is represented by a vector $x = (x_1, x_2, x_3)$ describing the quantities of Dna_{off}, Dna_{on} and $mRna$, respectively. The system evolves by means of the three reactions that change the state according to the following effects:

$$e_1 = (-1, 1, 0),\ e_2 = (1, -1, 0),\ e_3 = (0, 0, 1).$$

The intensities associated with the reactions are: $s_1(x) = \mu_1 x_1$, $s_2(x) = \mu_2 x_2$ and $s_3(x) = \mu_3 x_2$.

3. MARKOV REWARD MODEL

In this section, we provide first the definition of the applied Markov reward models together with the description of the accumulated reward and the completion time. Then we provide the necessary conditions for a CTMC to be transformable into a MRM and show that the transformation can be carried out automatically. At last, the expressions characterising the distribution of the accumulated reward are derived.

3.1 Definitions

Let $\{\mathcal{Z}(t), t \geq 0\}$ be a CTMC defined in the finite state space $\mathcal{S}$. This CTMC, called the underlying CTMC, governs the accumulation of W types of rewards as follows. In every state of the CTMC a number of activities are present whose occurrence can result in gain of reward and, eventually, in a state transition of the CTMC. The activities are identified by a vector of W integers describing the gain they provide and the total intensity of the activities providing g amount of reward and moving the CTMC from state i to state j is denoted by $r_{i,j}^{(g)}$ with $i, j \in \mathcal{S}$ and $g \in \mathbb{Z}^W$. (We denote by $\mathbb{Z}$ and $\mathbb{C}$ the set of non-negative integers and the set of complex numbers, respectively; the corresponding set of vectors of length W are denoted by $\mathbb{Z}^W$ and $\mathbb{C}^W$.) The intensities $r_{i,j}^{(g)}$ are organised into matrices as $\mathbf{R}^{(g)} = \left[r_{i,j}^{(g)}\right]_{i,j \in \mathcal{S}}$.

The *accumulated reward* (AR) is a discrete vector random variable, denoted with $\mathcal{B}(t) \in \mathbb{Z}^W$, which represents the quantity of reward which was gained up to time t. As an example, assume $W = 3$ and $\mathcal{B}(t) = (3, 1, 4)$. If an activity with reward vector $g = (1, 0, 2)$ occurs in the infinitesimal interval $[t, t + \Delta]$ then the vector random variable will take the value $\mathcal{B}(t + \Delta) = (3, 1, 4) + (1, 0, 2) = (4, 1, 6)$.

Since we do not consider activities with negative gain, the quantity of the produced reward can only grow or remain stable. The monotonicity of $\mathcal{B}(t)$ provides a relation between the AR and the *completion time* (CT) defined as the random variable $\mathcal{C}(w)$ representing the time needed to accumulate w amounts of reward, corresponding to $min\,[t \geq 0 : \mathcal{B}(t) \geq w]$. It is easy to see that between AR and CT the following duality like relation holds

$$Pr(\mathcal{B}(t) < w) = Pr(\mathcal{C}(w) > t).$$

3.2 Derivation of MRM from the original CTMC

Starting from the CTMC described in the previous section, the first step to build the MRM is to identify the set of species that have a monotonic growth and have no impact on the intensity of the reactions. Species i belongs to this set if the following property holds:

$$\forall n, 1 \leq n \leq R : a_{n,i} = 0 \text{ and } \exists n, 1 \leq n \leq R : b_{n,i} > 0. \quad (3)$$

If there are species satisfying the above property, then an MRM with a smaller state space than that of the original CTMC can be built. The construction of the MRM can be done in automatic manner as follows.

The species satisfying the property in (3) will be called *monotonic* and their set will be denoted by $\mathcal{M}$ while the rest of the species will be called *non-monotonic* and the corresponding set will be denoted by $\overline{\mathcal{M}}$. The cardinality of set $\mathcal{M}$, denoted by W, is the number of types of rewards of the MRM. In the MRM, the underlying CTMC, denoted by $\{\mathcal{Z}(t), t \geq 0\}$, models the non-monotonic species while the rewards take into account the growth of the monotonic species.

Next, the effect of each reaction has to be split into two parts. The first part gives the effect of the reaction on the species belonging to $\overline{\mathcal{M}}$ and gives rise to a transition in the underlying CTMC of the MRM. The effect of these transitions will be described by the vectors $e'_i, 1 \leq i \leq R$ which are obtained simply from the vectors $e_i, 1 \leq i \leq R$, introduced in Section 2, by taking those entries which refer to species belonging to $\overline{\mathcal{M}}$. The second part takes into account the growth of the monotonic species. The reward produced by a reaction $i, 1 \leq i \leq R$ can be simply described by a vector g_i collecting those entries of e_i which corresponds to monotonic species. To sum up, the effect of reaction $i, 1 \leq i \leq R$ described by e_i in the original CTMC is decomposed into two vectors e'_i and g_i refering to the non-monotonic and the monotonic species, respectively. Based on $e'_i, g_i, 1 \leq i \leq R$ and the corresponding intensities given in (1) the construction of the matrices $\mathbf{R}^{(g)}$ describing the MRM is straightforward. The entries are obtained as

$$r_{i,j}^{(g)} = \sum_{\forall n: j = i + e'_n \wedge g_n = g} s_n(i) \quad (4)$$

Note that the underlying CTMC of the MRM can have finite state space even if the state space of the original CTMC is infinite. This is the case for the gene transcription model introduced in Section 1 and the case study we provide in Section 5.1.

Considering the gene transcription model, we have two non-monotonic species, Dna_{on} and Dna_{off}, and one monotonic species, $mRna$. A state of the underlying CTMC of the MRM is given by a vector of two entries $x = (x_1, x_2)$ since it represents Dna_{on} and Dna_{off}. The effect of the transitions on the underlying CTMC is

$$e'_1 = (-1, 1),\ e'_2 = (1, -1),\ e'_3 = (0, 0).$$

We have a single type of reward corresponding to $mRna$. Accordingly, $W = 1$ and the vectors describing the effect of the reactions on the reward variable are composed of a single entry:

$$g_1 = (0),\ g_2 = (0),\ g_3 = (1).$$

Assuming that initially there is a single unit of Dna_{on} in the system, the matrices representing the MRM are simply

$$\mathbf{R}^{((0))} = \begin{vmatrix} 0 & \mu_1 \\ \mu_2 & 0 \end{vmatrix},\ \mathbf{R}^{((1))} = \begin{vmatrix} \mu_3 & 0 \\ 0 & 0 \end{vmatrix}.$$

Naturally, having an initial state with more units of Dna_{on} or Dna_{off} the state space of the underlying CTMC grows but it remains finite while the original CTMC is of infinite state space.

3.3 Accumulated reward, characterisation in time and transform domain

Given the matrices $\mathbf{R}^{(g)}$ for every possible gain vector g, the transient accumulated reward is characterised by the matrix $\mathbf{B}(t, w)$ with entries

$$B_{i,j}(t, w) = Pr\{\mathcal{B}(t) = w, \mathcal{Z}(t) = j | \mathcal{Z}(0) = i, \mathcal{B}(0) = 0\}$$

giving the probability that, having started in state i with 0 reward[1], at time t the reward is w and the underlying chain is in state j. Note that w is a vector: $w \in \mathbb{Z}^W$.

THEOREM 1. *The transient behaviour of the AR fulfills the following differential equation*

$$\frac{d\mathbf{B}(t, w)}{dt} = -\mathbf{B}(t, w)\mathbf{S} + \sum_{\forall g: w - g \geq 0} \mathbf{B}(t, w - g)\mathbf{R}^{(g)} \quad (5)$$

where $\mathbf{S}$ *is a diagonal matrix with entries*

$$S_{i,j} = \begin{cases} \sum_{\forall k \in \mathcal{S}} \sum_{\forall g} r_{i,k}^{(g)} & \text{if } i = j, \\ 0 & \text{otherwise.} \end{cases} \quad (6)$$

PROOF. In order to derive equation (5) let us consider first the change of $B_{i,j}(t, w)$ in an infinitesimal time interval. We have

$$B_{i,j}(t + \Delta, w) = B_{i,j}(t, w) \left(1 - \sum_{\forall k \in \mathcal{S}} \sum_{\forall g} r_{j,k}^{(g)} \Delta\right) + \sum_{\forall k \in \mathcal{S}} \sum_{\forall g: w - g \geq 0} \left(B_{i,k}(t, w - g) r_{k,j}^{(g)} \Delta\right) + o(\Delta)$$

where the first term is the probability that state j and w amount of reward have been reached by time t and no activity occurs in $[t, t + \Delta]$, the second term is the probability to get exactly the necessary amount to reach the target w and moving the process to the state j, meanwhile $o(\Delta)$ represents the fact that the probability of two events in $[t, t + \Delta]$ negligible.

[1] Our framework can be easily extended to starting the system from non-zero reward levels or with reward levels distributed according to some distribution but we avoid to handle these cases for sake of simplicity.

Dividing by Δ, taking the limit $\Delta \to 0$ and rearranging leads to

$$\frac{dB_{i,j}(t,w)}{dt} = -B_{i,j}(t,w) \sum_{\forall k \in \mathcal{S}} \sum_{\forall g} r_{j,k}^{(g)} + \sum_{\forall k \in \mathcal{S}} \sum_{\forall g: w-g \geq 0} \left(B_{i,k}(t,w-g) r_{k,j}^{(g)} \right)$$

from which introducing matrix notation the theorem follows. □

We mention here that matrix $\mathbf{S}$ represents the sojourn times whereas the matrices $\mathbf{R}^{(g)}$ represent the transition rates between states. Thus the infinitesimal generator of the underlying CTMC is

$$\mathbf{Q} = -\mathbf{S} + \sum_{\forall g} \mathbf{R}^{(g)}.$$

A compact solution of (5) can be provided only in transform domain. In the sequel the following transforms of $\mathbf{B}(t,w)$ will be applied: the Laplace transform according to the time variable given by

$$\mathbf{B}^*(s,w) = \int_0^\infty e^{-st} \mathbf{B}(t,w) dt$$

and the double continuous/discrete transform, i.e., Laplace transform according to the time variable and z-transform according to all the reward variables, defined by

$$\mathbf{B}^{**}(s,z) = \mathbf{B}^{**}(s,(z_1,\ldots,z_W)) = \sum_{\forall i \in \mathbb{Z}^W} \prod_{j=1}^W z_j^{i_j} \int_0^\infty e^{-st} \mathbf{B}(t,i) dt$$

with $z \in \mathbb{C}^W$. In the following, in order to abbreviate, having $z \in \mathbb{C}^W$ and $i \in \mathbb{Z}^W$ we will write $\prod_{j=1}^W z_j^{i_j}$ simply as z^i.

THEOREM 2. *The continuous/discrete transform of the accumulated reward is given by:*

$$\mathbf{B}^{**}(s,z) = \left[s\mathbf{I} + \mathbf{S} - \sum_{\forall g} z^g \mathbf{R}^{(g)} \right]^{-1} \tag{7}$$

where $\mathbf{I}$ *is the identity matrix.*

PROOF. The continuous/discrete transform of the left hand side of (5) with $z \in \mathbb{C}^W$ is given by

$$\sum_{\forall i \in \mathbb{Z}^W} z^i \int_0^\infty e^{-st} \frac{d\mathbf{B}(t,i)}{dt} = \sum_{\forall i \in \mathbb{Z}^W} z^i \left(s\mathbf{B}^*(s,i) - \mathbf{B}(0,i) \right) = s\mathbf{B}^{**}(s,z) - \mathbf{I} \tag{8}$$

because $\mathbf{B}(0,0) = \mathbf{I}$ and $\mathbf{B}(0,i) = \mathbf{0}$ when $i \neq 0$. The same operation on the right hand side of (5) leads to

$$\begin{aligned}
&\sum_{\forall i \in \mathbb{Z}^W} z^i \int_0^\infty e^{-st} \left(-\mathbf{B}(t,i)\mathbf{S} + \sum_{\forall g: i-g \geq 0} \mathbf{B}(t,i-g)\mathbf{R}^{(g)} \right) dt \\
&= \sum_{\forall i \in \mathbb{Z}^W} z^i \left(-\mathbf{B}^*(s,i)\mathbf{S} + \sum_{\forall g: i-g \geq 0} \mathbf{B}^*(s,i-g)\mathbf{R}^{(g)} \right) \\
&= -\mathbf{B}^{**}(s,z)\mathbf{S} + \sum_{\forall i \in \mathbb{Z}^W} z^i \left(\sum_{\forall g: i-g \geq 0} \mathbf{B}^*(s,i-g)\mathbf{R}^{(g)} \right) \\
&= -\mathbf{B}^{**}(s,z)\mathbf{S} + \sum_{\forall g} z^g \left(\sum_{\forall i \in \mathbb{Z}^W : i \geq g} z^{i-g} \mathbf{B}^*(s,i-g)\mathbf{R}^{(g)} \right) \\
&= -\mathbf{B}^{**}(s,z)\mathbf{S} + \sum_{\forall g} z^g \left(\sum_{\forall i \in \mathbb{Z}^W} z^i \mathbf{B}^*(s,i)\mathbf{R}^{(g)} \right) \\
&= -\mathbf{B}^{**}(s,z)\mathbf{S} + \sum_{\forall g} z^g \mathbf{B}^{**}(s,z)\mathbf{R}^{(g)}
\end{aligned} \tag{9}$$

From (8) and (9) we have

$$s\mathbf{B}^{**}(s,z) - \mathbf{I} = -\mathbf{B}^{**}(s,z)\mathbf{S} + \sum_{\forall g} z^g \mathbf{B}^{**}(s,z)\mathbf{R}^{(g)}$$

which by applying trivial algebra provides the theorem. □

4. MOMENTS OF THE ACCUMULATED REWARD

In this section we first define a method for the analysis of the factorial moments of the AR starting from the double transform expression given in (7). Since the numerical calculations of this method can easily be unstable, we make then modifications in order to define a numerically stable algorithm. Finally, we show that the truncation error is controllable and provide some indications for what concerns the computational complexity. Throughout the section we follow an approach similar to that of [26] extending it to the multiple reward variable case.

4.1 Recursion for the moments of the accumulated reward

Let us denote by $\mathcal{B}_{i,j}(t)$ the amount of the jth type of reward at time t given that the initial state is i. Then, having a vector $n \in \mathbb{Z}^W$, the associated joint factorial moment, assuming state i as initial state, is given by the expected value

$$f_i^{(n)}(t) = E\left[\prod_{j=1}^W \prod_{k=0}^{n_j-1} \left(\mathcal{B}_{i,j}(t) - k \right) \right]. \tag{10}$$

Let us illustrate the use of the factorial moments assuming $W = 2$. Using $n = (1,0)$ the expected value in (10) provides simply the mean quantity of the 1st type of reward. Using $n = (2,0)$ we obtain its second factorial moment which can be used to compute the second "normal" moment for the 1st type of reward as

$$E\left[\mathcal{B}_{i,1}(t)^2 \right] = f_i^{((2,0))}(t) + f_i^{((1,0))}(t).$$

For a general description of the relation between factorial moments and "normal" moments, see [11]. The formula in

(10) allows for expressing joint measures of the various reward types as well. For example, the covariance of the 1st and the 2nd type of rewards can be obtained as

$$E\left[\left(\mathcal{B}_{i,1}(t) - E\left[\mathcal{B}_{i,1}(t)\right]\right)\left(\mathcal{B}_{i,2}(t) - E\left[\mathcal{B}_{i,2}(t)\right]\right)\right] = f_i^{((1,1))}(t) - f_i^{((1,0))}(t) f_i^{((0,1))}(t).$$

The column vector formed by $f_i^{(n)}(t)$ will be denoted by $f^{(n)}(t) = \left(f_i^{(n)}(t)\right)$. Based on basic properties of the z-transform and denoting $\sum_{i=1}^{W} n_W$ by $\#n$ we can write

$$f^{(n)}(t) = \left.\frac{\partial^{\#n}\mathbf{B}^*(t,z)}{\prod_{i=1}^{W}\partial z_i^{n_i}}\right|_{z=1} \cdot \mathbf{1} \tag{11}$$

where $\mathbf{1}$ is the row vector of 1s. In the sequel, in order to abbreviate, the partial derivative in (11) will be written in "vector" notation leading to

$$f^{(n)}(t) = \left.\frac{\partial^{n}\mathbf{B}^*(t,z)}{(\partial z)^{n}}\right|_{z=1} \cdot \mathbf{1}. \tag{12}$$

From (7), based on basic properties of the Laplace-transform, we have

$$\mathbf{B}^*(t,z) = \exp\left(\left(-\mathbf{S} + \sum_{\forall g} z^g \mathbf{R}^{(g)}\right) t\right) \tag{13}$$

where $\exp(\bullet)$ denotes the matrix exponential function. Applying (13) in (12), using the definition of the matrix exponential function and changing the order of the derivative and the summation leads to

$$f^{(n)}(t) = \sum_{i=0}^{\infty} \frac{t^i}{i!} \frac{\partial^n}{(\partial z)^n} \left(-\mathbf{S} + \sum_{\forall g} z^g \mathbf{R}^{(g)}\right)^i \Bigg|_{z=1} \cdot \mathbf{1}$$

By using the notation

$$\mathbf{N}^{(n)}(i) = \frac{\partial^n}{(\partial z)^n} \left(-\mathbf{S} + \sum_{\forall g} z^g \mathbf{R}^{(g)}\right)^i \Bigg|_{z=1} \tag{14}$$

we clearly have

$$f^{(n)}(t) = \sum_{i=0}^{\infty} \frac{t^i}{i!} \mathbf{N}^{(n)}(i) \cdot \mathbf{1} \tag{15}$$

and in the following we show that $\mathbf{N}^{(n)}(i)$ can be computed in a recursive manner. We can write $\mathbf{N}^{(n)}(i) =$

$$\frac{\partial^n}{(\partial z)^n} \left(-\mathbf{S} + \sum_{\forall g} z^g \mathbf{R}^{(g)}\right) \left(-\mathbf{S} + \sum_{\forall g} z^g \mathbf{R}^{(g)}\right)^{i-1} \Bigg|_{z=1} =$$

$$-\frac{\partial^n}{(\partial z)^n} \mathbf{S} \left(-\mathbf{S} + \sum_{\forall g} z^g \mathbf{R}^{(g)}\right)^{i-1} \Bigg|_{z=1} + \tag{16}$$

$$\frac{\partial^n}{(\partial z)^n} \sum_{\forall g} z^g \mathbf{R}^{(g)} \left(-\mathbf{S} + \sum_{\forall g} z^g \mathbf{R}^{(g)}\right)^{i-1} \Bigg|_{z=1} \tag{17}$$

It is easy to see that the term in (16) equals $-\mathbf{S}\mathbf{N}^{(n)}(i-1)$. The term in (17), by changing the order of the summation and the derivative and by applying properties of derivatives of products, can be written as

$$\sum_{\forall g} \frac{\partial^n}{(\partial z)^n} z^g \mathbf{R}^{(g)} \left(-\mathbf{S} + \sum_{\forall g} z^g \mathbf{R}^{(g)}\right)^{i-1} \Bigg|_{z=1} =$$

$$\sum_{\forall g} \sum_{k \in \mathbb{Z}^W : k \le n} \left[\prod_{j=1}^{W} \binom{n_j}{k_j} \cdot \right. \tag{18}$$

$$\left. \left(\frac{\partial^k}{(\partial z)^k} z^g \mathbf{R}^{(g)} \cdot \frac{\partial^{n-k}}{(\partial z)^{n-k}} \left(-\mathbf{S} + \sum_{\forall g} z^g \mathbf{R}^{(g)}\right)^{i-1} \right) \right] \Bigg|_{z=1}$$

whose product of binomial coefficients will be abbreviated in the sequel as

$$\binom{n}{k} = \prod_{j=1}^{W} \binom{n_j}{k_j}.$$

The first derivative of the right hand side of (18) evaluated at $z = 1$ will be denoted by $c_{g,k}$ and results to be

$$c_{g,k} = \left.\frac{\partial^k}{(\partial z)^k} z^g\right|_{z=1} = \frac{\partial^{\#k} z_1^{g_1} z_2^{g_2} \dots z_W^{g_W}}{\partial z_1^{k_1} \partial z_2^{k_2} \dots \partial z_W^{k_W}} = \prod_{i=1}^{W} \prod_{j=0}^{k_i - 1} (g_i - j). \tag{19}$$

Based on (16), (17), (18) and (19) we have

$$\mathbf{N}^{(n)}(i) = -\mathbf{S}\mathbf{N}^{(n)}(i-1) + \sum_{k \in \mathbb{Z}^W : k \le n} \binom{n}{k} \sum_{\forall g} c_{g,k} \mathbf{R}^{(g)} \mathbf{N}^{(n-k)}(i-1) \tag{20}$$

which provides the required recursion. The initial condition for the recursion is $\mathbf{N}^{(0)}(0) = \mathbf{I}$ and $\mathbf{N}^{(n)}(0) = \mathbf{0}$ for any $n \neq 0$. Note that the recursion results in $\mathbf{N}^{(0)}(i) = \mathbf{Q}^i$ which corresponds to the fact that the factorial moment associated with the 0 vector provides the transient behaviour of the underlying CTMC.

4.2 Numerically stable recursion for the moments of the accumulated reward

The solution provided by (15) and (20) involves multiplication of matrices with positive and negative entries whose absolute value is larger than one and hence leads to a numerical computation with difficult error control. This problem can be solved by applying to (15) and (20) the idea of uniformisation [13, 24]. Uniformisation (called also randomisation) decomposes the behaviour of a continuous time Markov chain (CTMC) into a discrete time Markov chain (DTMC) and a Poisson process (PP). The DTMC takes into account the transitions of the CTMC while the PP provides the distribution of the number of transitions occuring in a given a time interval. The intensity of the PP, denoted by q, has to be larger or equal to the maximal entry of $\mathbf{S}$, i.e., $q \geq max_{i \in \mathcal{S}}(\mathbf{S}_{i,i})$. Based on this decomposition the distribution of a performance index at time t, denoted by $\mathcal{P}(t)$, can be written as

$$Pr\left\{\mathcal{P}(t) < x\right\} = \sum_{k=0}^{\infty} Pr\left\{\mathcal{P}(t) < x | k \text{ transitions in } [0,t]\right\} \cdot Pr\left\{k \text{ transitions in } [0,t]\right\}$$

where

$$Pr\{k \text{ transitions in } [0,t]\} = \frac{(qt)^i}{i!}e^{-qt}.$$

Algebraically the decomposition is represented by introducing the quantities

$$\mathbf{S}' = -\frac{\mathbf{S}}{q} + \mathbf{I} \text{ and } \mathbf{R}'^{(g)} = \frac{\mathbf{R}^{(g)}}{q} \tag{21}$$

whose entries are between zero and one and their sum

$$\mathbf{Q}' = \mathbf{S}' + \sum_{\forall g} \mathbf{R}'^{(g)}.$$

is the transition probability matrix of the corresponding DTMC. By using the quantities defined in (21), equation (13) can be written as

$$\mathbf{B}^*(t,z) = \exp\left(\left(q(\mathbf{S}'-\mathbf{I}) + \sum_{\forall g} z^g q\mathbf{R}'^{(g)}\right)t\right) = \tag{22}$$

$$\exp\left(\left(\mathbf{S}' + \sum_{\forall g} z^g \mathbf{R}'^{(g)}\right)qt - qt\mathbf{I}\right) =$$

$$\exp(-qt)\exp\left(\left(\mathbf{S}' + \sum_{\forall g} z^g \mathbf{R}'^{(g)}\right)qt\right)$$

from which, by introducing

$$\mathbf{N}'^{(n)}(i) = \frac{\partial^n}{(\partial z)^n}\left(\mathbf{S}' + \sum_{\forall g} z^g \mathbf{R}'^{(g)}\right)^i\Bigg|_{z=1}$$

we have

$$f^{(n)}(t) = \sum_{i=0}^{\infty} \frac{(qt)^i}{i!}e^{-qt}\mathbf{N}'^{(n)}(i)\cdot\mathbf{1}. \tag{23}$$

Following the same steps, given in (16-19), that lead to a recursion for $\mathbf{N}^{(n)}(i)$, the following recursive relation can be obtained for $\mathbf{N}'^{(n)}(i)$

$$\mathbf{N}'^{(n)}(i) = \begin{cases} \mathbf{I} & i=0, n=0 \\ \mathbf{0} & i=0, n\neq 0 \\ \mathbf{S}'\mathbf{N}'^{(n)}(i-1) + & \\ \sum\limits_{k\in\mathbb{Z}^W:k\leq n}\binom{n}{k}\sum\limits_{\forall g} c_{g,k}\mathbf{R}'^{(g)}\mathbf{N}'^{(n-k)}(i-1) & \\ & \text{otherwise} \end{cases} \tag{24}$$

In the next subsection we show that the recursion given in (24) together with (23) results in numerical computations with easy error control.

4.3 Error control

As in case of uniformisation based transient analysis of CTMCs, the infinite sum in (23) can be approximated by a finite sum. However, the error control is not as straightforward as in case of the transient analysis. For the transient probabilities, given by $f^{(0)}(t)$ in our framework, it is known that the sum of the entries is one. No such information is available in advance for the quantities $f^{(n)}(t)$ with $n \neq 0$.

The fact that the entries of $f^{(n)}(t)$ can be computed with arbitrary precision with a finite sum is ensured by the following trivial relation that holds entry-wise for the matrices $\mathbf{N}'^{(n)}(i)$

$$\mathbf{N}'^{(n)}(i) \leq (\mathbf{Q}')^i \prod_{j=1}^{W}\prod_{k=0}^{n_j-1}(ig_{max}-k)$$

where g_{max} denotes the maximal entries of the vectors representing the gains, i.e., $g_{max} = \max_{\forall g,\forall i:1\leq i\leq W} g_i$. For any $\epsilon > 0$ there exists such K that

$$\left|\left|\sum_{i=K}^{\infty}\frac{(qt)^i}{i!}e^{-qt}(\mathbf{Q}')^i\prod_{j=1}^{W}\prod_{k=0}^{n_j-1}(ig_{max}-k)\right|\right| \leq \epsilon \tag{25}$$

where $||v||$ is the sum of the entries of vector v. With such K we ensure

$$||f^{(n)}(t)|| - ||f_K^{(n)}(t)|| \leq \epsilon.$$

where $f_K^{(n)}(t)$ is the finite approximation given by

$$f_K^{(n)}(t) = \sum_{i=0}^{K}\frac{(qt)^i}{i!}e^{-qt}\mathbf{N}'^{(n)}(i)\cdot\mathbf{1}.$$

However, since not all reactions lead to maximal reward gain, the truncation point calculated based on (25) gives a pessimistic estimate for the number of terms that have to be considered for a given accuracy. A better approach in practice is to keep under control both the Poisson probabilities and the relative increment of the vectors $f^{(n)}(t)$. Accordingly, we truncate the infinite sum at K when

$$1 - \sum_{i=0}^{K}\frac{(qt)^i}{i!}e^{-qt} \leq \epsilon_1 \text{ and } \frac{||f_{K+1}^{(n)}(t)|| - ||f_K^{(n)}(t)||}{||f_K^{(n)}(t)||} \leq \epsilon_2.$$

4.4 Computational complexity

The computational complexity in time of the proposed method can be related to that of randomisation based transient analysis of CTMCs (which is not easy to characterize; the interested reader is referred to [7] for further information). As already mentioned, $f^{(0)}(t)$ provides the transient behaviour of the underlying CTMC and its computation requires as much effort as randomisation does. The calculation of a given factorial moment, $f^{(n)}(t)$, characterised by the vector n, necessitates the calculations of all factorial moments, $f^{(k)}(t)$, for which $k \in \mathbb{Z}^W : k \leq n$. Moreover, the larger n the more terms in (23) are needed to obtain the predefined complexity. This effect, however, depends heavily on the reward structure of the model and is hard to capture formally.

Let us report here our experimental findings for a few cases. The first l factorial moments of a single reward variable requires about $l+1$ times more calculations than randomisation. Having W reward variables, computing the first l factorial moments for all of them requires approximately $1+Wl$ times more time than randomisation. For what concerns joint moments, to compute the covariance for every pair of reward variables is about $1+W+\binom{W}{2}$ times heavier than randomisation.

For what concerns space requirements, two situations have to be distinguished. If we are interested in the behaviour for every possible initial state then the computation requires the

storage of square matrices whose size corresponds to the size of the state space. For a given factorial moments, $f^{(n)}(t)$, we need a matrix for every vector $k \in \mathbb{Z}^W : k \leq n$. If we are interested in the behaviour with a given initial situation (deterministic initial state or a particular initial distribution) then the calculations can be carried out on vectors. Once again, to compute $f^{(n)}(t)$ we need a vector for every $k \in \mathbb{Z}^W : k \leq n$. This means that the space requirement is as many times larger than that of randomisation as many vectors $k \in \mathbb{Z}^W : k \leq n$ we have to consider.

5. NUMERICAL ILLUSTRATIONS

In this section, in order to illustrate our method, we provide some numerical results obtained on two models. Since the scope is to provide a good test-bed for the method, the first model has been designed ad-hoc putting aside any biological meaning. On the contrary, the second case describes a real biological phenomenon. For both the models, starting from the factorial moments, we compute "normal" moments of all the *monotonic* species and the first joint moment $E\left[\mathcal{B}_{i,a}(t) \cdot \mathcal{B}_{i,b}(t)\right]$ for each couple of distinct *monotonic* species a, b. The results allow us to obtain directly measures of interest such as expectation, variance and covariance. Higher order moments can be used to compute bounds for the distribution of the monotonic species. In the following we provide figures with the behaviour of expectation, variance and covariance as function of time and figures with the bounds of the cumulative distribution function (*cdf*) for a given time point.

The solver for the MRM has been implemented in a prototype *JAVA* tool whereas the bounds of the distributions have been computed by using MRM Solve 2.0 [12, 25]. All the experiments have been performed on a common notebook powered by a *Intel Centrino Dual Core* with 4Gb of RAM.

5.1 Case 1

As anticipated above, the first model has been built ad-hoc to test our approach. Despite this, in order to be more realistic, we designed the model as a composition of common biological structures. In particular, we take inspiration from enzymatic reactions which are useful in this case due to their structure that gives rise naturally to MRMs. Roughly speaking, these kind of systems describe the production of one or more species, regulating their growth by the concentration of substrates and enzymes present in the system. Very often blocks of reactions describing the behaviour of enzymes are combined to model a biochemical phenomenon. For more details on these structures we refer the reader to [23] where a high number of enzymatic reactions systems are described.

Our system, depicted in Figure 2, contains two enzymes, E and E_1, competing for the substrate S with which both the enzymes are able to bind. The first enzyme, E, binds with S in order to produce P. The second enzyme E_1 is able instead to generate three different species, Q, R and P, after having bound with either subtrate S or B. When E_1 is bound with S, it can produce two units of Q and one unit of P and when it is bound with B a single unit of R plus one unit of P can be generated. We assume that there is such high amount of B present in the system that its quantity can be considered constant. Accordingly, B is present only when it is bound with E_1 (denoted as E_1B). Note that this way it is not possible to use up B and the

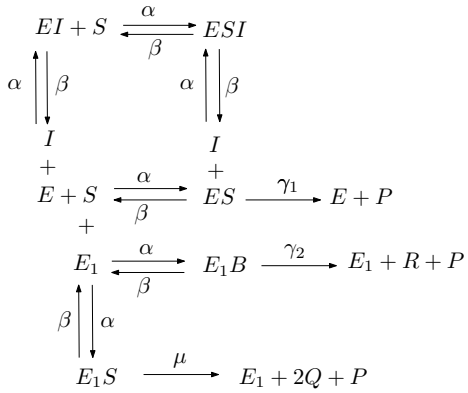

Figure 2: System of reactions of the ad-hoc

production of R and P is potentially infinite, giving rise to an infinite state space. A further assumption is that enzyme E can be inhibited by I in such way that the effectiveness of E gets lower in proportion of the quantity of I. The entire system is composed of 15 reactions. We assume mass action kinetics for all the reactions. The intensities of the binding and unbinding reactions are $\alpha = 1$ and $\beta = 0.1$, respectively. Whereas the production reactions are with intensity $\gamma_1 = \gamma_2 = 5$ and μ whose value will be 1, 5 or 10. The initial state is $E = E_1 = 5, I = S = 50$ and 0 for the other species.

It is clear that the *monotonic* species are Q, P and R and the "productive" activities are given by the reactions with intensities γ_1, γ_2, μ. Cutting off the *monotonic* species from the state descriptor the state space becomes finite with 55076 states. We computed 20 moments for Q, P, and R and the first joint moment for each couple of distinct variables in the time interval $[0, 25]$. We splitted the computation in 100 time intervals, each of them was computed in 3 minutes.

In Figure 3 we depicted the expectations and the variances as function of time. All the three species, Q, P and R, show faster growth for larger values of μ. This is not surprising for P and Q which are directly produced by a reaction whose intensity is μ. For what concerns R, the reason for which it grows faster with larger values of μ is the fact that with larger μ enzyme E_1 is released faster. For what concerns the variance patterns, one can observe that while there is substrate S in the system, the production of Q and R shows peaks of variability. Whereas, the variability of the production of P follows a more uniform pattern. The variance of Q returns then to lower level because its production is bounded.

The correlation coefficient (CC) is a particularly interesting measure for this kind of systems because it illustrates the degree and the kind of dependency between two species. It is computed as the ratio of the covariance of the random variables and the product of their standard deviations. In Figure 4 we show the CC as function of time for each couple of monotonic species. (Note that at time 0 the CC is undefined as its value is 0/0; in the figures we set to 0 the CC at time 0 and it results in some discontinuities of curves.) One can see that the consumption of substrate S has a strong impact on the correlation between the three species of interest. In fact, while S is not used up, Q and P are strongly related and, on the contrary, the correlation between P and R is low. The situation gets inverted when the quantity of S

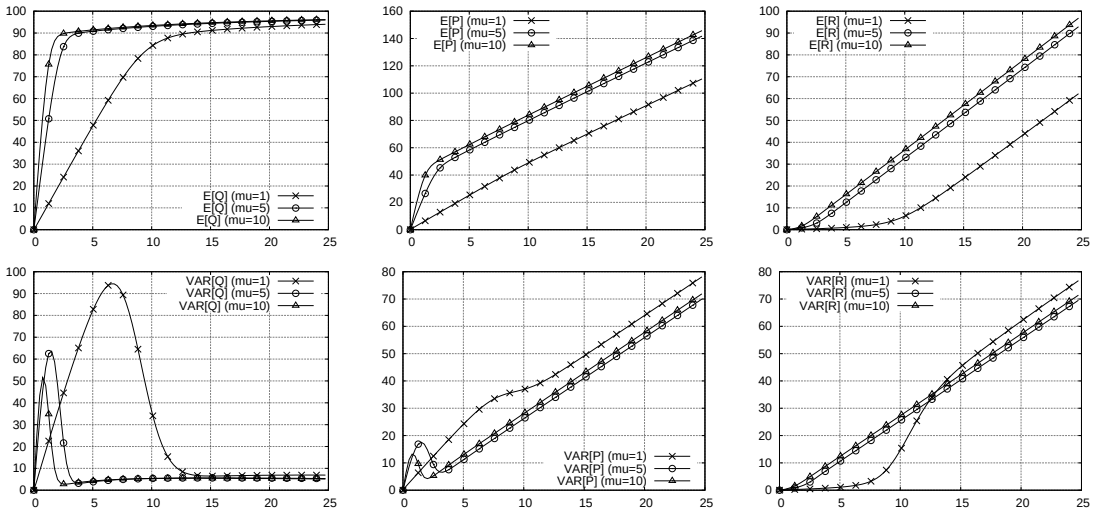

Figure 3: Ad-hoc model: expected values (upper part) and variances (lower part) of Q, R and P as function of time for the cases $\mu = 1, 5, 10$.

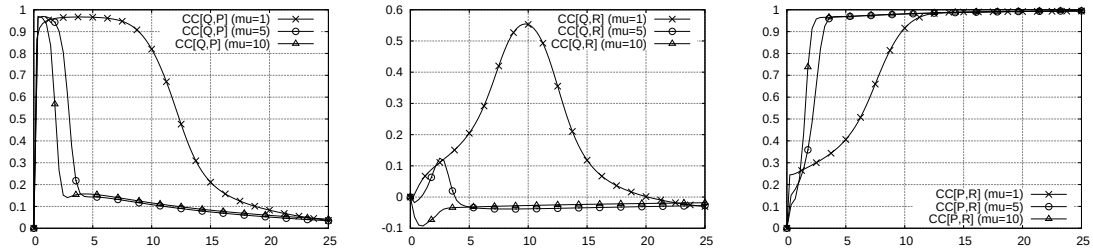

Figure 4: Ad-hoc model: correlation between each couple of *monotonic* species as function of time for the cases $\mu = 1,\ 5,\ 10$.

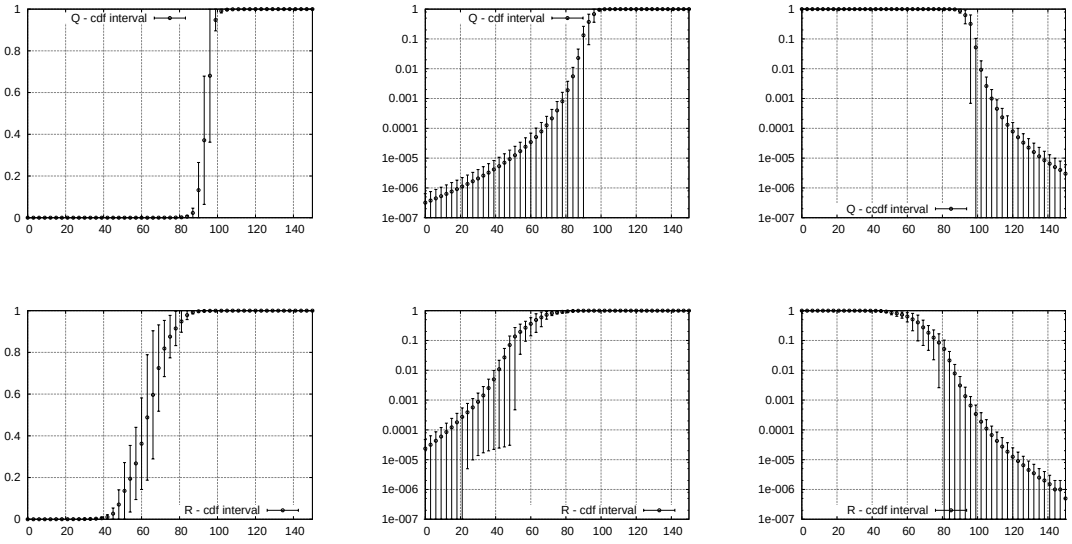

Figure 5: Ad-hoc model: bounds of the cdf of the quantity of Q and R at time 25; left: cdf with linear scale, middle: cdf with log scale, right: complementary cdf with log scale.

is close to zero due to the fact that the only possible production that can occur is through reaction γ_2 which produces P and R simultaneously. For what concerns the correlation of Q and R, the only case in which significant values occur is $\mu = 1$. This correlation is due to the fact that the more Q has been produced, the more E_1 has been unbound to produce R. This effect is not visible for larger values of μ because the initial phase where there is a significant amount of S is short.

As last measure we provide the bounds of the *cdf* obtained from the calculated moments by the method described in [25]. Given a point of interest c the estimation provides a lower bound and an upper bound for the probability $Pr\{X \leq c\}$. The bounds are tight at the extremes of the distribution and coarse near the mean value. The results are depicted in Figure 5 for Q and R for the situation after 25 time units with $\mu = 1$ (the results for P are similar to those for R). For both species we depicted the bounds of the cdf in linear scale (giving an overall view of the distribution), the bounds of the cdf with logarithmic y-axis (giving detailed view for values smaller than the mean), and the bounds of the complementary cdf with logarithmic y-axis (giving information on the tail of the distribution). As an example of interpreting these curves, consider Q at $c = 40$. The lower bound for the cdf at this point is 0 while the upper bound is about 10^{-5}. This implies that the probability of having less than 40 units of Q at time 25 is less than 10^{-5}. As for a value larger than the mean, we can read that the probability of having more than 100 units of R at time 25 is less than 0.001.

Let us mention here that obtaining bounds similar to those depicted in Figure 5 by simulation has high computational cost. Consider, for example, that having more than 150 units of Q at time 25 is less than 10^{-5}. This means that we need about 10^8 simulation runs to have a reasonable estimate of having more than 150 units of Q at time 25. This requires about 10 times more time than our approach.

As a last note on this case study, we mention that, since the original CTMC of the model is not finite, the results we provided in this sub-section are not straightforward to obtain using the original CTMC.

5.2 Case 2

The second model that we propose can be found in the database available on www.sbml.org, it models a real biological phenomenon with 14 species interacting through 16 reactions. The reactions are reported in Table 1.

Reactions	
$DFG \longrightarrow E1$	$DFG \longrightarrow E2$
$DFG \longrightarrow Gly + Cn$	$E1 \longrightarrow Gly + DG3$
$DG3 \longrightarrow Cn$	$DG3 \longrightarrow FA$
$E2 \longrightarrow Gly + DG1$	$DG1 \longrightarrow Cn$
$DG1 \longrightarrow AA$	$E1 \longrightarrow Gly + Man$
$E1 \longrightarrow Gly + Glu$	$Man \longrightarrow Glu$
$Glu \longrightarrow DG3$	$Gly + Cn \longrightarrow Mel$
$Cn \longrightarrow AA + FA + MG$	$E2 \longrightarrow Gly + Fru$

Table 1: Reactions of the DFG degradation pathway

The system models the N-(deoxy-D-fructos-1-y1)-glycine (DFG) degradation pathway, and tipically its transient analysis starts from the state with $DFG = n$, $n > 0$, and 0

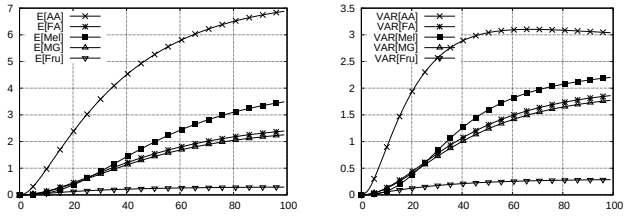

Figure 6: DFG Degradation: expected values (left) and variances (right) of AA, Mel, MG, FA, Fru, starting from the state $DFG = 13$.

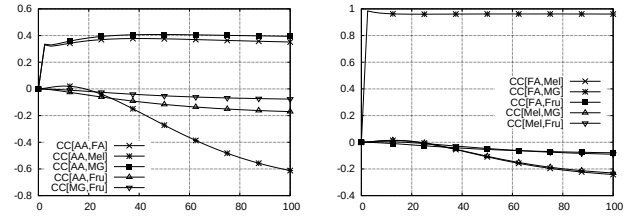

Figure 7: DFG Degradation: correlations between couple of *monotonic* species, starting from the state $DFG = 13$.

for the other species [16]. In this case, the state space of the original CTMC is bounded but even for low values of n its analysis is unfeasible because of the huge number of states. By using the approach proposed in this paper, we can analyse the system using a MRM whose state space is much smaller than the state space of the original CTMC. The monotonic species are AA, FA, MG, Mel and Fru and not considering them explicitely significantly reduces the state space. It is obvious that for larger values of n even our approach can become unfeasible but in several cases our method can make the difference between unfeasible and feasible.

We used the model with $n = 13$ in which case the original state space is composed of 5.200.300 states and, by using our method, it can be reduced to 497.420. In this case, we computed the first 2 moments and all the first joint moments in 40 equidistant points in the interval $[0, 100]$. Each time point needs about 5 minutes of time. The results are depicted in Figures 6 and 7. Based on Figure 7 one can figure out that species FA and MG have strong positive correlation, i.e., large (small) amount of FA implies large (small) amount of MG. Whereas, there is negative correlation between AA and Mel because there is competition between their production.

Since the original CTMC of this case study is finite, the results presented so far can be computed based on the original CTMC as well. In order to illustrate how much we gain using the proposed approach, in Table 2 we provide a comparison between the size of the state space of the original CTMC and that of the derived MRM.

6. CONCLUSION

In this paper we proposed a novel approach for the analysis of stochastic reaction networks. The approach is based on transforming the Markov chain representing the system into

n	CTMC	MRM
1	13	10
5	6.188	2.002
10	646.646	92.378
15	17.383.860	1.307.504

Table 2: Size of state space of the original CTMC and the derived MRM

a reward model whose underlying Markov chain is smaller than the original Markov chain. We provided an efficient method for the analysis of the moments of the accumulated reward of the resulting reward model. This method is an extension of an existing algorithm to the multiple reward variable case. Finally, we applied the approach to two case studies and showed that it can be used to gain insight into the mechanisms of complex reaction networks.

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