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► **To cite this version:**

Samuel Alexandre Vidal, Michel Petitot, François Boulier, François Lemaire, Celine Kuttler. Models of stochastic gene expression and Weyl algebra. Lecture Notes in Computer Science, 2010, Lecture Notes in Computer Science. hal-00492438v1

HAL Id: hal-00492438

<https://hal.science/hal-00492438v1>

Submitted on 11 Dec 2010 (v1), last revised 25 Jun 2011 (v2)

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Models of Stochastic Gene Expression and Weyl Algebra

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Abstract

This paper presents a symbolic algorithm for computing the ODE systems which describe the evolution of the moments associated to a chemical reaction system, considered from a stochastic point of view. The algorithm, which is formulated in the Weyl algebra, seems more efficient than the corresponding method, based on partial derivatives. In particular, an efficient method for handling conservation laws is presented. The output of the algorithm can be used for a further investigation of the system behaviour, by numerical methods. Relevant examples are carried out.

1 Introduction

This paper is concerned by the modeling of gene regulatory networks by chemical reaction systems, from a stochastic point of view. To such systems, one associates a time varying random variable, which counts the numbers of molecules of the various chemical species. It is well-known that the evolution, over the time t , of the moments (mean, variance, covariance) of this random variable, may be described by a system of ordinary differential equations (ODE), at least for first order chemical reaction systems. See [9] for an introduction to these topics. These systems of ODE can be built from the probability generating function associated to a given chemical reaction system, by performing, essentially, the three following steps:

1. compute a Schrödinger equation analog [2, Eq. (5.60)] for the probability generating function $\phi(t, z)$, where t denotes the time and z denote a vector of formal variables ;
2. compute iterated derivatives of this equation, with respect to t ;
3. evaluate the differentiated equation at $z = 1$.

This paper shows how to build these ODE systems by using Weyl algebra methods. The idea consists in formulating the Schrödinger equation analog using Euler derivation operators (of the form $z\partial/\partial z$) instead of more traditional partial derivatives (of the form $\partial/\partial z$). As far as we know, this use of Weyl algebra leads to a new algorithm which seems more efficient than the equivalent method, based on the use of partial derivatives. This claim is not proved in this paper. It was suggested to us by the following observations:

- (i) the formulation in the Weyl algebra permits to “combine in one step” steps 2 and 3 above, and thereby reduce the expression swell produced by step 2 (Formula (14) in Proposition 2) ;

- (ii) it is possible to encode, in the Schrödinger equation analog, the linear conservation laws of the system (Algorithm of Section 5.1), and thereby take advantage of them at the very first step of the method.

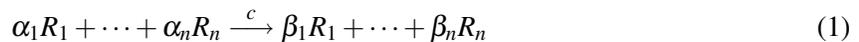
A software prototype has been developed by the second author in the MAPLE computer algebra software. It is available, for MAPLE 12, at <http://www2.lifl.fr/~petitot/publis/AB2010.zip>.

The paper is organized as follows. In Section 2, one recalls the classical theory. The material can essentially be found (often piecewise) in many texts such as [2, chapter 5] or [5]. We feel the need to recall it in order to avoid confusions, since, depending on slight variants on the underlying assumptions, or slight variants of notations, one may be led to different formula. Our presentation is based on stochastic Petri nets [10, 12]. In Section 3, one introduces Weyl algebra, Euler operators, and one reformulates the Schrödinger equation analog in this setting. In Section 4, the construction of the ODE system for the moments, from the differential operators, is explained (Proposition 1) and the algorithm is stated. In Section 5, the method for simplifying the Schrödinger equation analog using the conservation laws is provided. Section 6 provides a new, combined formula for steps 1 and 2 (Formula (14) in Proposition 2). Some properties of the algorithm, which depend on the order of the chemical reaction system under study are explored in Section 7. In particular, one recovers some well-known results (related to compartmental models), from the Weyl algebra theory. Some examples are carried out in Section 8. The problem of the “infinite cascade” is studied for order two systems. Many parts of this article can be found in [11, Annexe A].

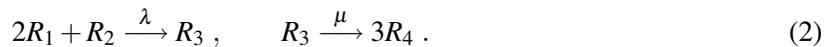
2 The Classical Theory

2.1 Chemical Reactions Systems

Definition 1. A chemical reaction system is given by a set of chemical species (R_1, R_2, \dots, R_n) , and, a set of chemical reactions, of the following form, where $\alpha = (\alpha_1, \alpha_2, \dots, \alpha_n)$, $\beta = (\beta_1, \beta_2, \dots, \beta_n)$ are multi-indices of nonnegative integers and c is a positive real valued kinetic constant¹.



Such a system, denoted \mathcal{R} , involves several reactions in general ; therefore it is a finite set of triples $(c, \alpha, \beta) \in \mathbb{R}_{>0} \times \mathbb{N}^n \times \mathbb{N}^n$. The state of the system $v = (v_1, v_2, \dots, v_n) \in \mathbb{N}^n$ is the number of molecules of the n chemical species at a given time. When reaction (1) occurs, the state vector instantaneously changes from the current value v to the new value $v' = v - \alpha + \beta$. The vector α indicates the quantities of the various species being consumed by the reaction while the vector β indicates the produced quantities. For a reaction to occur one needs $\alpha \leq v$, i.e. $\alpha_i \leq v_i$ for $i = 1 \dots n$. An example is provided by the following system, which is encoded by $\mathcal{R} = \{(\lambda, (2, 1, 0, 0), (0, 0, 1, 0)), (\mu, (0, 0, 1, 0), (0, 0, 0, 3))\}$.



2.2 Stochastic Petri Nets

Definition 2. A Petri net is a finite directed bipartite graph. Its nodes represent transitions (i.e. events that may occur, represented by boxes) and places (i.e. conditions for the events, represented by circles).

Denote $\mathcal{P} = \{p_1, p_2, \dots, p_n\}$ the set of places and $\mathcal{T} = \{t_1, t_2, \dots, t_m\}$ the set of transitions. At every instant, the place p_k , ($1 \leq k \leq n$) is supposed to contain v_k indistinguishable tokens. The state vector

¹Called *stochastic reaction constant* in [4].

$\mathbf{v} = (v_1, v_2, \dots, v_n) \in \mathbb{N}^n$ is the number of tokens a at given instant in the places. One denotes C^- and C^+ the integer matrices where $C_{i,j}^-$ is the number of arrows going from place p_j to transition t_i , and $C_{i,j}^+$ is the number of arrows going from transition t_i to place p_j . The *incidence matrix* is $C = C^+ - C^-$.

Definition 3. A stochastic Petri net is a Petri net enriched by a function $\rho : \mathcal{T} \rightarrow \mathbb{R}_{>0}$.

The category of the stochastic Petri nets is strictly equivalent to the category of chemical reaction systems. To each transition $t_i \in \mathcal{T}$, one associates a chemical reaction like (1) coded by a triple $(c, \alpha, \beta) \in \mathbb{R}_{>0} \times \mathbb{N}^n \times \mathbb{N}^n$ with $\alpha = (C_{ij}^-)_{j=1\dots n}$, $\beta = (C_{ij}^+)_{j=1\dots n}$ and $c = \rho(t_i)$. The incidence matrix C is then the transpose of the stoichiometry matrix of the chemical reaction system. The correspondence holds:

token	\longleftrightarrow	chemical molecule
place	\longleftrightarrow	chemical species
transition	\longleftrightarrow	chemical reaction

The chemical reaction system (2) corresponds to the Petri net of Figure 1 with associated matrices

$$C^- = \begin{pmatrix} 2 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \end{pmatrix} \quad C^+ = \begin{pmatrix} 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 3 \end{pmatrix} \quad C = \begin{pmatrix} -2 & -1 & 1 & 0 \\ 0 & 0 & -1 & 3 \end{pmatrix}$$

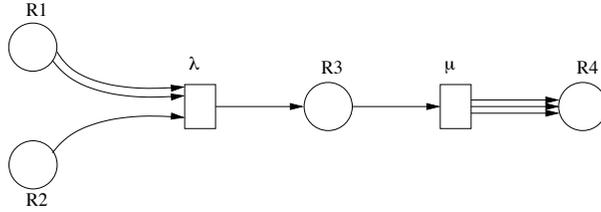


Figure 1: Petri net of Example (2)

2.3 Markov Chain of the Temporisation and Master Equation

One gives the “standard temporisation” of a stochastic Petri net by associating to it a continuous time Markov chain $\{N(t); t \in \mathbb{R}_{\geq 0}\}$ where the vector valued random variable $N(t)$ counts, at time t , the number of tokens in the places of the network. Let $\pi_{\mathbf{v}}(t)$ be the probability that the process be in state $N(t) = \mathbf{v}$ at time t . The *master-equation* [3] of a Markov chain is a linear differential system governing the evolution, over time, of the row vector $\pi(t) = (\pi_{\mathbf{v}}(t); \mathbf{v} \in \mathbb{N}^n)$. It is written as follows:

$$\frac{d}{dt} \pi(t) = \pi(t) A . \quad (3)$$

For each couple of multi-indices $(\alpha, \mathbf{v}) \in \mathbb{N}^n \times \mathbb{N}^n$, one defines the product of binomial coefficients

$$\binom{\mathbf{v}}{\alpha} = \binom{v_1}{\alpha_1} \binom{v_2}{\alpha_2} \dots \binom{v_n}{\alpha_n} . \quad (4)$$

The Markov chain $\{N(t); t \in \mathbb{R}_{\geq 0}\}$ associated to the stochastic Petri net \mathcal{R} , is defined on the discrete state space \mathbb{N}^n . For each triple $(c, \alpha, \beta) \in \mathcal{R}$ and for each state $\mathbf{v} \geq \alpha$ one builds an arrow going from \mathbf{v} to $\mathbf{v}' = \mathbf{v} - \alpha + \beta$, labeled by the transition rate $c \binom{\mathbf{v}}{\alpha}$. Schematically, this writes

$$(\mathbf{v} + \alpha - \beta) \xrightarrow{c \binom{\mathbf{v} + \alpha - \beta}{\alpha}} (\mathbf{v}) \xrightarrow{c \binom{\mathbf{v}}{\alpha}} (\mathbf{v} - \alpha + \beta) .$$

Assume that the system is in state $\mathbf{v} \in \mathbb{N}^n$ at time t . The probability that the chemical reaction (c, α, β) occurs over the time range $[t, t + \varepsilon[$ is $\varepsilon c \binom{\mathbf{v}}{\alpha} + o(\varepsilon)$. Then the master-equation (3) takes the form

$$\frac{d}{dt} \pi_{\mathbf{v}}(t) = \sum_{(c, \alpha, \beta) \in \mathcal{R}} c \binom{\mathbf{v} + \alpha - \beta}{\alpha} \pi_{\mathbf{v} + \alpha - \beta}(t) - c \binom{\mathbf{v}}{\alpha} \pi_{\mathbf{v}}(t) \quad (5)$$

According to Definition (4), the first term of the sum is zero whenever $\beta > \mathbf{v}$ and the second is zero whenever $\alpha > \mathbf{v}$. That differential system involves an infinite number of unknowns $\pi_{\mathbf{v}}(t)$ constrained by an infinite linear differential system. See Example (8).

2.4 The Schrödinger Equation Analog

For investigating models analytically one introduces the probability generating function [2, sect. 5.3]

$$\phi(t, z) = \sum_{\mathbf{v} \geq 0} \pi_{\mathbf{v}}(t) z^{\mathbf{v}}. \quad (6)$$

Note that $\phi(t, z)$ also equals $Ez^{N(t)}$ (i.e. the mean value of $z^{N(t)}$) since $Ez^{N(t)} = \sum_{\mathbf{v} \geq 0} \text{prob}(z^{\mathbf{v}} = z^{N(t)}) z^{\mathbf{v}}$. Given any chemical reaction system, it is possible to compute a general equation for ϕ [2, Eq. (5.60)]. This general equation is a Schrödinger equation analog. The differential operator H is a Hamiltonian.

$$\frac{\partial}{\partial t} \phi(z, t) = H \phi(z, t) \quad \text{where} \quad H = \sum_{(c, \alpha, \beta) \in \mathcal{R}} \frac{c}{\alpha!} (z^{\beta} - z^{\alpha}) \left(\frac{\partial}{\partial z} \right)^{\alpha}. \quad (7)$$

The Hamiltonian of Example (2) is

$$H = \frac{1}{2} \lambda (z_3 - z_1^2 z_2) \frac{\partial^2}{\partial z_1^2} \frac{\partial}{\partial z_2} + \mu (z_4^3 - z_3) \frac{\partial}{\partial z_3}.$$

By differentiating the probability generating function (6) and evaluating it at $z = 1$ i.e. at $z_1 = \dots = z_n = 1$, one obtains formulas which bind ϕ , the means and the variances of the number of molecules of the chemical species. Here are a few examples. By a mere evaluation, one gets: $\phi(t, z) |_{z=1} = 1$. Differentiate (6) with respect to any z_i and evaluate at $z = 1$, one gets the expected value of the number of molecules of species R_i , i.e. $EN_i(t)$

$$\left(\frac{\partial}{\partial z_i} \phi(z, t) \right)_{|z=1} = \sum \mathbf{v}_i \pi_{\mathbf{v}}(t) = EN_i(t).$$

Differentiate (6) twice with respect to some fixed z_i and evaluate at $z = 1$, one gets a formula featuring the expected value of the square of the number of molecules of R_i , denoted $EN_i(t)^2$, together with $EN_i(t)$:

$$\left(\frac{\partial}{\partial z_i} \frac{\partial}{\partial z_i} \phi(z, t) \right)_{|z=1} = \sum \mathbf{v}_i (\mathbf{v}_i - 1) \pi_{\mathbf{v}}(t) = \sum \mathbf{v}_i^2 \pi_{\mathbf{v}}(t) - \sum \mathbf{v}_i \pi_{\mathbf{v}}(t) = EN_i(t)^2 - EN_i(t).$$

The variance of the number of molecules of R_i satisfies the well-known formula: $\text{Var}N_i(t) = EN_i(t)^2 - (EN_i(t))^2$. The above formula can then be restated using $EN_i(t)$ and $\text{Var}N_i(t)$ only. Then, from the arguments above and the Schrödinger equation analog (7), one can compute an ODE system for the means and the variances $EN_i(t)$ and $\text{Var}N_i(t)$. The method is illustrated over the following example.



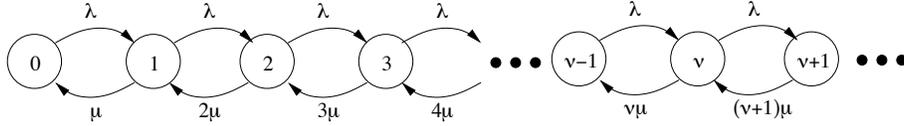


Figure 2: The Markov chain associated to System (8)

It corresponds to the creation and degradation of mRNA by an unregulated gene. It also corresponds to the $M/M/\infty$ client-server system [3]. The set of triples $\mathcal{R} = \{(\lambda, (0), (1)), (\mu, (1), (0))\}$ provides a description of that system. The Markov chain is described by the transition rates $\lambda \binom{v}{0} = \lambda$ and $\mu \binom{v}{1} = \mu v$ for all $v \in \mathbb{N}$. Using the convention $\pi_{-1}(t) = 0$, the master-equation (5) of that Markov chain is:

$$\frac{d}{dt} \pi_v(t) = \lambda [\pi_{v-1}(t) - \pi_v(t)] + \mu [(v+1)\pi_{v+1}(t) - v\pi_v(t)] \quad (v \geq 0), \quad (9)$$

The Schrödinger equation analog (7) is:

$$\frac{\partial}{\partial t} \phi(t, z) = \left[\lambda(z-1) + \mu(1-z) \frac{\partial}{\partial z} \right] \phi(t, z) = \lambda(z-1)\phi(t, z) + \mu(1-z)\phi_z(t, z).$$

In order to compute an ODE for the mean $EN(t)$, one differentiates that relation with respect to z ,

$$\frac{\partial}{\partial z} \frac{\partial}{\partial t} \phi(t, z) = \lambda [\phi(t, z) + (z-1)\phi_z(t, z)] + \mu [-\phi_z(t, z) + (1-z)\phi_{zz}(t, z)].$$

The partial derivatives $\frac{\partial}{\partial t}$ and $\frac{\partial}{\partial z}$ commute. At the point $z = 1$, this equation becomes,

$$\frac{\partial}{\partial t} \phi_z(t, z)|_{z=1} = \lambda - \mu \phi_z(t, z)|_{z=1}, \quad \frac{d}{dt} EN(t) = \lambda - \mu EN(t).$$

An ODE for $EN(t)$ is obtained. Similar computations provide an ODE for $\text{Var}N(t)$. The initial values are easily obtained since, at $t = 0$, the expected value of $N(t)$ is equal to the initial quantity n_0 of the chemical species and the variance of $N(t)$ is zero. The analysis of that dynamics can be done numerically or symbolically, depending on the instance of the problem.

Using this method, one can compute an ODE for any moment $EN^q(t)$ where $q \in \mathbb{N}$. In the particular case of *order 1* chemical reaction systems (definition 5), the ODE system is finite and one can compute exact values of the means and the variances [2, sect. 5.3.3]. The above example has order 1.

In the general case, the ODE system is infinite, since for any $q \in \mathbb{N}$, the evolutions of the moments of order q depend on moments of higher order (problem of the infinite cascade). It is sometimes possible to compute exact values for the means and the variances by *ad hoc* arguments. Otherwise, the ODE system needs to be truncated and one recovers a more or less usable approximation. The truncation, which is obtained by assuming that random variables $N_i(t)$ are independent, provides the classical deterministic model, which is used when the number of molecules is large.

3 Reformulation in the Weyl Algebra

In this section, one introduces the properties of the Weyl algebra, which are needed to understand the Algorithm of Section 4 and one reformulates the construction of the Hamiltonian (7).

The Weyl algebra $\text{Weyl}_{\mathbb{R}}(z_1, \dots, z_n) = \mathbb{R}[z_1, z_2, \dots, z_n][\partial_{z_1}, \partial_{z_2}, \dots, \partial_{z_n}]$ is the algebra of differential operators defined on the affine algebraic manifold \mathbb{R}^n . It is a non-commutative algebra generated by the

symbols z_k and ∂_{z_k} for $k = 1 \dots n$ constrained by the commutation relations $[\partial_{z_i}, z_j] = 1$ if $i = j$ else 0. For all $\alpha, \beta \in \mathbb{N}^n$, denote $z^\alpha = z_1^{\alpha_1} z_2^{\alpha_2} \dots z_n^{\alpha_n}$ and $\partial_z^\beta = \partial_{z_1}^{\beta_1} \partial_{z_2}^{\beta_2} \dots \partial_{z_n}^{\beta_n}$. For each element $z^\alpha \partial_z^\beta$, define the *degree* $\deg z^\alpha \partial_z^\beta$ as $|\alpha| - |\beta|$, and the *order* $\text{ord} z^\alpha \partial_z^\beta$ as $|\beta|$, where $|\alpha| = \alpha_1 + \alpha_2 + \dots + \alpha_n$ and $|\beta| = \beta_1 + \beta_2 + \dots + \beta_n$.

One now defines the evaluation of a differential operator. Any element $D \in \text{Weyl}_{\mathbb{R}}(z_1, \dots, z_n)$ can be written in a unique way as a finite sum of terms $f_\nu \partial_z^\nu$ where $\nu \in \mathbb{N}^n$, and where $f_\nu \in \mathbb{R}[z_1, z_2, \dots, z_n]$ defines a function $\mathbb{R}^n \rightarrow \mathbb{R}$. This allows to define the *evaluation* of D at a point $p \in \mathbb{R}^n$:

$$D|_p = \sum_{\nu} f_\nu(p) \partial_z^\nu. \quad (10)$$

The operator $D|_p : \mathbb{R}[z_1, z_2, \dots, z_n] \rightarrow \mathbb{R}$ is defined in a coordinate free way by setting $D|_p(h) = D(h)|_p$ for any function $h \in \mathbb{R}[z_1, z_2, \dots, z_n]$. The term $D(h)|_p$ denotes the real number obtained by evaluating the function $D(h)$ at p . The evaluation does not commute with the multiplication of the algebra $\text{Weyl}_{\mathbb{R}}(z)$.

One now reformulates the Schrödinger equation analog, using “falling powers” and Euler operators. Falling powers are defined by $x^{\underline{p}} = x(x-1)(x-2) \dots (x-p+1)$, where $p \in \mathbb{N}$. Then, binomial coefficients can be reformulated as follows: $\binom{x}{p} = (1/p!)x^{\underline{p}}$. Euler operators are defined by $\theta_k = z_k \partial / \partial z_k$. For any $\alpha \in \mathbb{N}^n$, one defines $\theta^\alpha = \theta_1^{\alpha_1} \theta_2^{\alpha_2} \dots \theta_n^{\alpha_n}$. The following lemma is well-known:

Lemma 1. For any $\alpha \in \mathbb{N}^n$, one has $\theta^\alpha = z^\alpha \left(\frac{\partial}{\partial z} \right)^\alpha$.

Given any chemical reaction system, the Schrödinger equation analog (7) which governs the probability generating function (6) can be formulated in the Weyl algebra as follows. The formula can be justified by using Formula (7) and Lemma 1. The Hamiltonian H belongs to $\text{Weyl}_{\mathbb{R}}(z)$. It is a linear operator acting on the formal series in the variables (z_1, z_2, \dots, z_n) .

$$H = \sum_{(c, \alpha, \beta) \in \mathcal{R}} \frac{c}{\alpha!} \left(z^{\beta - \alpha} - 1 \right) \theta^\alpha. \quad (11)$$

The Hamiltonian of Example (2) now writes:

$$H = \frac{1}{2} \lambda \left(\frac{z_3}{z_1^2 z_2} - 1 \right) \theta_1 (\theta_1 - 1) \theta_2 + \mu \left(\frac{z_4^3}{z_3} - 1 \right) \theta_3.$$

4 The Algorithm

One first proves Proposition 1, which permits our algorithm to convert differential operators into ordinary differential equations for the moments, hence for the desired means and variances. Then the algorithm is stated.

As $N(t)$ is a (time dependent) random variable taking values in \mathbb{N}^n , one can consider any random variable of the form $f(N(t))$ where $f : \mathbb{N}^n \rightarrow \mathbb{R}$ is a polynomial function coded by an element $f \in \mathbb{R}[\theta_1, \theta_2, \dots, \theta_n]$. Observe that f is also an element of the algebra $\text{Weyl}_{\mathbb{R}}(z)$. For example, to the polynomial $f = \theta_1^2 \theta_2 + 3\theta_1 \in \mathbb{R}[\theta_1, \theta_2]$, one can associate: the operator $f(\theta) = \theta_1^2 \theta_2 + 3\theta_1 \in \text{Weyl}_{\mathbb{R}}(z_1, z_2)$; the number $f(\nu) = \nu_1^2 \nu_2 + 3\nu_1 \in \mathbb{R}$; the random variable $f(N(t)) = N_1^2(t) N_2(t) + 3N_1(t)$ defined on \mathbb{N}^2 with value in \mathbb{R} ; the commutator $[f(\theta), H] = f(\theta)H - Hf(\theta)$; and the evaluated commutator, $[f(\theta), H]|_{z_1=z_2=1}$, which is a polynomial in $\mathbb{R}[\theta_1, \theta_2]$. The mean value of the random variable $f(N(t))$ is, by definition, $E f(N(t)) = \sum_{\nu} f(\nu) \pi_{\nu}(t)$.

Lemma 2. For any polynomial $f \in \mathbb{R}[\theta_1, \theta_2, \dots, \theta_n]$, interpreted as a differential operator acting on the generating series $\phi(t, z)$, one has: $\mathbb{E} f(N(t)) = f(\theta) \mathbb{E} z^{N(t)}|_{z=1}$.

Proof. One checks that for any $\nu \in \mathbb{N}^n$, one has $f(\theta) z^\nu = f(\nu) z^\nu$. It follows that $f(\theta) \phi(t, z) = \sum_\nu f(\nu) \pi_\nu(t) z^\nu$. Evaluating at $z = 1$, one gets: $f(\theta) \mathbb{E} z^{N(t)}|_{z=1} = \sum_\nu f(\nu) \pi_\nu(t) = \mathbb{E} f(N(t))$. \square

Proposition 1. Given any polynomial $f \in \mathbb{R}[\theta_1, \theta_2, \dots, \theta_n]$, denote $f_H(\theta) = [f(\theta), H]|_{z=1}$. Then

$$\frac{d}{dt} \mathbb{E} f(N(t)) = \mathbb{E} f_H(N(t)) .$$

Proof. One starts from the Schrödinger equation analog $\frac{\partial}{\partial t} \phi(t, z) = H \phi(t, z)$. The partial derivation $\partial/\partial t$ commutes with the operator $f(\theta)$ and the evaluation at $z = 1$. Thus $\partial/\partial t f(\theta) \phi(t, z)|_{z=1} = f(\theta) H \phi(t, z)|_{z=1}$. The first member is equal to $d/dt \mathbb{E} f(N(t))$ according to Lemma 2. In the second member, one can replace the product $f(\theta)H$ by the commutator $[f(\theta), H]$ since, according to Formula (11), the Hamiltonian H is zero at $z = 1$. The second member is equal to $\mathbb{E} f_H(N(t))$ by Lemma 2. \square

The Algorithm

Input: A stochastic Petri net \mathcal{R} and a maximum order $q \in \mathbb{N}$.

Output: A linear differential system characterizing the time evolution of moments, up to degree q .

(i) Compute the Hamiltonian H of \mathcal{R} using formula (11).

(ii) For all multi-indices $\kappa \in \mathbb{N}^n$ such that $|\kappa| \leq q$, compute the commutator evaluated at $z = 1$

$$f_\kappa = [\theta^\kappa, H]|_{z=1}, \quad (f_\kappa \in \mathbb{R}[\theta_1, \dots, \theta_n]) , \quad (12)$$

Then generate the linear differential equation $\frac{d}{dt} \mathbb{E} N^\kappa(t) = \mathbb{E} f_\kappa(N(t))$, using Proposition 1.

The polynomial f_κ in Formula (12) can be computed in different ways. It can be computed by using a smart computation of the Lie bracket (which avoids the expansion of the Lie bracket by computing $\theta^\kappa H$ and then subtracting $H \theta^\kappa$) and a specialization to $z = 1$. Otherwise, one can compute $f_\kappa = \theta^\kappa H|_{z=1}$ since the term $H \theta^\kappa|_{z=1}$ cancels. An even better formula is given in Section 6, which avoids Weyl algebra and only relies on basic operations on commutative polynomials in θ .

The returned ODE system is truncated. Thus, some ODE may, in general, depend on moments of order higher than q , for which no ODE is generated. This problem does not occur in Example (8). The Hamiltonian is

$$H = \lambda(z-1) + \mu \left(\frac{1}{z} - 1 \right) \theta \quad \text{with} \quad \theta = z \frac{\partial}{\partial z} .$$

The algorithm computes the brackets

$$[\theta, H]|_{z=1} = \lambda - \mu \theta , \quad [\theta^2, H]|_{z=1} = \lambda + (2\lambda + \mu) \theta - 2\mu \theta^2 .$$

and returns the differential system

$$\frac{d}{dt} \mathbb{E} N(t) = \lambda - \mu \mathbb{E} N(t) , \quad \frac{d}{dt} \mathbb{E} N^2(t) = \lambda + (2\lambda + \mu) \mathbb{E} N(t) - 2\mu \mathbb{E} N^2(t) .$$

The variance is computed using $\text{Var} N(t) = \mathbb{E} N^2(t) - (\mathbb{E} N(t))^2$. The dynamics of the mean $x(t) = \mathbb{E} N(t)$ and the variance $v(t) = \text{Var} N(t)$ follows immediately.

$$\frac{d}{dt} x(t) = \lambda - \mu x(t) , \quad \frac{d}{dt} v(t) = \lambda + \mu x(t) - 2\mu v(t) .$$

5 Model Reduction, Model Restriction and Conservation Laws

Definition 4. Let λ be a n -dimensional vector of integers. A conservation law I_λ is a linear combination of the following form, with integer coefficients, which is conserved by each transition of the considered Petri net.

$$I_\lambda(\mathbf{v}) = \lambda_1 v_1 + \lambda_2 v_2 + \cdots + \lambda_n v_n, \quad (\mathbf{v} \in \mathbb{N}^n, \lambda \in \mathbb{Z}^n)$$

This notion is independent of the temporisation, hence of the kinetic constants associated to chemical reactions. Recall that the incidence matrix of a Petri net is the transpose of the stoichiometry matrix of a chemical reaction system. The next lemma is then well-known [6].

Lemma 3. Let \mathcal{R} be a Petri net. The column vector $\lambda = (\lambda_1, \lambda_2, \dots, \lambda_n) \in \mathbb{Z}^n$ defines a conservation law iff $C\lambda = 0$ where $C = C^+ - C^-$ is the incidence matrix of \mathcal{R} .

5.1 Model Reduction

A conservation law I_λ induces a graduation w_λ of $w_\lambda(z_k) = \lambda_k$ and $w_\lambda(\partial/\partial z_k) = -\lambda_k$ for all $k = 1 \dots n$. One moreover defines $w_\lambda(z^v) = \sum_k \lambda_k v_k$, that is $I_\lambda(\mathbf{v})$, for all $\mathbf{v} \in \mathbb{N}^n$.

Lemma 4. Assume that a conservation law I_λ holds. Then, $\phi(t, z)$ is a formal power series, homogeneous for w_λ , with weight $w_\lambda(\phi(t, z)) = I_\lambda(\mathbf{v}_0)$, where $\mathbf{v}_0 \in \mathbb{N}^n$ denotes the initial state at $t = 0$.

Proof. As $I_\lambda(\mathbf{v})$ is independent of the time t , the fact that $I_\lambda(\mathbf{v}) \neq I_\lambda(\mathbf{v}_0)$ implies that $\pi_v(t) = 0$ for any $t \geq 0$. The series $\phi(t, z) = \sum_v \pi_v(t) z^v$ is thus w_λ -homogeneous of weight $w_\lambda(z^{\mathbf{v}_0})$. \square

One sets $C_0 = I_\lambda(\mathbf{v}_0)$. It is an element of \mathbb{Z} . Then the operator $I_\lambda(\theta) - C_0 = \sum_k \lambda_k \theta_k - C_0$ vanishes on the generating series $\phi(t, z)$ because, according to Lemma 4, one has $I_\lambda(\theta)\phi(t, z) = C_0\phi(t, z)$. Every operator of the left ideal generated in $\text{Weyl}_{\mathbb{R}}(z)$ by $I_\lambda(\theta) - C_0$ has therefore a null action on $\phi(t, z)$.

The Model Reduction Algorithm

Input: A Hamiltonian $H \in \text{Weyl}_{\mathbb{R}}(z_1, \dots, z_n)$ describing the evolution of $N(t) = (N_1(t), \dots, N_n(t))$ and a conservation law I_λ . To simplify the exposition, λ_n is assumed nonzero.

Output: A reduced Hamiltonian $H' \in \text{Weyl}_{\mathbb{R}}(z_1, \dots, z_{n-1})$ describing the evolution of $(N_1(t), \dots, N_{n-1}(t))$. The new Hamiltonian H' is obtained from H by the following substitution

$$\theta_n \mapsto \frac{1}{\lambda_n} [C_0 - (\lambda_1 \theta_1 + \lambda_2 \theta_2 + \cdots + \lambda_{n-1} \theta_{n-1})], \quad z_n \mapsto 1.$$

5.2 Model Restriction

The presence of conservation laws often enables us to bound some random variables of the model. Those bounds in general depend on the initial state $\mathbf{v}_0 \in \mathbb{N}^n$. In this situation, it is possible to restrict the model by taking a quotient of the Weyl algebra $\text{Weyl}_{\mathbb{R}}(z_1, \dots, z_n)$ by a left ideal. The method is presented over the following system of chemical reactions



together with initial conditions $\mathbf{v}_0 = (a, b, 0)$ for $a, b \in \mathbb{N}$. The Petri net \mathcal{R} admits two conservation laws $\mathbf{v}_1 + \mathbf{v}_3 = a$ and $\mathbf{v}_2 + \mathbf{v}_3 = b$. One can therefore consider the random variable $N_3(t)$ only, with the bound $0 \leq N_3(t) \leq \min(a, b)$. Our software computes the Hamiltonian:

$$H = \lambda \left(\frac{z_3}{z_1 z_2} - 1 \right) \theta_1 \theta_2 + \mu \left(\frac{z_1 z_2}{z_3} - 1 \right) \theta_3$$

Performing the substitutions $\theta_1 \mapsto a - \theta_3$, $\theta_2 \mapsto b - \theta_3$, $z_1 \mapsto 1$ and $z_2 \mapsto 1$, one gets, in $\text{Weyl}_{\mathbb{R}}(z_3)$, the reduced Hamiltonian $H' = \lambda (z_3 - 1)(b - \theta_3)(b - \theta_3) + \mu (z_3^{-1} - 1)\theta_3$. The bound $N_3(t) \leq m$ with $m = \min(a, b)$ implies that the function $f(v_3) = v_3(v_3 - 1) \cdots (v_3 - m)$ is zero at all time t . One then gets

$$f(\theta_3) \phi(t, z_3) = \sum_{0 \leq v_3 \leq m} \pi_{v_3}(t) f(v_3) z_3^{v_3} = 0, \quad \forall t \in \mathbb{R}_{\geq 0}.$$

The operator $f(\theta_3)$ vanishes on the generating series $\phi(t, z_3)$. All computations can therefore be done in the quotient of the algebra $\text{Weyl}_{\mathbb{R}}(z_3)$ by the left ideal generated by $f(\theta_3)$. From an algorithmic point of view, this can be achieved by Gröbner basis techniques on commutative polynomials in θ .

6 A combined formula for differentiating and evaluating

In this section, the explicit Formula (14) is given for computing f_{κ} (Formula (12)) which are commutators evaluated at $z = 1$. We believe that this formula has several advantages. First, this combined formula provides an improvement of the algorithm of Section 4. Indeed, Formula (14) can be implemented only with basic operations on commutative polynomials in θ . Moreover, Formula (14) does not need any specialization $z = 1$. Second, all computations in the Weyl algebra can be avoided, which makes the algorithm easier to implement since no library for computing in Weyl algebras is needed. Third, Formula (14) might help to find interesting formulas (as in Lemma 9). Fourth, the computation of Formula (14) can be easily mixed with the reductions detailed in section 5 by using modular exponentiations.

Lemma 5. *Let A and B be two elements of $\text{Weyl}_{\mathbb{R}}(z_1, \dots, z_n)$. Define $\text{ad}_A(B) = [A, B]$. Then*

$$A^k B = \sum_{i=0}^k \binom{k}{i} \text{ad}_A^i(B) A^{k-i}, \quad (13)$$

where ad_A^i denotes the ad_A function composed i times.

Proof. Let t be an indeterminate. The classical identity $\exp(tA)B \exp(-tA) = \exp(t \text{ad}_A)(B)$ between formal series in t holds (adjoint representation of a Lie group over its Lie algebra). This formula can be rewritten as $\exp(tA)B = \exp(t \text{ad}_A)(B) \exp(tA)$ and developed with a Taylor expansion. The result is proved by identifying the coefficients of t^k in each side of

$$\sum_{k \geq 0} \frac{t^k}{k!} A^k B = \sum_{i, j \geq 0} \frac{t^{i+j}}{i! j!} \text{ad}_A^i(B) A^j.$$

□

Lemma 6. *For all $m \in \mathbb{Z}$ and any $k \in \mathbb{N}$, one has $\theta^k z^m = z^m (m + \theta)^k$ with $\theta = z \frac{\partial}{\partial z}$.*

Proof. One has $\text{ad}_{\theta}(z^m) = [\theta, z^m] = m z^m$. Thus, one has $\text{ad}_{\theta}^i(z^m) = m^i z^m$ for any $i \geq 0$. The lemma then follows from Lemma 5 by taking $A = \theta$ and $B = z^m$. □

Let $\nu \in \mathbb{Z}^n$ and $\kappa \in \mathbb{N}^n$ be two multi-indices. Denote $(\nu + \theta)^{\kappa} = (\nu_1 + \theta_1)^{\kappa_1} (\nu_2 + \theta_2)^{\kappa_2} \cdots (\nu_n + \theta_n)^{\kappa_n}$.

Lemma 7. *The commutation relation between θ^{κ} and z^{ν} , in $\text{Weyl}_{\mathbb{R}}(z_1, z_2, \dots, z_n)$, writes*

$$\theta^{\kappa} z^{\nu} = z^{\nu} (\nu + \theta)^{\kappa}.$$

Proof. The proof relies on Lemma 6. One only gives it for $n = 3$.

$$\begin{aligned}\theta^\kappa z^v &= (\theta_1^{\kappa_1} \theta_2^{\kappa_2} \theta_3^{\kappa_3})(z_1^{v_1} z_2^{v_2} z_3^{v_3}) = (\theta_1^{\kappa_1} z_1^{v_1})(\theta_2^{\kappa_2} z_2^{v_2})(\theta_3^{\kappa_3} z_3^{v_3}) \\ &= z_1^{v_1} (v_1 + \theta_1)^{\kappa_1} z_2^{v_2} (v_2 + \theta_2)^{\kappa_2} z_3^{v_3} (v_3 + \theta_3)^{\kappa_3} \\ &= (z_1^{v_1} z_2^{v_2} z_3^{v_3})(v_1 + \theta_1)^{\kappa_1} (v_2 + \theta_2)^{\kappa_2} (v_3 + \theta_3)^{\kappa_3} = z^v (v + \theta)^\kappa.\end{aligned}$$

□

Proposition 2. *Let \mathcal{R} be a stochastic Petri net, the Hamiltonian of which is H . Then*

$$[\theta^\kappa, H]_{z=1} = \sum_{(c, \alpha, \beta) \in \mathcal{R}} \frac{c}{\alpha!} [(\beta - \alpha + \theta)^\kappa - \theta^\kappa] \theta^\alpha, \quad (\kappa \in \mathbb{N}^n). \quad (14)$$

Proof. The evaluated commutator $[\theta^\kappa, H]_{z=1}$ is linear in H . One assumes, for simplicity, that a single chemical reaction is involved, so that $H = (z^{\beta-\alpha} - 1) \theta^\alpha$. The proof reduces to the computation of $[\theta^\kappa, (z^{\beta-\alpha} - 1) \theta^\alpha]_{z=1}$. Lemma 7 is used to make the terms θ^κ and $z^{\beta-\alpha} - 1$ commute. Computations give the following formula

$$\theta^\kappa (z^{\beta-\alpha} - 1) = \theta^\kappa z^{\beta-\alpha} - \theta^\kappa = z^{\beta-\alpha} (\beta - \alpha + \theta)^\kappa - \theta^\kappa.$$

Evaluate it at $z = 1$ and apply the fact that $H|_{z=1} = 0$. The proposition is proved. □

7 Order of a Chemical Reaction System

In this section, one recovers well-known results on order 1 systems from the Weyl algebra theory. See [8] and [2, sect. 5.3.3]. First, one introduces some further theoretical developments on Weyl algebra.

The algebra $\text{Weyl}_{\mathbb{R}}(z) = \text{Weyl}_{\mathbb{R}}(z_1, \dots, z_n)$ is associative but noncommutative. It is graded by the *degree* and filtered by the *order* (in the sense of differential operators). It is readily checked that the product AB of two elements $A, B \in \text{Weyl}_{\mathbb{R}}(z)$ homogeneous by degree, is also homogeneous of degree $\deg(A) + \deg(B)$. The component $\mathcal{F}_q \subset \text{Weyl}_{\mathbb{R}}(z)$, $q \in \mathbb{N}$, of the growing filtration

$$\mathcal{F} : \mathcal{F}_0 \subset \mathcal{F}_1 \subset \mathcal{F}_2 \subset \dots \quad (15)$$

is the \mathbb{R} -vector space spanned by the elements $z^\alpha \partial_z^\beta$ of order *at most* q , i.e. such that $|\beta| \leq q$. One checks that $\mathcal{F}_k \mathcal{F}_l \subset \mathcal{F}_{k+l}$ for all $k, l \in \mathbb{N}$. The *graded* algebra associated to the filtration \mathcal{F} is commutative [1]. It is defined by

$$\text{gr Weyl}_{\mathbb{R}}(z) = \mathcal{F}_0 \oplus \mathcal{F}_1 / \mathcal{F}_0 \oplus \mathcal{F}_2 / \mathcal{F}_1 \oplus \dots \quad (16)$$

Definition 5. *A chemical reaction system \mathcal{R} is said to be of order $q \in \mathbb{N}$, if each reaction $(c, \alpha, \beta) \in \mathcal{R}$ satisfies $|\alpha| \leq q$ (where $|\alpha| = \alpha_1 + \alpha_2 + \dots + \alpha_n$ for any $\alpha \in \mathbb{N}^n$).*

Thus, a chemical reaction system \mathcal{R} is of order q if every reaction of \mathcal{R} consumes at most q molecules. The next lemma follows immediately from Formula (11).

Lemma 8. *A chemical reaction system is of order q iff its Hamiltonian H belongs to the \mathcal{F}_q component of the Weyl algebra filtration defined by (15).*

Any polynomial $f \in \mathbb{R}[\theta_1, \theta_2, \dots, \theta_n]$, homogeneous of degree d , defines a degree d moment $E f(N(t))$.

Proposition 3. *In a chemical reaction system of order q , the derivative with respect to the time of a degree d moment, only depends on other moments of order at most $q + d - 1$.*

Proof. Let $H \in \text{Weyl}_{\mathbb{R}}(z_1, z_2, \dots, z_n)$ be an order q operator i.e. $H \in \mathcal{F}_q$. If $f \in \mathbb{R}[\theta_1, \theta_2, \dots, \theta_n]$ is an homogeneous polynomial of degree d , then $[f(\theta), H] \in \mathcal{F}_{q+d-1}$. Evaluation at $z = 1$ provides an element $[f(\theta), H]_{z=1} \in \mathbb{R}[\theta_1, \theta_2, \dots, \theta_n]$ of degree at most $q + d - 1$. \square

Corollary 1. *In a chemical reaction system, the dynamics on the mean values $EN_k(t)$, $k = 1 \dots n$, (i.e. first order moments) writes as follows ($k \in \mathbb{N}$, $\alpha, \beta \in \mathbb{N}^n$). Moreover, the dynamics of a first order system is linear in the variables $EN_k(t)$.*

$$\frac{d}{dt} EN_k(t) = \sum_{(c, \alpha, \beta) \in \mathcal{R}} \frac{c}{\alpha!} (\beta_k - \alpha_k) EN(t)^\alpha$$

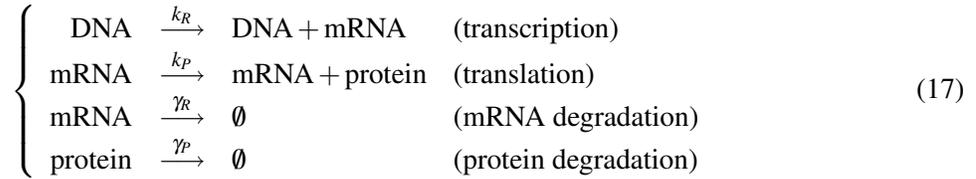
Proof. One deduces $\theta_k H = \sum_{(c, \alpha, \beta) \in \mathcal{R}} \frac{c}{\alpha!} (\beta_k - \alpha_k) z^{\beta - \alpha} \theta^\alpha + \frac{c}{\alpha!} (z^{\beta - \alpha} - 1) \theta_k \theta^\alpha$ from Formula (11). Evaluating at $z = 1$, one finds $\theta_k H|_{z=1} = \sum_{(c, \alpha, \beta) \in \mathcal{R}} \frac{c}{\alpha!} (\beta_k - \alpha_k) \theta^\alpha$. Applying Lemma 2 and Proposition 1, the formula is proved. Whenever $|\alpha| \leq 1$, $\alpha! = 1$ and $N(t)^\alpha = N(t)^\alpha$. Moreover $N(t)^\alpha = 1$ iff $\alpha = 0$ and $N(t)^\alpha = N_j(t)$ if $\alpha = (0, \dots, 0, 1, 0, \dots, 0)$, the “1” occurring in j^{th} position. \square

One recovers the deterministic models classically used in chemical kinetics (mass action law). For first order systems, the deterministic model corresponds to an unbiased averaging of the random variables $N_k(t)$. It does not apply to covariance matrices $\text{Cov}(N_i(t), N_j(t))$, where $i, j = 1 \dots n$.

8 Examples

8.1 First Order Systems

This model of non-regulated gene [7] is interesting because it was verified experimentally and because it shows the importance of random phenomena in gene expression. The transcription of the gene produces messenger RNAs (mRNA) which are translated into proteins:



The three chemical species are numbered: $R_1 = \text{DNA}$, $R_2 = \text{mRNA}$ and $R_3 = \text{protein}$. It admits the conservation law $v_1 = 1$, which means that there is only one gene involved in the network (at all time t). The model is reduced by setting $\theta_1 = 1$ and $z_1 = 1$. The reduced Hamiltonian is equal to

$$H = k_R(z_2 - 1) + k_P(z_3 - 1)\theta_2 + \gamma_R(z_2^{-1} - 1)\theta_2 + \gamma_P(z_3^{-1} - 1)\theta_3$$

Only two state variables remain $v = (v_2, v_3) \in \mathbb{N}^2$, the number of mRNA and the number of proteins at time t . Let $N(t) = (N_2(t), N_3(t))$, be the stochastic process associated to System (17). We are going to compute the means $x_2(t) = EN_2(t)$ et $x_3(t) = EN_3(t)$ and the covariance matrix $x_{ij}(t) = \text{Cov}(N_i(t), N_j(t))$ for $i, j = 2, 3$. According to the algorithm of Section 4, our software computes the commutators evaluated at the point $z_2 = z_3 = 1$:

$$\begin{aligned} [\theta_2, H]_{z=1} &= k_R - \gamma_R \theta_2 \\ [\theta_3, H]_{z=1} &= k_P \theta_2 - \gamma_P \theta_3 \\ [\theta_2^2, H]_{z=1} &= k_R + (2k_R + \gamma_R)\theta_2 - 2\gamma_R \theta_2^2 \\ [\theta_2 \theta_3, H]_{z=1} &= k_R \theta_3 + k_P \theta_2^2 + (-\gamma_R - \gamma_P)\theta_2 \theta_3 \\ [\theta_3^2, H]_{z=1} &= k_P \theta_2 + \gamma_P \theta_3 + 2k_P \theta_2 \theta_3 - 2\gamma_P \theta_3^2 \end{aligned}$$

and generates the system which describes the time evolution of the means and the covariances:

$$\begin{aligned}
\frac{d}{dt}x_2(t) &= k_R - \gamma_R x_2(t) \\
\frac{d}{dt}x_3(t) &= k_P x_2(t) - \gamma_P x_3(t) \\
\frac{d}{dt}x_{2,2}(t) &= \gamma_R x_2(t) + k_R - 2\gamma_R x_{2,2}(t) \\
\frac{d}{dt}x_{2,3}(t) &= (-\gamma_R - \gamma_P)x_{2,3}(t) + k_P x_{2,2}(t) \\
\frac{d}{dt}x_{3,3}(t) &= k_P x_2(t) - 2\gamma_P x_{3,3}(t) + 2k_P x_{2,3}(t) + \gamma_P x_3(t)
\end{aligned} \tag{18}$$

Since the chemical reaction system has order 1, one obtains a linear system and the phenomenon of the infinite cascade does not occur. For simplification, one selects a time scale such that $\gamma_R = 1$. The computation of the means and the variances at the stationary state give:

$$x_2 = k_R, \quad x_3 = \frac{k_P k_R}{\gamma_P}, \quad x_{2,2} = k_R, \quad x_{2,3} = \frac{k_P k_R}{1 + \gamma_P}, \quad x_{3,3} = \frac{k_P k_R (\gamma_P + k_P + 1)}{\gamma_P (1 + \gamma_P)}$$

This result is exact. The same formulas appear in [7] and are proved by using Langevin's technique: the two first equations of (18) are viewed as a deterministic model (arising from the mass action law). Then, one incorporates in the righthand sides, two white noises, of zero average. This method is difficult to justify theoretically. By solving the equations (18), by, sat, a Laplace transform technique, one obtains exact formulas for the means and the variances during the transient stage.

$$\begin{aligned}
x_2(t) &= k_R (-e^{-t} + 1) \\
x_3(t) &= \frac{k_P k_R (-1 + e^{-\gamma_P t} + \gamma_P (-e^{-t} + 1))}{\gamma_P (-1 + \gamma_P)} \\
x_{2,2}(t) &= k_R (-e^{-t} + 1) \\
x_{2,3}(t) &= \frac{(-e^{-t} (1 + \gamma_P) + \gamma_P + e^{-(1+\gamma_P)t}) k_R k_P}{\gamma_P (1 + \gamma_P)}
\end{aligned}$$

8.2 Second Order Systems

The dynamics on the degree d moments depends on moments of degree strictly greater than d : an infinite cascade occurs. This is the main source of difficulty. In order to break an infinite cascade there are two possible methods

1. One can operate an approximation assuming that the centered moments of degree d are zero for d great enough. This is a legitimate approximation whenever the number of tokens in each places (the number of chemical molecules of each chemical species) remains high at everytime t .
2. One has a relation expressing degree $d + 1$ moments in function of moments of degree at most d . This case occurs, in particular, whenever random variables only take a finite number of different values.

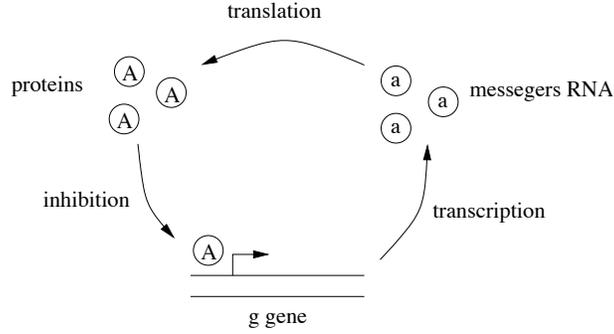
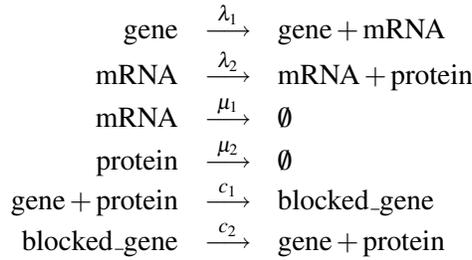


Figure 3: Autoregulated gene

8.2.1 Autoregulated Gene

The transcription of the gene produces messenger RNA, which in turn are translated in proteins. If a protein binds itself to the gene at the initialization of the transcription, then it is blocked (see Figure 3).



The four chemical species are numbered: $R_1 = \text{mRNA}$, $R_2 = \text{gene}$, $R_3 = \text{blocked gene}$, $R_4 = \text{protein}$. That system obeys the conservation law $I(v) = v_2 + v_3$, which means that the total number of “molecules” of type *gene* and *blocked_gene* remains constant. In practice, only one gene is involved. Therefore the Petri net gets initialized with the following assumption $v_2 + v_3 = 1$. Considering that at any time t , $v_2 + v_3 = 1$, we choose to remove the state variable v_3 putting $v_3 = 1 - v_2$. After model reduction, the Hamiltonian becomes,

$$\begin{aligned}
 H &= \lambda_1 (z_1 - 1) \theta_2 + \lambda_2 (z_4 - 1) \theta_1 \\
 &+ \mu_1 \left(\frac{1}{z_1} - 1 \right) \theta_1 + \mu_2 \left(\frac{1}{z_4} - 1 \right) \theta_4 + c_1 \left(\frac{1}{z_2 z_4} - 1 \right) \theta_2 \theta_4 + c_2 (z_2 z_4 - 1) (1 - \theta_2)
 \end{aligned}$$

One introduces the means $x_i(t) = \mathbb{E} N_i(t)$ for $i = 1, 2, 4$ and the covariance matrix $x_{ij}(t) = \text{Cov}(N_i(t), N_j(t))$ for $i, j = 1, 2, 4$. The random variable $N_2(t)$ is boolean ($v_2 = v_2^2$), the model restriction algorithm can therefore be applied. The algorithm computes the brackets $[\theta^\kappa, H]$ in the Weyl algebra quotiented by the left ideal spanned by the relation $\theta_2 = \theta_2^2$. The evaluation at $z = 1$ is performed afterwards. one gets:

$$\begin{aligned}
 [\theta_1, H]_{z=1} &= -\mu_1 \theta_1 + \lambda_1 \theta_2 \\
 [\theta_2, H]_{z=1} &= c_2 - c_2 \theta_2 - c_1 \theta_2 \theta_4 \\
 [\theta_4, H]_{z=1} &= c_2 + \lambda_2 \theta_1 - c_2 \theta_2 - \mu_2 \theta_4 - c_1 \theta_2 \theta_4 \\
 [\theta_1^2, H]_{z=1} &= \mu_1 \theta_1 + \lambda_1 \theta_2 - 2\mu_1 \theta_1^2 + 2\lambda_1 \theta_1 \theta_2 \\
 [\theta_2 \theta_1, H]_{z=1} &= c_2 \theta_1 + \lambda_1 \theta_2 - (\mu_1 + c_2) \theta_1 \theta_2 - c_1 \theta_1 \theta_2 \theta_4
 \end{aligned}$$

An infinite cascade occurs because the dynamics on the degree 2 moments involves two degree three moments, namely the moment coded by the following operators $\theta_1 \theta_2 \theta_4$ and $\theta_2 \theta_4^2$. To break this cascade, one can use as an approximation assumption that every centered moments of degree 3 is zero.

Consider three random variables (X_1, X_2, X_3) whose respective means are (x_1, x_2, x_3) . A routine computation gives the centered moment of order three $E((X_1 - x_1)(X_2 - x_2)(X_3 - x_3))$ as $E(X_1 X_2 X_3) - x_1 x_2 x_3 - x_1 \text{Cov}(X_2, X_3) - x_2 \text{Cov}(X_3, X_1) - x_3 \text{Cov}(X_1, X_2)$. We have no proof that this approximation is best fit. Our software computes the ordinary *non-linear* differential equation system:

$$\begin{aligned} \frac{d}{dt}x_1(t) &= -\mu_1 x_1(t) + \lambda_1 x_2(t) \\ \frac{d}{dt}x_2(t) &= c_2 - c_2 x_2(t) - c_1 x_4(t) x_2(t) - c_1 x_{2,4}(t) \\ \frac{d}{dt}x_4(t) &= c_2 + \lambda_2 x_1(t) - c_2 x_2(t) - c_1 x_4(t) x_2(t) \\ &\quad - \mu_2 x_4(t) - c_1 x_{2,4}(t) \\ \frac{d}{dt}x_{1,1}(t) &= \mu_1 x_1(t) + 2\lambda_1 x_{1,2}(t) + \lambda_1 x_2(t) - 2\mu_1 x_{1,1}(t) \\ \frac{d}{dt}x_{1,2}(t) &= \lambda_1 x_2(t) - c_1 x_{1,4}(t) x_2(t) - c_1 x_4(t) x_{1,2}(t) \\ &\quad - (\mu_1 + c_2) x_{1,2}(t) - \lambda_1 x_2(t)^2 \end{aligned}$$

The Figures 4, 5 and 6 show the results of the numerical simulations produced by our software. We used the following values for the parameters $\lambda_1 = 30.0$, $\lambda_2 = 10.0$, $\mu_1 = \mu_2 = 0.1$, $c_1 = c_2 = 1.0$ and the initial conditions $x_1(0) = 0$ (mRNA), $x_2(0) = 1$ (gene), $x_3(0) = 0$ (protein).

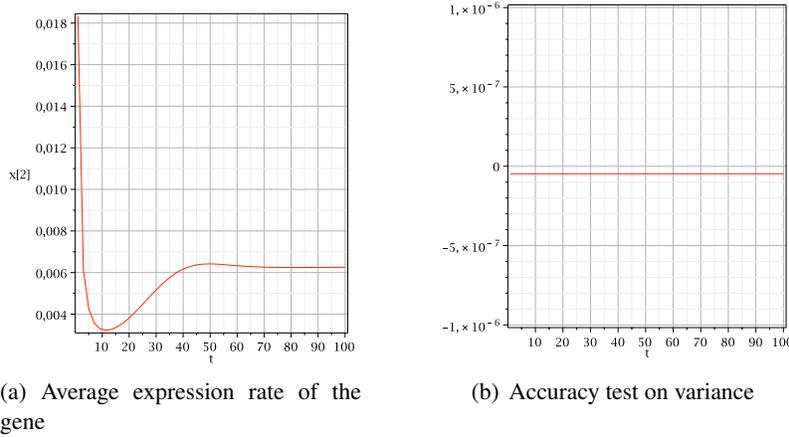


Figure 4: Autoregulated gene (boolean variable). Simulations are consistent with the fact that any boolean variable X satisfies $\text{Var}X = x(1 - x)$, where $x = EX$.

8.2.2 Second Order Degradation

One considers the chemical reaction



Using a time dilatation, one can assume that $\mu = 1$. The Hamiltonian is then, with $\theta = z \partial / \partial z$:

$$H = \frac{1}{2} \left(\frac{1}{z^2} - 1 \right) \theta(\theta - 1) = \frac{1}{2} (1 - z^2) \left(\frac{\partial}{\partial z} \right)^2.$$

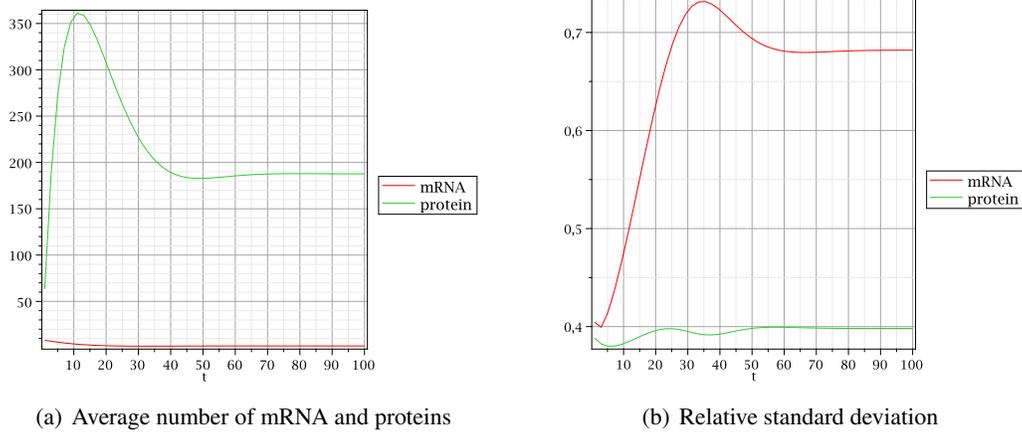


Figure 5: Joint evolution of mRNA and Protein number. The relative standard deviation of a random variable X is σ/x with $\sigma^2 := \text{Var}X$ and $x := E(X)$.

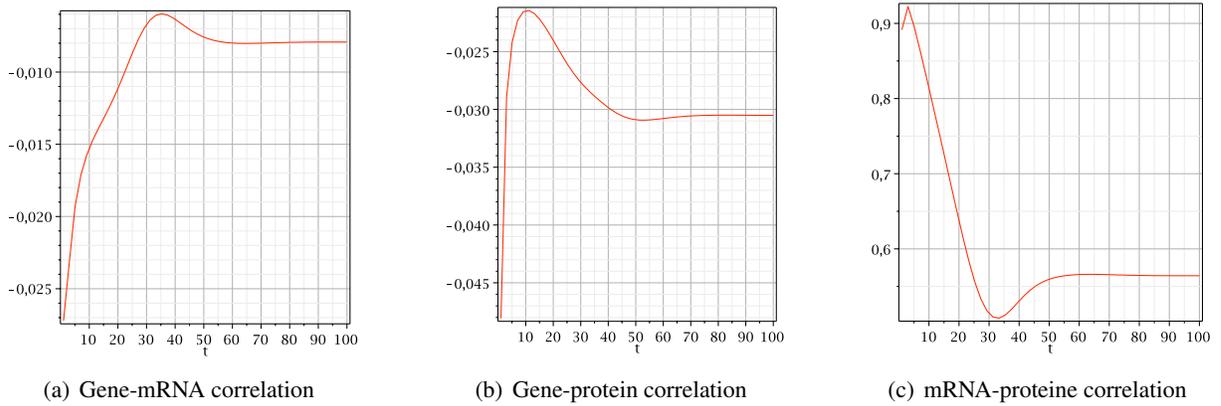


Figure 6: Evolution over time of correlation rates. The correlation rate $c(X, Y)$ between two random variables X and Y is defined by $c(X, Y) := \frac{\text{Cov}(X, Y)}{\sigma(X)\sigma(Y)}$.

On this example, the dynamics on the moments $EN(t)^k$, $k = 1 \dots 4$ is coded by

$$\begin{aligned}
 [\theta, H]_{z=1} &= -\theta^2 + \theta \\
 [\theta^2, H]_{z=1} &= -2\theta^3 + 4\theta^2 - 2\theta \\
 [\theta^3, H]_{z=1} &= -3\theta^4 + 9\theta^3 - 10\theta^2 + 4\theta \\
 [\theta^4, H]_{z=1} &= -4\theta^5 + 16\theta^4 - 28\theta^3 + 24\theta^2 - 8\theta
 \end{aligned} \tag{20}$$

Lemma 9. For all $m \in \mathbb{N}$, formulas (20) take the following closed form:

$$[\theta^m, H]_{z=1} = \frac{1}{2} [(-2 + \theta)^m - \theta^m] \theta(\theta - 1) \tag{21}$$

Proof. Apply Formula 14 for $(c, \alpha, \beta) := (1, (2), (0))$. □

Let $x(t)$ denote the mean and $v(t)$ the variance of $N(t)$. The previously developed approximation, obtained by killing centered order 3 moments, then gives

$$\frac{d}{dt}x(t) = x(t) - v(t) - (x(t))^2, \quad \frac{d}{dt}v(t) = -2x(t) + 4v(t) + 2(x(t))^2 - 4v(t)x(t).$$

This approximation method behaves badly at instants t where $EN(t)$ is close to 1 (see Figure 7). Unfortunately the situation does not improve if one keeps the centered moment up to a higher order.

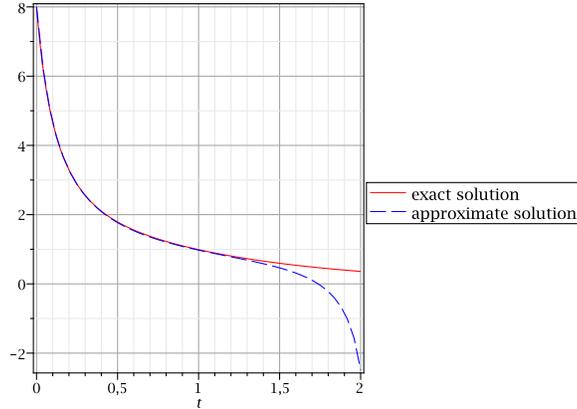


Figure 7: Evolution of the mean $x(t) = EN(t)$ over time, starting with state $n_0 = 8$. The approximation gets worse after $x(t)$ crosses the value 1 (around $t = 1$).

We show now how to get the *exact* dynamics on the moments of any order. Assume, as an example, that the initial state is $n_0 = 8$. The function $f(v) = v(v-2)(v-4)(v-6)(v-8)$ is zero at any instant t . According to Lemma 2 and Proposition 1, we have to quotient the algebra $\text{Weyl}_{\mathbb{R}}(z)$ by the left ideal spanned by the relation $f(\theta) = 0$. This gives $f(\theta) = \theta(\theta-2)(\theta-4)(\theta-6)(\theta-8)$. This one more relation added to System (20) enables us to get order 5 moments as functions of the moments of order at most 4. This way, one gets the exact dynamics, a linear system, describing the time evolution of the moments $x_k(t) = EN^k(t)$, for $k = 1 \dots 4$.

$$\begin{aligned} \frac{d}{dt}x_1(t) &= x_1(t) - x_2(t) \\ \frac{d}{dt}x_2(t) &= -2x_1(t) + 4x_2(t) - 2x_3(t) \\ \frac{d}{dt}x_3(t) &= 4x_1(t) - 10x_2(t) + 9x_3(t) - 3x_4(t) \\ \frac{d}{dt}x_4(t) &= 1528x_1(t) - 1576x_2(t) + 532x_3(t) - 64x_4(t) \end{aligned}$$

with the initial conditions: $x_1(0) = 8$, $x_2(0) = 64$, $x_3(0) = 512$, $x_4(0) = 4096$. These linear differential equations get solved by means of the Laplace transform:

$$\begin{aligned} x_1(t) &= \frac{8}{3}e^{-t} + \frac{112}{33}e^{-6t} + \frac{64}{39}e^{-15t} + \frac{128}{429}e^{-28t} \\ x_2(t) &= \frac{16}{3}e^{-t} + \frac{784}{33}e^{-6t} + \frac{1024}{39}e^{-15t} + \frac{3712}{429}e^{-28t} \\ x_3(t) &= \dots \end{aligned} \tag{22}$$

The infinite cascade is thereby broken by an exact method (see the simulations showed in Figure 8)

9 Conclusion

The algorithm presented in this paper permits to investigate the study of genetic regulatory networks, considered from a stochastic point of view. The symbolic part of the algorithm prepares further numerical

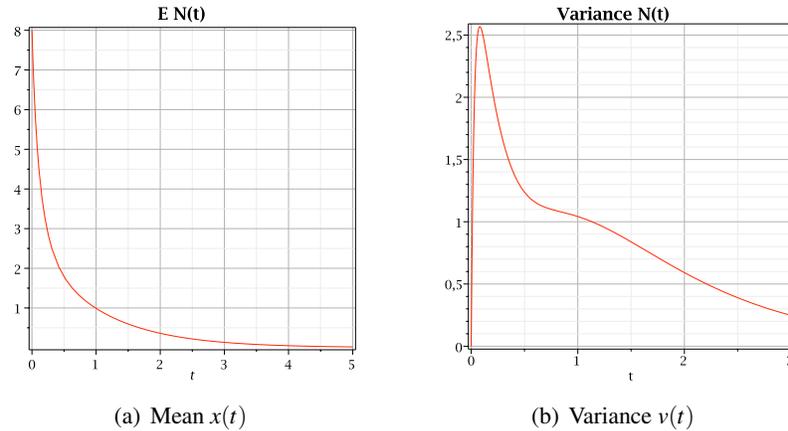


Figure 8: Simulation of System (19), starting with state $n_0 = 8$.

simulations. The algorithm and its theory are formulated in the Weyl algebra. However, Proposition 2 shows how to replace computations in Weyl algebra by basic operations on commutative polynomials. This seems to produce a more efficient algorithm which combines the differentiation and evaluation steps of the straightforward approach. The issue of the infinite cascade, well-known in statistical physics, reduces the usefulness of the overall method. Approximation techniques, useful to break it, still need some investigation.

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