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Solving the chemical master equation for monomolecular reaction systems analytically

Tobias Jahnke · Wilhelm Huisinga

Abstract The stochastic dynamics of a well-stirred mixture of molecular species interacting through different biochemical reactions can be accurately modelled by the chemical master equation (CME). Research in the biology and scientific computing community has concentrated mostly on the development of numerical techniques to approximate the solution of the CME via many realizations of the associated Markov jump process. The domain of exact and/or efficient methods for directly solving the CME is still widely open, which is due to its large dimension that grows exponentially with the number of molecular species involved. In this article, we present an exact solution formula of the CME for arbitrary initial conditions in the case where the underlying system is governed by monomolecular reactions. The solution can be expressed in terms of the convolution of multinomial and product Poisson distributions with time-dependent parameters evolving according to the traditional reaction-rate equations. This very structured representation allows to deduce easily many properties of the solution. The model class includes many interesting examples. For more complex reaction systems, our results can be seen as a first step towards the construction of new numerical integrators, because solutions to the monomolecular case provide promising ansatz functions for Galerkin-type methods.

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1 Introduction

The growing interest in stochastic models for biochemical reaction systems has lead to increasing activities in the design of efficient numerical methods for the solution of the underlying chemical master equation (CME) [1,3,4,10,12, 15,19,20]. Almost all current approaches *indirectly* approximate the CME by generating a statistically large number of realizations of the associated continuous-time, discrete state space Markov jump process, e.g. with the so-called stochastic simulation algorithm, cf. [11,22]. The domain of numerical or analytical techniques for *directly* solving the CME is still widely open, which is mainly due to the fact that the dimension increases exponentially with the number of molecular species involved. The CME can be understood as a huge system of coupled ordinary differential equations: There is one differential equation per *state* of the system, in contrast to the traditional reaction-rate approach where only one differential equation per *species* is required. For example, a rather small system of only three species with molecule numbers varying between, say, 0 and 99, contains 100^3 different states, and $1,000,000$ coupled differential equations have to be solved in order to determine evolution of the probability density in time! As a consequence, solving the CME with standard numerical integrators is usually cumbersome and often completely impossible.

Analytical solutions of the CME are only known for special reaction systems with particular initial conditions; these include, e.g., closed (mass conserving) linear reaction systems with multinomial initial distributions [6,8], open linear reaction systems with Poisson initial distribution [9], or a two-component, linear open system with deterministic initial conditions [21, Chap. 8.4]. Recently, Gadgil et al. [8] presented evolution equations for the mean and the variance of a general system of first-order reactions, but did not derive an analytical solution formula for the probability distribution. Concerning the limit behavior of the CME, it is known that the equilibrium distribution of a finite closed system of linear reactions is multinomial, while the equilibrium distribution of an open system of linear reactions is Poisson in each component (see, e.g., [8] and references therein), but to the best of our knowledge, nothing is known about the general time-dependent transient behavior for arbitrary initial conditions, including the important class of deterministic initial conditions.

In this article we consider chemical reaction systems with arbitrarily many species and states, but assume that only monomolecular reactions occur. Under this condition we derive an explicit formula for the *exact* solution of the CME. For the generic case of deterministic initial conditions, the solution turns out to be the convolution of multinomial and product Poisson distributions with time-dependent parameters evolving according to the traditional reaction-rate
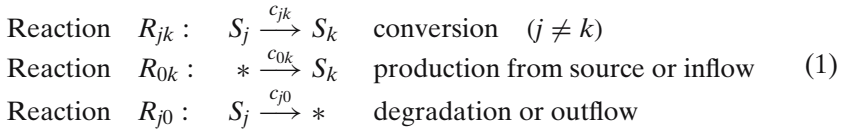
equations. All previously derived results on monomolecular reaction systems can be restated in terms of our representation. Although the vast majority of biochemical systems includes bimolecular or more complex reactions, many interesting applications belong to the class of monomolecular reaction systems: simplified models for the conformational dynamics of proteins and RNA, simple birth and death processes, bacteriophage dynamics, queing systems, migration processes, gating of ion chanels, hydrolysis etc. (see, e.g., [7,8] and references therein).

Moreover, we believe that studying monomolecular reactions is worthwhile for additional reasons: (1) Recent developments in speeding up the stochastic simulation algorithm by treating isolated subsystems (the so-called virtual fast process) analytically require the solution of the CME for these subsystems [5]. The virtual fast process will often be related to systems of monomolecular reactions (with rates depending on slow chemical species), although the overall system involves bimolecular reactions. (2) The performance of new numerical methods has to be evaluated, typically by applying the method to a problem with known solution. In this case, nontrivial, time-dependent solutions of chemical reactions systems are required. (3) The monomolecular case can be seen as a starting point for the construction of new numerical solvers for the general CME. Many numerical methods are devised in such a way that they yield the exact solution in special cases, like monomolecular reaction systems for the CME. Representing the solution as a linear combination of suitably chosen basis functions and exploiting linearity of the equation, such a representation would, at the cost of a hopefully small error, reduce the number of degrees of freedom considerably. Work in this direction is currently in progress.

Outline: Sect. 2 sets the scene and gives a short summary of the deterministic and the stochastic approach to reaction kinetics. In Sect. 3 explicit solution formulas for the monomolecular CME under special initial conditions are presented. For the convenience of the reader, we report two known results, namely that the solution of the CME for closed systems and multinomial initial conditions stays multinomial [8], and that a corresponding assertion holds for the Poisson distribution and open systems [9]. In our main theorem, both results are combined and extended in such a way that for *arbitrary* initial conditions an explicit solution formula of the monomolecular CME is obtained. In Sect. 4 we discuss properties of the solution distribution, like expectation, variance, convergence to steady states and marginal distributions. Our results are illustrated in Sect. 5 in application to some simple examples previously discussed in the literature. The last section sketches possible extensions and provides an outlook.

2 Stochastic and deterministic reaction kinetics

We study a reaction system with $n \in \mathbb{N}$ different species or substances $S_1, \ldots, S_n$ subject to the following reaction channels:

Reaction	R_{jk} :	$S_j \xrightarrow{c_{jk}} S_k$	conversion	$(j \neq k)$
Reaction	R_{0k} :	$* \xrightarrow{c_{0k}} S_k$	production from source or inflow	(1)
Reaction	R_{j0} :	$S_j \xrightarrow{c_{j0}} *$	degradation or outflow	

These reactions are referred to as *monomolecular* reactions. In comparison to general first-order reactions, we do not include (auto)catalytic reactions $S_j \xrightarrow{c} S_j + S_k$, nor splitting reactions $S_j \xrightarrow{c} S_l + S_k$ with $j \neq l, k$. For possible generalisations, see Sect. 6.

The rates c_{jk} are assumed to be nonnegative and can (but need not) be time dependent, i.e., $c_{jk} = c_{jk}(t)$. For simplicity of notation, let $c_{kk} \equiv 0$ for all $k \in \mathbb{N}$ in order to exclude the trivial reaction $S_k \xrightarrow{c_{kk}} S_k$. We suppose that all molecules are contained in a constant volume at constant temperature, and that the system is "well-mixed" in the sense that the molecules are uniformly distributed in space as explained in [11].

2.1 Deterministic reaction kinetics

In the traditional approach the concentration $C_k(t)$ of the substance S_k is the solution of the reaction-rate equation

$$\dot{C}_k(t) = c_{0k}(t) + \sum_{j=1}^{n} c_{jk}(t)C_j(t) - \sum_{j=0}^{n} c_{kj}(t)C_k(t). \tag{2}$$

Hence, the vector $C(t) = (C_1(t), \ldots, C_n(t))^{\mathrm{T}}$ of all concentrations evolves according to

$$\dot{C}(t) = A(t)C(t) + b(t) \tag{3}$$

where $b(t) \in \mathbb{R}^n$ is the vector

$$b(t) = (c_{01}(t), c_{02}(t), \ldots, c_{0n}(t))^{\mathrm{T}} \tag{4}$$

and $A(t)$ is the matrix with entries $a_{jk}(t)$ defined by

$$a_{jk}(t) = c_{kj}(t) \text{ for } j \neq k \geq 1, \quad a_{kk}(t) = -\sum_{j=0}^{n} c_{kj}(t). \tag{5}$$

The definition of A implies that the sum of each column is nonpositive, because

$$\sum_{j=1}^{n} a_{jk}(t) = -c_{k0}(t) \leq 0. \tag{6}$$

A matrix with property (6) and nonnegative off-diagonal elements is called a compartmental matrix [2]. Compartmental matrices have many nice features (see Proposition 4), for example that the solution $C(t)$ has nonnegative entries if the initial vector $C(0)$ has nonnegative entries. This can be readily seen from (2), because $C_k(t) = 0$ implies $\dot{C}_k(t) \geq 0$. Moreover, mass balance shows that $\sum_{k=1}^{n} C_k(t) \leq \sum_{k=1}^{n} C_k(0)$ for each $t = 0$, and "$\leq$" can be replaced by "$=$" if $c_{k0} = 0$ for all k.

2.2 Stochastic reaction kinetics

At any time t the state of the system is described by the number of molecules of each species. Since no positional information is available the state of the system is to be understood as a random variable $X(t) = (X_1(t), \dots, X_n(t))$ where $X_k(t)$ is the number of molecules of the kth species at time t.

The reactions are entirely defined by the stoichiometric vectors and the propensities. The stoichiometric vector $v^{(jk)} \in \mathbb{N}^n$ corresponds to the state change that occurs whenever the reaction channel R_{jk} fires. In case of the reaction system (1) we have

$$v^{(jk)} = \varepsilon_k - \varepsilon_j, \quad v^{(0k)} = \varepsilon_k, \quad v^{(j0)} = -\varepsilon_j,$$

where ε_k denotes the kth column of the identity matrix in $\mathbb{R}^{n \times n}$. The propensity $\alpha_{jk}(t, x)$ is related to the reaction probability in the following way: If the system is in state $X(t) = x \in \mathbb{N}^n$ at time t, then $\alpha_{jk}(t, x)dt$ is the probability that in the next "infinitesimal" time interval $[t, t + dt)$ the reaction channel R_{jk} will fire. According to [11] the propensities are given by

$$\alpha_{jk}(t, x) = \begin{cases} c_{jk}(t)x_j & \text{for reaction } R_{jk} \\ c_{0k}(t) & \text{for reaction } R_{0k} \\ c_{j0}(t)x_j & \text{for reaction } R_{j0} \end{cases}.$$

For ease of notation we define $\alpha_{jk}(t, x) = 0$ if $x \notin \mathbb{N}^n$.

In this article, we give an explicit formula for the probability distribution

$$P(t, x) = \mathbb{P}\Big(X_1(t) = x_1, \dots, X_n(t) = x_n\Big)$$

of the random variable $X(t)$. For convenience, we define $P(t, x) = 0$ for all $x \notin \mathbb{N}^n$. The distribution P is the solution of the chemical master equation (CME)

$$\partial_t P(t, x) = \sum_{j=0}^{n} \sum_{k=0}^{n} \Big(\alpha_{jk}(t, x - v^{jk}) P(t, x - v^{jk}) - \alpha_{jk}(t, x) P(t, x) \Big), \qquad (7)$$

which can be rewritten as

$$\partial_t P(t,x) = \sum_{k=1}^{n} c_{0k}(t)\Big(P(t,x-\varepsilon_k) - P(t,x)\Big)$$
$$+ \sum_{k=1}^{n} c_{k0}(t)\Big((x_k+1)P(t,x+\varepsilon_k) - x_k P(t,x)\Big)$$
$$+ \sum_{j=1}^{n}\sum_{k=1}^{n} c_{jk}(t)\Big((x_j+1)P(t,x+\varepsilon_j-\varepsilon_k) - x_j P(t,x)\Big). \qquad (8)$$

The first sum of the CME (8) corresponds to the inflow reactions R_{0k}, the second one to the degradation R_{k0}, and the double sum represents the conversions R_{jk}.

We suppose that the molecule numbers at time $t=0$ are specified in terms of some initial probability distribution μ, i.e.

$$P(0,x) = \mu(x) \quad \text{for all } x \in \mathbb{N}^n. \qquad (9)$$

By superposition, the problem of solving the CME for arbitrary initial distributions can be reduced to the corresponding problem with deterministic initial conditions, i.e.,

$$P(0,x) = \delta_\xi(x) = \begin{cases} 1 & \text{if } x = \xi \\ 0 & \text{otherwise} \end{cases} \qquad (10)$$

with $\delta_\xi(x)$ denoting the Kronecker symbol. To be more precise, if $P_\xi(t,\cdot)$ denotes the solution of (8) with initial condition (10), then the solution of (8) with initial condition (9) is given by

$$P(t,x) = \sum_{\xi \in \mathbb{N}^n} \mu(\xi)P_\xi(t,x), \qquad (11)$$

because the CME is linear and any $\mu(x)$ can be represented as

$$\mu(x) = \sum_{\xi \in \mathbb{N}^n} \mu(\xi)\delta_\xi(x).$$

Hence, our aim is to find a formula for the *exact* solution of the CME (8) with deterministic initial conditions (10).

3 Explicit solution formulas for the monomolecular chemical master equation

To start with, we briefly list some basic definitions. The convolution $P_1 \star P_2$ of two probability distributions P_1 and P_2 on the state space $\mathbb{N}^n$ is defined by

$$(P_1 \star P_2)(x) = \sum_z P_1(z)P_2(x - z) = \sum_z P_1(x - z)P_2(z),$$

where the sum is taken over all $z \in \mathbb{N}^n$ such that $(x - z) \in \mathbb{N}^n$.

Let $|x| := \sum_{k=1}^n |x_k|$ be the 1-norm of the vector x. For any $x \in \mathbb{N}^n$ and any $p = (p_1, \ldots, p_n) \in [0,1]^n$ with $|p| \leq 1$, the multinomial (or polynomial) distribution $\mathcal{M}(x, N, p)$ is given by

$$\mathcal{M}(x, N, p) = \begin{cases} N! \dfrac{(1 - |p|)^{N-|x|}}{(N - |x|)!} \displaystyle\prod_{k=1}^n \dfrac{p_k^{x_k}}{x_k!} & \text{if } |x| \leq N \text{ and } x \in \mathbb{N}^n \\ 0 & \text{otherwise.} \end{cases}$$

Finally, let $\mathcal{P}$ denote the product Poisson distribution

$$\mathcal{P}(x, \lambda) = \frac{\lambda_1^{x_1}}{x_1!} \cdots \frac{\lambda_n^{x_n}}{x_n!} \cdot e^{-|\lambda|}, \quad x \in \mathbb{N}^n$$

with parameter vector $\lambda = (\lambda_1, \ldots, \lambda_n) \in \mathbb{R}^n$ containing nonnegative entries, and for ease of notation let $\mathcal{P}(x, \lambda) = 0$ if $x \notin \mathbb{N}^n$.

3.1 Closed systems with multinomial initial distribution

In this section we assume that the system is closed[1] in the sense that all inflow reactions $R_{0k} : \ast \longrightarrow X_k$ are excluded by assuming $c_{0k} = 0$ for all k. Moreover, suppose that instead of the deterministic initial data (10), $P(0, x)$ is a multinomial distribution. Then, this is one of the few cases where the CME (8) can be solved analytically, cf. [8].

Proposition 1 *Consider the monomolecular reaction system* (1) *with a total number of $N \in \mathbb{N}$ molecules and suppose that $c_{0k} = 0$ for all k. If the initial distribution is the multinomial distribution*

$$P(0, x) = \mathcal{M}(x, N, p_0)$$

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[1] We call such a system closed in spite of the fact that some molecules can leave the system via the degradation reactions $R_{j0} : S_j \longrightarrow \ast$. We do so because, upon introducing a fictitious species $S_\ast$, reactions of type R_{j0} can be considered as conversion reactions $S_j \longrightarrow S_\ast$, and as a consequence the total number of molecules stays constant. The only particular thing about $S_\ast$ is that there is no reaction from $S_\ast$ back to any other species.

for some $p_0 \in [0,1]^n$, then the probability distribution at time $t > 0$ is still a multinomial distribution

$$P(t,x) = \mathcal{M}(x,N,p(t))$$

with parameter vector $p(t) = \left(p_1(t),\ldots,p_n(t)\right)^{\mathsf{T}}$ evolving according to the differential equation

$$\dot{p}(t) = A(t)p(t)$$
$$p(0) = p_0 \tag{12}$$

with A defined in (5).

Remark The differential equation (12) is the familiar deterministic rate equation (3) in the inflow-free case $b(t) \equiv (0,\ldots,0)^{\mathsf{T}}$. If all rates c_{jk} are constant the solution of (12) is simply $p(t) = \exp(tA)\,p_0$. If some of the rates are time-dependent, the matrix exponential $\exp(A(t))$ does generally *not* provide the solution, but the differential equation (12) can be solved numerically by using, e.g., a Magnus method [16].

Proof A proof based on random walks can be found in [8] (for constant rates). We give a different proof by verifying directly that $\mathcal{M}(x,N,p(t))$ solves indeed the CME (8). The initial condition is obviously met. Let $x \in \mathbb{N}^n$ be fixed, put $y = N - |x|$ and define $q(t) = 1 - |p(t)|$. We first consider the case that $x_k \neq 0$ and $y \neq 0$. Taking the derivative of the probability distribution gives

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathcal{M}(x,N,p(t)) = N!\frac{\mathrm{d}}{\mathrm{d}t}\left(\frac{q^y(t)}{y!}\prod_{k=1}^{n}\frac{p_k^{x_k}(t)}{x_k!}\right)$$

$$= N!\frac{q^{y-1}(t)}{(y-1)!}\dot{q}(t)\cdot\prod_{k=1}^{n}\frac{p_k^{x_k}(t)}{x_k!} + N!\frac{q^y(t)}{y!}\sum_{j=1}^{n}\frac{p_j^{x_j-1}(t)}{(x_j-1)!}\dot{p}_j(t)\cdot\prod_{k\neq j}\frac{p_k^{x_k}(t)}{x_k!}.$$

From (12) we obtain

$$\dot{p}_j = \sum_{i=1}^{n}c_{ij}p_i - \left(\sum_{i=0}^{n}c_{ji}\right)p_j, \quad \dot{q} = -\sum_{i=1}^{n}\dot{p}_i = \sum_{i=1}^{n}c_{i0}p_i$$

because $p_i(t) \geq 0$ for all i (cf. Sect. 2). This yields

$$\frac{d}{dt}\mathcal{M}(x,N,p) = N!\frac{q^{y-1}}{(y-1)!}\left(\sum_{i=1}^{n}c_{i0}p_i\right)\cdot\prod_{k=1}^{n}\frac{p_k^{x_k}}{x_k!}$$

$$+ N!\frac{q^y}{y!}\sum_{j=1}^{n}\frac{p_j^{x_j-1}}{(x_j-1)!}\left(\sum_{i=1}^{n}c_{ij}p_i\right)\cdot\prod_{k\neq j}\frac{p_k^{x_k}}{x_k!}$$

$$- N!\frac{q^y}{y!}\sum_{j=1}^{n}\frac{p_j^{x_j-1}}{(x_j-1)!}\left(\sum_{i=0}^{n}c_{ji}\right)p_j\cdot\prod_{k\neq j}\frac{p_k^{x_k}}{x_k!}$$

$$= N!\frac{q^{y-1}}{(y-1)!}\sum_{i=1}^{n}c_{i0}(x_i+1)\frac{p_i^{x_i+1}}{(x_i+1)!}\cdot\prod_{k\neq i}\frac{p_k^{x_k}}{x_k!}$$

$$+ N!\frac{q^y}{y!}\sum_{j=1}^{n}\sum_{i=1}^{n}c_{ij}\frac{p_j^{x_j-1}}{(x_j-1)!}(x_i+1)\frac{p_i^{x_i+1}}{(x_i+1)!}\cdot\prod_{k\neq j,k\neq i}\frac{p_k^{x_k}}{x_k!}$$

$$- \sum_{j=1}^{n}\sum_{i=0}^{n}c_{ji}x_j\mathcal{M}(x,N,p)$$

$$= \sum_{i=1}^{n}(x_i+1)c_{i0}\mathcal{M}(x+\varepsilon_i,N,p)$$

$$+ \sum_{j=1}^{n}\sum_{i=1}^{n}(x_i+1)c_{ij}M(x+\varepsilon_i-\varepsilon_j)$$

$$- \sum_{j=1}^{n}\sum_{i=0}^{n}c_{ji}x_j\mathcal{M}(x,N,p).$$

Rearranging these expressions gives

$$\frac{d}{dt}\mathcal{M}(x,N,p) = \sum_{i=1}^{n}c_{i0}\Big((x_i+1)\mathcal{M}(x+\varepsilon_i,N,p) - x_i\mathcal{M}(x,N,p)\Big)$$

$$+ \sum_{j=1}^{n}\sum_{i=1}^{n}c_{ij}\Big((x_i+1)\mathcal{M}(x+\varepsilon_i-\varepsilon_j) - x_i\mathcal{M}(x,N,p)\Big)$$

which is the CME (8) in the case $c_{0k} = 0$ for all $k = 1,\ldots,n$. If $y = 0$ and/or $x_k = 0$ for some k, then some of the terms in the above formulas vanish because $p_k(t)^0/0! \equiv 1$ and $\frac{d}{dt}p_k(t)^0/0! \equiv 0$, but the same calculation can be carried out *mutatis mutandis*. □

Proposition 1 states an explicit formula for the probability distribution under the assumption that there is no inflow into the system and that the initial distribution is multinomial. Both conditions, however, are very restrictive. Nevertheless, Proposition 1 will be helpful in the proof of our main result (Theorem 1).

3.2 Open systems with product Poisson initial distribution

In a next step towards this aim, we admit inflow reactions and quote a result similar to Proposition 1 for the Poisson distribution, cf. [9].

Proposition 2 *Consider the monomolecular reaction system* (1). *If the initial distribution is given by a product Poisson distribution*

$$P(0, x) = \mathcal{P}(x, \lambda_0)$$

with some parameter vector $\lambda_0 \in \mathbb{R}^n$ of nonnegative entries, then the probability distribution at time $t > 0$ is still a product Poisson distribution

$$P(t, x) = \mathcal{P}(x, \lambda(t))$$

with parameter vector $\lambda(t)$ evolving according to the reaction rate equation

$$\dot{\lambda}(t) = A(t)\lambda(t) + b(t)$$

$$\lambda(0) = \lambda_0$$

(13)

with $A(t)$ and $b(t)$ defined in (5) *and* (4).

Proof This result is derived in [9] using moment generating functions. For convenience of the reader, we give a direct proof. Let $x \in \mathbb{N}^n$ and, as in the proof of Proposition 1, assume first that $x_k \neq 0$ for all k. Since

$$\frac{d}{dt} \frac{\lambda_k^{x_k}}{x_k!} e^{-\lambda_k} = -\dot{\lambda}_k \frac{\lambda_k^{x_k}}{x_k!} e^{-\lambda_k} + \dot{\lambda}_k \frac{\lambda_k^{x_k-1}}{(x_k-1)!} e^{-\lambda_k}$$

the derivative of the Poisson distribution is

$$\frac{d}{dt} \mathcal{P}(x, \lambda) = -\sum_{k=1}^{n} \dot{\lambda}_k \mathcal{P}(x, \lambda) + \sum_{j=1}^{n} \dot{\lambda}_j \mathcal{P}(x - \varepsilon_j, \lambda).$$

(14)

From (13) and (6) we have

$$\dot{\lambda}_j = \sum_{i=1}^{n} a_{ji}\lambda_i + b_j = \sum_{i=1}^{n} c_{ij}\lambda_i - \sum_{i=0}^{n} c_{ji}\lambda_j + c_{0j}$$

and

$$\sum_{k=1}^{n} \dot{\lambda}_k = -\sum_{k=1}^{n} c_{k0}\lambda_k + |b|$$

which turns the first term on the right-hand side of (14) into

$$-\sum_{k=1}^{n} \dot{\lambda}_k \mathcal{P}(x, \lambda) = \left(\sum_{k=1}^{n} c_{k0}\lambda_k - |b|\right)\mathcal{P}(x, \lambda)$$

$$= \sum_{k=1}^{n} c_{k0}(x_k + 1)\mathcal{P}(x + \varepsilon_k, \lambda) - \sum_{k=1}^{n} c_{0k}\mathcal{P}(x, \lambda). \quad (15)$$

Using the relation $\lambda_j \mathcal{P}(x - \varepsilon_j, \lambda) = x_j \mathcal{P}(x, \lambda)$ we find that the second term of (14) equals

$$\sum_{j=1}^{n} \dot{\lambda}_j \mathcal{P}(x - \varepsilon_j, \lambda)$$

$$= \sum_{j=1}^{n}\sum_{i=1}^{n} c_{ij}\lambda_i \mathcal{P}(x - \varepsilon_j, \lambda) - \sum_{j=1}^{n}\sum_{i=0}^{n} c_{ji}\lambda_j \mathcal{P}(x - \varepsilon_j, \lambda) + \sum_{j=1}^{n} c_{0j}\mathcal{P}(x - \varepsilon_j, \lambda)$$

$$= \sum_{j=1}^{n}\sum_{i=1}^{n} c_{ij}(x_i + 1)\mathcal{P}(x + \varepsilon_i - \varepsilon_j, \lambda) - \sum_{j=1}^{n}\sum_{i=1}^{n} c_{ji}x_j \mathcal{P}(x, \lambda)$$

$$- \sum_{j=1}^{n} c_{j0}x_j \mathcal{P}(x, \lambda) + \sum_{j=1}^{n} c_{0j}\mathcal{P}(x - \varepsilon_j, \lambda). \quad (16)$$

Substituting (15) and (16) into (14) yields

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathcal{P}(x, \lambda) = \sum_{j=1}^{n} c_{0j}\Big(\mathcal{P}(x - \varepsilon_j, \lambda) - \mathcal{P}(x, \lambda)\Big)$$

$$+ \sum_{k=1}^{n} c_{k0}\Big((x_k + 1)\mathcal{P}(x + \varepsilon_k, \lambda) - x_k \mathcal{P}(x, \lambda)\Big)$$

$$+ \sum_{j=1}^{n}\sum_{i=1}^{n} c_{ij}\Big((x_i + 1)\mathcal{P}(x + \varepsilon_i - \varepsilon_j, \lambda) - x_i \mathcal{P}(x, \lambda)\Big),$$

which is exactly the CME (8). Now suppose that $x_k = 0$ for one or more k. Without loss of generality, it can be assumed, possibly after a suitable permutation of the indices, that there is an $m \in \mathbb{N}$ such that $x_k = 0$ for all $m < k \leq n$ and $x_k \neq 0$ for all $1 \leq k \leq m$. Then, the formula (14) for the derivative of $\mathcal{P}(x, \lambda)$ has to be adapted such that the second sum is only taken from 1 to m. Accordingly, (16) remains valid if "$\sum_{j=1}^{n}\ldots$" is replaced by "$\sum_{j=1}^{m}\ldots$" everywhere, and since we have defined $\mathcal{P}(x, \lambda) = 0$ for $x \notin \mathbb{N}^n$ the CME (8) is again recovered. □

Remarks 1. It is worth noticing that Proposition 2 remains valid if all inflow rates c_{0k} are set to zero, i.e. if the system is *closed*. In view of Proposition 1 this means

that, in case of a closed system, multinomial distributions stay multinomial whereas Poisson distributions stay Poisson. However, the occurrence of Poisson distributions for closed systems seems not to be very natural because in closed systems a finite state space is typically considered.

2. If $X_1, \ldots, X_n$ are independent Poisson variables with parameters $\lambda_1, \ldots, \lambda_n$, then it is known that the conditional distribution of $X(t) = (X_1, \ldots, X_n)$ given $\sum_{i=1}^{n} X_i = N$ is multinomial with parameters N and $p_i = \lambda_i / \sum_{i=1}^{n} \lambda_i$ (see, e.g., [17]). Combining this fact with Proposition 2 could also be used to prove Proposition 1 in a different way. However, we do not state any details here because the alternative proof is not shorter and requires some technical efforts.

3.3 General systems with arbitrary initial distribution

The above propositions state that "Poisson stays Poisson" and, in closed systems, that "multinomial stays multinomial". Though these results provide solutions of the CME their practical use is limited because in typical applications the initial data is neither a multinomial nor Poisson distribution but a deterministic condition of the form $P(0, x) = \delta_\xi(x)$. However, for some special parameter values the multinomial and Poisson distribution *are* indeed of this form, namely

$$
\begin{aligned}
\mathcal{P}(x, \lambda) = \delta_{\mathbf{0}}(x) &\iff \lambda = \mathbf{0} \\
\mathcal{M}(x, N, p) = \delta_{\mathbf{0}}(x) &\iff p = \mathbf{0} \\
\mathcal{M}(x, N, p) = \delta_{N\varepsilon_j}(x) &\iff p = \varepsilon_j
\end{aligned}
$$

where the symbol $\mathbf{0}$ denotes the zero vector $\mathbf{0} = (0, \ldots, 0)^T \in \mathbb{R}^n$. The first two lines correspond to the situation where no molecules exist at all, i.e. $\mathbb{P}(X = \mathbf{0}) = 1$. The third line is the situation where all N molecules belong to the same species S_j. Based on this observation we now derive an explicit formula for the solution $P(t, x)$ that holds if the initial condition is deterministic.

Theorem 1 *Consider the monomolecular reaction system* (1) *with initial distribution $P(0, \cdot) = \delta_\xi(\cdot)$ for some $\xi \in \mathbb{N}^n$. Then, the probability distribution at time $t > 0$ is*

$$
P(t, \cdot) = \mathcal{P}(\cdot, \lambda(t)) \star \mathcal{M}(\cdot, \xi_1, p^{(1)}(t)) \star \cdots \star \mathcal{M}(\cdot, \xi_n, p^{(n)}(t)). \tag{17}
$$

The vectors $p^{(k)}(t) \in [0, 1]^n$ and $\lambda(t) \in \mathbb{R}^n$ are the solutions of the reaction-rate equations

$$
\begin{aligned}
\dot{p}^{(k)}(t) &= A(t)p^{(k)}(t), & \dot{\lambda}(t) &= A(t)\lambda(t) + b(t), \\
p^{(k)}(0) &= \varepsilon_k, & \lambda(0) &= \mathbf{0},
\end{aligned}
\tag{18}
$$

with $A(t)$ and $b(t)$ defined in (5) *and* (4)*, respectively.*

Remark If the deterministic initial condition $P(0, \cdot) = \delta_\xi(\cdot)$ is replaced by $P(0, \cdot) = \mu(\cdot)$ for some arbitrary probability distribution μ, the solution can be obtained by superposition, as already mentioned in Sect. 2.2.

Proof Since only monomolecular reactions are considered, the evolution of each molecule does not depend on the evolution of the other molecules; cf. [8]. Therefore, we can split the set of all molecules into $n + 1$ disjoint subsets: A molecule belongs to the k-th subset if and only if it was a molecule of the species S_k ($1 \leq k \leq n$) at time $t = 0$. The zeroth subset contains all molecules that do not exist yet at $t = 0$ but are generated at some later time via one of the inflow reactions of type R_{0k}. As time evolves, any molecule can be transformed by one of the reactions to a molecule of some other species, but it will forever belong to the same subset determined by its initial state.

The molecule numbers within each subset of molecules is described by a vector valued-random variable denoted by $X^{(k)}(t)$ for all $k = 0, 1, \ldots, n$. By definition, the random variable $X(t)$ of the entire system is the sum

$$X(t) = X^{(0)}(t) + X^{(1)}(t) + \cdots + X^{(n)}(t).$$

The random variables $X^{(k)}(t)$ are *independent*: each subset of molecules evolves independently because only monomolecular reactions are considered. Thus, the joint probability distribution is given by the convolution

$$P(t, \cdot) = P^{(0)}(t, \cdot) \star P^{(1)}(t, \cdot) \star \cdots \star P^{(n)}(t, \cdot) \tag{19}$$

(see, e.g., [14]) where

$$P^{(k)}(t, x) = \mathbb{P}\left(X_1^{(k)}(t) = x_1, \ldots, X_n^{(k)}(t) = x_n\right)$$

is the probability distribution of $X^{(k)}(t)$. These probability distributions, however, are immediately obtained from the previous propositions.

For $k > 0$ the evolution of the kth subset is a *closed* system, because by definition any molecules generated by the inflow reactions R_{0j} does not belong to the kth subset. At the beginning, the subset contains exactly ξ_k molecules of S_k and no molecules of any other species. Hence, the initial distribution for the kth subset ($1 \leq k \leq n$) is

$$P^{(k)}(0, x) = \delta_{\xi_k \varepsilon_k}(x) = \mathcal{M}(x, \xi_k, \varepsilon_k),$$

and according to Proposition 1 we have

$$P^{(k)}(t, x) = \mathcal{M}\left(x, \xi_k, p^{(k)}(t)\right) \tag{20}$$

where $p^{(k)}$ is the solution of the left differential equation in (18).

The zeroth subset is the only open system, because here all molecules generated by any of the inflow reactions are collected. The initial distribution of this subset is

$$P^{(0)}(0,x) = \mathcal{P}(x,\mathbf{0}) = \delta_{\mathbf{0}}(x),$$

since the subset is empty at the beginning. Hence, Proposition 2 states that the probability distribution is

$$P^{(0)}(t,x) = \mathcal{P}\big(x,\lambda(t)\big) \tag{21}$$

with λ being the solution of the right differential equation in (18). The proof is now completed by inserting (21) and (20) into (19). Note that for $t = 0$ the formula yields the correct initial distribution because

$$P(0,\cdot) = \delta_{\mathbf{0}}(\cdot) \star \delta_{\xi_1 \varepsilon_1}(\cdot) \star \cdots \star \delta_{\xi_n \varepsilon_n}(\cdot) = \delta_{\xi}(\cdot).$$

$\square$

Remark Of course, Theorem 1 can also be shown by inserting (17) into the CME (8), but this requires long and tedious calculations. For a direct proof, it is more favourable (yet still quite lengthy) to use generating functions.

Our main result represents the exact solution of the CME (8) in terms of well-known probability distributions with parameters evolving according to reaction-rate equations. This very structured representation allows to deduce many properties of the solution, as exemplified in the next section.

4 Properties of the solution distribution

4.1 Marginal distributions

When the exact solution of the CME (8) is to be visualized, one is restricted to low-dimensional projections. Therefore, we derive mariginal distribution formulas for the solution distribution in this subsection.

For a vector-valued random variable $X = (X_1, \ldots, X_n)^{\mathrm{T}} \in \mathbb{N}^n$ and any number $j \in 1, \ldots, n-1$ we define two lower-dimensional random variables

$$Y = \big(X_1, \ldots, X_j\big)^{\mathrm{T}} \in \mathbb{N}^j, \quad Z = \big(X_{j+1}, \ldots, X_n\big)^{\mathrm{T}} \in \mathbb{N}^{n-j}$$

such that $X = (Y,Z)^{\mathrm{T}}$. Any other partition of X can be obtained by an appropriate permutation of the indices. Moreover, let

$$P(y,z) = \mathbb{P}(Y=y, Z=z), \quad F_Y(y) = \mathbb{P}(Y=y), \quad F_Z(z) = \mathbb{P}(Z=z)$$

be the corresponding probability distributions. Then F_Y and F_Z are called marginal distributions of P and are given by

$$\sum_{z \in \mathbb{N}^{n-j}} P(y, z) = F_Y(y), \quad \sum_{y \in \mathbb{N}^j} P(y, z) = F_Z(z),$$

cf. [14]. We show that the marginal distribution of the solution of (8) has the same form as the distribution (17) itself, but in a lower dimension.

Proposition 3 *Let $P(t, x)$ be the solution (17) of the CME (8). Moreover, fix $j \in 1, \ldots, n-1$ and define $x = (y, z)$ with $y = (x_1, \ldots, x_j)$ and $z = (x_{j+1}, \ldots, x_n)$. Then, the marginal distribution*

$$F_Y(t, y) = \sum_{z \in \mathbb{N}^{n-j}} P\big(t, (y, z)\big) = \sum_{x_{j+1}} \sum_{x_{j+2}} \cdots \sum_{x_n} P(t, x)$$

of $P(t, x)$ is given by

$$F_Y(t, y) = \left(\mathcal{P}\left(\cdot, \tilde{\lambda}(t)\right) \star \mathcal{M}\left(\cdot, \xi_1, \tilde{p}^{(1)}(t)\right) \right.$$

$$\left. \star \cdots \star \mathcal{M}\left(\cdot, \xi_n, \tilde{p}^{(n)}(t)\right) \right)(y) \tag{22}$$

where $\tilde{p}^{(k)} = (p_1^{(k)}, \ldots, p_j^{(k)})^{\mathrm{T}}$ and $\tilde{\lambda} = (\lambda_1, \ldots, \lambda_j)^{\mathrm{T}}$ only contain the first j entries of the parameter vectors $p^{(k)}(t) \in [0, 1]^n$ and $\lambda(t) \in \mathbb{R}^n$ defined by the differential equations (18).

Remark Note that (22) does not depend explicitly on neither $p_{j+1}^{(k)}, \ldots, p_n^{(k)}$ nor $\lambda_{j+1}, \ldots, \lambda_n$, but these values still have to be computed because they are coupled with the other entries via the differential equations (18).

Proof The marginal distributions of the multinomial and the Poisson distribution are

$$\sum_{z \in \mathbb{N}^{n-j}} \mathcal{M}\big((y, z), N, p\big) = \mathcal{M}(y, N, \tilde{p}),$$

$$\sum_{z \in \mathbb{N}^{n-j}} \mathcal{P}\big((y, z), \lambda\big) = \mathcal{P}\left(y, \tilde{\lambda}\right)$$

with $\tilde{p} = (p_1, \ldots, p_j)^{\mathrm{T}}$ and $\tilde{\lambda} = (\lambda_1, \ldots, \lambda_j)^{\mathrm{T}}$ (cf. [17]). Now, the statement follows from the fact that computing the convolution and passing to the marginal distribution commutes. □

4.2 Expectation and variance

The expectation $\mathbb{E}(X)$ and covariance $\text{Cov}(X_j, X_k) = \mathbb{E}(X_j - \mathbb{E}X_j)(X_k - \mathbb{E}X_k)$ of the probability distribution $P(t, x)$ can easily be calculated. It is known that an n-dimensional random variable Y with multinomial distribution $\mathcal{M}(x, N, p)$ has

$$\mathbb{E}(Y) = Np, \quad \text{Cov}(Y_j, Y_k) = \begin{cases} -Np_j p_k & \text{if } j \neq k \\ Np_k(1 - p_k) & \text{if } j = k \end{cases}$$

(see [17]). If Y is distributed according to the product Poisson distribution $\mathcal{P}(x, \lambda)$, then

$$\mathbb{E}(Y) = \lambda, \quad \text{Cov}(Y_j, Y_k) = 0 \text{ if } j \neq k, \quad \text{Cov}(Y_k, Y_k) = \lambda_k.$$

The sum of two independent random variables Y_1 and Y_2 has expectation $\mathbb{E}(Y_1 + Y_2) = \mathbb{E}(Y_1) + \mathbb{E}(Y_2)$ and covariance $\text{Cov}(Y_1, Y_2) = 0$ (cf. [14]). Together with the (bi-)linearity of Cov and $\mathbb{E}$, this yields

$$\mathbb{E}(X(t)) = \lambda(t) + \sum_{k=1}^{n} \xi_k p^{(k)}(t)$$

$$\text{Cov}(X_j, X_k) = \begin{cases} \displaystyle\sum_{i=1}^{n} \xi_i p_j^{(i)} (1 - p_j^{(i)}) + \lambda_j & \text{if } j = k \\ \displaystyle-\sum_{i=1}^{n} \xi_i p_j^{(i)} p_k^{(i)} & \text{otherwise} \end{cases}$$

with $p^{(k)}$ and $\lambda(t)$ from (18). It is well known that the expectation $\mathbb{E}(X)$ of the monomolecular reaction system (1) evolves according to the deterministic rate equation (3) used in traditional reaction kinetics. This can also easily be seen from the above expression: At $t = 0$ we have

$$\mathbb{E}(X(0)) = \lambda(0) + \sum_{k=1}^{n} \xi_k p^{(k)}(0) = \sum_{k=1}^{n} \xi_k \varepsilon_k = \xi, \tag{23}$$

and taking the derivative of $\mathbb{E}(X(t))$ yields via (18)

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathbb{E}(X(t)) = \dot{\lambda}(t) + \sum_{k=1}^{n} \xi_k \dot{p}^{(k)}(t) = A(t)\lambda(t) + b(t) + \sum_{k=1}^{n} \xi_k A p^{(k)}(t)$$
$$= A(t)\mathbb{E}(X(t)) + b(t). \tag{24}$$

This equation and a differential equation for the variance have been derived in [8].

4.3 Steady states and convergence

In this section we study the limit behaviour of the CME, in particular the convergence of its solution to a equilibrium distribution. For the remainder of this section we impose two additional and natural assumptions on the reaction system:

(A1) All reaction rates c_{jk} are constant.
(A2) The matrix A is irreducible, i.e., there is no permutation of indices such that A takes the form

$$A = \begin{pmatrix} A_{11} & 0 \\ A_{21} & A_{22} \end{pmatrix}.$$

Concerning (A1), a steady state might not exist if the rates are time-dependent, while (A2) guarantees that the system cannot be decomposed into two or more completely separated parts (see, e.g., [2]).

Under these conditions it is well–known that the equilibrium distribution of a finite closed system is multinomial, while it is product Poisson for open systems, cf. [8]. We show that these results can easily derived from Theorem 1. To do so, we quote some useful results about compartmental matrices.

Proposition 4 (Theorems 12.1, 12.3, 13.1, and 13.2 in [2])

– *The real part of any eigenvalue σ_k of A is nonpositive and there are no purely imaginary eigenvalues:*

$$Re(\sigma_k) \leq 0 \quad and \quad Re(\sigma_k) = 0 \iff \sigma_k = 0.$$

– *Let σ_1 be the eigenvalue with the smallest absolute value, i.e. $|\sigma_1| \leq |\sigma_k|$ for all k. Then $\sigma_1 = Re(\sigma_1)$ is real and nonpositive, and there is a corresponding eigenvector containing only nonnegative entries. Moreover, $Re(\sigma_k) < \sigma_1 \leq 0$ for all $k > 1$.*
– *If $c_{k0} \neq 0$ for one or more k, then $\sigma_1 < 0$ and A is invertible. All entries of A^{-1} are nonpositive.*

The proof is based on the Gerschgorin Circle Theorem and on the Perron-Frobenius Theorem, see [2, p. 55ff].

4.3.1 Closed systems

Suppose that there are no inflow reactions R_{0k}, i.e., $c_{0k} = 0$ for all k. If any of the degradation rates c_{k0} is nonzero, all molecules will disappear sooner or later and the system will tend to the trivial steady state $\lim_{t\to\infty} P(t, x) = \delta_0(x)$. Therefore, we only consider the more interesting case that $c_{k0} = c_{0k} = 0$ for all k.

Proposition 5 *Let $c_{k0} = c_{0k} = 0$ for all k. Under the assumptions* (A1) *and* (A2) *the solution of the CME* (8) *with initial data $P(0, \cdot) = \delta_\xi(\cdot)$ for $\xi \in \mathbb{N}^n$ converges to a multinomial distribution:*

$$\lim_{t \to \infty} P(t, x) = \mathcal{M}(x, |\xi|, \bar{p}).$$

The vector $\bar{p} \in [0, 1]^n$ is uniquely determined by the relations $A\bar{p} = \mathbf{0}$ and $|\bar{p}| = 1$.

A similar result can be found in [8].

Proof It follows from (6) that $\sum_{j=1}^n a_{jk} = 0$ for each k. Hence, $\sigma_1 = 0$ is an eigenvalue with left eigenvector $(1, \dots, 1)$. For $b = \mathbf{0}$ and constant A the solutions of (18) are simply

$$p^{(k)}(t) = \exp(tA)\varepsilon_k = T \exp(tJ)T^{-1}\varepsilon_k, \quad \lambda(t) \equiv \mathbf{0}$$

where $A = TJT^{-1}$ is the decomposition provided by the Jordan normal form (see, e.g., [18]). Thanks to the block structure of J we can treat the matrix exponential of each Jordan block separately. Since the eigenvalue σ_1 is simple according to Proposition 4, the first Jordan block consists of only one entry, namely $\sigma_1 = 0$, and hence

$$\exp(tJ_1) = \exp(\sigma_1 t) = 1.$$

For any other Jordan block it can be shown that

$$\lim_{t \to \infty} \exp(tJ_k) = 0$$

(where "0" denotes the corresponding zero matrix) because $\mathrm{Re}(\sigma_k) < 0$ for all $k > 1$ by Proposition 4. Hence, $\lim_{t \to \infty} \exp(tA) = TLT^{-1}$ with

$$L = \lim_{t \to \infty} \exp(tJ) = \begin{pmatrix} 1 & 0 & \cdots & 0 \\ 0 & 0 & & \vdots \\ \vdots & & \ddots & 0 \\ 0 & \cdots & 0 & 0 \end{pmatrix}.$$

As a consequence, the parameter vectors $p^{(k)}(t)$ tend to well-defined limits and the system converges to a unique steady state. The fact that $\exp(tA)$ converges implies that its derivative vanishes and thus

$$0 = \lim_{t \to \infty} \frac{d}{dt} \exp(tA) = \lim_{t \to \infty} \exp(tA)A = TLT^{-1}A.$$

If $v^{(k)}$ is the k-th row of TLT^{-1}, then $v^{(k)}A = (0, \dots, 0)$ which means that either $v^{(k)} = (0, \dots, 0)$ or $v^{(k)}$ is a left eigenvector of A to the eigenvalue $\sigma_1 = 0$. Since

this eigenvalue is simple, the corresponding left eigenspace is one-dimensional and only consists of vectors of the form $r \cdot (1, \ldots, 1)$ with some $r \in \mathbb{R}$. This yields that

$$TLT^{-1} = \begin{pmatrix} r_1 & r_1 & \cdots & r_1 \\ r_2 & r_2 & \cdots & r_2 \\ \vdots & \vdots & & \vdots \\ r_n & r_n & \cdots & r_n \end{pmatrix}$$

has n identical columns and all parameter vectors $p^{(k)}(t)$ converge to the same limit:

$$\lim_{t \to \infty} p^{(k)}(t) = \lim_{t \to \infty} \exp(tA)\varepsilon_k = TLT^{-1}\varepsilon_k = \begin{pmatrix} r_1 \\ \vdots \\ r_n \end{pmatrix} =: \bar{p}$$

The limit $\bar{p}$ lies in the kernel of A because $A\bar{p} = TJLT^{-1}\varepsilon_k = \mathbf{0}$. Moreover, it follows from (6) and $c_{k0} = 0$ that $|\bar{p}| = 1$. We insert $\bar{p}$ into the solution distribution given in Theorem 1 and use that

$$\mathcal{M}(\cdot, \xi_1, \bar{p}) \star \mathcal{M}(\cdot, \xi_2, \bar{p}) = \mathcal{M}(\cdot, \xi_1 + \xi_2, \bar{p})$$

(cf. [17]). This shows that the only steady state distribution is a multinomial distribution with parameters $\bar{p}$ and $|\xi|$. $\qquad\square$

Combining the above result with the representation (11), we obtain for every initial distribution μ and every $x \in \mathbb{N}^n$

$$\lim_{t \to \infty} P(t, x) = \sum_{\xi \in \mathbb{N}^n} \mu(\xi) \, \mathcal{M}(x, |\xi|, \bar{p}) = \sum_{N=0}^{\infty} \mu_N \, \mathcal{M}(x, N, \bar{p}), \qquad (25)$$

where $\bar{p} \in [0, 1]^n$ is uniquely determined by the relations $A\bar{p} = \mathbf{0}$ and $|\bar{p}| = 1$, and μ_N is defined by

$$\mu_N = \sum_{|\xi|=N} \mu(\xi)$$

for $N \in \mathbb{N}$. Equation (25) allows three interesting observations: (i) The steady state is not unique and does depend on the initial distribution μ, unless $c_{0k} > 0$ for some k. (ii) Fix some $N \in \mathbb{N}$. Then the limit distribution is unique and multinomial for the sub-class of initial distributions μ satisfying $\mu_N = 1$. (iii) Closed systems may evolve to Poissonian steady states (cf. Remark 1 following Proposition 2). As an example, consider the initial distribution $\mu = \mathcal{P}(\cdot, \lambda)$ for

some $\lambda \in [0, \infty)^n$. Then, μ can be interpreted as the joint probability distribution of n independent Poisson random variables $X_1, \ldots, X_n$. As a consequence

$$\mu_N = \mathbb{P}\Big(X_1 + \cdots + X_n = N\Big)$$

and

$$\mathbb{P}\Big(X_1 = x_1, \ldots, X_n = x_n \mid X_1 + \cdots + X_n = N\Big) = \mathcal{M}(x, N, p)$$

for $x \in \mathbb{N}^n$, see Remark 2 on p. 12. Now, by Bayes formula, we obtain

$$\lim_{t \to \infty} P(t, x) = \sum_{N=0}^{\infty} \mu_N \, \mathcal{M}(x, N, \bar{p}) = \mathcal{P}(x, \bar{\lambda})$$

with $\bar{\lambda} = |\lambda| \cdot \bar{p}_i$ for $i = 1, \ldots, n$.

4.3.2 Open systems

Proposition 6 *Let $c_{k0} \neq 0$ for one or more k and assume that* (A1) *and* (A2) *hold. Then, the solution of the CME* (8) *with initial data* (10) *converges to a Poisson distribution*

$$\lim_{t \to \infty} P(t, x) = \mathcal{P}(x, \bar{\lambda})$$

where $\bar{\lambda}$ is the solution of $A\bar{\lambda} = -b$ and contains only nonnegative numbers.

Remark This agrees with a result proven in [8] which states that the stationary distribution of any species in an open first-order conversion network is a Poisson distribution.

Proof By Proposition 4 the matrix A is invertible and all eigenvalues have negative real part. The solutions of the differential equations (18) are

$$p^{(k)}(t) = \exp(tA)\varepsilon_k, \quad \lambda(t) = \big(\exp(tA) - I\big)A^{-1}b$$

and since $\lim_{t \to \infty} \exp(tA) = 0$ (use the Jordan normal form as above) we obtain

$$\lim_{t \to \infty} p^{(k)}(t) = \mathbf{0}, \quad \lim_{t \to \infty} \lambda(t) = -A^{-1}b =: \bar{\lambda}.$$

All entries of $\bar{\lambda}$ are nonnegative because of Proposition 4. Inserting the limits into the solution distribution yields $\lim_{t \to 0} P(t, x) = \mathcal{P}(x, \bar{\lambda})$. $\qquad\square$

Combining the above result with the representation (11), we obtain for any given initial distribution $P(0, \cdot) = \mu(\cdot)$ and every $x \in \mathbb{N}^n$,

$$\lim_{t \to \infty} P(t, x) = \lim_{t \to \infty} \sum_{\xi \in \mathbb{N}^n} \mu(\xi) P_\xi(t, x) = \sum_{\xi \in \mathbb{N}^n} \mu(\xi) \, \mathcal{P}(x, \bar{\lambda}) = \mathcal{P}(x, \bar{\lambda}),$$
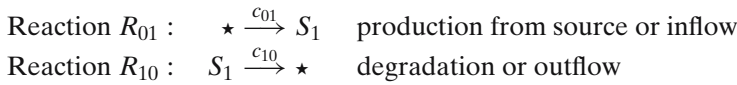
where $\bar{\lambda}$ is the solution of $A\bar{\lambda} = -b$ and contains only nonnegative numbers. Hence, for open systems the convergence and limit behavior is drastically different from that of closed systems. While in the latter case, the stationary distribution depends on the initial distribution, it is unique for open systems.

5 Some simple examples

In this subsection we illustrate our result by means of two well-known examples.

5.1 First example

Consider one single substance S_1 and the two reaction channels

Reaction R_{01} : $\star \xrightarrow{c_{01}} S_1$ production from source or inflow

Reaction R_{10} : $S_1 \xrightarrow{c_{10}} \star$ degradation or outflow

with constant reaction rates $c_{01} > 0$ and $c_{10} > 0$. Suppose that at $t = 0$ there are ξ molecules ($\xi \in \mathbb{N}$) and let $P(t, x)$ be the probability that at time t there are $x \in \mathbb{N}$ molecules of S_1. According to Theorem 1 this probability is given by

$$P(t, x) = \sum_{k=0}^{\min\{\xi, x\}} \binom{\xi}{k} p^k(t)(1 - p(t))^{\xi-k} \cdot \frac{\lambda^{x-k}(t)}{(x-k)!} e^{-\lambda(t)}$$

where $p(t) = e^{-c_{10}t}$ and $\lambda(t) = c_{01}(1 - e^{-tc_{10}})/c_{10}$ are the solutions of the differential equations

$$\dot{p}(t) = -c_{10}p(t), \quad \dot{\lambda}(t) = -c_{10}\lambda(t) + c_{01},$$
$$p(0) = 1, \quad \lambda(0) = 0.$$
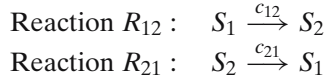
This result is stated in the books of Todorovic [21, Sect. 8.4] and Gardiner [9, Sect. 7.1]. Since $\lim_{t \to \infty} p(t) = 0$ and $\lim_{t \to \infty} \lambda(t) = c_{01}/c_{10}$, the limit distribution

$$\lim_{t \to \infty} P(t, x) = \frac{\bar{\lambda}^x}{x!} e^{-\bar{\lambda}}$$

is the Poisson distribution with parameter $\bar{\lambda} = c_{01}/c_{10}$.

5.2 Second example

Now we consider the isomerization process with two species S_1 and S_2 and the two conversions

$$\text{Reaction } R_{12}: \quad S_1 \xrightarrow{c_{12}} S_2$$
$$\text{Reaction } R_{21}: \quad S_2 \xrightarrow{c_{21}} S_1$$

with constant reaction rates $c_{12} > 0$ and $c_{21} > 0$. Suppose that at $t = 0$ there are ξ_1 molecules of S_1 and ξ_2 molecules of S_2. Let $P(t,x)$ be the probability that at time $t \geq 0$ there are x_1 molecules of S_1 and x_2 molecules of S_2. Then, according to Theorem 1,

$$P(t, \cdot) = \mathcal{M}\big(\cdot, \xi_1, p^{(1)}(t)\big) \, \star \, \mathcal{M}\big(\cdot, \xi_2, p^{(2)}(t)\big)$$

with parameter vectors $p^{(1)}(t)$ and $p^{(2)}(t)$ given by

$$p^{(1)}(t) = \exp(tA)\varepsilon_1, \quad p^{(2)}(t) = \exp(tA)\varepsilon_2, \quad A = \begin{pmatrix} -c_{12} & c_{21} \\ c_{12} & -c_{21} \end{pmatrix}.$$

The above formulas can be simplified if the diagonalisation $A = TDT^{-1}$ with

$$T = \begin{pmatrix} 1 & c_{21} \\ -1 & c_{12} \end{pmatrix}, \quad D = \begin{pmatrix} -d & 0 \\ 0 & 0 \end{pmatrix}, \quad T^{-1} = \frac{1}{d}\begin{pmatrix} c_{12} & -c_{21} \\ 1 & 1 \end{pmatrix}, \quad d = c_{12} + c_{21}$$

is used to compute the matrix exponential $\exp(tA) = T\exp(tD)T^{-1}$. This yields

$$p^{(1)}(t) = \frac{1}{d}\begin{pmatrix} e^{-td}c_{12} + c_{21} \\ (1 - e^{-td})c_{12} \end{pmatrix}, \quad p^{(2)}(t) = \frac{1}{d}\begin{pmatrix} (1 - e^{-td})c_{21} \\ e^{-td}c_{21} + c_{12} \end{pmatrix}.$$

Since $|p^{(1)}(t)| = |p^{(2)}(t)| = 1$ we find that

$$\left(1 - |p^{(k)}|\right)^{\xi_k - |x|} = 0^{\xi_k - |x|} = \delta_{\xi_k}(|x|).$$

As a consequence,

$$\mathcal{M}\big(x, \xi_k, p^{(k)}\big) = \frac{\xi_k!}{x_1! x_2! (1 - |x|)!} \left(p_1^{(k)}\right)^{x_1} \left(p_2^{(k)}\right)^{x_2} \left(1 - |p^{(k)}|\right)^{\xi_k - |x|}$$

$$= \delta_{\xi_k}(|x|) \frac{\xi_k!}{x_1!(1 - x_1)!} \left(p_1^{(k)}\right)^{x_1} \left(1 - p_1^{(k)}\right)^{\xi_k - x_1}$$

$$= \delta_{\xi_k}(|x|) \mathcal{B}\big(x_1, \xi_k, p_1^{(k)}\big)$$

for $k = 1$ or $k = 2$, where $\mathcal{B}(\cdot, \xi_k, p_1^{(k)})$ denotes the binomial distribution. This means that the total number of particles is constant, which is reasonable

for the above system. The two-dimensional convolution of two multinomial distribution now reduces to a one-dimensional convolution of two binomial distributions:

$$P(t,x) = \sum_z \delta_{\xi_k}(|z|) \mathcal{B}\left(z_1, \xi_1, p_1^{(1)}\right) \delta_{\xi_2}(|x-z|) \mathcal{B}\left(x_1 - z_1, \xi_2, p_1^{(2)}\right)$$

$$= \delta_{|\xi|}(|x|) \sum_{z_1} \mathcal{B}\left(z_1, \xi_1, p_1^{(1)}\right) \mathcal{B}\left(x_1 - z_1, \xi_2, p_1^{(2)}\right).$$

Since both $p_1^{(1)}(t)$ and $p_1^{(2)}(t)$ converge to the same value $\bar{p} = c_{21}/(c_{21} + c_{12})$ the stationary distribution is
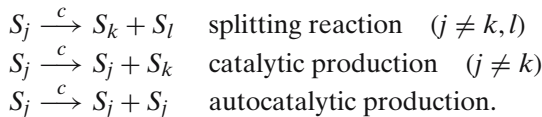
$$\lim_{t\to\infty} P(t,\cdot) = \delta_{|\xi|}(|x|)\left(\mathcal{B}\left(\cdot, \xi_1, \bar{p}\right) \star \mathcal{B}\left(\cdot, \xi_2, \bar{p}\right)\right) = \delta_{|\xi|}(x)\mathcal{B}\left(\cdot, |\xi|, \bar{p}\right)$$

because the convolution of two binomials with the same parameter is again a binomial (cf. [14]). In [13] the same stationary distribution was obtained in a different way.

6 Further development

In this article we derive an explicit formula for the *exact* solution of the CME under the assumption that only monomolecular reactions occur in the underlying reaction system. For the generic case of deterministic initial conditions, the solution turns out to be the convolution of multinomial and product Poisson distributions with time-dependent parameters evolving according to the traditional reaction-rate equations. To our knowlegde this is the first report of a general solution for arbitrary initial conditions. All previously derived results on monomolecular reaction systems can be restated in terms of our representation highlighting the structure of the system, as has been shown in Sect. 5. Exploiting the structure of the solution, many interesting features of the time-dependent distribution have been expressed in terms of the time-depending parameters specifying the multinomial and the product Poisson distribution.

Our results presented so far are applicable to reaction systems including conversion, production and degradation reactions, as specified in (1). The question arises whether Theorem 1 can be extended to a larger class of systems including, e.g.,

$$\begin{aligned} S_j &\xrightarrow{c} S_k + S_l & \text{splitting reaction} \quad (j \neq k, l) \\ S_j &\xrightarrow{c} S_j + S_k & \text{catalytic production} \quad (j \neq k) \\ S_j &\xrightarrow{c} S_j + S_j & \text{autocatalytic production.} \end{aligned}$$

As a first step in this direction, we discuss the case of one single species evolving according to an autocatalytic reaction with nonnegative rate $c(t)$. Theorem 1 cannot be applied to this situation because (26) is not a monomolecular reaction

in the sense of Sect. 2. Nevertheless, we can state an explicit formula for the probability distribution that solves the corresponding CME.

Proposition 7 *Suppose that at $t = 0$ there are $\xi \in \mathbb{N} \setminus \{0\}$ molecules of a species S taking part in the autocatalytic reaction*

$$S \xrightarrow{c} S + S \tag{26}$$

with rate $c(t) \geq 0$. If $P(t, m)$ denotes the probability to find $m \in \mathbb{N}$ molecules of S at time t, then

$$P(t, m) = \begin{cases} \binom{m-1}{m-\xi} p^{\xi}(t)\left(1 - p(t)\right)^{m-\xi} & \text{for } m \geq \xi \\ 0 & \text{for } m < \xi \end{cases} \tag{27}$$

with parameter $p(t)$ obtained by solving the differential equation $\dot{p}(t) = -c(t)p(t)$ with $p(0) = 1$.

Proof It has to be shown that (27) solves the CME

$$\frac{\partial}{\partial t} P(t, m) = c(t)(m - 1)P(t, m - 1) - c(t)mP(t, m) \tag{28}$$

with initial data $P(0, m) = \delta_{\xi}(m)$. Taking the derivative of (27) and omitting the argument "(t)" gives

$$
\begin{aligned}
\frac{\partial}{\partial t} P(t, m) &= \binom{m-1}{m-\xi} \left(\xi p^{\xi-1}(1-p)^{m-\xi} - p^{\xi}(m-\xi)(1-p)^{m-\xi-1} \right) \dot{p}(t) \\
&= \left(\frac{\xi}{p} - \frac{m-\xi}{1-p} \right) \dot{p} P(t, m) \\
&= \left(-c\xi + cp\frac{m-\xi}{1-p} \right) P(t, m) \\
&= -cmP(t, m) + c\frac{m-\xi}{1-p} P(t, m) \\
&= -cmP(t, m) + c(m-1)P(t, m-1)
\end{aligned}
$$

for all $m \geq \xi$, where we have used that $1 - p(t) > 0$ and $p(t) > 0$ for $t > 0$. At $t = 0$ we obtain

$$\binom{m-1}{m-\xi} p^{\xi}(0)\left(1 - p(0)\right)^{m-\xi} = \binom{m-1}{m-\xi} 1^{\xi} \delta_{\xi}(m) = \delta_{\xi}(m) = P(0, m).$$

This proves that (27) is indeed the solution of (28). □

Remark The distribution (27) is a shifted variant of the negative binomial distribution $\tilde{\mathcal{B}}$ defined by

$$\tilde{\mathcal{B}}(m, r, q) = \binom{r + m - 1}{m} p^r (1 - p)^m$$

for all $p \in [0, 1]$ and $r > 0$, see [14]. It is easy to see that $P(t, m) = \tilde{\mathcal{B}}(m - \xi, \xi, p)$. Since it is known that

$$\mathbb{E}\left(\tilde{\mathcal{B}}(\cdot, r, q)\right) = \sum_{m=0}^{\infty} m \tilde{\mathcal{B}}(m, r, q) = \frac{qr}{1 - q},$$

the expectation of $P(t, \cdot)$ is

$$\begin{aligned}
\mathbb{E}(P(t, \cdot)) &= \sum_{m=0}^{\infty} (m - \xi + \xi) \tilde{\mathcal{B}}(m - \xi, \xi, 1 - p(t)) \\
&= \mathbb{E}\left(\tilde{\mathcal{B}}(\cdot, \xi, 1 - p(t))\right) + \xi \\
&= \frac{(1 - p(t))\xi}{p(t)} + \xi = \frac{\xi}{p(t)} = \xi e^{ct}
\end{aligned}$$

which is again the solution of the traditional rate equation $\dot{y}(t) = cy(t)$ with initial value $y(0) = \xi$.

Proposition 7 provides an analytic solution for *isolated* autocatalytic reactions, but unfortunately we have not yet found a way to treat systems where autocatalytic reactions occur together with production, conversion or degradation reactions. For example, the joint probability distribution of the system

$$\begin{aligned}
* &\xrightarrow{c_1} S \\
S &\xrightarrow{c_2} * \\
S &\xrightarrow{c_3} S + S
\end{aligned}$$
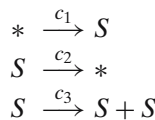
is beyond the scope of our results. We only know that somehow this distribution must "interpolate" between the Poisson, binomial and negative binomial distributions, because each of these is obtained in a special case. We believe, however, that Proposition 7 and Theorem 1 can be combined and extended in such a way that analytic solutions of the CME are obtained even when both monomolecular and autocatalytic reactions are possible.

References

1. Alfonsi, A., Cancès, E., Turinici, G., Ventura, B.D., Huisinga, W.: Adaptive simulation of hybrid stochastic and deterministic models for biochemical systems. ESAIM Proc. **14**, 1–13 (2005)
2. Anderson, D.H.: Compartmental Modeling and Tracer Kinetics. Number 50 in Lecture Notes in Biomathematics. Springer, Berlin Heidelberg New York (1983)
3. Burrage, K., Tian, T.: Poisson Runge–Kutta methods for chemical reaction systems. In: Proceedings of the Hong Kong Conference on Scientific Computing, 2003 (in press).
4. Burrage, K., Tian, T., Burrage, P.: A multi-scaled approach for simulating chemical reaction systems. Prog. Biophy. Mol. Biol. **85**, 217–234 (2004)
5. Cao, Y., Gillespie, D., Petzold, L.: The slow-scale stochastic simulation algorithm. J. Chem. Phys. **122**(1), 014116 (2005)
6. Darvey, I., Staff, P.: Stochastic approach to first-order chemical reaction kinetics. J. Chem. Phys. **44**(3), 990–997 (1966)
7. Fall, C.P., Marland, E.S., Wagner, J.M., Tyson, J.J.: Computational Cell Biology, volume 20 of Interdisciplinary Applied Mathematics. Springer, Berlin Heidelberg New York (2002)
8. Gadgil, C., Lee, C.-H., Othmer, H.G.: A stochastic analysis of first-order reaction networks. Bull. Math. Biol. **67**, 901–946 (2005)
9. Gardiner, C.W.: Handbook of Stochastic Methods. Springer, Berlin Heidelberg New York, 2nd enlarged edition (1985)
10. Gibson, M.A., Bruck, J.: Efficient exact stochastic simulation of chemical systems with many species and many channels. J. Phys. Chem. A **104**, 1876–1889 (2000)
11. Gillespie, D.T.: A general method for numerically simulating the stochastic time evolution of coupled chemical reactions. J. Comput. Phys. **22**, 403–434 (1976)
12. Gillespie, D.T.: Approximate accelerated stochastic simulation of chemically reacting systems. J. Chem. Phys. **115** (4), 1716–1733 (2001)
13. Gillespie, D.T.: The chemical Langevin and Fokker–Planck equations for the reversible isomerization reaction. J. Phys. Chem. **106**, 5063–5071 (2002)
14. Golberg, M.A.: An Introduction to Probability Theory with Statistical Applications. Plenum Press, New York and London (1984)
15. Haseltine, E.L., Rawlings, J.B.: Approximate simulation of coupled fast and slow reactions for stochastic chemical kinetics. J. Chem. Phys. **117** (15), 6959–6969 (2002)
16. Iserles, A., Nørsett, S.P.: On the solution of lienar differential equations in Lie groups. Philos. Trans. R. Soc. Lond., Ser. A, Math. Phys. Eng. Sci. **357**(1754), 983–1019 (1999)
17. Kotz, S. Johnson, N.L., Read, C.B.: editors. Encyclopedia of Statistical sciences, vol. 5. Wiley, New York, Chichester, Brisbane, Toronto, Singapore (1985)
18. Lang, S.: Linear algebra. Undergraduate Texts in Mathematics, 3rd edn. Springer, Berlin Heidelberg New York (1987)
19. Rao, C.V., Arkin, A.P.: Stochastic chemical kinetics and the quasi-steady-state assumption: application to the Gillespie algorithm. J. Chem. Phys. **118**(11), 4999–5010 (2003)
20. Salis, H., Kaznessis, Y.: Accurate hybrid simulation of a system of coupled chemical or biochemical reactions. J. Chem. Phys. **122** (2005)
21. Todorovic, P.: An Introduction to Stochastic Processes and their Applications. Springer, Berlin Heidelberg New York, (1992)
22. Turner, T.E., Schnell, S., Burrage. K.: Stochastic approaches for modelling in vivo reactions. Comput. Biol. Chem. **28**, 165–178 (2004)