

An analytical approach to solutions of master equations for stochastic nonlinear reactions

Chang Hyeong Lee · Pilwon Kim

Received: 12 August 2011 / Accepted: 22 February 2012 / Published online: 13 March 2012
© Springer Science+Business Media, LLC 2012

Abstract In this paper we consider a class of nonlinear reactions which are important in stochastic reaction networks. We find the exact solution of the chemical master equation for a class of irreversible and reversible nonlinear reactions. We also present the explicit form of the equilibrium probability solution of the reactions. The results can be used for analyzing stochastic dynamics of important reactions such as binding/unbinding reaction and protein dimerization.

Keywords Stochastic nonlinear reactions · Solutions of chemical master equations · Equilibrium probability

1 Introduction

Stochastic modeling of chemical or biochemical reaction networks is used when small biochemical reaction systems are studied. Traditionally, continuous description of the system has been utilized for long time. However, when the entire dynamics of the chemical system are characterized by interactions of small number of reactant molecules, the continuous description fails to explain the stochastic effects such as fluctuation. To capture such effects properly, discrete stochastic description has to be adopted. The discrete stochastic modeling describes how the molecular number of each species evolves in the system. A vector variable $\mathbf{n}(t) = (n_1(t), n_2(t), \dots, n_s(t))$ is used to denote the molecular number, where $n_i(t)$ is the molecular number of i th species at time t . Since the molecular interactions are stochastic in nature, $\mathbf{n}(t)$ is a random

C. H. Lee (✉) · P. Kim

School of Technology Management and School of Mechanical and Advanced Materials Engineering,
Ulsan National Institute of Science and Technology (UNIST), Ulsan Metropolitan City 689-798,
South Korea
e-mail: chlee@unist.ac.kr

vector. Under the Markovian assumption, $\mathbf{n}(t)$ is a continuous-time Markov process with discrete states. If we denote $Pr\{\mathbf{n}(t) = \mathbf{n}\}$ by $p(\mathbf{n}, t)$, we can write the governing equation, so-called chemical master equation as

$$\frac{d}{dt}p(\mathbf{n}, t) = \sum_{\ell} \mathcal{R}_{\ell}(\mathbf{n} - V_{\ell}) \cdot p(\mathbf{n} - V_{\ell}, t) - \sum_{\ell} \mathcal{R}_{\ell}(\mathbf{n}) \cdot p(\mathbf{n}, t), \quad (1)$$

where \mathcal{R}_{ℓ} is so-called the propensity function for the ℓ th reaction and V_{ℓ} is the ℓ th column of the stoichiometric matrix V that is the matrix whose (i, j) th component represents the stoichiometric amount of the i th species changed by the occurrence of the j th reaction [1]. The propensity $\mathcal{R}_{\ell}(\mathbf{n})$ is computed as

$$\mathcal{R}_{\ell}(\mathbf{n}) = c_{\ell} h_{\ell}(\mathbf{n}), \quad (2)$$

where c_{ℓ} is the probability that the ℓ th reaction occurs per unit time and $h_{\ell}(\mathbf{n})$ is the product of the numbers of reactants of the ℓ th reaction, which is computed by mass-action kinetics.

All accessible states of the system and transitions between them can be formulated in a Markov chain. We let the vector \mathbf{a}^i denote the i th state of \mathbf{n} and define the vector $\mathbf{p}(t)$ as $p_i(t) = Pr(\mathbf{n}(t) = \mathbf{a}^i)$, where $p_i(t)$ is the i th entry of $\mathbf{p}(t)$. By labeling all accessible states \mathbf{n} and computing transition rates $\mathcal{R}(\mathbf{n})$ between them, the evolution of the system can be completely described by a Kolmogorov equation of matrix form, which is equivalent to Eq. (1),

$$\frac{d\mathbf{p}(t)}{dt} = K\mathbf{p}(t), \quad (3)$$

where K is the matrix of transition rates between the states, defined as

$$K_{ij} = \begin{cases} \mathcal{R}_{\ell}(\mathbf{n}) & \text{if } \mathbf{a}^i = \mathbf{a}^j + V_{\ell} \text{ for some } \ell = 1, \dots, r \\ 0 & \text{otherwise.} \end{cases}$$

Here K is a Markov chain generator, i.e. $\sum_i K_{ij} = 0$ for each j , and $K_{ij} \geq 0$ for each $j \neq i$.

The formal solution of (3)

$$\mathbf{p}(t) = e^{Kt}\mathbf{p}(0) \quad (4)$$

describes how the system evolves exactly. However, if there are nonlinear reactions, it is difficult to find the analytic solution of (3), since it is not simple to identify the matrix K . Moreover, K is a big and sparse matrix for most of complex systems and is infinite-dimensional if the state space of the system is unbounded. In such cases, the solution of (4) is not easy to find even numerically.

The nonlinear reactions such as bimolecular reactions are ubiquitous and important chemical processes in biological networks. For example, the enzyme-substrate binding, ligand binding and dimerization can be considered as bimolecular reactions.

Although the exact solution of bimolecular reactions are hardly obtained as mentioned before, there have been works for finding the solution of master equations of some bimolecular reactions; McQuarrie found the equilibrium solutions of certain bimolecular reactions including $A + B \rightarrow C$, $2A \rightarrow B + C$, $A + B \rightarrow C + D$ by utilizing the generation function [2]. Laurenzi obtained the exact solution of the irreversible reaction $A + B \rightarrow C$ by applying Fourier transform and found the equilibrium probability of the reversible reaction $A + B \rightleftharpoons C$ [3].

In this paper we explicitly represent the solutions of nonlinear reactions including fundamental bimolecular reactions. This work is distinguished from the previous works in that all types of bimolecular reactions are considered in a unified framework. To authors' knowledge, no works about finding the exact solution of master equations of general nonlinear reactions have been done yet.

The outline of the paper is as follows. In Sect. 2, we find the exact solution of the general form of nonlinear irreversible reactions of the type $aA + bB \rightarrow cC + dD$ and study some exemplary cases. In Sect. 3, we present an explicit expression of stochastic solutions of reversible reactions $aA + bB \rightleftharpoons cC + dD$ and find the equilibrium solution of the reversible reactions. Throughout this paper, a vector and a matrix are denoted by a boldfaced small letter and a capital letter, respectively.

2 Irreversible reactions

2.1 Stochastic solution of general irreversible reactions

In this section we deal with a class of irreversible stochastic nonlinear reactions



involving four species. Here the species A , B , C and D are all distinct and a , b , c and d are nonnegative integers. c_1 is the probability rate constant for the reaction [1]. We denote the molecular number of species A , B , C and D as $n_i(t)$, $i = 1, 2, 3, 4$ at time t , respectively and initial molecular numbers as a_0 , b_0 , c_0 and d_0 , respectively. The stochastic dynamics of (5) are described by a Markov chain with transition diagram of all states as

$$\begin{aligned} (a_0, b_0, c_0, d_0) &\rightarrow (a_0 - a, b_0 - b, c_0 + c, d_0 + d) \rightarrow \cdots \\ &\rightarrow (a_0 - Ma, b_0 - Mb, c_0 + Mc, d_0 + Md), \end{aligned}$$

where M is the largest positive integer that satisfies $\min\{a_0 - Ma, b_0 - Mb\} \geq 0$. We denote each state of the above Markov chain by

$$\begin{aligned} S_i &= (a_0 - (i - 1)a, b_0 - (i - 1)b, c_0 + (i - 1)c, d_0 + (i - 1)d), \\ i &= 1, \dots, M + 1. \end{aligned}$$

Let α_i be the transition rate from S_i into S_{i+1} . That is, α_i is the propensity and by (2), it is computed as

$$\alpha_i = c_1 \binom{a_0 - (i-1)a}{a} \binom{b_0 - (i-1)b}{b},$$

for each $i = 1, \dots, M$ and α_i are all distinct [4]. Here

$$\binom{n}{k} = \frac{n!}{k!(n-k)!}.$$

Using these notations, one can describe the stochastic dynamics by

$$S_1 \xrightarrow{\alpha_1} S_2 \xrightarrow{\alpha_2} \dots \xrightarrow{\alpha_M} S_{M+1}. \quad (6)$$

Remark Note that the stoichiometry of (5) is $V = [-a, -b, c, d]^T$ and the basis matrix of the nullspace of V^T , $\mathcal{N}[V^T]$ is obtained as

$$A = \begin{bmatrix} c & 0 & a & 0 \\ 0 & d & 0 & b \\ d & 0 & 0 & a \end{bmatrix}.$$

From the matrix A , one can obtain the conservation quantities as

$$cn_1 + an_3 = L_1, \quad dn_2 + bn_4 = L_2, \quad dn_1 + an_4 = L_3,$$

where

$$L_1 = ca_0 + ac_0, \quad L_2 = db_0 + bd_0, \quad L_3 = da_0 + ad_0.$$

Using these conservation quantities, one can identify each state S_i by the state of one of the four species, say A .

The governing equation of the Markov chain (6) is

$$\frac{d\mathbf{p}}{dt} = K\mathbf{p} \quad (7)$$

and the transition-rate matrix K is given by

$$K = \begin{bmatrix} -\alpha_1 & 0 & 0 & 0 & \cdots & 0 \\ \alpha_1 & -\alpha_2 & 0 & 0 & \cdots & 0 \\ 0 & \alpha_2 & -\alpha_3 & 0 & \cdots & 0 \\ & & \ddots & \ddots & \ddots & \vdots \\ & & & \alpha_{M-1} & -\alpha_M & 0 \\ & & & & \alpha_M & 0 \end{bmatrix}. \quad (8)$$

To describe the stochastic dynamics, we find the exact solution of (7); Since K is a lower triangular matrix, all eigenvalues of K are the diagonal entries 0 and

$-\alpha_1, \dots, -\alpha_M$, and they are all real and distinct. The governing equation is written as

$$\frac{dp_1}{dt} = -\alpha_1 p_1 \quad (9)$$

$$\frac{dp_2}{dt} = \alpha_1 p_1 - \alpha_2 p_2 \quad (10)$$

$$\vdots = \vdots \quad (11)$$

$$\frac{dp_M}{dt} = \alpha_{M-1} p_{M-1} - \alpha_M p_M \quad (12)$$

$$\frac{dp_{M+1}}{dt} = \alpha_M p_M \quad (13)$$

If we assume $p(0) = \mathbf{e}_1$ where \mathbf{e}_1 is the unit vector $(1, 0, \dots, 0)$, then we find the solution of the above system as follows.

$$p_1(t) = e^{-\alpha_1 t} \quad (14)$$

$$p_2(t) = \frac{\alpha_1}{\alpha_1 - \alpha_2} (e^{-\alpha_2 t} - e^{-\alpha_1 t}) \quad (15)$$

After some computations, one can find the formula for general cases;

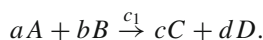
$$p_i(t) = \prod_{j=0}^{i-2} \alpha_{j+1} \sum_{k=0}^{i-1} \frac{e^{-\alpha_{k+1} t}}{\prod_{\substack{j=0 \\ j \neq k}}^{i-1} (\alpha_{j+1} - \alpha_{k+1})}, \quad (16)$$

for $i = 2, \dots, M$, and

$$p_{M+1}(t) = 1 - \sum_{i=1}^M p_i(t). \quad (17)$$

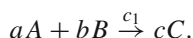
2.2 Special cases of irreversible reactions

Using the results in Sect. 2.1, we study some special cases of the reaction



(Case I) $d = 0$ and a, b, c are non-zero.

In this case, we have a reaction system



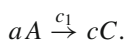
All possible states are $S_i = (a_0 - (i-1)a, b_0 - (i-1)b, c_0 + (i-1)c)$, $i = 1, \dots, M+1$, where M is the largest positive integer that satisfies $\min\{a_0 - Ma, b_0 - Mb\} \geq 0$.

$$\alpha_i = c_1 \binom{a_0 - (i-1)a}{a} \binom{b_0 - (i-1)b}{b},$$

for $i = 1, \dots, M$. The same argument is applied for the transition-rate matrix and the solution of the governing equation as in Sect. 2.1. Note that each state S_i can be identified by $(a_0 - (i-1)a)$ of species A , since there are conservation quantities $cn_1 + an_3 = L_1$, $cn_2 + bn_3 = L_2$ where $L_1 = ca_0 + ac_0$ and $L_2 = cb_0 + bc_0$ are constant.

(Case II) $b = d = 0$ and a, c are non-zero.

In this case, a reaction system is



All possible states are $S_i = (a_0 - (i-1)a, c_0 + (i-1)c)$, $i = 1, \dots, M+1$, where M is the largest positive integer that satisfies $a_0 - Ma \geq 0$. In this case, for each $i = 1, \dots, M$,

$$\alpha_i = c_1 \binom{a_0 - (i-1)a}{a}.$$

The conservation quantity is $cn_1 + an_2 = L_1$ where $L_1 = ca_0 + ac_0$. Using these conservation quantities, one can identify each state S_i by $(a_0 - (i-1)a)$ of species A .

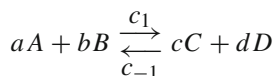
In Table 1, we find the state S_i and α_i for four typical irreversible reactions.

In Fig. 1, we illustrate the transient probability and the probability distribution obtained by the formulas in Table 1 for the binding reaction $A + B \rightarrow C$ under the initial condition $(40, 30, 0)$. The results are compared with simulation results by the direct method of the stochastic simulation algorithm.

3 Reversible bimolecular reactions

3.1 Solution of the general bimolecular reversible reactions

In this section, we deal with a class of reversible stochastic nonlinear reactions



involving four distinct species A, B, C and D and we find the exact solution of the master equation of the reactions.

Without loss of generality, we assume $a \geq b$ and $c \geq d$ and initial numbers of species A, B, C and D by a_0, b_0, c_0 and d_0 , respectively. All possible states can be denoted by

Table 1 Typical irreversible bimolecular reactions. S_i are accessible states in Markov chain of the type of the reaction

Reactions	Values of $S_i, i = 1, \dots, M + 1$ and $\alpha_i, i = 1, \dots, M$	
$A + B \xrightarrow{c_1} C$	S_i	$(a_0 - i + 1, b_0 - i + 1, c_0 + i - 1)$
	α_i	$c_1(a_0 - i + 1)(b_0 - i + 1)$
	M	$\min\{a_0 + 1, b_0 + 1\}$
$A + B \xrightarrow{c_1} C + D$	S_i	$(a_0 - i + 1, b_0 - i + 1, c_0 + i - 1, d_0 + i - 1)$
	α_i	$c_1(a_0 - i + 1)(b_0 - i + 1)$
	M	$\min\{a_0 + 1, b_0 + 1\}$
$2A \xrightarrow{c_1} C$	S_i	$(a_0 - 2(i - 1), c_0 + i - 1)$
	α_i	$\frac{c_1}{2}(a_0 - 2(i - 1))(a_0 - 2(i - 1) - 1)$
	M	$\frac{a_0}{2} + 1(\text{even } a_0), \frac{a_0 - 1}{2} + 1(\text{odd } a_0)$
$2A \xrightarrow{c_1} C + D$	S_i	$(a_0 - 2(i - 1), c_0 + i - 1, d_0 + i - 1)$
	α_i	$\frac{c_1}{2}(a_0 - 2(i - 1))(a_0 - 2(i - 1) - 1)$
	M	$\frac{a_0}{2} + 1(\text{even } a_0), \frac{a_0 - 1}{2} + 1(\text{odd } a_0)$

Since all α_i are identified, one can find the exact transient probability solution of the reaction by using (16) and (17)

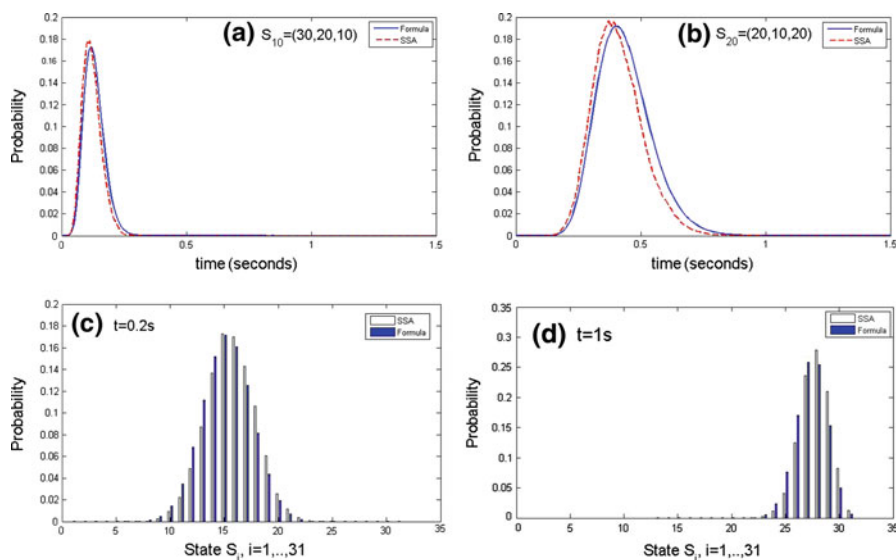


Fig. 1 Under the initial condition $(40, 30, 0)$ of $A + B \rightarrow C$, transient probabilities obtained by exact formulas (14)–(17) and the direct method of stochastic simulation algorithm (SSA) for **a** the state S_{10} and **b** S_{20} . Probability distribution for all accessible states $S_i, i = 1, \dots, 31$ at times **c** $t = 0.2s$ and **d** $t = 1s$. Here $S_i = (40 - i + 1, 30 - i + 1, i - 1)$. The results by SSA are based on 10,000 realizations

$$S_i = (a_0 + Na - (i - 1)a, b_0 + Nb - (i - 1)b, c_0 - Nc + (i - 1)c, d_0 - Nd + (i - 1)d),$$

for $i = 1, \dots, N + M + 1$. Here M is the largest positive integer that satisfies

$$M \leq \min \left\{ \frac{a_0}{a}, \frac{b_0}{b} \right\},$$

so that $a_0 - Ma \geq 0$ and $b_0 - Mb \geq 0$, and N is the largest positive integer that satisfies

$$N \leq \min \left\{ \frac{c_0}{c}, \frac{d_0}{d} \right\},$$

so that $c_0 - Nc \geq 0$ and $d_0 - Nd \geq 0$. We let α_i be the transition rate from the state S_i to S_{i+1} and let β_i be the transition rate from S_{i+1} into S_i . One can find

$$\alpha_i = c_1 \binom{a_0 + Na - (i-1)a}{a} \binom{b_0 + Nb - (i-1)b}{b},$$

and

$$\beta_i = c_{-1} \binom{c_0 - (N-i)c}{c} \binom{d_0 - (N-i)d}{d}.$$

for each $i = 1, \dots, N + M$. One can describe the stochastic dynamics by the Markov chain

$$S_1 \xrightleftharpoons[\beta_1]{\alpha_1} S_2 \xrightleftharpoons[\beta_2]{\alpha_2} \cdots \xrightleftharpoons[\beta_{N+M}]{\alpha_{N+M}} S_{N+M+1}. \quad (18)$$

The governing equation of the Markov Chain (18) is

$$\frac{d\mathbf{p}}{dt} = K\mathbf{p}, \quad (19)$$

and the transition-rate matrix K is

$$K = \begin{bmatrix} -\alpha_1 & \beta_1 & 0 & 0 & \cdots & 0 \\ \alpha_1 & -(\alpha_2 + \beta_1) & \beta_2 & 0 & \cdots & 0 \\ 0 & \alpha_2 & -(\alpha_3 + \beta_2) & \beta_3 & & \vdots \\ & & \ddots & \ddots & \ddots & \\ & & & \ddots & -(\alpha_{N+M} + \beta_{N+M-1}) & \beta_{N+M} \\ & & & & \alpha_{N+M} & -\beta_{N+M} \end{bmatrix}. \quad (20)$$

Note that K is a tridiagonal matrix. Before we do a detailed analysis on K , we briefly go over the properties of the tridiagonal matrix; A tridiagonal matrix is the matrix

which has zero entries below the first subdiagonal, and zero entries above the first superdiagonal. Thus the generic form of a tridiagonal matrix G is

$$\begin{bmatrix} g_{11} & g_{12} & 0 & 0 & \cdots & 0 \\ g_{21} & g_{22} & g_{23} & 0 & \cdots & 0 \\ 0 & g_{32} & g_{33} & g_{34} & & \\ & & \ddots & \ddots & \ddots & \\ & & & g_{n-1,n-2} & g_{n-1,n-1} & g_{n-1,n} \\ & & & & g_{n,n-1} & g_{n,n} \end{bmatrix}. \quad (21)$$

Note that if the matrix G is a real tridiagonal matrix and satisfies $g_{i,i+1}g_{i+1,i} > 0$ for all $i = 1, \dots, n-1$, then it is similar to a symmetric matrix [5]. Since a symmetric tridiagonal matrix without any zero off-diagonal elements has real distinct eigenvalues [7], all eigenvalues of the matrix G are real and distinct. Since the matrix K in (20) is a tridiagonal matrix with $\alpha_i\beta_i > 0$, $i = 1, \dots, N+M$, all eigenvalues of K are real and distinct.

We denote each eigenvector of K by \mathbf{u}_i , $i = 1, \dots, N+M$, and the corresponding eigenvalue by λ_i , $i = 1, \dots, N+M$. We write

$$K\mathbf{u}_i = \lambda_i\mathbf{u}_i, \quad K^2\mathbf{u}_i = \lambda_i^2\mathbf{u}_i, \quad \dots, \quad K^{N+M+1}\mathbf{u}_i = \lambda_i^{N+M+1}\mathbf{u}_i.$$

The matrix K has only one zero eigenvalue and we let $\lambda_1 = 0$. In the matrix form,

$$KU = U\Lambda, \quad K^2U = U\Lambda^2, \quad \dots, \quad K^{N+M+1}U = U\Lambda^{N+M+1}.$$

where

$$U = [\mathbf{u}_1 | \mathbf{u}_2 | \cdots | \mathbf{u}_{N+M+1}], \quad \Lambda = \text{diag}(\lambda_1, \dots, \lambda_{N+M+1}).$$

Since U is invertible, one finds

$$K^m = U\Lambda^mU^{-1},$$

for $m = 1, \dots, N+M+1$. That is, for $m = 1, \dots, N+M+1$,

$$[K^m]_{ij} = \sum_{k=1}^{N+M+1} \lambda_k^m \gamma_{i,j,k}, \quad (22)$$

where $\gamma_{i,j,k} = U_{ik}U_{kj}^{-1}$. Thus, to compute $\gamma_{i,j,k}$, we find all eigenvectors, which will require cumbersome computational works. Here we show how to find the constant $\gamma_{i,j,k}$ even without finding eigenvectors \mathbf{u}_i as follows;

First notice that (22) gives a system

$$\begin{aligned} \begin{bmatrix} K_{ij} \\ K_{ij}^2 \\ \vdots \\ K_{ij}^{N+M+1} \end{bmatrix} &= \begin{bmatrix} \lambda_1 & \lambda_2 & \cdots & \lambda_{N+M+1} \\ \lambda_1^2 & \lambda_2^2 & \cdots & \lambda_{N+M+1}^2 \\ \vdots & \vdots & \cdots & \vdots \\ \lambda_1^{N+M+1} & \lambda_2^{N+M+1} & \cdots & \lambda_{N+M+1}^{N+M+1} \end{bmatrix} \begin{bmatrix} \gamma_{i,j,1} \\ \gamma_{i,j,2} \\ \vdots \\ \gamma_{i,j,N+M+1} \end{bmatrix} \\ &= \begin{bmatrix} 1 & 1 & \cdots & 1 \\ \lambda_1 & \lambda_2 & \cdots & \lambda_{N+M+1} \\ \vdots & \vdots & \cdots & \vdots \\ \lambda_1^{N+M} & \lambda_2^{N+M} & \cdots & \lambda_{N+M+1}^{N+M} \end{bmatrix} \begin{bmatrix} \lambda_1 \gamma_{i,j,1} \\ \lambda_2 \gamma_{i,j,2} \\ \vdots \\ \lambda_{N+M+1} \gamma_{i,j,N+M+1} \end{bmatrix}. \end{aligned}$$

Since all λ_i are distinct, the Vandermonde matrix

$$H = \begin{bmatrix} 1 & 1 & \cdots & 1 \\ \lambda_1 & \lambda_2 & \cdots & \lambda_{N+M+1} \\ \vdots & \vdots & \cdots & \vdots \\ \lambda_1^{N+M} & \lambda_2^{N+M} & \cdots & \lambda_{N+M+1}^{N+M} \end{bmatrix}$$

has its inverse [5] and its inverse matrix W is explicitly written [6] as

$$W_{ij} = \frac{(-1)^{N+M+1-j} \sigma_{N+M+2-j,i}}{N+M+1 \prod_{\substack{j=1 \\ j \neq i}} (\lambda_i - \lambda_j)},$$

where $\sigma_{i,j}$ is defined for $j = 1, \dots, N+M+1$ as

$$\sigma_{1,j} = 1$$

and

$$\sigma_{i,j} = \sum_{\substack{r_1=1 \\ r_1 \neq j}}^{N+M+1} \sum_{\substack{r_2=r_1+1 \\ r_2 \neq j}}^{N+M+1} \cdots \sum_{\substack{r_{i-1}=r_{i-2}+1 \\ r_{i-1} \neq j}}^{N+M+1} \prod_{m=1}^{i-1} \lambda_{r_m}, \text{ for } i = 2, \dots, N+M+1.$$

Thus, from the equation

$$\begin{bmatrix} \lambda_1 \gamma_{i,j,1} \\ \lambda_2 \gamma_{i,j,2} \\ \vdots \\ \lambda_{N+M+1} \gamma_{i,j,N+M+1} \end{bmatrix} = H^{-1} \begin{bmatrix} K_{ij} \\ K_{ij}^2 \\ \vdots \\ K_{ij}^{N+M+1} \end{bmatrix},$$

one can obtain, for $k \geq 2$,

$$\gamma_{i,j,k} = \frac{\sum_{m=1}^{N+M+1} W_{k,m} K_{ij}^m}{\lambda_k}.$$

(Note that $\lambda_1 = 0$ and thus $\gamma_{i,j,1}$ is not defined from the above equation.) Therefore, the solution $P(t)$ is given by

$$\begin{aligned} P_{ij}(t) &= (e^{Kt})_{ij} = \sum_{m=0}^{\infty} \frac{t^m}{m!} (K^m)_{ij} \\ &= \sum_{m=0}^{\infty} \frac{t^m}{m!} \left(\sum_{k=1}^{N+M+1} \lambda_k^m \gamma_{i,j,k} \right) \\ &= \sum_{k=2}^{N+M+1} \gamma_{i,j,k} \sum_{m=0}^{\infty} \frac{(t\lambda_k)^m}{m!} + \gamma_{i,j,1}, \quad \text{since } \lambda_1 = 0 \\ &= \sum_{k=2}^{N+M+1} \gamma_{i,j,k} e^{\lambda_k t} + \gamma_{i,j,1} \\ &= \sum_{k=2}^{N+M+1} \frac{\sum_{m=1}^{N+M+1} W_{k,m} (K^m)_{ij}}{\lambda_k} e^{\lambda_k t} + \gamma_{i,j,1}. \end{aligned} \quad (23)$$

Here note that $\gamma_{i,j,1}$ is the equilibrium value of $P_{i,j}(t)$ as $t \rightarrow \infty$, since all $\lambda_k < 0$, $k \geq 2$, and if a deterministic initial condition $\mathbf{p}(0) = \mathbf{e}_1$ is given, $\gamma_{i,j,1}$ is explicitly computed as follows (see Sect. 3.3 for details);

$$\gamma_{i,j,1} = \frac{\left(\prod_{k=i}^{N+M} \beta_k \right) \left(\prod_{k=1}^{i-1} \alpha_k \right)}{\sum_{j=0}^{N+M} \left(\prod_{k=1}^j \alpha_k \right) \left(\prod_{k=j+1}^{N+M} \beta_k \right)}.$$

Thus, for a given initial condition $p(0)$, i -th entry of the solution $p(t)$ is

$$\begin{aligned} p_i(t) &= \sum_{j=1}^{N+M+1} \sum_{k=2}^{N+M+1} \gamma_{i,j,k} e^{\lambda_k t} p_j(0) + \sum_{j=1}^{N+M+1} \gamma_{i,j,1} p_j(0) \\ &= \sum_{j=1}^{N+M+1} \sum_{k=2}^{N+M+1} \frac{\sum_{m=1}^{N+M+1} W_{k,m} K_{ij}^m}{\lambda_k} e^{\lambda_k t} p_j(0) + \sum_{j=1}^{N+M+1} \gamma_{i,j,1} p_j(0). \end{aligned} \quad (24)$$

Especially, if a deterministic condition $\mathbf{p}(0) = \mathbf{e}_1$ is given, then

$$p_i(t) = \sum_{k=1}^{N+M+1} \gamma_{i,1,k} e^{\lambda_k t} = \sum_{k=1}^{N+M+1} \frac{\sum_{m=1}^{N+M+1} W_{k,m} (K^m)_{i1}}{\lambda_k} e^{\lambda_k t} + \gamma_{i,1,1}. \quad (25)$$

To find the eigenvalues λ_k in Eqs. (24) and (25), we consider a recursive formula for finding the determinant of a tridiagonal $n \times n$ matrix G [5]:

$$\det G = g_{n,n} \det G_{n-1} - g_{n,n-1} g_{n-1,n} \det G_{n-2}, \quad (26)$$

where $g_{i,j}$ denotes (i, j) th component of G and G_i denotes the submatrix formed by the first i rows and the first i columns of G . From the recursive formula (26) of a tridiagonal matrix, one can obtain recursive equations of the eigenvalues as follows; Let the characteristic polynomial $f_{N+M+1}(\lambda)$ of K be $f_{N+M+1}(\lambda) \equiv \det(\lambda I_{N+M+1} - K)$ and let the characteristic polynomial $f_i(\lambda)$ of the submatrix K_i be $f_i(\lambda) \equiv \det(\lambda I_i - K_i)$ for each $i = 1, \dots, N + M$. Since all matrices $(\lambda I_i - K_i)$ are tridiagonal, we have recursive formulas for $f_{N+M+1}(\lambda)$

$$f_{N+M+1}(\lambda) = -(\beta_{N+M} + \lambda) f_{N+M}(\lambda) - \alpha_{N+M} \beta_{N+M} f_{N+M-1}(\lambda) \quad (27)$$

$$f_i(\lambda) = -(\alpha_i + \beta_{i-1} + \lambda) f_{i-1}(\lambda) - \alpha_{i-1} \beta_{i-1} f_{i-2}(\lambda), \quad i = 3, \dots, N + M \quad (28)$$

$$f_2(\lambda) = (\alpha_2 + \beta_1 + \lambda)(\alpha_1 + \lambda) - \alpha_1 \beta_1, \quad f_1(\lambda) = -\alpha_1 - \lambda. \quad (29)$$

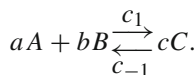
By solving the recursive formulas, one can find all eigenvalues of K .

In the next section, we focus on fundamental nonlinear reactions. Note that after identifying α_i and β_i , one can find the expression (23) of the solution of the bimolecular reactions.

3.2 Special cases of reversible reactions

In this section, we study some special cases of the reversible reactions in Sect. 3.1. We denote the initial number of species A , B and C by a_0 , b_0 and c_0 , respectively.

(Case I) Consider



$$S_i = (a_0 + Na - (i-1)a, b_0 + Nb - (i-1)b, c_0 - Nc + (i-1)c),$$

and for $i = 1, \dots, N + M$,

$$\alpha_i = c_1 \binom{a_0 + Na - (i-1)a}{a} \binom{b_0 + Nb - (i-1)b}{b}, \quad \beta_i = c_{-1} \binom{c_0 - (N-i)c}{c}.$$

Here M is the largest positive integer that satisfies $M \leq \min\{\frac{a_0}{a}, \frac{b_0}{b}\}$, and N is the largest positive integer that satisfies $N \leq \frac{c_0}{c}$.

(Case II) Consider

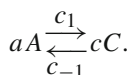


Table 2 Typical reversible bimolecular reactions

Type of reactions	Values of $S_i, i = 1, \dots, N + M + 1$ and $\alpha_i, \beta_i, i = 1, \dots, N + M$	
(I) $A + B \xrightleftharpoons[c_{-1}]{c_1} C$	S_i	$(a_0 + N - i + 1, b_0 + N - i + 1, c_0 - N + i - 1)$
	α_i	$c_1(a_0 + N - i + 1)(b_0 + N - i + 1)$
	β_i	$c_{-1}i$
	M, N	$M = \min\{a_0, b_0\}, N = c_0$
(II) $A + B \xrightleftharpoons[c_{-1}]{c_1} C + D$	S_i	$(a_0 + N - i + 1, b_0 + N - i + 1, c_0 - N + i - 1, d_0 - N + i - 1)$
	α_i	$c_1(a_0 + N - i + 1)(b_0 + N - i + 1)$
	β_i	$c_{-1}(c_0 - N + i)(d_0 - N + i)$
	M, N	$M = \min\{a_0, b_0\}, N = \min\{c_0, d_0\}$
(III) $2A \xrightleftharpoons[c_{-1}]{c_1} C$	S_i	$(a_0 + 2(N - i + 1), c_0 + i - 1 - N)$
	α_i	$\frac{c_1}{2}(a_0 + 2(N - i + 1))(a_0 + 2(N - i + 1))$
	β_i	$c_{-1}i$
	M, N	$M = \frac{a_0}{2}(\text{even } a_0), M = \frac{a_0-1}{2}(\text{odd } a_0), N = c_0$
(IV) $2A \xrightleftharpoons[c_{-1}]{c_1} C + D$	S_i	$(a_0 + 2(N - i + 1), c_0 + i - 1 - N, d_0 + i - 1 - N)$
	α_i	$\frac{c_1}{2}(a_0 + 2(N - i + 1))(a_0 + 2(N - i + 1))$
	β_i	$c_{-1}(c_0 + i - N)(d_0 + i - N)$
	M, N	$M = \frac{a_0}{2}(\text{even } a_0), M = \frac{a_0-1}{2}(\text{odd } a_0), N = \min\{c_0, d_0\}$

All accessible states S_i of Markov chain and the propensities α_i, β_i are identified for each type of reversible reactions. Using this table and Eqs. (24) and (25), one can find the exact transient probability solution of the reaction

We denote, for $i = 1, \dots, N + M + 1$,

$$S_i = (a_0 + Na - (i - 1)a, c_0 - Nc + (i - 1)c),$$

and for $i = 1, \dots, N + M$,

$$\alpha_i = c_1 \binom{a_0 + Na - (i - 1)a}{a}, \quad \beta_i = c_{-1} \binom{c_0 - (N - i)c}{c}.$$

Here M is the largest positive integer that satisfies $M \leq \frac{a_0}{a}$, and N is the largest positive integer that satisfies $N \leq \frac{c_0}{c}$.

In Table 2, we summarize four typical but important stochastic bimolecular reactions. Details are given in Appendix.

3.3 Equilibrium solution

Equilibrium probability distribution describes how the stochastic dynamics of a chemical reaction network are balanced at the end. It is a challenging problem to find analytic solutions of equilibrium probability for nonlinear reactions [2, 3, 8]. The equilibrium probability solutions of general bimolecular reactions can be obtained as explicit expressions by using linear operator theory and finding the term $a_{i,j,1}$ of the exact transient probability solution (23) in Sect. 3.1. Since the matrix K is diagonalizable, one can write from linear operator theory [9],

$$K = \sum_k (\lambda_k Q_k),$$

where Q_k is the eigenprojection corresponding to the eigenvalue λ_k that is defined as

$$Q_k = -\frac{1}{2\pi i} \int_{C_k} R(\lambda, K) d\lambda,$$

where C_k is a positively-oriented small circle enclosing λ_k but excluding other eigenvalues of K , and $R(\lambda_k)$ is the resolvent of K defined as $R(\lambda, K) = (K - \lambda I)^{-1}$. Since

$$P(t) = e^{Kt} = \sum_k e^{\lambda_k t} Q_k,$$

and $\lambda_k < 0$ except $\lambda_1 = 0$, $\lim_{t \rightarrow \infty} P(t) = Q_1$ at the equilibrium. Here Q_1 is the eigenprojection of the zero eigenvalue, and it is known from linear operator theory and Markov chain theory that Q_1 can be computed by $Q_1 = \Pi E$ [9]. Here Π is the $(N + M + 1) \times 1$ matrix, which is same as the column vector $\mathbf{p}(\infty)$ and E is the $1 \times (N + M + 1)$ matrix, which is same as the row vector of ones, i.e.

$$\Pi = \begin{bmatrix} p_1(\infty) \\ p_2(\infty) \\ \vdots \\ p_{N+M+1}(\infty) \end{bmatrix} \quad \text{and} \quad E = [1, 1, \dots, 1].$$

Thus, from Eq. (23), one obtains

$$\lim_{t \rightarrow \infty} P_{ij}(t) = a_{i,j,1} = (Q_1)_{i,j} = (\Pi E)_{i,j} = p_j(\infty).$$

Moreover, if a deterministic initial condition $\mathbf{p}(0) = \mathbf{e}_1$ is given, one can find the equilibrium probability $\mathbf{p}(\infty)$ explicitly; It is known that the exact solution is written as

$$\mathbf{p}(t) = \sum_{i=1}^{N+M+1} e^{\lambda_i t} (\mathbf{u}_i^*)_1 \mathbf{u}_i, \quad (30)$$

where $(\mathbf{u}_i^*)_1$ is the first entry of \mathbf{u}_i^* for a given deterministic initial condition $\mathbf{p}(0) = \mathbf{e}_1$ [10]. Thus, in Eq. (30), as $t \rightarrow \infty$, one obtains the solution at equilibrium

$$\mathbf{p}(\infty) = \lim_{t \rightarrow \infty} \mathbf{p}(t) = (\mathbf{u}_1^*)_1 \mathbf{u}_1, \quad (31)$$

where \mathbf{u}_1 and \mathbf{u}_1^* are eigenvectors of K and K^T corresponding to 0 eigenvalue. Since $\mathbf{u}_1 \equiv (u_1, \dots, u_{N+M+1})^T$ is the eigenvector corresponding to $\lambda_1 = 0$, one has

$$K\mathbf{u}_1 = 0. \quad (32)$$

If one solves Eq. (32), one can find a recursive formula

$$u_{i+1} = \frac{\alpha_i}{\beta_i} u_i,$$

for each $i = 1, \dots, N + M$. Thus, for each i ,

$$u_i = \frac{\alpha_{i-1}\alpha_{i-2} \cdots \alpha_1}{\beta_{i-1}\beta_{i-2} \cdots \beta_1} u_1.$$

By choosing $u_1 = 1$ and using $\sum_i p_i(\infty) = 1$, we can obtain

$$1 = (\mathbf{u}_1^*)_1 \sum_{i=1}^{N+M+1} u_i = (\mathbf{u}_1^*)_1 \left(1 + \frac{\alpha_1}{\beta_1} + \cdots + \frac{\alpha_{N+M}\alpha_{N+M-1} \cdots \alpha_1}{\beta_{N+M}\beta_{N+M-1} \cdots \beta_1} \right).$$

Thus,

$$(\mathbf{u}_1^*)_1 = \frac{1}{A},$$

where

$$A = \left(1 + \frac{\alpha_1}{\beta_1} + \cdots + \frac{\alpha_{N+M}\alpha_{N+M-1} \cdots \alpha_1}{\beta_{N+M}\beta_{N+M-1} \cdots \beta_1} \right). \quad (33)$$

Therefore, the equilibrium probability of the state i is

$$p_i(\infty) = \frac{1}{A} \left(\frac{\alpha_{i-1}\alpha_{i-2} \cdots \alpha_1}{\beta_{i-1}\beta_{i-2} \cdots \beta_1} \right),$$

or using (33), one obtains

Table 3 Equilibrium probability of reversible bimolecular reactions

Type of reactions	Equilibrium probability $p_i = \frac{Q}{P}$	
(I) $A + B \xrightleftharpoons[c_{-1}]{c_1} C$	Q	$(c_1)^{i-1} (c_{-1})^{N+M+1-i} \left[\prod_{k=i}^{N+M} (c_0 - N + k) \right]$ $\left[\prod_{k=1}^{i-1} (a_0 + N - k + 1)(b_0 + N - k + 1) \right]$ $P \sum_{j=0}^{N+M} \left((c_1)^j (c_{-1})^{N+M-j} \left[\prod_{k=1}^j (a_0 + N - k + 1)(b_0 + N - k + 1) \right] \right.$ $\left. \left[\prod_{k=j+1}^{N+M} (c_0 - N + k) \right] \right)$
(II) $A + B \xrightleftharpoons[c_{-1}]{c_1} C + D$	Q	$(c_1)^{i-1} (c_{-1})^{N+M+1-i} \left[\prod_{k=i}^{N+M} (c_0 - N + k)(d_0 - N + k) \right]$ $\left[\prod_{k=1}^{i-1} (a_0 + N - k + 1)(b_0 + N - k + 1) \right]$ $P \sum_{j=0}^{N+M} \left((c_1)^j (c_{-1})^{N+M-j} \left[\prod_{k=1}^j (a_0 + N - k + 1)(b_0 + N - k + 1) \right] \right.$ $\left. \left[\prod_{k=j+1}^{N+M} (c_0 - N + k)(d_0 - N + k) \right] \right)$
(III) $2A \xrightleftharpoons[c_{-1}]{c_1} C$	Q	$(c_1/2)^{i-1} (c_{-1})^{N+M+1-i} \left[\prod_{k=i}^{N+M} (c_0 - N + k) \right]$ $\left[\prod_{k=1}^{i-1} (a_0 + 2(N - k + 1))(a_0 + 2(N - k) + 1) \right]$ $P \sum_{j=0}^{N+M} \left((c_1/2)^j (c_{-1})^{N+M-j} \left[\prod_{k=1}^j (a_0 + 2(N - k + 1))(a_0 + 2(N - k) + 1) \right] \right.$ $\left. \left[\prod_{k=j+1}^{N+M} (c_0 - N + k) \right] \right)$
(IV) $2A \xrightleftharpoons[c_{-1}]{c_1} C + D$	Q	$(c_1/2)^{i-1} (c_{-1})^{N+M+1-i} \left[\prod_{k=i}^{N+M} (c_0 - N + k)(d_0 - N + k) \right]$ $\left[\prod_{k=1}^{i-1} (a_0 + 2(N - k + 1))(a_0 + 2(N - k) + 1) \right]$ $P \sum_{j=0}^{N+M} \left((c_1/2)^j (c_{-1})^{N+M-j} \left[\prod_{k=1}^j (a_0 + 2(N - k + 1))(a_0 + 2(N - k) + 1) \right] \right.$ $\left. \left[\prod_{k=j+1}^{N+M} (c_0 - N + k)(d_0 - N + k) \right] \right)$

Using Table 3, one can find the explicit expression for equilibrium probability p_i of each state S_i described in Table 2

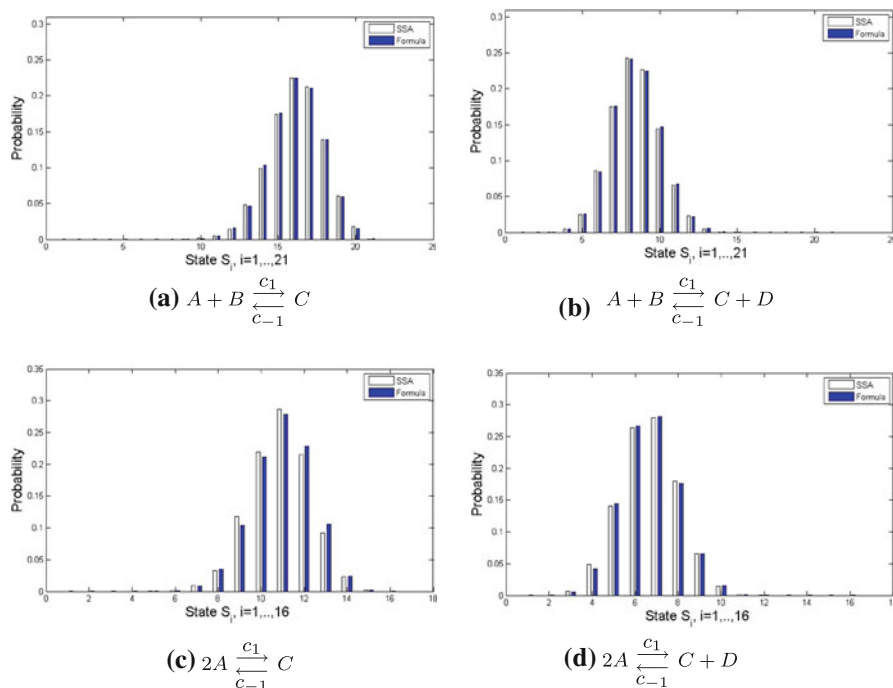


Fig. 2 Equilibrium probabilities of each case of Table 2, obtained by exact formulas in Table 2 and the direct method of stochastic simulation algorithm (SSA). $c_1 = 1s^{-1}$, $c_{-1} = 5s^{-1}$. Initial conditions are **a** $\mathbf{n}(0) = (30, 20, 0)$, **b** $\mathbf{n}(0) = (30, 20, 0, 0)$, **c** $\mathbf{n}(0) = (30, 0)$, **d** $\mathbf{n}(0) = (30, 0, 0)$. The states S_i are **a** $S_i = (30 - i + 1, 20 - i + 1, i - 1)$, $i = 1, \dots, 21$, **b** $S_i = (30 - i + 1, 20 - i + 1, i - 1, i - 1)$, $i = 1, \dots, 21$, **c** $S_i = (30 - 2(i - 1), i - 1)$, $i = 1, \dots, 16$, and **d** $S_i = (30 - 2(i - 1), i - 1, i - 1)$, $i = 1, \dots, 16$. The results by SSA are based on 10,000 realizations

$$p_i(\infty) = \frac{\left(e \prod_{k=i}^{N+M} \beta_k \right) \left(\prod_{k=1}^{i-1} \alpha_k \right)}{\sum_{j=0}^{N+M} \left(\prod_{k=1}^j \alpha_k \right) \left(\prod_{k=j+1}^{N+M} \beta_k \right)}, \quad (34)$$

for each $i = 1, \dots, N + M + 1$. Equation (34) can be used for finding any equilibrium probability of any type of reversible reactions $aA + bB \rightleftharpoons cC + dD$. Especially, in Table 3, we present the explicit expression for the equilibrium probability of the four bimolecular reactions in Table 2 by using (34). In Fig. 2, we compare the equilibrium probability of the four reactions under certain initial conditions.

4 Conclusion

In this paper, we presented the analytic methods for finding the solutions of stochastic master equations for a class of nonlinear reactions including typical bimolecular reactions such as binding and dimerization. We found the explicit formulas for time-dependent probability solution and equilibrium probability solution from chemical master equation of bimolecular reactions. The results can be used for finding exact

analytic solutions of the stochastic master equations for a class of bimolecular reactions without stochastic simulation. We expect that the methods presented in this paper will be helpful for analyzing complex reaction networks with nonlinear reactions.

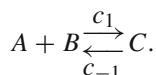
Acknowledgments C. H. Lee acknowledges that this work was supported by 2009 Research Fund of the UNIST (Ulsan National Institute of Science and Technology) and Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology(2011-0027047). The authors thank the reviewers for very useful comments on this paper.

Appendix

Important bimolecular reactions

(Case I) $A + B \rightleftharpoons C$

First we consider a reaction system



Suppose the initial condition $\mathbf{n}(0) = (a_0, b_0, c_0)$. Since there is a symmetry of A and B in the system, without loss of generality, we can assume $a_0 \geq b_0$. Transitions between all states are described by a Markov chain

$$(a_0, b_0, 0) \xrightleftharpoons{\quad} (a_0 - 1, b_0 - 1, 1) \xrightleftharpoons{\quad} (a_0 - 2, b_0 - 2, 2) \xrightleftharpoons{\quad} \cdots \\ \xrightleftharpoons{\quad} (a_0 - b_0, 0, b_0).$$

We define S_i as the state $(a_0 + c_0 - i + 1, b_0 + c_0 - i + 1, i - 1)$ for each $i = 1, \dots, b_0 + c_0 + 1$. By defining $\alpha_i = c_1(a_0 + c_0 - i + 1)(b_0 + c_0 - i + 1)$ and $\beta_i = c_{-1}i$, i.e., α_i = the transition rate from the state S_i to S_{i+1} and β_i = the transition rate from S_{i+1} into S_i , we have the Markov chain

$$S_1 \xrightleftharpoons[\beta_1]{\alpha_1} S_2 \xrightleftharpoons[\beta_2]{\alpha_2} \cdots \xrightleftharpoons[\beta_{n-1}]{\alpha_{n-1}} S_n,$$

where $n = b_0 + c_0 + 1$.

(Case II): $A + B \rightleftharpoons C + D$

Suppose the initial condition $\mathbf{n}(0) = (a_0, b_0, c_0, d_0)$. Without loss of generality, we assume $a_0 \geq b_0$ and $c_0 \geq d_0$. We define each state $S_i = (a_0 + d_0 - i + 1, b_0 + d_0 - i + 1, c_0 - d_0 + i - 1, i - 1)$ for $i = 1, 2, \dots, b_0 + d_0 + 1$. Then one can see a Markov chain

$$S_1 \xrightleftharpoons[\beta_1]{\alpha_1} S_2 \xrightleftharpoons[\beta_2]{\alpha_2} \cdots \xrightleftharpoons[\beta_{n-1}]{\alpha_{n-1}} S_n,$$

where $n = b_0 + d_0 + 1$. Thus, the transition rates are

$$\alpha_i = c_1(a_0 + d_0 - i + 1)(b_0 + d_0 - i + 1), \beta_i = c_{-1}(c_0 - d_0 + i)i,$$

for $i = 1, 2, \dots, b_0 + d_0$.

(Case III): $2A \rightleftharpoons C$

Suppose the initial condition $\mathbf{n}(0) = (a_0, c_0)$. Let

$$M = \begin{cases} \frac{a_0}{2}, & \text{if } a_0 \text{ is even} \\ \frac{a_0 - 1}{2}, & \text{if } a_0 \text{ is odd} \end{cases}$$

If we define each state $S_i = (a_0 + 2(c_0 - i + 1), i - 1)$, $i = 1, 2, \dots, M + c_0 + 1$, we obtain a Markov chain

$$S_1 \xrightleftharpoons[\beta_1]{\alpha_1} S_2 \xrightleftharpoons[\beta_2]{\alpha_2} \cdots \xrightleftharpoons[\beta_n]{\alpha_n} S_n,$$

where $n = M + c_0 + 1$. The transition rates are

$$\alpha_i = \frac{c_1}{2}(a_0 + 2(c_0 - i + 1))(a_0 + 2(c_0 - i) + 1), \beta_i = c_{-1}i,$$

for $i = 1, 2, \dots, M + c_0$.

(Case IV): $2A \rightleftharpoons C + D$

Suppose the initial condition $\mathbf{n}(0) = (a_0, c_0, d_0)$ and assume $c_0 \geq d_0$. Let

$$M = \begin{cases} \frac{a_0}{2}, & \text{if } a_0 \text{ is even} \\ \frac{a_0 - 1}{2}, & \text{if } a_0 \text{ is odd} \end{cases}$$

We let each state $S_i = (a_0 + 2(d_0 - i + 1), c_0 - d_0 + i - 1, i - 1)$, $i = 1, 2, \dots, M + d_0 + 1$. Then we have a Markov chain

$$S_1 \xrightleftharpoons[\beta_1]{\alpha_1} S_2 \xrightleftharpoons[\beta_2]{\alpha_2} \cdots \xrightleftharpoons[\beta_{n-1}]{\alpha_{n-1}} S_n,$$

where $n = M + d_0 + 1$. Thus, the transition rates are

$$\alpha_i = \frac{c_1}{2}(a_0 + 2(d_0 - i + 1))(a_0 + 2(d_0 - i) + 1), \beta_i = c_{-1}i(c_0 - d_0 + i),$$

for $i = 1, 2, \dots, M + d_0$.

References

1. D.T. Gillespie, A rigorous derivation of the chemical master equation. *Physica A* **188**, 404–425 (1992)
2. D.A. McQuarrie, Stochastic approach to chemical kinetics. *J. Appl. Probab.* **4**, 413–478 (1967)
3. I.J. Laurenzi, An analytical solution of the stochastic master equation for reversible bimolecular reaction kinetics. *J. Chem. Phys.* **113**, 3315 (2000)
4. O. Wolkenhauer, M. Ullah, W. Kolch, K.-H. Cho, Modelling and simulation of intra cellular dynamics: choosing an appropriate framework. *IEEE Trans. NanoBioSci.* **3**(3), 200–207 (2004)
5. R.A. Horn, C.R. Johnson, *Matrix Analysis* (Cambridge University Press, Cambridge, 1985)
6. M.E.A. El-Mikkawy, Explicit inverse of a generalized Vandermonde matrix. *Appl. Math. Comput.* **146**, 643–651 (2003)
7. A.S. Krishnakumar, Martin Morf, Eigenvalues of a symmetric tridiagonal matrix: a divide-and-conquer approach. *Numerische Mathematik* **48**, 349–368 (1986)
8. C.H. Lee, K. Kim, P. Kim, A moment closure method for stochastic reaction networks. *J. Chem. Phys.* **130**, 134107 (2009)
9. T. Kato, *Perturbation Theory for Linear Operators* (Springer, Berlin, 1976)
10. C. Gadgil, C.H. Lee, H.G. Othmer, A stochastic analysis of first-order reaction networks. *Bull. Math. Biol.* **67**, 901–946 (2005)