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ORIGINAL PAPER

A reduction method for multiple time scale stochastic reaction networks

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Abstract In this paper we develop a reduction method for multiple time scale stochastic reaction networks. When the transition-rate matrix between different states of the species is available, we obtain systems of reduced equations, whose solutions can successively approximate, to any degree of accuracy, the exact probability that the reaction system be in any particular state. For the case when the transition-rate matrix is not available, one needs to rely on the chemical master equation. For this case, we obtain a corresponding reduced master equation with first-order accuracy. We illustrate the accuracy and efficiency of both approaches by simulating several motivating examples and comparing the results of our simulations with the results obtained by the exact method. Our examples include both linear and nonlinear reaction networks as well as a three time scale stochastic reaction-diffusion model arising from gene expression.

Keywords Multiple time scale analysis · Chemical master equation · Stochastic simulation · Stochastic reaction-diffusion

1 Introduction

At thermal equilibrium, the evolution of a family of chemically reacting species is often described by a system of nonlinear ordinary differential equations of the form

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$$\frac{d\mathbf{c}}{dt} = VR(\mathbf{c}) \tag{1.1}$$

where $\mathbf{c}$ is an s-dimensional vector whose ith component is the concentration of species i, V is the *stoichiometric matrix* whose (i, j)th component represents the change of the stoichiometric amount of species i by the occurrence of reaction j, and $R(\mathbf{c})$ denotes the reaction rate function which is determined by mass-action kinetics. However, if some of the species consist of only a small number of molecules, then the stochastic fluctuations inherent in the molecular interactions may affect the dynamics of the system [10]. To capture these effects, one needs to model these species as a discrete random variable.

Let $n_i(t)$ denote the number of molecules of species i at time t and let $\mathbf{n}(t) = (n_1(t), n_2(t), \ldots, n_s(t))$ be a random vector with joint probability density $p(\mathbf{n}, t)$. For a system with r reactions, the *master equation* [6], which governs the evolution of $p(\mathbf{n}, t)$ is

$$\frac{dp(\mathbf{n}, t)}{dt} = \sum_{\ell=1}^{r} \left[Q_\ell(\mathbf{n} - V_\ell)p(\mathbf{n} - V_\ell, t) - Q_\ell(\mathbf{n})p(\mathbf{n}, t)\right] \tag{1.2}$$

where V_ℓ is the ℓth column of V and Q_ℓ is the *propensity function* of the ℓth reaction defined by

$$Q_\ell(\mathbf{n}) = c_\ell h_\ell(\mathbf{n})\,. \tag{1.3}$$

In (1.3), $c_\ell\,\Delta t$ is the probability that the ℓth-reaction occurs during the time interval $(t, t + \Delta t)$ and $h_\ell(\mathbf{n})$ is formed from the product of the reactants involved in the ℓth-reaction according to mass-action kinetics.

The master equation can also be written as a system of linear equations by writing down the *state diagram* which contains all the accessible states of $\mathbf{n}$ and the transition rates between them. Let $\mathbf{m}$ denote the k possible states of $\mathbf{n}$ and let $\mathbf{p}(t)$ be the k-vector with $p_i(t) = \mathrm{Prob}\{\mathbf{n}(t) = \mathbf{m}^i\}$, where $\mathbf{m}^i$ denotes ith state of $\mathbf{n}$. Then $\mathbf{p}$ satisfies the *Kolmogorov system*

$$\frac{d\mathbf{p}(t)}{dt} = K\,\mathbf{p}(t) \tag{1.4}$$

where K is the *transition-rate matrix* defined, for $i \neq j$, by

$$K_{ij} = \begin{cases} Q_\ell(\mathbf{n}) & \text{if} \quad \mathbf{m}^i = \mathbf{m}^j + V_\ell \text{ for some} \quad \ell = 1, \ldots, r \\ 0 & \qquad\qquad\qquad \text{otherwise} \end{cases} \tag{1.5}$$

and $K_{jj} = -\sum_{i \neq j} K_{ij}$. In (1.5), $\mathbf{m}^i = \mathbf{m}^j + V_\ell$ means that state $\mathbf{m}^i$ is accessible from state $\mathbf{m}^j$ by the occurrence of reaction ℓ.

Remark 1 A matrix K with the properties that $K_{ij} \geq 0$ for $i \neq j$ and $\sum_i K_{ij} = 0$ for all j is called a *Markov chain generator*. A vector $\mathbf{p}$ is called a *probability vector* if

$p_i \geq 0$ and $\sum p_i = 1$. Clearly if K is a Markov chain generator, then $\mathbf{1} = (1, \ldots, 1)$ is a left eigenvector corresponding to the eigenvalue 0. Furthermore, if K is irreducible, then 0 is a simple eigenvalue and the corresponding right eigenvector may be chosen to be a probability vector. This is well-known and can be proved from the Gerschgorin and Perron-Frobenius theorems. If K is a Markov chain generator and $\mathbf{p}$ is the solution to (1.4) with $\mathbf{p}(0)$ a probability vector, then $\mathbf{p}(t)$ is a probability vector for $t > 0$ [3, ch. 4.2]. The random vector $\mathbf{n}(t)$ is a *continuous-time Markov chain with discrete states*.

The solution of (1.4), namely $\mathbf{p}(t) = e^{Kt}\mathbf{p}(0)$, is difficult or impossible to compute if K is large or if it is infinite dimensional when there are infinitely many states. Therefore, one often resorts to the study of (1.2). The simulation of the master equation by Monte Carlo method is well known to be slow and inefficient. However, in many reaction networks, reactions may occur at different time scales and one can often exploit these properties to obtain an efficient and accurate approximation to the solutions of (1.2) and (1.4) [2,11,12,16,17]. All these references are based on the quasi-steady-state or similar assumption applied to stochastic systems. For example, Peleš et al. presented a finite state projection method and obtained an approximate master equation on slow time scale for certain linear reaction systems [11]. Cao et al. presented a slow time scale stochastic simulation algorithm for reaction systems and illustrated numerical results for a system with one independent fast species [2].

The purpose of this paper is to develop a reduction method for certain multiple time scale reaction networks with bounded state space[1] and illustrate how the reduction method, described in Theorems 1 and 2, can be applied to simulate real systems accurately and efficiently. For two time scale networks, the main assumption in Theorems 1 and 2 is that all components of the fast subsystem are strongly connected. Our reduction method may also be applied to three or more time scale reaction networks. We illustrate this by considering a stochastic reaction-diffusion model in Sect. 4.4.

There is a large body of recent literature on the simulations of two time scale stochastic reaction networks (see the references at the end of this paper). Our contribution is that we obtain a reduction method that can be applied to both linear and nonlinear, two or higher time scale systems. Our reduction method formally gives an approximation of the exact solution with error $O(\epsilon^i)$ for any $i = 1, 2, \ldots$, so that the approximation can be as accurate as desired. To the best of our knowledge, such reduction method has not been reported in the chemical reaction network literature before. Also, regarding diffusion as a medium time scale reaction and applying reduction method to simulate the resulting three time scale problem has not been done before. The usual way of handling diffusion in a stochastic system is given in [15]. All the networks considered in this paper, with the exception of Sect. 3.4, are nonlinear. Linear systems have been considered by Gadgil et al. [4].

The organization of the paper is as follows. Section 2 contains the development of our reduction method and the proofs of Theorems 1 and 2. The numerical implementation of the reduction method is explained in Sect. 3. Section 4 contains four examples to illustrate the efficiency and accuracy of the reduction method.

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[1] Every closed reaction network has bounded state space. Closed here means no molecules are being added to or removed from a system. However, a system with bounded state space is not necessarily closed, e.g. $A \rightleftarrows B \rightarrow \phi$.

We end this section by introducing some notations. For the rest of this paper, vectors are boldfaced and assumed vertical, $\mathbf{1}_m^T = [1, \ldots, 1]$ denotes a vector with m ones, matrices are capitalized, I_m is the identity matrix of size m, $\mathcal{N}(A)$ and $\mathcal{R}(A)$ denote the null space and range of the matrix A, respectively, and zero eigenvector means the eigenvector corresponding to the zero eigenvalue.

2 Multiple time scale stochastic reaction networks

We first consider the two time scale case. Let $0 < \epsilon \ll 1$ be the separation parameter between the two time scales. We assume that (1.1) can be written as

$$\frac{d\mathbf{c}}{dt} = \frac{1}{\epsilon} V^f R^f(\mathbf{c}) + V^s R^s(\mathbf{c}) \tag{2.1}$$

where R^f and R^s are the fast and slow reaction rate functions and V^f and V^s are the stoichiometric matrices for the fast and slow reactions, respectively. The two time scale master equation takes the form

$$\begin{aligned} \frac{dp(\mathbf{n},t)}{dt} &= \frac{1}{\epsilon} \sum_{\ell} \left[Q_\ell^f(\mathbf{n} - V_\ell^f)\, p(\mathbf{n} - V_\ell^f, t) - Q_\ell^f(\mathbf{n})\, p(\mathbf{n}, t) \right] \\ &\quad + \sum_k \left[Q_k^s(\mathbf{n} - V_k^s)\, p(\mathbf{n} - V_k^s, t) - Q_k^s(\mathbf{n})\, p(\mathbf{n}, t) \right] \end{aligned} \tag{2.2}$$

where Q^f and Q^s are the propensity functions for the fast and slow reactions, respectively. The two time scale system for (1.4) is

$$\frac{d\mathbf{p}(t)}{dt} = \left(\frac{1}{\epsilon} K^f + K^s \right) \mathbf{p}(t) \tag{2.3}$$

where K^f and K^s are the transition-rate matrices for the fast and slow reactions, respectively.

System (2.3), after multiplying throughout by ϵ, is an example of a singular perturbation problem. For such problems, there is usually an initial short period of time where there is a rapid change in $\mathbf{p}$ so that $\epsilon d\mathbf{p}/dt = O(1)$. This period is called the fast time scale. After this short initial period, we enter a long period of slow time scale where $d\mathbf{p}/dt$ is bounded and hence $K^f \mathbf{p} = O(\epsilon)$.

Reduction methods for the two time scale networks are given in the following theorems. The proof of Theorem 2 may be found in [9] but in order for the paper to be self-contained, we outline the proofs assuming that all the components of the fast subsystem are strongly connected. Fast subsystem means the resulting system obtained after removing all the slow reactions in a reaction network and a component of the fast subsystem means a maximal connected subgraph of the graph of the fast subsystem. A component is said to be strongly connected if there is a path from each node in the component to every other node. Note that an isolated node is a strongly connected component.

Remark 2 If we assume that all the components of a fast subsystem are strongly connected, then the state diagram may be decomposed to a collection of *fast components*, say $D_1, D_2, \ldots, D_m$, where within each fast component, only *fast reactions* occur and transformation between two fast components is via a single *slow reaction*. (See Sect. 4.2 for an example.) The transition rate matrix K^f is a block diagonal matrix and each fast component, D_i, gives rise to a block, K_i^f, which is an irreducible matrix and a Markov chain generator. The size of K_i^f is equal to the number of states in D_i. Suppose K^f has m blocks and K_i^f has dimension $m_i \times m_i$. Then clearly $\mathbf{1}_{m_i}^T$ is a left zero eigenvector of K_i^f. Let the right zero eigenvector be denoted by $\mathbf{\Pi}_i$ which, according to Remark 1, may be chosen to be a probability vector. If we pad $\mathbf{\Pi}_i$ with the right number of zeros, then it becomes a zero right eigenvector of K^f. Since 0 is a simple eigenvalue of K_i^f for each i, we conclude that $\mathcal{N}(K^f)$ has dimension m. The total number of states in the state diagram is equal to the sum of all the states in the fast components; i.e. $k = m_1 + \cdots + m_m$. Let $L = \operatorname{diag}(\mathbf{1}_{m_1}^T, \ldots, \mathbf{1}_{m_m}^T)$ which is an $m \times k$ matrix and let $\Pi = \operatorname{diag}(\mathbf{\Pi}_1, \ldots, \mathbf{\Pi}_m)$ which is a $k \times m$ matrix. Then $L\Pi = I_m$ and $LK^f = 0$ since each block of K^f is a Markov chain generator. Here I_m denotes the $m \times m$identity matrix.

In the next theorem, we obtain reduced equations in the slow time scale by utilizing a perturbation analysis.

Theorem 1 *Suppose each component of the fast subsystem is strongly connected. Then one can obtain a sequence of functions* $\{\tilde{\mathbf{r}}_i\,, i = 0, 1, 2, \ldots\}$ *such that in the slow time scale,* $\tilde{\mathbf{r}}_i$ *satisfies the reduced* $m \times m$ *system*

$$\frac{d\tilde{\mathbf{r}}_i}{dt} = LK^s\Pi\tilde{\mathbf{r}}_i + LK^s\mathbf{u}_i, \tag{2.4}$$

where $\mathbf{u}_0 = 0$ *and* $\mathbf{u}_i$ *is the unique solution of*

$$K^f\mathbf{u}_i = \frac{d\mathbf{u}_{i-1}}{dt} + (\Pi L - I)K^s(\mathbf{u}_{i-1} + \Pi\tilde{\mathbf{r}}_{i-1}) \text{ and } L\mathbf{u}_i = 0 \tag{2.5}$$

for $i = 1, 2, \ldots$. *The initial condition for each* $\tilde{r}_i$ *is given by* $\tilde{\mathbf{r}}_0(0) = L\mathbf{p}(0)$ *and* $\tilde{\mathbf{r}}_i(0) = 0$ *for* $i \geq 1$. *Furthermore, in the slow time scale, the error between the solutions of* (2.4) *and* (2.3) *is given formally by*

$$\|\sum_{k=0}^{i}\epsilon^k(\mathbf{u}_k + \Pi\tilde{\mathbf{r}}_k) - \mathbf{p}\| \approx O(\epsilon^{i+1})\,, \quad i = 0, 1, 2, \ldots. \tag{2.6}$$

Proof System (2.3) is a singular perturbation problem. After an initial time period of order ϵ, the fast reactions are in equilibrium and we consider the outer expansion $\mathbf{p}(t) \sim \sum_{i=0}^{\infty}\epsilon^i\mathbf{r}_i(t)$ in the slow time scale. Inserting the outer expansion into system

(2.3) and multiplying the result by ϵ, we obtain

$$\sum_{i=0}^{\infty} \epsilon^{i+1} \frac{d\mathbf{r}_i(t)}{dt} = \sum_{i=0}^{\infty} \epsilon^{i} (K^f + \epsilon K^s)\mathbf{r}_i(t)\,.$$

Comparing the coefficients of the ϵ^i terms, we have

$$\epsilon^0 : 0 = K^f \mathbf{r}_0 \tag{2.7}$$

$$\epsilon^1 : \frac{d\mathbf{r}_0}{dt} = K^s\mathbf{r}_0 + K^f\mathbf{r}_1 \tag{2.8}$$

$$\epsilon^2 : \frac{d\mathbf{r}_1}{dt} = K^s\mathbf{r}_1 + K^f\mathbf{r}_2 \tag{2.9}$$

$$\vdots \quad \vdots$$

$$\epsilon^{i+1} : \frac{d\mathbf{r}_i}{dt} = K^s\mathbf{r}_i + K^f\mathbf{r}_{i+1} \tag{2.10}$$

$$\vdots \quad \vdots$$

Recall the definitions and properties of K^f, L and Π from Remark 2. Let

$$\mathbf{R}^k = \mathcal{N}(K^f) \oplus \mathcal{R}((K^f)^T)\,. \tag{2.11}$$

From (2.7), we have $K^f\mathbf{r_0} = 0$ and thus $\mathbf{r}_0 = \Pi\,\tilde{\mathbf{r}}_0$ for some $\tilde{\mathbf{r}}_0$. Substituting this into (2.8) and multiplying the resulting system by L, we have

$$\frac{d\tilde{\mathbf{r}}_0(t)}{dt} = LK^s\Pi\,\tilde{\mathbf{r}}_0(t). \tag{2.12}$$

The proof of (2.4) for the case $i = 0$ is complete.

To find $\tilde{\mathbf{r}}_1$, from (2.8) and (2.12), we have

$$\begin{aligned} K^f\mathbf{r}_1 &= \frac{d\mathbf{r}_0}{dt} - K^s\mathbf{r}_0 = \Pi\frac{d\tilde{\mathbf{r}}_0}{dt} - K^s\Pi\tilde{\mathbf{r}}_0 = \Pi LK^s\Pi\tilde{\mathbf{r}}_0 - K^s\Pi\tilde{\mathbf{r}}_0 \\ &= (\Pi L - I)K^s\Pi\tilde{\mathbf{r}}_0. \end{aligned} \tag{2.13}$$

Let the right hand side of (2.13) be denoted by $\mathbf{j}_1$. From Remark 2, $L\Pi = I_m$. Hence, $L\mathbf{j}_1 = 0$ which implies that $\mathbf{j}_1 \in \mathcal{R}(K^f)$. Let $\tilde{\mathbf{r}}_1 = L\mathbf{r}_1$ and let $\mathbf{u}_1 = \mathbf{r}_1 - \Pi\tilde{\mathbf{r}}_1$ so that

$$\mathbf{r}_1 = \mathbf{u}_1 + \Pi\tilde{\mathbf{r}}_1. \tag{2.14}$$

Since $K^f\Pi = 0$ and $L\Pi = I_m$, it follows that

$$K^f\mathbf{u}_1 = K^f(\mathbf{r}_1 - \Pi\tilde{\mathbf{r}}_1) = K^f\mathbf{r}_1 = \mathbf{j}_1 \text{ and } L\mathbf{u}_1 = L(\mathbf{r}_1 - \Pi\tilde{\mathbf{r}}_1) = \tilde{\mathbf{r}}_1 - \tilde{\mathbf{r}}_1 = \mathbf{0}.$$

Since the nullspace of each block of K^f has dimension one, one sees that $\mathbf{u}_1$ is the unique solution of the linear systems $K^f\mathbf{x} = \mathbf{j}_1$ and $L\mathbf{x} = 0$. The equations $K^f\mathbf{u}_1 = \mathbf{j}_1$ and $L\mathbf{u}_1 = 0$ are system (2.5) with $i = 1$. After solving for $\mathbf{u}_1$ and multiplying Eq. 2.9 by L, we see that $\tilde{\mathbf{r}}_1$ satisfies the nonhomogeneous reduced system

$$\frac{d\tilde{\mathbf{r}}_1}{dt} = L\frac{d\mathbf{r}_1}{dt} = LK^s\mathbf{r}_1 = LK^s\Pi\tilde{\mathbf{r}}_1 + LK^s\mathbf{u}_1. \tag{2.15}$$

This completes the proof of (2.4) for $i = 1$. For the proof of the case $i = 2$, we first obtain from (2.14), (2.9) and (2.17)

$$\begin{aligned} K^f\mathbf{r}_2 &= \frac{d\mathbf{r}_1}{dt} - K^s\mathbf{r}_1 = \frac{d\mathbf{u}_1}{dt} + \Pi\frac{d\tilde{\mathbf{r}}_1}{dt} - K^s(\mathbf{u}_1 + \Pi\tilde{\mathbf{r}}_1) \\ &= \frac{d\mathbf{u}_1}{dt} + \Pi(LK^s\Pi\tilde{\mathbf{r}}_1 + LK^s\mathbf{u}_1) - K^s(\mathbf{u}_1 + \Pi\tilde{\mathbf{r}}_1) \\ &= \frac{d\mathbf{u}_1}{dt} + (\Pi L - I)K^s\mathbf{u}_1 + (\Pi L - I)K^s\Pi\tilde{\mathbf{r}}_1. \end{aligned} \tag{2.16}$$

Let the right hand side of (2.16) be denoted by $\mathbf{j}_2$. Let $\tilde{\mathbf{r}}_2 = L\mathbf{r}_2$ and let $\mathbf{u}_2 = \mathbf{r}_2 - \Pi\tilde{\mathbf{r}}_2$. Then

$$K^f\mathbf{u}_2 = K^f(\mathbf{r}_2 - \Pi\tilde{\mathbf{r}}_2) = K^f\mathbf{r}_2 = \mathbf{j}_2 \text{ and } L\mathbf{u}_2 = L(\mathbf{r}_2 - \Pi\tilde{\mathbf{r}}_2) = \tilde{\mathbf{r}}_2 - \tilde{\mathbf{r}}_2 = \mathbf{0}.$$

Hence $\mathbf{u}_2$ is the unique solution of linear systems $K^f\mathbf{x} = \mathbf{j}_2$ and $L\mathbf{x} = 0$. The equations $K^f\mathbf{u}_2 = \mathbf{j}_2$ and $L\mathbf{u}_2 = 0$ are system (2.5) with $i = 2$. Multiplying (2.10) for the case $i = 2$ by L, one obtains the reduced equation for $\tilde{\mathbf{r}}_2$

$$\frac{d\tilde{\mathbf{r}}_2}{dt} = L\frac{d\mathbf{r}_2}{dt} = LK^s\mathbf{r}_2 = LK^s\Pi\tilde{\mathbf{r}}_2 + LK^s\mathbf{u}_2, \tag{2.17}$$

which completes the proof of (2.4) for $i = 2$. The proof of cases $i \geq 3$ can be done similarly after defining $\tilde{\mathbf{r}}_i = L\mathbf{r}_i$ and $\mathbf{u}_i = \mathbf{r}_i - \Pi\tilde{\mathbf{r}}_i$ for each $i \geq 3$.

To obtain the initial condition for each $\tilde{\mathbf{r}}_i$, one should consider the matching condition between outer and inner expansions. The formal expression for the inner expansion is given by $\sum_{i=0}^{\infty}\epsilon^i\mathbf{s}_i\left(\frac{t}{\epsilon}\right)$. Substituting this into (2.3), multiplying by ϵ, and letting $\tau = t/\epsilon$, we have

$$\sum_{i=0}^{\infty}\epsilon^i\frac{d\mathbf{s}_i(\tau)}{d\tau} = \sum_{i=0}^{\infty}\epsilon^i(K^f + \epsilon K^s)\mathbf{s}_i(\tau)$$

Comparing the coefficients of ϵ^i, we obtain

$$\epsilon^0 : \frac{d\mathbf{s}_0}{d\tau} = K^f \mathbf{s}_0 \tag{2.18}$$

$$\vdots \quad \vdots$$

$$\epsilon^i : \frac{d\mathbf{s}_i}{d\tau} = K^f \mathbf{s}_i + K^s \mathbf{s}_{i-1} \tag{2.19}$$

$$\vdots \quad \vdots$$

From (2.18), $\frac{dL\mathbf{s}_0}{d\tau} = LK^f\mathbf{s}_0 = 0$ so that $L\mathbf{s}_0(t) = L\mathbf{s}_0(0) = L\mathbf{p}(0)$ for all $t > 0$. Since $\mathbf{r}_0(0) = \mathbf{s}_0(\infty)$, the initial condition for $\tilde{\mathbf{r}}_0$ is given by $\tilde{\mathbf{r}}_0(0) = L\mathbf{r}_0(0) = L\mathbf{p}(0)$. Moreover, for the initial condition to be matched, it should be satisfied that $\mathbf{r}_i(0) = 0$ for all $i \geq 1$. Thus, $\tilde{\mathbf{r}}_i(0) = L\mathbf{r}_i(0) = 0$ for all $i \geq 1$. Formal error estimate (2.6) follows from the outer expansion of $\mathbf{p}(t)$ and the relation $\mathbf{r}_i = \Pi\tilde{\mathbf{r}}_i + \mathbf{u}_i$. The proof of the theorem is complete. □

Remark 3 The assumption of Theorem 1 can be relaxed by only assuming that each fast component D_i has a unique equilibrium probability. This implies that 0 is a simple eigenvalue for each K_i^f and the argument given in Theorem 1 is valid. Note that if each component of the fast subsystem is strongly connected, i.e. if each block K_i^f is irreducible, then each fast component D_i has a unique equilibrium probability. Here is an example of a system for which there is a unique equilibrium probability but K^f is reducible, $A \to B$. Here is an example of a system for which there is not a unique equilibrium probability and the null space of K^f has dimension two, $A \to B,\ A \to C$.

Remark 4 From the paragraph after display (2.3), we see that in the slow time scale, $K^f\mathbf{p} = O(\epsilon)$. Quasi-steady state assumption (QSSA) for system (2.3) means assuming $K^f\mathbf{p} = 0$ which implies that $\mathbf{p} = \Pi\tilde{\mathbf{p}}$. Replacing $\mathbf{p}$ by $\Pi\tilde{\mathbf{p}}$ in system (2.3) and multiplying the result by the matrix L on the left, we obtain the reduced system $d\tilde{\mathbf{p}}/dt = LK^s\Pi\tilde{\mathbf{p}}$. However, QSSA alone cannot yield higher order approximations as given in Theorem 1.

Let A^f be the matrix whose rows form a basis of the vector space $\mathcal{N}((V^f)^T)$ and let $\tilde{\mathbf{n}} = A^f\mathbf{n}$. Then it is easy to see that $\tilde{\mathbf{n}}$ is constant in each fast component and only changes when a slow reaction occurs.

Theorem 2 *Let the hypotheses of Theorem 1 be satisfied. Then the reduced master equation in the slow time scale for* (2.2) *is*

$$\frac{d\tilde{p}(\tilde{\mathbf{n}},t)}{dt} = \sum_{\ell}\left[\tilde{Q}^s_\ell(\tilde{\mathbf{n}} - \tilde{V}^s_\ell)\,\tilde{p}(\tilde{\mathbf{n}} - \tilde{V}^s_\ell, t) - \tilde{Q}^s_\ell(\tilde{\mathbf{n}})\,\tilde{p}(\tilde{\mathbf{n}},t)\right] \tag{2.20}$$

where $\tilde{V}^s = A^f V^s$, $\tilde{Q}^s(\tilde{\mathbf{n}}) = E[Q^s(\mathbf{n})|\tilde{\mathbf{n}}]$, *and* $\tilde{p}(\tilde{\mathbf{n}},t)$ *is the joint density of the random vector* $\tilde{\mathbf{n}}(t)$.

Proof From Remark 2, K^s, which is a sparse matrix, can also be partitioned into blocks and the (i, j)th-block, K^s_{ij}, has dimension $m_i \times m_j$. One can easily show that the matrix $LK^s\Pi$ is a Markov chain generator by using the structures of the matrices L, Π, and a Markov chain generator K^s. The proof of this fact also may be found in [9] and will not be given here. The (i, j)th-component of $LK^s\Pi$ can be computed as follows,

$$\begin{aligned}(LK^s\Pi)_{ij} &= (\mathrm{diag}[\mathbf{1}_{m_1}^T, \ldots, \mathbf{1}_{m_m}^T]\; K^s\; \mathrm{diag}[\mathbf{\Pi}_1, \mathbf{\Pi}_2, \ldots, \mathbf{\Pi}_m])_{ij} \\ &= \mathbf{1}_{m_i}^T \begin{bmatrix} (K_{ij}^s)_{11} & \ldots & (K_{ij}^s)_{1m_j} \\ (K_{ij}^s)_{21} & \ldots & (K_{ij}^s)_{2m_j} \\ \vdots & \vdots & \vdots \\ (K_{ij}^s)_{m_i 1} & \ldots & (K_{ij}^s)_{m_i m_j} \end{bmatrix} \mathbf{\Pi}_j \\ &= \sum_{q=1}^{m_j} \sum_{p=1}^{m_i} (K_{ij}^s)_{pq} (\mathbf{\Pi}_j)_q. \end{aligned} \tag{2.21}$$

Recall from Remark 2 that in a state diagram, each row corresponds to a fast component D_i that has m_i states. The (i, j)th-block of K^s, K_{ij}^s, is the transition rate matrix from the fast component D_j to the fast component D_i by a slow reaction ℓ and its (p, q)th-entry, $(K_{ij}^s)_{pq}$, is the transition rate from the qth-state of D_j to the pth-state of D_i. Hence, given q, the summation over p in (2.21) consists of only one non-zero term. Also, $(\mathbf{\Pi}_j)_q = \mathrm{Prob}(\mathbf{n} = \tilde{\mathbf{n}}^{j,q} | \tilde{\mathbf{n}} = \tilde{\mathbf{n}}^j)$ where $\tilde{\mathbf{n}}^{j,q}$ is the qth-state of D_j. Therefore, from (2.21), we have

$$\begin{aligned}(LK^s\Pi)_{ij} &= \sum_q c_\ell h_\ell(\tilde{\mathbf{n}}^{j,q})\, \mathrm{Prob}(\mathbf{n} = \tilde{\mathbf{n}}^{j,q} | \tilde{\mathbf{n}} = \tilde{\mathbf{n}}^j) \\ &= c_\ell E[h_\ell(\mathbf{n}) | \tilde{\mathbf{n}} = \tilde{\mathbf{n}}^j] \\ &= E[Q_\ell^s(\mathbf{n}) | \tilde{\mathbf{n}} = \tilde{\mathbf{n}}^j]. \end{aligned} \tag{2.22}$$

System (2.12) is the analog of system (1.4) on slow time scale with $LK^s\Pi$ replacing K and the fast components $\{D_1, \ldots, D_m\}$ replacing the states $\{\mathbf{m}_1, \ldots, \mathbf{m}_k\}$. The relationship between the coefficient matrix K in (1.4) and the propensity function Q in (1.2) is given by (1.5). Therefore, $(LK^s\Pi)_{ij} = \tilde{Q}_\ell^s(\tilde{\mathbf{n}})$ if D_j is transformed to D_i via the slow reaction ℓ. From (2.22), $\tilde{Q}_\ell^s(\tilde{\mathbf{n}}) = E[Q_\ell^s(\mathbf{n}) | \tilde{\mathbf{n}}]$. The proof of Theorem 2 is complete. □

Higher time scale reaction networks may be reduced to several two time scale problems. For example, consider the three time scale reaction network

$$\frac{d\mathbf{p}}{dt} = \left(\frac{1}{\epsilon_2} K^f + \frac{1}{\epsilon_1} K^m + K^s \right) \mathbf{p} \tag{2.23}$$

where $0 < \epsilon_2 \ll \epsilon_1 \ll 1$ and $K^f, K^m, K^s \approx O(1)$. The first reduction is to assume that the fast reactions corresponding to $\frac{1}{\epsilon_2} K^f$ is in equilibrium. From Theorem 1, the reduced network is

$$\frac{d\mathbf{p}_1}{dt} = L_1\left(\frac{1}{\epsilon_1}K^m + K^s\right)\Pi_1\mathbf{p}_1 \equiv \left(\frac{1}{\epsilon_1}K_1^m + K_1^s\right)\mathbf{p}_1 \tag{2.24}$$

where L_1 and Π_1 are the matrices formed from the left and right zero eigenvectors of K^f. A second reduction is to assume that the fast reactions corresponding to $\frac{1}{\epsilon_1}K_1^m$ in Eq. 2.24 is in equilibrium. Doing so, we obtain

$$\frac{d\mathbf{p}_2}{dt} = L_2 K_s^1 \Pi_2 \mathbf{p}_2 \tag{2.25}$$

where L_2, Π_2 are matrices formed from the left and right zero eigenvectors of K_1^m.

One can also write Eq. 2.23 as a three time scale master equation

$$\begin{aligned}\frac{dp(\mathbf{n},t)}{dt} &= \frac{1}{\epsilon_2}\sum_i\left[Q_i^f(\mathbf{n}-V_i^f)\,p(\mathbf{n}-V_i^f,t) - Q_i^f(\mathbf{n})\,p(\mathbf{n},t)\right]\\ &\quad+\frac{1}{\epsilon_1}\sum_j\left[Q_j^m(\mathbf{n}-V_j^m)\,p(\mathbf{n}-V_j^m,t) - Q_j^m(\mathbf{n})\,p(\mathbf{n},t)\right]\\ &\quad+\sum_k\left[Q_k^s(\mathbf{n}-V_k^s)\,p(\mathbf{n}-V_k^s,t) - Q_k^s(\mathbf{n})\,p(\mathbf{n},t)\right]\end{aligned} \tag{2.26}$$

where V^f, V^m and V^s are the stoichiometric matrices and Q^f, Q^m and Q^s are the propensity functions for the fast, medium and slow reactions, respectively. Similar to a two time scale system, one can obtain a reduced equation for (2.26). To this end, we need to introduce some notations. We define the medium subsystem of a reaction network as the one obtained when all the fast and slow reactions are removed. Let A^f be a matrix whose rows form a (nonnegative integer valued) basis of $\mathcal{N}(V^f)^T$. Let $\tilde{\mathbf{n}} = A^f\mathbf{n}$, $\tilde{V}^m = A^f V^m$, $\tilde{V}^s = A^f V^s$, $\tilde{Q}^m(\tilde{\mathbf{n}}) = E[Q^m(\mathbf{n})|\tilde{\mathbf{n}}]$, $\tilde{Q}^s(\tilde{\mathbf{n}}) = E[Q^s(\mathbf{n})|\tilde{\mathbf{n}}]$, and let A^m be a matrix whose rows form a (nonnegative integer valued) basis of the vector space $\mathcal{N}((\tilde{V}^m)^T)$.

Theorem 3 *Suppose all the components of the fast and medium subsystems are strongly connected. Then the reduced master equation in the slow time scale for* (2.26) *is*

$$\frac{d\hat{p}(\hat{\mathbf{n}},t)}{dt} = \sum_k\left[\hat{Q}_k^s(\hat{\mathbf{n}}-\hat{V}_k^s)\,\hat{p}(\hat{\mathbf{n}}-\hat{V}_k^s,t) - \hat{Q}_k^s(\hat{\mathbf{n}})\,\hat{p}(\hat{\mathbf{n}},t)\right] \tag{2.27}$$

where $\hat{\mathbf{n}} = A^m\tilde{\mathbf{n}}$, $\hat{V}^s = A^m\tilde{V}^s$, $\hat{Q}_k^s(\hat{\mathbf{n}}) = E[\tilde{Q}_k^s(\tilde{\mathbf{n}})|\hat{\mathbf{n}}]$, *and* $\hat{p}(\hat{\mathbf{n}},t)$ *is the joint density of the random vector* $\hat{\mathbf{n}}(t)$.

Proof By considering the three time scale system as a two time scale system with fast and medium/slow reactions, one can rewrite Eq. 2.26 as

$$\begin{aligned}\frac{dp(\mathbf{n},t)}{dt} &= \frac{1}{\epsilon_2}\sum_i \left[Q_i^f(\mathbf{n}-V_i^f)\,p(\mathbf{n}-V_i^f,t) - Q_i^f(\mathbf{n})\,p(\mathbf{n},t)\right] \\ &\quad + \sum_\ell \left[Q_\ell^{ms}(\mathbf{n}-V_\ell^{ms})\,p(\mathbf{n}-V_\ell^{ms},t) - Q_\ell^{ms}(\mathbf{n})\,p(\mathbf{n},t)\right] \qquad (2.28)\end{aligned}$$

where $V^{ms} = [V^m|V^s]$ and Q_ℓ^{ms} is either the medium propensity function $\frac{1}{\epsilon_1}Q_j^m$ or the slow propensity function Q_k^s, depending on the corresponding stoichiometry. Applying Theorem 2 to Eq. 2.28, we obtain a reduced equation

$$\frac{d\tilde{p}(\tilde{\mathbf{n}},t)}{dt} = \sum_\ell \left[\tilde{Q}_\ell^{ms}(\tilde{\mathbf{n}}-\tilde{V}_\ell^{ms})\,\tilde{p}(\tilde{\mathbf{n}}-\tilde{V}_\ell^{ms},t) - \tilde{Q}_\ell^{ms}(\tilde{\mathbf{n}})\,\tilde{p}(\tilde{\mathbf{n}},t)\right] \qquad (2.29)$$

where $\tilde{V}^{ms} = A^f V^{ms}$, $\tilde{Q}_\ell^{ms}(\tilde{\mathbf{n}}) = E[Q_\ell^{ms}(\mathbf{n})|\tilde{\mathbf{n}}]$ and $\tilde{p}(\tilde{\mathbf{n}},t)$ is the joint density of the random vector $\tilde{\mathbf{n}}(t)$. If we split V^{ms} and Q^{ms} into medium and slow reaction parts, we can rewrite Eq. 2.29 as

$$\begin{aligned}\frac{d\tilde{p}(\tilde{\mathbf{n}},t)}{dt} &= \frac{1}{\epsilon_1}\sum_j \left[\tilde{Q}_j^m(\tilde{\mathbf{n}}-\tilde{V}_j^m)\,\tilde{p}(\tilde{\mathbf{n}}-\tilde{V}_j^m,t) - \tilde{Q}_j^m(\tilde{\mathbf{n}})\,\tilde{p}(\tilde{\mathbf{n}},t)\right] \\ &\quad + \sum_k \left[\tilde{Q}_k^s(\tilde{\mathbf{n}}-\tilde{V}_k^s)\,\tilde{p}(\tilde{\mathbf{n}}-\tilde{V}_k^s,t) - \tilde{Q}_k^s(\tilde{\mathbf{n}})\,\tilde{p}(\tilde{\mathbf{n}},t)\right] \qquad (2.30)\end{aligned}$$

where $\tilde{V}^m$, $\tilde{V}^s$, $\tilde{Q}^m(\tilde{\mathbf{n}})$ and $\tilde{Q}^s(\tilde{\mathbf{n}})$ are defined above. Note that Eq. 2.30 is the master equation of the reduced system obtained after removal of the fast reactions and it is a two time scale master equation. Let A^m be a matrix whose rows form a (nonnegative integer valued) basis of the vector space $\mathcal{N}((\tilde{V}^m)^T)$. Applying Theorem 2 to Eq. 2.30 again, we obtain

$$\frac{d\hat{p}(\hat{\mathbf{n}},t)}{dt} = \sum_k \left[\hat{Q}_k^s(\hat{\mathbf{n}}-\hat{V}_k^s)\,\hat{p}(\hat{\mathbf{n}}-\hat{V}_k^s,t) - \hat{Q}_k^s(\hat{\mathbf{n}})\,\hat{p}(\hat{\mathbf{n}},t)\right] \qquad (2.31)$$

where $\hat{\mathbf{n}}$, $\hat{V}^s$, $\hat{Q}_k^s(\hat{\mathbf{n}})$ and $\hat{p}(\hat{\mathbf{n}},t)$ are defined in the statement of the theorem. The proof of Theorem 3 is complete. □

3 Numerical methods

3.1 Finding the transition probability c_ℓ

We need to find c_ℓ, which is the probability that the ℓth-reaction occurs per unit time, from the reaction rate constant k_ℓ, which is what is usually given. For example, consider the second-order reaction $A + B \rightarrow P$. Then the number of molecules of P

produced per unit time is given by $\#P = c_\ell(\#A)(\#B)$ and the number of moles of P produced per unit time is $[P] = k_\ell[A][B]$. Since $\#X = [X]N_A V$ where N_A is the Avogadro's number and V is the volume, we have $k_\ell = c_\ell/(N_A V)$. Similarly, for the first-order reaction $A \to P$, $k_\ell = c_\ell$ and for the reaction $2A \to P$, $c_\ell = 2k_\ell/(N_A V)$.

3.2 Gillespie algorithm and the τ—leaping method

To simulate the full system (1.2), we follow the recipe in [5]. Suppose the state of the system at time t is $\mathbf{n}(t)$. Let $a_\nu = c_\nu h_\nu$ (see (1.3)) where a_ν is the propensity of νth reaction in the reaction network. Then the probability of the occurrence of the νth-reaction in the time interval $(t, t + dt)$ is $a_\nu(\mathbf{n})\, dt$. If $P_0(\tau)$ is the probability that no reaction occurred in the time interval $(t, t+\tau)$, then $P_0(\tau+d\tau) = P_0(\tau)[1-a_0 d\tau]$ where $a_0 = \sum_{\nu=1}^{r} a_\nu$. This implies that $dP_0/d\tau = -a_0 P_0$, $P_0(0) = 1$. Solving it, we have $P_0(\tau) = \exp[-a_0\tau]$. To find when the next reaction will occur and which one, we generate two random numbers r_1, r_2 from the unit-interval uniform random number generator. Let $\tau = (1/a_0)\ln(1/r_1)$ and let μ be the integer that satisfies $\sum_{\nu=1}^{\mu-1} a_\nu < r_2 a_0 \le \sum_{\nu=1}^{\mu} a_\nu$. Then the next reaction to occur will be reaction μ and it will occur at time $t + \tau$. One must then update $\mathbf{n}(t + \tau)$ from $\mathbf{n}(t)$ using reaction μ and the process is repeated. The same method may be used to simulate (2.20) except that one must find or approximate the propensity function $\tilde{Q}^s(\tilde{\mathbf{n}}) = E[Q^s(\mathbf{n})|\tilde{\mathbf{n}}]$ of the slow reaction which will be discussed in the next section.

While the Gillespie algorithm is exact and very general, it is well known that the algorithm is often computationally very intensive. This is because if a reaction is very fast, then the number of the reaction occurred in a given time interval will be very large. For such a system, the τ-leaping method may be employed to speed up the computations [7].

The τ-leaping method is based on the assumption that there exists $\tau > 0$ such that in the time interval $[t, t + \tau)$, the propensities $a_i(\mathbf{n}(t))$, $i = 1, \ldots, r$ for all reactions do not change appreciably and may be assumed to be constant. If this leaping condition is satisfied, then the number of occurrences of the ith-reaction in $[t, t+\tau)$ is a Poisson random variable with mean $a_i(\mathbf{n}(t))\tau$. The procedure of the tau-leaping formula is as follows:

Step 1: Choose a sample value b_i from the independent Poisson random variable $\mathcal{P}_i(a_i(\mathbf{n}(t)), \tau)$ for each $i = 1, \ldots, r$.
Step 2: Let $\mathbf{n}(t + \tau) = \mathbf{n}(t) + \sum_{i=1}^{r} V_i b_i$.
Step 3: Update $t = t + \tau$ and go back to Step 1.

We shall employ this method in Sect. 4.4.

3.3 Finding $E[Q^s(\mathbf{n}) \,|\, \tilde{\mathbf{n}}]$

We need to find Prob($\mathbf{n} = \tilde{\mathbf{n}}^{j,q} \,|\, \tilde{\mathbf{n}} = \tilde{\mathbf{n}}^{j}$) which is the same as $\mathbf{\Pi}_j$ according to the proof of Theorem 2. If one can construct K^f, then $\mathbf{\Pi}_j$ consists of the zero eigenvectors of K_j^f. If the matrix K^f is not available, then we have to write down the master equation of the fast subsystem and compute the equilibrium distribution as $t \to \infty$. This is because all the eigenvalues of K^f besides the zero eigenvalue, which is simple, are negative so that the solution of $\dot{\mathbf{q}} = K_i^f \mathbf{q}$ converges to $\mathbf{\Pi}_i$ as $t \to \infty$. An example of how to do this for the fast reaction $A + B \rightleftarrows C$ is given in Appendix 1. For many other fast subsystems, finding the equilibrium distribution is difficult if not impossible. For example, consider the fast reactions $A + B \underset{c_{-1}}{\overset{c_1}{\rightleftarrows}} C$ and $A + X \underset{c_{-3}}{\overset{c_3}{\rightleftarrows}} Y$. Let $n_1(t), n_2(t), n_3(t), n_4(t)$ and $n_5(t)$ denote the number of molecules of A, B, C, X and Y at time t, respectively, and let $\mathbf{n}(0) = (a_0, b_0, 0, x_0, 0)$. Then it is clear that $n_1(t) = a_0 - n_3(t) - n_5(t)$, $n_2(t) = b_0 - n_3(t)$, and $n_4(t) = x_0 - n_5(t)$. The master equation for the random vector $\mathbf{n} = (n_3, n_5)$ is

$$\begin{aligned}\frac{dp(\mathbf{n}, t)}{dt} &= c_1\,(a_0 - n_3 - n_5 + 1)(b_0 - n_3 + 1)p(n_3 - 1, n_5, t)\\ &\quad + c_{-1}\,(n_3 + 1)p(n_3 + 1, n_5, t) + c_3\,(a_0 - n_3 - n_5 + 1)(x_0 - n_5 + 1)\\ &\quad \times p(n_3, n_5 - 1, t) + c_{-3}\,(n_5 + 1)p(n_3, n_5 + 1, t) - [\,c_1(a_0 - n_3 - n_5)\\ &\quad \times (b_0 - n_3) + c_{-1}n_3 + c_3(a_0 - n_3 - n_5)(x_0 - n_5) + c_{-3}n_5\,]\,p(\mathbf{n}, t)\end{aligned}$$

with initial condition $p(0, 0) = 1$. The equilibrium distribution is $\lim_{t\to\infty} p(\mathbf{n}, t)$.

Let $G(z_1, z_2, t) = \sum z_1^i z_2^j\, p(i, j, t)$ be the moment generating function of p where the summation is over all non-negative integers i, j. Then $p(m, n, t) = (1/m!n!)\,\partial^{m+n} G(z_1, z_2, t)/\partial z_1^m \partial z_2^n$ evaluated at $z_1 = z_2 = 0$. If we multiply the above master equation by $z_1^i z_2^j$ and sum over all i, j, we obtain a partial differential equation for G. Let us assume that $\tilde{G}(z_1, z_2) = \lim_{t\to\infty} G(z_1, z_2, t)$ exists. Then formally $\tilde{G}$ satisfies the following equation

$$\begin{aligned}&c_1 z_1^2(z_1 - 1)\tilde{G}_{z_1 z_1} + c_3 z_2^2(z_2 - 1)\tilde{G}_{z_2 z_2} + z_1 z_2(c_1 z_1 + c_3 z_2 - c_1 - c_3)\tilde{G}_{z_1 z_2}\\ &+ A(z_1, z_2, c_1, c_{-1}, c_3, c_{-3}, b_0)\tilde{G}_{z_1} + A(z_2, z_1, c_3, c_{-3}, c_1, c_{-1}, x_0)\tilde{G}_{z_2}\\ &+ [c_1 a_0 b_0 z_1 + c_3 a_0 x_0 z_2 - a_0(c_1 b_0 + c_3 x_0)]\tilde{G} = 0\end{aligned}$$

where

$$\begin{aligned}A(z_1, z_2, c_1, c_{-1}, c_3, c_{-3}, b_0) &= c_1(1 - a_0 - b_0)z_1^2 - c_3 x_0 z_1 z_2\\ &\quad + [c_1(a_0 + b_0) - c_{-1} + c_3 x_0 - c_1]z_1 + c_{-1}.\end{aligned}$$

If we try to compute $\partial^{m+n}\tilde{G}/\partial z_1^m \partial z_2^n$, we will run into the so called moment-closure problem. Thus it is difficult to find the equilibrium distribution analytically and it has to be simulated.

3.4 Multiple time scale problems

In the reduction method of a three time scale reaction network, it is essential to compute the reduced propensity function $\hat{Q}_k^s(\hat{\mathbf{n}}) = E[\tilde{Q}_k^s(\tilde{\mathbf{n}})|\hat{\mathbf{n}}]$, where $\tilde{Q}_k^s(\tilde{\mathbf{n}}) = E[Q_k^s(\mathbf{n})|\tilde{\mathbf{n}}]$.

To find $\hat{Q}_k^s(\hat{\mathbf{n}})$, we first compute $\tilde{Q}_k^s(\tilde{\mathbf{n}})$ via a first reduction. This can be done by the computational method for a two time scale system described in the previous section. For the second reduction to compute $\hat{Q}_k^s(\hat{\mathbf{n}}) = E[\tilde{Q}_k^s(\tilde{\mathbf{n}})|\hat{\mathbf{n}}]$, one should note that the variable is not $\mathbf{n}$ but $\tilde{\mathbf{n}}$ after the first reduction. Thus, by replacing $\mathbf{n}$ by $\tilde{\mathbf{n}}$ and applying the argument in the previous section to the first reduced system, one can compute $\hat{Q}_k^s(\hat{\mathbf{n}}) = E[\tilde{Q}_k^s(\tilde{\mathbf{n}})|\hat{\mathbf{n}}]$ after finding the equilibrium probability of the medium subsystem in the first reduced system. Higher multiple time scale problems may be reduced similarly.

4 Applications

4.1 Enzyme-substrate model

This example is used to illustrate Theorem 2. The enzyme-substrate model,

$$E + S \underset{c_{-1}}{\overset{c_1}{\rightleftarrows}} ES \overset{c_2}{\to} E + P, \tag{4.1}$$

is a simple but important nonlinear reaction network. We assume that the reversible reaction between $E+S$ and ES is a fast reaction and the production of P from ES is a slow reaction. Then $V^f = [[-1,-1,1,0]^T, [1,1,-1,0]^T]$ and $V^s = [1,0,-1,1]^T$ and

$$A^f = \begin{bmatrix} 1 & 0 & 1 & 0 \\ 0 & 1 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix}. \tag{4.2}$$

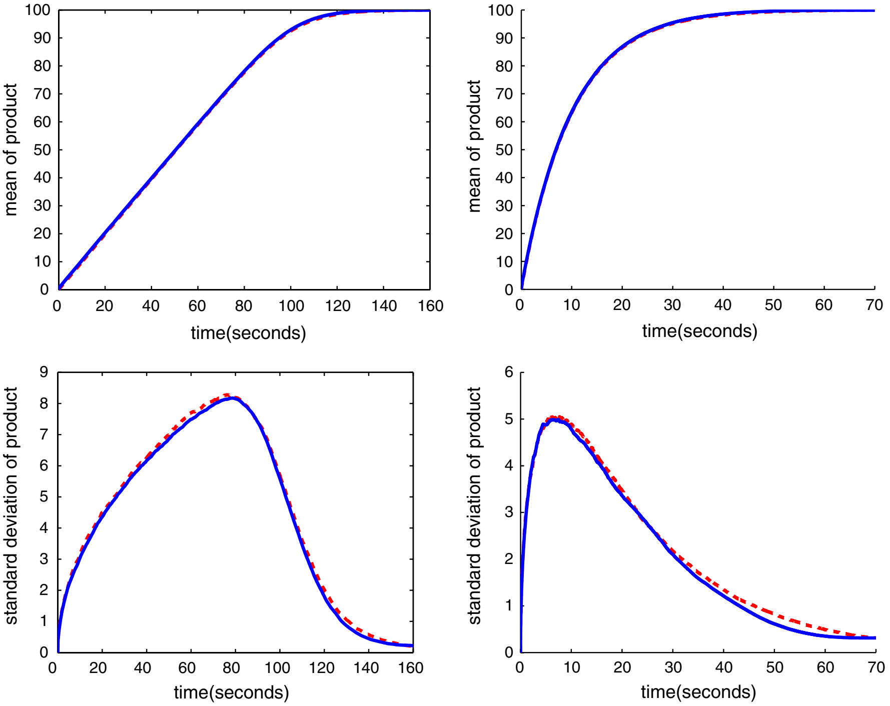
Note that the rows of A^f form a basis of $\mathcal{N}((V^f)^T)$. Let $\tilde{\mathbf{n}} = A^f \mathbf{n} = (n_1 + n_3, n_2 + n_3, n_4)^T$. Then the reduced master equation (2.20) is

$$\begin{aligned} \frac{d\tilde{p}(\tilde{\mathbf{n}}, t)}{dt} &= \sum_\ell \Big\{ E[Q_\ell^s(\mathbf{n} - \tilde{V}_\ell^s) \,|\, \tilde{\mathbf{n}} - \tilde{V}_\ell^s]\, \tilde{p}(\tilde{\mathbf{n}} - \tilde{V}_\ell^s, t) \\ &\quad - E[Q_\ell^s(\mathbf{n}) \,|\, \tilde{\mathbf{n}}]\, \tilde{p}(\tilde{\mathbf{n}}, t) \Big\} \\ &= c_2 E[n_3 | \tilde{\mathbf{n}} - \tilde{V}^s]\, \tilde{p}(\tilde{\mathbf{n}} - \tilde{V}^s, t) - c_2 E[n_3 | \tilde{\mathbf{n}}]\, \tilde{p}(\tilde{\mathbf{n}}, t). \end{aligned} \tag{4.3}$$

Let $\mathbf{n}(0) = (e_0, s_0, 0, 0)$. Then $n_1 + n_3 = e_0$ and $n_2 + n_3 + n_4 = s_0$. Since $\tilde{V}^s = A^f V^s = [0, -1, 1]^T$ and $\tilde{\mathbf{n}} - \tilde{V}^s = [n_1 + n_3, n_2 + n_3 + 1, n_4 - 1]^T = [e_0, s_0 - n_4 + 1, n_4 - 1]^T$, one can rewrite Eq. 4.3 as

$$\frac{d\tilde{p}(n_4, t)}{dt} = c_2 E[n_3 | n_4 - 1]\, \tilde{p}(n_4 - 1, t) - c_2 E[n_3 | n_4]\, \tilde{p}(n_4, t). \tag{4.4}$$

To implement a stochastic simulation algorithm using (4.4), we first compute the conditional probability $E[n_3|n_4] = \sum n_3 \tilde{p}(n_3|n_4)$ where the summation is taken over



(a) **(b)**

Fig. 1 Enzyme-substrate model. Comparisons of the mean and standard deviation of the product P with (dotted line) and without (solid line) the QSSA. Simulations are based on 5000 realizations with $c_1 = c_{-1} = 1$ and $c_2 = 0.1$. **a** $\mathbf{n}(0) = (10, 100, 0, 0)$. **b** $\mathbf{n}(0) = (1000, 100, 0, 0)$ (refer color figures for online)

all possible states of n_3. For the enzyme-substrate model, the conditional probability $\tilde{p}(n_3|n_4)$ is the equilibrium probability distribution of the fast subsystem

$$E + S \underset{c_{-1}}{\overset{c_1}{\rightleftarrows}} ES.$$

The formula and computations of $E[n_3|n_4]$ are given in Appendix 1. Figure 1 contains the simulation results of the mean and standard deviation of the product P with and without the QSSA. A similar numerical result was shown in [9]. Rao and Arkin have done similar work on the enzyme-substrate model using the stochastic version of Michaelis-Menten approximation [12]. However, their approximations are valid only when the substrate is in excess of the enzyme which is not needed in our method.

4.2 Enzyme-substrate-inhibitor model

This example is used to illustrate Theorem 1. The enzyme-substrate-inhibitor model is

$$E + S \underset{c_{-1}}{\overset{c_1}{\substack{\twoheadrightarrow \\ \twoheadleftarrow}}} ES \overset{c_2}{\rightarrow} E + P, \qquad E + I \underset{c_{-3}}{\overset{c_3}{\substack{\twoheadrightarrow \\ \twoheadleftarrow}}} EI. \tag{4.5}$$

where $\twoheadrightarrow$ indicates a fast reaction and $\rightarrow$ indicates a slow reaction. Let $n_1, n_2, n_3, n_4, n_5, n_6$ denote the number of molecules of species E, S, ES, I, EI, P, respectively, and let $\mathbf{n}(0) = (1, 3, 0, 2, 0, 0)$. Then the state diagram is

$$\begin{tikzcd}
(0,3,0,1,1,0) \arrow[r, shift left, ->>, "c_{-3}"] & (1,3,0,2,0,0) \arrow[l, shift left, ->>, "2c_3"] \arrow[r, shift left, ->>, "3c_1"] & (0,2,1,2,0,0) \arrow[l, shift left, ->>, "c_{-1}"] \arrow[d, "c_2"] & & \\
& (0,2,0,1,1,1) \arrow[r, shift left, ->>, "c_{-3}"] & (1,2,0,2,0,1) \arrow[l, shift left, ->>, "2c_3"] \arrow[r, shift left, ->>, "2c_1"] & (0,1,1,2,0,1) \arrow[l, shift left, ->>, "c_{-1}"] \arrow[d, "c_2"] & \\
& & (0,1,0,1,1,2) \arrow[r, shift left, ->>, "c_{-3}"] & (1,1,0,2,0,2) \arrow[l, shift left, ->>, "2c_3"] \arrow[r, shift left, ->>, "c_1"] & (0,0,1,2,0,2) \arrow[l, shift left, ->>, "c_{-1}"] \arrow[d, "c_2"] \\
& & & (0,0,0,1,1,3) \arrow[r, shift left, ->>, "c_{-3}"] & (1,0,0,2,0,3) \arrow[l, shift left, ->>, "2c_3"]
\end{tikzcd}$$

There are eleven states, labeled from top to bottom and from left to right as $\mathbf{m}^1, \ldots, \mathbf{m}^{11}$, respectively. Let $D_1 = \{\mathbf{m}^1, \mathbf{m}^2, \mathbf{m}^3\}$, $D_2 = \{(\mathbf{m}^4, \mathbf{m}^5, \mathbf{m}^6\}$, $D_3 = \{\mathbf{m}^7, \mathbf{m}^8, \mathbf{m}^9\}$ and $D_4 = \{\mathbf{m}^{10}, \mathbf{m}^{11}\}$. Under the QSSA, we obtain a reduced system in the slow time scale

$$D_1 \rightarrow D_2 \rightarrow D_3 \rightarrow D_4.$$

The propensity matrix K^f for the fast reactions is

$$K^f = \begin{bmatrix} K_1^f & & & \\ & K_2^f & & \\ & & K_3^f & \\ & & & K_4^f \end{bmatrix}$$

where

$$K_1^f = \begin{bmatrix} -c_{-3} & 2c_3 & 0 \\ c_{-3} & -(3c_1 + 2c_3) & c_{-1} \\ 0 & 3c_1 & -c_{-1} \end{bmatrix}, \quad K_2^f = \begin{bmatrix} -c_{-3} & 2c_3 & 0 \\ c_{-3} & -2(c_1 + c_3) & c_{-1} \\ 0 & 2c_1 & -c_{-1} \end{bmatrix}$$

$$K_3^f = \begin{bmatrix} -c_{-3} & 2c_3 & 0 \\ c_{-3} & -(c_1 + 2c_3) & c_{-1} \\ 0 & c_1 & -c_{-1} \end{bmatrix} \quad \text{and} \quad K_4^f = \begin{bmatrix} -c_{-3} & 2c_3 \\ c_{-3} & -2c_3 \end{bmatrix}.$$

are the propensity matrices for $D_i, i = 1, 2, 3, 4$, respectively. The eigenvectors corresponding to the zero eigenvalue of the K_i^f's are $\hat{\mathbf{\Pi}}_1 = [2\beta, 1, 3\alpha]^T$, $\hat{\mathbf{\Pi}}_2 = [2\beta, 1, 2\alpha]^T$, $\hat{\mathbf{\Pi}}_3 = [2\beta, 1, \alpha]$ and $\hat{\mathbf{\Pi}}_4 = [2\beta, 1]^T$ where $\alpha = c_1/c_{-1}$ and $\beta =$

c_3/c_{-3}. Let $\mathbf{\Pi}_i = \hat{\mathbf{\Pi}}_i/\|\hat{\mathbf{\Pi}}_i\|$ which is a probability vector. Here $\|\hat{\mathbf{\Pi}}_i\|$ denotes the sum of all components of $\hat{\mathbf{\Pi}}_i$. Then $LK^s\Pi$ is equal to

$$\begin{bmatrix} [1\ 1\ 1] & & & \\ & [1\ 1\ 1] & & \\ & & [1\ 1\ 1] & \\ & & & [1\ 1] \end{bmatrix} \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -c_2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & c_2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & -c_2 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & c_2 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -c_2 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & c_2 & 0 & 0 \end{bmatrix}$$

$$\begin{bmatrix} \mathbf{\Pi}_1 & & & \\ & \mathbf{\Pi}_2 & & \\ & & \mathbf{\Pi}_3 & \\ & & & \mathbf{\Pi}_4 \end{bmatrix} = \begin{bmatrix} -c_2(\mathbf{\Pi}_1)_3 & 0 & 0 & 0 \\ c_2(\mathbf{\Pi}_1)_3 & -c_2(\mathbf{\Pi}_2)_3 & 0 & 0 \\ 0 & c_2(\mathbf{\Pi}_2)_3 & -c_2(\mathbf{\Pi}_3)_3 & 0 \\ 0 & 0 & c_2(\mathbf{\Pi}_3)_3 & 0 \end{bmatrix}$$

where $(\mathbf{\Pi}_i)_3$ means the third component of the vector $\mathbf{\Pi}_i$. From Theorem 1, the reduced system is

$$\frac{d\tilde{\mathbf{p}}(t)}{dt} = LK^s\Pi\tilde{\mathbf{p}}(t) \tag{4.6}$$

where $\tilde{\mathbf{p}}(t)$ is an 11-dimensional vector and the ith-component $\tilde{p}_i(t) = \text{Prob}\{\tilde{\mathbf{n}}(t) = \mathbf{m}^i\}$. To find $\tilde{\mathbf{n}}$, we observe from (4.5) that

$$V^f = [[-1\ -1\ 1\ 0\ 0\ 0]^T,\ [1\ 1\ -1\ 0\ 0\ 0]^T,\ [-1\ 0\ 0\ -1\ 1\ 0]^T,\ [1\ 0\ 0\ 1\ -1\ 0]^T\ ].$$

Therefore,

$$A^f = \begin{bmatrix} 1 & 0 & 1 & 0 & 1 & 0 \\ 0 & 1 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 \end{bmatrix}, \quad \text{and} \quad \tilde{\mathbf{n}} = A^f\mathbf{n} = \begin{bmatrix} n_1 + n_3 + n_5 \\ n_2 + n_3 \\ n_4 + n_5 \\ n_6 \end{bmatrix}.$$

In Fig. 2, we compare the solutions of the full system with the solutions of the reduced system given by (4.6).

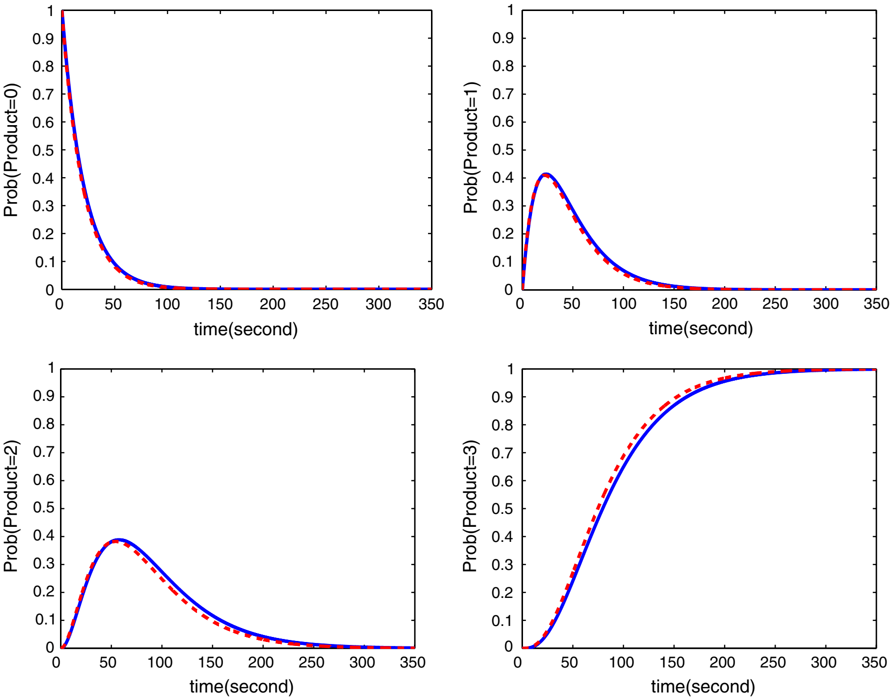


Fig. 2 Enzyme-substrate-inhibitor model. The four figures correspond to the time evolutions of Prob $(P = i)$ for $i = 0, 1, 2, 3$, respectively with $c_1 = c_{-1} = c_3 = 1$, $c_2 = 0.1$ and $\mathbf{n}(0) = (1, 3, 0, 2, 0, 0)$. Solutions without the QSSA are shown as solid line while solutions with the QSSA (4.6) are shown as dotted line (refer color figures for online)

4.3 Three time scale model of a linear system

In this section, we consider a three time scale reaction network with four species

$$A_1 \underset{k_{-1}/\epsilon^2}{\overset{k_1/\epsilon^2}{\rightleftarrows}} A_2 \underset{k_{-2}/\epsilon}{\overset{k_2/\epsilon}{\rightleftarrows}} A_3 \underset{k_{-3}}{\overset{k_3}{\rightleftarrows}} A_4 \tag{4.7}$$

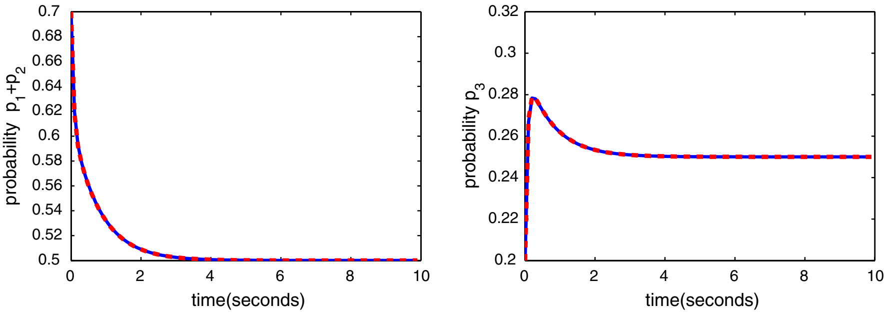
where k_i, $i = \pm 1, \pm 2, \pm 3$ have the same order of magnitude and $0 < \epsilon \ll 1$. Since all reactions in (4.7) are monomolecular reactions, the corresponding system of ordinary differential equations (2.1) is linear. Let p_i be the probability that a molecule is in the state A_i, $i = 1, 2, 3, 4$ and let $\mathbf{p} = (p_1, p_2, p_3, p_4)$. The master equation for this system is

$$\begin{aligned}\frac{d\mathbf{p}(t)}{dt} &= \left(\frac{1}{\epsilon^2}K_1 + \frac{1}{\epsilon}K_2 + K_3\right)\mathbf{p}(t)\\ &= \left(\frac{1}{\epsilon^2}\begin{bmatrix} -k_1 & k_{-1} & 0 & 0\\ k_1 & -k_{-1} & 0 & 0\\ 0 & 0 & 0 & 0\\ 0 & 0 & 0 & 0\end{bmatrix} + \frac{1}{\epsilon}\begin{bmatrix} 0 & 0 & 0 & 0\\ 0 & -k_2 & k_{-2} & 0\\ 0 & k_2 & -k_{-2} & 0\\ 0 & 0 & 0 & 0\end{bmatrix}\right.\\ &\quad \left. + \begin{bmatrix} 0 & 0 & 0 & 0\\ 0 & 0 & 0 & 0\\ 0 & 0 & -k_3 & k_{-3}\\ 0 & 0 & k_3 & -k_{-3}\end{bmatrix}\right)\mathbf{p}(t). \end{aligned} \tag{4.8}$$

To obtain a reduced system, we first apply the QSSA to the reaction between A_1 and A_2 in (4.7). Then the first reduced system is

$$\begin{aligned}\frac{d\mathbf{p_1}(t)}{dt} &= L_1\left(\frac{1}{\epsilon}K_1 + K_0\right)\Pi_1\mathbf{p}_1(t)\\ &= \begin{bmatrix} 1 & 1 & 0 & 0\\ 0 & 0 & 1 & 0\\ 0 & 0 & 0 & 1\end{bmatrix}\left(\frac{1}{\epsilon}\begin{bmatrix} 0 & 0 & 0 & 0\\ 0 & -k_2 & k_{-2} & 0\\ 0 & k_2 & -k_{-2} & 0\\ 0 & 0 & 0 & 0\end{bmatrix} + \begin{bmatrix} 0 & 0 & 0 & 0\\ 0 & 0 & 0 & 0\\ 0 & 0 & -k_3 & k_{-3}\\ 0 & 0 & k_3 & -k_{-3}\end{bmatrix}\right)\\ &\quad \times \begin{bmatrix} \frac{k_{-1}}{k_1 + k_{-1}} & 0 & 0\\ \frac{k_1}{k_1 + k_{-1}} & 0 & 0\\ 0 & 1 & 0\\ 0 & 0 & 1\end{bmatrix}\mathbf{p}_1(t)\\ &= \left(\frac{1}{\epsilon}\begin{bmatrix} -\frac{k_1 k_2}{k_1 + k_{-1}} & k_{-2} & 0\\ \frac{k_1 k_2}{k_1 + k_{-1}} & -k_{-2} & 0\\ 0 & 0 & 0\end{bmatrix} + \begin{bmatrix} 0 & 0 & 0\\ 0 & -k_3 & k_{-3}\\ 0 & k_3 & -k_{-3}\end{bmatrix}\right)\mathbf{p_1}(t) \end{aligned} \tag{4.9}$$

and the reduced chemical system is



(a) **(b)**

Fig. 3 Three time scale model (4.7) with $\mathbf{p}(0) = (.4, .3, .2, .1)$, each $k_i = 1$ and $\epsilon = 0.1$. Comparison between solutions obtained by solving system (4.8) (solid line) and the first reduced system (4.9) (dotted line). **a** probability that a molecule is in state A_1 or A_2, **b** probability that a molecule is in state A_3 (refer color figures for online)

$$B_1 \underset{k_{-2}/\epsilon}{\overset{k_2^*/\epsilon}{\rightleftarrows}} B_2 \underset{k_{-3}}{\overset{k_3}{\rightleftarrows}} B_3 \tag{4.10}$$

where $k_2^* = k_1k_2/(k_1 + k_{-1})$, B_1 is the reduced system of the fast reaction in (4.7), $B_2 = A_3$ and $B_3 = A_4$. Note that we can obtain the approximate value of the original probability p by using $p = \Pi_1 p_1$.

Next we apply the QSSA to the first reaction in (4.10) and obtain a second reduced system

$$\begin{aligned}\frac{d\mathbf{p}_2(t)}{dt} &= L_2K_0\Pi_2\mathbf{p}_2(t)\\ &= \begin{bmatrix}1 & 1 & 0\\ 0 & 0 & 1\end{bmatrix}\begin{bmatrix}0 & 0 & 0\\ 0 & -k_3 & k_{-3}\\ 0 & k_3 & -k_{-3}\end{bmatrix}\begin{bmatrix}b_1 & 0\\ b_2 & 0\\ 0 & 1\end{bmatrix}\mathbf{p}_2(t)\\ &= \begin{bmatrix}-k_3b_2 & k_{-3}\\ k_3b_2 & -k_{-3}\end{bmatrix}\mathbf{p}_2(t)\end{aligned} \tag{4.11}$$

where $b_1 = (k_1 + k_{-1})k_{-2}/(k_1k_{-2} + k_{-1}k_{-2} + k_1k_2)$ and $b_2 = k_1k_2/(k_1k_{-2} + k_{-1}k_{-2} + k_1k_2)$. Note that after the second reduction, one can obtain the approximate value of the original probability p by using $p = \Pi_1 p_1 = \Pi_1\Pi_2 p_2$. Results of our simulations are shown in Figs. 3 and 4.

4.4 A stochastic reaction-diffusion model

In this section, we give another example of a three time scale model. We consider the simulation of a three-dimensional stochastic reaction-diffusion equation based on the gene expression model in [13]. The idea here is to divide the spatial domain, which is assumed to be a cube, into equal compartments of size h and model diffusion between adjacent compartments as a first-order chemical reaction with reaction rate D/h^2

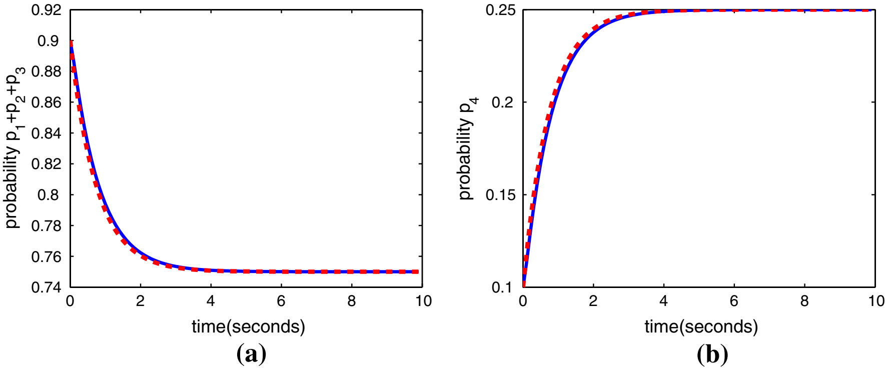


Fig. 4 Three time scales model with $(p_1, p_2, p_3, p_4) = (.4, .3, .2, .1)$, each $k_i = 1$ and $\epsilon = 0.1$. Comparison between solutions obtained by solving system (4.8) (solid line) and the second reduced system (4.11) (dotted line). **a** probability that a molecule is in state A_1, A_2, or A_3, **b** probability that a molecule is in state A_4 (refer color figures for online)

where D is bulk diffusion rate. For a more detail description of this method, see [4,8]. See also the mini survey on space in signaling pathways [14].

We consider a cell with a volume of $V = 1\,\mu\text{m}^3$. A DNA binding site is fixed at the center and is surrounded by freely diffusing RNA polymerase (RNAp) with bulk diffusion rate D. DNA and RNAp can bind with rate k_1 to form DNA-RNAp complex which can dissociates back to DNA and RNAp with rate k_{-1}, or produce, with rate k_2, a protein P with subsequent dissociation to DNA and RNAp. The protein is degraded with rate k_3. The model can be summarized by the following reaction network

$$DNA + RNAp \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} DNA\text{-}RNAp \overset{k_2}{\rightarrow} P + DNA + RNAp, \quad P \overset{k_3}{\rightarrow} \phi \tag{4.12}$$

with diffusion of RNAp. From [13], the reaction rate constants are $k_1 = 3 \times 10^9 M^{-1}\text{s}^{-1}$, $k_{-1} = 21.5\text{s}^{-1}$, $k_2 = 89.55\text{s}^{-1}$ and $k_3 = 0.04\text{s}^{-1}$. Bulk diffusion rate constant is $D = 1\,\mu\text{m}^2\text{s}^{-1}$. Initial numbers of molecules are $DNA = 1$, $RNAp = 18$, and $P = 0$. We need to convert the reaction rate constants to transition probabilities using the formulas in Sect. 3.1. Doing so, the transition probability

$$c_1 = \frac{k_1}{N_A \cdot V_h} = \frac{3 \times 10^9}{6.02214292 \times 10^{23} \times h^3 \times 10^{-15}}\,\text{s}^{-1} \approx \frac{4.9816}{h^3}\,\text{s}^{-1},$$

where V_h denotes the volume of a cubic compartment of size h. Since the reactions with transition rate constants k_{-1}, k_2 and k_3 are first order, their corresponding transition probabilities are $c_{-1} = 21.5\,\text{s}^{-1}$, $c_2 = 89.55\,\text{s}^{-1}$ and $c_3 = 0.04\,\text{s}^{-1}$.

To model diffusion, we divide the cell volume V into eight identical cubic compartments with size $h = 0.5\,\mu\text{m}$. Then we have

$$c_1 = \frac{4.9816}{h^3}\,\text{s}^{-1} = 39.8528\text{s}^{-1}$$

An analysis of the proper size of the compartment has been made in [8]. A proper size h of the compartment should satisfy the condition $\lambda \ll h \ll L$, where λ is the mean free path and L is the size of the whole system. In this system, $\lambda \approx 1/18 = 0.0556\,\mu\text{m}$ [13] and $L = 1\,\mu\text{m}$.

Since we distinguish between species in different compartments, the number of species in the whole system has increased from 4 to 32. Diffusion between adjacent compartments is modeled as a first-order reaction with reaction rate $D/h^2 = 1/h^2\,\text{s}^{-1} = 4\,\text{s}^{-1}$. Thus, considering the magnitude of each transition probability, one can consider the 'binding/unbinding of DNA and RNAp' and 'protein production' as fast reactions of order $O(10)$, 'diffusion' as a medium speed reaction of order $O(1)$, and 'decay of protein' as a slow reaction of order $O(10^{-2})$. This model is thus a three time scale model. However, the production of protein in the fast subsystem is not a reversible reaction and hence the graph of the fast subsystem is not strongly connected. To overcome this difficulty, we assume that the production of protein is a slow reaction with rate $c_2 = 0.1\,\text{s}^{-1}$ and then apply our reduction method to this modified gene expression model. We now briefly describe the first and second reduction methods for this model.

We denote the number of DNA, RNAp, DNA-RNAp complex and protein in ith compartment by n_1^i, n_2^i, n_3^i and n_4^i, respectively, for $i = 1, \ldots, 8$. Let $\mathbf{n} = (n_1^1, n_2^1, \cdots, n_3^8, n_4^8)$. In each compartment, the stoichiometries for the fast reactions and slow reactions are

$$W^f = \begin{bmatrix} -1 & 1 \\ -1 & 1 \\ 1 & -1 \\ 0 & 0 \end{bmatrix} \quad \text{and} \quad W^s = \begin{bmatrix} 1 & 0 \\ 1 & 0 \\ -1 & 0 \\ 1 & -1 \end{bmatrix},$$

respectively. Using them, one can write the stoichiometries V^f and V^s for the whole system in the form of tensor product

$$V^f = I_8 \otimes W^f, \qquad V^s = I_8 \otimes W^f.$$

For the diffusion of RNAp with medium speed, we denote its stoichiometry by V^m, which is a 32×24 matrix that can be obtained from the connectivity of the 8-compartment system. For example, if we write the stoichiometry of diffusion of RNAp from the first compartment into second compartment in the first column V_1^m of V^m, we have a 32×1 column vector

$$V_1^m = (0,\ -1,\ 0,\ 0,\ 0,\ 1,\ 0,\ 0,\ \cdots\ 0,\ 0,\ 0,\ 0)^T.$$

Similarly, we can find other columns of V^m. The entire matrix V^m is given in Appendix 2.

Let $\frac{1}{\epsilon_2} Q_i^f$, $i = 1, \ldots, 16$ be the propensities of the fast reactions in each compartment, let $\frac{1}{\epsilon_1} Q_j^m$, $j = 1, \ldots, 24$, be the propensities of RNAp diffusion between two adjacent compartments, and let Q_k^s, $k = 1, \ldots, 16$, be the propensities of the slow reactions in each compartment. Here $\epsilon_2 = 0.01$, $\epsilon_1 = 0.1$ and Q_i^f, Q_j^m and Q_k^s are of the same magnitude $O(0.1)$. Under these assumptions, the master equation is

$$\begin{aligned}\frac{dp(\mathbf{n},t)}{dt} &= \sum_{i=1}^{16} \frac{1}{\epsilon_2}\Big[Q_i^f(\mathbf{n}-V_i^f)\,p(\mathbf{n}-V_i^f,t) - Q_i^f(\mathbf{n})\,p(\mathbf{n},t)\Big] \\ &\quad + \frac{1}{\epsilon_1}\sum_{j=1}^{24}\Big[Q_j^m(\mathbf{n}-V_j^m)\,p(\mathbf{n}-V_j^m,t) - Q_j^m(\mathbf{n})\,p(\mathbf{n},t)\Big] \\ &\quad + \sum_{k=1}^{16}\big[Q_k^s(\mathbf{n}-V_k^s)\,p(\mathbf{n}-V_k^s,t) - Q_k^s(\mathbf{n})\,p(\mathbf{n},t)\big]. \end{aligned} \tag{4.13}$$

We now proceed to reduce Eq. 4.13.

First reduction : *elimination of fast reactions*

To eliminate the fast reactions, let B^f be the matrix whose rows form a basis of $N[(W^f)^T]$;

$$B^f = \begin{bmatrix} 1 & 0 & 1 & 0 \\ 0 & 1 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix}.$$

Then $A^f \equiv I_8 \otimes B^f$ is a matrix whose rows form a basis of $N[(V^f)^T]$. Let $\tilde{\mathbf{n}} = A^f\mathbf{n} = (n_1^1 + n_3^1, n_2^1 + n_3^1, n_4^1, \ldots, n_1^8 + n_3^8, n_2^8 + n_3^8, n_4^8)$, $\tilde{V}^m = A^f V^m$, and let $\tilde{V}^s = A^f V^s$. The master equation obtained after the first reduction is

$$\begin{aligned}\frac{d\tilde{p}(\tilde{\mathbf{n}},t)}{dt} &= \frac{1}{\epsilon_1}\sum_{j=1}^{24}\Big[\tilde{Q}_j^m(\tilde{\mathbf{n}}-\tilde{V}_j^m)\,\tilde{p}(\tilde{\mathbf{n}}-\tilde{V}_j^m,t) - \tilde{Q}_j^m(\tilde{\mathbf{n}})\,\tilde{p}(\tilde{\mathbf{n}},t)\Big] \\ &\quad + \sum_{k=1}^{16}\Big[\tilde{Q}_k^s(\tilde{\mathbf{n}}-\tilde{V}_k^s)\,\tilde{p}(\tilde{\mathbf{n}}-\tilde{V}_k^s,t) - \tilde{Q}_k^s(\tilde{\mathbf{n}})\,\tilde{p}(\tilde{\mathbf{n}},t)\Big] \end{aligned} \tag{4.14}$$

where $\tilde{Q}_j^m = E[Q_j^m(\mathbf{n})|\tilde{\mathbf{n}}]$ and $\tilde{Q}_j^s = E[Q_j^s(\mathbf{n})|\tilde{\mathbf{n}}]$. To find $\tilde{Q}_j^m$ and $\tilde{Q}_j^s$, we compute the equilibrium probability of the fast subsystem $DNA + RNAp \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} DNA\text{-}RNAp$ in each compartment. This can be done by using the method in Sect. 3.3.

Second reduction : *elimination of medium reactions*

In the second reduction, we eliminate the medium reactions in Eq. 4.14. To do so, we first find $\tilde{A}^m$ which is a matrix whose rows form a basis of $\mathcal{N}[(\tilde{V}^m)^T]$. (See the

Table 1

Method	Relative CPU time for single realization
Exact stochastic method	11250
Tau-leaping method	175
First reduction method	1062
Second reduction method	1

Appendix 2 for complete expression of $\tilde{V}^m$.)

$$\tilde{A}^m = \begin{bmatrix} B^m & & & \\ & B^m & & \\ & & \ddots & \\ & & & B^m \\ C^m & C^m & \cdots & C^m \end{bmatrix},$$

where $B^m = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 0 & 1 \end{bmatrix}$, $C^m = [0\ 1\ 0]$ and there are 8 blocks B^m and C^m. Let $\hat{n} = \tilde{A}^m \tilde{n} = (n_1^1 + n_3^1, n_4^1, \ldots, n_1^8 + n_3^8, n_4^8, n_2^1 + n_3^1 + \cdots + n_2^8 + n_3^8)$ and $\hat{V}^s = \tilde{A}^m \tilde{V}^s$. Then the reduced master equation is

$$\frac{d\hat{p}(\hat{\mathbf{n}}, t)}{dt} = \sum_{k=1}^{16} \left[\hat{Q}_k^s(\hat{\mathbf{n}} - \hat{V}_k^s)\, \hat{p}(\hat{\mathbf{n}} - \hat{V}_k^s, t) - \hat{Q}_k^s(\hat{\mathbf{n}})\, \hat{p}(\hat{\mathbf{n}}, t) \right] \tag{4.15}$$

where $\hat{Q}_k^s(\hat{\mathbf{n}}) = E[\tilde{Q}_k^s(\tilde{\mathbf{n}})|\hat{\mathbf{n}}]$. To compute $\hat{Q}_k^s(\hat{\mathbf{n}})$, we should find the equilibrium probability for the diffusion of RNAp which is a first-order reaction. It can be shown that the equilibrium probability distribution is multinomial [4]. Using this fact, one can compute $\hat{Q}_k^s(\hat{\mathbf{n}})$.

Results of our simulations are shown in Fig. 5. We show the results for proteins in the first and eighth compartments. Results in other compartments are almost the same. Since simulations by Gillespie algorithm requires a large amount of time, we use the tau-leaping method discussed in Sect. 3.2 to speed up the simulations. The relative CPU time spent for one realization is compared in the following table.

5 Discussion

The underlying assumption of this paper is that kinetics in the system can be identified as ones with distinct time scales. While the separation of time scales may not be obvious in certain reaction systems, many real biochemical or biological systems are known to evolve like a stiff system with distinct time scales in the region of interest in the whole state space. For such systems, our method can be utilized to approximate the solutions of the master equation accurately with considerably less computational load and time.

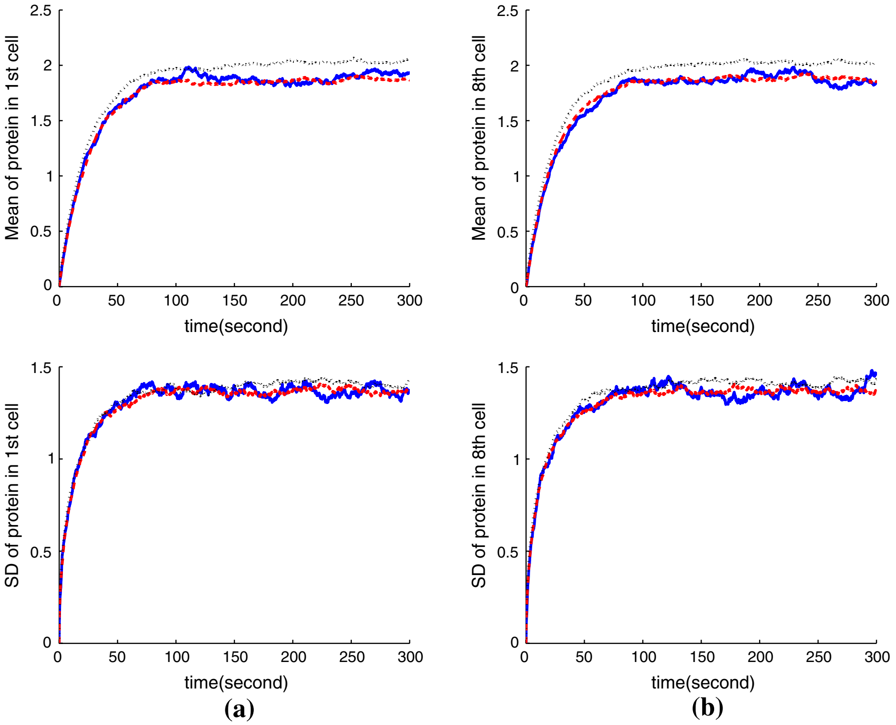


Fig. 5 Gene expression model with RNAp diffusion. Comparison between solutions obtained by Gillespie tau-leaping method (solid line), first reduction method (dashed line) and the second reduction method (dotted line). Tau-leaping and second reduction methods are based on 10000 realizations and first reduction method is based on 7000 realizations. **a** Mean and standard deviation of number of protein molecules in the first compartment. **b** Mean and standard deviation of number of protein molecules the eighth compartment (refer color figures for online)

When a system has unbounded state space, the dynamics of the system are described by transition between infinitely many possible states. In such a case, the transition matrix K and the probability vector $\mathbf{p}$ in the governing equation are infinite dimensional and very little is known about infinite dimensional ODE systems. Thus, developing a reduction method for such systems will be one of the major goal of our research in the future.

Acknowledgements This research was supported in part by the Institute for Mathematics and its Applications with funds provided by the National Science Foundation.

Appendix 1: Equilibrium distribution of a fast subsystem

Here we compute the equilibrium distribution of the reaction

$$A + B \underset{c_{-1}}{\overset{c_1}{\rightleftarrows}} C$$

by a method similar to [10]. Let $\mathbf{n} = (n_1, n_2, n_3)$ where n_1, n_2, n_3 denote the number of molecules of species A, B, C, respectively. Let $\mathbf{n}(0) = (a_0, b_0, c_0)$. Then since $n_1(t) + n_3(t) = a_0 + c_0$ and $n_2(t) + n_3(t) = b_0 + c_0$ for all $t > 0$, the random vector $\mathbf{n}$ may be represented by n_1 alone and the master equation for species A is

$$\begin{aligned}\frac{dP_a(t)}{dt} &= c_1[(a+1)(b_0 - a_0 + a + 1)P_{a+1}(t) - a(b_0 - a_0 + a)P_a(t)] \\ &\quad + c_{-1}[(a_0 + c_0 - a + 1)P_{a-1}(t) - (a_0 + c_0 - a)P_a(t)]\end{aligned}$$

where $P_a(t) = \text{Prob}\{n_1(t) = a\}$, $a = 0, 1, 2, \ldots$. Let $G(z,t) = \sum_a z^a P_a(t)$ be the moment generating function of $P_a(t)$. Multiplying the master equation by z^a and summing over a, we obtain

$$\begin{aligned}\sum_a z^a \frac{dP_a(t)}{dt} &= c_1 \sum_a z^a (a+1)(b_0 - a_0 + a + 1)P_{a+1} \\ &\quad - c_1 \sum_a z^a a(b_0 - a_0 + a)P_a + c_{-1} \sum_a z^a (a_0 + c_0 - a + 1)P_{a-1} \\ &\quad - c_{-1} \sum_a z^a (a_0 + c_0 - a)P_a. \qquad \text{(A.1)}\end{aligned}$$

The four terms on the right of (A.1) can be rewritten as

$$\begin{aligned}c_1 \sum_a z^a (a+1)(b_0 - a_0 + a + 1)P_{a+1} &= c_1(b_0 - a_0 + 1)G_z + c_1 z G_{zz} \\ -c_1 \sum_a z^a a(b_0 - a_0 + a)P_a &= -c_1(b_0 - a_0)zG_z - c_1 z^2 G_{zz} - c_1 z G_z \\ c_{-1} \sum_a z^a (a_0 + c_0 - a + 1)P_{a-1} &= c_{-1}(a_0 + c_0)zG - c_{-1} z^2 G_z \\ -c_{-1} \sum_a z^a (a_0 + c_0 - a)P_a &= -c_{-1}(a_0 + c_0)G + c_{-1} z G_z\end{aligned}$$

since

$$\sum_a z^a a(b_0 - a_0)P_a = (b_0 - a_0)zG_z$$

and

$$\sum_a z^a a^2 P_a = \sum_a z^a a(a-1)P_a + \sum_a z^a a P_a = z^2 G_{zz} + z G_z.$$

From (A.1), we obtain

$$G_t = c_1 z(1-z)G_{zz} - (c_{-1}z^2 + [c_1(b_0 - a_0 + 1) - c_{-1}]z - c_1(b_0 - a_0 + 1))G_z \\ + c_{-1}(a_0 + c_0)(z-1)G. \tag{A.2}$$

Therefore, the steady-state equation is

$$c_1 z(1-z)G_{zz} - (c_{-1}z^2 + (c_1(b_0 - a_0 + 1) - c_{-1})z - c_1(b_0 - a_0 + 1))G_z \\ + c_{-1}(a_0 + c_0)(z-1)G = 0. \tag{A.3}$$

Since

$$c_{-1}z^2 + (c_1(b_0 - a_0 + 1) - c_{-1})\,z - c_1(b_0 - a_0 + 1) \\ = (z-1)(c_{-1}z + c_1(b_0 - a_0 + 1)),$$

dividing both sides of (A.3) by $c_1 z(1-z)$, we obtain

$$G_{zz} + \left(\frac{b_0 - a_0 + 1}{z} + q\right)G_z - \frac{q(a_0 + c_0)}{z}G = 0 \tag{A.4}$$

where $q = c_{-1}/c_1$. By the change of variable $w = -qz$, Eq. A.4 becomes a Kummer's equation

$$w\frac{d^2 f}{dw^2} + (B - w)\frac{df}{dw} - Af = 0$$

which has two linearly independent solutions $M(A, B, w)$ and $U(A, B, w)$ [1, p. 504]. The function $U(A, B, w)$ is not defined at $w = 0$ while the function

$$M(a, b, w) = 1 + \frac{aw}{b} + \frac{(a)_2 w^2}{(b)_2 2!} + \cdots + \frac{(a)_n w^n}{(b)_n n!} + \cdots$$

where $(a)_n = a(a+1)(a+2)\ldots(a+n-1)$, $(a)_0 = 1$. Since $G(1) = 1$, the steady-state solution is

$$G(z) = \frac{M(-a_0 - c_0, b_0 - a_0 + 1, -qz)}{M(-a_0 - c_0, b_0 - a_0 + 1, -q)}, \qquad b_0 \ge a_0.$$

The condition $b_0 \ge a_0$ is necessary because $M(a, b, w)$ is undefined if a, b are both negative integers. If $b_0 < a_0$, then by the symmetry of the reaction system, one obtains

$$G(z) = \frac{M(-b_0 - c_0, a_0 - b_0 + 1, -qz)}{M(-b_0 - c_0, a_0 - b_0 + 1, -q)}, \qquad a_0 > b_0.$$

Since $P_a(t) = (1/a!)\,\partial^a G(z,t)/\partial z^a \mid_{z=0}$, the steady-state distribution of species A is

$$P_A(k) = D\frac{Q^k}{k!}\frac{(a_0 + c_0)(a_0 + c_0 - 1)\cdots(a_0 + c_0 - k + 1)}{(b_0 - a_0 + 1)(b_0 - a_0 + 2)\cdots(b_0 - a_0 + k)}, \quad k = 1, \ldots, a_0 + c_0$$

where D is a normalization constant. If $a_0 > b_0$, then the steady-state distribution of species B is

$$P_B(k) = D\frac{Q^k}{k!}\frac{(b_0+c_0)(b_0+c_0-1)\cdots(b_0+c_0-k+1)}{(a_0-b_0+1)(a_0-b_0+2)\cdots(a_0-b_0+k)}, \quad k = 1,\ldots,b_0+c_0.$$

Appendix 2: Matrices V_m and $\tilde{V}^m$ in reaction-diffusion model

$$V^m =$$

$$\begin{bmatrix}
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
-1 & 1 & -1 & 1 & -1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
1 & -1 & 0 & 0 & 0 & 0 & -1 & 1 & -1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 1 & -1 & 0 & 0 & -1 & 1 & -1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 1 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & -1 & 0 & 0 & -1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 1 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -1 & 1 & -1 & 1 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & -1 & 0 & 0 & -1 & 1 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & -1 & -1 & 1 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & -1 & 0 & 0 & 1 & -1 & 0 & 0 & 1 & -1 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0
\end{bmatrix}$$

$$\tilde{V}^m =$$

$$\begin{bmatrix}
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
-1 & 1 & -1 & 1 & -1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
1 & -1 & 0 & 0 & 0 & 0 & -1 & 1 & -1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 1 & -1 & 0 & 0 & -1 & 1 & -1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 1 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & -1 & 0 & 0 & -1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 1 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -1 & 1 & -1 & 1 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & -1 & 0 & 0 & -1 & 1 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & -1 & -1 & 1 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & -1 & 0 & 0 & 1 & -1 & 0 & 0 & 1 & -1 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0
\end{bmatrix}$$

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