

A reduction method for multiple time scale stochastic reaction networks with non-unique equilibrium probability

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Abstract We develop a reduction method for general closed multiple time scale stochastic reaction networks for which the fast subsystem may have non-unique equilibrium probability. We obtain a reduced ODE system with nonhomogeneous terms whose solutions can approximate the solutions of the full system accurately. We then apply this reduction method to general linear network and nonlinear networks for which the state diagram can be constructed. We illustrate the accuracy of the reduction method by comparing computational results of the full systems with the reduced ODE systems for several examples. Finally, we show how the reduction method may be extended to three or more time scale reaction networks.

Keywords Stochastic reaction network · Multiple time scale analysis · Non-unique equilibrium

1 Introduction

When the dynamics of a chemical reaction network are characterized by interactions of a small number of molecules, the network is modeled stochastically. The general form of the governing equation, called the chemical master equation, is

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$$\frac{dp(\mathbf{n}, t)}{dt} = \sum_{\ell=1}^r [Q_{\ell}(\mathbf{n} - V_{\ell})p(\mathbf{n} - V_{\ell}, t) - Q_{\ell}(\mathbf{n})p(\mathbf{n}, t)] \quad (1.1)$$

where $p(\mathbf{n}, t)$ is the joint density of the random vector \mathbf{n} , V_{ℓ} is the ℓ th column of the stoichiometry matrix V , and Q_{ℓ} is the *propensity function* of the ℓ th reaction [1]. The master Equation (1.1) can also be written as a linear *Kolmogorov system* by writing down the *state diagram* which consists all accessible states of \mathbf{n} and the transition rates between them [2].

Let \mathbf{m} denote the k possible states of \mathbf{n} and let $\mathbf{p}(t)$ be the k -vector with $p_i(t) = \text{Prob}\{\mathbf{n}(t) = \mathbf{m}^i\}$, where \mathbf{m}^i denotes the i th state of \mathbf{n} . Then \mathbf{p} satisfies the Kolmogorov system

$$\frac{d\mathbf{p}(t)}{dt} = K \mathbf{p}(t) \quad (1.2)$$

where K is the *transition rate matrix* whose off-diagonal entries are determined by the propensity function and diagonal entries are defined by $K_{jj} = -\sum_{i \neq j} K_{ij}$.

It is well-known that the exact solution of Eq. (1.1) is difficult, if not impossible, to obtain. The solution of (1.2) can be formally written as $\mathbf{p}(t) = e^{Kt} \mathbf{p}(0)$. For nonlinear networks, it is not easy to find K which is usually a large sparse matrix. Also, the solution of (1.2) requires an expensive computation of the matrix exponential. Due to these difficulties, one resorts to simulating the solutions of (1.1) by Monte Carlo methods such as the well-known Gillespie algorithm [3]. However, if the reaction network is stiff, simulations of the fast reactions by Monte Carlo methods are computationally inefficient and expensive. Recently, many researchers have proposed using reduction methods for fast reactions to reduce the computational intensity of the simulations [2, 4–6]. Most of these methods are based on the so called quasi-steady-state assumptions (QSSA) under which it is explicitly or implicitly assumed that the fast subsystem in the network has unique equilibrium probability. However, if this assumption is not satisfied, such reduction methods may not be applied. For example, branching of reactions is very common in reaction networks and many of them are fast reactions [8, 9]. If branching occurs in a reaction network, then the equilibrium probability cannot be found uniquely because the dimension of the null space of the fast transition matrix K^f is greater than one.

In this paper, we develop a reduction method for multiple time scale reaction networks whose fast subsystem have non-unique equilibrium probability. This work is an extension of the authors' previous work [2] to more general systems. To the authors' knowledge, such reduction method has not been reported elsewhere before. Outline of the paper is as follows. In Sect. 2, we present our theorem on reduction method for two time scale stochastic reaction networks. In Sect. 3, we apply our reduction method to linear reaction networks. In Sect. 4, we apply our method to nonlinear reaction networks and to a real example in chemistry. In Sect. 5, we discuss future work. In the appendix, we show how to extend our method to a three time scale reaction network.

For the rest of this section we define some terminology which will be used throughout this paper. First, we call the diagram of all the accessible states and transitions between them the state diagram. For example, if a stochastic reaction network is

$A + B \rightarrow C$ with initial condition $(2, 3, 0)$, then its state diagram is

$$(2, 3, 0) \rightarrow (1, 2, 1) \rightarrow (0, 1, 2).$$

Note that the structure of the state diagram depends on the initial condition as well as the stoichiometry of the reactions. Thus, if a large number of molecules are present initially or a variety of reactions occur in the reaction network, the state diagram is complex, which makes the analysis or computations of the system difficult. If the network is nonlinear, one should consider the state diagram to investigate its stochastic dynamics. On the other hand, for linear networks, the molecules are performing independent random walks and one can describe the dynamics of the network by only investigating the probabilistic movement of one molecule. Thus, there is no need to construct the state diagram.

2 Reduction of two time scale reaction networks

In this section we show how to obtain the *reduced ODE system* for a two time scale reaction network. Let $0 < \epsilon \ll 1$ be the separation parameter between the two time scales. The master equation for the two time scale reaction network is

$$\begin{aligned} \frac{dp(\mathbf{n}, t)}{dt} = & \frac{1}{\epsilon} \sum_{\ell} \left[Q_{\ell}^f(\mathbf{n} - V_{\ell}^f) p(\mathbf{n} - V_{\ell}^f, t) - Q_{\ell}^f(\mathbf{n}) p(\mathbf{n}, t) \right] \\ & + \sum_k \left[Q_k^s(\mathbf{n} - V_k^s) p(\mathbf{n} - V_k^s, t) - Q_k^s(\mathbf{n}) p(\mathbf{n}, t) \right] \end{aligned} \quad (2.1)$$

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

$$\frac{d\mathbf{p}(t)}{dt} = \left(\frac{1}{\epsilon} K^f + K^s \right) \mathbf{p}(t) \quad (2.2)$$

where K^f and K^s are the transition rate matrices for the fast and slow reactions, respectively. Before we state the main result of this paper, we need to provide some background. For more details, readers may consult [2].

A *fast component* in the state diagram is defined as the maximal subdiagram connected only by fast reactions. We denote the i th fast component in the state diagram by D_i and the j th state in D_i by $A_{i,j}$. The transition rate matrix K^f is a block diagonal matrix where each fast component, D_i , gives rise to a block, K_i^f . Let K_i^f have dimension $m_i \times m_i$ where m_i is equal to the number of states in D_i . Let K^f have m blocks. Then clearly the $1 \times m_i$ row vector $\mathbf{1}_{m_i}^T = (1, \dots, 1)$ is a left zero eigenvector of K_i^f . The total number of states in the state diagram is $k = m_1 + \dots + m_m$. Let $L = \text{diag}(\mathbf{1}_{m_1}^T, \dots, \mathbf{1}_{m_m}^T)$ which is an $m \times k$ matrix satisfying $LK^f = 0$.

In the next theorem, we obtain a reduced ODE system of (2.2) under the QSSA.

Theorem 1 Let \tilde{p}_i be the probability of D_i under the QSSA. Then there exist a matrix Π^* and a vector \mathbf{f}^* such that in the slow time scale, the reduced ODE system for (2.2) is

$$\frac{d\tilde{\mathbf{p}}}{dt} = LK^s\Pi^*\tilde{\mathbf{p}} + LK^s\mathbf{f}^* \tag{2.3}$$

where $\Pi^* = \text{diag}(\mathbf{e}_{m_1}, \dots, \mathbf{e}_{m_m})$ and each \mathbf{e}_{m_i} is an $m_i \times 1$ standard unit vector. The vector

$$\mathbf{f}^* = \mathbf{f} - \Pi^*\tilde{\mathbf{p}}$$

where $\mathbf{f} = (f_{1,1}, \dots, f_{1,m_1}, f_{2,1}, \dots, f_{m,1}, \dots, f_{m,m_m})^T$, and each $f_{i,j}$ is the probability of $A_{i,j}$ under the QSSA. Furthermore, the solutions of (2.3) and (2.2) satisfy

$$\|\tilde{\mathbf{p}} - L\mathbf{p}\| \approx O(\epsilon). \tag{2.4}$$

Proof By a singular perturbation method, we write the outer expansion of the solution of (2.2) in the slow time scale as $\mathbf{p}(t) \sim \sum_{i=0}^{\infty} \epsilon^i \mathbf{r}_i(t)$ after the fast reactions have reached equilibrium. Substituting $\sum_{i=0}^{\infty} \epsilon^i \mathbf{r}_i(t)$ into (2.2) and multiplying 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^0 and ϵ^1 terms, we have

$$\epsilon^0 : 0 = K^f \mathbf{r}_0 \tag{2.5}$$

$$\epsilon^1 : \frac{d\mathbf{r}_0}{dt} = K^s \mathbf{r}_0 + K^f \mathbf{r}_1 \tag{2.6}$$

Since $f_{i,j} = 0$ if $A_{i,j}$ is not an absorbing state, and the number of absorbing states in D_i is equal to the dimension of the null space of K_i^f , \mathbf{f} satisfies Eq. (2.5). Let $\mathbf{r}_0 = \mathbf{f}$. Then multiplying (2.6) by L and letting $\tilde{\mathbf{p}} = L\mathbf{r}_0 = L\mathbf{f}$, we have

$$\frac{d\tilde{\mathbf{p}}}{dt} = LK^s\mathbf{f}. \tag{2.7}$$

From the definition of L , $\tilde{p}_i(t) = \sum_{j=1}^{m_i} f_{i,j}(t)$ which is the probability of D_i under the QSSA.

In (2.7), we want to replace \mathbf{f} by $\tilde{\mathbf{p}}$. If the equilibrium probability of each fast component is unique, then $\mathbf{f} = \Pi\tilde{\mathbf{p}}$ where $\Pi = \text{diag}(\Pi_1, \dots, \Pi_m)$ and each Π_i satisfies $K_i^f \Pi_i = 0$ [2]. Hence, (2.7) becomes

$$\frac{d\tilde{\mathbf{p}}}{dt} = LK^s\Pi\tilde{\mathbf{p}}.$$

If the equilibrium probability of each fast component is not unique, then from the equation $\tilde{\mathbf{p}} = L\mathbf{f}$, for each i , we can choose one of $f_{i,j}$'s and express it in terms \tilde{p}_i and the rest of $f_{i,j}$'s. Suppose we express $f_{i,1}$ in terms of \tilde{p}_i and $f_{i,j}$, $j \neq 1$. Then

$$\begin{aligned}
 LK^s \mathbf{f} &= LK^s \begin{pmatrix} \tilde{p}_1 - \sum_{j \neq 1} f_{1,j} \\ f_{1,2} \\ \vdots \\ f_{1,m_1} \\ \tilde{p}_2 - \sum_{j \neq 1} f_{2,j} \\ \vdots \\ \tilde{p}_m - \sum_{j \neq 1} f_{m,j} \\ \vdots \\ f_{m,m_m} \end{pmatrix} \\
 &= LK^s \begin{bmatrix} 1 & 0 & 0 & \cdots & 0 \\ 0 & 0 & 0 & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ 0 & 0 & 0 & \cdots & 0 \\ 0 & 1 & 0 & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ 0 & 0 & 0 & \cdots & 1 \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ 0 & 0 & 0 & \cdots & 0 \end{bmatrix} \tilde{\mathbf{p}} + LK^s \begin{pmatrix} -\sum_{j \neq 1} f_{1,j} \\ f_{1,2} \\ \vdots \\ f_{1,m_1} \\ -\sum_{j \neq 1} f_{2,j} \\ \vdots \\ -\sum_{j \neq 1} f_{m,j} \\ \vdots \\ f_{m,m_m} \end{pmatrix} \\
 &\equiv LK^s \Pi^* \tilde{\mathbf{p}} + LK^s \mathbf{f}^*.
 \end{aligned}$$

Thus, the reduced ODE system (2.7) can be written as

$$\frac{d\tilde{\mathbf{p}}}{dt} = LK^s \mathbf{f} = LK^s \Pi^* \tilde{\mathbf{p}} + LK^s \mathbf{f}^*.$$

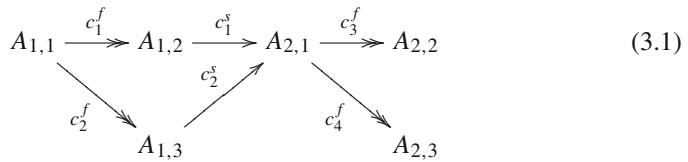
Finally, (2.4) follows from $\|\tilde{\mathbf{p}} - L\mathbf{p}\| = \|L\mathbf{r}_0 - L\mathbf{p}\| = O(\epsilon)$. The proof of the theorem is complete. □

Remark 1 The components of \mathbf{f}^* may be determined by solving a system of differential equations in the slow time scale. We shall show how to do this in the following sections.

3 Reduction of linear reaction networks

In this section we show how to find the reduced ODE system and *reduced network* for general linear reaction networks by applying Theorem 1. We first consider the

following two time scale stochastic reaction network with fast branching reactions and two slow reactions between the fast components



Throughout this section, we assume that there is no branching in the slow reactions even though the same method can be applied when there is branching in the slow reactions.

In the above network, $A_{1,2}, A_{1,3}, A_{2,2}, A_{2,3}$ are absorbing states while $A_{1,1}, A_{2,1}$ are not. Branching here means that molecules in $A_{1,1}$ may go to $A_{1,2}$ or $A_{1,3}$. Since the fast reactions are irreversible, the equilibrium state of the fast component $D_1 = \{A_{1,1}, A_{1,2}, A_{1,3}\}$ under the QSSA is not unique. The same applies to the fast component $D_2 = \{A_{2,1}, A_{2,2}, A_{2,3}\}$. Under the QSSA, the reduced network is $D_1 \rightarrow D_2$. Note that while D_1 approaches its equilibrium, some molecules are trapped in $A_{1,3}$ and they do not affect the slow reaction with rate constant c_1^s . The reduction method presented in previous works cannot capture such trapping behavior and previous reduction method will generate significant errors between the full ODE system (equations governing $p_{i,j}$) and the reduced ODE system. To obtain a correct reduced ODE system, one has to find the equilibrium probability of the fast subsystem which captures the probability of these trapped molecules.

To apply Theorem 1 to obtain the reduced ODE system for (3.1), we first find

$$L = \begin{bmatrix} 1 & 1 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 1 & 1 \end{bmatrix} \quad \text{and} \quad K^s = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -c_1^s & 0 & 0 & 0 & 0 \\ 0 & 0 & -c_2^s & 0 & 0 & 0 \\ 0 & c_1^s & c_2^s & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}.$$

From (3.1), we have $\tilde{p}_i = f_{i,2} + f_{i,3}, i = 1, 2$. If we choose $\mathbf{\Pi}_1^* = (0, 0, 1)^T$ and $\mathbf{\Pi}_2^* = (0, 0, 1)^T$, then $\mathbf{f}^* = (0, f_{1,2}, -f_{1,2}, 0, f_{2,2}, -f_{2,2})^T$, and we obtain from (2.3) the reduced ODE system

$$\begin{pmatrix} \tilde{p}'_1 \\ \tilde{p}'_2 \end{pmatrix} = \begin{bmatrix} -c_2^s & 0 \\ c_2^s & 0 \end{bmatrix} \begin{pmatrix} \tilde{p}_1 \\ \tilde{p}_2 \end{pmatrix} + \begin{pmatrix} (c_2^s - c_1^s)f_{1,2} \\ -(c_2^s - c_1^s)f_{1,2} \end{pmatrix}. \tag{3.2}$$

From (3.1), $f_{1,2}$ satisfies

$$\frac{df_{1,2}}{dt} = -c_1^s f_{1,2}, \quad f_{1,2}(0) = \frac{c_1^f}{c_1^f + c_2^f} p_{1,1}(0) + p_{1,2}(0).$$

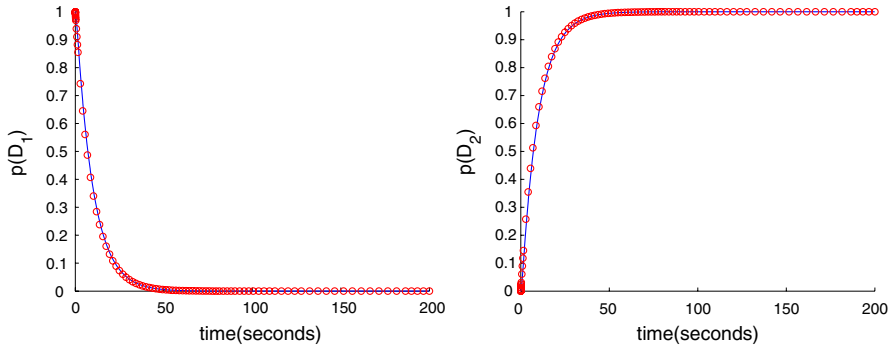
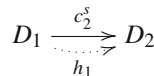


Fig. 1 Comparisons of solutions of the full (*solid*) and reduced (*circle*) systems for the network (3.1). $p(D_i)$ is the probability of $D_i, i = 1, 2$. We assume that $c_i^f = 1, i = 1, \dots, 4, c_1^s = 0.1, c_2^s = 0.11$ and initial condition $\mathbf{p}(0) = (1, 0, 0, 0, 0, 0)$

If we denote the linear reaction rate constant by a solid line arrow and nonhomogeneous rate by a dotted curve arrow, the reduced network is given by



where $h_1 = -(c_2^s - c_1^s)f_{1,2}$.

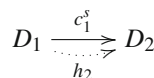
If we choose $\Pi_1^* = (0, 1, 0)^T$ and $\Pi_2^* = (0, 1, 0)^T$, then $\mathbf{f}^* = (0, -f_{1,3}, f_{1,3}, 0, -f_{2,3}, f_{2,3})^T$, and the reduced ODE system is

$$\begin{pmatrix} \tilde{p}'_1 \\ \tilde{p}'_2 \end{pmatrix} = \begin{bmatrix} -c_1^s & 0 \\ c_1^s & 0 \end{bmatrix} \begin{pmatrix} \tilde{p}_1 \\ \tilde{p}_2 \end{pmatrix} + \begin{pmatrix} (c_1^s - c_2^s)f_{1,3} \\ -(c_1^s - c_2^s)f_{1,3} \end{pmatrix}. \tag{3.3}$$

From (3.1), $f_{1,3}$ satisfies

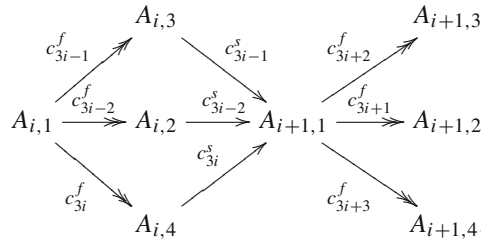
$$\frac{df_{1,3}}{dt} = -c_2^s f_{1,3}, \quad f_{1,3}(0) = \frac{c_2^f}{c_1^f + c_2^f} p_{1,1}(0) + p_{1,3}(0).$$

The reduced network is



where $h_2 = -(c_1^s - c_2^s)f_{1,3}$. Figure 1 compares the solutions of the full and reduced ODE systems for the above network.

The above analysis can be extended to the case of n fast components where each fast component has more than two absorbing states. Without out loss of generality, we assume that each D_i has three absorbing states and the network between D_i and D_{i+1} is given by



For this network, we find that $L = \text{diag}(\mathbf{1}_4^T, \mathbf{1}_4^T, \dots, \mathbf{1}_4^T)$ and $K^s = \text{diag}(K_1^s, K_2^s, \dots, 0_3)$ where

$$K_1^s = \begin{bmatrix} 0 & 0 & 0 & 0 \\ 0 & -c_1^s & 0 & 0 \\ 0 & 0 & -c_2^s & 0 \\ 0 & 0 & 0 & -c_3^s \\ 0 & c_1^s & c_2^s & c_3^s \end{bmatrix},$$

$$K_i^s = \begin{bmatrix} 0 & -c_{3i-2}^s & 0 & 0 \\ 0 & 0 & -c_{3i-1}^s & 0 \\ 0 & 0 & 0 & -c_{3i}^s \\ 0 & c_{3i-2}^s & c_{3i-1}^s & c_{3i}^s \end{bmatrix}, \quad i = 2, \dots, n - 1$$

and 0_3 is the 3×3 zero matrix. According to Theorem 1, the reduced ODE system is

$$\frac{d\tilde{\mathbf{p}}}{dt} = LK^s\Pi^*\tilde{\mathbf{p}} + LK^s\mathbf{f}^*.$$

If we choose $\Pi_i^* = (0, 1, 0, 0)^T$ for each i , then the reduced ODE system is

$$\begin{pmatrix} \tilde{p}'_1 \\ \tilde{p}'_2 \\ \vdots \\ \tilde{p}'_n \end{pmatrix} = \begin{bmatrix} -c_1^s & 0 & 0 & \dots & 0 & 0 \\ c_1^s & -c_4^s & 0 & \dots & 0 & 0 \\ 0 & c_4^s & -c_7^s & \dots & 0 & 0 \\ \vdots & \vdots & \ddots & \ddots & \vdots & \vdots \\ 0 & 0 & 0 & \dots & -c_{3n-2}^s & 0 \\ 0 & 0 & 0 & \dots & c_{3n-2}^s & 0 \end{bmatrix} \begin{pmatrix} \tilde{p}_1 \\ \tilde{p}_2 \\ \vdots \\ \tilde{p}_n \end{pmatrix} + \mathbf{g}$$

where \mathbf{g} is equal to

$$\begin{pmatrix} (c_1^s - c_2^s)f_{1,3} + (c_1^s - c_3^s)f_{1,4} \\ -(c_1^s - c_2^s)f_{1,3} - (c_1^s - c_3^s)f_{1,4} + (c_4^s - c_5^s)f_{2,3} + (c_4^s - c_6^s)f_{2,4} \\ \vdots \\ -(c_{3n-6}^s - c_{3n-5}^s)f_{n-2,3} - (c_{3n-6}^s - c_{3n-4}^s)f_{n-2,4} + (c_{3n-3}^s - c_{3n-2}^s)f_{n-1,3} \\ + (c_{3n-3}^s - c_{3n-1}^s)f_{n-1,4} - (c_{3n-3}^s - c_{3n-2}^s)f_{n-1,3} + (c_{3n-3}^s - c_{3n-1}^s)f_{n-1,4} \end{pmatrix}.$$

Also,

$$\begin{aligned}\frac{df_{1,2}}{dt} &= -c_1^s f_{1,2}, & f_{1,2}(0) &= p_{1,2}(0) + \frac{c_1^f}{c_1^f + c_2^f + c_3^f} p_{1,1}(0) \\ \frac{df_{1,3}}{dt} &= -c_2^s f_{1,3}, & f_{1,3}(0) &= p_{1,3}(0) + \frac{c_2^f}{c_1^f + c_2^f + c_3^f} p_{1,1}(0) \\ \frac{df_{1,4}}{dt} &= -c_3^s f_{1,4}, & f_{1,4}(0) &= p_{1,4}(0) + \frac{c_3^f}{c_1^f + c_2^f + c_3^f} p_{1,1}(0),\end{aligned}$$

$f_{i+1,2}$, $f_{i+1,3}$, $f_{i+1,4}$, $i = 1, \dots, n-2$ satisfy

$$\begin{aligned}\frac{df_{i+1,2}}{dt} &= c_{3i+1}^f \theta_i - c_{3i+1}^s f_{i+1,2}, \\ f_{i+1,2}(0) &= p_{i+1,2}(0) + \frac{c_{3i+1}^f}{c_{3i+1}^f + c_{3i+2}^f + c_{3i+3}^f} p_{i+1,1}(0) \\ \frac{df_{i+1,3}}{dt} &= c_{3i+2}^f \theta_i - c_{3i+2}^s f_{i+1,3}, \\ f_{i+1,3}(0) &= p_{i+1,3}(0) + \frac{c_{3i+2}^f}{c_{3i+1}^f + c_{3i+2}^f + c_{3i+3}^f} p_{i+1,1}(0) \\ \frac{df_{i+1,4}}{dt} &= c_{3i+3}^f \theta_i - c_{3i+3}^s f_{i+1,4}, \\ f_{i+1,4}(0) &= p_{i+1,4}(0) + \frac{c_{3i+3}^f}{c_{3i+1}^f + c_{3i+2}^f + c_{3i+3}^f} p_{i+1,1}(0)\end{aligned}$$

and

$$\begin{aligned}\frac{df_{n,2}}{dt} &= c_{3n-2}^f \theta_{n-1}, & f_{n,2}(0) &= p_{n,2}(0) + \frac{c_{3n-2}^f}{c_{3n-2}^f + c_{3n-1}^f + c_{3n}^f} p_{n,1}(0) \\ \frac{df_{n,3}}{dt} &= c_{3n-1}^f \theta_{n-1}, & f_{n,3}(0) &= p_{n,3}(0) + \frac{c_{3n-1}^f}{c_{3n-2}^f + c_{3n-1}^f + c_{3n}^f} p_{n,1}(0) \\ \frac{df_{n,4}}{dt} &= c_{3n}^f \theta_{n-1}, & f_{n,4}(0) &= p_{n,4}(0) + \frac{c_{3n}^f}{c_{3n-2}^f + c_{3n-1}^f + c_{3n}^f} p_{n,1}(0)\end{aligned}$$

where $\theta_i = (c_{3i-2}^s f_{i,2} + c_{3i-1}^s f_{i,3} + c_{3i}^s f_{i,4}) / (c_{3i+1}^f + c_{3i+2}^f + c_{3i+3}^f)$.

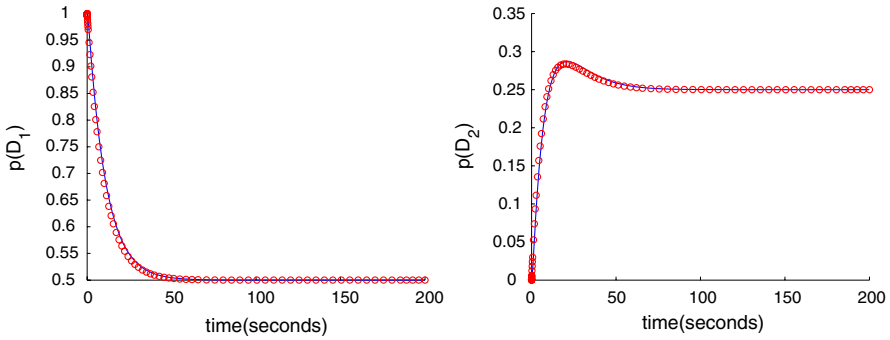
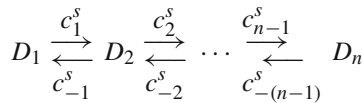
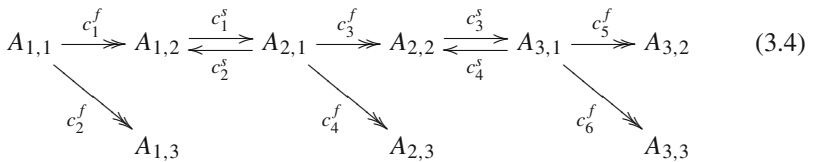


Fig. 2 Comparison of the solutions of the full (*solid*) and reduced (*circles*) systems for the network (3.4). $p(D_i)$ is the probability of D_i , $i = 1, 2$. We assume that $c_i^f = 1$, $i = 1, \dots, 6$, $c_j^s = 0.1$, $j = 1, \dots, 4$ and $p(0) = (1, 0, 0, 0, 0, 0, 0, 0)$

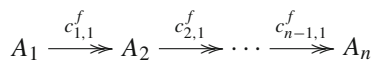
Remark 2 If a network consists of n fast components D_i , $i = 1, \dots, n$, which are connected by reversible reactions



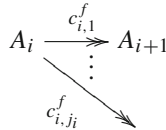
and each fast component D_i has the same network topology as in the previous cases, one sees that the same reduced ODE system is derived. Figure 2 compares the solutions of the full and the reduced ODE systems for a three component system with reversible slow reactions



Remark 3 In the reduced ODE system, the non-homogeneous terms involve $f_{i,j}$ of the absorbing states. These functions satisfy a separate ODE system and one needs to find the initial conditions for them. The initial conditions are the equilibrium probabilities of the absorbing states in the fast components under the QSSA. In this remark, we show how to find such equilibrium probabilities. Without loss of generality, consider the path



where there are j_i branching reactions from each species A_i with rate constant $c_{i,k}^f$, $k = 1, \dots, j_i$:



The governing equations are given by

$$p'_1 = - \left(\sum_{k=1}^{j_1} c_{1,k}^f \right) p_1, \quad p'_2 = c_{1,1}^f p_1 - \left(\sum_{k=1}^{j_2} c_{2,k}^f \right) p_2, \quad \dots, \quad p'_n = c_{n-1,1}^f p_{n-1}.$$

Integrating each equation over $[0, \infty]$, we have

$$\begin{aligned} \int_0^\infty p_1 dt &= \frac{p_1(0)}{\sum_k c_{1,k}^f}, \quad \int_0^\infty p_2 dt = \frac{1}{\sum_k c_{2,k}^f} \left(c_{1,1}^f \int_0^\infty p_1 dt + p_2(0) \right), \dots, \\ \int_0^\infty p_{n-1} dt &= \frac{1}{\sum_k c_{n-1,k}^f} \left(c_{n-2,1}^f \int_0^\infty p_{n-2} dt + p_{n-1}(0) \right), \quad p_n(\infty) = p_n(0) \\ &\quad + c_{n-1,1}^f \int_0^\infty p_{n-1} dt. \end{aligned}$$

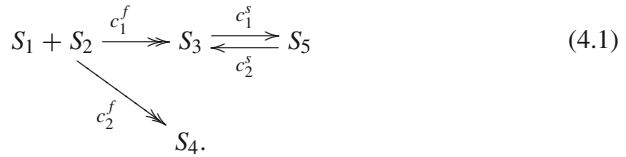
Solving the above equations, we have

$$p_n(\infty) = \left(\sum_{i=1}^{n-1} \frac{\prod_{\ell=i}^{n-1} c_{\ell,1}^f}{\prod_{\ell=i}^{n-1} (\sum_k c_{\ell,k}^f)} p_i(0) \right) + p_n(0).$$

By a similar approach, one can find the equilibrium probabilities of absorbing states in more complex networks.

4 Reduction of nonlinear reaction networks

In this section, we extend the reduction method developed in Sect. 2 to nonlinear reaction networks. To explain our method clearly, we consider the following example with five species S_1, \dots, S_5



The stoichiometry of the system is

$$V = [V^f \mid V^s] = \left[\begin{array}{cc|cc} -1 & -1 & 0 & 0 \\ -1 & -1 & 0 & 0 \\ 1 & 0 & -1 & 1 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & -1 \end{array} \right].$$

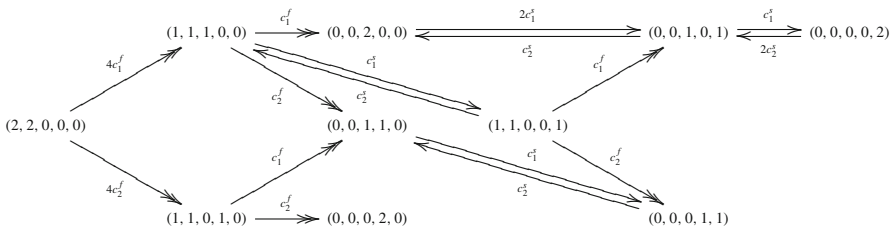
Let A^f be a matrix whose rows form a basis (with nonnegative integer components) of $\mathcal{N}((V^f)^T)$, the null space of V^f transpose [2]. Of course, A^f is not unique but one can always choose the set of independent maximal conserved-moiety vectors for a basis of $\mathcal{N}((V^f)^T)$ [7]. Doing so,

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

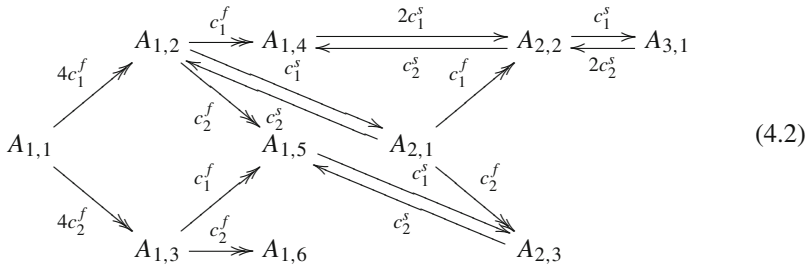
Under the QSSA, the new variable and stoichiometry are

$$\tilde{\mathbf{n}} = A^f \mathbf{n} = \begin{pmatrix} n_1 + n_3 + n_4 \\ n_2 + n_3 + n_4 \\ n_5 \end{pmatrix}, \quad \tilde{V}^s = A^f V^s = \begin{bmatrix} -1 \\ -1 \\ 1 \end{bmatrix}.$$

Let the initial condition be $(2, 2, 0, 0, 0)$. Then the state diagram is



which can be rewritten as



The fast components are $D_1 = \{A_{1,1}, \dots, A_{1,6}\}$, $D_2 = \{A_{2,1}, A_{2,2}, A_{2,3}\}$ and $D_3 = \{A_{3,1}\}$ which consist of states connected only by fast reactions. Also, the fast components can be identified by $\tilde{\mathbf{n}}$; namely, $\tilde{\mathbf{n}} = (2, 2, 0)^T$ for all states in D_1 , $\tilde{\mathbf{n}} = (1, 1, 1)^T$ for all states in D_2 , and $\tilde{\mathbf{n}} = (0, 0, 2)^T$ for all states in D_3 . We also find that $L = \text{diag}(\mathbf{1}_6^T, \mathbf{1}_3^T, 1)$ and K^s is the matrix with off-diagonal entries

$$K_{8,4}^s = 2c_1^s, \quad K_{4,8}^s = c_2^s, \quad K_{7,2}^s = c_1^s, \quad K_{2,7}^s = c_2^s, \quad K_{9,5}^s = c_1^s$$

$$K_{5,9}^s = c_2^s, \quad K_{10,8}^s = c_1^s, \quad K_{8,10}^s = 2c_2^s, \quad K_{i,j}^s = 0 \text{ otherwise}$$

and diagonal entries $K_{i,i}^s = -\sum_{j \neq i} K_{i,j}^s$.

By applying the reduction method in Sect. 3, the reduced ODE system for (4.2) under the QSSA is

$$\frac{d\tilde{\mathbf{p}}}{dt} = LK^s\Pi^*\tilde{\mathbf{p}} + LK^s\mathbf{f}^*.$$

If we choose $\Pi_1^* = (0, 0, 0, 1, 0, 0)^T$, $\Pi_2^* = (0, 1, 0)^T$, and $\Pi_3^* = 1$, then

$$\mathbf{f}^* = (0, 0, 0, -(f_{1,5} + f_{1,6}), f_{1,5}, f_{1,6}, 0, -f_{2,3}, f_{2,3}, 0)^T,$$

and the reduced ODE system is

$$\begin{pmatrix} \tilde{p}'_1 \\ \tilde{p}'_2 \\ \tilde{p}'_3 \end{pmatrix} = \begin{bmatrix} -2c_1^s & c_2^s & 0 \\ 2c_1^s & -(c_1^s + c_2^s) & 2c_2^s \\ 0 & c_1^s & -2c_2^s \end{bmatrix} \begin{pmatrix} \tilde{p}_1 \\ \tilde{p}_2 \\ \tilde{p}_3 \end{pmatrix} + \begin{pmatrix} c_1^s f_{1,5} + 2c_1^s f_{1,6} \\ -c_1^s f_{1,5} - 2c_1^s f_{1,6} + c_1^s f_{2,3} \\ -c_1^s f_{2,3} \end{pmatrix} \tag{4.3}$$

where $f_{1,5}$ and $f_{2,3}$ are the solutions of

$$f'_{1,5} = -c_1^s f_{1,5} + c_2^s f_{2,3}, \quad f'_{2,3} = c_1^s f_{1,5} - c_2^s f_{2,3},$$

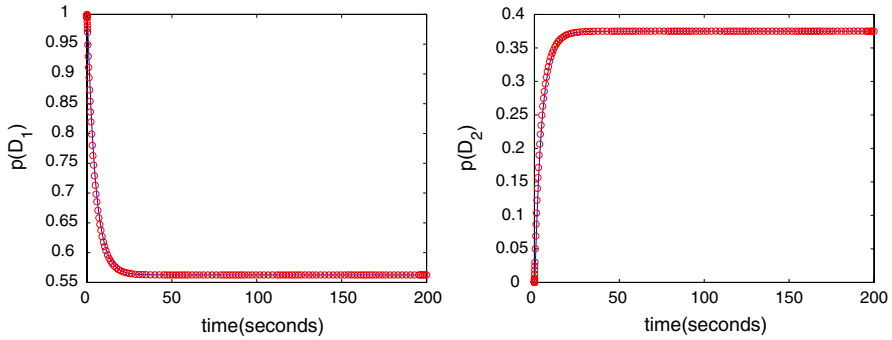


Fig. 3 Comparisons of solutions of the full (*solid*) and reduced (*circle*) systems for the nonlinear reaction network (4.1) where $c_1^f = c_2^f = 1$, $c_1^s = c_2^s = 0.1$. The initial condition is (2, 2, 0, 0, 0)

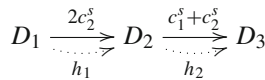
and $f_{1,6}(t) = f_{1,6}(0)$. The initial conditions are

$$f_{1,5}(0) = p_{1,5}(0) + \frac{2c_1^f c_2^f}{(c_1^f + c_2^f)^2} p_{1,1}(0) + \frac{c_2^f}{c_1^f + c_2^f} p_{1,2}(0) + \frac{c_1^f}{c_1^f + c_2^f} p_{1,3}(0)$$

$$f_{1,6}(0) = p_{1,6}(0) + \frac{(c_2^f)^2}{(c_1^f + c_2^f)^2} p_{1,1}(0) + \frac{c_2^f}{c_1^f + c_2^f} p_{1,3}(0), \quad \text{and}$$

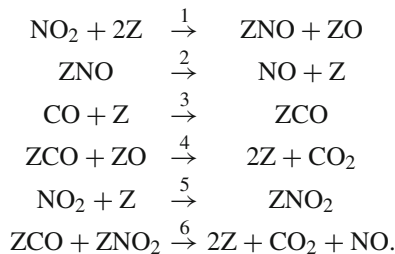
$$f_{2,3}(0) = p_{2,3}(0) + \frac{c_2^f}{(c_1^f + c_2^f)} p_{2,1}(0).$$

The reduced network under the QSSA is



where $h_1 = -(c_1^s f_{1,5} + 2c_1^s f_{1,6})$ and $h_2 = -c_1^s f_{2,3}$. Simulation results of this reduced network are shown in Fig. 3.

We end this section by showing an example of the reduction of NO₂ with CO to NO and CO₂ over metal catalyst Z [8]. There are two routes. One is by reactions 1, 2, 3, and 4 below and the other is by reactions 5, 3, 6 below.

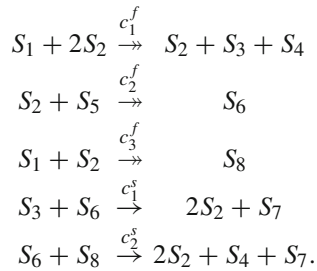


We identify the eight species as

$$S_1 = \text{NO}_2, S_2 = \text{Z}, S_3 = \text{ZO}, S_4 = \text{NO}, S_5 = \text{CO},$$

$$S_6 = \text{ZCO}, S_7 = \text{CO}_2, S_8 = \text{ZNO}_2.$$

We assume that ZNO is unstable and reaction 2 is instantaneous so that reactions 1 and 2 combine to become $\text{NO}_2 + 2\text{Z} \rightarrow \text{NO} + \text{Z} + \text{ZO}$. We also assume that 1,3,5 are fast reactions and 4, 6 are slow reactions. We write the above reactions as



The stoichiometry is given by

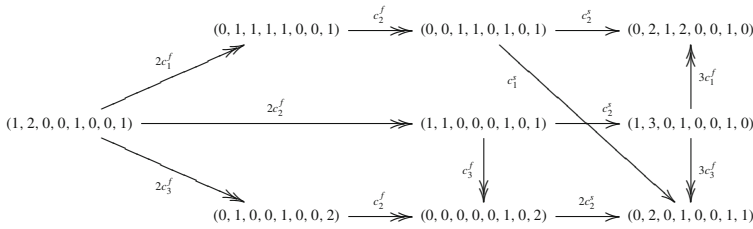
$$V = [V^f \mid V^s] = \left[\begin{array}{ccc|cc} -1 & 0 & -1 & 0 & 0 \\ -1 & -1 & -1 & 2 & 2 \\ 1 & 0 & 0 & -1 & 0 \\ 1 & 0 & 0 & 0 & 1 \\ 0 & -1 & 0 & 0 & 0 \\ 0 & 1 & 0 & -1 & -1 \\ 0 & 0 & 0 & 1 & 1 \\ 0 & 0 & 1 & 0 & -1 \end{array} \right] \quad \text{and}$$

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

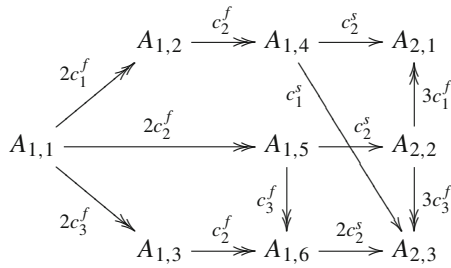
where the rows of A^f form a basis for $\mathcal{N}((V^f)^T)$. Thus, the slow variables and the new stoichiometry are

$$\tilde{\mathbf{n}} = A^f \mathbf{n} = \begin{pmatrix} n_1 + n_3 + n_8 \\ n_5 + n_6 \\ n_7 \\ n_2 + n_4 + n_6 + n_8 \\ n_1 + n_4 + n_8 \end{pmatrix}, \quad \tilde{V}^s = A^f V^s = \begin{bmatrix} -1 & -1 \\ -1 & -1 \\ 1 & 1 \\ 1 & 1 \\ 0 & 0 \end{bmatrix}.$$

Let $\mathbf{n}(0) = (1, 2, 0, 0, 1, 0, 0, 1)^T$. Then the state diagram is



which can be rewritten as



There are nine states $A_{1,1}, \dots, A_{2,3}$ and two fast components $D_1 = \{A_{1,1}, A_{1,2}, A_{1,3}, A_{1,4}, A_{1,5}, A_{1,6}\}$ and $D_2 = \{A_{2,1}, A_{2,2}, A_{2,3}\}$. Also, $\tilde{\mathbf{n}} = (2, 1, 0, 3, 2)^T$ for states in D_1 and $\tilde{\mathbf{n}} = (2, 0, 1, 4, 2)^T$ for states in D_2 . Note that the two columns of \tilde{V}^s are identical. This is because one of the slow reactions is dependent on other reactions as V has rank 4.

We find $L = \text{diag}(\mathbf{1}_6^T, \mathbf{1}_3^T)$ and K^s is the matrix with off-diagonal entries

$$K_{7,4}^s = c_2^s, K_{9,4}^s = c_1^s, K_{8,5}^s = c_2^s, K_{9,6}^s = 2c_2^s, K_{i,j}^s = 0 \text{ otherwise}$$

and diagonal entries $K_{i,i}^s = -\sum_{j \neq i} K_{i,j}^s$. The reduced equation is

$$\frac{d\tilde{\mathbf{p}}}{dt} = LK^s\Pi^*\tilde{\mathbf{p}} + LK^s\mathbf{f}^*$$

Since $\tilde{p}_1 = f_{1,4} + f_{1,6}$, there are two choices for Π^* . If we choose

$$\Pi_1^* = (0, 0, 0, 1, 0, 0)^T \quad \text{and} \quad \Pi_2^* = (1, 0, 0)^T,$$

then $\mathbf{f}^* = (0, 0, 0, -f_{1,6}, 0, f_{1,6}, -f_{2,3}, 0, f_{2,3})^T$, and the reduced ODE system is

$$\begin{pmatrix} \tilde{p}'_1 \\ \tilde{p}'_2 \end{pmatrix} = \begin{bmatrix} -(c_1^s + c_2^s) & 0 \\ c_1^s + c_2^s & 0 \end{bmatrix} \begin{pmatrix} \tilde{p}_1 \\ \tilde{p}_2 \end{pmatrix} + \begin{pmatrix} (c_1^s - c_2^s)f_{1,6} \\ -(c_1^s - c_2^s)f_{1,6} \end{pmatrix} \tag{4.4}$$

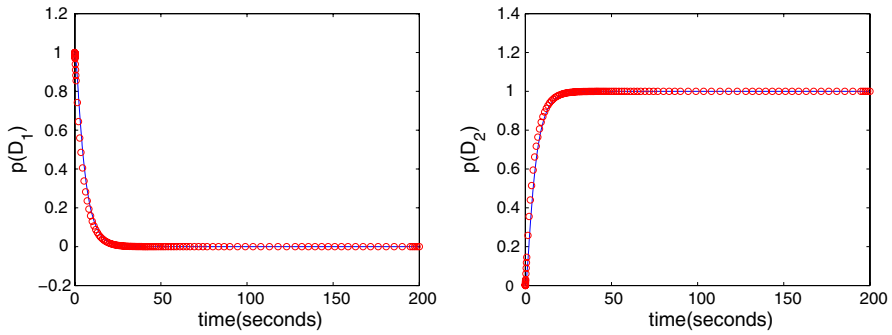


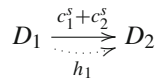
Fig. 4 Comparisons of the solutions of the full (*solid*) and reduced (*circle*) systems for the NO_2 reduction model with $c_1^f = c_2^f = c_3^f = 1$ and $c_1^s = c_2^s = 0.1$. The initial condition is $\mathbf{n}(0) = (1, 2, 0, 0, 1, 0, 0, 1)^T$

where $f_{1,6}(t)$ satisfies

$$f'_{1,6} = -2c_2^s f_{1,6},$$

$$f_{1,6}(0) = p_{1,6}(0) + p_{1,3}(0) + p_{1,5}(0) + \frac{c_3^f}{c_1^f + c_2^f + c_3^f} p_{1,1}(0) + \frac{c_2^f}{c_1^f + c_2^f + c_3^f} p_{1,1}(0).$$

The reduced network under the QSSA is



where $h_1 = -(c_1^s - c_2^s) f_{1,6}$. The simulation results are shown in Fig. 4.

If we choose

$$\Pi_1^* = (0, 0, 0, 0, 0, 1)^T, \quad \text{and} \quad \Pi_2^* = (0, 0, 1)^T,$$

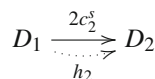
then $\mathbf{f}^* = (0, 0, 0, f_{1,4}, 0, -f_{1,4}, f_{2,1}, 0, -f_{2,1})^T$, and the reduced ODE system is

$$\begin{pmatrix} \tilde{p}'_1 \\ \tilde{p}'_2 \end{pmatrix} = \begin{bmatrix} -2c_2^s & 0 \\ 2c_2^s & 0 \end{bmatrix} \begin{pmatrix} \tilde{p}_1 \\ \tilde{p}_2 \end{pmatrix} + \begin{pmatrix} (c_2^s - c_1^s) f_{1,4} \\ -(c_2^s - c_1^s) f_{1,4} \end{pmatrix} \tag{4.5}$$

where $f_{1,4}(t)$ satisfies

$$f'_{1,4} = -(c_1^s + c_2^s) f_{1,4}, \quad f_{1,4}(0) = p_{1,4}(0) + p_{1,2}(0) + \frac{c_1^f}{c_1^f + c_2^f + c_3^f} p_{1,1}(0).$$

The reduced network under the QSSA is



where $h_2 = -(c_2^s - c_1^s) f_{1,4}$.

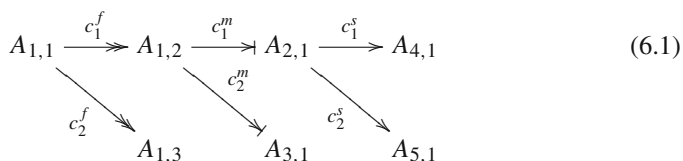
5 Discussion

In this paper we presented a reduction method for two time scale closed reaction networks whose fast subsystem has non-unique equilibrium probability. We showed that if the system is a closed linear network, one can obtain a reduced ODE system with non-homogeneous terms under the QSSA regardless of its network topology. We showed that this method can also be applied to the state diagram of a closed nonlinear network with small number of molecules. In case that the nonlinear network contains large number of molecules, its state diagram will consist of many states and transitions between them. It will require tremendous effort to identify all the states and transitions between them and so there is no practical benefit in obtaining a reduced ODE system for the Kolmogorov system. Thus, one has to rely on stochastic simulation algorithms (SSA) to simulate the reduced chemical master equation rather than the Kolmogorov system. The difficulty in utilizing SSA for such systems is that the propensity of the reduced master equation may not be found easily, since the propensity under the QSSA is expressed in terms of equilibrium probability of the fast subsystem that is not uniquely determined. The authors’ future work will be to use the method presented in this paper to formulate a reduced master equation and to implement a modified SSA for such equation.

6 Appendix: Three or more time scale reaction networks

The reduction method described in this paper can be applied to three or more time scale reaction networks. In this section, we show the procedure for a three time scale network. More complex three or higher time scale reaction networks may be treated similarly.

Consider the three time scale reaction network



where c_i^f , c_i^m and c_i^s denote the rate constants for fast, medium and slow reactions, respectively.

1. Reduction of fast reactions

One can consider the above system as a two time scale network, by identifying the medium and slow reactions as the slow reaction part. We define the fast components $D_{1,1} = \{A_{1,1}, A_{1,2}, A_{1,3}\}$, $D_{1,2} = A_{2,1}$, $D_{1,3} = A_{3,1}$, $D_{2,1} = A_{4,1}$, $D_{2,2} = A_{5,1}$.

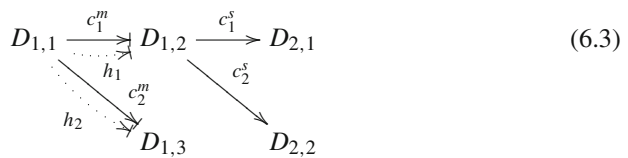
Applying the reduction method to the above network, one obtains the reduced ODE system

$$\begin{pmatrix} \tilde{p}'_1 \\ \tilde{p}'_2 \\ \tilde{p}'_3 \\ \tilde{p}'_4 \\ \tilde{p}'_5 \end{pmatrix} = \begin{bmatrix} -(c_1^m + c_2^m) & 0 & 0 & 0 & 0 \\ c_1^m & -(c_1^s + c_2^s) & 0 & 0 & 0 \\ c_2^m & 0 & 0 & 0 & 0 \\ 0 & c_1^s & 0 & 0 & 0 \\ 0 & c_2^s & 0 & 0 & 0 \end{bmatrix} \begin{pmatrix} \tilde{p}_1 \\ \tilde{p}_2 \\ \tilde{p}_3 \\ \tilde{p}_4 \\ \tilde{p}_5 \end{pmatrix} + \begin{pmatrix} (c_1^m + c_2^m) f_{1,3} \\ -c_1^m f_{1,3} \\ -c_2^m f_{1,3} \\ 0 \\ 0 \end{pmatrix} \tag{6.2}$$

where

$$f_{1,3}(t) = f_{1,3}(0) = p_{1,3}(0) + \frac{c_2^f}{c_1^f + c_2^f} p_{1,1}(0).$$

The reduced network for (6.1) after the first reduction is



where $h_1 = -c_1^m f_{1,3}$ and $h_2 = -c_2^m f_{1,3}$.

2. Reduction of medium reactions

We further reduce the two time scale system (6.3) by applying the reduction method. Let $g_{i,j}(t)$ be the probability of $D_{i,j}$ at time t under the QSSA and let $\hat{p}_i(t)$ be the probability of E_i , where $E_1 = \{D_{1,1}, D_{1,2}, D_{1,3}\}$, $E_2 = D_{2,1}$ and $E_3 = D_{2,2}$. Then, by applying the reduction method to (6.3), we have

$$g'_{1,2} = -(c_1^s + c_2^s)g_{1,2}, \quad g'_{2,1} = c_1^s g_{1,2}, \quad g'_{2,2} = c_2^s g_{1,2}.$$

Note that $g_{1,1}(t) = f_{1,3}(t) = f_{1,3}(0)$ since all the molecules in $D_{1,1}$ except for those in $A_{1,3}$ are moved to $D_{1,2}$ or $D_{1,3}$ after E_1 reaches equilibrium. Since $\hat{p}_1 = g_{1,1} + g_{1,2} + g_{1,3}$ and $g_{1,3}(t) = g_{1,3}(0)$, we have

$$\hat{p}'_1 = g'_{1,2} = -(c_1^s + c_2^s)g_{1,2} = -(c_1^s + c_2^s)\hat{p}_1 + (c_1^s + c_2^s)(g_{1,1} + g_{1,3}).$$

Furthermore,

$$\hat{p}'_2 = c_1^s g_{1,2} = c_1^s(\hat{p}_1 - g_{1,1} - g_{1,3}), \quad \hat{p}'_3 = c_2^s g_{1,2} = c_2^s(\hat{p}_1 - g_{1,1} - g_{1,3}).$$

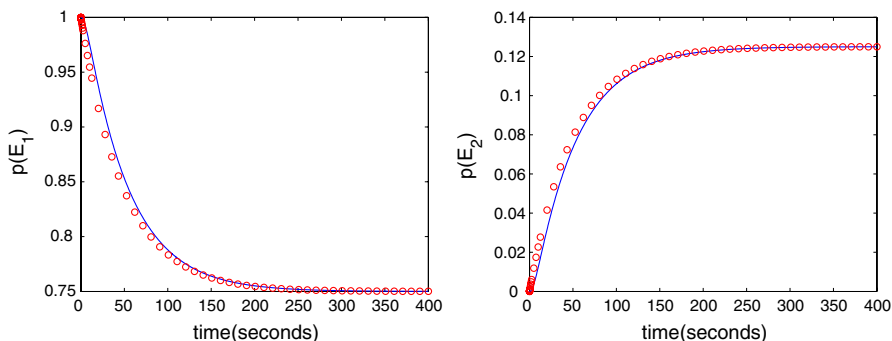


Fig. 5 Comparisons of solutions of the full (solid) and second reduced (circle) systems for the three time scale reaction network (6.1) where $c_1^f = c_2^f = 1, c_1^m = c_2^m = 0.1$ and $c_1^s = c_2^s = 0.01$. The initial condition is $(1, 0, 0, 0, 0, 0, 0)$

Thus, one obtains the reduced ODE system

$$\begin{pmatrix} \hat{p}'_1 \\ \hat{p}'_2 \\ \hat{p}'_3 \end{pmatrix} = \begin{bmatrix} -(c_1^s + c_2^s) & 0 & 0 \\ c_1^s & 0 & 0 \\ c_2^s & 0 & 0 \end{bmatrix} \begin{pmatrix} \hat{p}_1 \\ \hat{p}_2 \\ \hat{p}_3 \end{pmatrix} + \begin{pmatrix} (c_1^s + c_2^s)(g_{1,1} + g_{1,3}) \\ -c_1^s(g_{1,1} + g_{1,3}) \\ -c_2^s(g_{1,1} + g_{1,3}) \end{pmatrix} \quad (6.4)$$

where $g_{1,1}(t) = f_{1,3}(t)$ and

$$g_{1,3}(t) = g_{1,3}(0) = \frac{c_2^m}{c_1^m + c_2^m} \left(p_{1,2}(0) + \frac{c_1^f}{c_1^f + c_2^f} p_{1,1}(0) \right) + p_{2,2}(0).$$

The reduced network for (6.3) is



where $q_1 = -c_1^s(g_{1,1} + g_{1,3})$ and $q_2 = -c_2^s(g_{1,1} + g_{1,3})$.

Figure 5 compares the solutions of the full ODE system for (6.1) and the reduced ODE system (6.4).

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