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Model reduction of multi-scale chemical Langevin equations

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ABSTRACT

This paper addresses the model reduction problem for a class of stiff chemical Langevin equations that arise as models of biomolecular networks with fast and slow reactions and can be described as continuous Markov processes. Initially, a coordinate transformation is sought that allows the decoupling of fast and slow variables in the model equations. Necessary and sufficient conditions are derived for such a linear transformation to exist, along with an explicit change of variables which achieves the desired decoupling. For the systems for which this step is applicable, the method of adiabatic elimination is applied to determine a representation of the slow dynamics. Theoretical concepts and results are illustrated with simple examples.

1. Introduction

Biomolecular reaction networks that are far from the thermodynamic limit (i.e., that involve small species concentrations and infrequent reaction events) cannot be described accurately by classical deterministic kinetic models [1–3]. The inherent stochasticity of such systems becomes important and can be naturally accounted for by considering the vector of species numbers as a continuous-time discrete-state Markov process governed by the chemical master equation [4]. Assuming the existence of a macroscopically infinitesimal time increment, this model can be approximated by a continuous-time continuous-state Markov process governed by systems of chemical Langevin equations (CLEs) [4], which are stochastic differential equations (SDEs) with multiplicative noise terms.

Numerical simulation of kinetic models either in the deterministic regime or in the stochastic regime (and of course across different regimes) is hindered by the co-presence of reactions whose rates span widely different orders of magnitude. This results in stiffness of the underlying mathematical model and multi-time-scale behavior in the network dynamics. Model reduction is a natural tool to overcome this problem through the derivation of reduced non-stiff approximations of the network models in the appropriate time scales (see [5] for a recent comprehensive collection of papers on methods and applications of model reduction for multiscale systems).

In the case of deterministic kinetic models, described by systems of ordinary differential equations (ODEs), the model reduction problem has been extensively studied (see e.g. [6] and the references therein). Several attempts have also been devoted to the derivation of reduced-order models for networks modeled by chemical master equations. Reduced chemical master equations have been derived by projector methods [7–9], by generalizing the notion of quasi-steady-state assumption to stochastic systems in order to eliminate the fast intermediates [10], by introducing the concept of stochastic quasi-equilibrium to eliminate the fast reactions [11], and by approximating the evolution of the fast reactions by deterministic models or chemical Langevin equations [12]. Contrary to the other two descriptions of chemical reaction networks, the derivation of reduced-order models for stiff CLEs has not been investigated.

On the other hand, the mathematical literature offers model reduction techniques for SDEs with separated fast and slow variables of the following form:

$$\begin{aligned} \mathrm{d}\underline{Y}_s &= \underline{D}_s\left(\underline{Y}_s, \underline{Y}_f\right)\mathrm{d}t + \boldsymbol{\mathcal{B}}_s\left(\underline{Y}_s, \underline{Y}_f\right)\mathrm{d}\underline{W}_s \\ \mathrm{d}\underline{Y}_f &= \frac{1}{\epsilon}\underline{D}_f\left(\underline{Y}_s, \underline{Y}_f\right)\mathrm{d}t + \frac{1}{\sqrt{\epsilon}}\boldsymbol{\mathcal{B}}_f\left(\underline{Y}_s, \underline{Y}_f\right)\mathrm{d}\underline{W}_f, \end{aligned} \tag{1}$$

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where $\underline{Y}_s \in \mathbb{R}^{n_s}$ are referred to as slow variables and $\underline{Y}_f \in \mathbb{R}^{n_f}$ as fast variables, $\underline{W}_s$ (respectively, $\underline{W}_f$) is an m_s-dimensional (respectively, m_f-dimensional) vector of independent Wiener processes, and $\underline{D}_s$ and $\underline{D}_f$ (respectively, $\mathcal{B}_s$ and $\mathcal{B}_f$) are vectors (respectively, matrices) of the appropriate dimensions. For systems of this form, the fast variables may not converge in probability [13], which precludes the direct extension of the model reduction techniques available for ODEs [14], where the fast and slow dynamics are derived separately.

One approach followed in the literature is extending the averaging principle introduced for ODEs in to SDEs [15]. Several assumptions have been made to guarantee different types of convergence. In [16,17], convergence in distribution was proved when the coefficients satisfy Lipschitz and growth conditions. When the matrix $\mathcal{B}_s$ does not depend on the fast variables, stronger convergence results have been established. In [18], convergence in probability was proved provided that there was boundedness of the coefficients. In [19], under Lipschitz and linear growth conditions of the coefficients, the authors showed convergence in the mean-square sense, and the result was extended by one of the authors, in [20], to pth mean convergence for all $p \in [0, q]$ where the initial conditions of the system in Eq. (1) have finite qth mean.

Analytical asymptotic series for the probability density have also been proposed not only for the Kolmogorov equations associated to the SDE systems in Eq. (1) but also for more general Kolmogorov equations allowing mixed derivatives (i.e., with respect to both the fast and slow variables). However, this approach quickly becomes intensive, and has therefore been restricted to the Fokker–Planck (or Kolmogorov forward) equations for systems with one fast and one slow variable [21,22]. In the case of the Kolmogorov backward equation, multi-dimensional models have been studied, but they require a very involved approach combining probabilistic and analytic techniques [23].

Finally, the method of adiabatic elimination based on projector formalism has been developed for numerous SDE systems [24–28]. In this approach, the model reduction problem is recast in terms of the Fokker–Planck equation. The fast variables relax to the stationary distribution derived at fixed slow variables for a 'fast' Fokker–Planck operator. A projector is then defined by means of this stationary distribution in order to derive the Fokker–Planck equation for the probability density of the slow variables alone. The original distribution is computed by multiplying the fast variable stationary density by the slow variable density.

In this paper, we address the model reduction problem for stiff CLEs that arise as models of biomolecular networks with fast and slow reactions, and can be described as continuous Markov processes. The original formulations of such models result in stochastic differential equations whereby each variable may be affected by both fast and slow reactions; as a result, they require small time integration steps [29], and they do not have the explicit separation of fast and slow variables observed in Eq. (1). Motivated by this, initially, we seek a coordinate transformation that allows the decoupling of fast and slow variables. Necessary and sufficient conditions are derived for such a transformation to exist, along with an explicit change of variables which achieves the desired decoupling. For the systems for which this step is applicable, we treat each of the two subsets independently by extending the method of adiabatic elimination to the systems under consideration. Fast variables are assumed to relax to a pseudo-stationary density under the hypothesis that the slow variables remain constant. Slow variables are approximated through a Fokker–Planck equation which solely governs their probability density. The final step is to compute the approximated solution of the initial CLEs system by simply multiplying the two independent probability densities.

The paper is organized as follows. First, we define the problem of the two-time-scale CLE model. Then the reduction framework is formulated and the necessary theorems are presented and derived. Then theoretical concepts and results are illustrated with simple examples.

2. Two-time-scale CLE model

Consider a biomolecular network in which the following R reactions involving S species take place:

$$\sum_{s=1}^{S} r_s^j X_s \longrightarrow \sum_{s=1}^{S} p_s^j X_s \quad j = 1, \ldots, R. \tag{2}$$

Note that this notation allows for common reactants and products in a reaction (see examples in [26,4]). The SDEs describing such systems take the form [4]

$$\mathrm{d}\underline{X} = \sum_{j=1}^{R} \underline{\nu}_j k_j c_j(\underline{X})\mathrm{d}t + \sum_{j=1}^{R} \underline{\nu}_j \sqrt{k_j c_j(\underline{X})}\mathrm{d}W_j, \tag{3}$$

where $\underline{X}$ denotes the vector of species $\underline{X} = \begin{bmatrix} X_1 & \cdots & X_S \end{bmatrix}^T$, k_j the mesoscopic reaction rate of reaction j, $(W_1, \ldots, W_R)$ are R independent Wiener processes, the stoichiometric vector $\underline{\nu}_j$ associated to reaction j is defined as

$$\underline{\nu}_j = \begin{bmatrix} p_1^j - r_1^j \\ \vdots \\ p_S^j - r_S^j \end{bmatrix},$$

and

$$c_j(\underline{X}) = \prod_{s=1}^{S} \frac{X_s!}{r_s^j!\left(X_s - r_s^j\right)!}.$$

For simplicity, the notation $\mathrm{d}W_j$ for $1 \le j \le R$ is adopted instead of $\mathrm{d}W_j(t)$.

It is assumed that p fast reactions have been identified, and, without loss of generality, that these are the last p ones. In particular, the reaction rates are such that

$$\begin{aligned} &\frac{k_i}{k_j} \simeq O(1) \quad i, j \ge R - p + 1 \\ &k_{R-p+1} \gg k_i \quad i \le R - p. \end{aligned} \tag{4}$$

Corresponding to this distinction between fast and slow reactions, the $(S \times R)$ stoichiometric matrix $\mathcal{V} = \begin{bmatrix} \underline{\nu}_1 & \cdots & \underline{\nu}_R \end{bmatrix}$ can be written as $\mathcal{V} = \begin{bmatrix} \mathcal{V}_s & \mathcal{V}_f \end{bmatrix}$, where the $(S \times (R-p))$ matrix $\mathcal{V}_s$ (respectively, the $(S \times p)$ matrix $\mathcal{V}_f$) corresponds to the stoichiometric vectors associated with the slow reactions (respectively, fast reactions), i.e.,

$$\begin{aligned} \mathcal{V}_s &= \begin{bmatrix} \underline{\nu}_1 & \cdots & \underline{\nu}_{R-p} \end{bmatrix} \\ \mathcal{V}_f &= \begin{bmatrix} \underline{\nu}_{R-p+1} & \cdots & \underline{\nu}_R \end{bmatrix}. \end{aligned} \tag{5}$$

Observing that the SDE system is stiff owing to the co-existence of large and small reaction rates, we extract the large parameter $1/\epsilon$, where ϵ is defined as the inverse of the large representative reaction rate k_{R-p+1}, in order to isolate the source of stiffness. Thus, the SDEs with fast and slow reactions can be written in a matrix form:

$$\begin{aligned} \mathrm{d}\underline{X} = {} & \mathcal{V}_s \begin{bmatrix} k_1\, c_1(\underline{X}) \\ \vdots \\ k_{R-p}\, c_{R-p}(\underline{X}) \end{bmatrix} \mathrm{d}t + \mathcal{V}_s \begin{bmatrix} \sqrt{k_1\, c_1(\underline{X})}\mathrm{d}W_1 \\ \vdots \\ \sqrt{k_{R-p}\, c_{R-p}(\underline{X})}\mathrm{d}W_{R-p} \end{bmatrix} \\ & + \frac{1}{\epsilon} \mathcal{V}_f \begin{bmatrix} c_{R-p+1}(\underline{X}) \\ \vdots \\ \left(k_R/k_{R-p+1}\right) c_R(\underline{X}) \end{bmatrix} \mathrm{d}t \\ & + \frac{1}{\sqrt{\epsilon}} \mathcal{V}_f \begin{bmatrix} \sqrt{c_{R-p+1}(\underline{X})}\mathrm{d}W_{R-p+1} \\ \vdots \\ \sqrt{\left(k_R/k_{R-p+1}\right) c_R(\underline{X})}\mathrm{d}W_R \end{bmatrix}. \end{aligned} \tag{6}$$