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Layered decomposition for the model order reduction of timescale separated biochemical reaction networks

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HIGHLIGHTS

- Layering reaction networks is an alternative to modular decomposition.
- Layering identifies timescale-separated variables without transformations.
- Fast and slow subsystems can be expressed in terms of original variables.
- Approximated dynamics are interpreted as summed contributions from fast and slow layers.

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ABSTRACT

Biochemical reaction networks tend to exhibit behaviour on more than one timescale and they are inevitably modelled by stiff systems of ordinary differential equations. Singular perturbation is a well-established method for approximating stiff systems at a given timescale. Standard applications of singular perturbation partition the state variable into fast and slow modules and assume a quasi-steady state behaviour in the fast module. In biochemical reaction networks, many reactants may take part in both fast and slow reactions; it is not necessarily the case that the reactants themselves are fast or slow. Transformations of the state space are often required in order to create fast and slow modules, which thus no longer model the original species concentrations. This paper introduces a layered decomposition, which is a natural choice when reaction speeds are separated in scale. The new framework ensures that model reduction can be carried out without seeking state space transformations, and that the effect of the fast dynamics on the slow timescale can be described directly in terms of the original species.

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1. Introduction

A characteristic of many complex biological systems, including biochemical reaction networks, is that dynamical processes can occur on multiple, vastly different timescales (Southern et al., 2008; Jamshidi and Palsson, 2008). Modelling such a system by taking into account all of the timescales simultaneously results in stiff models. Simulation of these models requires fine temporal resolution to capture the fastest dynamics. If we are only interested in the behaviour of the system on a slower timescale, singular perturbation (Hinch, 1991; Murray, 2002) is a well-established model approximation technique which aims to capture the important dynamics at that timescale and remove the stiffness arising from the faster dynamics, making simulation and analysis more practical.

Fig. 1 represents the method of model reduction through singular perturbation as a sequence of steps. The first step is the identification of non-dimensional fast and slow variables, by which the system can be described by interconnected dynamic subsystems. The subsystem corresponding to the timescale which is not of interest is then approximated to be a static subsystem. The final step is the expression of the approximated system in terms of the original variables. In addition to approximating a stiff model with a non-stiff model, singular perturbation is also a model reduction technique. The reduction occurs because replacing a dynamic subsystem with a static subsystem (the second step in Fig. 1) removes differential equations from the recomposed system.

Grouping reactants into fast and slow subsets is an example of modular decomposition (Alexander et al., 2009). In the case of biochemical networks, this classification may be difficult. The variables are concentrations of reactants, but often the parameters are such that it is instead the reaction rate constants which separate in scale. If one reactant takes part in both fast and slow

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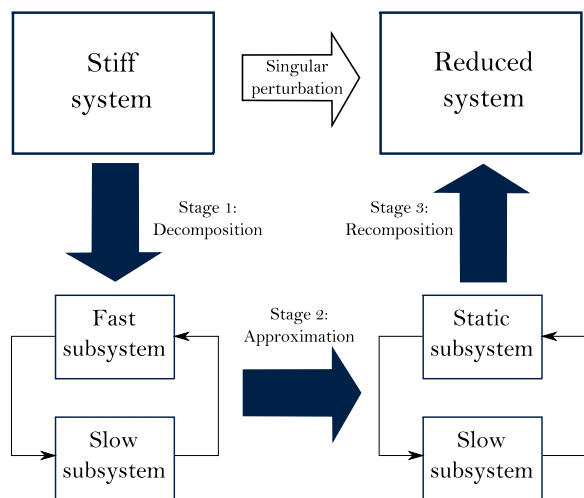


Fig. 1. The approximation of a stiff system through singular perturbation is broken down into three stages. First the system is decomposed into an interconnection of fast and slow subsystems, discussed in Section 2. In the second stage, discussed in Section 3, the fast subsystem is approximated by a static subsystem. Finally, the entire singularly perturbed system is formed from the recomposition of the original slow subsystem with the new static subsystem.

reactions, it cannot be classified as either fast or slow (Bennett et al., 2007; Lee and Othmer, 2010).

Up to now, the remedy for this has been to find a transformation of the state space to create pooled variables (Kumar et al., 1998). These are new variables, formed out of combinations of the reactant concentrations, whose dynamics allow them to be classified as fast or slow. For example, the well-known QSS approximation of the elementary enzyme reaction network is not valid when the enzyme concentration is on the same scale as that of the other reactants. The tQSS approximation (Tzafirri, 2003; Ciliberto et al., 2007) creates a new variable as a linear combination of two physical quantities that, for a given parameter range, allows a valid classification of variables as fast or slow. The improvement in approximation error (Prescott and Papachristodoulou, 2012) by taking the tQSS approach is at the expense of defining a new variable modelling a total concentration, rather than one of the original concentrations of interest.

This paper aims to perform singular perturbation of biochemical networks while avoiding finding transformations of the state variables. This will simplify the procedure of singular perturbation and also create fast and slow subsystems which have a biochemical interpretation in terms of the original variables. This is done by first reconsidering the decomposition of the system into subsystems in Section 2. It will be shown that an alternative decomposition method, termed *layering* (Prescott and Papachristodoulou, 2013), completes step 1 in Fig. 1 without requiring any transformations. We will then show in Section 3 how the approximation arising from such a decomposition results in reduced models, demonstrating our methods on two biological examples.

2. Decomposing biochemical reaction networks

This paper will focus on a standard ODE model for biochemical reaction networks (Palsson, 2006). Suppose such a network consists of N reactants X_i taking part in M reactions. The concentration of each reactant, denoted $x_i(t)$, is a component in the state variable $x(t) \in \mathbb{R}^N$. The rate at which reaction j occurs is denoted $v_j(x)$, where the argument is x to make explicit that each reaction rate may depend on the concentrations of any of the reactants at each point in time. The reaction rates form the components of the flux

vector $v(x) \in \mathbb{R}^M$. The stoichiometric coefficient of X_i in the j th reaction is denoted S_{ij} , which represents the change in concentration of X_i as reaction j proceeds. Each coefficient S_{ij} forms the stoichiometric matrix $S \in \mathbb{R}^{N \times M}$. These structures combine into a system of N coupled ODEs

$$\frac{dx}{dt} = Sv(x) \quad (1)$$

where the initial conditions are denoted $x(0) = x_0$.

In this section we will discuss how singular perturbation techniques can be interpreted as a decomposition of stiff systems into interconnected subsystems of characteristic time scales, as in Fig. 1. With this interpretation, we will show that established methods involving transformations correspond to a modular decomposition of the system. We then introduce a complementary decomposition, termed *layering*, which results in an alternative method for singular perturbation that avoids transformations and thus retains the natural coordinates (i.e. species concentrations) for each subsystem.

2.1. Modular decomposition of timescale-separated systems

The first stage of the approximation of a stiff non-dimensionalised ODE system through singular perturbation is the attempt to classify variables (i.e. reactants) as fast or slow. Suppose that the N components of the state variable x can be partitioned into two groups, where the components of $x_f \in \mathbb{R}^{N_f}$ are N_f fast reactants and the components of $x_s \in \mathbb{R}^{N_s}$ are N_s slow reactants. Assuming a re-ordering of the reactants index, we can write $x = (x_f^T, x_s^T)^T$. The classification into fast and slow reactants can be justified through the existence of a positive parameter $\epsilon \ll 1$ such that the non-dimensional system (1) can be written

$$\begin{bmatrix} \epsilon \dot{x}_f \\ \dot{x}_s \end{bmatrix} = \begin{bmatrix} S_f \\ S_s \end{bmatrix} v(x_f, x_s),$$

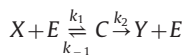
where the rows of S have been re-ordered and partitioned appropriately to the components of $x = (x_f^T, x_s^T)^T$. This representation makes clear the decomposition of the system into an interconnection of fast and slow modules:

$$\epsilon \dot{x}_f = S_f v(x_f, x_s),$$

$$\dot{x}_s = S_s v(x_f, x_s).$$

The full system state x can be recovered from the modular system states through the concatenation $x = (x_f^T, x_s^T)^T$.

However, often the parameters of the dynamical system are such that there is no decomposition of the state vector $x = (x_f, x_s)$ into variables with timescale-separated dynamics. For example, consider the enzyme kinetics network



modelling enzyme E converting X to Y via an intermediate complex C . If the initial concentration $[E(0)] = e(0)$ of enzyme is on a much smaller scale than that of the substrate $[X(0)] = x(0)$ then the non-dimensionalised variables do separate in timescale through the standard quasi-steady state (QSS) approximation. However, if $e(0)$ is on a similar scale to that of $x(0)$, it is no longer valid to assume that the non-dimensionalised variables separate in timescale, and another approximation must be found.

The standard technique in this case is to find a linear transformation T of the state vector so that the new state $z = Tx$ can be decomposed into fast and slow variables $z = (z_f, z_s)$. In general the required transformations are difficult to calculate, especially in the case of large-scale systems, and are often driven by intuition. Even when found, transformations of the state vector create linear

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