Determination of approximate lumping schemes by a singular perturbation method

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A singular perturbation method is employed for the determination of an approximate nonlinear lumped model for a chemical kinetic system described by a set of first order ordinary differential equations with a group of small positive parameters corresponding to different time scales. New variables, called purely fast variables, are introduced and determined. Substituting their explicit expressions into the original kinetic equation system yields a lumped differential equation system containing the independent variable t. The lumped system can reach any desired accuracy for any initial composition. A further approximation to this lumped system, obtained by omitting transient exponential functions of t, is shown to define the dynamics of the system on a slow invariant manifold. Two simple examples are used to illustrate this approach.

I. INTRODUCTION

The reduction in dimension of dynamic or kinetic equations describing a large system is a very important problem in many areas, such as chemical kinetics, chemical engineering, control theory, econometrics, and ecology.[1-4] This reduction is often achieved using *lumping* or *aggregation* techniques, in which the new dependent variables are certain functions of the original ones. The lumping is called *exact* or *approximate*, according to whether the solution of the lumped differential equation system does or does not contain errors compared to that of the original system. When the lumping transformation is linear, we call it linear lumping, otherwise nonlinear lumping. The authors have developed several approaches for exact and approximate linear lumping.[5-9] We have also presented a general analysis of exact nonlinear lumping, where linear lumping was included as a special case.[10]

It has been verified that exact nonlinear lumping schemes are related to global invariant manifolds of the original kinetic equation system, or to the eigenfunctions and generalized eigenfunctions of a linear partial differential operator A, which has a one-to-one relation with the original kinetic equation system. Unfortunately, there is no general approach to determine all the global invariant manifolds and eigenfunctions or generalized eigenfunctions for an arbitrary system. We need therefore to develop some approaches to determine lumped models approximately. There are several ways to do so. For example, using the theories of center manifolds,[11] inertial manifolds,[12-14] and slow manifolds,[15,16] some techniques have been developed. Some of these approaches make use of the separation in time scales which is common in chemical kinetic systems. The long time behavior of such systems can be described by an invariant manifold which is of a lower dimension

than the full state space. The dynamics of the original system when restricted to this manifold can therefore be described by a lower dimensional set of differential equations. This restriction to the slow/inertial manifold is equivalent to decoupling the fast modes in the original equations, and hence the lumped differential equation systems are valid only for initial compositions located in the center, inertial, or slow manifolds, respectively. When the initial composition is not in the manifolds, the lumped systems may have large errors before the solution trajectories enter them.

Even though the complete model gives a full description of all species, the higher dimension calls for a larger amount of computational effort. This problem becomes even more serious when the kinetic model is to be incorporated into a large physical model such as a computational fluid dynamics code. In practice, we are often concerned only with some selected species in a large system, such as initial reactants or main products. The concentrations of many intermediates are not usually of interest, and if we can find a simplified model containing only those species which are of interest, the amount of calculation needed to describe physical processes such as combustion will be greatly reduced. We will show that a singular perturbation method can be used for this purpose. Future work by the authors will illustrate the application of this approach to the $H_2 + O_2$ combustion system.[17]

In the present paper, we will employ a singular perturbation method to determine an approximately lumped model for a system whose kinetic equation system contains a group of small positive parameters corresponding to different time scales. We first introduce "*purely fast variables*" and find their explicit solutions by a singular perturbation method. In general, substituting these solutions into the original kinetic equation system will give a lower dimensional lumped differential equation system explicitly con-

taining the independent variable t. For many systems, such as combustion models, the decay of the purely fast variables occurs over such a small time scale that only the slow solution is necessary to represent the full equations. An autonomous set of equations can then be achieved containing a reduced set of variables.

This paper is organized as follows: In Sec. II, the theoretical basis of the singular perturbation method in approximate nonlinear lumping is presented. Two simple biochemical reactions are utilized as examples to illustrate this approach in Sec. III. Finally, Sec. IV presents conclusions and a comparison of the singular perturbation technique with other techniques such as inertial manifolds and the quasi-steady-state approximation.

II. DETERMINATION OF AN APPROXIMATELY LUMPED DIFFERENTIAL EQUATION SYSTEM BY A SINGULAR PERTURBATION METHOD

In this section, we will introduce the theoretical basis of a perturbation method[18] in the application of approximate nonlinear lumping. Suppose a kinetic system can be described by a set of first order ordinary differential equations of the following form:

$$\frac{d\mathbf{y}}{dt} = \mathbf{a}(\mathbf{y}) + A(\mathbf{y})\mathbf{z}, \tag{1}$$

$$\varepsilon \frac{d\mathbf{z}}{dt} = \mathbf{b}(\mathbf{y}) + B(\mathbf{y})\mathbf{z}, \tag{2}$$

where ε is an $n \times n$ diagonal matrix with a small positive parameter ε_i as its ith diagonal element; $\mathbf{y}$, $\mathbf{a}(\mathbf{y})$ and $\mathbf{z}$, $\mathbf{b}(\mathbf{y})$ are m- and n-dimensional vectors and function vectors; $A(\mathbf{y})$, and $B(\mathbf{y})$ are $m \times n$ and $n \times n$ function matrices, respectively. $B(\mathbf{y})$ is a matrix with negative eigenvalues and its inverse matrix can be given explicitly. The simplest case is a diagonal matrix with strictly negative diagonal elements. The restrictions on $\mathbf{z}$ and $B(\mathbf{y})$ come from the requirement for the determination of purely fast variables defined below. Even in this special form, Eqs. (1) and (2) can be used to describe some uni- and bimolecular or other reaction systems.

We wish to find an approximately lumped differential equation system which only contains the variable vector $\mathbf{y}$. In order to do so, we first define a purely fast variable vector ϕ by splitting off the slow part of $\mathbf{z}$ as follows:

$$\phi(t) = \mathbf{z}(t) + \mathbf{h}[\mathbf{y}(t)], \tag{3}$$

where $\phi(t)$ and $\mathbf{h}[\mathbf{y}(t)]$ are all n-dimensional vectors and $\mathbf{h}(\mathbf{y})$ is $\mathscr{C}^1$ (first order differentiable). Using Eqs. (1)–(3), we have

$$\varepsilon\dot{\phi} = \varepsilon\dot{\mathbf{z}} + \varepsilon\dot{\mathbf{h}}(\mathbf{y}) = \mathbf{b}(\mathbf{y}) + B(\mathbf{y})[\phi - \mathbf{h}(\mathbf{y})] + \varepsilon\mathbf{h}_\mathbf{y}(\mathbf{y})\dot{\mathbf{y}}$$

$$= \mathbf{b}(\mathbf{y}) + B(\mathbf{y})\phi - B(\mathbf{y})\mathbf{h}(\mathbf{y}) + \varepsilon\mathbf{h}_\mathbf{y}(\mathbf{y})\{\mathbf{a}(\mathbf{y}) + A(\mathbf{y})[\phi - \mathbf{h}(\mathbf{y})]\}$$

$$= [B(\mathbf{y}) + \varepsilon\mathbf{h}_\mathbf{y}(\mathbf{y})A(\mathbf{y})]\phi + \varepsilon\mathbf{h}_\mathbf{y}(\mathbf{y})[\mathbf{a}(\mathbf{y}) - A(\mathbf{y})\mathbf{h}(\mathbf{y})] - B(\mathbf{y})\mathbf{h}(\mathbf{y}) + \mathbf{b}(\mathbf{y}), \tag{4}$$

where a $\cdot$ represents the derivative with respect to t, and $\mathbf{h}_\mathbf{y}(\mathbf{y})$ is the Jacobian matrix of $\mathbf{h}(\mathbf{y})$ with respect to $\mathbf{y}$. We will obtain the purely fast and stable (as $\varepsilon \to 0$, i.e., every $\varepsilon_i \to 0$) differential equation system

$$\varepsilon\dot{\phi} = [B(\mathbf{y}) + \varepsilon\mathbf{h}_\mathbf{y}(\mathbf{y})A(\mathbf{y})]\phi \tag{5}$$

provided $\mathbf{h}(\mathbf{y})$ is selected as the solution of the following equation system:

$$\varepsilon\mathbf{h}_\mathbf{y}(\mathbf{y})[\mathbf{a}(\mathbf{y}) - A(\mathbf{y})\mathbf{h}(\mathbf{y})] - B(\mathbf{y})\mathbf{h}(\mathbf{y}) + \mathbf{b}(\mathbf{y}) = 0. \tag{6}$$

Let

$$\mathbf{h}(\mathbf{y}) = \sum_{i=0}^{\infty} \varepsilon^i \mathbf{h}_i(\mathbf{y}) \tag{7}$$

and then

$$\mathbf{h}_\mathbf{y}(\mathbf{y}) = \sum_{i=0}^{\infty} \varepsilon^i \mathbf{h}_{iy}(\mathbf{y}), \tag{8}$$

where $\mathbf{h}_i(\mathbf{y})$ is an n-dimensional function vector, $\mathbf{h}_{iy}(\mathbf{y})$ is the Jacobian matrix of $\mathbf{h}_i(\mathbf{y})$ with respect to $\mathbf{y}$, and

$$\varepsilon^i = \begin{pmatrix} \varepsilon_1^i & & & \\ & \varepsilon_2^i & & \\ & & \ddots & \\ & & & \varepsilon_n^i \end{pmatrix}, \tag{9}$$

where ε_j^i is the ith power of ε_j. Substituting Eqs. (7) and (8) into Eq. (6) yields

$$\varepsilon \sum_{i=0}^{\infty} \varepsilon^i \mathbf{h}_{iy}(\mathbf{y})\left[\mathbf{a}(\mathbf{y}) - A(\mathbf{y})\sum_{j=0}^{\infty} \varepsilon^j \mathbf{h}_j(\mathbf{y})\right]$$

$$- B(\mathbf{y})\sum_{i=0}^{\infty} \varepsilon^i \mathbf{h}_i(\mathbf{y}) + \mathbf{b}(\mathbf{y}) = 0. \tag{10}$$

Setting the coefficients with like powers of ε equal to the null vector will give some equations for the determination of $\mathbf{h}_i(\mathbf{y})$. From the terms with ε^0, we obtain the following equation:

$$-B(\mathbf{y})\mathbf{h}_0(\mathbf{y})+\mathbf{b}(\mathbf{y})=\mathbf{0}. \tag{11}$$

This gives

$$\mathbf{h}_0(\mathbf{y})=B^{-1}(\mathbf{y})\mathbf{b}(\mathbf{y}). \tag{12}$$

According to the definition above, the inverse $B^{-1}(\mathbf{y})$ can always be obtained. From the terms with ε^1, we have

$$\mathbf{h}_{0\mathbf{y}}(\mathbf{y})[\mathbf{a}(\mathbf{y})-A(\mathbf{y})\mathbf{h}_0(\mathbf{y})]-B(\mathbf{y})\mathbf{h}_1(\mathbf{y})=\mathbf{0}, \tag{13}$$

which gives

$$\mathbf{h}_1(\mathbf{y})=B^{-1}(\mathbf{y})\mathbf{h}_{0\mathbf{y}}(\mathbf{y})[\mathbf{a}(\mathbf{y})-A(\mathbf{y})\mathbf{h}_0(\mathbf{y})]. \tag{14}$$

Following the same procedure, we can obtain a recursion equation

$$\mathbf{h}_i(\mathbf{y})=B^{-1}(\mathbf{y})\left[\mathbf{h}_{(i-1)\mathbf{y}}(\mathbf{y})\mathbf{a}(\mathbf{y})-\sum_{j=0}^{i-1}\mathbf{h}_{j\mathbf{y}}A(\mathbf{y})\mathbf{h}_{i-1-j}(\mathbf{y})\right]$$
$$(i=1,2,...). \tag{15}$$

As the right-hand side is known from prior steps, $\mathbf{h}_i(\mathbf{y})$ can be obtained.

Now we will solve Eq. (5) by a singular perturbation method.[18] To obtain the outer solution, one needs to solve the equation

$$\varepsilon\frac{d\Phi(t)}{dt}=[B(\mathbf{y})+\varepsilon\mathbf{h}_\mathbf{y}(\mathbf{y})A(\mathbf{y})]\Phi(t). \tag{16}$$

Set

$$\Phi(t)=\sum_{i=0}^{\infty}\varepsilon^i\Phi_i(t), \tag{17}$$

where $\Phi_i(t)$ are n-dimensional vectors, and substitute it into Eq. (16). Comparing the terms with like powers of ε will give some equations to determine $\Phi_i(t)$. Notice that as $B(y)$ is nonsingular and the equation for Φ is homogeneous, the outer expansion $\Phi(t)$ for ϕ will be the trivial series (i.e., $\Phi_i\equiv\mathbf{0}$ for every i).

The stability of $B(\mathbf{y})$ implies that we can directly seek a solution consisting of only an initial layer expansion near $t=0$,

$$\phi(\tau,\varepsilon)=\sum_{i=0}^{\infty}\varepsilon^i\phi_i(\tau), \tag{18}$$

where $\phi_i(\tau)$ are n-dimensional vectors and

$$\tau=\begin{pmatrix}\tau_1\\ \vdots\\ \tau_n\end{pmatrix}=\begin{pmatrix}t/\varepsilon_1\\ \vdots\\ t/\varepsilon_n\end{pmatrix}. \tag{19}$$

To obtain the inner solution, one needs to solve the equation

$$\frac{d\phi(\tau,\varepsilon)}{d\tau}=[B(\mathbf{y})+\varepsilon\mathbf{h}_\mathbf{y}(\mathbf{y})A(\mathbf{y})]\phi(\tau,\varepsilon), \tag{20}$$

where

$$\frac{d\phi(\tau,\varepsilon)}{d\tau}=\begin{pmatrix}\dfrac{d\phi_1(\tau,\varepsilon)}{d\tau_1}\\ \vdots\\ \dfrac{d\phi_n(\tau,\varepsilon)}{d\tau_n}\end{pmatrix}, \tag{21}$$

and $\phi_j(\tau,\varepsilon)$ is the jth element of the vector $\phi(\tau,\varepsilon)$. Substituting Eq. (18) into Eq. (20) yields the equation for the determination of the initial layer expansion

$$\sum_{i=0}^{\infty}\varepsilon^i\frac{d\phi_i}{d\tau}=\left\{B[\mathbf{y}(0)]+\varepsilon\sum_{j=0}^{\infty}\varepsilon^j\mathbf{h}_{j\mathbf{y}}[\mathbf{y}(0)]A[\mathbf{y}(0)]\right\}$$
$$\times\sum_{i=0}^{\infty}\varepsilon^i\phi_i, \tag{22}$$

where

$$\frac{d\phi_i}{d\tau}=\begin{pmatrix}\dfrac{d\phi_{i1}}{d\tau_1}\\ \vdots\\ \dfrac{d\phi_{in}}{d\tau_n}\end{pmatrix} \tag{23}$$

and ϕ_{ij} is the jth element of the vector ϕ_i. By equating the coefficients with like powers of ε on both sides of Eq. (22), we obtain the equations for the determination of ϕ_i. For ϕ_0, we have

$$\frac{d\phi_0}{d\tau}=B[\mathbf{y}(0)]\phi_0. \tag{24}$$

Equating the coefficients with like powers of ε on both sides of Eq. (3) at $t=0$, we have the initial condition for Eq. (24)

$$\phi_0(0)=\mathbf{z}(0)+\mathbf{h}_0[\mathbf{y}(0)]. \tag{25}$$

Let us rewrite Eq. (24) as follows:

$$\frac{d\phi_0}{dt}=\varepsilon^{-1}B[\mathbf{y}(0)]\phi_0. \tag{26}$$

Its solution is

$$\phi_0(t)=\phi_0(\varepsilon\tau)=\phi_0(\tau)$$
$$=\exp\{\varepsilon^{-1}B[\mathbf{y}(0)]t\}\phi_0(0)$$
$$=\exp\{\varepsilon^{-1}B[\mathbf{y}(0)]\varepsilon\varepsilon^{-1}t\}\phi_0(0)$$
$$=\exp\{\varepsilon^{-1}B[\mathbf{y}(0)]\varepsilon\bar{\tau}\}\phi_0(0), \tag{27}$$

where

$$\bar{\tau}=\begin{pmatrix}\tau_1 & & \\ & \ddots & \\ & & \tau_n\end{pmatrix}. \tag{28}$$

When $B(\mathbf{y})$ is a diagonal matrix, we have

$$\phi_0(t)=\exp\{B[\mathbf{y}(0)]\varepsilon^{-1}t\}\phi_0(0)$$
$$=\exp\{B[\mathbf{y}(0)]\bar{\tau}\}\phi_0(0). \tag{29}$$

Here we used the commutative property for the product of two diagonal matrices. A similar treatment can be applied to other $\phi_i(\tau)$. For $\phi_1(\tau)$, we have

$$\frac{d\phi_1}{d\tau} = B[\mathbf{y}(0)]\phi_1 + \mathbf{h}_{0\mathbf{y}}[\mathbf{y}(0)]A[\mathbf{y}(0)]\phi_0$$

$$= B[\mathbf{y}(0)]\phi_1 + \mathbf{h}_{0\mathbf{y}}[\mathbf{y}(0)]A[\mathbf{y}(0)]$$

$$\times \exp\{\varepsilon^{-1}B[\mathbf{y}(0)]\varepsilon\bar{\tau}\}\phi_0(0) \qquad (30)$$

with the initial condition

$$\phi_1(0) = \mathbf{h}_1[\mathbf{y}(0)]. \qquad (31)$$

The solution is

$$\phi_1(\tau) = \exp\{\varepsilon^{-1}B[\mathbf{y}(0)]\varepsilon\bar{\tau}\}\mathbf{h}_1[\mathbf{y}(0)]$$

$$+ \int_0^t \exp\{\varepsilon^{-1}B[\mathbf{y}(0)]$$

$$\times (t-s)\}\varepsilon^{-1}\mathbf{h}_{0\mathbf{y}}[\mathbf{y}(0)]A[\mathbf{y}(0)]$$

$$\times \exp\{\varepsilon^{-1}B[\mathbf{y}(0)]s\}ds\,\phi_0(0). \qquad (32)$$

In summary, we successively obtain differential equation systems for $\phi_i(i=0,1,2,...)$ as follows:

$$\frac{d\phi_i}{d\tau} = B[\mathbf{y}(0)]\phi_i + \alpha_{i-1}(\tau) \qquad (33)$$

with the initial condition

$$\phi_i(0) = \mathbf{h}_i[\mathbf{y}(0)], \qquad (34)$$

where $\alpha_{-1}(\tau) \equiv 0$. As $\alpha_{i-1}(\tau)$ is known in terms of preceding coefficients as exponentially decaying vectors which tend to zero as $\tau \to \infty$, we obtain

$$\phi_i(\tau) = \exp\{\varepsilon^{-1}B[\mathbf{y}(0)]\varepsilon\bar{\tau}\}\mathbf{h}_i[\mathbf{y}(0)]$$

$$+ \int_0^t \exp\{\varepsilon^{-1}B[\mathbf{y}(0)](t-s)\}\varepsilon^{-1}\alpha_{i-1}(s,\varepsilon)ds.$$

$$(35)$$

Like the matrix $\exp\{\varepsilon^{-1}B[\mathbf{y}(0)]\varepsilon\bar{\tau}\}$, each vector ϕ_i satisfies that $\phi_i(\tau) = O(e^{-\sigma\tau})$ (where σ is a constant diagonal matrix with positive diagonal elements) under the prescribed condition of $B(\mathbf{y})$. Then the initial layer expansion $\phi(\tau,\varepsilon)$ matches the trivial outer solution $\Phi(t) \equiv 0$ as $\tau \to \infty$.

Substituting the result $\phi(t) = \phi(\tau,\varepsilon) = \phi(t,\varepsilon)$ into Eq. (1), we obtain a lumped differential equation system which only contains $\mathbf{y}$ and the independent variable t,

$$\frac{d\mathbf{y}}{dt} = \mathbf{a}(\mathbf{y}) - A(\mathbf{y})\mathbf{h}(\mathbf{y}) + A(\mathbf{y})\phi(t,\varepsilon). \qquad (36)$$

Usually we only take the first few terms of $\mathbf{h}_i(\mathbf{y})$ and $\phi_i(\tau)$, making the lumped system an approximate one.

Since the lumped differential equation system contains the initial values $\mathbf{z}(0)$ and $\mathbf{y}(0)$ in the expression for ϕ, it can be used only for a specified initial composition. This limitation will restrict its application. In many cases, e.g., where $\mathbf{z}$ represents the concentrations of radicals or complexes formed with catalysts, $\mathbf{z}(0) = \mathbf{0}$, and we have

$$\phi_i(0) = \mathbf{h}_i[\mathbf{y}(0)] \quad (i=0,1,2,...). \qquad (37)$$

Considering that ϕ is the purely fast variable vector and its solution only consists of the initial layer expansion near $t=0$, which approaches zero for a very small t, we can simply replace $\mathbf{y}(0)$ by $\mathbf{y}$ without introducing a significant error. We then have

$$\phi_i(\tau) = \exp[\varepsilon^{-1}B(\mathbf{y})\varepsilon\bar{\tau}]\mathbf{h}_i(\mathbf{y}) + \int_0^t \exp[\varepsilon^{-1}B(\mathbf{y})$$

$$\times (t-s)]\varepsilon^{-1}\alpha_{i-1}(s,\varepsilon)ds \qquad (38)$$

and treat $\mathbf{y}$ as a constant vector in the integration. The resultant lumped differential equation system can then be used for an arbitrary initial composition.

III. EXAMPLES

Two simple biochemical reactions will be used to illustrate the above method. In order to utilize the singular perturbation method, a group of small positive parameters ε_i corresponding to different time scales should be introduced into the original kinetic equation system. A nondimensionalization process is one way to reveal the relative time scales, but in general is a difficult task for large systems. For the application of the present approach, such a nondimensionalization process is not necessary As long as the variables $\mathbf{z}$, which react on a faster time scale than $\mathbf{y}$, can be identified, the small parameters effectively remain *hidden* and ε is introduced by simply writing it in front of $d\mathbf{z}/dt$ and finally set to I_n. If $\mathbf{z}$ are fast variables, then the higher order terms of the approximation for $\mathbf{h}$ and ϕ will converge even though ε is equal to I_n. Various methods exist for the identification of fast variables without nondimensionalization. For example, computational singular perturbation methods[19] can be used to investigate relative time scales before the application of analytical techniques. As shown in the following examples, it is sometimes not necessary for z to even be a fast variable. In certain cases, y and z can change on a similar time scale and the singular perturbation method can still be applied.

A. Example 1

The simplest and most commonly studied enzymatic reaction is the following:[20]

$$S + E \underset{k_{-1}}{\overset{k_1 \quad k_2}{\rightleftharpoons}} C \to P + E,$$
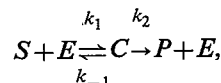
where S and P represent the substrate and product, respectively; E denotes the enzyme and C the complex formed between S and E; k_1, k_{-1}, and k_2 are rate constants. If we use lower-case letters to represent the species concentrations, the corresponding kinetic equation system is as follows:

$$\frac{ds}{dt} = -k_1 se + k_{-1}c, \qquad (39)$$

$$\frac{de}{dt} = -k_1 se + (k_{-1} + k_2)c, \qquad (40)$$

$$\frac{dc}{dt}=k_1 se-(k_{-1}+k_2)c, \tag{41}$$

$$\frac{dp}{dt}=k_2 c. \tag{42}$$

Note that $e+c$ is a constant. If at time $t=0$ $s=s_0$, $e=e_0$, and $c=p=0$, then

$$e+c=e_0. \tag{43}$$

As there are only two independent equations, we choose Eqs. (39) and (41). Substituting Eq. (43) into them yields

$$\frac{ds}{dt}=-k_1 e_0 s+(k_1 s+k_{-1})c, \tag{44}$$

$$\frac{dc}{dt}=k_1 e_0 s-(k_1 s+k_{-1}+k_2)c. \tag{45}$$

For this system, c is small and we are usually only concerned with the evolution of s. We wish to obtain an approximation for ds/dt which does not contain c. In the following, we use the variable $y=s/s_0$ instead of s. We will therefore use the perturbation method to construct an approximation of dy/dt which only contains y. First, we in-

troduce a small positive parameter ε. In order to do so, let us make Eqs. (44) and (45) dimensionless by taking

$$y=\frac{s}{s_0}, \quad z=\frac{c}{e_0}, \quad \varepsilon=\frac{e_0}{s_0}, \tag{46}$$

$$\bar{t}=k_1 e_0 t, \quad a=\frac{k_{-1}+k_2}{k_1 s_0}, \quad b=\frac{k_2}{k_1 s_0}. \tag{47}$$

The equations now have the desired form for the application of the singular perturbation method

$$\frac{dy}{dt}=-y+(y+a-b)z, \tag{48}$$

$$\varepsilon\frac{dz}{dt}=y-(y+a)z, \tag{49}$$

with the initial condition $y=1$, $z=0$ at $t=0$. For the sake of simplicity, in Eqs. (48) and (49) we still use t to represent $\bar{t}$.

First, we attempt to define a purely fast variable ϕ by splitting off the slow part of z. Let

$$\phi(t)=z(t)+h[y(t)]. \tag{50}$$

From Eqs. (48)–(50), we have

$$\varepsilon\dot{\phi}(t)=\varepsilon\dot{z}(t)+\varepsilon\dot{h}[y(t)]=y-(y+a)z+\varepsilon\frac{dh(y)}{dy}\dot{y}$$

$$=y-(y+a)\phi+(y+a)h(y)+\varepsilon\frac{dh(y)}{dy}[-y+(y+a-b)\phi-(y+a-b)h(y)]$$

$$=-\left[(y+a)-\varepsilon(y+a-b)\frac{dh(y)}{dy}\right]\phi+y+(y+a)h(y)-\varepsilon\frac{dh(y)}{dy}[y+(y+a-b)h(y)]. \tag{51}$$

We will obtain the purely fast and stable (as $\varepsilon\to0$) equation

$$\varepsilon\dot{\phi}(t)=-\left[(y+a)-\varepsilon(y+a-b)\frac{dh(y)}{dy}\right]\phi \tag{52}$$

provided $h(y)$ is selected as the solution of the following equation:

$$\varepsilon\frac{dh(y)}{dy}[y+(y+a-b)h(y)]-(y+a)h(y)-y=0. \tag{53}$$

Let

$$h(y)=\sum_{i=0}^{\infty}\varepsilon^i h_i(y). \tag{54}$$

Substituting for $h(y)$ in Eq. (53) and setting the coefficients of like powers of ε equal to zero gives equations to determine $h_i(y)$. For $h_0(y)$, we obtain

$$-(y+a)h_0(y)-y=0, \tag{55}$$

which gives

$$h_0(y)=-\frac{y}{y+a}. \tag{56}$$

The derivative of $h_0(y)$ with respect to y can be readily obtained as

$$\frac{dh_0(y)}{dy}=-\frac{a}{(y+a)^2}. \tag{57}$$

Similarly, for $h_1(y)$, we have

$$\frac{dh_0(y)}{dy}[y+(y+a-b)h_0(y)]-(y+a)h_1(y)=0. \tag{58}$$

This yields

$$h_1(y)=\frac{1}{y+a}\cdot\frac{dh_0(y)}{dy}[y+(y+a-b)h_0(y)]$$

$$=\frac{1}{y+a}\cdot\frac{-a}{(y+a)^2}\left[y-\frac{y(y+a-b)}{y+a}\right]$$

$$=-\frac{aby}{(y+a)^4}. \tag{59}$$

The derivative of $h_1(y)$ with respect to y is

$$\frac{dh_1(y)}{dy} = -\frac{ab(y+a)^4 - 4aby(y+a)^3}{(y+a)^8}$$

$$= \frac{4aby - ab(y+a)}{(y+a)^5}$$

$$= \frac{ab(3y-a)}{(y+a)^5} . \tag{60}$$

For $h_2(y)$, we have

$$\frac{dh_0(y)}{dy}(y+a-b)h_1(y) + \frac{dh_1(y)}{dy}[y+(y+a-b)h_0(y)]$$

$$- (y+a)h_2(y) = 0. \tag{61}$$

The solutions $h_2(y)$ and $dh_2(y)/dy$ are

$$h_2(y) = \frac{1}{y+a}\left\{\frac{dh_0(y)}{dy}(y+a-b)h_1(y) + \frac{dh_1(y)}{dy}[y+(y+a-b)h_0(y)]\right\}$$

$$= \frac{1}{y+a}\left\{\frac{-a}{(y+a)^2}(y+a-b)\frac{-aby}{(y+a)^4} + \frac{ab(3y-a)}{(y+a)^5}\left[y+(y+a-b)\frac{-y}{y+a}\right]\right\} = \frac{ab[(a+3b)y^2 + a(a-2b)y]}{(y+a)^7} \tag{62}$$

and

$$\frac{dh_2(y)}{dy} = \frac{ab[-5(a+3b)y^2 - 2a(2a-9b)y + a^2(a-2b)]}{(y+a)^8} . \tag{63}$$

In summary, we obtain the expressions for $h(y)$ and $dh(y)/dy$ as follows:

$$h(y) = h_0(y) + \varepsilon h_1(y) + \varepsilon^2 h_2(y) + \cdots = -\frac{y}{y+a} - \varepsilon\frac{aby}{(y+a)^4} + \varepsilon^2\frac{ab[(a+3b)y^2 + a(a-2b)y]}{(y+a)^7} + \cdots , \tag{64}$$

$$\frac{dh(y)}{dy} = \frac{dh_0(y)}{dy} + \varepsilon\frac{dh_1(y)}{dy} + \varepsilon^2\frac{dh_2(y)}{dy} + \cdots$$

$$= -\frac{a}{(y+a)^2} + \varepsilon\frac{ab(3y-a)}{(y+a)^5} + \varepsilon^2\frac{ab[-5(a+3b)y^2 - 2a(2a-9b)y + a^2(a-2b)]}{(y+a)^8} + \cdots . \tag{65}$$

Substituting Eq. (65) into Eq. (52) yields

$$\varepsilon\dot{\phi}(t) = -\left[(y+a) + \varepsilon\frac{a(y+a-b)}{(y+a)^2} - \varepsilon^2\frac{ab(3y-a)(y+a-b)}{(y+a)^5}\right.$$

$$\left. - \varepsilon^3\frac{ab(y+a-b)[-5(a+3b)y^2 - 2a(2a-9b)y + a^2(a-2b)]}{(y+a)^8} + \cdots\right]\phi(t) = -\omega(y,\varepsilon)\phi(t). \tag{66}$$

According to the discussion in Sec. II, the solution of $\phi(t)$ only consists of the initial layer expansion, and considering that ϕ is a scalar function, without expanding ϕ as a series, we immediately obtain

$$\phi(t) = \phi(0)\exp\{-\omega[y(0),\varepsilon]t/\varepsilon\}$$

$$= h[y(0)]\exp\{-\omega[y(0),\varepsilon]t/\varepsilon\}. \tag{67}$$

Here we have used the initial conditions, i.e., $\phi(0) = z(0) + h[y(0)]$ and $z(0) = 0$. If we require the lumped differential equation for y to be used for any initial composition [it does not have physical meaning in this example because $y(0)$ can only take the value 1], we replace $y(0)$ by y. Then we have

$$\phi(t) = h(y)\exp[-\omega(y,\varepsilon)t/\varepsilon]. \tag{68}$$

Substituting the solutions of $\phi(t)$ into Eq. (48), we obtain the lumped differential equation for $y(t)$ as

$$\frac{dy}{dt} = -y - (y+a-b)h(y) + (y+a-b)h[y(0)]$$

$$\times\exp\{-\omega[y(0),\varepsilon]t/\varepsilon\} \tag{69}$$

or

$$\frac{dy}{dt} = -y - (y+a-b)h(y) + (y+a-b)h(y)$$

$$\times\exp[-\omega(y,\varepsilon)t/\varepsilon]. \tag{70}$$

As we only take a few terms of the expansions of $h(y)$ and $dh(y)/dy$, the lumped differential equation is an approximate one. If we choose

$$h(y) = h_0(y) + \varepsilon h_1(y) + \varepsilon^2 h_2(y) + \cdots + \varepsilon^k h_k(y), \tag{71}$$

the lumped differential equation of $y(t)$ is the kth-order approximation of the original equation.

To show how good the resultant approximately lumped differential equations of $y(t)$ are, some calculations were done using the data from the hydrolysis of the benzoyl-L-arginine ethyl ester, catalyzed by trypsin.[20,21] $k_1=4\times10^6$, $k_{-1}=25$, and $k_2=15$ giving $a=1$ and $b=0.375$ when s_0 is equal to the Michaelis constant (k_{-1}

$+k_2)/k_1$. Suppose the initial values are $s(0)=s_0$ and $c(0)=0$. This gives $y(0)=1$ and $z(0)=0$. The value of $z(t)$ can be obtained by

$$z(t)=\phi(t)-h[y(t)]. \tag{72}$$

Under this condition, the lumped differential equations given by Eqs. (69) and (70) are as follows:

$$\frac{dy}{dt}=-\frac{0.375y}{y+1}+\varepsilon\frac{0.375y(y+0.625)}{(y+1)^4}-\varepsilon^2\frac{0.375y(y+0.625)(2.125y+0.25)}{(y+1)^7}+\cdots+(y+0.625)$$

$$\times(-0.5-0.0234\varepsilon+0.0070\varepsilon^2+\cdots)\exp\left[-\left(\frac{2}{\varepsilon}+0.4063-0.0381\varepsilon+0.0182\varepsilon^2+\cdots\right)t\right] \tag{73}$$

and

$$\frac{dy}{dt}=-y-(y+0.625)\left[-\frac{y}{y+1}-\varepsilon\frac{0.375y}{(y+1)^4}+\varepsilon^2\frac{0.375y(2.125y+0.25)}{(y+1)^7}+\cdots\right]\left(1-\exp\left\{-\left[\frac{y+1}{\varepsilon}+\frac{y+0.625}{(y+1)^2}\right.\right.\right.$$

$$-\varepsilon\frac{0.375(3y-1)(y+0.625)}{(y+1)^5}-\varepsilon^2\frac{0.375(y+0.625)(-10.625y^2+2.75y+0.25)}{(y+1)^8}+\cdots\right]t\right\}\right). \tag{74}$$

If we only take the terms of ε with powers equal to or less than 2, 1, and 0, the equations are referred to as the second, first, and zeroth order approximations. Typically, $\varepsilon\sim10^{-6}$, however, we used much larger values $\varepsilon=0.01$, 0.1, and 1.0. The results of Eq. (74) are given in Figs. 1–4. For comparison, we also show the solution obtained by the application of the quasisteady-state approximation to the variable z. A full discussion of the connections between the approaches is presented in the conclusions section. For $\varepsilon=0.01$, the zeroth order approximation gives essentially

the same $y(t)$ and $z(t)$ as those given by the original equations. For $\varepsilon=0.1$, the first order approximation is almost exact. For $\varepsilon=1.0$, the values of $y(t)$ and $z(t)$ given by the second order approximation are very close to the exact solutions. This shows that the singular perturbation method can be employed to construct a lumped differential equation system with any desired accuracy for an arbitrary initial composition of any system described by Eqs. (1) and (2) if one chooses enough terms of $\mathbf{h(y)}$ and ϕ. From this example, we see that ε can even take the value 1.
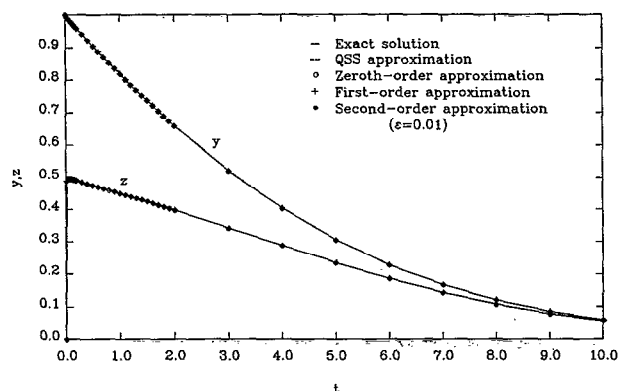

FIG. 1. A comparison between the solutions $y(t)$ and $z(t)$ given by the original differential equation system and the lumped differential equation [Eqs. (68) and (74)] for $\varepsilon=0.01$.
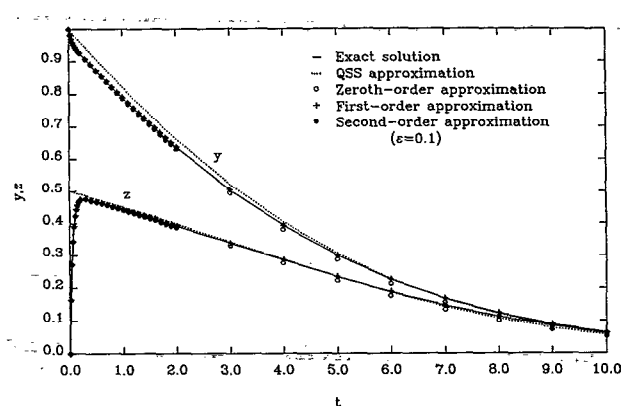

FIG. 2. A comparison between the solutions $y(t)$ and $z(t)$ given by the original differential equation system and the lumped differential equation [Eqs. (68) and (74)] for $\varepsilon=0.1$.
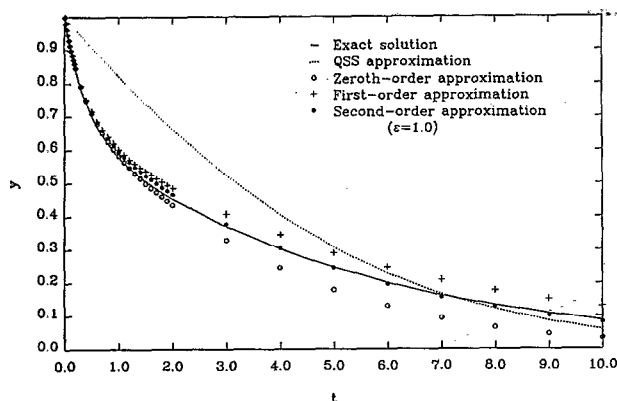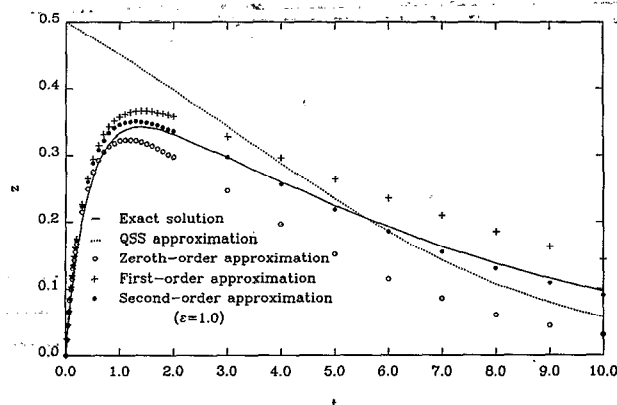
FIG. 3. A comparison between the solutions $y(t)$ given by the original differential equation system and the lumped differential equation [Eqs. (68) and (74)] for $\varepsilon = 1$.

The convergence rate of the expansion of $h(y)$ and ϕ can be accelerated by a special transformation. Let us define a linear partial differential operator A from Eq. (49) as

$$A = [y - (y+a)z] \frac{\partial}{\partial z}. \tag{75}$$

A function $\Phi(y,z)$ is called an invariant of A if

$$A\Phi(y,z) = 0. \tag{76}$$

A function $\varphi(y,z)$ is called an eigenfunction of A if

$$A\varphi(y,z) = \lambda(y,z)\varphi(y,z), \tag{77}$$

where $\lambda(y,z)$ is an invariant of A and referred to as the eigenvalue of A corresponding to $\varphi(y,z)$. Obviously, y is an invariant of A defined by Eq. (75). The eigenfunctions of A can be readily determined by solving the partial differential equation

$$[y - (y+a)z] \frac{\partial \varphi}{\partial z} = \lambda(y,z)\varphi(y,z). \tag{78}$$

The corresponding characteristic equation of Eq. (78) is

$$\frac{dz}{y-(y+a)z} = \frac{d\varphi}{\lambda(y,z)\varphi(y,z)}. \tag{79}$$

One solution is

FIG. 4. A comparison between the solutions $z(t)$ given by the original differential equation system and the lumped differential equation [Eqs. (68) and (74)] for $\varepsilon = 1$.

$$\varphi(y,z) = \frac{y}{y+a} - z \tag{80}$$

and

$$A\varphi(y,z) = -(y+a)\varphi(y,z). \tag{81}$$

This shows that

$$\lambda(y,z) = -(y+a). \tag{82}$$

Using y and φ as a new base, Eqs. (48) and (49) can be transformed to

$$\frac{dy}{dt} = -\frac{by}{y+a} - (y+a-b)\varphi, \tag{83}$$

$$\varepsilon \frac{d\varphi}{dt} = -\varepsilon \frac{aby}{(y+a)^3} - \left[(y+a) + \epsilon \frac{a(y+a-b)}{(y+a)^2} \right]\varphi. \tag{84}$$

Notice that here we used ϵ instead of ε on the right-hand side of Eq. (84), so it will not be considered in the determination of the expansion of $h(y)$. If we still use ε, the result will be identical to that obtained previously. Since Eqs. (83) and (84) have the same form as Eqs. (1) and (2), we can use the perturbation method to find the lumped differential equation for $y(t)$.

Similarly, we define a purely fast variable

$$\phi(t) = \varphi(t) + h[y(t)]. \tag{85}$$

Following the same procedure, we have

$$\varepsilon\dot{\phi}(t) = \varepsilon\dot{\varphi}(t) + \varepsilon\dot{h}[y(t)]$$

$$= -\left[(y+a) + \epsilon \frac{a(y+a-b)}{(y+a)^2} \right][\phi - h(y)] - \epsilon \frac{aby}{(y+a)^3} - \varepsilon \frac{dh(y)}{dy} \left[\frac{by}{y+a} + (y+a-b)[\phi - h(y)] \right]$$

$$= -\left[(y+a) + \epsilon \frac{a(y+a-b)}{(y+a)^2} + \varepsilon \frac{dh(y)}{dy}(y+a-b) \right]\phi + \left[(y+a) + \epsilon \frac{a(y+a-b)}{(y+a)^2} \right]h(y) - \epsilon \frac{aby}{(y+a)^3}$$

$$+ \varepsilon \frac{dh(y)}{dy} \left[\frac{-by}{y+a} + (y+a-b)h(y) \right]. \tag{86}$$

We will obtain a stable (as $\varepsilon \to 0$) equation for the purely fast variable ϕ,

$$\varepsilon\dot{\phi}(t) = -\left[(y+a) + \epsilon\frac{a(y+a-b)}{(y+a)^2} \right.$$
$$\left. + \varepsilon\frac{dh(y)}{dy}(y+a-b) \right]\phi \qquad (87)$$

provided $h(y)$ is selected as the solution of the following equation:

$$\varepsilon\frac{dh(y)}{dy}\left[\frac{-by}{y+a} + (y+a-b)h(y) \right]$$
$$+ \left[(y+a) + \epsilon\frac{a(y+a-b)}{(y+a)^2} \right]h(y) - \epsilon\frac{aby}{(y+a)^3} = 0. \qquad (88)$$

Let

$$h(y) = \sum_{i=0}^{\infty} \varepsilon^i h_i(y). \qquad (89)$$

Substituting for $h(y)$ in Eq. (88) and setting the coefficients of like powers of ε equal to zero gives equations to determine $h_i(y)$. For $h_0(y)$, we obtain

$$\left[(y+a) + \epsilon\frac{a(y+a-b)}{(y+a)^2} \right]h_0(y) - \epsilon\frac{aby}{(y+a)^3} = 0, \qquad (90)$$

which gives

$$h_0(y) = \frac{\epsilon aby}{(y+a)^4 + \epsilon a(y+a)(y+a-b)}. \qquad (91)$$

The derivative of $h_0(y)$ with respect to y can be readily obtained as

$$\frac{dh_0(y)}{dy}$$
$$= \frac{\epsilon ab[(y+a)^3(a-3y) - \epsilon ay(y+a) + \epsilon a^2(y+a-b)]}{[(y+a)^4 + \epsilon a(y+a)(y+a-b)]^2}. \qquad (92)$$

If we approximate $h(y)$ only by $h_0(y)$, the zeroth order approximation of dy/dt is the following:

$$\frac{dy}{dt} = -\frac{by}{y+a} + (y+a-b)h_0(y)$$
$$- (y+a-b)\phi(0)\exp\{-\omega[y(0),\varepsilon]t/\varepsilon\}$$
$$= -\frac{by}{y+a} + (y+a-b)h_0(y) - (y+a-b)\left\{ \frac{y(0)}{y(0)+a} \right.$$
$$\left. + h_0[y(0)] \right\}\exp\{-\omega[y(0),\varepsilon]t/\varepsilon\}, \qquad (93)$$

where

$$\omega(y,\varepsilon) = (y+a) + \varepsilon\frac{a(y+a-b)}{(y+a)^2} + \frac{\varepsilon^2 ab(y+a-b)[(y+a)^3(a-3y) - \varepsilon ay(y+a) + \varepsilon a^2(y+a-b)]}{[(y+a)^4 + \varepsilon a(y+a)(y+a-b)]^2}. \qquad (94)$$

In the resultant equation, we do not distinguish ϵ and ε. The lumped differential equation applicable for any initial composition has the form

$$\frac{dy}{dt} = -\frac{by}{y+a} + (y+a-b)h_0(y) - (y+a-b)$$
$$\times \left[\frac{y}{y+a} + h_0(y) \right]\exp[-\omega(y,\varepsilon)t/\varepsilon]. \qquad (95)$$

As the last term in Eq. (94) is quite complicated, but much smaller than the other terms, it will be omitted. From the calculations, it is clear that this omission does not influence the accuracy of the solution. The simplified $\omega(y,\varepsilon)$ is given by

$$\omega(y,\varepsilon) = (y+a) + \varepsilon\frac{a(y+a-b)}{(y+a)^2}. \qquad (96)$$

From Figs. 3 and 4, one sees that the different order approximations gradually approach the exact solution from both sides. The initial value of $\phi(0)$ for different order

approximations are around $y(0)/[y(0)+a] = 0.5$ in this example. Therefore, we can write the lumped differential equation for y as

$$\frac{dy}{dt} = -\frac{by}{y+a} + \frac{\varepsilon aby(y+a-b)}{(y+a)^4 + \varepsilon a(y+a)(y+a-b)}$$
$$- 0.5(y+a-b)\exp[-\omega(y,\varepsilon)t/\varepsilon], \qquad (97)$$

where $\omega(y,\varepsilon)$ is given by Eq. (96). For $a=1$, $b=0.375$, $y(0)=1$, $\varphi(0)=1/2$, and $\varepsilon=1$, the results of the zeroth order approximation (95) [$\omega(y,\varepsilon)$ are given by Eq. (94)], the simplified zeroth order approximation [$\omega(y,\varepsilon)$ is given by Eq. (96)] and Eq. (97) are given in Fig. 5. The accuracy of the zeroth order approximation for Eqs. (83) and (84) is the same as that given by the second order approximation for Eqs. (48) and (49). This shows that the convergence rate in the expansion of $h(y)$ and ϕ has been accelerated by the special transformation. Finally, the results of Eq. (97) are almost exact.
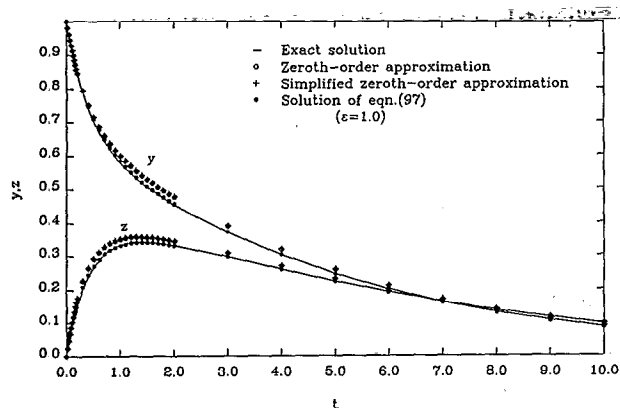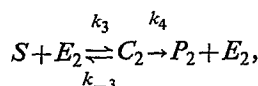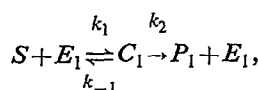
FIG. 5. A comparison between the solutions $y(t)$ and $z(t)$ given by the original differential equation system and the lumped differential equation [Eq. (95)] for $\varepsilon=1$.

B. Example 2

Let us consider another reaction, in which two enzymes act on one substrate

$$S+E_1 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C_1 \overset{k_2}{\rightarrow} P_1+E_1,$$

$$S+E_2 \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} C_2 \overset{k_4}{\rightarrow} P_2+E_2,$$

where E_i, C_i, and P_i ($i=1$ and 2) represent the two enzymes, complexes, and products, respectively. If we use lower-case letters to represent their concentrations, the corresponding kinetic equation system is as follows:

$$\frac{ds}{dt} = -k_1 s e_1 - k_3 s e_2 + k_{-1} c_1 + k_{-3} c_2, \qquad (98)$$

$$\frac{de_1}{dt} = -k_1 s e_1 + (k_{-1}+k_2) c_1, \qquad (99)$$

$$\frac{dc_1}{dt} = k_1 s e_1 - (k_{-1}+k_2) c_1, \qquad (100)$$

$$\frac{de_2}{dt} = -k_3 s e_2 + (k_{-3}+k_4) c_2, \qquad (101)$$

$$\frac{dc_2}{dt} = k_3 s e_2 - (k_{-3}+k_4) c_2, \qquad (102)$$

$$\frac{dp_1}{dt} = k_2 c_1, \qquad (103)$$

$$\frac{dp_2}{dt} = k_4 c_2. \qquad (104)$$

Notice that $e_i + c_i$ is a constant. If at time $t=0$ $s=s_0$, $e_i=e_{i0}$, and $c_i=p_i=0$, then

$$e_i + c_i = e_{i0} \quad (i=1,2). \qquad (105)$$

As there are only three independent equations, we choose Eqs. (98), (100), and (102). Substituting Eq. (105) into them yields

$$\frac{ds}{dt} = -(k_1 e_{10}+k_3 e_{20})s + (k_1 s+k_{-1})c_1 + (k_3 s+k_{-3})c_2, \qquad (106)$$

$$\frac{dc_1}{dt} = k_1 e_{10} s - (k_1 s+k_{-1}+k_2)c_1, \qquad (107)$$

$$\frac{dc_2}{dt} = k_3 e_{20} s - (k_3 s+k_{-3}+k_4)c_2. \qquad (108)$$

Now make the equations dimensionless by taking

$$y = \frac{s}{s_0}, \quad z_1 = \frac{c_1}{e_{10}+(k_3/k_1)e_{20}}, \quad z_2 = \frac{c_2}{(k_1/k_3)e_{10}+e_{20}}, \qquad (109)$$

$$\bar{t} = (k_1 e_{10}+k_3 e_{20})t, \quad \varepsilon_1 = \frac{k_1 e_{10}+k_3 e_{20}}{k_1 s_0},$$

$$\varepsilon_2 = \frac{k_1 e_{10}+k_3 e_{20}}{k_3 s_0}, \qquad (110)$$

$$a_1 = \frac{k_{-1}+k_2}{k_1 s_0}, \quad a_2 = \frac{k_{-3}+k_4}{k_3 s_0}, \quad b_1 = \frac{k_2}{k_1 s_0}, \quad b_2 = \frac{k_4}{k_3 s_0}, \qquad (111)$$

$$\mu = \frac{k_1 e_{10}}{k_1 e_{10}+k_3 e_{20}}. \qquad (112)$$

Then we obtain the desired form for the application of the singular perturbation method

$$\frac{dy}{dt} = -y + (y+a_1-b_1)z_1 + (y+a_2-b_2)z_2, \qquad (113)$$

$$\varepsilon_1 \frac{dz_1}{dt} = \mu y - (y+a_1)z_1, \qquad (114)$$

$$\varepsilon_2 \frac{dz_2}{dt} = (1-\mu)y - (y+a_2)z_2 \qquad (115)$$

with the initial condition $y=1$ and $z_1=z_2=0$ at $t=0$. For the sake of simplicity, we still use t to represent $\bar{t}$ in Eqs. (113)–(115).

Let us consider a numerical example of the above system. k_1, k_{-1}, and k_2 take the same values as those used in example 1, and $k_3=1\times10^6$, $k_{-3}=90$, $k_4=10$, and $e_{10}=e_{20}=e_0$. This gives $a_1=1$, $a_2=10$, $b_1=0.375$, $b_2=1$, and $\mu=0.8$ when s_0 is equal to the Michaelis constant $(k_{-1}+k_2)/k_1$ for the first reaction. In this case,

$$\varepsilon_1 = \frac{k_1+k_3}{k_1} \cdot \frac{e_0}{s_0} = 1.2\frac{e_0}{s_0}, \qquad (116)$$

$$\varepsilon_2 = \frac{k_1+k_3}{k_3} \cdot \frac{e_0}{s_0} = 5\frac{e_0}{s_0}. \qquad (117)$$

Using these data, Eqs. (113)–(115) become

$$\frac{dy}{dt} = -y + (y+0.625)z_1 + (y+9)z_2, \qquad (118)$$

$$\varepsilon_1 \frac{dz_1}{dt} = 0.8y - (y+1)z_1, \tag{119}$$

$$\varepsilon_2 \frac{dz_2}{dt} = 0.2y - (y+10)z_2. \tag{120}$$

Comparing these equations to Eqs. (1) and (2), we find that

$$a(y) = -y, \tag{121}$$

$$A(y) = (y + 0.625 \ y + 9), \tag{122}$$

$$b(y) = \begin{pmatrix} 0.8y \\ 0.2y \end{pmatrix}, \tag{123}$$

$$B(y) = \begin{bmatrix} -(y+1) & \\ & -(y+10) \end{bmatrix}, \tag{124}$$

$$B^{-1}(y) = \begin{bmatrix} -1/(y+1) & \\ & -1/(y+10) \end{bmatrix}, \tag{125}$$

$$\varepsilon = \begin{pmatrix} \varepsilon_1 & \\ & \varepsilon_2 \end{pmatrix}. \tag{126}$$

Similarly, we first define a purely fast variable vector ϕ by splitting off the slow part of z. Let

$$\phi(t) = \mathbf{z}(t) + \mathbf{h}[y(t)], \tag{127}$$

and

$$\mathbf{h}(y) = \sum_{i=0}^{\infty} \varepsilon^i \mathbf{h}_i(y), \tag{128}$$

$$\mathbf{h}_y(y) = \sum_{i=0}^{\infty} \varepsilon^i \mathbf{h}_{iy}(y), \tag{129}$$

$$\phi(\tau,\varepsilon) = \sum_{i=0}^{\infty} \varepsilon^i \phi_i(\tau). \tag{130}$$

$\mathbf{h}_0(y)$ and $\mathbf{h}_1(y)$ can be determined by Eqs. (12) and (14). The results are the following:

$$\mathbf{h}_0(y) = \begin{bmatrix} (-0.8y)/(y+1) \\ (-0.2y)/(y+10) \end{bmatrix}, \tag{131}$$

$$\mathbf{h}_1(y) = \begin{Bmatrix} [-0.4y(y+6.4)]/[(y+1)^4(y+10)] \\ [-y(y+6.4)]/[(y+1)(y+10)^4] \end{Bmatrix}. \tag{132}$$

The corresponding Jacobian matrices for $\mathbf{h}_0(y)$ and $\mathbf{h}_1(y)$ are

$$\frac{d\mathbf{h}_0(y)}{dy} = \begin{Bmatrix} [-0.8/(y+1)^2] \\ -2/[(y+10)^2] \end{Bmatrix}, \tag{133}$$

$$\frac{d\mathbf{h}_1(y)}{dy} = \begin{Bmatrix} (1.2y^3 + 17.84y^2 + 68.8y - 25.6)/[(y+1)^5(y+10)^2] \\ (3y^3 + 17.6y^2 - 0.8y - 64)/[(y+1)^2(y+10)^5] \end{Bmatrix}. \tag{134}$$

Similarly $\phi_i(i=0,1)$ can be determined by Eqs. (27) and (32). The results are the following:

$$\phi_0(t,\varepsilon) = \begin{Bmatrix} [(-0.8y)/(y+1)]\exp[-(y+1)t/\varepsilon_1] \\ [(-0.2y)/(y+10)]\exp[-(y+10)t/\varepsilon_2] \end{Bmatrix}, \tag{135}$$

$$\phi_1(t,\varepsilon) = \begin{Bmatrix} \omega_{11}(y,t,\varepsilon)\exp[-(y+1)t/\varepsilon_1] + \omega_{12}(y,t,\varepsilon)\exp[-(y+10)t/\varepsilon_2] \\ \omega_{21}(y,t,\varepsilon)\exp[-(y+1)t/\varepsilon_1] + \omega_{22}(y,t,\varepsilon)\exp[-(y+10)t/\varepsilon_2] \end{Bmatrix}, \tag{136}$$

where

$$\omega_{11}(y,t,\varepsilon) = -\frac{0.4y(y+6.4)}{(y+1)^4(y+10)} - \frac{0.16\varepsilon_2 y(y+9)}{(y+1)^2(y+10)[\varepsilon_2(y+1) - \varepsilon_1(y+10)]} + \frac{0.64y(y+0.645)}{\varepsilon_1(y+1)^3}t, \tag{137}$$

$$\omega_{12}(y,t,\varepsilon) = \frac{0.16\varepsilon_2 y(y+9)}{(y+1)^2(y+10)[\varepsilon_2(y+1) - \varepsilon_1(y+10)]}, \tag{138}$$

$$\omega_{21}(y,t,\varepsilon) = -\frac{1.6\varepsilon_1 y(y+0.625)}{(y+1)(y+10)^2[\varepsilon_2(y+1) - \varepsilon_1(y+10)]}, \tag{139}$$

$$\omega_{22}(y,t,\varepsilon) = -\frac{y(y+6.4)}{(y+1)(y+10)^4} + \frac{1.6\varepsilon_1 y(y+0.625)}{(y+1)(y+10)^2[\varepsilon_2(y+1) - \varepsilon_1(y+10)]} + \frac{0.4y(y+9)}{\varepsilon_2(y+10)^3}t. \tag{140}$$

If we want to obtain the special solution for $y(0)=1$, substituting $y=1$ into above equations yields

$$\phi_0(t,\varepsilon)=\begin{pmatrix} -0.4e^{-2t/\varepsilon_1} \\ -0.018\,18e^{-11t/\varepsilon_2} \end{pmatrix}, \qquad (141)$$

$$\phi_1(t,\varepsilon)=\begin{bmatrix} \omega_{11}(t,\varepsilon)e^{-2t/\varepsilon_1}+\omega_{12}(t,\varepsilon)e^{-11t/\varepsilon_2} \\ \omega_{21}(t,\varepsilon)e^{-2t/\varepsilon_1}+\omega_{22}(t,\varepsilon)e^{-11t/\varepsilon_2} \end{bmatrix}, \qquad (142)$$

where

$$\omega_{11}(t,\varepsilon)=-0.016\,82-\frac{0.036\,36\varepsilon_2}{2\varepsilon_2-11\varepsilon_1}+\frac{0.13}{\varepsilon_1}\,t, \qquad (143)$$

$$\omega_{12}(t,\varepsilon)=\frac{0.036\,36\varepsilon_2}{2\varepsilon_2-11\varepsilon_1}, \qquad (144)$$

$$\omega_{21}(t,\varepsilon)=-\frac{0.010\,74\varepsilon_1}{2\varepsilon_2-11\varepsilon_1}, \qquad (145)$$

$$\omega_{22}(t,\varepsilon)=-0.000\,253+\frac{0.010\,74\varepsilon_1}{2\varepsilon_2-11\varepsilon_1}+\frac{0.003}{\varepsilon_2}\,t. \qquad (146)$$

The lumped differential equation of $y(t)$ is

$$\frac{d\mathbf{y}}{dt}=\mathbf{a}(\mathbf{y})-A(\mathbf{y})\mathbf{h}(\mathbf{y})+A(\mathbf{y})\phi(t,\varepsilon)$$

$$=\mathbf{a}(\mathbf{y})-A(\mathbf{y})[\mathbf{h}_0(\mathbf{y})+\varepsilon\mathbf{h}_1(\mathbf{y})+\cdots]$$

$$+A(\mathbf{y})[\phi_0(t,\varepsilon)+\varepsilon\phi_1(t,\varepsilon)+\cdots]. \qquad (147)$$

Let $e_0/s_0=0.2$. This gives $\varepsilon_1=0.24$ and $\varepsilon_2=1.0$. In this case, we need consider only the first and zeroth order approximations. Actually, the first order approximation is almost exact. In Fig. 6, we show the profiles resulting from the lumped differential equation which is applicable for any initial composition, i.e., $\phi_i(i=0,1)$ given by Eqs. (135)–(140). For the specified initial composition, i.e., $\phi_i(i=0,1)$ given by Eqs. (141)–(146), the results are essentially the same.
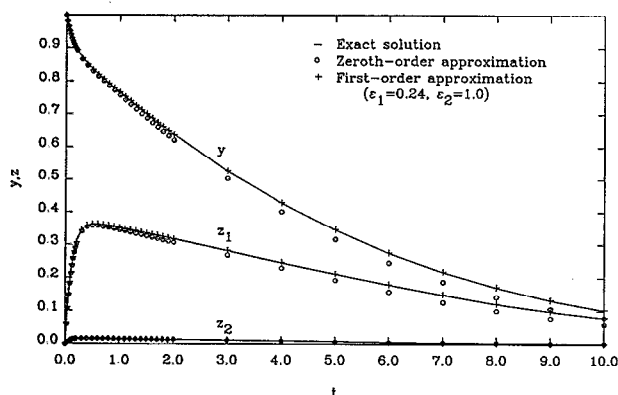

FIG. 6. A comparison between the solutions $y(t)$ and $z_i(t)$ given by the original differential equation system and the lumped differential equation (147) [ϕ_i are given by Eqs. (135)–(140)] for $\varepsilon_1=0.24$ and $\varepsilon_2=1$.

IV. CONCLUSIONS AND DISCUSSION

A singular perturbation method was presented for the determination of a nonlinear lumped model for a reaction system with kinetic equations in the form of Eqs. (1) and (2), containing a group of small positive parameters corresponding to different time scales. The key point of this approach is to separate a purely fast variable vector $\phi(t)$ from the vector $\mathbf{z}(t)$ which will not occur in the lumped differential equation system. The expansions of vector $\mathbf{h}(\mathbf{y})$ and $\phi(t)$ can be determined by the singular perturbation method.

Two simple biochemical reactions show that this approach can construct a lumped differential equation system with any desired accuracy and applicable for any initial composition. As the small parameters can take the value 1 in some cases, this approach is not restricted to systems containing such small parameters.

The transformation from $\mathbf{z}(t)$ to $\phi(t)$ has a clear geometric explanation. Consider the equation

$$\phi(t)=\mathbf{z}(t)+\mathbf{h}[\mathbf{y}(t)]. \qquad (148)$$

Notice that $\phi(t)$ is an exponential function vector and approaches $\mathbf{0}$ at small t. Then

$$\mathbf{z}(t)=-\mathbf{h}[\mathbf{y}(t)] \qquad (149)$$

represents an inertial manifold which attracts all solution trajectories. When the initial composition is located in this manifold, the solution will remain in it for all time and therefore it is an invariant manifold. When the initial composition is located out of the manifold, the solution will approach it exponentially fast. Hence

$$\frac{d\mathbf{y}}{dt}=\mathbf{a}(\mathbf{y})-A(\mathbf{y})\mathbf{h}(\mathbf{y}) \qquad (150)$$

and Eq. (149) are an approximation of Eqs. (1) and (2) giving the solutions in the inertial manifold of the original equation system. The term $A(\mathbf{y})\phi(t,\varepsilon)$ is the correction of this approximation and Eqs. (149) and (150) will be a good approximation if and only if ε has very small elements. By disregarding this correction term, we restrict the dynamics of the lumped system to the slow inertial manifold and therefore loose some information about the initial reaction period. Equations (149) and (150) provide both the equation of the manifold and the speed of motion along the manifold rather than a purely geometrical interpretation.

The above approach has close connections with the application of the quasisteady-state approximation (QSSA). In fact, the zeroth-order approximation to the invariant manifold

$$\mathbf{z}(t)=-\mathbf{h}_0[\mathbf{y}(t)] \qquad (151)$$

and the resulting approximation to Eqs. (1) and (2)

$$\frac{d\mathbf{y}}{dt}=\mathbf{a}(\mathbf{y})-A(\mathbf{y})\mathbf{h}_0(\mathbf{y}) \qquad (152)$$

are simply the equations resulting from the application of the QSSA to the species $\mathbf{z}$. It is clear from the application

of singular perturbation theory that the quasisteady-state approximation does not strictly describe the global invariant manifold of the system and that the error induced can have a significant effect.[22] Strictly, to define the invariant manifold, we must include all terms in the approximation for $h(y)$ and therefore the higher order terms

$$-\varepsilon h_1 - \varepsilon^2 h_2 - \cdots$$

describe the error in the steady-state species z induced by the application of the QSSA.

In Figs. 1–4, we have presented the quasisteady-state solution for comparison with the different order approximations obtained from the singular perturbation approach. As expected, the agreement is good for small values of ε such as $\varepsilon = 0.01$. As ε becomes larger, the quasisteady-state solution begins to differ significantly from the exact solution, where the higher order singular perturbation approximations do not. There are two reasons for this. First, the QSSA is not applicable over the whole reaction time. There is an induction period where it is not valid, which will become larger as ε increases. Second, for large ε, the higher order terms of h are important, and for $\varepsilon = 1$, can become comparable to h_0. The inclusion of both the exponential term and higher order terms for h means that the present approach provides a good approximation for larger values of ε over the whole reaction period when the QSSA does not. This can be seen immediately from the results shown in Figs. 3 and 4.

For many systems, it may not be trivial or even possible to define dimensionless variables which reveal relative time scales. The small parameter in some cases can be "hidden," but the above technique can still be applied and ε_i taken to be 1. As a general rule of thumb, we can say that the faster the variables z, the fewer terms needed in the approximation. It would be helpful to use techniques such as the computational singular perturbation method to obtain some knowledge about the relative time scales in order to identify the faster species to which the approximation will best apply.

In Sec. III A, we presented a method for accelerating the convergence rate of the expansion of $h(y)$ and ϕ. By first recasting the equations in new variables before applying singular perturbation methods, we were able to use only the zeroth order approximation to describe the behavior in the inertial manifold. The physical interpretation of the method is again clear and can be described as the double application of the quasisteady state. The new variable φ was effectively defined as

$$\varphi = -(h_0 + z) \tag{153}$$

[where h_0 is that from the application of the singular perturbation approach to the original equations (48) and (49)], the difference between the real value of z and its

quasisteady-state value $-h_0$. By finding the zeroth order approximation to Eqs. (83) and (84) describing y and φ, we are again applying the quasisteady state to φ, i.e., we find the effective error in the quasisteady state for z after an induction period and correct for it in the equation for y. In this way, we find a good approximation to the inertial manifold and again we can provide a further correction through an exponential term in order to describe the whole reaction period.

Even though this approach can give a very good lumped differential equation system, the form of Eqs. (1) and (2) is too restrictive in many cases. There can be no coupling between the species z_i and z_j as would occur in a radical–radical termination reaction, for example. In such a system only a subset of the radical species could be removed. For more general cases, we still need to consider approximate nonlinear lumping through the determination of the global invariant manifolds and eigenfunctions or generalized eigenfunctions.[10]

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