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Quasi-steady state reduction for compartmental systems

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ABSTRACT

We present a method to determine an asymptotic reduction (in the sense of Tikhonov and Fenichel) for singularly perturbed compartmental systems in the presence of slow transport. It turns out that the reduction can be derived from the individual interaction terms alone. We apply the result to spatially discretized reaction–diffusion systems and obtain (based on the reduced discretized systems) a heuristic to reduce reaction–diffusion systems in presence of slow diffusion.

1. Introduction

Quasi-steady state (QSS) phenomena occur frequently in the modeling and analysis of chemical or biological processes. They are particularly relevant for reduction of dimension. QSS is nowadays frequently seen as a singular perturbation problem. But the explicit computation of reductions may pose a substantial problem if no a priori separation into slow and fast variables is known. There are various methods of reduction (e.g. Kaper, Kaper and Zagaris [1], Lee and Othmer [2], Schauer and Heinrich [3], Stiefenhofer [4], Bothe [5], Lam and Goussis [6]), which are often based on the classical theories of Tikhonov [7] and Fenichel [8]. Following most of these references one will generally need to solve some implicit equation and therefore be forced to accept approximations for the reduced system on the slow manifold. The approach developed in [9,10] is applicable to the special case of (autonomous) polynomial or rational ODE systems and provides an explicit first order reduction in algorithmic manner, with the slow manifold being contained in an algebraic variety. Since many reaction systems are of this type (due to mass action kinetics) the range of applicability is reasonably broad. In the present paper we extend this approach to compartmental systems, i.e. ordinary differential equations which model systems that are governed by transport between subsystems and interaction within these subsystems. In particular, we determine an asymptotic reduction of such systems in presence of slow transport (with fast and slow interactions). As an important application, we develop a heuristical method to compute a reduction of reaction–diffusion systems in presence of slow diffusion.

The paper can be summarized as follows: In Section 2 we give a short review of Tikhonov–Fenichel reductions (in the sense of [9,10]) for autonomous ODEs. Assuming the existence of a kernel-image decomposition of $\mathbb{R}^m$ with respect to the Jacobian of the fast part of right-hand side h (e.g. the fast reactions of a reaction system) at certain points in its zero set, one can determine a reduced system in closed form by projecting the slow part of h to its kernel component relative to the above decomposition.

In Section 3 we extend this result to compartmental ODE systems. It turns out that the reduction can be derived from the individual interaction terms in the subsystems alone. An application to a SIR model is given.

In the context of reaction–diffusion systems it is known that already finding appropriate candidates for (asymptotically) reduced systems may be problematic. Our contribution to this problem – discussed in Section 4 – is a heuristical method to find such a candidate. Moreover, we show the consistency of the proposed reduction. Our heuristic starts from considering spatially discretized reaction–diffusion systems as compartmental systems.

In the final section, we discuss some examples. We compare our heuristical reduction to known results in the literature and discuss systems where no previous results seem to be known.

2. Review of Tikhonov–Fenichel reductions

While Tikhonov's theorem (see [11, Theorem 8.1]) is directly applicable only if the variables are separated into fast and slow ones, Fenichel overcame this problem, but generally gave no

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explicit form of the reduction. We briefly sketch a specialized approach for polynomial and rational systems developed in Noethen & Walcher [12,9].

Let $S \subset \mathbb{R}^m$ be open, $\varepsilon_0 > 0$ and $h\colon S \times [0, \varepsilon_0) \to \mathbb{R}^m$ a rational map with zero set $\mathcal{V}(h^{(0)}) = \{x \in U,\ h^{(0)}(x) = 0\}$ containing a submanifold of positive dimension. Consider singularly perturbed ODE systems of the type

$$\dot{x} = h(x, \varepsilon) = h^{(0)}(x) + \varepsilon h^{(1)}(x) + \cdots, \quad x \in S. \tag{2.1}$$

Rewriting (2.1) in slow time $\tau = \varepsilon t$, we get

$$x' = \varepsilon^{-1} h^{(0)}(x) + h^{(1)}(x) + \cdots, \quad x \in S. \tag{2.2}$$

In the following, we will refer to $h^{(0)}$ as the *fast part* of the evolution equation and $h^{(1)}$ as the *slow part*. For this type of systems, an explicit reduction formula was given in [10]. We state a variant of [10, Theorem 1] (see also [10, Remark 2]):

Theorem 2.1. *Consider system (2.1) with rational right-hand side h. Let x_0 be a point in the zero set $\mathcal{V}(h^{(0)})$ of $h^{(0)}$, such that* rank $Dh^{(0)}(x_0) = r$ *is maximal in a neighborhood of x_0. Thus, there exists a neighborhood $U \subset S$ of x_0, such that $\mathcal{U} = U \cap \mathcal{V}(h^{(0)})$ is a $(m-r)$-dimensional submanifold. Assume moreover that there exists a direct sum decomposition*

$$\mathbb{R}^m = \ker Dh^{(0)}(x_0) \oplus \operatorname{im} Dh^{(0)}(x_0).$$

Then the following holds:

(a) *There exists a product decomposition with*

$$P\colon U \to \mathbb{R}^{m\times r} \quad \text{and} \quad \mu\colon U \to \mathbb{R}^r$$

both rational, such that

$$h^{(0)}(x) = P(x)\mu(x), \quad x \in U$$

with rank $P(x_0) =$ rank $D\mu(x_0) = r$. *Moreover, the zero set Y of μ satisfies $Y \cap U = \mathcal{U}$. The entries of μ may be taken as any r entries of $h^{(0)}$ that are functionally independent in x_0.*

(b) *The following system is defined in U:*

$$x' = Q(x) \cdot h^{(1)}(x) \tag{2.3}$$

with

$$Q(x) = Id - P(x)(D\mu(x)P(x))^{-1} D\mu(x).$$

Every component of μ is a first integral of (2.3). In particular, $\mathcal{U}$ is an invariant set of (2.3).

(c) *If all nonzero eigenvalues of $Dh^{(0)}(x_0)$ have negative real part, then there exists $T > 0$ and a neighborhood $U^* \subset U$ of $\mathcal{U}$, such that solutions of (2.1) starting in U^* converge uniformly on $[t_0, T]$ to solutions of the reduced system (2.3) on $\mathcal{U}$ for $\varepsilon \to 0$ and any $t_0 > 0$.*

Remark 1. In the following we will use some notions and properties regarding algebraic varieties, which we briefly summarize (for details see Shafarevich [13]): The Zariski topology on $\mathbb{R}^m$ has as its closed sets common zeros of some collection of polynomial functions; these are also called (algebraic) varieties. Every such variety Y is the union of finitely many irreducible ones (i.e. ones that are not the union of two proper Zariski-closed sets). Each irreducible component of Y is in turn the union of finitely many submanifolds of $\mathbb{R}^m$. A point of Y is called simple if it is contained in just one irreducible component and in a submanifold of maximal dimension of that component.

Remark 2. (a) The approximation is of leading order only.

(b) More general types of invariant manifolds require a much more intricate theory (Fenichel [14,8]) and explicit reduction formulas (as opposed to iterative schemes) do not seem possible in this more general setting. However, our setting is sufficiently broad for application in the chemical and biological context.

(c) The submanifold $\mathcal{U}$ is often called (asymptotic) *slow manifold* [11,2,4,1]. In physics context it is also referred to as an adiabatic manifold [15]. We will also call $\mathcal{V}(h^{(0)})$ the slow manifold, even if this is technically incorrect.

(d) $Q(x)$ will be called the *projection operator* of $h^{(0)}$ with respect to x_0 as it projects every $y \in \mathbb{R}^m$ to its kernel component in the kernel-image decomposition with respect to $Dh^{(0)}(x_0)$. We want to stress that Q depends on the irreducible component containing x_0.

(e) The decomposition exists if and only if geometric and algebraic multiplicity of the eigenvalue zero are equal.

(f) If the eigenvalue condition in (c) in the theorem above is satisfied, we speak of a (convergent) *Tikhonov–Fenichel reduction*; otherwise, we speak of a *formal Tikhonov–Fenichel reduction*.

(g) There exists a constructive method to obtain the product decomposition of $h^{(0)}$ with rational P and μ (see [10, Appendix A.3]). Thus, the reduction procedure as a whole is algorithmically accessible. We note that in many applications one will obtain a decomposition by inspection.

(h) The question of projecting initial values was basically settled by Fenichel [8, Theorem 9.1] and was discussed in detail for this particular setting in [10] (see also the references given there; in particular Lee and Othmer [2], Schauer and Heinrich [3] and Stiefenhofer [4]). We briefly summarize: By [10, Proposition 2], the system $\dot{x} = h^{(0)}(x)$ admits $m - r$ first integrals in a neighborhood of x_0. Moreover, the intersection of a common level set of the first integrals with $\mathcal{V}(h^{(0)})$ consists (locally) of a single point. Thus, to project the initial values of system (2.1)–(2.3), one chooses the corresponding intersection point. (In general it will not be possible to determine the first integrals, but one can determine Taylor approximations; see [10, Remark 6].)

(i) The theorem stays true if h is only smooth. But the product decomposition can – in general – no longer be constructed algorithmically. In some settings (e.g. chemical reaction systems with more general kinetics) however, the decomposition may be found by inspection. Naturally, our results also apply to such situations.

One may write the reduced system (2.3) in the time scale t again:

$$\dot{x} = \varepsilon \cdot Q(x) \cdot h^{(1)}(x),$$

whenever this simplifies a comparison with other results in the literature (as in the next example).

The Michaelis–Menten model is possibly the best known example for a quasi-steady state reduction.

Example 2.2. The following reaction scheme for enzyme catalyzed formation of product goes back to Michaelis and Menten [16]

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C \overset{k_2}{\rightarrow} E + P.$$

Assuming the initial concentration (e_0) of enzyme E to be a small parameter $(e_0 = \varepsilon)$ and the initial concentration c_0 of the complex C to be zero, then the reaction system reads

$$\begin{pmatrix} \dot{s} \\ \dot{c} \end{pmatrix} = \underbrace{\begin{pmatrix} (k_1 s + k_{-1})c \\ -(k_1 s + k_{-1} + k_2)c \end{pmatrix}}_{:=h^{(0)}(s,c)} + e_0 \underbrace{\begin{pmatrix} -k_1 s \\ k_1 s \end{pmatrix}}_{:=h^{(1)}(s,c)}.$$

According to [17, Example 5], the (convergent) Tikhonov–Fenichel reduction is the result of a simple computation:

$$\dot{s} = -\frac{k_1 k_2 s e_0}{k_1 s + k_{-1} + k_2}, \qquad c \equiv 0.$$

This result coincides with the familiar reduction going back to Briggs and Haldane [18].