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Research article

Coordinate-independent singular perturbation reduction for systems with three time scales

Niclas Kruff and Sebastian Walcher*

Mathematik A, RWTH Aachen, 52056 Aachen, Germany

* **Correspondence:** Email: walcher@matha.rwth-aachen.de; Tel: +492418098132; Fax: +492418092212.

Abstract: On the basis of recent work by Cardin and Teixeira on ordinary differential equations with more than two time scales, we devise a coordinate-independent reduction for systems with three time scales; thus no a priori separation of variables into fast, slow etc. is required. Moreover we consider arbitrary parameter dependent systems and extend earlier work on Tikhonov-Fenichel parameter values – i.e. parameter values from which singularly perturbed systems emanate upon small perturbations – to the three time-scale setting. We apply our results to two standard systems from biochemistry.

Keywords: reaction network; dimension reduction; invariant set; multiple time scales

1. Introduction and overview

Ordinary differential equations involving a small parameter appear frequently in mathematics and in science. Their principal use in chemistry and biochemistry – which is the main topic of the present paper – is to find certain (attracting) invariant sets and to achieve reduction of dimension. The mathematical basis is singular perturbation theory, originally due to Tikhonov [1] and Fenichel [2], for systems with one small parameter ε (or, in other words, for systems with two time scales).

While Tikhonov's and Fenichel's theory is concerned with first order approximations in ε, there exist approaches to include higher order terms in ε, e.g. to improve accuracy in the approximation of invariant manifolds; see for instance the critical survey in Kaper and Kaper [3]. More recently, Noel et al. [4], Radulescu et al. [5], Samal et al. [6, 7] developed an algorithmic method to compute slow-fast scenarios in chemical reaction networks, using tropical geometry. Concerning the existence (or persistence) of invariant sets obtained by such (a priori formal) calculations one may invoke hyperbolicity properties; for instance Theorem 4.1 in Chicone [8] is very useful in this respect. A direct method for chemical reaction networks involving different orders of a single small parameter, given certain properties of the system, is due to Cappeletti and Wiuf [9].

A different perspective is the consideration of systems with more than two time scales by introducing, cum grano salis, several small parameters $\varepsilon_1, \varepsilon_2, \dots$, and to obtain invariant manifolds and reduction on this basis. (One has the option to set all parameters equal in the end.)

Recently Cardin and Teixeira [10] generalized Fenichel's fundamental theorems, proving results on invariant sets and reductions of systems with more than two time scales. Here, the differential equation systems are assumed to have variables separated into blocks of fast, slow, "very slow" ones, and so on.

The present paper is based, on the one hand, on Cardin and Teixeira [10]. On the other hand, we extend earlier work [11, 12] that is concerned with coordinate-independent reduction (not requiring an a priori separation of slow and fast variables), as well as with the basic question of finding – in arbitrary parameter dependent systems – critical parameter values from which singular perturbation reductions emanate.

We will focus on the three time-scale setting, essentially to keep notation manageable, and will only briefly sketch extensions to more than three time scales. Furthermore we will mostly consider systems that satisfy not only the normal hyperbolicity conditions from [10] but have the stronger feature of exponential attractivity. One reason for this restriction lies in our interest in chemical reaction networks. But beyond this practical consideration, the algorithm to compute critical parameter values for singular perturbation scenarios indeed requires this additional property.

The paper is organized as follows. In Section 2 we review the work by Cardin and Teixeira [10]. Section 3 generalizes the coordinate-independent reduction algorithm from [11] to three-time scale systems. In Section 4 we start from a general parameter dependent system and extend the work from [12] on critical parameter values (Tikhonov-Fenichel parameter values) to three time scales (resp. two "small parameters"), and in Section 5 we discuss two classical examples (cooperativity with two complexes, competitive inhibition) from biochemistry in detail. Section 6 contains a few remarks about more than three time scales, and finally, for the reader's convenience, we prove some essentially known facts in an Appendix.

2. Separated fast and slow variables

In this section we review and specialize results from Cardin and Teixeira [10] for a parameter dependent ordinary differential equation system

$$\begin{array}{rcccl} \dot{x}_1 & = & \frac{dx_1}{dt} & = & f_1(x, \varepsilon_1, \varepsilon_2) \\ \dot{x}_2 & = & \frac{dx_2}{dt} & = & \varepsilon_1 f_2(x, \varepsilon_1, \varepsilon_2) \ ; \quad \text{briefly } \dot{x} = f(x, \varepsilon_1, \varepsilon_2). \\ \dot{x}_3 & = & \frac{dx_3}{dt} & = & \varepsilon_1 \varepsilon_2 f_3(x, \varepsilon_1, \varepsilon_2) \end{array} \tag{2.1}$$

Here $x = (x_1, x_2, x_3)^{\mathrm{tr}} \in \mathbb{R}^n$ with $x_1 \in \mathbb{R}^{n_1}$, $x_2 \in \mathbb{R}^{n_2}$, and $x_3 \in \mathbb{R}^{n_3}$, and f is smooth on an open neighborhood of $U \times [0, \delta_1) \times [0, \delta_2)$, with $U \subseteq \mathbb{R}^n$ open and nonempty, and $\delta_1 > 0$, $\delta_2 > 0$.
We define

$$\mathcal{M}_1 := \{x \in U;\ f_1(x, 0, 0) = 0\} \tag{2.2}$$

and

$$\mathcal{M}_2 := \{x \in U;\ f_1(x, 0, 0) = f_2(x, 0, 0) = 0\}, \tag{2.3}$$

and we will assume throughout that these sets are nonempty. Cardin and Teixeira require some hyperbolicity conditions, which we state here in slightly stronger versions, for the sake of simplicity:

- *First hyperbolicity condition:* For every $x \in \mathcal{M}_1$, all the eigenvalues of $D_{x_1} f_1(x, 0, 0)^*$ have nonzero real parts.
  For sufficiently small $\varepsilon_1, \varepsilon_2$ this condition implies local solvability of the implicit equation $f_1(x, \varepsilon_1, \varepsilon_2) = 0$ in the form $x_1 = g(x_2, x_3, \varepsilon_1, \varepsilon_2)$, and one may furthermore write

$$\widetilde{f_2}(x_2, x_3, \varepsilon_1, \varepsilon_2) := f_2(g(x_2, x_3, \varepsilon_1, \varepsilon_2), x_2, x_3, \varepsilon_1, \varepsilon_2).$$

- *Second hyperbolicity condition:* For every $x \in \mathcal{M}_2$, all the eigenvalues of $D_{x_2} \widetilde{f_2}(x, 0, 0)$ have nonzero real parts.[†]

By suitable choice of U, δ_1 and δ_2 we may assume that $\mathcal{M}_1$ and $\mathcal{M}_2$ are submanifolds.
Continuing to follow [10] we introduce the *auxiliary system*

$$\begin{aligned} 0 &= \tfrac{dx_1}{d\tau_2} &&= f_1(x, 0, \varepsilon_2) \\ \dot{x}_2 &= \tfrac{dx_2}{d\tau_2} &&= f_2(x, 0, \varepsilon_2) \\ \dot{x}_3 &= \tfrac{dx_3}{d\tau_2} &&= \varepsilon_2 f_3(x, 0, \varepsilon_2) \end{aligned} \tag{2.4}$$

on

$$\mathcal{M}_2^{\varepsilon_2} := \{x \in U;\ f_1(x, 0, \varepsilon_2) = 0\},$$

and the *intermediate reduced system*

$$\begin{aligned} 0 &= \tfrac{dx_1}{d\tau_2} &&= f_1(x, 0, 0) \\ \dot{x}_2 &= \tfrac{dx_2}{d\tau_2} &&= f_2(x, 0, 0) \\ \dot{x}_3 &= \tfrac{dx_3}{d\tau_2} &&= 0 \end{aligned} \tag{2.5}$$

on $\mathcal{M}_1$. Thus in both equations (2.4) and (2.5) above the dot denotes differentiation with respect to $\tau_2 := \varepsilon_1 t$. By suitable choice of δ_2 we may also assume that every $\mathcal{M}_2^{\varepsilon_2}$ is a submanifold of $\mathbb{R}^n$.
Finally we define the *completely reduced system*

$$\begin{aligned} 0 &= \tfrac{dx_1}{d\tau_3} &&= f_1(x, 0, 0) \\ 0 &= \tfrac{dx_2}{d\tau_3} &&= f_2(x, 0, 0) \\ \dot{x}_3 &= \tfrac{dx_3}{d\tau_3} &&= f_3(x, 0, 0) \end{aligned} \tag{2.6}$$

on $\mathcal{M}_2$, hence the dot in (2.6) denotes differentiation with respect to $\tau_3 := \varepsilon_1 \varepsilon_2 t$. From here on we will follow [10] by just using dots for differentiations, with the appropriate time scale evident from the context.

We replace the hyperbolicity conditions from [10] by stronger requirements, since in our applications we focus on attracting invariant manifolds.

Definition 1. *We say that system* (2.1) *satisfies the hyperbolic attractivity condition* (HA) *if* $D_{x_1} f_1(x, 0, 0)$ *has only eigenvalues with negative real part on* $\mathcal{M}_1$ *and if furthermore* $D_{x_2} \widetilde{f_2}(x, 0, 0)$ *has only eigenvalues with negative real part on* $\mathcal{M}_2$.

[*] For a smooth function $g = g(x, y, \ldots)$ we denote the partial derivatives by $D_x g$, $D_y g$ etc.

[†] In [10] the second hyperbolicity condition is erroneously written for f_2 rather than $\widetilde{f_2}$. The authors are aware of this and will publish a corrigendum.

Our starting point is the following theorem, specialized from Cardin and Teixeira [10], Theorems A, B and Corollary A. Some of our statements are informal; for rigorous statements and pertinent definitions we refer to [10].

Theorem 1. *Let system* (2.1) *be given, with* (HA) *satisfied.*

(a) Let $\mathcal{N} \subseteq \mathcal{M}_2$ be a compact submanifold (with nonempty interior in the relative topology, and possibly with boundary). Then for all sufficiently small $\varepsilon_1, \varepsilon_2$ there exists a locally invariant manifold $\mathcal{N}_{\varepsilon_1,\varepsilon_2}$ for system (2.1) *which is $O(\varepsilon_1 + \varepsilon_2)$ close to $\mathcal{N}$, diffeomorphic to $\mathcal{N}$ and locally exponentially attracting. Given the appropriate time scales, solutions of* (2.1) *on $\mathcal{N}_{\varepsilon_1,\varepsilon_2}$ converge to solutions of* (2.6) *on $\mathcal{N}$.*

(b) Let ε_2 be sufficiently small and let $\mathcal{L} \subseteq \mathcal{M}_2^{\varepsilon_2}$ be a compact submanifold (with nonempty interior in the relative topology, and possibly with boundary). Then for all sufficiently small ε_1 there exists a locally invariant manifold $\mathcal{L}_{\varepsilon_1,\varepsilon_2}$ for system (2.1) *which is $O(\varepsilon_1 + \varepsilon_2)$ close to $\mathcal{L}$, diffeomorphic to $\mathcal{L}$ and locally exponentially attracting. Given the appropriate time scales, solutions of* (2.1) *on $\mathcal{L}_{\varepsilon_1,\varepsilon_2}$ converge to solutions of* (2.5) *on $\mathcal{L}$.*

Note that the passage from (2.1) to (2.6) may be seen as a singular perturbation reduction for two time scales. From this perspective, system (2.5) indeed represents an intermediate step. For systems with two time scales this leads to the question whether intermediates exist.
As given, the part regarding $\widetilde{f_2}$ in condition (HA) is not ready to use in applications. We provide two equivalent versions.

Proposition 1. *Condition* (HA) *is equivalent to either of the following conditions.*

(i) $D_{x_1} f_1(x, 0, 0)$ has only eigenvalues with negative real parts on $\mathcal{M}_1$, and

$$B_1(x) := -D_{x_1} f_2(x, 0, 0) D_{x_1} f_1(x, 0, 0)^{-1} D_{x_2} f_1(x, 0, 0) + D_{x_2} f_2(x, 0, 0)$$

has only eigenvalues with negative real parts on $\mathcal{M}_2$.

(ii) $D_{x_1} f_1(x, 0, 0)$ has only eigenvalues with negative real parts on $\mathcal{M}_1$, and for all sufficiently small $\varepsilon > 0$ the matrix

$$B_2(x, \varepsilon) := \begin{pmatrix} D_{x_1} f_1(x, 0, 0) & D_{x_2} f_1(x, 0, 0) \\ \varepsilon D_{x_1} f_2(x, 0, 0) & \varepsilon D_{x_2} f_2(x, 0, 0) \end{pmatrix}$$

has only eigenvalues with negative real parts on $\mathcal{M}_2$.

Proof. We use the notions introduced with the hyperbolicity condition (H) and Definition 1. From

$$f_1(g(x_2, x_3, \varepsilon_1, \varepsilon_2), x_2, x_3, \varepsilon_1, \varepsilon_2) = 0$$

one gets by the chain rule

$$D_{x_2} g(x_2, x_3) = -D_{x_1} f_1(x, , \varepsilon_1, \varepsilon_2)^{-1} D_{x_2} f_1(x, , \varepsilon_1, \varepsilon_2)$$

when $f_1(g(x_2, x_3, \varepsilon_1, \varepsilon_2), x_2, x_3, \varepsilon_1, \varepsilon_2) = 0$, and a further application of the chain rule shows the equivalence of (HA) and (i). The equivalence of (i) and (ii) follows from Lemma 3 in the Appendix.

□

Remark 1. *(a) One may rewrite systems* (2.1) *through* (2.6) *to some extent, with no effect on the reductions. Using Hadamard's lemma, one may restate* (2.1) *as*

$$\begin{aligned}\dot{x}_1 &= \widehat{f_1}(x,\varepsilon_2) + \varepsilon_1\widehat{f_{1,1}}(x,\varepsilon_1) + \varepsilon_1\varepsilon_2\widehat{f_{1,2}}(x,\varepsilon_1,\varepsilon_2)\\ \dot{x}_2 &= \varepsilon_1\widehat{f_2}(x,\varepsilon_1) + \varepsilon_1\varepsilon_2\widehat{f_{2,2}}(x,\varepsilon_1,\varepsilon_2)\\ \dot{x}_3 &= \varepsilon_1\varepsilon_2\widehat{f_3}(x,\varepsilon_1,\varepsilon_2)\end{aligned}$$

with only the $\widehat{f_i}$ remaining in the subsequent reductions. Thus the auxiliary system becomes

$$\begin{aligned}0 &= \widehat{f_1}(x,\varepsilon_2)\\ \dot{x}_2 &= \widehat{f_2}(x,0)\\ \dot{x}_3 &= \varepsilon_2 f_3(x,0,\varepsilon_2)\end{aligned}$$

and there are analogous modifications for the intermediate and the fully reduced system.

(b) The passage from (2.1) *to the completely reduced system* (2.6) *can evidently be obtained in the following manner: Fix $\varepsilon_1 > 0$ and reduce* (2.1) *with respect to the small parameter ε_2 (in time scale $\varepsilon_2 t$). Then let $\varepsilon_1 \to 0$, rescaling time once more to τ_3. We will use this observation later on.*

3. Coordinate-free reduction

In the present section we generalize the coordinate-independent reduction procedure from [11, 13] to the three-time scale setting. The first task is to intrinsically characterize those systems which admit a transformation to "standard form" (2.1). Reversing matters, applying a (local) smooth coordinate transformation to Eq (2.1) yields a smooth system

$$\dot{x} = g^{(0,0)}(x,\varepsilon_1,\varepsilon_2) + \varepsilon_1\left(g^{(1,0)}(x,\varepsilon_1,\varepsilon_2) + \varepsilon_2 g^{(1,1)}(x,\varepsilon_1,\varepsilon_2)\right) \tag{3.1}$$

on an open neighborhood of $\widetilde{U}\times[0,\delta_1)\times[0,\delta_2) \subseteq \mathbb{R}^n\times\mathbb{R}\times\mathbb{R}$ ($\widetilde{U}\subseteq\mathbb{R}^n$ open), evidently satisfying the following conditions:

(i) For all sufficiently small $\varepsilon_1 \geq 0$, $\varepsilon_2 \geq 0$, the zeros of $g^{(0,0)}(x,\varepsilon_1,\varepsilon_2)$ form a submanifold $\widetilde{\mathcal{M}_1} \subseteq \widetilde{U}$, of codimension n_1, $1 \leq n_1 < n$. Given any compact submanifold $\mathcal{P}_1 \subseteq \widetilde{\mathcal{M}_1}$, there exists $\theta_1 > 0$ such that at every $y \in \mathcal{P}_1$ the derivative $D_x g(y,\varepsilon_1,\varepsilon_2)$ admits the eigenvalue zero with algebraic and geometric multiplicity $n - n_1$, and the remaining eigenvalues have real parts $\leq -\theta_1$.

(ii) For all sufficiently small $\varepsilon_1 > 0$, $\varepsilon_2 \geq 0$ the zeros of

$$g^{(0,0)}(x,\varepsilon_1,\varepsilon_2) + \varepsilon_1 g^{(1,0)}(x,\varepsilon_1,\varepsilon_2)$$

form a submanifold $\widetilde{\mathcal{M}_2} \subseteq \widetilde{U}$, of codimension n_1+n_2, $1 \leq n_2 < n-n_1$. Moreover, for any compact submanifold $\mathcal{P}_2 \subseteq \widetilde{\mathcal{M}_2}$ there exists a $\theta_2 > 0$ with the following property: At every $y \in \mathcal{P}_2$ the derivative $D_x g^{(0,0)}(y,\varepsilon_1,\varepsilon_2) + \varepsilon_1 D_x g^{(1,0)}(y,\varepsilon_1,\varepsilon_2)$ admits the eigenvalue zero with algebraic and geometric multiplicity $n - n_1 - n_2$, and the remaining eigenvalues have real parts $\leq -\theta_2\varepsilon_1$.

By Remark 1 one may assume that system (3.1) is in the special form

$$\dot{x} = g^{(0,0)}(x,\varepsilon_2) + \varepsilon_1\left(g^{(1,0)}(x,\varepsilon_1) + \varepsilon_2 g^{(1,1)}(x)\right) + O(\varepsilon_2(\varepsilon_1+\varepsilon_2)), \tag{3.2}$$

adjusting conditions (i) and (ii) accordingly. Conditions (i) and (ii) are certainly necessary for (3.1) or (3.2) to be a transformed version of (2.1). The first part of the next lemma shows sufficiency.

Lemma 1. *(a) There exists a local diffeomorphism transforming system* (3.2) *to a system of type* (2.1) *with condition* (HA) *if and only if conditions (i) and (ii) above hold.*

(b) Condition (i) for system (3.2) *is equivalent to the following: For any* $y \in \widetilde{\mathcal{M}_1}$ *there exist a neighborhood* $U_{1,y}$*, a smooth map* $P_1 : U_{1,y} \to \mathbb{R}^{n\times n_1}$ *such that* $P_1(y, \varepsilon_2)$ *has rank* n_1*, and a smooth map* $\mu_1 : U_{1,y} \to \mathbb{R}^{n_1}$ *such that* $D_x\mu_1(y, \varepsilon_2)$ *has rank* n_1*, yielding a decomposition*

$$g^{(0,0)}(x, \varepsilon_2) = P_1(x, \varepsilon_2)\mu_1(x, \varepsilon_2),$$

and moreover there is a $\theta_1 > 0$ *such that*

$$A_1(x, \varepsilon_2) := D\mu_1(x, \varepsilon_2)P_1(x, \varepsilon_2)$$

has only eigenvalues with real part $\leq -\theta_1$*, for all* $x \in U_{1,y}$*.*

(c) In presence of condition (i), condition (ii) for system (3.2) *is equivalent to the following: For every (sufficiently small)* $\varepsilon_1 > 0$ *and any* $y \in \widetilde{\mathcal{M}_2}$ *there exist a neighborhood* $U_{2,y}$*, a smooth map* $P_2 : U_{2,y} \to \mathbb{R}^{n\times n_2}$ *such that* $(P_1(y, \varepsilon_2), \varepsilon_1 P_2(y, \varepsilon_1))$ *has rank* $n_1 + n_2$*, and a smooth map* $\mu_2 : U_{2,y} \to \mathbb{R}^{n_2}$ *such that* $(D_x\mu_1(y, \varepsilon_2), D_x\mu_2(y, \varepsilon_2))^{\mathrm{tr}}$ *has rank* $n_1 + n_2$*, yielding a decomposition*

$$g^{(0,0)}(x, \varepsilon_2) + \varepsilon_1 g^{(1,0)}(x, \varepsilon_1) = P_1(x, \varepsilon_2)\mu_1(x, \varepsilon_2) + \varepsilon_1 P_2(x, \varepsilon_1)\mu_2(x, \varepsilon_1),$$

and moreover there is a $\theta_2 > 0$ *such that*

$$A_2(x, \varepsilon_1, \varepsilon_2) := \begin{pmatrix} D\mu_1(x, \varepsilon_2) \\ D\mu_2(x, \varepsilon_1) \end{pmatrix} \begin{pmatrix} P_1(x, \varepsilon_2) & \varepsilon_1 P_2(x, \varepsilon_1) \end{pmatrix}$$

has only eigenvalues with real part $\leq -\theta_2\varepsilon_1$*, for all* $x \in U_{2,y}$*.*

Proof. The nontrivial assertion of part (a) follows from the existence of $n-n_1$ independent first integrals of $g^{(0,0)}$ in a neighborhood of y, which was noted by Fenichel [2], Lemma 5.3 for smooth vector fields, and shown in [13], Proposition 2.2 for the analytic setting, and likewise from the existence of $n-n_1-n_2$ independent first integrals of $g^{(0,0)} + \varepsilon_1 g^{(1,0)}$ in a neighborhood of y. These first integrals determine slow and "very slow" variables. Parts (b) and (c) are straightforward applications of [11], Theorem 1, Remark 4 and Remark 2. □

Remark 2. *The existence of the decomposition* $g^{(0,0)} = P_1\,\mu_1$ *in part (b) (as well as the decomposition in part (c)) is a consequence of the implicit function theorem in the smooth or analytic case. For polynomial or rational vector fields there exists a decomposition with rational functions as entries of* P_1 *and* μ_1*, and there is an algorithmic approach to its computation. See [11] for details.*

Next we use the decompositions to compute reductions.

Proposition 2. *(a) In arbitrary coordinates the reduction corresponding to the passage from system* (2.1) *to the auxiliary system may be obtained as follows:*
Given $\varepsilon_2 \geq 0$*, determine the projection matrix*

$$Q_1(x, \varepsilon_2) := I_n - P_1(x, \varepsilon_2)A_1(x, \varepsilon_2)^{-1}D_x\mu_1(x, \varepsilon_2).$$

The auxiliary system (2.4) *for* $\varepsilon_2 > 0$ *then corresponds to*

$$\dot{x} = Q_1(x, \varepsilon_2)\left(g^{(1,0)}(x, 0) + \varepsilon_2 g^{(1,1)}(x)\right)$$

on the local invariant manifold defined by $\mu_1(x, \varepsilon_2) = 0$. *The equation corresponding to the intermediate reduced system* (2.5) *is obtained by setting* $\varepsilon_2 = 0$.

(b) In arbitrary coordinates the reduction corresponding to the passage from system (2.1) *to the completely reduced system* (2.6) *may be obtained as follows:*
Given $\varepsilon_1 > 0$, *determine the projection matrix*

$$\widetilde{Q}_2(x, \varepsilon_1) := I_n - \left(P_1(x, 0), \quad \varepsilon_1 P_2(x, 0)\right) A_2(x, \varepsilon_1, 0)^{-1} \begin{pmatrix} D_x\mu_1(x, 0) \\ D_x\mu_2(x, 0) \end{pmatrix}.$$

Then $\widetilde{Q}_2(x, \varepsilon_1)$ *extends smoothly to a matrix valued function* $Q_2(x)$ *at* $\varepsilon_1 = 0$. *The equation corresponding to the completely reduced system in arbitrary coordinates is given by*

$$\dot{x} = Q_2(x)\, g^{(1,1)}(x)$$

on the local invariant manifold defined by $\mu_1(x, 0) = \mu_2(x, 0) = 0$.

Proof. Part (a) is a direct application of [11], Theorem 1. For part (b) this theorem is also applicable, but there is a technical problem involving $\widetilde{Q}_2$ as $\varepsilon_1 \to 0$, since $A_2(x, 0)$ is non-invertible. To resolve this difficulty, recall that $\widetilde{Q}_2(x, \varepsilon_1)$ is the projection map onto the kernel of

$$D_x g^{(0,0)}(x, 0) + \varepsilon_1 D_x g^{(1,0)}(x, \varepsilon_1)$$

along the image, for $x \in \widetilde{\mathcal{M}}_2$ (see [11], Remark 1). With the conditions given in Lemma 1 (c) the image is equal to the column space of $(P_1,\ \varepsilon_1 P_2)$, which in turn equals the column space W_1 of $(P_1,\ P_2)$. The latter matrix has full rank at $\varepsilon_1 = 0$, and its entries depend smoothly on ε_1 and x. Moreover the kernel is equal to the kernel of $(D_x\mu_1,\ D_x\mu_2)^{\mathrm{tr}}$, and we may assume w.l.o.g. that

$$\begin{pmatrix} D_x\mu_1 \\ D_x\mu_2 \end{pmatrix} = \begin{pmatrix} M_1 & M_2 \end{pmatrix}$$

with invertible M_1, whence the kernel is equal to the column space W_2 of the matrix

$$\begin{pmatrix} -M_1^{-1} M_2 \\ I \end{pmatrix}$$

with entries depending smoothly on ε_1. Thus there remains to verify that the matrix of the projection onto W_2 along W_1 depends smoothly on ε_1. For the sake of completeness we give a proof of this fact in Lemma 4, Appendix. □

We note that the reduction also works, including convergence properties, under the weaker assumption corresponding to (H) rather than (AH) for A_1 and A_2 in Lemma 1.

Remark 3. *While Proposition 2 provides the reduced equations, one also needs initial values for these, which may be obtained from an initial value y of system 3.2 with the help of the first integrals noted in the proof of Lemma 1(a); see [11], Proposition 2:*

- *Assuming that y is sufficiently close to* $\widetilde{\mathcal{M}}_1$ *, the corresponding initial value (up to an error of order* $\varepsilon_1 + \varepsilon_2$*) for the auxiliary system and for the intermediate reduced system is the (locally unique) intersection of* $\widetilde{\mathcal{M}}_1$ *and the level sets of* $n - n_1$ *independent first integrals of* $\dot{x} = g^{(0,0)}(x, 0)$ *which contain y.*
- *Assuming that y is sufficiently close to* $\widetilde{\mathcal{M}}_2$ *, the corresponding initial value (up to an error of order* $\varepsilon_1 + \varepsilon_2$*) for the auxiliary system and for the intermediate reduced system is the (locally unique) intersection of* $\widetilde{\mathcal{M}}_2$ *and the level sets of* $n - n_1 - n_2$ *independent common first integrals of* $\dot{x} = g^{(0,0)}(x, 0)$ *and* $\dot{x} = g^{(1,0)}(x, 0, 0)$ *which contain y. (A direct application of Proposition 2 in [11] would lead to simultaneous first integrals of* $\dot{x} = g^{(0,0)}(x, 0) + \varepsilon_1 g^{(1,0)}(x, \varepsilon_1, 0)$ *for all* ε_1*. This is equivalent to the condition stated.)*

To illustrate the procedure with an example, we recall the competitive inhibition network with substrate S, enzyme E, inhibitor I and two complexes C_1, C_2; see for instance Keener and Sneyd [14]. The reaction scheme is given by

$$\begin{aligned} E + S &\underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C_1 \overset{k_2}{\rightharpoonup} E + P, \\ E + I &\underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} C_2 \end{aligned}$$

which leads (with the usual assumptions of mass action kinetics, spatial homogeneity and constant thermodynamical parameters) to the differential equation system

$$\begin{aligned} \dot{s} &= k_{-1}c_1 - k_1 s(e_0 - c_1 - c_2) \\ \dot{c}_1 &= k_1 s(e_0 - c_1 - c_2) - (k_{-1} + k_2)c_1 \\ \dot{c}_2 &= k_3(e_0 - c_1 - c_2)(i_0 - c_2) - k_{-3}c_2 \end{aligned} \tag{3.3}$$

for the concentrations. (The original system is five dimensional; the two linear first integrals $e + c_1 + c_2$ and $i + c_2$ yield reduction to dimension three.) There is a familiar two time scale reduction for this system, viz. the quasi-steady state (QSS) reduction for both complexes; see Eqs (1.51–1.52) in Keener and Sneyd [14]. As was shown in [15], section 3.2 this QSS reduction is (up to irrelevant higher order terms) identical to the singular perturbation reduction with small parameter $e_0 = \varepsilon e_0^*$, hence Tikhonov guarantees its validity. (It is not generally true that QSS reductions amount to Tikhonov-Fenichel reductions. A sufficient condition is stated in [16], Prop. 5, and a list of possible QSS reductions for competitive inhibition - including a characterization which correspond to singular perturbation reductions - is given in section 5.2 of that paper.)

Example 1. In system (3.3) set $x = (s, c_1, c_2)^{\mathrm{tr}}$ and assume $k_2 = \varepsilon_1\varepsilon_2 k_2^*$, $k_3 = \varepsilon_1 k_3^*$ and $k_{-3} = \varepsilon_1 k_{-3}^*$. (Colloquially speaking, binding to the inhibitor and degradation from the inhibitor complex are slow, while degradation from the substrate complex to enzyme and product is very slow. The related two time scale reduction to a one dimensional equation corresponds to slow formation of enzyme and complex.) This is of the type (3.2), with

$$g^{(0,0)}(x) = \begin{pmatrix} k_{-1}c_1 - k_1 s(e_0 - c_1 - c_2) \\ k_1 s(e_0 - c_1 - c_2) - k_{-1}c_1 \\ 0 \end{pmatrix},$$

$$g^{(1,0)}(x,\varepsilon_1) = \begin{pmatrix} 0 \\ 0 \\ k_3^*(e_0 - c_1 - c_2)(i_0 - c_2) - k_{-3}^* c_2 \end{pmatrix},$$
$$g^{(1,1)}(x,\varepsilon_1,\varepsilon_2) = \begin{pmatrix} 0 \\ -k_2^* c_1 \\ 0 \end{pmatrix}.$$

Moreover $\widetilde{\mathcal{M}}_2$ is contained in the common zero set of

$$\mu_1 = k_{-1}c_1 - k_1 s(e_0 - c_1 - c_2) \text{ and } \mu_2 = k_3^*(e_0 - c_1 - c_2)(i_0 - c_2) - k_{-3}^* c_2,$$

$\widetilde{\mathcal{M}}_1$ is contained in the zero set of μ_1, and we have

$$P_1(x,\varepsilon_2) = \begin{pmatrix} 1 \\ -1 \\ 0 \end{pmatrix}, \quad P_2(x,\varepsilon_1) = \begin{pmatrix} 0 \\ 0 \\ 1 \end{pmatrix}.$$

We determine the auxiliary system and the intermediate reduced system. With

$$D\mu_1 = (-k_1(e_0 - c_1 - c_2,\ k_1 s + k_{-1}, k_1 s)$$

one has

$$D\mu_1 P_1 = -k_1(e_0 - c_1 - c_2 - (k_1 s + k_{-1}) =: -\nu_1$$

and furthermore

$$\begin{aligned} Q_1 &= I_3 + \tfrac{1}{\nu_1}\begin{pmatrix} * & k_1 s + k_{-1} & k_1 s \\ * & -(k_1 s + k_{-1}) & -k_1 s \\ 0 & 0 & 0 \end{pmatrix} \\ &= \tfrac{1}{\nu_1}\begin{pmatrix} * & k_1 s + k_{-1} & k_1 s \\ * & k_1(e_0 - c_1 - c_2) & -k_1 s \\ 0 & 0 & \nu_1 \end{pmatrix}. \end{aligned}$$

Application to

$$g^{(1,0)} + \varepsilon_2 g^{(1,1)} = \mu_2 \begin{pmatrix} 0 \\ 0 \\ 1 \end{pmatrix} - \varepsilon_2 k_2^* c_1 \begin{pmatrix} 0 \\ 0 \\ 1 \end{pmatrix}$$

yields the auxiliary system (in time scale $\varepsilon_1 t$) on $\widetilde{\mathcal{M}}_1$:

$$\begin{pmatrix} \dot{s} \\ \dot{c}_1 \\ \dot{c}_2 \end{pmatrix} = \frac{\mu_2}{\nu_1}\begin{pmatrix} k_1 s \\ -k_1 s \\ \nu_1 \end{pmatrix} - \varepsilon_2 \frac{k_2^* c_1}{\nu_1}\begin{pmatrix} k_1 s + k_{-1} \\ k_1(e_0 - c_1 - c_2) \\ 0 \end{pmatrix}.$$

Setting $\varepsilon_2 = 0$ one obtains the intermediate reduced system.
When the initial values for system (3.3) are given by $(s_0, c_{1,0}, c_{2,0})$, to obtain the approximate initial

values $(s_0^*, c_{1,0}^*, c_{2,0}^*)$ on $\widetilde{\mathcal{M}_1}$ one uses (according to Remark 3) the two first integrals $s + c_1$ and c_2 of $g^{(0,0)}$ and the defining equation for $\widetilde{\mathcal{M}_1}$, thus the system

$$\begin{aligned} s + c_1 &= s_0 + c_{1,0} \\ c_2 &= c_{2,0} \\ k_{-1}c_1 - k_1 s(e_0 - c_1 - c_2) &= 0 \end{aligned}$$

which leads to quadratic equations for s and c_1.

To find the fully reduced system one first computes

$$D\mu_2 = (0,\ -k_3^*(i_0 - c_2),\ -k_3^*(e_0 + i_0 - c_1 - 2c_2) - k_{-3}^*)$$

and

$$\begin{aligned} A_2 &= \begin{pmatrix} D\mu_1 \\ D\mu_2 \end{pmatrix}\begin{pmatrix} P_1, & \varepsilon_1 P_2 \end{pmatrix} \\ &= \begin{pmatrix} -k_1(e_0 - c_1 - c_2) - k_1 s - k_{-1} & \varepsilon_1 \cdot k_1 s \\ k_3^*(i_0 - c_2) & -\varepsilon_1 \cdot (k_3^*(e_0 + i_0 - c_1 - 2c_2) + k_{-3}^*) \end{pmatrix}. \end{aligned}$$

The computation of the projection matrix is straightforward (although a software system is helpful) but the output is sizeable. We just record the fully reduced system (in time scale $\varepsilon_1\varepsilon_2 t$). It is given by

$$\dot{x} = \frac{1}{\nu_2} \cdot \begin{pmatrix} \xi_1 \\ \xi_2 \\ \xi_3 \end{pmatrix}$$

with

$$\begin{aligned} \nu_2 =& sc_1k_1k_3^* + sc_2k_1k_3^* - se_0k_1k_3^* - c_1^2k_1k_3^* - 3c_1c_2k_1k_3^* + 2c_1e_0k_1k_3^* + c_1i_0k_1k_3^* - 2c_2^2k_1k_3^* \\ &+ 3c_2e_0k_1k_3^* + c_2i_0k_1k_3^* - e_0^2k_1k_3^* - e_0i_0k_1k_3^* - sk_{-3}^*k_1 + c_1k_{-3}^*k_1 + c_1k_{-1}k_3^* + c_2k_{-3}^*k_1 \\ &+ 2c_2k_{-1}k_3^* - e_0k_{-3}^*k_1 - e_0k_{-1}k_3^* - i_0k_{-1}k_3^* - k_{-3}^*k_{-1} \end{aligned}$$

and

$$\begin{aligned} \xi_1 =& k_2^*(se_0k_{-3}^*k_1 + c_1e_0k_{-1}k_3^* - c_1i_0k_{-1}k_3^* + c_2^2k_{-1}k_3^* - c_2e_0k_{-1}k_3^* - c_2i_0k_{-1}k_3^* \\ &+ e_0i_0k_{-1}k_3^* - c_2k_{-3}^*k_{-1}), \end{aligned}$$

$$\begin{aligned} \xi_2 =& \frac{k_1k_2^*}{k_3^*}(c_1^3(k_3^*)^2 - 2c_1^2e_0(k_3^*)^2 + 2c_1^2i_0(k_3^*)^2 + c_1e_0^2(k_3^*)^2 - 2c_1e_0i_0(k_3^*)^2 \\ &+ c_1i_0^2(k_3^*)^2 + c_2^3(k_3^*)^2 - c_2^2e_0(k_3^*)^2 - 2c_2^2i_0(k_3^*)^2 + 2c_2e_0i_0(k_3^*)^2 + c_2i_0^2(k_3^*)^2 - e_0i_0^2(k_3^*)^2 \\ &- c_1^2k_{-3}^*k_3^* + c_1e_0k_{-3}^*k_3^* + 2c_1i_0k_{-3}^*k_3^* - 3c_2^2k_{-3}^*k_3^* + 2c_2e_0k_{-3}^*k_3^* + 3c_2i_0k_{-3}^*k_3^* \\ &- 2e_0i_0k_{-3}^*k_3^* + 2c_2(k_{-3}^*)^2), \end{aligned}$$

$$\xi_3 = -\frac{k_{-3}^*k_1k_2^*}{k_3^*}(c_1i_0k_3^* - c_2^2k_3^* + c_2e_0k_3^* + c_2i_0k_3^* - e_0i_0k_3^* + c_2k_{-3}^*)$$

restricted to the invariant curve $\widetilde{\mathcal{M}_2}$.

Finally, given initial values $(s_0, c_{1,0}, c_{2,0})$ for system (3.3), approximate initial values for the fully reduced system may be determined by solving the algebraic equations $s + c_1 = s_0 + c_{1,0}$, $\mu_1 = 0$ and $\mu_2 = 0$.

4. Critical parameter values

Typically in applications one starts with a general parameter dependent system, rather than a system of type (2.1) or (3.1) with pre-assigned "small parameters". Therefore the first task is to determine critical parameter values, for which small perturbations lead to singular perturbation scenarios. Thus we consider *Tikhonov-Fenichel parameter values*, as defined in [12] for two time scales, and extend the notion to the three time scale setting.

4.1. Tikhonov-Fenichel parameter values

Tikhonov-Fenichel parameter values (TFPV) were introduced in [12] for polynomial (or rational) parameter dependent systems

$$\dot{x} = h(x, \pi), \quad x \in \mathbb{R}^n, \, \pi \in \Pi \subseteq \mathbb{R}^m. \tag{4.1}$$

A TFPV $\widehat{\pi}$ is characterized by the property that small perturbations $\pi = \widehat{\pi} + \varepsilon\rho + \cdots$ along a smooth curve in parameter space Π give rise to a singular perturbation reduction for

$$\dot{x} = h(x, \widehat{\pi} + \varepsilon\rho + \cdots) = h(x, \widehat{\pi}) + \varepsilon D_\pi h(x, \widehat{\pi})\rho + \cdots$$

with locally exponentially attracting critical manifold. (The definition extends easily to smooth systems but the algorithmic approach relies on the stronger assumption.) There exists an intrinsic characterization of TFPV's, see [12] Lemmas 1 and 2, for which the characteristic polynomial

$$\chi(\tau, x, \pi) = \tau^n + \sigma_{n-1}(x, \pi)\tau^{n-1} + \cdots + \sigma_1(x, \pi)\tau + \sigma_0(x, \pi) \tag{4.2}$$

of the Jacobian $D_x h(x, \pi)$ is relevant. We recall:

Lemma 2. *Given $0 < s < n$, a parameter value $\widehat{\pi}$ is a TFPV with locally exponentially attracting critical manifold Z_s (depending on $\widehat{\pi}$) of dimension s, and $x_0 \in Z_s$, if and only if the following hold:*

- $h(x_0, \widehat{\pi}) = 0$.
- *The characteristic polynomial $\chi(\tau, x, \pi)$ from* (4.2)*) satisfies*
  - *(i) $\sigma_0(x_0, \widehat{\pi}) = \cdots = \sigma_{s-1}(x_0, \widehat{\pi}) = 0$;*
  - *(ii) all roots of $\chi(\tau, x_0, \widehat{\pi})/\tau^s$ have negative real parts.*
- *The system $\dot{x} = h(x, \widehat{\pi})$ admits s independent local analytic first integrals at x_0.*

All the conditions in the lemma can be represented by polynomial equations and inequalities. The condition on the roots of $\chi(\tau, x_0, \widehat{\pi})/\tau^s$ is characterized by inequalities: There exist $n - s$ Hurwitz determinants (see e.g. Gantmacher [17], Ch. V, §6, Thm. 4 ff.) which must attain values > 0. Moreover, the existence requirement for s independent first integrals leads to a series of polynomial equations via degree by degree evaluation of Taylor expansions. While there are notable exceptions for chemical reaction networks, with possible first integrals from stoichiometry, this condition is the most problematic to verify in general. One may proceed as follows: For every $d > 0$ there is an induced action of $D_x h(x, \pi)$ on the space $S_1 + \cdots + S_d$ of polynomials in n variables with zero constant term and of degree $\leq d$. Extending condition (i), the characteristic polynomial of this action

(which coincides with (4.2) for $d = 1$) must have vanishing coefficients for all sufficiently small powers of the indeterminate. No further inequalities appear, due to the structure of the eigenvalues for this action, and thanks to Hilbert's *Basissatz*, finitely many of these equations suffice. With increasing dimension, one has to deal with feasibility problems. In applications the common procedure is step by step, looking for simplifications at every stage. A full account is given in [12].

For the remainder of this section we assume that $\Pi \subseteq \mathbb{R}^m_+$ is a semi-algebraic set, and that system (4.1) admits the positively invariant subset $\mathbb{R}^n_+$. Then, as was shown in [12], the Tikhonov-Fenichel parameter values for dimension s, $1 \leq s < n$ form a semi-algebraic subset $\Pi_s \subseteq \mathbb{R}^m$. We will denote the Zariski closure of Π_s by W_s. Thus the elements of W_s satisfy all defining equations for Π_s but not necessarily the defining inequalities.

4.2. Nested Tikhonov-Fenichel parameter values

Generalizing the approach to TFPV in [12]), and taking into account the special form of (3.1), it seems reasonable to consider surfaces in parameter space. Thus consider a smooth surface of the special form

$$\gamma(\varepsilon_1, \varepsilon_2) = \widehat{\pi} + \varepsilon_1 \left(\rho_1(\varepsilon_1) + \varepsilon_2 \rho_2(\varepsilon_1, \varepsilon_2)\right)$$

defined in some nighborhood of $(0,\ 0)$. Substitute $\gamma(\varepsilon_1,\ \varepsilon_2)$ for π in (4.1) to get

$$\begin{aligned} h\left(x, \gamma(\varepsilon_1, \varepsilon_2)\right) &= \underbrace{h(x, \widehat{\pi})}_{=:g^{(0,0)}} + \underbrace{h\left(x, \gamma(\varepsilon_1, 0)\right) - h(x, \widehat{\pi})}_{=:\varepsilon_1 \cdot g^{(1,0)}} \\ &+ \underbrace{\left(h(x, \gamma(\varepsilon_1, \varepsilon_2)) - h(x, \widehat{\pi})\right) - \left(h(x, \gamma(\varepsilon_1, 0)) - h(x, \widehat{\pi})\right)}_{=:\varepsilon_1 \varepsilon_2 g^{(1,1)}} \end{aligned} \tag{4.3}$$

with the $g^{(i,j)}$ smooth by Hadamard's lemma. In order to obtain a system (3.1) that also satisfies the conditions (i) and (ii) preceding Lemma 1, the following is necessary: There exist $s > 0$ and $k > 0$ such that $\widehat{\pi} \in \Pi_{s+k}$, and $\widehat{\pi} + \varepsilon_1 \cdot \rho_1(\varepsilon_1) \in \Pi_s$ for all sufficiently small $\varepsilon_1 > 0$. (Note that ε_2 plays no role in these conditions.) This observation gives rise to:

Definition 2. *Given system* (4.1) *and* $s,\ k > 0$ *with* $s + k < n$, *let* $\delta > 0$ *and let*

$$\beta : (-\delta, \delta) \longrightarrow \Pi,\ \varepsilon_1 \mapsto \beta(\varepsilon_1)$$

be a smooth curve such that

(i) $\beta(\varepsilon_1) \in \Pi_s$ *for all* $\varepsilon_1 > 0$,

(ii) $\widehat{\pi} := \beta(0) \in \Pi_{s+k}$.

Then we call $\widehat{\pi}$ *a Tikhonov-parameter value (for dimension* $s + k$*) nested in* $\overline{\Pi}_s$.

We note some properties of nested TFPV.

Proposition 3. *(a) Any TFPV* $\widehat{\pi} \in \Pi_{s+k}$ *which is nested in* $\overline{\Pi}_s$ *lies in the boundary of* Π_s *relative to its Zariski closure* W_s.

(b) Let β *as in Definition 2, and for* $\varepsilon_1 > 0$ *consider the decomposition*

$$h(x,\ \beta(\varepsilon_1)) = P^*(x,\ \varepsilon_1)\mu^*(x,\ \varepsilon_1)$$

according to [11], Theorem 1. Then

$$\det D\mu^*(x,\ 0)\, P^*(x,0)) = 0$$

on the critical manifold.

Proof. Part (a) is a direct consequence of the definition. As for part (b), at $\varepsilon_1 = 0$, with $\widehat{\pi} \in \Pi_{s+k}$ and $x_0 \in Z_{s+k}$ (using notation from Lemma 2), the coefficient $\sigma_s(x_0, \widehat{\pi})$ of the characteristic polynomial (4.2) of

$$D_x h(x_0, \widehat{\pi}) = P^*(x_0, 0) D\mu^*(x_0, 0)$$

must vanish. This is equivalent to non-invertibility of $D\mu^*(x,\ 0)\, P^*(x,0))$; see e.g. [11], Remark 4.

□

Remark 4. *Proposition 3 opens a starting point for the computation of nested TFPV: Start with system* (4.1) *corresponding to "generic" parameter values in* Π_s*, i.e. parameter values in the intersection of* Π_s *with an irreducible component of the Zariski closure* W_s*. In order to find nested parameters for higher dimension one only needs to look at the boundary of* $\overline{\Pi}_s$*, and one can use part (b) in order to obtain necessary conditions. Practically this may be realized by determining the decomposition* $P \cdot \mu$ *for generic* $\pi \in \Pi_s$ *and then looking at zeros of* $D\mu \cdot P$*, with parameters in the boundary. (The boundary may also contain further parameter values in* Π_s*.)*

4.3. Special settings for chemical reaction networks

For chemical reaction networks (CRN) the parameter region is usually given by $\Pi = \mathbb{R}^m_+$, thus

$$\pi = \begin{pmatrix} \pi_1 \\ \vdots \\ \pi_m \end{pmatrix} \in \mathbb{R}^m_+,$$

and for many such systems and given s, the irreducible components of W_s are just determined by the vanishing of certain of the π_i; see e.g. [12, 16, 18]. (The underlying reason for this fact is the subject of forthcoming work.) Thus we have, for π in a given irreducible component:

(i) Upon relabelling, there is an ℓ, $0 < \ell < m$ such that $\pi_i = 0$ for all $i \in \{\ell + 1, \cdots m\}$;

(ii) the remaining parameters are nonnegative.

In other words, the intersection of Π_s with the given irreducible component of W_s corresponds to some subset of $\overline{\mathbb{R}^\ell_+}$, with boundary $\overline{\mathbb{R}^\ell_+} \setminus \mathbb{R}^\ell_+$. This leads to an obvious case-by-case analysis. Note that boundary points may or may not be contained in Π_s, but there is no loss in starting with "generic" parameter values in the interior $\mathbb{R}^\ell_{>0}$. We look at a particular example.

Example 2. We again consider competitive inhibition; see Eq (3.3). Here the parameters are of the form

$$\pi = \begin{pmatrix} e_0 \\ k_1 \\ k_{-1} \\ k_2 \\ i_0 \\ k_3 \\ k_{-3} \end{pmatrix} \in \mathbb{R}^7_+.$$

From [12], Proposition 8 (see also Goeke's dissertation [18], section 9.3) we have the necessary condition $e_0k_1k_2k_{-3} = 0$ for a TFPV in Π_1, with each of the four cases (e.g. $e_0 = 0$ and all other parameter values ≥ 0) yielding a singular perturbation reduction with attracting one dimensional critical manifold. Hence W_1 has four irreducible components. For the cases with some $k_i = 0$, which amount to a distinction of slow and fast reactions, the two time scale reductions may be obtained using a computational procedure outlined in Heinrich and Schauer [19]; see also Stiefenhofer [22]. In order to find nested TFPV's for dimension 2 we perform a case-by-case investigation. We only consider one case here; see Section 5 for the remaining ones.
For the case $k_2 = 0$ the system is given by

$$\begin{aligned} \dot{s} &= k_{-1}c_1 - k_1se \\ \dot{c}_1 &= k_1se - k_{-1}c_1 \\ \dot{c}_2 &= k_3ei - k_{-3}c_2, \end{aligned}$$

where we have used the abbreviations $e = e_0 - c_1 - c_2$ and $i = i_0 - c_2$; note that $e \geq 0$ and $i \geq 0$ by design of (3.3). By Remark 4, nested TFPV's for dimension two and corresponding points in the critical manifold necesarily satisfy $\det(D\mu \cdot P) = 0$, with

$$\mu = \begin{pmatrix} k_{-1}c_1 - k_1se \\ k_3ei - k_{-3}c_2 \end{pmatrix}, \; P = \begin{pmatrix} 1 & 0 \\ -1 & 0 \\ 0 & 1 \end{pmatrix},$$

$$D\mu = \begin{pmatrix} -k_1e & k_1s + k_{-1} & k_1s \\ 0 & -k_3i & -(k_3i + k_3e + k_{-3}) \end{pmatrix}.$$

Proceeding according to Remark 4, we determine the vanishing set of

$$\begin{aligned} &\det \begin{pmatrix} -(k_1e + k_1s + k_{-1}) & k_1s \\ k_3i & -(k_3i + k_3e + k_{-3}) \end{pmatrix} \\ =&k_1k_3ie + k_1k_3e^2 + k_1k_{-3}e + k_1k_3se + k_1k_{-3}s + k_{-1}k_3i + k_{-1}k_3e + k_{-1}k_{-3}. \end{aligned}$$

Since all the variables and parameters are nonnegative, this sum equals zero if and only if every summand vanishes. In particular, $k_{-1} \cdot k_{-3}$ has to vanish for any nested TFPV. We look at the two ensuing cases.

(i) $k_{-1} = 0$: Then the remaining conditions are

$$k_1k_3ie = k_1k_3e^2 = k_1k_{-3}e = k_1k_3se = k_1k_{-3}s = 0.$$

If $k_1 = 0$ or $k_3 = k_{-3} = 0$ we obtain a two dimensional variety of stationary points. Checking the attractivity conditions (HA), one finds that these cases yield nested TFPV. If $e = s = 0$ holds then we get $e_0 - c_1 - c_2 = 0 = s$ which corresponds to a one dimensional variety. In case $e = k_{-3} = 0$ we get $c_1 = 0$ while c_2 and s are arbitrary, thus we have a two dimensional (attracting) variety of stationary points.

(ii) $k_{-3} = 0$: In this case there remains

$$k_1k_3ie = k_1k_3e^2 = k_1k_3se = k_{-1}k_3i = k_{-1}k_3e = 0.$$

In view of case (i) we only have to check $k_3 = 0$ or $e = i = 0$. In both cases we get a variety of dimension two.

The case $k_3 = k_{-3} = 0$ leads to system (3.3) with $k_3 = \varepsilon_1 k_3^*$, $k_{-3} = \varepsilon_1 k_{-3}^*$ and $k_2 = \varepsilon_1\varepsilon_2 k_2^*$, the reduction of which was discussed in Example 1.

5. Further examples

In this section we continue the discussion of the competitive inhibitor network, to some extent, and furthermore present a fairly complete investigation of a cooperative system with two complexes, following the strategy outlined in Remark 4. The mathematical analysis yields a rather large number of possible reductions, with parameter conditions that allow an interpretation in a biochemical context. It seems that most of these reductions have not been discussed before in the literature. Here one should note that the principal interest in biochemistry (as in the monograph by Keener and Sneyd) lies in identifying and discussing reaction velocities for given parameter constellations; thus the focus is different from the one in the present paper. (Noel et al. [4], Radulescu et al. [5], Samal et al. [6, 7] investigate questions related to those in the present paper.) Missing from a complete analysis are some cases concerned with boundary points in $\Pi_1 \subseteq W_1$ which themselves belong to Π_1, as well as certain degenerate cases for Π_2. Moreover we will not generally record routine calculations to verify conditions such as (HA), and for ease of notation we will frequently use the term "critical manifold" for the Zariski closure of this object, without mentioning the inequalities to be satisfied.

5.1. Competitive inhibition (cont.)

We continue to investigate the competitive inhibition network; see Eq (3.3), Examples 1 and 2. The analysis of TFPV which was started in Example 2 will be finished here. For Π_1 there are three remaining cases, viz. $e_0 = 0$, $k_1 = 0$ and $k_{-3} = 0$.

(a) For $e_0 = 0$, the system is given by

$$\begin{aligned} \dot{s} &= (k_1 s + k_{-1})c_1 + k_1 s c_2 \\ \dot{c}_1 &= -(k_1 s + k_{-1} + k_2)c_1 - k_1 s c_2 \\ \dot{c}_2 &= -k_3 i c_1 - (k_3 i + k_{-3})c_2 \end{aligned} \tag{5.1}$$

We only consider the generic case for Π_1, thus all the remaining parameters are > 0. Then the (only possible) decomposition $P \cdot \mu$ for the right hand side is given by

$$\mu = \begin{pmatrix} c_1 \\ c_2 \end{pmatrix}, \quad P = \begin{pmatrix} k_1 s + k_{-1} & k_1 s \\ -(k_1 s + k_{-1} + k_2) & -k_1 s \\ -k_3 i & -(k_3 i + k_{-3}) \end{pmatrix}.$$

For nested TFPV, a simple computation yields the necessary condition

$$0 = \det(D\mu \cdot P) = ik_{-1}k_3 + ik_2k_3 + sk_{-3}k_1 + k_{-3}k_{-1} + k_{-3}k_2,$$

with all terms positive; thus every summand must vanish, and in particular

$$\det(D\mu \cdot P) = 0 \;\Rightarrow\; (k_{-1} + k_2)k_{-3} = 0 \;\Rightarrow\; k_{-1} = k_2 = 0 \text{ or } k_{-3} = 0.$$

In case $k_{-1} = k_2 = 0$ system (5.1) admits a two dimensional variety of stationary points, with $k_1 s \neq 0$ only if $c_1 + c_2 = 0$. The intersection of this variety with the positive orthant is only one dimensional, thus we do not obtain a two dimensional critical manifold. The cases with $k_1 s = 0$ translate to $k_1 = \varepsilon k_1^*$ for the system with small parameters. (Otherwise the critical manifold would be given by $s = 0$, which does not contain the line given by $c_1 = c_2 = 0$.) Moreover we have $e_0 = \varepsilon_1\varepsilon_2 e_0^*$, hence every term $k_1 e_0 s$ is of the form $\varepsilon_1^2\varepsilon_2 \cdot (\cdots)$, and the completely reduced system is necessarily trivial. Likewise, the case $k_{-3} = 0$ in system (5.1) leads to $k_1 s = 0$.
To summarize, for the case $e_0 = 0$, which leads to the familiar QSS reduction in the two time scale setting, there are no interesting reductions for the three time scale scenario: No parameter value leads to an intermediate reduction to dimension two with nontrivial complete reduction.

(b) Next we consider the system with $k_1 = 0$, i.e.

$$\begin{aligned} \dot{s} &= k_{-1}c_1 \\ \dot{c}_1 &= -(k_{-1} + k_2)c_1 \\ \dot{c}_2 &= k_3 ei - k_{-3}c_2. \end{aligned}$$

Because of Example 2 we may assume that $k_2 \neq 0$, which yields $c_1 = 0$ for stationary points.
In case $k_{-3} = k_3 = 0$ we indeed have a two dimensional critical manifold. Turning to small parameters we have $k_1 = \varepsilon_1\varepsilon_2 k_1^*$, $k_3 = \varepsilon_1 k_3^*$ and $k_{-3} = \varepsilon_1 k_{-3}^*$, and (3.3) becomes

$$\begin{pmatrix} \dot{s} \\ \dot{c}_1 \\ \dot{c}_2 \end{pmatrix} = \begin{pmatrix} k_{-1}c_1 \\ -(k_{-1} + k_2)c_1 \\ 0 \end{pmatrix} + \varepsilon_1 \begin{pmatrix} 0 \\ 0 \\ k_3^* ei - k_{-3}^* c_2 \end{pmatrix} + \varepsilon_1\varepsilon_2 k_1^* es \begin{pmatrix} -1 \\ 1 \\ 0 \end{pmatrix} \tag{5.2}$$

We compute the reductions for this case. For the auxiliary system (on the critical variety defined by $c_1 = 0$) we obtain the decomposition

$$\begin{pmatrix} k_{-1}c_1 \\ -(k_{-1} + k_2)c_1 \\ 0 \end{pmatrix} = \underbrace{\begin{pmatrix} k_{-1} \\ -(k_{-1} + k_2) \\ 0 \end{pmatrix}}_{P_1} \cdot \underbrace{c_1}_{\mu_1},$$

and a straightforward computation yields the projection matrix

$$Q_1 = \begin{pmatrix} 1 & k_{-1}/(k_{-1}+k_2) & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 1 \end{pmatrix}$$

and the auxiliary system

$$\begin{pmatrix} \dot{s} \\ \dot{c}_1 \\ \dot{c}_2 \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ k_3^* ei - k_{-3^*} c_2 \end{pmatrix} + \varepsilon_2 \frac{k_1^* k_2 es}{k_{-1}+k_2} \begin{pmatrix} -1 \\ 0 \\ 0 \end{pmatrix}$$

on the variety defined by $c_1 = 0$. (This is a QSS reduction for complex C_1, according to [16], Proposition 5.) The intermediate reduced system is obtained setting $\varepsilon_2 = 0$.
Turning to the complete reduction, the decomposition of the "fast part" of (5.2) is given by

$$\begin{pmatrix} k_{-1} & 0 \\ -(k_{-1}+k_2) & 0 \\ 0 & \varepsilon_1 \end{pmatrix} \begin{pmatrix} c_1 \\ \mu_2 \end{pmatrix}, \quad \text{with } \mu_2 = k_3^* ei - k_{-3}^* c_2.$$

One obtains

$$A_2 = \begin{pmatrix} -(k_{-1}+k_2) & 0 \\ (k_{-1}+k_2)k_3 i & -\varepsilon_1 \left(k_3(e+i) + k_{-3}c_2\right) \end{pmatrix}$$

and may continue as prescribed by Proposition 2. There are shortcuts, though: First note that the critical manifold is given by $c_1 = 0$, and c_2 constant and equal to the smaller solution $\widetilde{c_2}$ of the quadratic equation

$$0 = \mu_2(0, c_2) = k_3^*(e_0 - c_2)(i_0 - c_2) - k_{-3}^* c_2.$$

The completely reduced system will automatically yield $\dot{c}_1 = 0$ and $\dot{c}_2 = 0$, hence only the first row of the projection matrix needs to be computed. As the final result of the reduction procedure we get the equation

$$\dot{s} = -\frac{k_1^* k_2}{k_{-1}+k_2}(e_0 - \widetilde{c_2})s,$$

with the dot denoting differentiation with respect to $\varepsilon_1\varepsilon_2 t$.

(c) Finally, we deal with the case $k_{-3} = 0$, which does not automatically yield a one dimensional variety of stationary points. System (3.3) becomes

$$\begin{aligned} \dot{s} &= k_{-1}c_1 - k_1 se \\ \dot{c}_1 &= k_1 se - (k_{-1}+k_2)c_1 \\ \dot{c}_2 &= k_3 ei. \end{aligned}$$

We may assume that $k_1 \neq 0$ and $k_2 \neq 0$, otherwise one would arrive at (non-generic) subcases of previously discussed systems. From this we obtain $c_1 = 0$ and $es = 0$ as necessary conditions. Now $e = 0$ and nonnegativity of varaibles imply $e_0 = 0$; a previously discussed case, therefore every stationary point satisfies $s = 0$. If $k_3 \neq 0$ then $i = 0$ forces $c_2 = i_0$; the corresponding parameter

values are not in Π_1. So the only case remaining is $k_3 = k_{-3} = 0$ (very slow binding to the inhibitor, very slow degradation of the inhibitor complex), with system

$$\begin{aligned}\dot{s} &= k_{-1}c_1 - k_1 se\\ \dot{c}_1 &= k_1 se - (k_{-1} + k_2)c_1\\ \dot{c}_2 &= 0.\end{aligned}$$

To obtain a two dimensional variety of stationary points one has to check the boundary of Π_1 for nested TFPV, which splits into four cases. We only discuss the case $k_1 = 0$ here, thus (3.3) with small parameters becomes

$$\begin{pmatrix}\dot{s}\\ \dot{c}_1\\ \dot{c}_2\end{pmatrix} = \begin{pmatrix}k_{-1}c_1\\ -(k_{-1}+k_2)c_1\\ 0\end{pmatrix} + \varepsilon_1 k_1^* es\begin{pmatrix}-1\\ 1\\ 0\end{pmatrix} + \varepsilon_1\varepsilon_2\begin{pmatrix}0\\ 0\\ k_3^* ei - k_{-3}^* c_2\end{pmatrix} \tag{5.3}$$

The computation of the auxiliary system runs similar to the reduction of (5.2) and yields

$$\begin{pmatrix}\dot{s}\\ \dot{c}_1\\ \dot{c}_2\end{pmatrix} = \frac{k_1^* k_2 es}{k_{-1}+k_2}\begin{pmatrix}-1\\ 0\\ 0\end{pmatrix} + \varepsilon_2\begin{pmatrix}0\\ 0\\ k_3^* ei - k_{-3^*} c_2\end{pmatrix},$$

on the invariant variety given by $c_1 = 0$. Finally, the completely reduced system lives on the variety defined by $c_1 = s = 0$ (a coordinate subspace), and therefore by [16], Proposition 5 the reduced system may be directly obtained via "classical" QSS reduction; yielding

$$\dot{c}_2 = k_3^*(e_0 - c_2)(i_0 - c_2) - k_{-3}^* c_2.$$

5.2. A cooperative system

In this subsection we study the standard cooperative system involving substrate S, two complexes C_1, C_2, enzyme E and product P. The reaction scheme

$$\begin{aligned} S + E &\underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C_1 \overset{k_2}{\rightharpoonup} E + P\\ S + C_1 &\underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} C_2 \overset{k_4}{\rightharpoonup} C_1 + P\end{aligned}$$

yields, with the usual assumptions and stoichiometry, the differential equation

$$\begin{aligned}\dot{s} &= -k_1 e_0 s + (k_{-1} + k_1 s - k_3 s)c_1 + (k_1 s + k_{-3})c_2\\ \dot{c}_1 &= k_1 e_0 s - (k_{-1} + k_2 + k_1 s + k_3 s)c_1 + (k_{-3} + k_4 - k_1 s)c_2\\ \dot{c}_2 &= k_3 s c_1 - (k_{-3} + k_4)c_2\end{aligned} \tag{5.4}$$

where all appearing constants are non-negative; see Keener and Sneyd [14], equations (1.62–64), where the QSS reduction for complexes C_1 and C_2 is discussed. A direct proof of validity via singular perturbation theory - for two time scales - is given in Murray [21], Section 6.5 when $e_0 = \varepsilon e_0^*$; alternatively [16], Proposition 5 is applicable. In [16], subsection 5.4 a list of parameter conditions for

various types of QSS is given, and their relation to Tikhonov-Fenichel reductions is discussed. Keener and Sneyd also mention the (partial) equilibrium approximation, by which one generally determines the product forming velocity given equilibrium in a certain subnetwork. In the present context [14], section 1.7, Exercise 10 this means that $k_2 = \varepsilon k_2^*$ and $k_4 = \varepsilon k_4^*$ are small. The discussion in 5.2.4 shows, among other things, that these conditions are not compatible with singular perturbation reductions. (One needs to add further "small parameters", and the resulting reduction formulas are more complicated.) Cooperative systems with three complexes are mentioned in [14], and the singular perturbation reduction in the case of arbitrary many complexes, with small $e_0 = \varepsilon e_0^*$, is derived in [16], section 5.3. Now we turn to the three time scale setting.
According to Goeke [18], Kap. 9.4, necessary conditions for TFPV are given by

$$e_0 k_1 k_2 (k_{-3} + k_4) = 0.$$

5.2.1. Case $k_1 = 0$

When we substitute $k_1 = 0$ in Eq (5.4) we obtain

$$\begin{aligned}
\dot{s} &= (k_{-1} - k_3 s)c_1 + k_{-3}c_2 \\
\dot{c}_1 &= -(k_{-1} + k_2 + k_3 s)c_1 + (k_{-3} + k_4)c_2 \\
\dot{c}_2 &= k_3 s c_1 - (k_{-3} + k_4)c_2.
\end{aligned}$$

Hence considering the generic case (all remaining parameters > 0) we obtain an irreducible component of W_1 given by $k_1 = 0$, and the critical manifold is given by $c_1 = c_2 = 0$. We get a decomposition with

$$P = \begin{pmatrix} -sk_3 + k_{-1} & k_{-3} \\ -(sk_3 + k_{-1} + k_2) & k_{-3} + k_4 \\ sk_3 & -(k_{-3} + k_4) \end{pmatrix}, \quad \mu = \begin{pmatrix} c_1 \\ c_2 \end{pmatrix},$$

and necessary conditions for nested TFPV from

$$0 = \det D\mu \cdot P = (k_{-1} + k_2)(k_{-3} + k_4) \Rightarrow k_{-1} = k_2 = 0 \text{ or } k_{-3} = k_4 = 0.$$

Thie first set of conditions does not, by itself, yield a two dimensional critical manifold, and we will not pursue it further here. The second set, i.e. $k_{-3} = k_4 = 0$, yields the two dimensional variety given by $c_1 = 0$.
Considering this setting, we introduce the small parameters in our original system by substituting $k_1 = \varepsilon_1\varepsilon_2 k_1^*$, $k_{-3} = \varepsilon_1 k_{-3}^*$, $k_4 = \varepsilon_1 k_4^*$. Ordering the parameters as $e_0, k_1, k_{-1}, k_2, , k_3, k_{-3}, k_4$, we thus consider the surface in parameter space given by

$$\gamma(\varepsilon_1, \varepsilon_2) = \begin{pmatrix} e_0 \\ 0 \\ k_{-1} \\ k_2 \\ k_3 \\ 0 \\ 0 \end{pmatrix} + \varepsilon_1 \cdot \left(\begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ k_{-3}^* \\ k_4^* \end{pmatrix} + \varepsilon_2 \begin{pmatrix} 0 \\ k_1^* \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix} \right),$$

and with $x = (s,\ c_1,\ c_2)^{\mathrm{tr}}$ we get

$$h(x, \varepsilon_1, \varepsilon_2) = g^{(0,0)}(x) + \varepsilon_1 \cdot \left(g^{(1,0)}(x, \varepsilon_1) + \varepsilon_2 \cdot g^{(1,1)}(x, \varepsilon_1, \varepsilon_2)\right) \tag{5.5}$$

with

$$g^{(0,0)}(x) = \begin{pmatrix} (-sk_3 + k_{-1})c_1 \\ -(sk_3 + k_{-1} + k_2)c_1 \\ k_3 s c_1 \end{pmatrix}$$

$$g^{(1,0)}(x, \varepsilon_1) = \begin{pmatrix} k^*_{-3} c_2 \\ (k^*_{-3} + k^*_4)c_2 \\ -(k^*_{-3} + k^*_4)c_2 \end{pmatrix}$$

$$g^{(1,1)}(x, \varepsilon_1, \varepsilon_2) = \begin{pmatrix} sk^*_1 c_1 + sk^*_1 c_2 - k^*_1 e_0 s \\ -(sk^*_1 c_1 + sk^*_1 c_2 - k^*_1 e_0 s) \\ 0 \end{pmatrix}.$$

For this system we compute the complete reduction on $c_1 = c_2 = 0$ and the intermediate reduction on $c_1 = 0$. In order to compute the completely reduced system, a factorization of $g^{(0,0)} + \varepsilon_1 g^{(1,0)}$ is given by

$$\left(P_1, \quad \varepsilon_1 P_2\right) \cdot \begin{pmatrix} \mu_1 \\ \mu_2 \end{pmatrix}$$

with $\mu_1 = c_1$, $\mu_2 = c_2$, and

$$P_1 = \begin{pmatrix} -sk_3 + k_{-1} \\ -(sk_3 + k_{-1} + k_2) \\ k_3 s \end{pmatrix}, \quad P_2 = \begin{pmatrix} k^*_{-3} \\ k^*_{-3} + k^*_4 \\ -(k^*_{-3} + k^*_4) \end{pmatrix}.$$

The projection matrix is

$$Q_2 = \begin{pmatrix} 1 & -\frac{-sk_3k^*_4 - k^*_{-3}k_{-1} - k_{-1}k^*_4}{k^*_{-3}k_{-1} + k_2k^*_{-3} + k_{-1}k^*_4 + k_2k^*_4} & -\frac{-sk_3k^*_4 - 2k^*_{-3}k_{-1} - k_2k^*_{-3} - k_{-1}k^*_4}{k^*_{-3}k_{-1} + k_2k^*_{-3} + k_{-1}k^*_4 + k_2k^*_4} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix},$$

and the fully reduced system in very slow time on the invariant manifold $c_1 = c_2 = 0$ is given by the equation

$$\dot{s} = -\frac{k_3k^*_4 s + k^*_{-3}k_2 + k^*_4k_2}{k^*_{-3}k_{-1} + k_2k^*_{-3} + k_{-1}k^*_4 + k_2k^*_4} \cdot k^*_1 e_0 s.$$

Similarly one computes the intermediate system on the two dimensional variety given by $c_1 = 0$ from the decomposition $P_1 \cdot \mu_1$:

$$\begin{pmatrix} \dot{s} \\ \dot{c}_1 \\ \dot{c}_2 \end{pmatrix} = \frac{1}{sk^*_3 + k_{-1} + k_2} \begin{pmatrix} -(sc_2k_3k^*_4 + 2k_{-1}c_2k^*_{-3} + k_2k^*_{-3}c_2 + c_2k^*_4k_{-1}) \\ 0 \\ -(k_{-1}c_2k^*_{-3} + k_2k^*_{-3}c_2 + c_2k^*_4k_{-1} + c_2k_2k^*_4) \end{pmatrix}.$$

In this context, a brief digression may be appropriate: In their discussion of reaction velocities, Keener and Sneyd [14] also derive a Hill function in Eq (1.69)) with arguments that could a priori be interpreted

as involving three time scales: They consider "$k_1 \to 0$ and $k_3 \to \infty$, with constant product $k_1 k_3$". Rescaling time, one might think of this as a case of very small k_1, with k_3 of order one. One system satisfying these conditions is (5.5), but the completely reduced equation manifestly does not follow Hill kinetics. One might also consider the case when k_3 is of order one, k_1 is very small and all the other k_i are small. This corresponds to a degenerate (but a priori legitimate) subcase of "$k_{-3} = k_4 = 0$" discussed above, with the surface in parameter space now given by

$$\gamma(\varepsilon_1, \varepsilon_2) = \begin{pmatrix} e_0 \\ 0 \\ 0 \\ 0 \\ k_3 \\ 0 \\ 0 \end{pmatrix} + \varepsilon_1 \cdot \left(\begin{pmatrix} 0 \\ 0 \\ k_{-1}^* \\ k_2^* \\ 0 \\ k_{-3}^* \\ k_4^* \end{pmatrix} + \varepsilon_2 \begin{pmatrix} 0 \\ k_1^* \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix} \right).$$

A straightforward analysis shows, however, that the resulting system does not satisfy the rank (or eigenvalue) conditions from Lemma 1(c), hence Tikhonov-Fenichel reduction is not applicable. To summarize: For the given cooperative network, a reaction velocity of Hill type cannot be obtained from time scale arguments.

5.2.2. Case $e_0 = 0$

From $e_0 = 0$ one also obtains a component of W_1, and system (5.4) specializes to

$$\begin{aligned} \dot{s} &= (k_{-1} + k_1 s - k_3 s)c_1 + (k_1 s + k_{-3})c_2 \\ \dot{c}_1 &= -(k_{-1} + k_2 + k_1 s + k_3 s)c_1 + (k_{-3} + k_4 - k_1 s)c_2 \\ \dot{c}_2 &= k_3 s c_1 - (k_{-3} + k_4)c_2. \end{aligned}$$

The right hand side has a factorization $P \cdot \mu$ with

$$\mu = \begin{pmatrix} c_1 \\ c_2 \end{pmatrix}, \qquad P = \begin{pmatrix} sk_1 - sk_3 + k_{-1} & sk_1 + k_{-3} \\ -sk_1 - sk_3 - k_{-1} - k_2 & -sk_1 + k_{-3} + k_4 \\ sk_3 & -k_{-3} - k_4 \end{pmatrix},$$

and in order to obtain nested TFPV we examine all variable-parameter configurations that satisfy

$$0 = \det(D\mu \cdot P) = sk_1 \cdot (sk_3 + k_{-3} + k_4) + (k_{-1} + k_2) \cdot (k_{-3} + k_4).$$

The plane given by $s = 0$ is not a viable candidate for a two dimensional critical manifold since it does not contain the line $c_1 = c_2 = 0$. This leaves the cases $k_1 = k_{-1} = k_2 = 0$, $k_1 = k_{-3} = k_4 = 0$ and $k_3 = k_{-3} = k_4 = 0$.

The first of these yields a two dimensional variety (defined by $k_3 s c_1 - k_{-3} c_2 = 0$) only under the additional condition $k_4 = 0$. The second case, whenever $k_1 \neq 0$, yields a variety whose intersection with the positive orthant has dimension one, hence is of no relevance. For the third case we obtain a two dimensional variety only if $k_1 = 0$ or $k_2 = 0$.

With the exception of this very last case, the completely reduced system will always be trivial, due

to $k_1 = \varepsilon_1 k_1^*$ and $e_0 = \varepsilon_1\varepsilon_2 e_0^*$, which implies $k_1 e_0 = O(\varepsilon_1^2\varepsilon_2)$. We consider one special case, viz. the intermediate reduction coresponding to the nested TFPV with $k_1 = k_3 = k_{-3} = k_4 = 0$; here $c_1 = 0$ defines the two dimensional critical manifold. Considering

$$\gamma(\varepsilon_1, \varepsilon_2) = \begin{pmatrix} 0 \\ 0 \\ k_{-1} \\ k_2 \\ 0 \\ 0 \\ 0 \end{pmatrix} + \varepsilon_1 \cdot \left(\begin{pmatrix} 0 \\ k_1^* \\ 0 \\ 0 \\ k_3^* \\ k_{-3}^* \\ k_4^* \end{pmatrix} + \varepsilon_2 \begin{pmatrix} e_0^* \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix} \right),$$

we compute:

$$g^{(0,0)} = \begin{pmatrix} c_1 k_{-1} \\ -(k_{-1} + k_2)c_1 \\ 0 \end{pmatrix}$$

$$g^{(1,0)} = \begin{pmatrix} (sk_1^* - sk_3^*)c_1 + (sk_1^* + k_{-3}^*)c_2 \\ -(sk_1^* + sk_3^*)c_1 + (-sk_1^* + k_{-3}^* + k_4^*)c_2 \\ k_3^* s c_1 - (k_{-3}^* + k_4^*)c_2 \end{pmatrix}$$

$$g^{(1,1)} = \begin{pmatrix} -\varepsilon_1 k_1^* e_0^* s \\ \varepsilon_1 k_1^* e_0^* s \\ 0 \end{pmatrix}.$$

The intermediate reduced system on the invariant variety $c_1 = 0$ is then:

$$\begin{pmatrix} \dot{s} \\ \dot{c}_1 \\ \dot{c}_2 \end{pmatrix} = \begin{pmatrix} \left(s c_2 k_1^* k_2 + 2 c_2 k_{-3}^* k_{-1} + c_2 k_{-3}^* k_2 + c_2 k_{-1} k_4^* \right)(k_{-1} + k_2) \\ 0 \\ -(k_{-3}^* + k_4^*)c_2 \end{pmatrix}.$$

5.2.3. Case $k_{-3} = k_4 = 0$

These conditions define a component of W_1, and generically the critical manifold is given by $s = c_1 = 0$. System (5.4) is given by

$$\begin{aligned} \dot{s} &= -k_1 e_0 s + (k_{-1} + k_1 s - k_3 s)c_1 + k_1 s c_2 \\ \dot{c}_1 &= k_1 e_0 s - (k_{-1} + k_2 + k_1 s + k_3 s)c_1 - k_1 s c_2 \\ \dot{c}_2 &= k_3 s c_1 \end{aligned}$$

and the product decomposition (which we do not write down here) yields

$$0 = \det D\mu \cdot P = k_1(e_0 - c_2)(k_2 + 2k_3 s).$$

as necessary conditions for nested TFPV. One possible case is $k_1 = 0$ with critical manifold $c_1 = 0$. The remaining cases are:

(i) $k_2 = k_{-1} = 0$ with variety $s = 0$;

(ii) $k_2 = k_3 = 0$ with variety $k_1(e_0 - c_1 - c_2)s - k_{-1}c_1 = 0$.

Note that the condition $e_0 - c_2 = 0$ does not yield a two dimensional critical variety.

5.2.4. Case $k_2 = 0$

In this situation system (5.4) simplifies to

$$\begin{aligned} \dot{s} &= -k_1 e_0 s + (k_{-1} + k_1 s - k_3 s)c_1 + (k_1 s + k_{-3})c_2 \\ \dot{c}_1 &= k_1 e_0 s - (k_{-1} + k_1 s + k_3 s)c_1 + (k_{-3} + k_4 - k_1 s)c_2 \\ \dot{c}_2 &= k_3 s c_1 - (k_{-3} + k_4)c_2. \end{aligned}$$

The condition $k_2 = 0$ by itself does not define an irreducible component of W_1; in other words it does not guarantee the existence of a one dimensional variety of stationary points. Therefore we first investigate sufficient conditions, using the observation $\dot{s} + \dot{c}_1 + 2\dot{c}_2 = -k_4 c_2$.

(a) For $k_4 \neq 0$ this observation implies that any stationary point satisfies $c_2 = 0$, and the remaining condition is $k_3 s c_1 = 0$.

(i) In case $k_3 \neq 0$ we have either $s = 0$, with the variety of stationary points given by $s = c_2 = 0$; in turn this yields the parameter configuration

$$k_{-1} = k_2 = 0.$$

(ii) Alternatively we have $c_1 = 0$, the variety is given by $c_1 = c_2 = 0$, and one must have $k_1 e_0 = 0$. We obtain the possible parameter configurations

$$k_1 = k_2 = 0 \text{ or } e_0 = k_2 = 0.$$

(b) In case $k_4 = 0$ the remaining system is

$$\begin{aligned} \dot{s} &= -k_1 e s + k_{-1} c_1 - k_3 s c_1 + k_{-3} c_2 \\ \dot{c}_1 &= k_1 e s - k_{-1} c_1 + k_3 s c_1 + k_{-3} c_2 \\ \dot{c}_2 &= k_3 s c_1 - k_{-3} c_2. \end{aligned}$$

Adding the first two equations for stationary points shows that $k_{-3} c_2 = 0$, and combining this with the third equation yields $k_3 s c_1 = 0$; in addition one has $k_1 e s - k_{-1} c_1 = 0$. Thus there are further conditions for the existence of a one dimensional critical variety.

(i) Given that $k_3 \neq 0$ and $k_{-3} \neq 0$, the variety is given either by $c_2 = s = 0$, which yields the parameter conditions

$$k_2 = k_{-1} = k_4 = 0;$$

or the variety is given by $c_1 = c_2 = 0$, with parameter conditions

$$k_2 = k_4 = k_1 = 0 \text{ or } k_2 = k_4 = e_0 = 0;$$

all of these are special cases from (a).

(ii) In case $k_3 = 0$ we obtain the one dimensional variety given by $c_2 = 0$ and $k_1(e_0 - c_1)s - k_{-1}c_1 = 0$; thus we have the parameter condition

$$k_2 = k_3 = k_4 = 0$$

which defines a component of W_1.

(iii) In case $k_{-3} = 0$ one obtains the variety $s = c_1 = 0$, with parameter conditions

$$k_2 = k_4 = k_{-3} = 0.$$

For all these parameters the next task is to discuss conditions for embedded TFPV. We will only do so for two cases.

1. In the case $k_{-1} = k_2 = 0$ one has a decomposition

$$\begin{pmatrix} -k_1 e - k_3 c_1 & k_{-3} \\ k_1 e - k_3 c_1 & k_{-3} + k_4 \\ k_3 c_1 & -(k_{-3} + k_4) \end{pmatrix} \cdot \begin{pmatrix} s \\ c_2 \end{pmatrix}$$

which yields

$$\det D\mu \cdot P = k_1(k_{-3} + k_4)e + k_3 k_4 c_1.$$

We take a closer look at the case $k_1 = k_3 = 0$, with critical variety $c_2 = 0$. The surface in parameter space

$$\gamma(\varepsilon_1, \varepsilon_2) = \begin{pmatrix} e_0 \\ 0 \\ 0 \\ 0 \\ 0 \\ k_{-3} \\ k_4 \end{pmatrix} + \varepsilon_1 \cdot \left(\begin{pmatrix} 0 \\ k_1^* \\ 0 \\ 0 \\ k_3^* \\ 0 \\ 0 \end{pmatrix} + \varepsilon_2 \begin{pmatrix} 0 \\ 0 \\ k_{-1}^* \\ k_2^* \\ 0 \\ 0 \\ 0 \end{pmatrix} \right)$$

yields

$$g^{(0,0)} = \begin{pmatrix} c_2 k_{-3} \\ (k_{-3} + k_4)c_2 \\ -(k_{-3} + k_4)c_2 \end{pmatrix}$$

$$g^{(1,0)} = \begin{pmatrix} -k_1^* e_0 s + (s k_1^* - s k_3^*)c_1 + s k_1^* c_2 \\ k_1^* e_0 s - (k_1^* s + k_3^* s)c_1 - k_1^* s c_2 \\ k_3^* s c_1 \end{pmatrix}$$

$$g^{(1,1)} = \begin{pmatrix} k_{-1}^* c_1 \\ -(k_{-1}^* + k_2^*)c_1 \\ 0 \end{pmatrix}.$$

The intermediate reduced system is as follows:

$$\begin{aligned} \dot{s} &= \frac{s c_1 k_{-3} k_1^* + k_4 k_1^* c_1 s - s c_1 k_3^* k_4 - k_1^* e_0 s k_{-3} - k_1^* e_0 s k_4}{k_{-3} + k_4} \\ \dot{c}_1 &= -s c_1 k_1^* + k_1^* e_0 s \\ \dot{c}_2 &= 0, \end{aligned}$$

and the completely reduced system (on $s = c_2 = 0$) is given by:

$$\dot{c}_1 = \frac{-c_1(c_1 k_{-3} k_1^* k_2^* - c_1 k_{-1}^* k_3^* k_4 + c_1 k_1^* k_2^* k_4 - c_1 k_2^* k_3^* k_4 - e_0 k_{-3} k_1^* k_2^* - e_0 k_1^* k_2^* k_4)}{c_1 k_{-3} k_1^* + c_1 k_1^* k_4 - c_1 k_3^* k_4 - e_0 k_1^* k_{-3} - e_0 k_1^* k_4}$$

2. In the case $k_2 = k_3 = k_4 = 0$ we have the one dimensional critical manifold

$$k_1 s \cdot (e_0 - c_1) - k_{-1} c_1 = 0,\ c_2 = 0$$

and the right hand side of the system at $k_2 = k_3 = k_4 = 0$ can be decomposed into $P \cdot \mu$, with

$$P = \begin{pmatrix} 1 & sk_1 + k_{-3} \\ -1 & -sk_1 + k_{-3} \\ 0 & -k_{-3} \end{pmatrix}$$
$$\mu = \begin{pmatrix} k_1 s \cdot (e_0 - c_1) - k_{-1} c_1 \\ c_2 \end{pmatrix}.$$

This yields

$$\det(D\mu \cdot P) = (k_1(e_0 - c_1) + k_1 s + k_{-4}) \cdot k_{-3}.$$

We investigate the case $k_{-3} = 0$. Additionally setting $k_{-3} = 0$ we obtain the two dimensional critical manifold defined by

$$\mu_2 := -k_1 e_0 s + (k_{-1} + k_1 s)c_1 + k_1 s c_2 = 0.$$

Following the usual procedure we consider the surface

$$\gamma(\varepsilon_1, \varepsilon_2) = \begin{pmatrix} e_0 \\ k_1 \\ k_{-1} \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix} + \varepsilon_1 \cdot \left(\begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ k^*_{-3} \\ 0 \end{pmatrix} + \varepsilon_2 \begin{pmatrix} 0 \\ 0 \\ 0 \\ k^*_2 \\ k^*_3 \\ 0 \\ k^*_4 \end{pmatrix} \right)$$

in parameter space, and thus

$$g^{(0,0)} = \begin{pmatrix} -k_1 e_0 s + (sk_1 + k_{-1})c_1 + k_1 s c_2 \\ k_1 e_0 s - (sk_1 + k_{-1})c_1 + -k_1 s c_2 \\ 0 \end{pmatrix}$$
$$g^{(1,0)} = \begin{pmatrix} k^*_{-3} c_2 \\ k^*_{-3} c_2 \\ -k^*_{-3} c_2 \end{pmatrix}$$
$$g^{(1,1)} = \begin{pmatrix} -sk^*_3 c_1 \\ -(sk^*_3 + k^*_2)c_1 + k^*_4 c_2 \\ sk^*_3 c_1 - k^*_4 c_2 \end{pmatrix}.$$

Here the intermediate reduced system is given by

$$\dot{s} = \frac{1}{sk_1 + k_1(e_0 - c_1 - c_2) + k_{-1}} \cdot (sc_2 k^*_{-3} k_1 + 2c_2 k^*_{-3} k_{-1})$$

$$\dot{c}_1 = \frac{1}{sk_1 + k_1(e_0 - c_1 - c_2) + k_{-1}} \cdot \left(sc_2 k^*_{-3} k_1 - 2k_1 c_2 k^*_{-3} c_1 - 2k_1 k^*_{-3} c_2^2 + 2e_0 k_1 k^*_{-3} c_2 \right)$$
$$\dot{c}_2 = -c_2 k^*_{-3}$$

on $\mu_2 = 0$, and the fully reduced system is given by

$$\dot{s} = \frac{1}{sk_1 + k_1(e_0 - c_1) + k_{-1}} \cdot (-se_0 k_1 k^*_2)$$
$$\dot{c}_1 = \frac{1}{sk_1 + k_1(e_0 - c_1) + k_{-1}} \cdot \left(k_1 k^*_2 c_1^2 - k^*_2 e_0 k_1 c_1 \right)$$
$$\dot{c}_2 = 0.$$

6. More time scales

In this section we give a brief outline on extending the coordinate-free approach to more than three time scales. Thus let $N \geq 3$ and first consider a system with $N - 1$ small parameters of the form

$$\dot{x}_i = \left(\prod_{1 \leq j < i} \varepsilon_j \right) \cdot f_i(x, \varepsilon_1, \ldots, \varepsilon_{N-1}), \quad 1 \leq i \leq N; \qquad \text{briefly } \dot{x} = f(x, \varepsilon) \tag{6.1}$$

with separated variables. By a smooth coordinate transformation this becomes

$$\dot{x} = g^{(0,\ldots,0)} + \varepsilon_1 \left(g^{(1,0,\ldots 0)} + \varepsilon_2 \left(g^{(1,1,0,\ldots,0)} + \varepsilon_3 \left(\cdots \right) \right) \right) \tag{6.2}$$

with the very last term in the embedded brackets being $\varepsilon_{N-1} g^{(1,\ldots,1)}$. Here all $g^{(i_1,\ldots,i_{N-1})}$ are functions of $(x, \varepsilon_1, \ldots, \varepsilon_{N-1})$. Moreover conditions (i), (ii) preceding Lemma 1 generalize in an obvious manner to the vanishing sets of

$$\begin{array}{lll} g^{(0,\ldots,0)} & & \\ g^{(0,\ldots,0)} & + & \varepsilon_1 g^{(1,0,\ldots 0)} \\ g^{(0,\ldots,0)} & + & \varepsilon_1 \left(g^{(1,0,\ldots 0)} + \varepsilon_2 g^{(1,1,0,\ldots,0)} \right) \\ & \text{etc.} & \end{array}$$

and as in Proposition 2 one obtains decompositions

$$\begin{aligned} g^{(0,\ldots,0)} &= P_1 \mu_1 \\ g^{(0,\ldots,0)} + \varepsilon_1 g^{(1,0,\ldots 0)} &= \begin{pmatrix} P_1, & \varepsilon_1 P_2 \end{pmatrix} \begin{pmatrix} \mu_1 \\ \mu_2 \end{pmatrix} \\ g^{(0,\ldots,0)} + \varepsilon_1 \left(g^{(1,0,\ldots 0)} + \varepsilon_2 g^{(1,1,0,\ldots,0)} \right) &= \begin{pmatrix} P_1, & \varepsilon_1 P_2, & \varepsilon_1 \varepsilon_2 P_3 \end{pmatrix} \begin{pmatrix} \mu_1 \\ \mu_2 \\ \mu_3 \end{pmatrix} \\ & \text{etc.} \end{aligned}$$

Likewise, one generalizes the definitions of A_1, A_2 and the constructions of the projection matrices Q_j, the latter extending smoothly to $\varepsilon_1 = \cdots \varepsilon_{N-1} = 0$. This yields the various (intermediate) reductions.

Given a general parameter dependent system (4.1), nested Tikhonov-Fenichel parameter values may be found via the ansatz

$$\gamma : (\varepsilon_1, \ldots, \varepsilon_{N-1}) \mapsto \widehat{\pi} + \varepsilon_1 (\rho_1(x, \varepsilon_1) + \varepsilon_2 (\rho_2(x, \varepsilon_1, \varepsilon_2) + \varepsilon_3 (\cdots)))$$

and the ensuing decomposition of $h(x, \gamma(\varepsilon_1, \ldots, \varepsilon_{N-1}))$ analogous to the one in (4.3). Thus the problem is to find $s > 0$, $0 < k_1 < \cdots < k_{N-1}$ with $s + k_{N-1} < n$ and a smooth map

$$\beta : (\varepsilon_1, \ldots, \varepsilon_{N-2}) \to \Pi,$$

defined in some neighborhood of 0, such that

$$\begin{aligned} \beta(\varepsilon_1, \ldots, \varepsilon_{N-2}) &\in \Pi_s \\ \beta(\varepsilon_1, \ldots, \varepsilon_{N-3}, 0) &\in \Pi_{s+k_1} \\ &\vdots \\ \beta(0, \ldots, 0) &\in \Pi_{s+k_{N-1}} \end{aligned}$$

whenever all $\varepsilon_j > 0$. Rather obvious generalizations of Proposition 3 hold, and the strategy outlined in Remark 4 remains applicable.

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Conflict of interest

Both authors declare no conflicts of interest in this paper.

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Appendix

For the reader's convenience we state and prove here two lemmas.

Lemma 3. *Let r_1, r_2 be positive integers and*

$$A \in \mathbb{R}^{r_1 \times r_1}, \quad B \in \mathbb{R}^{r_1 \times r_2}, \quad C \in \mathbb{R}^{r_2 \times r_1}, \quad D \in \mathbb{R}^{r_2 \times r_2}.$$

Moreover assume that all eigenvalues of A have real part < 0. Then the following are equivalent.

(i) All eigenvalues of $-CA^{-1}B + D$ have real part < 0.

(ii) There exists $\delta > 0$ such that, for every $\varepsilon \in (0, \delta)$, all eigenvalues of

$$\begin{pmatrix} A & B \\ \varepsilon C & \varepsilon D \end{pmatrix}$$

have real part < 0.

Proof. Consider the singularly perturbed linear differential equation

$$\begin{aligned} \dot{x} &= Ax + By \\ \dot{y} &= \varepsilon Cx + \varepsilon Dy \end{aligned}$$

Introducing $z := x + A^{-1}By$ one can rewrite this as

$$\begin{aligned} \dot{z} &= Az + \varepsilon(\cdots) \\ \dot{y} &= \varepsilon\left((-CA^{-1}B + D)y + Cz\right) \end{aligned}$$

Here the fast system is just given by $\dot{z} = Az$, and the slow system (on the critical manifold defined by $z = 0$) is given by

$$\dot{y} = \varepsilon(-CA^{-1}B + D)y.$$

Using Tikhonov's theorem (in the form given e.g. in Verhulst [23], Ch. 8), one sees that both conditions (i), (ii) are equivalent to exponential attractivity of the stationary point 0 for the linear system. □

Lemma 4. *Let $V \subseteq \mathbb{R}^n$ be open and nonempty, $0 < r < n$, $\delta > 0$ and*

$$\begin{aligned} B_1 :&\quad V \times [0, \delta) \to \mathbb{R}^{n \times r}, &&(x, \varepsilon) \mapsto B_1(x, \varepsilon) \\ B_2 :&\quad V \times [0, \delta) \to \mathbb{R}^{n \times (n-r)}, &&(x, \varepsilon) \mapsto B_2(x, \varepsilon) \end{aligned}$$

be smooth functions (defined in some neighborhood of $V \times [0, \delta)$) such that $\mathbb{R}^n$ is the sum of the image W_1 of B_1 and the image W_2 of B_2, for every (x, ε). Then the entries of the matrix $Q(x, \varepsilon) \in \mathbb{R}^{n \times n}$ which sends $v \in \mathbb{R}^n$ to its W_2-component with respect to the direct sum decomposition $W_1 \oplus W_2$ depend smoothly on (x, ε).

Proof. We suppress the arguments (x, ε) in the notation. By assumption $C := \begin{pmatrix} B_1, & B_2 \end{pmatrix}$ is invertible, and the entries of C^{-1} depend smoothly on (x, ε). With the projection matrix given by

$$Q = \begin{pmatrix} 0 & B_2 \end{pmatrix} C^{-1},$$

the assertion is obvious.

□

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