Quasi-steady state reduction for compartmental systems

Alexandra Goeke, Christian Lax*
Lehrstuhl A für Mathematik
RWTH Aachen
52056 Aachen, Germany

December 11, 2015

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.

MSC2010: 34E15, 92C45, 80A32, 35B40

Keywords: singular perturbations, reduction, reaction-diffusion equations

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 [59], Lee and Othmer [39], Schauer and Heinrich [31], Stiefenhofer [50],

*Corresponding author, email: christian.lax@matha.rwth-aachen.de

Bothe [11], Lam and Goussis [37]), which are often based on the classical theories of Tikhonov [52] and Fenichel [24]. 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 [27] and [29] 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 reasonable 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 [27,29]) 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 [53] 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 explicit form of the reduction. We briefly sketch a specialized approach for polynomial and rational systems developed in Noethen & Walcher [45], and [27].
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

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

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

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

In the following, we will refer to $h^{(0)}$ as the *fast part* of the evolution equation and to $h^{(1)}$ as the *slow part*. For this type of systems, an explicit reduction formula was given in [29]. We state a variant of [29] Theorem 1 (see also [29] 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* $\operatorname{rank} Dh^{(0)}(x_0) = r$ *is maximal in a neighborhood of* x_0. *Thus, there exists a neighborhood* U *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

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

both rational, such that

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

with $\operatorname{rank} P(x_0) = \operatorname{rank} D\mu(x_0) = r$. *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 [48]): 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 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 intrinsic theory (Fenichel [24, 25]) 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* [39, 50, 53, 59]. In physics context it is also refered to as an adiabatic manifold [47]. 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 [29] 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 [24] Theorem 9.1 and was discussed in detail for this particular setting in [29] (see also the references given there; in particular Lee and Othmer [39], Schauer and Heinrich [31] and Stiefenhofer [50]). We briefly summarize: By [29] 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) to (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 [29] 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 [42]*

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

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

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

According to [28] Example 5, the (convergent) Tikhonov-Fenichel reduction is the result of a simple computation:

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

This result coincides with the familiar reduction going back to Briggs and Haldane [16].

3 Compartmental systems

Compartmental systems date back to the original work by Teorell [51], who used them 1937 for pharmacokinetic models; i.e. for models describing the kinetics of drugs administered to an organism. Compartmental systems are used frequently in biology, chemistry and medicine [1, 34], e.g. for epidemic, population or ecosystem models. Mathematical descriptions can be found in Haddad et al. [30] and Contreras und Walter [54]; see also Brown [18] as well as Bernstein and Hyland [8]. While the notion of compartmental systems in the literature frequently refers to systems with transport between subsystems only, we consider systems that also allow interaction within the subsystems.

Consider a system governed by transport (or flow) of "species" $A_1, \ldots, A_m$ between N subsystems (compartments) and interaction within the subsystems. We denote the mass of A_i in compartment α with $a_{i;\alpha}$ and define $\Sigma := \{1, \ldots, N\}$. Moreover, define

$$a^*_\alpha := (a_{i;\alpha})_{1 \le i \le m} \in \mathbb{R}^m, \tag{3.1}$$

$$a^* := (a^*_\alpha)_{\alpha \in \Sigma} \in \mathbb{R}^M, \tag{3.2}$$

$$\tilde{a}_i := (a_{i;\alpha})_{\alpha \in \Sigma} \in \mathbb{R}^N \tag{3.3}$$

with $M = m \cdot N$, i numbering the species and α numbering the compartments. For our purpose, the following definition is convenient.

Definition 3.1. Let $D \subset \mathbb{R}^m$ be open and $D^N := D \times \cdots \times D$.

(a) Let the transport of species i from compartment α to compartment β be governed by $F_{i;\alpha\to\beta} \in C^1(D^N; \overline{\mathbb{R}}_+)$ satisfying

$$F_{i;\alpha\to\alpha}(a^*) = 0 \quad \text{for all } a^* \in D^N \text{ and } \alpha \in \Sigma,$$
$$F_{i;\alpha\to\beta}(a^*) = 0 \quad \text{for all } a^* \in D^N \text{ with } a_{i;\alpha} = 0 \text{ and } \alpha, \beta \in \Sigma.$$

i.e. there is no transport from any compartment in itself and there is no transport of a species from a compartment if it is not present in the compartment. Denote the total rate of change due to transport of species i in compartment α by

$$\mathcal{F}_{i;\alpha}(a^*) = \sum_{\beta\in\Sigma} \big(F_{i;\beta\to\alpha}(a^*) - F_{i;\alpha\to\beta}(a^*)\big), \quad 1 \le i \le m,\ \alpha \in \Sigma.$$

Moreover, define

$$\mathcal{F}_\alpha(a^*) := (\mathcal{F}_{i;\alpha}(a^*))_{1\le i\le m} \quad \text{and} \qquad \mathcal{F}_i(a^*) = (\mathcal{F}_{i;\alpha}(a^*))_{\alpha\in\Sigma}\,.$$

(b) Let the interaction term in a compartment be given by a smooth and essentially nonnegative map $\mathcal{R}_\alpha \colon D \to \mathbb{R}^m$, i.e. $\mathcal{R}_\alpha$ satisfies $\mathcal{R}_{i;\alpha}(x) \ge 0$ for all $x \in D \cap \overline{\mathbb{R}}^m_+$ with $x_i = 0$, for all $1 \le i \le m$.

(c) We call

$$\frac{d}{dt} a^*_\alpha = \mathcal{F}_\alpha(a^*) + \mathcal{R}_\alpha(a^*_\alpha), \quad \alpha \in \Sigma, \tag{3.4}$$

a *compartmental system with interaction* or simply a *compartmental system* on D^N.

Remark 3. (a) Frequently, D is an open neighborhood of $\overline{\mathbb{R}}^m_+$. In this case, the definitions of $\mathcal{F}_\alpha$ and $\mathcal{R}_\alpha$ imply that the positive orthant $\overline{\mathbb{R}}^M_+$ is positively invariant.

(b) As $\sum_{\alpha\in\Sigma} \mathcal{F}_{i;\alpha}(a^*) = 0$ for all $1 \le i \le m$, the total mass of every species is conserved by the transport. Degradation, out- or inflows may be modeled via the interaction terms $\mathcal{R}_\alpha$.

(c) The simplest type of transport term occurs when $\mathcal{F}_i$ is linear and depends only on $\tilde{a}_i$. Thus, we have $\mathcal{F}_i(a^*) = C^{[i]}\tilde{a}_i$ for a matrix $C^{[i]} \in \mathbb{R}^{N\times N}$. The definition implies that $C^{[i]}$ is a *W-matrix* (in the sense of van Kampen [36]), i.e. $a_{\alpha\beta} \le 0$ for $\alpha \ne \beta$ and $a_{\alpha\alpha} = -\sum_{\beta\ne\alpha} a_{\beta\alpha}$.

In [26] it has been shown that for every W-matrix the algebraic and geometric multiplicity of the eigenvalue zero is equal, and that every nonzero eigenvalue has negative real part. Note that a W-matrix is a negative singular M-matrix in the terminology of Berman and Plemmons [7].

Example 3.2. *Consider a variant of the SIR model [43, 54] for the spread of a nonlethal epidemic. Denote with x the number of persons susceptible for infection; with y those who are infected; and with z those who recovered and are immune. Then, the interaction in one compartment is described by*

$$\begin{aligned} \dot{x} &= -k_1 xy \\ \dot{y} &= k_1 xy - k_2 y \\ \dot{z} &= k_2 y, \end{aligned}$$

where $k_1 > 0$ is the rate of infection and $k_2 > 0$ is the rate of recovery. We are interested in the spread of the epidemic in n countries with different rates of infection and recovery. Thus, define $\mathcal{R}_\alpha$ by

$$\mathcal{R}_\alpha(x_\alpha, y_\alpha, z_\alpha) = \begin{pmatrix} -k_{1;\alpha} x_\alpha y_\alpha \\ k_{1;\alpha} x_\alpha y_\alpha - k_{2;\alpha} y_\alpha \\ k_{2;\alpha} y_\alpha \end{pmatrix}$$

Moreover, define $\tilde{x} := (x_1, \dots, x_n)^{\mathrm{tr}}$ ($\tilde{y}$, $\tilde{z}$ analogously). Lastly, assume that the transport terms

$$\mathcal{F}_x := \left(\mathcal{F}_{x;\alpha}\right)_{1 \le \alpha \le n}, \quad \mathcal{F}_y := \left(\mathcal{F}_{y;\alpha}\right)_{1 \le \alpha \le n}, \quad \mathcal{F}_z := \left(\mathcal{F}_{z;\alpha}\right)_{1 \le \alpha \le n}$$

between the countries are linear. Hence, we get

$$\mathcal{F}_x(\tilde{x}, \tilde{y}, \tilde{z}) = C^{[x]} \tilde{x}, \quad \mathcal{F}_y(\tilde{x}, \tilde{y}, \tilde{z}) = C^{[y]} \tilde{y}, \quad \mathcal{F}_z(\tilde{x}, \tilde{y}, \tilde{z}) = C^{[z]} \tilde{z},$$

with W-matrices

$$C^{[j]} = \begin{pmatrix} -\sum_{\alpha \neq 1} c^j_{\alpha 1} & c^j_{12} & \cdots & c^j_{1n} \\ c^j_{21} & \ddots & & \vdots \\ \vdots & & \ddots & c^j_{n-1,n} \\ c^j_{n1} & \cdots & c^j_{n,n-1} & -\sum_{\alpha \neq n} c^j_{\alpha n} \end{pmatrix}, \quad j = x, y, z.$$

We have $F_{j;\alpha \to \beta}(\tilde{x}, \tilde{y}, \tilde{z}) = c^j_{\beta\alpha} j_\alpha$ for $1 \le \alpha, \beta \le n$ and $j = x, y, z$.

In the following theorem we will apply Tikhonov-Fenichel reductions to compartmental systems. Since interaction in one compartment is independent of all other compartments, it is easy to give sufficient conditions with respect to the fast interaction term to ensure the existence of a reduction of the whole system (a slow transport provided): If we know the projection operator Q_α of the fast interaction $\mathcal{R}_{\alpha;fast}$ for all $\alpha \in \Sigma$, then we can give a reduction of (3.4). To simplify notation in the proof, we use $\mathrm{diag}(M_1, \ldots, M_k)$ for nonquadratic rectangular matrices $M_1, \ldots, M_k$ in the obvious way.

Theorem 3.3. *Consider a compartmental system* (3.4)*. Assume that in every compartment one part of the interaction $\mathcal{R}_{\alpha;fast}$ is fast with respect to all other parts of interaction $\mathcal{R}_{\alpha;slow}$ and the transport $(\mathcal{F}_\alpha)_{\alpha\in\Sigma}$, i.e.*

$$\frac{d}{dt}a^*_\alpha = \mathcal{R}_{\alpha;fast}(a^*_\alpha) + \varepsilon\big(\mathcal{R}_{\alpha;slow}(a^*_\alpha) + \mathcal{F}_\alpha(a^*)\big), \quad \alpha \in \Sigma. \tag{3.5}$$

Let $\bar{a}^* = (\bar{a}^*_\alpha)_{\alpha\in\Sigma}$ be a point in the zero set $\mathcal{V}(h^{(0)})$ of

$$h^{(0)}(a^*) := \left(\mathcal{R}_{\alpha;fast}(a^*_\alpha)\right)_{\alpha\in\Sigma}$$

such that for all $\alpha \in \Sigma$ a kernel-image decomposition of $\mathbb{R}^m$ (as in Theorem 2.1) exists in a neighborhood U_α of $\bar{a}^*_\alpha$. Then, for all $\alpha \in \Sigma$, there exists a submanifold $\mathcal{U}_\alpha \subset U_\alpha$ containing $\bar{a}^*_\alpha$ with properties as in Theorem 2.1. Let Q_α denote the projection operator of $\mathcal{R}_{\alpha;fast}$ at $\bar{a}^*_\alpha$ and let $\mathcal{R}_{\alpha;fast} = P_\alpha\mu_\alpha$ be the product decomposition in the sense of Theorem 2.1. Then:
There exists a formal Tikhonov-Fenichel reduction (in the sense of Remark 2) of system (3.5) *to*

$$\frac{d}{d\tau}a^*_\alpha = Q_\alpha(a^*_\alpha)\cdot\Big(\mathcal{R}_{\alpha;slow}(a^*_\alpha) + \mathcal{F}_\alpha(a^*)\Big), \quad \alpha \in \Sigma, \tag{3.6}$$

defined in $\widetilde{U} = U_1 \times \ldots \times U_N$. $\widetilde{\mathcal{U}} := \mathcal{U}_1 \times \cdots \times \mathcal{U}_N$ is an invariant set of (3.6)*. Moreover, if all Q_α induce convergent reductions, the reduction of* (3.5) *to* (3.6) *is also convergent, i.e. there exists $T > 0$ and a neighborhood $\widetilde{U}^* \subset \widetilde{U}$ of $\widetilde{\mathcal{U}}$, such that solutions of* (2.1) *starting in $\widetilde{U}^*$ converge uniformly on $[t_0, T]$ to solutions of the reduced system* (2.3) *on $\widetilde{\mathcal{U}}$ for $\varepsilon \to 0$ and any $t_0 > 0$.*

Proof. The conditions of Theorem 2.1 are satisfied. Thus, the projection operator $\widetilde{Q}$ of $h^{(0)}$ at $\bar{a}^*$ exists and is defined in $\widetilde{U}$. Defining

$$\widetilde{P}(a^*) := \mathrm{diag}\left(P_1(a^*_1), \ldots, P_N(a^*_N)\right)$$
$$\widetilde{\mu}(a^*) := \big(\mu_1(a^*_1), \ldots, \mu_N(a^*_N)\big)^{\mathrm{tr}},$$

we have $h^{(0)} = \widetilde{P}\widetilde{\mu}$ in $\widetilde{U}$. Hence, we have $\widetilde{Q} = \operatorname{diag}(Q_1, \ldots, Q_N)$ and every component of $\widetilde{\mu}$ is a first integral of (3.6). In particular, since $\mathcal{V}(\widetilde{\mu}) \cap \widetilde{U} = \widetilde{\mathcal{U}}$, $\widetilde{\mathcal{U}}$ is invariant. Moreover, since

$$Dh^{(0)}(a^*) = \operatorname{diag}\Big(D\mathcal{R}_{\alpha;fast}(a_1^*), \ldots, D\mathcal{R}_{\alpha;fast}(a_N^*)\Big),$$

the nonzero eigenvalues of $Dh^{(0)}(\bar{a}^*)$ have negative real part if and only if the same holds true for $D\mathcal{R}_{\alpha;fast}(\bar{a}_\alpha^*)$ and all $\alpha \in \Sigma$. □

Remark 4. (a) The theorem includes the case $\mathcal{R}_{\alpha;slow} \equiv 0$.

(b) The construction of the projection operator $\widetilde{Q}$ involves only $\mathcal{R}_{\alpha;fast}$. Thus, the theorem can be used in more general settings. To be more precise: The proof above works, if $Dh^{(0)}(\bar{a}^*)$ is a block diagonal matrix and if every block induces a direct sum decomposition of $\mathbb{R}^m$.

(c) If the reduction is convergent, then the positive invariance of the positive orthant $\overline{\mathbb{R}}_+^M$ under (3.5) implies that the positive orthant is still positively invariant under (3.6).

Example 3.4. *We continue the discussion of the SIR model. Assume that the interaction is fast with respect to the transport. Thus, consider the system*

$$\dot{x}_\alpha = -k_{1;\alpha} x_\alpha y_\alpha + \varepsilon \mathcal{F}_{x;\alpha}(\tilde{x}), \quad \alpha \in \Sigma \tag{3.7}$$

$$\dot{y}_\alpha = k_{1;\alpha} x_\alpha y_\alpha - k_{2;\alpha} y_\alpha + \varepsilon \mathcal{F}_{y;\alpha}(\tilde{y}), \quad \alpha \in \Sigma \tag{3.8}$$

$$\dot{z}_\alpha = k_{2;\alpha} y_\alpha + \varepsilon \mathcal{F}_{z;\alpha}(\tilde{z}), \quad \alpha \in \Sigma \tag{3.9}$$

on the positive orthant $\overline{\mathbb{R}}_+^{3n}$. Choosing $\mu_\alpha(x_\alpha, y_\alpha, z_\alpha) = y_\alpha$ and

$$P_\alpha(x_\alpha, y_\alpha, z_\alpha) = (-k_{1;\alpha} x_\alpha, k_{1;\alpha} x_\alpha - k_{2;\alpha}, k_{2;\alpha})^{\mathrm{tr}},$$

we get $D\mu_\alpha P_\alpha(x_\alpha, y_\alpha, z_\alpha) = k_{1;\alpha} x_\alpha - k_{2;\alpha}$. Thus, the convergence conditions are satisfied for $x_\alpha < \frac{k_{2;\alpha}}{k_{1;\alpha}}$. One verifies

$$Q_\alpha(x_\alpha, y_\alpha, z_\alpha) = \begin{pmatrix} 1 & \frac{k_{1;\alpha} x_\alpha}{k_{1;\alpha} x_\alpha - k_{2;\alpha}} & 0 \\ 0 & 0 & 0 \\ 0 & \frac{-k_{2;\alpha}}{k_{1;\alpha} x_\alpha - k_{2;\alpha}} & 1 \end{pmatrix}.$$

Hence, there exists a Tikhonov-Fenichel reduction of (3.7)–(3.9) to

$$x_\alpha = \mathcal{F}_{x;\alpha}(\tilde{x}), \quad \alpha \in \Sigma \tag{3.10}$$

$$y_\alpha = 0, \quad \alpha \in \Sigma \tag{3.11}$$

$$z_\alpha = \mathcal{F}_{z;\alpha}(\tilde{z}), \quad \alpha \in \Sigma \tag{3.12}$$

given on the slow manifold $\mathcal{U} = \{(\tilde{x}, 0, \tilde{z}) \in \overline{\mathbb{R}}^{3n}_+,\ x_\alpha < \frac{k_{2;\alpha}}{k_{1;\alpha}},\ \alpha \in \Sigma\}$ *(again denoting* $\tilde{x} := (x_1, \ldots, x_n)^{\mathrm{tr}}$ *and* $\tilde{y}$, $\tilde{z}$ *analogously). We can write* (3.10)–(3.12) *as*

$$\frac{d}{d\tau}\tilde{x} = C^{[x]}\tilde{x} \tag{3.13}$$

$$\frac{d}{d\tau}\tilde{y} = 0 \tag{3.14}$$

$$\frac{d}{d\tau}\tilde{z} = C^{[z]}\tilde{z}. \tag{3.15}$$

A solution $(X(t), Y(t), Z(t))$ *of* (3.13)–(3.15) *starting at any point of the slow manifold* $\mathcal{U}$ *converges to a stationary point* $(P_x, 0, P_z)$*, where* $P_x \in \overline{\mathbb{R}}^n_+ \cap \ker C^x$ *and* $P_z \in \overline{\mathbb{R}}^n_+ \cap \ker C^z$*. Moreover, since* $\psi_1(\tilde{x}, \tilde{y}, \tilde{z}) = \sum_{\alpha\in\Sigma} x_\alpha$ *and* $\psi_2(\tilde{x}, \tilde{y}, \tilde{z}) = \sum_{\alpha\in\Sigma} z_\alpha$ *are first integrals of the reduced system, we have*

$$\sum_{\alpha\in\Sigma} P_{x;\alpha} = \sum_{\alpha\in\Sigma} X_\alpha(0), \quad \sum_{\alpha\in\Sigma} P_{z;\alpha} = \sum_{\alpha\in\Sigma} Z_\alpha(0),$$

where $P_{j;\alpha}$ *is the* α*-component of* P_j*,* $j = x, z$*.*
To project the initial values on the slow manifold, note that we have $2n$ *independent first integrals for the fast system*

$$\begin{aligned}
\dot{x}_\alpha &= -k_{1;\alpha} x_\alpha y_\alpha, \quad \alpha \in \Sigma \\
\dot{y}_\alpha &= k_{1;\alpha} x_\alpha y_\alpha - k_{2;\alpha} y_\alpha, \quad \alpha \in \Sigma \\
\dot{z}_\alpha &= k_{2;\alpha} y_\alpha, \quad \alpha \in \Sigma
\end{aligned}$$

near $\mathcal{U}$*:*

$$\begin{aligned}
\varphi_{1,\alpha}(\tilde{x}, \tilde{y}, \tilde{z}) &= x_\alpha + y_\alpha + z_\alpha, && \alpha \in \Sigma \\
\varphi_{2,\alpha}(\tilde{x}, \tilde{y}, \tilde{z}) &= x_\alpha + y_\alpha - \frac{k_{2;\alpha}}{k_{1;\alpha}} \ln x_\alpha, && \alpha \in \Sigma.
\end{aligned}$$

Therefore, positive initial values $(x_{\alpha,0}, y_{\alpha,0}, z_{\alpha,0})$*,* $\alpha \in \Sigma$ *of* (3.7)–(3.9) *will be projected to* $(X_{\alpha,0}, 0, x_{\alpha,0} + y_{\alpha,0} + z_{\alpha,0} - X_{\alpha,0})$*,* $\alpha \in \Sigma$*, where* $X_{\alpha,0}$ *is the solution of*

$$X_{\alpha,0} - \frac{k_{2;\alpha}}{k_{1;\alpha}} \ln X_{\alpha,0} = x_{\alpha,0} + y_{\alpha,0} - \frac{k_{2;\alpha}}{k_{1;\alpha}} \ln x_{\alpha,0}$$

with $X_{\alpha,0} < \frac{k_{2;\alpha}}{k_{1;\alpha}}$*. Moreover, the solutions of the fast system converge to the corresponding intersection points (see [29] Proposition 2 or verify directly*

by using phase plane arguments). For a solution of system (3.13)–(3.15) *for small* $\varepsilon > 0$ *and initial data near* $\mathcal{U}$ *this means that after a short initial phase the solution will be near the corresponding solution of* (3.13)–(3.15) *for some time (Tikhonov only guarantees convergency on a compact interval). But, for system* (3.13)–(3.15) *transport may cause components* x_α *or* z_α *of a solution to move to a region containing stationary points with a nontrivial unstable manifold (thus* $x_\alpha > \frac{k_{2;\alpha}}{k_{1;\alpha}}$*). Therefore, the behaviour of solutions of* (3.7)–(3.9) *for small* $\varepsilon > 0$ *may be more complicated than convergence to an equilibrium. We will not discuss this in detail here.*

4 Reaction-diffusion systems

Consider a reaction between m chemical species $A_1, \dots, A_m$ in an open and bounded reactor $\Omega \subset \mathbb{R}^3$ with spatial inhomogeneity (i.e. Ω is not well-mixed) and no in- and outflow. If we assume that the reaction is modeled by mass action kinetics and that the diffusion is modeled by Fick's law, this leads to the *reaction-diffusion system*

$$\partial_t a = D\Delta a + \mathcal{R}(a), \qquad \text{in } (0,\infty)\times\Omega, \tag{4.1}$$

$$\frac{\partial a_i}{\partial \nu} = 0, \qquad \text{in } (0,\infty)\times\partial\Omega,\ 1 \le i \le m, \tag{4.2}$$

$$a(0,x) = a_0(x), \qquad \text{in } \Omega, \tag{4.3}$$

where $a_i = a_i(t,x)$ denotes the concentration of A_i, $a_0 \colon \overline{\Omega} \to \mathbb{R}^m$ is a function and $\frac{\partial \cdot}{\partial \nu}$ denotes the normal derivative. Mass action kinetics imply that the reaction part $\mathcal{R} \colon \mathbb{R}^m \to \mathbb{R}^m$ is polynomial and essentially nonnegative [20]. Moreover, $D := \operatorname{diag}(\delta_1, \dots, \delta_m)$ is the diffusion matrix with diffusion constants $\delta_i > 0$, $1 \le i \le m$. Note that – assuming $a_0 \in C^{1+\gamma}(\overline{\Omega}; \overline{\mathbb{R}}^m_+)$ for a $\gamma > 0$ and $\frac{\partial a_{i,0}}{\partial \nu} = 0$ on $\partial\Omega$ – Lunardi [40] Proposition 7.3.2 gives the existence of a local classical solution a, i.e.

$$a \in C^{1,2}((0,T)\times\Omega; \mathbb{R}^m) \cap C^{0,1}([0,T]\times\overline{\Omega}; \mathbb{R}^m)$$

for a $T > 0$, Moreover, Bothe und Pierre [13] Lemma 7 guarantees that the solution stays nonnegative for all $0 < t < T$. For general properties of reaction-diffusion systems, we refer to Smoller [49], Britton [17] and Pierre [46].

We want to reduce system (4.1)–(4.3) under the assumption that certain reactions are fast with respect to the diffusion and the other reactions, i.e. 4.1 reads

$$\partial_t a = \mathcal{R}_{fast}(a) + \varepsilon\big(D\Delta a + \mathcal{R}_{slow}(a)\big). \tag{4.4}$$

In the ODE case Tikhonov's theorem reduces the reduction problem to one of explicit computation, which we discussed above. In the PDE case the problem is twofold: finding and computing an explicit reduction and showing convergence. With our approach we are able to determine a candidate for a reduced PDE and we can make an argument that this candidate is the only one possible. Convergence problems are much harder in the PDE case. There is no counterpart to Tikhonov's theorem in infinite dimensions. Many results concerning reductions exist (see e.g. Bates et al. [5], Bothe et al. [9–15], Evans [21], Aulbach and Wanner [2–4]) and it is noticable that the proofs are quite hard or require very strict assumptions. We will not discuss convergence problems here (apart from giving references for some of the examples in the last section). The advantages of our ansatz are that only mild assumptions on the fast part are required, that it is frequently easy to compute the reduction in the context of chemical reactions and that it is based on the theorem of Tikhonov for the discretization of the PDE.
The heuristical method will consist of the following steps (see Figure 1):

1. Discretize the reaction-diffusion system (4.1) spatially. This leads to a compartmental system.
2. Reduce the compartmental system with the help of Section 3.
3. Interpret the reduced ODE system as the discretization of a PDE system.
4. The PDE system obtained in this way is the candidate for a limit system of (4.1).

We will give conditions that guarantee the existence of such a candidate. While proving convergence for solutions of (4.1) to solutions of the candidate of a reduction in general seems to be a problem, we will give a consistency result.

Remark 5. The diagram may remind the reader of asymptotic preserving schemes (see e.g. Jin [35]). There is indeed a close relation to the heuristics presented here, but it should be emphasized that the main purpose of our approach is the determination of a (possible) reduced system in the asymptotic limit.

4.1 Discretized reaction-diffusion systems

For the purpose of developing a heuristic, we assume Ω to be of the form

$$\Omega = (0, L_1) \times (0, L_2) \times (0, L_3).$$

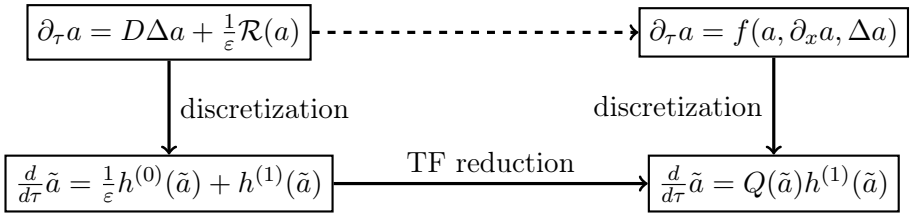


Figure 1: Schematical presentation of the heuristic

Let $L_i = n_i\rho$, where ρ is the mesh size, and $N := n_1 \cdot n_2 \cdot n_3$. We subdivide Ω in compartments of the form

$$\Omega_\alpha = ((\alpha_1 - 1)\rho, \alpha_1\rho) \times ((\alpha_2 - 1)\rho, \alpha_2\rho) \times ((\alpha_3 - 1)\rho, \alpha_3\rho)\,,$$

where $\alpha = (\alpha_1, \alpha_2, \alpha_3)$ is a multiindex:

$$\alpha \in \Sigma := \{1, \dots, n_1\} \times \{1, \dots, n_2\} \times \{1, \dots, n_3\} \subset \mathbb{N}^3.$$

Moreover, we identify α with the compartment Ω_α and define $a_{i,\alpha}$ as the concentration of species A_i in compartment α.
Again, define a^*_α, a^* and $\tilde{a}_i$ as in (3.1)-(3.3). In addition, let

$$\tilde{a} := \big(\tilde{a}_i\big)_{1\le i\le m} \in \mathbb{R}^M,$$

where (again) $M = N \cdot m$.
We choose a central difference discretization, i.e.

$$\begin{aligned}\mathcal{D}_\alpha(\tilde{a}_i) = &\frac{a_{i;\alpha_1-1,\alpha_2,\alpha_3} - 2a_{i;\alpha_1,\alpha_2,\alpha_3} + a_{i;\alpha_1+1,\alpha_2,\alpha_3}}{\rho^2}\\ &+ \frac{a_{i;\alpha_1,\alpha_2-1,\alpha_3} - 2a_{i;\alpha_1,\alpha_2,\alpha_3} + a_{i;\alpha_1,\alpha_2+1,\alpha_3}}{\rho^2}\\ &+ \frac{a_{i;\alpha_1,\alpha_2,\alpha_3-1} - 2a_{i;\alpha_1,\alpha_2,\alpha_3} + a_{i;\alpha_1,\alpha_2,\alpha_3+1}}{\rho^2}.\end{aligned}$$

To incorporate the Neumann conditions, we set

$$a_{0,n_2,n_3} = a_{1,n_2,n_3}, \quad a_{n_1+1,n_2,n_3} = a_{n_1,n_2,n_3}, \quad \text{etc.}$$

Lastly, let x_α denote the center of compartment α.
Now, the discretization of (4.1)–(4.3) reads

$$\begin{aligned}&\dot{a}_{i;\alpha} = \delta_i\mathcal{D}_\alpha(\tilde{a}_i) + \mathcal{R}_i(a^*_\alpha), \quad \alpha \in \Sigma \text{ and } 1 \le i \le m,\\ &a_{i;\alpha}(0) = a_i(0, x_\alpha), \quad \alpha \in \Sigma \text{ and } 1 \le i \le m\end{aligned}$$

or equivalently

$$\frac{d}{dt}a^*_\alpha = D\mathcal{D}_\alpha(\tilde{a}) + \mathcal{R}(a^*_\alpha), \quad \alpha \in \Sigma, \tag{4.5}$$

$$a^*_\alpha(0) = a(0, x_\alpha), \quad \alpha \in \Sigma, \tag{4.6}$$

with

$$\mathcal{D}_\alpha(\tilde{a}) := \big(D_\alpha(\tilde{a}_i)\big)_{1\le i\le m}.$$

Note that we write $\mathcal{D}_\alpha(\tilde{a})$ instead of $\mathcal{D}_\alpha(a^*)$ to emphasize that every $\mathcal{D}_\alpha(\tilde{a}_i)$ only depends on the concentrations of species A_i. In general one would need weight factors to account for different compartmental sizes (see [57] for an example of this), but in our case all compartments have the same size. Therefore, (4.5) is a compartmental system in the sense of Definition 3.1. Thus, we get the following consequence of Theorem 3.3:

Corollary 4.1. *(a) Consider the slowly diffusing reaction-diffusion system* (4.4) *with respect to conditions* (4.2)–(4.3) *and let*

$$\frac{d}{dt}a^*_\alpha = \mathcal{R}_{fast}(a^*_\alpha) + \varepsilon\big(\mathcal{R}_{slow}(a^*_\alpha) + D\mathcal{D}_\alpha(\tilde{a})\big), \quad \alpha \in \Sigma, \tag{4.7}$$

$$a^*_\alpha(0) = a(0, x_\alpha), \quad \alpha \in \Sigma \tag{4.8}$$

be its discretization, such that the conditions of Theorem 3.3 are satisfied for a point $\bar{a}^* = (\bar{a}^*_1, \dots, \bar{a}^*_N)$. *Then there exists a Tikhonov-Fenichel reduction of* (4.7) *to*

$$\frac{d}{d\tau}a^*_\alpha = Q_\alpha(a^*_\alpha) \cdot \Big(\mathcal{R}_{slow}(a^*_\alpha) + D\mathcal{D}_\alpha(\tilde{a})\Big), \quad \alpha \in \Sigma. \tag{4.9}$$

(b) Let $\bar{a} := \bar{a}^*_1 = \ldots = \bar{a}^*_N$ *and let* Q *denote the projection operator of* $\mathcal{R}_{fast}$ *at* $\bar{a}$. *This means that for every compartment the same component of the zero set of* $\mathcal{R}$ *is under consideration. Then* (4.9) *can be written as*

$$\frac{d}{d\tau}a^*_\alpha = Q(a^*_\alpha) \cdot \Big(\mathcal{R}_{slow}(a^*_\alpha) + D\mathcal{D}_\alpha(\tilde{a})\Big), \quad \alpha \in \Sigma. \tag{4.10}$$

Remark 6. The projected initial value in compartment α is again the intersection of the corresponding level sets of the first integrals of $\dot{a} = \mathcal{R}_{fast}(a)$ near a^*_α and $\mathcal{V}(\mathcal{R}_{fast})$ (see Remark 2 (e)).

We want to stress that Q_α may vary in different components of the zero set $\mathcal{V}(\mathcal{R}_{fast})$. (Recall that an algebraic variety is the union of finitely many irreducible components with respect to the Zariski topology; see [48].) Hence, in Corollary 4.1 (a) it may a-priori be difficult to get an interpretation of (4.9) as a discretization of a PDE. But, assuming smooth initial data a_0, it is reasonable to assume that the discretized initial data lies near the same component of $\mathcal{V}(\mathcal{R}_{fast})$ in every compartment, which corresponds to Corollary 4.1 (b). In this case, an interpretation is easily done. Moreover, one has no problems interpreting whenever there is only one irreducible component. We will make this clearer in the next section.

Remark 7. In [28] Proposition 3, it has been noted that the projection operator Q of $\mathcal{R}_{fast}$ exists at every positive stationary point of a reaction equation in the sense of Feinberg [23], if the following holds for the reaction system $\dot{a} = \mathcal{R}_{fast}(a)$:

(i) In every positive stoichiometric compatibility class exists exactly one stationary point.

(ii) Every stationary point is linearly asymptotically stable (with respect to the positive stoichiometric compatibility class).

In particular, due to the deficiency zero theorem by Feinberg [22, 23], if $\dot{a} = \mathcal{R}_{fast}(a)$ is weakly reversible and has deficiency zero, (i) is satisfied and every stationary point is asymptotically stable. One class of reaction networks which satisfies (i)-(ii) was discussed by Bothe [11].

Remark 8. (a) Suppose that the diffusion is fast with respect to the reaction, i.e.

$$\partial_t a = D\Delta a + \varepsilon \mathcal{R}(a).$$

Then there also exists a Tikhonov-Fenichel reduction of (4.5)–(4.6) and we get

$$\frac{d}{d\tau} a^*_\alpha = \mathcal{R}(a^*_\alpha),$$

on the slow manifold $\{a^* \in \mathbb{R}^M,\ a^*_\alpha = a^*_\beta \text{ for all } \alpha, \beta \in \Sigma\}$. The proof is analogous to the proof of Theorem 3.3: Choosing a different sorting of the equation – not by compartment but by species – $Dh^{(0)}$ is again a block diagonal matrix, where every block is a W-matrix, and thus satisfies the necessary existence and convergence conditions. The result is exactly as might be expected: The fast diffusion yields a homogenization of the concentrations, so that we have asymptotically

a reaction system in a well-mixed reactor.
In the same way, we can discuss the situation that the diffusion of some species is fast with respect to the reaction and that the diffusion of the other species is as slow as the reaction, e.g. we consider the system

$$\partial_t a_i = \delta_i \Delta a_i + \varepsilon \mathcal{R}_i(a), \quad 1 \le i \le p, \tag{4.11}$$

$$\partial_t a_i = \varepsilon \left(\delta_i \Delta a_i + \mathcal{R}_i(a) \right), \quad p+1 \le i \le m \tag{4.12}$$

(with respect to Neumann conditions and some initial conditions). Again, a (convergent) Tikhonov-Fenichel reduction of the discretization of (4.11)–(4.12) exists and the reduced system is given by

$$\frac{d}{d\tau} a_{i;1} = \frac{1}{N} \sum_{\alpha \in \Sigma} \mathcal{R}_i(a^*_\alpha), \quad 1 \le i \le p \tag{4.13}$$

$$\frac{d}{d\tau} a_{i;\alpha} = \delta_i \mathcal{D}_\alpha(\tilde{a}_i) + \mathcal{R}_i(a^*_\alpha), \quad p+1 \le i \le m,\ \alpha \in \Sigma \tag{4.14}$$

on the slow manifold $\mathcal{U} = \{a^* \in \mathbb{R}^m,\ a_{i;\alpha} = a_{i;1}, \quad 1 \le i \le p,\ \alpha \in \Sigma\}$. Thus, interpreting the right hand side of (4.13) as a discretization of

$$\frac{1}{|\Omega|} \int_\Omega \mathcal{R}_i(a)\, dx,$$

we gain the candidate

$$\frac{d}{d\tau} a_i(\tau) = \frac{1}{|\Omega|} \int_\Omega \mathcal{R}_i(a(\tau, x))\, dx, \quad 1 \le i \le p$$
$$\partial_\tau a_i(\tau, x) = \delta_i \Delta a_i(\tau, x) + \mathcal{R}_i(a(\tau, x)), \quad p+1 \le i \le m,$$

for a reduction of (4.11)–(4.12). Without further investigation it is unclear, whether the candidate is appropriate. This should be done in forthcoming work. (For details of computation and examples see [27, 38].)

(b) The heuristic depends on $D\mathcal{R}$ being in block diagonal form. Hence, in the case of fast reactions and some fast diffusing species, the heuristic does not work.

4.2 Reduction of continuous reaction-diffusion systems

The preceding subsection showed that the first two steps of the heuristic (indicated by the arrows marked by "discretization" and "TF reduction" in

Figure 1) work if the fast reaction is "well-behaved". Now, assuming smooth initial data a_0 near a simple point $\bar{a}$, we can use Corollary 4.1 (b) to find a candidate for the reduction of (4.4):

$$\partial_\tau a = Q(a) \cdot \big(\mathcal{R}_{slow}(a) + D\Delta a\big).$$

As in Theorem 2.1, the system is defined in a neighborhood of $\bar{a}$ and admits a particular invariant set.

Proposition 4.2. *Consider again* (4.4) *with respect to conditions* (4.2)–(4.3). *Assume that a_0 is smooth and close to a simple point $\bar{a}$ in an irreducible component V_1 of the zero set $\mathcal{V}(\mathcal{R}_{fast})$, such that the projection operator $Q = Id - P(D\mu P)^{-1}D\mu$ of $\mathcal{R}_{fast}$ exists at $\bar{a}$. Then*

$$\partial_\tau a = Q(a) \cdot \big(\mathcal{R}_{slow}(a) + D\Delta a\big), \quad \text{in } (0,\infty)\times\Omega, \tag{4.15}$$

$$\frac{\partial a_i}{\partial \nu} = 0, \quad \text{in } (0,\infty)\times\partial\Omega,\ 1 \le i \le m, \tag{4.16}$$

is well-defined in a neighborhood U of $\bar{a}$. Moreover, every component of μ defines a conservation law.

Proof. The well-definedness of (4.15)–(4.16) in U is a consequence of Theorem 2.1. The invariance is shown in the following way: One verifies

$$D\mu(a)Q(a) = 0$$

for all $a \in U$. Thus, we have for $x_0 \in \Omega$ with $a(0,x_0) \in U$

$$\begin{aligned}\frac{d}{d\tau}\mu(a(\tau,x_0)) &= D\mu(a(\tau,x_0)) \cdot \partial_\tau a(\tau,x_0)\\ &= D\mu(a(\tau,x_0)) \cdot Q(a(\tau,x_0)) \cdot (\mathcal{R}_{slow}(a(\tau,x_0)) + D\Delta a(\tau,x_0))\\ &= 0\end{aligned}$$

as long as a classical solution $a(\tau,x_0)$ exists. Hence, every component of μ defines a conservation law of (4.15). □

Remark 9. (a) $\mathcal{U} = U \cap \mathcal{V}(\mu)$ is a (positively time-) invariant set of (4.15)–(4.16) in the sense of Smoller [49], i.e. every local classical solution

$$a \in C^{1,2}((0,T)\times\Omega;\mathbb{R}^m) \cap C^{0,1}([0,T]\times\overline{\Omega};\mathbb{R}^m)$$

of (4.15)–(4.16) with respect to initial values in $\mathcal{U}$ (i.e. $a(0,x) \in \mathcal{U}$ for all $x \in \Omega$) satisfies $a(t,x) \in \mathcal{U}$ for all $t \in [0,T)$ and $x \in \Omega$.

(b) If convergence holds, then the positive orthant $\overline{\mathbb{R}}_+^m$ is still positively invariant under (4.15)–(4.16) as it is positively invariant under (4.4) with respect to conditions (4.2)–(4.3).

(c) In the spirit of the heuristic, one may proceed to determine initial conditions in the slow manifold $\mathcal{V}(\mathcal{R}_{fast})$ by taking the corresponding intersection point of the level sets of the first integrals of $\dot{a} = \mathcal{R}_{fast}(a)$ (considered as an ODE with parameter x) near a_α^* and $\mathcal{V}(\mathcal{R}_{fast})$.

As we have stated earlier, we are not able to provide a general convergence result. But we can show a consistency result: If the solution of the reaction-diffusion system (4.4) with respect to conditions (4.2)–(4.3) converges to the solution of the limit system (4.15)–(4.16) (with projected initial values), then its corresponding solution of the discretized reaction-diffusion system (4.7)–(4.8) converges to the corresponding solution of the discretized limit system (4.10) (again with projected initial values) in the following sense:
Let $\varepsilon_0 > 0$. Consider the PDEs

$$\partial_\tau a = f_1(a) \cdot D\Delta a + \varepsilon^{-1} f_2(a), \quad \text{in } (0,T) \times \Omega \tag{4.17}$$

and

$$\partial_\tau b = g_1(b) \cdot D\Delta b + g_2(b), \quad \text{in } (0,T) \times \Omega \tag{4.18}$$

for $0 < \varepsilon < \varepsilon_0$ and with f_i, g_i smooth. Let $T > 0$ and $K \subset \Omega$ be compact. Let $a(\cdot,\cdot,\varepsilon) \in C^{1,2}([0,T] \times K; \mathbb{R}^m)$ be a solution of (4.17) and $b \in C^{1,2}([0,T] \times K; \mathbb{R}^m)$ a solution of (4.18), both with respect to Neumann boundary conditions and smooth initial conditions, such that

$$\|a(\cdot,\cdot,\varepsilon) - b\|_{C^{1,2}([0,T]\times K;\mathbb{R}^m)} \to 0, \quad \varepsilon \to 0. \tag{4.19}$$

Now let

$$\frac{d}{d\tau} a_\alpha^* = f_{1,\rho}(a_\alpha^*) \cdot D\mathcal{D}_\alpha(\tilde{a}) + \varepsilon^{-1} f_{2,\rho}(a_\alpha^*) \tag{4.20}$$

and

$$\frac{d}{d\tau} b_\alpha^* = g_{1,\rho}(b_\alpha^*) \cdot D\mathcal{D}_\alpha(\tilde{b}) + g_{2,\rho}(b_\alpha^*) \tag{4.21}$$

be spatial discretizations with mesh size ρ (in the sense of Section 4.1) of (4.17) and (4.18) respectively, such that the solution

$$a^*(\cdot,\varepsilon,\rho) = (a_\alpha^*(\cdot,\varepsilon,\rho))_{\alpha\in\Sigma} \in C^1([0,T];\mathbb{R}^M)$$

of (4.20) and the solution $b^*(\cdot,\rho) \in C^1([0,T];\mathbb{R}^M)$ of (4.21) (with respect to the discretized initial conditions of (4.17) and (4.18)) satisfy

$$\|a(\cdot,x_\alpha,\varepsilon) - a^*_\alpha(\cdot,\varepsilon,\rho)\|_{C^1([0,T];\mathbb{R}^m)} \to 0, \quad \rho \to 0 \tag{4.22}$$

$$\|b(\cdot,x_\alpha) - b^*_\alpha(\cdot,\rho)\|_{C^1([0,T];\mathbb{R}^m)} \to 0, \quad \rho \to 0 \tag{4.23}$$

for all $\alpha \in \Sigma$, $\varepsilon \in (0,E)$ and some $E > 0$. Then we have:

Proposition 4.3. *For all $\varepsilon' > 0$ exist $\bar{\varepsilon} > 0$ and $\bar{\rho} > 0$ such that*

$$\|a^*(\cdot,\varepsilon,\rho) - b^*(\cdot,\rho)\|_{C^1([0,T];\mathbb{R}^m)} < \varepsilon'$$

for all $\varepsilon < \bar{\varepsilon}$ and $\rho < \bar{\rho}$.

Proof. Let $\varepsilon' > 0$. (4.19) implies that for all $\varepsilon'' > 0$ exists $\varepsilon_0 > 0$ such that

$$\|a(\cdot,\cdot,\varepsilon) - b\|_{C^{1,2}([0,T]\times K;\mathbb{R}^m)} < \varepsilon''$$

for all $\varepsilon < \varepsilon_0$. (4.22)-(4.23) imply that for all $\varepsilon''' > 0$ exists $\rho_0 > 0$ such that

$$\max_{\alpha\in\Sigma}\{\|a(\cdot,x_\alpha,\varepsilon) - a^*_\alpha(\cdot,\varepsilon,\rho)\|_{C^1([0,T];\mathbb{R}^m)}\} < \varepsilon'''$$

$$\max_{\alpha\in\Sigma}\{\|b(\cdot,x_\alpha) - b^*_\alpha(\cdot,\rho)\|_{C^1([0,T];\mathbb{R}^m)}\} < \varepsilon'''$$

for all $\rho < \rho_0$. Thus,

$$\begin{aligned}\|a^*(\cdot,\varepsilon,\rho) - b^*(\cdot,\rho)\|_{C^1([0,T];\mathbb{R}^m)} \le{}& \max_{\alpha\in\Sigma}\{\|a(\cdot,x_\alpha,\varepsilon) - a^*_\alpha(\cdot,\varepsilon,\rho)\|_{C^1([0,T];\mathbb{R}^m)}\} \\ &+ \|a(\cdot,\cdot,\varepsilon) - b\|_{C^{1,2}([0,T]\times K;\mathbb{R}^m)} \\ &+ \max_{\alpha\in\Sigma}\{\|b(\cdot,x_\alpha) - b^*_\alpha(\cdot,\rho)\|_{C^1([0,T];\mathbb{R}^m)}\}\end{aligned}$$

proves the result. □

We still have a problem with the interpretation of (4.9) when Q_α varies in different compartments. As we will see in the final example below, even if the initial data lies near different irreducible components of $\mathcal{V}$ for different $x \in \Omega$, one still may have a meaningful interpretation of (4.9).

5 Examples

5.1 Fast reactions of first order

Consider a reaction-diffusion system, where the reaction is of first order [32], i.e.

$$A_i \underset{k_{ij}}{\overset{k_{ji}}{\rightleftharpoons}} A_j \quad 1 \le i,j \le m,\ i \ne j.$$

Hence, we have a system of the form

$$\dot{a} = \varepsilon D \Delta a + K a. \tag{5.1}$$

Here, $K = (k_{ij})_{1 \le i,j \le m} \in \mathbb{R}^{m \times m}$ is the rate matrix, consisting of the rate constants with $k_{ij} \ge 0$ for $i \neq j$ and diagonal terms $k_{ii} := -\sum_{l \neq i} k_{li}$. Thus, K is a W-matrix and for every first order reaction there exists a convergent Tikhonov-Fenichel reduction. In the following, we make an additional assumption (motivated by chemistry), namely we require that the reaction satisfies the principle of detailed balance [33, 55], i.e.

$$k_{ij}\bar{a}_j = k_{ji}\bar{a}_i, \quad \text{for all stationary points } \bar{a} \in \mathbb{R}^m_+ \text{ and all } i \neq j.$$

This implies that K is (up to labelling) a block diagonal matrix with irreducible blocks. Moreover, Prater and Wei [56] noted that K is symmetric up to a scaling of variables. Without loss of generality, we assume that K is already irreducible and symmetric. Thus, we have $\ker K = \operatorname{span}\{(1, \dots, 1)^{\mathrm{tr}}\}$. As

$$x = \sum_{i=1}^{m} \frac{x_i}{m} \cdot \begin{pmatrix} 1 \\ \vdots \\ 1 \end{pmatrix} + \begin{pmatrix} x_1 - \sum_{i=1}^m \frac{x_i}{m} \\ \vdots \\ x_m - \sum_{i=1}^m \frac{x_i}{m} \end{pmatrix}$$

is a decomposition of $x \in \mathbb{R}^m$ into kernel and image components with respect to K, the projection operator Q onto the kernel of K is given by

$$Q(x) = \sum_{i=1}^{m} \frac{x_i}{m} \cdot \begin{pmatrix} 1 \\ \vdots \\ 1 \end{pmatrix}.$$

Hence, the Tikhonov-Fenichel reduction of the discretized reaction-diffusion system is given by

$$\frac{d}{d\tau} a^*_\alpha = Q(D\mathcal{D}_\alpha(\tilde{a})) = \sum_{i=1}^{m} \frac{\delta_i \mathcal{D}_\alpha(\tilde{a}_i)}{m} \cdot \begin{pmatrix} 1 \\ \vdots \\ 1 \end{pmatrix}, \quad \alpha \in \Sigma \tag{5.2}$$

on the slow manifold

$$\begin{aligned} \mathcal{U} &= \ker K \times \cdots \times \ker K \\ &= \{\tilde{a} \in \mathbb{R}^{N \cdot m} \colon \text{ for all } \alpha \in \Sigma \text{ holds } a_{i;\alpha} = a_{j;\alpha} \text{ for all } 1 \le i, j \le m\}. \end{aligned}$$

Defining

$$b_\alpha := \sum_{i=1}^{m} a_{i,\alpha} \quad \text{and} \quad \tilde{b} := (b_\alpha)_{\alpha\in\Sigma},$$

we get on $\mathcal{U}$

$$a_{i;\alpha} = \frac{1}{m} b_\alpha \text{ for all } \alpha \in \Sigma \Longrightarrow \tilde{a}_i = \frac{1}{m}\tilde{b}$$

for all $1 \le i \le m$. Thus, from (5.2) follows for all $\alpha \in \Sigma$

$$\frac{d}{d\tau} b_\alpha^* = m \cdot \sum_{i=1}^{m} \frac{\delta_i \mathcal{D}_\alpha(\tilde{a}_i)}{m} \tag{5.3}$$

$$\Longleftrightarrow \frac{d}{d\tau} b_\alpha^* = \left(\sum_{i=1}^{m} \frac{1}{m} \delta_i \right) \mathcal{D}_\alpha(\tilde{b}). \tag{5.4}$$

System (5.4) can be interpreted as the discretization of the one-dimensional diffusion equation

$$\partial_\tau b = \left(\sum_{i=1}^{m} \frac{1}{m} \delta_i \right) \Delta b. \tag{5.5}$$

In fact, a convergence result can be proven. The proof, which is given in [38], is similar to the one given by Bothe and Hilhorst [12] for two chemical species ($m = 2$) and more general kinetics.

Proposition 5.1. *Let $\Omega \subset \mathbb{R}^3$ be an open and bounded set with smooth boundary. Let $a_0 \in C^{1+\gamma}(\overline{\Omega}; \overline{\mathbb{R}}_+^m)$ for a $\gamma > 0$ and $\frac{\partial a_{i,0}}{\partial \nu} = 0$ on $\partial\Omega$ for all $1 \le i \le m$. Moreover, let K be an irreducible and symmetric W-matrix. Then, for every $\varepsilon > 0$ exists a classical solution*

$$a^\varepsilon \in C^{1,2}\big((0,\infty) \times \Omega; \mathbb{R}^m\big) \cap C^{0,1}\big([0,\infty) \times \overline{\Omega}); \mathbb{R}^m\big)$$

of

$$\begin{aligned}
&\partial_\tau a = D\Delta a + \varepsilon^{-1} K a, \quad \text{in } (0,\infty) \times \Omega \\
&\frac{\partial a_i}{\partial \nu} = 0, \quad \text{in } (0,\infty) \times \partial\Omega,\ 1 \le i \le m \\
&a_i(0,x) = a_{i,0}(x), \quad \text{in } \Omega,\ 1 \le i \le m.
\end{aligned}$$

The solution a^ε converges for all $T > 0$ in $L^2\big((0,T) \times \Omega; \mathbb{R}^m\big)$ to

$$a = \frac{1}{m}\big(b, \ldots, b\big)^{\mathrm{tr}}$$

as $\varepsilon \to 0$*, where*

$$b \in C^{1,2}((0,\infty) \times \Omega) \cap C^{0,1}([0,\infty) \times \overline{\Omega})$$

is the classical solution of the diffusion equation (5.5) *with respect to the initial data* $b_0 := \sum_{i=1}^m a_{i,0}$ *and the Neumann condition*

$$\frac{\partial b}{\partial \nu} = 0, \quad \text{in } (0,\infty) \times \partial\Omega.$$

Remark 10. (a) The principle of detailed balance implies that the reaction is (strongly) reversible, i.e. whenever there is a reaction from one complex to the other, then there is also a reaction from the latter to the former.

(b) If we include a slow reaction $\mathcal{R}_{slow}$, the system reads

$$\partial_\tau a = Ka + \varepsilon(\mathcal{R}_{slow}(a) + D\Delta a).$$

With the heuristic, a candidate for the reduction is given by

$$\partial_\tau b = \left(\sum_{i=1}^m \frac{1}{m}\delta_i\right)\Delta b + \sum_{i=1}^m \mathcal{R}_{i,slow}(\frac{b}{m},\dots,\frac{b}{m}).$$

In forthcoming work [38], a convergence result (given some mild technical assumptions) for this case will be shown.

5.2 A fast reversible reaction

Consider a reaction-diffusion system, where the reaction is given by

$$S + P \underset{k_-}{\overset{k_+}{\rightleftharpoons}} C,$$

i.e. a substrate S and a buffer P react to a complex C, which decays back to S and P. Assuming fast reactions, (4.4) reads

$$\partial_t s = \varepsilon\delta_s\Delta s - (k_+ sp - k_- c) \tag{5.6}$$

$$\partial_t p = \varepsilon\delta_p\Delta p - (k_+ sp - k_- c) \tag{5.7}$$

$$\partial_t c = \varepsilon\delta_c\Delta c + (k_+ sp - k_- c). \tag{5.8}$$

The (convergent) Tikhonov-Fenichel reduction of the discretized system reads

$$\begin{aligned}
\frac{d}{d\tau}s_\alpha &= \delta_s\mathcal{D}_\alpha(\tilde{s}) + \frac{K\delta_c\mathcal{D}_\alpha(\tilde{c}) - p_\alpha\delta_s\mathcal{D}_\alpha(\tilde{s}) - s_\alpha\delta_p\mathcal{D}_\alpha(\tilde{p})}{s_\alpha + p_\alpha + K}\\
\frac{d}{d\tau}p_\alpha &= \delta_p\mathcal{D}_\alpha(\tilde{p}) + \frac{K\delta_c\mathcal{D}_\alpha(\tilde{c}) - p_\alpha\delta_s\mathcal{D}_\alpha(\tilde{s}) - s_\alpha\delta_p\mathcal{D}_\alpha(\tilde{p})}{s_\alpha + p_\alpha + K}\\
\frac{d}{d\tau}c_\alpha &= \delta_c\mathcal{D}_\alpha(\tilde{c}) - \frac{K\delta_c\mathcal{D}_\alpha(\tilde{c}) - p_\alpha\delta_s\mathcal{D}_\alpha(\tilde{s}) - s_\alpha\delta_p\mathcal{D}_\alpha(\tilde{p})}{s_\alpha + p_\alpha + K},
\end{aligned}$$

with $K := \frac{k_-}{k_+}$ (see [27] for details of the computation).
This can be interpreted as the discretization of

$$\begin{aligned}
\partial_\tau s &= \delta_s\Delta s + \frac{K\delta_c\Delta c - p\delta_s\Delta s - s\delta_p\Delta p}{s + p + K}\\
\partial_\tau p &= \delta_p\Delta p + \frac{K\delta_c\Delta c - p\delta_s\Delta s - s\delta_p\Delta p}{s + p + K}\\
\partial_\tau c &= \delta_c\Delta c - \frac{K\delta_c\Delta c - p\delta_s\Delta s - s\delta_p\Delta p}{s + p + K}.
\end{aligned}$$

Moreover, $\mathcal{V} = \{(s, p, c) \in \mathbb{R}^3,\ sp = Kc\}$ is locally invariant.
Here, the convergence problem remains open at present.
Consider the special case that the buffer P and the complex C are immobile, i.e. $\delta_p = \delta_c = 0$. Thus, the evolution of S is given by

$$\partial_\tau s = \frac{\delta_s}{1 + \frac{p}{s+K}}\Delta s.$$

If we assume additionally that $s \ll K$ and that the initial concentration p_0 of P is very large, then we have $p \approx p_0$ and $s + K \approx K$. Thus, the reduction is approximately

$$\partial_\tau s = \frac{\delta_s}{1 + \frac{p_0}{K}}\Delta s.$$

This corresponds to a reduction proposed by Neher [44]. (See also Baumgartner [6] equations (9) and (10).)

5.3 Michaelis-Menten kinetics

Let us return to the Michaelis-Menten kinetics presented in Example 2.2. In the presence of diffusion, the overall quantity of enzyme and complex

$$E_0 = \int_\Omega e(0, x) + c(0, x)\, dx$$

is still conserved. But the "classical" QSS-assumption used in the example (i.e. a small initial concentration of enzyme) does not seem applicable to singular perturbation techniques in the general diffusion setting: Going back to the discretization,

$$\varphi(\tilde{e}, \tilde{s}, \tilde{c}, \tilde{p}) = \sum_{\alpha \in \Sigma} (e_\alpha + c_\alpha)$$

is a first integral of the discretized system and we can choose (again assuming $c_\alpha(0) = 0$)

$$\widetilde{E}_0 := \sum_{\alpha \in \Sigma} e_\alpha(0)$$

as a small parameter ($\widetilde{E}_0 = \varepsilon$). But in [38] it is shown that this ansatz yields no valuable information.
However, assuming that the enzyme E and the complex C are immobile (i.e. $\delta_e = \delta_c = 0$), the situation changes. Now, $e + c$ is constant in time for every point $x \in \Omega$. Thus, if we assume that the initial concentration of complex C is zero everywhere and if we define $e_0(x) := e(0, x)$, the system simplifies to

$$\begin{aligned} \partial_t s &= \varepsilon \delta_s \Delta s + (k_1 s + k_{-1}) c - k_1 s e_0 \\ \partial_t c &= -(k_1 s + k_{-1} + k_2) c + k_1 s e_0. \end{aligned}$$

Now assuming that e_0 is small everywhere (and the diffusion slow), the fast part $h^{(0)}$ is the same as in Example 2.2. Hence, the projection operator Q is also the same. One gets the possible limit system [38]

$$\partial_t s = \delta_s \Delta s - \frac{k_1 k_2 s e_0}{k_1 s + k_{-1} + k_2}, \quad c \equiv 0.$$

This coincides with the limit system given by Yannacopoulos et al. [58].

Moreover, in the general situation one still can study different QSS assumptions [38]. In the following we will consider a variant of the Michaelis-Menten mechanism:

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} E + P,$$

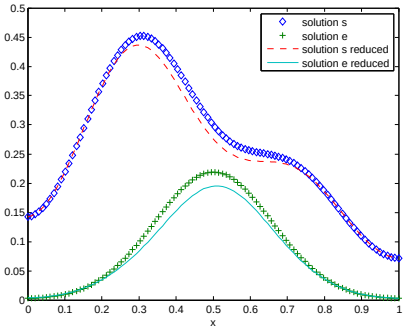
where we allow k_{-2} to be zero.
As an example, we consider the case of slow product formation, i.e.

$$\partial_t s = \varepsilon \delta_s \Delta s - k_1 s e + k_{-1} c \tag{5.9}$$

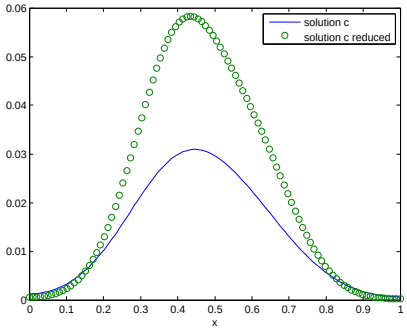
$$\partial_t e = \varepsilon(\delta_e \Delta e + k_2 c) - k_1 s e + k_{-1} c - k_{-2} e p \tag{5.10}$$

$$\partial_t c = \varepsilon(\delta_c \Delta c - k_2 c) + k_1 s e - k_{-1} c + k_{-2} e p \tag{5.11}$$

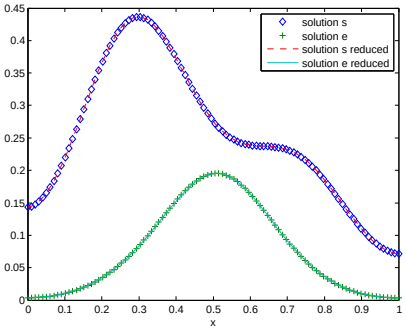
$$\partial_t p = \varepsilon(\delta_p \Delta p + k_2 c) - k_{-2} e p. \tag{5.12}$$



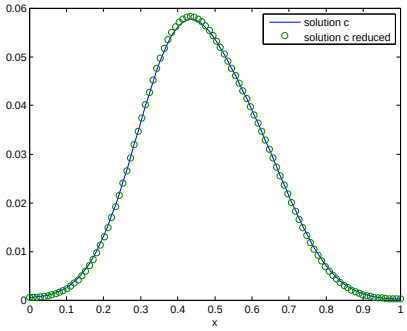
(a) Solutions s, e for $\varepsilon = 0.1$



(b) Solution c for $\varepsilon = 0.1$



(c) Solutions s, e for $\varepsilon = 0.001$



(d) Solution c for $\varepsilon = 0.001$

Figure 2: Solutions at $T = 0.01$ starting on the slow manifold. Note that the scaling of vertical axes is different in each image.

The irreversible case ($k_{-2} = 0$) leads to the situation of Example 5.2 above. In the reversible case ($k_{-2} > 0$) we get the following: The zero set $\mathcal{V}$ of $\mathcal{R}_{fast}$ (intersected with the positive orthant) is the union of $\mathcal{V}_1 = \{(s, e, c, p) \in \overline{\mathbb{R}}^4_+,\ e = c = 0\}$ and $\mathcal{V}_2 = \{(s, e, c, p) \in \overline{\mathbb{R}}^4_+,\ se = \frac{k_{-1}}{k_1}c,\ p = 0\}$. As there is no $x \in \mathcal{V}_1$ such that the direct sum decomposition exists, there also does not exist a Tikhonov-Fenichel reduction for any point in $\mathcal{V}_1$. However, near every point $x \in \mathcal{V}_2 \setminus \mathcal{V}_1$ a (convergent) Tikhonov-Fenichel reduction exists. Thus, one obtains the following candidate for a limit system

$$\begin{aligned}
\partial_\tau s &= \delta_s \Delta s + T(s, e, c, \Delta s, \Delta e, \Delta c) \\
\partial_\tau e &= \delta_e \Delta e + T(s, e, c, \Delta s, \Delta e, \Delta c) \\
\partial_\tau c &= \delta_c \Delta c - T(s, e, c, \Delta s, \Delta e, \Delta c),
\end{aligned}$$

with

$$T(s,e,c,\Delta s,\Delta e,\Delta c) := \frac{k_{-1}\delta_c\Delta c - k_1 s\delta_e\Delta e - k_1 e\delta_s\Delta s}{k_1(e+s)+k_{-1}},$$

where we explicitly used $p = 0$ to simplify the limit system. Numerical simulations (using a simple finite difference scheme and MATLAB [41]) for

$$\delta_s = \delta_e = \delta_c = \delta_p = k_1 = k_{-1} = k_2 = k_{-2} = 1$$

imply that the proposed reduction is well-grounded. Figure 2 depicts the situation, where the initial values of (5.9)–(5.12)

$$\begin{aligned}
s_0(x) &= \exp(-0.01(x-0.3)^2) + 0.5\exp(-0.01(x-0.7)^2),\\
e_0(x) &= 0.5\exp(-0.01(x-0.5)^2)\\
c_0(x) &= s_0(x)\cdot e_0(x),\\
p_0(x) &= 0
\end{aligned}$$

already lie on the slow manifold. Figure 3 gives an example for initial values of (5.9)–(5.12) not lying on the slow manifold, i.e.

$$\begin{aligned}
s_0(x) &= \exp(-0.01(x-0.5)^2),\\
e_0(x) &= 0.5\exp(-0.01(x-0.5)^2),\\
c_0(x) &= p_0(x) = 0.
\end{aligned}$$

These and other numerical experiments exhibited nice convergence properties, when the initial distribution lies on the slow manifold. Also, as shown by Figure 3, the same holds for certain initial distributions outside the slow manifold. But there are other initial values (e.g. choosing $c_0(x) = s_0(x)\cdot e_0(x) + 0.001$ instead of zero) which do not exhibit such a nice behaviour. The reason is probably that the chosen numerical procedure is not particularly specialized for singular scenarios.

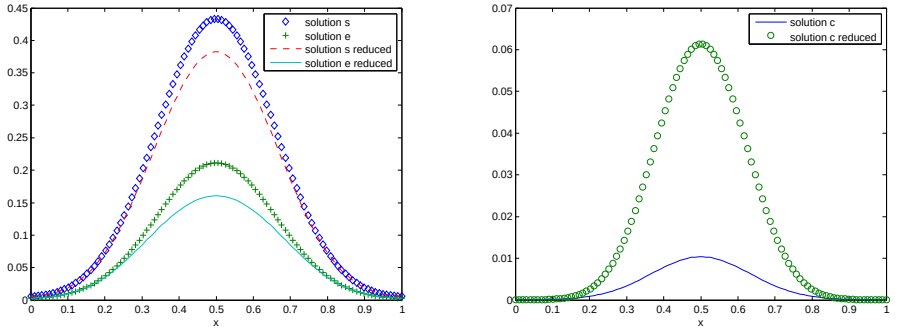
5.4 An irreversible fast reaction

Consider a reaction-diffusion system, where the irreversible reaction

$$S + P \xrightarrow{k} C$$

is fast with regard to the diffusion:

$$\begin{aligned}
\partial_t s &= \varepsilon\delta_s\Delta s - ksp\\
\partial_t p &= \varepsilon\delta_p\Delta p - ksp.
\end{aligned}$$



(a) Solutions s, e for $\varepsilon = 0.1$

(b) Solution c for $\varepsilon = 0.1$

(c) Solutions s, e for $\varepsilon = 0.001$

(d) Solution c for $\varepsilon = 0.001$

Figure 3: Solutions at $T = 0.01$ starting near the slow manifold. Note that the scaling of vertical axes is different in each image.

The zero set $\mathcal{V}$ of $\mathcal{R}$ in $\overline{\mathbb{R}}^m_+$ is given by the union of $\mathcal{V}_1 = \{(s, 0), s > 0\}$, $\mathcal{V}_2 = \{(0, p), p > 0\}$ and $\{0\}$. The computation of Q is the same as in the reversible case (see Example 5.2). Starting in a compartment with initial data of s, p near $\mathcal{V}_1$ the (convergent) reduction of the discretized reaction-diffusion system is given by

$$\frac{d}{d\tau} s_\alpha = \delta_s \mathcal{D}_\alpha(\tilde{s}), \quad p_\alpha = 0.$$

Starting in a compartment with initial data near $\mathcal{V}_2$ gives

$$\frac{d}{d\tau} p_\alpha = \delta_p \mathcal{D}_\alpha(\tilde{p}), \quad s_\alpha = 0.$$

A reduction near 0 does not exist.
Returning to continuous systems, the different reductions can be interpreted

as a spatial segregation of S and P. For an exact formulation as a free boundary problem [19] and convergence results we refer to Evans [21] and Bothe [10]. Thus, the existence of different components and reductions in the heuristic may be physically relevant.

6 Discussion

One principal result of the present paper shows that Tikhonov-Fenichel reductions for compartmental (interaction-transport) systems is feasible in the case of slow transport once the reduction for a single compartment is known. The heuristical method to find a candidate for a reduction of reaction-diffusion systems seems to be of some relevance: Reaction-diffusion systems with different time scales – especially slow diffusion – occur in the modeling of a broad spectrum of chemical and physical phenomena and have been studied widely in the literature from various perspectives (Verhulst [53] Chapter 9, Bothe et al. [9–15], Bates et al. [5], Yannacopoulos et al. [58]). As can be seen from inspection of these references, even finding and computing appropriate candidates for reduced systems may be problematic. This problem is solved here under relatively mild assumptions. Via a spatial discretization, we obtain the heuristic as follows: If the initial data is "smooth enough", the reduction of the discretized reaction-diffusion system can be interpreted as the discretization of a PDE system, which is our candidate for a reduction. This indicates that kernel-image decompositions and corresponding projections are of importance for a wide class of equations. Moreover, one can prove a convergence result for reaction-diffusion systems of abritrary size, if the reaction is detailed balanced and of first order (i.e. the reaction terms are linear and symmetric).

7 Acknowledgement

Both authors gratefully acknowledge support by the DFG-Graduiertenkolleg "Experimentelle und konstruktive Algebra" at RWTH Aachen. We would also like to thank Sebastian Walcher for useful discussions and Kerstin Küpper for advice with numerical simulations. Finally, our thanks go to two anonymous referees for detailed comments and suggestions.

References

[1] D.H. Anderson. *Compartmental modeling and tracer kinetics*. Lecture notes in biomathematics. Springer-Verlag, 1983.

[2] B. Aulbach and T. Wanner. Integral manifolds for Carathéodory type differential equations in Banach spaces. In *Six lectures on dynamical systems (Augsburg, 1994)*, pages 45–119. World Sci. Publ., River Edge, NJ, 1996.

[3] B. Aulbach and T. Wanner. The Hartman-Grobman theorem for Carathéodory-type differential equations in Banach spaces. *Nonlinear Anal.*, 40(1-8, Ser. A: Theory Methods):91–104, 2000. Lakshmikantham's legacy: a tribute on his 75th birthday.

[4] B. Aulbach and T. Wanner. Invariant foliations for Carathéodory type differential equations in Banach spaces. In *Advances in stability theory at the end of the 20th century*, volume 13 of *Stability Control Theory Methods Appl.*, pages 1–14. Taylor & Francis, London, 2003.

[5] P. Bates, K. Lu, and C. Zeng. Approximately invariant manifolds and global dynamics of spike states. *Inventiones mathematicae*, 174(2):355–433, 2008.

[6] W. Baumgartner. Electrodiffusion near an ion channel and the effect of mobile buffer. *Computational Biology and Chemistry*, 28(1):67 – 73, 2004.

[7] A. Berman and R. Plemmons. *Nonnegative matrices in the mathematical sciences*. Computer science and applied mathematics. Academic Press, New York, NY, 1979.

[8] D. Bernstein and D. Hyland. Compartmental modeling and second-moment analysis of state space systems. *SIAM Journal on Matrix Analysis and Applications*, 14(3):880–901, 1993.

[9] D. Bothe. Flow invariance for perturbed nonlinear evolution equations. *Abstract and Applied Analysis*, 1:417–433, 1996.

[10] D. Bothe. The instantaneous limit of a reaction-diffusion system. In *Evolution equations and their applications in physical and life sciences. Proceeding of the Bad Herrenalb (Karlsruhe) conference, Germany, 1999*, pages 215–224. New York, NY: Marcel Dekker, 2001.

[11] D. Bothe. Instantaneous limits of reversible chemical reactions in presence of macroscopic convection. *Journal of Differential Equations*, 193(1):27 – 48, 2003.

[12] D. Bothe and D. Hilhorst. A reaction-diffusion system with fast reversible reaction. *J. Math. Anal. Appl.*, 286(1):125–135, 2003.

[13] D. Bothe and M. Pierre. Quasi-steady-state approximation for a reaction-diffusion system with fast intermediate. *Journal of Mathematical Analysis and Applications*, 368(1):120–132), 2010-08-01.

[14] D. Bothe and M. Pierre. The instantaneous limit for reaction-diffusion systems with a fast irreversible reaction. *Discrete and Continuous Dynamical Systems Series S*, 5(1):49–59, Februar 2012.

[15] D. Bothe, M. Pierre, and G. Rolland. Cross-diffusion limit for a reaction-diffusion system with fast reversible reaction. *Comm. Partial Differential Equations*, 37(11):1940–1966, 2012.

[16] G. E. Briggs and J. B. S. Haldane. A note on the kinetics of enzyme action. *Biochem. J.*, 19:338–339, 1925.

[17] N. F. Britton. *Reaction-Diffusion Equations And Their Application to Biology*. Academic Press, London, 1986.

[18] R. F. Brown. Compartmental system analysis: State of the art. *Biomedical Engineering, IEEE Transactions on*, BME-27(1):1–11, Jan 1980.

[19] J. Cannon and C. Hill. On the movement of a chemical reaction interface. *Indiana Univ. Math. J.*, 20:429–454, 1971.

[20] V. Chellaboina, S. Bhat, W. Haddad, and D. Bernstein. Modeling and analysis of mass-action kinetics. *IEEE Control Systems*, 29(4):60–78, 2009.

[21] L.C. Evans. A convergence theorem for a chemical diffusion-reaction system. *Houston J. Math.*, 6(2):259–267, 1980.

[22] M. Feinberg. *Lectures on chemical reaction networks*. Chemical Engineering & Mathematics, The Ohio State University, 1979.

[23] M. Feinberg. The existence and uniqueness of steady states for a class of chemical reaction networks. *Archive for Rational Mechanics and Analysis*, 132(4):311–370, 1995.

[24] N. Fenichel. Geometric singular perturbation theory for ordinary differential equations. *J. Differential Equations*, 31(1):53–98, 1979.

[25] Neil Fenichel. Persistence and smoothness of invariant manifolds for flows. *Indiana Univ. Math. J.*, 21:193–226, 1972.

[26] D. Glasser, F. Horn, and R. Meidan. Properties of certain zero column-sum matrices with applications to the optimization of chemical reactors. *Journal of Mathematical Analysis and Applications*, 73(2):315 – 337, 1980.

[27] A. Goeke. *Reduktion und asymptotische Reduktion von Reaktionsgleichungen*. PhD thesis, RWTH Aachen, 2013.

[28] A. Goeke and S. Walcher. Quasi-steady state: Searching for and utilizing small parameters. In *Recent Trends in Dynamical Systems. Proceedings of a Conference in Honor of Jürgen Scheurle*, volume 35 of *Springer Proceedings in Mathematics & Statistics*. Springer-Verlag, New York, 2013.

[29] A. Goeke and S. Walcher. A constructive approach to quasi-steady state reductions. *J. Math. Chem.*, 52(10):2596–2626, 2014.

[30] W.M. Haddad, V.S. Chellaboina, and Q. Hui. *Nonnegative and Compartmental Dynamical Systems*. Princeton University Press, 2010.

[31] R. Heinrich and M. Schauer. Quasi-steady-state approximation in the mathematical modeling of biochemical networks. *Math. Biosci.*, 65:155–170, 1983.

[32] F. Horn. General first order kinetics. *Berichte der Bunsengesellschaft für physikalische Chemie*, 75(11):1191–1201, 1971.

[33] F. Horn and R. Jackson. General mass action kinetics. *Arch. Ration. Mech. Anal.*, 47:81–116, 1972.

[34] J.A. Jacquez. *Compartmental analysis in biology and medicine*. BioMedware, 1996.

[35] Shi Jin. Efficient asymptotic-preserving (ap) schemes for some multiscale kinetic equations. *SIAM Journal on Scientific Computing*, 21(2):441–454, 1999.

[36] N.G. Van Kampen. *Stochastic processes in physics and chemistry*. North Holland, 2007.

[37] SH Lam and DA Goussis. The csp method for simplifying kinetics. *International Journal of Chemical Kinetics*, 26(4):461–486, 1994.

[38] C. Lax. *Analyse und asymptotische Analyse von Modellen zur Reizübertragung an Synapsen*. PhD thesis, RWTH Aachen, in preparation.

[39] C. H. Lee and H. G. Othmer. A multi-time-scale analysis of chemical reaction networks: I. Deterministic systems. *J. Math. Biol.*, 60:387–450, 2009.

[40] A. Lunardi. *Analytic Semigroups and Optimal Regularity in Parabolic Problems*. Modern Birkhäuser Classics. Springer-Verlag, 1995.

[41] MATLAB. *version 8.3.0.532 (R2014a)*. The MathWorks Inc., Natick, Massachusetts, 2014.

[42] L. Michaelis and M. L.. Menten. Die Kinetik der Invertinwirkung. *Biochem. Z.*, 49:333–369, 1913.

[43] J. D. Murray. *Mathematical Biology. I: An Introduction*, volume 17 of *Interdisciplinary Applied Mathematics*. Springer-Verlag, Berlin Heidelberg New York, 3. edition, 2002.

[44] E. Neher. Concentration profiles of intracellular calcium in the presence of a diffusible chelator. *Exp. Brain Res. Ser.*, 14:80–96, 1986.

[45] L. Nöthen and S. Walcher. Tikhonov's theorem and quasi-steady state. *Discrete Contin. Dyn. Syst. Ser. B*, 16(3):945–961, 2011.

[46] Michel Pierre. Global existence in reaction-diffusion systems with control of mass: a survey. *Milan Journal of Mathematics*, 78(2):417–455, 2010.

[47] Anthony John Roberts. *Model emergent dynamics in complex systems*. SIAM, 2014.

[48] I. R. Shafarevich. *Basic algebraic geometry*. Springer-Verlag, Berlin-New York, study edition, 1977. Translated from the Russian by K. A. Hirsch, Revised printing of Grundlehren der mathematischen Wissenschaften, Vol. 213, 1974.

[49] J. Smoller. *Shock waves and reaction-diffusion equations*, volume 258 of *Grundlehren der mathematischen Wissenschaften*. Springer New York, 1983.

[50] M. Stiefenhofer. Quasi-steady-state approximation for chemical reaction networks. *J. Math. Biol.*, 36:593–609, 1998.

[51] T. Teorell. Kinetics of distribution of substances administered to the body, i: The extravascular modes of administration. *Archives internationales de pharmacodynamie et de therapie*, 57:205–225, 1937.

[52] A. N. Tikhonov. Systems of differential equations containing a small parameter multiplying the derivative (in russian). *Math. Sb.*, 31:575–586, 1952.

[53] F. Verhulst. *Methods and Applications of Singular Perturbations. Boundary Layers and Multiple Timescale Dynamics.* Springer, New York, 2005.

[54] G. Walter and M. Contreras. *Compartmental Modeling With Networks.* Modeling and simulation in science, engineering & technology. Springer, 1999.

[55] R. Wegscheider. Über simultane Gleichgewichte und die Beziehungen zwischen Thermodynamik und Reactionskinetik homogener Systeme. *Monatshefte für Chemie und verwandte Teile anderer Wissenschaften*, 32(8):849–906, 1911.

[56] J. Wei and C. D. Prater. The structure and analysis of complex reaction systems. In D. Elay, editor, *Advances in Catalysis*, volume 13, pages 203 – 392. Academic Press, 1962.

[57] J. Wolf and R. Heinrich. Dynamics of biochemical oscillators in a large number of interacting cells. *Nonlinear Analysis: Theory, Methods and Applications*, 30(3):1835 – 1845, 1997.

[58] A.N. Yannacopoulos, A.S. Tomlin, J. Brindley, J.H. Merkin, and M.J. Pilling. The use of algebraic sets in the approximation of inertial manifolds and lumping in chemical kinetic systems. *Physica D: Nonlinear Phenomena*, 83(4):421 – 449, 1995.

[59] Antonios Zagaris, Hans G. Kaper, and Tasso J. Kaper. Fast and slow dynamics for the computational singular perturbation method. *Multiscale Model. Simul.*, 2(4):613–638 (electronic), 2004.