Determining "small parameters" for quasi-steady state

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Abstract

For a parameter-dependent system of ordinary differential equations we present a systematic approach to the determination of parameter values near which singular perturbation scenarios (in the sense of Tikhonov and Fenichel) arise. We call these special values *Tikhonov parameter values*. The principal application we intend is to equations that describe chemical reactions, in the context of quasi-steady state (or partial equilibrium) settings. Such equations have rational (or even polynomial) right-hand side. We determine the structure of the set of Tikhonov parameter values as a semi-algebraic set, and present an algorithmic approach to their explicit determination, using Groebner bases. Examples and applications (which include the irreversible and reversible Michaelis-Menten systems) illustrate that the approach is rather easy to implement.

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1 Introduction and overview

The present paper is motivated by parameter dependent ordinary differential equations which model reaction networks in chemistry and biochemistry, the parameters representing rate constants or initial concentrations. In particular we are interested in the mathematical analysis of quasi-steady state (QSS) phenomena, either for certain chemical species, or for certain reactions in the given network (the latter case also is known as partial equilibrium approximation, briefly PEA). According to established practice we discuss these phenomena

within the mathematical framework of singular perturbation theory.
Given a quasi-steady state setting (or assumption), one will aim to reduce the system, by an ad-hoc approach or (on more solid mathematical ground) with the help of Tikhonov's and Fenichel's theorems, after identifying a suitable "small parameter". Thus, there are two issues when applying singular perturbation theory to QSS scenarios: Prior to reduction, one needs to determine (ideally all) parameter regions in which QSS phenomena occur. Most approaches to this problem invoke expertise (e.g. experimental data or educated guesswork) from chemistry, which then is transferred to workable mathematical conditions. A prominent example is the technique of estimating fast and slow time scales, which was initiated by Segel and Slemrod. But frequently, only relatively rough estimates can thus be obtained, and the obtained heuristics will, in turn, require further analysis. Time scale reasoning is also used in numerical schemes (even when all parameters are assigned numerical values), e.g. by Lam and Goussis.
For parameter-dependent systems it seems that all the approaches in the literature require an initial assumption, or a guess, about the existence of certain invariant sets, or about the magnitude of rate constants, or about time scales, which refers to the model underlying the equation. In the present paper, which is based on the first-named author's doctoral dissertation [13], we propose a different (and, to our knowledge, new) approach to finding "small parameters". This approach starts from the mathematical interpretation of QSS as a singular perturbation phenomenon, but within this framework we will present a self-contained (and to some extent algorithmic) method to finding all "small parameters" of a given system. The argument is rooted in ideas and approaches from the literature, but it works excusively via mathematical reasoning. The principle is to focus on those parameter tuples for which small perturbations provide a scenario such that Tikhonov's and Fenichel's theorems are applicable. The right-hand side of the differential equation features some degeneracy at such parameters, and this degeneracy in turn provides a computational approach to find them. This mathematical procedure seems simpler, both conceptually and computationally, than existing approaches. While there are some technicalities, examples show that the search for "small parameters" becomes less involved and more straightforward, and in principle one can find all the relevant parameter regions in this way.
We now give an overview of the contents. In Section 2 we provide a brief review of the literature, examples and introduce some terminology. In Section 3 we introduce – in the setting of smooth vector fields – the notion of a *Tikhonov parameter value (TPV)*; i.e., a parameter tuple such that every small deviation will lead to a singular perturbation scenario for which Tikhonov's and Fenichel's theorems are applicable. We discuss some properties of TPVs, relate them to other concepts in the literature, and indicate why TPVs are accessible via computations. In order to illustrate the inherent simplicity of the approach and its implementation, we discuss a linear chain reaction and the familiar irreversible Michaelis-Menten system as first examples. In Section 4 we specialize to systems with rational or polynomial right-hand side. In view of the intended applications to (bio-) chemistry, with mass action kinetics, this specialization is

not particularly restrictive. (To make the arguments and methods accessible to non-specialized readers, we include an intoduction and overview of some algebraic concepts and facts.) From a structural perspective we obtain the following characterization: If one considers the system on a semi-algebraic subset of phase and parameter space (e.g. the positive orthant) then the TPVs themselves form a semi-algebraic subset of parameter space, hence are determined by finitely many polynomial equations and inequalities. Moreover we describe a computational approach to finding TPVs via elimination ideals, which also allows for the use of algorithmic algebra techniques. Finally, in Section 5 we present several applications. For some systems we determine all Tikhonov parameter values, thus obtaining an exhaustive list of all quasi-steady state scenarios; in other cases we provide – in view of space considerations or due to computational complexity – partial lists, which include "small parameters" that seem to have been unnoticed so far.

It should be emphasized that the applicability of our approach is not limited to (bio–) chemistry and QSS. In particular the results of Section 3 are useful whenever one is interested in parameters that lead to a reduction via Tikhonov's and Fenichel's theorems.

2 Perspectives of QSS

We give a short summary of work on quasi-steady state (QSS) in the literature. This summary is necessarily incomplete with respect to the cited references, but – to the best of our knowledge – it includes all relevant approaches. From the perspective of chemical reaction equations, quasi-steady state is being considered either for certain chemical species that change slowly in comparison to the overall rate of change (QSS for species; cf. Atkins and de Paula [1], p. 812 ff. for details), or for certain reactions which proceed slowly when compared to the remaining ones (one also speaks of partial equilibrium approximation (PEA), or rapid equilibrium approximation; cf. e.g. Goussis [18], Heinrich and Schuster [22]). As an example to illustrate the notions and arguments, we take the standard Michaelis-Menten reaction: Substrate S and enzyme E reversibly combine to a complex C, which in turn degrades – reversibly or irreversibly – to E and product P; thus one has the reaction scheme

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

By mass action kinetics one arrives at the differential system

$$(1) \qquad \begin{array}{rcrcl} \dot{s} & = - & k_1 e_0 s & + & (k_1 s + k_{-1})c, \\ \dot{c} & = & k_1 e_0 s & - & (k_1 s + k_{-1} + k_2)c + k_{-2}(e_0 - c)(s_0 - s - c), \end{array}$$

for the concentrations, with initial values $s(0) = s_0 > 0$ and $c(0) = 0$. Moreover $k_{-2} = 0$ in the irreversible scenario, while $k_{-2} > 0$ in the reversible scenario; all

other parameters are greater than zero.
The notion of quasi-steady state goes back to the beginning of the 20th century. Henri [23] in 1903, Michaelis and Menten [30] in 1913, and Briggs and Haldane [5] in 1925 heuristically introduced and discussed two types of quasi-steady state for the irreversible reaction (1), and imposed conditions (on rate constants and initial concentrations) for the occurrence of QSS. Michaelis and Menten assumed instantaneous equilibrium between substrate and complex (in other words, slow degradation of complex to product and enzyme) and obtained the condition $k_2/k_{-1} \ll 1$. Briggs and Haldane assumed QSS for complex and found the condition $e_0/s_0 \ll 1$.
Heineken, Tsuchiya and Aris [19] were among the first to consider QSS (for irreversible Michaelis-Menten) from the mathematical perspective of singular perturbation theory. By scaling transformations and the (preset) "small parameter" $\varepsilon_H = e_0/s_0$, they obtained a reduced equation via Tikhonov's theorem. The approach by Segel and Slemrod [36] (see also Segel [35]) included a systematic determination of appropriate small parameters: They employed time scale arguments, comparing estimates for the initial phase and the quasi-stationary phase, to identify the "small parameter" $\varepsilon_S = e_0/(s_0 + M)$, with $M := (k_{-1} + k_2)/k_1$ for the irreversible system. Moreover they gave a direct proof that solutions of this system converge to solutions of the reduced equation, uniformly on any compact subinterval of $(0, \infty)$. (Earlier, the "small parameter" $\varepsilon_S^* = e_0/M$ was introduced heuristically for the reversible system by Seshadri and Fritzsch [37].) The time scale arguments introduced by Segel and Slemrod triggered a large number of publications. For instance, Borghans, de Boer und Segel [4] considered the irreversible Michaelis-Menten equation with a modified QSS assumption they called total QSS (tQSS). They obtained the small parameter $\varepsilon_B = k_2 e_0/\big(k_1(e_0 + s_0 + M)^2\big)$, which imposes less restrictive conditions on the parameters (in the sense that $\varepsilon_S \to 0$ implies $\varepsilon_B \to 0$). Tzafriri and Edelmann [40] discussed tQSS for the reversible Michaelis-Menten system, obtaining rather complicated estimates. A recent discussion of tQSS for reaction networks, and its application to reduction, is given in Kumar and Josic [25].
All the above approaches are conducted with singular perturbation phenomena in mind, but one should note that there exist alternative mathematical interpretations of QSS. Heinrich and Schauer [20] (for the irreversible system) focus on the approximate invariance of the set defined by $\dot{c} = 0$ in equation (1); this approach was formalized and extended in [33]. Thus the mathematical interpretation of QSS as a singular perturbation phenomenon is not the only possibility. However, we will restrict to the singular perturbation interpretation in the present paper.

When considering slow and fast chemical reactions, a singular perturbation approach is the natural choice, and it has been employed and investigated in various publications. We mention Heinrich and Schauer [21], as well as the more recent work by Lee and Othmer [28] where also the initial phase is discussed in detail, and the algorithmically oriented paper by Boulier et al. [3]. In the setting of slow and fast reactions the "small parameters" will be rate constants

of certain reactions (possibly pairs of forward and back reactions). Although the singular perturbation approach is less straightforward when it comes to QSS for chemical species, for many relevant reacting systems the hypotheses of Tikhonov's and Fenichel's theorems are satisfied. (In such scenarios we will briefly say that *Tikhonov-Fenichel reduction* is applicable.)

A different way to employ singular perturbation techniques, in the context of numerical schemes, can be found in Lam and Goussis [27], or in Duchêne und Rouchon [9]. In these works (where numerical values for the rate constants etc. are known) there is no chemical a priori motivation for separation of the system into fast and slow variables (or reactions). Instead the authors separate the linearized system into a "slow" and "fast" part (e.g. by separating the eigenvalues into "small" and "large" ones), and compute a reduced system (iteratively) by approximating a slow manifold by the sum of eigenspaces for the "small" eigenvalues. The link to Tikhonov and Fenichel is provided by assuming a limiting case with the "small" eigenvalues approaching zero. For the scenario to be discussed in the present paper (involving unknown parameters), this perspective is of considerable interest as a motivation, because it provides a cue where to search for singular perturbation settings.

3 Tikhonov parameter values

3.1 Background

Throughout this section we will consider a parameter-dependent ordinary differential equation

$$\dot{x} = h(x, \pi), \quad x \in U \subseteq \mathbb{R}^n, \quad \pi \in \Pi \subseteq \mathbb{R}^m \tag{2}$$

with U open and the right-hand side h smooth in the variable (x, π). (Most results hold under less restrictive differentiability assumptions.) If one is aware of (or suspects) a slow-fast separation of time scales within certain parameter ranges, then one will aim to reduce the system via the theorems of Tikhonov [39] and Fenichel [10]. The familiar approach is to first recast the system (e.g. by scaling transformations) into a special form

$$\dot{y} = g(y, \rho, \varepsilon), \quad y \in \widetilde{U} \subseteq \mathbb{R}^n, \quad \rho \in \widetilde{\Pi} \subseteq \mathbb{R}^p, \quad \varepsilon \in [0, \varepsilon_0) \tag{3}$$

with $\varepsilon_0 > 0$, and then fix $\rho = \rho^*$ and let the "small parameter" $\varepsilon \to 0$. Whenever the entries of y split into subsets of slow and fast variables, the standard version of Tikhonov's theorem (see e.g. Verhulst [41], Thm. 8.1) is directly applicable. But explicit knowledge of slow and fast variables is neither necessary to verify the existence of a Tihkonov-Fenichel reduction, nor is it necessary to compute a reduced equation. Actually, the relevant points are as follows; see [15] and [16].

(i) There exists $\rho^* \in \widetilde{\Pi}$ such that the zero set of $y \mapsto g(y, \rho^*, 0)$ contains a local submanifold $W \subseteq U$ of dimension s, $0 < s < n$.

(ii) For every $z \in W$, the partial derivative $D_1 g(z, \rho^*, 0)$ with respect to the first variable set determines a direct sum decomposition into kernel and image:

$$\mathbb{R}^n = \operatorname{Ker} D_1 g(z, \rho^*, 0) \oplus \operatorname{Im} D_1 g(z, \rho^*, 0).$$

(Equivalently, the algebraic and the geometric multiplicity of the eigenvalue 0 of $D_1 g(z, \rho^*, 0)$ coincide. The kernel then has dimension s.)

(iii) There exists a positive constant μ such that the nonzero eigenvalues of $D_1 g(z, \rho^*, 0)$, $z \in W$, have real part $\leq -\mu$.

We will call W an asymptotic slow manifold (briefly, slow manifold) of the system. Given these conditions, for sufficiently small ε there exists an attractive local manifold of the system which is close to W. The reduced equation which determines the asymptotic behavior on W can be computed explicitly according to [15], Thm. 8.2 (see also Remark 1 below and [16]). We note that all the necessary and sufficient conditions refer only to properties of the right-hand side g at $\varepsilon = 0$.
Due to Fenichel [10], an asymptotic invariant manifold exists whenever the first two conditions above are satisfied, and the nonzero eigenvalues have nonzero real parts. The reduction formula in [15] is still applicable even when only (i) and (ii) are satisfied; we will sometimes speak of *formal reduction* in this case.

For most applications of interest to us (e.g. chemical reaction equations with mass-action kinetics) the right-hand side of (2) will actually be a rational or polynomial function of (x, π). In particular the zeros of $x \mapsto h(x, \pi^*)$, with $\pi^* \in \Pi$ fixed, form an algebraic subvariety of $\mathbb{R}^n$. This observation indicates that methods of commutative algebra and algebraic geometry will be relevant for computations and for structural characterizations. We will return to this in Section 4; presently we discuss the smooth setting.

3.2 Definition and basic properties

For system (3) one sees that "small parameters" ε are in fact distinguished by properties at $\varepsilon = 0$. This observation suggests to focus on those parameter tuples $\pi \in \Pi$ in system (2) for which small deviations will give rise to a Tikhonov-Fenichel reduction.

Definition 1. *A parameter $\pi^* \in \Pi$ will be called a* Tikhonov parameter value (TPV) for dimension s *($1 \leq s \leq n-1$) of system* (2) *whenever the following hold:*

(i) The zero set $\mathcal{V}(h(\cdot, \pi^*))$ of $x \mapsto h(x, \pi^*)$ contains a local submanifold $\widetilde{Y}$ of dimension s.

(ii) There is a point $x_0 \in \widetilde{Y}$ such that

$$\mathbb{R}^n = \operatorname{Ker}\, D_1 h(x, \pi^*) \oplus \operatorname{Im}\, D_1 h(x, \pi^*), \quad \text{all } x \in \widetilde{Y} \text{ near } x_0.$$

(iii) The nonzero eigenvalues of $D_1 h(x_0, \pi^*)$ have real part < 0.

If only conditions (i) and (ii) hold then we will call π^* *a* weak Tikhonov parameter value *for dimension* s*.*

We first verify that this definition is in accordance with its motivation.

Proposition 1. *Let* $\pi^* \in \Pi$ *be a Tikhonov parameter value for dimension* s *of system* (2)*, and let* $x_0 \in \mathcal{V}(h(\cdot, \pi^*))$ *be such that the conditions in Definition 1 are satisfied. Then for any smooth curve* $\gamma\colon \mathbb{R} \to \Pi,\ \delta \mapsto \gamma(\delta)$ *in parameter space with* $\gamma(0) = \pi^*$*, the system*

$$\dot{x} = h(x, \gamma(\delta)) = h(x, \pi^*) + \delta \cdot D_2 h(x, \pi^*)\gamma'(0) + O(\delta^2) \tag{4}$$

admits a Tikhonov-Fenichel reduction for $\delta \to 0$*.*

Proof. Consider the Taylor expansion of $\delta \to h(x, \gamma(\delta))$ about 0. Then [15], Thm. 8.1 shows that, up to a coordinate transformation, the hypotheses of Tikhonov's theorem (as stated in Verhulst [41], Thm. 8.1) are satisfied. □

From this Proposition one sees that only the tangent direction of the curve γ in $\delta = 0$ matters; cf. also the following Remark. Frequently one will use straight lines in applications.

Remark 1. For the reader's convenience, and for later reference, we note some facts concerning the reduction. A more extensive account can be found in [15], Subsection 8.3 (see also [13], [16]).

(a) The reduced system corresponding to (4) is defined on a local submanifold $\widetilde{Y}$ of the vanishing set $\mathcal{V}(h(\cdot, \pi^*))$, and is determined by projecting $D_2 h(x, \pi^*)\gamma'(0)$ onto the kernel along the image of $D_1 h(x, \pi^*)$, for x near x_0. To find it explicitly, one uses a decomposition

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

in some neighborhood of x_0. Here P is an $\mathbb{R}^{n\times(n-s)}$-valued function of rank $n - s$ on $\widetilde{Y}$, and $\widetilde{Y}$ equals the vanishing set of the $\mathbb{R}^{(n-s)}$-valued function μ, and moreover $A(x,\, \pi^*) := D_1\mu(x,\, \pi^*)\, P(x,\, \pi^*)$ is invertible on $\widetilde{Y}$. The reduced system is given by

$$\dot{x} = \delta \cdot \big(I_n - P(x,\, \pi^*)A(x,\, \pi^*)^{-1} D_1\mu(x,\, \pi^*)\big)\, D_2 h(x,\, \pi^*)\gamma'(0) \tag{5}$$

on the invariant manifold $\widetilde{Y}$. We call

$$Q(x,\, \pi^*) := I_n - P(x,\, \pi^*)A(x,\, \pi^*)^{-1} D_1\mu(x,\, \pi^*)$$

the projection map corresponding to π^* (and $\widetilde{Y}$). For polynomial h all of this is algorithmically accessible; see [15], [16].

(b) The convergence property can be stated as follows: There is $L_{\pi^*} > 0$ such that for every $0 < d_{\pi^*} < L_{\pi^*}$ the solutions of system (4) rewritten in *slow*

time scale, i.e. for $\tau = \delta t$, converge to solutions of the reduced system (5) in slow time scale, viz.

$$\frac{dx}{d\tau} = \big(I_n - P(x,\, \pi^*)A(x,\, \pi^*)^{-1}D_1\mu(x,\, \pi^*)\big)\, D_2h(x,\, \pi^*)\gamma'(0)$$

as $\delta \to 0$, uniformly for $\tau \in [d_{\pi^*}, L_{\pi^*}]$; see Verhulst [41], Thm. 8.1.

(c) Given a weak Tikhonov parameter value $\pi^* \in \Pi$ for dimension s, the system $\dot{x} = h(x, \pi^*)$ admits a formal Tikhonov-Fenichel reduction (5) to an s-dimensional manifold $\widetilde{Z} \subset \mathcal{V}(h(\cdot, \pi^*))$. If the nonzero eigenvalues of $D_1h(x,\, \pi^*)$ have nonzero real part then for small δ there will be an invariant manifold close to $\widetilde{Z}$, and the dynamics on this invariant manifold is approximated by (5); see Fenichel [10]. For our purposes, weak TPVs will mostly be an intermediate step toward finding TPVs.

To emphasize the dependence on π^* we will sometimes speak of the local slow manifold of a (weak) Tikhonov parameter value.

Remark 2. Some authors prefer a different manner of writing down the reduced system. Let π^* a TPV of (2), with local slow manifold $\widetilde{Y}$, such that some neighborhood of π^* in Π is a submanifold of $\mathbb{R}^m$. Given a smooth curve $\gamma\colon \mathbb{R} \to \Pi,\ \delta \mapsto \gamma(\delta)$ with $\gamma(0) = \pi^*$, one may fix $\pi := \gamma(\delta)$ and replace (5) by

$$\dot{x} = \big(I_n - P(x,\, \pi^*)A(x,\, \pi^*)^{-1}D_1\mu(x,\, \pi^*)\big)\, D_2h(x,\, \pi^*)(\pi - \pi^*)$$

Since the right-hand sides of this equation and of (5) differ only by order δ^2, by familiar continuous dependence properties the convergence statement from Remark 1 (b) still applies. But note that Tikhonov covers only the case of π converging to π^* along a fixed tangent direction; there seems to be no sensible reduced system in slow time otherwise.

We give a first indication why TPVs are accessible via computations. The underlying reason is that an overdetermined parameter-dependent system will admit zeros only if the parameters satisfy certain conditions.
From now on, given system (2) and $(x, \pi)^T \in U \times \Pi$, we denote by

$$\chi(\tau) = \chi_{x,\pi}(\tau) := \tau^n + \sigma_{n-1}(x,\pi)\tau^{n-1} + \cdots + \sigma_1(x,\pi)\tau + \sigma_0(x,\pi) \tag{6}$$

the characteristic polynomial of the Jacobian $D_1h(x, \pi)$, in the indeterminate τ. The coefficients σ_i are smooth in x and π, and even rational (or polynomial) whenever the right-hand side h has this property.

Proposition 2. *If $\pi^* \in \Pi$ is a Tikhonov parameter value for dimension s (with $1 \le s \le n-1$) for system (2) then there exists $x_0 \in \mathbb{R}^n$ with the following properties.*

(i) $h(x_0, \pi^*) = 0$*;*

(ii) the Jacobian $D_1h(x_0, \pi^*)$ has rank $\le n - s$, thus for any $k > n - s$, all $k \times k$ minors vanish;

(iii) $\sigma_s(x_0, \pi^*) \neq 0$.

Proof. Let $\pi^* \in \Pi$ be a TPV for dimension s. According to Definition 1 there exists an s-dimensional local submanifold $\widetilde{Y}$ of $\mathcal{V}(h(\cdot, \pi^*))$ and an $x_0 \in Y$ such that (i) is satisfied, and

$$\mathbb{R}^n = \text{Ker } D_1 h(x, \pi^*) \oplus \text{Im } D_1 h(x, \pi^*) \quad \text{for all } x \in \widetilde{Y},\ x \text{ near } x_0.$$

The direct sum decomposition shows that geometric and algebraic multiplicity for the eigenvalue 0 of $D_1 h(x_0, \pi^*)$ coincide; denote this multiplicity by $\widetilde{s}$. Then $n - \widetilde{s}$ is equal to the rank of $D_1 h(x_0, \pi^*)$, which on the other hand equals $n - s$, due to $\dim \widetilde{Y} = s$. Thus $s = \widetilde{s}$, and properties (ii) and (iii) follow by linear algebra.

□

There is some redundancy in the statement of part (ii); it would suffice to require the vanishing of all minors for $k = n - s + 1$.
The notions and results provided so far already permit the discussion of relevant examples. If the reader is so inclined, she or he may pass over the next subsection in a first reading and proceed to these examples directly.

3.3 Technicalities

First, there remains to verify that the "small parameters" determined from the standard approaches in the literature (as outlined in Subsection 3.1) can be recovered by the TPV approach. To this end we state and prove a general result on coordinate transformations. We require smoothness of all functions and transformations involved, without explicitly saying so in every instance.

Proposition 3. *Let the open sets $U, V \subset \mathbb{R}^n$, $\Pi \subset \mathbb{R}^{m_1}$ and $\Sigma \subset \mathbb{R}^{m_2}$ be given. In addition to system (2) on $U \times \Pi$, consider also a system*

$$\dot{y} = g(y, \sigma), \quad y \in V,\ \sigma \in \Sigma, \tag{7}$$

and suppose that

$$\Gamma_1 \colon U \times \Pi \to V, \quad \Gamma_2 \colon \Pi \to \Sigma$$

define a transformation $\Gamma = (\Gamma_1, \Gamma_2)^T$ which maps solutions of the extended system

$$\begin{pmatrix} \dot{x} \\ \dot{\pi} \end{pmatrix} = \begin{pmatrix} h(x, \pi) \\ 0 \end{pmatrix}, \quad (x, \pi)^T \in U \times \Pi$$

to solutions of the extended system

$$\begin{pmatrix} \dot{y} \\ \dot{\sigma} \end{pmatrix} = \begin{pmatrix} g(y, \sigma) \\ 0 \end{pmatrix}, \quad (y, \sigma)^T \in V \times \Sigma.$$

Moreover assume that for every $\pi \in \Pi$ the map $\Gamma_1(\cdot, \pi) \colon U \to V$ locally has a smooth inverse. Then the following hold.

(a) *Any TPV (or weak TPV)* $\pi^* \in \Pi$ *for dimension* s *of* (2) *is mapped to a TPV (or weak TPV)* $\sigma^* = \Gamma_2(\pi^*) \in \Sigma$ *for dimension* s *of* (7).

(b) *There is an invertible solution-preserving map between the reduced equations corresponding to* (2) *for* π^* *and to* (7) *for* σ^**, respectively. In particular the local slow manifold of* (2) *for* π^* *is mapped to the local slow manifold of* (7) *for* σ^*.

Proof. We prove the statements simultaneously for TPVs and weak TPVs. Since Γ maps solutions to solutions we have the identity

$$\begin{pmatrix} g(\Gamma(x,\pi)) \\ 0 \end{pmatrix} = D\Gamma(x,\pi) \begin{pmatrix} h(x,\pi) \\ 0 \end{pmatrix}, \quad (x,\pi) \in U \times \Pi,$$

and in particular

$$g(\Gamma(x,\pi)) = D_1\Gamma_1(x,\pi)h(x,\pi) \quad \text{ for all } (x,\pi) \in U \times \Pi.$$

Differentiating this identity, and letting $x \in \mathcal{V}(h(\cdot,\pi))$ one finds

$$D_1 g(\Gamma(x,\pi))D_1\Gamma_1(x,\pi) = D_1\Gamma_1(x,\pi)D_1 h(x,\pi).$$

Due to the invertibility of $D_1\Gamma_1$, the Jacobians with respect to the first variable of g at $\Gamma(x,\pi)$ and of h at x are conjugate.

Now let $1 \le s \le n-1$, and let $\pi^* \in \Pi$ be a (weak) TPV for dimension s of (2). Then there exists an s-dimensional local submanifold $\widetilde{Y} \subseteq \mathcal{V}(h(\cdot,\pi^*))$ such that

$$\mathbb{R}^n = \text{Ker } D_1 h(x,\pi^*) \oplus \text{Im } D_1 h(x,\pi^*), \quad x \in \widetilde{Y}.$$

We show that $\sigma^* = \Gamma_2(\pi^*)$ is a TPV of (7) with slow manifold

$$\widetilde{Z} = \Gamma_1(\widetilde{Y},\pi^*) = \{\Gamma_1(x,\pi^*);\ x \in \widetilde{Y}\}.$$

Γ maps solutions to solutions, therefore $g \circ \Gamma$ vanishes at all (x,π^*), $x \in \widetilde{Y}$, and thus $\widetilde{Z} \subset \mathcal{V}(g(\cdot,\sigma^*))$. Since the map $\Gamma_1(\cdot,\,\pi^*)\colon U \to V$ is a local diffeomorphism, the dimensions of $\widetilde{Z}$ and $\widetilde{Y}$ are equal. From the direct sum decomposition induced by $D_1 h(x,\,\pi^*)$ one obtains

$$\mathbb{R}^n = D_1\Gamma_1(x,\pi^*) \cdot \text{Ker } D_1 h(x,\pi^*) \oplus D_1\Gamma_1(x,\pi^*) \cdot \text{Im } D_1 h(x,\pi^*), \quad x \in \widetilde{Y},$$

and by conjugacy of Jacobians one has the direct sum decomposition

$$\mathbb{R}^n = \text{Ker } D_1 g(y,\sigma^*) \oplus \text{Im } D_1 g(y,\sigma^*), \quad y \in \widetilde{Z}.$$

Therefore σ^* is a (weak) TPV for dimension s of (7). Moreover, the reduced equation

$$\dot{x} = \mathfrak{h}(x,\pi^*), \quad x \in \widetilde{Y}, \tag{8}$$

corresponding to (2) is obtained from the kernel–image decomposition with respect to $D_1 h(x, \pi^*)$ for $x \in \widetilde{Y}$, while the reduced equation

$$\dot{x} = \mathfrak{g}(x, \sigma^*), \quad x \in \widetilde{Y}, \tag{9}$$

corresponding to (7) is obtained from the kernel–image decomposition with respect to $D_1 g(x, \sigma^*)$ for $x \in \widetilde{Z}$. The above identities and Remark 1 (a) show that the projection map for g is conjugate by $D_1\Gamma_1(x, \pi^*)$ to the projection map for h. This in turn implies

$$D_1\Gamma_1(x, \pi^*)\mathfrak{h}(x, \pi^*) = \mathfrak{g}(\Gamma(x, \pi^*)) = \mathfrak{g}(\Gamma_1(x), \sigma^*), \quad x \in \widetilde{Y}.$$

Hence the invertible map Γ_1 sends solutions of (8) to solutions of (9). □

Remark 3. (a) Transformations from (2) to the special form (3) are included in Proposition 3, with $\sigma = (\rho, \varepsilon)$ and $\sigma^* = (\rho^*, 0)$. In addition, the TPV property is stable with respect to (non-singular) scaling of time. Indeed, given system (2) and a function $\kappa\colon \Pi \to \mathbb{R}_+$ without zeros, consider the parameter-dependent time scaling $\mathbb{R} \to \mathbb{R}$, $t \mapsto \kappa(\pi) \cdot t$. In time scale $\tau = \kappa(\pi) \cdot t$ equation (2) is given by

$$x' = \kappa(\pi)^{-1} h(x, \pi),$$

with $'$ denoting differentiation with respect to τ. Then $\pi^* \in \Pi$ is a TPV of (2) if and only if it is a TPV of the scaled system. The proof is straightforward from the definitions.

(b) The familiar scaling transformations (of variables and time), as for instance used in Heineken et al. [19], Segel and Slemrod [36], and frequently in Murray [31], are covered by Proposition 3. The reader may wonder why most of our results (as well as examples below) are stated without invoking any scaling. The principal reason is that in the present paper we focus mainly on convergence, and convergence of some sequence or function to zero is not influenced by multiplication with some positive constant. (Naturally in applications, with given numerical values for rate constants and concentrations, rates of convergence and estimates become important.)

(c) There is a secondary reason for omitting scalings here: They should be used with caution. Some of the transformations employed in the literature (for instance Goldbeter and Lefever [17]) involve singular Jacobians. Such transformations are not within the scope of our results, since they make a general application of singular perturbation theory impractical upon returning to original coordinates. The validity of asymptotic approximations obtained by such variants requires additional verification. One should also note that passing from fast to slow time scale in singular perturbation scenarios is not covered by the above results. But actually, zeros of κ should correspond to a TPV to be sensible.

We close this subsection with two more technical observations. The first of these will allow us to rewrite some reduced systems in a less cumbersome manner. Recall that the convergence statement in Remark 1 (b) is unaffected by changing the right-hand side of equation (5) by a term of order δ^2.

Remark 4. Let π^* be a TPV of system (2), with local slow manifold $\widetilde{Y}$.

(a) If $\delta \mapsto \gamma_0(\delta)$ is a smooth curve of TPVs with the same local slow manifold $\widetilde{Y}$, and $\gamma_0(0) = \pi^*$, then the projection maps $Q(x, \pi^*)$ and $Q(x, \gamma_0(\delta))$ differ only by $O(\delta)$. To see this, one may refer to [34], Lemma 2.4 and Prop. 2.5, which show that the entries are rational (hence smooth) functions in the coefficients of the characteristic polynomial (6) of $D_1h(x, \gamma_0(\delta))$, which in turn depend smoothly on the entries of D_1h. Thus the right-hand side of equation (5) with parameter π^* and the right-hand side with parameter $\gamma_0(\delta)$ differ by $O(\delta^2)$.

(b) By the same token, given a curve $\delta \mapsto \gamma(\delta) = \gamma_0(\delta)+\gamma_1(\delta)$, with γ_0 as above and γ_1 smooth with $\gamma_1(0) = 0$, one may replace $Q(x, \pi^*)$ by $Q(x, \gamma_0(\delta))$, with an error of order δ.

Finally we note that Tikhonov parameter values are not affected by augmenting a system with more "small parameters", keeping the "fast" part of the dynamics unchanged. This observation is of some interest for the determination of particular TPVs in reaction equations whenever a TPV for an equation describing a subsystem of these reactions is known, and all the additional reactions are slow. One possible application is to reversible systems with (some) slow reverse reactions. The proof is obvious.

Remark 5. Consider a system

$$\dot{x} = h(x, \pi, \rho), \quad x \in U \subseteq \mathbb{R}^n, \ (\pi, \rho)^T \in \Pi \times R \subset \mathbb{R}^{m_1+m_2}, \tag{10}$$

and a corresponding system with "truncated parameters", viz.

$$\dot{x} = \widehat{h}(x, \pi) := h(x, \pi, 0), \quad x \in U, \ \pi \in \Pi. \tag{11}$$

Then $(\pi^*, 0)^T \in \Pi \times R$ is a TPV for dimension s of (10) whenever $\pi^* \in \Pi$ is a TPV for dimension s of system (11). The slow manifolds coincide.

3.4 Example: A linear decay chain

The ideas underlying the concept of Tikhonov parameter values are rather straightforward, and so is their basic implementation in computations. We briefly illustrate this statement by a very simple application, viz., a linear chain reaction. The mathematical description of the decay chain is given by

$$\dot{x} = Mx,$$

with the vector $x = (x_1, \ldots, x_n)^T \in \mathbb{R}^n$ of concentrations, the decay rates $\lambda = (\lambda_1, \ldots, \lambda_n)^T \in \mathbb{R}^n$ and the matrix

$$M = \begin{pmatrix} -\lambda_1 & & & \\ \lambda_1 & -\lambda_2 & & \\ & \ddots & \ddots & \\ & & \lambda_{n-1} & -\lambda_n \end{pmatrix}.$$

The characteristic polynomial of M is equal to

$$\chi(\tau) = \prod_{i=1}^{n} (\tau + \lambda_i),$$

and $\det M$ is (up to sign) the product of all λ_i. Thus, according to Proposition 2 and Definition 1, a parameter tuple $0 \neq \lambda^* = (\lambda_1^*, \ldots, \lambda_n^*)^T \in \mathbb{R}^n$ is a weak TPV if and only if $\lambda_i^* = 0$ for at least one i, $1 \leq i \leq n$, and a weak TPV for dimension s if and only if exactly s of the λ_i^* are equal to 0. (One has a TPV if and only if all the remaining parameters are > 0.)

3.5 Example: Irreversible Michaelis-Menten

Turning to a more substantial illustration, we will discuss a familiar example, viz. the irreversible Michaelis-Menten system

$$\begin{array}{rcrcl} \dot{s} & = - & k_1 e_0 s & + & (k_1 s + k_{-1}) c \\ \dot{c} & = & k_1 e_0 s & - & (k_1 s + k_{-1} + k_2) c \end{array} \tag{12}$$

(with initial values $s(0) = s_0$, $c(0) = 0$) from the TPV perspective. According to the notation introduced in Subsection 3.2, we have the variable $x = (s, c)^T \in \mathbb{R}^2$, the parameter vector $\pi = (e_0, k_1, k_{-1}, k_2)^T \in \Pi \subseteq \mathbb{R}^4$ and

$$h(x, \pi) = \begin{pmatrix} -k_1 e_0 s + (k_1 s + k_{-1}) c \\ k_1 e_0 s - (k_1 s + k_{-1} + k_2) c \end{pmatrix}.$$

We do not a priori restrict the variable or parameter regions. The key to determining TPVs of this two-dimensional system (only dimension $s = 1$ is of interest) lies in Proposition 2: We compute the Jacobian matrix

$$D_1 h(x, \pi) = \begin{pmatrix} -k_1 e_0 + k_1 c & k_1 s + k_{-1} \\ k_1 e_0 - k_1 c & -k_1 s - k_{-1} - k_2 \end{pmatrix}$$

and its determinant

$$d(x, \pi) = \det D_1 h(x, \pi) = k_1 k_2 (e_0 - c).$$

Then any TPV is a common zero of d and the entries of h. This overdetermined system provides tight restrictions on the parameters.

Proposition 4. *A Tikhonov parameter value of the irreversible Michaelis-Menten system* (12) *satisfies the condition*

$$k_1 k_2 e_0 = 0.$$

Thus, every TPV has the form

$$\pi^* = \begin{pmatrix} 0 \\ k_1^* \\ k_{-1}^* \\ k_2^* \end{pmatrix} \in \Pi, \quad \pi^* = \begin{pmatrix} e_0^* \\ 0 \\ k_{-1}^* \\ k_2^* \end{pmatrix} \in \Pi, \quad \text{or} \quad \pi^* = \begin{pmatrix} e_0^* \\ k_1^* \\ k_{-1}^* \\ 0 \end{pmatrix} \in \Pi.$$

Proof. At a common zero of d, h_1 and h_2 one has $h_1(x,\pi)+h_2(x,\pi) = k_2 c = 0$. If $k_2 \neq 0$ then the slow manifold is necessarily defined by $c = 0$. Using $d(x,\, \pi) = 0$ one finds the asserted relation. □

We have found that (returning to common use of language) e_0, k_1 and k_2 are the only possible "small parameters" for the irreversible Michaelis-Menten system. There remain three cases, each of which is amenable to Tikhnonov-Fenichel reduction, and admits a biochemical interpretation.

- The case $e_0 \to 0$ (corresponding to a TPV with $e_0 = 0$) is most familiar, corresponding to small initial concentration of enzyme. This was discussed extensively; we mention the classical papers by Segel and Slemrod [36], who – assuming quasi-steady state for the complex – via scaling arguments obtained the small parameter ε_S and the earlier paper by Heineken et al. [19], who in a straightforward scaling procedure arrived at ε_H (recall Section 2). In these papers convergence to the solution of a reduced system was shown as $\varepsilon_S \to 0$ (with some restrictions), resp. $\varepsilon_H \to 0$. (The reduction procedure along the lines of Remark 1 is outlined in [15], Example 8.5.)

- The case $k_2 \to 0$ corresponds to slow product formation (and fast formation of complex); this was considered by Michaelis and Menten [30], and also in Schauer and Heinrich [21]. The corresponding reduction was discussed by Noethen [32], Subsection 5.2.4, Boulier et al. [3], Subsection 2.1, and in [15], Example 8.6.

- The case $k_1 \to 0$ admits a biochemical interpretation as well, viz., slow formation of complex. It seems that this has not been discussed explicitly in the literature. (While $k_1 \to 0$ is one of the cases corresponding to $\varepsilon_S \to 0$ in Segel and Slemrod's paper, and the hypotheses of the convergence theorem in [36], Section 6 are satisfied, the form of ε_S given in [36] seems to indicate that the authors did not consider the possibility of small k_1. Indeed, such behavior would be contrary to what is expected from the action of an enzyme.)

It should be emphasized that we arrived at those three cases from just one underlying assumption, i.e., the mathematical interpretation of QSS via Tikhonov

and Fenichel. The rest of the argument leading to Proposition 4 amounts to straightforward mathematics. Our approach recovers the familiar (and less familiar) QSS scenarios, as well as excluding the possibility of others.

Remark 6. The "small parameters" we obtained are not compatible with all the results found in the literature. On the one hand this may be due to our mathematical interpretation of QSS. But on the other hand, some of the heuristics employed in the literature provide only candidates for quasi-steady state, and additional verification is required. Moreover, when system parameters are combined to form a "small parameter" (such as ε_S or ε_H above), it may be necessary to define precisely the way in which the limit (such as $\varepsilon_S \to 0$) is attained. We take a look at some results.

(a) Heineken et al. [19] started from the irreversible Michaelis-Menten equation and scaled the dependent variables via $x := s/s_0$ and $y := c/e_0$, which yields the system

$$\begin{aligned} \dot{x} &= - \quad k_1 e_0 x \quad + \quad e_0(k_1 s_0 x + k_{-1})y \\ \dot{y} &= \quad\; k_1 s_0 x \quad - \quad (k_1 s_0 x + k_{-1} + k_2)y. \end{aligned}$$

Passing to slow time with a (singular) scaling $\tau = k_1 e_0 t$, they obtained a system in standard form for Tikhonov's theorem, with the small parameter $\varepsilon_H = e_0/s_0$. One might infer from this that $s_0 \to \infty$, which implies $\varepsilon_H \to 0$, will induce a reduction via singular perturbation theory. But the variable transformation becomes singular in this limit, hence the results obtained via Tikhonov are not directly transferrable to the original coordinates. Moreover, the initial value $(s_0, 0)$ of (12) leaves any bounded subset of the phase plane as $s_0 \to \infty$; the limit blows up the domain of interest. Finally the right-hand side of the reduced equation in [19] becomes trivial when $s_0 \to \infty$ (see also [15], Subsection 8.4.2).

(b) Segel and Slemrod [36] used a different scaling for c (so there is no blow-up of the relevant region in phase space when $e_0 \to 0$), and they did not assert convergence for the case $s_0 \to \infty$: Although $\varepsilon_S \to 0$ is a consequence of $s_0 \to \infty$ in their setting, the hypotheses of the convergence theorem in [36], Section 6 are not satisfied, since the parameter σ is not bounded when $s_0 \to \infty$.

(c) One example for an insufficient QSS condition obtained by time scale heuristics is the condition $k_{-1}/(e_0 k_1) \to 0$, specifically $k_{-1} \to 0$, for *reverse QSS* in Segel and Slemrod [36], and as a consequence some conditions on *total QSS* in Borghans et al. [4] should be considered with care. As indicated by a numerical example in [14], Section 4, there is no sensible QSS reduction in the limit $k_{-1} \to 0$ whenever the other parameters remain in a compact subset of the open positive orthant.

Of course QSS phenomena may occur outside the framework we are discussing (e.g. when certain parameters approach infinity), but these require a separate analysis.

Continuing the discussion of TPVs for irreversible Michaelis-Menten, we restrict to $\Pi = \mathbb{R}^4_+$ from here on, and consider only nonnegative solutions of the system. We will discuss the second and third of the TPV candidates found in Proposition 4, and the corresponding reduced equations. It should be emphasized that the reduction procedure outlined in Remark 1 is quite sensitive to the choice of "small parameters" (which determines the projection map), hence a case-by-case analysis is in order. Generally a TPV $\pi^* = (e_0^*, k_1^*, k_{-1}^*, k_2^*)^T \in \Pi$ induces a fast-slow decomposition

$$\begin{pmatrix} \dot{s} \\ c \end{pmatrix} = \begin{pmatrix} -k_1^* e_0^* s + (k_1^* s + k_{-1}^*)c \\ k_1^* e_0^* s - (k_1^* s + k_{-1}^* + k_2^*)c \end{pmatrix} + \begin{pmatrix} -k_1^* s & -(e_0^* - c)s & c & 0 \\ k_1^* s & (e_0^* - c)s & -c & -c \end{pmatrix} \begin{pmatrix} e_0 - e_0^* \\ k_1 - k_1^* \\ k_{-1} - k_{-1}^* \\ k_2 - k_2^* \end{pmatrix}$$

with

$$\begin{pmatrix} e_0 - e_0^* \\ k_1 - k_1^* \\ k_{-1} - k_{-1}^* \\ k_2 - k_2^* \end{pmatrix} = \delta \cdot \begin{pmatrix} \varepsilon_0 \\ \kappa_1 \\ \kappa_{-1} \\ \kappa_2 \end{pmatrix}.$$

(Thus we let the curve γ in Proposition 1 be a straight line.)

1. Consider $\pi^* := (e_0^*, 0, k_{-1}^*, k_2^*)^T$. Since

$$D_1 h(x, \pi^*) = \begin{pmatrix} 0 & k_{-1}^* \\ 0 & -(k_{-1}^* + k_2^*) \end{pmatrix}$$

we have the necessary and sufficient condition $k_{-1}^* + k_2^* > 0$ for π^* to be a TPV for dimension one (ensuring the kernel–image decomposition), and the slow manifold is given by $c = 0$ in any case. For the curve

$$\gamma(\delta) = \begin{pmatrix} e_0^* \\ 0 \\ k_{-1}^* \\ k_2^* \end{pmatrix} + \delta \begin{pmatrix} \varepsilon_0 \\ \kappa_1 \\ \kappa_{-1} \\ \kappa_2 \end{pmatrix}$$

in parameter space, a straightforward computation, as outlined in Remark 1, yields the reduced equation

$$\dot{s} = -\frac{\delta \kappa_1 e_0^* k_2^* s}{k_{-1}^* + k_2^*}; \quad c = 0.$$

With Remark 4 we may rewrite this in the more convenient form

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

up to an error of order δ^2, because $k_1 = \delta \kappa_1$ and

$$\gamma_0(\delta) = \begin{pmatrix} e_0^* \\ 0 \\ k_{-1}^* \\ k_2^* \end{pmatrix} + \delta \begin{pmatrix} \varepsilon_0 \\ 0 \\ \kappa_{-1} \\ \kappa_2 \end{pmatrix}$$

is a TPV with slow manifold $c = 0$, for every δ.
The degenerate case $e_0^* = 0$ still yields a TPV, but the right-hand side of the reduced equation is of order δ^2.

2. Now consider $\pi^* := (e_0^*, k_1^*, k_{-1}^*, 0)^T \in \Pi$; here

$$D_1 h(x,\, \pi^*) = \begin{pmatrix} -k_1^*(e_0 - c) & k_1^* s + k_{-1}^* \\ k_1^*(e_0 - c) & -(k_1^* s + k_{-1}^*) \end{pmatrix}$$

and we find the necessary and sufficient condition $k_1^* + k_{-1}^* > 0$ for π^* to be a TPV. The slow manifold is given by $c = k_1^* e_0^* s/(k_1^* s + k_{-1}^*)$. To avoid notational expenditure, we just consider the special curve

$$\gamma(\delta) = \begin{pmatrix} e_0^* \\ k_1^* \\ k_{-1}^* \\ 0 \end{pmatrix} + \delta \begin{pmatrix} 0 \\ 0 \\ 0 \\ \kappa_2 \end{pmatrix}$$

in parameter space, with the reduced equation

$$\dot{s} = -\frac{k_2 e_0 k_1 s(k_1 s + k_{-1})}{k_1 e_0 k_{-1} + (k_1 s + k_{-1})^2}, \quad s \in \mathbb{R}_+,\ c = \frac{k_1 e_0 s}{k_1 s + k_{-1}}.$$

Again degenerate cases occur, e.g. for $k_1 = 0$, which lead to right-hand side $O(\delta^2)$.

An extensive discussion of all Tikhonov parameter values and reductions for the irreversible Michaelis-Menten system is given in [13], Subsection 8.4.2.

At the end of this subsection, we use Tikhonov parameter values of the irreversible system to obtain some TPVs of the reversible system (1) by way of Remark 5. Thus we include a reaction of enzyme and product to complex, but with a small rate constant.

Example. Consider again system (1), i.e.,

$$\dot{x} = h(x, \pi, \rho) := \begin{pmatrix} -k_1 s e_0 + (k_1 s + k_{-1})c \\ k_1 s e_0 - (k_1 s + k_{-1} + k_2)c + k_{-2}(e_0 - c)(s_0 - s - c) \end{pmatrix}$$

in the variable $x = (s, c)^T$, with parameters

$$\pi = (e_0, k_1, k_{-1}, k_2, s_0)^T \in \mathbb{R}^5, \quad \rho = k_{-2} \in \mathbb{R}.$$

The corresponding system with "truncated parameters", viz.

$$\dot{x} = \widehat{h}(x, \pi) := h(x, \pi, 0),$$

is just the irreversible Michaelis-Menten equation (12). (Note that the term containing s_0 vanishes when $k_{-2} = 0$, and we may therefore introduce a "dummy pa-

rameter" s_0.) We obtain the following TPV candidates for reversible Michaelis-Menten:

$$\begin{pmatrix} 0 \\ k_1^* \\ k_{-1}^* \\ k_2^* \\ s_0^* \\ 0 \end{pmatrix}, \quad \begin{pmatrix} e_0^* \\ 0 \\ k_{-1}^* \\ k_2^* \\ s_0^* \\ 0 \end{pmatrix}, \quad \begin{pmatrix} e_0^* \\ k_1^* \\ k_{-1}^* \\ 0 \\ s_0^* \\ 0 \end{pmatrix}.$$

The restrictions found in the the above discussions (e.g. $k_{-1}^* + k_2^* > 0$ for the second candidate) are necessary and sufficient to yield TPVs. We will discuss the reversible Michaelis-Menten system in Section 5 below; the partial information obtained here will then be quite useful.

4 Structure and computation of TPVs

In this section we will specialize to systems (2) with polynomial or rational right-hand side, in view of our focus on reaction equations. Then the natural domain of definition for h is a Zariski-open (hence dense) subset of $\mathbb{R}^n \times \mathbb{R}^m$. We will characterize the set of TPVs, and from an algorithmic point of view we will describe a natural approach to their computation with the help of Groebner bases.

4.1 Special properties of rational systems

We will freely use some properties of affine algebraic varieties and some results from classical commutative algebra and algebraic geometry in this section. A rather concise introduction to the relevant notions and facts can be found in the first chapter of Kunz [26]. For local properties we refer to Shafarevich [38], Ch. II, and for computational issues (in particular, Groebner bases) to Cox, Little and O'Shea [7] as well as the implementation in the algorithmic algebra system SINGULAR; see [8]. The following account may serve as a short overview. Given that the right-hand side of (2) is rational or polynomial, the differential equation is defined on a Zariski-open subset of $\mathbb{R}^m \times \mathbb{R}^n$; i.e., the complement of the common zero set of some polynomials (actually, of one polynomial in this case). Moreover the set of stationary points is given by zeros of polynomials, thus is an (affine) algebraic variety. An algebraic variety is generally not a submanifold, but it is a finite union of submanifolds. (Examples of relevance here include the slow manifolds in reduction scenarios according to Section 3.) More precisely, a variety is a union of finitely many irreducible components, and the simple (or regular) points of each component (characterized by minimal dimension of the tangent space) form a Zariski-open and dense subset which is also a submanifold. For the discussion of zeros of polynomials, ideals are the natural objects. Thus given finitely many polynomials $q_1, \ldots, q_m \in \mathbb{R}[x_1, \ldots, x_n]$, their common zero set $\mathcal{V}(q_1, \ldots, q_m)$ coincides with the common zero set of the ideal

$$\langle q_1, \ldots, q_m \rangle := q_1\mathbb{R}[x_1, \ldots, x_n] + \cdots + q_m\mathbb{R}[x_1, \ldots, x_n].$$

This observation will be used frequently. More facts on varieties and ideals will be recalled below, whenever needed in proofs.

4.2 Structure of the TPV set

For the remainder of this section we will, in addition, assume that the domain under consideration in $\mathbb{R}^{n+m}$, which we call Δ, is a semi-algebraic subset of a Zariski-open set, thus defined by finitely many polynomial equations and polynomial inequalities. This further specialization is natural for applications to reaction equations, due to positivity of rate constants and initial concentrations. We will clarify structural properties of the set of Tikhonov parameter values. Our first observation is a consequence of Proposition 2.

Lemma 1. *Let $(x_0, \pi^*) \in \Delta$ be such that $h(x_0, \pi^*) = 0$, and let the characteristic polynomial of $D_1 h(x_0, \pi^*)$ be given by (6). Then $\pi^* \in \Pi$ is a Tikhonov parameter value for dimension s, and x_0 lies in the local slow manifold of π^*, only if the following hold.*

(i) One has $\sigma_0(x_0, \pi^*) = \cdots = \sigma_{s-1}(x_0, \pi^*) = 0$.

(ii) The polynomial

$$\widetilde{\chi}(\tau) = \tau^{n-s} + \sigma_{n-1}(x_0, \pi^*)\tau^{n-s-1} + \cdots + \sigma_s(x_0, \pi^*)$$

has only zeros with negative real part.

The points of Δ satisfying (i) and (ii) are defined by polynomial equations and inequalities (Routh-Hurwitz conditions for $\widetilde{\chi}$; cf. Gantmacher [12], Ch. V, §6). In particular they form a semi-algebraic subset of Δ.

The conditions in this Lemma are not sufficient for a TPV, as shown by the following example.

Example. Consider the parameter-dependent equation

$$\dot{x} = h(x, \alpha) := \begin{pmatrix} \alpha x_1 \\ x_1^2 - x_2^2 \end{pmatrix} \text{ on } \mathbb{R}^2$$

with $\alpha \in \mathbb{R}$. Then for any $\alpha < 0$ and $x_0 = 0$ the conditions of Lemma 1 are satisfied, but α is not a TPV for dimension 1, since the only stationary point 0 is isolated.

However, additional conditions ensure sufficiency; see [34], Prop. 2.2 or [29], Thm. 15 and Cor. 16 for proofs.

Lemma 2. *Let $(x_0, \pi^*) \in \Delta$ satisfy the conditions in Lemma 1. Then π^* is a TPV for dimension s, and x_0 in the local slow manifold of π^*, if and only if the system $\dot{x} = h(x, \pi^*)$ admits s functionally independent analytic (or formal) first integrals in a neighborhood of x_0. The lowest-degree terms of these first integrals may be chosen as (linearly independent) linear forms in $x - x_0$.*

Assuming $h(x_0, \pi^*) = 0$ we have a Taylor expansion with respect to $y := x - x_0$:

$$h(x, \pi^*) = \sum_{k \geq 1} h_k(x_0, \pi^*, y), \tag{13}$$

with h_k homogeneous of degree k in y, and in particular $h_1(x_0, \pi^*, y) = Dh(x_0, \pi^*)y$. Every h_k is rational in (x_0, π^*), since h is rational. A (formal) power series

$$\psi(y) = \sum_{j \geq 0} \psi_j(y), \quad \psi_j \text{ homogeneous of degree } j$$

is a first integral of h near $y = 0$ if and only if

$$L_h(\psi)(y) := D\psi(y)\, h(x_0, \pi^*, y) = 0,$$

equivalently if

$$\sum_{j=1}^{k} L_{h_j}(\psi_{k-j}) = 0 \text{ for all } k,$$

as follows from considering homogeneous parts with respect to y.

Definition 2. *Let h be rational, $(x_0, \pi^*) \in \mathcal{V}(h)$, and $d \geq 1$. Denote by S_k the space of homogeneous polynomials of degree k in y, and define the linear map*

$$L_h^{(d)} : S_1 + \cdots + S_d \to S_1 + \cdots + S_d$$

by sending $\psi = \psi_1 + \cdots + \psi_d$ to the truncation of $L_h(\psi)$ at degree d.

Proposition 5. *Let $(x_0, \pi^*) \in \Delta$ satisfy the conditions in Lemma 1.*

(a) The kernel of $L_h^{(d)}$ has dimension at most equal to

$$\vartheta_{s,d} := \sum_{j=1}^{d} \binom{s+j-1}{j}$$

(b) There exist s independent first integrals for $\dot{x} = h(x, \pi^*)$ near x_0 if and only if

$$\dim \operatorname{Ker} L_h^{(d)} = \vartheta_{s,d} \quad \text{for all } d \geq 1.$$

Proof. We abbreviate $B := D_1 h(x_0, \pi^*)$. Analogously to Definition 2 we also have maps

$$L_B^{(d)} : S_1 + \cdots + S_d \to S_1 + \cdots + S_d.$$

Let $\lambda_1 = \cdots = \lambda_s = 0$, $\lambda_{s+1}, \ldots, \lambda_n$ be the eigenvalues of B (in the complexification), counted according to their algebraic multiplicity. Let $\omega_1, \ldots, \omega_n$ be linearly independent linear forms such that the matrix of $L_B^{(1)}$ with respect to

this basis is in Jordan canonical form, with $\lambda_1, \ldots, \lambda_n$ on the diagonal. Then the monomials

$$\omega_1^{m_1} \cdots \omega_n^{m_n}; \quad m_1, \ldots, m_n \in \mathbb{Z}_{\geq 0} \text{ and } 0 < \sum m_i \leq d$$

form a basis of $S_1 + \cdots + S_d$, and with a suitable ordering (which in particular respects the degree), the matrix of $L_B^{(d)}$ with respect to this basis is in triangular form. (See, for instance, the argument in Bruno [6], Ch. III, 1.3.) Now L_{h_k}, with $k > 1$, maps S_j to S_{j+k-1}, therefore the matrix of $L_h^{(d)}$ with respect to the given basis and ordering is also triangular, and its eigenvalues (counted with multiplicity) are

$$m_1\lambda_1 + \cdots + m_n\lambda_n,$$

with $(m_1, \ldots, m_n)$ running through all tuples of nonnegative integers with $0 < \sum m_i \leq d$. Since the λ_i with $i > s$ have real part < 0, we have

$$m_{s+1}\lambda_{s+1} + \cdots + m_n\lambda_n \neq 0 \text{ whenever } m_{s+1} + \cdots + m_n > 0.$$

Thus only tuples of the form $(m_1, \ldots, m_s, 0, \ldots, 0)$ correspond to eigenvalue zero for $L_h^{(d)}$, hence its algebraic multiplicity is less than or equal to $\vartheta_{s,d}$. This proves part (a). As for part (b), first let $\dot{x} = h(x, \pi^*)$ admit s independent first integrals $\phi_1, \ldots, \phi_s$. We may assume that $\phi_j = \omega_j + \cdots$, with linearly independent $\omega_1, \ldots, \omega_s$. Then for every tuple $(m_1, \ldots, m_s)$,

$$\phi_1^{m_1} \cdots \phi_s^{m_s} = \omega_1^{m_1} \cdots \omega_s^{m_s} + \cdots$$

is a first integral of $\dot{x} = h(x, \pi^*)$, and its truncation at degree d lies in the kernel of $L_h^{(d)}$. Therefore the dimension of the kernel equals $\vartheta_{s,d}$. Conversely, assume that $\dim \operatorname{Ker} L_h^{(d)} = \vartheta_{s,d}$ for all d. Then for every d there exist

$$\phi_1^{(d)} = \omega_1 + \cdots \in \operatorname{Ker} L_h^{(d)}, \ldots, \phi_s^{(d)} = \omega_s + \cdots \in \operatorname{Ker} L_h^{(d)},$$

and one may choose every $\phi_j^{(d)}$ as truncation of $\phi_j^{(d+1)}$. This implies the existence of formal first integrals with initial terms $\omega_1, \ldots, \omega_s$, respectively.

□

Theorem 1. *Let $(x_0, \pi^*) \in \Delta$ satisfy the conditions in Lemma 1.*

(a) There exist finitely many polynomials in (x, π) with the following property: The parameter value π^* is a TPV of system (2) for dimension s, with x_0 in the local slow manifold of π^*, if and only if these polynomials vanish at (x_0, π^*). In particular, all such (x_0, π^*) form a semialgebraic subset of Δ.

(b) The Tikhonov parameter values of (2) for dimension s form a semialgebraic subset of $\mathbb{R}^m$.

Proof. Choose the basis of $S_1 + \cdots + S_d$ which consists of monomials in the y_j. The matrix of $L_h^{(d)}$ with respect to this basis has entries which are rational functions of (x_0, π^*) and is of size

$$\vartheta_{n,d} = \sum_{j=1}^{d} \binom{n+j-1}{j}.$$

The dimension of its kernel equals $\vartheta_{s,d}$ if and only if all minors of size $\vartheta_{n,d} - \ell$, $0 \leq \ell < \vartheta_{s,d}$ vanish. These conditions provide finitely many polynomials in (x, π) that must vanish at (x_0, π^*). Running through all d will provide necessary and sufficient conditions in view of Proposition 5, and finitely many of these polynomial conditions suffice, due to Hilbert's *Basissatz* (cf. Kunz [26]). In conjunction with Lemma 1, this argument proves part (a). Part (b) is a direct consequence of the Tarski-Seidenberg theorem (cf. e.g. Bierstone and Pierre [2], Thm. 1.5), which in particular states that the projection from $\mathbb{R}^n \times \mathbb{R}^m$ to the second component sends semialgebraic sets to semialgebraic sets. □

4.3 An algorithmic approach

In this subsection we further restrict attention to systems (2) with polynomial right-hand side. An extension to rational right-hand side is straightforward, but for the present account the extra expenditure (regarding notation and some case-by-case analysis) would seem too high.

A systematic determination of Tikhonov parameter values is obtained by employing some commutative algebra. Recall that we are interested in the zeros of $h(x, \pi)$, possibly augmented by some minors of $D_1 h(x, \pi)$; thus we consider the ideal generated by these polynomials. The following observation is our starting point; see Cox, Little, O'Shea [7], pp. 24–26 for a proof. (A Groebner basis of an ideal – with respect to a chosen monomial term order – is a special set of generators; see [7]. For the purpose of the following the relevant fact is that a Groebner basis can be determined algorithmically from any finite generator set. All computations in the following examples were performed with the help of SINGULAR.)

Lemma 3. *Consider a polynomial map*

$$Q : \mathbb{R}^n \times \mathbb{R}^m \to \mathbb{R}^p, (x, \pi) \mapsto \begin{pmatrix} q_1(x, \pi) \\ \vdots \\ q_p(x, \pi) \end{pmatrix}.$$

and the ideal $\mathcal{I}$ generated by the q_i in $\mathbb{R}[x, \pi]$.

(a) If (x_0, π^*) is a zero of Q (equivalently, of $\mathcal{I}$) then π^* is a zero of the elimination ideal $\mathcal{I} \cap \mathbb{R}[\pi]$.

(b) Given the lexicographic order on the variables $(x_1, \ldots, x_n, \pi_1, \ldots, \pi_m)$, a Groebner basis of $\mathcal{I} \cap \mathbb{R}[\pi]$ is obtained by intersecting $\mathbb{R}[\pi]$ with a Groebner basis of $\mathcal{I}$.

We note a direct consequence of this Lemma and Proposition 2.

Proposition 6. *Let $\pi^* \in \Pi$ be a TPV of the polynomial system* (2) *for dimension s, $1 \leq s \leq n-1$. Let $\gamma_1, \ldots, \gamma_{\ell_s} \in \mathbb{R}[x, \pi]$ denote all the $k \times k$ minors of $D_1 h(x, \pi)$, $n \geq k > n - s$, and let*

$$\mathcal{I} = \langle h_1, \ldots, h_n, \gamma_1, \ldots, \gamma_{\ell_s} \rangle \subseteq \mathbb{R}[x, \pi].$$

Then π^* is a zero of the elimination ideal $\mathcal{I}_\pi = \mathcal{I} \cap \mathbb{R}[\pi]$.

As noted earlier, it would suffice to include only the minors of size $n-s+1$ in the generator set, but using redundant information is sometimes helpful. Thus one may obtain weaker (but possibly more accessible) conditions by considering ideals that are generated by subsets of $h_1, \ldots, h_n, \gamma_1, \ldots, \gamma_{\ell_s}$; for instance:

Corollary. *Let the polynomial system* (2) *be given, and denote by*

$$\mathcal{J} = \langle h_1, \ldots, h_n, \det D_1 h(x, \pi) \rangle$$

the ideal generated by the entries of h and its Jacobian determinant. Then for every $s \geq 1$, a TPV π^* of system (2) *for dimension s is a zero of $\mathcal{J}_\pi := \mathcal{J} \cap \mathbb{R}[\pi]$.*

The above results yield necessary criteria for TPVs, which may be taken as a vantage point for further analysis. To illustrate the approach, we revisit the irreversible Michaelis-Menten system from an algorithmic perspective.

Example. Consider the irreversible Michaelis-Menten equation (12). The components h_1 and h_2 of h and their Jacobian determinant d generate the ideal

$$\mathcal{I} = \langle h_1, h_2, d \rangle,$$

in $\mathbb{R}[x, \pi]$. With respect to lexicographic order, SINGULAR will find the reduced Groebner basis

$$\begin{aligned} g_1(x, \pi) &= e_0 k_1 k_2, \\ g_2(x, \pi) &= k_2 c, \\ g_3(x, \pi) &= -k_1 s e_0 + (k_1 s + k_{-1}) c, \end{aligned}$$

with the elimination ideal $\mathcal{I}_\pi = \mathcal{I} \cap \mathbb{R}[\pi]$ generated by g_1. We thus have recovered Proposition 4, with a straightforward algorithmic proof.

Remark 7. One may use a variant of Proposition 6 for the matrix representations of $L_h^{(d)}$ (see Definition 2 and Proposition 5) to obtain necessary and sufficient conditions for TPVs, at least in principle. Indeed, assuming the conditions in Lemma 1, the kernel dimension equals $\vartheta_{s,d}$ if and only if certain determinants vanish. By Lemma 2, Proposition 5 and Hilbert's *Basissatz*, there is a finite (albeit a priori unknown) d^* so that the determinant conditions for $d = d^*$ imply the determinant conditions for all d, hence necessary and sufficient conditions for a TPV. (We will not discuss feasibility here.) Thus the procedure may be called pseudo-algorithmic: It terminates but there is no criterion at which point termination takes place.

To close this section, we note that the approach outlined in Proposition 6 ff. should not be seen as an exclusive path. For instance some combination of variables and parameters may be eliminated, thus providing partial information on the slow manifold. As a case in point we refer to the proof of Proposition 4, which actually starts by eliminating e_0, k_1, k_{-1} and s. Similar arguments will be used below.

5 Applications

The following applications both illustrate the efficiency (and feasibility) of our approach and provide relevant information about the reaction networks under consideration. When determining Tikhonov parameter values we will mostly use partial information obtained by methods from the previous section to obtain candidates, and then directly verify the TPV property.

5.1 Reversible Michaelis-Menten

We return to the reversible Michaelis-Menten system (1), and will determine all TPVs for this equation. Some information from Subsection 3.5 (in particular the last example) will be used. The entries of the right-hand side of (1) and the Jacobian determinant are given by

$$\begin{aligned} h_1(x,\pi) &= -k_1e_0s + (k_1s + k_{-1})c, \\ h_2(x,\pi) &= k_1e_0s - (k_1s + k_{-1} + k_2)c + k_{-2}(e_0 - c)(s_0 - s - c), \\ d(x,\pi) &= (e_0 - c)(k_1k_{-2}(2c - e_0 - s_0) - k_1k_2 - k_{-1}k_{-2}), \end{aligned}$$

with parameter tuple $(e_0, k_1, k_{-1}, k_2, s_0, k_{-2})^T \in \mathbb{R}^6_+$. We restrict attention to nonnegative parameters. The determinant factorizes, and this observation, together with positivity arguments, is the key to proving the following result.

Proposition 7. *Every Tikhonov parameter value of system* (1) *belongs to one of the following types:*

$$\begin{pmatrix} 0 \\ k_1^* \\ k_{-1}^* \\ k_2^* \\ s_0^* \\ k_{-2}^* \end{pmatrix}, \quad \begin{pmatrix} e_0^* \\ k_1^* \\ 0 \\ 0 \\ s_0^* \\ k_{-2}^* \end{pmatrix}, \quad \begin{pmatrix} e_0^* \\ 0 \\ 0 \\ k_2^* \\ s_0^* \\ k_{-2}^* \end{pmatrix}, \quad \begin{pmatrix} e_0^* \\ 0 \\ k_{-1}^* \\ k_2^* \\ s_0^* \\ 0 \end{pmatrix}, \quad \begin{pmatrix} e_0^* \\ k_1^* \\ k_{-1}^* \\ 0 \\ s_0^* \\ 0 \end{pmatrix}.$$

Proof. The Jacobian determinant is a product of two terms.

(i) If $e_0 - c = 0$ then $h_2 = -(k_{-1} + k_2)e_0$, thus $h_2 = 0$ forces either $e_0 = 0$ or $k_{-1} = k_2 = 0$. This corresponds to the first two parameter tuples in the list.

(ii) An auxiliary result: The four-dimensional system corresponding to the reversible Michaelis-Menten reaction scheme (for concentrations s, c, e and p) admits the linear first integrals $e+c$ and $s+c+p$. In view of the initial values one sees $e+c=e_0$ and $s+c+p=s_0$, and with positivity this yields a forward invariant set defined by $0 \leq c \leq e_0, \quad c \leq s_0$, which contains the semi-trajectories of interest to us. Within this set one has

$$2c - e_0 - s_0 \leq 0,$$

whence every summand in the second factor of $d(x,\pi)$ is ≤ 0. Thus the second factor vanishes if and only if every summand vanishes.

(iii) From $2c-e_0-s_0=0$ one obtains $c=e_0$ in particular, and we are back at case (i). Otherwise, one has $k_1 k_{-2}=0$, and taking the second and third summand into account one obtains the cases

$$\begin{array}{lll} k_1 = 0 & \text{and} & k_{-1} = 0; \\ k_1 = 0 & \text{and} & k_{-2} = 0; \\ k_{-2} = 0 & \text{and} & k_2 = 0. \end{array}$$

These correspond to the remaining tuples listed.

□

The Proposition provides only necessary conditions, but one can verify that each "generic" parameter tuple listed (i.e. all entries are > 0 unless explicitly set $= 0$) is in fact a TPV of the system. For the last two tuples this is a direct consequence of Subsection 3.5. Moreover, all these parameter values admit a biochemical interpretation (of varying relevance in applications).

(i) The case $e_0 \to 0$ (corresponding to a TPV with $e_0 = 0$) represents small initial concentration of enzyme.

(ii) The case $k_{-1} \to 0$, $k_2 \to 0$ corresponds to slow degradation of complex, in both directions.

(iii) The case $k_1 \to 0$, $k_{-1} \to 0$ represents slow formation of complex from enzyme and substrate, as well as slow degradation of complex to enzyme and substrate.

(iv) The case $k_1 \to 0$, $k_{-2} \to 0$ corresponds to slow formation of complex, from both directions.

(v) The case $k_2 \to 0$, $k_{-2} \to 0$ represents slow formation of complex from enzyme and product, as well as slow degradation of complex to enzyme and product.

We discuss the reduction procedure for case (iv) in this list.

Example. Consider the curve

$$\gamma(\delta) = \begin{pmatrix} e_0^* \\ 0 \\ k_{-1}^* \\ k_2^* \\ 0 \\ s_0^* \end{pmatrix} + \delta \cdot \begin{pmatrix} 0 \\ \kappa_1 \\ 0 \\ 0 \\ \kappa_{-2} \\ 0 \end{pmatrix}$$

in parameter space, with all parameters > 0 unless explicitly set $= 0$. Then

$$h(x, \gamma(\delta)) = \begin{pmatrix} k_{-1}c \\ -(k_{-1} + k_2)c \end{pmatrix} + \delta \cdot \begin{pmatrix} -\kappa_1(e_0 - c)s \\ \kappa_1(e_0 - c)s + \kappa_{-2}(e_0 - c)(s_0 - s - c) \end{pmatrix}.$$

A decomposition according to Remark 1 is given by

$$h(x, \gamma(0)) = \begin{pmatrix} k_{-1} \\ -(k_{-1} + k_2) \end{pmatrix} \cdot c,$$

with the slow manifold determined by $c = 0$. A straighforward calculation, using (5), yields the reduced equation

$$\dot{s} = \delta \frac{e_0^* s}{k_{-1}^* + k_2^*} \cdot \left(-\kappa_1 k_2^* s + \kappa_{-2} k_{-1}^* (s_0 - s)\right)$$

(and $\dot{c} = 0$).

5.2 Competitive inhibition

The reaction scheme of competitive inhibition augments the irreversible Michaelis-Menten reaction (enzyme-substrate complex C_1) with a reversible formation of enzyme-inhibitor complex C_2; see for instance Keener and Sneyd [24]. Thus

$$\begin{array}{rcccl} E + S & \rightleftharpoons & C_1 & \rightharpoonup & E + P, \\ E + I & \rightleftharpoons & C_2. & & \end{array}$$

Mass action kinetics and stoichiometry lead to a differential equation with variables $x = (s, c_1, c_2)^T \in \mathbb{R}^3$ and parameters

$$\pi = (e_0, k_1, k_{-1}, k_2, k_3, k_{-3}, i_0)^T \in \mathbb{R}^7;$$

the entries of the right-hand side are

$$\begin{array}{ll} h_1(x, \pi) & = k_{-1}c_1 - k_1 s(e_0 - c_1 - c_2), \\ h_2(x, \pi) & = k_1 s(e_0 - c_1 - c_2) - (k_{-1} + k_2)c_1, \\ h_3(x, \pi) & = k_3(e_0 - c_1 - c_2)(i_0 - c_2) - k_{-3}c_2, \end{array} \tag{14}$$

with Jacobian

$$d(x, \pi) = -k_1 k_2 (e_0 - c_1 + c_2)(k_{-3} + k_3(i_0 + e_0) - k_3(2c_2 - c_1)).$$

The h_k and d generate an ideal $\mathcal{I}$ in $\mathbb{R}[x, \pi]$. We proceed according to Proposition 6 and its Corollary.

Proposition 8. *For system* (14)*, with nonnegative parameter values, every Tikhonov parameter value belongs to one of the following classes.*

$$\pi_1^* = \begin{pmatrix} 0 \\ k_1^* \\ k_{-1}^* \\ k_2^* \\ k_3^* \\ k_{-3}^* \\ i_0^* \end{pmatrix}, \quad \pi_2^* = \begin{pmatrix} e_0^* \\ 0 \\ k_{-1}^* \\ k_2^* \\ k_3^* \\ k_{-3}^* \\ i_0^* \end{pmatrix}, \quad \pi_3^* = \begin{pmatrix} e_0^* \\ k_1^* \\ k_{-1}^* \\ 0 \\ k_3^* \\ k_{-3}^* \\ i_0^* \end{pmatrix}, \quad \pi_4^* = \begin{pmatrix} e_0^* \\ k_1^* \\ k_{-1}^* \\ k_2^* \\ k_3^* \\ 0 \\ i_0^* \end{pmatrix} \in \mathbb{R}_+^7.$$

For each of the tuples listed, some parameter ranges represent a TPV.

Proof. Elimination of the variables x in a Groebner basis of $\mathcal{I}$ yields the ideal $\mathcal{I}_\pi$ with a single generator, viz.,

$$\mathcal{I}_\pi = \langle e_0 k_1 k_2 k_{-3}(k_3^2(e_0 - i_0)^2 + k_{-3}(k_{-3} + 2k_3(e_0 + i_0)))\rangle.$$

For a TPV π^* one factor of the generator must vanish. The first four factors provide the candidates listed in the statement above. The last factor (due to nonnegativity) vanishes only when $k_{-3} = 0$, and this case is included in the previous ones. Inspection of the zero sets of $h(x, \pi^*)$ and of the matrices $D_1 h(x, \pi^*)$ shows the last assertion. □

The reduction for the TPV π_1^* was given in [14], including the reversible case.

Remark 8. The conditions in the Proposition must be satisfied for any TPV; generically they describe TPVs for dimension $s = 1$. The additional conditions for $s = 2$ (involving all 2×2-minors) are as follows.

$$\begin{aligned}
\theta_1 &= k_1 k_2 (e_0 - c_1 - c_2), \\
\theta_2 &= k_1 k_2 s, \\
\theta_3 &= k_1 k_3 (e_0 - c_1 - c_2), \\
\theta_4 &= k_1 (e_0 - c_1 - c_2)(k_3(e_0 + i_0 - c_1 - 2c_2) + k_{-3}), \\
\theta_5 &= k_2 (k_3(e_0 + i_0 - c_1 - 2c_2) + k_{-3}), \\
\theta_6 &= (k_1 s + k_{-1})(k_3(e_0 + i_0 - c_1 - 2c_2) + k_{-3}) + k_1 k_3 s.
\end{aligned}$$

All the conditions in the Proposition admit a natural biochemical interpretation. We will look at two scenarios in some detail.

Example. The case $k_{-3} \to 0$ corresponds to slow degradation of the enzyme-inhibitor complex. We will also assume that $i_0^* > e_0^*$ (the case $i_0^* < e_0^*$ yields a weak TPV but not a TPV). The slow manifold W is determined by $c_1 = 0$ and

$c_2 = e_0^*$; see the conditions for $h_3 = 0$. We consider the curve

$$\begin{pmatrix} e_0^* \\ k_1^* \\ k_{-1}^* \\ k_2^* \\ k_3^* \\ 0 \\ i_0^* \end{pmatrix} + \delta \cdot \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ \kappa_{-3} \\ 0 \end{pmatrix}$$

in parameter space, with all parameter values assumed > 0 unless explicitly set $= 0$. At $\pi = \pi^*$ we have a decomposition

$$h = P \cdot \mu; \quad P = \begin{pmatrix} k_{-1}^* & -k_1^* s \\ -(k_{-1}^* + k_2^*) & k_1^* s \\ 0 & k_3^*(i_0^* - c_2) \end{pmatrix}, \quad \mu = \begin{pmatrix} c_1 \\ e_0^* - c_1 - c_2 \end{pmatrix}$$

Furthermore, on the slow manifold W routine calculations show that

$$D\mu \cdot P = \begin{pmatrix} -(k_{-1}^* + k_2^*) & k_1^* s \\ k_{-1}^* + k_2^* & -k_1^* s - k_3^*(i_0^* - e_0^*) \end{pmatrix}$$

with determinant

$$\rho = (k_{-1}^* + k_2^*) k_3^* (i_0^* - e_0^*),$$

and projection matrix

$$I_3 - P \cdot (D\mu \cdot P)^{-1} \cdot D\mu = \begin{pmatrix} 1 & -k_1^* k_3^* (i_0^* - e_0^*)/\rho & -k_1^* k_2^* s/\rho \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}$$

To obtain the reduced system, this projection matrix is applied to

$$\delta \cdot \begin{pmatrix} 0 \\ 0 \\ \kappa_{-3} e_0^* \end{pmatrix}$$

and thus (replacing $\delta\kappa_{-3}$ by k_{-3}, k_1^* by k_1 and so on, for notational convenience) one arrives at the reduced equation

$$\dot{s} = -\frac{k_1 k_2 k_{-3} e_0 s}{(k_{-1} + k_2) k_3 (i_0 - e_0)}$$

(together with $\dot{c}_1 = \dot{c}_2 = 0$) on W.

Example. We discuss a TPV for dimension $s = 2$, viz.,

$$\pi^* = (e_0^*, 0, 0, 0, k_3^*, k_{-3}^*, i_0^*)^T \in \mathbb{R}_+^7.$$

In other words, we have $k_1 = k_{-1} = k_2 = 0$; the biochemical interpretation is that all reactions in the Michaelis-Menten subnetwork are slow. At π^* one has $h_1 = h_2 = 0$, and

$$h_3 = \sigma := k_3^*(e_0^* - c_1 - c_2)(i_0^* - c_2) - k_{-3}^* c_2.$$

The slow manifold is a parabolic cylinder given by $\sigma = 0$; one may rewrite this as

$$c_1 = e_0^* - c_2 - \frac{k_{-3}^* c_2}{k_3^*(i_0^* - c_2)}.$$

Choosing a straight line

$$\gamma(\delta) = \begin{pmatrix} e_0^* \\ 0 \\ 0 \\ 0 \\ k_3^* \\ k_{-3}^* \\ i_0^* \end{pmatrix} + \delta \cdot \begin{pmatrix} 0 \\ \kappa_1 \\ \kappa_{-1} \\ \kappa_2 \\ 0 \\ 0 \\ 0 \end{pmatrix}$$

in parameter space, one has

$$h = \begin{pmatrix} 0 \\ 0 \\ \sigma \end{pmatrix} + \delta \cdot \begin{pmatrix} \kappa_{-1} c_1 - \kappa_1 s(e_0^* - c_1 - c_2) \\ -(\kappa_{-1} + \kappa_2) c_1 + \kappa_1 s(e_0^* - c_1 - c_2) \\ 0 \end{pmatrix},$$

and at $\pi = \pi^*$ there is a decomposition

$$h = P \cdot \mu, \text{ with } P = \begin{pmatrix} 0 \\ 0 \\ 1 \end{pmatrix}, \quad \mu = \sigma.$$

Straightforward computations yield

$$D\mu \cdot P = -\rho := -\left(k_3^*(e_0^* + i_0^* - c_1 - 2c_2) + k_{-3}^*\right)$$

and the projection matrix

$$I_3 - P \cdot (D\mu \cdot P)^{-1} \cdot D\mu = \begin{pmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & -k_3^*(i_0^* - c_2)/\rho & 0 \end{pmatrix}$$

which in turn yields the reduced system

$$\begin{pmatrix} \dot{s} \\ \dot{c}_1 \\ \dot{c}_2 \end{pmatrix} = \delta \cdot \begin{pmatrix} \kappa_{-1} c_1 - \kappa_1 s(e_0^* - c_1 - c_2) \\ -(\kappa_{-1} + \kappa_2) c_1 + \kappa_1 s(e_0^* - c_1 - c_2) \\ (k_3^*(i_0^* - c_2)/\rho) \cdot ((\kappa_{-1} + \kappa_2) c_1 - \kappa_1 s(e_0^* - c_1 - c_2)) \end{pmatrix}$$

on W. Substituting the expression for c_1 from $\sigma = 0$, one finds the following planar system for s and c_2. (For notational convenience, we omit the asterisks and set $k_1 = \delta\kappa_1$, etc.)

$$\begin{aligned} \dot{s} &= k_{-1}(e_0 - c_2) - (k_1 s + k_{-1})\tfrac{k_{-3}c_2}{k_3(i_0 - c_2)} \\ \dot{c}_2 &= \theta \cdot \Big((k_{-1} + k_2)(e_0 - c_2) - (k_1 s + k_{-1} + k_2)\tfrac{k_{-3}c_2}{k_3(i_0 - c_2)}\Big) \end{aligned}$$

with

$$\theta = \frac{k_3(i_0 - c_2)^2}{k_3(i_0 - c_2)^2 + k_{-3}i_0}.$$

A straightforward discussion of this system shows the following. With c_2^* the smaller root of

$$\tau(c_2) = k_3(e_0 - c_2)(i_0 - c_2) - k_{-3}c_2,$$

the subset of the phase plane defined by $s \geq 0$, $0 \leq c_2 \leq c_2^*$ is forward invariant for the system, and every solution in this set converges to the stationary point $(0, c_2^*)^T$. Thus, for instance c_2^* indicates the amount of enzyme bound to inhibitor in equilibrium, and the degradation rate for s is eventually given by $k_1 k_{-3} c_2^*/(k_3(i_0 - c_2^*))$.

5.3 A Field-Noyes model

Finally we consider a Field-Noyes model [11] as discussed in Murray [31], Ch. 8. The reaction scheme is

$$\begin{array}{llll} A + Y \rightharpoonup X + P, & & X + Y \rightharpoonup 2P, & \\ A + X \rightharpoonup 2X + 2Z, & 2X \rightharpoonup A + P, & Z \rightharpoonup fY & \end{array}$$

for some $f \geq 0$. (This is to be understood as compounding a larger set of elementary reactions.) The usual procedure, together with the additional assumption that a is constant ([31], p. 260) yields a three-dimensional differential equation

$$\begin{aligned} \dot{x} &= k_1 a y - k_2 x y + k_3 a x - k_4 x^2 \\ \dot{y} &= -k_1 a y - k_2 x y + f k_5 z \\ \dot{z} &= 2k_3 a x - k_5 z \end{aligned} \tag{15}$$

(omitting the equation for p).

Proposition 9. *For system* (15)*, with nonnegative parameters*

$$\pi = (k_1, k_2, k_3, k_4, k_5, a, f)^T,$$

every Tikhonov parameter value belongs to one of the following classes.

$$\pi_1^* = \begin{pmatrix} 0 \\ k_2^* \\ k_3^* \\ k_4^* \\ k_5^* \\ a^* \\ f^* \end{pmatrix}, \pi_2^* = \begin{pmatrix} k_1^* \\ k_2^* \\ 0 \\ k_4^* \\ k_5^* \\ a^* \\ f^* \end{pmatrix}, \pi_3^* = \begin{pmatrix} k_1^* \\ k_2^* \\ k_3^* \\ k_4^* \\ 0 \\ a^* \\ f^* \end{pmatrix}, \pi_4^* = \begin{pmatrix} k_1^* \\ k_2^* \\ k_3^* \\ k_4^* \\ k_5^* \\ 0 \\ f^* \end{pmatrix}, \pi_5^* = \begin{pmatrix} k_1^* \\ 0 \\ k_3^* \\ 0 \\ k_5^* \\ a^* \\ f^* \end{pmatrix}.$$

Proof. Eliminating the variables x in a Groebner basis of the ideal $\mathcal{I}$ (generated by the entries of (15) and their Jacobian determinant) yields the ideal $\mathcal{I}_\pi$ with a single generator

$$k_1 k_3^2 k_5 a^3 \left(k_1^2 k_4^2 + (2+12f) k_1 k_2 k_3 k_4 + k_2^2 k_3^2 (2f-1)^2\right) (2f+1)^2.$$

For a TPV π^* one of the factors must vanish. The first four factors provide the first four candidates listed above. Due to nonnegativity of parameters, the last factor is always > 0, while the fifth term is equal to zero only if all three summands equal zero. The only two cases not included in previous ones are characterized by $k_2 = k_4 = 0$ (which yields π_5^*), or by $k_4 = 2f - 1 = 0$. Direct inspection of (15) in the latter case shows that the system admits non-isolated stationary points only if $k_1 k_3 k_5 a = 0$. □

Not all the candidates listed in the Proposition correspond to TPVs; for instance π_1^* is a weak TPV but not a TPV, and π_2^* is not a TPV (or weak TPV) when all entries except the third are > 0, but $k_4^* = 0$ will yield a TPV, with slow manifold given by $y = z = 0$. We will refrain from an exhaustive analysis here, and just discuss one case.

Example. Let $\pi^* = (k_1^*, 0, k_3^*, 0, k_5^*, 0, f^*)^T$. This is a TPV with slow manifold given by $z = 0$. One may interpret this scenario as a strong version of QSS for the variable x (with x being a first integral of the system at π^*). The right-hand side of (15) reduces to

$$\begin{pmatrix} 0 \\ f^* k_5 z \\ -k_5^* z \end{pmatrix} = \begin{pmatrix} 0 \\ f^* k_5 \\ -k_5^* \end{pmatrix} \cdot z,$$

with projection matrix

$$Q = \begin{pmatrix} 1 & 0 & 0 \\ 0 & 1 & f \\ 0 & 0 & 0 \end{pmatrix}.$$

Letting

$$\gamma(\delta) = \pi^* + \delta \ (0, \kappa_2, 0, \kappa_4, 0, \alpha, 0)^T$$

and abbreviating $k_1 := k_1^*$, $k_2 := \delta\kappa_2$ etc., one arrives at the two-dimensional differential equation

$$\begin{array}{rcllll} \dot{x} & = & k_3 a x & +k_1 a y & -k_2 x y & -k_4 x^2 \\ \dot{y} & = & 2f k_3 a x & -k_1 a y & -k_2 x y & \end{array}$$

This system admits a discussion by standard phase plane techniques. Assuming that all parameters are > 0, and letting

$$x^* := \max\left\{\frac{k_3}{k_4}, \frac{k_1}{k_2}\right\} \cdot a, \quad y^* := \frac{2f k_3}{k_1} x^*,$$

one verifies that the compact set defined by

$$0 \le x \le x^*, \quad 0 \le y \le y^*$$

is positively invariant for the system (and attracts all solutions starting in the positive quadrant). There is always exactly one stationary point in the positive quadrant, in addition to the unstable stationary point 0. This interior stationary point is always linearly asymptotically stable. In case $k_1 \geq k_3$, the trace

$$(k_3 - k_1)a - (k_1 + 2k_4)x - k_2 y$$

of the Jacobian is always negative, hence there can be no limit cycle due to Bendixson's criterion, and the positive stationary point is a global attractor. With more effort, this can also be shown for the remaining case.
(The discussion in Murray [31], Sections 8.4 and 8.5 covers a different parameter range; so no compatibility should be expected.)

To summarize, the examples discussed here are quite amenable to the methods developed in the previous section, and computations take little effort. Naturally, for systems with a higher number of variables or parameters, the analysis will become more cumbersome. But still, the method introduced in the present paper seems considerably less involved than the established approaches in the literature.

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