Quasi-steady state – Intuition, perturbation theory and algorithmic algebra

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Abstract. This survey of mathematical approaches to quasi-steady state (QSS) phenomena provides an analytical foundation for an algorithmic-algebraic treatment of the associated (parameter-dependent) ordinary differential systems, in particular for reaction networks. Topics include an ad hoc reduction procedure, singular perturbations, and methods to identify suitable parameter regions.
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1 Introduction

The notion quasi-steady state (QSS) characterizes the behavior of certain reaction networks with slow and fast species, or slow and fast reactions. It was introduced in the early 20^{th} century, with arguments based on scientific intuition. Mathematically, an intuitive approach prevailed for several decades as well, one reason being that the appropriate mathematical tools did not yet exist. With the emergence of singular perturbation theory, a possible appropriate translation from (bio-) chemical phenomenon to mathematical terms became available, and much of the subsequent work referred to singular perturbations. However, alternative interpretations and approaches do exist.

In the present paper we will survey two possible interpretations of QSS, and highlight the (perhaps surprising) fact that their implementation naturally leads to algorithmic algebra. "Naturally" in this context means that the familiar modelling of reaction networks by mass-action kinetics, and the subsequent reductions based on mathematical arguments, yield differential equations with polynomial or rational right-hand sides that are defined on algebraic varieties. (It is not necessary to invoke any additional assumptions.) From this perspective, QSS represents a very fitting example for "algebraic biology".

We will survey some recent work (mostly by the authors and co-workers) discussing the passage from (biological to) analytical to algebraic concepts. The

analytical results lead to problems which, at least initially, are amenable to standard methods of algorithmic algebra.

To illustrate the notions and arguments, we choose the Michaelis-Menten reaction system. (We do so with some reluctance, but this system is very relevant and very well-suited for brief illustrations.) In the Michaelis-Menten network, 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

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

Mass action kinetics and conservation laws yield the differential system

$$\begin{aligned} \dot{s} &= -k_1 e_0 s + (k_1 s + k_{-1})c, \\ \dot{c} &= \quad k_1 e_0 s - (k_1 s + k_{-1} + k_2)c + k_{-2}(e_0 - c)(s_0 - s - c), \end{aligned} \tag{1}$$

for the concentrations, usually with initial values $s(0) = s_0 > 0$ and $c(0) = 0$. Here $k_{-2} = 0$ defines the irreversible scenario, while a network with $k_{-2} > 0$ is called reversible; all other parameters are > 0.

We instantly employ this system to give readers with little or no background in biochemistry an impression of the arguments and problems arising in the practice of quasi-steady state.

As for a first example, consider the irreversible Michaelis-Menten system

$$\begin{aligned} \dot{s} &= -k_1 e_0 s + (k_1 s + k_{-1})c, \\ \dot{c} &= \quad k_1 e_0 s - (k_1 s + k_{-1} + k_2)c \end{aligned} \tag{2}$$

and assume (based on intuition or experiments) that the complex concentration c has a negligible rate of change, thus $0 \approx \dot{c} = k_1 e_0 s - (k_1 s + k_{-1} + k_2)c$, for an extended duration of time. This gives rise to a heuristic approach: Set $k_1 e_0 s - (k_1 s + k_{-1} + k_2)c = 0$ (i.e., make the stronger assumption that $\dot{c} = 0$ holds exactly), solve this relation for c and substitute into the first equation of (2). Using some high school algebra one obtains the so-called Michaelis-Menten equation

$$\dot{s} = -\frac{k_1 k_2 e_0 s}{k_1 s + k_{-1} + k_2}.$$

This heuristics clearly needs a justification.

As for a second example, assume (based, again, on intuition or experimental data) that the rate constants k_2 and k_{-2} in the reversible system (1) are very small, thus the "right half" of the reaction scheme proceeds at a much slower pace than the "left half". Here it is natural to consider the limit $k_2 \to 0$ and $k_{-2} \to 0$. Thus one obtains the system

$$\begin{aligned} \dot{s} &= -k_1 e_0 s + (k_1 s + k_{-1})c, \\ \dot{c} &= \quad k_1 e_0 s - (k_1 s + k_{-1})c. \end{aligned}$$

This system admits non-isolated stationary points, viz. a curve Z of equilibria corresponding to the fast reactions. In this approach the (presumed) interesting dynamics near Z is not being accounted for, hence more delicate limiting processes are necessary.

It goes without saying that a solid mathematical underpinning is necessary in both examples. One purpose of the present contribution is to sketch the underlying theory, and to set the heuristics on firm ground.

2 Transferring scientific to mathematical notions

The following short historical sketch of relevant contributions is necessarily incomplete, but it should serve to give an impression to non-expert readers.
Quasi-steady state assumptions for the irreversible reaction system (2) go back (among others) to Henri [19] in 1903, and Michaelis and Menten [25] in 1913. In the early stages, two incarnations of QSS materialized: One may say that Henri and Michaelis/Menten discussed QSS assuming slow and fast reactions (also known as partial equilibrium assumption, briefly PEA), while Briggs and Haldane [6] in 1925 considered QSS with a slow variable, and gave a heuristic derivation of the familiar Michaelis-Menten equation starting from the irreversible system (2). There was much work in the following decades, with arguments generally based on (bio-) chemical considerations; one representative is Laidler [22]. On the mathematical side, Tikhonov's work [36] on singular perturbations provided a solid mathematical foundation for slow-fast phenomena, as well as solid results. Heineken, Tsuchiya and Aris [18] were among the first to consider QSS (for irreversible Michaelis-Menten) from the perspective of singular perturbation theory; Schauer and Heinrich [30] gave a general discussion of slow-fast reactions from this point of view. One of Fenichel's [13] fundamental contributions to singular perturbation theory was a characterization with no reference to special coordinates. This was employed (and partly derived in an alternative way) by Stiefenhofer [35], as well as several others. The authors' work in [15–17] is also based on Fenichel's results. As for recent papers on slow/fast reactions one could mention Lee and Othmer [24] who included a discussion of the initial phase. A (quite efficient) numerical approach related to singular perturbation results, called computational singular perturbation (CSP), was introduced by Lam and Goussis [23] in the 1990s.
In addition to reducing a system with given small parameters, QSS also involves finding parameter regions where such phenomena occur (briefly, "finding small parameters"). Such lines of reasoning also go back to Henri, Michaelis/Menten, and Briggs/Haldane. Segel and Slemrod [32] in 1989 introduced an approach to determine appropriate small parameters via time scale heuristics, and their work triggered a large number of follow-up publications, such as Borghans et al. [5]. A different approach, to be discussed below, was recently introduced in [15, 17]. Generally, algebraic-algorithmic techniques for biological (and chemical) systems have been in the focus of attention since about 2000. An overview of early developments and an impression of the range of applications is provided in the conference proceedings [1, 20]. We mention only a few publications that are of relevance for reaction equations. Gatermann and Huber [14], as well as Shiu and Sturmfels [34] make use of the special structure of mass action systems to discuss the variety of stationary points, resp. siphons. Conditions for Hopf bifurcations

were considered by Niu and Wang [26], and by Errami et al. [9], among others. Parameter reduction from an algebraic perspective was discussed by Sedoglavic [31], and by Hubert and Labahn [21]. It seems that there exists relatively little work on algorithmic algebra aspects of quasi-steady state phenomena and reduction; one should, however, mention Boulier et al. [2–4].
The interpretation of QSS as a singular perturbation phenomenon is widely accepted but this does not seem to be a foregone conclusion. While a singular perturbation approach is natural for slow and fast chemical reactions, with the "small parameter" appearing in rate constants of certain reactions, it is less straightforward for QSS involving chemical species, and actually there exist alternative mathematical interpretations. Thus, Heinrich and Schauer [29] emphasized the approximate invariance of the set defined by $\dot{c} = 0$ in equation (1). This approximate invariance is implicitly assumed by practitioners who use the ad hoc reduction method as in Briggs/Haldane [6]. We will discuss both interpretations.

3 Preliminaries and notation

In this section we fix notation and recall a few notions and results. Throughout the paper we will consider a parameter-dependent ordinary differential equation

$$\dot{x} = h(x, \pi), \quad x \in U \subseteq \mathbb{R}^n, \quad \pi \in \Pi \subseteq \mathbb{R}^m \tag{3}$$

with U open and the right-hand side h smooth in the variable (x, π). (The case $m = 0$ describes parameter-independent systems.) Our principal interest lies in polynomial or rational systems; this is a natural assumption in the setting of chemical reaction equations. When appropriate, we will pass to the complexification.

3.1 Lie derivatives and invariance criteria

Given a smooth function $\psi : U \times \Pi \to \mathbb{R}$, we call $L_h(\psi)$, with

$$L_h(\psi)(x, \pi) = D_1\psi(x, \pi)h(x, \pi)$$

(note that only the partial derivative with respect to x is involved) the *Lie derivative* of ψ with respect to h. The Lie derivative describes the rate of change for ψ along solutions of (3); it is useful for invariance criteria such as the following.

Lemma 1. *(a) Let $\psi_1, \ldots, \psi_s$ be smooth on $U \times \Pi$, and assume that there are smooth functions μ_{jk} such that*

$$L_h(\psi_j) = \sum_{k=1}^{s} \mu_{jk}\psi_k, \quad 1 \le j \le s. \tag{4}$$

Then the common zero set Y of the ψ_j is an invariant set of (3); i.e., whenever $y \in Y$ then the solution trajectory through y is contained in Y.

(b) For complex polynomial functions and vector fields, the following converse holds: If the ψ_j generate a radical ideal, then invariance of the set Y will imply a relation (4)*, with polynomials μ_{jk}.*

3.2 Singular perturbations

Singular perturbation theory for ODEs starts with Tikhonov's theorem (for details see the monograph by Verhulst [37]; Theorem 8.1). We specialize it to smooth autonomous equations. Consider a system in *Tikhonov standard form* in "slow time"

$$\begin{aligned} y_1' &= f(y_1, y_2) + \varepsilon \ldots, \;\; y_1 \in D, \\ \varepsilon y_2' &= g(y_1, y_2) + \varepsilon \ldots, \;\; y_2 \in G, \end{aligned} \tag{5}$$

with small parameter $\varepsilon \geq 0$, defined on an open set $D \times G \subset \mathbb{R}^r \times \mathbb{R}^{n-r}$. Under some technical assumptions, the theorem guarantees that solutions of this system converge to solutions of a reduced system on the r-dimensional asymptotic slow manifold

$$\widetilde{Z} := \left\{ (y_1, y_2)^{\mathrm{tr}} \in D \times G;\, g(y_1, y_2) = 0 \right\};$$

the reduced system being given by

$$y_1' = f(y_1, y_2), \quad g(y_1, y_2) = 0, \tag{6}$$

on a suitable time interval as $\varepsilon \to 0$. A crucial technical assumption is satisfied whenever a uniform linear stability condition holds for the eigenvalues of the Jacobian $D_2 g(y_1, y_2)$ with respect to y_2. Generalizations for systems that are not in standard form, as well as less restrictive eigenvalue conditions (normal hyperbolicity), are due to Fenichel [13].

4 The ad hoc approach

The following classical reduction heuristic (which we call the *ad hoc reduction*) is directly related to an intuitive quasi-steady state assumption for chemical species, such as by Briggs and Haldane [6]: In the differential equation, set the negligible rates of change equal to zero, and use the subsequent algebraic relations to obtain a reduced system. The procedure may be formalized by introducing the notion of *enforced invariant sets.*

Definition 1. *Given system* (3)*, let $\psi_1, \ldots, \psi_{n-r}$ be smooth in a neighborhood of some $(x_0, \pi_0) \in U \times \Pi$, and assume that the rank of the Jacobian of $\Psi := (\psi_1, \ldots, \psi_{n-r})^{\mathrm{tr}}$ equals $n - r$ on this neighborhood. Let Y be (locally) the set of common zeros of these functions. Assume furthermore (w.l.o.g. upon relabelling) that the rank of $(x_1, \ldots, x_r, \psi_1, \ldots, \psi_{n-r})$ equals n on this neighborhood. Partition $x = (x^{[1]}, x^{[2]})$, with $x^{[1]} = (x_1, \ldots, x_r)^{\mathrm{tr}}$ and $x^{[2]} = (x_{r+1}, \ldots, x_n)^{\mathrm{tr}}$. Then we will call any system*

$$\begin{aligned} \dot{x}^{[1]} &= h^{[1]}(x, \pi) + \textstyle\sum_j m_j^{[1]} \psi_j \\ \dot{x}^{[2]} &= -D_2\Psi(x, \pi)^{-1} D_1 \Psi(x, \pi) h^{[1]}(x, \pi) + \textstyle\sum_j m_j^{[2]} \psi_j \end{aligned} \tag{7}$$

with arbitrary smooth $m_j^{[1]}$ *and* $m_j^{[2]}$, *a* system associated to (3) with enforced invariant set Y.

For the standard QSS setting, assuming "slow" variables $x_{r+1}, \ldots, x_n$ and $\psi_j = h_{r+j} = L_h(x_{r+j})$, this definition is applicable for ad hoc reduction. The common strategy is to consider only the first r equations, and to replace $x_{r+1}, \ldots, x_n$ in $h^{[1]}$ via $\Psi = 0$. System (7) on the invariant manifold Y provides an alternative to this (generally non-constructive) approach. In the polynomial or rational setting there remains to discuss a polynomial or rational system on an invariant algebraic variety; this seems more amenable to algebraic techniques. Boulier et al. [3, 4] present an algorithmic approach to ad hoc reduction using elimination; in [4] the authors specifically introduce a variant to describe the dynamics on invariant manifolds arising from slow and fast reactions.
One must note that such procedures are consistent only if Y is actually an invariant set. We record a few facts; the proof is straightforward with Lemma 1.

Lemma 2. *(a) The set* Y *is invariant for system* (7).
(b) If Y *is an invariant set for system* (3) *then its solutions on* Y *coincide with those of* (7).

Example 1. Ad hoc approach for the irreversible Michaelis-Menten system, assuming QSS for the variable s. A system with enforced invariant set Y defined by $\psi = L_h(s) = -k_1 e_0 s + (k_1 s + k_{-1})c = 0$ has the form

$$\begin{aligned} \dot{s} &= \tfrac{k_1 s + k_{-1}}{k_1 (e_0 - c)} \left(k_1 e_0 s + (k_1 s + k_{-1} + k_2) c\right), \\ \dot{c} &= k_1 e_0 s - (k_1 s + k_{-1} + k_2) c\,; \end{aligned} \tag{8}$$

here – in the notation of (7) – we chose $m^{[1]} = m^{[2]} = 0$. The choice $m^{[2]} = 1$ provides a more convenient version of the second equation on Y, viz. $\dot{c} = -k_2 c$.

We will return later to the crucial condition of invariance (or "approximate invariance") of the QSS set Y, which is fundamental for the ad hoc reduction.

5 Reduction in the SPT setting

In this section we discuss the (standard) singular perturbation approach to reduction. Thus we specialize system (3) to a smooth system with one small parameter, viz.

$$\dot{x} = h(x, \varepsilon) = h^{(0)}(x) + \varepsilon h^{(1)}(x) + \cdots \tag{9}$$

with ε in some neighborhood of 0. (One may think of other parameters as being "frozen".)

5.1 Conditions

Assume that system (9) is – in principle, after a coordinate change – amenable to reduction by Tikhonov's theorem. An obvious problem is to cast equations (9)

into standard form (5). Fenichel [13] discussed this, and the following local characterization of systems which admit a coordinate transformation to Tikhonov standard form is a consequence of his results. (An elementary proof is given in [28].)

Proposition 1. *Let system* (9) *be given, and denote by* $Z = \mathcal{V}(h^{(0)})$ *the zero set of* $h^{(0)}$*. Let* $a \in Z$ *and assume that there exists a neighborhood* U *of* a *in* $\mathbb{R}^n$ *such that* $Z \cap U$ *is an* r*-dimensional submanifold. Then there exists an invertible local coordinate transformation to standard form* (5)*, satisfying a linear stability condition in some neighborhood of* a*, if and only if the following hold.*

(i) The rank of $Dh^{(0)}(a)$ *is equal to* $n - r$*, and there exists a direct sum decomposition*

$$\mathbb{R}^n = \text{Ker } Dh^{(0)}(a) \oplus \text{Im } Dh^{(0)}(a).$$

(ii) The nonzero eigenvalues of $Dh^{(0)}(a)$ *have real part* < 0*.*

Adopting the nomenclature from subsection 3.2, we will refer to Z as the (asymptotic) slow manifold of (9).

As pointed out in [28], Proposition 1 guarantees the existence of a transformation to Tikhonov standard form, but generally one cannot determine such a transformation explicitly, even for polynomial systems. The main obstacle lies in the explicit determination of first integrals of system (9) when $\varepsilon = 0$. (There is an important exception to this rule for slow and fast reactions, if and when stoichiometry provides sufficiently many linear first integrals; see Schauer and Heinrich [30], Lee and Othmer [24] and the algorithmic implementation by Boulier et al. [2].) But even if such a transformation cannot be determined, for rational sytems one can compute a reduced system on Z explicitly.

5.2 Reduction of rational systems

The main result of this section (taken from [15, 16]) provides an algorithmic approach to the computation of reduced equations for general systems (9) with rational right-hand side, in particular for reaction equations with mass action kinetics. We will freely use some notions and results from commutative algebra and algebraic geometry. Underlying the reduction theorem is a fact from classical algebraic geometry; viz., a variety of dimension r can be represented as the zero set of $n - r$ regular functions in a Zariski-open neighborhood of a simple point (see e.g. Shafarevich [33], Ch.II, §3).

Theorem 1. (See [16]) *Consider system* (9) *with rational right-hand side* h*, and let* $a \in \mathbb{R}^n$ *be a simple point of* $\mathcal{V}(h^{(0)})$*, with* $n - r = \text{rank } Dh^{(0)}(a)$*. (Thus locally the dimension of* $\mathcal{V}(h^{(0)})$ *equals* r*.) Assume moreover a direct sum decomposition*

$$\mathbb{R}^n = \text{Ker } Dh^{(0)}(a) \oplus \text{Im } Dh^{(0)}(a).$$

Then the following hold.

(a) *There exist a Zariski-open neighborhood U_a of a in $\mathbb{R}^n$ and a product decomposition with matrices $\mu(x) \in \mathbb{R}(x)^{(n-r)\times 1}$, $P(x) \in \mathbb{R}(x)^{n\times(n-r)}$, such that*

$$h^{(0)}(x) = P(x)\mu(x), \quad x \in U_a \tag{10}$$

with rank $P(a) = n - r$, rank $D\mu(a) = n - r$, *and*

$$\mathcal{V}(h^{(0)}) \cap U_a = \mathcal{V}(\mu) \cap U_a$$

is an r–dimensional submanifold.

(b) *The following system is defined on a Zariski-open neighborhood of a in $\mathbb{R}^n$, and admits a relatively Zariski-open neighborhood $\mathcal{U}_a \subset \mathcal{V}(h^0)$ as an invariant set:*

$$x' = \left[I_n - P(x)A(x)^{-1}D\mu(x)\right] h^{(1)}(x), \tag{11}$$

with

$$A(x) := D\mu(x)P(x) \in \mathbb{R}(x)^{(n-r)\times(n-r)}.$$

(c) *If all the nonzero eigenvalues of $Dh^{(0)}(a)$ have negative real part then system* (11)*, restricted to $\mathcal{U}_a$, corresponds to the reduced system* (6) *in Tikhonov's theorem.*

If the condition in part (c) is not satisfied then formula (11) still defines a system with invariant set $\mathcal{U}_a$; we will call this a *formal reduction* of (9). (Fenichel's theory [13] implies convergence under mild hyperbolicity conditions.)

Example 2. In the Michaelis-Menten system, let $k_{-1} = \varepsilon\kappa_{-1}$ and $k_2 = \varepsilon\kappa_2$. Then

$$h^{(0)} = P \cdot \mu \text{ with } P = \begin{pmatrix} -k_1 s \\ k_1 s + k_{-2}(s_0 - s - c) \end{pmatrix} \text{ and } \mu = e_0 - c,$$

and $h^{(1)} = (\kappa_{-1}c, -(\kappa_{-1} + \kappa_2)c)^{\mathrm{tr}}$; thus the slow manifold is given by $c = e_0$. With the notation from Theorem 1 one has, for instance,

$$I_2 - P \cdot A^{-1} \cdot D\mu = \begin{pmatrix} 1 & -k_1 s/(k_1 s + k_{-2}(s_0 - s - c)) \\ 0 & 0 \end{pmatrix},$$

and the reduced equation on the slow manifold reads

$$\dot{s} = k_{-1}e_0 + k_1 s(k_{-1} + k_2)e_0/(k_1 s + k_{-2}(s_0 - e_0 - s))$$

together with $\dot{c} = 0$. This setting corresponds to slow degradation of complex; for biologically relevant parameter values the solution will eventually escape from the slow manifold.

The reduction of the irreversible Michaelis-Menten system with small k_2 is discussed by Schauer and Heinrich [30], who (essentially) employ a linear transformation to Tikhonov standard form, and by Boulier et al. [4] who take an approach via enforced invariant sets.

5.3 Algorithmic aspects

The decomposition in Theorem 1 (a) is found by inspection in many applications, but we point out that it can be determined constructively. First, according to Shafarevich [33], one may choose (any) $n - r$ functionally independent entries of $h^{(0)}$ for μ; thus a generator system of the vanishing ideal in the local ring of a is known. An algorithm to determine P (in effect, to express the remaining entries of $h^{(0)}$ by μ) uses standard bases and Mora's algorithm (see Decker and Lossen [11], Lecture 9). There is an implementation of Mora's algorithm in the computer algebra system SINGULAR [10]. Thus, to a great extent the reduction of rational systems is manageable by customary algorithms. Some restrictions apply, however, since inequations (to ensure rank conditions) and inequalities (to ensure negative real parts for eigenvalues) also play a role in the discussion. Moreover, one usually deals with semi-algebraic sets in phase and parameter space, due to nonnegativity conditions.

6 Identifying "small parameters"

In the previous section we assumed that a "small parameter" was known a priori for system (9). In some applications (such as networks with slow and fast reactions) this is the case, but in others it is not. In particular, for a quasi-steady state assumption for chemical species the designation of small parameters is not straightforward. In their influential paper on the irreversible Michaelis-Menten system, Segel and Slemrod [32] introduced a heuristics to identify and compare time scales, from which they derived appropriate "small parameters"; this laid the foundation for many publications on quasi-steady state phenomena. As it seems, all approaches in the literature to identify "small parameters" require some intuition (or initial assumption) about the reaction network. In recent work [15, 17] the authors proceeded differently, just assuming the existence of a singular perturbation scenario. A mathematical motivation for this approach was obtained from numerically oriented work, such as Lam and Goussis [23], Duchêne and Rouchon [12].

6.1 Definition and basic properties

Looking at a system in Tikhonov standard form (5) shows that "small parameters" ε are in fact distinguished by properties of the system at $\varepsilon = 0$, such as the existence of non-isolated stationary points.

Definition 2. *A $\pi^* \in \Pi$ will be called a* Tikhonov-Fenichel parameter value (TFPV) for dimension r *($1 \leq r \leq n-1$) of system* (3) *whenever the following hold:*

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

(ii) There is a point $x_0 \in Z$ *such that* rank $D_1h(x_0, \pi^*) = n - r$ *and*

$$\mathbb{R}^n = \text{Ker } D_1h(x, \pi^*) \oplus \text{Im } D_1h(x, \pi^*), \quad \textit{all } x \in Z \textit{ near } x_0.$$

(iii) The nonzero eigenvalues of $D_1h(x_0, \pi^*)$ *have real part* < 0.

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

A straightforward application of Theorem 1 shows:

Remark 1. Let $\pi^* \in \Pi$ be a Tikhonov-Fenichel parameter value for dimension r of system (3), and let $x_0 \in \mathcal{V}(h(\cdot, \pi^*))$ be such that the conditions in Definition 2 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

$$\dot{x} = h(x, \gamma(\delta)) = h(x, \pi^*) + \delta \cdot D_2h(x, \pi^*)\gamma'(0) + O(\delta^2) \tag{12}$$

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

6.2 Structure of the TFPV set

We turn to the computation of TFPV's for polynomial (or rational) vector fields; at the same time we will clarify the structure of the Tikhonov-Fenichel parameter value set. Thus we consider system (3) with a polynomial (or rational) right-hand side, and we will also assume that the domain of interest is a Zariski-open subset Δ of a semi-algebraic set in $\mathbb{R}^{n+m}$. (All proofs, as well as further details, may be found in [17].)

Given system (3) and $(x, \pi)^{\text{tr}} \in U \times \Pi$, we denote by

$$\chi(\tau) = \chi_{x,\pi}(\tau) := \tau^n + \sigma_{n-1}(x, \pi)\tau^{n-1} + \cdots + \sigma_1(x, \pi)\tau + \sigma_0(x, \pi) \tag{13}$$

the characteristic polynomial of the Jacobian $D_1h(x, \pi)$, in the indeterminate τ. The coefficients σ_i are polynomial (resp. rational) functions in x and π. We first list a few technical facts.

Lemma 3. *Let* $(x_0, \pi^*) \in \Delta$ *be such that* $h(x_0, \pi^*) = 0$*, and let the characteristic polynomial of* $D_1h(x_0, \pi^*)$ *be given by* (13)*. Then* $\pi^* \in \Pi$ *is a Tikhonov-Fenichel parameter value for dimension* r*, and* x_0 *lies in the local slow manifold of* π^**, only if the following hold.*

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

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

has only zeros with negative real part.

Note that the subset of Δ satisfying (i) and (ii) is defined by polynomial equations and inequalities (Routh-Hurwitz conditions for $\widetilde{\chi}$). The next auxiliary result is proven via Poincaré-Dulac normal form theory.

Lemma 4. *Let $(x_0, \pi^*) \in \Delta$ satisfy the conditions in Lemma 3. Then π^* is a TFPV for dimension r, and x_0 lies in the local slow manifold of π^*, if and only if the system $\dot{x} = h(x, \pi^*)$ admits r functionally independent analytic (equivalently, 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 $x - x_0$.*

There remains the task to restate these conditions by polynomial equalities or inequalities. Assuming $h(x_0, \pi^*) = 0$, consider the Taylor expansion with respect to $y := x - x_0$:

$$h(x, \pi^*) = \sum_{k \geq 1} h_k(x_0, \pi^*, y), \tag{14}$$

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 (comparing homogeneous parts with respect to y) if

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

Now denote by S_k the space of homogeneous polynomials of degree k in y. For any $d \geq 1$ 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 2. *Let $(x_0, \pi^*) \in \Delta$ satisfy the conditions in Lemma 3. There exist r independent first integrals for $\dot{x} = h(x, \pi^*)$ near x_0 if and only if*

$$\dim \operatorname{Ker} L_h^{(d)} = \vartheta_{r,d} := \sum_{j=1}^{d} \binom{r+j-1}{j} \quad \textit{for all } d \geq 1.$$

One knows that the kernel of $L_h^{(d)}$ has dimension at most $\vartheta_{r,d}$, hence the conditions may be restated, in a manner similar to Lemma 3(i), via coefficients of the characteristic polynomial of $L_h^{(d)}$. (The condition corresponding to (ii) is automatically satisfied.) Due to Hilbert's *Basissatz*, it is sufficient to check the dimension condition for some suitable $d = d^*$, which, however, is not known a priori. Hence we have the foundation for a pseudo-algorithm, rather than an algorithm. The above observations, in conjunction with Tarski-Seidenberg, also lead to a proof of the following structure theorem.

Theorem 2. *The Tikhonov-Fenichel parameter values of* (3) *for dimension r form a semialgebraic subset of $\mathbb{R}^m$.*

6.3 Algorithmic aspects

In this subsection we further restrict attention to systems (3) with polynomial right-hand side; for rational systems matters are similar, but the presentation is more cumbersome. Moreover we will only consider the setting of Lemma 3 (which also corresponds to the $d = 1$ case of Proposition 2), and we will only discuss the equations necessary for a TPFV (disregarding inequalities). This represents the first step in the general procedure.

Remark 2. If $\pi^* \in \Pi$ is a Tikhonov-Fenichel parameter value for dimension r (with $1 \leq r \leq n-1$) for system (3) then there exists $x_0 \in \mathbb{R}^n$ with the following properties.

(i) $h(x_0, \pi^*) = 0$;
(ii) the Jacobian $D_1 h(x_0, \pi^*)$ has rank $\leq n-r$, thus for any $k > n-r$, all $k \times k$ minors vanish;
(iii) $\sigma_r(x_0, \pi^*) \neq 0$.

There is some redundancy in the statement of part (ii) (clearly $k = n - r + 1$ suffices), which is harmless and sometimes even welcome for computations in small systems. To obtain TFPV's, it is natural to employ elimination ideals (see e.g. Cox, Little, O'Shea [8], pp. 24–26). Once more standard methods suffice for the initial computations.

Proposition 3. *Let $\pi^* \in \Pi$ be a TFPV of the polynomial system* (3) *for dimension r, $1 \leq r \leq n-1$. Let $\gamma_1, \ldots, \gamma_{\ell_r} \in \mathbb{R}[x, \pi]$ denote all the $k \times k$ minors of $D_1 h(x, \pi)$, $n \geq k > n - r$, and let*

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

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

Corollary 1. *For the polynomial system* (3)*, 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 $r \geq 1$, a TFPV π^* of system (3) *for dimension r is a zero of $\mathcal{J}_\pi := \mathcal{J} \cap \mathbb{R}[\pi]$.*

Example 3. Consider the irreversible Michaelis-Menten equation (2). The components h_1 and h_2 and the Jacobian determinant d of h generate the ideal

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

in $\mathbb{R}[x, \pi]$. With respect to lexicographic order, SINGULAR finds 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. The condition $g_1 = 0$ shows that the only possible "small parameters" in this system are e_0, k_1 and k_2. (One verifies that these actually yield Tikhonov-Fenichel reductions; furthermore g_2 and g_3 provide conditions on the slow manifold.)

7 The ad hoc approach revisited

We return to ad hoc QSS assumptions for chemical species, see Section 4. One motivation for this (as noted) lies in a possible different mathematical interpretation of QSS. But the strategy is also useful for finding certain TFPV's (keeping in mind that knowing partial solutions may be helpful when solving large polynomial systems). As noted above, constructing a differential equation with an enforced invariant set from a given one will only be relevant for the original when the set in question is "approximately invariant". Essentially this observation goes back to Schauer and Heinrich [29], who employed it to determine "small parameters" for the irreversible Michaelis-Menten system. In [27], the notion was investigated further, and an infinitesimal criterion was obtained. Recently in [7], the focus was on parameter values which force invariance (whence small perturbations force "approximate invariance"). These parameter values are algorithmically accessible for polynomial or rational vector fields.

7.1 Basics and approximation properties

Given the parameter-dependent system (3), we search for criteria to identify parameter regions where certain sets (defined by pre-imposed QSS conditions on certain species) are "approximately invariant" in the specific sense that a suitable nearby parameter will assure invariance. The following basic observation is a variant of [7], Prop. 4.1, with some details omitted.

Proposition 4. *Let $\pi^* \in \mathbb{R}^m$ such that the equations*

$$\psi_1(x, \pi^*) = \cdots = \psi_{n-r}(x, \pi^*) = 0$$

(with smooth functions and full rank) define a local r-dimensional submanifold Y_{π^*} of $\mathbb{R}^n$ which is invariant for the system (3) at $\pi = \pi^*$; moreover let $y^* \in Y_{\pi^*}$. Then there exist a compact neighborhood K of y^* and a neighborhood V of π^* such that for every $\pi \in V$ the set defined by the equations

$$\psi_1(x, \pi) = \cdots = \psi_{n-r}(x, \pi) = 0$$

contains an r-dimensional local submanifold Y_π which has nonempty compact intersection with K. As $\pi \to \pi^*$, solutions of (3) with initial value in $Y_\pi \cap K$ converge to solutions of any associated system (7) with enforced invariant set Y_{π^*}.

We will call π^* a *critical parameter value* with respect to $\psi_1, \ldots, \psi_{n-r}$ if the system of functions has full rank and defines an invariant r-dimensional local submanifold near some point (y^*, π^*).

7.2 Polynomial systems and algorithmic aspects

The algorithmic-algebraic implementation of critical parameter values has not been previously discussed. (The approach by Boulier et al. [4] to enforce certain

invariant manifolds, and to investigate the dynamics on these manifolds, has a different starting point, and uses different arguments.) The outline presented here (although based on arguments similar to section 6) may thus be considered new. Specializing to systems with polynomial right hand side, and keeping the maximal rank condition from Proposition 4, it is again natural to work in the local setting, as in subsection 5.2, and once more one obtains algebraic conditions on the parameters.

Proposition 5. *Given system* (3) *with polynomial right-hand side, and polynomials* $\psi_1, \ldots, \psi_{n-r}$ *as in Proposition 4, a critical parameter value lies in the ideal generated by all* $(n-r+1) \times (n-r+1)$ *minors of the Jacobians of*

$$\begin{pmatrix} \psi_1 \\ \vdots \\ \psi_{n-r} \\ L_h(\psi_j) \end{pmatrix}, \quad 1 \leq j \leq n-r.$$

Proof. We pass to the complexification, and choose $y \in Y_{\pi^*}$. By the rank condition, $\psi_1, \ldots, \psi_{n-r}$ locally define a variety of dimension r, and invariance, together with the local version of Hilbert's *Nullstellensatz* (see Shafarevich [33], Ch. III, §3) implies the existence of rational μ_{jk}, regular at y, such that

$$L_h(\psi_j) = \sum_{k=1}^{n-r} \mu_{jk} \psi_k, \quad 1 \leq j \leq n-r.$$

Differentiation of these identities with respect to x and using $\psi_j(z) = 0$ for $z \in Y_{\pi^*}$ shows that $D_1(L_h(\psi_j))(z, \pi^*)$ is a linear combination of the $D_1(\psi_k)(z, \pi^*)$ for all $z \in Y_{\pi^*}$. Therefore the Jacobian has rank $\leq n-r$.

Together with the $n-r+1$ equations $\psi_1 = \cdots = \psi_{n-r} = L_h(\psi_j) = 0$, these determinant conditions (of which there are at least r, so one has more than n equations in total) again allow to employ elimination ideals, with elimination of the variables. We discuss a small example to illustrate the procedure.

Example 4. We continue the example from section 4, searching for critical parameter values with respect to $\psi = -k_1 e_0 s + (k_1 s + k_{-1})c$, but we will consider the reversible case here. Elimination of s and c from the ideal generated by ψ, $L_h(\psi)$ and their Jacobian determinant yields an elimination ideal with one generator

$$g := e_0 k_{-1} \cdot p,$$

with

$$p = (k_1 k_2 + k_{-1} k_{-2})^2 + 2k_1 k_{-2}((e_0 + s_0) k_1 k_2 + k_{-1} k_{-2}) + k_1^2 k_{-2}^2 (e_0 - s_0)^2.$$

In view of nonnegativity conditions, this provides the following cases (and only these).

– $e_0 = 0$ (see Briggs-Haldane [6]);
– $k_{-1} = 0$; the invariant set is given here by $s = 0$;
– $k_1 = k_{-2} = 0$ (slow formation of complex);
– $k_2 = k_{-2} = 0$ (slow formation and degradation of product).

A comparison with [17], subsection 5.1 shows that (only) the second parameter value is not a TFPV. Thus, generally there exist critical parameter values which are not TFPV's.

A straightforward algorithmic search for critical parameter values via Proposition 5 seems to be more involved than a search for TFPV's. But a more detailed analysis will yield further (more convenient) conditions. This is the subject of ongoing work.

8 Conclusion

Readers with expertise in algorithmic algebra will have noticed that we did not discuss algorithmic-algebraic aspects in any depth or detail. Indeed, for a complete analysis of the relatively low-dimensional standard systems (involving relatively few parameters) from biochemistry that were discussed in [15–17], a combination of standard algorithms and case-by-case inspection of intermediate results turned out to be sufficient.

The principal purpose of the present note was to present and describe the basic analytical results which provide a natural foundation for algorithmic-algebraic work in the case of reaction equations. Indeed for this class all analytical conditions can be transferred to (semi-) algebraic ones, and the pertinent results of [15–17] were outlined here.

The (semi-) algebraic conditions we gave are quite likely not stated in an optimal manner, and it may be advisable for further analysis to use more special properties of reaction systems in a general discussion. (We essentially only required polynomiality of the systems and certain positivity conditions.) Certainly a general approach will take a substantially bigger effort to become feasible, and much work remains to be done. The authors hope that the present paper will provide a stimulus for such work.

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