

Reduction of chemical reaction networks

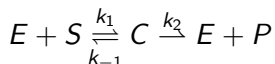
Sebastian Walcher, RWTH Aachen

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PART ONE: BACKGROUND AND MOTIVATION

A standard example: Michaelis-Menten

Chemical reaction network (CRN) with mass action kinetics:



Differential equation for concentrations by standard procedure:

$$\begin{aligned}\dot{s} &= -k_1 es + k_{-1}c, \\ \dot{c} &= k_1 es - (k_{-1} + k_2)c, \\ \dot{e} &= -k_1 es + (k_{-1} + k_2)c, \\ \dot{p} &= k_2c.\end{aligned}$$

Initial values $s(0) = s_0$, $c(0) = 0$, $e(0) = e_0$, $p(0) = 0$ and **stoichiometry** (linear first integrals $e + c$ and $s + c + p$):

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

QSS for Michaelis-Menten: Ancient history

Differential equation

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

Quasi-Steady State (QSS); Briggs and Haldane (1925):

QSS for complex C means $\dot{c} = 0$; more precisely

$$0 = k_1 e_0 s - (k_1 s + k_{-1} + k_2)c \implies c = \dots$$

(Briggs and Haldane: Biochemical argument for QSS assumption, for small e_0 .)

Substitution into $\dot{s} = \dots$ yields the **Michaelis-Menten equation**

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

QSS for Michaelis-Menten: More recent history

Heineken, Tsuchiya und Aris (1967): Singular perturbation reduction of

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

Small enzyme concentration; interpretation $e_0 = \varepsilon e_0^*$, $\varepsilon \rightarrow 0$.

Scaling: Set $c^* := c/\varepsilon$; then

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

ready for application of Tikhonov's theorem. Reduction yields Michaelis-Menten equation.

PART TWO: SINGULAR PERTURBATION REDUCTION FOR CHEMICAL REACTION NETWORKS

Work by and with
Alexandra Goeke
Lena Nöthen
Eva Zerz

Tikhonov and Fenichel: Basic theorem

System with small parameter ε in *standard form*

$$\begin{aligned}\dot{x}_1 &= f_1(x_1, x_2) + \varepsilon(\dots), & x_1 &\in D \subseteq \mathbb{R}^r, \\ \dot{x}_2 &= \varepsilon f_2(x_1, x_2) + \varepsilon^2(\dots), & x_2 &\in G \subseteq \mathbb{R}^s.\end{aligned}$$

Slow time $\tau = \varepsilon t$: $\varepsilon x'_1 = f_1(x_1, x_2) + \dots$, $x'_2 = f_2(x_1, x_2) + \dots$.

Assumptions: (i) Nonempty *critical manifold*

$$\tilde{Z} := \left\{ (y_1, y_2)^T \in D \times G; f_1(y_1, y_2) = 0 \right\};$$

(ii) there exists $\nu > 0$ such that every eigenvalue of $D_1 f_1(y_1, y_2)$, $(y_1, y_2) \in \tilde{Z}$ has real part $\leq -\nu$.

Theorem. There exist $T > 0$ and a neighborhood of $\tilde{Z}$ in which, as $\varepsilon \rightarrow 0$, all solutions converge uniformly to solutions of

$$x'_2 = f_2(x_1, x_2), \quad f_1(x_1, x_2) = 0 \quad \text{on } [t_0, T] \quad (t_0 > 0 \text{ arbitrary}).$$

Differential equations for CRN

Typical for chemical reaction networks: Parameter dependent ordinary differential equation

$$\dot{x} = h(x, \pi), \quad x \in \mathbb{R}^n, \quad \pi \in \mathbb{R}^m$$

with polynomial right hand side.

Why? Mass action kinetics, thermodynamical conditions fixed; spatially homogeneous. Parameters: Rate constants, initial concentrations.

Question: How do singular perturbation reductions enter this picture? (A priori: No ε , no slow-fast separation.)

Transfer to standard setting

Parameter dependent system

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

versus

$$\begin{aligned}\dot{x}_1 &= f_1(x_1, x_2) + \varepsilon (\dots), \\ \dot{x}_2 &= \varepsilon f_2(x_1, x_2) + \varepsilon^2 (\dots).\end{aligned}$$

Preliminary step: For suitable $\hat{\pi}$ (to be determined) consider system

$$\dot{x} = h(x, \hat{\pi} + \varepsilon \rho + \dots) =: g^{(0)}(x) + \varepsilon g^{(1)}(x) + \varepsilon^2 \dots$$

Suitability of $\hat{\pi}$ implies: Scenario is *singular*, i.e. the vanishing set of $g^{(0)}$ contains a submanifold Z of dimension $s > 0$.
(*Proof.* Look at standard system when $\varepsilon = 0$.)

Tikhonov-Fenichel: Identification

Proposition. Assume $\dim Z = s > 0$. Then

$$\dot{x} = g^{(0)}(x) + \varepsilon g^{(1)}(x) + \varepsilon^2 \dots$$

admits a coordinate transformation into standard form and subsequent Tikhonov-Fenichel reduction near every point of Z if and only if

- (i) $\text{rank } Dg^{(0)}(x) = r := n - s$ for all $x \in Z$;
- (ii) for each $x \in Z$ there exists a direct sum decomposition $\mathbb{R}^n = \text{Ker } Dg^{(0)}(x) \oplus \text{Im } Dg^{(0)}(x)$;
- (iii) for each $x \in Z$ the nonzero eigenvalues of $Dg^{(0)}(x)$ have real parts $\leq -\nu < 0$.

Remaining problem: Explicit computation of coordinate transformation is generally impossible.

Tikhonov-Fenichel: Coordinate-free reduction

Singularly perturbed system

$$x' = \varepsilon^{-1} g^{(0)}(x) + g^{(1)}(x) + \dots$$

with $Z \subseteq \mathcal{V}(g^{(0)})$ satisfying conditions (i), (ii) und (iii); $a \in Z$.

Decomposition: There is a Zariski-open neighborhood U_a of a such that

$$g^{(0)}(x) = P(x)\mu(x),$$

with $\mu(x) \in \mathbb{R}(x)^{r \times 1}$, $P(x) \in \mathbb{R}(x)^{n \times r}$, $\text{rank } P(a) = r$,
 $\text{rank } D\mu(a) = r$, and (w.l.o.g.) $\mathcal{V}(g^{(0)}) \cap U_a = \mathcal{V}(\mu) \cap U_a = Z$.

Reduction: The system

$$x' = \left[I_n - P(x)A(x)^{-1}D\mu(x) \right] g^{(1)}(x), \quad \text{with } A(x) := D\mu(x)P(x)$$

is defined on U_a and admits Z as invariant set. The restriction to Z corresponds to the reduction via Tikhonov's theorem as $\varepsilon \rightarrow 0$.

Finding suitable parameter values

Definition: We call $\hat{\pi}$ a *Tikhonov-Fenichel parameter value* (TFPV) for dimension s ($1 \leq s \leq n - 1$) of $\dot{x} = h(x, \pi)$ if the following hold:

- (i) The vanishing set $\mathcal{V}(h(\cdot, \hat{\pi}))$ of $x \mapsto h(x, \hat{\pi})$ contains a component $\tilde{Y}$ of dimension s ;
- (ii) there is $a \in \tilde{Y}$ and neighborhood Z of a in $\tilde{Y}$ such that $\text{rank } D_x h(x, \hat{\pi}) = n - s$ and

$$\mathbb{R}^n = \text{Ker } D_x h(x, \hat{\pi}) \oplus \text{Im } D_x h(x, \hat{\pi}), \quad \text{for all } x \in Z;$$

- (iii) the nonzero eigenvalues of $D_x h(a, \hat{\pi})$ have real parts < 0 .

Note: Conditions by copy-and-paste (more or less) from characterization above. Therefore reduction works for small perturbations $\hat{\pi} + \varepsilon \rho + \dots$.

TFPV: Characterization

Denote the characteristic polynomial of the Jacobian $D_x h(x, \pi)$ by

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

Proposition. A parameter value $\hat{\pi}$ is a TFPV with locally exponentially attracting critical manifold $Z = Z_s$ of dimension $s > 0$, and $x_0 \in Z_s$, if and only if the following hold:

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

Why the first integrals?

Proposition. A parameter value $\hat{\pi}$ is a TFPV, and $x_0 \in Z_s$, if and only if the following hold:

- ▶ ...
- ▶ The system $\dot{x} = h(x, \hat{\pi})$ admits s independent local analytic first integrals at x_0 .

Underlying reason: Consider Poincaré–Dulac normal form for

$$\dot{y} = By + \dots, B = \begin{pmatrix} 0 & 0 \\ 0 & B^* \end{pmatrix}, \quad B^* \in \mathbb{R}^{(n-s) \times (n-s)}, \operatorname{Re} \operatorname{Spec} B^* < 0.$$

System admits an s -dimensional local manifold of stationary points iff there are s independent first integrals. (Convergence? QNF!)

Note. First integrals appear naturally in CRN (stoichiometry).

TFPV: Computation and structure

Properties of TFPV $\hat{\pi}$ for dimension s :

- ▶ Vanishing set Z of $h(\cdot, \hat{\pi})$ has dimension s : “More equations in x than variables”; elimination theory allows a start.
- ▶ All nonzero eigenvalues of $D_x h(x, \hat{\pi})$, $x \in Z$, have real parts < 0 : Hurwitz-Routh provides inequalities.
- ▶ Further conditions from existence of first integrals.

Theorem. The TFPV for dimension s of a polynomial (or rational) system $\dot{x} = h(x, \pi)$ with nonnegative parameters (and x in the nonnegative orthant) form a semi-algebraic subset $\Pi_s \subseteq \mathbb{R}^m$.

TFPV for Michaelis-Menten

System

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

with **Jacobian determinant** $d = k_1 k_2 (e_0 - c)$.

Three equations (also $d = 0$): Eliminate s and c .

Result: A TFPV $(\hat{e}_0, \hat{k}_1, \hat{k}_{-1}, \hat{k}_2)$ satisfies

$$\hat{e}_0 \hat{k}_2 \hat{k}_1 = 0.$$

Small perturbations yield all relevant cases:

$$\begin{pmatrix} \varepsilon e_0^* \\ \hat{k}_1 \\ \hat{k}_{-1} \\ \hat{k}_2 \end{pmatrix} \text{ or } \begin{pmatrix} \hat{e}_0 \\ \varepsilon k_1^* \\ \hat{k}_{-1} \\ \hat{k}_2 \end{pmatrix} \text{ or } \begin{pmatrix} \hat{e}_0 \\ \hat{k}_1 \\ \hat{k}_{-1} \\ \varepsilon k_2^* \end{pmatrix} \text{ or } \begin{pmatrix} \hat{e}_0 \\ \hat{k}_1 \\ \varepsilon k_{-1}^* \\ \varepsilon k_2^* \end{pmatrix}$$

Michaelis-Menten: Some reductions

- ▶ Small enzyme concentration $e_0 = \varepsilon e_0^*$: Familiar result.
- ▶ Slow product formation:

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

Decomposition $\hat{g}^{(0)} = P \cdot \mu$ with

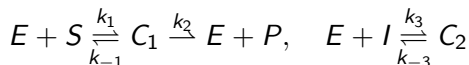
$$P = \begin{pmatrix} 1 \\ -1 \end{pmatrix}, \quad \mu = k_1 e_0 s - (k_1 s + k_{-1})c.$$

Reduced equation (on $Z = \mathcal{V}(\mu)$):

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

Further example: Competitive inhibition

Michaelis-Menten network with inhibitor:



Mass action kinetics and stoichiometry lead to ODE

$$\begin{aligned}\dot{s} &= k_{-1}c_1 - k_1s(e_0 - c_1 - c_2), \\ \dot{c}_1 &= k_1s(e_0 - c_1 - c_2) - (k_{-1} + k_2)c_1, \\ \dot{c}_2 &= k_3(e_0 - c_1 - c_2)(i_0 - c_2) - k_{-3}c_2.\end{aligned}$$

Competitive inhibition: TFPV

System

$$\begin{aligned}\dot{s} &= k_{-1}c_1 - k_1s(e_0 - c_1 - c_2), \\ \dot{c}_1 &= k_1s(e_0 - c_1 - c_2) - (k_{-1} + k_2)c_1, \\ \dot{c}_2 &= k_3(e_0 - c_1 - c_2)(i_0 - c_2) - k_{-3}c_2\end{aligned}$$

with Jacobian determinant

$$d(x, \pi) = -k_1k_2(e_0 - c_1 + c_2)(k_{-3} + k_3(i_0 + e_0) - k_3(2c_2 - c_1)).$$

Four equations for three variables: **Elimination ideal** has radical

$$\mathcal{I} = \langle e_0k_1k_2k_{-3}(k_3^2(e_0 - i_0)^2 + k_{-3}(k_{-3} + 2k_3(e_0 + i_0))) \rangle$$

with single generator. This yields candidates for Π_1 by setting $e_0 = 0$, resp. $k_1 = 0$, ...

Competitive inhibition: One of the reductions

System with “small” $e_0 = \varepsilon e_0^*$. Here

$$g^{(0)} = \begin{pmatrix} k_1 s + k_{-1} & k_1 s \\ -(k_1 s + k_{-1} + k_2) & -k_1 s \\ -k_3(i_0 - c_2) & -k_3(i_0 - c_2) - k_{-3} \end{pmatrix} \cdot \begin{pmatrix} c_1 \\ c_2 \end{pmatrix},$$

$$g^{(1)} = \begin{pmatrix} -k_1 s e_0^* \\ k_1 s e_0^* \\ k_3 e_0^*(i_0 - c_2) \end{pmatrix}.$$

Critical variety Z defined by $c_1 = c_2 = 0$; reduced system

$$s' = -\frac{k_1 k_2 k_{-3} e_0^* s}{k_1 k_{-3} s + (k_{-1} + k_2)(k_3 i_0 + k_{-3})}, \quad c_1' = c_2' = 0.$$

Note: “Classical” QSS reduction procedure yields the same result.

PART THREE: APPLICATION TO A POPULATION MODEL

Joint work with
Niclas Kruff
Christian Lax
Volkmar Liebscher

A well-known predator - prey system

Rosenzweig and MacArthur:

$$\begin{aligned}\dot{B} &= \rho B(1 - B) - \frac{\alpha\theta}{\theta+B}BR, \\ \dot{R} &= -\delta R + \frac{\zeta\alpha\theta}{\theta+B}BR.\end{aligned}$$

(B stands for prey, R stands for predator. All parameters positive.)

Questions:

- ▶ How to derive this specific equation from “first principles”?
- ▶ Biological interpretation of the parameters?

Approach presented here:

- ▶ Start from individual-based (stochastic) model with mass action type interactions (“first principles”).
- ▶ Pass to ODE (“large volume limit”)
- ▶ Look at singular perturbation reductions.

Start from individual based model

Three dimensional model with prey B , saturated predators S and hungry predators H ; $R = H + S$.

Differential equation derived from stochastic model:

$$\begin{aligned}\dot{B} &= \rho B(1 - B) - \alpha BH \\ \dot{S} &= -\eta S + \gamma BH \\ \dot{H} &= \beta S - \delta H + \eta S - \gamma BH.\end{aligned}$$

Parameters have clear biological interpretation;
e.g. ρ is birth rate of prey, η is rate of transition from saturated to hungry, ...

Rosenzweig-MacArthur via reduction

Educated guess: The system

$$\begin{aligned}\dot{B} &= \rho B(1 - B) - \alpha BH \\ \dot{S} &= -\eta S + \gamma BH \\ \dot{H} &= \beta S - \delta H + \eta S - \gamma BH\end{aligned}$$

admits the TFPV

$$\hat{\pi} := (0, \hat{\alpha}, 0, \hat{\gamma}, 0, \hat{\delta});$$

thus $\rho = \eta = \beta = 0$.

Singular perturbation reduction (straightforward) yields Rosenzweig-MacArthur.

Problem (non-mathematical): Biological interpretation of small parameters (slow vs. fast processes).

TFPV and reductions of 3D system

Systematic approach rather than guesswork: Determine all TFPV of

$$\begin{aligned}\dot{B} &= \rho B(1 - B) - \alpha BH \\ \dot{S} &= -\eta S + \gamma BH \\ \dot{H} &= \beta S - \delta H + \eta S - \gamma BH\end{aligned}$$

for dimension $s = 2$ of the critical manifold.

- ▶ Necessary conditions (via elimination ideals):

$$\rho\eta\delta = \rho\gamma\delta = \alpha\eta\delta = \rho\gamma\beta = 0.$$

- ▶ Roughly two dozen cases, not all yielding a TF reduction.
- ▶ 15 TF reductions; among these four interesting ones.
- ▶ One of these is Rosenzweig-MacArthur (above).
- ▶ Another one to be discussed next.

A variant of Rosenzweig-MacArthur

One result of systematic approach: The differential equation

$$\begin{aligned}\dot{B} &= \rho B(1 - B) - \alpha BH \\ \dot{S} &= -\eta S + \gamma BH \\ \dot{H} &= \beta S - \delta H + \eta S - \gamma BH\end{aligned}$$

admits the TFPV

$$\hat{\pi} := (0, 0, \hat{\eta}, \hat{\gamma}, 0, 0)$$

with reduced equation (here $\rho = \varepsilon\rho^*$ etc.)

$$\begin{aligned}B' &= \rho^* B(1 - B) - \frac{\alpha^* \theta}{\theta + B} BR \\ R' &= -\delta^* \frac{\theta}{\theta + B} R + \frac{\beta^*}{\theta + B} BR.\end{aligned}$$

More satisfactory from biological (modelling) perspective.

PART FOUR: SOME RECENT RESULTS

Joint work with
Elisenda Feliu
Niclas Kruff
Christian Lax
Carsten Wiuf

“Classical” QSS reduction

“**Classical**” **QSS reduction**, following Briggs/Haldane (1925) in more general setting: Consider system

$$\begin{aligned}\dot{x} &= a_0(x) + A_0(x)z + \varepsilon (a_1(x) + A_1(x)z) + \dots \\ \dot{z} &= b_0(x) + B_0(x)z + \varepsilon (b_1(x) + B_1(x)z) + \dots\end{aligned}$$

and assume that $B_0(x)$ is invertible for all x . (Not the most general setting but the most relevant.)

Elimination of z via QSS assumption:

Solve “ $\dot{z} = 0$ ” and substitute expression for z in first equation.

Observation: Reduction is not necessarily meaningful!

Minimal requirement for consistency:

$$\left(Db_0(x) - DB_0(x)(B_0(x)^{-1}b_0(x)) \right) \left(a_0(x) - A_0(x)B_0(x)^{-1}b_0(x) \right) = 0.$$

“Classical” QSS vs. singular perturbations

System

$$\begin{aligned}\dot{x} &= a_0(x) + A_0(x)z + \varepsilon(a_1(x) + A_1(x)z) + \dots \\ \dot{z} &= b_0(x) + B_0(x)z + \varepsilon(b_1(x) + B_1(x)z) + \dots\end{aligned}$$

with $B_0(x)$ is invertible for all x .

- **Minimal requirement** for consistency of QSS reduction:

$$\left(Db_0 - DB_0(B_0^{-1}b_0)\right) \left(a_0 - A_0B_0^{-1}b_0\right) = 0.$$

(Argument x suppressed.)

- **Necessary** for Tikhonov–Fenichel reduction with critical manifold Y prescribed by $b_0(x) + B_0(x)z = 0$:

$$a_0(x) - A_0(x)B_0(x)^{-1}b_0(x) = 0$$

for all x .

Tikhonov-Fenichel reduction

Reduction with prescribed critical manifold Y : With

$$w(x) := B_0(x)^{-1}b_0(x), \text{ thus } z = -w(x) \text{ on } Y$$

one has

$$\begin{aligned} b_0(x) + B_0(x)z &= B_0(x)(w(x) + z), \\ a_0(x) + A_0(x)z &= A_0(x)(w(x) + z). \end{aligned}$$

Use reduction theorem for

$$g^{(0)}(x, z) = \begin{pmatrix} a_0(x) + A_0(x)z \\ b_0(x) + B_0(x)z \end{pmatrix}, \quad g^{(1)}(x, z) = \begin{pmatrix} a_1(x) + A_1(x)z \\ b_1(x) + B_1(x)z \end{pmatrix}.$$

Reduced systems

Abbreviation:

$$M := Dw A_0 B_0^{-1} + I_p.$$

Proposition.

- (a) The reduced equation by singular perturbation theory, in slow time $\tau = \varepsilon t$, on Y yields the system

$$\begin{aligned} \frac{dx}{d\tau} &= \left(I_n - A_0 B_0^{-1} M^{-1} Dw \right) (a_1 - A_1 w) \\ &\quad - \left(A_0 B_0^{-1} M^{-1} \right) (b_1 - B_1 w). \end{aligned}$$

- (b) The reduction by the classical QSS procedure yields, in slow time, the system

$$\frac{dx}{d\tau} = \left(a_1 - A_1 w - A_0 B_0^{-1} (b_1 - B_1 w) \right) + \varepsilon(\cdots).$$

Agreement and disagreement

Corollary. The classical QSS reduction agrees with the singular perturbation reduction (up to higher order terms in ε) if and only if

$$A_0 B_0^{-1} M^{-1} Dw (A_0 B_0^{-1} (B_1 w - b_1) - (A_1 w - a_1)) = 0.$$

Given this, Tikhonov's theorem also applies to the QSS reduction.

The condition holds in the following scenarios:

- ▶ $Dw = 0$, thus w is constant.
- ▶ $A_0 = 0$: System is in Tikhonov standard form.
- ▶ $A_0 B_0^{-1} (B_1 w - b_1) = A_1 w - a_1$: Both reductions trivial.

But in general QSS heuristic and singular perturbation reduction yield substantially different results, and reduction by QSS is incorrect.

An incorrect QSS reduction

Popular example: Irreversible Michaelis-Menten equation

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

with *slow product formation*; $k_2 = \varepsilon k_2^*$.

Tikhonov-Fenichel reduction on critical manifold Y (given by $k_1 e_0 s - (k_1 s + k_{-1})c = 0$):

$$\dot{s} = -\frac{k_2 k_1 e_0 s (k_1 s + k_{-1})}{k_{-1} e_0 + (k_1 s + k_{-1})^2}.$$

QSS reduction for complex:

$$\dot{s} = -\frac{k_2 k_1 e_0 s}{k_1 s + k_{-1} + k_2} = -\frac{k_2 k_1 e_0 s}{k_1 s + k_{-1}} + \varepsilon(\dots)$$

These differ significantly (and **QSS is wrong**)!

Reduction for parameterized critical manifolds

Recall coordinate-free reduction for system

$$x' = \varepsilon^{-1}g^{(0)}(x) + g^{(1)}(x) + \dots$$

on critical manifold Z : Use decomposition $g^{(0)}(x) = P(x)\mu(x)$ to get reduced system

$$x' = Q(x)g^{(1)}(x), \quad Q(x) := \left[I_n - P(x)A(x)^{-1}D\mu(x) \right].$$

Problem: Feasibility for the computation of projection matrix Q .

Alternative approach when parameterization known:

Given open set $W \subseteq \mathbb{R}^s$ and smooth parameterization

$$\Phi: W \rightarrow Z, \quad \text{rank } D\Phi(v) = s \text{ for all } v \in W.$$

Reduction for parameterized CM

Observation: Every solution $x(t)$ of the reduced system with initial value in $\Phi(W)$ can be written as $x(t) = \Phi(v(t))$. Thus

$$D\Phi(v(t)) v'(t) = x'(t) = Q(\Phi(v(t))) \cdot g^{(1)}(\Phi(v(t))).$$

Theorem.

(a) For every $v \in W$ there exists a unique $R(v) \in \mathbb{R}^{s \times n}$ such that

$$Q(\Phi(v)) = D\Phi(v) \cdot R(v).$$

(b) The reduced system, in parameterized version, is given by

$$v' = R(v) \cdot g^{(1)}(\Phi(v)).$$

(c) For every $x \in Z$ let $L(x) \in \mathbb{R}^{s \times n}$ be of full rank s and such that $L(x)P(x) = 0$. Then

$$R(v) = (L(\Phi(v)) D\Phi(v))^{-1} L(\Phi(v)).$$

Application to CRN: Fast and slow reactions

Differential equation for network with slow and fast reactions:

$$\dot{x} = N_f \cdot (K_f \circ x^{Y_f}) + \varepsilon N_s \cdot (K_s \circ x^{Y_s})$$

Notation: N_f and N_s are stoichiometric matrices, and one has rate vectors

$$w_f(x) = K_f \circ x^{Y_f}, \quad w_s(x) = K_s \circ x^{Y_s}$$

with vectors of reaction constants K_f, K_s . (Here $\circ$ denotes elementwise product, $x^a = \prod x_i^{a_i}$ for vectors, similarly for matrix exponents.)

Observation: If r denotes the rank of $Dg^{(0)}(x)$, $x \in Z$, then $\text{rank } N_f \geq r$, but inequality may be strict.

Rank condition. We impose that $\text{rank } N_f = \text{rank } Dh^{(0)}(x) = r$, for all $x \in Z$.

Reduction for fast and slow reaction systems

Proposition. Given the system with slow and fast reactions, and a parameterization Φ of the critical manifold, assume the rank condition holds on $\Phi(W)$.

Let $L_f \in \mathbb{R}^{s \times n}$ be a matrix whose rows form a basis of the left-kernel of N_f . Then $R(v) = (L_f D\Phi(v))^{-1} L_f$, and the reduced system is given by

$$v' = (L_f D\Phi(v))^{-1} L_f N_s \cdot (K_s \circ \Phi(v)^{Y_s}), \quad v \in W.$$

Remark.

- ▶ Parameterization Φ of the stationary points for the fast system is needed. But for many relevant reaction networks such parameterizations are known.
- ▶ Closed form reductions like the above are preferable from an applied perspective.

Thank you for your attention!

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