Quasi-steady state –
A mathematical characterization

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The topic

- Quasi-steady state (QSS) reduction: Strange method to reduce dimension of (bio-)chemical reaction equations.
- Pragmatic view: Strange but often successful.
- Today: The mathematical side of QSS.

First example

Michaelis-Menten equation ("irreversible")

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

with positive parameters.

Quasi-steady state for complex concentration c:

- Assume $\dot{c} = 0$, thus $k_1 e_0 s - (k_1 s + k_{-1} + k_2)c = 0$.
- Solve for c as function of s.
- Substitute in first equation to get $\dot{s} = -k_1 k_2 e_0 s/(k_1 s + k_{-1} + k_2)$.
- Is this legal? If it is, why?

Objects

Parameter-dependent ordinary differential equations

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

with *polynomial* (or *rational*) right-hand side.

Motivation: Chemical reaction networks, mass action kinetics, thermodynamic parameters fixed.

Bonus: Explicit computations become feasible (algorithmic algebra).

Objectives

- Take this strange reduction procedure seriously.
- Determine conditions so that procedure is (approximately) legal from a mathematical perspective.
- Determine (all) parameters for which procedure is legal.
- Relation to singular perturbation reductions (Tikhonov, Fenichel).

Benchmark example: Reversible Michaelis-Menten

Reaction scheme

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

leads to differential equation system for the concentrations:

$$\begin{aligned}
\dot{s} &= -k_1 es + (k_1 s + k_{-1})c,\\
\dot{c} &= k_1 es - (k_1 s + k_{-1} + k_2)c + k_{-2}ep,\\
\dot{e} &= -k_1 es + (k_1 s + k_{-1} + k_2)c - k_{-2}ep,\\
\dot{p} &= k_2 c - k_{-2}ep.
\end{aligned}$$

Stoichiometry (linear first integrals $e + c$ and $s + c + p$) and initial conditions:

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

QSS for reversible Michaelis-Menten

Differential equation

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

QSS reduction for complex C:
Condition $\dot{c} = 0$ yields quadratic equation for $c = c(s)$, etc. (Manageable, but unwieldy.)

Singular perturbation reduction with "small parameter" $e_0 \to 0$ yields reduced equation

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

Correspondence: This is the first order term in expansion of QSS reduction!

QSS reduction in general I

Given a (polynomial or rational) system

$$\dot{x} = h(x, \pi) = \begin{pmatrix} h_1(x, \pi) \\ \vdots \\ h_n(x, \pi) \end{pmatrix}$$

Notation: For $1 \leqslant r < n$ set

$$\begin{aligned} x^{[1]} &:= (x_1, \ldots, x_r)^{\mathrm{tr}}; \quad x^{[2]} := (x_{r+1}, \ldots, x_n)^{\mathrm{tr}}; \\ h^{[1]} &:= (h_1, \ldots, h_r)^{\mathrm{tr}}; \quad h^{[2]} := (h_{r+1}, \ldots, h_n)^{\mathrm{tr}}; \\ Y_\pi &:= \{x \in \mathbb{R}^n;\ h^{[2]}(x, \pi) = 0\}. \end{aligned}$$

The reduction procedure (underlying reasoning):

- Underlying assumption: QSS with respect to "chemical species" $x^{[2]} := (x_{r+1}, \ldots, x_n)^{\mathrm{tr}}$.
- Solve $h^{[2]} = 0$ for $x^{[2]}$ as function of $x^{[1]}$. Substitute in $h^{[1]}$.
- This should work on the zero set Y_π of $h^{[2]}$.

QSS reduction in general II

Necessary conditions for existence of reduction (with $\pi = \pi^*$ fixed):

- The zero set Y_{π^*} should be nonempty. Let $y^* \in Y_{\pi^*}$.
- Full rank of $(x_1, \ldots, x_r, h_{r+1}, \ldots, h_n)^{\mathrm{tr}}$ at y^*.

Definition. For π near π^* the following equation will be called a *QSS-reduced equation* of $\dot{x} = h(x, \pi)$ on U_π, given QSS for $x_{r+1}, \ldots, x_n$:

$$\begin{array}{rcl} \dot{x}^{[1]} & = & h^{[1]}(x, \pi) \\ \dot{x}^{[2]} & = & -D_2 h^{[2]}(x, \pi)^{-1} D_1 h^{[2]}(x, \pi) h^{[1]}(x, \pi) \end{array}; \text{ briefly } \dot{x} = h_{\mathrm{red}}(x, \pi).$$

(Here D_i denotes the partial derivative with respect to $x^{[i]}$.)

Note. This is an equivalent implicit version of $\dot{x}^{[1]} = h^{[1]}(x^{[1]}, \Psi(x^{[1]}))$ whenever $h^{[1]}(x^{[1]}, x^{[2]}) = 0$ is being solved to yield $x^{[2]} = \Psi(x^{[1]})$.

(When) does QSS reduction make sense?

Consider

$$\dot{x} = h(x,\ \pi) \text{ versus } \begin{array}{rcl} \dot{x}^{[1]} & = & h^{[1]}(x,\pi) \\ \dot{x}^{[2]} & = & -D_2h^{[2]}(x,\pi)^{-1}D_1h^{[2]}(x,\pi)h^{[1]}(x,\pi) \end{array}$$

Minimal requirement: Approximate correctness.

Proposition. The solutions of both systems starting on U_π are equal if and only if U_π is invariant for the first.

Definition: Call π^* a *QSS parameter value* with respect to the species $x_{r+1}, \ldots, x_n$ if the rank condition holds at some y^* for $h^{[2]} = (h_{r+1}, \ldots, h_n)$ and U_{π^*} is invariant.

Proposition. The solutions of both systems starting on U_π are approximately equal (in a well-defined sense) if and only if π is close to a QSS parameter value π^*.

Consequence: It suffices to search for QSS parameter values.

Finding QSS parameter values I

Exploit invariance and rank conditions for U_π to get:

Proposition. Let the polynomial system $\dot{x} = h(x, \pi)$ be given, let π^* be a QSS parameter value with respect to $x_{r+1}, \ldots, x_n$, and let $y^* \in Y_{\pi^*}$ satisfy the rank condition. Then (y^*, π^*) lies in the ideal $J \subseteq \mathbb{R}[x, \pi]$ generated by the polynomials

- $h_{r+1}, \ldots, h_n$;
- $L_h(h_{r+1}), \ldots, L_h(h_n)$ (Here L_h denotes the Lie derivative);
- all $(n - r + 1) \times (n - r + 1)$ minors of the Jacobians of

$$\begin{pmatrix} h_{r+1} \\ \vdots \\ h_n \\ L_h(h_k) \end{pmatrix}, \quad r + 1 \leqslant k \leqslant n.$$

Finding QSS parameter values II

Notation. Call π^* a *QSS-critical parameter value* if $(y^*, \pi^*) \in J$ for some y^*. Then π^* is a QSS parameter value if and only if y^* can be chosen such that the the rank condition holds.

Observations.

- The number of defining equations for the ideal J is greater than the number of variables $x_1, \ldots, x_n$. ("More equations than variables!")
- The elimination ideal $J \cap \mathbb{R}[\pi]$ provides conditions on parameters.
- Algorithmic algebra (Groebner bases etc.) can be put to work. (Initially standard methods suffice.)

Example

QSS-critical parameter values for irreversible Michaelis-Menten;
QSS *for substrate* s:

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

Consider ideal J generated by

$$\theta, \quad L_h(\theta) = -(k_1(e_0 - c) + k_1 s + k_{-1})\theta - (k_1 s + k_{-1})k_2 c$$

and their Jacobian determinant. Eliminate s and c.

Result: The radical of the elimination ideal is generated by $e_0 k_1 k_2 k_{-1}$. In other words, any QSS-critical parameter value $\pi^* = (e_0^*, k_1^*, k_2^*, k_{-1}^*)$ must have one entry zero.

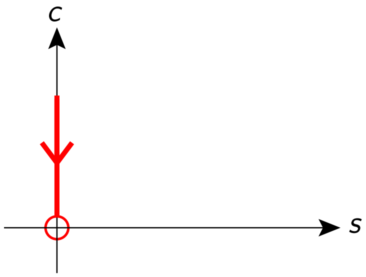
Remark: This yields "small parameters" e_0, resp. k_1, resp. k_2, resp. k_{-1}.

Example (cont.)

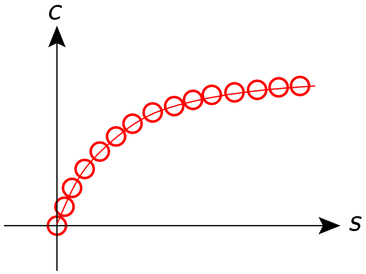
Irreversible Michaelis-Menten, QSS for s; QSS-critical parameters.

Some cases:

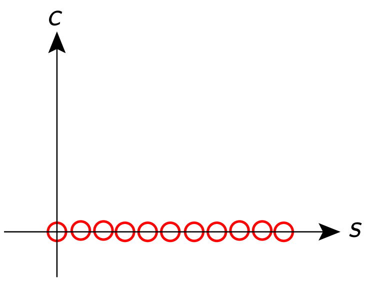
- For $k_{-1} = 0$ (other parameters > 0) one has invariant set given by $s = 0$. (Regular perturbation problem for small k_{-1}.)



- For $k_2 = 0$ (other parameters > 0) one has invariant set given by $k_1 e_0 s - (k_1 s + k_{-1})c = 0$. All points on this set are stationary: Singular perturbation problem!



- For $e_0 = 0$ (other parameters > 0) one has invariant set given by $c = 0$. All points on this set are stationary: Singular perturbation problem!



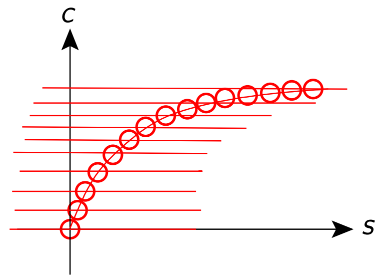
Structure in greater detail

QSS parameter values provide further invariant sets:

Proposition. Given $\dot{x} = h(x, \pi)$, consider QSS with respect to species $x_{r+1}, \ldots, x_n$, and let π^* be a QSS parameter value, with local invariant manifold U_{π^*}. Then every set

$$U_{\pi^*} \cap \{x;\ x_{r+1} = \gamma_{r+1}, \ldots, x_n = \gamma_n\}$$

(with constants $\gamma_{r+1}, \ldots, \gamma_n$) is also invariant for $\dot{x} = h(x, \pi^*)$.



Remarks.

- This property frequently forces singular settings, i.e. existence of non-isolated stationary points.
- Natural question: How reliable is QSS reduction in singular circumstances?

Singular settings: A view of the problem

Notation. Near a QSS parameter value π^*, consider $\pi^* + \delta\rho$ with some $\rho \in \mathbb{R}^m$, $\delta \geqslant 0$ and write

$$h(x, \pi^*) =: h_0(x), \quad h(x, \pi^* + \delta\rho) = h_0(x) + \delta h_1(x) + \cdots ;$$

similarly for $h^{[1]}$ and $h^{[2]}$. QSS reduction up to first order in δ:

$$\begin{aligned} \dot{x}^{[1]} &= h_0^{[1]}(x) + \delta h_1^{[1]}(x) \\ \dot{x}^{[2]} &= -D_2 h_0^{[2]}(x)^{-1} D_1 h_0^{[2]}(x) h_0^{[1]}(x) + \delta q(x) \end{aligned}$$

with some (complicated) q.

Singular setting: $h_0^{[1]}$ has non-isolated zeros on U_{π^*}.

Fully singular setting: If $h_0^{[1]}$ vanishes on U_{π^*} then we have reduction

$$\begin{aligned} \dot{x}^{[1]} &= \delta h_1^{[1]}(x) \\ \dot{x}^{[2]} &= -\delta D_2 h_0^{[2]}(x)^{-1} D_1 h_0^{[2]}(x) h_1^{[1]}(x) \end{aligned}$$

Realistic? Dependence theorem guarantees only order zero in δ!

Digression: Singular perturbations (slow/fast separation given)

Classical singular perturbation theory (Tikhonov, Fenichel): System in standard form with "fast and slow variables" separated:

$$\begin{aligned} \dot{y}^{[1]} &= \epsilon f_1(y^{[1]}, y^{[2]}) + \epsilon^2 \cdots ; \\ \dot{y}^{[2]} &= g_0(y^{[1]}, y^{[2]}) + \epsilon \cdots ; \end{aligned} \qquad \begin{aligned} {y^{[1]}}' &= f_1(y^{[1]}, y^{[2]}) + \epsilon \cdots ; \\ \epsilon^{-1} {y^{[2]}}' &= g_0(y^{[1]}, y^{[2]}) + \epsilon \cdots \end{aligned}$$

(in fast and slow time scales); $\epsilon > 0$ parameter. Interest in behavior near $\epsilon = 0$.

Conditions.

- $Z := \{y;\, g_0(y) = 0\} \neq \emptyset$ and $D_2 g_0(y)$ invertible for all $y \in Z$.
- There is $\sigma > 0$ so that all eigenvalues of $D_2 g_0(y)$, $y \in Z$ have real part $\leq -\sigma$.
- By implicit function theorem: Parameterization $y \in Z \Leftrightarrow y^{[2]} = \Gamma(y^{[1]})$.

Theorem. Given above conditions, there is a compact interval J such that solutions of system (in slow time) converge toward solutions of reduced system

$$ {y^{[1]}}' = f_1(y^{[1]}, \Gamma(y^{[1]}))$$

on J, uniformly in ϵ. Moreover, for every small ϵ the system admits an invariant "slow manifold" near Z.

Digression: Singular perturbations “in the wild”

Given system $\dot{x} = h(x, \pi)$, a parameter $\widehat{\pi}$ is called a *Tikhonov-Fenichel (TF) parameter value for dimension s* $(1 \leqslant s \leqslant n-1)$ of the system whenever the following hold:

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

(ii) There is a point $x_0 \in \widetilde{V}$ such that $Dh(x, \widehat{\pi})$ has rank $n-s$ and

$$\mathbb{R}^n = \mathrm{Ker}\ Dh(x, \widehat{\pi}) \oplus \mathrm{Im}\ Dh(x, \widehat{\pi}) \text{ for all } x \in \widetilde{V} \text{ near } x_0.$$

(iii) The nonzero eigenvalues of $Dh(x_0, \widehat{\pi})$ have real part < 0.

TF parameter values: Properties

Motivation. If $\widehat{\pi}$ is a TF parameter value, and $\rho \in \mathbb{R}^m$, then one has classical singular perturbation scenario for

$$\dot{x} = h(x, \widehat{\pi} + \varepsilon\rho) \quad \text{as} \ \ \varepsilon \to 0.$$

Note: This holds up to a coordinate transformation!

Remark. TF parameter values are accessible to algorithmic algebra; see Condition (i) on non-isolated stationary points.

Theorem. The TF parameter values form a semi-algebraic variety in parameter space.

Singular perturbations "in the wild" (reduction)

Given $\dot{x} = h(x, \pi)$ with TF parameter value $\widehat{\pi}$ and some (suitable) $\rho \in \mathbb{R}^m$:

- One has reduction for
$$\dot{x} = h(x, \widehat{\pi} + \epsilon\rho) = h(x, \widehat{\pi}) + \epsilon q(x) + \cdots, \text{ as } \epsilon \to 0.$$
- To determine a reduced system on $\widetilde{V}$ explicitly, use a decomposition
$$h(x, \widehat{\pi}) = P(x, \widehat{\pi})\, \mu(x, \widehat{\pi})$$
in some neighborhood of $x_0 \in \widetilde{V}$; P is $\mathbb{R}^{n\times(n-s)}$-valued, and $\widetilde{V}$ is the vanishing set of the $\mathbb{R}^{(n-s)}$-valued function μ.
(Algorithmic algebra: standard bases.)
- $A(x, \widehat{\pi}) := D\mu(x, \widehat{\pi})\, P(x, \widehat{\pi})$ is invertible on $\widetilde{V}$. Reduced system $\widetilde{V}$ in fast time:
$$\dot{x} = \epsilon \cdot \left(I_n - P(x, \widehat{\pi})A(x, \widehat{\pi})^{-1} D\mu(x, \widehat{\pi})\right) q(x).$$
(Only linear algebra involved!)

Matching QSS and SPT – Experimental observations

- QSS and singular perturbation reduction coincide in some relevant cases (e.g. irreversible Michaelis-Menten, small parameter e_0).
- The reductions coincide up to lowest order in small parameter in even more cases (such as reversible Michaelis-Menten, small parameter e_0):

$$\begin{aligned}\dot{s} &= \text{something complicated involving square roots}\\ &= -e_0(k_1k_2s + k_{-1}k_{-2}(s - s_0))/(k_1s + k_{-1} + k_2 + k_{-2}(s_0 - s)) + \text{t.h.o.}\end{aligned}$$

(expand in powers of e_0).

- This fact explains the usefulness and popularity of QSS reduction.

Matching QSS and SPT – Counterexample

Irreversible Michaelis-Menten with slow product formation.

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

small parameter $\epsilon = k_2$; other parameters > 0.

Tikhonov-Fenichel reduction on $\widetilde{V}$ (determined by $\mu := k_1 e_0 s - (k_1 s + k_{-1})c = 0$) provides

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

Counterexample, continued

QSS reduction for complex with small parameter k_2 yields

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

(lowest order in k_2).

Compare with Tikhonov-Fenichel reduction (slightly rewritten):

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

Considerable discrepancy: QSS reduction procedure yields incorrect result!

Matching QSS and SPT II

Definition. Let π^* be a QSS parameter value of $\dot{x} = h(x, \pi)$, with respect to species $x_{r+1}, \ldots, x_n$.

We say that QSS near π^* is *consistent with the singular perturbation reduction* if:

- π^* is also a Tikhonov-Fenichel parameter value;
- the (asymptotic) slow manifold $\widetilde{V}$ coincides locally with U_{π^*};
- the reductions are in agreement up to first order.

Matching QSS and SPT III

A consistency result:

Proposition. Let π^* be a QSS parameter value of $\dot{x} = h(x, \pi)$, which is also a TF parameter value.
If $\widetilde{V}$ coincides locally with U_{π^*}, and if U_{π^*} is open-dense in some "affine coordinate subspace" $Z_{\gamma^*} = \{x;\ x_{r+1} = \gamma^*_{r+1}, \ldots, x_n = \gamma^*_n\}$ with constants γ^*_i, then the QSS reduction is consistent with the singular perturbation reduction.

Note. This explains Michaelis-Menten for small e_0.

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Application: A problem vanishes

Frequent (frequently suppressed) **problem** with QSS reduction: There may be no explicit solution $x^{[2]} = \Psi(x^{[1]})$ for $h^{[1]}(x^{[1]}, x^{[2]}) = 0$. (Recall Abel's theorem.)

Example. (Pantea et al.)

$$\begin{aligned}
\dot{a} &= k_2 by - k_4 ax + 2k_5 z^2 \\
\dot{b} &= 2k_1 y^2 - 2k_{-1} b^2 - k_2 by - k_3 bz + k_{-3} x^2 + k_4 ax \\
\dot{x} &= 2k_3 bz - 2k_{-3} x^2 - k_4 ax \\
\dot{y} &= -2k_1 y^2 + 2k_{-1} b^2 - k_2 by + k_4 ax \\
\dot{z} &= k_2 by - k_3 bz + k_{-3} x^2 - 2k_5 z^2
\end{aligned}$$

QSS assumption and reduction with respect to x, y, z: Polynomial system not solvable via radicals.

But: For QSS parameter value $k_{-1} = 0$ (all other parameters > 0) we have invariant plane given by $x = y = z = 0$, and QSS reduction is consistent with singular perturbation reduction.

A problem vanishes (cont.)

Use singular perturbation reduction with small parameter k_{-1} and decomposition

$$\begin{pmatrix}\dot{x}\\ \dot{y}\\ \dot{z}\end{pmatrix} = \begin{pmatrix}-k_4a & 0 & 2k_3b\\ k_4a & -k_2b & 0\\ 0 & k_2b & -k_3b\end{pmatrix}\begin{pmatrix}x\\ y\\ z\end{pmatrix} + \begin{pmatrix}\vdots\end{pmatrix} + k_{-1}\begin{pmatrix}0\\ 2b^2\\ 0\end{pmatrix}$$

etc. to arrive at reduced system

$$\begin{aligned}\dot{a} &= 2k_{-1}b^2\\ \dot{b} &= -2k_{-1}b^2\end{aligned}$$

Conclusion: There are cases where QSS reduction provides incorrect results (and, in addition, algebraic problems may persist). But in many relevant applications one has a feasible alternative approach (and essentially no algebraic obstacles).

Some open questions

Among other things:

- Workable version of conditions for QSS (and TF) parameter values.
- Make use of special properties of reaction systems to improve algorithms.
- Compare to other approaches to QSS (slow-fast heuristics).

Thank you for your attention!

Some references

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