Structure of CRN and critical parameters for singular perturbation reductions

Sebastian Walcher, RWTH Aachen

SYMBIONT Closing Event, Bonn, March 2022

The objective

- Reduce the dimension of an ODE system that models CRN.
- But first: Identify parameter regions that allow for reductions.
- Toolbox (of choice): Singular perturbation methods.

Pre-Symbiont

Recalling work by and with

Alexandra Goeke
Christian Lax
Lena Nöthen
Eva Zerz

Tikhonov and Fenichel: Basic theorem

System with small parameter ε in *standard "slow-fast" 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 $\tau = \varepsilon t$: $\quad \varepsilon x_1' = f_1(x_1, x_2) + \cdots, \quad x_2' = f_2(x_1, x_2) + \cdots$.

Assumptions: (i) Nonempty *critical manifold*

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

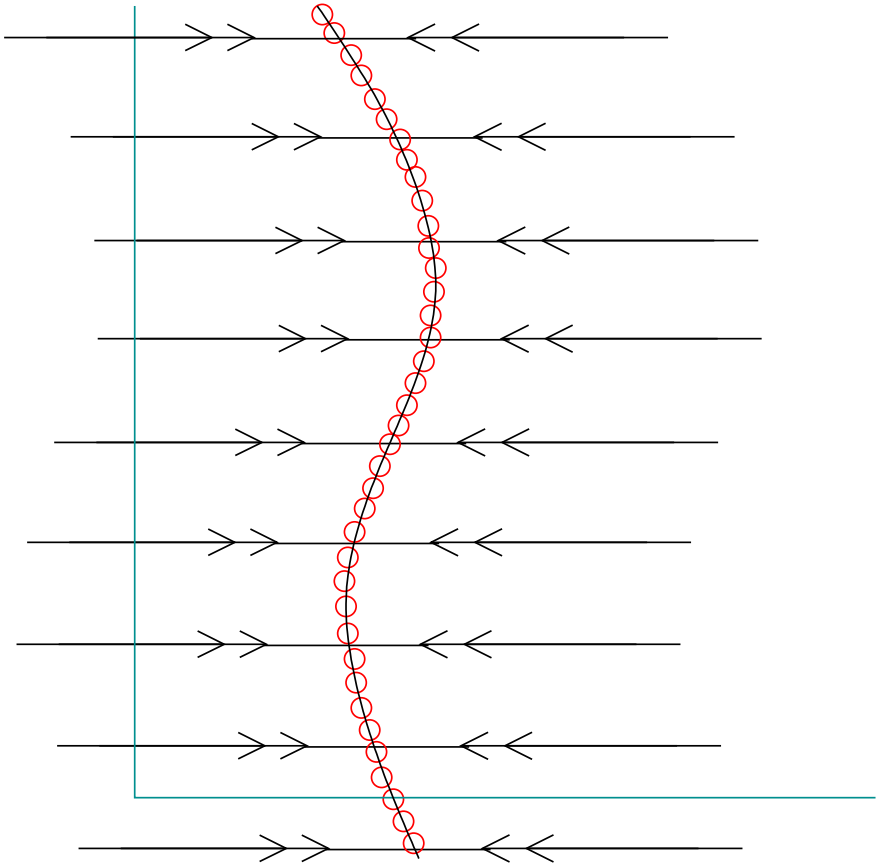
(ii) there exists $\nu > 0$ such that every eigenvalue of $D_1 f_1(y_1, y_2)$, $(y_1, y_2) \in \widetilde{Z}$ has real part $\leq -\nu$.

Theorem. There exist $T > 0$ and a neighborhood of $\widetilde{Z}$ in which, as $\varepsilon \to 0$, all solutions (in slow time) converge uniformly to solutions of

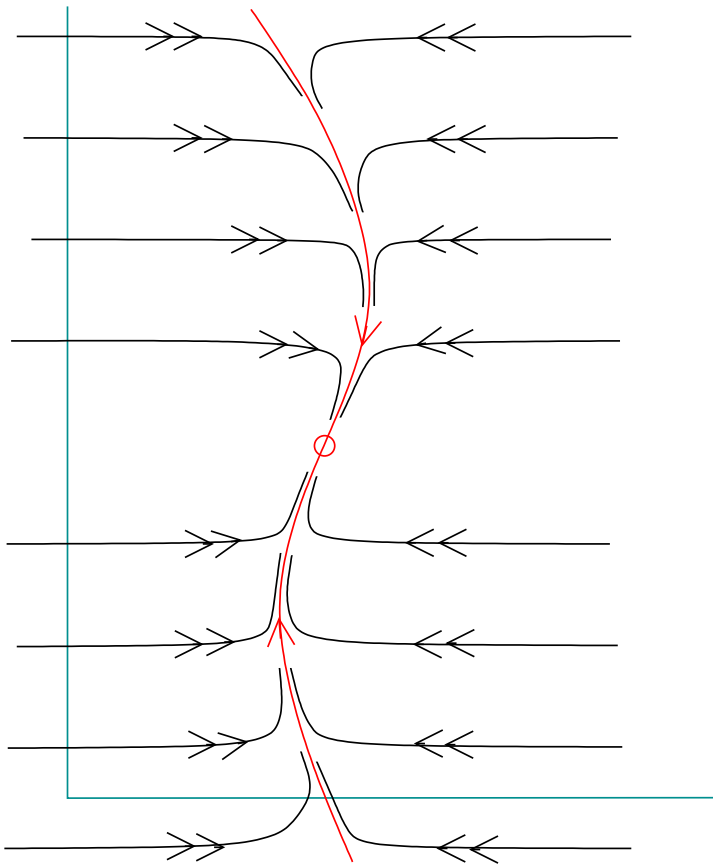
$$x_2' = f_2(x_1, x_2), \quad f_1(x_1, x_2) = 0 \quad \text{on } [t_0, T] \quad (t_0 > 0 \text{ arbitrary}).$$

Tikhonov-Fenichel: A visualization

$\varepsilon = 0$ (degenerate)



$\varepsilon > 0$ (for instance)



Chemical reaction networks

CRN model from a distance: 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.

Questions:

- How do singular perturbation reductions enter this picture?
- More to the point: Where is that ε?

Transferability to standard form

Parameter dependent system

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

versus system in Tikhonov standard form

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

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

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

Re suitability of $\widehat{\pi}$: Scenario must be *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) $\operatorname{rank} Dg^{(0)}(x) = r := n - s$ for all $x \in Z$;

(ii) for each $x \in Z$ there exists a direct sum decomposition $\mathbb{R}^n = \operatorname{Ker}\ Dg^{(0)}(x) \oplus \operatorname{Im}\ Dg^{(0)}(x)$;

(iii) for each $x \in Z$ the nonzero eigenvalues of $Dg^{(0)}(x)$ have real parts $\leq -\nu < 0$.

Caveat: Explicit computation of coordinate transformation is generally impossible (but we don't mind).

Finding suitable parameter values, part 1

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

(i) The vanishing set $\mathcal{V}(h(\cdot,\widehat{\pi}))$ of $x \mapsto h(x\,,\widehat{\pi})$ contains a component $\widetilde{Y}$ of dimension s;

(ii) there is $a \in \widetilde{Y}$ and neighborhood Z of a in $\widetilde{Y}$ such that $\operatorname{rank}\, D_x h(x,\widehat{\pi}) = n - s$ and

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

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

Note: Conditions essentially by copy-and-paste from characterization above. Therefore reduction works for small perturbations $\widehat{\pi} + \varepsilon\rho + \cdots$.

[1] For generic parameters there should be only isolated stationary points.

Finding suitable parameter values, part 2

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 $\widehat{\pi}$ 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:

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

TFPV for irreversible 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** $d = \sigma_2 = k_1 k_2 (e_0 - c)$.

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

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

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

Small perturbations yield all relevant cases:

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

Finding suitable parameter values, part 3

- Characterization above provides an algorithmic access: For a TFPV $\widehat{\pi}$, one has more equations for x than variables. Elimination (e.g. via Gröbner) is possible.
- For CRN this works better than expected (see MM example above), but limitations exist.
- Desideratum (as they say in the humanities): Relate TFPV to structure of CRN.

Some pre-SYMBIONT references

- A. Goeke, S. Walcher: *A constructive approach to quasi-steady state reduction.* J. Math. Chem. **52**, 2596 - 2626 (2014).
- A. Goeke, S. Walcher, E. Zerz: *Determining "small parameters" for quasi-steady state.* J. Diff. Equations **259**, 1149–1180 (2015).
- A. Goeke, S. Walcher, E. Zerz: *Classical quasi-steady state reduction – A mathematical characterization.* Physica D **343**, 11 - 26 (2017).

Part Two:
Symbiont and Post-Symbiont

Joint work with

Elisenda Feliu
Niclas Kruff
Christian Lax
Carsten Wiuf

Some SYMBIONT products

- C. Lax, S. Walcher: *Singular perturbations and scaling.* Discrete Contin. Dyn. Syst. Ser. B **25**, 1 - 29 (2020).
- E. Feliu, N. Kruff, S. Walcher: *Tikhonov-Fenichel reduction for parameterized critical manifolds with applications to chemical reaction networks*, J. Nonlinear Sci. **30**, 1355 - 1380 (2020).
- E. Feliu, C. Lax, S. Walcher, C. Wiuf: *Quasi-steady state and singular perturbation reduction for reaction networks with non-interacting species.* SIAM J. Appl. Dyn. Sys. (to appear).
- E. Feliu, S. Walcher, C. Wiuf: *Critical parameters for singular perturbation reductions of chemical reaction networks.* In revision (2022).

ODEs for mass action networks: A closer look

Proposition (Horn, Jackson). The dynamics of a mass action CRN is determined by the ordinary differential equation

$$\dot{x} = F(x, \kappa) := Y \cdot A(\kappa) \cdot v(x)$$

for the concentrations x_i of the chemical species X_i.

- $\kappa \in \mathbb{R}^m_{\geq 0}$ stands for the reaction rate parameters.
- Complexes $Y_j = \sum_i y_{ij} X_i$, $1 \leq j \leq d$, with $y_{ij} \in \mathbb{Z}_{\geq 0}$.
- $Y := (y_{ij}) \in \mathbb{R}^{n \times d}$ is the complex matrix of the network.
- Moreover

$$v(x) = (v_j(x))_{1 \leq j \leq d}, \quad v_j(x) = \prod_{1 \leq i \leq n} x_i^{y_{ij}}; \quad \text{briefly } v(x) = x^Y.$$

- $A(\kappa)$ is called the reaction rate matrix.

Structure of the reaction rate matrix

Laplacian matrix

$$A(\kappa) := \begin{pmatrix} -\sum_\ell \gamma_{1\ell} & \gamma_{21} & \cdots & \gamma_{d1} \\ \gamma_{12} & & \ddots & \vdots \\ \vdots & \ddots & \ddots & \gamma_{d,d-1} \\ \gamma_{1d} & \cdots & \gamma_{d-1,d} & -\sum_\ell \gamma_{d\ell} \end{pmatrix} \in \mathbb{R}^{d\times d}$$

with nonnegative γ_{ij}.

Note: All non-diagonal entries ≥ 0 and all column sums $= 0$; thus $(1, \ldots, 1) \cdot A(\kappa) = 0$.

Laplacians: Some facts

- **Reducibility:** A Laplacian matrix is reducible (decomposable) if it can be written (up to permutation of indices) as

$$A = \begin{pmatrix} A_{11} & A_{12} \\ 0 & A_{22} \end{pmatrix} \quad \text{resp.} \quad A = \begin{pmatrix} A_{11} & 0 \\ 0 & A_{22} \end{pmatrix}.$$

  Further refinements may be possible.

- **Proposition.** An irreducible Laplacian A has left kernel spanned by

$$(1, \ldots, 1)\,.$$

- The kernel dimension of any Laplacian is well understood.
- Alle nonzero eigenvalues have real part < 0.

CRN, Laplacians and graphs

- A CRN with mass action kinetics may be seen as a labelled digraph: The complexes are nodes, the reactions are arrows, the rate parameters are labels.
- Properties of the graph correspond to properties of the reaction rate matrix. For instance, the graph is disconnected if and only if the matrix is decomposable.

Notion of TFPV - An adjustment for CRN

Definition: Let $\dot{x} = h(x, \pi)$ admit $s^* \geq 0$ independent stoichiometric first integrals for all π. We call $\widehat{\pi}$ a TFPV for dimension s ($s^* + 1 \leq s \leq n - 1$) of $\dot{x} = h(x, \pi)$ if the following hold:

(i) The vanishing set $\mathcal{V}(h(\cdot, \widehat{\pi}))$ of $x \mapsto h(x, \widehat{\pi})$ contains a component $\widetilde{Y}$ of dimension s;

(ii) there is $a \in \widetilde{Y}$ and neighborhood Z of a in $\widetilde{Y}$ such that $\operatorname{rank} D_x h(x, \widehat{\pi}) = n - s$ and

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

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

This yields the original definition for restrictions to stoichiometric compatibility classes (SCC).

TFPV from CRN structure - Where to look?

Recall structure of ODE:

$$\dot{x} = Y \cdot A(\kappa) \cdot x^Y$$

with Laplacian matrix $A(\kappa)$. Need to understand variety of stationary points.

- First approach: $\operatorname{Ker} A(\kappa)$ is well understood; dimension apparent from reducibility properties or graph connectivity. (But what about $\operatorname{Ker} Y \cdot A(\kappa)$?)
- Second approach: Stationary points from $x^Y = 0$, regardless of other ingredients. (In general, one gets more than $\{0\}$).

Example: Reversible Michaelis-Menten

Reaction network $G(\kappa)$:

$$X_1 + X_2 \underset{\kappa_{-1}}{\overset{\kappa_1}{\rightleftarrows}} X_3 \underset{\kappa_{-2}}{\overset{\kappa_2}{\rightleftarrows}} X_4 + X_2.$$

Differential equation:

$$\begin{pmatrix} \dot{x}_1 \\ \dot{x}_2 \\ \dot{x}_3 \\ \dot{x}_4 \end{pmatrix} = \begin{pmatrix} 1 & 0 & 0 \\ 1 & 0 & 1 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix} \cdot \begin{pmatrix} -\kappa_1 & \kappa_{-1} & 0 \\ \kappa_1 & -(\kappa_{-1} + \kappa_2) & \kappa_{-2} \\ 0 & \kappa_2 & -\kappa_{-2} \end{pmatrix} \cdot \begin{pmatrix} x_1 x_2 \\ x_3 \\ x_1 x_4 \end{pmatrix},$$

with

$$Y = \begin{pmatrix} 1 & 0 & 0 \\ 1 & 0 & 1 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix}, A(\kappa) = \begin{pmatrix} -\kappa_1 & \kappa_{-1} & 0 \\ \kappa_1 & -(\kappa_{-1} + \kappa_2) & \kappa_{-2} \\ 0 & \kappa_2 & -\kappa_{-2} \end{pmatrix}, v = \begin{pmatrix} x_1 x_2 \\ x_3 \\ x_2 x_4 \end{pmatrix}.$$

For this system, $\operatorname{Ker} Y \cdot A(\kappa) = \operatorname{Ker} A(\kappa)$.

Deficiency zero networks

$$\dot{x} = Y \cdot A(\kappa) \cdot v(x).$$

Definition. One says that the network has deficiency zero when $\mathrm{Ker}\, Y \cdot A(\kappa) = \mathrm{Ker}\, A(\kappa)$ for generic κ.

Note: This property is inherited by all specializations $\widehat{\kappa}$.

A consequence of Horn-Jackson-Feinberg structure theory:

Theorem. Let a weakly reversible network $G(\kappa)$ of deficiency zero be given, with n species and d complexes. Let $\widehat{\kappa} \in \mathbb{R}^m_{\geq 0}$ be such that the induced subnetwork $G(\widehat{\kappa})$ is weakly reversible and has more connected components than G.
Then $\widehat{\kappa}$ is a TFPV of the system for dimension $n - d + r$, with d and r the number of complexes, respectively, connected components of $G(\widehat{\kappa})$.

Example: Competitive inhibition

Competitive inhibition network with reversible product formation:

$$X_1 + X_2 \underset{\kappa_{-1}}{\overset{\kappa_1}{\rightleftharpoons}} X_3 \underset{\kappa_{-2}}{\overset{\kappa_2}{\rightleftharpoons}} X_4 + X_2, \quad X_5 + X_2 \underset{\kappa_{-3}}{\overset{\kappa_3}{\rightleftharpoons}} X_6.$$

This reaction network is weakly reversible with deficiency zero.

By the Theorem, setting either $\kappa_1 = \kappa_{-1} = 0$, or $\kappa_2 = \kappa_{-2} = 0$, or $\kappa_3 = \kappa_{-3} = 0$, the number of connected components increases by one, and the resulting rate parameters are TFPVs for dimension 4. In addition, choosing two of the three pairs to be zero, one obtains TFPVs for dimension 5.

For restrictions to (three dimensional) SCC: TFPVs for dimension one and two, respectively.

Note: We have found TFPV without recourse to algorithmic algebra.

The other approach: Canonical scalings

Genuinely nonlinear heuristic for mass action systems

$$\dot{x} = Y \cdot A(\kappa) \cdot x^Y.$$

- **Fact.** The irreducible components of the variety defined by $x^Y = 0$ are coordinate subspaces, i.e. defined by equations

$$x_{i_1} = \cdots = x_{i_r} = 0$$

with some $r < n$ and $1 \leq i_1 < \cdots < i_r \leq n$.

- **Heuristic:** For every nontrivial choice of such a coordinate subspace the scaling

$$x_{i_k} = \varepsilon x^*_{i_k}$$

yields a slow-fast system for which Tikhonov may apply.

- **Fact.** Under suitable conditions, such scalings correspond to stoichiometric first integrals and TFPV on SCC's.

Example revisited: Reversible Michaelis-Menten

Differential equation:

$$\begin{pmatrix} \dot{x}_1 \\ \dot{x}_2 \\ \dot{x}_3 \\ \dot{x}_4 \end{pmatrix} = \begin{pmatrix} 1 & 0 & 0 \\ 1 & 0 & 1 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix} \cdot \begin{pmatrix} -\kappa_1 & \kappa_{-1} & 0 \\ \kappa_1 & -(\kappa_{-1}+\kappa_2) & \kappa_{-2} \\ 0 & \kappa_2 & -\kappa_{-2} \end{pmatrix} \cdot \begin{pmatrix} x_1 x_2 \\ x_3 \\ x_1 x_4 \end{pmatrix},$$

with

$$x^Y = \begin{pmatrix} x_1 x_2 \\ x_3 \\ x_2 x_4 \end{pmatrix}.$$

- The variety defined by $x^Y = 0$ has two components $x_2 = x_3 = 0$ resp. $x_1 = x_3 = x_4 = 0$.
- These correspond to the first integrals $x_2 + x_3$ and $x_1 + x_3 + x_4$.

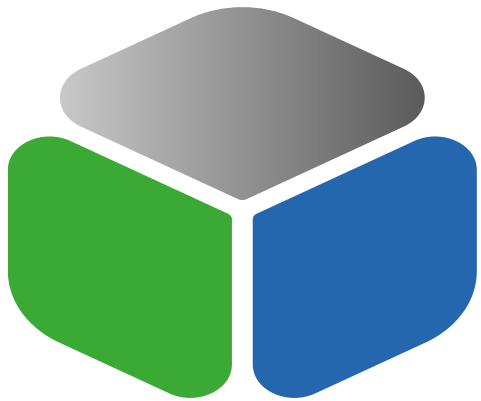
Reversible MM: Scalings

Scaling $x_2 = \varepsilon\, x_2^*$ and $x_3 = \varepsilon\, x_3^*$ yields the slow-fast system

$$\begin{aligned}
\dot{x}_1 &= \varepsilon\left(-\kappa_1 x_1 x_2^* + \kappa_{-1} x_3^*\right),\\
\dot{x}_2^* &= -\kappa_1 x_1 x_2^* + \left(\kappa_{-1} + \kappa_2\right) x_3^* - \kappa_{-2} x_2^* x_4,\\
\dot{x}_3^* &= \kappa_1 x_1 x_2^* - \left(\kappa_{-1} + \kappa_2\right) x_3^* + \kappa_{-2} x_2^* x_4,\\
\dot{x}_4 &= \varepsilon\left(\kappa_2 x_3^* - \kappa_{-2} x_2^* x_4\right).
\end{aligned}$$

After reducing with first integral $x_2^* + x_3^*$, Tikhonov theorem is applicable.
Resulting slow system admits another first integral (inherited from $x_1 + x_3 + x_4$), total reduction to dimension one.

Thank you for your attention!



SYMBIONT PROJECT