Model Reduction and the Quasi-Steady State Approximation (QSSA)

Carsten Wiuf

Department of Mathematical Sciences
University of Copenhagen

Joint with: Elisenda Feliu, Meritxell Sáez, Sebastian Walcher

SMB, June 14, 2021

The tale of the non-interacting species

Michaelis-Menten mechanism and the QSSA

Conversion of substrate S to product P

$$S + E \underset{k_2}{\overset{k_1}{\rightleftharpoons}} Y, \qquad Y \xrightarrow{k_3} P + E$$

$$\begin{aligned}
\dot{c}_S &= -k_1 c_S c_E + k_2 c_Y \\
\dot{c}_P &= \quad k_3 c_Y \\
\dot{c}_E &= -k_1 c_S c_E + k_2 c_Y + k_3 c_Y \\
\dot{c}_Y &= \quad k_1 c_S c_E - k_2 c_Y
\end{aligned}$$

$$\widehat{T} = c_S + c_P + c_Y, \quad T = c_E + c_Y$$

Our interest is the accumulation of P in terms of S, so the species E, Y are nuisance species

Segal & Slemrod (1989)

Michaelis-Menten mechanism and the QSSA

A standard heuristic procedure to reduce a model to a simpler model by elimination of variables (species) is that of QSSA

It assumes quasi-stationarity of the species to eliminate

$$\begin{aligned}
\dot{c}_S &= -k_1 c_S c_E + k_2 c_Y \\
\dot{c}_P &= \quad k_3 c_Y \\
\dot{c}_E &= -k_1 c_S c_E + k_2 c_Y + k_3 c_Y \\
\dot{c}_Y &= \quad k_1 c_S c_E - k_2 c_Y
\end{aligned}$$

$$\widehat{T} = c_S + c_P + c_Y, \quad T = c_E + c_Y$$

Michaelis-Menten mechanism and the QSSA

A standard heuristic procedure to reduce a model to a simpler model by elimination of variables (species) is that of QSSA

It assumes quasi-stationarity of the species to eliminate

$$\begin{aligned}
\dot{c}_S &= -k_1 c_S c_E + k_2 c_Y \\
\dot{c}_P &= \quad k_3 c_Y \\
0 &= -k_1 c_S c_E + k_2 c_Y + k_3 c_Y \\
0 &= \quad k_1 c_S c_E - k_2 c_Y
\end{aligned}$$

$$\widehat{T} = c_S + c_P + c_Y, \quad T = c_E + c_Y$$

Michaelis-Menten mechanism and the QSSA

A standard heuristic procedure to reduce a model to a simpler model by elimination of variables (species) is that of QSSA

It assumes quasi-stationarity of the species to eliminate

$$\begin{aligned} \dot{c}_S &= -k_1 c_S c_E + k_2 c_Y \\ \dot{c}_P &= \quad k_3 c_Y \\ 0 &= -k_1 c_S c_E + k_2 c_Y + k_3 c_Y \\ 0 &= \quad k_1 c_S c_E - k_2 c_Y \end{aligned}$$

$$\widehat{T} = c_S + c_P + c_Y, \quad T = c_E + c_Y$$

We solve the red equations in terms of c_E, c_Y, and plug the solution back into the remaining equations to get

$$\dot{c}_S = -\dot{c}_P = \frac{T k_1 k_3 c_s}{k_1 c_s + k_2 + k_3}$$

Segal & Slemrod (1989)

Michaelis-Menten mechanism and the QSSA

The QSSA claims the trajectories of the reduced system are close to the trajectories of the original system

For this, some assumptions are made on the speed of the reactions (k_i) and the total amounts of the eliminated species (T)

The method of verification in general (if any is given!) is reference to Tikhonov's theorem

Michaelis-Menten mechanism and the QSSA

The QSSA claims the trajectories of the reduced system are close to the trajectories of the original system

For this, some assumptions are made on the speed of the reactions (k_i) and the total amounts of the eliminated species (T)

The method of verification in general (if any is given!) is reference to Tikhonov's theorem

However, QSSA is not in general a valid procedure and cannot be verified generally[1]

My interest is to give a simple procedure that guarantees the QSSA is valid[2]

[1]Lax, Seliger & Walcher (2018); [2]Feliu, Lax, Walcher & Wiuf (2021)

Two-substrate mechanism

Two-substrate example with mass-action kinetics (Cornish-Bowden, 2012)

Substrate binding: $E + A \underset{k_2}{\overset{k_1}{\rightleftharpoons}} EA \qquad EA + B \underset{k_4}{\overset{k_3}{\rightleftharpoons}} EAB$

Transformation: $EAB \underset{k_6}{\overset{k_5}{\rightleftharpoons}} EPQ$

Product release: $EPQ \underset{k_8}{\overset{k_7}{\rightleftharpoons}} EQ + P \qquad EQ \underset{k_{10}}{\overset{k_9}{\rightleftharpoons}} E + Q$

Two-substrate mechanism

Two-substrate example with mass-action kinetics (Cornish-Bowden, 2012)

Substrate binding: $E + A \underset{k_2}{\overset{k_1}{\rightleftharpoons}} EA \qquad EA + B \underset{k_4}{\overset{k_3}{\rightleftharpoons}} EAB$

Transformation: $EAB \underset{k_6}{\overset{k_5}{\rightleftharpoons}} EPQ$

Product release: $EPQ \underset{k_8}{\overset{k_7}{\rightleftharpoons}} EQ + P \qquad EQ \underset{k_{10}}{\overset{k_9}{\rightleftharpoons}} E + Q$

Two-substrate mechanism

Two-substrate example with mass-action kinetics (Cornish-Bowden, 2012)

Substrate binding: $E + A \underset{k_2}{\overset{k_1}{\rightleftharpoons}} EA \qquad EA + B \underset{k_4}{\overset{k_3}{\rightleftharpoons}} EAB$

Transformation: $EAB \underset{k_6}{\overset{k_5}{\rightleftharpoons}} EPQ$

Product release: $EPQ \underset{k_8}{\overset{k_7}{\rightleftharpoons}} EQ + P \qquad EQ \underset{k_{10}}{\overset{k_9}{\rightleftharpoons}} E + Q$

$$A + B \underset{r_2}{\overset{r_1}{\rightleftharpoons}} P + Q \qquad r_1(c) = \frac{T_E c_A c_B}{p(c)}, \quad r_2(c) = \frac{T_E c_P c_Q}{p(c)}$$

Two-substrate mechanism

Two-substrate example with mass-action kinetics (Cornish-Bowden, 2012)

Substrate binding: $E + A \underset{k_2}{\overset{k_1}{\rightleftharpoons}} EA \qquad EA + B \underset{k_4}{\overset{k_3}{\rightleftharpoons}} EAB$

Transformation: $EAB \underset{k_6}{\overset{k_5}{\rightleftharpoons}} EPQ$

Product release: $EPQ \underset{k_8}{\overset{k_7}{\rightleftharpoons}} EQ + P \quad EQ \underset{k_{10}}{\overset{k_9}{\rightleftharpoons}} E + Q$

$$A + B \underset{r_2}{\overset{r_1}{\rightleftharpoons}} P + Q \qquad r_1(c) = \frac{T_E c_A c_B}{p(c)}, \quad r_2(c) = \frac{T_E c_P c_Q}{p(c)}$$

The red species are non-interacting (stoichiometric coefficients are one and they are never on the same side of a reaction)

Two-substrate mechanism

Two-substrate example with mass-action kinetics (Cornish-Bowden, 2012)

$$\text{Substrate binding:}\quad E + A \underset{k_2}{\overset{k_1}{\rightleftharpoons}} EA \qquad EA + B \underset{k_4}{\overset{k_3}{\rightleftharpoons}} EAB$$

$$\text{Transformation:}\quad EAB \underset{k_6}{\overset{k_5}{\rightleftharpoons}} EPQ$$

$$\text{Product release:}\quad EPQ \underset{k_8}{\overset{k_7}{\rightleftharpoons}} EQ + P \qquad EQ \underset{k_{10}}{\overset{k_9}{\rightleftharpoons}} E + Q$$

$$A + B \underset{r_2}{\overset{r_1}{\rightleftharpoons}} P + Q \qquad r_1(c) = \frac{T_E c_A c_B}{p(c)}, \quad r_2(c) = \frac{T_E c_P c_Q}{p(c)}$$

The red species are non-interacting (stoichiometric coefficients are one and they are never on the same side of a reaction)

Eliminated species: E, EA, EAB, EPQ, EQ Core species: A, B, P, Q

Reduction theorem

Let a mass-action reaction network and a set of non-interacting species be given.

Reduction theorem

Let a mass-action reaction network and a set of non-interacting species be given. Further suppose

- the non-interacting species are consumed and produced

Reduction theorem

Let a mass-action reaction network and a set of non-interacting species be given. Further suppose

- the non-interacting species are consumed and produced
- the rate constants of the reactions involving non-interacting species in the reactant scale as $k_i = \frac{1}{\epsilon}\kappa_i$ ('fast' reactions)

Reduction theorem

Let a mass-action reaction network and a set of non-interacting species be given. Further suppose

- the non-interacting species are consumed and produced
- the rate constants of the reactions involving non-interacting species in the reactant scale as $k_i = \frac{1}{\epsilon}\kappa_i$ ('fast' reactions)
- the conserved quantity of any conservation law involving only non-interaction species scales as $T = \epsilon\tau$

Reduction theorem

Let a mass-action reaction network and a set of non-interacting species be given. Further suppose

- the non-interacting species are consumed and produced
- the rate constants of the reactions involving non-interacting species in the reactant scale as $k_i = \frac{1}{\epsilon}\kappa_i$ ('fast' reactions)
- the conserved quantity of any conservation law involving only non-interaction species scales as $T = \epsilon\tau$

There exists a mass-action-like reduced reaction network (w/o the non-interacting species) and a time $t > 0$, such that the trajectories of original network converge to the trajectories of the reduced on finite time intervals $[u, t]$, for any $0 < u < t$, as $\epsilon \to 0$. The reaction rates of the reduced system are rational functions, depending on κ_i, τ

Reduction theorem

Let a mass-action reaction network and a set of non-interacting species be given. Further suppose

- the non-interacting species are consumed and produced
- the rate constants of the reactions involving non-interacting species in the reactant scale as $k_i = \frac{1}{\epsilon}\kappa_i$ ('fast' reactions)
- the conserved quantity of any conservation law involving only non-interaction species scales as $T = \epsilon\tau$

There exists a mass-action-like reduced reaction network (w/o the non-interacting species) and a time $t > 0$, such that the trajectories of original network converge to the trajectories of the reduced on finite time intervals $[u, t]$, for any $0 < u < t$, as $\epsilon \to 0$. The reaction rates of the reduced system are rational functions, depending on κ_i, τ

Moreover, the QSSA is valid

Feliu & Wiuf (2012,2013a,b); Sáez, Wiuf & Feliu (2016); Feliu, Lax, Walcher & Wiuf (2021)

Related work: King & Altman (1956); Horiuti & Nakamura (1957); Wong & Hanes (1962)

Returning to the example

Substrate binding: $E + A \underset{\frac{1}{\epsilon}\kappa_2}{\overset{\frac{1}{\epsilon}\kappa_1}{\rightleftharpoons}} EA \qquad EA + B \underset{\frac{1}{\epsilon}\kappa_4}{\overset{\frac{1}{\epsilon}\kappa_3}{\rightleftharpoons}} EAB$

Transformation: $EAB \underset{\frac{1}{\epsilon}\kappa_6}{\overset{\frac{1}{\epsilon}\kappa_5}{\rightleftharpoons}} EPQ$

Product release: $EPQ \underset{\frac{1}{\epsilon}\kappa_8}{\overset{\frac{1}{\epsilon}\kappa_7}{\rightleftharpoons}} EQ + P \qquad EQ \underset{\frac{1}{\epsilon}\kappa_{10}}{\overset{\frac{1}{\epsilon}\kappa_9}{\rightleftharpoons}} E + Q$

$$\epsilon\tau_E = c_E + c_{EA} + c_{EAB} + c_{EPQ} + c_{EQ}$$

Michaelis-Menten mechanism

$$S + E \underset{k_2}{\overset{k_1}{\rightleftharpoons}} Y, \qquad Y \xrightarrow{k_3} P + E.$$

Non-interacting species E, Y

All reactions involve E or Y in the reactant and $T = c_Y + c_E$, so

$$k_i = \tfrac{1}{\epsilon}\kappa_i, \quad i = 1, 2, 3, \qquad T = \epsilon\tau$$

The reduced system corresponds to the system $S \to P$ with kinetics

$$\dot{c}_S = -\dot{c}_P = \frac{\tau\kappa_1\kappa_3 c_s}{\kappa_1 c_s + \kappa_2 + \kappa_3}$$

The proof

There are three steps in the proof

- Derive the reduced ODE system using QSSA[1]
- Identify a mass-action-like reaction network for the reduced ODE system[2]
- Apply Tikhonov theory to deduce convergence of trajectories[3]

All three steps rely on the eliminated species being non-interacting

[1] Feliu & Wiuf (2012,2013a,b); [2] Sáez, Wiuf, Feliu (2016); [3] Feliu, Walcher & Wiuf (2018)

ODE system and QSSA

$$E + A \underset{k_2}{\overset{k_1}{\rightleftharpoons}} EA$$
$$EA + B \underset{k_4}{\overset{k_3}{\rightleftharpoons}} EAB$$
$$EAB \underset{k_6}{\overset{k_5}{\rightleftharpoons}} EPQ$$
$$EPQ \underset{k_8}{\overset{k_7}{\rightleftharpoons}} EQ + P$$
$$EQ \underset{k_{10}}{\overset{k_9}{\rightleftharpoons}} E + Q$$

$$\begin{aligned}
\dot{c}_E &= -k_1 c_E c_A - k_{10} c_E c_Q + k_2 c_{EA} + k_9 c_{EQ} \\
\dot{c}_A &= -k_1 c_E c_A + k_2 c_{EA} \\
\dot{c}_B &= -k_3 c_B c_{EA} + k_4 c_{EAB} \\
\dot{c}_P &= -k_8 c_P c_{EQ} + k_7 c_{EPQ} \\
\dot{c}_Q &= -k_{10} c_E c_Q + k_9 c_{EQ} \\
\dot{c}_{EA} &= -k_3 c_B c_{EA} - k_2 c_{EA} + k_1 c_E c_A + k_4 c_{EAB} \\
\dot{c}_{EAB} &= -k_4 c_{EAB} - k_5 c_{EAB} + k_3 c_B c_{EA} + k_6 c_{EPQ} \\
\dot{c}_{EPQ} &= -k_6 c_{EPQ} - k_7 c_{EPQ} + k_8 c_P c_{EQ} + k_5 c_{EAB} \\
\dot{c}_{EQ} &= -k_9 c_{EQ} - k_8 c_P c_{EQ} + k_{10} c_E c_Q + k_7 c_{EPQ}
\end{aligned}$$

ODE system and QSSA

$$E + A \underset{k_2}{\overset{k_1}{\rightleftharpoons}} EA$$
$$EA + B \underset{k_4}{\overset{k_3}{\rightleftharpoons}} EAB$$
$$EAB \underset{k_6}{\overset{k_5}{\rightleftharpoons}} EPQ$$
$$EPQ \underset{k_8}{\overset{k_7}{\rightleftharpoons}} EQ + P$$
$$EQ \underset{k_{10}}{\overset{k_9}{\rightleftharpoons}} E + Q$$

$$\begin{aligned}
\dot{c}_E &= -k_1 c_E c_A - k_{10} c_E c_Q + k_2 c_{EA} + k_9 c_{EQ} \\
\dot{c}_A &= -k_1 c_E c_A + k_2 c_{EA} \\
\dot{c}_B &= -k_3 c_B c_{EA} + k_4 c_{EAB} \\
\dot{c}_P &= -k_8 c_P c_{EQ} + k_7 c_{EPQ} \\
\dot{c}_Q &= -k_{10} c_E c_Q + k_9 c_{EQ} \\
\dot{c}_{EA} &= -k_3 c_B c_{EA} - k_2 c_{EA} + k_1 c_E c_A + k_4 c_{EAB} \\
\dot{c}_{EAB} &= -k_4 c_{EAB} - k_5 c_{EAB} + k_3 c_B c_{EA} + k_6 c_{EPQ} \\
\dot{c}_{EPQ} &= -k_6 c_{EPQ} - k_7 c_{EPQ} + k_8 c_P c_{EQ} + k_5 c_{EAB} \\
\dot{c}_{EQ} &= -k_9 c_{EQ} - k_8 c_P c_{EQ} + k_{10} c_E c_Q + k_7 c_{EPQ}
\end{aligned}$$

Conservation laws :

$$\begin{aligned}
T_E &= c_E + c_{EA} + c_{EAB} + c_{EPQ} + c_{EQ} \\
T_{A+Q} &= c_A + c_Q + c_{EA} + c_{EAB} + c_{EPQ} + c_{EQ} \\
T_{B+Q} &= c_B + c_Q + c_{EAB} + c_{EPQ} + c_{EQ} \\
T_{B+P} &= c_B + c_P + c_{EAB} + c_{EPQ}
\end{aligned}$$

ODE system and QSSA

$$E + A \underset{k_2}{\overset{k_1}{\rightleftharpoons}} EA$$
$$EA + B \underset{k_4}{\overset{k_3}{\rightleftharpoons}} EAB$$
$$EAB \underset{k_6}{\overset{k_5}{\rightleftharpoons}} EPQ$$
$$EPQ \underset{k_8}{\overset{k_7}{\rightleftharpoons}} EQ + P$$
$$EQ \underset{k_{10}}{\overset{k_9}{\rightleftharpoons}} E + Q$$

$$\begin{aligned}
\dot{c}_E &= -k_1 c_E c_A - k_{10} c_E c_Q + k_2 c_{EA} + k_9 c_{EQ} \\
\dot{c}_A &= -k_1 c_E c_A + k_2 c_{EA} \\
\dot{c}_B &= -k_3 c_B c_{EA} + k_4 c_{EAB} \\
\dot{c}_P &= -k_8 c_P c_{EQ} + k_7 c_{EPQ} \\
\dot{c}_Q &= -k_{10} c_E c_Q + k_9 c_{EQ} \\
\dot{c}_{EA} &= -k_3 c_B c_{EA} - k_2 c_{EA} + k_1 c_E c_A + k_4 c_{EAB} \\
\dot{c}_{EAB} &= -k_4 c_{EAB} - k_5 c_{EAB} + k_3 c_B c_{EA} + k_6 c_{EPQ} \\
\dot{c}_{EPQ} &= -k_6 c_{EPQ} - k_7 c_{EPQ} + k_8 c_P c_{EQ} + k_5 c_{EAB} \\
\dot{c}_{EQ} &= -k_9 c_{EQ} - k_8 c_P c_{EQ} + k_{10} c_E c_Q + k_7 c_{EPQ}
\end{aligned}$$

Conservation laws :

$$\begin{aligned}
T_E &= c_E + c_{EA} + c_{EAB} + c_{EPQ} + c_{EQ} \\
T_{A+Q} &= c_A + c_Q + c_{EA} + c_{EAB} + c_{EPQ} + c_{EQ} \\
T_{B+Q} &= c_B + c_Q + c_{EAB} + c_{EPQ} + c_{EQ} \\
T_{B+P} &= c_B + c_P + c_{EAB} + c_{EPQ}
\end{aligned}$$

Interpretation as a linear system

Steady state equations of $c_E, c_{EA}, c_{EAB}, c_{EPQ}$ and c_{EQ}

$$
\begin{aligned}
\dot{c}_E = \quad 0 &= -k_1 c_E c_A - k_{10} c_E c_Q + k_2 c_{EA} + k_9 c_{EQ} \\
\dot{c}_{EA} = \quad 0 &= -k_2 c_{EA} - k_3 c_B c_{EA} + k_1 c_E c_A + k_4 c_{EAB} \\
\dot{c}_{EAB} = \quad 0 &= -k_4 c_{EAB} - k_5 c_{EAB} + k_3 c_B c_{EA} + k_6 c_{EPQ} \\
\dot{c}_{EPQ} = \quad 0 &= -k_6 c_{EPQ} - k_7 c_{EPQ} + k_8 c_P c_{EQ} + k_5 c_{EAB} \\
\dot{c}_{EQ} = \quad 0 &= -k_8 c_P c_{EQ} - k_9 c_{EQ} + k_{10} c_E c_Q + k_7 c_{EPQ} \\
T_E &= c_E + c_{EA} + c_{EAB} + c_{EPQ} + c_{EQ}
\end{aligned}
$$

The system is linear in $c_E, c_{EA}, c_{EAB}, c_{EPQ}, c_{EQ}$ and has a unique solution

... because the species are non-interacting

Solution

$$q(c) = (k_4k_6+k_4k_7+k_5k_7)k_2k_9+k_2k_4k_6k_8c_P+k_3k_5k_7k_9c_B+(k_4k_6+k_4k_7+k_5k_7)k_2k_{10}c_Q+(k_4k_6+k_5k_7+k_4k_7)k_1k_9c_A$$
$$+(k_5k_9+k_7k_9+k_5k_7+k_6k_9)k_1k_3c_Ac_B+k_3k_5k_7k_{10}c_Bc_Q+k_1k_4k_6k_8c_Ac_P+(k_5+k_6)k_1k_3k_8c_Ac_Bc_P$$
$$+(k_5k_2+k_4k_2+k_6k_2+k_6k_4)k_8k_{10}c_Pc_Q+(k_5+k_6)k_3k_8k_{10}c_Bc_Pc_Q$$

$$c_E = \frac{T_E}{q(c)}\Big((k_4k_6+k_4k_7+k_5k_7)k_2k_9+k_3k_5k_7k_9c_B+k_2k_4k_6k_8c_P\Big)$$

$$c_{EA} = \frac{T_E}{q(c)}\Big((k_4k_6+k_5k_7+k_4k_7)k_1k_9c_A+k_4k_6k_8k_{10}c_Pc_Q+k_1k_4k_6k_8c_Ac_P\Big)$$

$$c_{EAB} = \frac{T_E}{q(c)}\Big((k_6+k_7)k_1k_3k_9c_Ac_B+k_2k_6k_8k_{10}c_Pc_Q+k_3k_6k_8k_{10}c_Bc_Pc_Q$$
$$+k_1k_3k_6k_8c_Ac_Bc_P\Big)$$

$$c_{EPQ} = \frac{T_E}{q(c)}\Big(k_1k_3k_5k_9c_Ac_B+(k_4+k_5)k_2k_8k_{10}c_Pc_Q+k_3k_5k_8k_{10}c_Bc_Pc_Q$$
$$+k_1k_3k_5k_8c_Ac_Bc_P\Big)$$

$$c_{EQ} = \frac{T_E}{q(c)}\Big((k_4k_6+k_5k_7+k_4k_7)k_2k_{10}c_Q+k_3k_5k_7k_{10}c_Bc_Q+k_1k_3k_5k_7c_Ac_B\Big)$$

Non-negative solution because the species are non-interacting

The reduced reaction network

Inserting these expressions into the remaining equations yields

$$\begin{aligned}
\dot{c}_A &= \tfrac{T_E}{q(c)}\left(-\alpha_1 c_A c_B + \alpha_2 c_P c_Q\right) \qquad & \alpha_1 &= k_1 k_3 k_5 k_7 k_9 \\
\dot{c}_B &= \tfrac{T_E}{q(c)}\left(-\alpha_1 c_A c_B + \alpha_2 c_P c_Q\right) \qquad & \alpha_2 &= k_2 k_4 k_6 k_8 k_{10} \\
\dot{c}_P &= \tfrac{T_E}{q(c)}\left(\ \ \alpha_1 c_A c_B - \alpha_2 c_P c_Q\right) \\
\dot{c}_Q &= \tfrac{T_E}{q(c)}\left(\ \ \alpha_1 c_A c_B - \alpha_2 c_P c_Q\right)
\end{aligned}$$

This system in invariant in the non-negative orphant

. . . because the species are non-interacting

Reduced ODE system

Linear elimination of non-interacting species

The concentrations of a set of non-interacting species can be non-negatively eliminated from the steady state equations.
That is, the concentrations of the non-interacting species are rational functions of the remaining species, and furthermore, they are non-negative for non-negative concentrations of the remaining species

ODE system without the non-interacting species

By insertion of the rational expressions obtained for the non-interacting species into the original ODE system, an ODE system for the remaining species is obtained

[1] Feliu & Wiuf (2012,2013a,b)

The reduced reaction network

Returning to the reduced ODE system

$$\begin{aligned}
\dot{c}_A &= \tfrac{T_E}{q(c)}\left(-\alpha_1 c_A c_B + \alpha_2 c_P c_Q\right) & \alpha_1 &= k_1 k_3 k_5 k_7 k_9 \\
\dot{c}_B &= \tfrac{T_E}{q(c)}\left(-\alpha_1 c_A c_B + \alpha_2 c_P c_Q\right) & \alpha_2 &= k_2 k_4 k_6 k_8 k_{10} \\
\dot{c}_P &= \tfrac{T_E}{q(c)}\left(\ \ \alpha_1 c_A c_B - \alpha_2 c_P c_Q\right) & & \\
\dot{c}_Q &= \tfrac{T_E}{q(c)}\left(\ \ \alpha_1 c_A c_B - \alpha_2 c_P c_Q\right) & &
\end{aligned}$$

Reactions and kinetics

$$\begin{aligned}
A + B &\xrightarrow{r_1} P + Q & r_1(c) &= \tfrac{T_E}{q(c)}\alpha_1 c_A c_B \\
P + Q &\xrightarrow{r_2} A + B & r_2(c) &= \tfrac{T_E}{q(c)}\alpha_2 c_P c_Q
\end{aligned}$$

The kinetics is mass-action-like ... because of the non-interacting species

Reduction theorem

Let a mass-action reaction network and a set of non-interacting species be given. Further suppose

- the non-interacting species are consumed and produced
- the rate constants of the reactions involving non-interacting species in the reactant scale as $k_i = \frac{1}{\epsilon}\kappa_i$ ('fast' reactions)
- the conserved quantity of any conservation law involving only non-interaction species scales as $T = \epsilon\tau$

There exists a mass-action-like reduced reaction network (w/o the non-interacting species) and a time $t > 0$, such that the trajectories of original network converge to the trajectories of the reduced on finite time intervals $[u, t]$, for any $0 < u < t$, as $\epsilon \to 0$. The reaction rates of the reduced system are rational functions, depending on κ_i, τ

Moreover, the QSSA is valid

Feliu & Wiuf (2012,2013a,b); Sáez, Wiuf & Feliu (2016); Feliu, Lax, Walcher & Wiuf (2021)

Related work: King & Altman (1956); Horiuti & Nakamura (1957); Wong & Hanes (1962)

THANKS

to the audience

also to the Danish Research Councils
and the Lundbeck Foundation

Tikhonov reduction

Tikhonov's theorem assume 'fast' and 'slow' variables

$$\dot{x} = f(x, y), \quad \epsilon\dot{y} = g(x, y)$$

We have 'fast' and 'slow' reactions, defined by the reaction rate constants

$$\dot{x} = \frac{1}{\epsilon} f_1(x, y) + f_2(x, y), \quad \dot{y} = \frac{1}{\epsilon} g_1(x, y) + g_2(x, y)$$

There exist conditions under which a reaction network with fast and slow reactions can be transformed into Tikhonov form[1]

Assuming mass-action kinetics and that the eliminated species are non-interacting then the conditions are fulfilled

[1] Lax, Seliger & Walcher (2018)

Application of Tikhonov theory

Tikhonov reduction (non-interacting species)[1]

Let a mass-action reaction network and a set of non-interacting species be given. Further suppose

- the eliminated-species graph consists of strongly connected components
- the rate constants of the reactions involving non-interacting species in the reactant scale as $k_i = \frac{1}{\epsilon}\kappa_i$
- the conserved quantity of any conservation law involving only non-interaction species fulfils $T = \epsilon\tau$

The trajectories of the ODE system converge to the trajectories of the reduced ODE system on finite time intervals $[t_1, t_2]$, $0 < t_1 < t_2$, as $\epsilon \to 0$. The reaction rates of the reduced system depend on κ_i, τ_i

[1] Feliu, Walcher & Wiuf (2018)

Eliminated-species graph

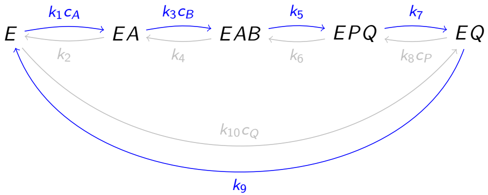
$$E + A \underset{k_2}{\overset{k_1}{\rightleftharpoons}} EA \qquad EA + B \underset{k_4}{\overset{k_3}{\rightleftharpoons}} EAB \qquad EAB \underset{k_6}{\overset{k_5}{\rightleftharpoons}} EPQ$$

$$EPQ \underset{k_8}{\overset{k_7}{\rightleftharpoons}} EQ + P \qquad EQ \underset{k_{10}}{\overset{k_9}{\rightleftharpoons}} E + Q$$

$$\begin{tikzcd}
E \arrow[r, shift left, "k_1 c_A"] \arrow[rrrr, bend right=40, "k_{10} c_Q"] & EA \arrow[l, shift left, "k_2"] \arrow[r, shift left, "k_3 c_B"] & EAB \arrow[l, shift left, "k_4"] \arrow[r, shift left, "k_5"] & EPQ \arrow[l, shift left, "k_6"] \arrow[r, shift left, "k_7"] & EQ \arrow[l, shift left, "k_8 c_P"] \arrow[llll, bend left=50, "k_9"]
\end{tikzcd}$$

Reactions in the reduced reaction network

i) Consider a directed cycle and the corresponding reactions

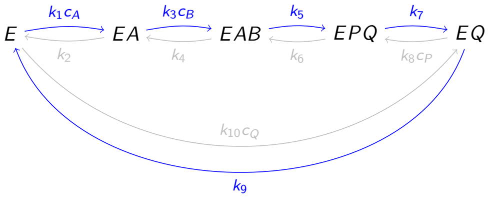


$$
\begin{array}{ccc}
E+A & \xrightarrow{k_1 c_A} & EA \\
EA+B & \xrightarrow{k_3 c_B} & EAB \\
EAB & \xrightarrow{k_5} & EPQ \\
EPQ & \xrightarrow{k_7} & EQ+P \\
EQ & \xrightarrow{k_9} & E+Q \\
\hline
\end{array}
$$

Reactions in the reduced reaction network

i) Consider a directed cycle and the corresponding reactions

ii) Cancel the eliminated species on both sides



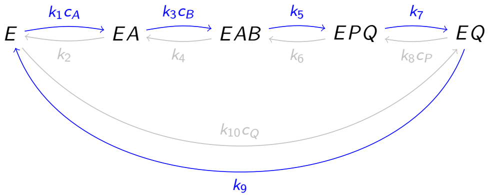
$$\begin{array}{ccc}
A & \xrightarrow{k_1 c_A} & \\
B & \xrightarrow{k_3 c_B} & \\
 & \xrightarrow{k_5} & \\
 & \xrightarrow{k_7} & P \\
 & \xrightarrow{k_9} & Q \\
\hline
\end{array}$$

Reactions in the reduced reaction network

i) Consider a directed cycle and the corresponding reactions

ii) Cancel the eliminated species on both sides

iii) Add the remaining reactants and products



$$
\begin{array}{ccc}
A & \xrightarrow{k_1 c_A} & \\
B & \xrightarrow{k_3 c_B} & \\
 & \xrightarrow{k_5} & \\
 & \xrightarrow{k_7} & P \\
 & \xrightarrow{k_9} & Q \\
\hline
A + B & \longrightarrow & P + Q
\end{array}
$$

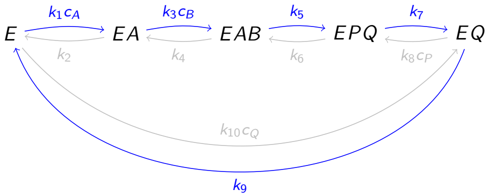
Reactions in the reduced reaction network

i) Consider a directed cycle and the corresponding reactions

ii) Cancel the eliminated species on both sides

iii) Add the remaining reactants and products

iv) Define the rate function as $\frac{T_E}{q(c)} r(c)$



$$r(c) = k_1 k_3 k_5 k_7 k_9 c_A c_B$$

$$\begin{array}{ccc}
A & \xrightarrow{k_1 c_A} & \\
B & \xrightarrow{k_3 c_B} & \\
 & \xrightarrow{k_5} & \\
 & \xrightarrow{k_7} & P \\
 & \xrightarrow{k_9} & Q \\
\hline
A + B & \xrightarrow{\frac{T_E}{q(c)} r(c)} & P + Q
\end{array}$$

Reactions in the reduced reaction network

Reduced reaction network (non-interacting species)[1]

The reduced ODE system can always be interpreted as a reaction network on the core species.
The reactions are derived from the cycles of the eliminated-species graph

Kinetic of the reduced reaction network (non-interacting species)[1]

If the original system has mass-action kinetics then the reaction rates are of the form $\frac{p(c)}{q(c)}$, where p, q are polynomials in c, and $\frac{p(c)}{q(c)}$ is irreducible.
Furthermore, the numerator $p(c)$ has mass-action form

[1] Sáez, Wiuf & Feliu (2017)

King & Altman (1956); Horiuti & Nakamura (1957); Wong & Hanes (1962); Temkin (1965); Temkin & Bonchev (1992)