Engineering model reduction of bio-chemical kinetic models

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Outline

- Introduction to RKN
- Cascade activation reactions
- Variable lumping of cascade activation reactions
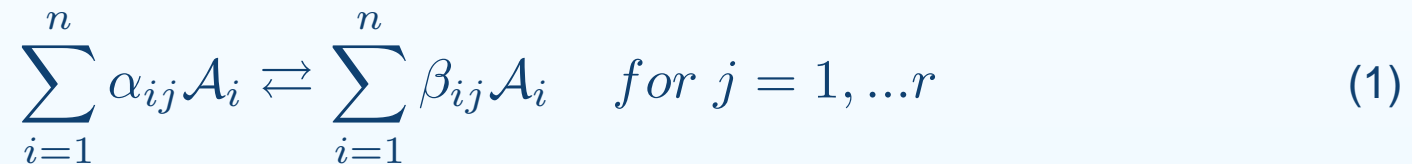- Generalizations and example
- Conclusions

Chemical reaction networks

Number of species: n
Number of reactions: r
Number of complexes: m
Stoichiometric mechanism:

$$\sum_{i=1}^{n} \alpha_{ij} \mathcal{A}_i \rightleftarrows \sum_{i=1}^{n} \beta_{ij} \mathcal{A}_i \quad for \ j = 1, ...r \tag{1}$$

where
- $\alpha_{ij}, \beta_{ij} \in \mathbb{N}$ are the constant stoichiometric coefficients for specie $\mathcal{A}_i$ in the reaction step j.

- The linear combinations of species (i.e. the terms $\sum_{i=1}^{n} \alpha_{ij} \mathcal{A}_i$) in (1) are called the *complexes* of the reaction network and denoted by $c_1, \ldots, c_m$.

Reaction network:
Species: $\mathcal{S} = \{\mathcal{A}_1, \ldots, \mathcal{A}_n\}$
Complexes: $\mathcal{C} = \{c_1, \ldots, c_m\}$
Reactions: $\mathcal{R} \subset \mathcal{C} \times \mathcal{C}$

Mass action reaction kinetics

The reaction rate obeys the Mass Action Law, therefore it can be expressed as:

$$W_j(x) = k_{mn} \prod_{i=1}^{n} x_i^{\alpha_{ij}} - k_{nm} \prod_{i=1}^{n} x_i^{\beta_{ij}} \tag{2}$$

where x_i denotes the concentration of species (state variables) and $k_{mn}, k_{nm} \in \mathbb{R}^+$ are the rate constant of the direct and inverse reaction rates of the j-th reaction step between complexes c_m and c_n.

Irreversible steps: choosing the appropriate k-s to be zero.

$$\frac{dx}{dt} = \mathcal{N}W(x) \tag{3}$$

where

$$\mathcal{N} = \mathcal{N}_\alpha - \mathcal{N}_\beta \tag{4}$$

where

$$[\mathcal{N}_\alpha]_{ij} = \alpha_{ij}, \quad [\mathcal{N}_\beta]_{ij} = \beta_{ij}, \quad i = 1, \ldots, n, \quad j = 1, \ldots, r \tag{5}$$

The reaction graph of a reaction network

- **(Weighted) directed graph**
  $D = (V_d, E_d)$, where
  $V_d = \{c_1, c_2, \ldots c_n\}$: finite nonempty set of vertices (the complexes)
  E_d: finite nonempty set of directed edges (reactions), $(c_i, c_j) \in E_d$ if complex c_i is transformed to c_j
  Weights: reaction rates, i.e. k_{ij} can be assigned to (c_i, c_j)

- **Undirected graph**
  $U = (V_u, E_u)$, where $V_u = V_d$ and the undirected edge $(c_i, c_j) \in E_u$ if $(c_i, c_j), (c_j, c_i) \in E_d$

Cascade activation reactions

In the following a set of enzymatic reaction levels, where the product of a higher level acts as an enzyme in the next reaction level will be called **cascade activation reaction**.

The most simple reaction scheme of cascade activation can be seen in figure 6.
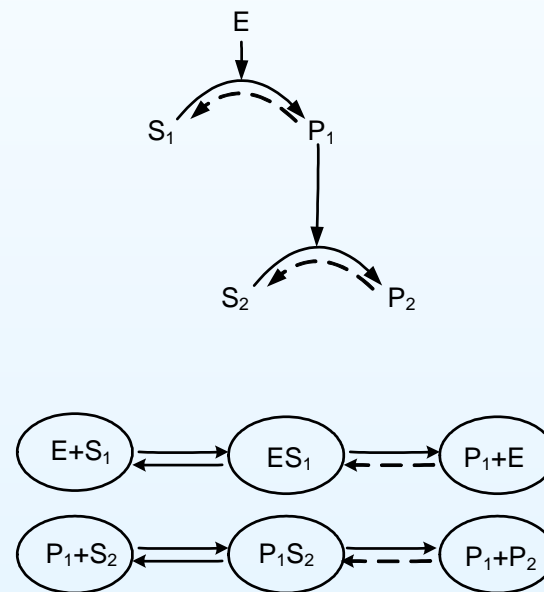
The activation scheme and reaction graph of the cascade activation reaction. The dashed lines denote the reversible case

The variable lumping transformation in linear case

$$\frac{dx}{dt} = Ax + Bu \quad y = Cx$$

Applied to variables with similar behavior: $x_j = Kx_l$

$x_j, x_l \rightarrow \hat{x}_j \quad \hat{x}_j = \frac{x_j + x_l}{2}$

System parameters:

For $i, k \neq j, l$:

$$\hat{a}_{ik} = a_{ik} \quad \hat{b}_{ik} = b_{ik} \quad \hat{c}_{ik} = c_{ik}$$

and for all elements with index j:

$$\hat{a}_{jk} = \frac{a_{jk} + a_{lk}}{2} \quad \hat{b}_{jk} = \frac{b_{jk} + b_{lk}}{2}$$

$$\hat{a}_{jj} = \frac{K(a_{jj} + a_{jl}) + (a_{jl} + a_{ll})}{K + 1}$$

$$\hat{a}_{ij} = \frac{2Ka_{ij} + 2a_{il}}{K + 1} \quad \hat{c}_{ij} = \frac{2Kc_{ij} + 2c_{il}}{K + 1}$$

Nonlinear lumping of cascade activation reactions

The original system is described by the following reactions:

The basic idea is to shorten the way between the beginning and the end of the signaling path ($E \rightarrow P_1 \rightarrow P_2$), and eliminate the intermediate component in a way, which approximately preserves the dynamic properties of the system, as it can be seen in the right sub-figure of figure 1.
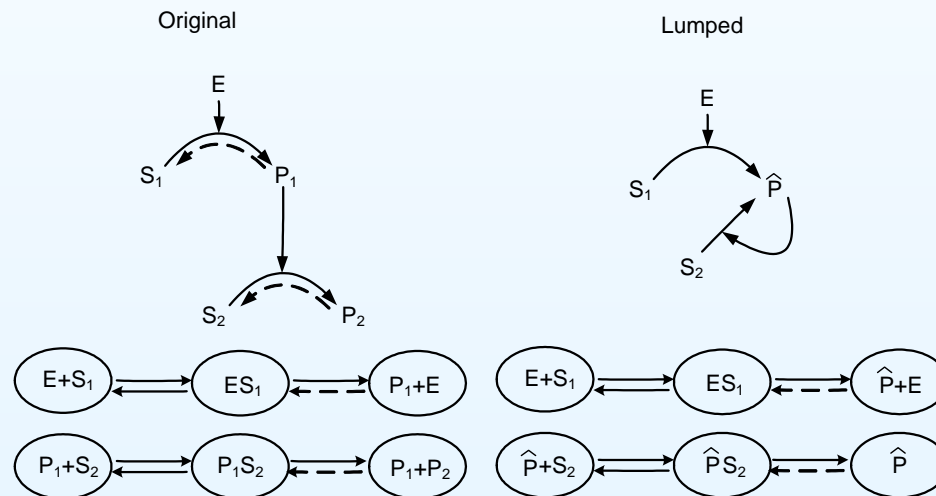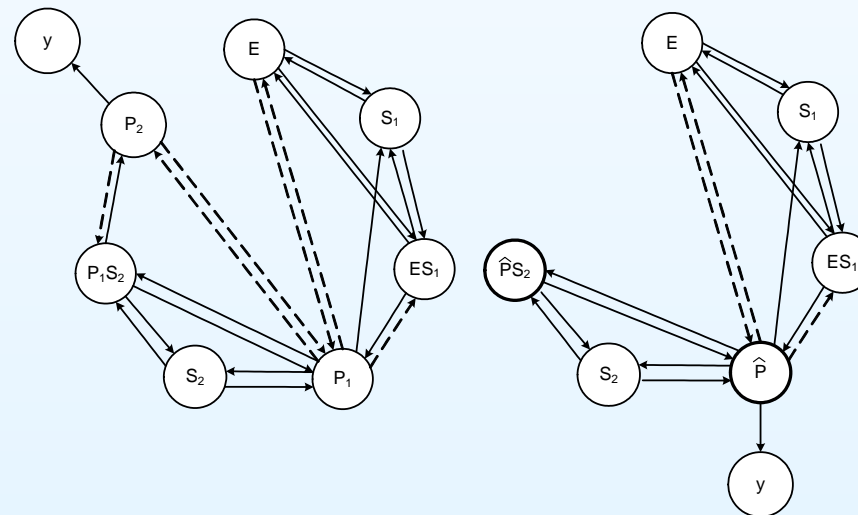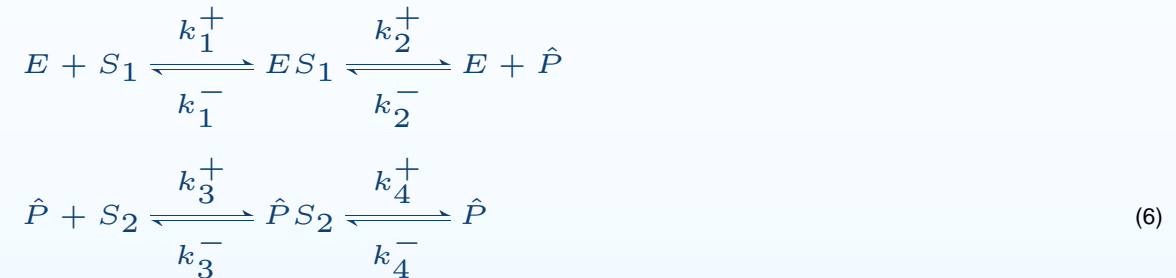

Figure 1: The activation scheme and reaction graph of the original and lumped reaction. The dashed lines denote the reversible case

Nonlinear lumping of cascade activation reactions II

This new reaction scheme implies the following reactions:

$$E + S_1 \underset{k_1^-}{\overset{k_1^+}{\rightleftharpoons}} ES_1 \underset{k_2^-}{\overset{k_2^+}{\rightleftharpoons}} E + \hat{P}$$

$$\hat{P} + S_2 \underset{k_3^-}{\overset{k_3^+}{\rightleftharpoons}} \hat{P}S_2 \underset{k_4^-}{\overset{k_4^+}{\rightleftharpoons}} \hat{P} \tag{6}$$

The structure graph of the original and the lumped reaction. The dashed lines denote the reversible case

Variation of stochiometric coefficients I

In the original case: $S_1 + ES_1 + P_1 = 1$, $S_2 + P_1 S_2 + P_2 = 1$.

Transformations: $S_1 \rightarrow P_1 \quad S_2 \rightarrow P_2$ We can observe that S_1 and S_2 will be transformed into P_1 and P_2 which ones will reach the concentration value of 1. In the case of the lumped reaction scheme, $S_1 \rightarrow \hat{P}$, and S_2 is eliminated via $\hat{P}$. In this case the stochiometric coefficients are changed, according to the final concentration of the final product of the original reaction. In this case one unit of both substrates are transformed into half unit of the product.
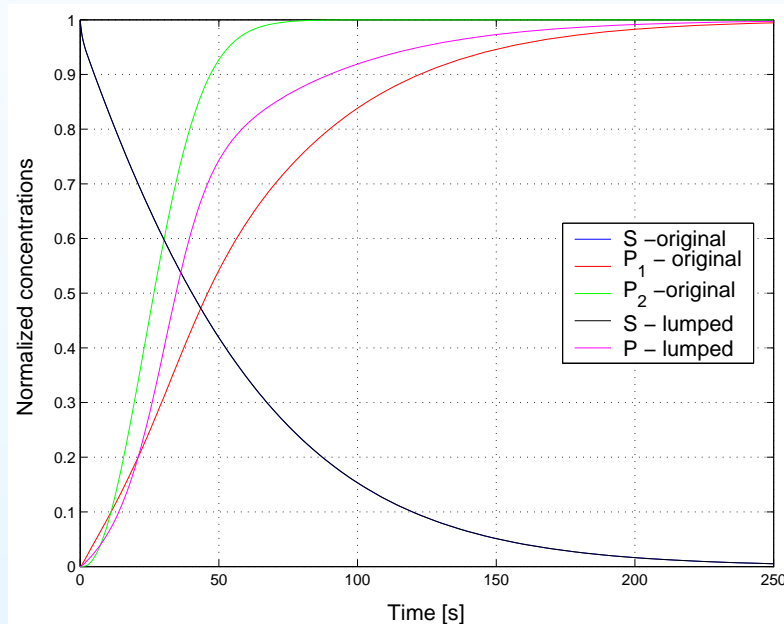
$$E + S_1 \underset{k_1^-}{\overset{k_1^+}{\rightleftharpoons}} ES_1 \underset{k_2^-}{\overset{k_2^+}{\rightleftharpoons}} E + 0.5\hat{P}$$

$$\hat{P} + S_2 \underset{k_3^-}{\overset{k_3^+}{\rightleftharpoons}} \hat{P}S_2 \underset{k_4^-}{\overset{k_4^+}{\rightleftharpoons}} 1.5\hat{P} \tag{7}$$
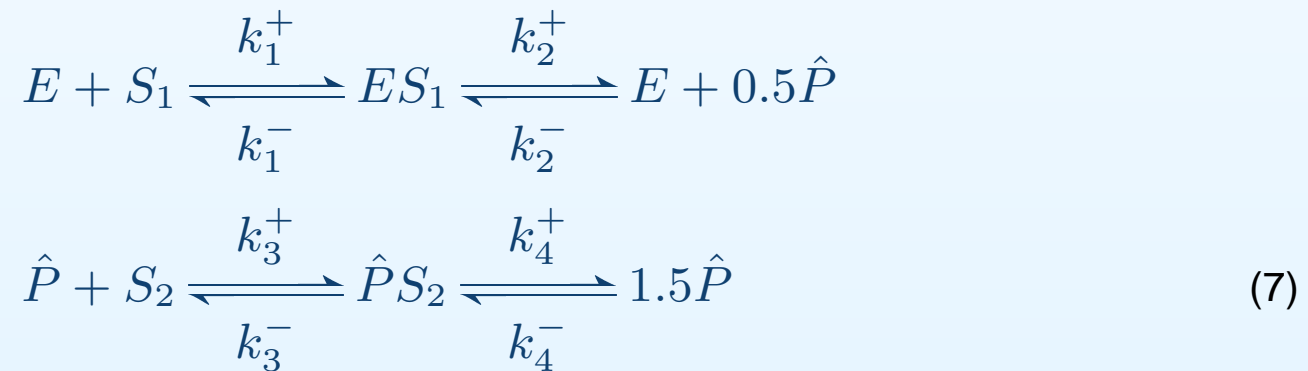
This reactions will imply the final concentration of 1 for $\hat{P}$.

$$y = \hat{P}$$

Variation of stochiometric coefficients II

- Original model - 3 conservation equations, lumped -2

- Both models are of degree of freedom 4 (7/6 state eq., 3/2 conservation eq.)
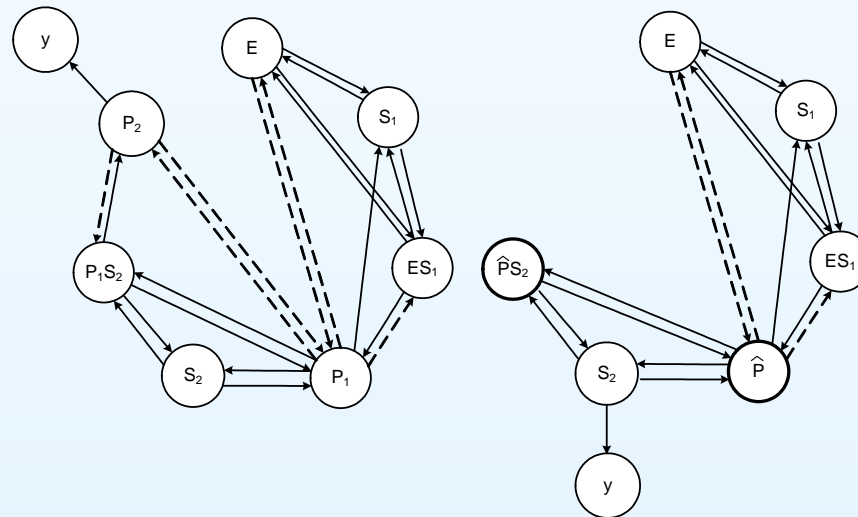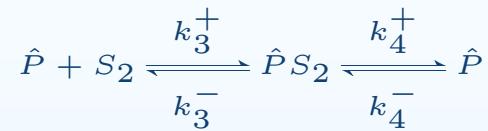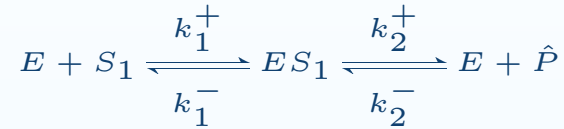 Simulation results
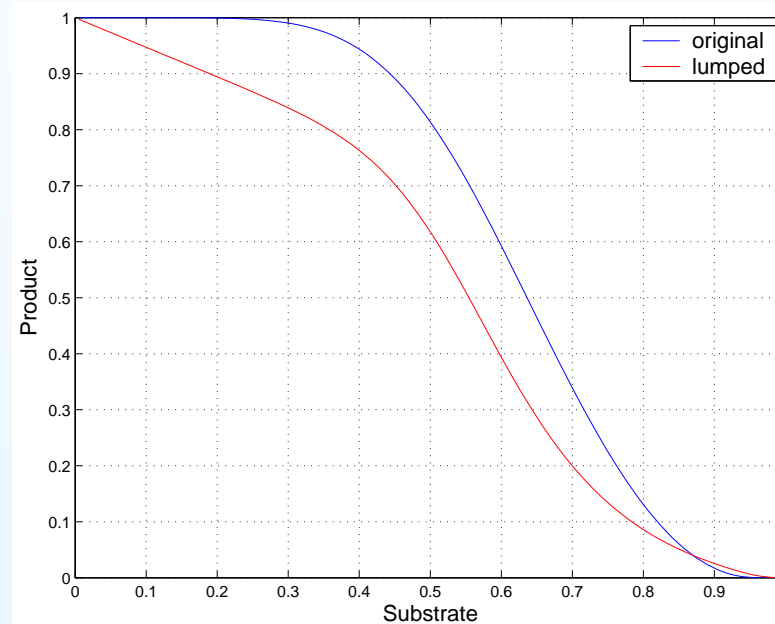
The normalized concentrations of the substrates and the products in the case of the original and the lumped reaction as functions of time and as state trajectory
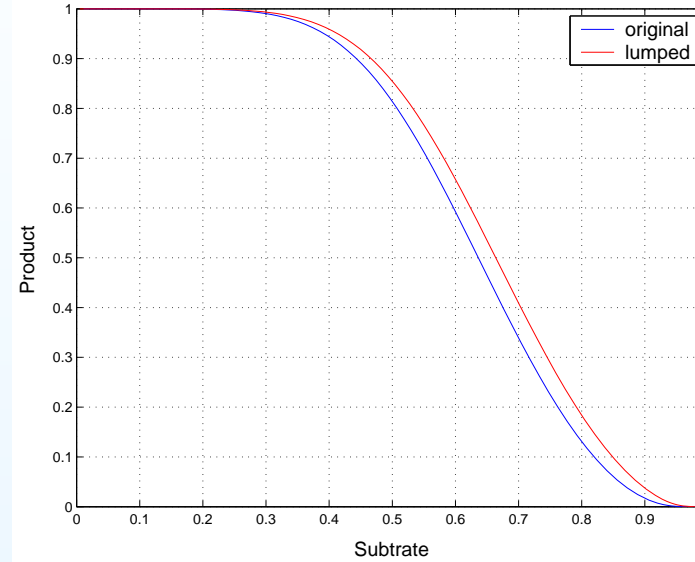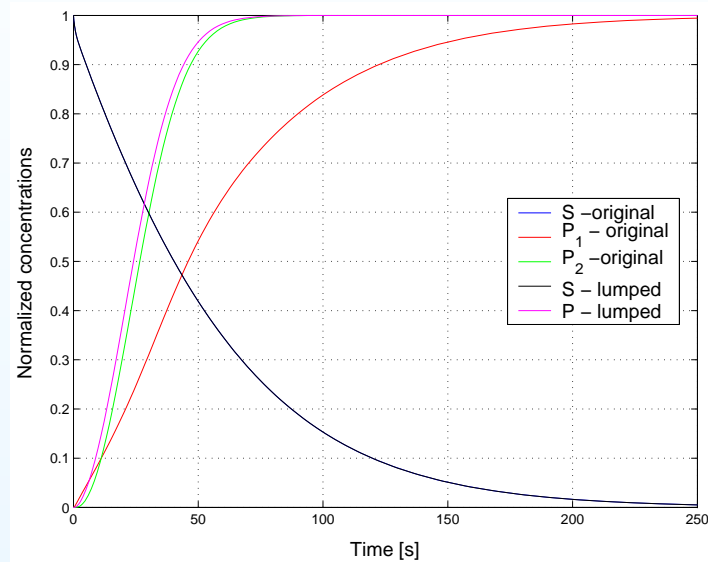
Output transformation I

y=transformed S_2 $(=S_2^{tot} - S_2)$

$$E + S_1 \underset{k_1^-}{\overset{k_1^+}{\rightleftharpoons}} ES_1 \underset{k_2^-}{\overset{k_2^+}{\rightleftharpoons}} E + \hat{P}$$

$$\hat{P} + S_2 \underset{k_3^-}{\overset{k_3^+}{\rightleftharpoons}} \hat{P}S_2 \underset{k_4^-}{\overset{k_4^+}{\rightleftharpoons}} \hat{P}$$

The structure graph of the original and the lumped reaction. The dashed lines denote the reversible case

Output transformation II

Simulation results:
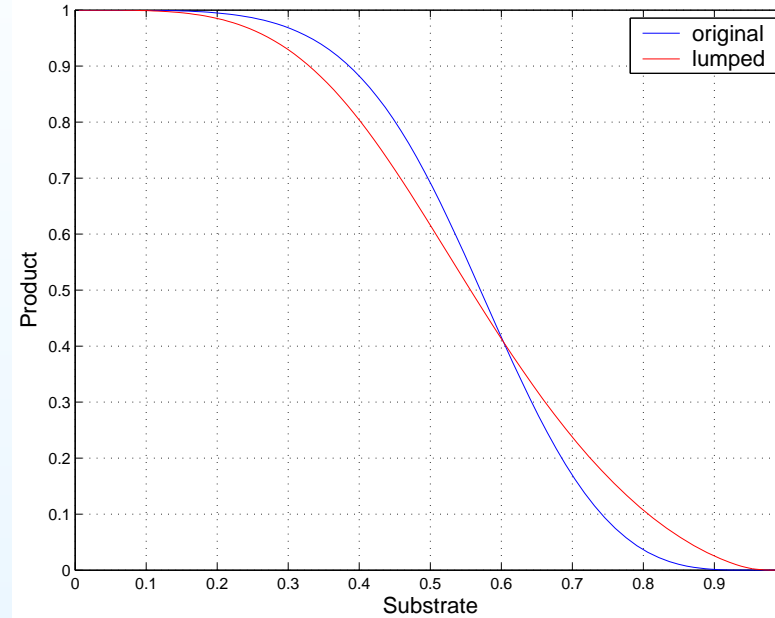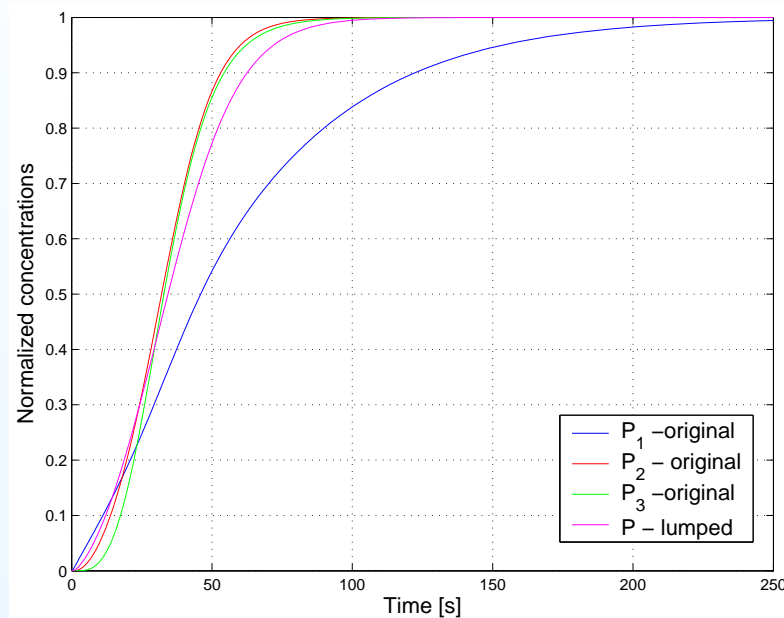
Generalizations I - Two step cascade

We can generalize the state-variable lumping method also for a two-step cascade.
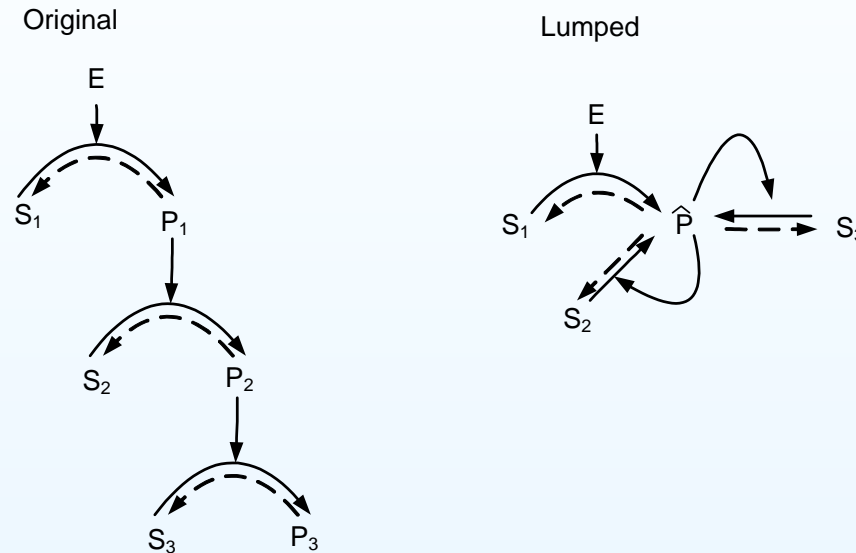
Original

Lumped

The activation scheme of the original and the lumped reaction

Generalizations II - Simulation results

Simulation results in the case of the output transformation method:

Better approximation of input-output behavior is achieved compared to the method of the variation of stochiometric coefficients.
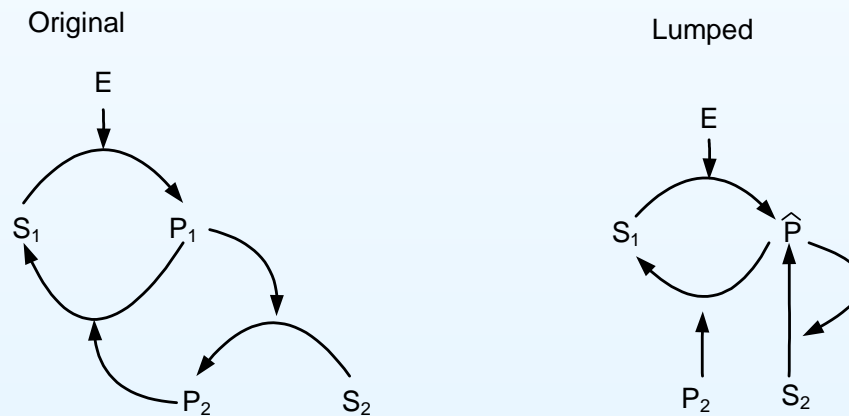
Generalizations III - Feedback regulated cascade

One important example: MAPK cascade - central signaling cascade playing part in DNA expression control, cell cycle, etc.

Activation sequence: Ras $\to$ Raf $\to$ MEK $\to$ ERK

+ FEEDBACK REGULATION

We can generalize the state-variable lumping method also for a feedback regulated cascade.
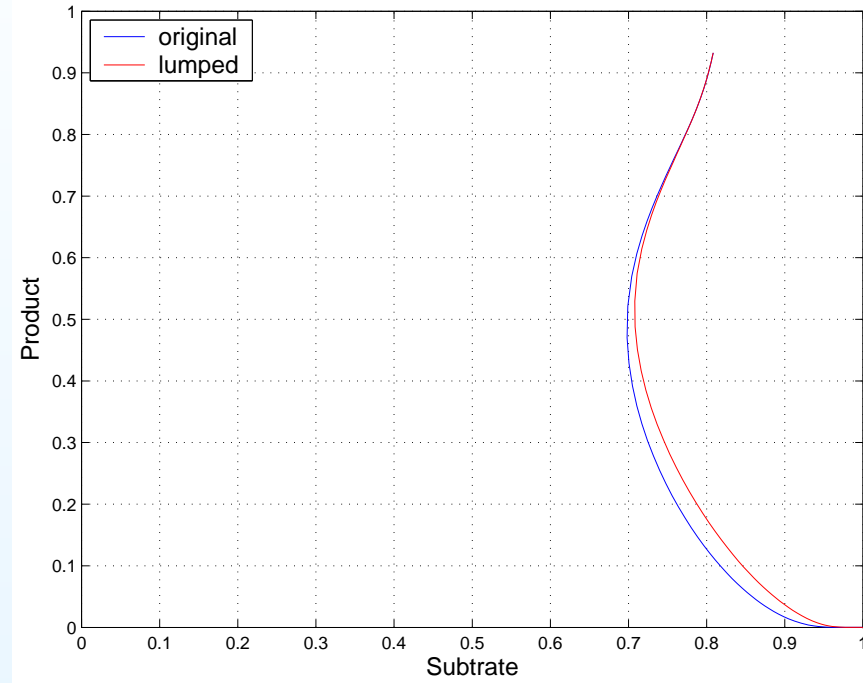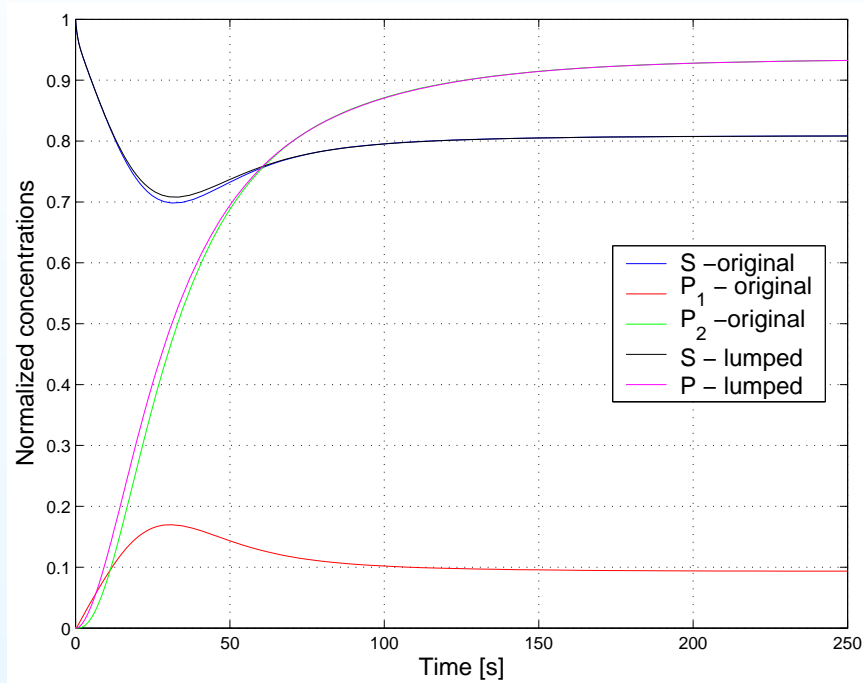
Original

Lumped

The activation scheme of the original and the lumped reaction

Generalizations IV - Simulation results

Simulation results in the case of the output transformation method:

Conclusions

Conclusions

- A step towards minimal input-output model based on structural properties (Gray-box modeling).

- Acceptable results in the case of various parameter sets, in the case of identical parameters.

- Output transformation - better results in the case of irreversible reactions.

- Can be applied also for two step and feedback regulated reactions.