Computation of dynamically equivalent and linearly conjugate reaction networks using optimization methods

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Contents

Introduction

- **(bio)chemical reaction networks** (CRNs): useful class of nonnegative nonlinear systems
  - dynamical description of (bio)chemical reactions in a laboratory or industrial environment
  - interesting from the viewpoint of nonlinear systems theory: description of complex behaviour
- **optimization**: important area, fast scientific and HW/SW development:
  - essential for the solution of numerous engineering/technical problems,
  - deciding feasibility and searching for feasible solutions can be possible when the problem is hard or impossible to treat analytically (LMIs, BMIs, SOS problems in control, diagonal stabilizability etc.)
- **approach**: the dynamics is given, we are searching for preferred CRN structures that "realize" it

Some motivating facts

- dynamics is essential for understanding complex phenomena in biological/biochemical systems
- kinetic systems form a wide class within nonnegative polynomial models
- many important features like deficiency, (weak) reversibility, complex/detailed balance etc. are not intrinsically encoded in the kinetic ODEs, but they are realization properties
- the strong structure-dependent results of CRNT can often be extended to other models through appropriate dynamically equivalent realizations

Original problem statement and starting analogies

- Problem statement of computing CRN topologies corresponding to a set of kinetic differential equations with required properties appeared about 30 years ago in: Hárs and Tóth, "On the inverse problem of reaction kinetics", *Qualitative Theory of Differential Equations*, 30:363-369, 1981.
- Similar (unsolved) problem in the theory of electrical circuits: constructing a linear electrical network with a minimal number of R, L, C elements corresponding to a given transfer function (R.E. Kalman, probably substantially more complex than our problem)
- The idea of terminology 'realization' came from linear control theory, where matrices (A, B, C, D) are called a realization of a transfer function $H(s)$, if

$$H(s) = C(sI - A)^{-1}B + D$$

1. Introduction and motivation

2. **Basic notions and tools**
   - Positive (nonnegative) dynamical systems
   - Reaction networks obeying the mass action law (MAL)
   - Dynamical equivalence (macro-equivalence)
   - Combining logic with mixed integer linear programming (MILP)

3. Computing CRN realizations with preferred properties
   - Computing "dense" and "sparse" realizations
   - Minimizing/maximizing the number of complexes
   - Computation of reversible realizations
   - Detailed and complex balance
   - Finding weakly reversible realizations
   - Linearly conjugate networks

4. Conclusions

Essentially nonnegative systems

- the function $f = [f_1 \ \ldots \ f_n]^T : [0,\infty)^n \to \mathbb{R}^n$ is *essentially nonnegative*, if whenever $x_i = 0$, $f_i(x) \geq 0 \ \forall \ x \in [0,\infty)^n$ for $i = 1, \ldots, n$
- linear case: $f(x) = Ax$, A is a so-called *Metzler-matrix* (off-diagonal elements are nonnegative)
- Consider the following nonlinear autonomous system:

$$\dot{x} = f(x), \ x(0) = x_0 \tag{1}$$

where $f : \mathcal{X} \to \mathbb{R}^n$ is locally Lipschitz, $\mathcal{X}$ is an open subset of $\mathbb{R}^n$, and $x_0 \in \mathcal{X}$. Assume furthermore that $[0,\infty)^n = \bar{\mathbb{R}}^n_+ \subset \mathcal{X}$. Then the nonnegative orthant is invariant for the dynamics (1) **if and only if** f is essentially nonnegative.

- Kinetic systems are (naturally) essentially nonnegative

characterization of mass action type CRNs

Usual definition for CRNs:

- **Species**: $\mathcal{S} = \{X_1, X_2, \ldots, X_n\}$
- **Complexes**: $\mathcal{C} = \{C_1, C_2, \ldots, C_m\}$, where

$$C_i = \sum_{j=1}^{n} \alpha_{ij} X_j, \quad i = 1, \ldots, m$$

  and the $\alpha_{ij} \geq 0$ are the *stoichiometric coefficients*
- **Reactions**: $\mathcal{R} = \{(C_i, C_j) \mid C_i \to C_j\}$
  weighted by *reaction rate coefficients* k_{ij}

Reaction rate with mass action law (MAL) for the elementary reaction step $C_i \overset{k_{ij}}{\to} C_j$, where $C_i = \sum_{j=1}^{n} \alpha_{ij} X_j$:

$$\rho_{ij}(x) = k_{ij} \prod_{i=1}^{n} [X_i]^{\alpha_{ij}} = k_{ij} \prod_{i=1}^{n} x_i^{\alpha_{ij}}$$

Weighted directed graph of a reaction network

- *directed graph* G consists of a finite nonempty set V_d of vertices and a finite set E_d of ordered pairs of distinct vertices (directed edges), i.e. $G = (V_d, E_d)$
- *vertices* correspond to complexes:
  $V_d = \{C_1, C_2, \ldots C_m\}$
- *directed edges* represent reactions:
  $(C_i, C_j) \in E_d$ if complex C_i is transformed to C_j
- *reaction rate coeffs.*: $k_j \geq 0$, $j = 1, \ldots, r$ (weights of the corresponding directed edges)
- *linkage class*: connected component (complexes of the set are linked to each other in the reaction graph but not to any other complex)
- *reversible reaction*: both $C_i \to C_j$ and $C_j \to C_i$ are present
- *weakly reversible network*: linkage classes are the strongly connected components

Dynamical description (ODEs)

Stoichiometric matrix (Y) and the reaction monomials

$$Y_{ij} = \alpha_{ij}, \quad \varphi_j(x) = \prod_{i=1}^{n} x_i^{Y_{ij}} \quad , \; j = 1, .., m; \; i = 1, ..., n$$

Kirchhoff (or kinetic) matrix of a CRN: $A_k \in \mathbb{R}^{m \times m}$

$$[A_k]_{ij} = \begin{cases} -\sum_{l=1, l \neq i}^{m} k_{il} & \text{if} \quad i = j \\ k_{ji} & \text{if} \quad i \neq j \end{cases}$$

(column conservation matrix with nonpositive diagonal and nonnegative off-diagonal entries)

Dynamic state equations:

$$\frac{dx}{dt} = \underbrace{Y \cdot A_k}_{M} \cdot \varphi(x) = M \cdot \varphi(x) \tag{2}$$

Kinetic polynomial systems

- An autonomous system of the form $\dot{x} = f(x)$ is *kinetic*, if $f(x) = Y \cdot A_k \cdot \phi(x)$, where (Y, A_k) are such that they encode a CRN (constraints!) $\Longrightarrow$ (Y, A_k) is called the *kinetic realization* of the function f
- Necessary and sufficient conditions for kinetic realizability:

$$f_i(x) = -x_i g_i(x) + h_i(x), \;\; i = 1, \ldots, n$$

  where g_i and h_i are polinomials with nonnegative coefficients
- There exists a *systematic algorithm* for determining one possible CRN structure from kinetic polynomial equations (Hárs és Tóth, 1981)
  But: in general, it inserts more complex/reactions into the graph than the necessary minimum (but it is very important to determine an initial realization)
- What to do with nonnegative but not kinetic polynomial systems?
  a) state dependent time-rescaling, b) embedding into (generalized) Lotka-Volterra form $\Longrightarrow$ **the set of polynomial systems that are kinetic or are transformable to kinetic form is quite wide**

Realization of kinetic systems: algorithm

Form of coordinates functions:

$$f_i(x) = \sum_{j=1}^{r_i} m_{ij} \prod_{k=1}^{n} x^{b_{jk}} \tag{3}$$

Realization algorithm (Tóth J. és Hárs V., 1981)
for each $i = 1, \ldots, n$ and for each $j = 1, \ldots, r_i$ do:

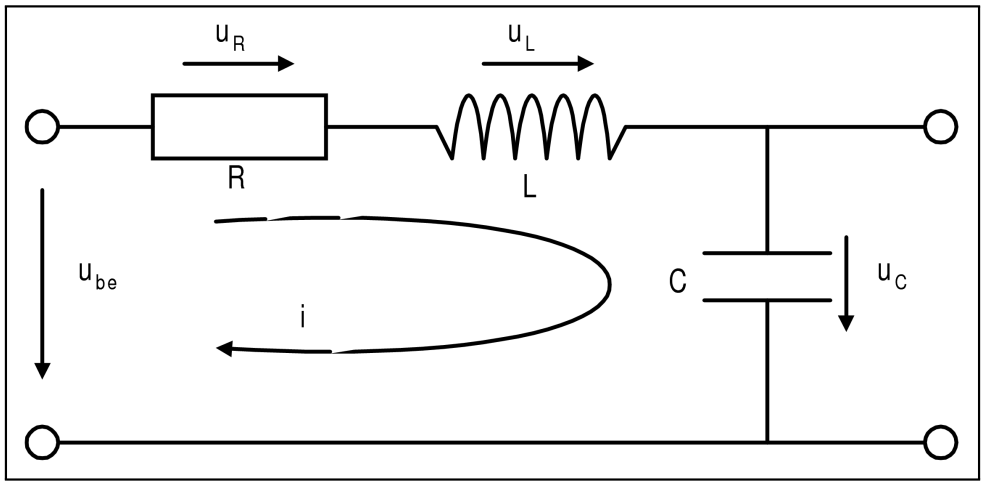
1. $C_j = B_j + \text{sign}(m_{ij}) \cdot e_i$
2. Add the following reaction to the CRN graph:

$$\sum_{k=1}^{n} b_{jk} \mathbf{X}_k \longrightarrow \sum_{k=1}^{n} c_{jk} \mathbf{X}_k$$

where the reaction rate coefficient is $|m_{ij}|$, and
$C_j = [c_{j1} \ \ldots \ c_{jn}]$.

Example: "kinetic RLC circuit" – 1

Original system:



Example: "kinetic RLC circuit" – 2

Physical model and state equations:
Voltage along a loop: $-u_{be} + u_R + u_L + u_C = 0$
Ohm's law: $U_R = R \cdot i$
Dynamics of linear capacitor and inductor:

$$u_L = L \cdot \frac{di}{dt}, \quad i = C \cdot \frac{dU_C}{dt}$$

state equations

$$\begin{aligned} \frac{di}{dt} &= -\frac{R}{L} \cdot i - \frac{1}{L} u_C + \frac{1}{L} u_{be} \\ \frac{du_C}{dt} &= \frac{1}{C} \cdot i \end{aligned}$$

Example: "kinetic RLC circuit" – 3

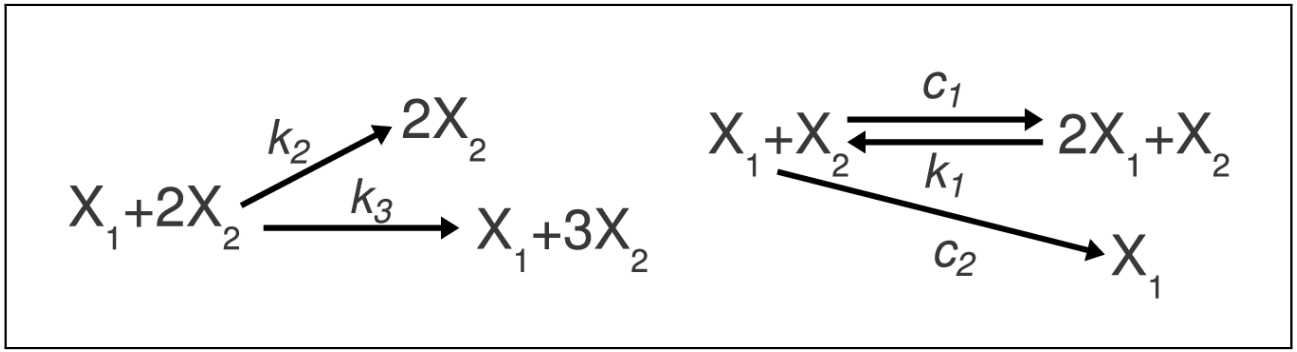
Model equations (after coordinates shift (x_1^*, x_2^*) and time-rescaling):
variables: $i \rightsquigarrow x_1$, $u_C \rightsquigarrow x_2$, $(u_{be} = 0)$

$$x_1' = -k_1 x_1^2 x_2 - k_2 x_1 x_2^2 + c_1 x_1 x_2 \tag{4}$$

$$x_2' = k_3 x_1 x_2^2 - c_2 x_1 x_2 \tag{5}$$

where: $k_1 = R/L$, $k_2 = 1/L$, $k_3 = 1/C$, $c_1 = (R/L)x_1^* + (1/L)x_2^*$, $c_2 = (1/C)x_2^*$

Output of realization algorithm:



Example: "kinetic RLC circuit" – 4

Operation of the realization algorithm

$$x_1' = -k_1 x_1^2 x_2 - k_2 x_1 x_2^2 + c_1 x_1 x_2$$
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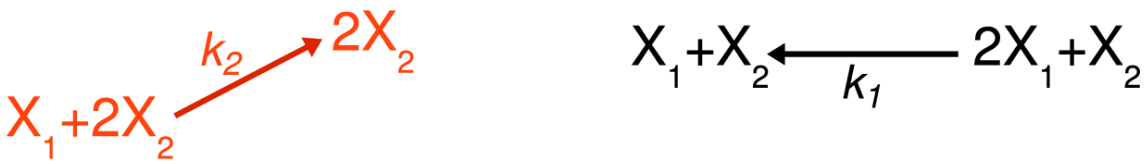

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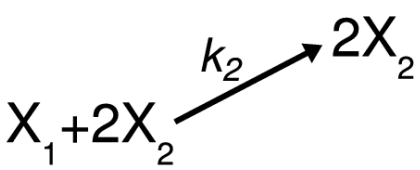

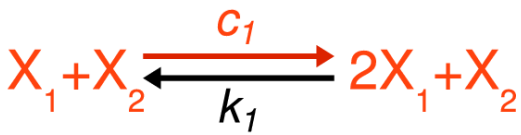

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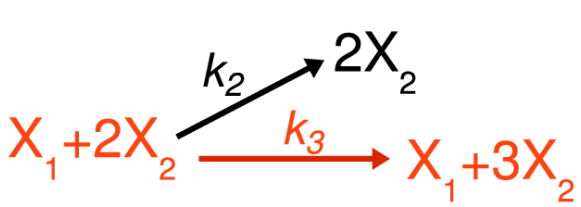

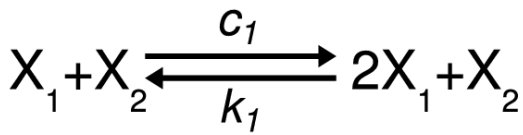

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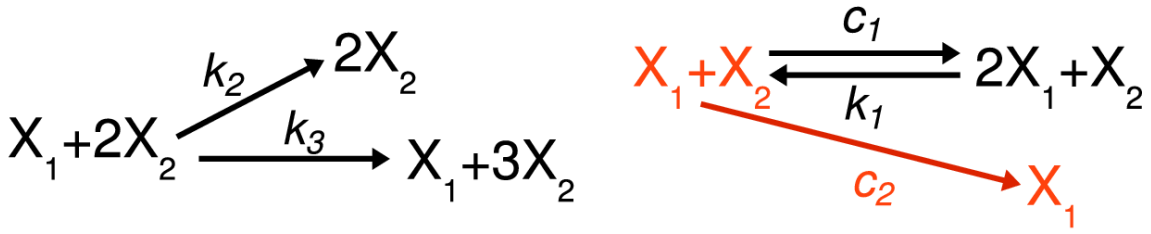
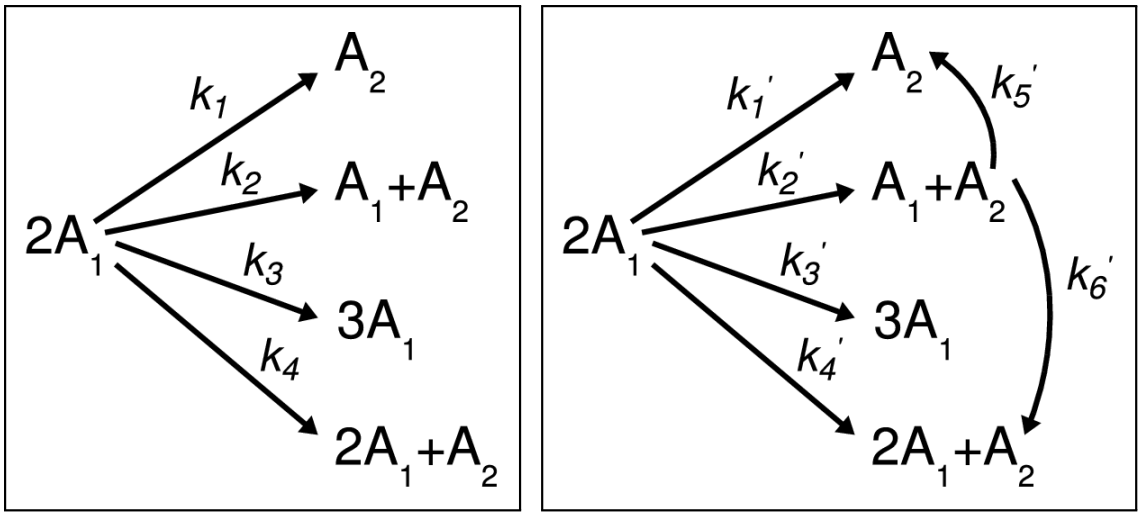


Distinguishability, dynamical equivalence

- G. Craciun and C. Pantea. Identifiability of chemical reaction networks. *Journal of Mathematical Chemistry*, 44:244-259, 2008.
  Original (unfortunately erroneous) **claim**:
  Under the mass-action kinetics assumption, two chemical reaction networks $(\mathcal{S}, \mathcal{C}', \mathcal{R}')$ *and* $(\mathcal{S}, \mathcal{C}'', \mathcal{R}'')$ *are confoundable if and only if* ***they have the same source complexes*** *and* $Cone_{\mathcal{R}'}(y) \cap Cone_{\mathcal{R}''}(y)$ *is nonempty for every source complex* y.
- **Counterexample**:
  G. Szederkényi. Comment on "Identifiability of chemical reaction networks" by G. Craciun and C. Pantea. *Journal of Mathematical Chemistry*, 45: 1172-1174, 2009.

Dynamical equivalence – Example 1

- *known (?) property*: CRNs with different structures may have exactly the same dynamics (*dynamically equivalent* networks)



Both give the following equations:

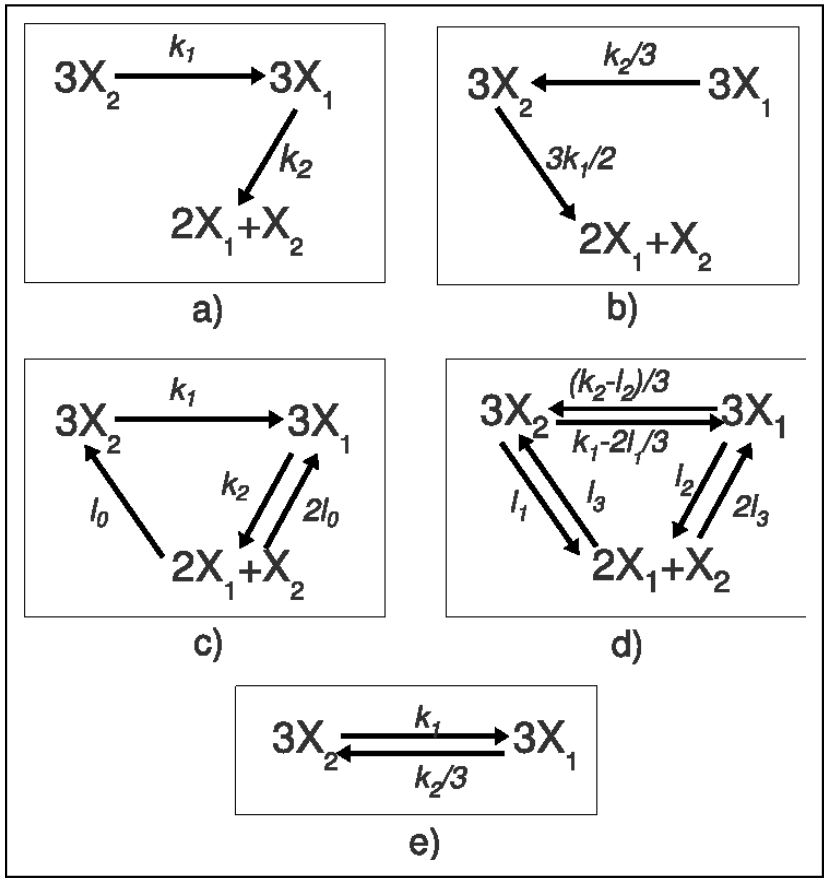
$$\begin{bmatrix} \dot{x}_1 \\ \dot{x}_2 \end{bmatrix} = \begin{bmatrix} -2x_1^2 \\ 3x_1^2 \end{bmatrix} \tag{6}$$

with the parameters

$k_i = 1, \quad i = 1, 2, 3, 4; \quad k_1' = 1, \; k_2' = k_3' = k_5' = k_6' = 0.1, \; k_4' = 1.9$

Dynamical equivalence – Example 2

Dynamically equivalent networks (realizations)



Dynamics:

$$\dot{x}_1 = 3k_1x_2^3 - k_2x_1^3$$

$$\dot{x}_2 = -3k_1x_2^3 + k_2x_1^3$$

Mixed integer linear programming

- A *mixed integer linear program* (MILP) with k variables (denoted by $y \in \mathbb{R}^k$) and p constraints can be written as:

$$\begin{aligned} &\text{minimize } c^T y \\ &\text{subject to:} \\ &A_1 y = b_1 \\ &A_2 y \leq b_2 \\ &l_i \leq y_i \leq u_i \text{ for } i = 1, \ldots, k \\ &y_j \text{ is integer for } j \in I,\ I \subseteq \{1, \ldots, k\} \end{aligned} \tag{7}$$

  where $c \in \mathbb{R}^k$, $A_1 \in \mathbb{R}^{p_1 \times k}$, $A_2 \in \mathbb{R}^{p_2 \times k}$, and $p_1 + p_2 = p$.
- if there are no integer variables, then (7) is a simple LP problem (polynomial)
- if any of the variables is integer: the problem is NP-hard (efficient free and commercial solvers exist)

MILP and propositional calculus

- *literal*: a statement (such as $x \leq 0$) that can have a truth value of "T" (true) or "F" false
- *compound statement*: literals combined into more complex expressions using the following *connectives*: "$\wedge$" (and), "$\vee$" (or), "$\sim$" (not), "$\rightarrow$" (implies), "$\leftrightarrow$" (if and only if), "$\oplus$" (exclusive or)
- a propositional logic problem, where a statement S_1 must be proved to be true given a set of compound statements containing literals $S_1, \ldots, S_n$, can be solved by means of a linear integer program:
  - logical variables δ_i ($\delta_i \in \{0, 1\}$) are associated with the literals S_i
  - compound statements can be algorithmically translated to linear inequalities involving the logical variables δ_i

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4. Conclusions

Dense and sparse realizations: goals

- **Given**: (Y, A_k) CRN or kinetic polynomial system
- **Goal**: computing the following:
  - *sparse realization* (Y^S, A_k^s) (containing the minimal number of reactions)
  - *dense realization* (Y^S, A_k^s) (containing the maximal number of reactions)
- **Assumption**: the set of possible complexes is given in advance

Dense and sparse realizations: computation

Kinetic constraints

$$
\begin{aligned}
&Y \cdot A_k = M \\
&\textstyle\sum_{i=1}^{m} [A_k]_{ij} = 0, \quad j = 1, \ldots, m \\
&[A_k]_{ij} \geq 0, \quad i, j = 1, \ldots, m, \quad i \neq j \\
&[A_k]_{ii} \leq 0, \quad i = 1, \ldots, m
\end{aligned}
$$

Lower/upper bounds

$$
\begin{aligned}
&0 \leq [A_k]_{ij} \leq l_{ij}, \quad i, j = 1, \ldots, m, \quad i \neq j \\
&l_{ii} \leq [A_k]_{ii} \leq 0, \quad i = 1, \ldots, m
\end{aligned}
$$

Density/sparsity

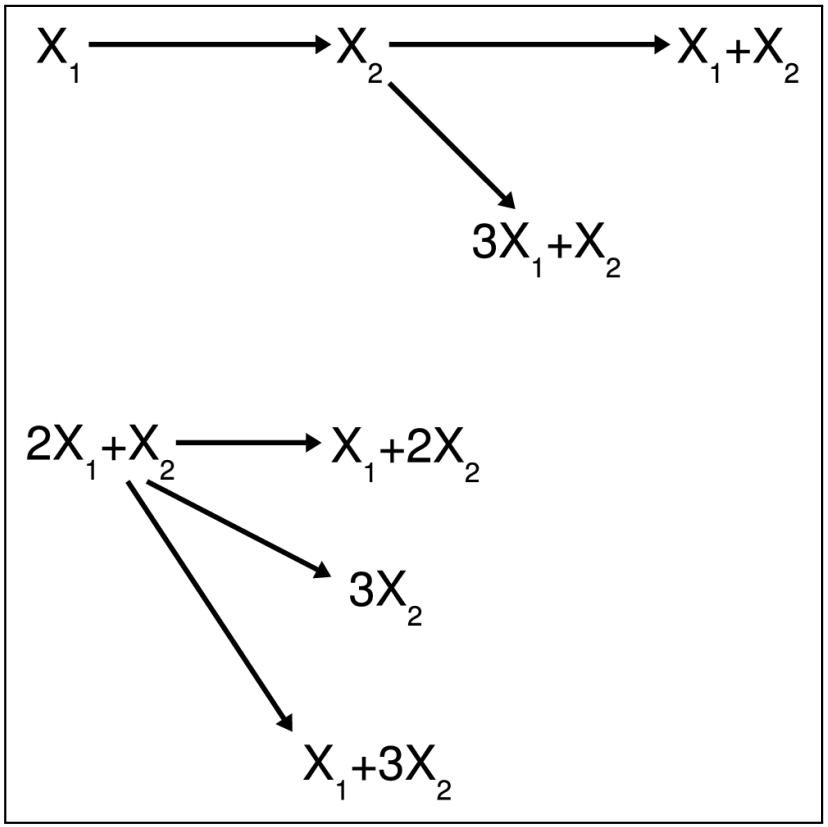
$$
\begin{aligned}
&\delta_{ij} = 1 \leftrightarrow [A_k]_{ij} > \epsilon, \quad i, j = 1, \ldots, m, \quad i \neq j \\
&C_1(\delta) = \sum_{\substack{i,j=1 \\ i \neq j}}^{m} \delta_{ij} \quad \text{(objective function)}
\end{aligned}
$$

Computations can be parallelized! (column-by-column)

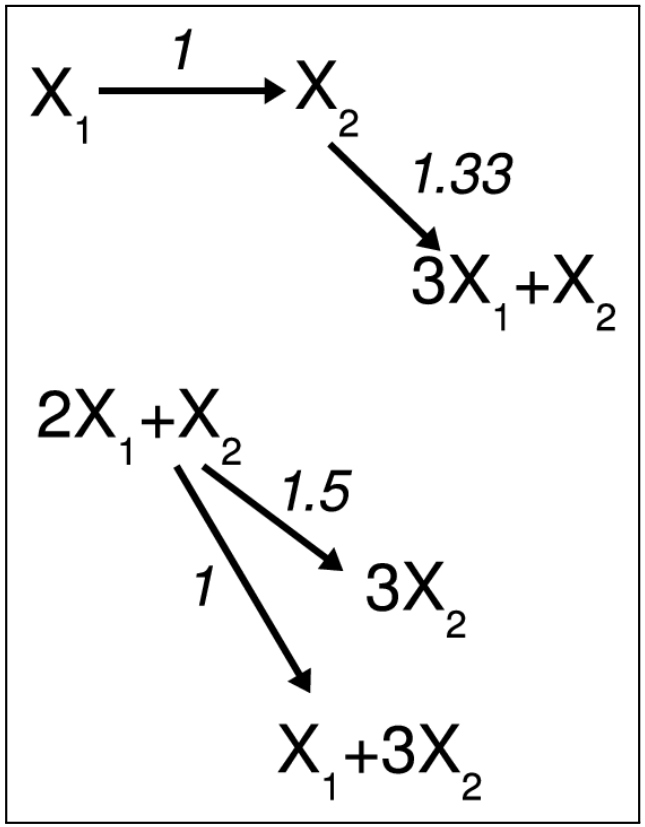
Dense and sparse realizations: example

"Pathological" example (2 components, higher deficiency)

Reaction network ($\delta = 4$):

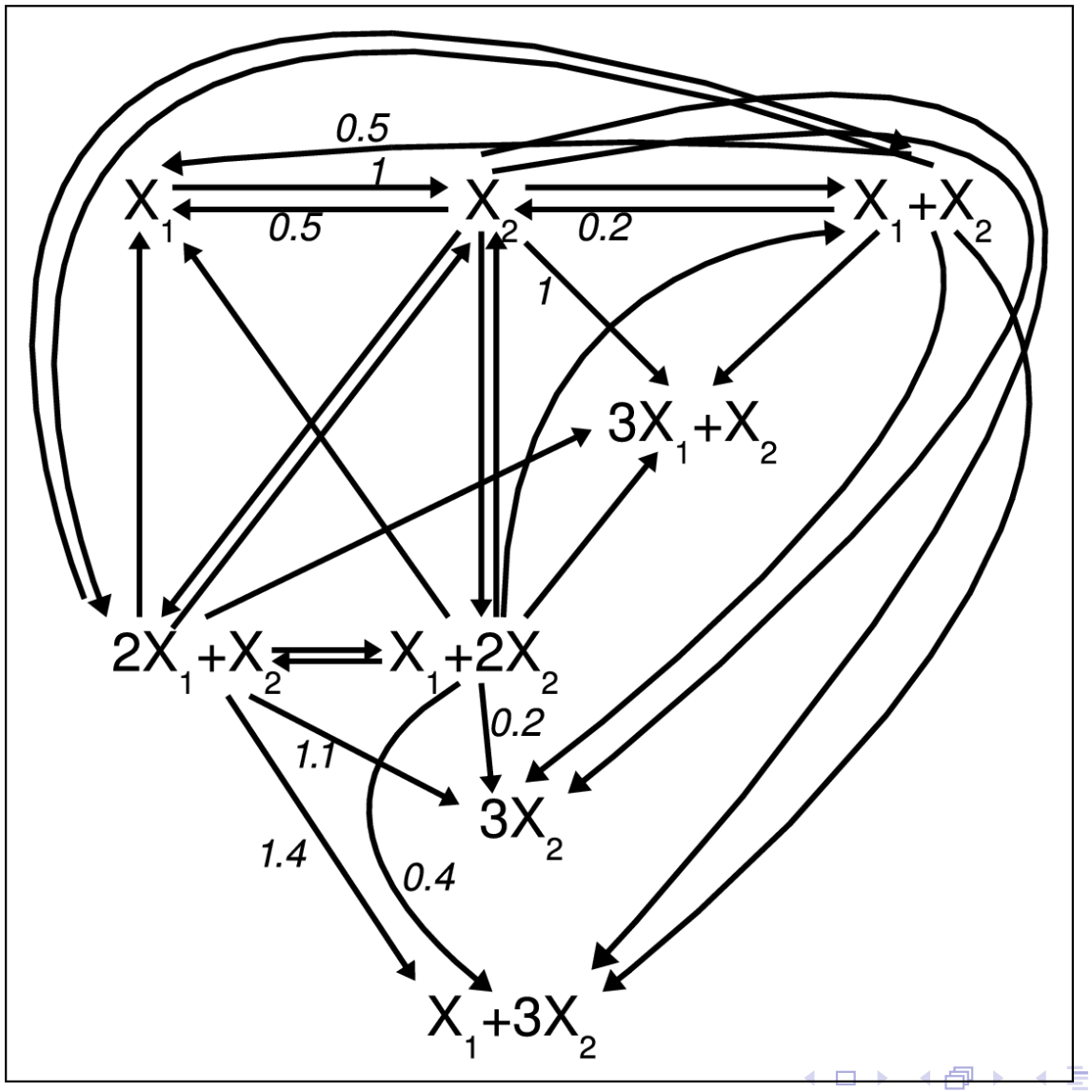


Sparse realization ($\delta = 2$):



Dense and sparse realizations: example

Dense realization ($\delta = 5$):



Further results and properties

We have managed to prove:

- if a kinetic system Σ is given with matrices M and Y, then the directed unweighted graph of any realization is a subgraph of the directed unweighted graph of the dense realization (maximal superstructure)
- the structure of the dense realization (directed unweighted graph) is unique if the set of complexes is given
- the structure of a CRN is unique if and only if the structures of the dense and sparse realizations are identical if the set of complexes is given (easy to check computationally!)

Other (sometimes trivial) remarks:

- reactions not present in the dense realization cannot be parts of any other realizations
- dense realizations are parametrically not unique in general
- the structure of sparse realizations is not unique in general
- dense/sparse realizations are not only theoretical constructions (we gave an easily usable computation method)
- more complex problems can also be solved using the proposed computation framework

Minimizing/maximizing the number of complexes

- constraints of MAL kinetics: same as before
- a complex becomes isolated in the graph (i.e. it can be omitted from the model), if the corresponding row/column of A_k is zero
- m boolean variables are assigned to the colums/rows of A_k:

$$\delta_i = 1 \leftrightarrow \sum_{j_1=1}^{m} A_k(i, j_1) + \sum_{j_2=1}^{m} A_k(j_2, i) > \epsilon, \quad i = 1, \ldots, m$$

  (can be transformed to linear (in)equalities)
- The goal is the following:

$$\text{min. } \pm \sum_{i=1}^{m} \delta_i$$

- the problem is not straightforward to parallelize in its original form, but the number of integers here is only m (instead of the previous m^2)

Reversible realizations

Further condition: $[A_k]_{i,j} > \epsilon_2 \leftrightarrow [A_k]_{j,i} > \epsilon_2, \quad \forall i > j$
Corresponding inequalities:

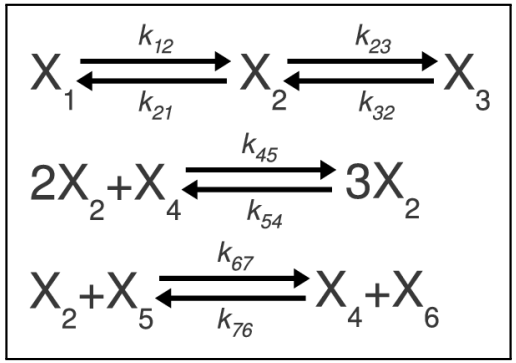
$$0 \leq (\epsilon_2 - \epsilon) - [A_k]_{ij} + (l_{ij} - \epsilon_2) \cdot \delta_{ij}^{(1)}, \quad \forall i > j$$
$$0 \leq (\epsilon_2 - \epsilon) - [A_k]_{ji} + (l_{ji} - \epsilon_2) \cdot \delta_{ij}^{(1)}, \quad \forall i > j$$
$$0 \leq [A_k]_{ij} - \epsilon_2 \cdot \delta_{ij}^{(1)}, \quad \forall i > j$$
$$0 \leq [A_k]_{ji} - \epsilon_2 \cdot \delta_{ij}^{(1)}, \quad \forall i > j$$

Assuring numerical stability: $[A_k]_{ij} < \epsilon$ OR $[A_k]_{ij} > \epsilon_2 + \gamma$, i.e.:

$$0 \leq \delta_{ij}^{(2)}, \quad i \neq j$$
$$0 \leq l_{ij} - [A_k]_{ij} - (l_{ij} - \epsilon) \cdot \delta_{ij}^{(3)}, \quad i \neq j$$
$$0 \leq [A_k]_{ij} - (\epsilon_2 + \gamma) \cdot \delta_{ij}^{(4)}, \quad i \neq j$$
$$0 \leq -\delta_{ij}^{(2)} + \delta_{ij}^{(3)} + \delta_{ij}^{(4)}, \quad i \neq j$$
$$0 \leq \delta_{ij}^{(2)} - \delta_{ij}^{(3)}, \quad i \neq j$$
$$0 \leq \delta_{ij}^{(2)} - \delta_{ij}^{(4)}, \quad i \neq j$$

Brusselator example

Starting network: reversible Brusselator (well known)



Corresponding kinetic ODEs:

$$\dot{x}_1 = -k_{12}x_1 + k_{21}x_2$$
$$\dot{x}_2 = k_{12}x_1 - (k_{21}+k_{23})x_2 + k_{32}x_3 + k_{45}x_2^2x_4 - k_{54}x_2^3 - k_{67}x_2x_5 + k_{76}x_4x_6$$
$$\dot{x}_3 = k_{23}x_2 - k_{32}x_3$$
$$\dot{x}_4 = -k_{45}x_2^2x_4 + k_{54}x_2^3 + k_{67}x_2x_5 - k_{76}x_4x_6$$
$$\dot{x}_5 = -k_{67}x_2x_5 + k_{76}x_4x_6$$
$$\dot{x}_6 = k_{67}x_2x_5 - k_{76}x_4x_6$$

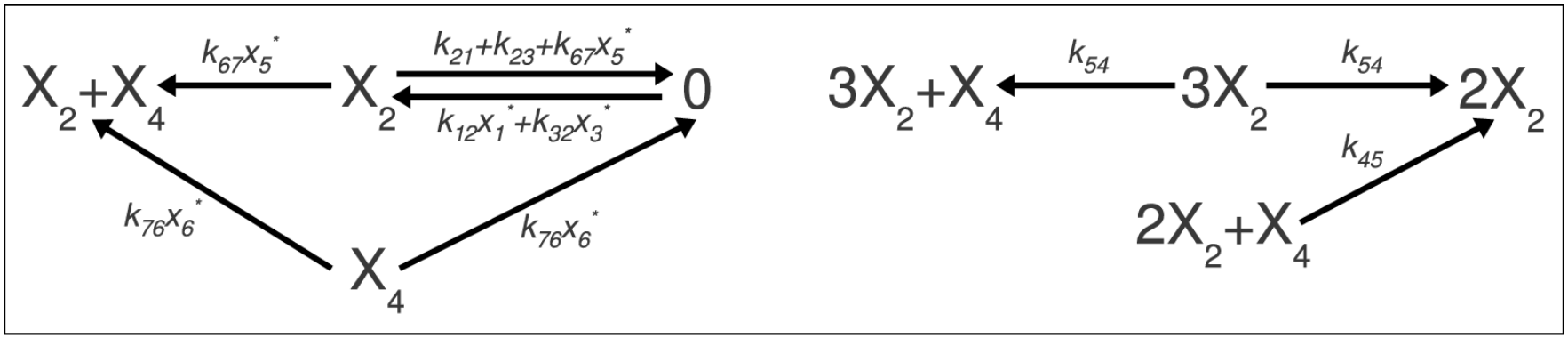
Brusselator example

Oscillation condition: $x_i = x_i^*, \quad i = 1, 3, 5, 6$
Remaining dynamics (kinetic):

$$\dot{x}_2 = (k_{12}x_1^* + k_{32}x_3^*) + (-k_{21} - k_{23} - k_{67}x_5^*)x_2 - k_{54}x_2^3 + k_{45}x_2^2x_4 + (k_{76}x_6^*)x_4$$

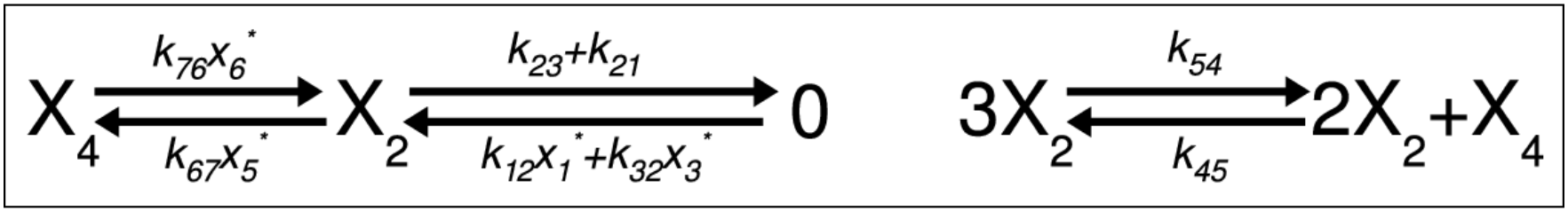
$$\dot{x}_4 = -k_{45}x_2^2x_4 + k_{54}x_2^3 + k_{67}x_5^*x_2 - k_{76}x_6^*x_4$$

Realizing reaction network:



Brusselator example

Does there exist a fully reversible dyn. eq. realization? YES!



Detailed and complex balance

- The realization (Y, A_k) is *complex balanced* at the point $x^* \in \mathbb{R}^n_+$, if $A_k \varphi(x^*) = 0$.
- The reversible realization (Y, A_k) is *detailed balanced* at the point $x^* \in \mathbb{R}^n_+$, if

$$\rho_{ij}(x^*) = \rho_{ji}(x^*), \quad \forall i, j \text{ for which } C_i \leftrightarrows C_j \text{ exists}$$

Most important properties:

- detailed/complex balance at $x^* \Longrightarrow x^*$ is an equilibrium point
- detailed (complex) balance at $x^* \Longrightarrow$ detailed (complex) balance in **any** equilibrium point
- complex balance $\Longrightarrow$ weak reversibility (strong connectivity)
- complex balance for any positive value of reaction rate coeffs: $\Longleftrightarrow$ weak reversibility AND 0 deficiency
- complex balance $\Longrightarrow$ at least local stability with known Lyapunov function

Two important conjectures

- **Global attractor conjecture**: Complex balance $\Longrightarrow$ global stability with known Lyapunov function
- **Persistency conjecture**: Weak reversibility (strong connectivity) $\Longrightarrow$ persistence of dynamics

Computation of complex balanced realizations

Given: (Y, A_k), x^*, $\varphi^* = \varphi(x^*)$
We are searching for: elements of A_k (y)
Solution: LP problem
Objective function: $h = c^T y$
Constraints:

$$\begin{aligned} -a_{11}\varphi_1^* + a_{12}\varphi_2^* + \cdots + a_{1m}\varphi_m^* &= 0 \\ a_{21}\varphi_1^* - a_{22}\varphi_2^* + \cdots + a_{2m}\varphi_m^* &= 0 \\ &\vdots \\ a_{m1}\varphi_1^* + \cdots + a_{m(m-1)}\varphi_{m-1}^* - a_{mm}\varphi_m^* &= 0 \end{aligned}$$

Computation of detailed balanced realizations

Given: (Y, A_k), x^*, $\varphi^* = \varphi(x^*)$
We are searching for: elements of A_k (y)
Let $G = \mathrm{diag}(\varphi^*)$
Solution: LP problem
Objective function: $h = c^T y$
Constraints:

$$G \cdot A_k^T = A_k \cdot G$$

i.e.

$$\varphi_i^* y_{(i-1)m+j} - \varphi_j^* y_{(j-1)m+i} = 0, \quad \forall i > j,$$

Weakly reversible realizations – principles

Basic principle (roughly): the dense realization contains all possible reactions $\Rightarrow$ compute it and discard the unnecessary edges (if possible)
More precisely:

- If each strongly connected component of a directed graph G is contracted to a single vertex, the resulting directed graph is a directed acyclic graph. (*acyclic graph*: has no nontrivial strongly connected subgraphs)
- The structure of the dense realization of any CRN is unique, and the directed unweighted graph of any CRN realization is a subgraph of the directed unweighted graph of the dense realization, if the set of complexes is fixed.

Directed edges linking different strong components have to be removed while maintaining dynamical equivalence.

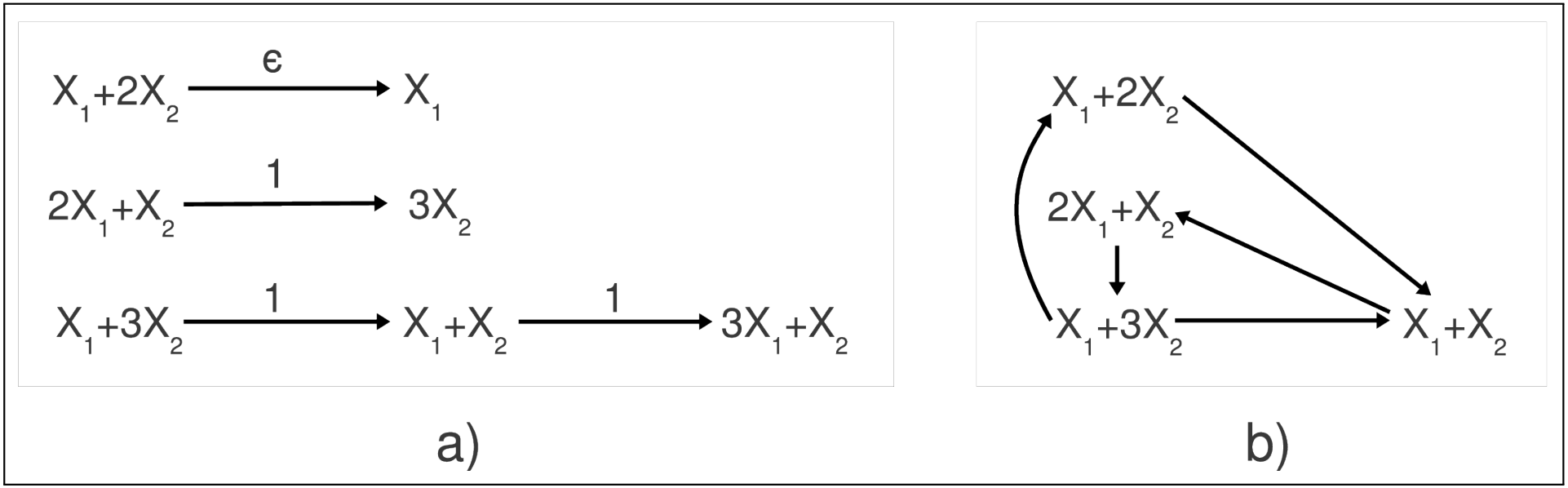
The proposed algorithm – pseudocode

A_k^{out}=FindWeaklyReversibleRealization($Y^{(0)}$,$A_k^{(0)}$)

```
1   A_k^out := 0 ∈ ℝ^{m×m}; ExitCondition:=false;
2   Y := Y^(0); A_k := A_k^(0); F_out:=true; 𝒦 := {}; L := {};
3   while (ExitCondition=false) do
4   begin
5      if (𝒦 ≠ {}) then F_out:=IsRemovable(Y,A_k,𝒦);
6      if (F_out =true) then
7      begin
8         A_k:=FindConstrDenseRealization(Y,A_k,𝒦);
9         L:=FindCrossComponentEdges(A_k);
10        if (L = {}) then ExitCondition:=true; A_k^out:=A_k;
11        else 𝒦 := 𝒦 ∪ L;
12     end
13     else ExitCondition:=true;
14  end
15  return A_k^out;
```

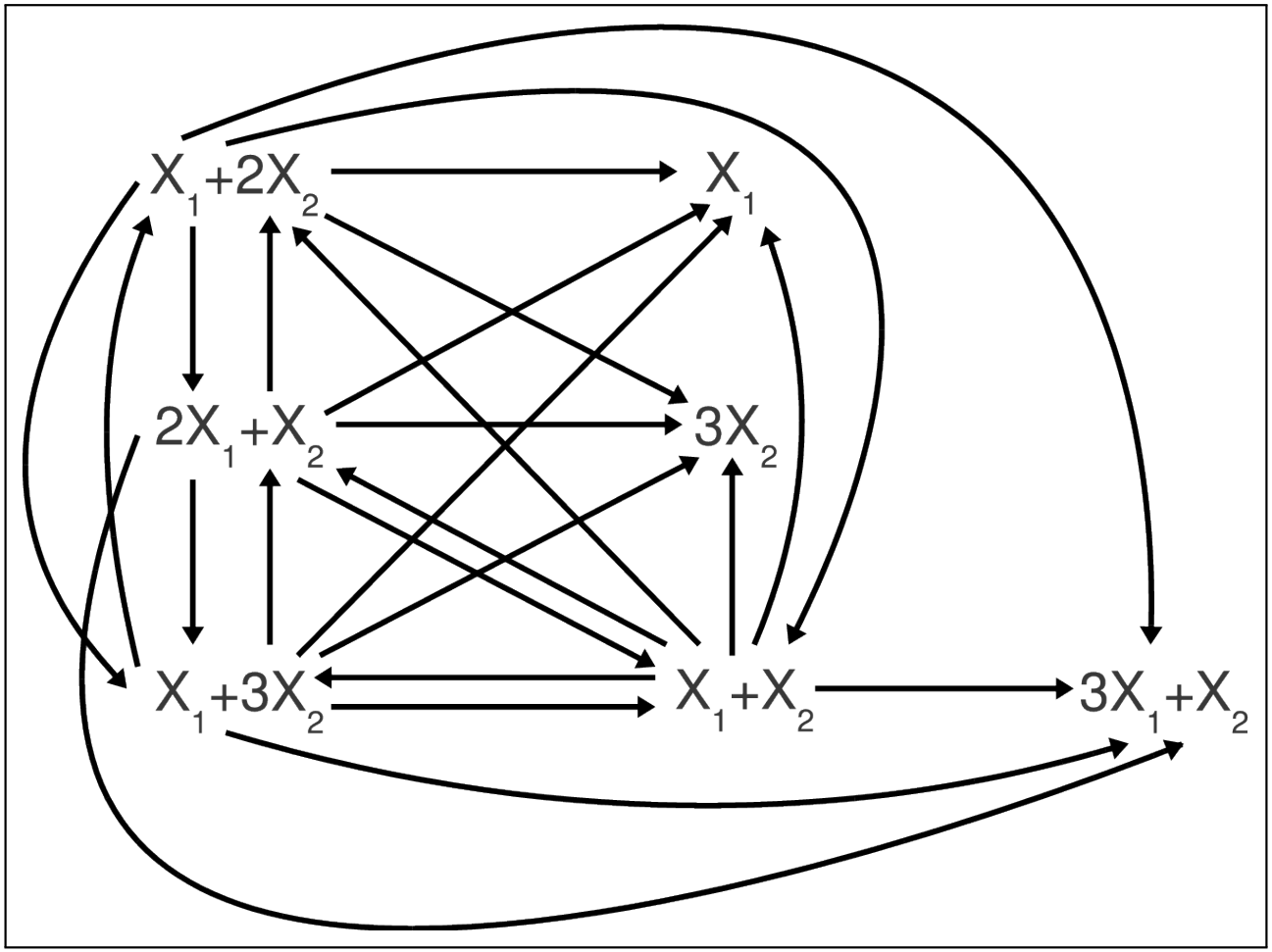
Weak reversibility example – 1

a) Original network from (Johnston and Siegel, 2011), and
b) its published weakly reversible realization structure



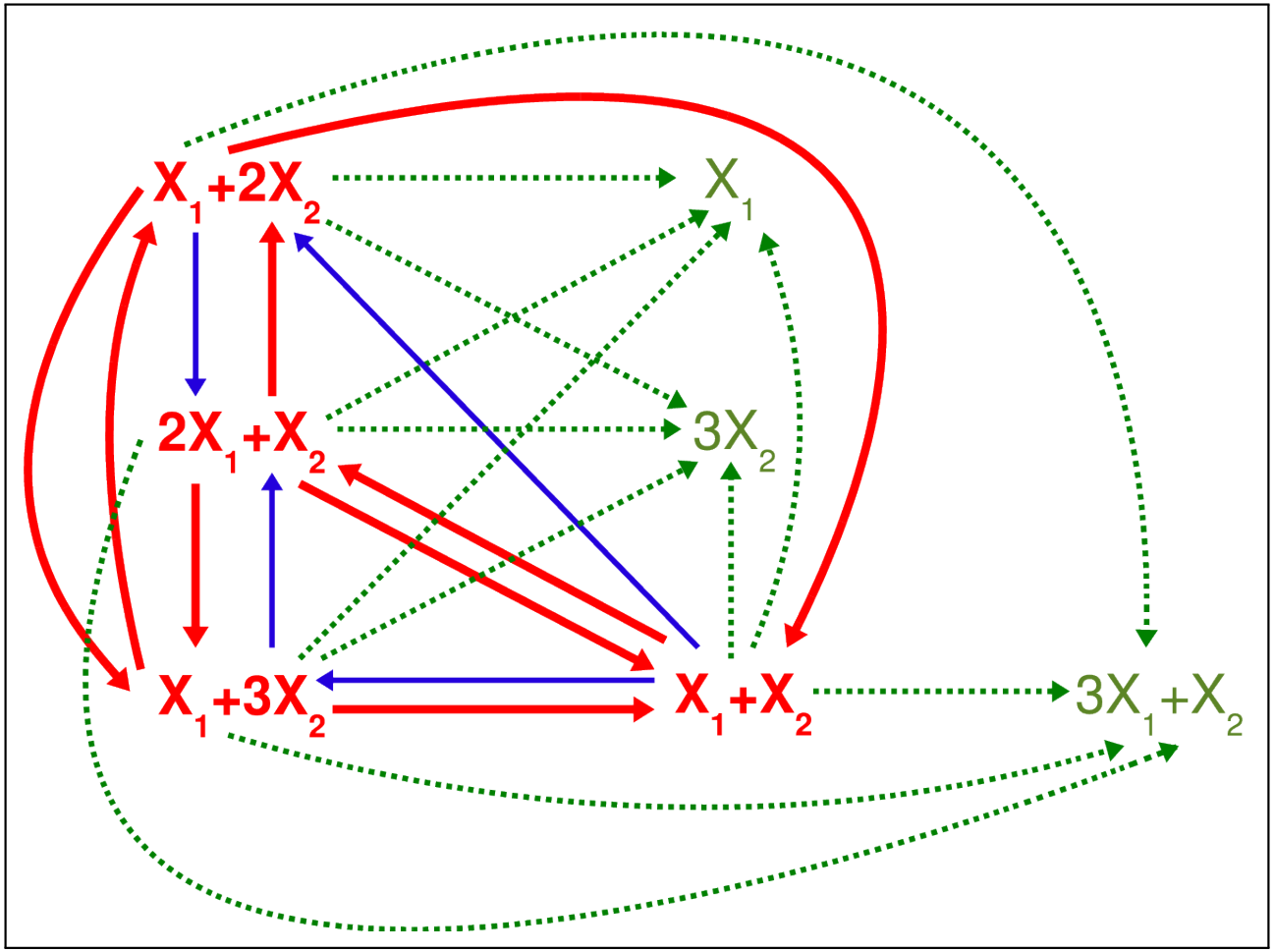
Weak reversibility example – 2

Structure of dense realization



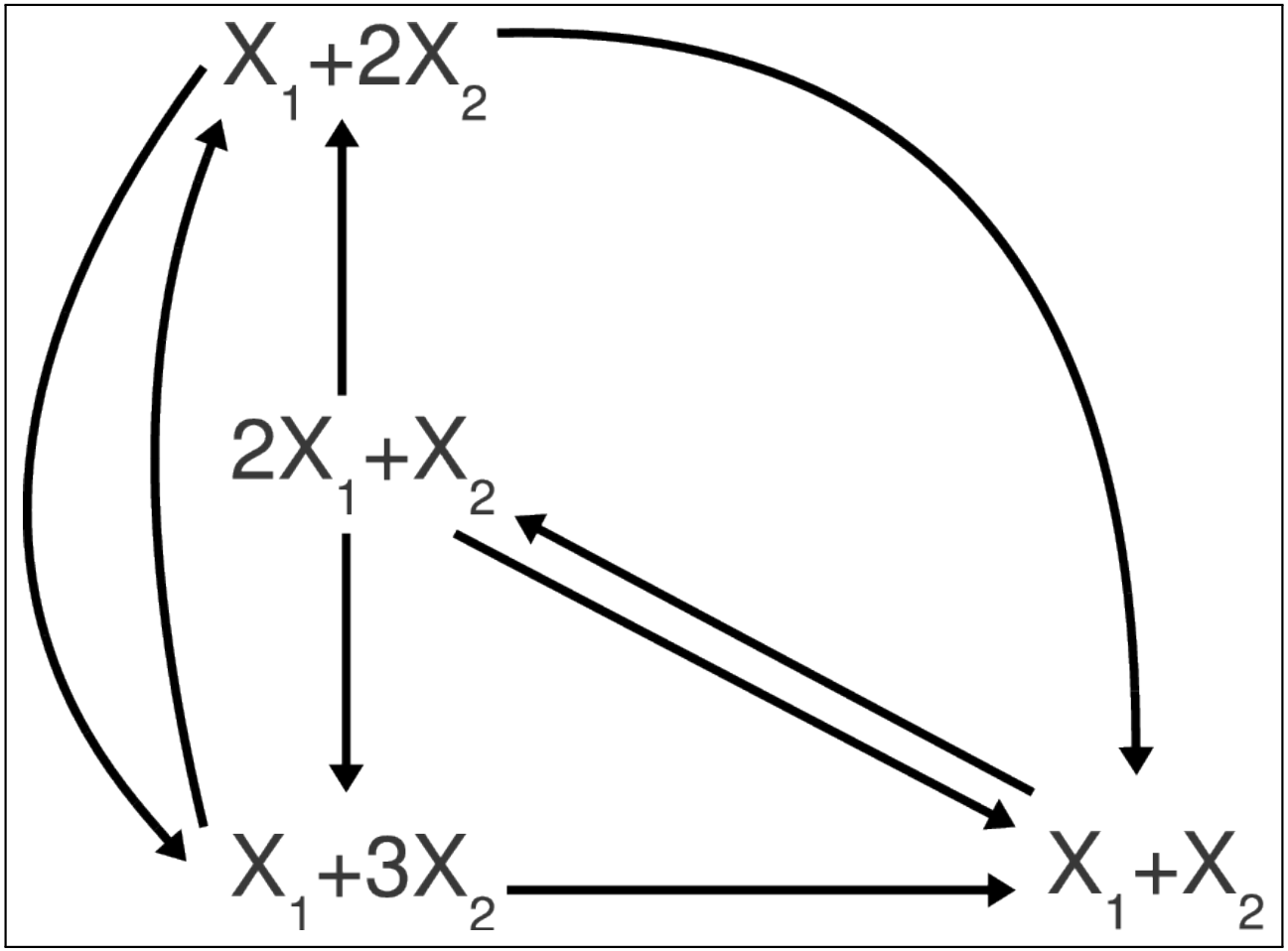
Weak reversibility example – 3

Operation of the algorithm



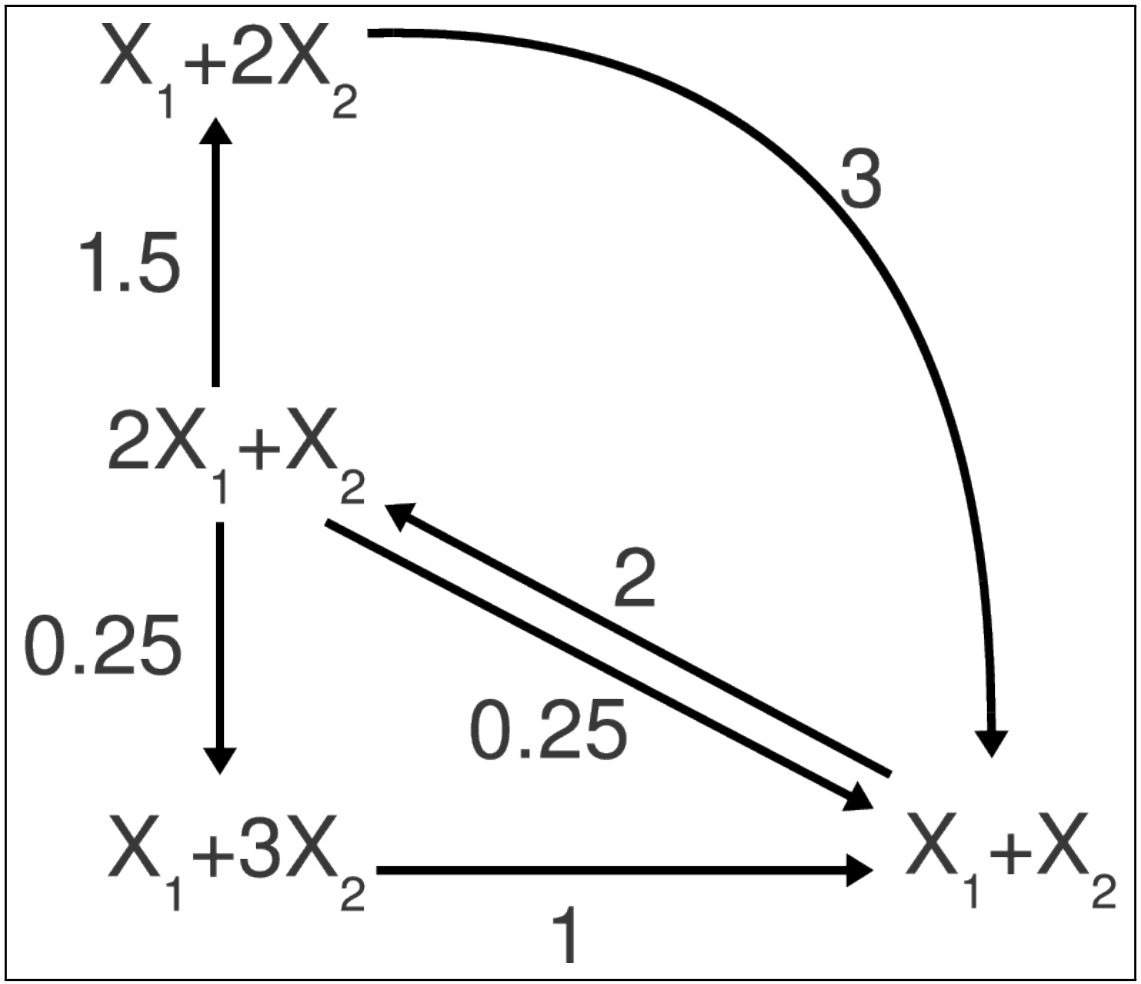
Weak reversibility example – 4

The dense dynamically equivalent weakly reversible structure (not complex balanced with the obtained parameters)



Weak reversibility example – 5

Complex balanced realization (computed with pure LP)
(structure is the subgraph of the dense one)



Linear conjugacy – 1

- Special case of kinetic lumpings
- Two CRNs denoted by Σ and Σ' are said to be *linearly conjugate* if there is a positive diagonal linear mapping which takes the flow of one network to the other (dynamical equivalence is a special case)
- Consider two mass-action systems $\Sigma = (\mathcal{S}, \mathcal{C}, \mathcal{R})$ and $\Sigma' = (\mathcal{S}, \mathcal{C}', \mathcal{R}')$ and let Y be the stoichiometric matrix corresponding to the complexes in either network. Consider a kinetics matrix A_k corresponding to Σ and suppose that there is a kinetics matrix A_b with the same structure as Σ' and a vector $c \in \mathbb{R}^n_{>0}$ such that

$$\underbrace{Y \cdot A_k}_{M} = T \cdot Y \cdot A_b \tag{8}$$

where $T = \text{diag}\{c\}$. Then Σ is linearly conjugate to Σ' with kinetics matrix

$$A'_k = A_b \cdot \text{diag}\left\{\psi(c)\right\}. \tag{9}$$

Linear conjugacy – 2

Corresponding calculation: Let $\Phi(x_0, t)$ correspond to the flow of (2) associated to the reaction network Σ. Consider the linear mapping $\mathbf{h}(x) = T^{-1} \cdot x$ where $T = \text{diag}\{c\}$. Now define $\tilde{\Phi}(y_0, t) = T^{-1} \cdot \Phi(x_0, t)$ so that $\Phi(x_0, t) = T \cdot \tilde{\Phi}(y_0, t)$.
Since $\Phi(x_0, t)$ is a solution of (2), we have

$$\frac{d}{dt}\tilde{\Phi}(y_0, t) = T^{-1} \cdot \frac{d}{dt}\Phi(x_0, t) = T^{-1} \cdot Y \cdot A_k \cdot \psi(\Phi(x_0, t)) =$$
$$= T^{-1} \cdot T \cdot Y \cdot A_b \cdot \psi(T \cdot \tilde{\Phi}(y_0, t)) = Y \cdot A_b \cdot \text{diag}\{\psi(c)\} \cdot \psi(\tilde{\Phi}(y_0, t)).$$

It is clear that $\tilde{\Phi}(y_0, t)$ is the flow of (2) corresponding to the reaction network Σ' with the kinetics matrix given by (9). We have that $\mathbf{h}(\Phi(x_0, t)) = \tilde{\Phi}(\mathbf{h}(x_0), t)$ for all $x_0 \in \mathbb{R}^n_{>0}$ and $t \geq 0$ where $y_0 = \mathbf{h}(x_0)$ since $y_0 = \tilde{\Phi}(y_0, 0) = T^{-1} \cdot \Phi(x_0, 0) = T^{-1} \cdot x_0$. It follows that the networks Σ and Σ' are linearly conjugate.

Linear conjugacy – optimization constraints

$$\textbf{(LC)} \quad \begin{cases} Y \cdot A_b = T^{-1} \cdot M \\ \sum_{i=1}^{m} [A_b]_{ij} = 0, \quad j = 1, \ldots, m \\ [A_b]_{ij} \geq 0, \quad i, j = 1, \ldots, m, \ i \neq j \\ [A_b]_{ii} \leq 0, \quad i = 1, \ldots, m \\ \epsilon \leq c_j \leq 1/\epsilon, \quad j = 1, \ldots, n \end{cases} \tag{10}$$

where $M = Y \cdot A_k$, $T = \text{diag}\{\mathbf{c}\}$, and $0 < \epsilon \ll 1$, and

$$\textbf{(LC-S)} \quad \begin{cases} 0 \leq [A_b]_{ij} - \epsilon\delta_{ij}, \quad i, j = 1, \ldots, m, \quad i \neq j \\ 0 \leq -[A_b]_{ij} + u_{ij}\delta_{ij}, \quad i, j = 1, \ldots, m, \quad i \neq j \\ \delta_{ij} \in \{0, 1\}, \quad i, j = 1, \ldots, m, i \neq j, \end{cases} \tag{11}$$

where $u_{ij} > 0$ for $i, j = 1, \ldots, m, i \neq j$.

Linear conjugacy – Example 1

Consider the kinetics scheme:

$$\begin{aligned}\dot{x}_1 &= x_1 x_2^2 - 2x_1^2 + x_1 x_3^2 \\ \dot{x}_2 &= -x_1^2 x_2^2 + x_1 x_3^2 \\ \dot{x}_3 &= x_1^2 - 3x_1 x_3^2\end{aligned} \tag{12}$$

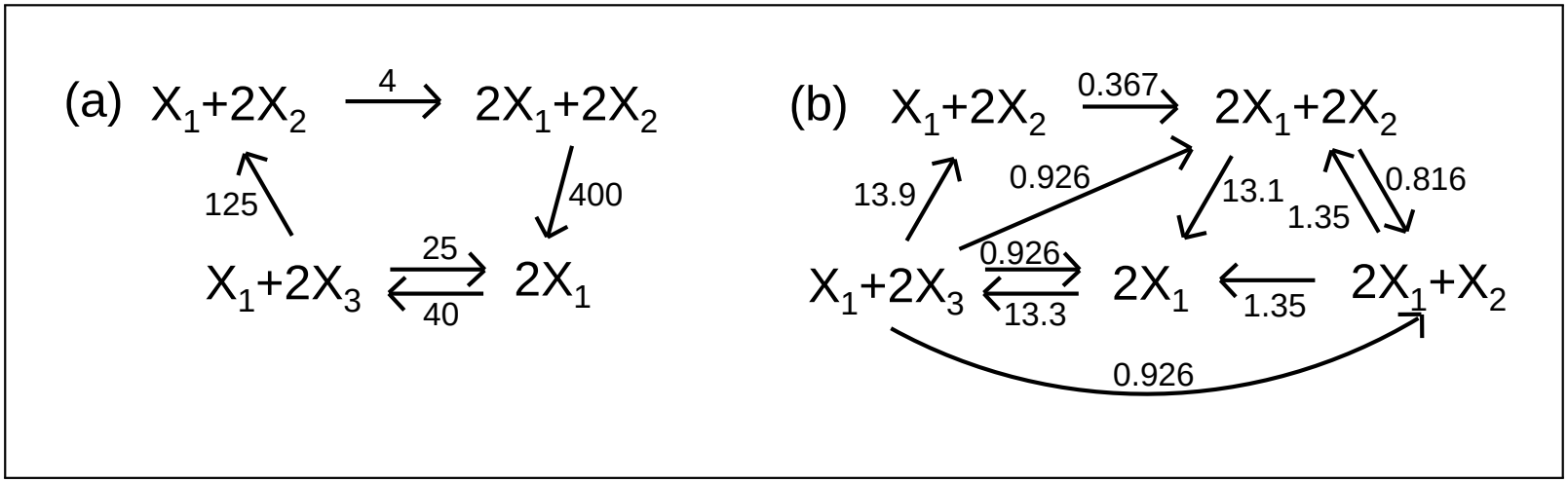
Generated complex set:

$$C_1 = X_1 + 2X_2,\ C_2 = 2X_1 + 2X_2,\ C_3 = 2X_1 + X_2,$$
$$C_4 = 2X_1,\ C_5 = X_1,\ C_6 = 2X_1 + X_3,\ C_7 = X_1 + 2X_3,$$
$$C_8 = 2X_1 + 2X_3,\ C_9 = X_1 + X_2 + 2X_3,\ C_{10} = X_1 + X_3$$

There is no WR dynamically equivalent realization with this complex set
But ...

Linear conjugacy – Example 1

Sparse and dense linearly conjugate WR realizations:



Computed transformation constants:

(a) $c_1 = 20,\ c_2 = 2,\ c_3 = 5$

(b) $c_1 = 20/3,\ c_2 = 20/33,\ c_3 = 5/3$

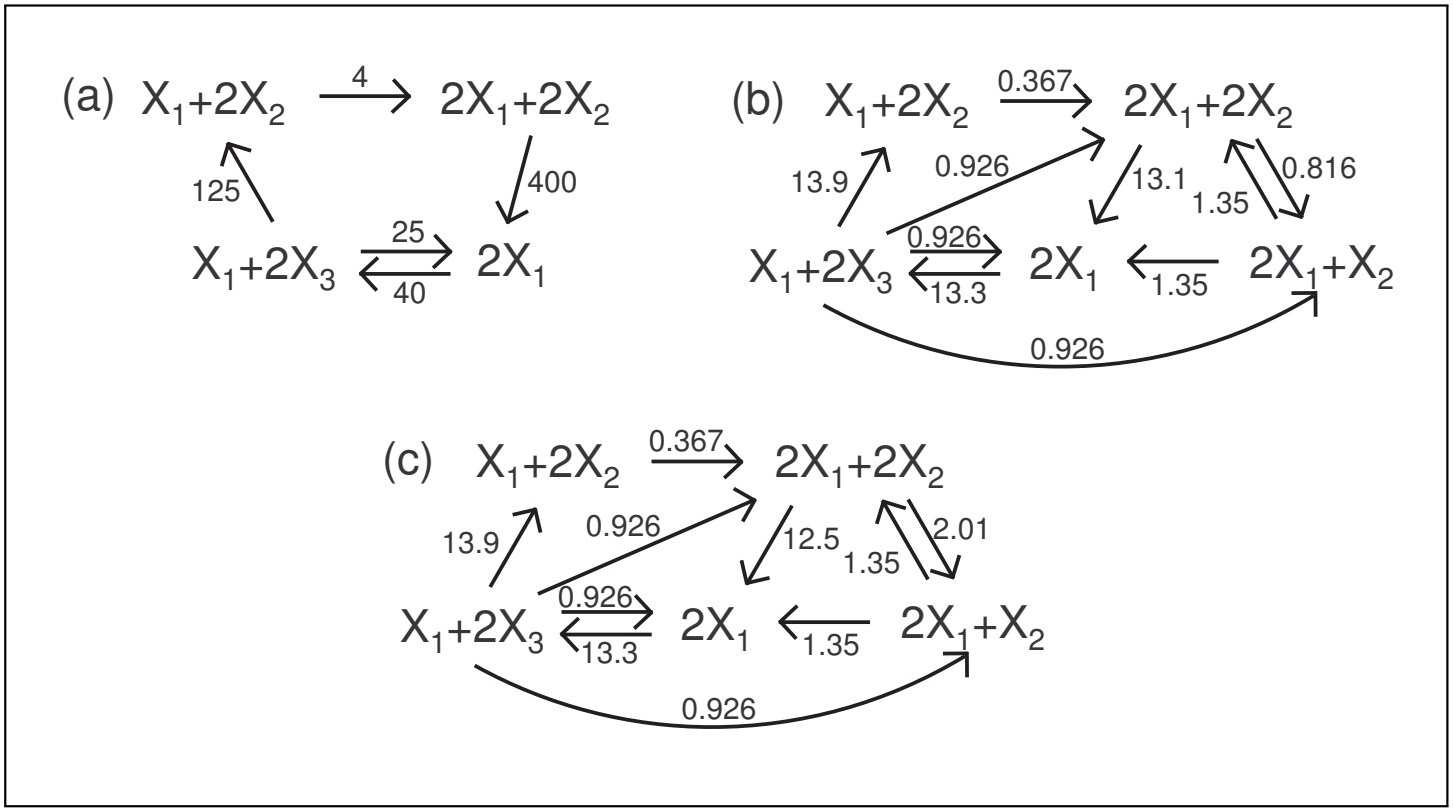
Linear conjugacy – some further results

- **Any eq. point can be selected for the computation of linearly conjugate complex balanced realizations:**
  Suppose $\mathcal{N}$ is linearly conjugate to $\mathcal{N}'$ with transformation matrix $T = \operatorname{diag}\{\mathbf{c}\}$ where $\mathbf{c} \in \mathbb{R}^n_{>0}$ and suppose $\mathcal{N}'$ is complex balanced at $\mathbf{y}^* = T^{-1}\mathbf{x}^*$ where $\mathbf{x}^* \in \mathbb{R}^n_{>0}$ and $Y \cdot A_k \cdot \Psi(\mathbf{x}^*) = \mathbf{0}$. Then $\mathcal{N}'$ is complex balanced at $\bar{\mathbf{y}}^* = T^{-1}\bar{\mathbf{x}}^*$ for all $\bar{\mathbf{x}}^* \in \mathbb{R}^n_{>0}$ satisfying $Y \cdot A_k \cdot \Psi(\bar{\mathbf{x}}^*) = \mathbf{0}$.
- **For a given CRN, the unweighted directed reaction graph of any linearly conjugate realization is the subgraph of that of the dense one** $\Longrightarrow$ The structure of the dense linearly conjugate realization is unique.

Linear conjugacy – Example 2

Consider the kinetic system of Example 1 again

Linearly conjugate realizations:



(a) Sparse, complex balanced (WR, deficiency 0)

(b) Dense, weakly reversible, not complex balanced

(c) Dense, complex balanced

1. Introduction and motivation

2. Basic notions and tools
   - Positive (nonnegative) dynamical systems
   - Reaction networks obeying the mass action law (MAL)
   - Dynamical equivalence (macro-equivalence)
   - Combining logic with mixed integer linear programming (MILP)

3. Computing CRN realizations with preferred properties
   - Computing "dense" and "sparse" realizations
   - Minimizing/maximizing the number of complexes
   - Computation of reversible realizations
   - Detailed and complex balance
   - Finding weakly reversible realizations
   - Linearly conjugate networks

4. **Conclusions**

Summary

Conclusions

- some important properties of CRNs are not encoded in the ODEs
- the scope of strong CRNT results can be extended through dynamical equivalence and linear conjugacy
- solution motivation: widespread optimization-based feasibility analysis (e.g. in systems and control theory)
- thermodynamical point of view: interesting/useful even in the case of non-(bio)chemically originated (but mathematically kinetic) models
- existence analysis and computation of CRN structures with preferred properties: optimization (LP, MILP)
- properties of system class, prescribed features: constraints
- proposed methods do not substitute rigorous (algebraic, geometric) analysis in any way

Work in progress: developing algorithms to be numerically more efficient

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