

Analysis and control of positive systems using kinetic realizations: dynamics, structure, and optimization

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Background and goals

"If all you have is a hammer, everything looks like a nail."

Background: computer science/engineering, (nonlinear) systems and control theory (applied to thermodynamical, biochemical systems)

Aims

- to illustrate the notion and significance of dynamical systems
- a (draft) overview of the approach of systems and control theory
- a more detailed introduction to kinetic models
- to summarize our contributions

Motivation

- to know and describe new system classes
- a deep understanding of certain interesting phenomena in technological and living systems
- to improve/develop methods in modeling, analysis and control

- 1 Motivation and introduction
- 2 Basic notions: kinetic systems (CRNs) and optimization
- 3 Properties and computation of CRN structures
 - Computation of "dense" and "sparse" realizations
 - Computation of weakly reversible realizations
 - Computing linearly conjugate WR realizations with minimal deficiency
- 4 Kinetic feedbacks for polynomial systems
- 5 Conclusions

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Introductory remarks and notions

- the construction and application of mathematical models is essential during the design/operation of technological systems and the analysis/control of complex processes in living systems
- description of quantities changing in space/time: dynamical models (in a system and control theoretic framework)
- the handling of nonlinearities is often necessary \Rightarrow it is advantageous to choose model classes with good descriptive power but having relatively simple mathematical structure
- nonnegative (positive) systems : physical, chemical, biological, pharmacokinetical (compartmental), transportation or process models with nonnegative (positive) state variables (non-positive systems can often be transformed to nonnegative form)

autonomous nonlinear model: $\dot{x} = f(x)$, $x \in \mathbb{R}^n$,

nonnegativity condition: for $x_i = 0$, $f_i(x) \geq 0 \forall x \in [0, \infty)^n$,

$i = 1, \dots, n$

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Ingredients and approach

(bio)chemical reaction networks (CRNs)

interesting/useful class of nonnegative systems

- **dynamical description** of (bio)chemical processes in a laboratory or industrial environment
- **interesting from the point of view of nonlinear systems theory** : suitable to describe complex dynamical behaviour

optimization

important decision support tool, fast HW/SW development

- **essential** in the solution of many scientific/engineering problems
- **deciding solvability** and searching for certain solutions is often possible, even if the problem is hard (or impossible) to treat algebraically (e.g. LMIs, BMIs, SOS problems, diagonal stabilizability etc.)

chosen approach

the dynamics is given, and we are searching for CRN structures that "realize" this

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Essentially nonnegative systems

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

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

where $f : \mathcal{X} \rightarrow \mathbb{R}^n$ 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

The notion of CRNs with mass action kinetics

Elementary reaction step (example)



Definition of CRNs

- *species* : $\mathcal{S} = \{X_1, X_2, \dots, X_n\}$
- *complexes* : $\mathcal{C} = \{C_1, C_2, \dots, C_m\}$, where

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

and $\alpha_{ij} \geq 0$ are the *stoichiometric coefficients*

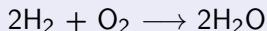
- *reactions* : $\mathcal{R} = \{(C_i, C_j) \mid C_i \rightarrow C_j\}$, weighted by k_{ij} *reaction rate coefficients*

the *reaction rate* corresponding to the $C_i \xrightarrow{k_{ij}} C_j$ elementary reaction step:

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

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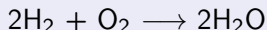
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Weighted directed graph of a reaction network

- *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:
 $V_d = \{C_1, C_2, \dots, C_m\}$
- *directed edges* represent reactions:
 $(C_i, C_j) \in E_d$ if complex C_i is transformed to C_j
- *reaction rate coeffs.* : $k_j \geq 0, j = 1, \dots, r$ (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 $C_i \rightarrow C_j$ and $C_j \rightarrow C_i$ are present
- *weakly reversible network* : linkage classes are the strongly connected components

Dynamical description

- *stoichiometric matrix* (Y) and *reaction monomials* :

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

- *Kirchhoff-matrix* of a CRN: $A_k \in \mathbb{R}^{m \times m}$

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

(column conservation matrix with non/positive diagonal and non-negative off-diagonal entries)

- ODEs:

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

- When is a set of polynomial ODEs "kinetic"? \implies simple necessary and sufficient conditions with a constructive proof containing the algorithm to build the so-called canonical CRN structure. (Hárs & Tóth, 1981)

Kinetic polynomial systems

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

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

where g_i and h_i are polynomials 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 \implies **the set of polynomial systems that are kinetic or are transformable to kinetic form is quite wide**

Realization of kinetic systems: algorithm

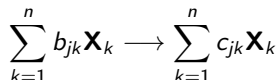
Form of coordinates functions:

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

Realization algorithm (Tóth J. és Hárs V., 1981)

for each $i = 1, \dots, n$ and for each $j = 1, \dots, r_i$ do:

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

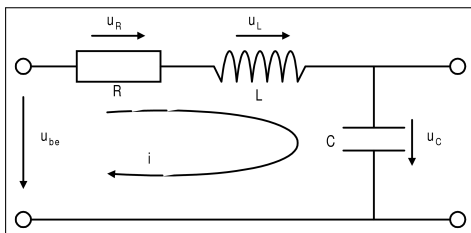


where the reaction rate coefficient is $|m_{ij}|$, and

$$C_j = [c_{j1} \ \dots \ c_{jn}].$$

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

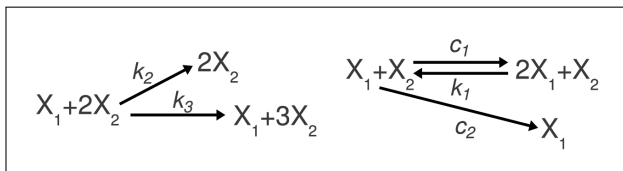
Model equations (after coordinates shift (x_1^*, x_2^*) and time-rescaling):
variables: $i \rightsquigarrow x_1$, $u_C \rightsquigarrow x_2$, ($u_{be} = 0$)

$$x_1' = -k_1 x_1^2 x_2 - k_2 x_1 x_2^2 + c_1 x_1 x_2 \quad (4)$$

$$x_2' = k_3 x_1 x_2^2 - c_2 x_1 x_2 \quad (5)$$

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

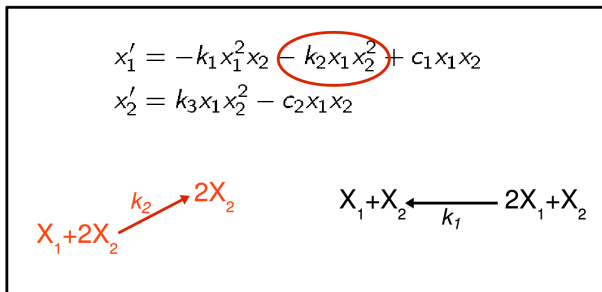
Operation of the realization algorithm

$$x_1' = -k_1 x_1^2 x_2 - k_2 x_1 x_2^2 + c_1 x_1 x_2$$
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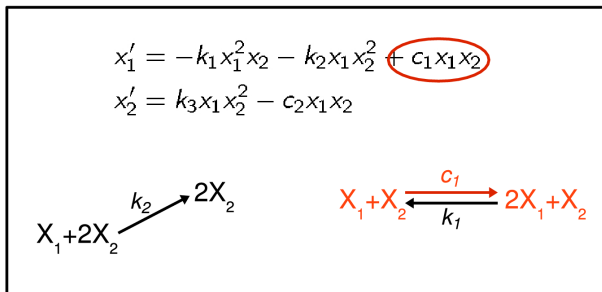
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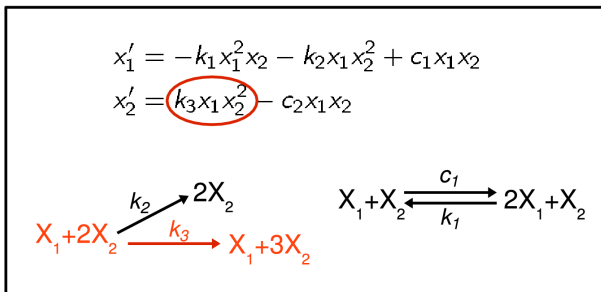
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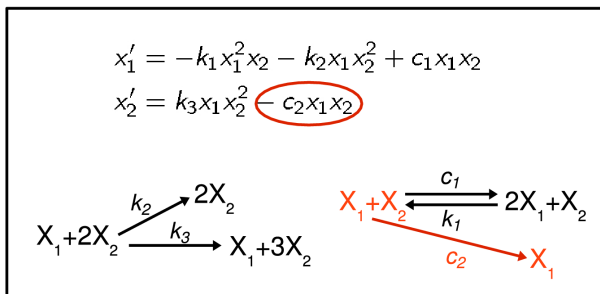
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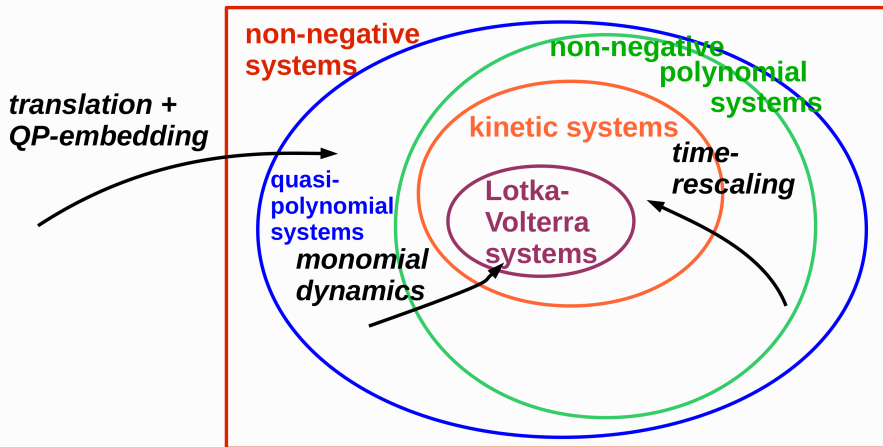
Example: "kinetic RLC circuit" – 4

Operation of the realization algorithm



The above CRN is the so-called **canonical structure**

Summary of some non-negative system classes



Mixed integer linear programming

- *mixed integer linear programming (MILP) problem* with k variables ($y \in \mathbb{R}^k$) and p constraints:

$$\min. c^T y$$

subject to:

$$A_1 y = b_1$$

$$A_2 y \leq b_2$$

$$l_i \leq y_i \leq u_i \quad i = 1, \dots, k$$

$$y_j \text{ is integer for } j \in I, \quad I \subseteq \{1, \dots, k\}$$

(6)

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 $p_1 + p_2 = p$.

- generally NP-hard (but there exist efficient solvers)
- certain **propositional logic problems** can be (algorithmically) rewritten into MILP problems

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, \dots, 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

Compound statements and corresponding linear (in)equalities

truth table of connectives:

S_1	S_2	$\sim S_1$	$S_1 \vee S_2$	$S_1 \wedge S_2$	$S_1 \rightarrow S_2$	$S_1 \leftrightarrow S_2$	$S_1 \oplus S_2$
T	T	F	T	T	T	T	F
T	F	F	T	F	F	F	T
F	T	T	T	F	T	F	T
F	F	T	F	F	T	T	F

compound statements and linear (in)equalities:

compound statement	equivalent linear equality/inequality
$S_1 \vee S_2$	$\delta_1 + \delta_2 \geq 1$
$S_1 \wedge S_2$	$\delta_1 = 1, \delta_2 = 1$
$\sim S_1$	$\delta_1 = 0$
$S_1 \rightarrow S_2$	$\delta_1 - \delta_2 \leq 0$
$S_1 \leftrightarrow S_2$	$\delta_1 - \delta_2 = 0$
$S_1 \oplus S_2$	$\delta_1 + \delta_2 = 1$

Stoichiometric subspace and deficiency

- *reaction vectors* : $v_{ij} = \begin{cases} [Y]_{\cdot,j} - [Y]_{\cdot,i} & \text{for } (C_i, C_j) \in \mathcal{R} \\ 0 & \text{otherwise} \end{cases}$
- *stoichiometric space* : $S = \text{span}\{v_{ij} \mid (C_i, C_j) \in \mathcal{R}\}$
- the trajectories are restricted to the *stoichiometric compatibility classes* : $(\mathbf{x}_0 + S) \cap \mathbb{R}_{>0}^n$
- *deficiency of a CRN* : $\delta = m - \ell - s$,
where m is the number of stoichiometrically distinct complexes, ℓ is the number of linkage classes, and s is the dimension of the stoichiometric subspace (**depends only on stoichiometry and network structure** but not on the parameters, **realization property**)
- an equilibrium concentration $\mathbf{x}^* \in \mathbb{R}_{>0}^n$ of a mass-action system is called a *complex balanced equilibrium concentration* if $A_k \cdot \varphi(\mathbf{x}^*) = \mathbf{0}$.
(**system property** : there exists a complex balanced equilibrium \Rightarrow all equilibrium concentrations are complex balanced)

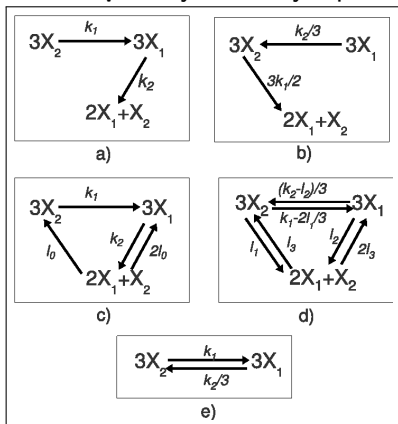
Relations between network structure and dynamics

- complex balance \Rightarrow weak reversibility
- complex balance \Rightarrow precisely one equilibrium point in each positive stoichiometric compatibility class that is (at least) locally asymptotically stable relative to its compatibility class with a known logarithmic Lyapunov function
- **Deficiency Zero Theorem** : a CRN with any positive parameters (rate coefficients) is complex balanced \iff the network is weakly reversible and has a deficiency of zero (**robust stability property**)
- **Deficiency One Theorem** : ordered structure of equilibrium points
- **Global Attractor Conjecture** : complex balance \Rightarrow (?) global stability
- **Persistency Conjecture** : weak reversibility \Rightarrow (?) persistent dynamics
- **Boundedness Conjecture** : weak reversibility \Rightarrow (?) bounded trajectories

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Dynamical equivalence (macro-equivalence)

- CRNs with different structure/parametrization but giving exactly the same dynamics
- example:** dynamically equivalent networks (realizations)



Dynamics:

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

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

Dyn. eq. condition:

$$Y^{(1)} A_k^{(1)} \varphi^{(1)}(x) = Y^{(2)} A_k^{(2)} \varphi^{(2)}(x),$$

$$\forall x \in \mathbb{R}_+^n$$

- it is of interest to search for such dyn. eq. structures (if they exist) from which we obtain useful information about the system dynamics

Linearly conjugate networks

Introduction of **linear conjugacy** : (Johnston and Siegel, J. Math. Chem. 2011)

- known: *the kinetic structure is preserved up to the positive rescaling and/or reordering of the variables*
- generalization of linear equivalence
- 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 $\Sigma = (S, \mathcal{C}, \mathcal{R})$ and $\Sigma' = (S, \mathcal{C}', \mathcal{R}')$ 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 $c \in \mathbb{R}_{>0}^n$ such that

$$\underbrace{Y \cdot A_k}_M = T \cdot Y \cdot A_b \quad (7)$$

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

$$A'_k = A_b \cdot \text{diag}\{\varphi(c)\}. \quad (8)$$

Dynamical equivalence and linear conjugacy – literature

- F. Horn and R. Jackson. General mass action kinetics. *Arch. Rational Mech. Anal.*, 47:81-116, 1972.
- V. Hárs and J. Tóth. On the inverse problem of reaction kinetics, *Qualitative Theory of Differential Equations*, 30:363-369, 1981.
- G. Craciun and C. Pantea. Identifiability of chemical reaction networks. *Journal of Mathematical Chemistry*, 44:244-259, 2008.
- M. D. Johnston and D. Siegel. Linear conjugacy of chemical reaction networks. *Journal of Mathematical Chemistry*, 49:1263-1282, 2011.

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

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

Dense and sparse realizations: goals

- **Given:** (Y, A_k) CRN or kinetic polynomial system
- **Aim:** to compute the following linearly conjugate networks:
 - *sparse realization* (Y^S, A_k^S) (contains the minimal number of reactions)
 - *dense realization* (Y^S, A_k^S) (contains the maximal number of reactions)
- **Assumption:** the set of usable complexes is given

Dense and sparse realizations: computation

kinetic constraints:

$$M = Y \cdot A_k$$
$$Y \cdot A_b = T^{-1} \cdot M, \quad T = \text{diag}(c_1, \dots, c_n),$$
$$\sum_{i=1}^m [A_b]_{ij} = 0, \quad j = 1, \dots, m$$
$$[A_b]_{ij} \geq 0, \quad i, j = 1, \dots, m, \quad i \neq j$$
$$[A_b]_{ii} \leq 0, \quad i = 1, \dots, m$$

lower/upper bounds:

$$0 \leq [A_b]_{ij} \leq l_{ij}, \quad i, j = 1, \dots, m, \quad i \neq j$$
$$l_{ii} \leq [A_b]_{ii} \leq 0, \quad i = 1, \dots, m$$
$$\epsilon \leq c_i \leq 1/\epsilon, \quad i = 1, \dots, n$$

density/sparsity:

$$\delta_{ij} = 1 \Leftrightarrow [A_b]_{ij} > \epsilon, \quad i, j = 1, \dots, m, \quad i \neq j$$
$$F_{obj}(\delta) = \sum_{\substack{i,j=1 \\ i \neq j}}^m \delta_{ij} \quad (\text{obj. function})$$

Given: Y, A_k , constraints

To be computed: $A_b, T \implies A'_k$

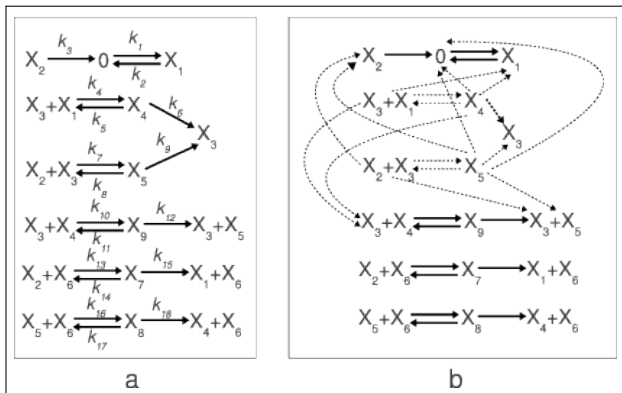
Problem: using MILP for computing CRN realizations can be problematic for large networks (number of integer variables is too high)

(Computations can be parallelized (columnwise) in the case of dyn. eq.)

Dense realization: a biological example

Biochemical switch in yeast cells (Conradi et al., PNAS, 2007)

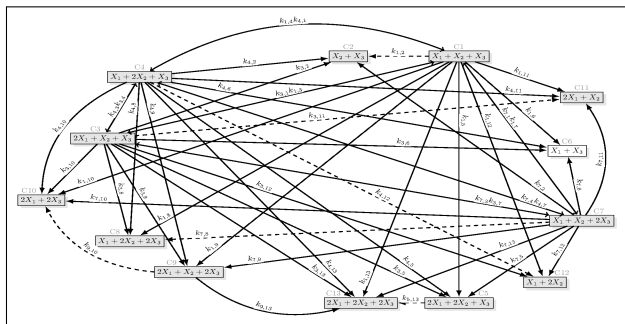
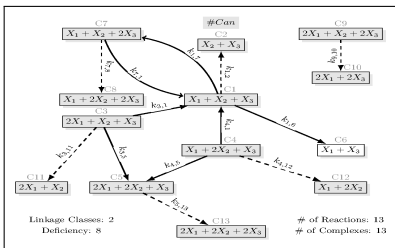
Original system and dense realization:



Different realizations: the Lorenz system

$$\begin{aligned}\dot{x}_1 &= \sigma(x_2 - x_1) \\ \dot{x}_2 &= \rho x_1 - x_2 - x_1 x_3 \\ \dot{x}_3 &= x_1 x_2 - \beta x_3\end{aligned}$$

not nonnegative : coordinates shift
+ 2 possible transformations



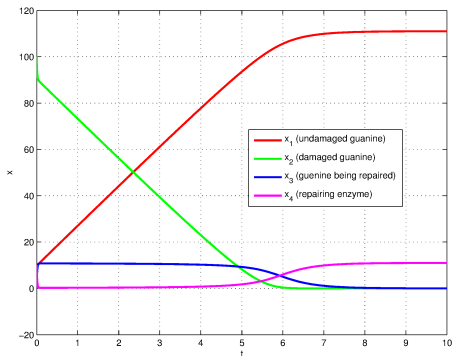
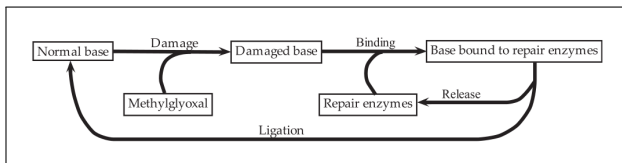
Different realizations: the Lorenz system

Summary of results for the different kinetic realizations of the Lorenz system

Feature	SD-TS	X-factorable
R_d	51	44
R_s	13	12
R_c	6	4
C_c	12	8
no. of complexes in the canonical realization	13	15
no. of valid sparse realizations	5376	48
no. of realizations containing only core complexes	504	0
minimal no. of linkage classes	1	1
maximal no. of linkage classes	3	3
no. of weakly reversible realizations	0	0
minimal deficiency	7	8
maximal deficiency	9	9

Example: a simple DNA repairing mechanism

(Karschau et al., Biophysical Journal, 2011)



Sparse realizations of the DNA repairing system

System model:

kinetic equations:

$$\dot{x}_1 = k_3 x_3 - k_1 x_1$$

$$\dot{x}_2 = k_1 x_1 - k_2 x_2 x_4$$

$$\dot{x}_3 = k_2 x_2 x_4 - k_3 x_3$$

$$\dot{x}_4 = k_3 x_3 - k_2 x_2 x_4,$$

variables: x_1 - undamaged guanin bases,
 x_2 - damaged guanin bases, x_3 - guanin
bases under repair, x_4 - free repairing
enzymes

realizing complexes:

$$C_1 = X_3, C_2 = X_1 + X_3, C_3 = X_1,$$

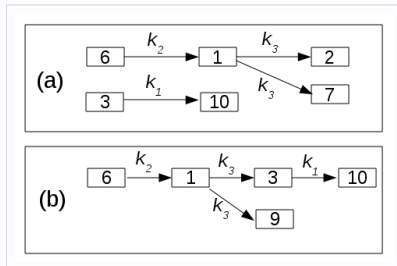
$$C_4 = 0, C_5 = X_1 + X_2, C_6 = X_2 + X_4,$$

$$C_7 = X_4, C_8 = X_2 + X_3 + X_4,$$

$$C_9 = X_3 + X_4, C_{10} = X_2$$

computation results

Dynamically equivalent sparse
realizations:



assuming sparsity is not enough for
structural uniqueness in general

Sparse realizations of the DNA repairing system

System model:

kinetic equations:

$$\dot{x}_1 = k_3 x_3 - k_1 x_1$$

$$\dot{x}_2 = k_1 x_1 - k_2 x_2 x_4$$

$$\dot{x}_3 = k_2 x_2 x_4 - k_3 x_3$$

$$\dot{x}_4 = k_3 x_3 - k_2 x_2 x_4,$$

variables: x_1 - undamaged guanine bases, x_2 - damaged guanine bases, x_3 - guanine bases under repair, x_4 - free repairing enzymes

realizing complexes:

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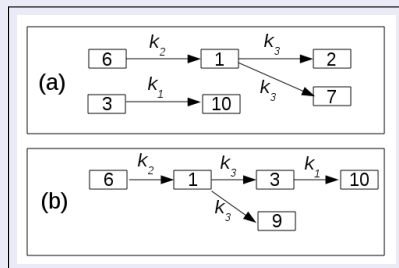
$$C_4 = 0, C_5 = X_1 + X_2, C_6 = X_2 + X_4,$$

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$$C_9 = X_3 + X_4, C_{10} = X_2$$

computation results

Dynamically equivalent sparse realizations:



assuming sparsity is not enough for structural uniqueness in general

Dense lin. conj. realizations: maximal super-structure

For a given complex set, the structure of dense realizations is unique and it contains all possible linearly conjugate CRN structures as subgraphs

Theorem (Johnston, Siegel, Szederkényi, 2012)

Consider a CRN given by the pair (Y, A_k) and assume that A'_k is such a Kirchhoff matrix that contains the maximal number of nonzero off-diagonal elements for which there exists a positive definite diagonal T matrix such that

$$Y \cdot A_k = T \cdot Y \cdot A'_k. \quad (9)$$

Then the directed unweighted reaction graph corresponding to any Kirchhoff matrix A''_k for which there exists a positive definite diagonal T'' such that $Y \cdot A_k = T'' \cdot Y \cdot A''_k$ is the subgraph of the reaction graph defined by A'_k .

Proof.

(Indirect) Assume that A''_k is such that

$$Y \cdot A_k = T'' \cdot Y \cdot A''_k, \quad (10)$$

where T'' is a positive definite diagonal matrix, A''_k is Kirchhoff matrix, and $\exists(i, j), i \neq j$ for which $[A''_k]_{ij} > 0$, but $[A'_k]_{ij} = 0$. Then $T'' = Q \cdot T$ for a positive diagonal Q matrix with $Q = T'' \cdot T^{-1}$, and using (9) we can write:

$$T'' \cdot Y \cdot A'_k = Q \cdot T \cdot Y \cdot A'_k = Q \cdot Y \cdot A_k. \quad (11)$$

Now we proceed with the calculations as:

$$T'' \cdot Y \cdot A'_k + T'' \cdot Y \cdot A''_k = T'' \cdot Y \cdot (A'_k + A''_k) = T'' \cdot Y \cdot \bar{A}_k, \quad (12)$$

where $\bar{A}_k = A'_k + A''_k$ is clearly a valid Kirchhoff matrix. □

Dense dyn. eq. realizations can be computed in polynomial time

The problem can be solved using $m(m-1)$ parallel LP steps (plus one final one):

Determining reactions in the dense realization

for each $p, q = 1, \dots, m$, $p \neq q$ do:

$$\text{maximize } f_{pq} = [A_k]_{p,q}$$

subject to :

$$Y \cdot A_k = M,$$

$$\sum_{i=1}^m [A_k]_{i,j} = 0, \quad j = 1, \dots, m, \quad (13)$$

$$0 \leq [A_k]_{i,j} \leq U_{ij}, \quad i, j = 1, \dots, m, \quad i \neq j,$$

$$[A_k]_{i,i} \leq 0, \quad i = 1, \dots, m,$$

decision variables: off-diagonal entries of A_k

role of U_{ij} : to avoid unbounded feasible solutions

$$C_q \rightarrow C_p \text{ is in the dense realization} \iff \max f_{pq} > 0$$

Dense dyn. eq. realizations can be computed in polynomial time

A lower bound for the elements of A_k

Constraints in the previous LP steps are convex (trivially) \implies

$$\epsilon_{ij} = \left[\frac{1}{m(m-1)} \sum_{\substack{p, q = 1 \\ p \neq q}}^m \bar{A}_k^{pq} \right]_{i,j}, \quad i \neq j. \quad (14)$$

The last LP step

$$Y \cdot A_k = M,$$

$$\sum_{i=1}^m [A_k]_{i,j} = 0, \quad j = 1, \dots, m,$$

$$\epsilon_{ij} \leq [A_k]_{i,j} \leq U_{ij}, \quad i, j = 1, \dots, m, \quad i \neq j, \quad (15)$$

$$[A_k]_{i,i} \leq 0, \quad i = 1, \dots, m.$$

The dense dyn. eq. WR realization can be found in polynomial time

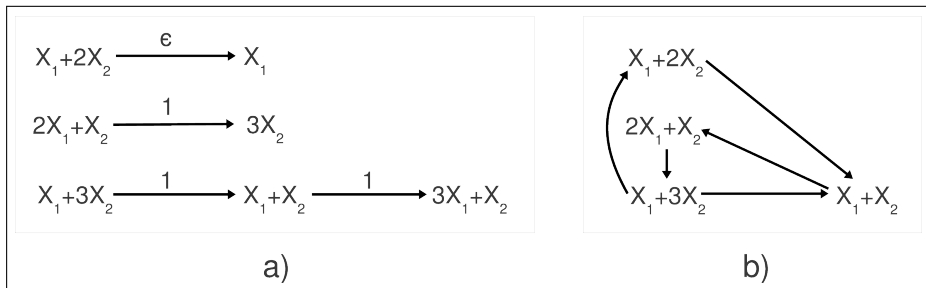
(G. Szederkényi, Zs. Tuza, K. M. Hangos. MATCH Comm. Math. Comp. Chem. 2012)

```
 $A_k^{out} = \text{FindWeaklyReversibleRealization}(Y^{(0)}, A_k^{(0)})$   
1  $A_k^{out} := 0 \in \mathbb{R}^{m \times m}$ ;  $ExitCondition := false$ ;  
2  $Y := Y^{(0)}$ ;  $A_k := A_k^{(0)}$ ;  $F_{out} := true$ ;  $\mathcal{K} := \{\}$ ;  $L := \{\}$ ;  
3 while ( $ExitCondition = false$ ) do  
4   begin  
5     if ( $\mathcal{K} \neq \{\}$ ) then  $F_{out} := IsRemovable(Y, A_k, \mathcal{K})$ ;  
6     if ( $F_{out} = true$ ) then  
7       begin  
8          $A_k := \text{FindConstrDenseRealization}(Y, A_k, \mathcal{K})$ ;  
9          $L := \text{FindCrossComponentEdges}(A_k)$ ;  
10        if ( $L = \{\}$ ) then  $ExitCondition := true$ ;  $A_k^{out} := A_k$ ;  
11        else  $\mathcal{K} := \mathcal{K} \cup L$ ;  
12        end  
13      else  $ExitCondition := true$ ;  
14    end  
15  return  $A_k^{out}$ ;
```

Weak reversibility: example (1)

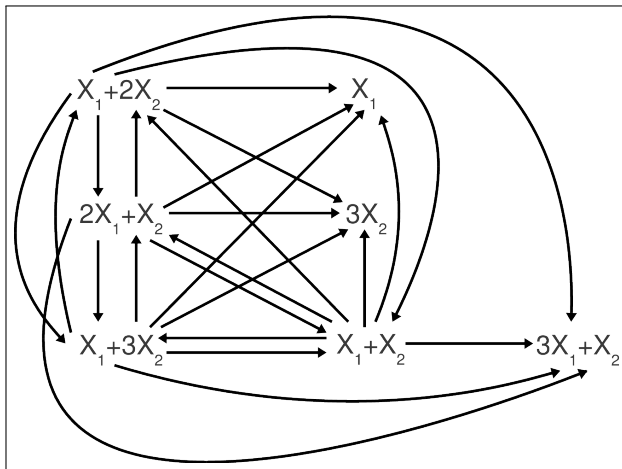
a) Original irreversible network (Johnston and Siegel, 2011)

b) published dyn. eq. WR realization



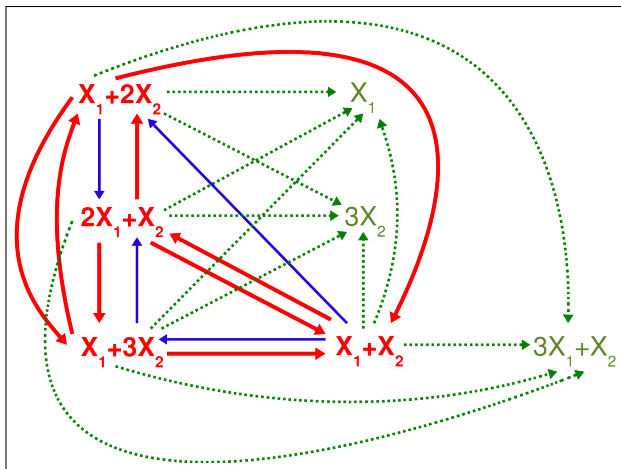
Weak reversibility: example (2)

Structure of dense realization



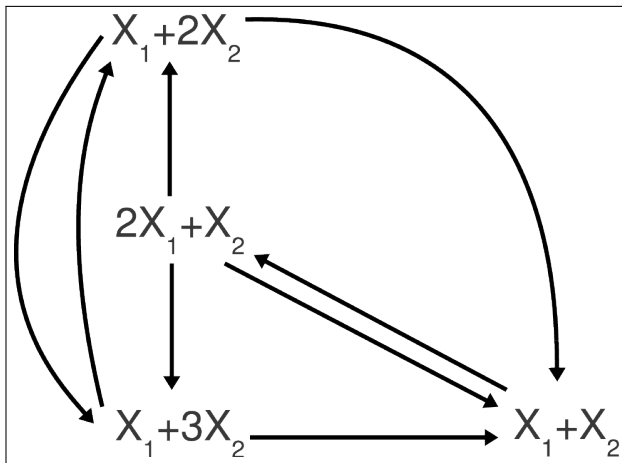
Weak reversibility: example (3)

Operation of the algorithm



Weak reversibility: example (4)

Structure of the computed dyn. eq. dense WR realization
(not complex balanced with the obtained parameters)



A simple example

Consider the kinetic system (Johnston, Siegel, Szederkényi, 2012)

$$\begin{aligned}\dot{x}_1 &= x_1 x_2^2 - 2x_1^2 + x_1 x_3^2 \\ \dot{x}_2 &= -x_1^2 x_2^2 + x_1 x_3^2 \\ \dot{x}_3 &= x_1^2 - 3x_1 x_3^2.\end{aligned}\tag{16}$$

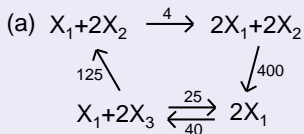
Realizing complex set:

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

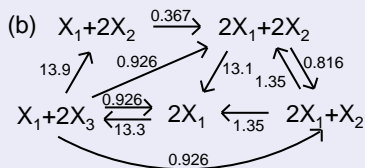
Linearly conjugate WR realizations

A simple example (continued)

optimization result: There is no dynamically equivalent WR realization
However, there exist several linearly conjugate WR realizations :



sparse ($c_1 = 20, c_2 = 2, c_3 = 5$)



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

Further solved problems

Solved for both the dynamically equivalent and the linearly conjugate cases:

- Minimizing/maximizing the number of complexes from a given set (it can be decided whether a reacting complex can be added to the system or not)
- Computing fully reversible realizations
- Computing complex balanced realizations
- Computing detailed balanced realizations
- Computing *core reactions* and *core complexes*
- Handling monomial coefficient intervals
- Computing *all* sparse realizations (efficiently)
- Computing **WR realizations with the minimal deficiency**
- Computing **kinetic feedbacks for polynomial systems**

- 1 Motivation and introduction
- 2 Basic notions: kinetic systems (CRNs) and optimization
- 3 Properties and computation of CRN structures**
 - Computation of "dense" and "sparse" realizations
 - Computation of weakly reversible realizations
 - Computing linearly conjugate WR realizations with minimal deficiency
- 4 Kinetic feedbacks for polynomial systems
- 5 Conclusions

Min. def. realizations: basis of the solution

to be minimized: $\delta = m - l - s$

- the set of complexes is given
- we allow isolated (non-reacting) complexes: they increase both m and l and do not change the deficiency
- weakly reversible networks: the dimension of the largest invariant linear space of the dynamics is equal to the dimension of the stoichiometric subspace s (known from literature)
- linear conjugacy (trivially) preserves the dimension of invariant linear spaces of mass-action systems



- the dimension of s is the same for all linearly conjugate weakly reversible realizations



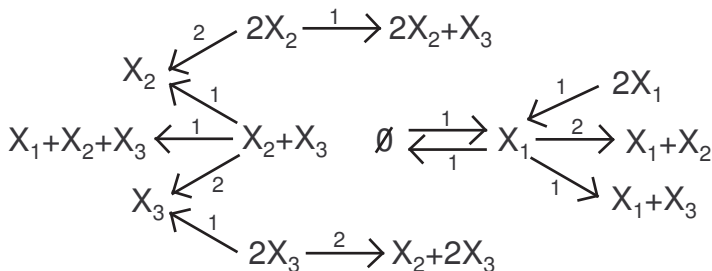
- it is enough to maximize the number of linkage classes (l)

Example: min. def. realizations

consider the kinetic system:

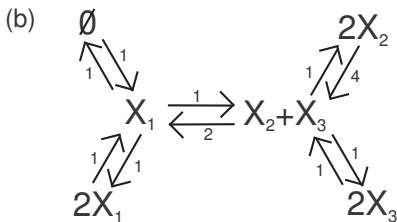
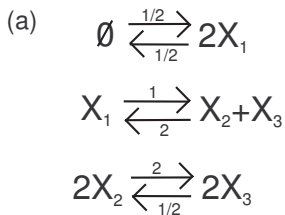
$$\begin{aligned}\frac{dx_1}{dt} &= 1 - x_1^2 - x_1 + x_2x_3 \\ \frac{dx_2}{dt} &= 2x_1 - 2x_2x_3 - 2x_2^2 + 2x_3^2 \\ \frac{dx_3}{dt} &= x_1 - x_2x_3 + x_2^2 - x_3^2.\end{aligned}\tag{17}$$

canonical realization:



Example: min. def. realizations

def. zero and def. two linearly conjugate WR realizations:



System representation (special): input-affine form
set of nonlinear ODEs parameterized by inputs

$$\dot{x} = f(x) + \sum_{i=1}^p g_i(x)u_i = f(x) + g(x)u$$
$$y = h(x)$$

$$x(t) \in \mathbb{R}^n, u(t) \in \mathbb{R}^p, y(t) \in \mathbb{R}^r, \forall t \geq 0$$
$$f, g_i \in \mathbb{R}^n \rightarrow \mathbb{R}^n, h \in \mathbb{R}^n \rightarrow \mathbb{R}^r$$

The concept of control and feedback

Control: sensing + feedback computation + actuation



may fundamentally change the behaviour (dynamical properties) of the original system

Feedback equivalence of input-affine systems

Ingredients:

- 1 *System model:*

$$\dot{x} = f(x) + g(x)u$$

- 2 *Feedback:*

$$u = \alpha(x) + \beta(x)\tilde{u}$$

- 3 *Coordinates transformation* (local or global diffeomorphism):

$$\tilde{x} = \phi(x)$$

Goal: the controlled system (in the new coordinates) has some preferred property (e.g. stability, linearity, passivity, Hamiltonian structure etc.)

Feedback equivalence of input-affine systems

Controlled system model (input-affine):

$$\dot{\tilde{x}} = \tilde{f}(\phi(x)) + \tilde{g}(\phi(x))\tilde{u}$$

$$\tilde{f}(\phi(x)) = \frac{\partial \phi}{\partial x}(x)(f(x) + g(x)\alpha(x))$$

$$\tilde{g}(\phi(x)) = \frac{\partial \phi}{\partial x}(x)(g(x)\beta(x))$$

Our goal: to obtain a weakly reversible kinetic system (with minimal deficiency)

Kinetic feedback

- **goal:** to transform a polynomial control system to (advantageous) kinetic form using feedback (i.e. **feedback equivalence** problem to a **kinetic system**)
- **open loop model form:**

$$\dot{x} = M \cdot \psi_1(x) + Bu, \quad (18)$$

where $x \in \mathbb{R}^n$, is the state vector, $u \in \mathbb{R}^p$ is the input, $\psi_1 \in \mathbb{R}^n \rightarrow \mathbb{R}^{m_1}$ contains the monomials of the open-loop system, $B \in \mathbb{R}^{n \times p}$ and $M \in \mathbb{R}^{n \times m_1}$.

- **feedback form:**

$$u = K \cdot \bar{\psi}(x), \quad (19)$$

where $\bar{\psi}(x) = [\psi_1^T(x) \ \psi_2^T(x)]^T$ with $\psi_2 \in \mathbb{R}^n \rightarrow \mathbb{R}^{m_2}$ containing possible additional monomials for the feedback, $B \in \mathbb{R}^{n \times m}$, and $K = [K_1 \ K_2] \in \mathbb{R}^{p \times (m_1 + m_2)}$.

- closed loop dynamics

$$\dot{x} = \underbrace{\begin{bmatrix} M + BK_1 & BK_2 \end{bmatrix}}_{\bar{M}} \begin{bmatrix} \psi_1(x) \\ \psi_2(x) \end{bmatrix} = \bar{M} \cdot \bar{\psi}(x). \quad (20)$$

- aim:** to factorize \bar{M} as $\bar{M} = \bar{Y} \cdot \bar{A}_k$ where $\bar{Y} \in \mathbb{Z}_{\geq 0}^{n \times (m_1+m_2)}$, and $\bar{A}_k \in \mathbb{R}^{(m_1+m_2) \times (m_1+m_2)}$ is a valid Kirchhoff matrix (can be written as a [linear programming problem](#), while other structural conditions might require MILP)
- It is straightforward to use a [dynamic extension](#) to increase the degrees of freedom

Dynamic kinetic feedback

Open loop system form:

$$\dot{x}^{(1)} = M_{11}\psi_1(x^{(1)}) + Bu, \quad (21)$$

where $x^{(1)} \in \mathbb{R}^n$, $M_{11} \in \mathbb{R}^{n \times m_1}$, $\psi_1 : \mathbb{R}^n \rightarrow \mathbb{R}^{m_1}$, $B \in \mathbb{R}^{n \times p}$, and $u \in \mathbb{R}^p$.
Equations of the **dynamic extension**:

$$\dot{x}^{(2)} = M_{21}\psi_1(x^{(1)}) + M_{22}\psi_2(x), \quad (22)$$

where $x^{(2)} \in \mathbb{R}^k$, $M_{21} \in \mathbb{R}^{k \times m_1}$, $M_{22} \in \mathbb{R}^{k \times m_2}$. Moreover,

$$x = \begin{bmatrix} x^{(1)} \\ x^{(2)} \end{bmatrix} \in \mathbb{R}^{n+k}, \quad \bar{\psi}(x) = \begin{bmatrix} \psi_1(x^{(1)}) \\ \psi_2(x) \end{bmatrix}, \quad (23)$$

where $\psi_2 : \mathbb{R}^{n+k} \rightarrow \mathbb{R}^{m_2}$.

Monomial feedback:

$$u = K\bar{\psi}(x) = K_1\psi_1 + K_2\psi_2, \quad (24)$$

where $K_1 \in \mathbb{R}^{p \times m_1}$, $K_2 \in \mathbb{R}^{p \times m_2}$, and $K = [K_1 \ K_2]$.

Controlled (closed loop) system:

$$\dot{x} = \underbrace{\begin{bmatrix} M_{11} + BK_1 & BK_2 \\ M_{21} & M_{22} \end{bmatrix}}_{\bar{M}} \cdot \bar{\psi}(x) = \bar{M} \cdot \bar{\psi}(x) \quad (25)$$

such that

$$\bar{M} = \bar{Y} \cdot \bar{A}_k \quad (26)$$

where \bar{Y} is the new complex composition matrix and \bar{A}_k is the Kirchhoff matrix of a weakly reversible CRN

Kinetic feedback: example

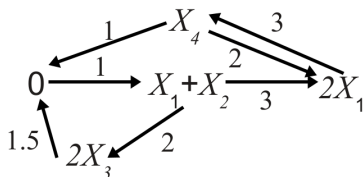
Consider the polynomial system:

$$\dot{x}_1 = 1 + x_1x_2 + u \quad (27)$$

$$\dot{x}_2 = 1 - 5x_1x_2 \quad (28)$$

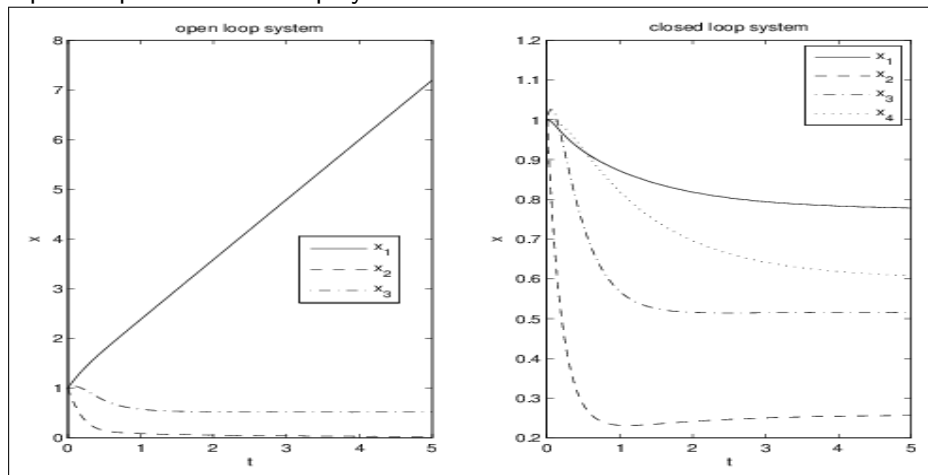
$$\dot{x}_3 = 4x_1x_2 - 3x_3^2 \quad (29)$$

The feedback $u = -6x_1^2 + 4x_4$, and the dynamic extension: $\dot{x}_4 = 3x_1^2 - 3x_4$ results in a weakly reversible closed loop system:



Kinetic feedback: simulation results

Open loop and closed loop system



Summary

- a wide class of dynamical systems /phenomena can be described in the kinetic framework (strong results on the relation between stoichiometric composition, graph structure and dynamics)
- representation /coordinates system is important to solve certain system analysis/synthesis tasks stoichiometric composition, graph structure and dynamics)
- numerous important qualitative properties of CRN dynamics are not directly visible from the kinetic ODEs
- the directed graph structure corresponding to a given kinetic dynamics is non-unique (dynamical equivalence, linear conjugacy)
- preferred reaction graph structures can be found using appropriate factorization and optimization (LP, MILP), often large networks can also be handled
- dense linearly conjugate realizations form a maximal super-structure with a fixed complex set (can be found in polynomial time)
- first steps towards 'kinetic' feedbacks for polynomial systems to achieve robust stability

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Selected recent publications



G. Szederkényi, K. M. Hangos and Z. Tuza.

Finding weakly reversible realizations of chemical reaction networks using optimization.

MATCH Commun. Math. Comput. Chem., 67:193-212, 2012.



M. D. Johnston, D. Siegel and G. Szederkényi.

Computing weakly reversible linearly conjugate chemical reaction networks with minimal deficiency.

Mathematical Biosciences, 241:88-98, 2013.



Z. A. Tuza, G. Szederkényi, K. M. Hangos, A. A. Alonso and J. R. Banga.

Computing all sparse kinetic structures for a Lorenz system using optimization.

International Journal of Bifurcation and Chaos, 23:1350141, 2013.



J. Rudan, G. Szederkényi, K. M. Hangos and T. Péni.

Polynomial time algorithms to determine weakly reversible realizations of chemical reaction networks.

Journal of Mathematical Chemistry, 52:1386-1404, 2014.



G. Lipták, G. Szederkényi and K. M. Hangos.

Kinetic feedback computation for polynomial systems to achieve weak reversibility and minimal deficiency.

Proc. of 13th European Control Conference, ECC 2014, 06. 24 - 06. 27, 2014, Strasbourg, France, 2691-2696, 2013.