

# **Control and System Theory for Biochemical Reaction Networks**

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29 November 2005  
CWI BRICKS Day  
Amsterdam

## Outline

- Example *Trypanosoma brucei*.
- Modeling of biochemical reaction networks.
- Rational positive systems.
- Problem 1. Control.
- Problem 2. System reduction.
- Problem 3. Dynamical system properties.
- Problem 4. Decompositions of rational positive systems.
- Problem 5. Observers.
- Problem 6. Realization.
- Concluding remarks.

## Example Glycolysis in *Trypanosoma brucei*

- *Trypanosoma brucei* (Tb). Unicellular eukaryote (with nucleus). Parasite in humans and other mammals. Lives in blood and tissue.
- Subspecies cause African Sleep Disease. 200.000 new infections a year. Lethal unless treated. Damage to livestock.
- Need for medicines. Existing drugs have severe side effects.

## Research

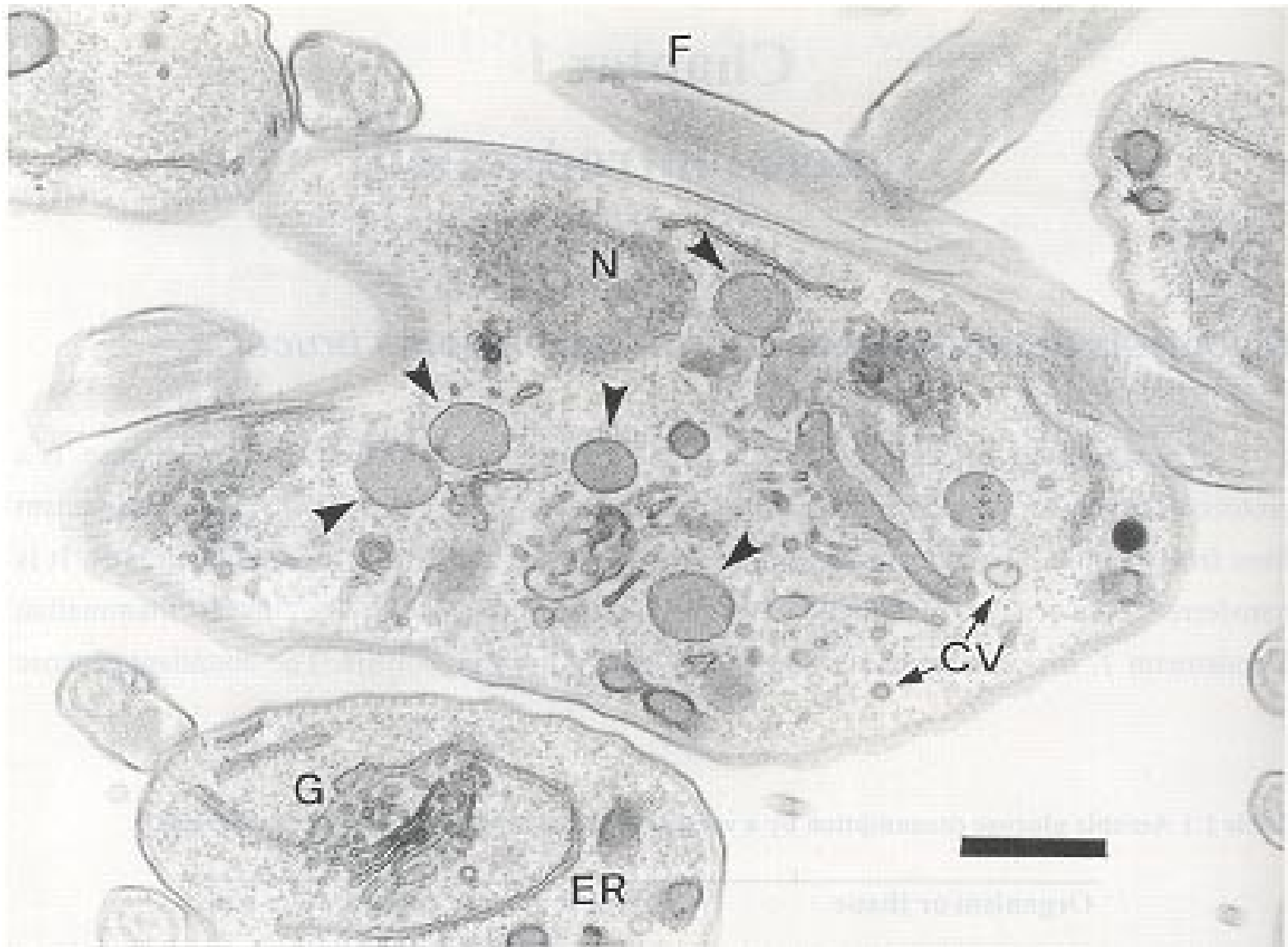
- Paul Michels and Fred Opperdoes (Institute of Cellular Pathology, Université Catholique de Louvain, Brussels, Belgium).
- Barbara M. Bakker and Hans V. Westerhoff (Department of Biology, Vrije Universiteit, Amsterdam, The Netherlands).

**Example** Glycolysis in *T. brucei*.

- *T. brucei* gets free energy from host in the form of glucose. It is processed only by glycolysis.
- **Glycolysis:**  
From **glucose** (sugar) to **ATP**, to **pyruvate** (90%), and to **glycerol** (10%).
- Uniquely in this organism, glycolysis is largely performed in organelles called **glycosomes**.
- Mathematical and computer model of metabolic network.
- Research for medicines directed at which enzymes/reactions limit most the setting free of the free energy (ATP).

Next page: Figure of *T. brucei* from (B. Bakker (1998), p. 8).

Original source I. Coppens (IPC, Brussels).

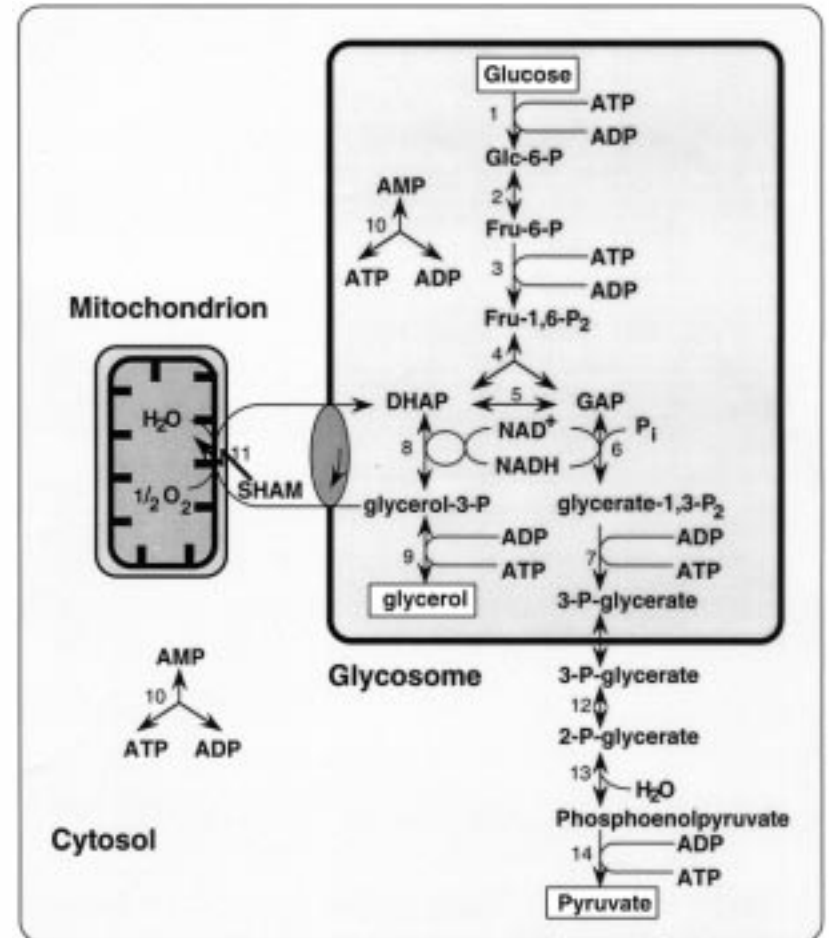


# Trypanosoma brucei

Biochemical reaction network.

Source 1: (I. Coppens (ICP, Brussels))

Source 2: (B.M. Bakker, Ph.D. thesis, VU, Amsterdam, 1998, p. 9).



## Glycolysis in *T. brucei*

**Glycolysis** = splitting of sugar (glucose) into  $C_3$  molecules.

In human red-blood cells,



**ATP = Adenosine Triphosphate** used elsewhere in cell for activities.

Conversion  $ATP \rightarrow ADP + \text{phosphate}$  delivers free energy.

**Example** Glycolysis in *T. brucei*. Mathematical model.

- 36 states (concentrations of chemical compounds),  
1 external input, 3 outputs.
- 21 reactions and corresponding enzymes.
- Differential algebraic system of equations. Details below.  
Differential equation,

$$\dot{x}(t) = B \text{Diag}(r(x(t), x_{ex}(t)))u(t), \quad x(t_0) = x_0.$$

**Example** Glycolysis in *T. brucei*.

States represent concentrations of chemical substances:

$$\begin{aligned}x_1 &= [GLC]_g, & x_2 &= [Glc]_{ex}, & x_3 &= [Glc - 6 - P]_g, \\x_4 &= [Fru - 6 - P]_g, & x_5 &= [Fru - 1, 6 - BP]_g, & x_6 &= [ATP]_g, \\x_7 &= [ADP]_g, & x_8 &= [AMP]_g, & x_9 &= [DHAP]_g, \dots\end{aligned}$$

Enzymes and corresponding input components:

- $u_1$  transport of glucose through the plasma and glycosome membrane,
- $u_2$  HK,  $u_3$  PGI,,  $u_4$  PFK,
- $u_5$  ALD,  $u_6$  TIM,  $u_7$  GAPDH, ...

**Example** Glycolysis in *T. brucei*.

Rate functions  $v_i = r_i u_i$ :

$$r_1(x, x_{ex}) = c_2 \frac{c_{21}x_{ex} - c_{22}x_1}{c_{23} + x_1 + x_{ex} + c_{24}x_1x_{ex}},$$

$$r_2(x, x_{ex}) = c_1 \frac{c_3x_{13}c_4x_1}{(1 + c_3x_{12} + c_5x_{11})(1 + c_4x_1)},$$

$$r_7(x, x_{ex}) = c_1 \frac{[c_9x_{17}c_{10}x_{16} - c_6c_7x_5c_8x_8]}{(1 + c_9x_{17} + c_7x_5)(1 + c_{10}x_{16} + c_8x_8)},$$

$$r_8(x, x_{ex}) = c_1 \frac{[c_{11}x_5c_{12}x_{11} - c_{13}c_{14}x_{13}c_{15}x_{12}]}{(1 + c_{11}x_5 + c_{14}x_{13})(1 + c_{12}x_{11} + c_{15}x_{12})}.$$

Differential equation,

$$\begin{aligned} \dot{x}(t) &= \sum_{i=1}^m \sum_{j=1}^m (b_i - b_j) r_{i,j}(x(t), x_{ex}(t)) u_{i,j}(t), \\ &= \sum_{k=1}^m (b_k^+ - b_k^-) r_k(x(t), x_{ex}(t)) u_k(t), \quad (k \sim (i, j)), \\ &= B \text{Diag}(r(x(t), x_{ex}(t))) u(t), \quad x(t_0) = x_0. \end{aligned}$$

## Rational positive system for *Trypanosoma brucei*

$$\begin{aligned}\dot{x}(t) &= B\text{Diag}(r(x(t), x_{ex}(t)))u(t), \quad x(t_0) = x_0, \\ z(t) &= H\text{Diag}(r(x(t), x_{ex}(t)))u(t), \quad \text{outflow rate.}\end{aligned}$$

10 ordinary differential equations,

17 algebraic equations of rational positive type,

(7 molecular conservation relations, 5 pools, 5 fast dynamics)

After algebraic operations one obtains 10 differential equations.

### Questions

- Is system positive? Yes!
- Steady states? One unique steady state, apparently!
- Graph? Two irreducible components (sizes 9,1).

## Modeling of biochemical reaction networks

Distinguish:

- **Microscopic modeling**: Interaction of individual molecules.
- **Macroscopic modeling**: Concentrations and reaction rates.  
(Used below.)

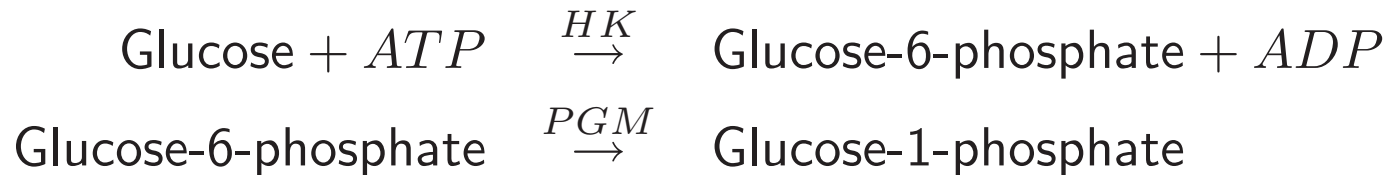
Characteristic for biochemical reactions:

- Hyperbolic (saturable) in substrate concentration.
- Reversible (rate can change sign).
- Product inhibited.

Sources: A. Cornish-Bowden (2004), I.H. Segel (1993),  
R. Heinrich, S. Schuster (1996).  
B. Alberts et al (1994).

## Modeling of biochemical reaction networks

**Example** Reactions of liver cells



**Enzymes:** HK = Hexokinase, PGM = Phosphoglucomatase.

**Stoichiometric matrix**, (stoikheion = elements (from Greek))

$$B = \begin{pmatrix} & HK & PGM & & \\ -1 & & 0 & \text{Gluc} & \\ 1 & & -1 & \text{G6P} & \\ 0 & & 1 & \text{G1P} & \\ -1 & & 0 & \text{ATP} & \\ 1 & & 0 & \text{ADP} & \end{pmatrix} \cdot$$

Column of  $B$  represents chemical substances produced or used,  
row of  $B$  represents one substance involved in all reactions.

## Modeling of biochemical reaction networks

### Differential equation

Reaction rate models (enzyme kinetics with general mass action):

**Polynomial model** (HW: not realistic),

$$\begin{aligned}\dot{x}(t) &= \sum_{j=1}^m (B_j^+ - B_j^-) \left[ (c_j^+ \prod_{k=1}^n x_k^{B_{k,j}^-}) - (c_j^- \prod_{k=1}^n x_k^{B_{k,j}^+}) \right] u_j(t), \\ &= \sum_{j=1}^m B_j r_j(x(t)) u_j(t), \\ B_{i,j}^+ &= \begin{cases} B_{i,j}, & B_{i,j} \geq 0, \\ 0, & B_{i,j} < 0, \end{cases} \quad B_{i,j}^- = \begin{cases} 0, & B_{i,j} \geq 0, \\ -B_{i,j}, & B_{i,j} < 0, \end{cases}\end{aligned}$$

## Modeling of biochemical reaction networks

### Forms of the rate functions

- **Polynomial form** (See previous page).
- **Rational form**  
**Michaelis-Menten kinetics**, rational function representing inhibition by product, for example,

$$r(x) = \frac{V_m^+(x_1/c_1) - V_m^-(x_2/c_2)}{1 + (x_1/c_1) + (x_2/c_2)}.$$

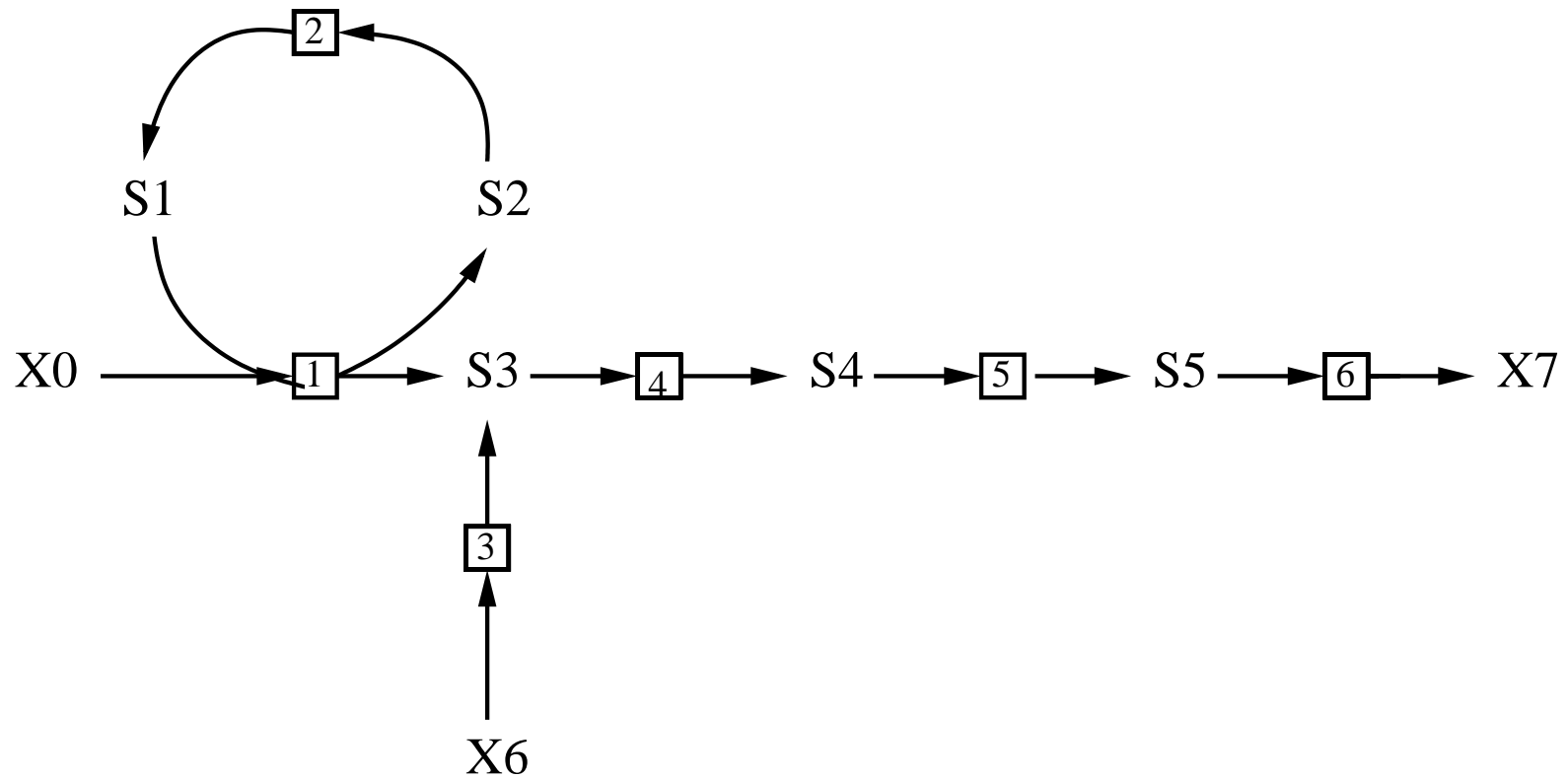
L. Michaelis, M.L. Menten (1913)  $r(x) = cx/(k + x)$ .

- Distinguish **factorizable** functions (E.D. Sontag (2001) and **nonfactorizable** functions.

Example Tb has nonfactorizable (strict) rate functions.

## Example Rohwer's network

Small cell reaction network. (J.M. Rohwer, 1997, pp. 32, 37).



**Example** Rohwer's network (Continued)

**States and matrices**

$$n = 5, n_{ex} = 2, n_z = 1, m = 6,$$

$$x_1 = S_1, \dots, x_5 = S_5, \text{ concentrations} = \text{states},$$

$$x_{ex,1} = X_0, x_{ex,2} = X_6, \text{ external concentrations},$$

$$Z = dX/dt, \text{ outflow rate.}$$

$$B = \begin{pmatrix} -1 & 1 & 0 & 0 & 0 & 0 \\ 1 & -1 & 0 & 0 & 0 & 0 \\ 1 & 0 & 1 & -1 & 0 & 0 \\ 0 & 0 & 0 & 1 & -1 & 0 \\ 0 & 0 & 0 & 0 & 1 & -1 \end{pmatrix}, \text{ stoichiometric matrix,}$$

$$H = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 & 1 \end{pmatrix}, \text{ outflow matrix.}$$

## Example Rohwer's network (Continued)

### Rate functions

$$\begin{aligned}r_1(x, x_{ex}) &= \frac{10x_{ex,1}x_1}{1 + x_{ex,1}x_1 + x_2x_3} - \frac{x_2x_3}{1 + x_{ex,1}x_1 + x_2x_3} \\ &= \frac{p_1^+(x, x_{ex})}{q_1^+(x, x_{ex})} - \frac{p_1^-(x, x_{ex})}{q_1^-(x, x_{ex})}, \\ r_2 &= \frac{10x_2 - x_1}{1 + x_1 + x_2}, \quad r_3 = \frac{5x_{ex,2} - x_3}{1 + x_3 + x_{ex,2}}, \\ r_4 &= \frac{10x_3 - x_4}{1 + x_3 + x_4}, \quad r_5 = \frac{10x_4 - x_5}{1 + x_4 + x_5}, \quad r_6 = \frac{10x_5}{1 + x_5}.\end{aligned}$$

Differential equation of system,

$$\begin{aligned}\dot{x}(t) &= B \text{Diag}(r(x(t), x_{ex}))u(t), \quad x(t_0) = x_0, \\ z(t) &= H \text{Diag}(r(x(t), x_{ex}))u(t).\end{aligned}$$

## Modeling of biochemical cell reaction networks

### Types of networks

- Metabolic networks.
- Signal transduction networks.
- Gene networks (DNA  $\rightarrow$  RNA  $\rightarrow$  mRNA).

### Model for all reactions in a cell

- Hierarchical model: genetic level, signal level, metabolic level.
- Interactions between levels.
- Realistic and mathematically treatable small models?

## Main problem: Realistic models of low complexity?

- Numbers are huge:  
Humans: 30.000 genes, 15.000 enzymes/reactions, 10.000 conc.  
E. coli, 4000, 2000, 1000. Yeast 6000.
- Dynamic behavior rich in types.  
Feedback in networks limits dynamic behavior considerably.
- Values of parameters are difficult to obtain. Large uncertainty in values.
- Control and system theory should base a theory on structure and general properties of models rather than on values of parameters.

## **Aim of research program in control and system theory for cell biology**

- Gain understanding of dynamics and control of cell reaction networks.
- Decomposition and role of feedback in networks.
- Realization, controllability, and observability.
- Assist with medical drug research. Control.
- Assist with cell factory biotechnology (beer, bread).

## Positive linear algebra

$$\mathbb{Z}, \quad \mathbb{Z}_+, \mathbb{N},$$

$$\mathbb{Z}_n = \{1, 2, \dots, n\}, \quad \mathbb{N}_n = \{0, 1, 2, \dots, n\}, \quad \forall n \in \mathbb{Z}_+,$$

$$\mathbb{R}_+ = [0, \infty), \quad \text{positive real numbers,}$$

$$\mathbb{R}_{s+} = (0, \infty) \quad \text{strictly positive real numbers,}$$

$$(\mathbb{R}_+, +, \times, 0, 1) \quad \text{semi-ring and integral domain,}$$

$$(\mathbb{R}_+, \mathbb{R}_+^n) \quad \text{positive vector space,}$$

$$V \subseteq \mathbb{R}_+^n \quad \text{cone if (1) } V + V \subseteq V; \quad (2) \mathbb{R}_+ V \subseteq V;$$

$$V \subseteq \mathbb{R}_+^n \quad \text{polyhedral cone (geometric object)}$$

if it equals intersection of finite number of half spaces;

equivalently,  $\exists v_1, \dots, v_m \in \mathbb{R}_+^n$ , such that

$$V = \text{cone}(\{v_1, \dots, v_m\}).$$

## Positive polynomials

$$k = (k_1, \dots, k_n) \in \mathbb{N}^n, \text{ multi index,}$$

$$p(x) = \sum_{k \in \mathbb{N}^n} c_p(k) \prod_{j=1}^n x_j^{k(j)} = \sum_{k \in \mathbb{N}^n} c_p(k) x^k,$$

$\forall k \in \mathbb{N}^n, c_p(k) \in \mathbb{R}_+,$  finite number non zero,

$p \in \mathbb{R}_+[x_1, \dots, x_n] = \mathbb{R}_+[x],$  **positive polynomial.**

(polynomial with positive coefficients)

$$p(x) = 3.1x_1^2x_2^3x_3^4 + 2x_1^3x_3^1 + 5x_2^4x_4^2, \text{ example positive polynomial.}$$

$(\mathbb{R}_+[x], +, \times, 0, 1)$  dioid.

$$\deg(p) = \max_{\{k \in \mathbb{N}^n | c_p(k) \neq 0\}} \left\{ \sum_{i=1}^n k(i) \right\} \in \mathbb{N}, \text{ degree of } p.$$

## Special rational positive functions

$$\mathbb{R}_{+,s}(x) = \{p/q \mid p, q \in \mathbb{R}_+[x], c_p(0) = 0, c_q(0) = 1, \},$$

$$\frac{p(x)}{q(x)} = \frac{c_1x_1 + c_2x_2}{1 + c_3x_1 + c_4x_2}, \text{ example.}$$

## Definitions

### Def. Rational positive system for cell reaction network

$$\dot{x}(t) = N \text{Diag}(r(x(t), x_{ex}(t)))u(t), \quad x(t_0) = x_0,$$

$$z(t) = H \text{Diag}(r(x(t), x_{ex}(t)))u(t), \quad \text{outflow rate,}$$

$$y(t) = Cx(t), \quad \text{output,}$$

$$T = [t_0, \infty), \quad n, m \in \mathbb{Z}_+, \quad n_{ex}, n_z \in \mathbb{N},$$

$$X = \mathbb{R}_+^n, \quad X_{ex} = \mathbb{R}_+^{n_{ex}}, \quad U = \mathbb{R}_+^m,$$

$$r_j(x, x_{ex}) = \frac{p_j^+(x, x_{ex})}{q_j(x, x_{ex})} - \frac{p_j^-(x, x_{ex})}{q_j(x, x_{ex})},$$

$$(p_j^+/q_j), (p_j^-/q_j) \in \mathbb{R}_{+,s}(x, x_{ex}), \quad \forall j \in \mathbb{Z}_m,$$

$$\dot{x}(t) = \sum_{j=1}^m (B_j^+ - B_j^-) \left[ \frac{p_j^+(x(t), x_{ex})}{q_j(x(t), x_{ex})} - \frac{p_j^-(x(t), x_{ex})}{q_j(x(t), x_{ex})} \right] u_j(t).$$

**Def.** Rational positive system (Continued). **Conditions imposed:**

1. (Relative primeness)

$\forall j \in \mathbb{Z}_m, (p_j^+, q_j), (p_j^-, q_j)$  relatively prime in  $\mathbb{R}_+[x]$ .

2. (Forward invariance)  $\forall i \in \mathbb{Z}_n, j \in \mathbb{Z}_m,$

$$x_i = 0 \wedge B_{i,j}^+ - B_{i,j}^- > 0 \Rightarrow p_j^-(x) = 0,$$

$$x_i = 0 \wedge B_{i,j}^+ - B_{i,j}^- < 0 \Rightarrow p_j^+(x) = 0.$$

$$H_{i,k} > 0 \Rightarrow p_j^- = 0, \forall k \in \mathbb{Z}_m.$$

3. (Linear independence)  $\{r_j(\cdot) \in \mathbb{R}[x], j \in \mathbb{Z}_m\}$ .

4. (Existence and uniqueness solution)

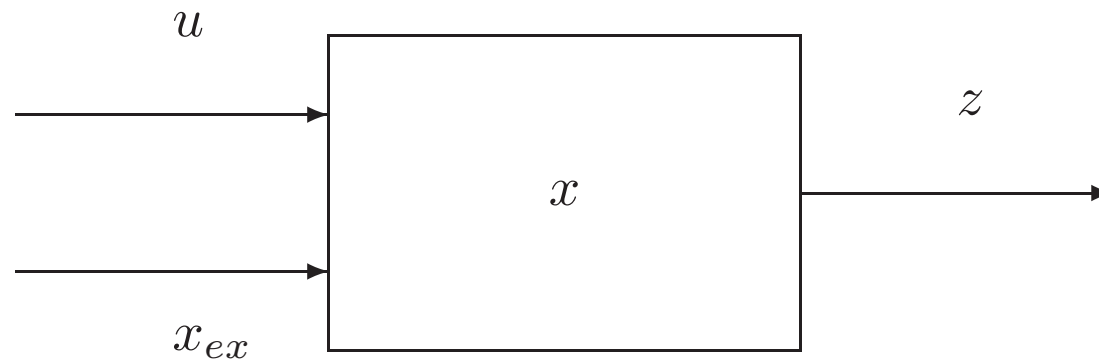
For all  $T = [t_0, \infty), x_0 \in \mathbb{R}^n, x_{ex}, u,$

there exists an unique solution of the ODE.

## Problem 1 Control of large networks

How does the cell regulate its biochemical reaction network?

For example, the metabolic network?



## Subproblems

- (a) Which enzymes concentration(s) to put to zero so as to achieve a zero outflow for one of its controlled outputs?  
Motivated by rational drug design.
- (b) How does the cell determine the enzymes to be increased to achieve the control objective of a higher value for one of its functions?  
Conjecture: The genetic network has the information for this.
- (c) How does the biochemical reaction network react against abrupt changes in its food supply (changes in  $x_{ex}$ ).

## Motivation for control problems

**Needs** of cell biologists for control:

1. Understanding role of feedback in cell reaction networks.  
Gene networks, metabolic networks, signal transduction networks.
2. Research for medical drugs.

**Networked-based drug research.** Phases:

1. Model reaction network of cell for phenomenon.
2. Select reaction and corresponding enzyme to inhibit.
3. Select chemical compounds to attach to active site.
4. Study side effects.

## Remark

Metabolic control theory developed by H.V. Westerhoff and many others.

## Control actuation based on inhibition of a chemical reaction

- Biochemical reaction catalyzed by an enzyme.  
**Enzyme** is a large molecule.
- **Active site** on enzyme is used to assemble new molecules from elements.
- Chemical substances introduced into cell via a drug may attach to active site. Substance will stay there for a long time.
- **Inhibition** of biochemical reaction:  
regular reaction cannot take place because active site is occupied by chemical substance.

## Approaches to control of reaction networks

### Approach of biochemists

- Approach to zeroing output for drug design:  
(1) Simulation. (2) Metabolic control theory (sensitivity analysis).

### Approach of control theory

- One, two, or more reactions inhibited:  
Select  $u_i = 0$  for  $i \in I \subset \mathbb{Z}_m$ . Computation of steady states.
- Graph for zeroing outflow.
- Determine feedback or zero input signal such that the zero dynamics of the controlled output is globally attractive.
- Inverse system for control of particular outflows.
- Decoupling for control of particular outflows.

**Problem Minimal set of input components to diminish outflow rate**

Consider  $k \in \mathbb{Z}_{n_z}$ . Determine,

$$J_0 \subseteq \mathbb{Z}_m, \text{ such that,}$$
$$\{u_j = 0, \forall j \in J_0\} \Rightarrow z_k = 0.$$

**Motivation** Networked based drug design.

**Def.** Consider a graph of a biochemical reaction network.

(Nodes, edges) = ((states, outflows, inflows), reactions).

A **special-cut-set** is a set of edges all to the same destination node(s) which, when these edges are deleted from the network, result in a graph without path from the inflows to the outflow.

**Problem** (Continued)

**Problem** The **minimal special-cut-set** problem is to determine a special-cut-set with the minimal number of destination nodes.

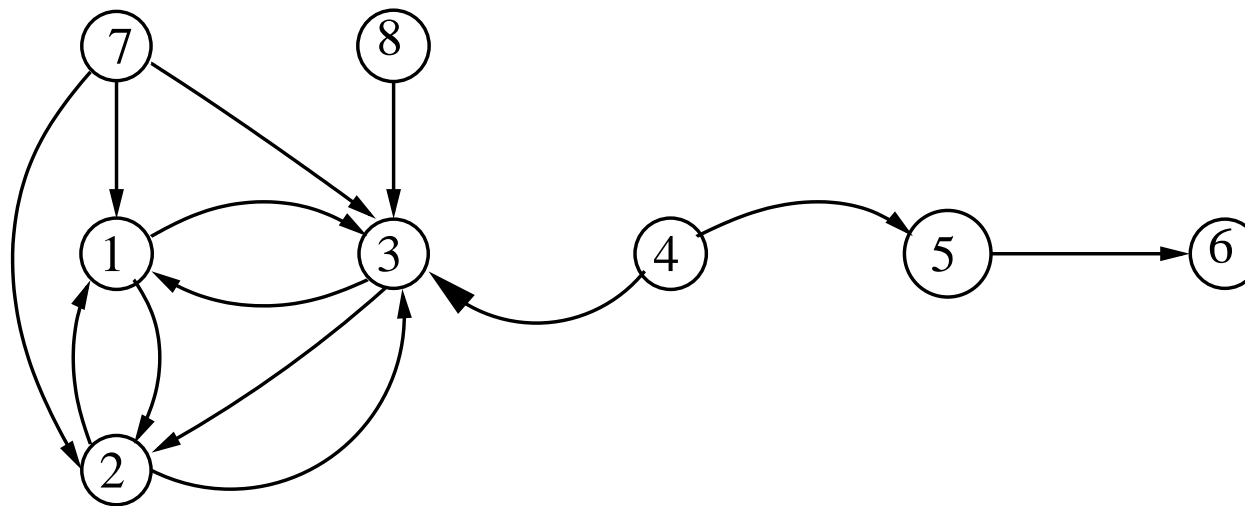
**Remark** Theory and algorithms of combinatorial optimization.

**Case study Tb** Graph based on reaction network.

Computation of existence of a path if one or more enzymes are inhibited.  
Yields all combinations of enzymes to inhibit.

**Minimal set of nodes for outflow**

**Example Rohwer's network**



**Example** *T. brucei* Computations to be carried out.

B. Bakker: Special-cut-set consisting of two nodes, corresponding to two enzymes.

**Problem 2 System reduction** Consider the rational positive system

$$\begin{aligned}\dot{x}(t) &= B \text{Diag}(r(x(t), x_{ex}(t)))u(t), \quad x(t_0) = x_0, \\ z(t) &= H \text{Diag}(r(x(t), x_{ex}(t)))u(t), \quad x(t) \in \mathbb{R}_+^{n_1}, \quad n_1 \in \mathbb{Z}_+.\end{aligned}$$

Determine an algorithm which produces a second rational positive system of lower order than the original one

$$\begin{aligned}\dot{\bar{x}}(t) &= \bar{B} \text{Diag}(\bar{r}(\bar{x}(t), x_{ex}(t)))u(t), \quad \bar{x}(t_0) = \bar{x}_0, \\ z(t) &= \bar{H} \text{Diag}(\bar{r}(\bar{x}(t), x_{ex}(t)))u(t), \quad \bar{x}(t) \in \mathbb{R}_+^{\bar{n}}, \quad \bar{n} \ll n,\end{aligned}$$

such that the external behavior of both system is close in terms of a prespecified norm.

**Remarks** System reduction for biochemical reaction networks differs from that for control systems due to reversibility of reactions.

## Motivation

- Analyse large networks.
- Conjecture is that feedback in the network simplifies the dynamics.
- Control for drug design.

## Approach to system reduction

1. System reduction for linear positive systems.  
Used much in engineering, for example chip design.  
Research in progress (HH). Book A.C. Antoulas (2005).
2. System reduction for irreducible subsystems.
3. Algorithms analogous to algorithm for subspace identification but adjusted to positive systems.

Research project System Reduction

Hanna Härdin, Hans V. Westerhoff, JHvS (Vrije Universiteit and CWI).

### Problem 3 Dynamical system properties

- Existence and uniqueness of solution to ODE.  
Existence due to local Lipschitz conditions.  
Global Lipschitz condition does not hold.
- Steady states. Existence? Uniqueness? Multiple steady states?
- Global asymptotic stability of the steady state (if unique).  
Approaches:
  - Horn, Jackson (1972); Feinberg (1987, 1995a, 1995b). Results not complete.
  - E.D. Sontag (2001), D. Angeli, E.D. Sontag (2004). Monotone systems, inspired by M. Hirsch.
- Conservation.

## Dynamical system properties

**Def.** Positive orthant,  $\mathbb{R}_+^n$ , said to be **forward invariant** for ODE if for all  $x_0 \in \mathbb{R}_+^n$ ,  $x_{ex}$ ,  $v$ ,  $u$ , which are positive, the solution satisfies  $x(t) \in \mathbb{R}_+^n$ ,  $\forall t \in T$ .

**Theorem** The positive orthant is forward invariant.

**Argument** Condition (2) of rational positive system.

**Problem** Existence and uniqueness of steady states for fixed enzyme input?  
Research in progress.

#### **Problem 4. Decomposition of rational positive systems**

Decompose the rational positive system into an ordered set of irreducible subsystems.

Graph is a further abstracted representation of the positive system.

**Remark** Properties of rational positive systems are best investigated in terms of irreducible components of the system.

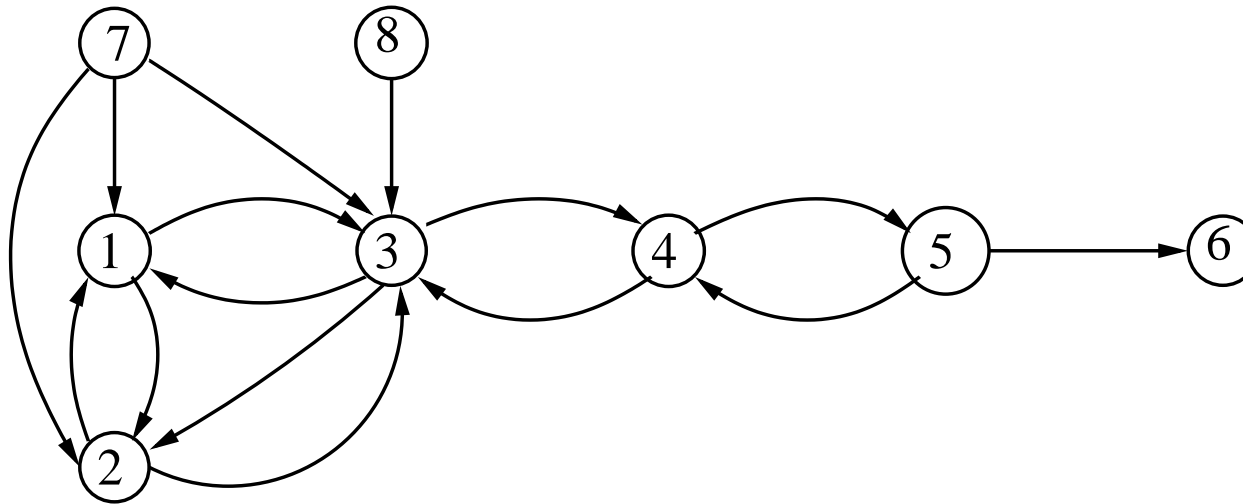
**Example** Positive matrices.

Concepts of reducible matrix, irreducible matrix, and completely reduced matrix.

Irreducible positive matrix can be decomposed into superdiagonal block-shift matrix corresponding to cycles.

## Rational systems and their graphs

**Example** Rohwer's network.



$V = \{1, 2, 3, 4, 5, 6, 7, 8\}$ , nodes,  
    {states (1-5), outflow rate (6), external concentrations (7-8)},

$E \subset V \times V$ .

**Def. System graph** defined as directed graph,

$$V = \{\text{states, outflow rates, external concentrations}\},$$

$$E \subset V \times V,$$

$$(i, k) \in E, \text{ if (1) } \exists j \in \mathbb{Z}_m \text{ such that } N_{i,j}^+ > 0,$$

$$\frac{p_j^+(x(t), x_{ex}(t))}{q_j(x(t), x_{ex}(t))}, \text{ depends on } x_k,$$

if (2) it depends on  $x_{ex,k}$ ,

and if (3) formula for  $z_i$  depends on  $x_k$ , or on  $x_{ex,k}$ .

$$A \in \{0, 1\}^{(n+n_z) \times (n+n_z+n_{ex})},$$

$$A_{i,k} = \begin{cases} 1, & (i, k) \in E, \\ 0, & \text{else.} \end{cases}$$

**Example** *T. brucei*. Graph.

## Steady states

**Problem** Existence and uniqueness of **steady state**.

For  $x_{ex} \in X_{ex}$ ,  $\{u(t) = u_s \in \mathbb{R}_+^m, \forall t \in T\}$ ,

does there exist

$x_s$  **steady state** such that

$$0 = B\text{Diag}(r(x_s, x_{ex,s}))u_s.$$

$z_s$  **steady outflow rate** corresponding to  $x_s$ ,

$$z_s = H\text{Diag}(r(x_s, x_{ex,s}))u_s \in \mathbb{R}_+^{n_z}.$$

## Approach to steady state problem

1. Decompose the system in terms of irreducible components.
2. Solve steady state problem per irreducible component, proceeding along graph through all such components.

## Conditions for solvability of irreducible components

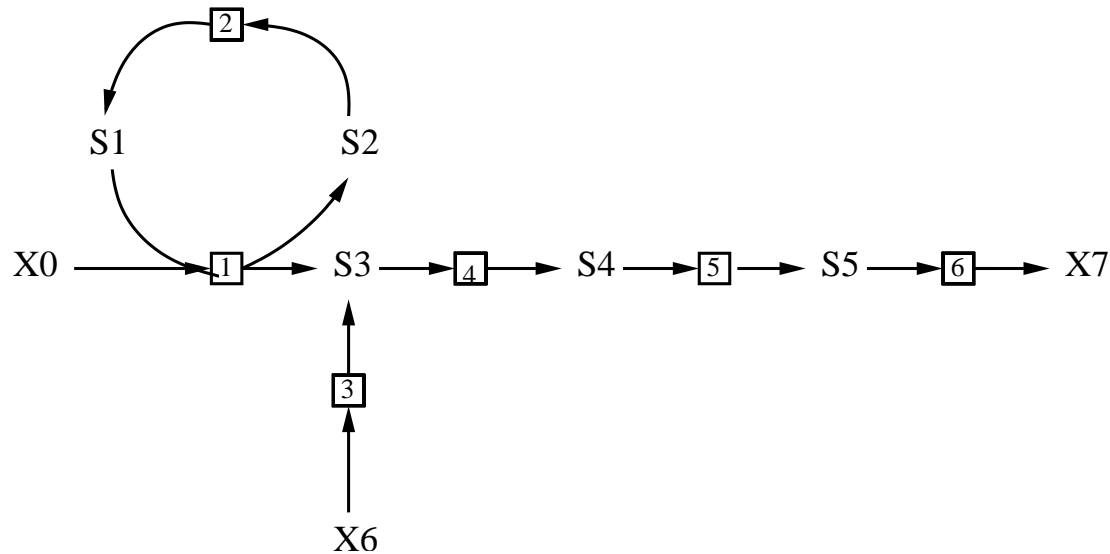
1. **Conservation** Examples:
  - (1) Rational positive systems for biochemical reaction networks.
  - (2) Compartmental systems.
2. **Contraction** or **expansion**.  
Steady state zero or no steady state respectively.

**Further research** Dynamic system properties.

Rational positive systems: Periodic solutions, chaotic dynamics?

## Steady states for rational positive system

### Example Rohwer's network



Network consists of cycle followed by series network.

Cycle of reactions: conserved moiety:  $x_1 + x_2 = c$ .

Choose  $u_s = 1 \in \mathbb{R}_+^6$ . Transformation,

$$0 = Br(x) \Rightarrow 0 = SBr(x) = Kr(x) = \bar{r}(x),$$

## Steady states for rational positive system

### Example Rohwer's network

Symbolic calculations with MAPLE on polynomials  $\bar{r}$  yield,

$$x_4 = 11x_5(1 + x_5)/10, \quad x_3 = (121x_5^2 + 132x_5 + 111)/100,$$

$$x_1 = c - x_2,$$

$$x_2 \quad \text{rational function of } x_5, x_{ex,1}, x_{ex,2}, c,$$

$$x_5 \quad \text{solution of polynomial of degree 11 with parameters } x_{ex,1}, x_{ex,2}, c,$$

$$x_{ex} = 1, \quad c = 10, \quad \text{arbitrary choices,}$$

$$x_5 \quad \text{unique real root in } (0, \infty),$$

$$x = (5.74, 4.26, 1.88, 1.33, 0.71).$$

### Example *T. brucei*

B.M. Bakker: If cycle conservation is taken care of then the solution is unique in computations. Proof?

## Problem 5 Observer problem

Construct an observer for a rational positive system, possibly of the form,

$$\begin{aligned}\dot{\hat{x}}(t) &= f(\hat{x}(t), y(t), u(t)) \\ &= B\text{Diag}(r(\hat{x}(t))u(t) + k(y(t) - H\text{Diag}(r(\hat{x}(t))u(t))), \\ \hat{x}(t_0) &= \hat{x}_0.\end{aligned}$$

such that for all initial conditions  $\hat{x}_0 \in \mathbb{R}_+^n$ :

$$\lim_{t \rightarrow \infty} [\hat{x}(t; t_0, \hat{x}_0) - x(t)] = 0.$$

**Motivation** To be used in identification.

In the cell no direct measurements can take place, only indirectly.

## Problem 6. Realization

Consider a relation,

$$\begin{aligned} u &: T \rightarrow \mathbb{R}_+^m, \quad y : T \rightarrow \mathbb{R}_+^p, \\ 0 &= f(u(t), \dots, u^{(r)}(t), y(t), \dots, y^{(s)}(t)). \end{aligned}$$

Does there exist a rational positive system, called a **realization**,

$$\begin{aligned} \dot{x}(t) &= B \text{Diag}(r(x(t)))u(t), \quad x(t_0) = x_0 \in X_0, \\ y(t) &= Cx(t), \end{aligned}$$

such that the external behavior of this system equals the relation?

- Existence of realization (conditions on  $f$ ).
- Minimality characterization (reachability, observability).
- Classification of all minimal realizations.

## Positive polynomials - Factorization

$$\mathbb{R}_{+,1}[x] = \{p \in \mathbb{R}_+[x] \mid c_p(0) = 1\},$$

$$\{1\} \subseteq \mathbb{R}_{+,1}[x], \text{ set of units (invertible elements),}$$

$$p \in \mathbb{R}_{+,1} \text{ irreducible if,}$$

$$(1) \quad p \neq 1, \quad (2) \quad p = p_1 p_2 \Rightarrow p_1 = 1 \text{ or } p_2 = 1.$$

$$\mathbb{R}_{+,1}[x] \text{ integral domain.}$$

**Unique factorization domain** if

$$(1) \quad q \in \mathbb{R}_{+,1} \Rightarrow q = \prod_{r=1}^n p_i, \quad p_i \in \mathbb{R}_{+,1}, \text{ irreducible,}$$

$$(2) \quad \text{factorization unique upto reordering.}$$

$$\mathbb{R}_{+,1}[x] \text{ not unique factorization domain,}$$

$$p(x) = (x + 2b)(x + 3b)(x^2 - bx + 4b^2), \quad b \in (0, \infty),$$

$$= (x + 2b)(x^3 + 2bx^2 + b^2x + 12b^3)$$

$$= (x + 3b)(x^3 + bx^2 + 2b^2x + 8b^3).$$

## Def. Positive polynomials

**Common multiple** of  $\{p_j \in \mathbb{R}_+[x_1, \dots, x_n], j \in \mathbb{Z}_m\}$ ,  
 $p \in \mathbb{R}_+[x]$  such that  $\forall j \in \mathbb{Z}_m, \exists q_j \in \mathbb{R}_+[x], p = q_j p_j$ .

**Least common multiple** of  $\{p_j \in \mathbb{R}_+[x], j \in \mathbb{Z}_m\}$ ,  
 $p \in \mathbb{R}_+[x]$  such that it is a common multiple  
and for any other common multiple  $\bar{p} \in \mathbb{R}_+[x]$ ,

$\text{order}(p) \leq \text{order}(\bar{p})$ , for example, lexicographic ordering on  $x_1, \dots, x_n$ .

Notation,

$$p = \text{lcm}(\{p_j \in \mathbb{R}_+[x], j \in \mathbb{Z}_m\}; \mathbb{R}_+[x], \text{order}).$$

$$\mathbb{R}_{+,1}[x] = \{p \in \mathbb{R}_+[x] \mid c_p(0) = 1\},$$

$$\mathbb{R}_0[x] = \{p \in \mathbb{R}[x] \mid c_p(0) = 0\}.$$

## Theorem Existence realization

$$\begin{aligned} 0 &= f(y(t), y^{(1)}(t), u(t)), \forall t \in T = \mathbb{R}_+, \\ u &: T \rightarrow U = \mathbb{R}_+^m, \quad y : T \rightarrow \mathbb{R}_+^n, \text{ continuously diff.}, \end{aligned}$$

There exists a realization of the relation  $f$ ,  
in the form of a rational positive system, except Conditions (1-4),

$$\begin{aligned} \dot{x}(t) &= B \text{Diag}(r(x(t)))u(t), \quad x(t_0) = x_0, \\ y(t) &= x(t), \end{aligned}$$

if and only if  $f$  can be transformed to,

$$\begin{aligned} q(y(t))y_i^{(1)} &= \sum_{j=1}^m B_{i,j}k_j(y(t))p_j(y(t))u_j(t), \quad \forall i \in \mathbb{Z}_n, \\ q &\in \mathbb{R}_{+,1}[x], \quad k_j \in \mathbb{R}_{+,1}[x], \quad p_j \in \mathbb{R}_0[x], \quad \forall i \in \mathbb{Z}_n, j \in \mathbb{Z}_m, \\ q &= \text{lcm}(\{k_j \in \mathbb{R}_+[y], \quad \forall j \in \mathbb{Z}_m\}, \mathbb{R}_+[x], \text{order}). \end{aligned}$$

**Remark** Further research needed on  
differential algebra for positive polynomials.

## Problem State-space isomorphism problem

Which class of functions  $s : \mathbb{R}_+^n \rightarrow \mathbb{R}_+^n$ , state-space transformations, leave the class of rational positive systems invariant?

**Theorem** Consider the rational positive system

$$\dot{x}_i(t) = \sum_{j=1}^m (B_{i,j}^+ - B_{i,j}^-) \left[ \frac{p_j^+(x(t))}{q_j^+(x(t))} - \frac{p_j^-(x(t))}{q_j^-(x(t))} \right] u_j(t), \quad \forall i \in \mathbb{Z}_n.$$

Assume  $s \in \mathbb{R}_{+,s}$  and inverse exists  $s^{-1} \in \mathbb{R}_{+,s}(x)$ . Then

$$\begin{aligned} \bar{x}(t) &= s(x(t)), \\ \dot{\bar{x}}_i(t) &= \sum_{j=1}^m (B_{i,j}^+ - B_{i,j}^-) \left[ \frac{p_j^+(\bar{x}(t))}{q_j^+(\bar{x}(t))} - \frac{p_j^-(\bar{x}(t))}{q_j^-(\bar{x}(t))} \right] u_j(t), \quad \forall i \in \mathbb{Z}_n, \end{aligned}$$

if and only if

$$s'(x)Br(x) = Br(s(x)), \quad \forall x \in X, \text{ where,}$$

$$s'(x)_{i,k} := \partial s_i(x) / \partial x_k, \quad \forall i, k \in \mathbb{Z}_n, \quad \forall x \in X.$$

## Realization theory - Further research

- Existence of realization. Differential algebra for positive polynomials.
- Reachability and observability of rational positive systems.

Literature on realization of polynomial and rational systems, not necessarily positive. (Incomplete list)

(E.D. Sontag (1979, Ph.D. thesis))

(Z. Bartosiewicz (1987))

(Yuan Wang, E.D. Sontag (1992))

## Research problems

- Experience with a variety of biochemical networks.
- **Control** for networked-based drug design and other purposes.
- **System reduction.**
- **Observers.**
- **Algebraic structure and algorithms**  
for polynomials with positive coefficients.
- **Decompositions** of rational positive systems.
- **Realization.**
- **Computer tools** for modeling, realization, and control.

## **Acknowledgements**

- Barbara M. Bakker, Hanna Härdin, Hans V. Westerhoff (VU.SystemsBio).
- Ilona Verburg, André C.M. Ran (VU.Math).
- Dorina Jibeteau (CWI).

## **Financial support in part**

- CWI (Amsterdam, The Netherlands).
- Vrije Universiteit (Amsterdam).
- European Commission via EU.TMR.SI.

**The End!**