Rational Positive Systems for Cell Reaction Networks

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Outline

- Example *Trypanosoma brucei*.
  Modeling of cell reaction networks.
- Rational positive systems.
- Interconnections and decompositions.
- Dynamical system properties.
- Realization.
- Control.
- Research problems.

Example Glycolysis in Trypanosoma brucei

- *Trypanosoma brucei*. Unicellular eukaryote (with nucleus). Parasite in humans and other mammals. Lives in blood and tissue.
- Subspieces cause African Sleep Disease. 200.000 new infections a year. Lethal unless treated. Damage to lifestock.
- 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 **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).

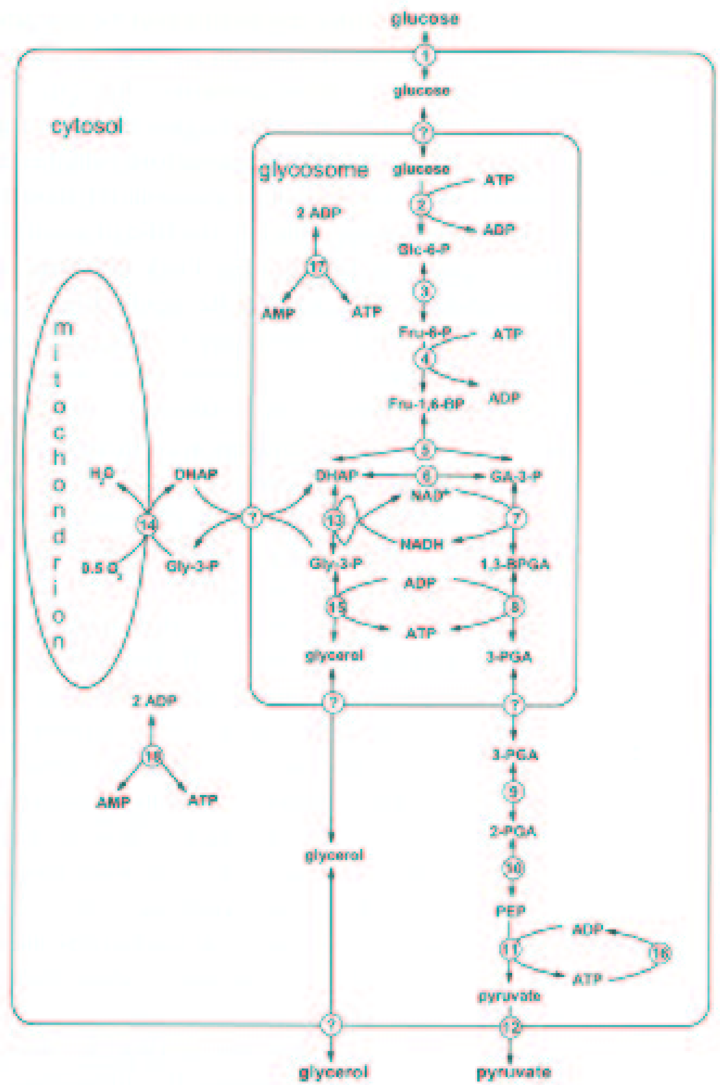

F
N
G
ER
CV

Trypanosoma brucei

Biochemical reaction network.

Source1: (B.M. Bakker, Ph.D. thesis, VU, Amsterdam, 1998, p. 9).

Source2: (I. Coppens (ICP, Brussels)).



Glycolysis in T. brucei

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

In our red blood cells,

$$C_6H_{12}O_6 \;\rightarrow\; 2C_3H_6O_3\text{(lactic acid)} \;+\; \text{Gibbs free energy (ATP)}.$$

ATP = Adenosine Triphosphate used elsewhere in cell for activities.

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

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

- 28 chemical compounds, 1 external input, 2 output flows.
- 20 reactions and corresponding enzymes.
- Differential algebraic system of equations.
  8 Reactions treated as in 'equilibrium'. Details below.
  Differential equation,

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

Example Glycolysis in *T. brucei*.

States represent concentrations of chemical substances:

$$
\begin{array}{lll}
x_1 = GLC_{in}, & x_2 = [hexose - P], & x_3 = [Fru - 1,6 - BP]_g, \\
x_4 = [triose - P], & x_5 = [1,3 - BPGA]_g, & x_6 = N, \\
x_7 = [PYR]_c, & x_8 = [NADH]_g, & x_9 = P_g, \\
x_{10} = [P_c], & x_{11} = ADP, & x_{12} = ATP, \\
x_{13} = [3 - PGA], & x_{14} = DHAP, & x_{15} = [Gly - 3 - P], \\
x_{16} = NAD^+, & x_{17} = [GA - 3 - P], & x_{18} = Gly. \\
x_{ex} = GLC_{out}. & &
\end{array}
$$

Enzymes and corresponding input components:

u_1 transport of glucose through the plasma and glycosome membrane,

u_2 HK, u_4 PFK, u_5 ALD, u_7 GAPDH, u_8 PGK, u_{10} PYK,

u_{11} transport of pyruvate across the plasma membrane,

u_{12} GDH, u_{14} GPO, u_{16} GK, u_{18} ATP utilization.

Example Glycolysis in *T. brucei*.

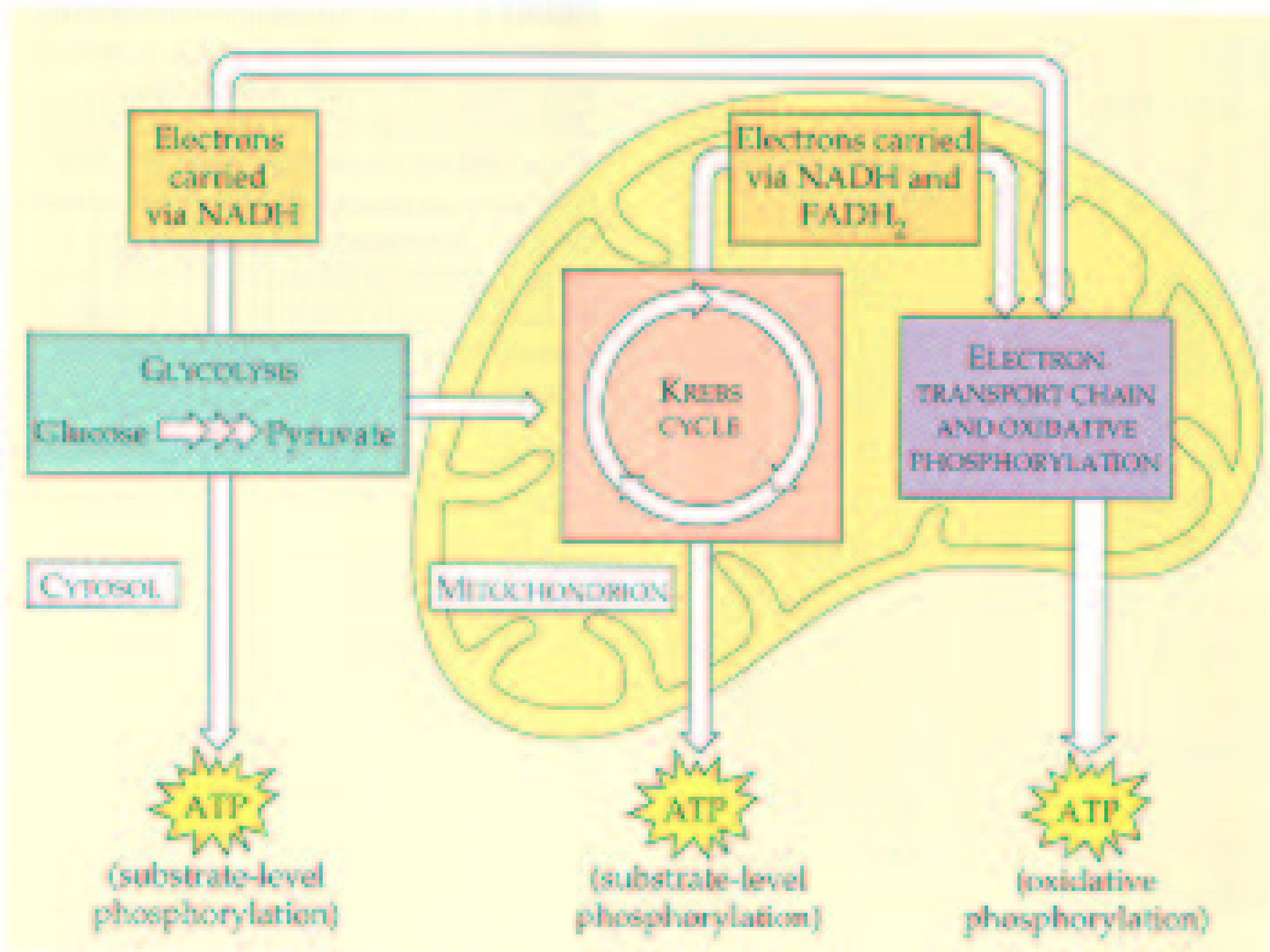
Rate functions $v_i = r_i u_i$:

$$
\begin{aligned}
r_1 &= c_2 \frac{c_{21} x_{ex} - c_{22} x_1}{c_{23} + x_1 + x_{ex} + c_{24} x_1 x_{ex}}, \\
r_2 &= c_1 \frac{c_3 x_{13} c_4 x_1}{(1 + c_3 x_{12} + c_5 x_{11})(1 + c_4 x_1)}, \\
r_7 &= c_1 \frac{[c_9 x_{17} c_{10} x_{16} - c_6 c_7 x_5 c_8 x_8]}{(1 + c_9 x_{17} + c_7 x_5)(1 + c_{10} x_{16} + c_8 x_8)}, \\
r_8 &= c_1 \frac{[c_{11} x_5 c_{12} x_{11} - c_{13} c_{14} x_{13} c_{15} x_{12}]}{(1 + c_{11} x_5 + c_{14} x_{13})(1 + c_{12} x_{11} + c_{15} x_{12})}.
\end{aligned}
$$

Differential equation,

$$\dot{x}(t) = N \mathrm{Diag}(r(x(t), x_{ex}(t))) u(t), \; x(t_0) = x_0.$$

Glycolysis in most cells (Campbell, Reece, Mitchell (1999)).



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: (R. Heinrich, S. Schuster (1996)). (B. Alberts etal (1994)). (F. Horn, R. Jackson (1972)).

Modeling of biochemical reaction networks

Example Reactions of liver cells

$$\begin{aligned} \text{Glucose} + ATP &\overset{HK}{\to} \text{Glucose-6-phosphate} + ADP \\ \text{Glucose-6-phosphate} &\overset{PGM}{\to} \text{Glucose-1-phosphate} \end{aligned}$$

Enzymes: HK = Hexokinase, PGM = Phosphoglucomatase.

Stoichiometric matrix, (stoikheion = (Greek) elements)

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

Column of N represents concentrations produced by a reaction,
row of N represents use/production of one substance by all reactions.

Modeling of biochemical reaction networks

Differential equation

Reaction rate models (general mass action kinetics):

Polynomial model (HW: not realistic),

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

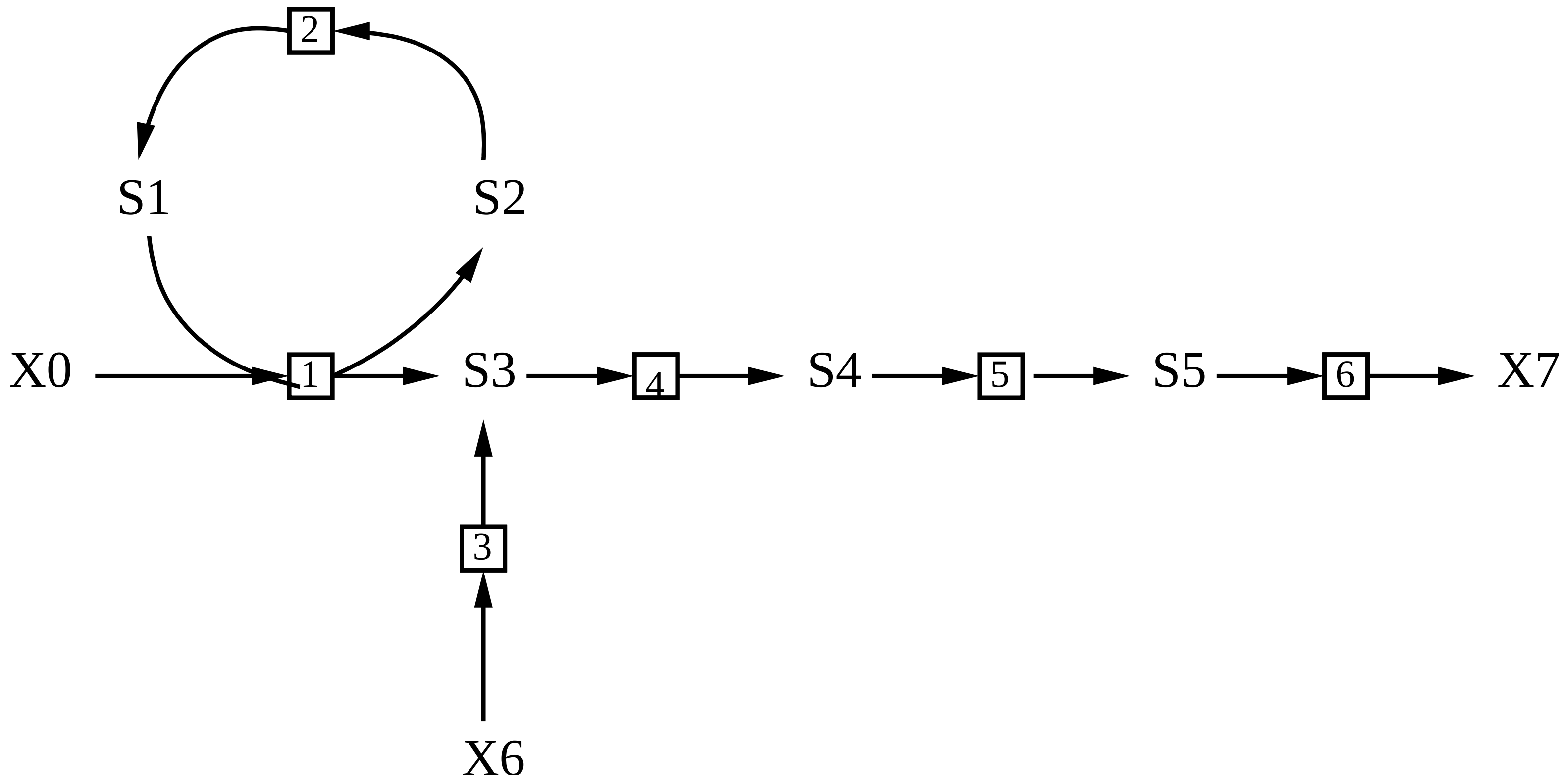
Michaelis-Menten kinetics, rational function, for example,

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

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

Example Rohwer's network

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



Example Rohwer's network (Continued)

States and matrices

$$
\begin{aligned}
n &= 5,\ n_{ex} = 2,\ n_z = 1,\ m = 6, \\
x_1 &= S_1,\ \ldots,\ x_5 = S_5,\ \text{concentrations} = \text{states}, \\
x_{ex,1} &= X0,\ x_{ex,2} = X6,\ \text{external concentrations}, \\
Z &= dX7/dt,\ \text{outflow rate.} \\
N &= \begin{pmatrix} -1 & 1 & 0 & 0 & 0 & 0 \\ 1 & -1 & 0 & 0 & 0 & 0 \\ 1 & 0 & 1 & -1 & 0 & 0 \\ 0 & 0 & 0 & 1 & -1 & 0 \\ 0 & 0 & 0 & 0 & 1 & -1 \end{pmatrix},\ \textbf{stoichiometric matrix,} \\
H &= \begin{pmatrix} 0 & 0 & 0 & 0 & 0 & 1 \end{pmatrix},\ \textbf{outflow matrix.}
\end{aligned}
$$

Example Rohwer's network (Continued)

Rate functions

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

Differential equation of system,

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

Modeling of biochemical cell reaction networks
Types of networks

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

Remarks on research for networks

- Numbers are large:
  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.
- Assist with medical drug research. Control.
- Assist with cell factory biotechnology (beer, bread).

Positive linear algebra

$$\begin{array}{rcl} \mathbb{Z}, & & \mathbb{Z}_+,\ \mathbb{N}, \\ \mathbb{Z}_n & = & \{1,2,\ldots,n\},\ \mathbb{N}_n = \{0,1,2,\ldots,n\}, \quad \forall n \in \mathbb{Z}_+, \\ \mathbb{R}_+ & = & [0,\infty),\ \textbf{positive real numbers,} \\ (0,\infty) & & \textbf{strictly positive real numbers,} \\ (\mathbb{R}_+,+,\times,0,1) & & \textbf{semi-ring and integral domain,} \\ (\mathbb{R}_+,\mathbb{R}_+^n) & & \textbf{positive vector space,} \\ V & \subseteq & \mathbb{R}_+^n \ \textbf{cone if}\ (1)\ V+V \subseteq V;\ (2)\ \mathbb{R}_+ V \subseteq V; \\ V & \subseteq & \mathbb{R}_+^n \ \textbf{polyhedral cone} \\ & & \text{if it equals intersection of finite number of half spaces;} \\ & & \text{equivalently, } \exists v_1,\ldots,v_m \in \mathbb{R}_+^n, \\ V & = & \text{cone}(\{v_1,\ldots,v_m\}). \end{array}$$

Positive polynomials

$$
\begin{aligned}
k &= (k_1,\ldots,k_n) \in \mathbb{N}^n, \text{ \textbf{multi index,}} \\
p(x) &= \sum_{k\in\mathbb{N}^n} c_p(k) \prod_{j=1}^{n} x_j^{k(j)} = \sum_{k\in\mathbb{N}^n} c_p(k) x^k, \\
& \forall k \in \mathbb{N}^n,\ c_p(k) \in \mathbb{R}_+,\ \text{finite number non zero,} \\
& p \in \mathbb{R}_+[x_1,\ldots,x_n] = \mathbb{R}_+[x],\ \text{\textbf{positive polynomial.}} \\
& \text{(polynomial with positive coefficients)} \\
p(x) &= 3.1 x_1^2 x_2^3 x_3^4 + 2 x_1^3 x_3^1 + 5 x_2^4 x_4^2,\ \text{example positive polynomial.} \\
& (\mathbb{R}_+[x], +, \times, 0, 1)\ \text{dioid.} \\
\deg(p) &= \max_{\{k\in\mathbb{N}^n \mid c_p(k)\neq 0\}} \{\sum_{i=1}^{n} k(i)\} \in \mathbb{N},\ \text{\textbf{degree of} } p.
\end{aligned}
$$

Special rational positive functions

$$
\begin{aligned}
\mathbb{R}_{+,s}(x) &= \{p/q \mid p, q \in \mathbb{R}_+[x],\ c_p(0) = 0,\ c_q(0) = 1,\ \}, \\
\frac{p(x)}{q(x)} &= \frac{c_1 x_1 + c_2 x_2}{1 + c_3 x_1 + c_4 x_2},\ \text{example.}
\end{aligned}
$$

Definitions

Def. Rational positive system for cell reaction network

$$
\begin{aligned}
\dot{x}(t) &= N\mathrm{Diag}(r(x(t),x_{ex}(t)))u(t) + Bv(t),\ x(t_0) = x_0,\\
z(t) &= H\mathrm{Diag}(r(x(t),x_{ex}(t)))u(t),\ \textbf{outflow rate,}\\
y(t) &= Cx(t),\ \textbf{output},\\
T &= [t_0,\infty),\ n,m \in Z_+,\ n_v,n_{ex},n_z \in \mathbb{N},\\
X &= \mathbb{R}_+^n,\ X_{ex} = \mathbb{R}_+^{n_{ex}},\ V = \mathbb{R}_+^{n_v},\ U = \mathbb{R}_+^m,\\
r_j(x,x_{ex}) &= \frac{p_j^+(x,x_{ex})}{q_j(x,x_{ex})} - \frac{p_j^-(x,x_{ex})}{q_j(x,x_{ex})},\\
&\quad (p_j^+/q_j),(p_j^-/q_j) \in \mathbb{R}_{+,s}(x,x_{ex}),\ \forall j \in \mathbb{Z}_m,\\
\dot{x}_i(t) &= \sum_{j=1}^{m}(N_{i,j}^+ - N_{i,j}^-)\left[\frac{p_j^+(x(t),x_{ex})}{q_j(x(t),x_{ex})} - \frac{p_j^-(x(t),x_{ex})}{q_j(x(t),x_{ex})}\right]u_j(t) + B_i v(t).
\end{aligned}
$$

Distinguish: **External input rate** v and **external concentration** x_{ex}.

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) $\forall i \in \mathbb{Z}_n$, $j \in \mathbb{Z}_m$,

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

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

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

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

4. (Existence and uniqueness solution)
   For all $T = [t_0, \infty)$, $x_0 \in \mathbb{R}^n$, x_{ex}, v, u,
   there exists an unique solution of the ODE.

Dynamical system properties

- Existence and uniqueness of solution to ODE.
  Existence due to local Lipschitz conditions.
  Global Lipschitz condition does not hold.
- Steady states.
- Conservation.
- Stability. Not discussed. See (M. Feinberg, 1995) and others.

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, solution satisfies $\forall t \in T, \; x(t) \in \mathbb{R}_+^n$.

Theorem The positive orthant is forward invariant.
Argument Condition (2) of rational positive system,

Interconnections and decompositions of cell reaction networks

Theorem Consider two rational positive systems,

$$\begin{aligned}
\dot{x}_1(t) &= N_1 \mathrm{Diag}(r_1(x_1(t))u_1(t) + B_1 v_1(t), \;\; x_1(t_0) = x_{1,0}, \\
z_1(t) &= H_1 \mathrm{Diag}(r_1(x_1(t)))u_1(t), \\
\dot{x}_2(t) &= N_2 \mathrm{Diag}(r_2(x_2(t))u_2(t) + B_2 v_2(t), \;\; x_2(t_0) = x_{2,0}, \\
z_2(t) &= H_2 \mathrm{Diag}(r_2(x_2(t)))u_2(t).
\end{aligned}$$

Class of rational positive systems is closed with respect to:

(a) **Series connection** of System 1 and 2 for external input rate with

$$v_2(t) = K z_1(t).$$

(b) **Feedback connection** around System 1 for external input rate with

$$v_1(t) = F z_1(t) + v_3(t).$$

Decomposition of rational positive systems

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

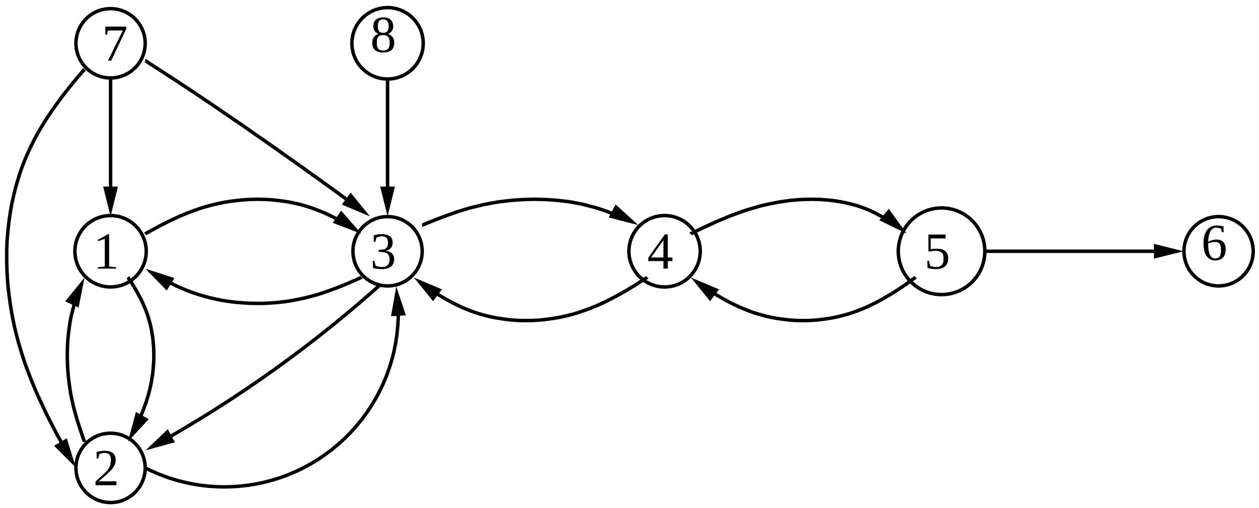
Decomposition of rational positive systems

- Graph.
- Decomposition into ordered set of irreducible components.

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.



$$
\begin{aligned}
V &= \{1,2,3,4,5,6,7,8\}, \text{ nodes}, \\
&\quad \{\text{states (1-5), outflow rate (6), external concentrations (7-8)}\}, \\
E &\subset V \times V.
\end{aligned}
$$

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

$$
\begin{aligned}
V &= \{\text{states, outflow rates, external concentrations}\}, \\
E &\subset V \times V, \\
(i,k) &\in E, \text{ if } \exists j \in \mathbb{Z}_m \text{ such that } N^+_{i,j} > 0, \\
&\quad \frac{p^+_j(x(t), x_{ex}(t))}{q_j(x(t), x_{ex}(t))}, \text{ depends on } x_k \\
&\quad \text{if it depends on } x_{ex,k}, \\
&\quad \text{if formula for } z_i \text{ depends on } x_k, \text{ or on } x_{ex,k}. \\
A &\in \{0,1\}^{(n+n_z)\times(n+n_z+n_{ex})}, \\
A_{i,k} &= \begin{cases} 1, & (i,k) \in E, \\ 0, & \text{else.} \end{cases}
\end{aligned}
$$

Example *T. brucei*. Graph under construction.

Dissipation and conservation

Remarks Distinguish:

- Models based on moity conservation. Used below.
- Models based on Gibbs free energy.
  Reactions due to free energy differences.
  Not discussed below.

Mathematical models of biochemical cell reaction networks based on mass action kinetics are by definition conservative.
Rational positive system should have this property.

Def. Consider rational positive system,

$$\begin{aligned} \dot{x}(t) &= N\text{Diag}(r(x(t))u(t) + Bv(t),\ x(t_0) - x_0, \\ z(t) &= H\text{Diag}(r(x(t))u(t). \end{aligned}$$

System called **dissipative** or **conservative** with
inflow rate LBv, $L \in \mathbb{R}^{1 \times n_v}$, and outflow rate Kz, $K \in \mathbb{R}^{1 \times n_z}$
if there exists a storage function $S : X \to \mathbb{R}_+$
such that for all $t_1, t_2 \in T$, $t_1 < t_2$, $T_1 = [t_1, t_2]$,
$x_1 \in X$, $u : T_1 \to \mathbb{R}_+^m$, $v : T_1 \to \mathbb{R}_+^{n_v}$,

$$\begin{aligned} S(x(t_2)) + \int_{t_1}^{t_2} Kz(s)ds &\leq S(x_1) + \int_{t_1}^{t_2} LBv(s)ds, \\ \text{storage at } t_2 \ + \ \text{outflow} &\leq \text{storage at } t_1 \ + \ \text{inflow;} \\ &\leq \text{(dissipation inequality)}, \\ &= \text{(conservation equality)}. \end{aligned}$$

Remark Concept special case of (J.C. Willems, 1972).

Theorem Consider rational positive system.

(a) System is dissipative respectively conservative
with inflow and outflow rates LBv and Kz respectively
and with storage function $S(x) = Sx$, $S \in \mathbb{R}_+^{1\times n}$
if and only if

$$\begin{aligned} (SN + KH)r(x) &\leq 0, \; \forall x \in X, \\ (S - L)B &\leq 0, \; \text{respectively} = 0, \;\; = 0. \end{aligned}$$

(b) System is conservative with ...
if and only if

$$SN + KH = 0, \;\; (S - L)B = 0.$$

This condition holds for biochemical reaction networks based on conservation of moity due to modeling.

Remark
Storage function for example counts atoms of particular type.

Dissipation and conservation

Example Rohwer's network

External concentration present.

$$
\begin{aligned}
r_{ex,1} &= \frac{10x_1x_{ex,1} - x_2x_3}{1 + x_1x_{ex,1} + x_2x_3}, \; r_{ex} : X \times X_{ex} \to \mathbb{R}^m_+, \\
r_{ex,3} &= \frac{5x_{ex,2} - x_3}{1 + x_{ex,2} + x_3}, \; r_{ex,i} = 0, \text{ otherwise}, \\
& \int_{t_1}^{t_2} H_{ex}\mathrm{Diag}(r_{ex}(x, x_{ex}))u(s)ds, \\
& \text{term added to dissipation inequality}, \\
H_{ex} &= (1\ 0\ 1\ 0\ 0\ 0), \; S = (1\ 1\ 1\ 1\ 1), \; K = 1, \; L = S, \\
0 &= [SN + KH]r(x, x_{ex}) - H_{ex}r_{ex}(x, x_{ex}).
\end{aligned}
$$

Steady states

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

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

$$
\begin{aligned}
x_s & \quad \textbf{steady state} \text{ such that} \\
0 &= N\mathrm{Diag}(r(x_s, x_{ex,s})u_s + Bv_s. \\
z_s & \quad \textbf{steady outflow rate} \text{ corresponding to } x_s, \\
z_s &= H\mathrm{Diag}(r(x_s, x_{ex,s})u_s \in \mathbb{R}_+^{n_z}.
\end{aligned}
$$

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

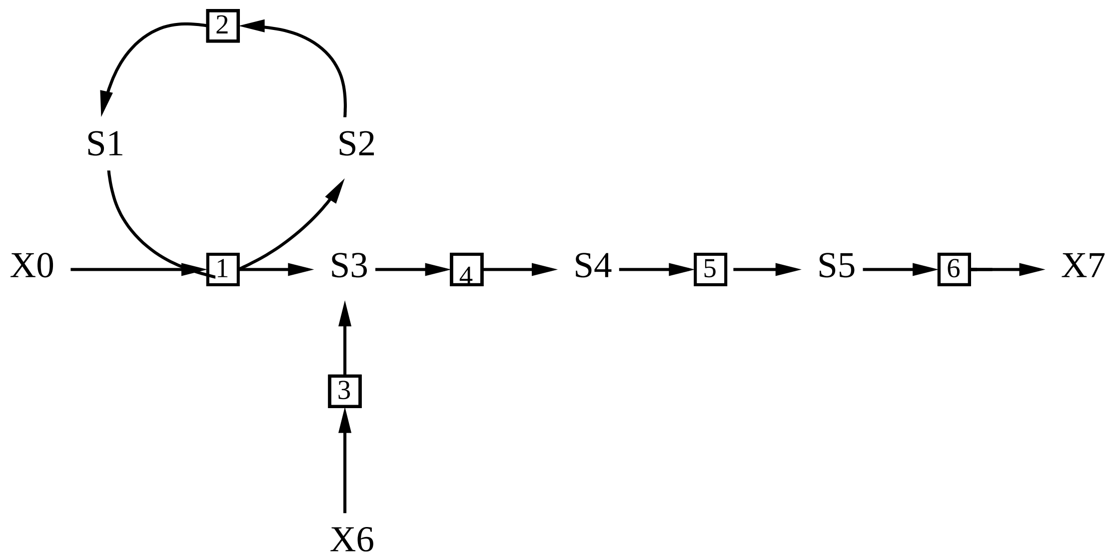
1. **Conservation** Examples:
   (1) Rational positive systems for biochemical reaction networks.
   (2) Compartmental systems.
2. **Contraction** or **expansion**.
   Steady state zero or no steady state respectively.

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 moity: $x_1 + x_2 = c$.

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

$$0 = Nr(x) \;\Rightarrow\; 0 = SNr(x) = Kr(x) = \bar{r}(x),$$

Steady states for rational positive system

Example Rohwer's network

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

$$
\begin{aligned}
x_4 &= 11x_5(1+x_5)/10, \quad x_3 = (121x_5^2 + 132x_5 + 111)/100, \\
x_1 &= c - x_2, \\
x_2 & \quad \text{rational function of } x_5, x_{ex,1}, x_{ex,2}, c, \\
x_5 & \quad \text{solution of polynomial of degree 11 with parameters } x_{ex,1}, x_{ex,2}, c, \\
x_{ex} &= 1, \; c = 10, \; \text{arbitrary choices}, \\
x_5 & \quad \text{unique real root in } (0, \infty), \\
x &= (5.74, \; 4.26, \; 1.88, \; 1.33, \; 0.71).
\end{aligned}
$$

Example *T. brucei*

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

Realization

Problem Realization

Consider a relation,

$$
\begin{aligned}
& u : T \to \mathbb{R}_+^m,\ v : T \to \mathbb{R}_+^{n_v},\ y : T \to \mathbb{R}_+^p, \\
0 &= f(u(t), \ldots, u^{(r)} r(t), v(t), \ldots, v^{(q)}(t), y(t), \ldots, y^{(s)}(t)).
\end{aligned}
$$

Does there exists a rational positive systems, called a **realization**,

$$
\begin{aligned}
\dot{x}(t) &= N\mathrm{Diag}(r(x(t))u(t) + Bv(t),\ x(t_0) = x_0 \in X_0, \\
y(t) &= Cx(t),
\end{aligned}
$$

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

$$
\begin{aligned}
\mathbb{R}_{+,1}[x] &= \{p \in \mathbb{R}_+[x] | c_p(0) = 1\}, \\
\{1\} &\subseteq \mathbb{R}_{+,1}[x], \ \textbf{set of units} \text{ (invertible elements)}, \\
p &\in \mathbb{R}_{+,1} \ \textbf{irreducible} \text{ if}, \\
(1) & \quad p \neq 1, \ (2) \ p = p_1 p_2 \ \Rightarrow \ p_1 = 1 \text{ or } p_2 = 1. \\
\mathbb{R}_{+,1}[x] & \quad \textbf{integral domain.} \\
& \quad \textbf{Unique factorization domain} \text{ if} \\
(1) & \quad q \in \mathbb{R}_{+,1} \ \Rightarrow \ q = \prod_{r=1}^{n} p_i, \ p_i \in \mathbb{R}_{+,1}, \ \text{irreducible}, \\
(2) & \quad \text{factorization unique upto reordering.} \\
\mathbb{R}_{+,1}[x] & \quad \text{not unique factorization domain}, \\
p(x) &= (x+2b)(x+3b)(x^2 - bx + 4b^2), \ b \in (0, \infty), \\
&= (x+2b)(x^3 + 2bx^2 + b^2 x + 12b^3) \\
&= (x+3b)(x^3 + bx^2 + 2b^2 x + 8b^3).
\end{aligned}
$$

Def. Positive polynomials

Common multiple of $\{p_j \in \mathbb{R}_+[x_1,\ldots,x_n], j \in \mathbb{Z}_m\}$,

$p \in \mathbb{R}_+[x]$ 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 $\bar{p} \in \mathbb{R}_+[x]$,

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

Notation,

$$
\begin{aligned}
p &= \mathrm{lcm}(\{p_j \in \mathbb{R}_+[x], j \in \mathbb{Z}_m\}; \mathbb{R}_+[x], \mathrm{order}). \\
\mathbb{R}_{+,1}[x] &= \{p \in \mathbb{R}_+[x] \mid c_p(0) = 1\}, \\
\mathbb{R}_0[x] &= \{p \in \mathbb{R}[x] \mid c_p(0) = 0\}.
\end{aligned}
$$

Theorem Existence realization

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

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

$$\begin{aligned} \dot{x}(t) &= N \mathrm{Diag}(x(t)) u(t),\ x(t_0) = x_0, \\ y(t) &= x(t), \end{aligned}$$

if and only if f can be transformed to,

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

Remark Further research needed on
differential algebra for positive polynomials.

Problem State-space isomorphism problem

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

Theorem Consider the rational positive system

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

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

$$\begin{aligned} \bar{x}(t) &= s(x(t)), \\ \dot{\bar{x}}_i(t) &= \sum_{j=1}^{m} (N_{i,j}^+ - N_{i,j}^-) \left[\frac{p_j^+(\bar{x}(t))}{q_j^+(\bar{x}(t))} - \frac{p_j^-(\bar{x}(t))}{q_j^-(\bar{x}(t))} \right] u_j(t), \ \forall i \in \mathbb{Z}_n, \\ & \text{if and only if} \\ s'(x) N r(x) &= N r(s(x)), \ \forall x \in X, \ \text{where,} \\ s'(x)_{i,k} &:= \partial s_i(x) / \partial x_k, \ \forall i, k \in \mathbb{Z}_n, \ \forall x \in X. \end{aligned}$$

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))

Control

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.

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.
- **Inhibition** of biochemical reaction:
  regular reaction cannot take place because active site is occupied by chemical substance.

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.

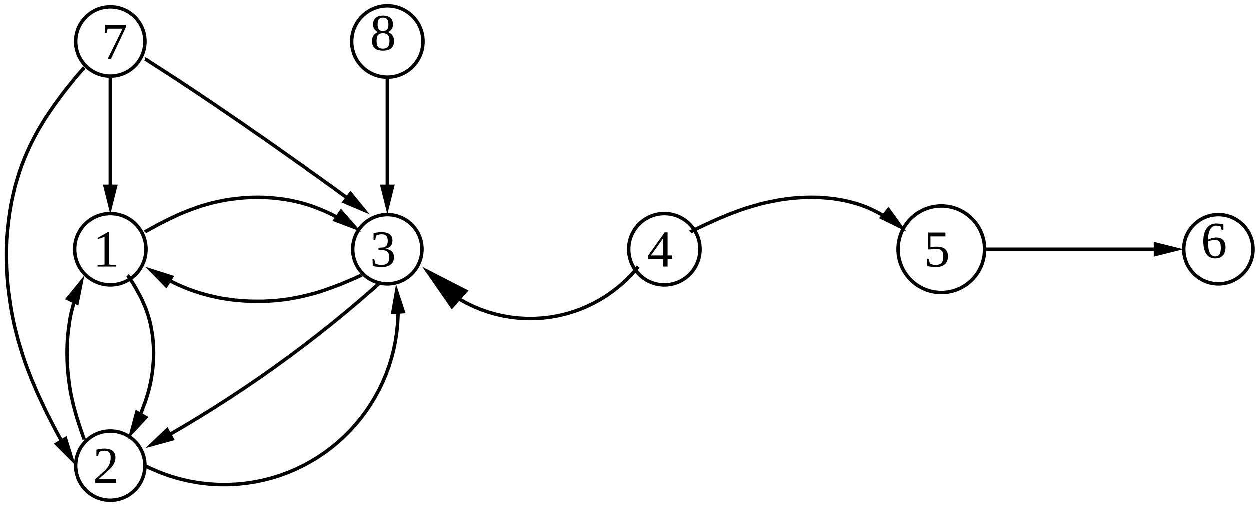
Def. Consider a graph of a biochemical reaction network.
(Nodes, edges) = ((states, outflows, inflows), reactions).
A **special-cut-set** is a set of edges all to the same destination node(s) which, when these edges are deleted from the network, result in a graph without path from the inflows to the outflow.

Problem 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.

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 Control steady outflow rate

Determine which enzymes (input components) effectively limit, but not necessarily zero, outflow rate $z_r \in \mathbb{R}_+^{n_z}$.

Def. Rational positive system. Fix $v_s \in \mathbb{R}_+^{n_v}$.
Assume $\forall u_s \in U$, $\exists ! z_s(u_s) \in \mathbb{R}_+^{n_z}$.

Required outflow rate $z_r \in \mathbb{R}_+^{n_z}$.

Set of required inputs for (steady input) $z_r \in \mathbb{R}_+^{n_z}$,

$$U(z_r) = \{u_s \in U | z_r \leq z_s(u_s)\}.$$

Infimal input for $z_r \in \mathbb{R}_+^{n_z}$,

$$\begin{aligned} u_{inf}(z_r) &= (u_{inf,1}(z_r), \ldots, u_{inf,m}(z_r)) \in \mathbb{R}_+^m, \\ u_{inf,k}(z_r) &= \inf_{u \in U(z_r)} u_k, \quad \forall k \in \mathbb{Z}_m. \end{aligned}$$

Index set of limiting input components

$$I(z_r, u) = \{k \in \mathbb{Z}_m | u_k = u_{inf,k}(z_r)\}, \quad z_r \in \mathbb{R}_+^{n_z}, \ u \in U(z_r).$$

Research problems

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

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The End!