Cycle structure in SR and DSR graphs: implications for multiple equilibria and stable oscillation in chemical reaction networks

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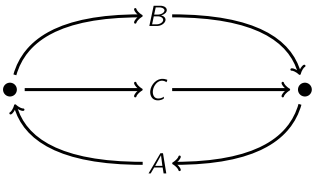
BioPPN, Braga, 21st June 2010

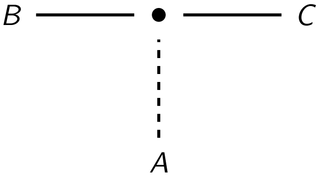
Representing chemical reactions

Consider the single reversible chemical reaction:

$$\mathrm{A} \rightleftharpoons \mathrm{B} + \mathrm{C}$$

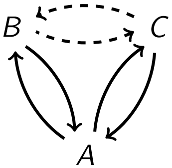


Petri net graph



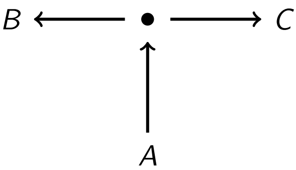
SR/DSR graph

I-graph



From Petri net graph to DSR graph I

$$\mathrm{A} \to \mathrm{B} + \mathrm{C}$$



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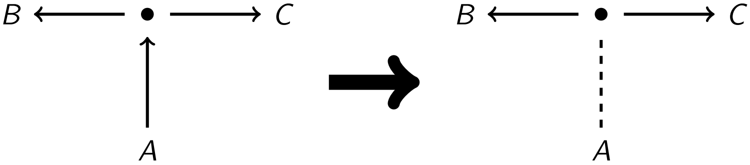

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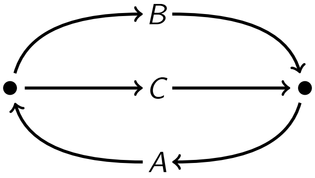

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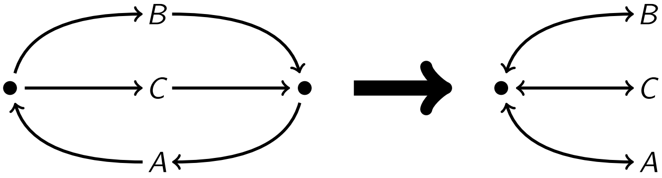

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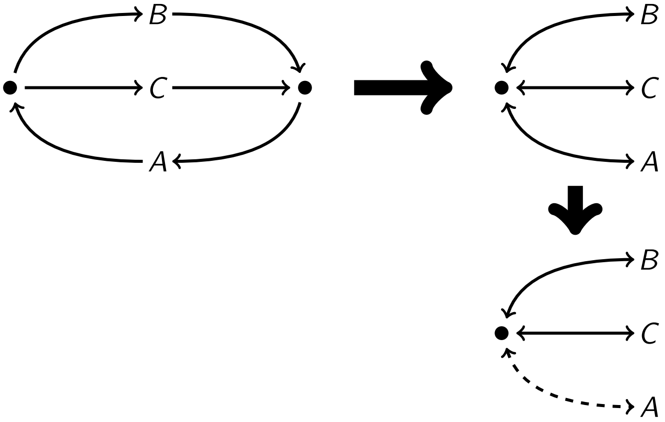

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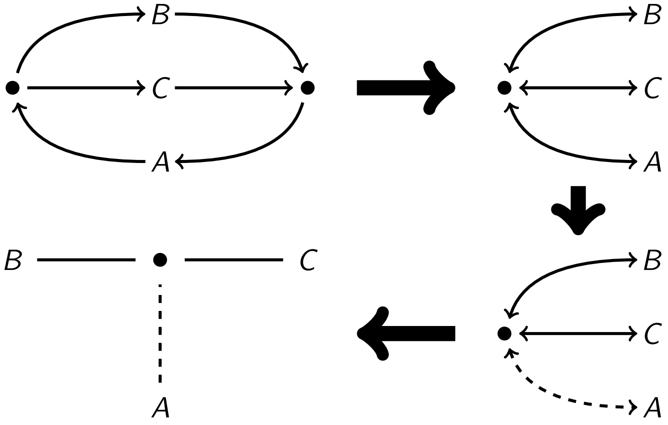


Terminology

- Place $\Leftrightarrow$ chemical species $\Leftrightarrow$ S-vertex
- Transition $\Leftrightarrow$ reaction $\Leftrightarrow$ R-vertex
- Arc weights $\Leftrightarrow$ stoichiometric coefficients $\Leftrightarrow$ edge labels
- marking $\Leftrightarrow$ concentration $\Leftrightarrow$?

Dynamical systems from CRNs

CRNs give dynamical systems of the form:

$$\dot{x} = \Gamma \, v(x)$$

reactant concentrations

stoichiometric matrix

reaction rates

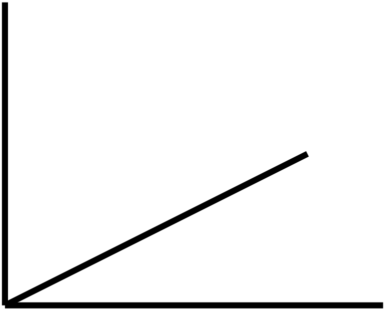
The Jacobian has a natural factorisation

$$J(x) = \Gamma \, Dv(x)$$

Stoichiometry classes

$\boxed{\dot{x} \;=\; \Gamma\; v(x)}$ $\quad \mathrm{Im}(\Gamma) =$ **stoichiometric subspace**.

Trajectories lie on the intersection of cosets of $\mathrm{Im}(\Gamma)$ with the nonnegative orthant, termed **stoichiometry classes**.



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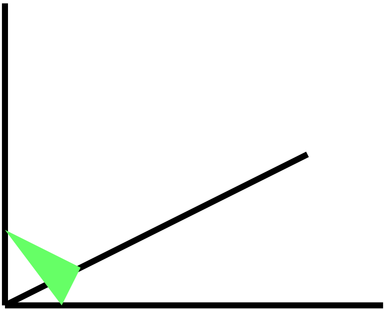

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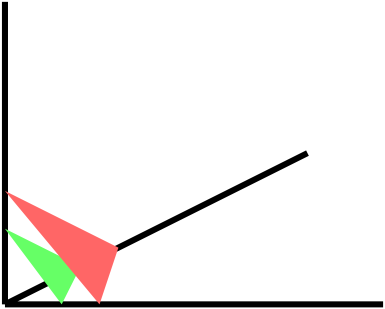

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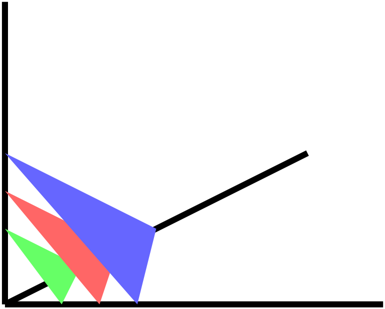

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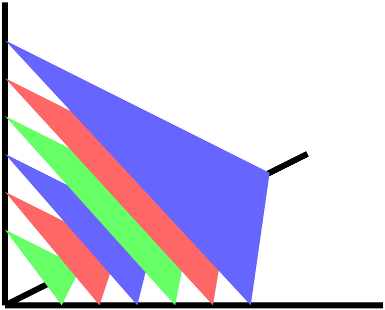

Jacobian factorisation

$$\dot{x} = \Gamma v(x)$$

$$J(x) = \Gamma \; Dv(x)$$

This Jacobian factorisation is the starting point for much of modern CRN theory. Under mild physical assumptions,

$$\Gamma_{ij} = 0 \Rightarrow Dv_{ji} = 0 \quad \text{and} \quad \Gamma_{ij} Dv_{ji} \leq 0 \qquad (\mathbf{N1C})$$

$$\Gamma = \begin{bmatrix} 0 & * & * \\ - & * & - \\ * & * & + \end{bmatrix} \quad -Dv^T = \begin{bmatrix} 0 & * & * \\ 0 & * & - \\ * & * & + \end{bmatrix}$$

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SR/DSR graphs

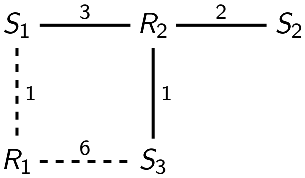
Formal construction: SR graphs and matrices

We can associate with any matrix an object termed an SR graph. The core structure is a

- bipartite graph
- with signs on its edges
- and labels on its edges

For example

$$\begin{bmatrix} -1 & 3 \\ 0 & 2 \\ -6 & 1 \end{bmatrix} \Leftrightarrow$$



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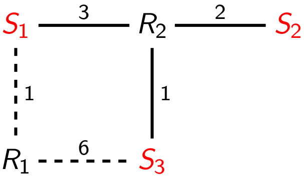

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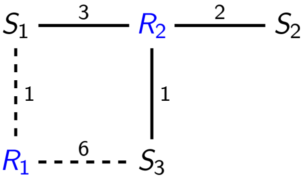

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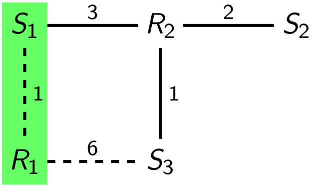

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Given a matrix and a sign-pattern of the same dimension we can construct an object termed a DSR graph.

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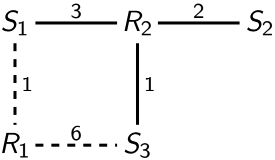
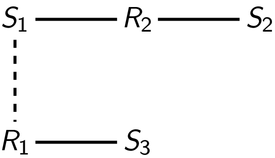


$$\begin{bmatrix} - & + \\ 0 & + \\ + & 0 \end{bmatrix}$$



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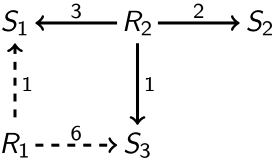

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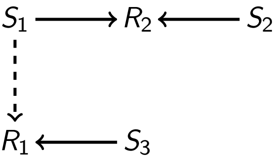

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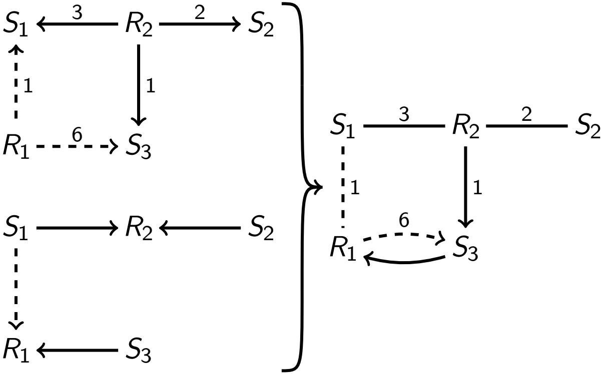

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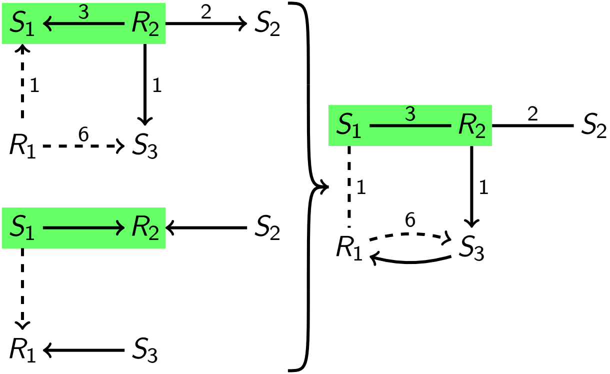

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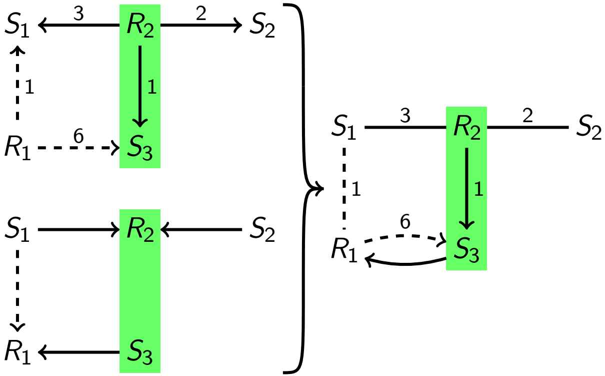

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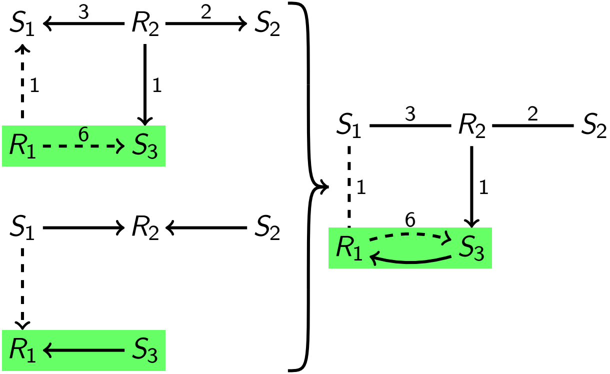


DSR graph for a CRN

$$\dot{x} = \Gamma v(x)$$

$$J(x) = \Gamma \; Dv(x)$$

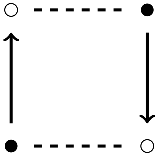
Use the matrix Γ and the sign pattern of $-Dv^T$ to construct the DSR graph at each x.

Cycles in DSR graphs: e-cycles and o-cycles

Since all edges in a DSR graph are signed, all cycles have a sign. Define the **parity** of any cycle E to be

$$P(E) := (-1)^{|E|/2}\mathrm{sign}(E).$$

All cycles have even length and so $P(E)$ is defined. E is an **e-cycle** if $P(E) = 1$, and an **o-cycle** if $P(E) = -1$.



This is an e-cycle, because

$$(\#\text{ edges})/2 \;+\; \#\text{ odd edges} = 4$$

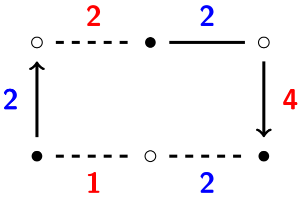
which is even.

Cycles in DSR graphs: s-cycles

We define the **value** of an edge to be its edge label. When all edges e_i in a cycle $C = [e_1, e_2, \ldots, e_{2r}]$ have an edge-label, we can define:

$$\mathrm{s}(C) = \left| \prod_{i=1}^{r} \mathrm{val}(e_{2i-1}) - \prod_{i=1}^{r} \mathrm{val}(e_{2i}) \right| .$$

(This definition is independent of the starting point chosen on the cycle.) A cycle with $\mathrm{s}(C) = 0$ is termed an **s-cycle**.

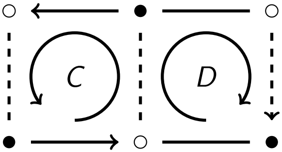


This cycle is an s-cycle, because

$$1 \times 2 \times 4 = 2 \times 2 \times 2.$$

Cycles in DSR graphs: S-to-R intersection

S-to-R intersection between cycles. Two cycles in a DSR graph are said to have S-to-R intersection if they have compatible orientation, and moreover each component of their intersection has odd length, i.e. it is either an S-to-R path or an R-to-S path.



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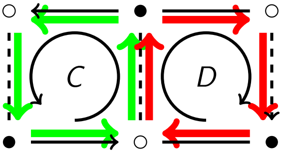

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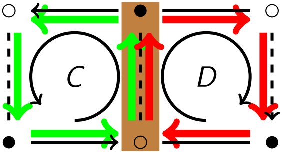

Cycles C and D have S-to-R intersection.

Main injectivity result

Condition (∗): All e-cycles in a DSR graph are s-cycles, and no two e-cycles have S-to-R intersection.
Condition (∗∗): A DSR graph contains no e-cycles.

Then the associated CRN cannot have multiple nondegenerate positive equilibria on any stoichiometry class.

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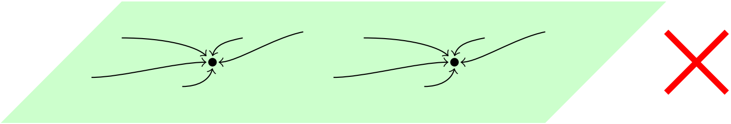
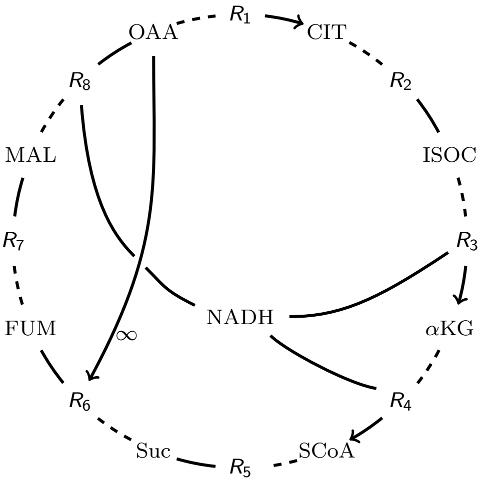


A nontrivial example: the TCA cycle



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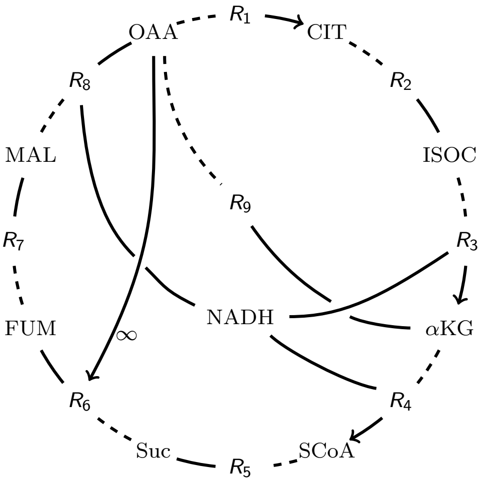

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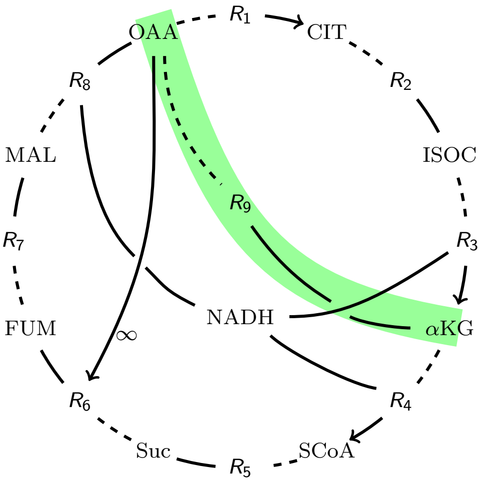


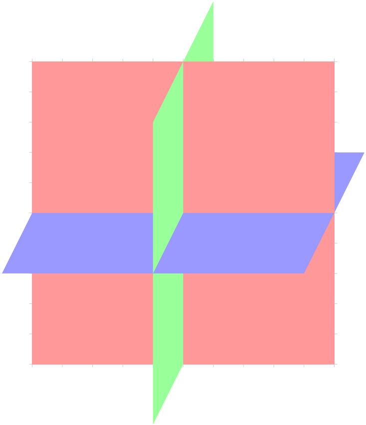
Theme 2: monotonicity

A function f is monotone, or order preserving, if

$$x \leq y \Rightarrow f(x) \leq f(y)$$

If the evolution of a dynamical system preserves some order, then this has various dynamical implications. For example, attracting periodic orbits are ruled out, except perhaps on the boundary of the state space.

Proper cones



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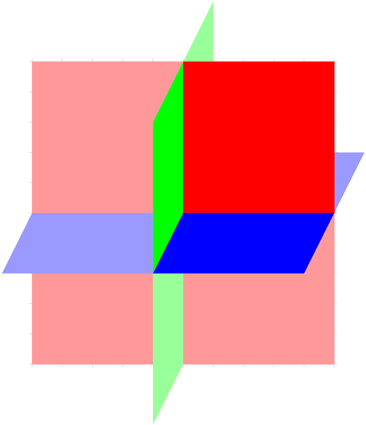

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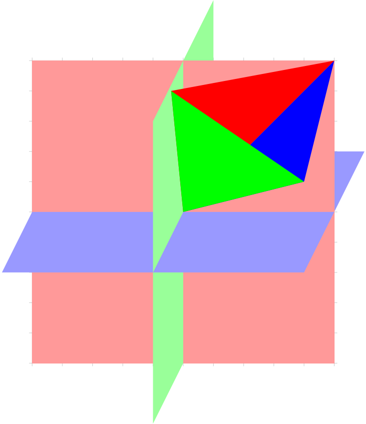

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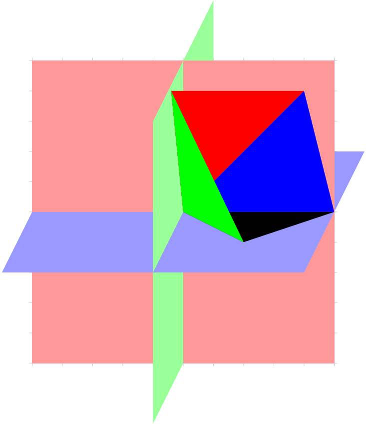

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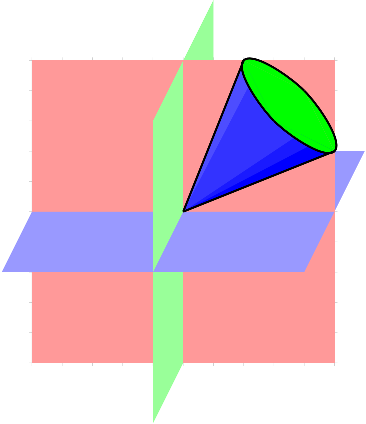

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general

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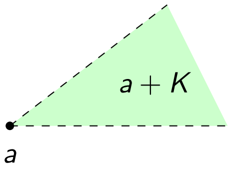

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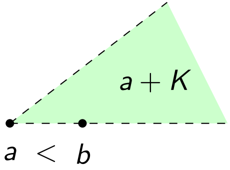

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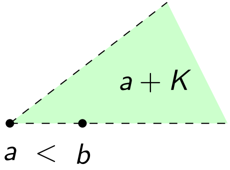
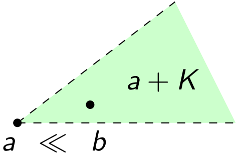
- $a < b \Leftrightarrow a \leq b$ and $a \neq b$



- $a \ll b \Leftrightarrow b \in a + \mathrm{int}\ K$



A monotone dynamical system

Let K be a proper cone in $\mathbb{R}^n$ with $K \supset Y$. From now on, all inequalities are with respect to the ordering defined by K.

A local semiflow ϕ is **monotone** with respect to K, if

$$x > y \Rightarrow \phi_t(x) > \phi_t(y)$$

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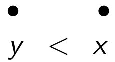

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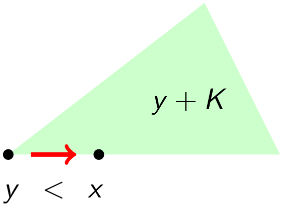

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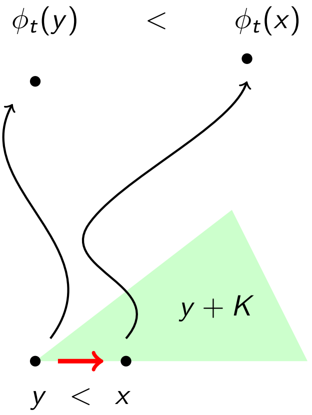

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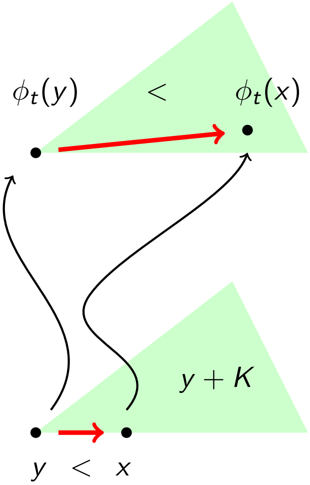


Monotonicity

Consider any ODE

$$\dot{x} = f(x)$$

A sufficient condition for monotonicity of the associated local semiflow with respect to some cone K is

$$\boxed{\mathbf{y} \in K \Rightarrow \exists \alpha \in \mathbb{R} \text{ s.t. } Df\,\mathbf{y} + \alpha\mathbf{y} \in K} \qquad (***)$$

If K is polyhedral, then $(***)$ is both necessary and sufficient for monotonicity.

Consider a CRN, and define local coordinates on some invariant set (perhaps a stoichiometry class). When does the Jacobian of the system in local coordinates fulfil $(***)$?

Sufficient condition

For N1C systems, a sufficient condition for monotonicity of the local semiflow on each stoichiometry class is:

1. Γ has linearly independent columns
2. SR graph has maximum S-degree 2
3. SR graph contains no o-cycles.

This condition **not** necessary.

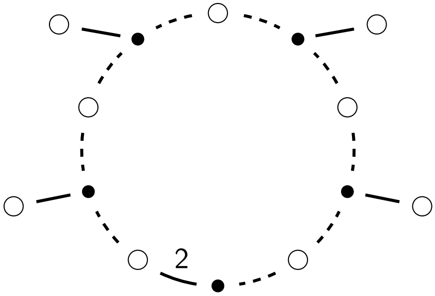
Example: system and stoichiometric matrix

$$\begin{array}{c} A_1 + A_2 \rightleftharpoons B_1 \\ A_2 + A_3 \rightleftharpoons B_2 \\ A_3 + A_4 \rightleftharpoons B_3 \\ A_4 + A_5 \rightleftharpoons B_4 \\ A_5 \rightleftharpoons 2A_1 \end{array}$$

$$\Gamma = \begin{pmatrix} -1 & 0 & 0 & 0 & 2 \\ -1 & -1 & 0 & 0 & 0 \\ 0 & -1 & -1 & 0 & 0 \\ 0 & 0 & -1 & -1 & 0 \\ 0 & 0 & 0 & -1 & -1 \\ 1 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 \end{pmatrix}$$

1. Γ is easily checked to have rank 5.

$$A_1 + A_2 \rightleftharpoons B_1$$
$$A_2 + A_3 \rightleftharpoons B_2$$
$$A_3 + A_4 \rightleftharpoons B_3$$
$$A_4 + A_5 \rightleftharpoons B_4$$
$$A_5 \rightleftharpoons 2A_1$$



2. The SR graph has maximum S-degree 2 and no o-cycles. So the system is order preserving.

Summary and conclusions

1. There are many similarities, but also some important differences, between PT graphs and SR graphs, as these have evolved to make different kinds of claims.
2. SR/DSR graphs can be used to make rigorous claims about injectivity and monotonicity of associated continuous time, continuous state, dynamical systems.
3. The extent to which such theory can be applied to discrete event systems is unclear.
4. Work in this area still has a long way to go.

Some references

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