

Delft Center for Systems and Control



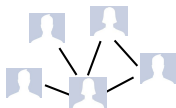
**Control-theoretic tools for the structural  
analysis of biological systems**

**Giulia Giordano**

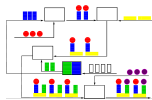
Università degli Studi di Padova, Control Days 2019

May 10, 2019

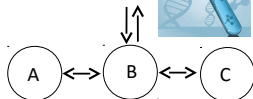
# Dynamical networks



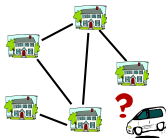
social networks



production and  
distribution systems

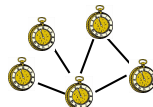


(bio)chemical processes

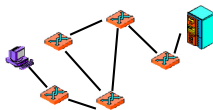


traffic management

## DYNAMICAL NETWORKS



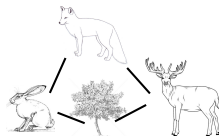
synchronization



telecommunication / data  
communication networks

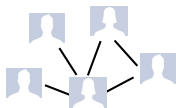


water distribution  
networks

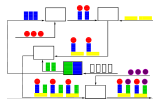


biological systems  
and ecosystems

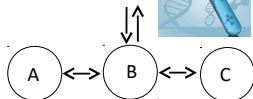
# Dynamical networks: graph representation



social networks



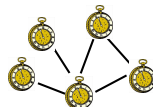
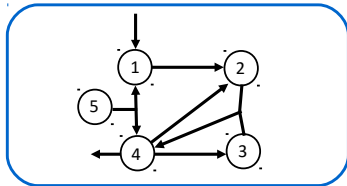
production and distribution systems



(bio)chemical processes



traffic management



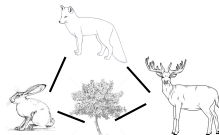
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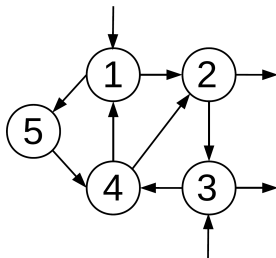


water distribution networks



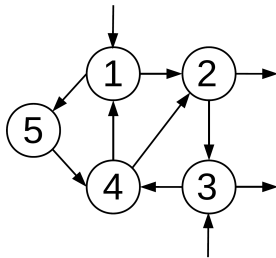
biological systems and ecosystems

Graph:

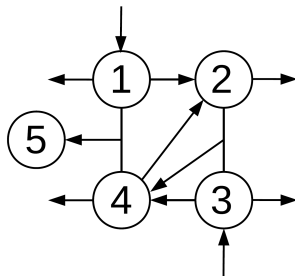


# Structure

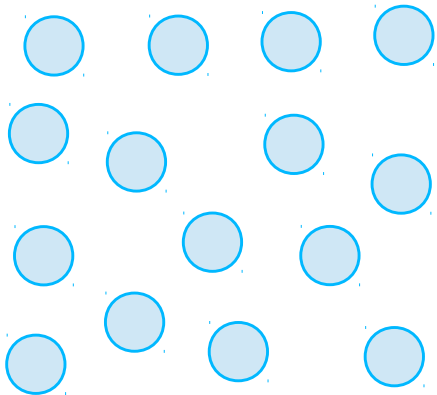
Graph:



Hypergraph:

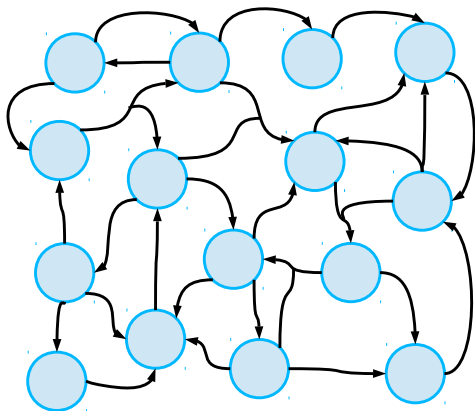


# Graph representation: nodes



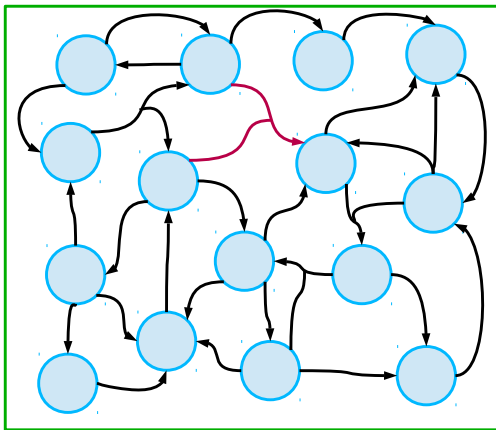
Nodes: Agents

# Graph representation: arcs



Arcs: Interactions

# Local interactions $\Rightarrow$ Global behaviour



Local Interactions

Global Behaviour



# Dynamical networks: structural analysis and control

A twofold goal

**Structural Analysis  
of Dynamical  
Networks**

**Network-  
Decentralised  
Control Synthesis**

...especially meant for...

**Natural Systems**

**Man-made Systems**

## Structural analysis

- Looking for **structural, parameter-free properties**.

# Structural: more than robust

## Definition

$\mathcal{F}$ : family of systems,  $\mathcal{P}$ : relevant property

$\mathcal{P}$  is **robust** if any element  $f \in \mathcal{F}$  has the property  $\mathcal{P}$

Moreover,  $\mathcal{P}$  is **structural** if  $\mathcal{F}$  is specified by a structure without numerical bounds

## Example

Let  $a, b, c, d > 0$ .

$$A_1 = \begin{bmatrix} -a & b \\ c & -d \end{bmatrix} \quad A_2 = \begin{bmatrix} -a & -b \\ c & -d \end{bmatrix}$$

- $A_1$  is robustly stable if  $0 \leq b, c \leq 1$ ,  $2 \leq a, d \leq 3$ ;
- Conversely  $A_2$  is structurally stable.

# Structural properties

- Parameter-free approach: **system structure**

## Structural analysis

Explain behaviours based on the system inherent **structure** (graph)

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- **Structurally assess fundamental properties**

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Satisfied by **all** the systems of a **family** specified by a **structure**, without numerical bounds.

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Explain behaviours based on the system inherent **structure** (graph)

- **Structurally assess fundamental properties**

## Structural properties

Satisfied by **all** the systems of a **family** specified by a **structure**, without numerical bounds.

- Applications to **biochemical systems**

## Structural properties in nature

Biological systems → extremely **robust**: fundamental properties **preserved** despite **huge uncertainties and parameter variations**.

# (Bio)chemical reaction networks

**Species:**  $A, B, C$

**Concentrations:**  $a, b, c$

**ODE system:**

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Species:  $A, B, C$

Reactions:  $\emptyset \xrightarrow{a_0} A$

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ODE system:

$$\dot{a} = a_0$$

$$\dot{b} =$$

$$\dot{c} =$$



# (Bio)chemical reaction networks

Species:  $A, B, C$

Reactions:  $\emptyset \xrightarrow{a_0} A, A \xrightarrow{g_a} B + C$

Concentrations:  $a, b, c$

ODE system:

$$\dot{a} = a_0 - g_a(a)$$

$$\dot{b} = g_a(a)$$

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$$\dot{a} = a_0 - g_a(a) - g_{ac}(a, c)$$

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$$\begin{bmatrix} \dot{a} \\ \dot{b} \\ \dot{c} \end{bmatrix} = \underbrace{\begin{bmatrix} -1 & -1 & 0 \\ 1 & 0 & -1 \\ 1 & -1 & 0 \end{bmatrix}}_{\text{stoichiometric matrix}} \underbrace{\begin{bmatrix} g_a(a) \\ g_{ac}(a, c) \\ g_b(b) \end{bmatrix}}_{\text{rate vector}} + \underbrace{\begin{bmatrix} a_0 \\ 0 \\ 0 \end{bmatrix}}_{\text{input vector}}$$

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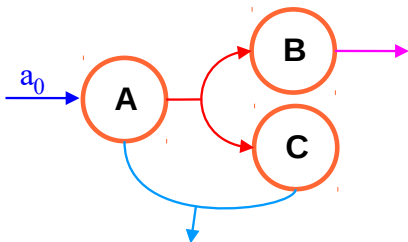
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$$\dot{x}(t) = Sg(x(t)) + g_0, \quad g \text{ monotonic functions}$$

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## Local BDC-decomposition

The Jacobian can be decomposed as:

$$J(x) = \frac{\partial Sg(x)}{\partial x} = B\Delta(x)C, \quad \Delta(x) = \text{diag} \left\{ \left| \frac{\partial g_k}{\partial x_h} \right| \right\} \succ 0.$$

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## Global BDC-decomposition

Given the equilibrium  $\bar{x}$  ( $0 = Sg(\bar{x}) + g_0$ ),  $z \doteq x - \bar{x}$ .

The system can be rewritten as:

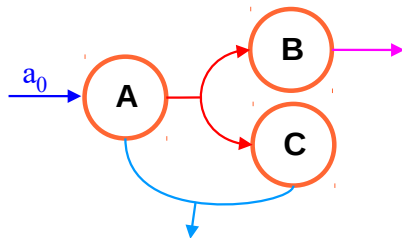
$$\dot{z}(t) = Sg(z(t) + \bar{x}) - Sg(\bar{x}) = [BD(z)C] z(t), \quad D(z) \succ 0.$$

For any vector  $\bar{x}$

$$\begin{aligned} Sg(x) - Sg(\bar{x}) &= \left[ \int_0^1 J(\bar{x} + \sigma(x - \bar{x})) d\sigma \right] (x - \bar{x}) \\ &= B \left[ \int_0^1 D(\bar{x} + \sigma(x - \bar{x})) d\sigma \right] C (x - \bar{x}) \end{aligned}$$

# BDC-decomposition: example

$$\begin{bmatrix} \dot{a} \\ \dot{b} \\ \dot{c} \end{bmatrix} = \begin{bmatrix} -1 & -1 & 0 \\ 1 & 0 & -1 \\ 1 & -1 & 0 \end{bmatrix} \begin{bmatrix} g_a(a) \\ g_{ac}(a, c) \\ g_b(b) \end{bmatrix} + \begin{bmatrix} a_0 \\ 0 \\ 0 \end{bmatrix}$$



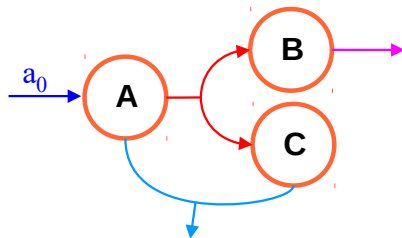
$$\dot{z} = BDCz$$

$$D = \text{diag} \left\{ \frac{\partial g_a}{\partial a}, \frac{\partial g_{ac}}{\partial a}, \frac{\partial g_{ac}}{\partial c}, \frac{\partial g_b}{\partial b} \right\} \succ 0$$

$$B = \begin{bmatrix} -1 & -1 & -1 & 0 \\ 1 & 0 & 0 & -1 \\ 1 & -1 & -1 & 0 \end{bmatrix} \quad \text{and} \quad C = \begin{bmatrix} 1 & 0 & 0 \\ 1 & 0 & 0 \\ 0 & 0 & 1 \\ 0 & 1 & 0 \end{bmatrix}$$

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Structure: parameter free, no numerical bounds.

## Assumption

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*Monotonic functions  $g$  and dissipative reactions  $\frac{\partial \dot{x}_i}{\partial x_i} < 0$*

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Matrix  $S$  and qualitative information on  $g(\cdot) \Leftrightarrow$  structure  $\Leftrightarrow$  graph.  
A structural result depends on the associated graph and stability must hold for all networks with the same graph.

How can we **structurally** assess **stability**?

F. Blanchini and G. Giordano, "Piecewise-linear Lyapunov Functions for Structural Stability of Biochemical Networks", *Automatica*, 2014

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We exploit the *BDC*-decomposition! Structurally  $\Leftrightarrow$  for **any**  $D_i > 0$

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Idea:  $D(z(t)) \rightarrow D(t)$

Absorb the nonlinear system in a Linear Differential Inclusion

$$\dot{z}(t) = [BD(t)C] z(t), \quad D(t) \succ 0. \quad (LDI)$$

Any trajectory of the original system is also a trajectory of (LDI).

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To analyse stability we can assume  $0 \leq D_i \leq 1$ .

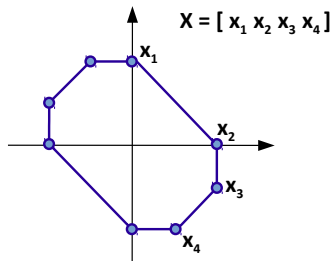
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# Structurally assess stability: polyhedral Lyapunov functions

$$V_X(x) = \inf \{ \|w\|_1 : Xw = x \}$$

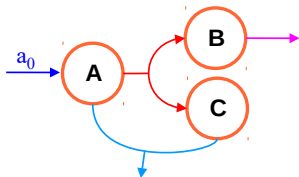
$X$  full row rank

Based on a discrete difference inclusion, a numerical algorithm computes the **unit ball of the polyhedral Lyapunov function** (if any) via set iteration.

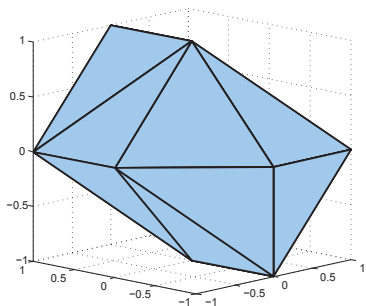


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# Structurally assess stability: example



The procedure converges  $\implies$  structurally stable



# Local and global asymptotic stability

**Problem:** For  $\dot{x} = 0$  the procedure stops successfully!

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## Proposition

*If the procedure produces a PLF, then there exists an equilibrium that is locally asymptotically stable iff BDC is robustly nonsingular, namely*

$$\det[-BDC] > 0$$

*for all  $D > 0$ . We have a vertex-type algorithm.*

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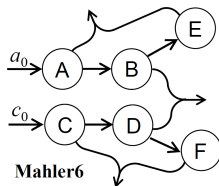
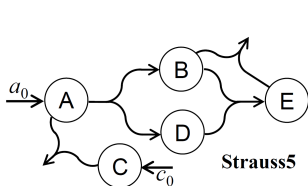
## Proposition

*Let  $\varepsilon > 0$  (Infinitesimal dissipativity):*

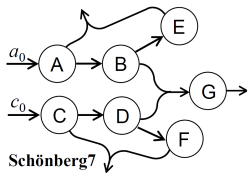
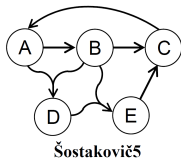
$$\dot{x} = -\varepsilon x + Sg(x) + g_0$$

*A PLF implies that there exists an equilibrium that is globally asymptotically stable. **With  $\varepsilon = 0$ , the equilibrium is globally asymptotically stable iff BDC is robustly nonsingular.***

## Networks with positive test outcome

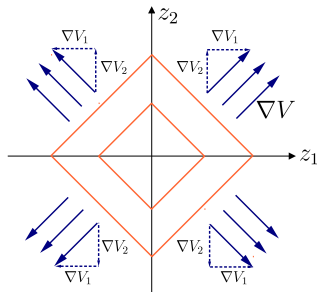
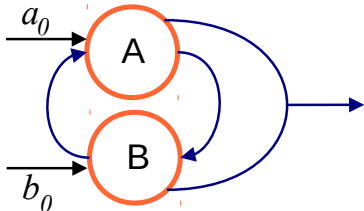


## Networks with negative test outcome





# Structurally assess stability: polyhedral... why?



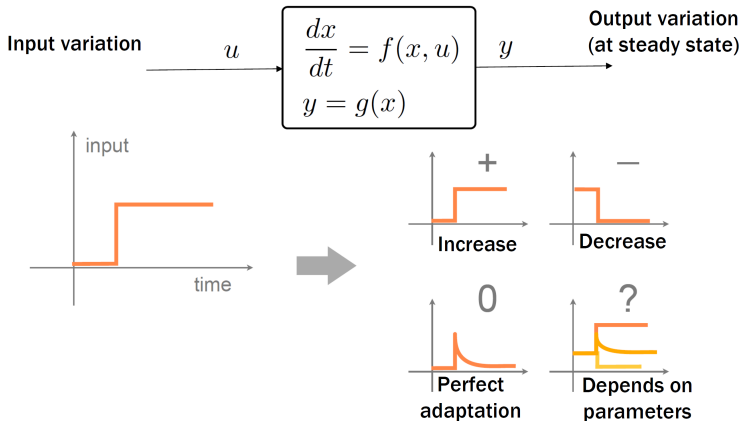
## Claim

The only **structural** Lyapunov function is **polyhedral**!

There are no other rate-independent Lyapunov functions.

F. Blanchini, G. Giordano, "Polyhedral Lyapunov functions structurally ensure global asymptotic stability of dynamical networks iff the Jacobian is non-singular", *Automatica*, 2017

# Structural steady-state analysis: the influence matrix



G. Giordano, C. Cuba Samaniego, E. Franco, F. Blanchini, "Computing the Structural Influence Matrix for Biological Systems", *J. Math. Biol.*, 2015

# The structural influence matrix

## Structural influence of variable $j$ on variable $i$

Assuming stability,  $\Sigma_{ij} \in \{+, -, 0, ?\}$ : sign of the steady-state variation of  $x_i(\infty)$  due to a step input acting on  $x_j$ .

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## For systems admitting a $BDC$ decomposition

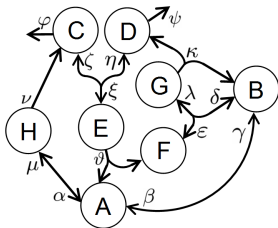
$$\Sigma_{ij} = H_i(-BDC)^{-1}E_j,$$

$H$  output matrix,  $E$  input matrix  $\rightarrow$  efficient **vertex algorithm**

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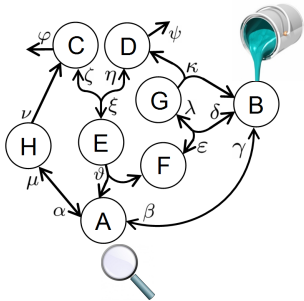
Network from Shinar&Feinberg (2010)



+	+	+	+	+	+	+	+
+	+	+	+	+	+	+	+
+	+	+	0	+	0	+	+
0	0	0	+	+	+	+	0
+	+	+	+	+	+	+	+
?	?	?	?	?	?	?	?
+	+	+	+	+	+	+	+
+	+	+	+	+	+	+	+

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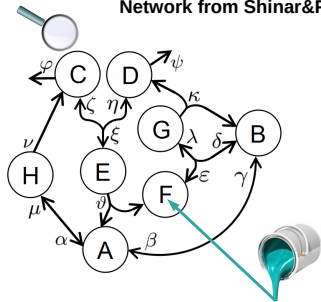
Network from Shinar&Feinberg (2010)



+	+	+	+	+	+	+	+
+	+	+	+	+	+	+	+
+	+	+	0	+	0	+	+
0	0	0	+	+	+	+	0
+	+	+	+	+	+	+	+
?	?	?	?	?	?	?	?
+	+	+	+	+	+	+	+
+	+	+	+	+	+	+	+

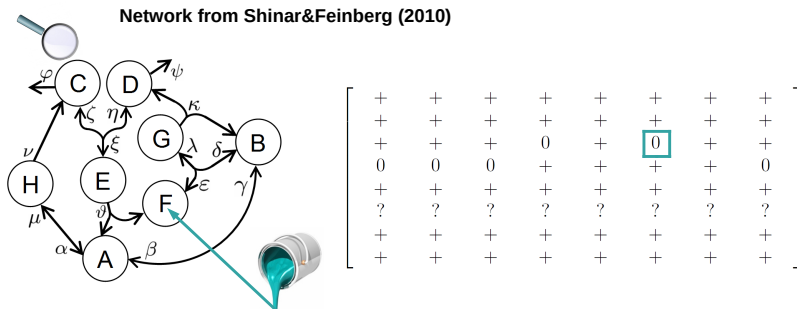
# The structural influence matrix

Network from Shinar&Feinberg (2010)



+	+	+	+	+	+	+	+
+	+	+	+	+	+	+	+
+	+	+	0	+	0	+	+
0	0	0	+	+	+	+	0
+	+	+	+	+	+	+	+
?	?	?	?	?	?	?	?
+	+	+	+	+	+	+	+
+	+	+	+	+	+	+	+

# The structural influence matrix



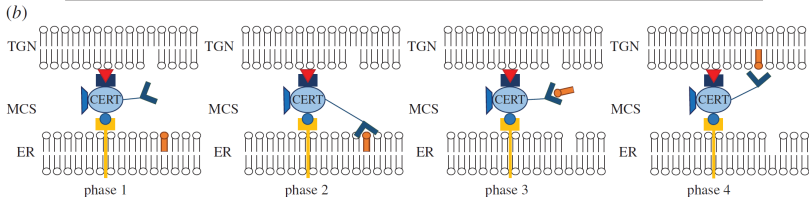
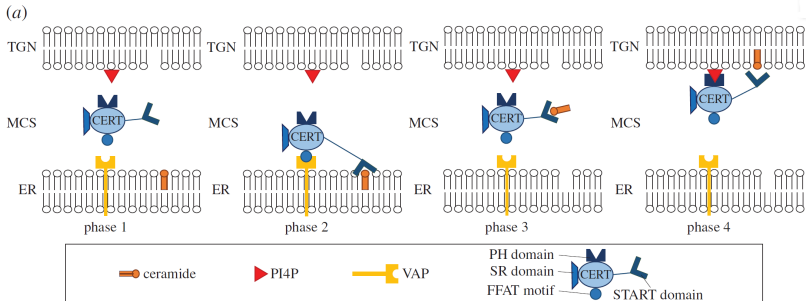
**Can be important for model falsification!**

Compare structural influence matrix and experimental results!



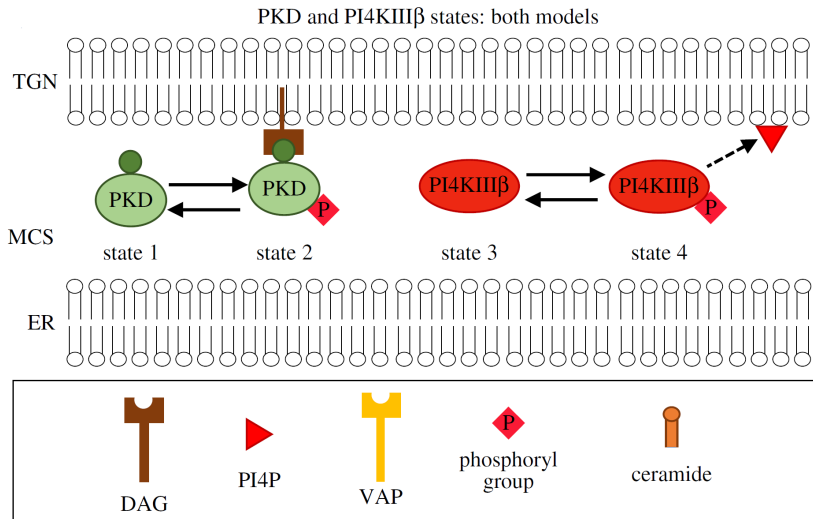
# Intracellular ceramide transport: a case study

## Short distance shuttle model



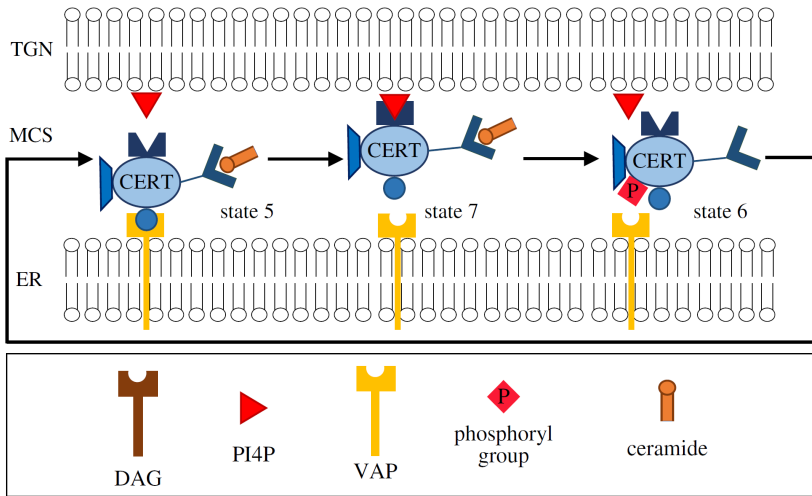
## Neck swinging model

# Intracellular ceramide transport: a case study

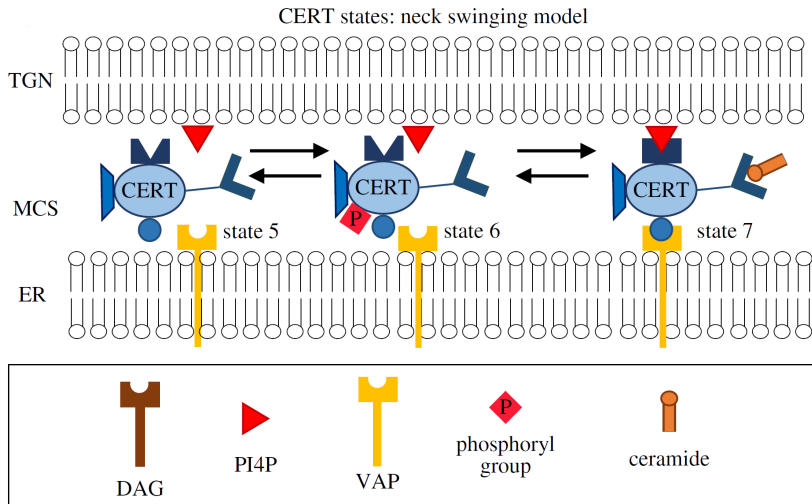


# Intracellular ceramide transport: a case study

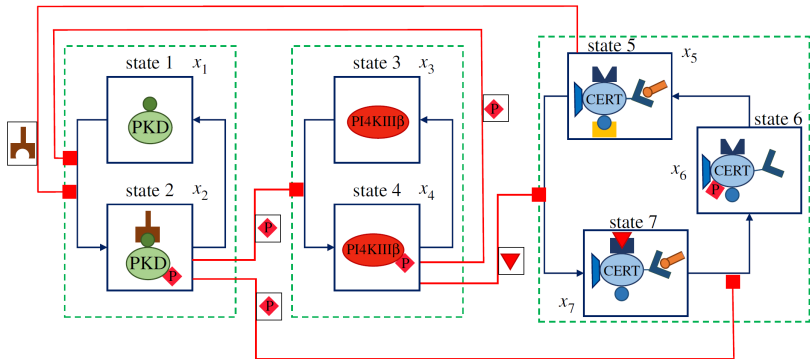
CERT states: short distance shuttle model



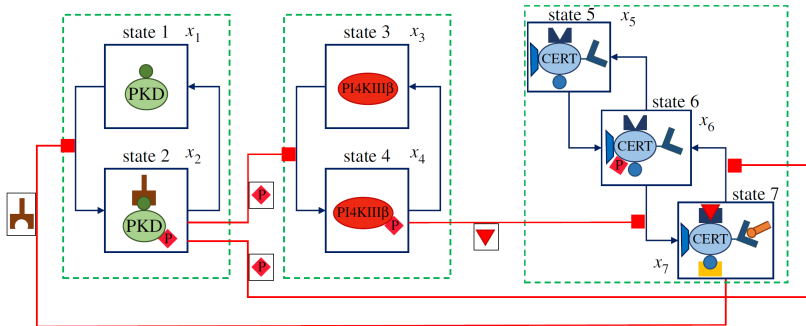
# Intracellular ceramide transport: a case study



# Short distance shuttle model



# Neck swinging model



# Model comparison: influence matrices

$$\Sigma_{\text{SDS}} = \begin{bmatrix} ? & ? & ? & ? & - & - & - \\ + & + & ? & ? & + & + & + \\ - & - & ? & ? & - & - & - \\ + & + & ? & ? & + & + & + \\ ? & ? & ? & ? & ? & ? & ? \\ + & + & ? & ? & ? & ? & ? \\ ? & ? & ? & ? & ? & ? & ? \end{bmatrix} \quad \text{and} \quad \Sigma_{\text{NS}} = \begin{bmatrix} ? & ? & - & - & - & - & - \\ + & + & + & + & + & + & + \\ - & - & ? & ? & - & - & - \\ + & + & + & + & + & + & + \\ ? & ? & - & - & ? & ? & ? \\ ? & ? & - & - & ? & ? & ? \\ ? & ? & + & + & + & + & + \end{bmatrix}$$

**NOT CONFLICTING!**

# Model comparison: input influence matrices

Inputs:

$u_1$  increases the flow from  $x_1$  to  $x_2$

$u_2$  increases the flow from  $x_2$  to  $x_1$

$$\begin{array}{l} \text{SDS} \end{array} \begin{array}{c} x_1 \{ \\ x_2 \{ \\ x_3 \{ \\ x_4 \{ \\ x_5 \{ \\ x_6 \{ \\ x_7 \{ \end{array} \begin{array}{cc} \overbrace{\quad}^{u_1} & \overbrace{\quad}^{u_2} \\ \left[ \begin{array}{cc} - & + \\ + & - \\ - & + \\ + & - \\ ? & ? \\ + & - \\ ? & ? \end{array} \right] \end{array} \quad \text{and} \quad \text{NS} \begin{array}{c} x_1 \{ \\ x_2 \{ \\ x_3 \{ \\ x_4 \{ \\ x_5 \{ \\ x_6 \{ \\ x_7 \{ \end{array} \begin{array}{cc} \overbrace{\quad}^{u_1} & \overbrace{\quad}^{u_2} \\ \left[ \begin{array}{cc} - & + \\ + & - \\ - & + \\ + & - \\ ? & ? \\ ? & ? \\ ? & ? \end{array} \right] \end{array}$$



# Model comparison: flow influence matrices

## Short distance shuttle model

$$\Phi_{\text{SDS}} = \lambda x_6 + x_7 g_2(x_2) + x_5 g_4(x_4)$$
$$\Phi_{\text{SDS}} \left\{ \begin{array}{ccccccccc} \overbrace{u_1} & \overbrace{u_2} & \overbrace{x_1} & \overbrace{x_2} & \overbrace{x_3} & \overbrace{x_4} & \overbrace{x_5} & \overbrace{x_6} & \overbrace{x_7} \\ + & - & + & + & ? & ? & ? & ? & ? \end{array} \right\}$$

## Neck swinging model

$$\Phi_{\text{NS}} = x_6 g_4(x_4) + x_7 g_2(x_2)$$
$$\Phi_{\text{NS}} \left\{ \begin{array}{ccccccccc} \overbrace{u_1} & \overbrace{u_2} & \overbrace{x_1} & \overbrace{x_2} & \overbrace{x_3} & \overbrace{x_4} & \overbrace{x_5} & \overbrace{x_6} & \overbrace{x_7} \\ + & - & + & + & + & + & + & + & + \\ x_7 \left\{ \begin{array}{ccccccccc} ? & ? & ? & ? & + & + & + & + & + \end{array} \right. \end{array} \right\}$$

# CERT-mediated ceramide transfer: wrap up

**Both models:** flow-inducing systems; flows between pairs of species are tuned by the concentrations of other species, and suitable external inputs can **structurally** regulate ceramide transfer

**Short distance shuttle:** amount of transferred ceramide **structurally tuned by PKD**, both directly and indirectly, in a **coherent feed-forward loop** motif

**Neck-swinging:** amount of transferred ceramide **structurally tuned by active PI4KIII $\beta$** .

**Active PKD** directly inhibits ceramide transfer and indirectly promotes it: **incoherent feed-forward loop**. It **structurally favours CERT mobility in the cytosol**. Possible explanation: if CERT bound to ER+TGN in the same location, area soon depleted of ceramide; increased mobility in the cytosol helps it detach and bind again where ceramide more abundant.

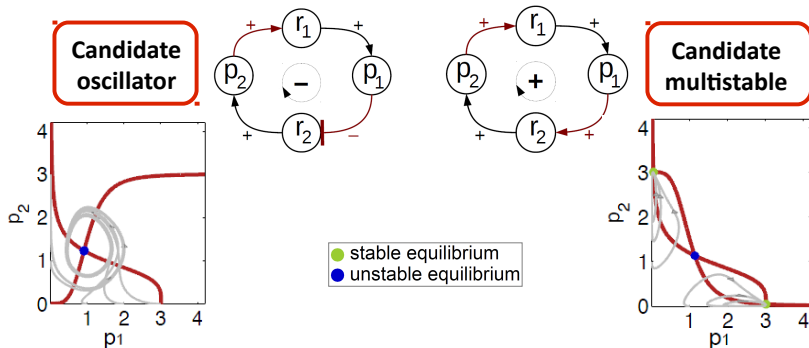
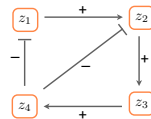
The influences in the two models are **not conflicting**.

Often structurally determined steady-state signs, which can **help falsify the models against experimental traces**.

G. Giordano, "CERT-mediated ceramide transfer is a structurally tunable flow-inducing mechanism with structural feed-forward loops", *Royal Society Open Science*, 2018

# Oscillatory/multistationary systems: structural classification

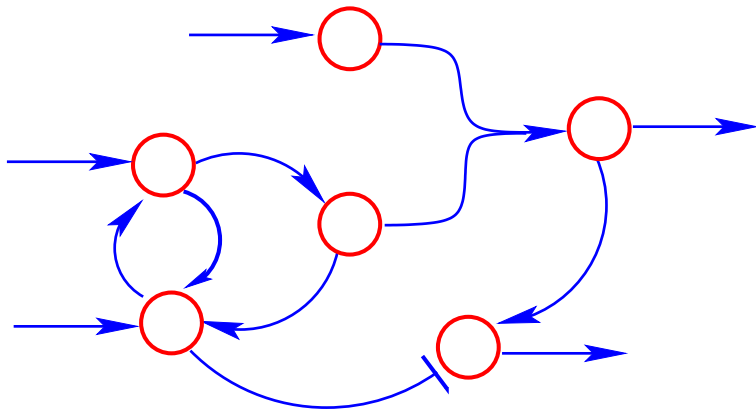
	Candidate oscillator	Candidate multistationary
Weak	A negative cycle exists	A positive cycle exists
Strong	All cycles are negative	All cycles are positive



F. Blanchini, E. Franco and G. Giordano, "A Structural Classification of Candidate Oscillators and Multistationary Biochemical Systems", *Bull. Math. Biol.*, 2014

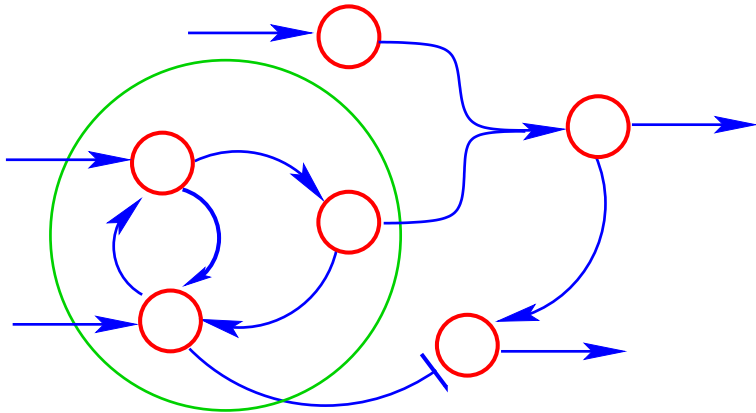
# Aggregation of monotone/PIR subsystems

We can recognize and aggregate subsystems that are stable  
Input-Output Monotone Systems  
or Positive Impulse Response Systems



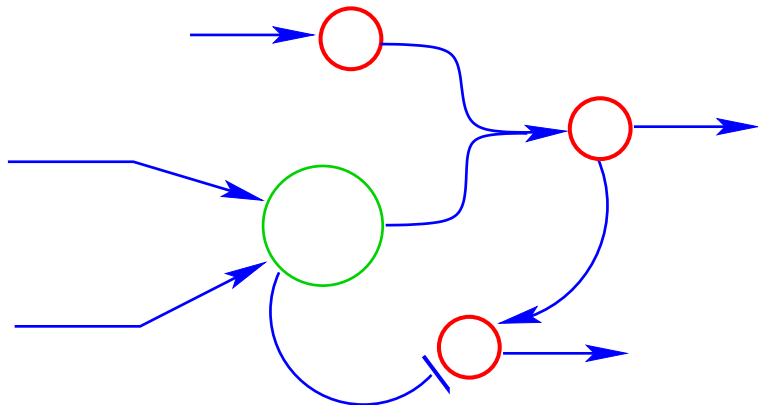
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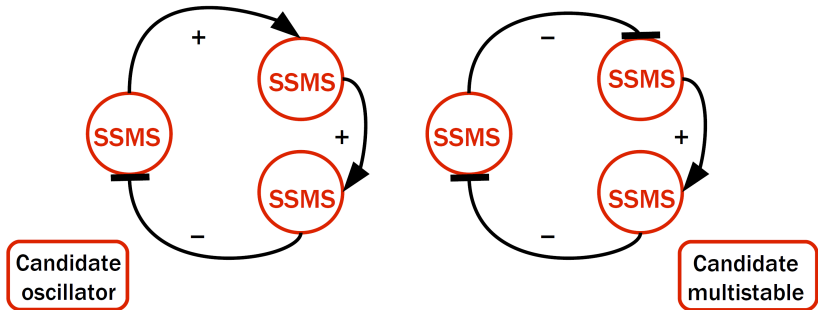
# Aggregation of monotone/PIR subsystems

The same results  
(classification, influence)  
hold for the aggregate system



# Oscillatory/multistationary aggregate monotone systems

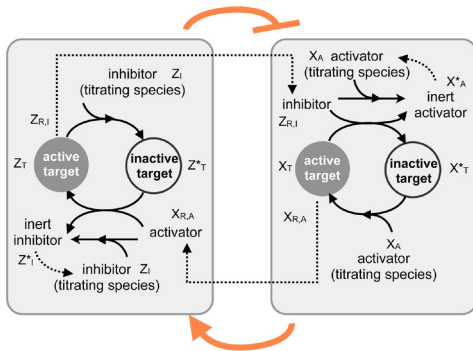
Analogous results for the **sign-definite interconnection** of **Structurally Stable Monotone Subsystems**



F. Blanchini, E. Franco and G. Giordano, "Structural Conditions for Oscillations and Multistationarity in Aggregate Monotone Systems", *IEEE CDC*, 2015



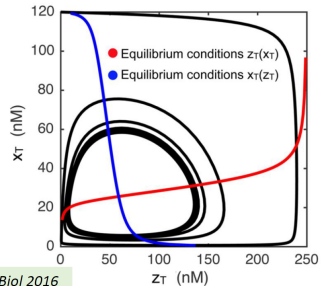
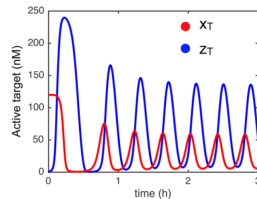
# Biomolecular clocks



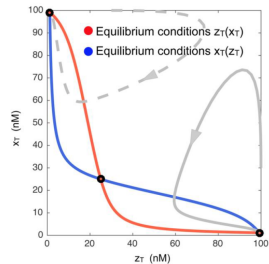
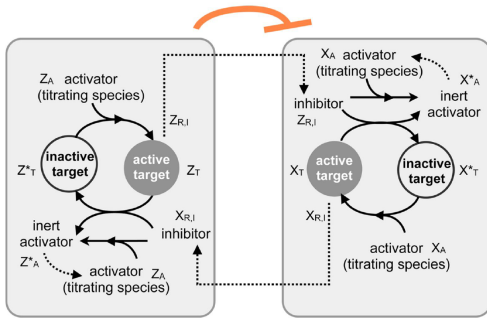
[Kim&Winfree]

C. Cuba Samaniego, G. Giordano, F. Blanchini, E. Franco, *J Biol Dyn* 2017

C. Cuba Samaniego, G. Giordano, J. Kim, F. Blanchini, E. Franco, *ACS Synth Biol* 2016



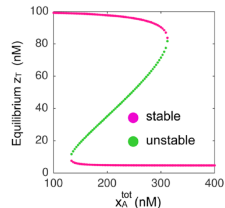
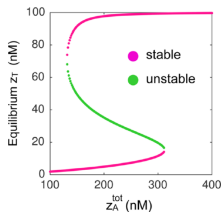
# Biomolecular switches



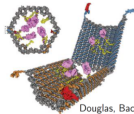
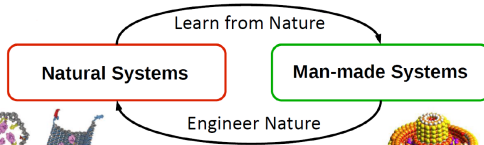
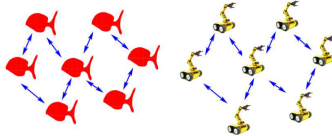
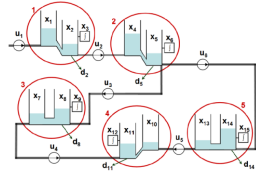
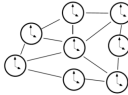
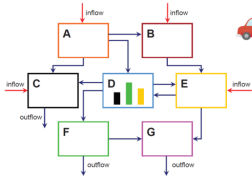
[Kim, White & Winfree]

E. Franco, G. Giordano, P.O. Forsberg, R.M. Murray, *ACS Synth Biol* 2014

C. Cuba Samaniego, G. Giordano, J. Kim, F. Blanchini, E. Franco, *ACS Synth Biol* 2016



# Learn from nature and engineer nature



Douglas, Bachelet, Church (2012)



Institute for Molecular Manufacturing 1997

Joint work with **Franco Blanchini**,  
Christian Cuba Samaniego, Elisa Franco

## Grazie!

Joint work with **Franco Blanchini**,  
Christian Cuba Samaniego, Elisa Franco

