54th IEEE Conference on Decision and Control
Osaka, Japan

December 15, 2015

Structural conditions for oscillations and multistationarity in aggregate monotone systems

Franco Blanchini, Elisa Franco, Giulia Giordano

Oscillatory and multistationary dynamics are ubiquitous

Oscillatory and **multistationary** dynamics are ubiquitous

Biological models plagued by **uncertainty**
Can we **robustly** assess their dynamic behaviour?

Oscillations and multistationarity in biological systems

Oscillatory and **multistationary** dynamics are ubiquitous

Biological models plagued by **uncertainty**
Can we **robustly** assess their dynamic behaviour?

Structural approach

Parameter-free criteria to evaluate possible **dynamic outcomes**

Oscillatory and **multistationary** dynamics are ubiquitous

Biological models plagued by **uncertainty**
Can we **robustly** assess their dynamic behaviour?

Structural approach

Parameter-free criteria to evaluate possible **dynamic outcomes**

Can the system **structurally** (independent of parameters) exhibit **oscillations** / **multistationarity**?

Framework

$$\dot{x}(t) = f(x(t)), \qquad x \in \mathbb{R}^n$$

Framework

$$\dot{x}(t) = f(x(t)), \qquad x \in \mathbb{R}^n$$

1. globally asymptotically bounded solutions $\Rightarrow$ **equilibrium**

Framework

$$\dot{x}(t) = f(x(t)), \qquad x \in \mathbb{R}^n$$

1. globally asymptotically bounded solutions $\Rightarrow$ **equilibrium**
2. $\frac{\partial f_i}{\partial x_j}$ always $+$, always $-$, always 0 $\Rightarrow$ **sign-definite Jacobian**

Framework

$$\dot{x}(t) = f(x(t)), \qquad x \in \mathbb{R}^n$$

1. globally asymptotically bounded solutions $\Rightarrow$ **equilibrium**
2. $\frac{\partial f_i}{\partial x_j}$ always $+$, always $-$, always 0 $\Rightarrow$ **sign-definite Jacobian**
3. **non-autocatalytic**: $\frac{\partial f_i}{\partial x_i} < 0$

$$\dot{x}(t) = f(x(t)), \qquad x \in \mathbb{R}^n$$

1. globally asymptotically bounded solutions $\Rightarrow$ **equilibrium**
2. $\frac{\partial f_i}{\partial x_j}$ always $+$, always $-$, always 0 $\Rightarrow$ **sign-definite Jacobian**
3. **non-autocatalytic**: $\frac{\partial f_i}{\partial x_i} < 0$

Problem

What kind of instability does the system admit?

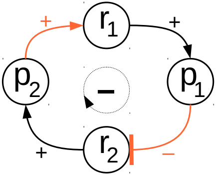
Strong candidate oscillator

$$\begin{bmatrix} \dot{r}_1 \\ \dot{p}_1 \\ \dot{r}_2 \\ \dot{p}_2 \end{bmatrix} = \begin{bmatrix} - & 0 & 0 & + \\ + & - & 0 & 0 \\ 0 & - & - & 0 \\ 0 & 0 & + & - \end{bmatrix} \begin{bmatrix} r_1 \\ p_1 \\ r_2 \\ p_2 \end{bmatrix}$$

$$(s+1)^4 - K, \; K < 0$$

Strong candidate oscillator

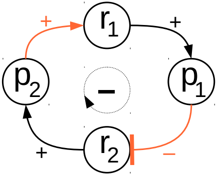
$$\begin{bmatrix}\dot r_1\\ \dot p_1\\ \dot r_2\\ \dot p_2\end{bmatrix} = \begin{bmatrix} - & 0 & 0 & + \\ + & - & 0 & 0 \\ 0 & - & - & 0 \\ 0 & 0 & + & - \end{bmatrix} \begin{bmatrix} r_1\\ p_1\\ r_2\\ p_2\end{bmatrix}$$



$$(s+1)^4 - K, \; K < 0$$

Strong candidate oscillator

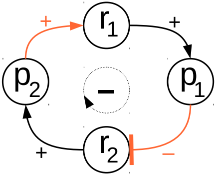
$$\begin{bmatrix} \dot r_1 \\ \dot p_1 \\ \dot r_2 \\ \dot p_2 \end{bmatrix} = \begin{bmatrix} - & 0 & 0 & + \\ + & - & 0 & 0 \\ 0 & - & - & 0 \\ 0 & 0 & + & - \end{bmatrix} \begin{bmatrix} r_1 \\ p_1 \\ r_2 \\ p_2 \end{bmatrix}$$

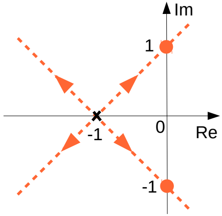


$(s+1)^4 - K$, $K < 0$

Negative cycles only

$$\begin{bmatrix} \dot{r}_1 \\ \dot{p}_1 \\ \dot{r}_2 \\ \dot{p}_2 \end{bmatrix} = \begin{bmatrix} - & 0 & 0 & + \\ + & - & 0 & 0 \\ 0 & - & - & 0 \\ 0 & 0 & + & - \end{bmatrix} \begin{bmatrix} r_1 \\ p_1 \\ r_2 \\ p_2 \end{bmatrix}$$

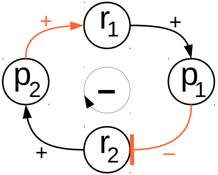


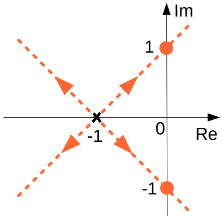


$(s+1)^4 - K$, $K < 0$

Negative cycles only

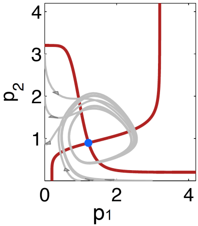
$$\begin{bmatrix} \dot r_1 \\ \dot p_1 \\ \dot r_2 \\ \dot p_2 \end{bmatrix} = \begin{bmatrix} - & 0 & 0 & + \\ + & - & 0 & 0 \\ 0 & - & - & 0 \\ 0 & 0 & + & - \end{bmatrix} \begin{bmatrix} r_1 \\ p_1 \\ r_2 \\ p_2 \end{bmatrix}$$



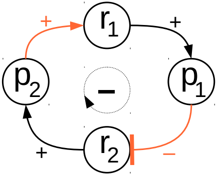


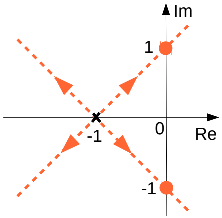
$(s+1)^4 - K$, $K < 0$

Negative cycles only



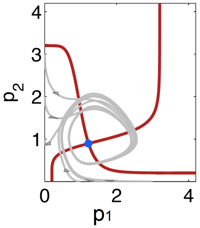
$$\begin{bmatrix} \dot{r}_1 \\ \dot{p}_1 \\ \dot{r}_2 \\ \dot{p}_2 \end{bmatrix} = \begin{bmatrix} - & 0 & 0 & + \\ + & - & 0 & 0 \\ 0 & - & - & 0 \\ 0 & 0 & + & - \end{bmatrix} \begin{bmatrix} r_1 \\ p_1 \\ r_2 \\ p_2 \end{bmatrix}$$





$(s+1)^4 - K$, $K < 0$

Negative cycles only



Strong Candidate Oscillator

The only admissible transitions to instability are **oscillatory**

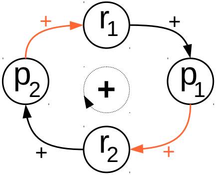
Strong candidate multistable

$$\begin{bmatrix} \dot{r}_1 \\ \dot{p}_1 \\ \dot{r}_2 \\ \dot{p}_2 \end{bmatrix} = \begin{bmatrix} - & 0 & 0 & + \\ + & - & 0 & 0 \\ 0 & + & - & 0 \\ 0 & 0 & + & - \end{bmatrix} \begin{bmatrix} r_1 \\ p_1 \\ r_2 \\ p_2 \end{bmatrix}$$

$$(s+1)^4 - K, \; K > 0$$

Strong candidate multistable

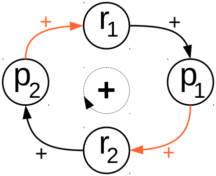
$$\begin{bmatrix} \dot{r}_1 \\ \dot{p}_1 \\ \dot{r}_2 \\ \dot{p}_2 \end{bmatrix} = \begin{bmatrix} - & 0 & 0 & + \\ + & - & 0 & 0 \\ 0 & + & - & 0 \\ 0 & 0 & + & - \end{bmatrix} \begin{bmatrix} r_1 \\ p_1 \\ r_2 \\ p_2 \end{bmatrix}$$



$$(s+1)^4 - K, \; K > 0$$

Strong candidate multistable

$$\begin{bmatrix} \dot{r}_1 \\ \dot{p}_1 \\ \dot{r}_2 \\ \dot{p}_2 \end{bmatrix} = \begin{bmatrix} - & 0 & 0 & + \\ + & - & 0 & 0 \\ 0 & + & - & 0 \\ 0 & 0 & + & - \end{bmatrix} \begin{bmatrix} r_1 \\ p_1 \\ r_2 \\ p_2 \end{bmatrix}$$

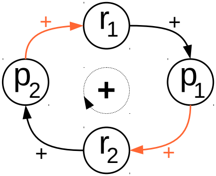


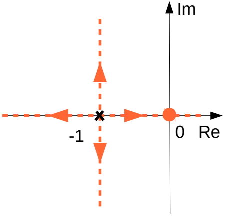
$$(s+1)^4 - K, \; K > 0$$

Positive cycles only

Strong candidate multistable

$$\begin{bmatrix} \dot r_1 \\ \dot p_1 \\ \dot r_2 \\ \dot p_2 \end{bmatrix} = \begin{bmatrix} - & 0 & 0 & + \\ + & - & 0 & 0 \\ 0 & + & - & 0 \\ 0 & 0 & + & - \end{bmatrix} \begin{bmatrix} r_1 \\ p_1 \\ r_2 \\ p_2 \end{bmatrix}$$



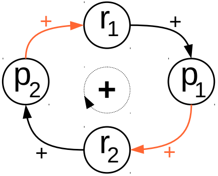


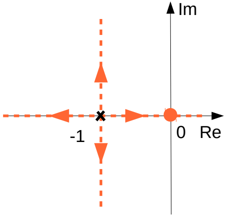
$(s+1)^4 - K$, $K > 0$

Positive cycles only

Strong candidate multistable

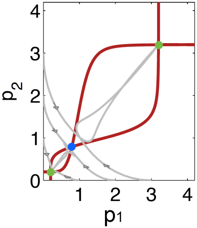
$$\begin{bmatrix} \dot{r}_1 \\ \dot{p}_1 \\ \dot{r}_2 \\ \dot{p}_2 \end{bmatrix} = \begin{bmatrix} - & 0 & 0 & + \\ + & - & 0 & 0 \\ 0 & + & - & 0 \\ 0 & 0 & + & - \end{bmatrix} \begin{bmatrix} r_1 \\ p_1 \\ r_2 \\ p_2 \end{bmatrix}$$





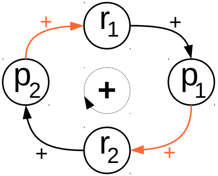
$(s+1)^4 - K$, $K > 0$

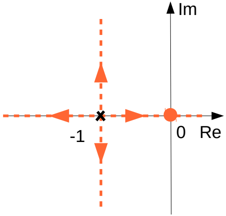
Positive cycles only



Strong candidate multistable

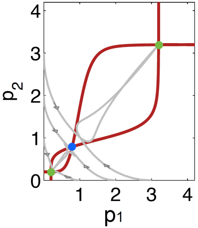
$$\begin{bmatrix} \dot{r}_1 \\ \dot{p}_1 \\ \dot{r}_2 \\ \dot{p}_2 \end{bmatrix} = \begin{bmatrix} - & 0 & 0 & + \\ + & - & 0 & 0 \\ 0 & + & - & 0 \\ 0 & 0 & + & - \end{bmatrix} \begin{bmatrix} r_1 \\ p_1 \\ r_2 \\ p_2 \end{bmatrix}$$





$(s+1)^4 - K$, $K > 0$

Positive cycles only



Strong Candidate Multistable

The only admissible transitions to instability are **real**

Structural classification

Jacobian sign-pattern $\longleftrightarrow$ **structure**

Sign-definite networks can be **structurally** classified based on the **sign of the cycles** in the **Jacobian graph**

Blanchini, Franco & Giordano, "A structural classification of candidate oscillators and multistationary biochemical systems", *Bull. Math. Biol.*, 2014

Structural classification

Jacobian sign-pattern $\longleftrightarrow$ **structure**

Sign-definite networks can be **structurally** classified based on the **sign of the cycles** in the **Jacobian graph**

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

Strong candidate: **exclusively** admits oscillatory/real instability
Weak candidate: **possibly** admits oscillatory/real instability

Blanchini, Franco & Giordano, "A structural classification of candidate oscillators and multistationary biochemical systems", *Bull. Math. Biol.*, 2014

And for **interconnections of stable monotone subsystems**?

And for **interconnections of stable monotone subsystems**?

System formed by N subsystems

$$\dot{z}_i(t) = F_{ii}(z_i(t)) + \sum_j G_{ij}(w_{ij}(t)), \qquad w_{ki}(t) = H_{ki}(z_i(t))$$

And for **interconnections of stable monotone subsystems**?

System formed by N subsystems

$$\dot{z}_i(t) = F_{ii}(z_i(t)) + \sum_j G_{ij}(w_{ij}(t)), \qquad w_{ki}(t) = H_{ki}(z_i(t))$$

$G_{ij}(\cdot)$ either non-decreasing or non-increasing; $H_{ij}(\cdot)$ non-decreasing

And for **interconnections of stable monotone subsystems**?

System formed by N subsystems

$$\dot{z}_i(t) = F_{ii}(z_i(t)) + \sum_j G_{ij}(w_{ij}(t)), \qquad w_{ki}(t) = H_{ki}(z_i(t))$$

$G_{ij}(\cdot)$ either non-decreasing or non-increasing; $H_{ij}(\cdot)$ non-decreasing

1. **unconditionally stable**
   for constant $\bar{w}_{ij}$, a single equilibrium $\bar{z}_i$ asymptotically stable

Aggregate monotone systems

And for **interconnections of stable monotone subsystems**?

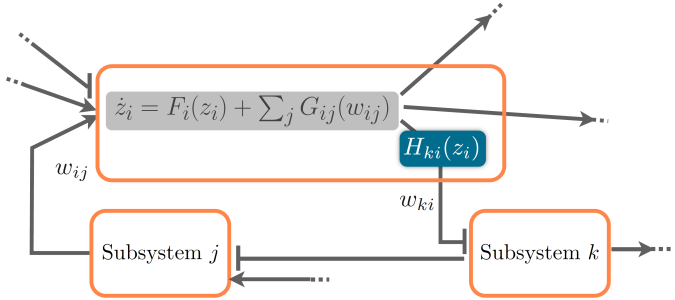
System formed by N subsystems

$$\dot{z}_i(t) = F_{ii}(z_i(t)) + \sum_j G_{ij}(w_{ij}(t)), \qquad w_{ki}(t) = H_{ki}(z_i(t))$$

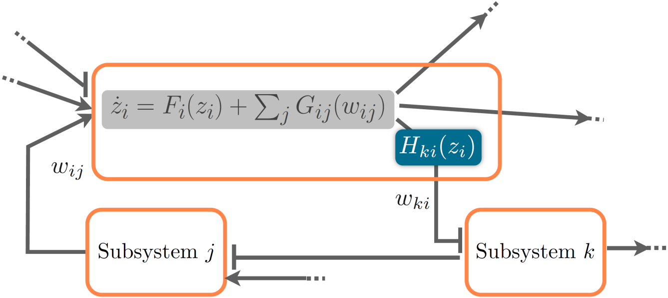
$G_{ij}(\cdot)$ either non-decreasing or non-increasing; $H_{ij}(\cdot)$ non-decreasing

1. **unconditionally stable**
   for constant $\bar{w}_{ij}$, a single equilibrium $\bar{z}_i$ asymptotically stable
2. **input-to-state monotone**
   for $w_{ij}(t) \geq \tilde{w}_{ij}(t)$, either
   $z_i(0) \geq \tilde{z}_i(0) \implies z_i(t) \geq \tilde{z}_i(t)$ for $t \geq 0$, or
   $z_i(0) \leq \tilde{z}_i(0) \implies z_i(t) \leq \tilde{z}_i(t)$ for $t \geq 0$

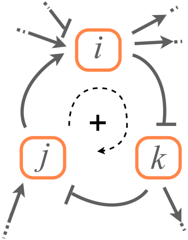
Aggregate graph

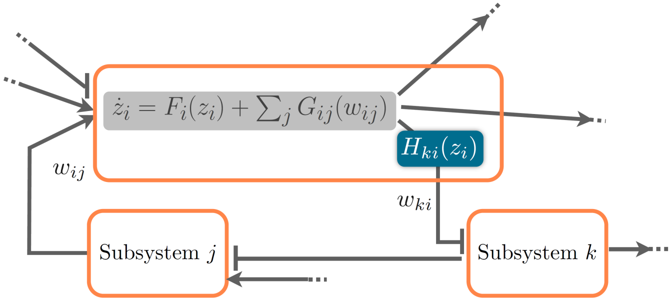


Aggregate graph

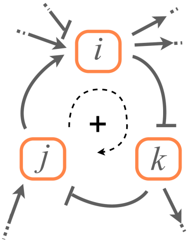


Aggregate graph representation: **nodes** $\longleftrightarrow$ **subsystems**





Aggregate graph representation: **nodes** $\longleftrightarrow$ **subsystems**



Strongly connected graph

An **oriented** path connects each pair of nodes

Structural classification for aggregate monotone systems

Theorem

An aggregate system formed by the interconnection of strongly connected monotone unconditionally stable components is structurally a strong candidate

- oscillator **if and only if**
  all the cycles in the aggregate graphs are negative
- multistable **if and only if**
  all the cycles in the aggregate graphs are positive

Structural classification for aggregate monotone systems

Theorem

An aggregate system formed by the interconnection of strongly connected monotone unconditionally stable components is structurally a strong candidate

- oscillator **if and only if**
  all the cycles in the aggregate graphs are negative
- multistable **if and only if**
  all the cycles in the aggregate graphs are positive

Proof exploits two main facts

- sign $\frac{\partial w_{ki}}{\partial w_{ij}} = - \left.\frac{\partial H_{ki}}{\partial z_i}\right|_{\bar{z}_i} \left(\left.\frac{\partial F_{ii}}{\partial z_i}\right|_{\bar{z}_i} \right)^{-1} \left.\frac{\partial G_{ij}}{\partial w_{ij}}\right|_{\bar{w}_{ij}}$ depends on sign $\left.\frac{\partial G_{ij}}{\partial w_{ij}}\right|_{\bar{w}_{ij}}$
- suitable differential scaling maps can alter $f(x)$ around 0 (with unaltered structure, equilibrium and boundedness) to scale the Jacobian entries, hence the magnitude of cycles

Structural classification for aggregate monotone systems

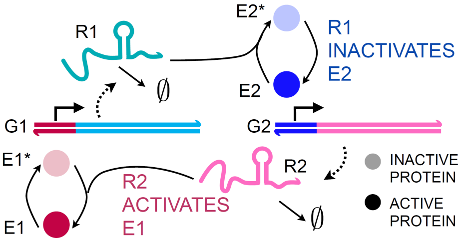
Theorem

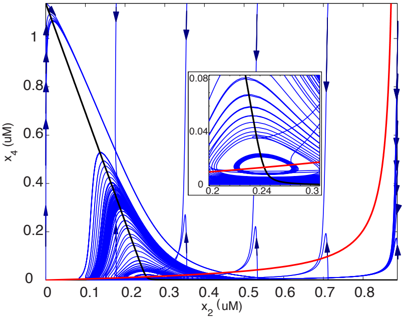
An aggregate system formed by the interconnection of strongly connected monotone unconditionally stable components is structurally a strong candidate

- oscillator **if and only if**
  all the cycles in the aggregate graphs are negative
- multistable **if and only if**
  all the cycles in the aggregate graphs are positive

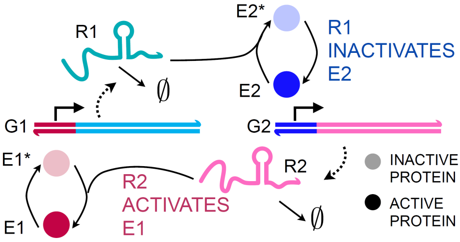
Interactions between unconditionally stable monotone components must be independent!

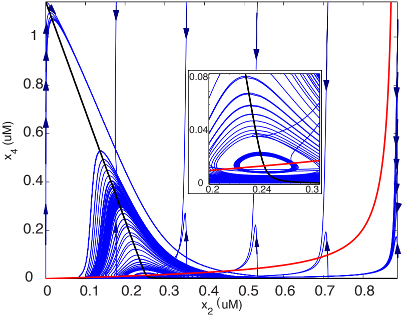
Biomolecular oscillator:
Blanchini, Cuba Samaniego, Franco & Giordano, "Design of a molecular clock with RNA-mediated regulation", *CDC 2014*





Biomolecular oscillator:
Blanchini, Cuba Samaniego, Franco & Giordano, "Design of a molecular clock with RNA-mediated regulation", *CDC 2014*





Strong candidate oscillator ?

Analyse the system Jacobian...

$$\begin{bmatrix} -\gamma_1(x_2^{tot}-\bar{x}_2)-\delta_2 & \gamma_1\bar{x}_3 & \kappa_2 & 0 \\ \gamma_1(x_2^{tot}-\bar{x}_2) & -\beta_1-\gamma_1\bar{x}_3 & 0 & 0 \\ 0 & 0 & -\beta_2-\gamma_2\bar{x}_1 & \gamma_2\bar{x}_4 \\ 0 & -\kappa_1 & \gamma_2\bar{x}_1 & -\gamma_2\bar{x}_4-\delta_1 \end{bmatrix}$$

Strong candidate oscillator ?

Analyse the system Jacobian...

$$\begin{bmatrix} -\gamma_1(x_2^{tot}-\bar{x}_2)-\delta_2 & \gamma_1\bar{x}_3 & \kappa_2 & 0 \\ \gamma_1(x_2^{tot}-\bar{x}_2) & -\beta_1-\gamma_1\bar{x}_3 & 0 & 0 \\ 0 & 0 & -\beta_2-\gamma_2\bar{x}_1 & \gamma_2\bar{x}_4 \\ 0 & -\kappa_1 & \gamma_2\bar{x}_1 & -\gamma_2\bar{x}_4-\delta_1 \end{bmatrix}$$

monotone aggregate
1

Strong candidate oscillator ?

Analyse the system Jacobian...

$$\begin{bmatrix} -\gamma_1(x_2^{tot} - \bar{x}_2) - \delta_2 & \gamma_1 \bar{x}_3 & \kappa_2 & 0 \\ \gamma_1(x_2^{tot} - \bar{x}_2) & -\beta_1 - \gamma_1 \bar{x}_3 & 0 & 0 \\ 0 & 0 & -\beta_2 - \gamma_2 \bar{x}_1 & \gamma_2 \bar{x}_4 \\ 0 & -\kappa_1 & \gamma_2 \bar{x}_1 & -\gamma_2 \bar{x}_4 - \delta_1 \end{bmatrix}$$

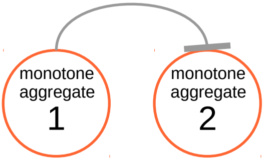
monotone aggregate 1

monotone aggregate 2

Strong candidate oscillator ?

Analyse the system Jacobian...

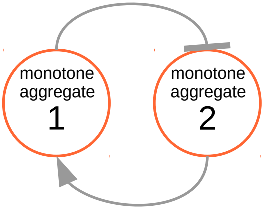
$$\begin{bmatrix} -\gamma_1(x_2^{tot}-\bar{x}_2)-\delta_2 & \gamma_1\bar{x}_3 & \kappa_2 & 0 \\ \gamma_1(x_2^{tot}-\bar{x}_2) & -\beta_1-\gamma_1\bar{x}_3 & 0 & 0 \\ 0 & 0 & -\beta_2-\gamma_2\bar{x}_1 & \gamma_2\bar{x}_4 \\ 0 & -\kappa_1 & \gamma_2\bar{x}_1 & -\gamma_2\bar{x}_4-\delta_1 \end{bmatrix}$$



Strong candidate **oscillator** ?

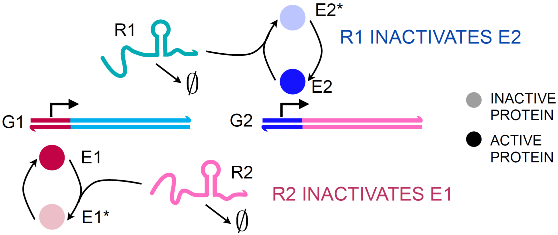
Negative feedback of unconditionally stable monotone systems

$$\begin{bmatrix} -\gamma_1(x_2^{tot}-\bar{x}_2)-\delta_2 & \gamma_1\bar{x}_3 & \kappa_2 & 0 \\ \gamma_1(x_2^{tot}-\bar{x}_2) & -\beta_1-\gamma_1\bar{x}_3 & 0 & 0 \\ 0 & 0 & -\beta_2-\gamma_2\bar{x}_1 & \gamma_2\bar{x}_4 \\ 0 & -\kappa_1 & \gamma_2\bar{x}_1 & -\gamma_2\bar{x}_4-\delta_1 \end{bmatrix}$$

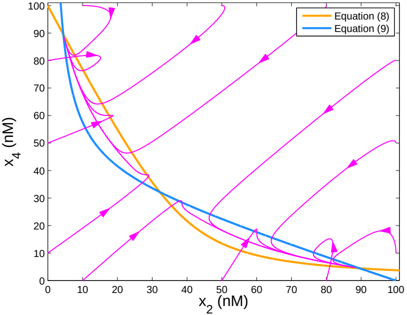


Strong candidate oscillator !

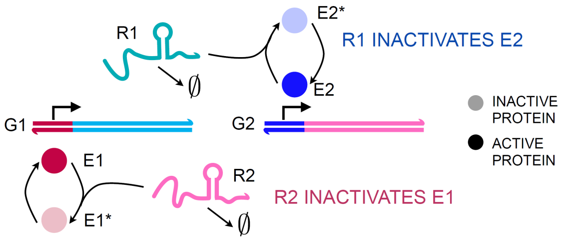
Bistable monotone aggregate: a biomolecular example



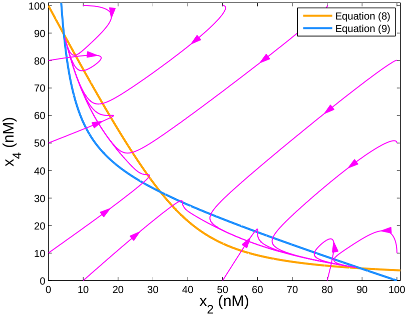
Biomolecular bistable: Mardanlou, Tran & Franco, "Design of a molecular bistable system with RNA-mediated regulation", *CDC 2014*



Bistable monotone aggregate: a biomolecular example



Biomolecular bistable: Mardanlou, Tran & Franco, "Design of a molecular bistable system with RNA-mediated regulation", *CDC 2014*



Strong candidate **bistable** ?

Bistable monotone aggregate: a biomolecular example

Analyse the system Jacobian...

$$\begin{bmatrix} -\beta-\gamma\bar{x}_3 & \gamma\bar{x}_2 & 0 & 0 \\ \gamma\bar{x}_3 & -\gamma\bar{x}_2-\delta & \kappa_2 & 0 \\ 0 & 0 & -\beta-\gamma\bar{x}_1 & \gamma\bar{x}_4 \\ \kappa_1 & 0 & \gamma\bar{x}_1 & -\gamma\bar{x}_4-\delta \end{bmatrix}$$

Strong candidate **bistable** ?

Bistable monotone aggregate: a biomolecular example

Analyse the system Jacobian...

$$\begin{bmatrix} -\beta - \gamma\bar{x}_3 & \gamma\bar{x}_2 & 0 & 0 \\ \gamma\bar{x}_3 & -\gamma\bar{x}_2 - \delta & \kappa_2 & 0 \\ 0 & 0 & -\beta - \gamma\bar{x}_1 & \gamma\bar{x}_4 \\ \kappa_1 & 0 & \gamma\bar{x}_1 & -\gamma\bar{x}_4 - \delta \end{bmatrix}$$

monotone aggregate
1

Strong candidate **bistable** ?

Bistable monotone aggregate: a biomolecular example

Analyse the system Jacobian...

$$\begin{bmatrix} -\beta - \gamma\bar{x}_3 & \gamma\bar{x}_2 & 0 & 0 \\ \gamma\bar{x}_3 & -\gamma\bar{x}_2 - \delta & \kappa_2 & 0 \\ 0 & 0 & -\beta - \gamma\bar{x}_1 & \gamma\bar{x}_4 \\ \kappa_1 & 0 & \gamma\bar{x}_1 & -\gamma\bar{x}_4 - \delta \end{bmatrix}$$

monotone aggregate 1

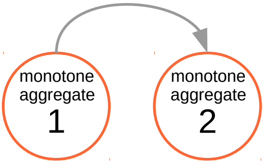
monotone aggregate 2

Strong candidate **bistable** ?

Bistable monotone aggregate: a biomolecular example

Analyse the system Jacobian...

$$\begin{bmatrix} -\beta-\gamma\bar{x}_3 & \gamma\bar{x}_2 & 0 & 0 \\ \gamma\bar{x}_3 & -\gamma\bar{x}_2-\delta & \kappa_2 & 0 \\ 0 & 0 & -\beta-\gamma\bar{x}_1 & \gamma\bar{x}_4 \\ \kappa_1 & 0 & \gamma\bar{x}_1 & -\gamma\bar{x}_4-\delta \end{bmatrix}$$

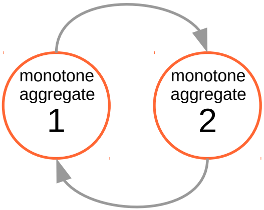


Strong candidate **bistable** ?

Bistable monotone aggregate: a biomolecular example

Positive feedback of unconditionally stable monotone systems

$$
\begin{bmatrix}
-\beta-\gamma\bar{x}_3 & \gamma\bar{x}_2 & 0 & 0 \\
\gamma\bar{x}_3 & -\gamma\bar{x}_2-\delta & \boxed{\kappa_2} & 0 \\
0 & 0 & -\beta-\gamma\bar{x}_1 & \gamma\bar{x}_4 \\
\boxed{\kappa_1} & 0 & \gamma\bar{x}_1 & -\gamma\bar{x}_4-\delta
\end{bmatrix}
$$



Strong candidate bistable !

Conclusions

- Several systems in nature are **interconnections of monotone subsystems** (MAPK pathway, Goldbeter oscillator...)

Conclusions

- Several systems in nature are **interconnections of monotone subsystems** (MAPK pathway, Goldbeter oscillator...)
- **Structural** (parameter-free) criteria are crucial for **biomolecular systems** (highly **uncertain**)

Conclusions

- Several systems in nature are **interconnections of monotone subsystems** (MAPK pathway, Goldbeter oscillator...)
- **Structural** (parameter-free) criteria are crucial for **biomolecular systems** (highly **uncertain**)
- **Structural** necessary and sufficient conditions for **oscillations / multistationarity** in **aggregate monotone** systems: only **negative / positive cycles** in the aggregate graph

Conclusions

- Several systems in nature are **interconnections of monotone subsystems** (MAPK pathway, Goldbeter oscillator...)
- **Structural** (parameter-free) criteria are crucial for **biomolecular systems** (highly **uncertain**)
- **Structural** necessary and sufficient conditions for **oscillations / multistationarity** in **aggregate monotone** systems: only **negative / positive cycles** in the aggregate graph
- **Structurally analyse** the dynamics of biomolecular networks

Conclusions

- Several systems in nature are **interconnections of monotone subsystems** (MAPK pathway, Goldbeter oscillator...)
- **Structural** (parameter-free) criteria are crucial for **biomolecular systems** (highly **uncertain**)
- **Structural** necessary and sufficient conditions for **oscillations / multistationarity** in **aggregate monotone** systems: only **negative / positive cycles** in the aggregate graph
- **Structurally analyse** the dynamics of biomolecular networks
- **Design** artificial biomolecular circuits that are **structurally well suited** to achieve the desired dynamics

Conclusions

- Several systems in nature are **interconnections of monotone subsystems** (MAPK pathway, Goldbeter oscillator...)
- **Structural** (parameter-free) criteria are crucial for **biomolecular systems** (highly **uncertain**)
- **Structural** necessary and sufficient conditions for **oscillations / multistationarity** in **aggregate monotone** systems: only **negative / positive cycles** in the aggregate graph
- **Structurally analyse** the dynamics of biomolecular networks
- **Design** artificial biomolecular circuits that are **structurally well suited** to achieve the desired dynamics

どうもありがとうございます