ANALYSIS OF MODULAR ORGANISATION OF INTERACTION NETWORKS BASED ON ASYMPTOTIC DYNAMICS

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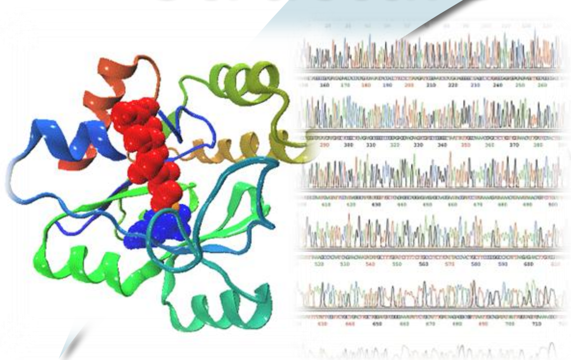
Trends in systems biology

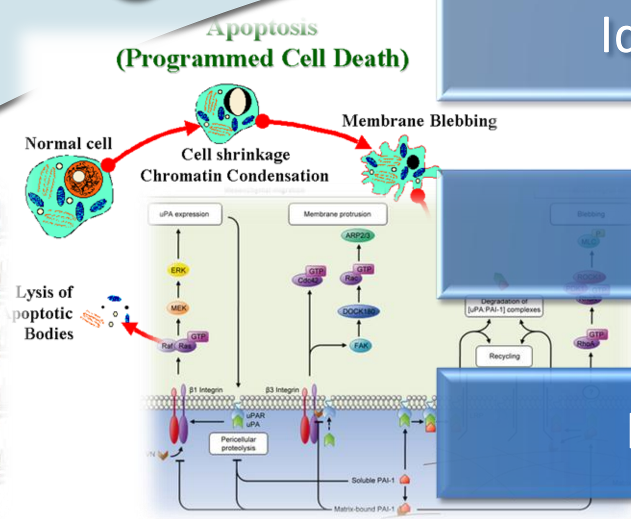
Modularity of biological system

System

Function

Structure





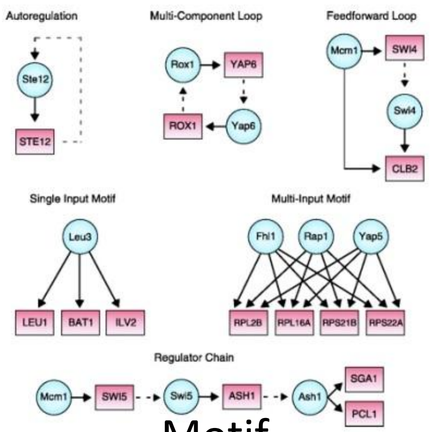
Identification of parts

Interaction of parts

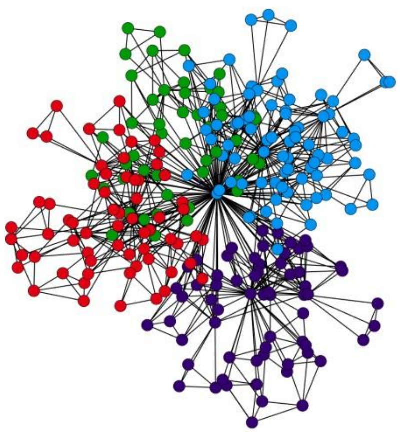
Integration of parts

Modularity in biological networks

Structure driven

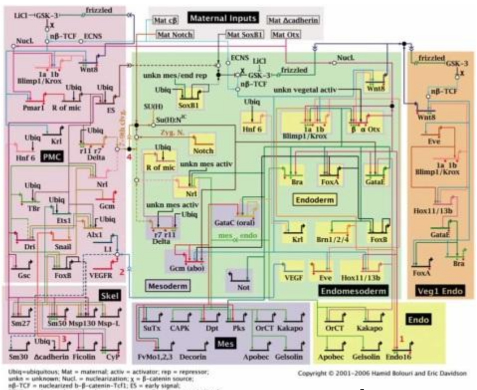


Motif
Over expressed pattern [Allon]

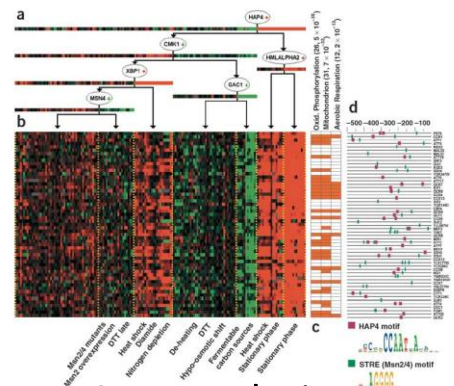


Structure prop.: Scale free – cliques - SCCs

Behavior driven



Experimental
Morphogenesis [Davidson]

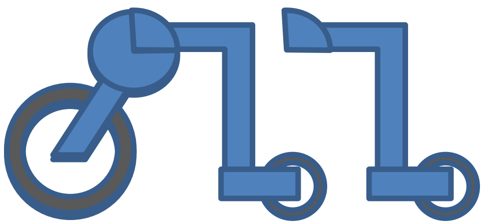


Co- regulation:
Statistical analysis – RNA Chips [Segal]

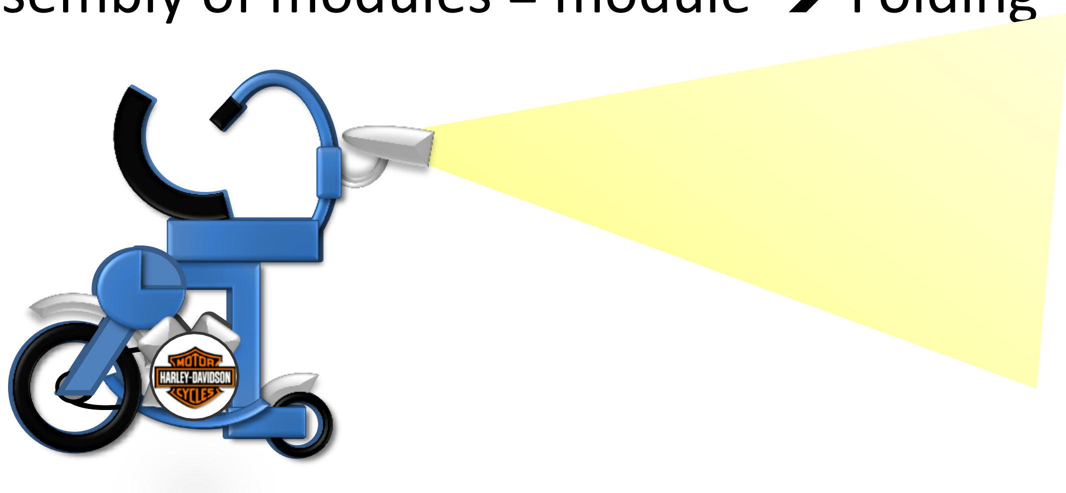
Modularity

What are the module properties ?

Structure assembly = function composition ➔ Compositionality



Assembly of modules = module ➔ Folding



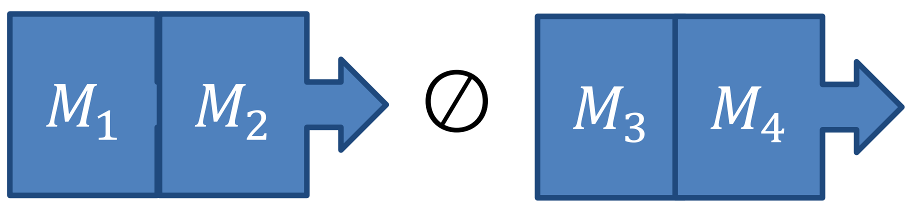
Behavioral hierarchy on modules ➔ Hierarchy

Modularity properties

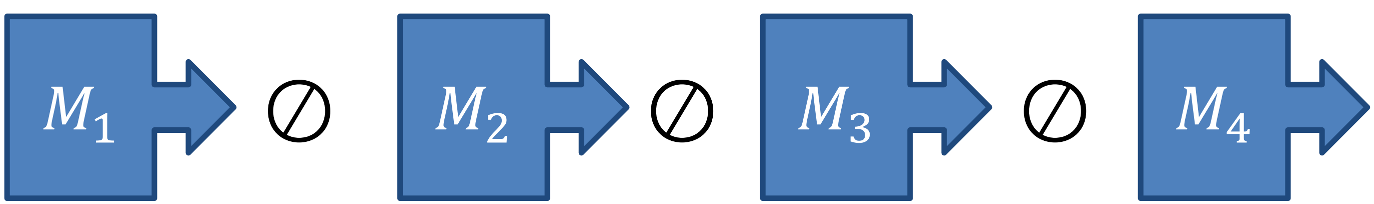
Compositionality Homomorphism Struct. (::) ➔Fun. ∅

$$\mathrm{B}(\boldsymbol{M}) = \mathrm{B}(M_1 :: M_2) = \mathrm{B}(M_1) \varnothing B(M_2)$$

Folding – Assembly of modules = module ➔ Associativity of ∅



Hierarchy - Order on composition = modular organisation



Network ➔ Discrete dynamics

A= agents, S= states of agents

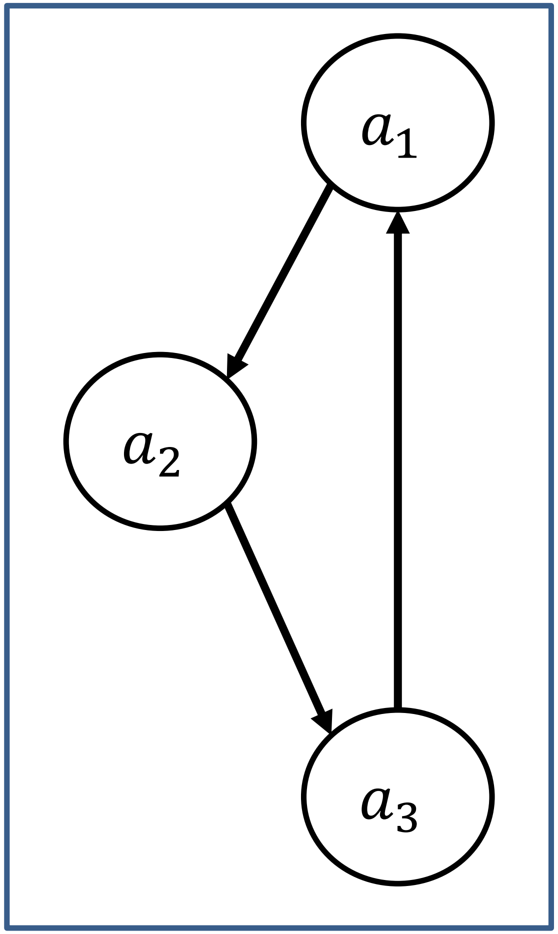
Networks = family of functions

$$\eta = \{\eta_{a_i}\}_{a_i \in A} \qquad \eta_{a_i} : S \to S_{a_i}$$

Example : Boolean network

$$\eta \begin{cases} s(a_1) = \neg s(a_3) \\ s(a_2) = \quad s(a_1) \\ s(a_3) = \neg s(a_2) \end{cases}$$

Interaction Graph



Dynamics = Asynchronous Model

Labeled transition system

$$\langle A, S, \rightharpoonup \rangle$$

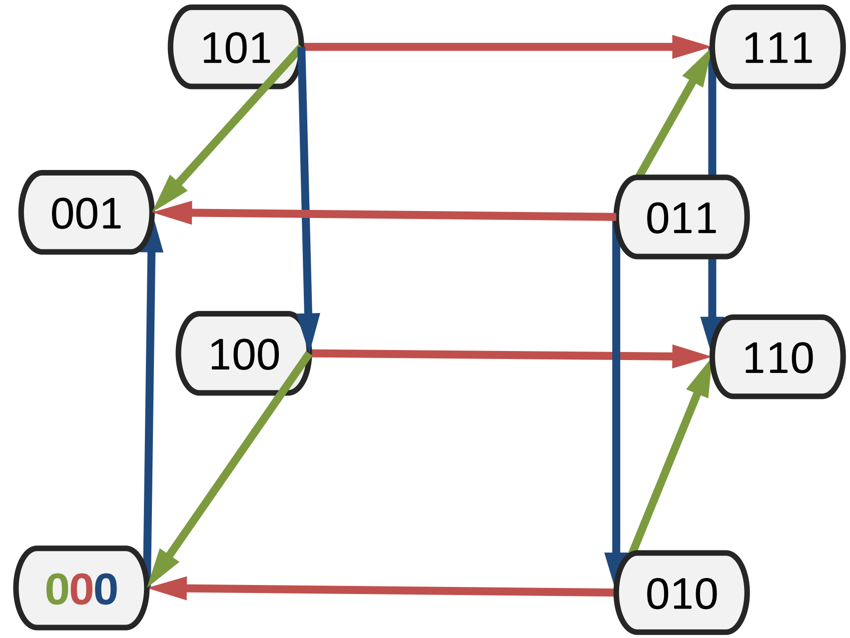
$$\rightharpoonup \subseteq S \times A \times S$$

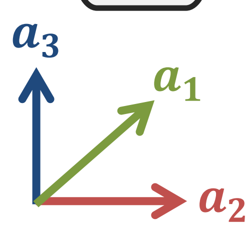
Collective transition

$$\rightharpoonup_X = \bigcup_{a_i \in X} \rightharpoonup_{a_i}$$

Model of a network

$$\left\langle A, S, \overset{\eta}{\rightharpoonup} \right\rangle$$





$$\eta \begin{cases} s(a_1) = \neg s(a_3) \\ s(a_2) = \quad s(a_1) \\ s(a_3) = \neg s(a_2) \end{cases}$$

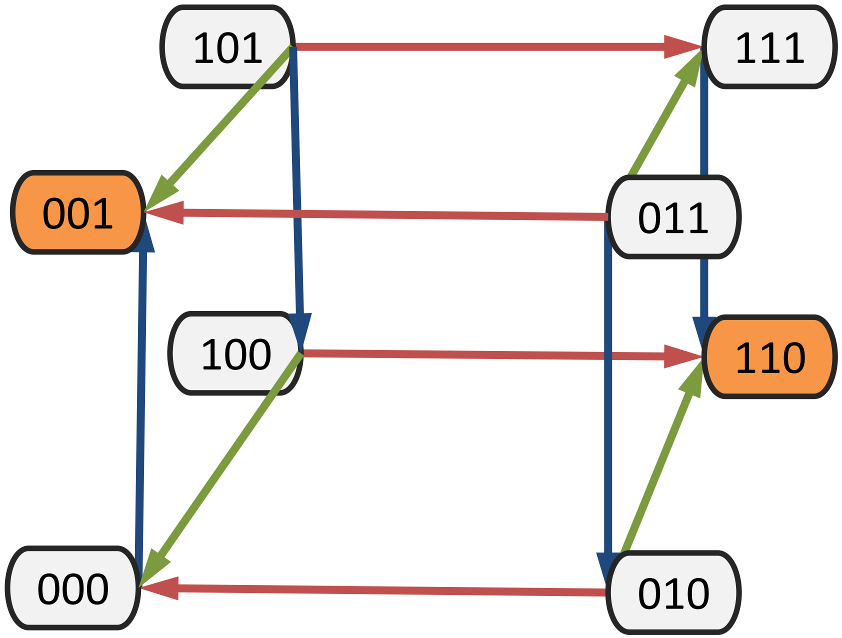
$$s_1 \overset{\eta}{\rightharpoonup}_{a_i} s_2 \triangleq \textit{only the state of } a_i \textit{ is updated, s.t. } s_2(a_i) = \eta_{a_i}(s_1)$$

Equilibrium

Equilibrium

State endlessly met once reached

$$\forall s' \in S\colon\ s \rightharpoonup^{*} s' \Rightarrow s' \rightharpoonup^{*} s.$$



Equilibria function

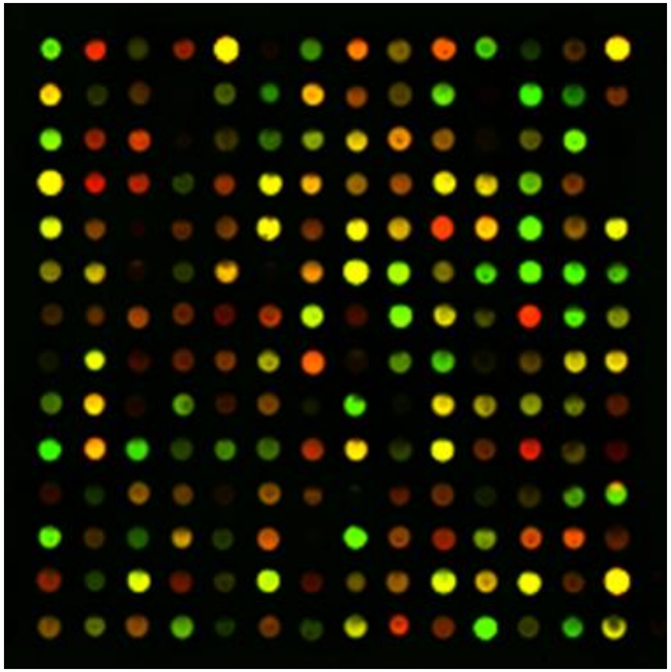
Set of equilibria reachable from a set of states

$$\eta \begin{cases} s(a_1) = \neg s(a_3) \\ s(a_2) = \quad s(a_1) \\ s(a_3) = \neg s(a_2) \end{cases}$$

$$\Psi_X(S') = \{s \in (S' \rightharpoonup_X{}^{*}) \mid \forall s' \in S\colon\ s \rightharpoonup_X{}^{*} s' \Rightarrow s' \rightharpoonup_X{}^{*} s\}$$

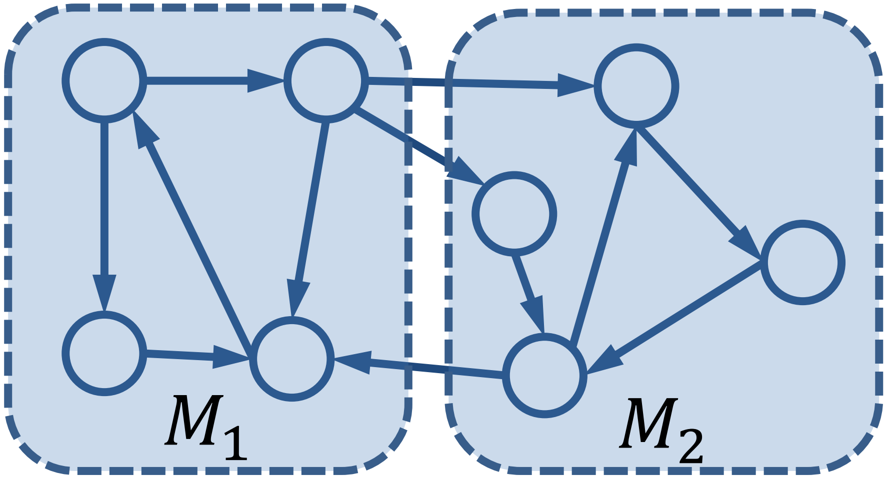
Basic modeling hypothesis

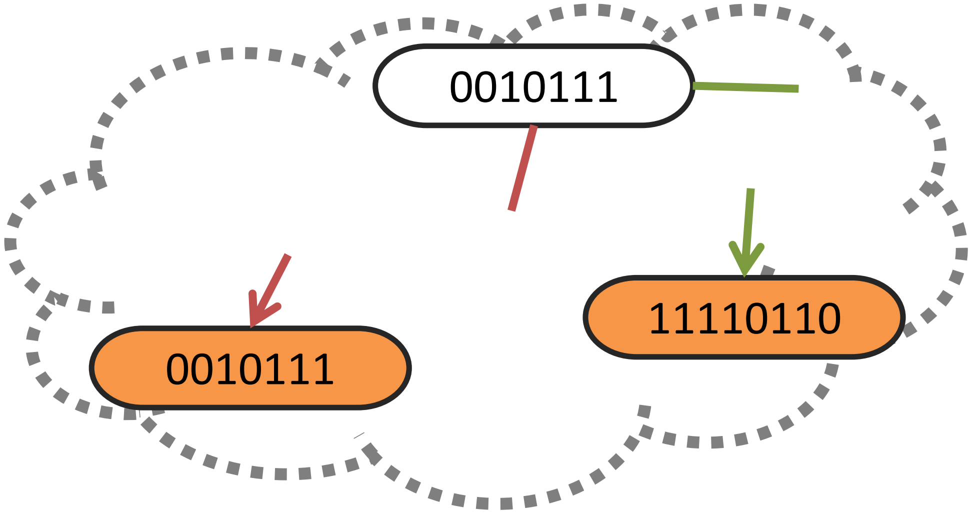
- **Observation of biological function =**
  Asymptotic behavior of a molecular process.
- **Equilibrium = Signature of a biological function in a model.**



Modules on networks

$$B(\boldsymbol{M}) = B(M_1 :: M_2) = B(M_1) \oslash B(M_2)$$

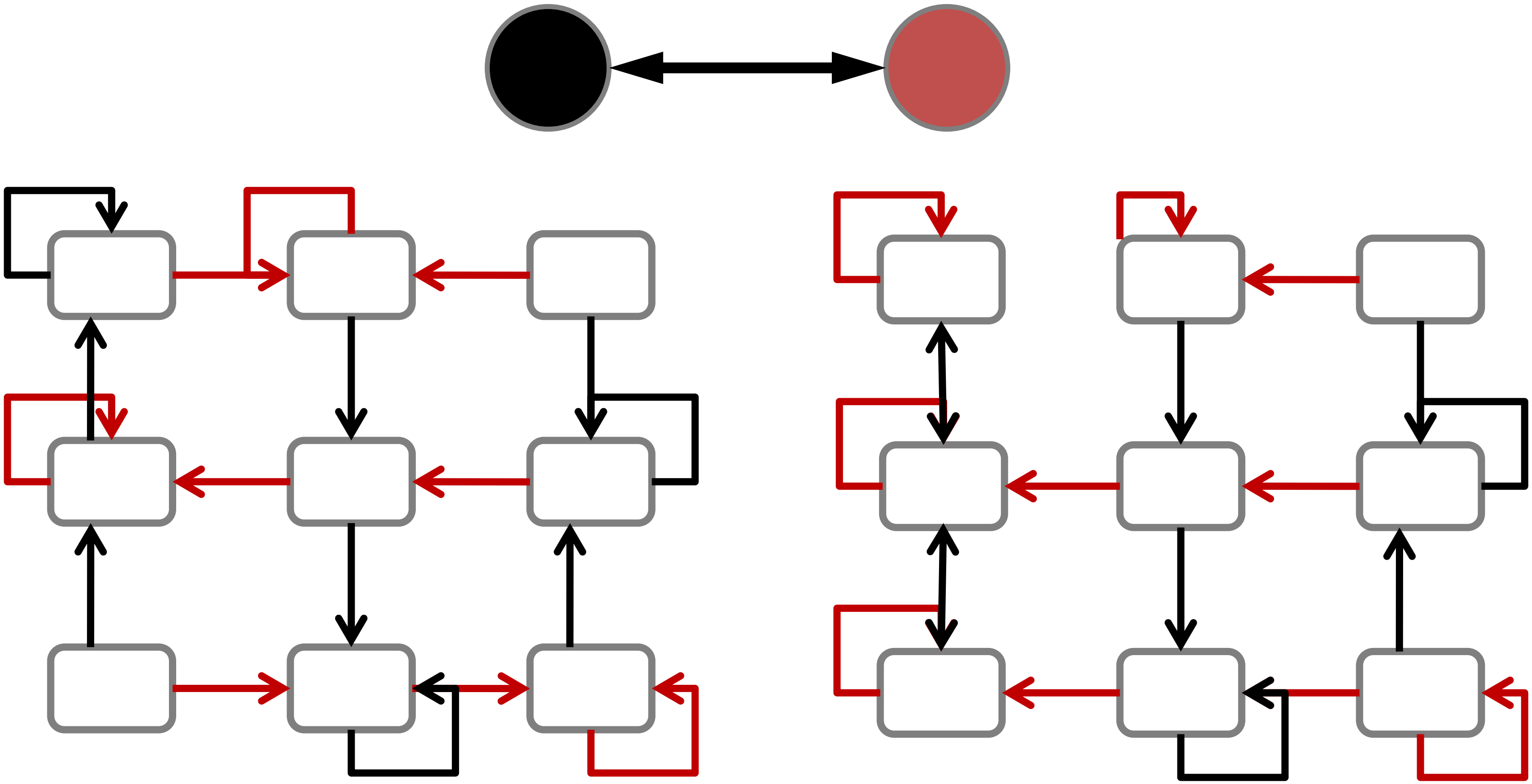




$$\Psi_{\boldsymbol{M}} = \Psi_{M_1 \cup M_2} = \Psi_{M_1} \oslash \Psi_{M_2}$$

1. Identifying modular composition operator ?
2. Characterizing modules formally ?

Behavior inclusion → M-relation



M-relation

$$M_i \rightsquigarrow M_{i+1} = \forall S' \subseteq S: \Psi_{M_{i+1}} \circ \Psi_{M_i \cup M_{i+1}}(S') \subseteq \Psi_{M_i} \circ \Psi_{M_i \cup M_{i+1}}(S')$$

Module based equilibria composition

Under the condition

$$M_1 \rightsquigarrow M_2 \ldots \rightsquigarrow M_m$$

Compositional modular equilibria computation

$$\Psi_{\bigcup_{i=1,m} M_i} = \Psi_{M_1} \oslash \Psi_{M_2} \oslash \cdots \oslash \Psi_{M_m}$$

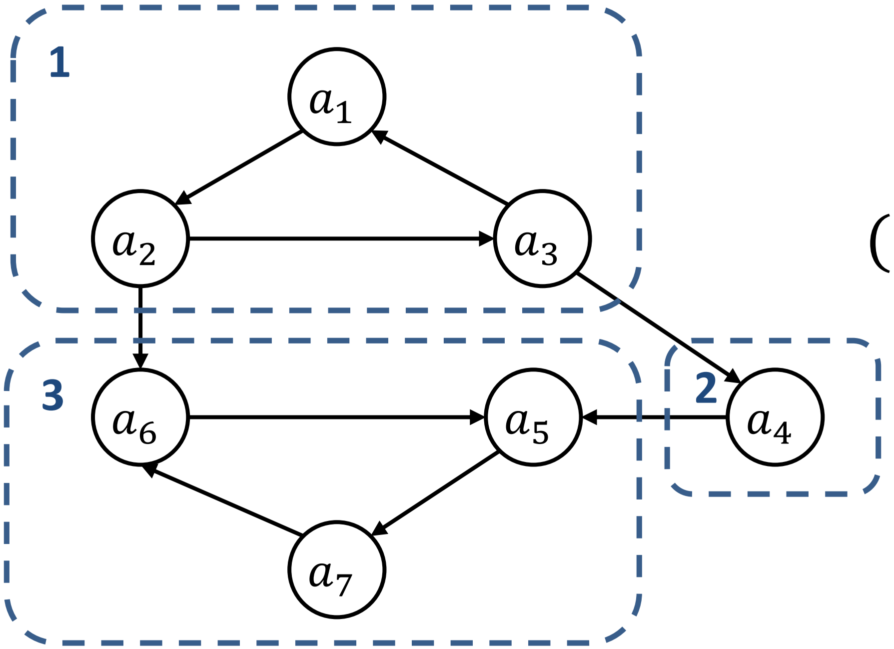
$$\Psi_{X_i} \oslash \Psi_{X_j} = \mathsf{Flatten} \circ [\widetilde{\Psi_{X_j}}]_{\rightleftharpoons_{X_i}} \circ \Psi_{X_i},$$

$$[\widetilde{\Psi_{X_j}}]_{\rightleftharpoons_{X_i}}(S') \triangleq \{e \in [S']_{\rightleftharpoons_{X_i}} \mid ((e[\rightharpoonup_{X_j}]^{*}_{\rightleftharpoons_{X_i}}) \subseteq [S']_{\rightleftharpoons_{X_i}}) \wedge (\forall e' \in [S]_{\rightleftharpoons_{X_i}} : e[\rightharpoonup_{X_j}]^{*}_{\rightleftharpoons_{X_i}} e' \implies e'[\rightharpoonup_{X_j}]^{*}_{\rightleftharpoons_{X_i}} e)\}.$$

Back to the structure: some results

Can we identify modules from structures ?

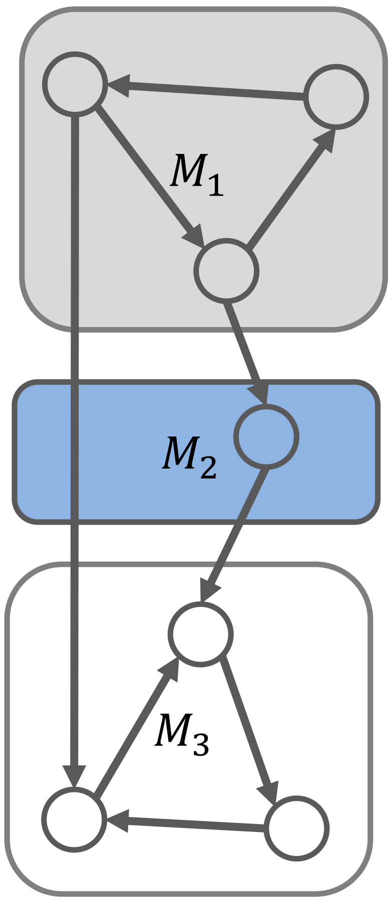
- A Strongly connected component is a module
- A topological order of the SCC quotient graph of the interaction graph is a modular organization



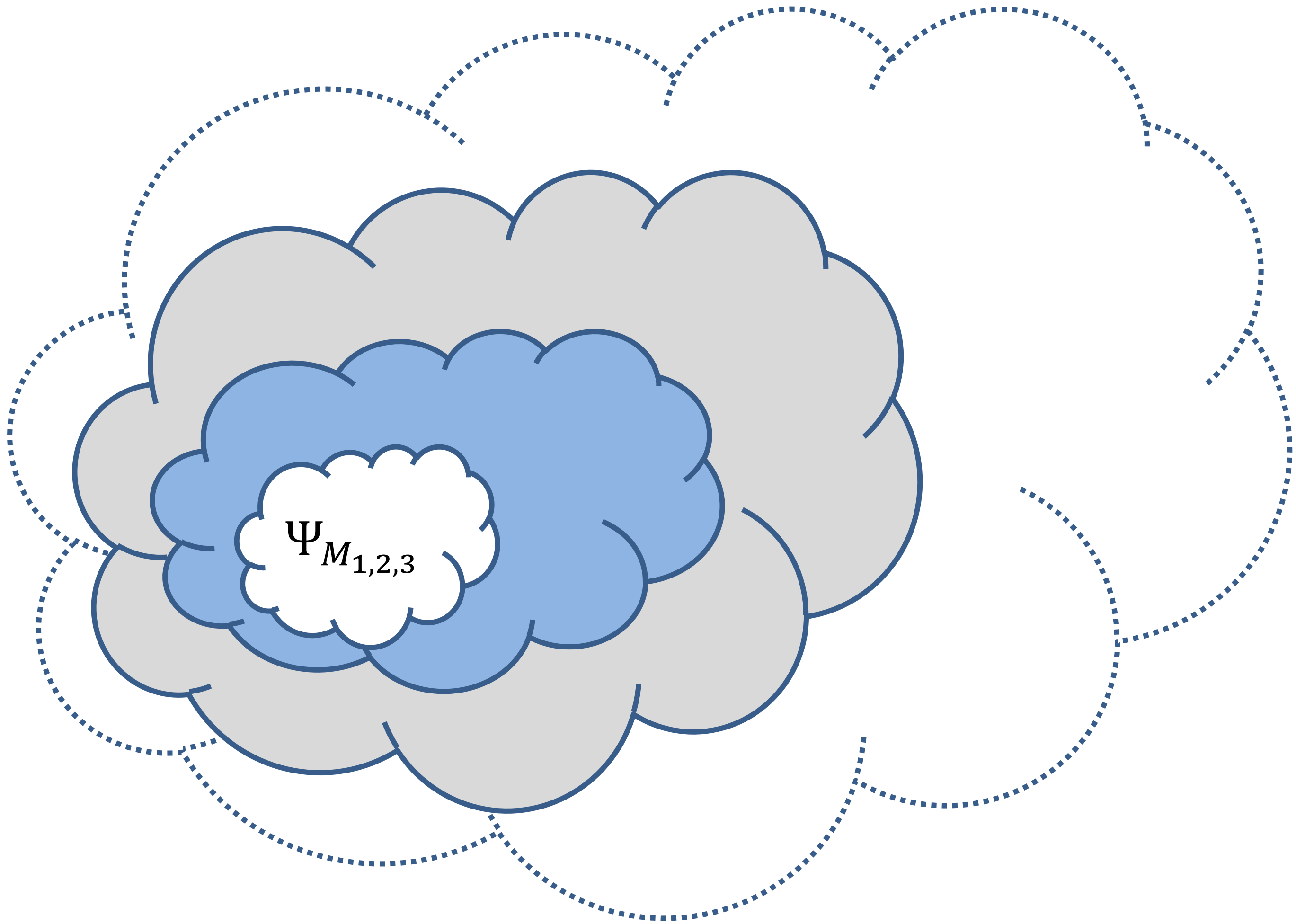
Modular Organisation

$$(\{a_1, a_2, a_3\}, \{a_4\}, \{a_5, a_6, a_7\})$$

Modular computation of equilibria



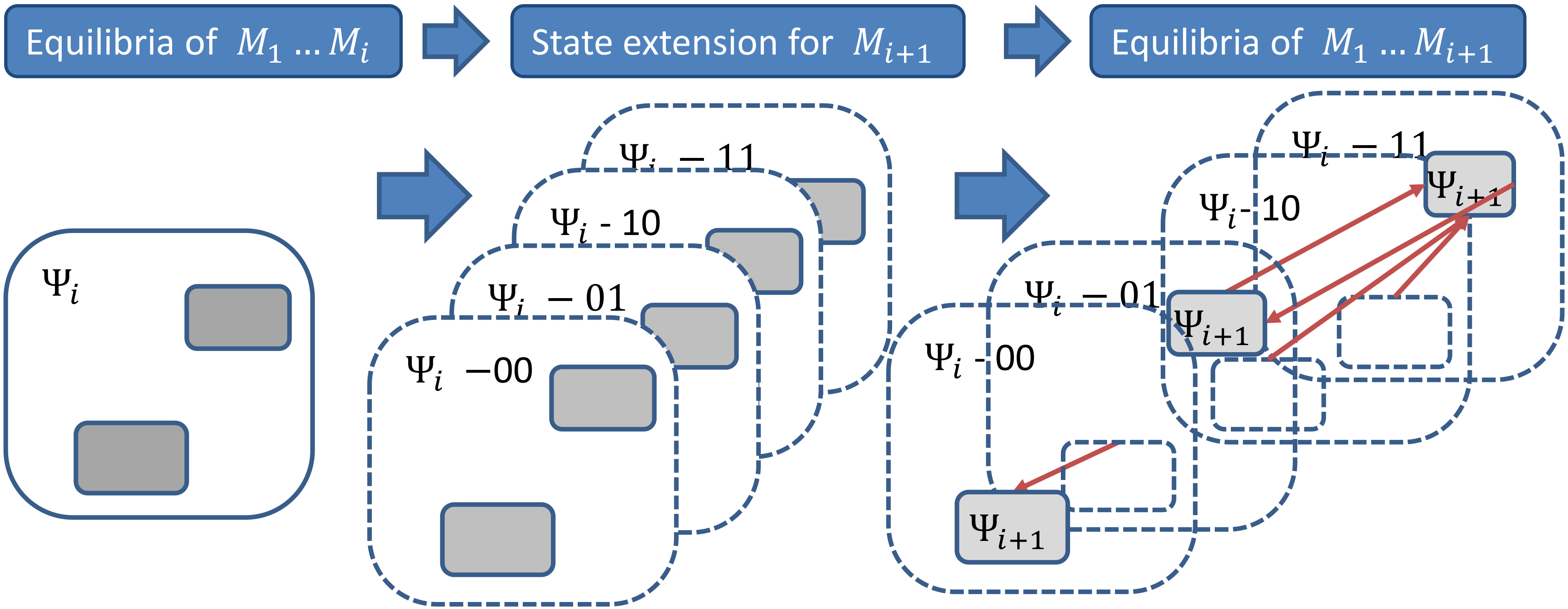
Modular Organization



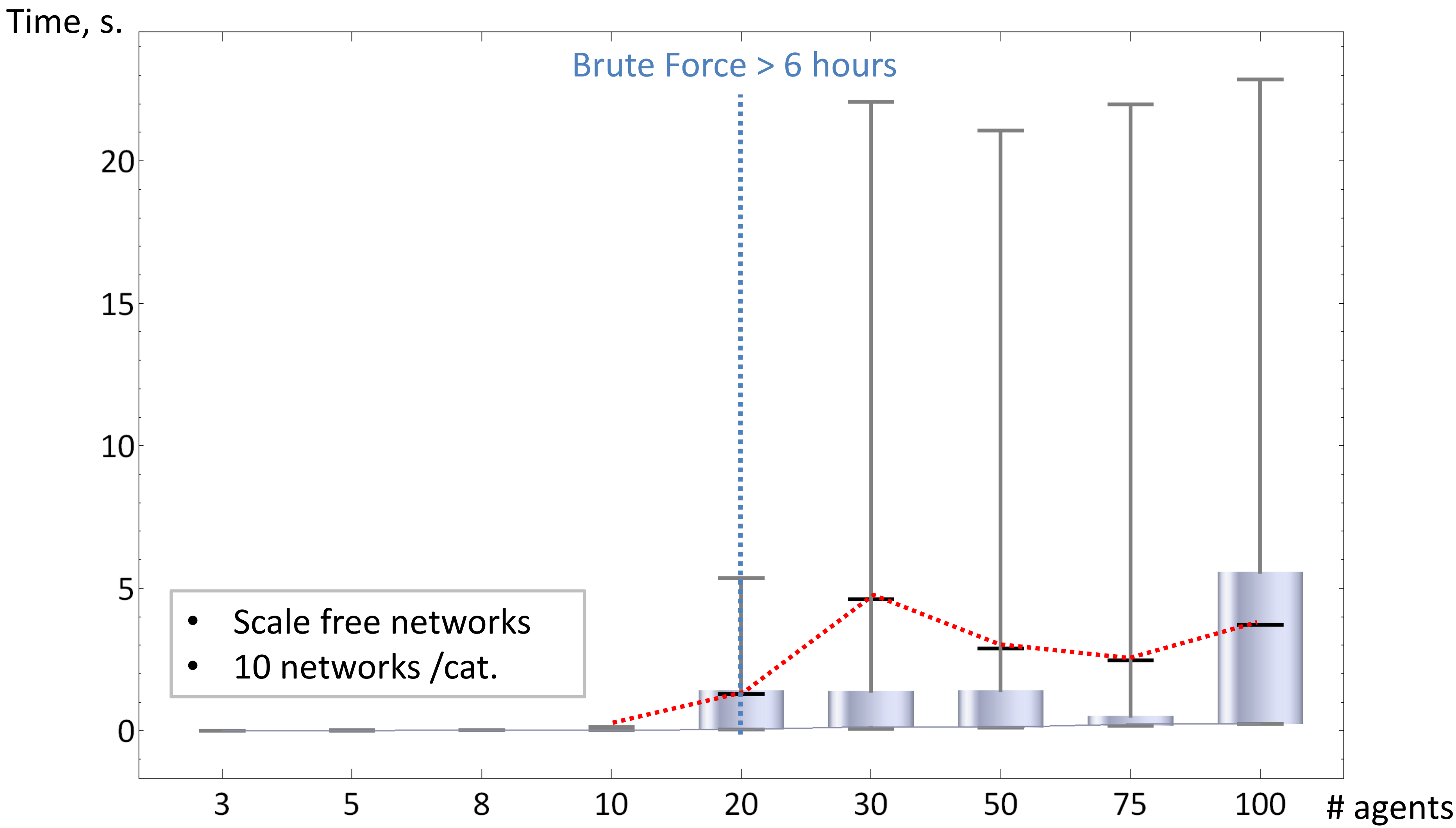
State Graph

Modular computation of equilibria

- **Parsimonious state extension** for equilibria computation
- Efficient algorithm in practice $O(2^{\beta}.\alpha)$, (Brute-force $O(2^{|A|})$)
  β= Cardinality of the greatest SCC, α = max. # equilibria for a module

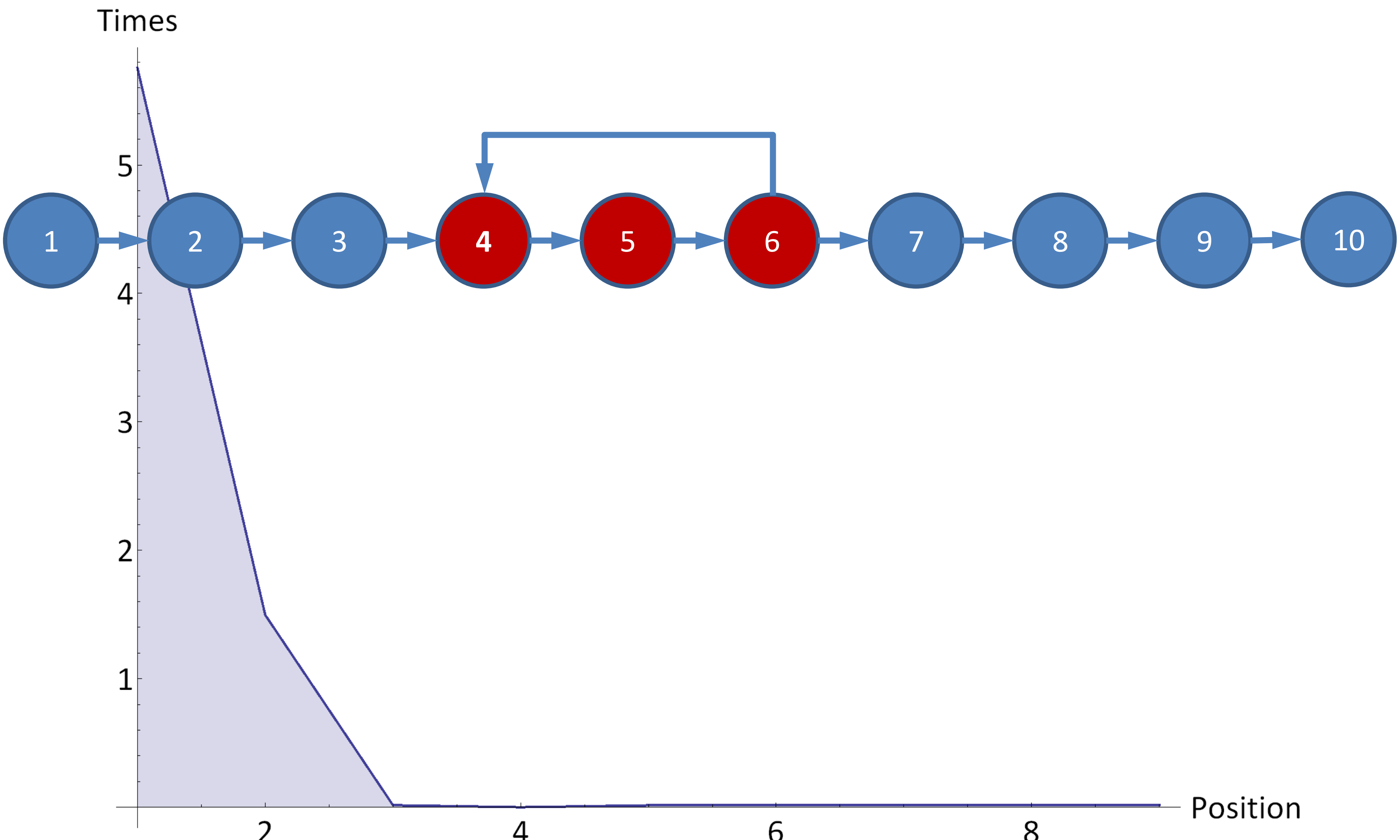


Experimental results – Positive circuits



Experiments - K. Rosasz

Experimental results - Negative circuits



Experiments - K. Rosasz

Summary remarks

- The modularity is underpinned by the M-relation.
  - A module refines the behavior (equilibrium) of a module located backward in the organisation
- Modular decomposition is a reductionnist approach
  - A composition of equilibrium is a selection of equilibria
- The parameters of the algorithms are:
  - The size of the SCC extended to its frontier of regulator
  - The number equilibria carried through the different steps of computation

Conclusion

Objective
- Formalization of modularity tackling with the relation of structure and behavior
- Based on equilibria analysis

Result
- Structural identification of modules = SCCs
- Efficient modular computation of equilibria

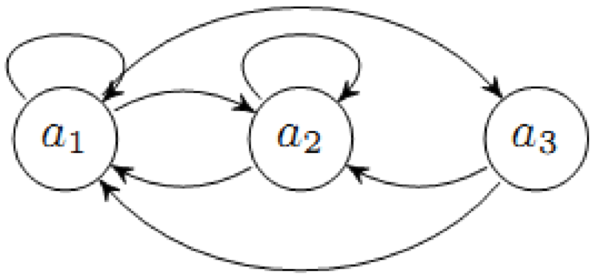
Application
- biological validation of our hypothesis ?

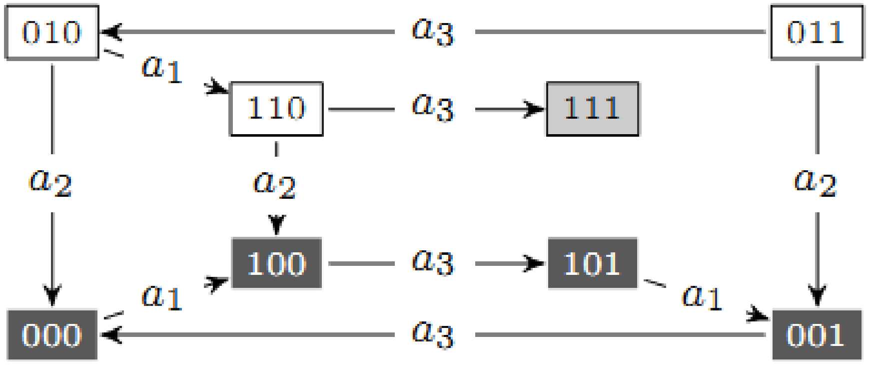
Perspective
- Symbolic version
- Extension of the separation condition

Towards elementary modules

- SCC ➔ currently the modular unit
- SCC separation ➔ possible while preserving M-relation

$$\eta = \begin{cases} \eta_{a_1}(s) = (s_{a_1} \wedge s_{a_2}) \vee \neg s_{a_3} \\ \eta_{a_2}(s) = s_{a_1} \wedge s_{a_2} \wedge s_{a_3} \\ \eta_{a_3}(s) = s_{a_1} \end{cases}$$





Modular organisation = $(\{a_2\}, \{a_1, a_3\})$

ANALYSIS OF M… NISATION OF INTERACTION N… D ON ASYMPTOTIC DY…

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Types of biomolecular networks

	Vertex	Edge	Char.
Gene GRN	Gene	Proteins Fix. (TF. Fact.) Regulation	Oriented Labeled
Metabolism	Chemical (substrate)	Bio-chemical reactions	Oriented Labeled
Signal Trans.	Proteins	Information Transmission	Oriented Labeled
Proteins	Proteins	Phys. Inter. (Binding)	UnOriented