Symmetry-inspired building blocks perform core logic computations in biological networks

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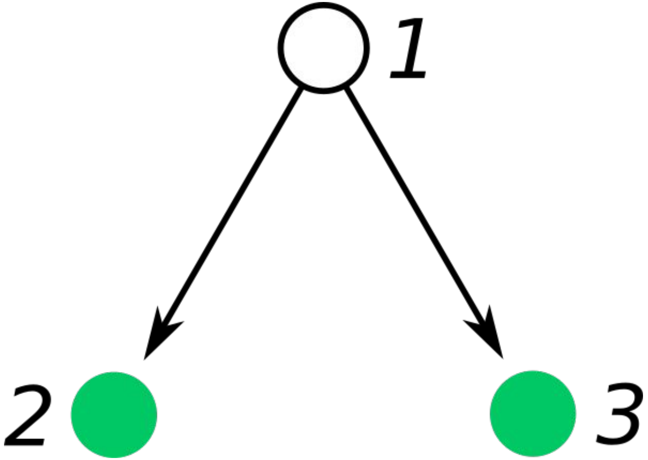
Introduction

- A major ambition of system science is to decompose the complex system into the fundamental building blocks and study the way the collective behavior emerges from their interactions
- Network motifs represent circuits that appear more frequently in certain networks, yet they don't allow the network decomposition and their function is undefined
- Symmetry considerations provide a novel way to find building blocks originating from the synchronization in the network dynamics in real large-scale networks
- Symmetry fibrations have first been introduced in category theory by Alexander Grothendieck in 1958 and later studied in computer science, chaos theory and graph theory providing us with the well-developed mathematical machinery
- Disclaimer: we talk about applications to transcriptional regulatory networks and use examples from bacteria, but this approach can be applied to any directed network

Admissible ODEs

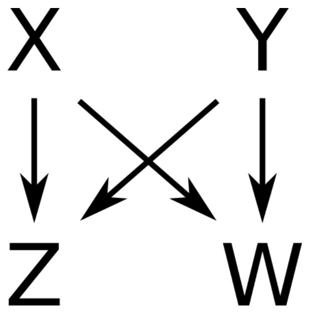
Set of ODEs is said to be admissible if they respect the network structure.



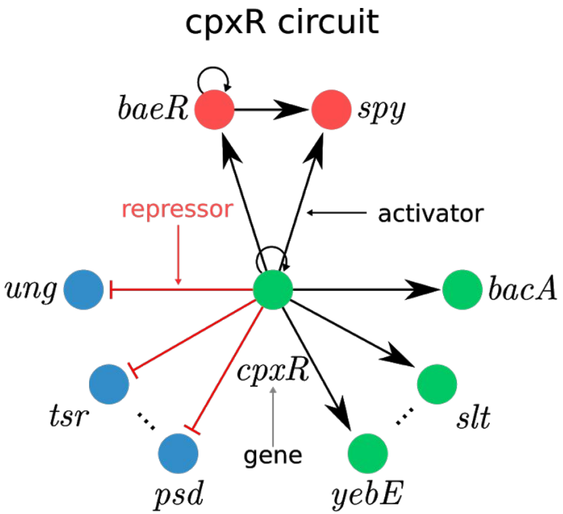
$$\begin{aligned} \dot{x}_1 &= f(x_1) \\ \dot{x}_2 &= g(x_2, x_1) \\ \dot{x}_3 &= g(x_3, x_1) \end{aligned}$$

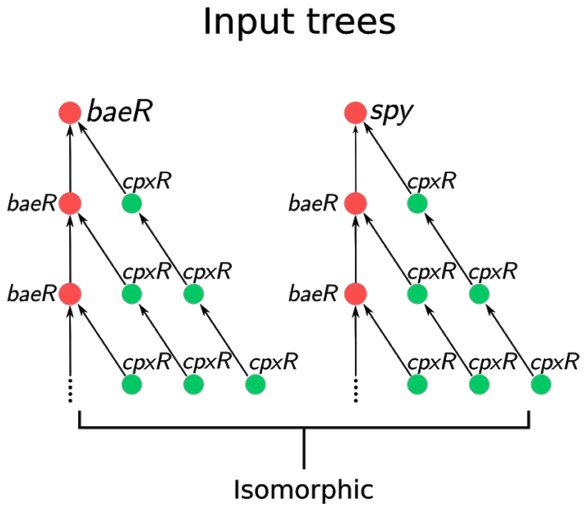
Why do network motifs fail to be functional?

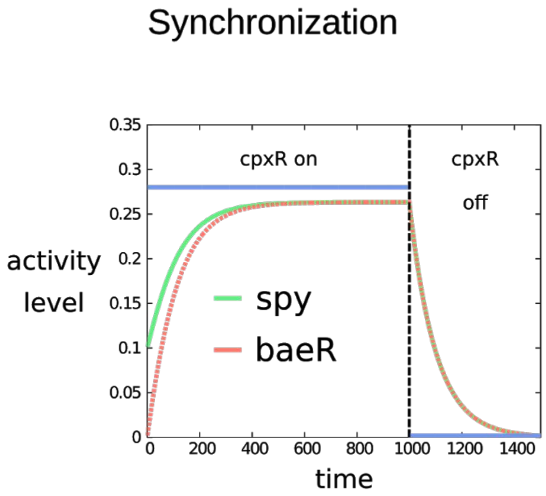
- Subgraph of graph $G=(N,E)$ is a graph $G'=(N', E')$ such that $N' \in N$ and $E' \in E$.
- To count the number of occurrences of motif G' in graph G, we count the number of subgraphs of G isomorphic to G'.
- The state of the node is defined by the state of the set of nodes that send to it.
- Each node of the motif can have extra inputs from inside and outside the motif drastically changing the dynamics.



Input-trees, fibers, synchronization





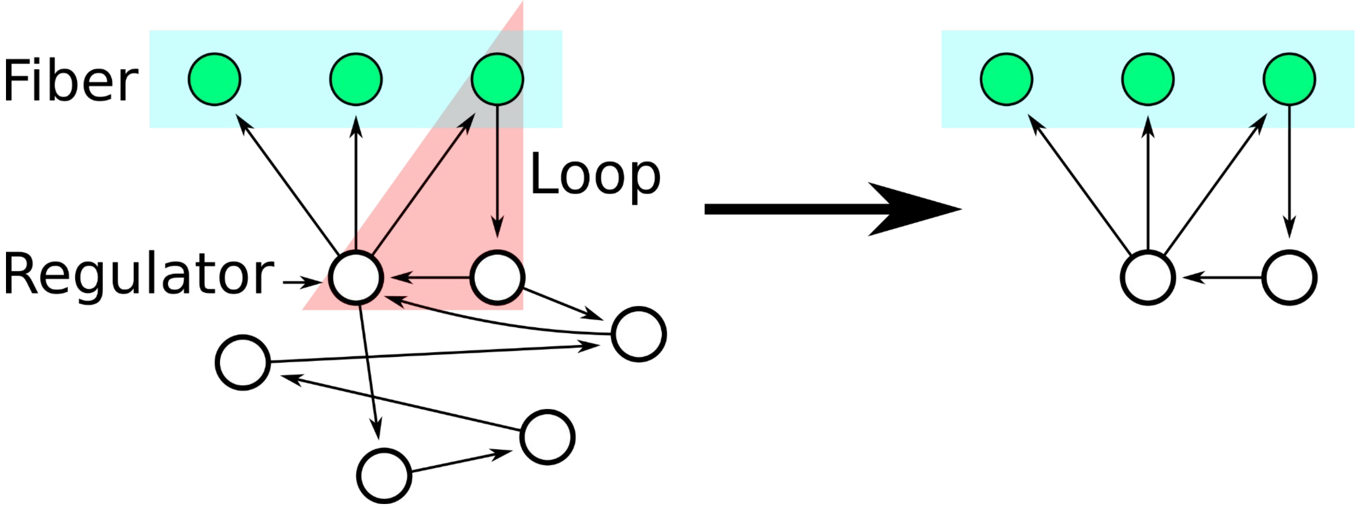


[1] L. DeVille, E. Lerman. Dynamics on Networks of Manifolds. Symmetry, Integrability and Geometry: Methods and Applications. 11 (2015).

Fiber Building blocks

An induced subgraph of $G = (N, E)$ induced by the vertex set $N' \in N$ is the graph $G'=(N', E')$ such that $E' = \{e = (n1, n2) \in E \mid n1, n2 \in N'\}$.

Fiber building block is an induced subgraph induced by: all the nodes in the fiber, all regulators that send inputs to the fiber and, if any node in a fiber is a part of a loop, the shortest loop including this node.

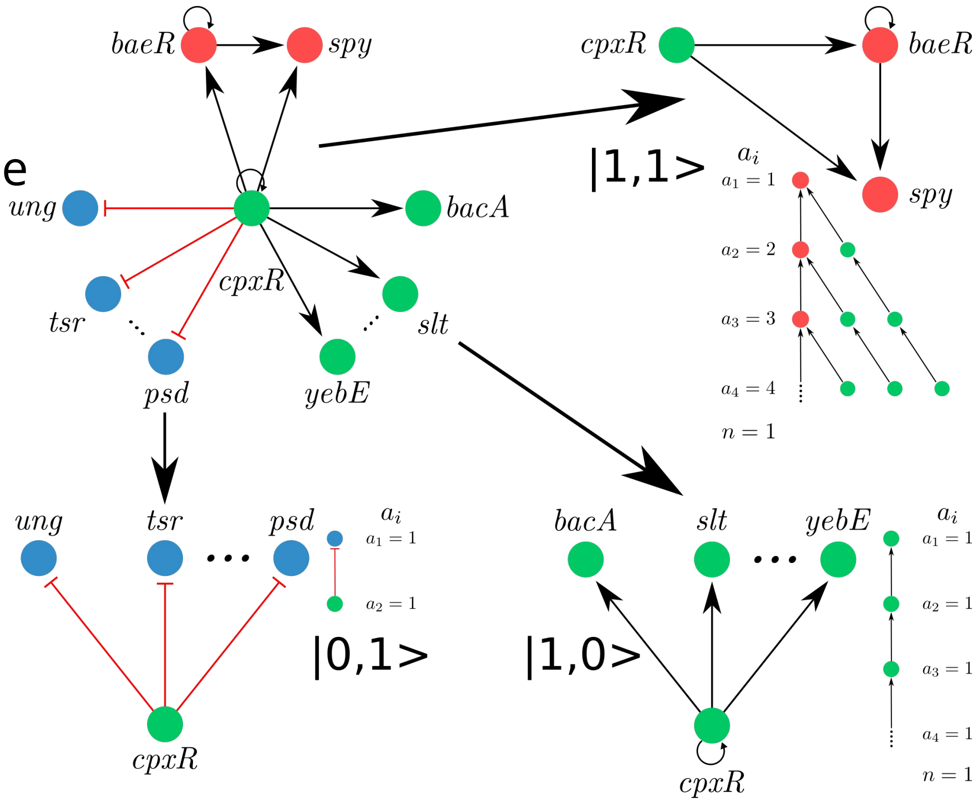


Building blocks fiber numbers

Building blocks are classified using 'fiber numbers' denoted |*n*, *l*>. *n* is the branching ratio of the input tree

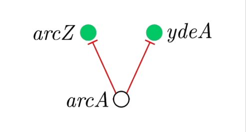
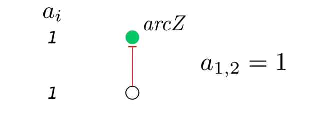
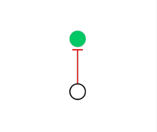
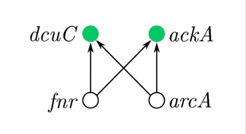
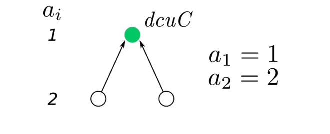
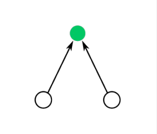
$$n = lim_{i \to \infty} \frac{a_{i+1}}{a_i}$$

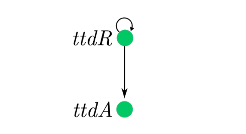
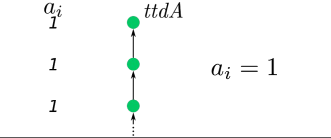
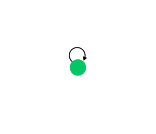
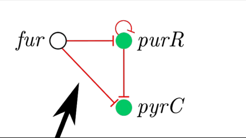
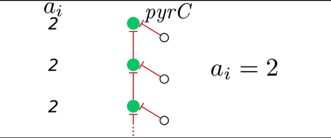
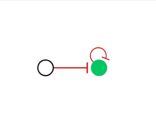
and *l* is the number of external regulators of the fiber



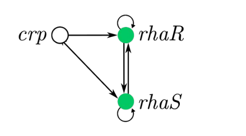
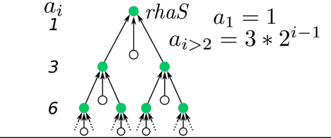
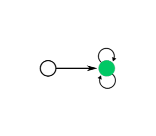
[1] F. Morone, I. Leifer, HA Mákse. Fibration symmetries uncover the building blocks of biological networks. Proc Natl Acad Sci USA. 117(15):83068314 (2020)

Building blocks. Integer |n, l>

$\|n,\ell\rangle$	Genetic circuit	Input tree	Base
$\|0,1\rangle$			
$\|0,2\rangle$			

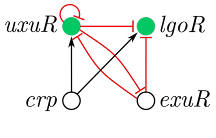
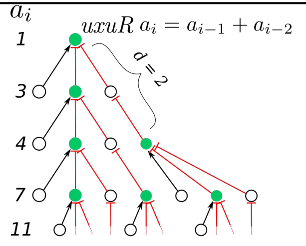
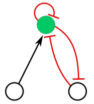
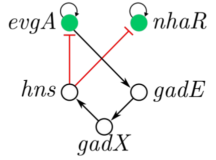
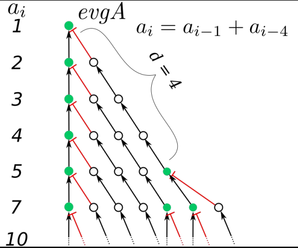
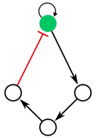
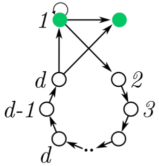
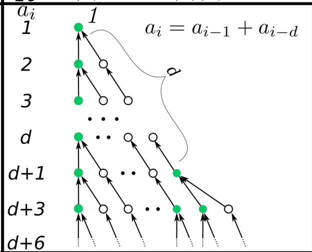
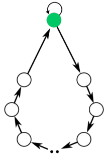
$\|n,\ell\rangle$	Genetic circuit	Input tree	Base
$\|1,0\rangle$			
$\|1,1\rangle$			

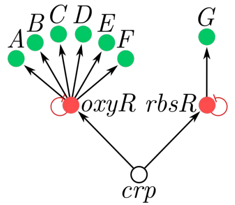
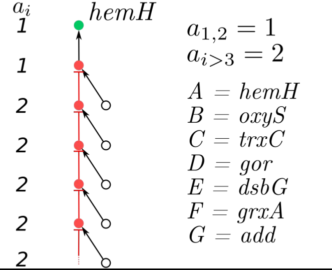
FFF

$\|n,\ell\rangle$	Genetic circuit	Input tree	Base
$\|2,1\rangle$			

[1] F. Morone, I. Leifer, HA Mákse. Fibration symmetries uncover the building blocks of biological networks. Proc Natl Acad Sci USA. 117(15):83068314 (2020)

Building blocks. Fibonacci and composite fibers

$\|\varphi_d, \ell\rangle$	Genetic circuit	Input tree	Base
$\|1.6180..., 2\rangle$	 2-Fibonacci Fiber (2-FF)		
$\|1.3802..., 1\rangle$	 4-Fibonacci Fiber (4-FF)		
$\|\varphi_d, \ell\rangle$	 d-Fibonacci Fiber (d-FF)		

$\|\varphi_d, \ell\rangle$	Genetic circuit	Input tree	Base
$\|0,1\rangle \oplus \|1,1\rangle$	 Multi-layer composite fiber		

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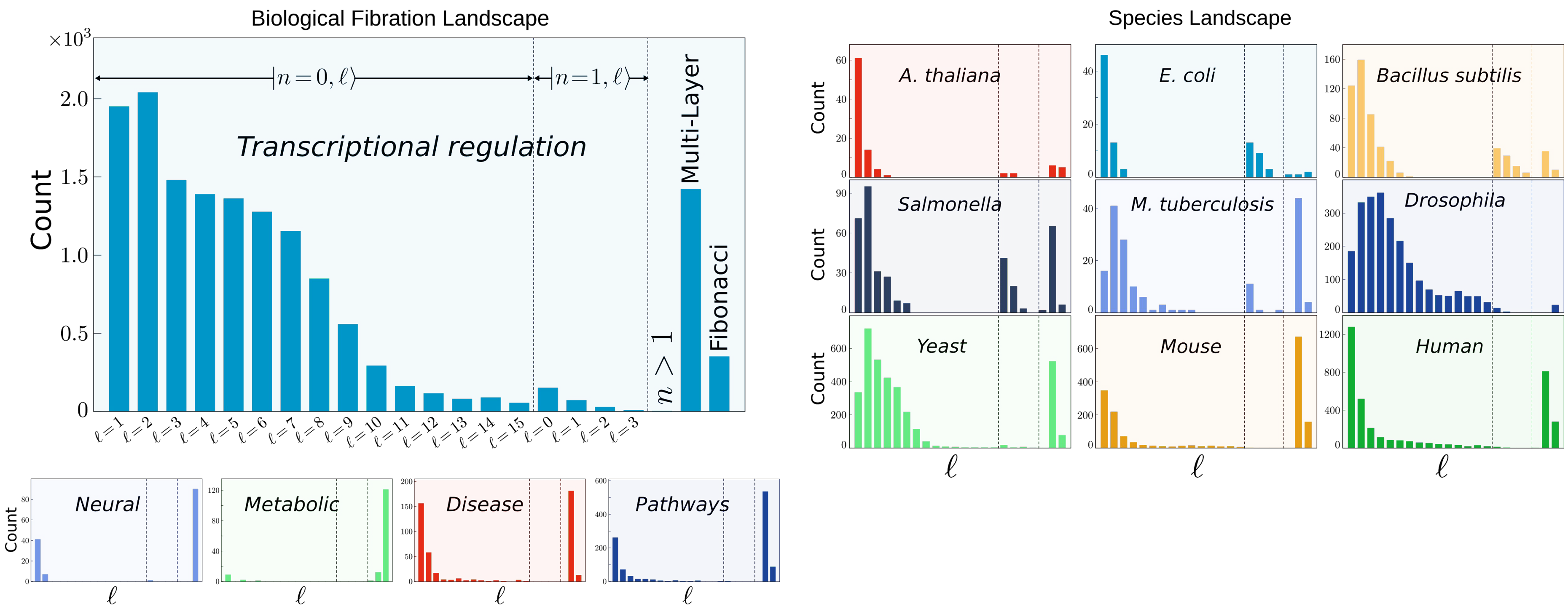
Building block landscape



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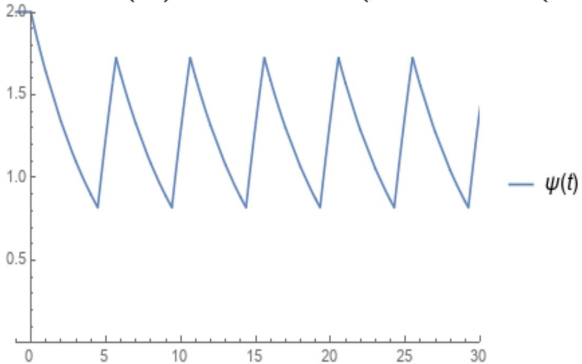
Dynamics of the autorepression loop (clock)

Repressor Autoregulator Loop $|1,0\rangle$

Genetic network | Q_t Input-tree | *Base* | Logic circuit

Continuous model

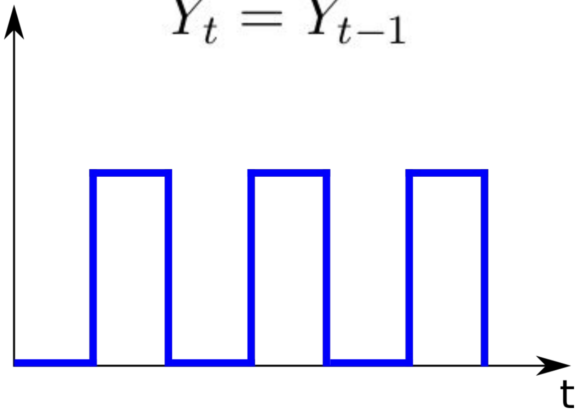
$$\dot{\psi} = -\alpha\psi(t) + \delta\ \theta(1 - \psi(t-\tau))$$



Boolean model

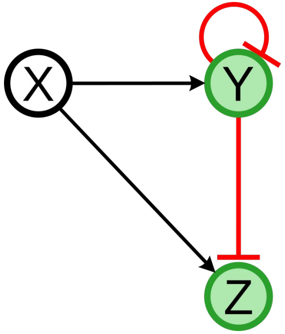
t	Y_t
0	1
1	0
2	1
3	0
4	1

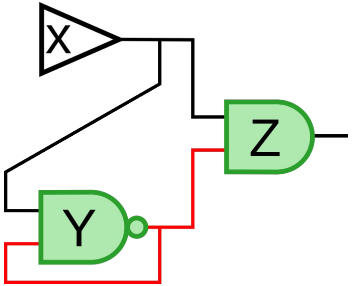
$$Y_t = \overline{Y_{t-1}}$$



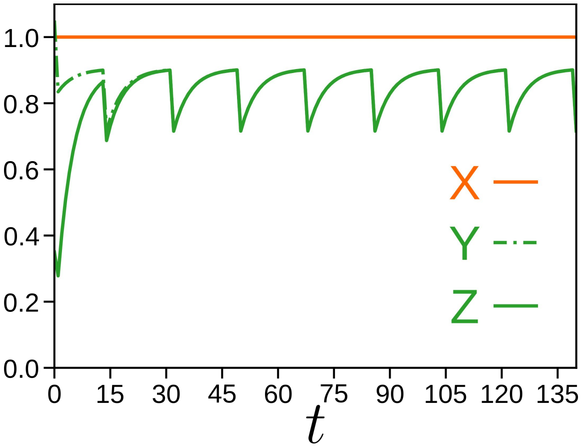
[1] I. Leifer, F. Morone, SDS Reis, JS Andrade, M. Sigman, HA Mákse. Circuits with broken fibration symmetries perform core logic computations in biological networks. PLoS Comput Biol 16(6):e1007776 (2020).

UNSAT-FFF synchronization and oscillation





$$Y_t = \overline{Y_{t-1}} \text{ AND } X_{t-1}$$
$$Z_t = \overline{Y_{t-1}} \text{ AND } X_{t-1}$$

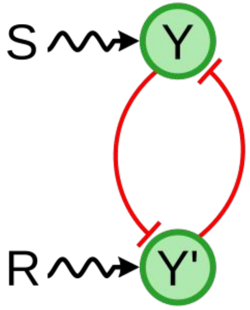


t	X_t	Y_t	Z_t
0	0	1	1
1	0	0	0
0	0	1	0
1	0	0	0
0	0	0	1
1	0	0	0

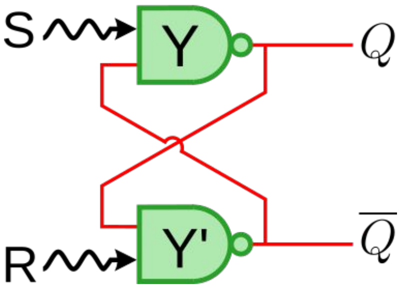
t	X_t	Y_t	Z_t
0	1	1	0
1	1	0	0
2	1	1	1
3	1	0	0
4	1	1	1
5	1	0	0

[1] I. Leifer, F. Morone, SDS Reis, JS Andrade, M. Sigman, HA Mákse. Circuits with broken fibration symmetries perform core logic computations in biological networks. PLoS Comput Biol 16(6):e1007776 (2020).

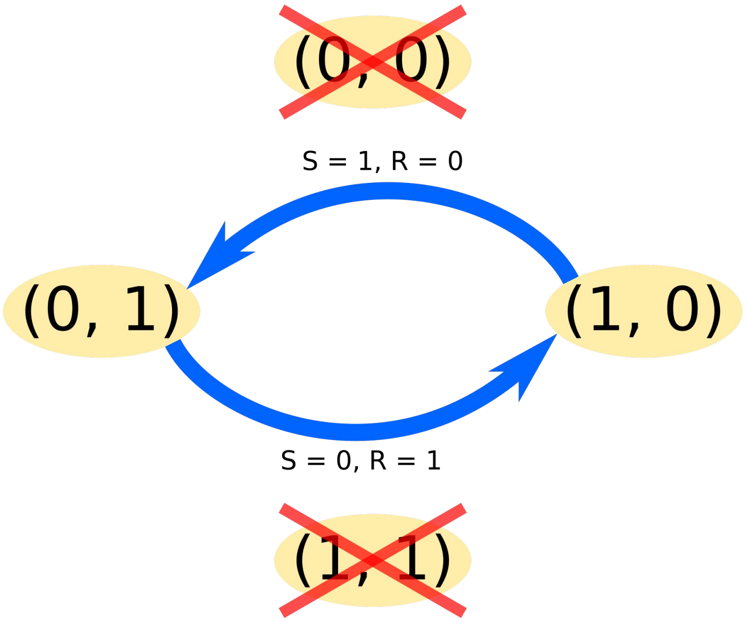
Dynamics of the genetic flip-flop (memory)



SR flip-flop



Boolean model



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Conclusion

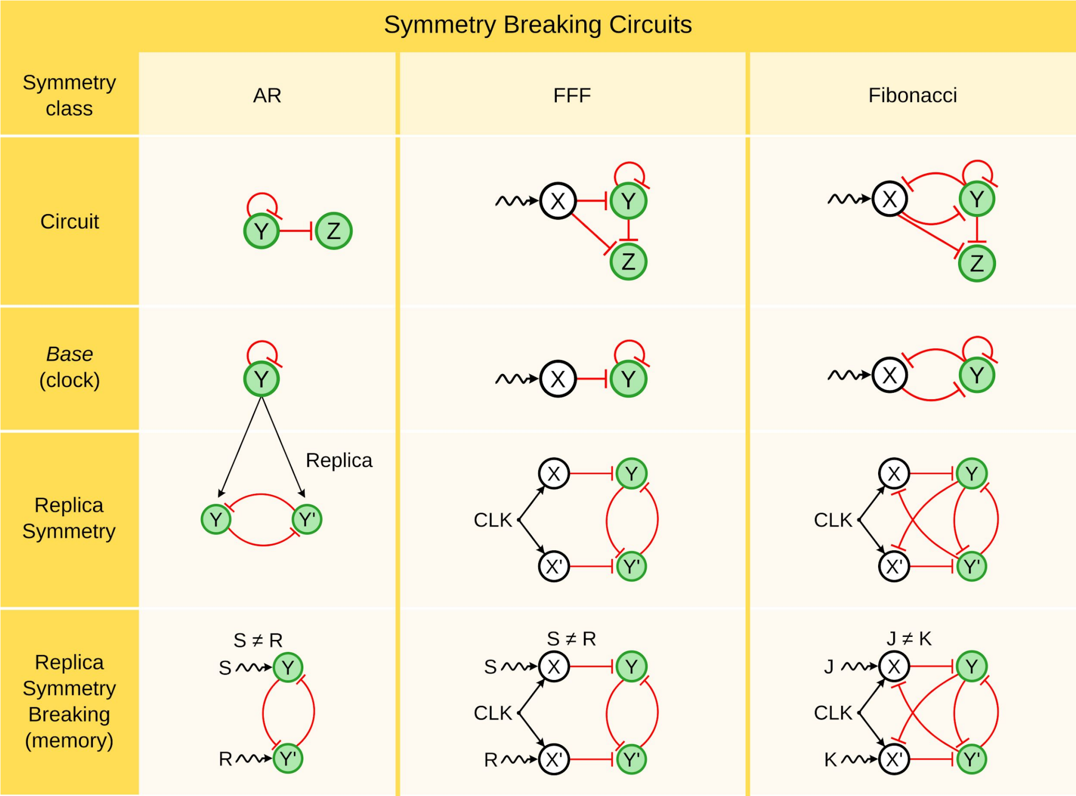
- Fibration symmetry provides the novel way to analyze a biological network
- Symmetries of the network help uncover new functional building blocks related to synchronization
- Along with synchronization functional building blocks play the role of clock and memory
- This is a theoretically principled and algorithmically supported strategy to search for computational building blocks in directed networks

Further reading:
Morone, Leifer, Makse, PNAS (2020)
Leifer et al. Plos. Comp. bio (2020)
Leifer et al. BMC Bioinformatics (2021)

Algorithm availability:
https://github.com/makselab

Thank you for your attention!

Constructing symmetry breaking circuits



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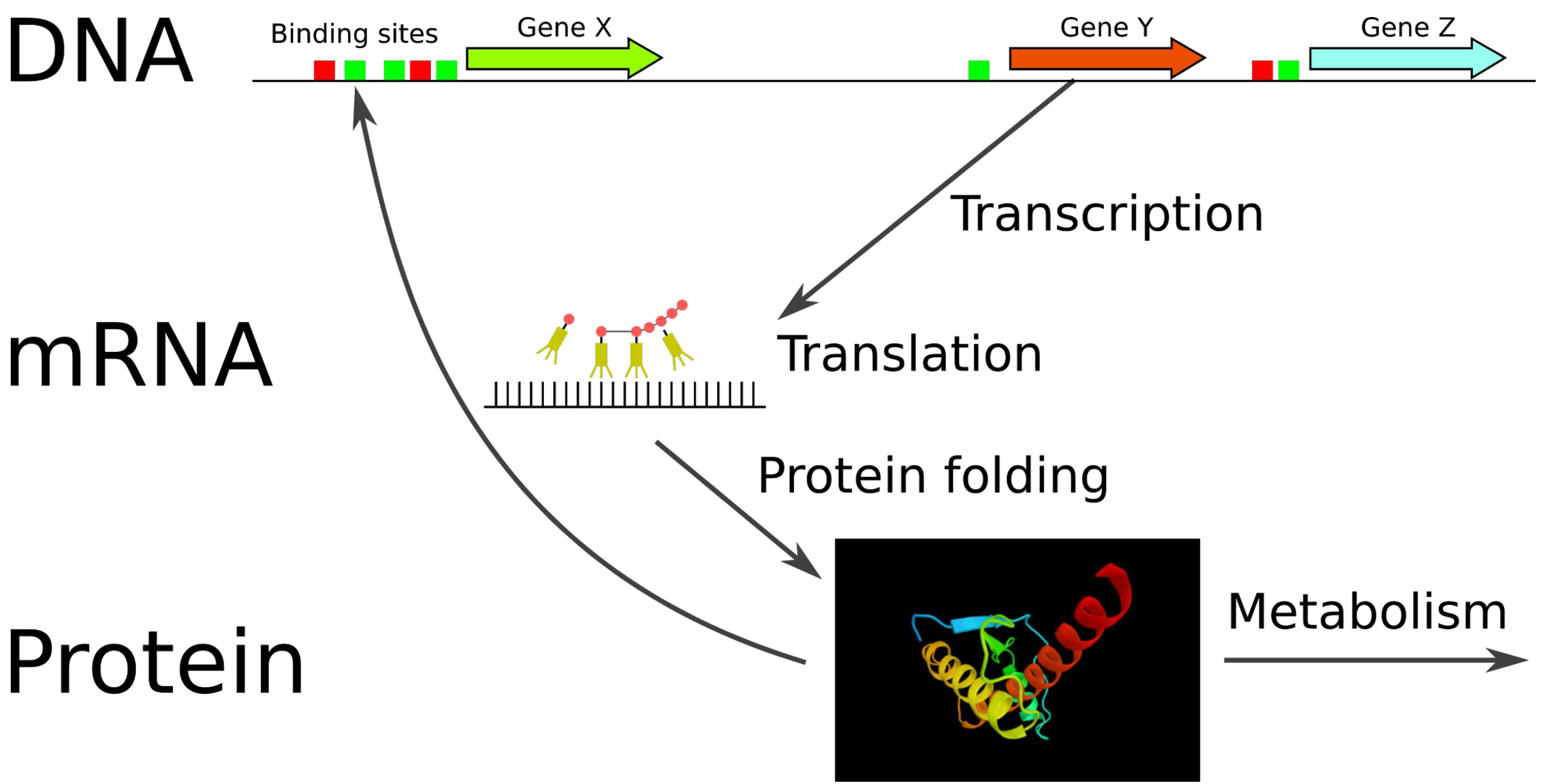
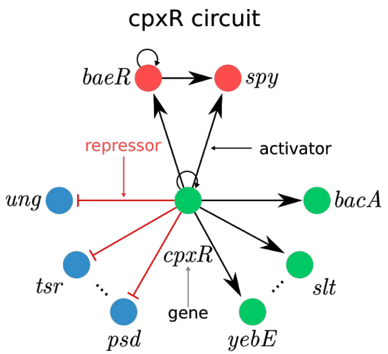
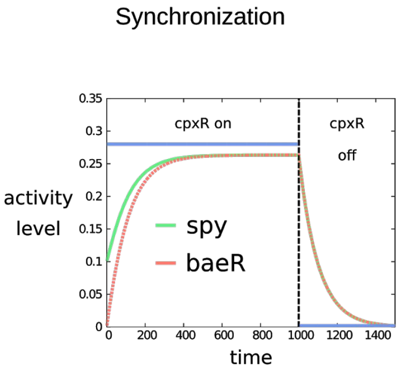
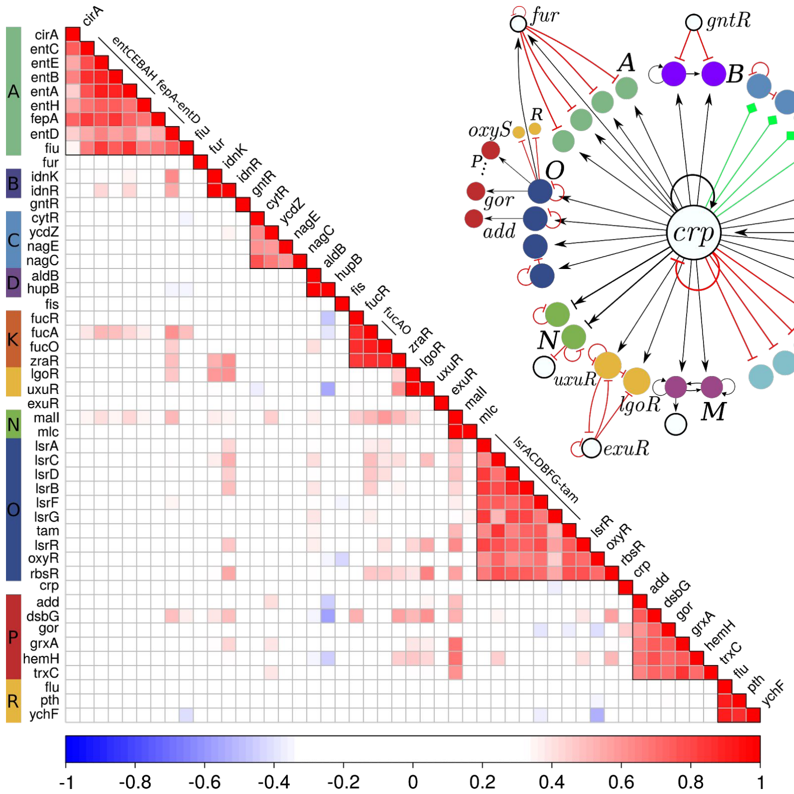
What is a transcriptional regulatory network?

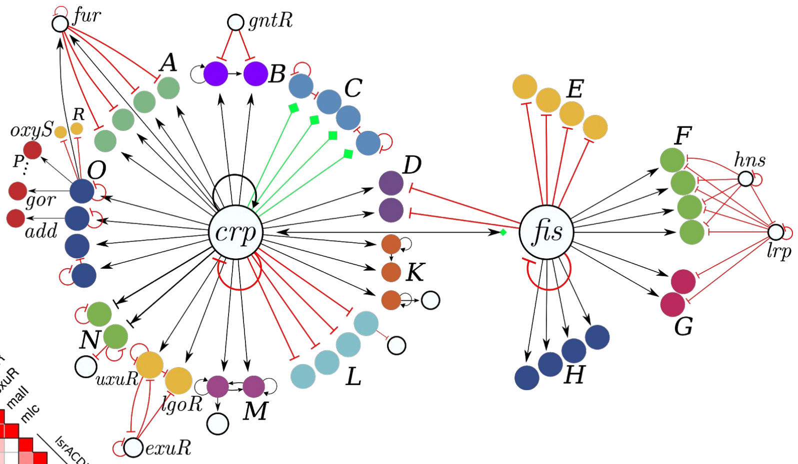


Symmetry Fibration Leads to Synchronization.









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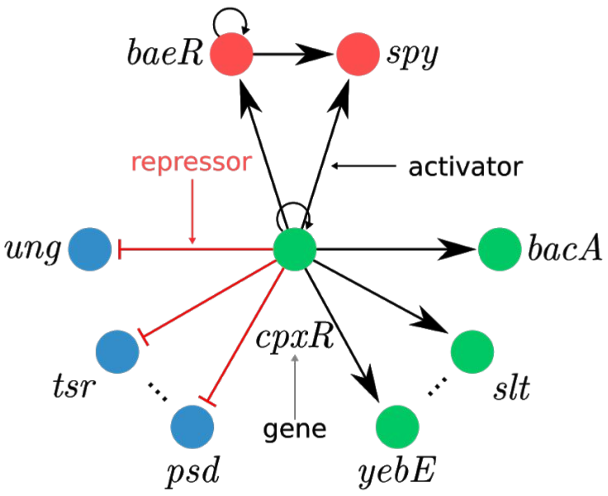
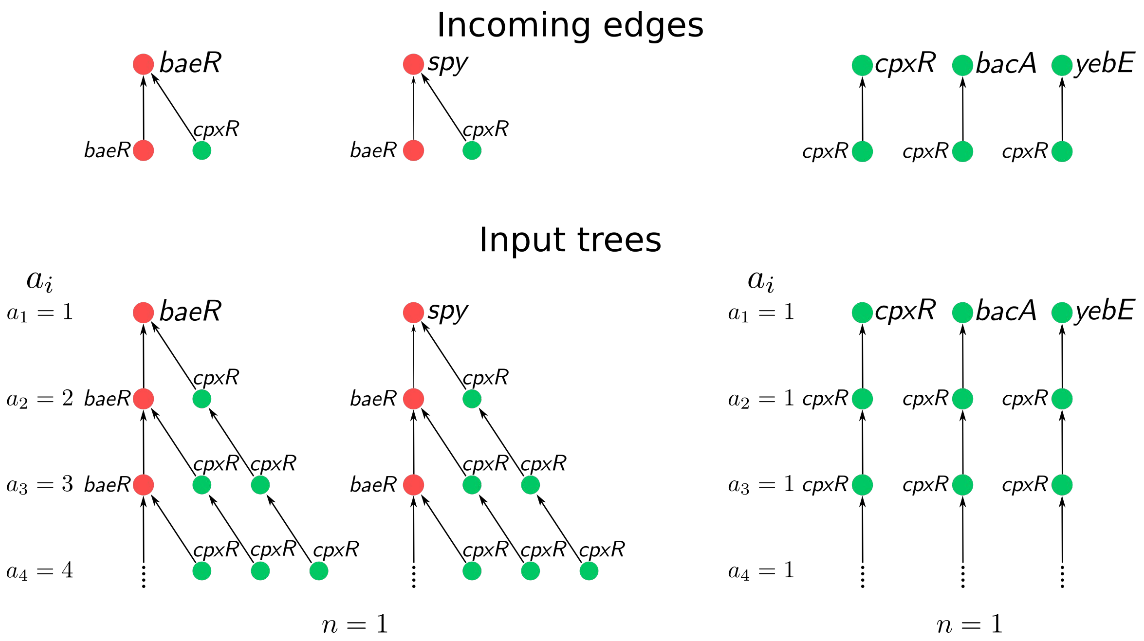
Input trees, branching ratio

cpxR circuit



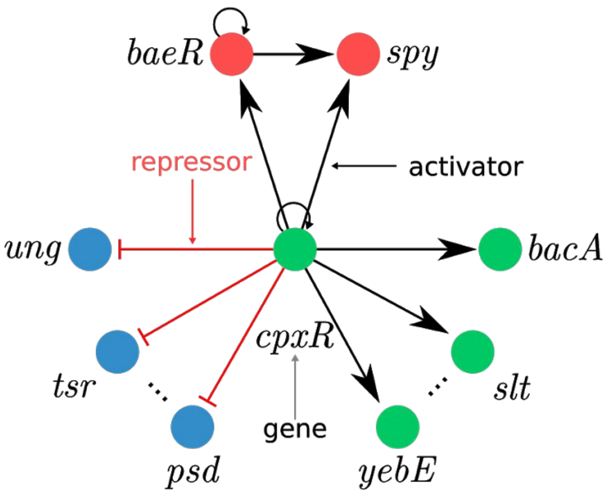


$$n = lim_{i \to \infty} \frac{a_{i+1}}{a_i}$$

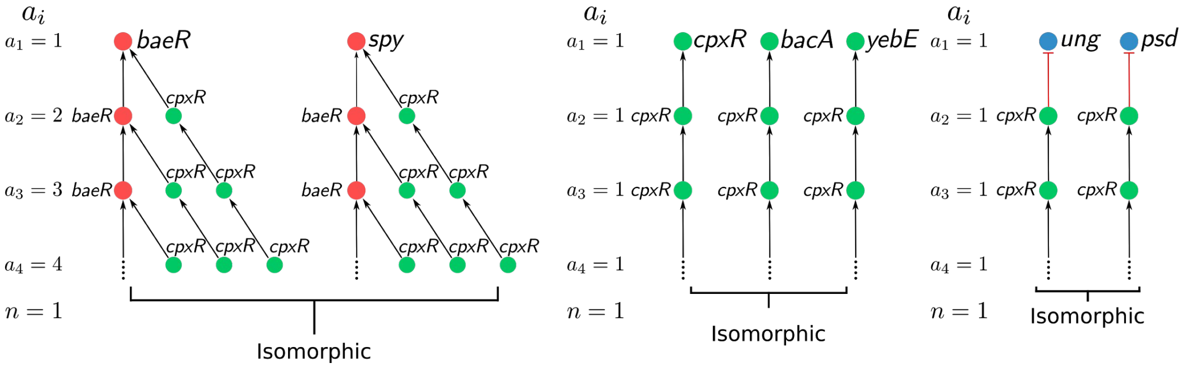
[1] A. Grothendieck, Technique de descente et theoremes d'existence en geometrie algebrique, I. Generalites. Descente par morphismes fidelement plats. Seminaire N. Bourbaki 5, 299–327 (1958–1960).
[2] P. Boldi, S. Vigna, Fibrations of graphs. Discrete Math. 243, 21–66 (2001)
[3] F. Morone, I. Leifer, HA Mákse. Fibration symmetries uncover the building blocks of biological networks. Proc Natl Acad Sci USA. 117(15):83068314 (2020)

Input tree isomorphism, fibers

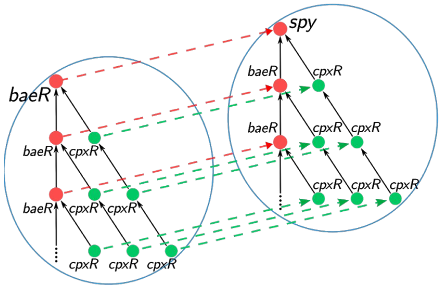
cpxR circuit



Input trees



Isomorphism



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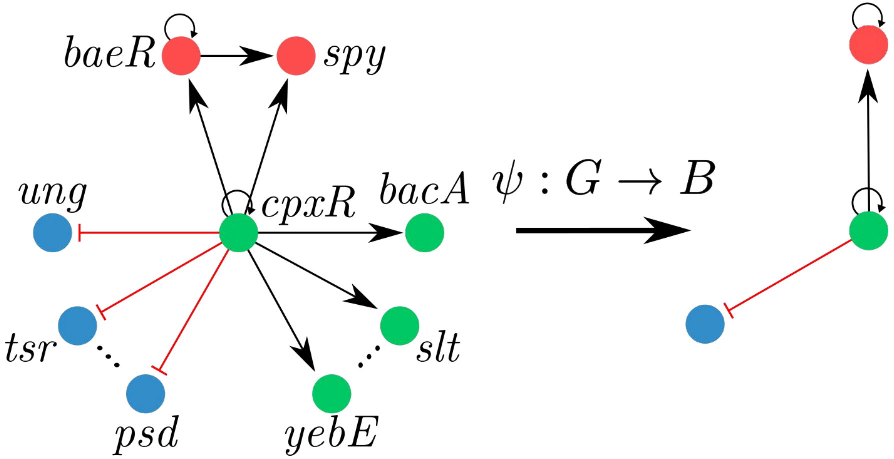
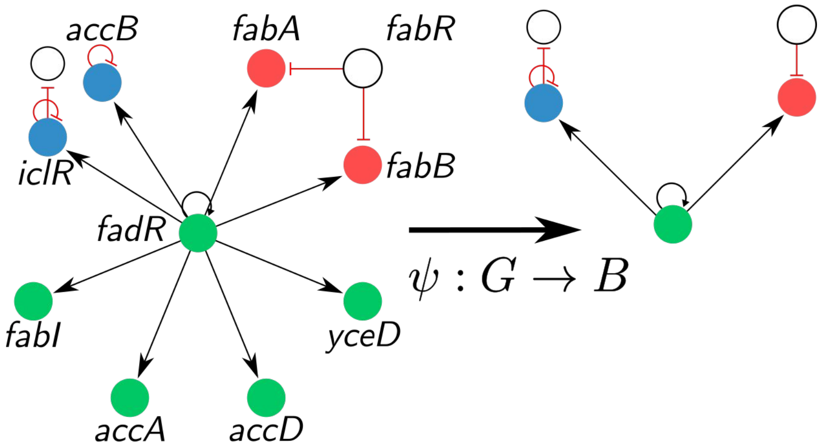
[2] P. Boldi, S. Vigna, Fibrations of graphs. Discrete Math. 243, 21–66 (2001)
[3] F. Morone, I. Leifer, HA Mákse. Fibration symmetries uncover the building blocks of biological networks. Proc Natl Acad Sci USA. 117(15):83068314 (2020)

Symmetry fibration

Symmetry fibration of the cpxR circuit



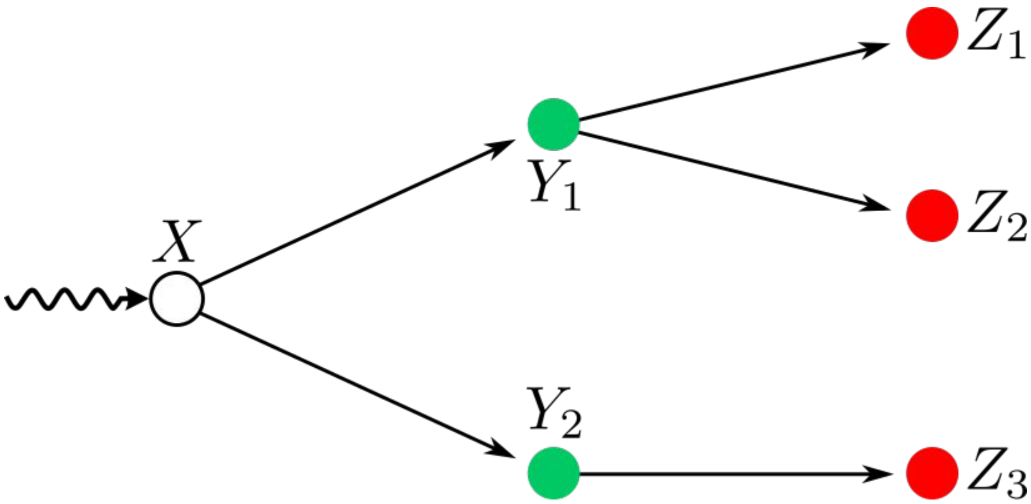
Fibration of the fadR circuit



Symmetry fibration is a map between two graphs that satisfies the lifting property [2].

[1] A. Grothendieck, Technique de descente et theoremes d'existence en geometrie algebrique, I. Generalites. Descente par morphismes fidelement plats. Seminaire N. Bourbaki 5, 299–327 (1958–1960).
[2] P. Boldi, S. Vigna, Fibrations of graphs. Discrete Math. 243, 21–66 (2001)
[3] F. Morone, I. Leifer, HA Mákse. Fibration symmetries uncover the building blocks of biological networks. Proc Natl Acad Sci USA. 117(15):83068314 (2020)

Network is the representation of the system of ODEs



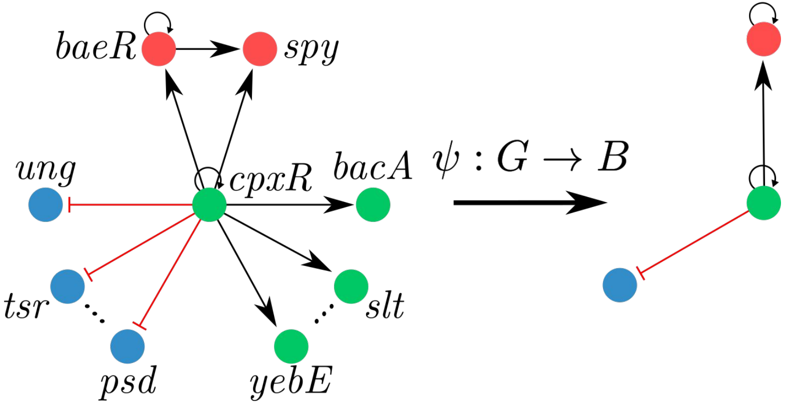
$$
\begin{cases}
\frac{dx}{dt} = -k(x) + f(t) \\
\frac{dy_1}{dt} = -k(y_1) + g(x) \\
\frac{dy_2}{dt} = -k(y_2) + g(x) \\
\frac{dz_1}{dt} = -k(z_1) + g(y_1) \\
\frac{dz_2}{dt} = -k(z_2) + g(y_1) \\
\frac{dz_3}{dt} = -k(z_3) + g(y_2)
\end{cases}
$$

$$k(x) = -\alpha x$$

$$g(x) = \gamma_x \theta(x - k_x)$$

Symmetry Fibration Leads to Synchronization

Symmetry fibration of the cpxR circuit



$$\begin{cases} \frac{dx_1}{dt} = -\alpha x_1 + \gamma_{x_1}\theta(x_1 - k_{x_1}) \times \gamma_{y_1}\theta(y_1 - k_{y_1}) \\ \frac{dx_2}{dt} = -\alpha x_2 + \gamma_{x_1}\theta(x_1 - k_{x_1}) \times \gamma_{y_1}\theta(y_1 - k_{y_1}) \\ \frac{dy_1}{dt} = -\alpha y_1 + \gamma_{y_1}\theta(y_1 - k_{y_1}) \\ \frac{dy_2}{dt} = -\alpha y_2 + \gamma_{y_1}\theta(y_1 - k_{y_1}) \\ \dots \\ \frac{dz_1}{dt} = -\alpha z_1 + \gamma_{y_1}\theta(k_{y_1} - y_1) \\ \frac{dz_2}{dt} = -\alpha z_2 + \gamma_{y_1}\theta(k_{y_1} - y_1) \\ \dots \end{cases}$$

$$\begin{cases} x_1(t) = x(t) \\ x_2(t) = x(t) \\ y_1(t) = y(t) \\ y_2(t) = y(t) \\ \dots \\ z_1(t) = z(t) \\ z_2(t) = z(t) \\ \dots \end{cases}$$

$$x_1 = baeR, \; x_2 = spy$$
$$y_1 = cpxR, \; y_2 = bacA$$
$$z_1 = ung, \; z_2 = tsr$$

$$\begin{cases} \frac{dx}{dt} = -\alpha x + \gamma_{x_1}\theta(x - k_{x_1}) \times \gamma_{y_1}\theta(y - k_{y_1}) \\ \frac{dy}{dt} = -\alpha y + \gamma_{y_1}\theta(y - k_{y_1}) \\ \frac{dz}{dt} = -\alpha z + \gamma_{y_1}\theta(k_{y_1} - y) \end{cases}$$

[1] Stewart I, Golubitsky M, Pivato M. Symmetry Groupoids and Patterns of Synchrony in Coupled Cell Networks. SIAM J. Appl. Dynam. Sys. 2(4),609-646 (2003).
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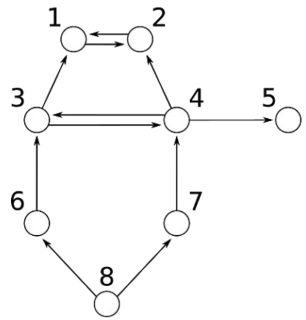
Algorithms to find fibers

Initial partition

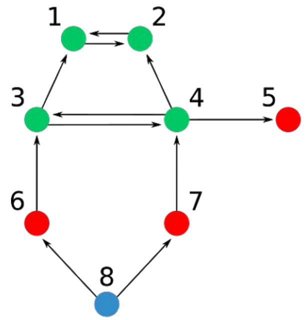


	1	2	3	4	5	6	7	8
⚪	2	2	2	2	1	1	1	0
New color	🟢	🟢	🟢	🟢	🔴	🔴	🔴	🔵

Input Set Color Vector (ISCV) of a node is a vector of length equal to the number of colors in the graph. Each entry of the ISCV of a given node counts how many nodes of each color are in the k-in of this node. The balanced coloring is achieved when all nodes of the same color have the same ISCVs.

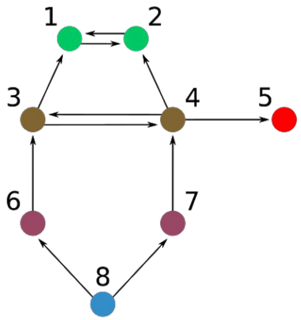
Algorithm availability:
https://github.com/ianleifer/fibrationSymmetries
https://github.com/makselab

Second partition



	1	2	3	4	5	6	7	8
🟢	2	2	1	1	1	0	0	0
🔴	0	0	1	1	0	0	0	0
🔵	0	0	0	0	0	1	1	0
New color	🟢	🟢	🟤	🟤	🔴	🟣	🟣	🔵

Last partition



	1	2	3	4	5	6	7	8
🟢	1	1	0	0	0	0	0	0
🟤	1	1	1	1	1	0	0	0
🔴	0	0	0	0	0	0	0	0
🟣	0	0	1	1	0	0	0	0
🔵	0	0	0	0	0	1	1	0
Final color	🟢	🟢	🟤	🟤	🔴	🟣	🟣	🔵

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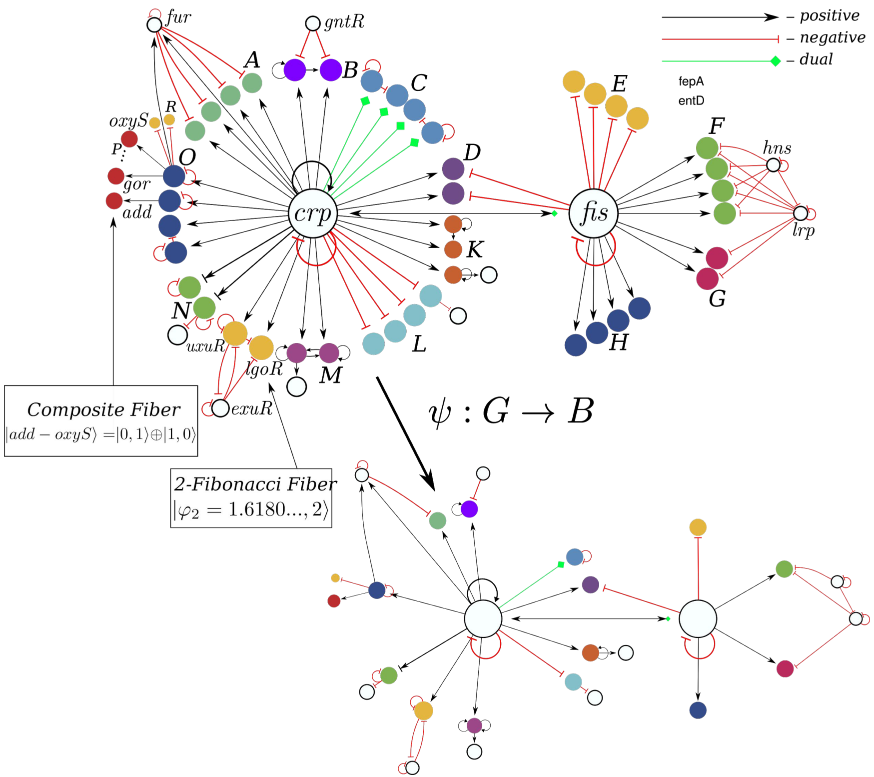
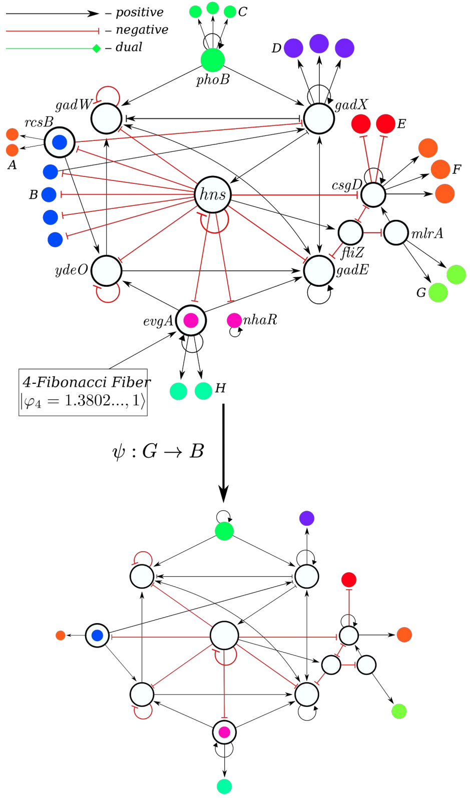
Strongly Connected Components

crp-fis connected component

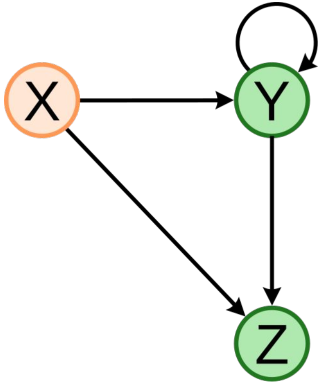


pH connected component

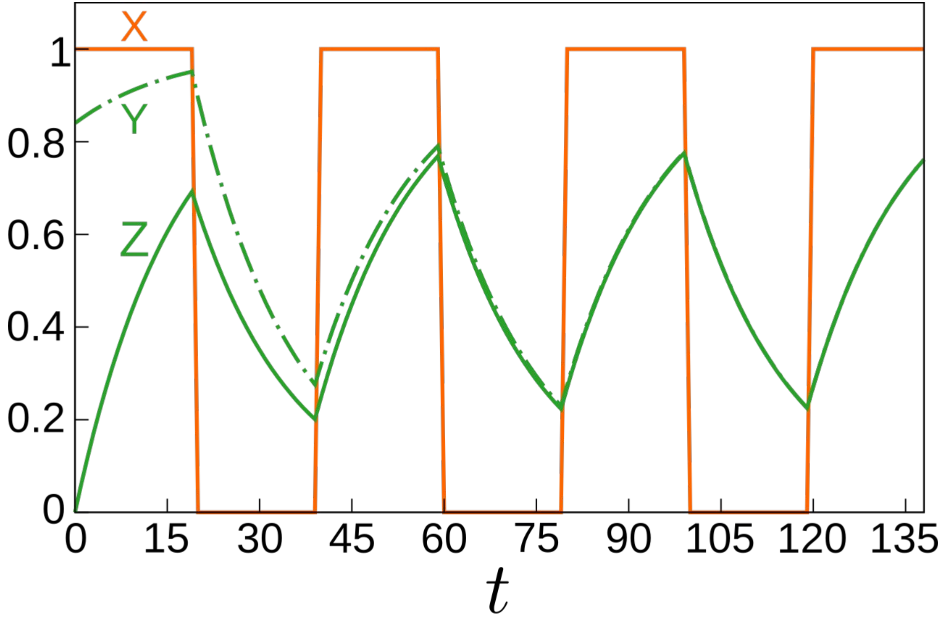


[1] F. Morone, I. Leifer, HA Mákse. Fibration symmetries uncover the building blocks of biological networks. Proc Natl Acad Sci USA. 117(15):83068314 (2020)

SAT-FFF and it's synchronization



$$\begin{cases} \dot{y} = -\alpha y(t) + \gamma_x \theta(x(t) - k_x) \times \gamma_y \theta(y(t) - k_y), \\ \dot{z} = -\alpha z(t) + \gamma_x \theta(x(t) - k_x) \times \gamma_y \theta(y(t) - k_y). \end{cases}$$



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