
Symmetry-inspired analysis of biological networks

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Introduction

Introduction

- The centerpiece in science is to decompose the complex system into the fundamental building blocks and study the way the collective behavior emerges from their interactions
- Two approaches are popular in biology: modularity by the biological function that parts perform together and network motifs
- Symmetry fibrations provide a novel way to look for building blocks originating from the synchronization in the network dynamics
- 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 to be applied
- Disclaimer: we talk about applications to transcriptional regulatory networks and use examples from bacteria, but this approach can be applied to any directed network

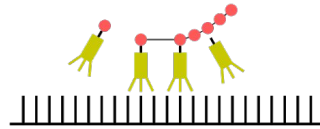
Methods

What is a transcriptional regulatory network?

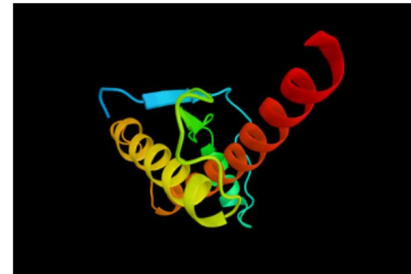
DNA



mRNA



Protein



Transcription

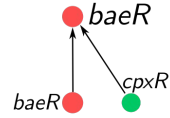
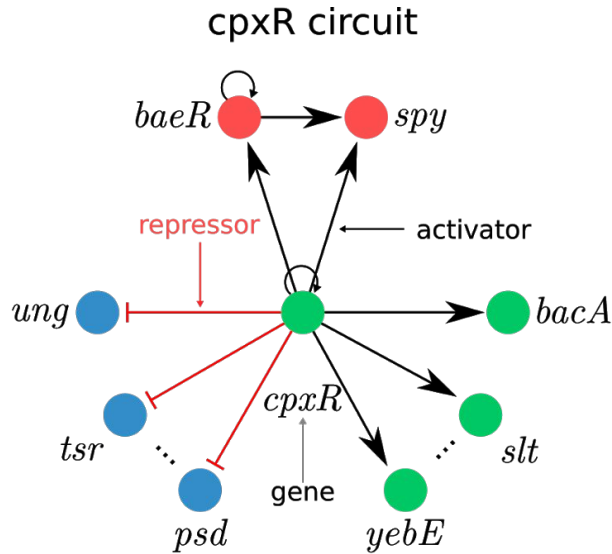
Translation

Protein folding

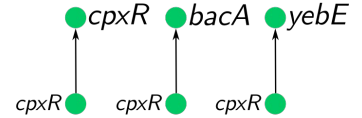
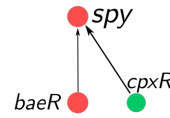
Metabolism



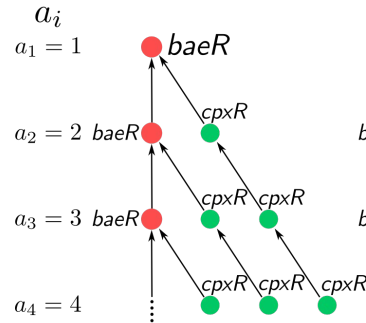
Input trees, branching ratio



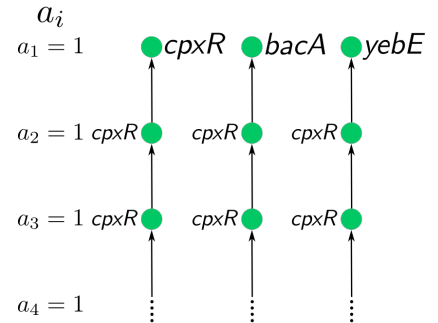
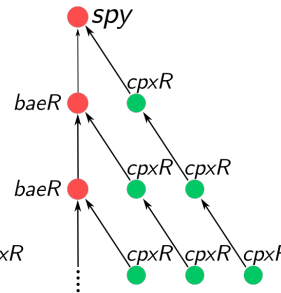
Incoming edges



Input trees



$n = 1$

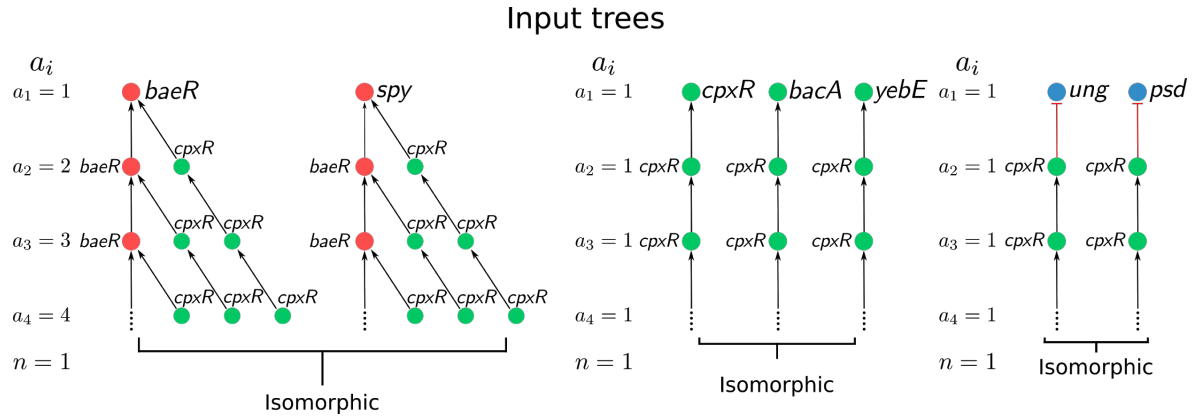
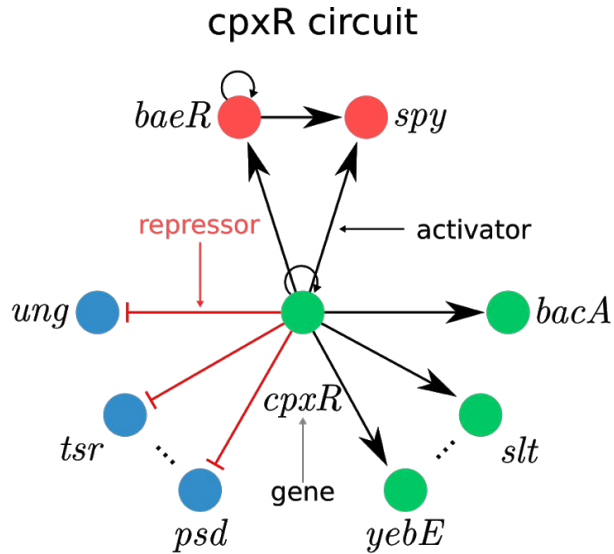


$n = 1$

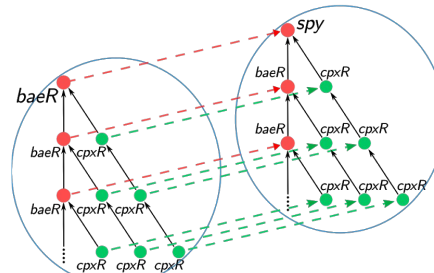
[1] A. Grothendieck, Technique de descente et theoremes d'existence en geometrie algebrique, I. Generalites. Descente par morphismes fidelement plats. Seminaire N. Bourbaki 5, 299–327 (1958–1960).
 [2] P. Boldi, S. Vigna, Fibrations of graphs. Discrete Math. 243, 21–66 (2001)
 [3] F. Morone, I. Leifer,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

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

Input tree isomorphism, fibers



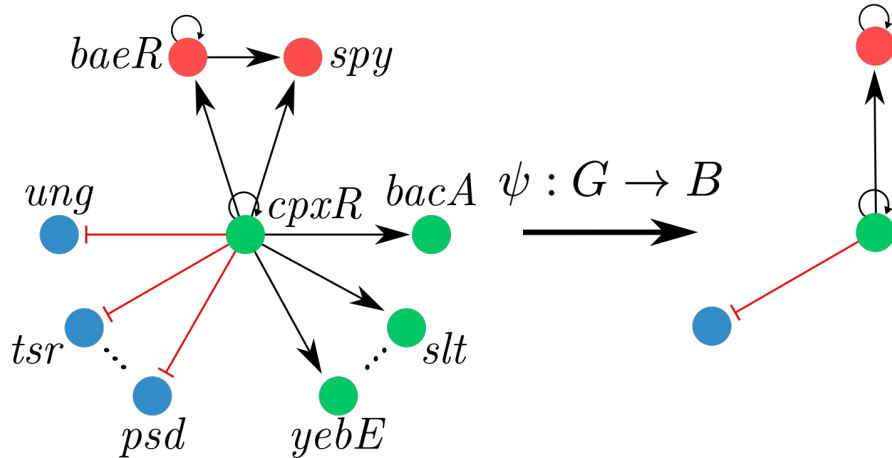
Isomorphism



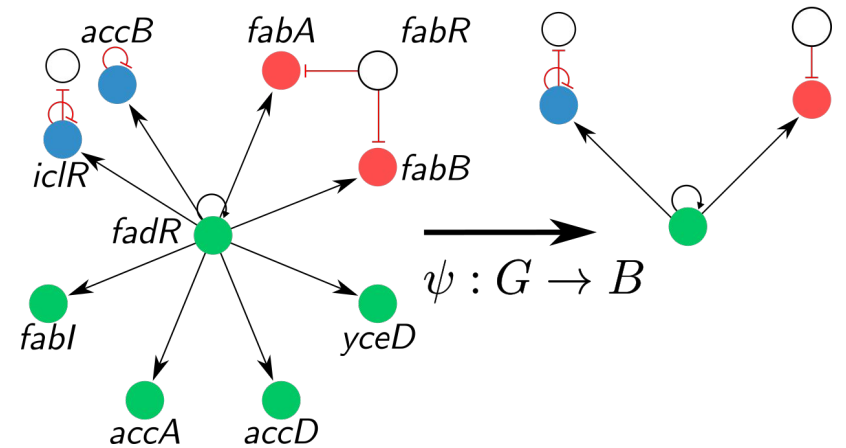
- [1] A. Grothendieck, Technique de descente et theoremes d'existence en geometrie algebrique, I. Generalites. Descente par morphismes fidelement plats. Seminaire N. Bourbaki 5, 299–327 (1958–1960).
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 [3] F. Morone, I. Leifer, HA Mákse. Fibration symmetries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

Symmetry fibration

Symmetry fibration of the *cpxR* circuit



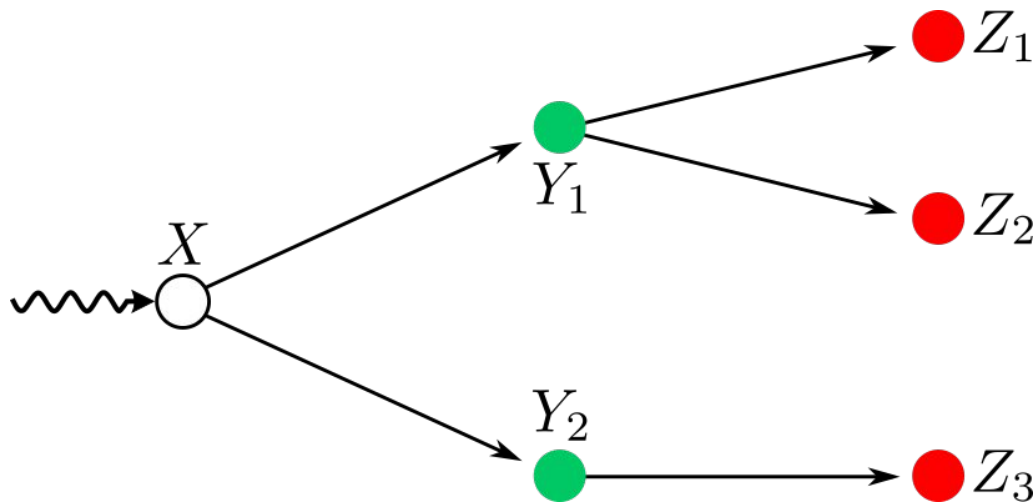
Fibration of the *fadR* circuit



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



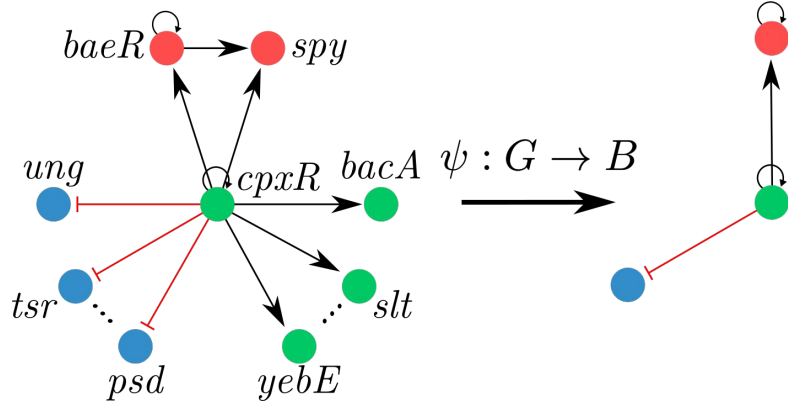
$$\left\{ \begin{array}{l} \frac{dx}{dt} = -k(x) + f(t) \\ \frac{dy_1}{dt} = -k(y_1) + g(x) \\ \frac{dy_2}{dt} = -k(y_2) + g(x) \\ \frac{dz_1}{dt} = -k(z_1) + g(y_1) \\ \frac{dz_2}{dt} = -k(z_2) + g(y_1) \\ \frac{dz_3}{dt} = -k(z_3) + g(y_2) \end{array} \right.$$

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

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

Symmetry Fibration Leads to Synchronization

Symmetry fibration of the cpxR circuit

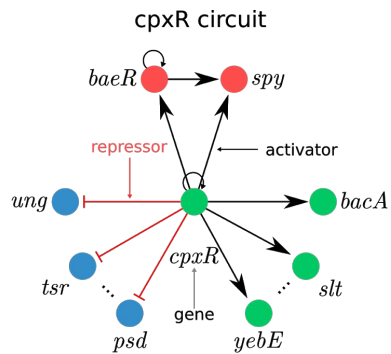


$$\begin{aligned} x_1 &= baeR, & x_2 &= spy \\ y_1 &= cpxR, & y_2 &= bacA \\ z_1 &= ung, & z_2 &= tsr \end{aligned}$$

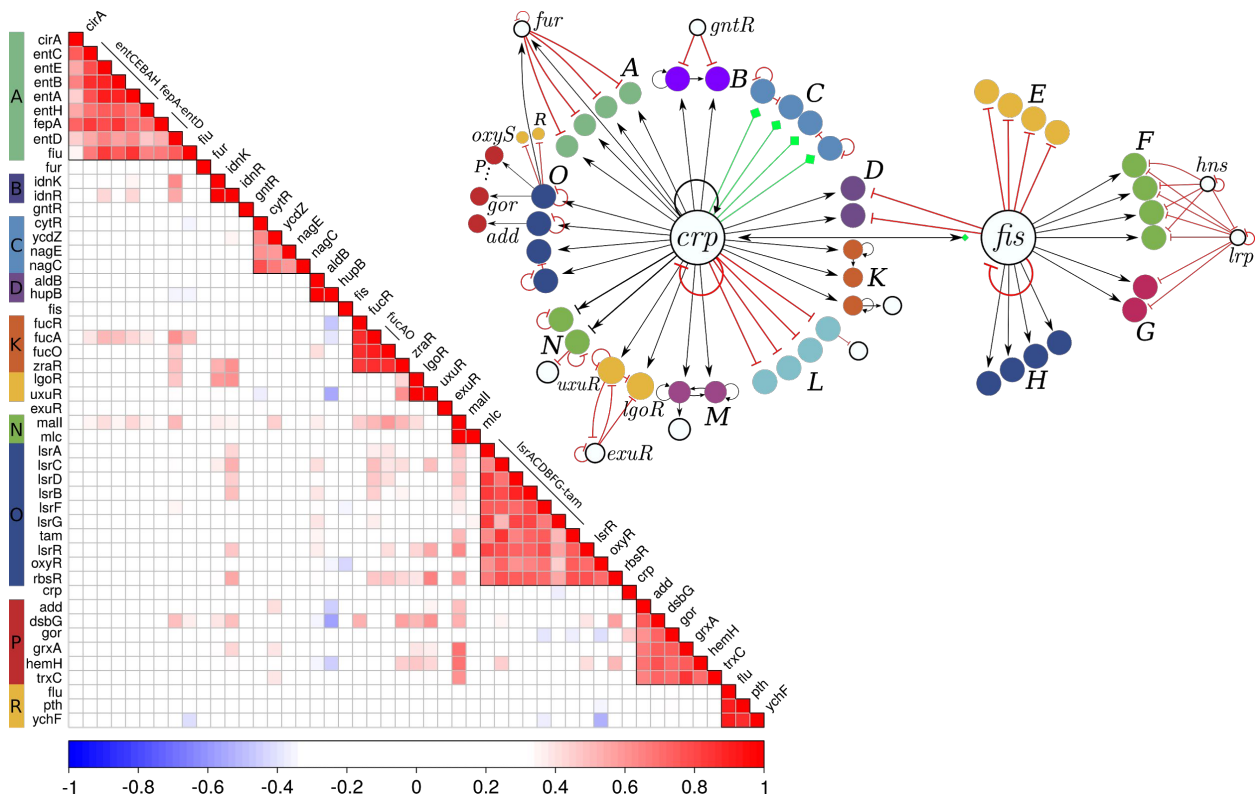
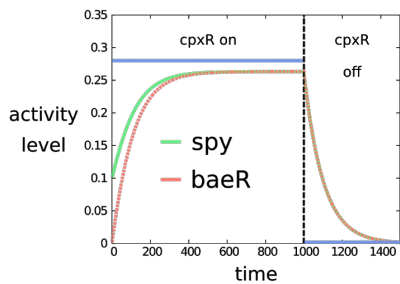
$$\begin{cases} \frac{dx_1}{dt} = -\alpha x_1 + \gamma_{x_1} \theta(x_1 - k_{x_1}) \times \gamma_{y_1} \theta(y_1 - k_{y_1}) \\ \frac{dx_2}{dt} = -\alpha x_2 + \gamma_{x_1} \theta(x_1 - k_{x_1}) \times \gamma_{y_1} \theta(y_1 - k_{y_1}) \\ \frac{dy_1}{dt} = -\alpha y_1 + \gamma_{y_1} \theta(y_1 - k_{y_1}) \\ \frac{dy_2}{dt} = -\alpha y_2 + \gamma_{y_1} \theta(y_1 - k_{y_1}) \\ \dots \\ \frac{dz_1}{dt} = -\alpha z_1 + \gamma_{y_1} \theta(k_{y_1} - y_1) \\ \frac{dz_2}{dt} = -\alpha z_2 + \gamma_{y_1} \theta(k_{y_1} - y_1) \\ \dots \end{cases} \quad \left\{ \begin{array}{l} x_1(t) = x(t) \\ x_2(t) = x(t) \\ y_1(t) = y(t) \\ y_2(t) = y(t) \\ \dots \\ z_1(t) = z(t) \\ z_2(t) = z(t) \\ \dots \end{array} \right.$$

- [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).
 [2] L. DeVille, E. Lerman. Dynamics on Networks of Manifolds. Symmetry, Integrability and Geometry: Methods and Applications. 11 (2015).
 [3] E. Nijholt, BW Rink, JM Sanders. Graph fibrations and symmetries of network dynamics. Journal of Differential Equations, 261,4861-4896 (2014).
 [4] I. Belykh, M. Hasler. Mesoscale and clusters of synchrony in networks of bursting neurons. Chaos. 21(1):016106 (2011).

Symmetry Fibration Leads to Synchronization.

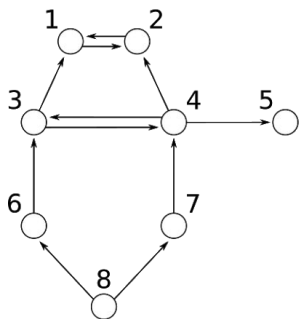


Synchronization



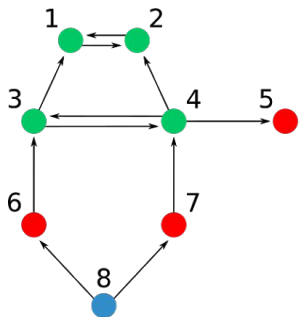
Algorithms to find fibers

Initial partition



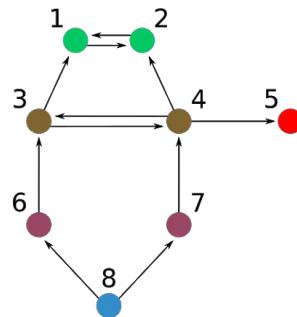
	1	2	3	4	5	6	7	8
○	2	2	2	2	1	1	1	0
New color	●	●	●	●	●	●	●	●

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	●	●	●	●	●	●	●	●

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>

Building blocks

Definition of building block and fiber numbers

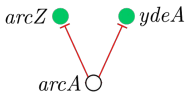


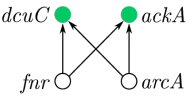
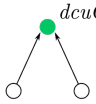

Building block of a fiber is comprised by the genes in the fiber plus all regulators that are needed to establish the synchronization in the fiber and, in case if any node in the fiber belongs to the SCC, the shortest loop.




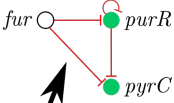
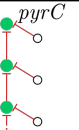

Building blocks are classified using 'fiber numbers' denoted $|n, l\rangle$. n is the branching ratio of the input tree (when an input tree is finite, then $n = 0$)

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

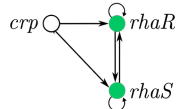
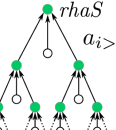

and l is the number of external regulators of the fiber

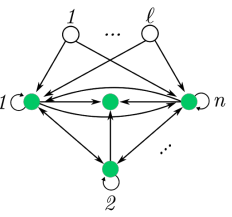
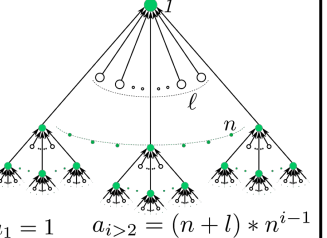
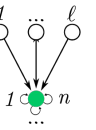
Building blocks. Integer branching ratios

$ n, \ell\rangle$	Genetic circuit	Input tree	Base
$ 0, 1\rangle$		a_i 1  $a_{1,2} = 1$	
$ 0, 2\rangle$		a_i 1  $a_1 = 1$ 2 $a_2 = 2$	

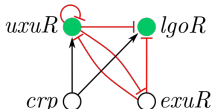
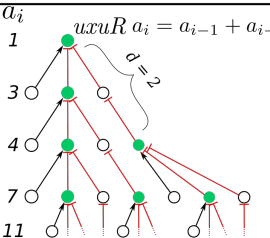
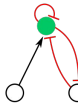
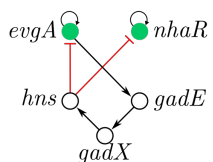
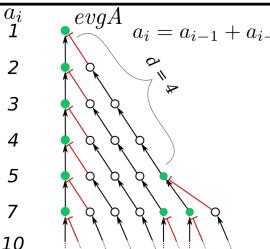
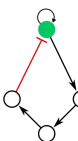
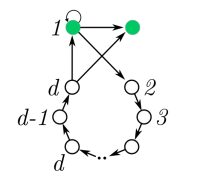
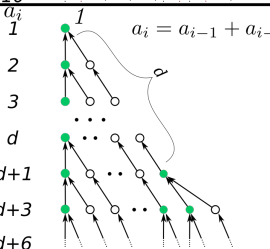

$ n, \ell\rangle$	Genetic circuit	Input tree	Base
$ 1, 0\rangle$		a_i 1  $a_i = 1$	
$ 1, 1\rangle$		a_i 2  $a_i = 2$	

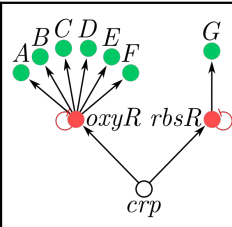
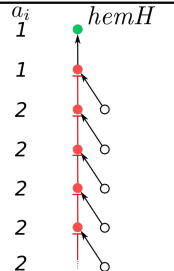

FFF

$ n, \ell\rangle$	Genetic circuit	Input tree	Base
$ 2, 1\rangle$		a_i 1  $a_1 = 1$ 3 $a_{i>2} = 3 * 2^{i-1}$ 6	

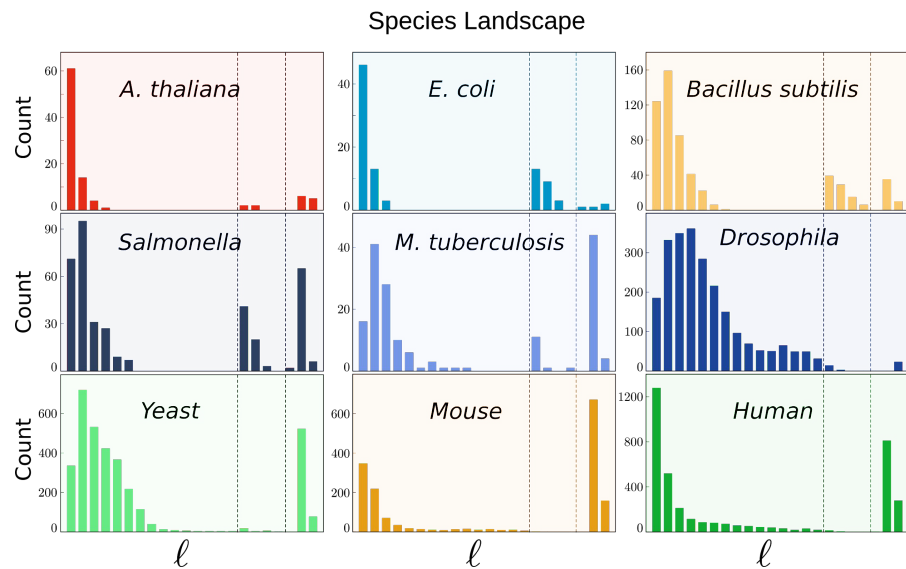
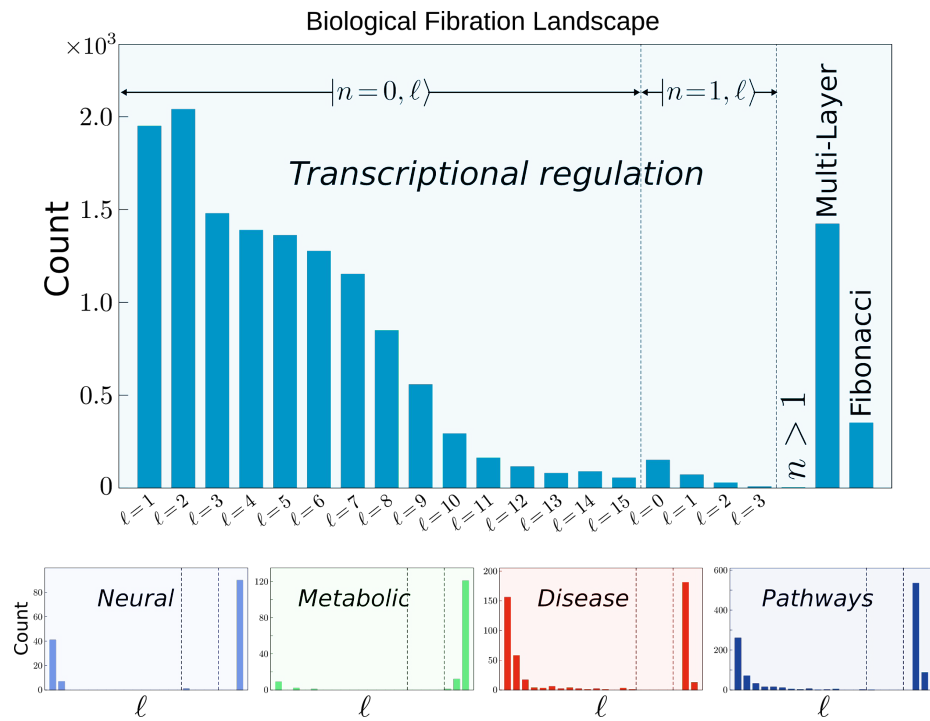
$ n, \ell\rangle$	Genetic circuit	Input tree	Base
$ n \geq 3, \ell\rangle$		 $a_1 = 1$ $a_{i>2} = (n + l) * n^{i-1}$	

Building blocks. Fibonacci and composite fibers

$ \varphi_d, \ell\rangle$	Genetic circuit	Input tree	Base
$ 1.6180\dots, 2\rangle$	 <p>2-Fibonacci Fiber (2-FF)</p>	 <p>$a_i = a_{i-1} + a_{i-2}$</p>	
$ 1.3802\dots, 1\rangle$	 <p>4-Fibonacci Fiber (4-FF)</p>	 <p>$a_i = a_{i-1} + a_{i-4}$</p>	
$ \varphi_d, \ell\rangle$	 <p>d-Fibonacci Fiber (d-FF)</p>	 <p>$a_i = a_{i-1} + a_{i-d}$</p>	

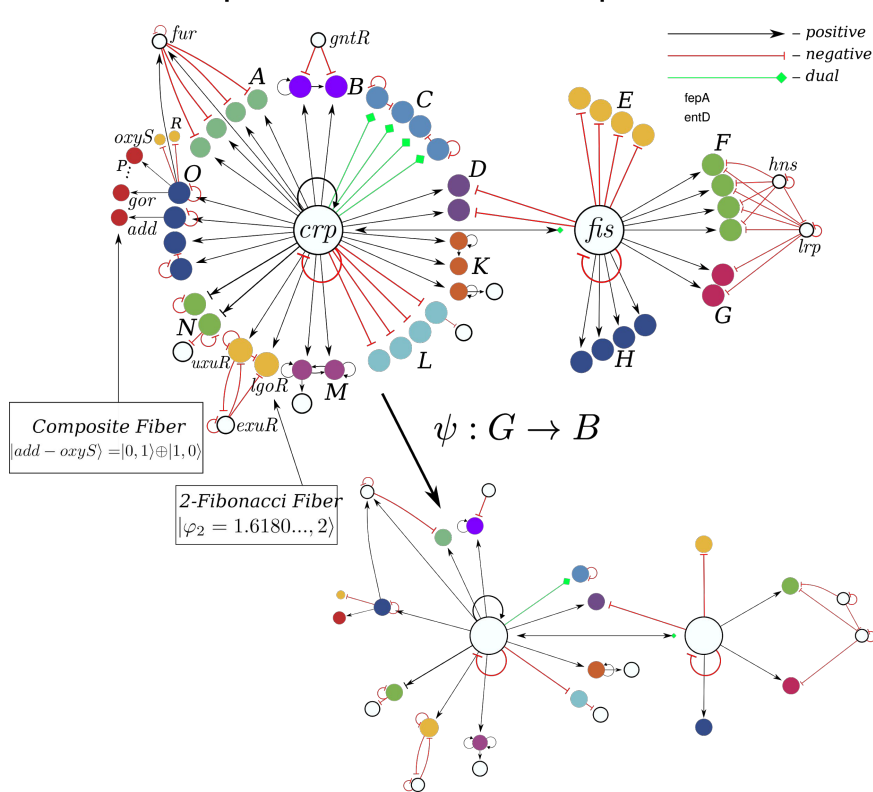
$ \varphi_d, \ell\rangle$	Genetic circuit	Input tree	Base
$ 0, 1\rangle \oplus$ $ 1, 1\rangle$	 <p>Multi-layer composite fiber</p>	 <p>$a_{1,2} = 1$ $a_{i>3} = 2$</p> <p> $A = hemH$ $B = oxyS$ $C = trxC$ $D = gor$ $E = dsbG$ $F = grxA$ $G = add$ </p>	

Building block landscape

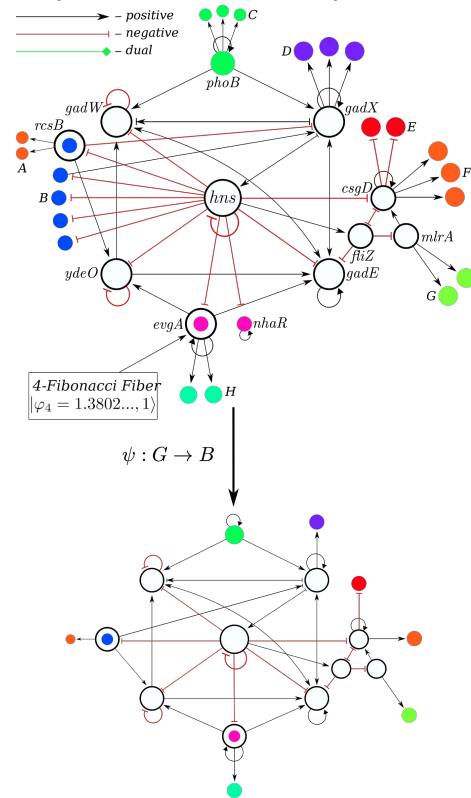


Strongly Connected Components

crp-fis connected component

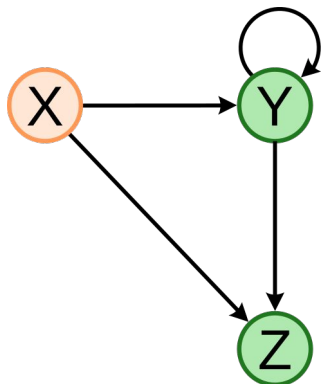


pH connected component

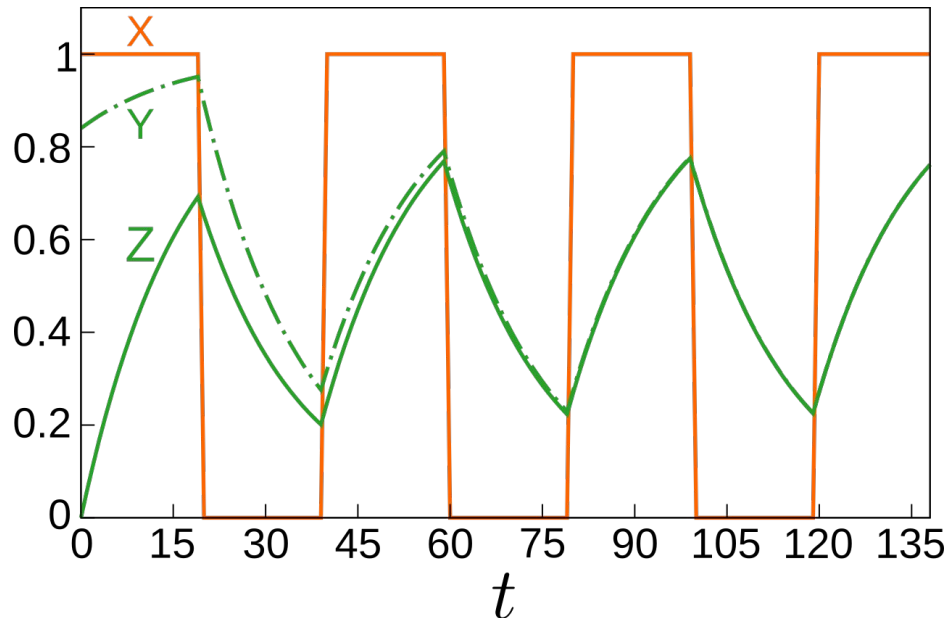


Dynamical results

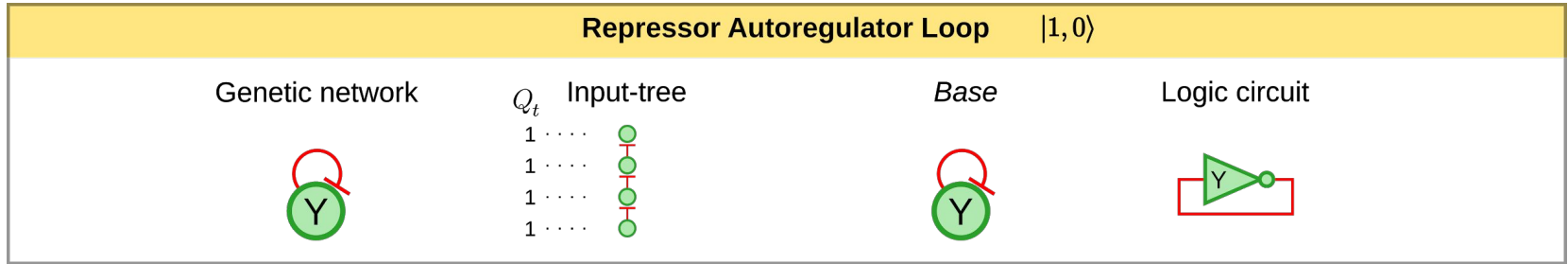
SAT-FFF and it's synchronization



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

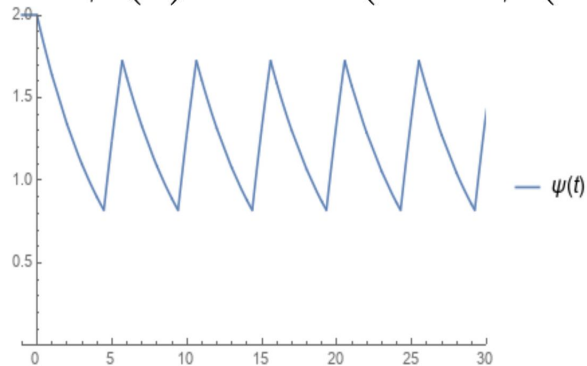


Analogy to electronic circuits (clock)



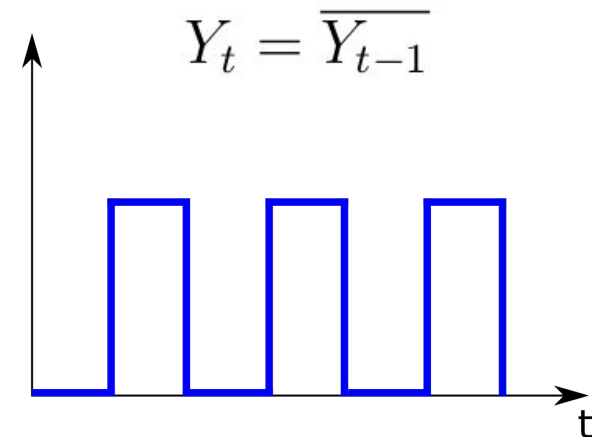
Continuous model

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

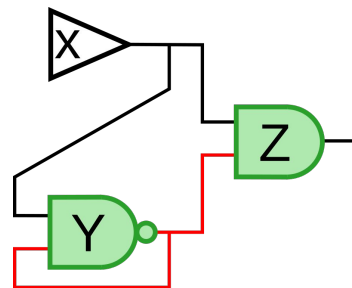
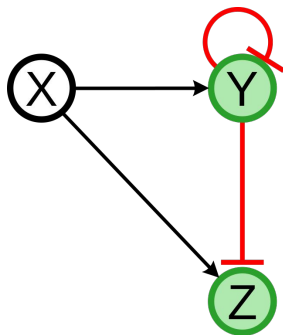


Boolean model

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

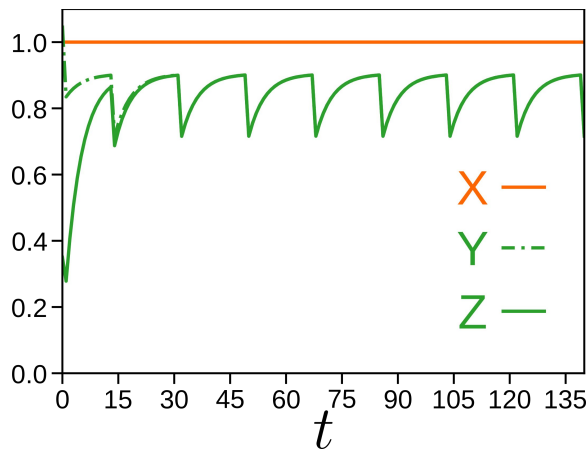


UNSAT-FFF synchronization and oscillation



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

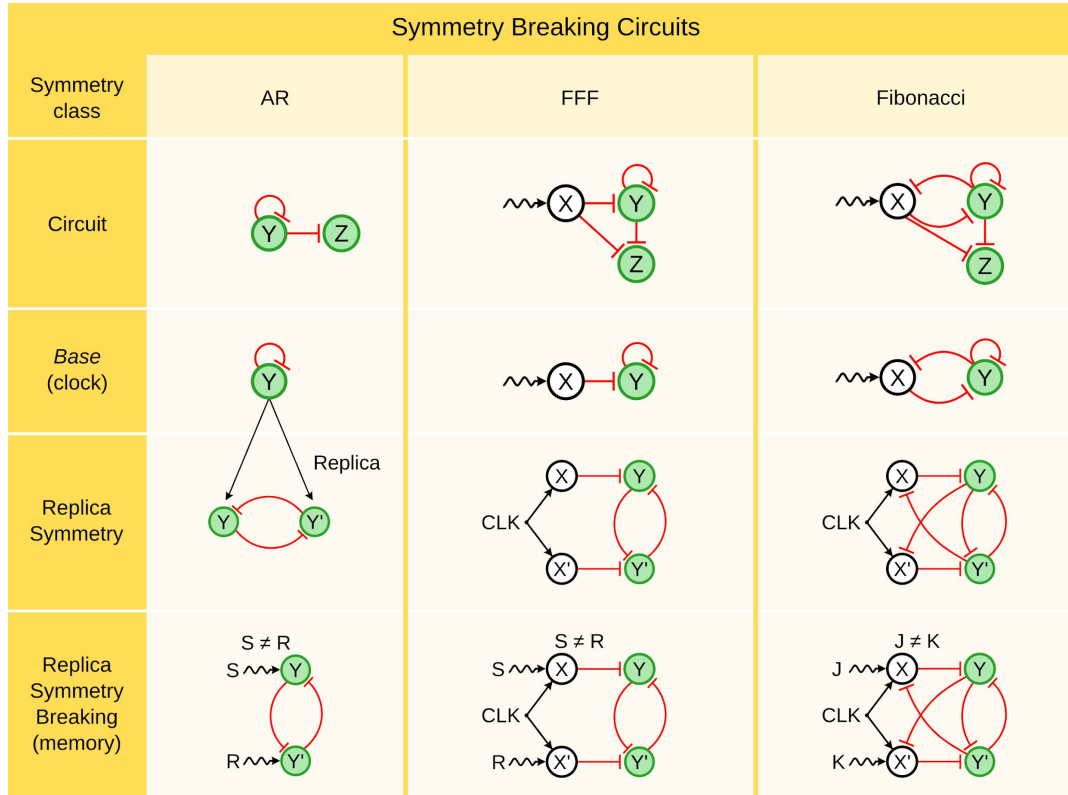
$$Z_t = \overline{Y_{t-1}} \text{ AND } X_{t-1}$$



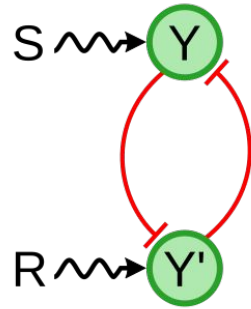
t	X _t	Y _t	Z _t
0	0	1	1
1	0	0	0
0	0	1	0
1	0	0	0
0	0	0	1
1	0	0	0

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

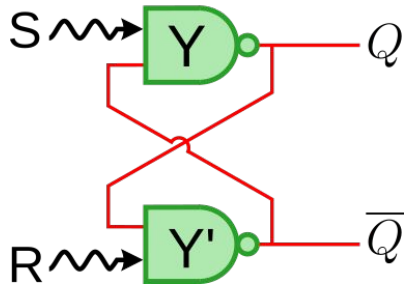
Constructing symmetry breaking circuits



Analogy to electronic circuits (memory)



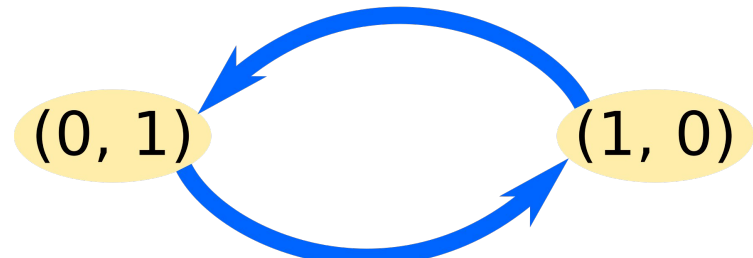
SR flip-flop



Boolean model



$S = 1, R = 0$



$S = 0, R = 1$



Conclusion and proposed research

Conclusion

- Fibration symmetry provides the novel way to analyze biological (or any other directed) 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 biological networks

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

Proposed research

