Characterizing robust dynamics in regulatory networks

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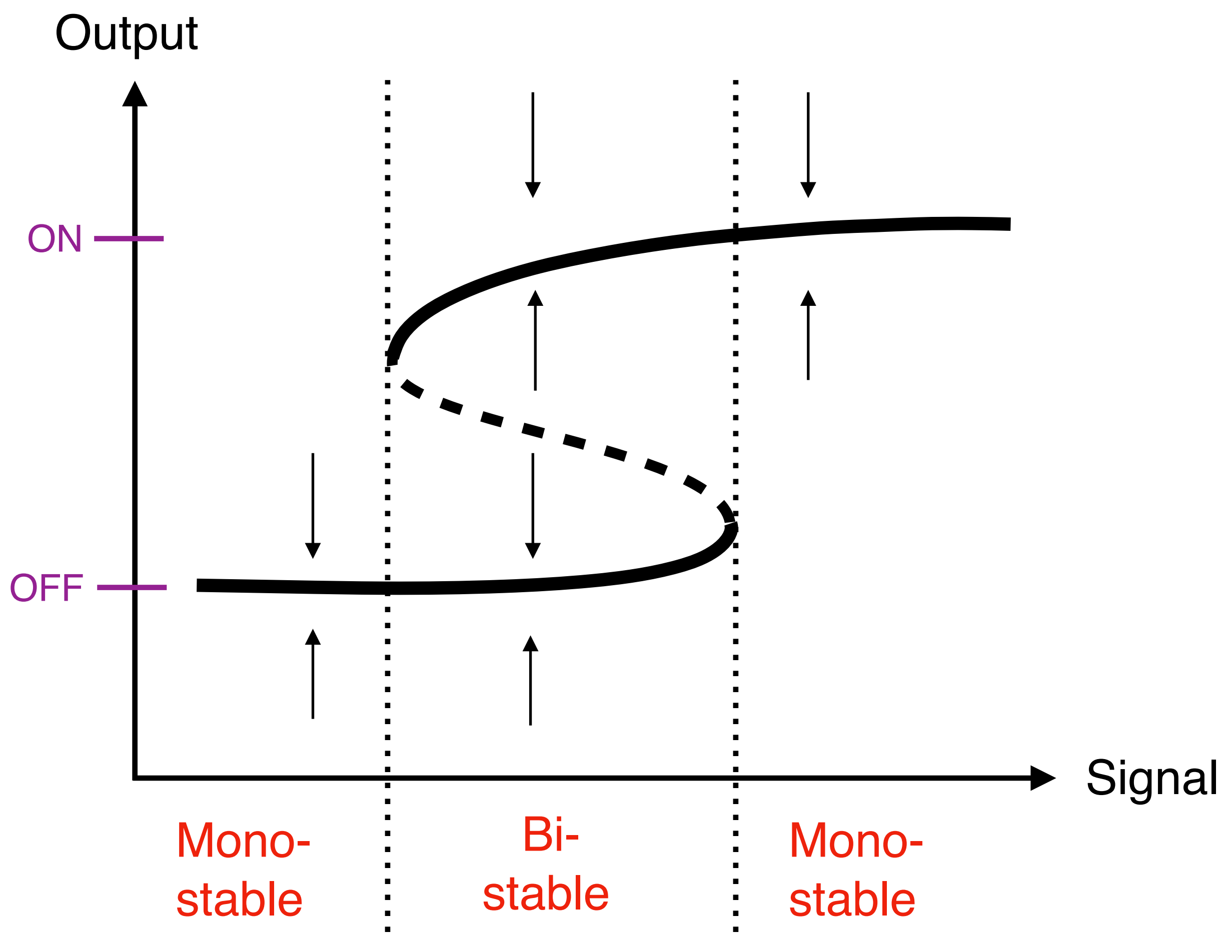
Bistable hysteretic switch

What is a switch?



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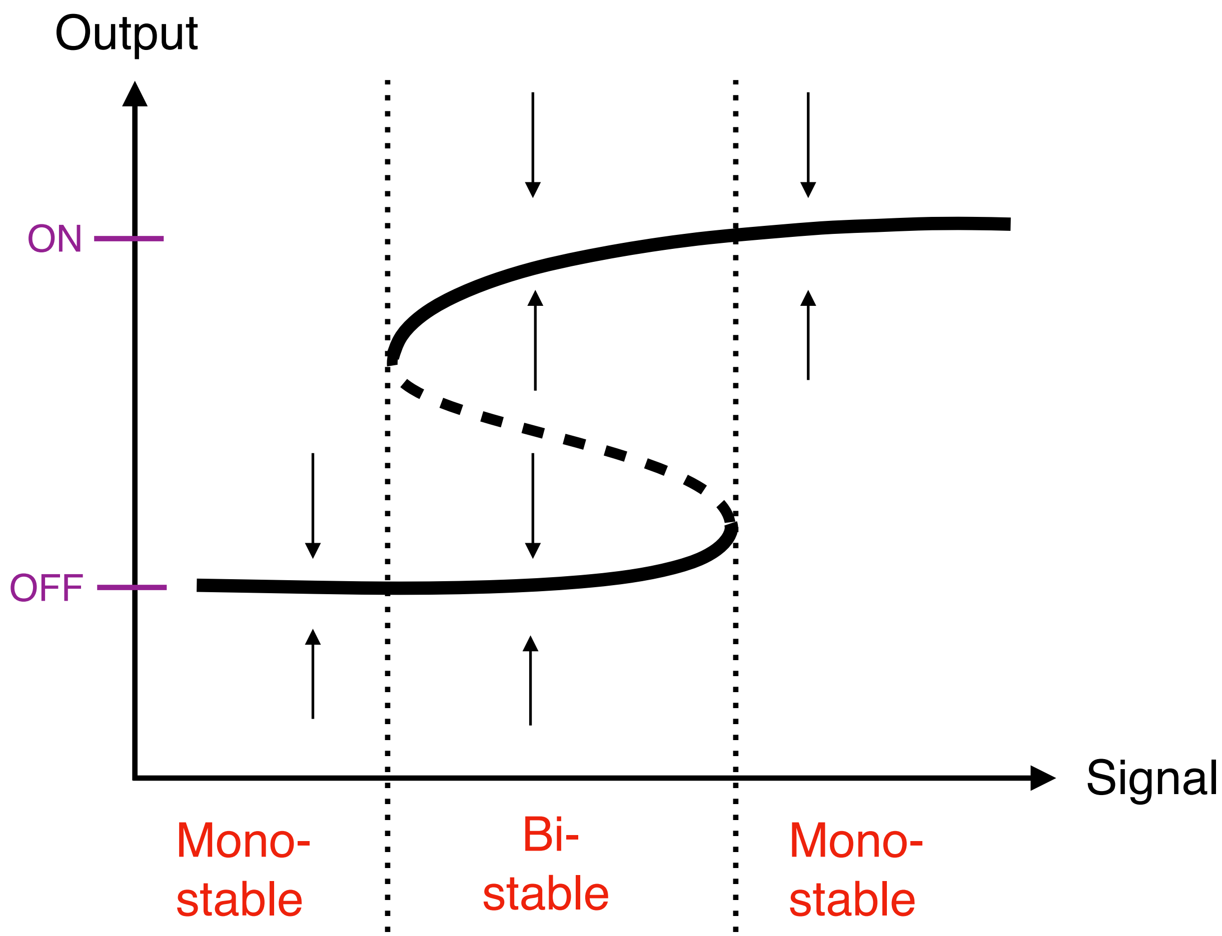

Goal: Design 3-node networks that function as robust bi-stable hysteretic switches.

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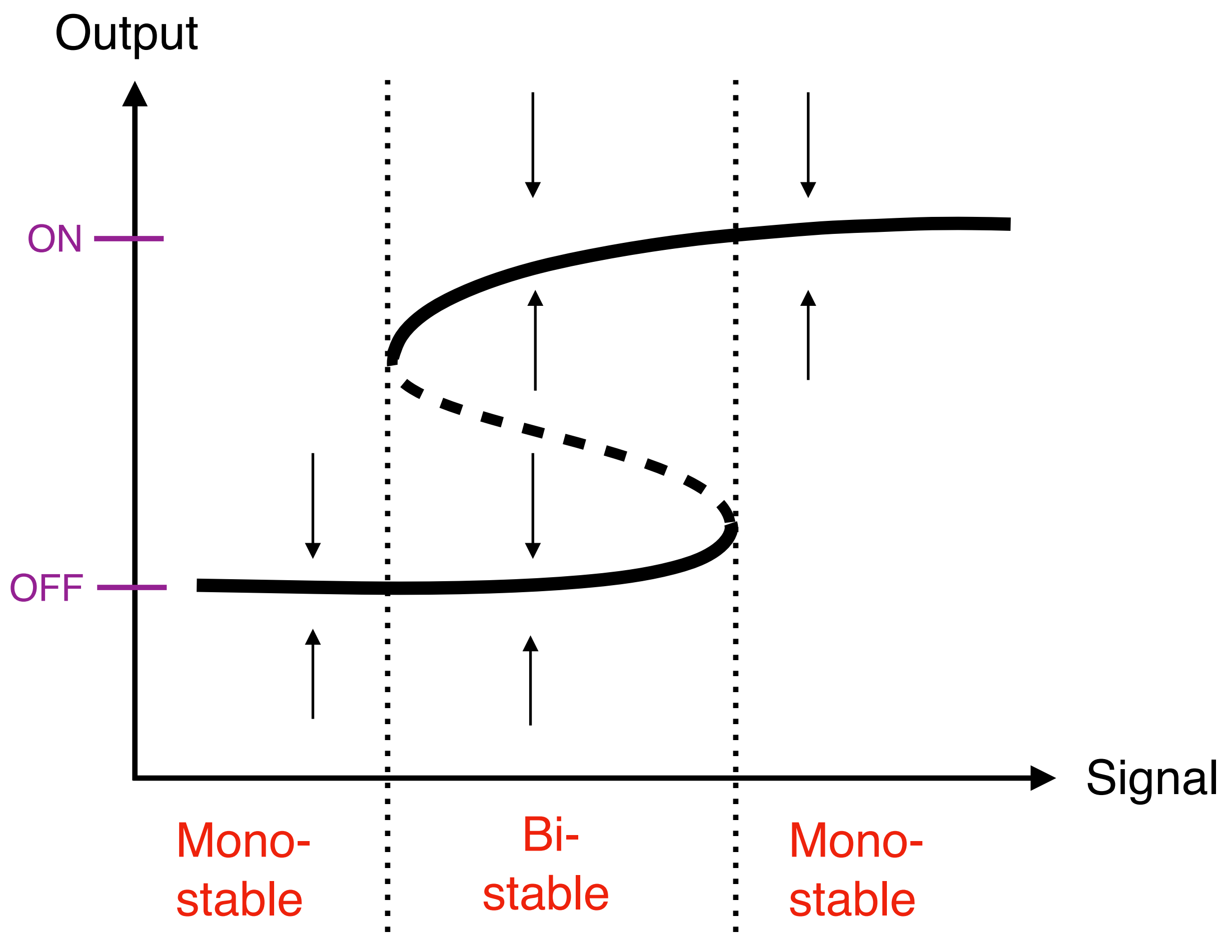

Goal: Design 3-node networks that function as robust bi-stable hysteretic switches.

Robust in the sense that it should function across a wide range of parameters (stable under perturbations).

Networks with robust hysteresis

DSGRN (Dynamic Signatures Generated by Regulatory Networks) can compute a coarse description of dynamics of a network that is valid for all of parameter space.

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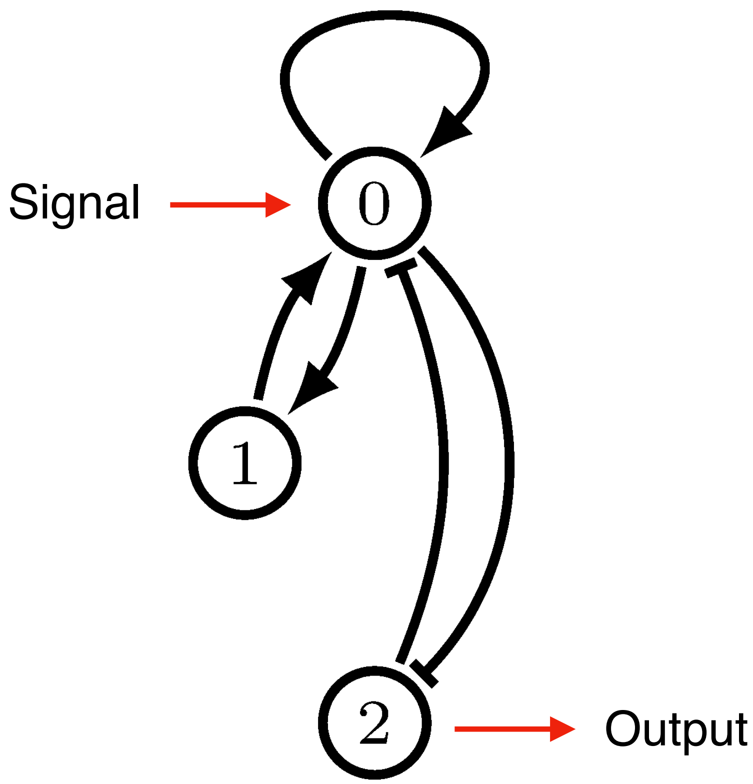
DSGRN can evaluate robustness across all of parameter space.

We rank all 3-node networks according to their ability to function as a robust bi-stable switch.

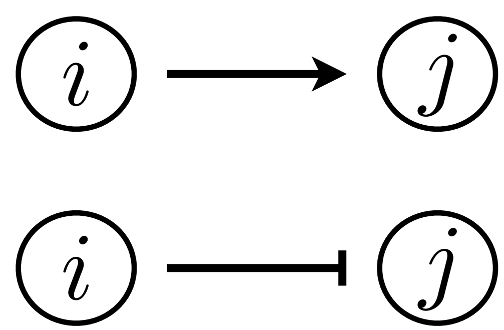
Networks with robust hysteresis

All three-node networks



Total number of networks $3^9 = 19,683$

Networks considered: $14,068$



Activating

Repressing

Networks with robust hysteresis

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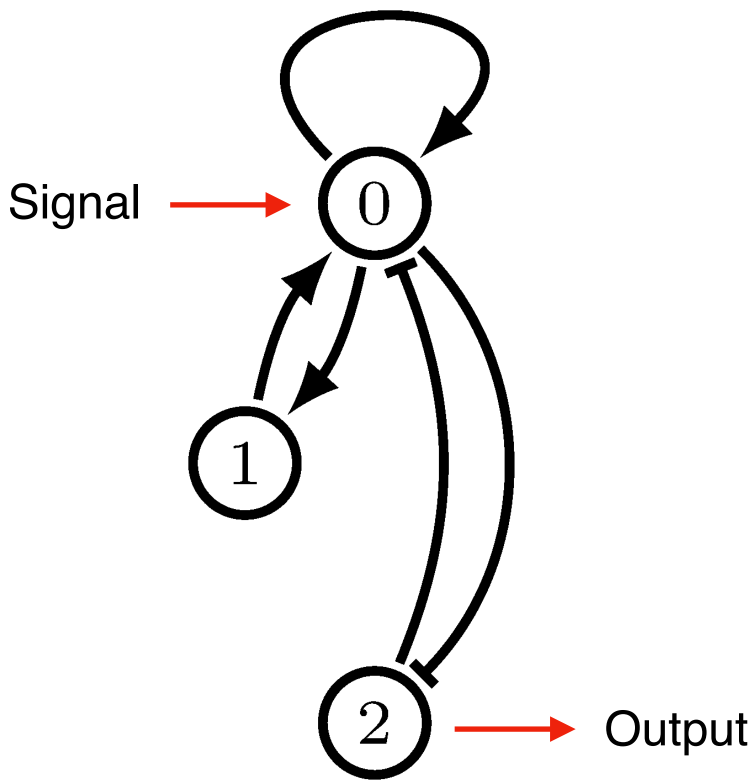

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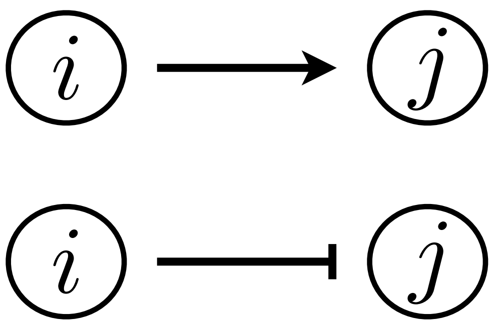


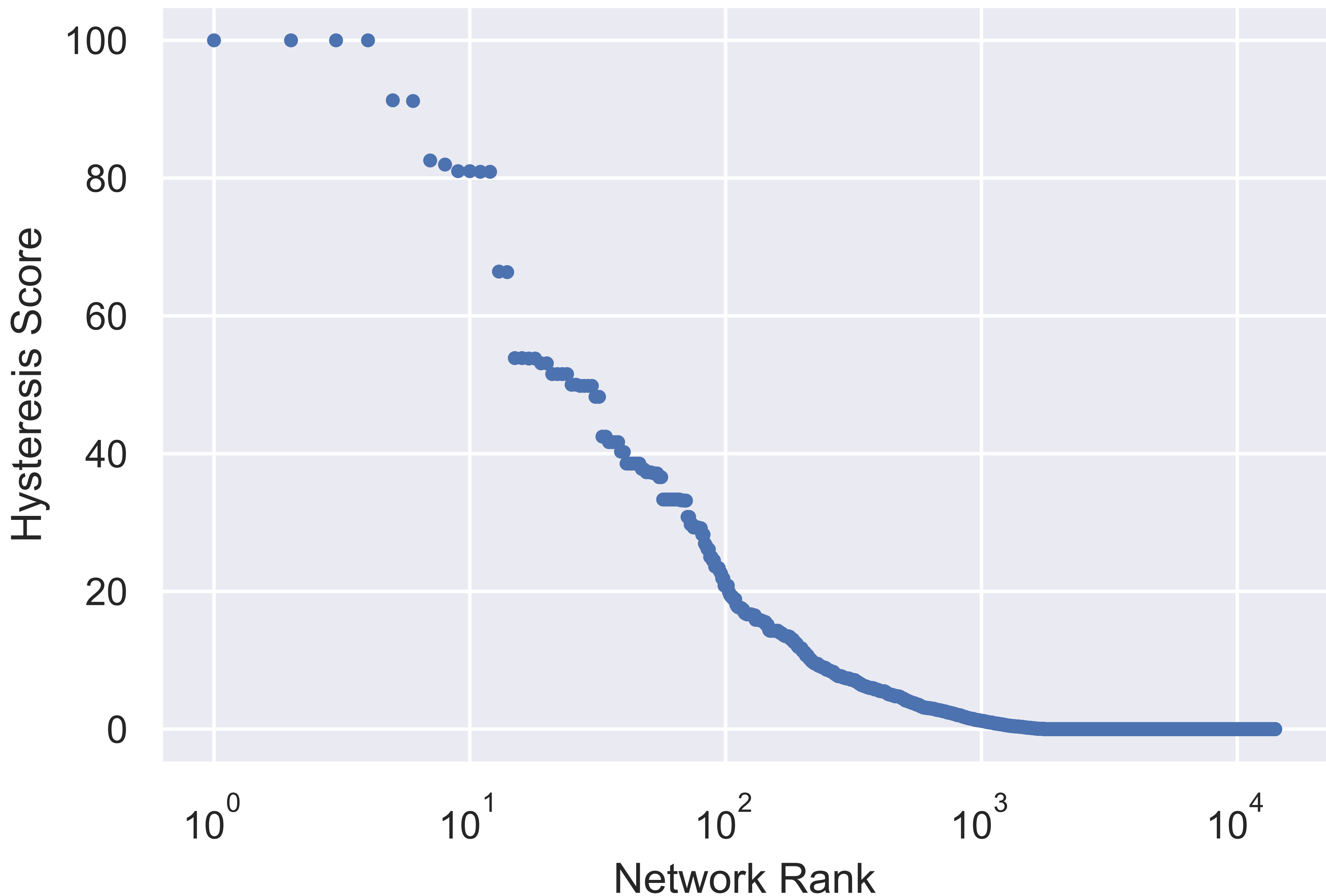
Activating

Repressing

Score: "percent" of parameters exhibiting hysteresis

Hysteresis score

Hysteresis scores of all (14,068) three node networks



G., Gedeon, Kepley, Mischaikow, PLoS Comp Bio, 2021

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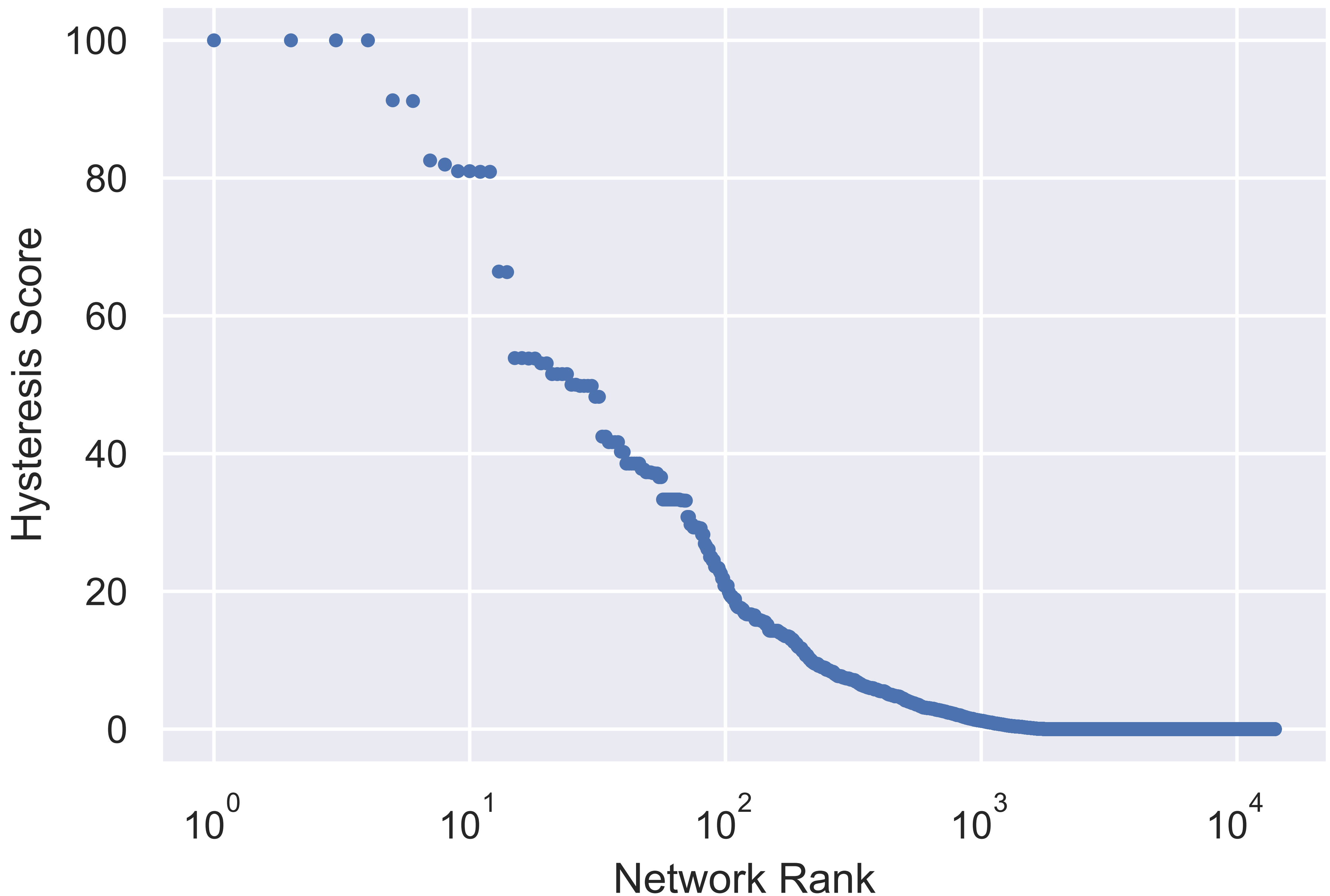

How about robustness under perturbation?

G., Gedeon, Kepley, Mischaikow, PLoS Comp Bio, 2021

DSGRN

There is no “the right” model for a biological network

If a model is selected it is very difficult and expensive to obtain parameter values and dynamics can vary widely with parameters

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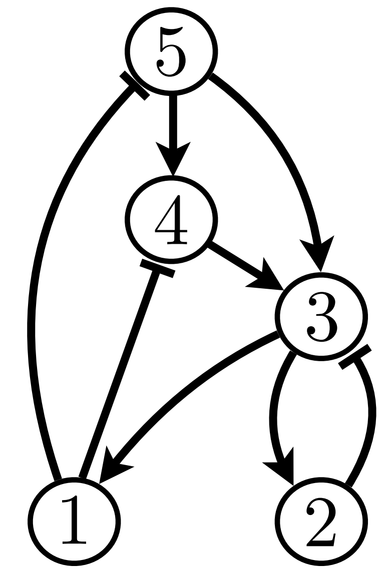
Description of dynamics does not dependent on a particular ODE model

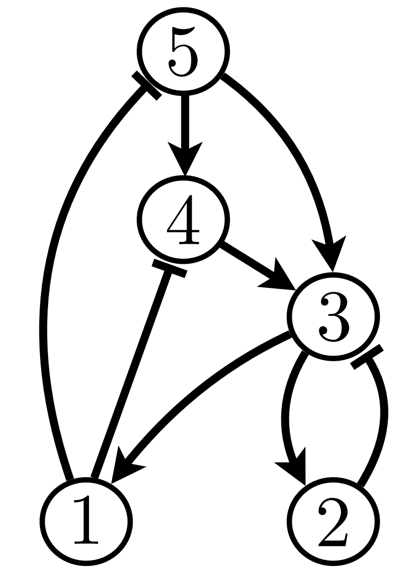
DSGRN

Denote by x_n a quantity associated with node n and assume that:



Cummins, et. al., SIADS, 2016

DSGRN



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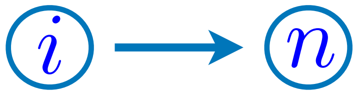
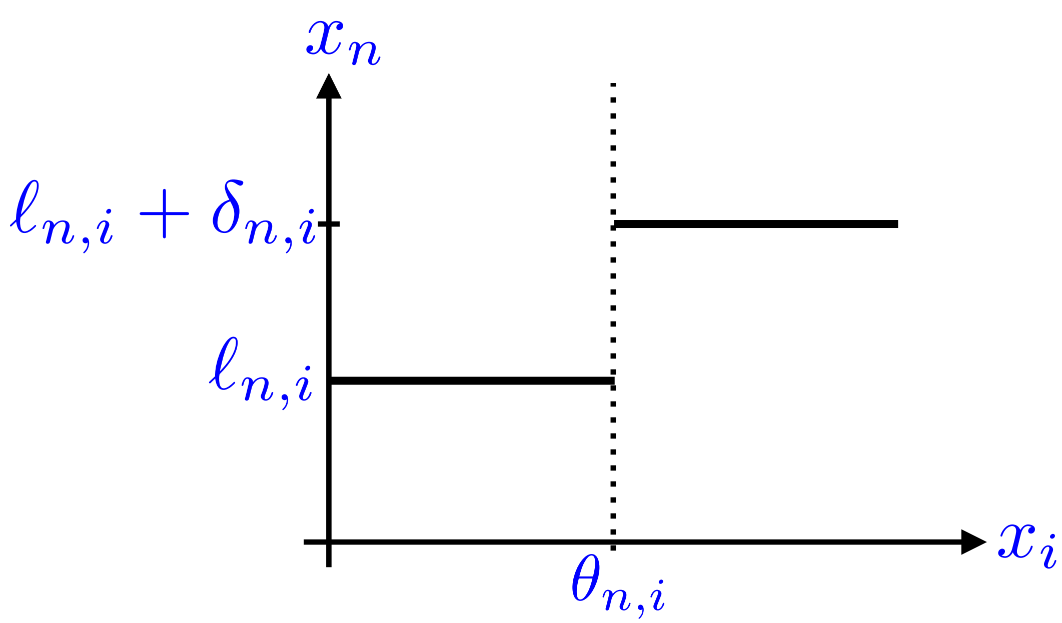


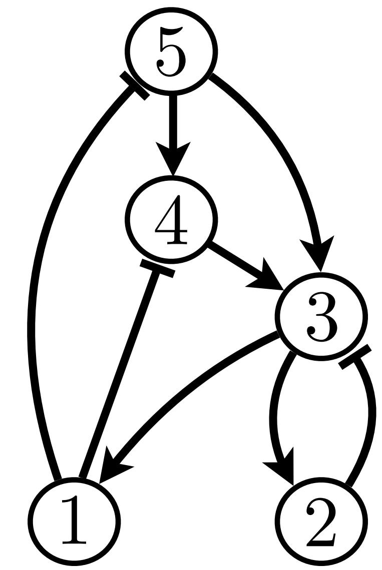
An increase in x_i increases the rate of production of x_n



$$\sigma^+_{n,i}(x_i) = \begin{cases} \ell_{n,i}, & \text{if } x_i < \theta_{n,i} \\ \ell_{n,i} + \delta_{n,i}, & \text{if } x_i > \theta_{n,i} \end{cases}$$

Cummins, et. al., SIADS, 2016

DSGRN



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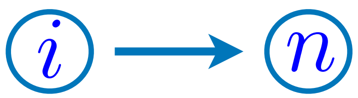

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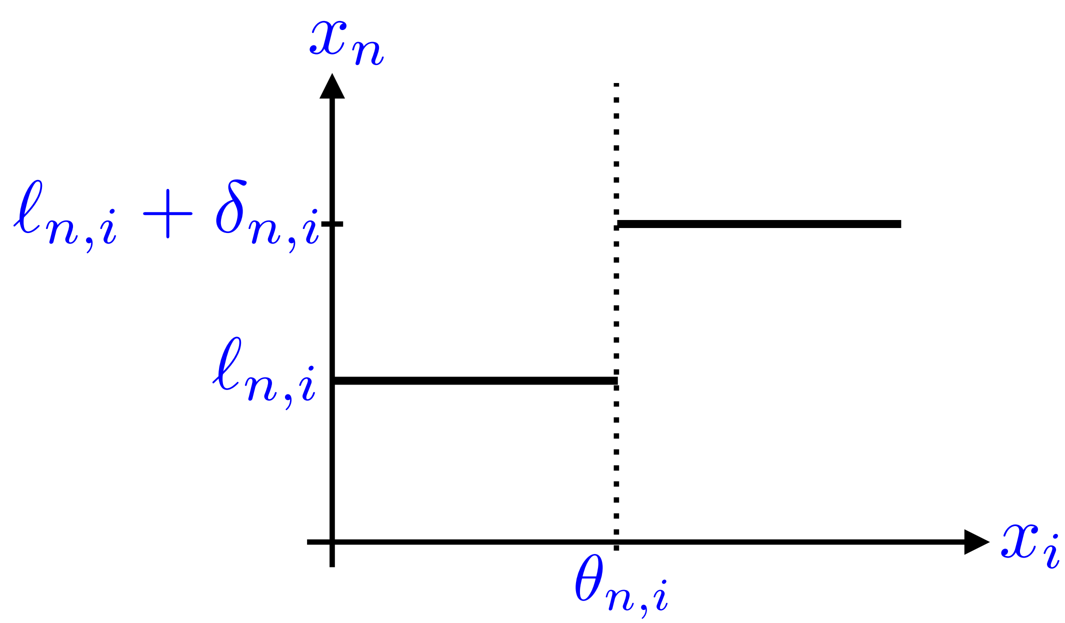

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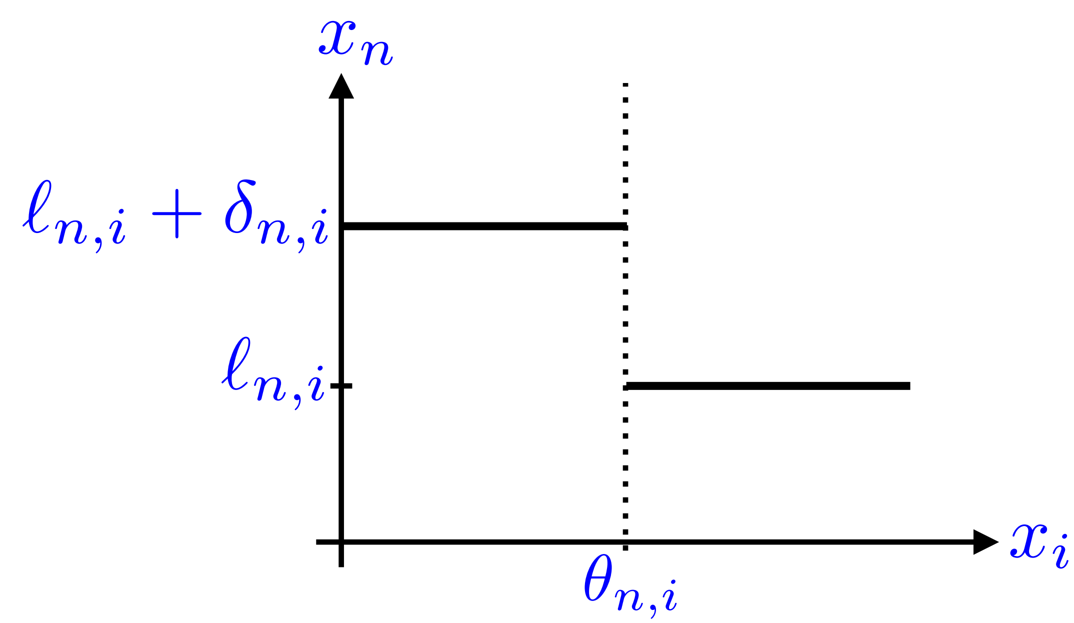

$$\sigma^-_{n,i}(x_i) = \begin{cases} \ell_{n,i} + \delta_{n,i}, & \text{if } x_i < \theta_{n,i} \\ \ell_{n,i}, & \text{if } x_i > \theta_{n,i} \end{cases}$$

Cummins, et. al., SIADS, 2016

DSGRN

The rate of change of x_n is given by

$$-\gamma_n x_n + \Lambda_n(x)$$

decay

production

Product of sums of switching functions $\sigma^{\pm}_{n,i}(x_i)$

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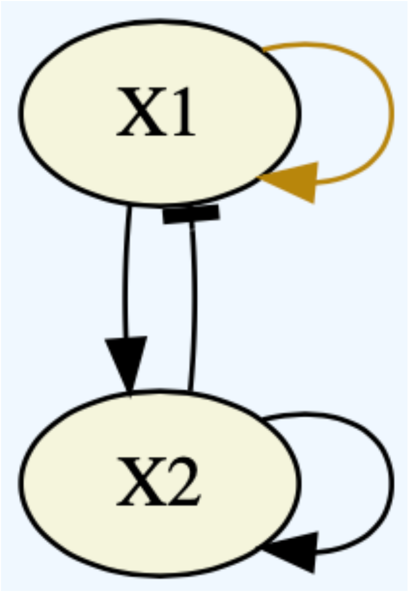
Example:



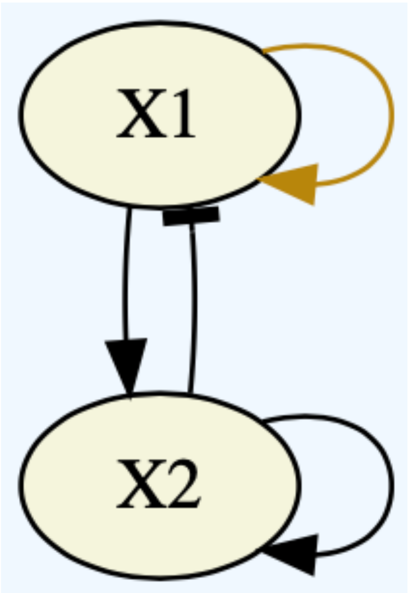
$$\begin{cases} -\gamma_1 x_1 + \sigma^{+}(x_1)\sigma^{-}(x_2) \\ -\gamma_2 x_2 + \sigma^{+}(x_1) + \sigma^{+}(x_2) \end{cases}$$

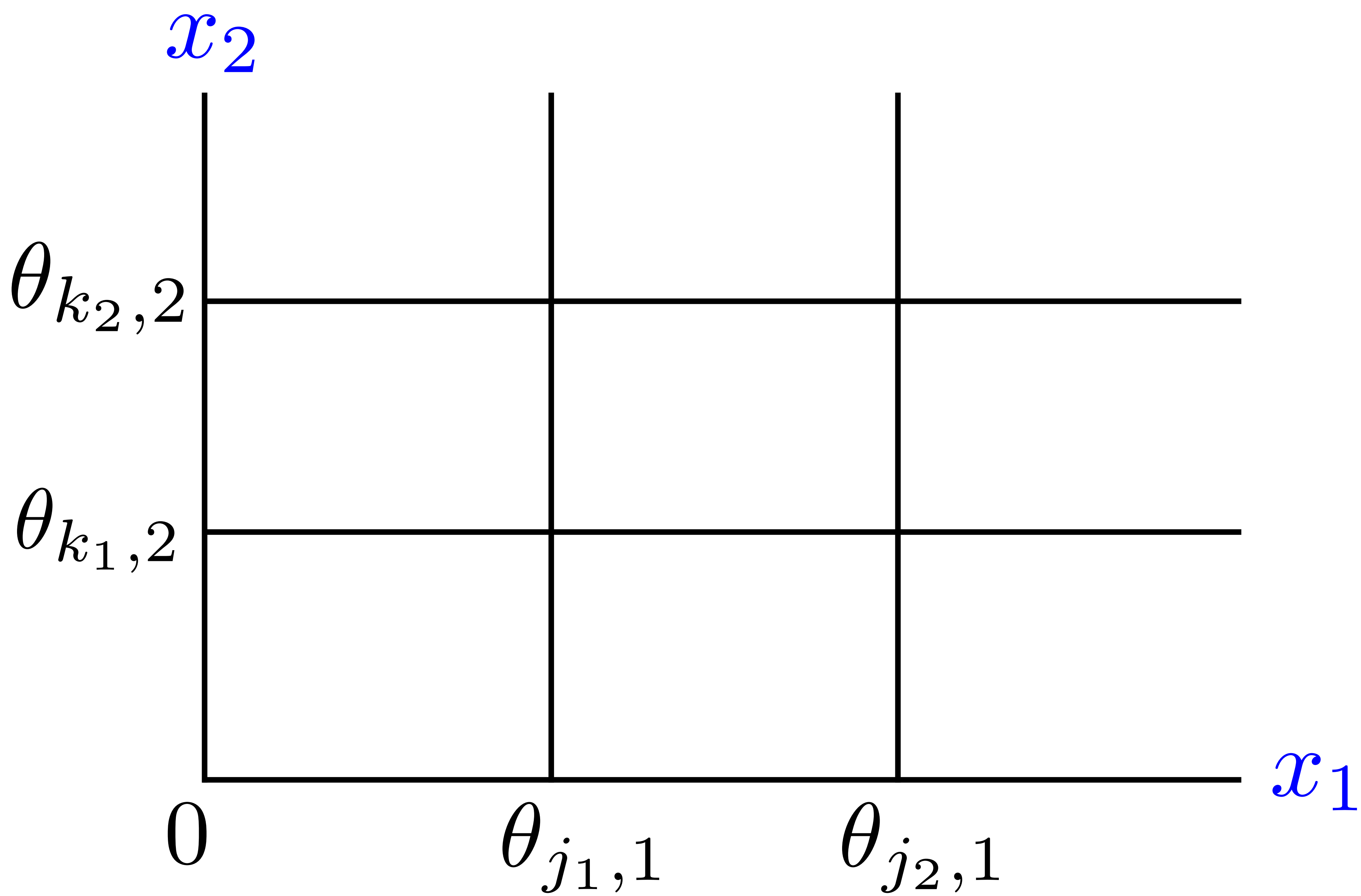
DSGRN

The function $\Lambda_n(x)$ is constant off the hyperplanes $x_i = \theta_{n,i}$

out-edge threshold

Hence we have a natural decomposition of phase space into rectangular regions





DSGRN

We want to determine whether x_n is increasing or decreasing within one of these regions

That is we want to determine the sign of

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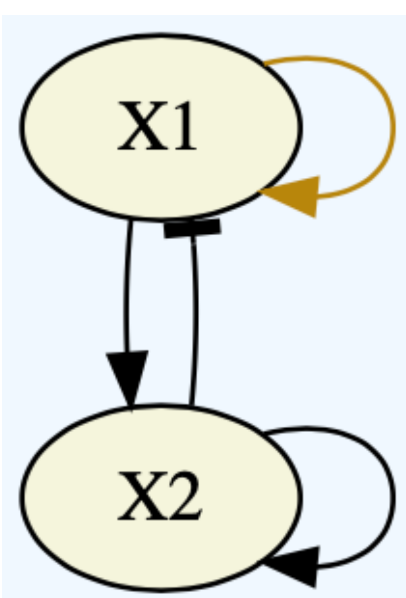
Note that $\Lambda_1(x) = \sigma^+(x_1)\sigma^-(x_2)$ can take on the values



$$p_0 = \ell_{1,1}\ell_{1,2}$$

$$p_1 = (\ell_{1,1} + \delta_{1,1})\ell_{1,2}$$

$$p_2 = \ell_{1,1}(\ell_{1,2} + \delta_{1,2})$$

$$p_3 = (\ell_{1,1} + \delta_{1,1})(\ell_{1,2} + \delta_{1,2})$$

Parameter graph

Hence if we determine all admissible total orders of

$$\{p_0, p_1, p_2, p_3\}$$

Kepley, et. al., SIAM J. Appl. Algebra Geometry, 2021

Parameter graph

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Total orders $p_0 < p_1 < p_2 < p_3$ and $p_0 < p_2 < p_1 < p_3$

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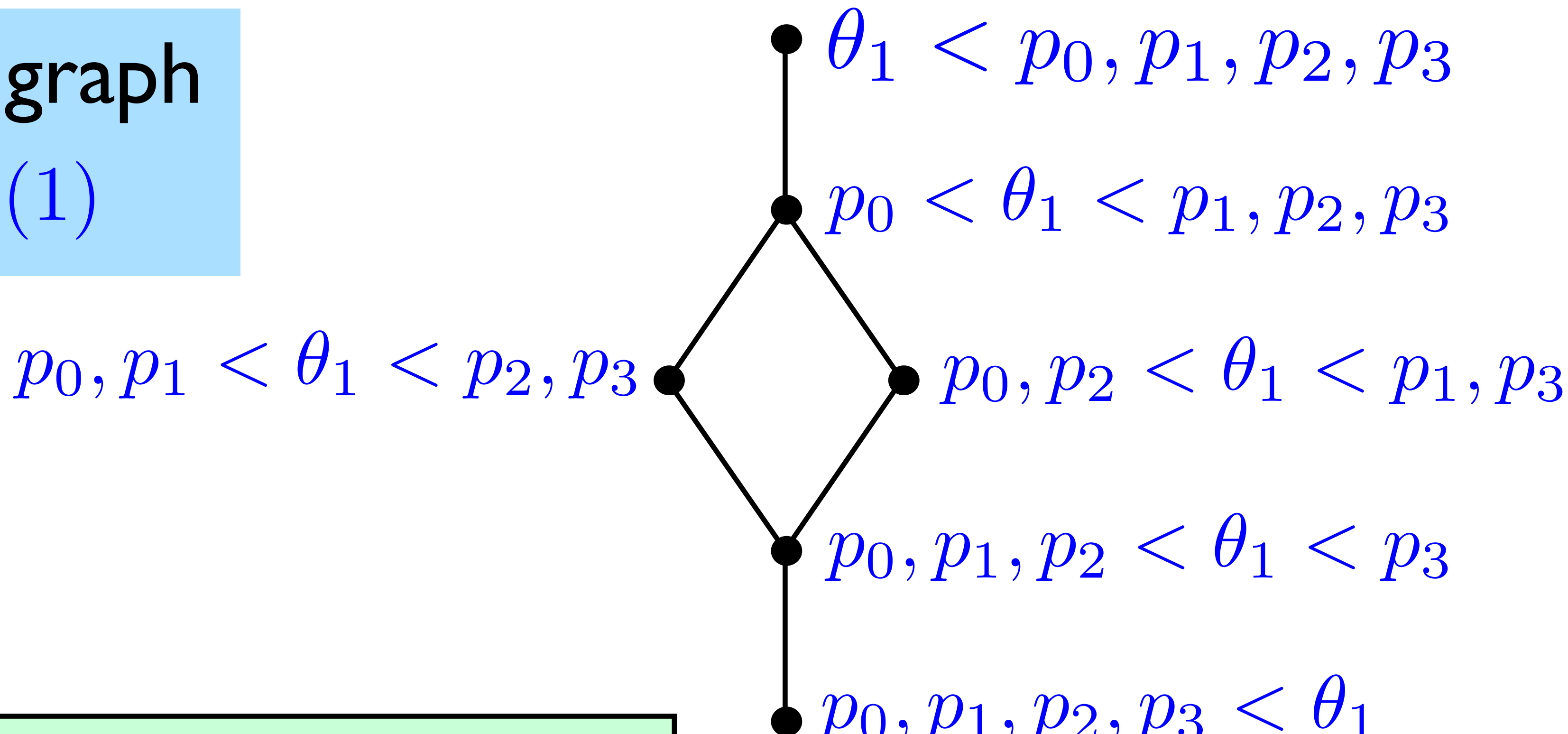
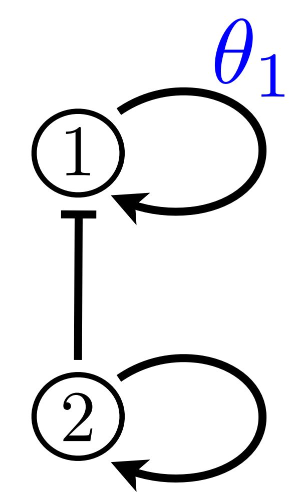
Factor graph

$PG(1)$



Poset



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Parameter graph

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$$PG = \prod_{n=1}^{N} PG(n)$$

Each node determines all possible signs of

$$-\gamma_n \theta_{*,n} + \Lambda_n(x)$$

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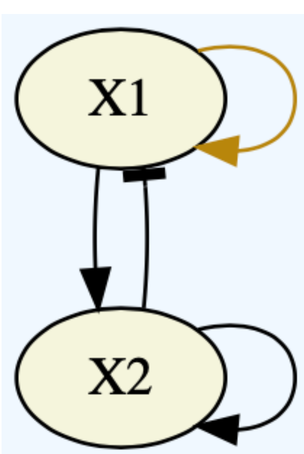
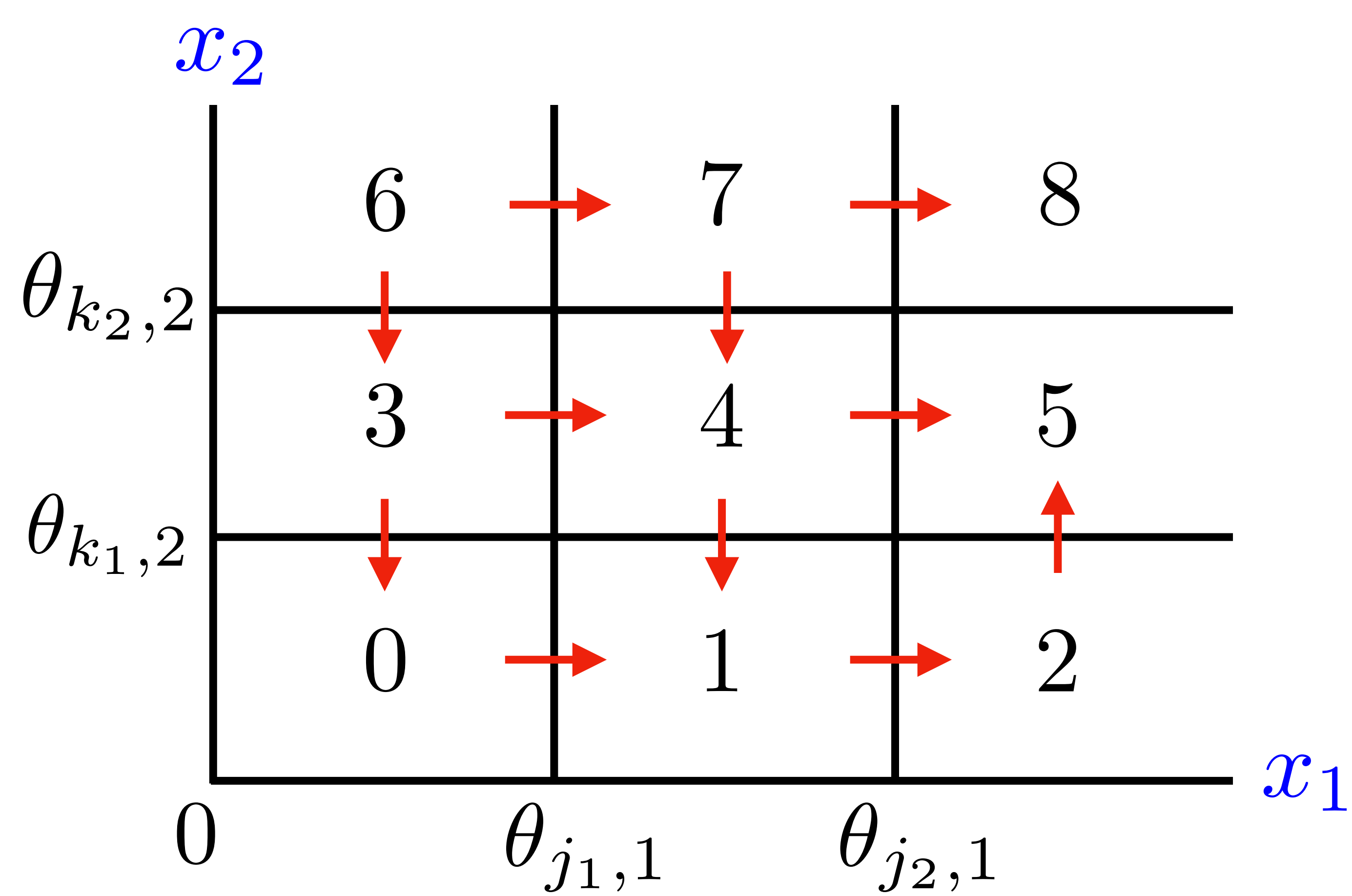


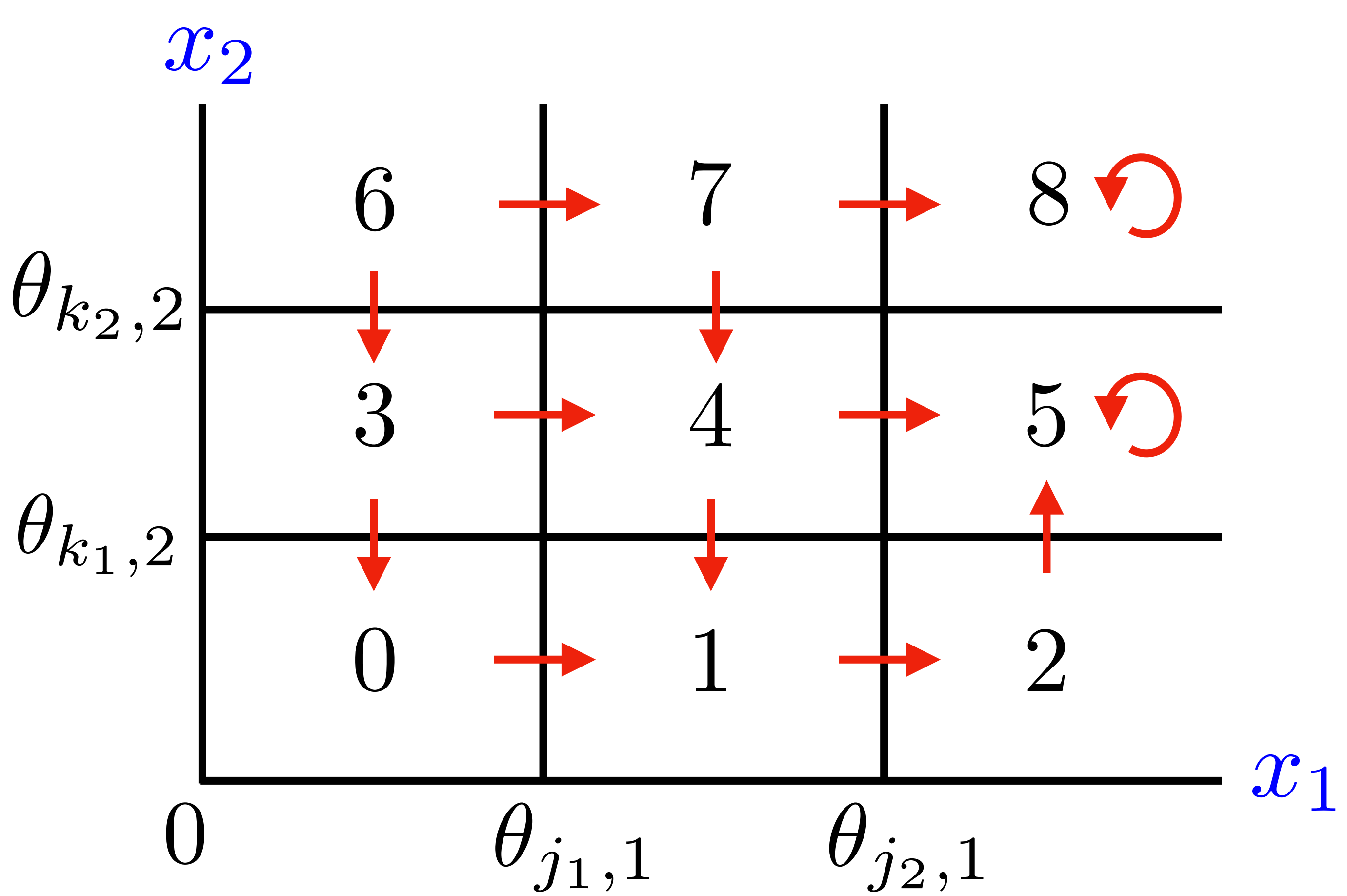
Parameter graph size: 1600

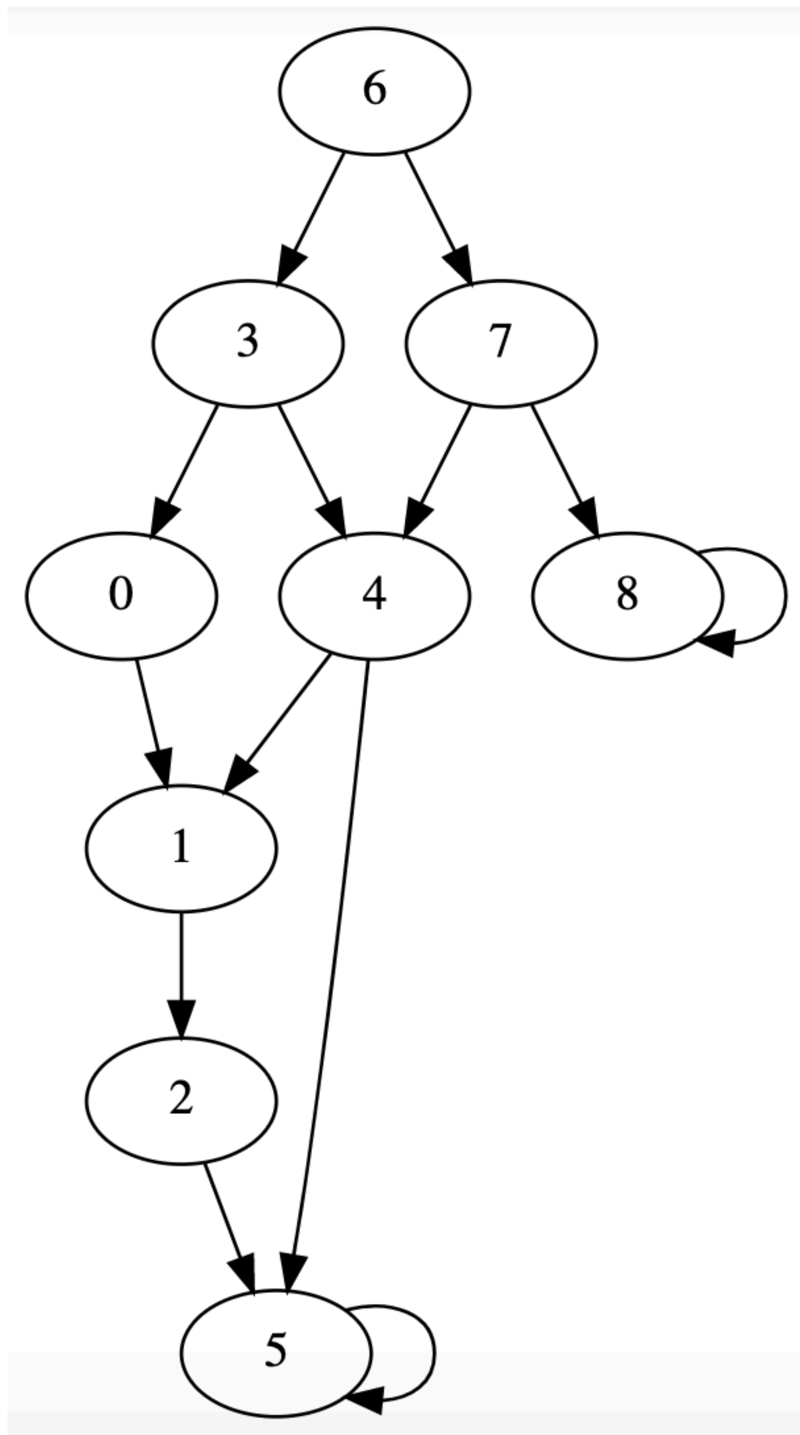
Parameter space dim: 14



State transition graph

Signs of $-\gamma_n\theta_{*,n} + \Lambda_n(x)$ determine the state transition graph

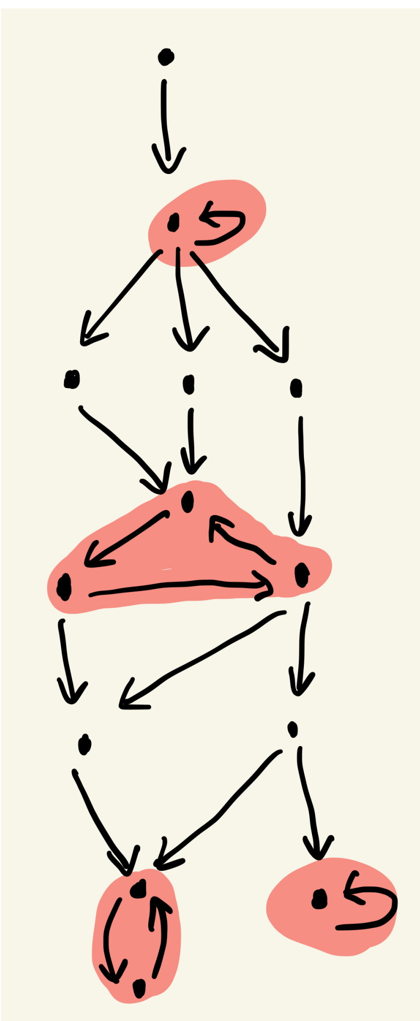




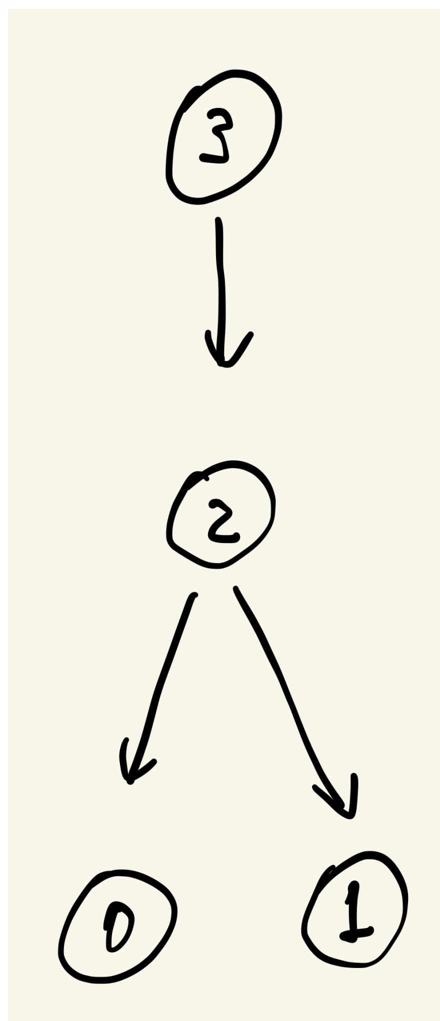
State transition graph (STG) or
Combinatorial multi-valued map $\mathcal{F}$

Morse graph

The nontrivial strongly connected components (SCC) capture the recurrent dynamics



SCC



Morse Graph

Linear time algorithm to compute SCC

Vertices: Morse sets (Recurrent Dynamics)

Edges: Non-recurrent (gradient-like) dynamics

Software and examples

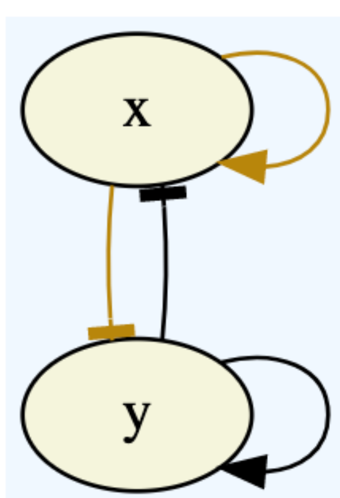
GitHub repository

https://github.com/marciogameiro/DSGRN

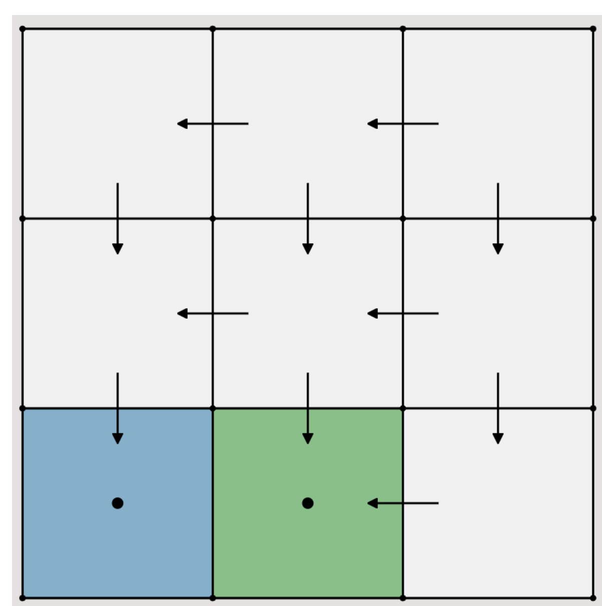
Install with `pip install DSGRN`

DSGRN Visualization

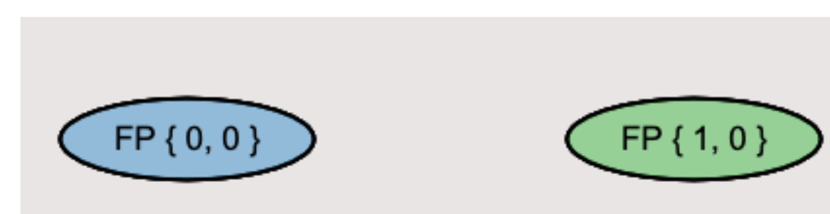
http://chomp.rutgers.edu/projects/dsgrn_viz/



Network

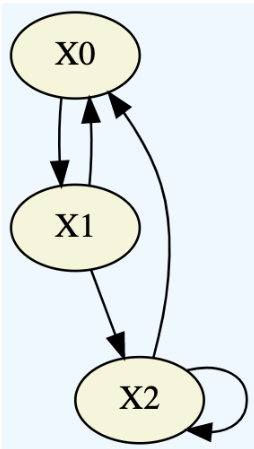


Multivalued map



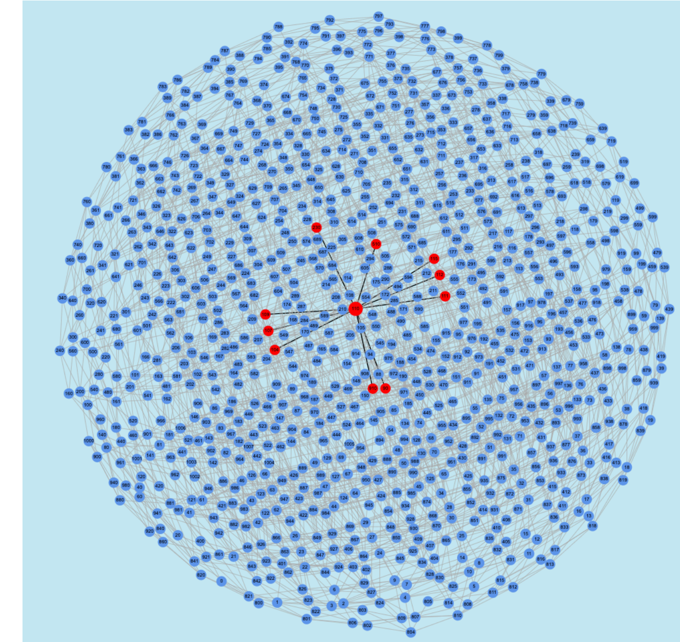
Morse graph

3D example



Parameter space:
$(0, \infty)^{18}$

Parameter Graph:



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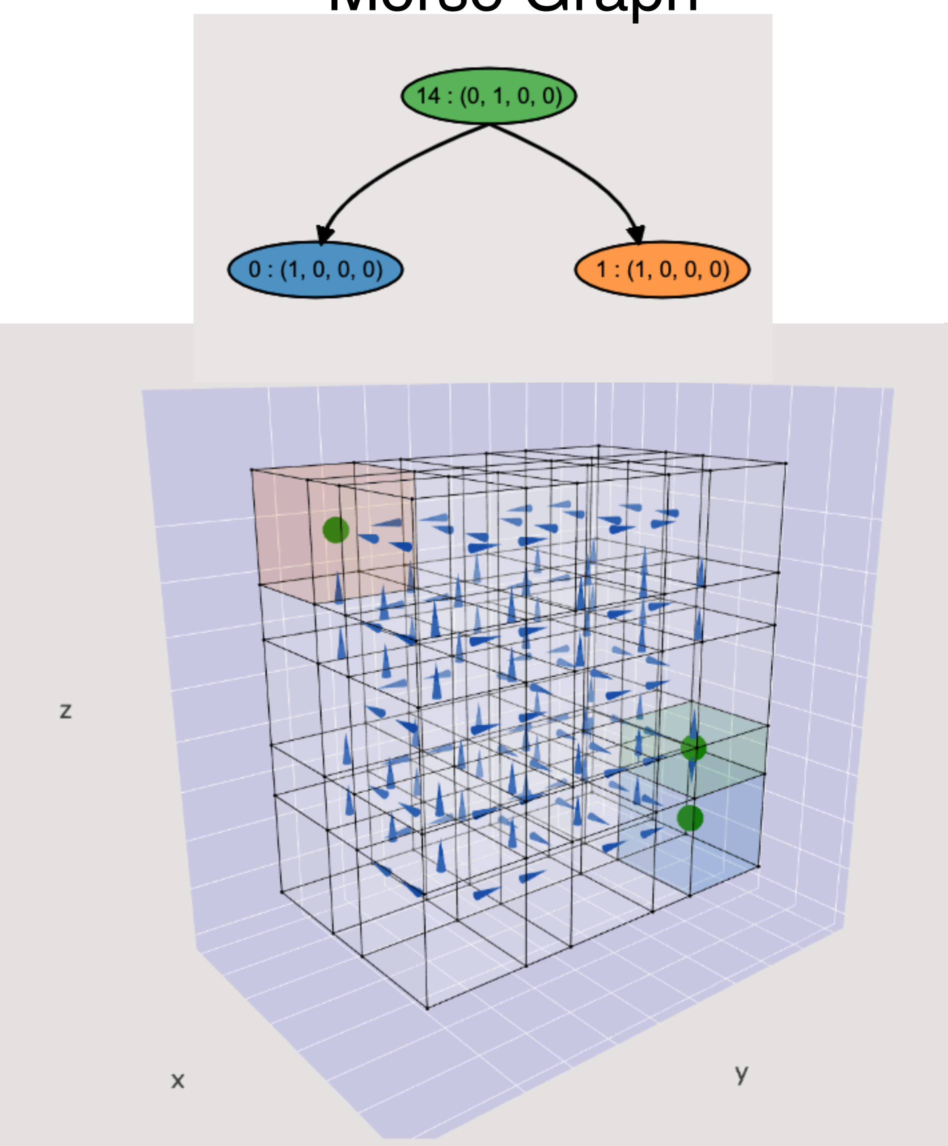
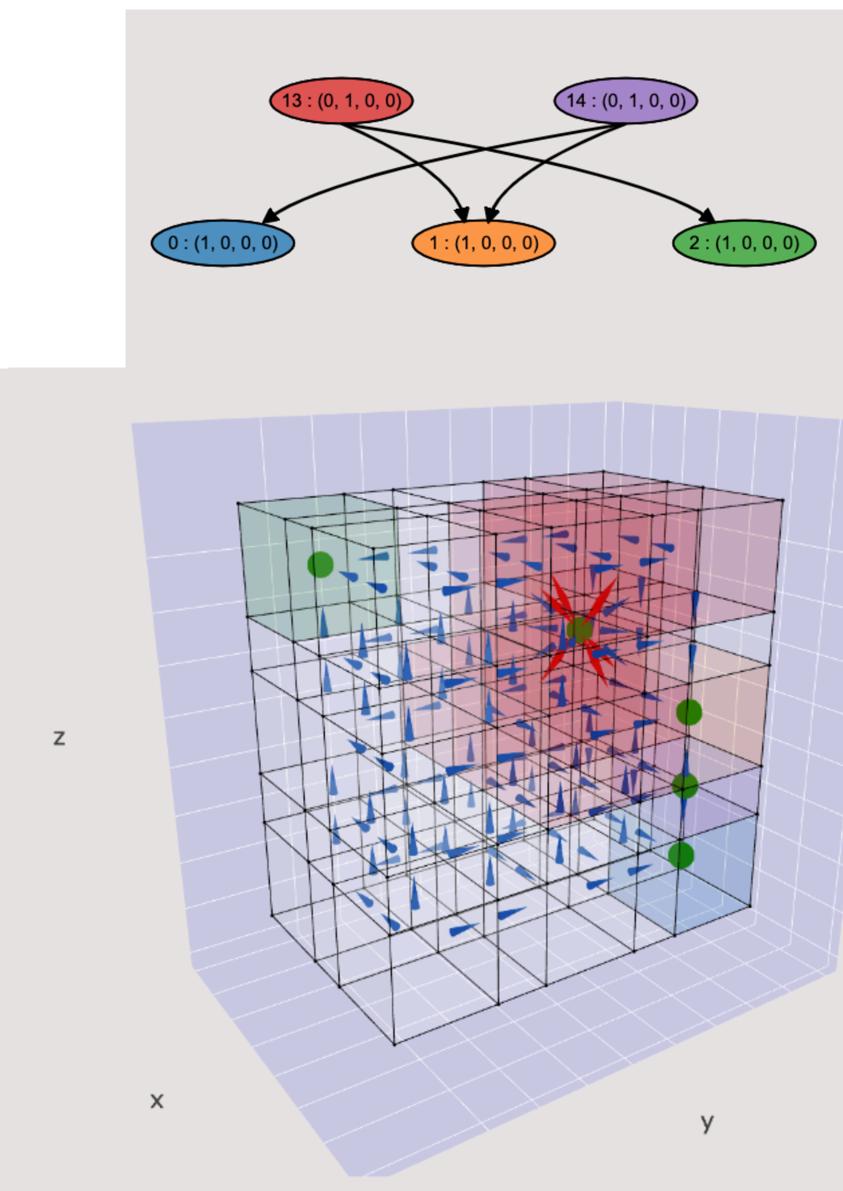
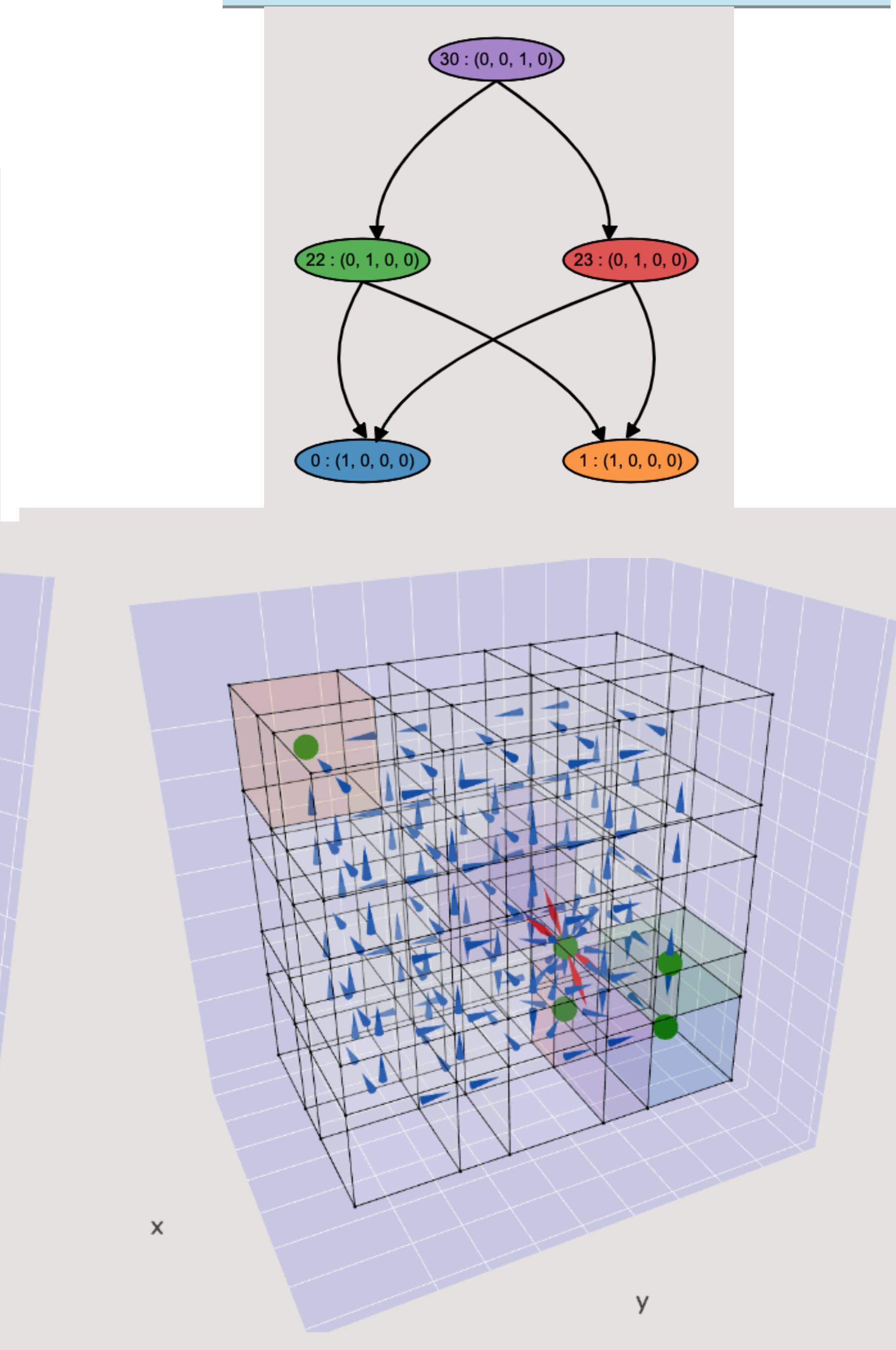
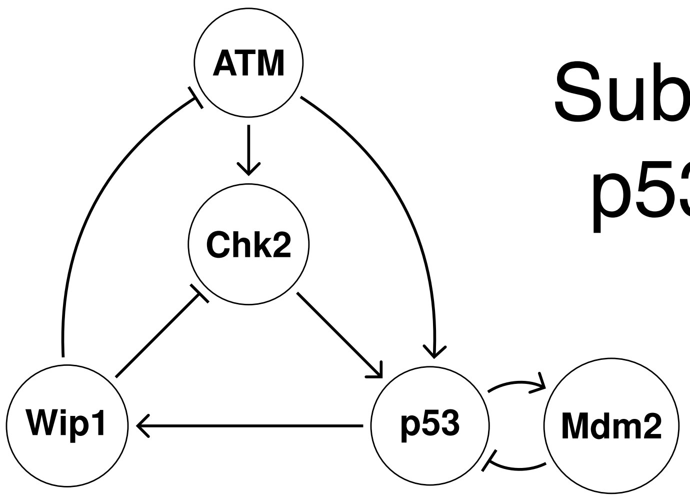






Examples

Can this network produce stable oscillation involving all five variables?



Subnetwork of p53 network

Cummins, et. al., SIADS, 2016

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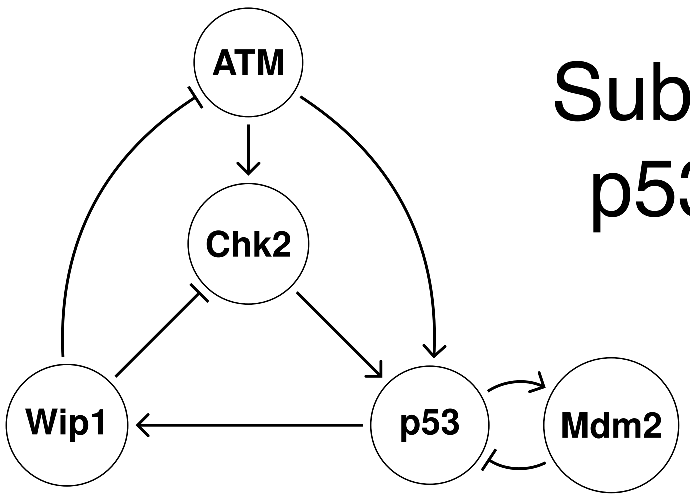

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Answer: Yes for 6904 regions.

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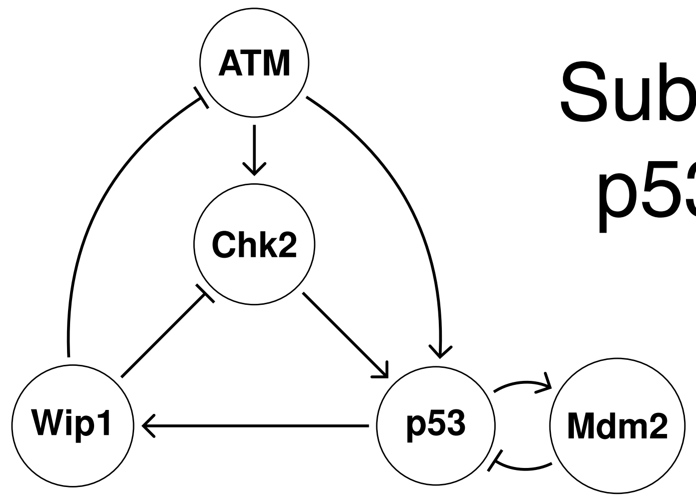

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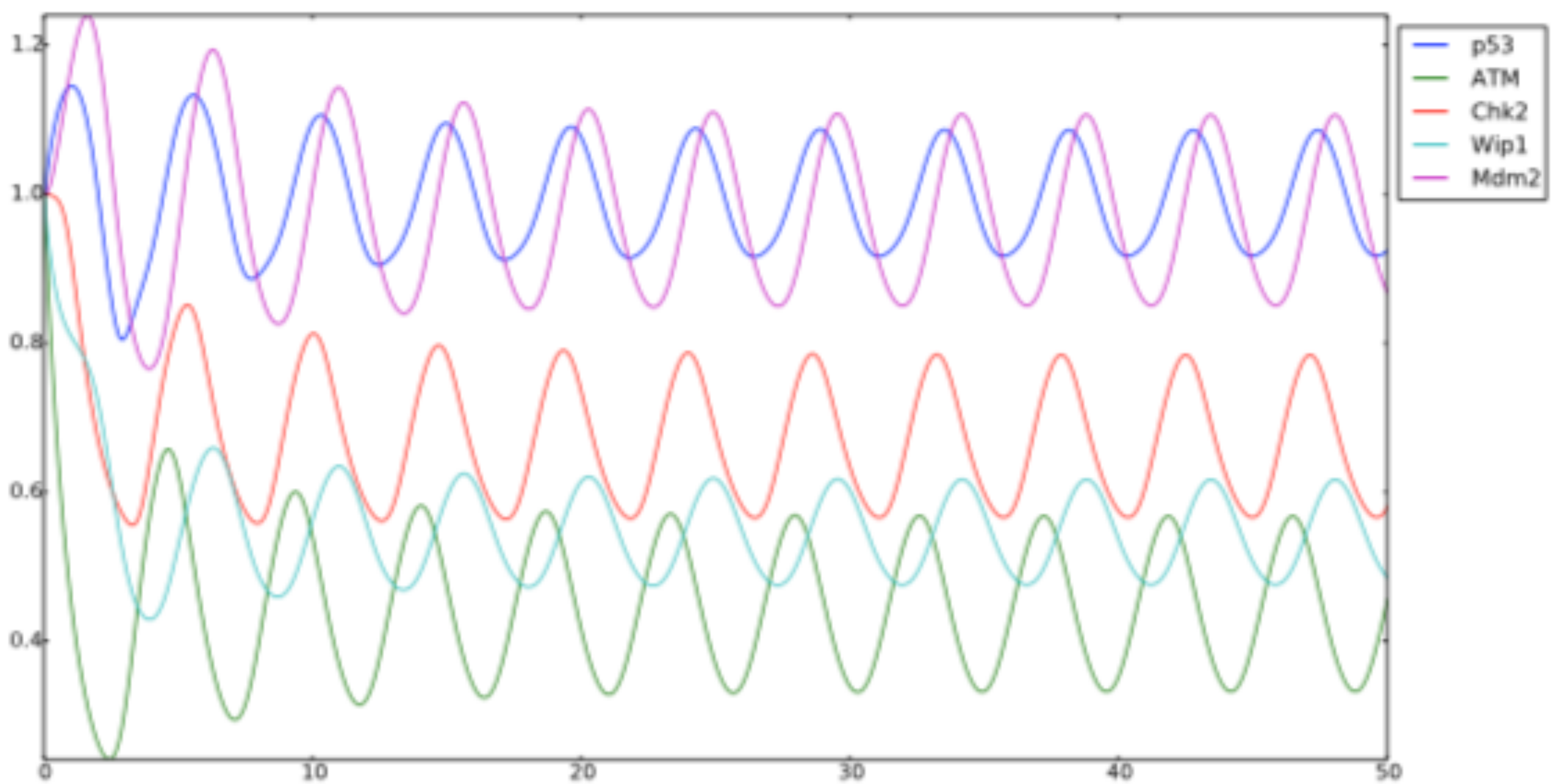

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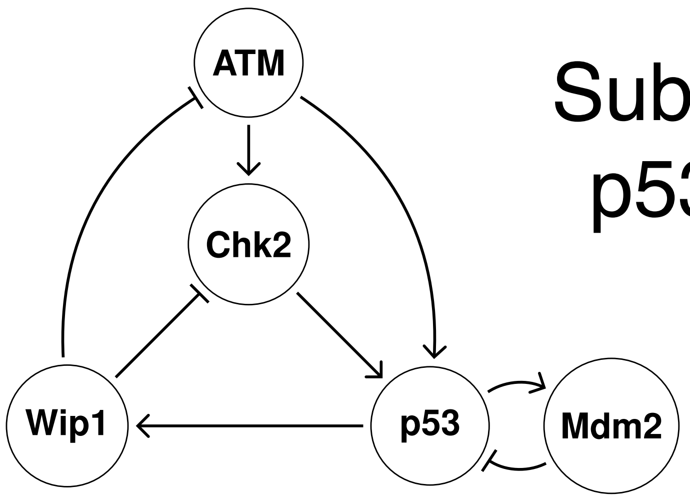

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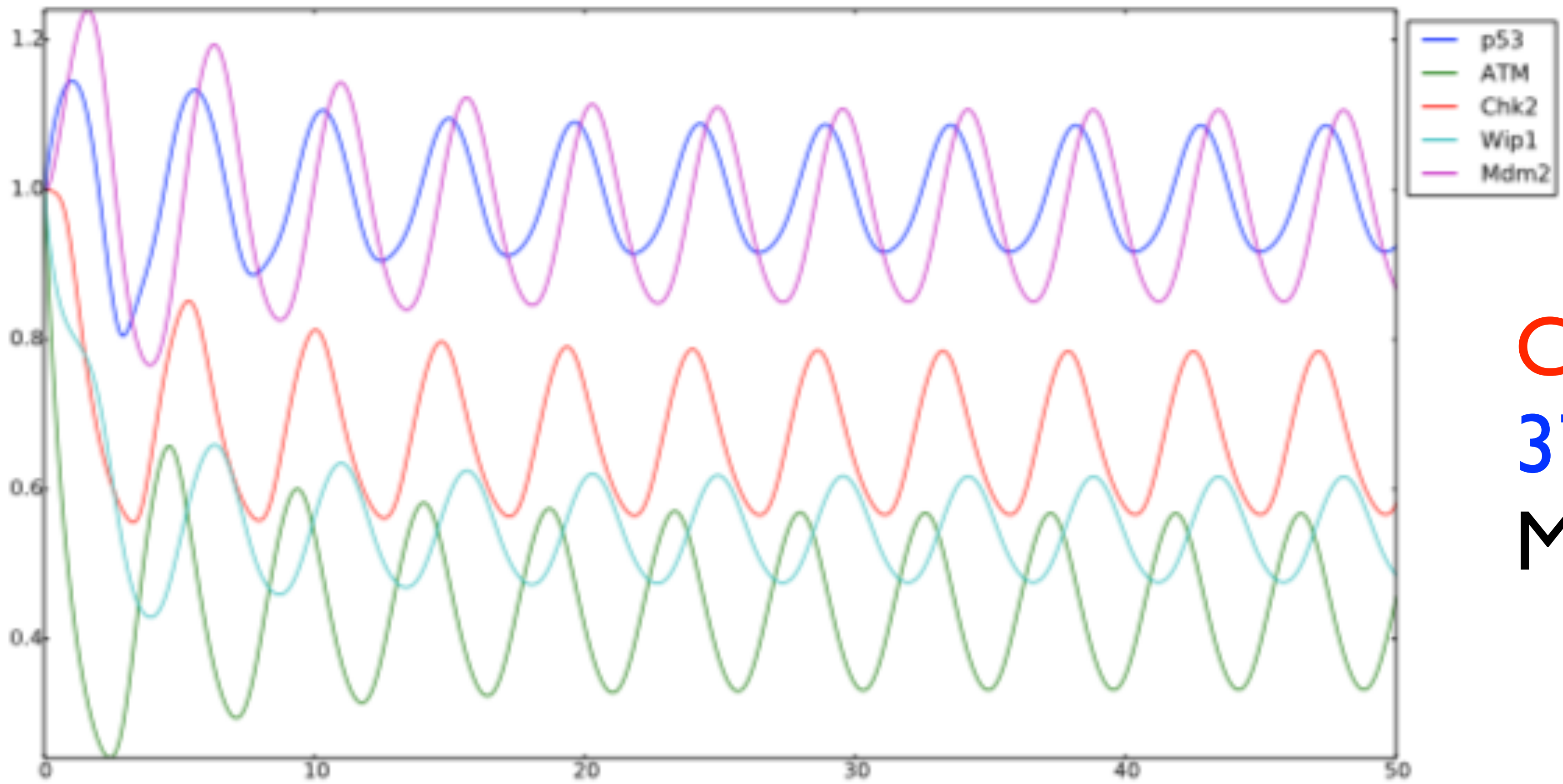
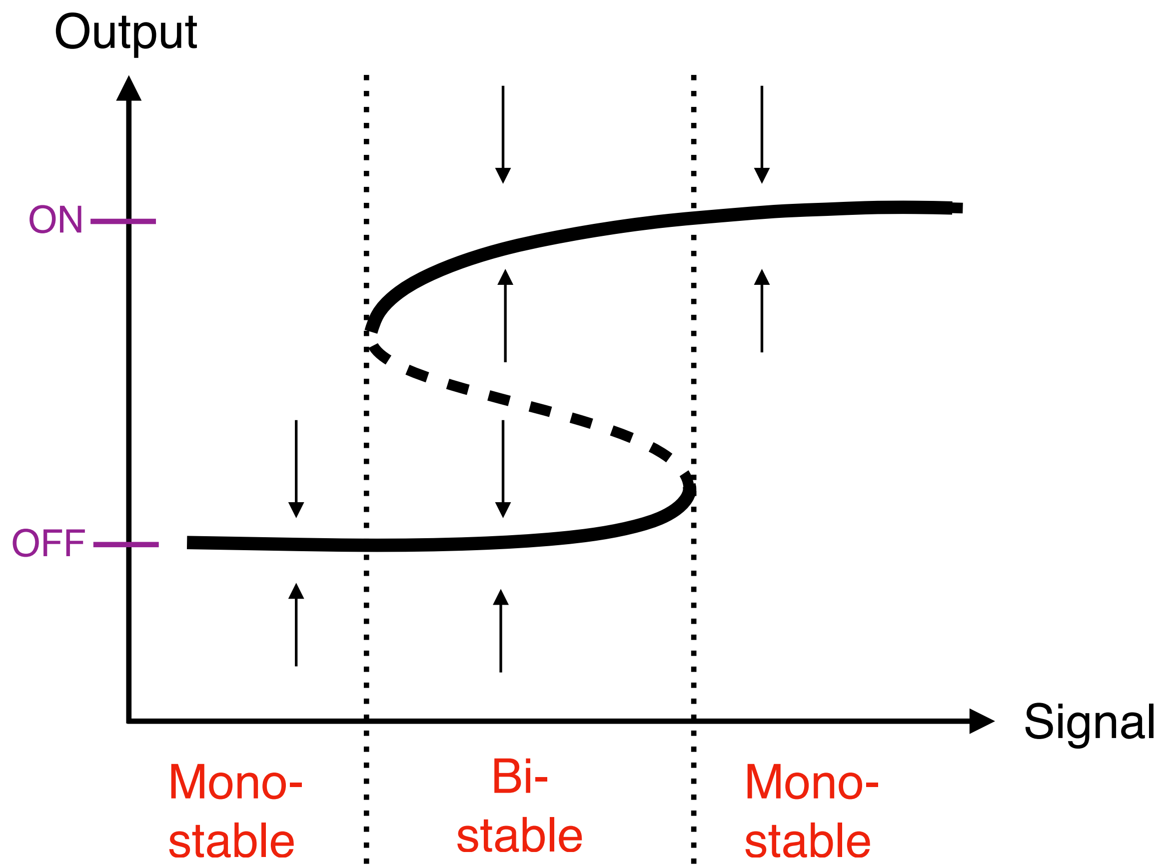


Computational Cost: 37 seconds on a 2014 MacBook pro laptop.

Cummins, et. al., SIADS, 2016

Networks with robust hysteresis

Classical hysteresis



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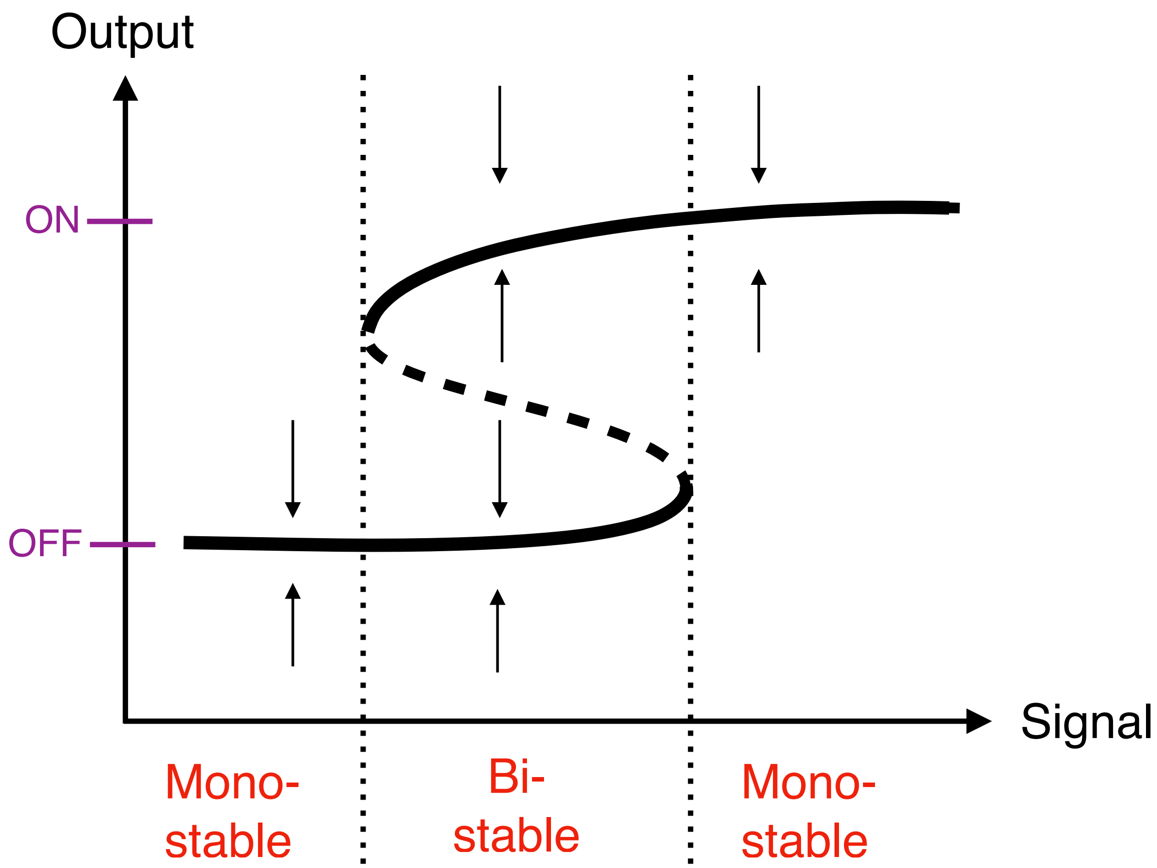
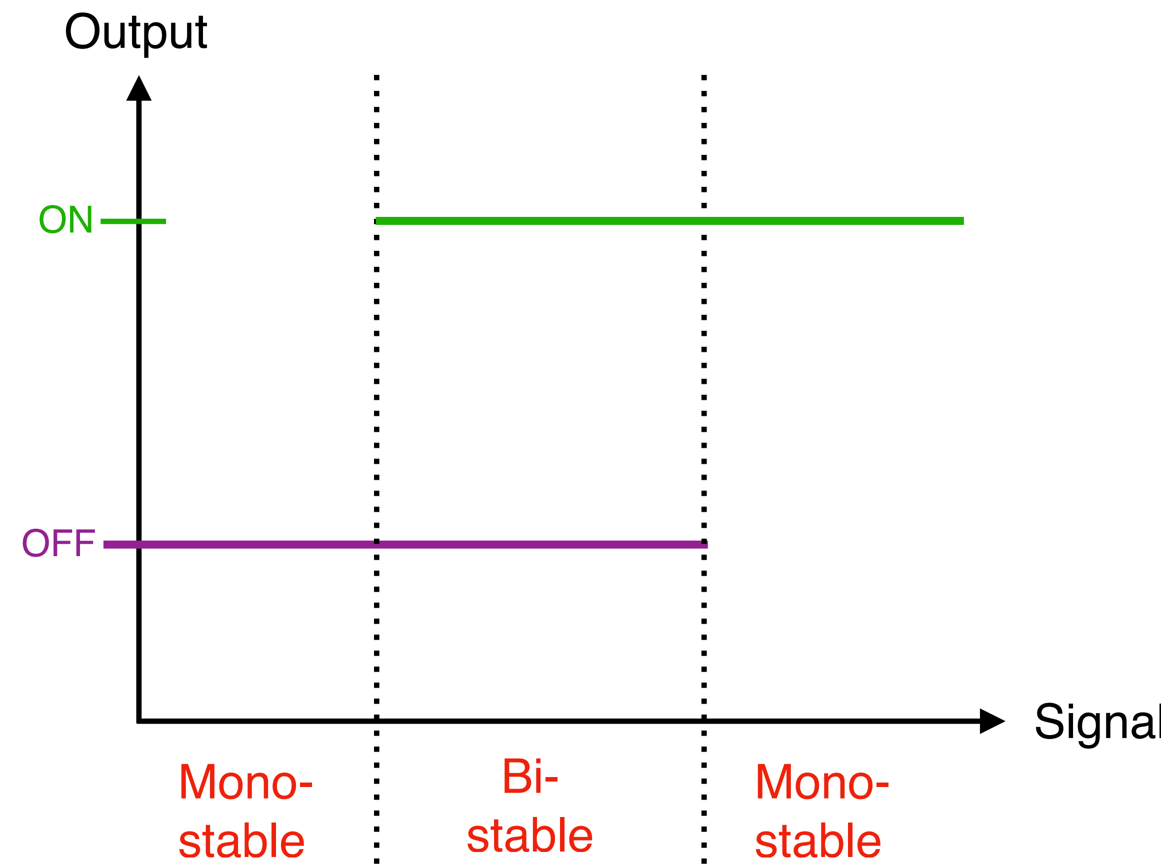


Combinatorial hysteresis



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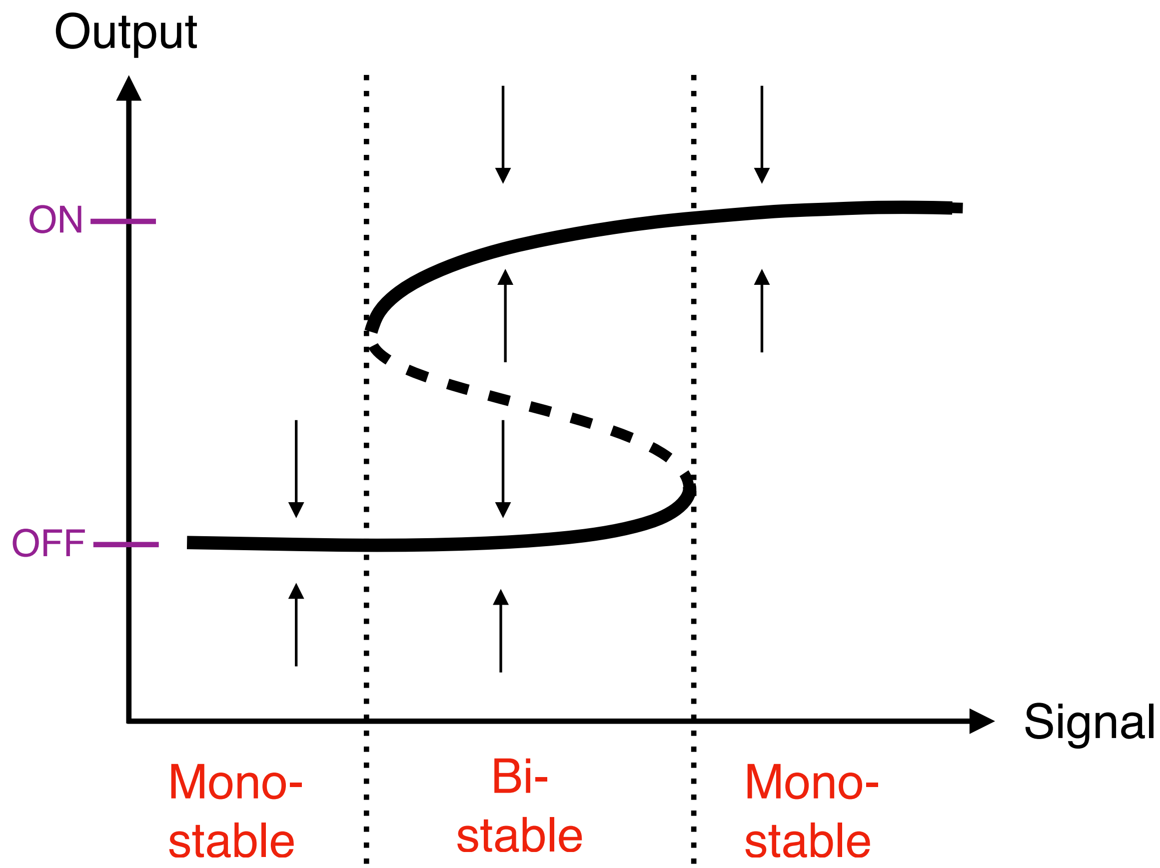

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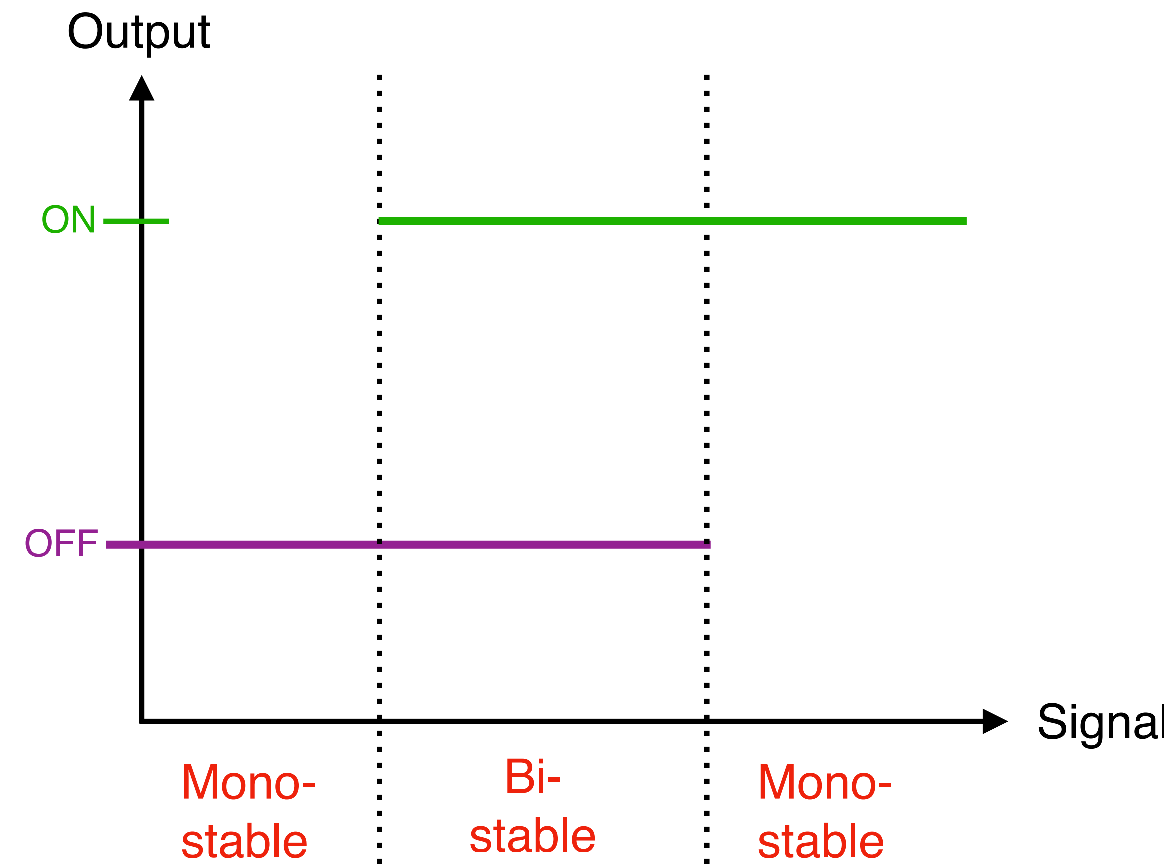
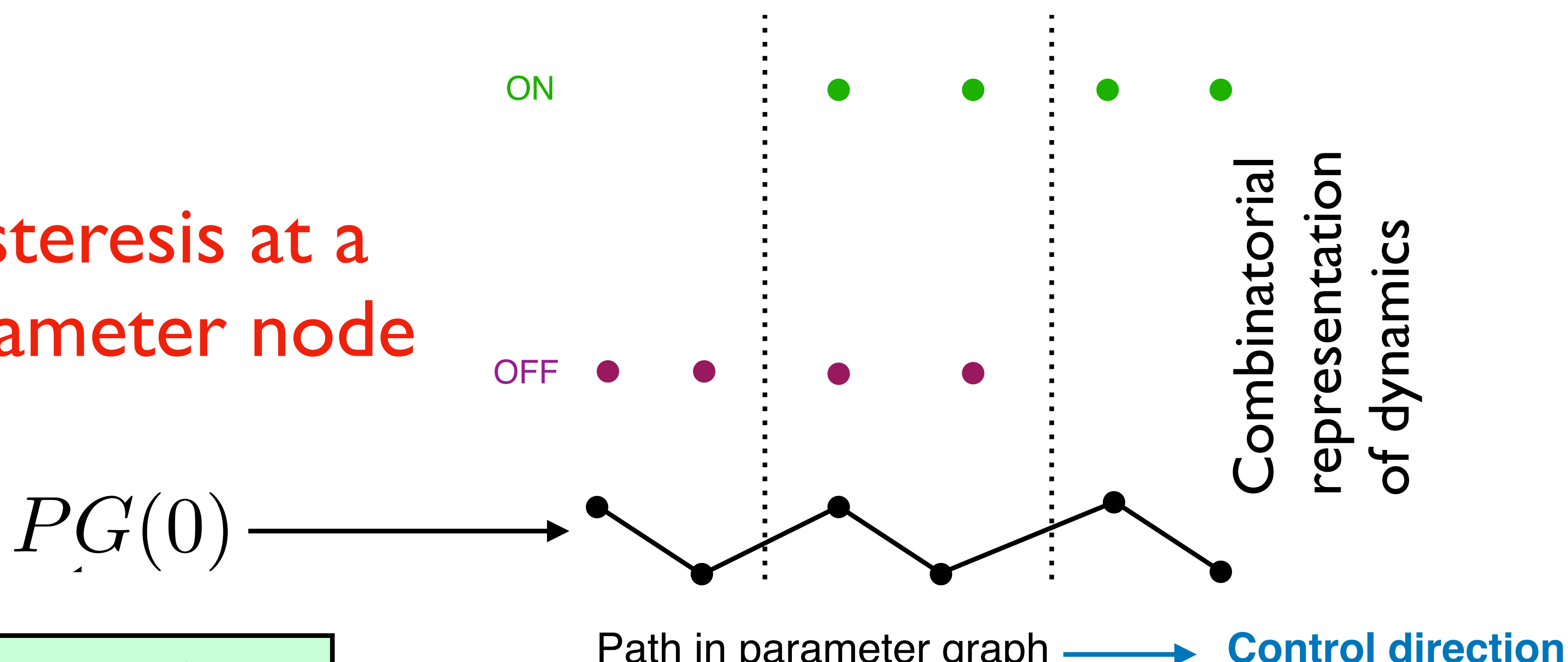


Hysteresis at a parameter node



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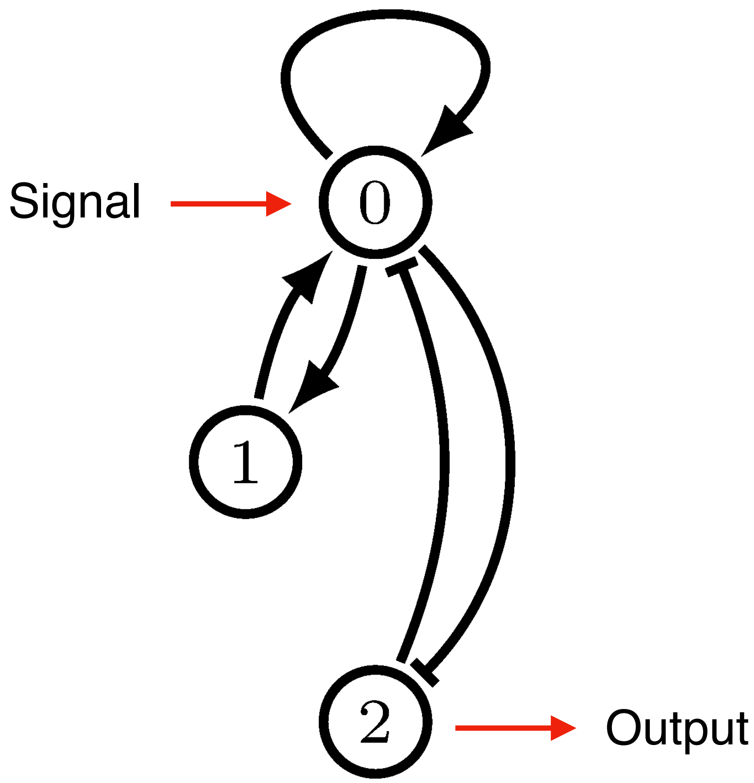
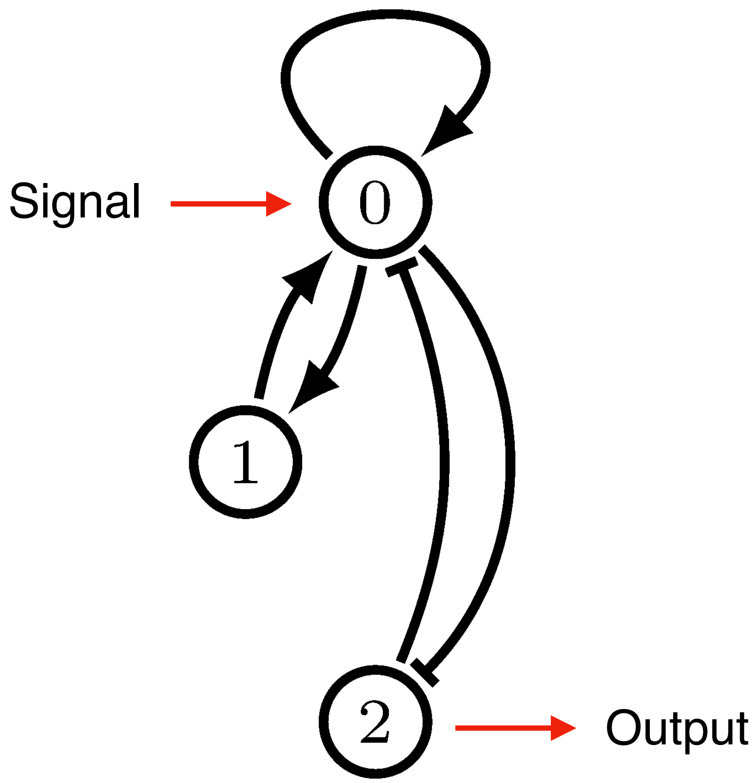


14,068 Networks

Parameter spaces: 12D to 30D

Size of parameter graphs: 27 to 93,329,542,656

Networks with robust hysteresis



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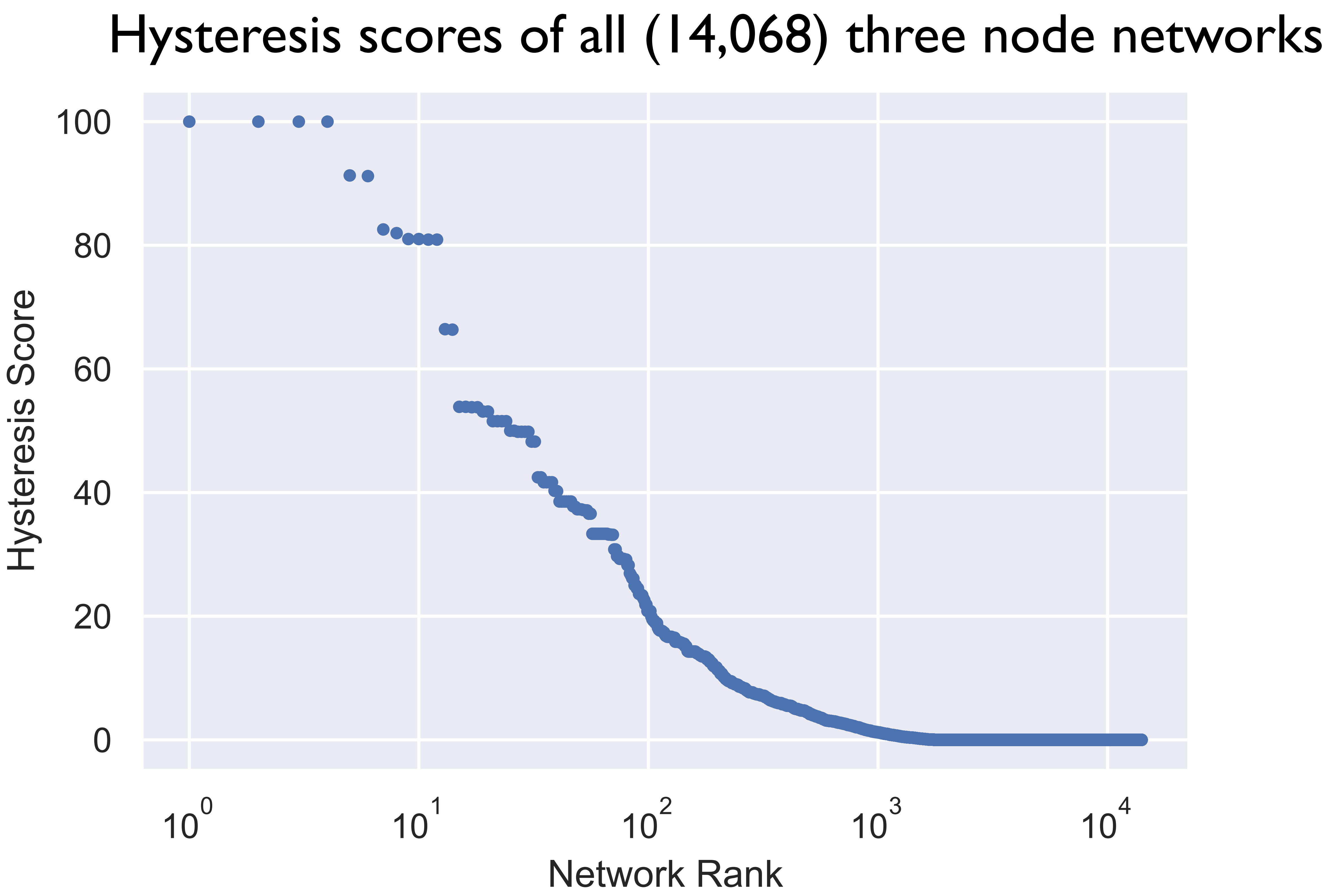
$$\text{Hysteresis score} = \frac{\#\ \text{paths exhibiting hysteresis}}{\#\ \text{of directed paths in } PG(0)}$$

poset

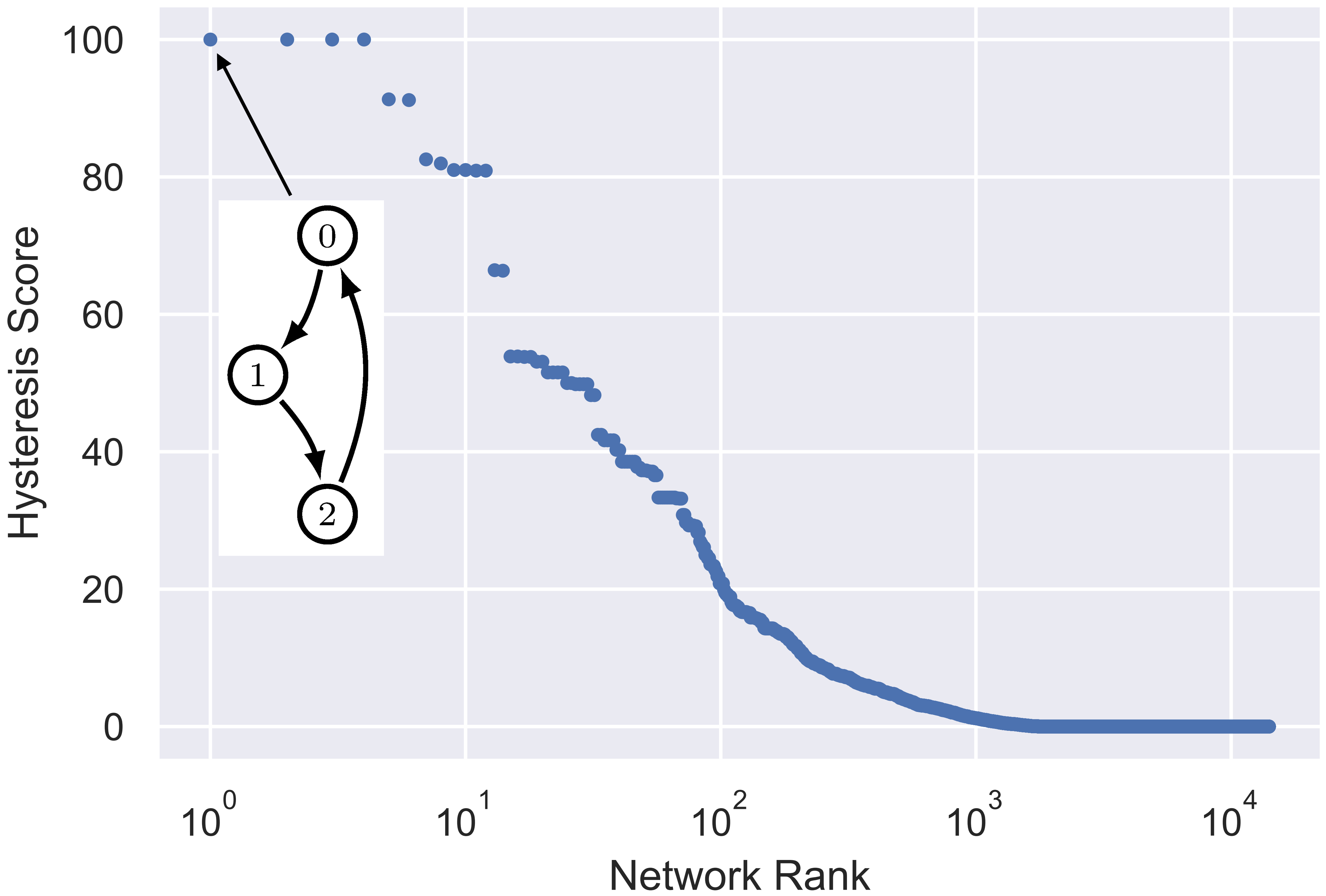
Hysteresis score



G., Gedeon, Kepley, Mischaikow, PLoS Comp Bio, 2021

Hysteresis score

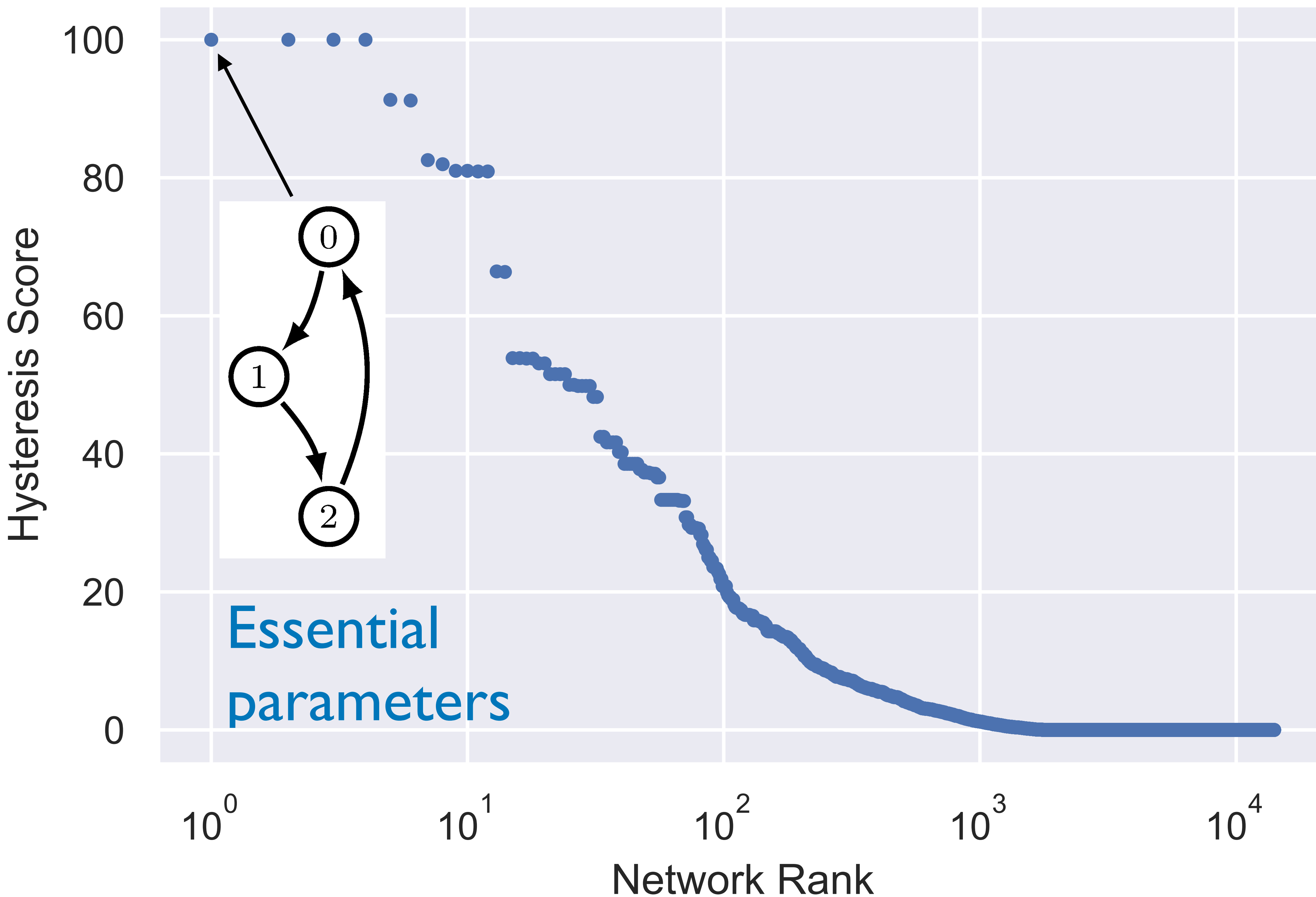
Hysteresis scores of all (14,068) three node networks



G., Gedeon, Kepley, Mischaikow, PLoS Comp Bio, 2021

Hysteresis score

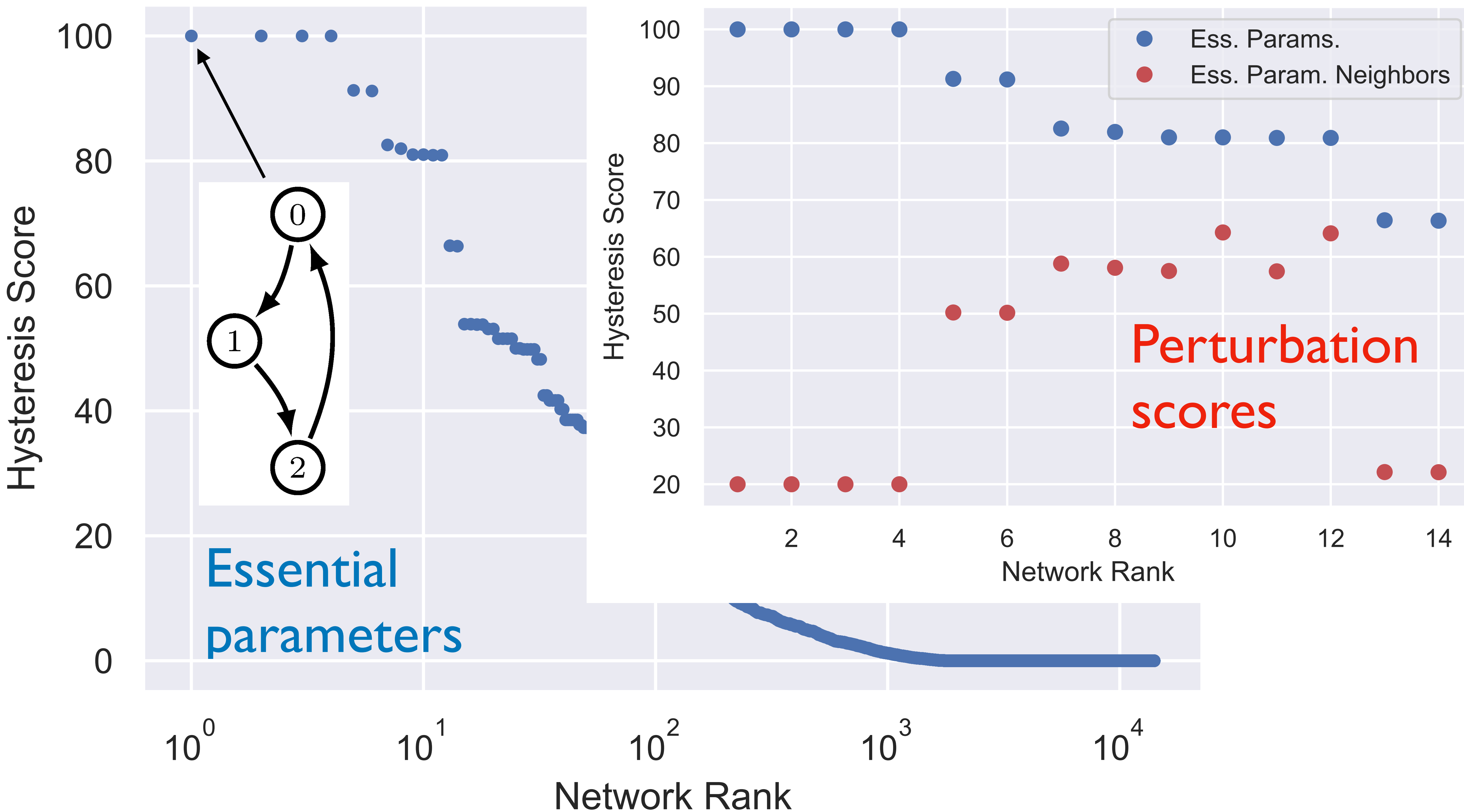
Hysteresis scores of all (14,068) three node networks



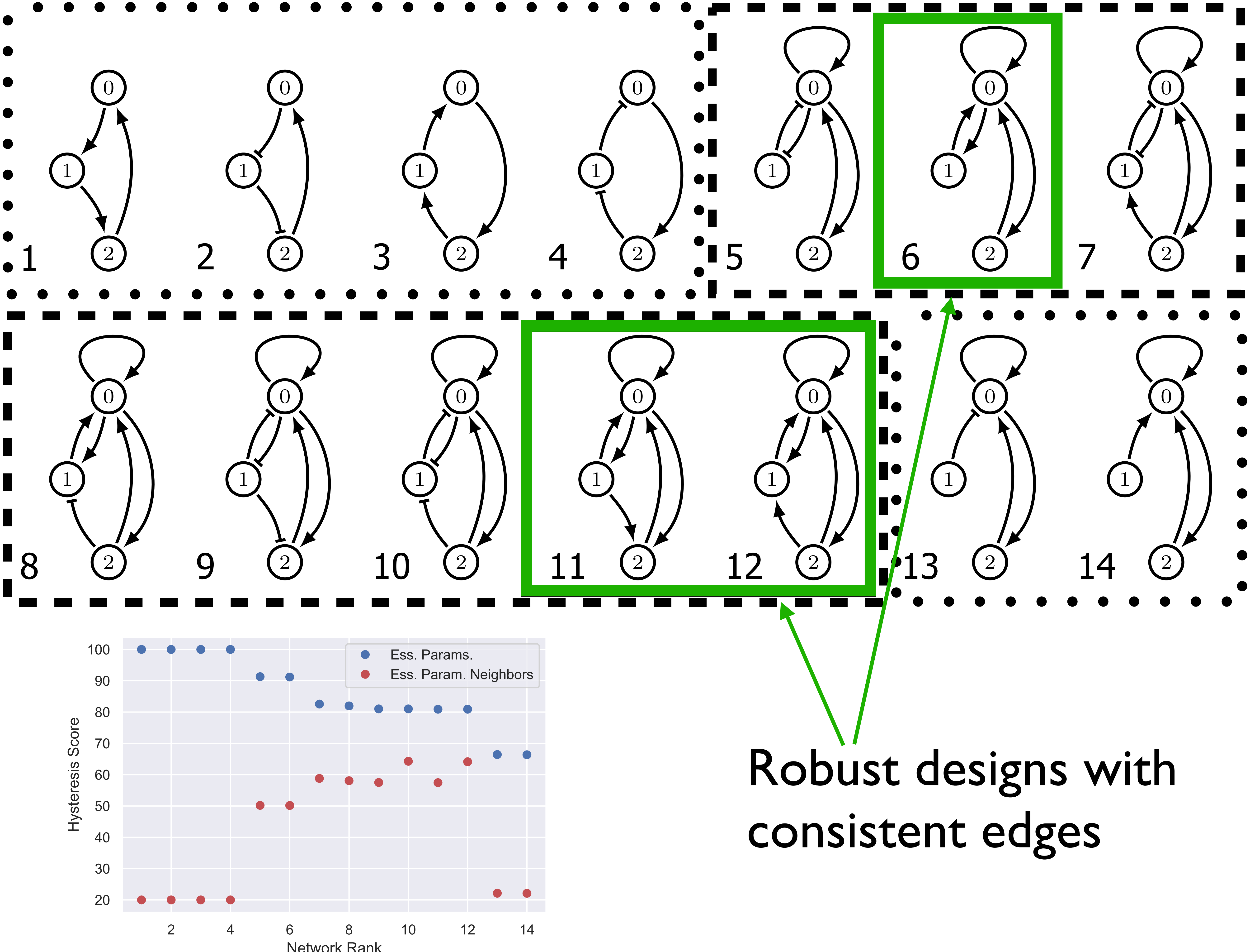
G., Gedeon, Kepley, Mischaikow, PLoS Comp Bio, 2021

Hysteresis score

Hysteresis scores of all (14,068) three node networks



G., Gedeon, Kepley, Mischaikow, PLoS Comp Bio, 2021



1
2
3
4
5
6
7
8
9
10
11
12
13
14
Hysteresis Score
Network Rank
Ess. Params.
Ess. Param. Neighbors
Robust designs with consistent edges

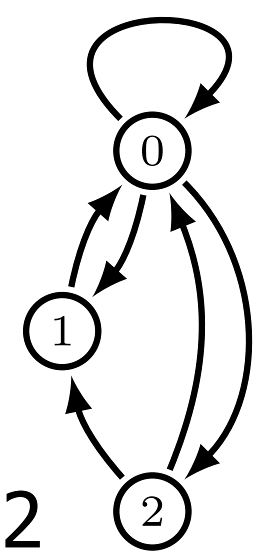
Hill model ODE simulations

$$\dot{x}_0 = -\gamma_0 x_0 + H_0(x) + s$$
$$\dot{x}_1 = -\gamma_1 x_1 + H_1(x)$$
$$\dot{x}_2 = -\gamma_2 x_2 + H_2(x)$$

Hill function nonlinearities

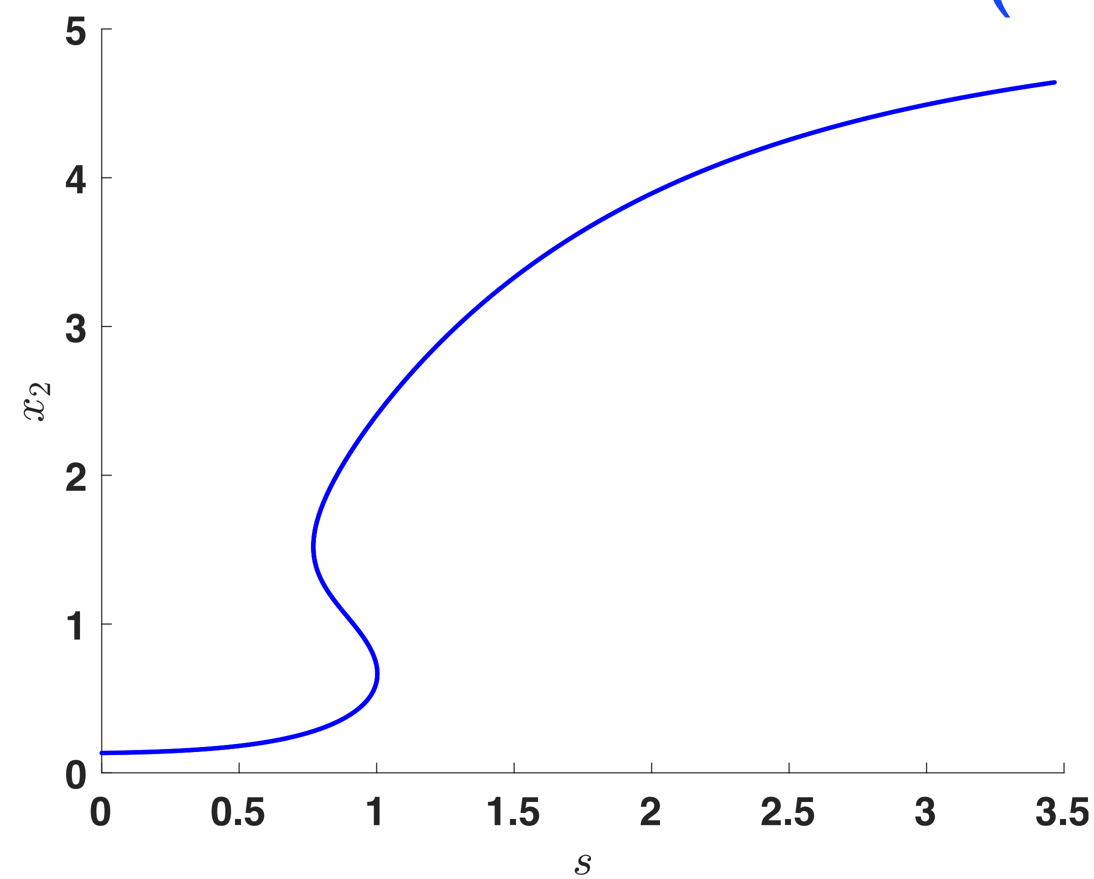
Example

$$\dot{x}_0 = -\gamma_0 x_0 + L_0 + \frac{\delta_{0,0} x_0^n}{\theta_{0,0}^n + x_0^n} + \frac{\delta_{0,1} x_1^n}{\theta_{0,1}^n + x_1^n} + \frac{\delta_{0,2} x_2^n}{\theta_{0,2}^n + x_2^n} + s$$
$$\dot{x}_1 = -\gamma_1 x_1 + L_1 + \frac{\delta_{1,0} x_0^n}{\theta_{1,0}^n + x_0^n} + \frac{\delta_{1,2} x_2^n}{\theta_{1,2}^n + x_2^n}$$
$$\dot{x}_2 = -\gamma_2 x_2 + L_2 + \frac{\delta_{2,0} x_0^n}{\theta_{2,0}^n + x_0^n}$$



Network 12

Numerical continuation (n=4)



Hill model ODE simulations

Regulatory Network	12		33		108		4346	
Hill function exponent n	Hysteresis Score	Perturbed Score	Hysteresis Score	Perturbed Score	Hysteresis Score	Perturbed Score	Hysteresis Score	Perturbed Score
30	81.2 %	51.7 %	84.4 %	41.2 %	57.9 %	56.1 %	0 %	0 %
20	70.8 %	41.3 %	74.9 %	34.0 %	45.4 %	46.8 %	0 %	0 %
10	39.7 %	18.8 %	45.3 %	16.6 %	18.2 %	21.8 %	0 %	0 %
5	7.3 %	2.1 %	7.6 %	2.2 %	1.3 %	2.4 %	0 %	0 %
4	3.1 %	0.6 %	2.2 %	0.5 %	0.2 %	0.3 %	0 %	0 %
DSGRN (full path)	100 %	79.1 %	83.3 %	61.7 %	33.9 %	25.1 %	0 %	0 %
DSGRN (partial path)	80.9 %	64.1 %	42.5 %	27.7 %	18.9 %	13.3 %	0 %	0 %

DSGRN scores

Hill model simulations with sampled parameter values (1,000 curves per entry) - 12-30 dimensional parameter space

DSGRN takes a fraction of the time and covers all of the parameter space

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DSGRN software

https://github.com/marciogameiro/DSGRN

DARPA

NIH National Institute of General Medical Sciences

NSF