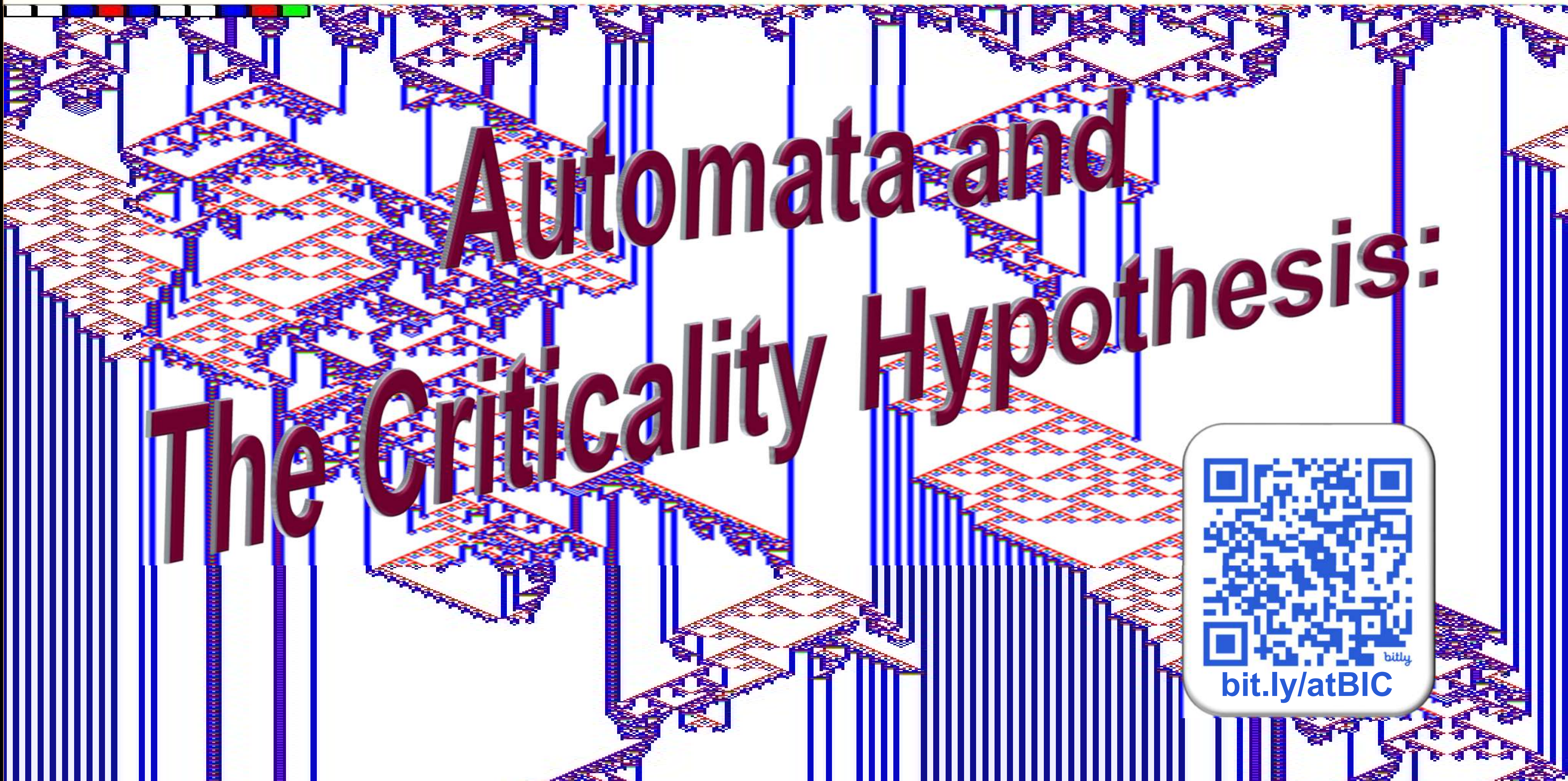
Automata and The Criticality Hypothesis:



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key events coming up

- Labs: 35% (ISE-483)
  - Complete 5 (best 4 graded) assignments based on algorithms presented in class
    - Lab 3: March 11th
      - Cellular Automata and Boolean Networks (Assignment 3)
        - Delivered by SSIE583 Group 3
        - Due: March 25th
- SSIE – 583 -Presentation and Discussion: 25%
  - Present and lead the discussion of an article related to the class materials
    - Enginet students post/send video or join by Zoom
  - Dates TBA
    - Conrad, M. [1990]. "The geometry of evolution." *Biosystems* **24**: 61-81.
      - Mario Franco
    - Stanley, Kenneth O., Jeff Clune, Joel Lehman, and Risto Miikkulainen. "Designing Neural Networks through Neuroevolution." *Nature Machine Intelligence* **1**, no. 1 (January 2019): 24–35.
      - Jessica Lasebikan
    - Lindgren, K. [1991]."Evolutionary Phenomena in Simple Dynamics." In: *Artificial Life II*. Langton et al (Eds). Addison-wesley, pp. 295-312.
      - Akshay Gangadhar
    - Salahshour, Mohammad. "Interaction between Games Give Rise to the Evolution of Moral Norms of Cooperation." *PLOS Computational Biology* **18**, no. 9 (September 29, 2022): e1010429
      - Srikanth Iyer
    - Discussion by all

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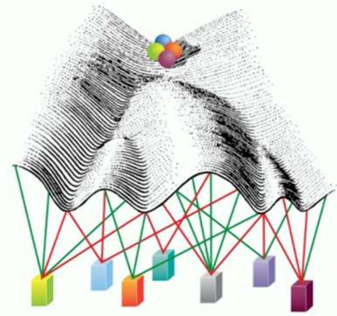
until now

- Class Book
  - Floreano, D. and C. Mattiussi [2008]. *Bio-Inspired Artificial Intelligence: Theories, Methods, and Technologies*. MIT Press. Preface, **Chapter 2.**
    - Nunes de Castro, Leandro [2006]. *Fundamentals of Natural Computing: Basic Concepts, Algorithms, and Applications*. Chapman & Hall. **Chapter 1**, pp. 1-23. Chapter 7, sections **7.1-7.4**, **Appendix B.3.1**, **Chapter 2**, Chapter 8, sections **8.1, 8.2, 8.3.10**
- Lecture notes
  - Chapter 1: What is Life?
  - Chapter 2: The logical Mechanisms of Life
  - Chapter 3: Formalizing and Modeling the World
  - Chapter 4: Self-Organization and Emergent Complex Behavior
    - posted online @ http://informatics.indiana.edu/rocha/i-bic



- Papers and other materials
  - Dynamical Systems
    - Kauffman, S.A. [1969]. "Metabolic stability and epigenesis in randomly constructed genetic nets". Journal of Theoretical Biology 22(3):437-467.
  - Optional
    - Prusinkiewicz and Lindenmeyer [1996] *The algorithmic beauty of plants*.
      - Chapter 1
    - Flake's [1998], *The Computational Beauty of Life*. MIT Press.
      - Chapters 10, 11, 14 – Dynamics, Attractors and chaos

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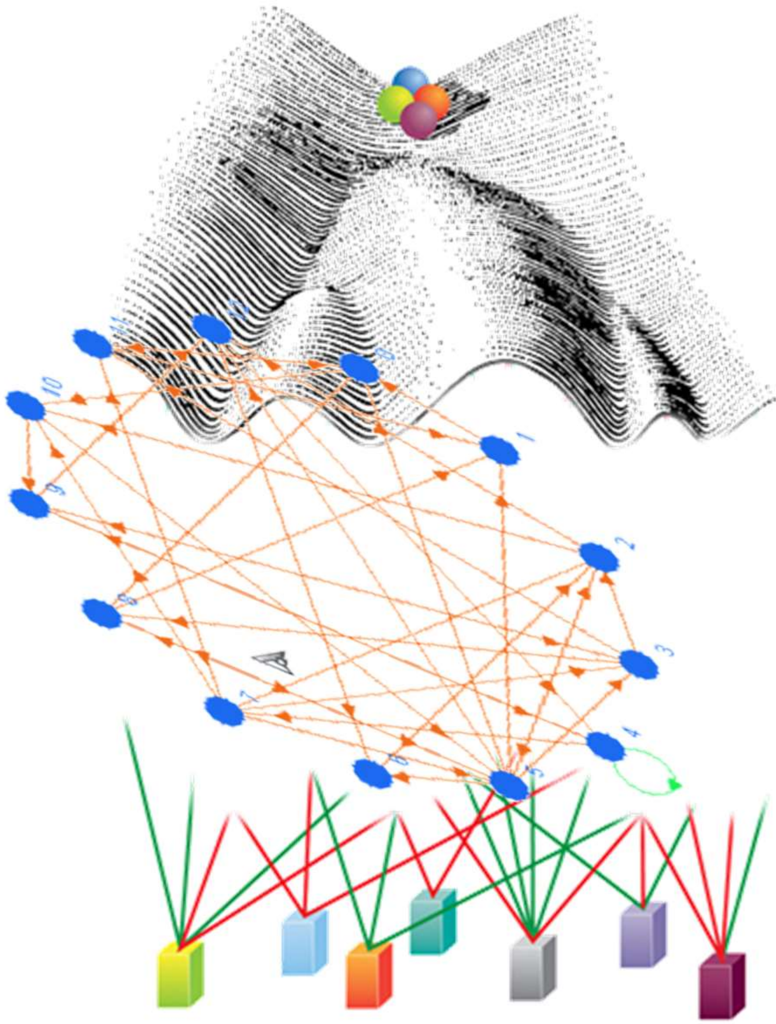
- Projects
  - Due by May 6th in Brightspace, "Final Project Paper" assignment
    - ALIFE 2023
      - Not to submit to actual conference due date (April 3rd , 2024)
      - https://2024.alife.org/
      - 8 pages, author guidelines:
      - https://2024.alife.org/call_paper.html
      - MS Word and Latex/Overleaf templates
    - Preliminary ideas **by March 15**
      - Submit to "Project Idea" assignment in Brightspace.
  - Individual or group
    - With very definite tasks assigned per member of group

ALIFE 2024

Tackle a real problem using bio-inspired algorithms, such as those used in the labs.

evolution requires life in critical regime which is small, how come life is not chaotic?



Kauffman, S. A. (1984). *Phys. D Nonlinear Phen*.**10**,145–156.

Waddington CH (1942). *Nature*.**150** (3811):563–565

robustness of phenotypes is the result of a ***buffering*** of the developmental process.

dynamics of gene networks provides buffering (***self-organization***). But still easily chaotic.

Structure (***topological organization***), can provide larger stable or critical universe, but still easily chaotic.

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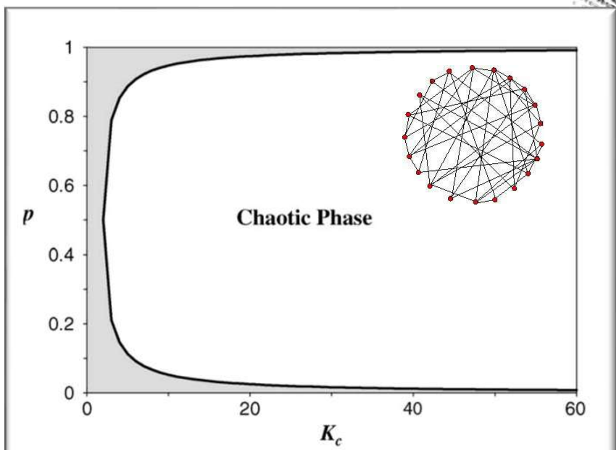
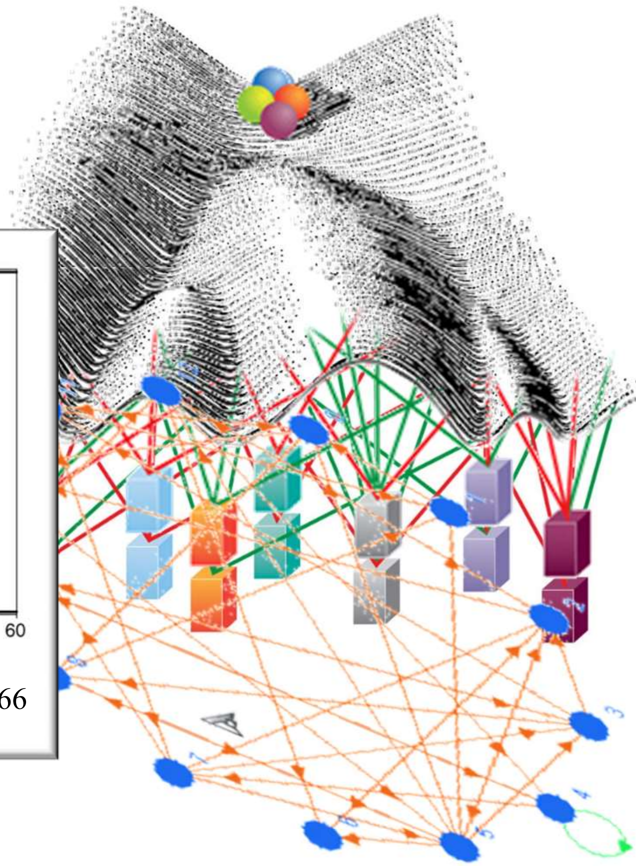


Aldana, M. [2003]. *Physica D.* **185**: 45–66



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The Criticality Hypothesis

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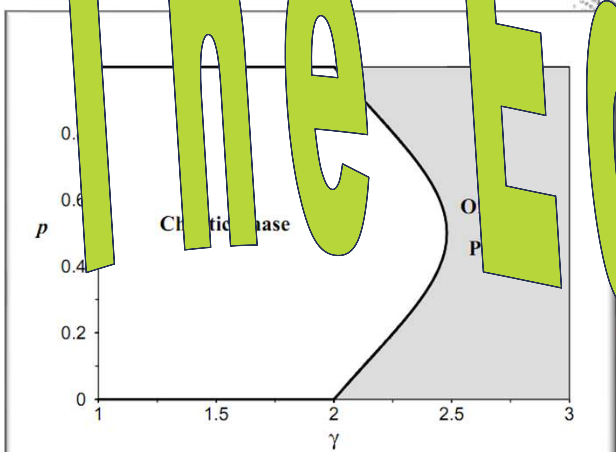
The Edge of Chaos?



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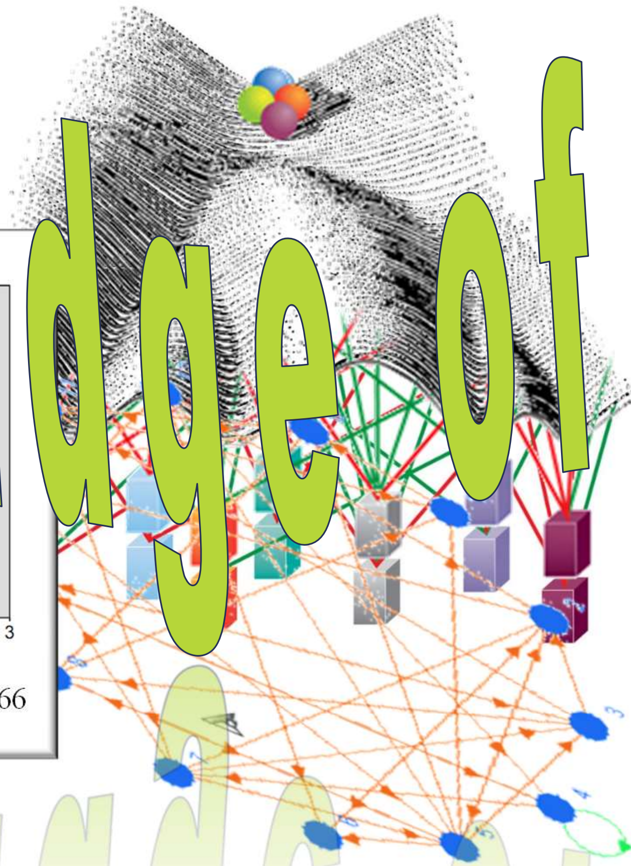

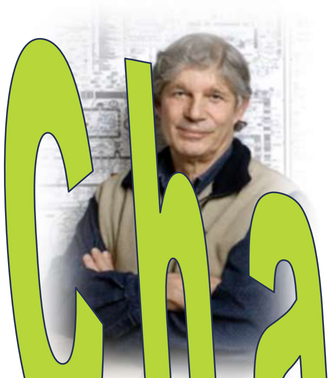

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The Criticality Hypothesis

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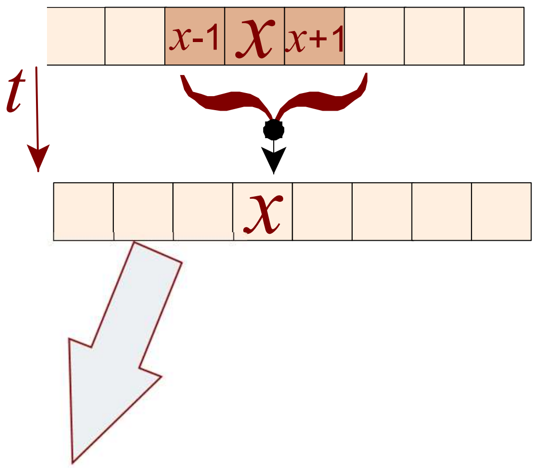
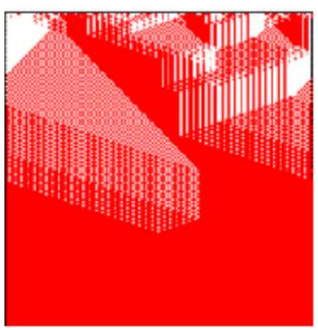
Cellular automata

homogenous lattice of state-determined systems

Cellular Automata



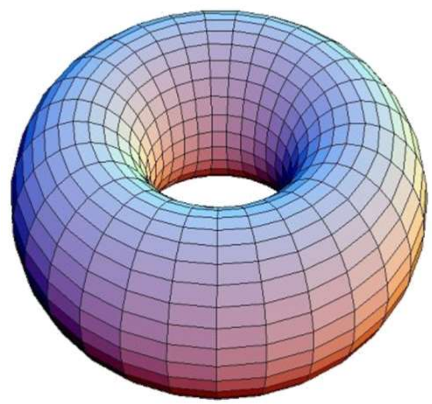


Space-time diagram

1-D

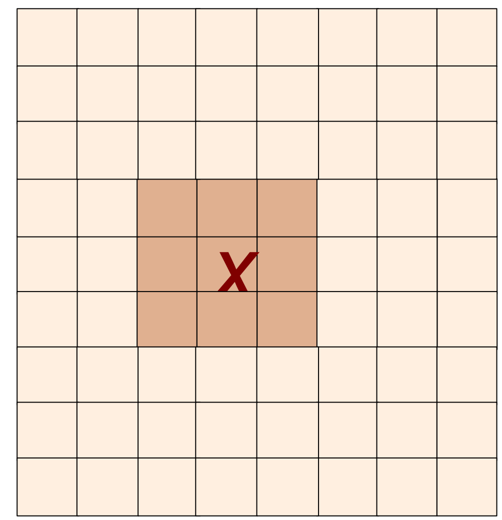
$$x_i^t = f\left(x_{i-r},\ldots,x_i,\ldots x_{i+r}\right)^{t-1}$$

$$x \in \{0,1,2,\ldots s\}$$



Toroidal Lattice

2-D



$$x_{i,j}^t = f\left(x_{i-r_x,j-r_y},\ldots,x_{i,j},\ldots x_{i+r_x,j+r_y}\right)^{t-1}$$

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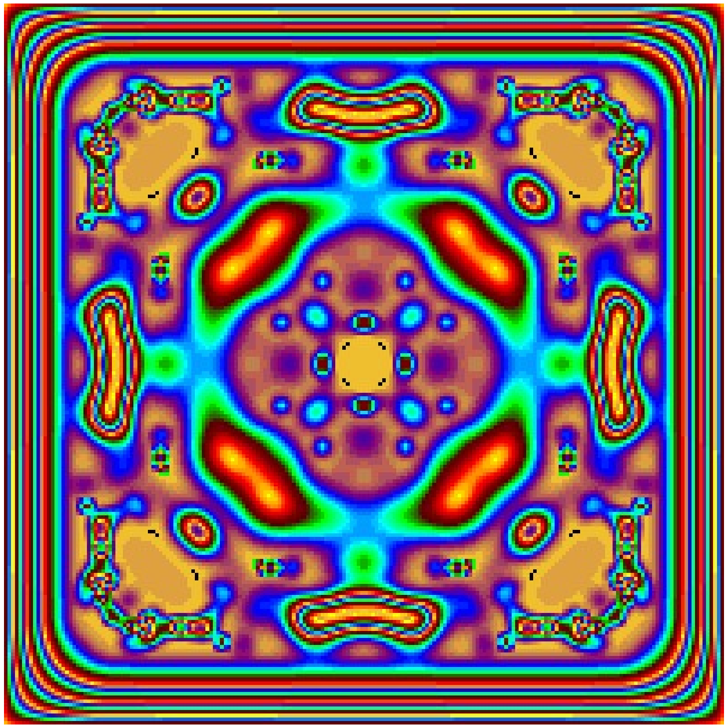
- Parallel updating
- Artificial physics
  - Local interactions only
    - No actions at a distance
  - Homogeneous
- Unpredictable global behavior
  - Emergence
    - 2-levels: rules (micro-level) and attractor behavior (macro-level)
  - Irreversible
- Self-organization
- Example rules
  - Rug (diffusion)
    - 256 states
    - Average of 8 neighbors in 2-d grid, if state is 255 -> 0.
  - Vote/majority
    - binary



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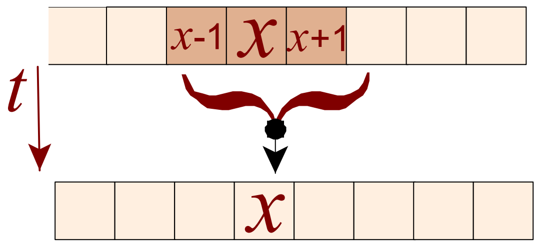
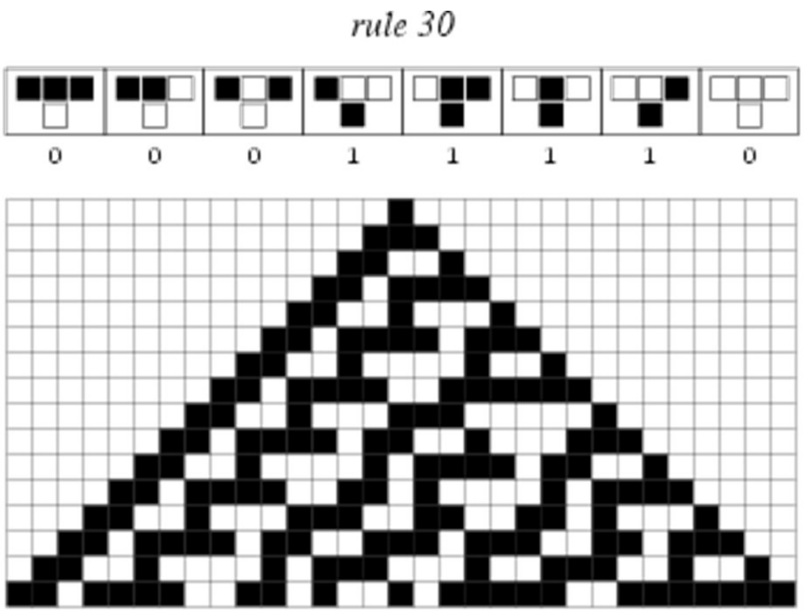
Cellular Automata



- Radius 1
  - Neighborhood =3
- Binary
  - 2^3 = 8 input neighborhoods
  - 2^8 = 256 rules



http://mathworld.wolfram.com/CellularAutomaton.html

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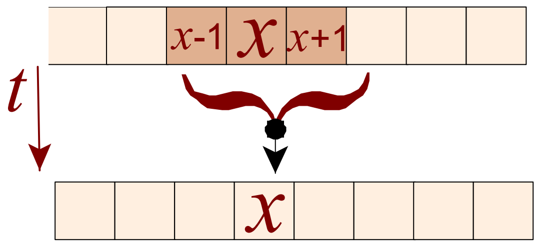
Cellular Automata



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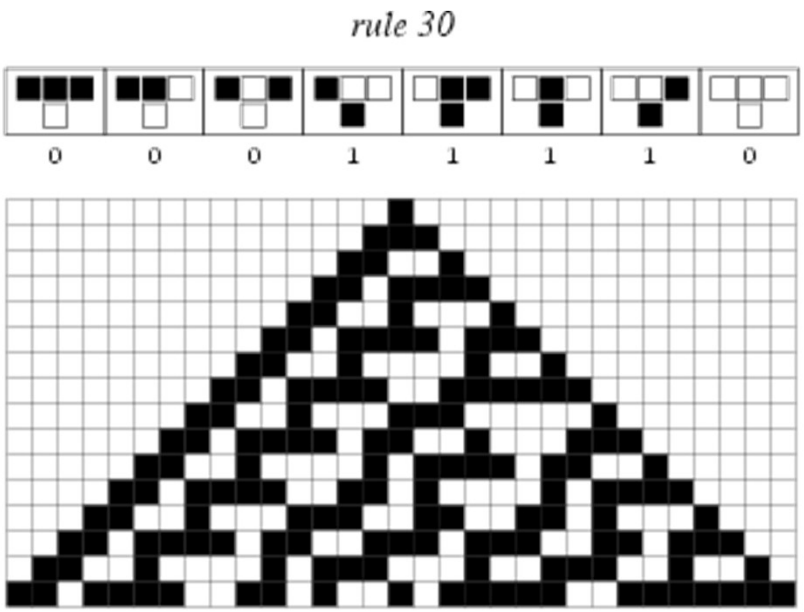

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state-determined transitions

if a cell and its neighbours look like this at time **t**

s_i

s_{i-1} ☐ ☐ ☐ s_{i+1}

condition

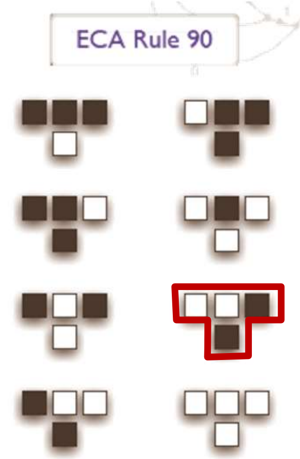
then the cell will look like this on the next row (at time **t+1**)

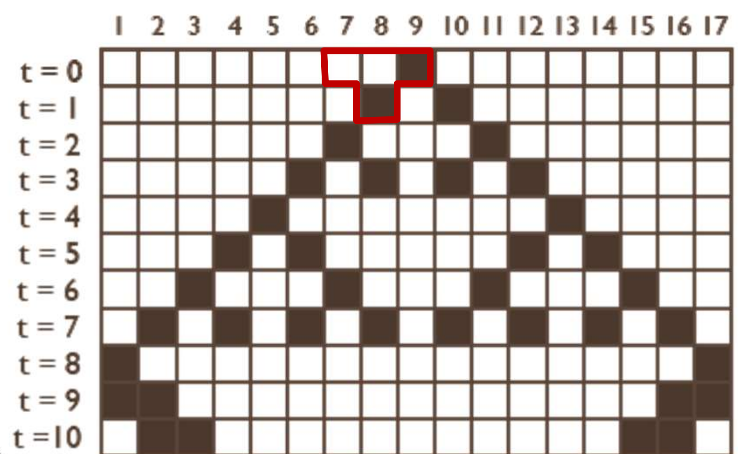
s_i

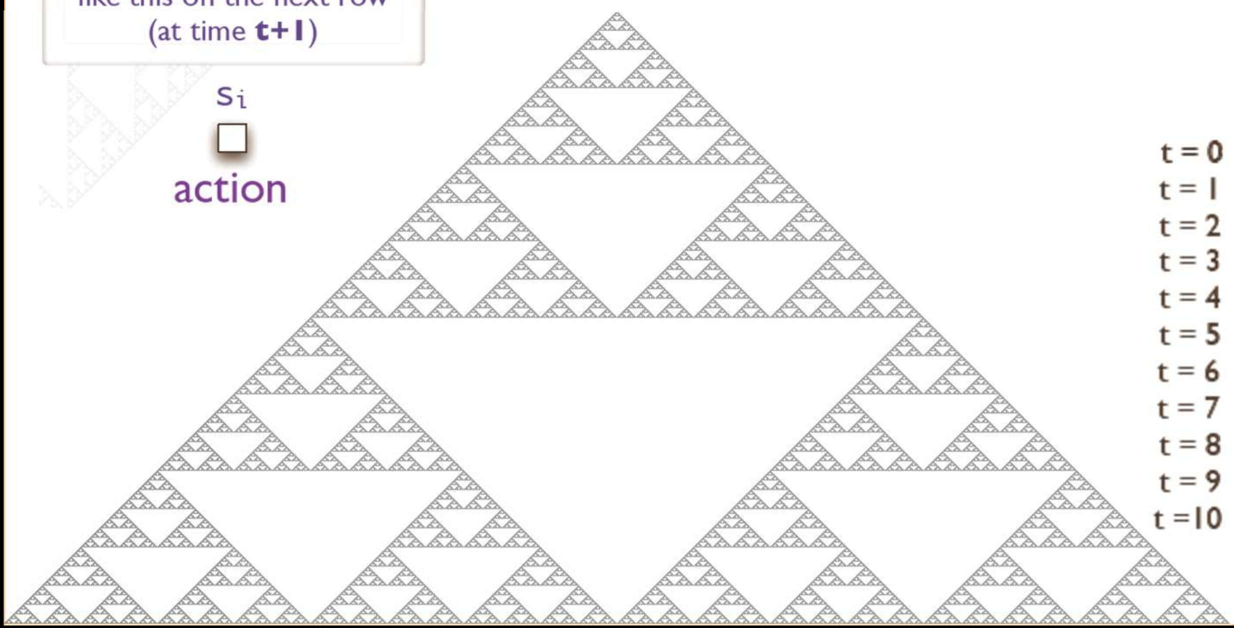
☐

action

look-up table
each entry is a
condition-action rule







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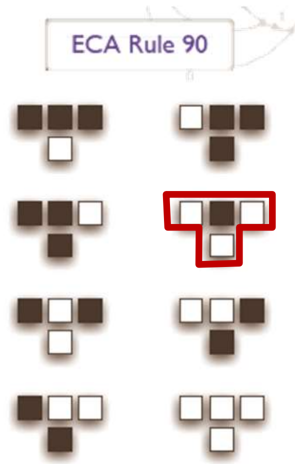

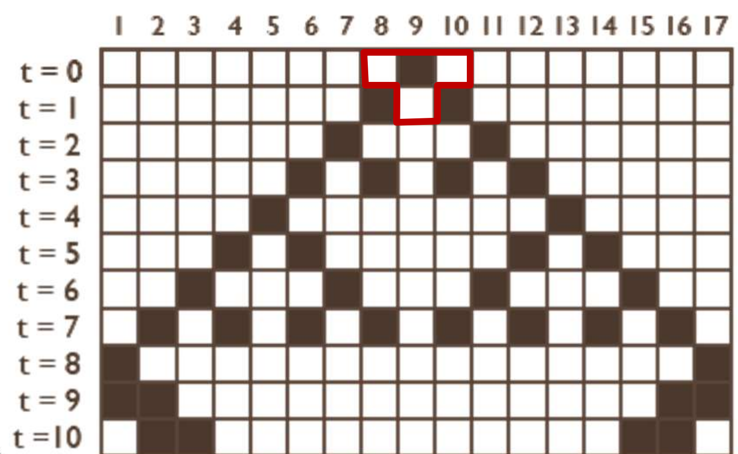

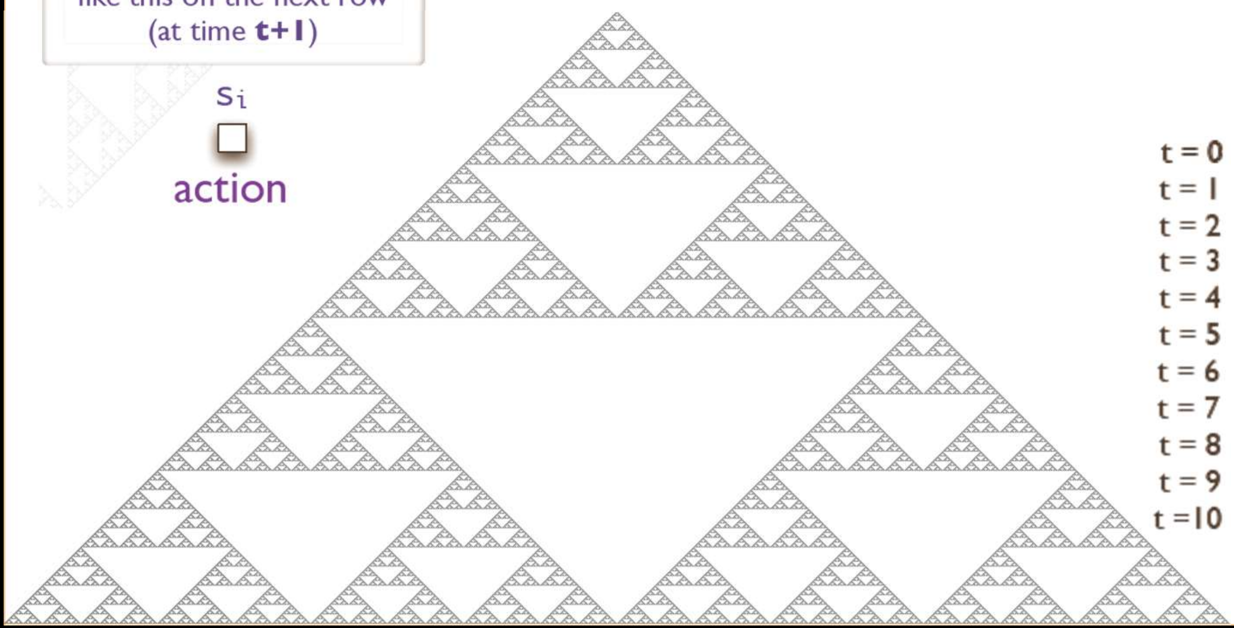

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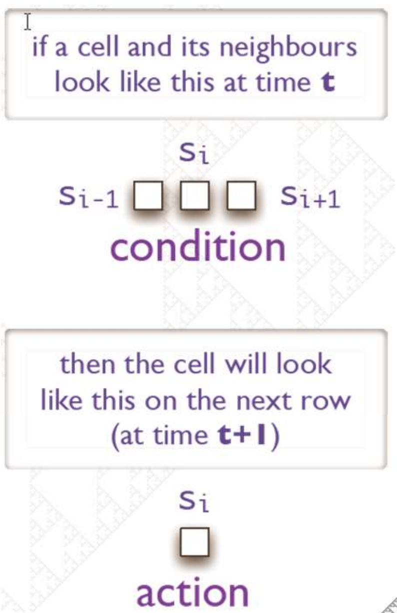

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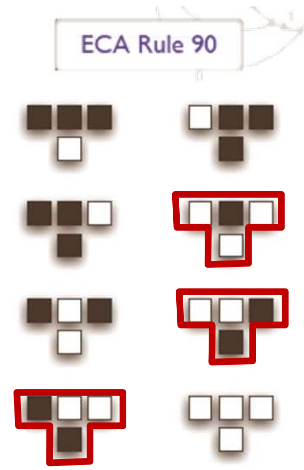

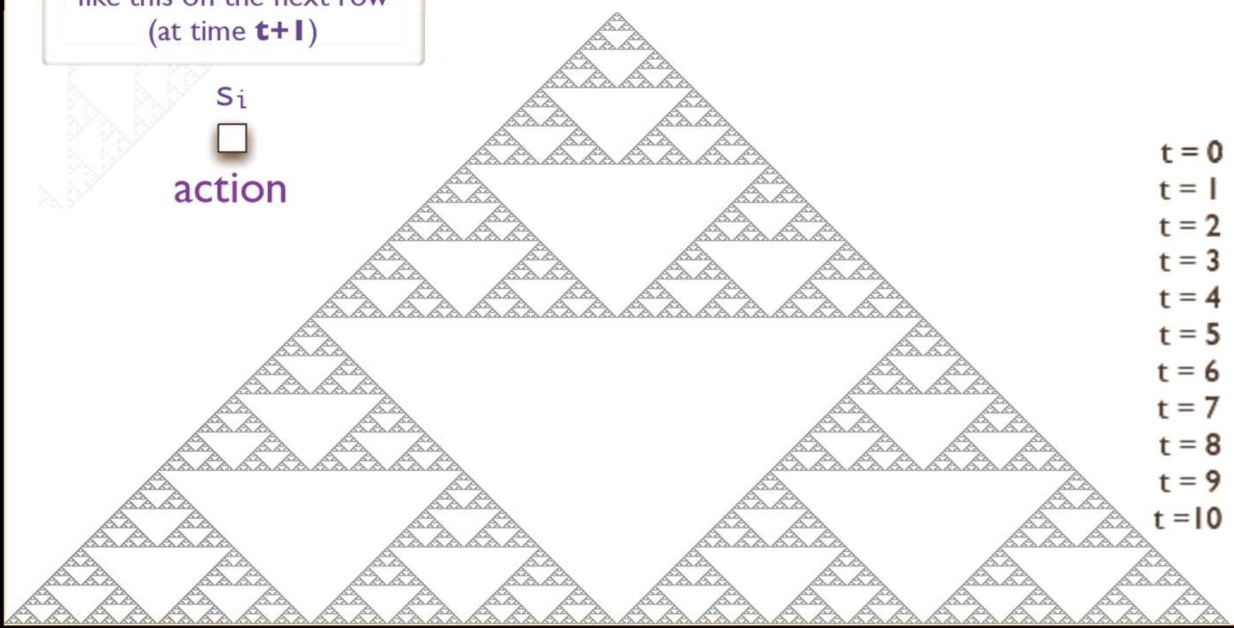

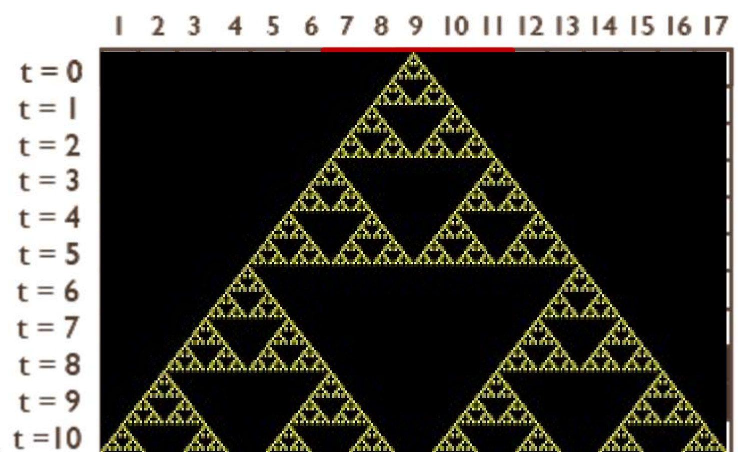

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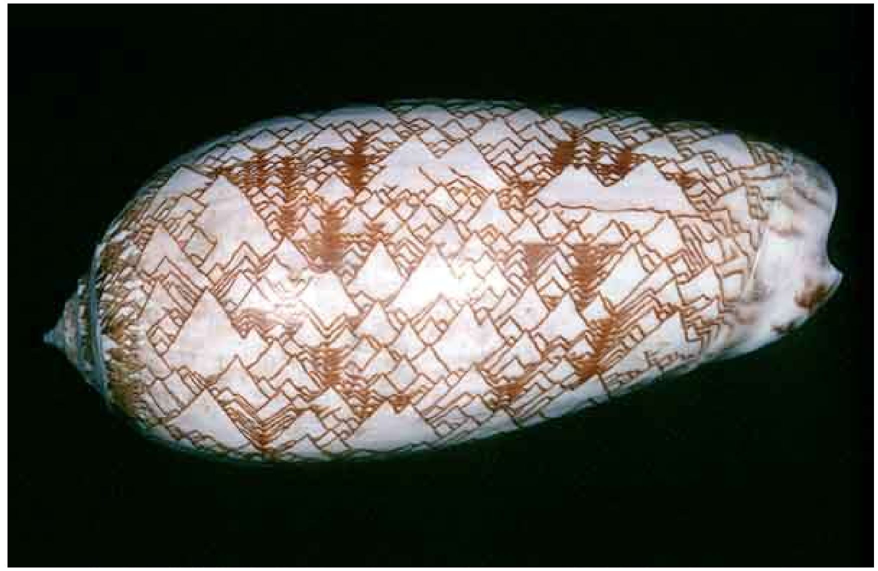

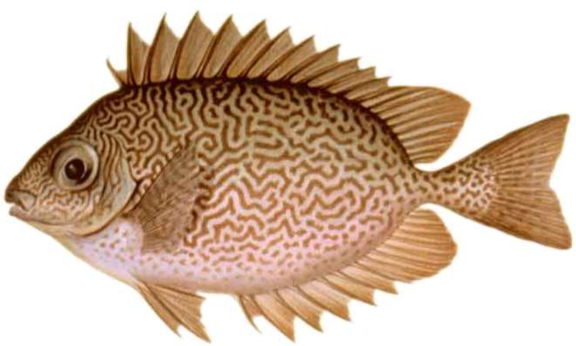

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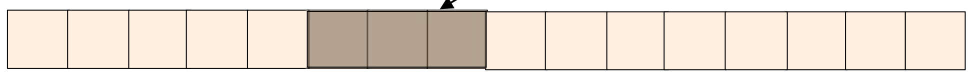
more formally

D-dimensional lattice *L* with a finite ***automaton*** in each lattice site (cell)

Neighborhood template *N*



- State-determined system
  - finite number of states Σ: K=| Σ|
    - E.g. Σ = {0,1}
  - finite input alphabet α
  - transition function Δ: α→Σ
    - uniquely ascribes state s in Σ to input patterns α

Example (ECA)

K=2, N=3,

$|\alpha|=2^3=8$

$D = 2^8=256$

$$\alpha \in \Sigma^N, |\alpha| = K^N$$

Number of possible neighborhood states

$$D = K^{K^N}$$

Number of possible transition functions

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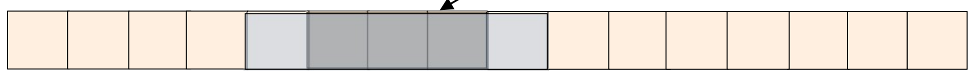

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$D = 2^8=256$

Example

K=8

N=5

|α|=37,768

$D \approx 10^{30,000}$

$$\alpha \in \Sigma^N, |\alpha| = K^N$$

Number of possible neighborhood states

$$D = K^{K^N}$$

Number of possible transition functions

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Finding the structure of all possible transition functions

- Statistical analysis
  - Identify classes of transition functions with similar behavior
    - Similar dynamics (statistically)
  - Via Higher level statistical observables
    - Like Kauffman
- The Lambda Parameter (similar to bias in BN)
  - Select a subset of D characterized by λ
    - Arbitrary ***quiescent state***: s_q
      - Usually 0
    - A particular function Δ has n transitions to this state and $(K^N\text{-}n)$ transitions to other states s of Σ
    - $(1\text{-}\lambda)$ is the probability of having a s_q *in every position of the rule table*

$$\lambda = \frac{K^N - n}{K^N}$$

λ = 0: all transitions lead to s_q ($n = K^N$)

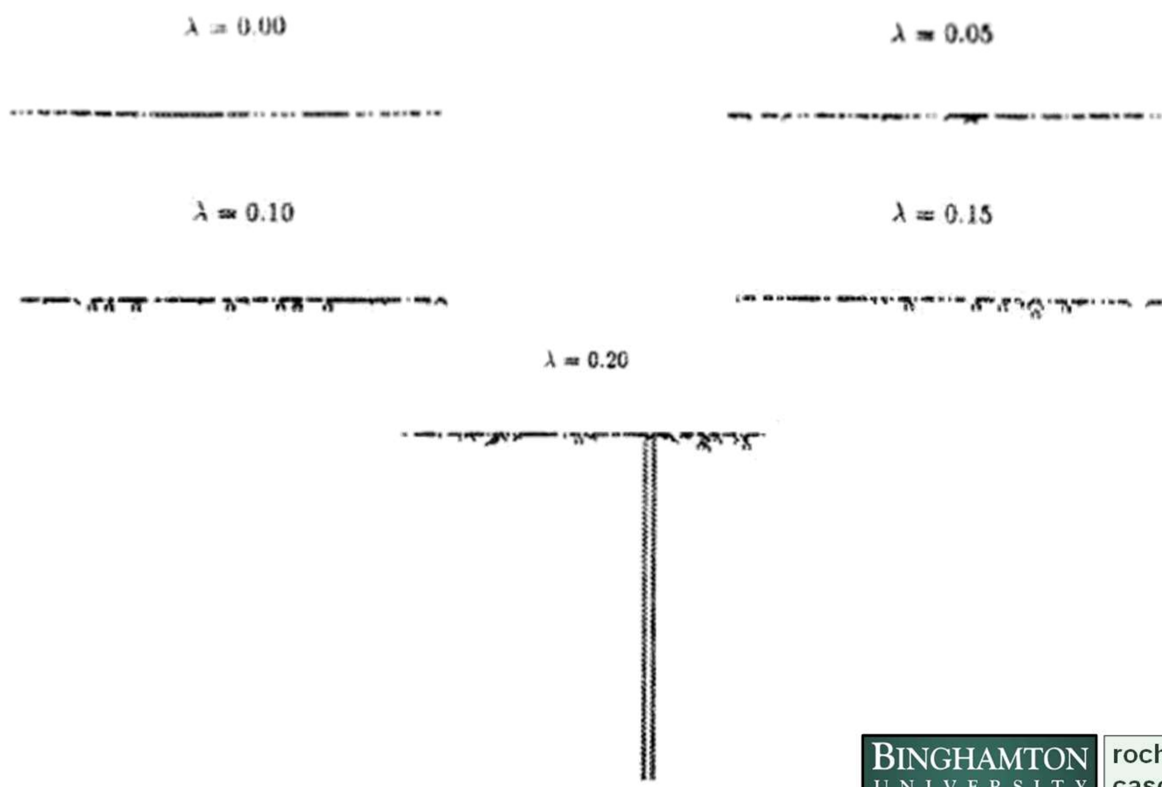
λ = 1: no transitions lead to s_q ($n = 0$)

λ = 1-1/K: equally probable states ($n = 1/K \cdot K^N$)

Range: from most homogeneous to most heterogeneous

Langton, C.G. [1990]. "Computation at the edge of chaos: phase transitions and emergent computation". *Artificial Life II*. Addison-Wesley.

- λ only correlates well with dynamic behavior for fairly large values of K and N
  - E.g. K≥4 and N≥5
- Experiments
  - K=4, N=5



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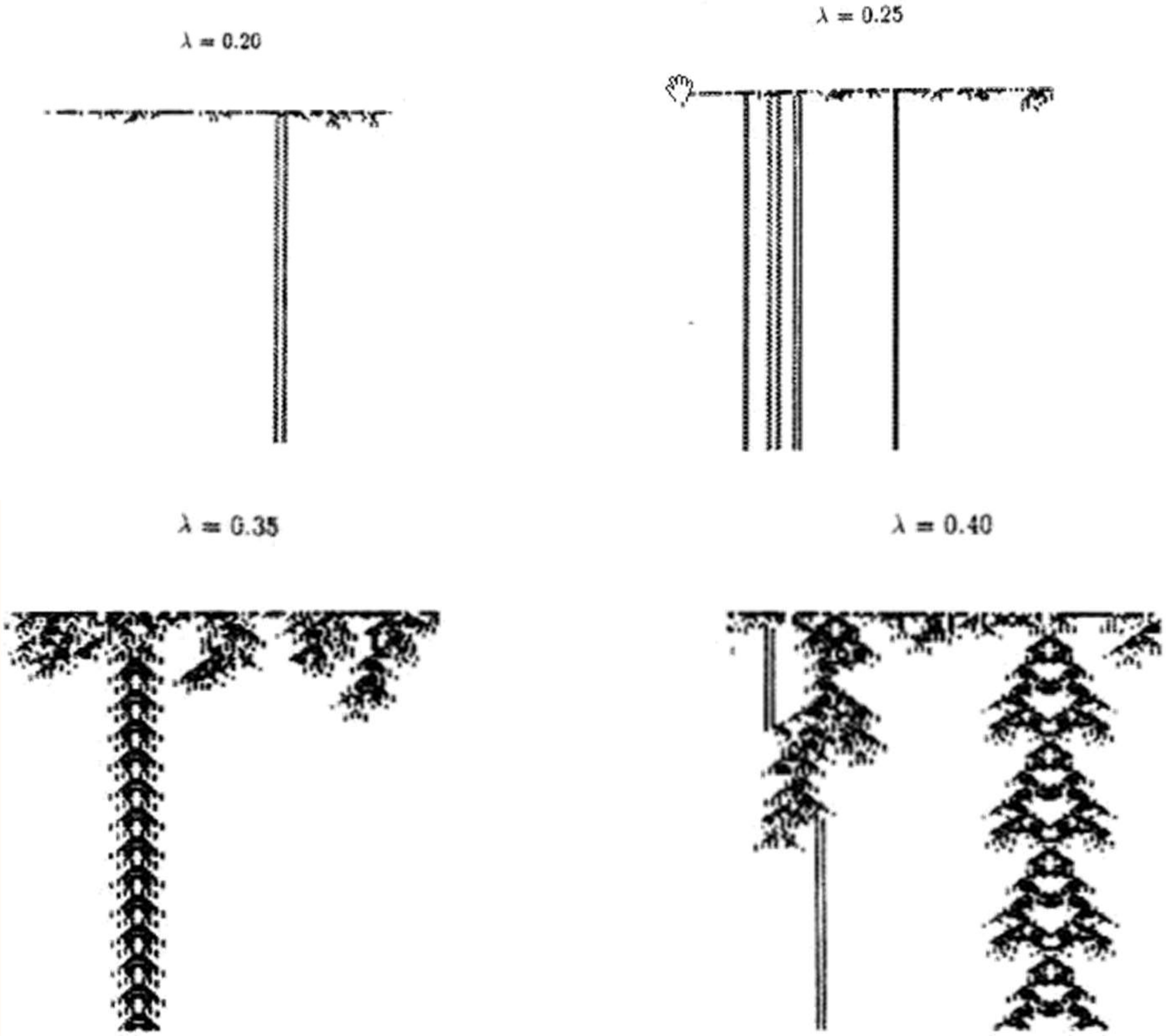
Langton's results



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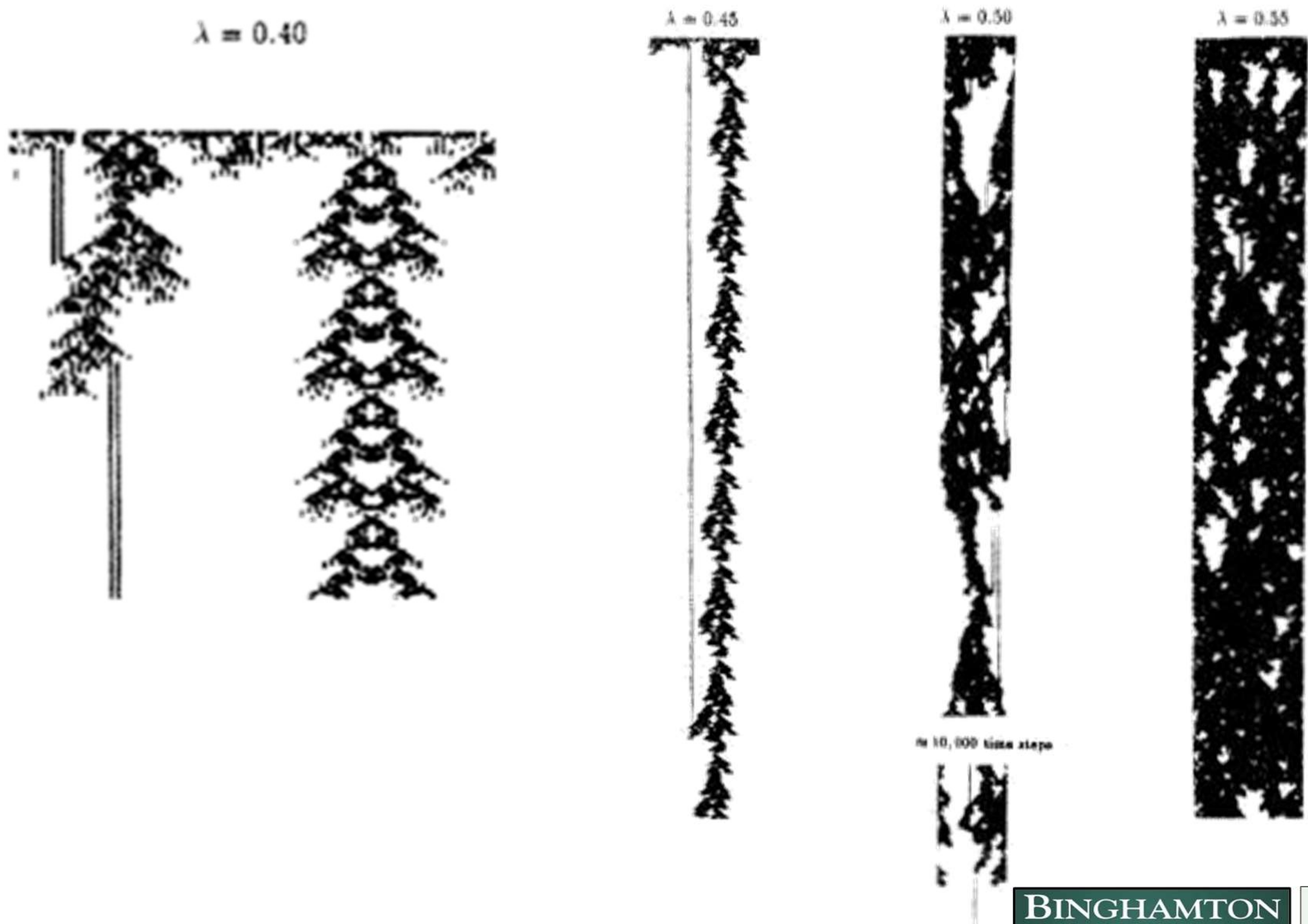

← Approximate time when density is within 1% of long-term behavior

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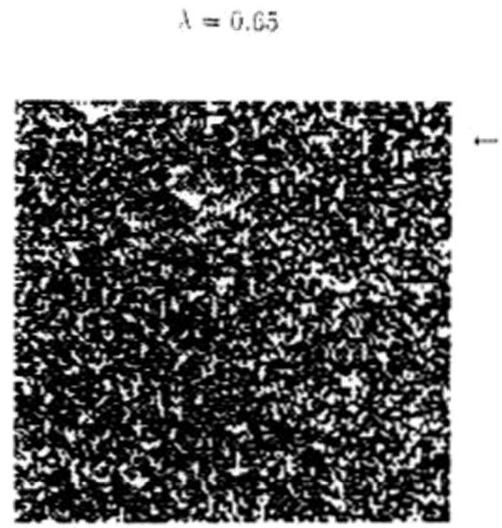

Approximate time when density is within 1% of long-term behavior

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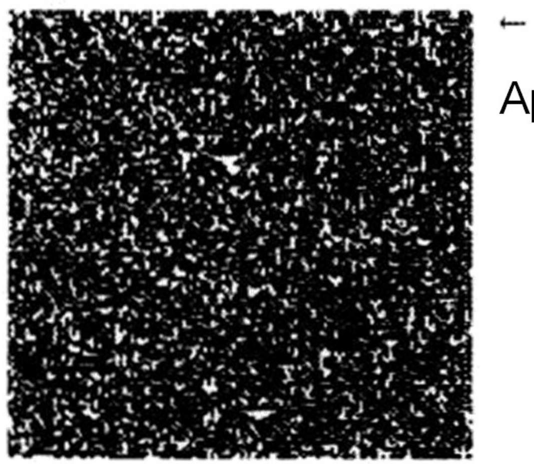
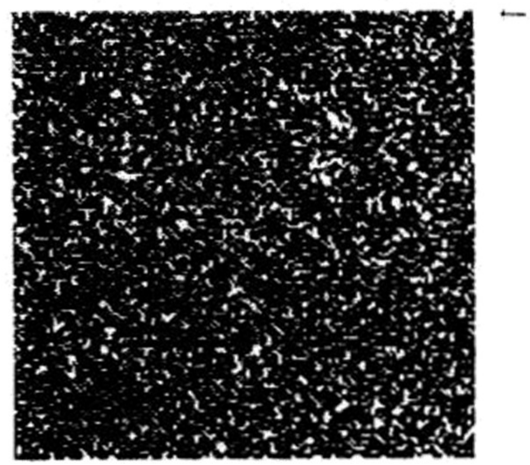
$\lambda = 0.70$



$\lambda = 0.75$



Approximate time when density is within 1% of long-term behavior

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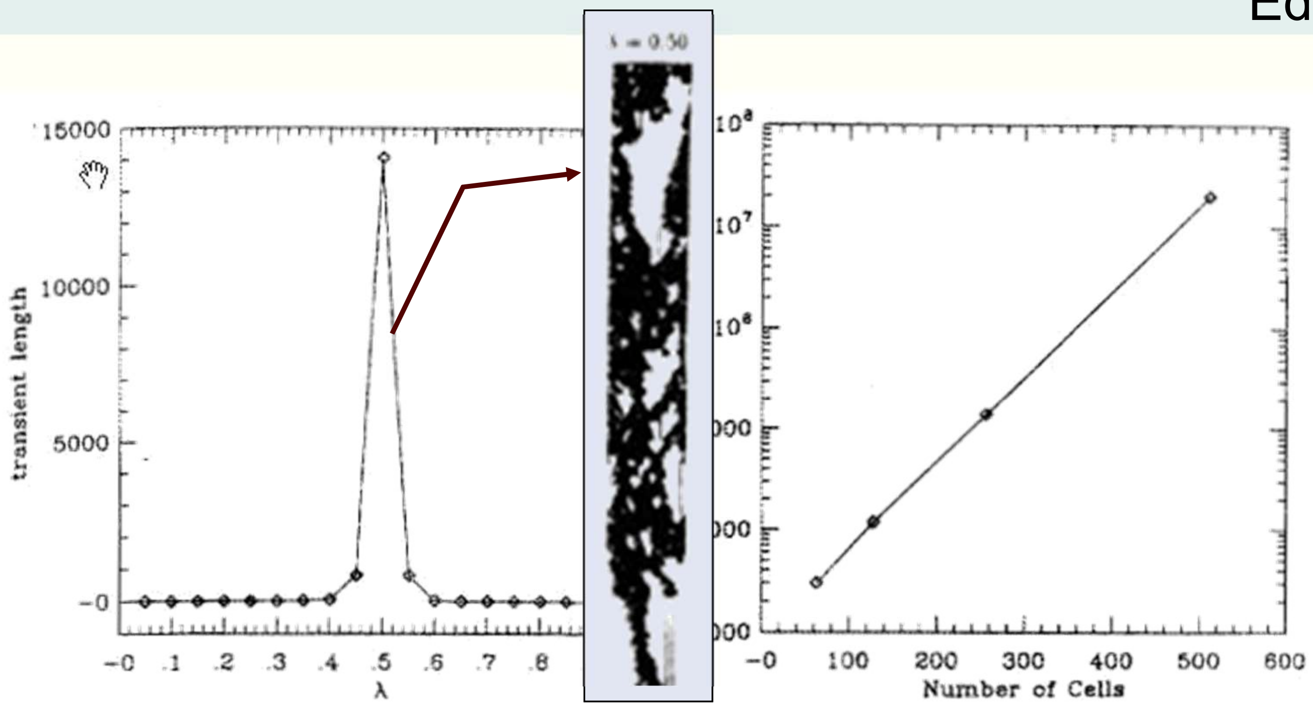
A phase transition?



- Transient growth in the vicinity of phase transitions
  - Length of CA lattice only relevant around phase transition (λ=0.5)
- Conclusion: more complicated behavior found in the phase transition between order and chaos
  - Patterns that move across the lattice

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- Transition region
  - Supports both static and propagating structures
    - λ =0.4+
  - Propagating waves (“signals”?) across the CA lattice
    - Necessary for computation?
    - Signals and storage?
- Computation
  - Requires storage and transmission of information
  - Any dynamical system supporting computation must exhibit long-range signals in space and time
- Wolfram’s CA classes
  - I: homogeneous state
    - Steady-state
  - II: periodic state
    - Limit cycles
  - III: chaotic
  - IV: complex patterns of localized structures
    - Long transients
    - Capable of universal computation

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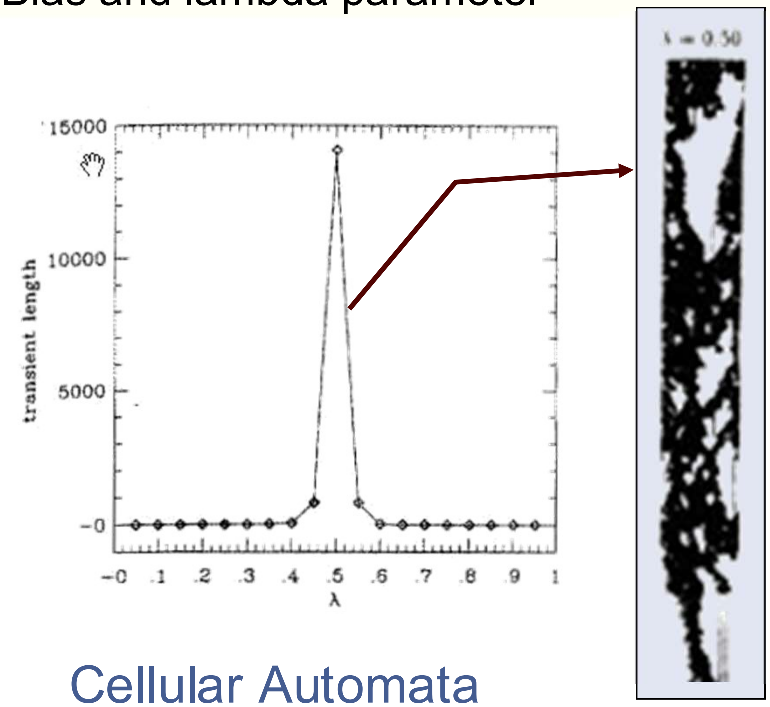
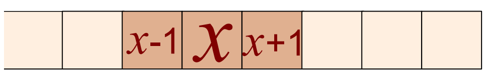
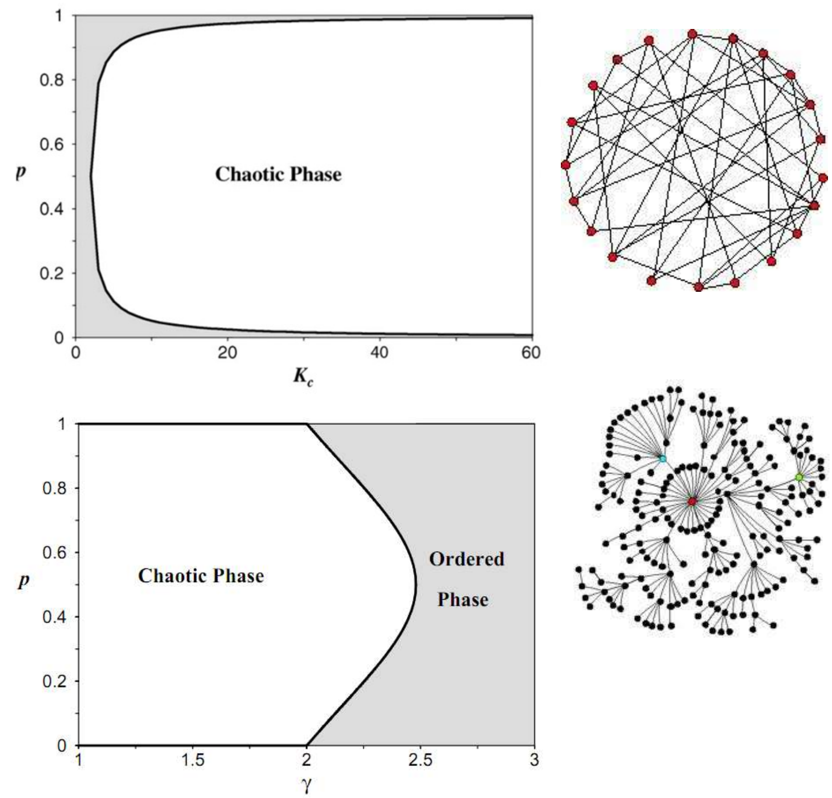
Bias and lambda parameter



Cellular Automata





Boolean Networks

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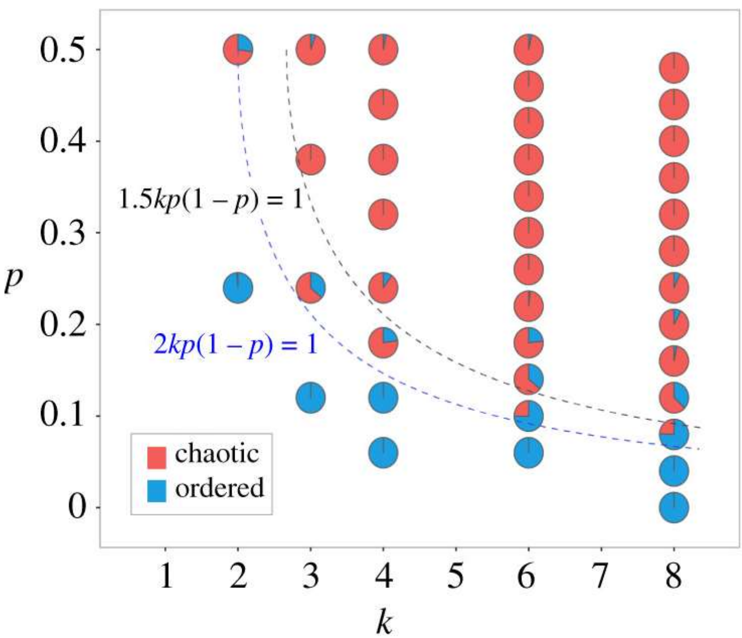
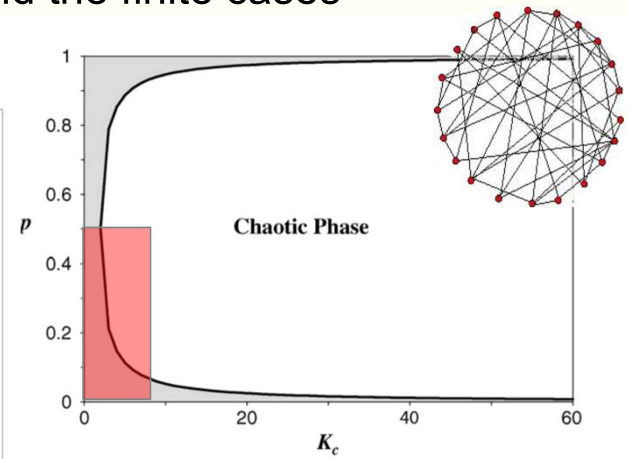
current theory for random networks and the finite cases

homogeneous networks

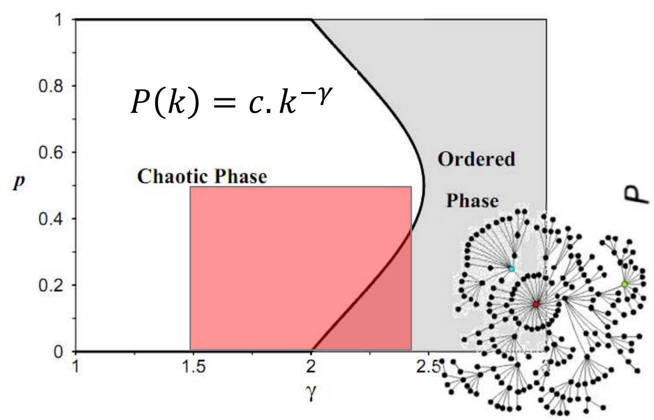


$$2.k.p(1-p)=1$$

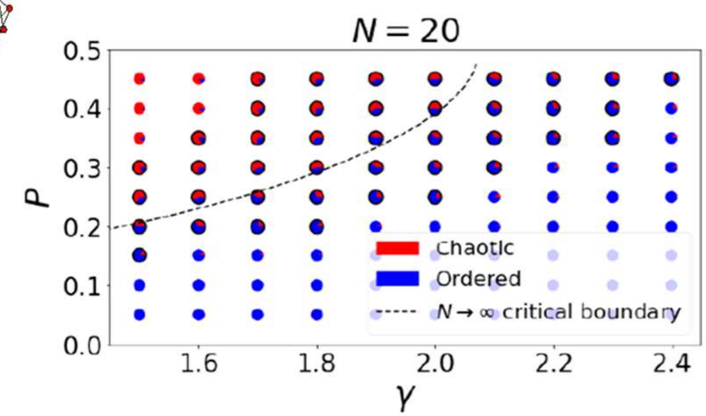
Derrida & Pomeau. [1986] *EPL* . **1.2**: 45.

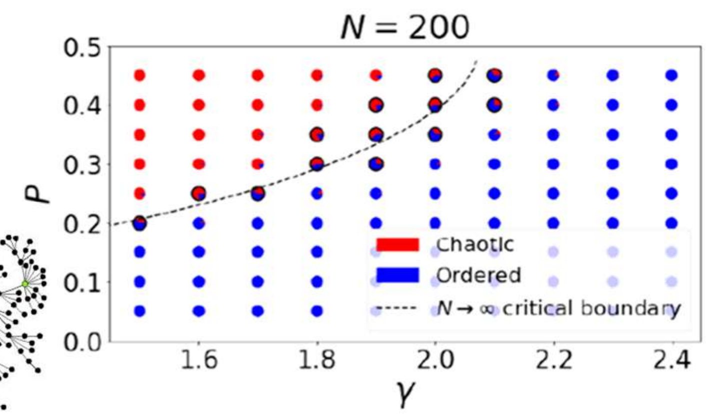


Aldana, M. [2003]. *Physica D*. **185**: 45–66



heterogenous networks





Manicka, Marques-Pita, & Rocha, [2022]. *J. Royal Society Interface*. **19**(186):20210659.
Costa, Rozum, Marcus, & Rocha[2023]. *Entropy*. **25**(2):374.

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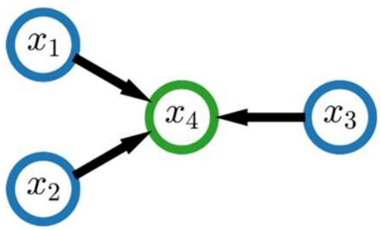
effective graph: nonlinear measure of effective connectivity



look-up-table (LUT)

$F(x_4)$

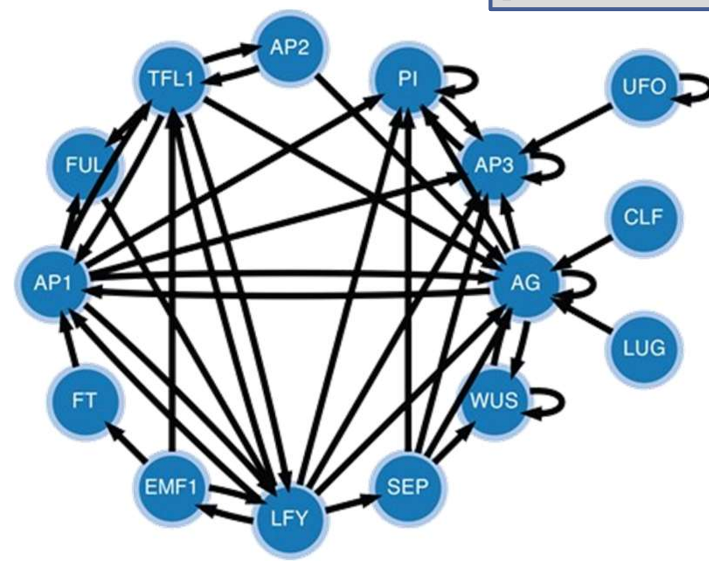
	x_1	x_2	x_3		x_4
f_1	0	0	0	:	0
f_2	0	0	1	:	0
f_3	0	1	0	:	0
f_4	0	1	1	:	0
f_5	1	0	0	:	0
f_6	1	0	1	:	0
LUT entry/input condition → f_7	1	1	0	:	1
f_8	1	1	1	:	1

↖ on/off state

Measuring dynamical ***redundancy*** and its dual ***effectiveness***

$p(x) = 2/8 = 0.25$

p: bias, ratio of “1’s” in output



Correia, Gates, Wang & Rocha [2018]. *Frontiers in Physyology* **9:** 1046.
Gates, Correia, Wang & Rocha [2021]. *PNAS*. **118** (12): e2022598118.
Marques-Pita & Rocha, [2013]. *PLoS ONE*, **8**(3): e55946.
Chaos et al [2006]. *J. of Plant Growth Regulation*. **25**(4): 278-289.

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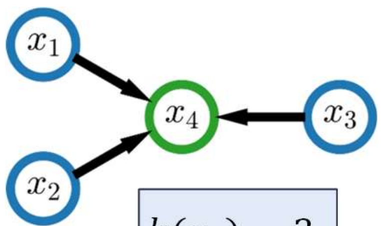
redundancy in causal logic of automata (canalization)

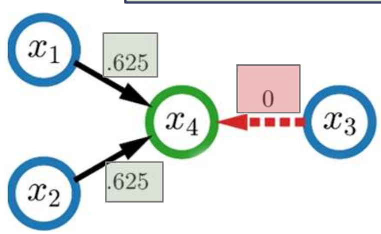
effective graph: nonlinear measure of effective connectivity

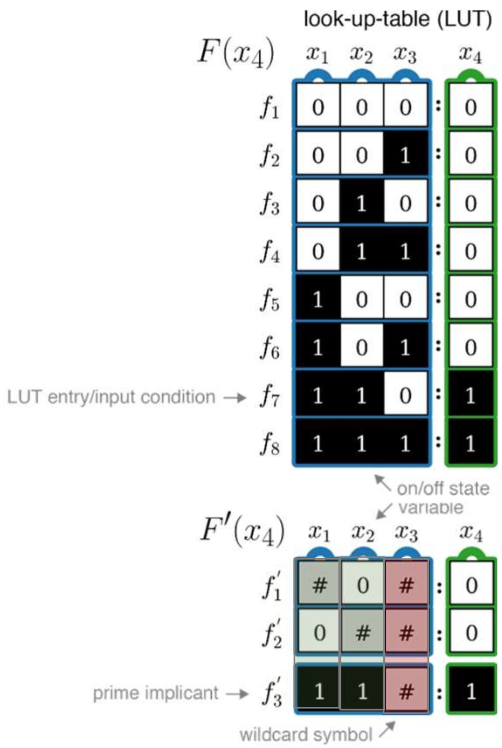


$k(x_4) = 3$

$x_4 = x_1 \wedge x_2$

$k_e(x_4) = 1.25$





Prime Implicants (Quine-McCluskey)

github.com/CASCI-lab/CANA

Measuring dynamical ***redundancy*** and its dual ***effectiveness***

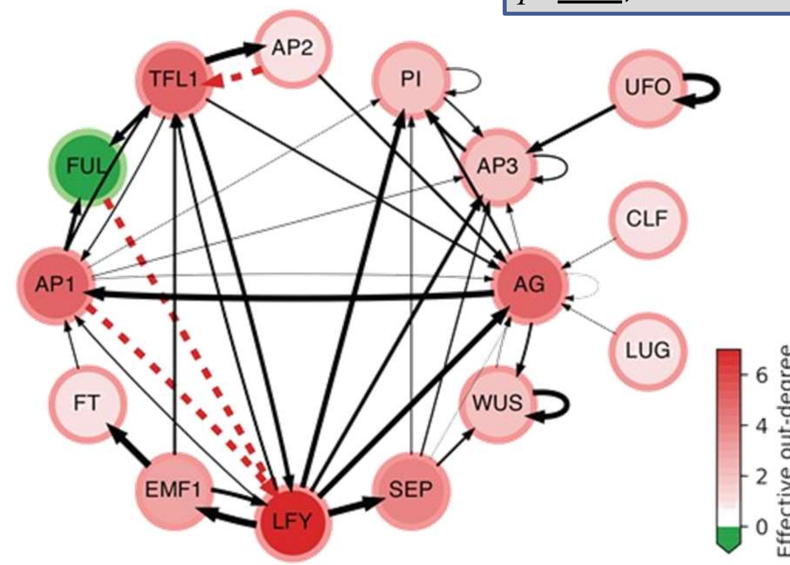
input redundancy:
$k_r(x)$ = mean number of "#" in LUT

$k_r(x_4) = 1.75$

effective connectivity:
$k_e(x) = k(x) - k_r(x)$

$p(x) = 2/8 = 0.25$

p: bias, ratio of "1's" in output



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arabidopsis thaliana network

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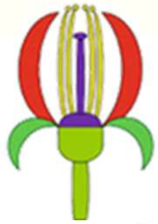
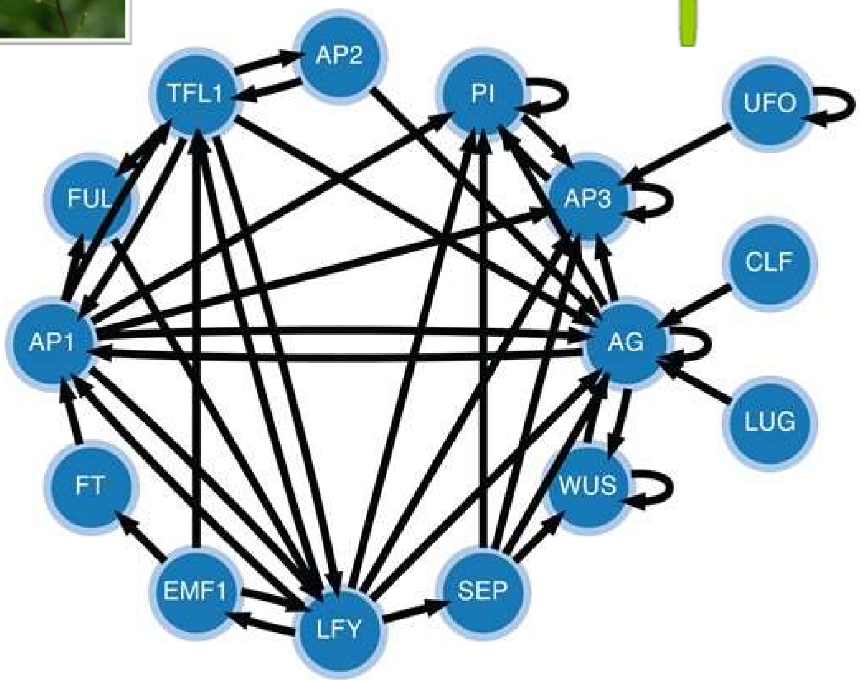
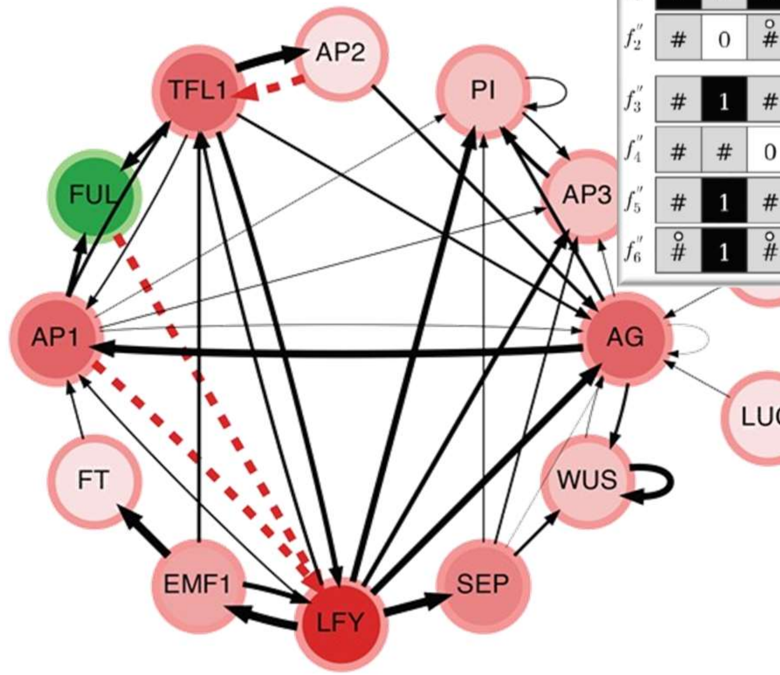


redundant variables and more effective control pathways revealed

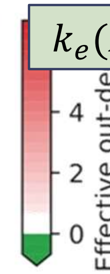




	AP1	LFY	AP2	WUS	AG	LUG	CLF	TFL1	SEP	:	AG
f''_1	1	#	1	0	$\mathring{0}$	1	1	#	$\mathring{\#}$	:	0
f''_2	#	0	$\mathring{\#}$	#	#	#	#	$\dot{1}$	#	:	0
f''_3	#	1	#	1	#	#	#	#	#	:	1
f''_4	#	#	0	#	#	#	#	0	#	:	1
f''_5	#	1	#	#	1	#	#	#	1	:	1
f''_6	$\mathring{\#}$	1	$\mathring{\#}$	#	#	$\mathring{\#}$	$\mathring{0}$	#	#	:	1

$k(AG) = 9$

$k_e(AG) = 2.1$



Gates, Correia, Wang & Rocha [2021]. *PNAS*. **118** (12): e2022598118.
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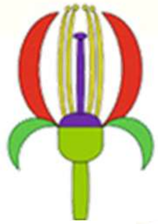

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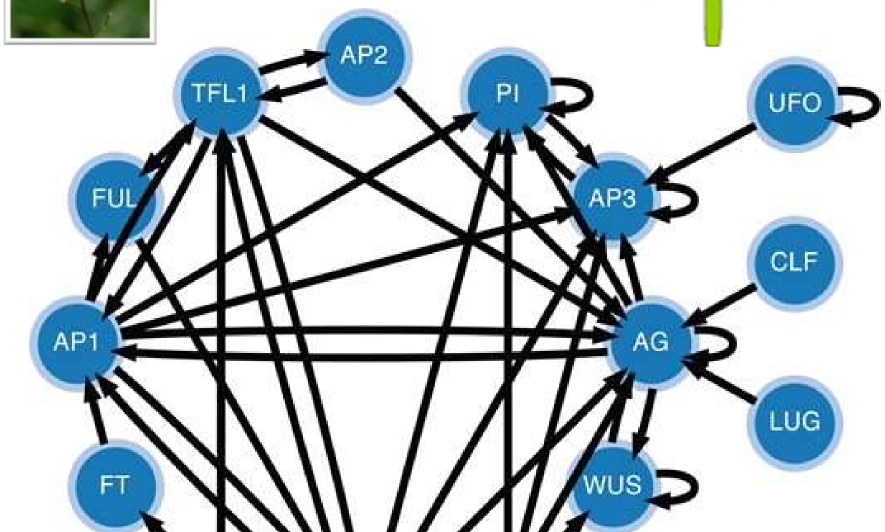

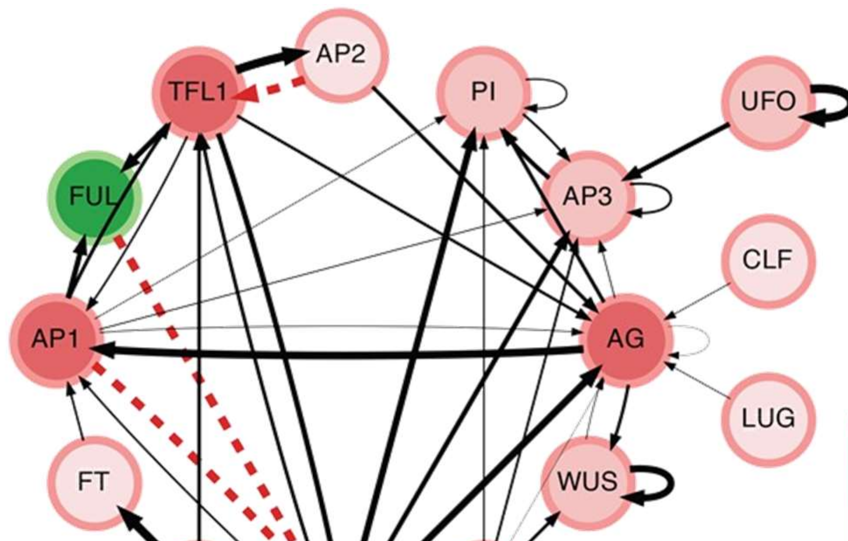

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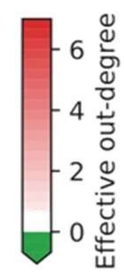

Interaction graph obtained from pairwise estimation of interaction. No dynamics represented in graph; many dynamics fit same structure.

Effective graph redundancy in (nonlinear) dynamics is integrated probabilistically (not estimated). Provides **causal explanation** of how **likely** dynamical perturbation and control signals propagate in biochemical pathways.

Gates, Correia, Wang & Rocha [2021]. *PNAS*. **118** (12): e2022598118.
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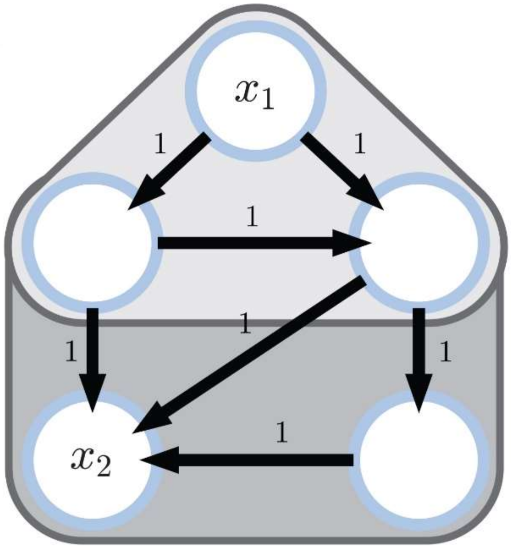
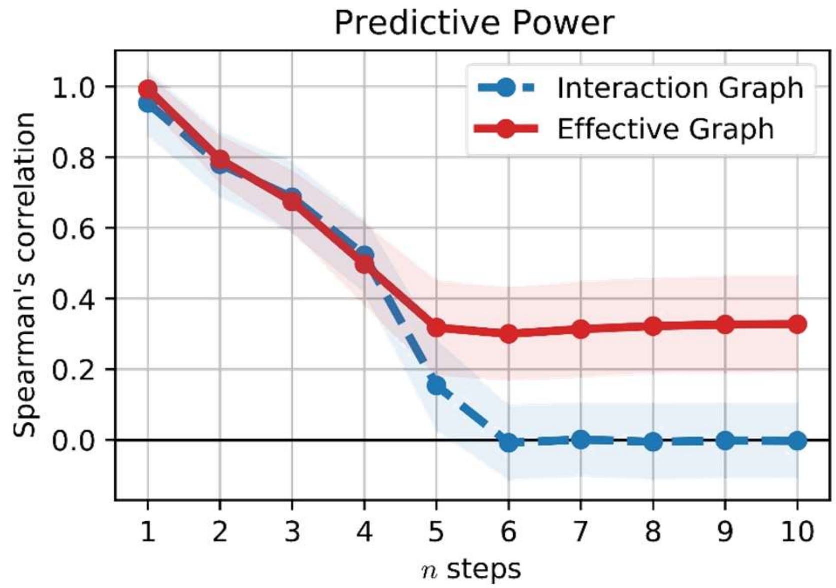
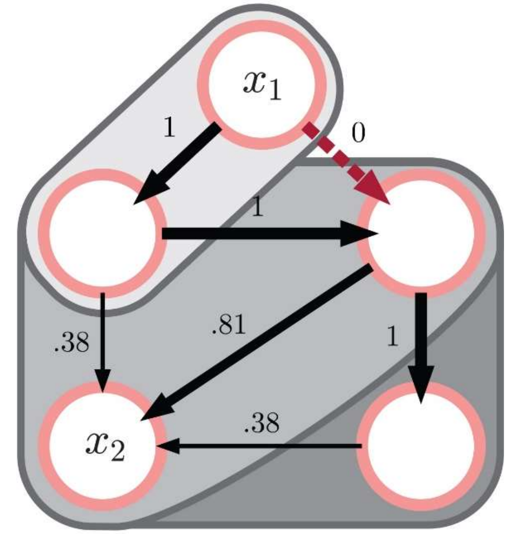
probabilistic and precise characterization of causal (nonlinear) dynamics



$p_3(x_1, x_2) = 1 \times 1 = 1$





$p_3(x_1, x_2) = 1 \times 1 \times 0.81 = 0.81$

Interaction graph typically obtained from (qualitative) pairwise estimation of interaction. No dynamics represented in graph; many dynamics fit same structure.

Effective graph redundancy in dynamics is integrated probabilistically (not estimated). Reveals network of nonlinear interactions that escapes pairwise estimation. Provides **causal explanation** of how dynamical perturbation and control signals propagate in biochemical pathways.

Gates, Correia, Wang & Rocha [2021]. *PNAS*. **118** (12): e2022598118.

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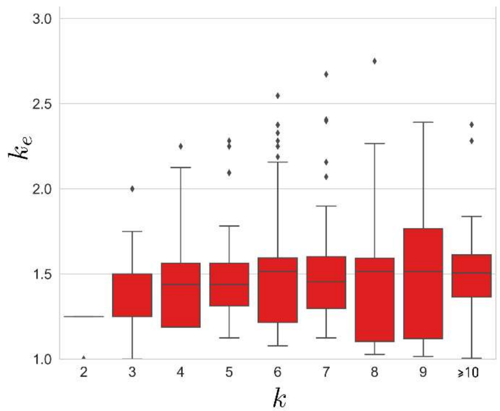
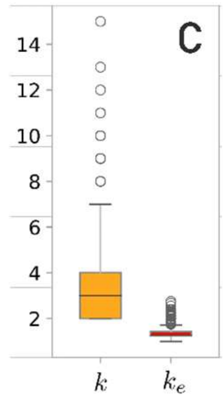
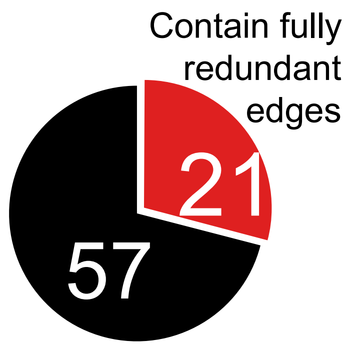
redundant pathways are ubiquitous in biochemical regulation

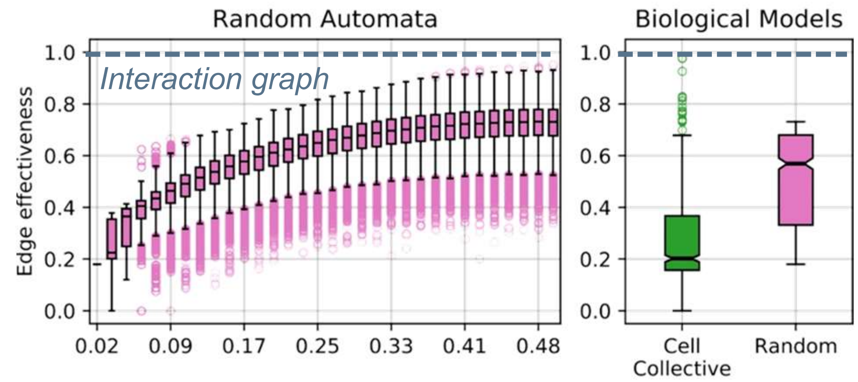
node-level





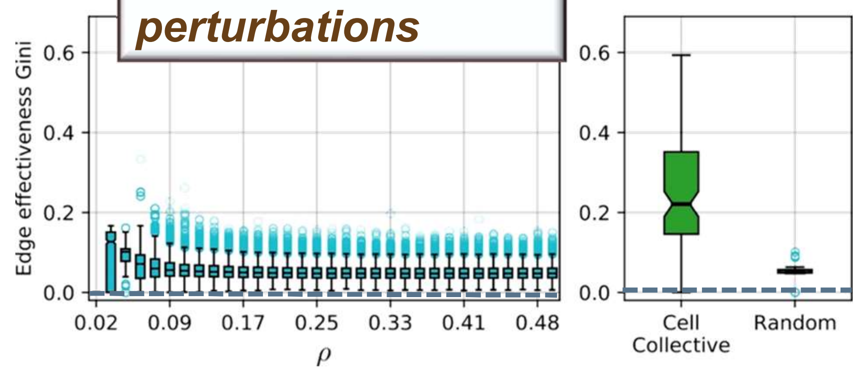


edge-level



dynamical redundancy is pervasive in systems biology models of regulation and signaling: biochemical variables are controlled by substantially fewer inputs than interaction graph suggests.

robustness to most perturbations



effectiveness is heterogenous: only few inputs are very effective, most are ineffective or redundant.

Cell Collective

8,220 interactions (of over 3K automata) in 78 models

Gates & Rocha [2016]. *Scientific Reports* **6**, 24456.
Manicka, Marques-Pita, & Rocha, [2021]. *J. Royal Society Interface*. **19**(186):20210659.
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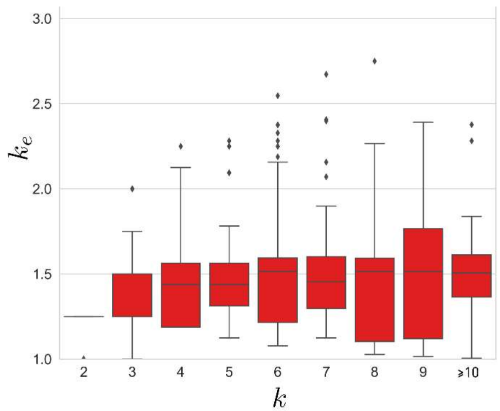
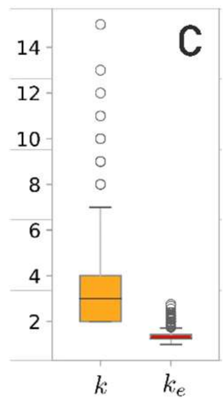
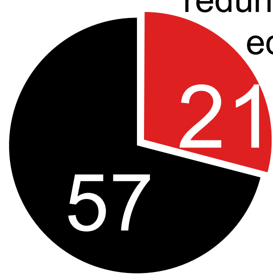
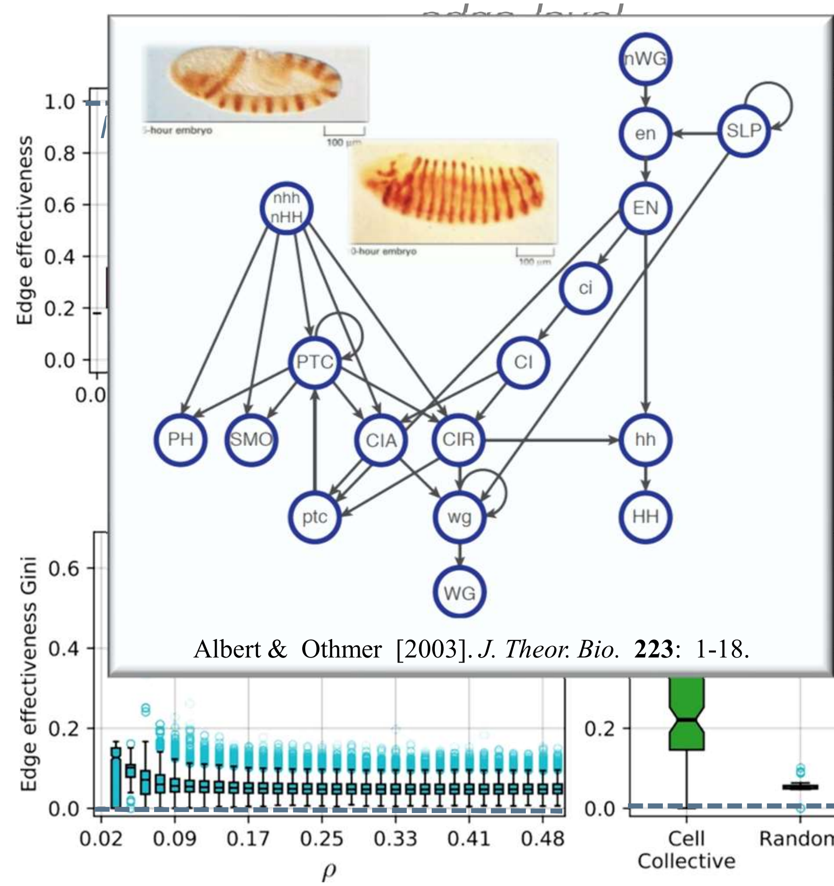
node-level





Contain fully redundant edges





Albert & Othmer [2003]. *J. Theor. Bio.* **223**: 1-18.

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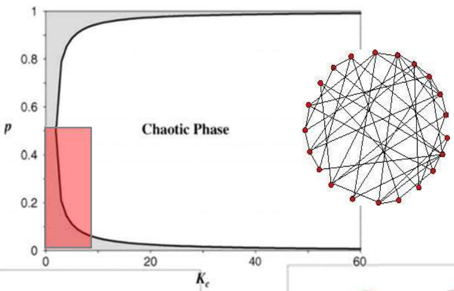
effective connectivity enables greater robustness (random ensembles)

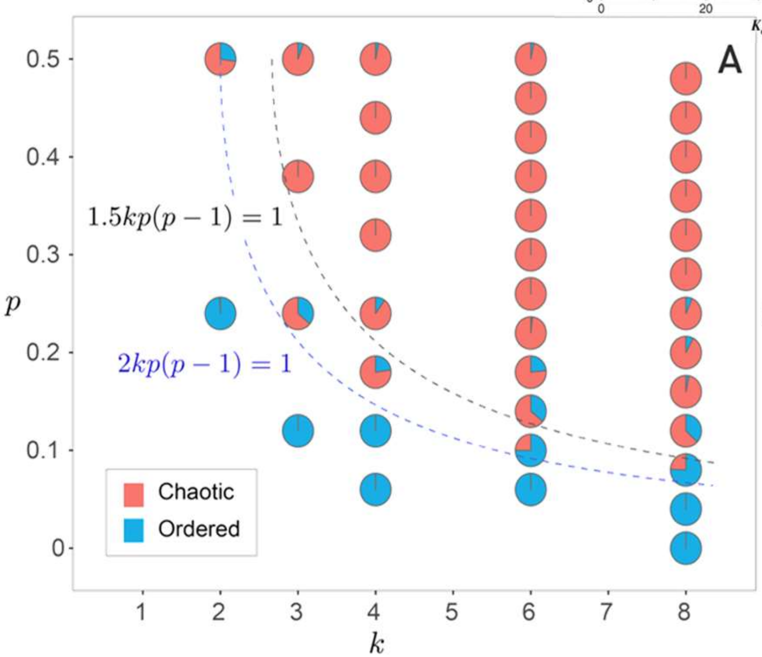
Derrida & Pomeau. [1986] *EPL* . **1.2**: 45.
Aldana, M. [2003]. *Physica D.* **185**: 45–66

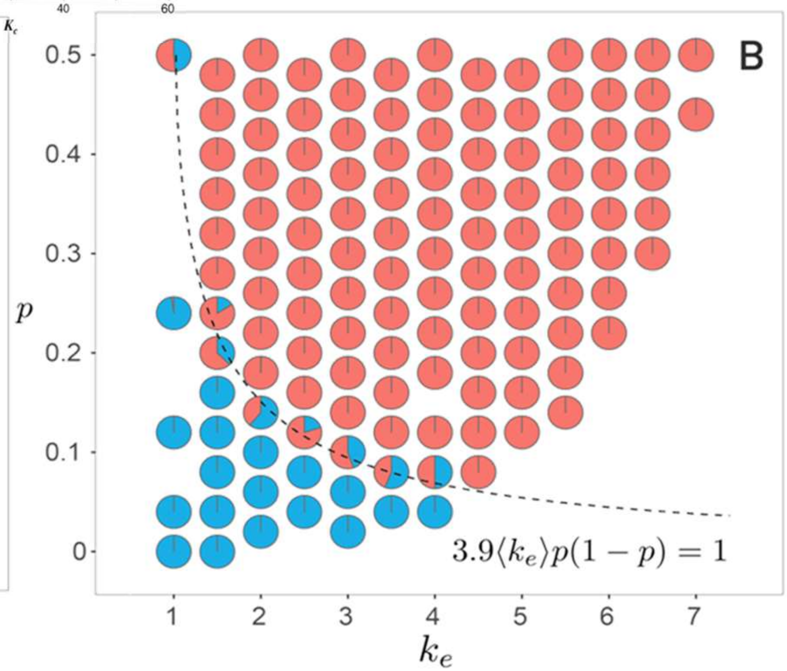
$$c.\,k.\,p(1-p) = 1$$



$$k_e(x) = k(x) - k_r(x)$$

$$c.\,k_e.\,p(1-p) = 1$$





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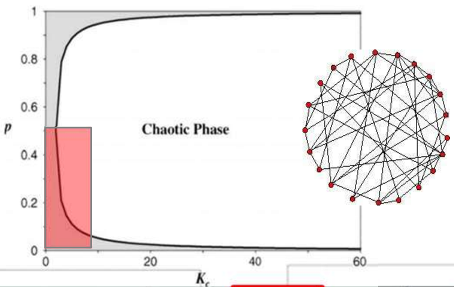
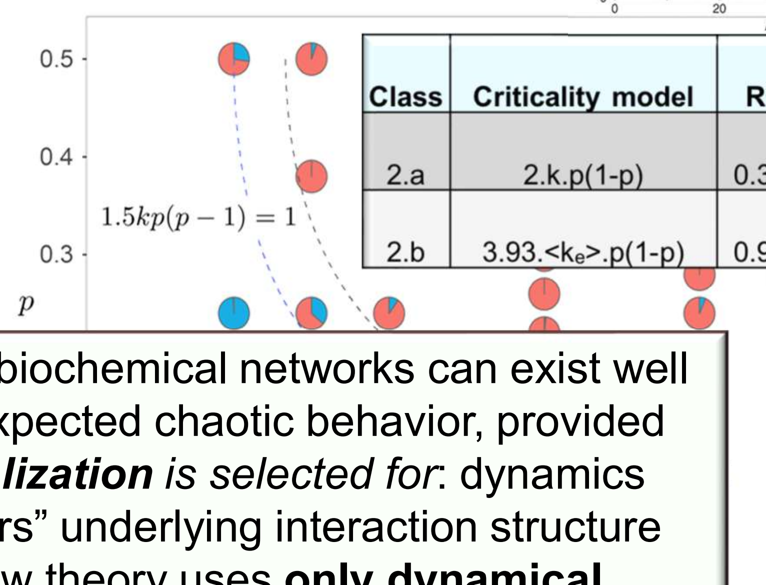
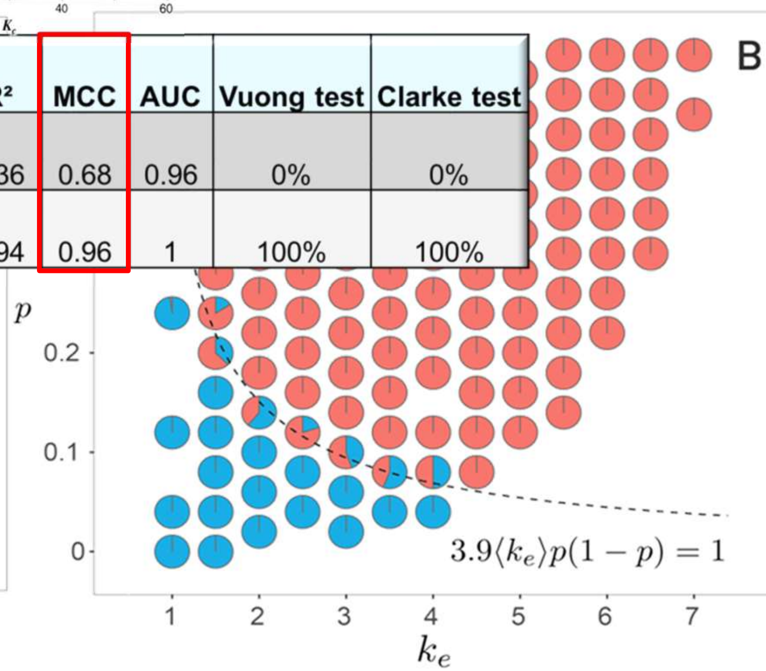


$$k_e(x) = k(x) - k_r(x)$$

$$c.\,k_e.\,p(1-p) = 1$$



Class	Criticality model	R^2	MCC	AUC	Vuong test	Clarke test
2.a	2.k.p(1-p)	0.36	0.68	0.96	0%	0%
2.b	3.93.<k$_e$>.p(1-p)	0.94	0.96	1	100%	100%



Stable biochemical networks can exist well into expected chaotic behavior, provided ***canalization*** *is selected for*: dynamics "buffers" underlying interaction structure
New theory uses **only dynamical redundancy properties**

Manicka, Marques-Pita, & Rocha, [2021]. *J. Royal Society Interface*. **19**(186):20210659.

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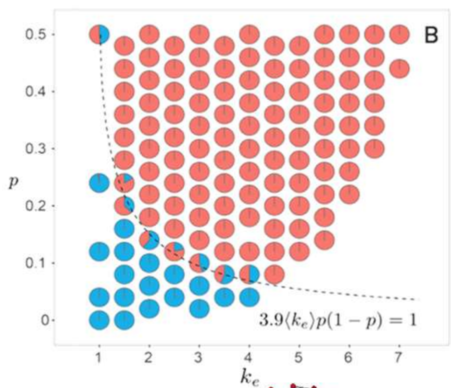
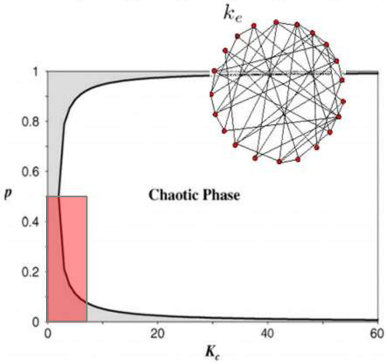
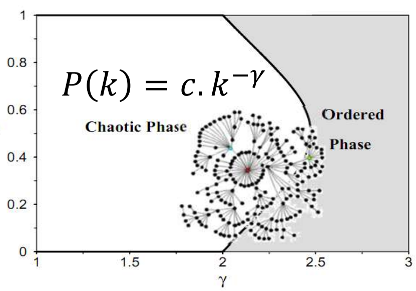
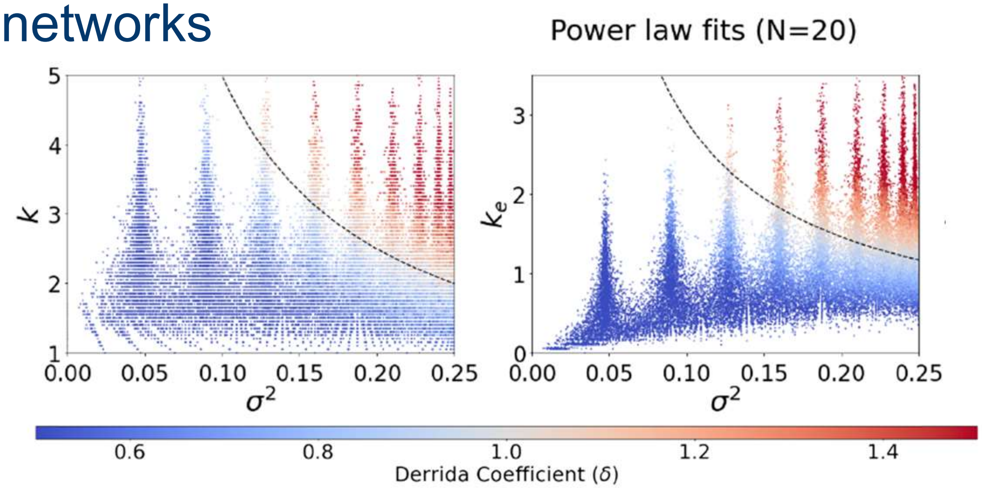




$c.\,k_e.\,p(1-p) = 1$

heterogenous networks





Stable biochemical networks can exist well into expected chaotic behavior, provided ***canalization** is selected for*: dynamics "buffers" underlying interaction structure

$\sigma^2 = p(1-p)$

N	20	50	100	200
$\sigma^2 k$	93.83	95.04	95.88	96.71
$\sigma^2 k_e$	96.09	96.35	96.53	96.8

Costa, Rozum, Marcus, & Rocha[2023]. *Entropy*. **25**(2):374.
Manicka, Marques-Pita, & Rocha, [2021]. *J. Royal Society Interface*. **19**(186):20210659.

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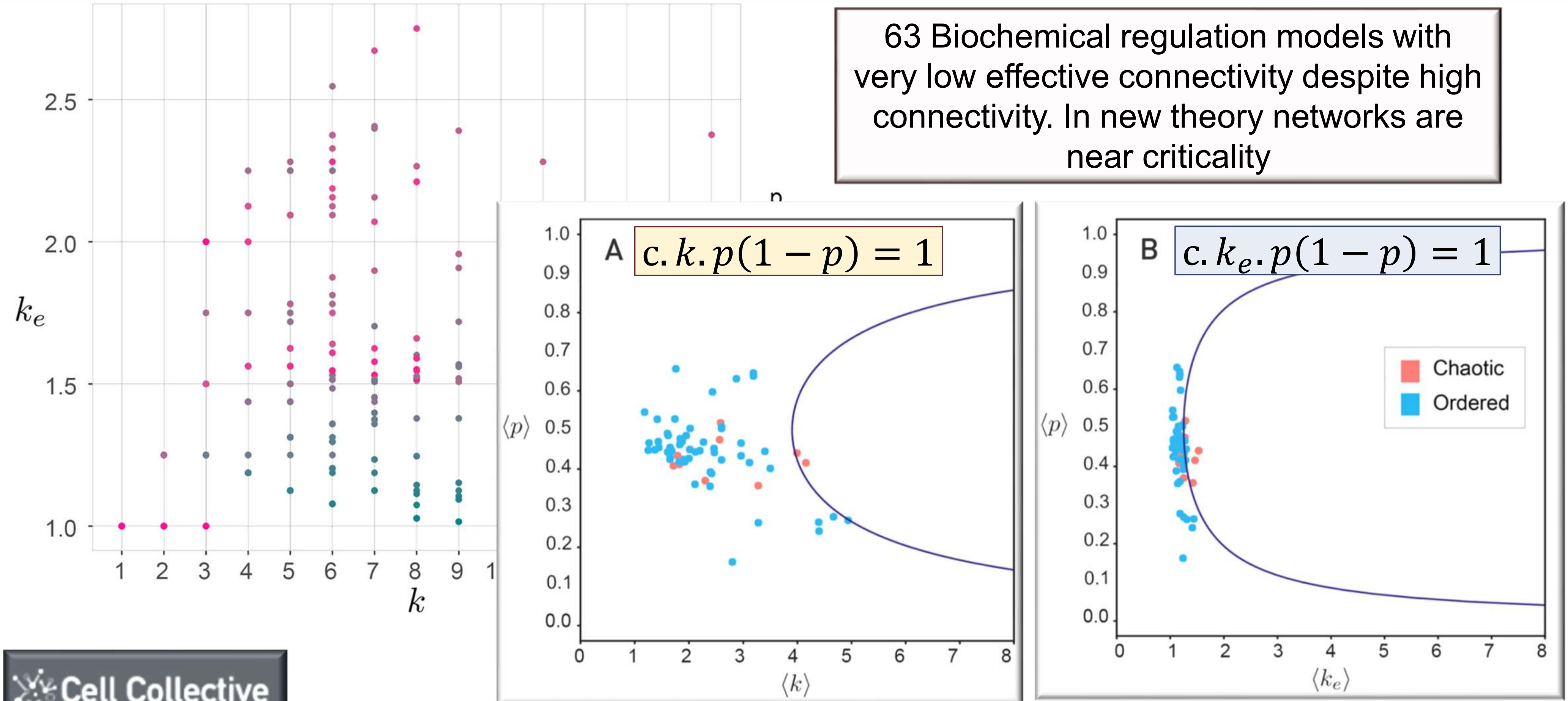
low effective connectivity leads networks closer to "edge of chaos"

63 Biochemical regulation models with very low effective connectivity despite high connectivity. In new theory networks are near criticality



Cell Collective

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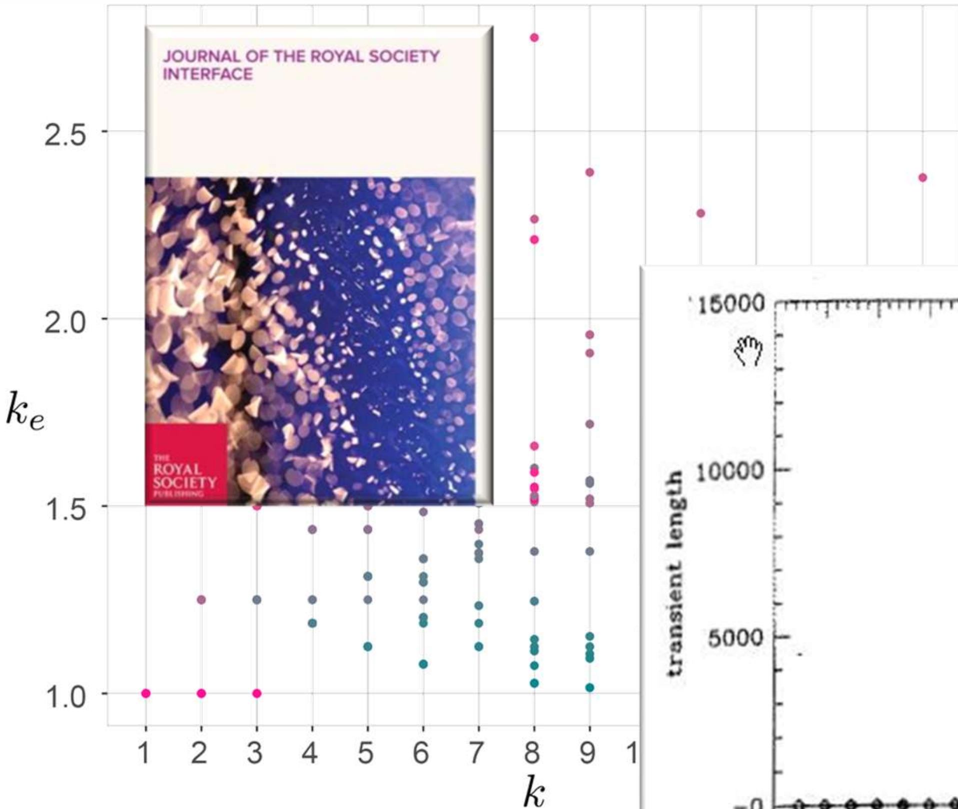
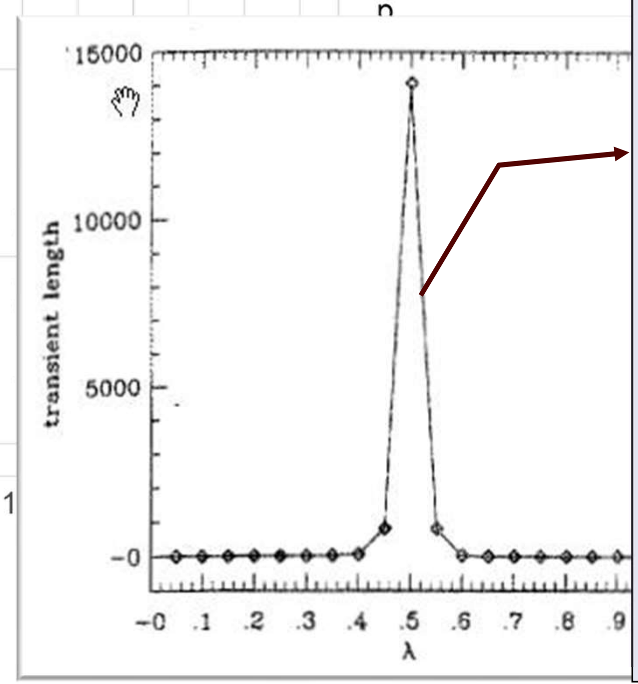
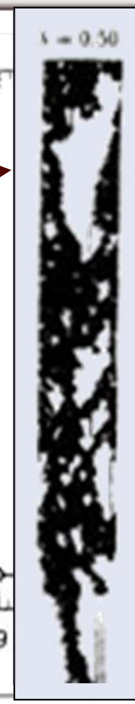
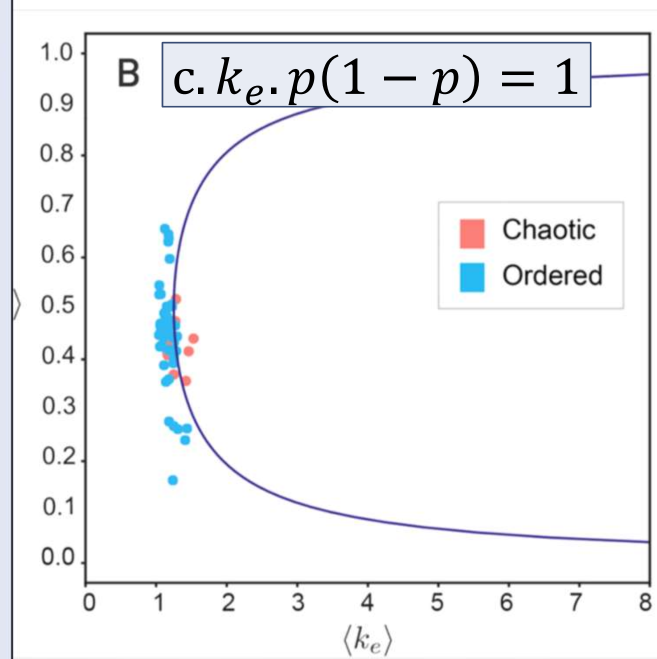


63 Biochemical regulation models with very low effective connectivity despite high connectivity. In new theory networks are near criticality







Cell Collective

Manicka, Marques-Pita, & Rocha, [2022]. *J. Royal Society Interface*. **19**(186):20210659.

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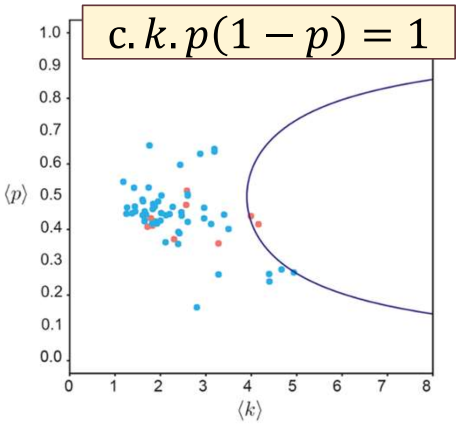
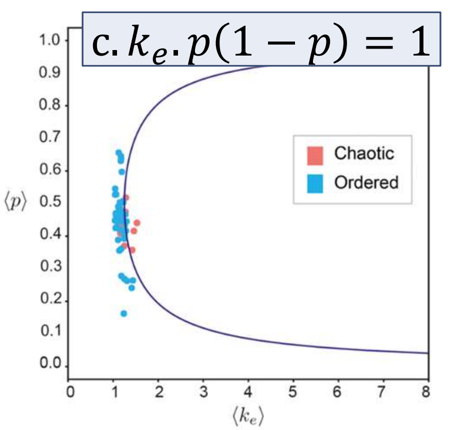
ubiquitous canalization in (experimentally-validated) systems biology models

effective connectivity better predicts critical transition

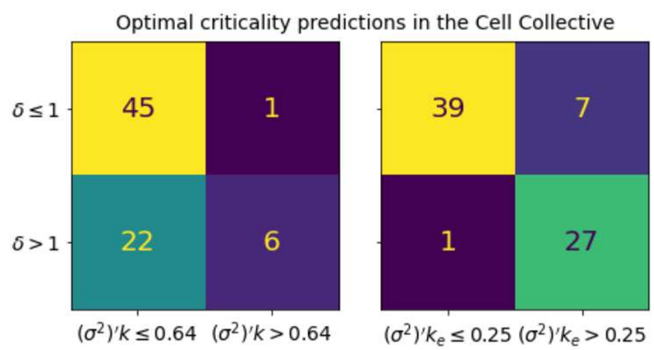
homogeneous networks



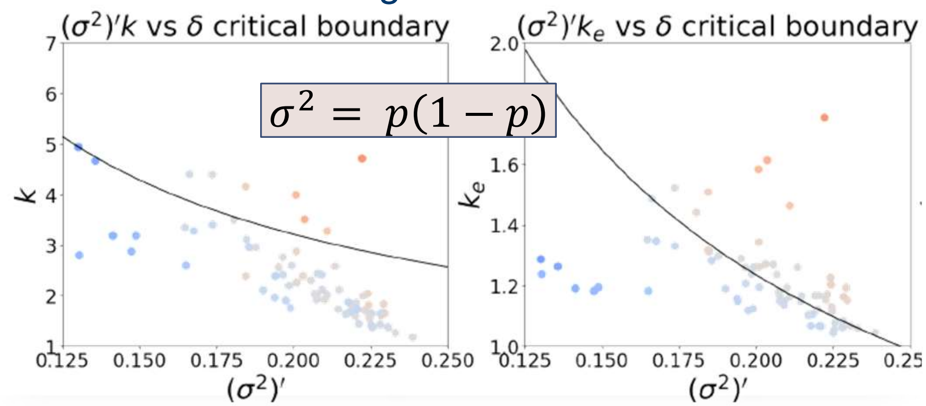


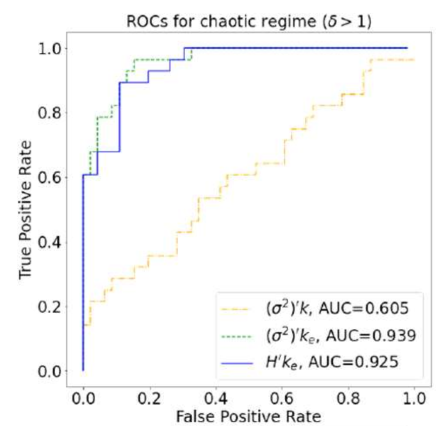
Biochemical regulation models have very low effective connectivity despite high connectivity. Accounting for heterogeneity and canalization better predicts dynamical regime

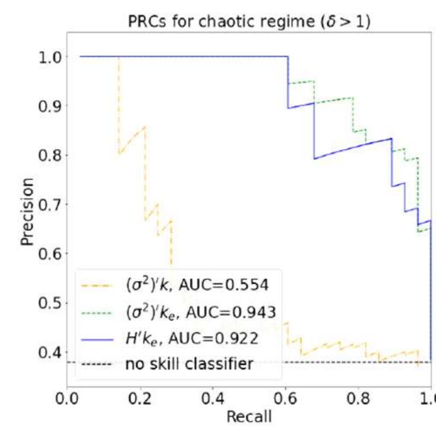
Cell Collective



heterogenous networks







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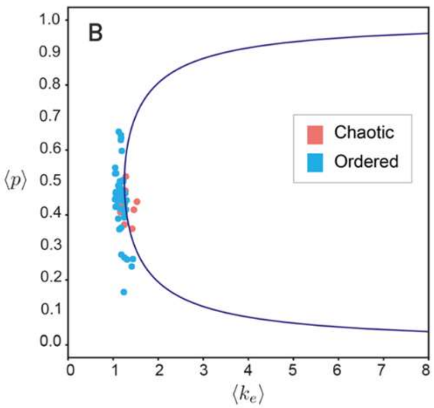
ubiquitous canalization in (experimentally-validated) systems biology models

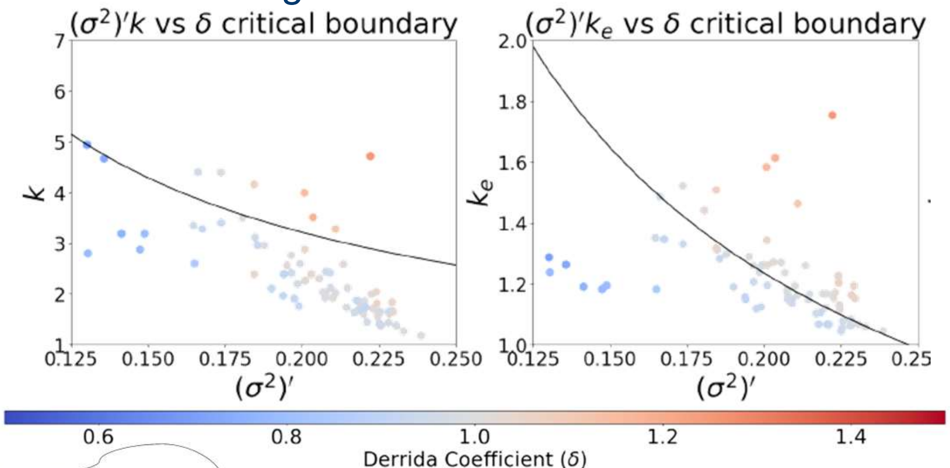
but is there an edge of chaos boundary?

homogeneous networks



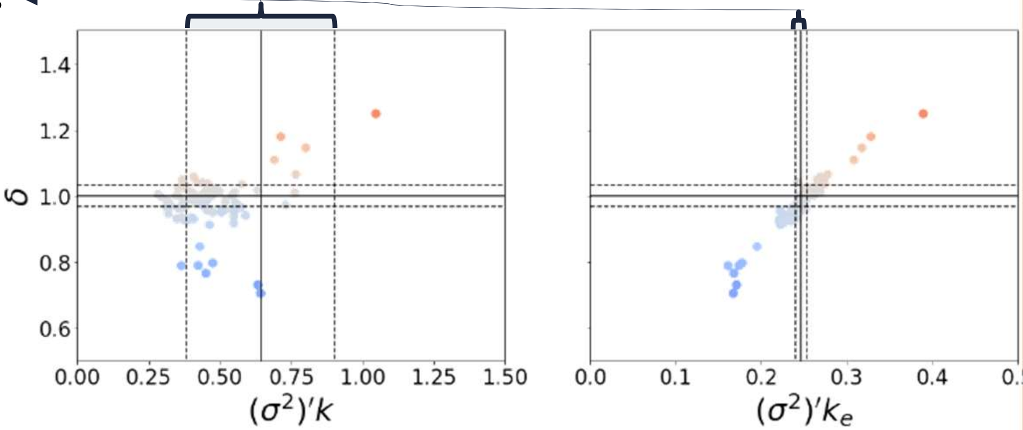
Once canalization (dynamical redundancy) is considered optimal critical region very small and dynamical range is better predicted.

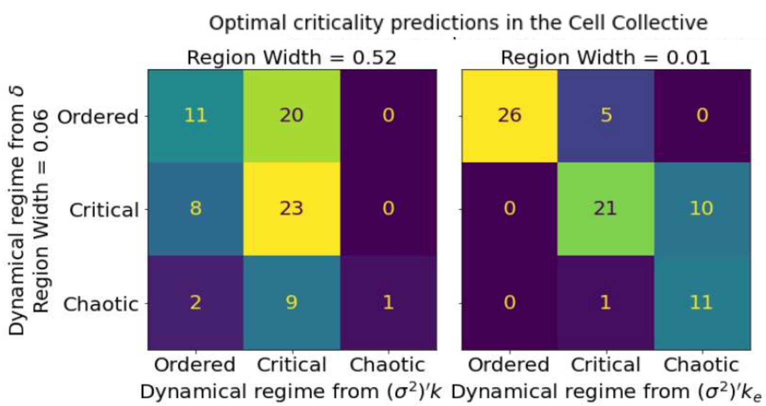
heterogenous networks



Optimal classification thresholds

IQR Of Derrida





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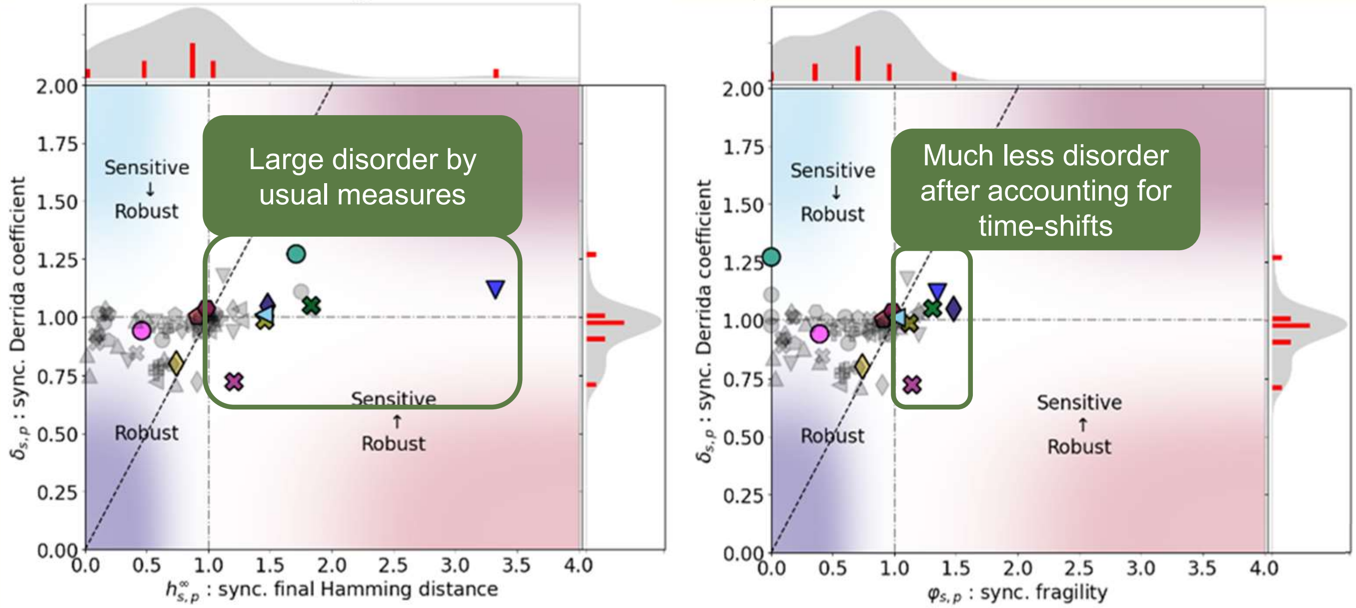
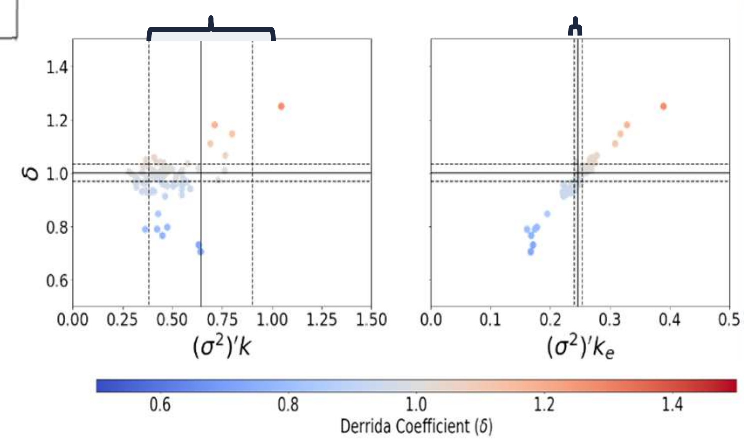


Criticality might arise from interactions of amongst largely stable modules

Cell Collective



More accurate measures of dynamical regime show that experimentally-validated systems biology are far from the edge of chaos

Park, Costa, Rocha, Albert, & Rozum [2023]. *PRX Life*. **1**, 023009.
Costa, Rozum, Marcus, & Rocha[2023]. *Entropy*. **25**(2):374.
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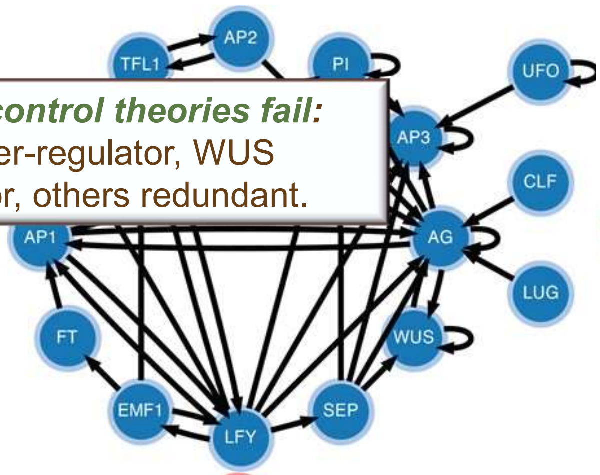
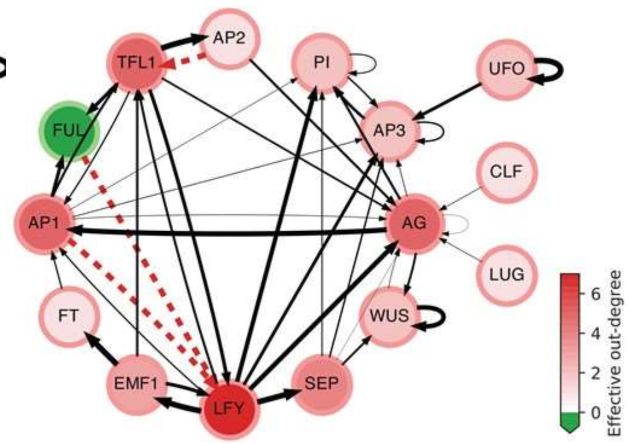
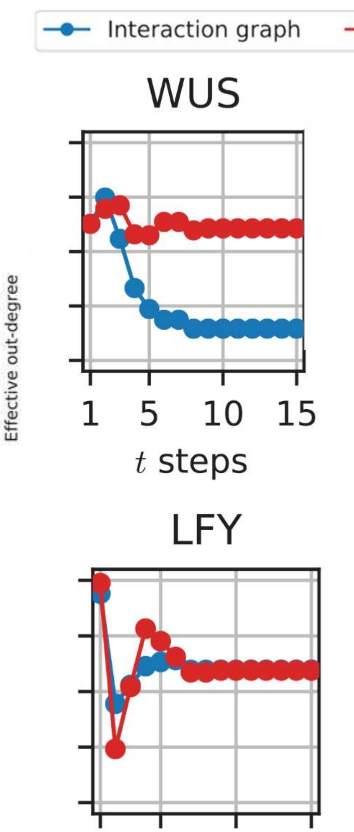
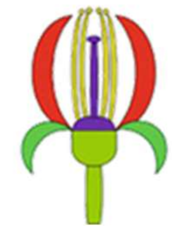
Thaliana control pathways (using structure and dynamics information)

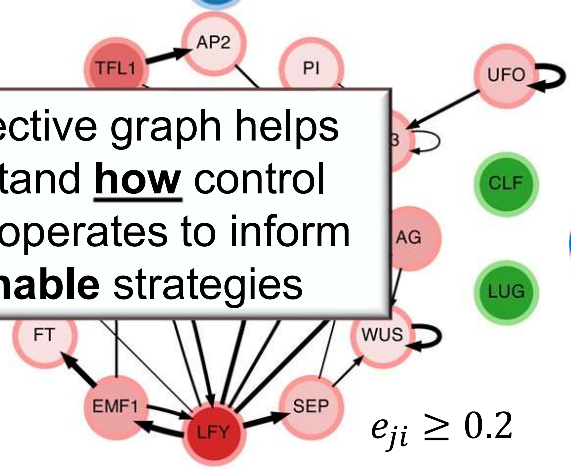


Structural control theories fail:
LFY is master-regulator, WUS autoregulator, others redundant.



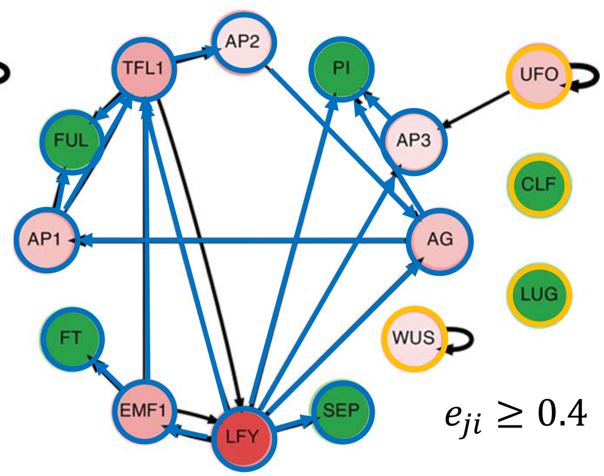






The effective graph helps understand **how** control actually operates to inform **actionable** strategies

$e_{ji} \geq 0.2$



$e_{ji} \geq 0.4$

Chaos et al [2006]. *J. of Plant Growth Regulation*. **25**(4): 278-289.

Gates & Rocha [2016]. *Sci. Rep.* **6**, 24456.
Gates, Correia, Wang & Rocha [2021]. *PNAS*. **118** (12): e2022598118.

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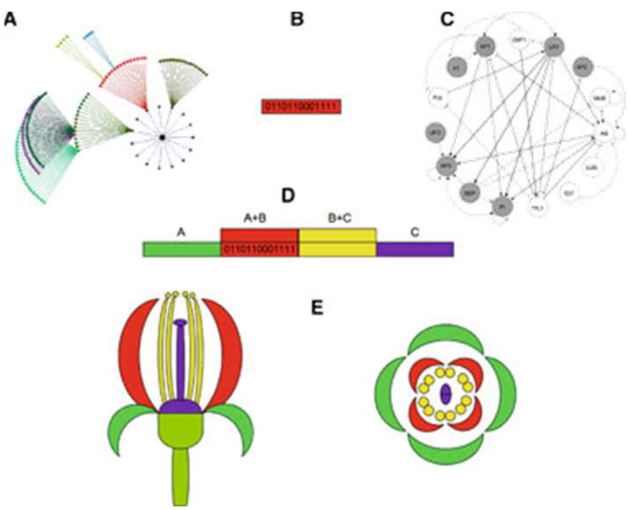
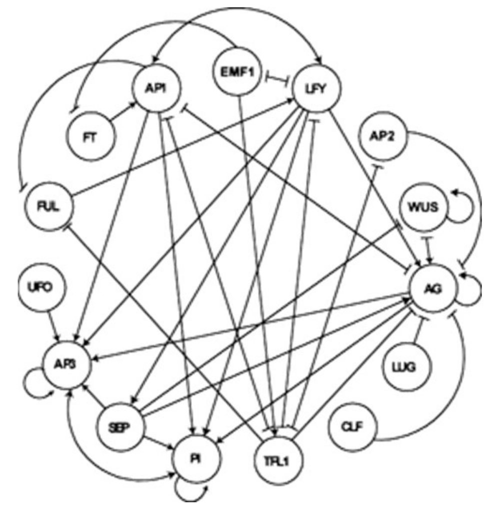
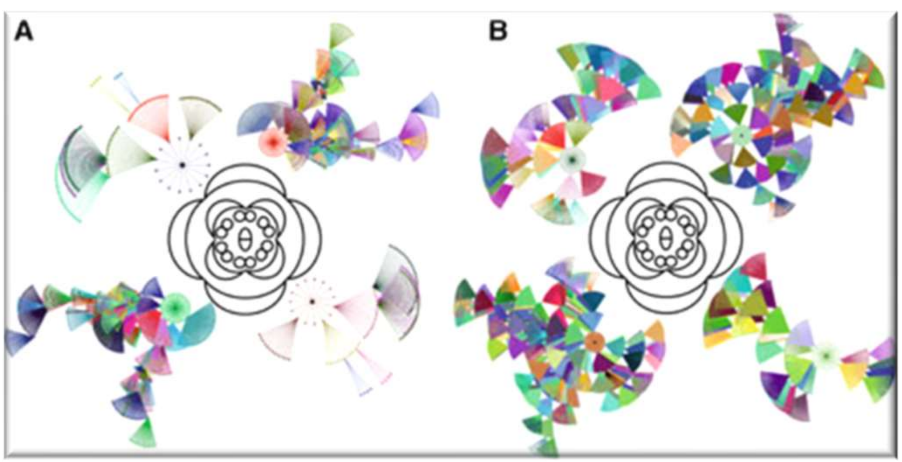
Boolean networks, control, sound, art, and education







Chaos et al [2006]. “From Genes to Flower Patterns and Evolution: Dynamic Models of Gene Regulatory Networks”. *Journal of Plant Growth Regulation*. **25**(4): 278-289.

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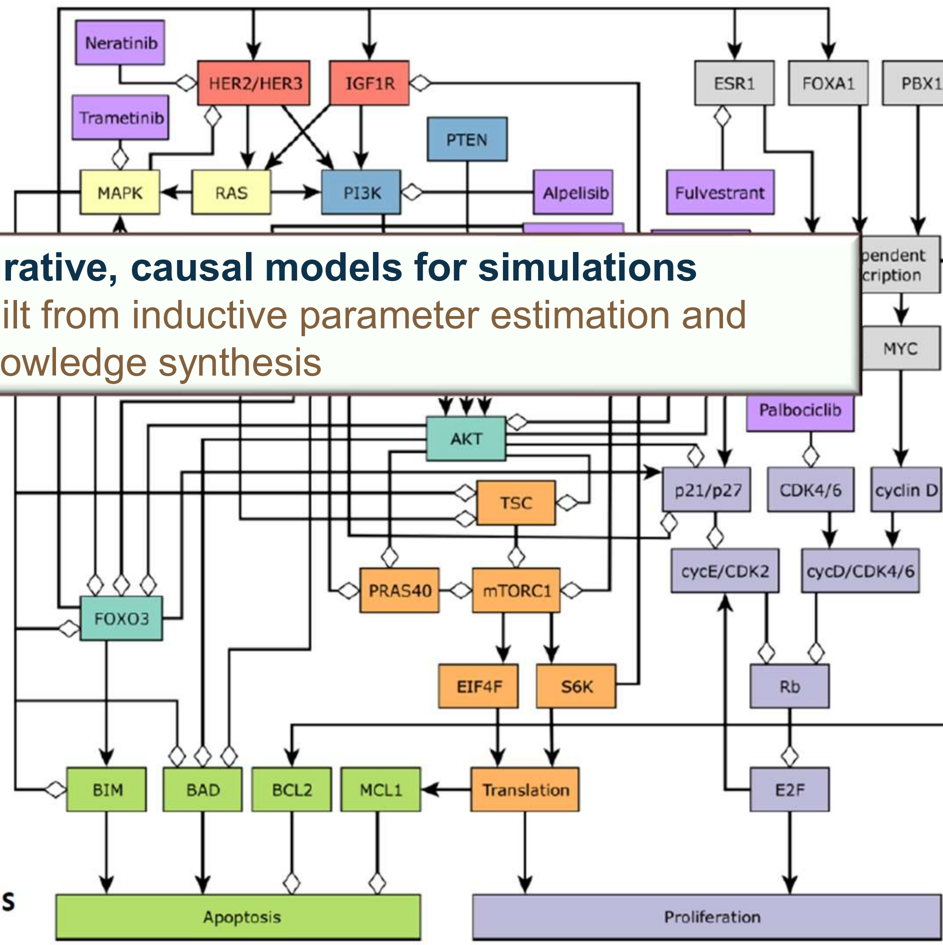
Boolean networks, control, sound, art, and education

Boolean networks, control, sound, art, and education

predicting drug and therapy targets in causal models

discrete modeling of within-cell **oncogenic signal transduction**, recapitulates known resistance PI3K inhibitors. Suggests novel combinatorial interventions.



Integrative, causal models for simulations
- built from inductive parameter estimation and knowledge synthesis

A network modeling approach to elucidate drug resistance mechanisms and predict combinatorial drug treatments in breast cancer

Jorge G. T. Zañudo[1,2,3,*] and Réka Albert[1,4,&]

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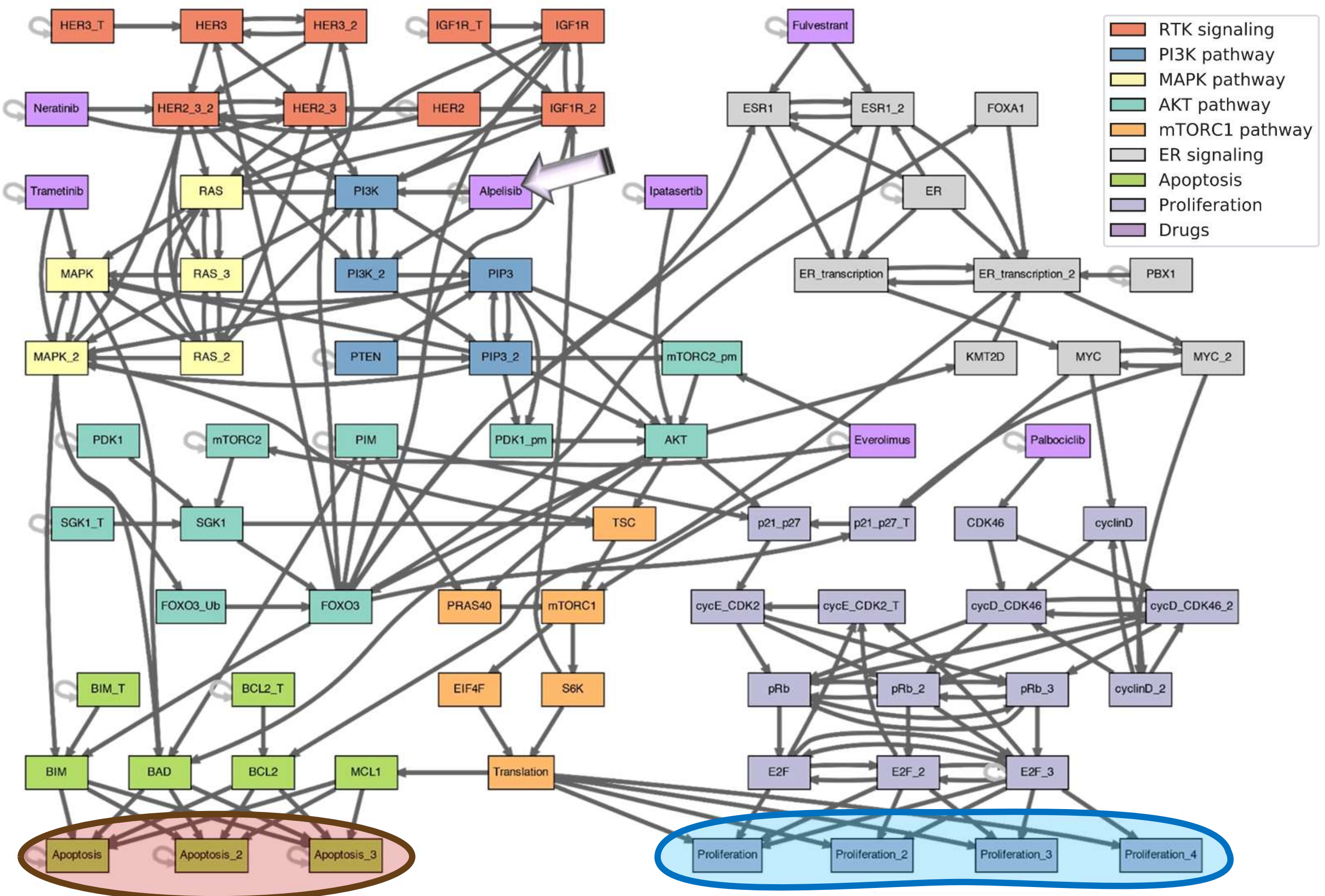
ER+ breast cancer model

uncovering and characterizing control pathways for drug therapy



Gates,Correia, Wang & Rocha [2021]. *PNAS*. **118** (12): e2022598118.

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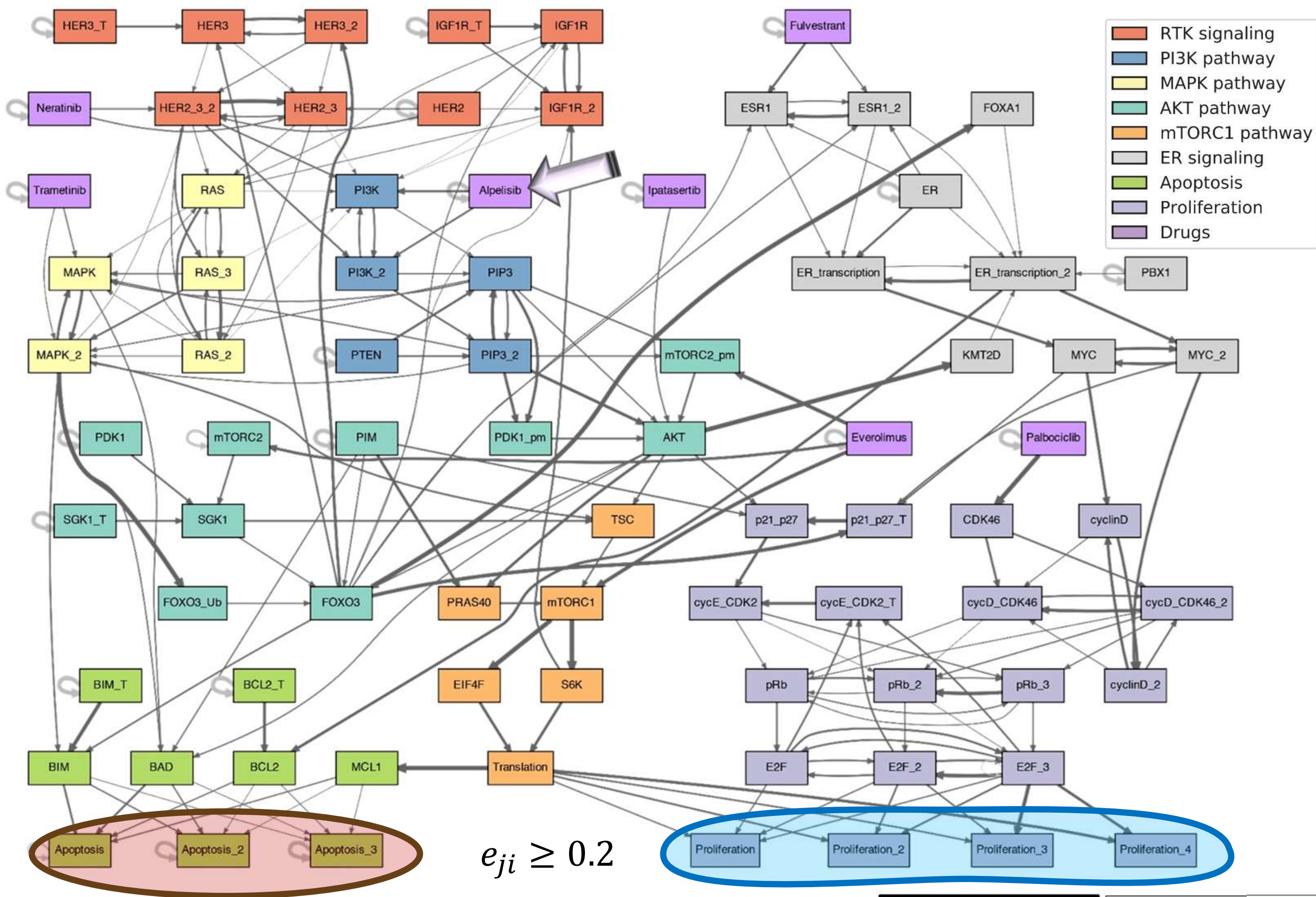

$e_{ji} \geq 0.2$

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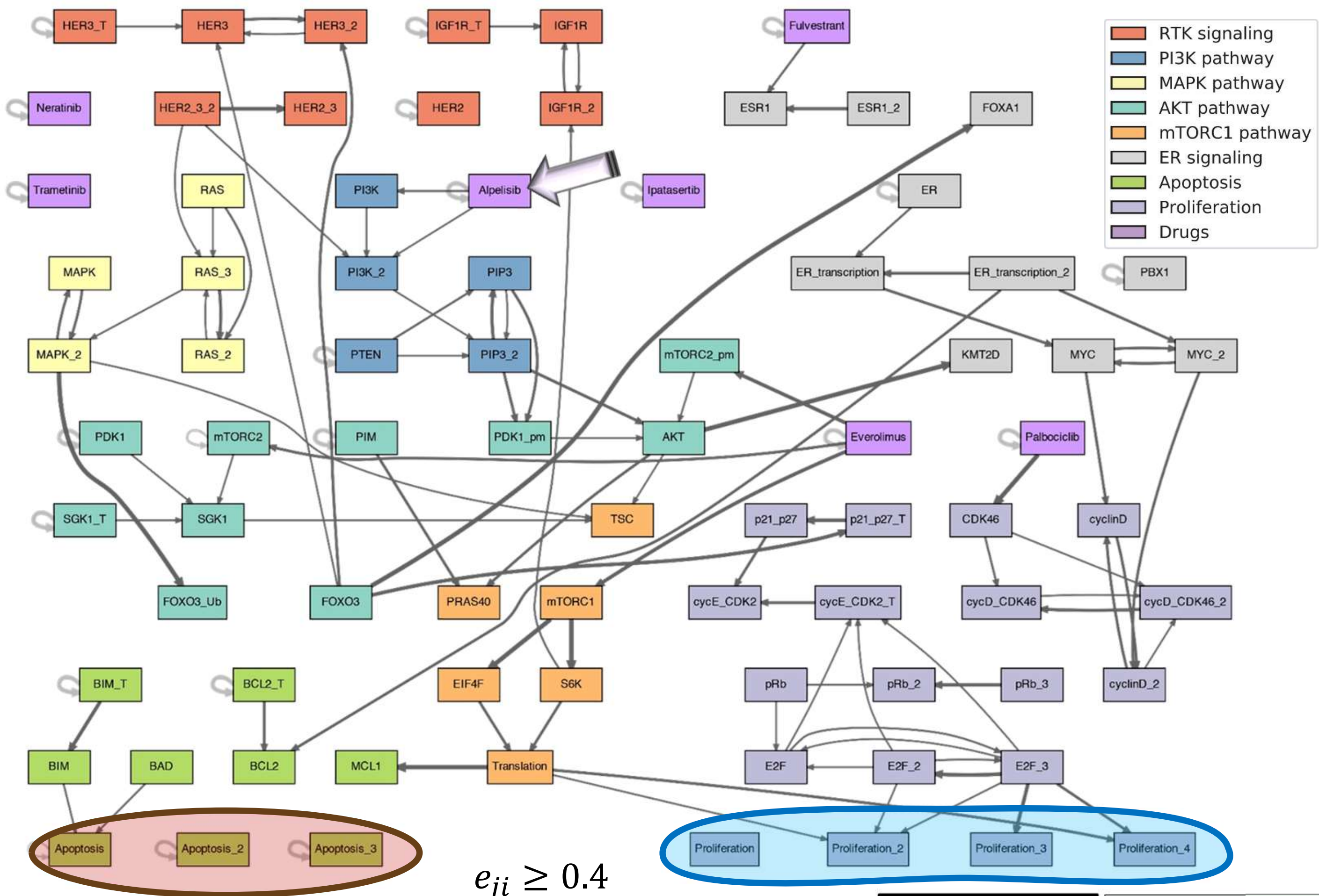

$e_{ji} \geq 0.4$

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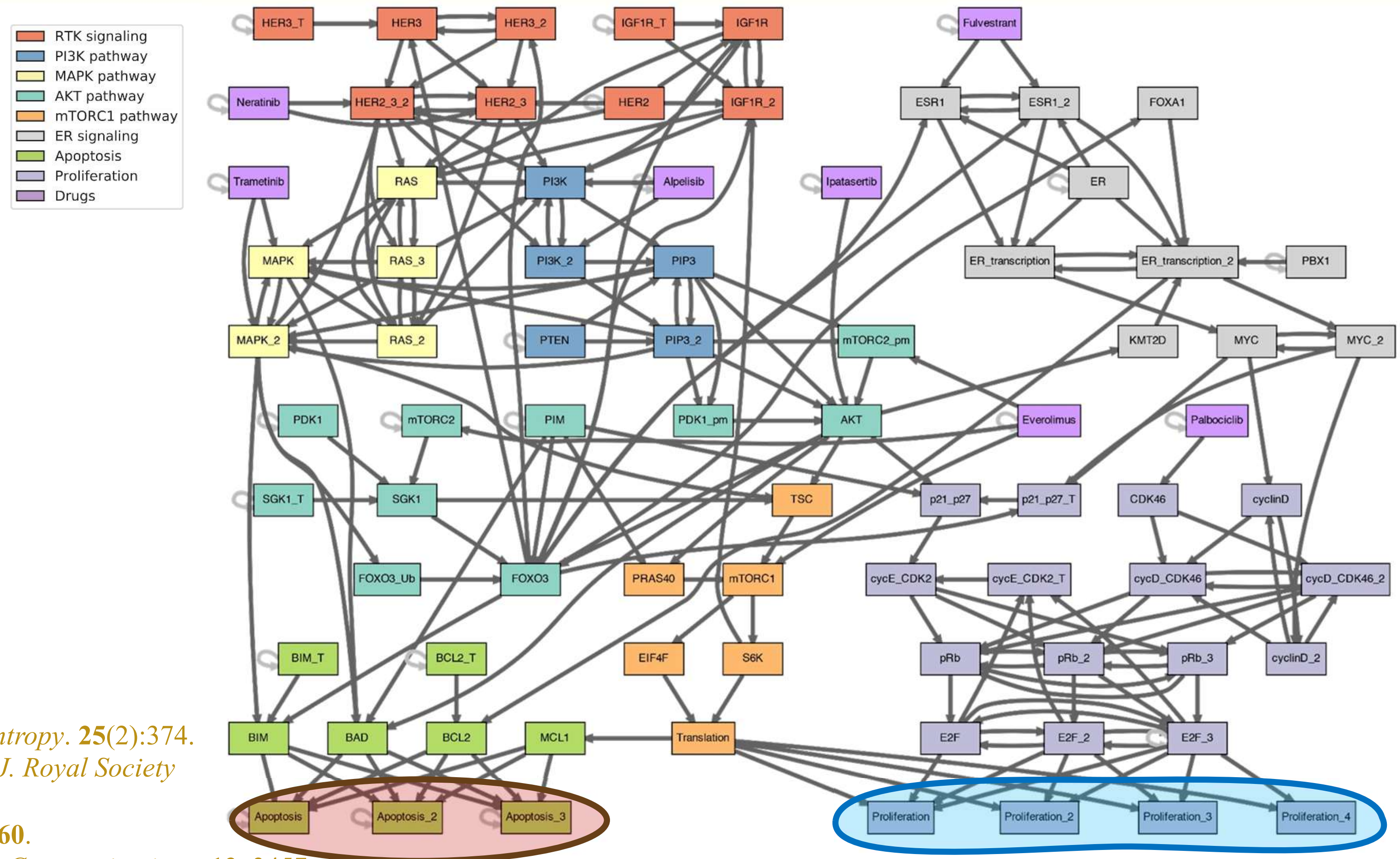
causal (modular) dynamics via conditional effective connectivity



Costa, Rozum, Marcus, & Rocha[2023]. *Entropy*. **25**(2):374.
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Parmer, Rocha & Radicchi [2022]. *Nature Communications*. **13**, 3457.
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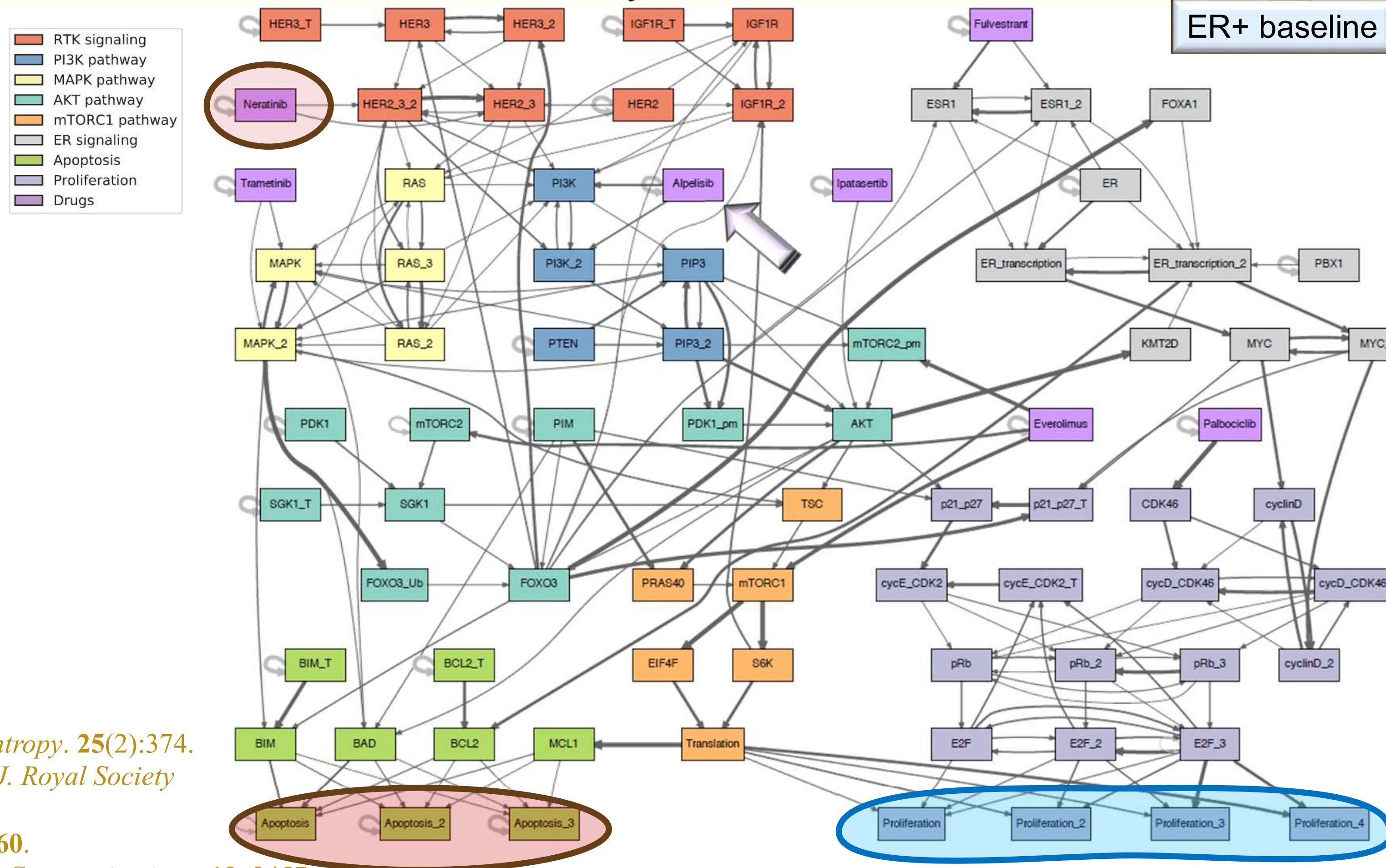

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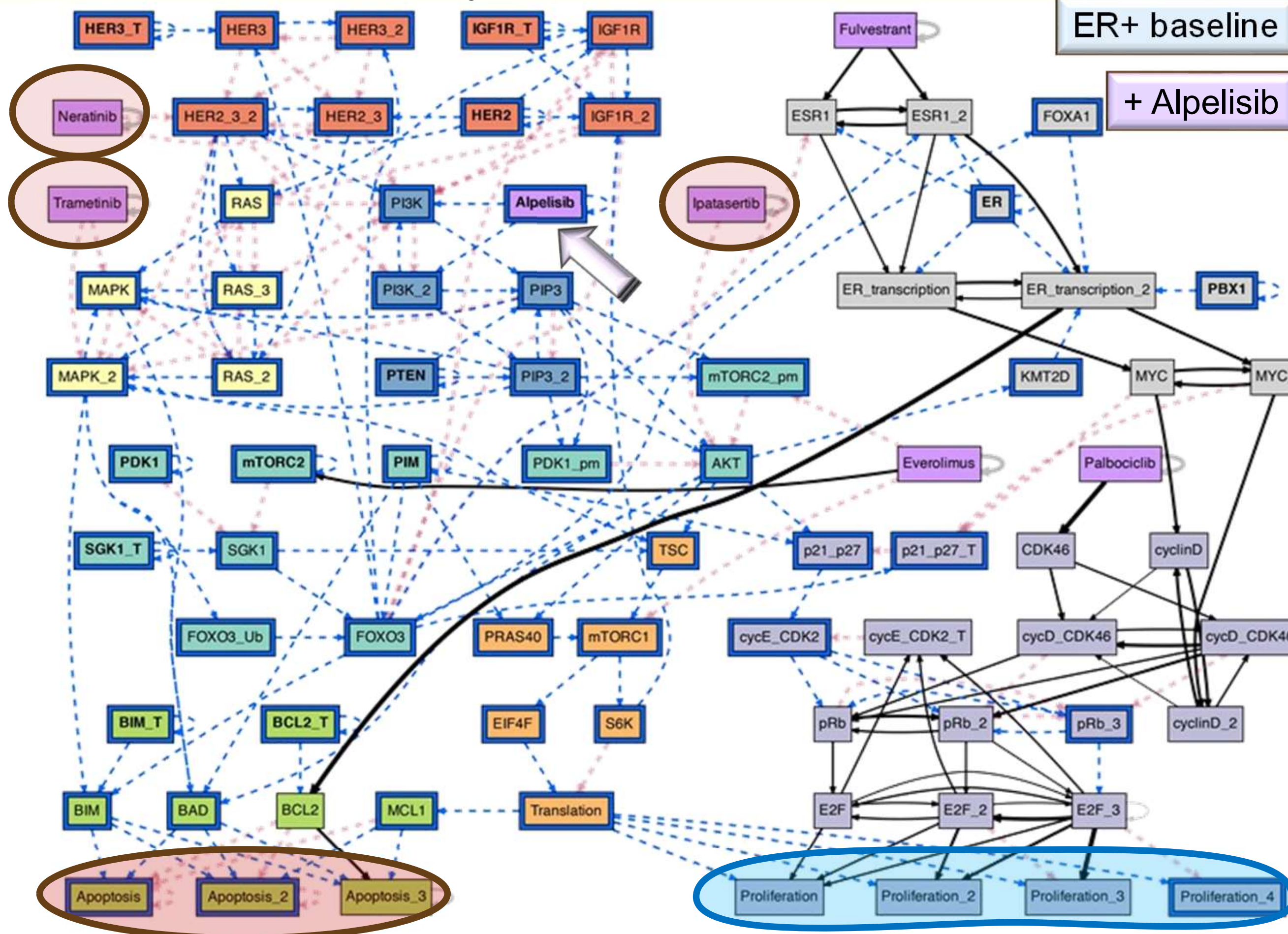
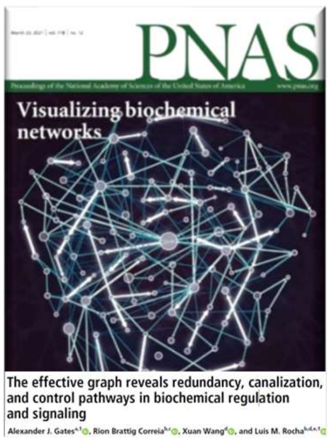
causal (modular) dynamics via conditional effective connectivity

- RTK signaling
- PI3K pathway
- MAPK pathway
- AKT pathway
- mTORC1 pathway
- ER signaling
- Apoptosis
- Proliferation
- Drugs





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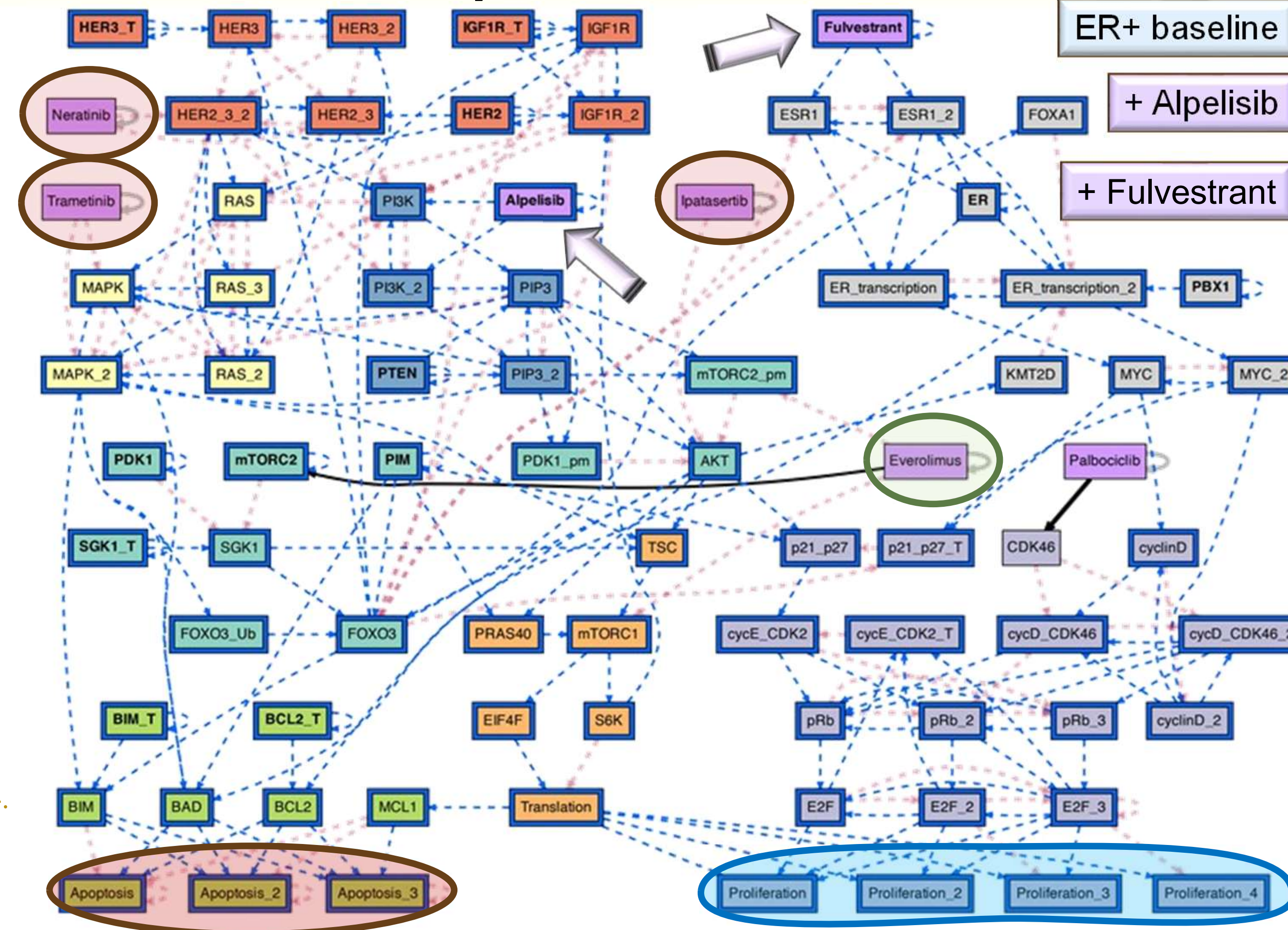

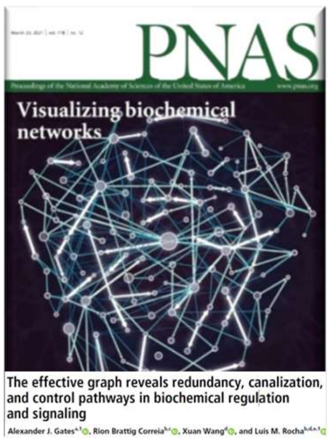

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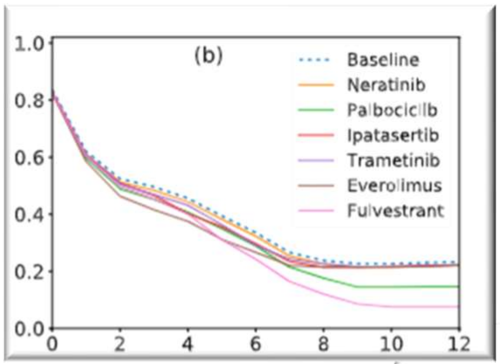

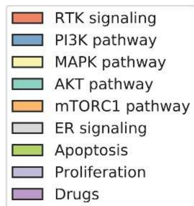

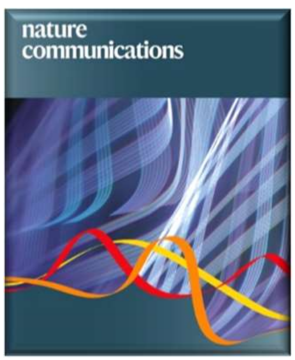

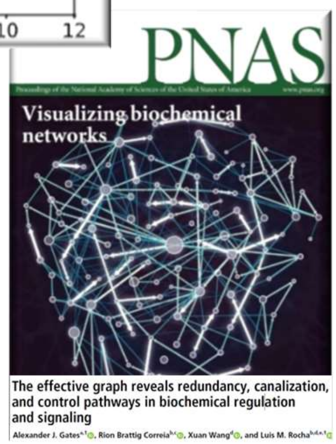

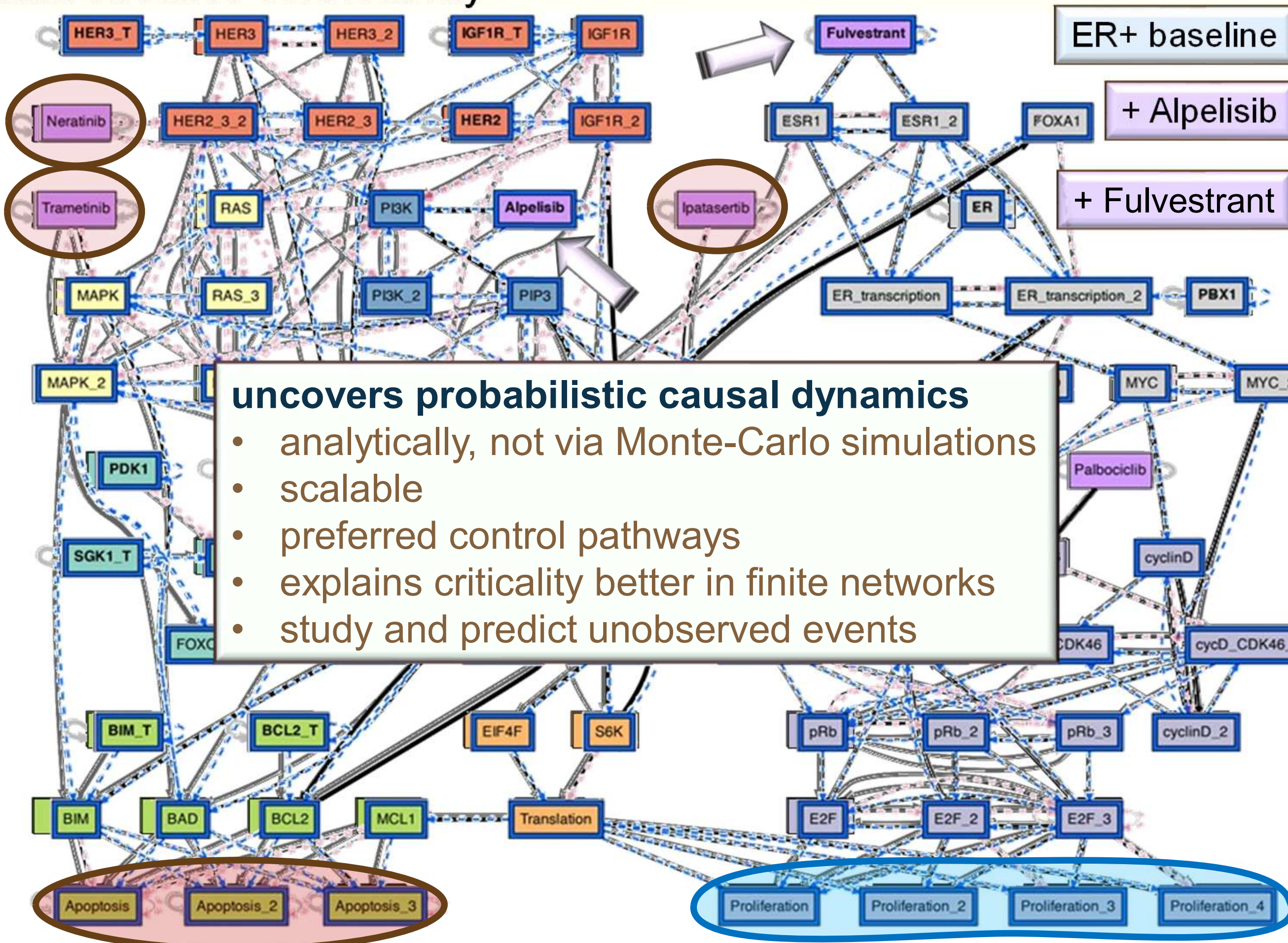

uncovers probabilistic causal dynamics

- analytically, not via Monte-Carlo simulations
- scalable
- preferred control pathways
- explains criticality better in finite networks
- study and predict unobserved events

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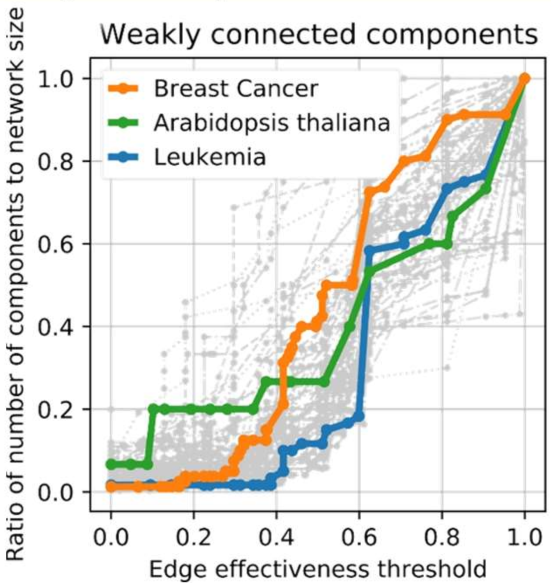
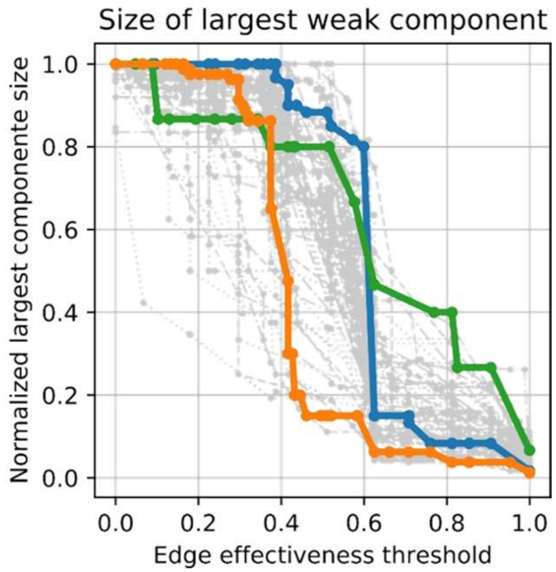
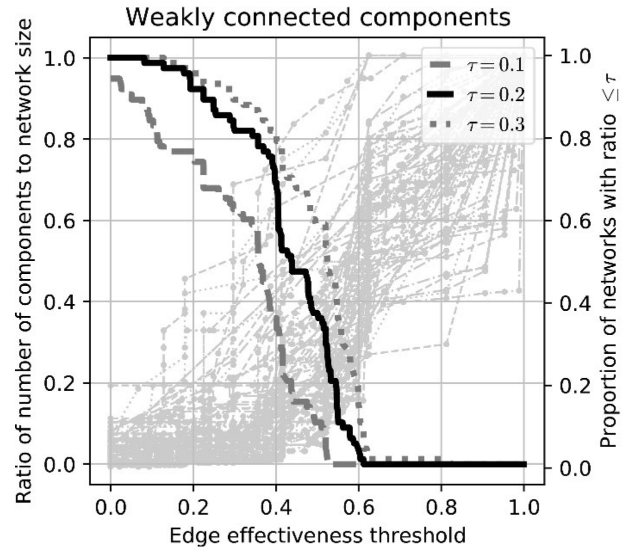
dynamically-decoupled modules







Most networks preserve a large weakly connected component up to edge effectiveness ≤ 0.4.

Cell Collective

Allows comparisons between networks regarding the ability to effectively propagate signals.

But most break into dynamically-decoupled modules for edge effectiveness > [0.4, 0.6].

Experimentally-validated models suggest biochemical regulation highly ***modular*** with low effectiveness interactions between modules granting robustness to perturbations.

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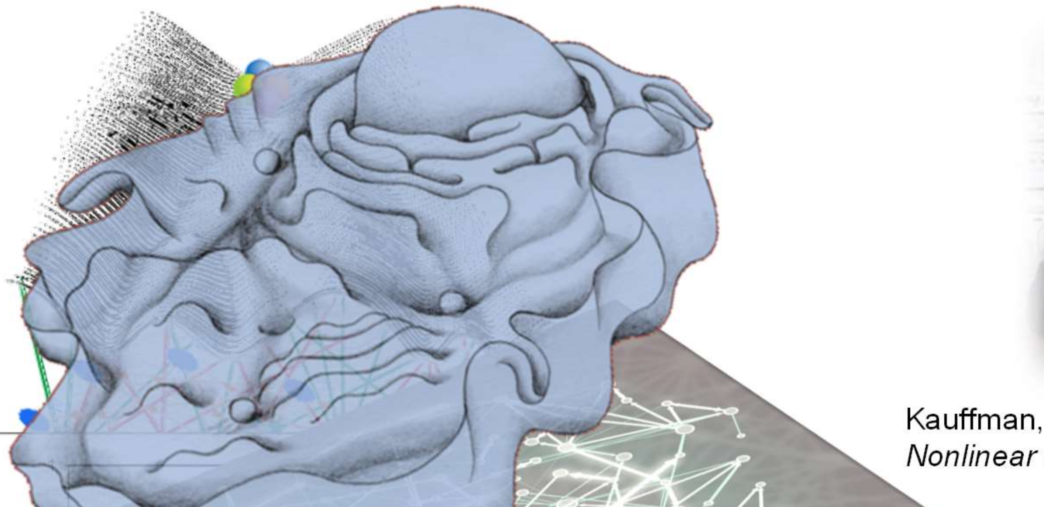
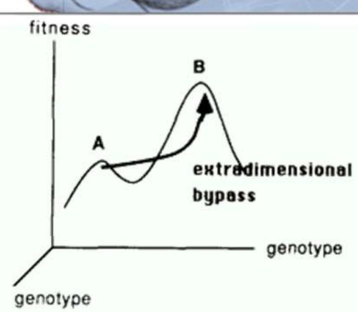
from evolutionary robustness to network and dynamical redundancy



Kauffman, S. A. (1984). *Phys. D Nonlinear Phen.* **10**,145–156.

Waddington CH (1942). *Nature*. **150** (3811):563–565

Michael Conrad



Evolvability: extradimensional bypass, neutrality, redundancy, controllability and robustness tradeoff.

…bustness of phenotypes is the result of a ***buffering*** of …velopmental process.

…dynamics of gene networks provides buffering (***self-organization***). But still easily chaotic.

Structure (***topological organization***), can provide larger stable or critical universe, but still easily chaotic.

canalized genetic **control** ignores some inputs (***redundancy***) to attain necessary resilience (tradeoff stability/evolvability)

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