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Morphisms of Reaction Networks

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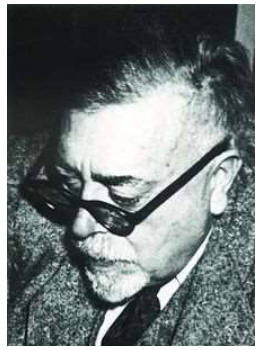
Beilstein Symposium 2018-06-07

Mapping one network into another

- We would like *simple* understanding of *complex* systems
  - Subnetworks, motifs, model reduction, …
- But we also want to preserve meaning
  - What is a good model of a cat?
- Understanding how complex systems may arise from simpler systems
- How to reconcile?
  - Look for relationships between large (complex) and small (simple) networks that preserve *structure* and *function*.



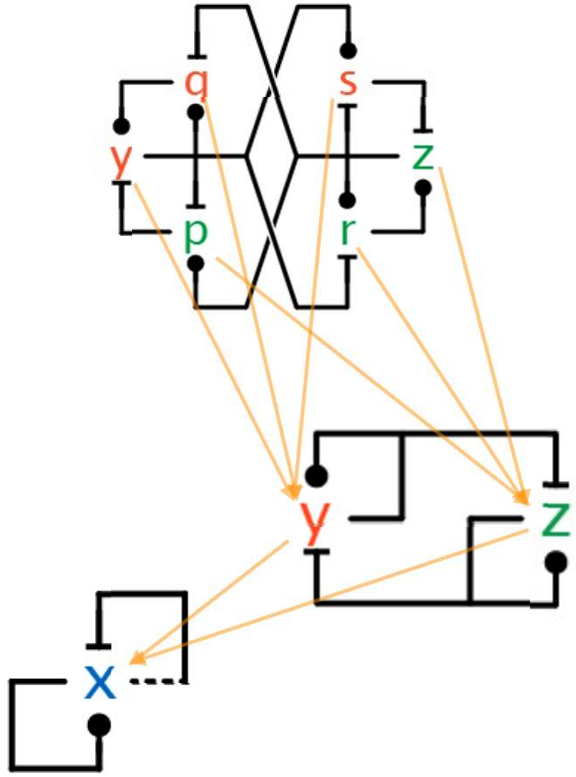
Norbert Wiener

Pioneer of stochastic processes and inventor of Cybernetics.

"The best material model of a cat is another, or preferably the same, cat"

Comparing networks by morphing them

- How can we compare different networks?
  - Different number of species
  - Different number of reactions
  - Apparently unrelated connectivity
- How is structure related to function and performance?
  - Does antagonism (in network structure) guarantee bistability (in function)?
- We *morph* networks onto one another (structurally) so that they *emulate* each other ('s function)
  - Deterministic version of simulation of reactive systems



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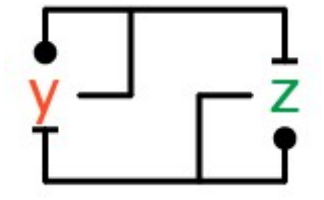
Morphisms of Antagonistic Networks

Antagonistic Networks

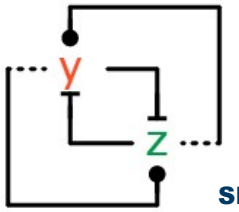
activation
inhibition

1 vs. 1
Mutual Inhibition & Self Activation



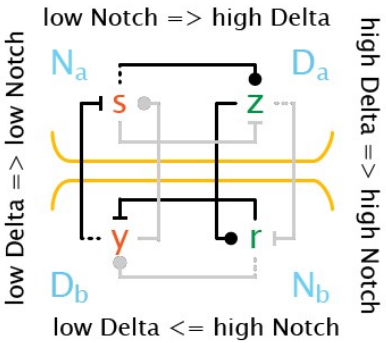
MI

1 vs. 1
Mutual Inhibition & Mutual Anti-activation

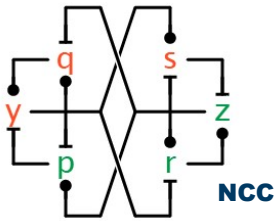


SI

2 vs. 2



3 vs. 3



NCC

Cell cycle transitions

Molecular mechanisms creating bistable switches at cell cycle transitions

Anael Verdugo, P. K. Vinod, John J. Tyson and Bela Novak

Open Biol. 2013 3, 120179, published 13 March 2013

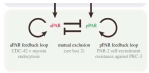
Polarity establishment

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B

rstb.royalsocietypublishing.org

The PAR network: redundancy and robustness in a symmetry-breaking system

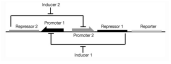
Fumio Motegi[2,3] and Geraldine Seydoux[4]



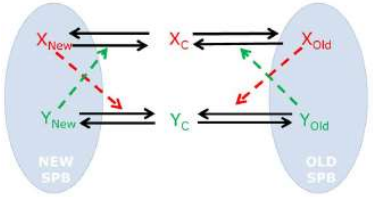
Gene networks

Construction of a genetic toggle switch in *Escherichia coli*

Timothy S. Gardner[1-2], Charles R. Cantor[3] & James J. Collins[1-2]



Septation Initiation

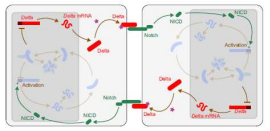


Dynamics of SIN Asymmetry Establishment

Archana Bajpai[1], Anne Fankhänel[2], Jun-Song Chen[2], Damrel McCollum[2], Masamitsu Sato[4,5], Rafael E. Carazo-Salas[6], Kathleen L. Gould[2], Attila Csikasz-Nagy[1,7]*

PLOS Computational Biology | www.ploscompbiol.org

Delta-Notch



Patterning embryos with oscillations: structure, function and dynamics of the vertebrate segmentation clock

Andrew C. Oates[1,2], Luis G. Morelli[1,2] and Saúl Ares[3,4,*]

Lateral Inhibition through Delta-Notch Signaling: A Piecewise Affine Hybrid Model*

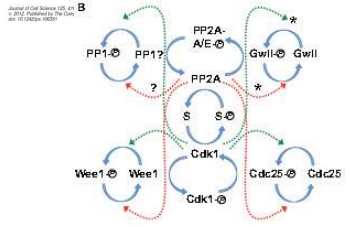
Ronojoy Ghosh and Claire J. Tomlin

M.D. Di Benedetto, A. Sangiovanni-Vincentelli (Eds.): HSCC 2001, LNCS 2034, pp. 232–246, 2001.
© Springer-Verlag Berlin Heidelberg 2001

The "new" cell cycle switch

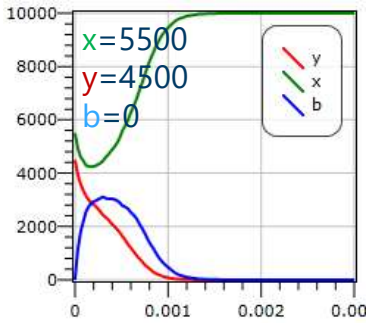
Phosphorylation network dynamics in the control of cell cycle transitions

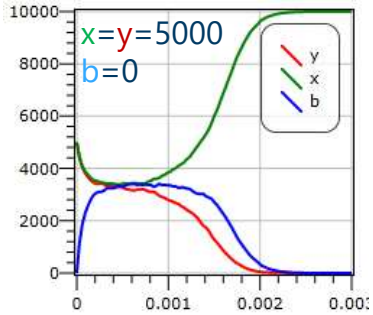
Daniel Fisher[1,*], Liliana Krasinska[1,2], Damien Coudreuse[2,3] and Béla Novák[3,*]



A Consensus Algorithm

- Approximate Majority (AM) Algorithm
  - Uses a third "undecided" population b
  - Disagreements cause agents to become undecided
  - Undecided agents agree with any non-undecided agent

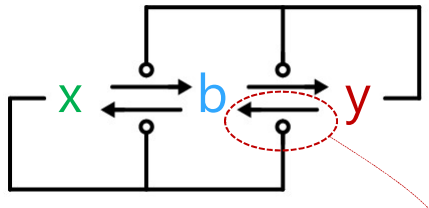




Dana Angluin · James Aspnes · David Eisenstat

A Simple Population Protocol for Fast Robust Approximate Majority

catalysis



chemical reaction network

$x + y \to^{r} y + b$

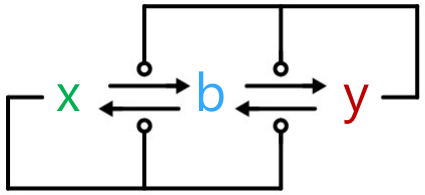
$y + x \to^{r} x + b$

$b + x \to^{r} x + x$

$b + y \to^{r} y + y$

A Biological Implementation

Approximate Majority (AM)



1) Bistable
   Even when initially x=y (stochastically)

2) Fast (asymptotically optimal)
   O(*log n*) convergence time

3) Robust to perturbation
   above a threshold, initial majority wins *whp*

Dana Angluin · James Aspnes · David Eisenstat

A Simple Population Protocol for Fast Robust Approximate Majority

2007

Epigenetic Switch

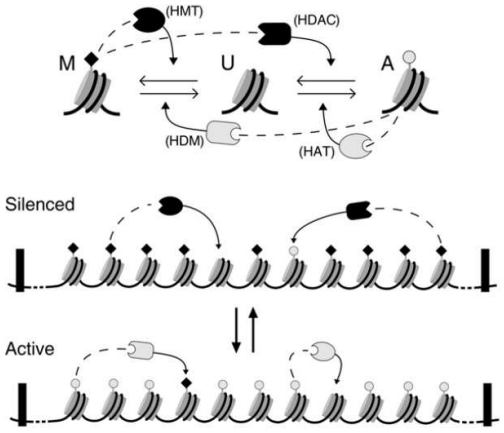
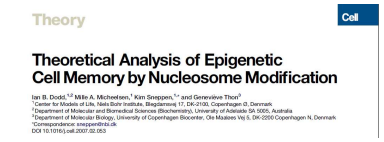


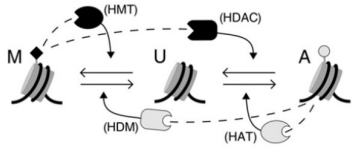
Figure 1. Basic Ingredients of the Model



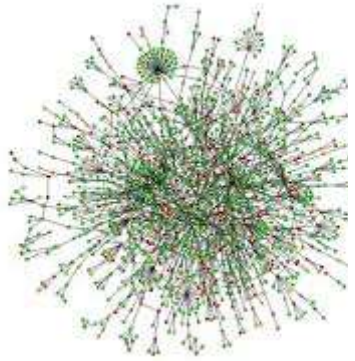
2007

Not always that simple

- The epigenetic switch seems a *direct* biological implementation of an algorithm
  - Although we may have to qualify that with some notion of approximation of the (enzymatic) kinetics

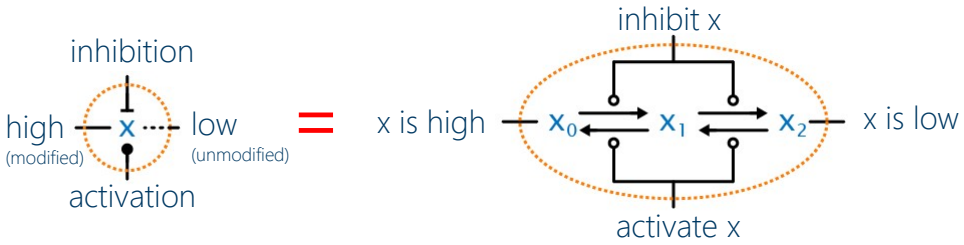


- In most cases the biological implementation seems more *indirect* or *obfuscated*
  - *"Nature is subtle but not malicious - Einstein"* Ha! think again!
  - Other implementations of Approximate Majority seem more convoluted and approximate



The Triplet Model of Influence

activation
inhibition
(mass action) catalysis

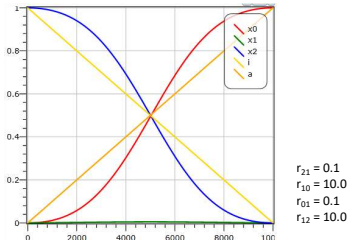


Usually modeled by sigmoid (e.g. Hill or Reinitz) functions

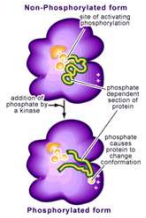
triplet motif

We model them by 4 mass action reactions over 3 species x_0, x_1, x_2

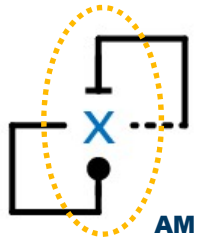
They actually implement a Hill function of coefficient 2:



biological mechanism: (e.g.:) multisite phosphorylation



For example:



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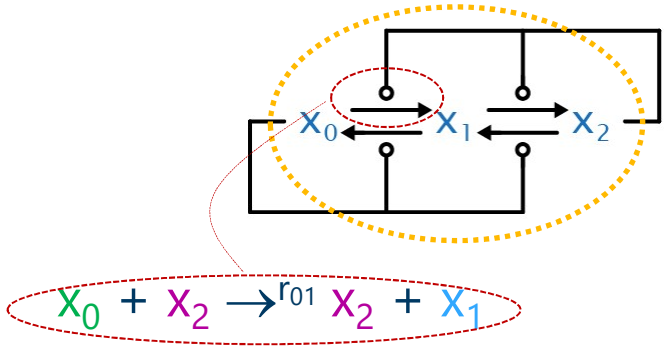
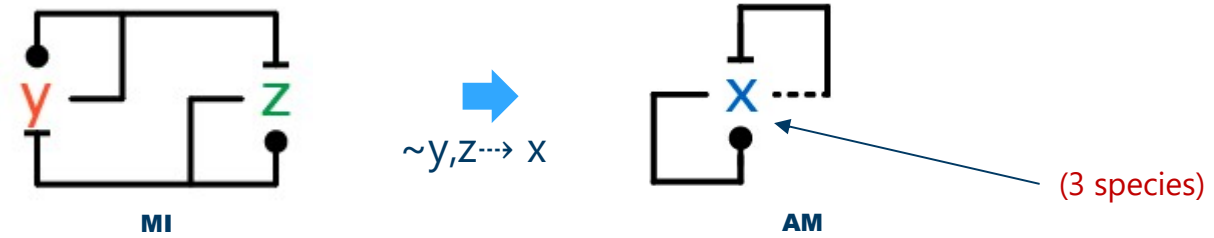
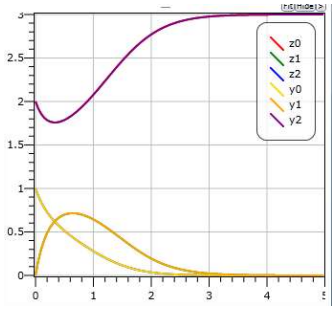


Approximate Majority

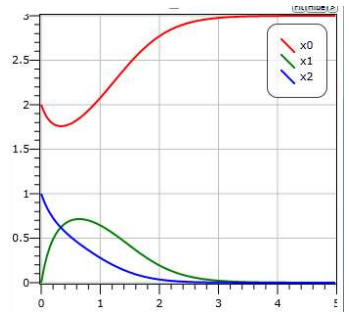
Network Emulation MI emulates AM

- For *any* rates and initial conditions of AM, we can find *some* rates and initial conditions of MI such that the (6) trajectories of MI retrace those (3) of AM:





(6 species on 3 trajectories)



(3 species on 3 trajectories)

initialize:
z = x
~y = x

($y_2 = x_0$
$y_1 = x_1$
$y_0 = x_0$)

- How do we find these matching parameters? By a network morphism!

CRN Morphisms

A *CRN morphism* from (S, R) to $(\hat{S}, \hat{R})$
written $m \in (S, R) \to (\hat{S}, \hat{R})$

is a pair of maps $m = (m_S, m_R)$

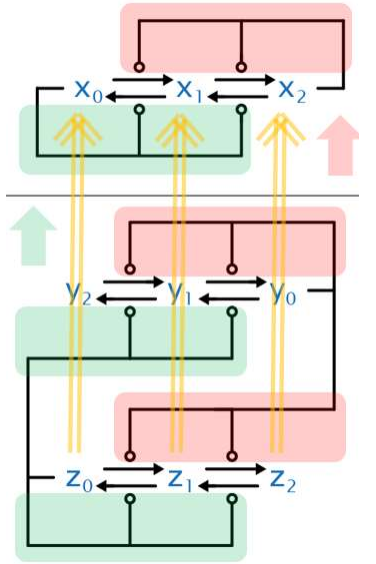
a *species map* $m_S \in S \to \hat{S}$

a *reaction map* $m_R \in R \to \hat{R}$

reactant morphism $\boldsymbol{m_S{}^{\mathrm{T}} \cdot \rho = \hat{\rho} \cdot m_R{}^{\mathrm{T}}}$ preserve enough network structure

stoichiomorphism $\boldsymbol{\varphi \cdot m_R = m_S \cdot \hat{\varphi}}$ preserve enough chemical stoichiometry

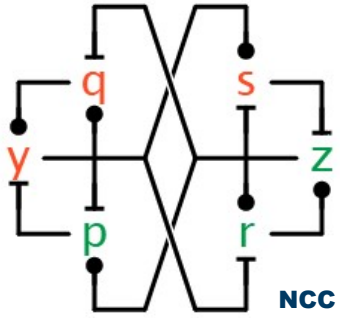
Mappings (symmetries) between two networks

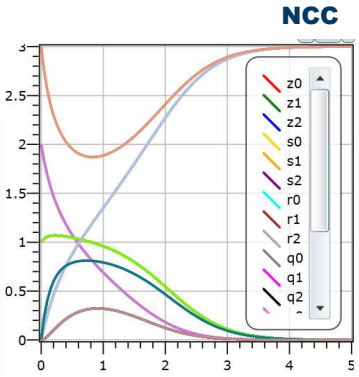


$\boldsymbol{\varphi}$ is the stoichiometric matrix and $\boldsymbol{\rho}$ is the related reactant matrix. $\boldsymbol{m_S}$ and $\boldsymbol{m_R}$ are the characteristic 0-1 matrices of the morphism maps m_S (on species) and m_R (on reactions). $-^{\mathrm{T}}$ is transpose.

Network Emulation: NCC emulates MI

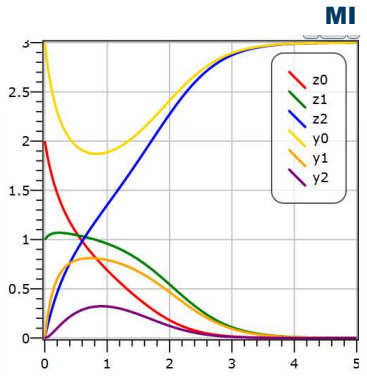
- For *any* rates and initial conditions of MI we can find *some* rates and initial conditions of NCC such that the (18) trajectories of NCC retrace those (6) of MI





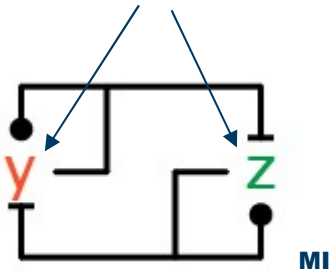
(18 species on 6 trajectories)

z,r,p ⇢ z
y,q,s ⇢ y



(6 species on 6 trajectories)

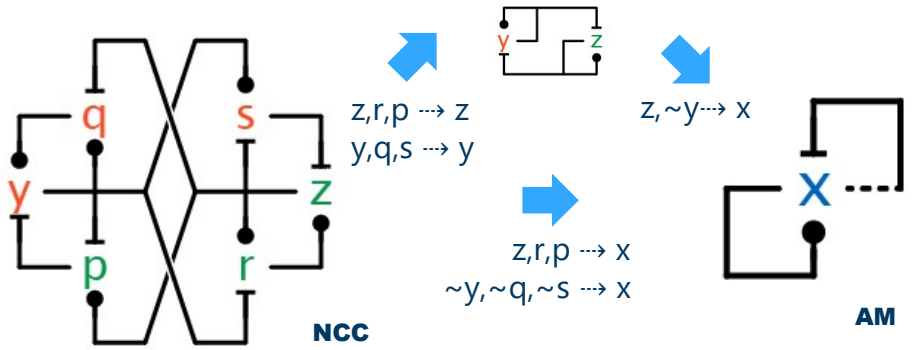
(3 species each)

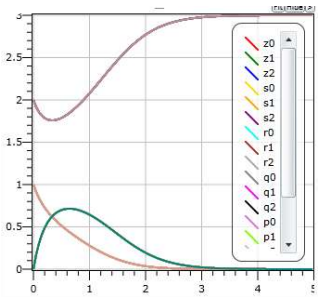


initialize
z,r,p = z
y,q,s = y

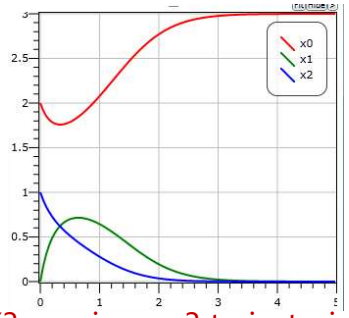
Emulations Compose

- The (18) trajectories **NCC** can *always* retrace those (3) of **AM**





(18 species on 3 trajectories)



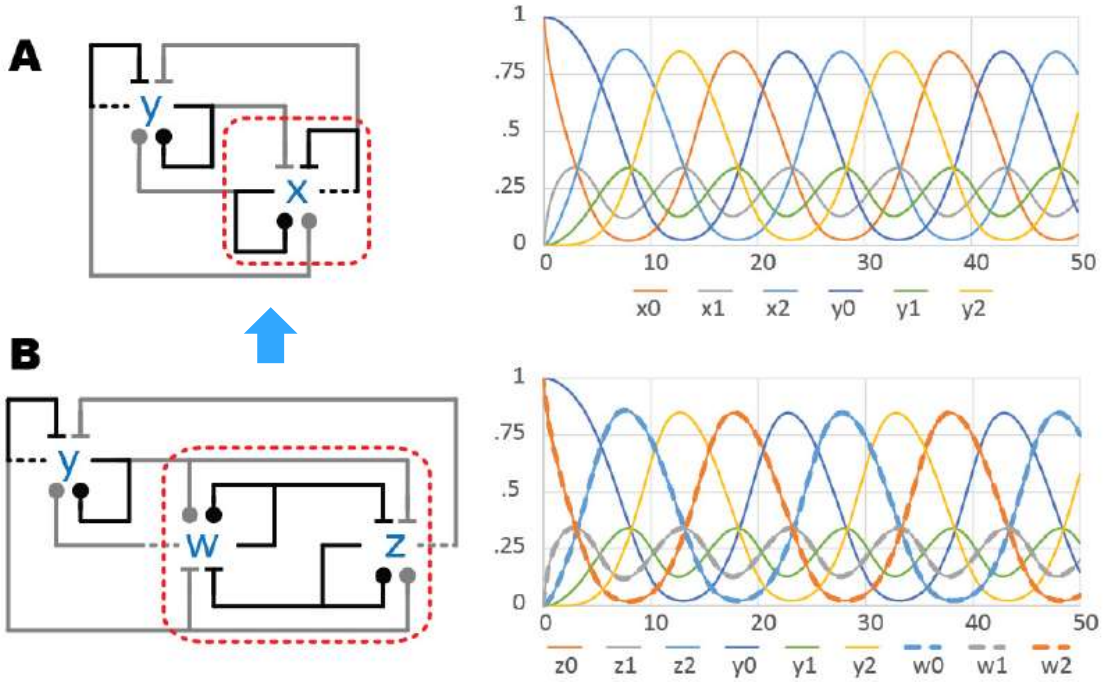
(3 species on 3 trajectories)

The new cell cycle switch can emulate AM *exactly*.

For *any* initial conditions of AM.

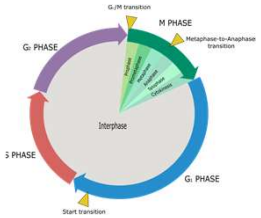
And for *any* rates of AM.

Emulations are Modular

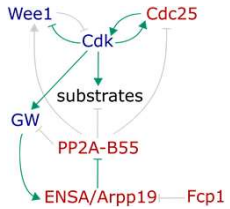


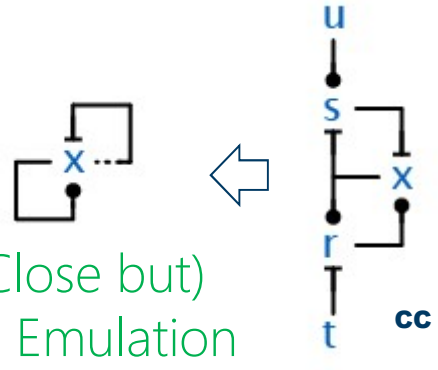
Nature seems to like good algorithms

Cell Cycle

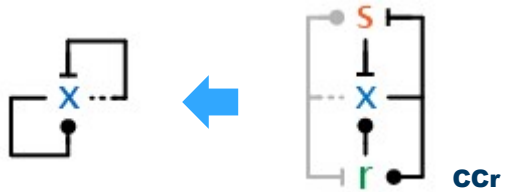


G_2/M Transition





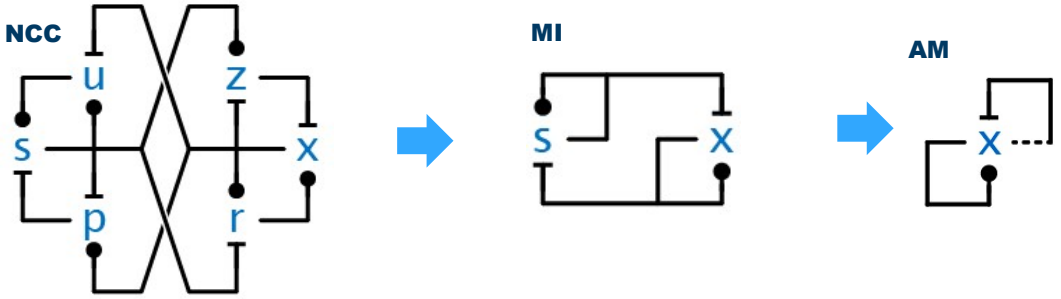
(Close but)
No Emulation



Exact Emulation

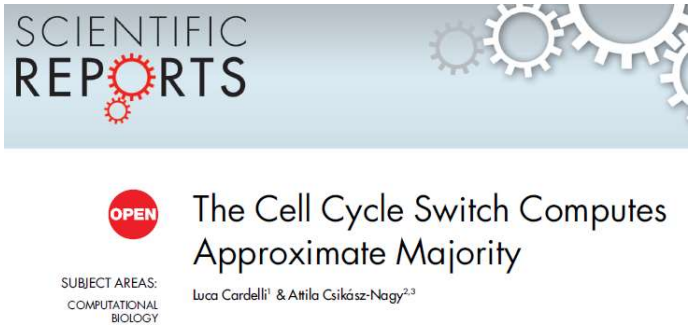
These additional feedbacks *do exist* in real cell cycles (via indirections)

The cell cycle switch *can* exactly emulate AM



Nature seems to like good algorithms

- The cell cycle switch emulates approximate majority
  - Hence it can switch as fast as Approximate Majority (it can follow the same trajectories)
    - And Approximate Majority is optimal!
  - And it is as robust to perturbation as Approximate Majority
    - Which can resist large fluctuations



How to check for emulation

- How do we check a potential emulation morphism for all possible initial conditions of the target?
  - Statically! Check conditions on the joint stoichiometric matrices of the two networks under the mapping.
- How do we check a potential emulation morphism for all possible rates of the target?
  - Can't; but if one emulation is found, then the rates of the target network can be changed *arbitrarily* and a related emulation will again exist.


Cardelli *BMC Systems Biology* 2014, **8**:84
http://www.biomedcentral.com/1752-0509/8/84

BMC Systems Biology

RESEARCH ARTICLE Open Access

Morphisms of reaction networks that couple structure to function

Luca Cardelli[1,2]

Applications of Emulation

- Model Reduction
  - Find reduced networks
  - Compute quotient CRNs
  - Find network symmetries that may be of biological interest
- Morphism Generation
  - Find morphisms between networks (e.g. all the ones for a fixed rate assignment)

Benchmarks from
Sneddon et al., Nature Methods, 2011

Model	Reactions	Species	FB	Time (s)	BB	Time (s)
e9	3538944	262146	222	4.61E+4	222	7.65E+4
e8	786432	65538	167	1.92E+3	167	3.68E+3
e7	172032	16386	122	8.15E+1	122	1.77E+2
e6	36864	4098	86	3.00E+0	86	7.29E+0
e5	7680	1026	58	1.54E-1	58	4.06E-1
e4	1536	258	37	9.00E-3	37	1.09E-1
e3	288	66	22	1.00E-3	22	3.00E-3
e2	48	18	12	1.00E-3	12	2.00E-3

Aggregation reduction | Emulation reduction

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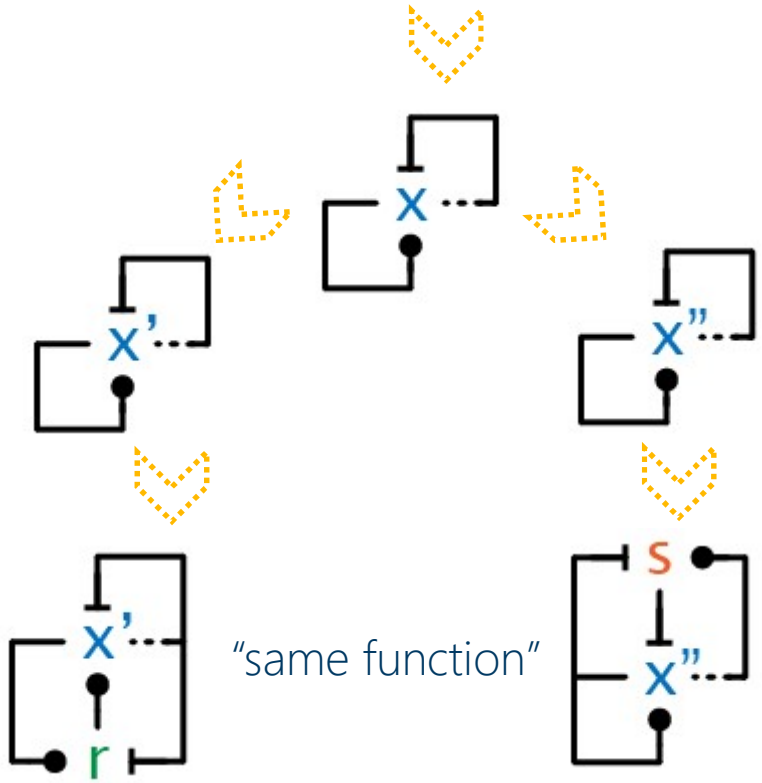
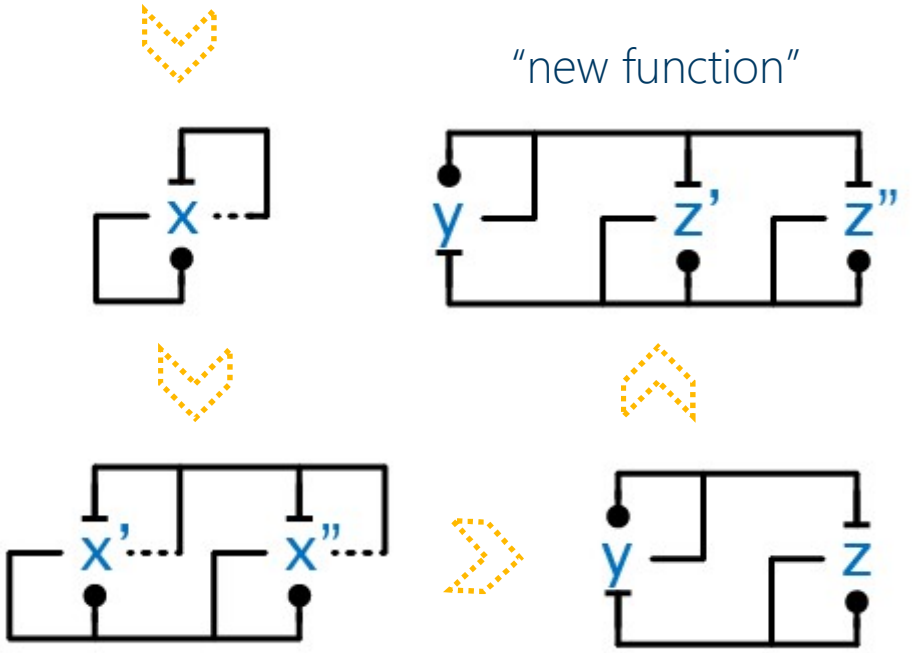
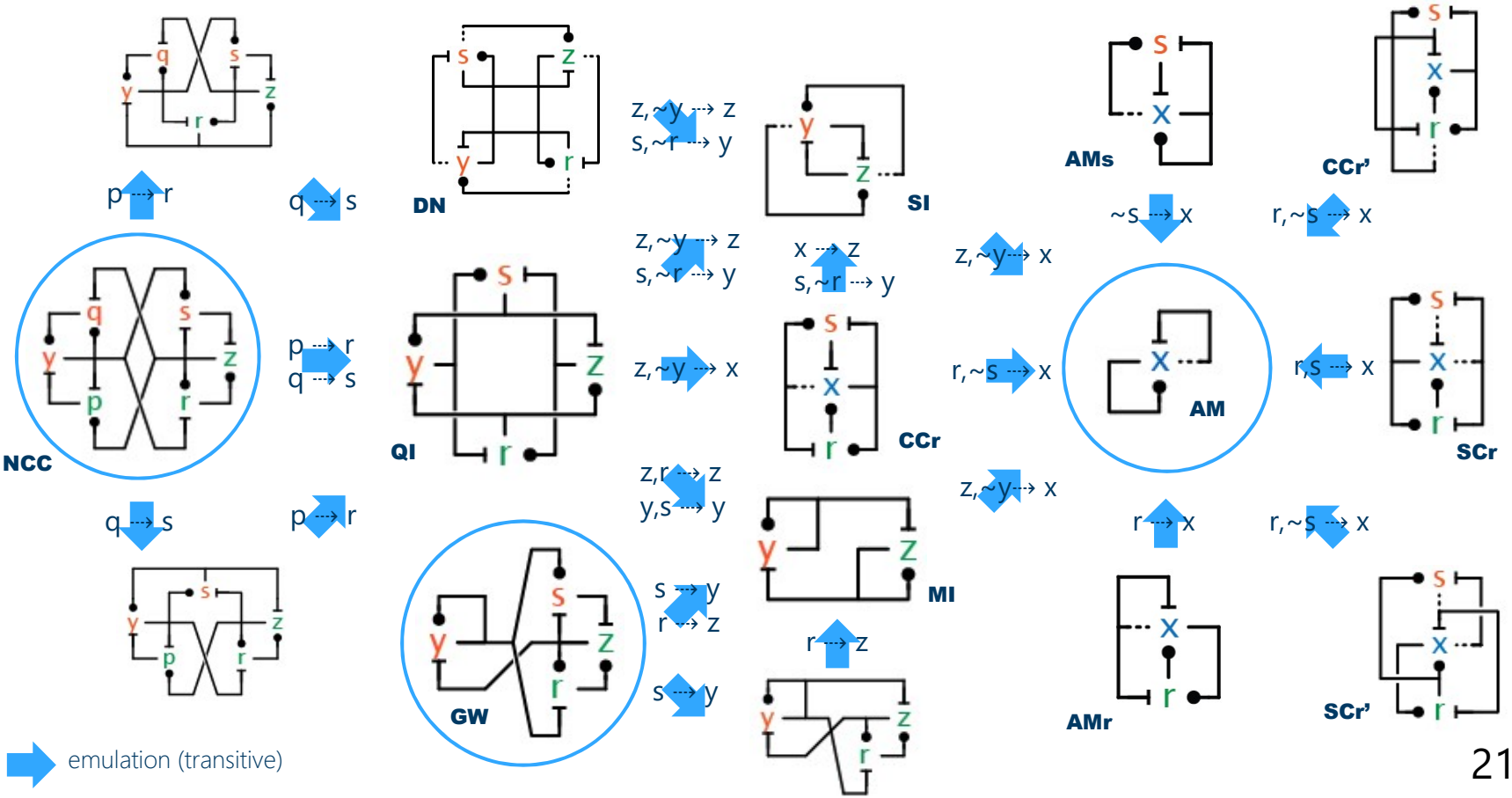
Network Morphisms as Evolutionary Paths

Network Evolution

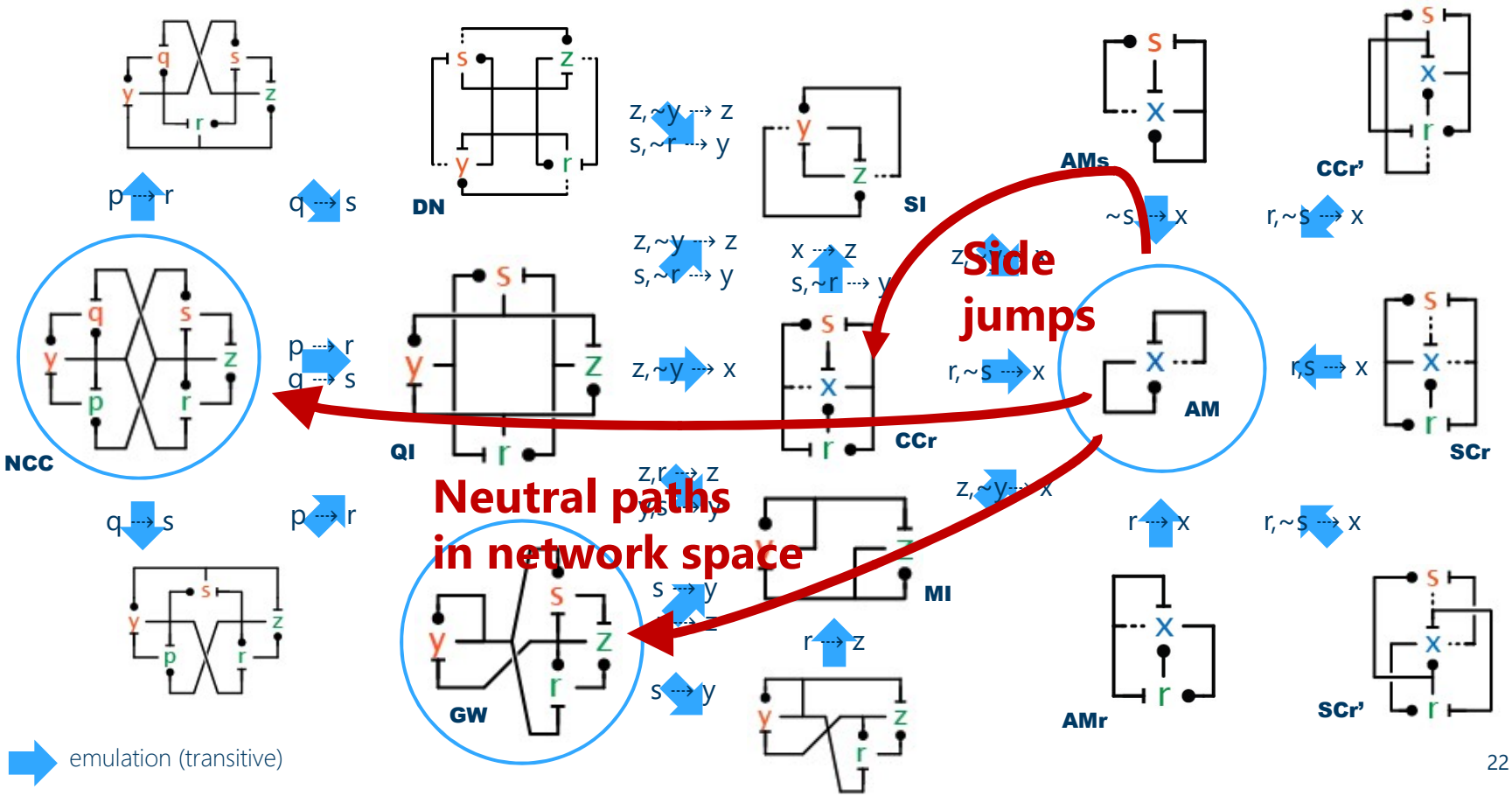




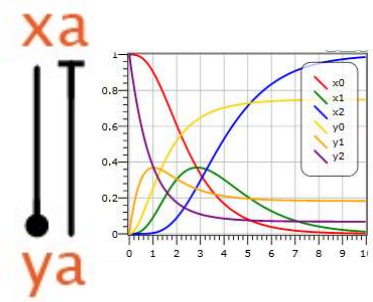
Emulation Zoo



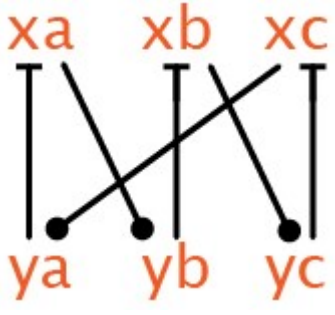
Walks in Network Space

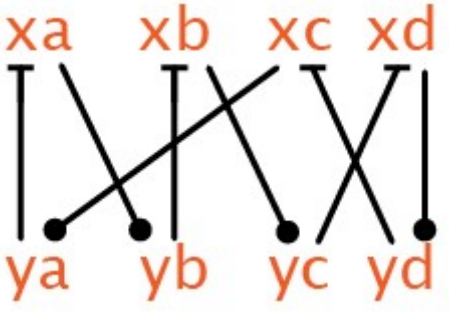


Another Zoo


xa
ya
x0
x1
x2
y0
y1
y2


xa xb
ya yb


xa xb xc
ya yb yc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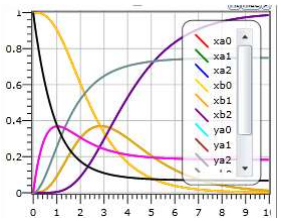
ya yb yc yd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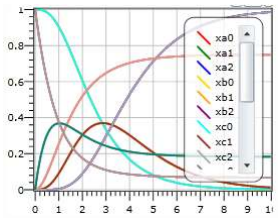
xa1
xa2
xb0
xb1
xb2
ya0
ya1
ya2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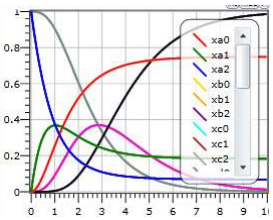
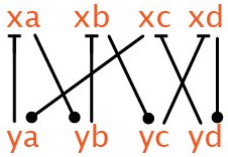
xc1
xc2


xa0
xa1
xa2
xb0
xb1
xb2
xc0
xc1
xc2

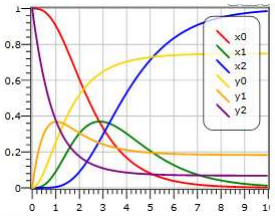
Network Perturbations

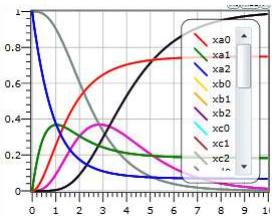
Network



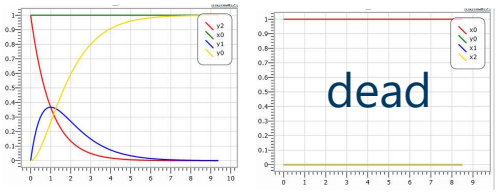
A complex but robust implementation of the simple network

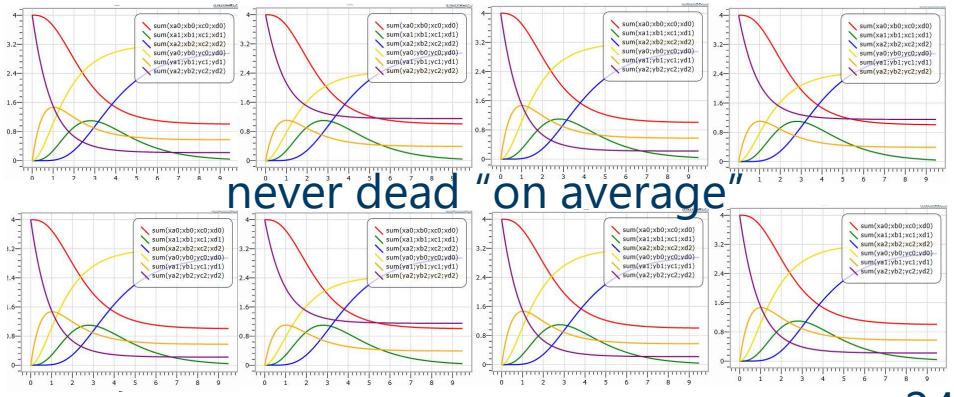
Normal Behavior





Removing each link in turn





never dead “on average”

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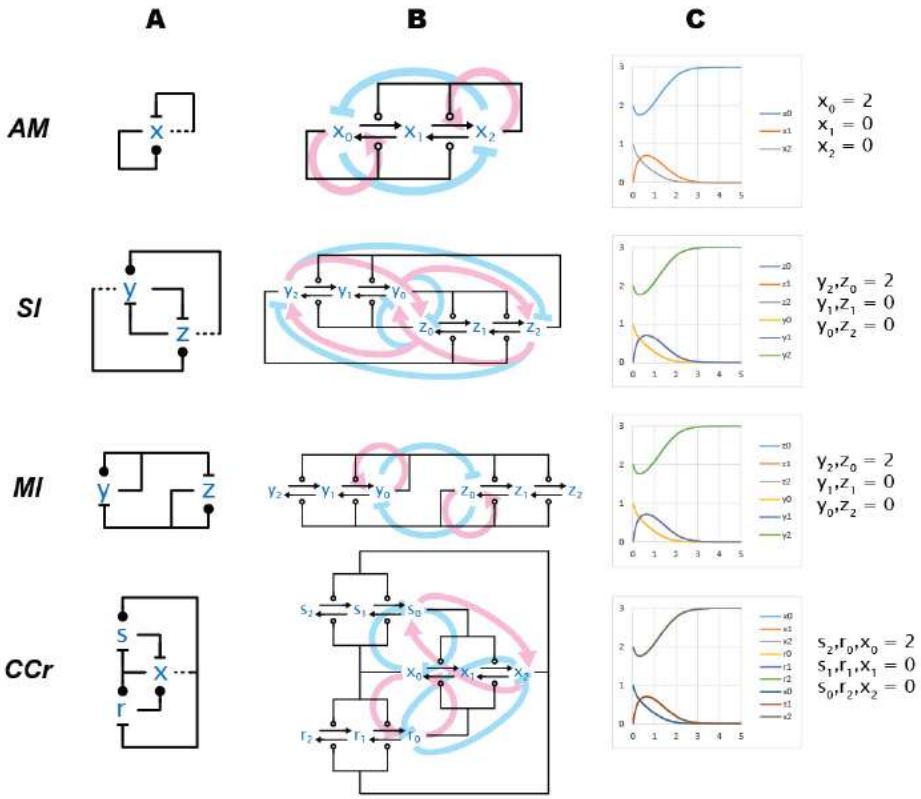
Noise Reduction in Biochemical Switches

Basic Switches (deterministic)



(A) Influence network diagrams

(B) Chemical reaction network diagrams and feedback loops

(C) Numerical solutions of the deterministic kinetics of the networks:
Horizontal axis is time
Vertical axis is species concentration

First some arbitrary initial conditions are chosen for AM.

Then the initial conditions of the other networks are chosen in such a way that each trace of each of the other networks retraces exactly one trace of AM.

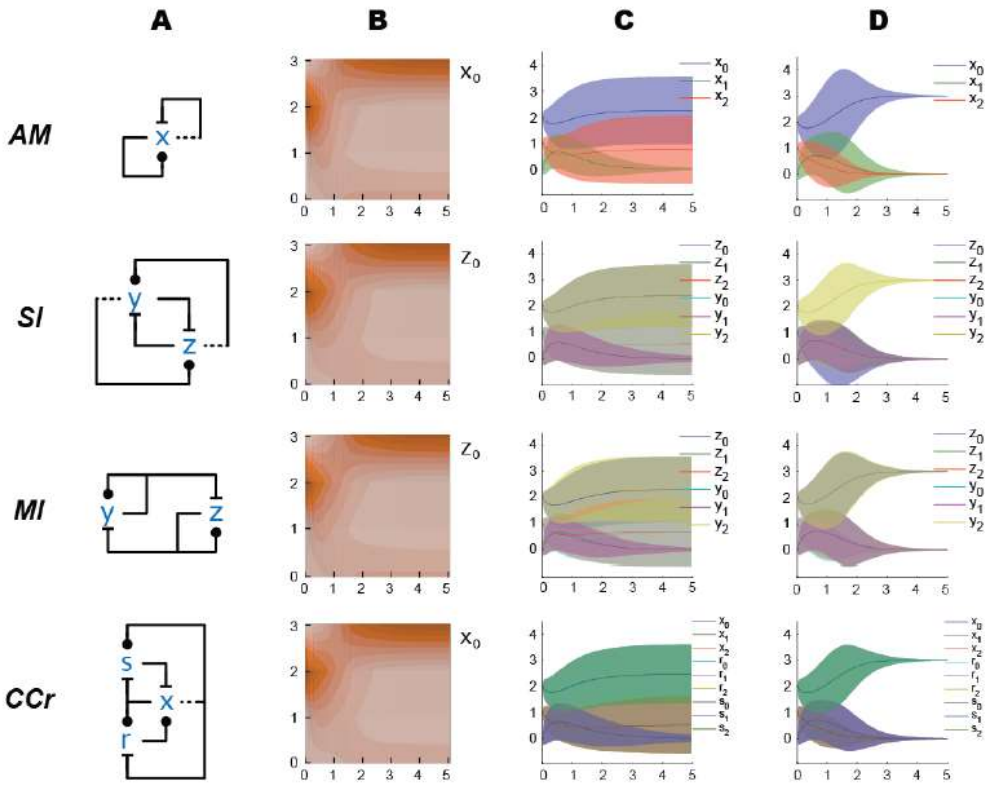
This can be done for any initial conditions chosen for AM, and indicates the potential of each of the other networks to operate as a simpler switch.

Noise Reduction in Complex Biological Switches

Luca Cardelli[1,2,¶,*], Attila Csikász-Nagy[3,4,¶], Neil Dalchau[1,¶], Mirco Tribastone[5,¶], Max Tschaikowski[5,¶]

(To appear.)

Basic Switches (stochastic)



Horizontal axes is time

Vertical axes is number of molecules.

(A) Influence networks.

(B) Chemical Master Equation solution: probability distribution, with color (in 10 bands from light = 0 to dark = 1) indicating the probability that at time t there are y molecules of the single indicated species.

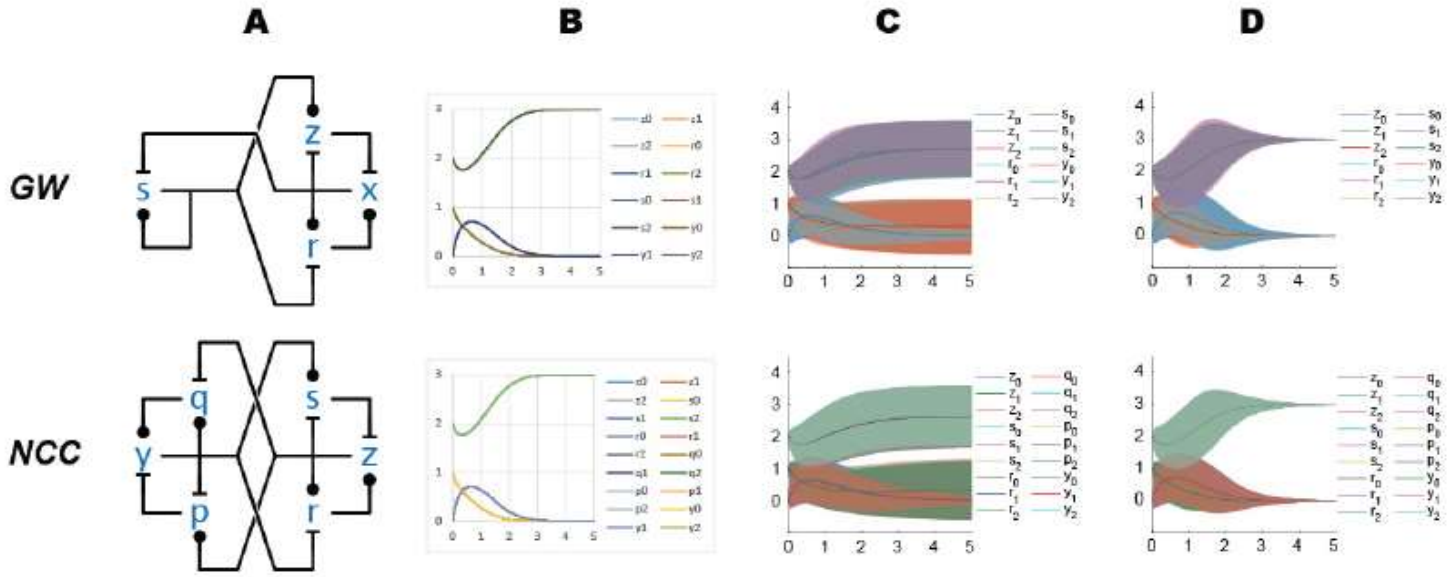
(C) Chemical Master Equation solution: mean (solid lines) and standard deviation (color bands) for the species in the network.

(D) Central Limit Approximation solution: mean (solid lines) and standard deviation (color bands) for the species in the network.

Disentangle the contribution of complexity to stochasticity

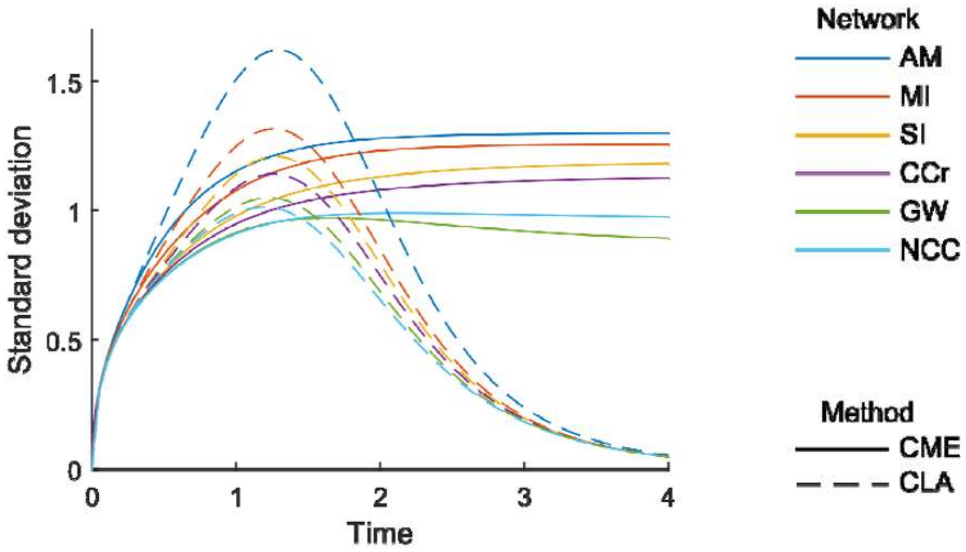
Compare network noise on the baseline of deterministic emulation, across networks of different size and structure

More Complex Switches



Horizontal axes are time, vertical axes are number of molecules.
(A) Influence networks.
(B) ODE solutions for comparison
(C) Chemical Master Equation solution: mean (solid lines) and standard deviation (color bands) for the species in the network.
(D) Central Limit Approximation solution: mean (black lines) and standard deviation (color bands) for the species in the network.

Intrinsic Noise



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Noise Reduction in Complex Biological Switches

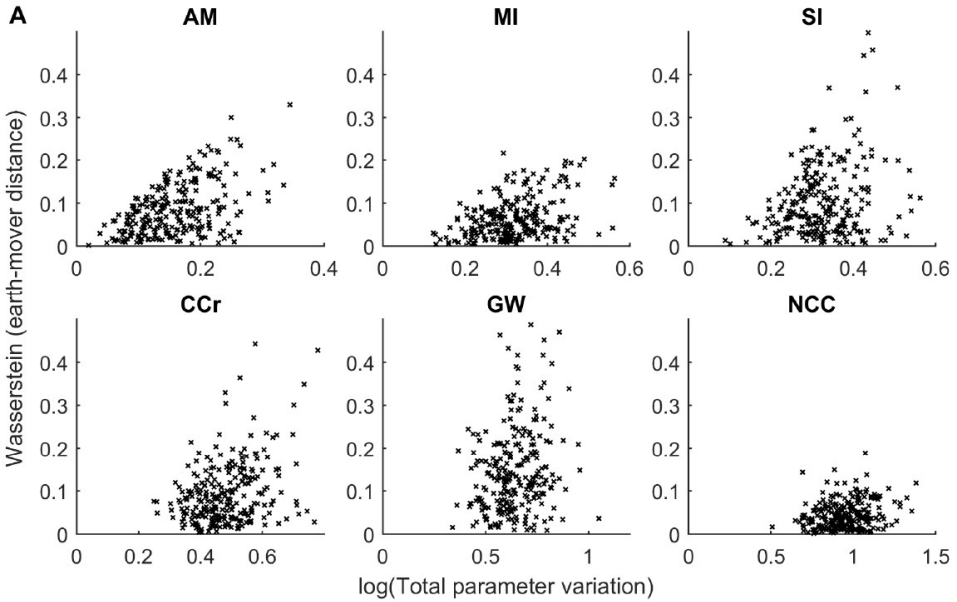
Luca Cardelli, Attila Csikász-Nagy, Neil Dalchau, Mirco Tribastone & Max Tschaikowski

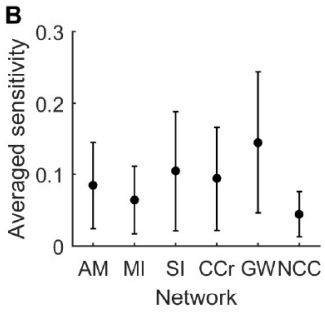
Scientific Reports **6**, Article number: 20214 (2016)
doi:10.1038/srep20214

Received: 21 August 2015
Accepted: 29 December 2015
Published online: 08 February 2016

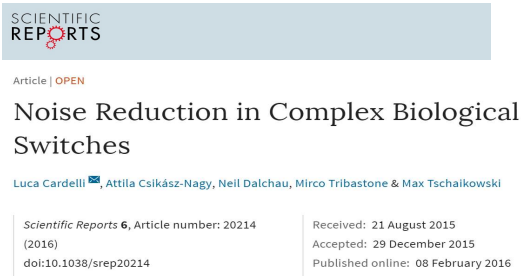
Complexity improves overall performance of the cell cycle switch. The performance of different networks was evaluated by calculating the standard deviation of the main molecular states over time.
Standard deviations are calculated via numerical integration of the chemical master equation (CME) using the Visual GEC software, and via numerical integration of the central limit approximation (CLA) in Matlab.

Extrinsic Noise





MI and SI have the same number of species and reactions.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Complexity *can* confer robustness to extrinsic noise.

Extrinsic noise is introduced by randomly perturbing all the reaction rates (separately but from the same distribution) of each model. (So the total variation in more complex models is actually *higher*.)

Variations in network behaviour is assessed in comparison to the default parameters, in which allr eaction rates are set equal to 1.

Network variation is quantified using the summed Wasserstein metric over the whole probability distribution over time.

Noise vs. Complexity

- With corresponding initial conditions, all studied networks show the same mean behavior
- CCr emulating AM is the simplest explanation of the core cell cycle switching function
- Many other biological switches can be so reduced to an algorithm with well-understood properties
- On the basis of kinetic similarity of mean behavior, we show variations in noise behavior (both intrinsic and extrinsic).
- Noise tends to decrease with complexity, but this also depends on network structure and *not* directly on total molecular counts

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Conclusions

Networks are Algorithms

- They are *methods* for achieving a function
  - We need to understand how these methods relate to each other
  - In addition to how and how well they implement function
  - Algorithms can be obfuscated, and nature can obfuscate networks
- Network emulation can be checked *statically*
  - By stoichiometric/reaction-rate (*structural*) properties
  - That is, no need to compare ODE (*functional*) properties
  - For *any* initial conditions and rates of (one of) the networks
- We can efficiently discover emulations
  - Automatic model reduction of large networks

Interpretations of Network Morphisms

- Explanation of network structure
  - E.g. we know that the main function of Delta-Notch is to stabilize the system in one of two states. AM is the quintessential network that embodies fast robust bistability. The stoichiomorphism from Delta-Notch to AM "explains" what Delta-Notch (normally) does, and exactly how well it can do it.
- Robust implementation of simpler function
  - Redundant symmetries are implicit in the stoichiomorphism relationships
- Neutral paths in network space (evolution)
  - If an evolutionary event happens to be a stoichiomorphism, or close to it, it will not be immediately selected against, because it is "kinetically neutral".
  - This allows the network to increase its complexity without kinetic penalty.
  - Later, the extra degrees of freedom can lead to kinetic differentiation.
  - But meanwhile, the organism can explore variations of network structure.
- Network refinement
  - Emulations are not about abstraction / coarse-graining that preserve behavior, on the contrary, they are about *refinement* / *fine-graining* that preserve behavior.
  - They map out *successive refinements* of simple networks.

Network Emulation Morphism FAQ

- What guarantees emulation?
  - Reactant morphism + stoichiomorphism: static, state-independent (*structural*) conditions
- How do you find them?
  - Emulation Theorem => they do not depend on initial conditions
  - Change of Rates Theorem => can look for rate-1 morphisms
  - E.g. test all possible rate-1 homomorphism between two networks to see if they are stoichiomorphisms
- How common are they?
  - Likely relatively rare, but still many useful ones => richness of networks space
  - Approximate emulations exist too
- How useful are they?
  - Establish structural, algorithmic, (non-accidental) *reasons* for kinetic similarity
  - Explain simple behavior "facets" of complicated networks
  - Investigate evolutionary paths (maybe)
- How brittle are they?
  - Will a perturbed trajectory of the source network converge to a trajectory of the target network?
  - What about other reaction kinetics?