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Biochemical Algorithms

Luca Cardelli, Microsoft Research & Oxford University

related work: Attila Csikász-Nagy, Neil Dalchau, Mirco Tribastone, Max Tschaikowski, Andrea Vandin

IMT Lucca, 2017-03-30

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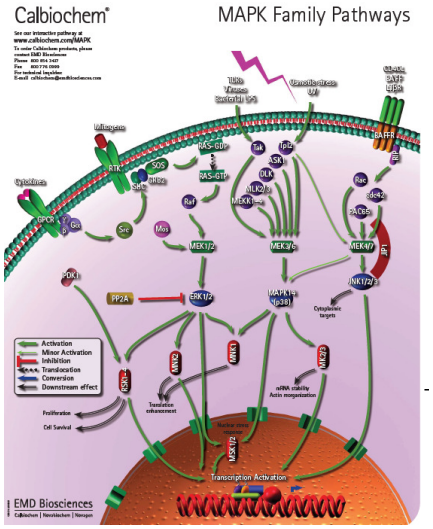
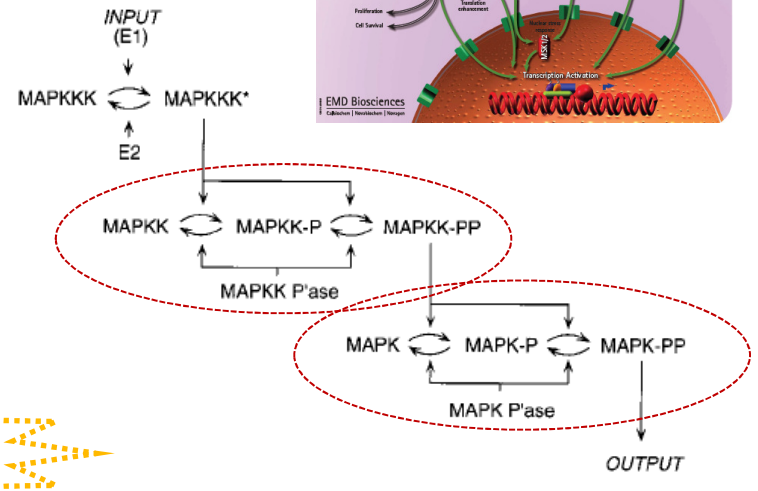
Introduction

Cellular Computation

- No survival without computation!
  - Finding food
  - Avoiding predators
- How do cells compute?
  - *Clearly* doing "information processing"
  - What are their computational principles?
  - What are their algorithms?

Computer Science!

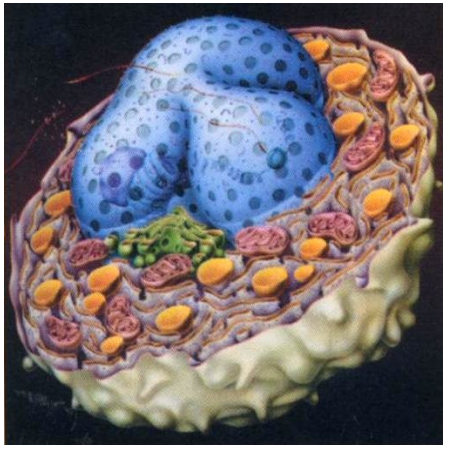




Ultrasensitivity in the mitogen-activated protein cascade, Chi-Ying F. Huang and James E. Ferrell, Jr., 1996, *Proc. Natl. Acad. Sci. USA*, 93, 10078-10083.

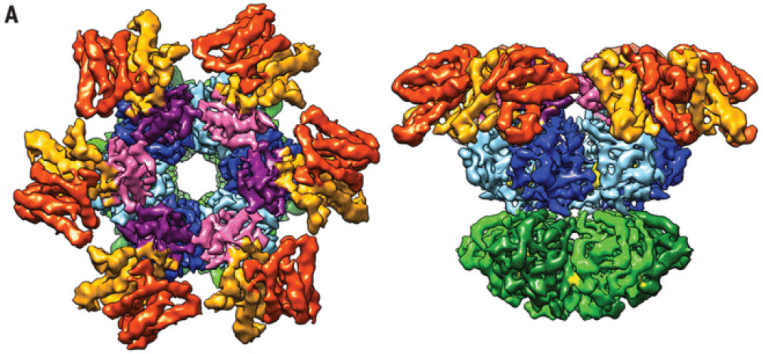
More concretely

- Give substance to the claim that "cells compute"
  - Yes, but *what* do they compute?
- Catch nature red-handed in the act of running a computational task
  - Something that a computer scientist would recognize as an *algorithm*



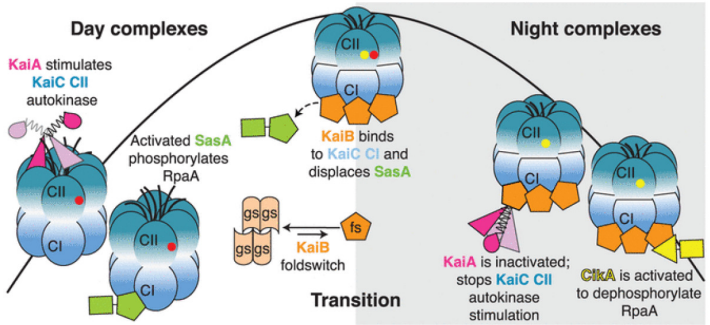
Reality is Complicated

- *Every* biochemical species that we may just call "X" is actually a sophisticated machine that has evolved for billions of years



Structures of the cyanobacterial circadian oscillator frozen in a fully assembled state

Joost Snijder,[1*†] Jan M. Schuller,[2*‡] Anika Wiegard,[3] Philip Lössl,[1] Nicolas Schmelling,[3] Ilka M. Axmann,[3] Jürgen M. Plitzko,[2] Friedrich Förster,[2,4§] Albert J. R. Heck[1§]



Structural basis of the day-night transition in a bacterial circadian clock

Roger Tseng,[1*] Nicolette F. Goularte,[2*] Archana Chavan,[3*] Jansen Luu,[2] Susan E. Cohen,[4] Yong-Gang Chang,[3] Joel Heisler,[6] Sheng Li,[7] Alicia K. Michael,[2] Sarvind Tripathi,[2] Susan S. Golden,[4,5] Andy LiWang,[1,3,4,6,8†] Carrie L. Partch[2,4†]

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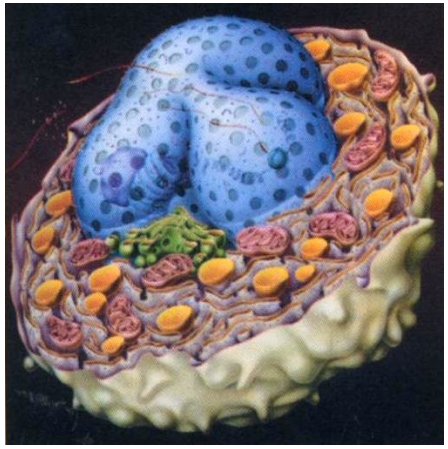
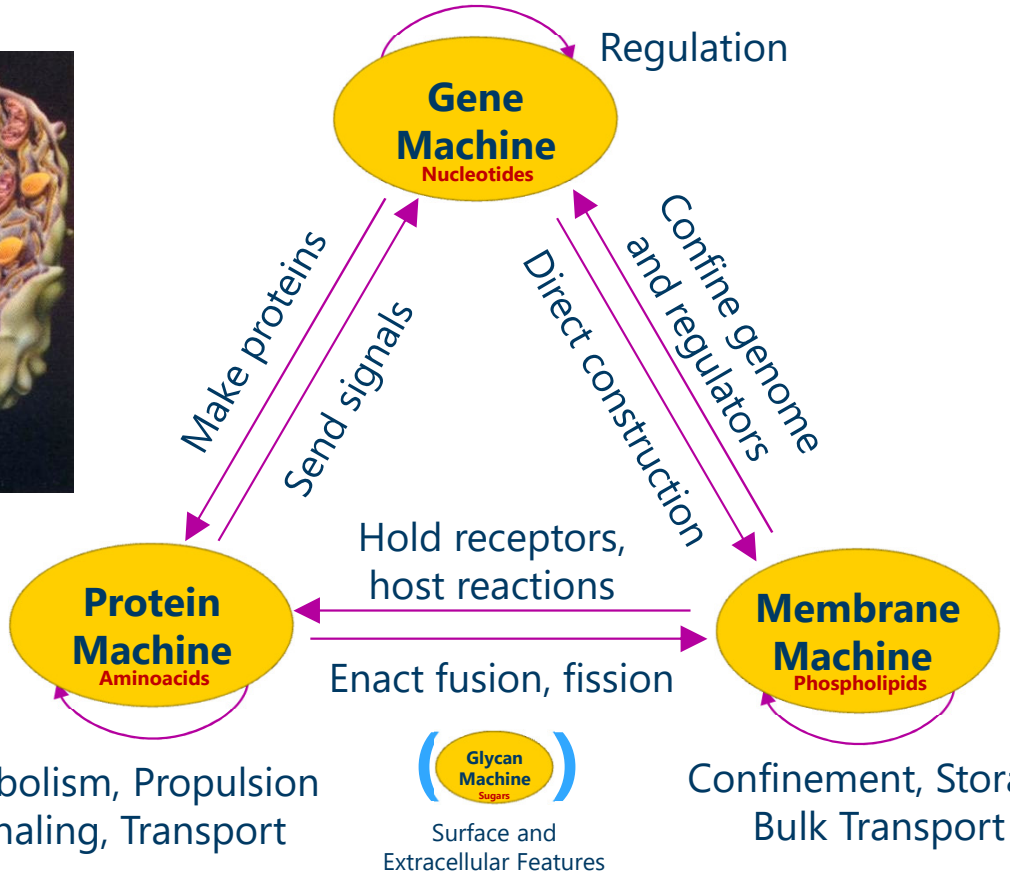
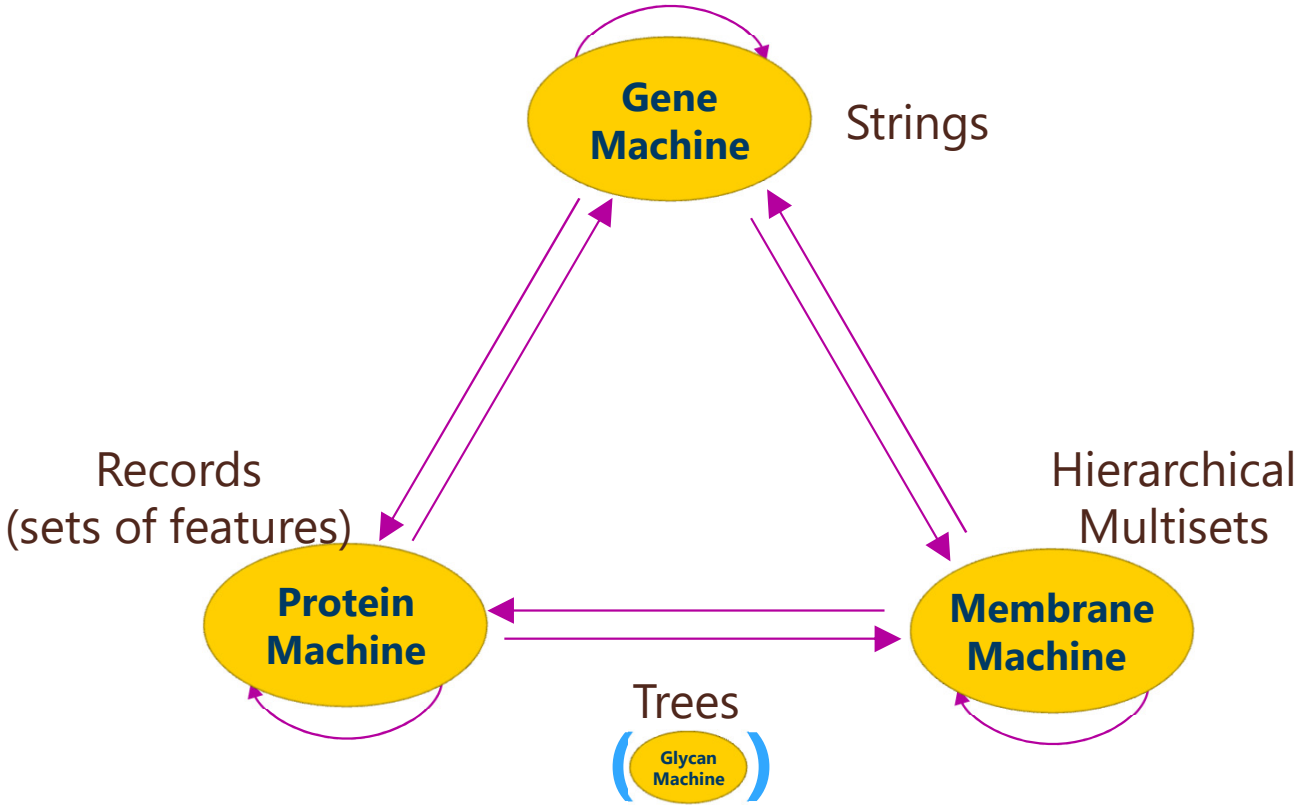
Biochemical Networks

Abstract Machines of Biochemistry

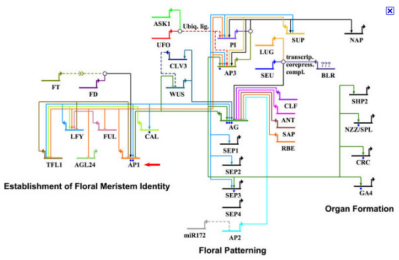




Bioinformatics View (Data Structures)



Systems Biology View (Networks)

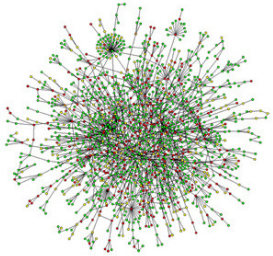


Gene Machine

Gene Regulatory Networks

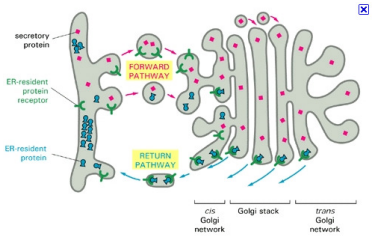
Biochemical Networks

Transport Networks

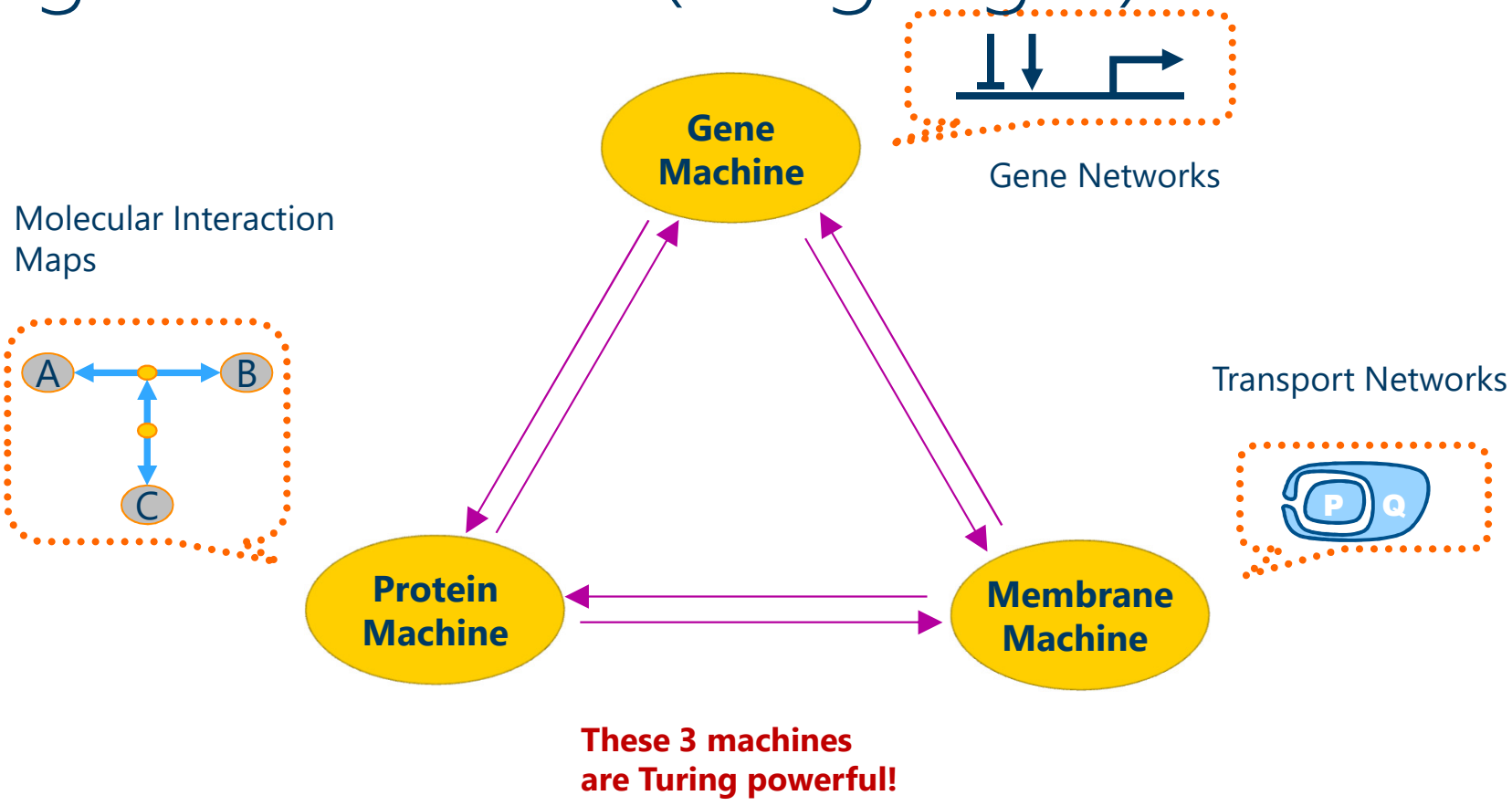


Protein Machine

Membrane Machine

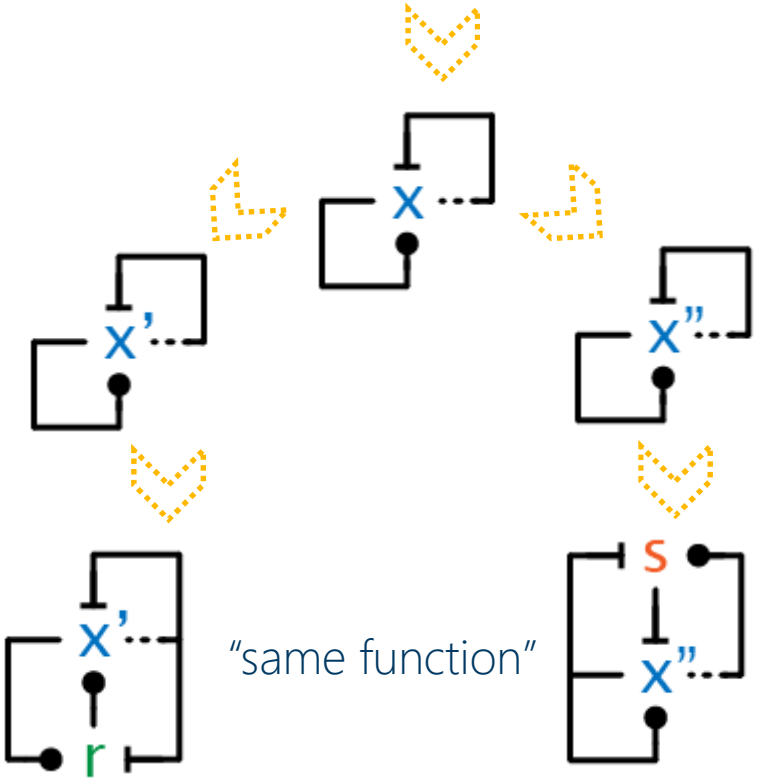


Algorithmic View (Languages)

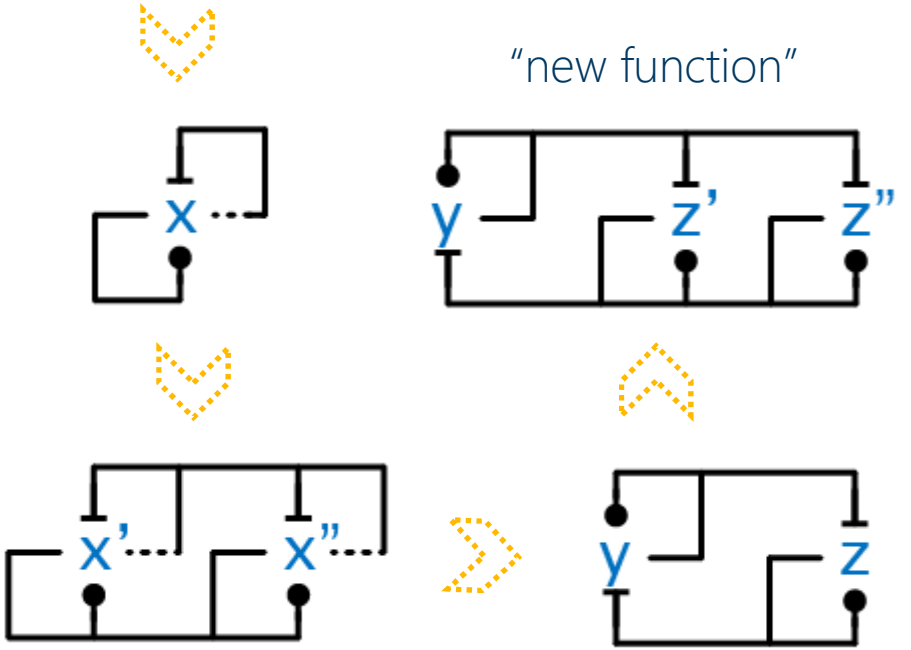


Network Evolution

Across species: *Ortholog genes*



Within species: *Paralog genes*



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Influence Networks

How to model "Influence"

"True" molecular interactions.

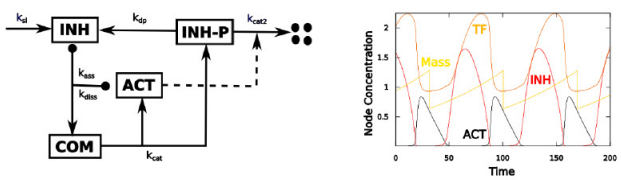


Figure 3: a) Schematic diagram of a simplified SIMM model [17]. The activa-

"Equivalent" influence interactions.

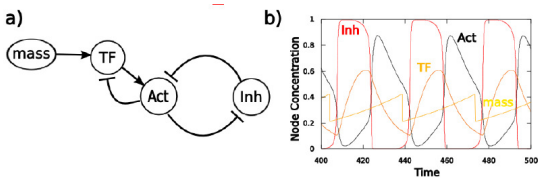


Figure 4: a) Schematic diagram of a primitive cell cycle in the reinitz framework.

Chemical Reaction Network ⟷ Influence Network

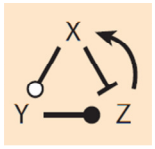
Evolving a Primitive Eukaryotic Cell Cycle Model

Malte Lücken, Jotun Hein, Bela Novak

Instead of modeling basic interactions, such as binding, synthesis, and degradation of molecular components, this framework models interactions simply as activation or inhibition. This approach also reduces the number of nodes necessary in the network, as e.g. the inhibitor binding tightly to the activator to form a complex, which produces phosphorylated inhibitor to be degraded under catalysis by the activator, is now simply a double negative feedback loop shown in Figure 1. This type of interaction is the basis of both aforementioned molecular model, therefore they can both be summarized in a single Reinitz model.

The Reinitz Model of Influence

- Based on early connectionist (neural network) modeling
  - Each activation/inhibition interaction is modeled as a flexible sigmoid function with 4+ parameters per node



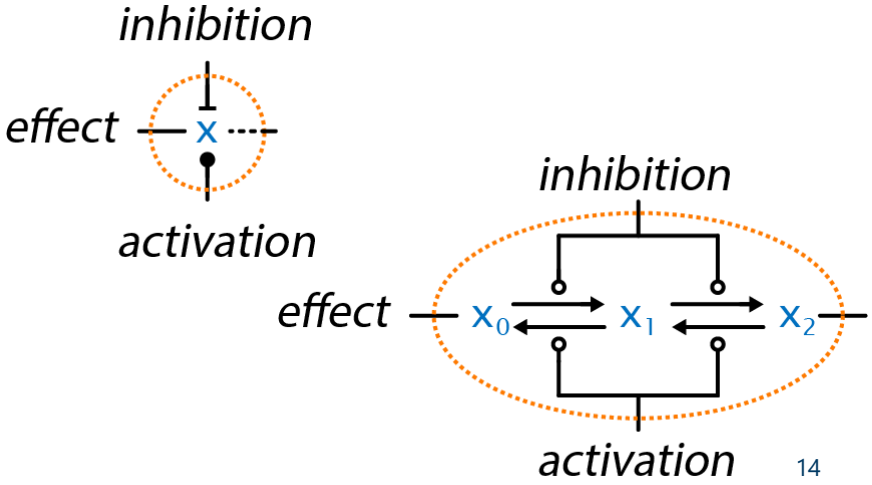
Functional Motifs in Biochemical Reaction Networks

John J. Tyson[1] and Béla Novák[2]

$$\frac{dX_i}{dt} = \gamma_i \frac{[A_i(1 - X_i) - B_i X_i]}{A_i + B_i}, \quad i = 1, \ldots, N,$$

$$A_i = \exp\left\{\sigma_i\left(\alpha_{i0} + \sum_{j=1}^{N} \alpha_{ij} X_j\right)\right\}, \quad B_i = \exp\left\{\sigma_i\left(\beta_{i0} + \sum_{j=1}^{N} \beta_{ij} X_j\right)\right\}. \tag{4}$$

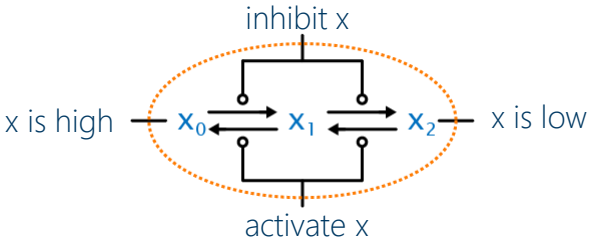
- We prefer to stick to mass action kinetics
  - It will later become clear why
- We model activation/inhibition nodes by a mass action motif:
  - Using 4 rate parameters per node
  - Akin to multisite modification



The Triplet Model of Influence

activation
inhibition
catalysis

=



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

Functional Motifs in Biochemical Reaction Networks

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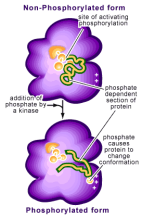
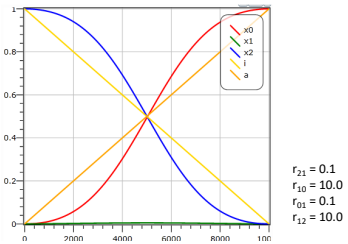
biological mechanism:
(e.g.:) multisite phosphorylation



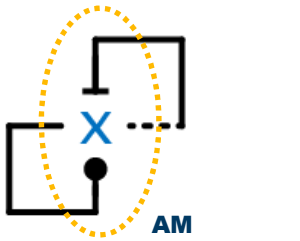
triplet motif

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:



For example:



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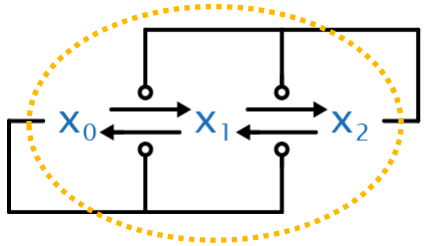
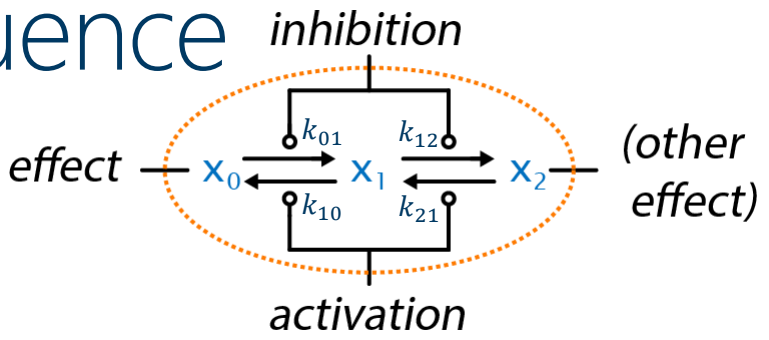


Approximate Majority

The Triplet Model of Influence



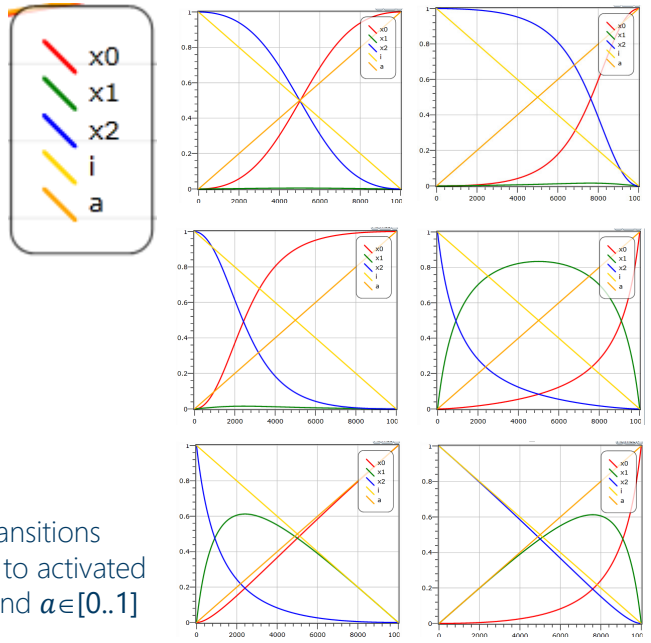
- Solving this mass action model at steady state with $tot = x_0 + x_1 + x_2$, obtain x_0 as a function of a and i :

$$x_0 = \frac{k_{10}k_{21}tot\ a^2}{k_{10}k_{21}a^2 + k_{01}k_{21}ai + k_{01}k_{12}i^2}$$

- Assuming $i = tot - a$ (inhibition decreases as activation increases) obtain x_0 as a function of $a \in [0..tot]$ (max stimulus = max response)

$$x_0 = \frac{k_{10}k_{21}tot\ a^2}{(k_{10}k_{21} - k_{01}k_{21} + k_{01}k_{12})a^2 + (k_{01}k_{21} - 2k_{01}k_{12})tot\ a + k_{01}k_{12}\ tot^2}$$

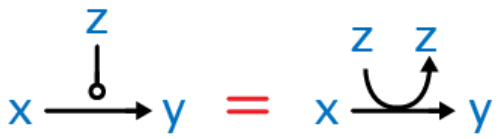
- By regulating the rates of flow through x_1 within 2 orders of magnitude we can obtain a range of linear, hyperbolic and sigmoid responses in the range [0..1] to linear activation $a \in [0..1]$.



steady state transitions from inhibited to activated with $tot = 1$ and $a \in [0..1]$

Influence Network Notation

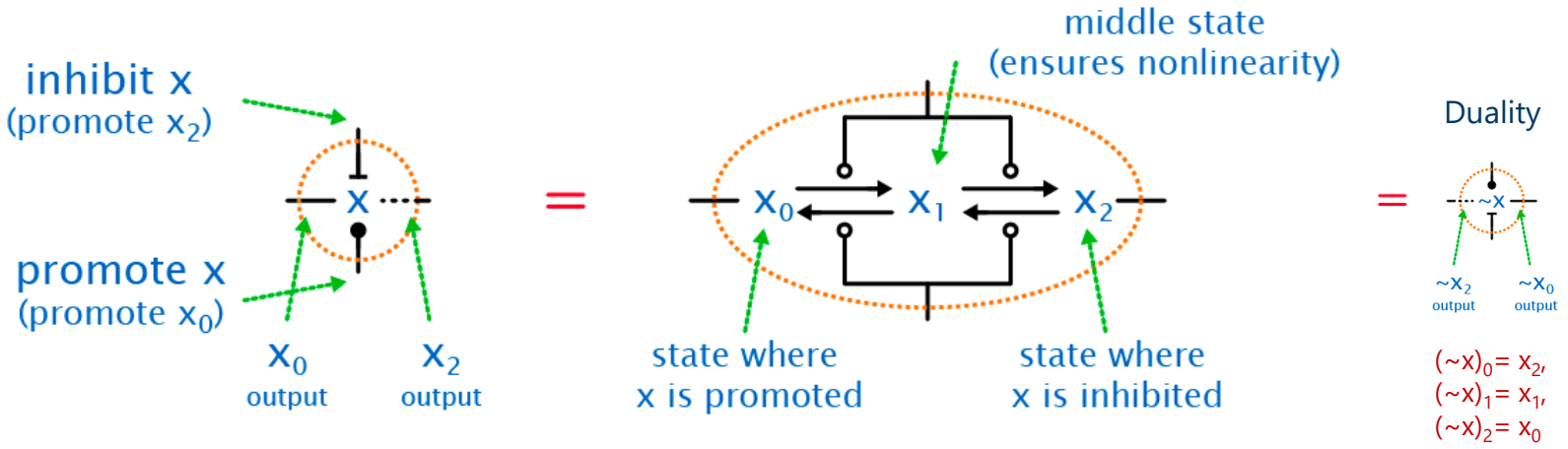
- Catalytic reaction



z is the catalyst

$x + z \rightarrow z + y$

- Triplet motif



influence node catalytic node

Influence Network Duality

- Let ~x be the species such that

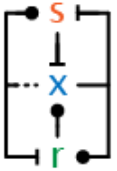
  $(\sim x)_0 = x_2$, $(\sim x)_1 = x_1$, $(\sim x)_2 = x_0$

  so that promoting x is the same as inhibiting ~x etc. Then:

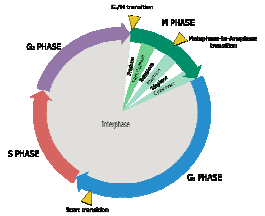
Network model

- Influence networks
  - Influence species: two main molecular states (high/low or modified/unmodified)
  - High-low transitions are nonlinear (e.g. sigmoidal)
  - Transition kinetics may vary (but we fix one uniformly)

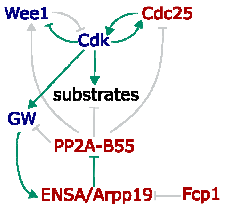
Nodes



Ex.: a cell cycle switch model



G_2/M Transition



  - Very much like gene regulatory networks, but with the extra option of the "unmodified" state being active too

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Consensus Networks

A Consensus Problem

- Population Consensus
  - Given two populations of x and y "agents"
  - We want them to "reach consensus"
  - By converting *all* agents to x or to y depending on which population was in majority initially
- Population Protocols Model
  - Finite-state identity-free agents (molecules) interact in randomly chosen pairs ($\Rightarrow$ stochastic symmetry breaking)
  - Each interaction (collision) can result in state changes
  - Complete connectivity, no centralized control (well-mixed solution)

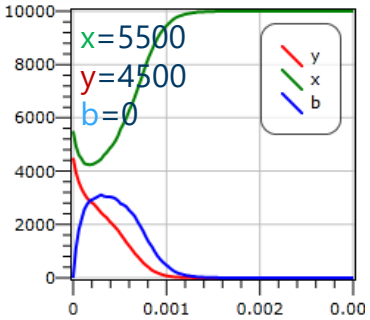
specification

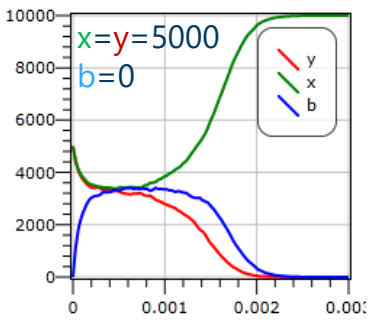
$X,Y := X+Y, 0 \quad \text{if} \quad X_0 \geq Y_0$

$X,Y := 0, X+Y \quad \text{if} \quad Y_0 \geq X_0$

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





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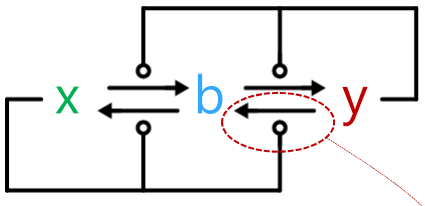
A Simple Population Protocol for Fast Robust Approximate Majority

catalysis



chemical reaction network

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

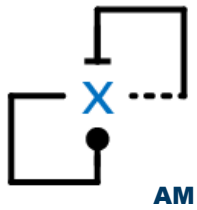
$y + x \to^r x + b$

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

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

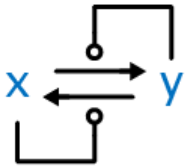
activation

inhibition



Consensus Algorithms

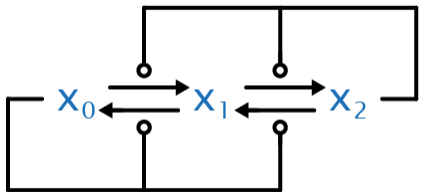
Direct Competition



DC

$x + y \rightarrow y + y$
$y + x \rightarrow x + x$

Approximate Majority

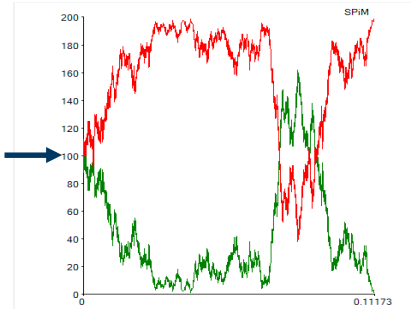


AM

$x_2 + x_0 \rightarrow x_0 + x_1$
$x_1 + x_0 \rightarrow x_0 + x_0$
$x_0 + x_2 \rightarrow x_2 + x_1$
$x_1 + x_2 \rightarrow x_2 + x_2$

Bad: O(n)

x=y



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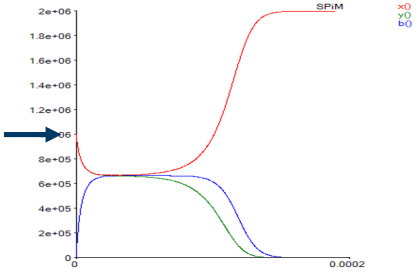
A Simple Population Protocol for Fast Robust Approximate Majority

Good: O(log n)

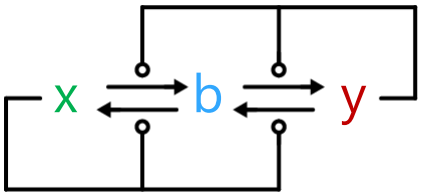
$x_0=x_2$



Worse-case scenario example, starting with $x_0=x_2$, $x_1=0$:

A Biological Implementation

Approximate Majority (AM)



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

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

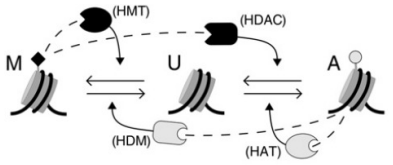
3) Robust to perturbation
   above a threshold, initial majority wins *whp*

Dana Angluin · James Aspnes · David Eisenstat

A Simple Population Protocol for Fast Robust Approximate Majority

2007

Epigenetic Switch



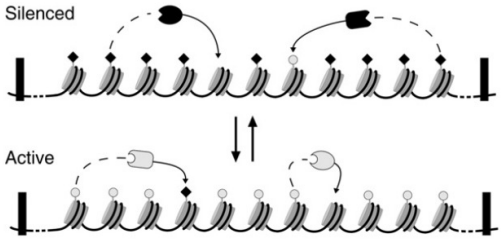
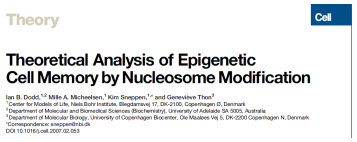


Figure 1. Basic Ingredients of the Model


Theory

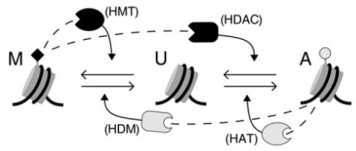
Cell

Theoretical Analysis of Epigenetic Cell Memory by Nucleosome Modification

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

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Antagonistic Networks

Antagonistic Networks

- Let's generalize:
  - AM is based on antagonism between two species (inside the triplet)
  - So (essentially) are many standard biological networks
- Are they somehow related?
  - We could try the same empirical analysis as for CC/AM
  - But we can do better

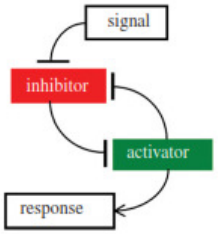
Mutual Inhibition (1 vs. 1)

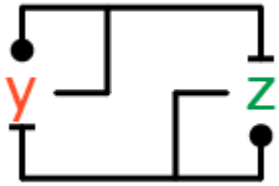
- "All" cellular switches in all phases of the cell cycle follow (abstractly) a mutual inhibition pattern:

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





MI

- Also found in other areas (cell polarity establishment):

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B

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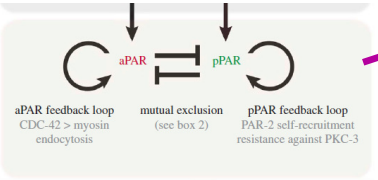
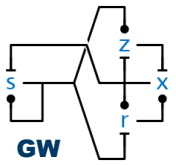
The PAR network: redundancy and robustness in a symmetry-breaking system

Fumio Motegi[1,2,3] and Geraldine Seydoux[4]

[1]Temasek Lifesciences Laboratory, [2]Mechanobiology Institute, and [3]Department of Biological Sciences, National University of Singapore, 1 Research Link, Singapore 117604, Republic of Singapore
[4]Department of Molecular Biology and Genetics and HHMI, Johns Hopkins University School of Medicine, Baltimore MD 21205, USA



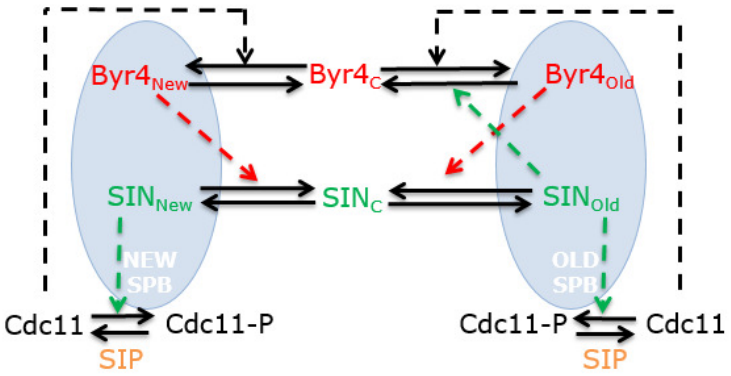
cf.:



GW

Septation Initiation (1 vs. 1)

- Other (inherently different) biological networks are based on mutual inhibition, and share characteristics with AM



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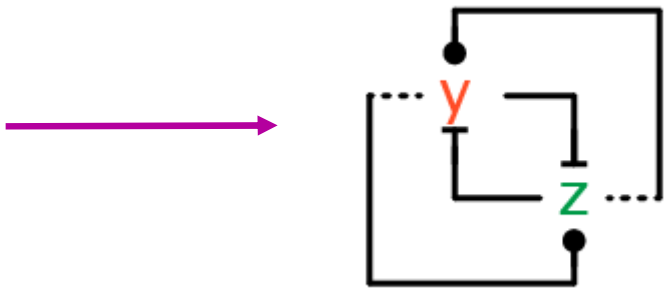
PLOS | COMPUTATIONAL BIOLOGY

Dynamics of SIN Asymmetry Establishment

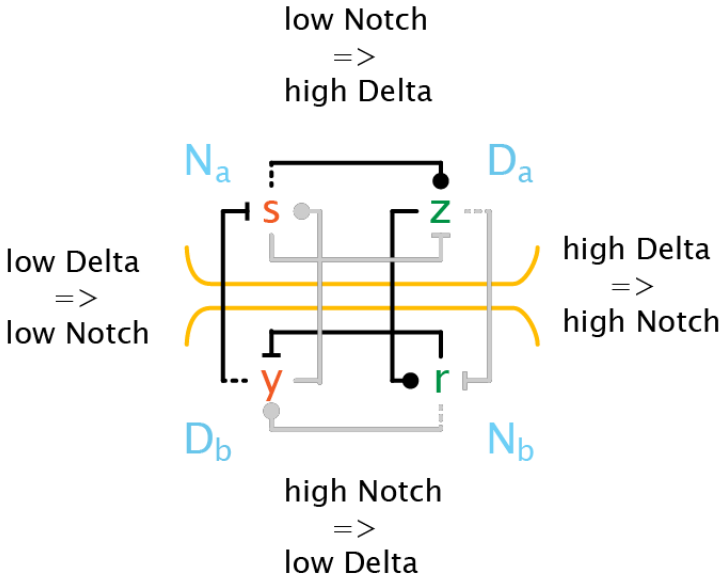
Archana Bajpai[1], Anna Feoktistova[2], Jun-Song Chen[2], Dannel McCollum[3], Masamitsu Sato[4,5], Rafael E. Carazo-Salas[6], Kathleen L. Gould[2], Attila Csikász-Nagy[1,7,8*]



SIN inhibiting Byr4,
absence of SIN promoting Byr4
Byr4 inhibiting SIN,
absence of Byr4 promoting SIN

Delta-Notch (2 vs. 2)

- A mutual inhibition pattern
  - Involving *two* species in each cell
- In two cells a,b
  - D_a,N_b antagonize D_b,N_a



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.
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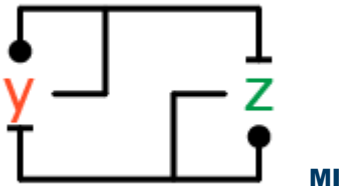
Antagonistic Networks

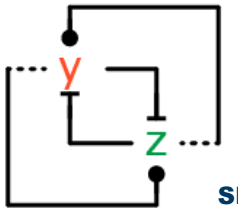
activation
inhibition

1 vs. 1
Mutual Inhibition & Self Activation



MI

1 vs. 1
Mutual Inhibition & Mutual Anti-activation



SI

Cell cycle transitions

Molecular mechanisms creating bistable switches at cell cycle transitions

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

Polarity establishment

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B

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

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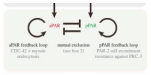
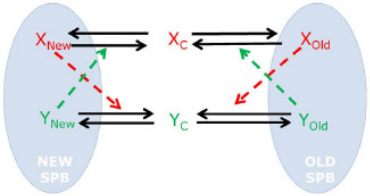


Gene networks

Construction of a genetic toggle switch in *Escherichia coli*

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

Septation Initiation



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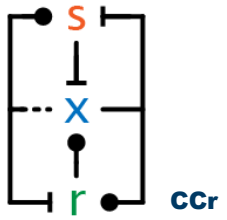
PLOS Computational Biology | www.ploscompbiol.org 1 July 2013 | Volume 9 | Issue 7 | e1003147

Antagonistic Networks

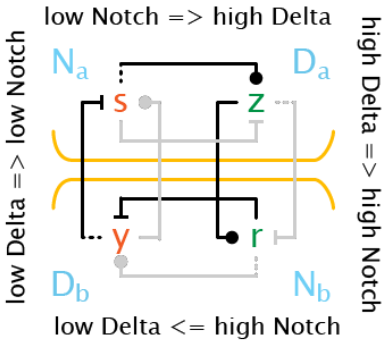
activation
inhibition

1 vs. 2

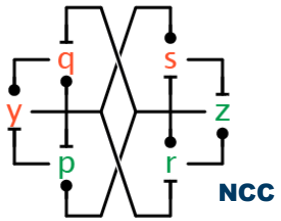


CCr

2 vs. 2

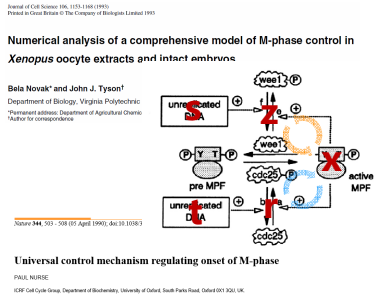


3 vs. 3



NCC

The G_2/M cell cycle switch



Numerical analysis of a comprehensive model of M-phase control in *Xenopus* oocyte extracts and intact embryos

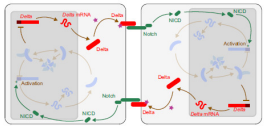
Bela Novak* and John J. Tyson†

Department of Biology, Virginia Polytechnic

Universal control mechanism regulating onset of M-phase

PAUL NURSE

Delta-Notch



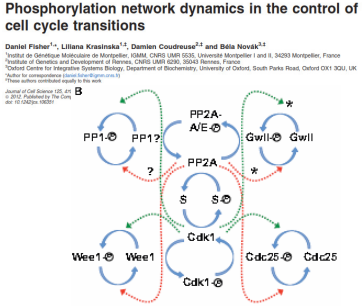
Patterning embryos with oscillations: structure, function and dynamics of the vertebrate segmentation clock

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

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

Ronojoy Ghosh and Claire J. Tomlin

The "new" cell cycle switch



Phosphorylation network dynamics in the control of cell cycle transitions

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

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The Cell Cycle Switch

Decisions, decisions…

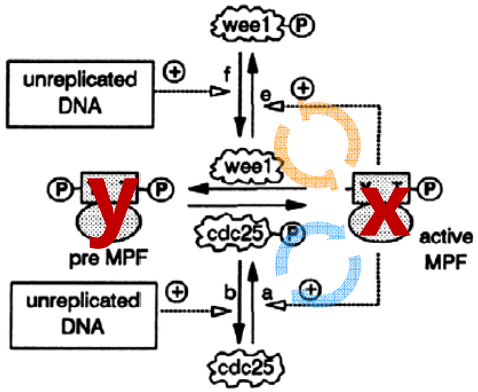
- The AM algorithm has ideal properties for settling a population into one of two states
- Seems like this would be useful in Biology
  - Can we find biological implementations of this algorithm?
  - Could it be related to the cell cycle switch?

The Cell Cycle Switch

Universal control mechanism regulating onset of M-phase

Paul Nurse

- This basic network is universal in Eukaryotes [P. Nurse]
  - The *switching function* and the *basic network* is *the same* from yeast to us.
  - In particular detail, in frog eggs, G_2/M transition:



Double positive feedback on x
Double negative feedback on x
No feedback on y. Why ???

Journal of Cell Science 106, 1153-1168 (1993)
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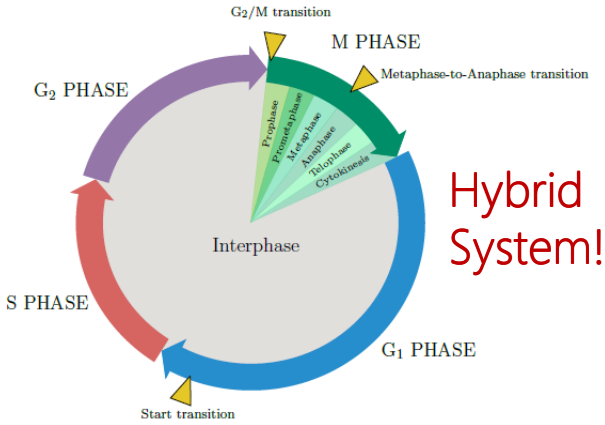
Numerical analysis of a comprehensive model of M-phase control in *Xenopus* oocyte extracts and intact embryos

Bela Novak* and John J. Tyson†
Department of Biology, Virginia Polytechnic Institute and State University, Blacksburg, Virginia 24060-0406, USA
*Permanent address: Department of Agricultural Chemical Technology, Technical University of Budapest, 1521 Budapest Gellert Ter 4, Hungary
†Author for correspondence



Hybrid System!

  - The function is very well-studied. But why this network structure?
  - That is, why this peculiar *algorithm*?

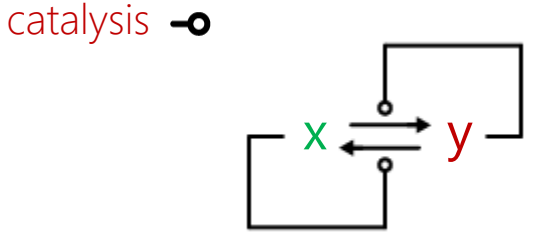
How to Build a Good Switch

- What is a "good" switch?
  - We need first a bistable system: one that has two *distinct* and *stable* states. I.e., given any initial state the system must settle into one of two states
  - The settling must be fast (not get stuck in the middle for too long) and robust (must not spontaneously switch back)
  - Finally, we need to be able to flip the switch by external inputs
- "Population protocol" switches
  - Identical agents ('molecules') in a population start in some state, say x or y
  - A pair of agents is chosen randomly at each step, they interact ('collide') and change state
  - The whole population must eventually agree on a majority value (all-x or all-y) with probability 1

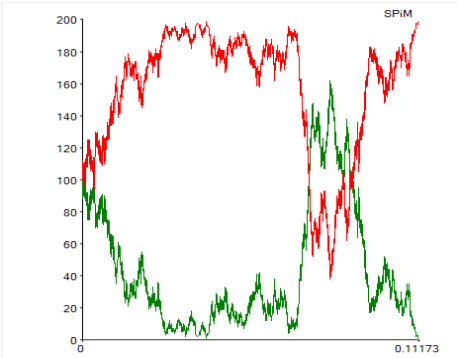
A Bad Algorithm

- Direct Competition
  - x catalyzes the transformation of y into x
  - y catalyzes the transformation of x into y
  - when all-x or all-y, it stops

- This system has two end states, but
  - Convergence to an end state is slow (a random walk)
  - Any perturbation of an end state can start a random walk to the other end state (hence not really *bistable*)



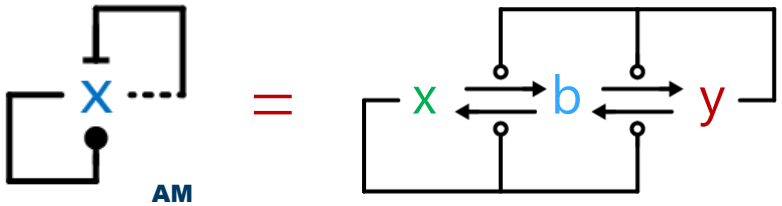
$$y + x \rightarrow x + x$$
$$x + y \rightarrow y + y$$



A Good Algorithm

activation
inhibition
catalysis

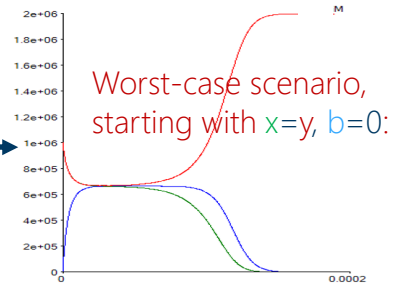
- Approximate Majority (AM)
  - Third, undecided, state b
  - Disagreements cause agents to become undecided
  - Undecided agents believe any non-undecided agent



$x + y \rightarrow y + b$
$y + x \rightarrow x + b$
$b + x \rightarrow x + x$
$b + y \rightarrow y + y$

- With high probability, for *n* agents
  - The total number of interactions before converging is $O(n \log n)$
    ⇒ fast (optimal)
  - The final outcome is correct if the initial disparity is $\omega(\sqrt{n} \log n)$
    ⇒ solution states are robust to perturbations
- Logarithmic time bound in parallel time
  - *Parallel time* is the number of steps divided by the number of agents
  - In parallel time the algorithm converges with high probability in $O(\log n)$

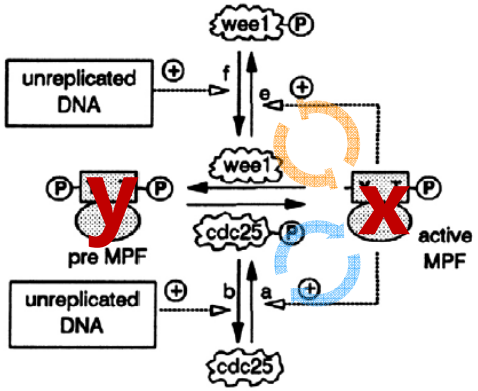
x=y →



Worst-case scenario, starting with x=y, b=0:

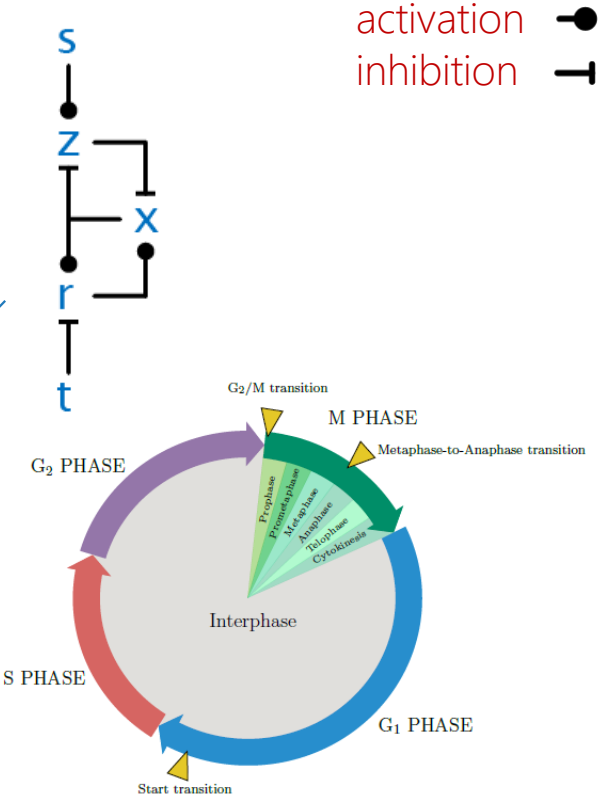
Dana Angluin · James Aspnes · David Eisenstat
A Simple Population Protocol for Fast Robust Approximate Majority

An "Ugly" Algorithm: Cell Cycle Switch



Nobel-prize winning network

Obfuscation of a distributed algorithm?



- Is it a good algorithm? Is it bad?
- Is it optimal or suboptimal?

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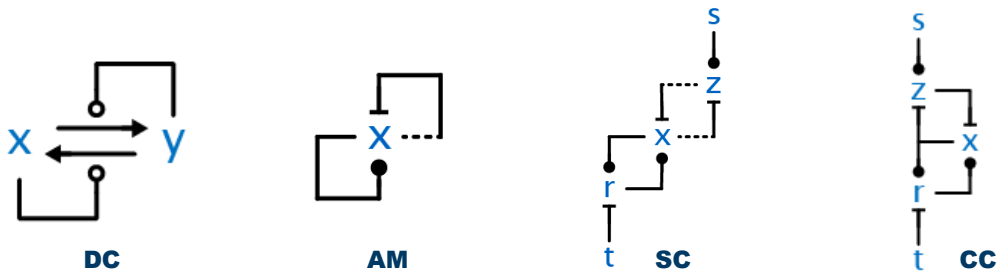
†Author for correspondence

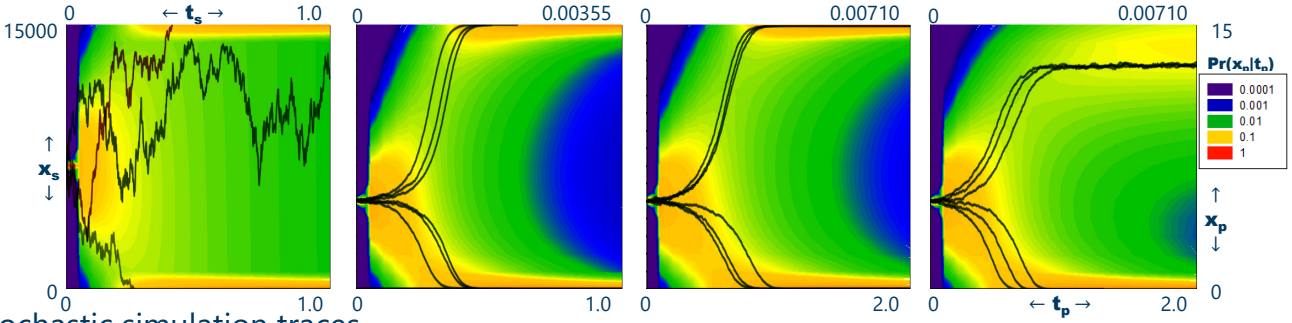
Convergence Analysis - CONSENSUS

- Switches as computational systems

CC converges in O(log n) time (like AM)
(but 2x slower than AM, and does not fully switch)



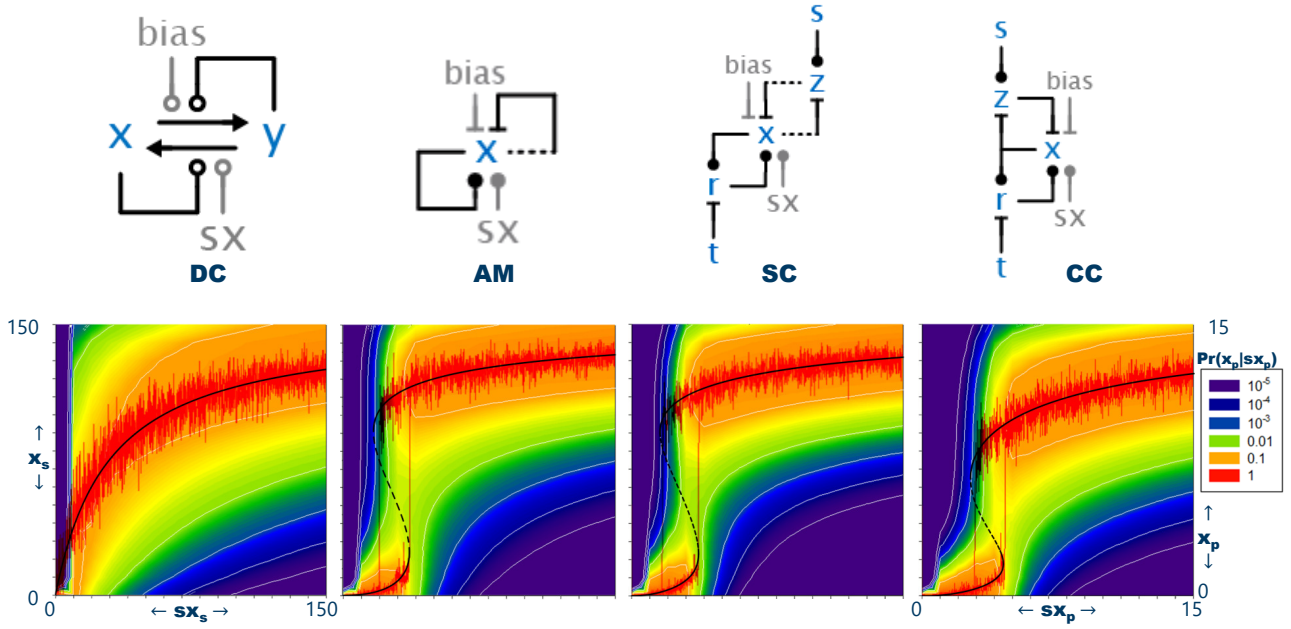
Start symmetrical
(x_0=x_1=x_2 etc.)



Black lines: several stochastic simulation traces
Color: full probability distribution of small-size system

Steady State Analysis - SWITCH

- Switches as dynamical systems



Black lines: deterministic ODE bifurcation diagrams
Red lines: noisy stochastic simulations
Color: full probability distribution of small-size system

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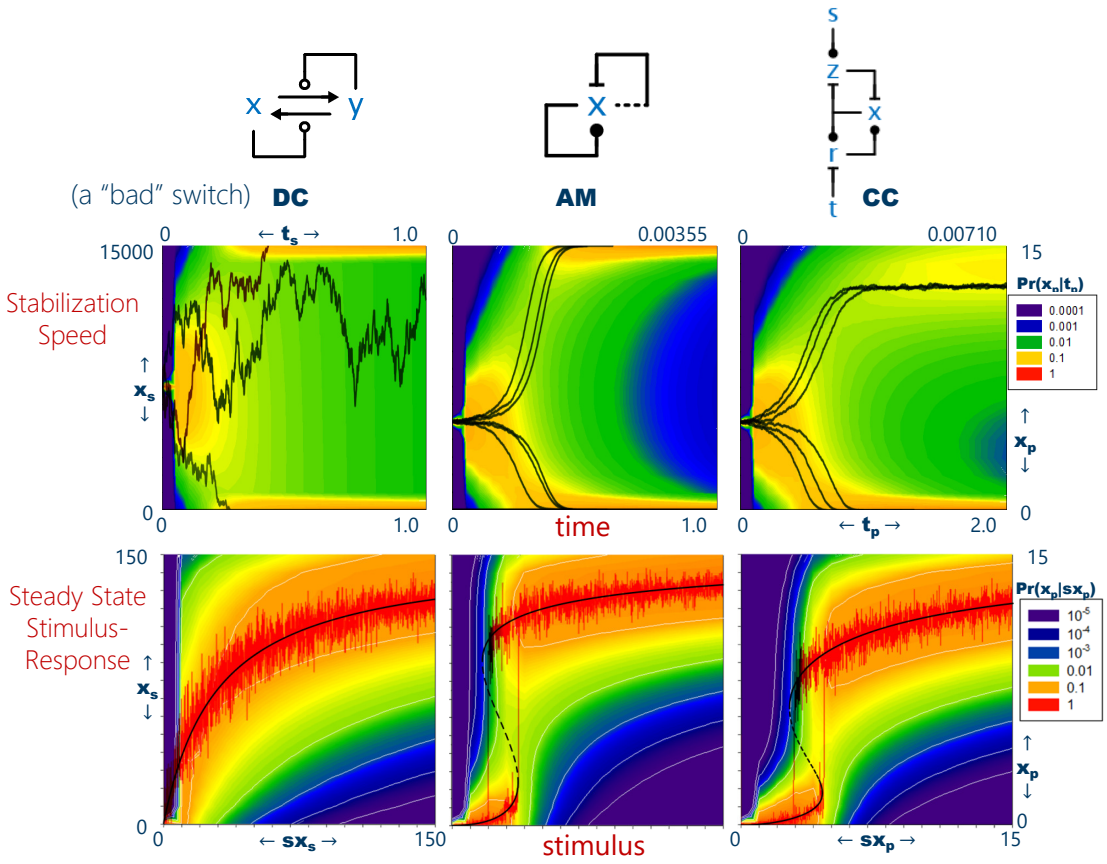
A Bug in the Algorithm

In Summary

activation
inhibition
catalysis



The "classical" Cell Cycle Switch CC approximates AM performance

SCIENTIFIC REPORTS

OPEN

The Cell Cycle Switch Computes Approximate Majority

SUBJECT AREAS: COMPUTATIONAL BIOLOGY

Luca Cardelli[1] & Attila Csikász-Nagy[2,3]

CC converges in O(log n) time (like AM)
(but 2x slower than AM, and does not fully switch)

Symmetrical initial conditions ($x_0=x_1=x_2$)

Black lines: high-count stochastic simulation traces
Color: full probability distribution of low-count system

Hor axis is *time*.

AM shows hysteresis (like CC)

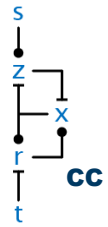
Black lines: deterministic ODE bifurcation diagrams
Red lines: medium-count stochastic simulations
Color: full probability distribution of low-count system

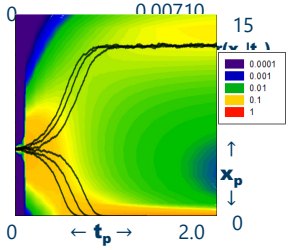
Hor axis is *stimulus* pushing towards x_0 against fixed bias.

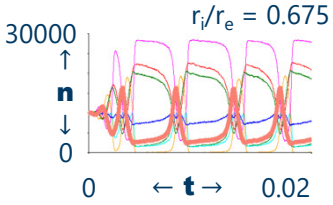
But there is a *deficiency* in CC performance!

Why is CC worse than AM?

- The classical CC has an algorithmic "bug"
  - It works ok but never as well as AM
  - Because s continuously inhibits x through z, so that x cannot fully express





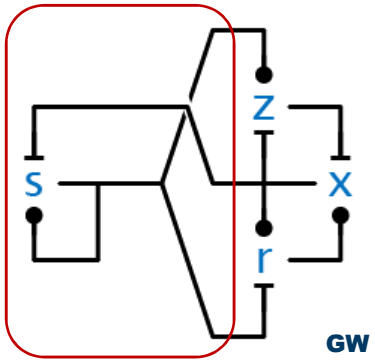


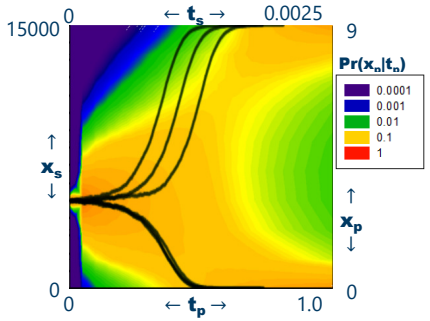
The corresponding cell cycle oscillator is also depressed

- So let's fix the bug!
  - Easy: let x inhibit s and t "in retaliation"
  - Q: Why didn't nature fix it?

Nature fixed it!

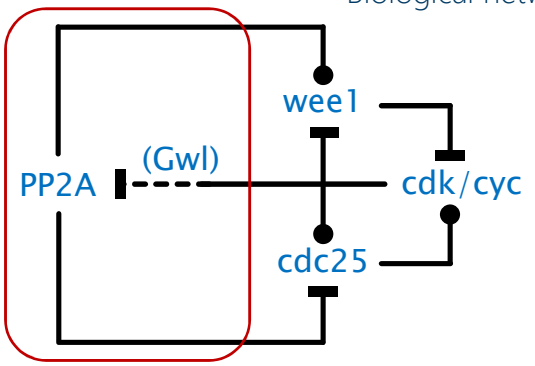
- There is another known feedback loop
  - By which x suppresses s "in retaliation" via the so-called Greatwall loop
  - Also, s and t happen to be the same molecule (=s)





Full activation!

Biological network



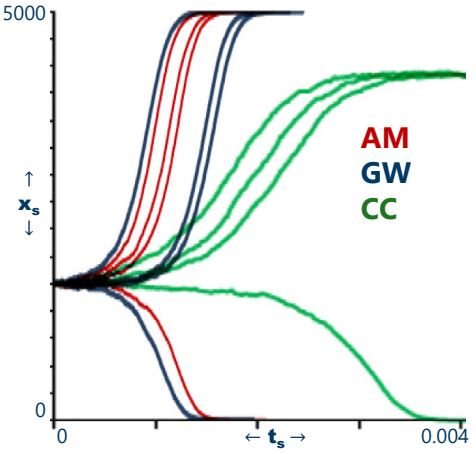
- s and x now are antagonists: they are the two halves of the switch, mutually inhibiting each other (through intermediaries).

More surprisingly

- The fix makes it faster too!
  - The extra feedback also speeds up the decision time of the switch, making it about as good as the 'optimal' AM switch:

Conclusion:
Nature is trying as hard as it can to implement an AM-class algorithm!

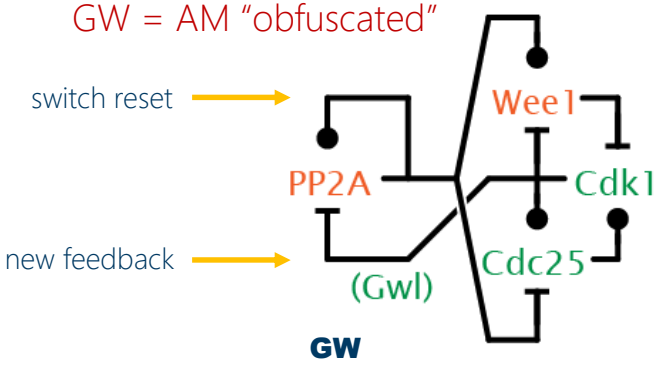
The "classical" cell cycle switch is only half of the picture: the extra feedback completes it *algorithmically*.



The Greatwall Loop

- Our paper appeared, suggesting GW is a better cell cycle switch than CC:

GW = AM "obfuscated"



OPEN

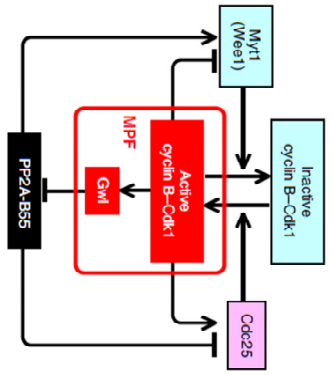
SUBJECT AREAS:
COMPUTATIONAL BIOLOGY

The Cell Cycle Switch Computes Approximate Majority

Luca Cardelli[1] & Attila Csikász-Nagy[2,3]

Sep 2012

- Another paper appeared that *same* week:



Showing experimentally that the Greatwall loop is a necessary component of the switch.
The not-as-good-as-AM network has been 'refuted'

ARTICLE

Received 6 Jul 2012 | Accepted 14 Aug 2012 | Published 11 Sep 2012
DOI:10.1038/ncomms2062

Greatwall kinase and cyclin B-Cdk1 are both critical constituents of M-phase-promoting factor

Masatoshi Hara[1,†], Yusuke Abe[1,†], Toshiaki Tanaka[2], Takayoshi Yamamoto[1,†], Eiichi Okumura[1] & Takeo Kishimoto[1]

Sep 2012

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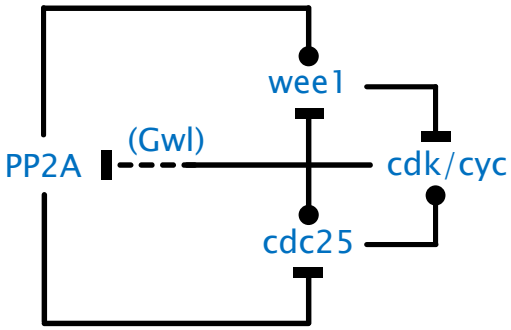
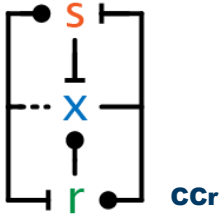
More Recent Developments

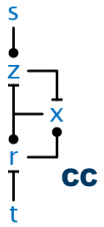
The basic "revised" Cell Cycle Switch





This is an AM-class algorithm (identical performance)

Vs.



New Cell Cycle Switch Network

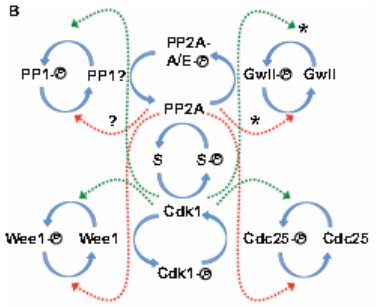
- A recent paper presents a more complete view of the cell cycle switch
- N.B. "phosphorylation network dynamics" here is the same as our x_0-x_1-x_2 motif

Phosphorylation network dynamics in the control of cell cycle transitions

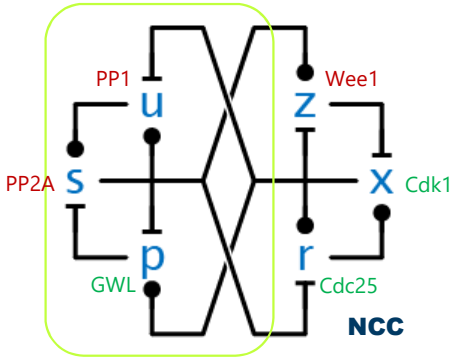
Daniel Fisher[1,*], Liliana Krasinska[1,‡], Damien Coudreuse[2,‡] and Béla Novák[3,‡]
[1]Institut de Génétique Moléculaire de Montpellier, IGMM, CNRS UMR 5535, Université Montpellier I and II, 34293 Montpellier, France
[2]Institute of Genetics and Development of Rennes, CNRS UMR 6290, 35043 Rennes, France
[3]Oxford Centre for Integrative Systems Biology, Department of Biochemistry, University of Oxford, South Parks Road, Oxford OX1 3QU, UK
*Author for correspondence (daniel.fisher@igmm.cnrs.fr)
‡These authors contributed equally to this work

Journal of Cell Science 125, 4703–4711

doi: 10.1242/jcs.106351

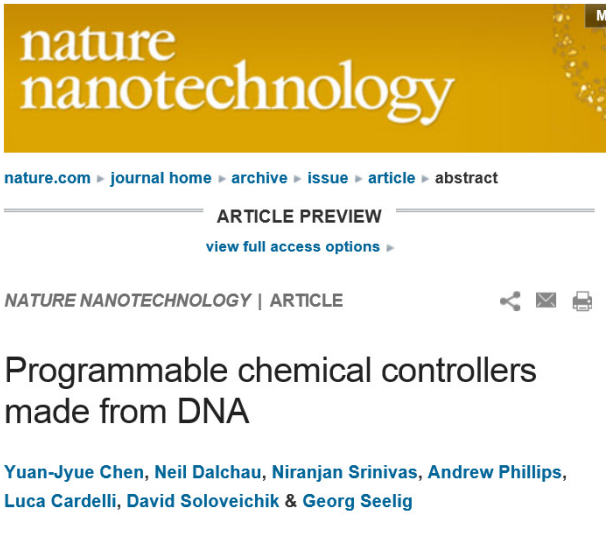


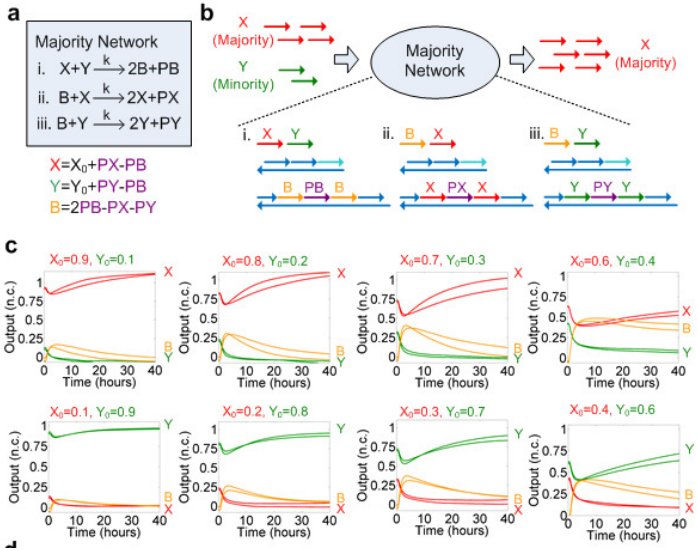
Mutual inhibition between *three* species each



Molecular Implementation of AM

- We produced a chemical implementation of AM using DNA gates
- I.e., a 'synthetic reimplementation' of the central cell-cycle switch.





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Network Equivalences

What we learned

- The network structure of AM implements an input-driven switching function (in addition to the known majority function).
- The network structure of CC/GW implements a input-less majority function (in addition to the known switching function).

- The behavior of AM and CC/GW in isolation are related.
- The behavior of AM and CC/GW in oscillator contexts are related.

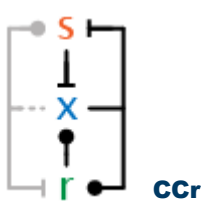
- A refinement (GW) of the core CC network, known to occur in nature, improves its switching performance and brings it in line with AM performance.

Can we make this precise?

- Our evidence for computational content of biochemical networks is so far
  - Quantitative, covering both kinetic and steady state behavior of *what* networks do
  - But empirical (based on simulations/numerical solutions)
  - And it does not yet explain *how* the CC/GW network relates to the AM network, that is, how each *piece* of CC/GW corresponds to each *piece* of AM
- Analytical evidence is harder to obtain
  - The proofs of the computational properties (optimality etc.) for the AM algorithm are hard and do not generalize easily to more complex networks
  - Quantitative theories of behavioral equivalence and behavioral approximation, e.g. in process algebra, are still lacking (although rich qualitative theories exist)
- How exactly is CC (or CCr, GW, etc.) the "same" as AM?

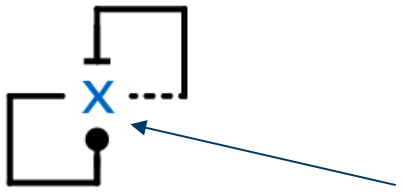
Network Emulation CCr emulates AM

- For *any* rates and initial conditions of **AM**, we can find *some* rates and initial conditions of **CCr** such that the (9) trajectories of **CCr** retrace those (3) of **AM**:



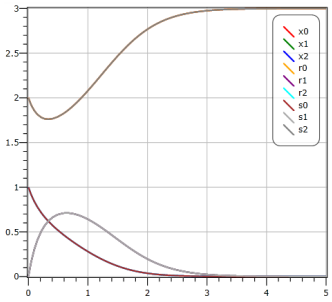
CCr

~s,r⇢ x

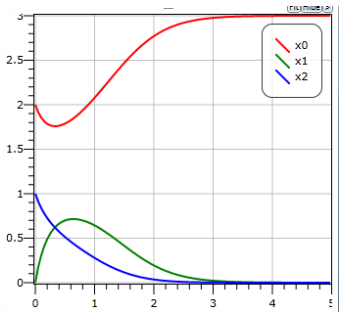


(3 species)

AM



(9 species on 3 trajectories)



(3 species on 3 trajectories)

initialize:
$z = x$
$\sim y = x$

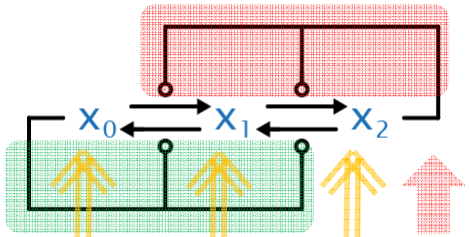
$(y_2 = x_0$
$y_1 = x_1$
$y_0 = x_0)$

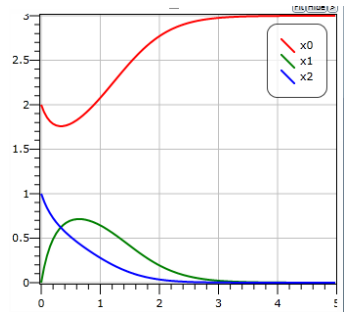
- How do we find these matching parameters? By a network morphism!

Network Emulation: MI emulates AM

A mapping of species and reactions

AM



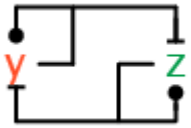


any initial conditions

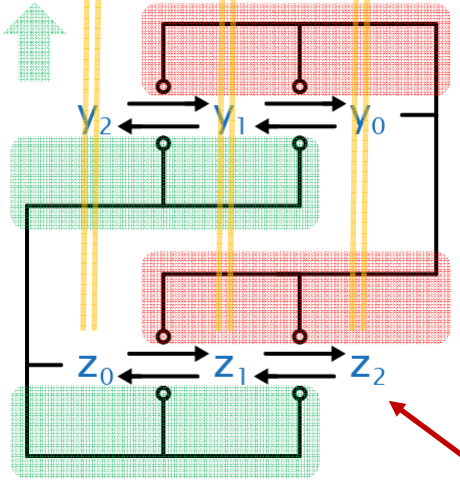
homomorphic mapping

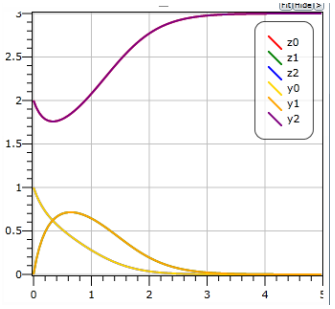
z -> x

~y -> x



MI





initial conditions:

$z_0 = y_2 = x_0$

$z_1 = y_1 = x_1$

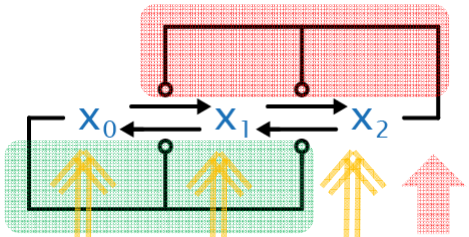
$z_2 = y_0 = x_2$

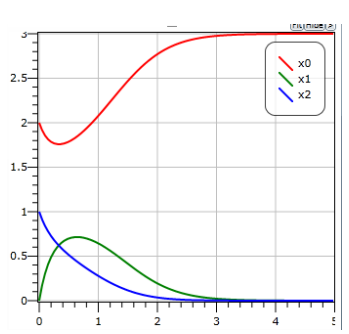
less trivial than you might think:
it need not preserve the out-degree of a node!

Network Emulation: SI emulates AM

A mapping of species and reactions

AM

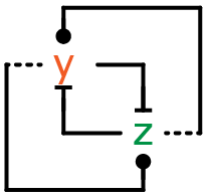




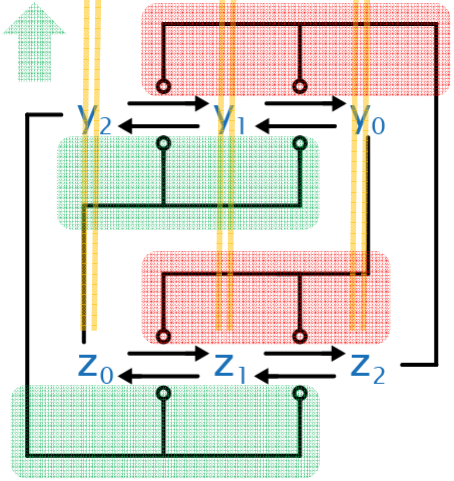
any initial conditions

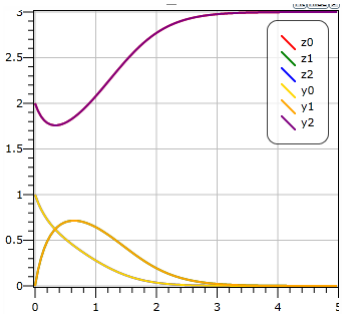
homomorphic mapping

z -> x
~y -> x



SI





initial conditions:

$z_0 = y_2 = x_0$
$z_1 = y_1 = x_1$
$z_2 = y_0 = x_2$

How to find emulations

- How do we check a potential mapping 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)

Models from the BioNetGen database

	Original model		*Forward reduction*				*Backward reduction*			
Id	$\|R\|$	$\|S\|$	*Red.(s)*	$\|R\|$	$\|S\|$	*Speed-up*	*Red.(s)*	$\|R\|$	$\|S\|$	*Speed-up*
M1	3538944	262146	4.61E+4	990	222	—	7.65E+4	2708	222	—
M2	786432	65538	1.92E+3	720	167	—	3.68E+3	1950	167	—
M3	172032	16386	8.15E+1	504	122	1.16E+3	1.77E+2	1348	122	5.34E+2
M4	48	18	1.00E–3	24	12	1.00E+0	2.00E–3	45	12	1.00E+0
M5	194054	14531	3.72E+1	142165	10855	1.03E+0	1.32E+3	93033	6634	1.03E+0
M6	187468	10734	3.07E+1	57508	3744	1.92E+1	2.71E+2	144473	5575	3.53E+0
M7	32776	2506	1.26E+0	16481	1281	6.23E+0	1.66E+1	32776	2506	x
M8	41233	2562	1.12E+0	33075	1897	1.12E+0	1.89E+1	41233	2562	x
M9	5033	471	1.91E–1	4068	345	1.04E+0	4.35E–1	5033	471	x
M10	5797	796	1.61E–1	4210	503	1.47E+0	7.37E–1	5797	796	x
M11	5832	730	3.89E–1	1296	217	1.32E+1	6.00E–1	2434	217	7.55E+0
M12	487	85	2.00E–3	264	56	1.88E+0	6.00E–3	426	56	1.31E+0
M13	24	18	1.20E–2	24	18	x	7.00E–3	6	3	1.00E+0

Aggregation reduction

Emulation reduction

Forward and Backward Bisimulations for Chemical Reaction Networks

Luca Cardelli[1], Mirco Tribastone[2], Max Tschaikowski[3], and Andrea Vandin[4]

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2-4 University of Southampton, UK
{m.tribastone,m.tschaikowski,a.vandin}@soton.ac.uk

Concur 2015

Satisfiability Modulo Differential Equivalence Relations

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POPL 2016

Comparing Chemical Reaction Networks: A Categorical and Algorithmic Perspective

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LICS 2016

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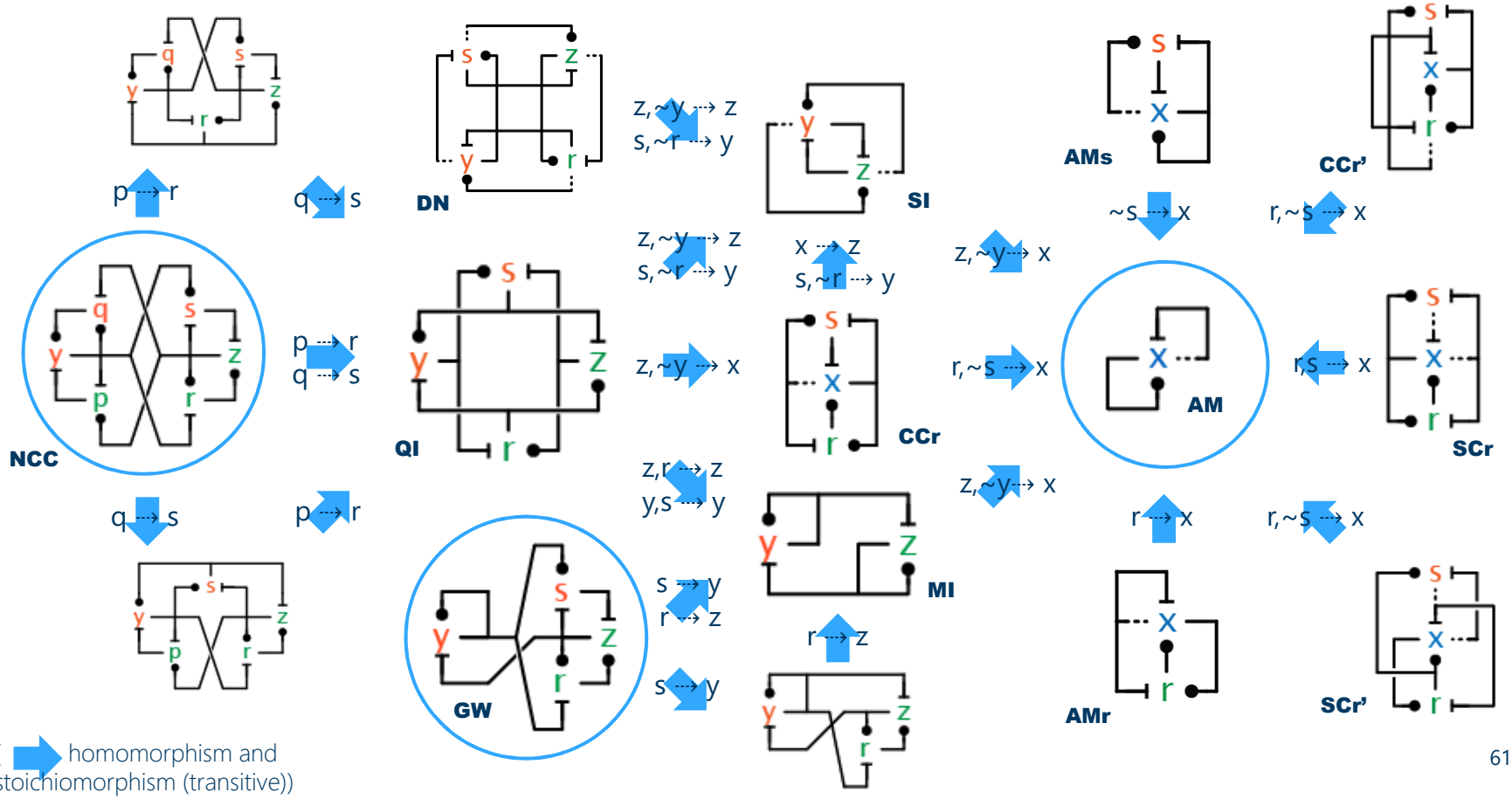
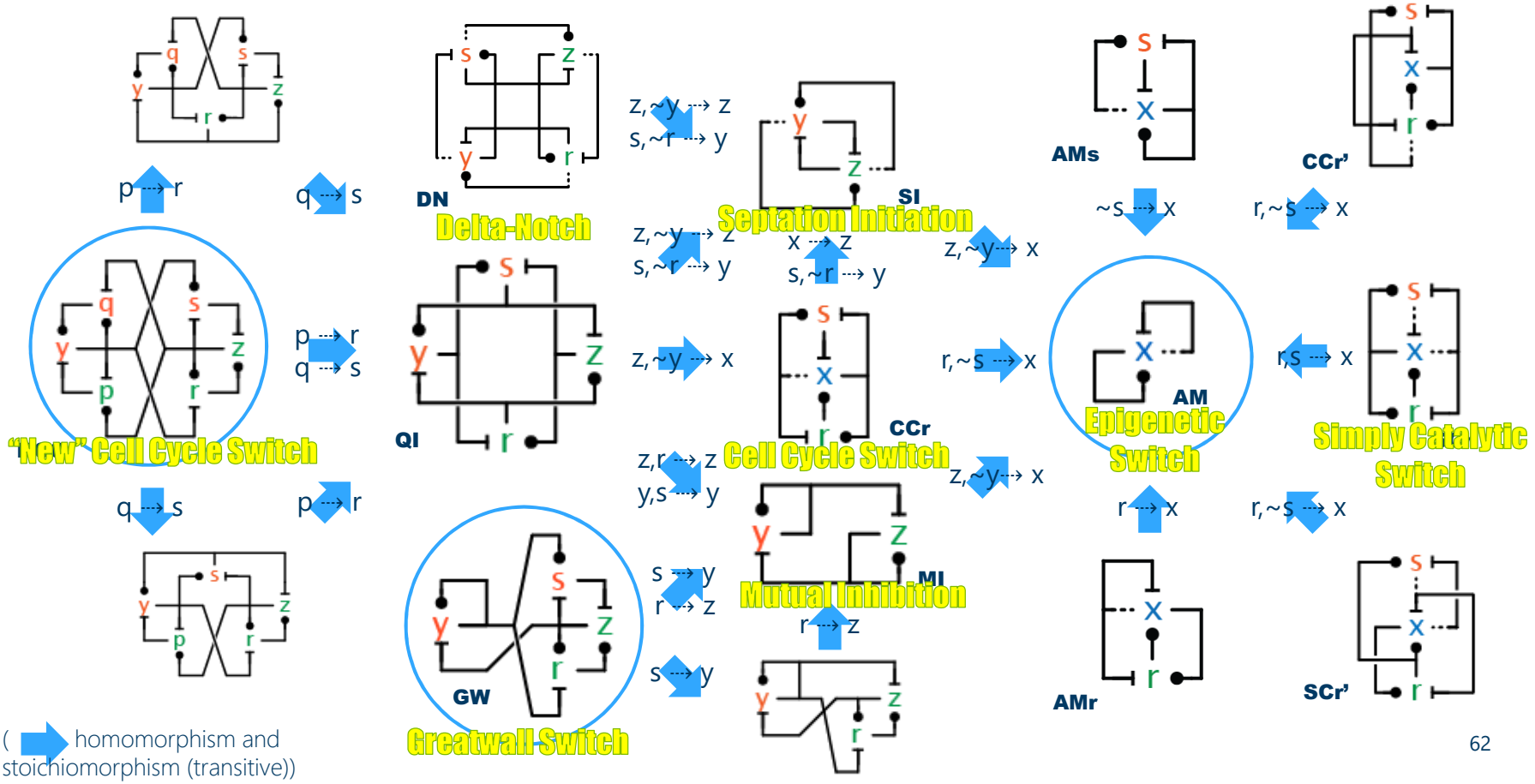
Network Evolution and Network Robustness

Walks in Network Space



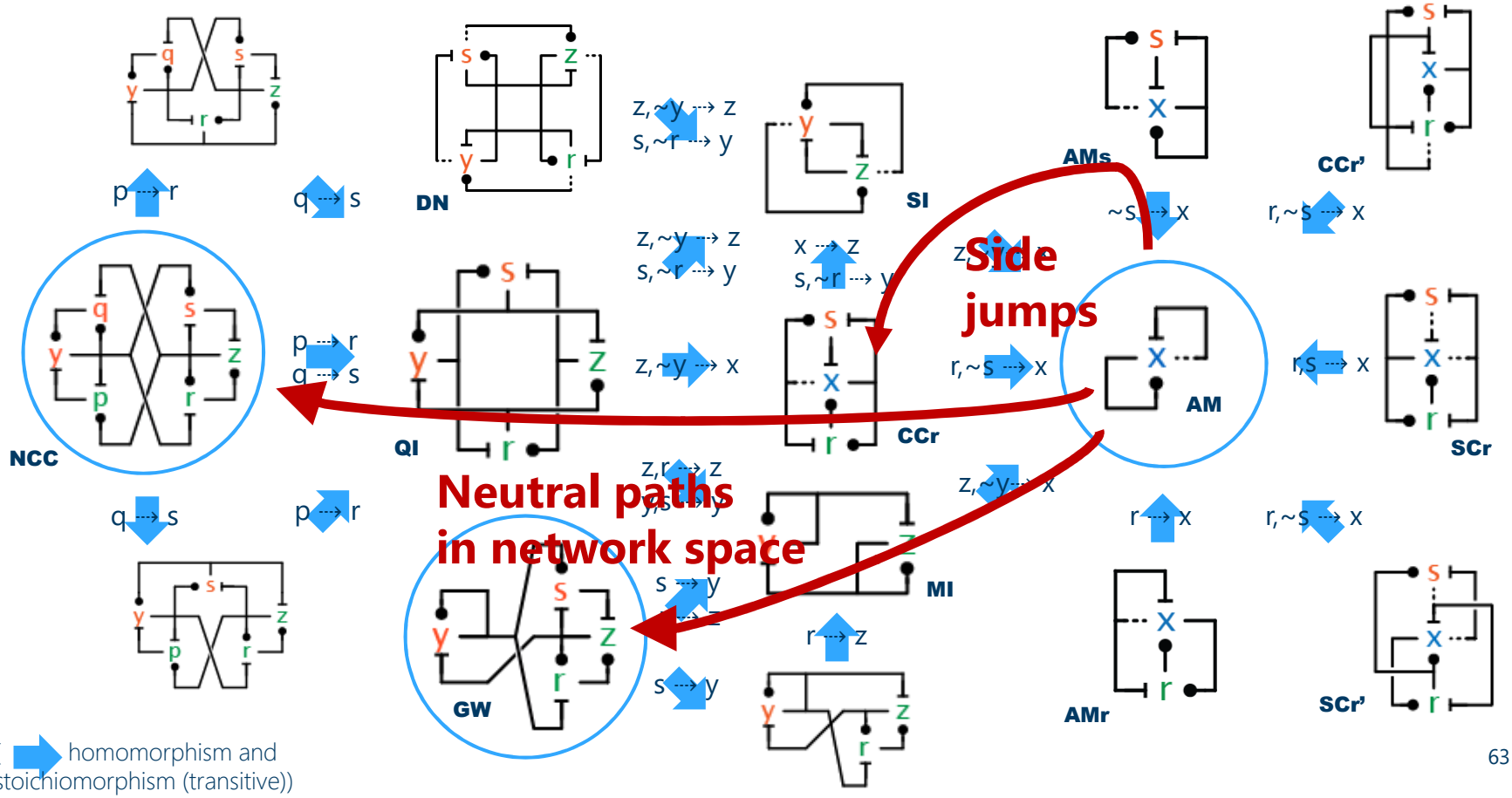
(⇢ homomorphism and stoichiomorphism (transitive))

Walks in Network Space



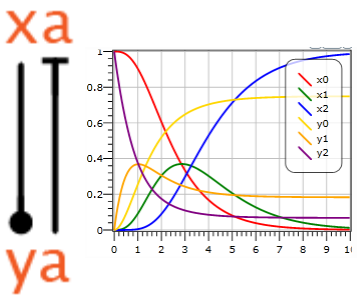
(➡ homomorphism and stoichiomorphism (transitive))

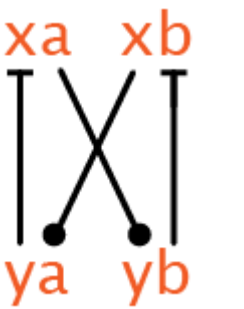
Walks in Network Space



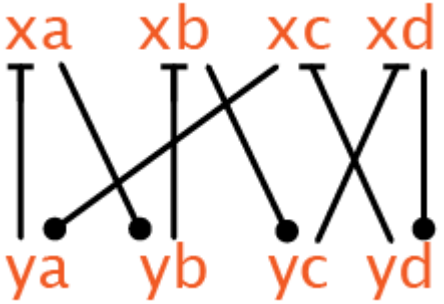
(homomorphism and stoichiomorphism (transitive))

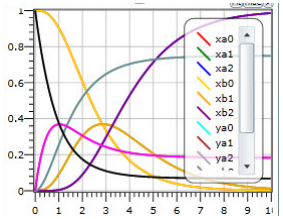
Another Zoo

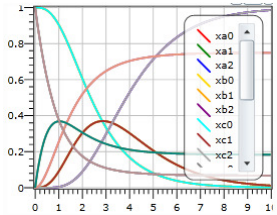

xa
ya
x0
x1
x2
y0
y1
y2

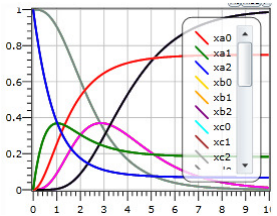

xa xb
ya yb


xa xb xc
ya yb yc


xa xb xc xd
ya yb yc yd

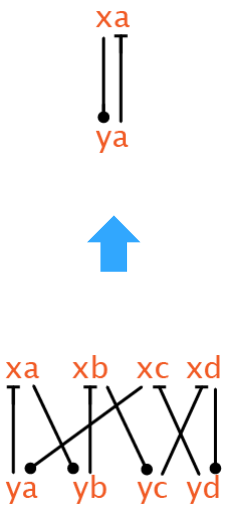

xa0
xa1
xa2
xb0
xb1
xb2
ya0
ya1
ya2


xa0
xa1
xa2
xb0
xb1
xb2
xc0
xc1
xc2


xa0
xa1
xa2
xb0
xb1
xb2
xc0
xc1
xc2

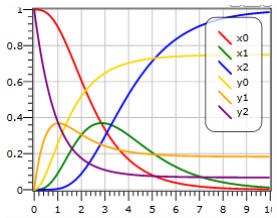
Network Perturbations

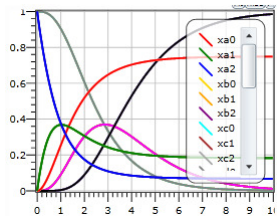
Network



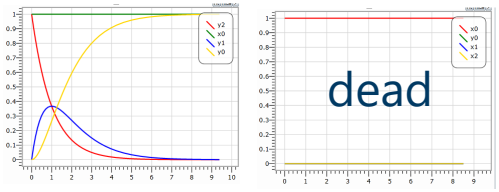
A complex but robust implementation of the simple network

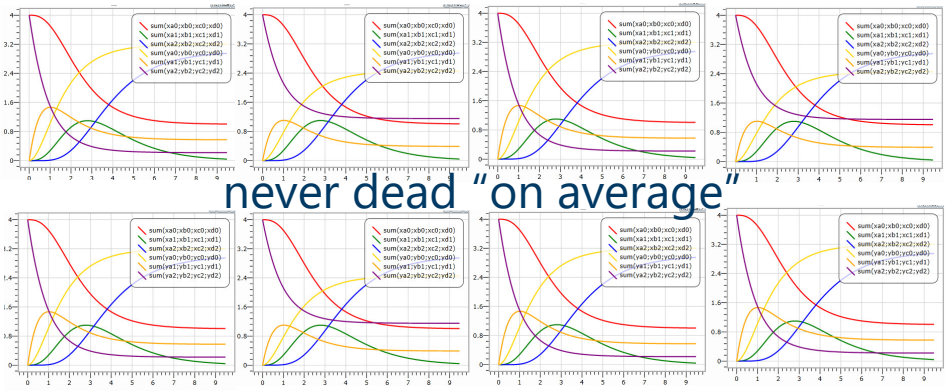
Normal Behavior





Removing each link in turn





never dead "on average"

Microsoft Research

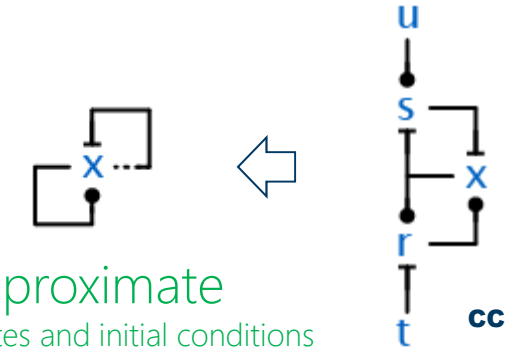
UNIVERSITY OF OXFORD

Conclusion

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 (to what end?)
- 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

Nature likes good algorithms



Approximate

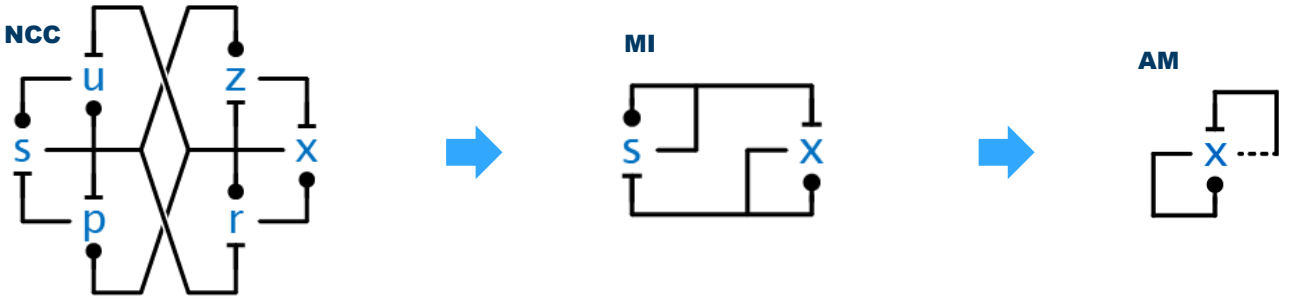
"default" rates and initial conditions

Exact

any rates and initial conditions

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

The cell cycle switch *can* exactly emulate AM



What Contributes to Complexity?

- Indifference? (does not really cost much)
- Robustness? (resist point failures)
- Adaptability? (neutral paths)
- Noise resistance? (improve signal processing)
- Temperature compensation?
- Etc.