Microsoft Research

The Cell Cycle Switch Computes Approximate Majority

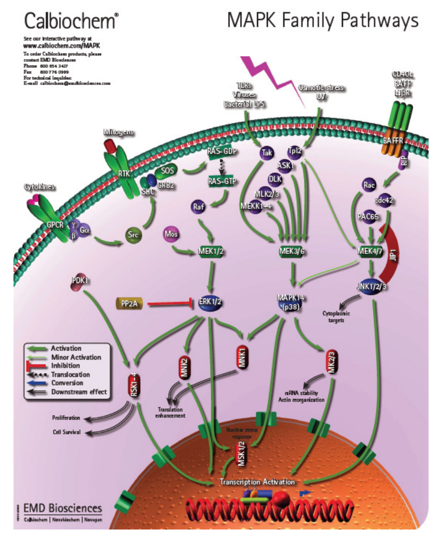
Luca Cardelli, Microsoft Research

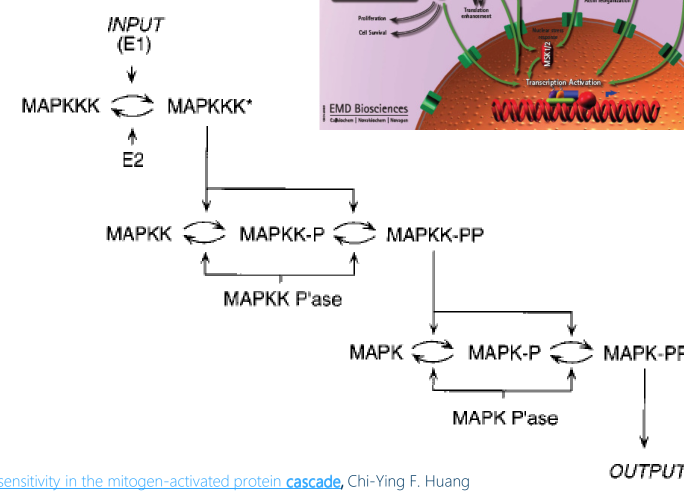
Joint work with Attila Csikász-Nagy, CoSBi & King's College London

Emergence in Chemical Systems 3.0, Anchorage, 2013-06-17

Cells Compute

- No survival without computation!
  - Finding food
  - Avoiding predators
- How do they compute?
  - Clearly doing “information processing”
  - Based on complex, higher-order interactions
    - MAPKKK = MAP Kinase Kinase Kinase = *that which operates on that which operates on that which operates on protein.*
  - How ‘sophisticated’ are natural algorithms?





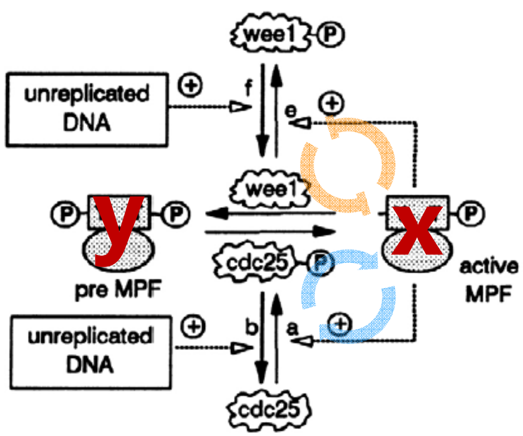
Ultrasensitivity in the mitogen-activated protein **cascade**, Chi-Ying F. Huang and James E. Ferrell, Jr., 1996, *Proc. Natl. Acad. Sci. USA*, 93, 10078-10083.

Outline

- Analyzing biomolecular networks
  - Try do understand the function of a network
  - But also try to understand its *structure*, and what determines it
- The Cell-Cycle Switches
  - Some of the best studied molecular networks
  - Important because of their fundamental function (cell division) and the stability of the network across evolution
- We ask:
  - What does the cell cycles switch compute?
  - How does it compute it?

The Cell Cycle Switch

- This network is universal in all Eukaryotes [P. Nurse]
  - I.e., the *network* at the core of cell division is *the same* from yeast to us
  - *Not the components* of the network, *nor the rates*



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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†

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†Author for correspondence

Double positive feedback on x
Double negative feedback on x
No feedback on y
What on earth … ???

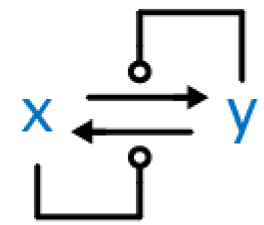
- The function is very well-studied. But why this structure?
- I.e., why this algorithm?

How to Build a Good Switch

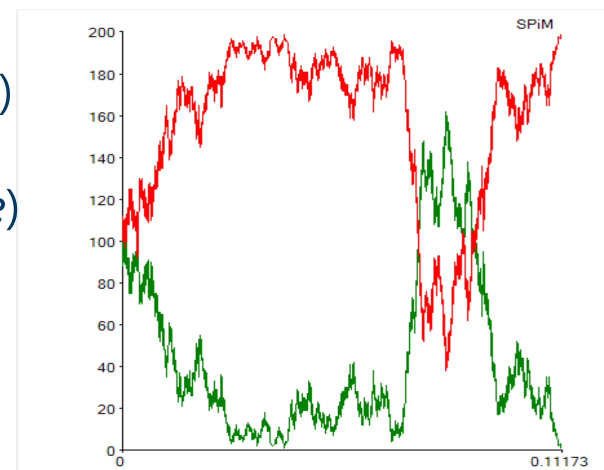
- What is a "good" switch?
  - We need first a bistable system: one that has two *distinct* and *stable* states. I.e., given any initial state the system must settle into one of two states
  - The settling must be fast (not get stuck in the middle for too long) and robust (must not spontaneously switch back)
  - Finally, we need to be able to flip the switch by external inputs
- "Population" Switches
  - Populations of identical agents (molecules) with the whole population switching from one state to another as a whole
  - Highly concurrent (stochastic)

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 Very Good Algorithm

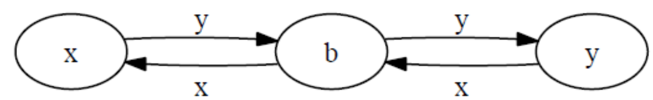
- Approximate Majority (AM)
  - Decide which of two populations is in majority
- A fundamental 'population protocol'
  - Agents in a population start in state x or state y
  - A pair of agents is chosen randomly at each step, they interact ('collide') and change state
  - The whole population must eventually agree on a majority value (all-x or all-y) with probability 1

Dana Angluin · James Aspnes · David Eisenstat

A Simple Population Protocol for Fast Robust Approximate Majority

We analyze the behavior of the following population protocol with states $Q = \{b, x, y\}$. The state b is the **blank** state. Row labels give the initiator's state and column labels the responder's state.

	x	b	y
x	(x, x)	(x, x)	(x, b)
b	(b, x)	(b, b)	(b, y)
y	(y, b)	(y, y)	(y, y)



Third 'undecided' state

1) Disagreements cause agents to become undecided
2) Undecided agents believe any non-undecided agent they meet

Properties

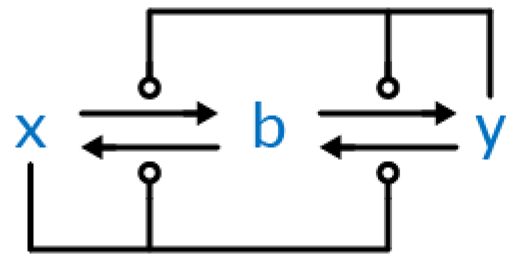
[Angluin et al., http://www.cs.yale.edu/homes/aspnes/papers/disc2007-eisenstat-slides.pdf]

- With high probability, for *n* agents
  - The total number of interactions before converging is $O(n \log n)$
    $\Rightarrow$ fast
  - The final outcome is correct if the initial disparity is $\omega(\mathit{sqrt}(n) \log n)$
    $\Rightarrow$ 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 $O(\log n)$

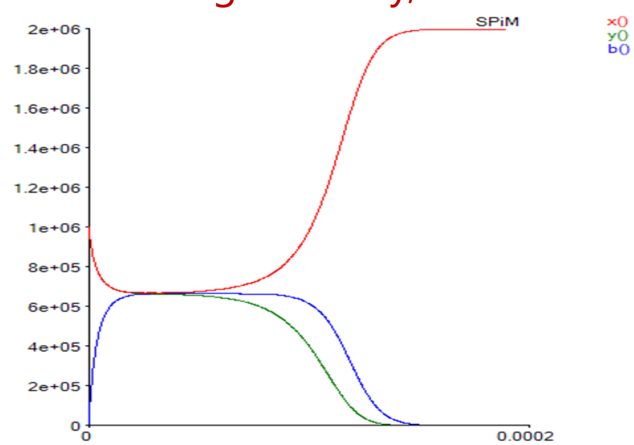
Chemical Implementation

Chemistry as a programming language for population algorithms!

x + y → y + b
y + x → x + b
b + x → x + x
b + y → y + y



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



Bistable
 Even when x=y! (stochastically)

Fast
 O(*log n*) convergence time

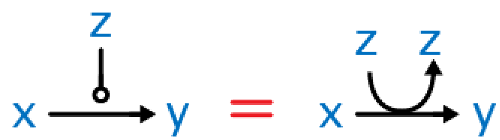
Robust to perturbation
 above a threshold, initial majority wins *whp*

Back to the Cell Cycle

- The AM algorithm has ideal properties for settling a population into one of two states
- But that is not what the cell cycle uses
- Or is it?

Influence Network Notation

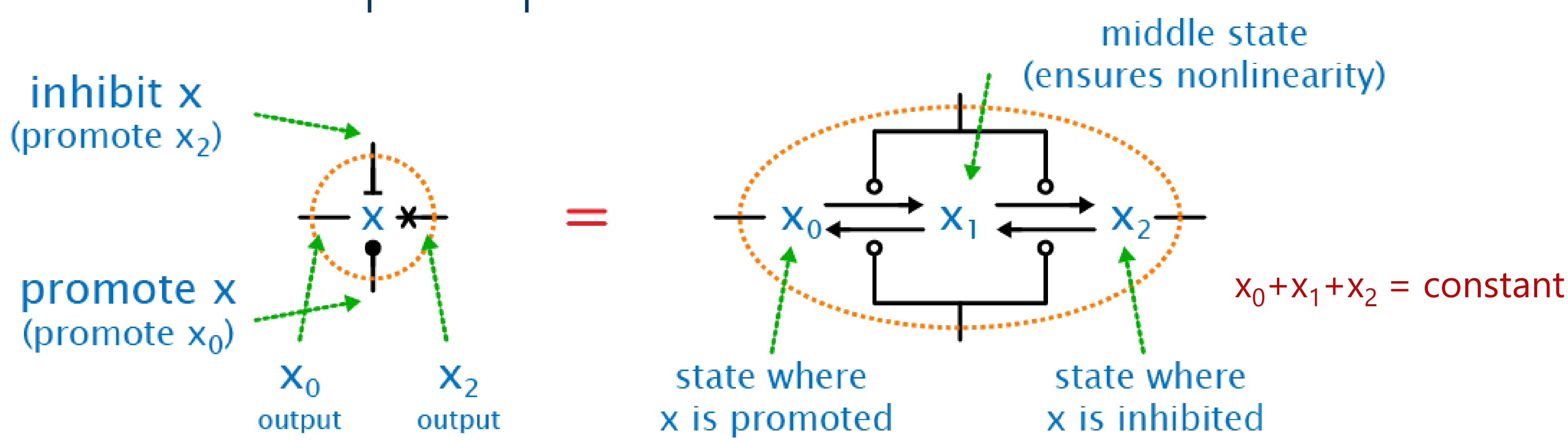
- Catalytic reaction



z is the catalyst

$x + z \rightarrow z + y$

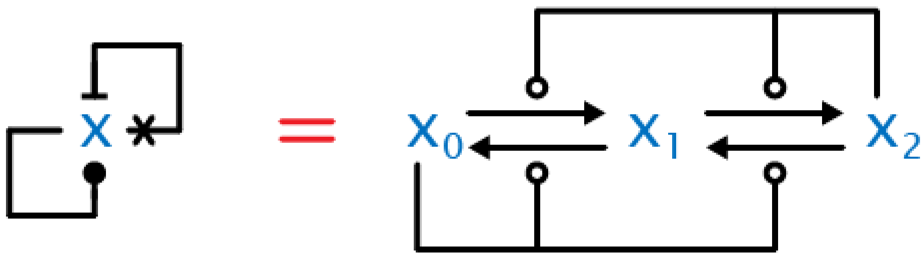
- 'Double kinase-phosphatase' motif



influence node

catalytic node

Step 1: the AM Network



(x_2 promotes x_2)

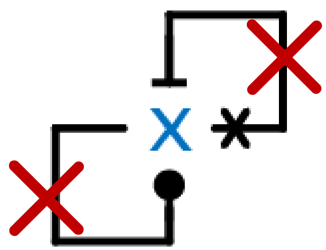
(x_0 promotes x_0)

- … not biochemically plausible

Natural Constraint #1

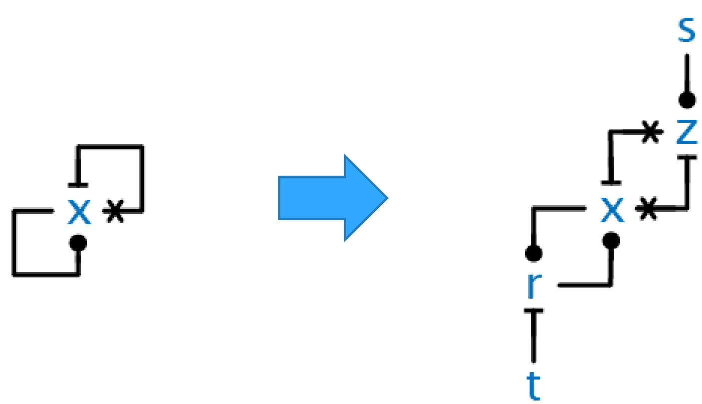
- Direct autocatalysis is not commonly seen in nature

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



Step 2: remove auto-catalysis

- Replace autocatalysis
  - By *mutual* (simple) catalysis, introducing intermediate species z and r
  - z and r need to ‘relax back’ when they are not being promoted:
    s and t provide the back pressure for such relaxation



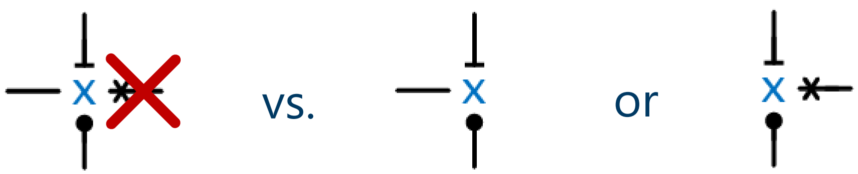
(x_2 promotes z_2, promotes x_2)

(x_0 promotes r_0, promotes x_0)

- … still not biochemically plausible.

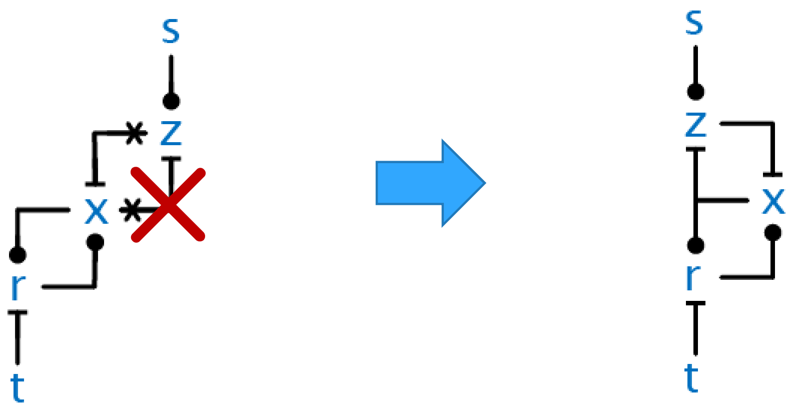
Natural Constraint #2

- x_0 and x_2 (usually two states of the same molecule) are both active catalysts in that network
- That is not commonly seen in nature



Step 3: only one active state per species

- Remove the catalytic activity of x_2
  - By "flipping the z feedback to the other side"



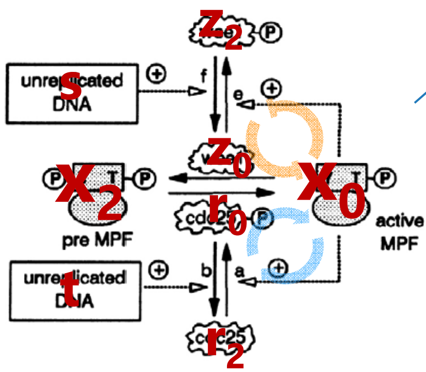
(x_2 promotes z_0 via s bias,
z_0 promotes x_2 via inhibiting x_0)

(x_0 promotes r_0, promotes x_0)

- All species now have one active (x_0,z_0,r_0) and one inactive (x_2,z_2,r_2) form
- This is 'biochmically plausible'

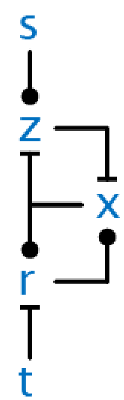
Network Structure

- … and that is the cell-cycle switch!



Nobel-prize winning network

Variation on a distributed algorithm

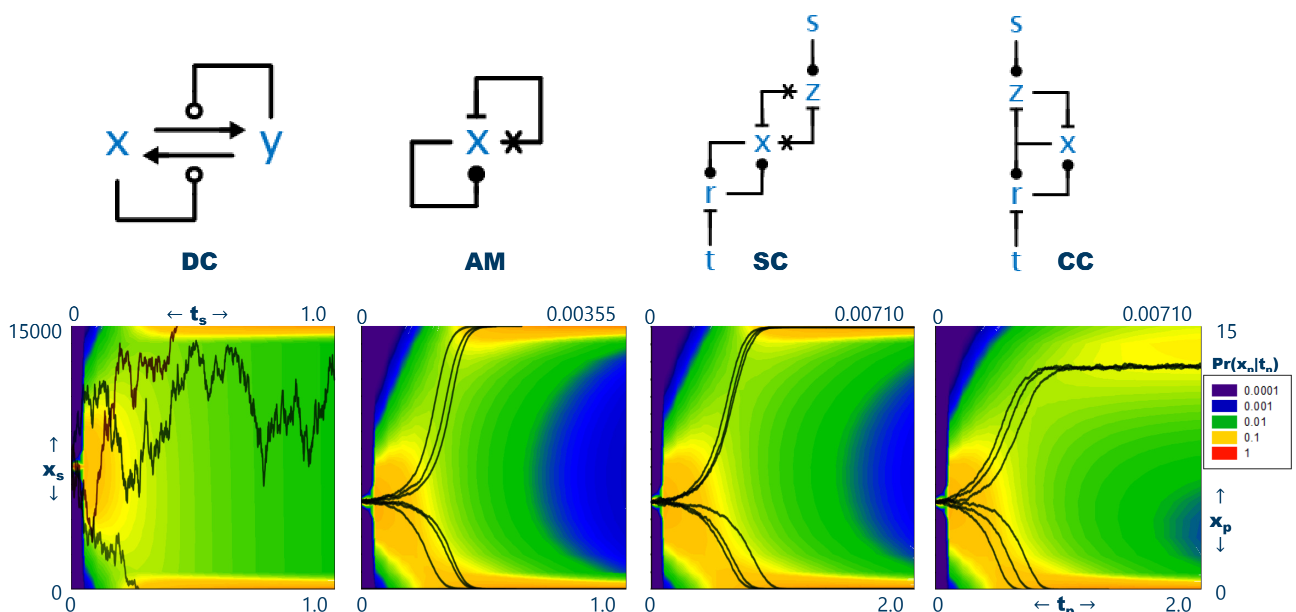


- But did we preserve the AM function through our network transformations?
- Ideally: prove either that the networks are 'contextually equivalent' or that the transformations are 'correct'
- Practically: compare their 'typical' behavior

Convergence Analysis

- Switches as computational systems

Start symmetrical
(x_0=x_1=x_2 etc.)

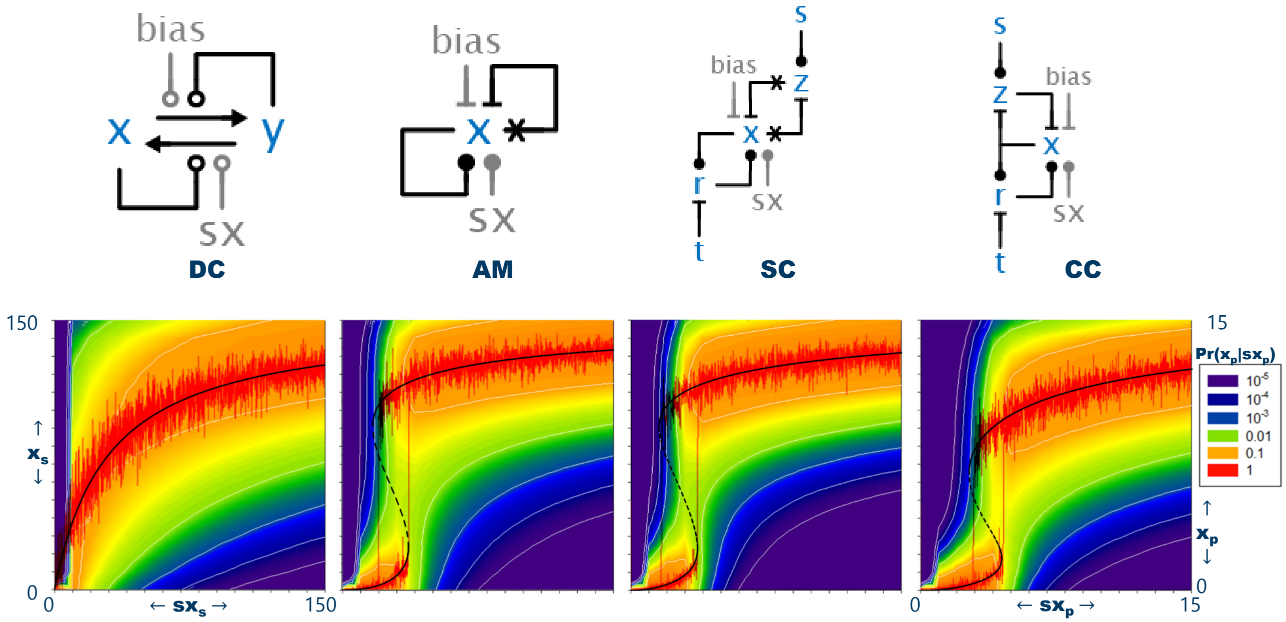


Black lines: several stochastic simulation traces
Color: full probability distribution of small-size system

NEW!
CC appears to converge in log time

Steady State Analysis

- Switches as dynamical systems

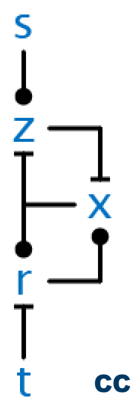


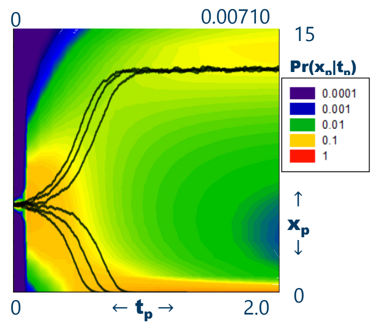
Black lines: deterministic ODE bifurcation diagrams
Red lines: noisy stochastic simulations
Color: full probability distribution of small-size system

NEW!
AM shows hysteresis

Evidence that CC is ‘similar’ to AM

- But there was a difference
  - The output of CC does not go ‘fully on’ like AM:

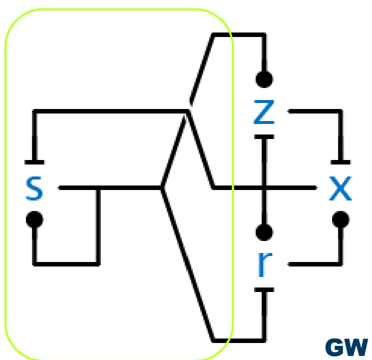


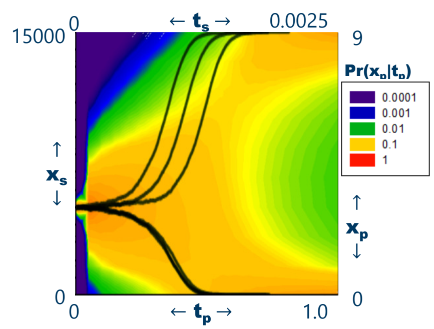


  - Because s continuously inhibits x through z, so that x cannot fully express
  - Q: Why didn’t nature do better than that?

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





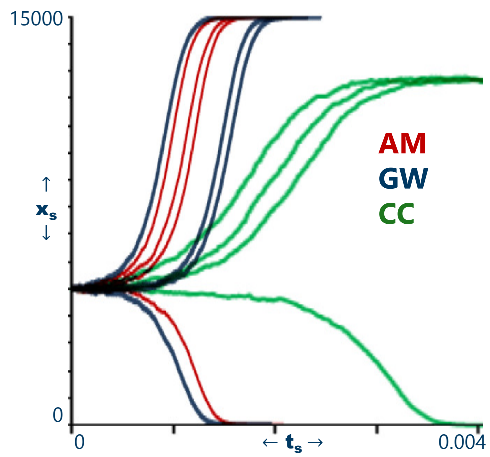
Full activation!

- (As usual, there are many more details in real biological networks; this is one of the many details people knew about without fully understanding its function)

More surprisingly

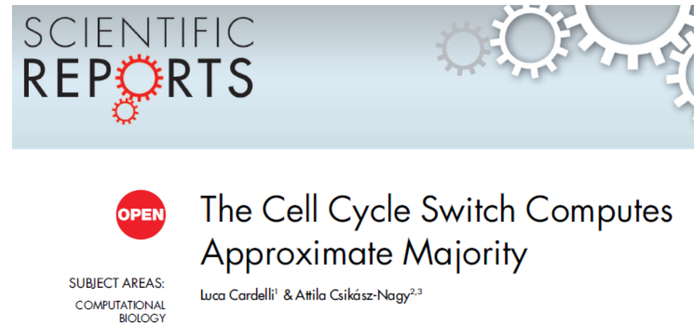
- Made it faster too!
  - The extra feedback also speeds up the decision time of the switch, making it about as good as the 'optimal' AM switch:

Conclusion (in our published paper):
Nature is trying as hard as it can to implement an AM-class algorithm!



The Greatwall Kinase

- Our paper appeared:
  - Suggesting GW is a better switch than CC, also in the context of oscillators



SCIENTIFIC REPORTS

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SUBJECT AREAS:
COMPUTATIONAL BIOLOGY

The Cell Cycle Switch Computes Approximate Majority

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

- Another paper the same week:
  - Showing experimentally that the Greatwall loop is a necessary component of the switch, i.e. the not-as-good-as-AM network has been 'refuted'

nature COMMUNICATIONS

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ARTICLE

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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]

But what about network equivalence?

- Our evidence is empirical
  - Although quantitative and covering both kinetic and steady state behavior
  - Also, contextual equivalence holds in the context of oscillators (see paper)
- Analytical evidence is harder to obtain
  - The proof techniques 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)

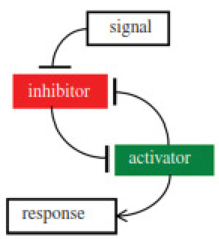
Mutual Inhibition

- A new paper suggests that all cellular switches in all phases of the cell cycle follow (abstractly) a mutual inhibition pattern:

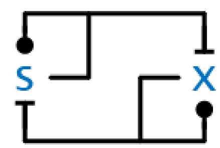
Molecular mechanisms creating bistable switches at cell cycle transitions

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

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

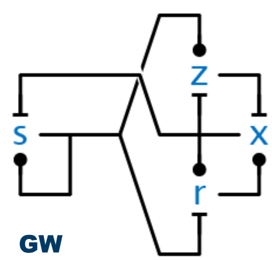


In our notation:



MI

cf.:



GW

New Cell Cycle Network

- A new paper presents a more complete view of the cell cycle switch
- N.B. “phosphorylation network dynamics” 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
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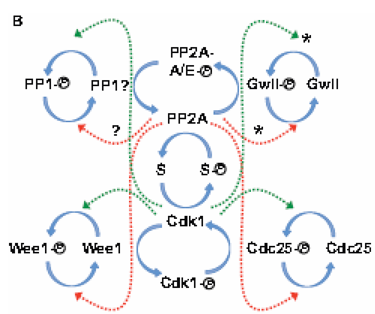
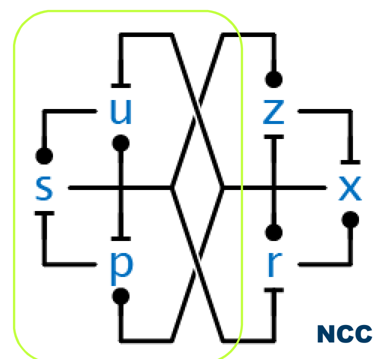
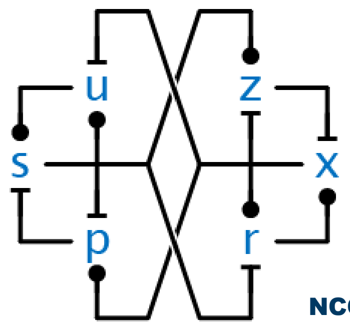


In our notation:



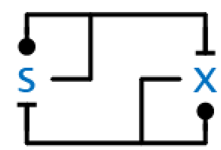
Network Emulation

- For chosen (uniform) initial conditions, the ODEs (and hence trajectories) of **NCC** collapse to those of **MI** (thanks to David Soloveichik):

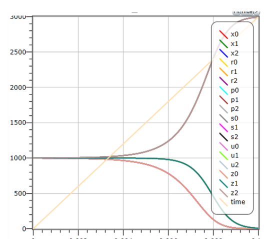


NCC

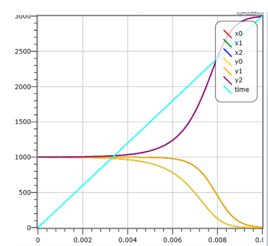
x,r,p ⇢ x
s,u,z ⇢ s



MI



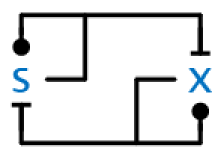
(18 species on 3 trajectories)



(6 species on 3 trajectories)

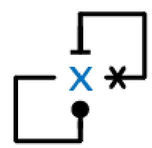
Network Emulation

- For chosen (uniform) initial conditions, the ODEs (and hence trajectories) of **MI** collapse to those of **AM**:

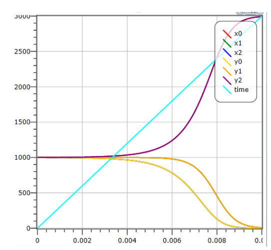


MI

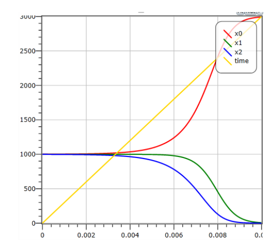
s,x⇢ x



AM



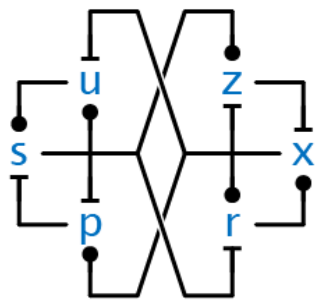
(6 species on 3 trajectories)



(3 species on 3 trajectories)

Conclusions

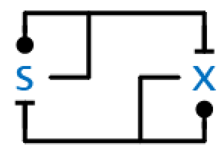
- The cell cycle switch *can* exactly emulate AM



NCC

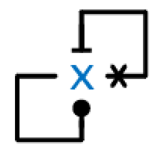
(New) cell cycle switch

emulates:



MI

emulates:



AM

Approximate majority algorithm

- Nature likes a good algorithm!

Microsoft