Microsoft Research

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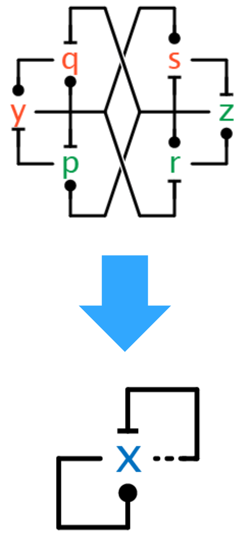
Analysis of Biological Switches as Algorithms

Luca Cardelli, Microsoft Research & Oxford University

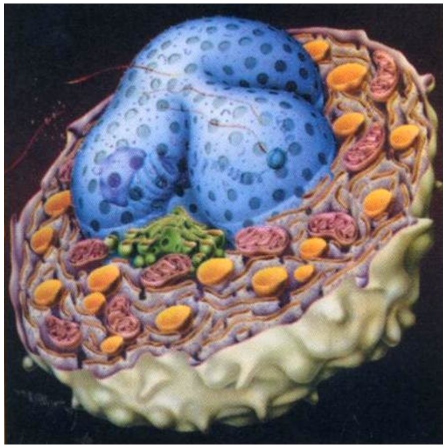
Joint work with Attila Csikász-Nagy, Fondazione Edmund Mach & King's College London

CANES launch event, 2014-10-08



Motivation

- 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*

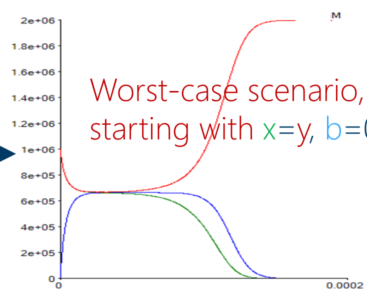


A Consensus Algorithm

- Population Consensus Problem
  - Find which state x or y is in majority in the population
  - By converting the *whole* population to either x or y

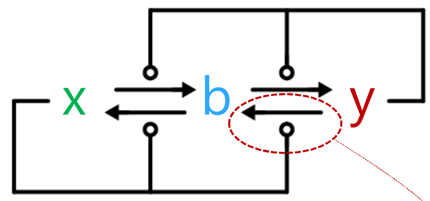
- Approximate Majority (AM) Algorithm
  - Uses a third "undecided" state b
  - Disagreements cause agents to become undecided
  - Undecided agents believe any non-undecided agent

x=y →



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

catalysis



$$x + y \to y + b$$
$$y + x \to x + b$$
$$b + x \to x + x$$
$$b + y \to y + y$$

Dana Angluin · James Aspnes · David Eisenstat

A Simple Population Protocol for Fast Robust Approximate Majority

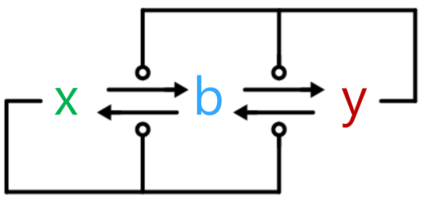
Population Protocols

- Computational model
  - Finite-state identity-free agents (molecules) interact in randomly chosen pairs
  - Each interaction (collision) can result in state changes
  - Complete connectivity, no centralized control (well-mixed solution)

- AM properties: With high probability, for n agents
  - The total number of interactions is $O(n \log n)$ ⇒ fast (optimal)
  - Correct outcome if the initial disparity is $\omega(\mathrm{sqrt}(n) \log n)$ ⇒ robust
  - In parallel time, converges in $O(\log n)$

A Plain Biological Implementation

Approximate Majority (AM)



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A Simple Population Protocol for Fast Robust Approximate Majority

2007

Epigenetic Switch

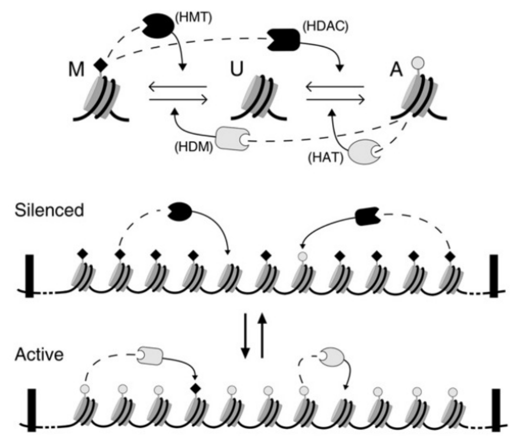

Figure 1. Basic Ingredients of the Model

2007

Theory

Cell

Theoretical Analysis of Epigenetic Cell Memory by Nucleosome Modification

Ian B. Dodd,[1,2] Mille A. Micheelsen,[1] Kim Sneppen,[1,*] and Geneviève Thon[3]
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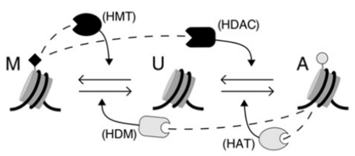
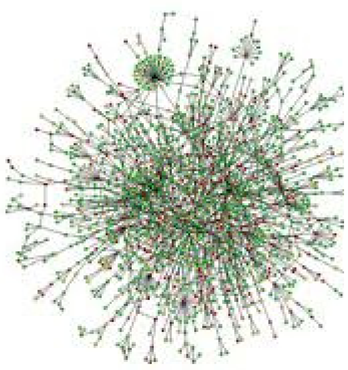
Motivation (cont'd)

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

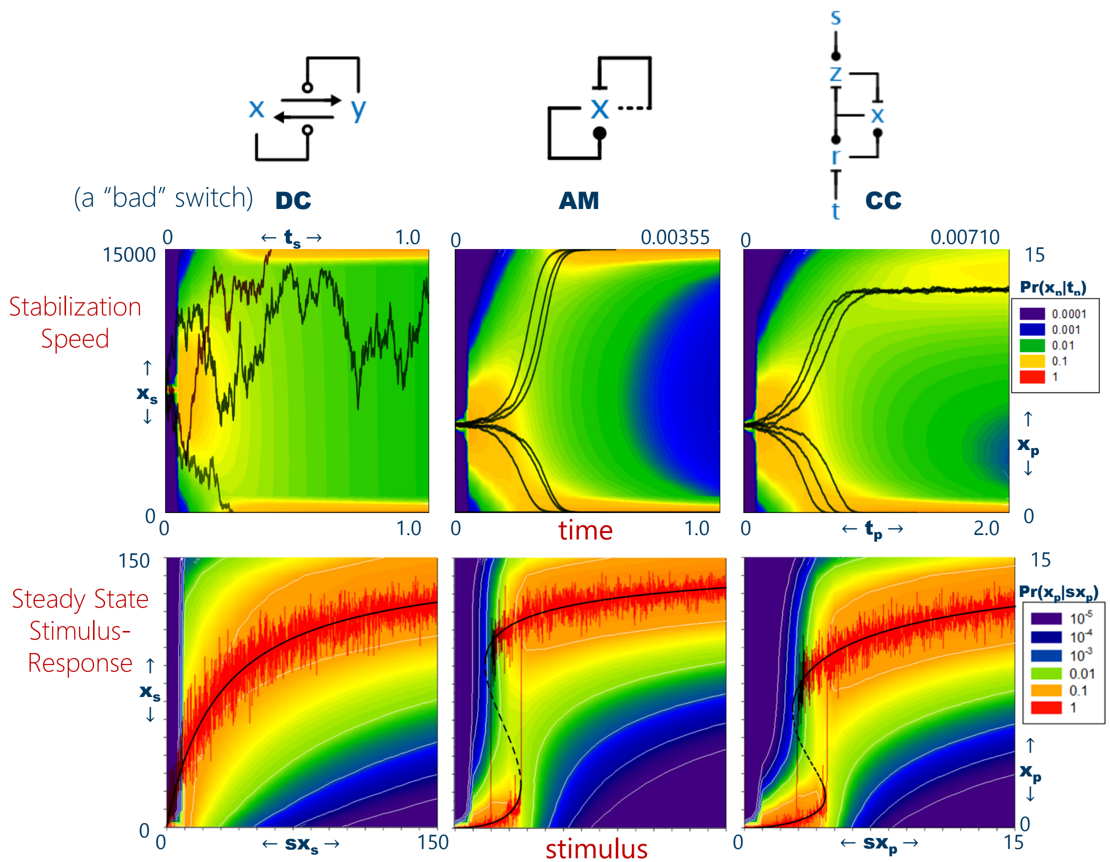


- In most cases the biological implementation seems more *indirect* or *obfuscated*
  - *"Nature is subtle but not malicious - Einstein"* Ha! think again!
  - Other implementations of Approximate Majority seem convoluted and... approximate
  - Like finding an algorithm in a haystack...

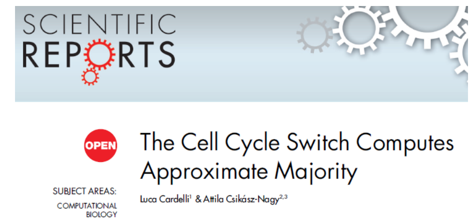


In Previous Work

activation
inhibition
catalysis



The "classical" Cell Cycle Switch **CC** approximates AM performance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The Cell Cycle Switch Computes Approximate Majority

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)

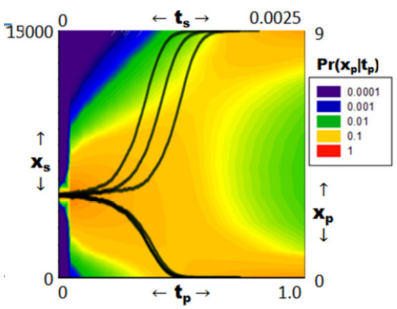
Black lines: deterministic ODE bifurcation diagrams
Red lines: medium-count stochastic simulations
Color: full probability distribution of low-count system

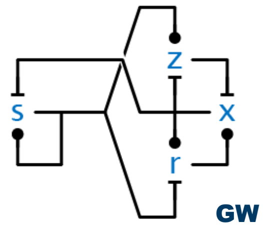
Hor axis is *stimulus* pushing towards x_0 against fixed bias.

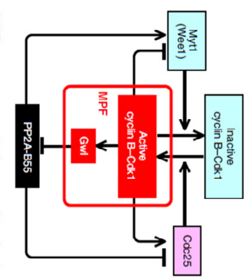
There is an *obvious* bug in CC performance!

In Previous Work

- GW is better!
  - Fully switchable, just as fast as AM
  - GW *emulates* AM







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The Cell Cycle Switch Computes Approximate Majority

SUBJECT AREAS: COMPUTATIONAL BIOLOGY

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

nature COMMUNICATIONS

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ARTICLE

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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]

- That same week:
  - The Greatwall loop is a necessary component of the switch
  - So, nature fixed CC!

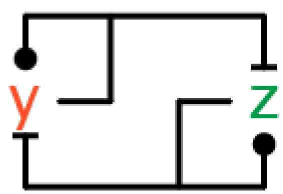
Motivation (cont'd)

- When does a biologically messy network X "implement" some ideal algorithm Y?

- Some networks behave similarly because "their ODEs are just equivalent"
  - When do trajectories of one CRN "collapse" into trajectories of another?
  - This can be answered on the *static structure* of CRNs as opposed to their kinetics.
  - Independently on rates and initial conditions (of one of the two networks).

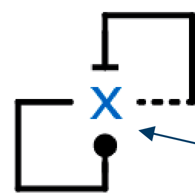
Network Emulation: MI emulates AM

- 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:



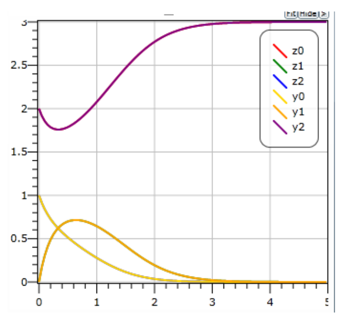
MI

~y,z⇢ x

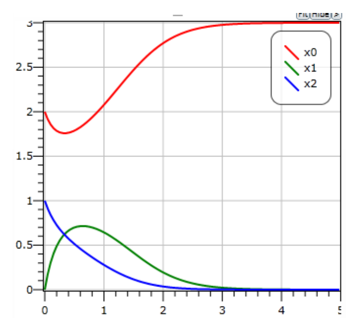


(3 species)

AM



(6 species on 3 trajectories)



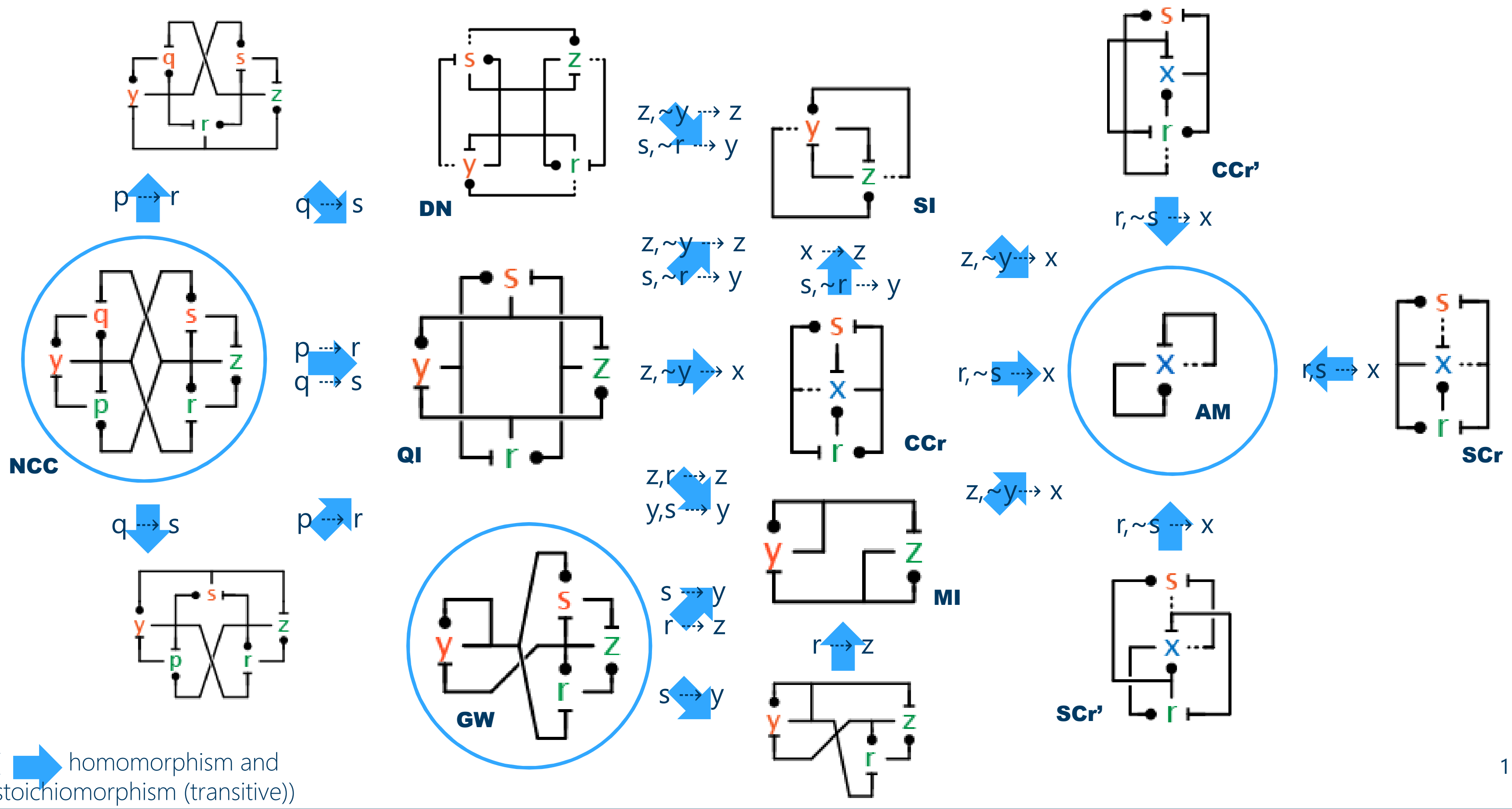
(3 species on 3 trajectories)

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

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

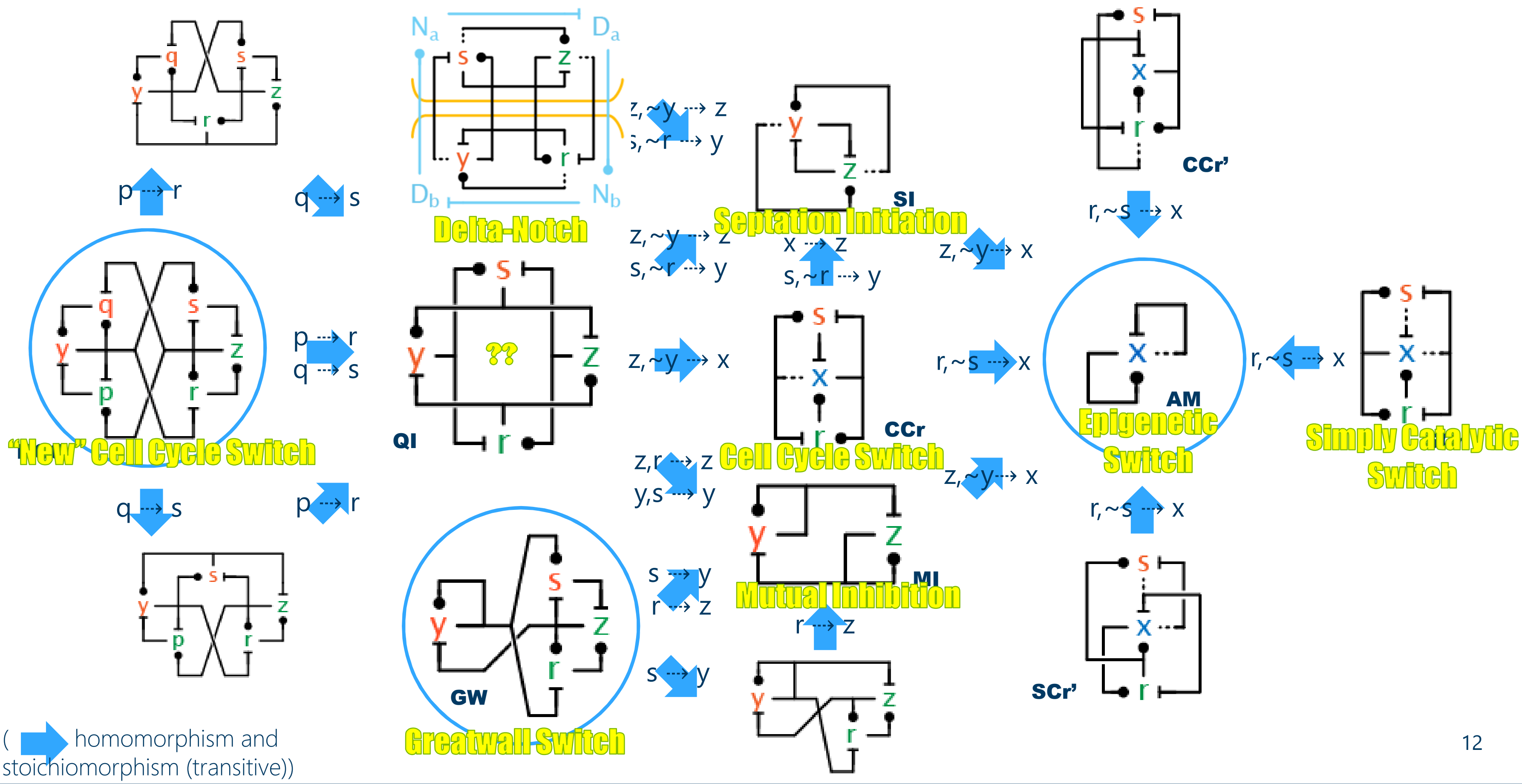
- How do we find these matching parameters? By a network morphism!

Approximate Majority Emulation Zoo



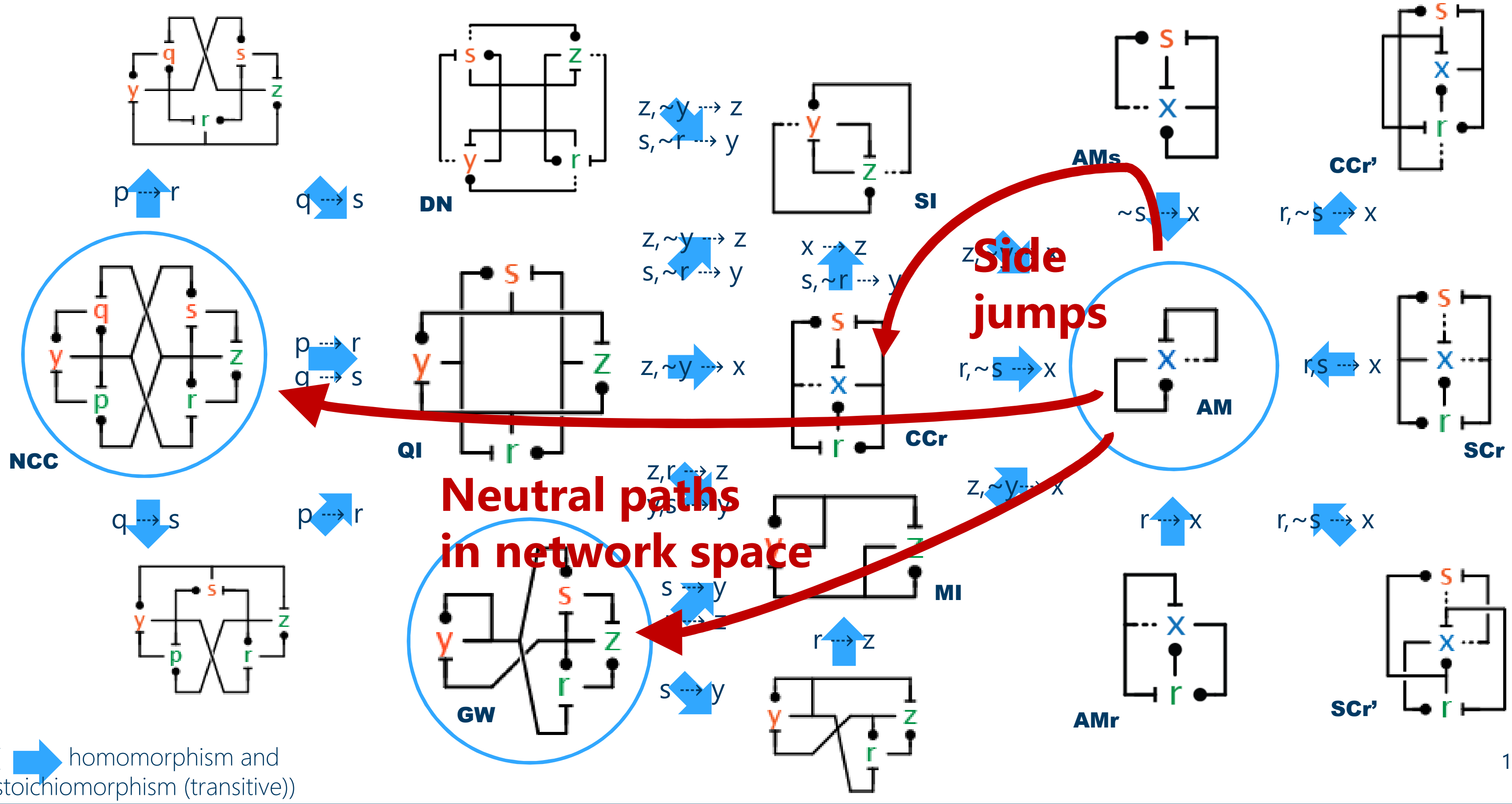
(homomorphism and stoichiomorphism (transitive))

Approximate Majority Emulation Zoo



(homomorphism and stoichiomorphism (transitive))

Approximate Majority Emulation Zoo



(homomorphism and stoichiomorphism (transitive))

Emulation Theorem

Theorem: If $m \in (S,R) \to (\hat{S},\hat{R})$ is a CRN reactant morphism and stoichiomorphism then it is a CRN emulation

reactant morphism $\quad \boldsymbol{m_{\mathcal{S}}}^{\mathbf{T}} \cdot \boldsymbol{\rho} = \boldsymbol{\hat{\rho}} \cdot \boldsymbol{m_{\mathcal{R}}}^{\mathbf{T}}$

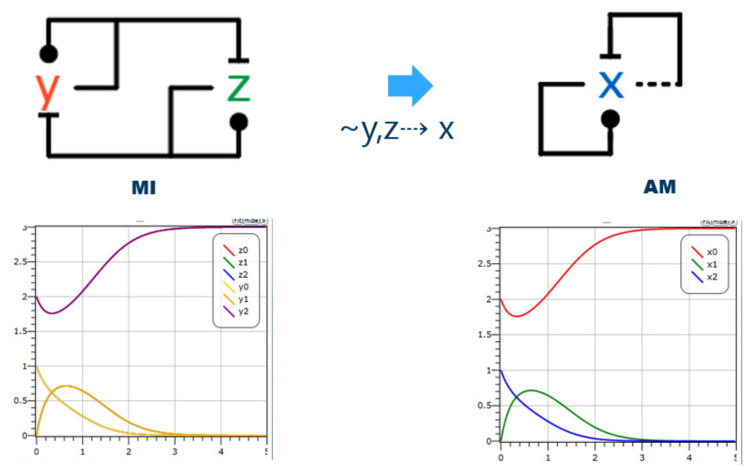
stoichiomorphism $\quad \boldsymbol{\varphi} \cdot \boldsymbol{m_{\mathcal{R}}} = \boldsymbol{m_{\mathcal{S}}} \cdot \boldsymbol{\hat{\varphi}}$

$$\Downarrow$$

emulation $\quad \forall \boldsymbol{\hat{v}}.\ \ F(\boldsymbol{\hat{v}} \circ m_{\mathcal{S}}) = \hat{F}(\boldsymbol{\hat{v}}) \circ m_{\mathcal{S}}$

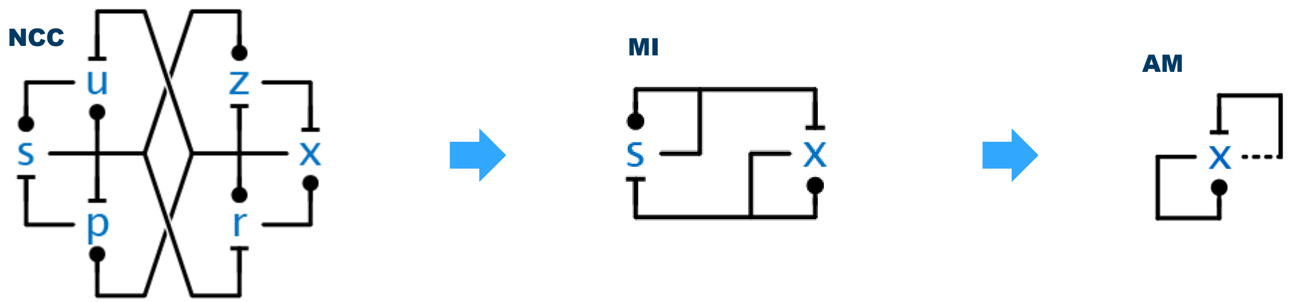
F is the *differential system* of (S,R), given by the law of mass action, $\boldsymbol{\hat{v}}$ is a state of $(\hat{S},\hat{R})$. $\boldsymbol{\varphi}$ is the stoichiometric matrix and $\boldsymbol{\rho}$ is the related reactant matrix. $\boldsymbol{m_{\mathcal{S}}}$ and $\boldsymbol{m_{\mathcal{R}}}$ are the characteristic 0-1 matrices of the morphism maps $m_{\mathcal{S}}$ (on species) and $m_{\mathcal{R}}$ (on reactions).
Homomorphism implies reactant morphism.

Thus, for *any initial conditions* of $(\hat{S},\hat{R})$ we can initialize (S,R) to match its trajectories. And also (another theorem), for *any rates* of $(\hat{S},\hat{R})$ we can choose rates of (S,R) that lead to emulation.



Nature likes a good algorithm

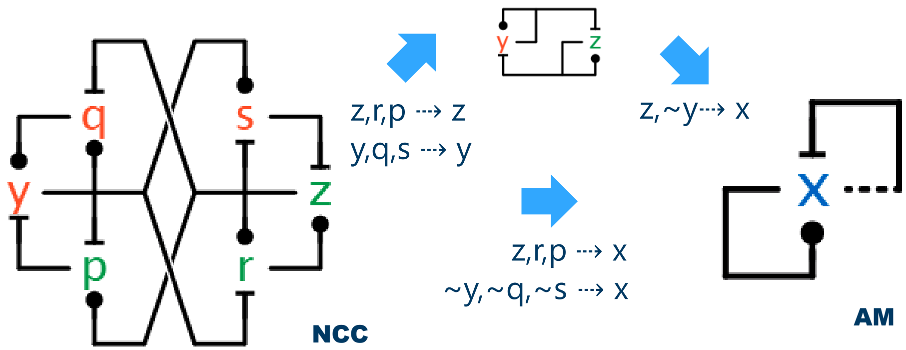
The cell cycle switch *can* exactly emulate Approximate Majority

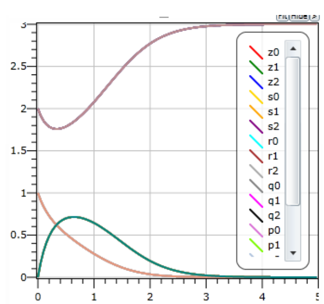


Now we can show this analytically via the Emulation Theorem

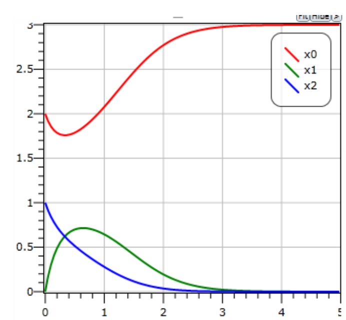
Emulations Compose: NCC emulates AM

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



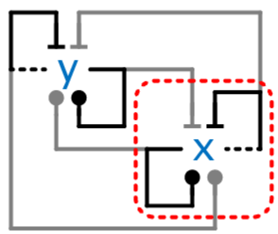


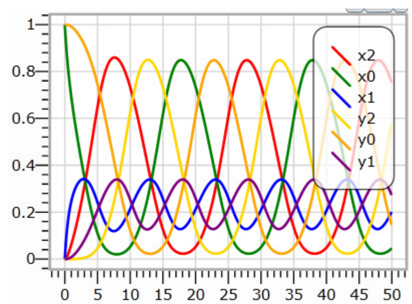
(18 species on 3 trajectories)



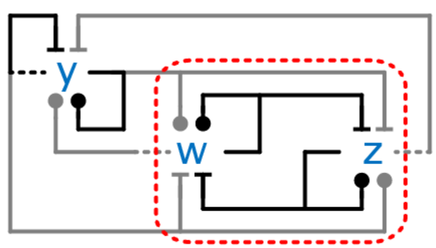
(3 species on 3 trajectories)

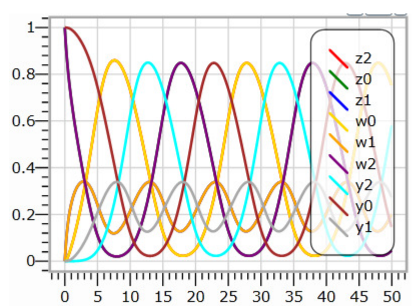
Emulation in Context





AM-AM Oscillator





AM-MI Oscillator

$m \in \mathrm{MI} \to \mathrm{AM}$ is an emulation:
it maps $z \to x$ and $\sim w \to x$

We can replace AM with MI in a context. The mapping m tells us how to wire MI to obtain an overall emulation:

Each influence crossing the dashed lines into x is replaced by a similar influence into *both* z *and* $\sim w$. The latter is the same as an opposite influence into w (shown).

Each influence crossing the dashed lines out of x is replaced by a similar influence from the same side of *either* z *or* $\sim w$. The latter is the same as a similar influence from the opposite side of w (shown), and the same as an opposite influence from the same side of w.

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 implementation (not abstraction!)
  - Stoichiomorphisms are not about abstraction / coarse-graining that preserve behavior, on the contrary, they are about *refinement* / *fine-graining* that preserve behavior.
  - They describe *implementations* of abstract networks, where the abstract networks themselves may not be (biologically) implementable because of excessive demands on species interactions.