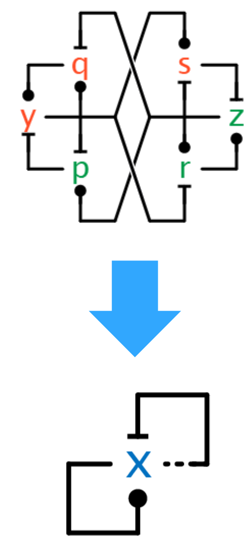
Finding Algorithms in Biological Networks



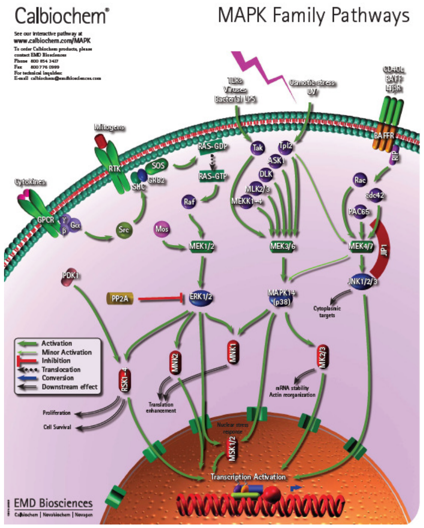
Luca Cardelli, Microsoft Research & Oxford University

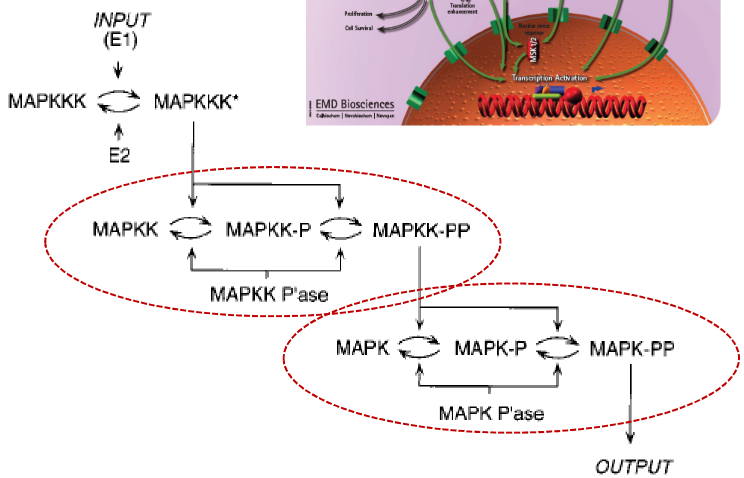
Joint work with Attila Csikász-Nagy, Fondazione Edmund Mach & King's College London

MSRC TAB, 2014-05-12

Cells Compute

- No survival without computation!
  - Finding food
  - Avoiding predators
- How do they compute?
  - *Clearly* doing "information processing"
  - But can we actually catch nature running an (optimal) *algorithm*?

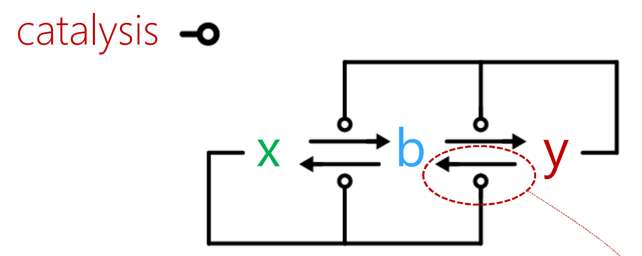




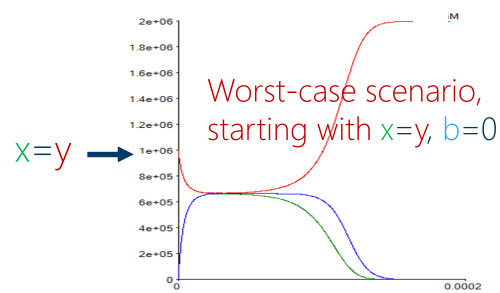
[Ultrasensitivity in the mitogen-activated protein cascade](), Chi-Ying F. Huang and James E. Ferrell, Jr., 1996, *[Proc. Natl. Acad. Sci. USA]()*, 93, 10078-10083.

A Consensus Algorithm

- Population Protocols
  - 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)
- A Population Consensus Problem
  - Find which state x or y is in majority in the population
  - By converting the *whole* population to 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
- 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 $O(\log n)$



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

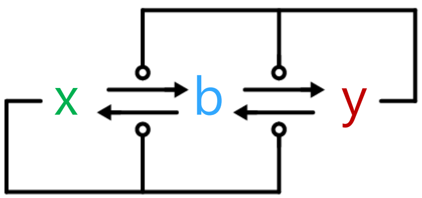


Dana Angluin · James Aspnes · David Eisenstat

A Simple Population Protocol for Fast Robust Approximate Majority

A Plain Biological Implementation

Approximate Majority (AM)



Dana Angluin · James Aspnes · David Eisenstat

A Simple Population Protocol for Fast Robust Approximate Majority

2007

Epigenetic Switch

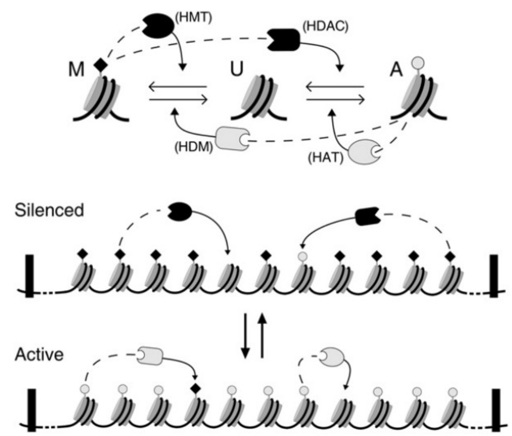


Figure 1. Basic Ingredients of the Model

2007

Theory

Cell

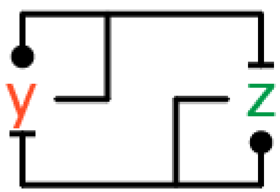
Theoretical Analysis of Epigenetic Cell Memory by Nucleosome Modification

Ian B. Dodd,[1,2] Mille A. Micheelsen,[1] Kim Sneppen,[1,*] and Geneviève Thon[3]
[1]Center for Models of Life, Niels Bohr Institute, Blegdamsvej 17, DK-2100, Copenhagen Ø, Denmark
[2]Department of Molecular and Biomedical Sciences (Biochemistry), University of Adelaide SA 5005, Australia
[3]Department of Molecular Biology, University of Copenhagen Biocenter, Ole Maaløes Vej 5, DK-2200 Copenhagen N, Denmark
*Correspondence: sneppen@nbi.dk
DOI 10.1016/j.cell.2007.02.053

Obfuscated Implementations?

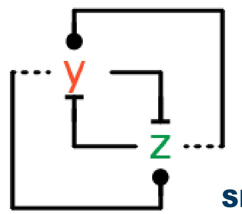
activation
inhibition

Mutual Inhibition & Self Activation



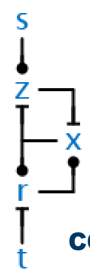
MI

Mutual Inhibition & Mutual Anti-activation



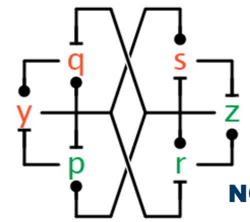
SI

Switching



CC

Better Switching



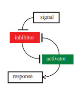
NCC

Cell cycle transitions

Molecular mechanisms creating bistable switches at cell cycle transitions

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

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



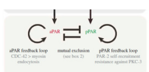
Polarity establishment

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B

rstb.royalsocietypublishing.org

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

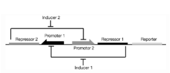
Fumio Motegi and Geraldine Seydoux



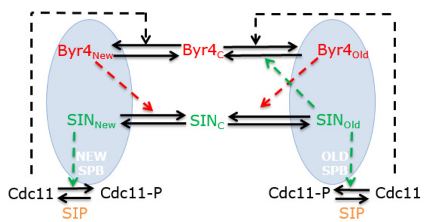
Gene networks

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



SIN inhibiting Byr4,
absence of SIN activating Byr4

Dynamics of SIN Asymmetry Establishment

Archana Bajpai, Anna Feoktistova, Jun-Song Chen, Dannel McCollum, Masamitsu Sato, Rafael E. Carazo-Salas, Kathleen L. Gould, Attila Csikász-Nagy

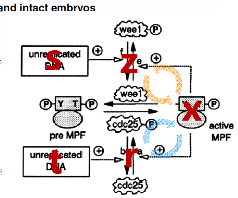
The G_2/M cell cycle switch

Journal of Cell Science 106, 1153-1168 (1993)

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



Nature 344, 503 - 508 (05 April 1990)

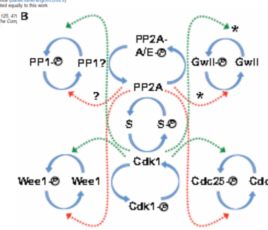
Universal control mechanism regulating onset of M-phase

PAUL NURSE

The "new" cell cycle switch

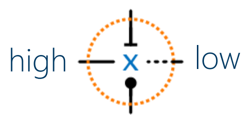
Phosphorylation network dynamics in the control of cell cycle transitions

Daniel Fisher, Liliana Krasinska, Damien Coudreuse and Béla Novák



Influence Networks

activation
inhibition
catalysis



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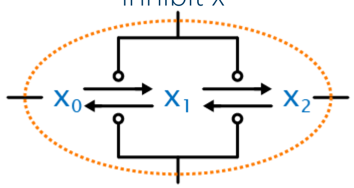
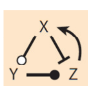


Usually modeled by sigmoid (e.g. Hill or Reinitz) functions



Functional Motifs in Biochemical Reaction Networks

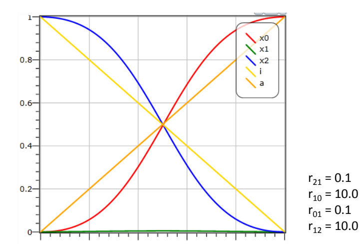
John J. Tyson[1] and Béla Novák[2]

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

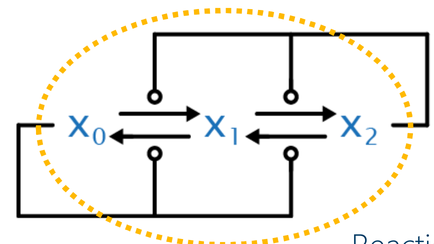
$$A_i = \exp\left\{\sigma_i\left(\alpha_{i0} + \sum_{j=1}^{N} \alpha_{ij} X_j\right)\right\}, \quad B_i = \exp\left\{\sigma_i\left(\beta_{i0} + \sum_{j=1}^{N} \beta_{ij} X_j\right)\right\}, \qquad (4)$$

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:



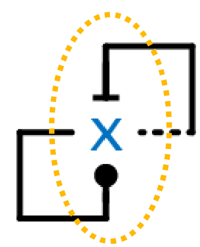
Approximate Majority



Reaction Network

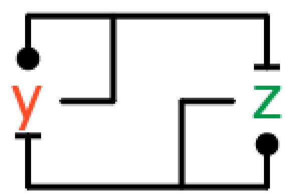
=

Influence Network



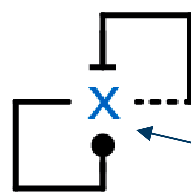
Network Emulation: MI emulates AM

- 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:



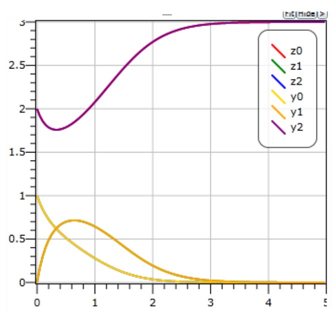
MI

~y,z⇢ x

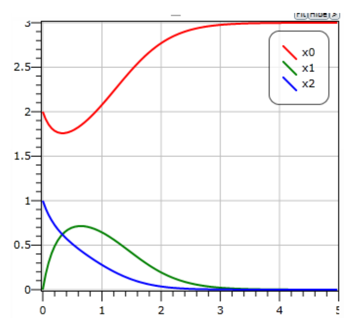


AM

(3 species)



(6 species on 3 trajectories)



(3 species on 3 trajectories)

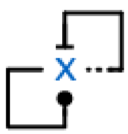
initialize:
$z = x$
$\sim y = x$

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

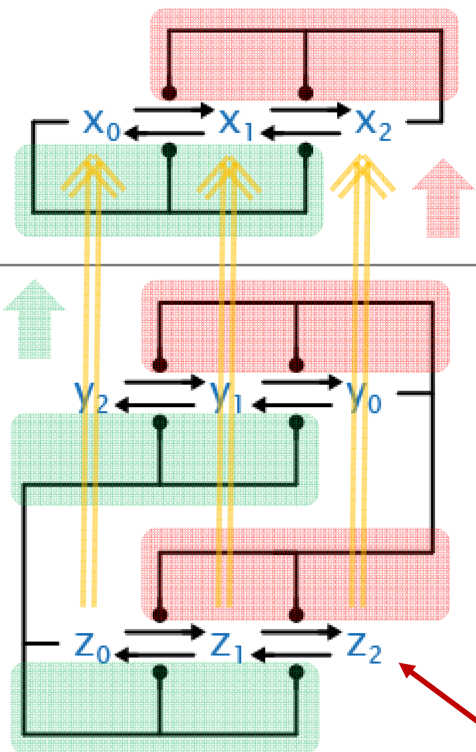
- How do we find these matching parameters? By a network morphism!

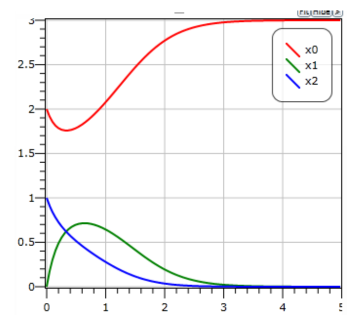
Emulation is a Network Morphism

A mapping of species and reactions



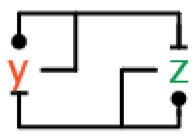
AM



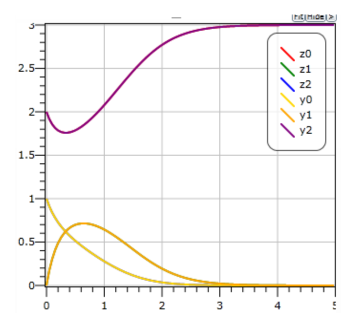


any initial conditions

homomorphic mapping



MI

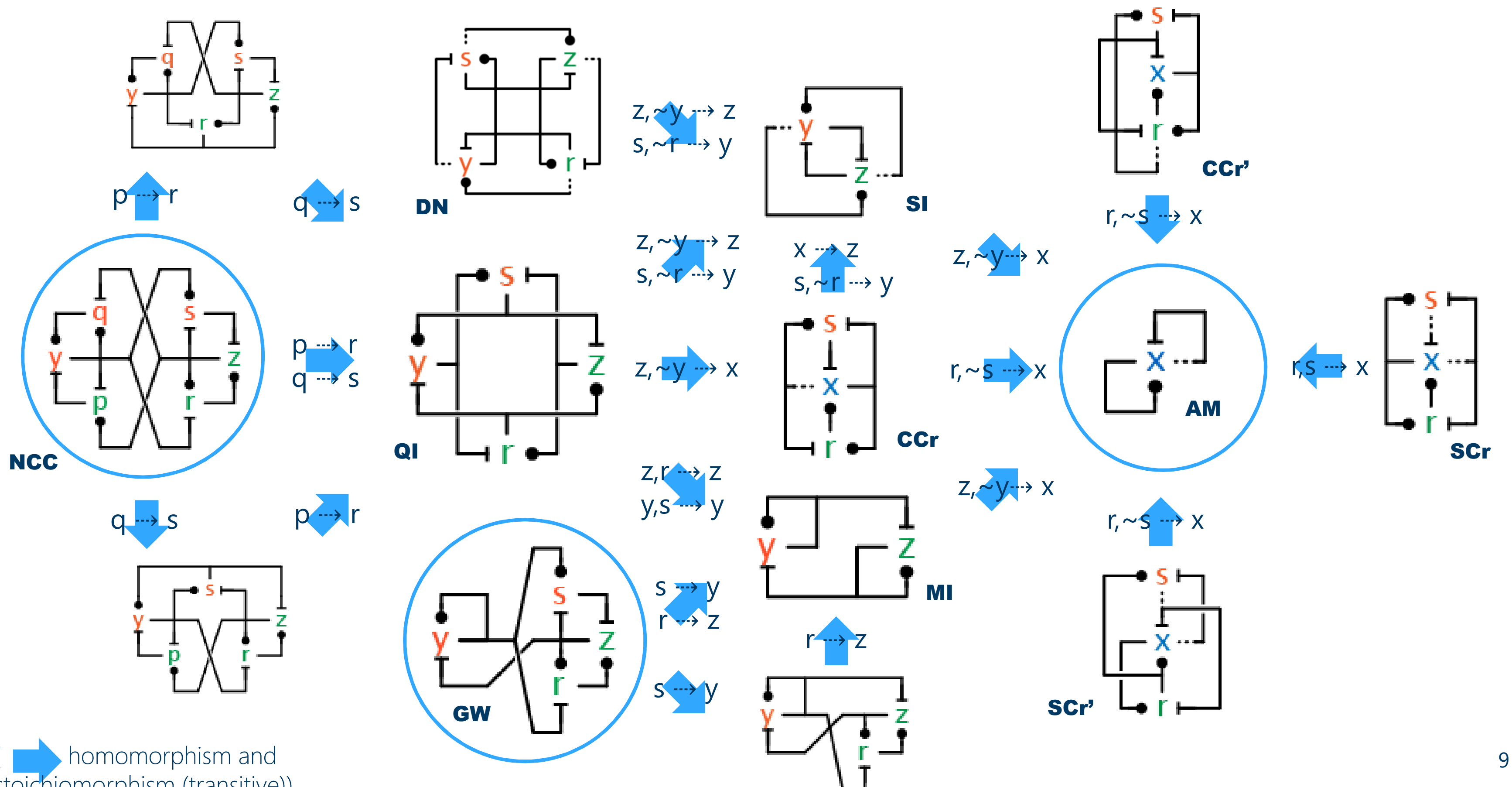


initial conditions:

$z_0 = y_2\ (= x_0)$
$z_1 = y_1\ (= x_1)$
$z_2 = y_0\ (= x_2)$

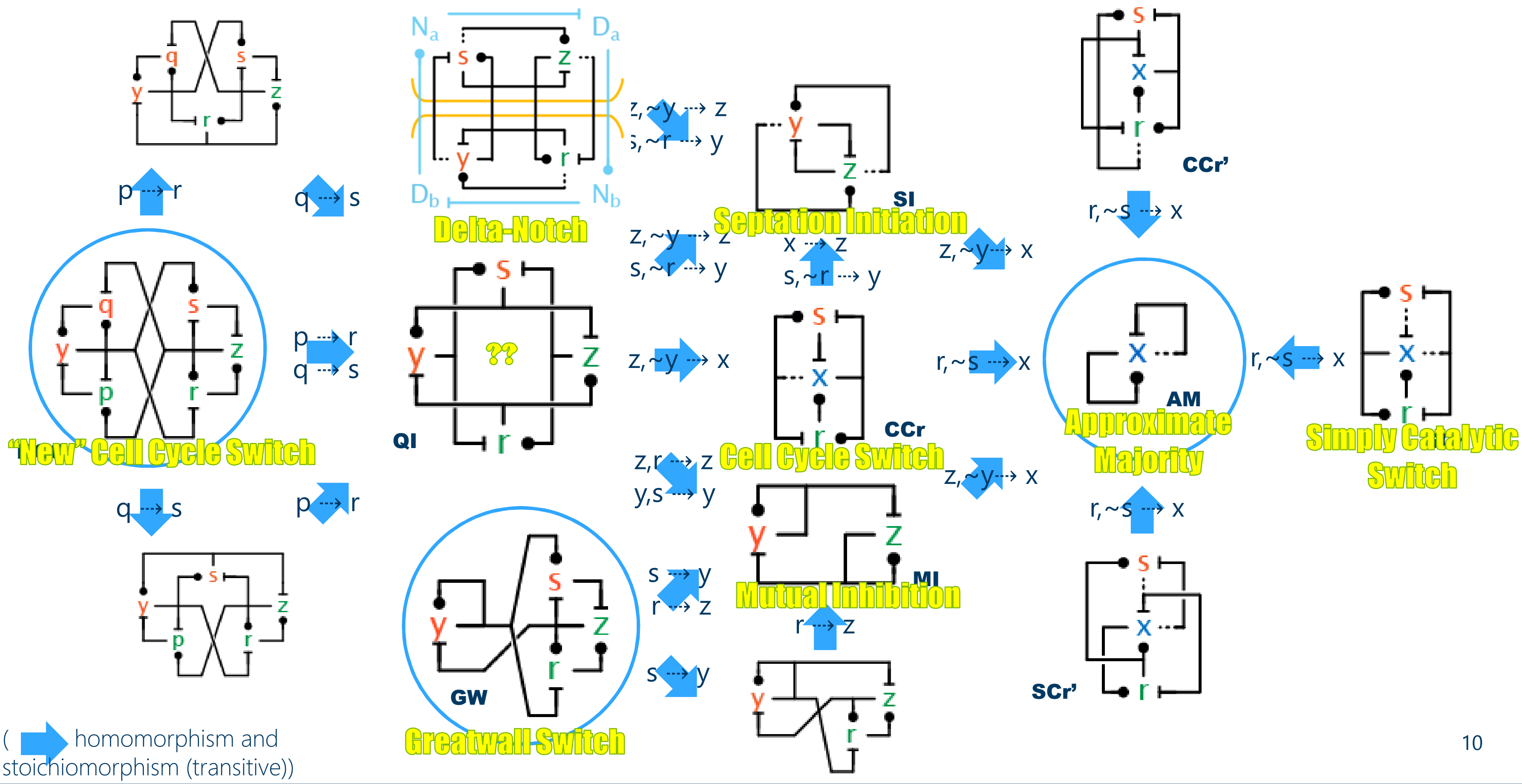
less trivial than you might think:
it need not preserve the out-degree of a node!

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 $\boldsymbol{m_{\mathcal{S}}}^{\mathbf{T}} \cdot \boldsymbol{\rho} = \widehat{\boldsymbol{\rho}} \cdot \boldsymbol{m_{\mathcal{R}}}^{\mathbf{T}}$

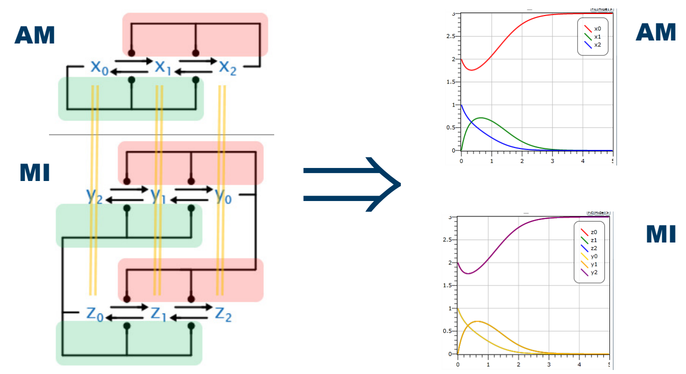
stoichiomorphism $\boldsymbol{\varphi} \cdot \boldsymbol{m_{\mathcal{R}}} = \boldsymbol{m_{\mathcal{S}}} \cdot \widehat{\boldsymbol{\varphi}}$

$$\Downarrow$$

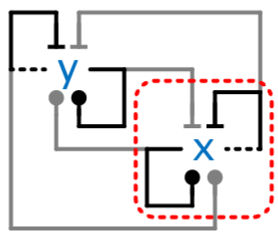
emulation $\forall \widehat{\boldsymbol{v}}.\ \ F(\widehat{\boldsymbol{v}} \circ m_{\mathcal{S}}) = \hat{F}(\widehat{\boldsymbol{v}}) \circ m_{\mathcal{S}}$

F is the *differential system* of (S,R), given by the law of mass action, $\widehat{\boldsymbol{v}}$ 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.

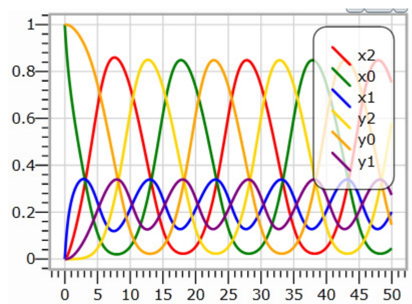
Thus, for *any initial conditions* of $(\hat{S},\hat{R})$ we can initialize (S,R) to match its trajectories. And also (another theorem), for *any rates* of $(\hat{S},\hat{R})$ we can choose rates of (S,R) that lead to emulation.

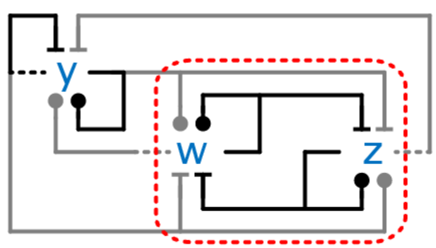


Emulation in Context

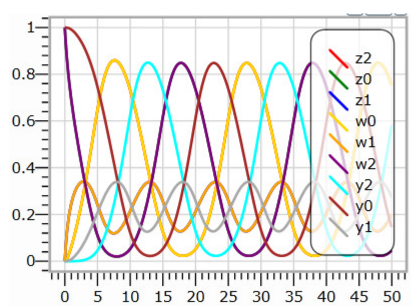


AM-AM Oscillator





AM-MI Oscillator



$m \in \mathbf{MI} \to \mathbf{AM}$ 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.

Nature likes a good algorithm

The cell cycle switch *can* exactly emulate Approximate Majority