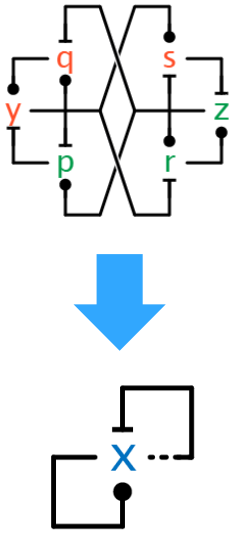
Microsoft Research

UNIVERSITY OF OXFORD

# The Cell Cycle Switch Computes Approximate Majority



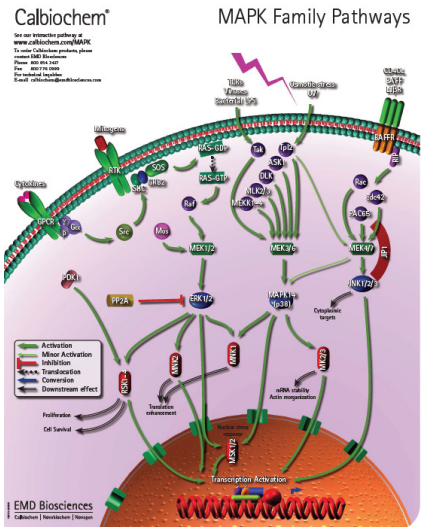

Luca Cardelli, Microsoft Research & Oxford University

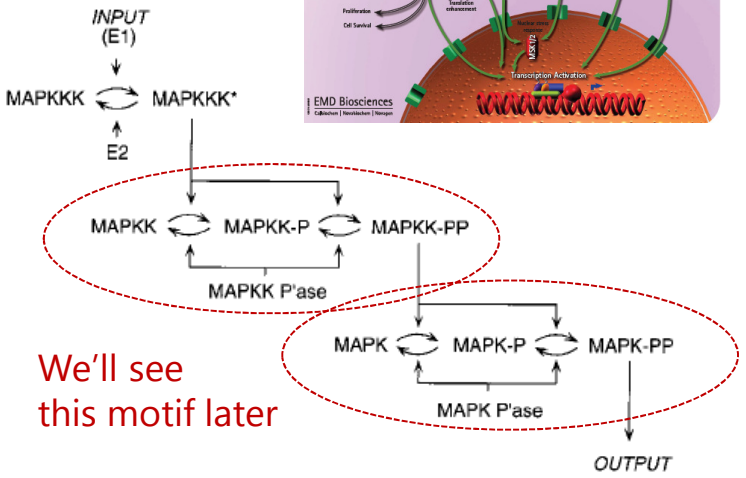
Joint work with Attila Csikász-Nagy, Fondazione Edmund Mach & King's College London

Northwestern University, CS+X Colloquium, 2014-04-29

# 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*?

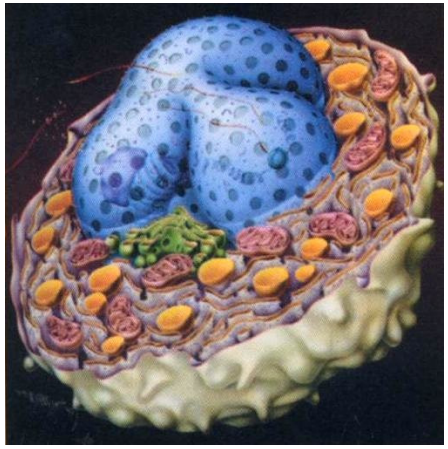


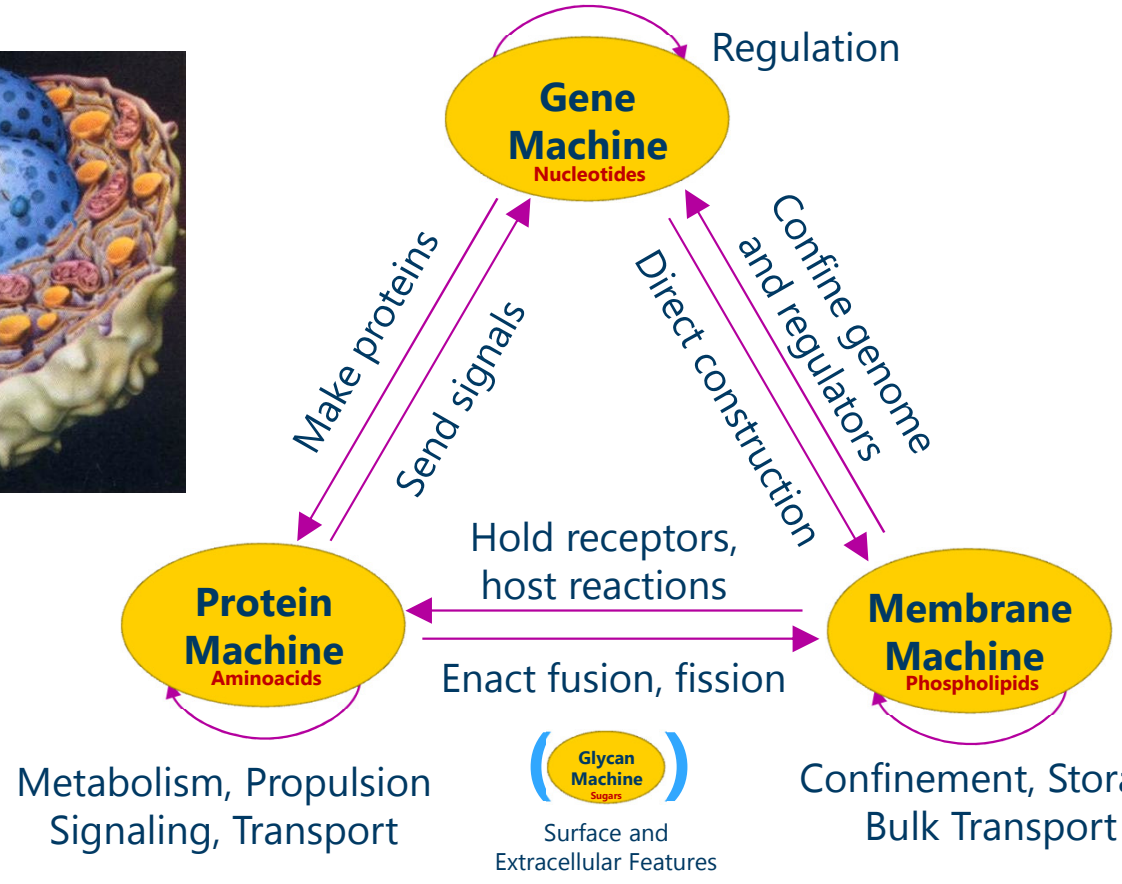




We'll see this motif later

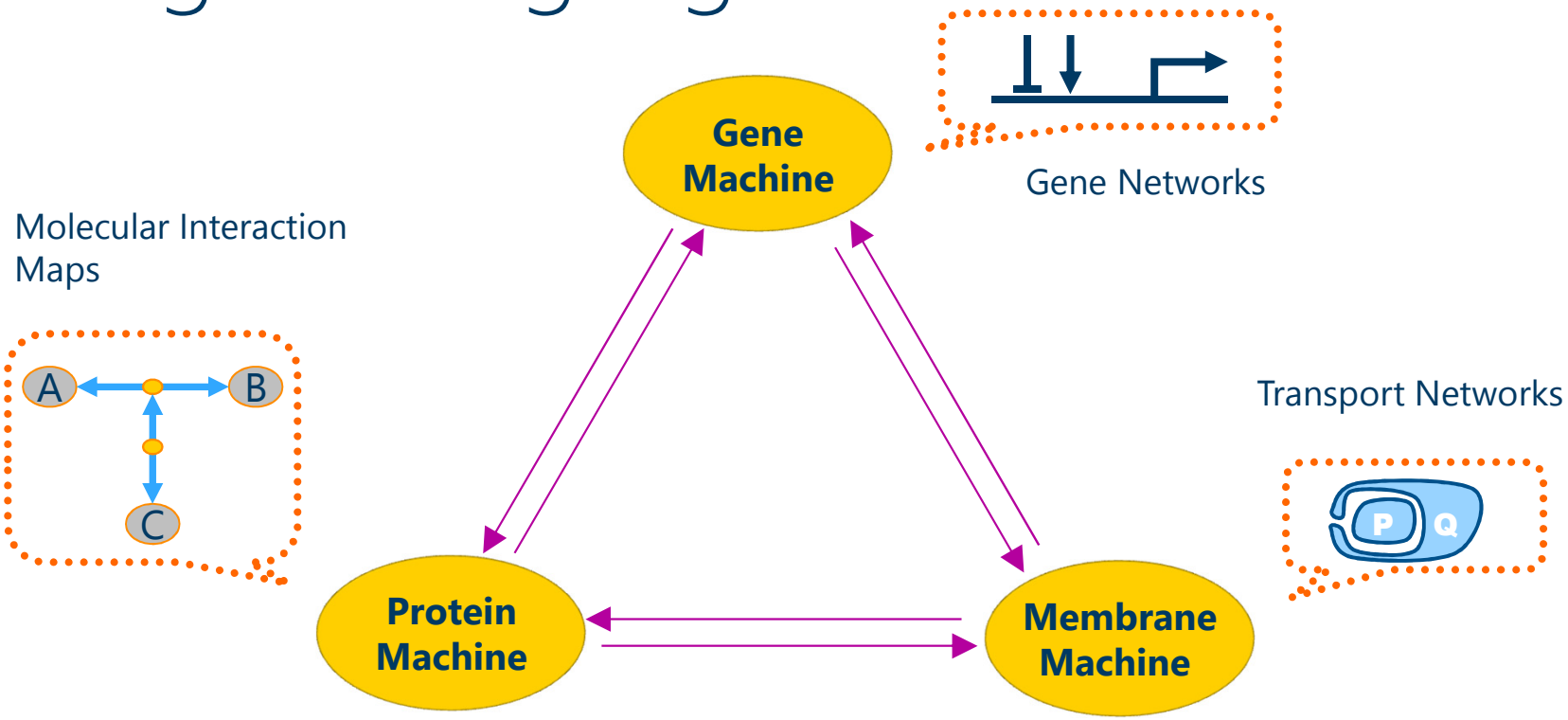
Ultrasensitivity in the mitogen-activated protein cascade, Chi-Ying F. Huang and James E. Ferrell, Jr., 1996, *Proc. Natl. Acad. Sci. USA*, 93, 10078-10083.

# Abstract Machines of Biology





# Biological Languages

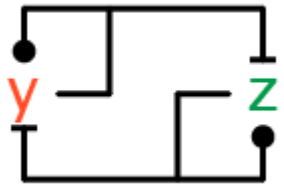



⇒ algorithms

# Biological Networks

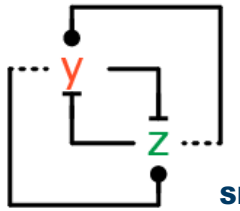
activation
inhibition

## Mutual Inhibition & Self Activation




MI

## Mutual Inhibition & Mutual Anti-activation

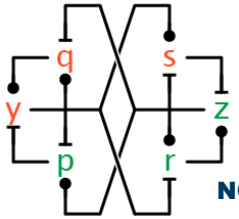



SI

## Something Mysterious

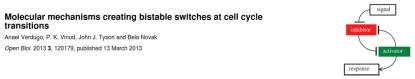

CC

## Something Complicated




NCC

### Cell cycle transitions



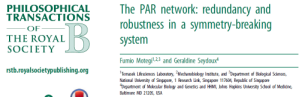
Molecular mechanisms creating bistable switches at cell cycle transitions

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

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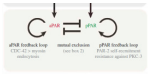
The PAR network: redundancy and robustness in a symmetry-breaking system

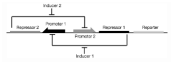
Fumio Matsogi[1,2] and Geraldine Seydoux[3]



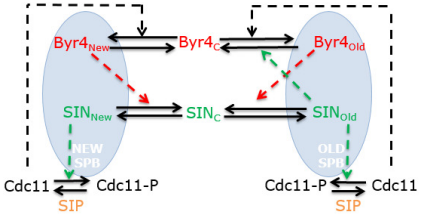
### Gene networks

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

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

### The $G_2$/M cell cycle switch

Journal of Cell Science 106, 1153-1168 (1993)
Printed in Great Britain © The Company of Biologists Limited 1993

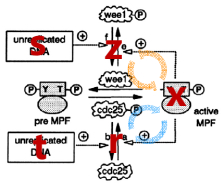
Numerical analysis of a comprehensive model of M-phase control in *Xenopus* oocyte extracts and intact embryos

Bela Novak* and John J. Tyson†

Department of Biology, Virginia Polytechnic

*Permanent address: Department of Agricultural Chemico

†Author for correspondence




*Nature* **344**, 503 - 508 (05 April 1990); doi:10.1038/3

Universal control mechanism regulating onset of M-phase

PAUL NURSE

ICRF Cell Cycle Group, Department of Biochemistry, University of Oxford, South Parks Road, Oxford OX1 3QU, UK

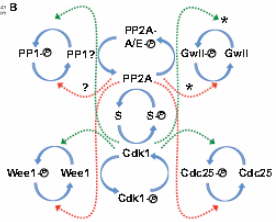
### The "new" cell cycle switch

Phosphorylation network dynamics in the control of cell cycle transitions

Daniel Fisher[1,*], Liliana Krasinska[1,2], Damien Coudreuse[3,4] and Béla Novák[3,5]

[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, 4…
© 2012. Published by The Com…
doi: 10.1242/jcs.106351



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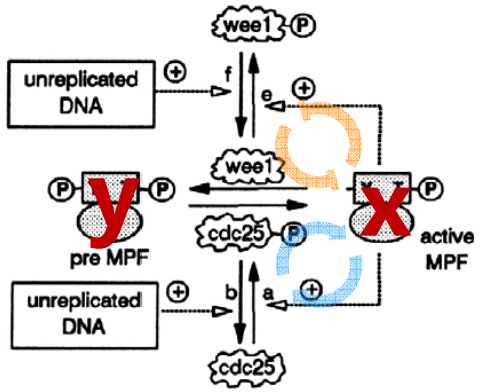
# How to build a good switch

# 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:




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

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

# How to Build a Good Switch

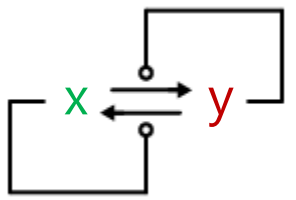
- What is a "good" switch?
  - We need first a bistable system: one that has two *distinct* and *stable* states. I.e., given any initial state the system must settle into one of two states
  - The settling must be fast (not get stuck in the middle for too long) and robust (must not spontaneously switch 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

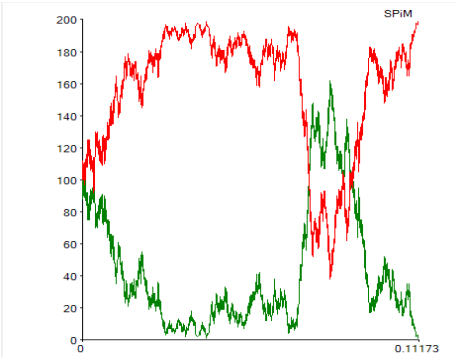
- This system has two end states, but
  - Convergence to an end state is slow (a random walk)
  - Any perturbation of an end state can start a random walk to the other end state (hence not really *bistable*)

catalysis




$y + x \rightarrow x + x$

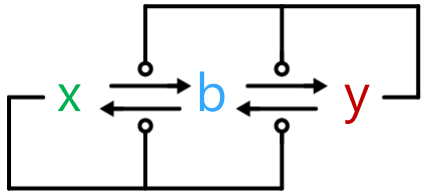
$x + y \rightarrow y + y$



# A Very Good Algorithm

- Approximate Majority (AM)
  - 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 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 $O(\log n)$

catalysis



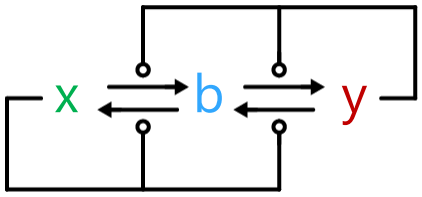

$$x + y \rightarrow y + b$$
$$y + x \rightarrow x + b$$
$$b + x \rightarrow x + x$$
$$b + y \rightarrow y + y$$


Dana Angluin · James Aspnes · David Eisenstat

A Simple Population Protocol for Fast Robust Approximate Majority

# A Biological Implementation

## Approximate Majority (AM)




Bistable
  Even when x=y (stochastically)

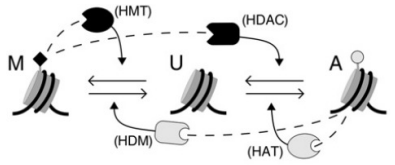
Fast
  *O*(*log n*) convergence time

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

## Epigenetic Switch



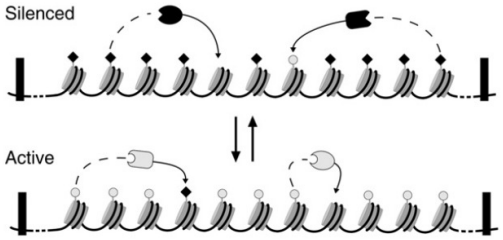
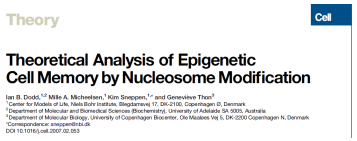




Figure 1. Basic Ingredients of the Model


Theory

Cell

Theoretical Analysis of Epigenetic Cell Memory by Nucleosome Modification

# Back to Biology

- 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?

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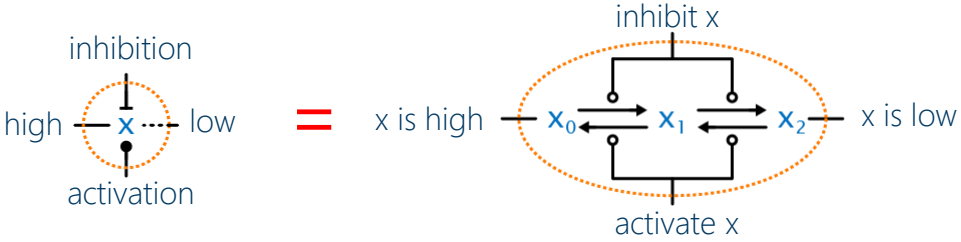
# Algorithms and Dynamical Systems

# Influence Nodes

activation
inhibition
catalysis




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

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

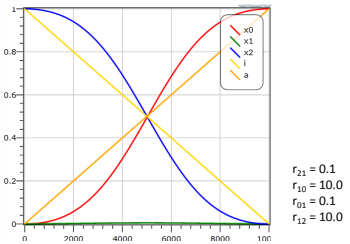

Functional Motifs in Biochemical Reaction Networks

John J. Tyson[1] and Béla Novák[2]

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

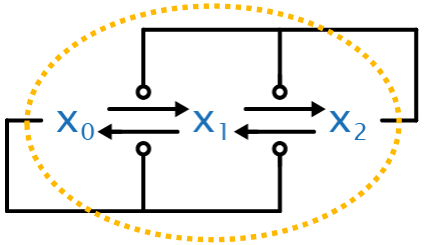
$$A_i = \exp\left\{\sigma_i\left(\alpha_{i0} + \sum_{j=1}^{N} \alpha_{ij} X_j\right)\right\}, \quad B_i = \exp\left\{\sigma_i\left(\beta_{i0} + \sum_{j=1}^{N} \beta_{ij} X_j\right)\right\}, \qquad (4)$$

They actually implement a Hill function of coefficient 2:




$r_{21} = 0.1$
$r_{10} = 10.0$
$r_{01} = 0.1$
$r_{12} = 10.0$

## Approximate Majority

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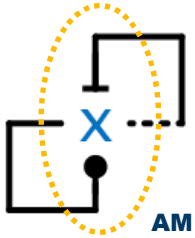
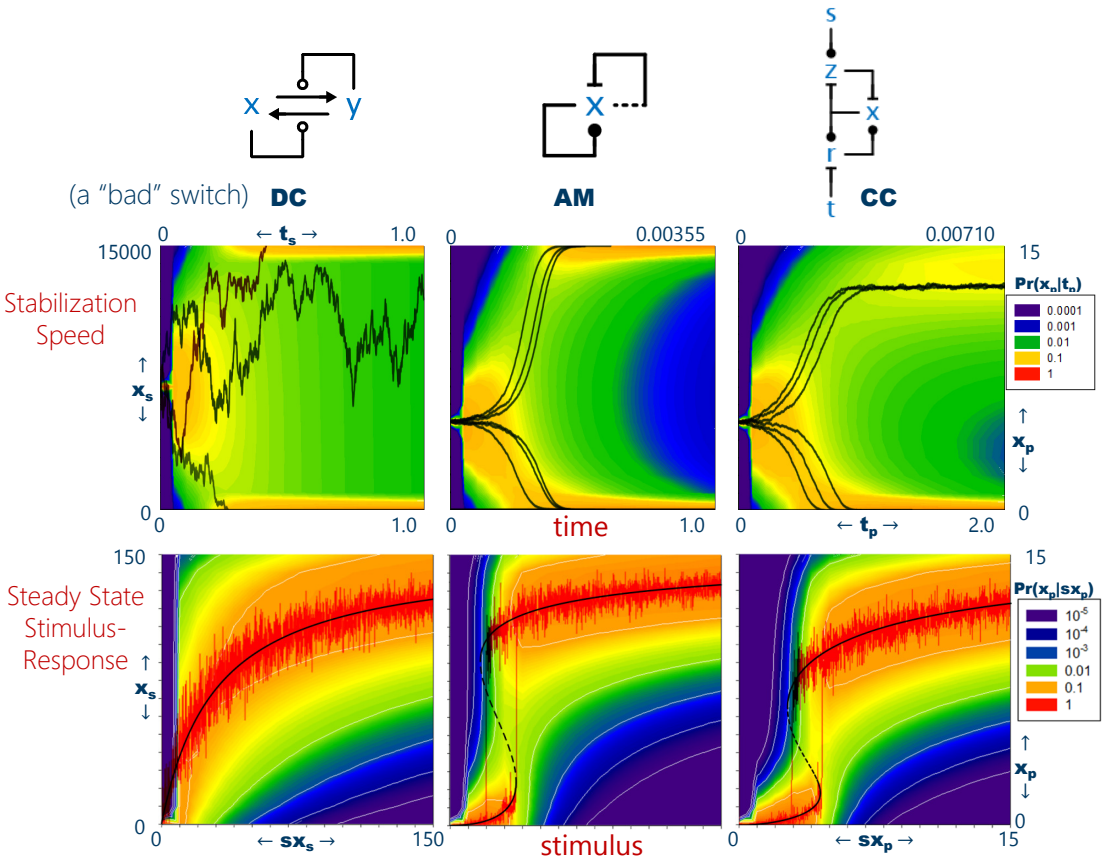


# In Previous Work

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)

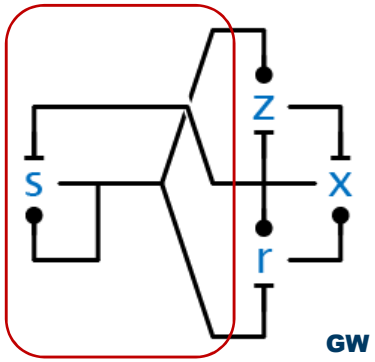
Black lines: deterministic ODE bifurcation diagrams
Red lines: medium-count stochastic simulations
Color: full probability distribution of low-count system

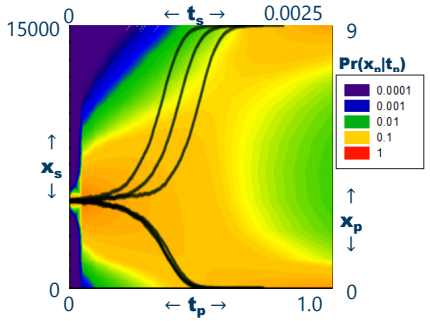
Hor axis is *stimulus* pushing towards $x_0$ against fixed bias.

There is an *obvious* bug in CC performance!

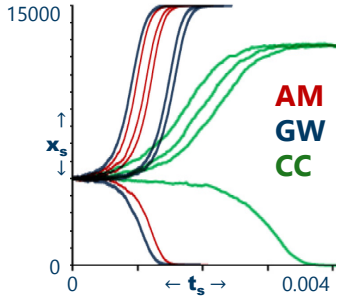
# Nature fixed the bug!

- There is another known feedback loop by which x suppresses s "in retaliation" via the so-called Greatwall loop; s and x are antagonists: they are the two halves of the switch, mutually inhibiting each other (through intermediaries).
- Also, s and t happen to be the same molecule (=s)




Full activation!

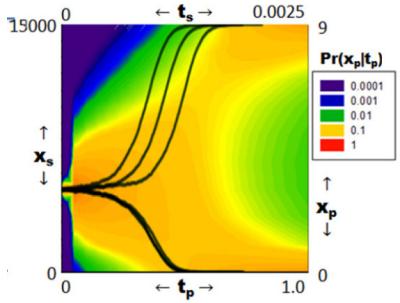



Faster too!

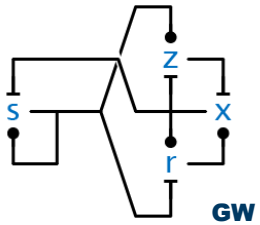
- The "classical" cell cycle switch seems to be only half of the picture: the extra feedback completes it algorithmically and makes it as good as AM.

# In Previous Work

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




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



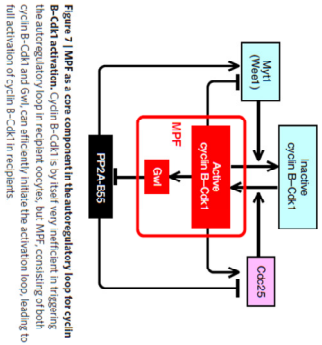




**Figure 7 | MPF as a core component in the autoregulatory loop for cyclin B–Cdk1 activation.** Cyclin B–Cdk1 s by itself very inefficient in triggering the autoregulatory loop in recipient oocytes, but MPF, consisting of both cyclin B–Cdk1 and Gwl, can efficiently initiate the activation loop, leading to full activation of cyclin B–Cdk1 in recipients

SCIENTIFIC REPORTS

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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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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]

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# Networks and Morphisms

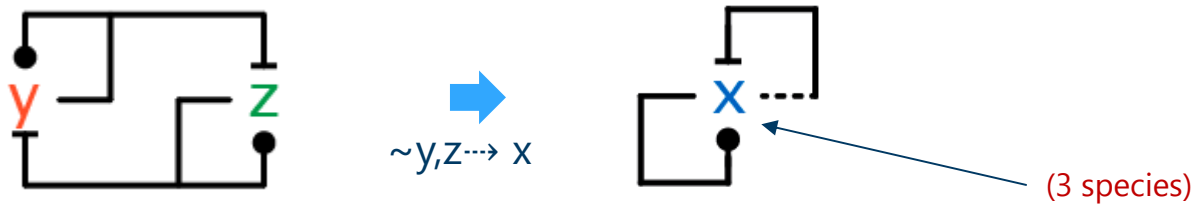
# A Theory of Network Emulation

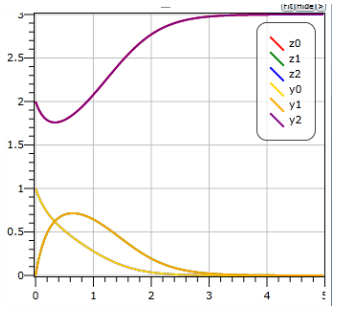
(with thanks to David Soloveichik)

- So far, evidence is empirical
  - Specific simulations based on a choice of parameters
- But indeed…
  - We can show that, GW, NCC, etc. are *exactly* and *always* as good as AM
  - Where *exactly* means *numerically* as good, not just in the same complexity class
  - And *always* means for *any* choice of rates and initial conditions
- A network *emulates* another network:
  - When it can *exactly* reproduce the kinetics of another network for *any* choice of rates and initial conditions
  - We aim to show that the cell cycle switch can emulate AM in that sense
  - And moreover that the emulation is algorithmic: it is determined by network structure

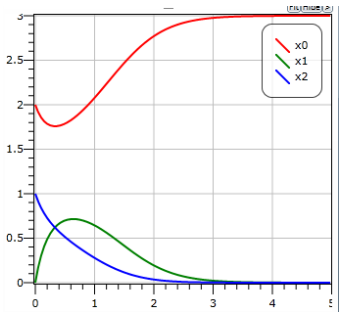
# Network Emulation: MI emulates AM

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




(6 species on 3 trajectories)




(3 species on 3 trajectories)

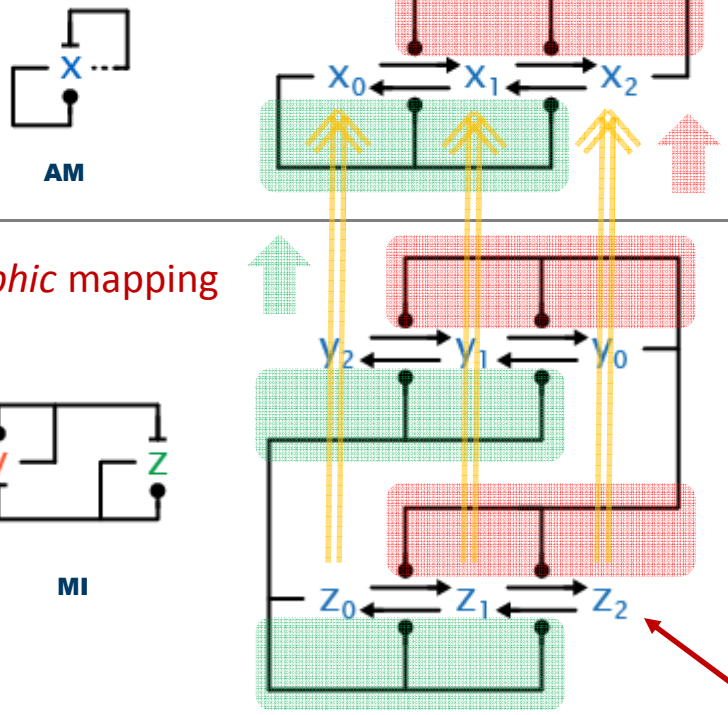
initialize:
$z = x$
$\sim y = x$

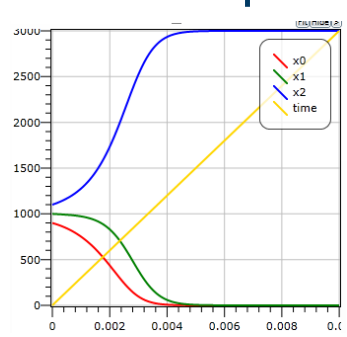
($y_2 = x_0$
$y_1 = x_1$
$y_0 = x_0$)

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

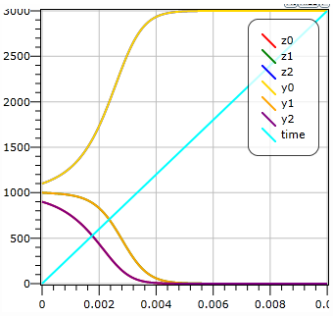
# Emulation is a Network Morphism

A mapping of species and reactions




any initial conditions



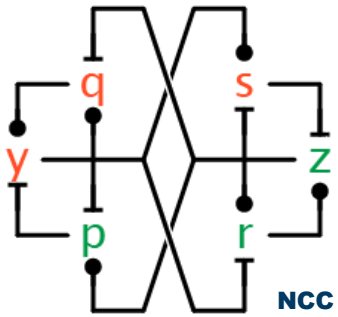

initial conditions:

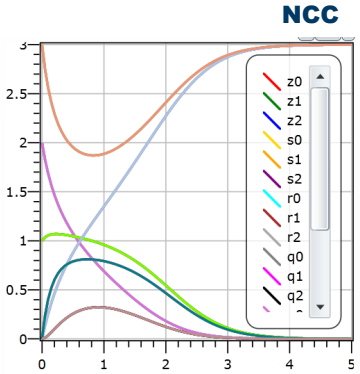
$z_0 = y_2 = x_0$
$z_1 = y_1 = x_1$
$z_2 = y_0 = x_2$

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

# Network Emulation: NCC emulates MI

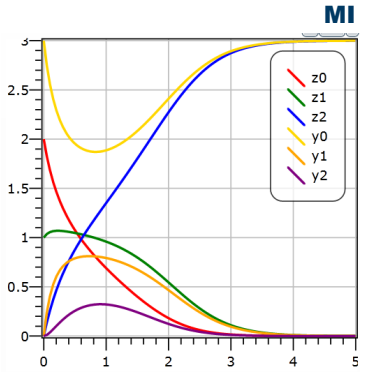
- For *any* rates and initial conditions of MI we can find *some* rates and initial conditions of NCC such that the (18) trajectories of NCC retrace those (6) of MI



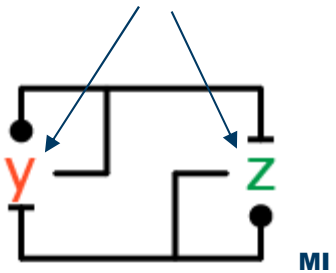

(18 species on 6 trajectories)

z,r,p ⇢ z
y,q,s ⇢ y




(6 species on 6 trajectories)

(3 species each)




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

- Why does this work so well?

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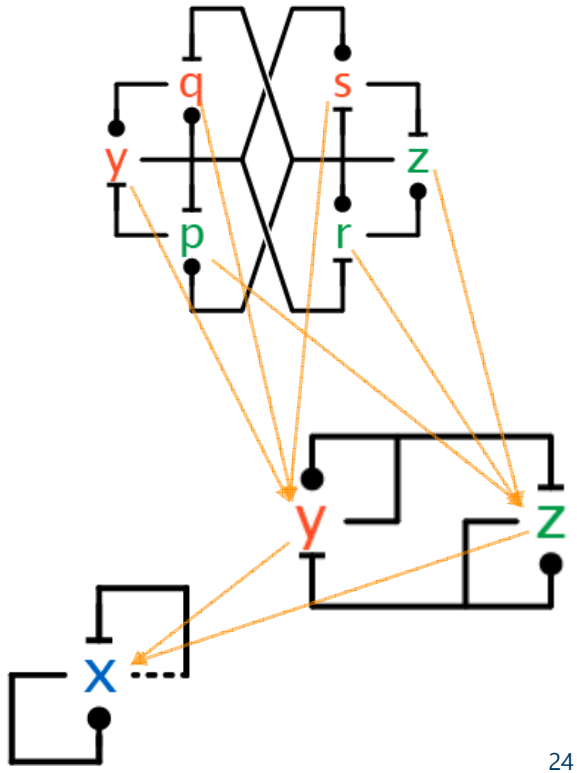
# Kinetic Emulation

# When can a Network Emulate Another?

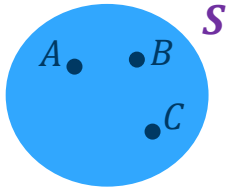
- What kind of morphisms guarantee emulation?
  - do they preserve network structure?
  - do they preserve stoichiometry?



# Chemical Reaction Networks

- A CRN is a pair $(S, R)$ where
  - $S = \{s_1, \dots, s_n\}$ a finite set of *species*
  - $R = \{r_1, \dots, r_m\}$ a finite set of *reactions*

$S = \{A, B, C\}$
$R = \{r\}$

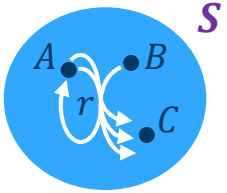



- Reactions $r =$

$$\rho \to^k \pi$$

with *stoichiometric numbers* $\rho, \pi \in \mathbb{N}^S$

$r = 2A + B \to^k A + 3C$
$\rho_A = 2,\ \rho_B = 1,\ \rho_C = 0$
$\pi_A = 1,\ \pi_B = 0,\ \pi_C = 3$




- The *stoichiometry* of $s$ in $\rho \to^k \pi$ is:

$$\eta(s, \rho \to^k \pi) = \pi_s - \rho_s$$
$$\varphi(s, \rho \to^k \pi) = k \cdot (\pi_s - \rho_s)$$

$\eta(A, r) = -1$ *net stoichiometry*
$\varphi(A, r) = -k$ *(instantaneous) stoichiometry*

# CRN Morphisms

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

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

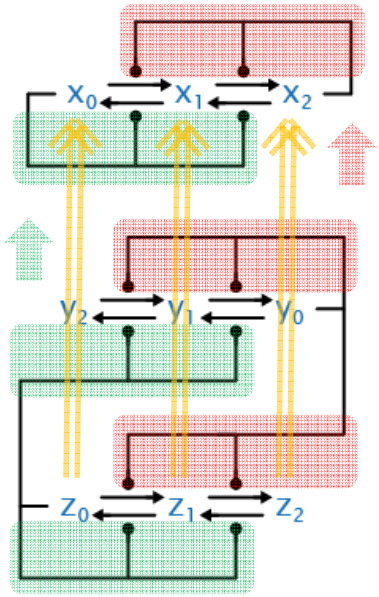
a species map $m_S \in S \to \hat{S}$

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

(sometimes omitting the subscripts on $m$)

We are interested in morphisms that are *not* injective, that represent *refinements* of simpler networks

Mappings (symmetries) between two networks



# 3 Key Morphisms

- A morphism $m \in (S, R) \to (\hat{S}, \hat{R})$ is
  - a *CRN homomorphism* if $m_{\mathcal{R}}$ is determined by $m_{\mathcal{S}}$:

$$m_{\mathcal{R}}(\rho \to^k \pi) = m_{\mathcal{S}}(\rho) \to^k m_{\mathcal{S}}(\pi) \quad \Rightarrow \quad \boldsymbol{m_{\mathcal{S}}{}^{\mathrm{T}} \cdot \varphi = \hat{\varphi} \cdot m_{\mathcal{R}}{}^{\mathrm{T}}}$$

  - a *CRN reactant morphism* if $m_{\mathcal{R}}$ is determined by $m_{\mathcal{S}}$ on reactants. $\exists \hat{k}, \hat{\pi}$:

$$m_{\mathcal{R}}(\rho \to^k \pi) = m_{\mathcal{S}}(\rho) \to^{\hat{k}} \hat{\pi} \quad \Leftrightarrow \quad \boldsymbol{m_{\mathcal{S}}{}^{\mathrm{T}} \cdot \rho = \hat{\rho} \cdot m_{\mathcal{R}}{}^{\mathrm{T}}}$$

  - a *CRN stoichiomorphism* if:

*def.* $\quad \boldsymbol{\varphi \cdot m_{\mathcal{R}} = m_{\mathcal{S}} \cdot \hat{\varphi}}$

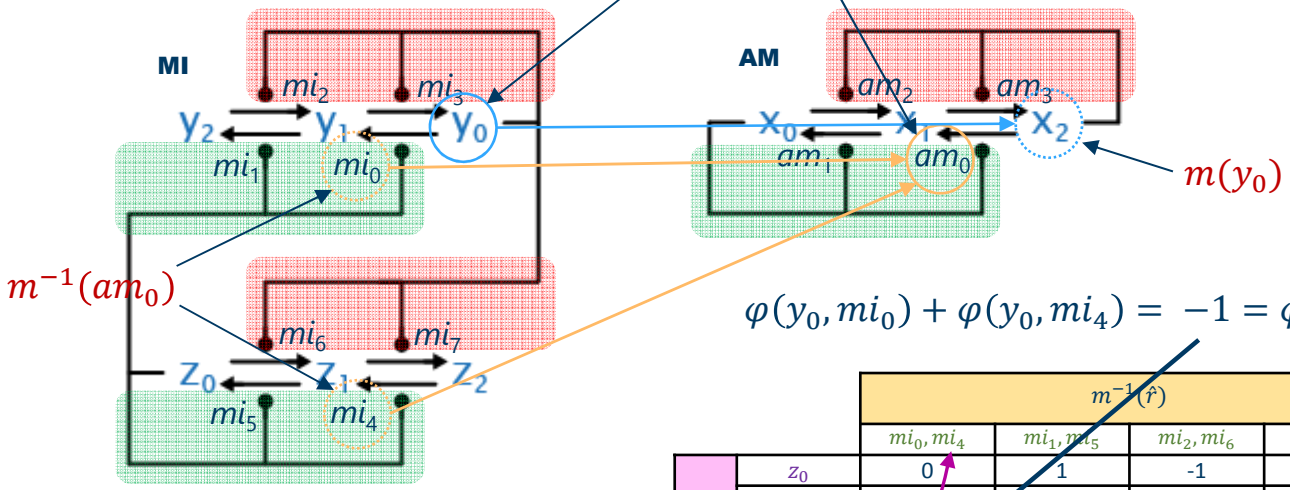
$\boldsymbol{\varphi}, \hat{\boldsymbol{\varphi}}$ are the respective stoichiometric matrices
$\boldsymbol{\rho}, \hat{\boldsymbol{\rho}}$ are the respective reactant matrices
$\boldsymbol{m_{\mathcal{S}}}, \boldsymbol{m_{\mathcal{R}}}$ are the characteristic 0-1 matrices of $m_{\mathcal{S}}, m_{\mathcal{R}}$
$\boldsymbol{m_{\mathcal{S}}}(s, \hat{s}) = 1$ if $m_{\mathcal{S}}(s) = \hat{s}$ else 0

$m_{\mathcal{S}}(\rho)_{\hat{s}} = \Sigma_{s \in m_{\mathcal{S}}{}^{-1}(\hat{s})} \rho_s$

# Checking the Stoichiomorphism Condition

$m \in \mathrm{MI} \to \mathrm{AM}$

$\forall s \in S.\ \ \forall \hat{r} \in \hat{R}.\ \ \Sigma_{r \in m^{-1}(\hat{r})} \varphi(s,r) = \varphi(m(s),\hat{r})$




$\varphi(y_0, mi_0) + \varphi(y_0, mi_4) = -1 = \varphi(x_2, am_0)$

| | | $m^{-1}(\hat{r})$ | | | | |
|---|---|---|---|---|---|---|
| | | $mi_0, mi_4$ | $mi_1, mi_5$ | $mi_2, mi_6$ | $mi_3, mi_7$ | |
| $\forall s \in \mathrm{MI}$ | $z_0$ | 0 | 1 | -1 | 0 | $x_0$ |
| | $z_1$ | 1 | -1 | 1 | -1 | $x_1$ |
| | $z_2$ | -1 | 0 | 0 | 1 | $x_2$ |
| | $y_0$ | -1 | 0 | 0 | 1 | $x_2$ |
| | $y_1$ | 1 | -1 | 1 | -1 | $x_1$ |
| | $y_2$ | 0 | 1 | -1 | 0 | $x_0$ |
| | | $am_0$ | $am_1$ | $am_2$ | $am_3$ | |
| | | $\forall \hat{r} \in \mathrm{AM}$ | | | | $m(s)$ |

All unit rates (sufficient because of another theorem)

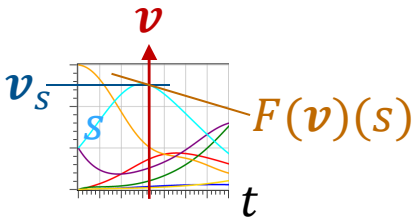
This is both a homomorphism and a stoichiomorphism

# CRN Kinetics

A *state* of a CRN $(S, R)$ is a $\boldsymbol{v} \in \mathbb{R}_+^S$

a vector of concentrations for each species

The *differential system* of a CRN $(S, R)$, $F \in \mathbb{R}_+^S \to \mathbb{R}^S$




$F(\boldsymbol{v})(s)$ gives the instantaneous change of concentration of a species in a given state

Given by the law of mass action:

$$F(\boldsymbol{v})(s) = \Sigma_{r=(\rho \to^{k} \pi) \in R} \ \varphi(s, r) \cdot \Pi_{\acute{s} \in S} \ \boldsymbol{v}_{\acute{s}}^{\ \rho_{\acute{s}}}$$

sum over all reactions of the stoichiometry of species in reaction times the product of reagent concentrations according to their stoichiometric numbers

Usually written as a system of coupled concentration ODEs, integrated over time: $\frac{d\boldsymbol{v}_s}{dt} = F(\boldsymbol{v})(s)$

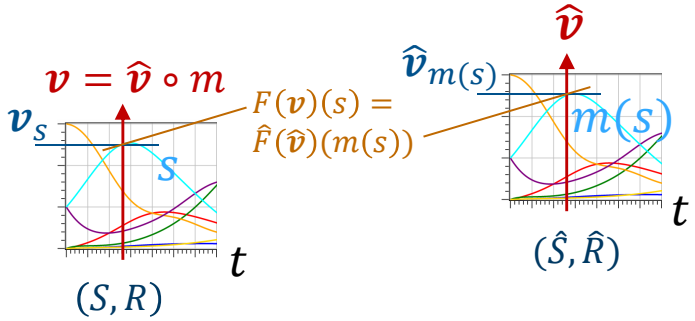
# Kinetic Emulation

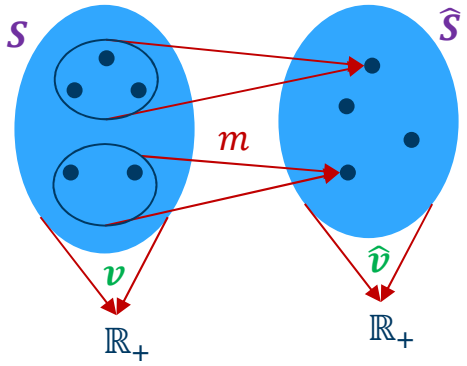
A morphism $m \in (S,R) \to (\hat{S},\hat{R})$ is a *CRN emulation* if for the respective differential systems $F, \hat{F}$, $\forall \hat{\boldsymbol{v}} \in \mathbb{R}_+^{\hat{S}}$:

$$F(\hat{\boldsymbol{v}} \circ m) = \hat{F}(\hat{\boldsymbol{v}}) \circ m$$

$$\begin{array}{ccc} \mathbb{R}^{S}_{\hat{\boldsymbol{v}} \circ m} & \xrightarrow{F} & \mathbb{R}^{S} \\ {\scriptstyle -\circ m}\uparrow & & \uparrow{\scriptstyle -\circ m} \\ \mathbb{R}^{\hat{S}}_{\hat{\boldsymbol{v}}} & \xrightarrow{\hat{F}} & \mathbb{R}^{\hat{S}}_{\hat{F}(\hat{\boldsymbol{v}})} \end{array}$$

That is: $\forall s \in S.\ F(\hat{\boldsymbol{v}} \circ m)(s) = \hat{F}(\hat{\boldsymbol{v}})(m(s))$




if the derivative of $\boldsymbol{s}$ (in state $\hat{\boldsymbol{v}} \circ \boldsymbol{m}$) equals the derivative of $\boldsymbol{m}(\boldsymbol{s})$ (in state $\hat{\boldsymbol{v}}$)

if we *start* the two systems in states $\boldsymbol{v} = \hat{\boldsymbol{v}} \circ \boldsymbol{m}$ (which is a *copy* of $\hat{\boldsymbol{v}}$ according to $\boldsymbol{m}$) and $\hat{\boldsymbol{v}}$ resp., for each $\boldsymbol{s}$ the solutions are equal and the derivatives are equal, hence they will have identical trajectories by determinism

# 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 $\boldsymbol{m_S}^{\mathbf{T}} \cdot \boldsymbol{\rho} = \hat{\boldsymbol{\rho}} \cdot \boldsymbol{m_{\mathcal{R}}}^{\mathbf{T}}$

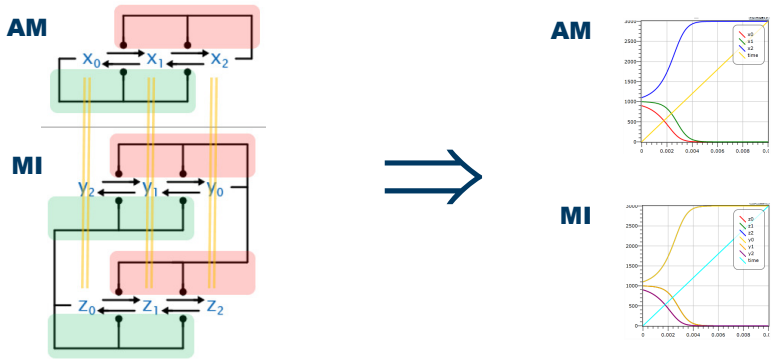
stoichiomorphism $\boldsymbol{\varphi} \cdot \boldsymbol{m_{\mathcal{R}}} = \boldsymbol{m_S} \cdot \hat{\boldsymbol{\varphi}}$

$\Downarrow$

emulation $F(\hat{\boldsymbol{v}} \circ m) = \hat{F}(\hat{\boldsymbol{v}}) \circ m$

N.B. homomorphism implies reactant morphism, implies $\boldsymbol{m_S}^{\mathbf{T}} \cdot \boldsymbol{\rho} = \hat{\boldsymbol{\rho}} \cdot \boldsymbol{m_{\mathcal{R}}}^{\mathbf{T}}$.

thus, for *any initial conditions* of $(\hat{S}, \hat{R})$ we can match trajectories



# Change of Rates Theorem

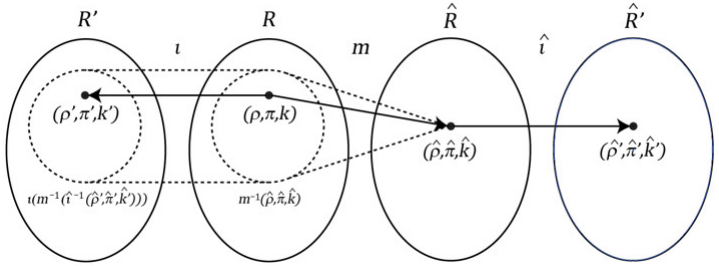
A *change of rates* for $(S, R)$ is morphism $\iota \in (S, R) \to (S, R')$ such that $\iota(S)$ is the identity and $\iota(\rho, \pi, k) = (\rho, \pi, k')$.

a morphism that modifies rates only

**Theorem**: If $m \in (S, R) \to (\hat{S}, \hat{R})$ is a stoichiomorphism, then for *any* change of rates $\hat{\imath}$ of $(\hat{S}, \hat{R})$ there is a change of rates $\iota$ of $(S, R)$ such that $\hat{\imath} \circ m \circ \iota^{-1}$ is a stoichiomorphism.

thus, for *any rates* of $(\hat{S}, \hat{R})$ we can match trajectories

In fact, $\iota$ changes rates by the ratio with which $\hat{\imath}$ changes rates:
$\iota(\rho, \pi, k) = \left(\rho, \pi, k \cdot \frac{\hat{k}'}{\hat{k}}\right)$ where $m(\rho, \pi, k) = (\hat{\rho}, \hat{\pi}, \hat{k})$ and $\hat{\imath}(\hat{\rho}, \hat{\pi}, \hat{k}) = (\hat{\rho}, \hat{\pi}, \hat{k}')$.



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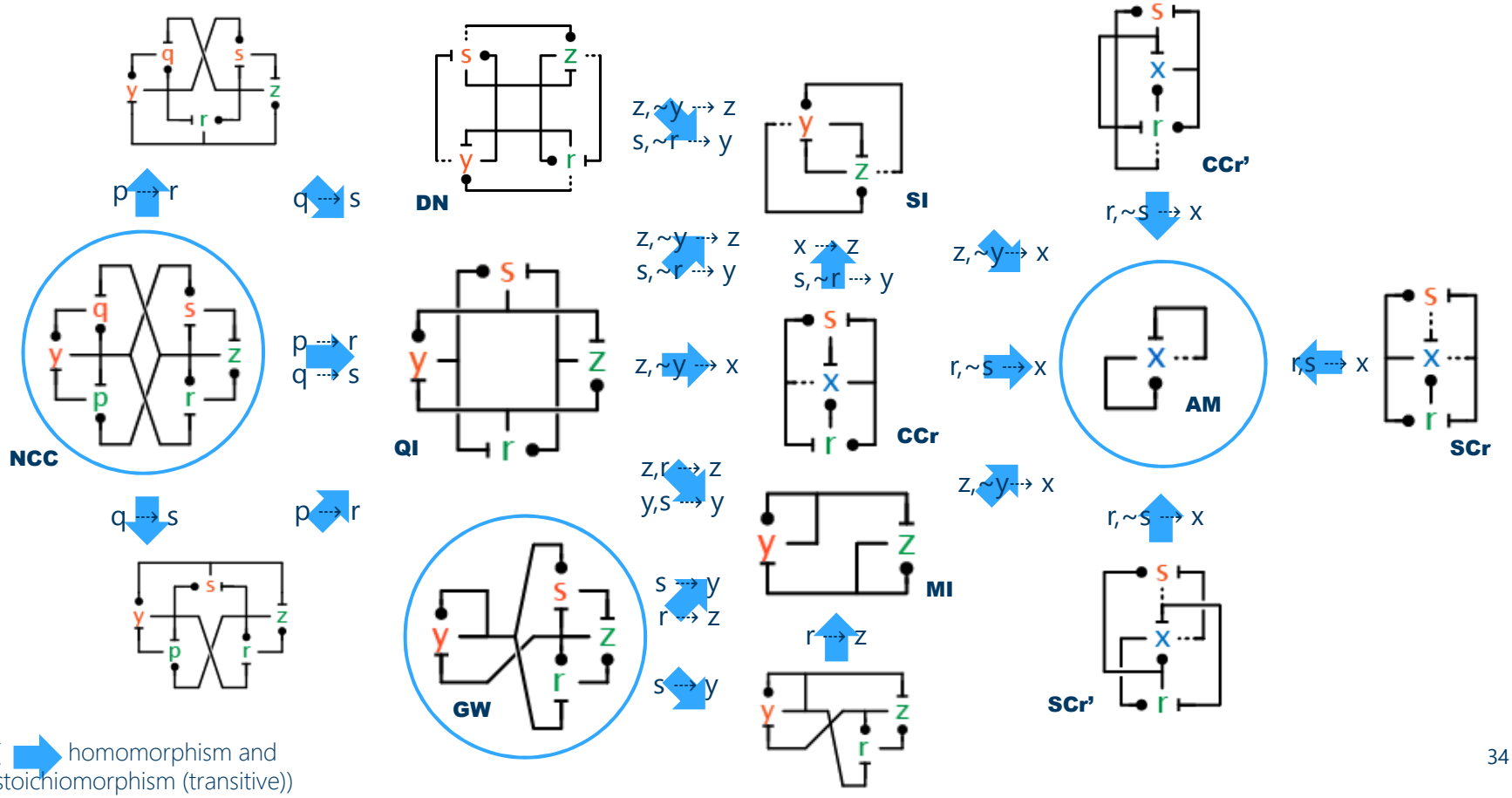
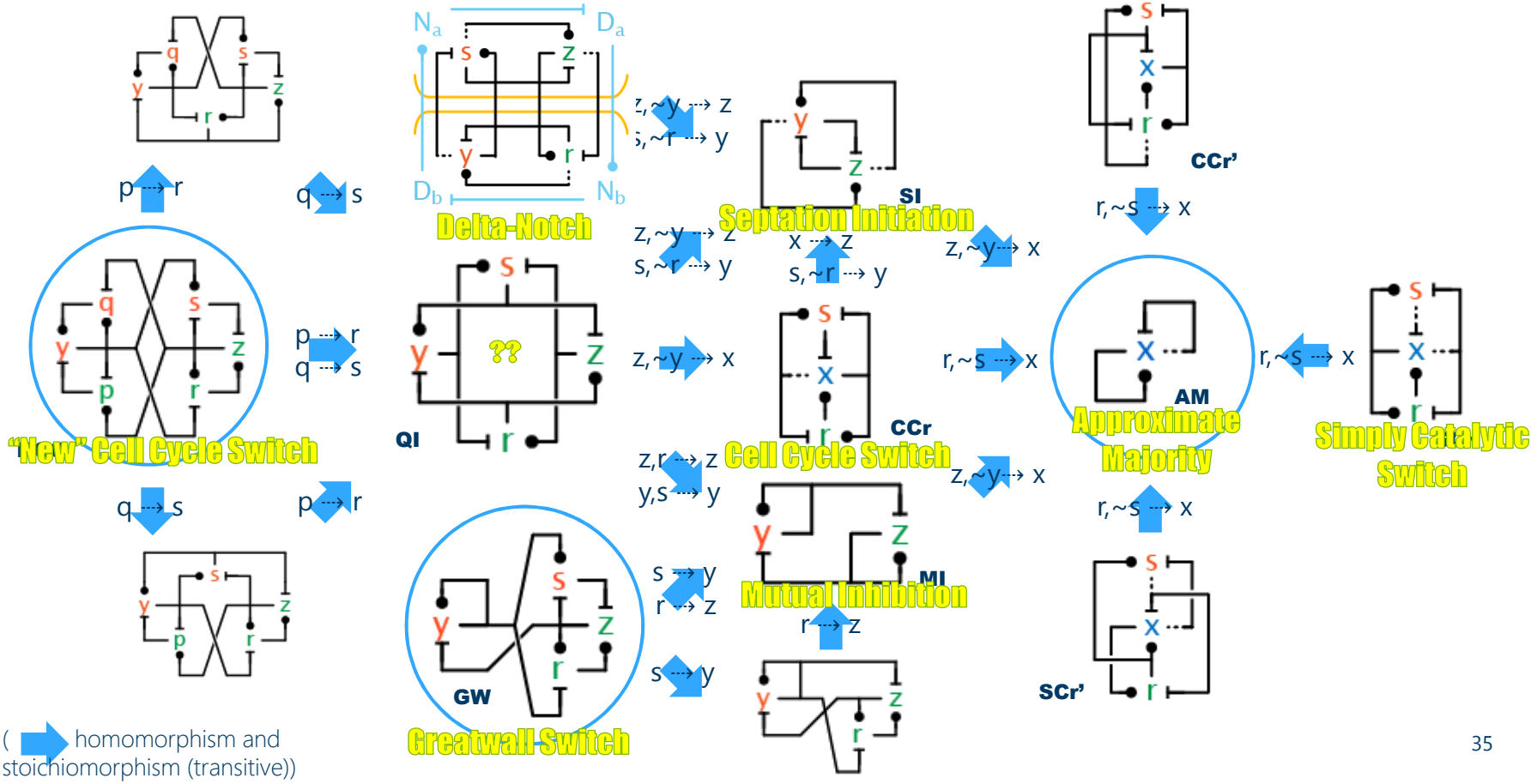
# Network Zoos

# Approximate Majority Emulation Zoo




( homomorphism and stoichiomorphism (transitive))

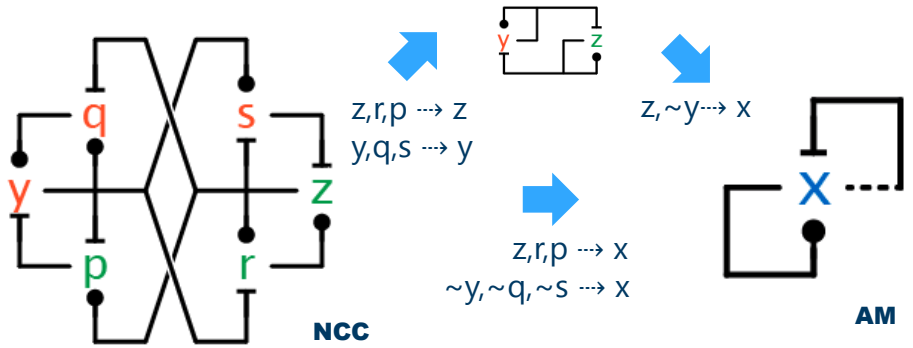
# Approximate Majority Emulation Zoo

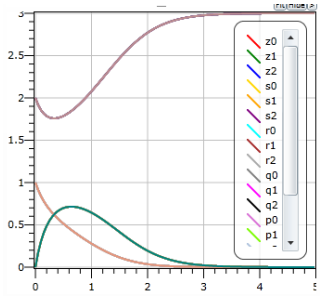



( homomorphism and stoichiomorphism (transitive))

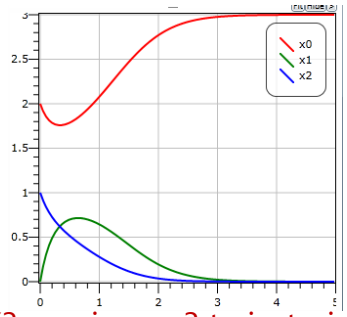
# Emulations Compose: NCC emulates AM

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



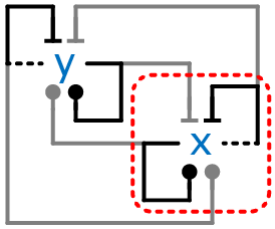




(18 species on 3 trajectories)

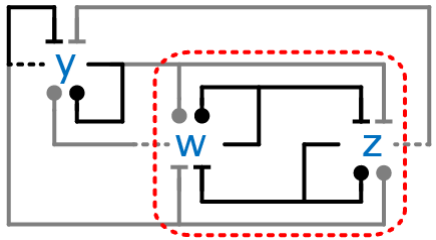



(3 species on 3 trajectories)

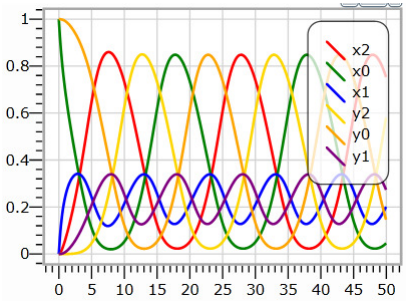
# Emulation in Context

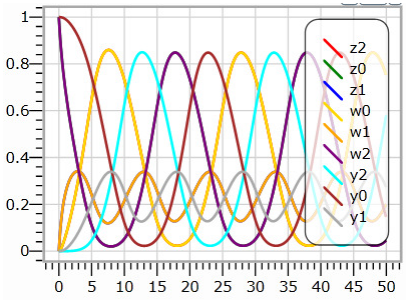



AM-AM Oscillator




AM-MI Oscillator



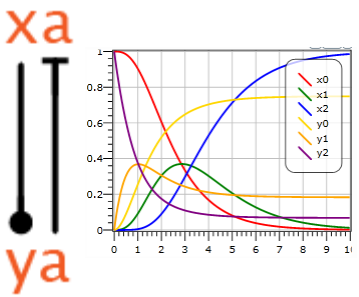

$m \in \mathbf{MI} \to \mathbf{AM}$ is an emulation:
it maps $z \to x$ and $\sim w \to x$

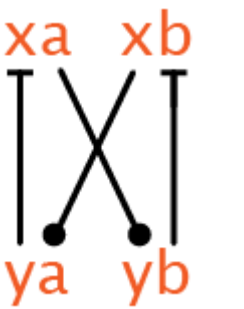
We can replace AM with MI in a context. The mapping $m$ tells us how to wire MI to obtain an overall emulation:

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).

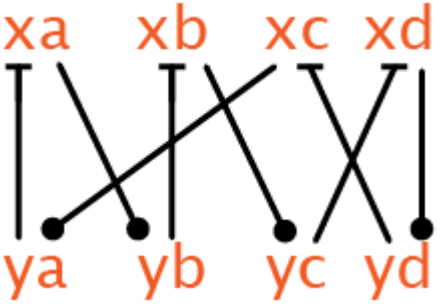
Each influence crossing the dashed lines out of $x$ is replaced by a similar influence from the same side of *either* $z$ *or* $\sim w$. The latter is the same as a similar influence from the opposite side of $w$ (shown), and the same as an opposite influence from the same side of $w$.

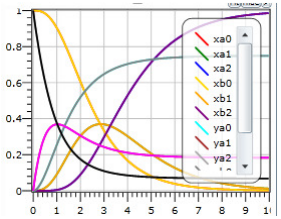
# Another Zoo

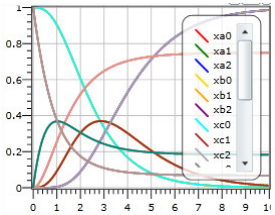

xa
ya
x0
x1
x2
y0
y1
y2

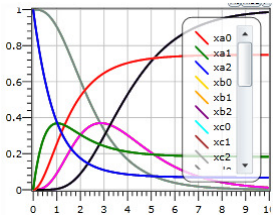

xa xb
ya yb


xa xb xc
ya yb yc


xa xb xc xd
ya yb yc yd

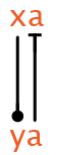

xa0
xa1
xa2
xb0
xb1
xb2
ya0
ya1
ya2

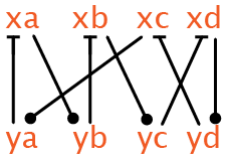

xa0
xa1
xa2
xb0
xb1
xb2
xc0
xc1
xc2


xa0
xa1
xa2
xb0
xb1
xb2
xc0
xc1
xc2

# Network Perturbations

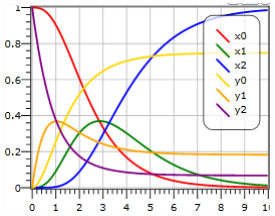
Network

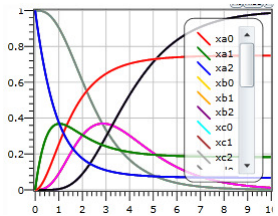


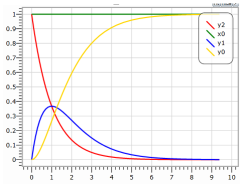

A complex but robust implementation of the simple network

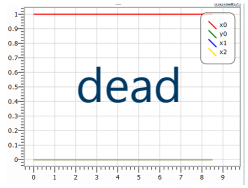
Normal Behavior

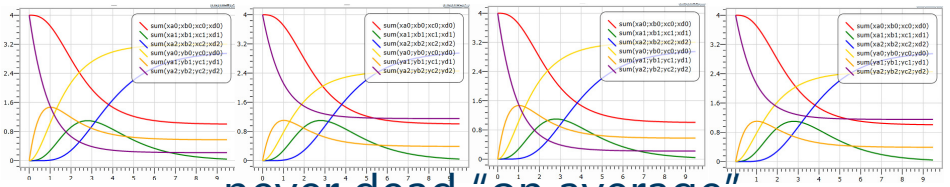


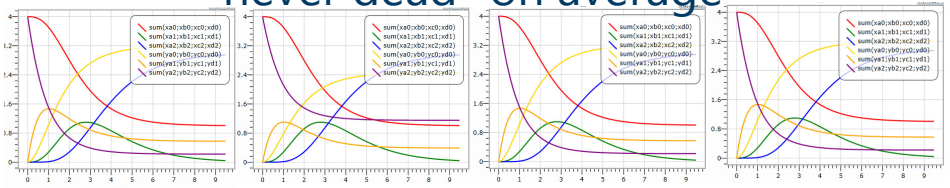

Removing each link in turn





never dead "on average"



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# Conclusions

# Interpretations of Stoichiomorphism

- 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.

# Nature likes a good algorithm

First part

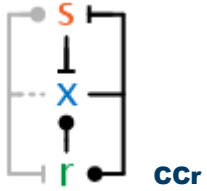

Approximate

"default" rates and initial conditions


Second part

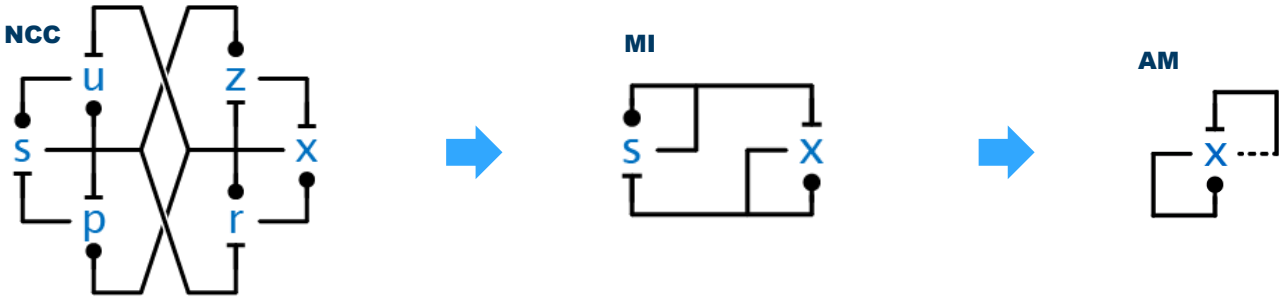

Exact

*any* rates and initial conditions




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

The cell cycle switch *can* exactly emulate AM



# In separate work…

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