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The Cell Cycle Switch Computes Approximate Majority

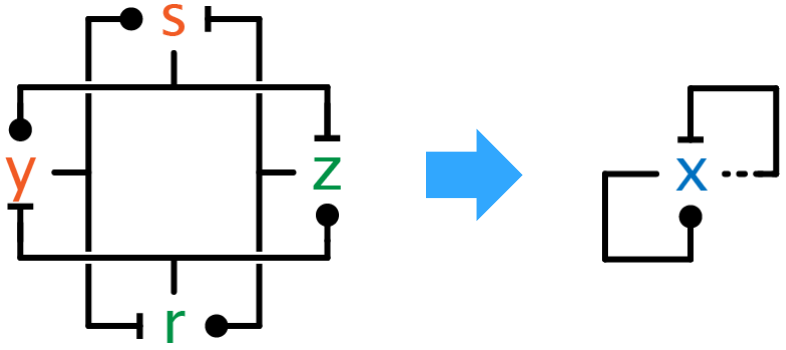
Luca Cardelli, Microsoft Research & Oxford University

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

Middlesex Algorithms Day, 2014-03-14

Outline

- Algorithms and Dynamical Systems
- Networks and Morphisms
- Kinetic Emulation
- Network Zoos
- Conclusions



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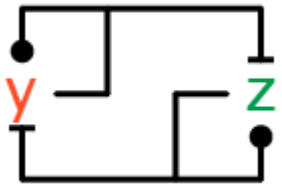
Algorithms and Dynamical Systems

Biological Networks

activation
inhibition

Mutual Inhibition & Self Activation



MI

Cell cycle transitions

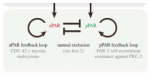
Molecular mechanisms creating bistable switches at cell cycle transitions

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

Polarity establishment

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B

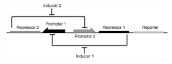
The PAR network: redundancy and robustness in a symmetry-breaking system



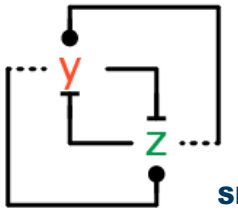
Gene networks

Construction of a genetic toggle switch in *Escherichia coli*

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

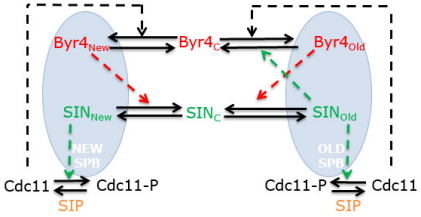


Mutual Inhibition & Mutual Anti-activation



SI

Septation Initiation



SIN inhibiting Byr4,
absence of SIN activating Byr4

Dynamics of SIN Asymmetry Establishment

Something Mysterious

CC

The G_2/M cell cycle switch

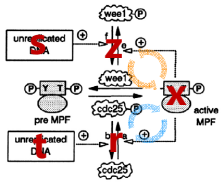
Numerical analysis of a comprehensive model of M-phase control in *Xenopus* oocyte extracts and intact embryos

Bela Novak* and John J. Tyson†

Department of Biology, Virginia Polytechnic

*Permanent address: Department of Agricultural Chemico

†Author for correspondence

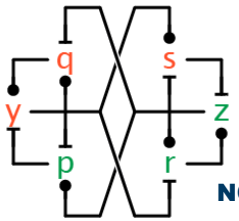


Universal control mechanism regulating onset of M-phase

PAUL NURSE

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

Something Complicated



NCC

The "new" cell cycle switch

Phosphorylation network dynamics in the control of cell cycle transitions

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

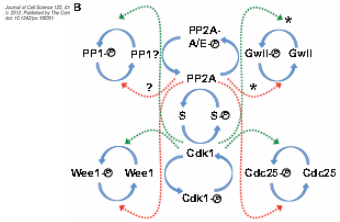
[1]Institut de Génétique Moléculaire de Montpellier, IGMM, CNRS UMR 5535, Université Montpellier I and II, 34293 Montpellier, France

[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

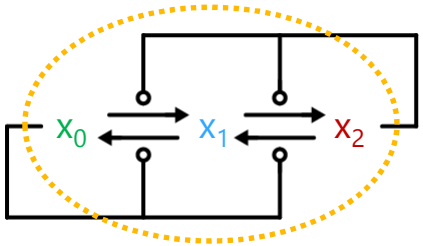


Consensus Algorithms

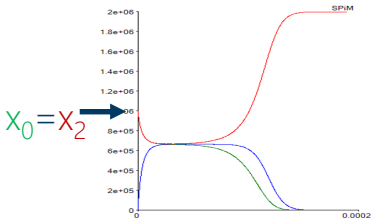
catalysis 

Approximate Majority (AM)

Two initial populations: some x_0 + some x_2
One final population: all x_0 or all x_2
One intermediate population: x_1 (undecided)



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



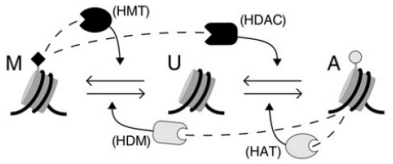
Worst-case scenario,
starting with $x_0=x_2$, $x_1=0$:

Provably fast: O(log n)
and robust to perturbations

Dana Angluin · James Aspnes · David Eisenstat

A Simple Population Protocol for Fast Robust Approximate Majority

Epigenetic Switch



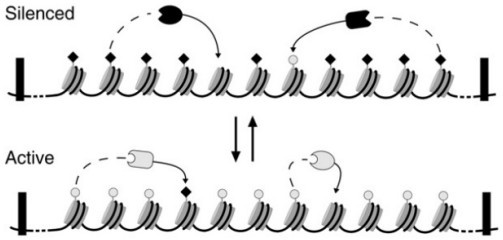
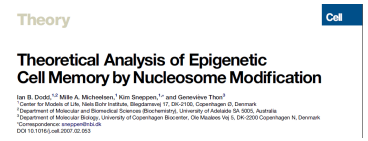


Figure 1. Basic Ingredients of the Model

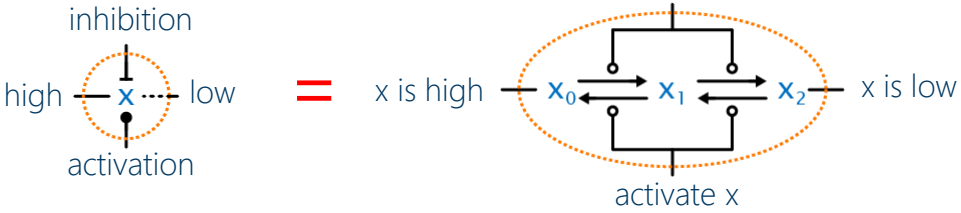

Theory

Cell

Theoretical Analysis of Epigenetic Cell Memory by Nucleosome Modification

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

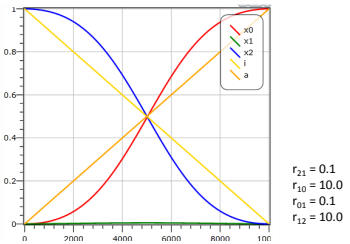
Functional Motifs in Biochemical Reaction Networks

John J. Tyson[1] and Béla Novák[2]

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

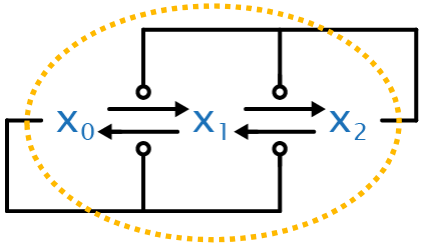
$$A_i = \exp\left\{\sigma_i\left(\alpha_{i0} + \sum_{j=1}^{N} \alpha_{ij} X_j\right)\right\}, \quad B_i = \exp\left\{\sigma_i\left(\beta_{i0} + \sum_{j=1}^{N} \beta_{ij} X_j\right)\right\}, \qquad (4)$$

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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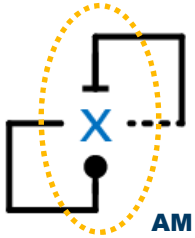
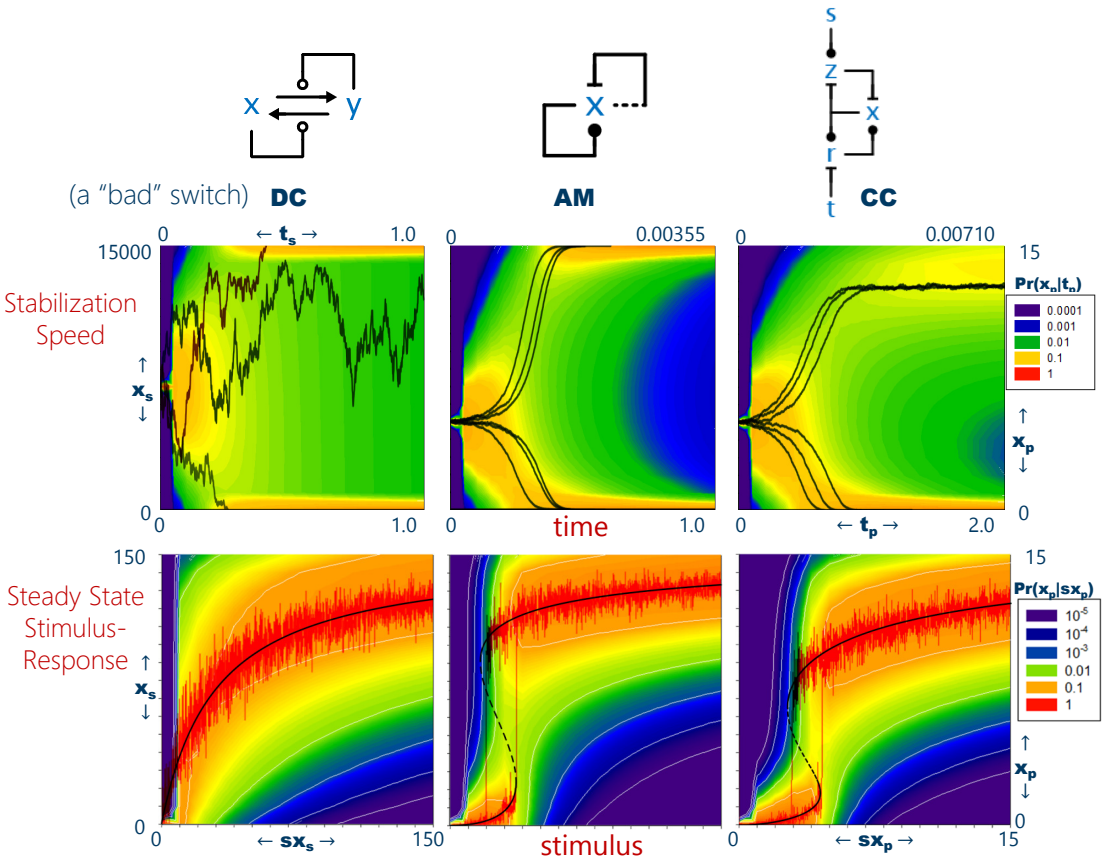


In Previous Work

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)

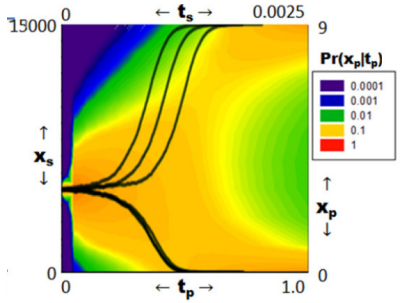
Black lines: deterministic ODE bifurcation diagrams
Red lines: medium-count stochastic simulations
Color: full probability distribution of low-count system

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

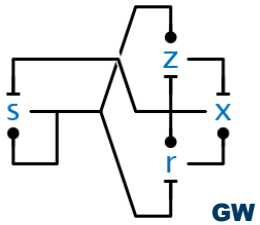
There is an obvious bug in CC performance: let's fix it!

In Previous Work

- But 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!



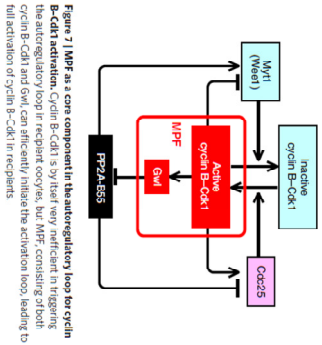


Figure 7 | MPF as a core component in the autoregulatory loop for cyclin B–Cdk1 activation. Cyclin B–Cdk1 s by itself very inefficient in triggering the autoregulatory loop in recipient oocytes, but MPF, consisting of both cyclin B–Cdk1 and Gwl, can efficiently initiate the activation loop, leading to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

Received 6 Jul 2012 | Accepted 14 Aug 2012 | Published 11 Sep 2012

DOI:10.1038/ncomms2062

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

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

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Networks and Morphisms

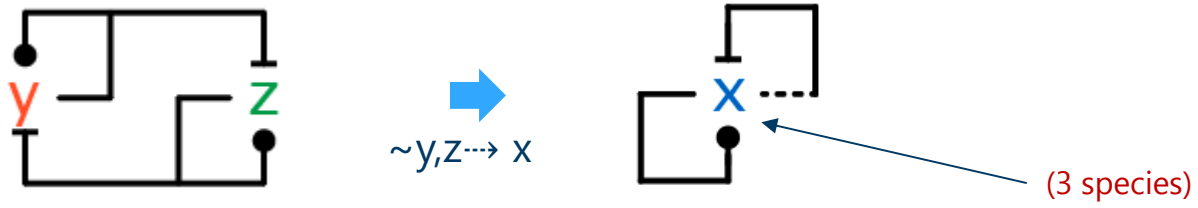
A Theory of Network Emulation

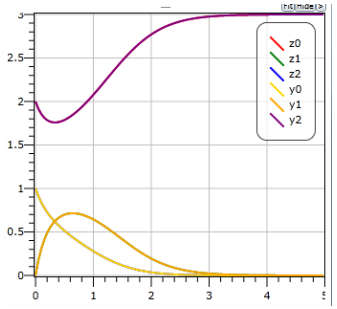
(with thanks to David Soloveichik)

- So far, evidence is empirical
  - 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

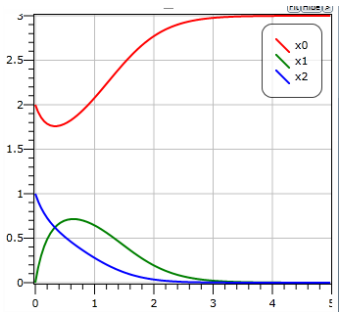
Network Emulation: MI emulates AM

- 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)



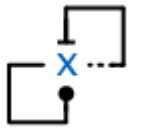
(3 species on 3 trajectories)

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

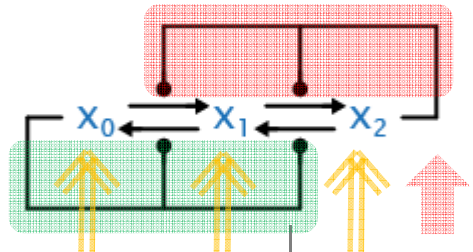
($y_2 = x_0$
$y_1 = x_1$
$y_0 = x_0$)

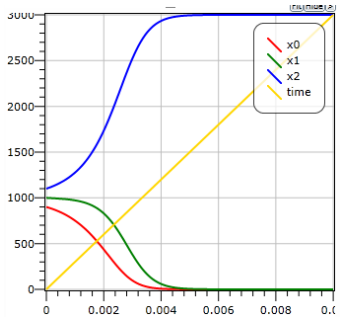
Emulation is a Network Morphism

A mapping of species and reactions



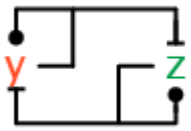
AM



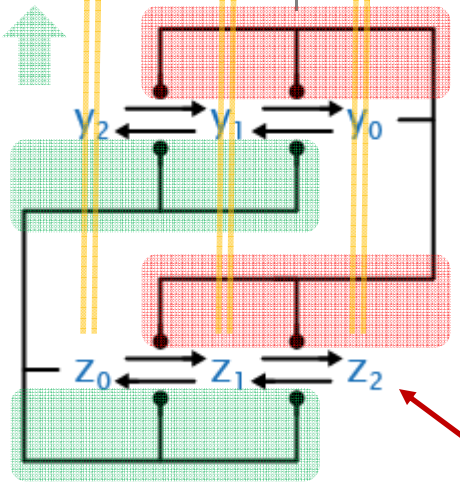


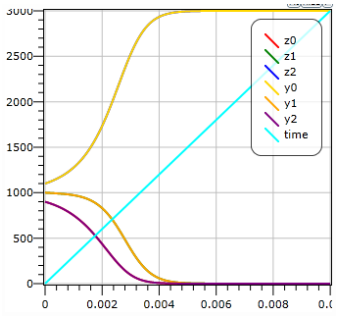
any initial conditions

homomorphic mapping



MI





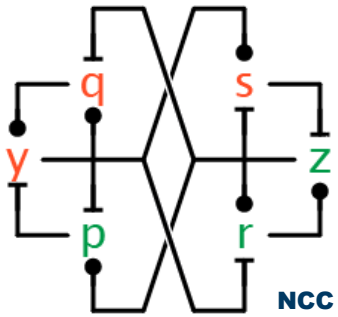
initial conditions:

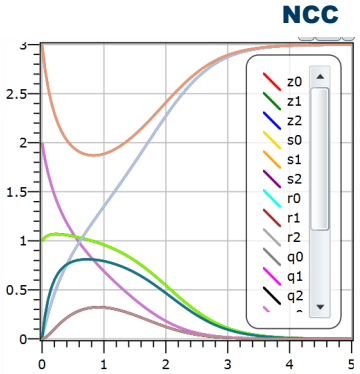
$z_0 = y_2 = x_0$
$z_1 = y_1 = x_1$
$z_2 = y_0 = x_2$

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

Network Emulation: NCC emulates MI

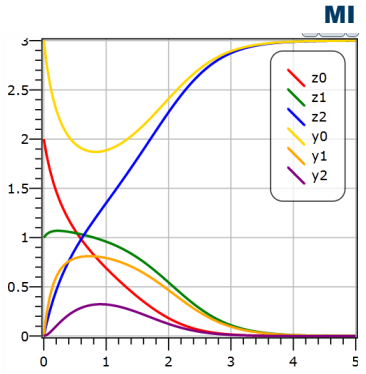
- For *any* rates and initial conditions of MI we can find *some* rates and initial conditions of NCC such that the (18) trajectories of NCC retrace those (6) of MI





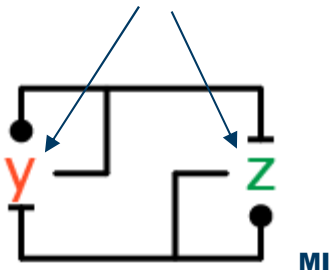
(18 species on 6 trajectories)

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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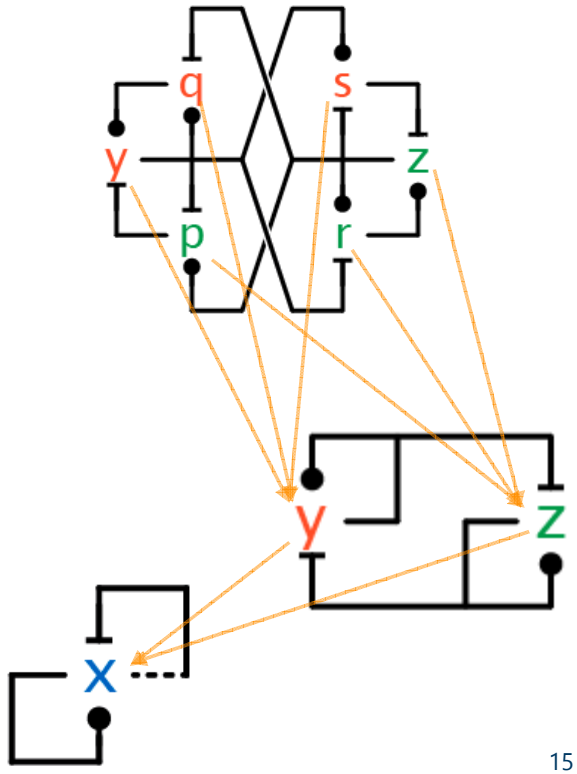
Kinetic Emulation

When can a Network Emulate Another?

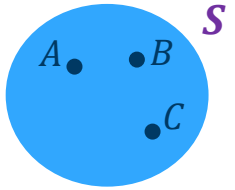
- What kind of morphisms guarantee emulation?
  - do they preserve network structure?
  - do they preserve stoichiometry?



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*

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

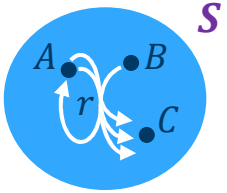


- Reactions $r =$

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

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 $m = (m_S, m_R)$

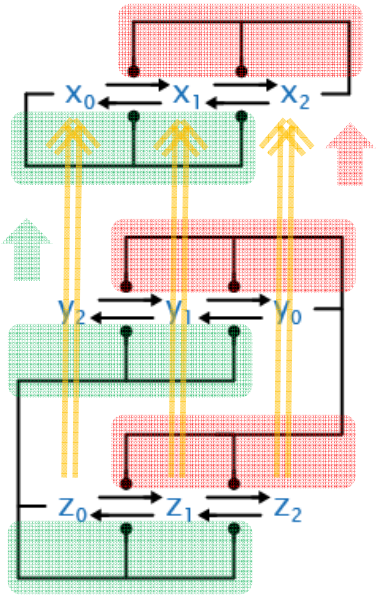
a species map $m_S \in S \to \hat{S}$

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

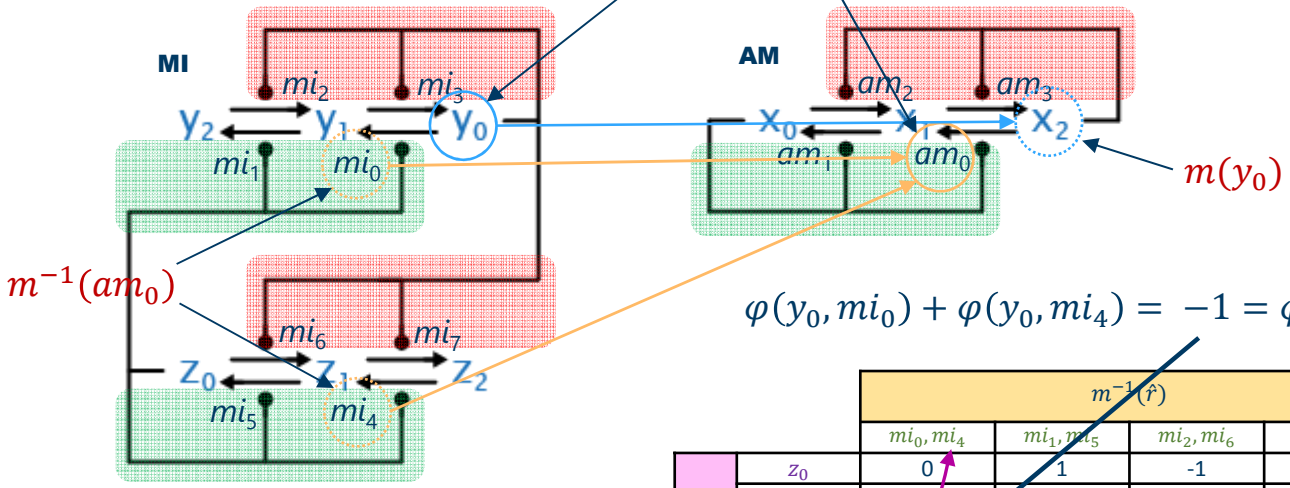
$\boldsymbol{\varphi}, \hat{\boldsymbol{\varphi}}$ are the respective stoichiometric matrices
$\boldsymbol{\rho}, \hat{\boldsymbol{\rho}}$ are the respective reactant matrices
$\boldsymbol{m_{\mathcal{S}}}, \boldsymbol{m_{\mathcal{R}}}$ are the characteristic 0-1 matrices of $m_{\mathcal{S}}, m_{\mathcal{R}}$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

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

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



All unit rates (sufficient because of another theorem)

This is both a homomorphism and a stoichiomorphism

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

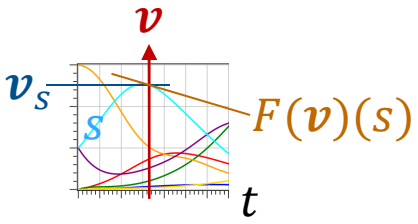
		$m^{-1}(\hat{r})$				
		mi_0, mi_4	mi_1, mi_5	mi_2, mi_6	mi_3, mi_7	
$\forall s \in$ MI	z_0	0	1	-1	0	x_0
	z_1	1	-1	1	-1	x_1
	z_2	-1	0	0	1	x_2
	y_0	-1	0	0	1	x_2
	y_1	1	-1	1	-1	x_1
	y_2	0	1	-1	0	x_0
		am_0	am_1	am_2	am_3	
		$\forall \hat{r} \in$ AM				$m(s)$

CRN Kinetics

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

a vector of concentrations for each species

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



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

Given by the law of mass action:

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

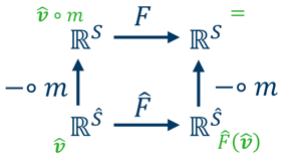
sum over all reactions of the stoichiometry of species in reaction times the product of reagent concentrations according to their stoichiometric numbers

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

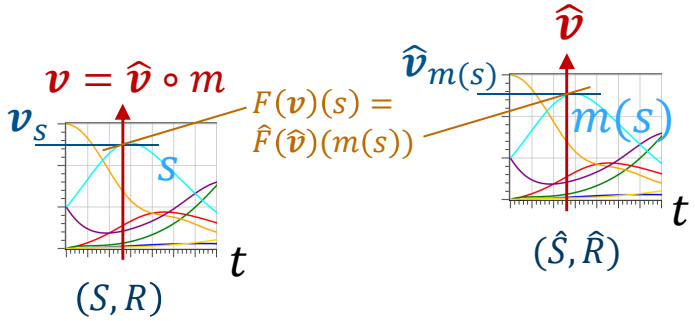
Kinetic Emulation

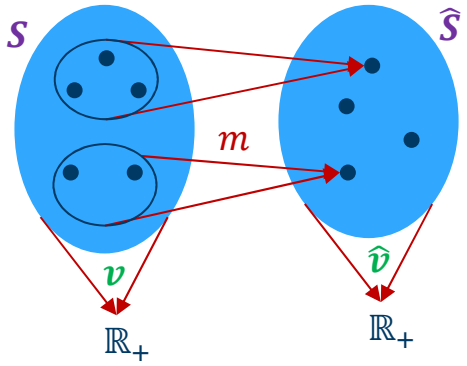
A morphism $m \in (S,R) \to (\hat{S},\hat{R})$ is a *CRN emulation* if for the respective differential systems $F, \hat{F}$, $\forall \hat{v} \in \mathbb{R}_+^{\hat{S}}$:

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



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





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

if we *start* the two systems in states $v = \hat{v} \circ m$ (which is a *copy* of $\hat{v}$ according to m) and $\hat{v}$ resp., for each 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 $\boldsymbol{m_S}^{\mathbf{T}} \cdot \boldsymbol{\rho} = \hat{\boldsymbol{\rho}} \cdot \boldsymbol{m_{\mathcal{R}}}^{\mathbf{T}}$

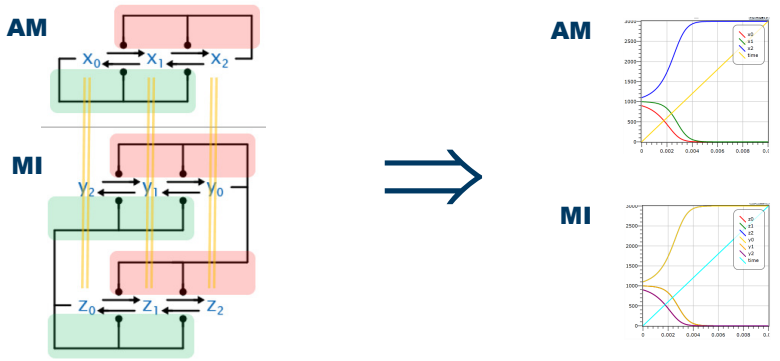
stoichiomorphism $\boldsymbol{\varphi} \cdot \boldsymbol{m_{\mathcal{R}}} = \boldsymbol{m_S} \cdot \hat{\boldsymbol{\varphi}}$

$\Downarrow$

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

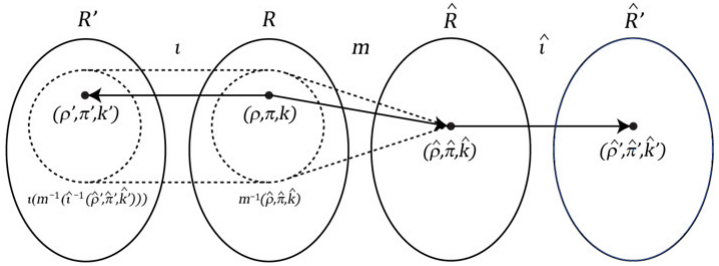
A *change of rates* for (S, R) is morphism $\iota \in (S, R) \to (S, R')$ such that $\iota(S)$ is the identity and $\iota(\rho, \pi, k) = (\rho, \pi, k')$.

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 $\hat{\iota}$ of $(\hat{S}, \hat{R})$ there is a change of rates ι of (S, R) such that $\hat{\iota} \circ m \circ \iota^{-1}$ is a stoichiomorphism.

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

In fact, ι changes rates by the ratio with which $\hat{\iota}$ 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 $\hat{\iota}(\hat{\rho}, \hat{\pi}, \hat{k}) = (\hat{\rho}, \hat{\pi}, \hat{k}')$.



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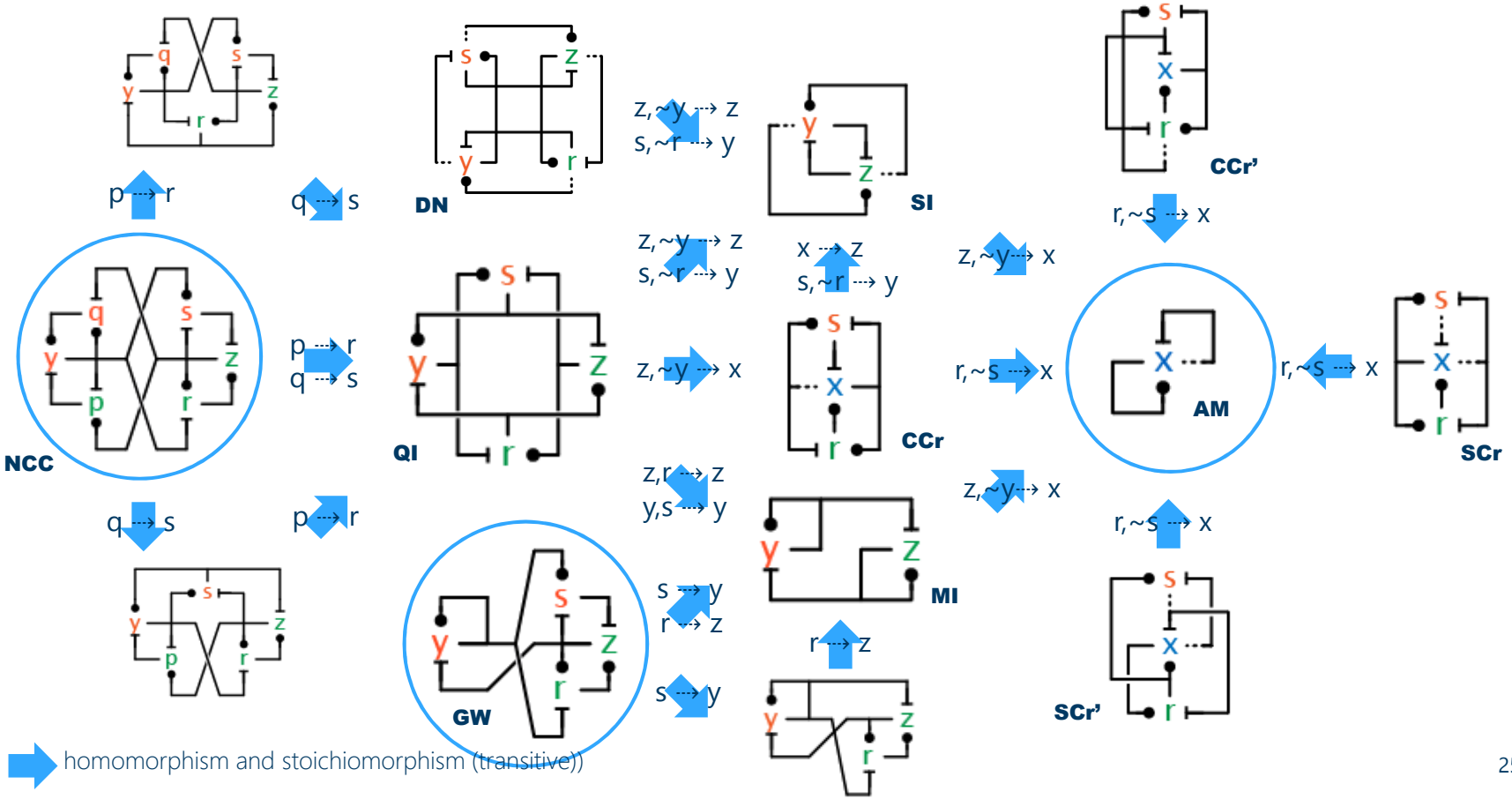
Network Zoos

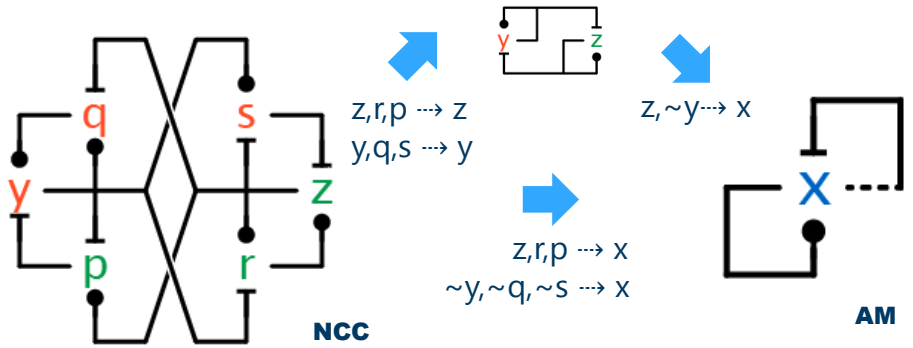
Approximate Majority Emulation Zoo

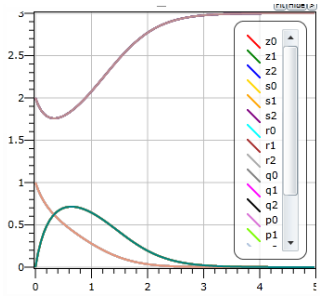


(homomorphism and stoichiomorphism (transitive))

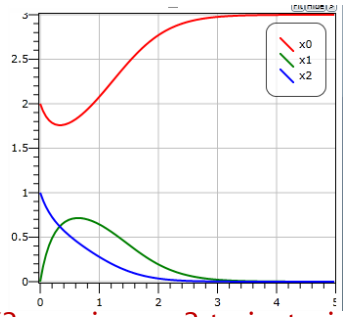
Emulations Compose: NCC emulates AM

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



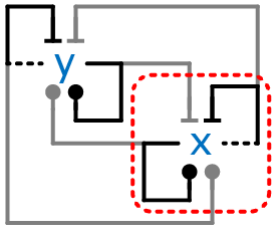


(18 species on 3 trajectories)

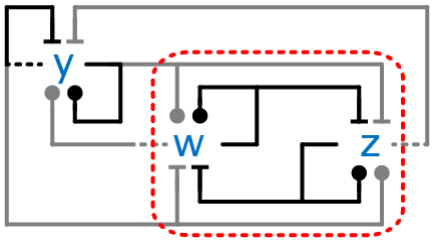


(3 species on 3 trajectories)

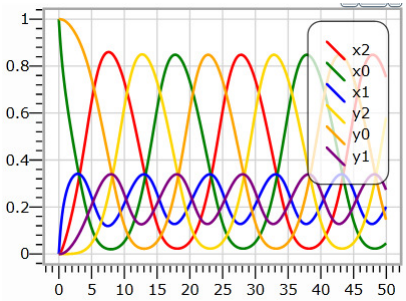
Emulation in Context

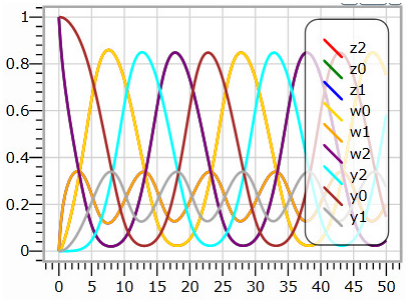


AM-AM Oscillator



AM-MI Oscillator





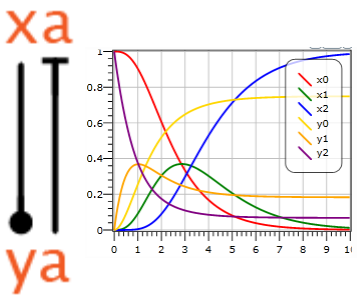
$m \in \mathbf{MI} \to \mathbf{AM}$ is an emulation:
it maps $z \to x$ and $\sim w \to x$

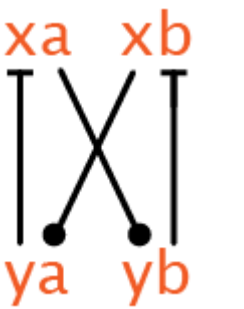
We can replace AM with MI in a context. The mapping m tells us how to wire MI to obtain an overall emulation:

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).

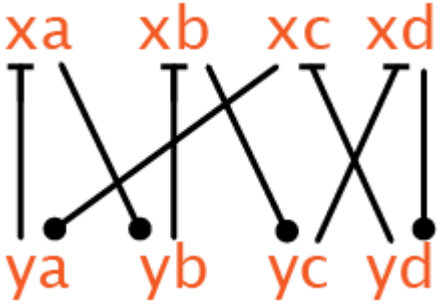
Each influence crossing the dashed lines out of x is replaced by a similar influence from the same side of *either* z *or* $\sim w$. The latter is the same as a similar influence from the opposite side of w (shown), and the same as an opposite influence from the same side of w.

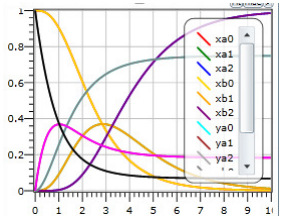
Another Zoo

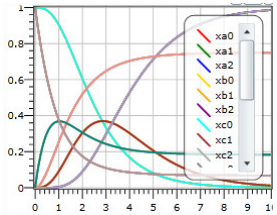

xa
ya
x0
x1
x2
y0
y1
y2

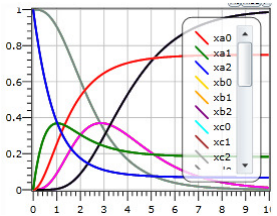

xa xb
ya yb


xa xb xc
ya yb yc


xa xb xc xd
ya yb yc yd

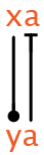

xa0
xa1
xa2
xb0
xb1
xb2
ya0
ya1
ya2

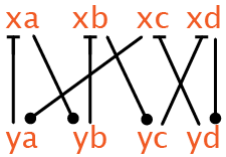

xa0
xa1
xa2
xb0
xb1
xb2
xc0
xc1
xc2


xa0
xa1
xa2
xb0
xb1
xb2
xc0
xc1
xc2

Network Perturbations

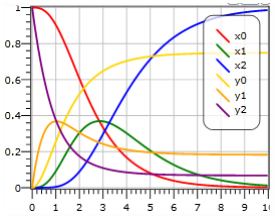
Network

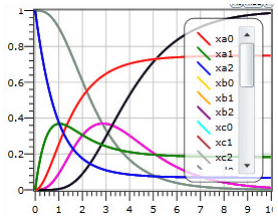




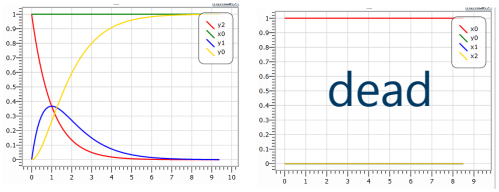
A complex but robust implementation of the simple network

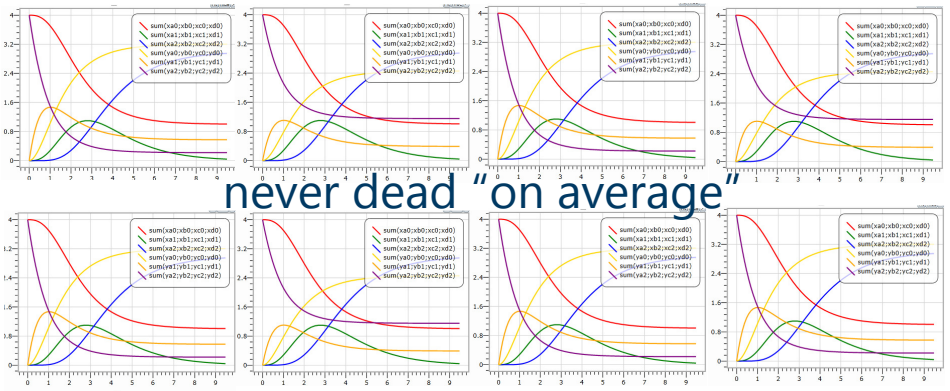
Normal Behavior





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

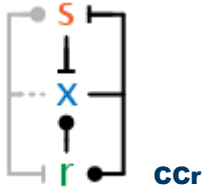
Approximate

"default" rates and initial conditions

Second part

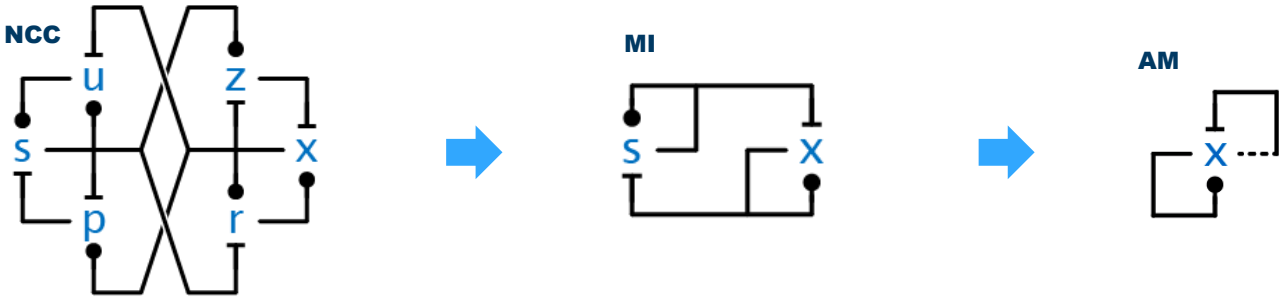
Exact

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.