Microsoft Research

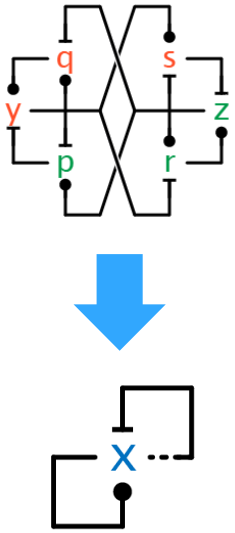
UNIVERSITY OF OXFORD

# Morphisms of Reaction Networks

Luca Cardelli, Microsoft Research & Oxford University

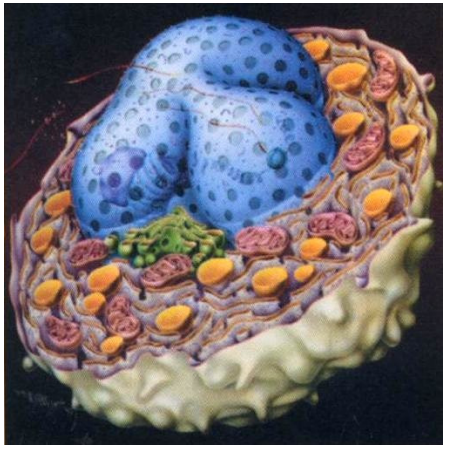
Joint work with Attila Csikász-Nagy, Fondazione Edmund Mach & King's College London

Iowa State University, Robert Stewart Distinguished Lecture, 2014-05-01



# Motivation

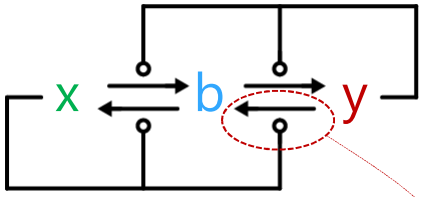
- Give substance to the claim that "cells compute"
  - Yes, but *what* do they compute?
- Catch nature red-handed in the act of running a computational task
  - Something that a computer scientist would recognize as an *algorithm*



# A Consensus Algorithm

- Population 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 $O(n \log n) \Rightarrow$ fast (optimal)
  - Correct outcome if the initial disparity is $\omega(\sqrt{n} \log n) \Rightarrow$ robust
  - In parallel time, converges in $O(\log n)$

catalysis




chemical reaction network

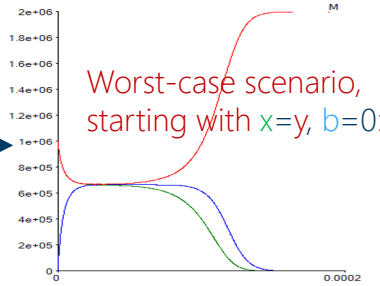
$x + y \rightarrow^{r} y + b$

$y + x \rightarrow^{r} x + b$

$b + x \rightarrow^{r} x + x$

$b + y \rightarrow^{r} y + y$

x=y



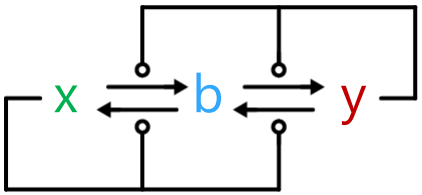

Worst-case scenario, starting with x=y, b=0:

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

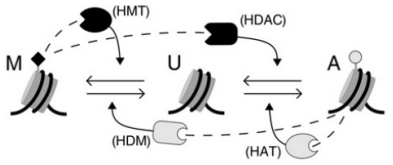
Robust to perturbation
  above a threshold, initial majority wins *whp*

Dana Angluin · James Aspnes · David Eisenstat

A Simple Population Protocol for Fast Robust Approximate Majority

2007

## Epigenetic Switch



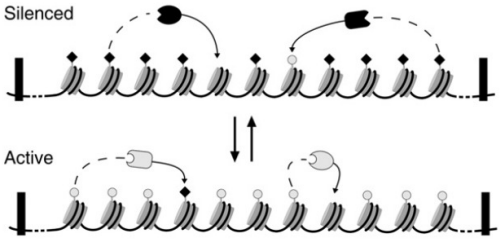
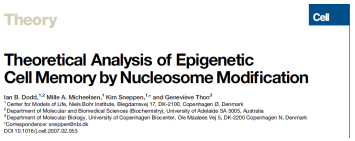



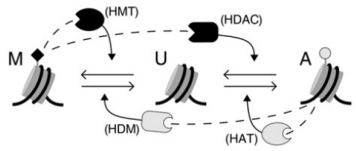

Figure 1. Basic Ingredients of the Model




2007

# Motivation (cont'd)

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

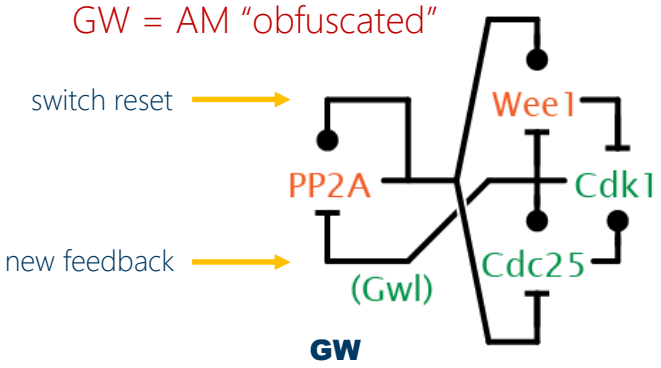



- In most cases the biological implementation seems more *indirect* or *obfuscated*
  - *"Nature is subtle but not malicious - Einstein"* Ha! think again!
  - Other implementations of Approximate Majority seem convoluted and… approximate

# Obfuscated Implementations

- GW is a better cell cycle switch than [the traditional switch]

GW = AM "obfuscated"




SCIENTIFIC REPORTS

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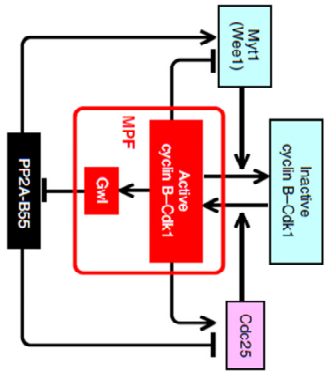
SUBJECT AREAS: COMPUTATIONAL BIOLOGY

The Cell Cycle Switch Computes Approximate Majority

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

Sep 2012

- GW is how the cell cycle switch "really works"




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]

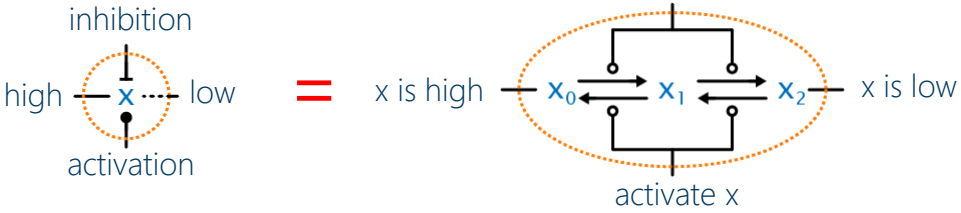
Sep 2012

# Motivation (cont'd)

- When does a biologically messy network X "implement" some ideal algorithm Y?
  - Pushed coauthors into thinking about approximate stochastic bisimulation metrics for CTMCs
  - But they didn't come back…
- Some networks behave similarly because "their ODEs are just equivalent" [David S.]
  - When are CRNs "deterministically equivalent"?
  - Or better, when do trajectories of one CRN "collapse" into trajectories of another?
  - This can be answered on the *static structure* of CRNs as opposed to their kinetics.
  - Independently on rates and initial conditions (of one of the two networks).

# Influence Networks

activation
inhibition
catalysis

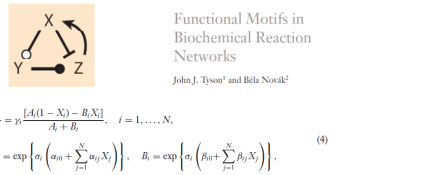



Usually modeled by sigmoid (e.g. Hill or Reinitz) functions

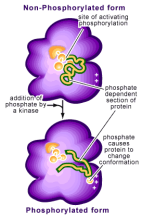
triplet motif

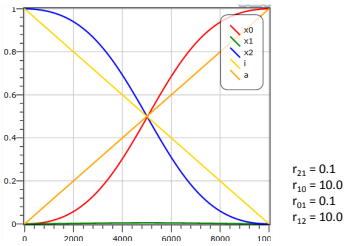
We model them by 4 mass action reactions over 3 species $x_0$, $x_1$, $x_2$

They actually implement a Hill function of coefficient 2:

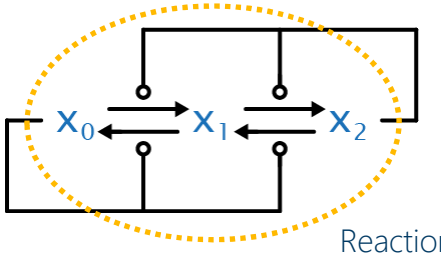



biological mechanism: (e.g.:) multisite phosphorylation



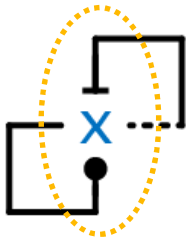




## Approximate Majority




Reaction Network

=

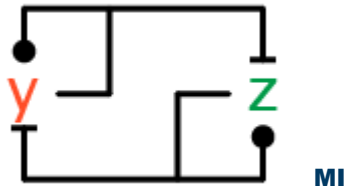



Influence Network

# Biological Influence Networks

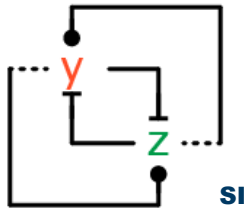
activation
inhibition

## Mutual Inhibition & Self Activation




MI

## Mutual Inhibition & Mutual Anti-activation

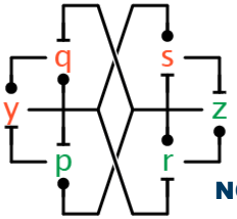



SI

## Cell Cycle Switching

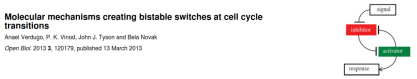

CC

## Better Switching




NCC

### Cell cycle transitions



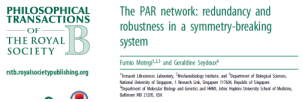
Molecular mechanisms creating bistable switches at cell cycle transitions

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

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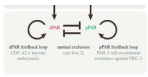
The PAR network: redundancy and robustness in a symmetry-breaking system

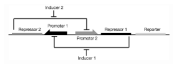
Fumio Motegi[1,2] and Geraldine Seydoux[3]



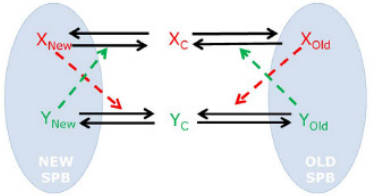
### Gene networks

Construction of a genetic toggle switch in *Escherichia coli*

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



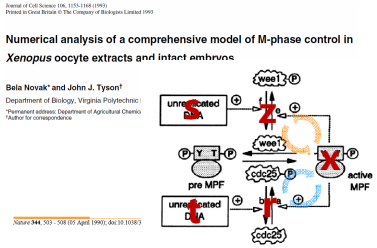
### Septation Initiation




Dynamics of SIN Asymmetry Establishment

Archana Bajpai[1], Anna Fookstova[2], Jun-Song Chen[2], Dannel McCollum[3], Masamitsu Sato[4,5], Rafael E. Carazo-Salas[6], Kathleen L. Gould[2], Attila Csikasz-Nagy[1,7]*

### 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 Chemic

†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[3,2] and Béla Novák[2,†]

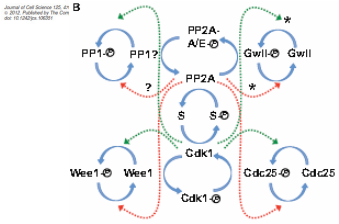
[1]Institut de Génétique Moléculaire de Montpellier, IGMM, CNRS UMR 5535, Université Montpellier I and II, 34293 Montpellier, France

[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



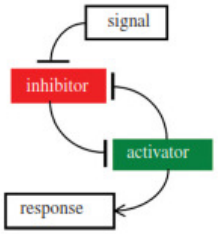
# Mutual Inhibition

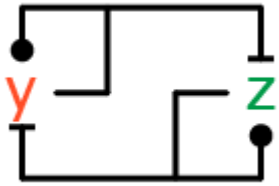
- A recent paper suggests that all cellular switches in all phases of the cell cycle follow (abstractly) a mutual inhibition pattern:

**Molecular mechanisms creating bistable switches at cell cycle transitions**

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

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




MI

- Also found in other areas (cell polarity establishment):

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B

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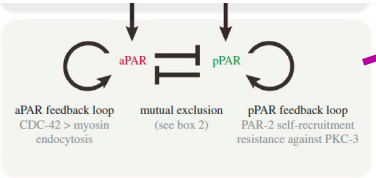
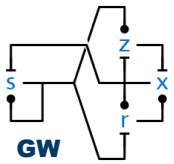
The PAR network: redundancy and robustness in a symmetry-breaking system

Fumio Motegi[1,2,3] and Geraldine Seydoux[4]

[1]Temasek Lifesciences Laboratory, [2]Mechanobiology Institute, and [3]Department of Biological Sciences, National University of Singapore, 1 Research Link, Singapore 117604, Republic of Singapore
[4]Department of Molecular Biology and Genetics and HHMI, Johns Hopkins University School of Medicine, Baltimore MD 21205, USA



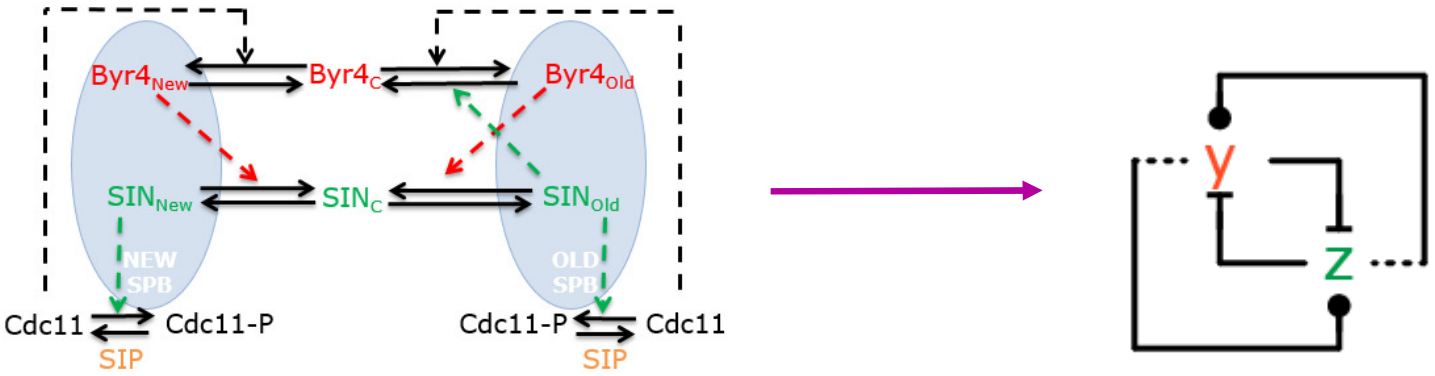

cf.:




GW

# Septation Initiation

- Other (inherently different) biological networks are based on mutual inhibition, and share characteristics with AM




SIN inhibiting Byr4,
absence of SIN promoting Byr4

# New Cell Cycle Network

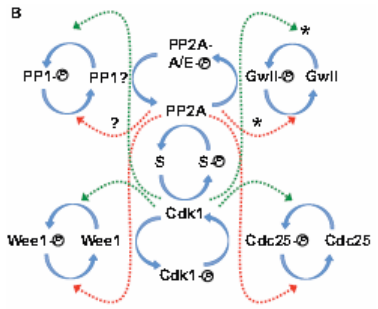
- A new paper presents a more complete view of the cell cycle switch
- N.B. "phosphorylation network dynamics" is the same as our $x_0$-$x_1$-$x_2$ motif

**Phosphorylation network dynamics in the control of cell cycle transitions**

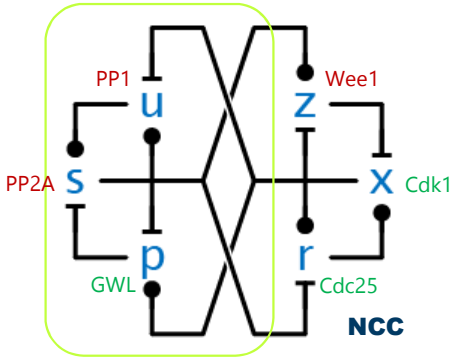
Daniel Fisher[1,*], Liliana Krasinska[1,‡], Damien Coudreuse[2,‡] and Béla Novák[3,‡]
[1]Institut de Génétique Moléculaire de Montpellier, IGMM, CNRS UMR 5535, Université Montpellier I and II, 34293 Montpellier, France
[2]Institute of Genetics and Development of Rennes, CNRS UMR 6290, 35043 Rennes, France
[3]Oxford Centre for Integrative Systems Biology, Department of Biochemistry, University of Oxford, South Parks Road, Oxford OX1 3QU, UK
*Author for correspondence (daniel.fisher@igmm.cnrs.fr)
‡These authors contributed equally to this work

Journal of Cell Science 125, 4703–4711

doi: 10.1242/jcs.106351

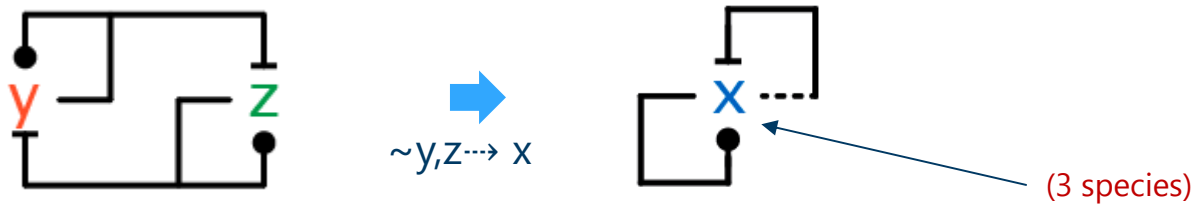


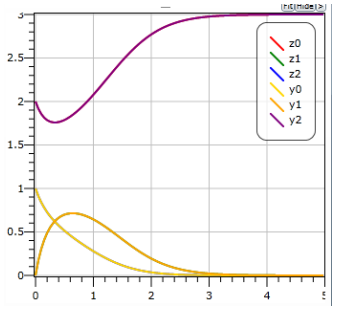

In our notation:



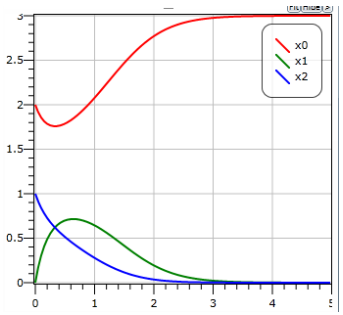
# Network Emulation: MI emulates AM

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

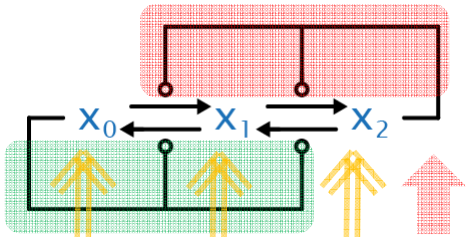
($y_2 = x_0$
$y_1 = x_1$
$y_0 = x_0$)

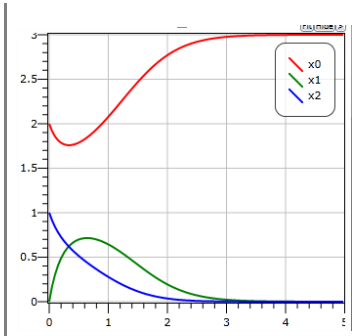
- How do we find these matching parameters? By a network morphism!

# MI to AM Emulation: Network Morphism

## A mapping of species and reactions


AM



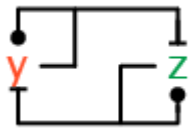




any initial conditions

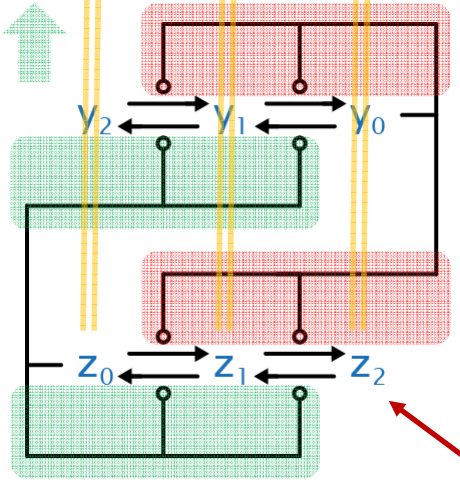
*homomorphic* mapping

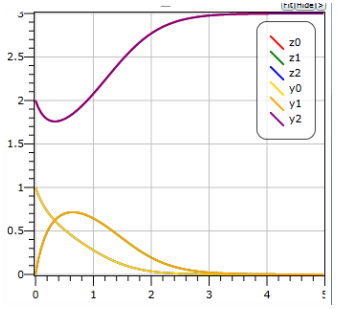
z -> x

~y -> x




MI




initial conditions:

$z_0 = y_2 = x_0$

$z_1 = y_1 = x_1$

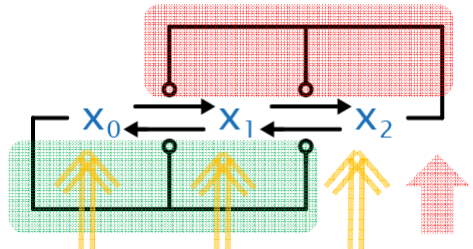
$z_2 = y_0 = x_2$

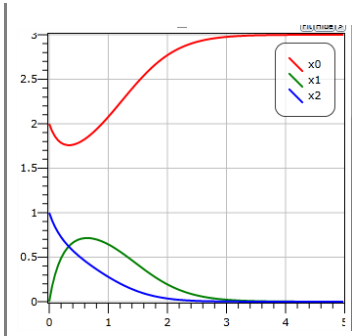
less trivial than you might think:
it need not preserve the out-degree of a node!

# SI to AM Emulation: Network Morphism

## A mapping of species and reactions


AM



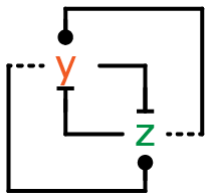




any initial conditions

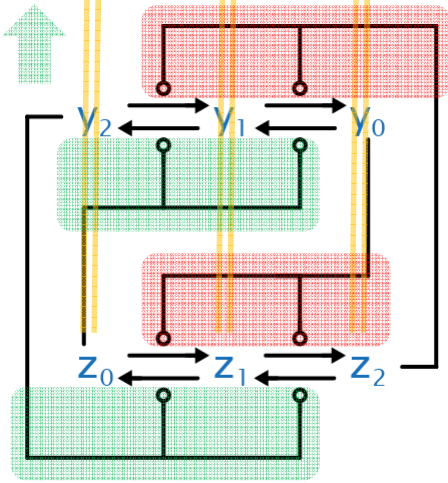
*homomorphic* mapping

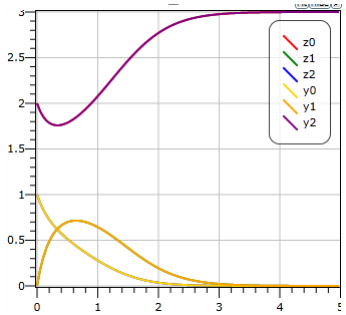
z -> x

~y -> x




SI




initial conditions:

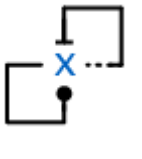
$z_0 = y_2 = x_0$

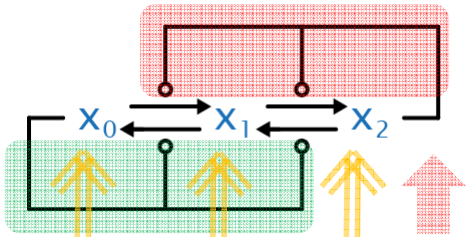
$z_1 = y_1 = x_1$

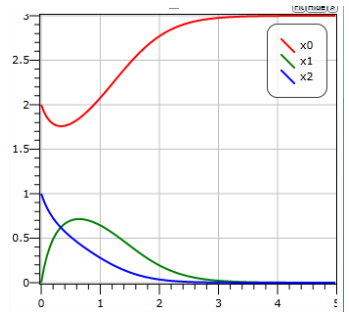
$z_2 = y_0 = x_2$

# AMr to AM Emulation: Network Morphism

## A mapping of species and reactions



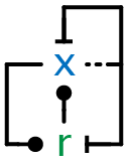



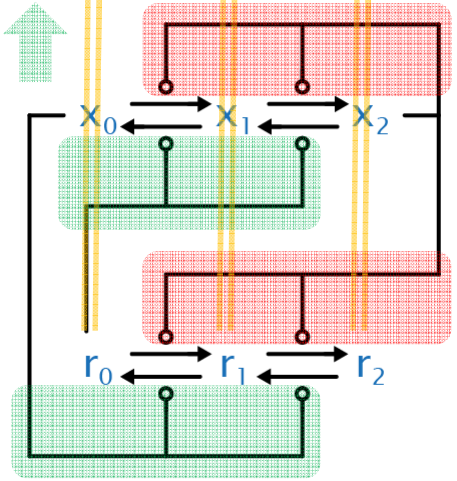



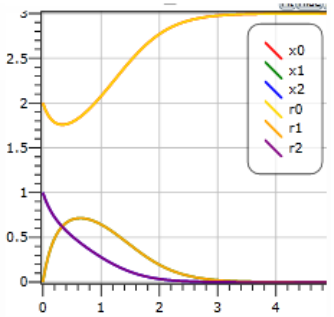

any initial conditions

*homomorphic* mapping

x -> x
r -> x



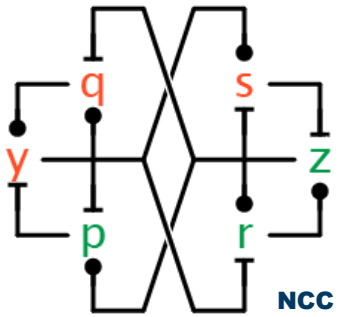

initial conditions:

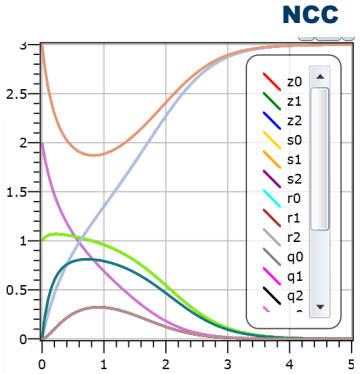
$r_0 = x_0 = x_0^{AM}$
$r_1 = x_1 = x_1^{AM}$
$r_2 = x_2 = x_2^{AM}$

(AMr adds an indirection to the x positive loop; if we also add an indirection to the x negative loop, we obtain a prototypical cell cycle switch that also emulates AM: CCR)

# Network Emulation: NCC emulates MI

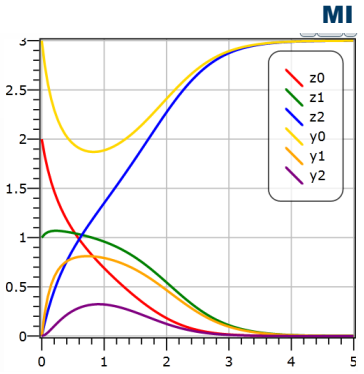
- For *any* rates and initial conditions of MI we can find *some* rates and initial conditions of NCC such that the (18) trajectories of NCC retrace those (6) of MI



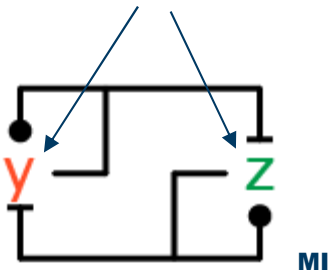

(18 species on 6 trajectories)

z,r,p ⇢ z
y,q,s ⇢ y




(6 species on 6 trajectories)

(3 species each)

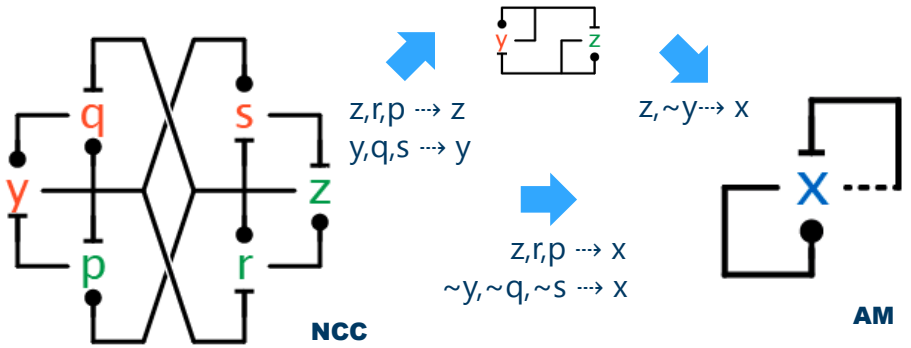


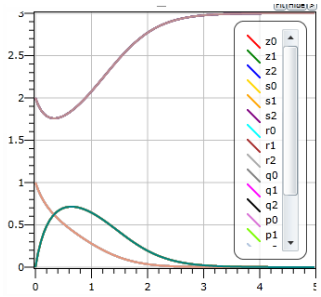

initialize
z,r,p = z
y,q,s = y

- Why does this work so well?

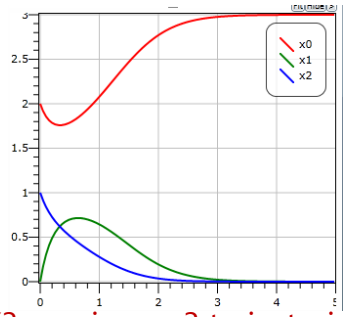
# Emulations Compose: NCC emulates AM

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




(18 species on 3 trajectories)



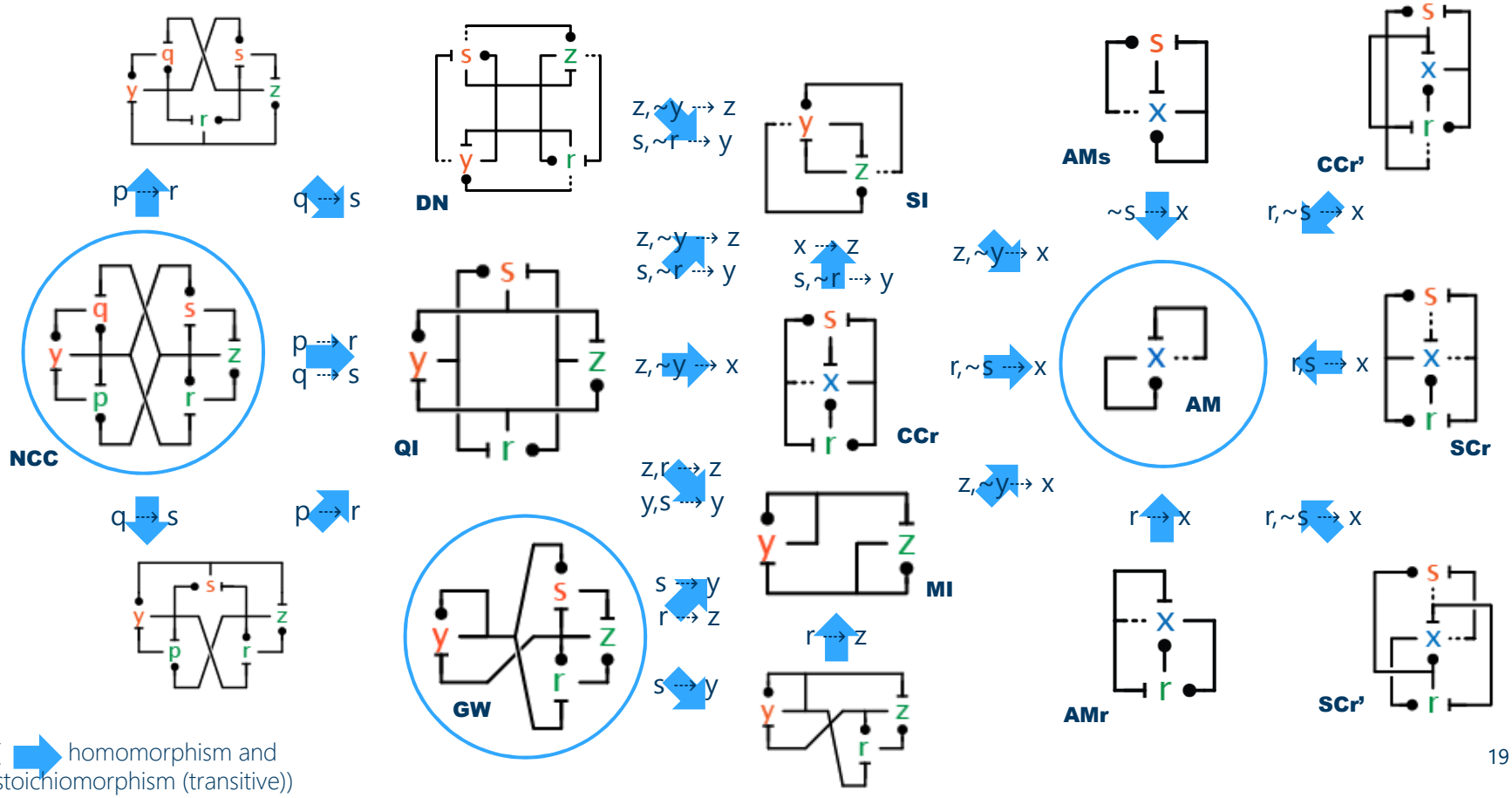

(3 species on 3 trajectories)

The new cell cycle switch can emulate AM *exactly*.

For *any* initial conditions of AM.

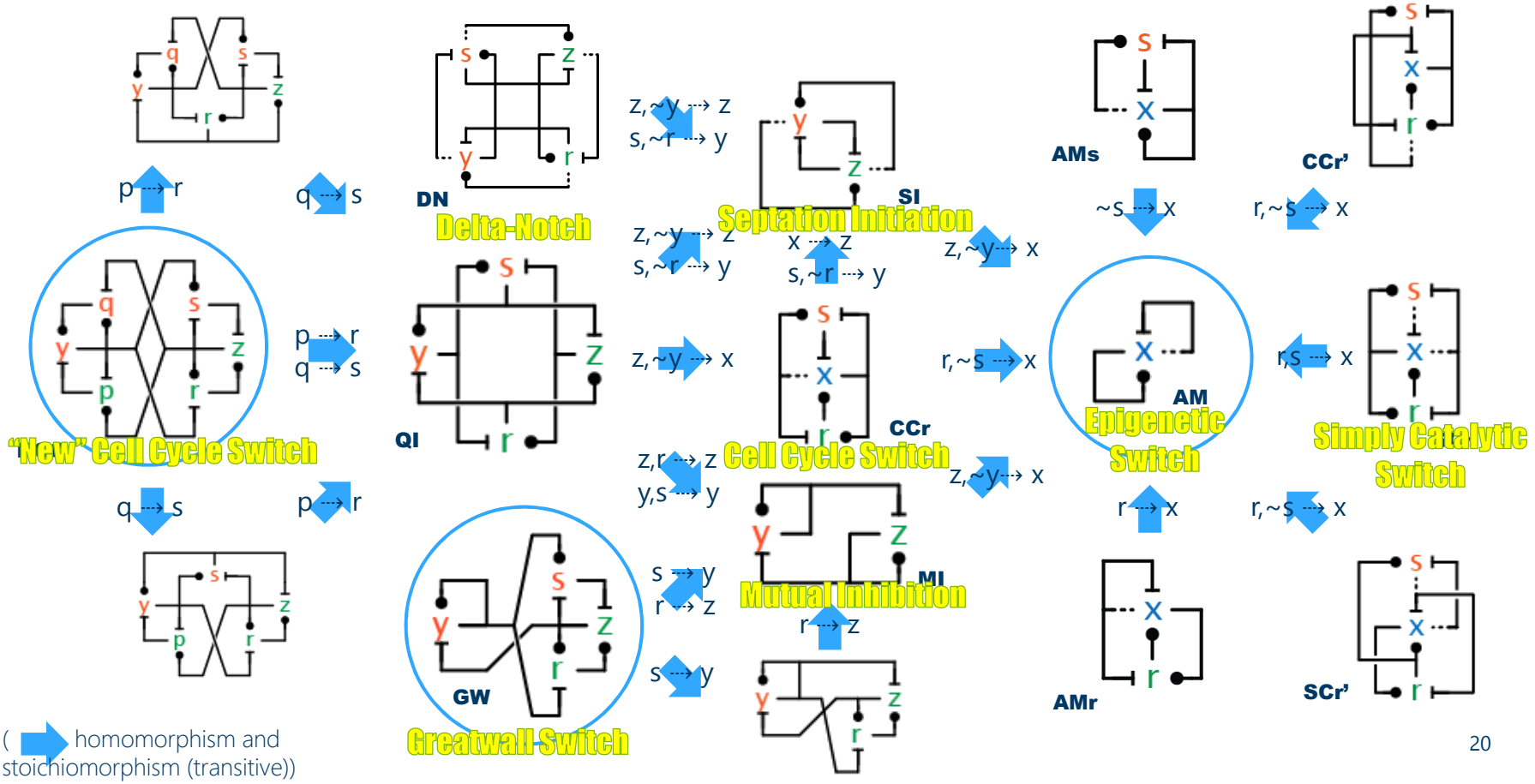
And for *any* rates of AM.

# Approximate Majority Emulation Zoo



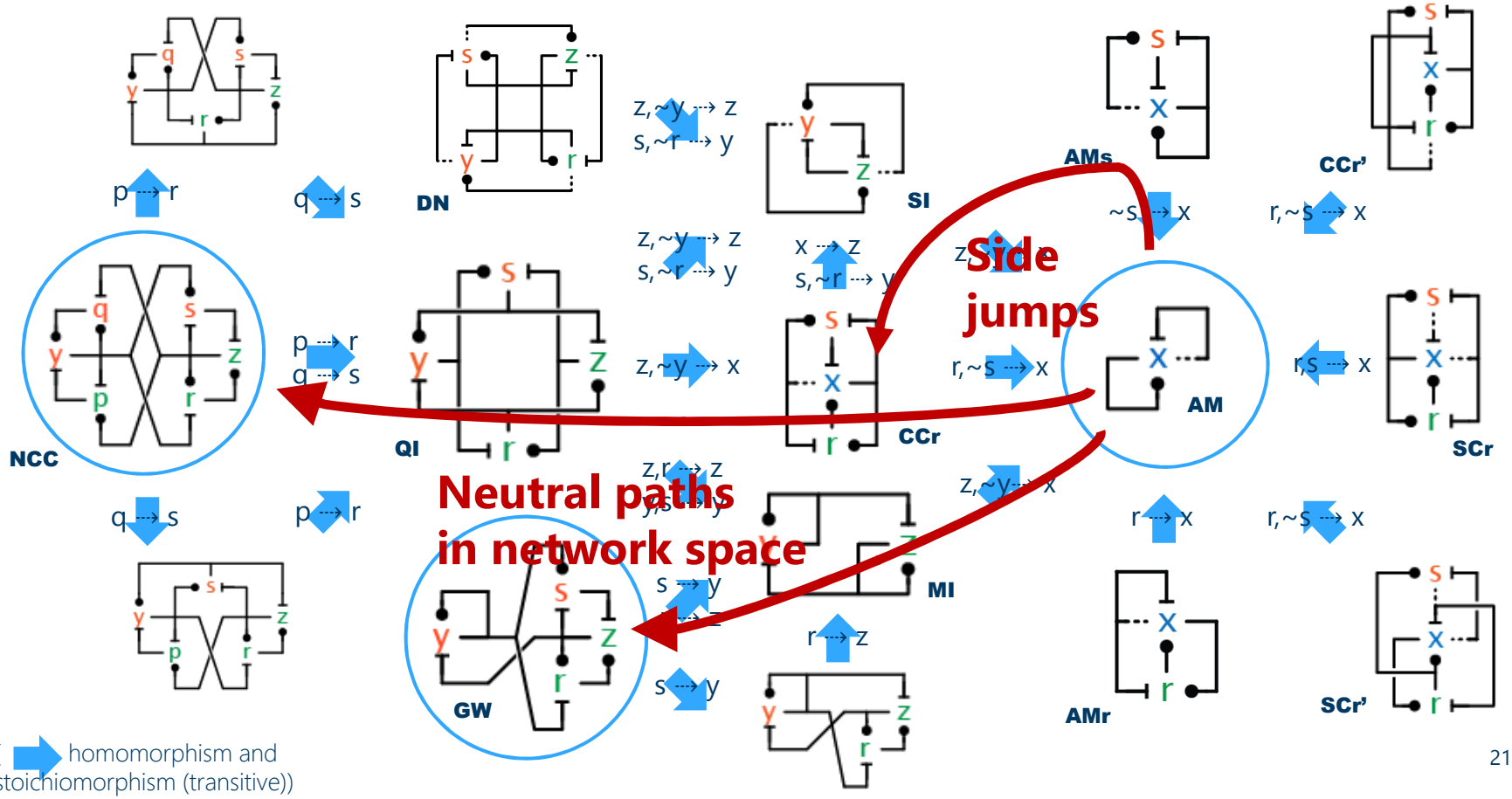

( homomorphism and stoichiomorphism (transitive))

# Approximate Majority Emulation Zoo



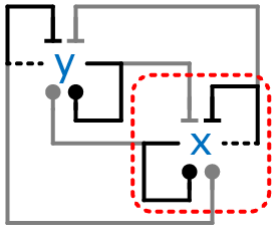

( ➡ homomorphism and stoichiomorphism (transitive))

# Approximate Majority Emulation Zoo

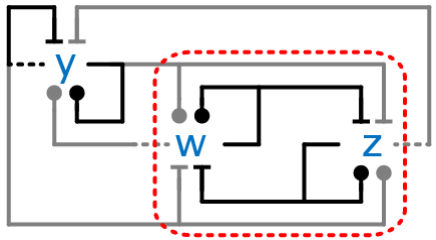



( ⇢ homomorphism and stoichiomorphism (transitive))

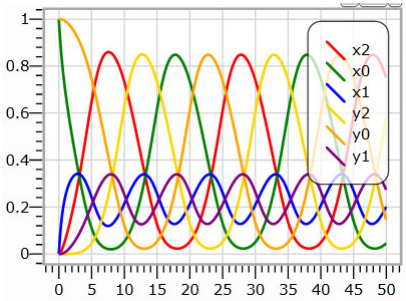
# Emulation in Context

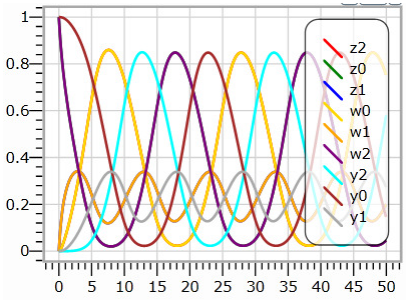



AM-AM Oscillator




AM-MI Oscillator



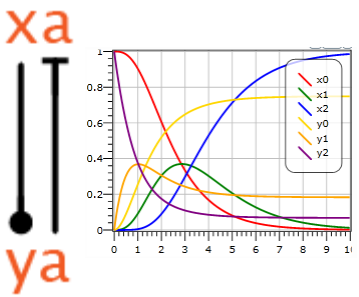

$m \in \mathbf{MI} \to \mathbf{AM}$ is an emulation:
it maps $z \to x$ and $\sim w \to x$

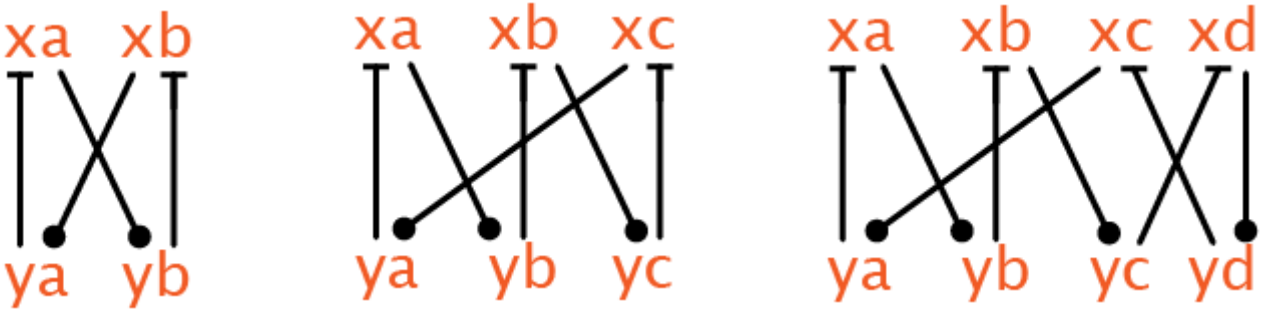
We can replace AM with MI in a context. The mapping $m$ tells us how to wire MI to obtain an overall emulation:

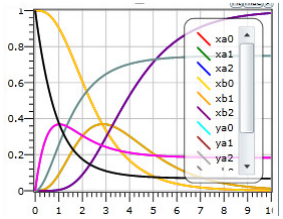
Each influence crossing the dashed lines into $x$ is replaced by a similar influence into *both* $z$ *and* $\sim w$. The latter is the same as an opposite influence into $w$ (shown).

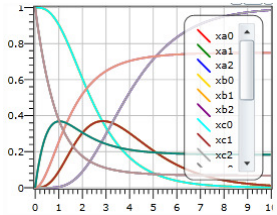
Each influence crossing the dashed lines out of $x$ is replaced by a similar influence from the same side of *either* $z$ *or* $\sim w$. The latter is the same as a similar influence from the opposite side of $w$ (shown), and the same as an opposite influence from the same side of $w$.

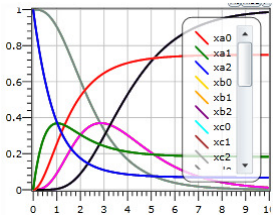
# Another Zoo


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

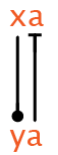

xa0
xa1
xa2
xb0
xb1
xb2
ya0
ya1
ya2

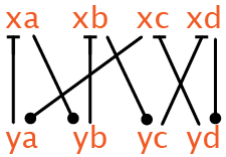

xa0
xa1
xa2
xb0
xb1
xb2
xc0
xc1
xc2


xa0
xa1
xa2
xb0
xb1
xb2
xc0
xc1
xc2

# Network Perturbations

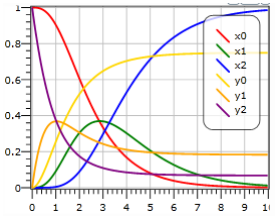
Network

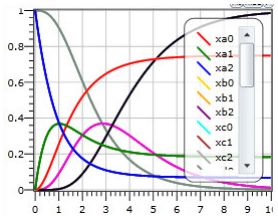


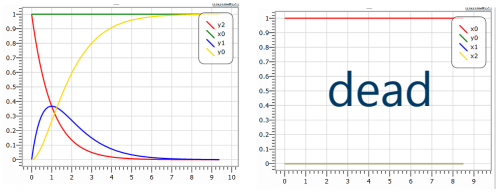

A complex but robust implementation of the simple network

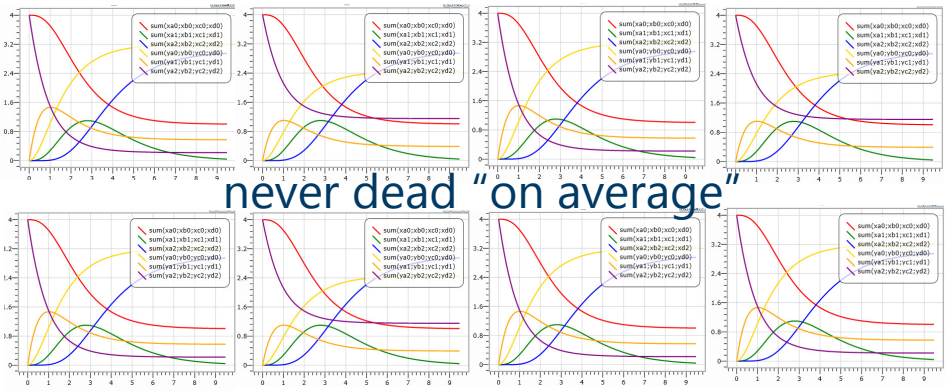
Normal Behavior



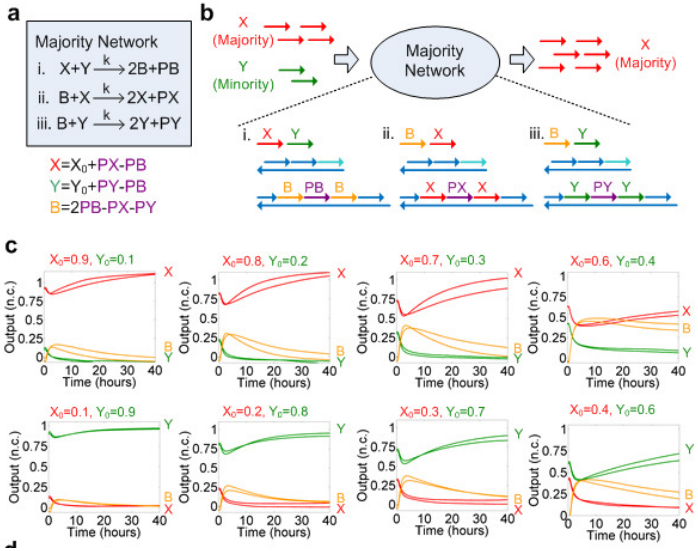

Removing each link in turn



# In separate work…

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

Microsoft Research

UNIVERSITY OF OXFORD

# Morphisms of CRNs

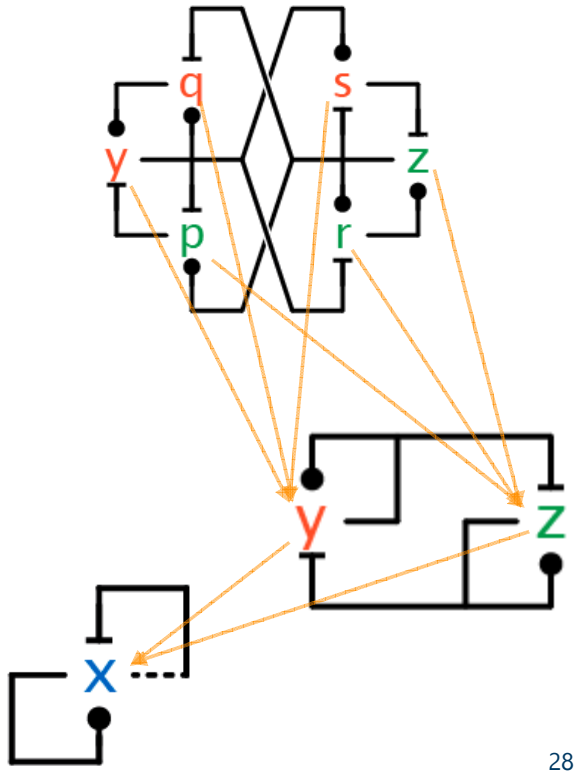
# A Theory of Network Emulation

(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

# When can a Network Emulate Another?

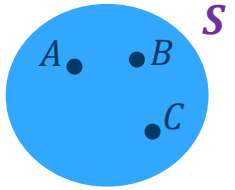
- What kind of morphisms guarantee emulation?
  - do they preserve network structure?
  - do they preserve stoichiometry?



# Chemical Reaction Networks

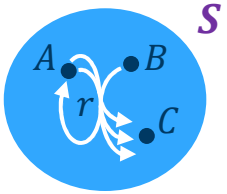
- A CRN is a pair $(S, R)$ where
  - $S = \{s_1, \dots, s_n\}$ a finite set of *species*
  - $R = \{r_1, \dots, r_m\}$ a finite set of *reactions*(*)

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




- Reactions $r = \rho \to^k \pi \in R$
  with *complexes* $\rho, \pi \in \mathbb{N}^S$
  *stoichiometric numbers* $\rho_s, \pi_s$ for $s \in S$
  and *rate constants* $k > 0$

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




- 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*

(*) $\rho \to^k \pi, \rho \to^{k'} \pi \in R \quad \Rightarrow \quad k = k'$

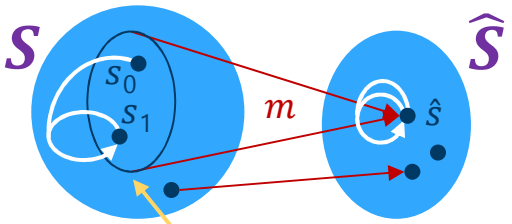
# Species Maps and Reaction Maps

- A *species map* is a map $m_{\mathcal{S}} \in S \to \hat{S}$
- Lifted to a *complex map*:

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

- It induces a canonical *reaction map* $m_{\mathcal{R}} \in R \to \hat{R}$

$$m_{\mathcal{R}}(\rho \to^k \pi) = m_{\mathcal{S}}(\rho) \to^k m_{\mathcal{S}}(\pi)$$




the *fiber* of $\hat{s}$: $m^{-1}(\hat{s})$

$$m_{\mathcal{S}}(s_0) = m_{\mathcal{S}}(s_1) = \hat{s}$$

$$r = s_0 + s_1 \to^1 s_1$$

where $\rho_{s_0} = 1,\ \rho_{s_1} = 1$

$$m_{\mathcal{R}}(r) = 2\hat{s} \to^1 \hat{s}$$

becuase $m_{\mathcal{S}}(\rho)_{\hat{s}} = \rho_{s_0} + \rho_{s_1} = 2$

# CRN Morphisms

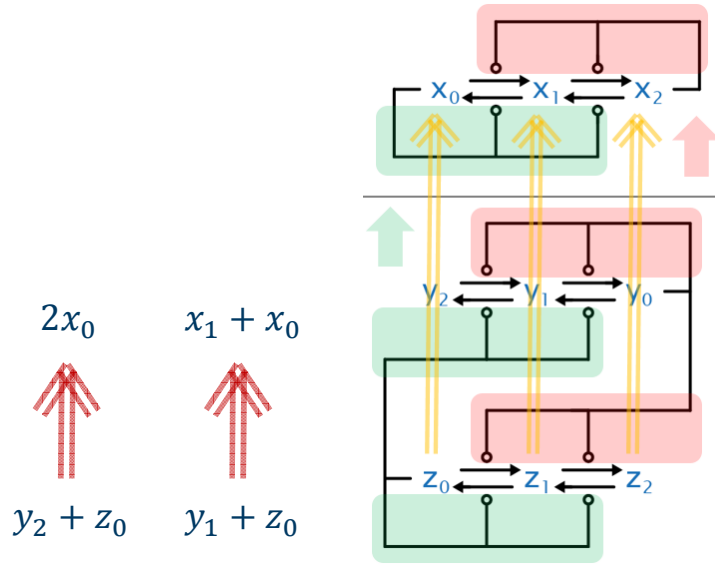
A *CRN morphism* from $(S, R)$ to $(\hat{S}, \hat{R})$
written $m \in (S, R) \to (\hat{S}, \hat{R})$

is a pair of maps $m = (m_S, m_R)$
- a *species map* $m_S \in S \to \hat{S}$
- a *reaction map* $m_R \in R \to \hat{R}$

extended to a *complex map* $m_S \in \mathbb{N}^S \to \mathbb{N}^{\hat{S}}$
linearly: $m_S(\rho)_{\hat{s}} = \Sigma_{s \in m_S^{-1}(\hat{s})} \rho_s$

(sometimes omitting the subscripts on $m$)

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

# CRN Homomorphisms

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

$$m_{\mathcal{R}}(\rho \to^k \pi) = m_{\mathcal{S}}(\rho) \to^k m_{\mathcal{S}}(\pi)$$

It implies that stoichiometries are connected:

$$\boldsymbol{m_{\mathcal{S}}}^{\mathbf{T}} \cdot \boldsymbol{\varphi} = \hat{\boldsymbol{\varphi}} \cdot \boldsymbol{m_{\mathcal{R}}}^{\mathbf{T}}$$

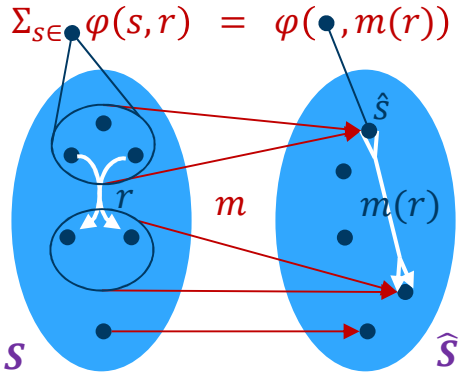
$\boldsymbol{\varphi}, \hat{\boldsymbol{\varphi}}$ are the respective stoichiometric matrices

$\boldsymbol{m_{\mathcal{S}}}$, $\boldsymbol{m_{\mathcal{R}}}$ 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 $0$

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

Preserves the graph structure of the network: the reaction mapping is all made of canonical maps that 'agree' with the species mapping $\forall \hat{s} \in \hat{S}, \forall r \in R$:




It therefore preserves some of the stoichiometry: $\boldsymbol{\varphi}$ agrees with $\boldsymbol{m}$ when *summed over species*

.

# CRN Reactant Morphism

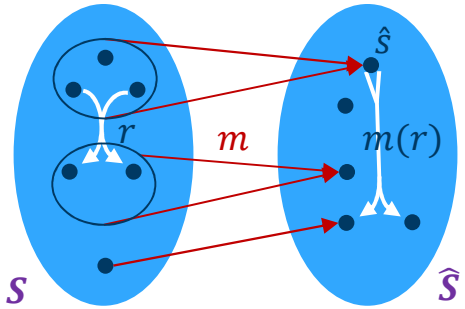
$m \in (S, R) \to (\hat{S}, \hat{R})$ is a *CRN reactant morphism* if $m_{\mathcal{R}}$ is determined by $m_{\mathcal{S}}$ on reactants. $\exists \hat{k}, \hat{\pi}$:

$$m_{\mathcal{R}}(\rho \to^{k} \pi) = m_{\mathcal{S}}(\rho) \to^{\hat{k}} \hat{\pi}$$

iff ($\boldsymbol{\rho}, \hat{\boldsymbol{\rho}}$ are the respective reactant matrices):

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

Preserves just the "left hand side" graph structure of the network, on the source side of the reaction edges




A homomorphism is a reactant morphism

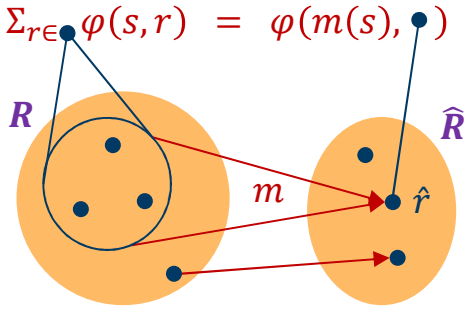
# CRN Stoichiomorphisms

$m \in (S, R) \to (\hat{S}, \hat{R})$ is a *CRN stoichiomorphism* if:

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

That *can be checked on the syntax of the networks* without any consideration of the kinetics

Preserves the stoichiometry of the network: $\boldsymbol{\varphi}$ agrees with $\boldsymbol{m}$ when *summed over reactions* $\forall s \in S, \forall \hat{r} \in \hat{R}$:

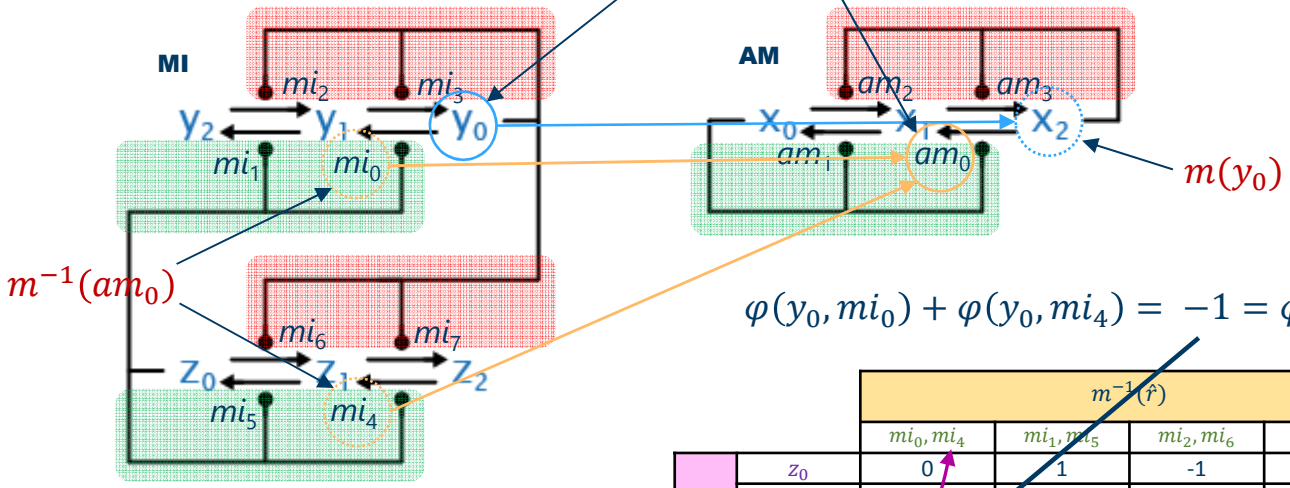



Together with reactant morphism, this preserves *enough* of the stoichiometric structure to ensure the emulation property

# 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

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

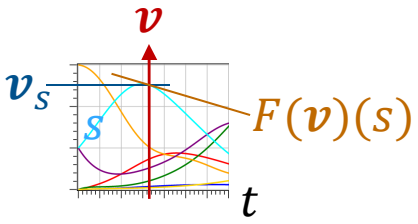
| | | $m^{-1}(\hat{r})$ | | | | |
|---|---|---|---|---|---|---|
| | | $mi_0, mi_4$ | $mi_1, mi_5$ | $mi_2, mi_6$ | $mi_3, mi_7$ | |
| $\forall s \in \mathrm{MI}$ | $z_0$ | 0 | 1 | -1 | 0 | $x_0$ |
| | $z_1$ | 1 | -1 | 1 | -1 | $x_1$ |
| | $z_2$ | -1 | 0 | 0 | 1 | $x_2$ |
| | $y_0$ | -1 | 0 | 0 | 1 |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

# 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:

$$F(\boldsymbol{v})(s) = \Sigma_{r \in R}\ \varphi(s, r) \cdot [\mathrm{r}]_{\boldsymbol{v}}$$

sum over all reactions of the stoichiometry of the species in the reaction times the mass action of the reaction in the state

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

the mass action of a reaction in state is the product of reagent concentrations according to their stoichiometric numbers:

$[\rho \to^k \pi]_{\boldsymbol{v}} = \boldsymbol{v}^{\rho} = \Pi_{s \in S}\ \boldsymbol{v}_s{}^{\rho_s}$

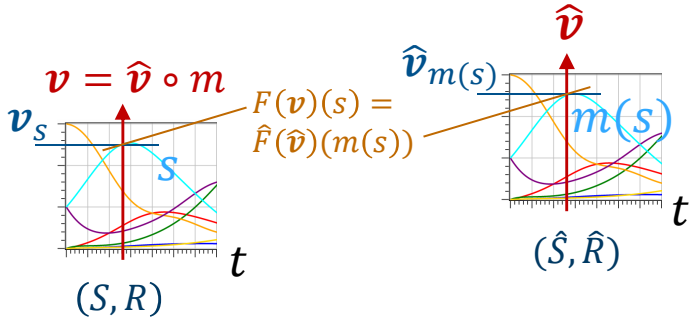
# Kinetic Emulation

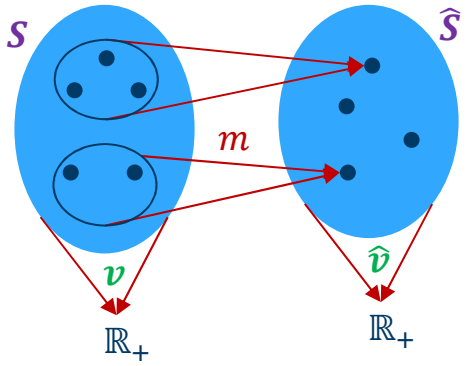
A morphism $m \in (S,R) \to (\hat{S},\hat{R})$ is a *CRN emulation* if for the respective differential systems $F, \hat{F}$, $\forall \hat{v} \in \mathbb{R}_+^{\hat{S}}$:

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

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

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 $\boldsymbol{m_S}^{\mathbf{T}} \cdot \boldsymbol{\rho} = \hat{\boldsymbol{\rho}} \cdot \boldsymbol{m_R}^{\mathbf{T}}$ preserve enough network structure

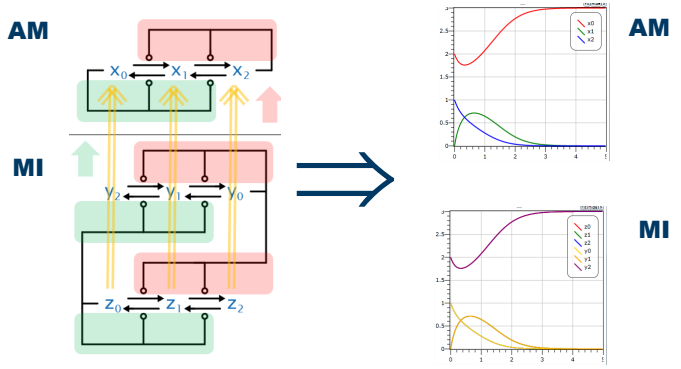
stoichiomorphism $\boldsymbol{\varphi} \cdot \boldsymbol{m_R} = \boldsymbol{m_S} \cdot \hat{\boldsymbol{\varphi}}$ preserve enough chemical stoichiometry

$\Downarrow$

emulation $\forall \hat{\boldsymbol{v}}.\ F(\hat{\boldsymbol{v}} \circ m_S) = \hat{F}(\hat{\boldsymbol{v}}) \circ m_S$ preserve derivatives

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



# Change of Rates Theorem

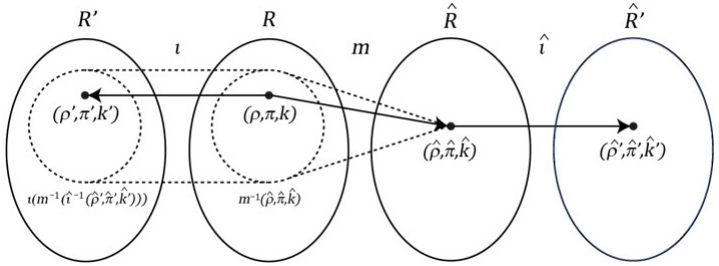
A *change of rates* for $(S, R)$ is morphism $\iota \in (S, R) \to (S, R')$ such that $\iota(S)$ is the identity and $\iota(\rho, \pi, k) = (\rho, \pi, k')$.

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.

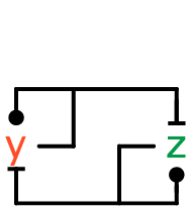
thus, for *any rates* of $(\hat{S}, \hat{R})$ we can match trajectories

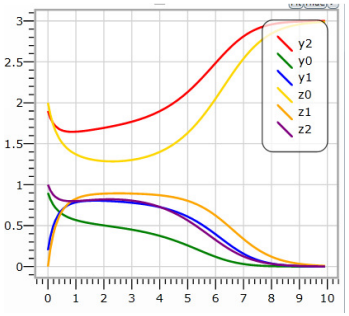
In fact, $\iota$ changes rates by the ratio with which $\hat{\imath}$ changes rates:
$\iota(\rho, \pi, k) = \left(\rho, \pi, k \cdot \frac{\hat{k}'}{\hat{k}}\right)$ where $m(\rho, \pi, k) = (\hat{\rho}, \hat{\pi}, \hat{k})$ and $\hat{\imath}(\hat{\rho}, \hat{\pi}, \hat{k}) = (\hat{\rho}, \hat{\pi},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



# Any Rates, Any Initial Conditions

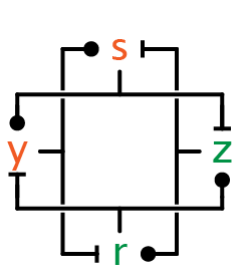
- A stoichiomorphism $m \in (S, R) \rightarrow (\hat{S}, \hat{R})$ that is also a homomorphism, determines an emulation for any choice of rates of $(\hat{S}, \hat{R})$.
- Those emulations can match any initial conditions of any choice of rates of $(\hat{S}, \hat{R})$ with some initial conditions of some choice of rates of $(S, R)$.
- Automatically substitutive for catalytic networks
  - Rewire in larger network according to $m$ (shared inputs, single copy outputs).

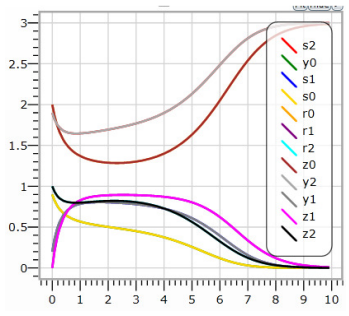



```
directive sample 10.0 100

init z0 2 |
init z1 0 |
init z2 1 |
init y0 0.9 |
init y1 0.2 |
init y2 1.9 |

y2 + y0 ->{0.9} y0 + y1 |
y1 + y0 ->{1.0} y0 + y0 |
z0 + y0 ->{1.1} y0 + z1 |
z1 + y0 ->{1.2} y0 + z2 |

y0 + z0 ->{0.7} z0 + y1 |
y1 + z0 ->{0.8} z0 + y2 |
z2 + z0 ->{0.5} z0 + z1 |
z1 + z0 ->{0.6} z0 + z0
```

MI with completely heterogeneous rates and initial conditions



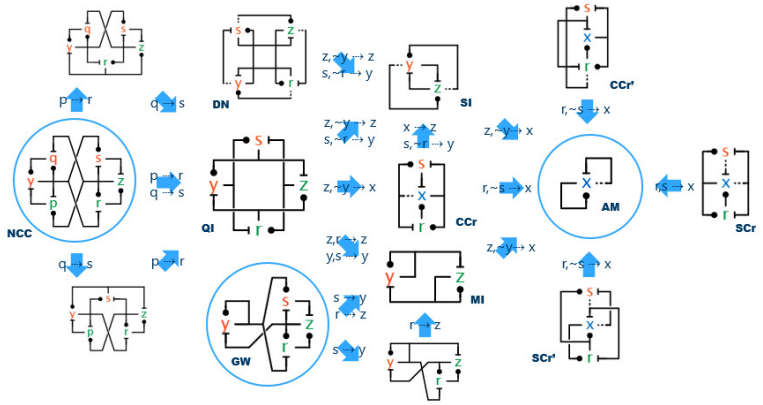




```
directive sample 10.0 100

init z0 2 |
init z1 0 |
init z2 1 |

init s0 0.9 |
init s1 0.2 |
init s2 1.9 |

init r0 2 |
init r1 0 |
init r2 1 |

init y0 0.9 |
init y1 0.2 |
init y2 1.9 |

s2 + y0 ->{0.9} y0 + s1 |
s1 + y0 ->{1.0} y0 + s0 |
r0 + y0 ->{1.1} y0 + r1 |
r1 + y0 ->{1.2} y0 + r2 |

s0 + z0 ->{0.7} z0 + s1 |
s1 + z0 ->{0.8} z0 + s2 |
r2 + z0 ->{0.5} z0 + r1 |
r1 + z0 ->{0.6} z0 + r0 |

y2 + s0 ->{0.9} s0 + y1 |
y1 + s0 ->{1.0} s0 + y0 |
z0 + s0 ->{1.1} s0 + z1 |
z1 + s0 ->{1.2} s0 + z2 |

y0 + r0 ->{0.7} r0 + y1 |
y1 + r0 ->{0.8} r0 + y2 |
z2 + r0 ->{0.5} r0 + z1 |
z1 + r0 ->{0.6} r0 + z0
```

QI with matching rates and initial conditions

# Corollaries

- By checking only static network and morphism properties we can learn that:
  - All these networks are (at least) bistable
  - (We do not have to reanalyze the steady states of all these dynamical systems)
  - All these networks can perform *exactly* as fast as AM
  - (We do not have to reprove the complexity bounds for all these networks)



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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.

# Network Emulation Morphisms

- What guarantees emulation?
  - Reactant morphism + stoichiomorphism: static, state-independent (*structural*) conditions
- How do you find them?
  - Emulation Theorem => they do not depend on initial conditions
  - Change of Rates Theorem => can look for rate-1 morphisms
  - E.g. test all possible rate-1 homomorphism between two networks to see if they are stoichiomorphisms
- How common are they?
  - Likely relatively rare, but still many useful ones => richness of networks space
- How useful are they?
  - Establish structural, algorithmic, (non-accidental) *reasons* for kinetic similarity
  - Explain simple behavior "facets" of complicated networks
  - Investigate evolutionary paths (maybe)
- How brittle are they?
  - Will a perturbed trajectory of the source network converge to a trajectory of the target network?
  - What about other reaction kinetics?
- What about stochastic?
  - Is there a CME Emulation Theorem?

# Nature likes a good algorithm

First part

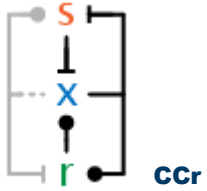

Approximate

"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