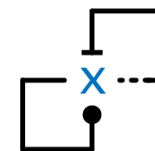
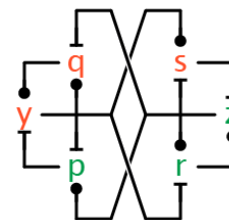


# Morphisms of Reaction Networks

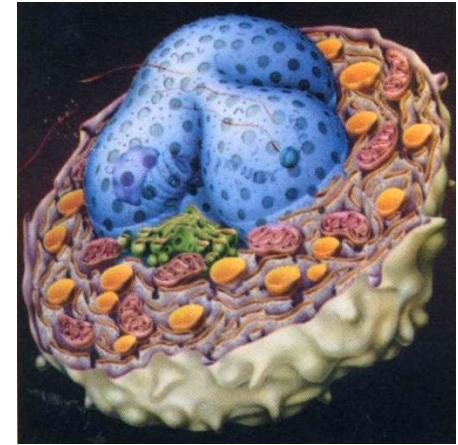
Luca Cardelli, Microsoft Research & Oxford University

Verification of Engineered Molecular Devices and Programs, Vienna, 2014-07-17



# Motivation

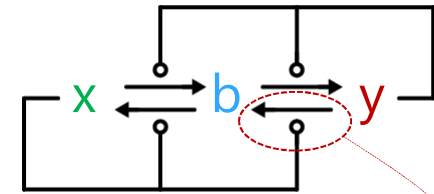
- Give substance to the claim that “cells compute”
  - Yes, but *what* do they compute?
- Catch nature red-handed in the act of running a computational task
  - Something that a computer scientist would recognize as an *algorithm*



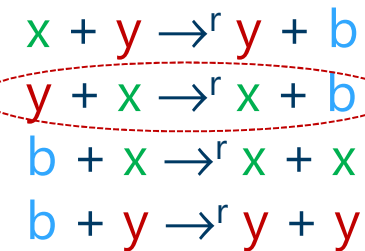
# A Consensus Algorithm

- 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  $\rightarrow$



chemical reaction network

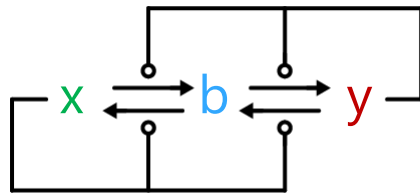


Dana Angluin · James Aspnes · David Eisenstat

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

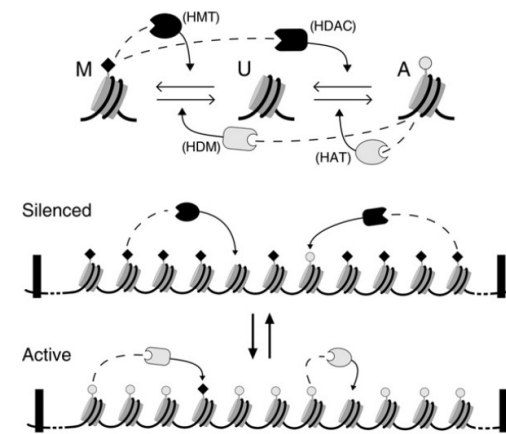


Figure 1. Basic Ingredients of the Model

Theory

Cell

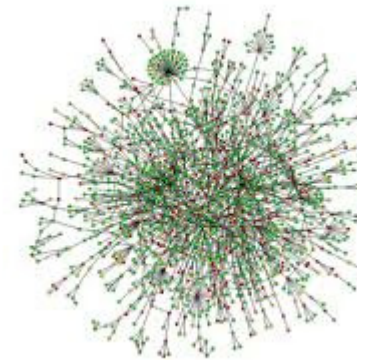
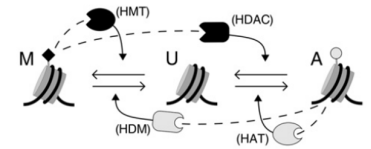
Theoretical Analysis of Epigenetic  
Cell Memory by Nucleosome Modification

Ben B. Doak,<sup>1,2</sup> Misha A. Michor,<sup>1,3</sup> Kim Sjögreen,<sup>1,4</sup> and Genevieve Thori  
<sup>1</sup>Center for Molecular Life, Niels Bohr Institute, Copenhagen Ø, Denmark  
<sup>2</sup>Department of Molecular and Biomedical Science, University of Adelaide, SA 5005, Australia  
<sup>3</sup>Department of Molecular Biology, University of Copenhagen, Copenhagen N, Denmark  
Correspondence: sjoegreen@biol.ku.dk  
DOI: 10.1016/j.cel.2007.02.012

2007

# Motivation (cont'd)

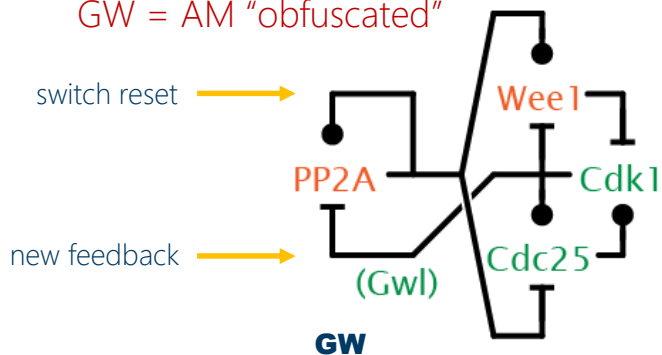
- We can claim that the epigenetic switch is a *direct* biological implementation of an algorithm
  - Although we may have to qualify that with some notion of approximation of the (enzymatic) kinetics
- In most cases the biological implementation seems more *indirect* or *obfuscated*
  - "Nature is subtle but not malicious - Einstein" Ha! think again!
  - Other implementations of Approximate Majority seem convoluted and... approximate
  - Like finding an algorithm in a haystack...



# Obfuscated Implementations

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

GW = AM "obfuscated"



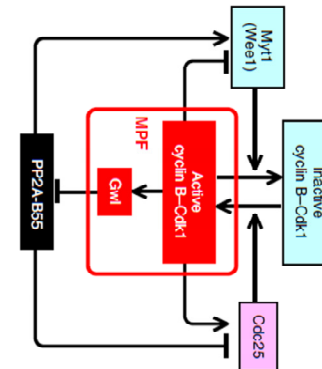
The Cell Cycle Switch Computes Approximate Majority

SUBJECT AREAS:  
COMPUTATIONAL  
BIOLOGY

Luca Cardelli<sup>1</sup> & Attila Csikász-Nagy<sup>2,3</sup>

Sep 2012

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



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

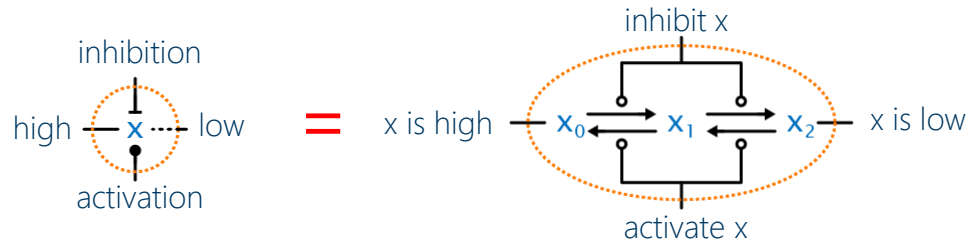
Masatoshi Hara<sup>1,†</sup>, Yusuke Abe<sup>1,†</sup>, Toshiaki Tanaka<sup>2</sup>, Takayoshi Yamamoto<sup>1,†</sup>, Eiichi Okumura<sup>1</sup> & Takeo Kishimoto<sup>1</sup>

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.]
  - Epiphany! Forget stochastic! Forget approximate! When are CRNs “deterministically equivalent”?
  - Or better, when do trajectories of one CRN “collapse” into trajectories of another?
  - Much simpler! And can be solved 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



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

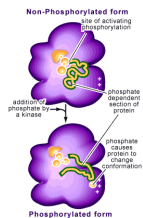


Functional Motifs in Biochemical Reaction Networks  
John J. Tyson<sup>1</sup> and Bela Novak<sup>2</sup>

$$\frac{dx_i}{dt} = \gamma_i \frac{[A_i(1-x_i) - B_i x_i]}{A_i + B_i}, \quad i = 1, \dots, N.$$

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

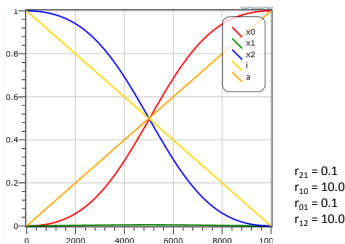
biological mechanism: (e.g.:) multisite phosphorylation



triplet motif

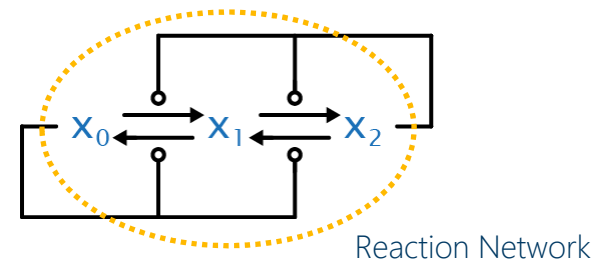
We model them by 4 mass action reactions over 3 species  $x_0, x_1, x_2$

They actually implement a Hill function of coefficient 2:

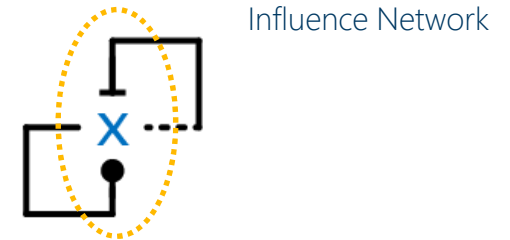


activation ●  
inhibition T  
catalysis ○

## Approximate Majority



=

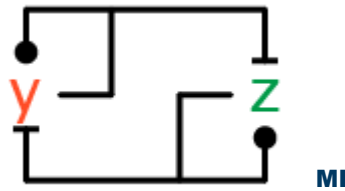




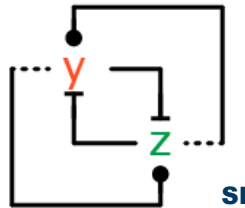
# Biological Influence Networks

activation ●  
inhibition ⊣

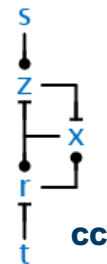
## Mutual Inhibition & Self Activation



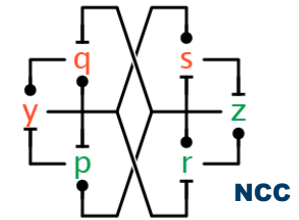
## Mutual Inhibition & Mutual Anti-activation



## Cell Cycle Switching



## Better Switching



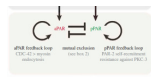
## Cell cycle transitions

Molecular mechanisms creating bistable switches at cell cycle transitions  
Amal Vengalil, P. K. Sirock, J. Tyson and Bela Novak  
Open Biol 2013, 9: 130178, published 15 March 2013



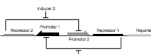
## Polarity establishment

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY  
The PAR network redundancy and robustness in a symmetry-breaking system  
Ferdin Merys<sup>1,2</sup> and Caroline Slaughter<sup>1</sup>  
<sup>1</sup>Group in Systems Biology, Theoretical Biology and Biophysics, National Institute of Standards and Technology, Gaithersburg, Maryland, USA; <sup>2</sup>Department of Biology, University of Cambridge, Cambridge, UK

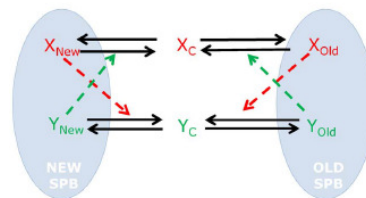


## Gene networks

Construction of a genetic toggle switch in *Escherichia coli*  
Timothy S. Gardner<sup>1,2</sup>, Charles R. Cantor<sup>1,2</sup> & James J. Collins<sup>1,2</sup>



## Septation Initiation



### Dynamics of SIN Asymmetry Establishment

Archana Rajgarh<sup>1</sup>, Arava Farkhoulou<sup>2</sup>, Jun-Sung Cha<sup>2</sup>, Daniel McCollum<sup>1</sup>, Massimo Saito<sup>1,3</sup>, Ralf-Dieter Jahn<sup>1</sup>, Ashwin Vigneri<sup>1</sup>, Qing-Qing Li<sup>1</sup>, Armin Eichler<sup>1</sup>, David R. Nelson<sup>1,3</sup>  
<sup>1</sup>Department of Biology, <sup>2</sup>Department of Chemistry, <sup>3</sup>Department of Physics, Harvard University, Cambridge, MA 02138

## The G<sub>2</sub>/M cell cycle switch

Journal of Cell Science 116, 1053-1061 (2003)  
Printed in Great Britain © The Company of Biologists Limited 2003

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

Bela Novak<sup>1</sup> and John J. Tyson<sup>1</sup>  
<sup>1</sup>Department of Biology, Virginia Polytechnic Institute, Blacksburg, VA 24061, USA  
<sup>2</sup>Present address: Department of Agricultural Chemistry, University of Cambridge, Cambridge, UK  
\*Author for correspondence



Novak, B. & Tyson, J. J. (2003) *Journal of Cell Science*, 116, 1053-1061.

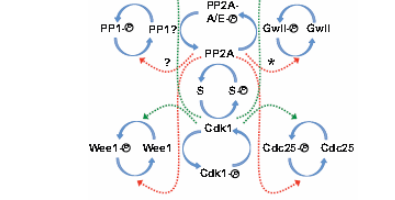
### Universal control mechanism regulating onset of M-phase

PNAS 100, 1053-1058 (2003)  
100th Anniversary Issue  
100th Anniversary Issue  
100th Anniversary Issue

## The "new" cell cycle switch

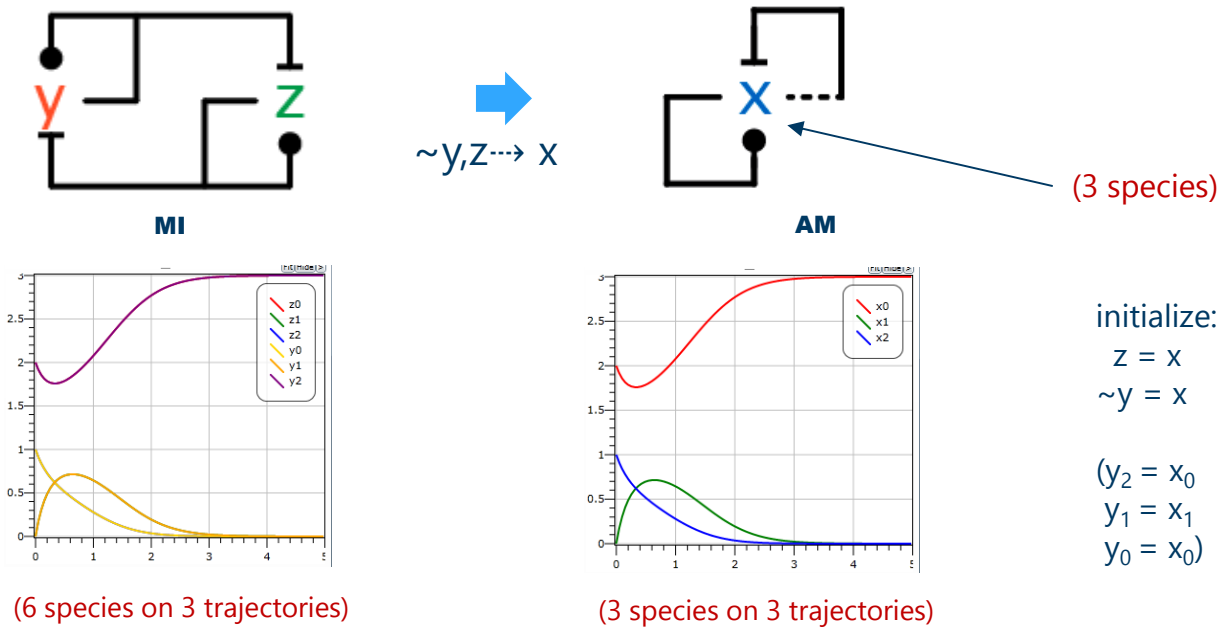
### Phosphorylation network dynamics in the control of cell cycle transitions

Daniel Fisher<sup>1,2</sup>, Liliana Krasinska<sup>1,2</sup>, Damien Coudreuse<sup>1,2</sup> and Bela Novak<sup>1,2</sup>  
<sup>1</sup>Unit of Systems Biology, Massachusetts Institute of Technology, Cambridge, MA 02139, USA; <sup>2</sup>Department of Biology, Virginia Polytechnic Institute, Blacksburg, VA 24061, USA  
<sup>3</sup>Department of Biology, University of Cambridge, Cambridge, UK  
\*Author for correspondence



# Network Emulation: MI emulates AM

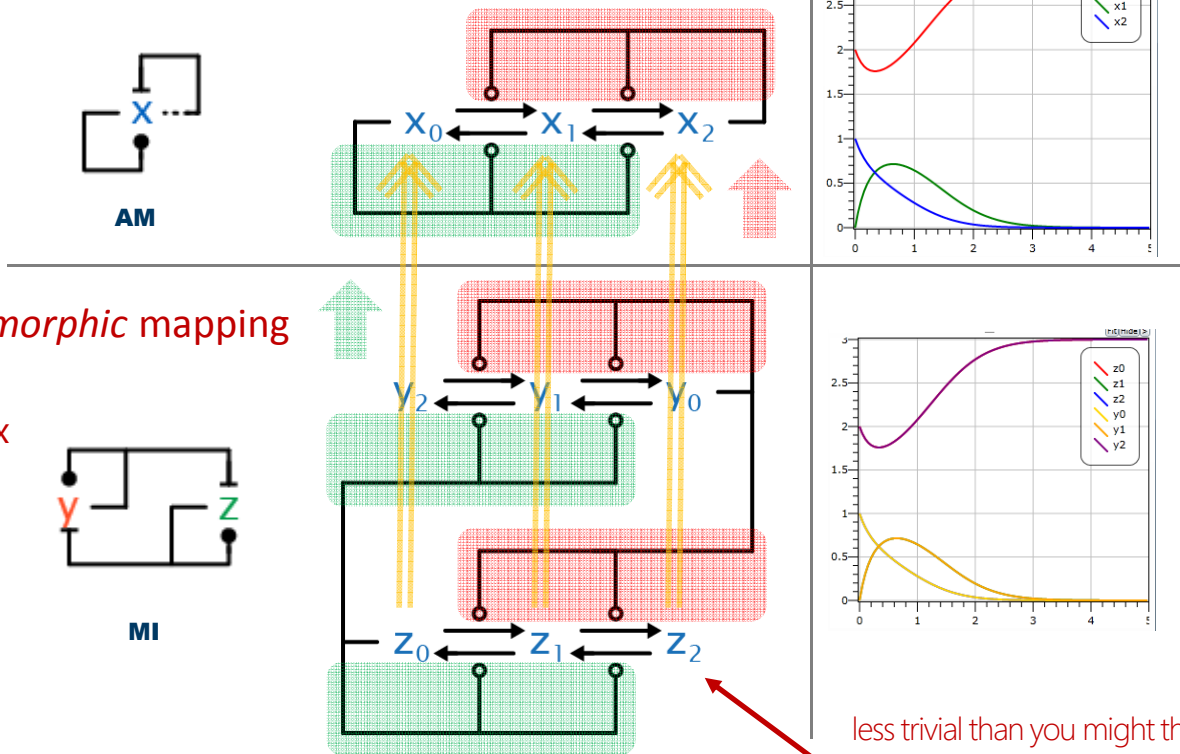
- For **any rates and initial conditions** of AM, we can find *some* rates and initial conditions of MI such that the (6) trajectories of MI retrace those (3) of AM:



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

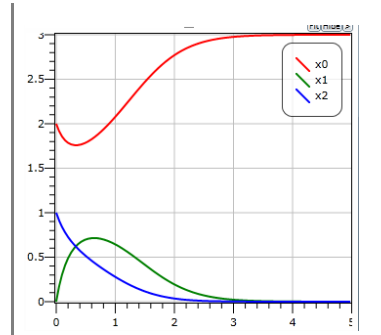
# MI to AM Emulation: Network Morphism

A mapping of species and reactions

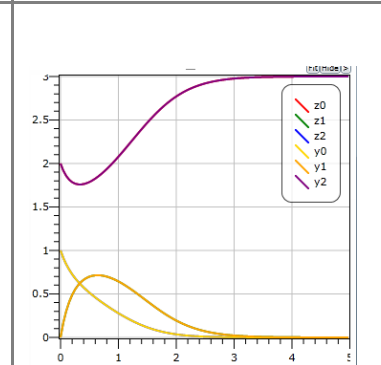


homomorphic mapping

$z \rightarrow x$   
 $\sim y \rightarrow x$



any initial conditions



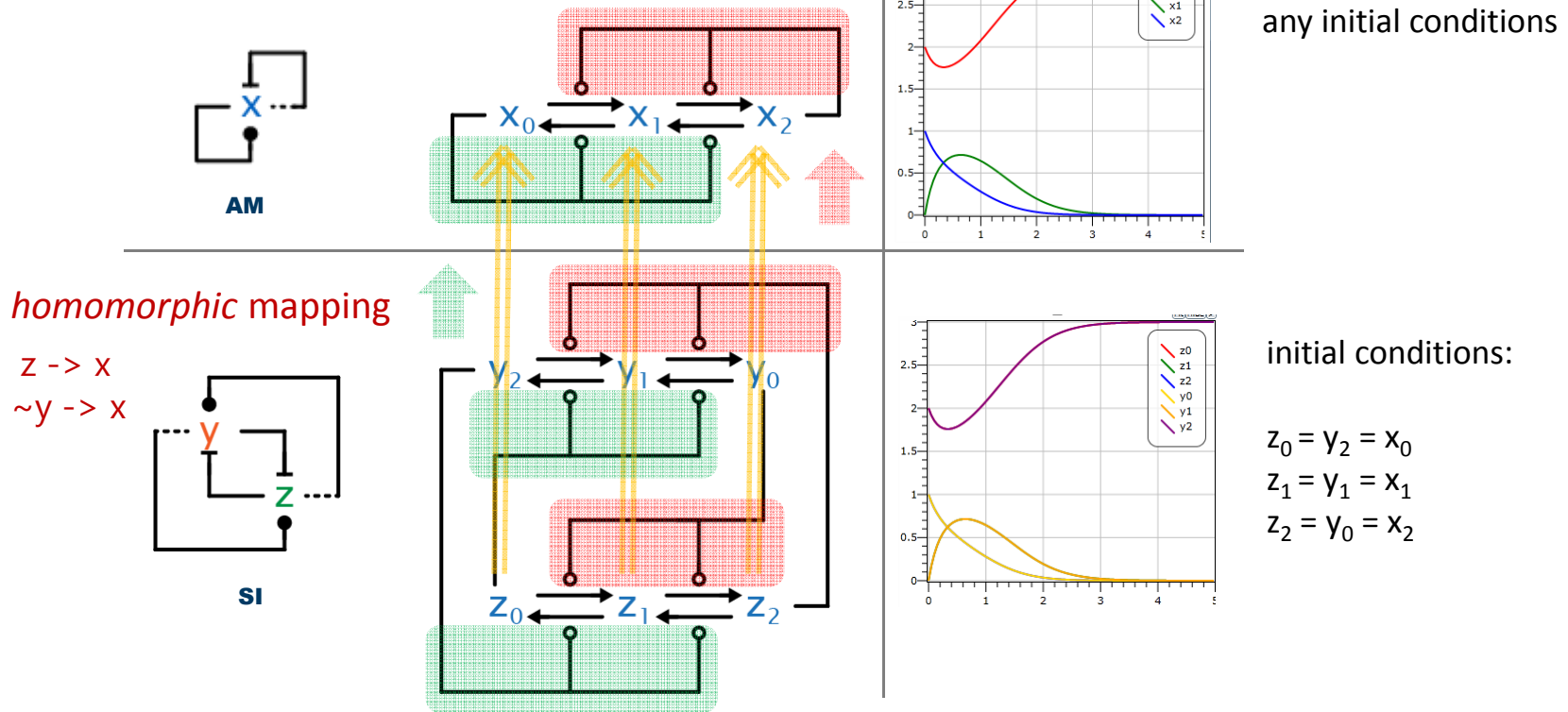
initial conditions:

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

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

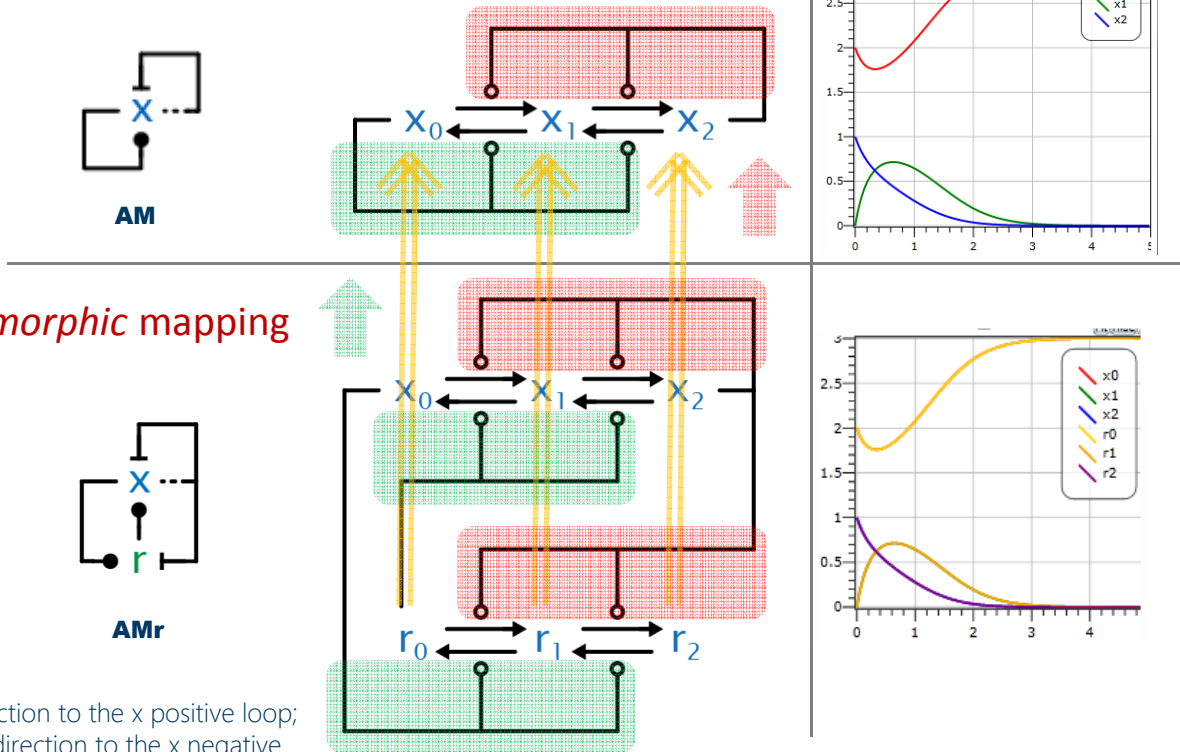
# SI to AM Emulation: Network Morphism

A mapping of species and reactions



# AMr to AM Emulation: Network Morphism

A mapping of species and reactions



any initial conditions

initial conditions:

$$r_0 = x_0 = x_0^{AM}$$

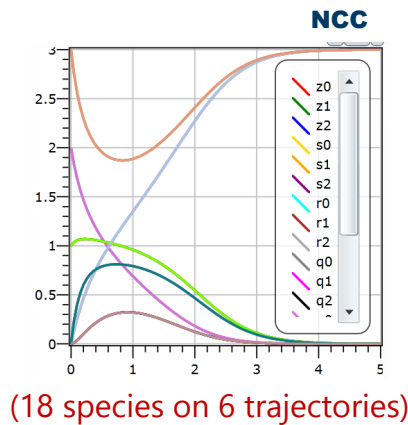
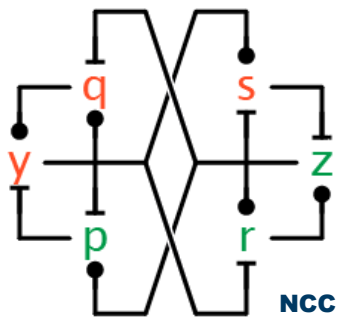
$$r_1 = x_1 = x_1^{AM}$$

$$r_2 = x_2 = x_2^{AM}$$

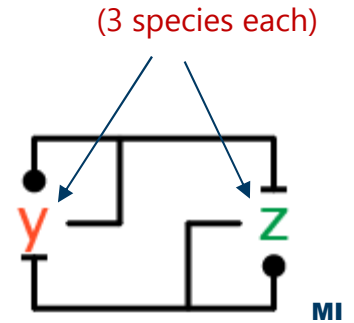
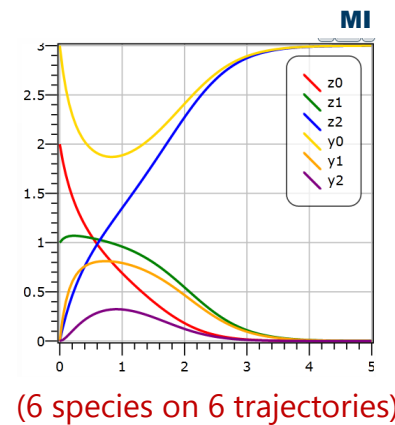
(AMr adds an indirection to the x positive loop; if we also add an indirection to the x negative loop, we obtain a prototypical cell cycle switch that also emulates AM: CCR)

# 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



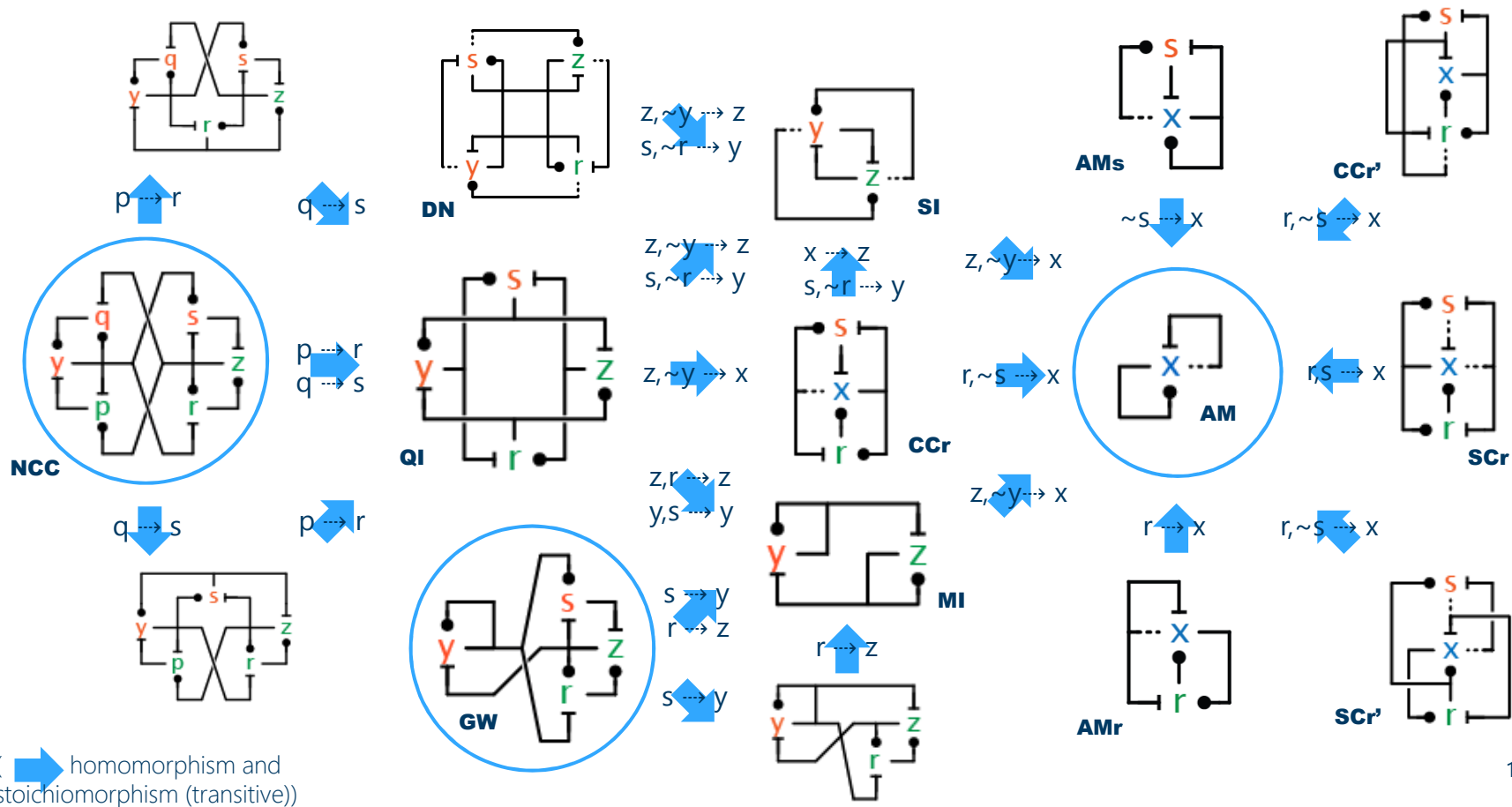
$z, r, p \rightsquigarrow z$   
 $y, q, s \rightsquigarrow y$



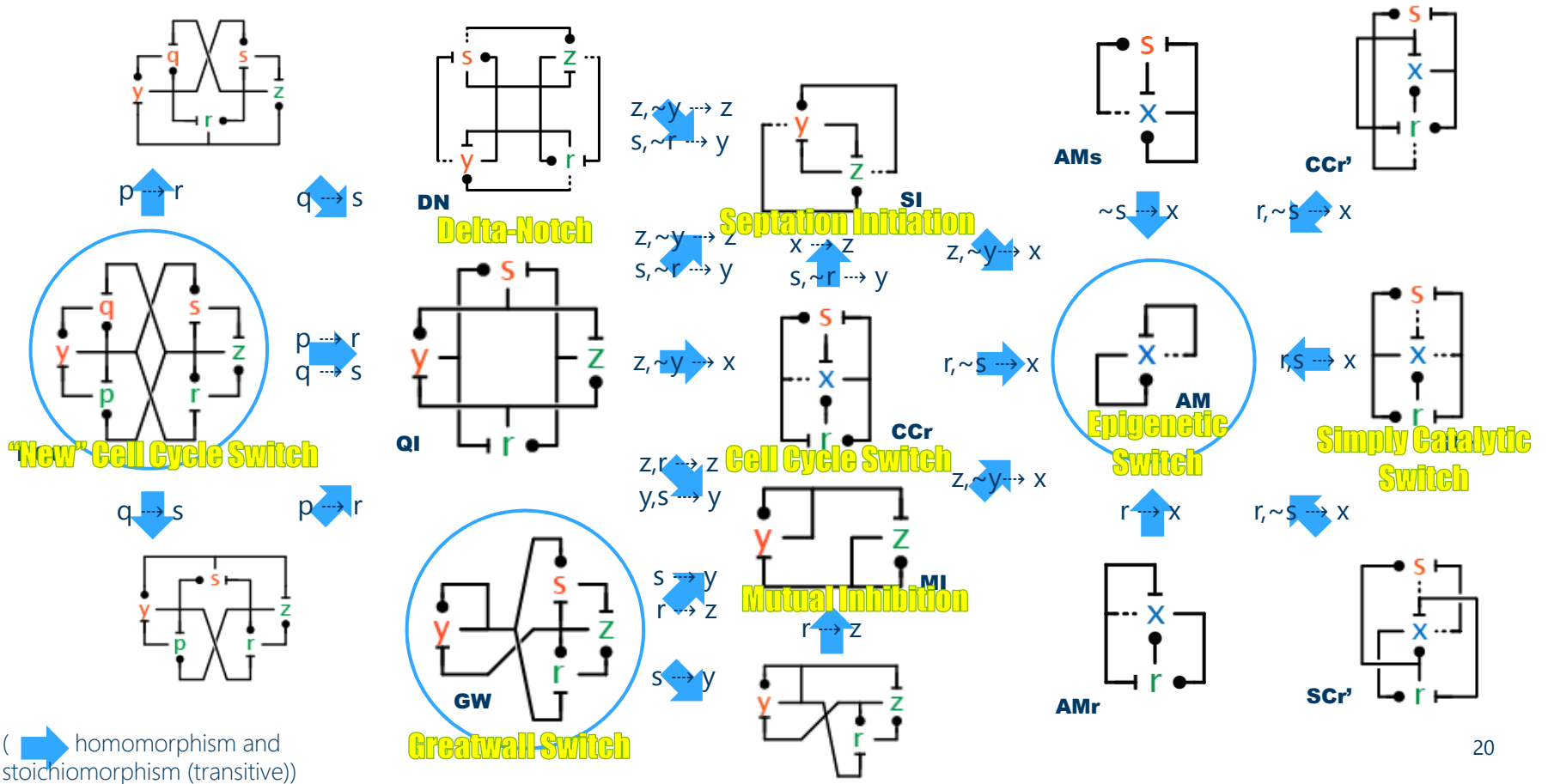
initialize  
 $z, r, p = z$   
 $y, q, s = y$

- Why does this work so well?

# Approximate Majority Emulation Zoo



# Approximate Majority Emulation Zoo

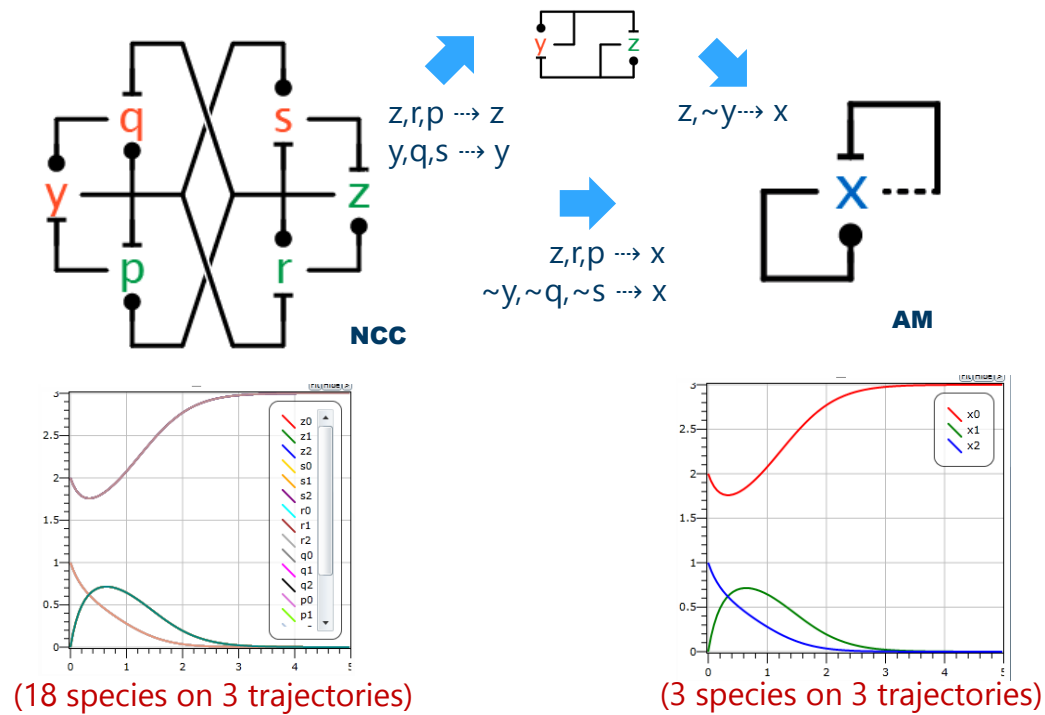




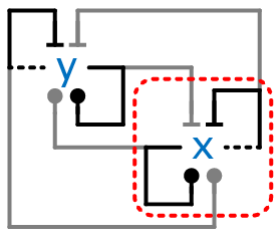


# Emulations Compose: NCC emulates AM

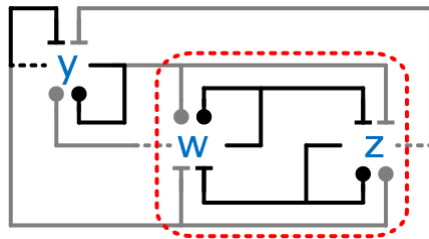
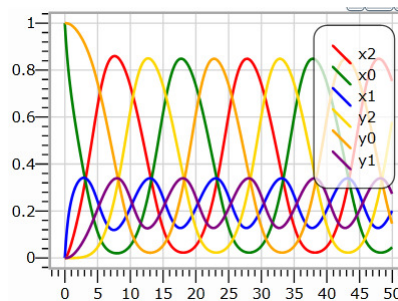
- The (18) trajectories NCC can *always* retrace those (3) of AM



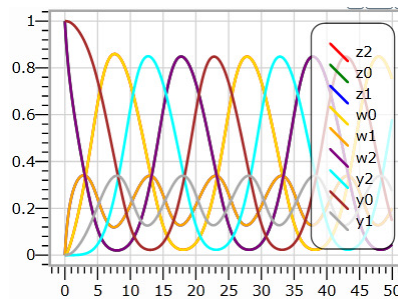
# Emulation in Context



AM-AM Oscillator



AM-MI Oscillator



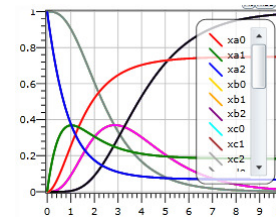
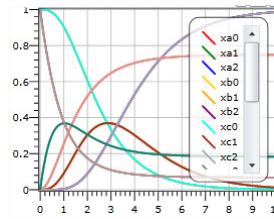
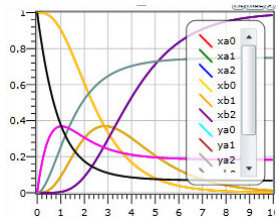
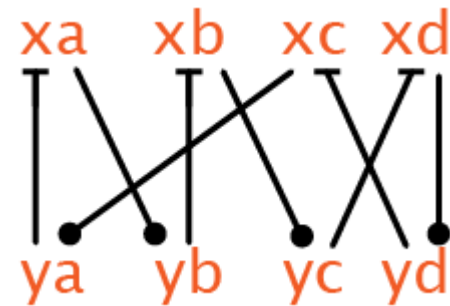
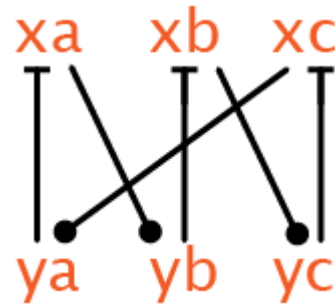
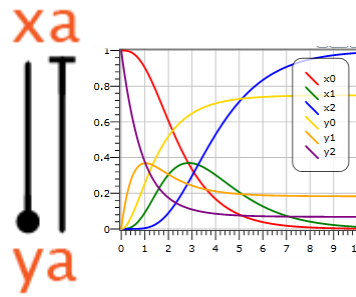
$m \in \text{MI} \rightarrow \text{AM}$  is an emulation:  
it maps  $z \rightarrow x$  and  $\sim w \rightarrow x$

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).

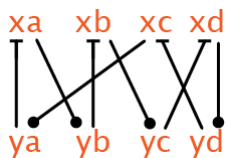
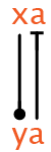
Each influence crossing the dashed lines out of  $x$  is replaced by a similar influence from the same side of *either*  $z$  or  $\sim w$ . The latter is the same as a similar influence from the opposite side of  $w$  (shown), and the same as an opposite influence from the same side of  $w$ .

# Another Zoo



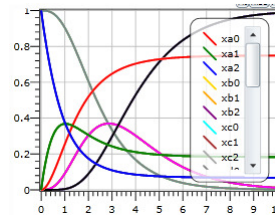
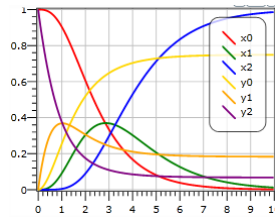
# Network Perturbations

Network

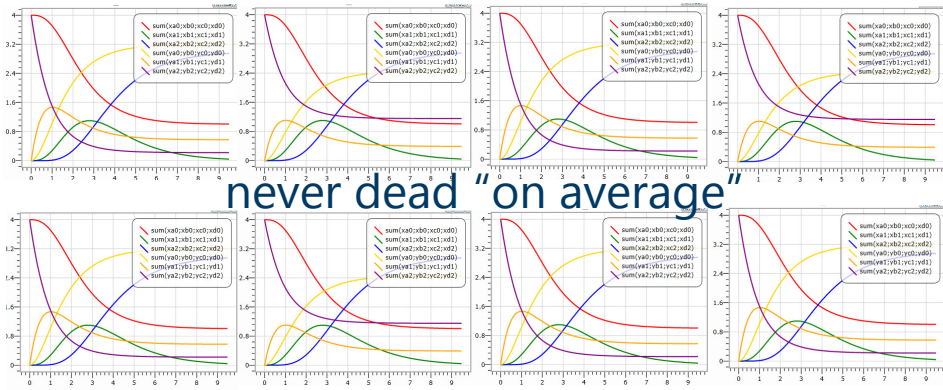
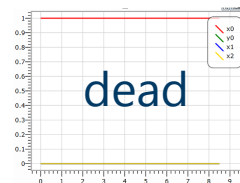
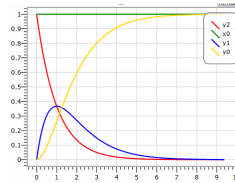


A complex but robust implementation of the simple network

Normal Behavior



Removing each link in turn



never dead "on average"

# Morphisms of CRNs

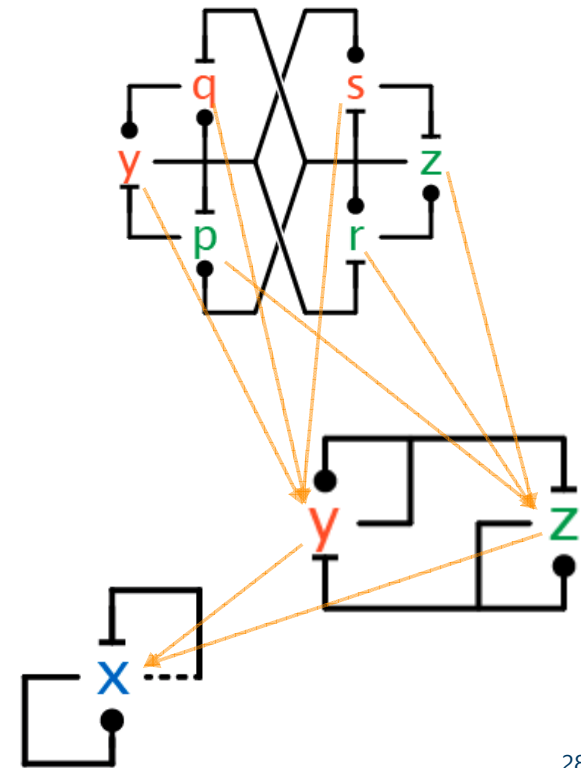
# A Theory of Network Emulation

(with thanks to David Soloveichik)

- So far, evidence is empirical
  - Specific simulations based on a choice of parameters
- But indeed...
  - We can show analytically 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 (of the target network)
- A network *emulates* another network:
  - When it can *exactly* reproduce the kinetics of another network for *any* choice of rates and initial conditions (of the other network)
  - We aim to show that e.g. the cell cycle switch can emulate AM in that sense
  - And moreover that the emulation is *algorithmic*: it is determined by static network *structure* (including rate constants and stoichiometric constants), not by random kinetic

# When can a Network Emulate Another?

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



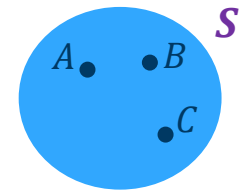


# Chemical Reaction Networks

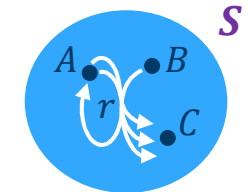
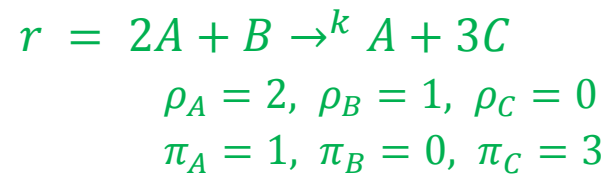
- A CRN is a pair  $(S, R)$  where
  - $S = \{s_1, \dots, s_n\}$  a finite set of *species*
  - $R = \{r_1, \dots, r_m\}$  a finite set of *reactions*<sup>(\*)</sup>

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

$$R = \{r\}$$



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



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

$$\eta(s, \rho \rightarrow^k \pi) = \pi_s - \rho_s$$

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

$$\eta(A, r) = -1 \quad \text{net stoichiometry}$$

$$\varphi(A, r) = -k \quad \text{(instantaneous) stoichiometry}$$

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

# CRN Morphisms

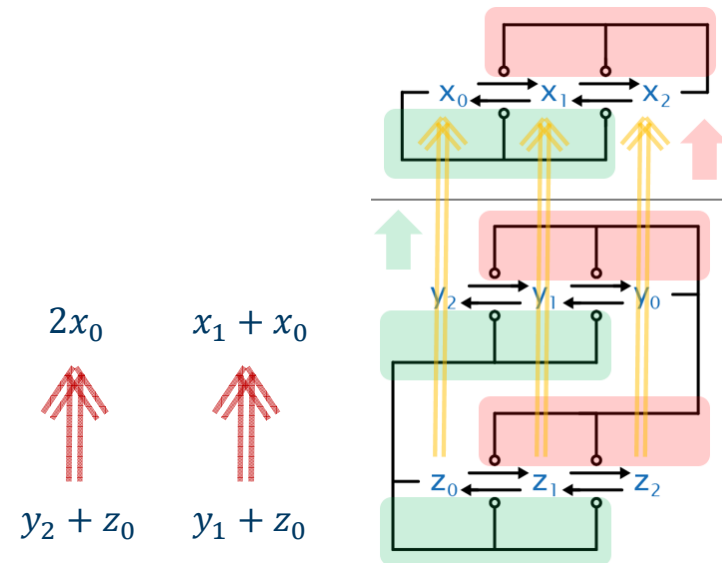
A *CRN morphism* from  $(S, R)$  to  $(\hat{S}, \hat{R})$   
 written  $m \in (S, R) \rightarrow (\hat{S}, \hat{R})$

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

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

(sometimes omitting the subscripts on  $m$ )

Mappings (symmetries)  
 between two networks



# 3 Key Morphisms

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

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

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

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

- a *CRN stoichiomorphism* if:

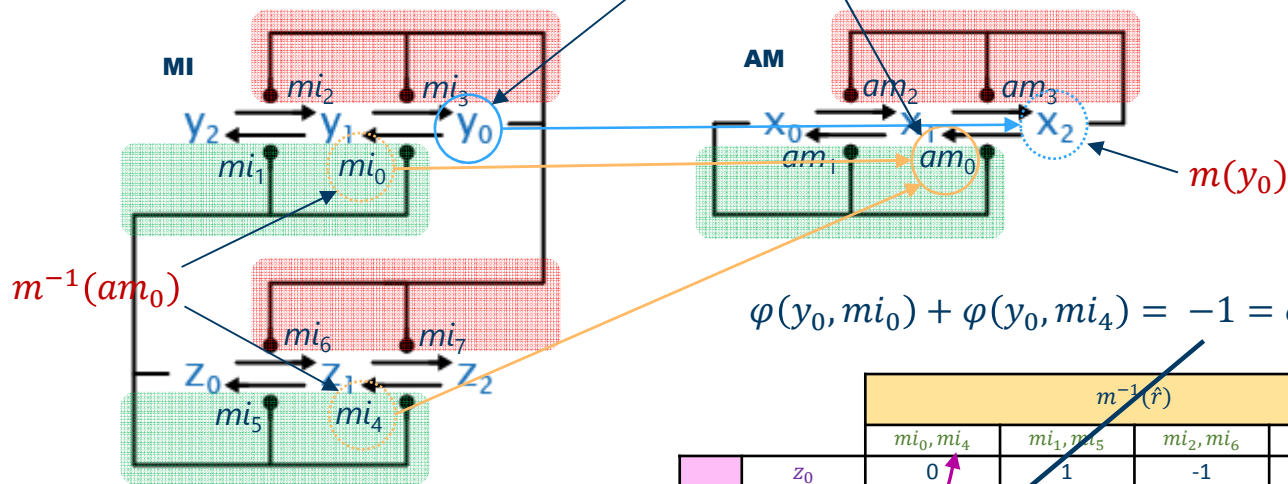
def.  $\varphi \cdot m_{\mathcal{R}} = m_{\mathcal{S}} \cdot \hat{\varphi}$

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

# Checking the Stoichiomorphism Condition

$m \in \text{MI} \rightarrow \text{AM}$

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



All unit rates (sufficient because of another theorem)

This is both a homomorphism and a stoichiomorphism

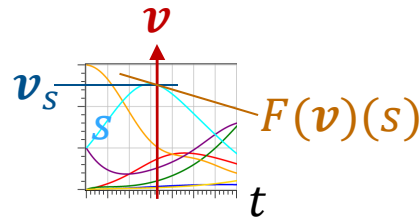
		$m^{-1}(\hat{r})$				$m(s)$
		$mi_0, mi_4$	$mi_1, mi_5$	$mi_2, mi_6$	$mi_3, mi_7$	
$\forall s \in \text{MI}$	$z_0$	0	1	-1	0	$x_0$
	$z_1$	1	-1	1	-1	$x_1$
	$z_2$	-1	0	0	1	$x_2$
	$y_0$	-1	0	0	1	$x_2$
	$y_1$	1	-1	1	-1	$x_1$
	$y_2$	0	1	-1	0	$x_0$
			$am_0$	$am_1$	$am_2$	$am_3$
		$\forall \hat{r} \in \text{AM}$				

# CRN Kinetics

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

a vector of concentrations for each species

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



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

Given by the *law of mass action*:

$$F(\mathbf{v})(s) = \sum_{r \in R} \varphi(s, r) \cdot [\mathbf{r}]_{\mathbf{v}}$$

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:

$$\frac{d\mathbf{v}_s}{dt} = F(\mathbf{v})(s)$$

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

$$[\rho \rightarrow^k \pi]_{\mathbf{v}} = \mathbf{v}^{\rho} = \prod_{s \in S} \mathbf{v}_s^{\rho_s}$$

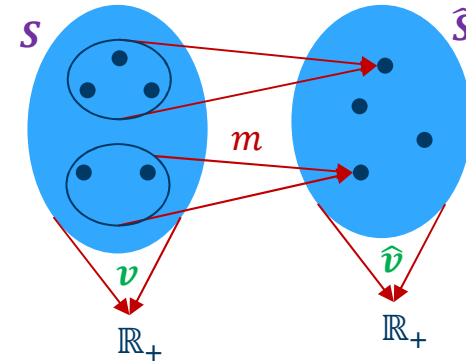
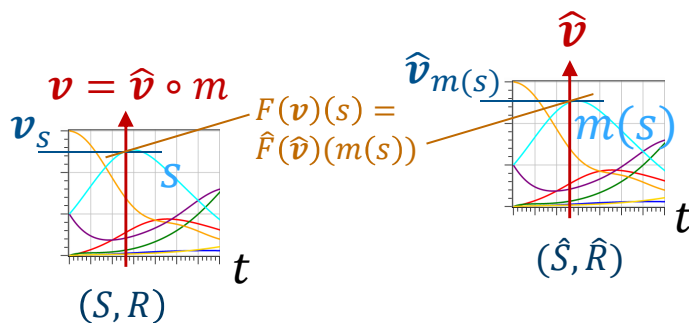
# Kinetic Emulation

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

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

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

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

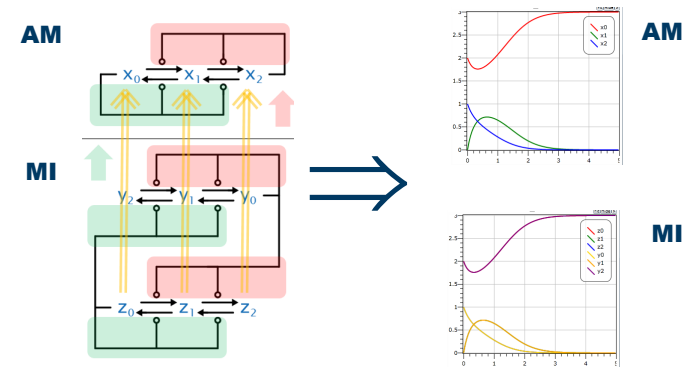
# Emulation Theorem

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

reactant morphism	$\mathbf{m}_S^T \cdot \boldsymbol{\rho} = \hat{\boldsymbol{\rho}} \cdot \mathbf{m}_R^T$	preserve enough network structure
stoichiomorphism	$\boldsymbol{\varphi} \cdot \mathbf{m}_R = \mathbf{m}_S \cdot \hat{\boldsymbol{\varphi}}$	preserve enough chemical stoichiometry
⇓		
emulation	$\forall \hat{\mathbf{v}}. F(\hat{\mathbf{v}} \circ \mathbf{m}_S) = \hat{F}(\hat{\mathbf{v}}) \circ \mathbf{m}_S$	preserve derivatives

$F$  is the differential system of  $(S, R)$ , given by the law of mass action,  $\hat{\mathbf{v}}$  is a state of  $(\hat{S}, \hat{R})$ .  $\boldsymbol{\varphi}$  is the stoichiometric matrix and  $\boldsymbol{\rho}$  is the related reactant matrix.  $\mathbf{m}_S$  and  $\mathbf{m}_R$  are the characteristic 0-1 matrices of the morphism maps  $\mathbf{m}_S$  (on species) and  $\mathbf{m}_R$  (on reactions).  $-^T$  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  $\iota \in (S, R) \rightarrow (S, R')$  such that  $\iota(S)$  is the identity and  $\iota(\rho, \pi, k) = (\rho, \pi, k')$ .

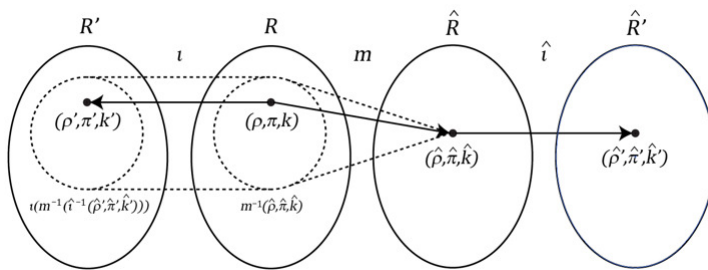
a morphism that modifies rates only

**Theorem:** If  $m \in (S, R) \rightarrow (\hat{S}, \hat{R})$  is a stoichiomorphism, then for *any* change of rates  $\hat{\iota}$  of  $(\hat{S}, \hat{R})$  there is a change of rates  $\iota$  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,  $\iota$  changes rates by the ratio with which  $\hat{\iota}$  changes rates:

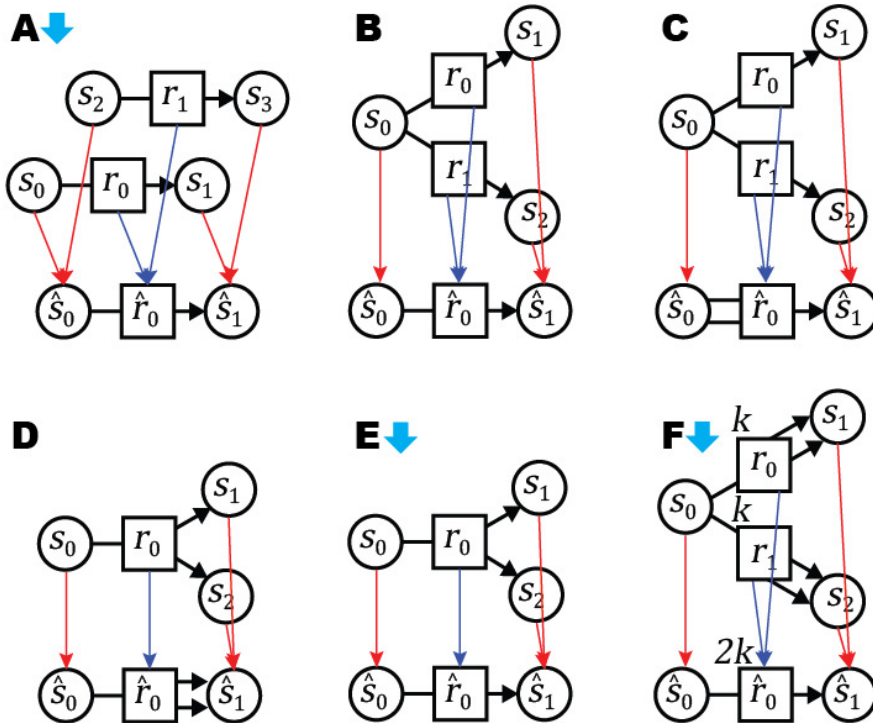
$$\iota(\rho, \pi, k) = \left(\rho, \pi, k \cdot \frac{\hat{k}'}{\hat{k}}\right) \text{ where } m(\rho, \pi, k) = (\hat{\rho}, \hat{\pi}, \hat{k}) \text{ and } \hat{\iota}(\hat{\rho}, \hat{\pi}, \hat{k}) = (\hat{\rho}', \hat{\pi}', \hat{k}').$$







# Examples of CRN morphisms



Circles are species and squares are reactions. Red arrows are species mappings  $m_S$  and blue arrows are reaction mappings  $m_R$ . Solid arrows indicate morphisms that are emulations.

**(A)** A simple stoichiomorphism: the species in the source reactions are distinct. In general, multiple separate copies of a system will map to it via a trivial map that is a homomorphism and stoichiomorphism.

**(B)** This is a homomorphism, but is not a stoichiomorphism. For  $s_0, \hat{r}_0$ :  $\sum_{r \in m_R^{-1}(\hat{r}_0)} \varphi(s_0, r) = -2 \neq -1 = \varphi(m_S(s_0), \hat{r}_0)$ .

**(C)** This is a stoichiomorphism, but is not a homomorphism or a reactant morphism.  $r_0 = \rho \rightarrow \pi$  with  $\rho_{s_0} = 1$  but  $m_R(r_0) = \hat{r}_0 = \hat{\rho} \rightarrow \hat{\pi}$  with  $\hat{\rho}_{m_S(s_0)} = \hat{\rho}_{\hat{s}_0} = 2$ , so  $\hat{\rho} \neq m_S(\rho)$  and  $m_R(r_0) \neq m_S(\rho) \rightarrow \hat{\pi}$ .

**(D)** This is a homomorphism but not a stoichiomorphism. For  $s_1, \hat{r}_0$ :  $\sum_{r \in m_R^{-1}(\hat{r}_0)} \varphi(s_1, r) = 1 \neq 2 = \varphi(m_S(s_1), \hat{r}_0)$ .

**(E)** This stoichiomorphism is not a homomorphism, but is a reactant morphism.  $r_0 = \rho \rightarrow \pi$  and  $m_R(r_0) = \hat{r}_0 = \hat{\rho} \rightarrow \hat{\pi}$  with  $\hat{\rho} = m_S(\rho)$  and  $m_R(r_0) = m_S(\rho) \rightarrow \hat{\pi}$ .

**(F)** This reactant morphism is not a homomorphism but is a stoichiomorphism. E.g., for  $s_1, \hat{r}_0$ :  $\sum_{r \in m_R^{-1}(\hat{r}_0)} \varphi(s_1, r) = \varphi(s_1, r_0) + \varphi(s_1, r_1) = 2 \cdot k + 0 \cdot k = 1 \cdot 2k = \varphi(m_S(s_1), \hat{r}_0)$ .

# Conclusions

# 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?

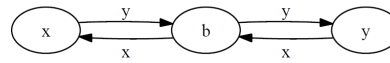
# Population Majority

2004: **Computation in networks of passively mobile finite-state sensors.** Dana Angluin, James Aspnes, Zoë Diarmadi, Michael J. Fischer, René Peralta. PODC'04.

**Majority.**  
The value of the majority function is 1 if there are more 1's than 0's in the input; otherwise, it is 0.  
The states of our protocol consist of a live bit and a counter with values in the set  $\{-1, 0, 1\}$ . Initially, the live

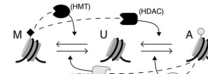
**Exact Majority** - 6-state  
**Nondeterministic.**  
(population protocol)

2007: **A Simple Population Protocol for Fast Robust Approximate Majority.** Dana Angluin, James Aspnes, David Eisenstat. DISC'07.



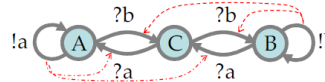
**Approximate Majority** - 3-state  
**Stochastic,** discrete time  
(DTMC) Fundamental results.

2007: **Theoretical Analysis of Epigenetic Cell Memory by Nucleosome Modification.** Ian B. Dodd, Mille A. Micheelsen, Kim Sneppen, Genevieve Thon. Cell.



Approximate Majority - 3-state  
Stochastic, discrete time  
(ad-hoc)

2009. **Artificial Biochemistry.** Luca Cardelli. Algorithmic Bioprocesses, Springer.



Approximate Majority - 3-state  
Stochastic, **continuous time**  
(CTMC). Simulations.

2009: **Robust Stochastic Chemical Reaction Networks and Bounded Tau Leaping (Appendix 4).** David Soloveichik. J.Comput.Biol.

Transfer complexity results from discrete time population protocols to continuous time **stochastic chemical reaction networks.**

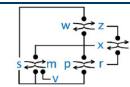
2009. **Using Three States for Binary Consensus on Complete Graphs.** Etienne Perron, Dinkar Vasudevan, and Milan Vojnovic. IEEE Infocom.

Approximate Majority - 3-state  
Stochastic, **continuous time**  
(CTMC) Fundamental results.

2010: **Convergence Speed of Binary Interval Consensus.** Moez Draief, Milan Vojnovic. Infocom'10.

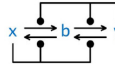
**Exact Majority** - 4-state  
Stochastic, **continuous time.**  
(similar to 2004 paper)

2012: **The Cell Cycle Switch Computes Approximate Majority.** Luca Cardelli, Attila Csikász-Nagy. Scientific Reports.



The biological cell cycle switch is a (non-obvious) implementation of approximate majority. Simulations.

2014: **Morphisms of Reaction Networks that Couple Structure to Function.** Luca Cardelli.



Approximate Majority - 3-state  
**Continuous space,** continuous time  
(Deterministic ODE). Emulation theorem.