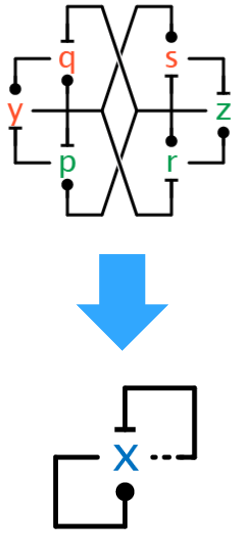
Microsoft Research

UNIVERSITY OF OXFORD

Morphisms of Reaction Networks

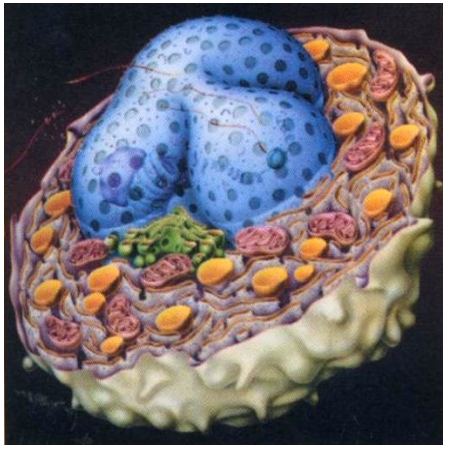


Luca Cardelli, Microsoft Research & Oxford University

IMT Lucca, 2014-07-08

Motivation

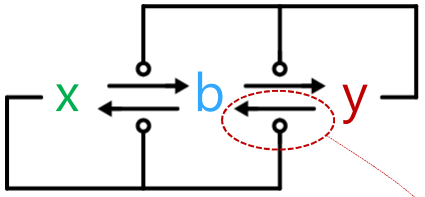
- Give substance to the claim that "cells compute"
  - Yes, but *what* do they compute?
- Catch nature red-handed in the act of running a computational task
  - Something that a computer scientist would recognize as an *algorithm*



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

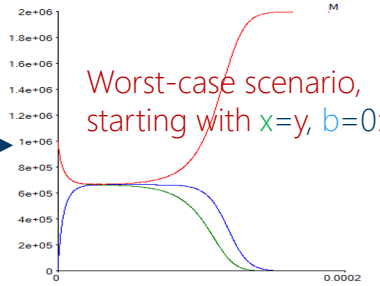
$x + y \rightarrow^{r} y + b$

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

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

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

x=y



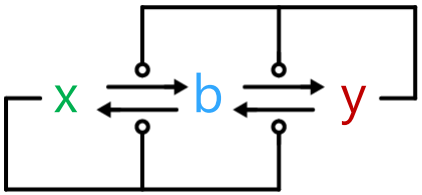
Worst-case scenario, starting with x=y, b=0:

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

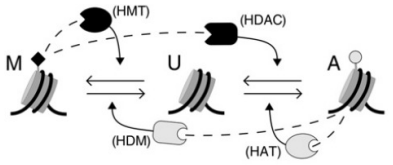
Robust to perturbation
  above a threshold, initial majority wins *whp*

Dana Angluin · James Aspnes · David Eisenstat

A Simple Population Protocol for Fast Robust Approximate Majority

2007

Epigenetic Switch



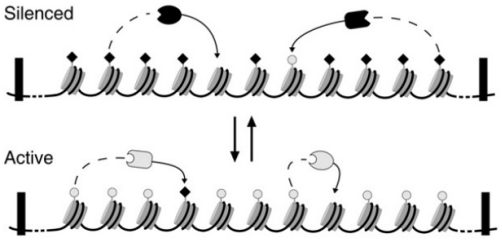
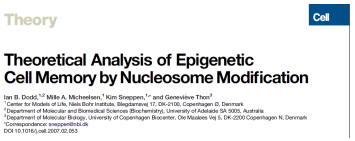


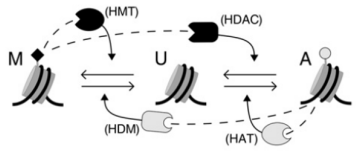
Figure 1. Basic Ingredients of the Model



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

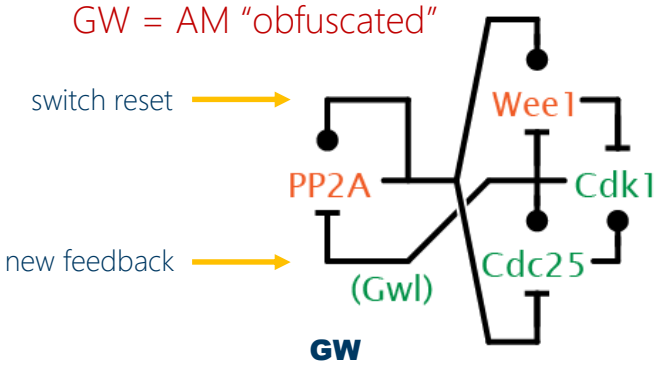


- In most cases the biological implementation seems more *indirect* or *obfuscated*
  - *"Nature is subtle but not malicious - Einstein"* Ha! think again!
  - Other implementations of Approximate Majority seem convoluted and… approximate
  - Like finding an algorithm in a haystack…

Obfuscated Implementations

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

GW = AM "obfuscated"



SCIENTIFIC REPORTS

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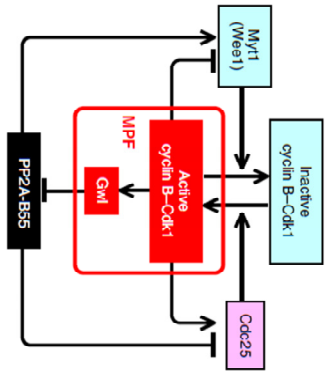
SUBJECT AREAS: COMPUTATIONAL BIOLOGY

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

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

DOI:10.1038/ncomms2062

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

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

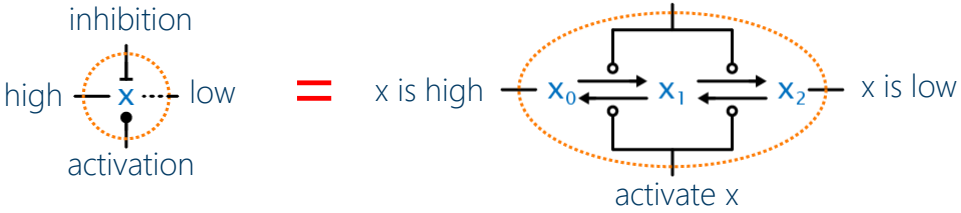
Sep 2012

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

activation
inhibition
catalysis

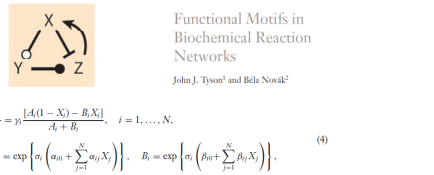


Usually modeled by sigmoid (e.g. Hill or Reinitz) functions

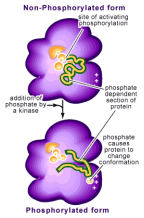
triplet motif

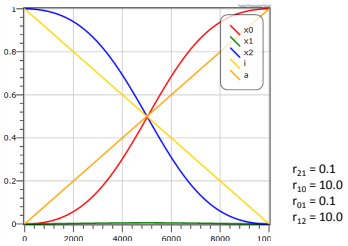
We model them by 4 mass action reactions over 3 species x_0, x_1, x_2

They actually implement a Hill function of coefficient 2:

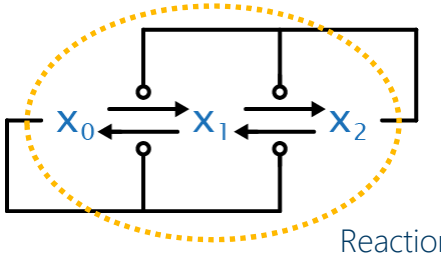


biological mechanism: (e.g.:) multisite phosphorylation



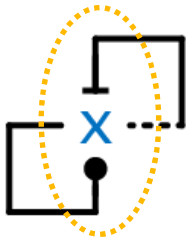


Approximate Majority



Reaction Network

=

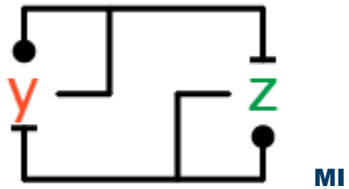


Influence Network

Biological Influence Networks

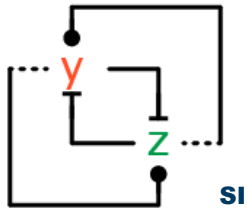
activation
inhibition

Mutual Inhibition & Self Activation



MI

Mutual Inhibition & Mutual Anti-activation

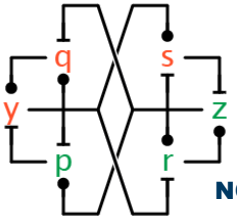


SI

Cell Cycle Switching

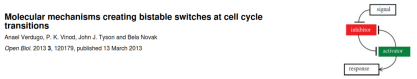
CC

Better Switching



NCC

Cell cycle transitions

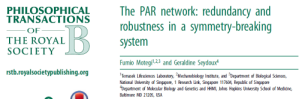


Molecular mechanisms creating bistable switches at cell cycle transitions

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

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

Polarity establishment

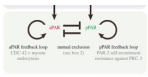


PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B

rstb.royalsocietypublishing.org

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

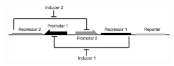
Fumio Motegi[1,2] and Geraldine Seydoux[3]



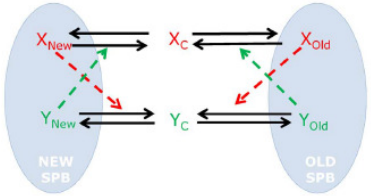
Gene networks

Construction of a genetic toggle switch in *Escherichia coli*

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



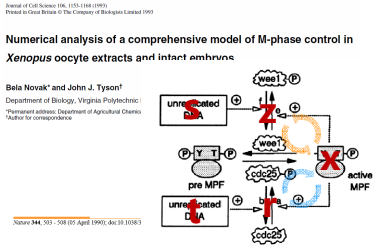
Septation Initiation



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,†]

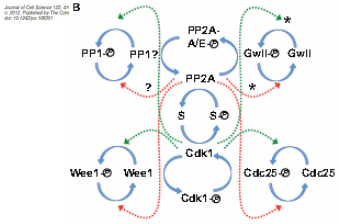
[1]Institut de Génétique Moléculaire de Montpellier, IGMM, CNRS UMR 5535, Université Montpellier I and II, 34293 Montpellier, France

[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

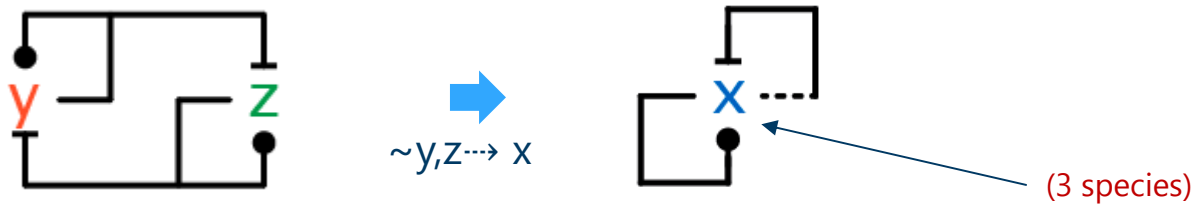
*Author for correspondence (daniel.fisher@igmm.cnrs.fr)

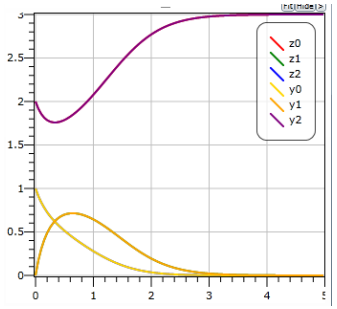
†These authors contributed equally to this work



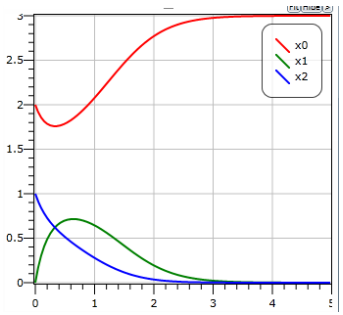
Network Emulation: MI emulates AM

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

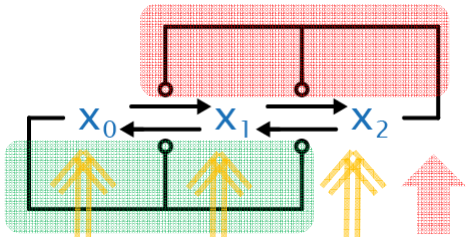
($y_2 = x_0$
$y_1 = x_1$
$y_0 = x_0$)

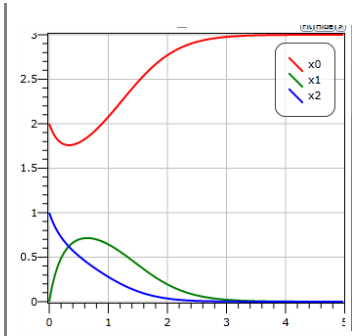
- How do we find these matching parameters? By a network morphism!

MI to AM Emulation: Network Morphism

A mapping of species and reactions

AM



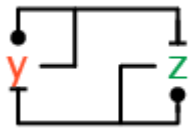


any initial conditions

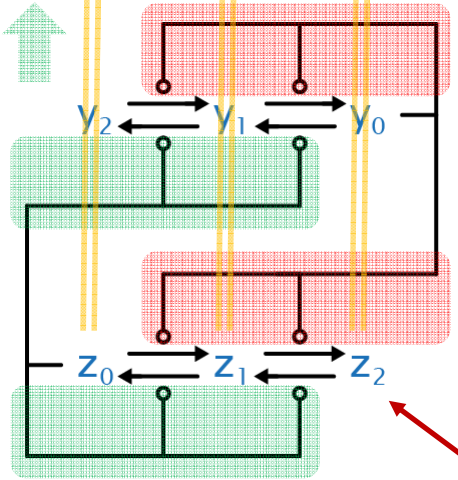
homomorphic mapping

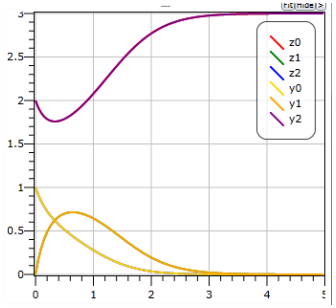
z -> x

~y -> x



MI





initial conditions:

$z_0 = y_2 = x_0$

$z_1 = y_1 = x_1$

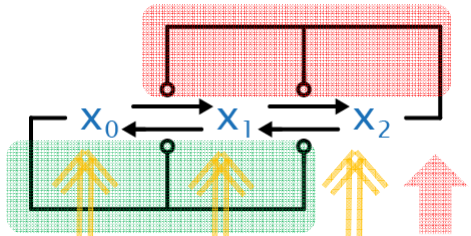
$z_2 = y_0 = x_2$

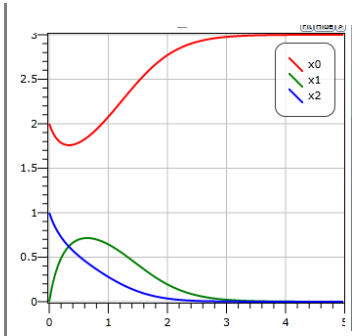
less trivial than you might think:
it need not preserve the out-degree of a node!

SI to AM Emulation: Network Morphism

A mapping of species and reactions

AM

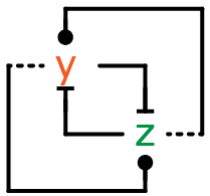




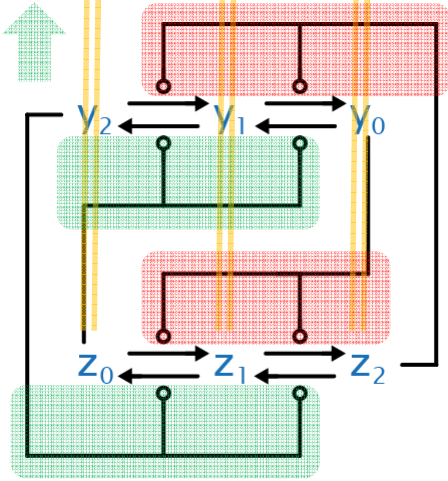
any initial conditions

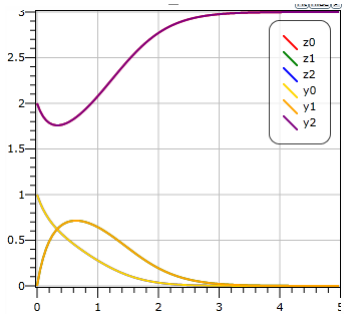
homomorphic mapping

z -> x
~y -> x



SI



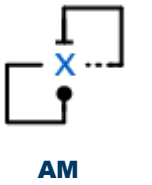


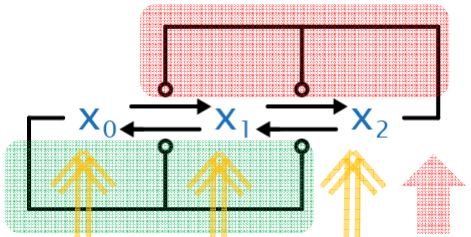
initial conditions:

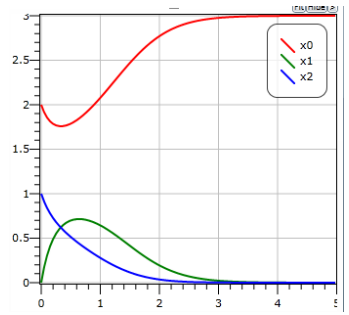
$z_0 = y_2 = x_0$
$z_1 = y_1 = x_1$
$z_2 = y_0 = x_2$

AMr to AM Emulation: Network Morphism

A mapping of species and reactions



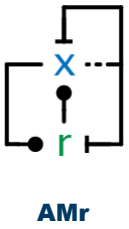


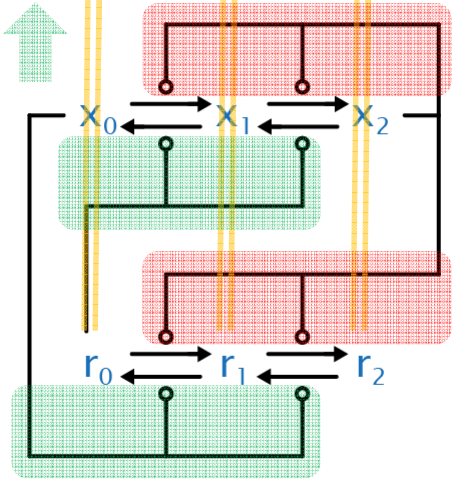


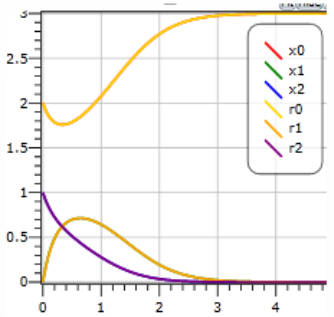
any initial conditions

homomorphic mapping

x -> x
r -> x







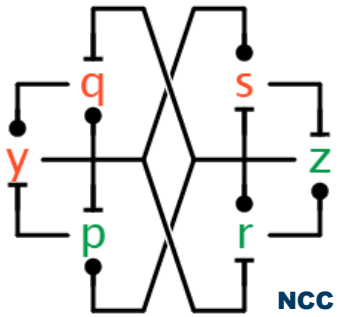
initial conditions:

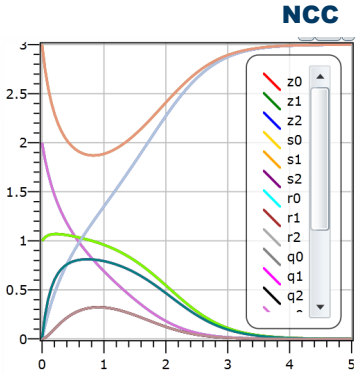
$r_0 = x_0 = x_0^{AM}$
$r_1 = x_1 = x_1^{AM}$
$r_2 = x_2 = x_2^{AM}$

(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

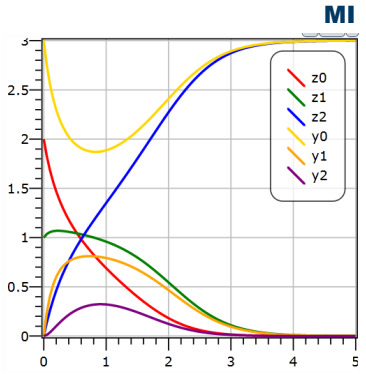
- For *any* rates and initial conditions of MI we can find *some* rates and initial conditions of NCC such that the (18) trajectories of NCC retrace those (6) of MI





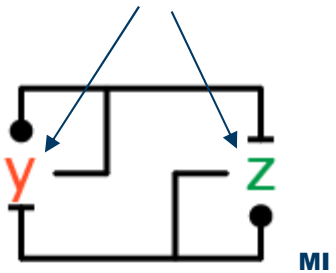
(18 species on 6 trajectories)

z,r,p ⇢ z
y,q,s ⇢ y



(6 species on 6 trajectories)

(3 species each)

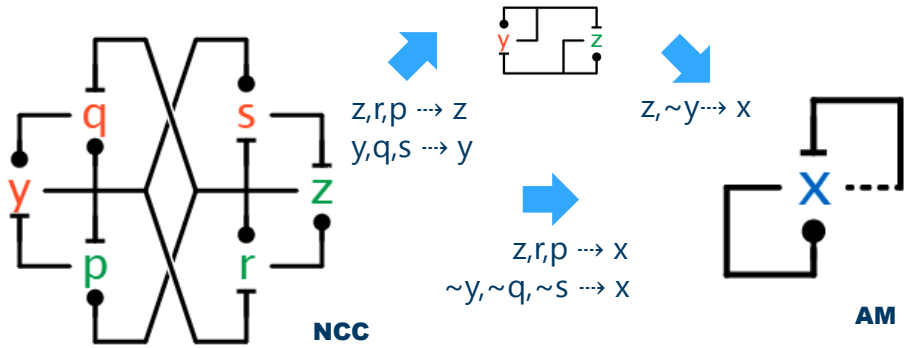


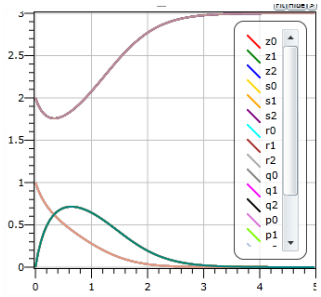
initialize
z,r,p = z
y,q,s = y

- Why does this work so well?

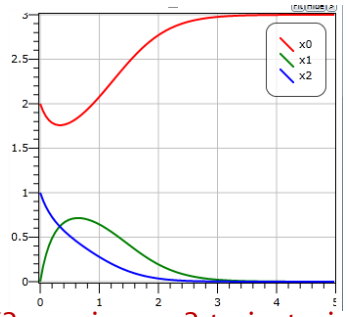
Emulations Compose: NCC emulates AM

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



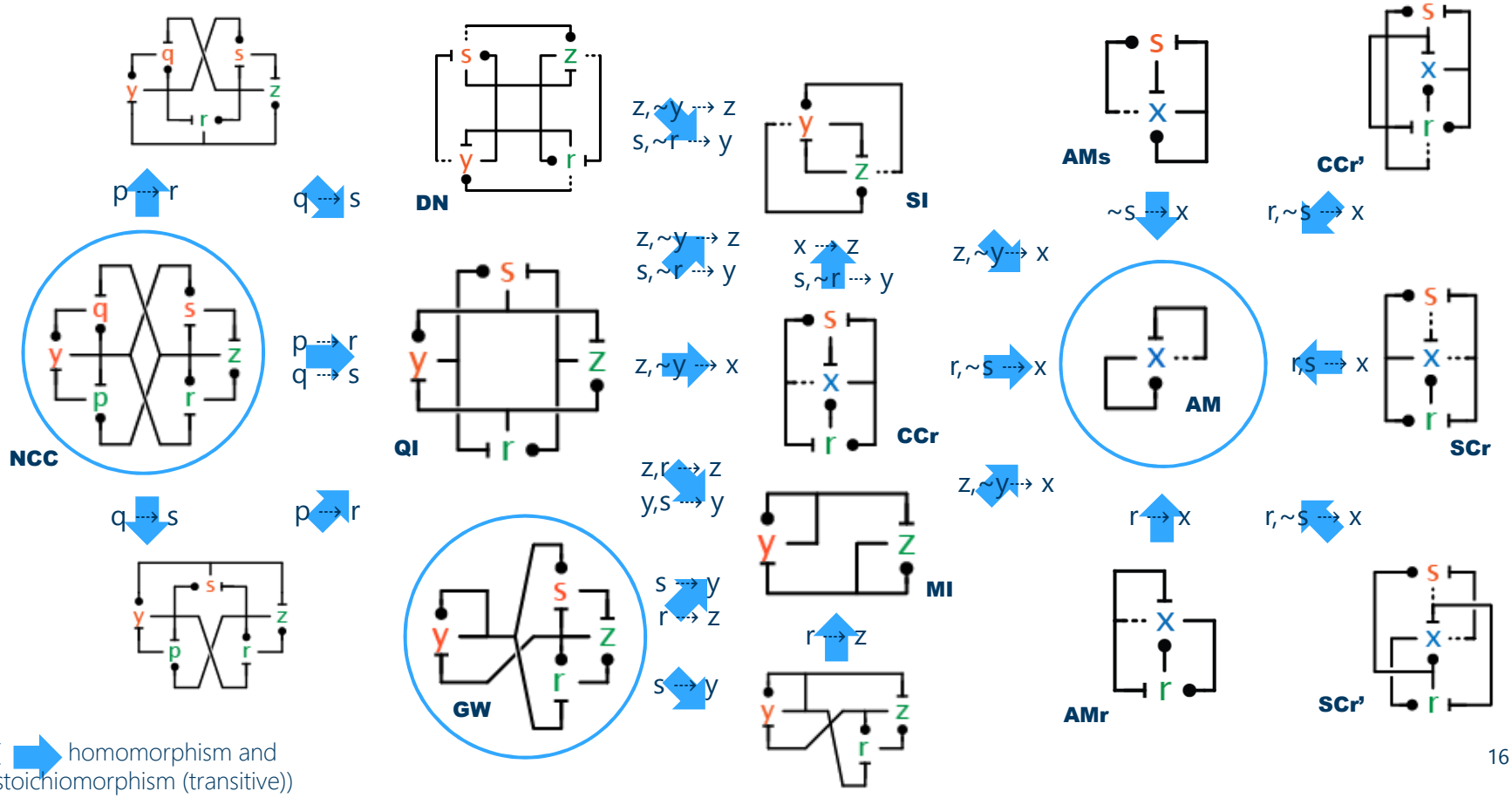


(18 species on 3 trajectories)



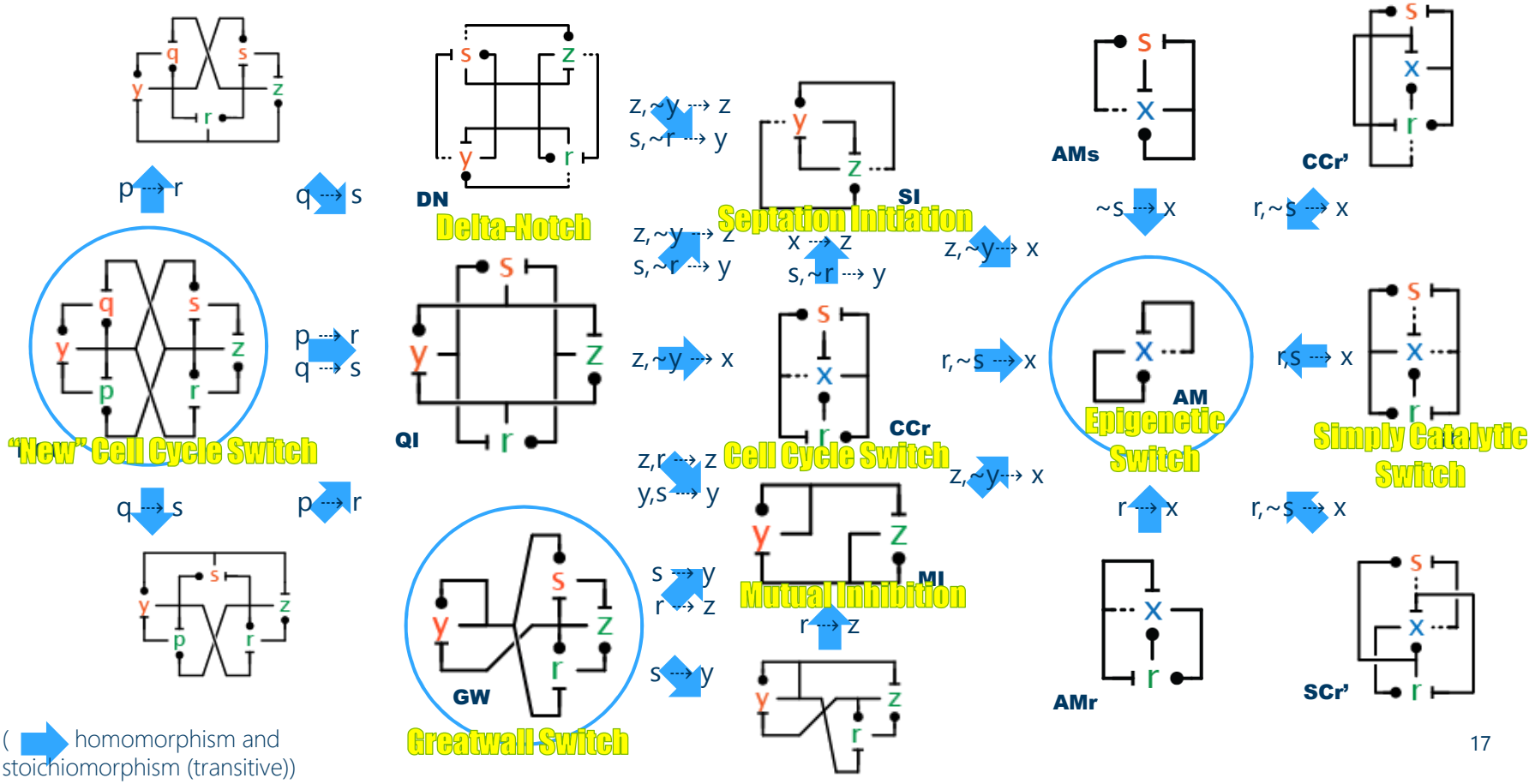
(3 species on 3 trajectories)

Approximate Majority Emulation Zoo



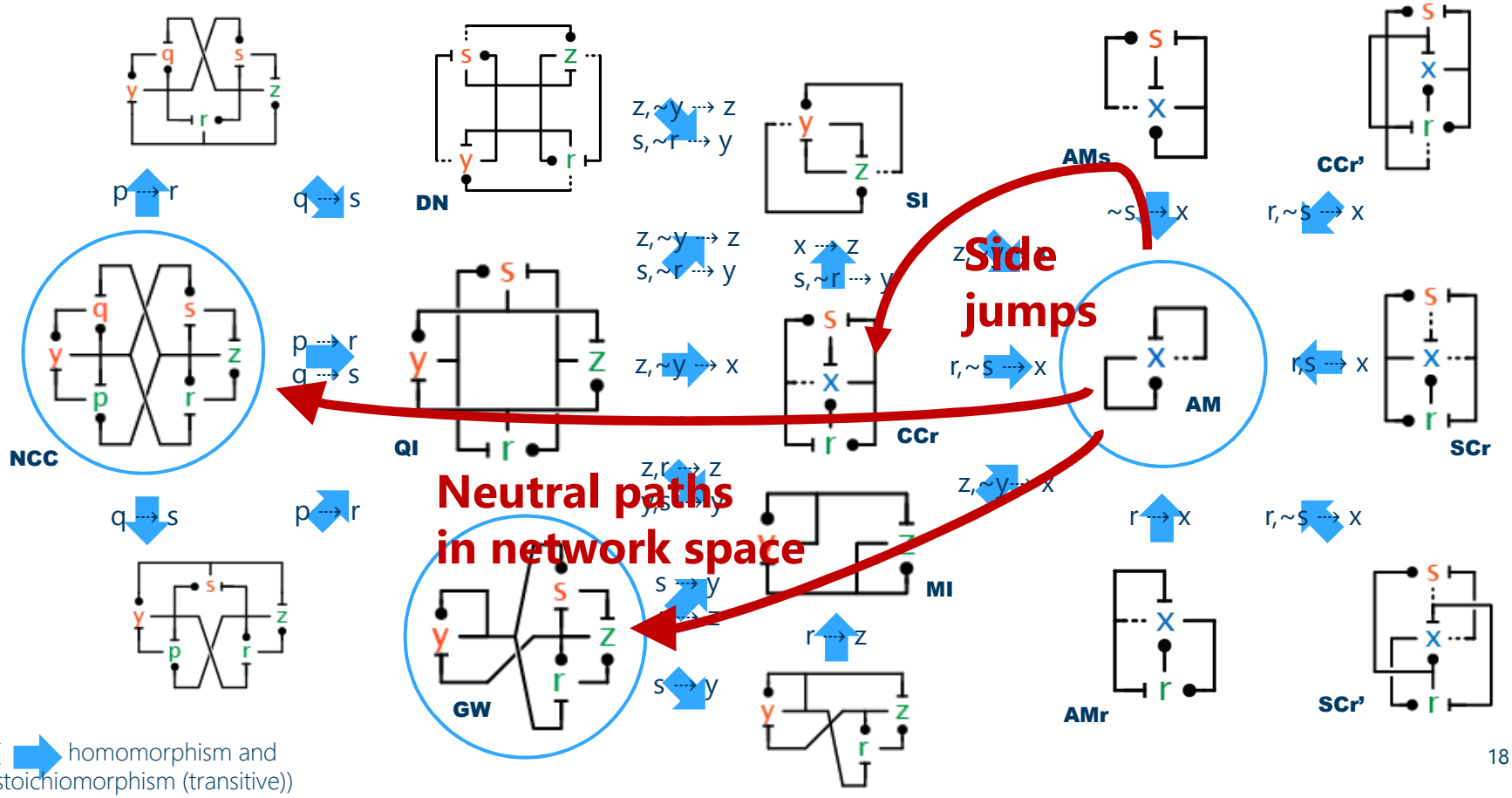
(homomorphism and stoichiomorphism (transitive))

Approximate Majority Emulation Zoo



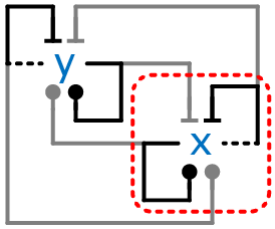
(homomorphism and stoichiomorphism (transitive))

Approximate Majority Emulation Zoo

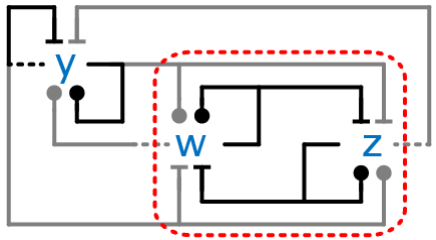


(homomorphism and stoichiomorphism (transitive))

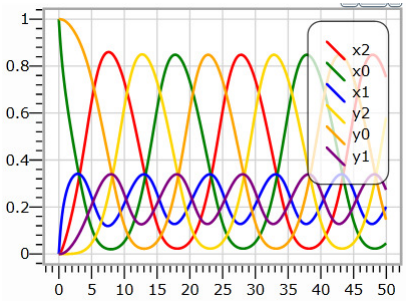
Emulation in Context

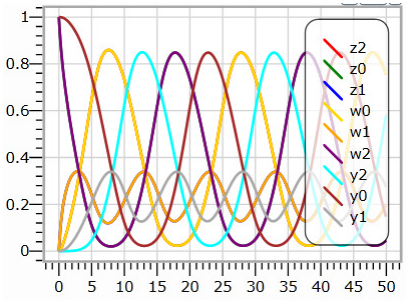


AM-AM Oscillator



AM-MI Oscillator





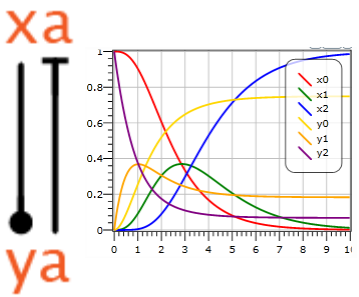
$m \in \mathbf{MI} \to \mathbf{AM}$ is an emulation:
it maps $z \to x$ and $\sim w \to x$

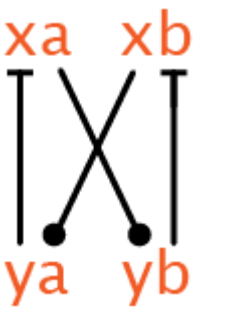
We can replace AM with MI in a context. The mapping m tells us how to wire MI to obtain an overall emulation:

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).

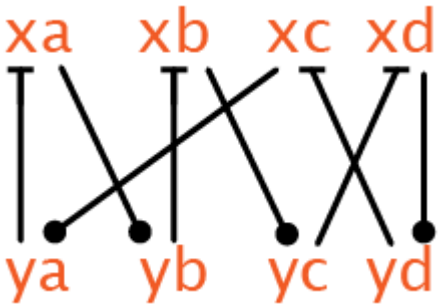
Each influence crossing the dashed lines out of x is replaced by a similar influence from the same side of *either* z *or* $\sim w$. The latter is the same as a similar influence from the opposite side of w (shown), and the same as an opposite influence from the same side of w.

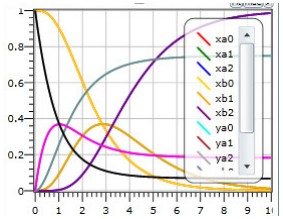
Another Zoo

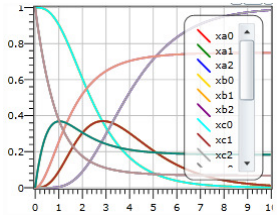

xa
ya
x0
x1
x2
y0
y1
y2

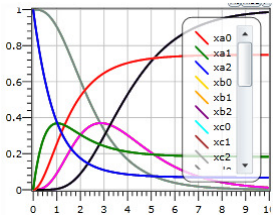

xa xb
ya yb


xa xb xc
ya yb yc


xa xb xc xd
ya yb yc yd

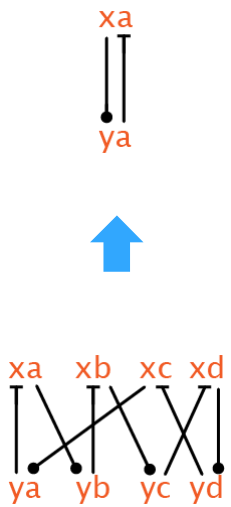

xa0
xa1
xa2
xb0
xb1
xb2
ya0
ya1
ya2


xa0
xa1
xa2
xb0
xb1
xb2
xc0
xc1
xc2


xa0
xa1
xa2
xb0
xb1
xb2
xc0
xc1
xc2

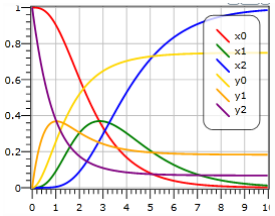
Network Perturbations

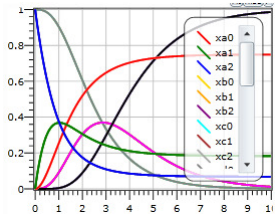
Network



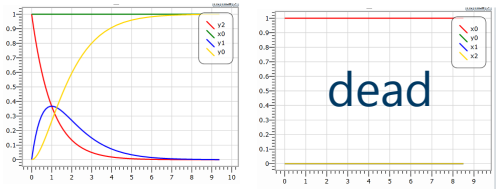
A complex but robust implementation of the simple network

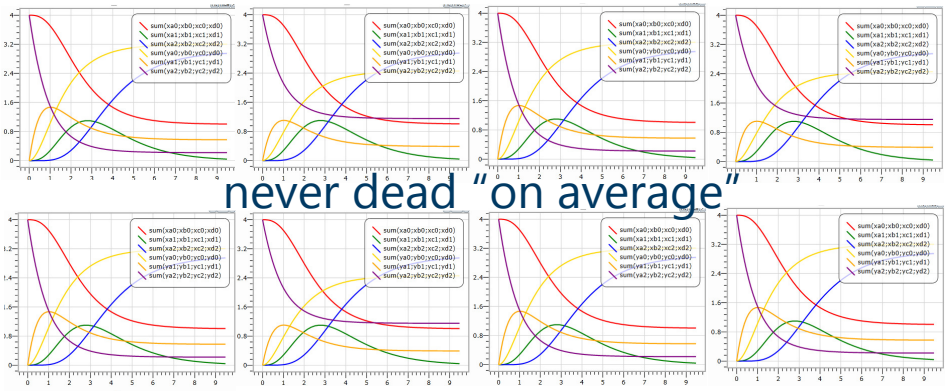
Normal Behavior





Removing each link in turn





Microsoft Research

UNIVERSITY OF OXFORD

Morphisms of CRNs

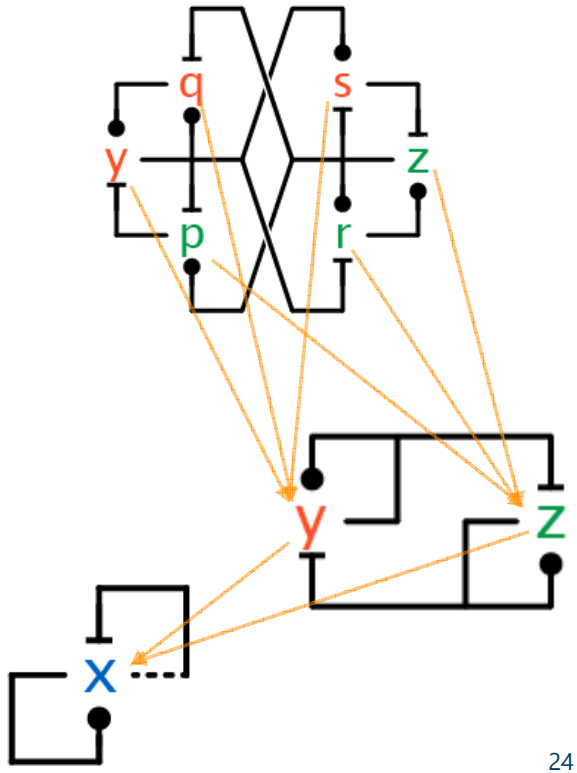
A Theory of Network Emulation

(with thanks to David Soloveichik)

- So far, evidence is empirical
  - Specific simulations based on a choice of parameters
- But indeed…
  - We can show 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?

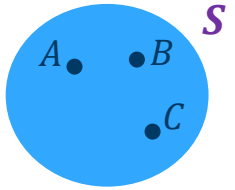
- What kind of morphisms guarantee emulation?
  - do they preserve network structure?
  - do they preserve stoichiometry?



Chemical Reaction Networks

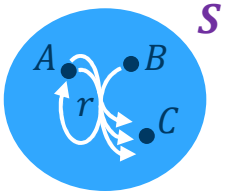
- A CRN is a pair (S, R) where
  - $S = \{s_1, \dots, s_n\}$ a finite set of *species*
  - $R = \{r_1, \dots, r_m\}$ a finite set of *reactions*(*)

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



- Reactions $r = \rho \to^k \pi \in R$
  with *complexes* $\rho, \pi \in \mathbb{N}^S$
  stoichiometric numbers ρ_s, π_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*

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

CRN Morphisms

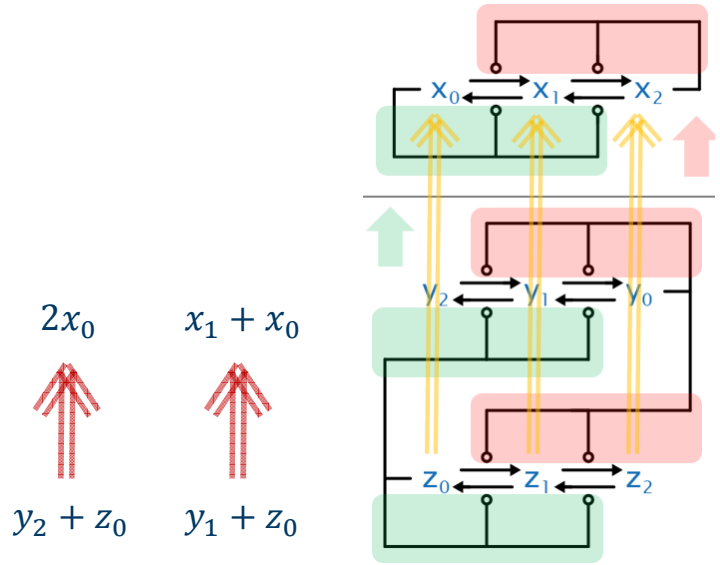
A *CRN morphism* from (S, R) to $(\hat{S}, \hat{R})$
written $m \in (S, R) \to (\hat{S}, \hat{R})$

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:

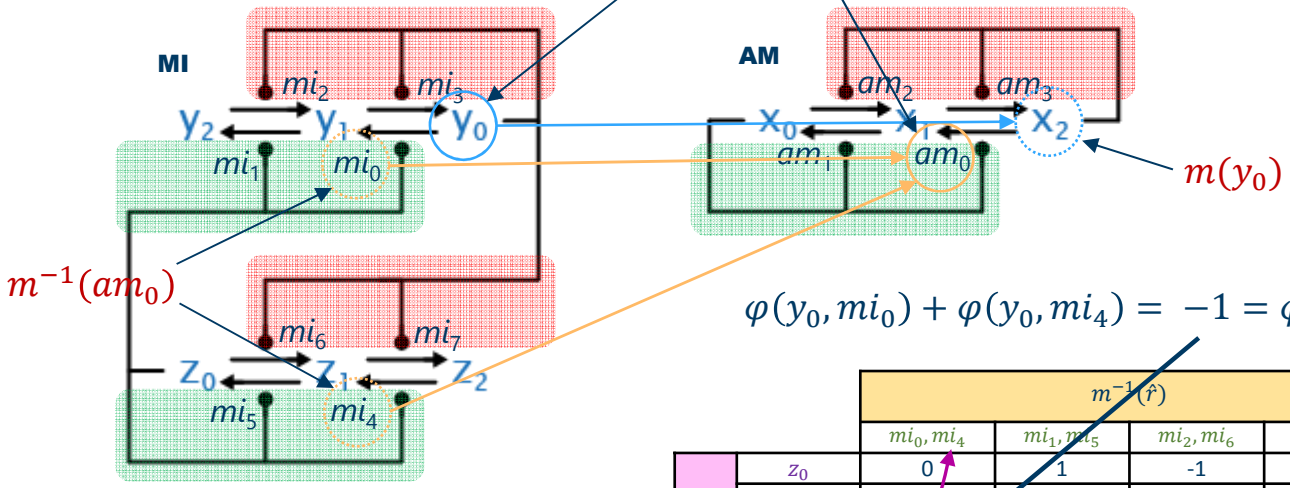
def. $\quad \boldsymbol{\varphi \cdot m_{\mathcal{R}} = m_{\mathcal{S}} \cdot \hat{\varphi}}$

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

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

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

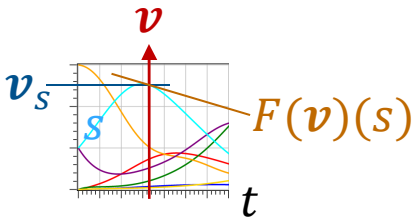
		$m^{-1}(\hat{r})$				
		mi_0, mi_4	mi_1, mi_5	mi_2, mi_6	mi_3, mi_7	
$\forall s \in \mathrm{MI}$	z_0	0	1	-1	0	x_0
	z_1	1	-1	1	-1	x_1
	z_2	-1	0	0	1	x_2
	y_0	-1	0	0	1	x_2
	y_1	1	-1	1	-1	x_1
	y_2	0	1	-1	0	x_0
		am_0	am_1	am_2	am_3	
		$\forall \hat{r} \in \mathrm{AM}$				$m(s)$

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:

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

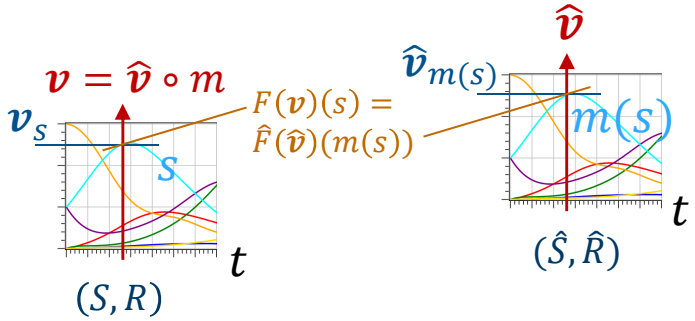
Kinetic Emulation

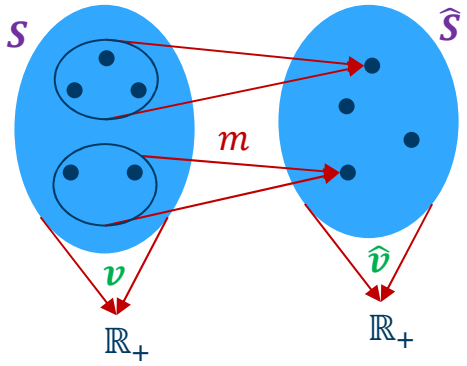
A morphism $m \in (S,R) \to (\hat{S},\hat{R})$ is a *CRN emulation* if for the respective differential systems $F, \hat{F}$, $\forall \hat{\boldsymbol{v}} \in \mathbb{R}_+^{\hat{S}}$:

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

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

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





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

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

Emulation Theorem

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

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

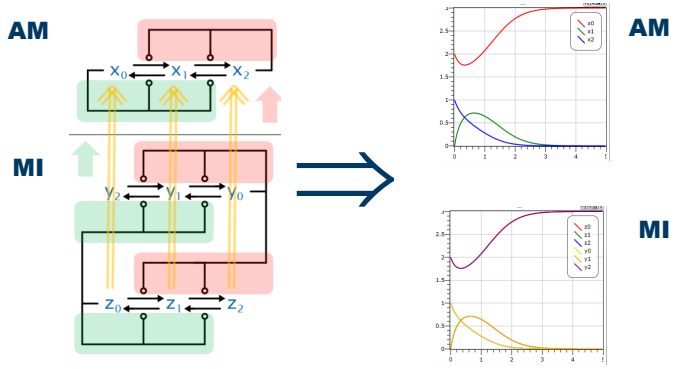
stoichiomorphism $\boldsymbol{\varphi} \cdot \boldsymbol{m_R} = \boldsymbol{m_S} \cdot \hat{\boldsymbol{\varphi}}$ preserve enough chemical stoichiometry

$\Downarrow$

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

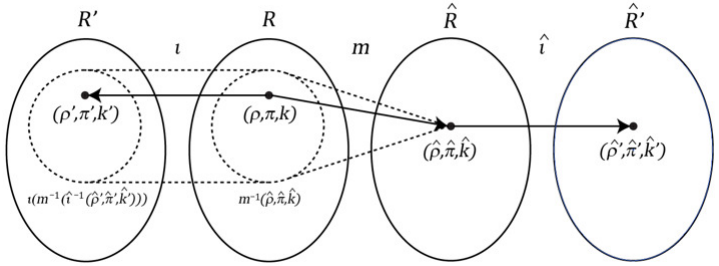
A *change of rates* for (S, R) is morphism $\iota \in (S, R) \to (S, R')$ such that $\iota(S)$ is the identity and $\iota(\rho, \pi, k) = (\rho, \pi, k')$.

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

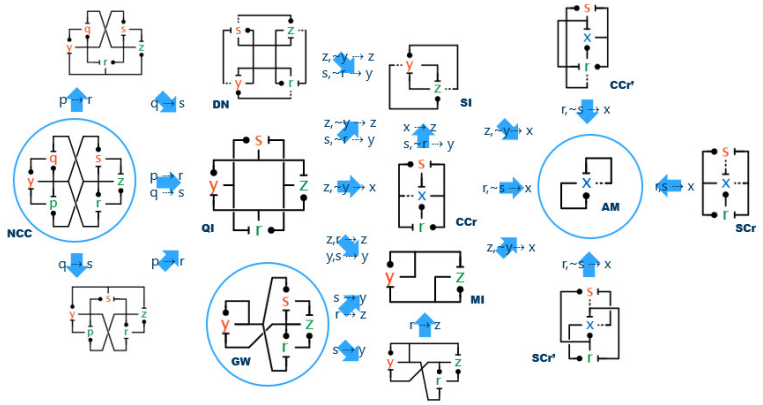
thus, for *any rates* of $(\hat{S}, \hat{R})$ we can match trajectories

In fact, ι 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 $\hat{\imath}(\hat{\rho}, \hat{\pi}, \hat{k}) = (\hat{\rho}, \hat{\pi}, \hat{k}')$.

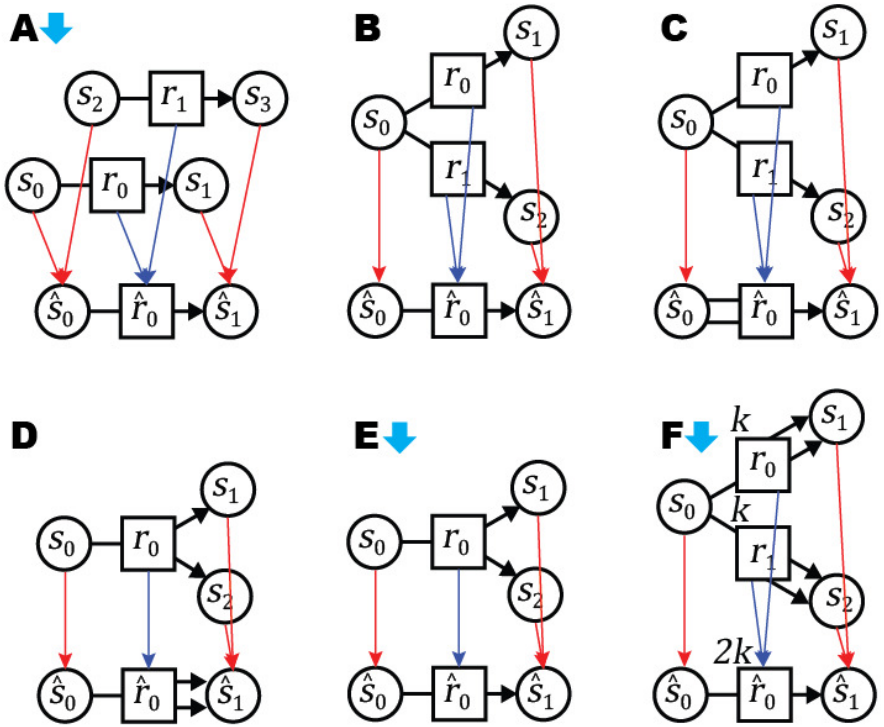


Corollaries

- 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)



Examples of CRN morphisms



Circles are species and squares are reactions. Red arrows are species mappings $m_{\mathcal{S}}$ and blue arrows are reaction mappings $m_{\mathcal{R}}$. 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* $s_0, \hat{r}_0$: $\Sigma_{r \in m_{\mathcal{R}}(\hat{r}_0)}\ \varphi(s_0, r) = -2 \neq -1 = \varphi(m_{\mathcal{S}}(s_0), \hat{r}_0)$.

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

(D) *This is a homomorphism but not a stoichiomorphism. For* $s_1, \hat{r}_0$: $\Sigma_{r \in m_{\mathcal{R}}^{-1}(\hat{r}_0)}\ \varphi(s_1, r) = 1 \neq 2 = \varphi(m_{\mathcal{S}}(s_0), \hat{r}_0)$.

(E) *This stoichiomorphism is not a homomorphisms, but is a reactant morphism.* $r_0 = \rho \to \pi$ *and* $m_{\mathcal{R}}(r_0) = \hat{r}_0 = \hat{\rho} \to \hat{\pi}$ *with* $\hat{\rho} = m_{\mathcal{S}}(\rho)$ *and* $m_{\mathcal{R}}(r_0) = m_{\mathcal{S}}(\rho) \to \hat{\pi}$.

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

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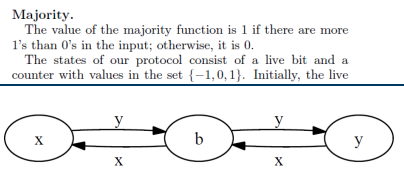
Conclusions

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 Diamadi, Michael J. Fischer, René Peralta. PODC'04.

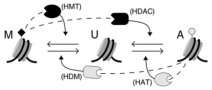

Majority.
The value of the majority function is 1 if there are more 1's than 0's in the input; otherwise, it is 0.
The states of our protocol consist of a live bit and a counter with values in the set $\{-1, 0, 1\}$. Initially, the live

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.

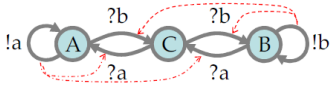
Approximate Majority - 3-state
Stochastic, discrete time
(DTMC) Fundamental results.

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 Soloveichick. J.Comput.Biol.

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

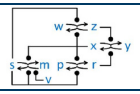
2009. **Using Three States for Binary Consensus on Complete Graphs.** Etienne Perron, Dinkar Vasudevan, and Milan Vojnovic. IEEE Infocom.

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

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

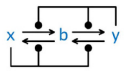
Exact Majority - 4-state
Stochastic, **continuous time**.
(similar to 2004 paper)

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.