Microsoft Research

UNIVERSITY OF OXFORD

The Cell Cycle Switch Computes Approximate Majority

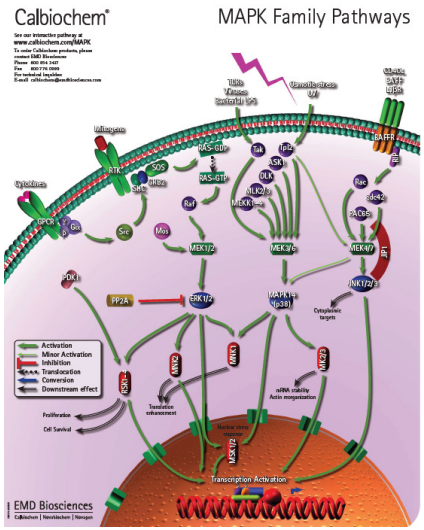
Luca Cardelli, Microsoft Research & Oxford University

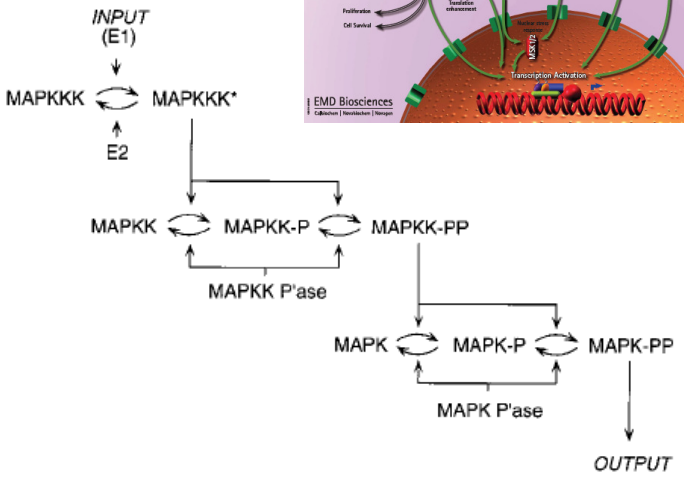
Joint work with Attila Csikász-Nagy, Fondazione Edmund Mach & King's College London

Oxford, 2014-02-14

Cells Compute

- No survival without computation!
  - Finding food
  - Avoiding predators
- How do they compute?
  - *Clearly* doing "information processing"
  - But can we actually catch nature running an (optimal) *algorithm*?





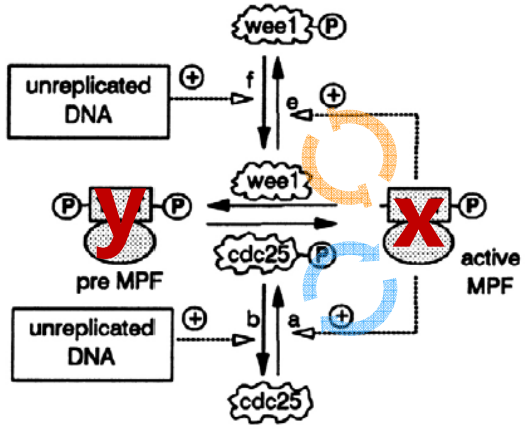
Ultrasensitivity in the mitogen-activated protein cascade, Chi-Ying F. Huang and James E. Ferrell, Jr., 1996, *Proc. Natl. Acad. Sci. USA*, 93, 10078-10083.

Outline

- Analyzing biomolecular networks
  - Try do understand the *function* of a network
  - But also try to understand its *structure*, and what determines it
- The Cell-Cycle Switches
  - Some of the best studied molecular networks
  - Important because of their fundamental function (cell division) and the stability of the network across evolution
- We ask:
  - What does the cell cycles switch compute?
  - How does it compute it?

The Cell Cycle Switch

- This network is universal in all Eukaryotes [P. Nurse]
  - I.e., the *network* at the core of cell division is *the same* from yeast to us
  - *Not the components* of the network, *nor the rates*



Journal of Cell Science 106, 1153-1168 (1993)
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Numerical analysis of a comprehensive model of M-phase control in *Xenopus* oocyte extracts and intact embryos

Bela Novak* and John J. Tyson†

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Double positive feedback on x
Double negative feedback on x
No feedback on y
Why ???

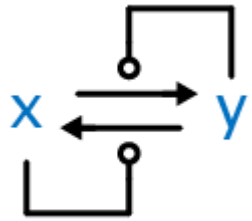
- The function is very well-studied. But why this structure?
- I.e., why this algorithm?

How to Build a Good Switch

- What is a "good" switch?
  - We need first a bistable system: one that has two *distinct* and *stable* states. I.e., given any initial state the system must settle into one of two states
  - The settling must be fast (not get stuck in the middle for too long) and robust (must not spontaneously switch back)
  - Finally, we need to be able to flip the switch by external inputs
- "Population" Switches
  - Populations of identical agents (molecules) with the whole population switching from one state to another as a whole
  - Highly concurrent. Stochastic symmetry breaking

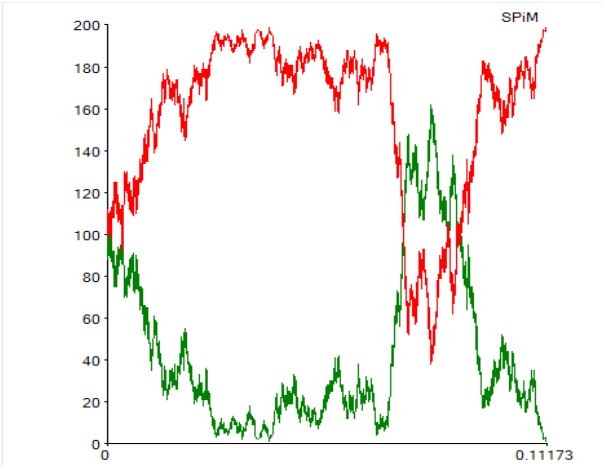
A Bad Algorithm

- Direct Competition
  - x catalyzes the transformation of y into x
  - y catalyzes the transformation of x into y
  - when all-x or all-y, it stops
- This system has two end states, but
  - Convergence to an end state is slow (a random walk)
  - Any perturbation of an end state can start a random walk to the other end state (hence not really *bistable*)



$y + x \rightarrow x + x$

$x + y \rightarrow y + y$

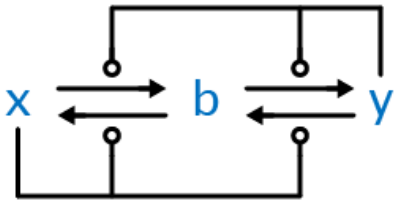


A Very Good Algorithm

- Approximate Majority (AM)
  - Decide which of two populations is in majority
- A fundamental 'population protocol'
  - Agents in a population start in state x or state y
  - A pair of agents is chosen randomly at each step, they interact ('collide') and change state
  - The whole population must eventually agree on a majority value (all-x or all-y) with probability 1

Dana Angluin · James Aspnes · David Eisenstat

A Simple Population Protocol for Fast Robust Approximate Majority



Third 'undecided' state

1) Disagreements cause agents to become undecided
2) Undecided agents believe any non-undecided agent they meet

Properties

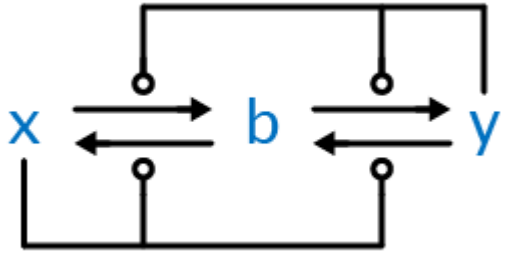
- With high probability, for *n* agents
  - The total number of interactions before converging is $O(n \log n)$
    ⇒ fast (optimal)
  - The final outcome is correct if the initial disparity is $\omega(\sqrt{n} \log n)$
    ⇒ solution states are robust to perturbations
- Logarithmic time bound in parallel time
  - *Parallel time* is the number of steps divided by the number of agents
  - In parallel time the algorithm converges with high probability in $O(\log n)$

[Angluin et al., http://www.cs.yale.edu/homes/aspnes/papers/disc2007-eisenstat-slides.pdf]

Chemical Implementation

Chemistry as a programming language for population algorithms!

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

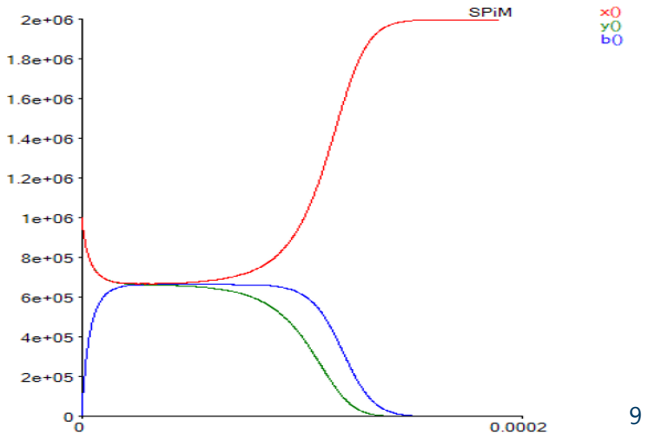


Bistable
Even when x=y! (stochastically)

Fast
$O(\log n)$ convergence time

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

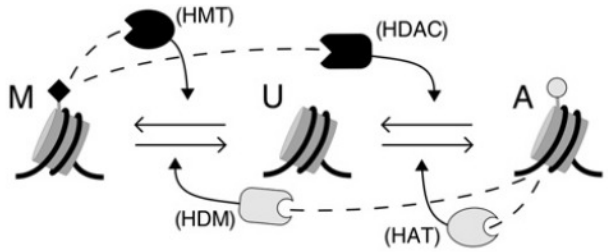
Worse-case scenario example, starting with x=y, b=0:

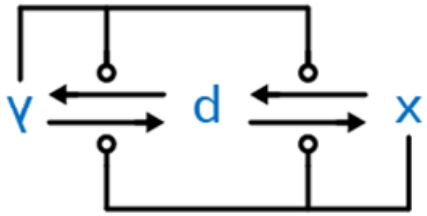


Back to Biology

- The AM algorithm has ideal properties for settling a population into one of two states
- Seems like this would be useful in Biology
  - Can we find biological implementations of this algorithm?
  - Can that explain some biological features?
  - Could the cell cycle switch be operating this way? (Looks unlikely…)

(Aside) A Biological Implementation





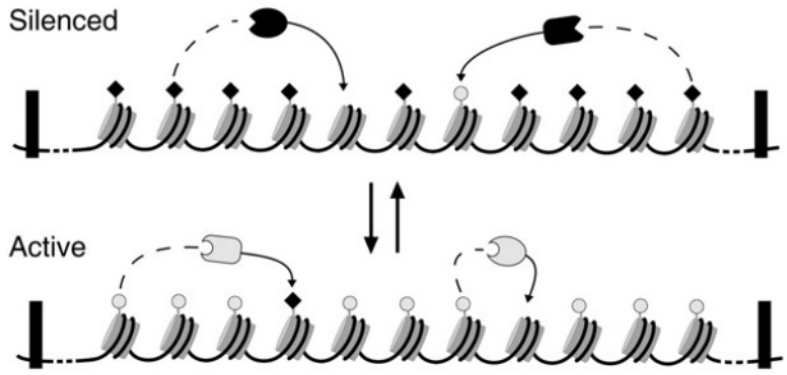
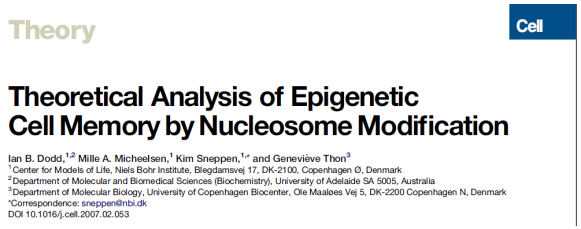


Figure 1. Basic Ingredients of the Model

Population of histones reaching agreement



Theory

Cell

Theoretical Analysis of Epigenetic Cell Memory by Nucleosome Modification

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DOI 10.1016/j.cell.2007.02.053

(Detour) How to model "Influence"

"True" molecular interactions.

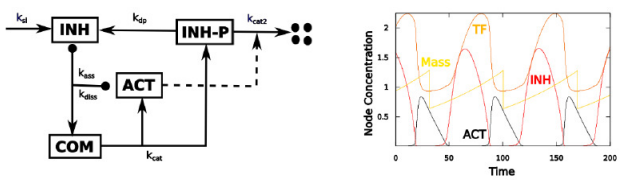


Figure 3: a) Schematic diagram of a simplified SIMM model [17]. The activa-

"Equivalent" influence interactions.

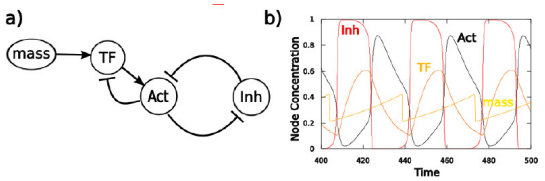


Figure 4: a) Schematic diagram of a primitive cell cycle in the reinitz framework.

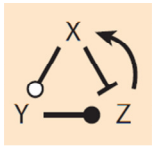
Evolving a Primitive Eukaryotic Cell Cycle Model

Malte Lücken, Jotun Hein, Bela Novak

Instead of modeling basic interactions, such as binding, synthesis, and degradation of molecular components, this framework models interactions simply as activation or inhibition. This approach also reduces the number of nodes necessary in the network, as e.g. the inhibitor binding tightly to the activator to form a complex, which produces phosphorylated inhibitor to be degraded under catalysis by the activator, is now simply a double negative feedback loop shown in Figure 1. This type of interaction is the basis of both aforementioned molecular model, therefore they can both be summarized in a single Reinitz model.

The Reinitz Model of Influence

- Based on early connectionist (neural network) modeling
  - Each activation/inhibition interaction is modeled as a flexible sigmoid function with 4+ parameters per node



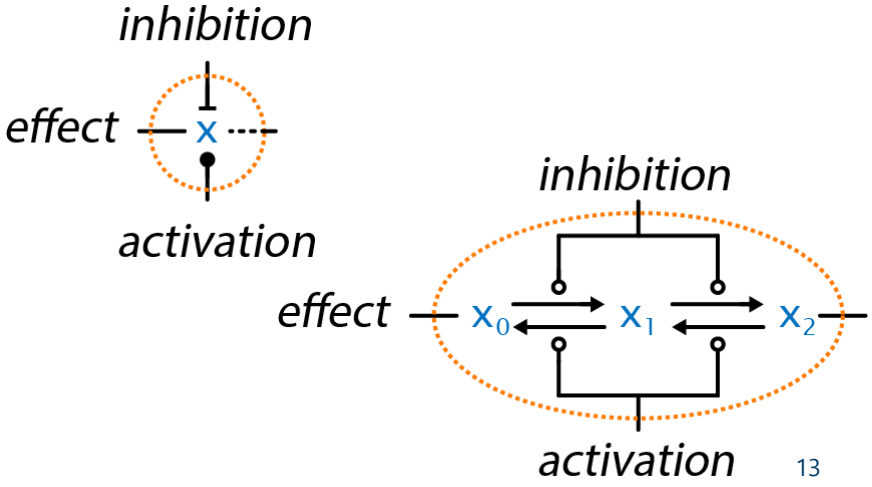
Functional Motifs in Biochemical Reaction Networks

John J. Tyson[1] and Béla Novák[2]

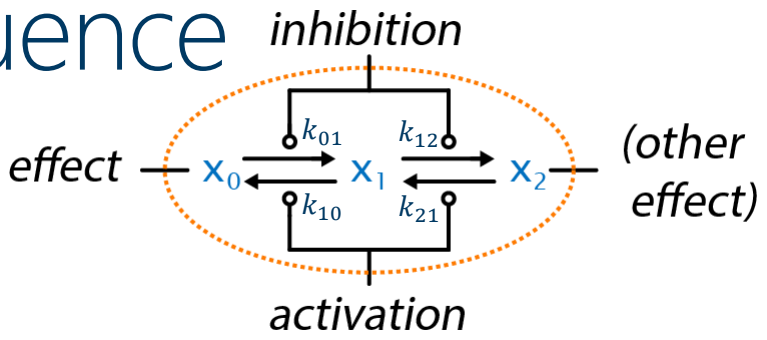
$$\frac{dX_i}{dt} = \gamma_i \frac{[A_i(1 - X_i) - B_i X_i]}{A_i + B_i}, \quad i = 1, \ldots, N,$$

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

- We prefer to stick to mass action kinetics
  - It will later become clear why
- We model activation/inhibition nodes by a mass action motif:
  - Using 4 rate parameters per node
  - Akin to multisite modification



The Triplet Model of Influence



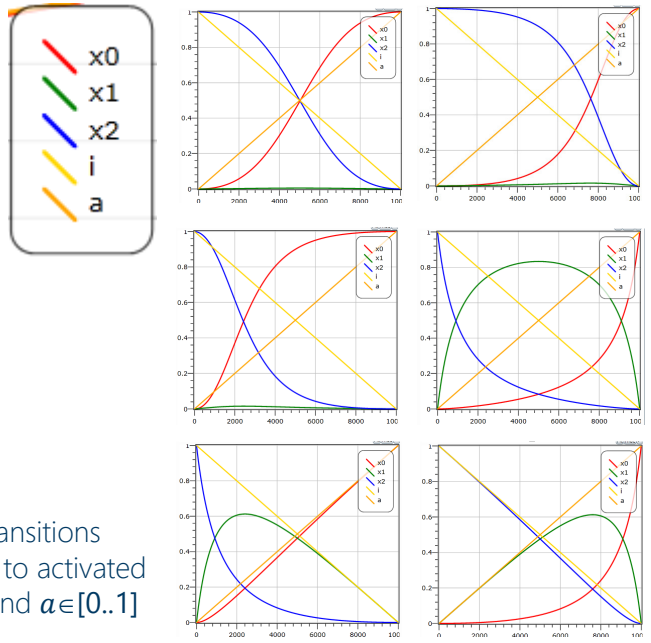
- Solving this mass action model at steady state with $tot = x_0 + x_1 + x_2$, obtain x_0 as a function of a and i :

$$x_0 = \frac{k_{10}k_{21}tot\ a^2}{k_{10}k_{21}a^2 + k_{01}k_{21}ai + k_{01}k_{12}i^2}$$

- Assuming $i = tot - a$ (inhibition decreases as activation increases) obtain x_0 as a function of $a \in [0..tot]$ (max stimulus = max response)

$$x_0 = \frac{k_{10}k_{21}tot\ a^2}{(k_{10}k_{21} - k_{01}k_{21} + k_{01}k_{12})a^2 + (k_{01}k_{21} - 2k_{01}k_{12})tot\ a + k_{01}k_{12}\ tot^2}$$

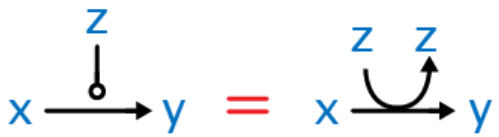
- By regulating the rates of flow through x_1 within 2 orders of magnitude we can obtain a range of linear, hyperbolic and sigmoid responses in the range [0..1] to linear activation $a \in [0..1]$.



steady state transitions from inhibited to activated with $tot = 1$ and $a \in [0..1]$

Influence Network Notation

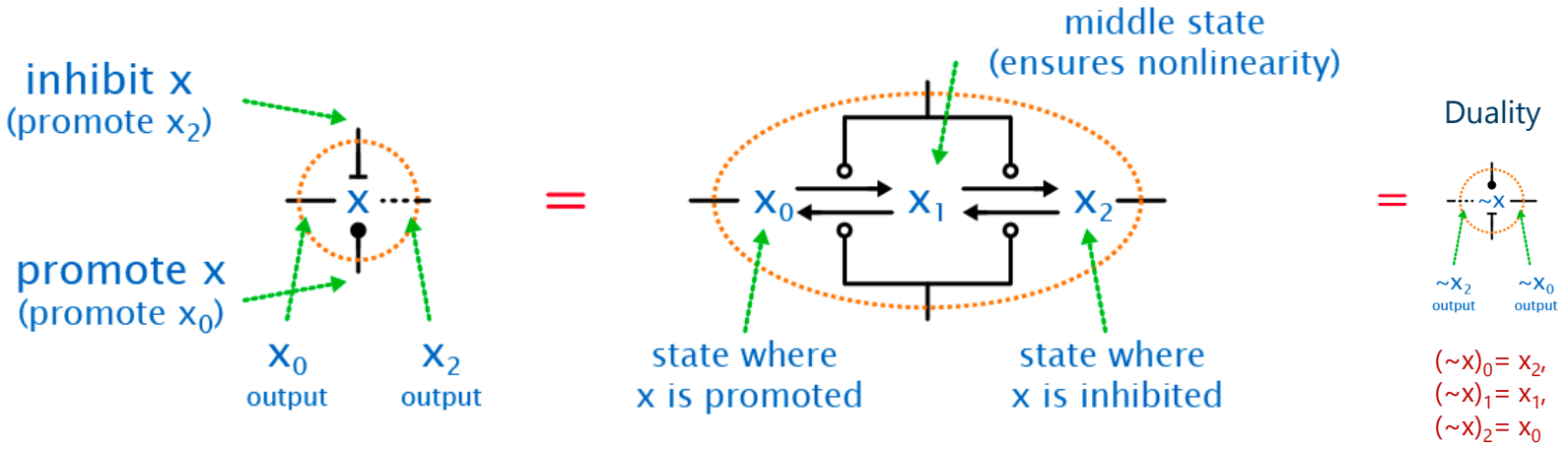
- Catalytic reaction



z is the catalyst

$x + z \rightarrow z + y$

- Triplet motif

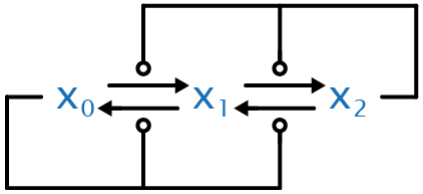


influence node catalytic node

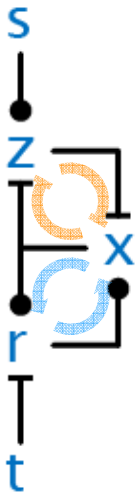
Cell Cycle Switch vs. AM

AM

=



CC



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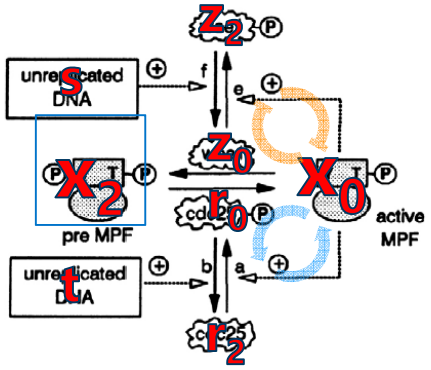
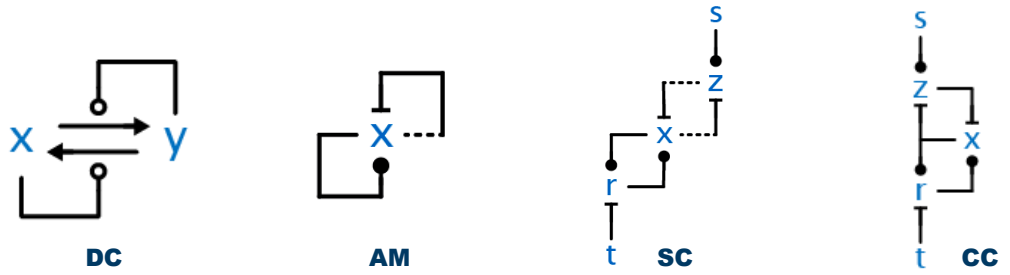
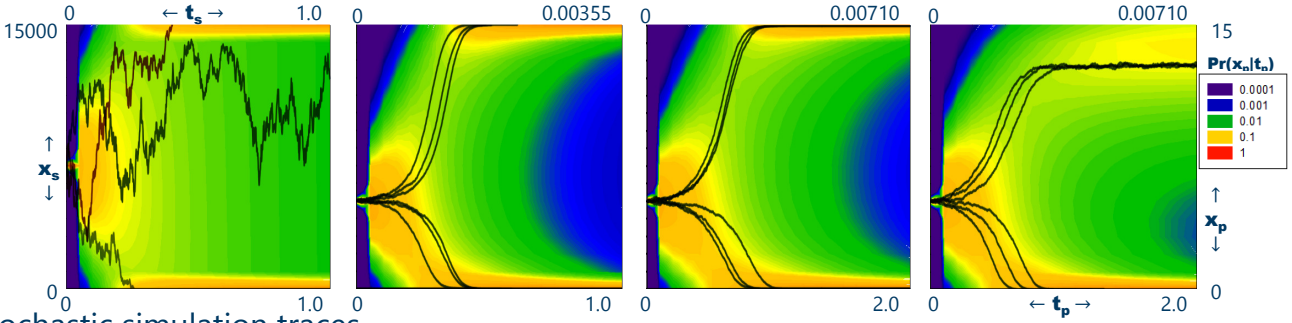


Convergence Analysis

- Switches as computational systems



Start symmetrical
(x_0=x_1=x_2 etc.)

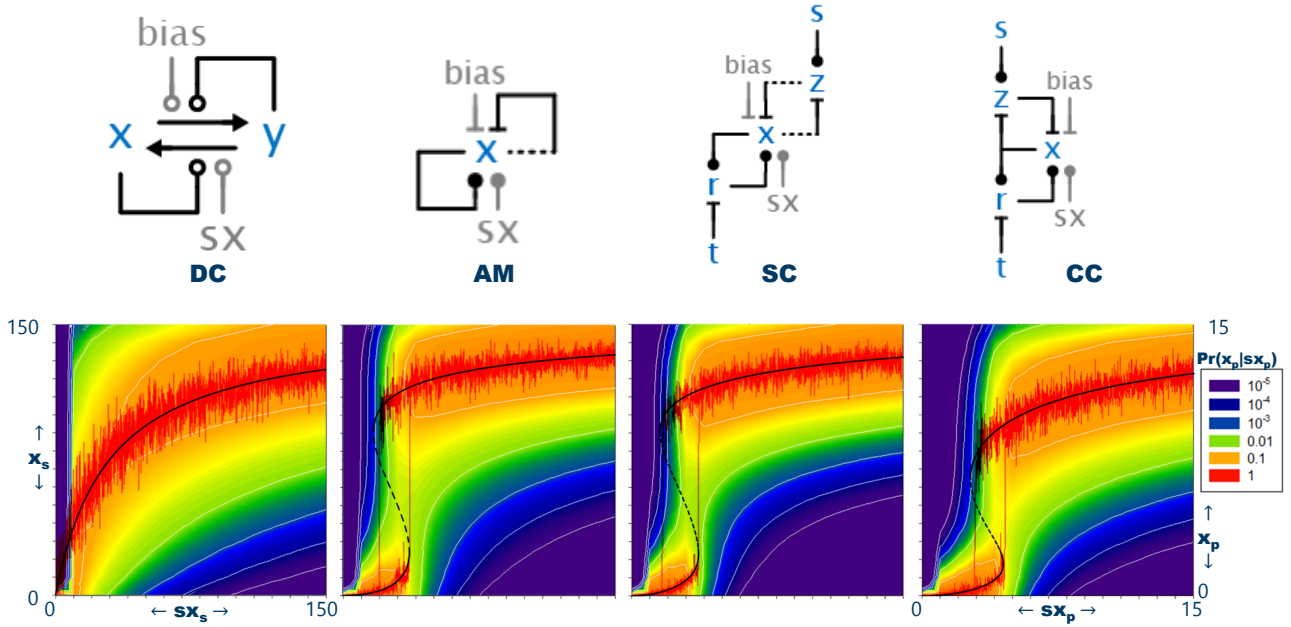


Black lines: several stochastic simulation traces
Color: full probability distribution of small-size system

NEW!
CC appears to converge in log time

Steady State Analysis

- Switches as dynamical systems

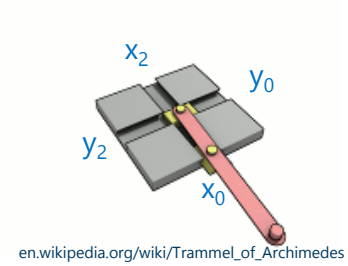


Black lines: deterministic ODE bifurcation diagrams
Red lines: noisy stochastic simulations
Color: full probability distribution of small-size system

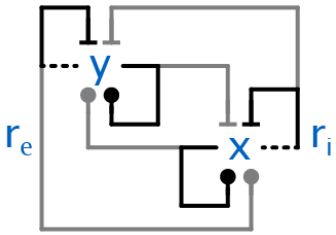
NEW!
AM shows hysteresis

Contextual Analysis

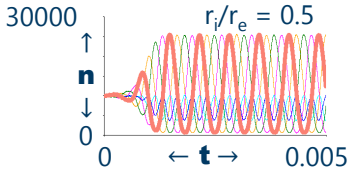
- AM switches in the context of oscillators

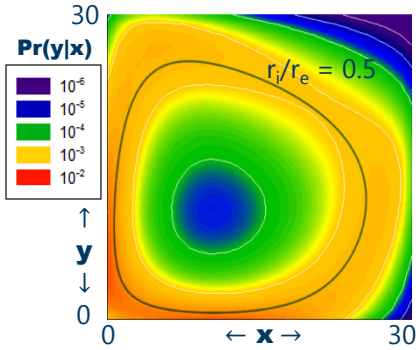


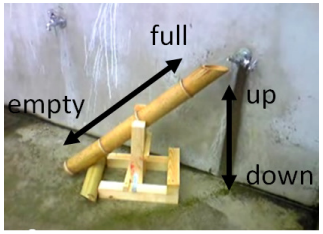
en.wikipedia.org/wiki/Trammel_of_Archimedes

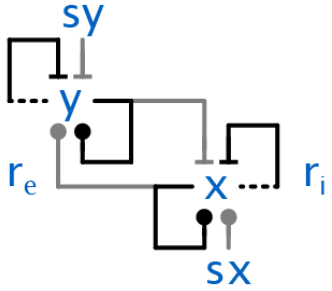


Trammel of Archimedes

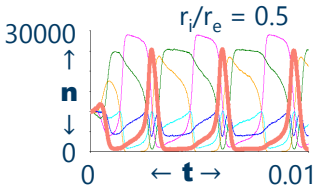


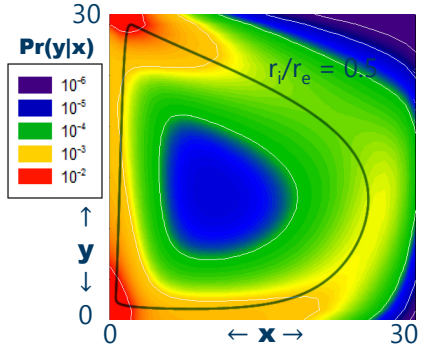






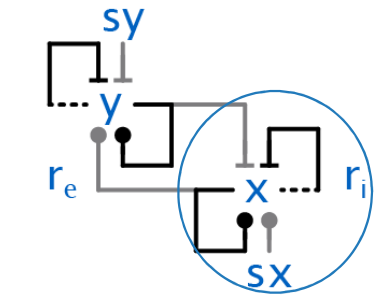
Shishi Odoshi

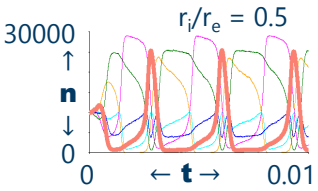


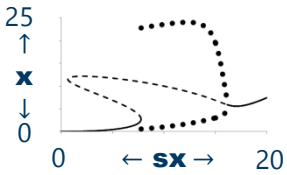


Modularity Analysis

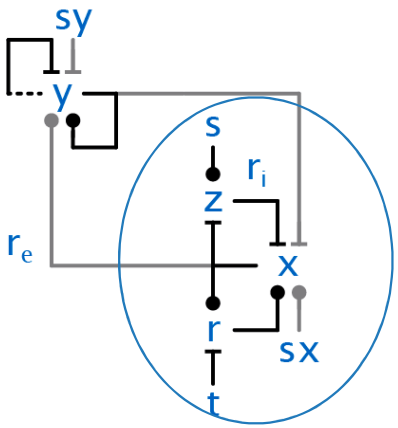
- CC swapped in for AM

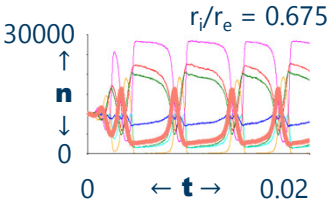


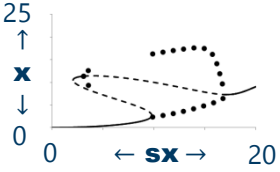




ri/re = 0.6
sy = 10



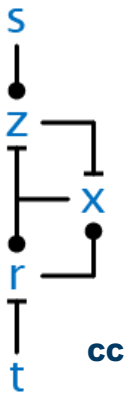


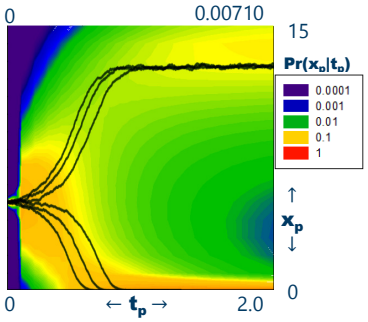


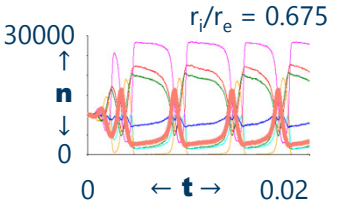
ri/re = 0.675
sy = 10

Evidence that CC is 'similar' to AM

- But there is a difference
  - The classical cell cycle switch, CC, works ok but never as well as AM
  - The output of CC does not go 'fully on':



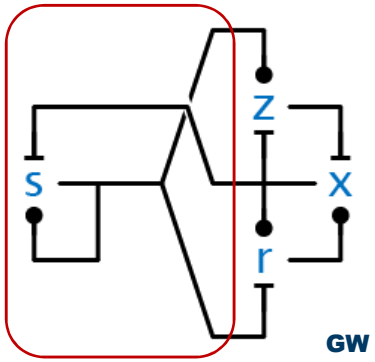


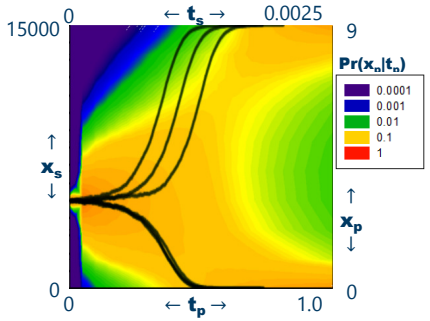


  - Because s continuously inhibits x through z, so that x cannot fully express
  - Engineering question: could *we* fix it? (Yes: let x inhibit s and t)
  - Q: Why didn't nature fix it?

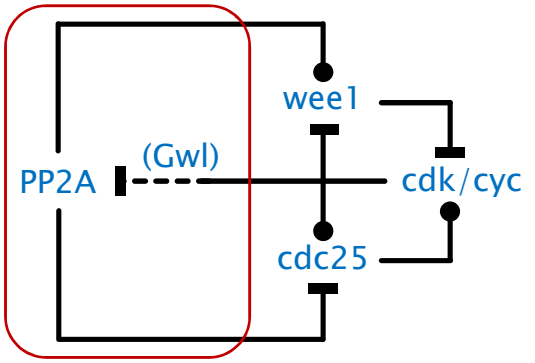
Nature did!

- There is another known feedback loop
  - By which x suppresses s "in retaliation" via the so-called Greatwall loop
  - Also, s and t happen to be the same molecule (=s)





Full activation!



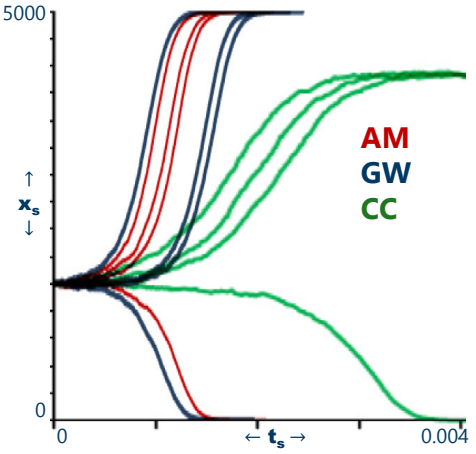
  - s and x now are antagonists: they are the two halves of the switch, mutually inhibiting each other (through intermediaries).

More surprisingly

- Makes it faster too!
  - The extra feedback also speeds up the decision time of the switch, making it about as good as the 'optimal' AM switch:

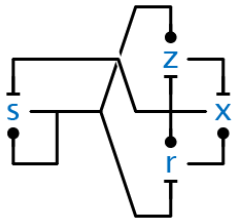
Conclusion (in our published paper):
Nature is trying as hard as it can to implement an AM-class algorithm!

The "classical" cell cycle switch seems to be only half of the picture: the extra feedback completes it *algorithmically*.



The Greatwall Kinase

- Our paper appeared:
  - Suggesting GW is a better switch than CC. *September 2012*



OPEN

SUBJECT AREAS:
COMPUTATIONAL BIOLOGY

The Cell Cycle Switch Computes Approximate Majority

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

- Another paper that same week:
  - Showing experimentally that the Greatwall loop is a necessary component of the switch, i.e. the not-as-good-as-AM network has been 'refuted'

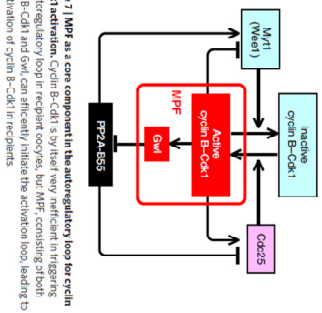


Figure 7 | MPF as a core component in the autoregulatory loop for cyclin B–Cdk1 activation. Cyclin B–Cdk1 's by itself very inefficient in triggering the autoregulatory loop in recipient oocytes, but MPF, consisting of both cyclin B–Cdk1 and Gwl, can efficiently initiate the activation loop, leading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

ARTICLE

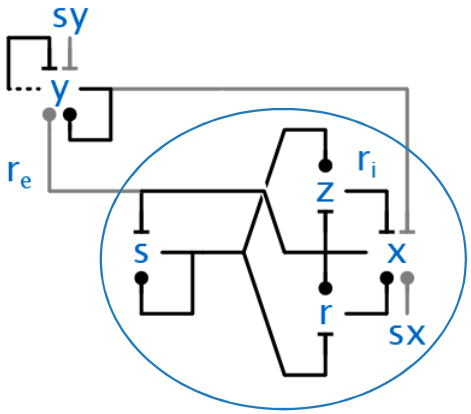
Received 6 Jul 2012 | Accepted 14 Aug 2012 | Published 11 Sep 2012 DOI: 10.1038/ncomms2062

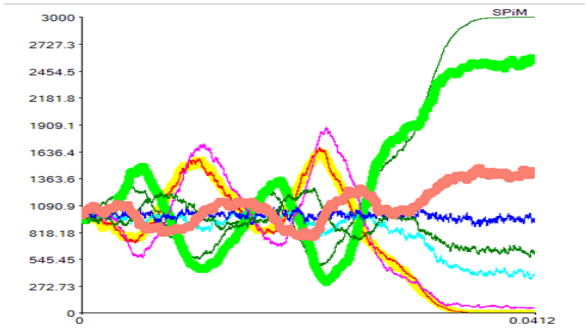
Greatwall kinase and cyclin B-Cdk1 are both critical constituents of M-phase-promoting factor

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

A new cell cycle switch candidate: GW

- Will it work in the normally-wired oscillator?

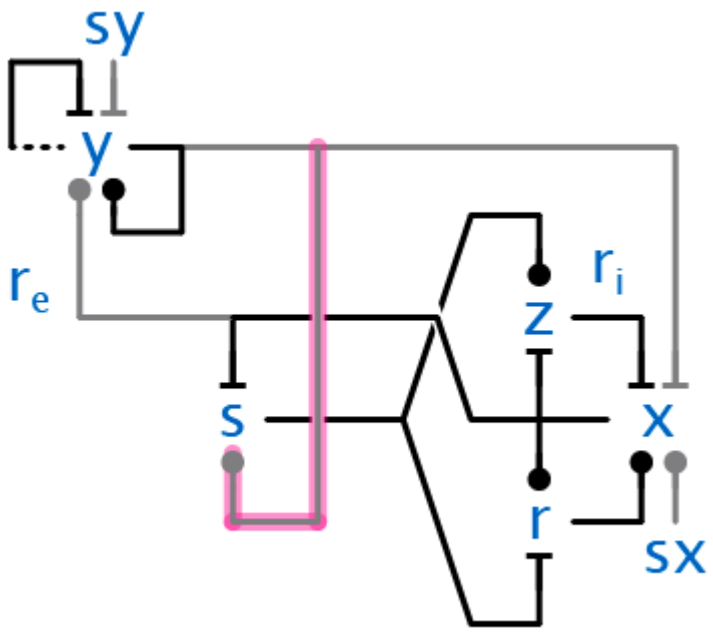


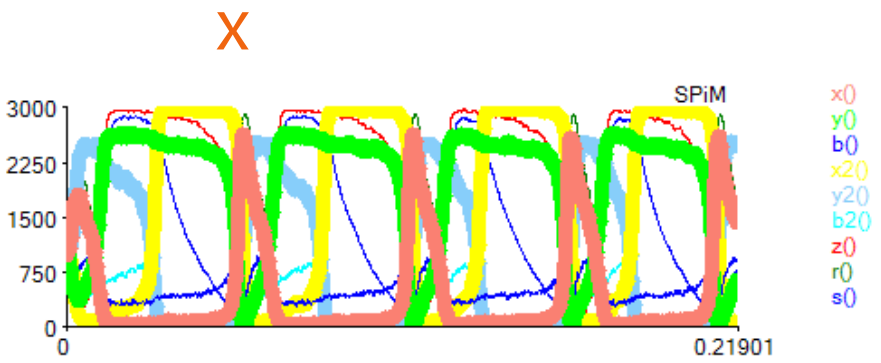


- Absolutely not! ☹
  - The x stable state is just too strong: a high x will shut down s completely; which means that r will be fully on, and it in turn will reinforce x fully. And y can never be strong enough to push down x when x-r are in such a strong mutual feedback. No amount of fiddling seems to give enough control on that situation.

However this will

- Put s under control of y so it can undermine x

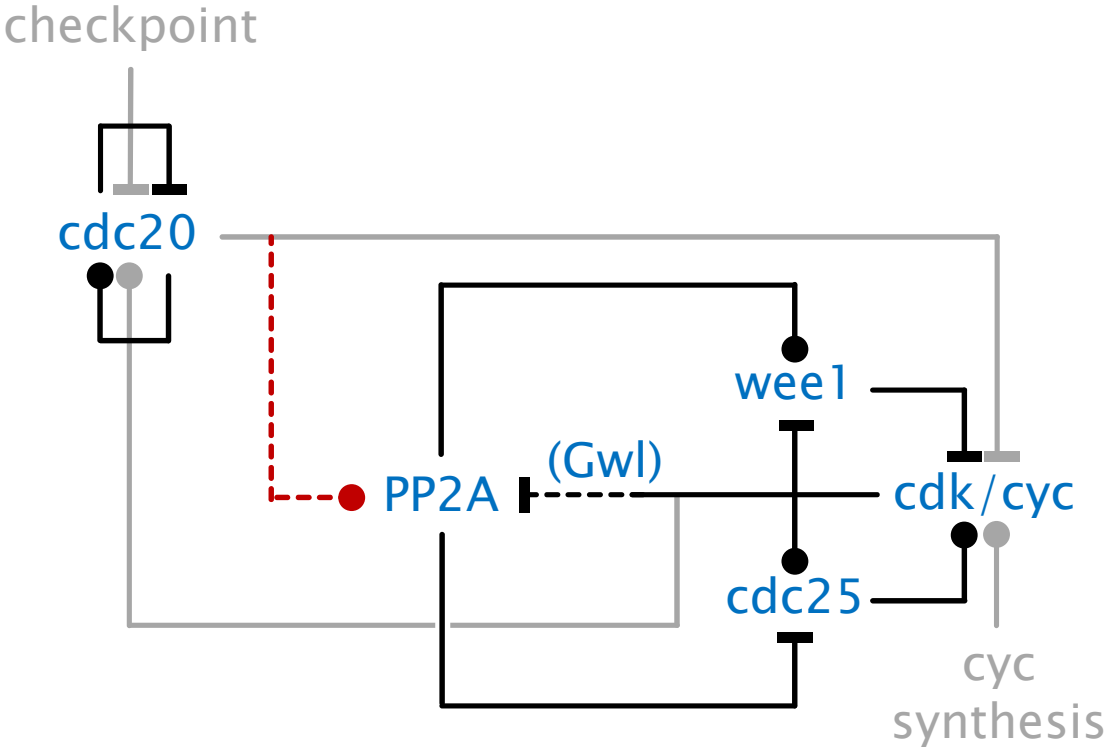




Robust full-on oscillation with all-default parameters (all black rates 1.0, all gray rates 0.5, all initial quantities equal)

Suggests a new interaction

- Either Gwl or PP2A or something along that path must be under control of cdc20.
- There are some hints in the literature that this may be the case, but no direct experimental validation.



Part II: What is network structure *really* telling us about kinetics?

An Analytical Theory of Network Emulation (with thanks to David Soloveichik)

- So far, our evidence is empirical
  - Although based on numerical simulations and covering both kinetic and steady state behavior
- Analytical evidence is harder to obtain
  - The proof techniques for the AM algorithm are hard and do not generalize easily to more complex networks
  - Quantitative theories of behavioral equivalence and behavioral approximation, e.g. in process algebra, are still lacking (although rich qualitative theories exist)

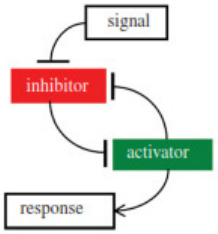
Mutual Inhibition

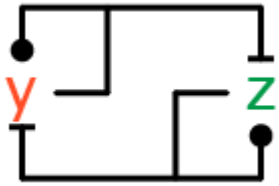
- A recent paper suggests that all cellular switches in all phases of the cell cycle follow (abstractly) a mutual inhibition pattern:

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):

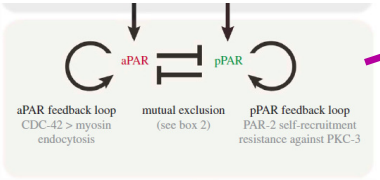
PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B

rstb.royalsocietypublishing.org

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

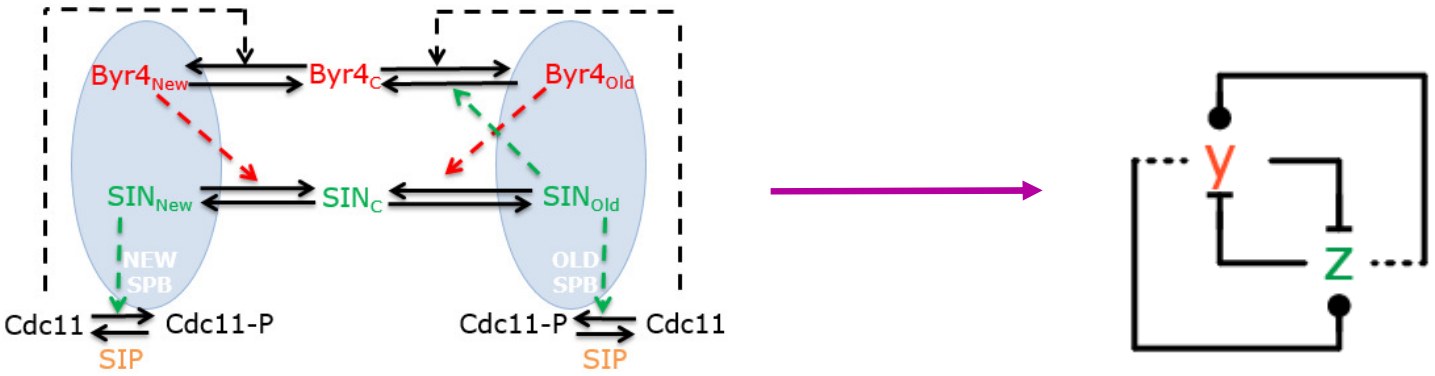
Fumio Motegi[1,2,3] and Geraldine Seydoux[4]

[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



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

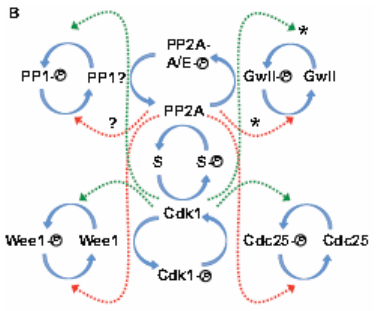
- A recent paper presents a more complete view of the cell cycle switch
- N.B. "phosphorylation network dynamics" is the same as our x_0-x_1-x_2 motif

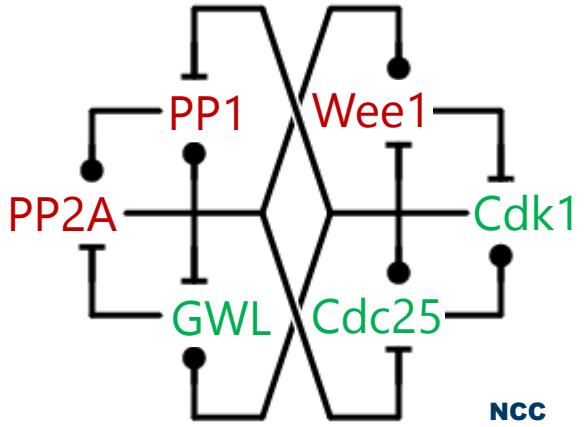
Phosphorylation network dynamics in the control of cell cycle transitions

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

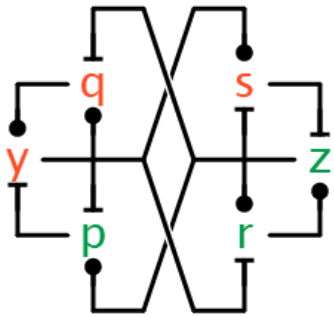
doi: 10.1242/jcs.106351

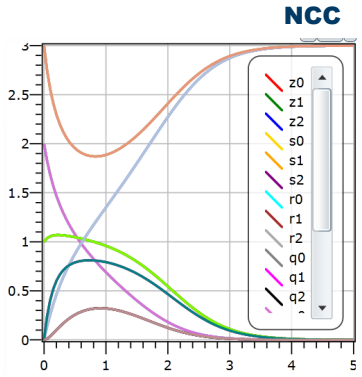




Network Emulation: NCC to MI

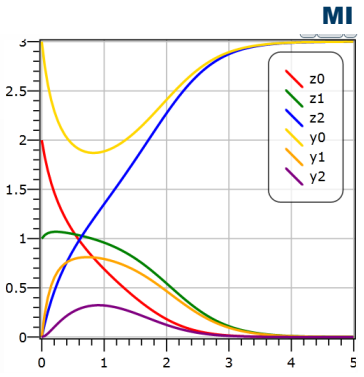
- For *any* initial state of MI we can find *some* initial state of NCC (actually by *copying* the state of MI) such that NCC *exactly* emulates MI





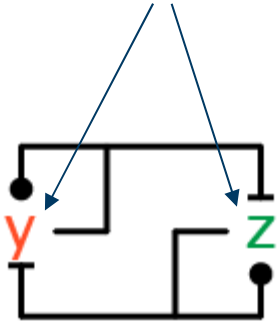
(18 species on 6 trajectories)

z,r,p ⇢ z
y,q,s ⇢ y



(6 species on 6 trajectories)

(3 species each)



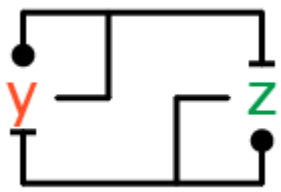
initialize z,r,p, identically to z;

initialize y,q,s identically to y

- Also for *any* rates of MI we can find rates for NCC such that the *average* behavior is *exactly* the same
- Why does this work so well?

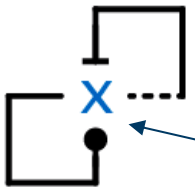
Network Emulation: MI to AM

- For chosen initial conditions of MI, the (6) trajectories of MI emulate those (3) of AM: MI *exactly* emulates AM



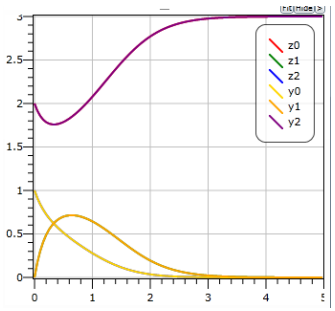
MI

~y,z⇢ x

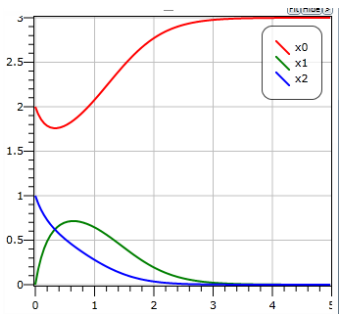


AM

(3 species)



(6 species on 3 trajectories)



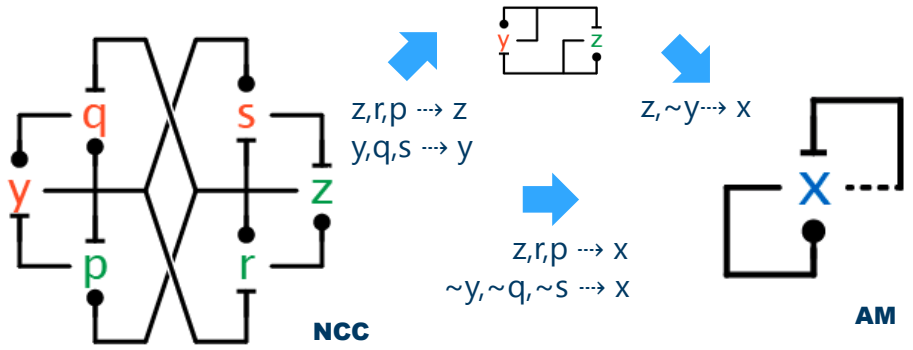
(3 species on 3 trajectories)

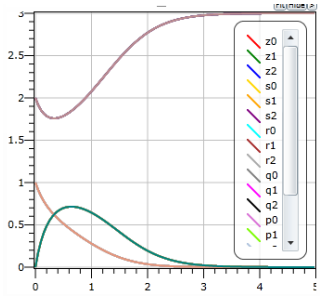
initialize ~y,z, identically to x

Network Emulations Compose: NCC to AM

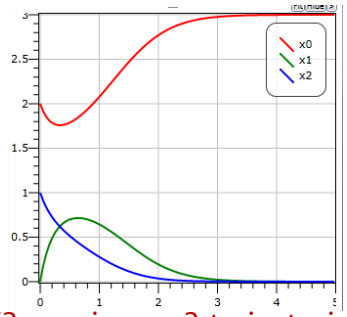
- For chosen initial conditions of **NCC**, the (18) trajectories of **NCC** emulate those (3) of **AM**

NCC *exactly* emulates **AM**





(18 species on 3 trajectories)



(3 species on 3 trajectories)

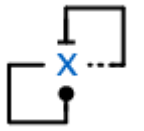
The new cell cycle switch can emulate AM *exactly*.

For *any* initial conditions of AM.

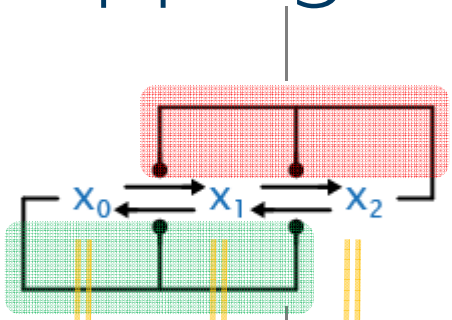
And for *any* rates of AM.

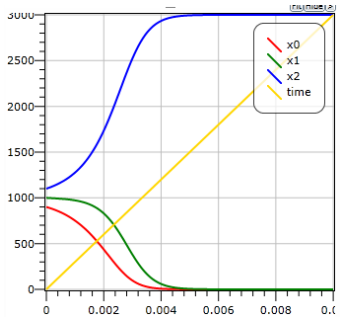
Why?

MI to AM mapping in detail



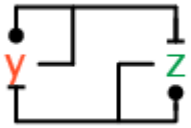
AM



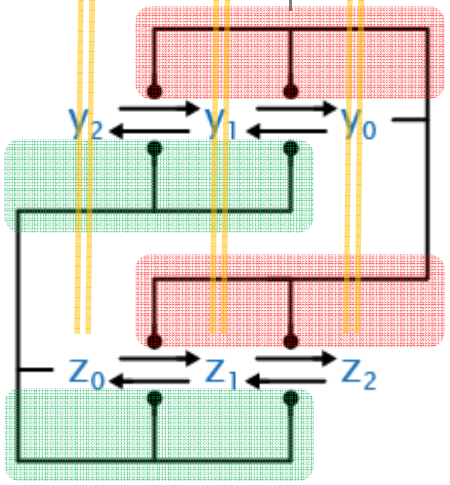


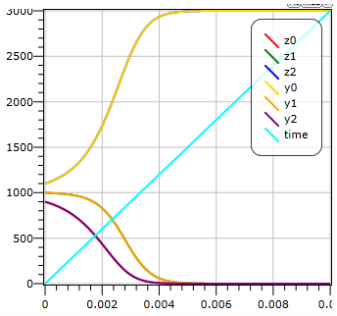
any initial conditions

homomorphic mapping



MI





initial conditions:

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

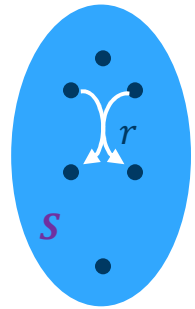
An Analytical Theory of Network Emulation

- An emulation is an "implementation"
  - "for every input produces the same output" (algorithms)
    "for every initial conditions produces the same trajectories" (dynamical systems)
  - A refined network that works just as well as the coarser network
    in the context of the inputs of the coarser network (not arbitrary inputs)

- When can a network emulate another one?
  - Theories of behavioral equivalence and behavioral approximation,
    e.g. like in process algebra, are still lacking in this quantitative field ☹
  - So we look at the continuous-state semantics of these networks,
    and see what we can do there ☺

- If you get lost, just read the green stuff!

Chemical Reaction Networks



- A CRN is a pair (S, R) where
  - $S = \{s_1, \ldots, s_n\}$ is a finite set of *species*
  - $R = \{r_1, \ldots, r_m\}$ is a finite set of *reactions* over S
- Reactions $r = (\rho, \pi, k)$ written $\Sigma_{s \in S}\ \rho_s \cdot s \rightarrow^k \Sigma_{s \in S}\ \pi_s \cdot s$
  - Ex.: $r = 2A + B \rightarrow^k A + 3C$
  - *with* $\rho_A = 2,\ \rho_B = 1,\ \rho_C = 0$ *reactant stoichiometric numbers*
    $\pi_A = 1,\ \pi_B = 0,\ \pi_C = 3$ *product stoichiometric numbers*
- The *stoichiometry* of a species s in a reaction r is:

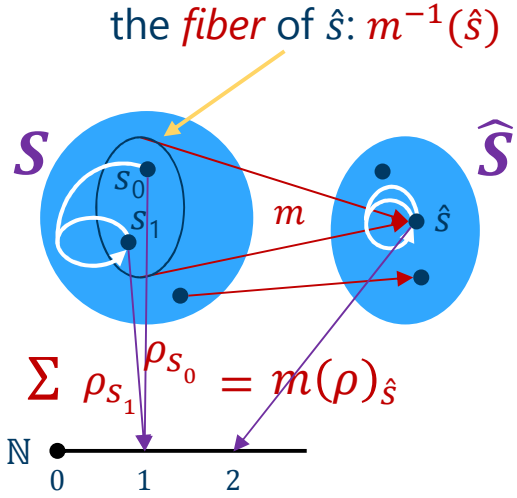
$\eta(s, (\rho, \pi, k)) = \pi_s - \rho_s$ *net stoichiometry* $\eta(A, r) = -1$

$\varphi(s, (\rho, \pi, k)) = k \cdot (\pi_s - \rho_s)$ *(instantaneous) stoichiometry* $\varphi(A, r) = -k$

Species Maps and Reaction Maps

- A *species map* is a map $m \in S \to \hat{S}$
  - Ex: $m(s_0) = m(s_1) = \hat{s}$
- It induces a canonical *reaction map* $R \to \hat{R}$
  - Ex: $m(s_0 + s_1 \to^1 s_1) = 2\hat{s} \to^1 \hat{s}$
- Where $m(\rho, \pi, k) = (m(\rho), m(\pi), k)$
- And $m(\rho)$ (similarly $m(\pi)$) is the sum over fibers:

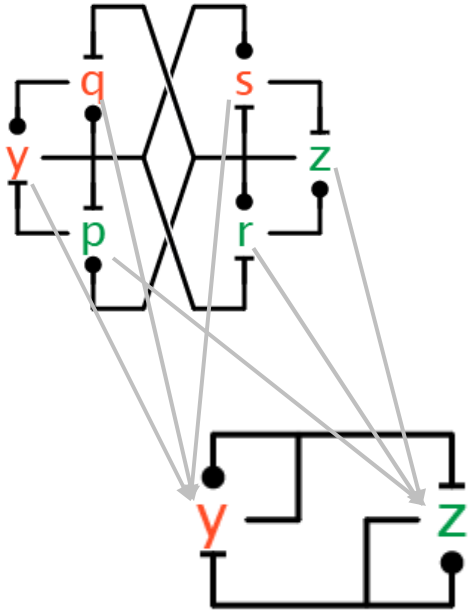
$$m(\rho)_{\hat{s}} = \Sigma_{s \in m^{-1}(\hat{s})}\, \rho_s$$



in case two species in the same reaction are mapped to the same species.

CRN Morphisms

- *Mappings (potential symmetries) between two networks*
- A *CRN morphism* is a map $m \in (S, R) \rightarrow \left(\hat{S}, \hat{R}\right) = (m_S, m_R)$ with $m_S \in S \rightarrow \hat{S}$ and $m_R \in R \rightarrow \hat{R}$.
  - We are interested in morphisms that are *not* injective, that represent *implementations* or *refinements* of simpler networks



CRN Homomorphisms

- *Preserve the graph structure of the network*
- $m \in (S, R) \to (\hat{S}, \hat{R})$ is a *CRN homomorphism* if $m_{\mathcal{R}}$ is determined by $m_{\mathcal{S}}$:

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

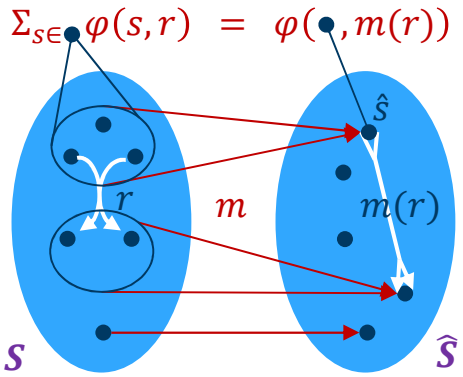
- Ex:

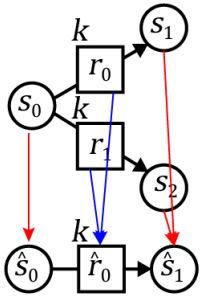
r_0: $m_{\mathcal{R}}(s_0, s_1, k) = (\hat{s}_0, \hat{s}_1, k) = (m_{\mathcal{S}}(s_0), m_{\mathcal{S}}(s_1), k)$
r_1: $m_{\mathcal{R}}(s_0, s_2, k) = (\hat{s}_0, \hat{s}_1, k) = (m_{\mathcal{S}}(s_0), m_{\mathcal{S}}(s_2), k)$

- It implies that *for each reaction m preserves stoichiometry summed over species fibers*

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

- But it may not preserve stoichiometry
  $\varphi(s_0, r_0) + \varphi(s_0, r_1) = -2k \neq -1k = \varphi(\hat{s}_0, \hat{r}_0)$ (see next slide)





Homomorphism

CRN Stoichiomorphisms

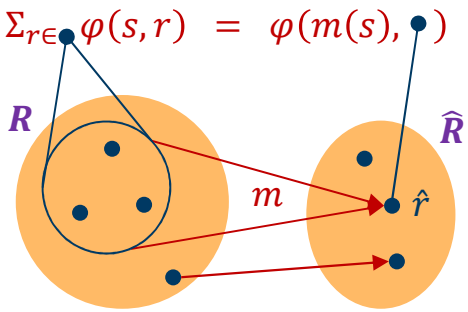
- *Preserve the stoichiometry of the network*
- $m \in (S, R) \to (\hat{S}, \hat{R})$ is a *CRN stoichiomorphism* if *for each species m preserves stoichiometry summed over reaction fibers*

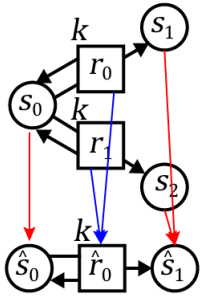
$$\forall s \in S.\ \ \forall \hat{r} \in \hat{R}.\ \ \Sigma_{r \in m^{-1}(\hat{r})}\, \varphi(s, r) = \varphi(m(s), \hat{r})$$

- This condition can be checked over the *syntax* of CRNs, without any consideration of their kinetics
  - Ex:

$$\begin{aligned} s_0, \hat{r}_0&: \quad \varphi(s_0, r_0) + \varphi(s_0, r_1) = 0 = \varphi(\hat{s}_0, \hat{r}_0) \\ s_1, \hat{r}_0&: \quad \varphi(s_1, r_0) + \varphi(s_1, r_1) = 1k = \varphi(\hat{s}_1, \hat{r}_0) \\ s_2, \hat{r}_0&: \quad \varphi(s_2, r_0) + \varphi(s_2, r_1) = 1k = \varphi(\hat{s}_1, \hat{r}_0) \end{aligned}$$

- We will show that existence of a stoichiomorphism implies identical network kinetics (in certain conditions).





Homomorphism and stoichiomorphism.

CRN Morphism Conditions

- Homomorphism: *preserves the graph structure of the network*

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

- Stoichiomorphism: *preserves the stoichiometry of the network*

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

- If m is an isomorphism (injective and surjective, with singleton fibers) then both properties reduce to the simple property:
  preserves the stoichiometry of each species in each reaction

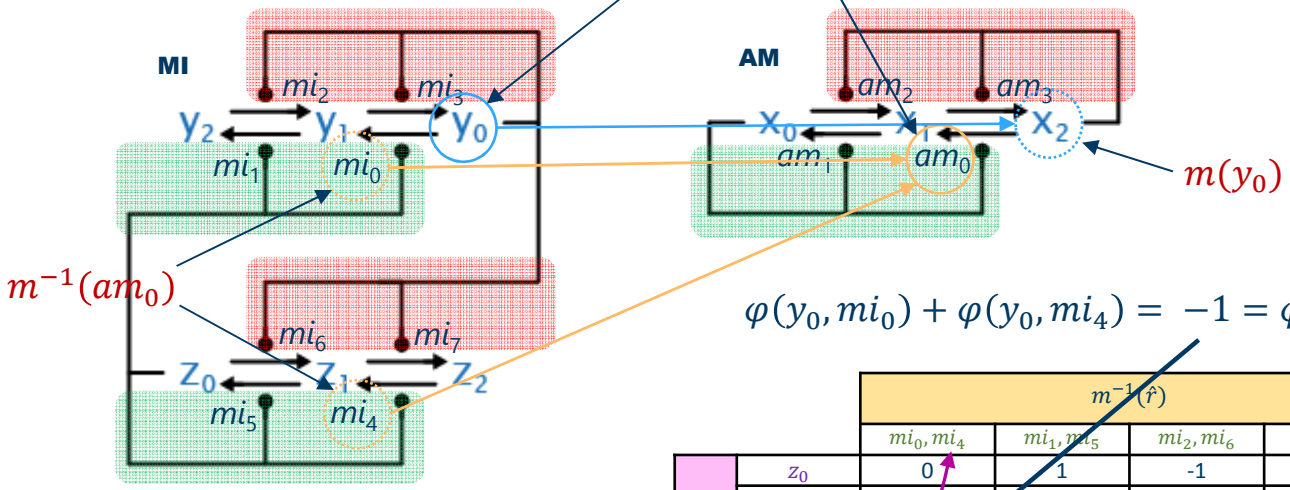
$$\forall s \in S.\ \ \forall r \in R.\ \ \varphi(s, r) = \varphi\big(m(s), m(r)\big)$$

- The above are thus generalization for when m is not injective.

Checking the Stoichiomorphism Condition

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

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



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

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

All unit rates (for simplicity)

This is both a homomorphism and a stoichiomorphism

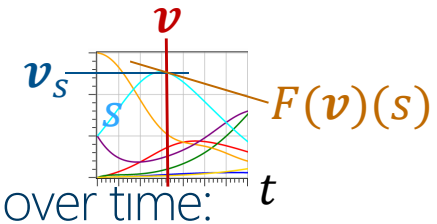
CRN Kinetics

- A *state* of a CRN (S, R) is a vector of concentrations for each species: $\boldsymbol{v} \in \mathbb{R}_+^S$.
- The *mass action* $[r] \in \mathbb{R}_+^S \to \mathbb{R}^+$ of a reaction $r \in R$ is:

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

- The *differential system* of a CRN (S, R) is the map $F \in \mathbb{R}_+^S \to \mathbb{R}^S$
  (for each state, gives the differential of concentration for each species):

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



- Normally written as a system of concentration ODEs, integrated over time:

$$\frac{d\boldsymbol{v}_s}{dt} = F(\boldsymbol{v})(s) = \Sigma_{(\rho,\pi,k) \in R}\ k \cdot (\pi_s - \rho_s) \cdot \boldsymbol{v}^{\rho}$$

Kinetic Emulation

- A map $m \in (S,R) \to (\hat{S},\hat{R})$ is a *CRN emulation* if the following holds for the respective differential systems $F, \hat{F}$:

$$\forall \hat{v} \in \mathbb{R}_{+}^{\hat{S}}.\ \forall s \in S.\ F(\hat{v} \circ m)(s) = \hat{F}(\hat{v})\big(m(s)\big)$$

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

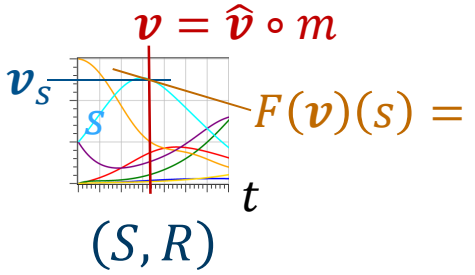
- It follows that for *any* initial state $\hat{v}$ of $(\hat{S},\hat{R})$ there is an initial state v (=$\hat{v} \circ m$) of (S,R) such that the trajectory of any s in (S,R) is identical to (*emulates*) the trajectory of $m(s)$ in $(\hat{S},\hat{R})$.

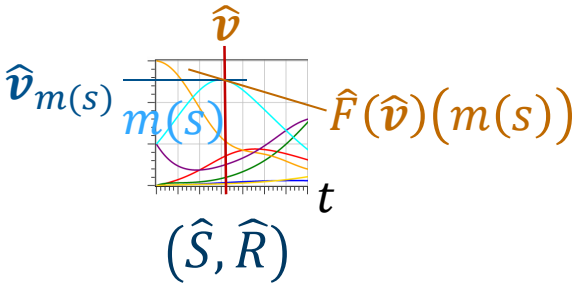
(the trajectory of s from $\hat{v} \circ m$ equals the trajectory of $m(s)$ from $\hat{v}$)

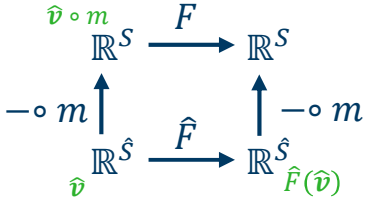
-

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

(With minor caveats if m is not surjective.)

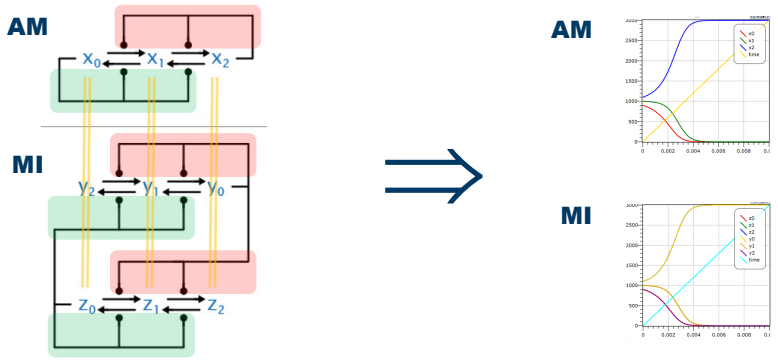






Emulation Theorem

- Theorem: If $\boldsymbol{m}$ is a CRN homomorphism and stoichiomorphism then it is a CRN emulation.



That is, for *any initial conditions* we can match trajectories.

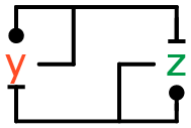
- Actually, $\boldsymbol{m}$ need not be a homomorphism for this to hold: it is enough for $\boldsymbol{m}$ to be a *reactant morphism* and a stoichiomorphism. A reactant morphism agrees with the species map on the reactant species, but allows rates and product species to disagree. This allows a wider range of network mappings that preserve kinetics.

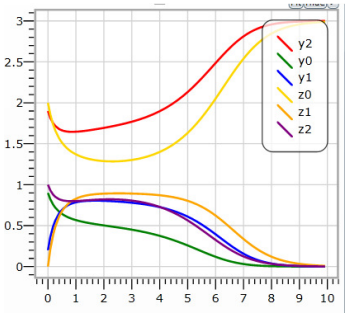
Change of Rates Theorem

- A *change of rates* for (S, R) is bijection $\iota \in (S, R) \to (S, R')$ such that $\iota(S)$ is the identity and $\iota(\rho, \pi, k) = (\rho, \pi, k')$.
- Theorem: If $m \in (S, R) \to (\hat{S}, \hat{R})$ is a stoichiomorphism, then for *any* change of rates $\hat{\iota}$ of $(\hat{S}, \hat{R})$ there is a change of rates ι of (S, R) such that $\hat{\iota} \circ m \circ \iota^{-1}$ is a stoichiomorphism.
  - In fact, ι changes rates by the ratio with which $\hat{\iota}$ changes rates: $\iota(\rho, \pi, k) = \left(\rho, \pi, k \cdot \frac{\hat{k}'}{\hat{k}}\right)$ where $m(\rho, \pi, k) = (\hat{\rho}, \hat{\pi}, \hat{k})$ and $\hat{\iota}(\hat{\rho}, \hat{\pi}, \hat{k}) = (\hat{\rho}, \hat{\pi}, \hat{k}')$.
- Corollary: If $m \in (S, R) \to (\hat{S}, \hat{R})$ is a stoichiomorphism and homomorphism, then for *any change of rates* $\hat{\iota}$ of $(\hat{S}, \hat{R})$ there is a change of rates ι of (S, R) such that $\hat{\iota} \circ m \circ \iota^{-1}$ is an emulation.
- That is, for *any rates* we can match trajectories.

Any Rates, Any Initial Conditions

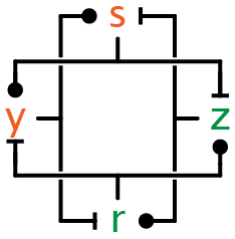
- A stoichiomorphism $m \in (S, R) \rightarrow (\hat{S}, \hat{R})$ that is also a homomorphism, determines an emulation for any choice of rates of $(\hat{S}, \hat{R})$.
- Those emulations can match any initial conditions of any choice of rates of $(\hat{S}, \hat{R})$ with some initial conditions of some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

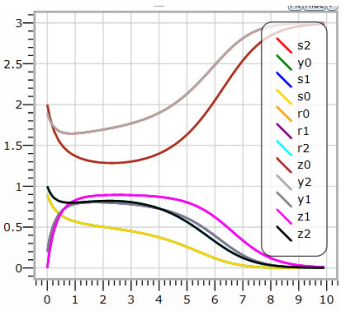





```
directive sample 10.0 100

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

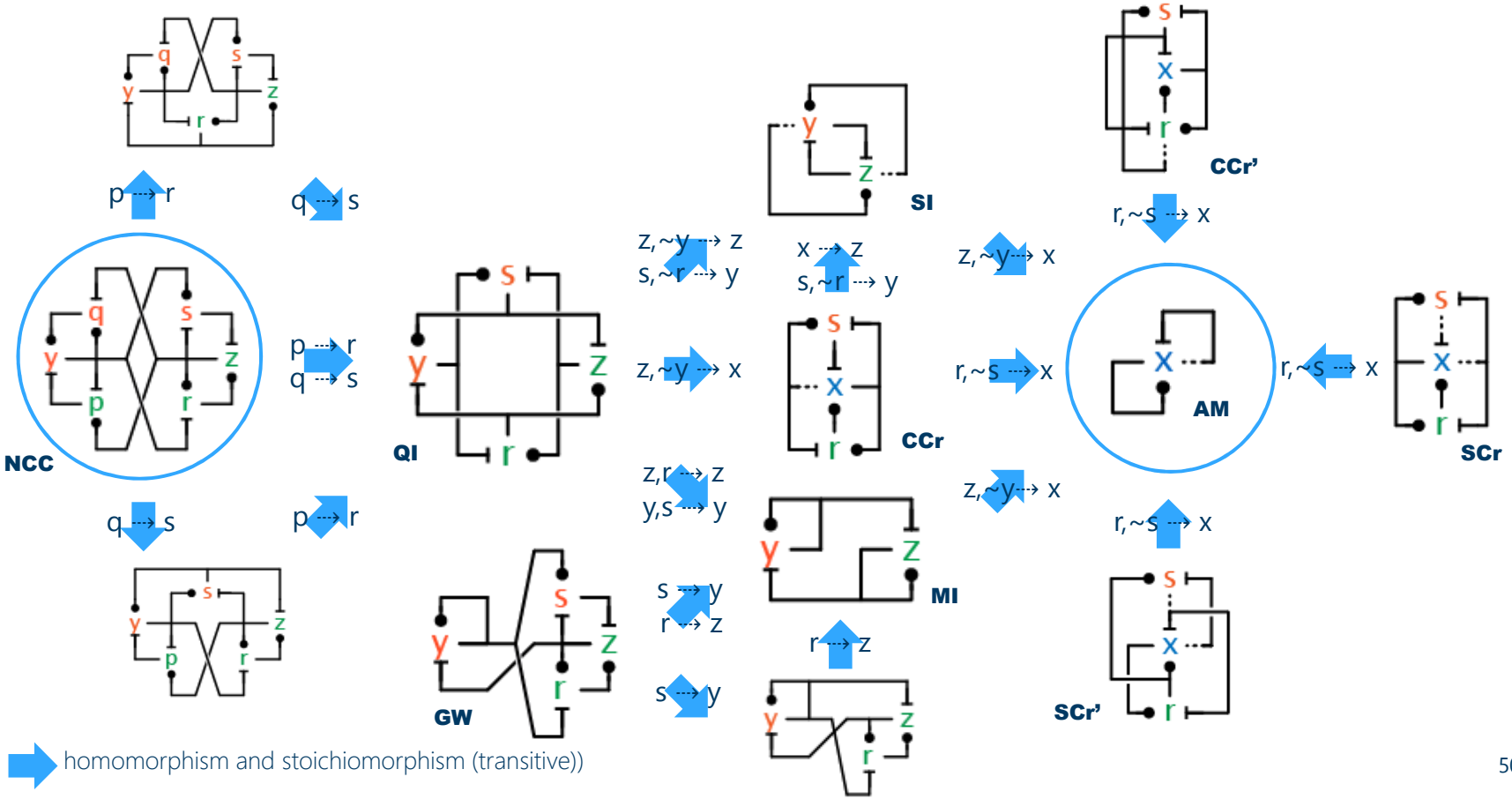





```
directive sample 10.0 100

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

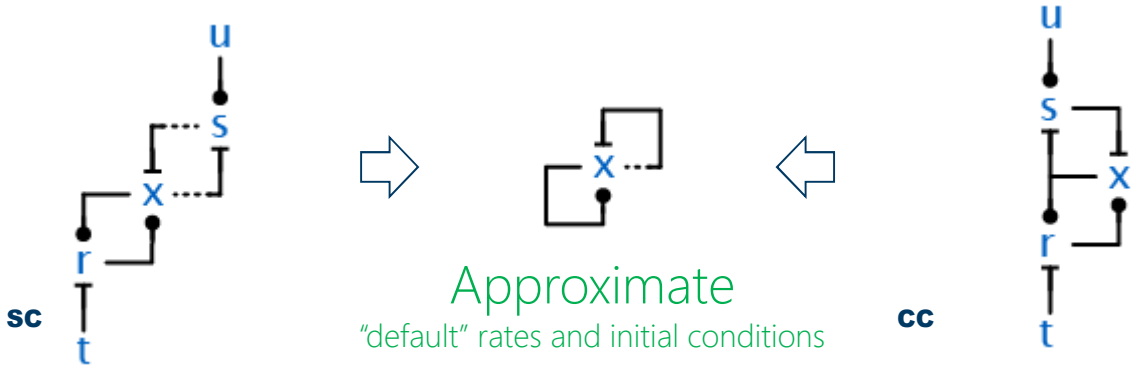
Cell Cycle Stoichiomorphism Zoo



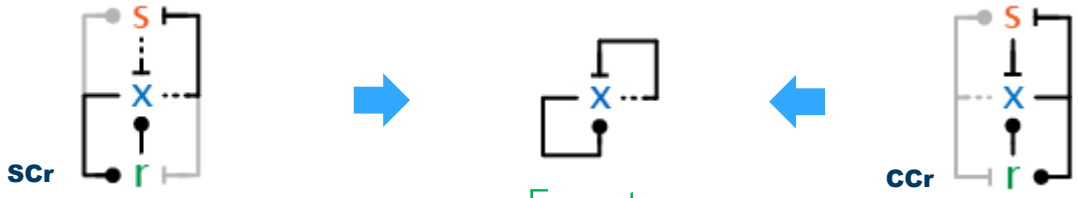
(homomorphism and stoichiomorphism (transitive))

From Empirical to Analytical

First part of talk:

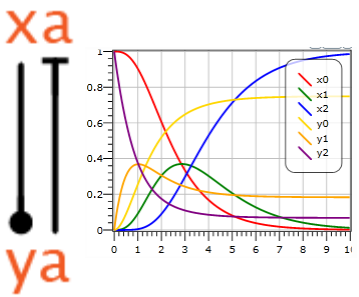


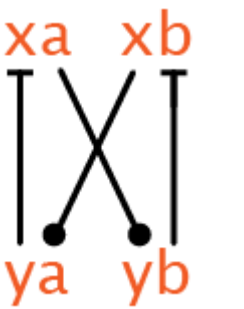
Second part of talk:



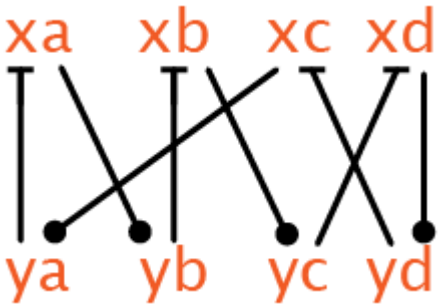
These additional feedbacks *do exist* in real cell cycles (via indirections)

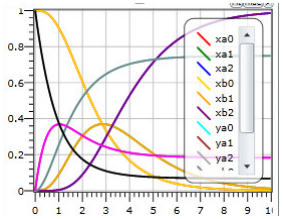
Another Zoo

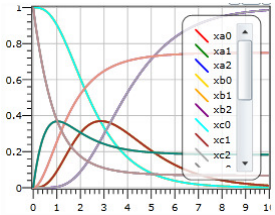

xa
ya
x0
x1
x2
y0
y1
y2

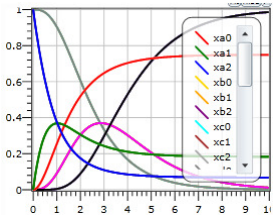

xa xb
ya yb


xa xb xc
ya yb yc


xa xb xc xd
ya yb yc yd

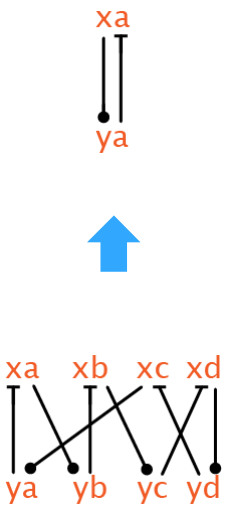

xa0
xa1
xa2
xb0
xb1
xb2
ya0
ya1
ya2


xa0
xa1
xa2
xb0
xb1
xb2
xc0
xc1
xc2


xa0
xa1
xa2
xb0
xb1
xb2
xc0
xc1
xc2

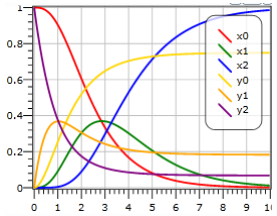
Network Perturbations

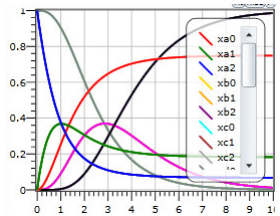
Network



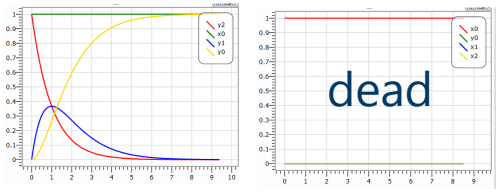
A complex but robust implementation of the simple network

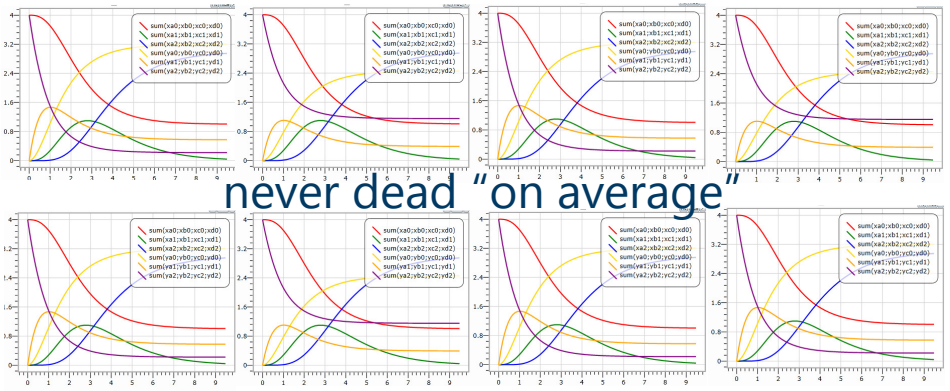
Normal Behavior





Removing each link in turn



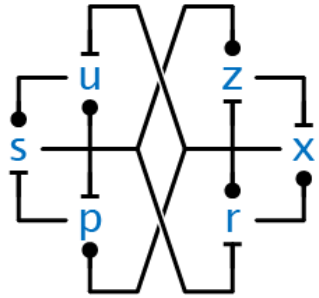


Interpretation of Stoichiomorphism

- Ignorance about initial conditions
  - We may not know the concentrations of species in the more complex network, but at least we know that if they satisfy certain conditions, then it behaves like the simpler network.
- 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.

Conclusions

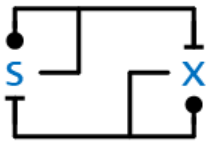
- The cell cycle switch *can* exactly emulate AM



NCC

(New) cell cycle switch

emulates:



MI

emulates:

AM

Approximate majority algorithm

- Nature likes a good algorithm!

In separate work…

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