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Morphisms of Reaction Networks

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Outline

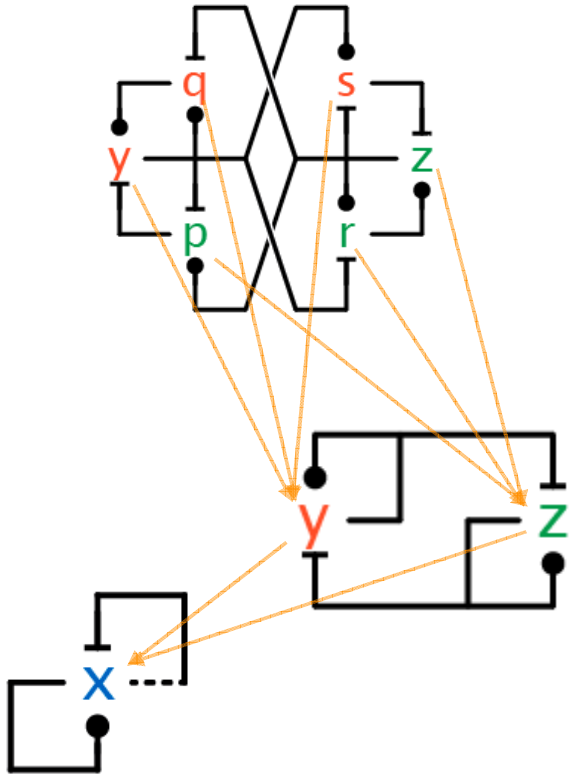
- Computational Methods
  - Comparing Networks
  - Network Bisimulations (and Morphisms)
  - Finding Bisimulations by Theorem Proving
- Systems Biology
  - Morphisms of Antagonistic Networks
  - Network Morphisms as Evolutionary Paths
  - Noise Reduction in Complex Biochemical Switches

Comparing Networks

- High-value activity:
  - 2001 Nobel prize in Physiology for the discovery of *"Key regulators of the cell cycle … they have identified key molecules that regulate the cell cycle in all eukaryotic organisms, including yeast, plants, animals, and human."*
  - These are *not* the same molecules in all organisms, but it is still "the same network"
- Network differences expose evolution
  - Tracing back ancestral networks from current ones
- Networks are algorithms
  - Algorithms fall in different performance classes (is nature "optimal"?)
  - Different networks for the same function may or may not be in the same class

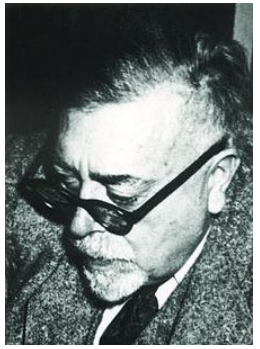
Morphing networks

- How can we compare different networks?
  - Different number of species
  - Different number of reactions
  - Apparently unrelated connectivity
- So that we can compare their function?
  - Does antagonism (in network structure) guarantee bistability (in function)?
- We do it by *mapping* networks onto one another so that they *emulate* each other ('s traces)
  - Deterministic version of simulation of reactive systems



Mapping one network into another

- A formal notion was strangely missing from the literature
  - Seen in Biology: single-network analysis (e.g. structure of feedback loops) and network reduction (e.g. while preserving steady states). Study of common or frequent subnetworks.
  - Seen in C.S.: comparing network *behaviors* (e.g. morphisms of event structures).
  - Nothing much resembling (bi)simulation "on the syntax" (structure) of whole biochemical networks.
- Model reduction is unavoidable and pervasive, but
  - Often criticized/ignored by biologists when it leads to quantities that are "not biologically meaningful". E.g. a fusion or change a variables in the ODEs where the new variables do not correspond to biological parts. The reduced model should "inform" the original one.
- Science's ethos
  - The "truth" is the big network, not the small one!
    If you depart from the truth in any way, you have to explain how you can get back to it.
  - The point is not to reduce the size of the network (although that's neat),
    but to understand aspects of *the big network* by reference to a smaller one.
  - The mapping is more important than either networks.



Norbert Wiener

Pioneer of stochastic processes and inventor of Cybernetics.

"The best material model of a cat is another, or preferably the same, cat"

Chemical Reaction Networks

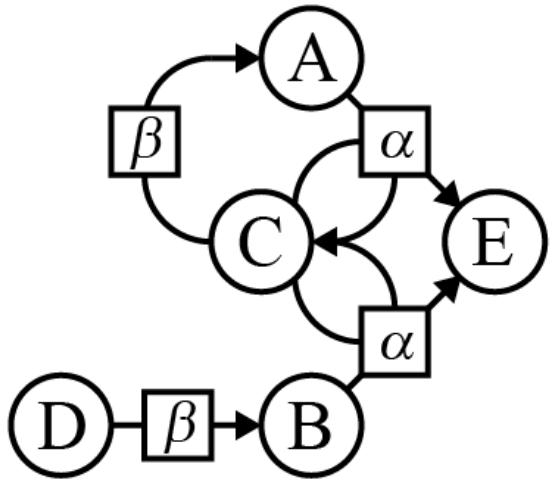
$A + C \xrightarrow{\alpha} C + E$

$B + C \xrightarrow{\alpha} C + E$

$C \xrightarrow{\beta} A$

$D \xrightarrow{\beta} B$

$$\dot{V}_A = -\alpha V_A V_C + \beta V_C$$
$$\dot{V}_B = -\alpha V_B V_C + \beta V_D$$
$$\dot{V}_C = -\beta V_C$$
$$\dot{V}_D = -\beta V_D$$
$$\dot{V}_E = \alpha V_A V_C + \alpha V_B V_C$$



The (autonomous) ODE system $\dot{V} = F(V)$ underlying a CRN (S, R) is $F : \mathbb{R}^S_{\geq 0} \to \mathbb{R}^S$, where each component F_X, with $X \in S$ is defined as:

$$F_X(V) := \sum_{\rho \xrightarrow{\alpha} \pi \in R} (\pi(X) - \rho(X)) \cdot \alpha \cdot \prod_{Y \in S} V_Y^{\rho(Y)} .$$

This represents the well-known *mass-action* kinetics, where the reaction rate is proportional to the concentrations of the reactants involved. Since the ODE system of a CRN is given by polynomials, the vector field F is locally Lipschitz. Hence, the theorem of Picard-Lindelöf ensures that for any $V(0) \in \mathbb{R}^S_{\geq 0}$ there exists a unique non-continuable solution of $\dot{V} = F(V)$.

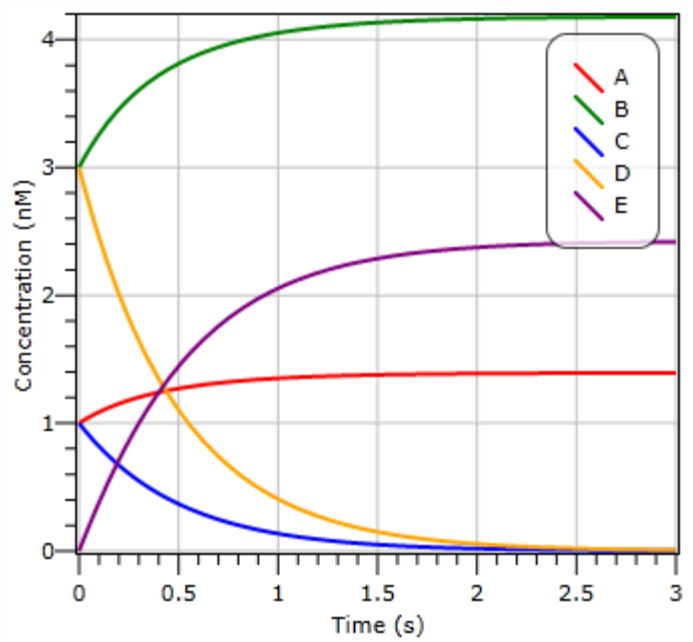
Behavior

```
directive sample 3.0 100
directive simulation deterministic
directive plot A; B; C; D; E

rate a = 1;
rate b = 2;

init A 1 |
init B 3 |
init C 1 |
init D 3 |
init E 0 |

A + C ->{a} C + E |
B + C ->{a} C + E |
C ->{b} A |
D ->{b} B
```



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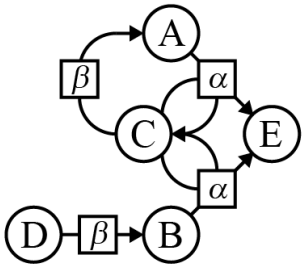
Network Bisimulation

A Bisimulation Approach

- For discrete transition systems
  - Nondeterministic: If two systems are in "equivalent" states, and one system can step from one state to another, then the other system can make a similar step and end up in an "equivalent" state. And vice-versa.
  - Stochastic: If two systems are in "equivalent" states, and one system can step from one state to an equivalence class of states (with some collective probability), then the other system can make a similar step and end up again in an "equivalent" equivalence class of states. And vice-versa.
  - Syntactic characterizations (bisimulation is definable over Process Algebras rather than their state spaces).
- For continuous transition systems
  - Continuous: If two systems are in "equivalent" states (e.g. identical states (BB), or up to sum of variables (FB)), and one system takes an infinitesimal step into another state, then the other system can take a similar infinitesimal step and end up in the "equivalent" state. And vice-versa.
  - Defined on traces: no syntactic characterization.
- What we contribute:
  - We define bisimulation (actually two of them) over a syntax for continuous transition systems, where the syntax is that of CRNs.
  - This allows us to both compare and minimize CRNs, via fast algorithms based on partition refinement (Tarjan - CONCUR) or theorem proving (Tarski - POPL).

Forward Bisimulation

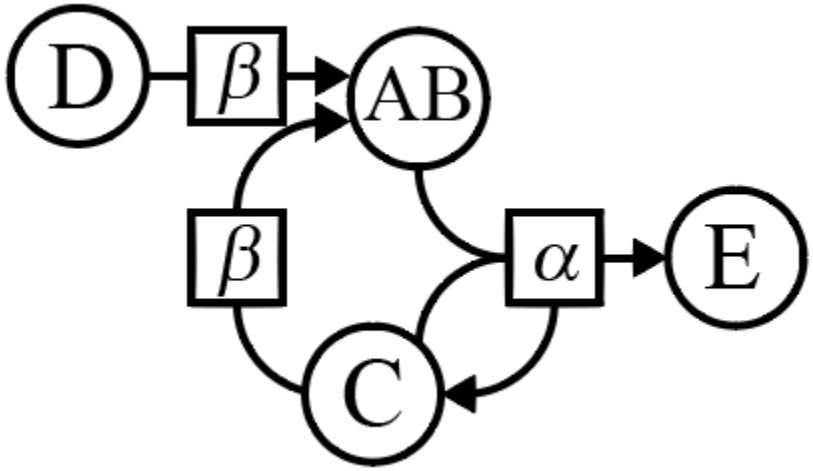
- Consider a partition (lumping) of species:
  {{A, B}, {C}, {D}, {E}}
- It may induce a collapse of the CRN:



$AB + C \xrightarrow{\alpha} C + E$

$C \xrightarrow{\beta} AB$

$D \xrightarrow{\beta} AB$



In the sense that AB represents A+B

Reduction works for that partition

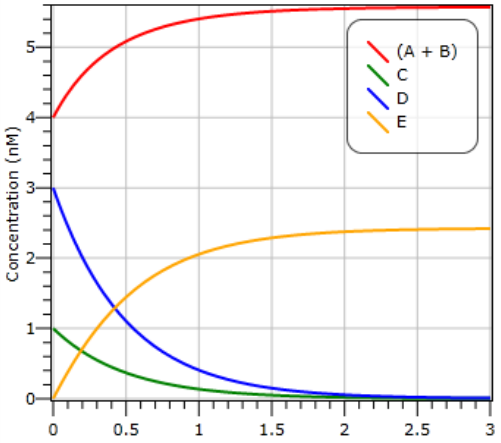
Original CRN, plotting A+B

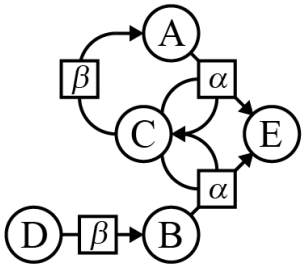
```
directive sample 3.0 100
directive simulation deterministic
directive plot sum(A; B); C; D; E

rate a = 1;
rate b = 2;

init A 1 |
init B 3 |
init C 1 |
init D 3 |
init E 0 |

A + C ->{a} C + E |
B + C ->{a} C + E |
C ->{b} A |
D ->{b} B
```





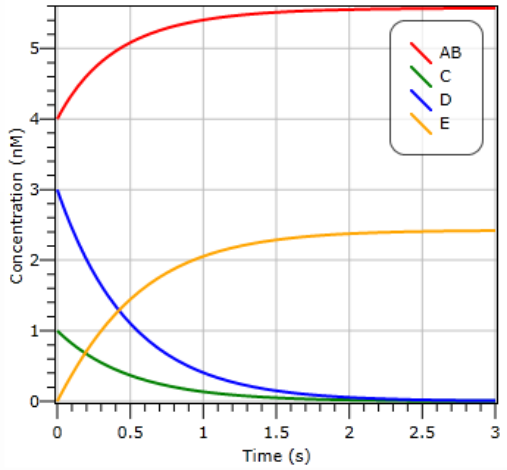
Reduced CRN with $AB_0 = A_0 + B_0$

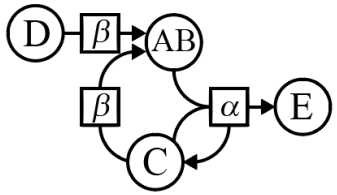
```
directive sample 3.0 100
directive simulation deterministic
directive plot AB; C; D; E

rate a = 1;
rate b = 2;

init AB 4 |
init C 1 |
init D 3 |
init E 0 |

AB + C ->{a} C + E |
C ->{b} AB |
D ->{b} AB
```





Because it works on the ODEs

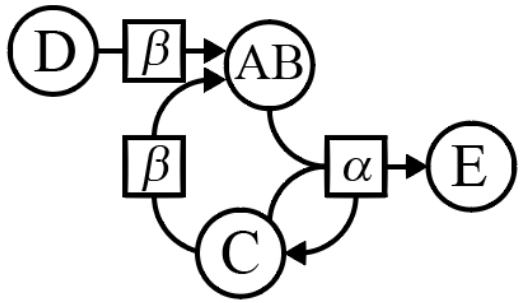
- We can consider AB = A + B and express the system just in terms of AB, dropping A and B

$$\dot{V}_{AB} = \dot{V}_A + \dot{V}_B = -\alpha V_{AB} V_C + \beta V_C + \beta V_D$$

$$\dot{V}_C = -\beta V_C$$

$$\dot{V}_D = -\beta V_D$$

$$\dot{V}_E = \alpha V_{AB} V_C$$



- And these are the ODEs of the reduced CRN

When does it work, in general?

- A partition H of the ODE (variables) is an (*ordinary-*) *lumping* if one can derive an ODE for the partition from the ODE of the original system, in terms of sums of the variables in the partition.

▶ **Definition 2** (Ordinary fluid lumpability). Let (S, R) be a CRN, F be its vector field, and $\mathcal{H} = \{H_1, \ldots, H_m\}$ a partition of S. Then, $\mathcal{H}$ is *ordinary fluid lumpable* if for all $H \in \mathcal{H}$ there exists a polynomial $\wp_H$ in $|\mathcal{H}|$ variables such that $\sum_{X \in H} F_X(V) = \wp_H(\sum_{X \in H_1} V_X, \ldots, \sum_{X \in H_m} V_X)$ for all $V \in \mathbb{R}^S_{\geq 0}$.

- Thm: A partition of CRN species that is a Forward Bisimulation is an ordinary lumping of the corresponding ODEs.

▶ **Theorem 11** (Forward bisimulation implies ordinary fluid lumpability). *Let (S, R) be a CRN. Then, $\mathcal{H}$ is an ordinarily fluid lumpable partition of S if $\mathcal{H}$ is an FB of S.*

- A partition of CRN species is a Forward Bisimulation if the fluxes of the CRN match up in a certain way (checkable just by looking at the CRN, not its ODEs):

▶ **Definition 7** (Reaction and production rates). Let (S, R) be a CRN, $X, Y \in S$, and $\rho \in \mathcal{MS}(S)$. The *ρ-reaction rate* of X, and the *ρ-production rate* of Y-elements by X are defined respectively as

$$\mathbf{crr}[X, \rho] := (\rho(X) + 1) \sum_{X + \rho \xrightarrow{\alpha} \pi \in R} \alpha, \qquad \mathbf{pr}(X, \rho, Y) := (\rho(X) + 1) \sum_{X + \rho \xrightarrow{\alpha} \pi \in R} \alpha \cdot \pi(Y)$$

Finally, for $H \subseteq S$ we define $\mathbf{pr}[X, \rho, H] := \sum_{Y \in H} \mathbf{pr}(X, \rho, Y)$.

▶ **Definition 8** (Forward CRN Bisimulation). Let (S, R) be a CRN, $\mathcal{R}$ an equivalence relation over S and $\mathcal{H} = S/\mathcal{R}$. Then, $\mathcal{R}$ is a forward CRN bisimulation (abbreviated FB) if for all $(X, Y) \in \mathcal{R}$, all $\rho \in \mathcal{MS}(S)$, and all $H \in \mathcal{H}$ it holds that

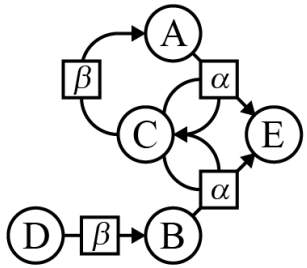
$$\mathbf{crr}[X, \rho] = \mathbf{crr}[Y, \rho] \quad \text{and} \quad \mathbf{pr}[X, \rho, H] = \mathbf{pr}[Y, \rho, H] \tag{1}$$

Forward and Backward Bisimulations for Chemical Reaction Networks.
Luca Cardelli, Mirco Tribastone, Max Tschaikowski, Andrea Vandin. [CONCUR'15]

Comparing Chemical Reaction Networks: A Categorical and Algorithmic Perspective.
Luca Cardelli, Mirco Tribastone, Max Tschaikowski, Andrea Vandin. [LICS'16]

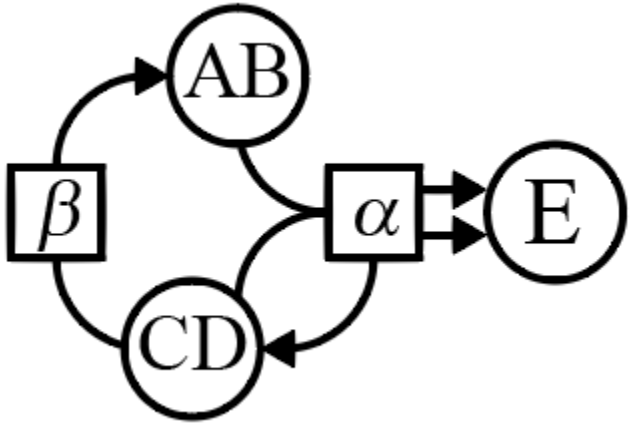
Backward Bisimulation

- Consider a partition (lumping) of species:
  {{A, B}, {C, D}, {E}}
- It may induce a collapse of the CRN:



$AB + CD \rightarrow^{\alpha} CD + 2E$

$CD \rightarrow^{\beta} AB$



In the sense that AB represents A *and* B *equally*

Reduction works for that partition

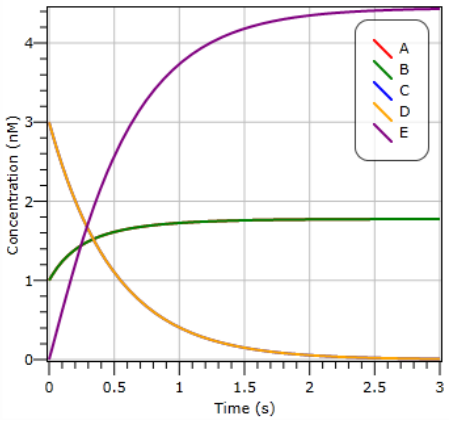
Original CRN, setting $A_0=B_0$, $C_0=D_0$

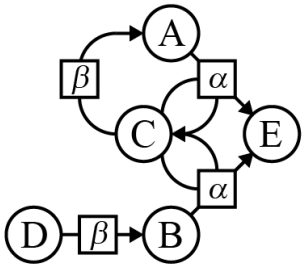
```
directive sample 3.0 100
directive simulation deterministic
directive plot A; B; C; D; E

rate a = 1;
rate b = 2;

init A 1 |
init B 1 |
init C 3 |
init D 3 |
init E 0 |

A + C ->{a} C + E |
B + C ->{a} C + E |
C ->{b} A |
D ->{b} B
```





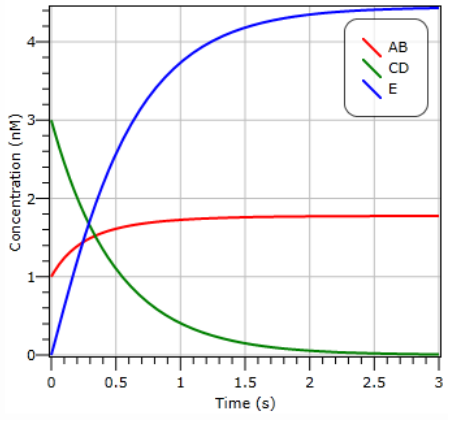
Reduced CRN with $AB_0=A_0=B_0$, $CD_0=C_0=D_0$

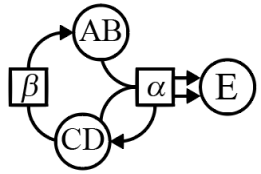
```
directive sample 3.0 100
directive simulation deterministic

rate a = 1;
rate b = 2;

init AB 1 |
init CD 3 |
init E 0 |

AB + CD ->{a} CD  + 2 E |
CD ->{b} AB
```



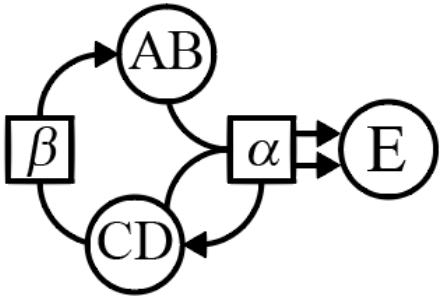


Because it works on the ODEs

- If $V_A(0) = V_B(0)$ and $V_C(0) = V_D(0)$ then $V_A(t) = V_B(t)$ and $V_C(t) = V_D(t)$

$$\dot{V}_A = -\alpha V_A V_C + \beta V_C$$
$$\dot{V}_B = -\alpha V_B V_C + \beta V_D$$
$$\dot{V}_C = -\beta V_C$$
$$\dot{V}_D = -\beta V_D$$
$$\dot{V}_E = \alpha V_A V_C + \alpha V_B V_C$$

$$\dot{V}_A = -\alpha V_A V_C + \beta V_C$$
$$\dot{V}_C = -\beta V_C$$
$$\dot{V}_E = 2\alpha V_A V_C$$



- And these are the ODEs of the reduced CRN

When does it work, in general?

- A partition H of the ODE (variables) is an (*exact-*) *lumping* if the derivatives are equal in each partition whenever the concentrations are equal in each partition.

► **Definition 4** (Exact fluid lumpability). Let (S, R) be a CRN, F its vector field, and $\mathcal{H}$ a partition of S. We call $V \in \mathbb{R}^S$ *constant on* $\mathcal{H}$ if $V_{X_i} = V_{X_j}$ for all $H \in \mathcal{H}$, and all $X_i, X_j \in H$. Then, $\mathcal{H}$ is *exactly fluid lumpable* if $F(V)$ is constant on $\mathcal{H}$ whenever V is constant on $\mathcal{H}$.

- Thm: A partition of CRN species that is a Backward Bisimulation is an exact lumping of the corresponding ODEs.

► **Theorem 17** (Backward bisimulation characterizes exact fluid lumpability). *Let (S, R) be a CRN. Then, $\mathcal{H}$ is an exactly fluid lumpable partition of S if and only if $\mathcal{H}$ is a BB of S.*

- A partition of CRN species is a Backward Bisimulation if the fluxes of the CRN match up in a certain way (checkable just by looking at the CRN, not its ODEs):

► **Definition 13** (Cumulative flux rate). Let (S, R) be a CRN, $X \in S$, $\rho \in \mathcal{MS}(S)$, and $\mathcal{M} \subseteq \mathcal{MS}(S)$. Then, we define

$$\mathbf{fr}(X, \rho) := \sum_{\rho \xrightarrow{\alpha} \pi \in R} (\pi(X) - \rho(X)) \cdot \alpha, \qquad \mathbf{fr}[X, \mathcal{M}] := \sum_{\rho \in \mathcal{M}} \mathbf{fr}(X, \rho).$$

We call $\mathbf{fr}(X, \rho)$ and $\mathbf{fr}[X, \mathcal{M}]$ *ρ-flux rate* and *cumulative $\mathcal{M}$-flux rate* of X, respectively.

► **Definition 14** (Backward CRN bisimulation). Let (S, R) be a CRN, $\mathcal{R}$ an equivalence relation over S, $\mathcal{H} = S/\mathcal{R}$ and μ the choice function of $\mathcal{H}$. Then, $\mathcal{R}$ is a backward CRN bisimulation (BB) if for any $(X, Y) \in \mathcal{R}$ it holds that

$$\mathbf{fr}[X, \mathcal{M}] = \mathbf{fr}[Y, \mathcal{M}] \quad \text{for all} \quad \mathcal{M} \in \{\rho \mid \rho \xrightarrow{\alpha} \pi \in R\}/\approx_{\mathcal{H}}, \tag{2}$$

where any two $\rho, \sigma \in \mathcal{MS}(S)$ satisfy $\rho \approx_{\mathcal{H}} \sigma$ if $\mu(\rho) = \mu(\sigma)$.

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Comparing Chemical Reaction Networks: A Categorical and Algorithmic Perspective.
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Applications of Bisimulation

- Model Reduction
  - Find reduced networks
  - Compute quotient CRNs
  - Find network symmetries that may be of biological interest
- Morphism Generation
  - Find morphisms between networks (e.g. all the ones for a fixed rate assignment)

Benchmarks from
Sneddon et al., Nature Methods, 2011

Model	Reactions	Species	FB	Time (s)	BB	Time (s)
e9	3538944	262146	222	4.61E+4	222	7.65E+4
e8	786432	65538	167	1.92E+3	167	3.68E+3
e7	172032	16386	122	8.15E+1	122	1.77E+2
e6	36864	4098	86	3.00E+0	86	7.29E+0
e5	7680	1026	58	1.54E-1	58	4.06E-1
e4	1536	258	37	9.00E-3	37	1.09E-1
e3	288	66	22	1.00E-3	22	3.00E-3
e2	48	18	12	1.00E-3	12	2.00E-3

Aggregation reduction | Emulation reduction

How does it work?

- Partition refinement!
  - Start from the coarsest partition: {{A, B, C, D, E}}
  - Thm: There is always a coarsest FB or BB partition
  - Find a reason why that partition is *not* an FB or BB (e.g., ask Z3)
  - Split the partition: {{A, B, C}, {D, E}} (this is the clever part)
  - Iterate
  - In the worst case we end up with {{A}, {B}, {C}, {D}, {E}}
- Customizable
  - If we know that we want to observe A separately, we can start the algorithm e.g. with the partition {{A}, {B, C, D, E}}

Microsoft Research

Finding Network Bisimulations by Theorem Proving for "general" kinetics

Differential Equations

- Linear ODE systems
  - Control theory
  - Electrical engineering
  - Kolmogorov equation for Continuous Time Markov Chains
    a.k.a. the *Chemical Master Equation* for discrete (-molecule count) chemistry
- Nonlinear ODE systems
  - Quantitative models of computing:
    (continuous) Petri Nets, (mean-field) PEPA, …
  - Chemical Reaction Networks for continuous (-concentration) chemistry
    (with Mass Action or with Hill kinetics)

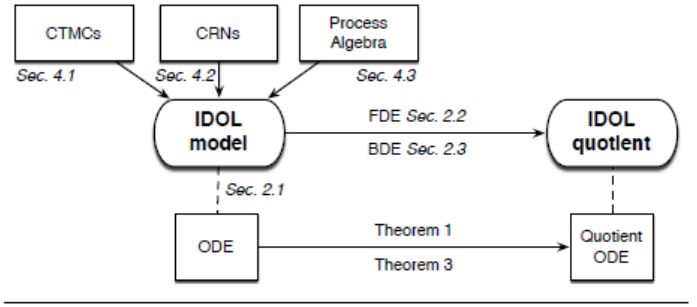


Figure 1. Paper overview.

IDOL: Intermediate Drift-Oriented Language

$$p ::= \varepsilon \mid \dot{x}_i = f,\ p \qquad\qquad n, m \in \mathbb{Z}\ and\ m \neq 0$$

$$f ::= n \mid x_i \mid f + f \mid f \cdot f \mid f^{\frac{1}{m}}$$

- Each IDOL program is a list of variable drifts $\dot{x}_i = f$
- The semantics is:

$$[\![x]\!]_c^p : [0;T] \to \mathbb{R}^{\mathcal{V}_p} \qquad [\![x_i]\!]_c^p(t) = \hat{\sigma}(x_i) + \int_0^t [\![f_i]\!]_c^p([\![x]\!]_c^p(s))ds$$

  - where p is the full program, $c = (T, \hat{\sigma})$ is the time horizon and initial conditions. and x is the vector of all the x_i.
  - Provided there is a unique solution (there are sufficient conditions for that).

We <3 Tarski

- IDOL is within Tarski's decidable fragment of reals
  - The Law of Mass action has drifts like $x_1 \cdot x_2$
  - Hill kinetics has drifts like $x_1^2/(1+x_1^2)$
  - PEPA uses drifts like $\min(x_1, x_2) := \frac{1}{2}(x_1 + x_2 - |x_1 - x_2|), \quad \text{with } |x| := (x \cdot x)^{\frac{1}{2}}$

    where $y = x^{\frac{1}{2}} = \exists y(y^2 = x)$
  - No trigonometry, no exponentials, etc. in our ODEs.

- Bisimulations over CRNs [CONCUR'15]
  - Are also formulas within Tarski's fragment.

Differential Equivalence Relations

- We encode equivalences over IDOL programs
  - As first-order logic formulas containing IDOL terms.
- Z3 has a solver for them

  D. Jovanovic and L. M. de Moura. Solving non-linear arithmetic. In *IJCAR*, pages 339–354, 2012.
- We use Z3 to minimize ODE (IDOL) systems
  - And, indirectly, to minimize Chemical Reaction Networks
  - On biological networks, Z3 is often faster than specialized polynomial algorithms!
- For Backward Bisimulation in particular:
  - We use a counter-example guided partition refinement algorithm.
- The IDOL solver uses Z3 as a subroutine
  - Possibly iteratively, e.g. for counter-example guided partitioning

Benchmarks

Original model			*Largest FB*		*Largest FDE*	
Model	$\|R\|$	$\|S\|$	*Red.(s)*	*Size*	*Red.(s)*	*Size*
M1 [34, 70]	8620	745	6.54E–1	745	7.85E+3	105
M2 [34, 70]	3680	354	2.81E–1	354	3.22E+3	105
M3 [1]	4944	411	1.29E–1	411	6.46E+2	47
M4 [8]	3447	348	2.46E–1	348	5.22E+3	215

Table 1. FDE reduces more than forward bisimulation (FB).

Original model			*Reduction*		
Model	$\|R\|$	$\|S\|$	*BB (s)*	*BDE (s)*	$\|S\|$
M5 [70]	786432	65538	3.68E+3	1.01E+3	167
M6 [70]	172032	16386	1.77E+2	3.01E+2	122
M7 [70]	48	18	2.00E–3	6.00E–2	12
M8 [73]	194054	14531	1.32E+3	3.45E+3	6634
M9 [34, 70]	187468	10734	2.71E+2	1.57E+3	5575
M10 [22, 23]	5832	730	6.00E–1	3.22E+0	217
M11 [53]	487	85	6.00E–3	2.71E–1	56
M12 [18]	24	18	7.00E–3	5.20E–2	3

Table 2. BDE has runtimes similar to backward bisimulation (BB).

Automated model reduction for

- Continuous Time Markov Chains
  - By their forward Kolmogorov equation
- Chemical Reaction Networks
  - By their nonlinear ODE mass action kinetics
- Stochastic Process Algebra
  - Including PEPA, which has a min-based interaction law
- Chemical Master Equation
  - By the (linear) Kolmogorov equation
- Linear Control Systems
  - They are "just" linear ODEs
- Electronic Circuits
  - Kirchhoff's laws …

Just compile them to IDOL

Symbolic Computation of Differential Equivalences.
Luca Cardelli, Mirco Tribastone, Max Tschaikowski, Andrea Vandin [POPL'16]

Further improvements

- General theorem proving is very appealing
  - We can leave some model components undefined or underconstrained, and let Z3 "figure them out".
- Still, specialized algorithms can do better
  - By using a version of Tarjan's Partition Refinement algorithm, we are getting amazing speedups in the computation of bisimulations for bimolecular CRNs.

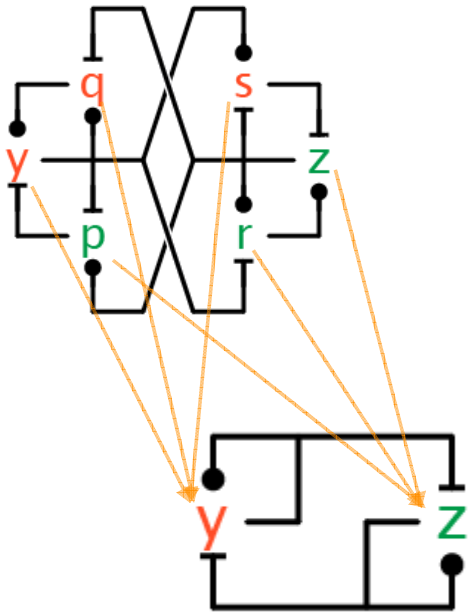
Efficient Syntax-Driven Lumping of Differential Equations.
Luca Cardelli, Mirco Tribastone, Max Tschaikowski, Andrea Vandin [TACAS'16]

Microsoft Research

Morphisms of Antagonistic Networks

Bisimulations (partitions) of 1 network, vs. Morphisms (mappings) between 2 networks

- A morphism between two CRNs that preserves traces can be understood as a (backward) bisimulation over the species of a "union CRN".
- Conversely, from a (many-to-one, backward) bisimulation we can reconstruct a canonical morphism between two networks.

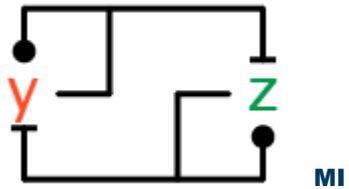


- Such a bisimulation is called an emulation morphism: one network can exactly reproduce all the traces of the other network.

Antagonistic Networks

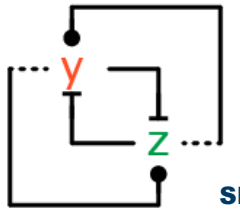
activation
inhibition

1 vs. 1
Mutual Inhibition & Self Activation



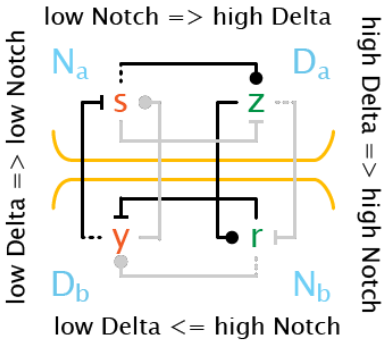
MI

1 vs. 1
Mutual Inhibition & Mutual Anti-activation

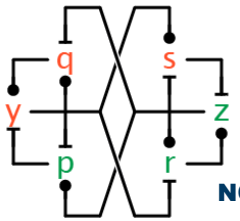


SI

2 vs. 2

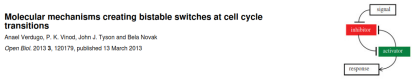


3 vs. 3



NCC

Cell cycle transitions

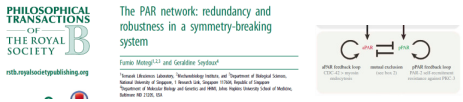


Molecular mechanisms creating bistable switches at cell cycle transitions

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

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

Polarity establishment



PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B

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

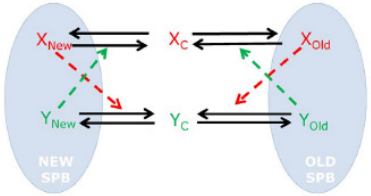
rstb.royalsocietypublishing.org

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

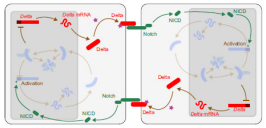


Dynamics of SIN Asymmetry Establishment

Archana Bajpai[1], Anna Fookstsova[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]*

PLOS Computational Biology | www.ploscompbiol.org

Delta-Notch



Patterning embryos with oscillations: structure, function and dynamics of the vertebrate segmentation clock

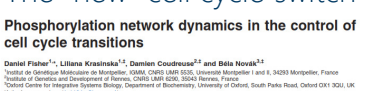
Andrew C. Oates[1,3], Luis G. Morelli[1,2] and Saúl Ares[3,4,*]

Lateral Inhibition through Delta-Notch Signaling: A Piecewise Affine Hybrid Model*

Ronojoy Ghosh and Claire J. Tomlin

M.D. Di Benedetto, A. Sangiovanni-Vincentelli (Eds.): HSCC 2001, LNCS 2034, pp. 232–246, 2001.
© Springer-Verlag Berlin Heidelberg 2001

The "new" cell cycle switch

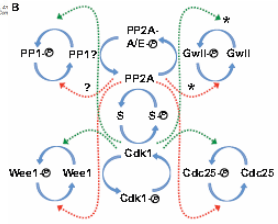


Phosphorylation network dynamics in the control of cell cycle transitions

Daniel Fisher[1,*], Liliana Krasinska[1,2], Damien Coudreuse[3,4] and Béla Novák[1,2]

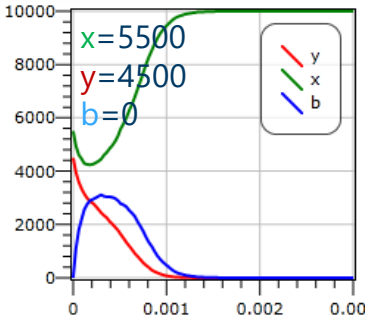
[1]Institut de Génétique Moléculaire de Montpellier, IGMM, CNRS UMR 5535, Université Montpellier I and II, 34293 Montpellier, France
[2]Institute of Genetics and Development of Rennes, CNRS UMR 6290, 35043 Rennes, France
[3]Oxford Centre for Integrative Systems Biology, Department of Biochemistry, University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

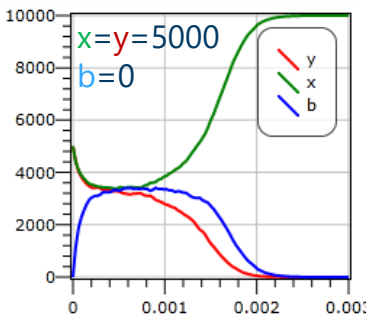
Journal of Cell Science 122, 419–423 © 2012. Published by The Company of Biologists Ltd doi: 10.1242/jcs.106351



A Consensus Algorithm

- Approximate Majority (AM) Algorithm
  - Uses a third "undecided" population b
  - Disagreements cause agents to become undecided
  - Undecided agents agree with any non-undecided agent

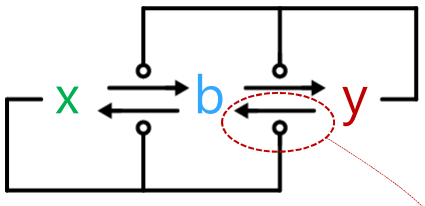




Dana Angluin · James Aspnes · David Eisenstat

A Simple Population Protocol for Fast Robust Approximate Majority

catalysis



chemical reaction network

$x + y \to^r y + b$

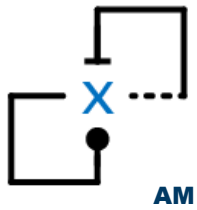
$y + x \to^r x + b$

$b + x \to^r x + x$

$b + y \to^r y + y$

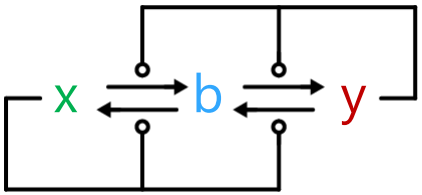
activation

inhibition



A Biological Implementation

Approximate Majority (AM)



1) Bistable
   Even when initially x=y (stochastically)

2) Fast (asymptotically optimal)
   O(*log n*) convergence time

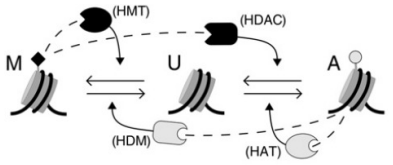
3) Robust to perturbation
   above a threshold, initial majority wins *whp*

Dana Angluin · James Aspnes · David Eisenstat

A Simple Population Protocol for Fast Robust Approximate Majority

2007

Epigenetic Switch



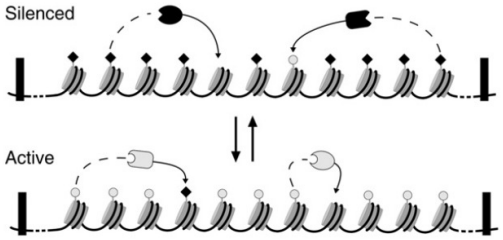
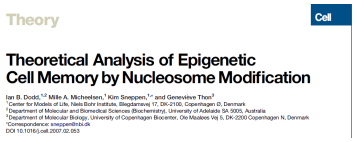


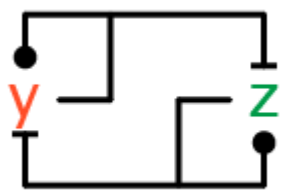
Figure 1. Basic Ingredients of the Model



2007

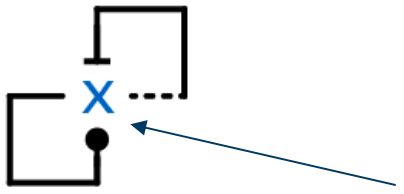
Network Emulation MI emulates AM

- 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**:



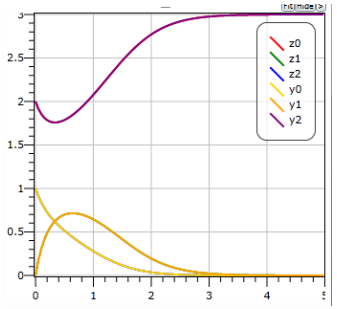
MI

~y,z⇢ x

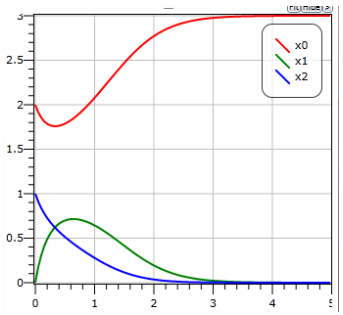


AM

(3 species)



(6 species on 3 trajectories)



(3 species on 3 trajectories)

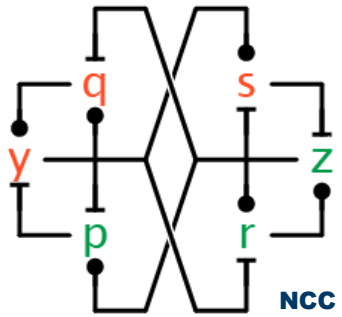
initialize:
z = x
~y = x

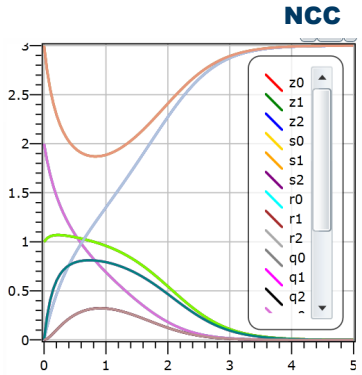
($y_2 = x_0$
$y_1 = x_1$
$y_0 = x_0$)

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

Network Emulation: NCC emulates MI

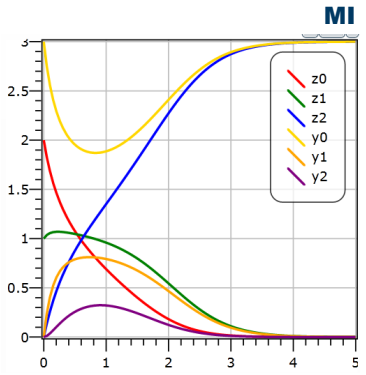
- For *any* rates and initial conditions of MI we can find *some* rates and initial conditions of NCC such that the (18) trajectories of NCC retrace those (6) of MI





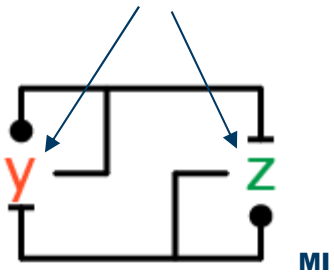
(18 species on 6 trajectories)

z,r,p ⇢ z
y,q,s ⇢ y



(6 species on 6 trajectories)

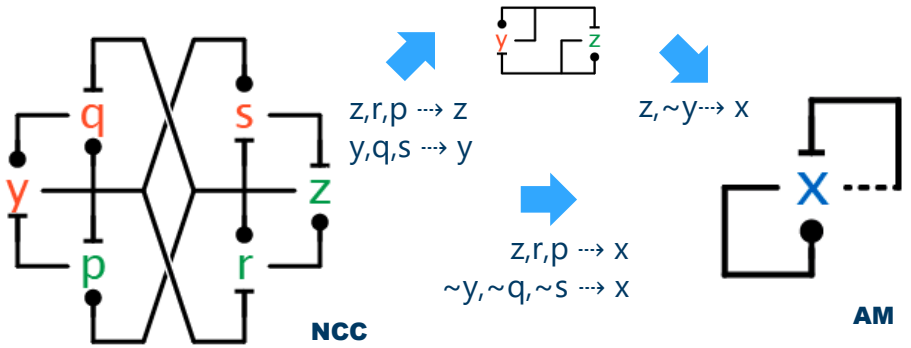
(3 species each)

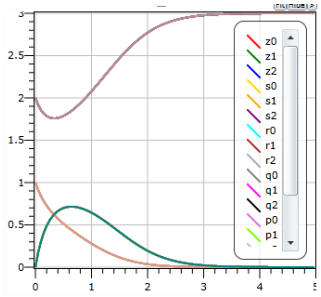


initialize
z,r,p = z
y,q,s = y

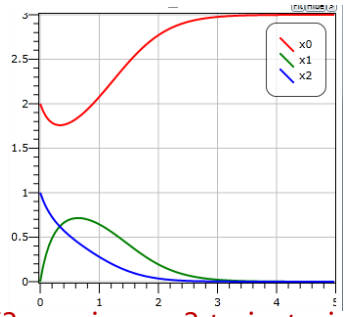
Emulations Compose

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





(18 species on 3 trajectories)



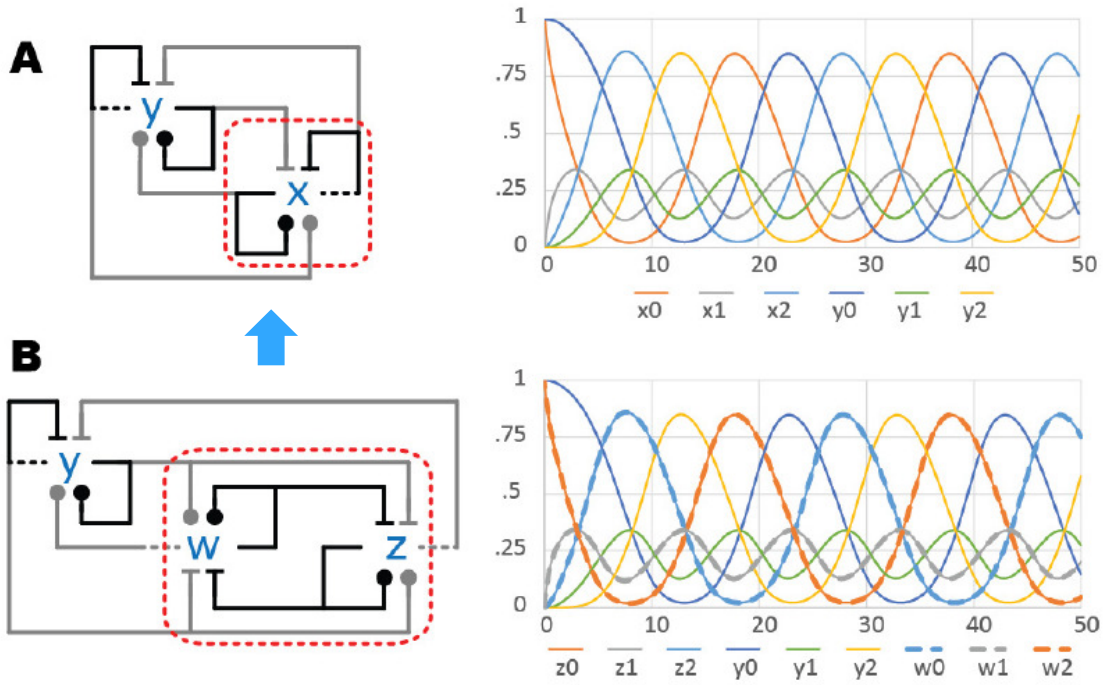
(3 species on 3 trajectories)

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

For *any* initial conditions of AM.

And for *any* rates of AM.

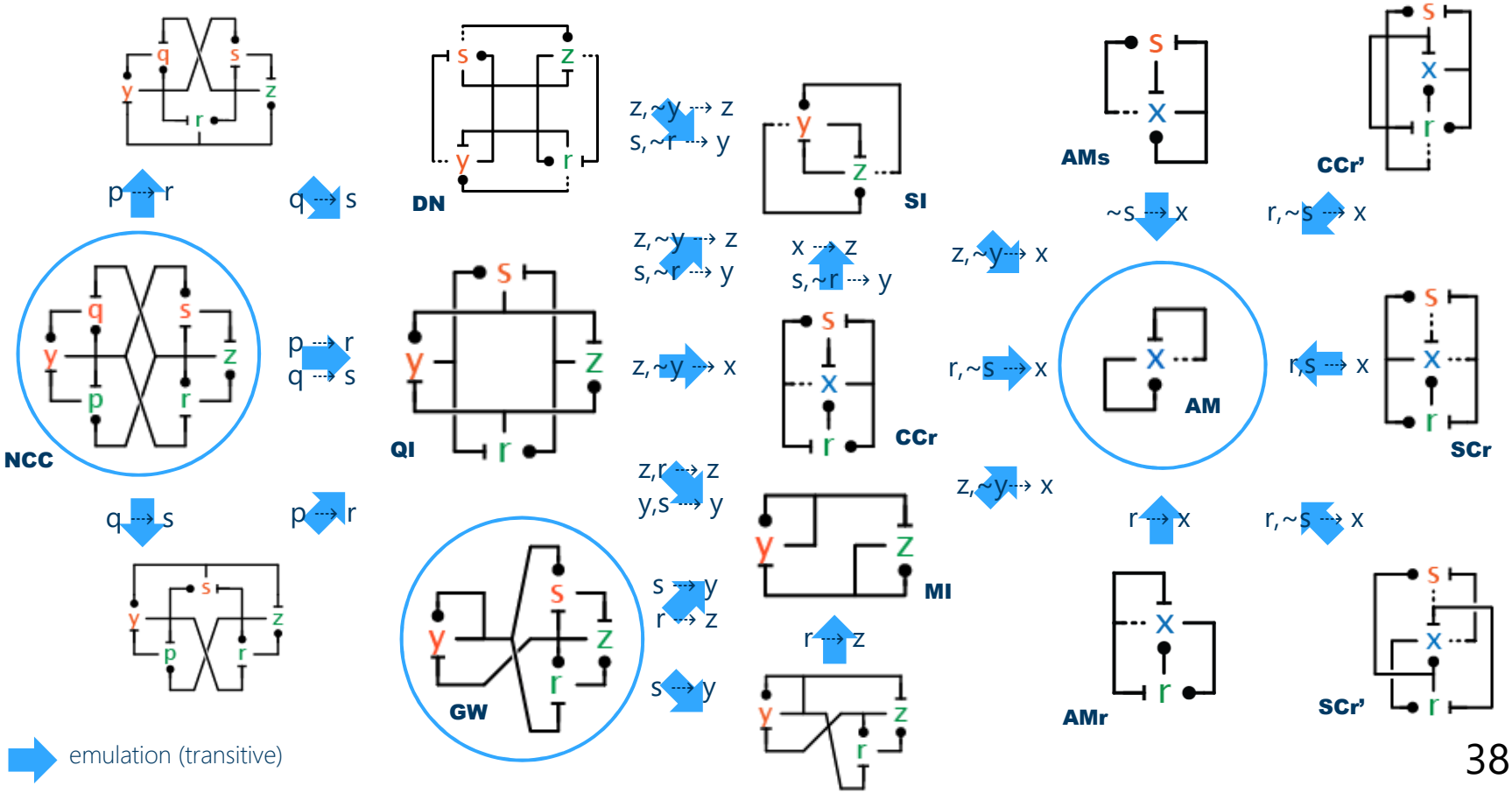
Emulations are Modular



How to check for emulation

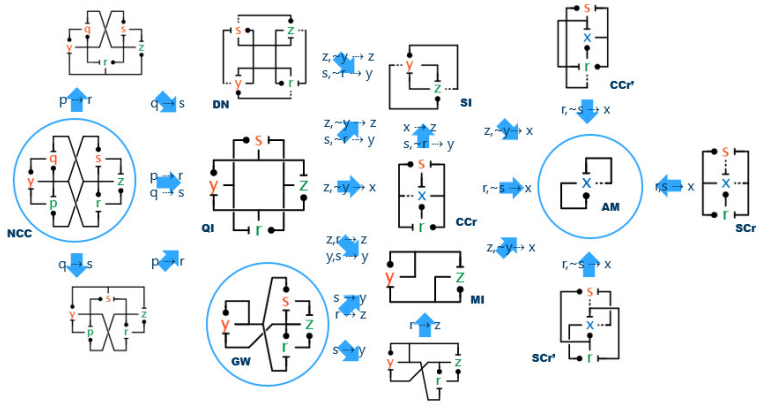
- How do we check a potential emulation morphism for all possible initial conditions of the target?
  - Statically! Check conditions on the joint stoichiometric matrices of the two networks under the mapping.
- How do we check a potential emulation morphism for all possible rates of the target?
  - Can't; but if one emulation is found, then the rates of the target network can be changed *arbitrarily* and a related emulation will again exist.

Emulation Zoo



Biological 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)



Network Emulation Morphism FAQ

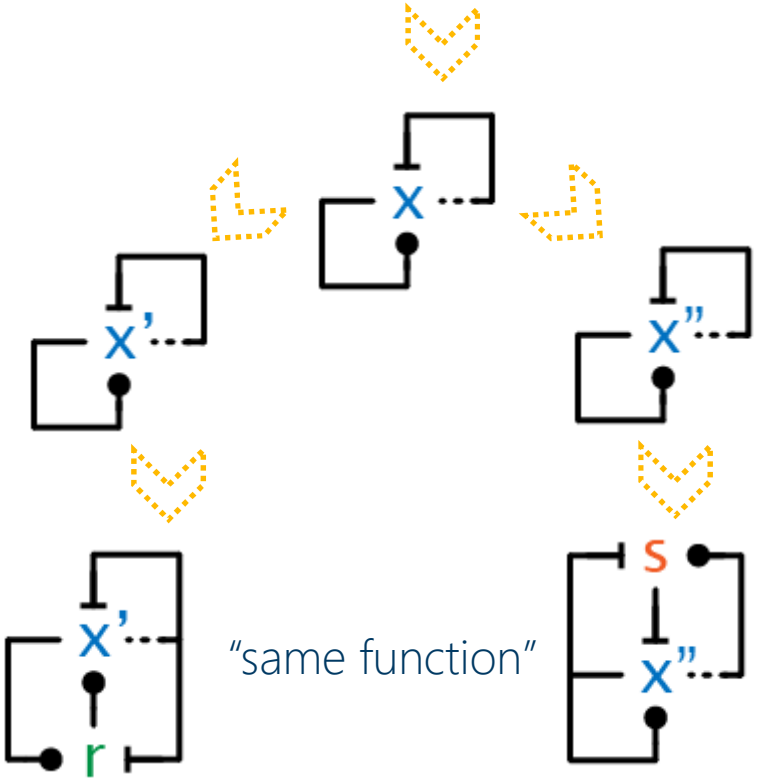
- What guarantees emulation?
  - Reactant morphism + stoichiomorphism: static, state-independent (*structural*) conditions
- How do you find them?
  - Emulation Theorem => they do not depend on initial conditions
  - Change of Rates Theorem => can look for rate-1 morphisms
  - E.g. test all possible 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?

Microsoft Research

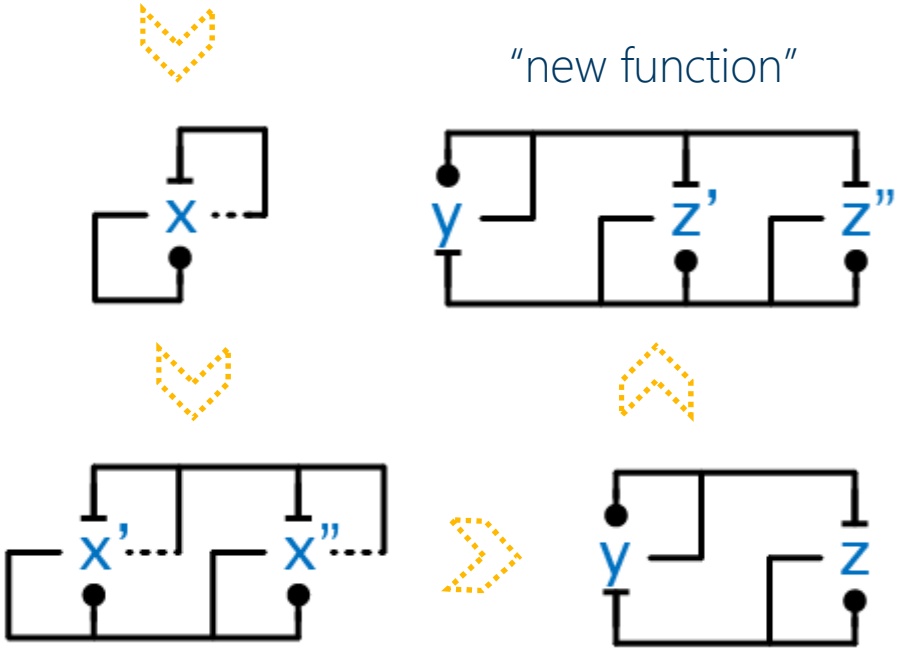
Network Morphisms as Evolutionary Paths

Network Evolution

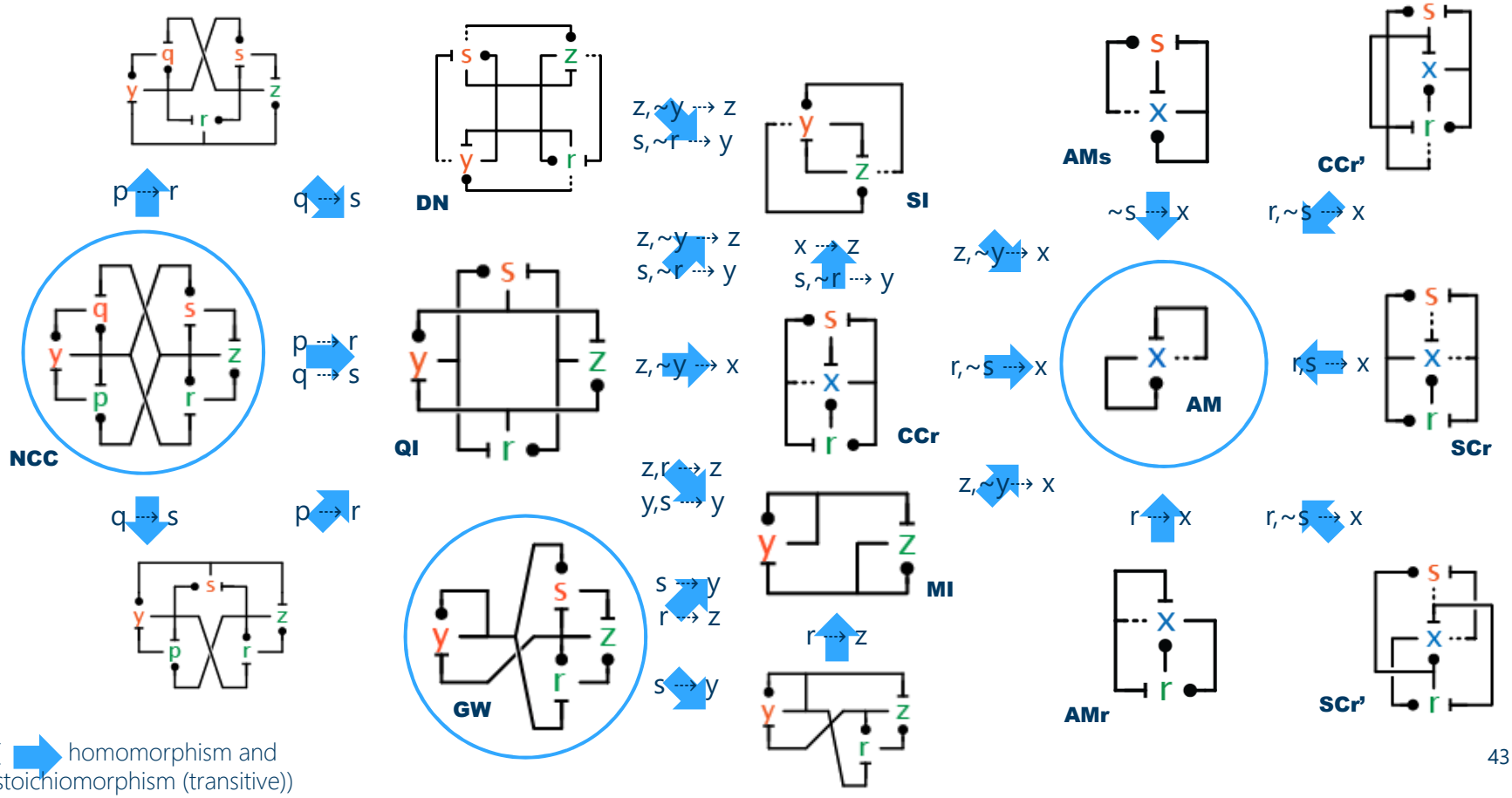
Across species: *Ortholog genes*



Within species: *Paralog genes*

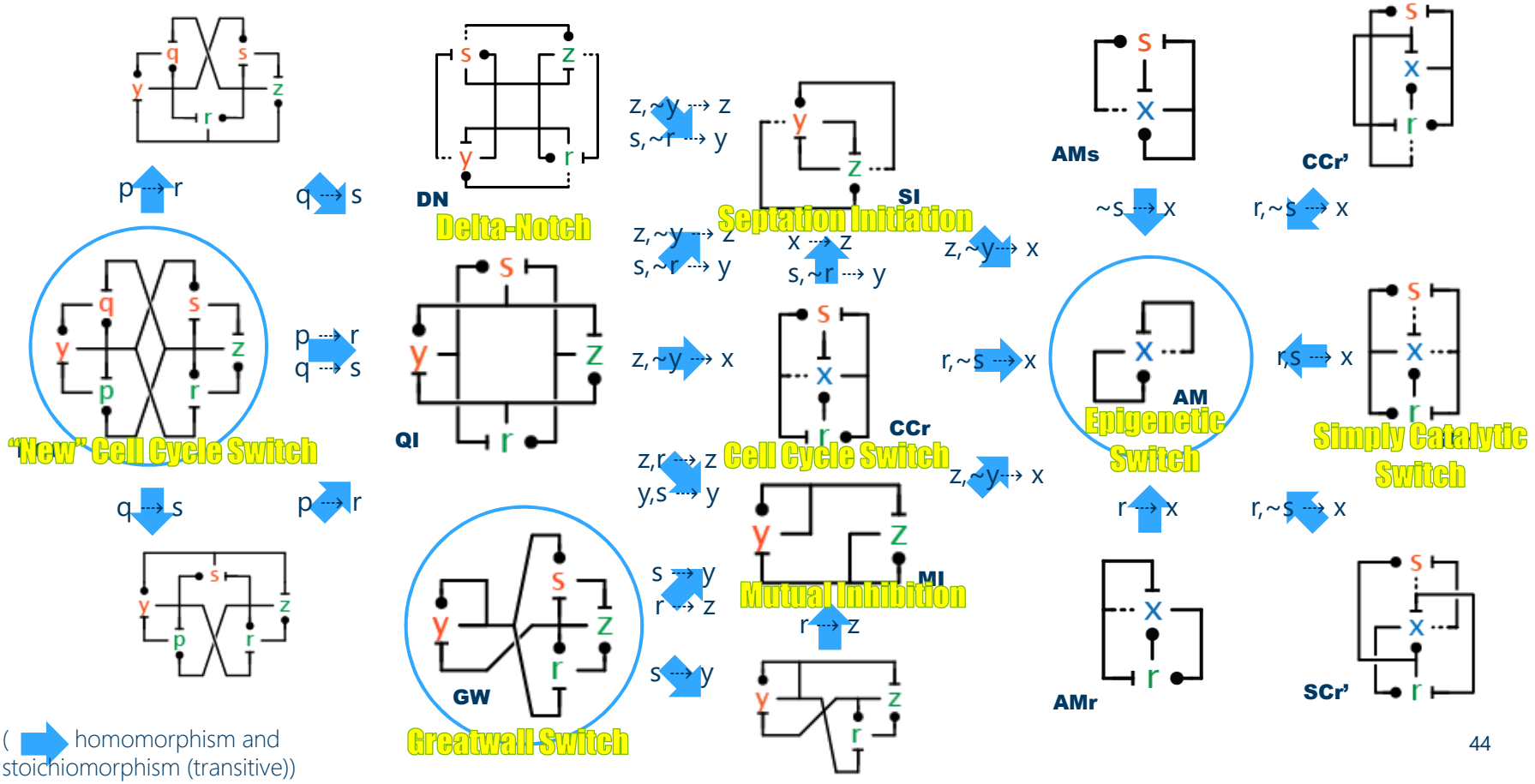


Walks in Network Space



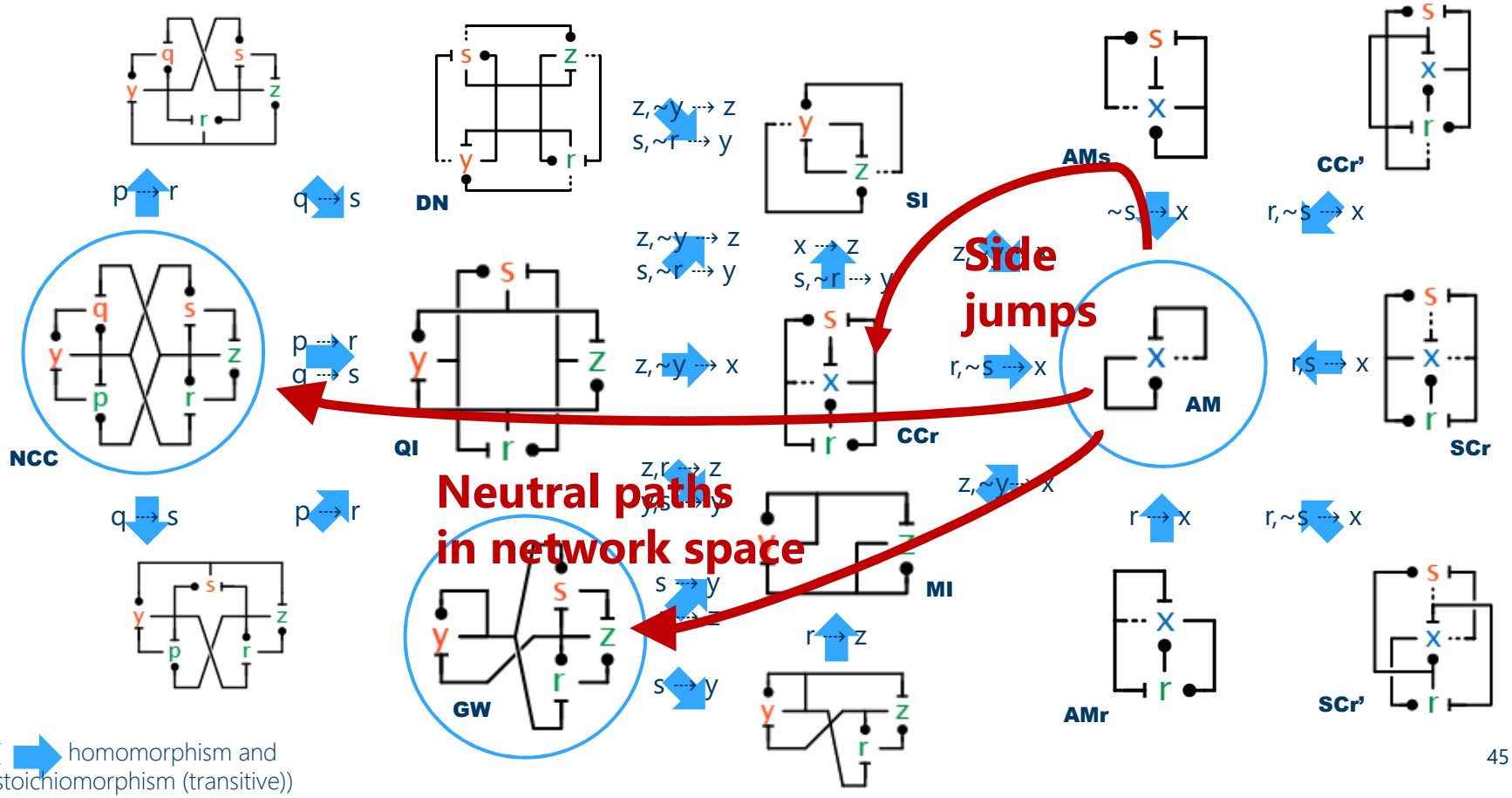
(⇢ homomorphism and stoichiomorphism (transitive))

Walks in Network Space



(➡ homomorphism and stoichiomorphism (transitive))

Walks in Network Space

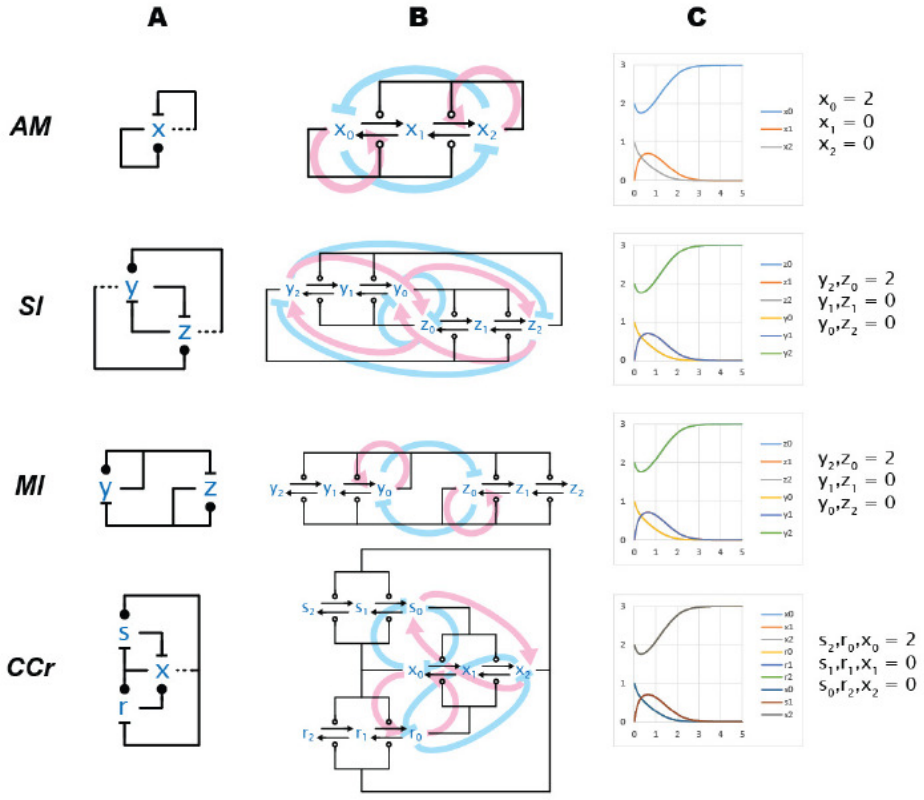


(homomorphism and stoichiomorphism (transitive))

Microsoft Research

Noise Reduction in Biochemical Switches

Basic Switches (deterministic)



(A) Influence network diagrams

(B) Chemical reaction network diagrams and feedback loops

(C) Numerical solutions of the deterministic kinetics of the networks:
Horizontal axis is time
Vertical axis is species concentration

First some arbitrary initial conditions are chosen for AM.

Then the initial conditions of the other networks are chosen in such a way that each trace of each of the other networks retraces exactly one trace of AM.

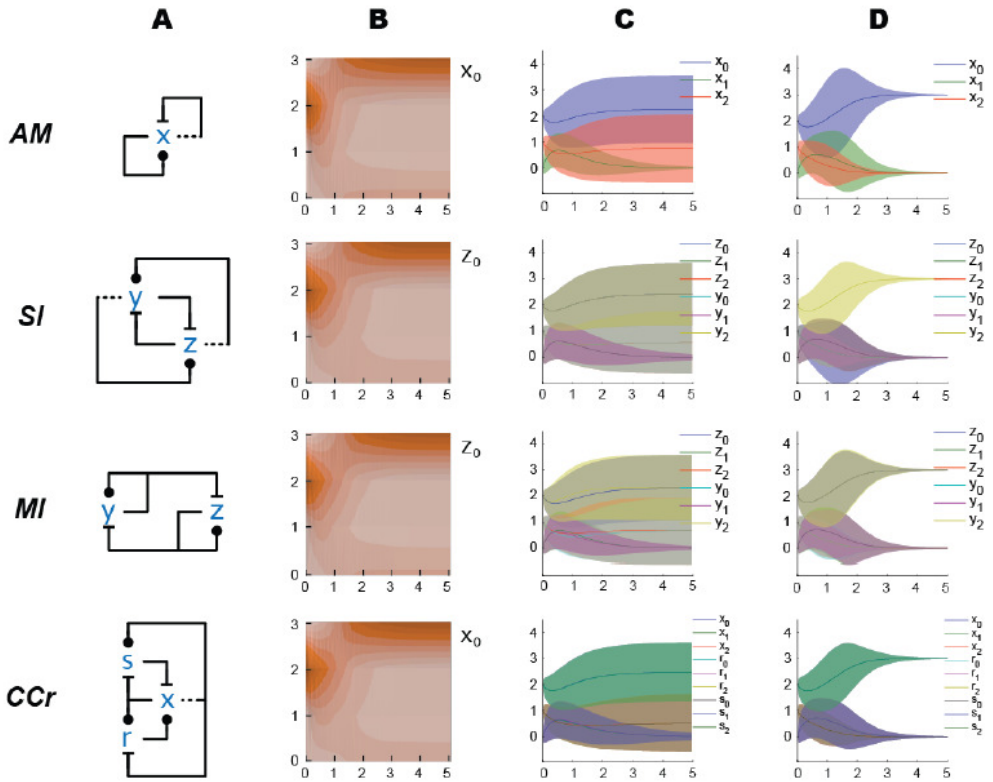
This can be done for any initial conditions chosen for AM, and indicates the potential of each of the other networks to operate as a simpler switch.

Noise Reduction in Complex Biological Switches

Luca Cardelli[1,2,¶,*], Attila Csikász-Nagy[3,4,¶], Neil Dalchau[1,¶], Mirco Tribastone[5,¶], Max Tschaikowski[5,¶]

(To appear.)

Basic Switches (stochastic)



Horizontal axes is time

Vertical axes is number of molecules.

(A) Influence networks.

(B) Chemical Master Equation solution: probability distribution, with color (in 10 bands from light = 0 to dark = 1) indicating the probability that at time t there are y molecules of the single indicated species.

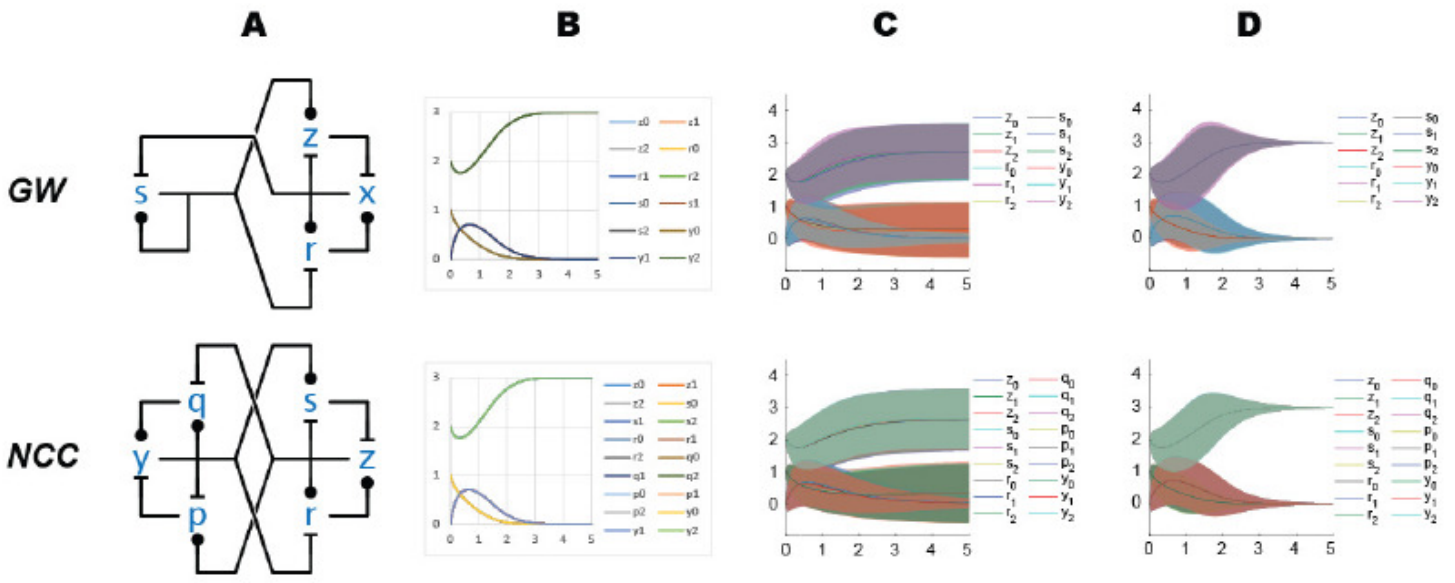
(C) Chemical Master Equation solution: mean (solid lines) and standard deviation (color bands) for the species in the network.

(D) Central Limit Approximation solution: mean (solid lines) and standard deviation (color bands) for the species in the network.

Disentangle the contribution of complexity to stochasticity

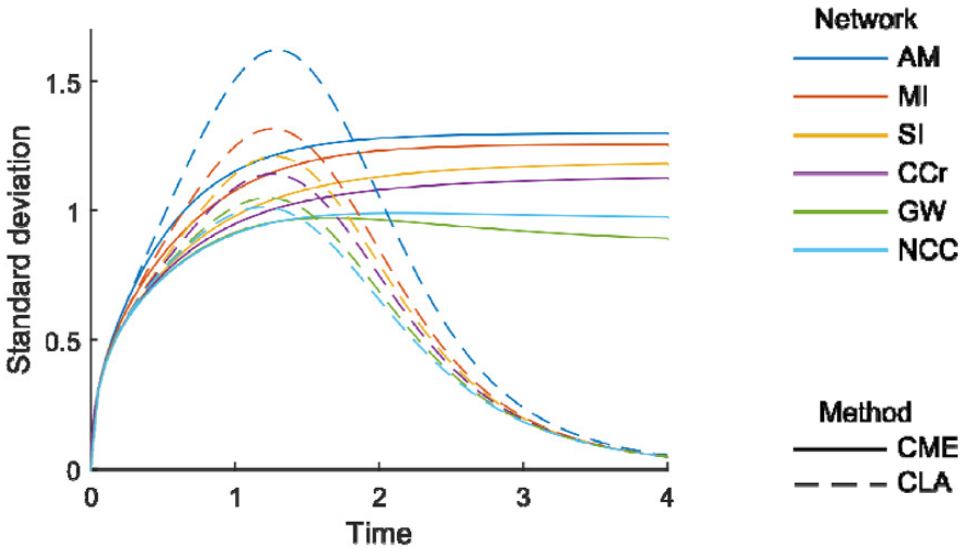
Compare network noise on the baseline of deterministic emulation, across networks of different size and structure

More Complex Switches



Horizontal axes are time, vertical axes are number of molecules.
(A) Influence networks.
(B) ODE solutions for comparison
(C) Chemical Master Equation solution: mean (solid lines) and standard deviation (color bands) for the species in the network.
(D) Central Limit Approximation solution: mean (black lines) and standard deviation (color bands) for the species in the network.

Intrinsic Noise



Complexity improves overall performance of the cell cycle switch. The performance of different networks was evaluated by calculating the standard deviation of the main molecular states over time.
Standard deviations are calculated via numerical integration of the chemical master equation (CME) using the Visual GEC software, and via numerical integration of the central limit approximation (CLA) in Matlab.

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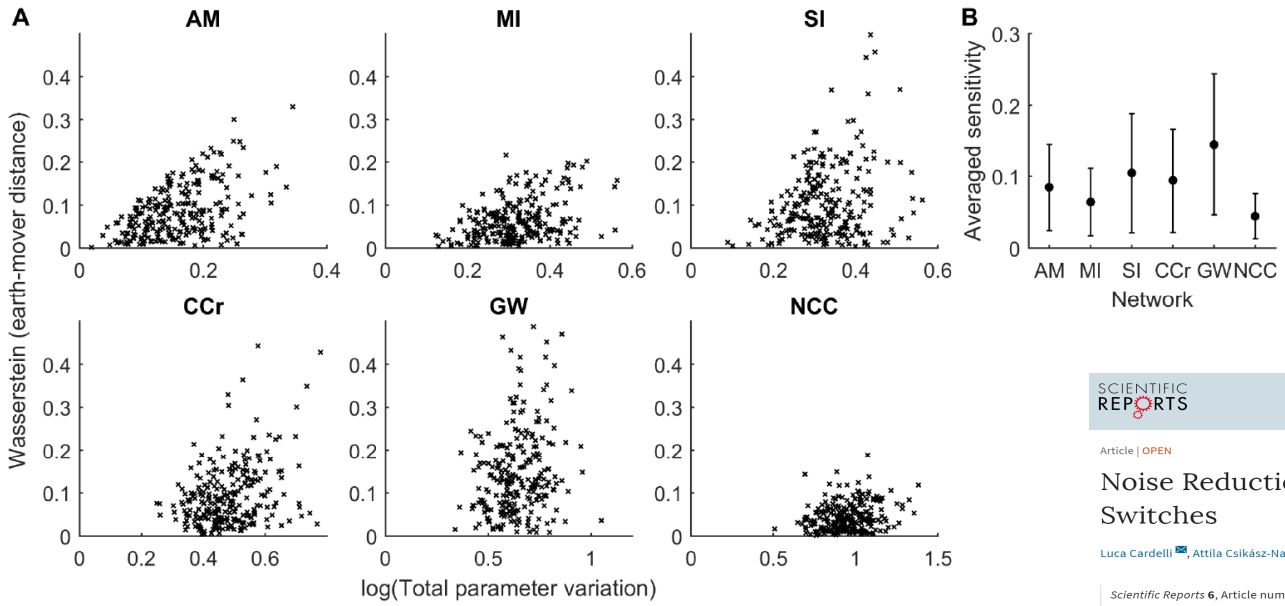
Extrinsic Noise



MI and SI have the same number of species and reactions.

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Complexity *can* confer robustness to extrinsic noise.

Extrinsic noise is introduced by randomly perturbing all the reaction rates (separately but from the same distribution) of each model. (So the total variation in more complex models is actually *higher*.)

Variations in network behaviour is assessed in comparison to the default parameters, in which allr eaction rates are set equal to 1.

Network variation is quantified using the summed Wasserstein metric over the whole probability distribution over time.

Noise vs. Complexity

- With corresponding initial conditions, all studied networks show the same mean behavior
- CCr emulating AM is the simplest explanation of the core cell cycle switching function
- Many other biological switches can be so reduced to an algorithm with well-understood properties
- On the basis of kinetic similarity of mean behavior, we show variations in noise behavior (both intrinsic and extrinsic).
- Noise tends to decrease with complexity, but this also depends on network structure and *not* directly on total molecular counts

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Conclusions

Computational Methods

- Comparing Networks
  - Explanation of network structure (*how* functionality is achieved)
- Network Bisimulations (and Morphisms)
  - Feasible for large networks by partition refinement algorithms
- Finding Bisimulations by Theorem Proving
  - Also feasible for large networks by "magical" theorem proving
  - Supports kinetics other than mass action

Systems Biology

- Morphisms of Antagonistic Networks
  - Entail deep properties of complex networks (bistability, optimality)
- Network Morphisms as Evolutionary Paths
  - Neutral paths in network space
- Noise Reduction in Complex Biochemical Switches
  - Deterministic morphisms as a baseline for making stochastic comparisons between networks of different sizes