

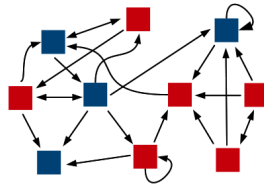
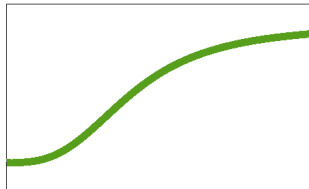
Boolean versus continuous dynamics on small and large model networks



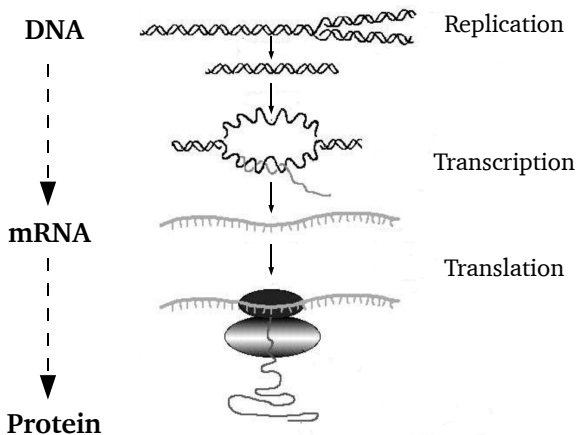
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VS.

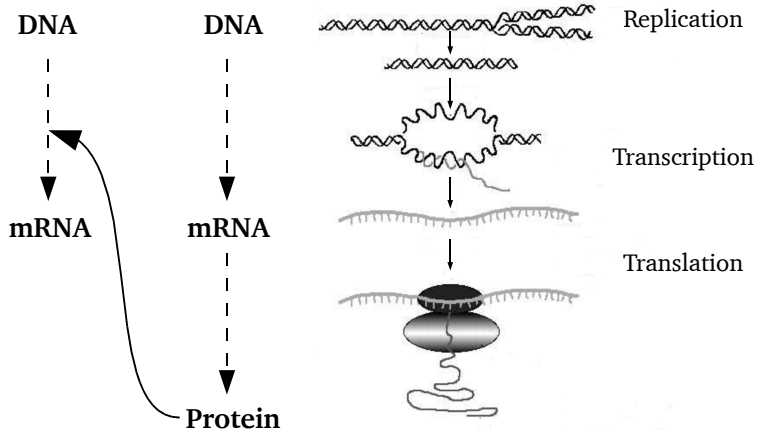


Biological background: Gene regulatory networks



based on: D. Del Vecchio & E. Sontag
Dynamics and Control of Synthetic Bio-molecular Networks
Proceedings of American Control Conference, 2007

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- Toy-model: on-off states
- Parallel update
- Deterministic dynamics

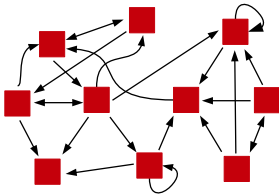
- Toy-model: on-off states
- Parallel update
- Deterministic dynamics

Dynamics of individual nodes depends on update functions:

In	\mathcal{F}		\mathcal{C}_1				\mathcal{C}_2								\mathcal{R}		
00	1	0	0	1	0	1	1	0	0	0	0	1	1	1	1	0	0
01	1	0	0	1	1	0	0	1	0	0	1	0	1	1	0	1	1
10	1	0	1	0	0	1	0	0	1	0	1	1	0	1	0	1	1
11	1	0	1	0	1	0	0	0	0	1	1	1	1	0	1	0	0

Boolean and continuous dynamics for gene regulatory networks

Boolean model

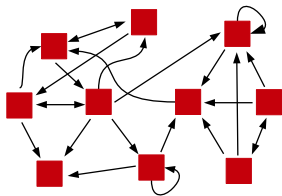


$$\sigma_i = \{0, 1\}$$

$$\sigma_i(t+1) = F_i(\sigma(t))$$

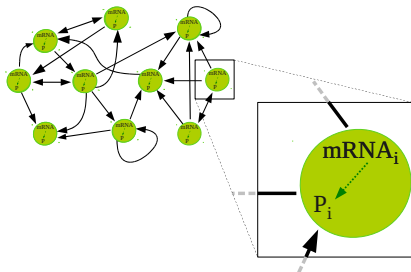
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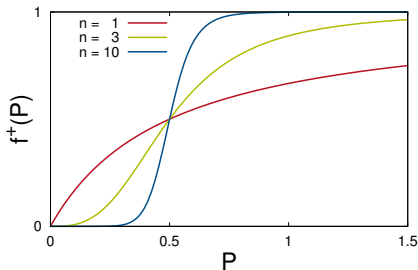
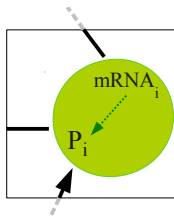
Continuous model



$$mRNA_i = F_i(\mathbf{P}) - \alpha mRNA_i$$
$$\dot{P}_i = \beta mRNA_i - \delta P_i$$

Hill function

Regulation by single gene



$$mRNA_i = F_i(\mathbf{P}) - \alpha mRNA_i$$

$$F_i(\mathbf{P}) = f^+(P) = \frac{P^n}{P^n + k^n}$$

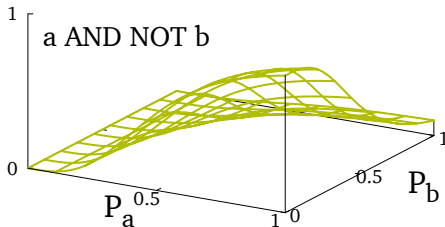
Generalization to more inputs: Hill cubes

Hill cubes

Standardized method for converting any Boolean function into a continuous function

gene _a	gene _b	output
0	0	0
0	1	0
1	0	1
1	1	0

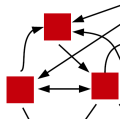
$$F(P_a, P_b) = f^+(P_a) \cdot f^-(P_b)$$



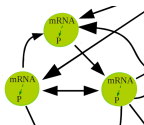
D. Wittmann et al.
*Transforming boolean models to continuous models:
Methodology and application to t-cell receptor signaling.*
BMC Systems Biology, **3** (1) (2009)

Comparison:

Fixed points and oscillations

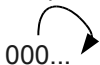


Boolean

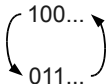


Continuous

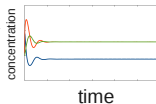
- Fixed points



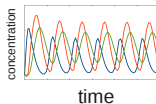
- Cycles



- Fixed points



- Oscillations





- Steady-state concentrations: $mRNA_i^*$, P_i^*
- Normalized state variables: $r_i = \frac{mRNA_i}{mRNA_i^*}$, $p_i = \frac{P_i}{P_i^*}$ and functions: $\tilde{f}_j(p_i) = \frac{F_j(P_i^* p_i)}{F_j(P_i^*)}$

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$$J_{N=2} = \begin{pmatrix} \alpha & & & \\ & \alpha & & \\ & & \beta & \\ & & & \beta \end{pmatrix} \begin{pmatrix} \begin{pmatrix} -1 & 0 \\ 0 & -1 \end{pmatrix} \\ \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix} \end{pmatrix} \begin{pmatrix} \begin{pmatrix} \frac{\partial \tilde{f}_a}{\partial p_a} & \frac{\partial \tilde{f}_a}{\partial p_b} \\ \frac{\partial \tilde{f}_b}{\partial p_a} & 0 \end{pmatrix} \\ \begin{pmatrix} -1 & 0 \\ 0 & -1 \end{pmatrix} \end{pmatrix}$$

- $\frac{\alpha}{\beta} \equiv \lambda$: ratio of time scales between mRNA and protein dynamics



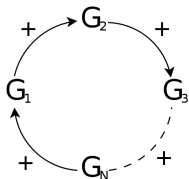
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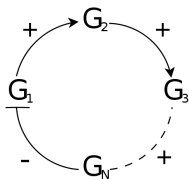
- $\frac{\alpha}{\beta} \equiv \lambda$: ratio of time scales between mRNA and protein dynamics
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T. Gross, U. Feudel
*Generalized models as a universal approach to
the analysis of nonlinear dynamical systems*
Physical Review E **73** (1) (2006)

- *Even loops*: even number of inhibitors



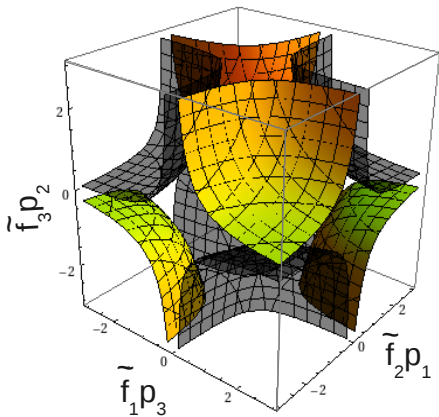
- *Odd loops*: odd number of inhibitors



Simple Loops

Example: Three gene network

Even loop:

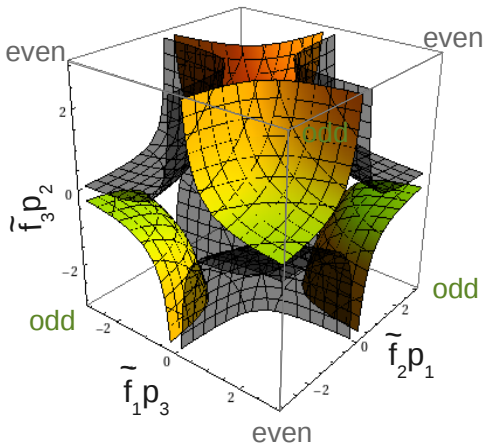


Odd loop:

Simple Loops

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Even loop:

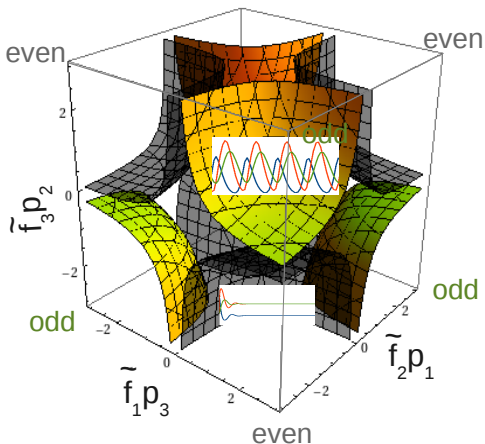


Odd loop:

Simple Loops

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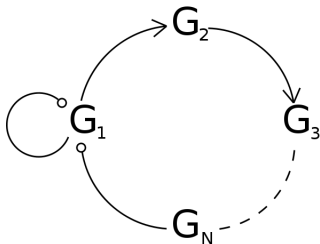
Even loop:



Odd loop:

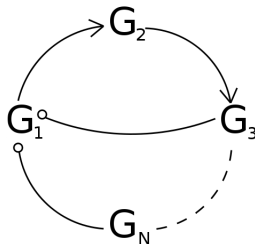
Loops with an additional input

$$x = 1$$



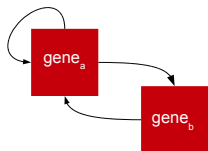
Loops with an additional input

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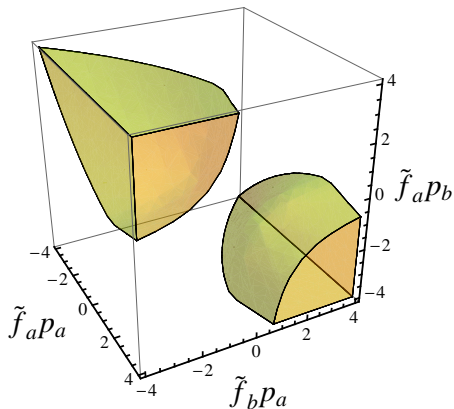


Loops with an additional input

Example: Two gene network

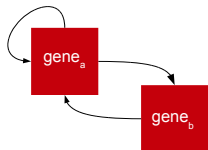


E. Gehrmann, B. Drossel
*Boolean versus continuous dynamics
on simple two-gene modules*
Physical Review E **82** (4) (2010)

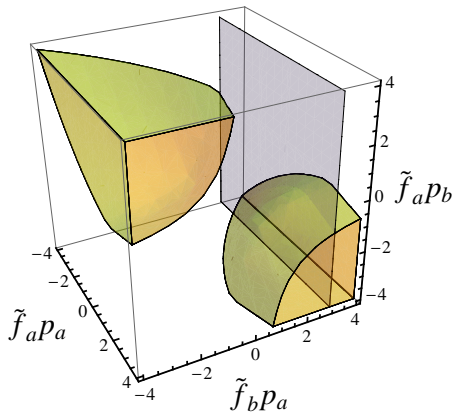


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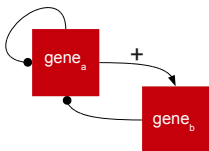
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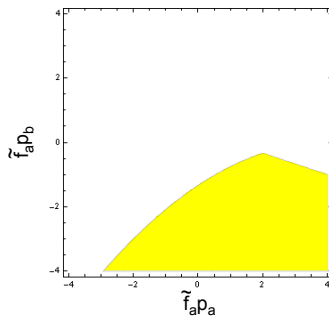
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 Oscillations

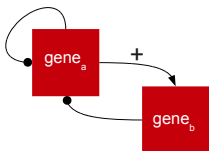


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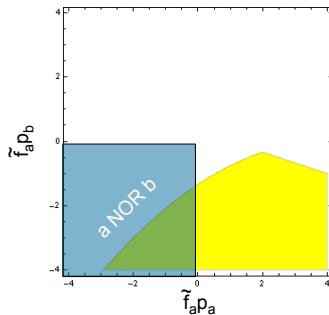
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- Oscillations
- Boolean cycle

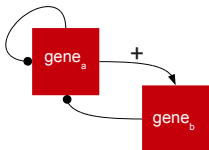


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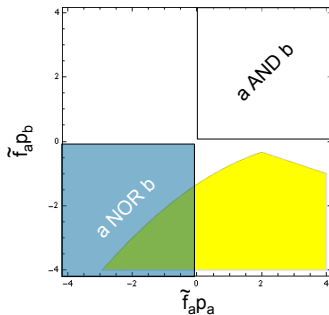
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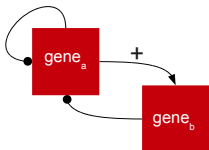


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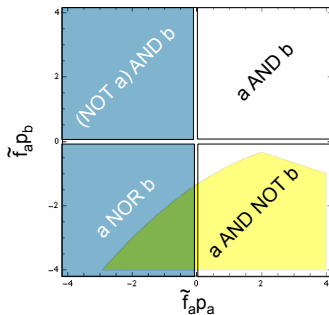
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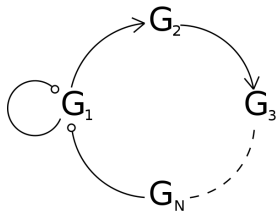
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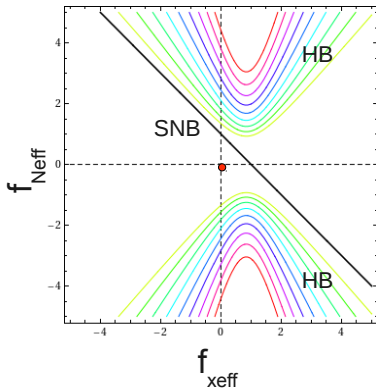
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N-gene networks with self-input or crosslink

$$x = 1$$



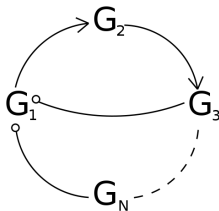
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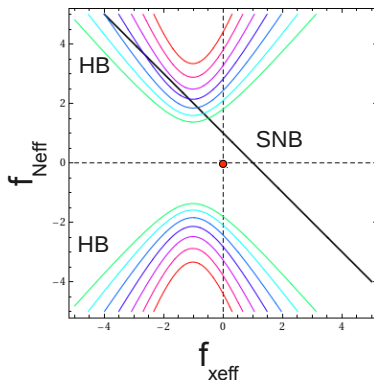
E. Ackermann, E.M. Weiel, T. Pfaff, B. Drossel
*Boolean versus continuous dynamics
in modules with two feedback loops*
In preparation

N-gene networks with self-input or crosslink

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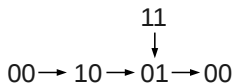
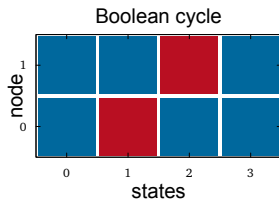
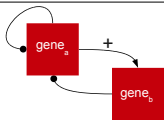
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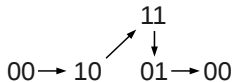
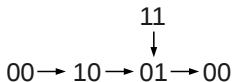
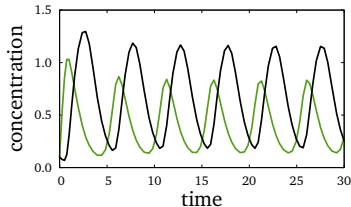
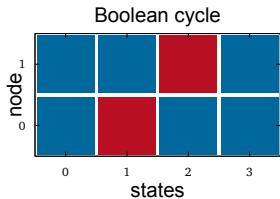
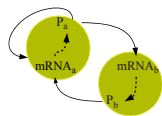
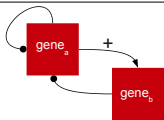
Hamming distance

Example: Two-gene network with $F = a \text{ NOR } b$



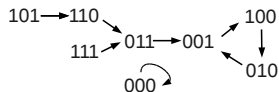
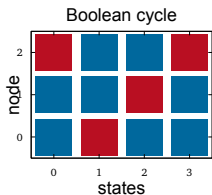
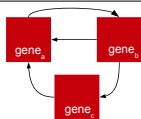
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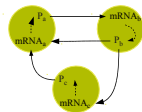
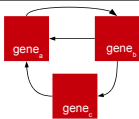
Hamming distance

Example: Three-gene network with $F = \text{NOT } b \text{ AND } c$

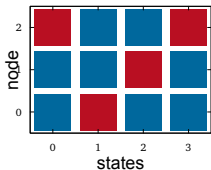


Hamming distance

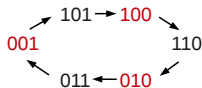
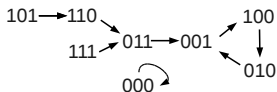
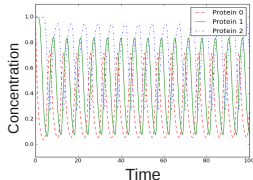
Example: Three-gene network with $F = \text{NOT } b \text{ AND } c$



Boolean cycle



Continuous oscillations



- Boolean vs. continuous dynamics
 - Conditions for oscillations in terms of
 - regulating functions' signs
 - steepness of response functions
- ⇒ Not size and topology, but dynamical features of a network are relevant

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 - Conditions for oscillations in terms of
 - regulating functions' signs
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- ⇒ Not size and topology, but dynamical features of a network are relevant
- Hamming distance = 1: Cycle found in Boolean dynamics are in continuous model
 - Hamming distance > 1 : Intermediate states must not coincide with fixed point
-
- Assumption: For entirely reliable trajectories the Boolean description reflects continuous dynamics

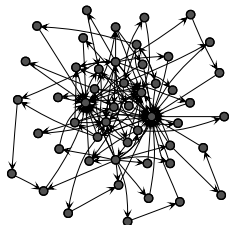
Entirely reliable trajectories



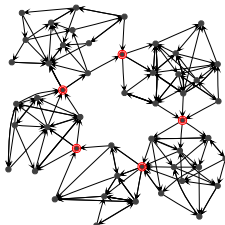
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DARMSTADT

Hamming distance $h = 1$ between to subsequent states:
Only one nodes flips per time step

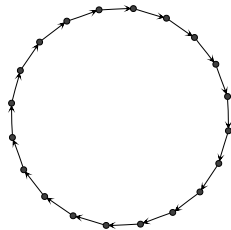
Three general types of dynamics under random update schedule



Stochastic dynamics



"Checkpoint" states

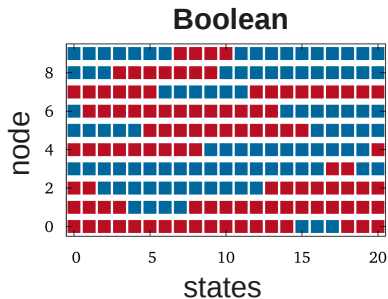


Entirely reliable
trajectory

Our interest is best possible case:
Entirely reliable trajectories with Hamming distance $h = 1$

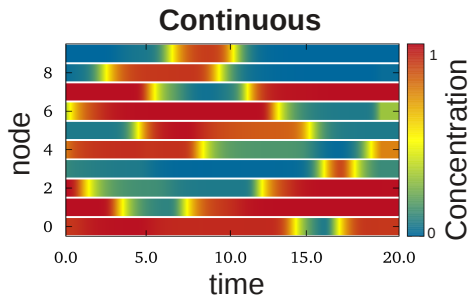
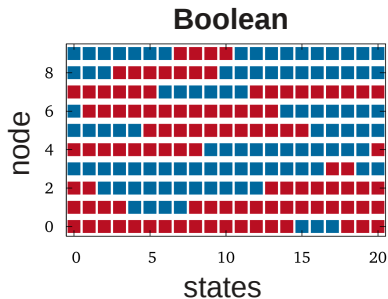
Entirely reliable trajectories

Hamming distance $h = 1$



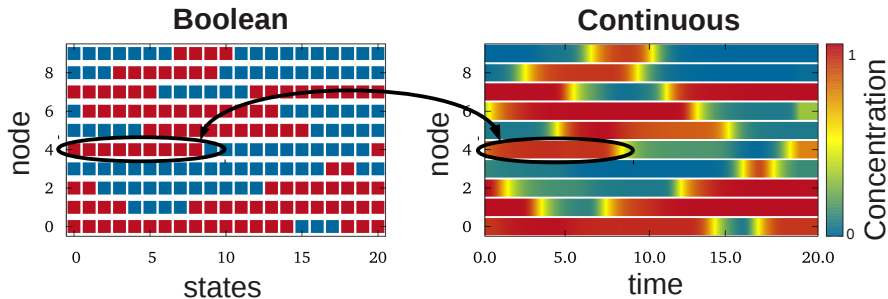
Entirely reliable trajectories

Hamming distance $h = 1$



Entirely reliable trajectories

Hamming distance $h = 1$



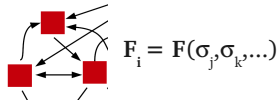
1. Variables

Number of nodes: N
Length of trajectory: L
Hamming distance: h

2. Trajectory

0 1 1 1 1 0 ...
0 0 1 1 0 0 ...
1 1 1 0 0 0 ...
...

3. Topology & Functions

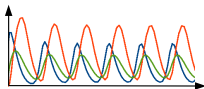


4. Continuous model



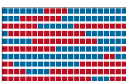
Hill coefficient n

5. Time series

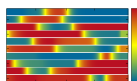


6. Comparison

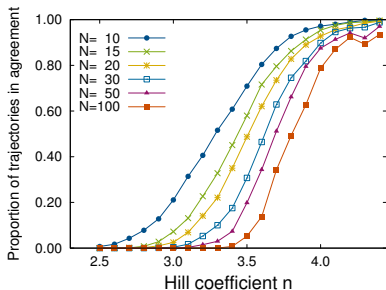
Boolean



Continuous

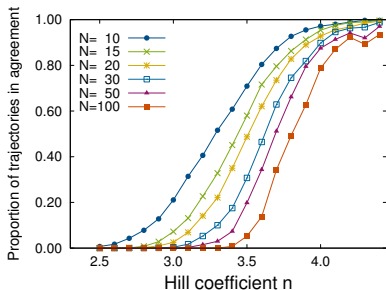


Results: Hamming distance $h = 1$

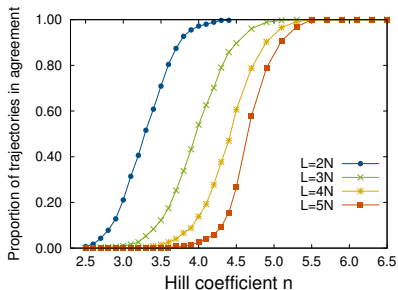


Variation: Number of nodes N
(with $L = 2N$)

Results: Hamming distance $h = 1$

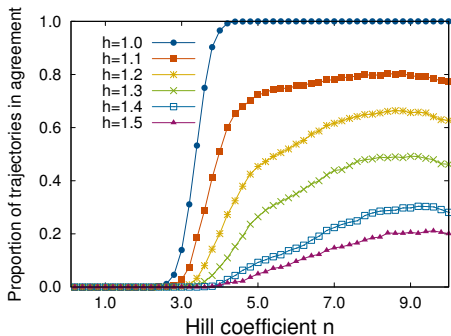


Variation: Number of nodes N
(with $L = 2N$)



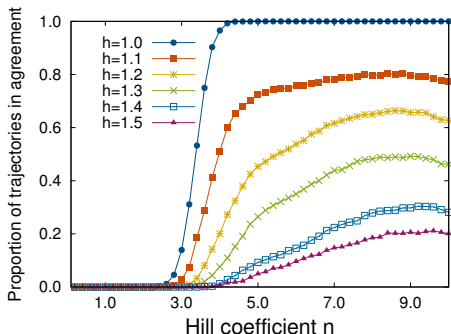
Variation: Length of trajectory L
(with $N = 10$)

Results: Hamming distance $h > 1$



Variation: Hamming distance h
($N = 10$, $L = 20$)

Results: Hamming distance $h > 1$



Features of robust trajectories [1]

- “Catcher states“: Only one node changes its state
- Activity states are kept for an extended time

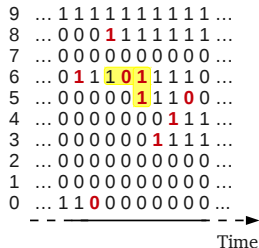
[1] S. Braunevell & S. Bornholdt
*Superstability of the yeast cell-cycle dynamics:
Ensuring causality in the presence of biochemical stochasticity*
Journal of Theoretical Biology, 2007

Variation: Hamming distance h
($N = 10, L = 20$)

Results: Features of consistent trajectories

Duration of node states must not be too short

$N = 10, L = 20, h = 1.1$

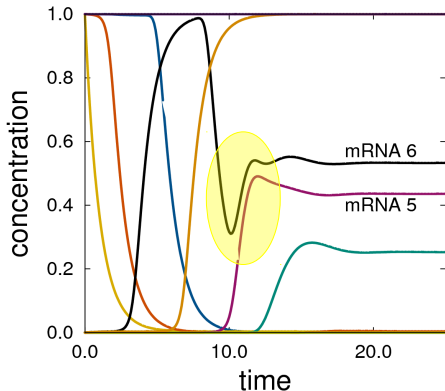
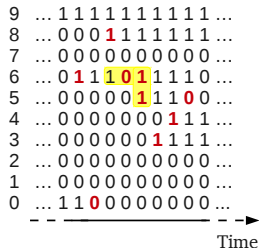


Example: Duration of node states too short and simultaneous update of 2 nodes
⇒ No oscillations in continuous model

Results: Features of consistent trajectories

Duration of node states must not be too short

$N = 10, L = 20, h = 1.1$



Example: Duration of node states too short and simultaneous update of 2 nodes
⇒ No oscillations in continuous model

- Entirely reliable trajectories
 - ⇒ Boolean description reflects continuous dynamics
- Increased Hamming distance
 - ⇒ Agreement of continuous dynamics with Boolean dynamics becomes worse
- Features of robust trajectories
 - Catcher states
 - Duration of node states are not too short
- Biological relevance: Processes in biological networks must be reliable despite fluctuations affecting the timing of different steps

Thank you for your attention



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Thank you for your attention



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