Reconciling qualitative and abstract (and scalable) reasoning with Boolean networks

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Overview

Discrete Dynamical Systems

(Boolean Networks)

+

Systems Biology

(Signalling/regulation networks)

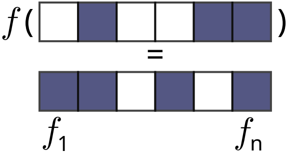
Concurrency Theory

(Semantics)

Introduction

Boolean Network (BN) $f : \mathbb{B}^n \to \mathbb{B}^n$

Configuration: $x \in \mathbb{B}^n$



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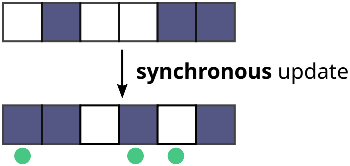

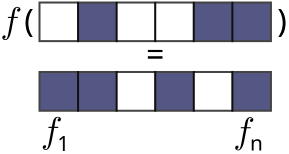

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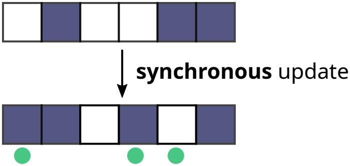
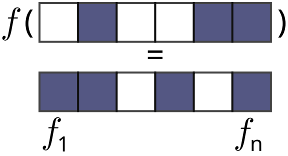
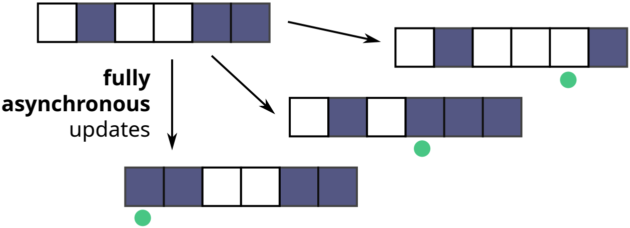
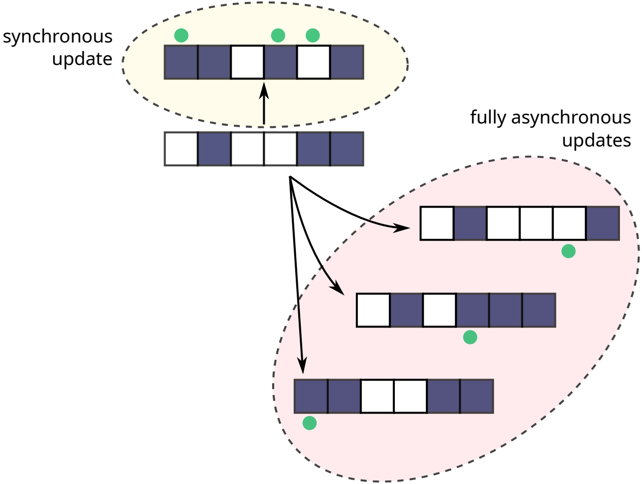






Asynchronous updates



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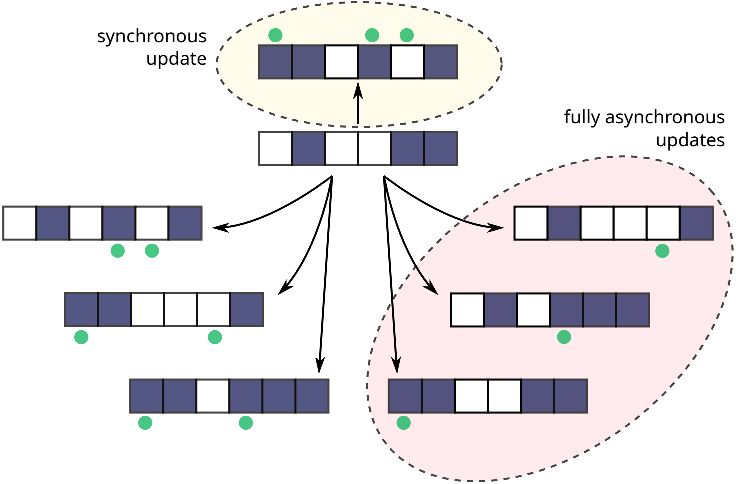
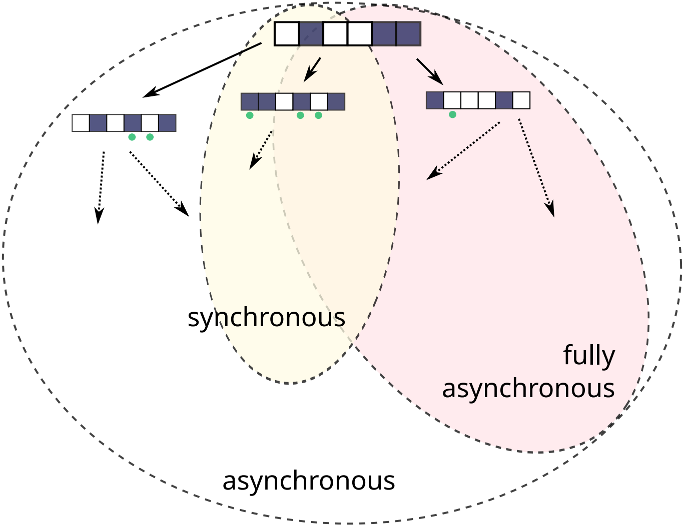


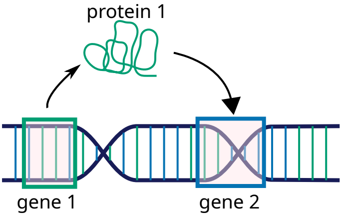
Reachable configurations



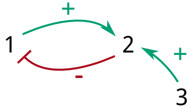
Boolean networks for biological processes

Example with gene regulation

[Since 70's - Kauffman, Thomas]



Influence graph



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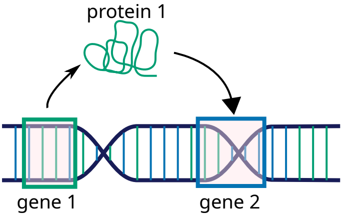

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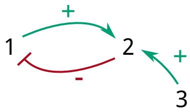


Reachable configurations

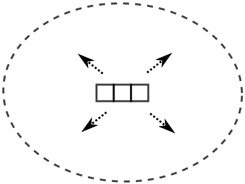
Boolean network

$$f_1(x) \triangleq \neg x_2$$

$$f_2(x) \triangleq x_1 \wedge x_3$$

$$f_3(x) \triangleq \dots$$

+ update mode =



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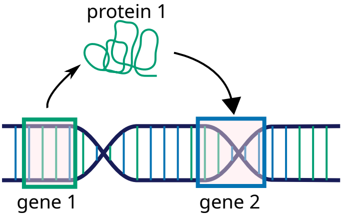

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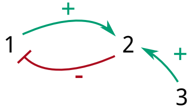

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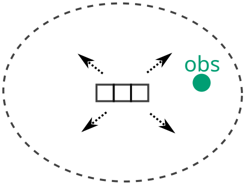


Validation w.r.t. observations (e.g. time series data)

⇒ we expect measurements match with reachable configurations

Properties of Boolean networks for biology

Given a Boolean network f of dimension n

Reachability (seq. of transitions from conf. x to y)
⇒ PSPACE-complete with update modes
Potential behaviours/capabilities of the cell

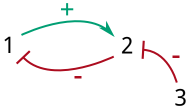
Fixpoints ($f(x) = x$)
⇒ NP-complete for sync/async/gasync
Steady states/phenotypes

Attractors (smallest sets of conf. closed by transitions)
⇒ PSPACE-complete with update modes
Steady states/phenotypes

Qualitative vs abstract modelling

information

Influence graph

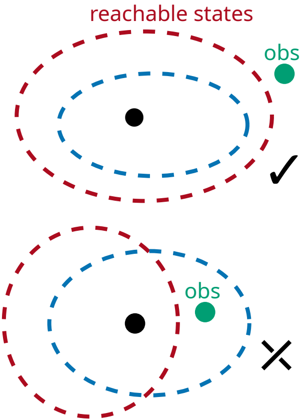


Boolean network
- logic of activity w.r.t. regulators
- *update mode* (sync, async, etc.)

Multilevel network
+ define activation thresholds

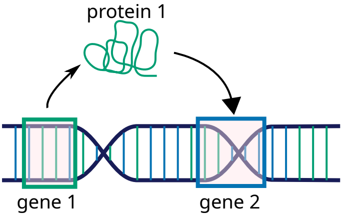
Quantitative model

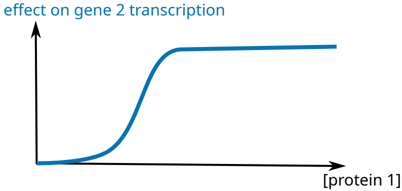
Consistency
analysis at Boolean level
transposable to multilevel?



Gene expression is not Boolean

Qualitative modelling: Boolean vs multivalued networks





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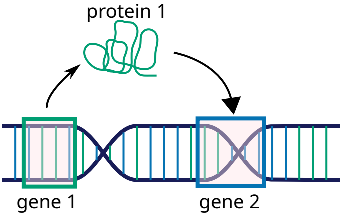

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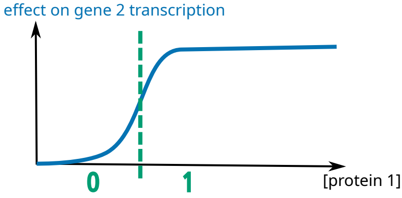

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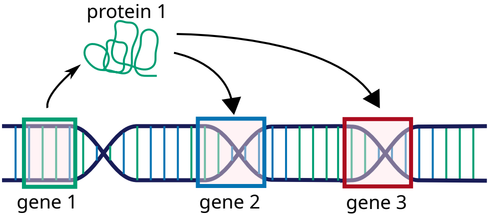

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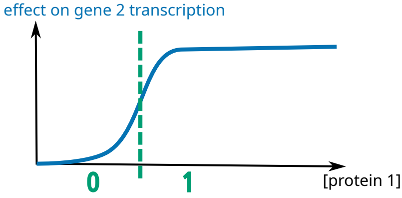

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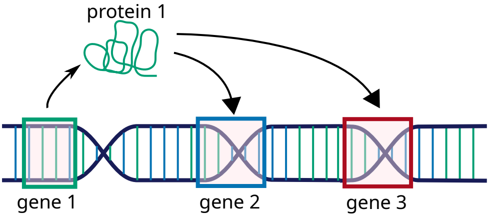

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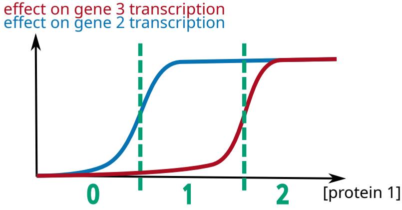


Multivalued network

$$F_2(x) \triangleq (x_1 \geq 1)$$

$$F_3(x) \triangleq (x_1 \geq 2)$$

Multivalued Networks

$$F : \mathbb{M}^n \to \{-1, 0, 1\}^n \qquad \mathbb{M} \triangleq \{0, 1, ..., m\}$$

Asynchronous semantics

$$x \in \mathbb{M}^n \xrightarrow[\mathrm{a}]{F} y \in \mathbb{M}^n$$

$$\overset{\Delta}{\Longleftrightarrow}$$

$$\forall i \in \Delta(x, y), y_i = x_i + F_i(x)$$

To ease notations,

$$F_i(x) \triangleq 1 \text{ if } P(x) \text{ else } -1 \quad \equiv \quad F_i(x) \triangleq P(x)$$

Remark: very similar to ODEs ($\mathbb{R}^n_{\geq 0} \to \mathbb{R}^n$)

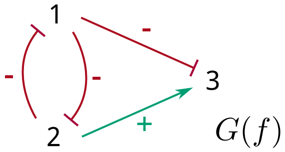
Asynchronous

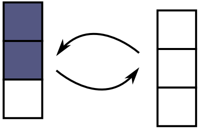
Boolean networks:

a **bug**…

Motivating example
(embedded in many actual biological networks)

$$f_1(x) \triangleq \neg x_2$$
$$f_2(x) \triangleq \neg x_1$$
$$f_3(x) \triangleq \neg x_1 \wedge x_2$$





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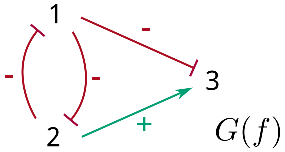

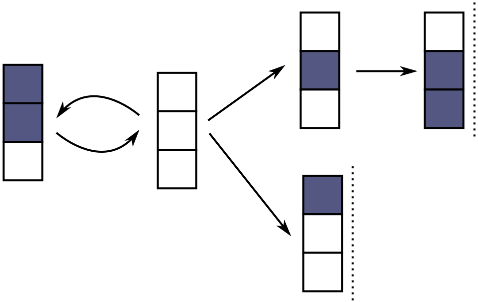

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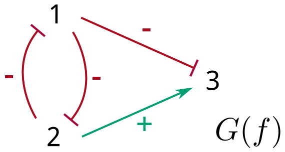

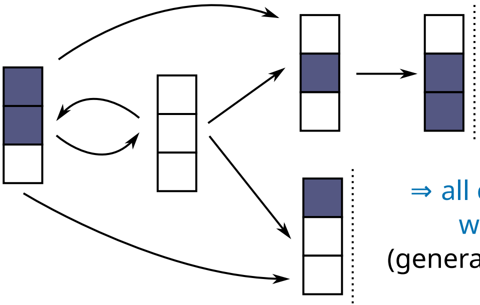

⇒ all configurations reachable
with any update mode
(generalized) asynchronous mode

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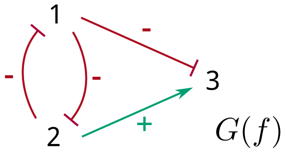
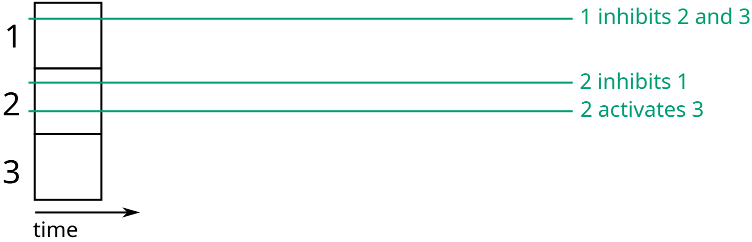


Compatible continuous/multilevel model:



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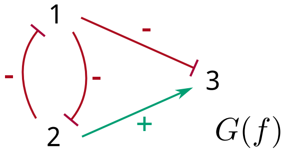

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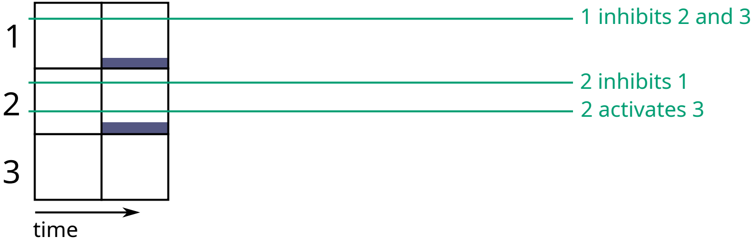

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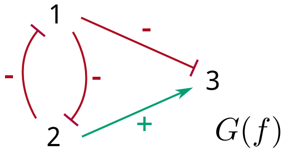

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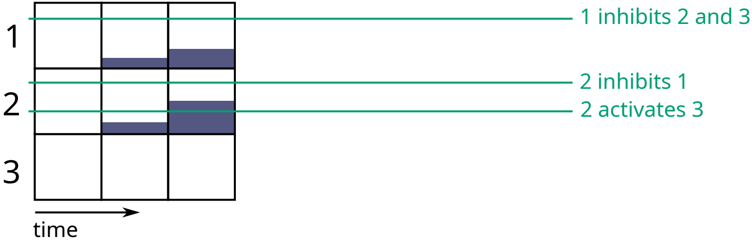

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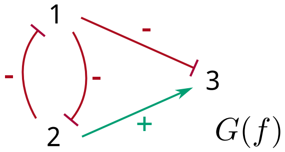

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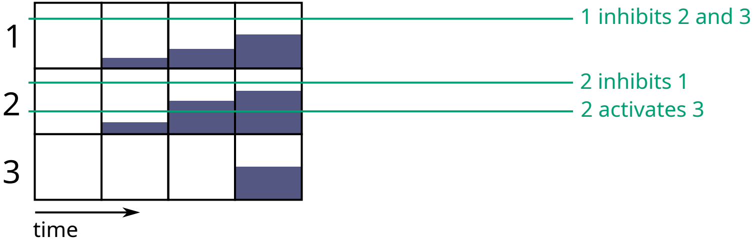

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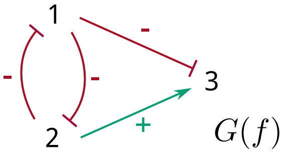

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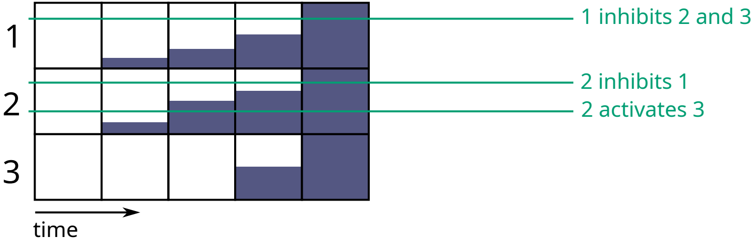

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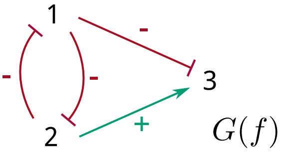

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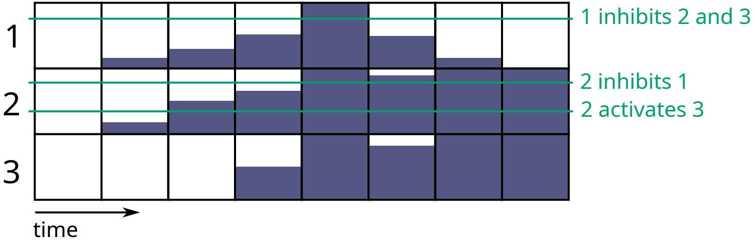

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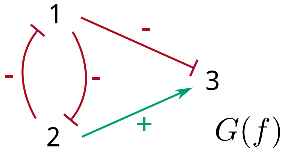

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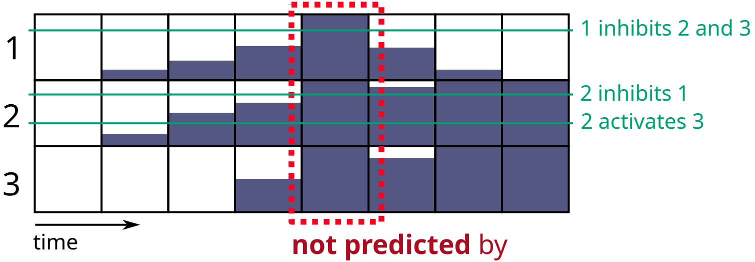


not predicted by
update modes in Boolean

Most Permissive

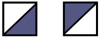
Boolean networks

enabling new behaviours

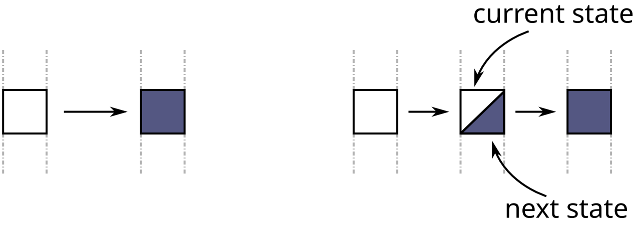
Most permissive semantics

- delay between firing and application of state change

  ⇒ allow interleaving other state changes

- in "intermediate" states 

  other components choose what they see



Most permissive semantics

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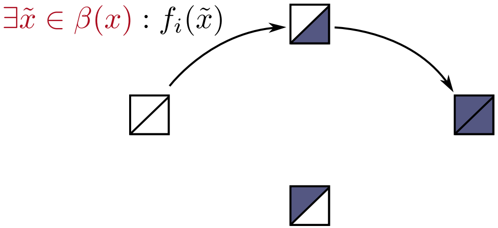

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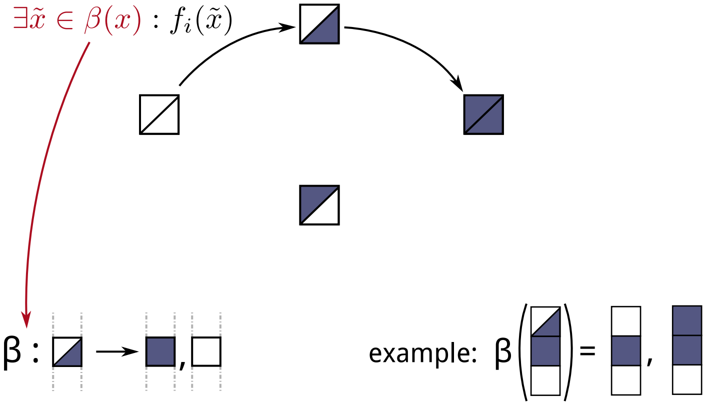

Choose value of "changing" components
(act as choosing an activation threshold)

Most permissive semantics

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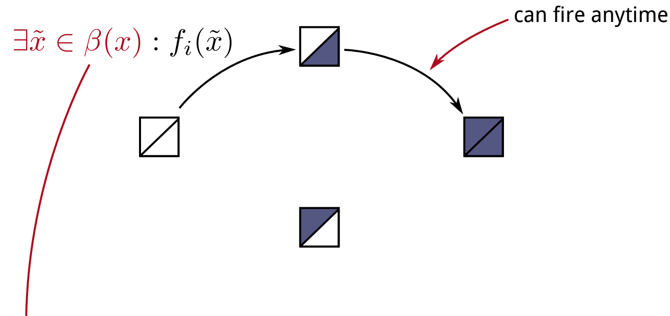
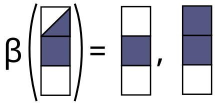


example: 

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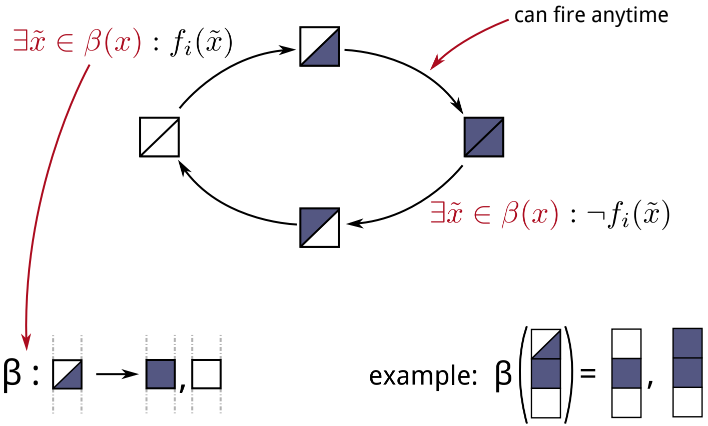

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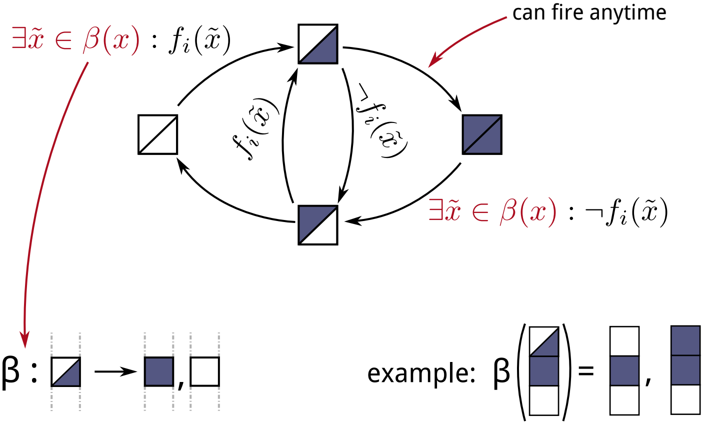

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Application to motivating example

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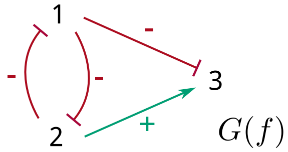
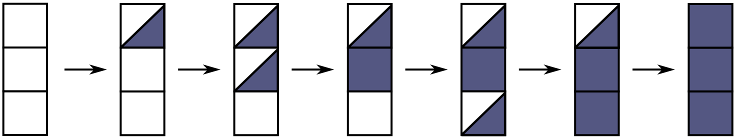
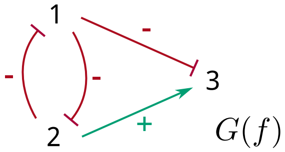
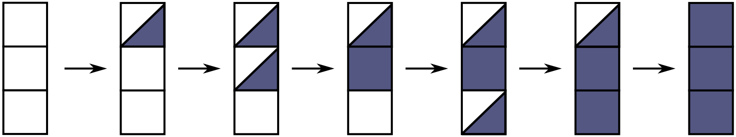




Application to motivating example

$$f_1(x) \triangleq \neg x_2$$
$$f_2(x) \triangleq \neg x_1$$
$$f_3(x) \triangleq \neg x_1 \wedge x_2$$





⇒ valid with respect to multivalued refinements

Properties of the most permissive semantics

Correct abstraction of multilevel/quantitative systems:

- includes all the transitions of every update mode
- multilevel refinements only remove behaviours

- Reachability can be decided in quadratic nb of transitions

(PTIME with locally-monotonic networks, or encoded as BDDs/Petri nets/...; NP-complete otherwise; instead of PSPACE-complete with update modes)

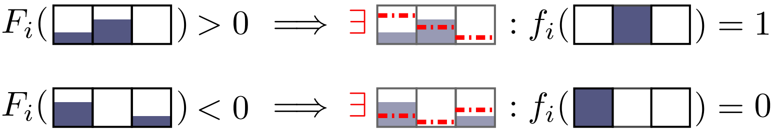
- Attractors are hypercubes (minimal trap spaces)
  - ⇒ finding attractors is NP-complete (instead of PSPACE-complete)
  - ⇒ fixpoints are the same as with update modes

Refinements of Boolean Networks

A multivalued network

$$F : \mathbb{M}^n \to \{-1, 0, 1\}^n$$

is a refinement of a Boolean network *f* iff

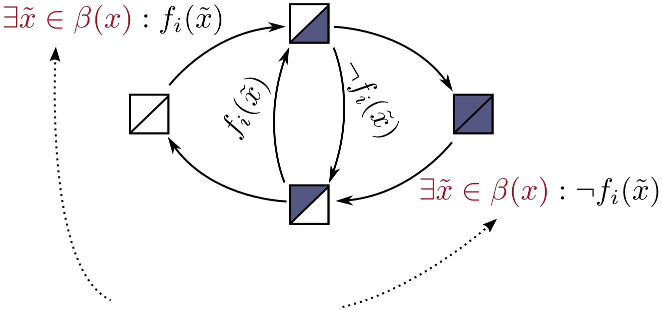


Most permissive semantics weakly simulates any multivalued refinement with *any update mode*

(can be extended to ODEs)

Reachability with the most permissive semantics

Cost of one transition in component i



NP (SAT) in general;
Linear with
- locally-monotonic networks (f_i are monotone)
- when f is encoded as BDDs/Petri nets/...

Reachability with the most permissive semantics

Deciding reachability requires quadratic nb of transitions

Main property:
y reachable from x ⇔ there exists a path of length ≤3n transitions

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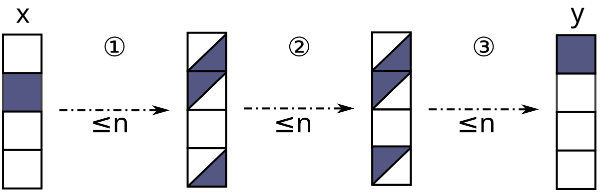

① - only transitions to "in-between" states*
② - orient towards final states
③ - converge to final states

*: some components must not be updated!

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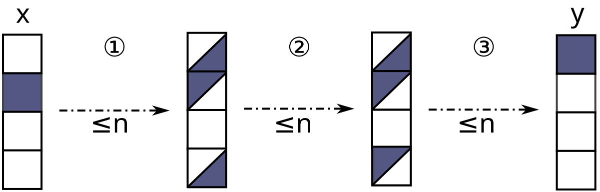

① - only transitions to "in-between" states*
② - orient towards final states
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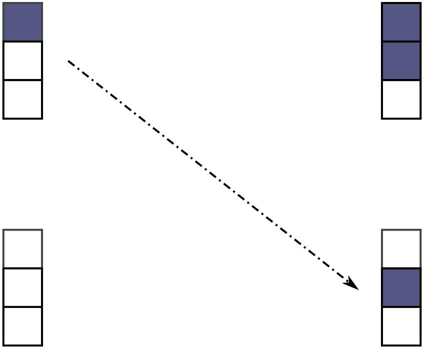
*: some components must not be updated!

NP in general
PTIME w/ locally-monotonic; BDDs; Petri nets..

Attractors with the most permissive semantics

Attractor: smallest set of configurations closed by transitions

Attractors are hypercubes



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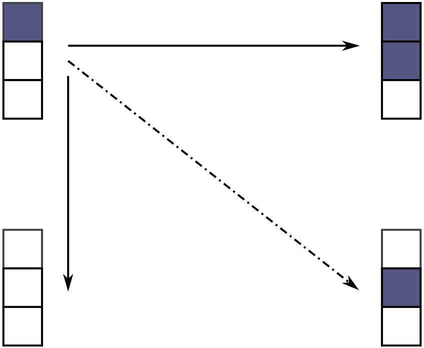

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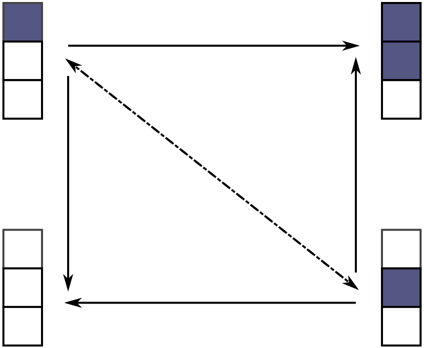

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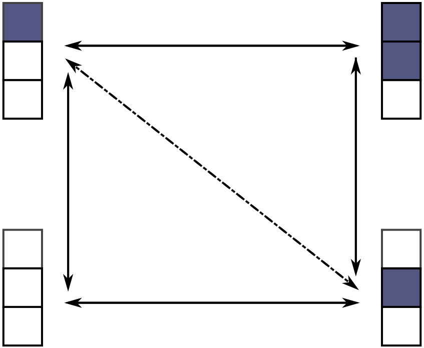
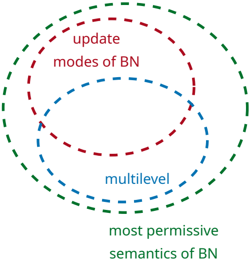


Attractors of most permissive semantics = minimal trap spaces

Deciding if trap space is minimal = 2 reachability checking

Is most permissive semantics restrictive?



Minimality of abstraction

to any "most permissive" transition,

there is corresponding multilevel transition

(work in progress w/ "most permissive" paths: non-minimal, but tricky counter-examples)

- fixpoints (stable states) are preserved (identical)
- trap spaces: known to be relevant for reasoning with attractors

  [Klarner et al in Nat. Comp. 2015] [Naldi in Front. Phys. 2018]

⇒ most permissive semantics seems still adequate to model differentiation processes !

Boolean network synthesis

WiP (PhD studies of Stéphanie Chevalier LRI-LaBRI-Curie)

Constraints

- Putative influences (domain of Boolean functions)
- +/- reachability between partial configurations
- existence of (reachable) attractors

Output

- Exhaustive enumeration of compatible Boolean networks

SAT approach (Answer-Set Programming)

- Application to cellular differentiation data
- Scalable to >100 nodes (>1000 w/o neg. reachability)

Conclusion

Update modes of Boolean networks (sync, async, etc.):

• difficult to justify for biology (strong implications on dynamics)

• can miss important behaviours [CHP at AUTOMATA'18]

⇒ lead to reject valid models of biological systems...

• have limited tractability (model-checking, ...)

Most permissive semantics:

• correct abstraction: guarantees that multilevel/quantitative refinements only remove behaviours

• simpler complexity: reachability PTIME, attractors NP

⇒ genome-scale tractability

WiP: assess non-minimality (Juraj Kolčák, LSV-LaBRI PhD student)