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

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Overview

Discrete Dynamical Systems
(Boolean Networks)

+

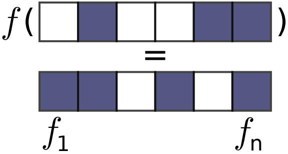
Systems Biology
(Signalling/regulation networks)

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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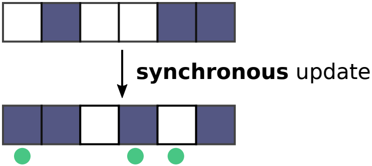

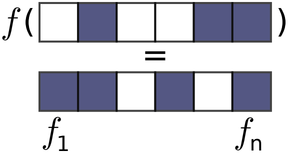

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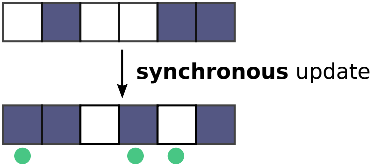
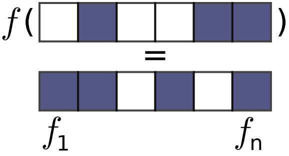
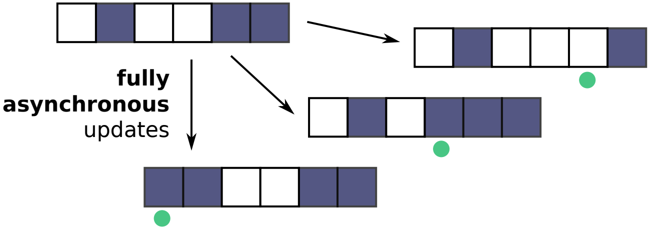
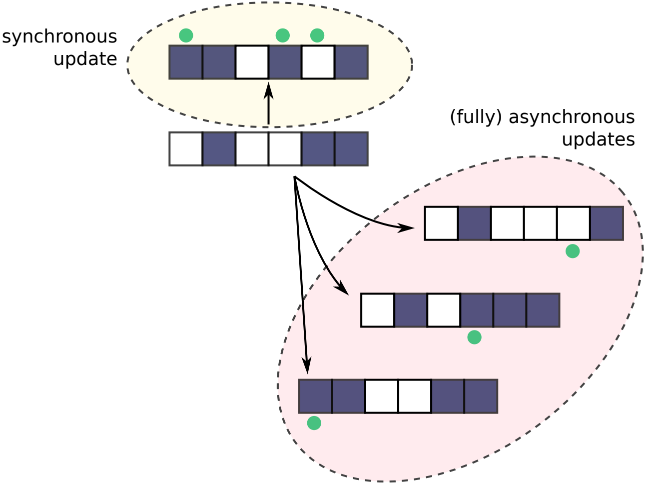






Generalized Asynchronicity



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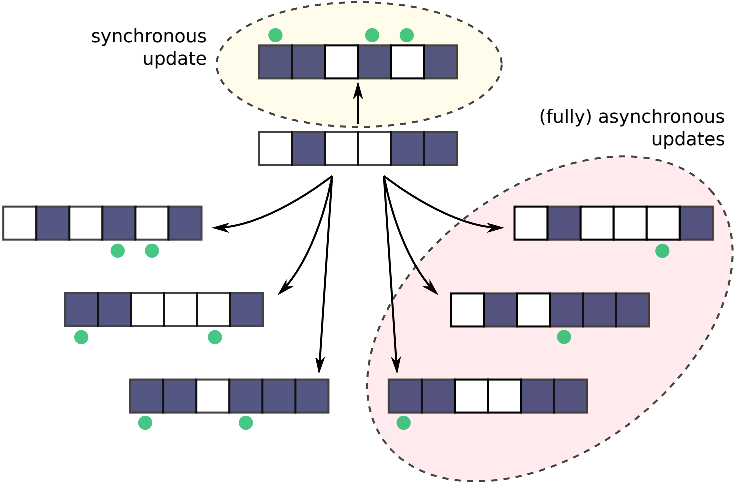
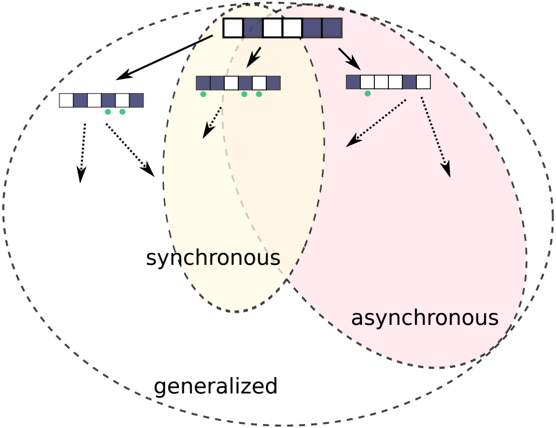


Reachable configurations



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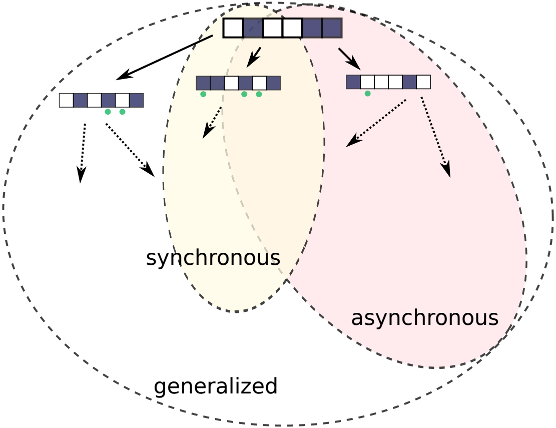
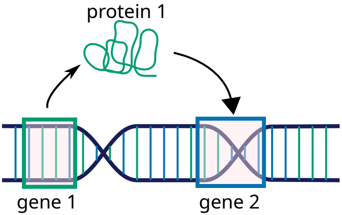


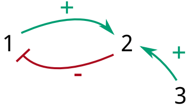
Should we reach configurations beyond generalized asynchronicity?

Boolean networks for biological processes

Example with gene regulation



Influence graph



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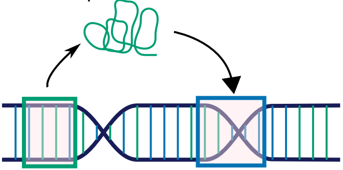

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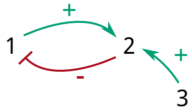


Reachable configurations

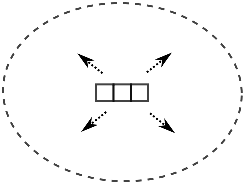
Boolean network

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

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

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

\+ update mode =



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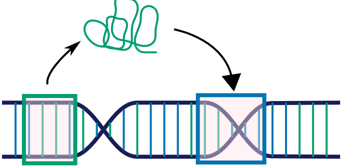

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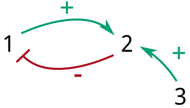

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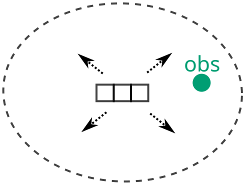
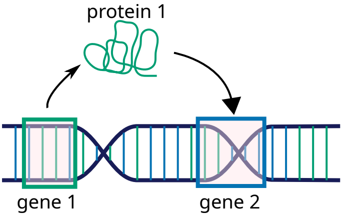
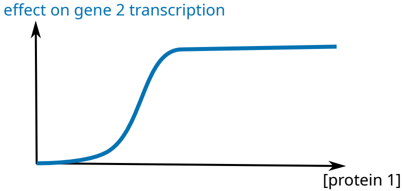


Validation w.r.t. observations (e.g. time series data)
⇒ we expect measurements match with reachable configurations

Gene expression is not Boolean

Qualitative modelling: Boolean vs multivalued networks





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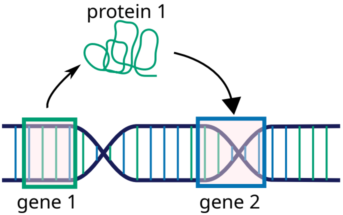

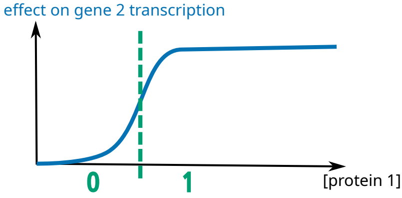

Boolean network

$$f_2(x) \triangleq x_1$$

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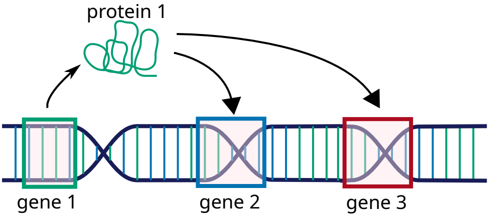

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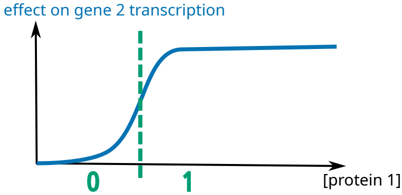

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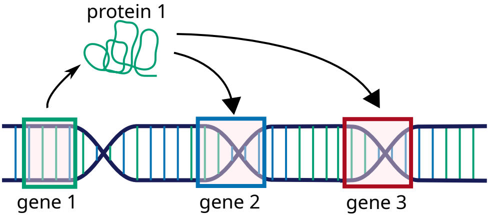

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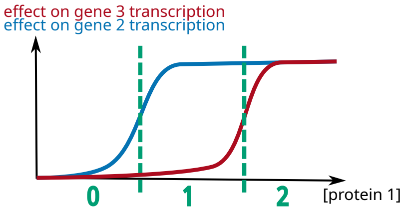


Multivalued network

$$f_2(x) \triangleq (x_1 \geq 1)$$

$$f_3(x) \triangleq (x_1 \geq 2)$$

Remark: Multivalued models can require different thresholds for each target

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

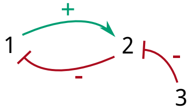
Fixpoints ($f(x) = x$)
⇒ NP-complete for sync/async/gasync
Steady states/phenotypes

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

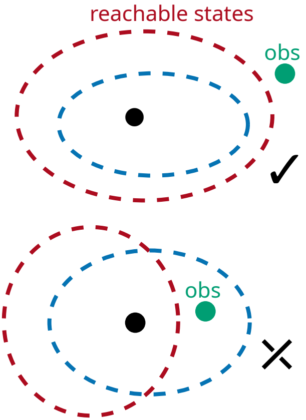
Qualitative vs abstract modelling

information

Influence graph



Consistency
analysis at Boolean level
transposable to multilevel?



Boolean network

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

Multilevel network

+ define activation thresholds

Quantitative model

Update modes

of Boolean networks:

a **bug**…

Motivating example

(embedded in many actual biological networks)

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

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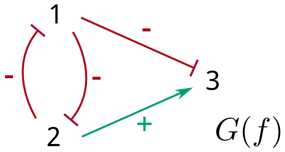
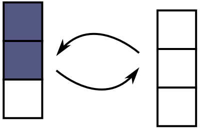
$$f_3(x) \triangleq \neg x_1 \wedge x_2$$





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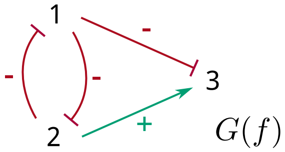

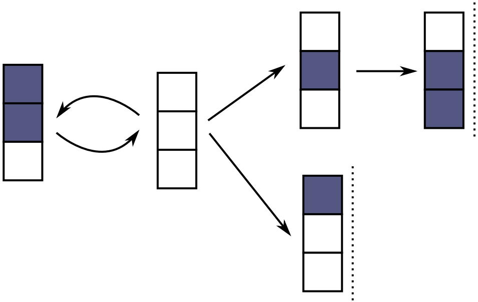

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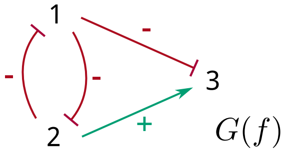

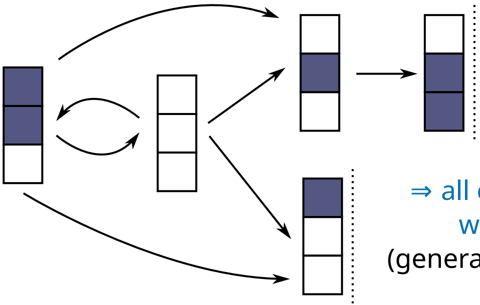

⇒ all configurations reachable
with any update mode
(generalized) asynchronous mode

Motivating example

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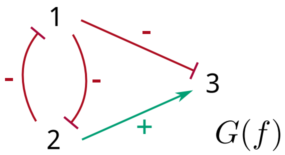
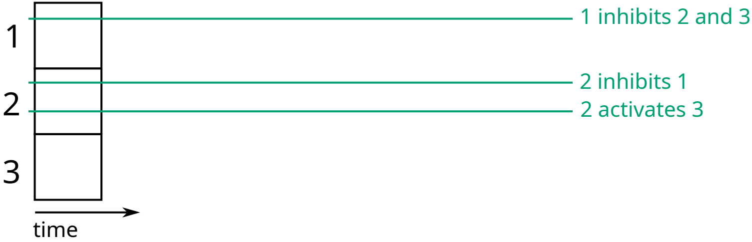


Compatible continuous/multilevel dynamics:



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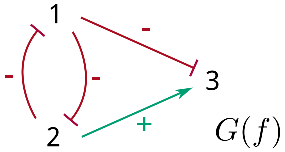

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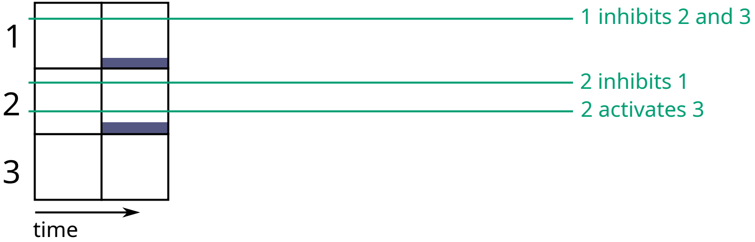

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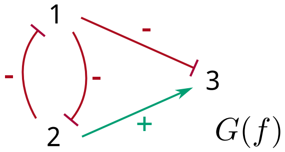

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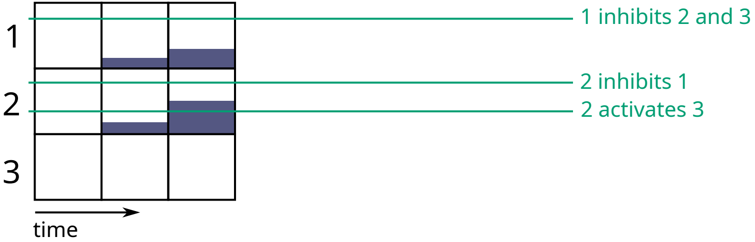

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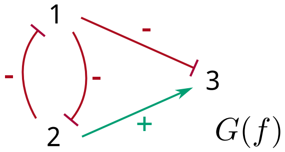

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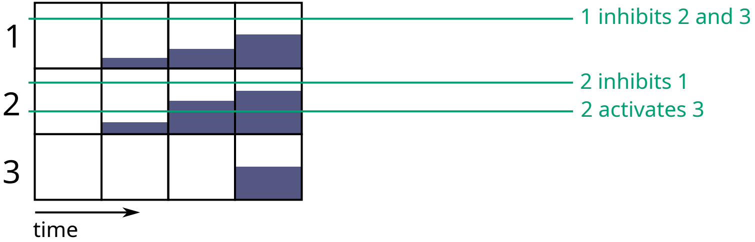

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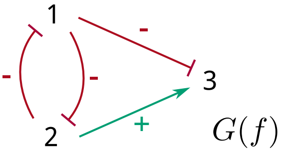

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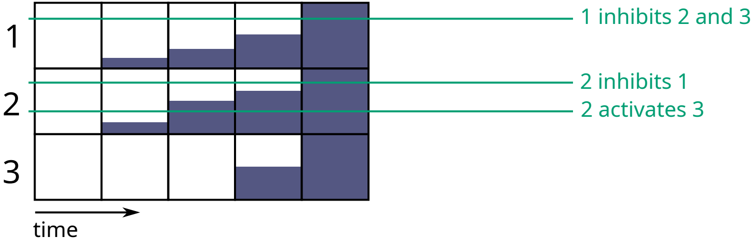

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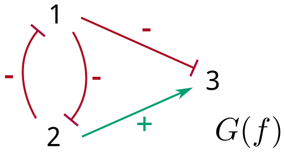

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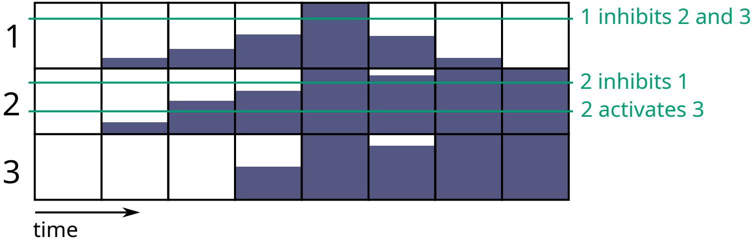

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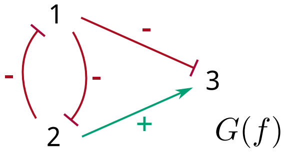

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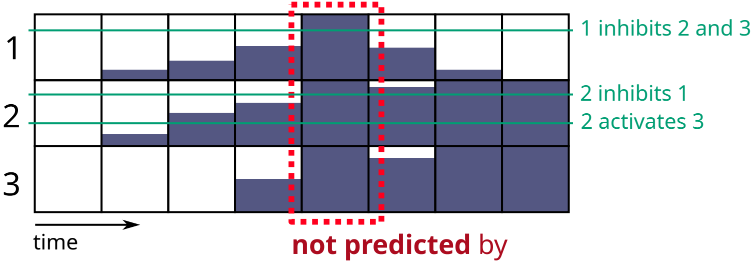


not predicted by
update modes in Boolean

Practical implications

Update modes can miss admissible transitions

Model synthesis from observations

⇒ Reject valid solutions (false negatives)

(wrongly concludes on reachability)

Prediction for reprogramming (control)

Find mutations such that

1. y (goal phenotype) is reachable from x

⇒ False negatives

2. z (bad phenotype) is not reachable from x

⇒ False positives

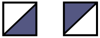
Most permissive semantics of Boolean networks

enabling new behaviours

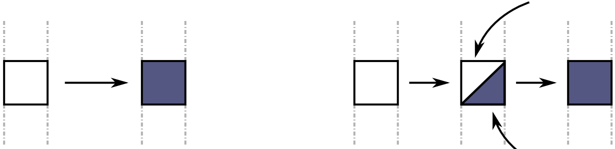
Most permissive semantics

- delay between firing and application of state change

  ⇒ allow interleaving other state changes

- in "intermediate" states 

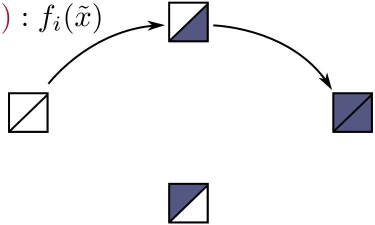
  other components choose what they see



Most permissive semantics

Rules for state of component i:

$\exists \tilde{x} \in \beta(x) : f_i(\tilde{x})$



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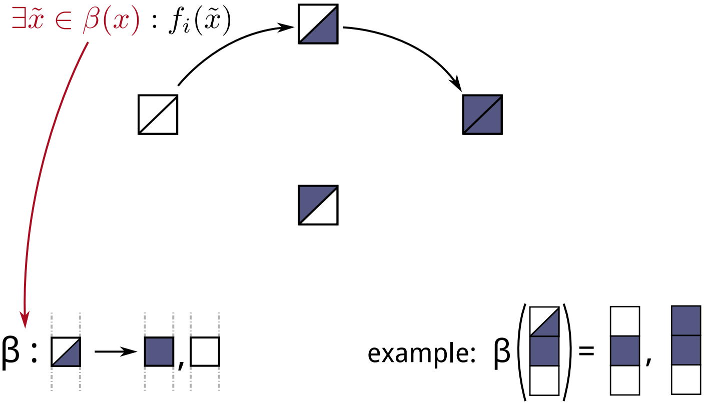

Choose value of "changing" components
(act as choosing an activation threshold)

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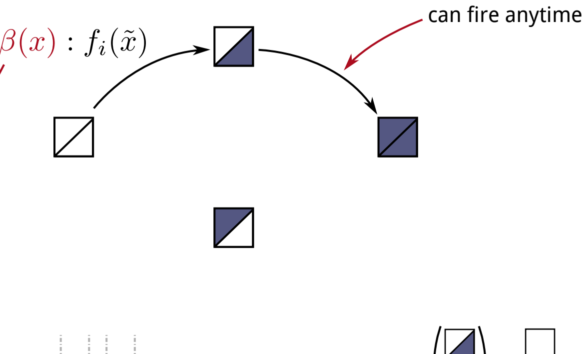
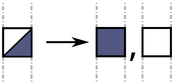
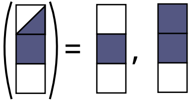


β :



example: β



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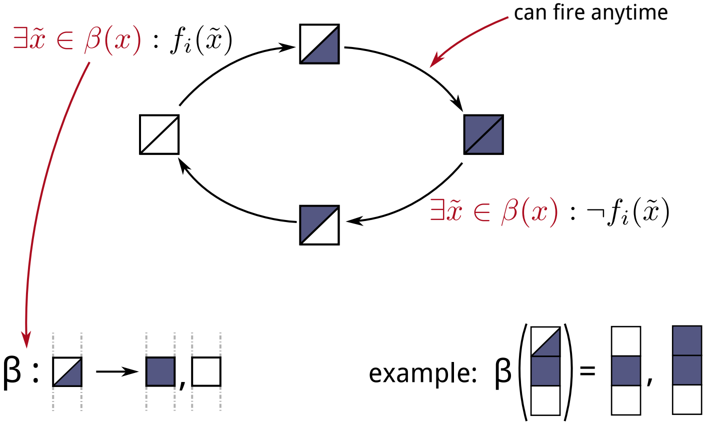

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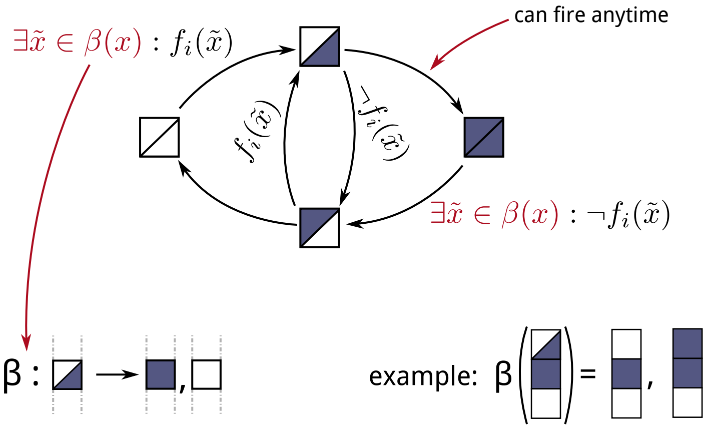
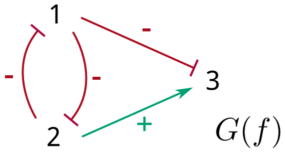
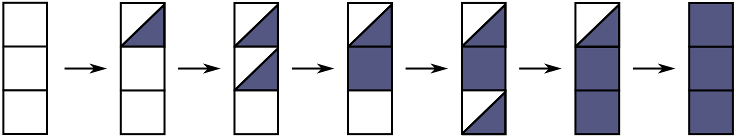


Choose value of "changing" components
(act as choosing an activation threshold)

Application to motivating example

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





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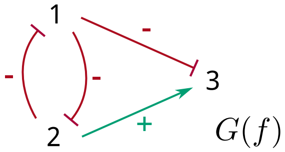
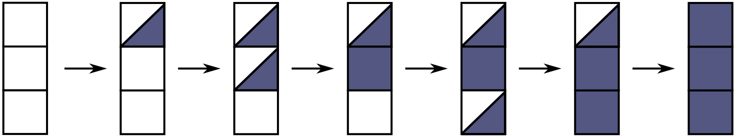




⇒ valid with respect to multivalued refinements

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)

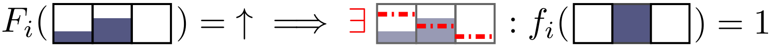
- Attractors are hypercubes (minimal trap spaces)
  - ⇒ finding attractors is NP-complete (instead of PSPACE-complete)
  - ⇒ fixpoints are the same as with update modes

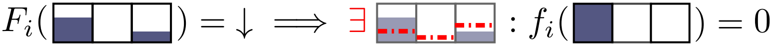
Refinements of Boolean Networks

A multivalued network

$$F : \mathbb{M}^n \to \{\uparrow, -, \downarrow\}$$

is a refinement of a Boolean network *f* iff



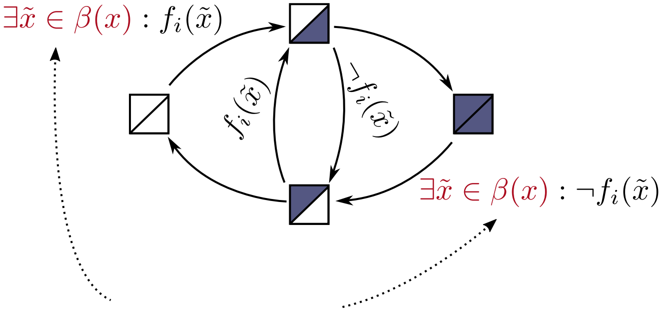


Most permissive semantics weakly simulates
any multivalued refinement with *any update mode*

(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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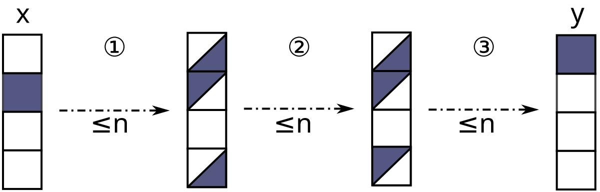

① - only transitions to "in-between" states*
② - orient towards final states
③ - converge to final states

*: some components must not be updated!

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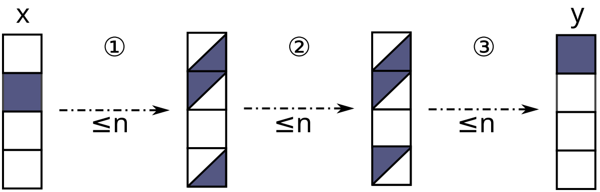

① - only transitions to "in-between" states*
② - orient towards final states
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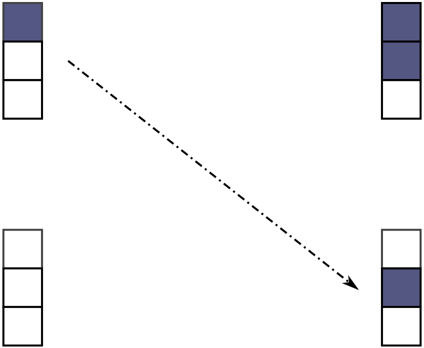
*: some components must not be updated!

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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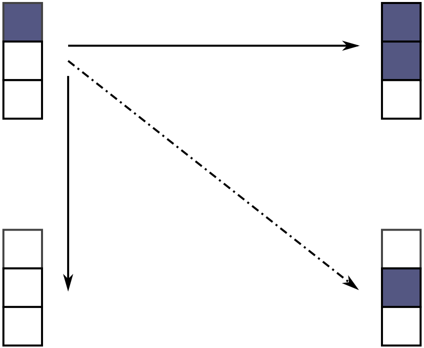

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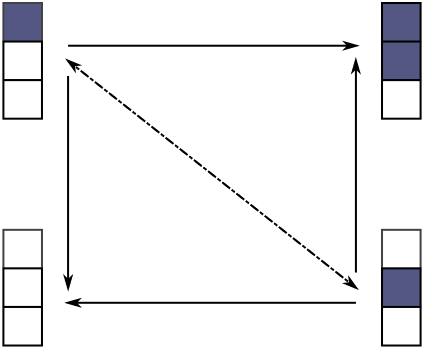

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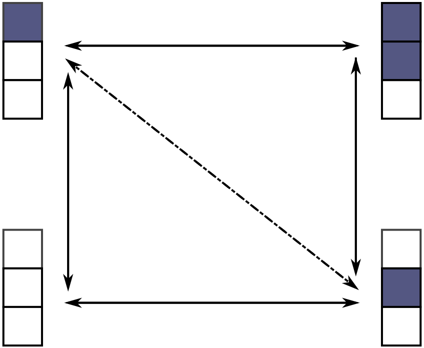
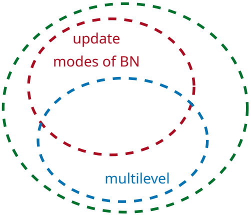


Attractors of most permissive semantics = minimal trap spaces

Existence of attractor within hypercube is NP-complete

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 !

Applications

Prototype python library + ASP (SAT) implementation
https://github.com/pauleve/mpbn

Boolean network synthesis from reachability properties
⇒ becomes NP
⇒ CaspoTS implements most permissive reachability (ASP)
https://github.com/bioasp/caspots

Computation of reachable attractors
⇒ In the order of ms for networks tested so far (~100 nodes)

WiP with most permissive semantics:

- model synthesis from differentiation data [Stéphanie Chevalier]
- prediction for cellular reprogramming

Conclusion

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

- difficult to justify (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 adding information (multilevel, thresholds) will only remove behaviours
- simpler complexity: reachability PTIME, attractors NP

⇒ much higher tractability

Future work: most permissive for multilevel networks