Most Permissive Semantics of Boolean Networks

Reconciling Qualitative and Abstract Modelling

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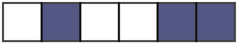
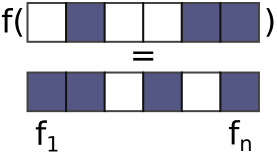
Introduction

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

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





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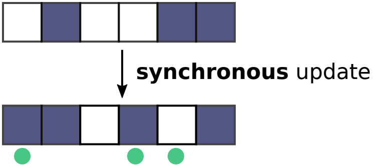

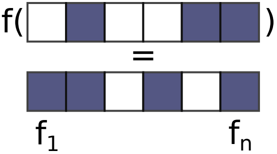

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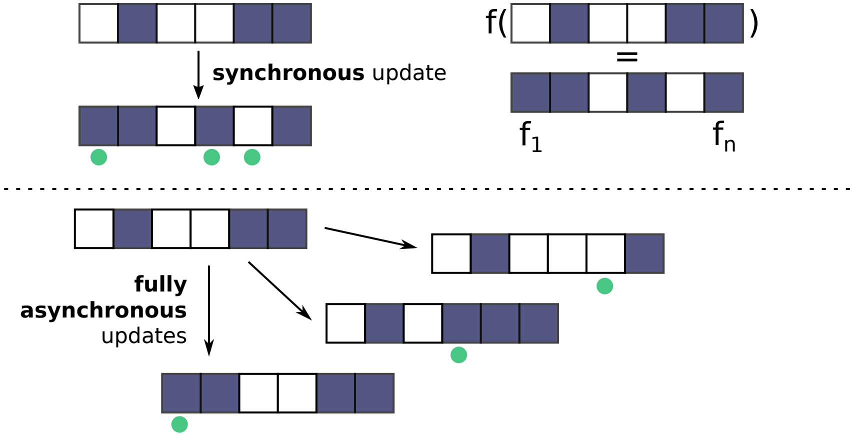
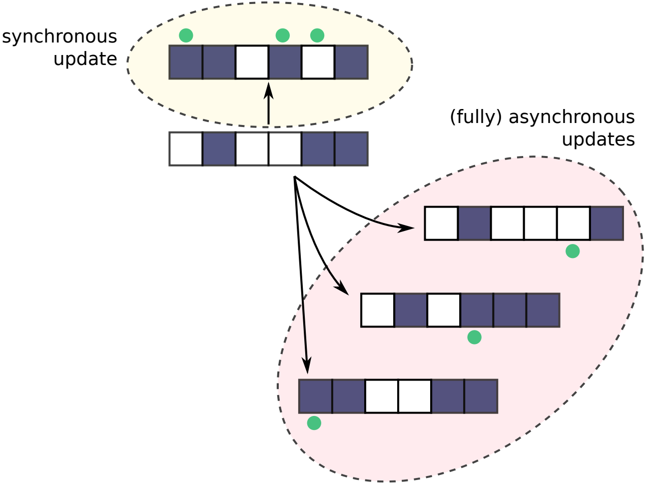


Generalized Asynchronicity



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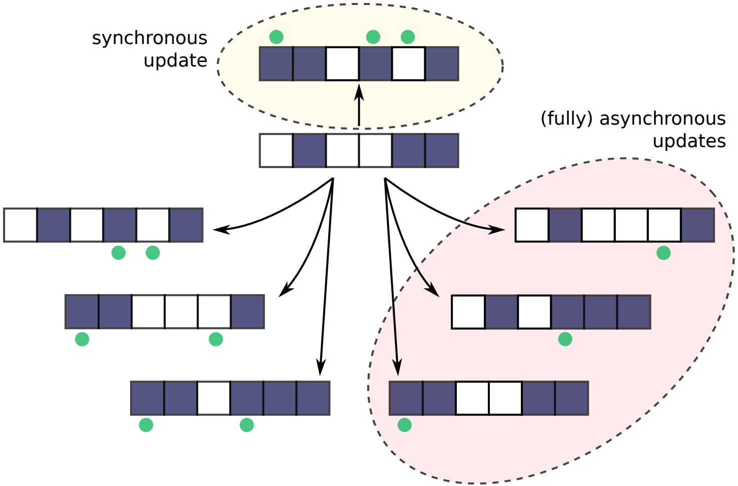
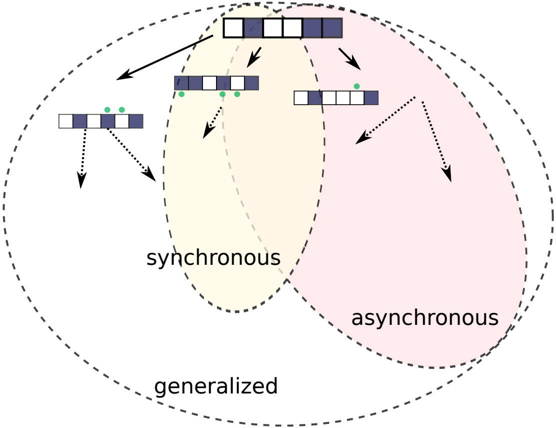


Is configuration x is reachable from y?

⇒ **PSPACE-complete** with update modes

Reachable configurations



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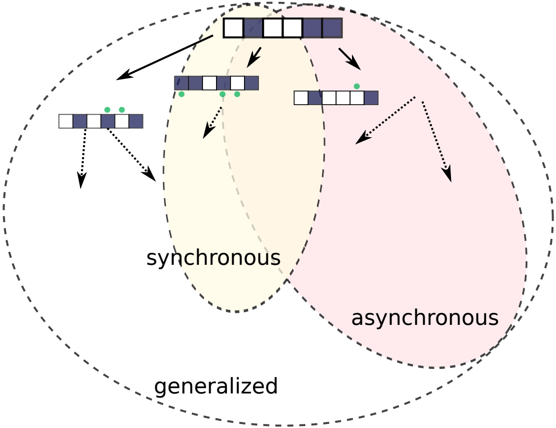
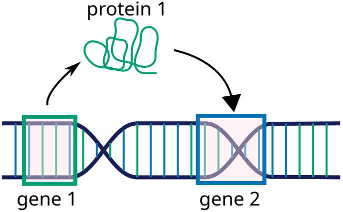


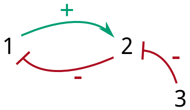
Can we reach configurations
beyond generalized asynchronicity?

Boolean networks for biological processes

Example with gene regulation



Influence graph



Boolean networks for biological processes

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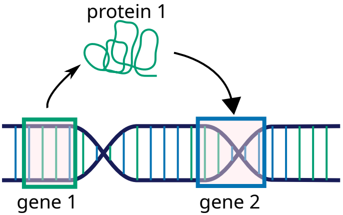

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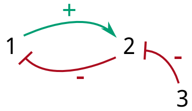
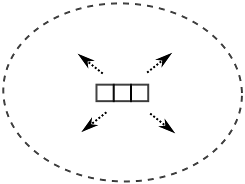


Reachable configurations

Boolean network

$$f_1(x) \triangleq \cdots$$
$$f_2(x) \triangleq \cdots$$
$$f_3(x) \triangleq \cdots$$

+ update mode =



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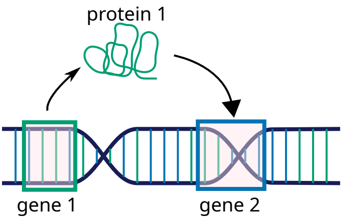

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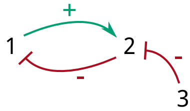

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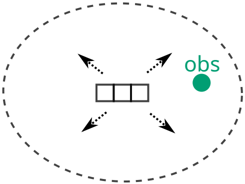
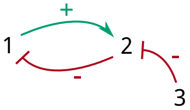
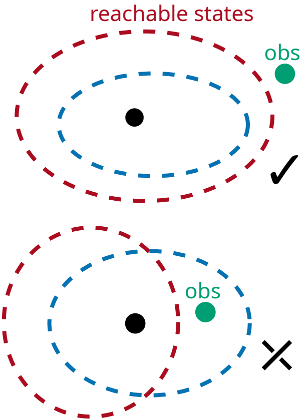


Validation w.r.t. observations (e.g. time series data)
⇒ we expect measurements match with reachable configurations

Qualitative vs abstract modelling



Consistency
analysis at Boolean level
transposable to multilevel?



information

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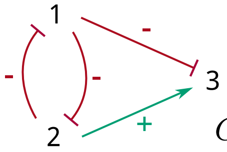
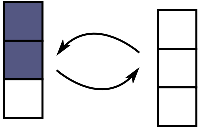
$$f_3(x) \triangleq \neg x_1 \wedge x_2$$



$G(f)$



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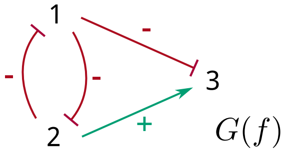

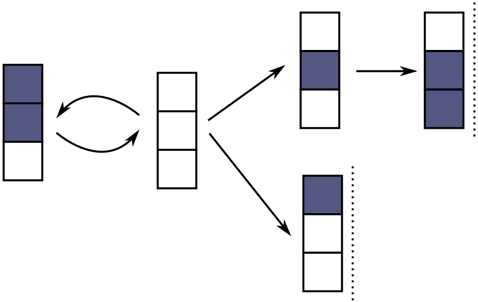

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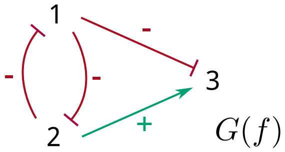

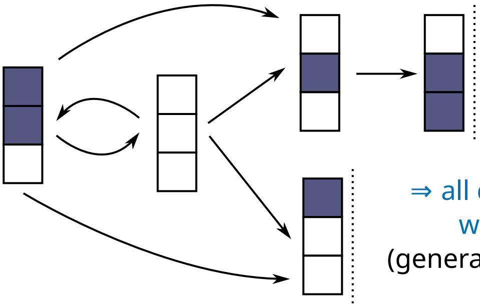

⇒ all configurations reachable
with any update mode
(generalized) asynchronous mode

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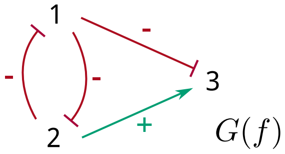
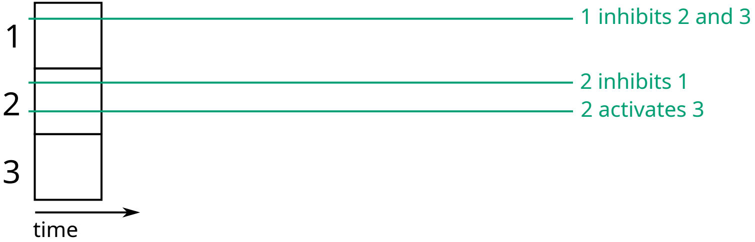


Compatible continuous/multilevel dynamics:



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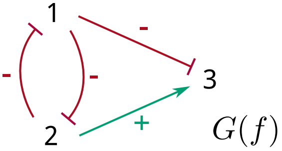

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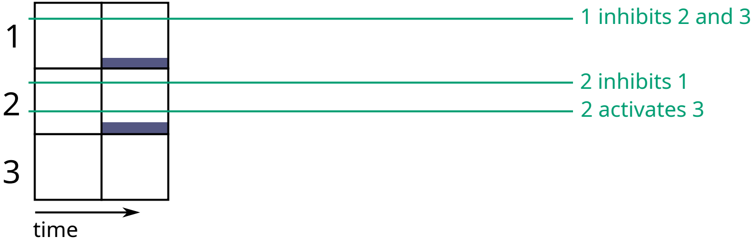

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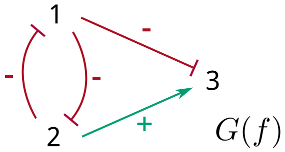

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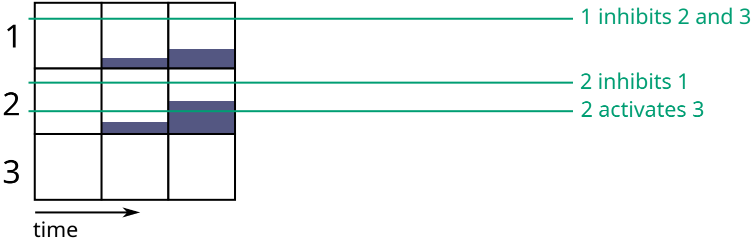

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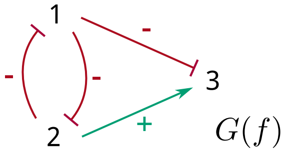

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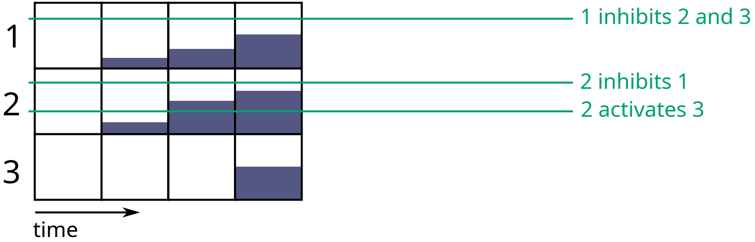

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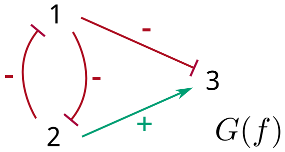

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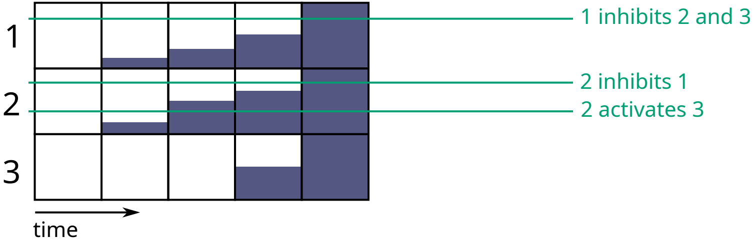

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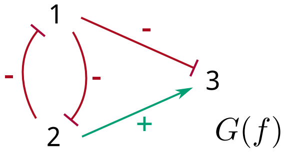

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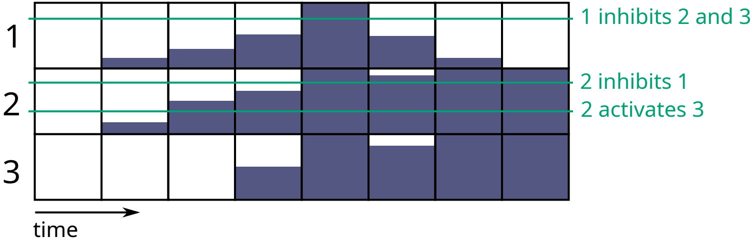

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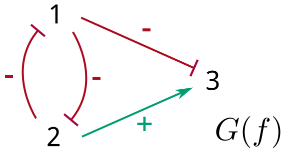

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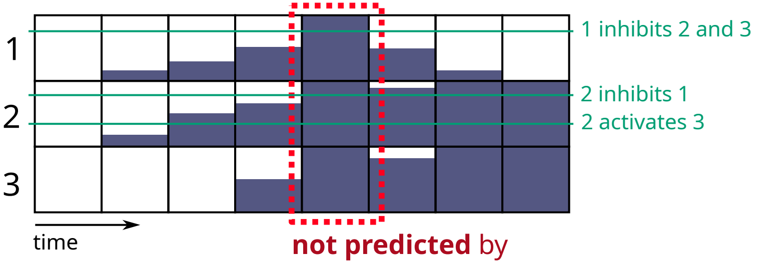


not predicted by
update modes in Boolean

Practical implications

Any update modes can miss possible transitions

Model inference from observations

⇒ Reject valid models (false negatives)

(wrongly conclude that some state are not reachable)

Prediction for reprogramming

Find mutations such that

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

⇒ False positives (2)

⇒ False negatives (1)

Most permissive semantics of Boolean networks

enabling new behaviours

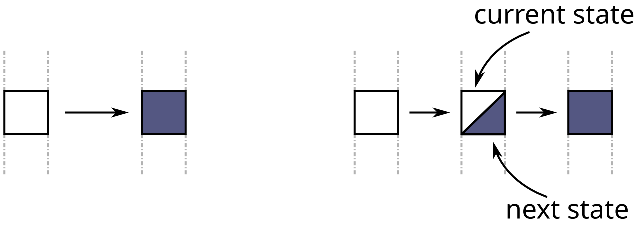
Most permissive semantics

- delay between firing and application of state change

  ⇒ allow interleaving other state changes

- in "intermediate" states

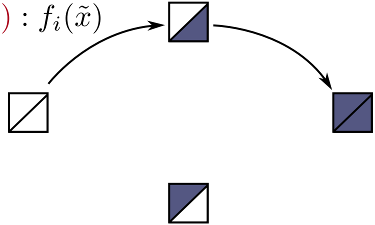
  other components choose what they see



Most permissive semantics

Rules for state of component i:

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



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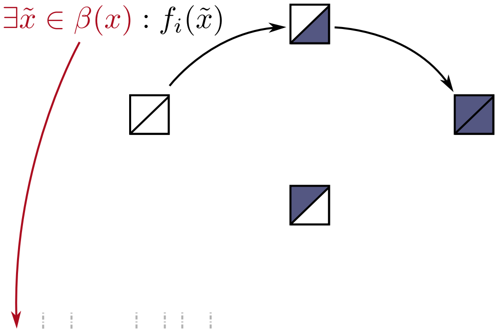

Choose value of "changing" components
(act as choosing an activation threshold)

Most permissive semantics

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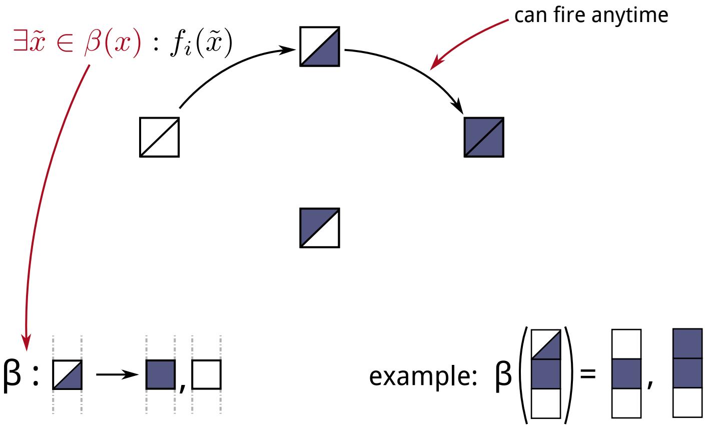

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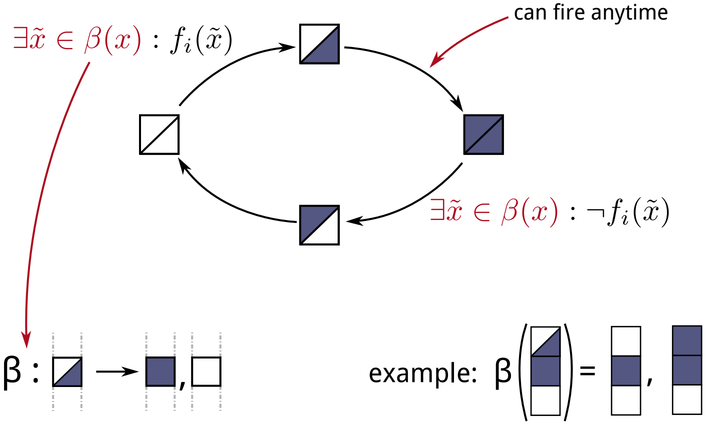

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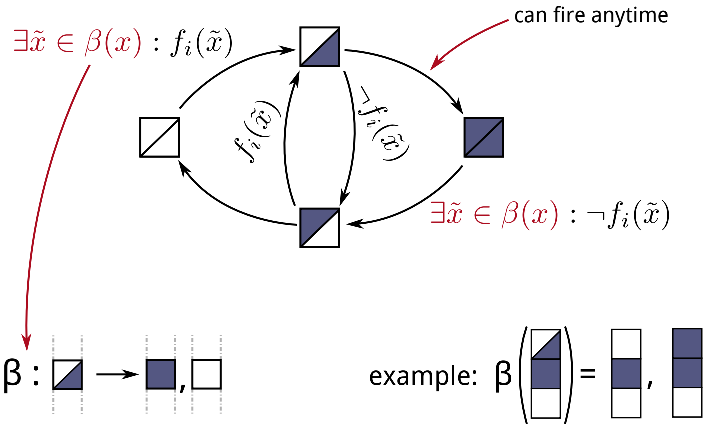

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Application to motivating example

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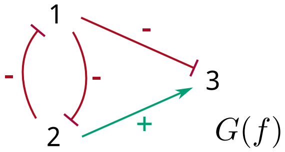

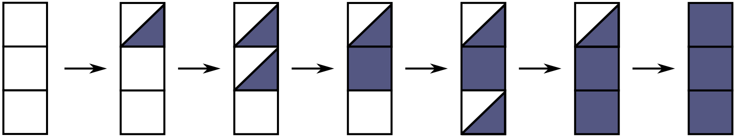

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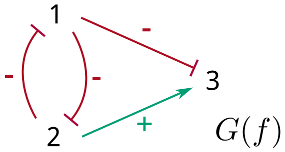
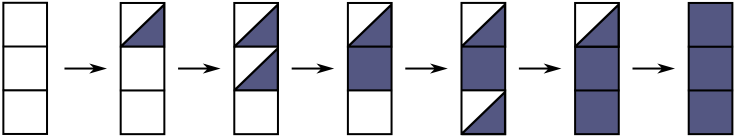




⇒ valid with respect to multivalued refinements

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 (configuration y is reachable from x):

  ⇒ comput. in quadratic iterations

(PTIME with locally-monotonic networks, or encoded as BDDs/Petri nets/...;

NP otherwise; instead of PSPACE-complete with update modes)

  ⇒ no need for simulations / model-checking / ...

  ⇒ scalable to thousands of components

- Attractors are hypercubes (minimal trap spaces)

  ⇒ finding attractors is in NP (instead of PSPACE-complete)

Refinements of Boolean Networks

A multivalued network

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

is a refinement of a Boolean network *f* iff

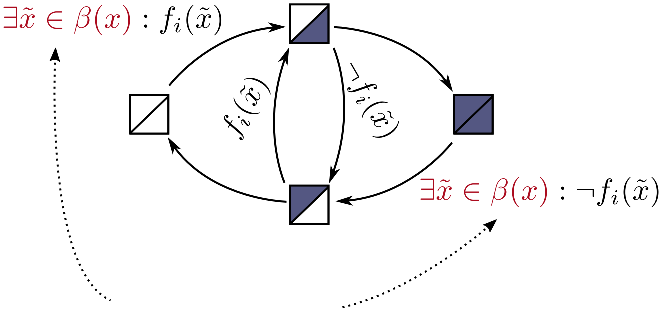
$$F_i(x) = \uparrow \implies \exists x' \in \beta(x) : f_i(x') = 1$$
$$F_i(x) = \downarrow \implies \exists x' \in \beta(x) : f_i(x') = 0$$

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
- when *f* is encoded as BDDs/Petri nets/...

Reachability with the most permissive semantics

Deciding reachability requires quadratic transitions

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

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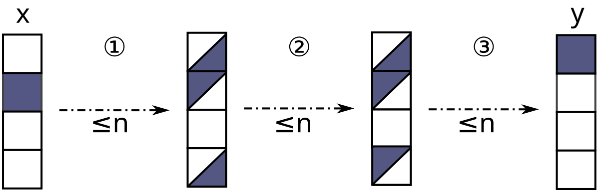

① - only transitions to "in-between" states*
② - orient towards final states
③ - converge to final states

*: some components must not be updated!

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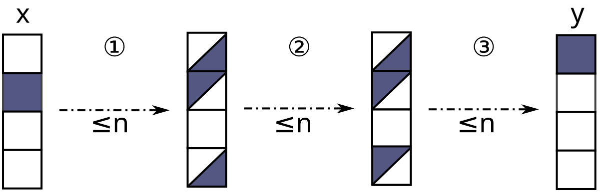

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NP in general
PTIME w/
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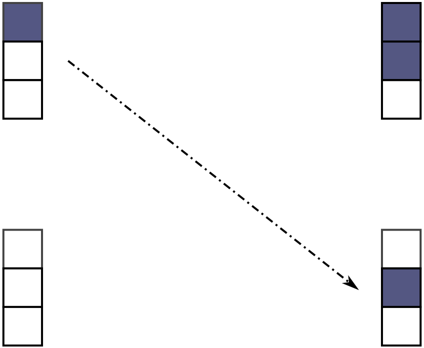
BDDs; Petri nets..

Attractors with the most permissive semantics

Attractor: smallest set of configurations without outgoing transitions

Attractors are hypercubes



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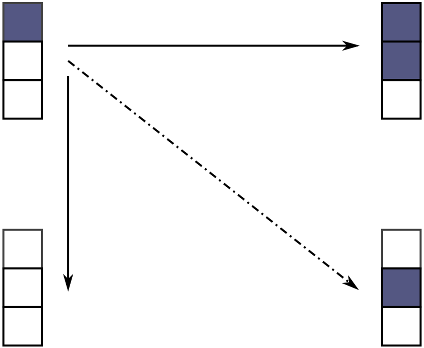
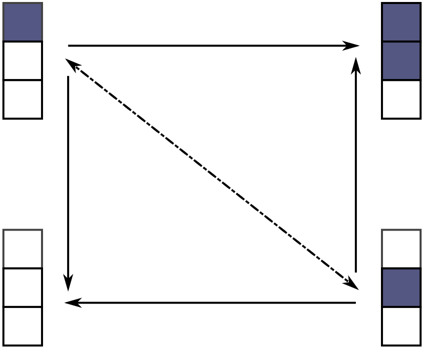


Attractors with the most permissive semantics

Attractor: smallest set of configurations without outgoing transitions

Attractors are hypercubes



Attractors with the most permissive semantics

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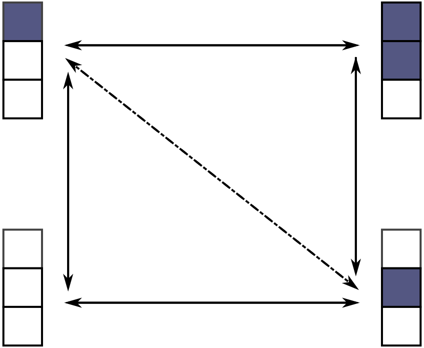
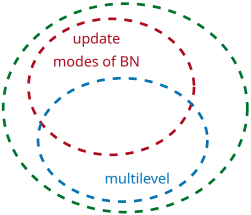


Attractors of most permissive semantics = minimal trap spaces

Existence of attractor within hypercube is in NP

Is most permissive semantics restrictive?



Minimality of abstraction

to any "most permissive" transition,

there is corresponding multilevel transition

(future work: "most permissive" paths)

- fixpoints (stable states) are preserved
- 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

Model inference from time series (reachabilty)

⇒ CaspoTS implements most permissive reachability

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 inference from differentiation data [Stéphanie Chevalier]
- prediction for 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