# Buffering of Boolean Networks

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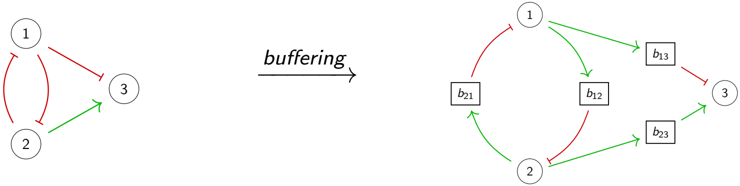
# Buffer networks

*Idea:* add a "buffer" or "delay" to each interaction




- each buffer is a copy of its regulator
  e.g., $f_{b_{12}}(x_1, x_2, b_{12}, b_{13}, b_{21}, b_{23}) = x_1$
- regulators are replaced by buffers in the regulation of their targets
  e.g., $f_3(x_1, x_2) = \bar{x}_1 \wedge x_2$ becomes
  $f_3(x_1, x_2, b_{12}, b_{13}, b_{21}, b_{23}) = \bar{b}_{13} \wedge b_{23}$
- buffer dynamics = asynchronous dynamics of the extended Boolean network

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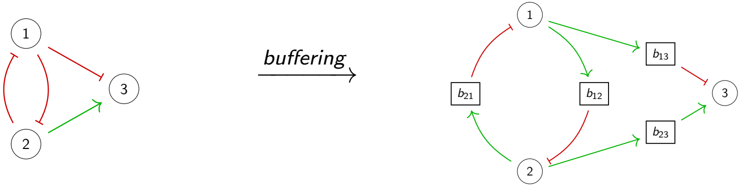


1. **Motivation**
   - trajectories
   - attractors
2. **Properties**
3. **Some open questions**

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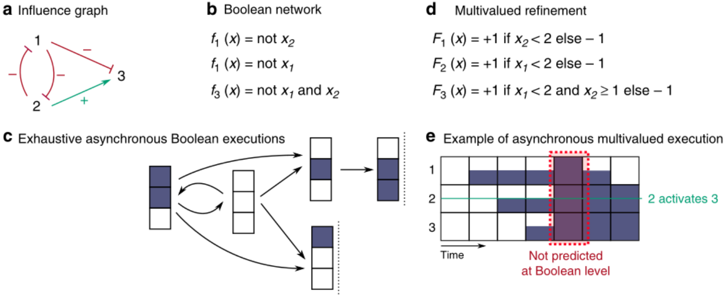
# Motivation: trajectories

*Boolean networks do not capture all behaviours of multivalued or continuous models*

**most permissive semantics** (Paulevé et al., *Nature Comm.*, 2020)



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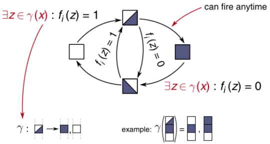


- states space is $\{0, 1, \nearrow, \searrow\}^n$
- all multivalued (and continuous) behaviours captured
- good computational properties

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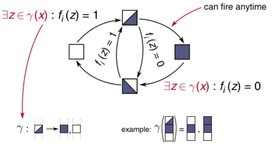


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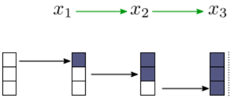


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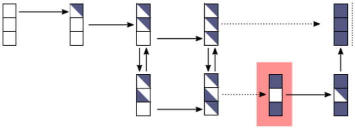

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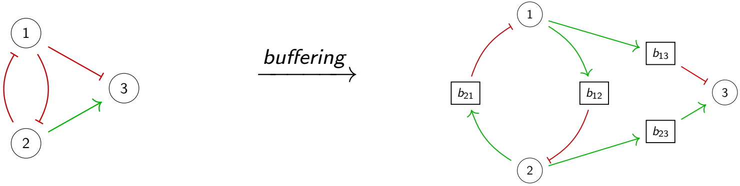


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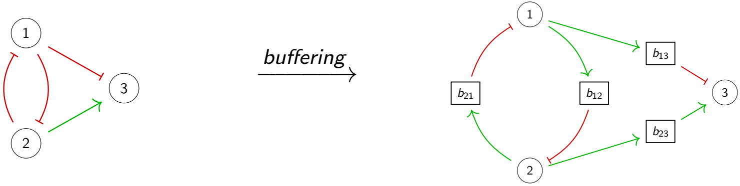
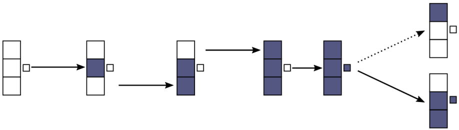



- separating thresholds by introducing “buffer” or “delay” variables
- still a Boolean network. **core** vs **buffer** components
- capture *some* multivalued behaviours:



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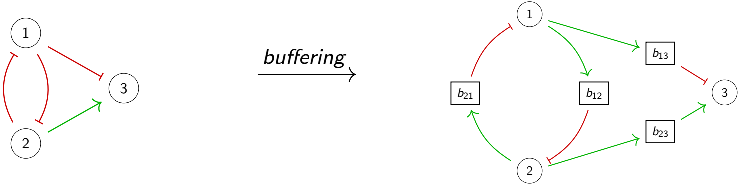


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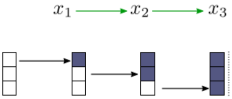


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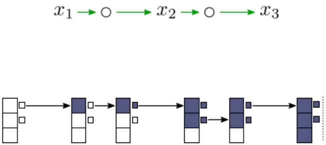
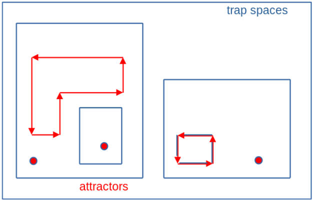


# Motivation: attractors

Attractors of asynchronous Boolean networks:

- *fixed points* and
- *complex/cyclic attractors*




- fixed points are easier to find
- trap spaces (subspaces closed for the dynamics; can be seen as partial fixed points) can also be found "easily"
- in biological networks, minimal trap spaces are *often* good approximations of attractors

- Most permissive semantics: attractors = minimal trap spaces.
- Buffer networks: attractors are in one-to-one correspondence with minimal trap spaces.

1 Motivation
- trajectories
- attractors

2 Properties

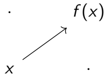
3 Some open questions

# Definitions of dynamics

Given $f\colon \{0,1\}^n \to \{0,1\}^n$

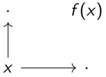
- synchronous dynamics:

$$x \mapsto f(x) \mapsto f^2(x) \mapsto \dots$$



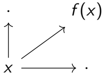

- asynchronous dynamics: for all $i \in \Delta(x, f(x)) = \{i \mid x_j \neq f_j(x)\}$

$$x \to x + e^i$$




- generalised asynchronous dynamics: for all $I \subseteq \Delta(x, f(x))$

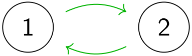
$$x \to x + \sum_{i \in I} e^i$$

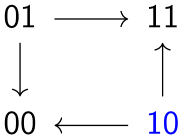


# Buffer networks and canonical states

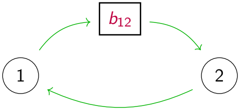
- add buffer variables that replace and copy their regulators
- *canonical*: states where buffer variables coincide with their regulators
- from every non-canonical state there is a path to a canonical

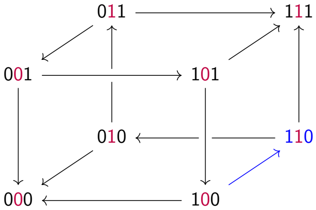
*Example:* $f(x_1, x_2) = (x_2, x_1)$




$f^b(x_1, b_{12}, x_2) = (x_2, x_1, b_{12})$



# Buffer networks: properties (1)

- asynchronous buffer dynamics contain all trajectories of generalised asynchronous dynamics

given $I \subseteq \Delta(x, f(x))$, $x \to \bar{x}^I$ transition in generalised dynamics, there exists a path from $x$ to $\bar{x}^I$ in the buffer asynchronous dynamics

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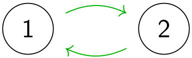


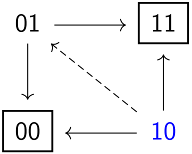


$f(10) = 01$

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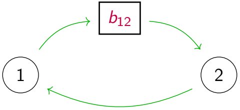


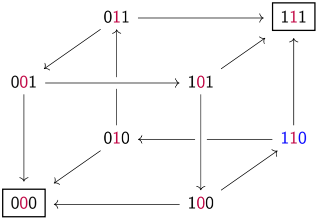

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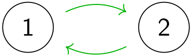


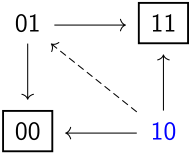


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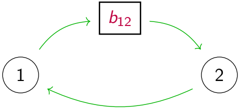


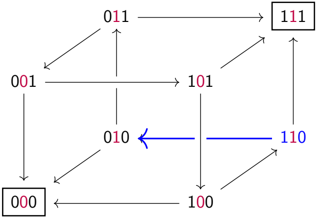

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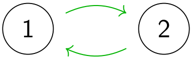


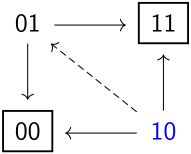


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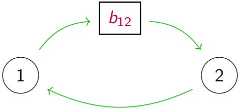


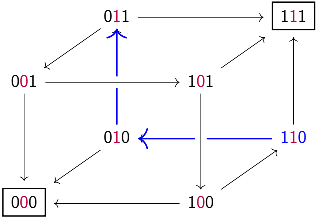

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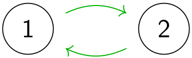


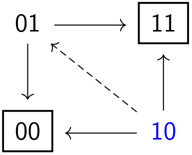


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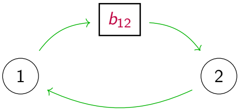


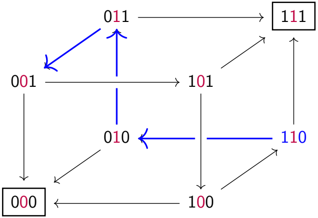

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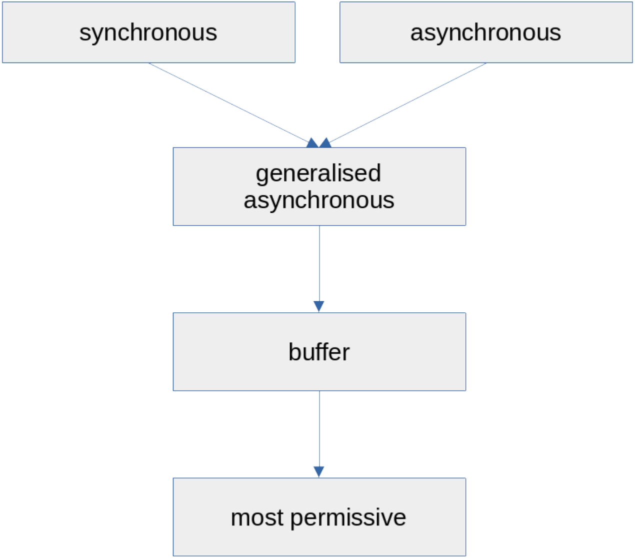
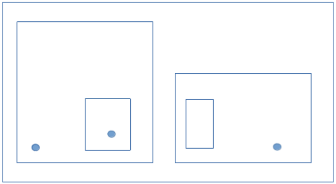


# Buffer networks: properties (2)

- reachability of trap spaces

original



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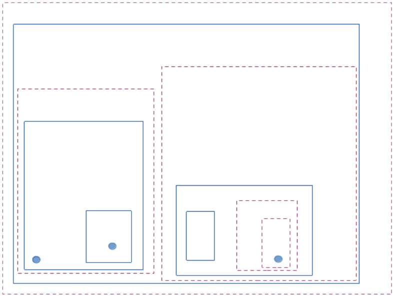
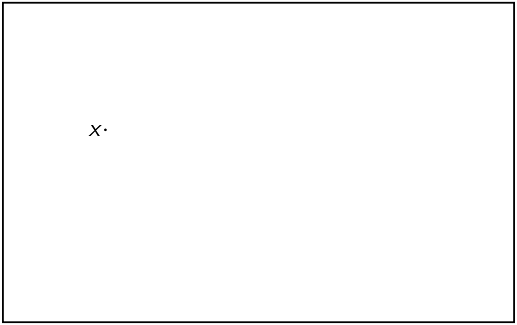


- trap space in Boolean network $\leftrightarrow$ canonical trap space in buffer network
- min. trap spaces in Boolean network $\leftrightarrow$ min. trap spaces in buffer network

# Buffer networks: properties (2)

- reachability of trap spaces: given an initial condition $x$, all trap spaces contained in the minimal trap space containing $x$ are reachable (canonical $x$, canonical trap spaces)



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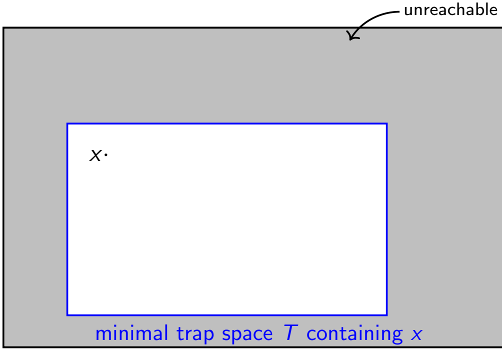

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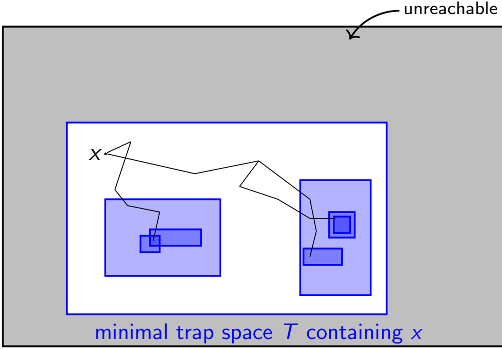


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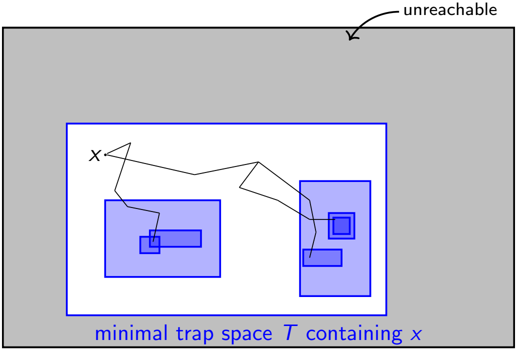
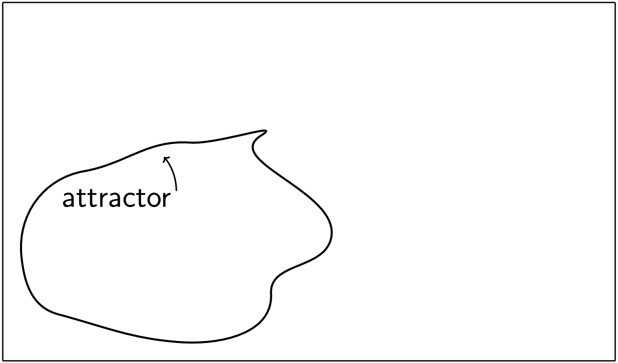



*all trap spaces in $T$ are reachable from $x$*

<u>*No attractors outside minimal trap spaces*</u>

# Buffer networks: properties (3)

- Each minimal trap space contains exactly one attractor



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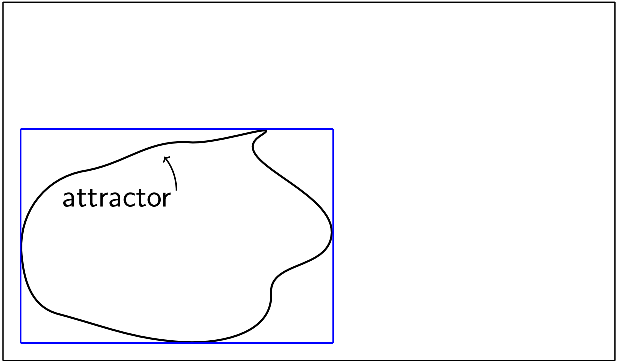


minimal subspace $T$ containing the attractor $\rightarrow$ *trap space*

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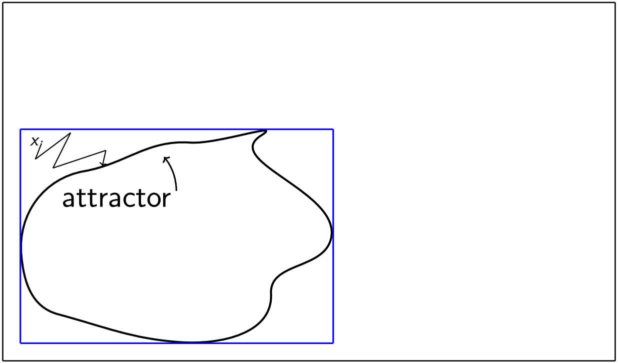


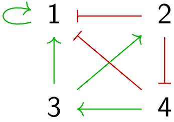

minimal subspace $T$ containing the attractor → *trap space*

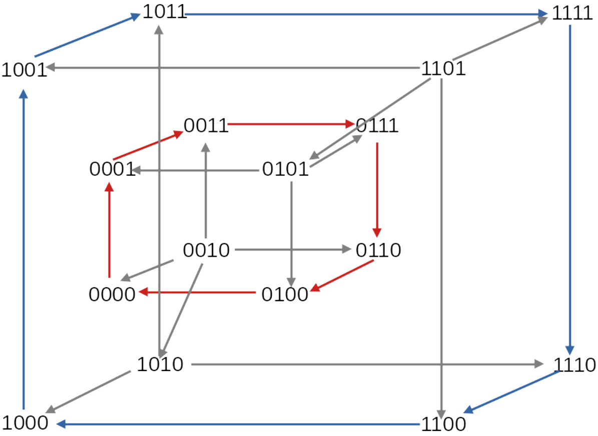
attractor reachable from all $x$ in $T$

# Buffer networks: properties (3) - example

- original network: two attractors in a minimal trap space (full space)

$f_1(x) =$
$x_1\bar{x}_2|x_1x_3|x_1\bar{x}_4|\bar{x}_2x_3\bar{x}_4$

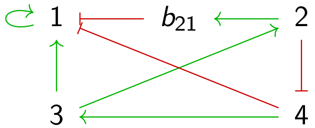


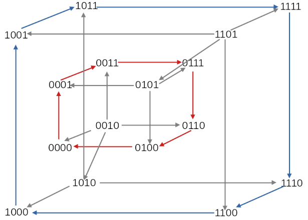



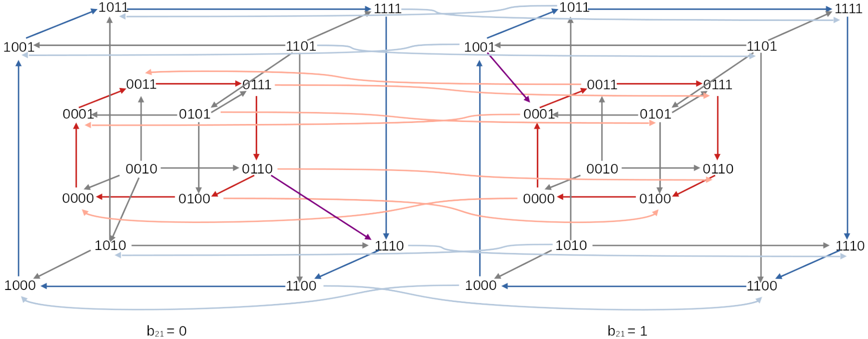
# Buffer networks: properties (3) - example

- buffered network: one attractor

$$f_1^b(x) = x_1 \bar{b}_{21} | x_1 x_3 | x_1 \bar{x}_4 | \bar{b}_{21} x_3 \bar{x}_4$$

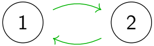


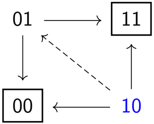



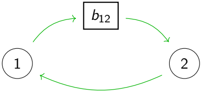



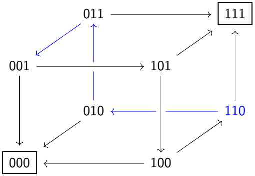
# How many buffers?

Do we need buffer $i \to j$ if $i$ has only one target?



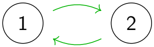

Only so that **all cycles are buffered**

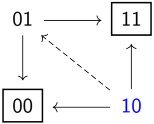
we call this type of extensions *buffer-separated*

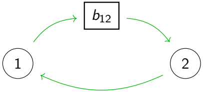
- all interactions from regulators with multiple targets are buffered
- all cycles are buffered

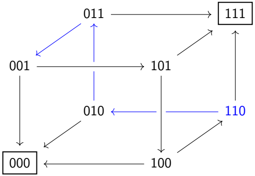
# How many buffers?

Do we need buffer $i \to j$ if $i$ has only one target?

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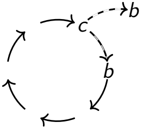
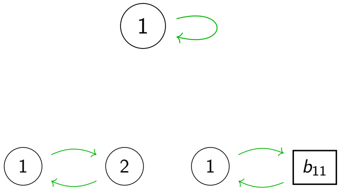
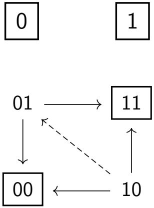


# What if the network is already bipartite?

× Reachability: clarify which variables are *core* and which variables are *buffer*.




✓ Attractors ↔ minimal trap spaces

1 Motivation
- trajectories
- attractors

2 Properties

3 Some open questions

# Open questions: bounds on path lengths?

$x, y \in \{0,1\}^n$ Boolean states

**most permissive**
if there exists a path from $x$ to $y$, then there exists a path from $x$ to $y$ with at most $3n$ transitions

**buffer-separated**
Example:

$$f(x_1, x_2, x_3, x_4) = (\bar{x}_3, \bar{x}_4, x_2, x_1 \wedge x_3)$$

4 core variables, 5 buffer variables

no path $0000 \rightsquigarrow 0101$ in asynchronous dynamics

paths $0000 \rightsquigarrow 0101$ in buffered network require *at least 18 updates of core variables*

# Open questions: comparison to multivalued

multivalued network

$$F\colon M = X_1 \times \cdots \times X_n \to M, \quad X_i = \{0, \ldots, m_i\}$$

$F$ is a *refinement* of $f\colon \{0,1\}^n \to \{0,1\}^n$ if "it can be seen as a multivalued version of $f$"

**most permissive**
For any asynchronous transition in any multivalued refinement, a corresponding trajectory exists

**buffer-separated**
For any asynchronous transition in a *single-threshold* refinement, a corresponding trajectory exists

# Summary

*Definition:*

- Network buffering allows to separate regulation thresholds
- No buffer needed if only one target and all cycles are buffered
- Some networks can be seen as buffer networks

*Properties:*

- General asynch. $\subseteq$ buffer asynch. $\subseteq$ most permissive dynamics
- Minimal trap spaces are good approximations of attractors
- All trap spaces "visible" from a given initial condition are reachable

A. Naldi, H. Siebert and E. T., Buffer extensions of Boolean networks, in preparation

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