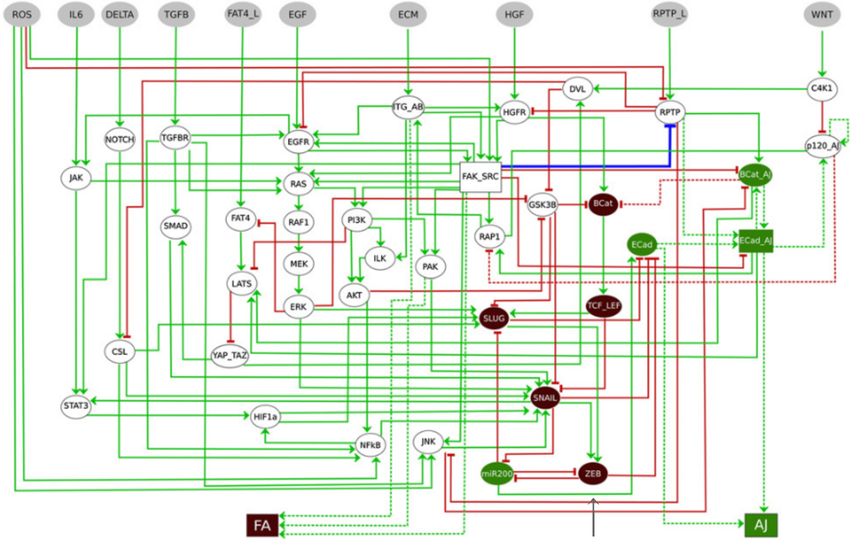
Structure and dynamics of discrete interaction networks: some recent trends

Elisa Tonello

Department of Mathematics and Computer Science
Freie Universität Berlin

elisa.tonello@fu-berlin.de

Boolean modelling



not(miR200) and (SNAIL or SLUG)

EMT network, from Selvaggio et al., *Cancer Research*, 2020

Outline

Boolean networks

n species

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

Example: $n = 2$

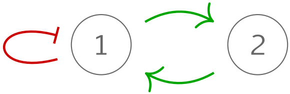
$f(x_1, x_2) = ((1 - x_1)x_2, x_1)$

Interaction graph

- vertices $\{1, \ldots, n\}$
- edge $j \xrightarrow{s} i$ at x if

$$\frac{f_i(\bar{x}^j) - f_i(x)}{\bar{x}^j_j - x_j} = s \in \{-1, 1\}$$

where $\bar{x}^j_k = x_k$ for $k \neq j$, $\bar{x}^j_j = 1 - x_j$



$1 \xrightarrow{1} 2$ at $x = 00$:

$$\frac{f_2(10) - f_2(00)}{1 - 0} = 1$$

Boolean networks

n species

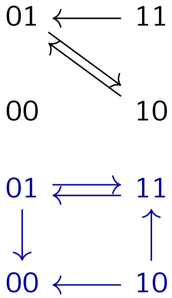
$f\colon \{0,1\}^n \to \{0,1\}^n$

Example: $n = 2$

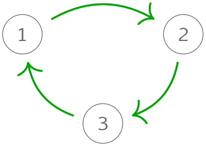
$f(x_1, x_2) = ((1 - x_1)x_2, x_1)$

State transition graph

- vertices $\{0,1\}^n$
- edges (*transitions*)
  - **synchronous**:
    $x \mapsto f(x) \mapsto f^2(x) \mapsto \dots$
  - **asynchronous**:
    $x \to \bar{x}^i$ if $f_i(x) \neq x_i$
  - ...

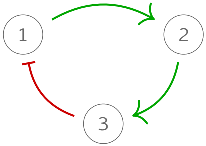


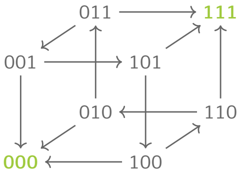
Examples and definition of attractor



interaction graph

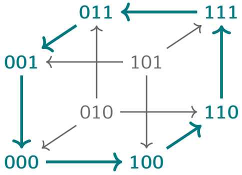
n vertices





asynchronous state transition graph

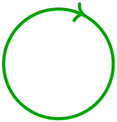
2^n states



Attractors = terminal strongly connected components

- fixed points or stable states
- cyclic attractors

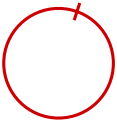
Interaction cycles and attractors



isolated positive cycle

⇓

two fixed points



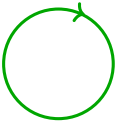
isolated negative cycle

⇓

one cyclic attractor

Remy et al. 2003

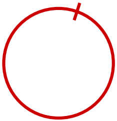
Interaction cycles and attractors



isolated positive cycle

⇓

two fixed points



isolated negative cycle

⇓

one cyclic attractor

Remy et al. 2003

∃ positive local cycle

⇑

multiple attractors

∃ negative "global" cycle

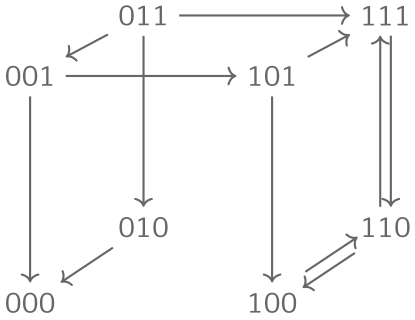
⇑

∃ cyclic attractor

"rules of Thomas" overview: Richard 2019

Attractors and trap spaces

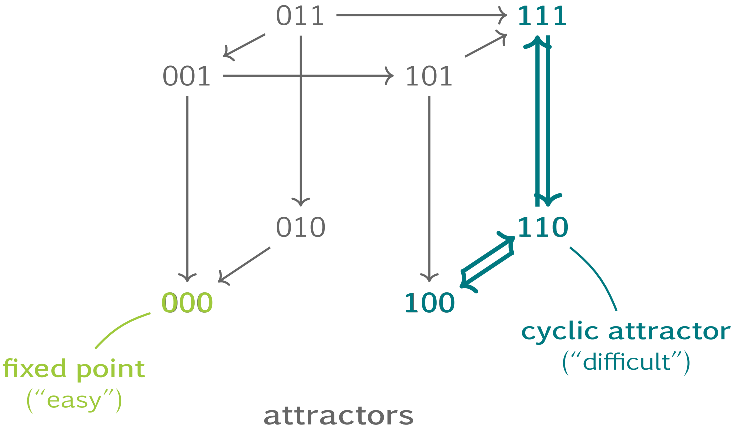
$f(x_1, x_2, x_3) = (x_1 \vee x_3, x_1 \wedge (\neg x_2 \vee x_3), x_1 \wedge x_2 \wedge \neg x_3)$



asynchronous dynamics

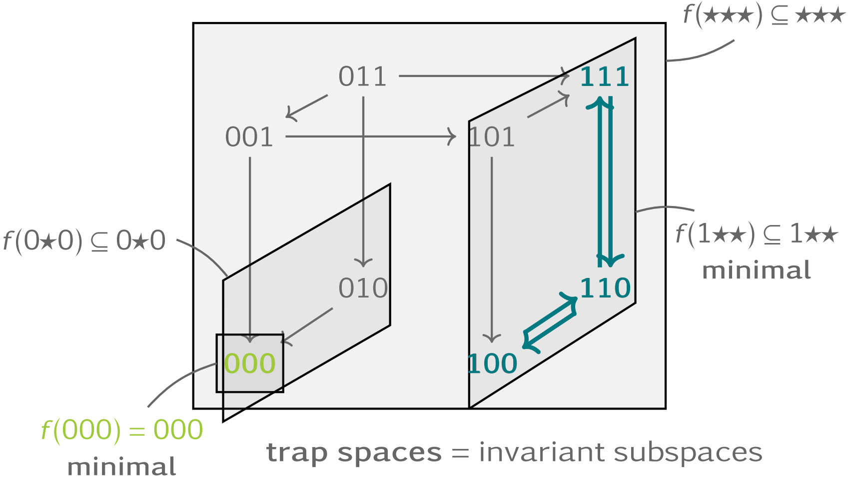
Attractors and trap spaces

$f(x_1, x_2, x_3) = (x_1 \vee x_3, x_1 \wedge (\neg x_2 \vee x_3), x_1 \wedge x_2 \wedge \neg x_3)$



Attractors and trap spaces

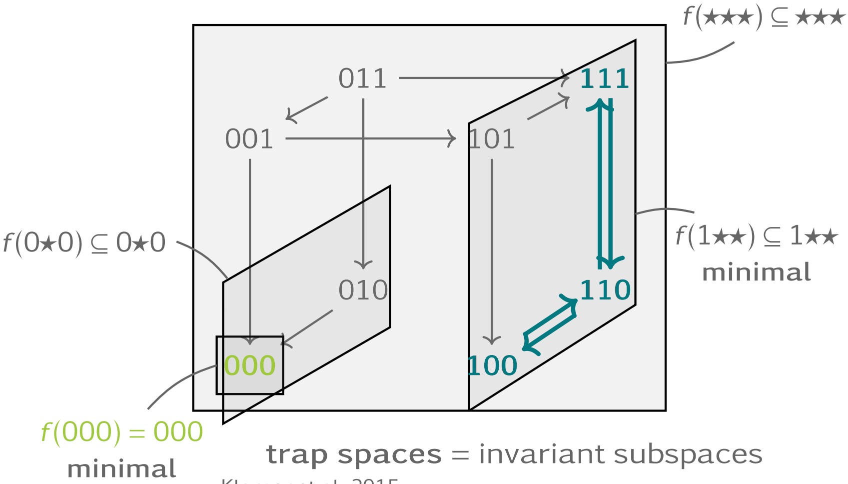
$f(x_1, x_2, x_3) = (x_1 \vee x_3, x_1 \wedge (\neg x_2 \vee x_3), x_1 \wedge x_2 \wedge \neg x_3)$



trap spaces = invariant subspaces

Attractors and trap spaces

$f(x_1, x_2, x_3) = (x_1 \vee x_3, x_1 \wedge (\neg x_2 \vee x_3), x_1 \wedge x_2 \wedge \neg x_3)$



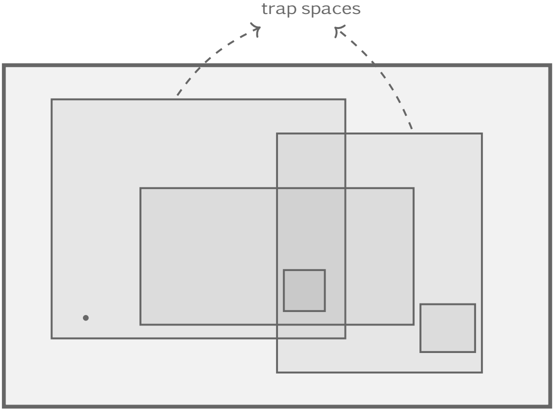
trap spaces = invariant subspaces

Klarner et al. 2015

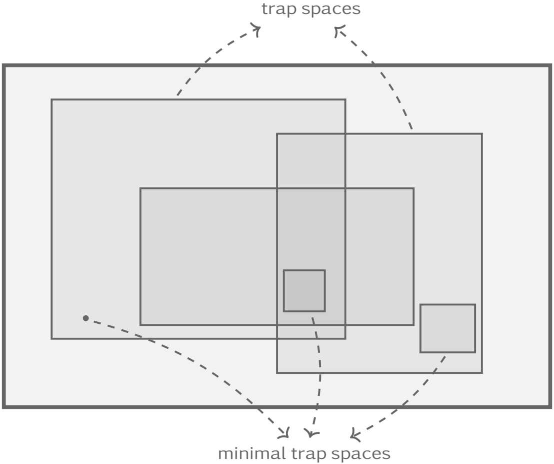
Trinh et al. 2022: trap spaces = siphons of Petri netri encoding

Moon et al. 2023: computational complexity

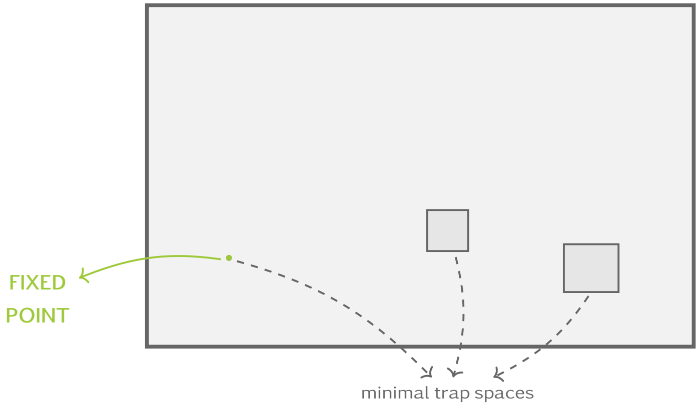
A taxonomy of asynchronous attractors



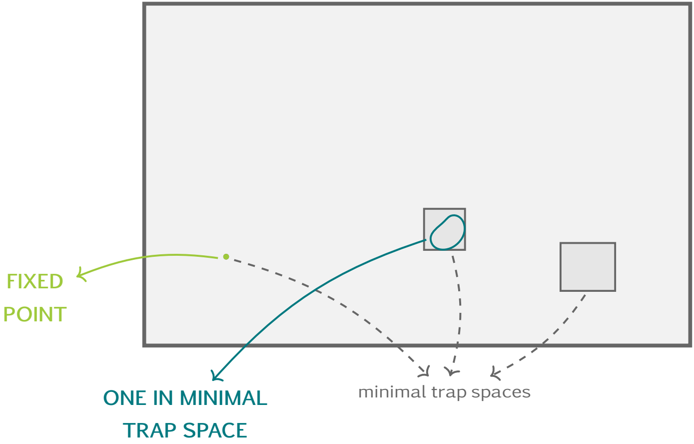
A taxonomy of asynchronous attractors



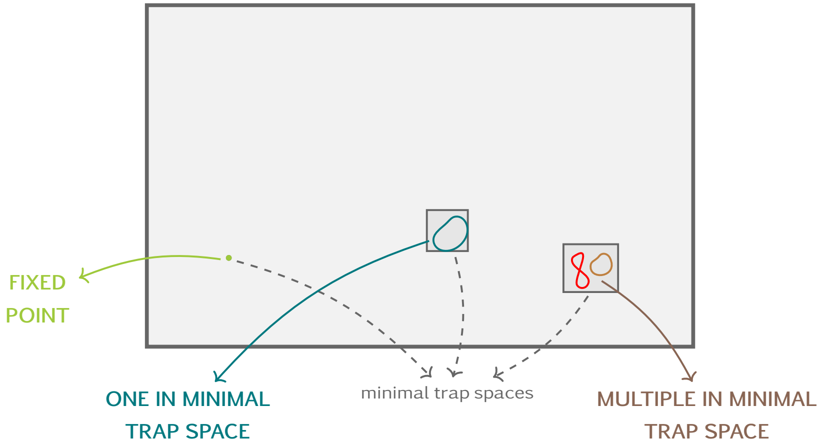
A taxonomy of asynchronous attractors



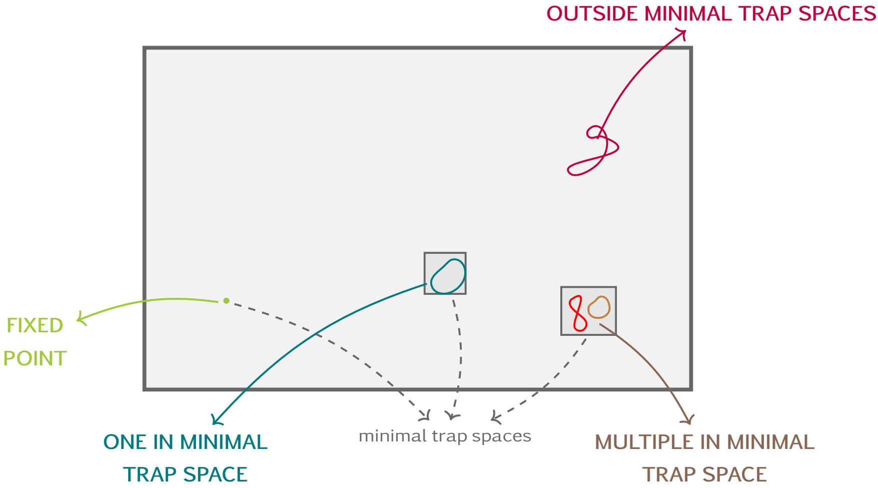
A taxonomy of asynchronous attractors



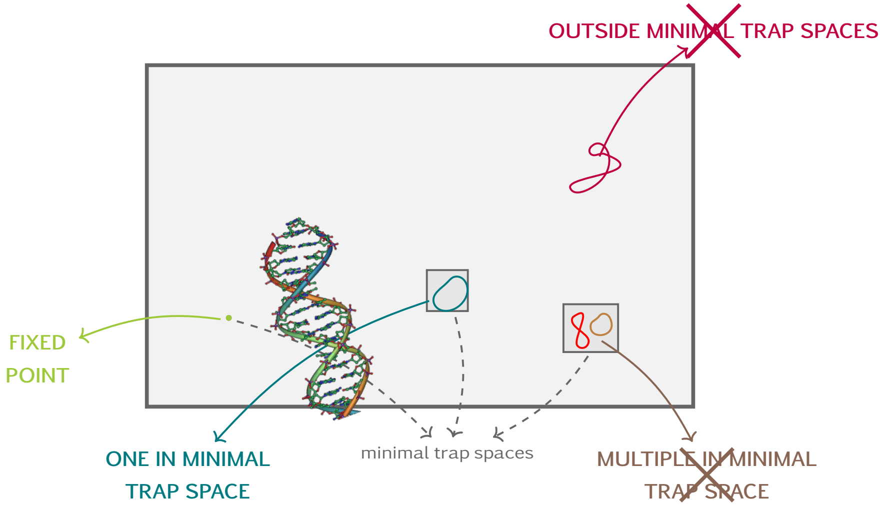
A taxonomy of asynchronous attractors



A taxonomy of asynchronous attractors

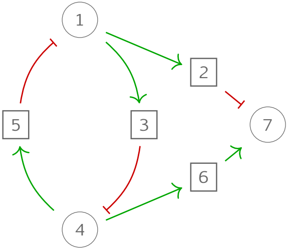


A taxonomy of asynchronous attractors



Conditions for “nice” asynchronous attractors?

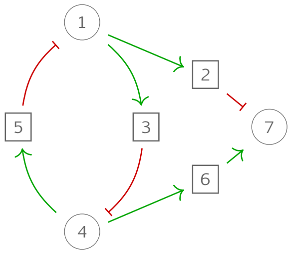
Networks with linear cuts (Naldi, Richard and Tonello 2023)



- ✓ $\{2, 3, 5, 6\}$ are *linear* (one regulator, one target)
- ✓ they are a feedback vertex set (if removed, no cycles)
- ✓ intercept all paths from variables with multiple targets to variables with multiple regulators

Conditions for "nice" asynchronous attractors?

Networks with linear cuts (Naldi, Richard and Tonello 2023)



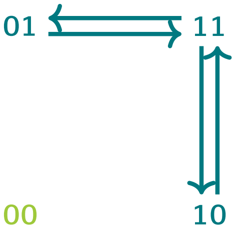
- ✓ $\{2, 3, 5, 6\}$ are *linear* (one regulator, one target)
- ✓ they are a feedback vertex set (if removed, no cycles)
- ✓ intercept all paths from variables with multiple targets to variables with multiple regulators

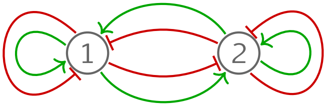
- ▹ attractors 1-to-1 with minimal trap spaces
- ▹ attractor reachability from initial condition x: if linear variables are "copies" of their regulators, all attractors contained in the minimal trap space containing x are reachable from x

Conditions for "nice" asynchronous attractors?

Separating attractors (Richard and Tonello 2023)

- conditions for each attractor in a separate subspace/trap space?

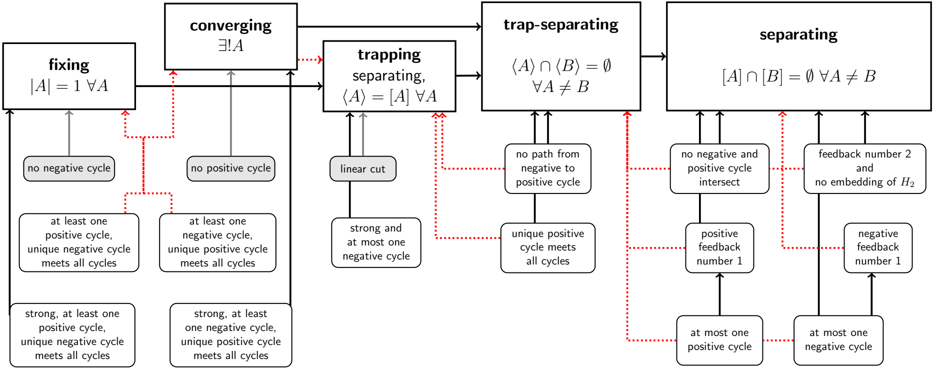




Conditions for "nice" asynchronous attractors?

Separating attractors (Richard and Tonello 2023)

- conditions for each attractor in a separate subspace/trap space?



Problem 1: finding attractors

- using symbolic computation (AEON): Beneš et al. 2021, 2022
- breaking negative cycles and using trap spaces (mtsNFVS): Trinh et al. 2021, 2021
- reduction: Tonello and Paulevé 2023

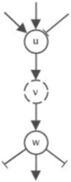
	original			reduced			
Model	nodes	AEON	mtsNFVS	nodes	reduction	AEON	mtsNFVS
MAPK	53	5.7	28.9 ±5.7 (3 DNF)	10	0.0	0.3	0.7
IL-6	55	774.6	14.8 ±1.8	17	0.0	6.0	7.4
EMT	56	25.6	DNF	17	0.1	0.7	1.4
T-LGL	58	17.5	2.2	18	0.0	0.9	1.9
CACC	66	9.3	0.5	11	0.0	0.3	0.7
AD	74	361.9	0.7	10	0.0	0.4	0.8
AGS	83	1.7	0.6	2	0.0	0.3	0.7
CC	87	DNF	8.2 ±3.5	35	0.3	11.1	6.0
SP	102	DNF	DNF	33	0.1	0.8	1.1
SIPC	116	DNF	1664.7 ±506.3	32	0.6	6.9	53.7 ±7.4
DSP	144	DNF	2.3	10	0.0	0.4	0.7
C3.0	176	DNF	2.1	14	0.1	0.4	1.0
EP	183	DNF	62.7 ±64.2	25	0.1	0.6	2.4

Attractors and reduction

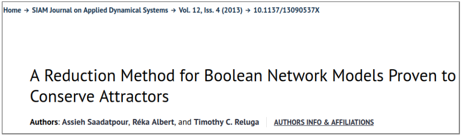
Home → SIAM Journal on Applied Dynamical Systems → Vol. 12, Iss. 4 (2013) → 10.1137/13090537X

A Reduction Method for Boolean Network Models Proven to Conserve Attractors

Authors: Assieh Saadatpour, Réka Albert, and Timothy C. Reluga | AUTHORS INFO & AFFILIATIONS

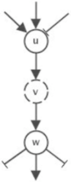


Attractors and reduction


Home → SIAM Journal on Applied Dynamical Systems → Vol. 12, Iss. 4 (2013) → 10.1137/13090537X

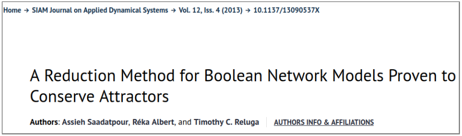
A Reduction Method for Boolean Network Models Proven to Conserve Attractors

Authors: Assieh Saadatpour, Réka Albert, and Timothy C. Reluga | AUTHORS INFO & AFFILIATIONS



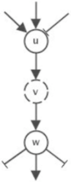
counterexamples: Schwieger and Tonello 2024

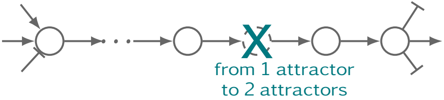
Attractors and reduction


Home → SIAM Journal on Applied Dynamical Systems → Vol. 12, Iss. 4 (2013) → 10.1137/13090537X

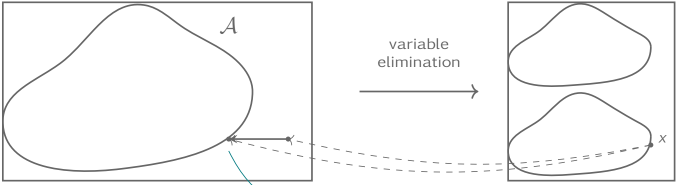
A Reduction Method for Boolean Network Models Proven to Conserve Attractors

Authors: Assieh Saadatpour, Réka Albert, and Timothy C. Reluga | AUTHORS INFO & AFFILIATIONS





counterexamples: Schwieger and Tonello 2024



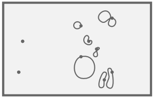
$(x_1, \ldots, f_i(x_1, \ldots, \cancel{x_i}, \ldots, x_n), \ldots, x_n)$

Tonello and Paulevé 2023

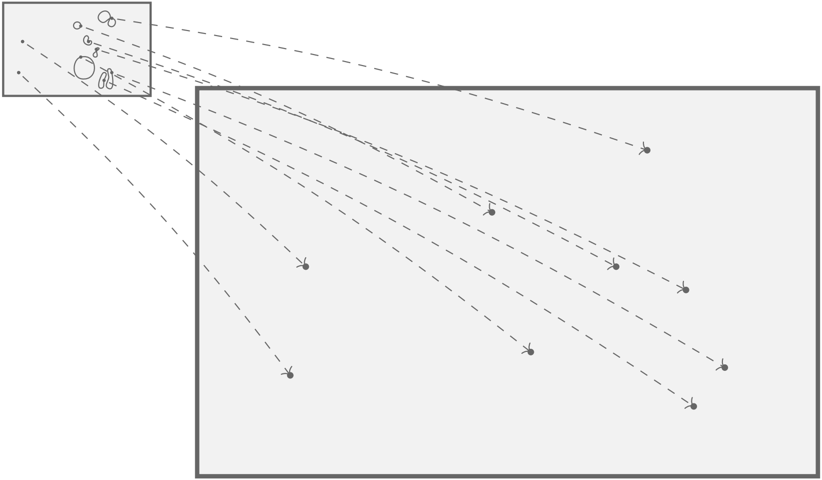
Theorem: states in attractors can be reconstructed from states in attractors of the reduction

Reduction approach: idea

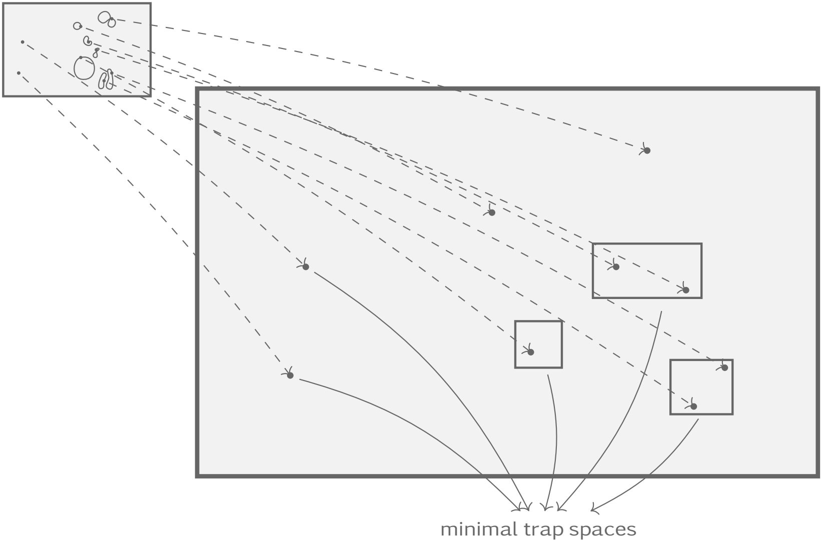
Reduction approach: idea



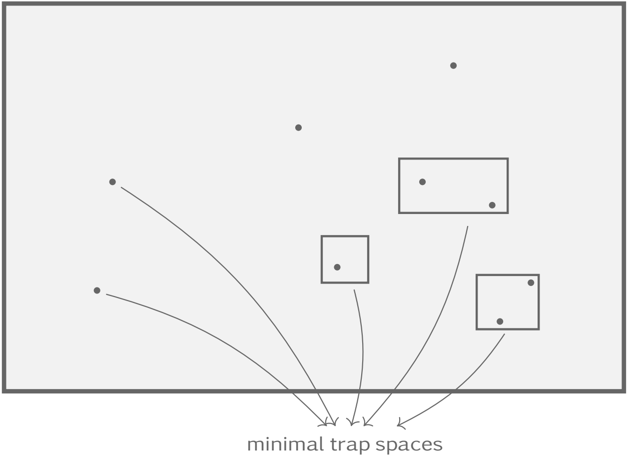
Reduction approach: idea



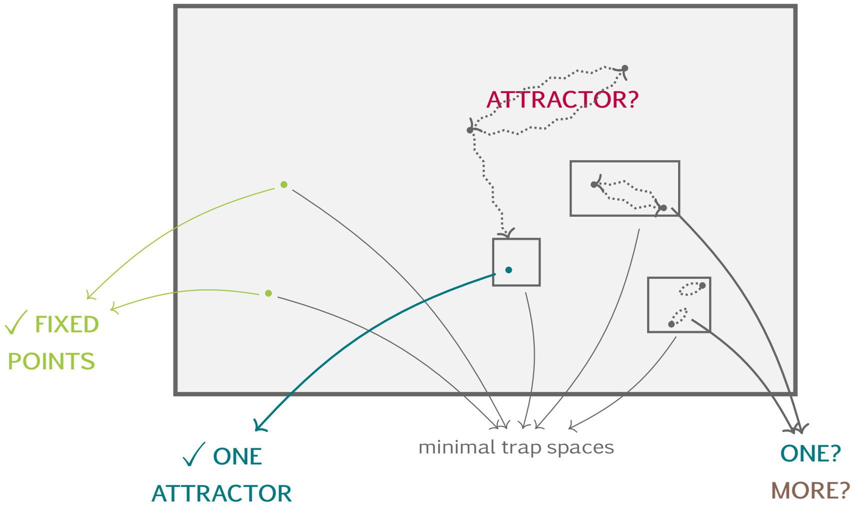
Reduction approach: idea



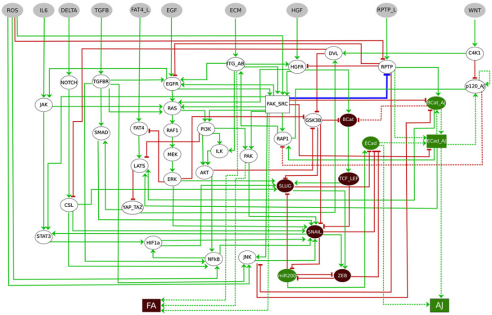
Reduction approach: idea



Reduction approach: idea



Problem 2: control strategy identification



EMT network, from Selvaggio et al., *Cancer Research*, 2020

phenotypes

e.g. $M1 = \{AJ_1 = 0, AJ_2 = 0, FA_1 = 1, FA_2 = 0, FA_3 = 0\}$

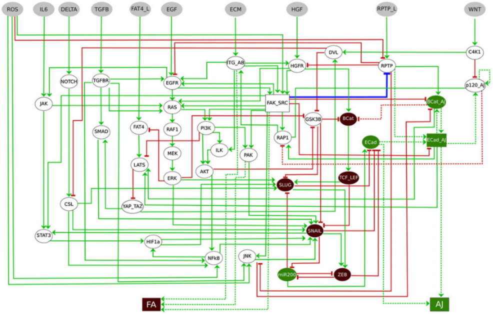
node interventions

e.g. $\{ROS = 1, PAK = 0\}$

identify (minimal number of) node or edge interventions s.t.

- all attractors contained in a given phenotype
- no attractors contained in a given phenotype
- attractors reachable from some given initial conditions . . .
- . . .

Problem 3: marker set identification



EMT network, from Selvaggio et al., *Cancer Research*, 2020

P = *phenotype variables*

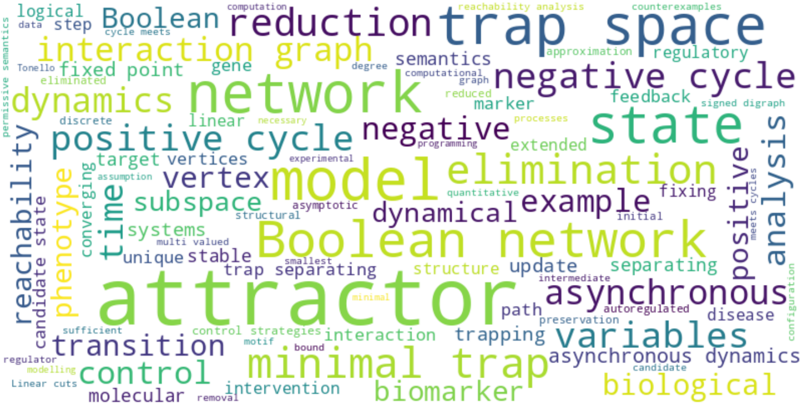
for x in attractor,
$\pi_P(x)$ identifies the phenotype

identify (minimal number of) *marker variables* M:
for all x, y attractor states

$$\pi_M(x) = \pi_M(y) \implies \pi_P(x) = \pi_P(y)$$

Klarner et al. 2021

The end



Thank you

elisa.tonello@fu-berlin.de, elisa@tonello.me