Logical modelling: Inferring structure from dynamics

Ling Sun, Therese Lorenz and Alexander Bockmayr
Freie Universität Berlin

Speaker: Ling Sun
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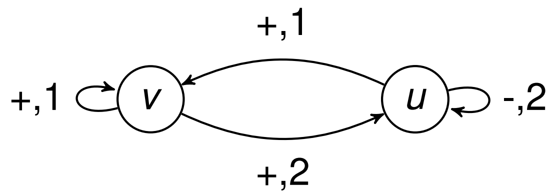
Logical formalism: structure, a model $M = (I, K)$

Interaction graph (IG)

A directed graph with

- V: nodes
- E: edges, **no multiple edges**
- ε: signs
- ϑ: thresholds
- max: maximal activity levels



Logical parameter $K(v, \omega)$

Tendency of each component v under every possible combination ω of its positive influences

ω	$K(v,\omega)$	ω	$K(u,\omega)$
$\emptyset$	0	$\emptyset$	0
$\{u\}$	1	$\{u\}$	0
$\{v\}$	1	$\{v\}$	0
$\{v,u\}$	2	$\{v,u\}$	2

Alternative: logical rules, $\wedge$, $\vee$ and $\neg$

Logical formalism: dynamics, ASTG $T_M = (X, S)$

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State transitions

- asynchronous
- unitary

State $x = (x_{v_1}, x_{v_2})$

10

$Res(v_1, 20) = \emptyset$

$K(v_1, \emptyset) = 0$

$\delta(v_1, 20) = \text{sign}(0 - 2) = -1$

20 → 21

$Res(v_2, 20) = \{v_1, v_2\}$

$K(v_2, \{v_1, v_2\}) = 2$

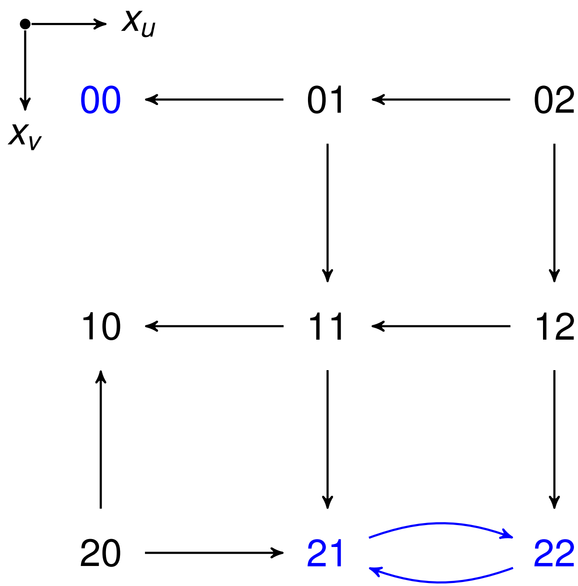
$\delta(v_2, 20) = \text{sign}(2 - 0) = 1$

Asynchronous state transition graph (ASTG)

$T_M = (X, S)$, X: state space, S: state transitions

$$S := \bigcup_{x \in X} \{(x, x + \delta(u, x)\, \mathbf{e}^u) \mid u \in V : \delta(u, x) \neq 0\}$$

($\mathbf{e}^u$ is the u-th unit vector in X)



attractors: terminal strongly connected components

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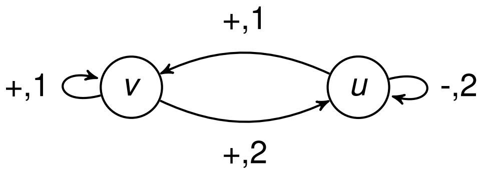
Structure (Model) — Logical modelling → **Dynamics** (ASTG)

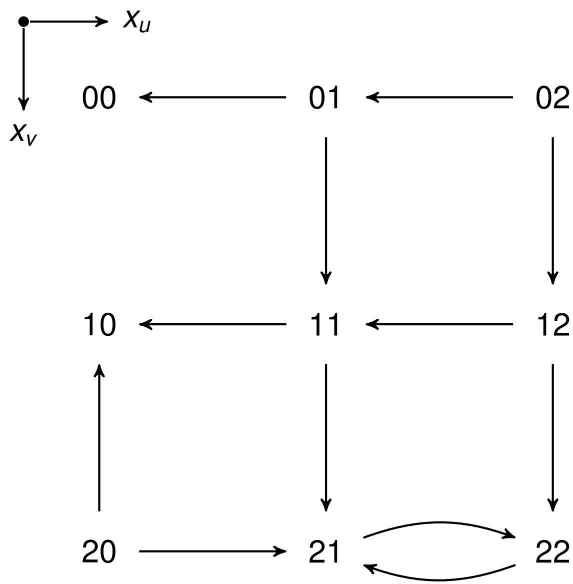
← Reverse engineering [T. Lorenz, 2011]



Interaction graph (IG) I

ω	$K(v,\omega)$	$K(u,\omega)$
$\emptyset$	0	0
$\{u\}$	1	0
$\{v\}$	1	0
$\{v,u\}$	2	2

Logical parameter function K



Asynchronous state transition graph (ASTG) $T_M = (X, S)$

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Row-types in ASTGs

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Proposition [1,2]

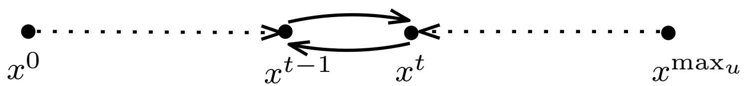
Given an ASTG T_M, for each u-row $\tau^u = (x^0, \ldots, x^{\max_u})$, exactly one of the following situations holds:

In an ASTG, this indicates:

1. τ^u has the form

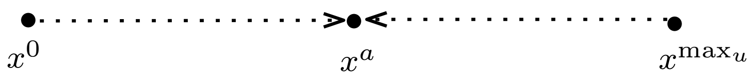
$\Longrightarrow \varepsilon(u,u) = +,\ \vartheta(u,u) = t,$
pos-type

2. τ^u has the form



$\Longrightarrow \varepsilon(u,u) = -,\ \vartheta(u,u) = t,$
neg-type

3. τ^u has the form



$\Longrightarrow (u,u) \notin E$ or $\varepsilon(u,u) = +$ or $-$,
open-type

[1] T. Lorenz. *Vergleich von zwei- und mehrwertigen Modellen...*. Diploma Thesis, Freie Universität Berlin, 2011.
[2] T. Lorenz, H. Siebert and A. Bockmayr. *Analysis and characterization of asynchronous ...*. Bull. of Math. Biol., 2013.

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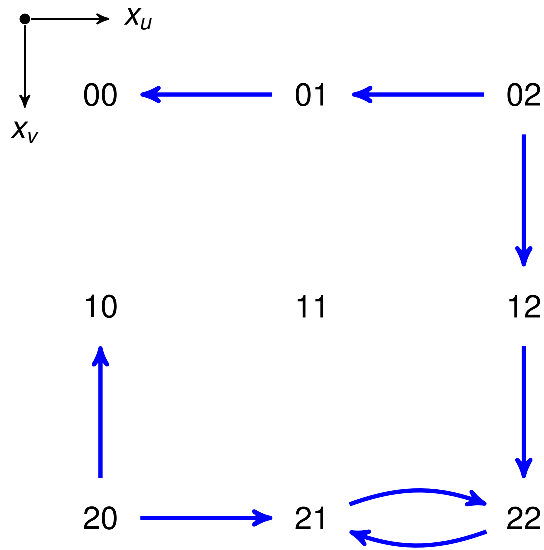
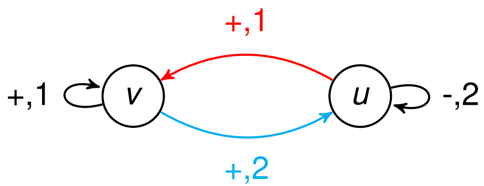
Theorem [2]

For any model $M = (I, K)$, the ASTG T_M is uniquely determined by its extremal rows and the interaction graph I.

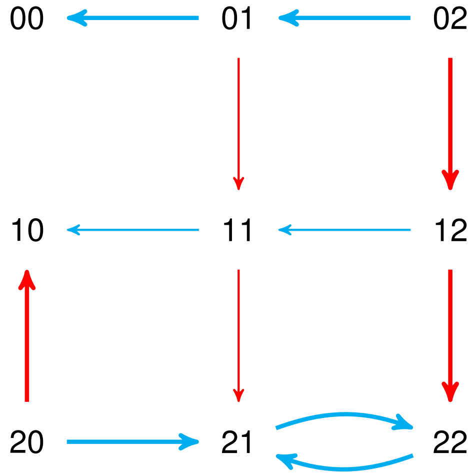


Extremal rows

+



⇗



Parallel rows in one direction can change at most once.

Characterise ASTGs by necessary and sufficient conditions: *u*-hypercube[3]

[2] T. Lorenz, H. Siebert and A. Bockmayr. *Analysis and characterization of asynchronous ....* Bull. of Math. Biol., 2013.
[3] L. Sun *Relating the structures and dynamics....* Doctoral Thesis, Freie Universität Berlin, 2017.

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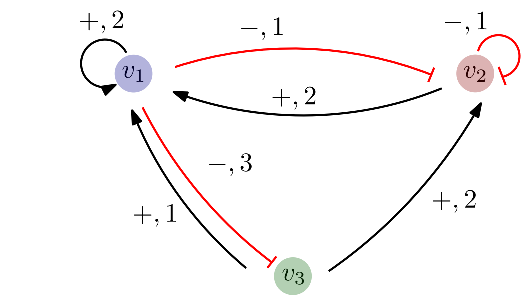
ASTG example: a model with 3 nodes

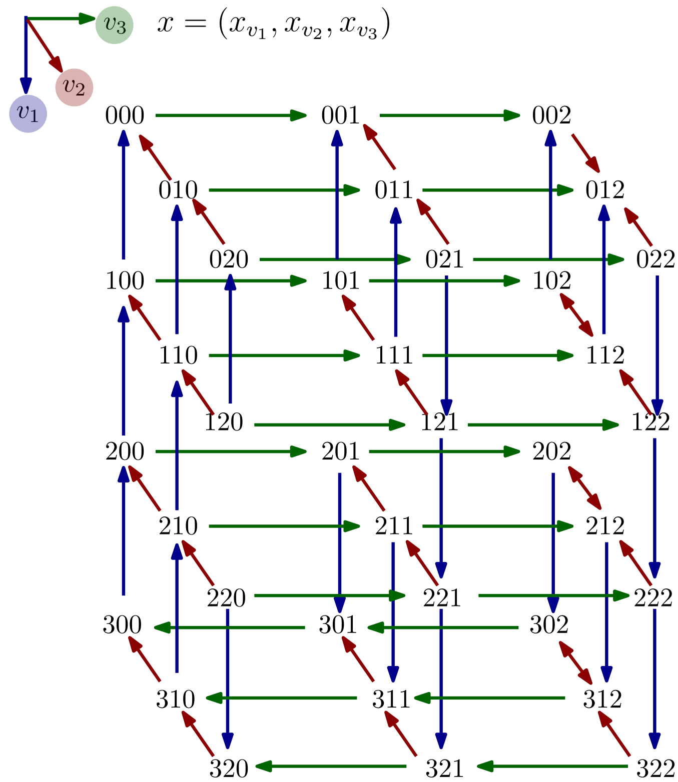


ω	$K(v_1,\omega)$
$\emptyset$	0
$\{v_3\}$	0
$\{v_2\}$	0
$\{v_2, v_3\}$	2
$\{v_1\}$	1
$\{v_1, v_3\}$	3
$\{v_1, v_2\}$	3
$\{v_1, v_2, v_3\}$	3

ω	$K(v_2,\omega)$
$\emptyset$	0
$\{v_3\}$	0
$\{v_2\}$	0
$\{v_2, v_3\}$	1
$\{v_1\}$	0
$\{v_1, v_3\}$	1
$\{v_1, v_2\}$	0
$\{v_1, v_2, v_3\}$	2

ω	$K(v_3,\omega)$
$\emptyset$	0
$\{v_1\}$	2

Model



ASTG

ASTG example: a model with 3 nodes, v_2-rows

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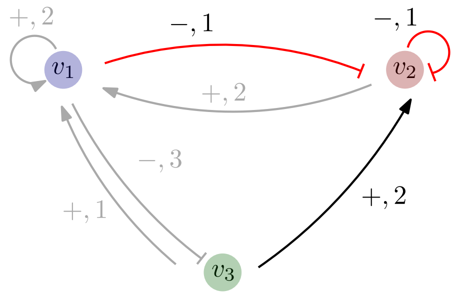
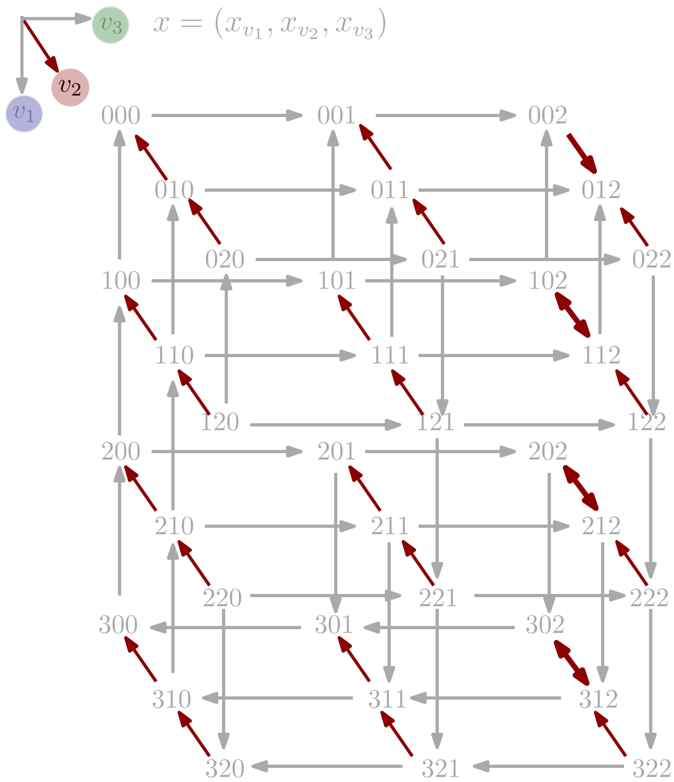


ω	$K(v_1,\omega)$
$\emptyset$	0
$\{v_3\}$	0
$\{v_2\}$	0
$\{v_2, v_3\}$	2
$\{v_1\}$	1
$\{v_1, v_3\}$	3
$\{v_1, v_2\}$	3
$\{v_1, v_2, v_3\}$	3

ω	$K(v_2,\omega)$
$\emptyset$	0
$\{v_3\}$	0
$\{v_2\}$	0
$\{v_2, v_3\}$	1
$\{v_1\}$	0
$\{v_1, v_3\}$	1
$\{v_1, v_2\}$	0
$\{v_1, v_2, v_3\}$	2

ω	$K(v_3,\omega)$
$\emptyset$	0
$\{v_1\}$	2

Model



ASTG

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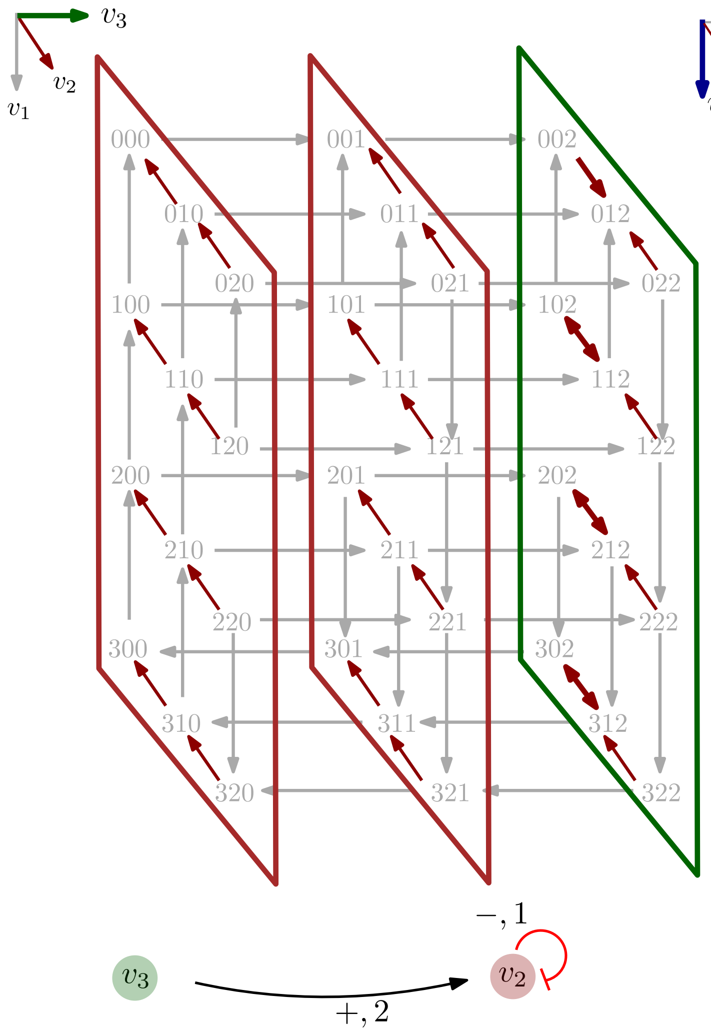
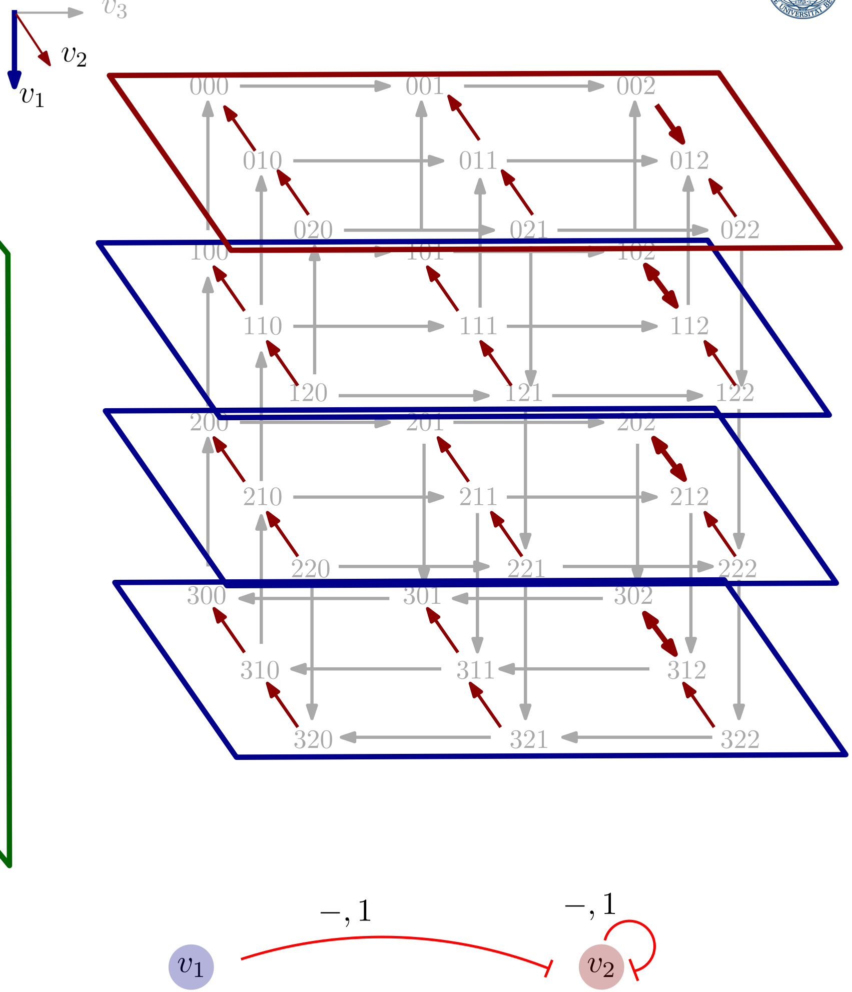
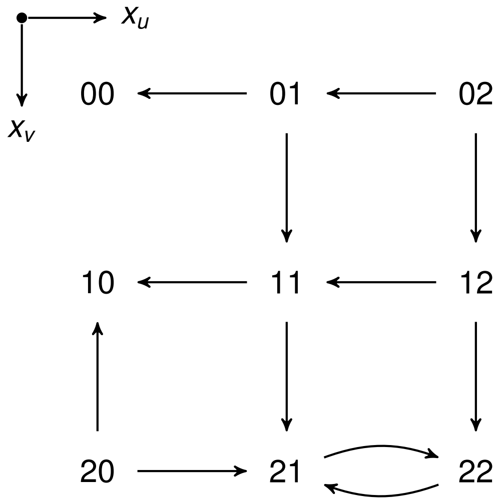
Extremal rows + interaction graph $\Longrightarrow$ ASTG: isomorphic slices





Parallel slices in one direction can change at most once.

Reverse engineering algorithms: model inference from given dynamics [2,3]

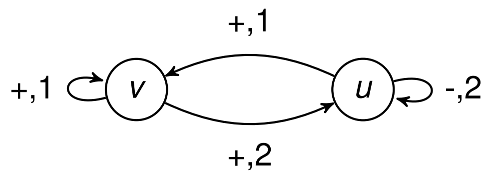


Input

A graph based on the state space, $G = (X, S)$

Output

For valid input (ASTG):
A model $M = (I, K)$ with minimal number of edges, ASTG $(M) \cong G$.



ω	$K(v, \omega)$	$K(u, \omega)$
$\emptyset$	0	0
$\{u\}$	1	0
$\{v\}$	1	0
$\{v, u\}$	2	2

[2] T. Lorenz, H. Siebert and A. Bockmayr. *Analysis and characterization of asynchronous ....* Bull. of Math. Biol., 2013.
[3] L. Sun *Relating the structures and dynamics....* Doctoral Thesis, Freie Universität Berlin, 2017.

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Initialise

V: nodes,
max: maximal activity levels of V
A: attractors, the desired behaviour

Enumerate

all ASTGs based on the state space X with desired A (*in low dimension*)

Infer models

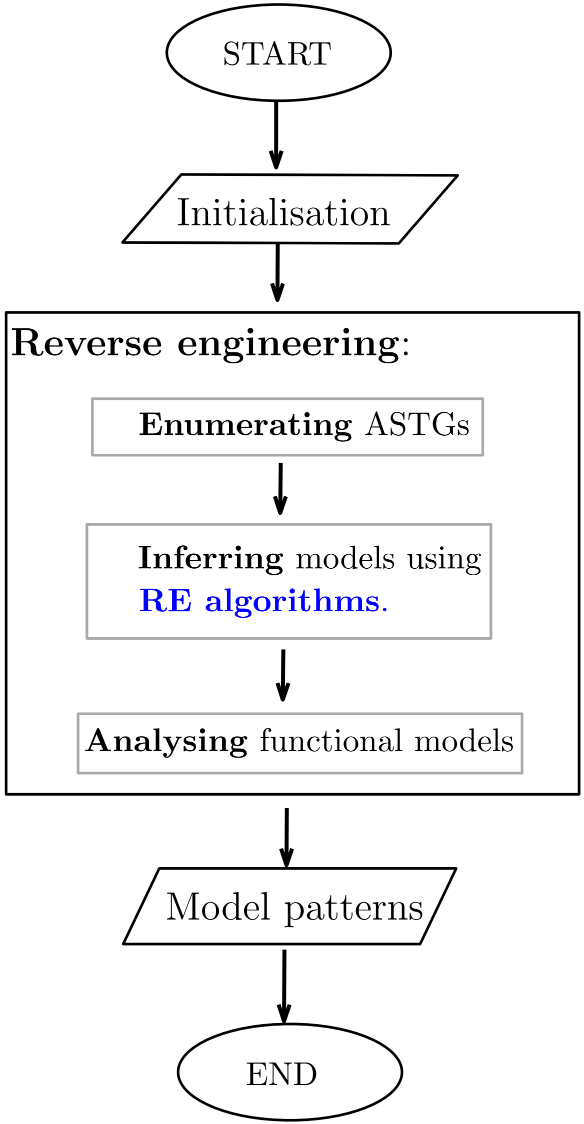
Reverse engineering algorithms

Analyse

Structural and logical **analysis** methods

Model patterns

Interaction patterns, building blocks, minimal logical representations



Structures producing a cyclic attractor

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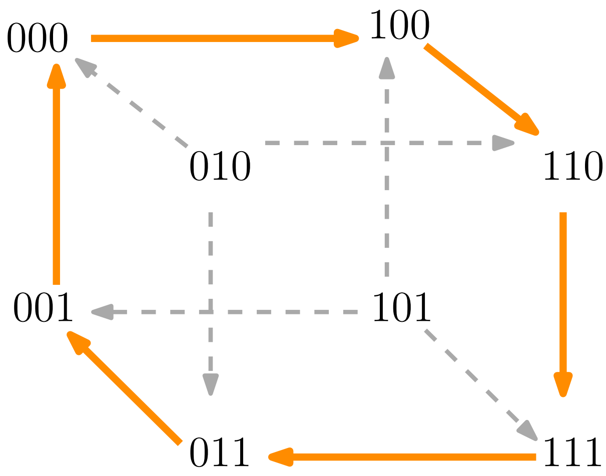
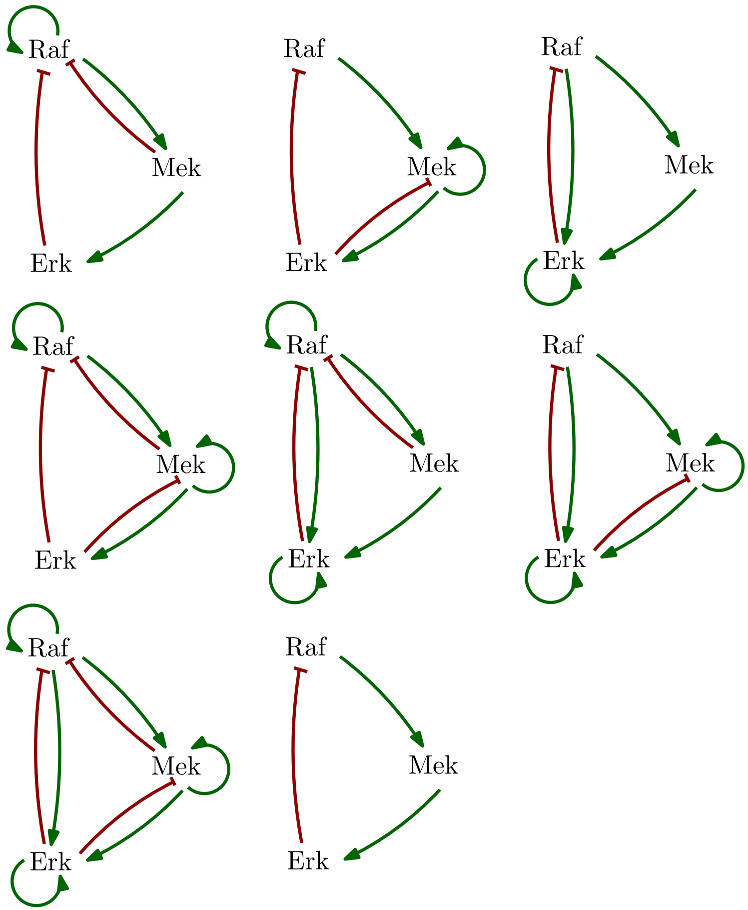
Simplified MAPK-cascade [4]

State $x = (x_{Raf}, x_{Mek}, x_{Erk})$



a cyclic attractor

Result: 64 models including 8 IGs



[4] K. Thobe, et al. *Model integration and crosstalk analysis*... Springer International Publishing, Cham, 2014.

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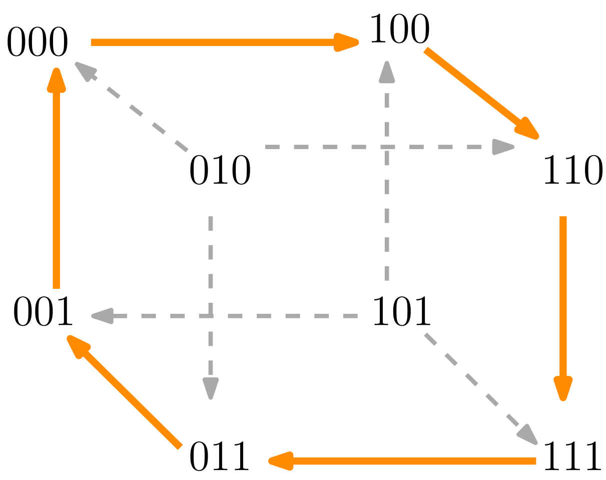
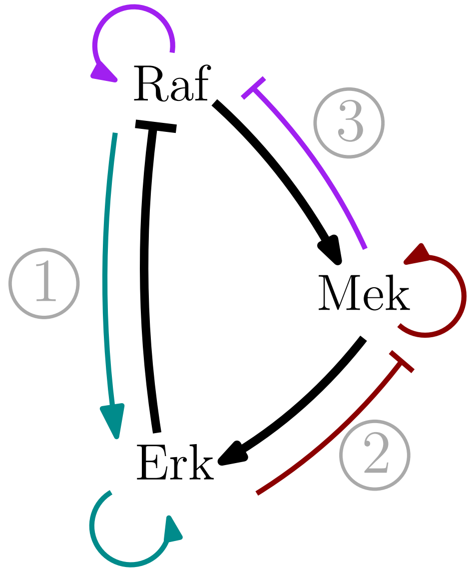
State $x = (x_{Raf}, x_{Mek}, x_{Erk})$



a cyclic attractor

Core (must be present)
Building block 1 (optional)
Building block 2 (optional)
Building block 3 (optional)



Logical representation

core	building block 1	building block 2	building block 3
$x^+_{EM}x^-_{RE}x^+_{MR}$	$(x^+_{EE}x^+_{ER} + \overline{x^+_{ER}}\;\overline{x^+_{EE}})$	$(x^+_{MM}x^-_{ME} + \overline{x^+_{MM}}\;\overline{x^-_{ME}})$	$(x^+_{RR}x^-_{RM} + \overline{x^+_{RR}}\;\overline{x^-_{RM}})$

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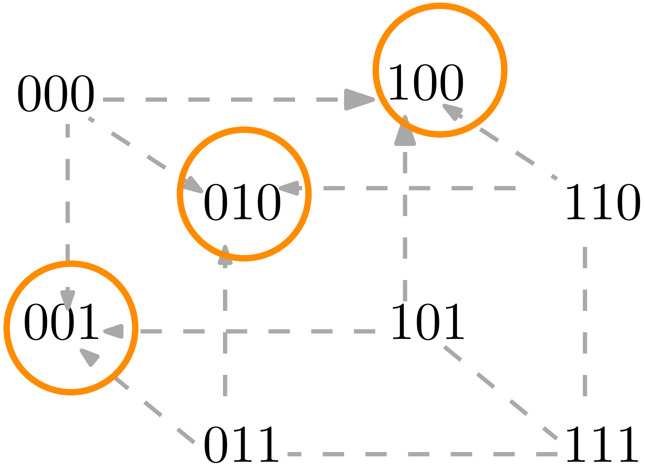
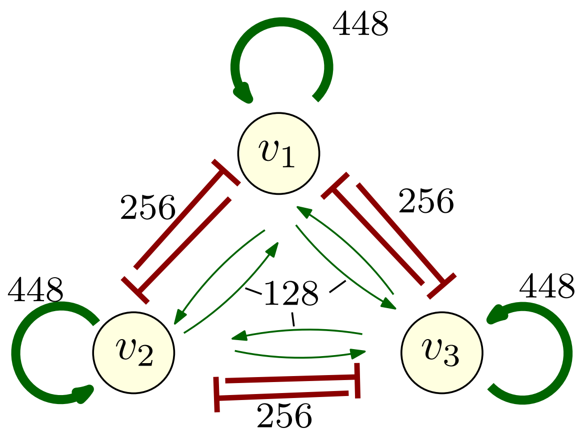
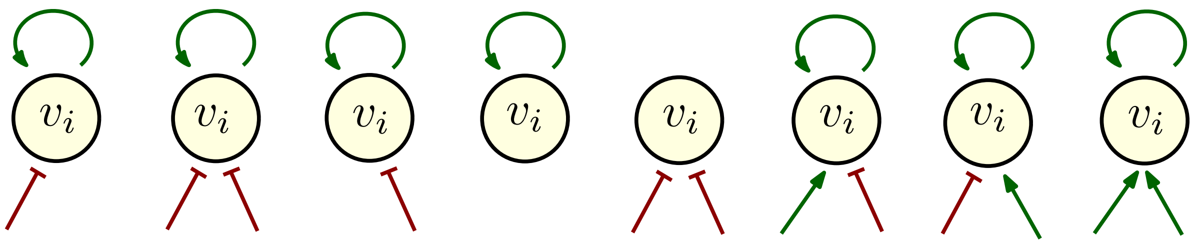
State space $\{0,1\}^3$,
three steady states[5] $\{010, 001, 100\}$



Result: 512 IGs, sum up



Building blocks: incoming edges for v_i, $i \in \{1,2,3\}$
(can be combined freely)



[5] Breindl et al.. *Structural requirements and discrimination of cell differentiation networks.* IFAC Proceedings Volumes, 2011

ASTG construction in low dimension

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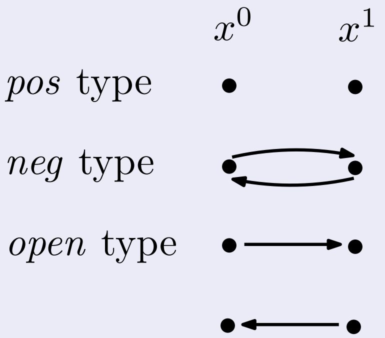
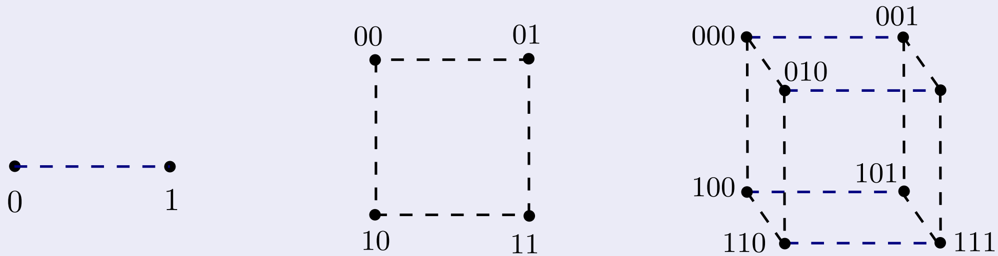
Boolean rows



State spaces



(a) 1-D (b) 2-D (c) 3-D

Number of ASTGs

(1) 4: 4 Boolean rows, 1 row in (a).

(2) 4^4: 4 Boolean rows, 4 rows in (b).

(3) $4^{4\times3}$: 4 Boolean rows, 4×3 rows in (c).

ASTG enumeration in low dimension

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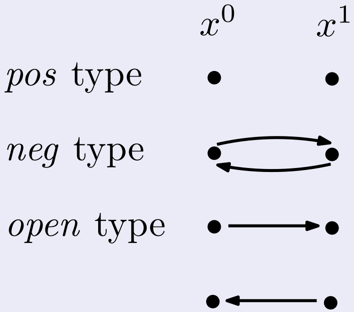
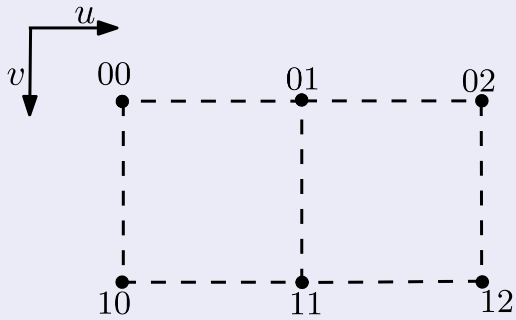
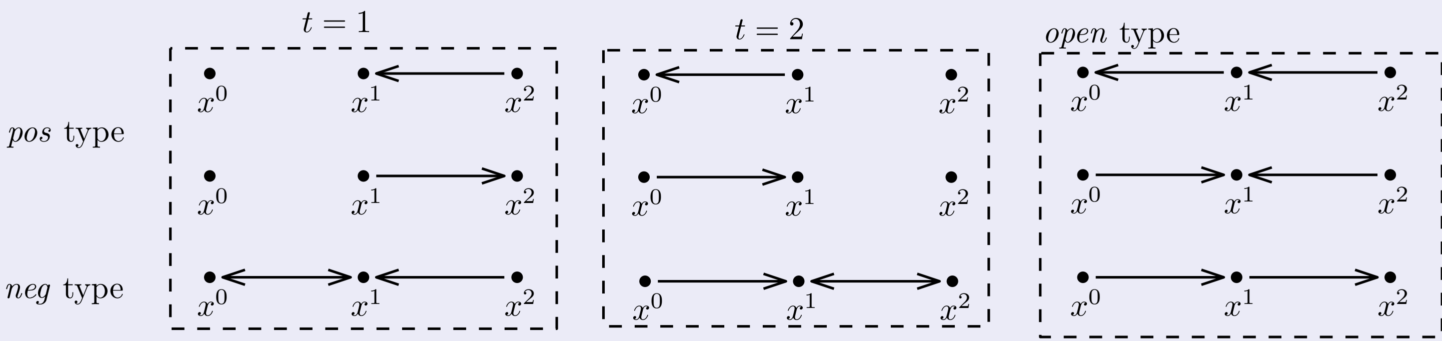
Boolean rows



State space X



Multi-valued rows of 3 states



Number of ASTGs on X

1764: 28×63

v-rows: $(4^2 \times 2 - 4) = 28$

u-rows: $(6^2 + 6^2 - 3^2) = 63$

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Conclusion

1. Methods
   - Characterise ASTGs: extremal rows, necessary and sufficient conditions
   - Reverse engineering algorithms: network inference
   - Reverse engineering workflow
2. Applications
   - Biological case study
     - homeostasis: a cyclic attractor from a simplified MAPK-cascade
     - multistability: three stable states, cell differentiation
   - ASTG enumeration in low dimension

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Thank you for your attention!

Ευχαριστώ!

Work groups *Mathematics in Life Science & Discrete Biomathematics*

References

- Lorenz, Therese. *Vergleich von zwei- und mehrwertigen Modellen bioregulatorischer Netzwerke*. Diploma Thesis, Freie Universität Berlin, 2011.
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- Thobe, K., Streck, A., Klarner, H., and Siebert, H. *Model integration and crosstalk analysis of logical regulatory networks*. pages 32–44. Springer International Publishing, Cham., 2014.
- Breindl, C., Schittler, D., Waldherr, S., and Allgöwer, F. *Structural requirements and discrimination of cell differentiation networks.* IFAC Proceedings Volumes, 44(1):11767–11772, 2011.