Computing Symbolic Steady States of Boolean Networks

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Overview

1: Background

Boolean Networks

- **Boolean domain** $\mathbb{B} = \{0, 1\}$
- **Boolean Expression** $f ::= 0 \mid 1 \mid v \mid \overline{f} \mid f_1 \cdot f_2 \mid f_1 + f_2$
- **Boolean network** $V = \{v_1, \ldots, v_n\}, F = \{f_1, \ldots, f_n\}$
- **States** $S = \{s : V \to \mathbb{B}\}$
- Notation for states: 0011
- **Evaluation** $f(s) \in \mathbb{B}$ and $F(s) \in S$
- **Steady states** $\mathcal{S} = \{s \in S \mid F(s) = s\}$

1: Background

Running Example

$$f_1 = v_1 + v_2 \qquad f_1(1101) = 1 + 1 = 1$$
$$f_2 = v_1 \cdot v_4 \qquad f_2(1101) = 1 \cdot 1 = 1$$
$$f_3 = \overline{v_1} \cdot v_4 \qquad f_3(1101) = \overline{1} \cdot 1 = 0$$
$$f_4 = \overline{v_3} \qquad f_4(1101) = \overline{0} = 1$$

$$F(1101) = 1101$$
$$F(0000) = 0001$$
$$\mathcal{S} = \{1101\}$$

- **Symbolic State** $PS = \{p : U_p \subseteq V \to \mathbb{B}\}$
- Notation for symbolic states $0_2 1_3$
- **Reference** $S[p] = \{s \in S \mid \forall v \in U_p : s(v) = p(v)\}$

- **Size** $|p| := |U_p|$
- p and q are **consistent** if $\forall v \in U_p \cap U_q : p(v) = q(v)$
- **Partial ordering** $p \leq q$ if p, q are consistent and $U_p \subseteq U_q$
- If p, q are consistent then the **union** $p \sqcup q$ exists, e.g.

$$0_1 \sqcup 0_2 = 0_1 0_2$$

1: Background

Symbolic Steady States and Seeds

- $f[p]$ denotes the expression obtained from f by **substituting** p
- The **image** $F[p]$ of p under $F = \{f_1, \dots, f_n\}$ is $q : U_q \to \mathbb{B}$ defined by
  - $U_q := \{v_i \in V \mid f_i[p] \text{ is constant}\}$
  - $q(v_i) := f_i[p]$, for all $v_i \in U_q$
- **Symbolic Steady States** $Sym\mathcal{S} = \{p \in PS | F[p] = p\}$
- **Seeds** $\{p \in PS | F[p] \geq p\}$
- **Percolation** $p \in Seeds$ implies $F[p], F^2[p], F^3[p] \dots \in Seeds$
- Note that

$$\mathcal{S} \subseteq Sym\mathcal{S} \subseteq Seeds$$

1: Background

Running Example

$$\begin{array}{lll}
p := 1_1 & q := 0_1 0_2 & r := 1_3 1_4 \\
f_1[p] = 1 & f_1[q] = 0 & f_1[r] = v_1 + v_2 \\
f_2[p] = 1 \cdot v_4 & f_2[q] = 0 & f_2[r] = v_1 \cdot 1 \\
f_3[p] = 0 & f_3[q] = \overline{0} \cdot v_4 & f_3[r] = \overline{v_1} \cdot 1 \\
f_4[p] = \overline{v_3} & f_4[q] = \overline{v_3} & f_4[r] = 0 \\
F[p] = 1_1 0_3 > p & F[q] = 0_1 0_2 = q & F[r] = 0_4 \not\geq r
\end{array}$$

- p is a **seed**, q is a **symbolic steady state**, r is neither
- $Seeds = \{\varnothing, 1_1, 0_1 0_2, 1101\}$
- $Sym\mathcal{S} = \{\varnothing, 0_1 0_2, 1101\}$

Overview

Applications

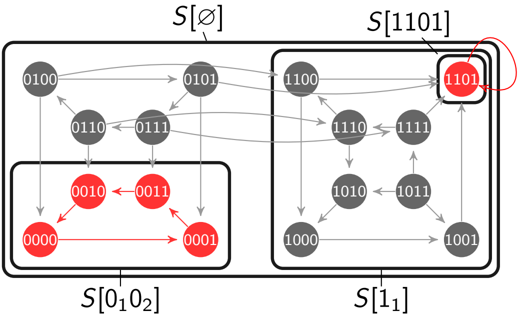
- Model Reduction
- Cyclic Attractors

- **State transition graph** $(S, \to)$
- **Asynchronous**
  - $s \hookrightarrow t$ iff $\Delta(s,t) = 1$ and $\Delta(t, F(s)) < \Delta(s, F(s))$
- **Trap set** $R \subseteq S$ s.t. for all $s \to t : s \in R \implies t \in R$
- **Attractor** $X \subseteq S$ is an inclusion-wise minimal trap set
  - $|X| = 1$ steady state
  - $|X| > 1$ cyclic attractor

Theorem: *If* $p \in Seeds$ *then* $S[p]$ *is a trap set.*

2: Application

Running Example



The asynchronous state transition graph $(S, \hookrightarrow)$

- **Trap set induced symbolic state** $p = Stab(R)$
  - $U_p := \{v \in V \mid \forall r, s \in R : r(v) = s(v)\}$
  - $p(v) := r(v)$ for arbitrary $r \in R$
- Note $S[Stab(R)] \supseteq R$
- **Model reduction**
  - R a trap set and $p := Stab(R)$
  - Trajectories with initial state $s_1 \in R$ are governed by

$$V_p := \{v \in V \mid v \notin U_p\}$$
$$F_p := \{f_i[p] \mid f_i \in F, v_i \in V_p\}$$

Model reduction with seeds: $p \in Seeds$ *implies* $Stab(p) = p$

2: Application

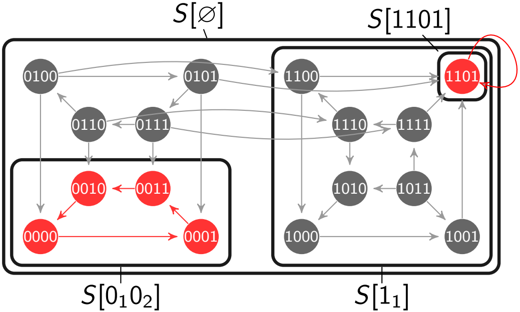
Running Example

$$f_3 = v_4$$
$$f_4 = \overline{v_3}$$

Reduction by $p = 0_1 0_2$

$$f_2 = v_4$$
$$f_3 = 0$$
$$f_4 = \overline{v_3}$$

Reduction by $q = 1_1$



- **Maximal symbolic steady states** $\max(Sym\mathcal{S})$ (w.r.t. $\leq$)
- $Sym\mathcal{S} = \{\varnothing, 0_1 0_2, 1101\}$
- $\max(Sym\mathcal{S}) = \{0_1 0_2, 1101\}$

Theorem: *$|\{p \in \max(Sym\mathcal{S}) \mid |p| < n\}|$ is a lower bound for cyclic attractors.*

Overview

Computing Symbolic Steady States

- Prime Implicants
- 0-1 Optimization Problem

- **Prime implicant** p is a c-prime implicant of f if
  - $f[p] = c$
  - for all $q \leq p : f[q] \neq c$
- The prime implicants PI of (V, F)

$$PI := \{(p, c, v_i) \in PS \times \mathbb{B} \times V \mid p \text{ is a } c\text{-prime implicant of } f_i\}$$

Prime Implicant Graph $(\mathcal{N}, \mathcal{A})$ where

- $\mathcal{N} := \{p \in PS \mid |p| = 1\}$
- $\mathcal{A} \subseteq 2^{\mathcal{N}} \times 2^{\mathcal{N}}$ is defined by

  $$\alpha : PI \to 2^{\mathcal{N}} \times 2^{\mathcal{N}}, (p, c, v_i) \mapsto (\{p_1, \dots, p_{|p|}\}, \{q\})$$

  where

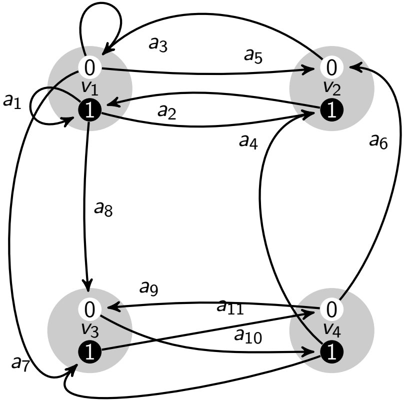
  - $p = p_1 \sqcup \dots \sqcup p_{|p|}$
  - $q \in PS$ is defined by $U_q := \{v_i\}$ and $q(v_i) := c$.

- The **head** of $a \in \mathcal{A}$ is $H(a) := q$
- The **tail** of $a \in \mathcal{A}$ is $T(a) := p$

3: Computing Symbolic Steady States

Running Example

PI	$\mathcal{A}$
$(1_1, 1, v_1)$	a_1
$(1_2, 1, v_1)$	a_2
$(0_1 0_2, 0, v_1)$	a_3
$(1_1 1_4, 1, v_2)$	a_4
$(0_1, 0, v_2)$	a_5
$(0_4, 0, v_2)$	a_6
$(0_1 1_4, 1, v_3)$	a_7
$(1_1, 0, v_3)$	a_8
$(0_4, 0, v_3)$	a_9
$(0_3, 1, v_4)$	a_{10}
$(1_3, 0, v_4)$	a_{11}



3: Computing Symbolic Steady States

Arcs and Symbolic States

- $A \subseteq \mathcal{A}$ is **consistent** if

$$\forall a, b \in A : H(a) \text{ and } H(b) \text{ are consistent}$$

- **Induced symbolic state** of consistent $A = \{a_1, \ldots, a_m\} \subseteq \mathcal{A}$

$$H(A) := H(a_1) \sqcup \cdots \sqcup H(a_m)$$

- $A \subseteq \mathcal{A}$ is **stable** if

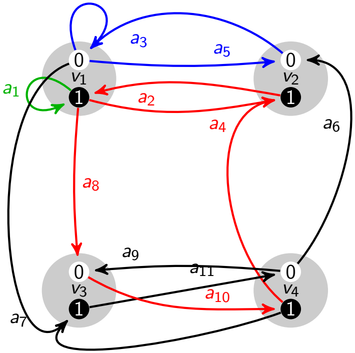
$$\forall a \in A : \exists B \subseteq A : T(A) \leq H(B)$$

3: Computing Symbolic Steady States

Running Example

$$B = \{a_3, a_5\}$$
$$C = \{a_1\}$$
$$D_1 = \{a_1, a_4, a_8, a_{10}\}$$
$$D_2 = \{a_2, a_4, a_8, a_{10}\}$$
$$D_3 = \{a_1, a_2, a_4, a_8, a_{10}\}$$

$$H(B) = 0_1 0_2$$
$$H(C) = 1_1$$
$$H(D_i) = 1101$$



3: Computing Symolic Steady States

0-1 Optimization Problem

Theorem: *$p \in$ Seeds if and only if there is a stable and consistent $A \subseteq \mathcal{A}$ such that $H(A) = p$.*

Corollary: *Inclusion-wise maximal stable and consistent arc sets induce maximal seeds and therefore maximal symbolic steady states.*

- Can solve the 0-1 optimization problem with ILP formulation

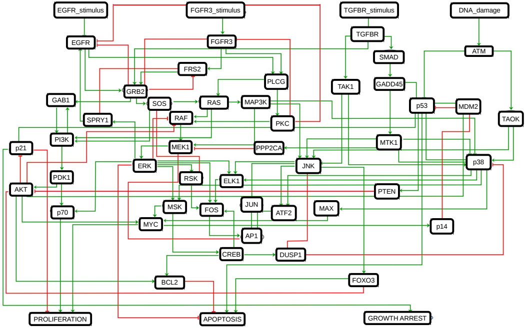
Overview

Case Studies

- MAPK Signaling Network
- Performance

4: Case Studies

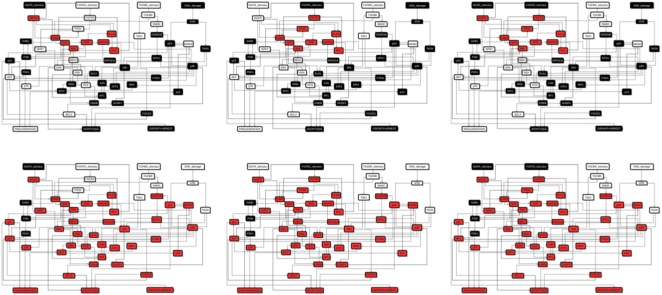
MAPK Signaling Pathway



G. Luca, et al. "Integrative Modelling of the Influence of MAPK Network on Cancer Cell Fate Decision." PLoS Computational Biology, 2013.

4: Case Studies

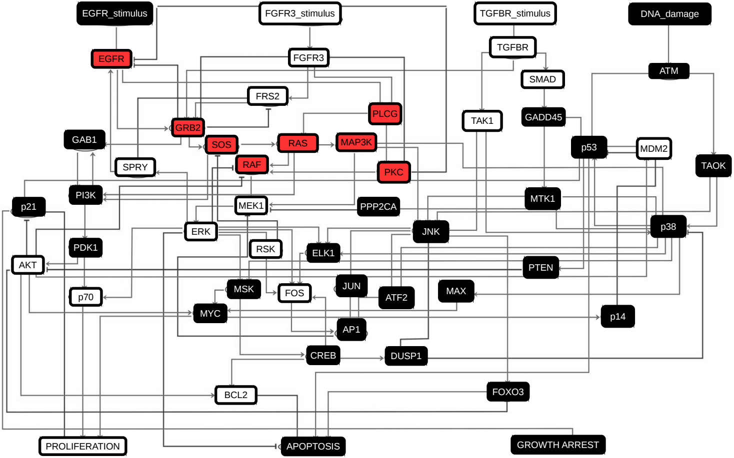
MAPK Signaling Pathway



- $n = 53, \quad |PI| = 181$ solved in < 1 sec.
- $|\max(Sym\mathcal{S})| = 18, \quad |\mathcal{S}| = 12$
- $\Rightarrow$ Lower bound on cyclic attractors: 6

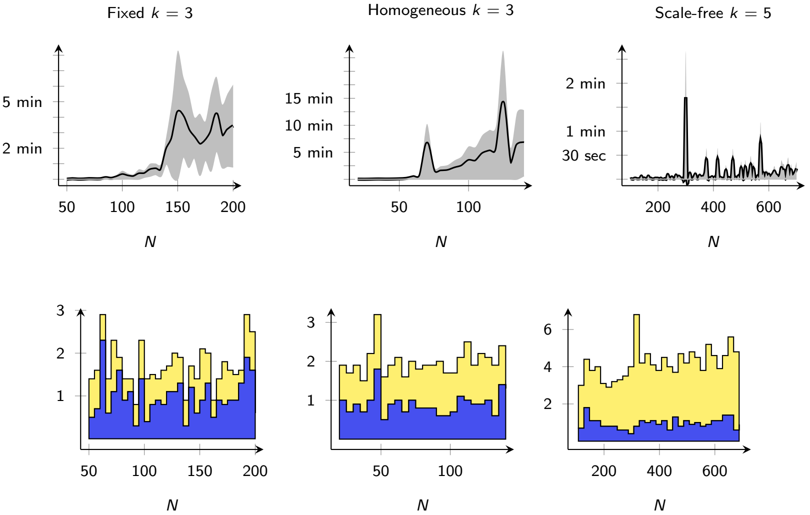
4: Case Studies

MAPK Signaling Pathway



4: Case Studies

Performance



Summary

- **Python script**: *sourceforge.net/projects/boolnetfixpoints*
- **Preprint**: *nbn-resolving.de/urn:nbn:de:0296-matheon-12823*

Thank You!

- **Alexander Bockmayr** PhD supervisor
- **Heike Siebert** group leader