Enumeration and extension of non-equivalent deterministic update schedules in Boolean networks

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joint work with
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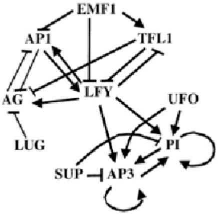
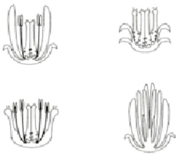
Contents

Boolean Network as model of a GRN

A genetic regulatory network consists of a set of genes, proteins, small molecules, and their mutual interactions.

(L. Mendoza and E. Alvarez, 1998)





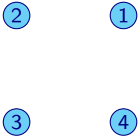
Elements:

Vertex = A gene or a gene product.
States = 1 (activated), 0 (inactivated).
Interaction Graph = Interaction of genes and genes products each other.
Activation function = Regulation function.
Iteration = parallel (in the most cases).
Attractors = Cellular phenotypes and mitotic cycles.

Boolean networks

Boolean Networks

- A finite set V of n element and n states variables $x_v \in \{0,1\},\ v \in V$



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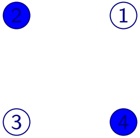

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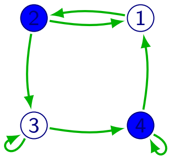

$$f_1(x) = x_2 \wedge x_4$$
$$f_2(x) = x_1$$
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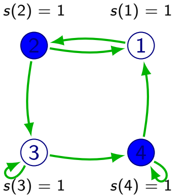

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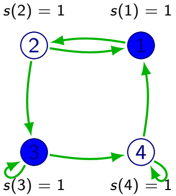

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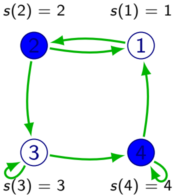

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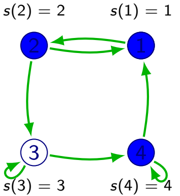

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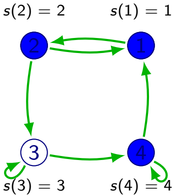

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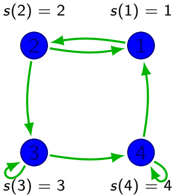

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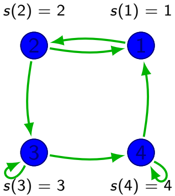

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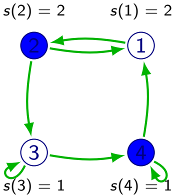

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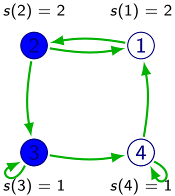

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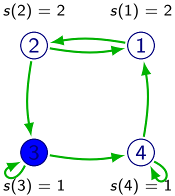

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Dynamical behavior

The iteration of the Boolean network is given by:

$$x_v^{k+1} = f_v(x_u^{l_u} \colon u \in V), \quad l_u = \begin{cases} k & \text{if } s(v) \leq s(u) \\ k+1 & \text{if } s(v) > s(u) \end{cases}$$

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Dynamical behavior

$F^s : \{0,1\}^n \to \{0,1\}^n$:

$$f_v^s(x) = f_v(g_{v,u}^s(x) \colon u \in V), \quad g_{v,u}^s(x) = \begin{cases} x_u & \text{if } s(v) \leq s(u) \\ f_u^s(x) & \text{if } s(v) > s(u) \end{cases}$$

Example of dynamical behavior

$s_1 = \{1, 2, 3, 4\}$

$$
\begin{aligned}
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\end{aligned}
$$

Example of dynamical behavior

$s_1 = \{1, 2, 3, 4\}$ $\qquad$ $s_2 = \{1\}\{2\}\{3\}\{4\}$

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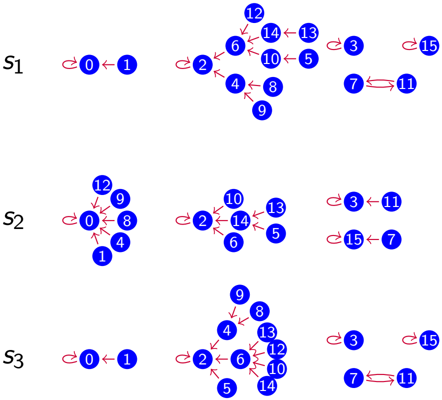
Dynamics

$s_1 = \{1, 2, 3, 4\}$
$s_2 = \{1\}\{2\}\{3\}\{4\}$
$s_3 = \{3, 4\}\{1, 2\}$

	State	F^{s_1}	F^{s_2}	F^{s_3}
0	0000	0000	0000	0000
1	0001	0000	0000	0000
2	0010	0010	0010	0010
3	0011	0011	0011	0011
4	0100	0010	0000	0010
5	0101	1010	1110	0010
6	0110	0010	0010	0010
7	0111	1011	1111	1011
8	1000	0100	0000	0100
9	1001	0100	0000	0100
10	1010	0110	0010	0110
11	1011	0111	0011	0111
12	1100	0110	0000	0110
13	1101	1110	1110	0110
14	1110	0110	0010	0110
15	1111	1111	1111	1111



Dynamical problems related to schedule

- Does there exist two different update schedules s_1, s_2 such that the function F updated with s_1 has the same dynamical behavior, that F updated with s_2?

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- Does there exist two update schedules s_1, s_2 such that the function F updated with s_1 has the same attractors that F updated with s_2?

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- Does there exist an update schedule s such that the function F updated with s does not have limit cycles?

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- Does there exist an update schedule s such that the function F updated with s does not have limit cycles?
- Does there exist an update schedule s such that the function F updated with s has limit cycles?
- Does there exist an update schedule s such that given $x^1, \ldots, x^k, y^1, \ldots, y^k \in \{0,1\}^n$, $F^s(x^i) = y^i$?

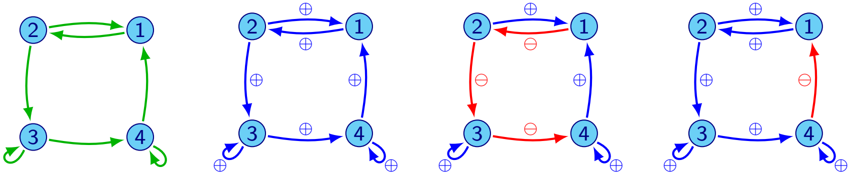
Update digraph

A labeled digraph is a graph G with a label function lab, (G, lab) such that: $lab : A(G) \to \{\oplus, \ominus\}$

We say that a labeled digraph is an update digraph if there exists $s : V(G) \to \{1, \ldots, n\}$, an update function such that:

$$\forall (u,v) \in A(G), lab(u,v) = \oplus \iff s(u) \geq s(v)$$

$s_1 = \{1,2,3,4\}$ $s_2 = \{1\}\{2\}\{3\}\{4\}$ $s_3 = \{3,4\}\{1,2\}$



Why are we interested in update digraphs?

Theorem (Aracena, Goles, Moreira, Salinas (2009))

Given two Boolean networks $N_1 = (F, s)$ *and* $N_2 = (F, s')$ *which differ only in the update schedule. If the update digraphs associated to them are equal, then both networks have the same dynamical behavior.*

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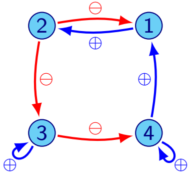
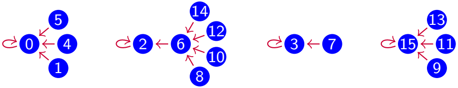
$s = \{2\}\{1\}\{3\}\{4\}$ and $s' = \{2\}\{3\}\{1\}\{4\}$





Of this way, we say that two update schedules are equivalent if and only if they have the same update digraph.

New questions

- Given a labeled digraph. Is it an update digraph?

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New questions

- Given a labeled digraph. Is it an update digraph?
- If it is an update digraph. How do we find un update shedule with this update digraph?
- How many non-equivalent update schedules are there? How many elements does each have?
- Given a certain dynamical property. Is there an equivalence class that holds it?

Labels and Update digraphs

Reverse Digraph

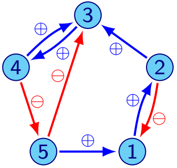
Given (G, lab) a labeled digraph, we define the reverse digraph as (G_r, lab_r), where:

$$V(G_r) = V(G)$$

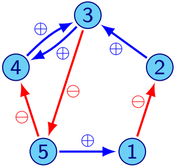
$$A(G_r) = \{(u,v)/((v,u) \in A(G) \wedge lab(v,u) = \ominus) \vee ((u,v) \in A(G) \wedge lab(u,v) = \oplus)\}$$

$$lab_r(u,v) = \begin{cases} \ominus & (v,u) \in A(G) \wedge lab(v,u) = \ominus \\ \oplus & \text{otherwise} \end{cases}$$

Labeled digraph



Reverse digraph

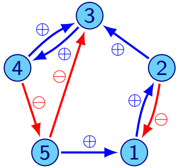


Labels and Update digraphs

Reverse Path

A reverse path is a path in the reverse graph.

Labeled digraph



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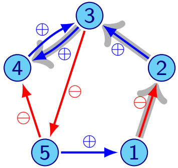


Labels and Update digraphs

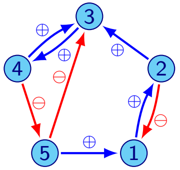
Reverse Path

A reverse path is a path in the reverse graph.

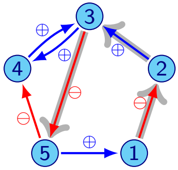
Negative Reverse Path

A negative reverse path is a path with an arc labeled ⊖ in the reverse graph.

Labeled digraph



Reverse digraph



Labels and Update digraphs

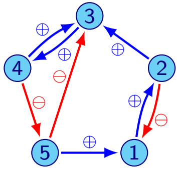
Forbidden cycle

A forbidden cycle is a cycle with an arc labeled $\ominus$ in the reverse graph.

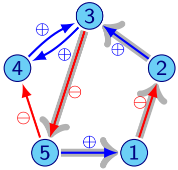
Theorem (Montalva (2012))

A labeled digraph is an update digraph if and only if there does not exist a forbidden cycle in its reverse digraph.

Labeled digraph

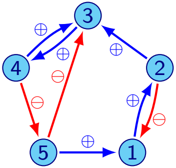


Reverse digraph



Is it an update digraph?

G :



Is it an update digraph?

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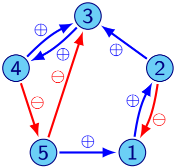
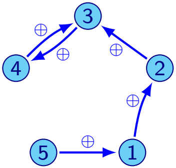
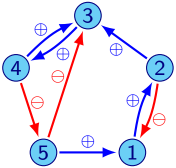


$G_{\oplus}$:



Is it an update digraph?

G :



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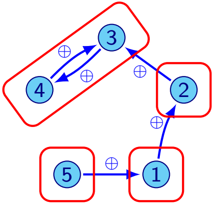

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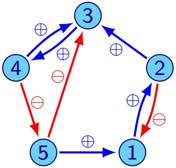

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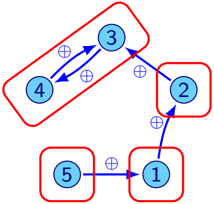
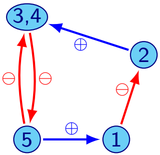


G_R :



Is it an update digraph?

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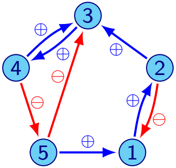

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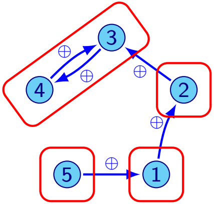

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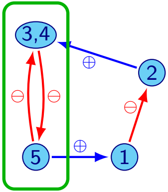

Forbidden cycle

How I find the update schedule of a label?

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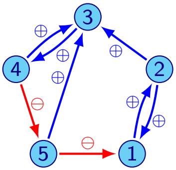

How I find the update schedule of a label?

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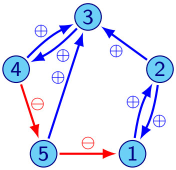

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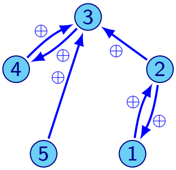

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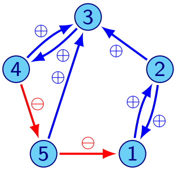

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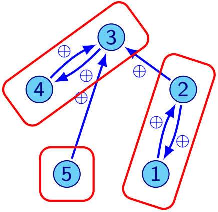

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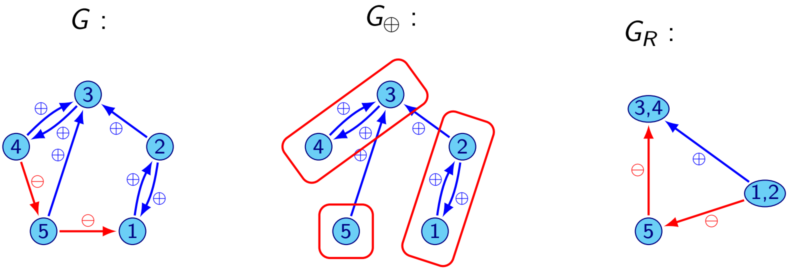

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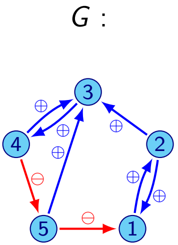

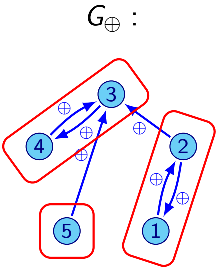

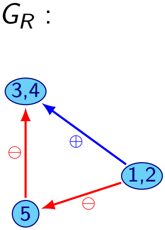

$$s = \{3,4\}\,\{5\}\,\{1,2\}$$

Transition problem

Does there exist an update schedule s such that given $x^1, \dots, x^k, y^1, \dots, y^k \in \{0,1\}^n$, $F^s(x^i) = y^i$?

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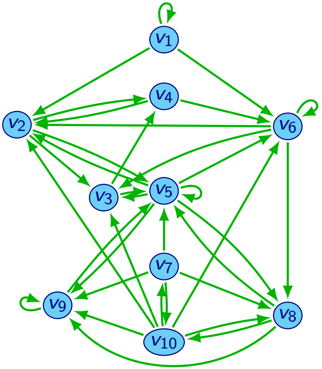

Limit cycle										
$v \in V(G^F)$	v_1	v_2	v_3	v_4	v_5	v_6	v_7	v_8	v_9	v_{10}
x^0	1	0	1	0	0	0	0	1	1	0
x^1	1	0	1	1	0	0	0	1	0	0
x^2	1	0	1	1	1	0	0	1	0	0
x^3	1	0	0	1	1	0	0	0	0	0
x^4	1	0	0	0	1	0	0	0	1	1
x^5	1	0	0	0	1	0	1	0	1	1
x^6	1	0	0	0	0	0	1	1	1	0
x^7	1	0	1	0	0	0	0	1	1	0

$$
\begin{aligned}
f_{v_1}(x) &= x_{v_1} \\
f_{v_2}(x) &= (\neg x_{v_1} \wedge \neg x_{v_{10}}) \wedge ([\neg x_{v_4} \wedge \neg x_{v_5}] \vee x_{v_6}) \\
f_{v_3}(x) &= (\neg x_{v_2} \wedge \neg x_{v_5} \wedge \neg x_{v_{10}}) \vee (x_{v_6} \wedge \neg x_{v_2} \wedge \neg x_{v_{10}}) \\
f_{v_4}(x) &= x_{v_3} \wedge \neg x_{v_2} \\
f_{v_5}(x) &= (\neg x_{v_2} \wedge \neg x_{v_7} \wedge \neg(x_{v_8} \wedge x_{v_9})) \wedge (x_{v_3} \vee x_{v_5}) \\
f_{v_6}(x) &= (\neg x_{v_1} \wedge \neg x_{v_{10}}) \wedge ([\neg x_{v_4} \wedge \neg x_{v_5}] \vee [x_{v_6} \wedge \neg(x_{v_4} \wedge x_{v_5})]) \\
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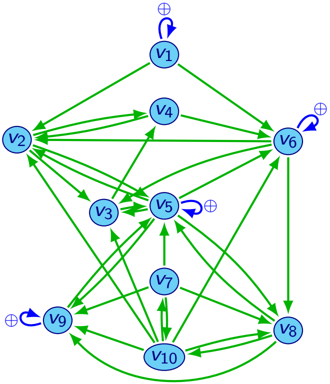

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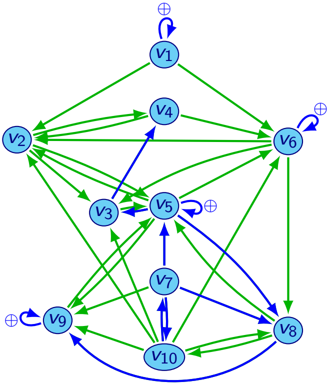

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x^2	1	0	1	1	1	0	0	1	0	0
x^3	1	0	0	1	1	0	0	0	0	0
x^4	1	0	0	0	1	0	0	0	1	1
x^5	1	0	0	0	1	0	1	0	1	1
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Update Digraph Extension Problem

UDE

Given a labeled digraph (G, lab), find the set $\mathcal{S}(G, lab)$ of all fully labeled extensions lab' of lab such that (G, lab') is an update digraph.

Complexity

CUDE

Given (G, lab) a labeled digraph, to determine the cardinality of the set $\mathcal{S}(G, lab)$.

Complexity

CUDE

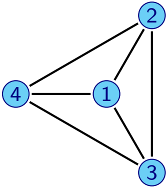
Given (G, lab) a labeled digraph, to determine the cardinality of the set $\mathcal{S}(G, lab)$.

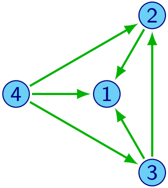
Theorem

CUDE is #P-complete

Acyclic orientation problem

Given a graph to determine the number of acyclic orientations is #P-complete





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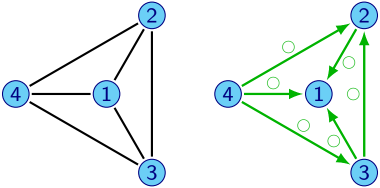

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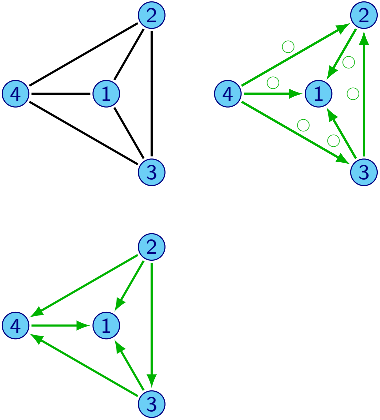

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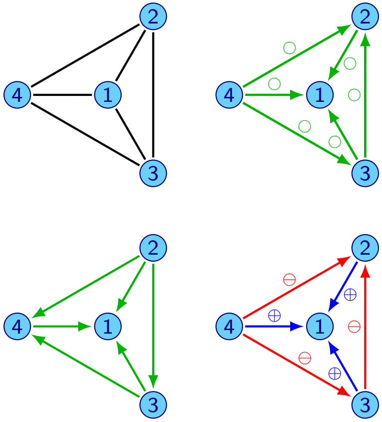

Extension existence

Theorem (Extension)

Given G a digraph and G' a subdigraph of G. if (G', lab') is an update digraph, then there exists $lab : A(G) \to \{\oplus, \ominus\}$ such that (G, lab) is an update digraph and $lab|_{A(G')} = lab'$.

Force

Proposition

Given a labeled digraph (G, lab) and an arc (i,j) with $lab(i,j) = \bigcirc$:

- *If there exists a reverse path from i to j, then the arc (i,j) must be labeled $\oplus$*
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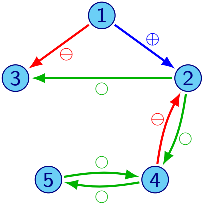

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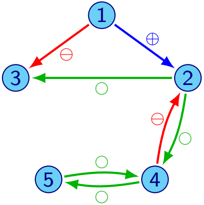

Matrix M

$V(G)$	1	2	3	4	5
1	∞	1	∞	-1	∞
2	∞	∞	∞	-1	∞
3	-1	-1	∞	-1	∞
4	∞	∞	∞	∞	∞
5	∞	∞	∞	∞	∞

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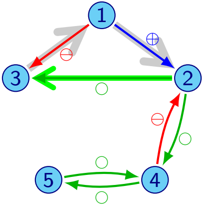
Given a labeled digraph (G, lab) and an arc (i,j) with $lab(i,j) = \bigcirc$:

- *If there exists a reverse path from i to j, then the arc (i,j) must be labeled $\oplus$*
- *If there exists a negative reverse path from j to i, then the arc (i,j) must be labeled $\ominus$*



Matrix M

$V(G)$	1	2	3	4	5
1	∞	1	∞	-1	∞
2	∞	∞	∞	-1	∞
3	-1	**-1**	∞	-1	∞
4	∞	∞	∞	∞	∞
5	∞	∞	∞	∞	∞

Force

Proposition

Given a labeled digraph (G, lab) and an arc (i, j) with $lab(i, j) = \bigcirc$:

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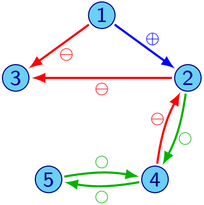

Matrix M

$V(G)$	1	2	3	4	5
1	∞	1	∞	-1	∞
2	∞	∞	∞	-1	∞
3	-1	-1	∞	-1	∞
4	∞	∞	∞	∞	∞
5	∞	∞	∞	∞	∞

Force

Proposition

Given a labeled digraph (G, lab) and an arc (i,j) with $lab(i,j) = \bigcirc$:

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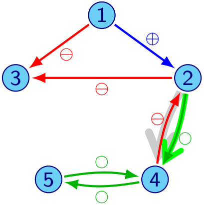

Matrix M

$V(G)$	1	2	3	4	5
1	∞	1	∞	-1	∞
2	∞	∞	∞	-1	∞
3	-1	-1	∞	-1	∞
4	∞	∞	∞	∞	∞
5	∞	∞	∞	∞	∞

Force

Proposition

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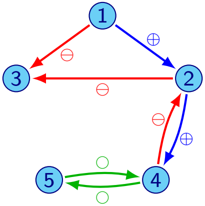

Matrix M

$V(G)$	1	2	3	4	5
1	∞	1	∞	-1	∞
2	∞	∞	∞	-1	∞
3	-1	-1	∞	-1	∞
4	∞	∞	∞	∞	∞
5	∞	∞	∞	∞	∞

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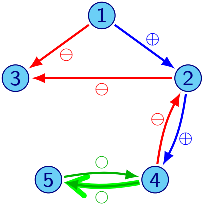
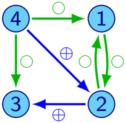


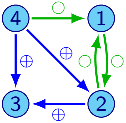
Matrix M

$V(G)$	1	2	3	4	5
1	∞	1	∞	-1	∞
2	∞	∞	∞	-1	∞
3	-1	-1	∞	-1	∞
4	∞	∞	∞	∞	∞
5	∞	∞	∞	∞	∞

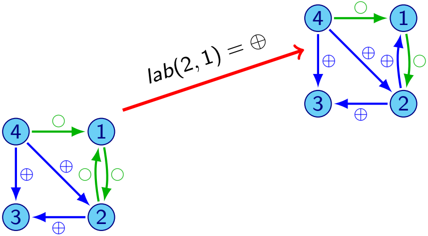
Example of SimpleLabel



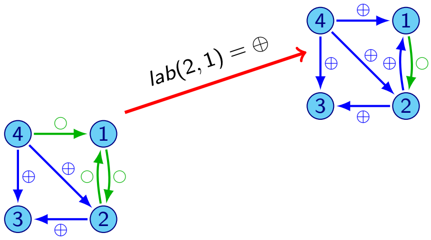
Example of SimpleLabel



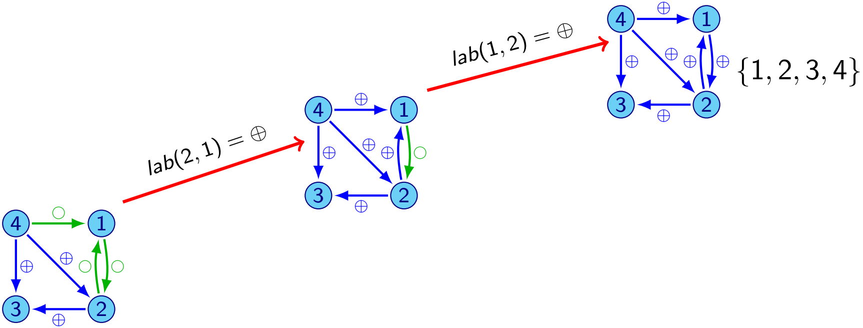
Example of SimpleLabel



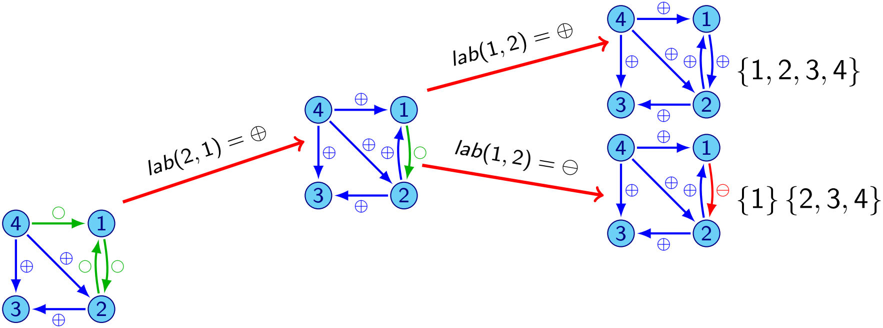
Example of SimpleLabel



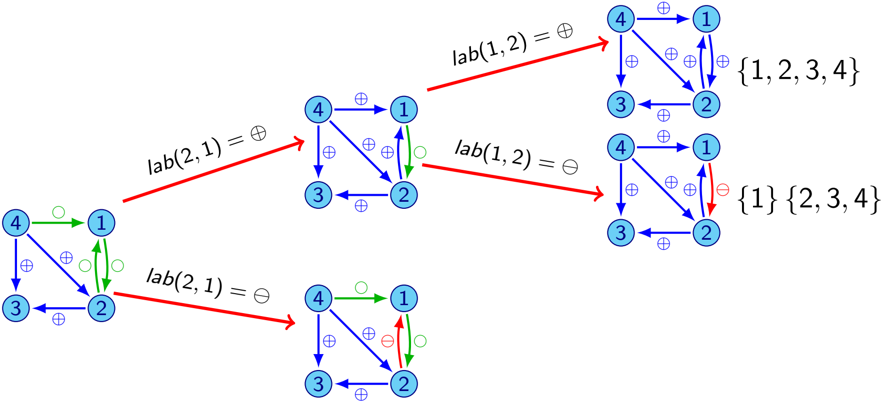
Example of SimpleLabel



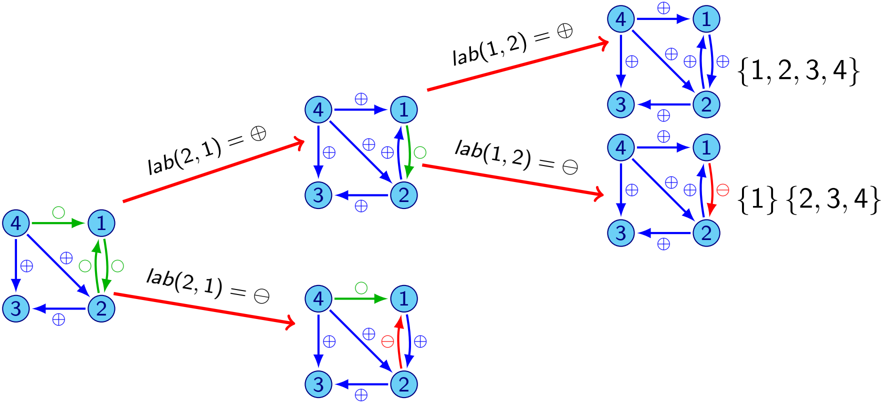
Example of SimpleLabel



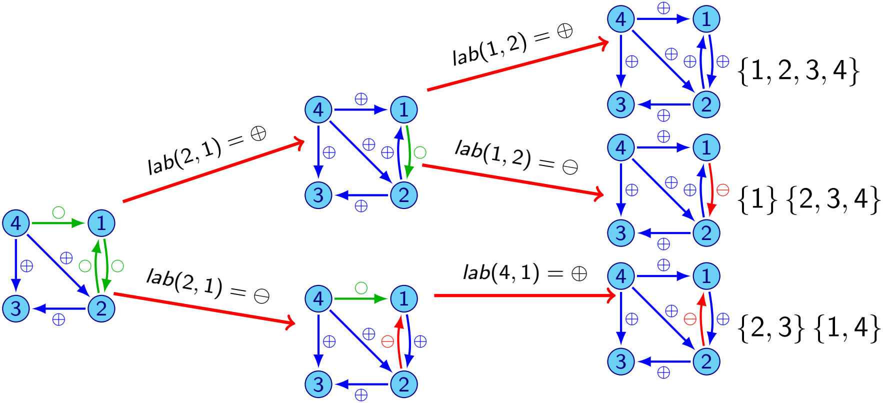
Example of SimpleLabel



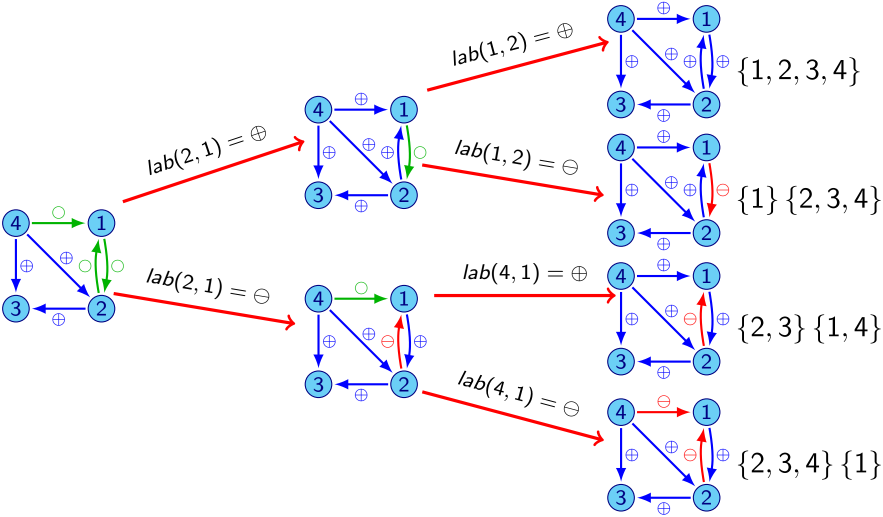
Example of SimpleLabel



Example of SimpleLabel



Example of SimpleLabel



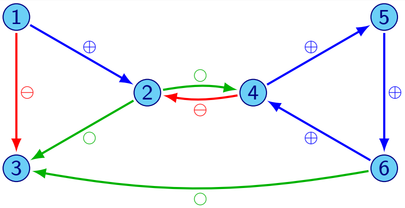
Reduce

Definition

Let (G, lab) be an update digraph and $\{G_1, \dots, G_k\}$ its positive strongly connected components. We define its reduced labeled digraph by $R(G, lab) = (G_{rd} = (V_{rd}, A_{rd}), lab_{rd})$, where:

- $V_{rd} = \{v_1, \dots, v_k\}$
- $A_{rd} = \{(v_i, v_j) | \exists (u, v) \in A(G) \cap (V(G_i) \times V(G_j))\}$

$lab_{rd}(v_i, v_j) = lab(u, v)$, if there exists $(u, v) \in (V(G_i) \times V(G_j)) \cap \text{Sup}(lab)$ and $lab_{rd}(v_i, v_j) = \bigcirc$ otherwise



Reduce

Definition

Let (G, lab) be an update digraph and $\{G_1, \ldots, G_k\}$ its positive strongly connected components. We define its reduced labeled digraph by $R(G, lab) = (G_{\text{rd}} = (V_{\text{rd}}, A_{\text{rd}}), lab_{\text{rd}})$, where:

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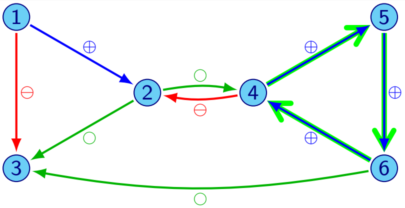
$lab_{\text{rd}}(v_i, v_j) = lab(u, v)$, if there exists $(u, v) \in \big(V(G_i) \times V(G_j)\big) \cap \text{Sup}(lab)$ and
$lab_{\text{rd}}(v_i, v_j) = \bigcirc$ otherwise



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Let (G, lab) be an update digraph and $\{G_1, \ldots, G_k\}$ its positive strongly connected components. We define its reduced labeled digraph by $R(G, lab) = (G_{\mathrm{rd}} = (V_{\mathrm{rd}}, A_{\mathrm{rd}}), lab_{\mathrm{rd}})$, where:

- $V_{\mathrm{rd}} = \{v_1, \ldots, v_k\}$
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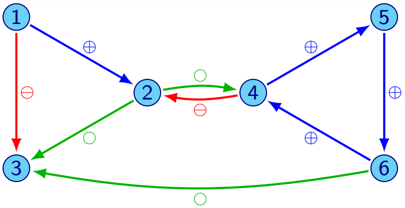
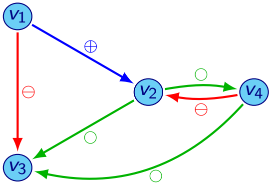
$lab_{\mathrm{rd}}(v_i, v_j) = lab(u, v)$, if there exists $(u, v) \in \big(V(G_i) \times V(G_j)\big) \cap \mathrm{Sup}(lab)$ and $lab_{\mathrm{rd}}(v_i, v_j) = \bigcirc$ otherwise



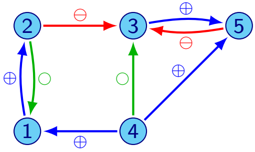


Strongly connected components

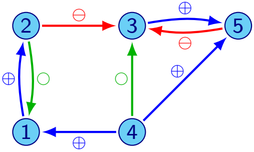
Divide by SCC

Let (G, lab) an update digraph with SCC $G_1, \dots, G_k$ (ordered) over its reverse extended digraph, then:

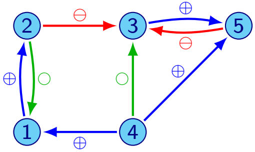
$$\mathcal{S}(G, lab) = \mathcal{S}\left(\widetilde{G}_1, lab|_{A(G_1)}\right) \circ_n \cdots \circ_n \mathcal{S}\left(\widetilde{G}_k, lab|_{A(G_k)}\right)$$

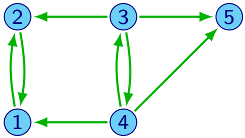


Example: Division by SCC

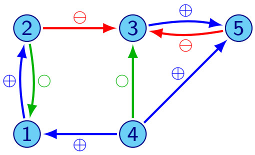


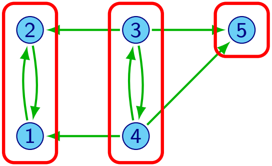
Example: Division by SCC



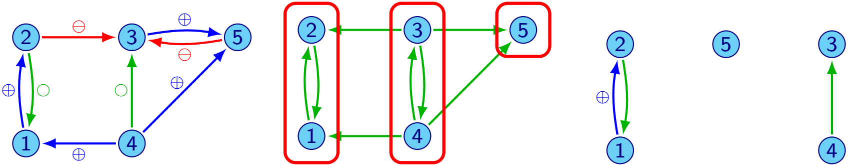


Example: Division by SCC

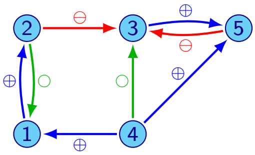


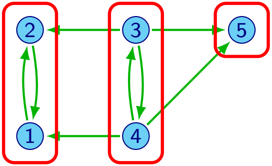


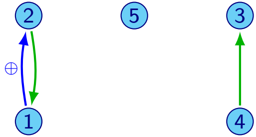
Example: Division by SCC



Example: Division by SCC

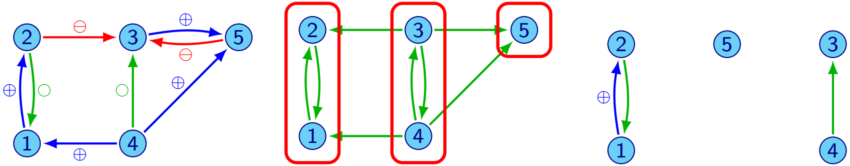






$$\mathcal{S}(G[1,2], lab) = \{\{1,2\}, \{2\}\{1\}\}$$
$$\mathcal{S}(G[5], lab) = \{\{5\}\}$$
$$\mathcal{S}(G[3,4], lab) = \{\{3\}\{4\}, \{4\}\{3\}\}$$

Example: Division by SCC



$$\mathcal{S}(G[1,2], lab) = \{\{1,2\}, \{2\}\{1\}\}$$
$$\mathcal{S}(G[5], lab) = \{\{5\}\}$$
$$\mathcal{S}(G[3,4], lab) = \{\{3\}\{4\}, \{4\}\{3\}\}$$

Then,

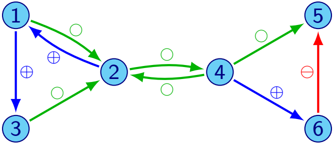
$$\begin{aligned}\mathcal{S}(G, lab) &= \mathcal{S}(G[1,2], lab) \circ_n \mathcal{S}(G[5], lab) \circ_n \mathcal{S}(G[3,4], lab)\\ &= \{\{1,2\}\{5\}, \{2\}\{1\}\{5\}\} \circ_n \{\{3\}\{4\}, \{4\}\{3\}\}\\ &= \Big\{ \{1,2\}\{5\}\{3\}\{4\}, \{1\}\{2\}\{5\}\{3\}\{4\},\\ &\quad \{1,2\}\{5\}\{4\}\{3\}, \{1\}\{2\}\{5\}\{4\}\{3\} \Big\}\end{aligned}$$

Bridges

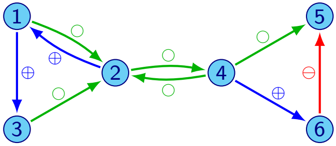
Divide by Bridges

Let (G, lab) a connected digraph, G_U the underlying digraph of G and $uv \in E(G_U)$ a bridge that divide G in G_1 and G_2, then

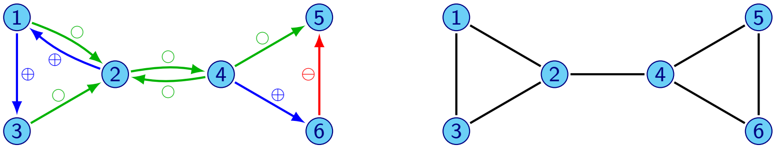
$$\mathcal{S}(G, lab) = \mathcal{S}(G_1, lab|_{A(G_1)}) \circ_{\{u,v\}} \mathcal{S}(G_2, lab|_{A(G_2)})$$



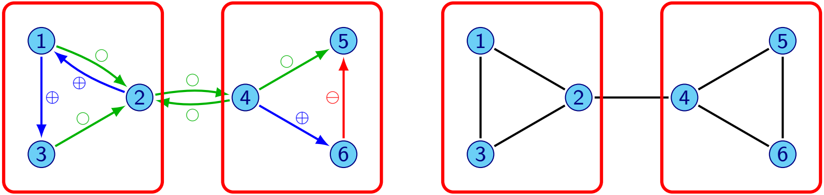
Example: Division by Bridges



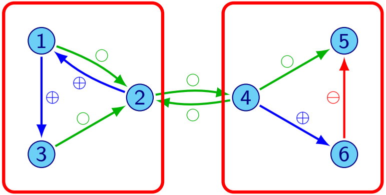
Example: Division by Bridges

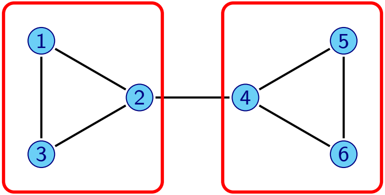


Example: Division by Bridges



Example: Division by Bridges

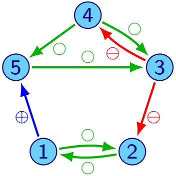




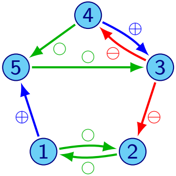
$$S_1 \circ_{nrm_{2,4}} S_2 = \{\{1,2,3\},\{3\}\{1,2\},\{3\}\{1\}\{2\}\} \circ_{nrm_{2,4}} \{\{6\}\{5\}\{4\},\{6\}\{4\}\{5\}\}$$

$\{1,2,3\}\{6\}\{5\}\{4\}$	$\{6\}\{5\}\{4\}\{1,2,3\}$	$\{6\}\{5\}\{4,1,2,3\}$
$\{3\}\{1,2\}\{6\}\{5\}\{4\}$	$\{6\}\{5\}\{4\}\{3\}\{1,2\}$	$\{3\}\{6\}\{5\}\{4,1,2\}$
$\{3\}\{1\}\{2\}\{6\}\{5\}\{4\}$	$\{6\}\{5\}\{4\}\{3\}\{1\}\{2\}$	$\{3\}\{1\}\{6\}\{5\}\{4,2\}$
$\{1,2,3\}\{6\}\{4\}\{5\}$	$\{6\}\{4\}\{5\}\{1,2,3\}$	$\{6\}\{4,1,2,3\}\{5\}$
$\{3\}\{1,2\}\{6\}\{4\}\{5\}$	$\{6\}\{4\}\{5\}\{3\}\{1,2\}$	$\{3\}\{6\}\{4,1,2\}\{5\}$
$\{3\}\{1\}\{2\}\{6\}\{4\}\{5\}$	$\{6\}\{4\}\{5\}\{3\}\{1\}\{2\}$	$\{3\}\{1\}\{6\}\{4,2\}\{5\}$

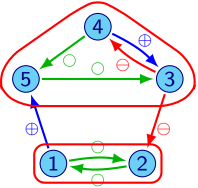
Example: UpdateLabel



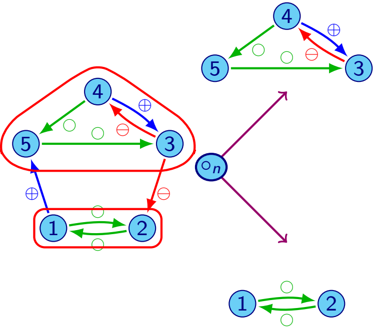
Example: UpdateLabel



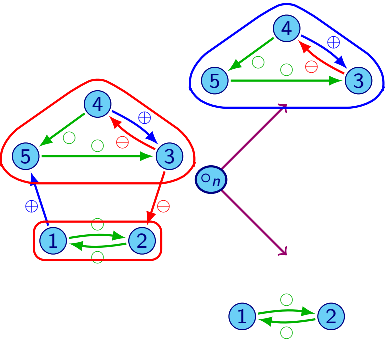
Example: UpdateLabel



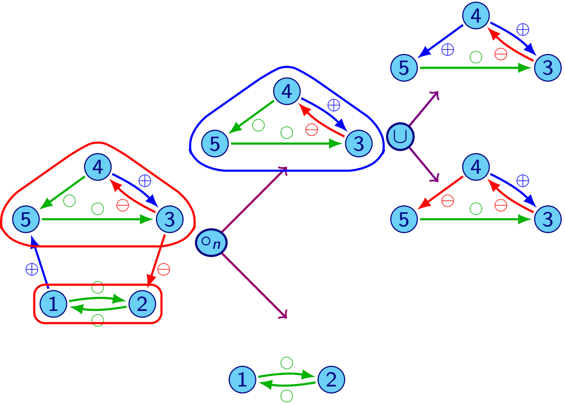
Example: UpdateLabel



Example: UpdateLabel



Example: UpdateLabel



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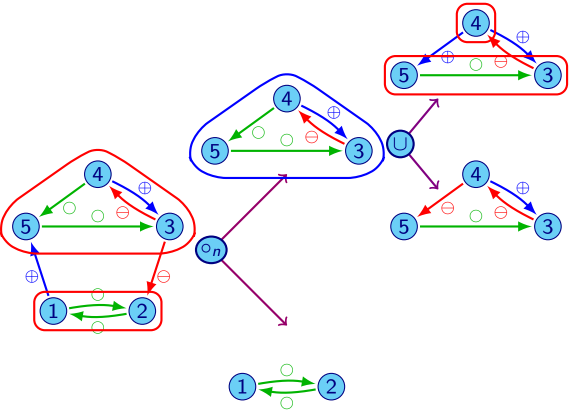

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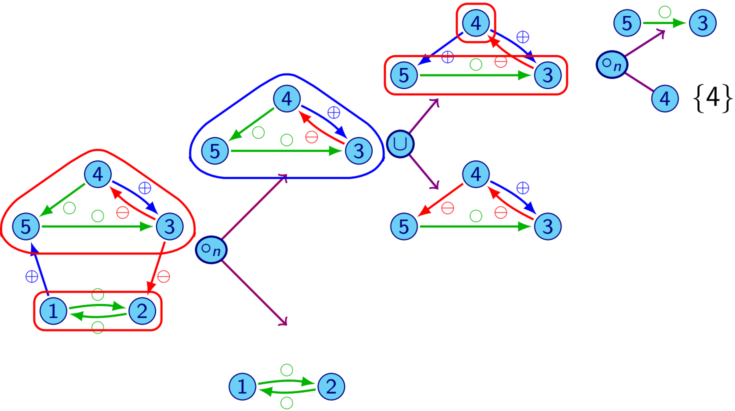
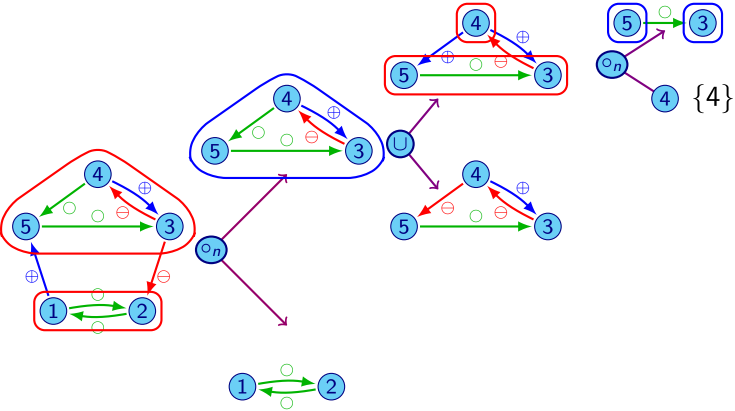


Example: UpdateLabel



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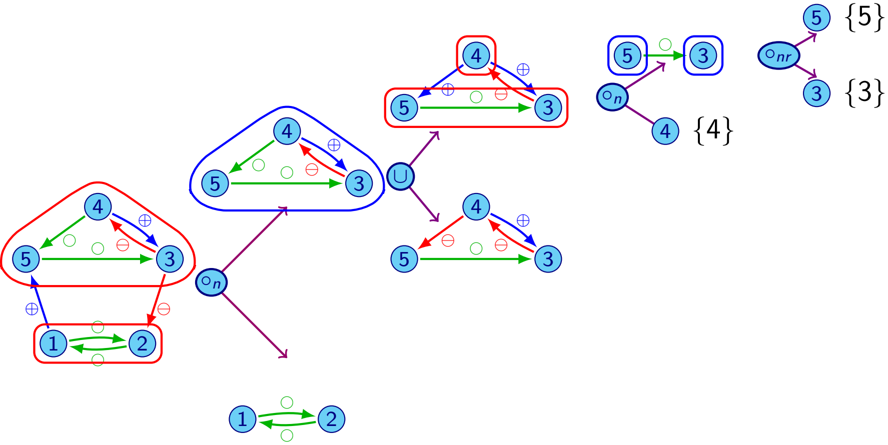

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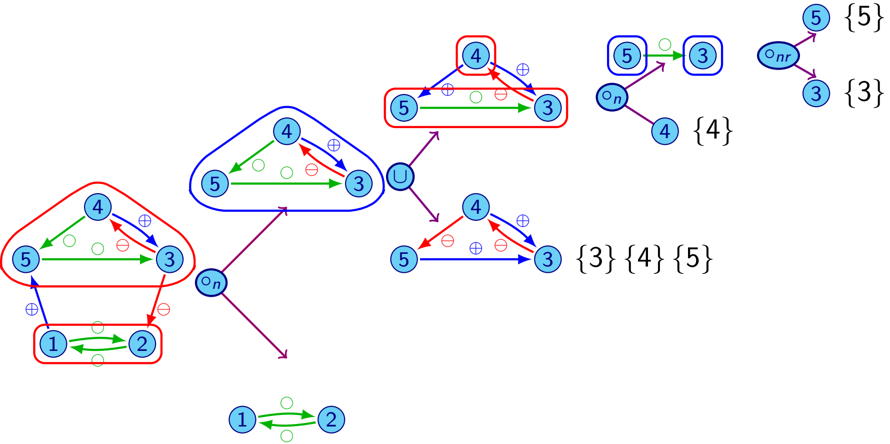
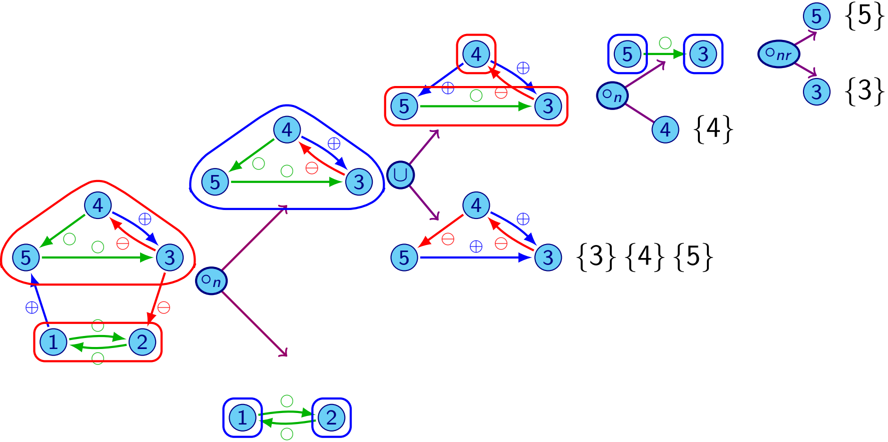
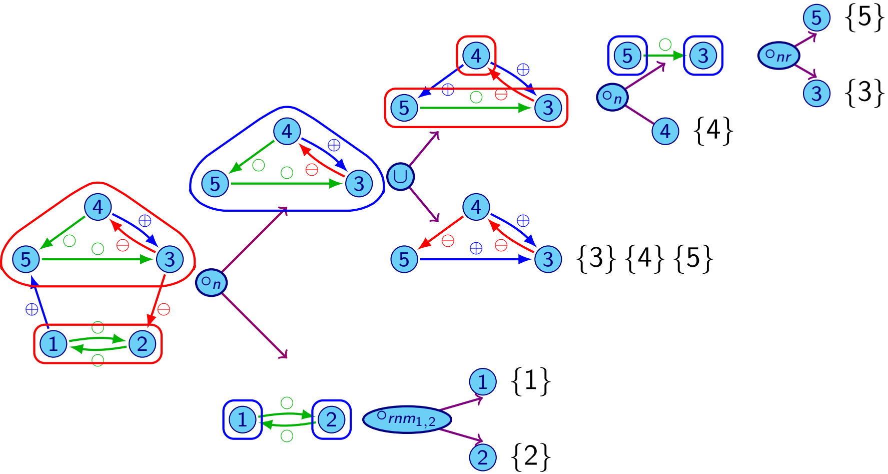


Example: UpdateLabel



Example: UpdateLabel



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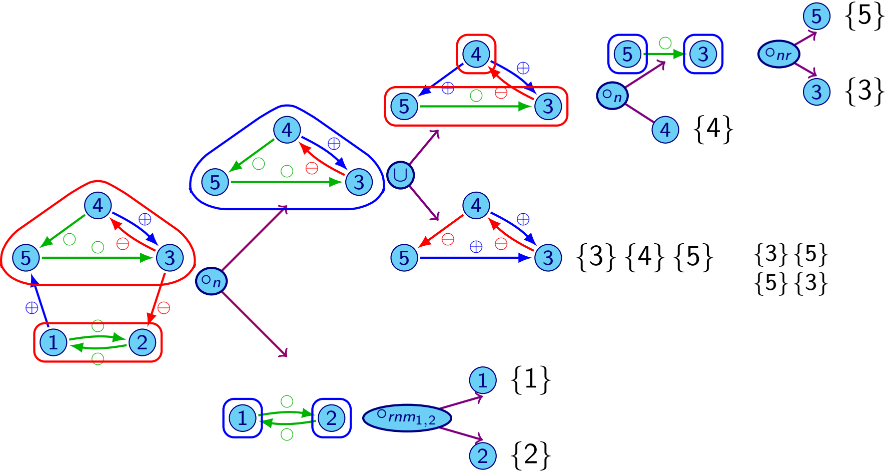
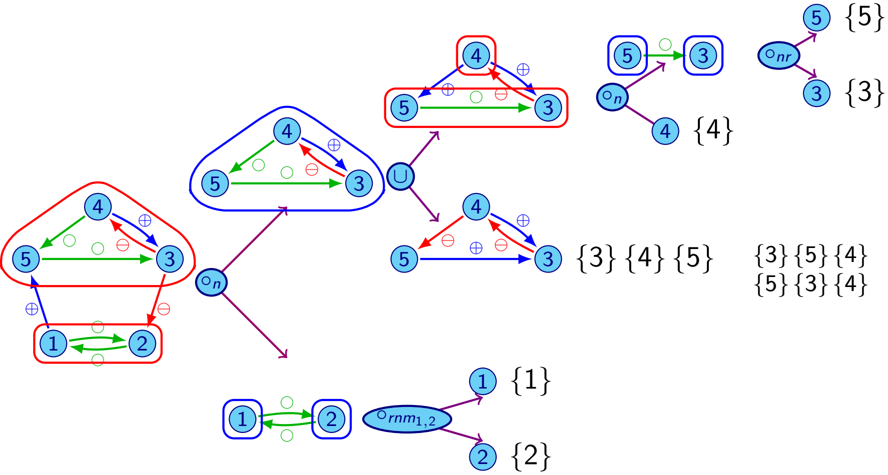
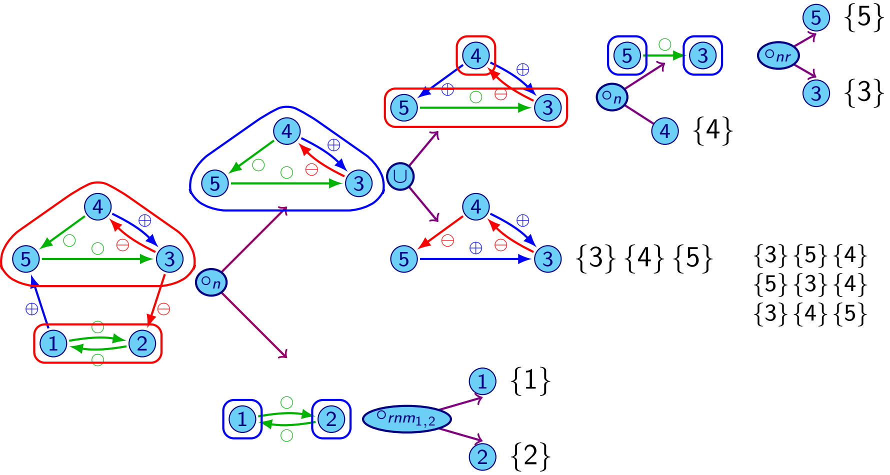


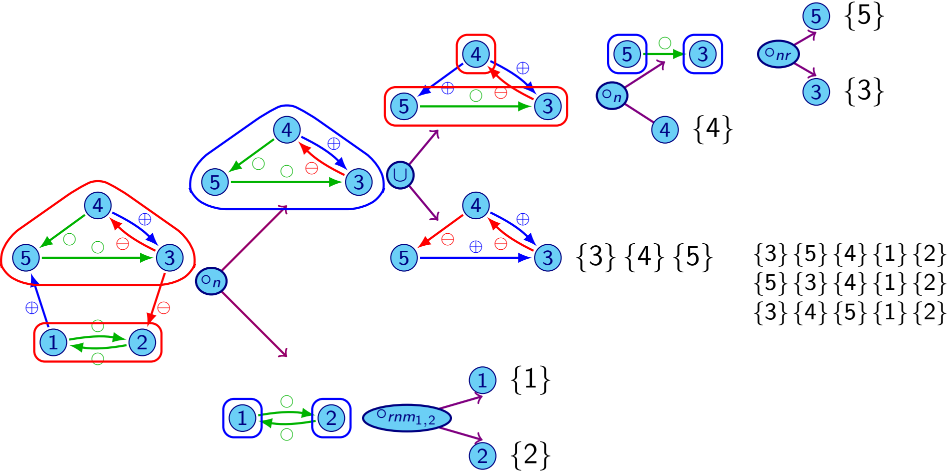
Example: UpdateLabel



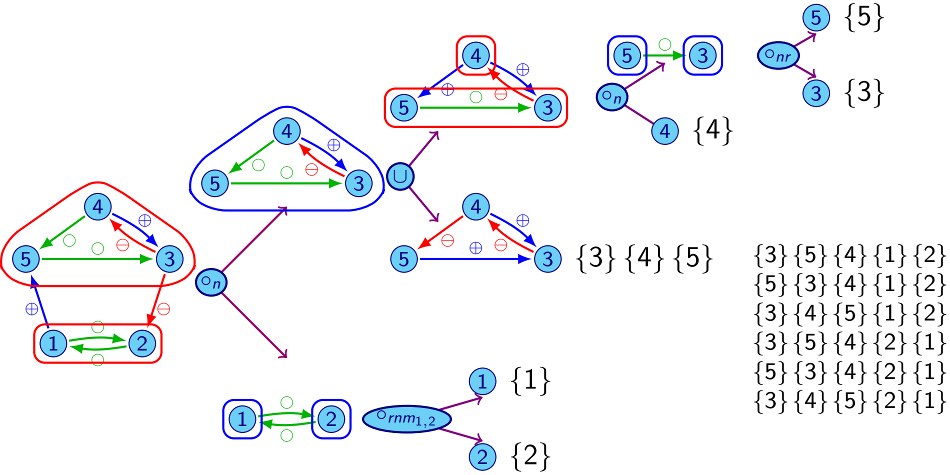
Example: UpdateLabel



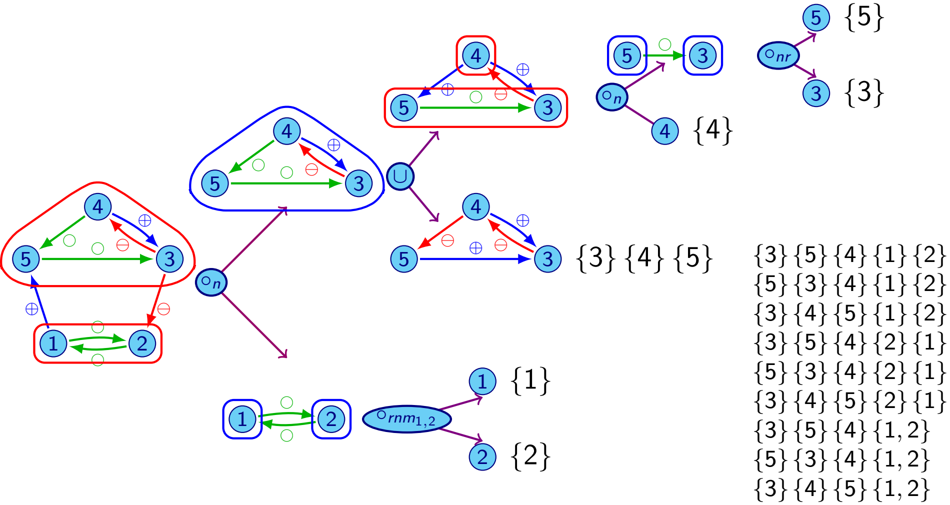
Example: UpdateLabel



Example: UpdateLabel



Example: UpdateLabel



Results

Graph	Nodes	Arcs	$\lvert\mathcal{S}(G, lab)\rvert$	SimpleLabel	Label
K_3	3	6	13	0.02	0.02
K_5	5	20	541	0.18	0.13
K_7	7	42	47 293	140.76	0.79
K_8	8	56	545 835	$>$ 22 200.00	1.90
P_{10}	10	18	19 683	4.43	0.02
P_{12}	12	22	177 147	313.68	0.02
P_{50}	50	98	3^{49}	–	0.09
P_{200}	200	398	3^{199}	–	0.17

Results for the network of mammalian cell cycle

		SimpleLabel (sec)	Label (sec)
Number of update schedule:	466 712	5.230	2.966
Number of extensions:	1 440	0.016	0.033

Finally, only 216 non-equivalent update schedules have this cycle as an attractor.

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