Abstractions for Capturing Dynamics of Very Large Biological Networks

JFLI-LRI-NII - 10th October 2013

Loïc Paulevé

CNRS / LRI

loic.pauleve@lri.fr

http://loicpauleve.name

Overview

Formal verification of dynamical properties

- Validate/refute a model.
- Exhaustive analysis.
- How to handle large-scale networks?

Process Hitting

- Qualitative modelling of biological networks dynamics.
- Subclass of automata networks/Petri nets.
- Supports partial knowledge on cooperations between components.

Abstract Interpretation of Dynamics

- Compact approximate representation of possible dynamics.
- Over-approximation and under-approximation of dynamics.
- Application: reachability verification, cut sets computation.

Outline

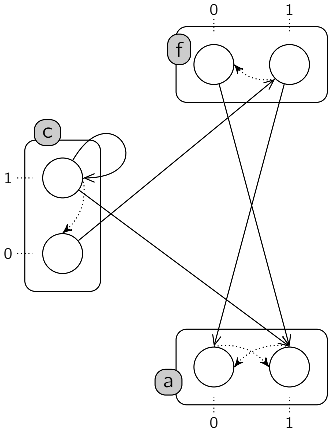
Outline

1. Fixed points
2. Reachability
3. Cut sets for reachability

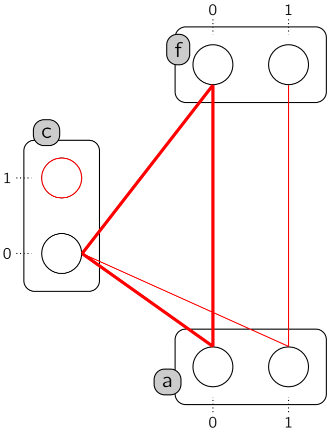
Fixed Points

[Paulevé, Magnin, Roux in TCSB 2011]

Process Hitting



Hitless graph

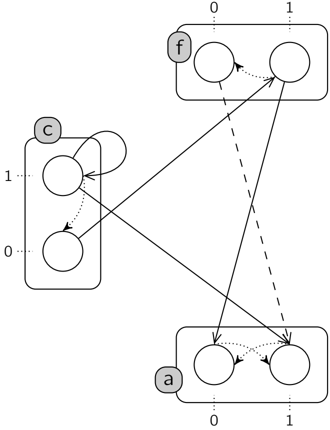


n-cliques <u>are</u> fixed points

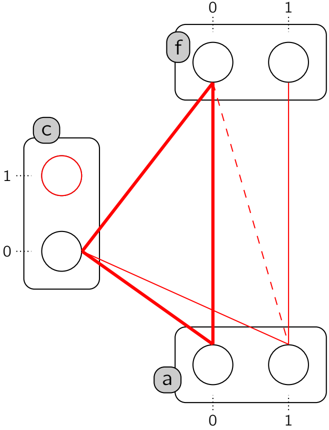
Fixed Points

[Paulevé, Magnin, Roux in TCSB 2011]

Process Hitting



Hitless graph

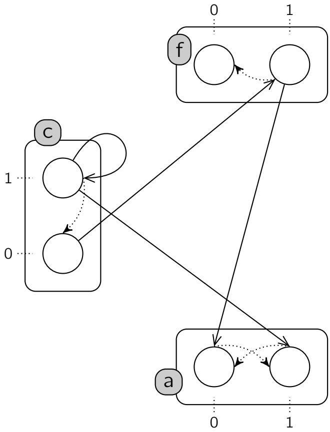


n-cliques are fixed points

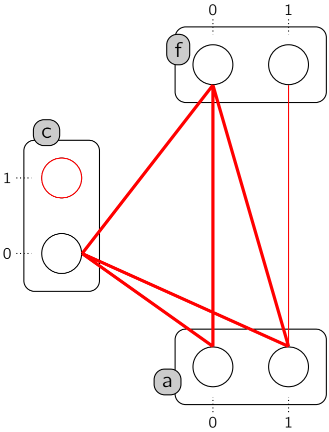
Fixed Points

[Paulevé, Magnin, Roux in TCSB 2011]

Process Hitting



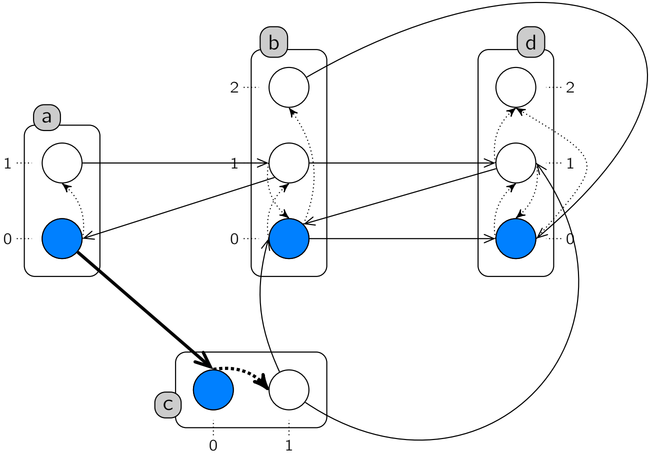
Hitless graph



n-cliques are fixed points

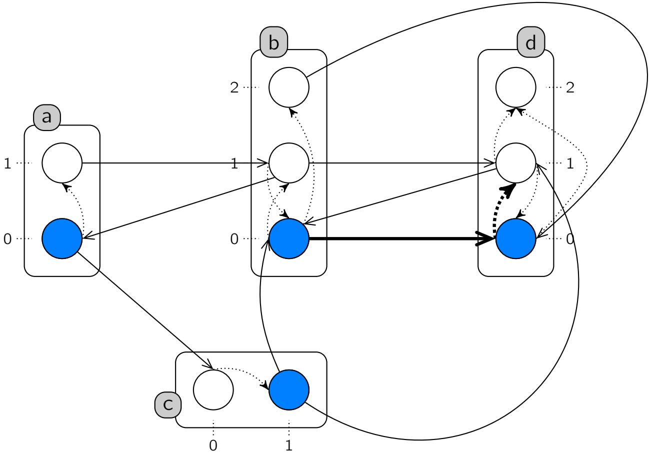
Outline

Scenarios



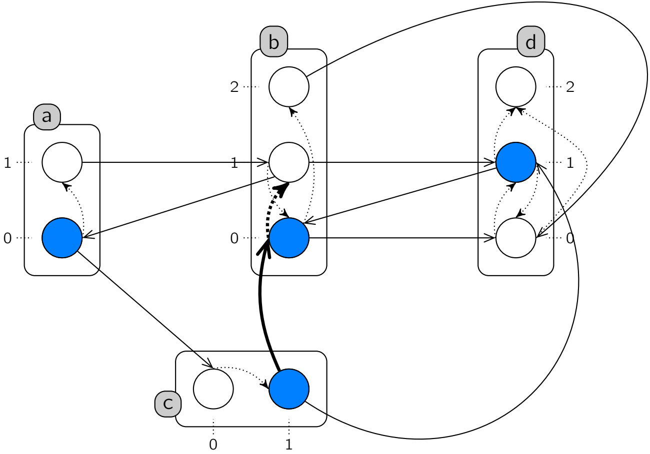
$\mathbf{a_0} \rightarrow \mathbf{c_0} \upharpoonright \mathbf{c_1} :: b_0 \rightarrow d_0 \upharpoonright d_1 :: c_1 \rightarrow b_0 \upharpoonright b_1 :: b_1 \rightarrow d_1 \upharpoonright d_2$

Scenarios



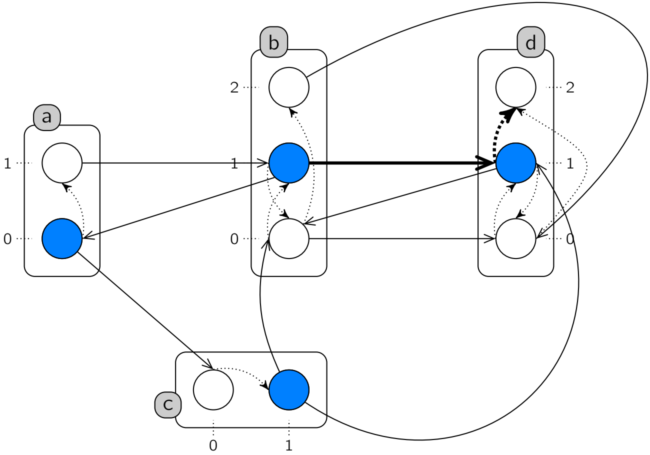
$a_0 \rightarrow c_0 \Rsh c_1 :: \mathbf{b_0 \rightarrow d_0 \Rsh d_1} :: c_1 \rightarrow b_0 \Rsh b_1 :: b_1 \rightarrow d_1 \Rsh d_2$

Scenarios



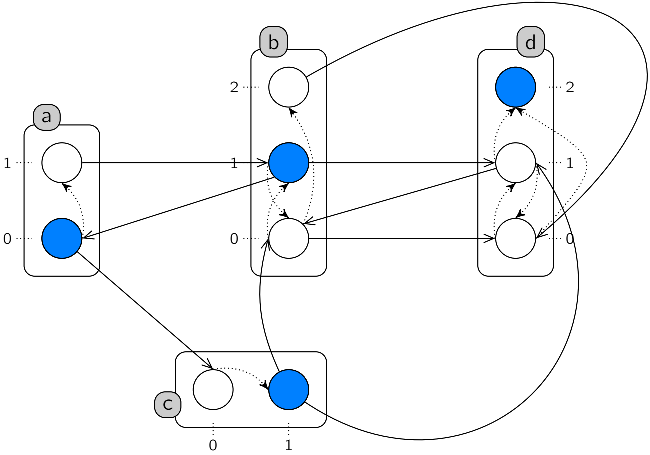
$a_0 \rightarrow c_0 \Rsh c_1 :: b_0 \rightarrow d_0 \Rsh d_1 :: \mathbf{c_1 \rightarrow b_0 \Rsh b_1} :: b_1 \rightarrow d_1 \Rsh d_2$

Scenarios



$$a_0 \rightarrow c_0 \Rsh c_1 :: b_0 \rightarrow d_0 \Rsh d_1 :: c_1 \rightarrow b_0 \Rsh b_1 :: \mathbf{b_1 \rightarrow d_1 \Rsh d_2}$$

Scenarios



$$a_0 \rightarrow c_0 \upharpoonright c_1 :: b_0 \rightarrow d_0 \upharpoonright d_1 :: c_1 \rightarrow b_0 \upharpoonright b_1 :: b_1 \rightarrow d_1 \upharpoonright d_2$$

Static Analysis of Successive Reachability Properties

[Paulevé, Magnin, Roux in MSCS 2012]

Successive Reachability ω

- Given a Process Hitting $\mathcal{PH}$ with an initial state,
- is it possible to reach the process a_i? ...
- then the process b_j? ... etc.

Static Analysis of Successive Reachability Properties

[Paulevé, Magnin, Roux in MSCS 2012]

Successive Reachability ω

- Given a Process Hitting $\mathcal{PH}$ with an initial state,
- is it possible to reach the process a_i? ...
- then the process b_j? ...etc.

Difficulties: combinatorial explosion of dynamics to explore.

Static Analysis of Successive Reachability Properties

[Paulevé, Magnin, Roux in MSCS 2012]

Successive Reachability ω

- Given a Process Hitting $\mathcal{PH}$ with an initial state,
- is it possible to reach the process a_i? ...
- then the process b_j? ...etc.

Difficulties: combinatorial explosion of dynamics to explore.

Chosen approach

Over-approximations

$\mathcal{PH}$ does not satisfy $\mathcal{P} \implies \omega$ is impossible.

Under-approximations

$\mathcal{PH}$ satisfies $\mathcal{Q} \implies \omega$ is possible.

Requirement: checking $\mathcal{P}$ ($\mathcal{Q}$) is fast.

Two Complementary Abstractions of Scenarios

$$a_0 \rightarrow \mathbf{c_0} \upharpoonright \mathbf{c_1} :: b_0 \rightarrow \mathbf{d_0} \upharpoonright \mathbf{d_1} :: c_1 \rightarrow \mathbf{b_0} \upharpoonright \mathbf{b_1} :: b_1 \rightarrow \mathbf{d_1} \upharpoonright \mathbf{d_2}$$

Abstraction by Objective Sequences

- $c_0 \upharpoonright^* c_1 :: d_0 \upharpoonright^* d_1 :: b_0 \upharpoonright^* b_1 :: d_1 \upharpoonright^* d_2$;

Two Complementary Abstractions of Scenarios

$$a_0 \rightarrow c_0 \Rsh c_1 :: b_0 \rightarrow \mathbf{d_0} \Rsh d_1 :: c_1 \rightarrow \mathbf{b_0} \Rsh \mathbf{b_1} :: b_1 \rightarrow d_1 \Rsh \mathbf{d_2}$$

Abstraction by Objective Sequences

- $c_0 \Rsh^* c_1 :: d_0 \Rsh^* d_1 :: b_0 \Rsh^* b_1 :: d_1 \Rsh^* d_2$;
- $b_0 \Rsh^* b_1 :: d_0 \Rsh^* d_2$

Two Complementary Abstractions of Scenarios

$$a_0 \rightarrow c_0 \Rsh c_1 :: b_0 \rightarrow \mathbf{d_0} \Rsh d_1 :: c_1 \rightarrow b_0 \Rsh b_1 :: b_1 \rightarrow d_1 \Rsh \mathbf{d_2}$$

Abstraction by Objective Sequences

- $c_0 \Rsh^* c_1 :: d_0 \Rsh^* d_1 :: b_0 \Rsh^* b_1 :: d_1 \Rsh^* d_2$;
- $b_0 \Rsh^* b_1 :: d_0 \Rsh^* d_2$
- $d_0 \Rsh^* d_2$, ...

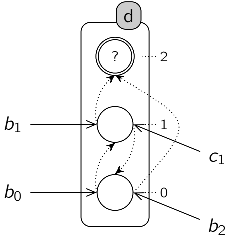
Two Complementary Abstractions of Scenarios

$$a_0 \rightarrow c_0 \upharpoonright c_1 :: \mathbf{b_0 \rightarrow d_0 \upharpoonright d_1} :: c_1 \rightarrow b_0 \upharpoonright b_1 :: \mathbf{b_1 \rightarrow d_1 \upharpoonright d_2}$$

Abstraction by Objective Sequences

- $c_0 \upharpoonright^* c_1 :: d_0 \upharpoonright^* d_1 :: b_0 \upharpoonright^* b_1 :: d_1 \upharpoonright^* d_2$;
- $b_0 \upharpoonright^* b_1 :: d_0 \upharpoonright^* d_2$
- $d_0 \upharpoonright^* d_2$, ...

Abstraction by Bounce Sequences



E.g.: $b_0 \rightarrow d_0 \upharpoonright d_1 :: b_1 \rightarrow d_1 \upharpoonright d_2$ ($d_0 \upharpoonright^* d_2$)

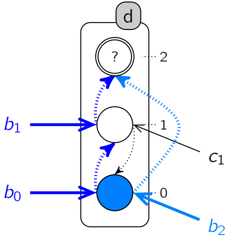
Two Complementary Abstractions of Scenarios

$$a_0 \rightarrow c_0 \Rsh c_1 :: b_0 \rightarrow d_0 \Rsh d_1 :: c_1 \rightarrow b_0 \Rsh b_1 :: b_1 \rightarrow d_1 \Rsh d_2$$

Abstraction by Objective Sequences

- $c_0 \Rsh^* c_1 :: d_0 \Rsh^* d_1 :: b_0 \Rsh^* b_1 :: d_1 \Rsh^* d_2$;
- $b_0 \Rsh^* b_1 :: d_0 \Rsh^* d_2$
- $d_0 \Rsh^* d_2$, ...

Abstraction by Bounce Sequences



E.g.: $b_0 \rightarrow d_0 \Rsh d_1 :: b_1 \rightarrow d_1 \Rsh d_2$ $(d_0 \Rsh^* d_2)$
$\Rightarrow$ can be computed off-line:

- $\mathrm{sol}(d_0 \Rsh^* d_2) = \{b_0 \rightarrow d_0 \Rsh d_1 :: b_1 \rightarrow d_1 \Rsh d_2,$
  $b_2 \rightarrow d_0 \Rsh d_2\}$;
- $\mathrm{sol}^{\wedge}(d_0 \Rsh^* d_2) = \{\{b_0, b_1\}, \{b_2\}\}$.

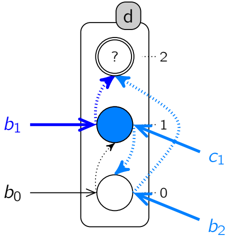
Two Complementary Abstractions of Scenarios

$$a_0 \rightarrow c_0 \Rsh c_1 :: b_0 \rightarrow d_0 \Rsh d_1 :: c_1 \rightarrow b_0 \Rsh b_1 :: b_1 \rightarrow d_1 \Rsh d_2$$

Abstraction by Objective Sequences

- $c_0 \Rsh^* c_1 :: d_0 \Rsh^* d_1 :: b_0 \Rsh^* b_1 :: d_1 \Rsh^* d_2$;
- $b_0 \Rsh^* b_1 :: d_0 \Rsh^* d_2$
- $d_0 \Rsh^* d_2$, ...

Abstraction by Bounce Sequences

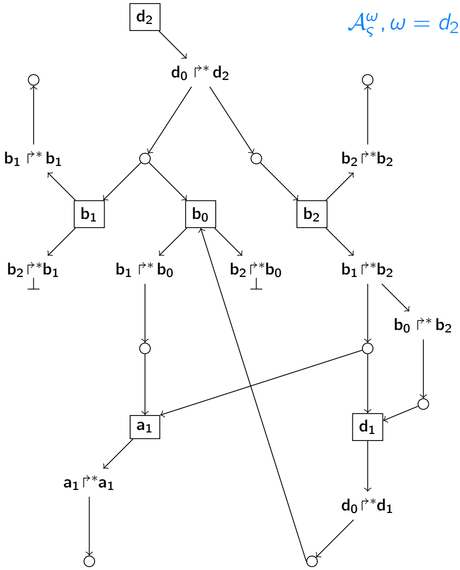


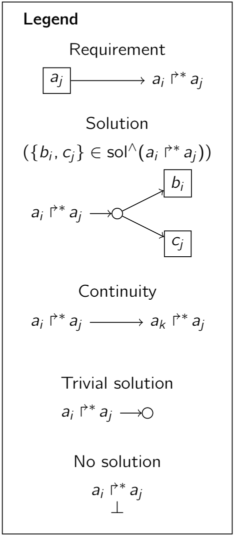
E.g.: $b_0 \rightarrow d_0 \Rsh d_1 :: b_1 \rightarrow d_1 \Rsh d_2$ $(d_0 \Rsh^* d_2)$
$\Rightarrow$ can be computed off-line:

- $\mathrm{sol}(d_0 \Rsh^* d_2) = \{b_0 \rightarrow d_0 \Rsh d_1 :: b_1 \rightarrow d_1 \Rsh d_2,$
  $b_2 \rightarrow d_0 \Rsh d_2\}$;
- $\mathrm{sol}^\wedge(d_0 \Rsh^* d_2) = \{\{b_0, b_1\}, \{b_2\}\}$.
- $\mathrm{sol}(d_1 \Rsh^* d_2) = \{b_1 \rightarrow d_1 \Rsh d_2,$
  $c_1 \rightarrow d_1 \Rsh d_0 :: b_2 \rightarrow d_0 \Rsh d_2\}$;
- $\mathrm{sol}^\wedge(d_1 \Rsh^* d_2) = \{\{b_1\}, \{b_2, c_1\}\}$.

Graph of Local Causality

$\mathcal{A}_{\varsigma}^{\omega}, \omega = d_2, \varsigma = \langle a_1, \{b_1, b_2\}, c_1, d_0 \rangle$





Abstract Interpretation

- ω: successive reachability property (e.g. $a_i :: b_j :: \cdots z_l$).
- ς: set of initial states.

$$\gamma_\varsigma(\omega) = \{\delta \in \mathbf{Sce} \mid \delta \text{ concretizes } \omega \wedge \delta \text{ starts in } \varsigma\}$$

Objective refinement using $\mathrm{sol}^\wedge$**:** $\rho^\wedge$

$\mathbf{Obj} \times \wp(\mathrm{sol}^\wedge)$	$\wp(\mathbf{OS})$
$d_0 \Rsh^* d_2$, $\{\{b_0, b_1\}, \{b_2\}\}$	$\star \Rsh^* b_0 :: b_0 \Rsh^* b_1 :: d_0 \Rsh^* d_2$, $\star \Rsh^* b_1 :: b_1 \Rsh^* b_0 :: d_0 \Rsh^* d_2$, $\star \Rsh^* b_2 :: d_0 \Rsh^* d_2$
$\gamma_\varsigma(d_0 \Rsh^* d_2)$	$= \gamma_\varsigma(\rho^\wedge(d_0 \Rsh^* d_2, \mathrm{sol}^\wedge(d_0 \Rsh^* d_2)))$

Abstract Interpretation

- ω: successive reachability property (e.g. $a_i :: b_j :: \cdots z_l$).
- ς: set of initial states.

$$\gamma_\varsigma(\omega) = \{\delta \in \mathbf{Sce} \mid \delta \text{ concretizes } \omega \wedge \delta \text{ starts in } \varsigma\}$$

Objective refinement using $\mathrm{sol}^\wedge$**:** $\rho^\wedge$

$\mathbf{Obj} \times \wp(\mathrm{sol}^\wedge)$	$\wp(\mathbf{OS})$
$d_0 \Rsh^* d_2$, $\{\{b_0, b_1\}, \{b_2\}\}$	$\star \Rsh^* b_0 :: b_0 \Rsh^* b_1 :: d_0 \Rsh^* d_2$, $\star \Rsh^* b_1 :: b_1 \Rsh^* b_0 :: d_0 \Rsh^* d_2$, $\star \Rsh^* b_2 :: d_0 \Rsh^* d_2$
$\gamma_\varsigma(d_0 \Rsh^* d_2)$	$= \gamma_\varsigma(\rho^\wedge(d_0 \Rsh^* d_2, \mathrm{sol}^\wedge(d_0 \Rsh^* d_2)))$

Generalization to OS refinements: $\widetilde{\rho}$

$\mathbf{OS} \times \wp(\mathrm{sol}^\wedge)$	$\wp(\mathbf{OS})$
$\omega, \mathrm{sol}^\wedge$	interleave $\begin{pmatrix} \omega' \\ \omega_{1..n-1} \end{pmatrix} :: \omega_{n..\lvert\omega\rvert}$ where $n \in \mathbb{I}^\omega$ and $\omega' :: \omega_n \in \rho^\wedge(\omega_n, \mathrm{sol}^\wedge(\omega_n))$
$\gamma_\varsigma(\omega)$	$= \gamma_\varsigma(\widetilde{\rho}(\omega, \mathrm{sol}^\wedge))$

Approximations of Successive Reachability

Over-approximations

- Un-ordered approximation.
- Ordered approximation.
- Ordered approximation with occurences order constraints.

No / Inconc

$\Uparrow$

Successive Process Reachability (reach a_i, then b_k, etc.)

$\Uparrow$

Under-approximations

- Un-ordered approximation.
- Ordered approximation.

Yes / Inconc

Approximations of Successive Reachability

Over-approximations

- Un-ordered approximation.
- Ordered approximation.
- Ordered approximation with occurences order constraints.

No / Inconc

$\Uparrow$

Successive Process Reachability (reach a_i, then b_k, etc.)

$\Uparrow$

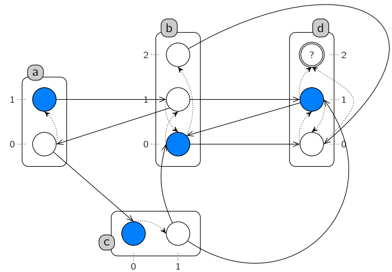
Under-approximations

- Un-ordered approximation.
- Ordered approximation.

Yes / Inconc

Over-approximation of Reachability

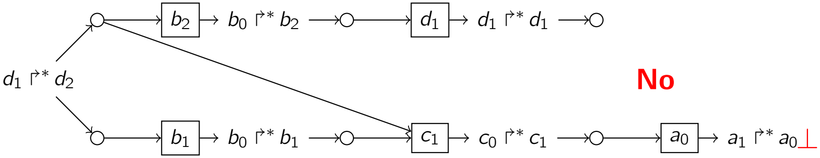
Example



Necessary condition for reaching d_2:

There exists a traversal of the GLC s.t.:

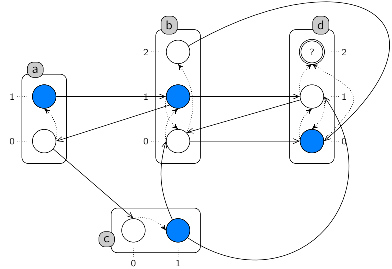
- objective → follow at least one solution;
- process → follow all objectives;
- no cycle.



No

Over-approximation of Reachability

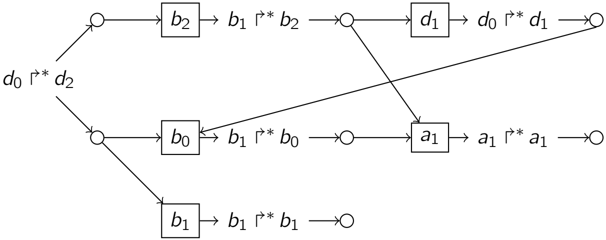
Example



Necessary condition for reaching d_2:

There exists a traversal of the GLC s.t.:

- objective → follow at least one solution;
- process → follow all objectives;
- no cycle.



Inconc

Approximations of Successive Reachability

Over-approximations

- Un-ordered approximation.
- Ordered approximation.
- Ordered approximation with occurences order constraints.

No / Inconc

$\Uparrow$

Successive Process Reachability (reach a_i, then b_k, etc.)

$\Uparrow$

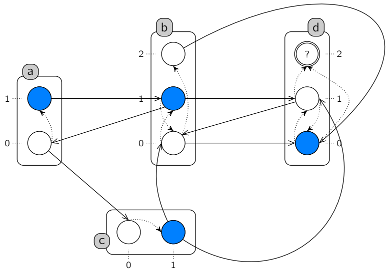
Under-approximations

- Un-ordered approximation.
- Ordered approximation.

Yes / Inconc

Un-ordered Under-approximation

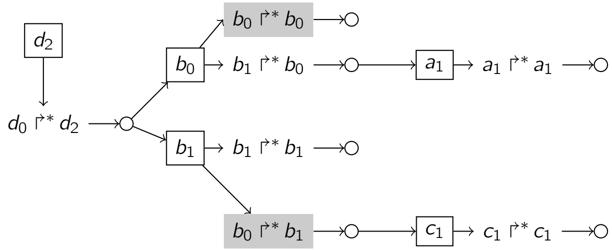
Example



Sufficient condition for reaching d_2:

- $\lceil \mathcal{B}_\varsigma^\omega \rceil$ has no cycle;
- each objective has at least one solution.

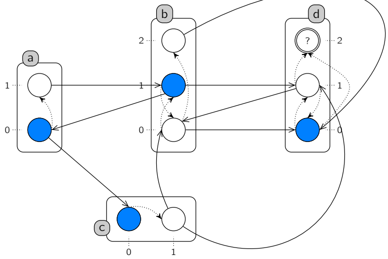
$\lceil \mathcal{B}_\varsigma^\omega \rceil$: saturated $\mathcal{A}_\varsigma^\omega$.



Yes

Un-ordered Under-approximation

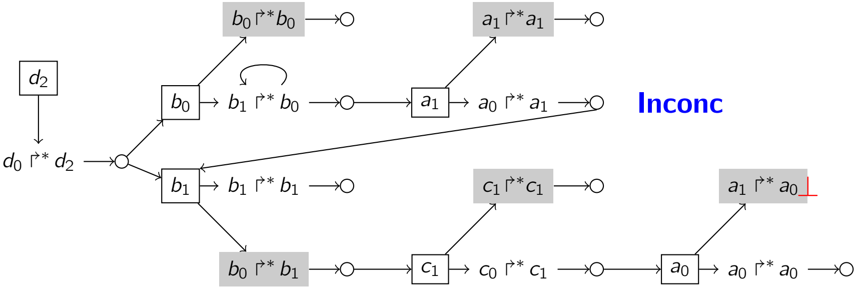
Example



Sufficient condition for reaching d_2:

- $\lceil \mathcal{B}_\varsigma^\omega \rceil$ has no cycle;
- each objective has at least one solution.

$\lceil \mathcal{B}_\varsigma^\omega \rceil$: saturated $\mathcal{A}_\varsigma^\omega$.



Static Analysis of Successive Reachability

Over-approximations

- Un-ordered approximation.
- Ordered approximation.
- Ordered approximation with occurences order constraints.

No / Inconc

$\Uparrow$

Successive Process Reachability (reach a_i, then b_k, etc.)

$\Uparrow$

Under-approximations

- Un-ordered approximation.
- Ordered approximation.

Yes / Inconc

Static Analysis of Successive Reachability

Over-approximations

- Un-ordered approximation.
- Ordered approximation.
- Ordered approximation with occurences order constraints.

No / Inconc

$\Uparrow$

Successive Process Reachability (reach a_i, then b_k, etc.)

$\Uparrow$

Under-approximations

- Un-ordered approximation.
- Ordered approximation.

Yes / Inconc

Still inconclusive?

- Require new analyses of the abstract structure
- $\Rightarrow$ drive refinements of ω.

Complexity

Abstract Strutures $\mathcal{A}^{\omega}_{\varsigma}$, $\lceil \mathcal{B}^{\omega}_{\varsigma} \rceil$

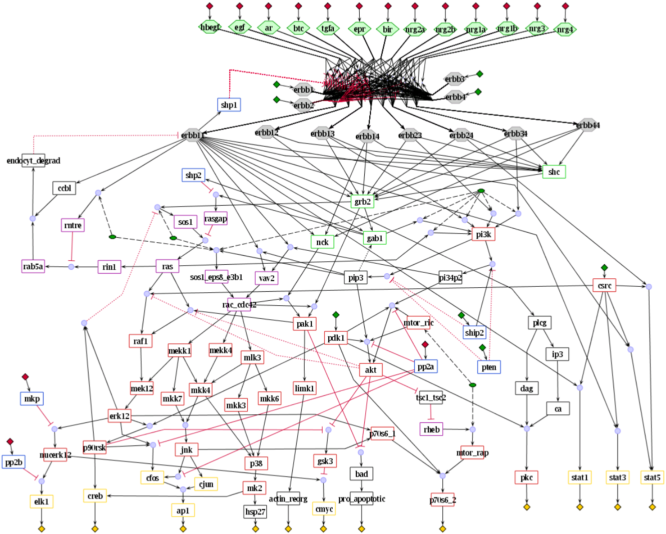
- $\text{sol}^{\wedge}$ computation: exponential in the number of processes within a single sort.
- Size of $\text{sol}^{\wedge}$: combinaisons of $|\mathbf{LS}_a|$ processes $\binom{|\mathbf{LS}|}{|\mathbf{LS}_a|}$.
- Size of $\mathcal{A}^{\omega}_{\varsigma}$ (and $\lceil \mathcal{B}^{\omega}_{\varsigma} \rceil$): polynomial in processes number $\times$ size of $\text{sol}^{\wedge}$.

Analyses

- Over-approximations: polynomial in the size of $\mathcal{A}^{\omega}_{\varsigma}$.
- Different strategies of under-approximation:
  - global: polynomial in the size of $\lceil \mathcal{B}^{\omega}_{\varsigma} \rceil$;
  - per solution: $\times$ exponential in the size of $\text{sol}^{\wedge}$.

$\Longrightarrow$ efficient with a small number of processes per sort, while a very large number of sorts can be handled.

EGFR/ErbB Signalling Network
(104 components)



[Samaga, *et al.* in PLoS Comput Biol, 2009]

Process Hitting

193 sorts,
748 processes,
2356 actions:
$\approx 2 \cdot 10^{96}$ states.

Execution times

- Real biological models.
- Wide-range of biological/arbitrary reachability analysis.
- Always conclusive.

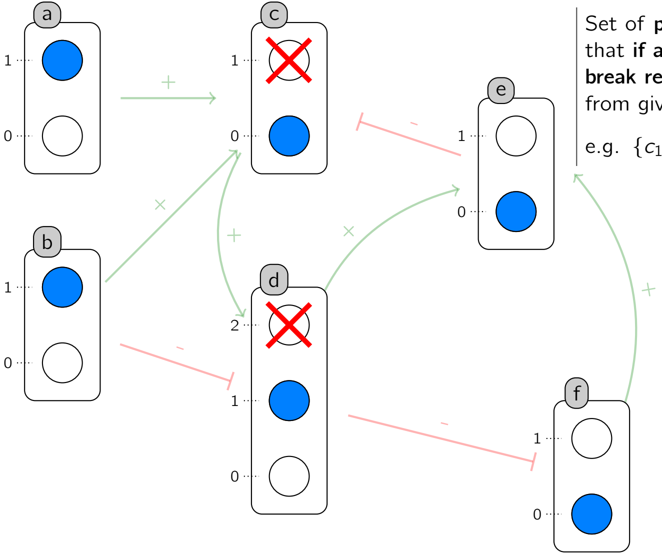
Model	sorts	procs	actions	states	Biocham[1]	libDDD[2]	PINT[3]
egfr20	35	196	670	2^{64}	[3s-KO]	[1s-150s]	0.007s
tcrsig40	54	156	301	2^{73}	[1s-KO]	[0.6s-KO]	0.004s
tcrsig94	133	448	1124	2^{194}	KO	KO	0.030s
egfr104	193	748	2356	2^{320}	KO	KO	0.050s

[1] `http://contraintes.inria.fr/biocham` (using NuSMV2)
[2] `http://move.lip6.fr/software/DDD`
[3] `http://loicpauleve.name/pint`

Outline

Cut Sets for Reachability

[Paulevé et al. at CAV'13]

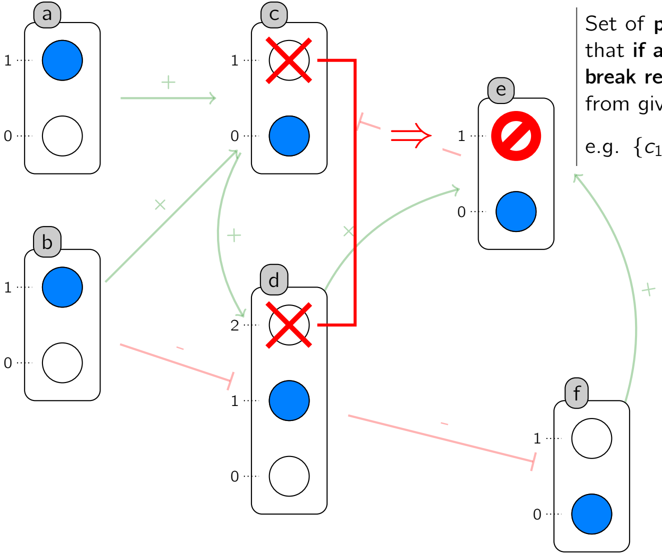


Set of **processes** that **if all disabled break reachability** from given initial states

e.g. $\{c_1, d_2\}$

Cut Sets for Reachability

[Paulevé et al. at CAV'13]

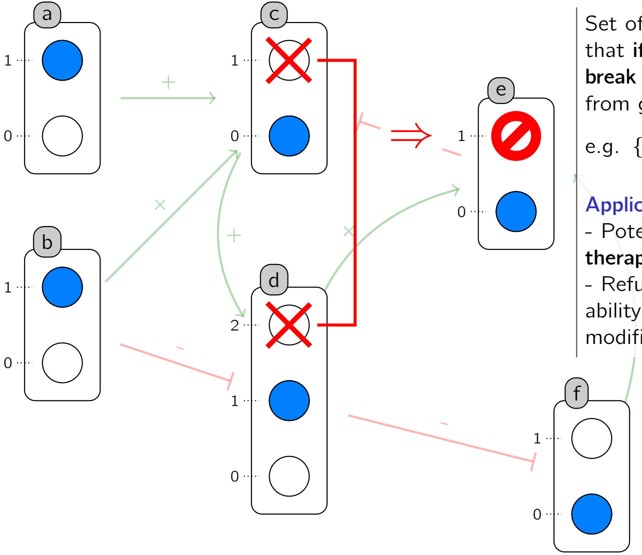


Set of **processes**
that **if all disabled**
break reachability
from given initial states

e.g. $\{c_1, d_2\}$

Cut Sets for Reachability

[Paulevé et al. at CAV'13]



Set of **processes** that **if all disabled break reachability** from given initial states

e.g. $\{c_1, d_2\}$

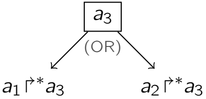
Applications

- Potential **therapeutic targets**
- Refute model if reachability still occurs in the modified (real) system

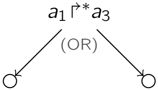
Cut Sets Under-Approximation

Associate to each node sets of processes intersecting *any* trace from given context.

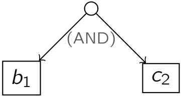
$$\mathbb{V} : \text{nodes} \mapsto \wp(\wp^{\leq N}(\mathcal{O}bs)), \mathcal{O}bs \subset \mathbf{LS}$$



$$\mathbb{V}(a_3) = \mathbb{V}(a_1 \Rsh^* a_3) \tilde{\times} \mathbb{V}(a_2 \Rsh^* a_3) \cup \{\{a_3\}\}$$



$$\mathbb{V}(a_1 \Rsh^* a_3) = \mathbb{V}(sol^1) \tilde{\times} (sol^2)$$



$$\mathbb{V}(sol^1) = \mathbb{V}(b_1) \cup \mathbb{V}(c_2)$$

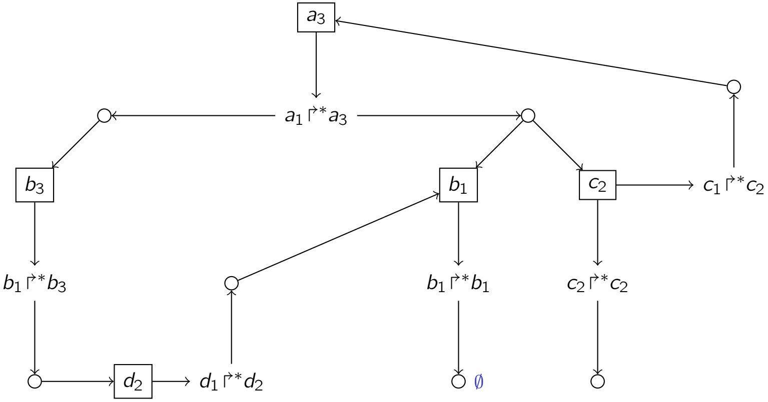
$\{e^1, \ldots, e^n\} \tilde{\times} \{f^1, \ldots, f^m\} \triangleq \{e^i \cup f^j \mid i \in [1;n] \wedge j \in [1;m]\}$; $e^i, f^j \in \wp^{\leq N}(\mathcal{O}bs)$

Cut Sets Under-approximation

Example

Sketch

- Follow the topological order of GLC.
- SCCs: arbitrary/random order for updating nodes having child modified.
- Always converges.

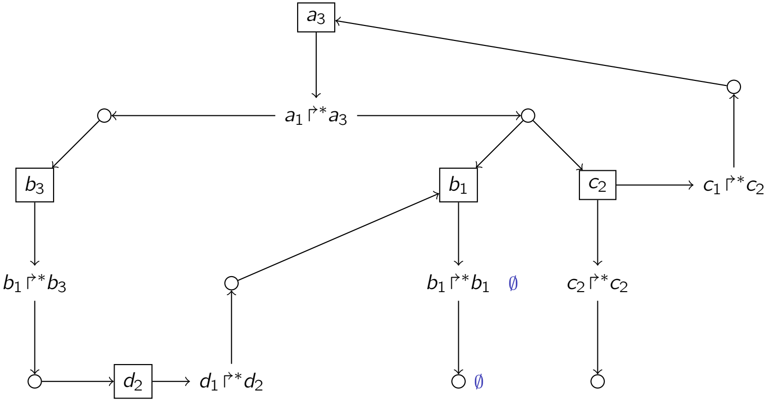


Cut Sets Under-approximation

Example

Sketch

- Follow the topological order of GLC.
- SCCs: arbitrary/random order for updating nodes having child modified.
- Always converges.

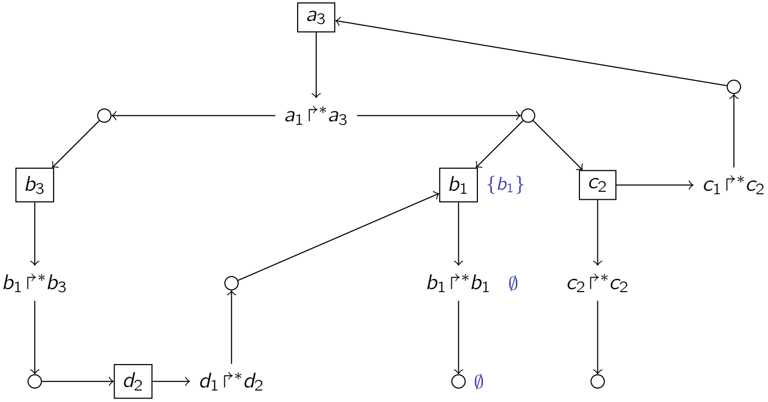


Cut Sets Under-approximation

Example

Sketch

- Follow the topological order of GLC.
- SCCs: arbitrary/random order for updating nodes having child modified.
- Always converges.

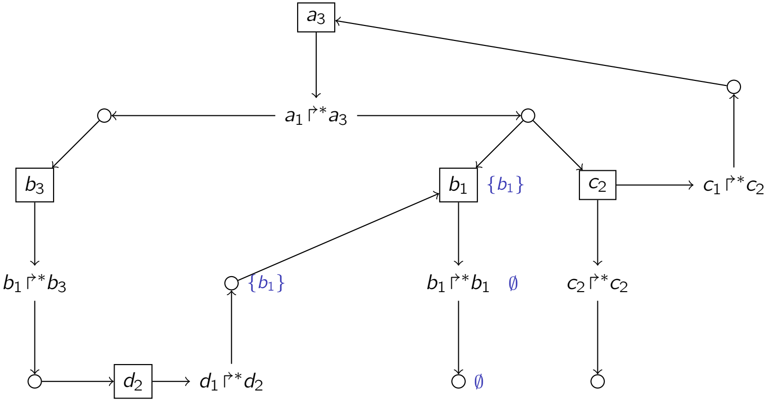


Cut Sets Under-approximation

Example

Sketch

- Follow the topological order of GLC.
- SCCs: arbitrary/random order for updating nodes having child modified.
- Always converges.

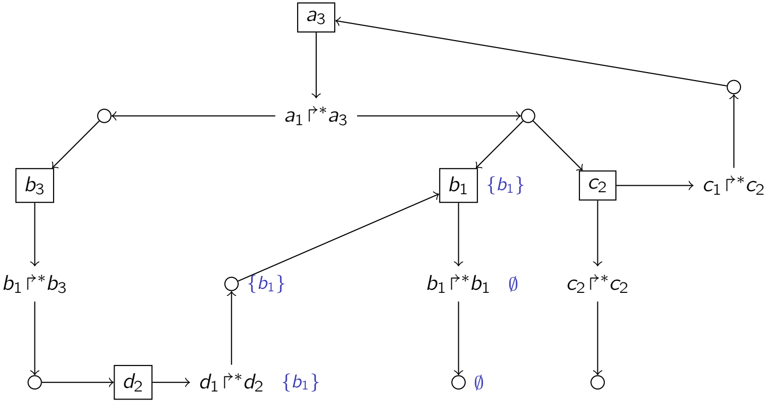


Cut Sets Under-approximation

Example

Sketch

- Follow the topological order of GLC.
- SCCs: arbitrary/random order for updating nodes having child modified.
- Always converges.

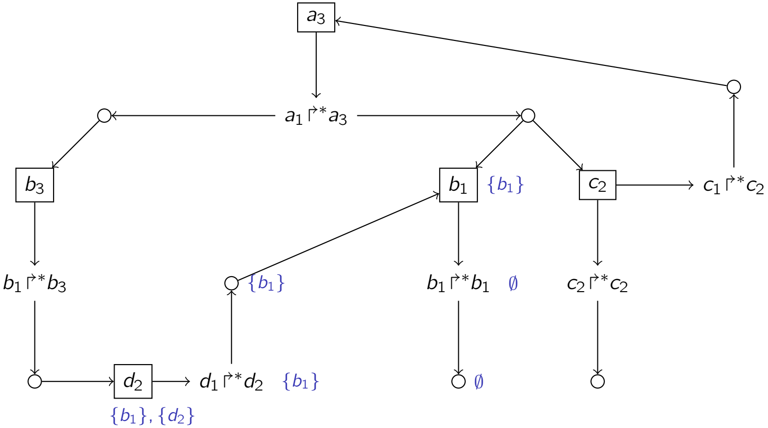


Cut Sets Under-approximation

Example

Sketch

- Follow the topological order of GLC.
- SCCs: arbitrary/random order for updating nodes having child modified.
- Always converges.

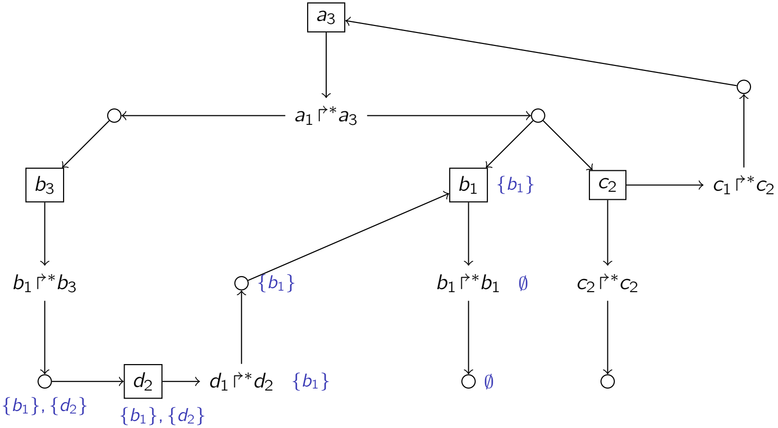


Cut Sets Under-approximation

Example

Sketch

- Follow the topological order of GLC.
- SCCs: arbitrary/random order for updating nodes having child modified.
- Always converges.

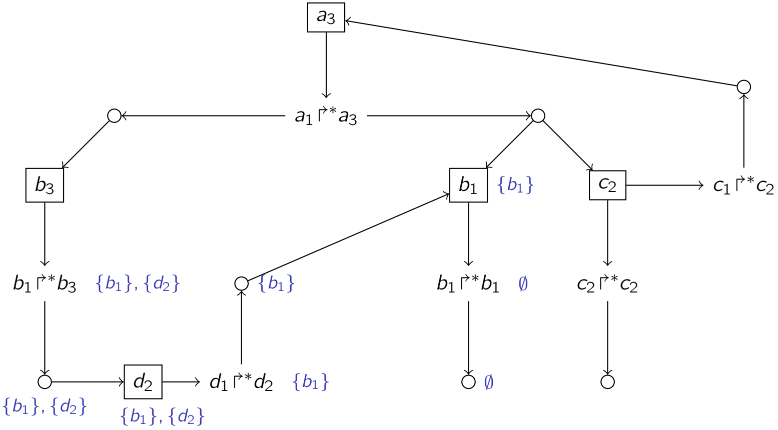


Cut Sets Under-approximation

Example

Sketch

- Follow the topological order of GLC.
- SCCs: arbitrary/random order for updating nodes having child modified.
- Always converges.

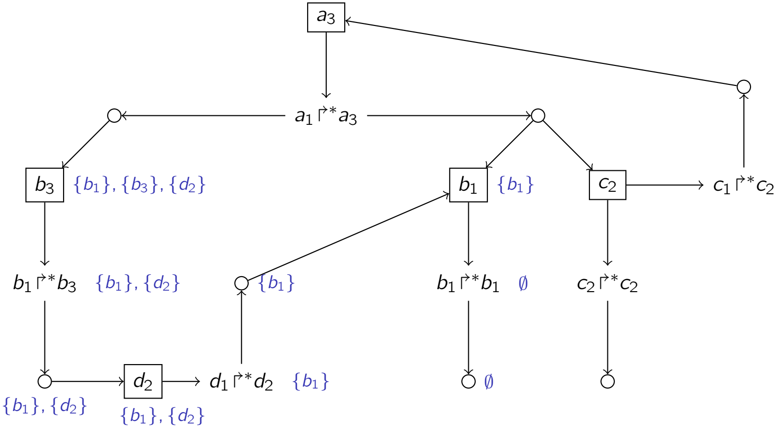


Cut Sets Under-approximation

Example

Sketch

- Follow the topological order of GLC.
- SCCs: arbitrary/random order for updating nodes having child modified.
- Always converges.

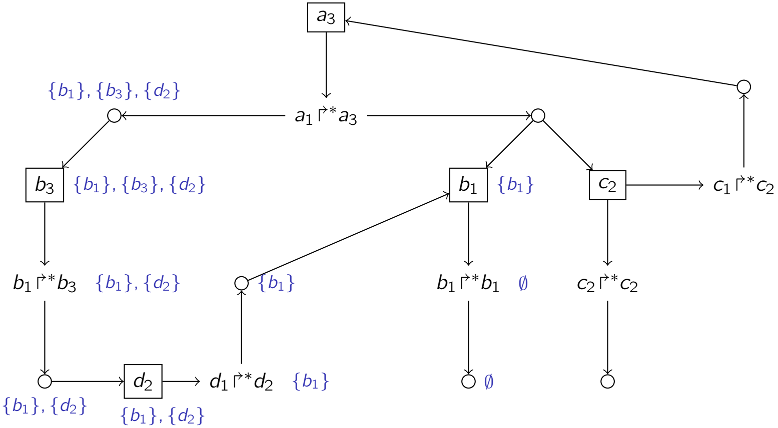


Cut Sets Under-approximation

Example

Sketch

- Follow the topological order of GLC.
- SCCs: arbitrary/random order for updating nodes having child modified.
- Always converges.

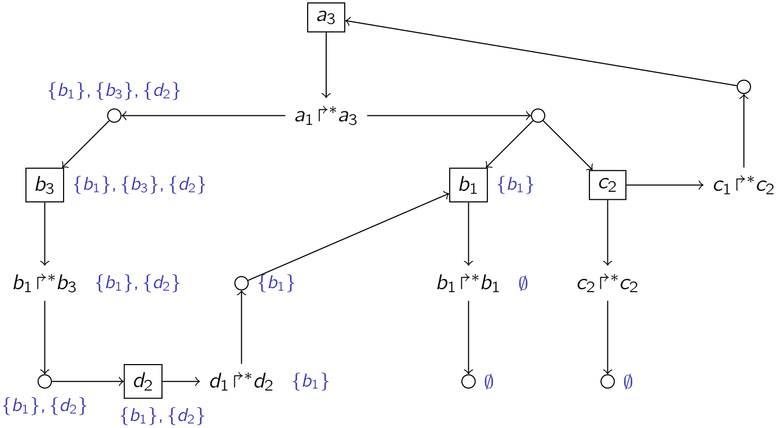


Cut Sets Under-approximation

Example

Sketch

- Follow the topological order of GLC.
- SCCs: arbitrary/random order for updating nodes having child modified.
- Always converges.

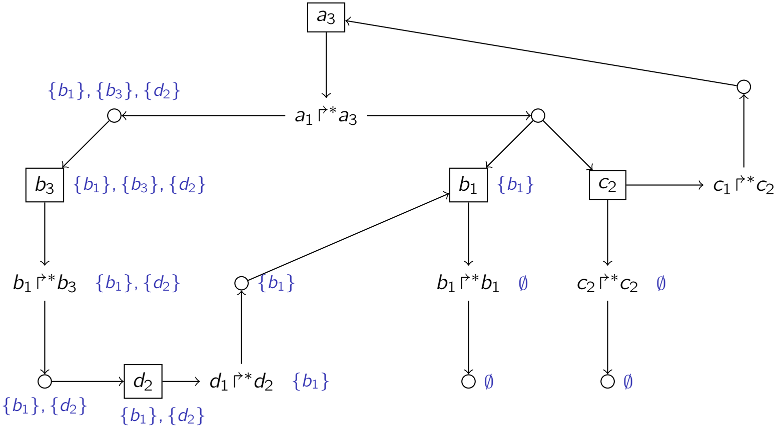


Cut Sets Under-approximation

Example

Sketch

- Follow the topological order of GLC.
- SCCs: arbitrary/random order for updating nodes having child modified.
- Always converges.

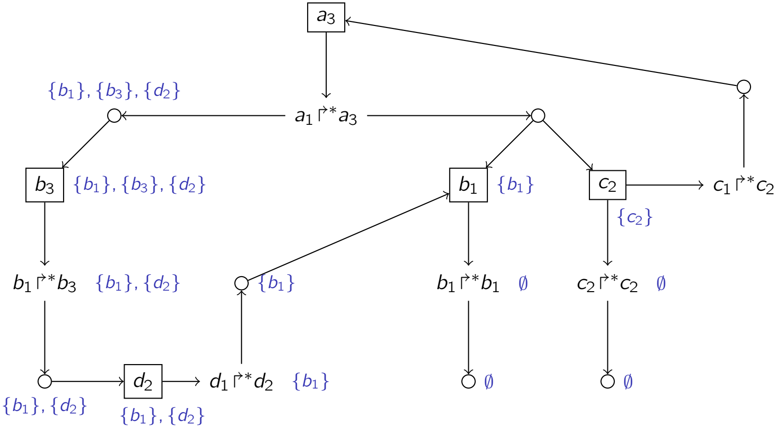


Cut Sets Under-approximation

Example

Sketch

- Follow the topological order of GLC.
- SCCs: arbitrary/random order for updating nodes having child modified.
- Always converges.

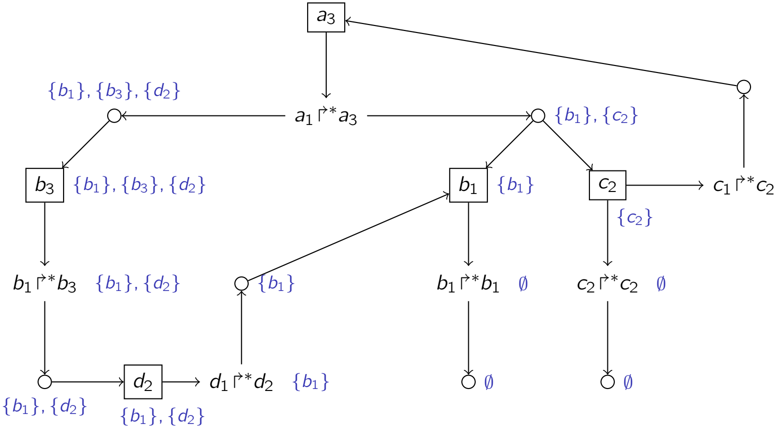


Cut Sets Under-approximation

Example

Sketch

- Follow the topological order of GLC.
- SCCs: arbitrary/random order for updating nodes having child modified.
- Always converges.

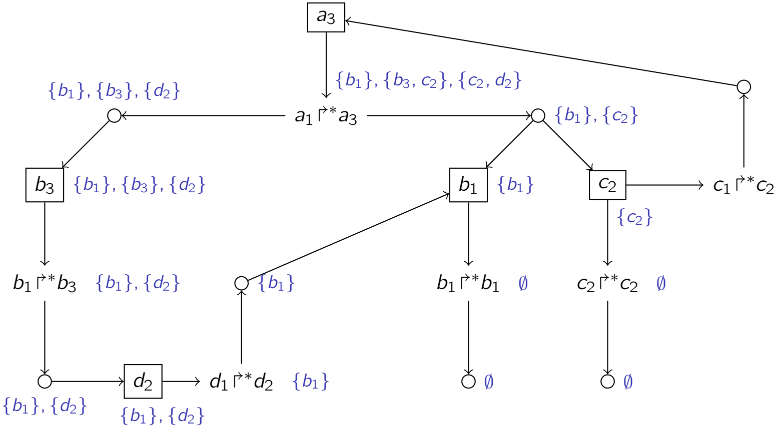


Cut Sets Under-approximation

Example

Sketch

- Follow the topological order of GLC.
- SCCs: arbitrary/random order for updating nodes having child modified.
- Always converges.

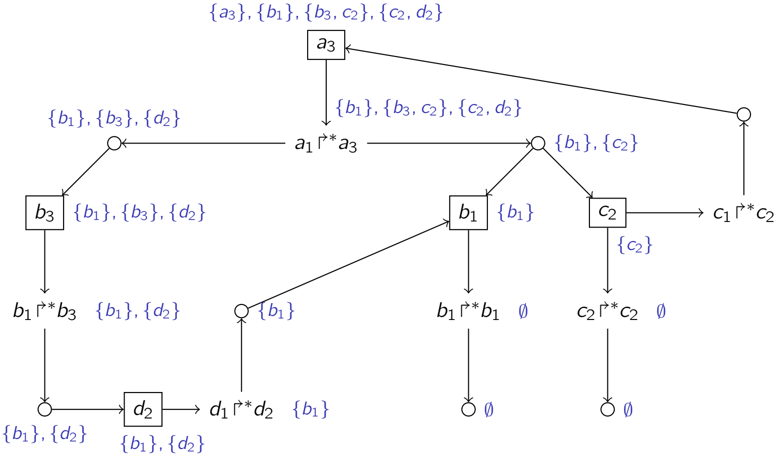


Cut Sets Under-approximation

Example

Sketch

- Follow the topological order of GLC.
- SCCs: arbitrary/random order for updating nodes having child modified.
- Always converges.

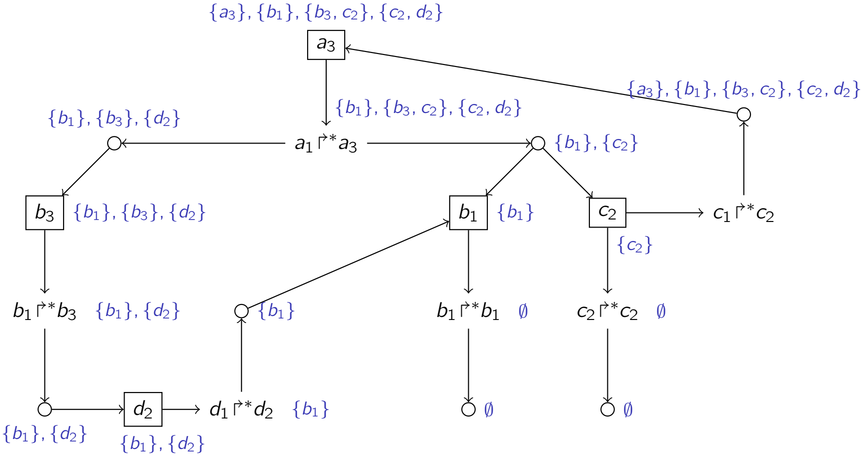


Cut Sets Under-approximation

Example

Sketch

- Follow the topological order of GLC.
- SCCs: arbitrary/random order for updating nodes having child modified.
- Always converges.

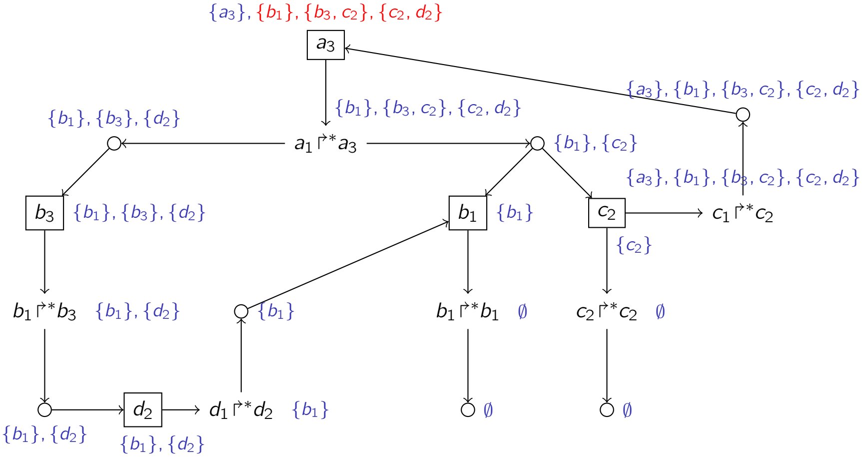


Cut Sets Under-approximation

Example

Sketch

- Follow the topological order of GLC.
- SCCs: arbitrary/random order for updating nodes having child modified.
- Always converges.



Formal analysis of the whole PID

Pathway Interaction Database `http://pid.nci.nih.gov`

- Inductions, inhibitions, transcriptional regulation, complex formations, . . .
- +9,000 interacting components.

Graph of Local Causality for (independent) reachability of active SNAIL, p15, p21

- From Process Hitting model (sub-class of Asynchronous ANs)
  +21,000 concurrent automata (biological and logical); largest: 16 local states.
- ≈20,000 nodes involving ≈1,600 biological components.

Extracted Cut Sets

N	Visited nodes	Exec. time	$SNAIL_1$	$p15INK4b_1$	$p21CIP1_1$
1	29,022	0.9s	1	1	1
2	36,602	1.6s	+6	+6	+0
3	44,174	5.4s	+0	+92	+0
4	54,322	39s	+30	+60	+0
5	68,214	8.3m	+90	+80	+0
6	90,902	2.6h	+930	+208	+0

Implemented in PINT `http://loicpauleve.name/pint` (OCaml);
Dedicated data structures to efficiently compute cross products between million of sets.

Conclusion

Abstract interpretation of dynamics

- Do not build (even symbolically) the transition graph.
- Compact static structure for representing the possible transitions.
  ⇒ Graph of Local Causality (GLC)

Static analysis using the GLC

- Over-approximation: successive reachability properties + cut sets
  Can be defined for any automata network/Petri net.
- Under-approximation: successive reachability properties
  Specific to Process Hitting

Extensions

- Process Hitting with Priorities (Maxime Folschette)
  ⇒ new under-approximation conditions.
- Other dynamical properties: complex attractors, etc.

Thank you for your attention.