Pint, a static analyzer for dynamics of Automata Networks

Loïc Paulevé

Pint • Static Analyzer for Dynamics of Automata Networks

http://loicpauleve.name/pint

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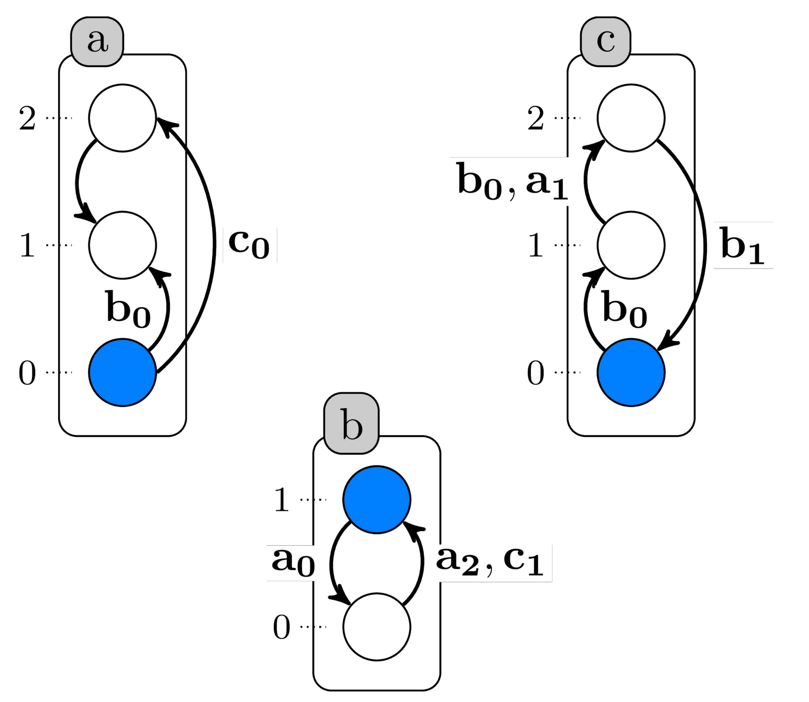
Input Model

- Asynchronous **Automata Networks** [1]




```
a [0,1,2]
b [0,1]
c [0,1,2]

a 0 -> 1 when b=0
a 0 -> 2 when c=0
a 2 -> 1
b 1 -> 0 when a=0
b 0 -> 1 when a=2 and c=1
c 0 -> 1 when b=0
c 1 -> 2 when a=1 and b=0
c 2 -> 0 when b=1

initial_state a=0,b=1,c=0
```

- Encoding of **Boolean networks** and multi-valued.
- Import from **SBML-qual/GINsim** using LogicalModel
  https://github.com/colomoto/logicalmodel

```
$ logicalmodel sbml:an model.sbml model.an
```

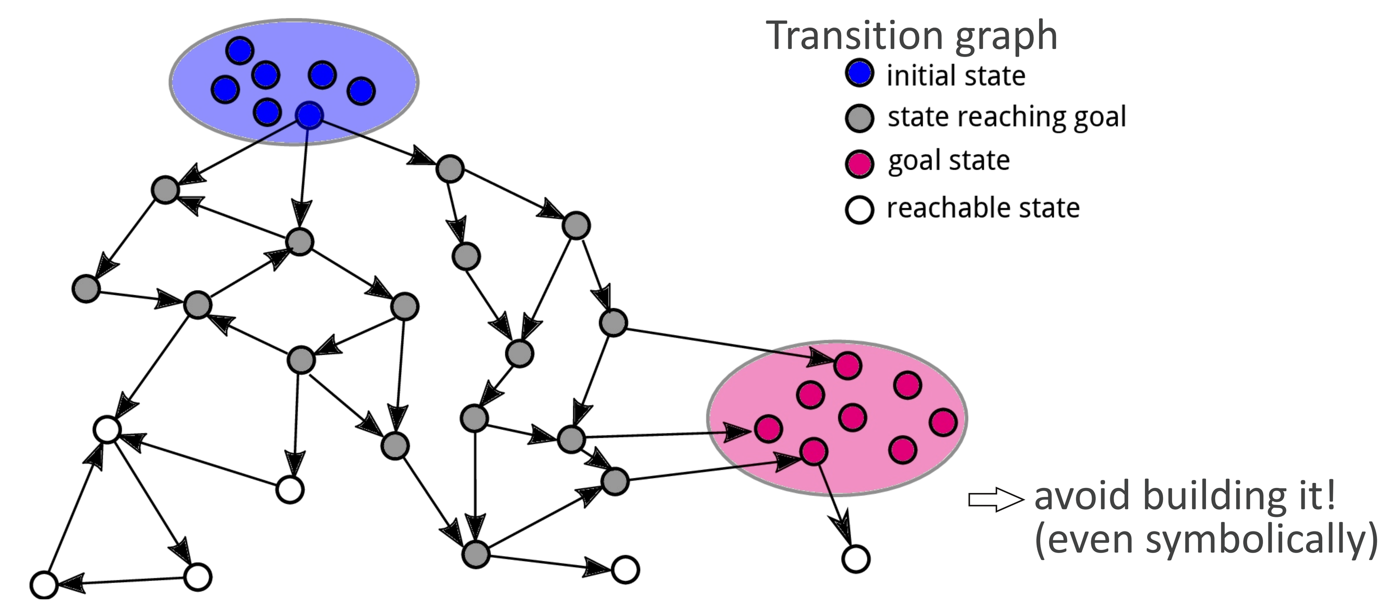
- Other formats: SBGN-PD [2], Biocham, CellNetAnalyzer

Technologies

- **Abstract interpretation**: traces abstraction
  causality analysis (Local Causality Graphs)
  formal over-/under-approximations of reachability
- **Answer-Set Programming** (ASP)
  logic programming for enumeration problems (NP)

- Implemented with **OCaml** programming language
- Free software: CeCILL licence

Main Features



- Static analysis of **transient reachability**
  Combines over- and under-approximation [3]

```
$ pint-reach -i model.an g=1
True/False/Inconc
```

- Identification of **cut sets**: mutations for breaking goal
  Static analysis for under-approximation [4]

```
$ pint-reach --cutsets 4 -i TCell-d.an BCL6=1
"GP130"=1
"STAT5"=0
"CD28"=1,"IL6R"=1
...
```

- Identification of **bifurcation transitions** for goal
  Static analysis for under-approximation [5]

```
$ pint-reach --bifurcations -i TCell-d.an BCL6=1
"STAT5" 0 -> 1 when "IL2R"=1
...
```

- **Model reduction** preserving goal reachability [1]

```
$ pint-export --reduce-for-goal g=1 -i model.an
      -o reduced.an
```

- Other features : **fixed points** (SAT) ; transition graph analysis (**attractors**) ; stochastic **simulation** ; embedded Boolean/Thomas networks (contrib M. Folschette) ; **C bindings** ; interface with **model-checkers** (NuSMV, ITS, mole)

Applications to Biological Networks

- Gene regulatory networks ; signalling pathways ; etc.
- Tractable on **very large networks** (100-10,000 comp.)
  complexity of causality analysis: poly(nb automata,trs), exp(nb levels)

- Identification of cut sets for goal (mutations)

	TCell-d (101)	RBE2F (370)	MAPK (309)	PID (21,000)
≤4-cutsets	0.03s (27)	0.06s (57)	0.1s (34)	39s (37)
≤6-cutsets	0.03s (27)	0.76s (334)	0.5s (43)	2.6h (1257)

- Identification of bifurcations for goal

				NuSMV		Pint	
Model	local trs	nb states	goal	$\|t_b\|$	time	$\|t_b\|$	time
TCell-d (101) s_0=Th17	384	$\approx 4 \cdot 10^9$	RORGT=1	18	48s	8	26s
			BCL6=1	7	26s	4	24s
TCell-d (101) s_0=HTG	384	KO	BCL6=1	KO		6	61s
			GATA3=1			7	34s

- Goal-oriented reduction: **make life easier for model-checking**

			Verification of goal reachability		Verification of cut set	
Model	local trs	nb states	NuSMV (EF g)	its-reach	NuSMV	its-ctl
TCell-d (101)	384	$\approx 2.7 \cdot 10^8$	3s 40Mb	0.5s 24Mb		
profile 1	**0**	**1**				
TCell-d (101)	384	KO	KO	0.5s 23Mb	KO	KO
profile 2	**161**	**75,947,684**	**474s 260Mb**	**0.3s 19Mb**	**600s 360Mb**	**KO**
EGF-r (104)	378	$\approx 2.7 \cdot 10^{16}$	KO	1.36s 60Mb	KO	KO
	69	**62,914,560**	**11s 33Mb**	**0.3s 17Mb**	**13s 33Mb**	**21s 875Mb**
RBE2F (370)	742	KO	KO	KO	KO	KO
	56	**2,350,494**	**5s 377Mb**	**5s 170Mb**	**6s 29Mb**	**180s 1.8Gb**

In all cases, reduction took less than 0.1s.
Properties are equivalent in the reduced models.

Computations performed on Intel® Core™ i7-4770 3.40GHz CPU with 16GB of RAM

[TCell-d] Abou-Jaoudé et al, Frontiers in Bioengineering and Biotechnology 2015
[EGF-r] Samaga et al, PLOS Computational Biology 2009
[RBE2F] RB/E2F Pathway http://bioinfo-out.curie.fr/projects/rbpathway/
[MAPK] Schoeberl et al, Nature Biotechnology, 2002
[PID] Pathway interaction database http://pid.nci.nih.gov

For more information

[1] Paulevé, *Goal-Oriented Reduction of Automata Networks* at CMSB 2016
[2] Rougny, Froidevaux, Calzone, Paulevé. *Qualitative dynamics semantics for SBGN process description* in BMC Systems Biology 2016
[3] Paulevé, Magnin, Roux. *Static analysis of biological regulatory networks using abstract interpretation* in Math. Struct. in Comp. Sci. 2012
[4] Paulevé, Andrieux, Koeppl. *Under-approximating cut sets for reachability in large scale automata networks* at CAV 2013
[5] Fitime, Roux, Guziolowski, Paulevé. *Identification of bifurcations in biological regulatory networks using ASP* at WCB 2016

Source .zip .deb .dmg docker