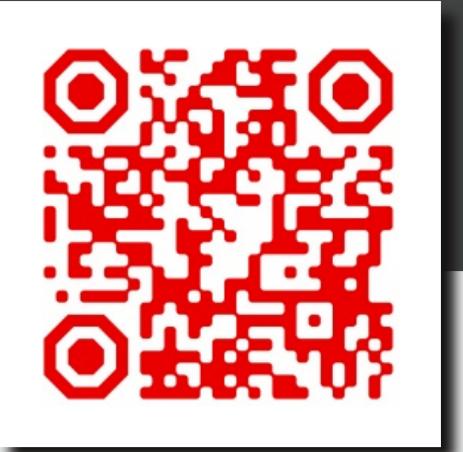


# Pint • Static Analyzer for Dynamics of Automata Networks

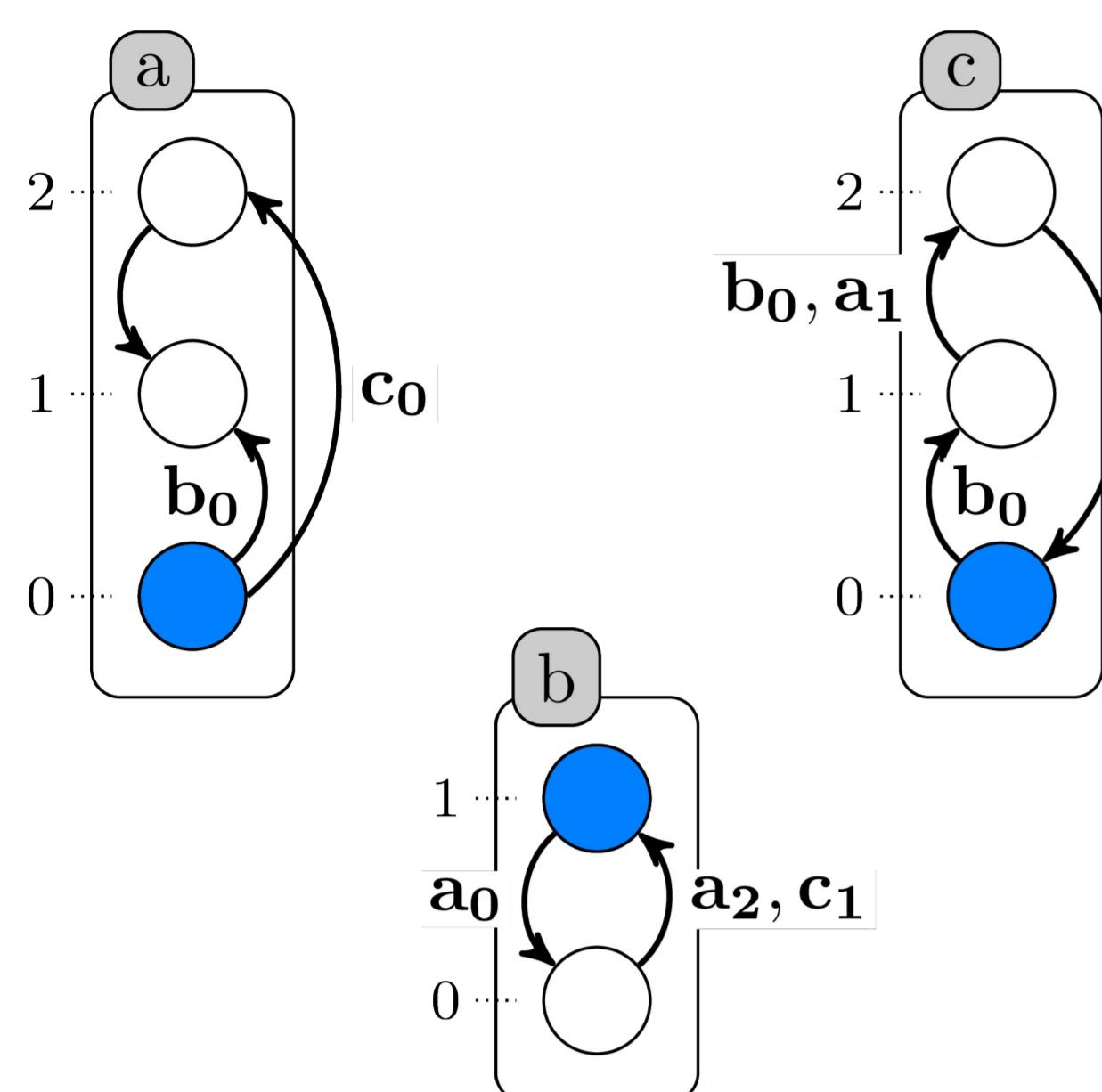
<http://loicpauleve.name/pint>



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## Input Model

- Asynchronous **Automata Networks** [1]



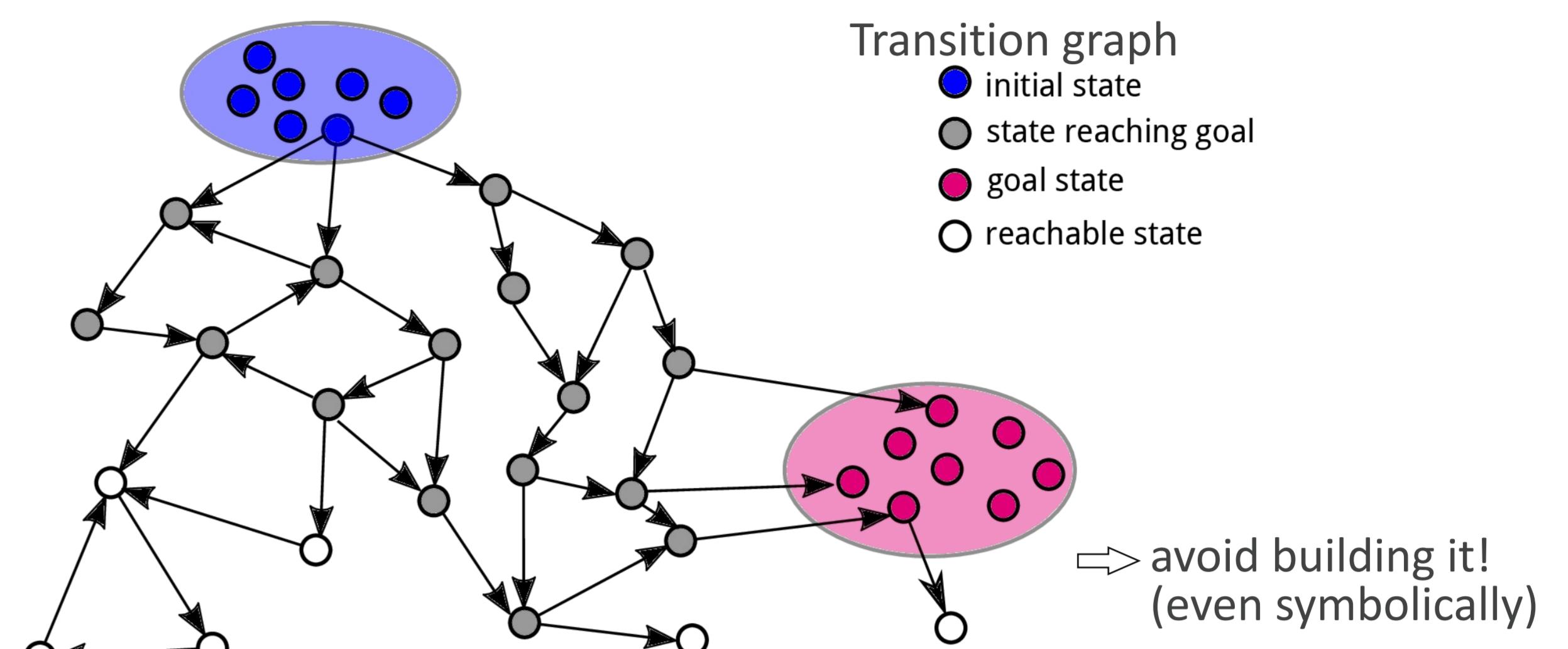
a [0, 1, 2]  
b [0, 1]  
c [0, 1, 2]  
  
a 0 -> 1 when b=0  
a 0 -> 2 when c=0  
a 2 -> 1  
b 1 -> 0 when a=0  
b 0 -> 1 when a=2 and c=1  
c 0 -> 1 when b=0  
c 1 -> 2 when a=1 and b=0  
c 2 -> 0 when b=1  
  
initial\_state a=0,b=1,c=0

- 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

## 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)

## 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

## 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) |
|-------------------|---------------|-------------|------------|--------------|
| $\leq 4$ -cutsets | 0.03s (27)    | 0.06s (57)  | 0.1s (34)  | 39s (37)     |
| $\leq 6$ -cutsets | 0.03s (27)    | 0.76s (334) | 0.5s (43)  | 2.6h (1257)  |

- Identification of bifurcations for goal

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

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

| Model                                | local trs | nb states                   | Verification of goal reachability |            | Verification of cut set |            |
|--------------------------------------|-----------|-----------------------------|-----------------------------------|------------|-------------------------|------------|
|                                      |           |                             | NuSMV (EF g)                      | its-reach  | NuSMV                   | its-ctl    |
| TCell-d (101)<br>$s_0 = \text{Th17}$ | 384       | $\approx 2.7 \cdot 10^8$    | 3s 40Mb                           | 0.5s 24Mb  |                         |            |
| TCell-d (101)<br>$s_0 = \text{HTG}$  | 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, Guziowski, Paulevé. *Identification of bifurcations in biological regulatory networks using ASP* at WCB 2016

