Scalable and formal control of reachability in qualitative networks with PINT

Loïc Paulevé

CNRS/LRI, Univ. Paris-Sud, Univ. Paris-Saclay – BioInfo team

loic.pauleve@lri.fr

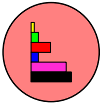
http://loicpauleve.name

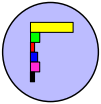
[BC]^2 workshop on logical modelling of biological regulatory networks

12 September 2017

Cellular Dynamics

Cell state
of interest

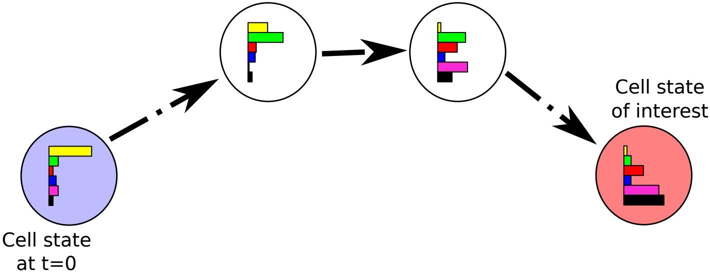




Cell state
at t=0

Initial state(s)/Goal state(s)

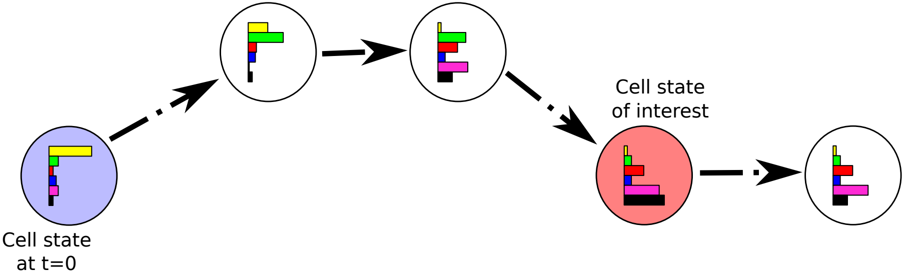
Cellular Dynamics



Initial state(s)/Goal state(s)

- Trajectory existence (reachability)

Cellular Dynamics



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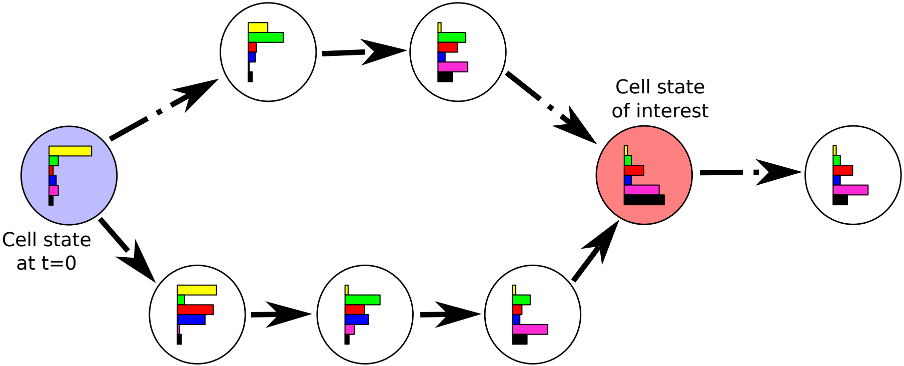

Initial state(s)/Goal state(s)

- Trajectory existence (reachability)
- Reasoning on all trajectories: e.g., **common features**
- Control: **perturbations** to avoid/enforce goal reachability

Analysis with the software PINT

Settings

- Qualitative models: state of components is Boolean/with a few levels
- Consider sets of initial conditions
- Goal states specified by the activity of narrow number of components (markers)

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Contribution

- Avoid *in silico* screening of candidate perturbation
- Static analysis of traces: instead of computing (symbolic) state transition graph PINT computes a compact abstraction of it [Paulevé et al in Math Struct in Comp Sci 2012]
- Results are formal (guaranteed) but can be incomplete due to the abstraction

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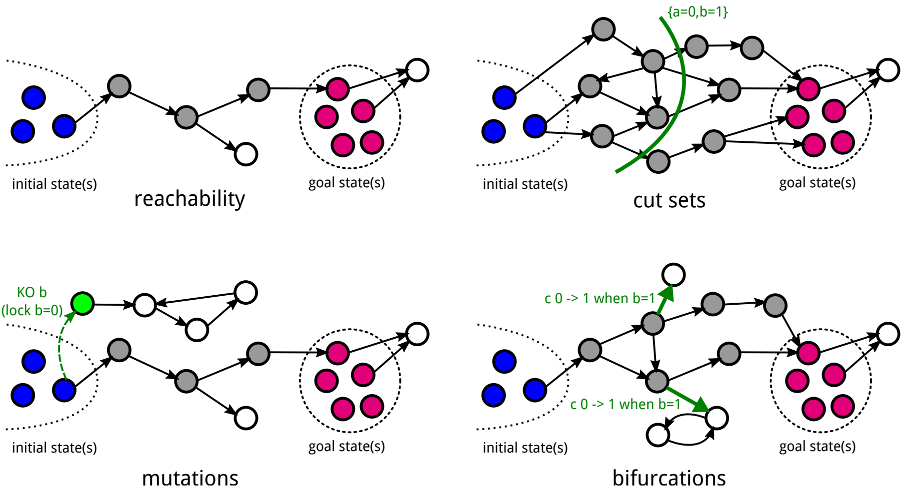
Model input for PINT

- Main framework: automata networks (transition-centered specification)
- Boolean networks, multi-valued networks, 1-bounded Petri nets, . . .
- Uses BioLQM [Naldi et al] to import GINsim, SBML-Qual, BoolSim, . . .
  + other custom importations (BIOCHAM, SBGN-PD, . . .)

Remark: the following results do not depend on the updating schedule ((a)synchronous)

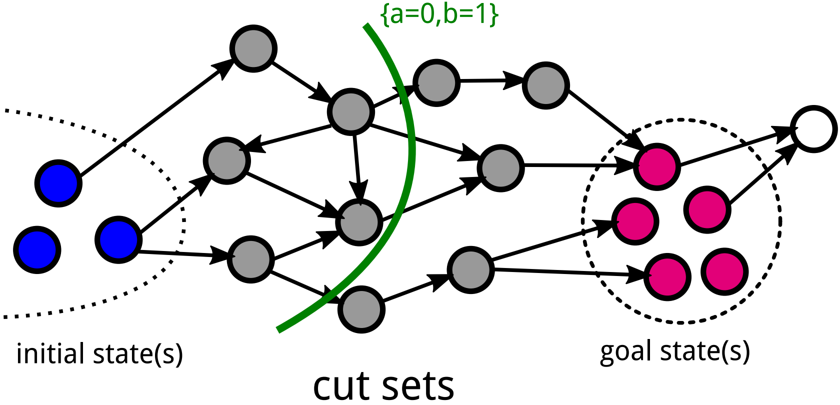
Static analysis of automata networks with Pint



Software Pint - `http://loicpauleve.name/pint` [Paulevé at CMSB 2017]

Scalability: networks with 100 - 10,000 components

Static analysis of automata networks with Pint



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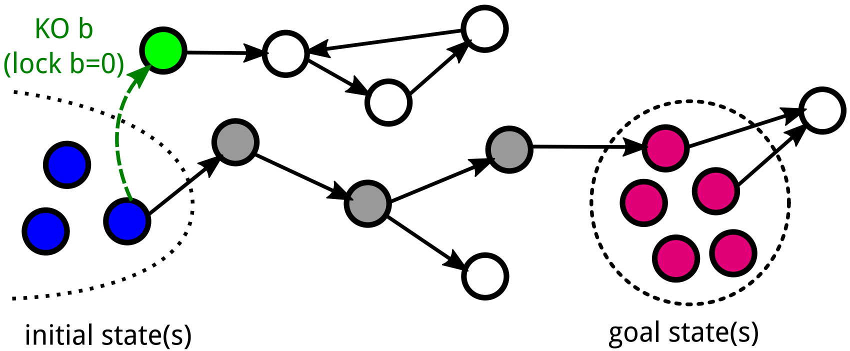
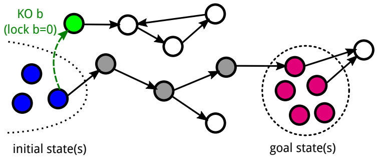


mutations

Mutations



Definition

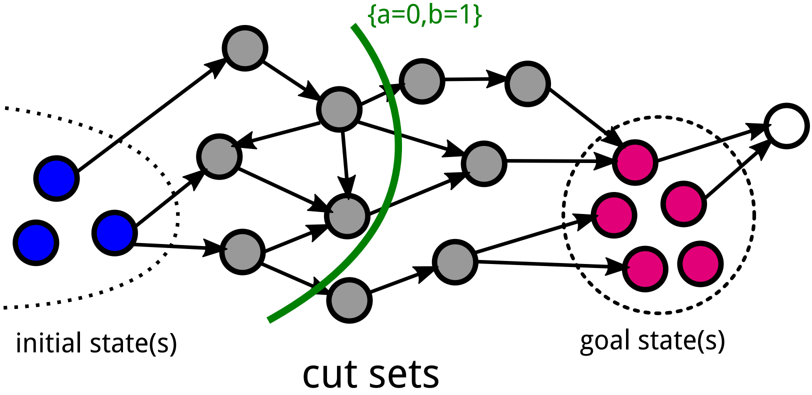
- Set of nodes with value to lock. E.g., $\{\mathbf{lock}(b = 0), \mathbf{lock}(c = 1)\}$.
- Goal is not reachable when applied to the initial state.

Implementation in PINT

- Answer-Set Programming (ASP) – similar to SAT.
- Encodes jointly the (abstracted) dynamics and the mutation property.
- Solutions are derived from the ASP logical model
  $\Rightarrow$ no screening.

(PINT approximates a PSPACE-complete problem into an NP problem)

Cut sets: common features of traces to goal

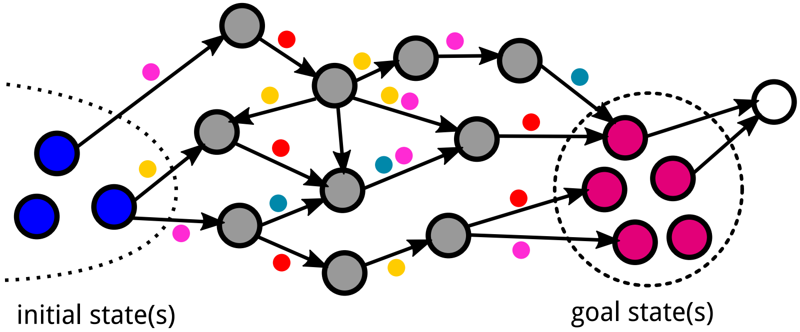


Interpretation: any trace requires at some point either $a = 0$ or $b = 1$.

Cut sets in the state transition graph

- From classical graph theory on labeled (multiple) directed graph
- Cut set = set of labels which **disconnects** initial states and goal states

Labeled directed graph:



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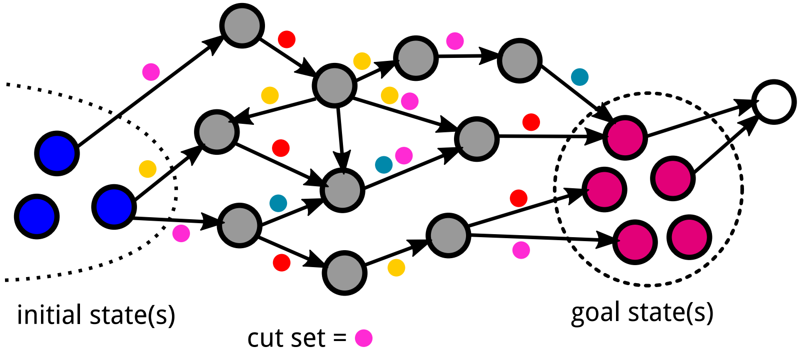

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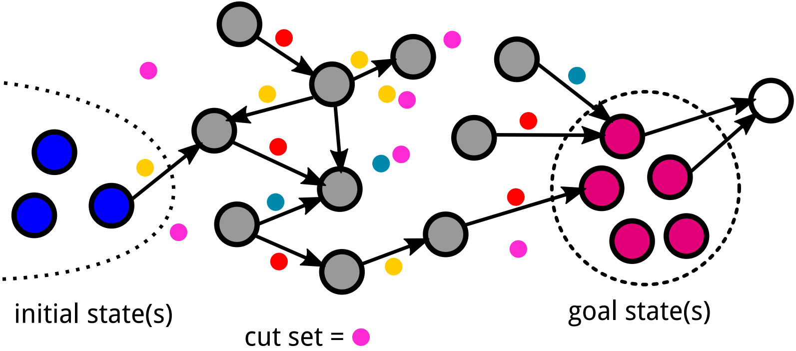

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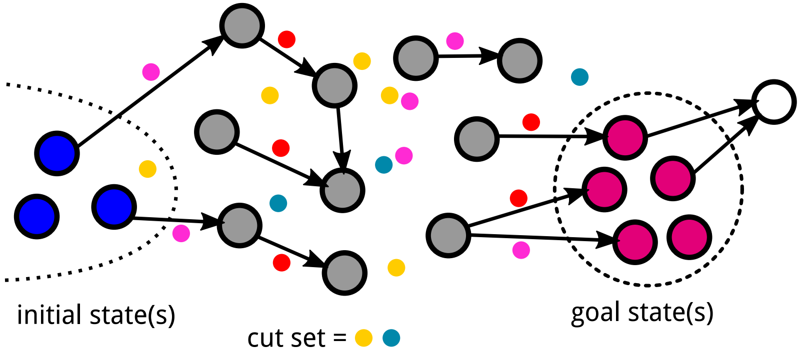
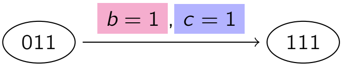


Transitions labels for Boolean networks

Labels = minimal cause of transitions

$$f_a(x) = x_b \text{ or } x_c$$

Labels for the transition $\langle 011\rangle \rightarrow \langle 111\rangle$



Remark: these labels come for free with automata networks/Petri nets

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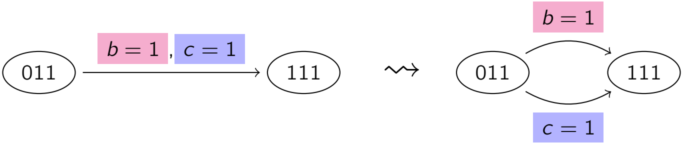

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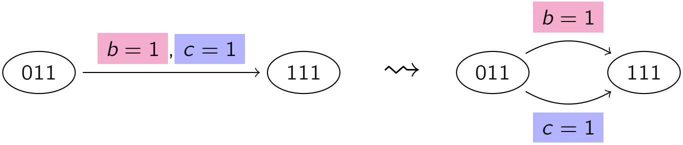

$\Rightarrow$ **1 cut set** to disconnect $\langle 011 \rangle$ and $\langle 111 \rangle$: $\{ b = 1, c = 1 \}$.

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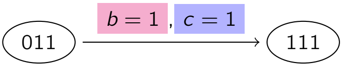
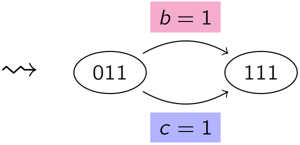
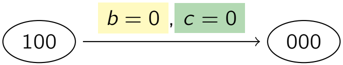




⇒ **1 cut set** to disconnect $\langle 011\rangle$ and $\langle 111\rangle$: $\{ b = 1, c = 1 \}$.

Labels for the transition $\langle 100\rangle \rightarrow \langle 000\rangle$



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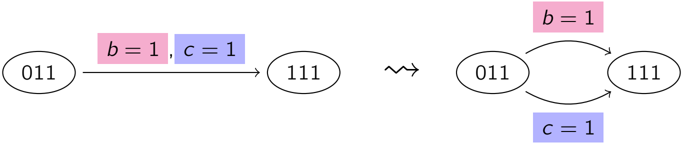

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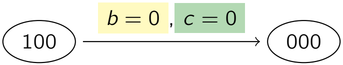


$\Rightarrow$ **2 cut sets** to disconnect $\langle 100 \rangle$ and $\langle 000 \rangle$: $\{ b = 0 \}$, $\{ c = 0 \}$.

Remark: these labels come for free with automata networks/Petri nets

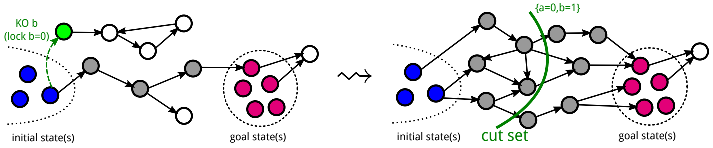
Cut sets in PINT

Implementation

- Does not build the state transition graph.
- Dedicated algorithm on its abstraction (3-partite graph) [Paulevé et al at CAV 2013].
- Solutions are derived, no candidate enumeration (no screening).

An alternative implementation with ASP could be considered as well.

Mutations vs Cut sets



From mutations to cut sets

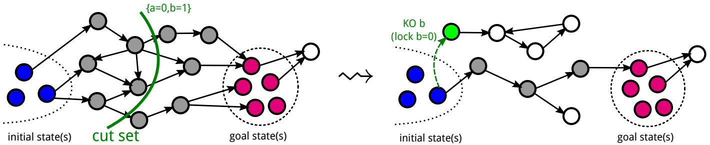
- lock($a = i$) cuts transitions using $a = j$, $j \neq i$
- To any mutation set corresponds a cut set
- ... *but* for a potentially different initial state

E.g., consider the mutation set

$$\begin{aligned} & \{\text{lock}(b = 0), \text{lock}(c = 1)\} \\ \Rightarrow \quad & \{b = 1, c = 0\} \end{aligned}$$

is a cut set for the goal from the initial state with $b = 0$ and $c = 1$.

Mutations vs Cut sets



From cut sets to mutations

- Idea: if every trace to goal uses either $a = 1$ or $c = 1$,
  KO of a and b prevents goal reachability
- ...*but* a cut set can include both active and inactive state of a same node
- ...the mutation should not change the initial state.

$\Rightarrow$ a cut set does not always gives a mutation

E.g., considering the initial state $\langle a = 0, b = 1, c = 0 \rangle$,

- $\{a = 1, c = 1\}$ gives guaranteed mutation $\{\text{lock}(a = 0), \text{lock}(c = 0)\}$;
- $\{a = 1, a = 0, b = 0\}$ gives no mutation;
- $\{a = 1, b = 1\}$ gives non-proven mutation $\{\text{lock}(a = 0), \text{lock}(b = 0)\}$.

Scalability of implementations

Computations with PINT:

- *k*-cut sets: OCaml implementation (algorithm on abstract structure)
- *k*-mutations: Answer-Set Programming (ASP) with clingo

k: limit results to sets with at most *k* elements.

Goal	TCell-d (101) FOXP3=1		MAPK (309) ERK-PP=1		PID (10,229) SNAIL=1	
3-cut sets	0.06s	35	0.06s	24	1.2s	7
4-cut sets	0.10s	101	0.1s	48	5s	37
6-cut sets	0.60s	495	1s	60	10m	907
3-mutations	0.30s	15	5s	222	50m	7
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6-mutations	0.30s	15	Too many		50m	367

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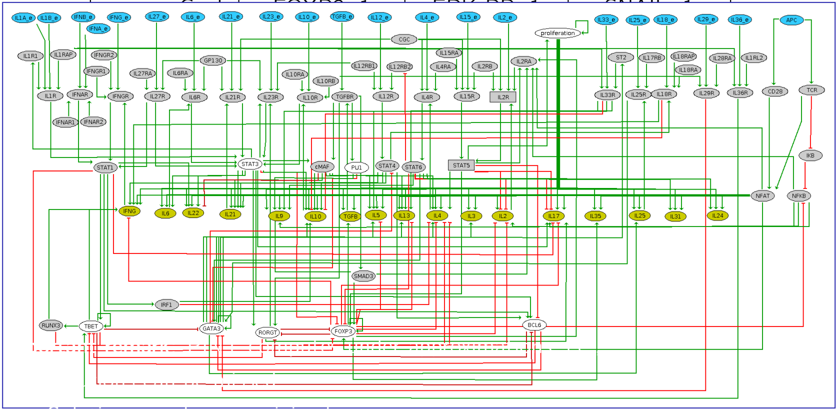

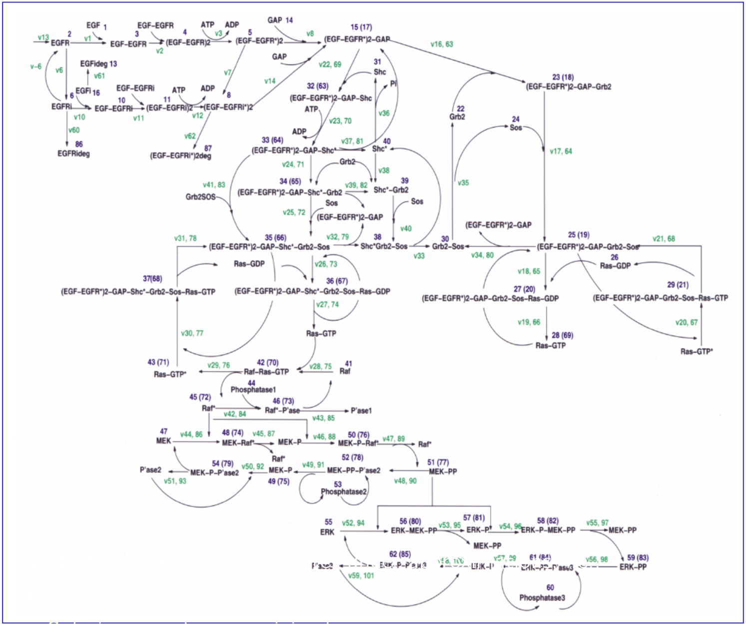
EGF 1
EGF–EGFR
ATP
ADP
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v13
2 EGFR
v1
3 EGF–EGFR
4 (EGF–EGFR)2
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v3
5 (EGF–EGFR*)2
v8
15 (17) (EGF–EGFR*)2–GAP
v16, 63
GAP
v–6
v6
EGFIdeg 13
v61
EGFI 16
6 EGFRi
EGF–EGFRi
10 EGF–EGFRi
11 (EGF–EGFRi)2
v10
v11
v12
8 (EGF–EGFRi*)2
v7
v14
v22, 69
31 Shc
Pi
32 (63) (EGF–EGFR*)2–GAP–Shc
ATP
ADP
v23, 70
v36
23 (18) (EGF–EGFR*)2–GAP–Grb2
22 Grb2
24 Sos
v17, 64
v60
86 EGFRideg
v62
87 (EGF–EGFRi*)2deg
33 (64) (EGF–EGFR*)2–GAP–Shc*
v37, 81
40 Shc*
v24, 71
Grb2
v38
v41, 83
Grb2SOS
34 (65) (EGF–EGFR*)2–GAP–Shc*–Grb2
v39, 82
39 Shc*–Grb2
Sos
v25, 72
(EGF–EGFR*)2–GAP
v40
v35
(EGF–EGFR*)2–GAP
v31, 78
35 (66) (EGF–EGFR*)2–GAP–Shc*–Grb2–Sos
v32, 79
38 Shc*Grb2–Sos
v33
30 Grb2–Sos
v34, 80
25 (19) (EGF–EGFR*)2–GAP–Grb2–Sos
v21, 68
Ras–GDP
v26, 73
26 Ras–GDP
v18, 65
37(68) (EGF–EGFR*)2–GAP–Shc*–Grb2–Sos–Ras–GTP
36 (67) (EGF–EGFR*)2–GAP–Shc*–Grb2–Sos–Ras–GDP
27 (20) (EGF–EGFR*)2–GAP–Grb2–Sos–Ras–GDP
29 (21) (EGF–EGFR*)2–GAP–Grb2–Sos–Ras–GTP
v27, 74
v19, 66
v20, 67
v30, 77
Ras–GTP
28 (69) Ras–GTP
Ras–GTP*
43 (71) Ras–GTP*
v29, 76
42 (70) Raf–Ras–GTP
v28, 75
41 Raf
44 Phosphatase1
45 (72) Raf*
46 (73) Raf*–P'ase
P'ase1
v42, 84
v43, 85
47 MEK
v44, 86
48 (74) MEK–Raf*
v45, 87
MEK–P
v46, 88
50 (76) MEK–P–Raf*
v47, 89
Raf*
Raf*
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51 (77) MEK–PP
P'ase2
54 (79) MEK–P–P'ase2
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MEK–P
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49 (75)
v48, 90
v51, 93
53 Phosphatase2
55 ERK
v52, 94
56 (80) ERK–MEK–PP
v53, 95
57 (81) ERK–P
v54, 96
58 (82) ERK–P–MEK–PP
v55, 97
MEK–PP
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62 (85)
v57, 99
61 (84)
v56, 98
59 (83) ERK–PP
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60 Phosphatase3

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Important remark: PINT computes under-approximations, i.e.,

- Solutions can be missed
- Solutions can be non-minimal

Demo

There is a public instance of Jupyter/pint at
`http://tmpnb.loicpauleve.name`

Be aware that

- For short tests only (limited session durations)
- It runs in a virtual machine with limited resources on a personal server

You can install Pint locally either with binary packages or using docker
`http://loicpauleve.name/pint/doc/`

Conclusion

Mutations vs Cut sets from initial states to goal states

- Mutations: block reachability of the goal
- Cut sets: common features of all the trajectories to the goal
- Mutations give cut sets, but (some are) for different initial states
- Some cut sets cannot be transformed into mutations
  (if they change the initial state; if they use both the active and inactive form of a node)

PINT implementation

- No screening of candidates, solutions are deduced by static analysis
- Scalable to networks >1,000 components
- Under-approximation (no magic)

On-going and future work

- Compute temporal mutations
- Static quantification of the effect of a partial mutation/cut sets

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- Maxime Folschette

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