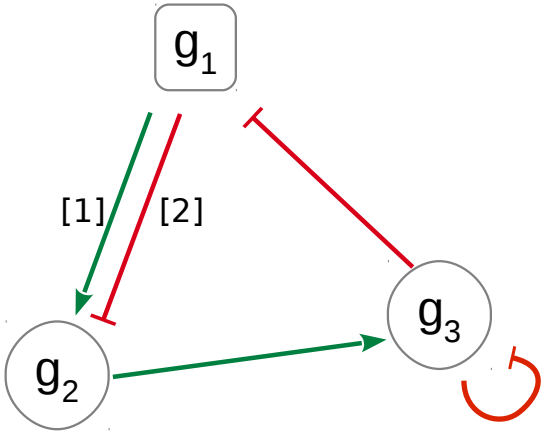
CoLoMoTo, SBML qual and LogicalModel: building bridges for qualitative models

Aurélien Naldi

Logical modeling



- Nodes: genes, proteins...

  Activity level (Boolean, MV)

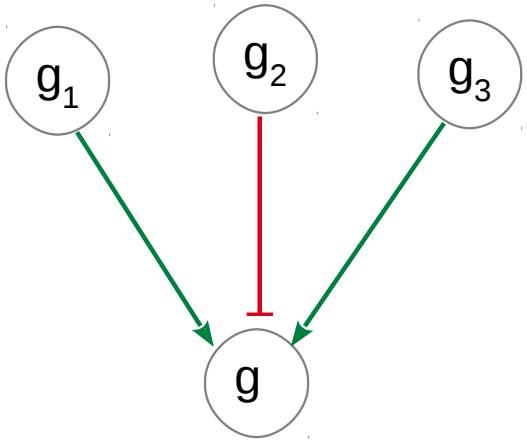
- Edges: interactions

  Threshold for MV source

- Logical rules

  next(G3) = G2 and not G3

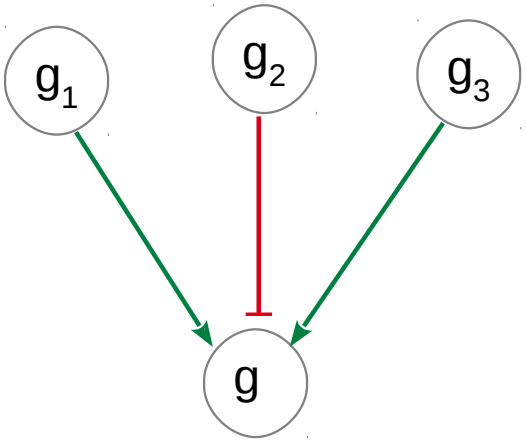
Discrete modelling methods



$(g_1 \mid g_3) \,\&\, !\, g_2$

g1	g2	g3	g
0	0	0	0
0	0	1	1
0	1	0	0
0	1	1	0
1	0	0	1
1	0	1	1
1	1	0	0
1	1	1	0

Discrete modelling methods



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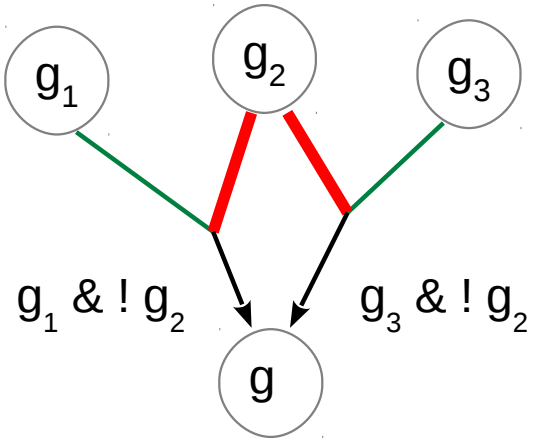
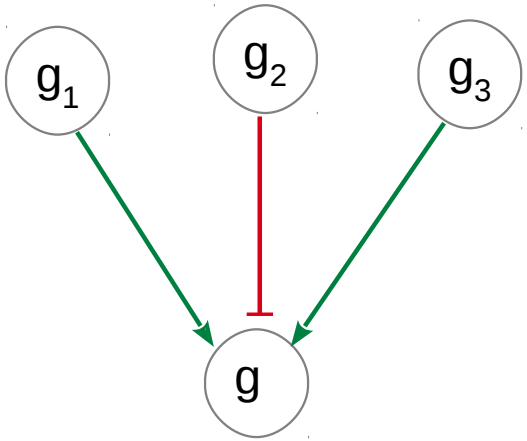


Discrete modelling methods



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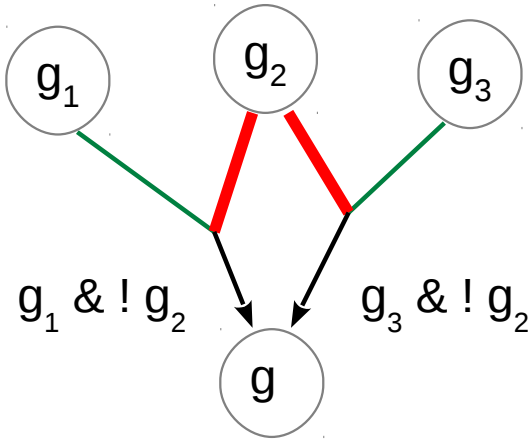
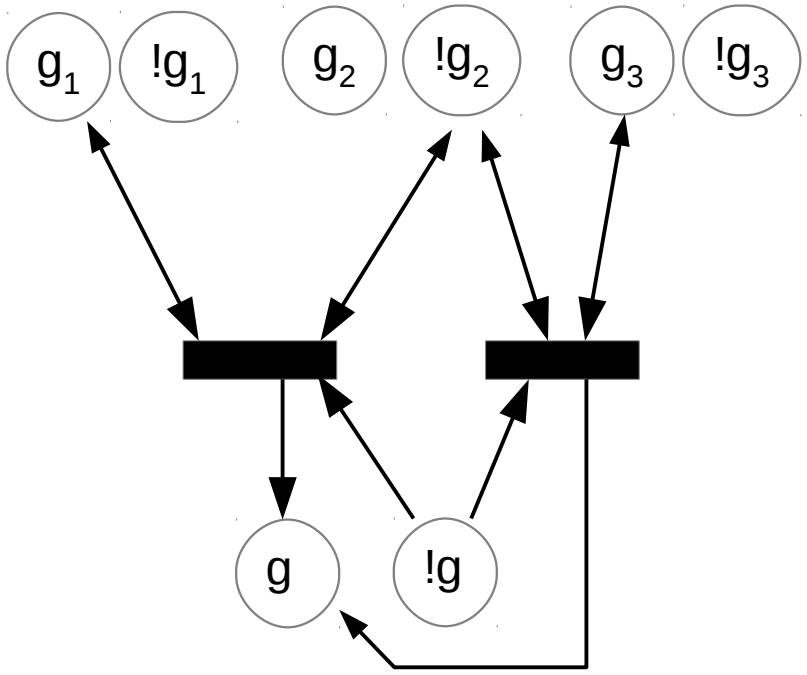
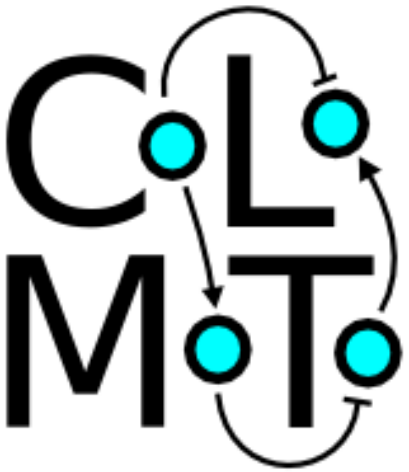


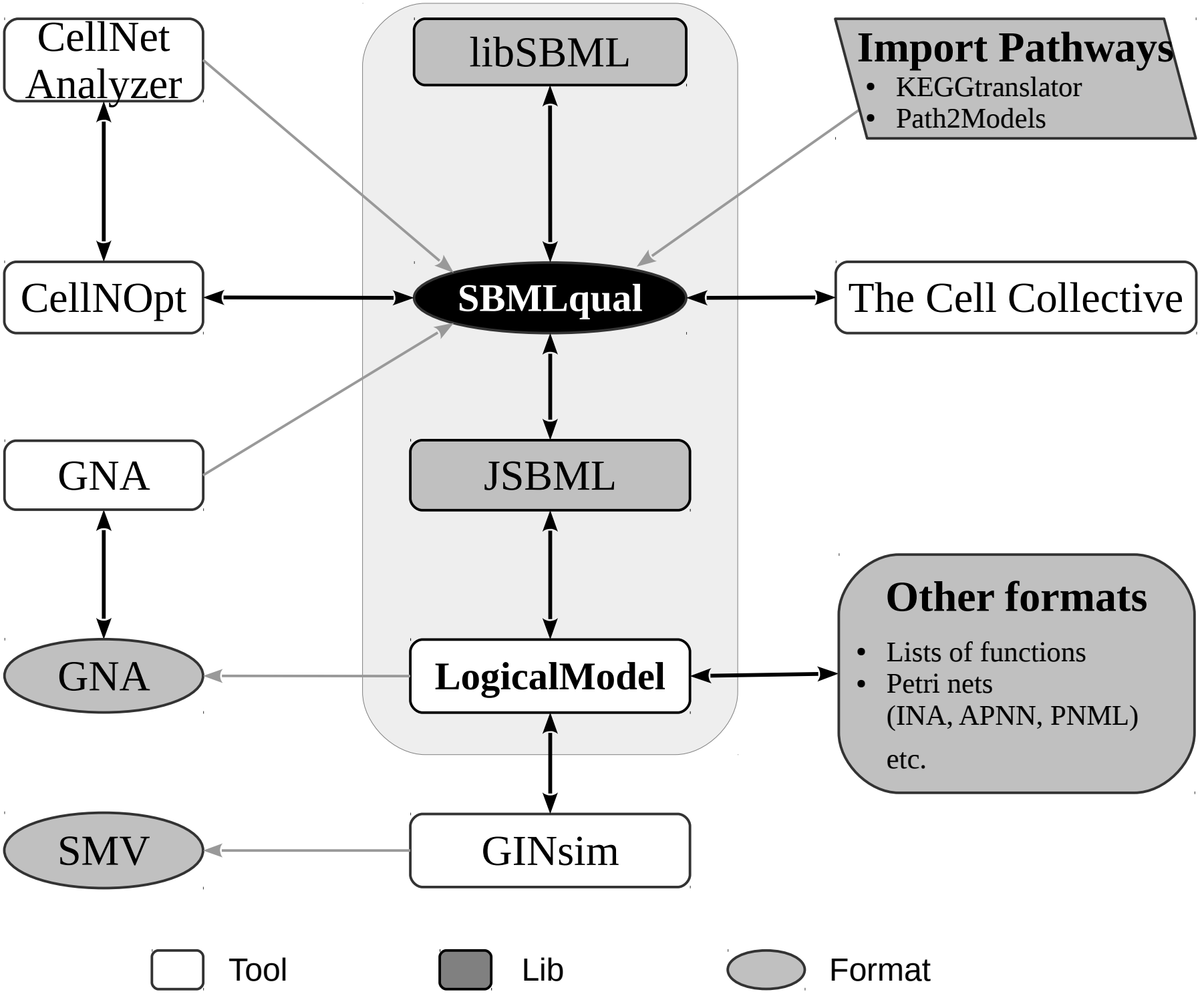


Petri net

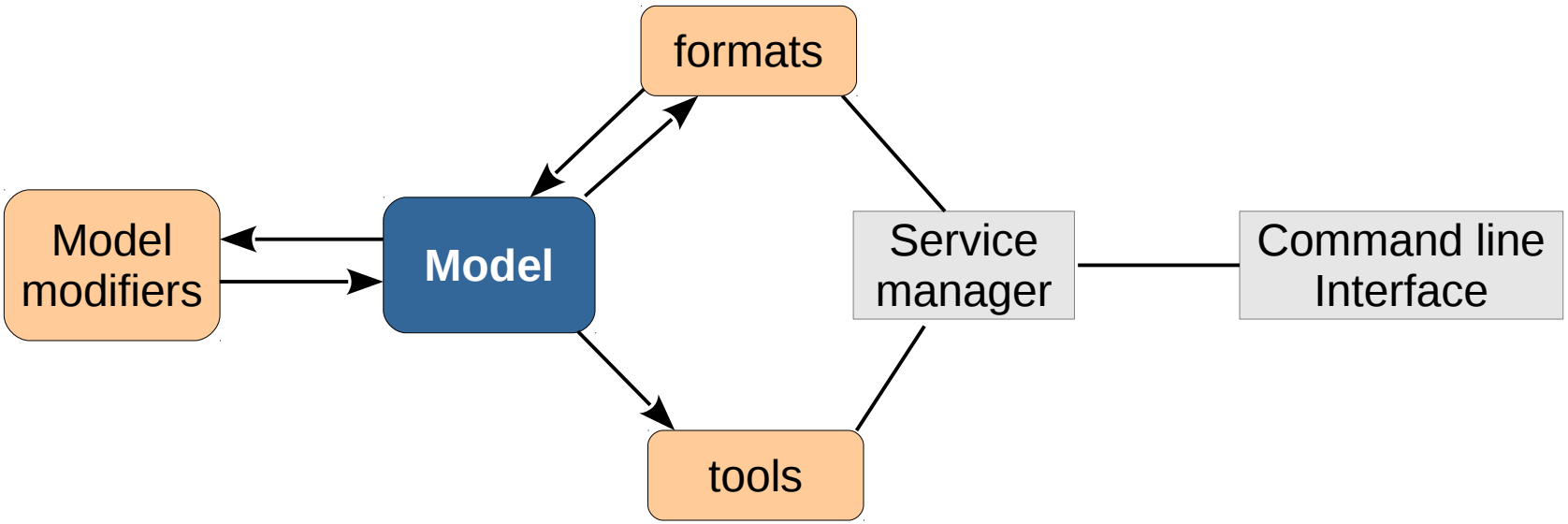
CoLoMoTo: exchanging models

- SBML qual extension: common exchange format
- Conversion tool
  - Read/write SBML qual and a few simple formats
  - Write several other formats
  - Can be extended
- Existing tools
  - Write SBML qual




CellNet Analyzer
libSBML
Import Pathways
• KEGGtranslator
• Path2Models
CellNOpt
SBMLqual
The Cell Collective
GNA
JSBML
Other formats
• Lists of functions
• Petri nets (INA, APNN, PNML)
etc.
GNA
LogicalModel
SMV
GINsim
Tool
Lib
Format

Organisation



Implemented

Model

Core and extra components
Multivalued Decision Diagrams

Model modifiers

Perturbations

Reduction
Output stripping

Formats

B <> boolsim
B <> Raw functions

M <> SBML qual

M > GINML
M > GNA
M > Petri net

M < Truth table

Tools

Stable state search

How to use?

As command-line tool

java -jar LogicalModel.jar model.sbml model.pnt -r stable model.sbml

- Search stable states
- Format conversion

As (Java) library

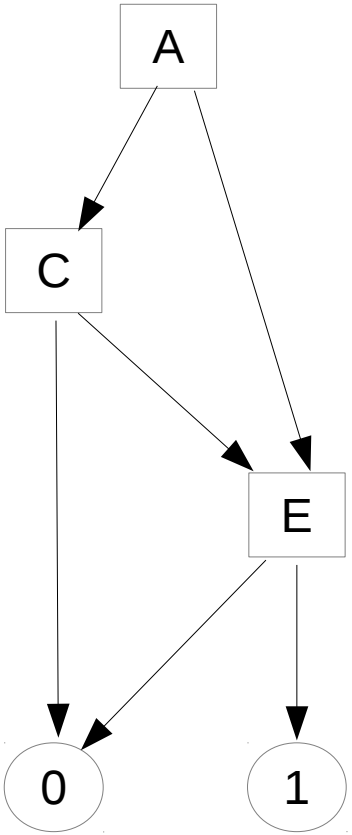
- GINsim (general qualitative modelling tool)
  - Data structure for simulation
  - Import/export backend (adds SBML layout markup)
  - Some tools backend (stable search, reduction)
- EpiLog (specialised for networks of epithelial cells)

Adding a format: minimal boilerplate

```
@ProviderFor(LogicalModelFormat.class)
public class YourFormat extends AbstractFormat {

	public YourFormat() {
		super("extension", "your description", true);
	}

	@Override
	public void export(LogicalModel model, OutputStream out) throws IOException {
		new YourFormatWriter(model).export(out);
	}

	@Override
	public LogicalModel importFile(File f) throws IOException {
		Return new YourFormatImporter.import(f);
	}
}
```

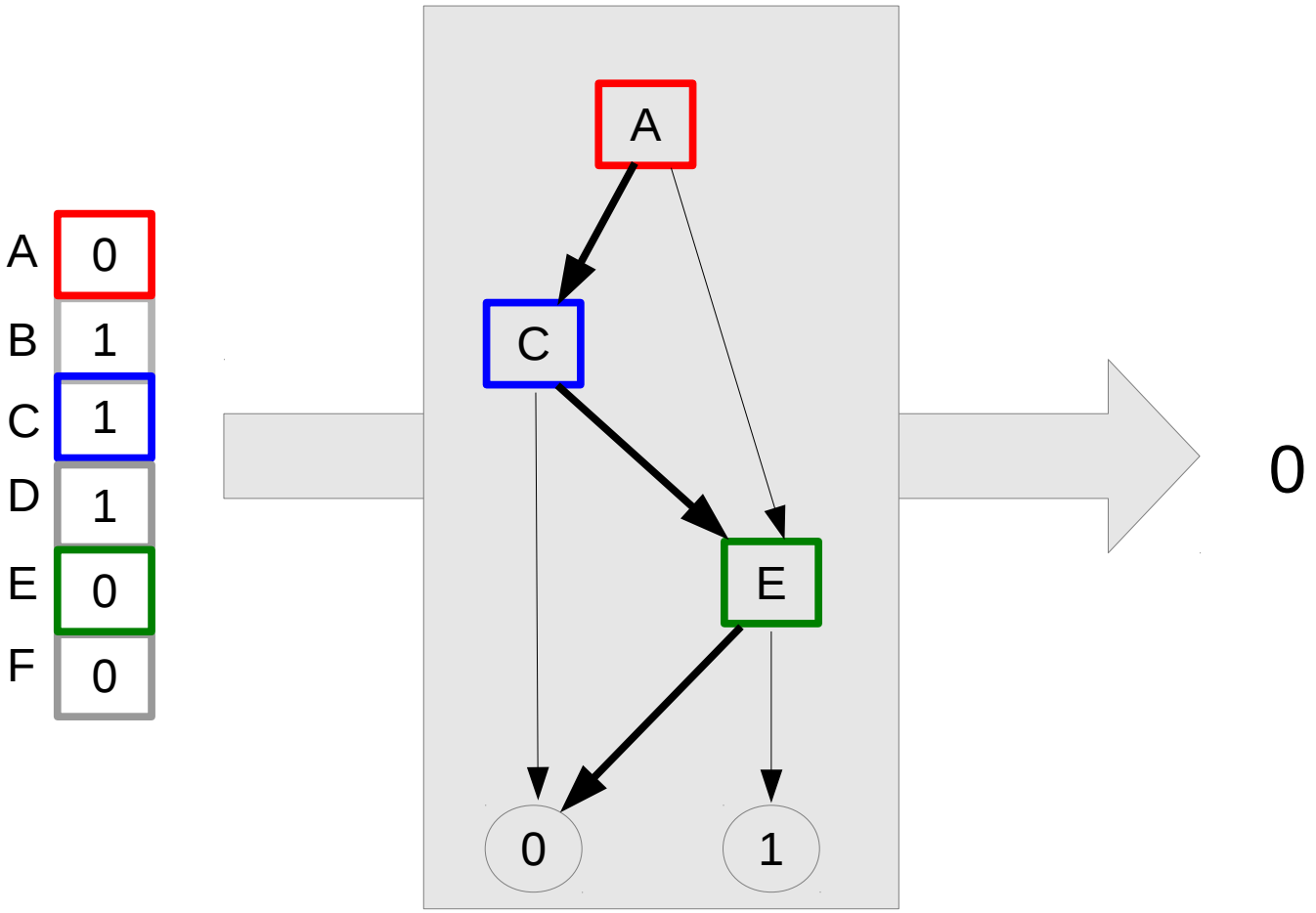
Decision Diagrams (MDD)

(A or C) and E



- A,B,C,D,E,F: ordered
- Fast (at most 6 tests, here 3)
- Predictable
- Picking order is hard

MDD query



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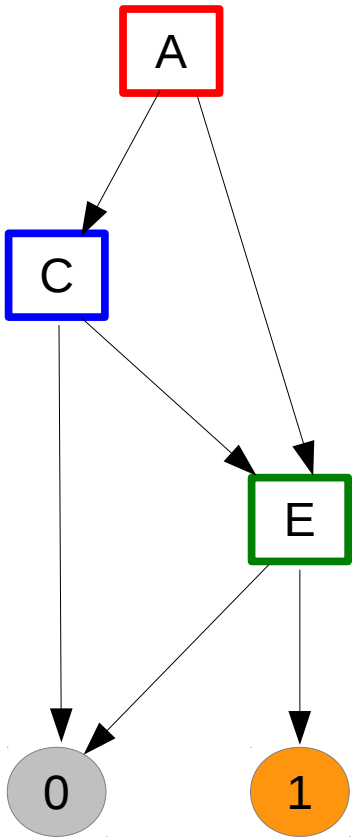
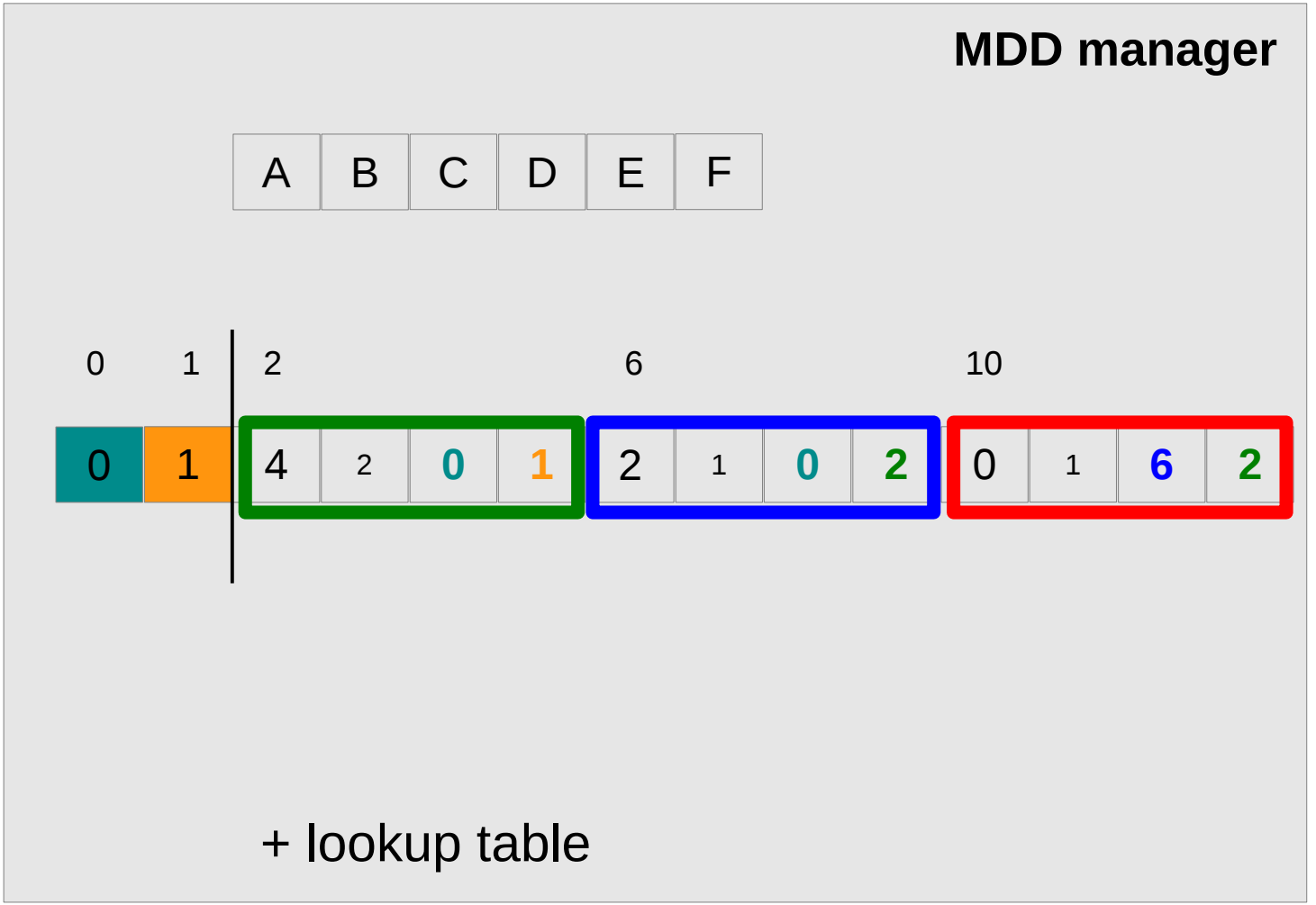
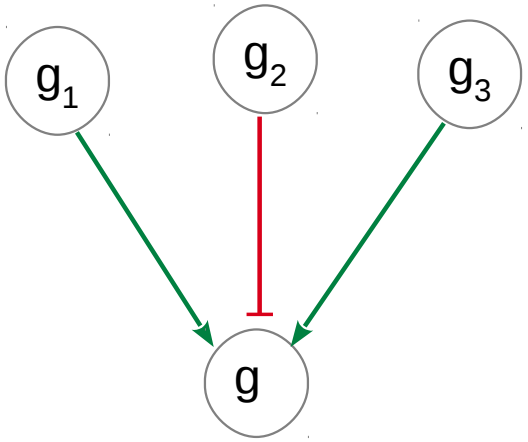




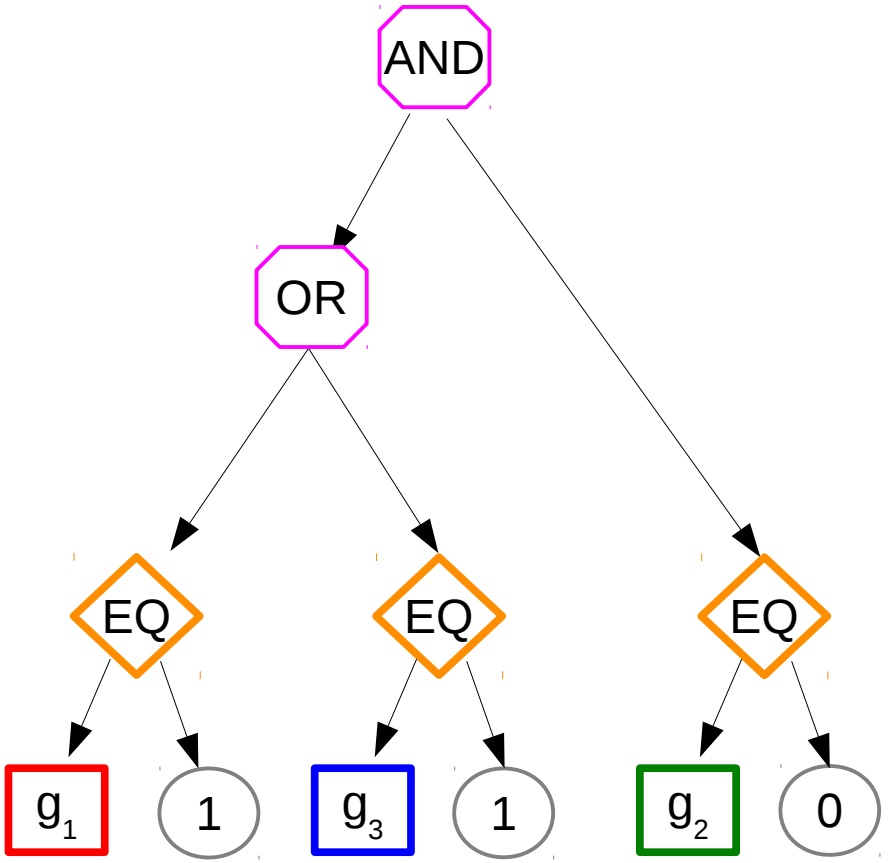
Multi-valued: some variables have more than two children

Functions in SBML-qual (and other)



$(g_1 \mid g_3) \,\&\, !\, g_2$

$(g_1{=}1 \mid g_3{=}1) \,\&\, g_2{=}0$



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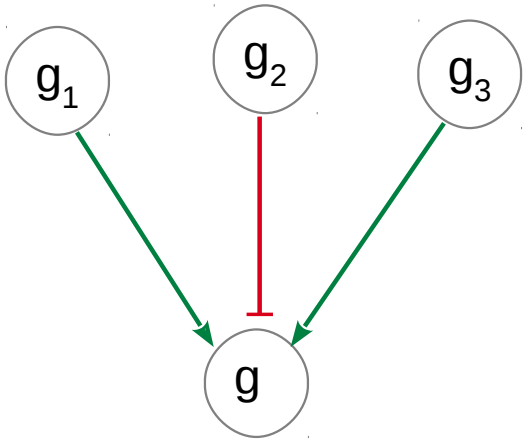

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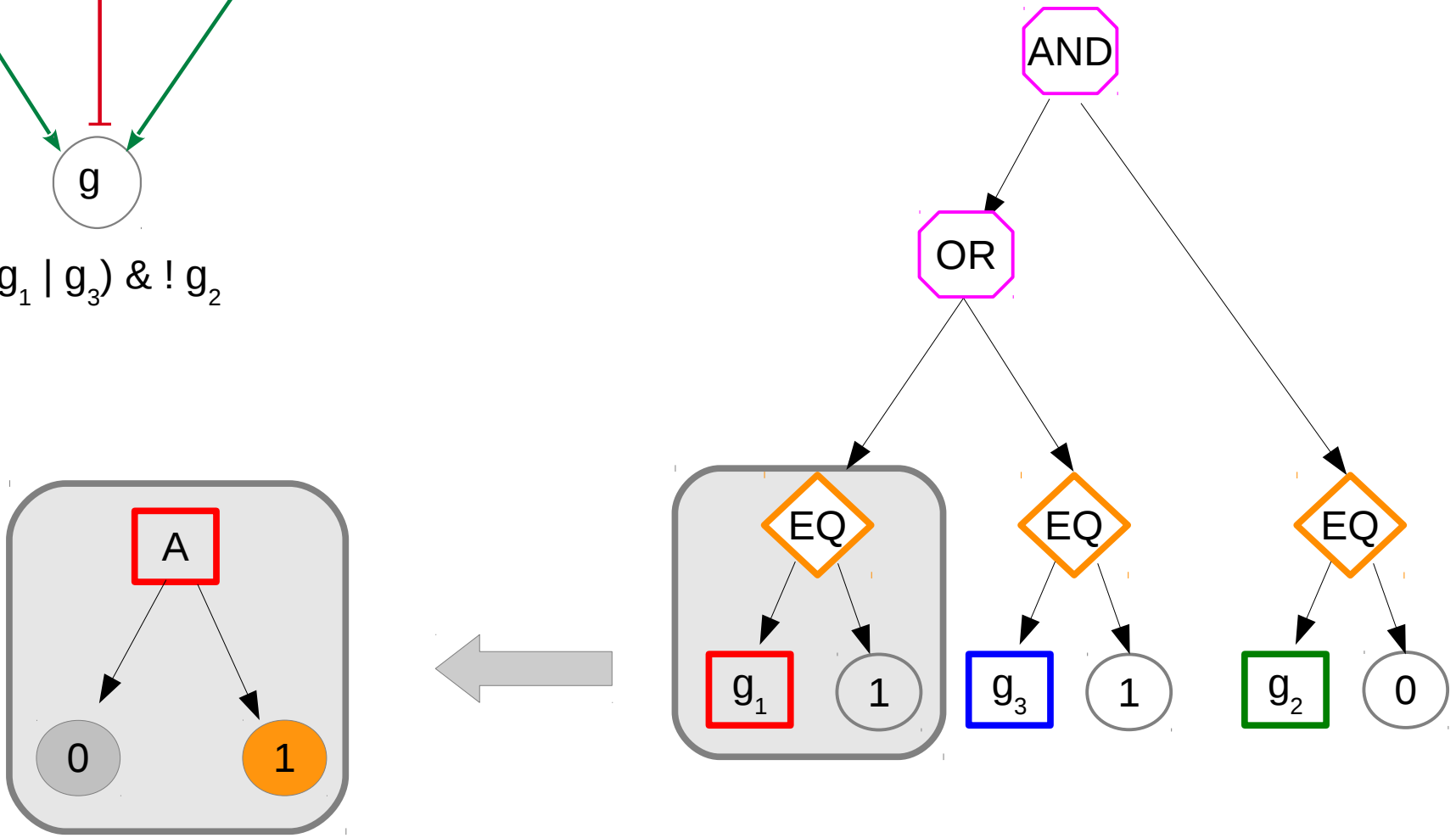


MDD manipulation for “OR”, “AND” operators

Helpers

Little MDDs knowledge required

- Extract list of regulators from function
- Iterate paths in the MDD
- Construct a function?

Iterate paths in a MDD

```
// input: LogicalModel model
MDDManager ddmanager = model.getMDDManager();
PathSearcher searcher = new PathSearcher(ddmanager);

for (int function: model.getLogicalFunctions()) {

   int[] path = searcher.setNode(functions[idx]);
   for (int leaf: searcher) {
      // leaf gives the value of the function
      // path gives the value of the components
   }
}
```

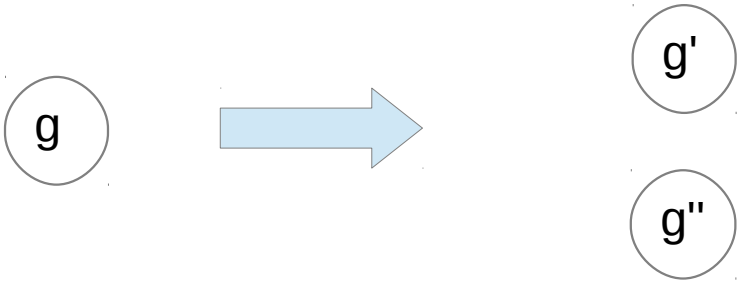
Future extensions

- Model modifiers
  - Transform multi-valued to Boolean
- Data
  - Documentation (SBML, GINML, JSON file)
  - Visual information (positions, styles?)
- Tools
  - state → successors: (a)synchronous, sequential

From multivalued to Boolean

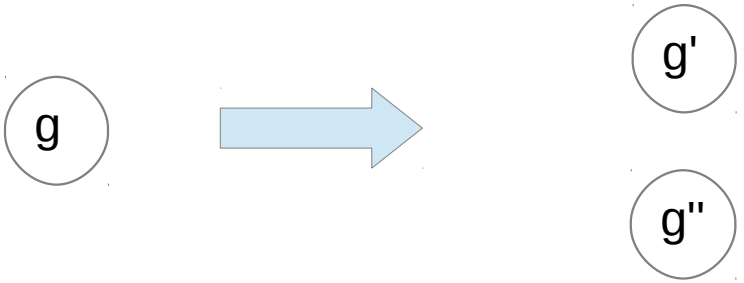
- Some tools support only Boolean models
- Multivalued models getting more common
- “Boleanize” a multivalued model when needed:
  - Multiply components
  - Rewrite functions

From multivalued to Boolean



g'	g''	g'''	g
0			0
1			1
0	1		2
1	1		3
0	0	1	4
1	0	1	5
0	1	1	6
1	1	1	7

From multivalued to Boolean



g'	g''	g'''	g
0			0
1			1
0	1		2
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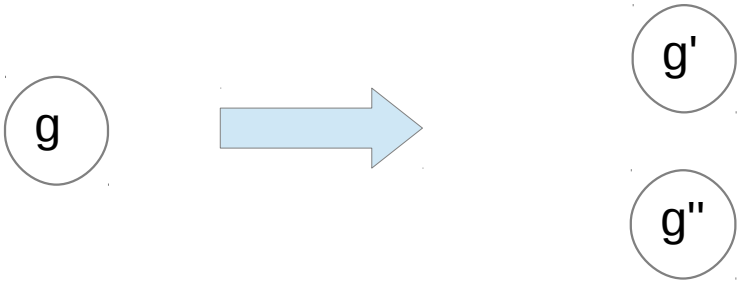
g'	g''	g'''	g
0			0
1			1
1	1		2
0	1		3
0	1	1	4
1	1	1	5
1	0	1	6
0	0	1	7

From multivalued to Boolean



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1	0	1	6
0	0	1	7

g'	g''	g'''	g''''	g
0				0
1				1
1	1			2
1	1	1		3
1	1	1	1	4

Acknowledgements

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github.com/colomoto