Compaction of logical state transition graphs

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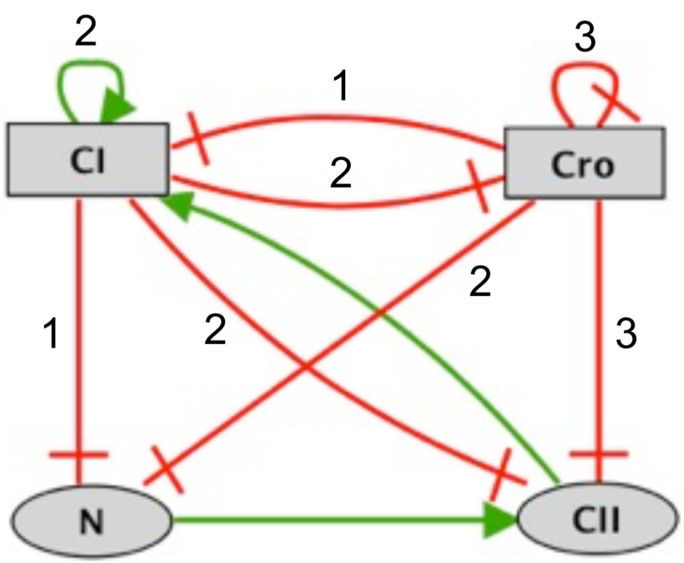
Coping with the exponential growth of logical state transition graphs

- Model reduction
- Attractor identification
- Temporisation (e.g. priorities, delays, etc.)
- **Compaction of state transition graphs**

Bacteriophage lambda: regulatory graph



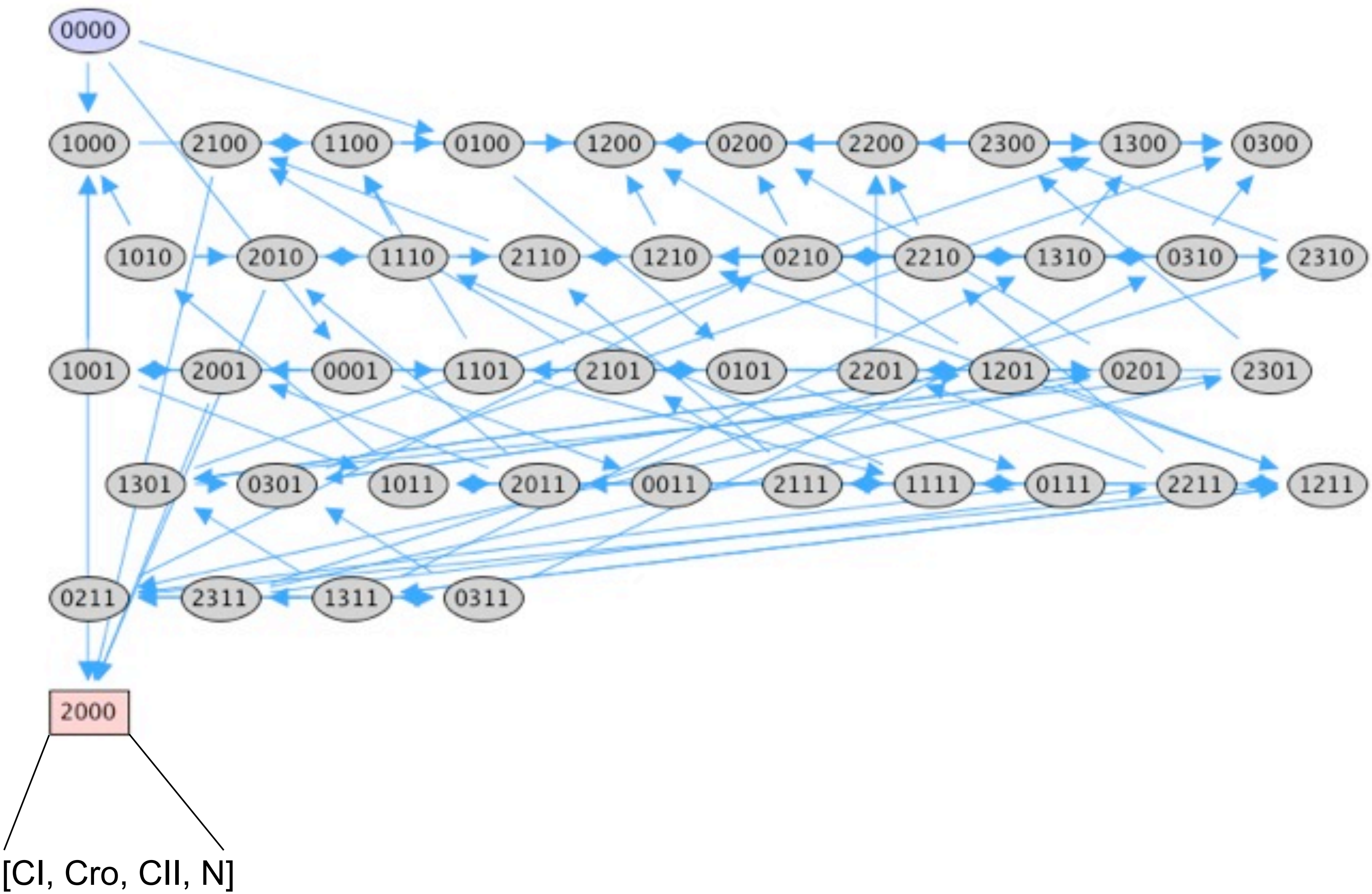
Thieffry & Thomas (1995)

Phage lambda model : logical rules

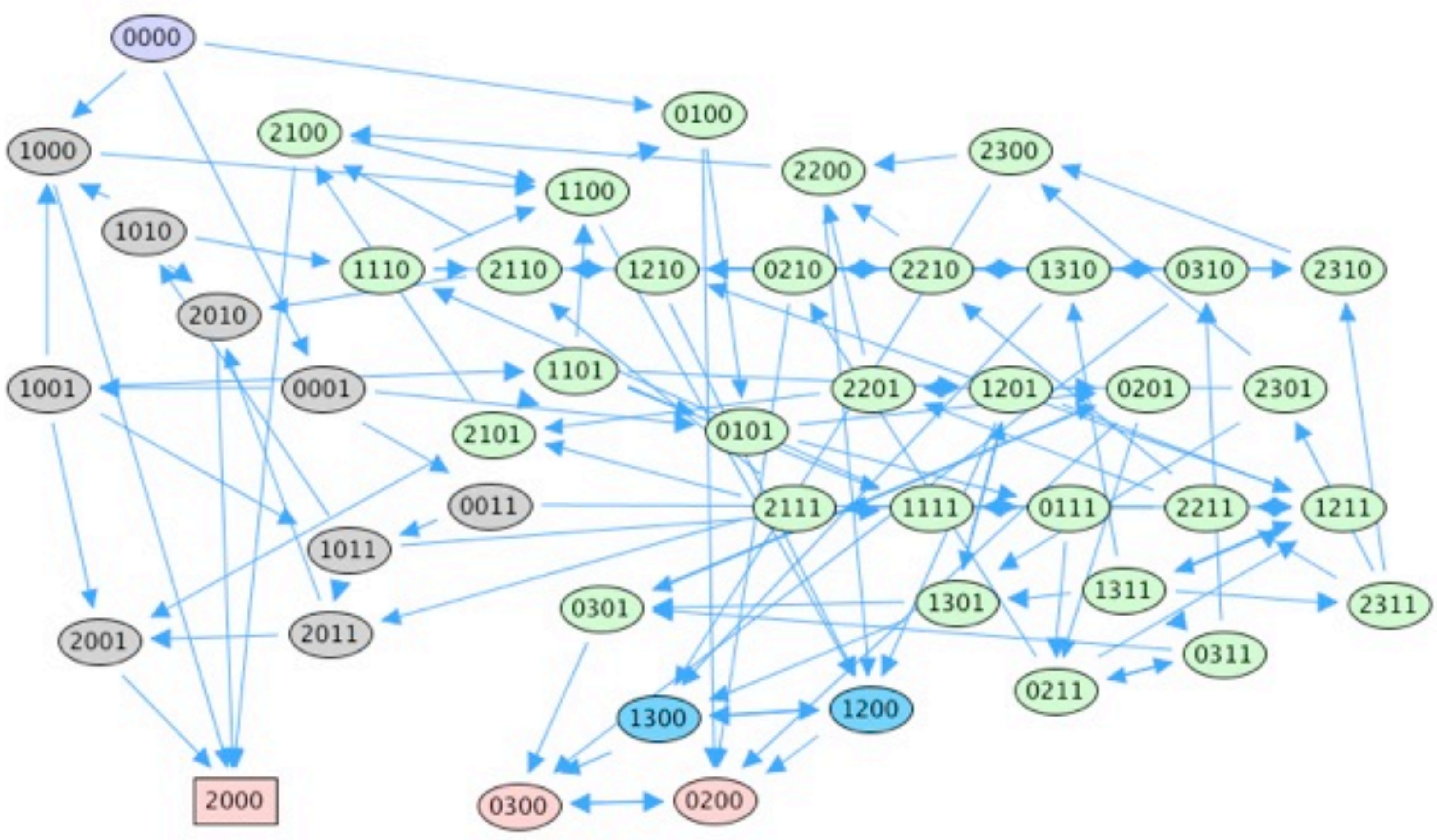
<table>
<tr><th>Node => target value</th><th>Logical Rule</th></tr>
<tr><td>CI => 2
CI => 0</td><td>!Cro | CII
Otherwise</td></tr>
<tr><td>Cro => 3
Cro => 2
Cro => 0</td><td>!CI & !Cro
!CI & Cro
CI</td></tr>
<tr><td>CII => 1
CII => 0</td><td>!CI & !Cro & N
Otherwise</td></tr>
<tr><td>N => 1
N => 0</td><td>!CI & !Cro
Otherwise</td></tr>
</table>

Thieffry & Thomas (1995)

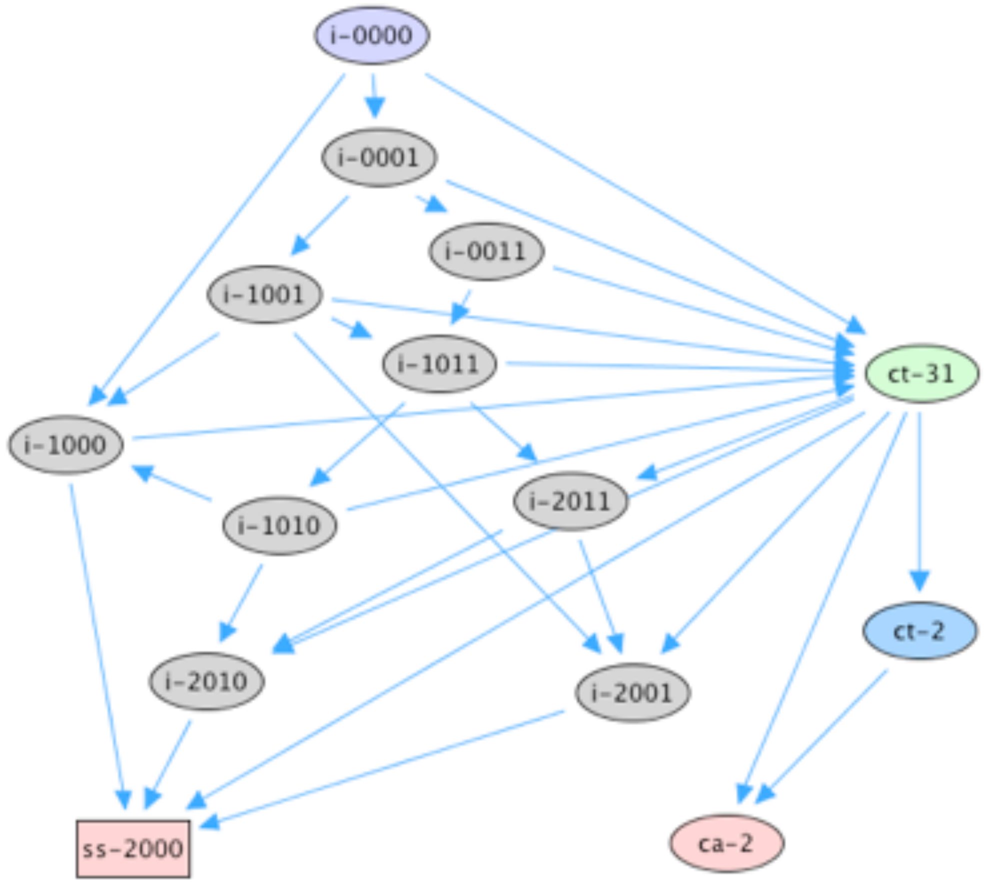
Lambda phage model: state transition graph (STG)



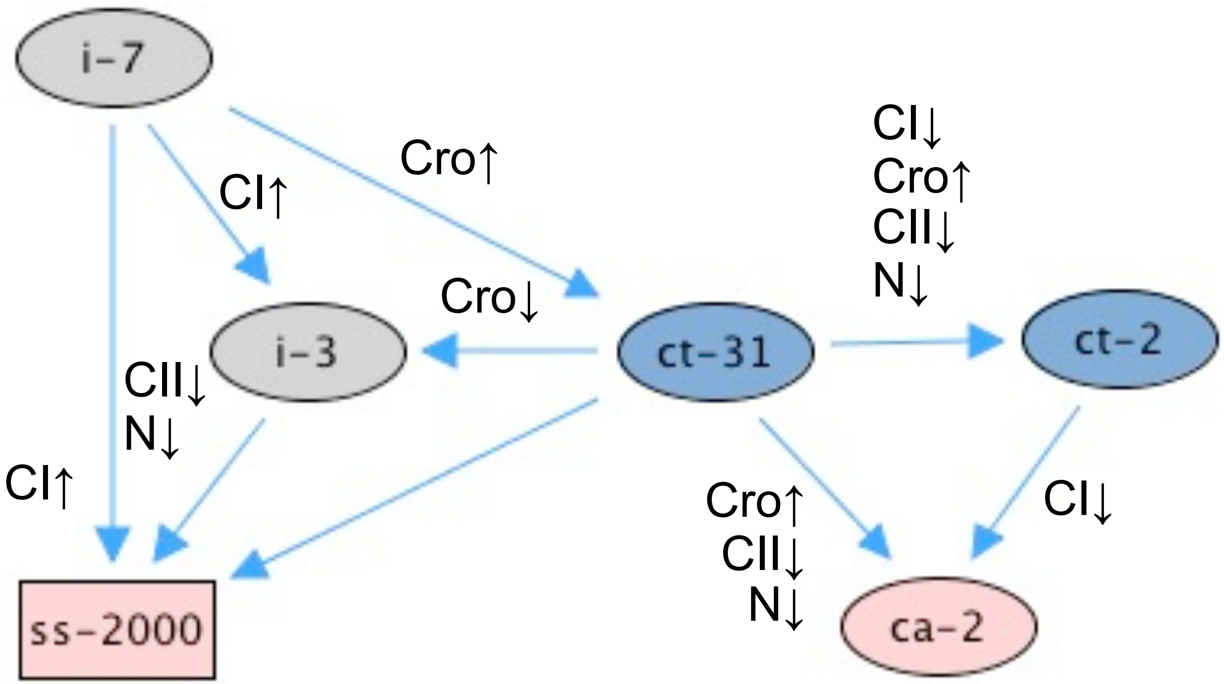
Lambda phage model: state transition graph (STG)



Lambda phage model:
graph of strongly connected components (GSCC)



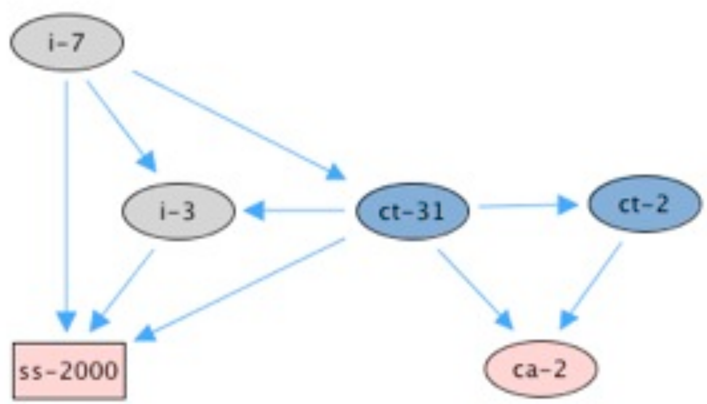
Lambda phage model: hierarchical state transition graphs (HTG)



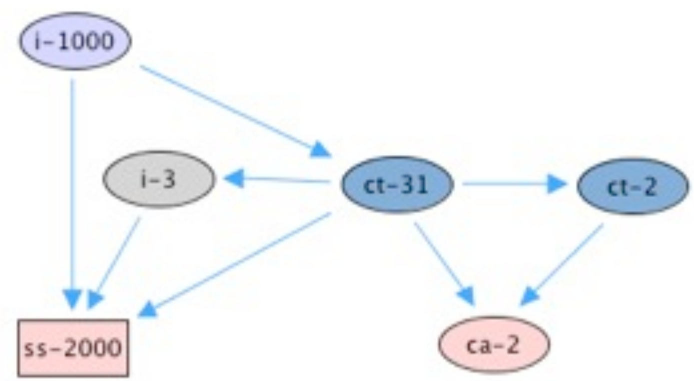
Content of HTG components (schemata)

Component	CI	Cro	CII	N
#11	0	0	0	*
	0	0	1	1
	1	0	*	*
#47	0	1	0	*
	0	1	1	1
	0	2	0	1
	0	2	1	*
	0	3	0	1
	0	3	1	*
	1	1	*	*
	1	2	0	1
	1	2	1	*
	1	3	0	1
	1	3	1	*
	2	1	*	*
	2	2	*	*
	2	3	*	*
#2	1	2	0	0
	1	3	0	0
#3	2	0	0	1
	2	0	1	*
#2 (terminal)	0	2	0	0
	0	3	0	0
2000	2	0	0	0

Over-approximation



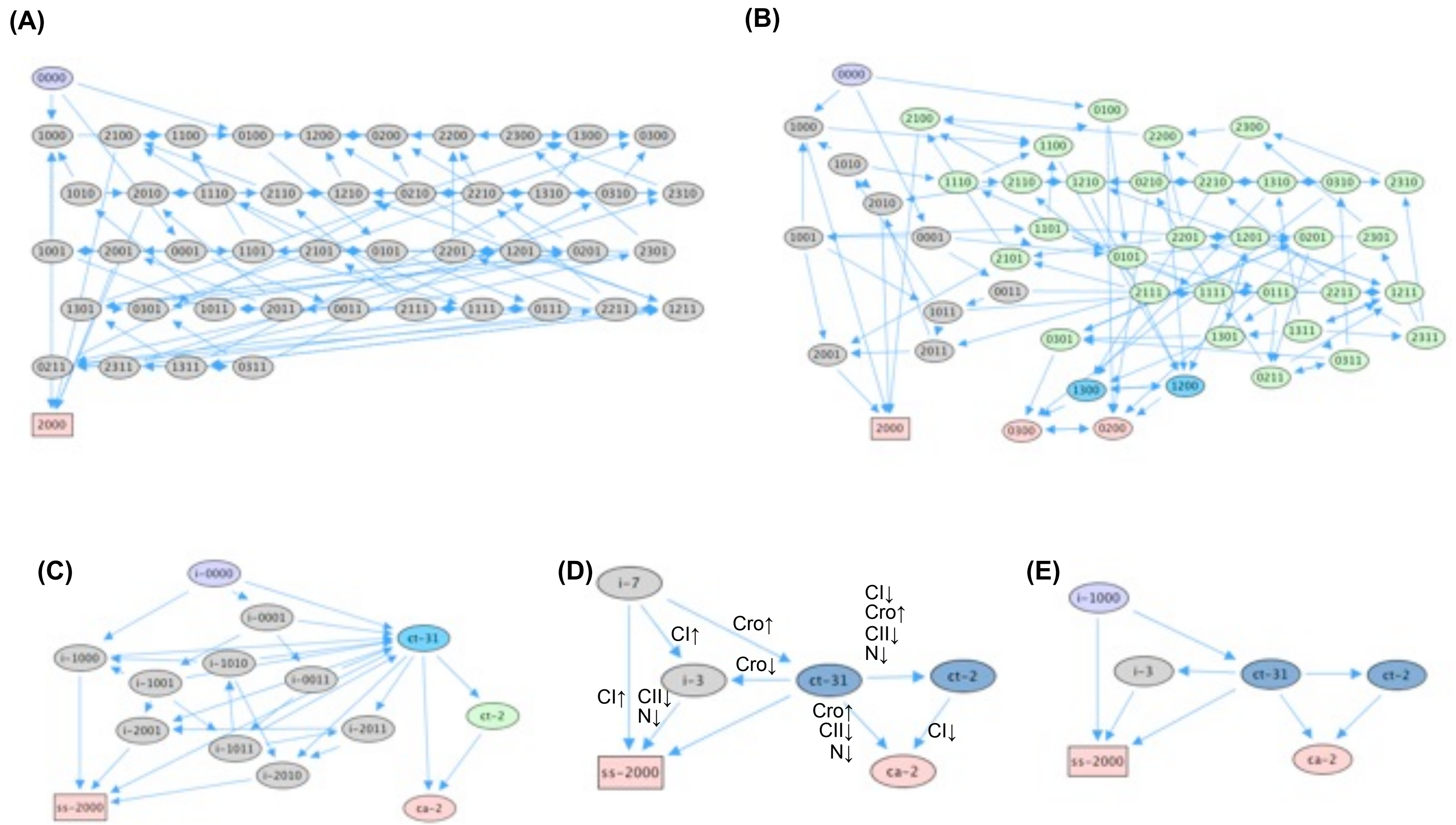
Asynchronous STG starting from initial state 0000



Asynchronous STG starting from initial state 1000

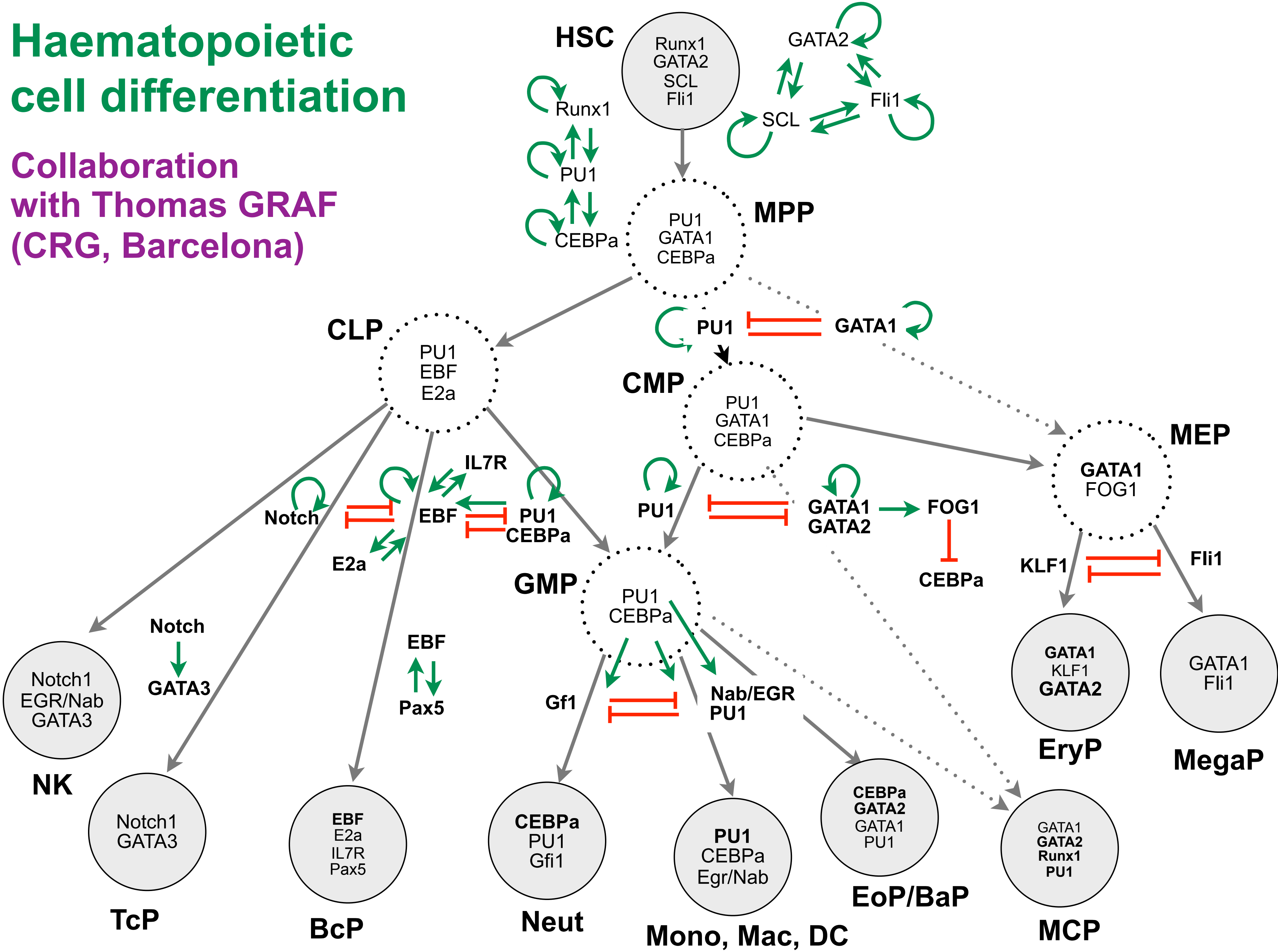
To a path between two states in the STG correspond always a path in the HTG, but the reverse is not always true

STG vs GSCC vs HTG



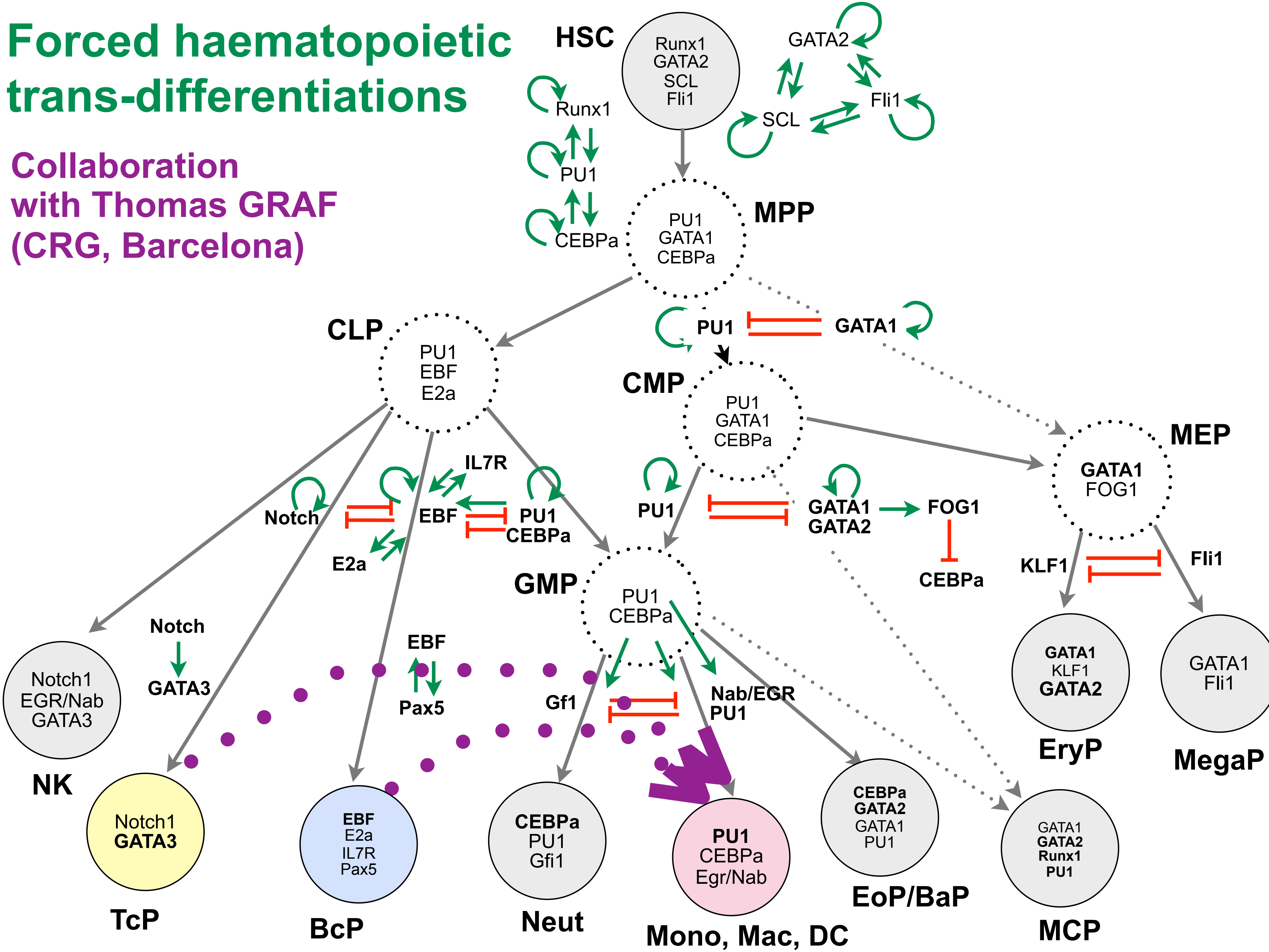
Haematopoietic cell differentiation

Collaboration with Thomas GRAF (CRG, Barcelona)

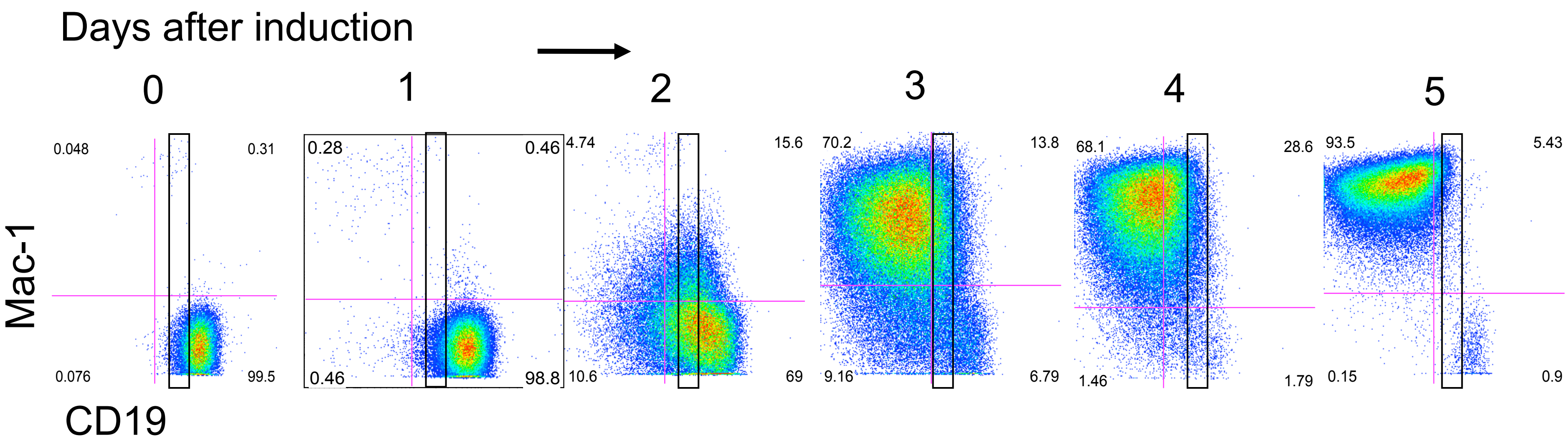


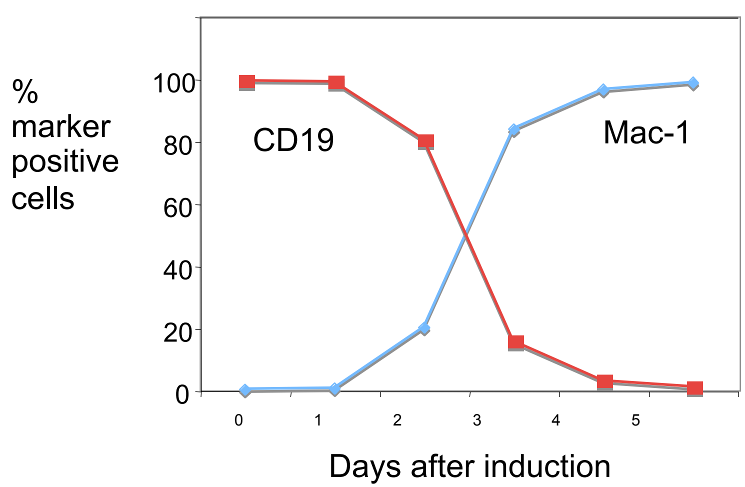
Forced haematopoietic trans-differentiations

Collaboration with Thomas GRAF (CRG, Barcelona)



An inducible form of C/EBPα permits highly efficient reprogramming of pre-B cells into macrophages

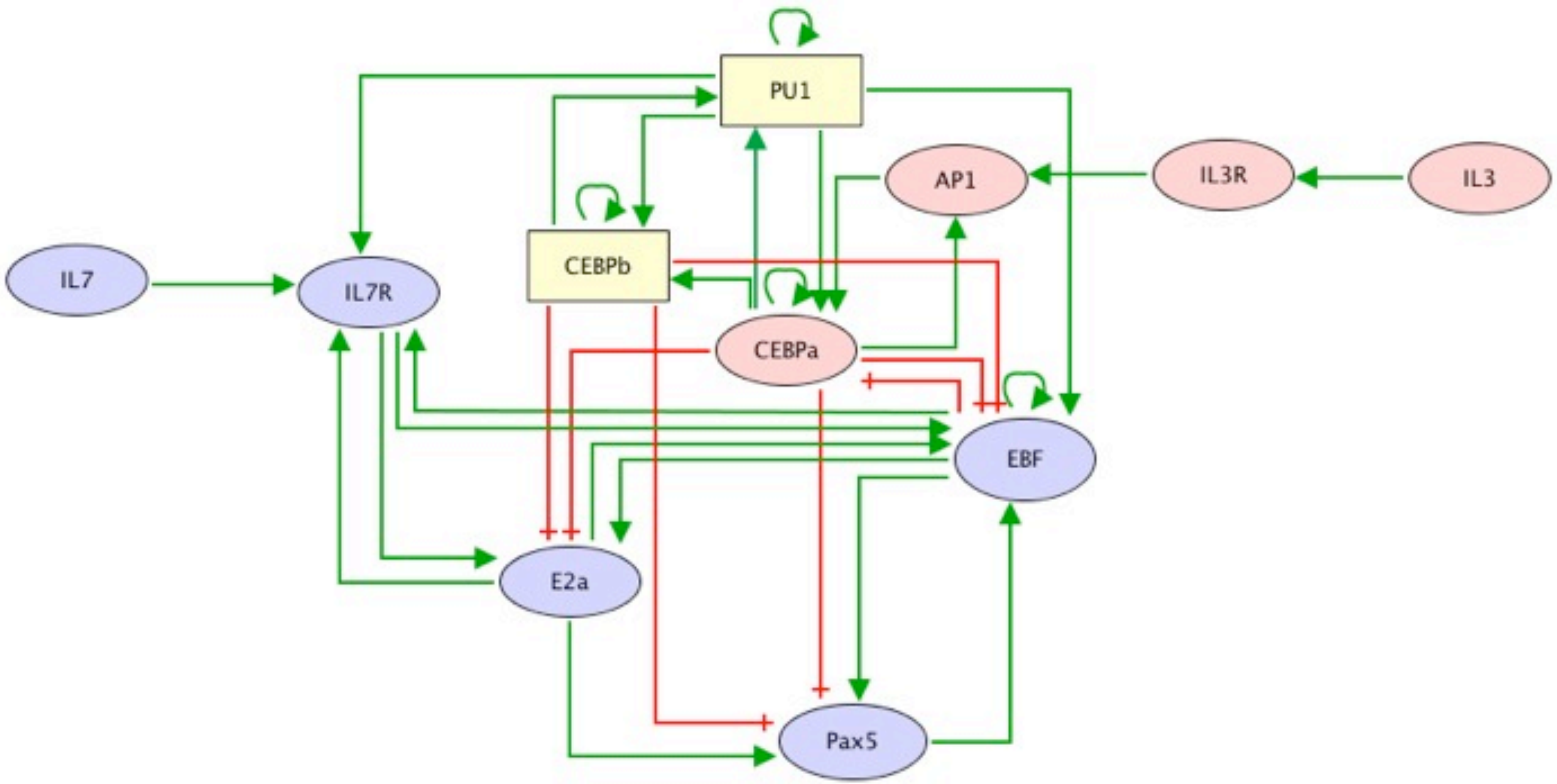




Courtesy T Graf

Xie *et al* (2004) *Cell*
Bussman *et al* (2009) *Cell Stem Cell*

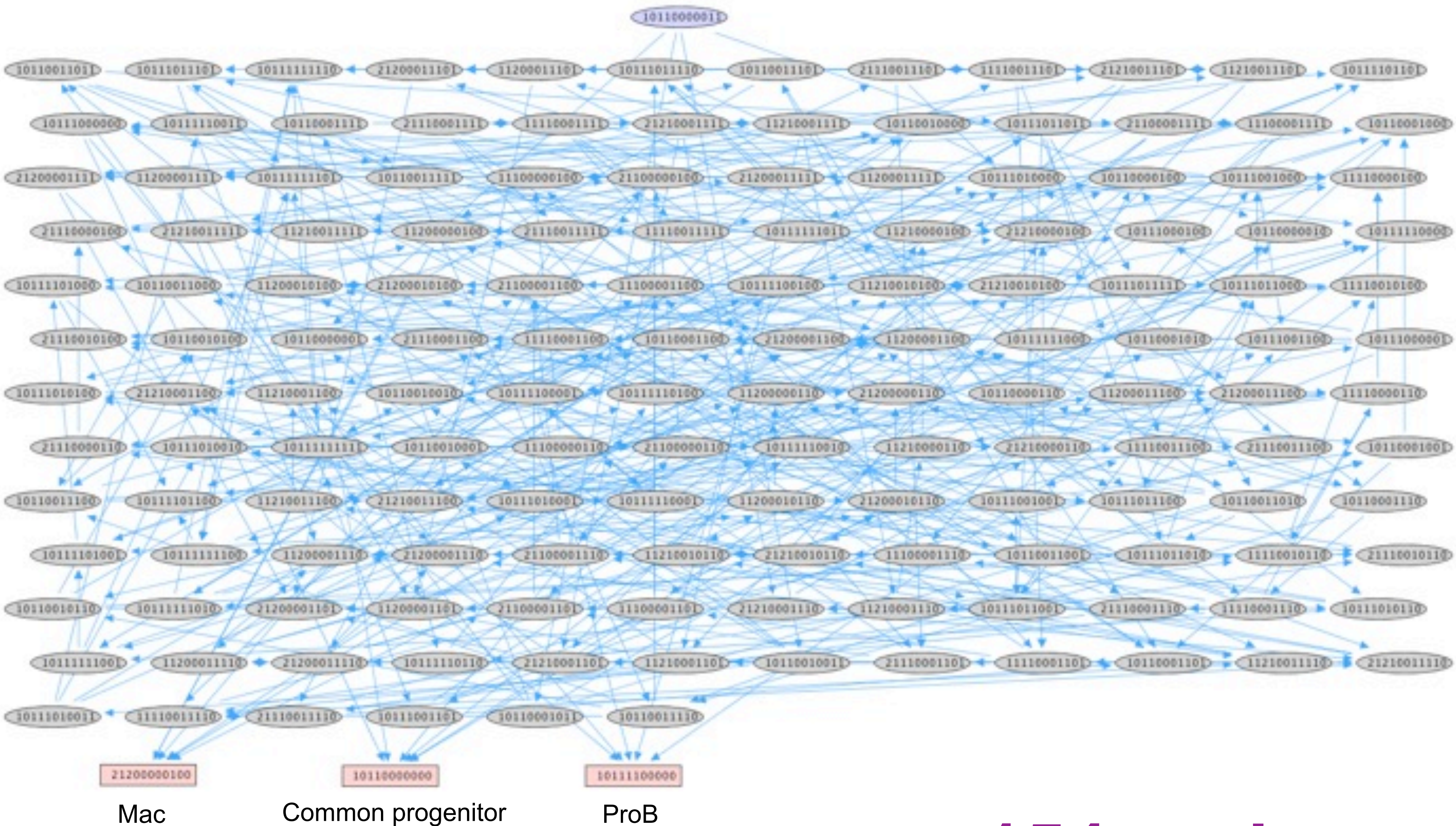
ProB reprogramming model: regulatory graph



ProB reprogramming model: logical rules

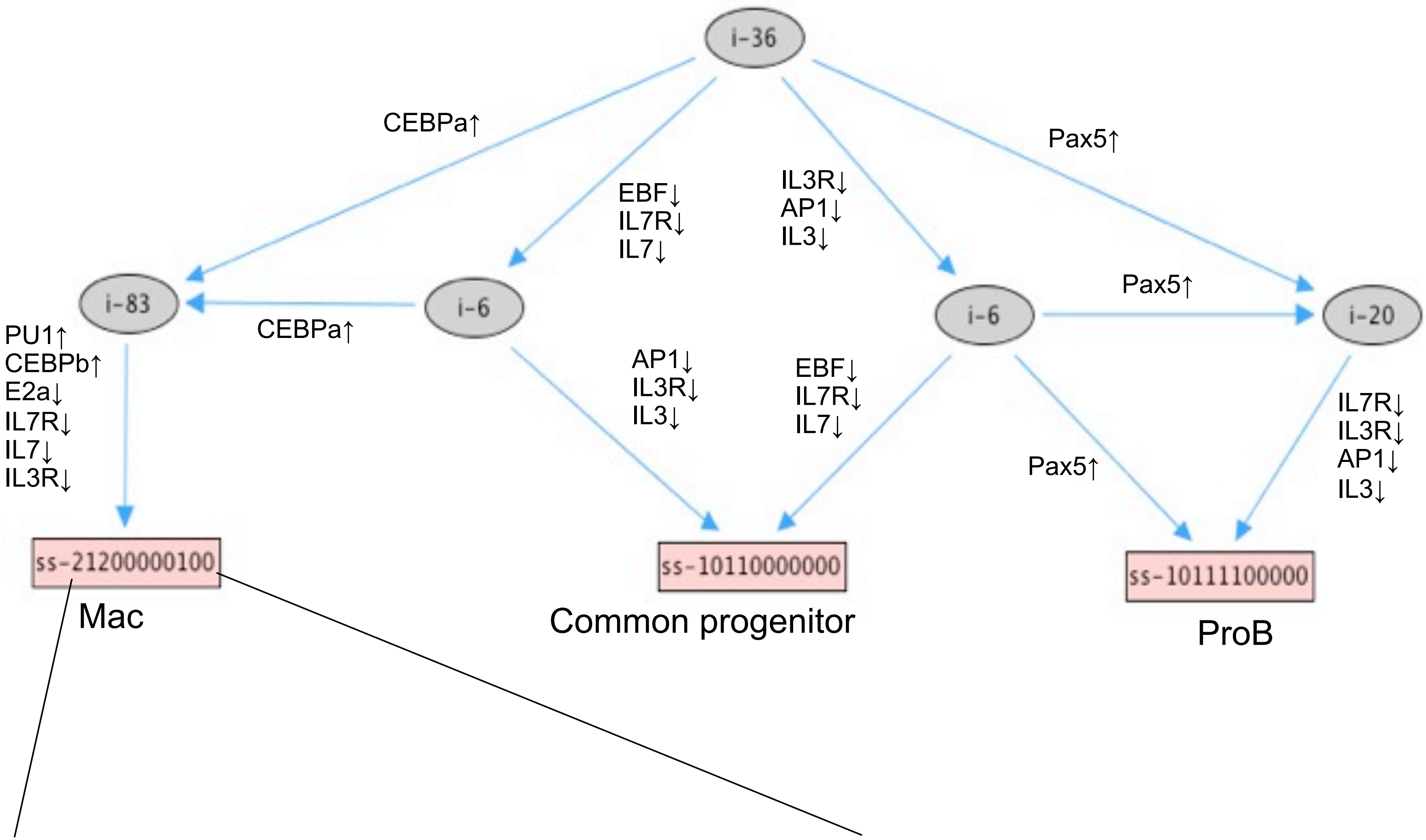
<table>
<tr><th>Node => target value</th><th>Logical Rule</th></tr>
<tr><td>PU1 =>2
PU1=>1</td><td>(CEBPa & CEBPb & PU1) | (PU1 & CEBPb:2)
(CEBPa | CEBPb | PU1) & !(CEBPa & CEBPb & PU1)
& !(PU1 & CEBPb:2)</td></tr>
<tr><td>CEBPa=>1</td><td>(AP1 & !EBF) | (PU1 & AP1 & CEBPa) | (PU1 & CEBPa & !EBF)</td></tr>
<tr><td>CEBPb=>2
CEBPb=>1</td><td>PU1 & CEBPa & CEBPb
(CEBPa | CEBPb) & PU1 & !(CEBPa & CEBPb & PU1)</td></tr>
<tr><td>E2A=> 1</td><td>(!CEBPa | EBF | IL7R) & !CEBPb</td></tr>
<tr><td>EBF=> 1</td><td>(PU1 & E2a & IL7R & !CEBPa & !CEBPb) |
(PU1 & EBF & Pax5 & !CEBPa & !CEBPb) |
(PU1 & E2a & IL7R & Pax5 & CEBPb & !CEBPa)</td></tr>
<tr><td>Pax5=> 1</td><td>E2a & EBF & !CEBPa & !CEBPb</td></tr>
<tr><td>IL7R=> 1</td><td>PU1 & E2a & IL7</td></tr>
<tr><td>IL3R=> 1</td><td>IL3</td></tr>
<tr><td>AP1=> 1</td><td>IL3R | CEBPa</td></tr>
<tr><td>IL7 => 0</td><td>Input</td></tr>
<tr><td>IL3 => 0</td><td>Input</td></tr>
</table>

STG (=GSCC) for initial state 1011000011



154 nodes

ProB reprogramming model: HTG for IS= 1011000011



[Pu1, CEBPa, CEBPb, E2a, EBF, Pax5, IL7R, IL3R, AP1, IL7, IL3]

8 nodes

Content of HTG components (schemata)

Component	PU1	CEBPa	CEBPb	E2a	EBF	Pax5	IL7R	IL3R	AP1	IL7	IL3
#36	1	0	1	1	1	1	0	0	0	0	1
	1	0	1	1	1	1	0	0	1	0	0
	1	0	1	1	1	1	0	1	*	0	*
	1	0	1	1	1	1	1	0	0	*	*
	1	0	1	1	1	1	1	0	1	*	0
	1	0	1	1	1	1	1	1	*	*	*
#83	1	1	1	0	0	0	0	0	1	*	0
	1	1	1	0	0	0	0	1	1	*	*
	1	1	1	1	0	0	*	0	1	*	0
	1	1	1	1	0	0	*	1	1	*	*
	1	1	2	*	0	0	*	0	1	*	0
	1	1	2	*	0	0	*	1	1	*	*
	2	1	1	0	0	0	0	0	1	*	0
	2	1	1	0	0	0	0	1	1	*	*
	2	1	1	1	0	0	*	0	1	*	0
	2	1	1	1	0	0	*	1	1	*	*
	2	1	2	0	0	0	0	0	1	1	0
	2	1	2	0	0	0	0	1	1	*	*
	2	1	2	0	0	0	1	0	1	*	0
	2	1	2	0	0	0	1	1	1	*	*
	2	1	2	1	0	0	*	0	1	*	0
	2	1	2	1	0	0	*	1	1	*	*
#6	1	0	1	1	0	0	0	0	0	1	0
	1	0	1	1	0	0	1	0	0	*	0
	1	0	1	1	1	0	0	0	0	0	0
	1	0	1	1	1	0	1	0	0	*	0
#20	1	0	1	1	1	1	0	0	0	0	1
	1	0	1	1	1	1	0	0	1	0	0
	1	0	1	1	1	1	0	1	*	0	*
	1	0	1	1	1	1	1	0	0	*	*
	1	0	1	1	1	1	1	0	1	*	0
	1	0	1	1	1	1	1	1	*	*	*
#6	1	0	1	1	0	0	0	0	0	0	1
	1	0	1	1	0	0	0	0	1	0	0
	1	0	1	1	0	0	0	1	*	0	*

Outlook

- ★ Computation of GSCC ad HTG *on the fly*
- ★ Implementation into *GINsim*
- ★ Gain in simulation storing space
- ★ Gain in computing time thanks to data structure compaction (decision diagrams)
- ★ Emphasis on crucial transitions
- ★ HTG as a tools to study attractor basins

Contributors & supports

- ★ **ENS (Paris)**
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Bioinformatics and Modelling : from Genomes to Networks