A circuit-preserving mapping from multilevel to Boolean dynamics

Adrien Fauré, Shizuo Kaji, Yamaguchi university, Japan

Thomas' conjectures:

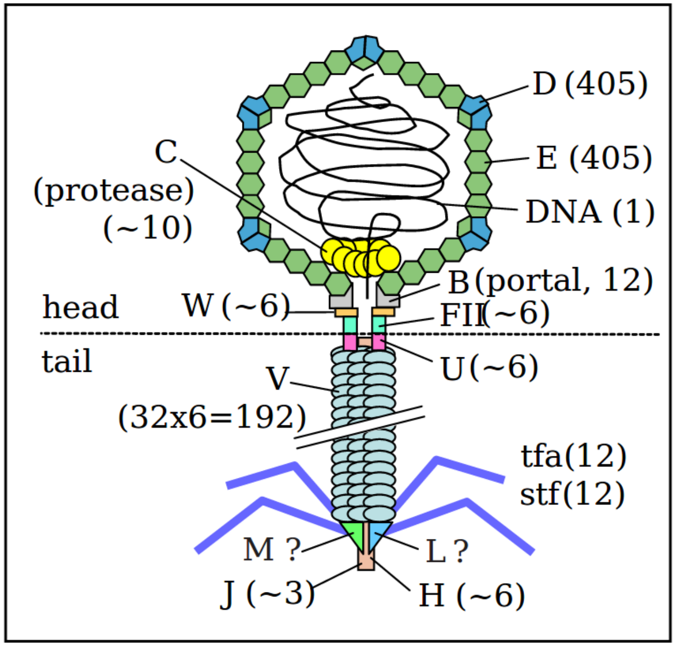
"As far as one can extrapolate from the hundreds of networks analyzed so far, *the presence of a **negative** loop in the logical structure of a system is a necessary, although not sufficient, condition for a **permanent periodic behaviour**, and the presence of a **positive** loop is a necessary, although not sufficient, condition for **multiple stable steady states**.*"

René Thomas, On the Relation Between the Logical Structure of Systems and Their Ability to Generate Multiple Steady States or Sustained Oscillations.
In Numerical Methods in the Study of Critical Phenomena, **1981**

Sign of a circuit: product of the sign of its arcs

Oscillations and multistationarity

Lambda phage example



Rajagopala et al. 2011, BMC Microbiology 11: 213

- bacteriophage (~virus)

- infects E. coli

- lysis / lysogeny switch:

→ dormant | cI

→ multiplies and kills the cell | cro

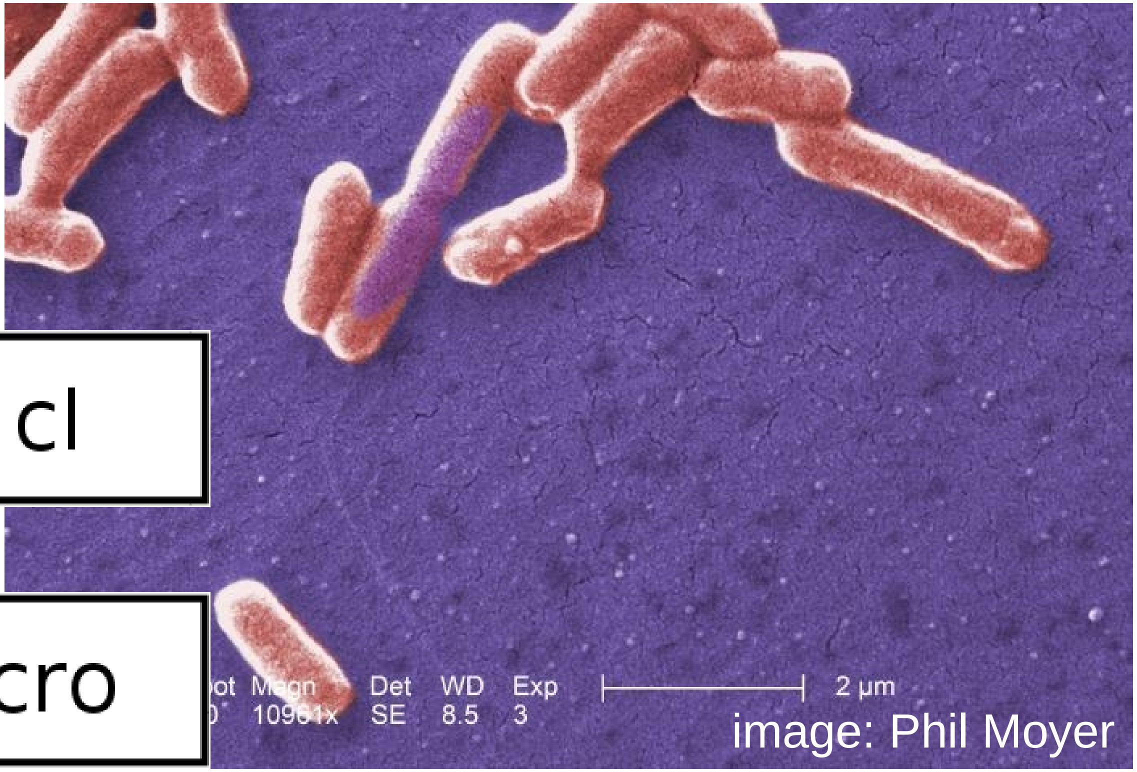
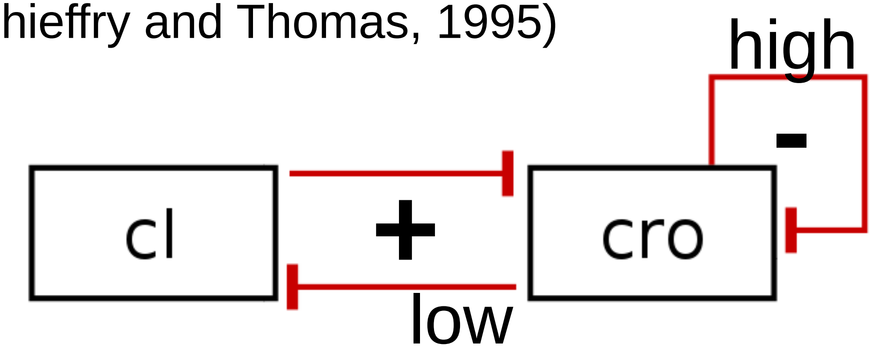


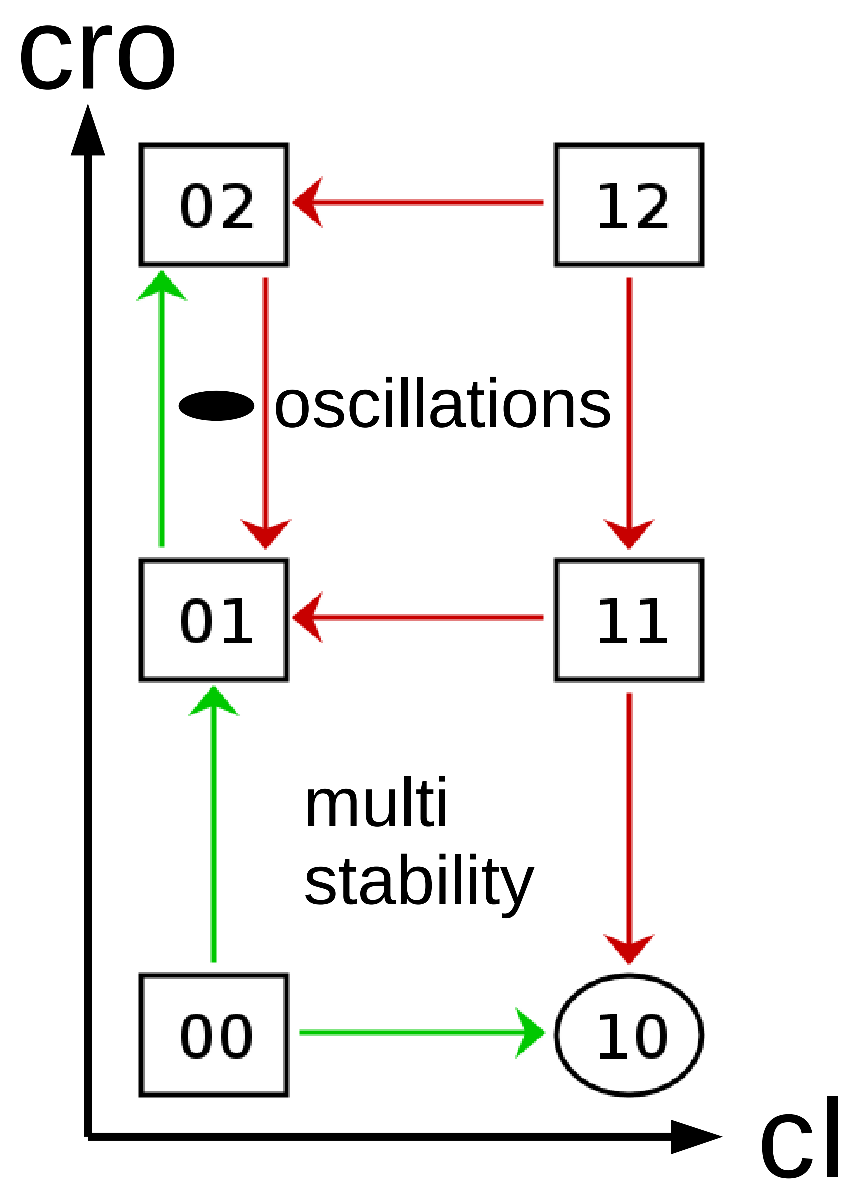
image: Phil Moyer

Oscillations and multistationarity

Lambda phage example

(Thieffry and Thomas, 1995)





$\mathbf{f_{cl}}$ = 1 if NOT **cro**

0 otherwise

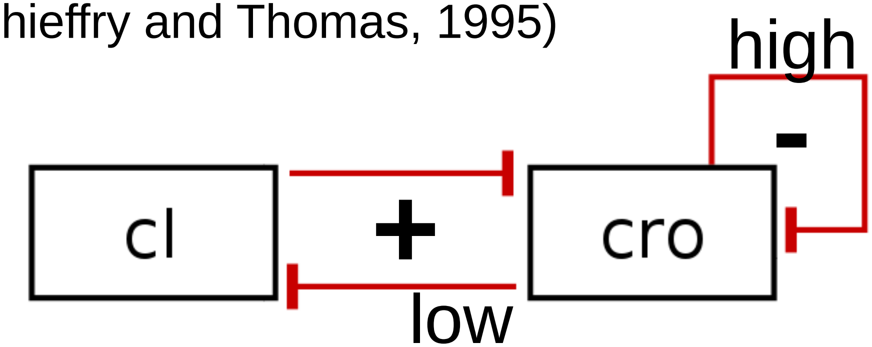
$\mathbf{f_{cro}}$ = 2 if NOT **cl** AND NOT **cro:2**

0 otherwise

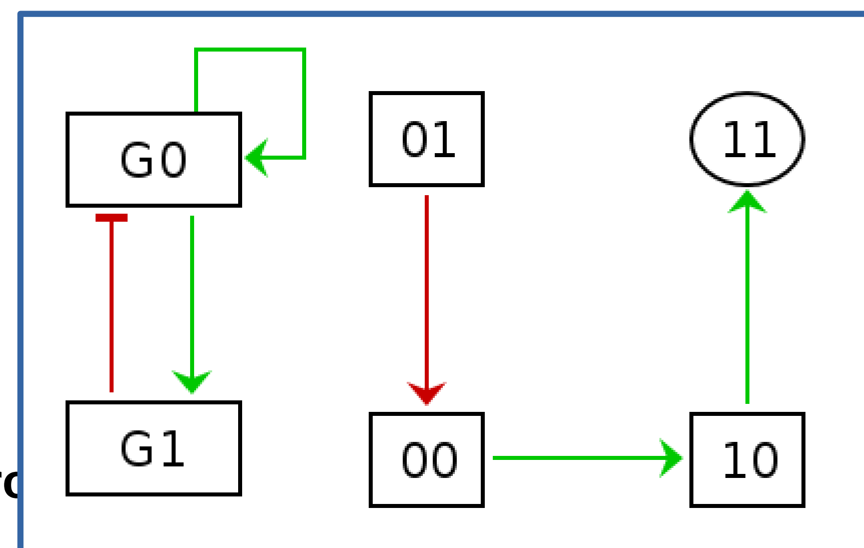
Oscillations and multistationarity

Lambda phage example

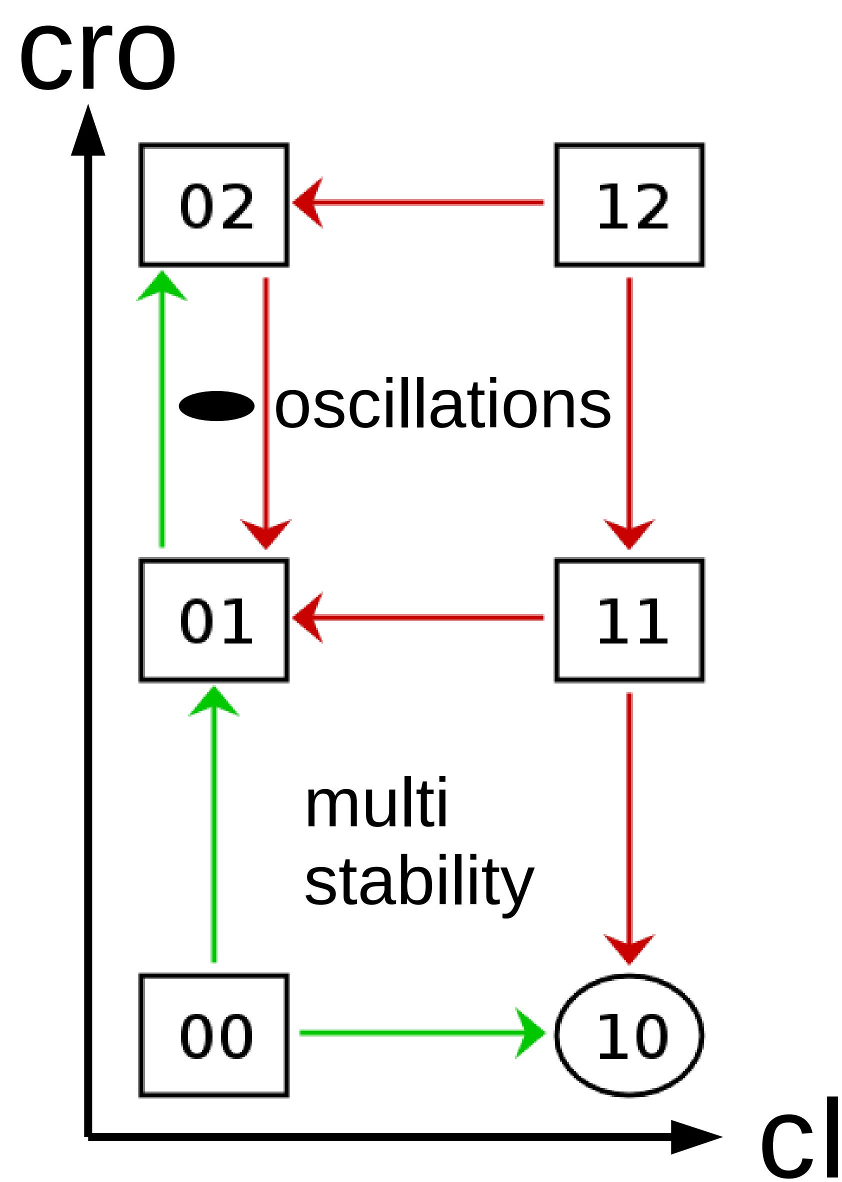
(Thieffry and Thomas, 1995)



f_{cl}



f_{cr} o:2



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Vol. 22 no. 14 2006, pages e124–e131
doi:10.1093/bioinformatics/btl210

Dynamical analysis of a generic Boolean model for the control of the mammalian cell cycle

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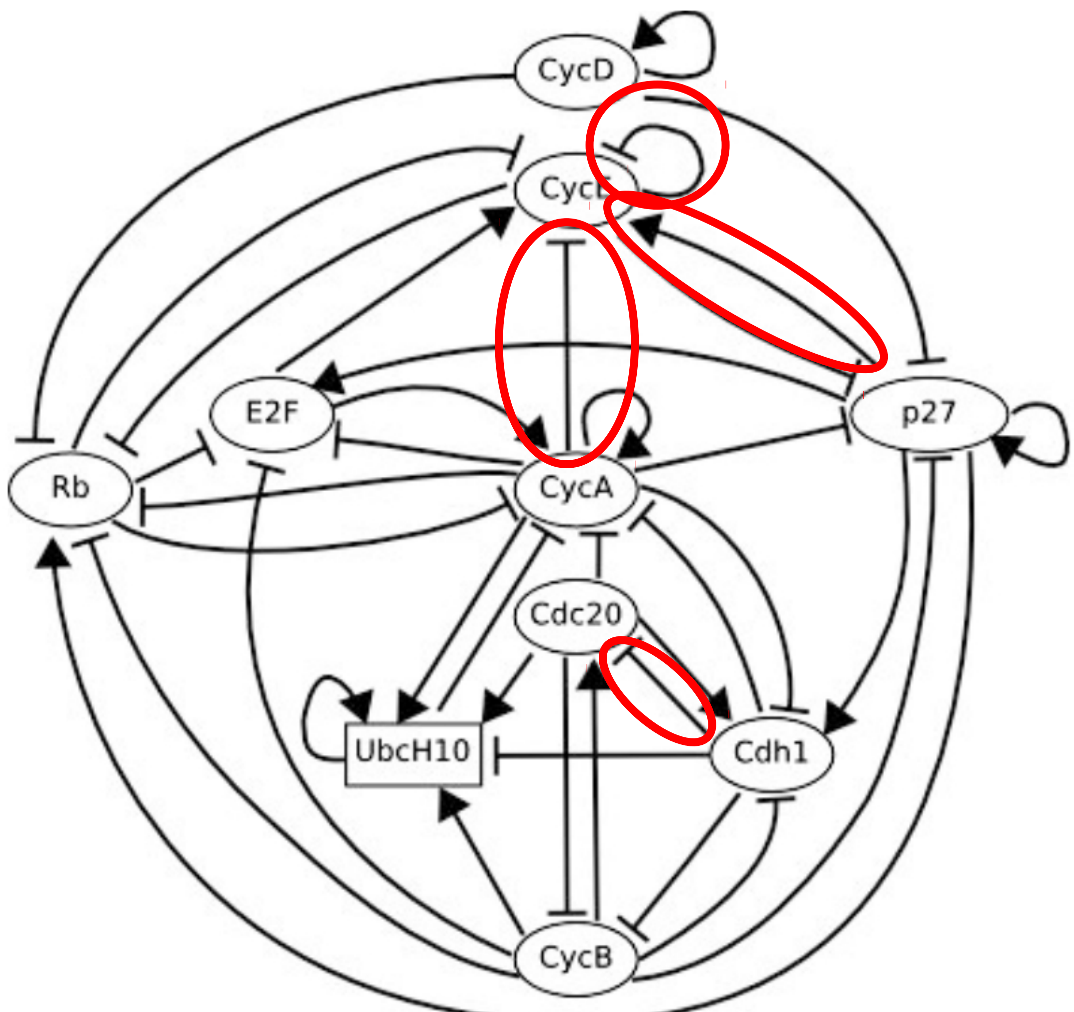


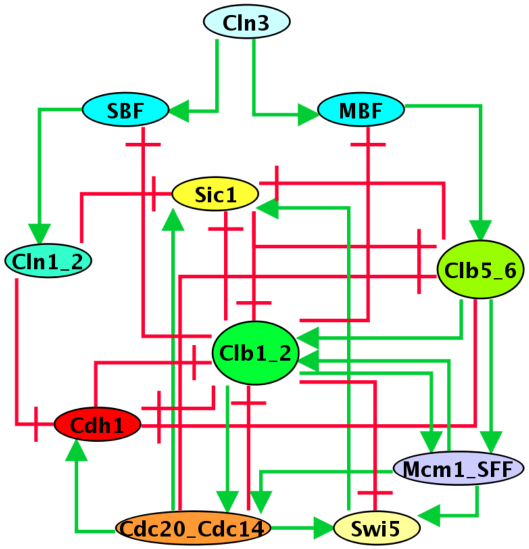
Main reference: ODE-based model by Novák and Tyson (2004)
+UbcH10

Some arcs are
not functional!

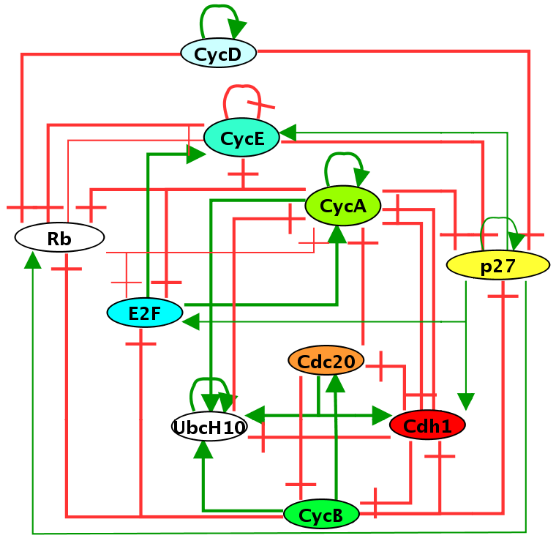
(Have no influence on the dynamics)

Logical modelling of cell cycle control in eukaryotes: a comparative study.

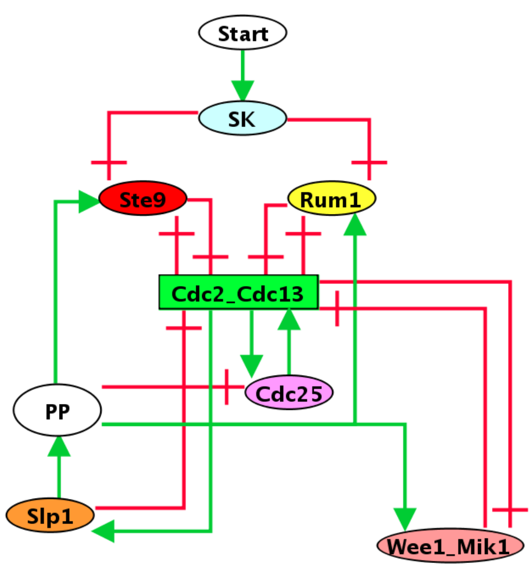
Fauré A and Thieffry D (2009) Mol Biosyst. 5:1569–81



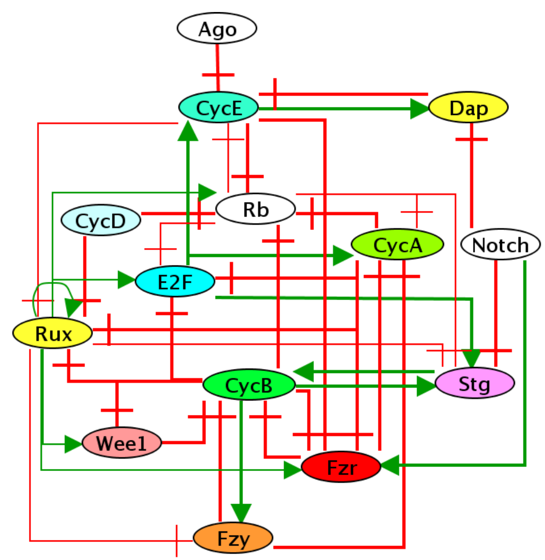
Budding yeast
(Li *et al.*, 2004)



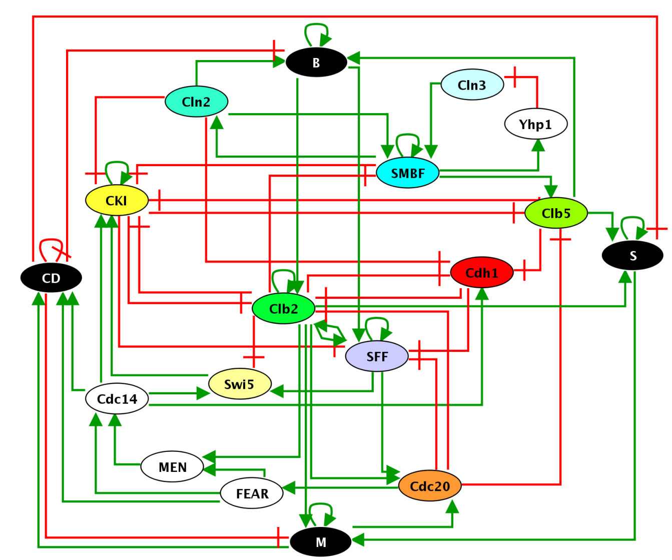
Mammals
(Fauré *et al.*, 2006)



Fission yeast
(Davidich *et al.*, 2008)



Drosophila
(Fauré & Thieffry, 2009)



Budding yeast
(Irons, 2009)

Conservation of functional circuits in logical cell cycle models in different organisms

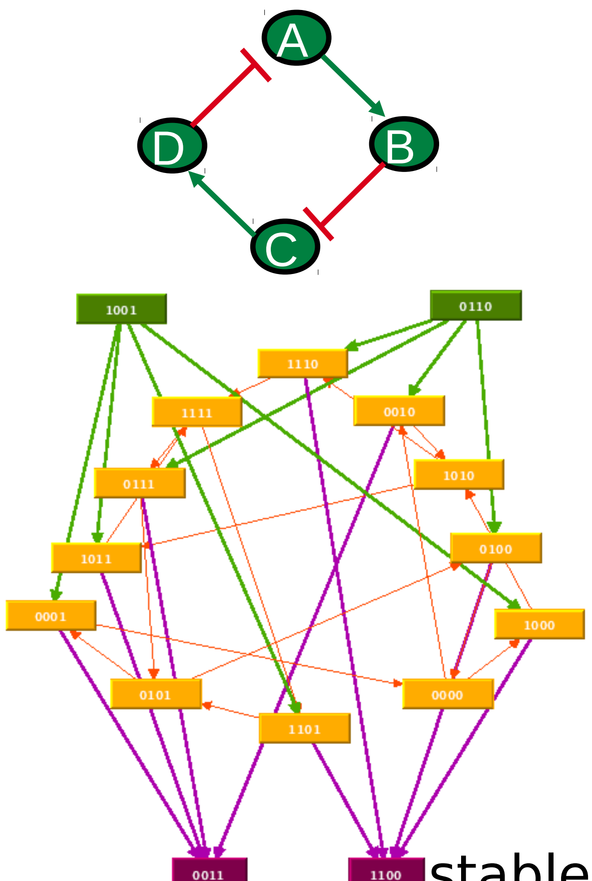
Model	*Budding yeast* (Li et al , 2004)	*Fission yeast* (Davidich et al, 2008)	*Mammals* (Fauré et al, 2006	*Budding yeast* (Irons, 2009)	*Drosophila* (Fauré et al)
Total number of circuits	64	9	132	701	199
Functional negative circuits	**Clb1,2/MBF/Clb5,6** **Cdc20/Clb5,6/Mcm1** **Clb1,2/Cdc20**	**Cdc13/Slp1**	**CycB/Cdc20**	**Cdc20/FEAR/Cdc14 /CKI /Clb2** **SFF/Swi5/CKI** **CKI/Clb2/MEN/Cdc14** **Clb2/MEN/Cdc14/Cdh1** **Cdc20/Clb2**	**CycA/E2F** **CycB/Fzy** **CycE/Dap**
Functional positive circuits	**Clb1,2/Cdh1** **Clb1,2/Sic1** **Clb5,6/Sic1**	**Cdc13/Rum1** **Cdc13/Ste9** **Cdc13/Cdc25**	**CycB/Cdh1** **CycA/Rb** **CycA/Cdh1** **CycE/Rb**	**CKI/Clb2** **Clb2/Cdh1**	**CycB/Fzr** **Fzr/CycA** **CycE/Rb** **CycB/Stg** **CycA/Rb** **CycB/Wee1**

Circuit functionality

A positive (resp. negative) circuit is functional (or effective, operative) if it **generates** multistationarity (resp. a cyclic attractor)

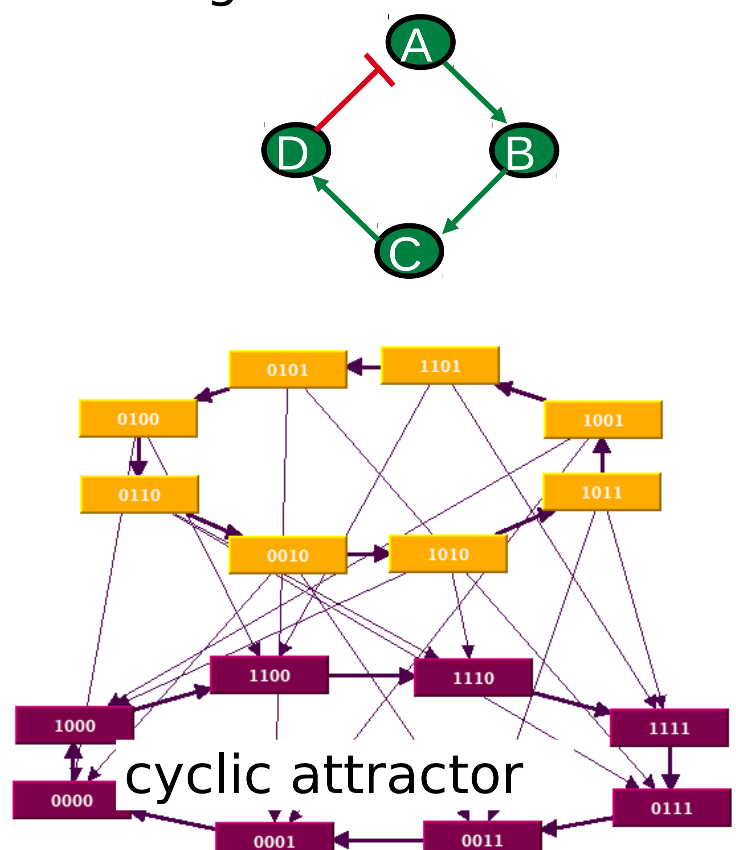
Discrete dynamics of simple feedback circuits

Positive circuit



stable states

Negative circuit



Remy E, Mosse B, Chaouiya C, Thieffry D (2003). Bioinformatics 10: ii172-8.

Circuit functionality

A positive (resp. negative) circuit is functional (or effective, operative) if it **generates** multistationarity (resp. a cyclic attractor)

- if several circuits, which one?
- predict behaviour?
- meaning of “generate”?

Bottom-up definition:

a circuit is functional if all its arcs are functional

if and **where** ? different definitions, with different properties

How can we reconcile the two notions?

Bull Math Biol (2013) 75:906–919
DOI 10.1007/s11538-013-9829-2

Society for Mathematical Biology

ORIGINAL ARTICLE

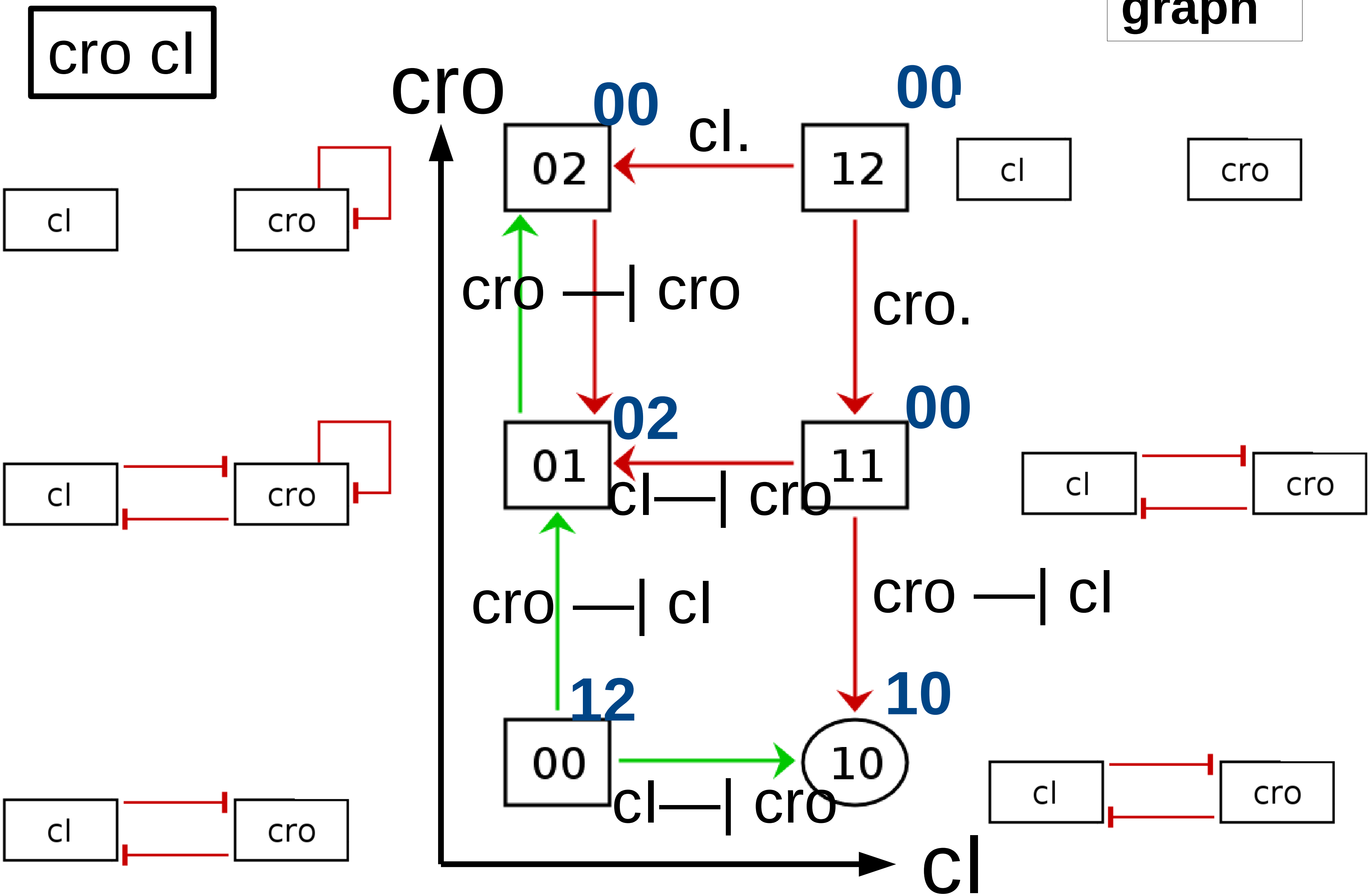
On Circuit Functionality in Boolean Networks

Jean-Paul Comet · Mathilde Noual · Adrien Richard · Julio Aracena · Laurence Calzone · Jacques Demongeot · Marcelle Kaufman · Aurélien Naldi · El Houssine Snoussi · Denis Thieffry

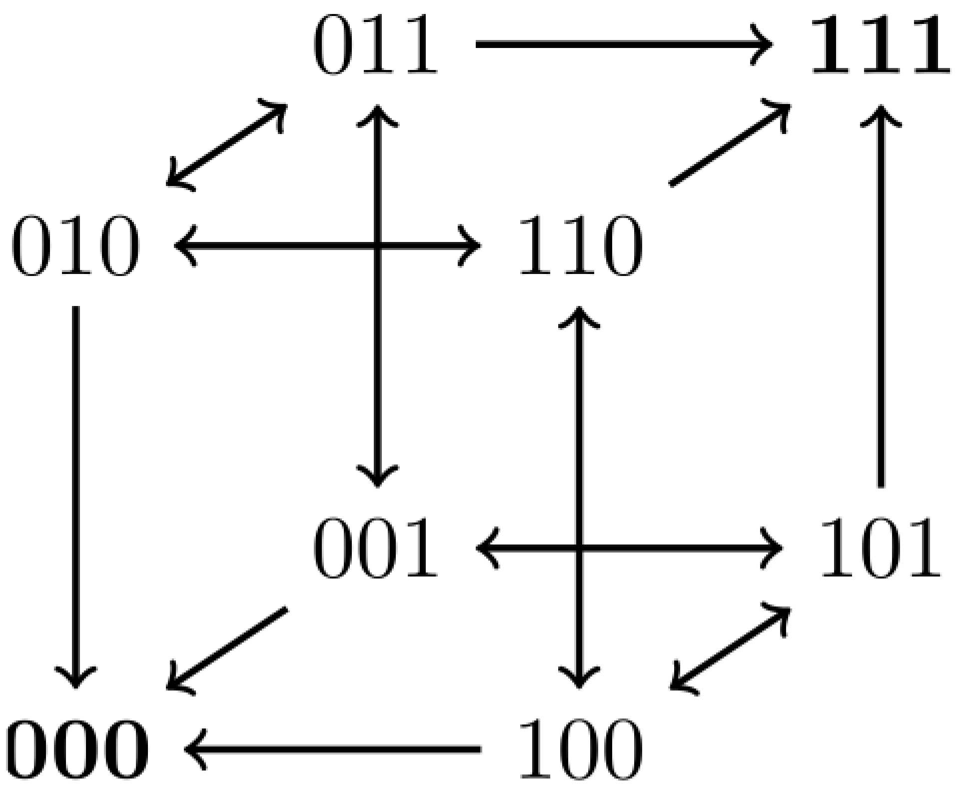
"In this paper, we review and discuss different notions of circuit functionality leading to such necessary conditions. We start by introducing a natural definition of the functionality of an arc along with the localization of this functionality in the phase space. Next, we propose different definitions of the functionality of a circuit based on where, in the phase space, the arcs composing the circuit are functional."

Functionality of a circuit

Local graph



Local functionality?

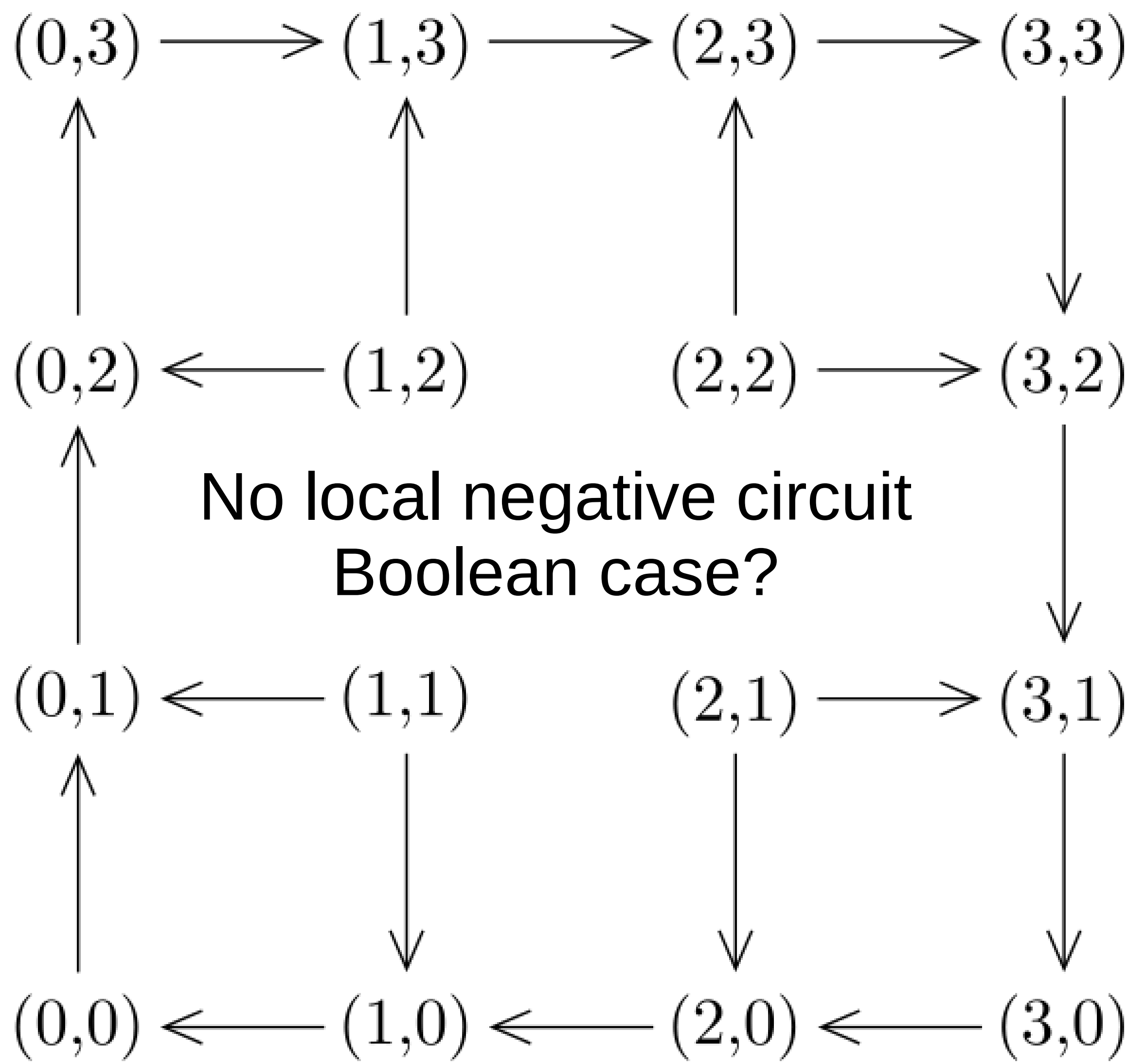


local functional **positive** circuit
necessary for **multistationarity**

Advances in Applied Mathematics 44 (2010) 378–392

Negative circuits and sustained oscillations in asynchronous automata networks

Adrien Richard *



Mapping multivalued onto Boolean dynamics

Gilles Didier[a,*], Elisabeth Remy[a], Claudine Chaouiya[b,c,1]

[a] Institut de Mathématiques de Luminy, Marseille, France
[b] Instituto Gulbenkian de Ciência, Oeiras, Portugal
[c] Inserm U928 - TAGC, Marseille, France

CHAPTER XV

How to deal with variables with more than two levels

P. VAN HAM[+]

5. Logical structure of the multilevel variable

A multilevel variable has an underlying logical structure which can be expressed by a set of logical equations of the following form :

$$Y_i = y_{i-1} \cdot f_i + y_{i+1}$$

$$i = 1, \ldots, p$$

$$\text{with } y_0 = 1 \text{ and } y_p = 0$$

Mapping multivalued onto Boolean dynamics

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x_g	$\mathrm{b}_0(x)h_1^g$	$\mathrm{b}_0(x)h_2^g$	$\mathrm{b}_0(x)h_3^g$	$\mathrm{b}_0(x)h_4^g$	$\dots$	$\mathrm{b}_0(x)h_{\mathbf{m}_g}^g$
0	0	0	0	0	$\dots$	0
1	1	0	0	0	$\dots$	0
2	1	1	0	0	$\dots$	0
3	1	1	1	0	$\dots$	0
$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\ddots$	$\vdots$
$\mathbf{m}_g$	1	1	1	1	$\dots$	1

Journal of Theoretical Biology 270 (2011) 177–184

Mapping multivalued onto Boolean dynamics

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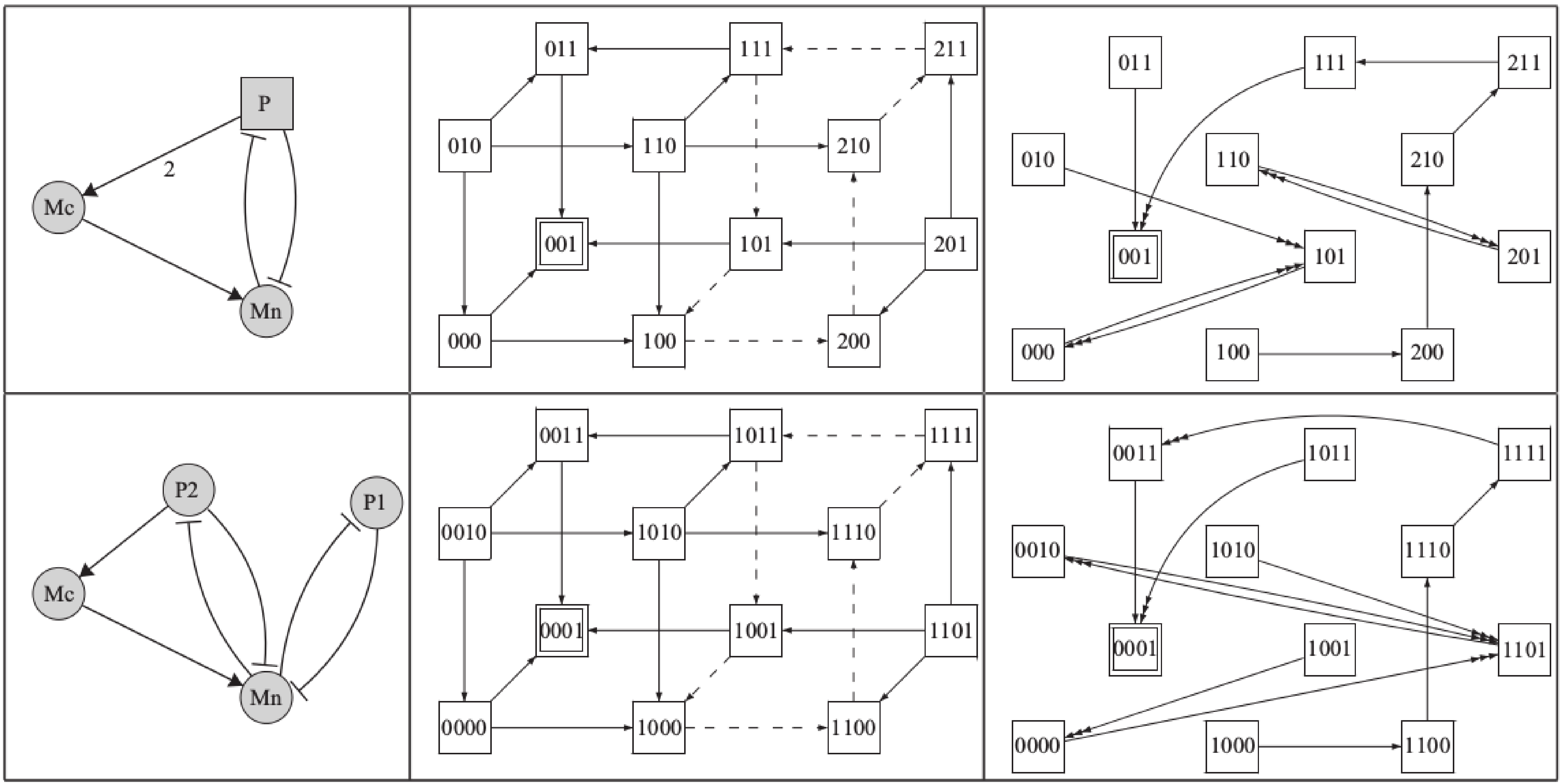
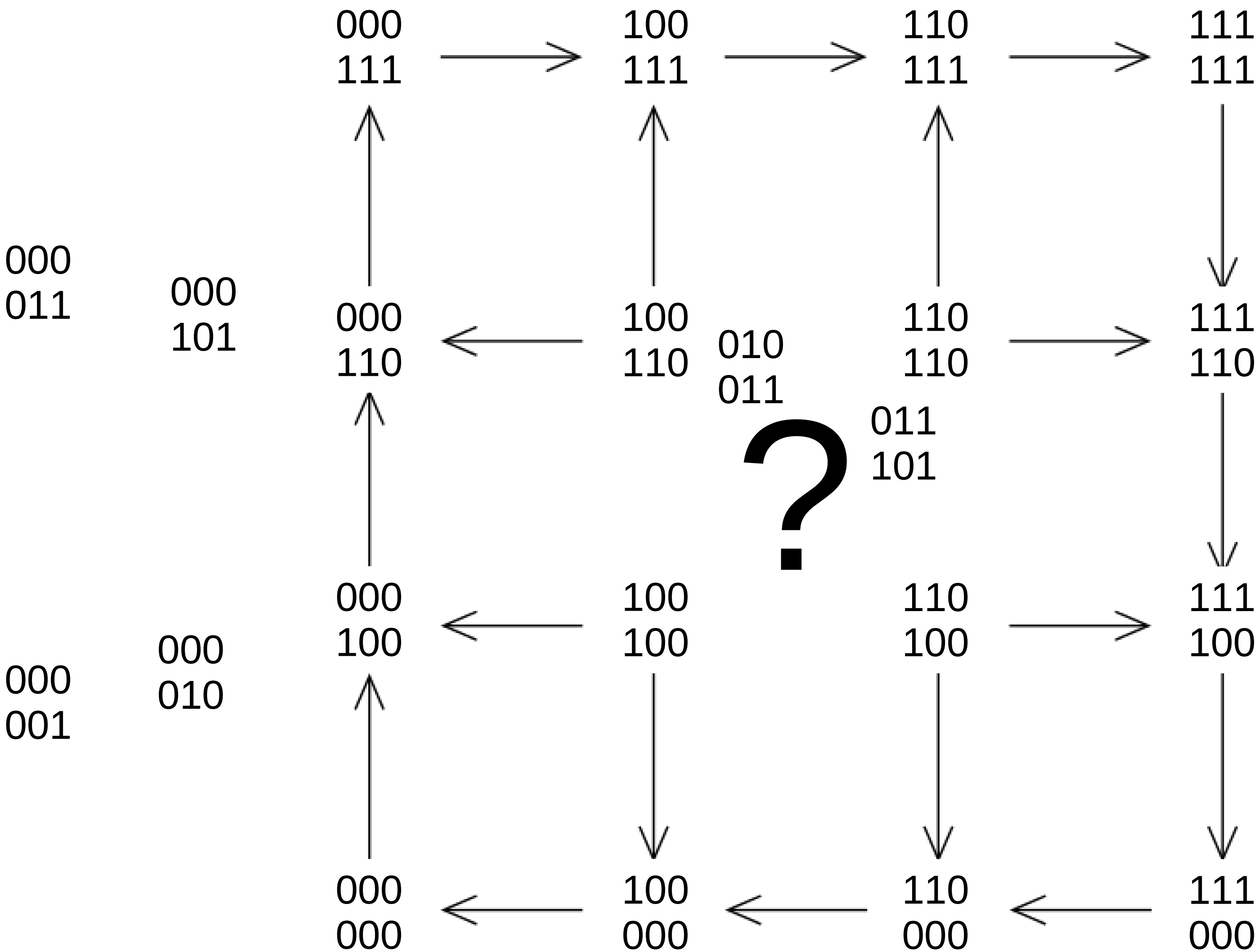


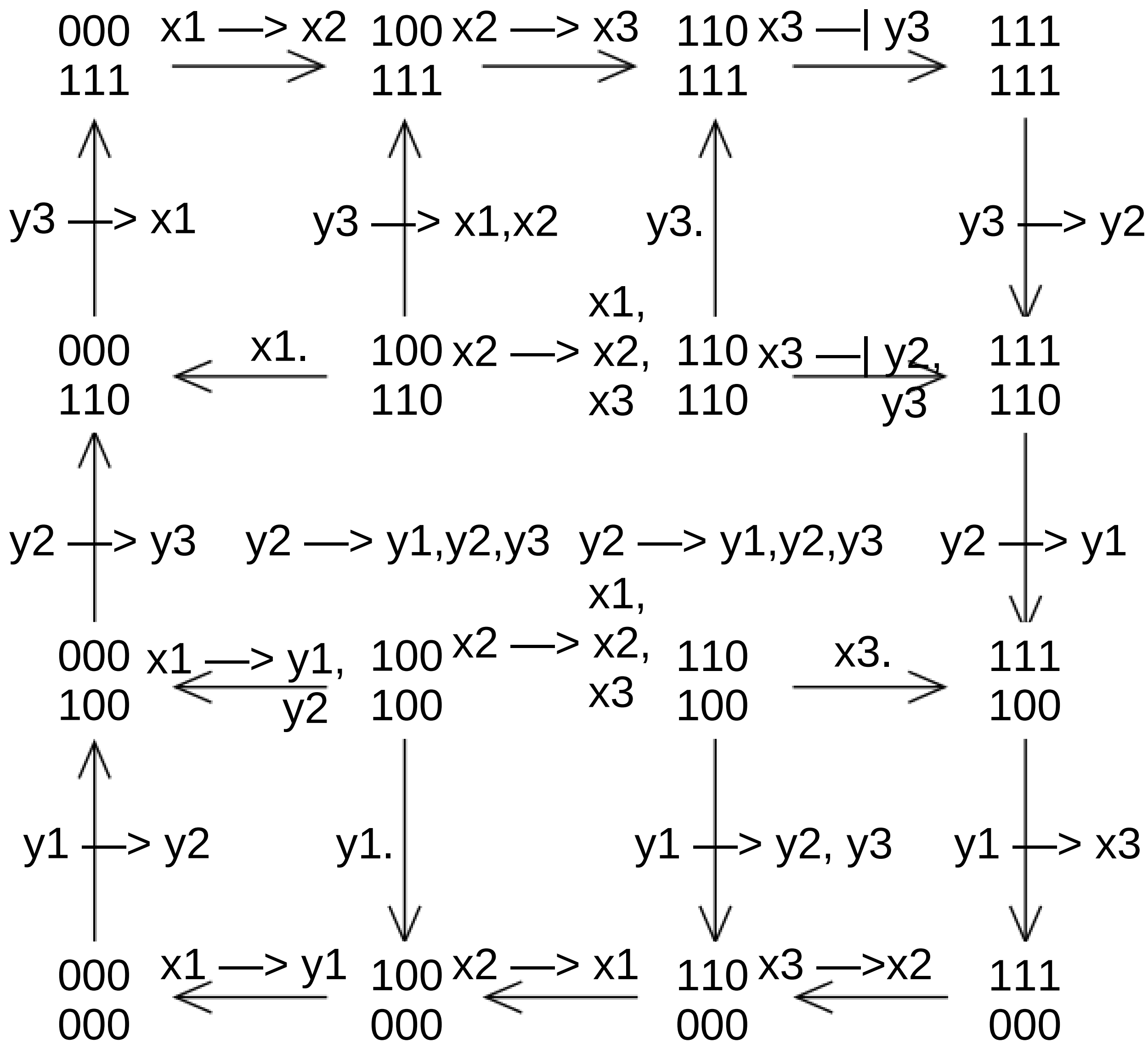
Family of models

x1x2x3
y1y2y3



Within the admissible region

x1x2x3
y1y2y3

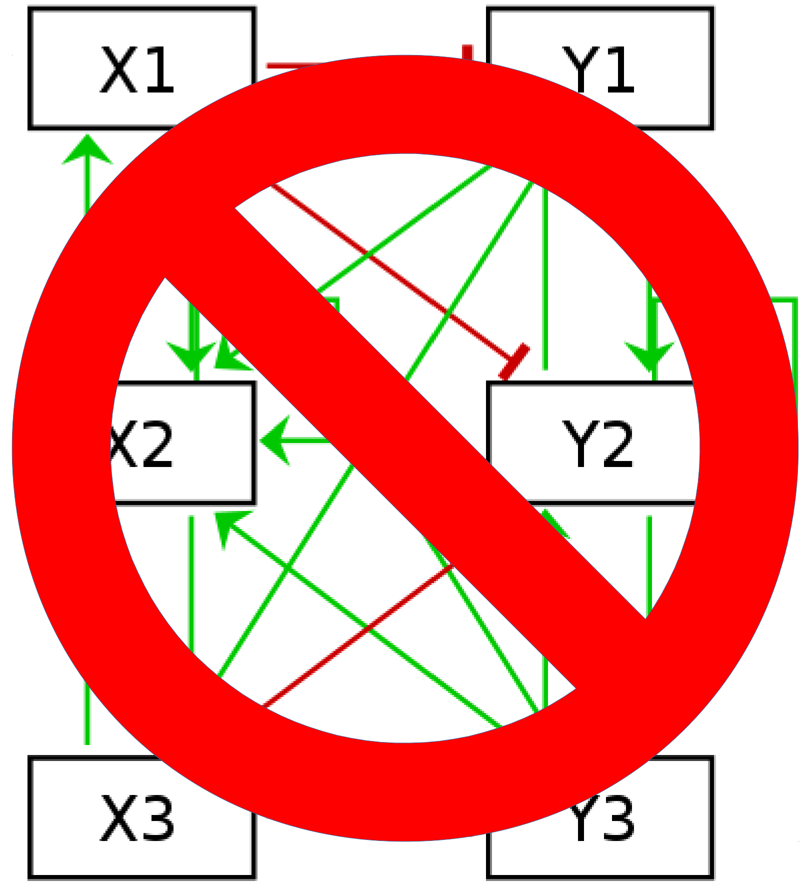


x1x2x3
y1y2y3

Simplest rules?

x1 —> x2　　x2 —> x3　　x3 —| y3

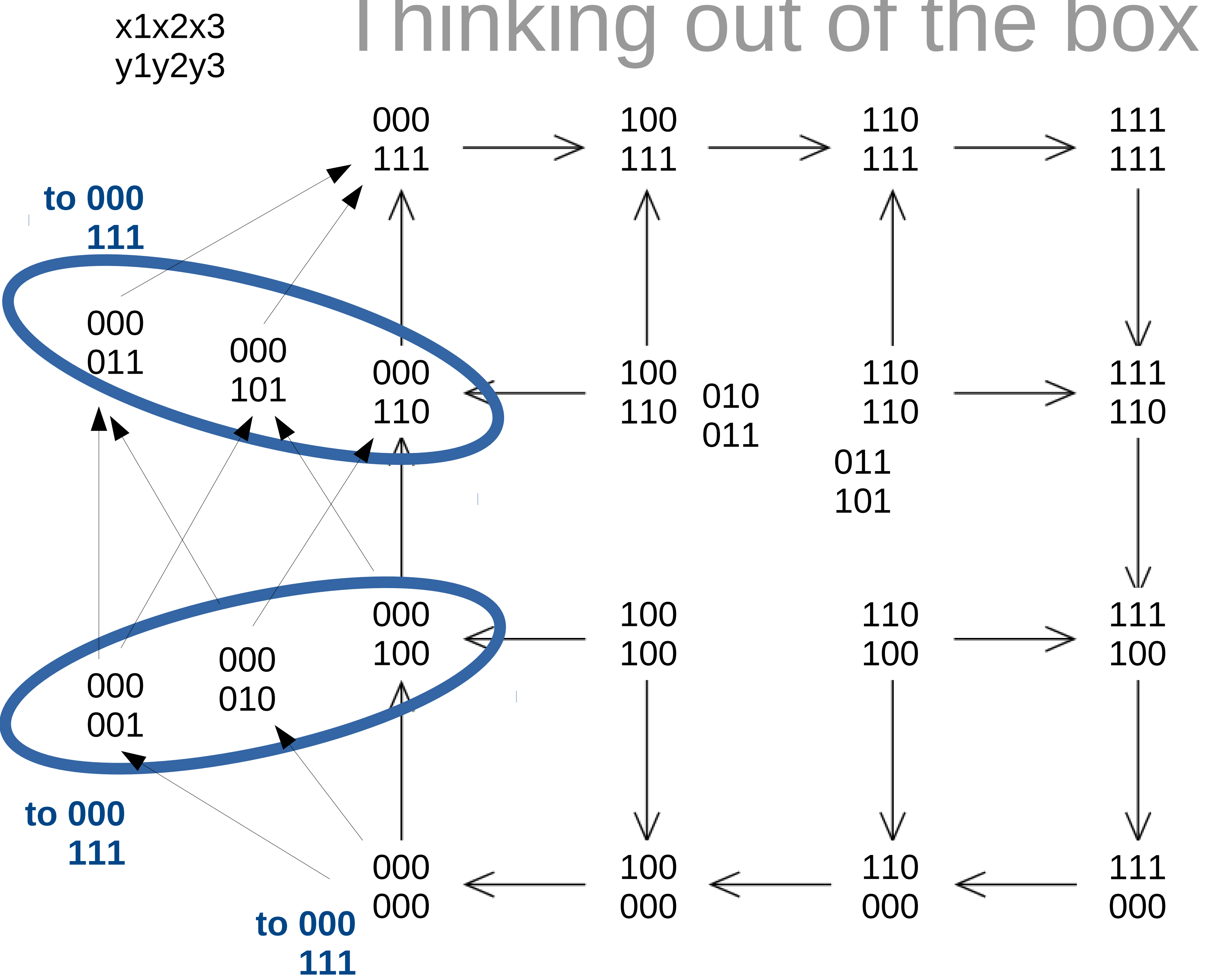
y3 —> x
y2 —> y
x:
y1 —> y



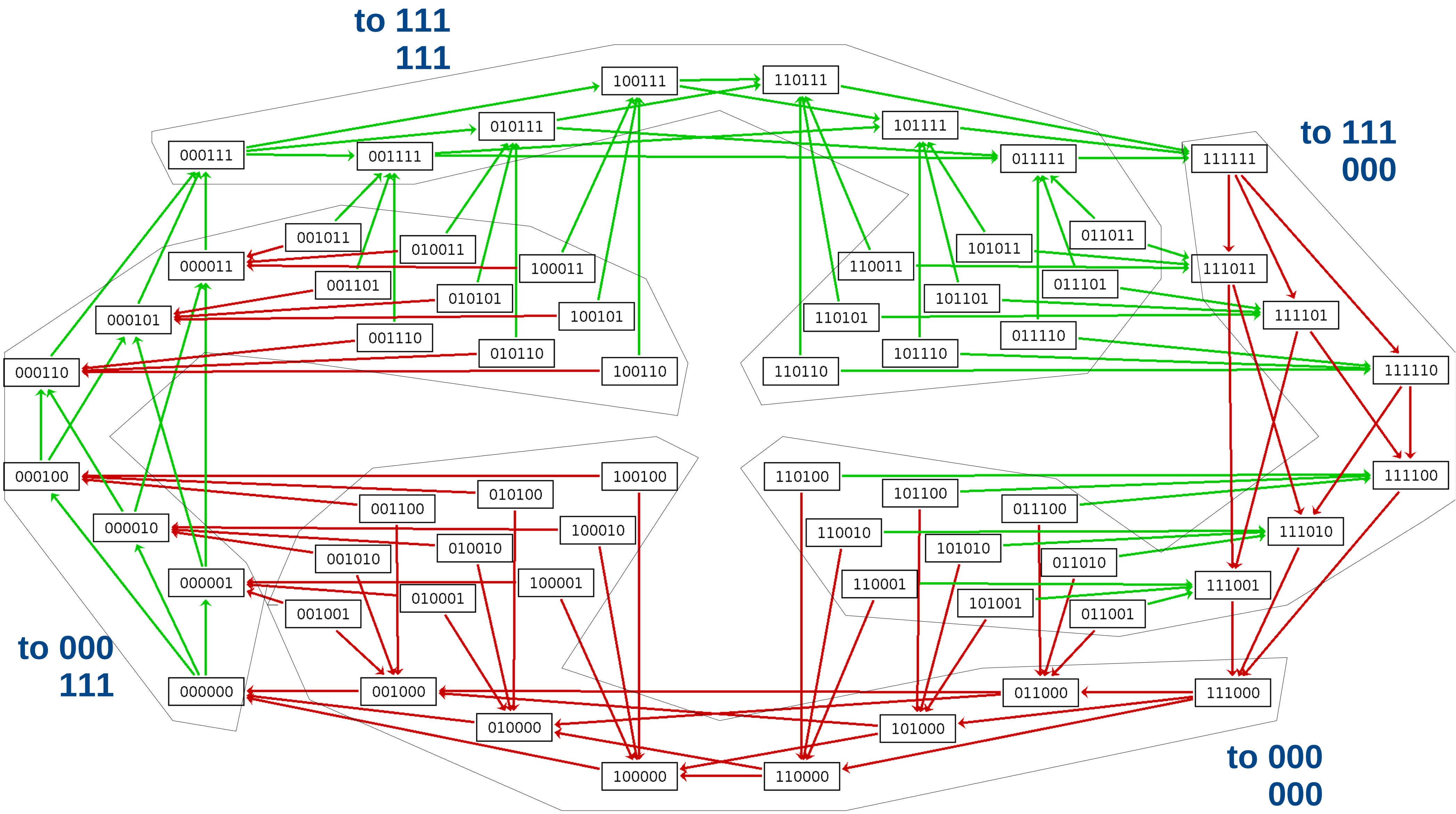
3 —> y2
—> y1
. —> x3

x1 —> y1　　x2 —> x1　　x3 —>x2

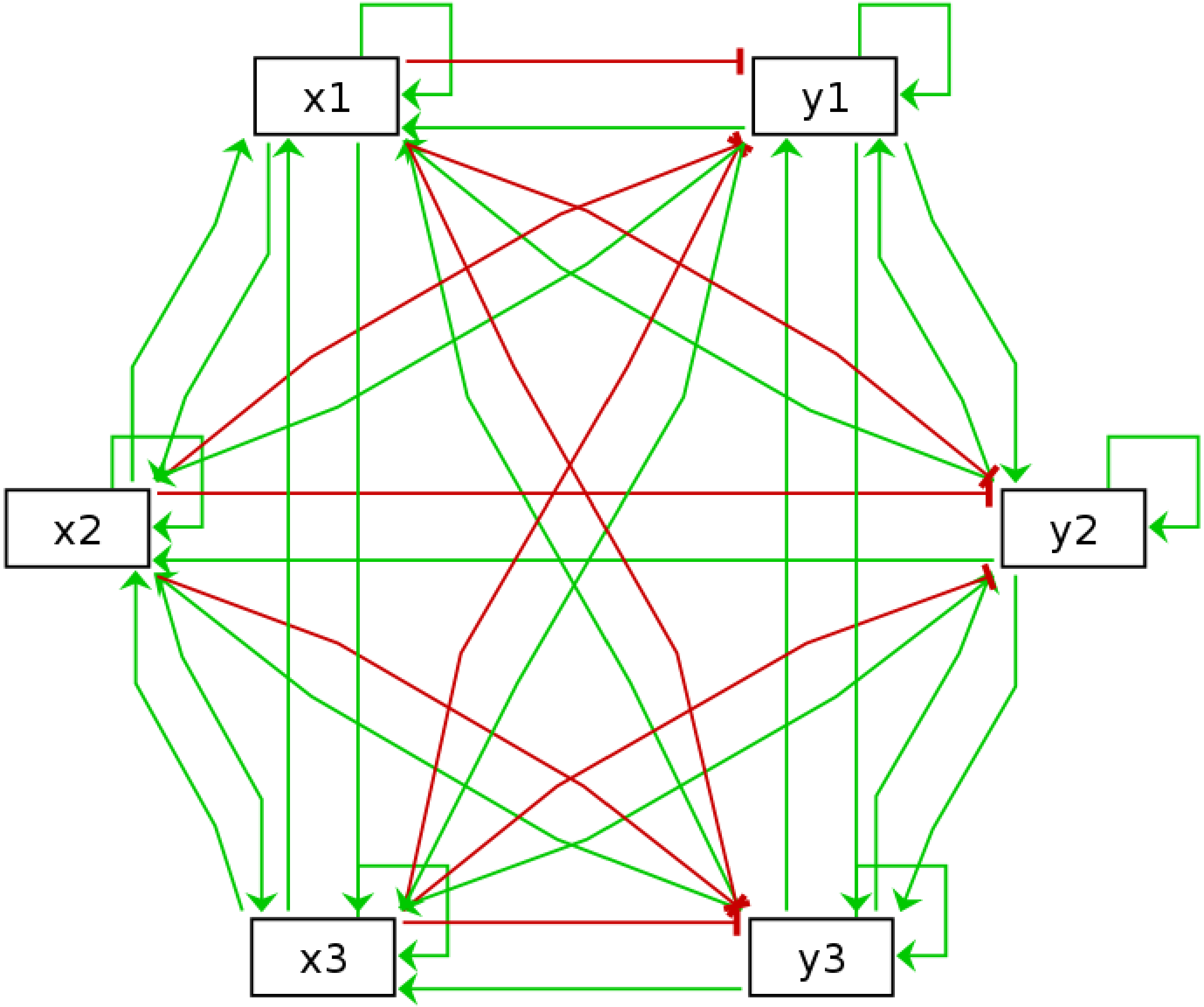
Thinking out of the box



Boolean model, sustained oscillations

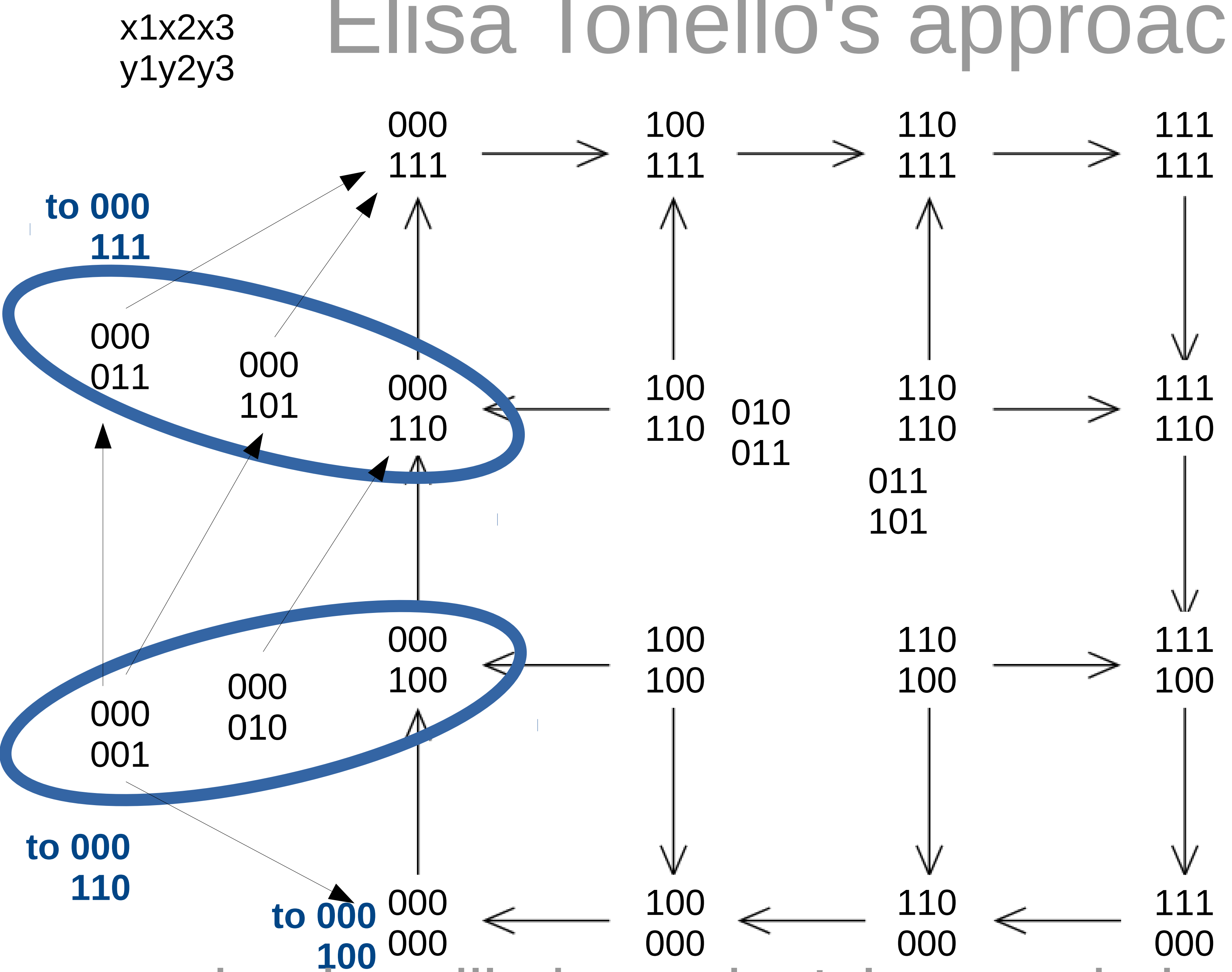


no negative circuit



x1
y1
x2
y2
x3
y3

Elisa Tonello's approach



sustained oscillations, don't leave admissible region

no negative circuit

Conclusion

A circuit-preserving mapping from multilevel to Boolean dynamics (Adrien Fauré, Shizuo Kaji)

On the conversion of multivalued gene regulatory networks to Boolean dynamics (Elisa Tonello)

Local negative circuits NOT necessary for **sustained oscillations**

Find a definition that satisfies Thomas' conjectures?