Logic-Based Modeling in Systems Biology

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DFG Research Center Matheon
Mathematics for key technologies

Outline

I. Systems biology

II. Logic modeling of regulatory networks

   A. Boolean logic

   B. Multi-valued logic

III. Logical analysis of network dynamics

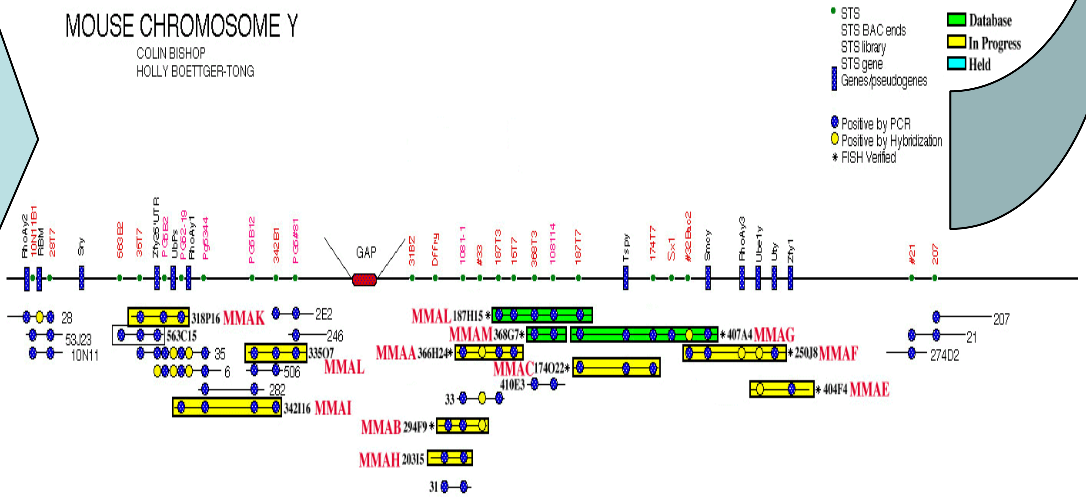
IV. Application: Bio-Logic

I. Systems biology

Systems biology

Molecular biology

Systems biology



Very active interdisciplinary research field

Various types of biological networks

- metabolic
- regulatory
- signaling, ...

Various modeling approaches

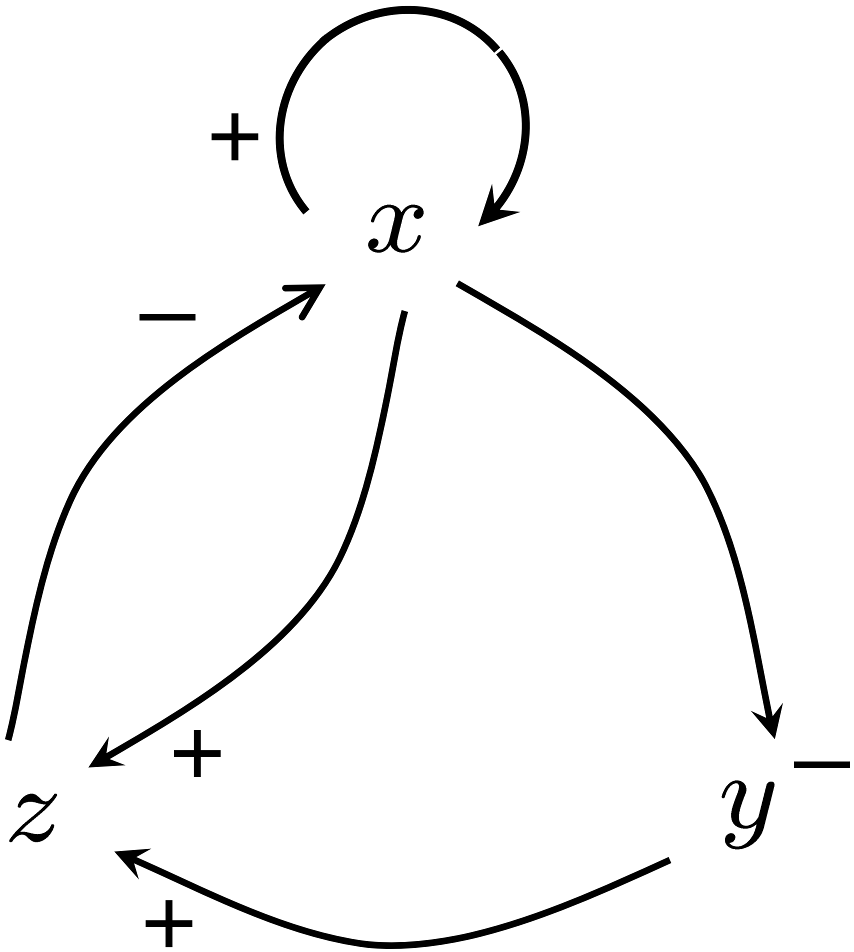
- continuous (ordinary/partial differential equations)
- stochastic (chemical master equation)
- discrete (logic, Petri nets, process calculi, ...)
- hybrid (continuous/stochastic, discrete/continuous)

Here: Logic-based discrete modeling of regulatory networks

1. Logic modeling of the network structure
   - Boolean logic
   - Multi-valued logic
2. Logical analysis of the dynamics
   - Non-determinism
   - Temporal logic
   - Model checking

II. Logic modeling of regulatory networks

A) Boolean logic



Nodes

$$X_1, \ldots, X_n \in \{0, 1\}$$

(component is active or not)

Arcs

Activation: $X_i \overset{+}{\longleftarrow} X_j$

Inhibition: $X_i \overset{-}{\longleftarrow} X_j$

Sugita 61, Kauffman 69

1. Boolean variables $X_1, \ldots, X_n \in \{0, 1\}$
2. Boolean mapping $F : \{0, 1\}^n \to \{0, 1\}^n$

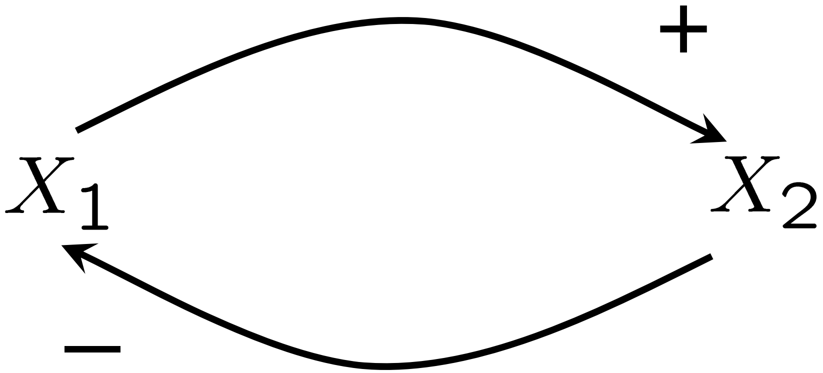
$F_i(X_1,\ldots,X_n)$ describes how the next state of X_i depends on the current state of $(X_1,\ldots,X_n)$.

$$X_i^{\to} = F_i(X_1, \ldots, X_n)$$

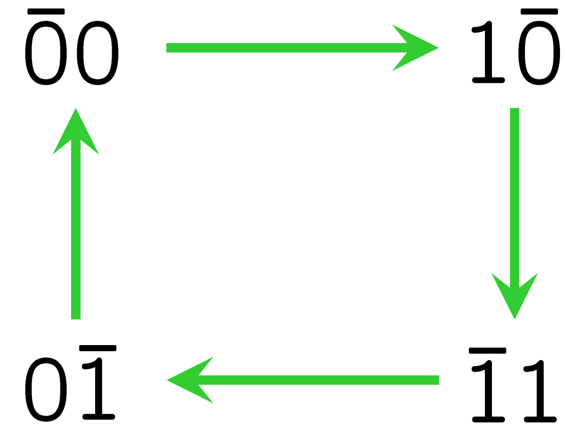
⇨ discrete dynamics

Two-element negative circuit

Interaction graph



State transition graph



$$X_1, X_2 \in \{0, 1\}$$

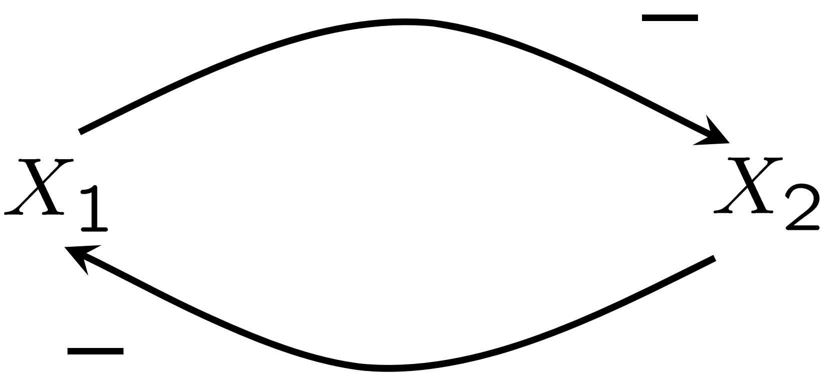
$$X_1^{\rightarrow} = F_1(X_1, X_2) = \neg X_2$$

$$X_2^{\rightarrow} = F_2(X_1, X_2) = X_1$$

X_1	X_2	$X_1^{\rightarrow}$	$X_2^{\rightarrow}$
0	0	1	0
0	1	0	0
1	0	1	1
1	1	0	1

Two-element positive circuit

Interaction graph



$$X_1, X_2 \in \{0, 1\}$$

$$X_{\overrightarrow{1}} = F_1(X_1, X_2) = \neg X_2$$

$$X_{\overrightarrow{2}} = F_2(X_1, X_2) = \neg X_1$$

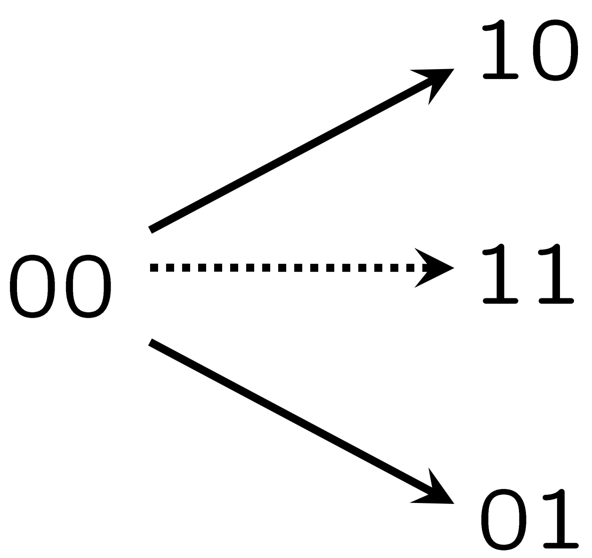
X_1	X_2	$X_{\overrightarrow{1}}$	$X_{\overrightarrow{2}}$
0	0	1	1
0	1	0	1
1	0	1	0
1	1	0	0

Synchronous vs. asynchronous

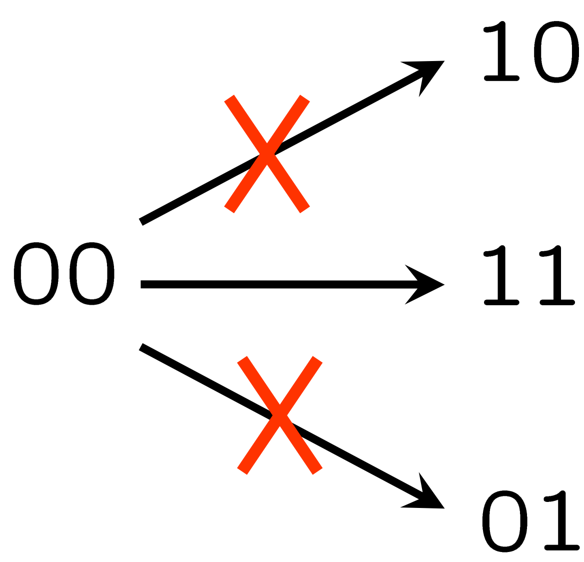
$$(X_1, X_2) = (0,0), (X_1^{\rightarrow}, X_2^{\rightarrow}) = (1,1)$$

Thomas´73: Update only one variable at a time.

Nondeterminism: Several successor states possible



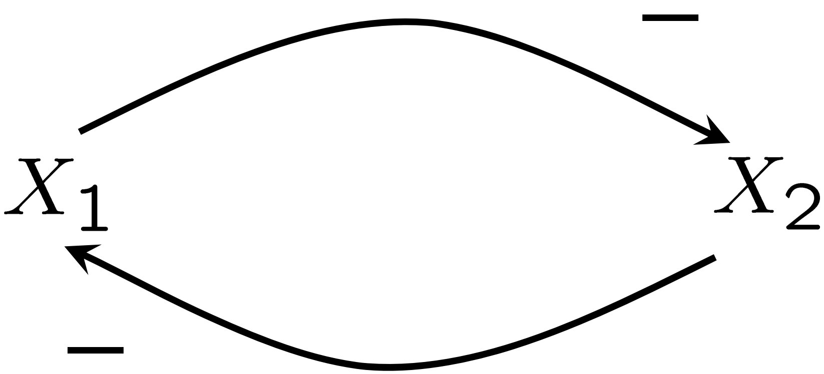
asynchronous



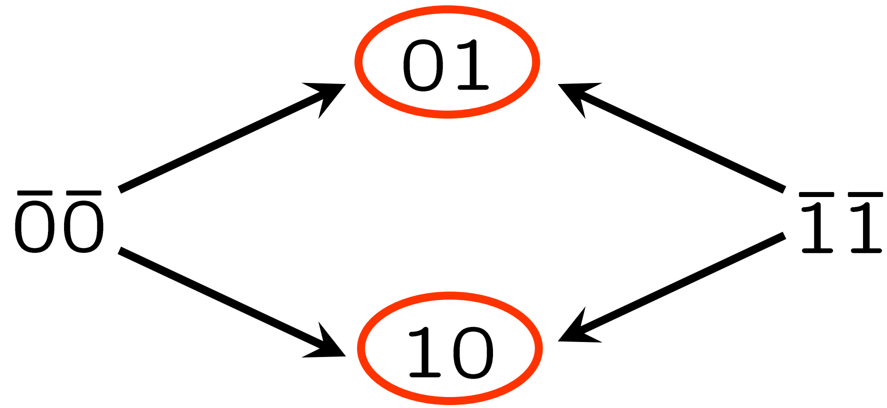
synchronous

Two-element positive circuit

Interaction graph



State transition graph



$$X_1, X_2 \in \{0, 1\}$$

$$X_1^{\rightarrow} = F_1(X_1, X_2) = \neg X_2$$

$$X_2^{\rightarrow} = F_2(X_1, X_2) = \neg X_1$$

X_1	X_2	$X_1^{\rightarrow}$	$X_2^{\rightarrow}$
0	0	1	1
0	1	0	1
1	0	1	0
1	1	0	0

II. Logic modeling of regulatory networks

B) Multi-valued logic

Thresholds and activity levels

Thomas/Snoussi 88

If component j acts on n_j other components

(up to) n_j thresholds: $X_j \in D_j = \{0, \ldots, n_j\}$

$X_j = k$: activity level of component j is above the k-th threshold and below the (k+1)-th.

discrete update function

$$F : D_1 \times \ldots \times D_n \to D_1 \times \ldots \times D_n$$

$$\overrightarrow{X_i} = F_i(X_1, \ldots, X_n) = F_i(X, \mathbf{K})$$

with discrete parameter vector $\mathbf{K}$.

State

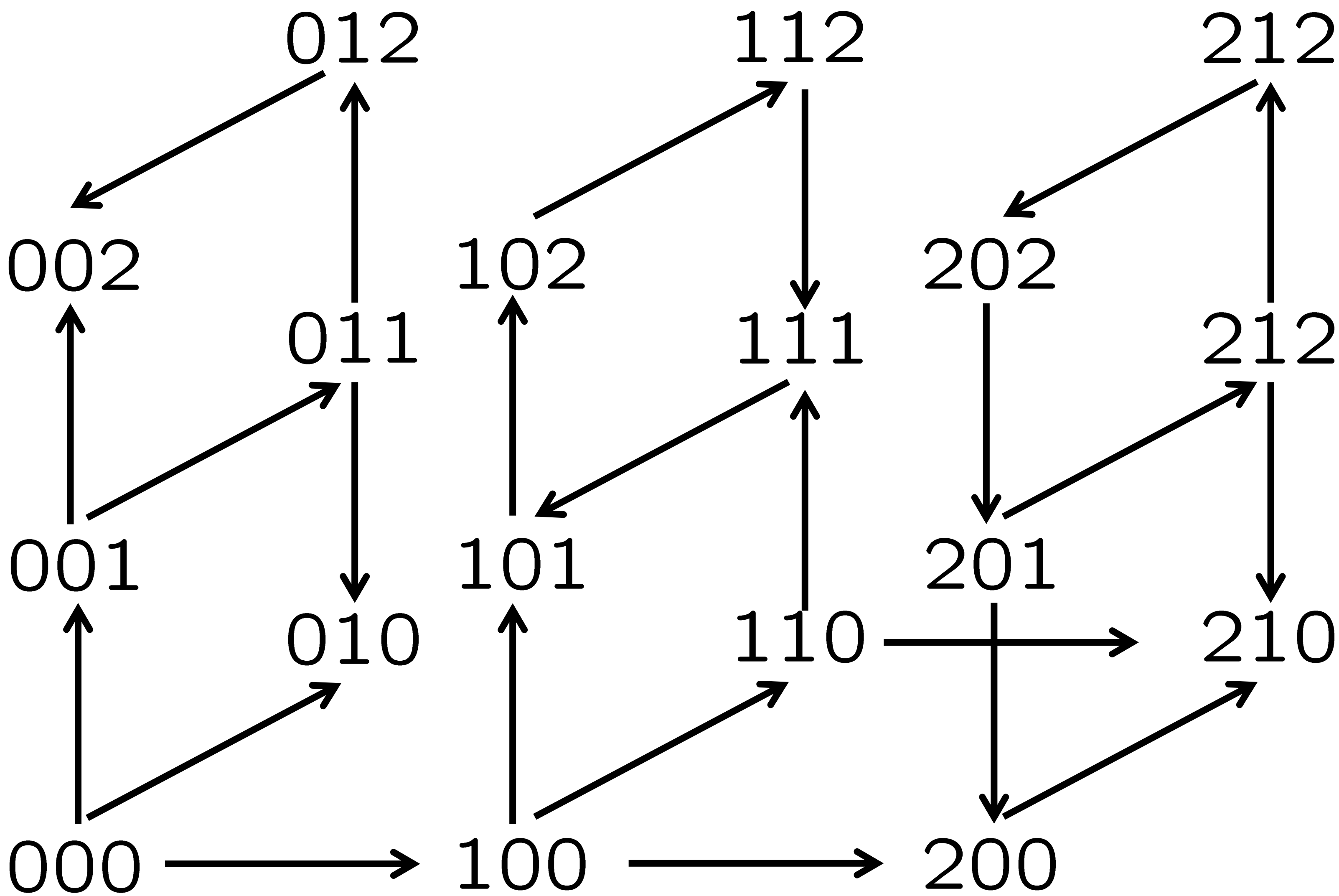
$$X = (X_1, \ldots, X_n),\ X_i \in \{0, \ldots, n_i\}$$

State transitions

$$(X_1, \ldots, X_n) \longrightarrow (X_1, \ldots, X_i \pm 1, \ldots, X_n)$$

if $X_i^{\rightarrow} > X_i$ resp. $X_i^{\rightarrow} < X_i$

⇒ discrete non-deterministic dynamics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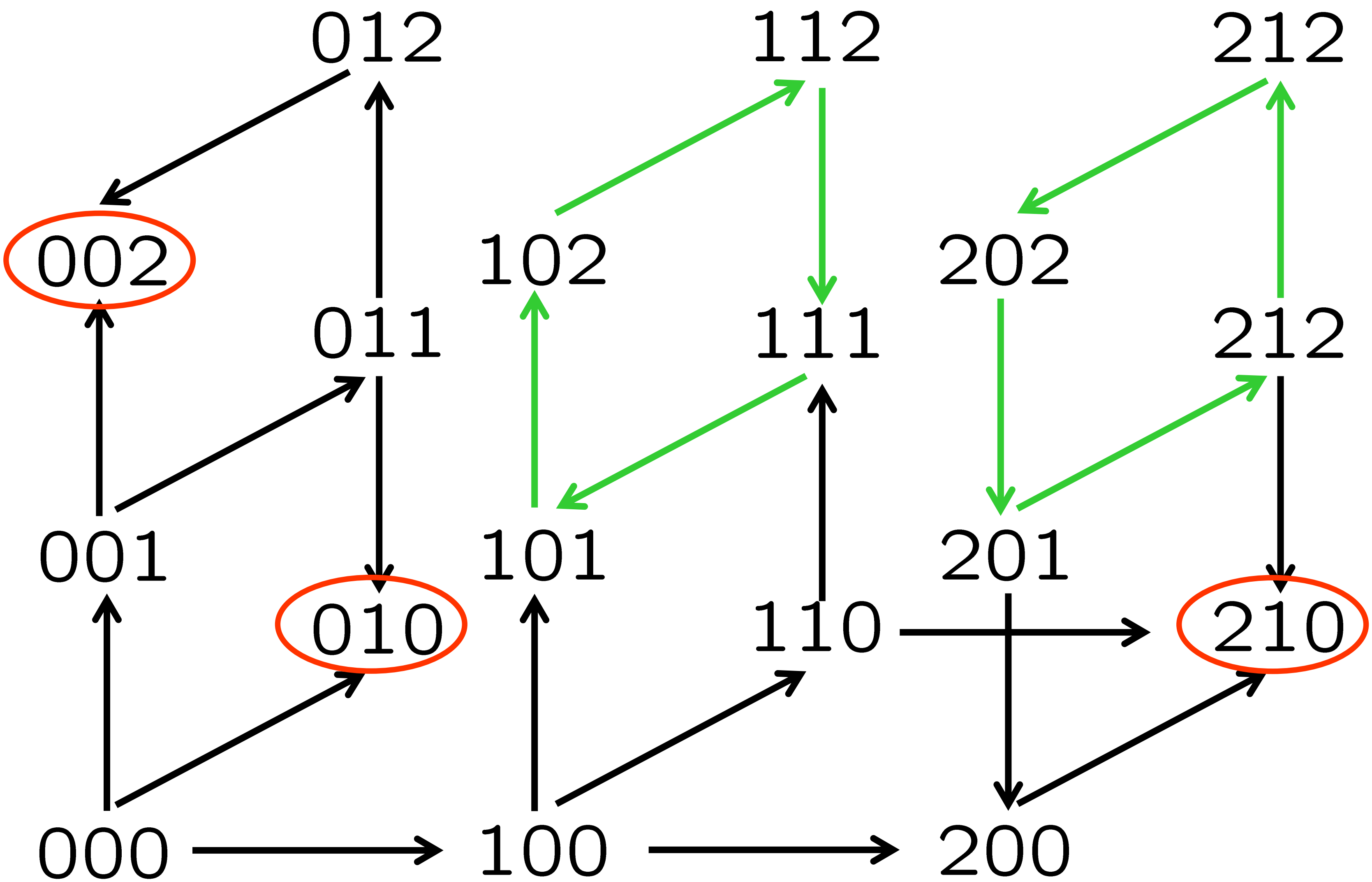
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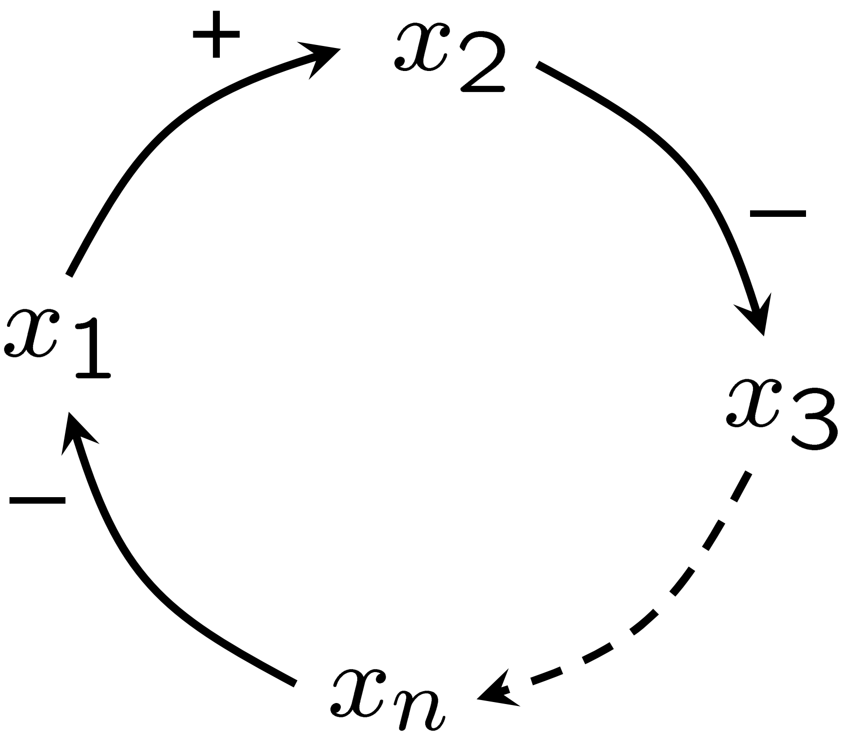
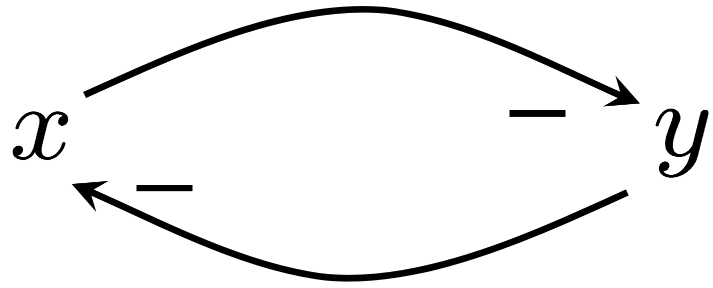
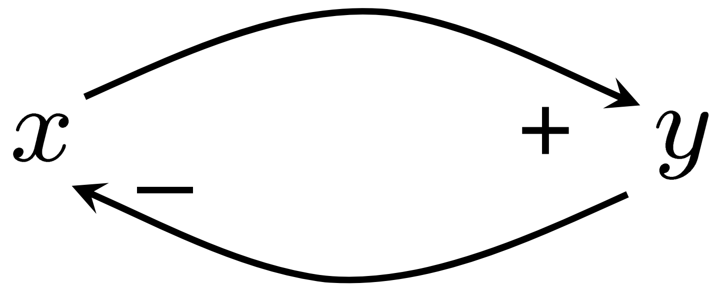




Positive 2-circuit



Negative 2-circuit

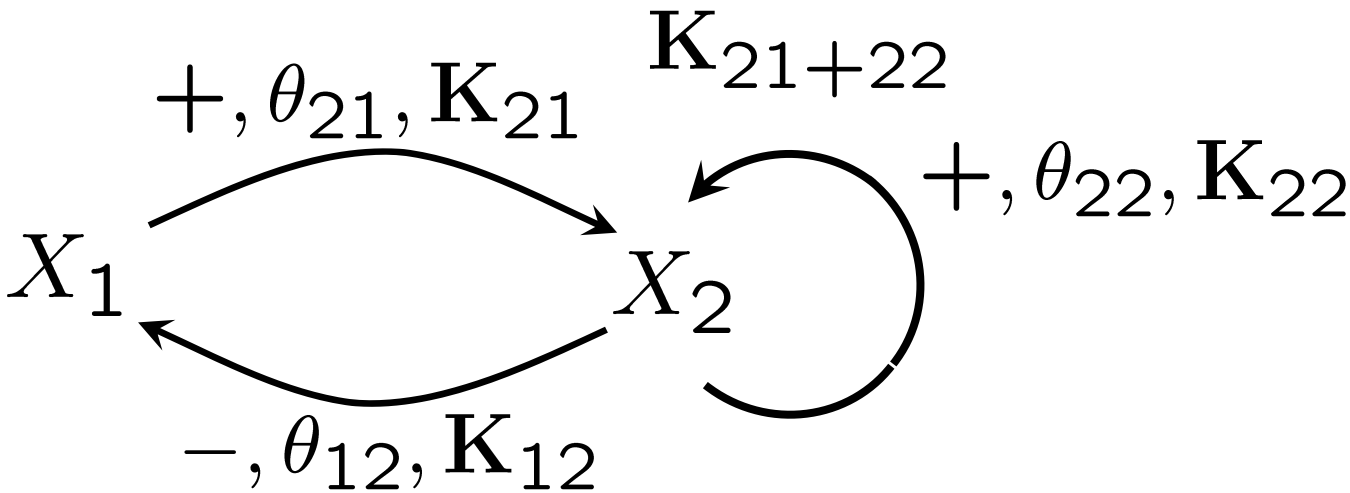
Sign of circuit =
Product of signs of arcs

Thomas´81

A positive circuit in the interaction graph is a necessary condition for multistationarity.

A negative circuit in the interaction graph is a necessary condition for stable periodic behavior.

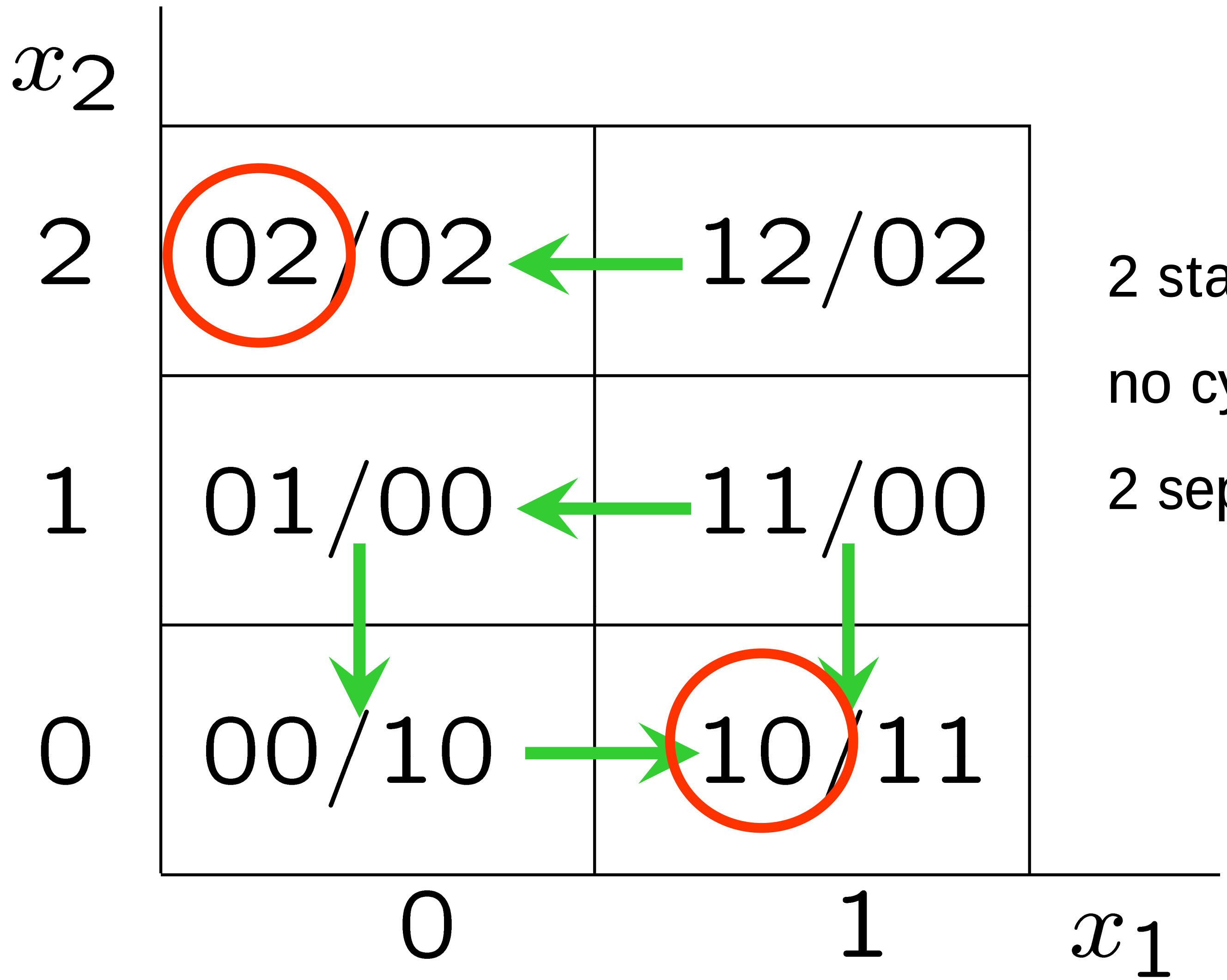
[Proofs exist in various scenarios.]



- $X_1 \in \{0,1\}$
- $X_2 \in \{0,1,2\}$
- Assume $\theta_{12} < \theta_{22}$, i.e., when activated, X_2 acts first on X_1, then on itself.

X_1	X_2	$X_1^{\rightarrow}$	$X_2^{\rightarrow}$
0	0	$\mathbf{K}_{12}$	0
0	1	0	0
0	2	0	$\mathbf{K}_{22}$
1	0	$\mathbf{K}_{12}$	$\mathbf{K}_{21}$
1	1	0	$\mathbf{K}_{21}$
1	2	0	$\mathbf{K}_{21+22}$

$K_{12} = 1$, $K_{21} = 0$, $K_{22} = K_{21+22} = 2$

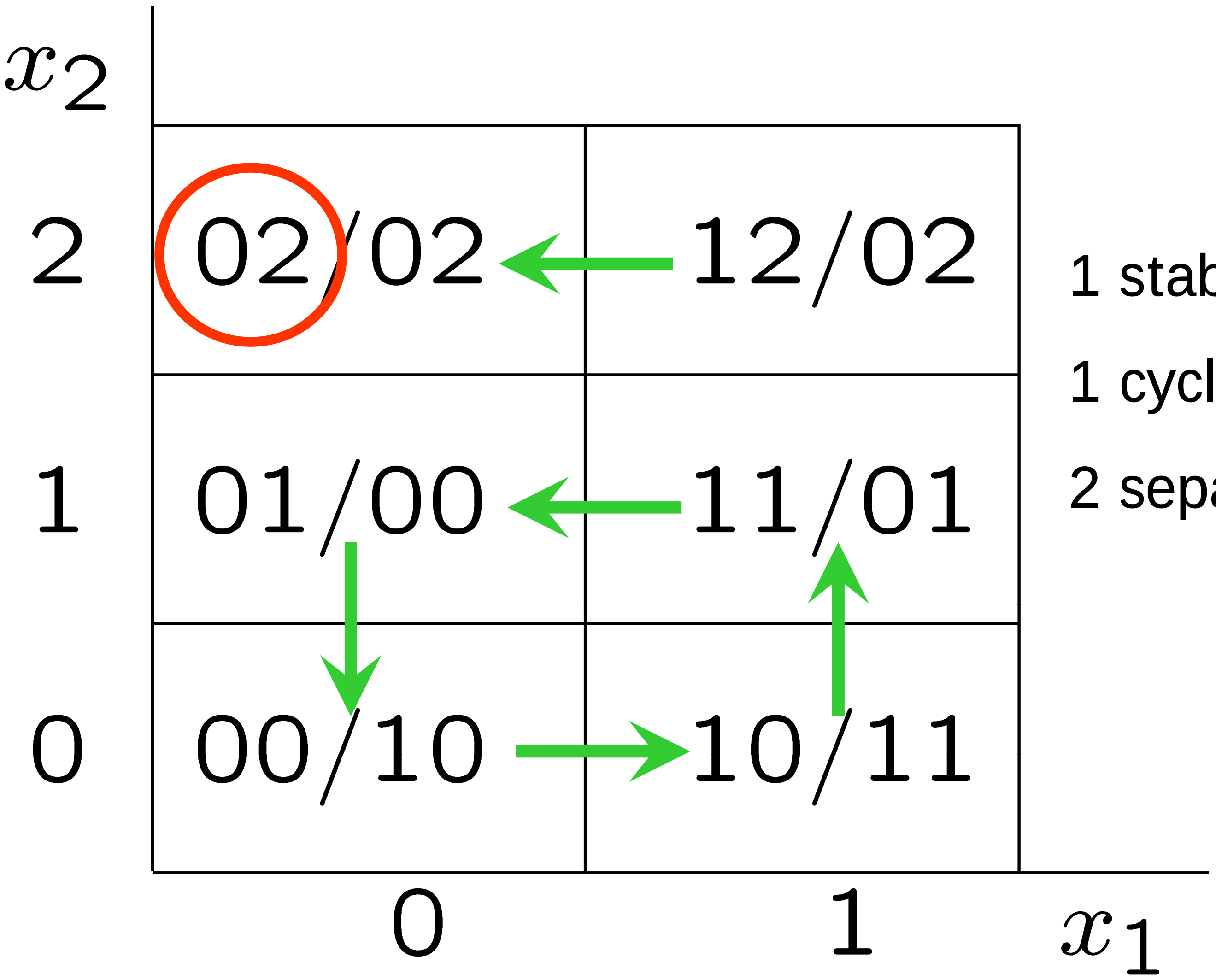


2 stable states

no cycle

2 separate domains

$K_{12}=1, K_{21} = 1, K_{22} = K_{21+22} = 2$

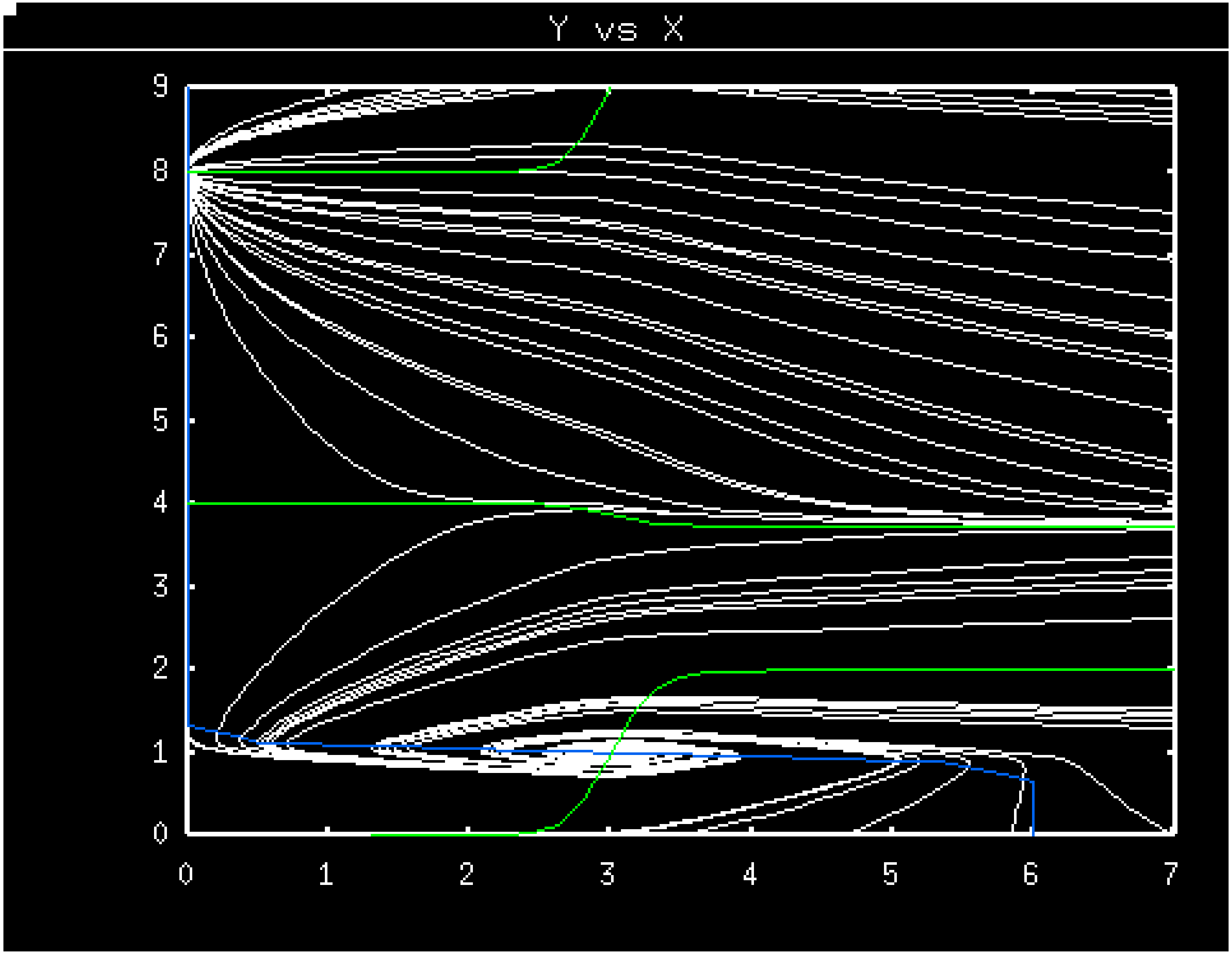


1 stable state

1 cycle

2 separate domains

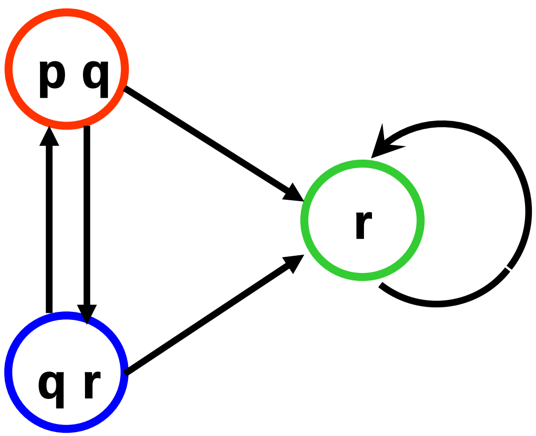
Continuous model



III. Logical analysis of the dynamics

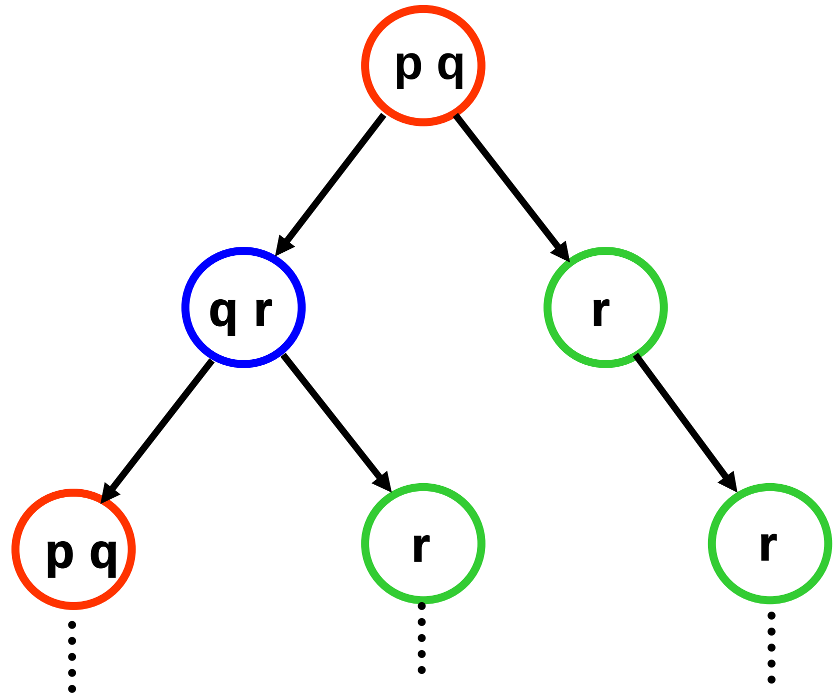
Clarke/Emerson and Sifakis 81

State transition graph
(Kripke model)



exponentially large

Infinite computation tree



⇒ check properties expressed in some temporal logic.

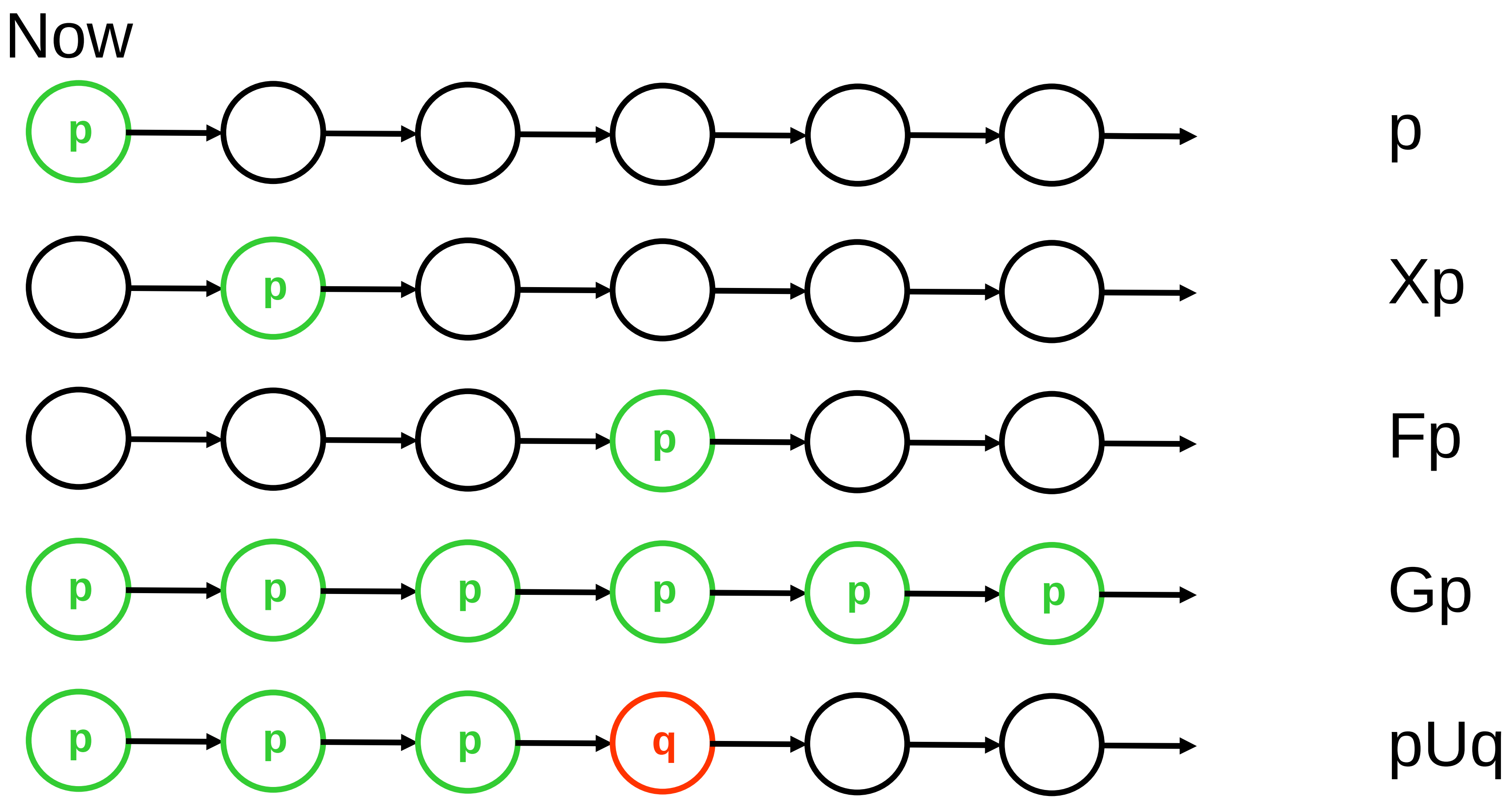
Atomic formulae : p, q, r, ..., e.g. $X_i = 1$

Linear time operators :

- X p : p holds next time
- F p : p holds sometimes in the future
- G p : p holds globally in the future
- p U q : p holds until q holds

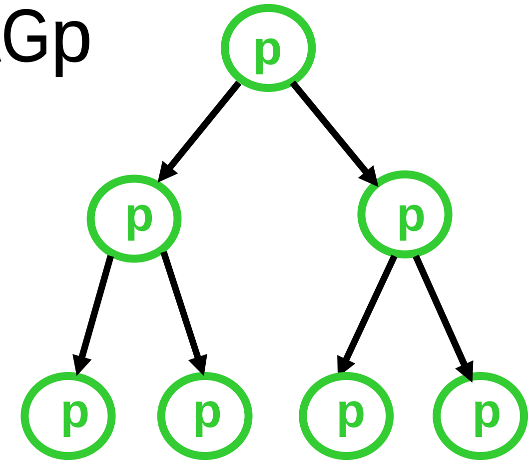
Path quantifiers :

- A : for every path
- E : there exists a path

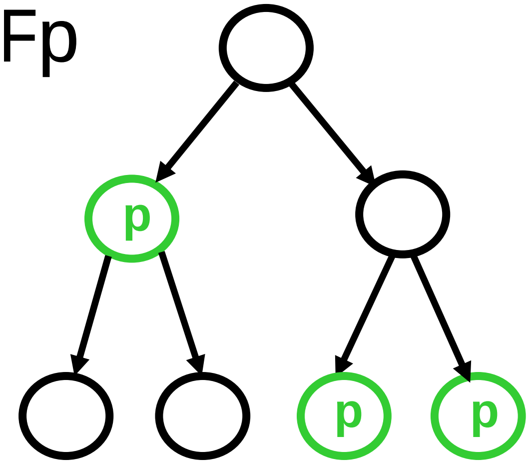

Now
p
p
Xp
p
Fp
p
Gp
p
p
p
p
p
p
pUq
p
p
p
q

Path quantifiers

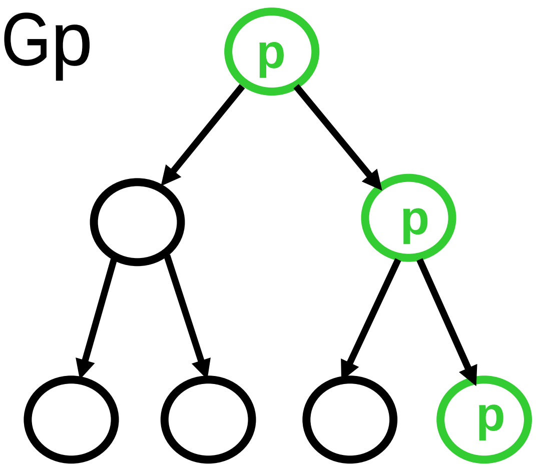
AGp



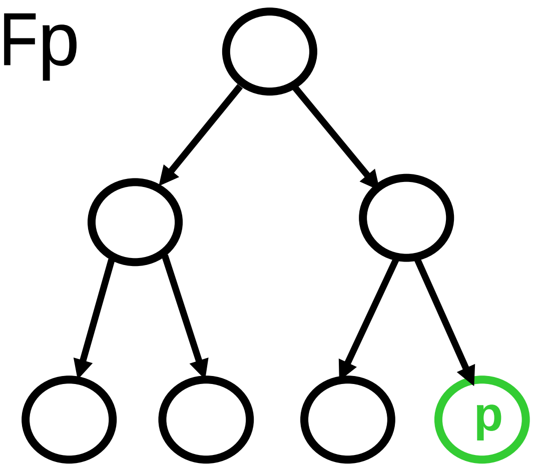
AFp



EGp



EFp



CTL model checking for regulatory networks

Bernot/Comet/Richard/Guespin 04

Input

- Interaction graph / state transition graph
- Temporal logic formula (CTL)

Output

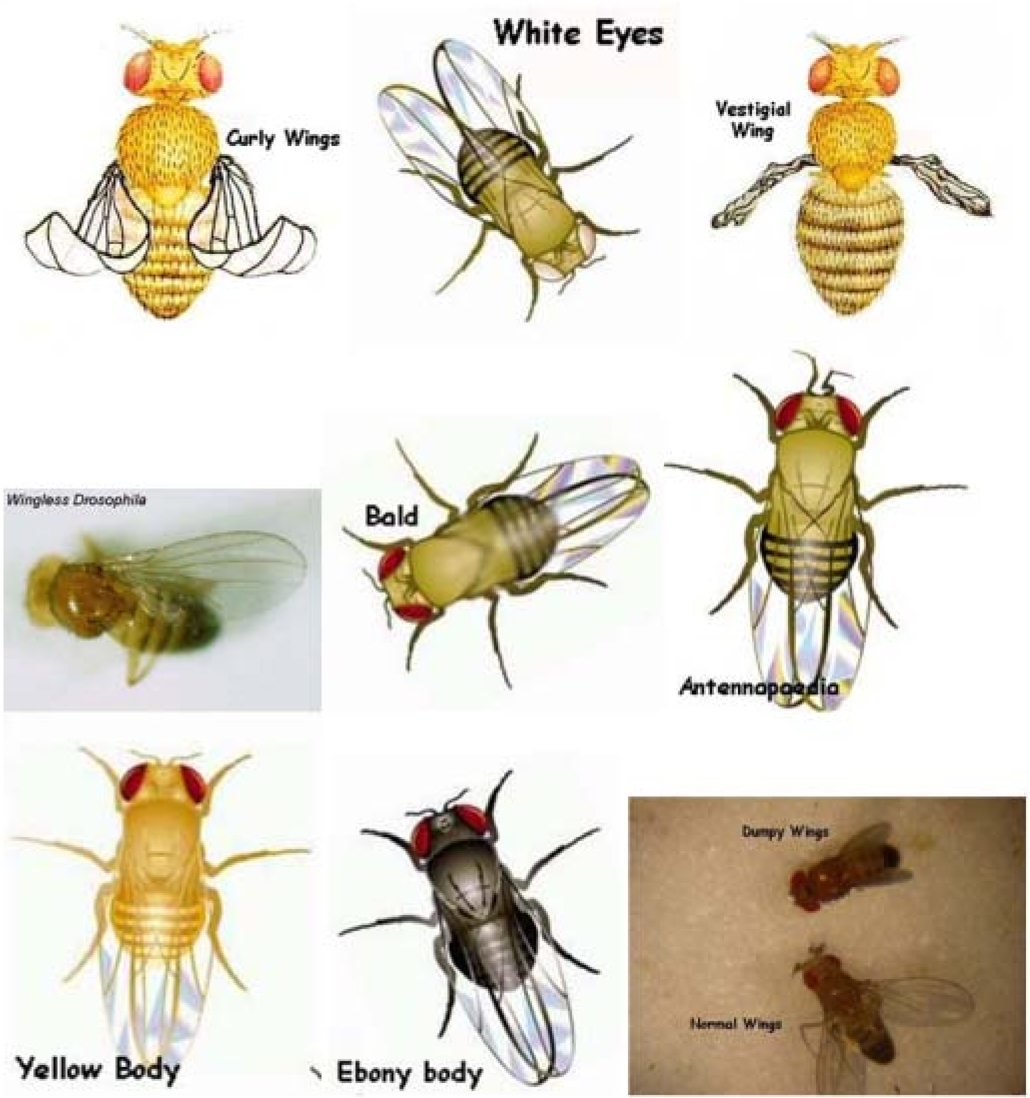
Set of states in which the formula is true

Example

$$(x = 0) \Rightarrow AG(\neg(x = 2))$$
$$(x = 2) \Rightarrow AX\,AF(x = 2)$$
$$\neg E(\neg(x = 2)\,U\,(x = 1))$$

Can also be used for network inference.

IV. Application: Bio-Logic



Source: www.chaosscience.org.uk

Understand the regulatory logic underlying developmental and other biological processes

Conclusion

- Molecular systems biology
- Logical modeling of regulatory structures
  - ❖ Boolean logic
  - ❖ Multi-valued logic
- Logical analysis of the dynamics
  - ❖ Non-determinism
  - ❖ Temporal logic
  - ❖ Model checking
- Bio-Logic