Constraint-based modeling in systems biology

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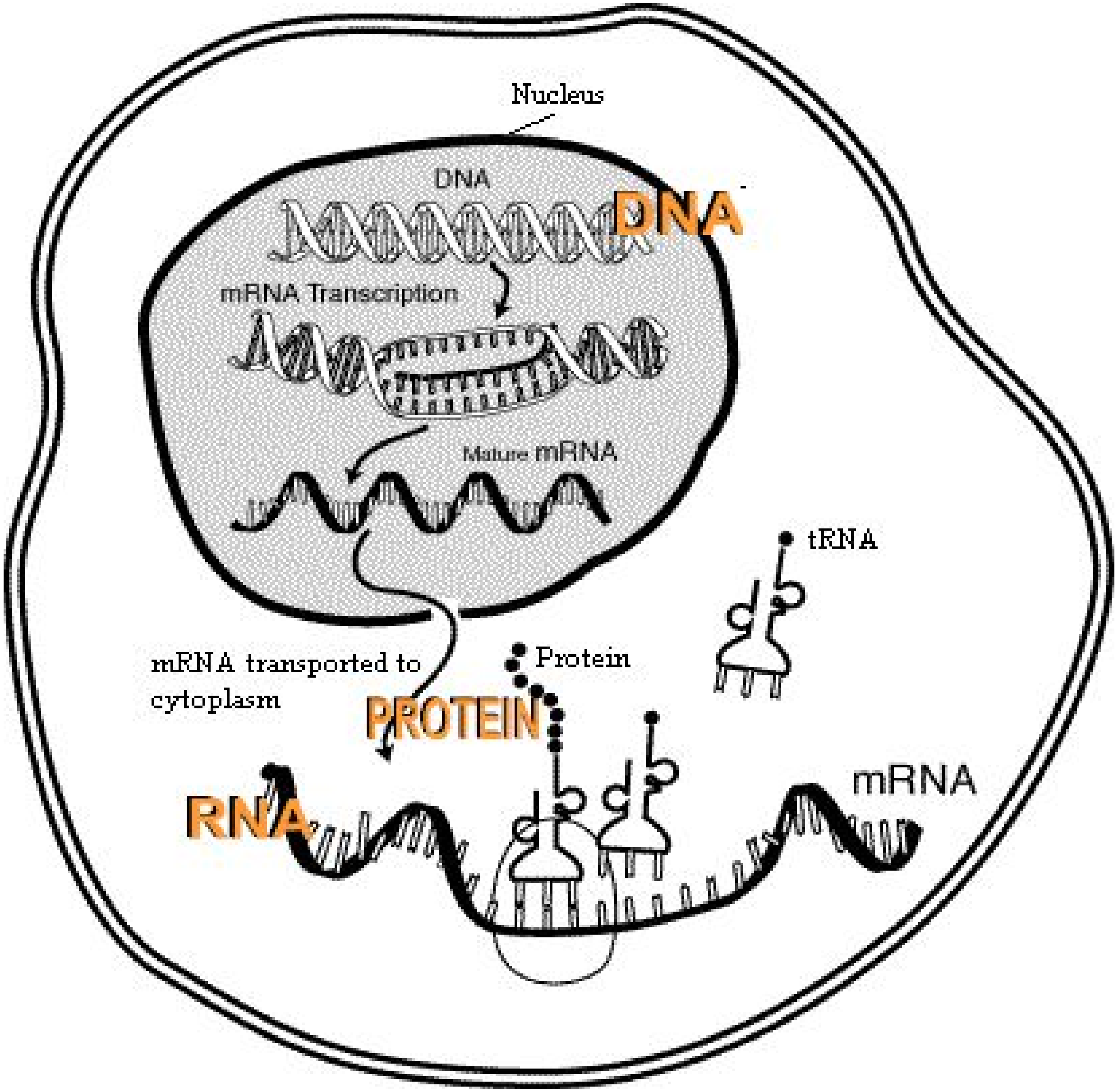
DFG Research Center Matheon
Mathematics for key technologies

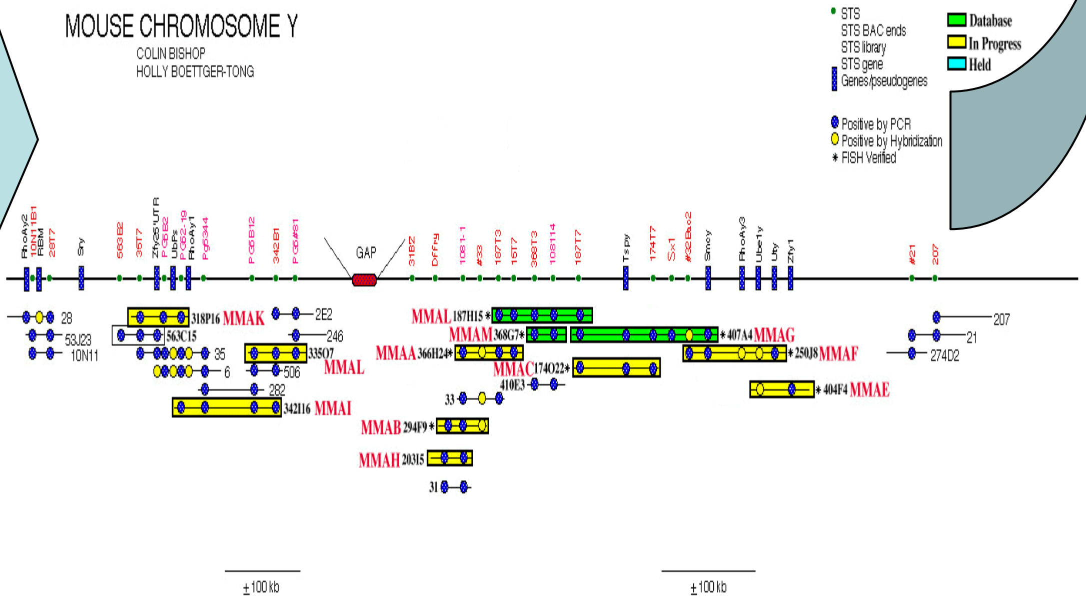
I. Systems biology
II. Constraint-based modeling
III. Regulatory networks: structure
IV. Regulatory networks: dynamics
V. Temporal logic and model checking
VI. Temporal constraints and time delays

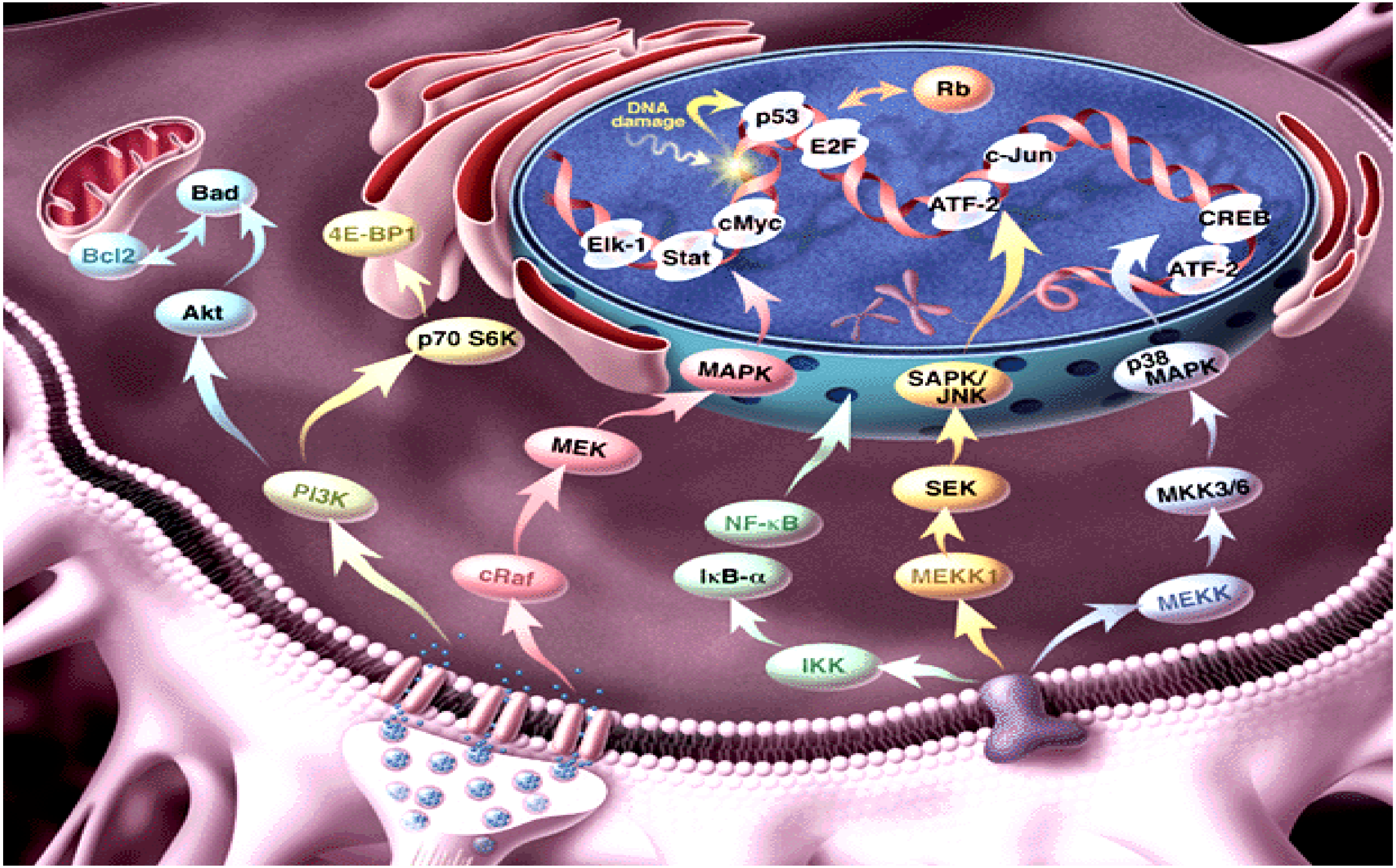
I. Systems biology


Nucleus
DNA
DNA
mRNA Transcription
Mature mRNA
tRNA
Protein
mRNA transported to cytoplasm
PROTEIN
RNA
mRNA

Molecular biology

Systems biology




Rb
DNA damage
p53
E2F
c-Jun
ATF-2
CREB
ATF-2
Elk-1
Stat
cMyc
Bad
Bcl2
4E-BP1
Akt
p70 S6K
MAPK
SAPK/ JNK
p38 MAPK
MEK
PI3K
SEK
MKK3/6
NF-κB
IκB-α
cRaf
MEKK1
MEKK
IKK

Various network types

- 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)

Traditional approach

- Kinetic modeling
- Deterministic or stochastic mathematical model
- Numerical simulation (ODE, Gillespie, ...)

- Requires detailed knowledge of the network (rate laws, kinetic parameters, ...)
- Often not available

II. Constraint-based modeling

Palsson, Nature Biotech.,2000

“ Because biological information is incomplete, it is necessary to take into account the fact that cells are subject to certain constraints that limit their possible behaviors. By imposing these constraints in a model, one can then determine what is possible and what is not, and determine how a cell is likely to behave, but never predict its behavior precisely.”

⇨ COBRA toolbox

Saraswat´89

Constraint system = system of inference with pieces of partial information

... in systems biology

Constraint-based modeling in systems biology

- State constraints on a biological network
  - ❖ structure/topology
  - ❖ dynamics
- Make inferences about the set of possible behaviors
  - ❖ non-determinism
- Forward + backward reasoning
  - ❖ structure $\rightsquigarrow$ dynamics
  - ❖ dynamics $\rightsquigarrow$ structure
- Formal reasoning vs. numerical simulation

Discrete modeling formalism of René Thomas (1973)

- Interaction graphs — Structure
- State transition graphs — Dynamics

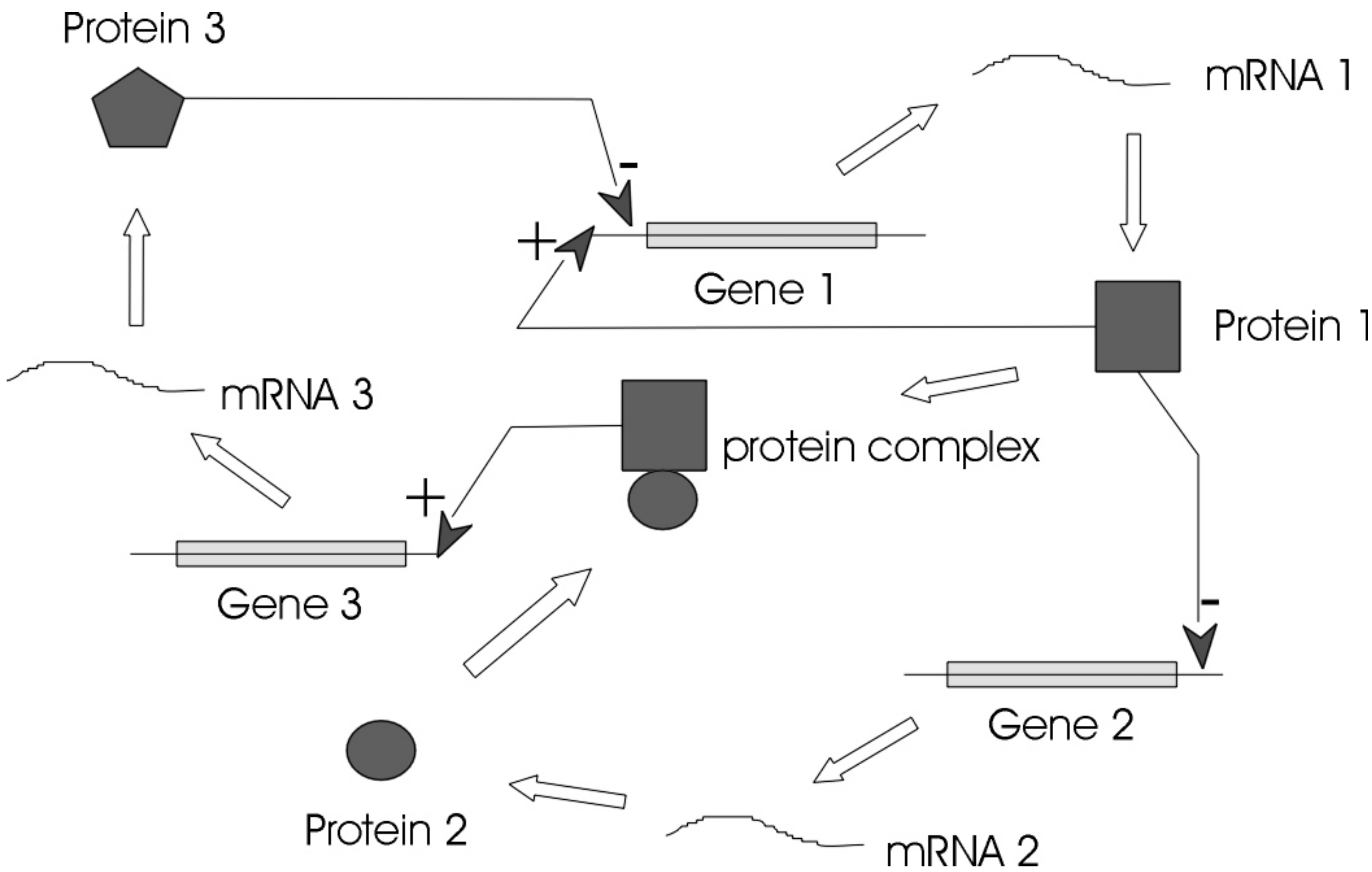
Constraint-based analysis of the dynamics

- Temporal logic
- Model checking — Formal reasoning

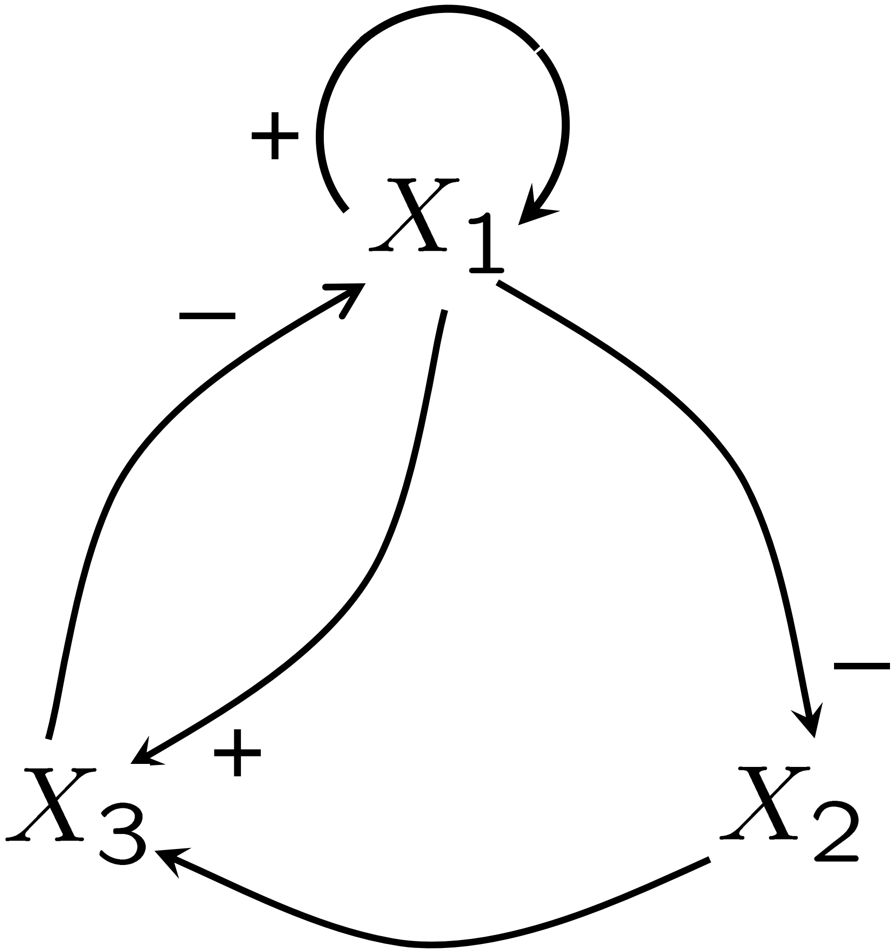
Adding time delays

- Temporal constraints
- Hybrid discrete-continuous modeling

III. Regulatory networks: structure



http://www.zaik.uni-koeln.de/AFS/



+
x_1
−
x_3
+
x_2
−

Regulatory components: Variables

$$X_1, \ldots, X_n$$

X_j represents activity level of component j.

Regulatory interactions: Activation/inhibition

$$X_i \xleftarrow{+} X_j \qquad X_i \xleftarrow{-} X_j$$

Component i is influenced by component j only if the activity level X_j is above a certain threshold θ_{ij}.

Thomas/Snoussi 88

If component j acts on n_j other components

⇒ (up to) n_j thresholds θ_{ij}:

$$X_j \in \{0, \ldots, n_j\}$$

$X_j = k$: activity level of component j is above

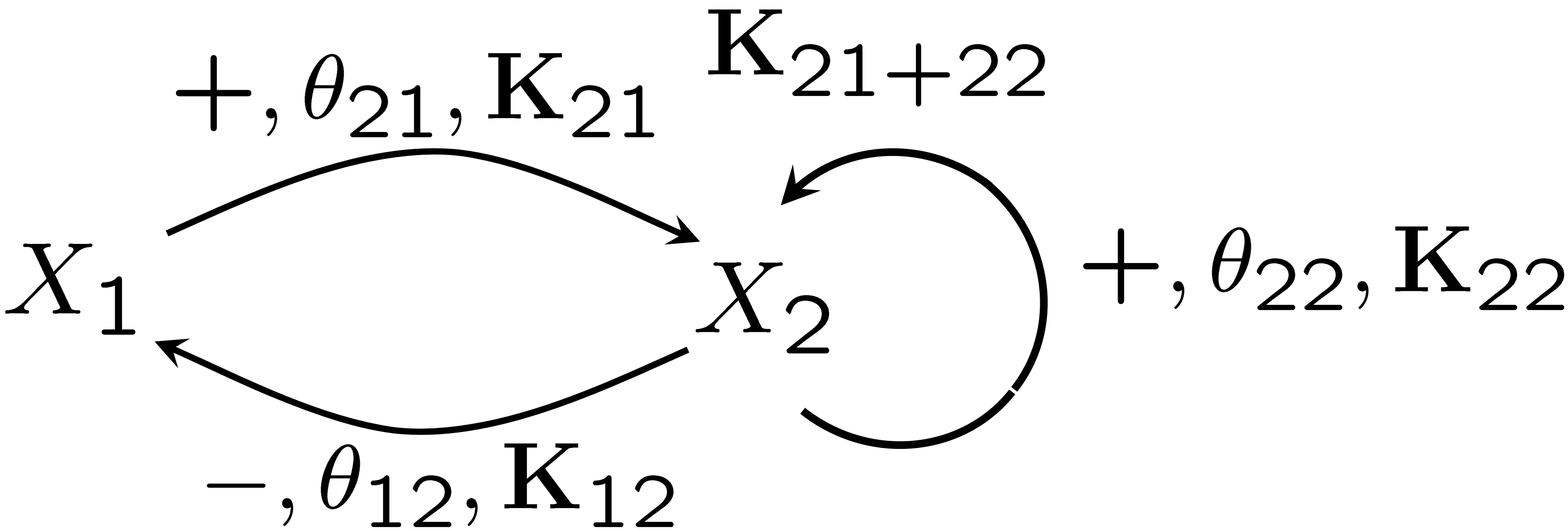
the k-th threshold and below the (k+1)-th.

$\mathbf{K}_{ij} \in \{0, \ldots, n_i\}$: weight given to the action on X_i by X_j

$\mathbf{K}_{ij+ik} \in \{0, \ldots, n_i\}$: weight given to the common action on X_i by X_j and X_k

- finitely many possible parameter values
- discrete update function

$$X_i^{\rightarrow} = f_i(X_1, \ldots, X_n, \mathbf{K}_{i*})$$



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

$$X_2 \in \{0, 1, 2\}$$

IV. Regulatory networks: dynamics

Thomas 73, Thomas/Snoussi 89

State

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

State transitions

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

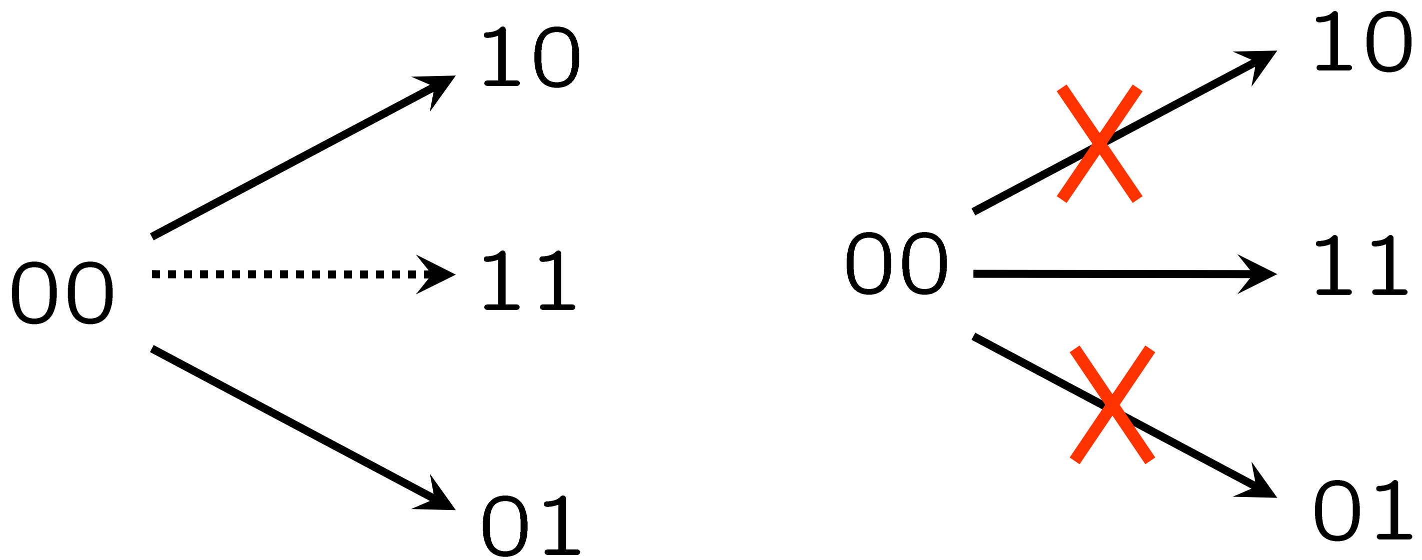
if $X_i^{\rightarrow} > X_i$ resp. $X_i^{\rightarrow} < X_i$

(where $X_i^{\rightarrow}$ is the update value for X_i).

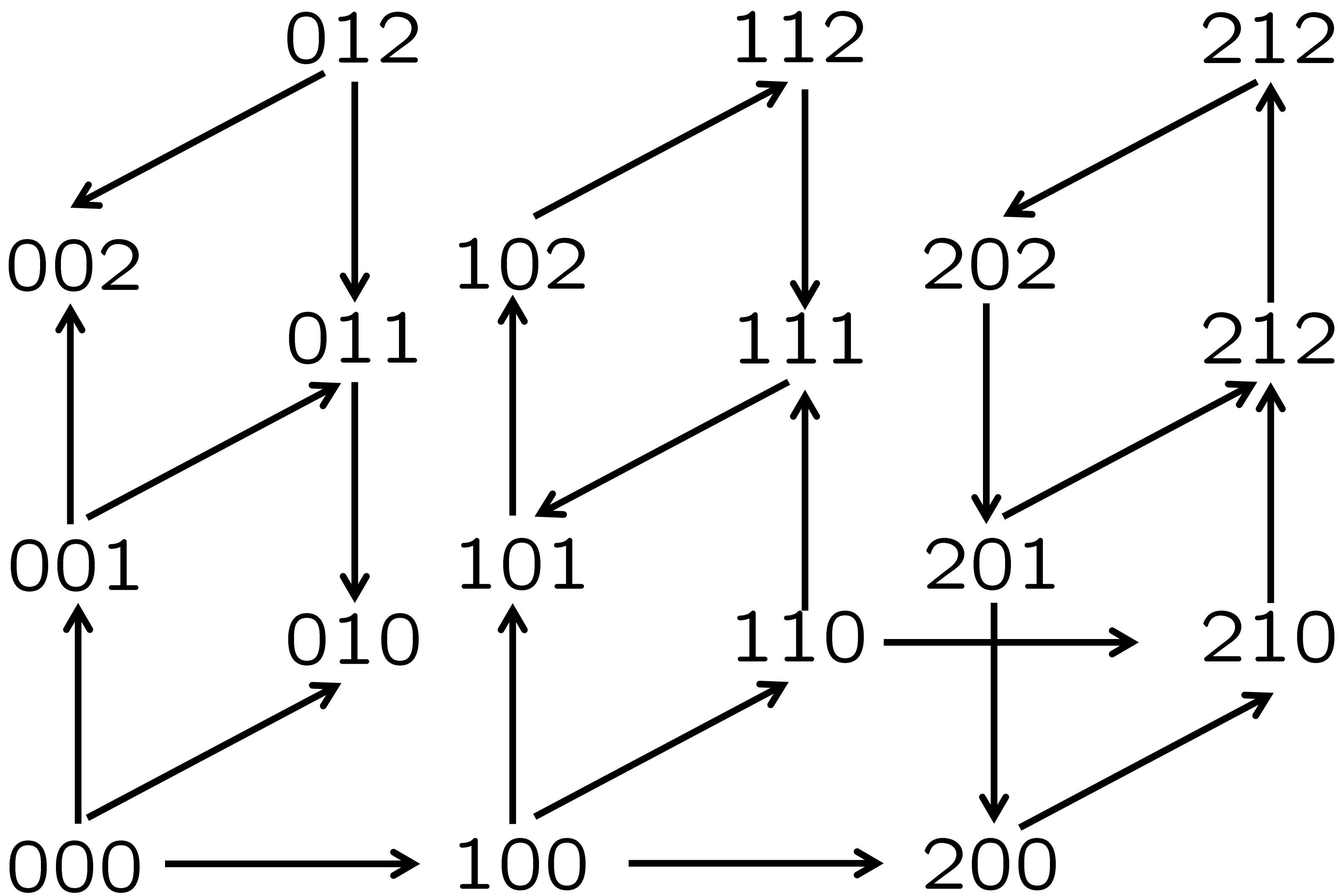
$$(X_1, X_2) = (0,0), (X_1^{\rightarrow}, X_2^{\rightarrow}) = (1,1)$$

Only one variable updated at a time.

Nondeterminism: Several successor states possible



asynchronous synchronous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000
100
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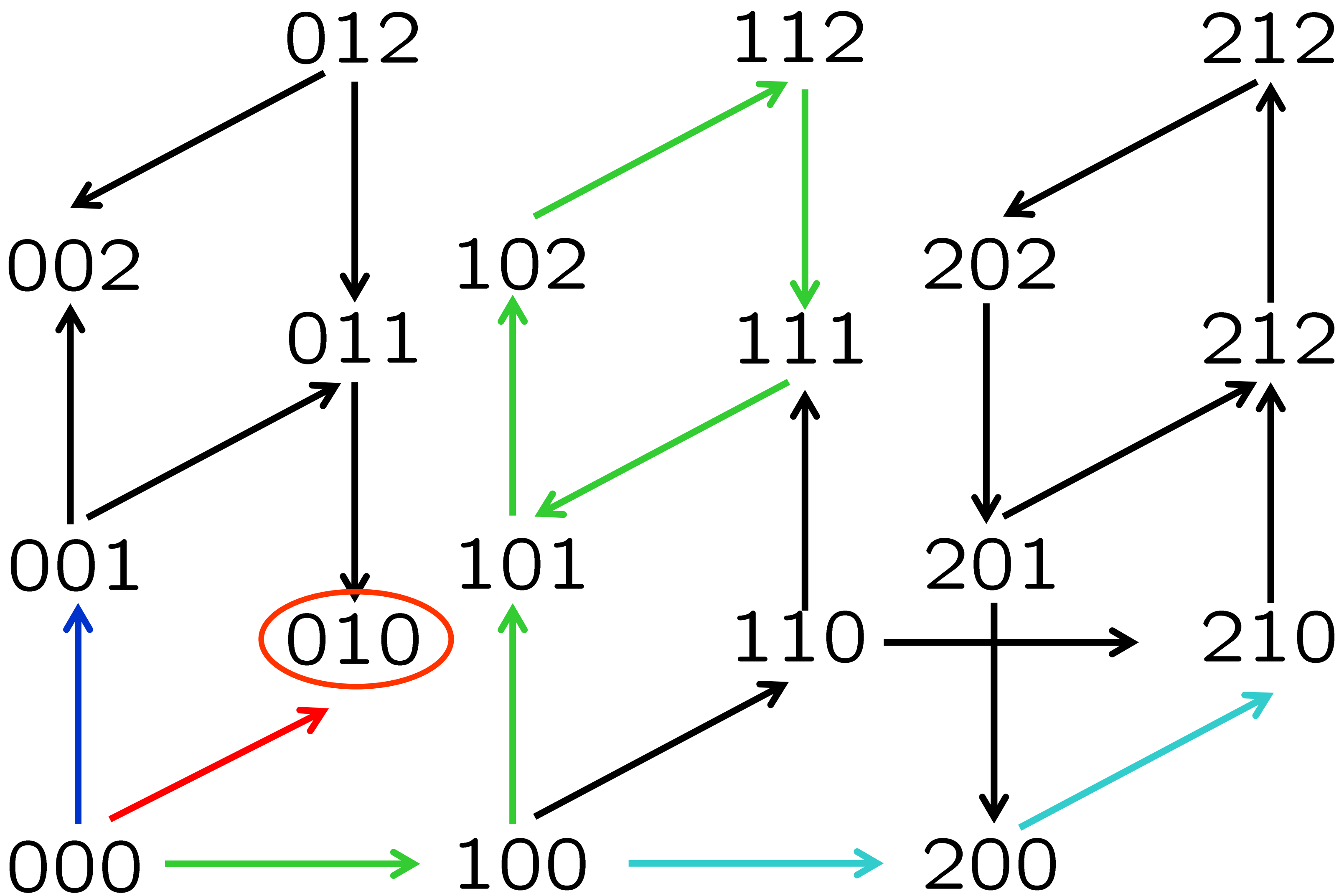
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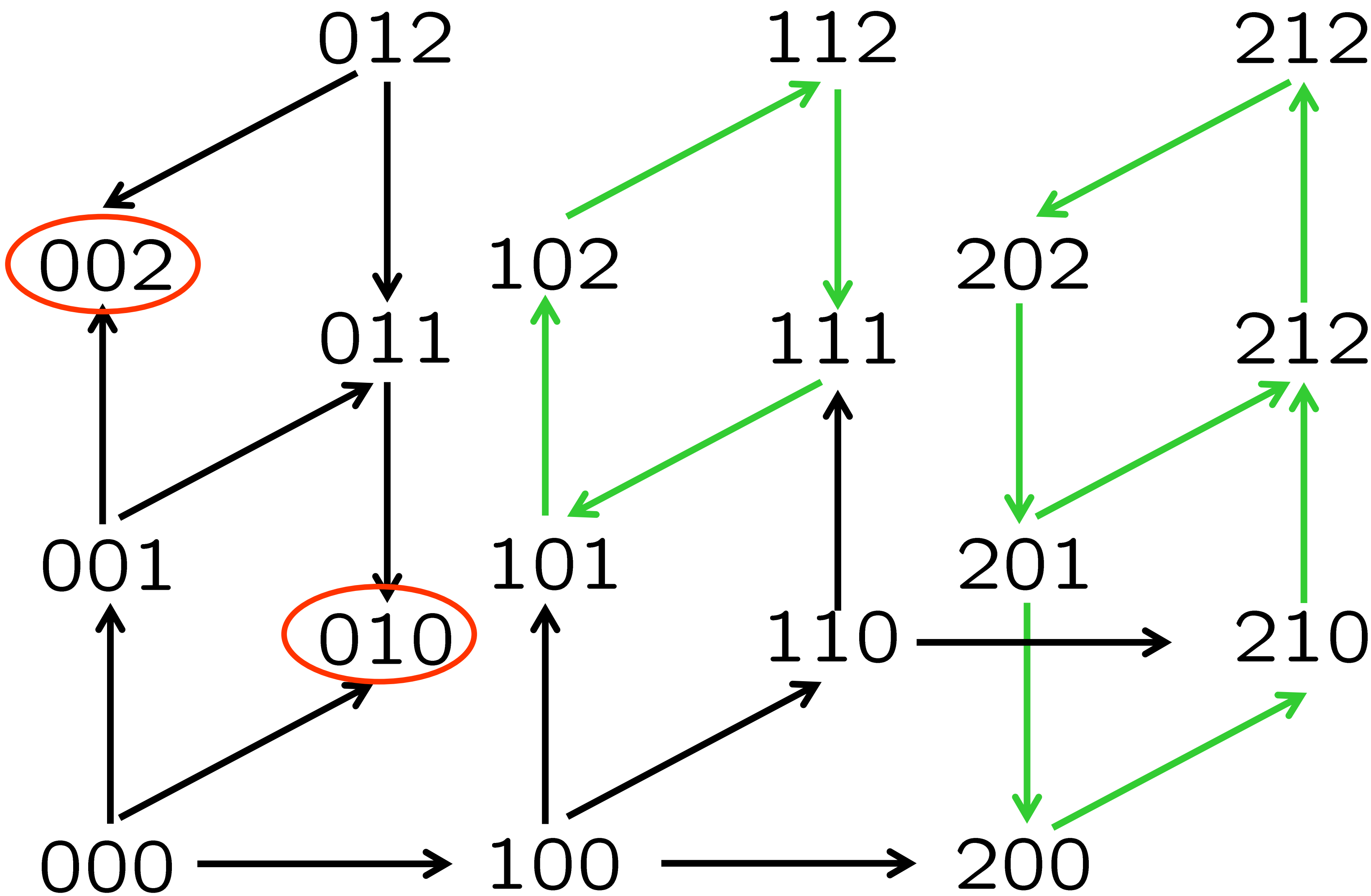
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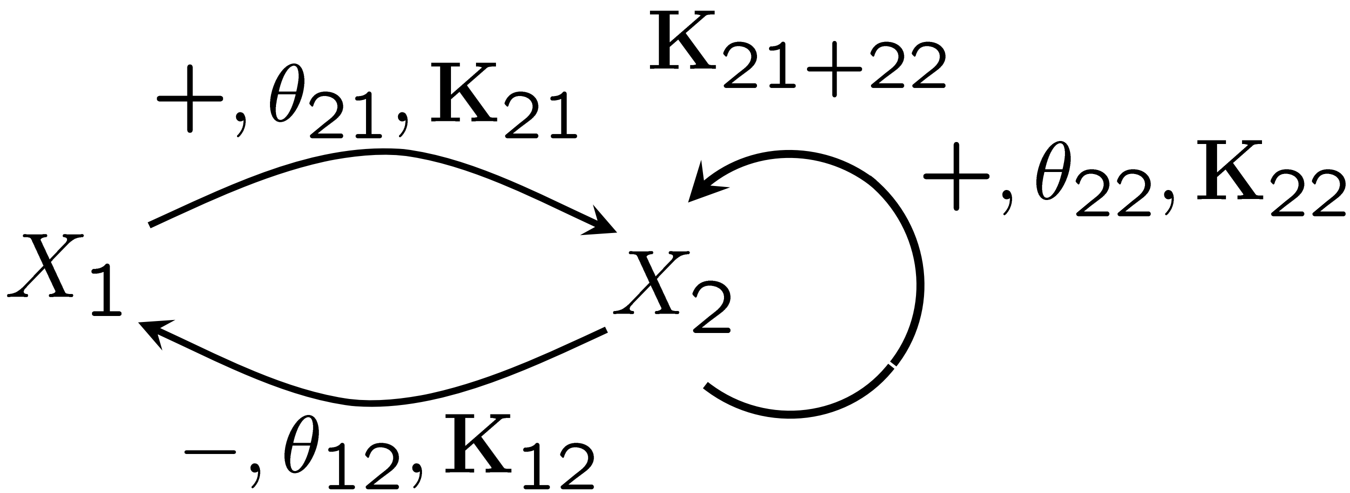
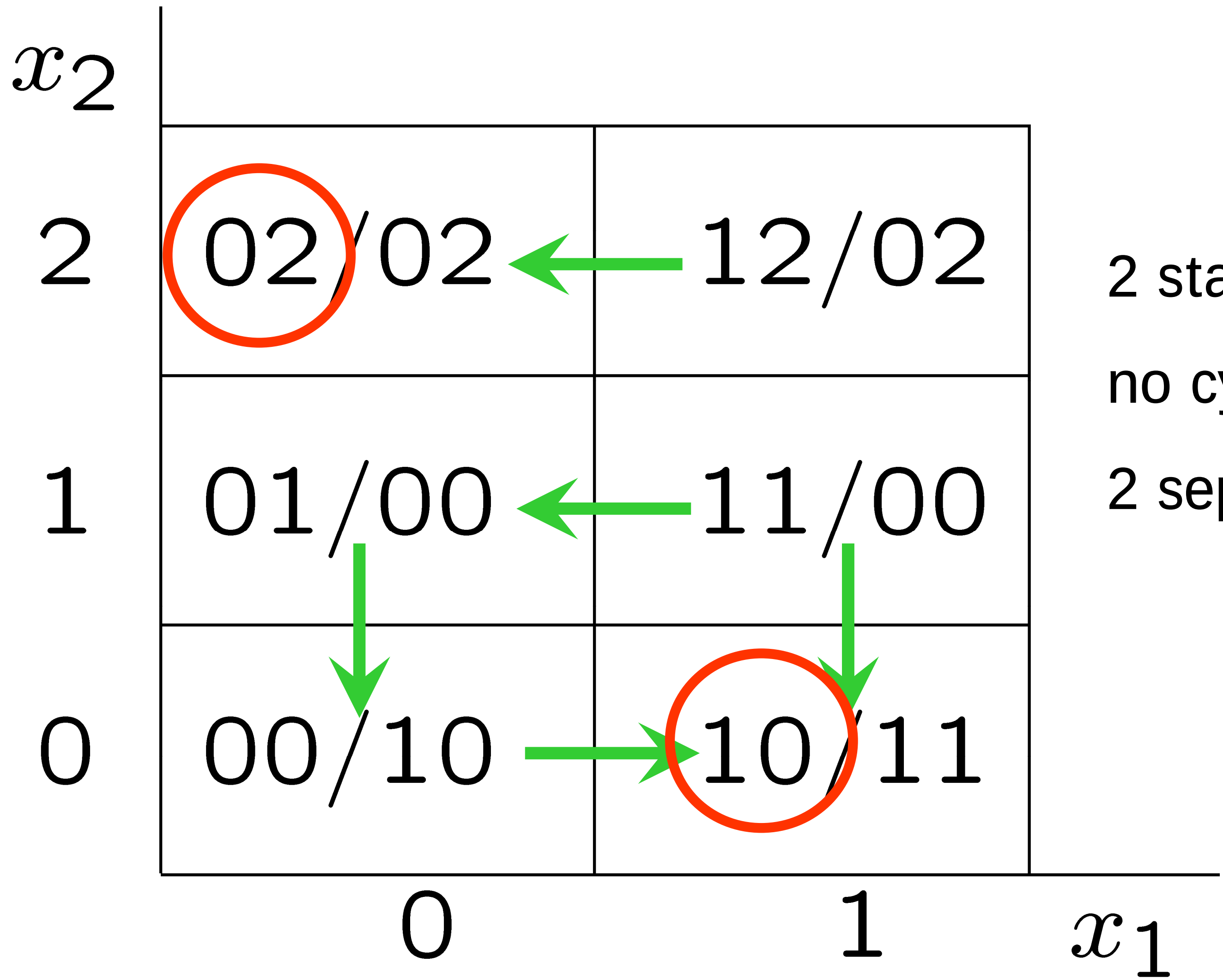


X_1	X_2	$X_1^{\rightarrow}$	$X_2^{\rightarrow}$
0	0	$\mathbf{K}_{12}$	0
0	1	0	0
0	2	0	$\mathbf{K}_{22}$
1	0	$\mathbf{K}_{12}$	$\mathbf{K}_{21}$
1	1	0	$\mathbf{K}_{21}$
1	2	0	$\mathbf{K}_{21+22}$

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

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

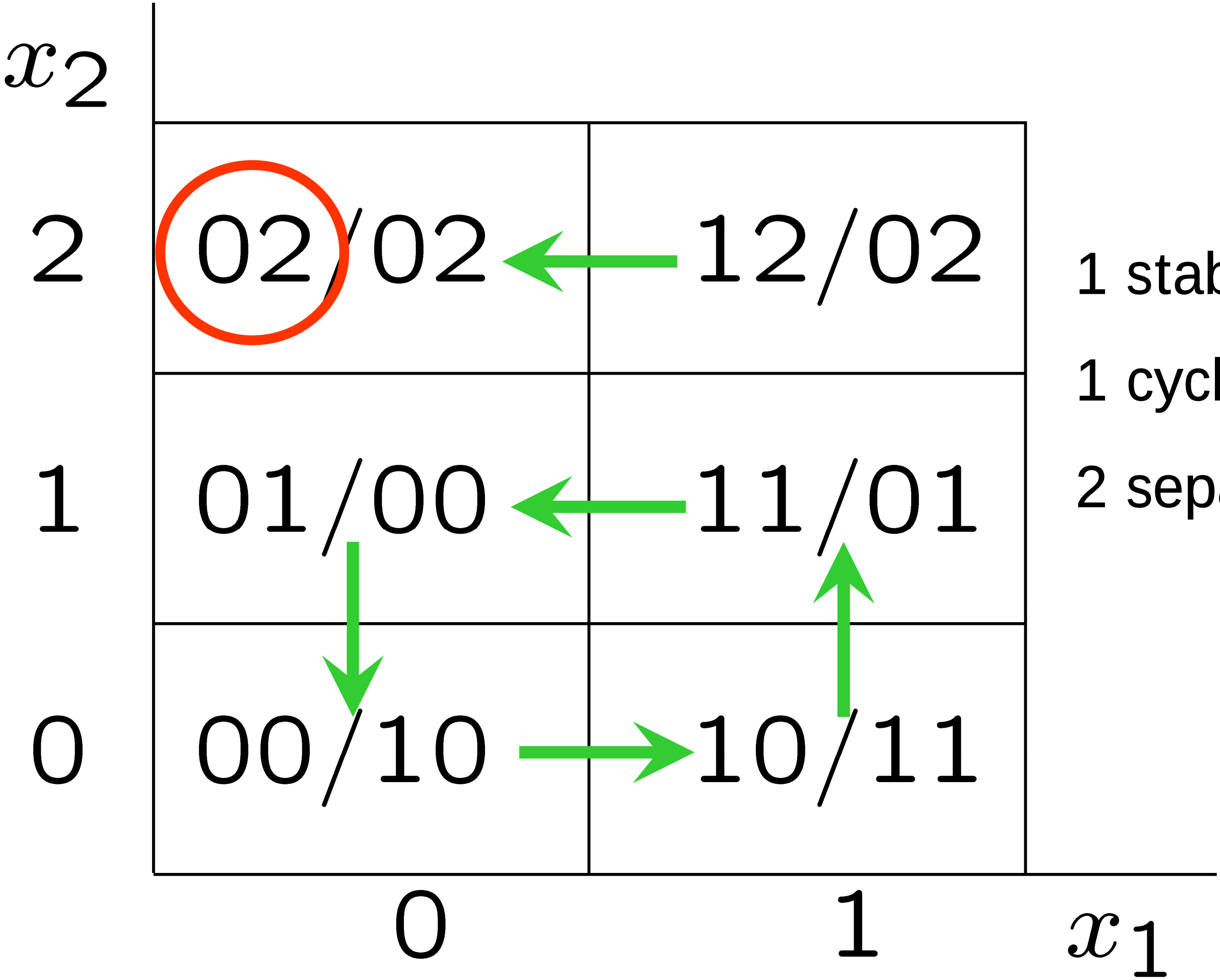


2 stable states

no cycle

2 separate domains

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

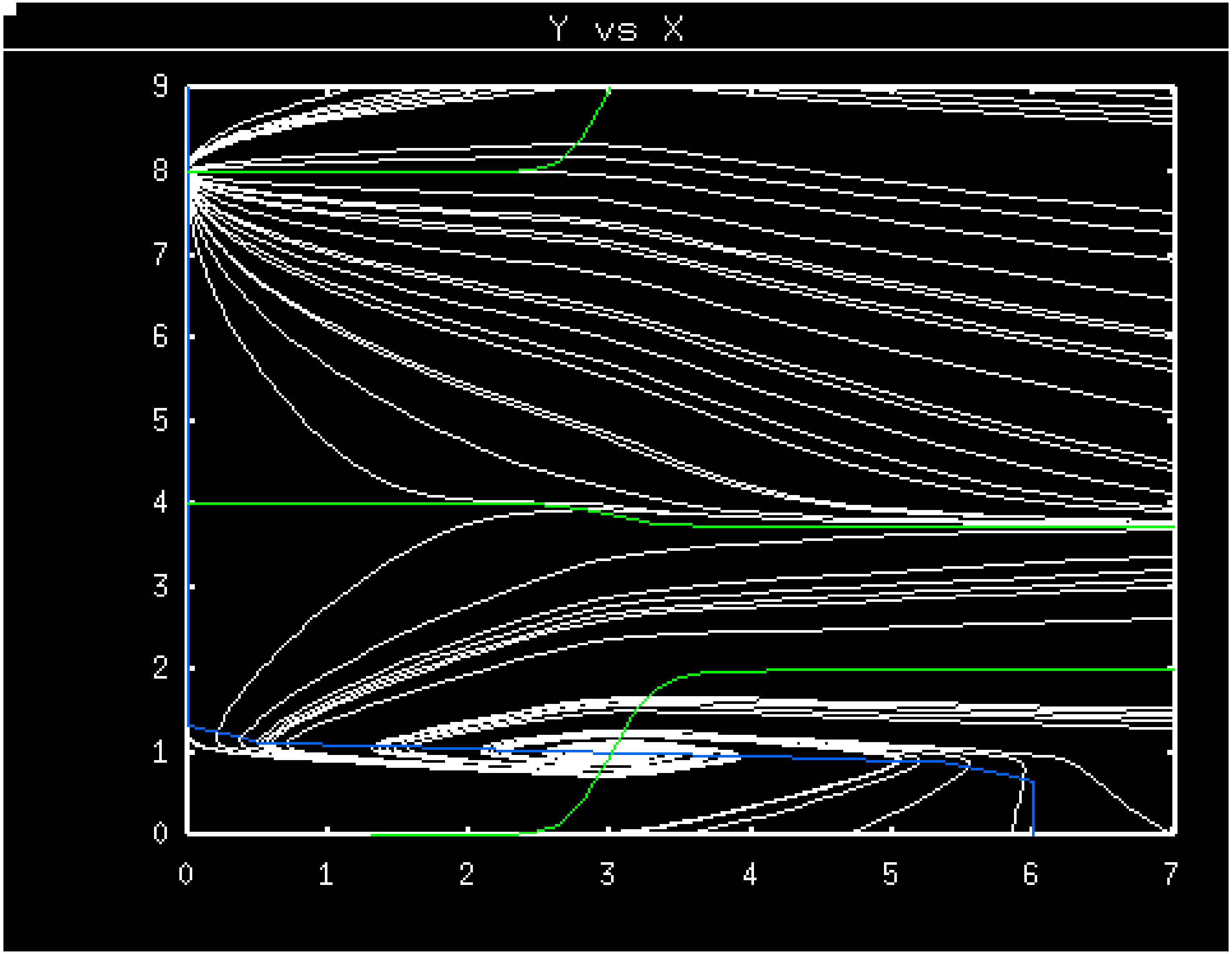


1 stable state

1 cycle

2 separate domains

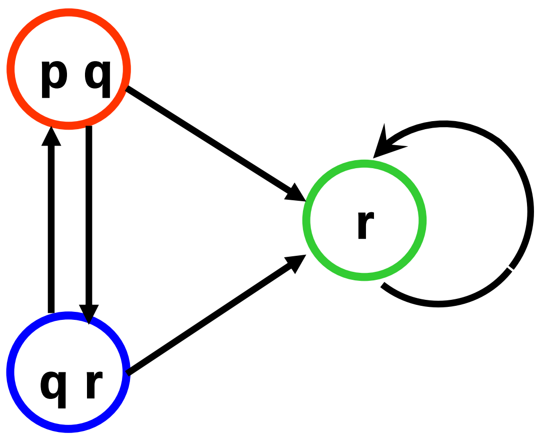
Continuous model



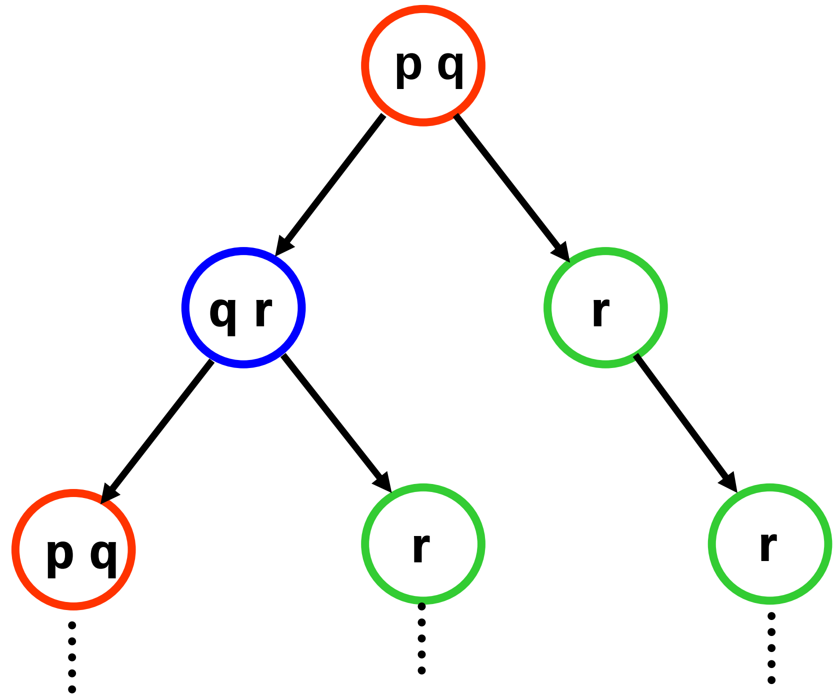
V. Temporal logic and model checking

Clarke/Emerson and Sifakis 81

State transition graph
(Kripke model)



Infinite computation tree



exponentially large

⇒ check dynamics properties expressed in suitable temporal logic

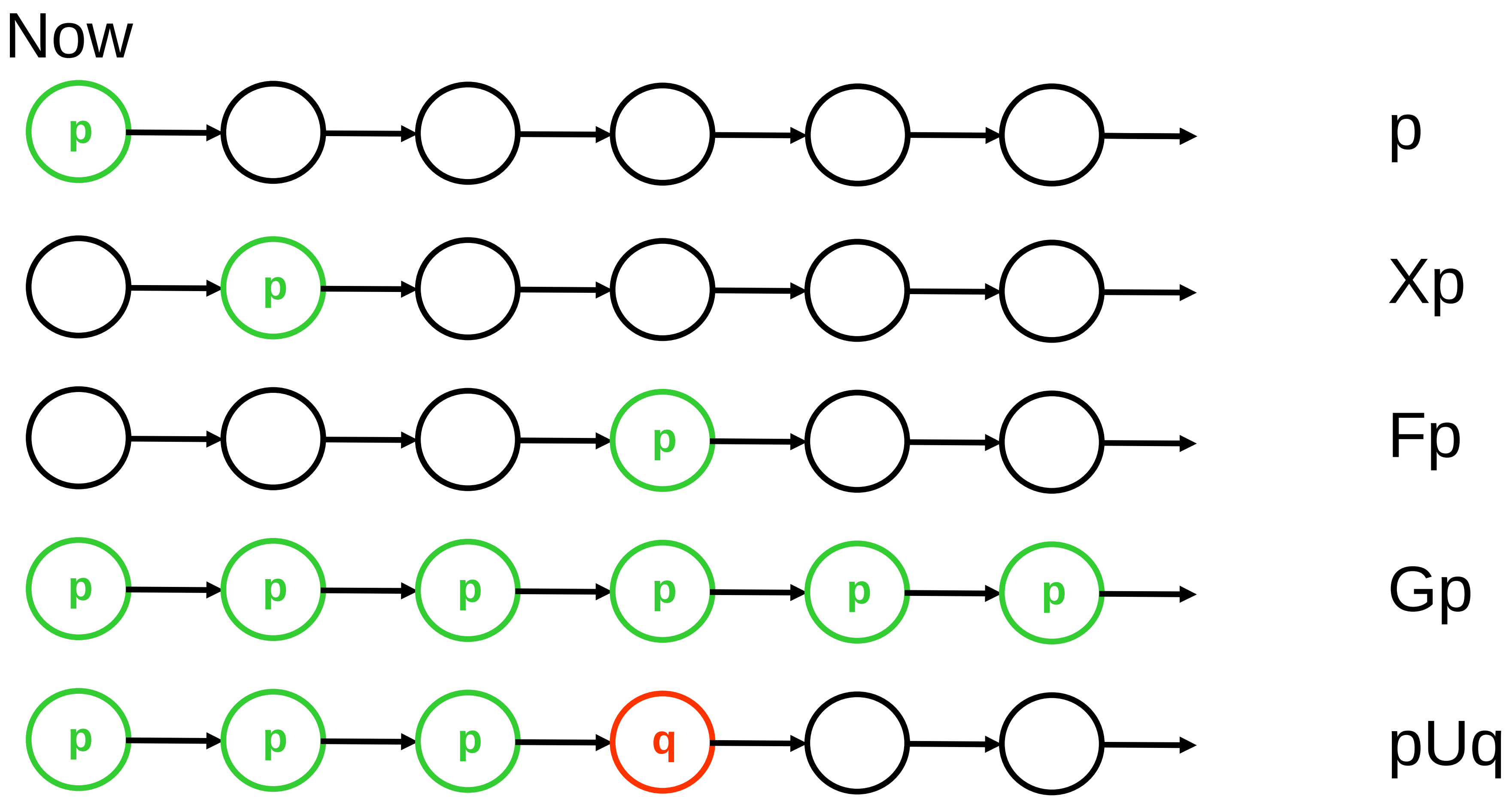
Atomic formulae : p, q, r, ..., e.g. $X_i = 1$

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

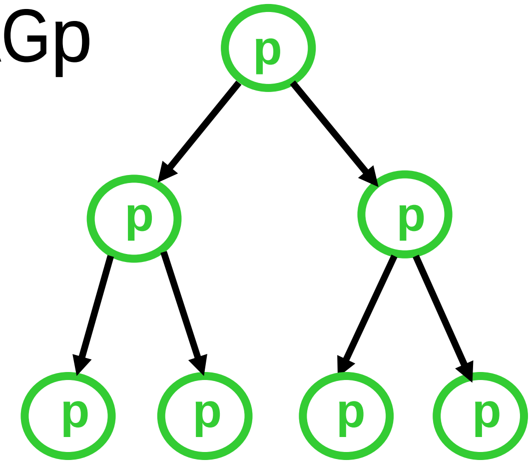
Path quantifiers :

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

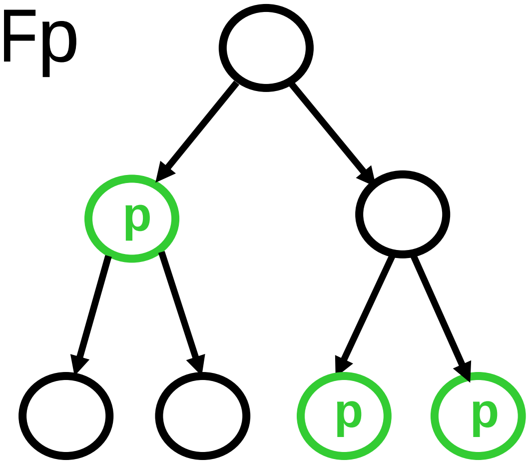

Now
p
p
p
p p p p p p
p p p q
p
Xp
Fp
Gp
pUq

Path quantifiers

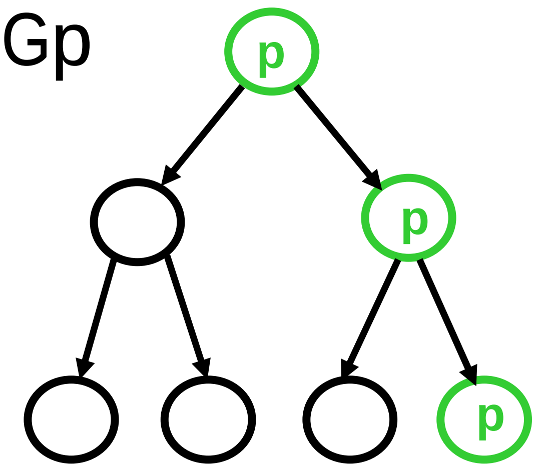
AGp



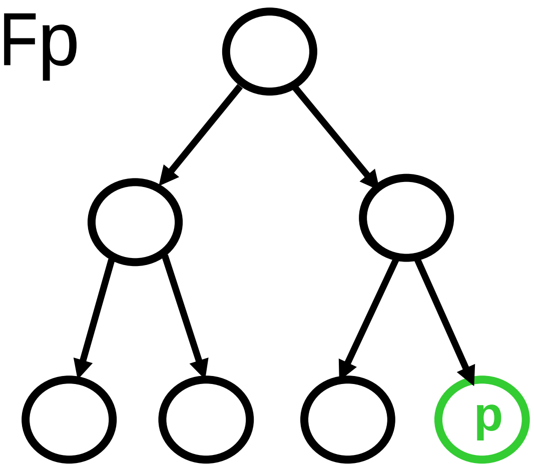
AFp



EGp



EFp



Input

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

Output

Set of states in which the formula is true

Very efficient software available (e.g. NuSMV)

Forward reasoning: Structure $\rightsquigarrow$ dynamics

What are the possible trajectories/dynamics compatible with the given structure ?

Bernot/Comet/Richard/Guespin 04

Specify dynamic properties using CTL formulas

$$(x = 0) \Rightarrow AG(\neg(x = 2))$$

$$(x = 2) \Rightarrow AX\,AF(x = 2)$$

$$\neg E(\neg(x = 2)\,U\,(x = 1))$$

Find compatible logical parameter values (SMBioNet)

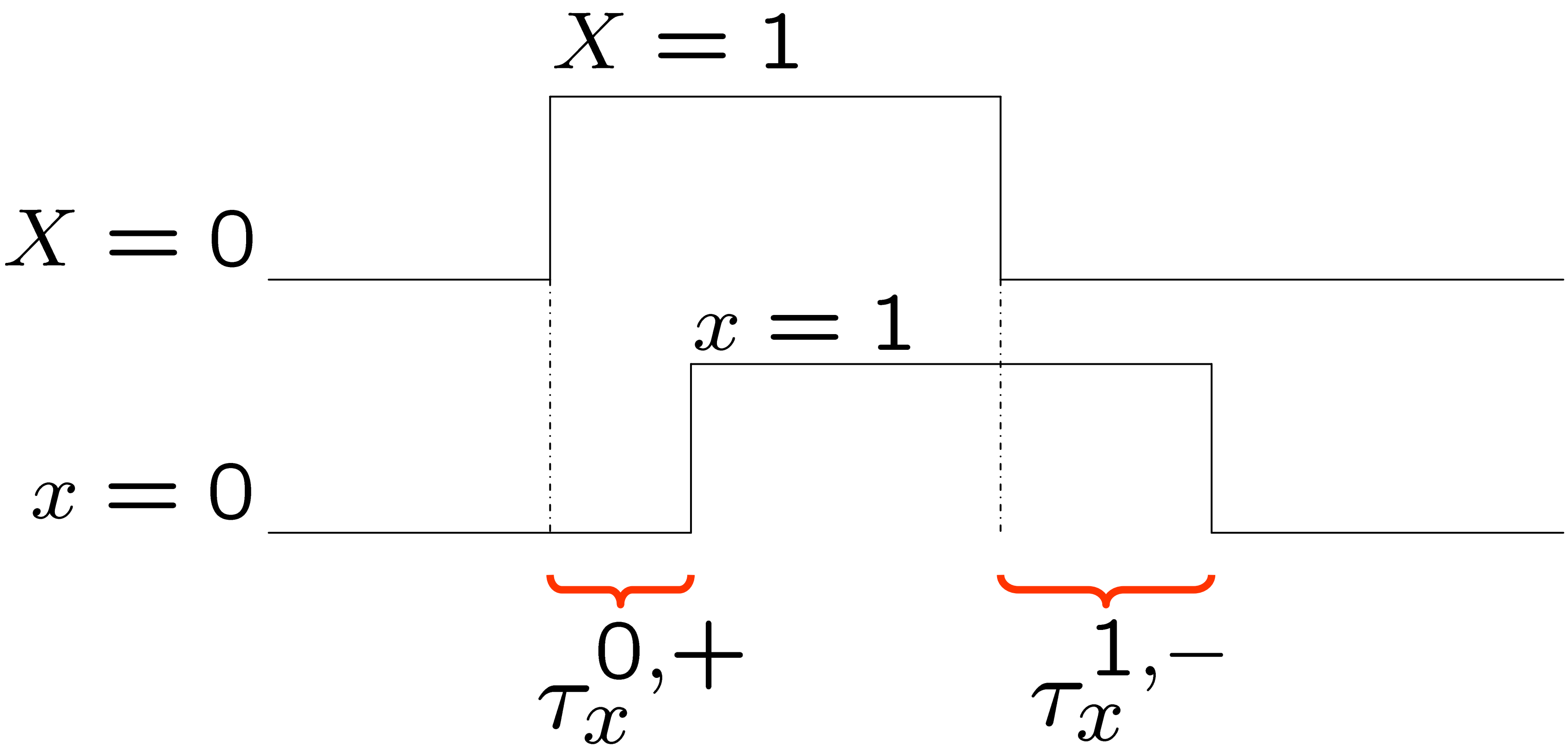
$$\mathbf{K}_{12} = 1, \mathbf{K}_{21} = 0, \mathbf{K}_{22} = \mathbf{K}_{21+22} = 2\ ?$$

$$\mathbf{K}_{12} = 1, \mathbf{K}_{21} = 1, \mathbf{K}_{22} = \mathbf{K}_{21+22} = 2\ ?$$

Alternative: Infer constraints on logical parameters

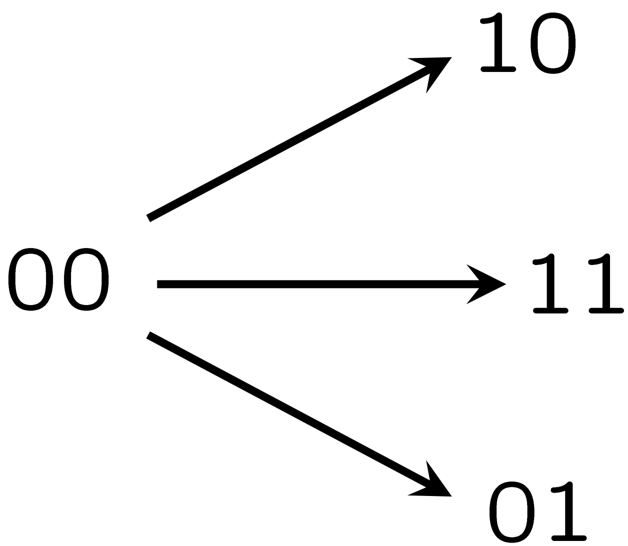
Backward reasoning: Dynamics $\rightsquigarrow$ structure

VI. Temporal constraints on time delays


$X = 1$
$X = 0$
$x = 1$
$x = 0$
$\tau_x^{0,+}$
$\tau_x^{1,-}$

Reducing non-determinism

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

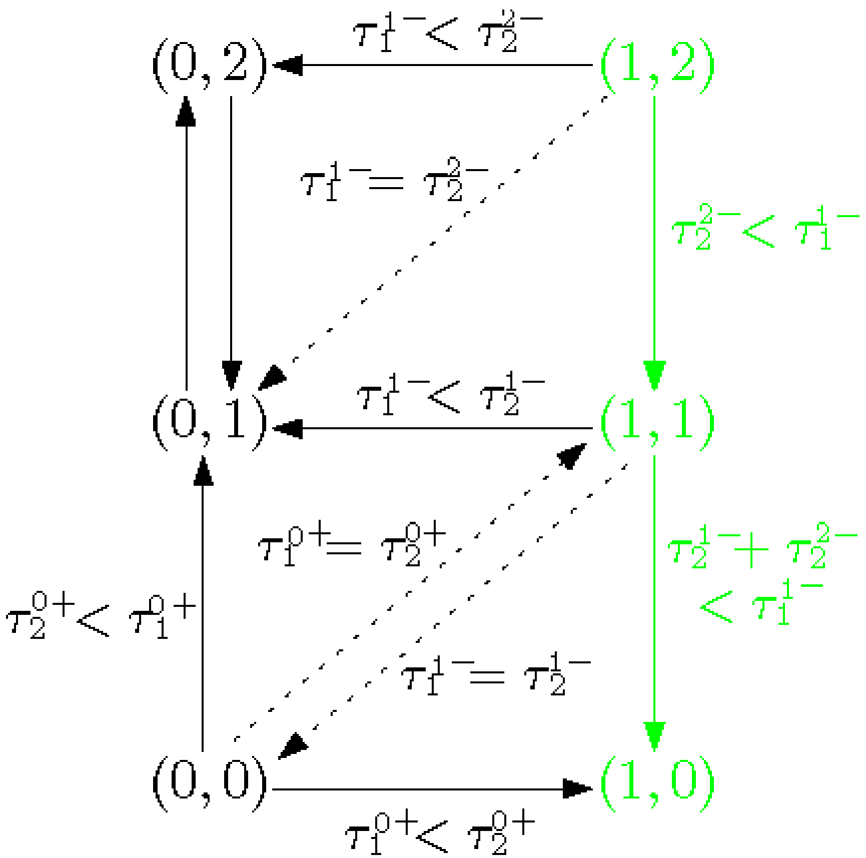


if $\tau_1^{0,+} < \tau_2^{0,+}$

if $\tau_1^{0,+} = \tau_2^{0,+}$

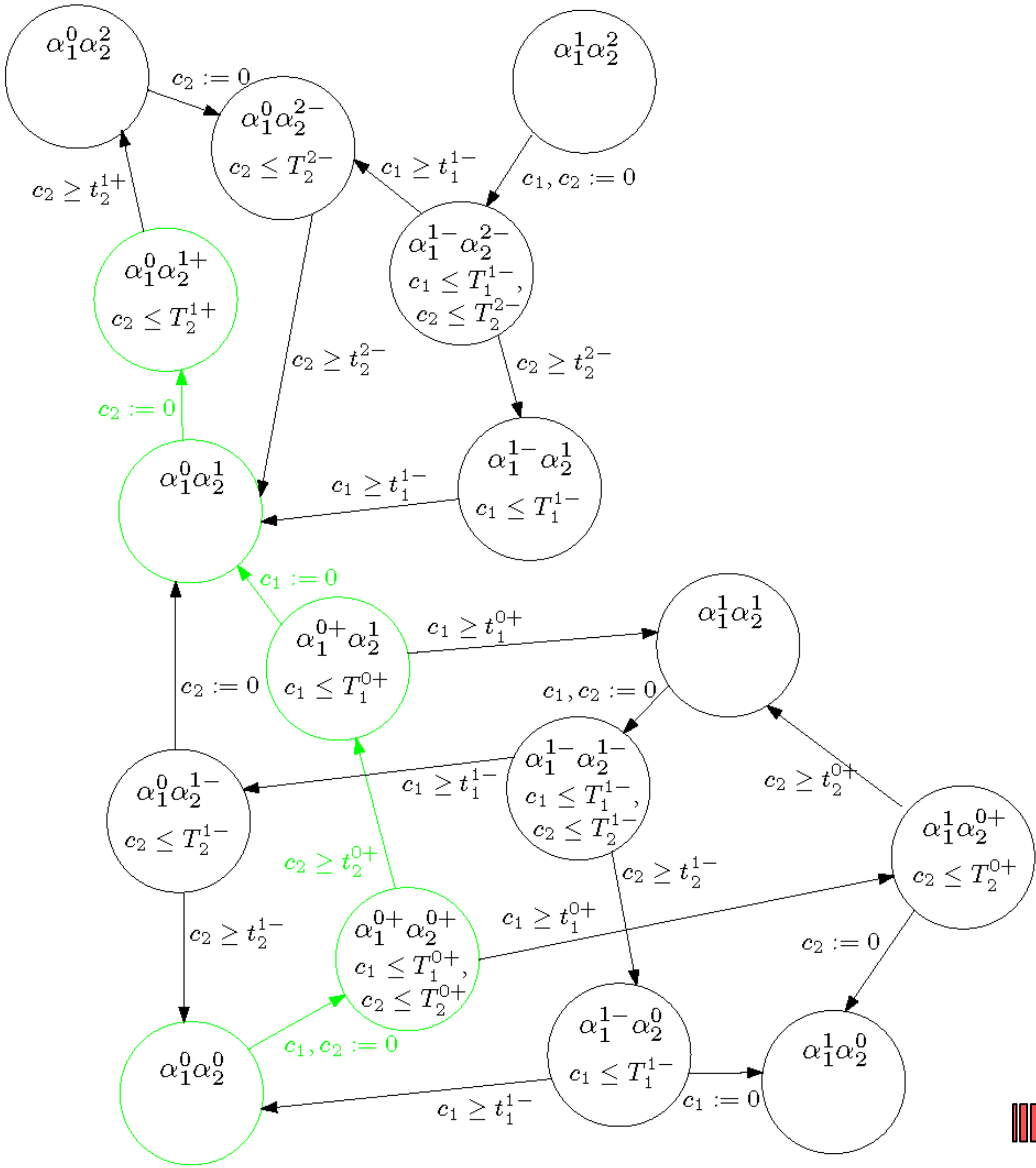
if $\tau_1^{0,+} > \tau_2^{0,+}$

- Time delays may depend on
  - the component
  - the activity level
  - activation/inhibition
- Temporal constraints on time delays
- Temporal constraints along a pathway
- Hybrid discrete/continuous modeling



Formal analysis using timed automata

Siebert/Bockmayr 08



$$((\alpha_1^0, \alpha_2^0), (0,0))$$

$$((\alpha_1^{0+}, \alpha_2^{0+}), (0,0))$$

$t \leq T_1^{0+}, T_2^{0+}$

$$((\alpha_1^{0+}, \alpha_2^{0+}), (t,t))$$

$t \geq t_2^{0+},\ t \leq T_1^{0+}$

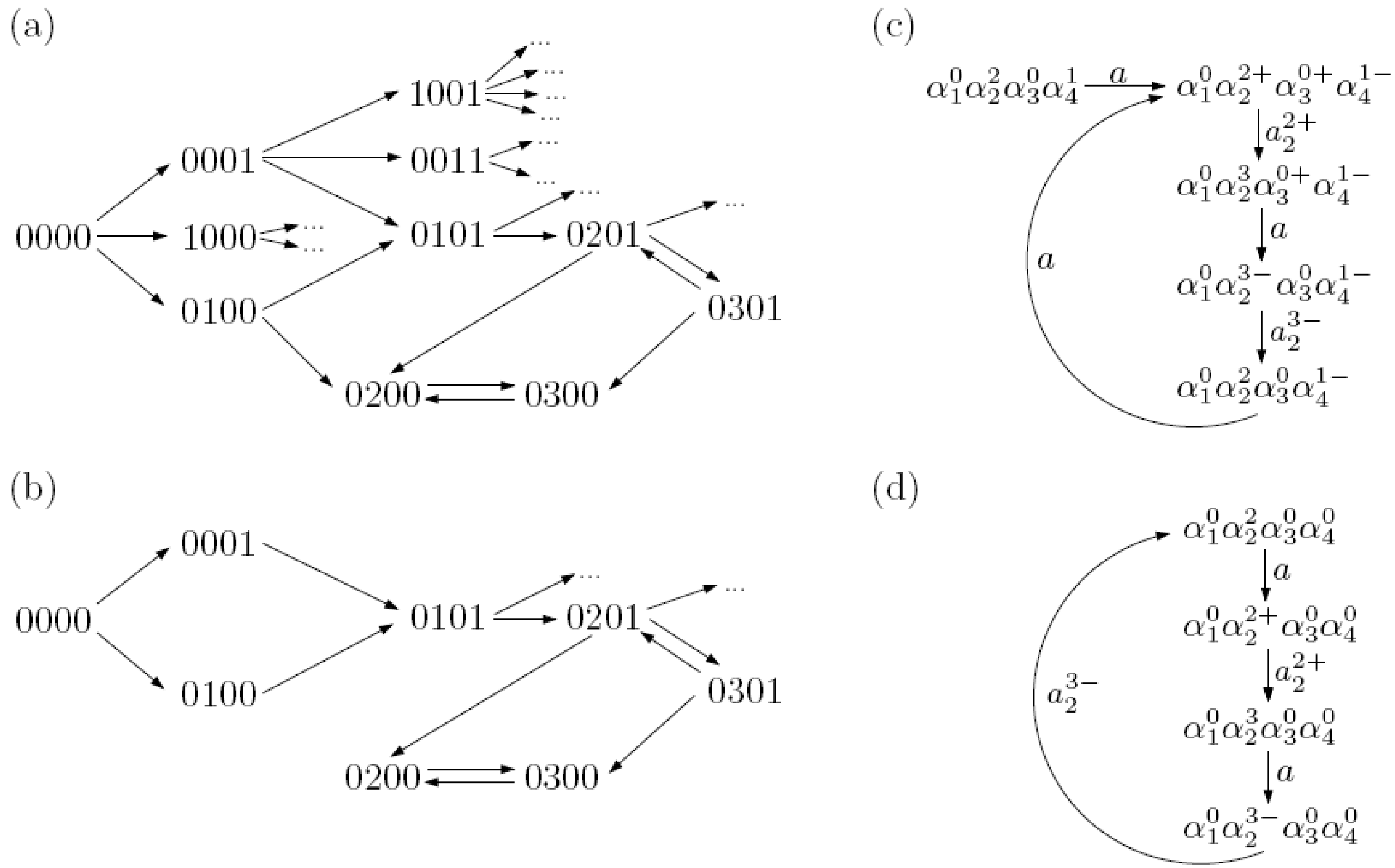
$$((\alpha_1^{0+}, \alpha_2^{1}), (t,t))$$

$$((\alpha_1^{0}, \alpha_2^{1}), (0,t))$$

$$((\alpha_1^{0}, \alpha_2^{1+}), (0,0))$$

⇒ reduce non-determinism

- Elimination of pathways violating temporal constraints
- Feasibility, stability of certain dynamic behaviors
- Additional information on gene activity



Conclusion

- Constraint-based modeling of regulatory networks
- Interaction graph — Structure
- State transition graph — Dynamics
- Temporal logic and model checking
- Reducing non-determinism: time delays, temporal constraints, hybrid automata

- Deterministic/stochastic vs. constraint-based modeling
- Numerical simulation vs. formal reasoning