Logical Modeling with Time Delays

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Toward Systems Biology
Grenoble
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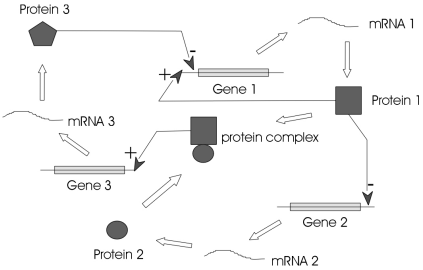
Why logical modeling?

- lack of quantitative information on kinetic parameters and molecular concentrations
- biochemical reaction mechanisms underlying interactions not or incompletely known
- resulting systems of differential equations mostly not analytically solvable

$\Rightarrow$ discrete modeling based on qualitative data



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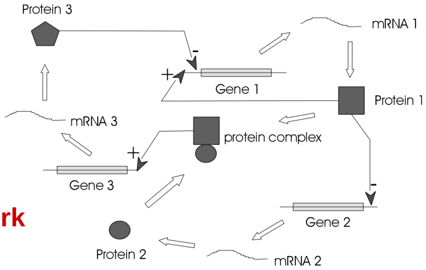


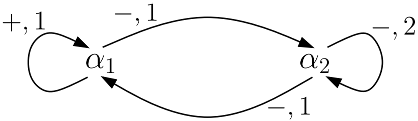
allow for the incorporation of temporal data concerning network processes

Thomas Formalism

[R. Thomas, 1973]

Structure: interaction graph

- discrete variables $\alpha_1, \ldots \alpha_n$
- expression levels $0, \ldots, p_j$ associated with each α_j
- labeled interactions



$\alpha_1 \in \{0, 1\},\ \alpha_2 \in \{0, 1, 2\}$

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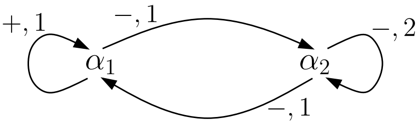

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Dynamics: state space and evolution

- state space $S := \{0,\dots,p_1\} \times \dots \times \{0,\dots,p_n\}$
- discrete function $f : S \to S$ determines behavior of the system

$s = (s_1, s_2), f(s) = (f_1(s), f_2(s))$

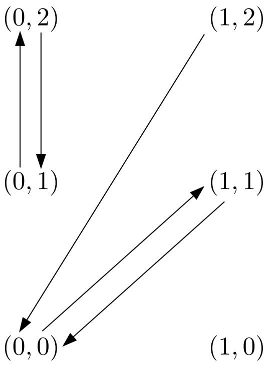
$$f_1(s) = \begin{cases} 1 & , \quad s_2 = 0 \\ 0 & , \quad \text{else} \end{cases}$$

$$f_2(s) = \begin{cases} 2 & , \quad s_1 = 0 \wedge s_2 \le 1 \\ 1 & , \quad s_1 = 0 \wedge s_2 = 2 \\ 0 & , \quad \text{else} \end{cases}$$

Thomas Formalism

Dynamics: state transition graph

- vertex set S
- edges derived from parameter values



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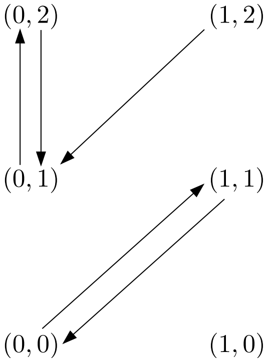
    - corresponding component values differ at most by 1



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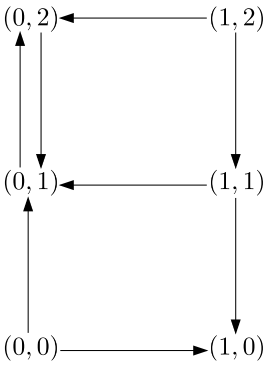
  - states differ from their successors in one component only
    asynchronous update: sole assumption about time delays



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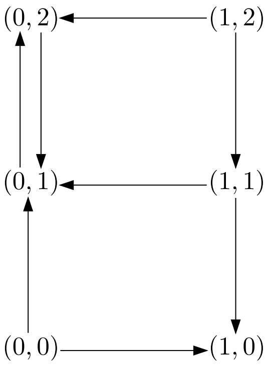
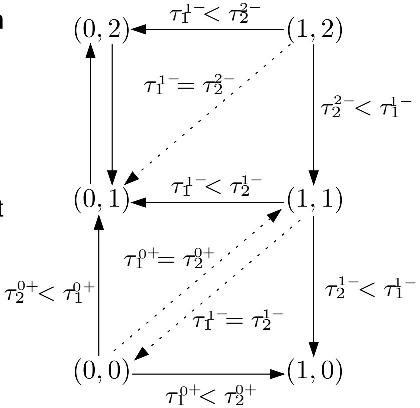


non-deterministic representation of the network dynamics

Considering Time Delays

Command to change for more than one component

- compare time delays associated with different processes
  - distinguish between components
  - distinguish between production and decay processes
  - take expression levels into account
- allow for the possibility of time delay equality



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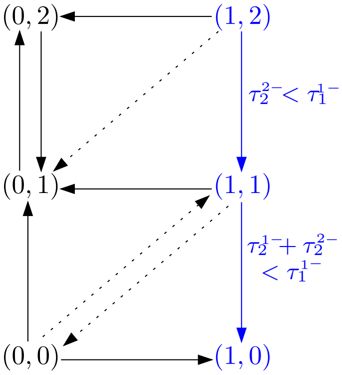
- complexity of time constraints may increase with path length



Introducing Time

Timed Automata [R. Alur, D. Dill, 1994]

- clocks measure time, progress linear and synchronously
- clock constraints are formulated in the grammar

$$\varphi ::= c \leq q \mid c \geq q \mid c < q \mid c > q \mid \varphi_1 \wedge \varphi_2$$

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  - vertices (locations) represent states
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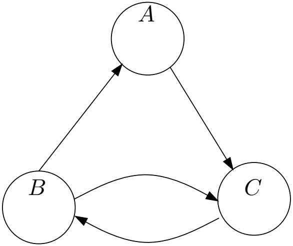

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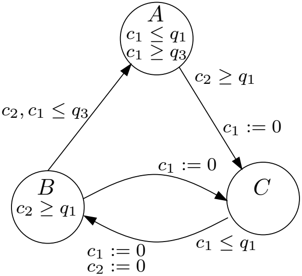
  - edges represent (discrete) state changes
  - time constraints may be posed on states and edges, clocks may be reset



Modus Operandi

1. Model each component incorporating information on
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2. Combine the components to a model supplying information on
   - the state space of the network,
   - state changes induced by the structure and parameter specification of the network,
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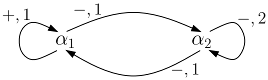
3. Evaluate the data inherent in the network model to obtain a representation of the dynamical behavior in agreement with all given constraints.

Modeling Each Component

- one clock for each component



$f : S \to S$

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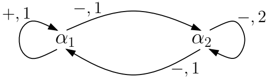

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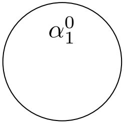

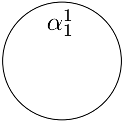

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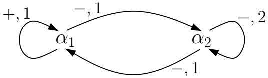
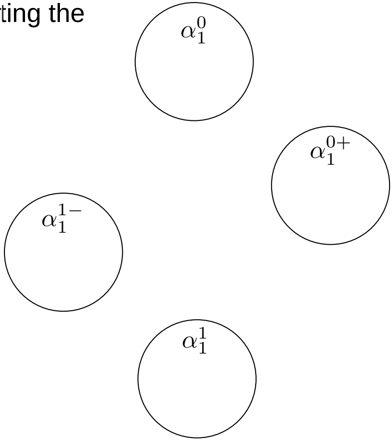


$f : S \rightarrow S$

- one clock for each component
- expression levels – distinction between stationary states and states representing the process of expression level change



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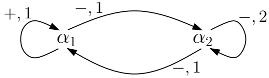

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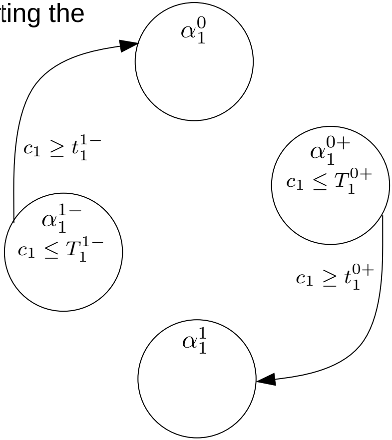
- location changes due to elapse of time



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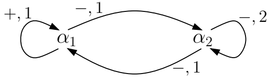

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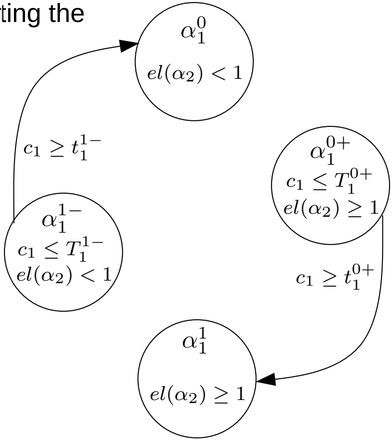

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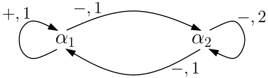

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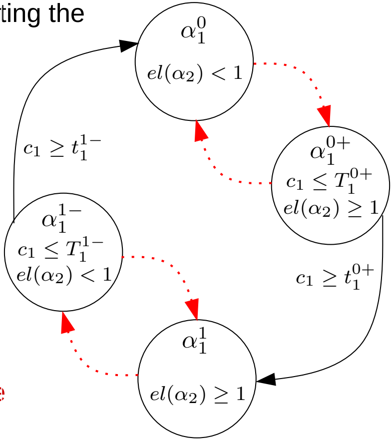
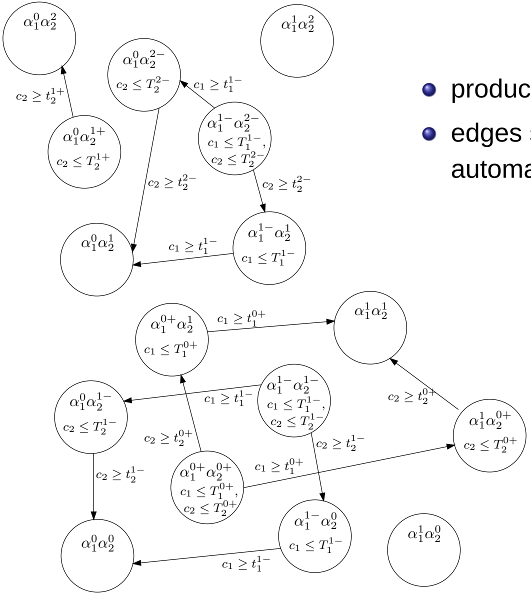
  induced location changes can only be evaluated in the network context



Connecting the Parts



- product locations
- edges specified in component automata

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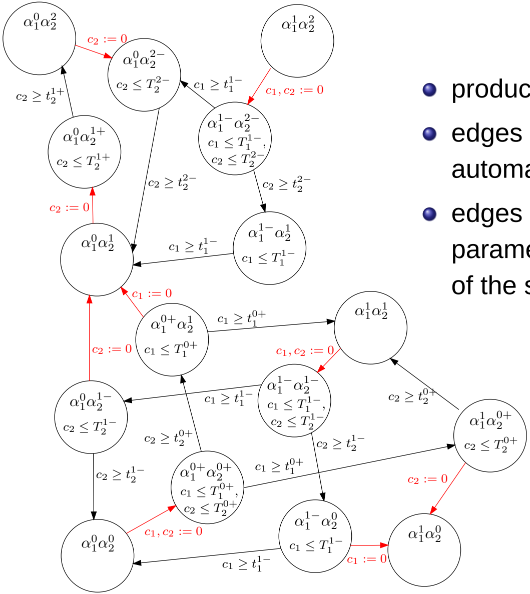
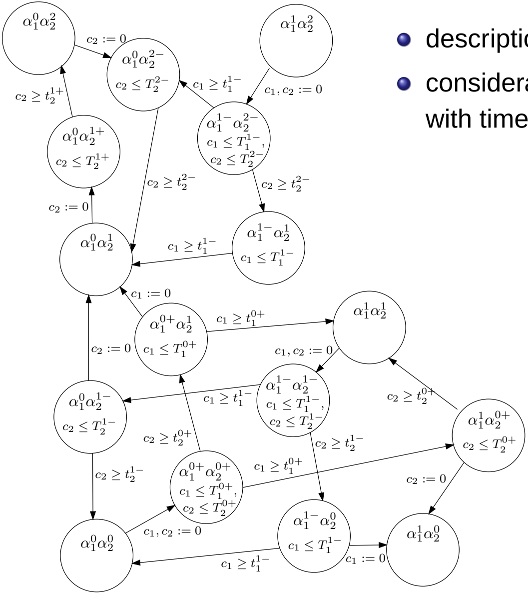


- product locations
- edges specified in component automata
- edges due to network interactions, parameters and current state of the system

Dynamics



- description includes time component
- consideration of behavior in agreement with time constraints

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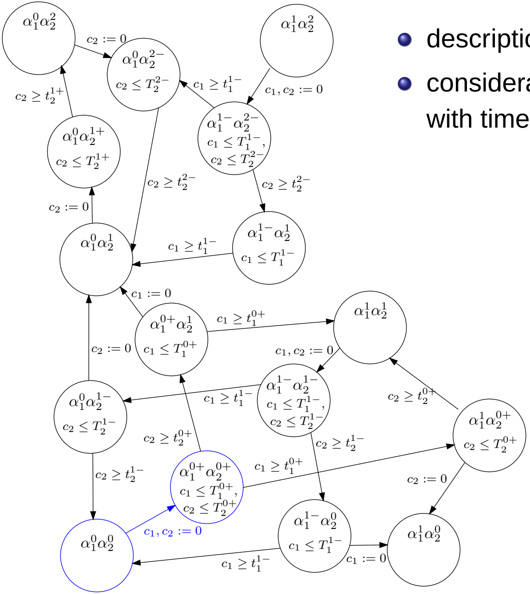

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$$((\alpha_1^0, \alpha_2^0), (0, 0))$$
$$\downarrow$$
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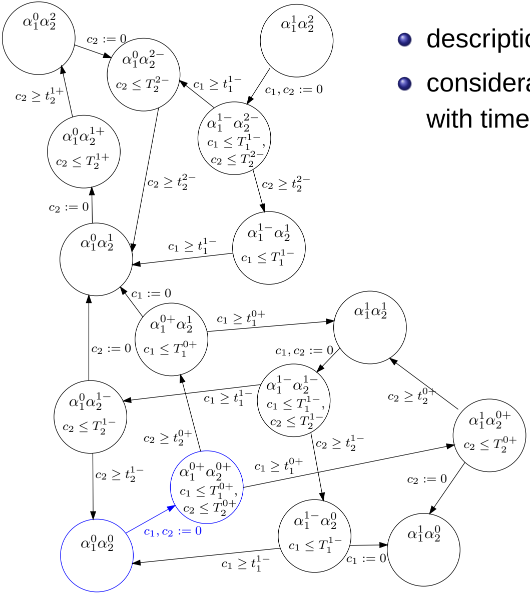

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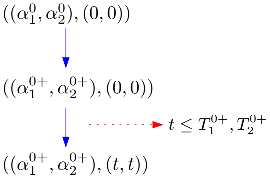

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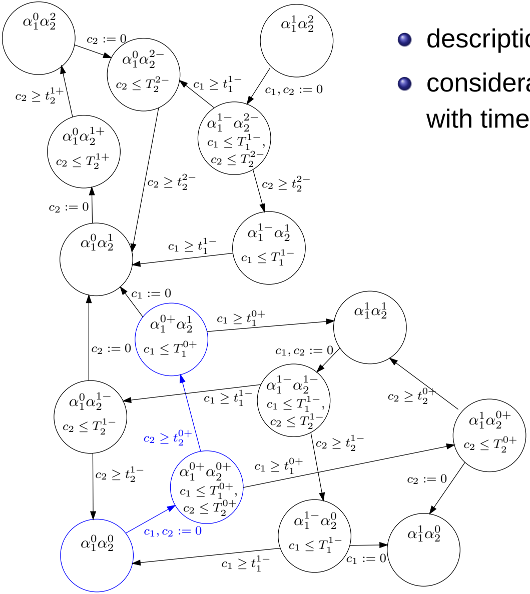

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$$\downarrow \quad \cdots\cdots \rightarrow t \leq T_1^{0+}, T_2^{0+}$$

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

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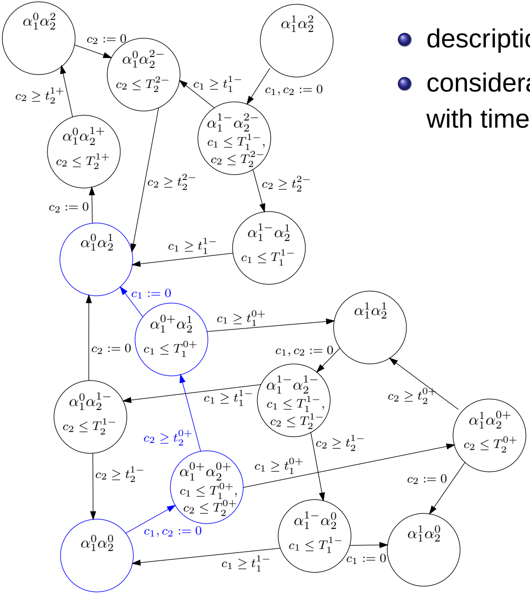

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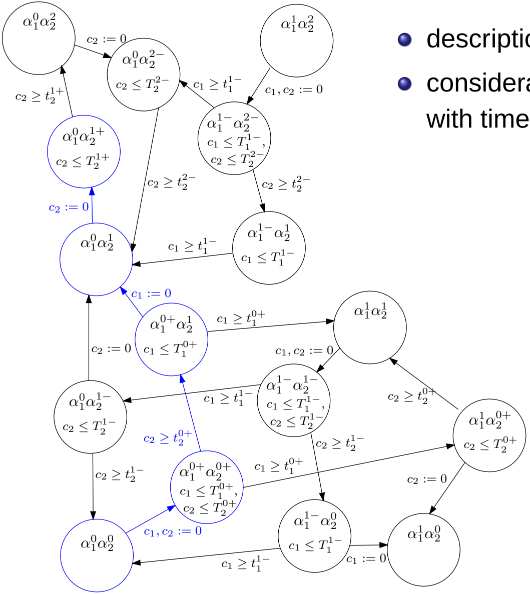

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Analyzing the Transition System

Dynamics captured in a transition system

- infinite due to time component
- non-deterministic

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Consistency: state transition graph of the Thomas formalism can be recovered from the dynamics of a suitable timed automata model

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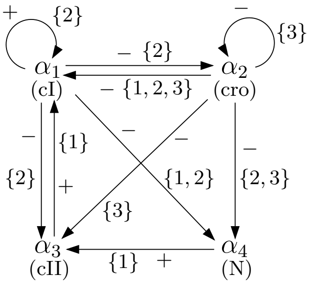
Possible approach:

- analysis and verification by means of model checking techniques
- software for editing, simulating and verification of timed automata available
- implementation in UPPAAL

Bacteriophage λ
[D. Thieffry, R. Thomas, 1995]



$$
\begin{aligned}
K_{1,\{e_{21}\}} &= 2 & K_{2,\{e_{12}\}} &= 2\\
K_{1,\{e_{31}\}} &= 2 & K_{2,\{e_{12},e_{22}\}} &= 3\\
K_{1,\{e_{11},e_{21}\}} &= 2 & &\\
K_{1,\{e_{11},e_{31}\}} &= 2 & K_{3,\{e_{13},e_{23},e_{43}\}} &= 1\\
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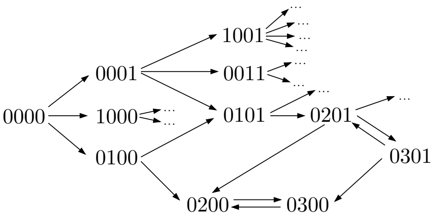
K_{1,\{e_{11},e_{21},e_{31}\}} &= 2 & K_{4,\{e_{14},e_{24}\}} &= 1
\end{aligned}
$$

Bacteriophage λ



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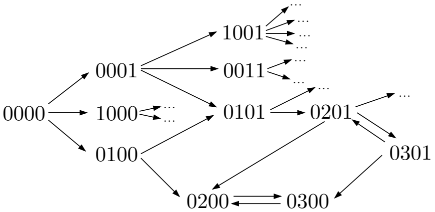
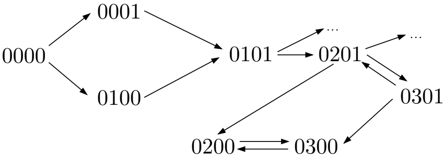


- elimination of pathways violating clock constraints based on temporal data



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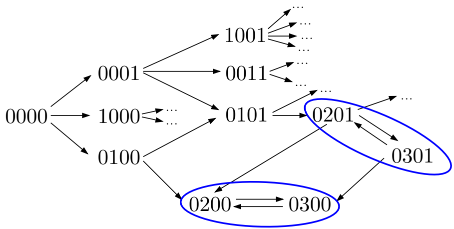

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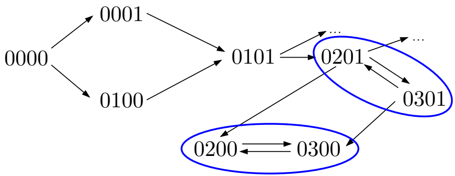
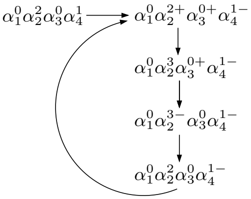
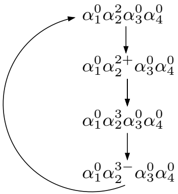


- additional information on the status of component activity





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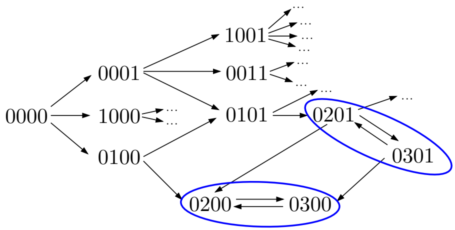

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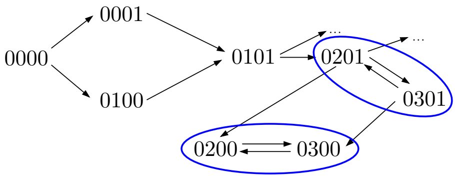

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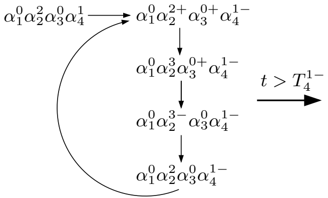

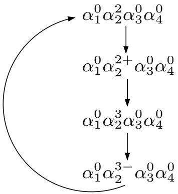

- evaluation of feasibility and stability of behavior

Conclusion

Modeling formalism

- modular logical modeling of regulatory networks
- incorporating time delays

$\Rightarrow$ refined analysis of the network dynamics

Outlook

- applying the formalism
- developing precise concepts to evaluate feasibility and stability of dynamical behavior
- consideration of more expressive modeling frameworks