Logical Modeling with Time Delays

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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

⇒ discrete modeling based on qualitative data
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- lack of quantitative information on kinetic parameters and molecular concentrations
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⇒ discrete modeling based on qualitative data

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 $\alpha_j$
- labeled interactions

\[ S = \{0, \ldots, p_1\} \times \cdots \times \{0, \ldots, p_n\} \]

\[ f : S \to S \]

\[ f_1(s) = \begin{cases} 1 & s_2 = 0 \\ 0 & \text{else} \end{cases} \]

\[ f_2(s) = \begin{cases} 2 & s_1 = 0 \land s_2 \leq 1 \\ 0 & \text{else} \end{cases} \]
Thomas Formalism
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Structure: interaction graph

- discrete variables $\alpha_1, \ldots, \alpha_n$
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  associated with each $\alpha_j$
- labeled interactions

Dynamics: state space and evolution

- state space
  $S := \{0, \ldots, p_1\} \times \cdots \times \{0, \ldots, p_n\}$
- discrete function $f : S \rightarrow S$
  determines behavior of the system
**Dynamics:** state transition graph

- vertex set $S$
- edges derived from parameter values

Graph:

- Vertex set $S = \{(0, 0), (0, 1), (0, 2), (1, 0), (1, 1), (1, 2)\}$
- Edges:
  - $(0, 0) \rightarrow (1, 0)$
  - $(0, 1) \rightarrow (1, 1)$
  - $(0, 2) \rightarrow (1, 2)$

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Thomas Formalism

**Dynamics:** state transition graph
- vertex set \( S \)
- edges derived from parameter values
  - corresponding component values differ at most by 1

\[
\begin{align*}
(0, 2) & \rightarrow (1, 2) \\
(0, 1) & \rightarrow (1, 1) \\
(0, 0) & \rightarrow (1, 0)
\end{align*}
\]
Thomas Formalism

**Dynamics:** state transition graph

- vertex set $S$
- edges derived from parameter values
  - corresponding component values differ at most by 1
  - states differ from their successors in one component only

**asynchronous update:** sole assumption about time delays

![State transition graph](image)
**Thomas Formalism**

**Dynamics:** state transition graph

- vertex set $S$
- edges derived from parameter values
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  - states differ from their successors in one component only

**asynchronous update:** sole assumption about time delays

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

\[
\begin{align*}
\tau_2^- &< \tau_1^- \\
\tau_1^- &< \tau_2^- \\
\tau_1^- &= \tau_2^- \\
\tau_2^- &< \tau_1^- \\
\tau_1^+ &< \tau_2^+ \\
\tau_2^+ &< \tau_1^+ \\
\tau_1^- &= \tau_2^- \\
\tau_2^- &< \tau_1^- \\
\tau_1^+ &< \tau_2^+ \\
\tau_2^+ &< \tau_1^+ \\
\end{align*}
\]
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
- 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

\[ \varphi ::= c \leq q \mid c \geq q \mid c < q \mid c > q \mid \varphi_1 \land \varphi_2 \]
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- timed automata may be visualized as digraphs where
  - vertices (locations) represent states
  - edges represent (discrete) state changes
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- timed automata may be visualized as digraphs where
  - vertices (locations) represent states
  - edges represent (discrete) state changes
  - time constraints may be posed on states and edges, clocks may be reset
1. Model each component incorporating information on
   - expression levels,
   - interactions,
   - parameter values,
   - time delays.
Modus Operandi

1. Model each component incorporating information on
   - expression levels,
   - interactions,
   - parameter values,
   - time delays.

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,
   - constraints on time delays associated with state changes.
Modus Operandi

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   ▶ interactions,
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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,
   ▶ constraints on time delays associated with state changes.

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
Modeling Each Component

- one clock for each component
- expression levels

\[ f : S \rightarrow S \]
Modeling Each Component

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

\[ f : S \rightarrow S \]

\[ \alpha_0 \]

\[ \alpha_1^{-} \]

\[ \alpha_1^{+} \]

\[ \alpha_1^{0+} \]

\[ \alpha_1^{0} \]

\[ \alpha_1^{1} \]
Modeling Each Component

- one clock for each component
- expression levels – distinction between stationary states and states representing the process of expression level change
- maximal and minimal time delays associated with expression level change
- location changes due to elapse of time

\[ f : S \rightarrow S \]

\[ \alpha_1^0 \]

\[ \alpha_1^1 \]

\[ \alpha_1^{0+} \]

\[ \alpha_1^{1-} \]

\[ c_1 \geq t_1^{1-} \]

\[ c_1 \leq T_1^{1-} \]

\[ c_1 \leq T_1^{0+} \]

\[ c_1 \geq t_1^{0+} \]
Modeling Each Component

- one clock for each component
- expression levels – distinction between stationary states and states representing the process of expression level change
- maximal and minimal time delays associated with expression level change
- location changes due to elapse of time
- corresponding network interactions and parameters (“switch conditions”),
Modeling Each Component

- one clock for each component
- expression levels – distinction between stationary states and states representing the process of expression level change
- maximal and minimal time delays associated with expression level change
- location changes due to elapse of time
- corresponding network interactions and parameters (“switch conditions”), induced location changes can only be evaluated in the network context

\[ f : S \rightarrow S \]

\[ \alpha_1^{0+}, \alpha_1^{1-} \]
\[ c_1 \geq t_1^{1-} \]
\[ c_1 \leq T_1^{1-} \]
\[ el(\alpha_2) < 1 \]
\[ el(\alpha_2) \geq 1 \]

\[ \alpha_2^{0+} \]
\[ c_1 \leq T_1^{0+} \]
\[ el(\alpha_2) \geq 1 \]

\[ +, 1 \xrightarrow{1} -, 1 \]
\[ \alpha_1 \]
\[ -, 2 \xrightarrow{2} -, 1 \]
\[ \alpha_2 \]
Connecting the Parts

- product locations
- edges specified in component automata
Connecting the Parts

- 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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- consideration of behavior in agreement with time constraints

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

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

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

\[((\alpha_0, \alpha_0), (0, 0))\]
\[((\alpha_0^+, \alpha_0^+), (0, 0))\]
\[t \leq T_1^0 +, T_2^0+\]
\[((\alpha_0^+, \alpha_0^+), (t, t))\]
- description includes time component
- consideration of behavior in agreement with time constraints

\[
((\alpha_0^0, \alpha_0^0), (0, 0)) \quad \Rightarrow \quad t \leq T_1^{0+}, T_2^{0+}
\]

\[
((\alpha_1^0, \alpha_2^0), (0, 0)) \quad \Rightarrow \quad t \geq t_1^{0+}, t \leq T_1^{0+}
\]

\[
((\alpha_0^+, \alpha_2^+), (t, t)) \quad \Rightarrow \quad t \geq t_2^{0+}, t \leq T_1^{0+}
\]

\[
((\alpha_0^+, \alpha_1^2), (t, t))
\]
- description includes time component
- consideration of behavior in agreement with time constraints

\[
\begin{align*}
(\alpha_{0+}^0, \alpha_{0+}^2), (0, 0)) \\
(\alpha_{1+}^0, \alpha_{2+}^0), (0, 0)) \\
(\alpha_{1+}^0, \alpha_{2+}^0), (t, t)) \\
(\alpha_{0+}^0, \alpha_{1+}^2), (t, t)) \\
(\alpha_{0+}^0, \alpha_{1+}^2), (0, t)) \\
\end{align*}
\]
- description includes time component
- consideration of behavior in agreement with time constraints

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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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Dynamics captured in a transition system

- infinite due to time component
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Consistency: state transition graph of the Thomas formalism can be recovered from the dynamics of a suitable timed automata model

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]

\[ \alpha_1, \alpha_2, \alpha_3, \alpha_4 \]

\[ \begin{align*}
K_1,\{e_{21}\} & = 2 \\
K_1,\{e_{31}\} & = 2 \\
K_1,\{e_{11},e_{21}\} & = 2 \\
K_1,\{e_{11},e_{31}\} & = 2 \\
K_1,\{e_{21},e_{31}\} & = 2 \\
K_1,\{e_{11},e_{21},e_{31}\} & = 2 \\
K_2,\{e_{12}\} & = 2 \\
K_2,\{e_{12},e_{22}\} & = 3 \\
K_3,\{e_{13},e_{23},e_{43}\} & = 1 \\
K_4,\{e_{14},e_{24}\} & = 1 
\end{align*} \]
Bacteriophage $\lambda$
Bacteriophage $\lambda$

- elimination of pathways violating clock constraints based on temporal data
Bacteriophage $\lambda$

- elimination of pathways violating clock constraints based on temporal data
- additional information on the status of component activity

\[
\begin{align*}
\alpha^0_1 &\alpha^2_2 \alpha^0_3 \alpha^1_4 \\
\rightarrow & \\
\alpha^0_1 &\alpha^2_2 \alpha^0_3 + \alpha^1_4 \\
\rightarrow & \\
\alpha^0_1 &\alpha^2_2 \alpha^0_3 - \alpha^1_4 \\
\rightarrow & \\
\alpha^0_1 &\alpha^2_2 \alpha^0_3 \alpha^1_4 \\
\end{align*}
\]
Bacteriophage λ

- elimination of pathways violating clock constraints based on temporal data
- additional information on the status of component activity
- evaluation of feasibility and stability of behavior
Conclusion

Modeling formalism

- modular logical modeling of regulatory networks
- incorporating time delays

⇒ 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