MDSC team seminar

Qualitative modeling and dynamical analysis of Biological Regulatory Networks using Asynchronous Automata Networks

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The Modeling/Analysis duality

Modeling a system is the first step towards its comprehension
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The required analysis has an impact on modeling
- The modeling tools must be adapted to the observed properties
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  • The modeling tools must be adapted to the observed properties

Modeling choices have an impact on the results of the analysis
  • The level of details changes the quantity of obtained info
  • The size of the model increases the analysis duration
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The modeling and analysis steps of a system are strongly linked
Abstracting biological models

- Abstraction of biological components
- Discrete, asynchronous and unitary representations
Abstracting biological models

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- Discrete, asynchronous and unitary representations

Examples of discrete models

- Discrete Networks (Thomas modeling)
- Asynchronous Automata Networks
- Other extensions of the Process Hitting formalism
Abstracting biological models

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Examples of discrete models

- Discrete Networks (Thomas modeling)
- Asynchronous Automata Networks
- Other extensions of the Process Hitting formalism

Analysis of the dynamics of discrete models

- Static analysis on the structure
- Abstract interpretation
- A $\mu$-calculus approach
Abstractions of the Representation
Abstractions of the Representation
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Discretization and Asynchronism

Discretization and Asynchronism

[Richard, Advances in Applied Mathematics, 2010]
Discretization and Asynchronism


- Unknown real values of concentrations or continuous activity levels
  → Abstracted as thresholds or **discrete levels**
Qualitative modeling and dynamical analysis of BRNs using AANs

Introduction

Discretization and Asynchronism

[Richard, Advances in Applied Mathematics, 2010]

- Unknown real values of concentrations or continuous activity levels
  → Abstracted as thresholds or discrete levels
- Continuous variations of the real values
  → Unitary dynamics
Discretization and Asynchronism

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- Unknown real values of concentrations or continuous activity levels
  → Abstracted as thresholds or discrete levels
- Continuous variations of the real values
  → Unitary dynamics
- Simultaneous crossings of two thresholds never occurs
  → Asynchronous dynamics
Discrete Networks / Thomas Modeling

[Kauffman in *Journal of Theoretical Biology*, 1969]
[Thomas in *Journal of Theoretical Biology*, 1973]

- A set of components \( N = \{a, b, z\} \)
Discrete Networks / Thomas Modeling

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- A set of components \( N = \{a, b, z\} \)
- A set of discrete expression levels for each component \( a \in F^a = \{0; 2\} \)
- The set of global states \( F = F^a \times F^b \times F^z \)
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- The set of global states \( F = F^a \times F^b \times F^z \)
- An evolution function for each component \( f^z : F \rightarrow F^z \)

\[
\begin{array}{c|c}
  a & f^b(a) \\
  \hline
  0 & 0 \\
  1 & 1 \\
  2 & 1 \\
\end{array}
\quad
\begin{array}{c|c|c}
  z & b & f^a(z, b) \\
  \hline
  0 & 0 & 1 \\
  0 & 1 & 0 \\
  1 & 0 & 1 \\
  1 & 1 & 2 \\
\end{array}
\quad
\begin{array}{c|c|c}
  a & b & f^z(a, b) \\
  \hline
  0 & 0 & 0 \\
  0 & 1 & 0 \\
  1 & 0 & 0 \\
  1 & 1 & 0 \\
  2 & 0 & 0 \\
  2 & 1 & 1 \\
\end{array}
\]
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![Diagram](attachment:image.png)
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- The set of global states \( F = F^a \times F^b \times F^z \)
- Signs on the edges \( a \rightarrow z \) or signs + thresholds \( a \rightarrow^{2,+} z \)
- Discrete parameters / evolution functions \( f^a : F \rightarrow F^a \)

<table>
<thead>
<tr>
<th>( a )</th>
<th>( f^b(a) )</th>
<th>( z )</th>
<th>( b )</th>
<th>( f^a(z, b) )</th>
<th>( a )</th>
<th>( b )</th>
<th>( f^z(a, b) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
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<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
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</tbody>
</table>

Maxime FOLSCHEETTE 6/35 MDSC seminar — 2015/09/28
Several semantics exist regarding the updates:

- Synchronous (deterministic)
- **Asynchronous** (non-deterministic)
- Generalized (even more non-deterministic)

In every case, exponential size in the number of components
Qualitative modeling and dynamical analysis of BRNs using AANs

Classical Analysis of Discrete Networks

State-graph of a Discrete Network

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```
abz
000 ← 010 ← 001 ← 011
|     |     |     |
|     | 110 |     | 111
| 100 |     | 101 |     | 200 |     | 201 |     | 210 |     | 211

Attractor = minimal set of states from which the dynamics cannot escape
= terminal strongly connected component

- Stable state (state with no successors)
- Complex attractor (loop or composition of loops)
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Static Analysis of Discrete Networks


Conjectures of René Thomas:

![Diagram](attachment:image.png)
Conjectures of René Thomas:

- Multiple **stable states** $\Rightarrow$ positive cycle in the graph
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- Multiple **stable states** $\Rightarrow$ positive cycle in the graph

\[ a \xrightarrow{[0; 2]} b \xrightarrow{[0; 1]} z \xrightarrow{[0; 1]} a \]

Proofs:
- [Remy, Ruet, Thieffry in *Advances in Applied Mathematics*, 2008]
- [Richard, Comet in *Discrete Applied Mathematics*, 2007]

Other results:
- Lower & upper bounds of the number of attractors
- Functionality of the cycles
- Sufficient condition for no stable state / Topological stable states
Conjectures of René Thomas:

- Multiple **stable states** ⇒ positive cycle in the graph
- Sustained oscillations (**complex attractor**) ⇒ negative cycle in the graph
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Dynamic Analysis of Discrete Networks

- These static analysis results are not sufficient to predict the dynamics of independent components.

Examples that cannot be tackled:

1) From the initial state \((a, b, z) = (0, 0, 0)\), is it possible to reach \(z = 2\)?
2) Does \((0, 0, 0)\) belong to an attractor?
3) What is the set of attractors of the model?
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- Temporal logics (LTL, CTL, CTL*)

More precise but require to compute the whole state graph

Examples:
1) \((a = 0 \land b = 0 \land z = 0) \Rightarrow EF(z = 2)\)
2) \((a = 0 \land b = 0 \land z = 0) \Rightarrow AG(EF(a = 0 \land b = 0 \land z = 0))\)
3) ???
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3) ???

- Applications of CTL and LTL

Check a property on a given model: NuSMV, LibDDD, ...
Create a model for which a property holds: SMBioNet, SPuTNIk, ...
[Bernot, Comet, Richard, Guespin in *Journal of Theoretical Biology, 2004*]
The Enriched Process Hitting

Synchronized Automata Networks

- Process Hitting
- Discrete Networks (Thomas)
The Enriched Process Hitting

Synchronized Automata Networks

- Process Hitting
  - Abstract interpretation

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Qualitative modeling and dynamical analysis of BRNs using AANs

Analysis with Asynchronous Automata Networks

The Enriched Process Hitting

Synchronized Automata Networks

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The Enriched Process Hitting
Example of enriched Process Hitting Model
Example of enriched Process Hitting Model
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Model from [François et al. in Molecular Systems Biology, 2007]
Static analysis

- No conflict
- All leaves are $\emptyset$

![Diagram of AANs and BRNs](diagram.png)
Qualitative modeling and dynamical analysis of BRNs using AANs — Analysis with Asynchronous Automata Networks

Static analysis

- No conflict
- All leaves are $\emptyset$

$$\{c_0, f_1\} \rightarrow a_0 \Rightarrow a_1$$
Static analysis

- No conflict
- All leaves are $\emptyset$

\[
\begin{align*}
\{c_0, f_1\} &\rightarrow a_0 \rightarrow a_1 \\
\{c_0, f_1\} &\rightarrow c_0 \rightarrow c_0
\end{align*}
\]
Static analysis

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\[ \{c_0, f_1\} \rightarrow a_0 \rhd a_1 \]
Static analysis

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\[ \{c_0, f_1\} \rightarrow a_0 \rightarrow a_1 \]
Qualitative modeling and dynamical analysis of BRNs using AANs • Analysis with Asynchronous Automata Networks

Static analysis

- No conflict
- All leaves are \( \emptyset \)

\[ \{ c_0, f_1 \} \rightarrow a_0 \xrightarrow{\sim} a_1 \]

\[ f_1 \rightarrow f_1 \xrightarrow{\sim} f_1 \rightarrow \emptyset \]

\[ c_0 \rightarrow c_0 \xrightarrow{\sim} c_0 \rightarrow \emptyset \]
Static analysis

- No conflict
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\[
\begin{align*}
\{c_0, f_1\} &\rightarrow a_0 \rightarrow a_1 \\
c_0 &\rightarrow c_0 \\
f_1 &\rightarrow f_1 \\
\end{align*}
\]
Static analysis

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\[
\begin{align*}
\{a_1, f_1\} & \rightarrow c_0 \triangleright c_1 \quad :: \quad \{c_1\} \rightarrow a_1 \triangleright a_0
\end{align*}
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Qualitative modeling and dynamical analysis of BRNs using AANs

Analysis with Asynchronous Automata Networks

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$$\{a_1, f_1\} \rightarrow c_0 \vdash c_1 :: \{c_1\} \rightarrow a_1 \uparrow a_0$$
Qualitative modeling and dynamical analysis of BRNs using AANs

Analysis with Asynchronous Automata Networks

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\[ \{a_0\} \rightarrow c_1 \uparrow c_0 :: \{c_0, f_1\} \rightarrow a_0 \uparrow a_1 \]
Qualitative modeling and dynamical analysis of BRNs using AANs • Analysis with Asynchronous Automata Networks

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\[
\begin{align*}
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\end{align*}
\]
Qualitative modeling and dynamical analysis of BRNs using AANs • Analysis with Asynchronous Automata Networks

Static analysis

- No conflict
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$$\{a_0\} \rightarrow c_1 \uparrow c_0 :: \{c_0, f_1\} \rightarrow a_0 \uparrow a_1$$
Implementation of the Static Analysis Into PINT

Complexity:

- Computation of the local causality graph:
  - Polynomial in the number of sorts
  - Exponential in the number of processes of each sort
- Analysis of the graph (sufficient condition):
  - Polynomial in the size of the graph
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  - Polynomial in the size of the graph

Makes the study of large networks tractable:

<table>
<thead>
<tr>
<th>Model</th>
<th>Automata</th>
<th>Actions</th>
<th>States</th>
<th>libddd$^1$</th>
<th>GINsim$^2$</th>
<th>PINT</th>
</tr>
</thead>
<tbody>
<tr>
<td>egfr20</td>
<td>35</td>
<td>670</td>
<td>$2^{64}$</td>
<td>&lt;1s</td>
<td>0.02s</td>
<td></td>
</tr>
<tr>
<td>tcrsig40</td>
<td>54</td>
<td>301</td>
<td>$2^{73}$</td>
<td>$\infty$</td>
<td>0.02s</td>
<td></td>
</tr>
<tr>
<td>tcrsig94</td>
<td>133</td>
<td>1124</td>
<td>$2^{194}$</td>
<td>(&gt;1min – $\infty$)</td>
<td>0.03s</td>
<td></td>
</tr>
<tr>
<td>egfr104</td>
<td>193</td>
<td>2356</td>
<td>$2^{320}$</td>
<td>(&gt;1min – $\infty$)</td>
<td>0.16s</td>
<td></td>
</tr>
</tbody>
</table>

$^1$ LIP6/Move [Couvreur et al., Lecture Notes in Computer Science, 2002]
$^2$ TAGC/IGC [Chaouiya, Naldi, Thieffry, Methods in Molecular Biology, 2012]

egfr20 : Epithelial Growth Factor Receptor (20 components) [Sahin et al., 2009]
egfr104 : Epithelial Growth Factor Receptor (104 components) [Samaga et al., 2009]
tcrgsig40 : T-Cell Receptor (40 composants) [Klamt et al., 2006]
tcrgsig94 : T-Cell Receptor (94 composants) [Saez-Rodriguez et al., 2007]
Classes of priorities

[Folschette et al. in *Theoretical Computer Science*, 2015b]

- Each action is associated to a discrete priority
- An action is playable only if no other action with higher priority is playable

\[a \xrightarrow{1} b \xrightarrow{1} \quad \text{cannot be reached}\]
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- Each action is associated to a discrete priority
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\[ a \xrightarrow{1} b \]

\[
\begin{array}{c}
1 & 2 & 3 & \cdots & n \\
\text{highest priority} & & & & \text{lowest priority}
\end{array}
\]

\[ \rightarrow b_1 \text{ cannot be reached} \]
Temporal Simulation
[Paulevé (PhD thesis), 2011]

- Simulation with stochastic parameters:

\begin{align*}
\text{a} & = [0.742; 1.29] \text{ (mean 1)} \\
\text{c} & = [1.48; 2.59] \text{ (mean 2)} \\
\text{f} & = [23.9; 35.4] \text{ (mean 30)}
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  \[
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Spatial Simulation

Paulevé (PhD thesis), 2011

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\(a = [0.742; 1.29]\) (mean 1)
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\(\Rightarrow a < c < f\)

Stochastic parameters:
Temporal Simulation
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\end{align*}
Example with Classes of Priorities
Example with Classes of Priorities
Neutralizing Edges

- Integration of temporal data about relative reaction speeds
- Atomistic preemptions between actions similar to “atomistic priorities”

\[ c_0 \rightarrow d_0 \uparrow d_1 \text{ cannot be plays while } a_0 \rightarrow b_0 \uparrow b_1 \text{ is playable} \]

\[ \rightarrow d_1 \text{ is always reached after } b_1 \]
Neutralizing Edges

- Integration of temporal data about relative reaction speeds
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$c_0 \rightarrow d_0 \uparrow d_1$ cannot be plays while $a_0 \rightarrow b_0 \uparrow b_1$ is playable

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Neutralizing Edges

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Example with Neutralizing Edges
Equivalence Between Process Hitting Extensions

- Synchronous Automata Networks
- Asynchronous Automata Networks
- Process Hitting with neutralizing edges
- Process Hitting with classes of priority
- Standard Process Hitting

All developed enrichments have the same expressivity

- Expressive power improved
- Can always be translated to the canonical form
- But sometimes at the cost of an exponential translation
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Translation From and To Other Discrete Models

- Equivalence with Discrete Networks / Thomas modeling
- Translation towards (bounded) Petri nets with inhibitor arcs
- Translation from the Boolean semantics of Biocham
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Inferring a BRN with Thomas’ parameters

\[
\begin{align*}
\omega & \quad | \quad k_{z,\omega} \\
- & \quad + & \quad 1 \\
- & \quad - & \quad 0 \\
+ & \quad + & \quad 2 \\
+ & \quad - & \quad 1
\end{align*}
\]
Inferring a BRN with Thomas’ parameters

\begin{align*}
    a & \rightarrow b \\
    b & \rightarrow c \\
    c & \rightarrow a
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Inferring the Interaction Graph

[Folschette et al. in *Theoretical Computer Science*, 2015a]
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→ Exhaustive search in all possible configurations
Inferring the Interaction Graph

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→ Exhaustive search in all possible configurations

1. Pick one regulator \([a]\), and choose an active process for all the others \([b_0]\).
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1. Pick one regulator $[a]$, and choose an active process for all the others $[b_0]$.
2. Change the active process of the regulator $[a_0, a_1]$ and watch the evolution.
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Inferring the Interaction Graph

[Folschette et al. in *Theoretical Computer Science*, 2015a]

→ Exhaustive search in all possible configurations

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4. Iterate
Qualitative modeling and dynamical analysis of BRNs using AANs

Links with Other formalisms

Inferring the Interaction Graph

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\{b = 1\} \Rightarrow \sim
\{b = 0\} \Rightarrow 1+
Inferring the Interaction Graph

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Inferring the Interaction Graph

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4. Iterate and conclude globally.

Problematic cases:
→ No focal processes (cycle)
→ Opposite influences (\(+ & -\)) \(\Rightarrow\) Unsigned edge
Inferring Parameters

[Folschette et al. in *Theoretical Computer Science, 2015a*]
Inferring Parameters

[Folschette et al. in *Theoretical Computer Science*, 2015a]

1. For each configuration of resources \( \omega = \{a^+, b^-\} \)
Inferring Parameters

[Folschette et al. in Theoretical Computer Science, 2015a]

1. For each configuration of resources find the focal processes.

\[ \omega = \{ a^+, b^- \} \]
Inferring Parameters

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1. For each configuration of resources \( \omega = \{a^+, b^-\} \)
find the **focal processes**. If possible, conclude. \( k_z, \{a^+, b^-\} = 1 \)
Inferring Parameters

[Folschette et al. in *Theoretical Computer Science*, 2015a]

1. For each configuration of resources $\omega = \{a^+, b^-\}$ find the focal processes. If possible, conclude. $[k_{z,\omega}, \{a^+, b^-\} = 1]$

Inconclusive cases:
- Behavior cannot be represented as a BRN
- Lack of cooperation (no focal processes)
1. For each configuration of resources $[\omega = \{a^+, b^-\}]$ find the **focal processes**. If possible, conclude. $[k_z,\{a^+, b^-\} = 1]$

**Inconclusive cases:**
- Behavior cannot be represented as a BRN
- Lack of cooperation (no focal processes)

2. If some parameters could not be inferred, enumerate all admissible parametrizations, regarding:
   - Biological constraints [Bernot et al. in *Concurrent Models in Molecular Biology*, 2007]
   - The dynamics of the Process Hitting

   
   $[k_z,\{a^+, b^-\} \in \{0; 1; 2\}; k_z,\{a^-, b^+\} \in \{0; 1; 2\}]$
Translation to Thomas Modeling

[Folschette et al. in *Theoretical Computer Science*, 2015a]

- Two successive inferences: 1) interaction graph; 2) parameters
- Exhaustive analysis of the local dynamics for each regulator
- Enumeration of all parametrizations compatible with the dynamics

**Complexity:**
- Linear in the number of genes,
- Exponential in the number of regulators of one component
Qualitative modeling and dynamical analysis of BRNs using AANs

Links with Other formalisms

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<table>
<thead>
<tr>
<th>Models</th>
<th>Inference the IG</th>
<th>Inference of parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name</td>
<td>Sorts</td>
<td>Processes</td>
</tr>
<tr>
<td>egfr20</td>
<td>42</td>
<td>152</td>
</tr>
<tr>
<td>tcrsig40</td>
<td>54</td>
<td>156</td>
</tr>
<tr>
<td>tcrsig94</td>
<td>133</td>
<td>448</td>
</tr>
<tr>
<td>egfr104</td>
<td>193</td>
<td>744</td>
</tr>
</tbody>
</table>

egfr20 : Epithelial Growth Factor Receptor (20 components) [Sahin et al., 2009]
egfr104 : Epithelial Growth Factor Receptor (104 components) [Samaga et al., 2009]
tcrsig40 : T-Cell Receptor (40 composants) [Klamt et al., 2006]
tcrsig94 : T-Cell Receptor (94 composants) [Saez-Rodriguez et al., 2007]
Qualitative modeling and dynamical analysis of BRNs using AANs ▪ Analysis with μ-calculus

The Modal μ-calculus

**LTL:** Example of the “Until” operator

\[ p U q \equiv \text{“Either q, or } p \text{ and the next state also verifies } p U q” \]

⇒ Implicit fixed point

(Modal) μ-calculus makes such fixed points explicit

\[ \varphi = p \mid \neg \varphi \mid \varphi \land \varphi \mid \varphi \lor \varphi \mid \diamond \varphi \mid \Box \varphi \mid \mu X.\varphi \mid \nu X.\varphi \mid X \]

• Basic property: \( p \) (“\( p \) is verified in this node”)
• Modal operators: \( \Box \) (“for all successors”), \( \diamond \) (“there exists a successor”)
• Fixed points: \( \mu \) (least fixed point), \( \nu \) (greatest fixed point)

Polyadic (modal) μ-calculus allows to manipulate several tokens in parallel

\[ \varphi = p_i \mid i \leftarrow j \mid i = j \mid \neg \varphi \mid \varphi \land \varphi \mid \varphi \lor \varphi \mid \diamond_i \varphi \mid \Box_i \varphi \mid \mu X.\varphi \mid \nu X.\varphi \mid X \]

• Token manipulation:
  \( i = j \) (“tokens \( i \) and \( j \) point to the same node”)
  \( i \leftarrow j \) (“move token \( i \) to the position of token \( j \)”)

Maxime FOLSCHE TTE 27/35 MDSC seminar — 2015/09/28
Qualitative modeling and dynamical analysis of BRNs using AANs  ○ Analysis with \( \mu \)-calculus

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The Modal $\mu$-calculus

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Polyadic (modal) $\mu$-calculus allows to manipulate several tokens in parallel
Examples with Modal $\mu$-calculus

No tokens: only one evolution is studied

**Atomic property** $(p, q, r)$

\[
\begin{align*}
[p] &= \{p\} \\
[q \lor r] &= \{q; r\}
\end{align*}
\]

**Possible future** ("may")

\[
\Box q = \{p\}
\]

**Necessary future** ("must")

\[
\begin{align*}
\Box q &= \emptyset \\
\Box p &= \{q; r\}
\end{align*}
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Examples with Modal $\mu$-calculus

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Qualitative modeling and dynamical analysis of BRNs using AANs

Analysis with $\mu$-calculus

Examples with Polyadic $\mu$-calculus

Atomic property $(p, q, r)$

\[
[p_1 \land r_2] = \{(p, r)\} \\
[p_1] = \{(p, p); (p, q); (p, r)\}
\]

Token affectation $(i \leftarrow j)$

\[
\{2 \leftarrow 1\} p_1 \land p_2 = \{(p, p); (p, q); (p, r)\}
\]

Token comparison $(i = j)$

\[
[1 = 2] = \{(p, p); (q, q); (r, r)\}
\]

Possible future (“may”)

\[
[\Diamond_1 q] = \{(p, p); (p, q); (p, r)\}
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Examples with Polyadic $\mu$-calculus

Atomic property $(p, q, r)$
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[\mu p_1 \land r_2] = \{(p, r)\} \\
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Token affectation $(i \leftarrow j)$
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Examples with Polyadic μ-calculus

Least fixed point ($\mu$)

$$\phi = \mu X.(\Box_1 \bot \land \Box_2 \bot) \lor \Diamond_1 \Diamond_2 X$$

Iterations:

$$\begin{align*}
[\phi]_0 &= \emptyset \\
[\phi]_1 &= \{(a_1, b_1)\} \\
[\phi]_2 &= \{(a_1, b_1); (a_2, b_2)\} \\
[\phi]_3 &= \{(a_1, b_1); (a_2, b_2); (a_3, b_3)\} \\
&\vdots
\end{align*}$$

Generalization:

$$[\phi] = \{(a_i, b_i) \mid i \in [1; \min(m, n)]\}$$

Idea: use one (or $n$) token per automata
Examples with Polyadic $\mu$-calculus

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Examples with Polyadic $\mu$-calculus

Least fixed point ($\mu$)

$$\phi = \mu X.(\square_1 \perp \land \square_2 \perp) \lor \diamond_1 \diamond_2 X$$

Iterations:

- $[\phi]_0 = \emptyset$
- $[\phi]_1 = \{(a_1, b_1)\}$
- $[\phi]_2 = \{(a_1, b_1); (a_2, b_2)\}$
- $[\phi]_3 = \{(a_1, b_1); (a_2, b_2); (a_3, b_3)\}$
  ...

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Examples with Polyadic $\mu$-calculus

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Search for Attractors with Polyadic $\mu$-calculus

\[
\phi_{\text{att}} = \{ y \leftarrow x \} \nu W. (\mu Z. (x = y) \lor (\Diamond_x Z)) \land (\Box_x W)
\]

\[
\phi_{\text{reach}} \lor \phi_{\text{explore}}
\]

- $\llbracket \phi_{\text{reach}} \rrbracket = \{ (s; t) | s \rightarrow^* t \}$
  $\phi_{\text{reach}} \equiv \text{“There exists a path from } x \text{ to } y \text{”}$

- $\llbracket \phi_{\text{explore}} \rrbracket = \{ (s; t) | \forall s', s \rightarrow^* s' \Rightarrow s' \rightarrow^* t \}$
  $\phi_{\text{explore}} \equiv \text{“All successors of } x \text{ can reach } y \text{”}$

- $\llbracket \phi_{\text{att}} \rrbracket = \{ (s; s) | \forall s', s \rightarrow^* s' \Rightarrow s' \rightarrow^* s \}$
  $\phi_{\text{att}} \equiv \text{“} x \text{ belongs to an attractor”}$
Search for Attractors with Polyadic $\mu$-calculus

$\phi_{att} = \{y \leftarrow x\} \nu W. (\mu Z. (x = y) \lor (\Box x Z)) \land (\Box x W)$

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  $\varphi_{\text{att}} \equiv \text{"} x \text{ belongs to an attractor\"}
Search for Switches with Polyadic μ-calculus

\[ \varphi_{\text{switch}}(a) = (\mu W. (x = a) \lor (\Diamond_x W)) \land \Diamond_x \{x \leftarrow y\}(\nu Z. \neg(y = a) \land (\Box_y Z)) \]

- \([\varphi_{\text{reach}}] = \{(s; t) \mid s \rightarrow^* a\}\)
  \(\varphi_{\text{reach}} \equiv \text{“There exists a path from } x \text{ to } a\)

- \([\varphi_{\text{noreach}}] = \{(s; t) \mid \neg(t \rightarrow^* a)\}\)
  \(\varphi_{\text{noreach}} \equiv \text{“There exists no path from } y \text{ to } a\)

- \([\varphi_{\text{switch}}] = \{(s; t) \mid s \rightarrow t \land s \rightarrow^* a \land \neg(t \rightarrow^* a)\}\)
  \(\varphi_{\text{switch}} \equiv \text{“There is a switch between } x \text{ and } y\)
Search for Switches with Polyadic $\mu$-calculus

$\varphi_{\text{switch}}(a) = \left( \mu W.(x = a) \lor (\Diamond_x W) \right) \land \\
\Diamond_x \{x \leftarrow y\} \left( \nu Z.\neg(y = a) \land (\Box_y Z) \right)$

$[\varphi_{\text{reach}}] = \{(s; t) | s \rightarrow^* a\}$
$\varphi_{\text{reach}} \equiv \text{“There exists a path from } x \text{ to } a\text{”}$

$[\varphi_{\text{noreach}}] = \{(s; t) | \neg(t \rightarrow^* a)\}$
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$\varphi_{\text{switch}} \equiv \text{“There is a switch between } x \text{ and } y\text{”}$
Search for Switches with Polyadic $\mu$-calculus

Let $\varphi_{\text{reach}}$ be the property:

$$\varphi_{\text{reach}} = (\mu W. (x = a) \lor (\Diamond x W)) \land (\Box x \{x \leftarrow y\} (\nu Z. \neg (y = a) \land (\Box y Z)))$$

- $\varphi_{\text{reach}}$ equals "There exists a path from $x$ to $a$"

Let $\varphi_{\text{noreach}}$ be the property:

$$\varphi_{\text{noreach}} = \{ (s; t) | \neg(t \rightarrow^* a) \}$$

- $\varphi_{\text{noreach}}$ equals "There exists no path from $y$ to $a$"

Let $\varphi_{\text{switch}}$ be the property:

$$\varphi_{\text{switch}} = \{ (s; t) | s \rightarrow t \land s \rightarrow^* a \land \neg(t \rightarrow^* a) \}$$

- $\varphi_{\text{switch}}$ equals "There is a switch between $x$ and $y$"
Search for Switches with Polyadic μ-calculus

\[ \varphi_{\text{switch}}(a) = \left( \mu W. (x = a) \lor (\diamond x W) \right) \land \diamond_x \{x \leftarrow y\}(\nu Z. \lnot (y = a) \land (\square y Z)) \]

- \( [\varphi_{\text{reach}}] = \{(s; t) \mid s \rightarrow^* a\} \)
  \( \varphi_{\text{reach}} \equiv \) “There exists a path from \( x \) to \( a \)”

- \( [\varphi_{\text{noreach}}] = \{(s; t) \mid \lnot (t \rightarrow^* a)\} \)
  \( \varphi_{\text{noreach}} \equiv \) “There exists no path from \( y \) to \( a \)”

- \( [\varphi_{\text{switch}}] = \{(s; t) \mid s \rightarrow t \land s \rightarrow^* a \land \lnot (t \rightarrow^* a)\} \)
  \( \varphi_{\text{switch}} \equiv \) “There is a switch between \( x \) and \( y \)”
Generic bisimulation between two models:

\[
\varphi_{\text{bisim}} = \nu X. \left( \bigwedge_{p \in P} p_1 \leftrightarrow p_2 \right) \land \left( \Box_1 \Diamond_2 X \land \Box_2 \Diamond_1 X \right)
\]

Bisimulation only on two sets of observable components \(O\) and \(O'\):

\[
\varphi_{\text{bisim-obs}} = \nu X. \left( \bigwedge_{p \in P} \bigwedge_{(i,j) \in C} p_i \leftrightarrow p_j \right) \land \left( \Box^* \Box^* O \Diamond^* \Diamond^* O' X \right)
\]
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  - Discrete Networks / Thomas modeling
  - Asynchronous Automata Networks
  - Other extensions of the Process Hitting

- Static analysis based on the structure
  - Results on attractors (multiple stable states / complex attractors)
  - But results are not always fine enough

- Static analysis by abstract interpretation
  - Reachability properties
  - Very efficient (polynomial complexity)
  - Broad rand of models (+ translations)
  - But only one kind of property (CTL operator $EF$)

- $\mu$-calculus
  - More generic than CTL*
  - Example: enumeration of attractors
  - More ongoing work: cycles, switches...
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Thank you