Colored Petri Nets to Model and Simulate Biological Systems

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Outline

- Motivation
- Colored Petri nets-based framework
- Functionalities and features
- Constructing colored Petri net models
- Outlook
Motivation
Low-level Petri nets do not scale,
Mainly restricted to relatively small models,
Difficult to manage and understand large-scale nets,
Increasing risk of modeling errors for large-scale nets.
Colored Petri nets

- Compact and readable representation,
- Increasing net size = increasing color sets,
- Analysis techniques of low-level Petri nets by automatic unfolding,
- Analysis techniques of high-level Petri nets.
Example: the repressilator
Example: the repressilator

- **gene_a**: generate, proteine_a, block_a, unblock, degrade
- **gene_b**: generate, proteine_b, block_b, unblock, degrade
- **gene_c**: generate, proteine_c, block_c, unblock, degrade
Colored Petri net model for the repressilator

Declarations

Colorset Gene = enum with a-c
Variable x: Gene
Colored Petri net model for the generalized repressilator

Declarations

Colorset Gene = enum with a-i

Variable x: Gene
Colored Petri nets-based framework
Colored Petri nets-based framework

![Diagram showing the relationship between Colored Petri nets (CPNs) and Quantitative Petri nets (QPNs)]

- \( \text{SPN}^C \)
- \( \text{QPN}^C \)
- \( \text{CPN}^C \)

**Axes:**
- **Discrete State Space**
- **Continuous State Space**

**Annotations:**
- **Time-free**
- **Timed, Quantitative**

**Arrows:**
- **Approximation**
- **Abstraction**
Colored qualitative Petri net (\(QPN^C\))

- A colored extension of extended P/T net,
  e.g., inhibitor arc, read arc, equal arc and reset arc,
- Predefined data types for color set definition:
  - Basic types: dot, integer, string, Boolean, enumeration, index,
  - Structured types: product, union.
Colored stochastic Petri net ($SPN^C$)

- A colored extension of biochemicaly interpreted extended stochastic Petri nets,
- Many features helpful for modeling biological systems, e.g., initial marking definition, rate function definition.
Functionalities and features
Functionalities

- Colored Petri net models drawn as usual.
- Automatic syntax checking of declarations and expressions.
- Qualitative animation
  - Automatic animation,
  - Single-step animation by manually choosing a binding.
- Stochastic simulation:
  - Done on an automatically unfolded Petri net,
  - Several algorithms, e.g. Gillespie stochastic simulation algorithm (SSA),
  - Results for colored or uncolored places/transitions.
- $QPN^C$ and $SPN^C$ are exported to different net formalisms.
Features for modeling biological systems

1. Concise specification of initial markings,
2. Rate function for each instance of a colored transition,
3. Special arc types:
   - inhibitor arc,
   - read arc,
   - equal arc,
   - reset arc,
   - modifier arc,
4. Transition types:
   - stochastic transitions with freestyle rate functions,
   - immediate firing,
   - deterministic firing delay,
   - scheduled firing.
1. Specification of initial markings

- Specifying colors and their corresponding tokens as usual,
- Specifying a set of colors with the same number of tokens,
- Using a predicate to choose a set of colors and then specifying the same number of tokens,
- Using the `all()` function to specify all colors with a specified number of tokens.

<table>
<thead>
<tr>
<th>Color/Predicate/Function</th>
<th>marking</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>4,5,7</td>
<td>2</td>
</tr>
<tr>
<td>$x &gt; 10$</td>
<td>3</td>
</tr>
<tr>
<td>all()</td>
<td>4</td>
</tr>
</tbody>
</table>

Colorset $CS = \text{int with 1-100}$;
2. Rate function for each instance of a colored transition

Declarations:
Colorset CS = int with 1-2;
Variable x : CS;

[x=1] MassAction( 0.01 )
[x=2] LevelInterpretation(0.1,16)
3. Special arc types

Declarations:
Colorset CS=int with 1,2;
Variable x:CS;
Constructing colored Petri net models
Basic colored Petri net components

(a)

Declarations:

colorset CS = int with 1,2;
variable x : CS ;

(b)

decalarations:

colorset CS = int with 1,2;
variable x : CS ;

(c)

(d)
Cooperative binding of oxygen to hemoglobin

- Binding of oxygen to the four subunits of a hemoglobin heterotetramer,
- Oxygen (O2) is represented in the form of multiple copies of one logical place

Cooperative binding of oxygen to hemoglobin

- Subnet partition,
- Node set partition.
Cooperative binding of oxygen to hemoglobin

- Define color sets and variables,
- Assign color sets to places,
- Define guards/rate functions for transitions
- Write arc expressions.
Cooperative binding of oxygen to hemoglobin
Cooperative binding of oxygen to hemoglobin: declarations for the colored models

Declarations

Colorset Dot = dot;
Colorset HbO2 = int with 0-4;
Colorset Level = enum with H,L;
Colorset P = product with HbO2 × Level;
Variable x: HbO2;
Variable y: Level;
C. elegans vulval development model
C. elegans vulval development model
C. elegans vulval development model

Colorset Dot = dot;
Colorset Cell = enum with c3,c4,c5,c6,c7,c8;
Variable x: Cell;
Colored stochastic Petri net model for the repressilator

Declarations

Colorset Gene = enum with a-c

Variable x: Gene
Colored stochastic Petri net model for the repressilator

<table>
<thead>
<tr>
<th>Transition</th>
<th>Rate function</th>
</tr>
</thead>
<tbody>
<tr>
<td>generate</td>
<td>0.1 ( \times ) gene</td>
</tr>
<tr>
<td>block</td>
<td>1.0 ( \times ) proteine</td>
</tr>
<tr>
<td>unblock</td>
<td>0.0001 ( \times ) blocked</td>
</tr>
<tr>
<td>degrade</td>
<td>0.001 ( \times ) proteine</td>
</tr>
</tbody>
</table>

Stochastic Result: repressilatorex.colstochpn
Colored stochastic Petri net model for the repressilator

[Diagram of a colored stochastic Petri net model]

Stochastic Result: repressilatorex.colstochpn

[Graph showing time vs. value for different proteins]
Outlook
Outlook

- Improving $QPN^C$ and $SPN^C$ prototypes,
- Developing analysis tools for $SPN^C$,
- Developing the $CPN^C$ prototype,
- Considering how to automatically create colored Petri nets from non-coloured Petri nets (automatic folding),
- Working on a $SPN^C$ model for C. elegans vulval development,
- Working on a case study, the underlying uncolored model: about 110,000 places and 135,000 transitions.
Acknowledgments

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Thanks for your attention!

Begin to demonstrate $QPN^C/SPN^C$