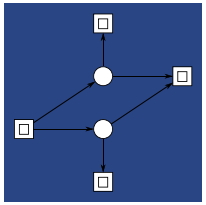

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Colored Petri Nets to Model and Simulate Biological Systems

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BioPPN, Braga
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Outline

- Motivation
- Colored Petri nets-based framework
- Functionalities and features
- Constructing colored Petri net models
- Outlook

Motivation

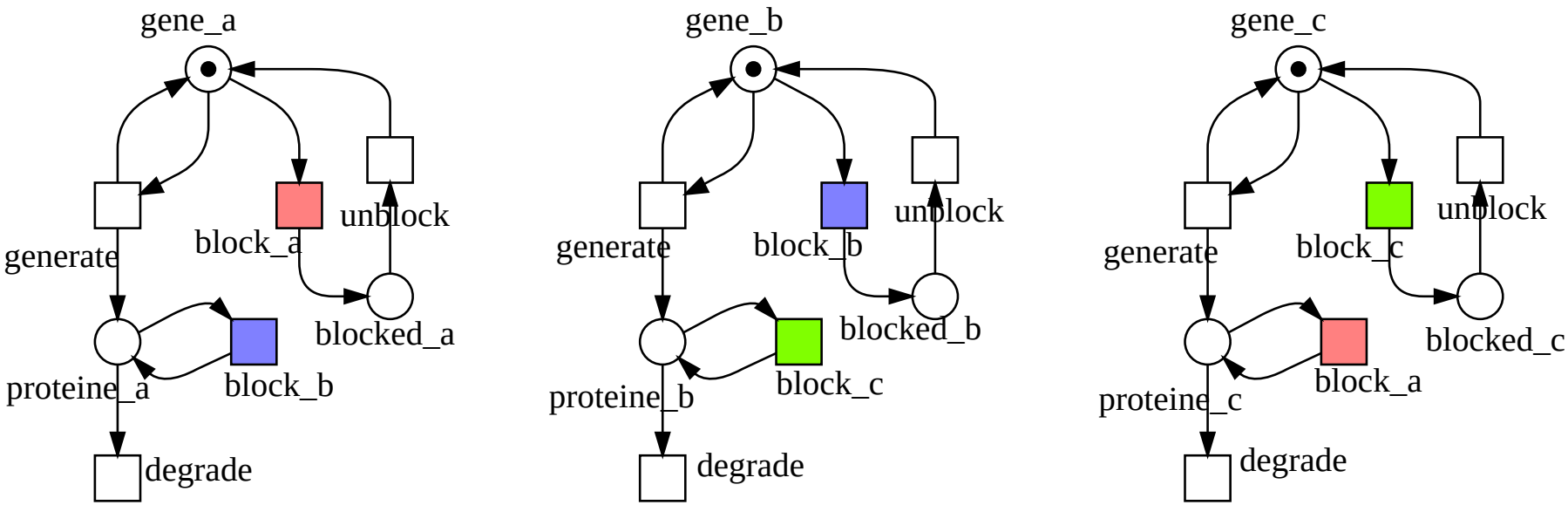
Low-level Petri nets

- 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.

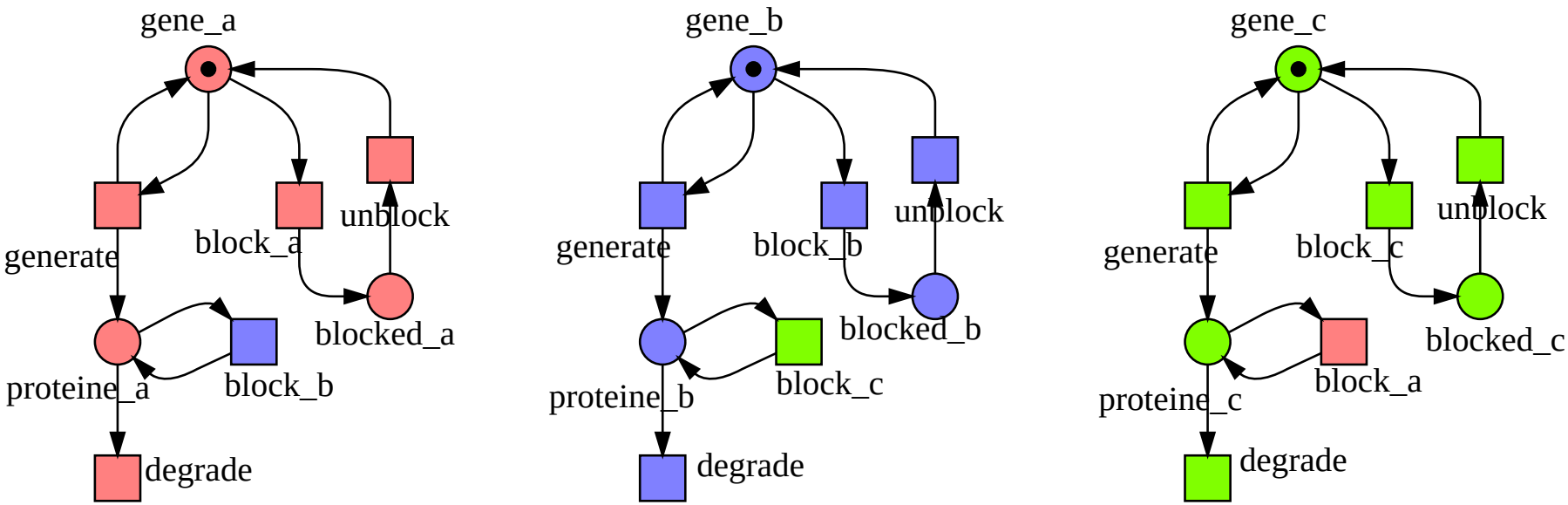
Colored Petri nets

- 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.

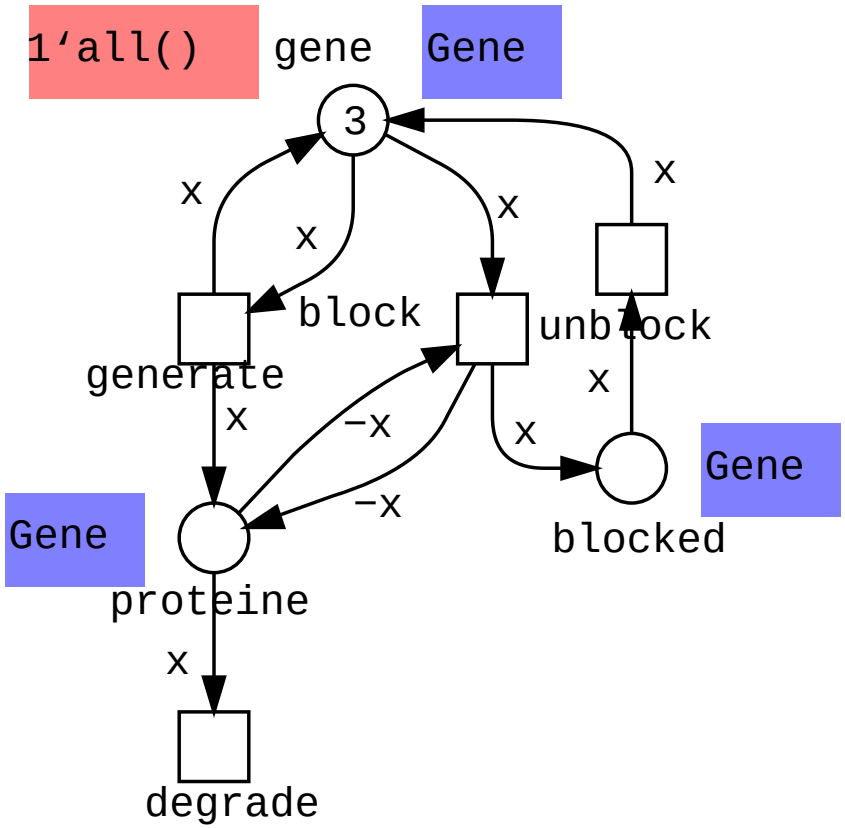
Example: the repressilator



Example: the repressilator



Colored Petri net model for the repressilator

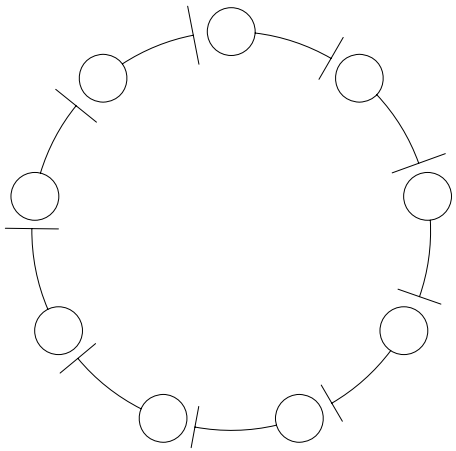


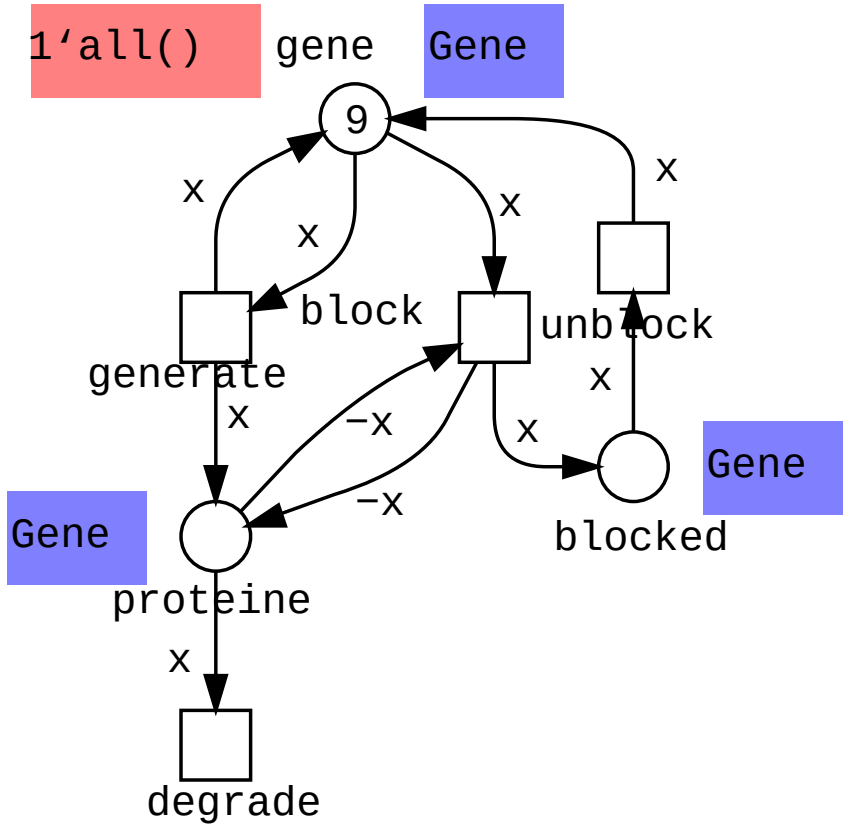
Declarations

Colorset Gene = enum with a-c

Variable x: Gene

Colored Petri net model for the generalized repressilator





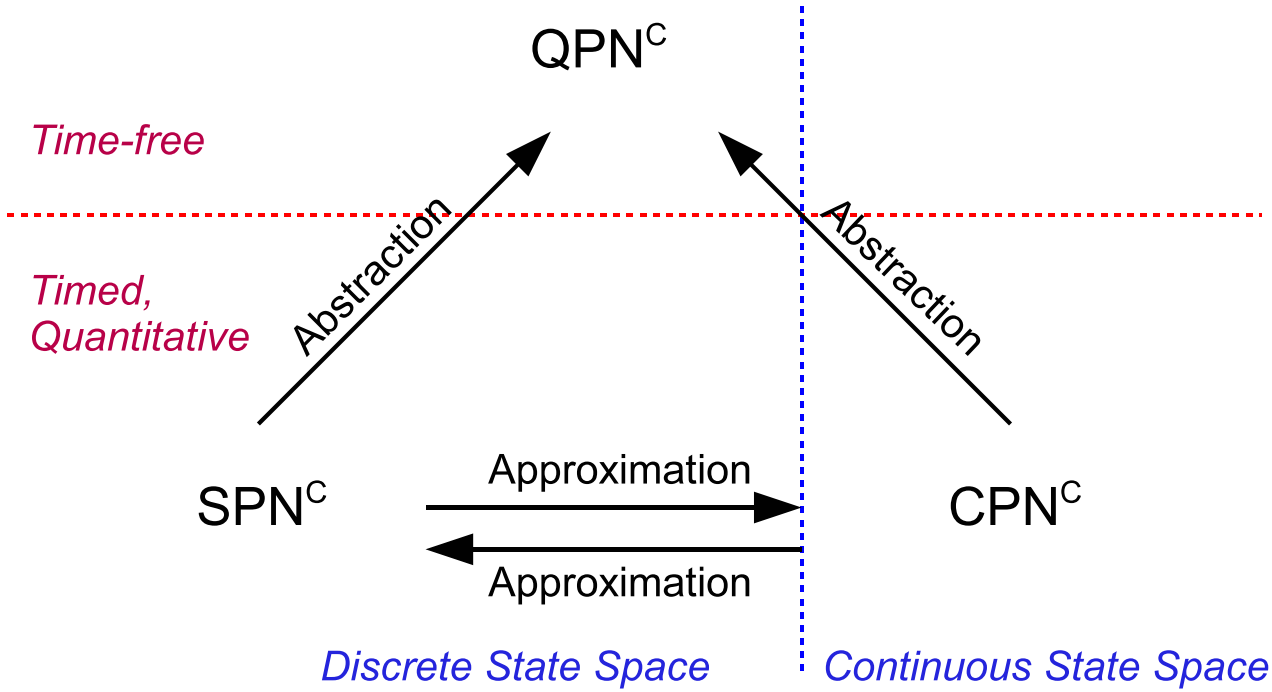
Declarations

Colorset Gene = enum with a-i

Variable x: Gene

Colored Petri nets-based framework

Colored Petri nets-based framework



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

  biochemically interpreted extended stochastic Petri nets,
- Many features helpful for modeling biological systems,

  e.g., initial marking definition, rate function definition.

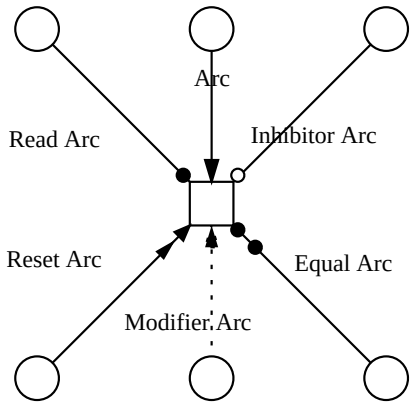
Functionalities and features

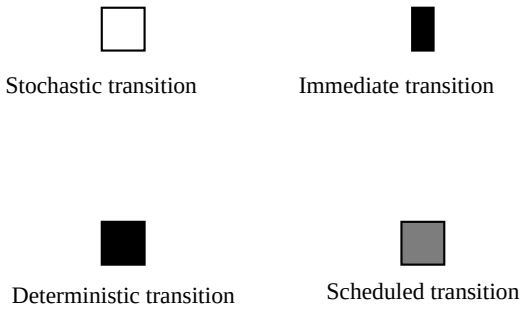
Functionalities

- 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. Gilespie 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.





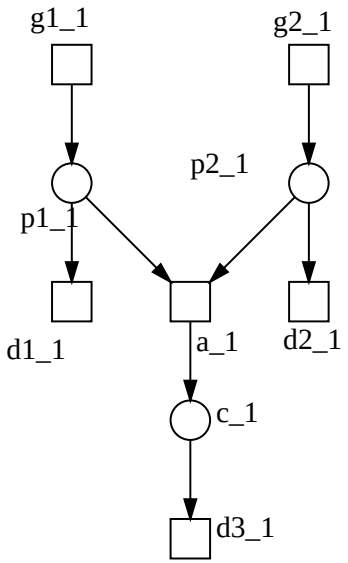
1. Specification of initial markings

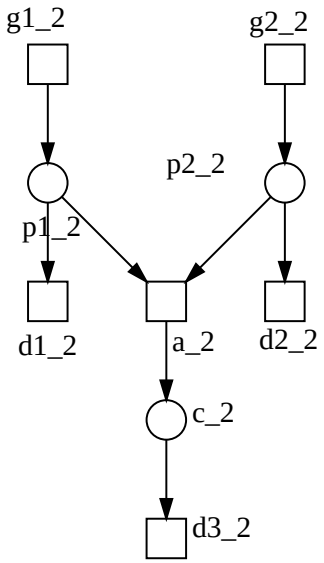
- Specifying colors and their corresponding tokens as usual,
- Specifying a set of colors with the same number of tokens,
- Using a predicate to choose a set of colors and then specifying the same number of tokens,
- Using the *all*() function to specify all colors with a specified number of tokens.

Color/Predicate/Function	marking
1	1
4,5,7	2
$x > 10$	3
all()	4

Colorset CS = int with 1-100;

2. Rate function for each instance of a colored transition





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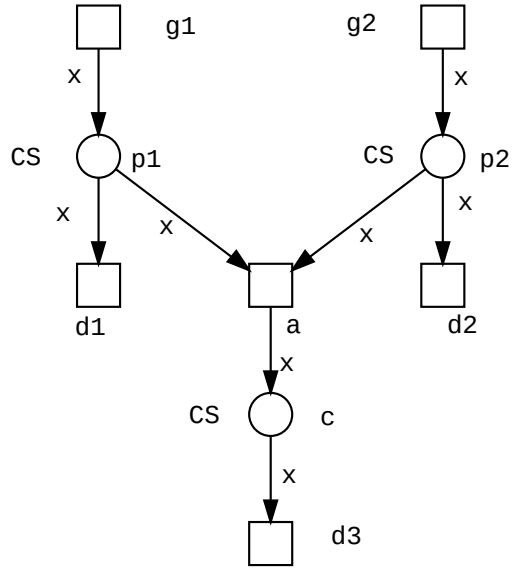
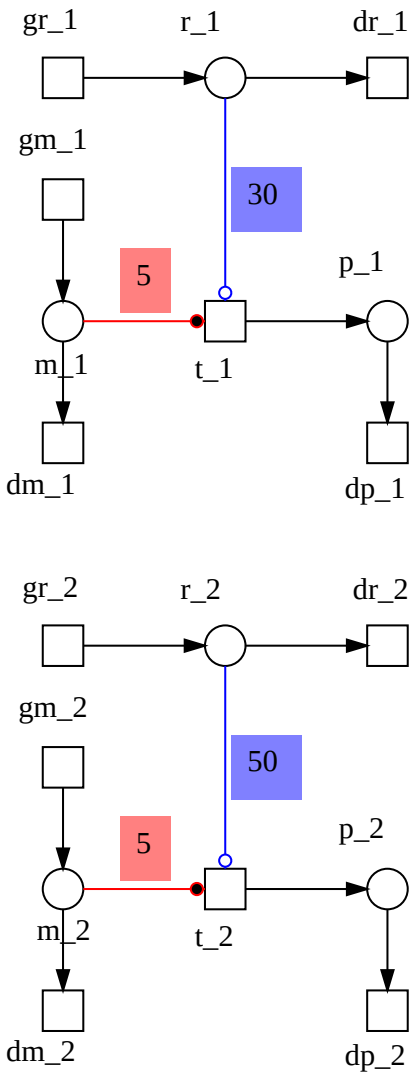
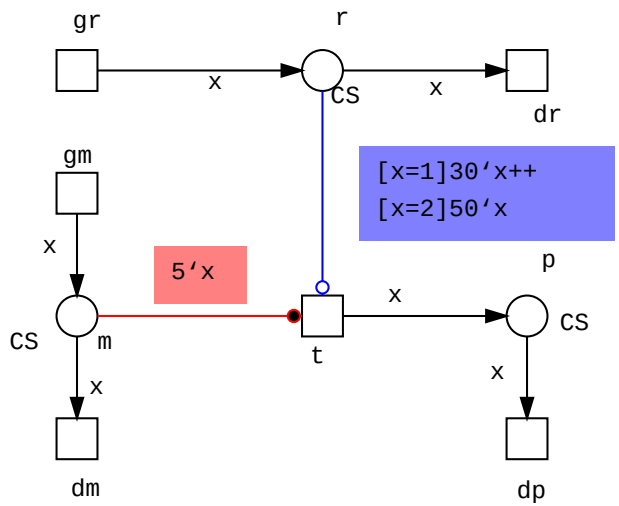



```
Declarations:
Colorset CS = int with 1-2;
Variable x : CS;
```

```
[x=1] MassAction( 0.01 )
[x=2] LevelInterpretation(0.1,16)
```

3. Special arc types

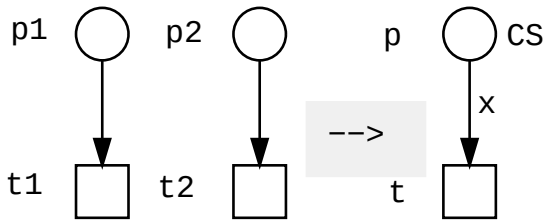




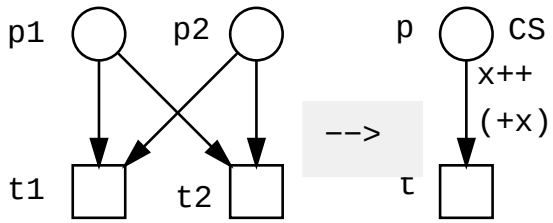

```
Declarations:
Colorset CS=int with 1,2;
Variable x:CS;
```

Constructing colored Petri net models

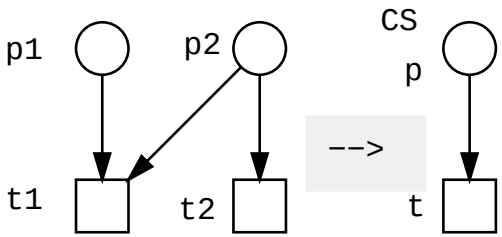
Basic colored Petri net components



(a)



(b)



[x=1](x+(+x))++
[x=2]x

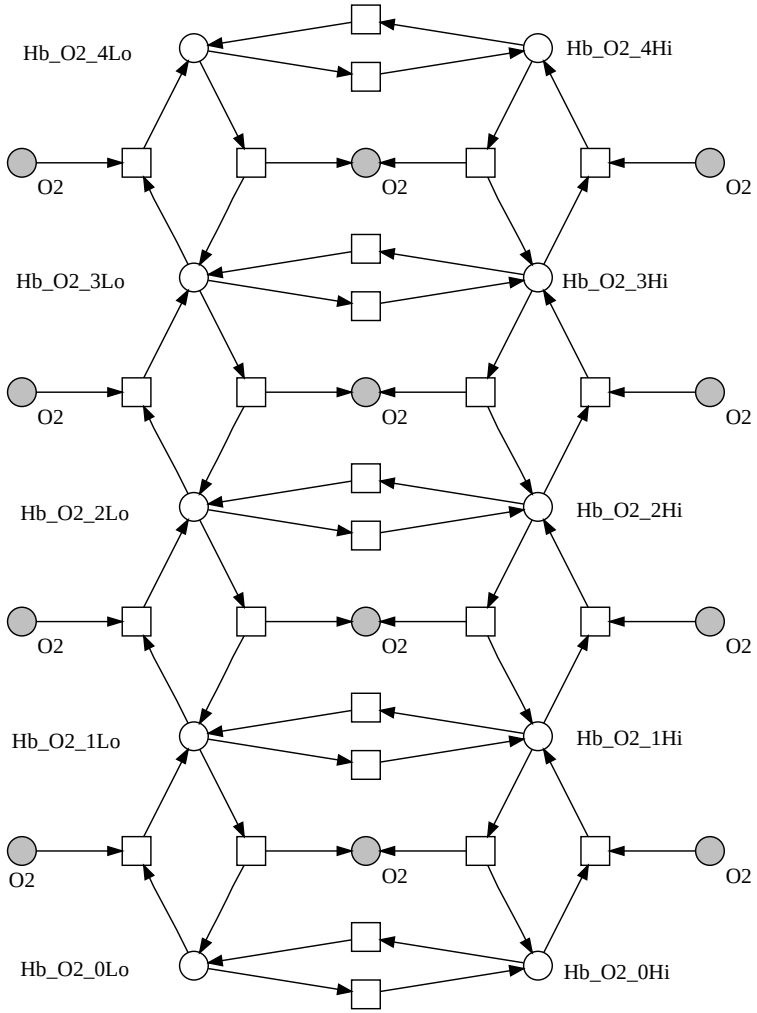
(c)

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

(d)

Cooperative binding of oxygen to hemoglobin

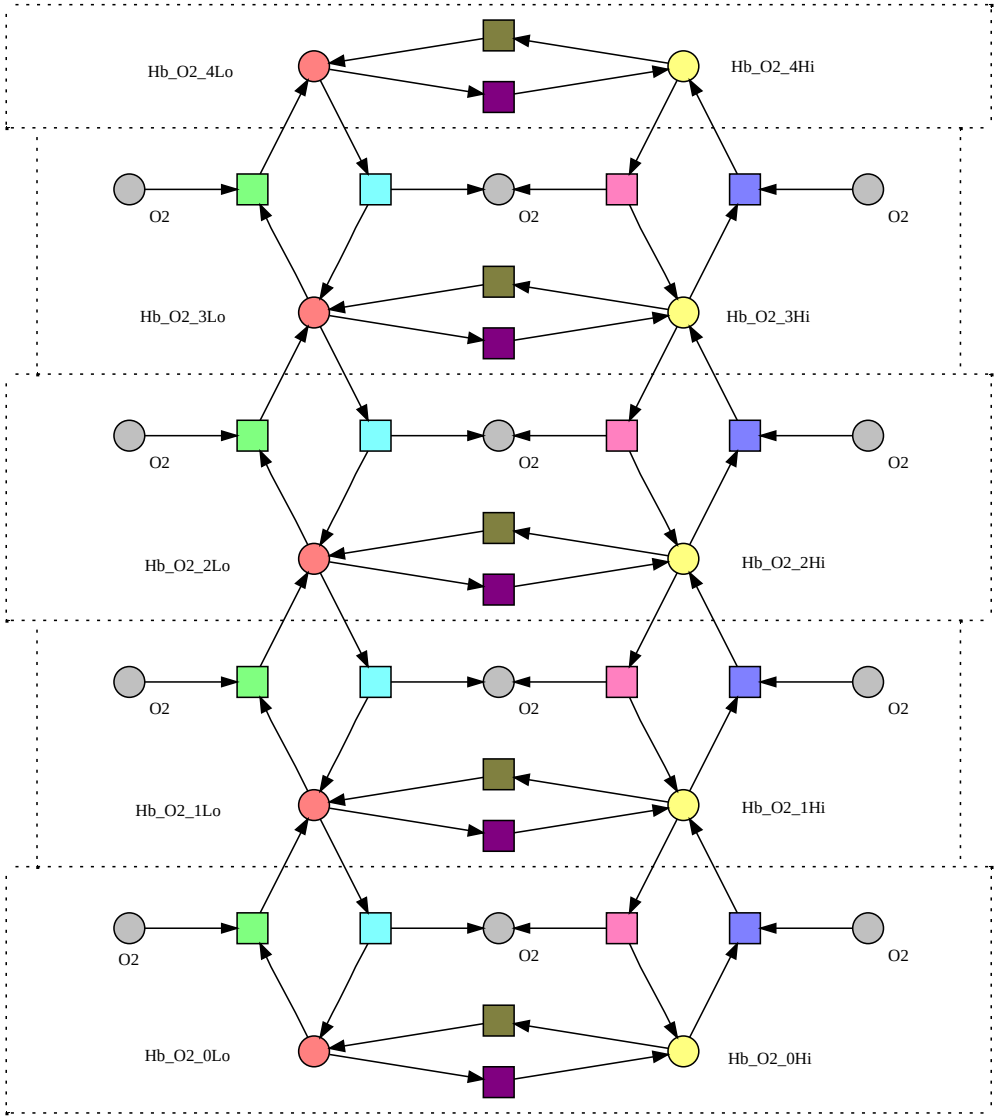
- Binding of oxygen to the four subunits of a hemoglobin heterotetramer,
- Oxygen (O2) is represented in the form of multiple copies of one logical place



Reference: W. Marwan, A. Wagler, R. Weismantel: Petri Nets as a Framework for the Reconstruction and Analysis of Signal Transduction Pathways and Regulatory Networks. Natural Computing. 9 (2009)

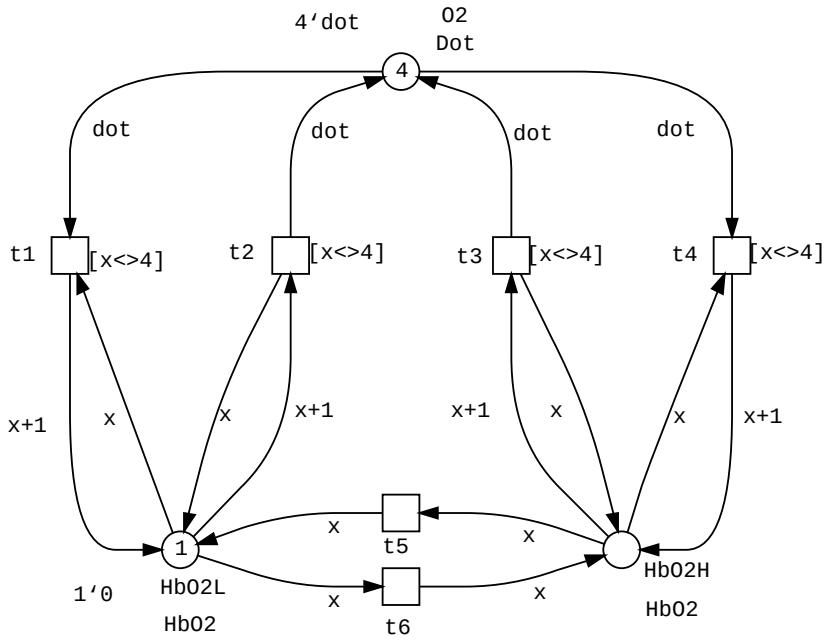
Cooperative binding of oxygen to hemoglobin

- Subnet partition,
- Node set partition.

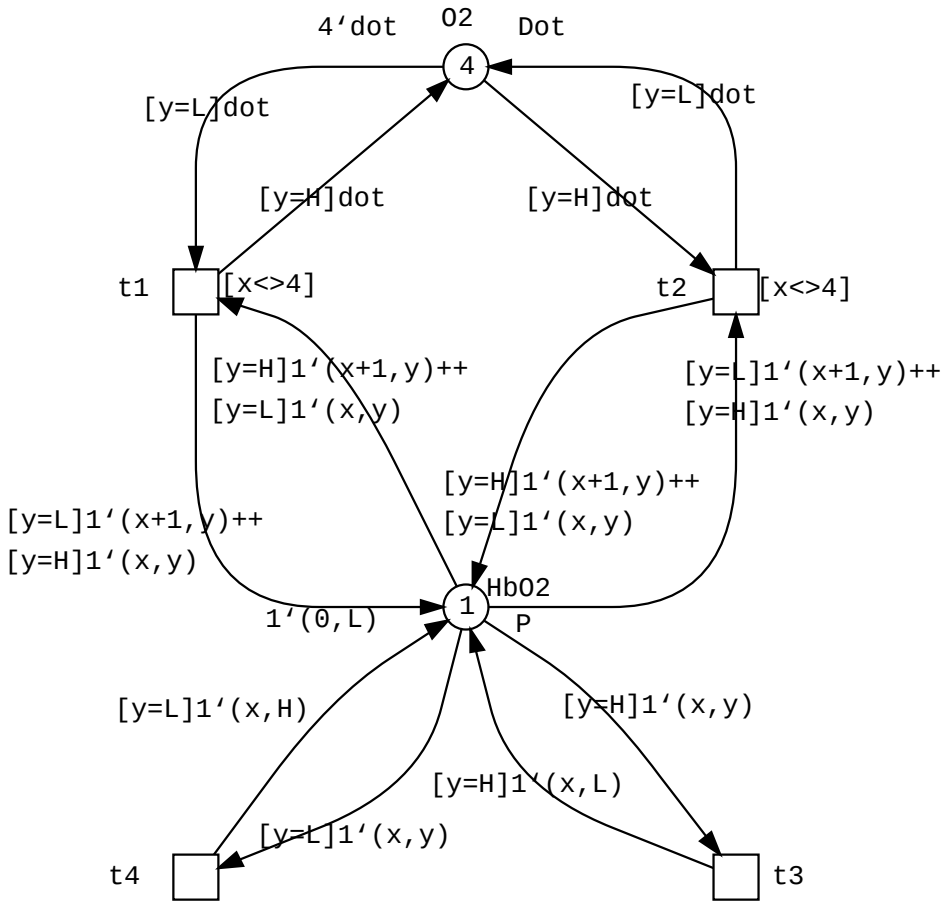


Cooperative binding of oxygen to hemoglobin

- Define color sets and variables,
- Assign color sets to places,
- Define guards/rate functions for transitions
- Write arc expressions.



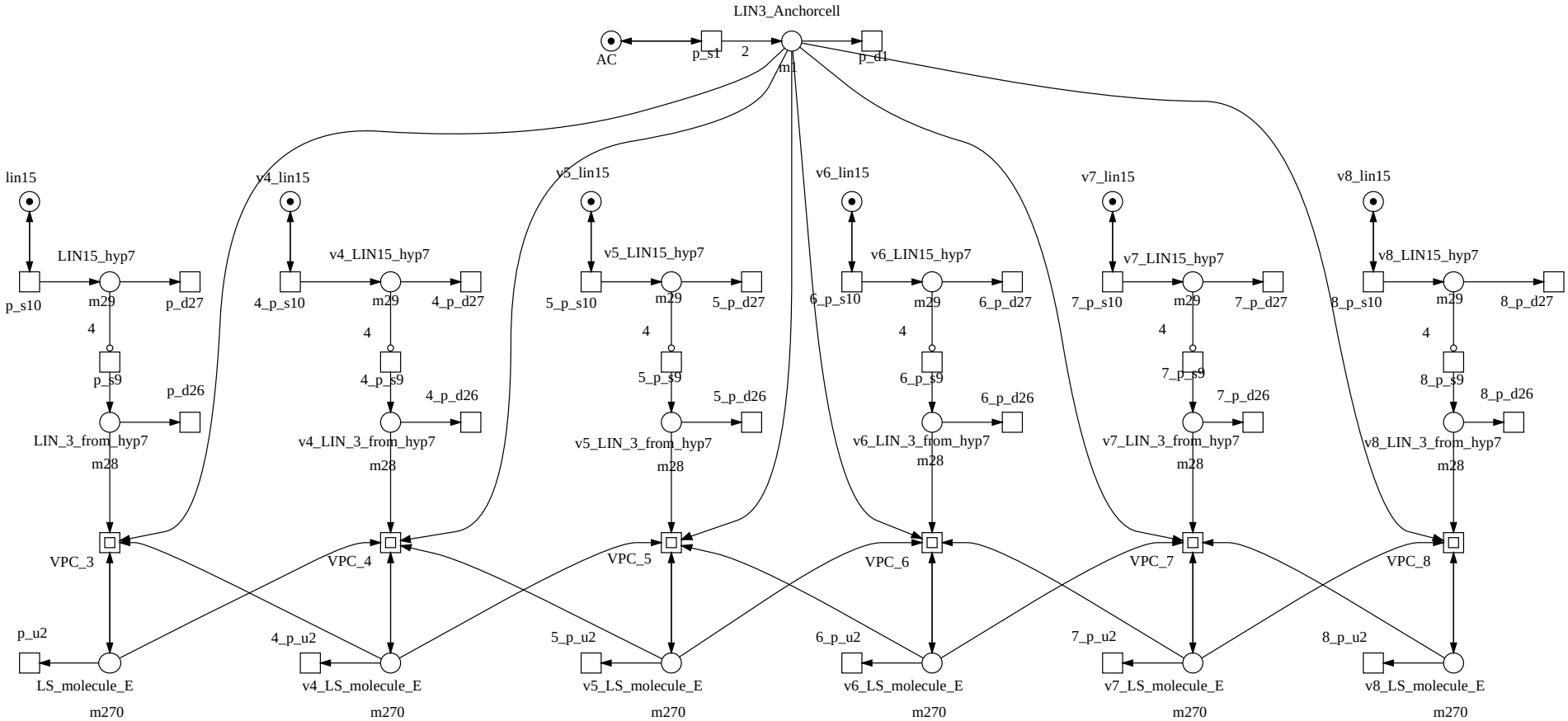
Cooperative binding of oxygen to hemoglobin



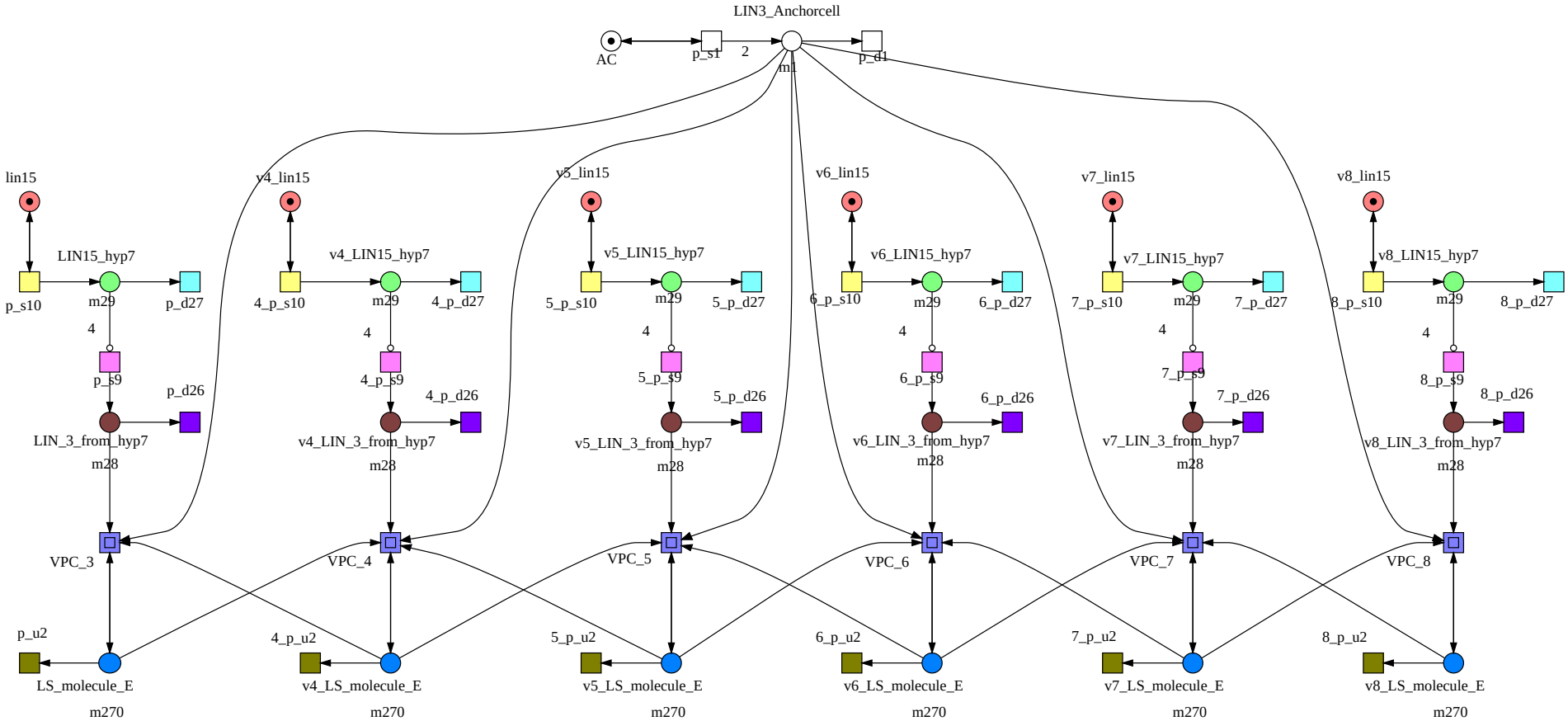
Cooperative binding of oxygen to hemoglobin: declarations for the colored models

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;

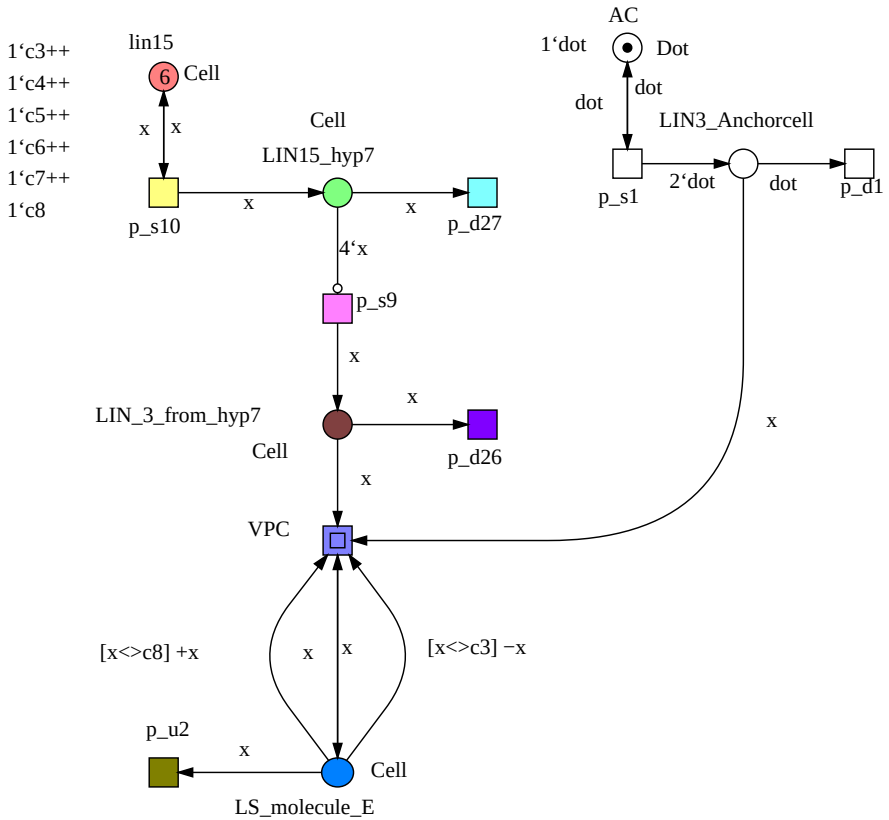
C. elegans vulval development model



C. elegans vulval development model



C. elegans vulval development model

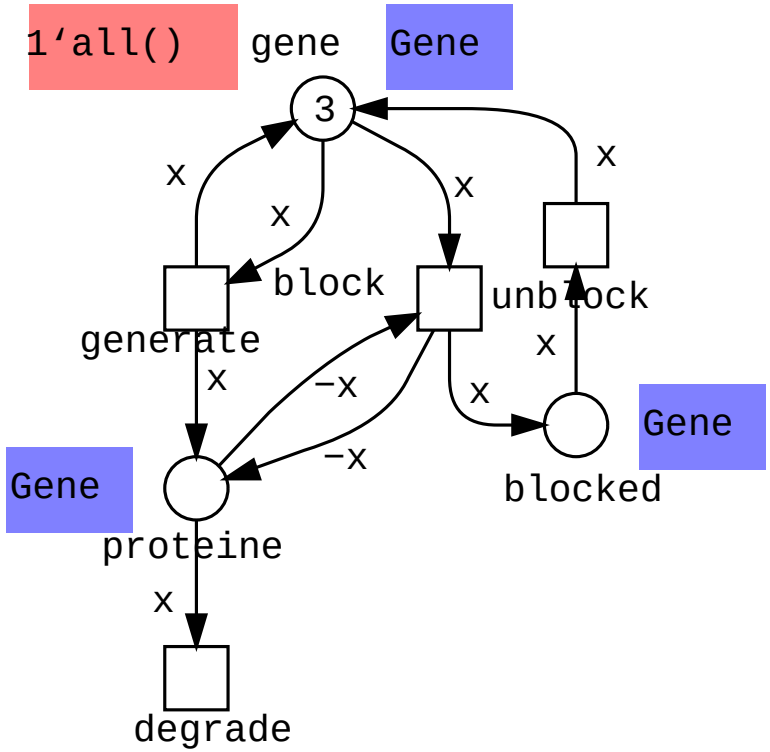


Colorset Dot = dot;

Colorset Cell = enum with c3,c4,c5,c6,c7,c8;

Variable x: Cell;

Colored stochastic Petri net model for the repressilator



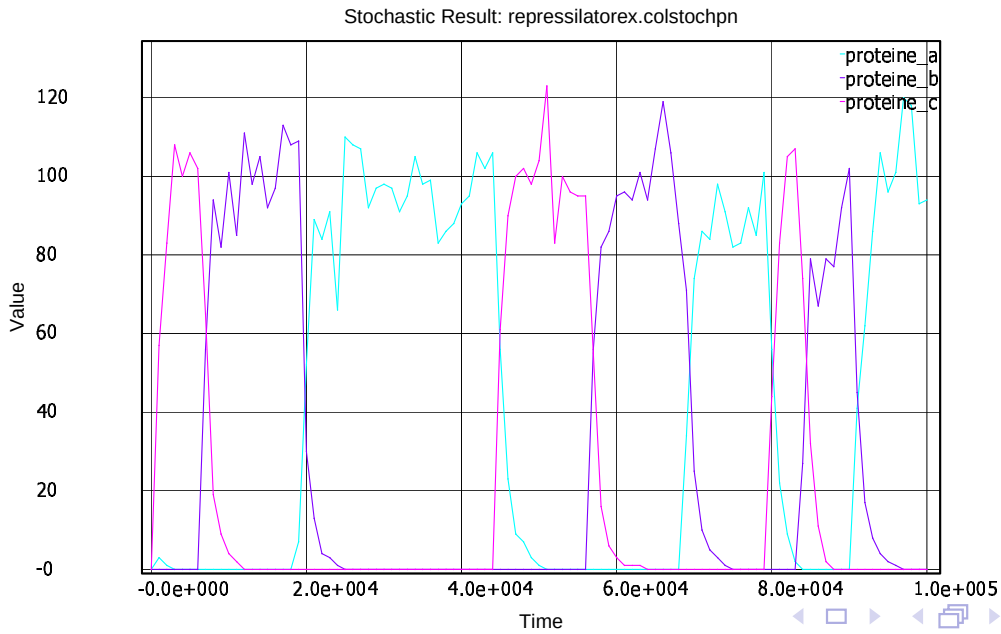
Declarations

Colorset Gene = enum with a-c

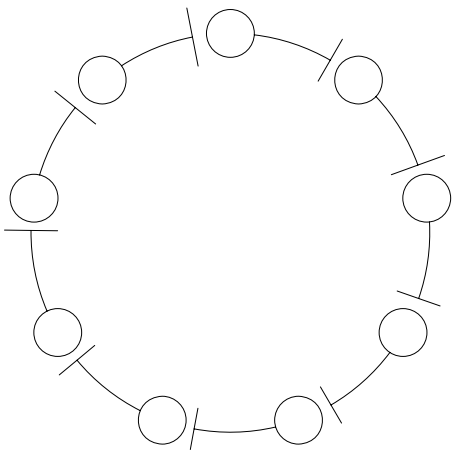
Variable x: Gene

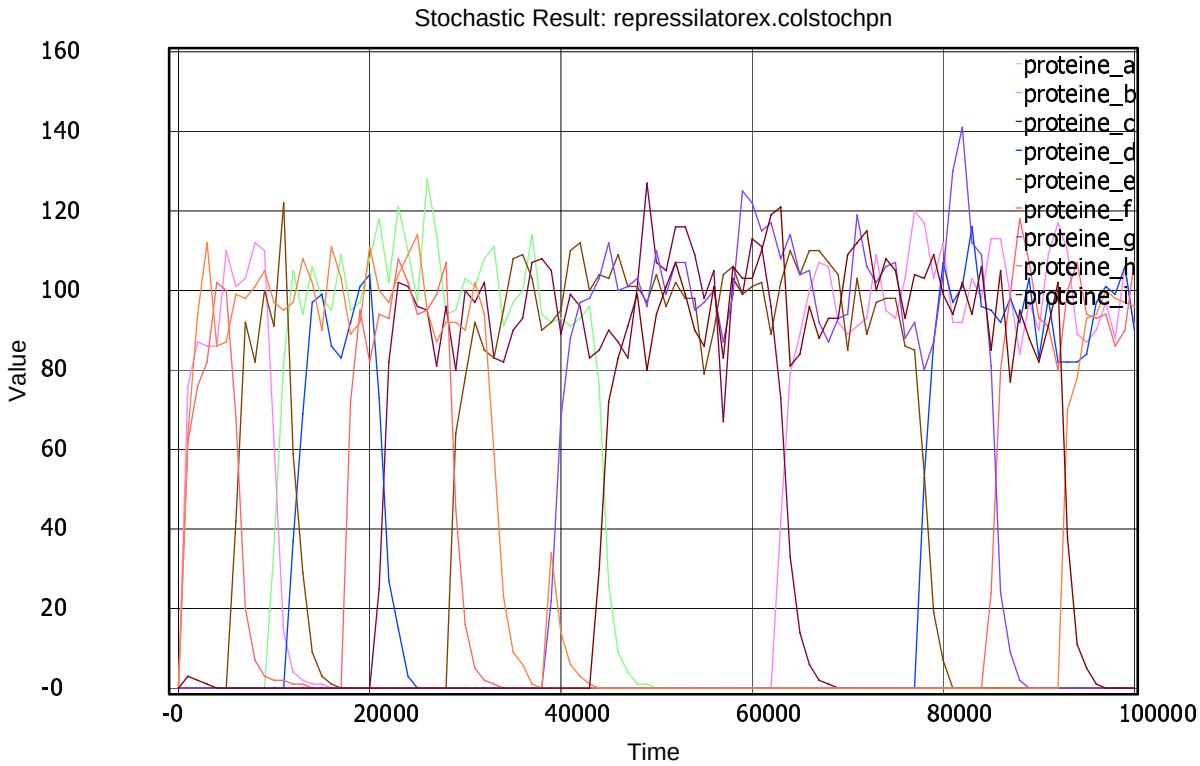
Colored stochastic Petri net model for the repressilator

Transition	Rate function
generate	$0.1 * gene$
block	$1.0 * proteine$
unblock	$0.0001 * blocked$
degrade	$0.001 * proteine$



Colored stochastic Petri net model for the repressilator





Outlook

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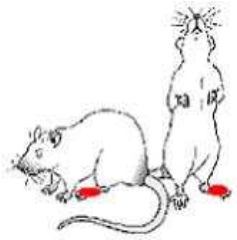
- Improving QPN^C and SPN^C prototypes,
- Developing analysis tools for SPN^C,
- Developing the CPN^C prototype,
- Considering how to automatically create colored Petri nets from non-coloured Petri nets (automatic folding),
- working on a SPN^C model for C. elegans vulval development,
- Working on a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

Acknowledgments



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- Thank the anonymous referees for many constructive comments.

Thanks for your attention !

Begin to demonstrate QPN^C / SPN^C