A Framework for Modular Modeling and Analysis of Signaling Networks

Kiel
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Project Milestones

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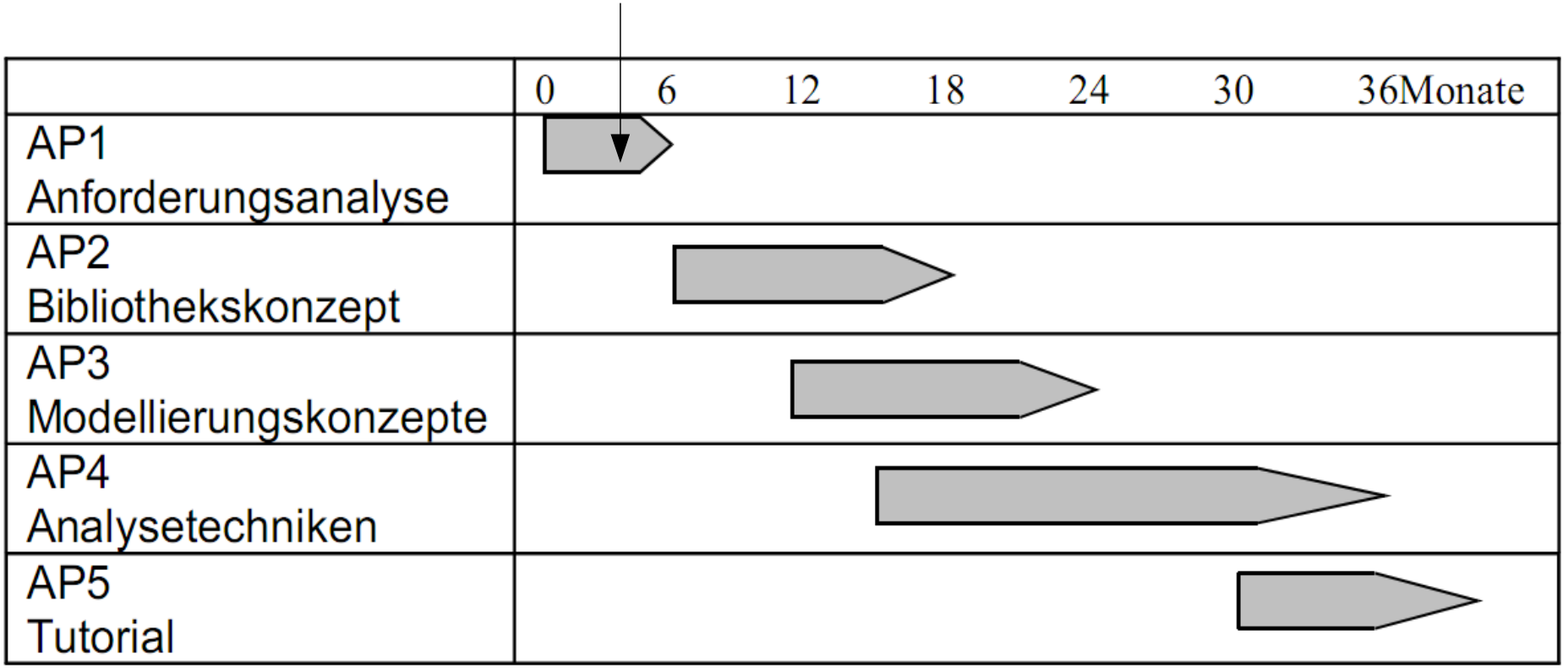
- WP1 - Requirements analysis
- WP2 - Library approach for generic model components
- WP3 - Modelling concepts for dealing with model alternatives
- WP4 - Analysis techniques for identification and behaviour comparison of model components
- WP5 - Tutorial

Schedule


0
6
12
18
24
30
36Monate
AP1
Anforderungsanalyse
AP2
Bibliothekskonzept
AP3
Modellierungskonzepte
AP4
Analysetechniken
AP5
Tutorial

- Building a collection of relevant network examples which are fully documented in the literature;
- Literature search for techniques to identify structure-based modules; evaluation on automatability, tool availability, and expense of implementation;
- Identification of structural components, manually or using tools, if possible;
- Identification of classes of structural components, which can be grouped together as generic model components;
- Develop a concept for the coupling with the database developed in M2;

Project Results

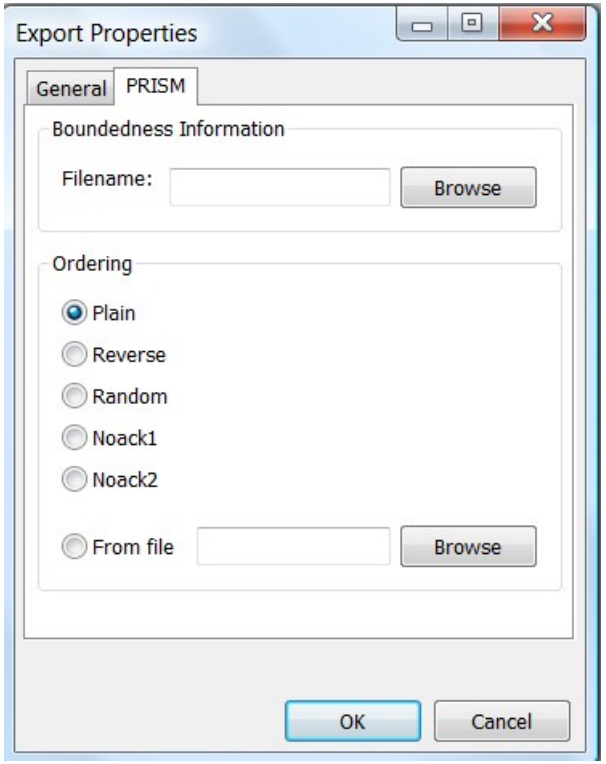
February 2009 --- June 2009

- Designed and implemented the Snoopy2Prism export module

  -> Translating Stochastic PN models to Prism files,

  -> Analyzed by PRISM tool (a probabilistic model checker),

  -> Finished the Snoopy2Prism export manual.

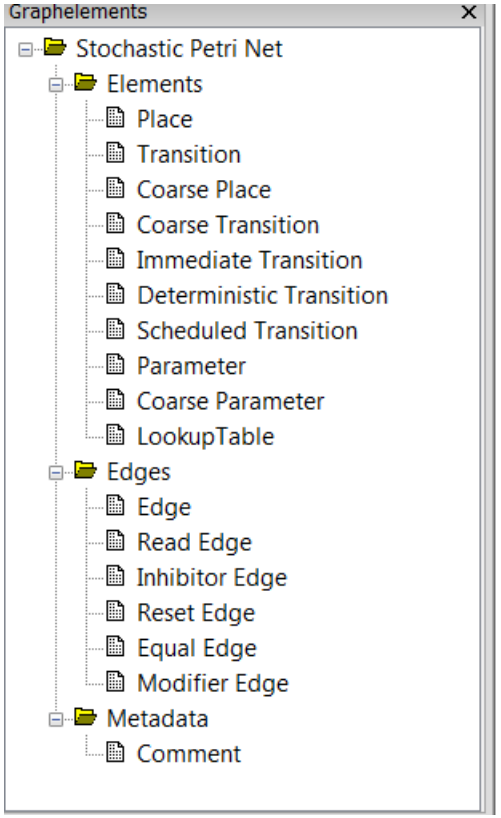


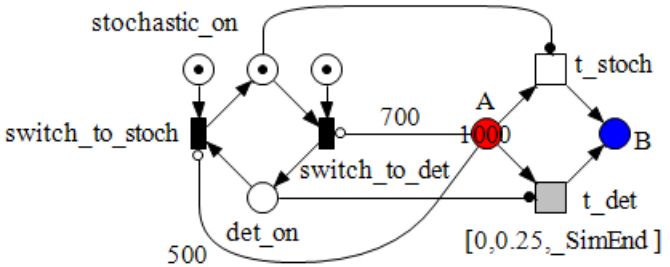

```
ctmc
const int Max;
const int N;
module  Noack1export

P6:   [ 0..Max ]  init 0;
P4:   [ 0..Max ]  init 0;
P5:   [ 0..Max ]  init 0;
P2:   [ 0..Max ]  init 0;
P1:   [ 0..Max ]  init 0;
P3:   [ 0..Max ]  init 10*N;

[k1]
(P1 >= 1) & (P3 <= Max-1 )
 -> 1 * P1 :
(P1' = P1-1) & (P3' = P3+1);

[k2]
(P3 >= 1) & (P4 <= Max-1 )
 -> 0.4 * P3 :
(P3' = P3-1) & (P4' = P4+1);

[k3]
(P2 >= 1) & (P4 >= 1) & (P6 >= 1) & (P5 >= 1) & (P1 <= Max-1 )
 -> 0.1 * P2 * P4 * P6 * P5 :
(P2' = P2-1) & (P4' = P4-1) & (P6' = P6-1) & (P5' = P5-1) & (P1' = P1+1);

[k4]
(P3 >= 1) & (P6 <= Max-1 )
 -> 0.5 * P3 :
(P3' = P3-1) & (P6' = P6+1);

[k5]
(P3 >= 1) & (P2 <= Max- 1 ) & (P5 <= Max-1 )
 -> 0.5 * P3 :
(P3' = P3-1) & (P2' = P2+1) & (P5' = P5+1);

endmodule
```

➔ Adding additional features for stochastic Petri nets in Snoopy

-> Adding three types of transitions: immediate, deterministic, and scheduled.

-> Adding special arcs: equal, reset.

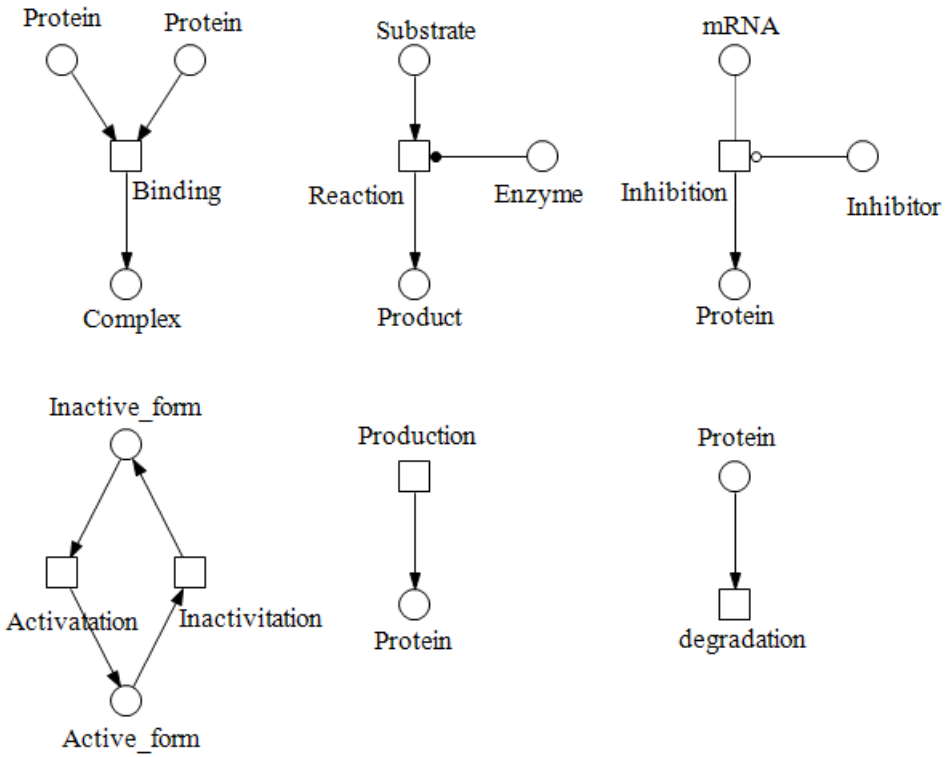




Collecting basic biological functions

-> binding, enzymatic reaction, inhibition,

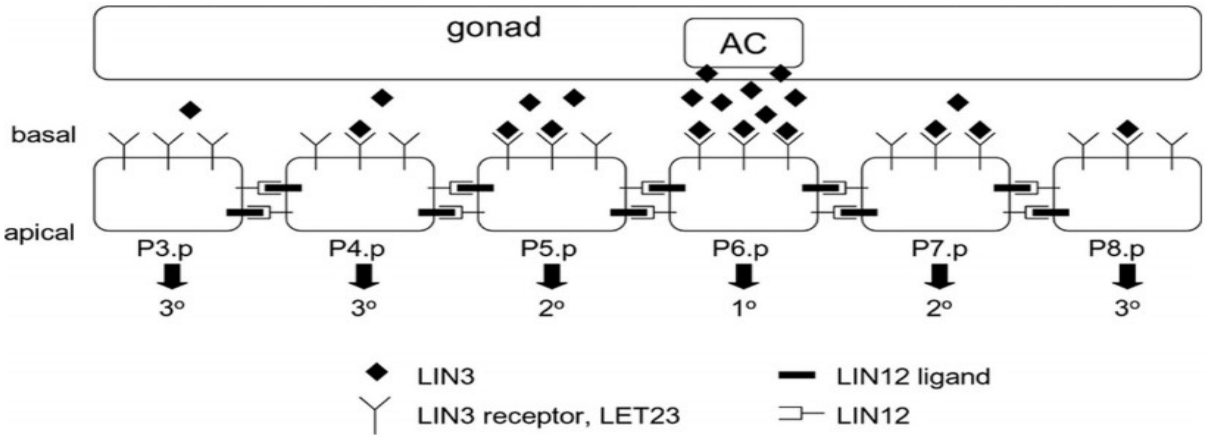
-> activation, inactivation, production, degradation



➔ Modeling C. elegans vulval development process

-> to study how multiple pathways, in multiple cells, interact to produce developmental patterns

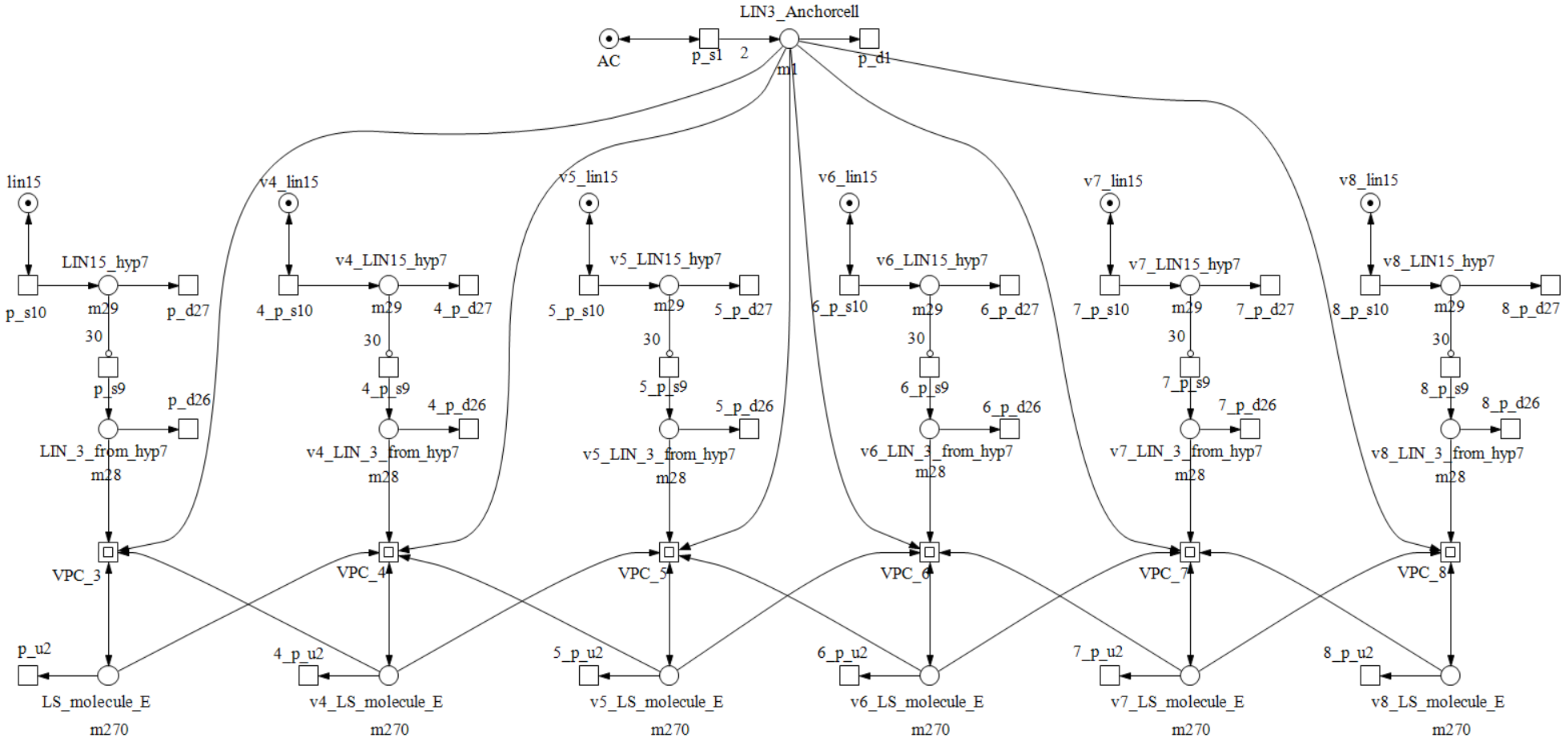
-> Ras/MAPK pathway, Notch/LIN-12 pathway



Spatial patterning of VPCs in *C. elegans*. The AC in the gonad releases LIN-3, which distributes across the linear array of VPCs (P3.p–P8.p). This factor binds its receptor LET-23 on the basal surface of the precursor cells and provides an inductive signal for fate specification. The interplay between the inductive signal (LIN-3:LET-23 complexes) and lateral coupling between neighboring cells mediated by LIN-12 and its ligands specifies P3.p–P8.p cells to three distinct cell fates (1°, 2°, and 3°).

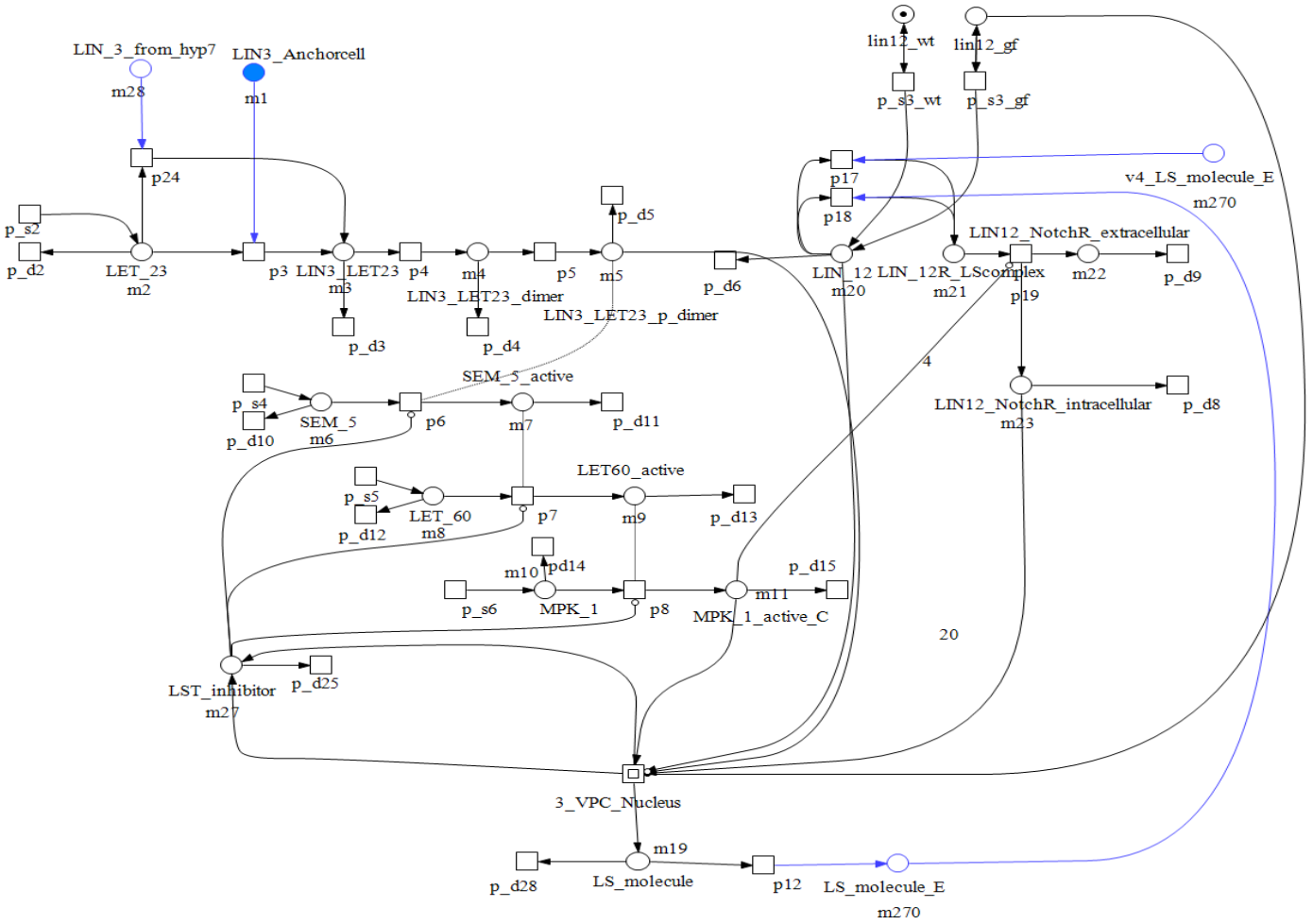
➔ Modeling C. elegans vulval development process

Places: 206
Transitions: 360
Kinetics: mass action



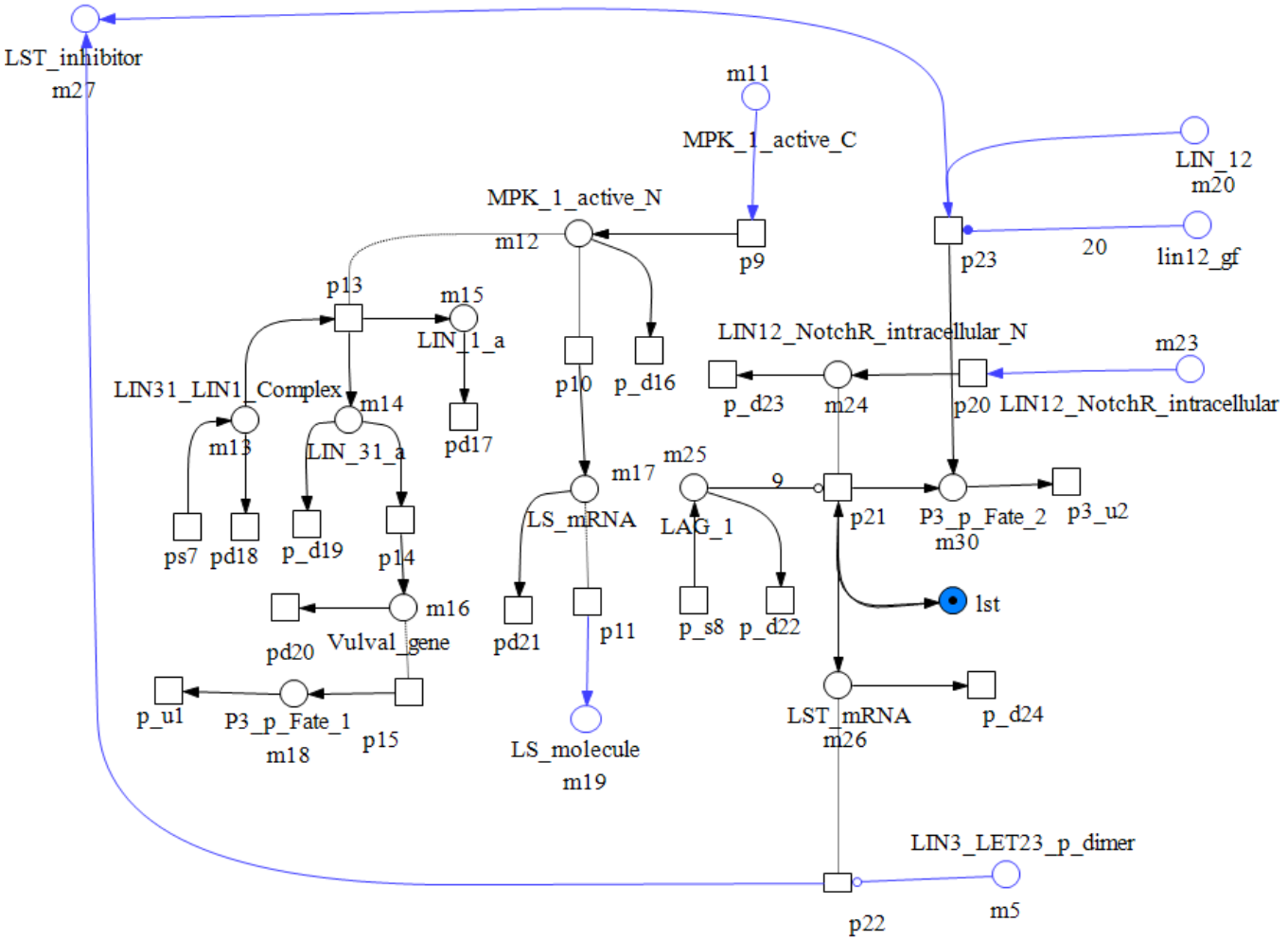
➔ Modeling C. elegans vulval development process

-> one VPC (vulval precursor cell)



➔ Modeling C. elegans vulval development process

-> Nucleus of one VPC

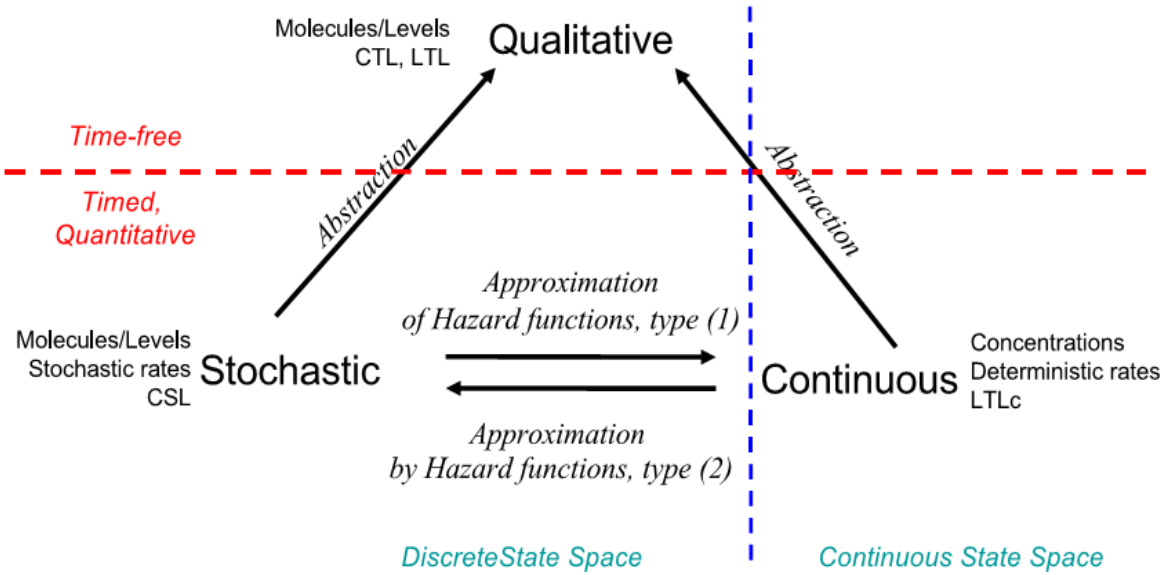


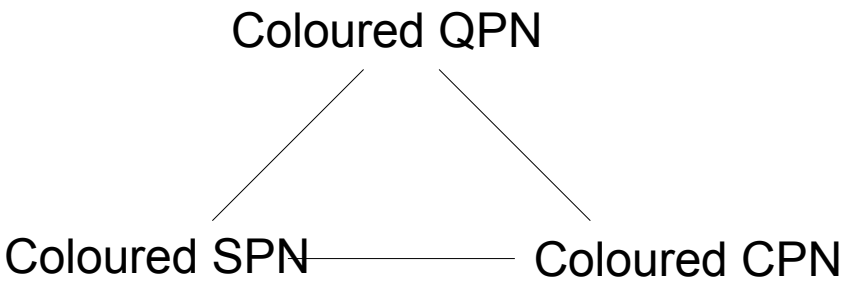
- Different types of Petri nets, supported by different tools
- Unifying framework for modeling and analyzing biochemical network

  -> unifying the qualitative, stochastic and continuous paradigms,

  -> complementing each other to accomplish modeling and analysis

  -> realized by Snoopy





- Considering Coloured QPN (CQPN), SPN (CSPN), CPN (CCPN)

  -> *Requirements analysis for coloured Petri nets*

  -> *Precisely defining different types of coloured PN*

  -> *Considering implementation details: data types or colours, arc expressions, guard functions, unfolding algorithms, ...*

Tools survey

- CPN tools
- GreatSPN
- TimeNet
- Cell Illustrator

Tools survey – CPN tools

- Source: University of Aarhus, Denmark.
- Coloured Petri nets
- Simulation, occurrence graphs, place invariants
- OS: Windows/XP, Linux

Tools survey - GreatSPN

- Source: Università di Torino, Italy
- Generalized Stochastic Petri Nets, Stochastic Well-formed Nets
- Coloured and symbolic reachability graph, simulation
- OS: SunOS, Mac OS, Linux

Tools survey - TimeNet

- Source: Technische Universität Ilmenau
- Stochastic Petri nets, stochastic coloured Petri nets
- Simulation, token game
- OS: Windows/XP, Linux

Tools survey - Cell Illustrator

- Source: GNI and University of Tokyo, Japan
- Hybrid functional Petri nets
- Simulation, token game
- OS: Windows, Linux, Mac, Unix

- Comparing tools in terms of the following aspects:
  - -> *functions, analysis capabilities,*
  - -> *data types, expressions for arcs and guards, ...*
- Analyzing the capabilities and equivalence of Cell Illustrator (CI) and Snoopy in terms of:
  - -> *Continuous model in CI – Stochastic model in Snoopy*
  - -> *Discrete model in CI – Timed model in Snoopy*
  - -> *Hybrid model (continuous and discrete) in CI – stochastic and timed model in Snoopy*

Next Steps

Next steps

- Precisely define three types of coloured Petri nets:
  CQPN, CSPN, CCPN
- Consider more network examples, especially from the collaborators
- Continue to analyze the capabilities and equivalence of Cell Illustrator and Snoopy
- Coupling with the database developed by M2, needs to be discussed

Thank You !