A Unifying Framework for Modelling and Analysing Biochemical Pathways Using Petri Nets

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Groningen, NL, London, UK, Cottbus, DE

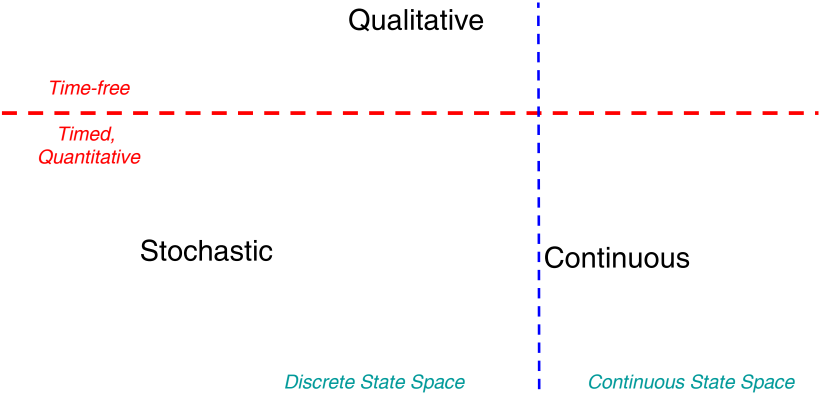
BME Tutorial, Part 4
Paris, June 2009

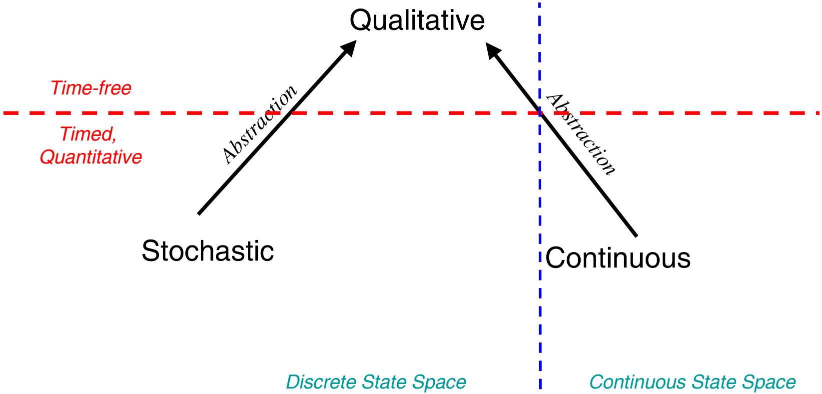
Qualitative

Stochastic

Continuous

Framework


Qualitative
Time-free
Timed,
Quantitative
Stochastic
Continuous
Discrete State Space
Continuous State Space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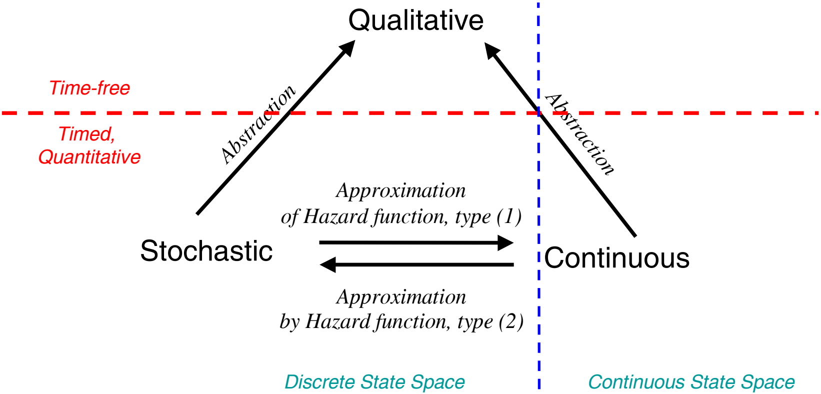
Qualitative
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Approximation
of Hazard function, type (1)
Stochastic
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Approximation
by Hazard function, type (2)
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Definition :

A **place/transition Petri net** is a quadruple $\mathcal{PN} = (P, T, f, m_0)$, where

- P, T - finite, non empty, disjoint sets *(places, transitions)*

(Qualitative) Petri Net

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Interleaving Semantics : reachability graph / CTL, LTL
Partial Order Semantics : prefix / CTL, LTL

Definition :

A **biochemically interpreted stochastic Petri net** is a quintuple $\mathcal{SPN}_{Bio} = (P, T, f, v, m_0)$, where

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- $m_0 : P \rightarrow \mathbb{N}_0$ *(***initial marking***)*
- $v : T \rightarrow H$ *(***stochastic firing rate functions***)* with
  - $H := \left\{ h_t \mid h_t : \mathbb{N}_0^{|^{\bullet}t|} \rightarrow \mathbb{R}^+, t \in T \right\}$
  - $v(t) = h_t$ for all transitions $t \in T$

Stochastic Petri Net

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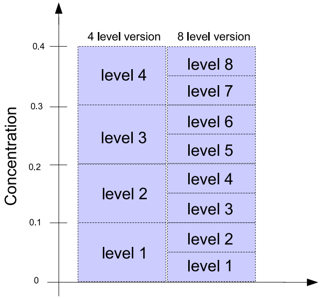
Semantics : Continuous Time Markov Chain / CSL, PLTLc

Interpretation of tokens :

- *tokens = molecules*
- *tokens = concentration levels*



Stochastic Petri Net

Specialised stochastic firing rate function, two examples :

- *molecules semantics*

$$h_t := c_t \cdot \prod_{p \in {}^\bullet t} \binom{m(p)}{f(p,t)} \tag{1}$$

- *concentration levels semantics*

$$h_t := k_t \cdot N \cdot \prod_{p \in {}^\bullet t} \left(\frac{m(p)}{N}\right) \tag{2}$$

Stochastic Petri Net - Semantics

- a transition t is enabled as usual : $\forall p \in {}^\bullet t : m(p) > 0$.
- an enabled transition t has to wait
- *transition's waiting time* is an exponentially distributed random variable X_t with the *probability density function* :

$$f_{X_t}(\tau) = \lambda_t(m) \cdot e^{(-\lambda_t(m) \cdot \tau)}, \qquad \tau \geq 0.$$

- while waiting, the transition may loose its enabled state
- firing itself does not consume time, follows standard firing rule

Semantics : Continuous Time Markov Chain / CSL, PLTLc

Definition :

A **biochemically interpreted continuous Petri net** is a quintuple $\mathcal{CPN}_{Bio} = (P, T, f, v, m_0)$, where

- P, T - finite, non empty, disjoint sets *(places, transitions)*
- $f : ((P \times T) \cup (T \times P)) \to \mathbb{R}_0^+$ *(weighted directed arcs)*
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Semantics : ODEs / LTLc

- A continuous transition t is enabled in m, if $\forall p \in {}^{\bullet}t : m(p) > 0$.
- each place p subject to changes gets its own equation

$$\frac{dm(p)}{dt} = \sum_{t \in {}^{\bullet}p} f(t,p)\, v(t) - \sum_{t \in p^{\bullet}} f(p,t)\, v(t),$$

- each equation corresponds to a line in the incidence matrix

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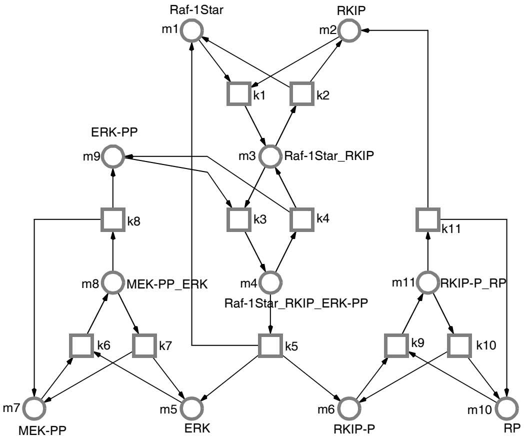
- each equation corresponds to a line in the incidence matrix
- *continuous Petri net = structured description of ODEs.*

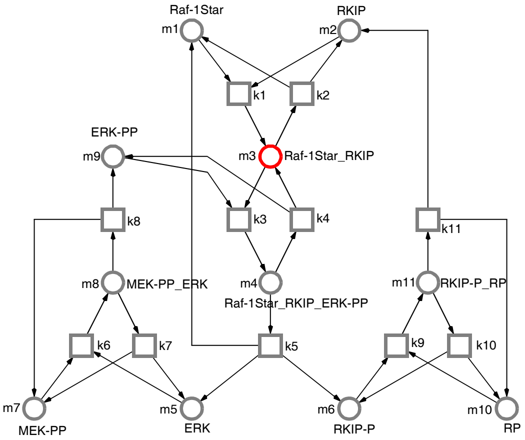
Semantics : ODEs / LTLc

Continuous Petri Net - Example



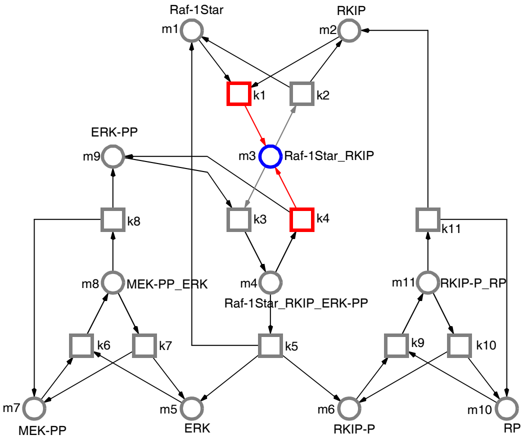
Continuous Petri Net - Example

$$\frac{dm3}{dt} =$$

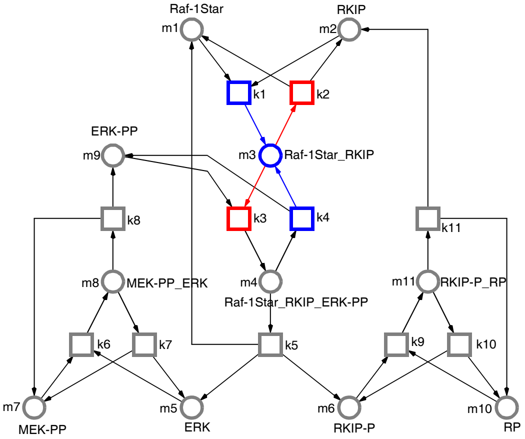


Continuous Petri Net - Example

$$\frac{dm3}{dt} = +r1 + r4$$

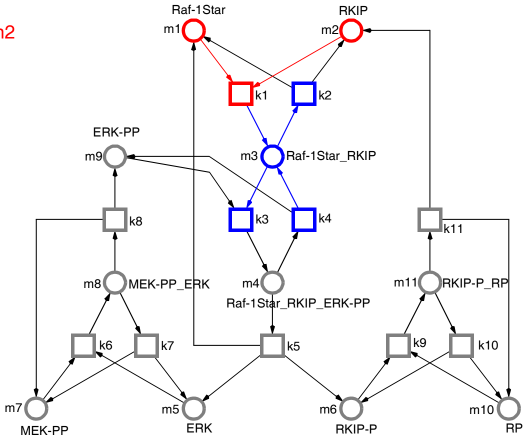


$$\frac{dm3}{dt} = +r1 + r4 - r2 - r3$$

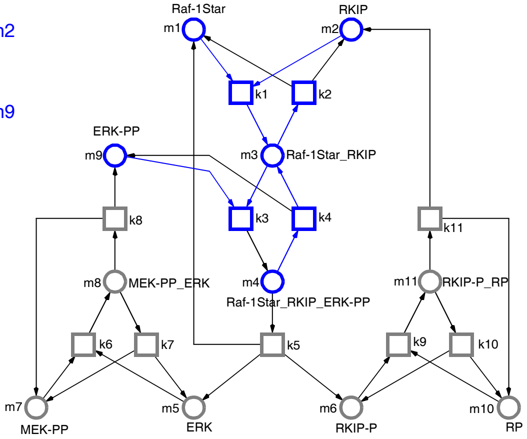


Continuous Petri Net - Example

$$\frac{dm3}{dt} = + k1 * m1 * m2 + r4 - r2 - r3$$



$$\frac{dm3}{dt} = + k1 * m1 * m2 + k4 * m4 - k2 * m3 - k3 * m3 * m9$$



Continuous Petri Net - Example, ODEs

$$\frac{dm_1}{dt} = r_2 + r_5 - r_1$$
$$\frac{dm_2}{dt} = r_2 + r_{11} - r_1$$
$$\frac{dm_3}{dt} = r_1 + r_4 - r_2 - r_3$$
$$\frac{dm_4}{dt} = r_3 - r_4 - r_5$$
$$\frac{dm_5}{dt} = r_5 + r_7 - r_6$$
$$\frac{dm_6}{dt} = r_5 + r_{10} - r_9$$

$$\frac{dm_7}{dt} = r_7 + r_8 - r_6$$
$$\frac{dm_8}{dt} = r_6 - r_7 - r_8$$
$$\frac{dm_9}{dt} = r_4 + r_8 - r_3$$
$$\frac{dm_{10}}{dt} = r_{10} + r_{11} - r_9$$
$$\frac{dm_{11}}{dt} = r_9 - r_{10} - r_{11}$$

Continuous Petri Net - Example, ODEs

$$
\begin{aligned}
r_1 &= k_1 * m_1 * m_2 \\
r_2 &= k_2 * m_3 \\
r_3 &= k_3 * m_3 * m_9 \\
r_4 &= k_4 * m_4 \\
r_5 &= k_5 * m_4 \\
r_6 &= k_6 * m_5 * m_7
\end{aligned}
$$

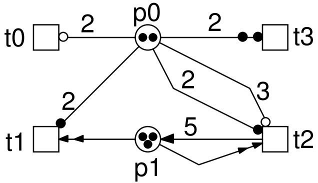
$$
\begin{aligned}
r_7 &= k_7 * m_8 \\
r_8 &= k_8 * m_8 \\
r_9 &= k_9 * m_6 * m_{10} \\
r_{10} &= k_{10} * m_{11} \\
r_{11} &= k_{11} * m_{11}
\end{aligned}
$$

References

- *M Heiner, D Gilbert, R Donaldson :*
  Petri Nets for Systems and Synthetic Biology ;
  SFM 2008, Springer LNCS 5016, pp. 215Ð264, 2008.
- M Heiner ; R Donaldson ; D Gilbert :
  Petri Nets for Systems Biology ;
  in MS Iyengar (ed.) : Symbolic Systems Biology : Theory and Methods, Jones & Bartlett Publishers, LLC, in Press.
- D Gilbert, M Heiner, S Rosser, R Fulton, X Gu, M Trybilo :
  A Case Study in Model-driven Synthetic Biology ;
  IFIP WCC 2008/BICC 2008, Springer Boston, IFIP, Vol . 268, pp. 163-175, 2008.
- D Gilbert, M Heiner, S Lehrack :
  A Unifying Framework for Modelling and Analysing Biochemical Pathways Using Petri Nets ;
  Proc. CMSB 2007, LNCS/LNBI 4695, pp. 200-216.

(Qualitative) Petri net + special arcs :

- *read arc*
- *inhibitor arc*
- equal arc
- reset arc



- read/inhibitor/equal arcs :
  influence on enabling, tested place is not changed by the firing
- reset arc :
  no influence on enabling, tested place is reset to zero

Stochastic Petri Net - Extensions

- *special arcs* : read, inhibitor, equal, reset

- *immediate transitions* - highest priority
- *deterministic transitions* :
  deterministic waiting time/delay - relative time points
- *scheduled transitions* : *start(repetition)end*
  schedule specifies absolute points of the simulation time
  where the transition may fire, if enabled

- *remark : immediate transition* $\neq$
  deterministic transition with zero waiting time

Definition, part 1 :
A **biochemically interpreted deterministic and stochastic Petri net** is a septuple $\mathcal{DSPN}_{Bio} = (P, T, f, g, v, d, m_0)$, where

- P, T - finite, non empty, disjoint sets (**places**, **transitions**)
- The set T is the union of three disjunctive transition sets : $T := T_{stoch} \cup T_{im} \cup T_{timed}$ with :
  - T_{stoch} - set of stochastic transitions with exponentially distributed waiting time,
  - T_{im} - set of immediate transitions,
  - T_{timed} - set of transitions with deterministic waiting time.

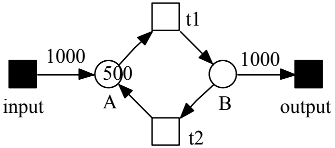
. . . *continued on next slide*

Definition, part 2 :

- $f : ((P \times T) \cup (T \times P)) \rightarrow \mathbb{N}_0$ **(weighted directed arcs)**
- $g : (P \times T) \rightarrow \mathbb{N}_0$ ***(weighted directed inhibitor arcs)***
- $v : T \rightarrow H$ **(stochastic firing rate functions)** with
  - $H := \bigcup_{t \in T} \left\{ h_t \mid h_t : \mathbb{N}_0^{|^\bullet t|} \rightarrow \mathbb{R}^+ \right\}$
  - $v(t) = h_t$ for all transitions $t \in T$
- $d : T_{timed} \rightarrow \mathbb{R}^+$ ***(deterministic waiting time)***
- $m_0 : P \rightarrow \mathbb{N}_0$ **(initial marking)**

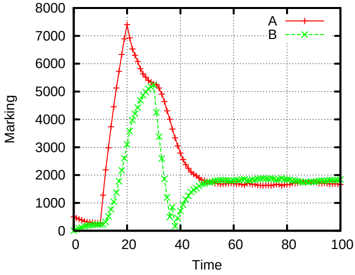
Semantics : CTMC ? $\rightarrow$ *simulative MC/PLTLc*

EX1 : time-controlled inflow/outflow

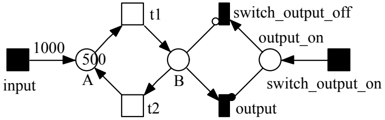


input - scheduled(11,1,20)

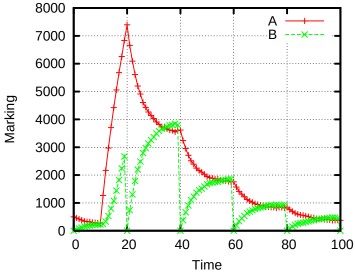
output - scheduled(31,1,40)



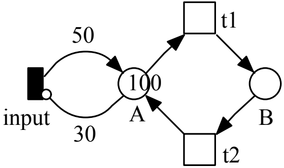
EX2 : time-controlled inflow/outflow

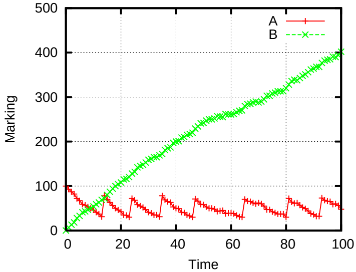


input - scheduled(11,1,20)
switch_output_on -
scheduled(20,20,_SimEnd)



EX3 : Token-controlled Inflow

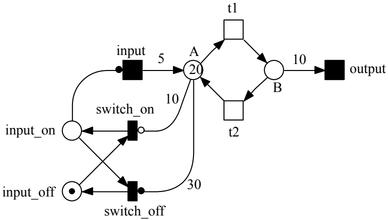


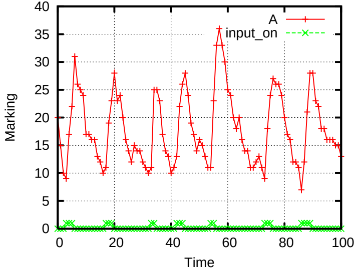


*t*1 - *BioMassAction(0.1)*

*t*2 - *BioMassAction(0.005)*

EX4 : Token-controlled Inflow

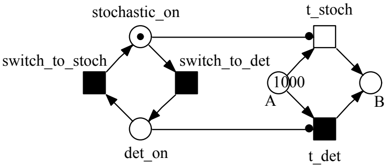


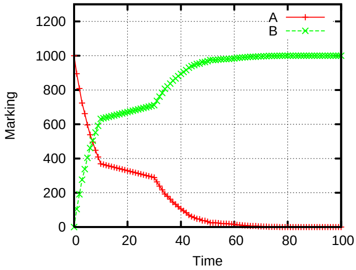


input - delay(0.5)

output - scheduled(5,5,_SimEnd)

EX5 : time-controlled switch between deterministic and stochastic behaviour

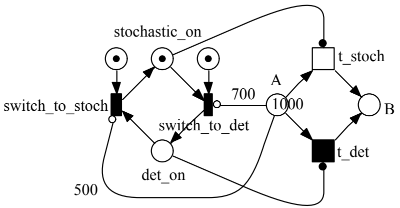


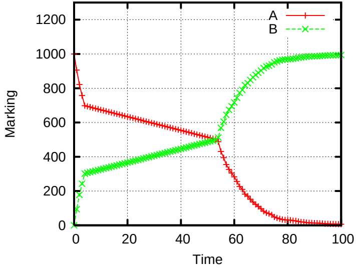


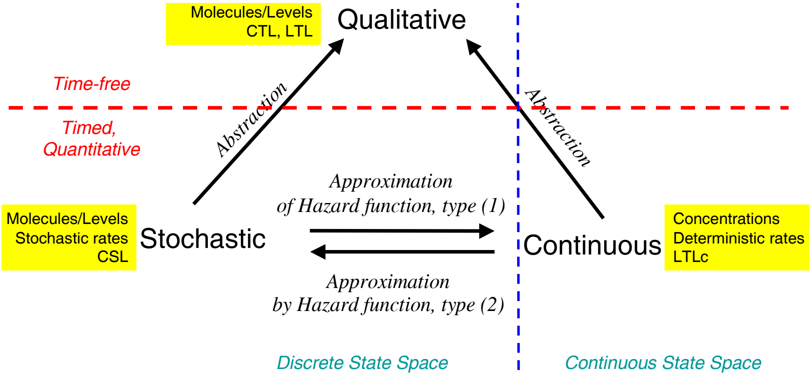
switch_to_det - scheduled(10)

switch_to_stoch - scheduled(30)

EX6 : token-controlled switch between deterministic and stochastic behaviour






Molecules/Levels
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Approximation
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Molecules/Levels
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Stochastic
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Concentrations
Deterministic rates
LTLc
Approximation
by Hazard function, type (2)
Discrete State Space
Continuous State Space

Tools

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  - BioNessi (London)
  - Snoopy (CB)

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  - INA (HUB), Charlie (CB)
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  - PRISM/CSL (Oxford) , IDD-CSL (CB)
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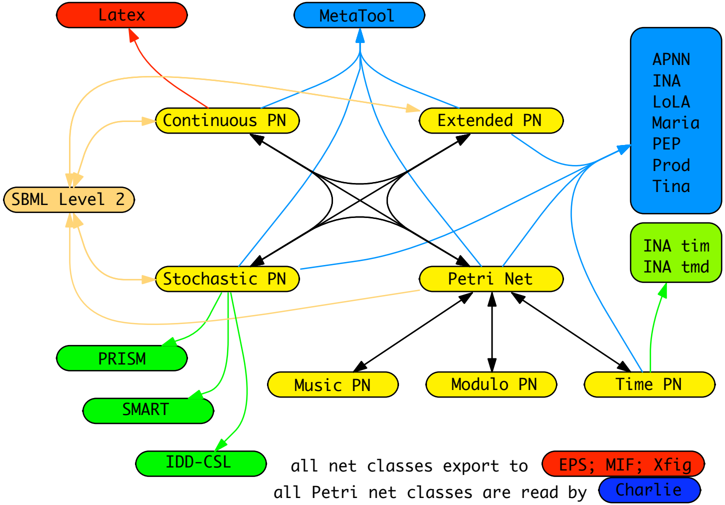
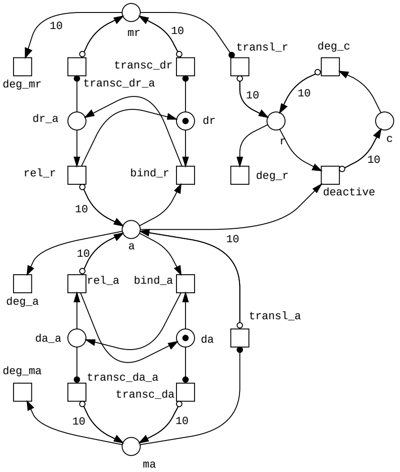
- *continuous analysis*
  - MATLAB
  - BIOCHAM/LTLc (INRIA/Paris), MC2/LTLc (Glasgow)

Tools - Snoopy's Export Features



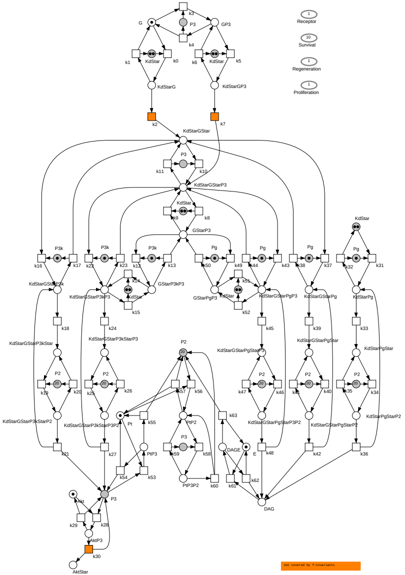
Circadian Clock ;
PRISM web page

places : 9
transitions : 16



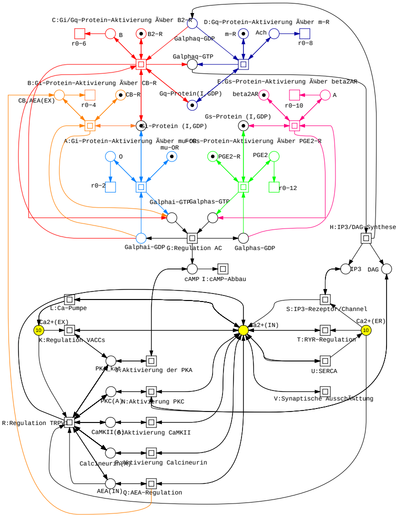
. . . , Balbo :
Angiogenesis Process ;
CMSB 2009

places : 39
transitions : 64



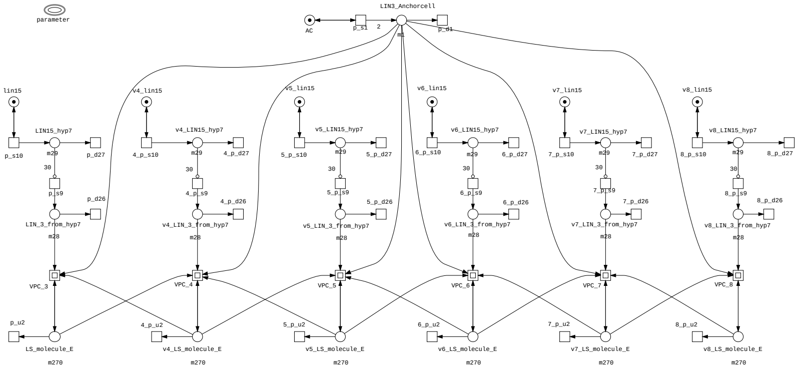
Pain-related pathways ;
MOSS project,
MD project group, 2009

places : 132
transitions : 152



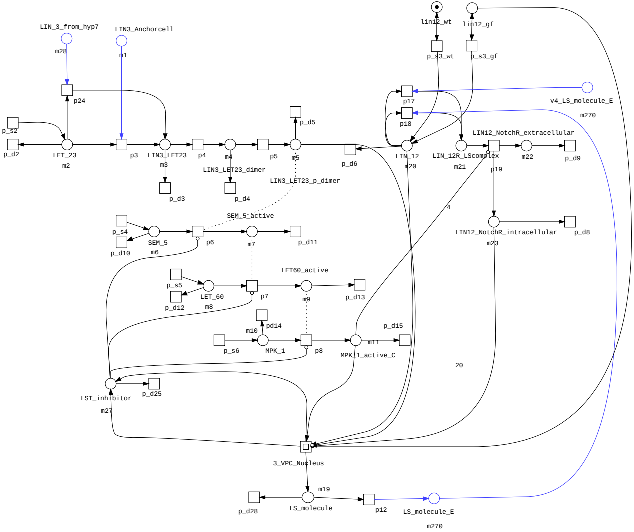
C. elegance vulval development : *places : 206, transitions : 366*

- Miyano et al., BMC Syst. Biol. 2009 ;
- Bonzanni et al., Bioinformatics 2009 ;



. . . some more examples

C. elegance vulval development :



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