

PART II

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

Monika Heiner

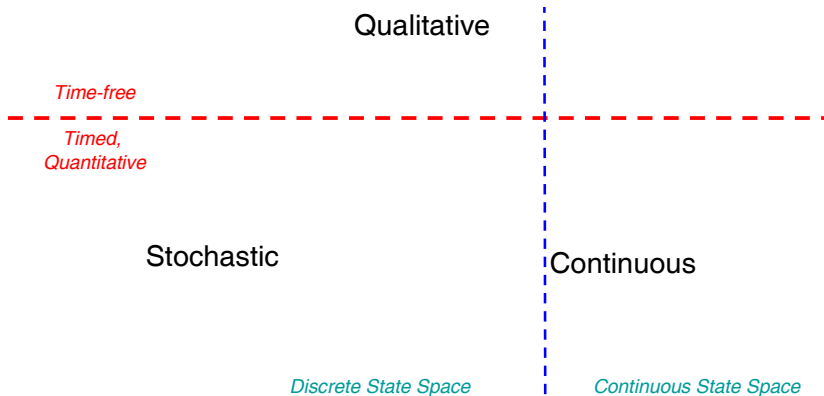
joined work with Rainer Breitling (Glasgow/UK), David Gilbert (London/UK),
BME Tutorial, Part 4, Paris, June 2009

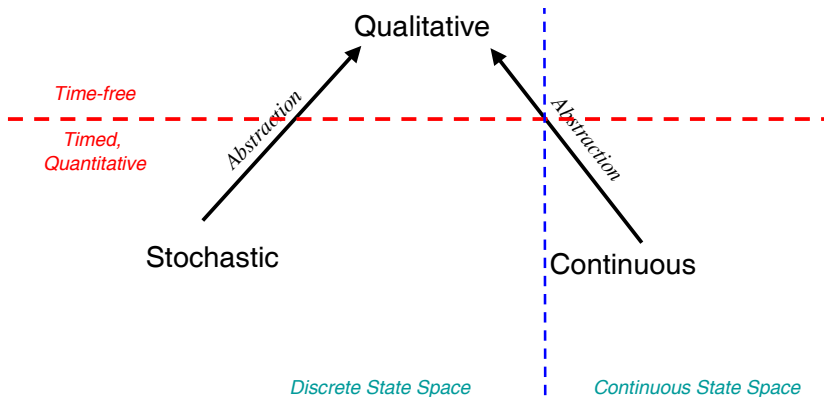
Universidad de Zaragoza, February 22, 2010

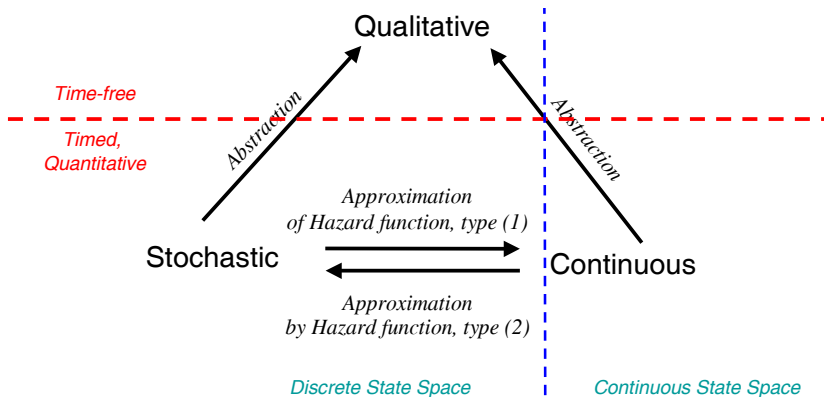
Qualitative

Stochastic

Continuous







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**)

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

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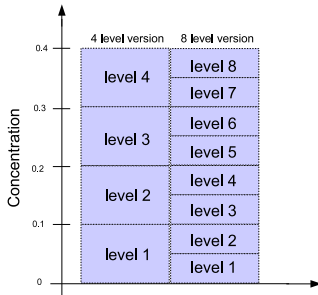
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Semantics : Continuous Time Markov Chain / CSL, PLTLc

Interpretation of tokens :

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



Specialised stochastic firing rate function, two examples :

- *molecules semantics*

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

- *concentration levels semantics*

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

- 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* :

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

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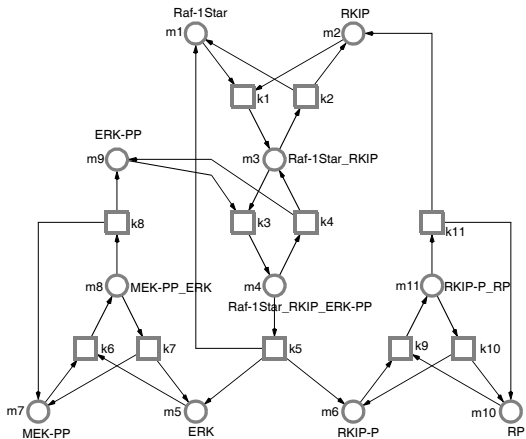
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- each equation corresponds to a line in the incidence matrix
- *continuous Petri net = structured description of ODEs.*

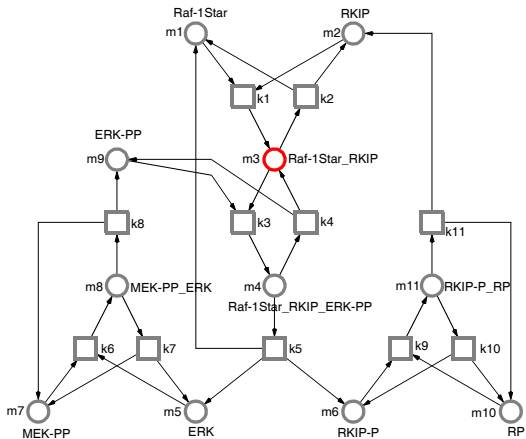
Semantics : ODEs / LTLc

Continuous Petri Net - Example



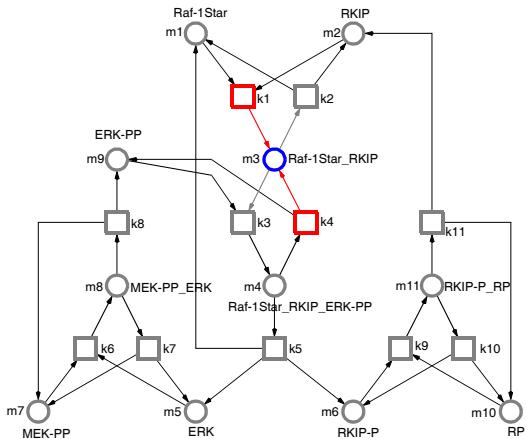
Continuous Petri Net - Example

$$\frac{dm_3}{dt} =$$



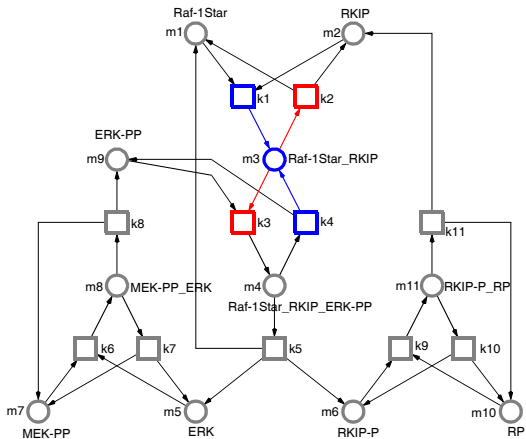
Continuous Petri Net - Example

$$\frac{dm_3}{dt} = +r_1 + r_4$$



Continuous Petri Net - Example

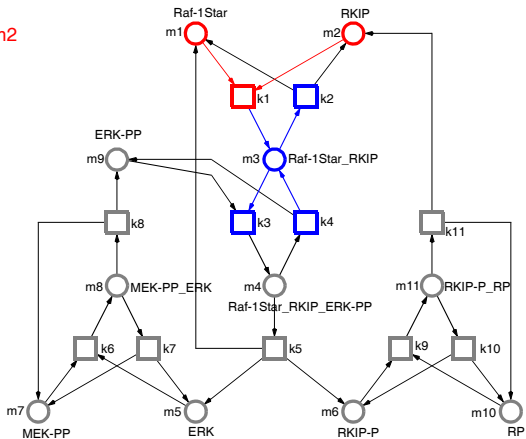
$$\frac{dm_3}{dt} = +r_1 + r_4 - r_2 - r_3$$



Continuous Petri Net - Example

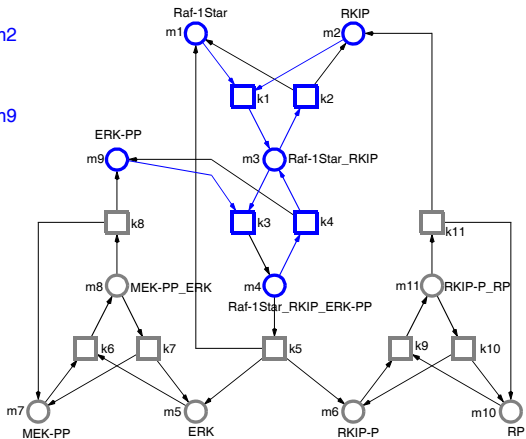
$$\frac{dm_3}{dt} = +k_1 * m_1 * m_2$$

+ r4
- r2
- r3



Continuous Petri Net - Example

$$\begin{aligned}\frac{dm_3}{dt} = & + k_1 * m_1 * m_2 \\ & + k_4 * m_4 \\ & - k_2 * m_3 \\ & - k_3 * m_3 * m_9\end{aligned}$$



$$\frac{dm_1}{dt} = r_2 + r_5 - r_1$$

$$\frac{dm_2}{dt} = r_2 + r_{11} - r_1$$

$$\frac{dm_3}{dt} = r_1 + r_4 - r_2 - r_3$$

$$\frac{dm_4}{dt} = r_3 - r_4 - r_5$$

$$\frac{dm_5}{dt} = r_5 + r_7 - r_6$$

$$\frac{dm_6}{dt} = r_5 + r_{10} - r_9$$

$$\frac{dm_7}{dt} = r_7 + r_8 - r_6$$

$$\frac{dm_8}{dt} = r_6 - r_7 - r_8$$

$$\frac{dm_9}{dt} = r_4 + r_8 - r_3$$

$$\frac{dm_{10}}{dt} = r_{10} + r_{11} - r_9$$

$$\frac{dm_{11}}{dt} = r_9 - r_{10} - r_{11}$$

$$r_1 = k_1 * m_1 * m_2$$

$$r_2 = k_2 * m_3$$

$$r_3 = k_3 * m_3 * m_9$$

$$r_4 = k_4 * m_4$$

$$r_5 = k_5 * m_4$$

$$r_6 = k_6 * m_5 * m_7$$

$$r_7 = k_7 * m_8$$

$$r_8 = k_8 * m_8$$

$$r_9 = k_9 * m_6 * m_{10}$$

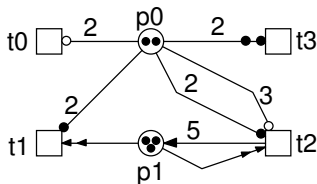
$$r_{10} = k_{10} * m_{11}$$

$$r_{11} = k_{11} * m_{11}$$

- *M Heiner, D Gilbert, R Donaldson :
Petri Nets for Systems and Synthetic Biology ;
SFM 2008, Springer LNCS 5016, pp. 215-264, 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

- *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 $DSPN_{Bio} = (P, T, f, g, v, d, m_0)$, 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.

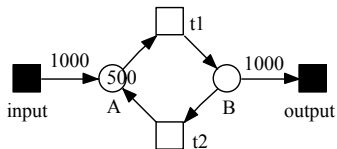
... *continued on next slide*

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
 - $H := \bigcup_{t \in T} \{h_t \mid h_t : \mathbb{N}_0^{|\bullet t|} \rightarrow \mathbb{R}^+\}$
 - $v(t) = h_t$ for all transitions $t \in T$
- $d : T_{timed} \rightarrow \mathbb{R}^+$ (deterministic waiting time)
- $m_0 : P \rightarrow \mathbb{N}_0$ (initial marking)

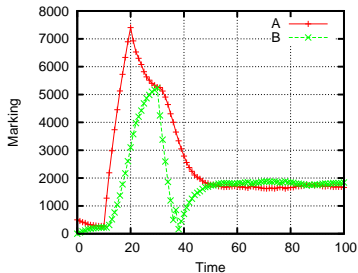
Semantics : CTMC ? \rightarrow *simulative MC/PLTLc*

EX1 : time-controlled inflow/outflow

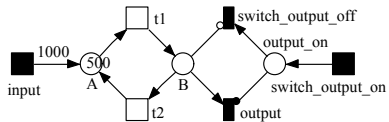


input - scheduled(11,1,20)

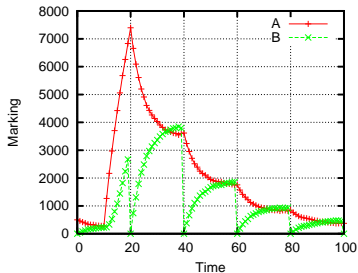
output - scheduled(31,1,40)



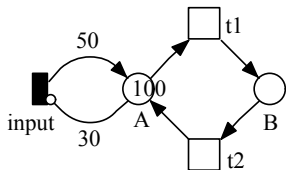
EX2 : time-controlled inflow/outflow



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

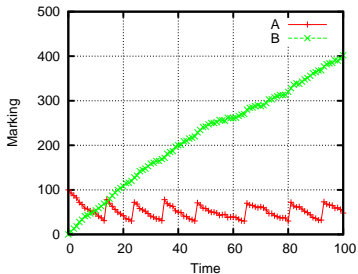


EX3 : Token-controlled Inflow

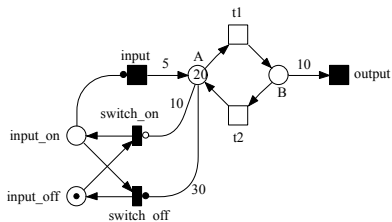


$t1$ - $BioMassAction(0.1)$

$t2$ - $BioMassAction(0.005)$

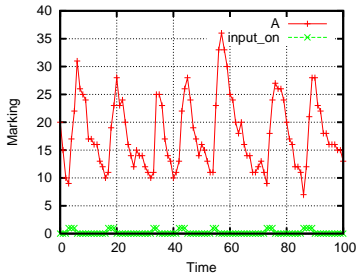


EX4 : Token-controlled Inflow

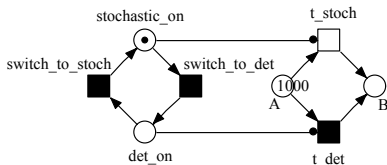


input - delay(0.5)

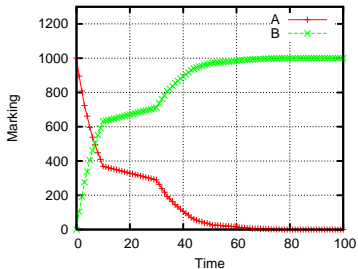
output - scheduled(5,5,_SimEnd)



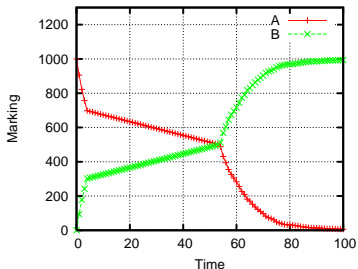
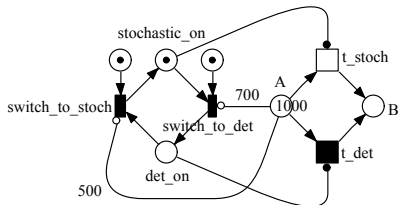
EX5 : time-controlled switch between deterministic and stochastic behaviour

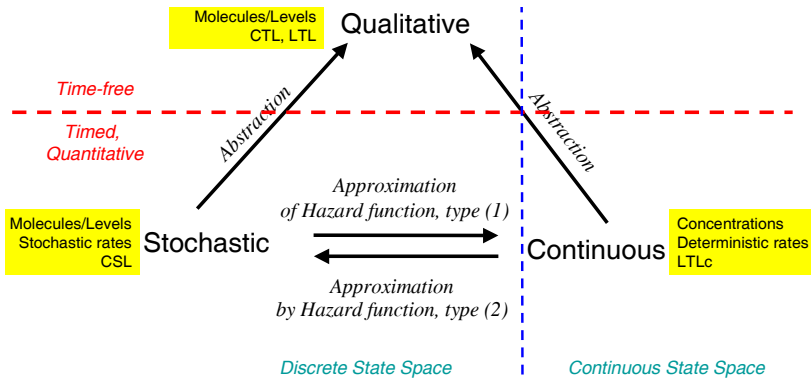


switch_to_det - *scheduled*(10)
switch_to_stoch - *scheduled*(30)



EX6 : token-controlled switch between deterministic and stochastic behaviour





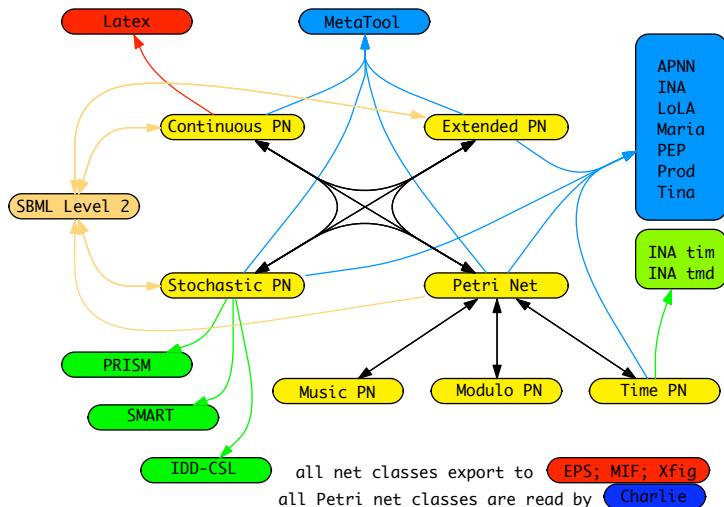
- *model construction*
 - BioNessi (London)
 - Snoopy (CB)

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 - PRISM/CSL (Oxford) , IDD-CSL (CB)
 - MC2/PLTLc (Glasgow)

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- *stochastic analysis*
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 - MC2/PLTLc (Glasgow)
- *continuous analysis*
 - MATLAB
 - BIOCHAM/LTLc (INRIA/Paris), MC2/LTLc (Glasgow)

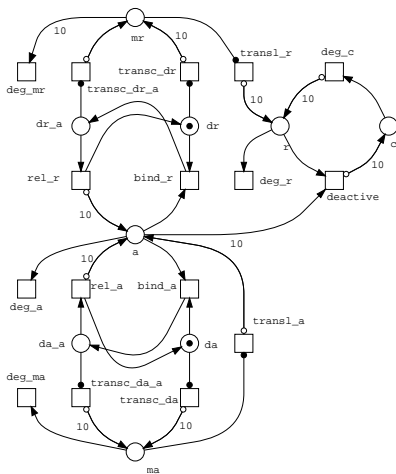
Tools - Snoopy's Export Features



... some more examples

Circadian Clock ;
PRISM web page

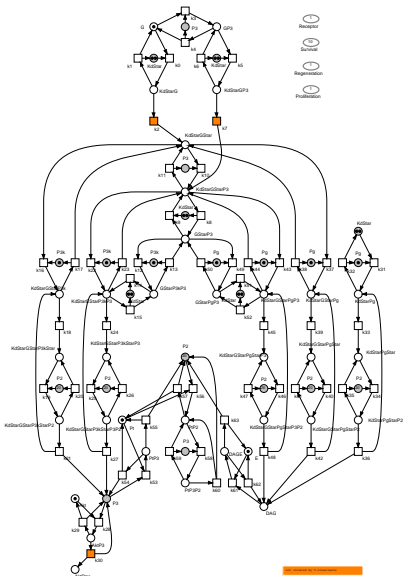
places : 9
transitions : 16



... some more examples

..., Balbo :
Angiogenesis Process;
CMSB 2009

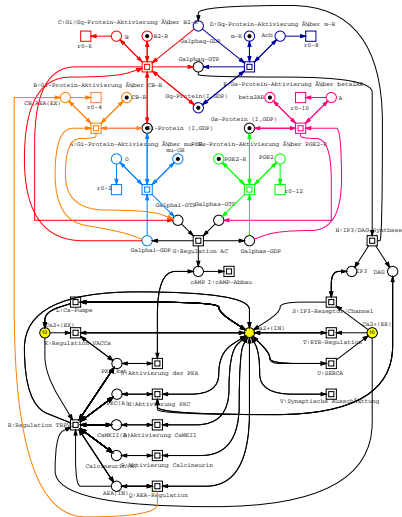
places : 39
transitions : 64



... some more examples

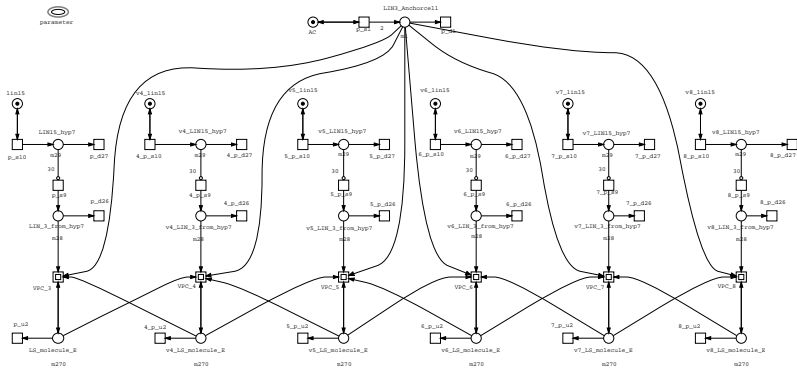
Pain-related pathways;
MOSS project,
MD project group, 2009

places : 132
transitions : 152

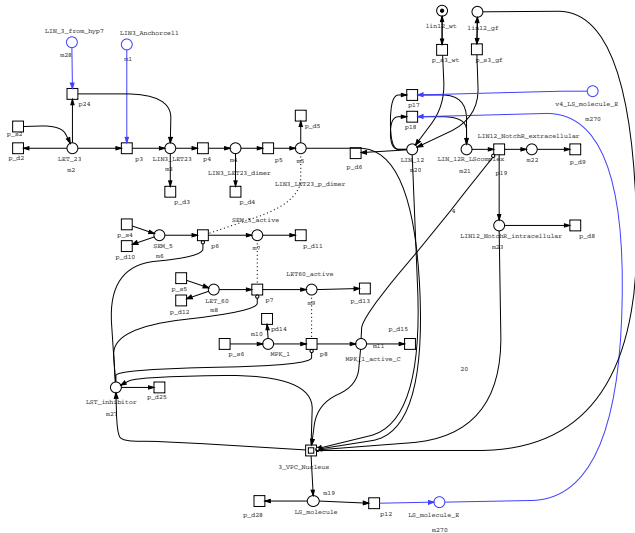


C. elegans vulval development : *places* : 206, *transitions* : 366

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



C. elegans vulval development :



C. elegans vulval development :

