

**SNOOPY -
A UNIFYING PETRI NET FRAMEWORK
TO INVESTIGATE
BIOMOLECULAR NETWORKS**

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PRELIMINARIES

- ❑ **predecessor: Petri Net Editor PED, 1992 - 2004**
- ❑ **initial implementation concepts**
 - > *Thomas Menzel, Master Thesis, 1997*
- ❑ **core implementation**
 - > *Markus Fieber, Master Thesis, 2004*
- ❑ **Master Theses supervised by staff members**
 - > *Denny Bayer, Matthias Dube, Anja Kurth, Sebastian Lehrack, Ronny Richter, **Christian Rohr**, Daniel Scheibler, Krispin Schulz, Marcel Schwarze, Alexey Tovchigrechko, Katja Winder, . . . and many students' projects*
- ❑ **now about 120,000 lines of code (without running extensions)**
- ❑ **many features influenced by**
 - > *Wolfgang Marwan, Otto von Guericke University & Magdeburg Centre for Systems Biology & MPI*

supported operating systems

- > *MAC OS X*
- > *Windows*
- > *Linux (selected distributions)*

free of charge for non-commercial use

reference for acknowledgements

C Rohr, W Marwan, M Heiner:

Snoopy - a unifying Petri net framework to investigate biomolecular networks;

Bioinformatics 2010 26(7): 974-975

source code available on request

- > *close cooperation partners*

further information

<http://www-dssz.informatik.tu-cottbus.de/software/snoopy.html>

❑ **platform-independent**

-> *implementation in C++*

-> *wxWidgets (<http://www.wxwidgets.org>)*

❑ **extensible**

generic design facilitates the addition of new graph classes

❑ **adaptive**

-> *simultaneous use of several graph types in a homogeneous environment*

-> *GUI adopts dynamically to graph type in active window*

❑ **open**

-> *export to many foreign (qualitative) analysis tools, among them*

Charlie (<http://www-dssz.informatik.tu-cottbus.de/charlie.html>)

METATOOL (<http://penguin.biologie.uni-jena.de/bioinformatik/networks>)

-> *import of a few formats + automatic layout*

-> *import / export of SBML, Level 2, Version 3 (<http://sbml.org>)*

- ❑ **qualitative Petri nets**
 - QPN
 - > *Petri net* - PN
 - > *extended Petri net* - xPN

- ❑ **quantitative Petri nets**
 - > *stochastic Petri net* - SPN (xSPN)
 - > *continuous Petri net* - CPN
 - > *timed Petri nets (duration Petri, reaction Petri net)*

- ❑ **other Petri net classes**
 - > *modulo Petri net, music Petri net*

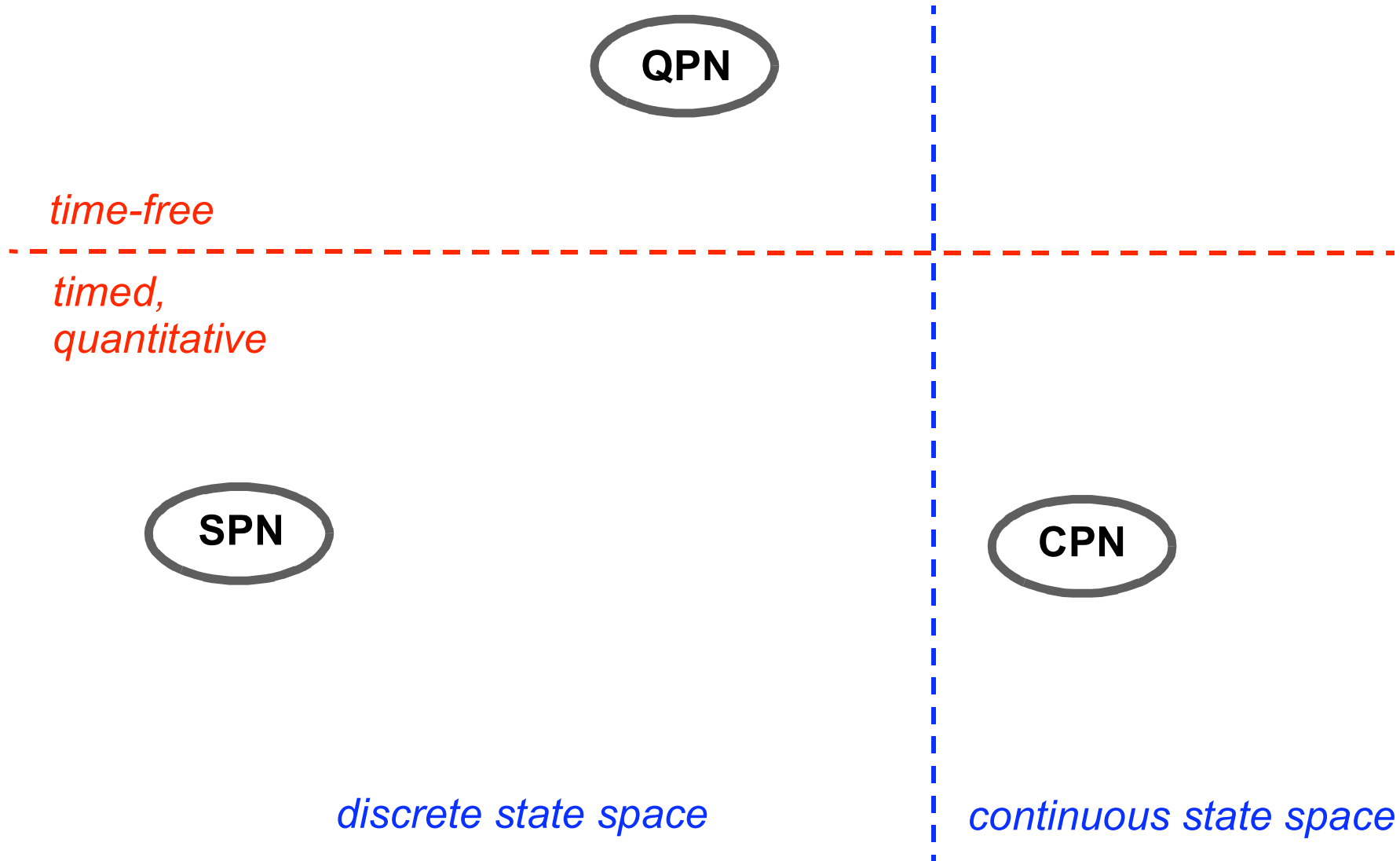
- ❑ **other graph types**
 - > *reachability graph, fault tree, extended fault tree, MTBDD, MTIDD, freestyle net*

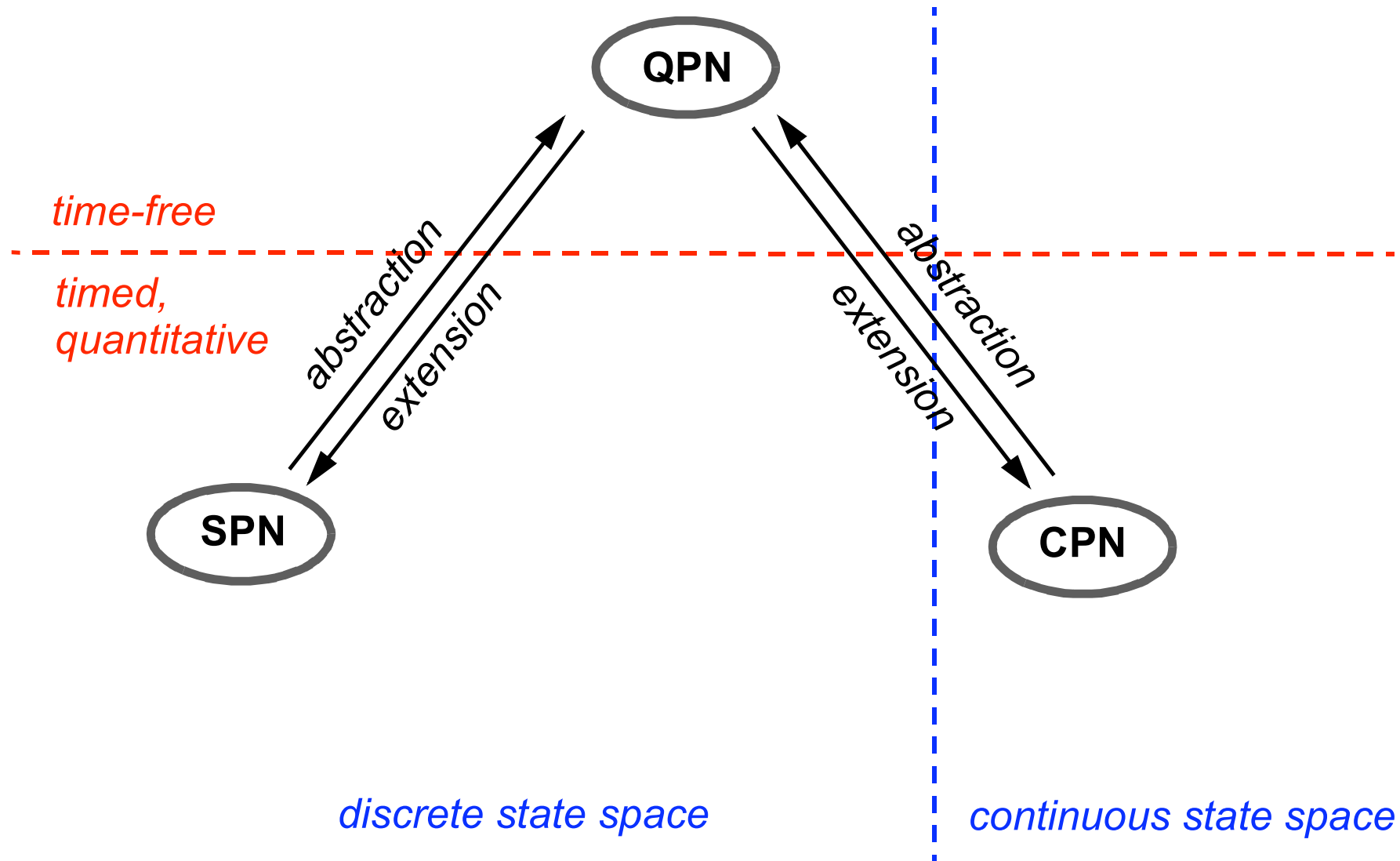
- ❑ **outlook**
 - coloured Petri nets, hybrid Petri nets*

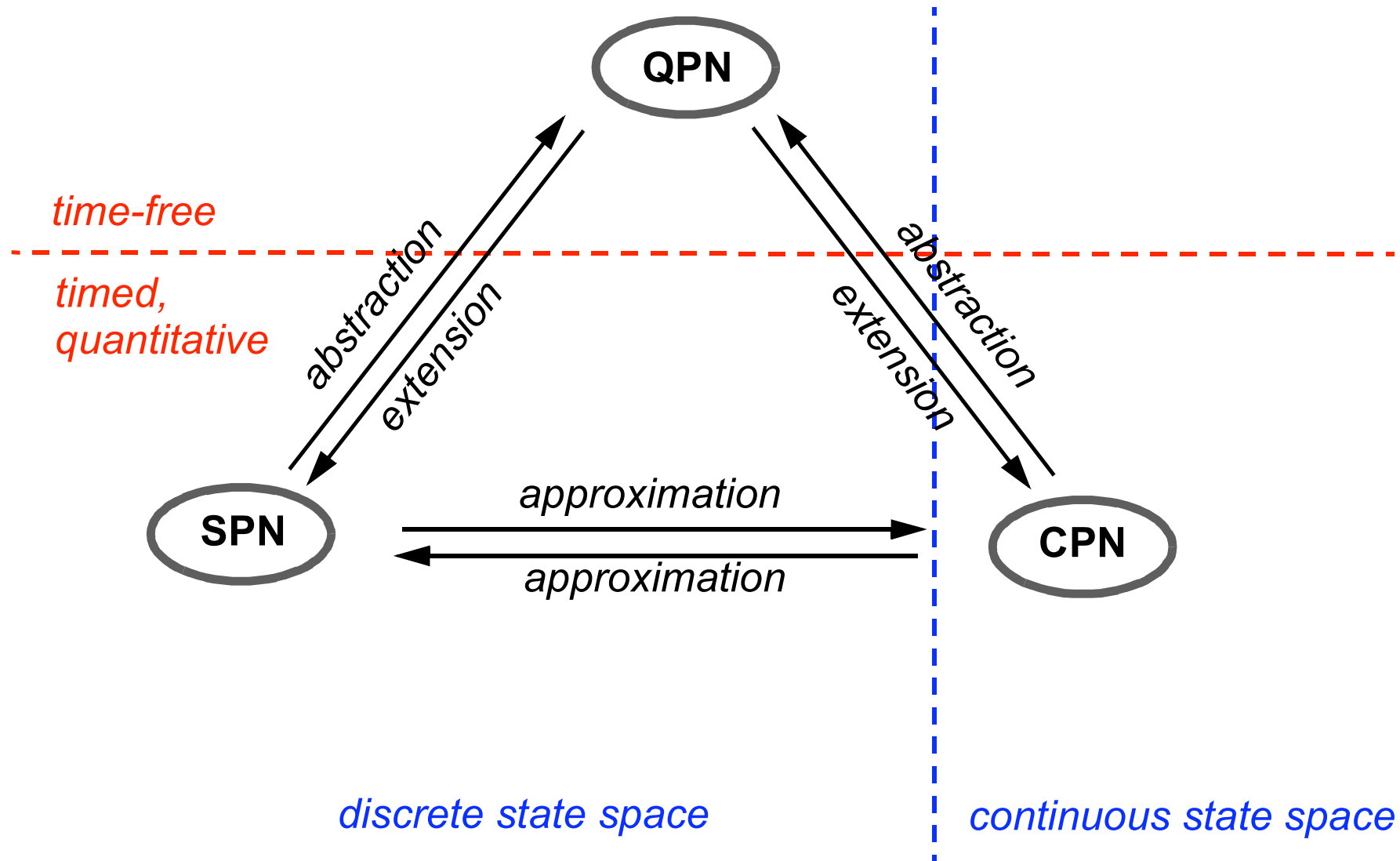
QPN

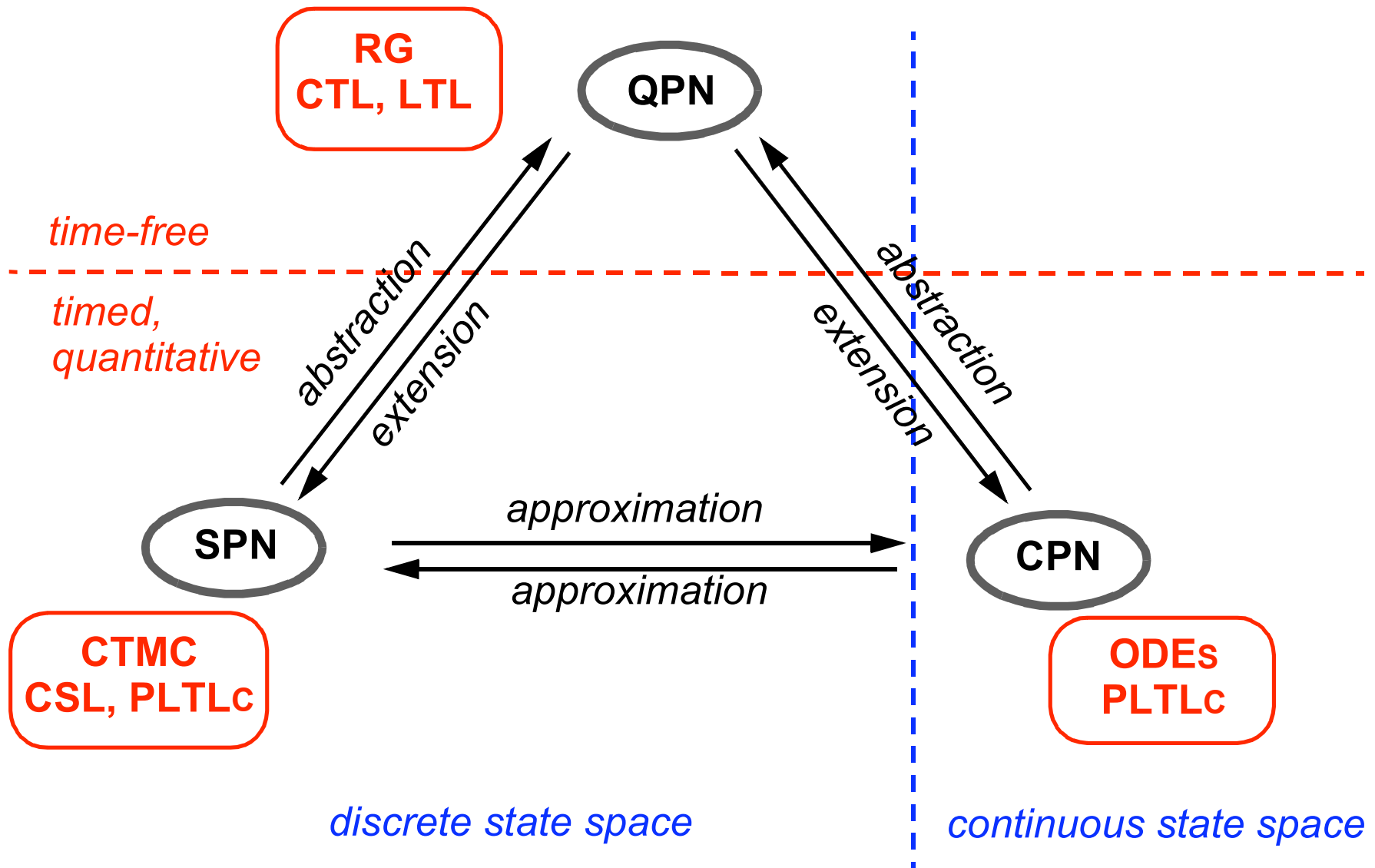
SPN

CPN







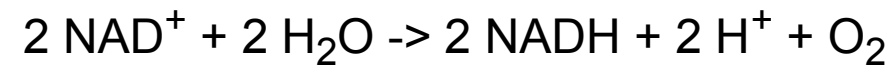


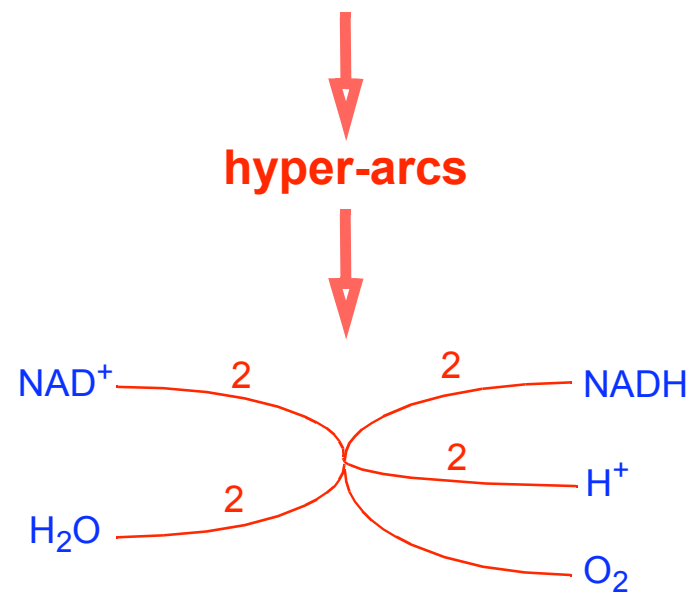
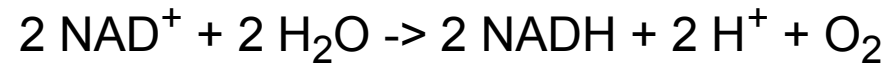
THREE MODELS SHARING STRUCTURE

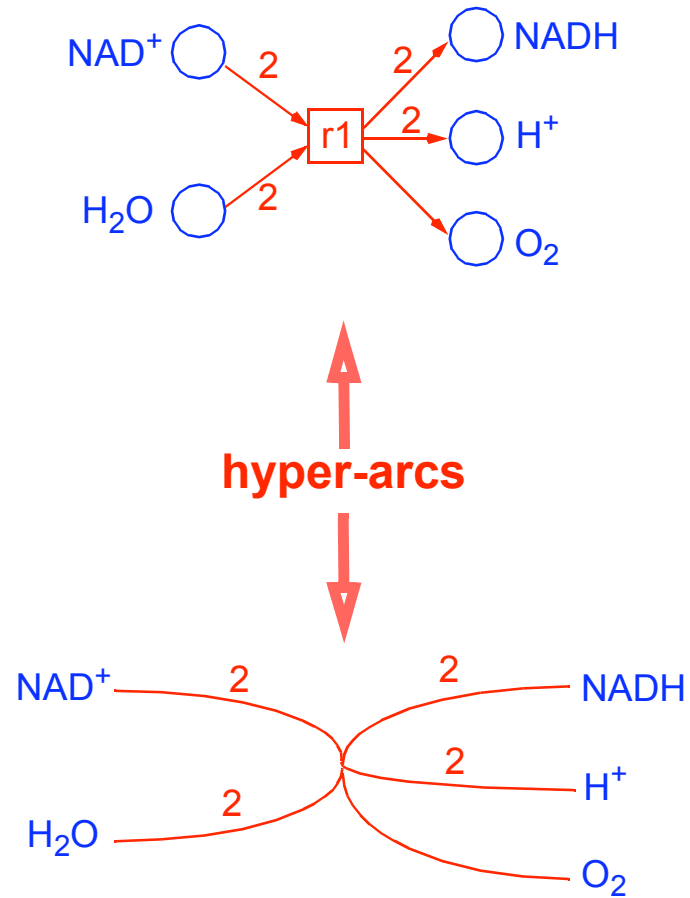
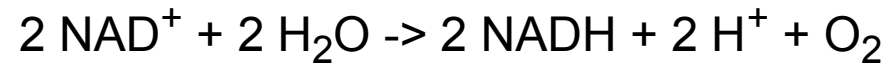


**quantitative model = qualitative model
+
quantitative parameters (kinetics)**

QUALITATIVE PETRI NETS - QPN -





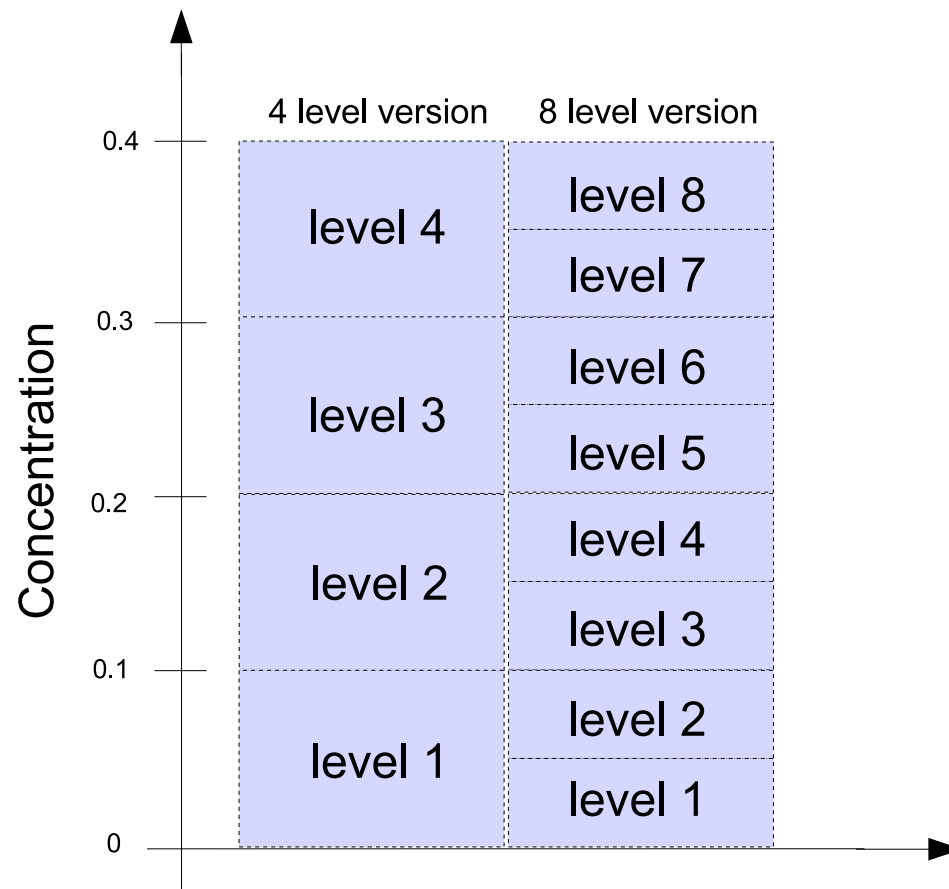


- ❑ **metabolic networks**
 - signal transduction networks**
 - gene regulatory networks**

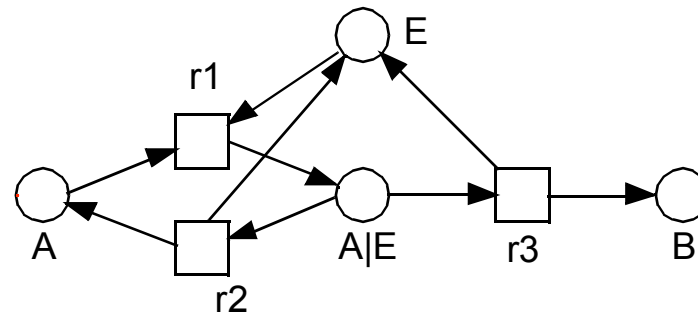
- ❑ **transitions**
 - > *(reversible, stoichiometric) chemical reactions,*
 - > *enzyme-catalyzed conversions of metabolites, proteins, . . .*
 - > *complexations/decomplexations, de-/phosphorylations, . . .*

- ❑ **places**
 - > *(primary, secondary) chemical compounds,*
 - > *(various states of) proteins, protein complex, genes, . . .*

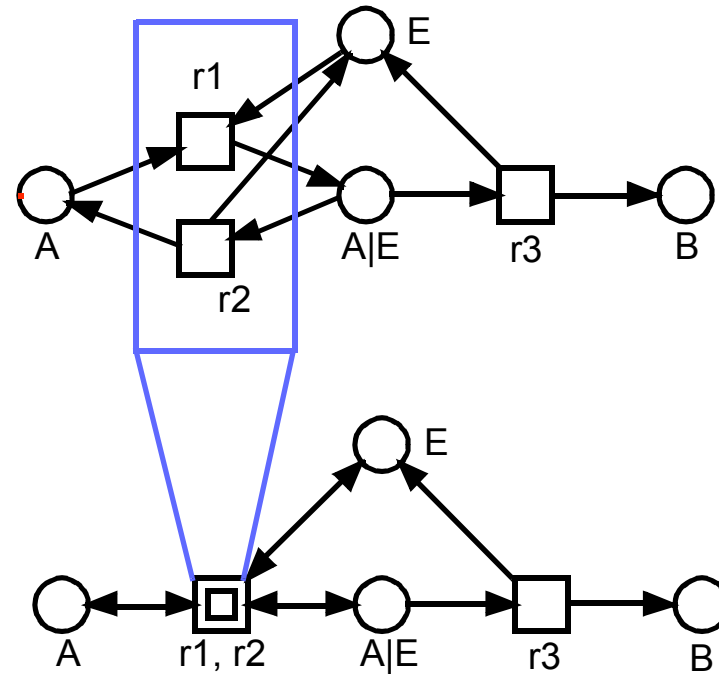
- ❑ **tokens**
 - > *molecules, moles, . . .*
 - > *concentration levels, gene expression levels, . . .*
 - e.g., high/low = present/not present, or any finite integer number*



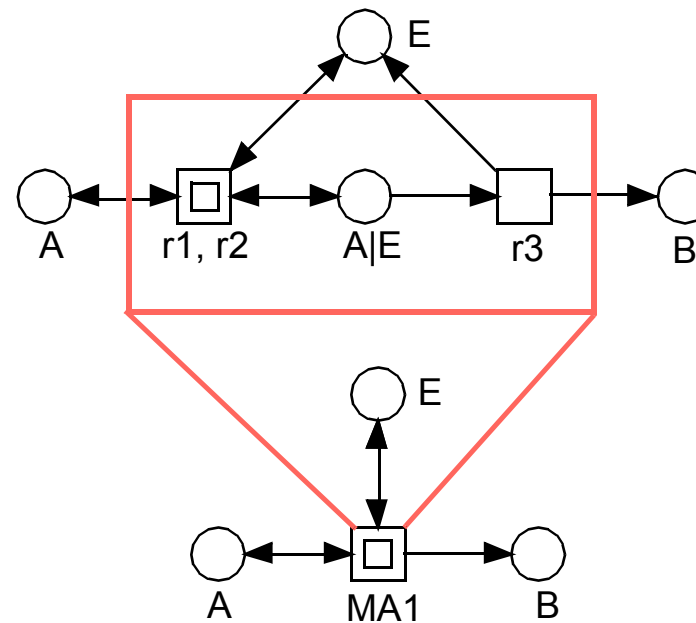
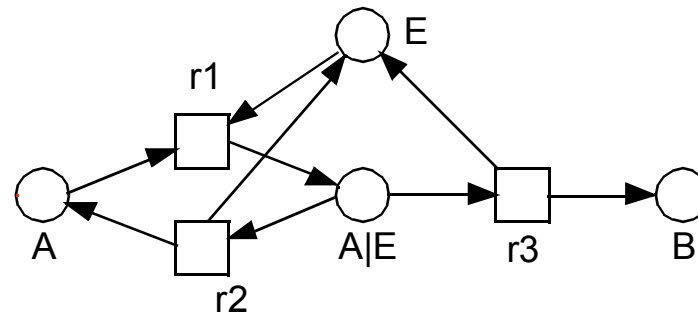
*enzymatic reaction,
mass-action approach 1*



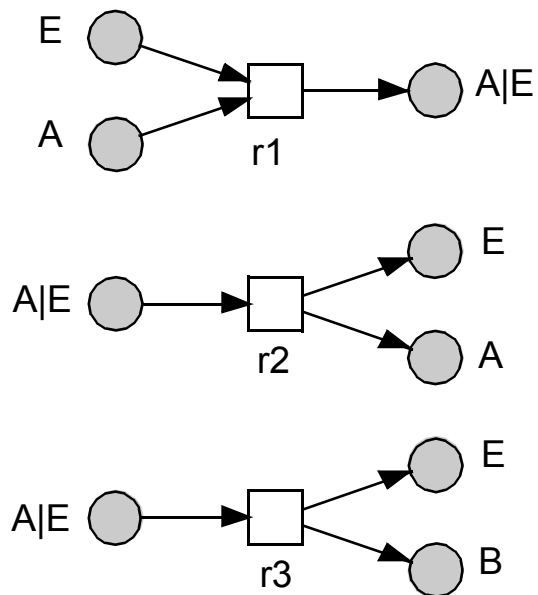
*enzymatic reaction,
mass-action approach 1*



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mass-action approach 1*

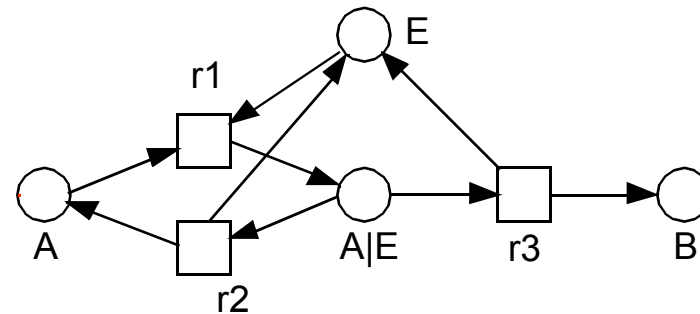


reaction-centred view

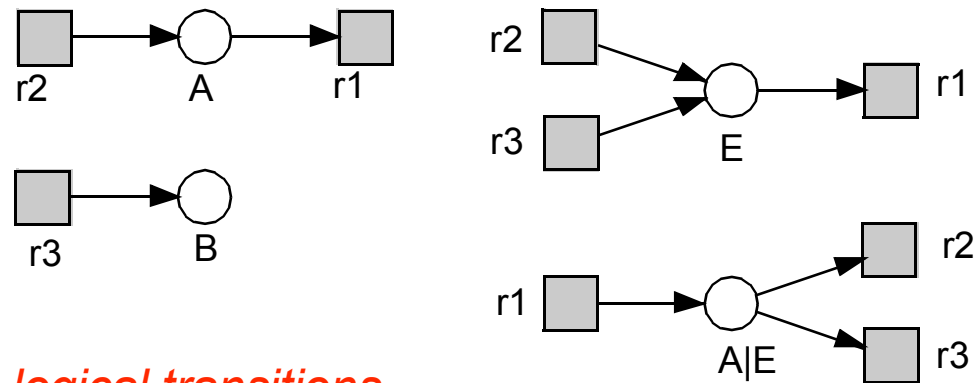


logical places

process-oriented view

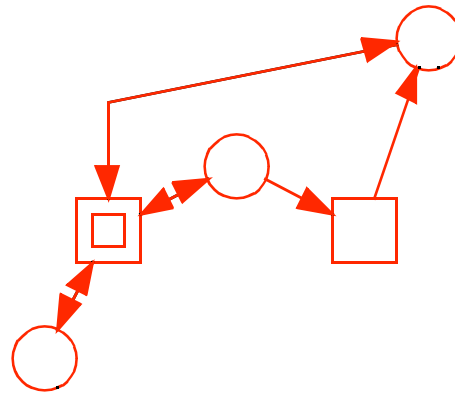


species-centred view



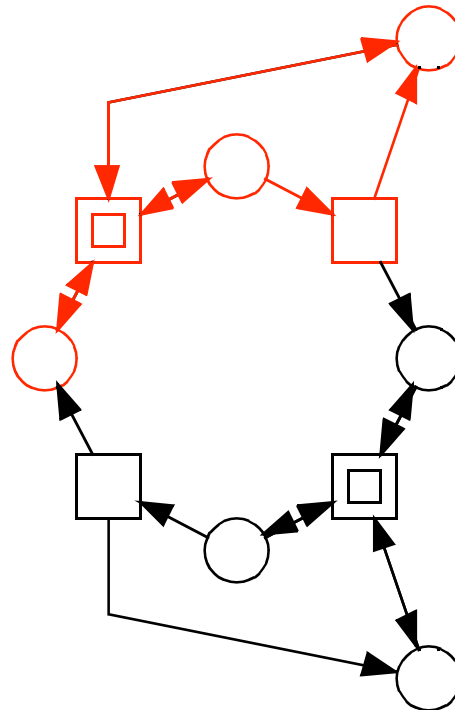
logical transitions

SINGLE
MASS-ACTION STEP

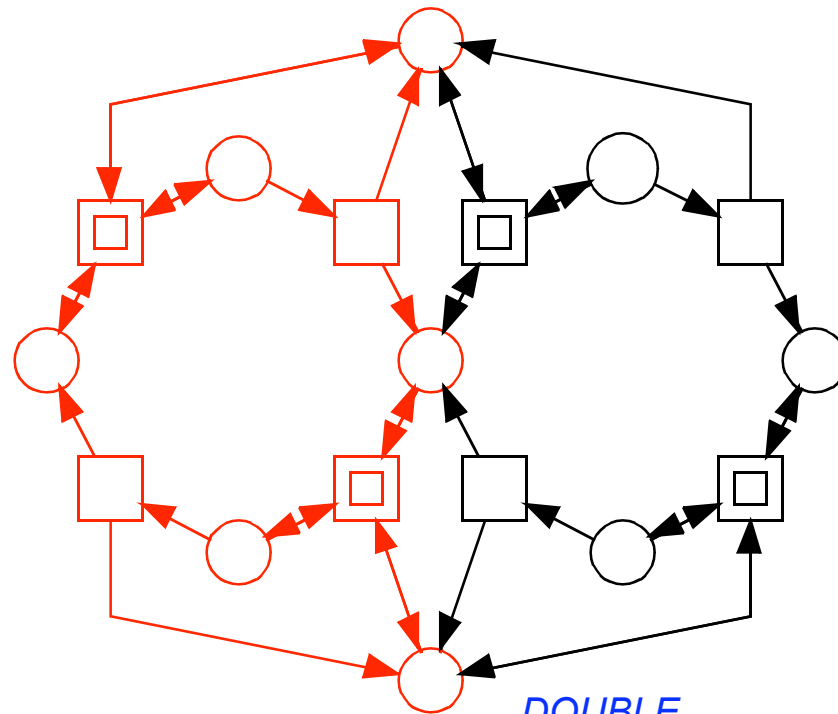


SINGLE PHOSPHORYLATION / DEPHOSPHORYLATION

SINGLE
MASS-ACTION STEP



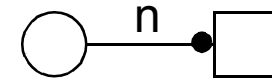
SINGLE PHOSPHOYLATION / DEPHOSPHORYLATION



DOUBLE PHOSPHOYLATION / DEPHOSPHORYLATION

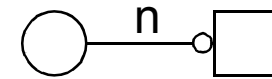
❑ Read arcs with arc weight n

-> *enabled, if tested place contains at least n tokens*



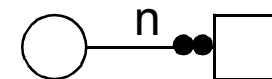
❑ inhibitor arcs with arc weight n

-> *enabled, if tested place contains less than n tokens*



❑ equal arcs with arc weight n

-> *enabled, if tested place contains exactly n tokens*



-- no marking change upon firing --

❑ reset arcs

-> *do not restrict enabledness*

-> *upon firing all tokens are removed*



**STOCHASTIC
PETRI NETS
- SPN (*xSPN*) -**

- ❑ **stochastic transitions get a stochastic waiting time**
 - > *exponential distribution with parameter lambda*

- ❑ **state-dependent lambda defined by propensity function**
 - > *any arithmetic function including the transition's pre-places as integer variables and user-defined real-valued parameters*
 - > *modifier arcs*
 - > *popular kinetics: mass-action semantics, level semantics*

- ❑ **multiple initial markings, parameter sets, and function sets**

- ❑ **deterministically timed transitions**
 - > *immediate transitions* - *zero waiting time*
 - > *deterministic transitions* - *delay relative to the enabling time*
 - > *scheduled transitions* - *scheduled at absolute time points*

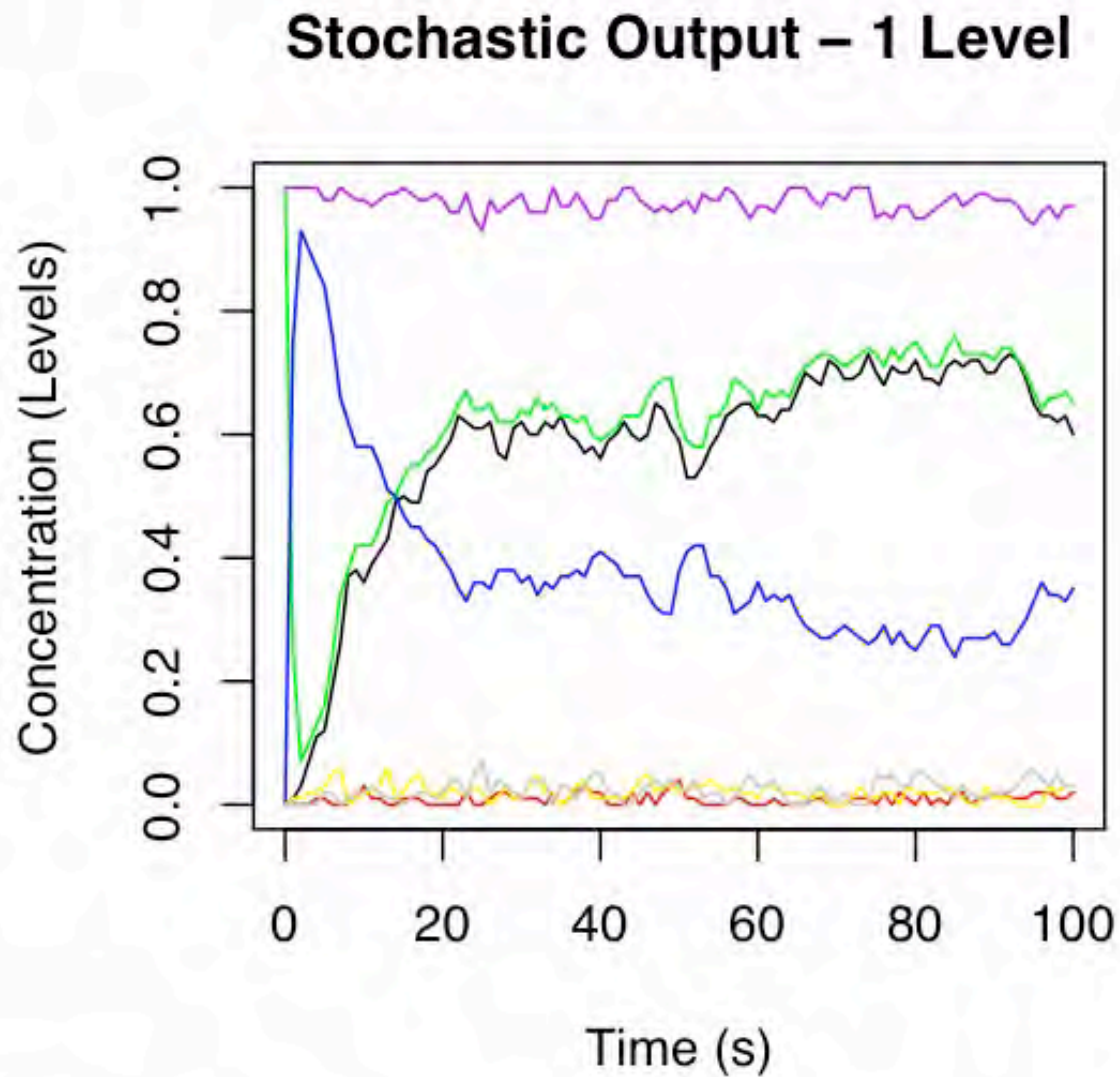
- ❑ **stochastic simulation algorithms (SSA), e.g. Gillespie's SSA**

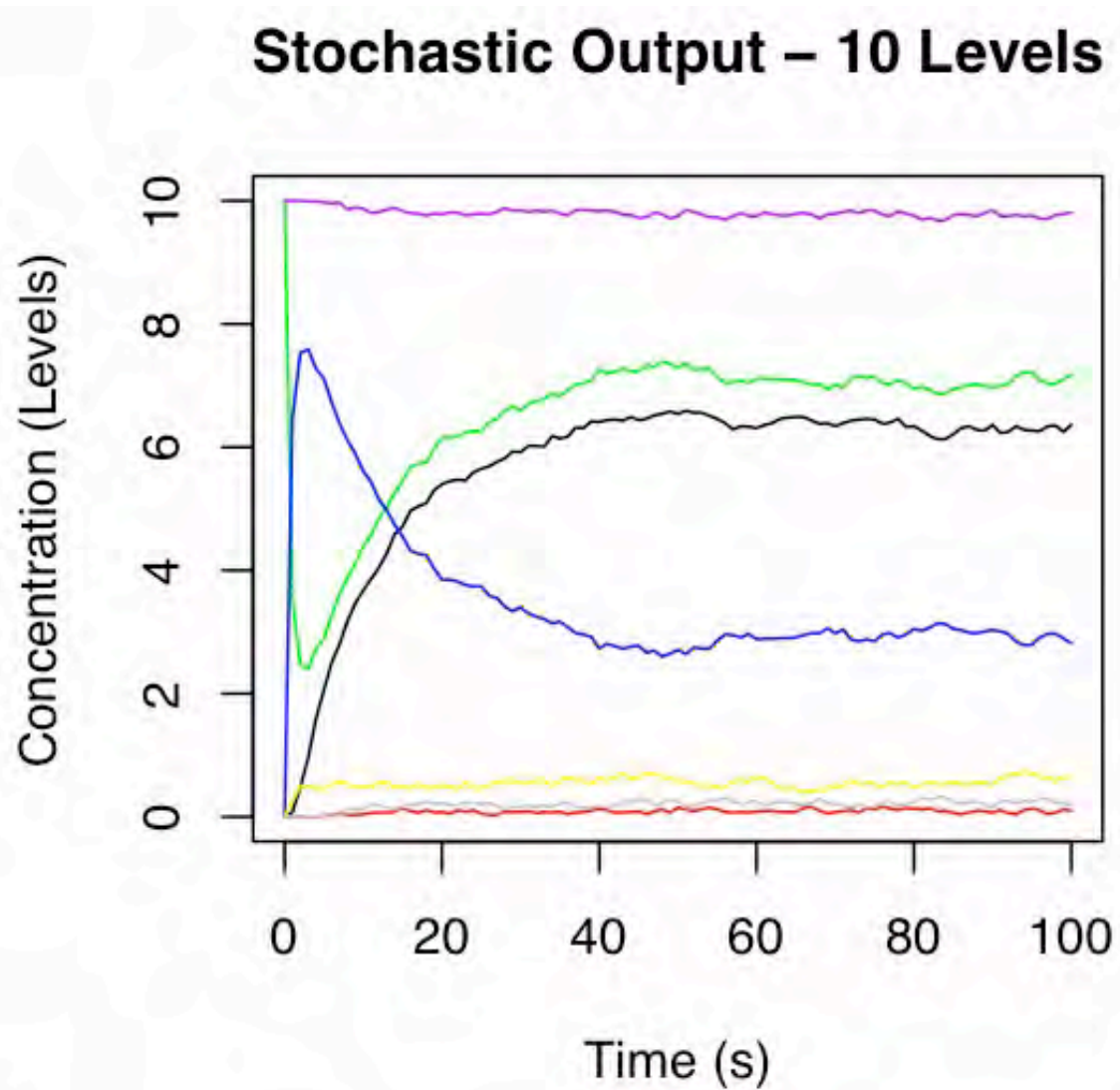
- *molecules semantics*

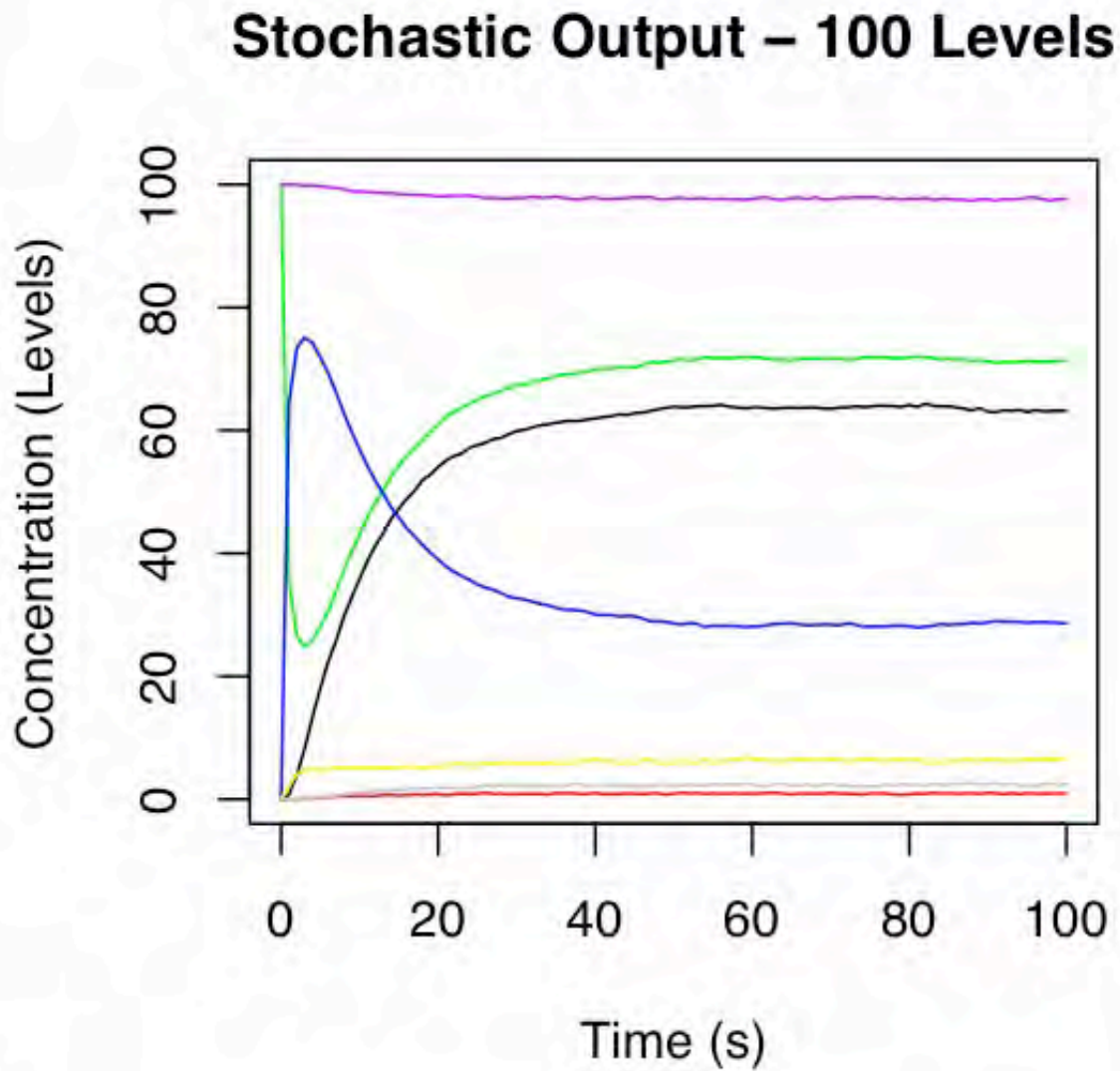
$$h_t := c_t \cdot \prod_{p \in \bullet t} \binom{m(p)}{f(p, t)}$$

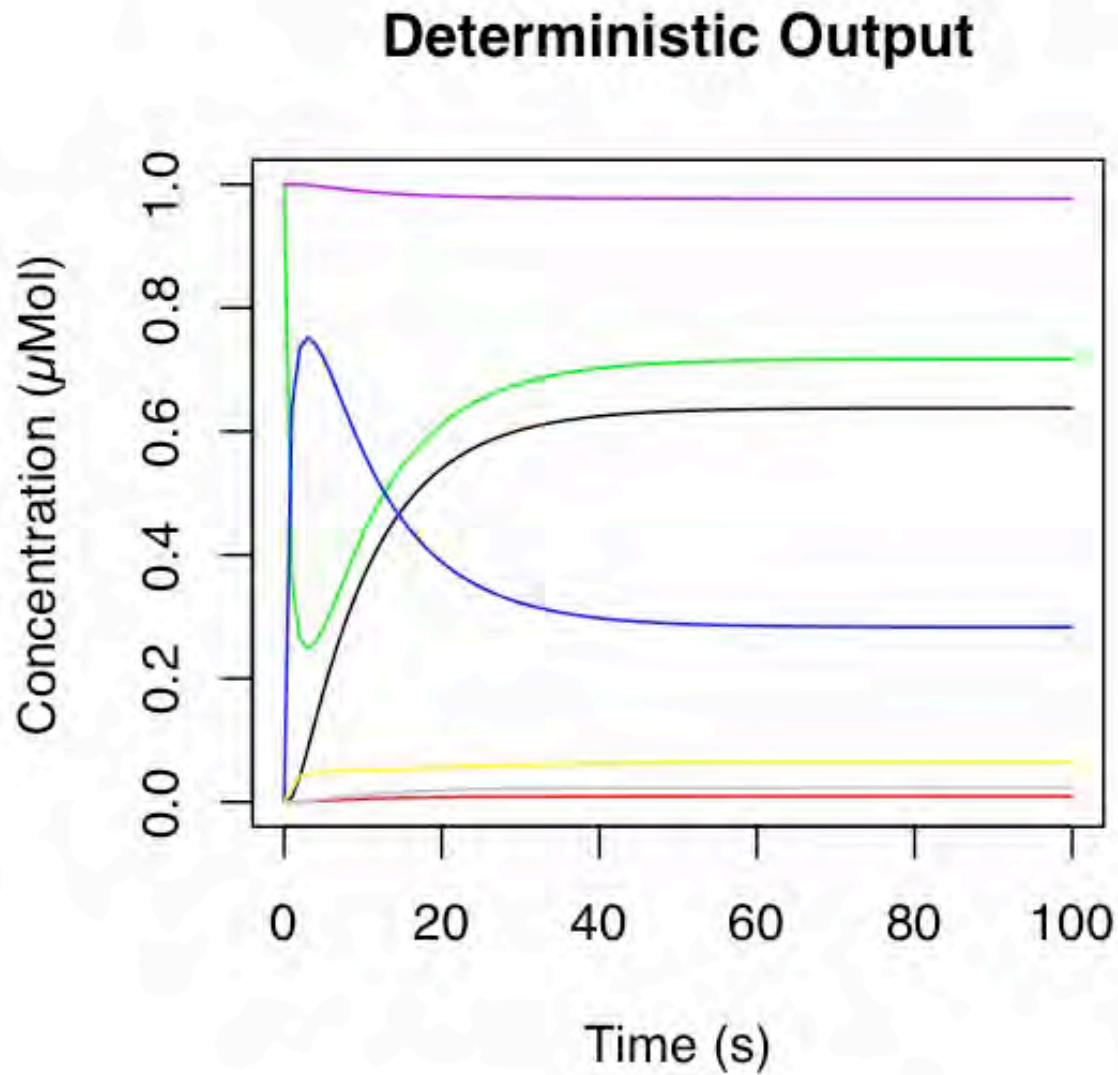
- *concentration levels semantics*

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



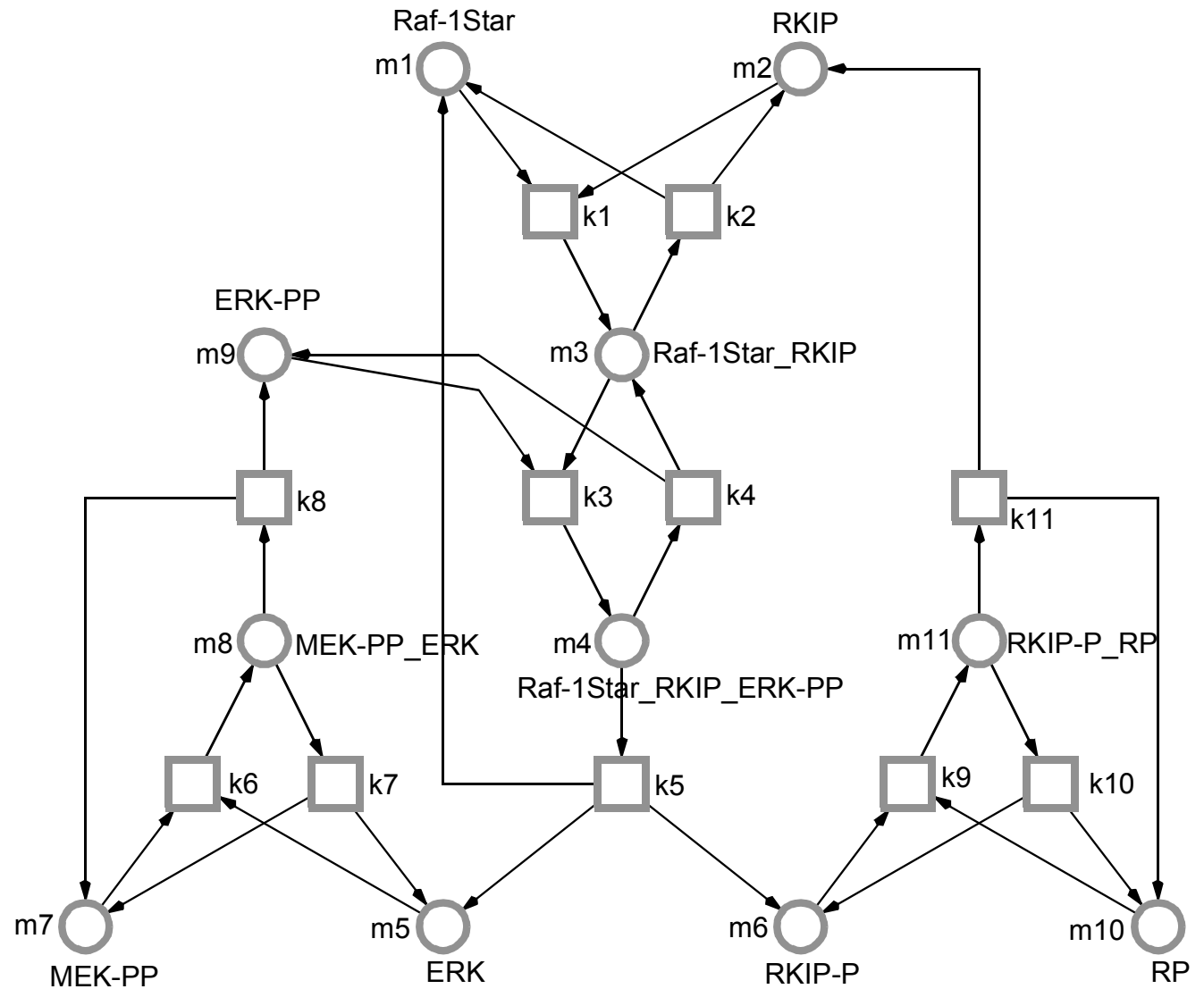






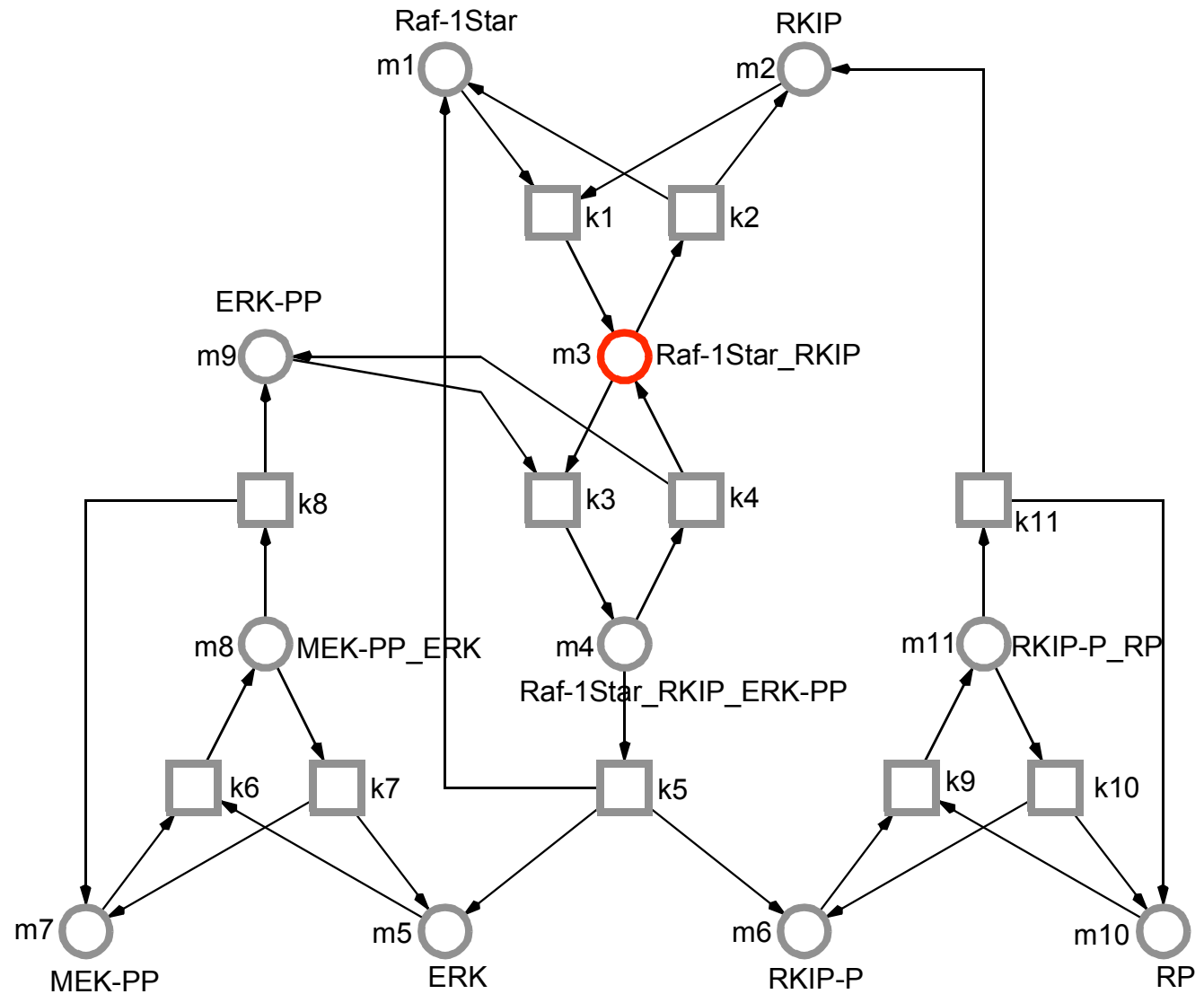
CONTINUOUS PETRI NETS - CPN -

- ❑ **transitions fire continuously**
- ❑ **rate functions**
 - > *any arithmetic function including the transition's pre-places as real-valued variables and user-defined real-valued parameters*
- ❑ **real-valued tokens**
 - > *concentrations*
- ❑ **multiple initial markings, parameter sets, function sets (not yet)**
- ❑ **a CPN defines uniquely a set of ordinary differential equations (ODEs), but not vice versa**
 - > *export of the generated ODEs to Latex and ASCII*
- ❑ **simulation (numerical integration)**
 - > *six stiff and six unstiff solvers*



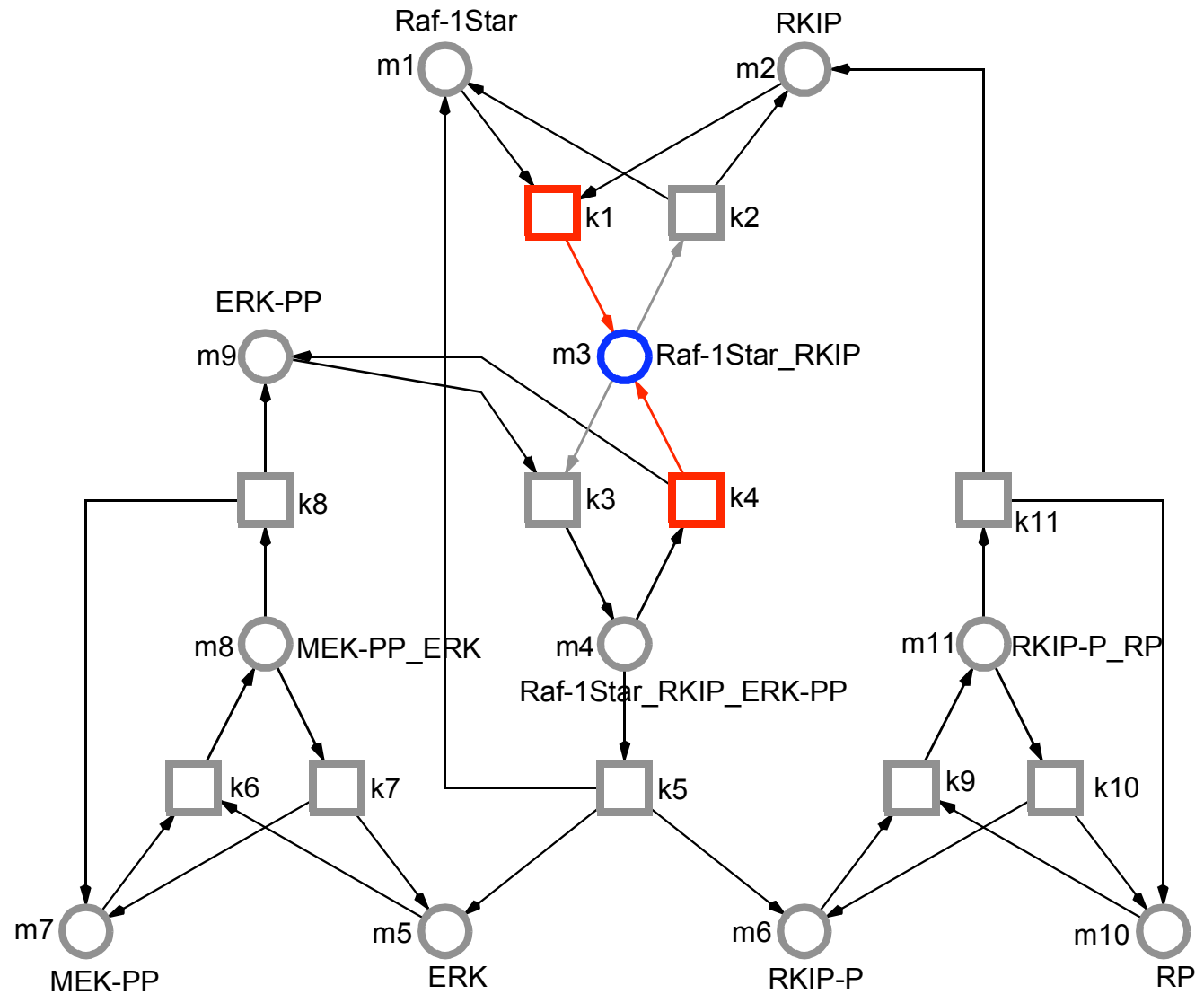
CONTINUOUS PETRI NET DEFINES ODES

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



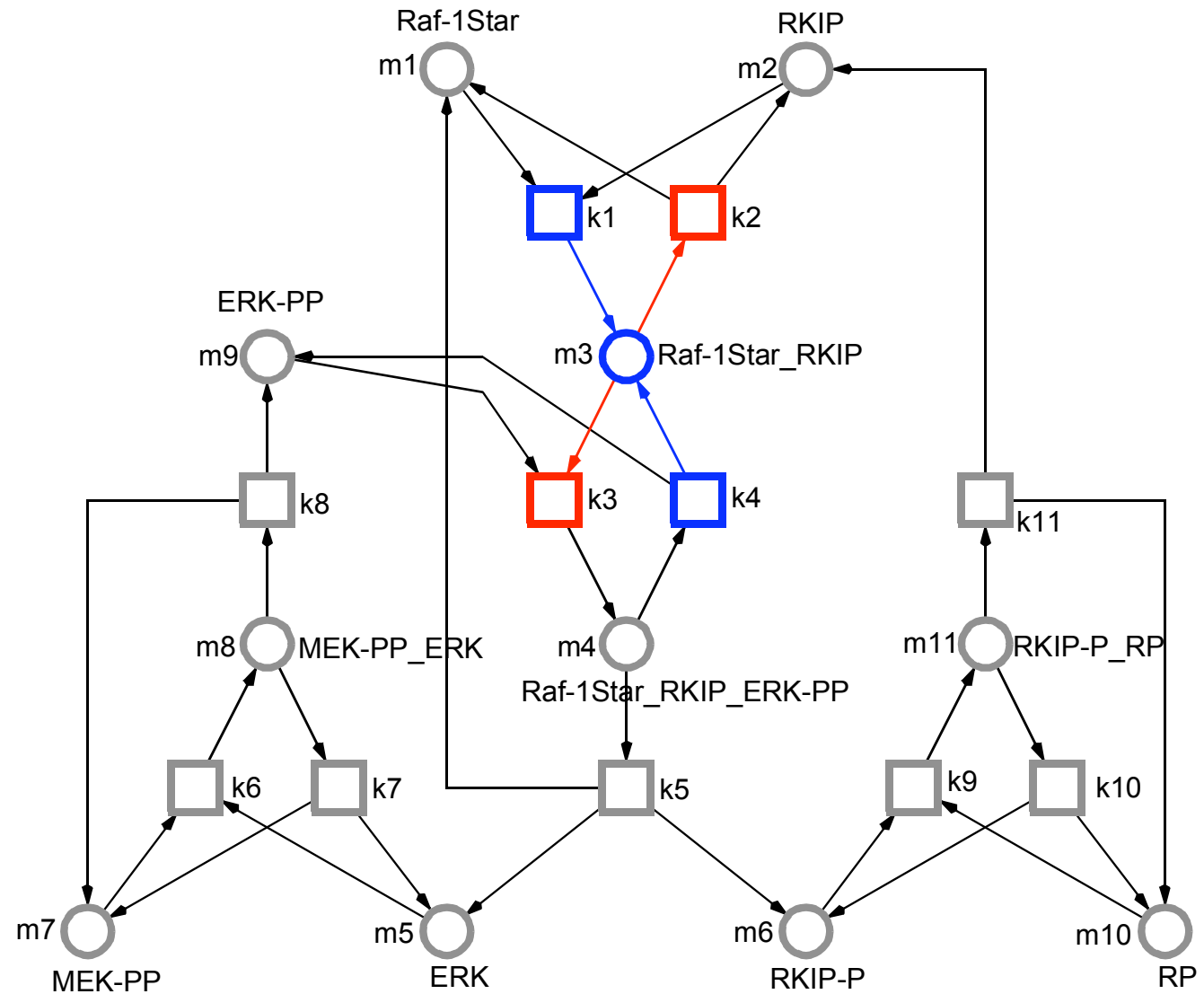
CONTINUOUS PETRI NET DEFINES ODES

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



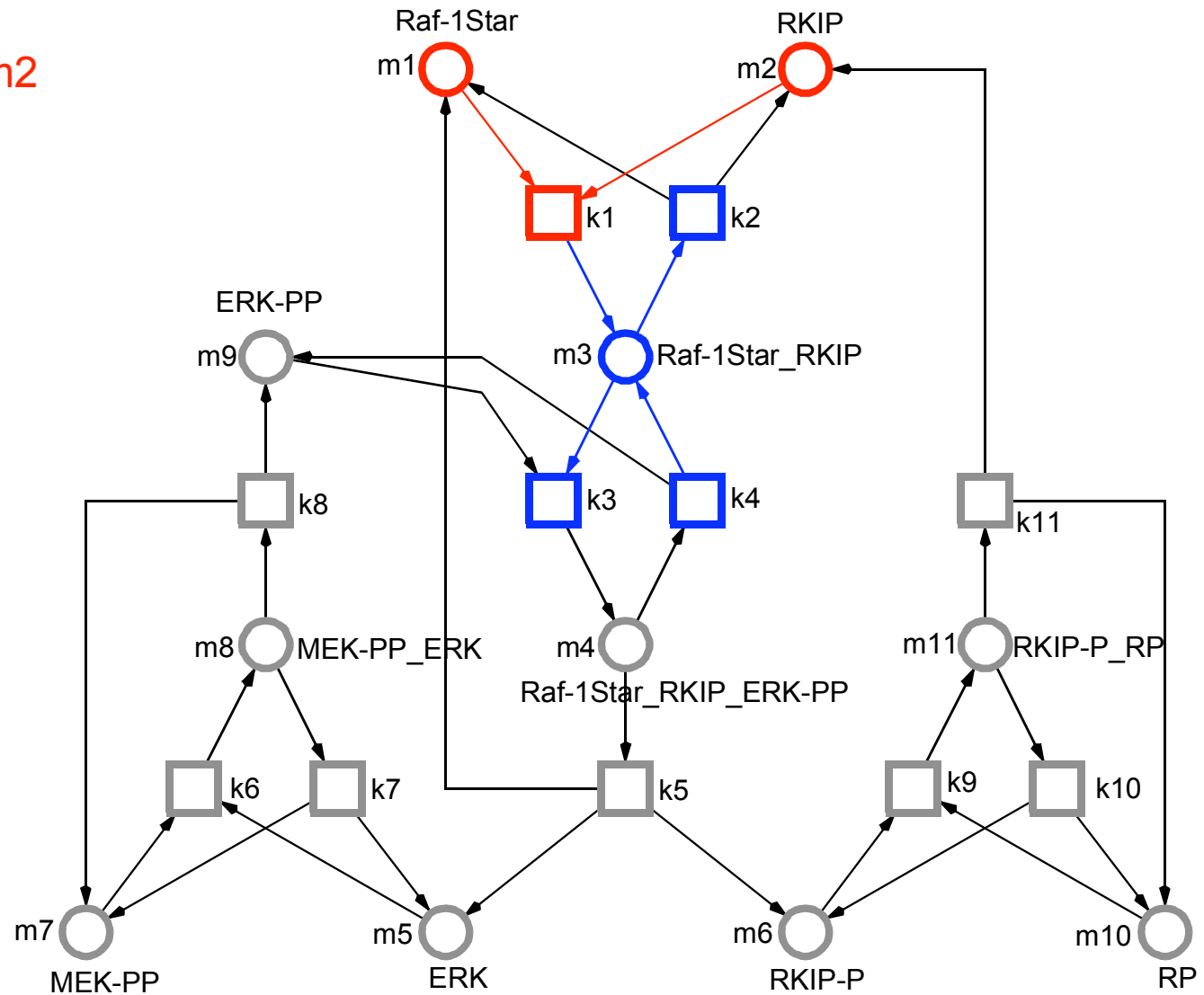
CONTINUOUS PETRI NET DEFINES ODES

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



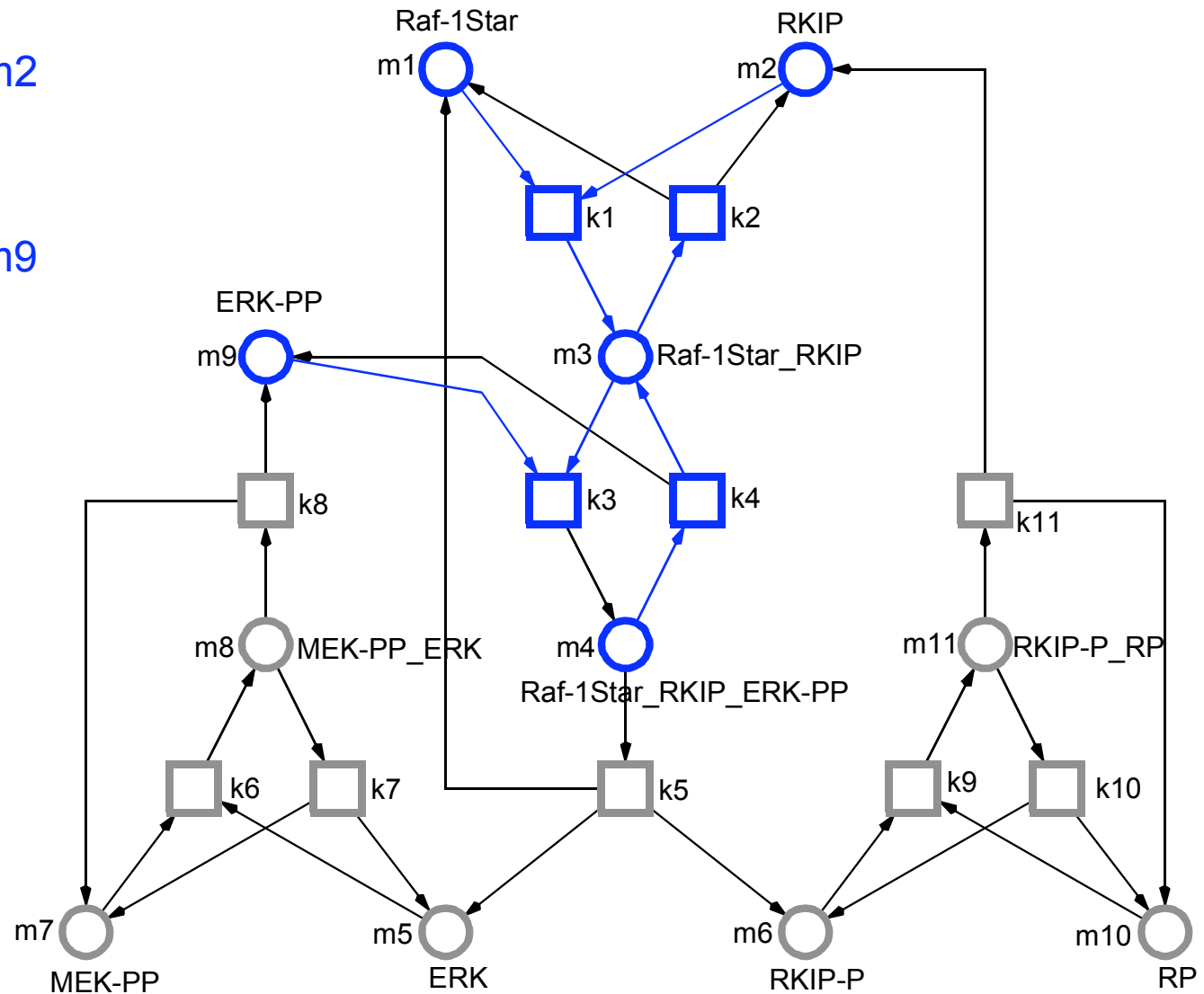
CONTINUOUS PETRI NET DEFINES ODES

$$\frac{dm_3}{dt} = +k_1 * m_1 * m_2 + r_4 - r_2 - r_3$$



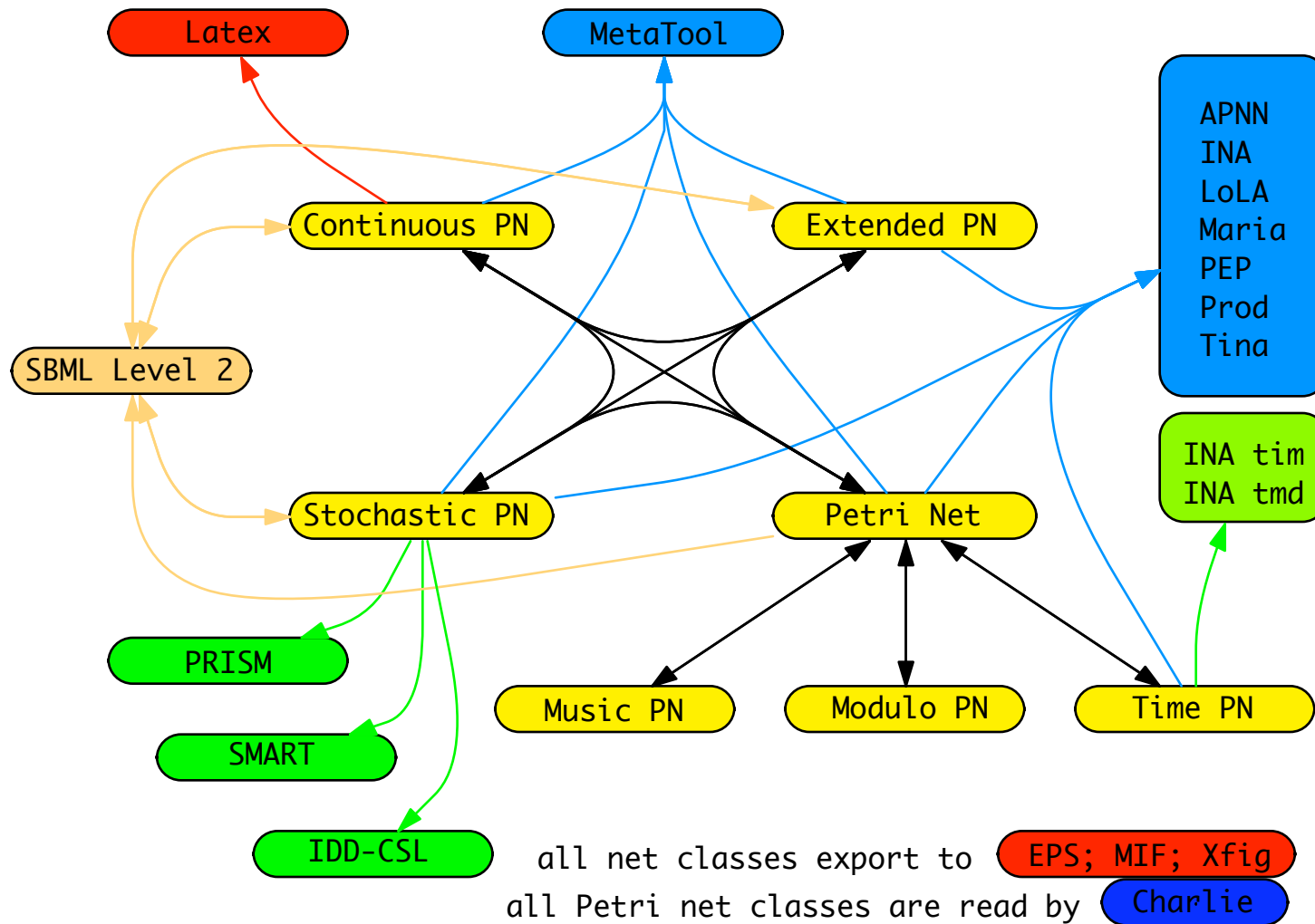
CONTINUOUS PETRI NET DEFINES ODES

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



SUMMARY

SNOOPY'S EXPORT FEATURES



□ representation of bionetworks by Petri nets

-> *partial order representation*

-> *formal semantics*

-> *unifying view*

-> *better comprehension*

-> *sound analysis techniques*

❑ representation of bionetworks by Petri nets

- > *partial order representation*
- > *formal semantics*
- > *unifying view*

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❑ purposes

- > *animation*
- > *model validation against consistency criteria*
- > *qualitative / quantitative behaviour prediction*

- > *to experience the model*
- > *to increase confidence*
- > *experiment design,
new insights*

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❑ step-wise model development

- > *qualitative model*
- > *discrete quantitative model*
- > *continuous quantitative model*

- > *discrete Petri nets*
- > *stochastic Petri nets*
- > *continuous Petri nets = ODEs*

❑ **Rainer Breitling**

*University Glasgow, Integrative and Systems Biology &
University of Groningen, Groningen Bioinformatics Centre*

❑ **David Gilbert**

*Brunel University London/Uxbridge,
School of Information Systems, Computing and Mathematics*

❑ **Wolfgang Marwan**

*Otto von Guericke University & Magdeburg Centre for Systems Biology &
Max Planck Institute for Dynamics of Complex Technical Systems*

❑ **Louchka Popova-Zeugmann**

Humboldt University Berlin, Computer Science Institute

- ❑ M Heiner; R Donaldson; D Gilbert:
Petri Nets for Systems Biology; MS Iyengar (ed.): Symbolic Systems Biology: Theory and Methods, Jones & Bartlett Publishers, LLC, 2010.
- ❑ 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, Milano, Sept. 2008, Springer Boston, IFIP, Vol . 268, pp. 163-175, 2008.
- ❑ M Heiner, D Gilbert, R Donaldson:
Petri Nets for Systems and Synthetic Biology; M Bernardo, P Degano, and G Zavattaro (eds.): SFM 2008, Springer LNCS 5016, pp. 215–264, 2008.
- ❑ R Breitling, D Gilbert, M Heiner, R Orton:
A structured approach for the engineering of biochemical network models, illustrated for signalling pathways; Briefings in Bioinformatics, September 2008; 9: 404 - 421.
- ❑ D Gilbert, M Heiner, S Lehrack:
A Unifying Framework for Modelling and Analysing Biochemical Pathways Using Petri Nets; Proc. CMSB 2007, Edinburgh, Springer LNCS/LNBI 4695, pp. 200-216.

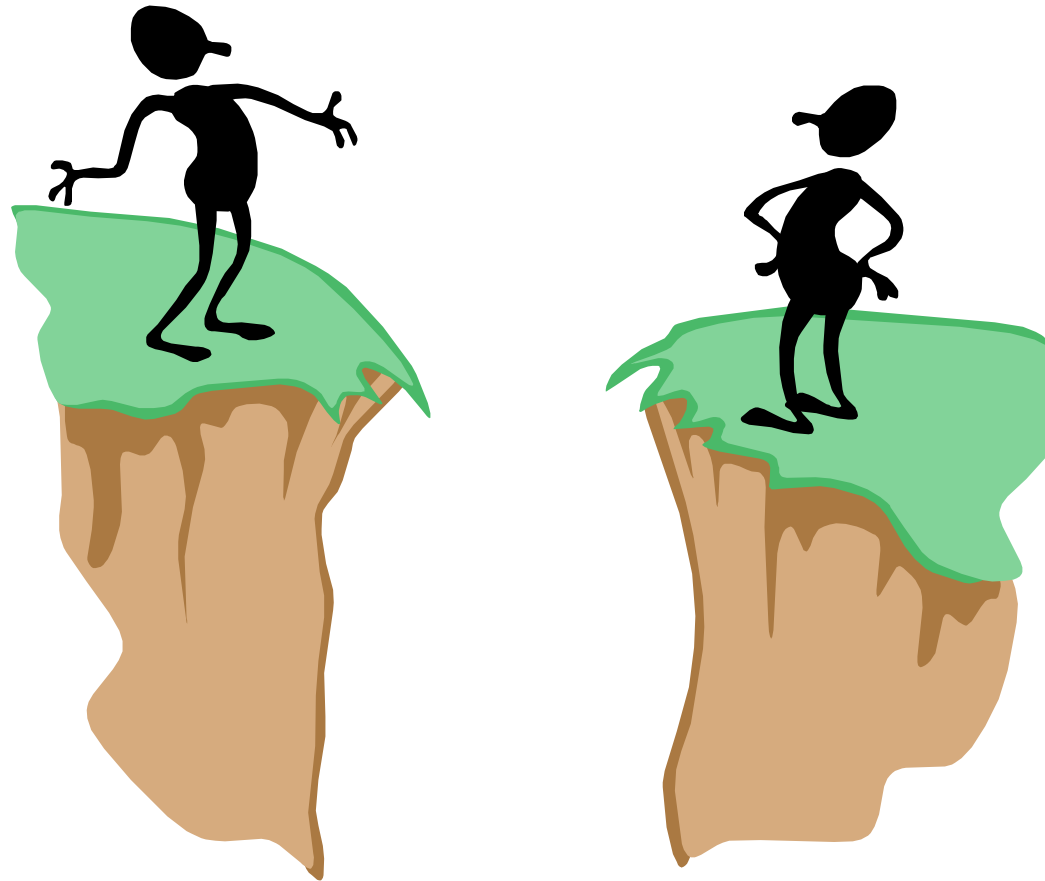
- ❑ C Rohr, W Marwan, M Heiner:
[Snoopy - a unifying Petri net framework to investigate biomolecular networks;](#)
Bioinformatics 2010 26(7): 974-975

- ❑ M Heiner, R Richter, C Rohr, M Schwarick:
[Snoopy - A Tool to Design and Execute Graph-Based Formalisms.](#)
Petri Net Newsletter 74 (April 2008), pp. 8-22.
extended version of Proc. PNTAP 2008, Marseille, ACM digital library.

- ❑ M Heiner, S Lehrack, D Gilbert, W Marwan:
[Extended Stochastic Petri Nets for Model-based Design of Wet-lab Experiments;](#)
Trans. on Computational Systems Biology XI, Springer LNBI 5750, pp. 138-163,
2009.

- ❑ W Marwan, C Rohr, M Heiner:
[Petri nets in Snoopy: A unifying framework for the graphical display, computational modelling, simulation, and bioinformatic annotation of bacterial regulatory networks;](#)
in Jv Helden, A Toussaint, D Thieffry (eds): *Methods in Molecular Biology - Bacterial Molecular Networks*, Humana Press, chapter 24, submitted.

THANKS



[HTTP://WWW-DSSZ.INFORMATIK.TU-COTTBUS.DE](http://www-dssz.informatik.tu-cottbus.de)