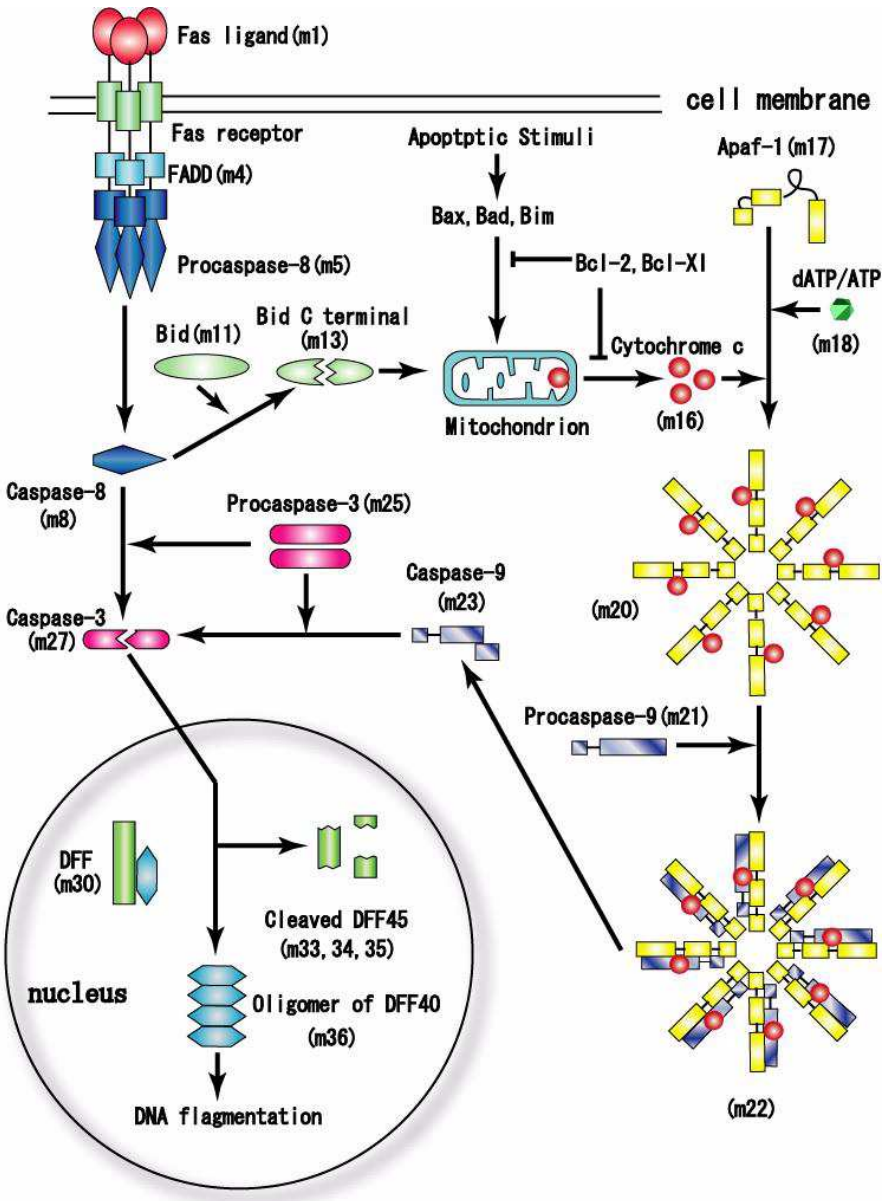
MODULAR MODELLING WITH PETRI NETS

Monika Heiner

Brandenburg University of Technology
Computer Science Institute

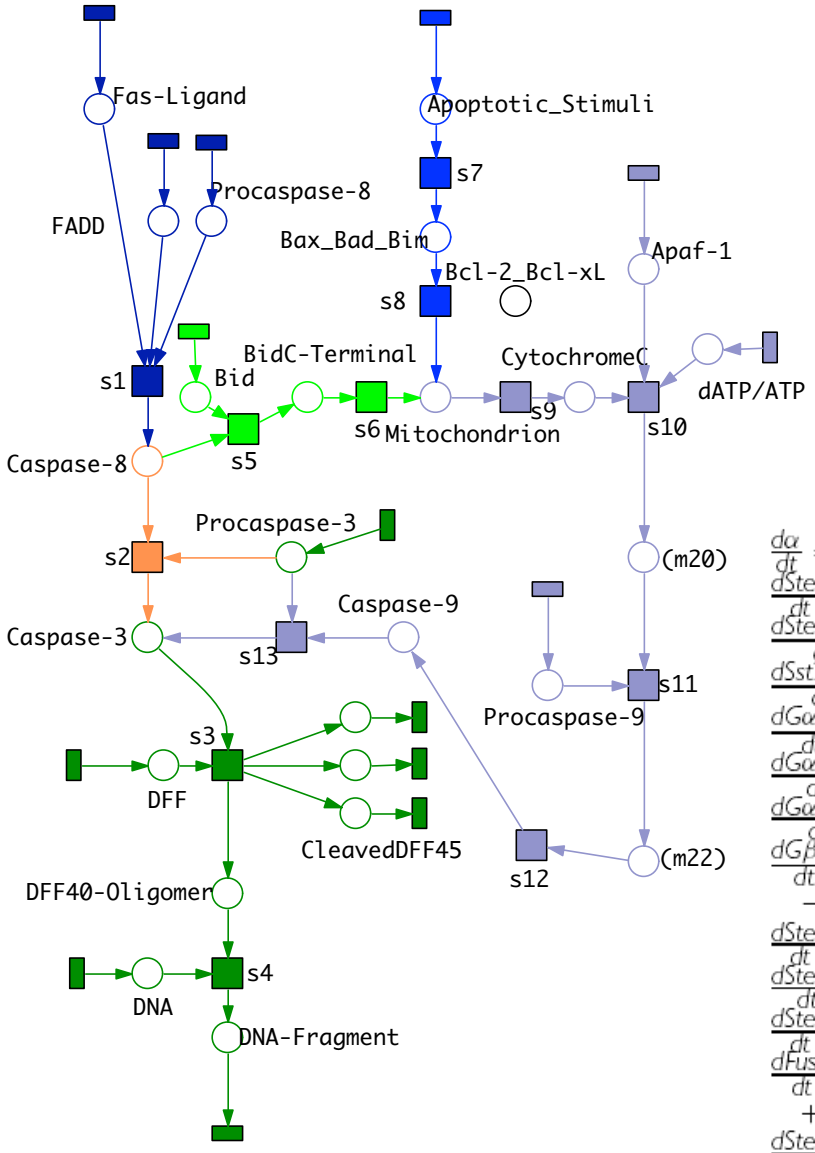
joined work with Mary Ann Blätke, Wolfgang Marwan
Otto-von-Guericke University Magdeburg

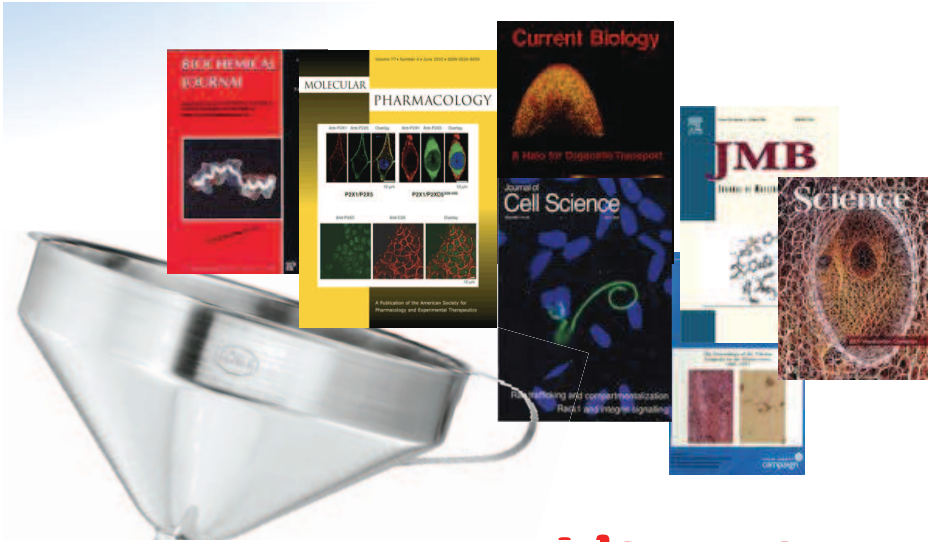

Fas ligand(m1)
cell membrane
Fas receptor
Apoptptic Stimuli
Apaf-1(m17)
FADD(m4)
Bax, Bad, Bim
Procaspase-8(m5)
Bcl-2, Bcl-Xl
dATP/ATP
Bid(m11)
Bid C terminal (m13)
Cytochrome c
(m18)
Mitochondrion
(m16)
Caspase-8 (m8)
Procaspase-3(m25)
Caspase-9 (m23)
(m20)
Caspase-3 (m27)
Procaspase-9(m21)
DFF (m30)
Cleaved DFF45 (m33, 34, 35)
nucleus
Oligomer of DFF40 (m36)
DNA flagmentation
(m22)


Current Biology
MOLECULAR PHARMACOLOGY
Cell Science
JMB
Science

Literature

PROLOGUE



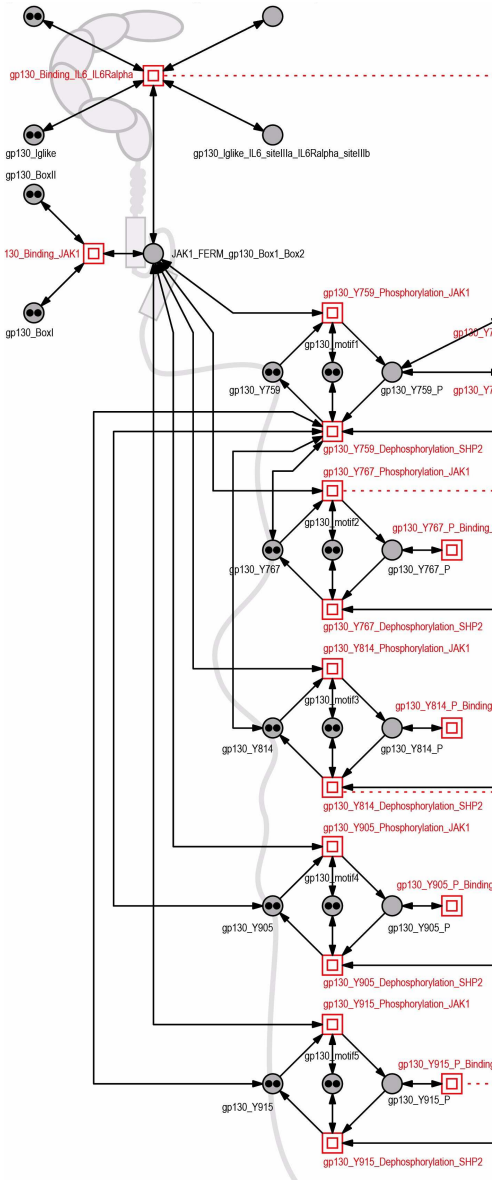


$$\frac{d\alpha}{dt} = -v_1$$
$$\frac{dSte2}{dt} = -v_2 + v_3 - v_5$$
$$\frac{dSte2_{active}}{dt} = v_2 - v_3 - v_4$$
$$\frac{dSst2_{active}}{dt} = v_{46} - v_{47}$$
$$\frac{dG\alpha\beta\gamma}{dt} = -v_6 + v_9$$
$$\frac{dG\alpha GTP}{dt} = v_6 - v_7 - v_8$$
$$\frac{dG\alpha GDP}{dt} = v_7 + v_8 - v_9$$
$$\frac{dG\beta\gamma}{dt} = v_6 - v_9 - v_{10} + v_{11} + v_{21} + v_{23} + v_{25} + v_{27} + v_{32} - v_{42} + v_{43}$$
$$\frac{dSte5}{dt} = -v_{12} + v_{13} + v_{17} + v_{21} + v_{23} + v_{25} + v_{27} + v_{32}$$
$$\frac{dSte11}{dt} = -v_{12} + v_{13} + v_{17} + v_{21} + v_{23} + v_{25} + v_{27} + v_{32}$$
$$\frac{dSte7}{dt} = -v_{14} + v_{15} + v_{17} + v_{21} + v_{23} + v_{25} + v_{27} + v_{32}$$
$$\frac{dFus3}{dt} = -v_{14} + v_{15} + v_{17} + v_{21} + v_{23} + v_{25} + v_{27} - v_{29} + v_{30} + v_{33}$$
$$\frac{dSte20}{dt} = -v_{18} + v_{19} + v_{21} + v_{23} + v_{25} + v_{27} + v_{32}$$

$$v_1 = \alpha[t] \cdot Bar1_{active}[t] \cdot k_1$$
$$v_2 = Ste2[t] \cdot \alpha[t] \cdot k_2$$
$$v_3 = Ste2_{active}[t] \cdot k_3$$
$$v_4 = Ste2_{active}[t] \cdot k_4$$
$$v_5 = Ste2[t] \cdot k_5$$
$$v_6 = Ste2_{active}[t] \cdot G\alpha\beta\gamma[t] \cdot k_6$$
$$v_7 = G\alpha GTP[t] \cdot k_7$$
$$v_8 = G\alpha GTP[t] \cdot Sst2_{active}[t] \cdot k$$
$$v_9 = G\alpha GDP[t] \cdot G\beta\gamma[t] \cdot k_9$$
$$v_{10} = G\beta\gamma[t] \cdot C[t] \cdot k_{10}$$
$$v_{11} = D[t] \cdot k_{11}$$
$$v_{12} = Ste5[t] \cdot Ste11[t] \cdot k_{12}$$
$$v_{13} = A[t] \cdot k_{13}$$
$$v_{14} = Ste7[t] \cdot Fus3[t] \cdot k_{14}$$
$$v_{15} = B[t] \cdot k_{15}$$
$$v_{16} = A[t] \cdot B[t] \cdot k_{16}$$
$$v_{17} = C[t] \cdot k_{17}$$
$$v_{18} = D[t] \cdot Ste20[t] \cdot k_{18}$$

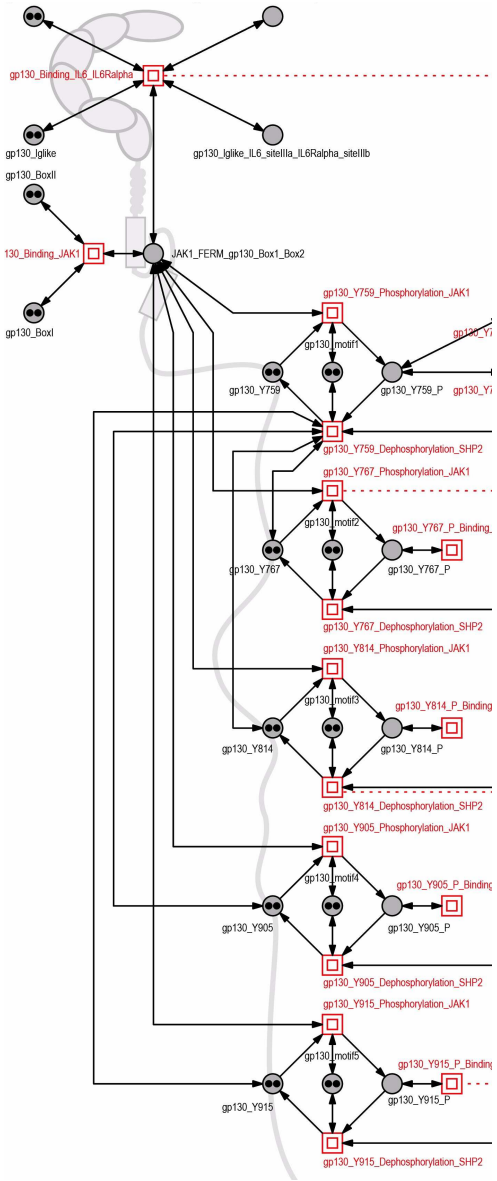
- **monolithic models**
  - -> *a posteriori modularisation - numerous approaches*
  - -> *process-oriented view*
  - -> *it's difficult to*
    - *reuse network components*
    - *combine networks*

- **modular models**
  - -> *a priori modular network design*
  - -> *object-oriented view*
    - *object = protein*
    - *well-defined object interfaces = composionality*
  - -> *targets*
    - *reusability of models*
    - *step-wise construction of larger networks*
    - *automatic mutation of networks . . .*



OUTLINE

- **PETRI NETS**
  - -> *basic notions*
  - -> *Petri Net Framework: QPN - SPN - CPN - HPN*
- **MODELLING COMFORT**
  - -> *hierarchical structuring by macro nodes*
  - -> *composition by logical nodes*
- **MODULAR MODELLING**
  - -> *module = protein*
  - -> *composition via interfaces = subnets*
  - -> *case studies*
- **DATABASE WITH WEB INTERFACE**
- **SUMMARY & OUTLOOK**



PETRI NETS
- CRASH COURSE -

monika.heiner@tu-cottbus.de

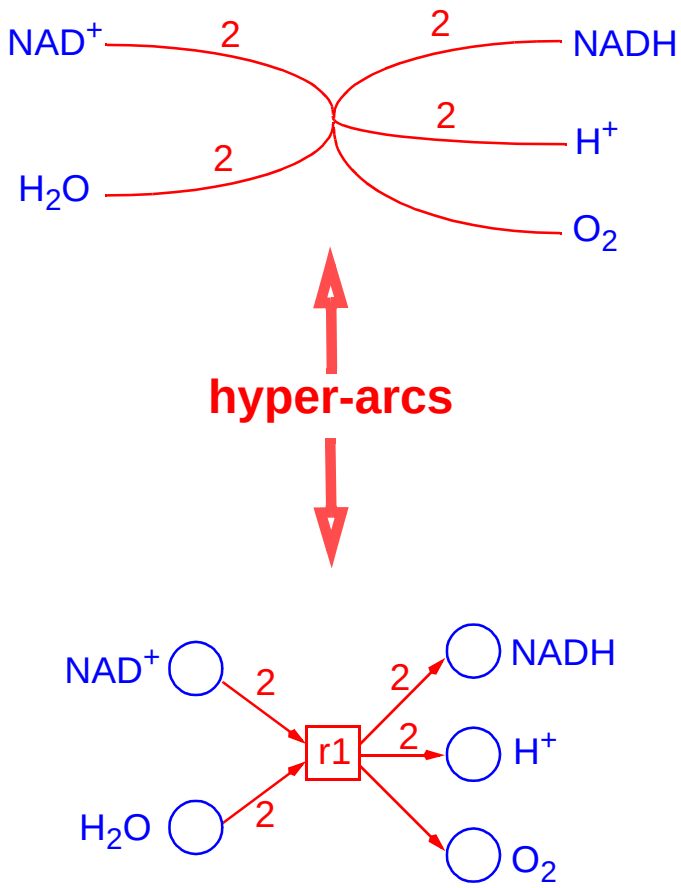
. . .

ARE NETWORKS OF BIOCHEMICAL REACTIONS

. . .

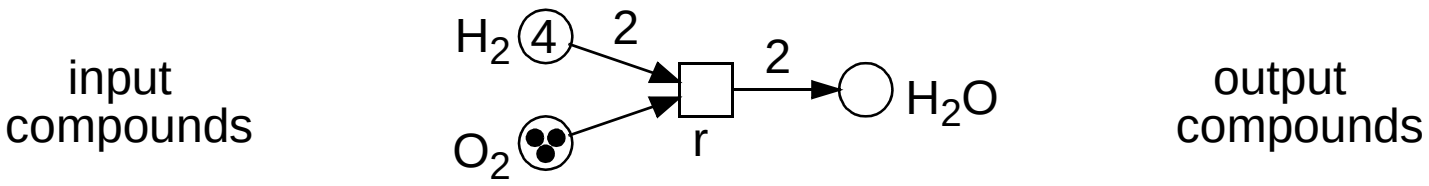
NATURALLY EXPRESSIBLE AS PETRI NETS

$$2\ NAD^+ + 2\ H_2O \rightarrow 2\ NADH + 2\ H^+ + O_2$$



- **atomic actions -> Petri net transitions -> chemical reactions**

$$2\ H_2 + O_2 \rightarrow 2\ H_2O$$

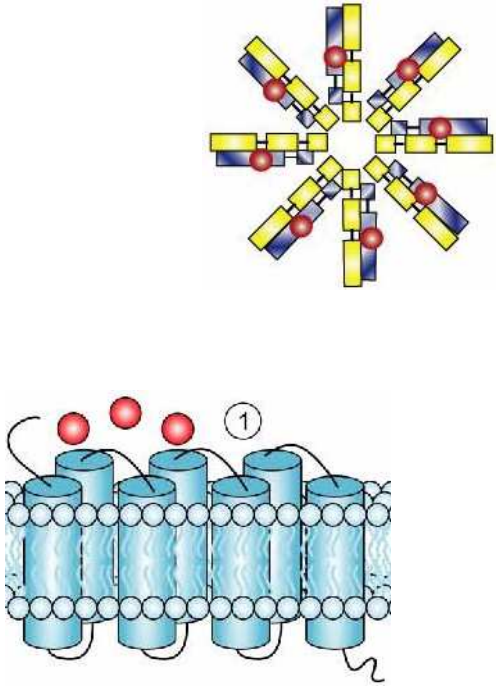


- **local conditions -> Petri net places -> chemical compounds**
- **multiplicities -> Petri net arc weights -> stoichiometric relations**
- **condition's state -> token(s) in its place -> available amount (e.g. mol)**
- **system state -> marking -> compounds distribution**
- **PN = (P, T, F, m_0), F: (P x T) U (T x P) -> N_0, m_0: P -> N_0**

PLACES, TRANSITIONS - SOME BIO INTERPRETATIONS

- **places -> model variables**
  - -> *(bio-) chemical compounds*
  - -> *proteins*
  - -> *protein conformations*
  - -> *complexes*
  - -> *genes, . . . , etc.*
  - *. . . in different locations*

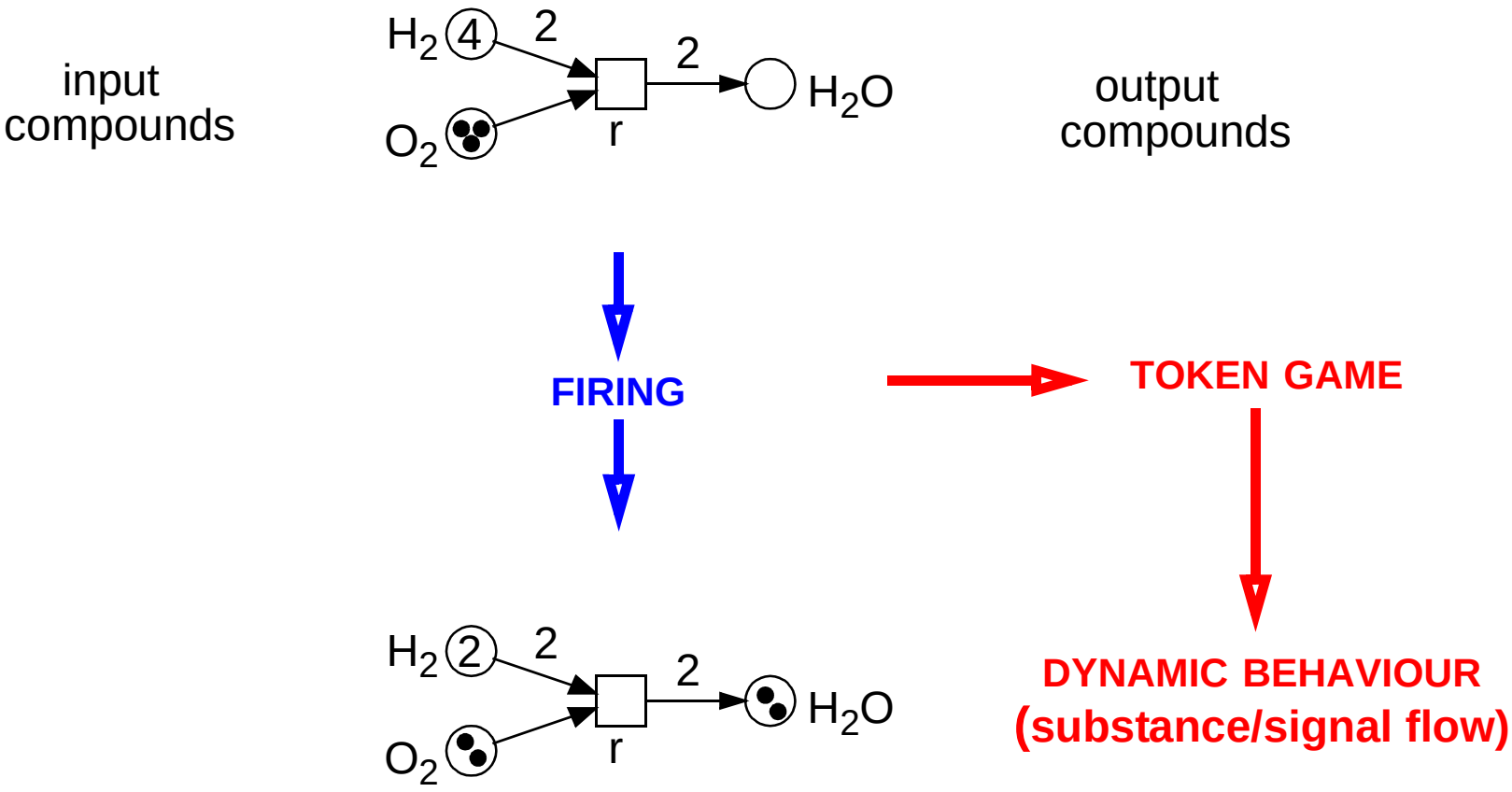
- **transitions -> atomic events**
  - -> *(stoichiometric) chemical reaction*
  - -> *complexation / decomplexation*
  - -> *phosphorylation / dephosphorylation*
  - -> *conformational change*
  - -> *transport step, . . . , etc.*
  - *. . . in different locations*



- **an action may happen, if** **-> prerequisite**
  - -> *all preconditions are fulfilled (corresponding to the arc weights);*
- **if an action happens, then** **-> firing behaviour**
  - -> *tokens are removed from all preconditions (corresponding to the arc weights), and*
  - -> *tokens are added to all postconditions (corresponding to the arc weights);*
- **action happens (firing of a transition)** **-> model assumptions**
  - -> *atomic*
  - -> *time-less*

- **atomic actions -> Petri net transitions -> chemical reactions**

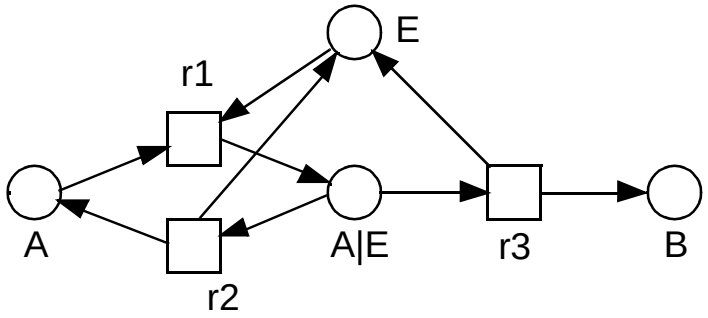
$$2\ H_2 + O_2 \rightarrow 2\ H_2O$$



TYPICAL BASIC STRUCTURES I

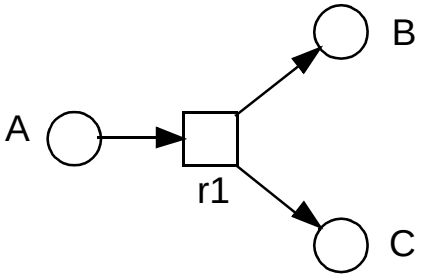
$$A \xleftrightarrow{E} A|E \rightarrow B$$

enzymatic reaction,
mass-action kinetics

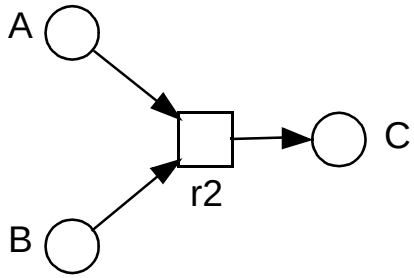


TYPICAL BASIC STRUCTURES II

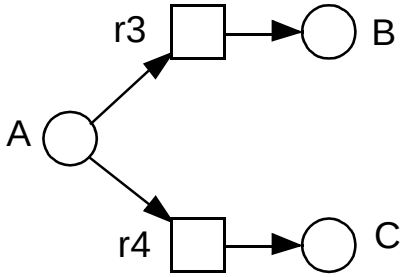
A --> B + C



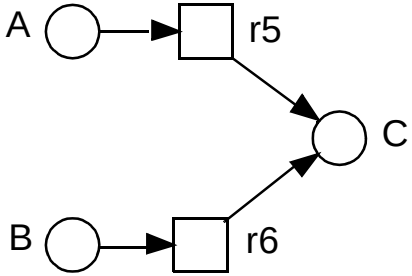
A + B --> C



A --> B,
A --> C

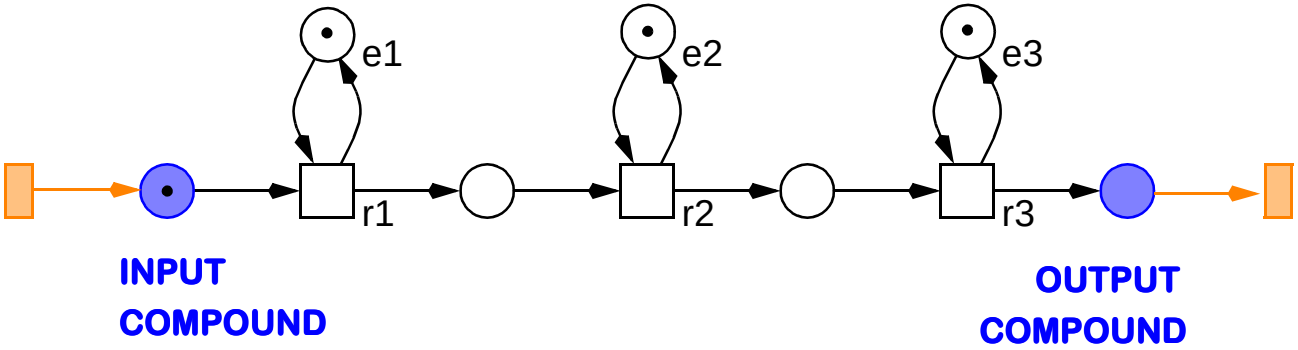


A --> C,
B --> C

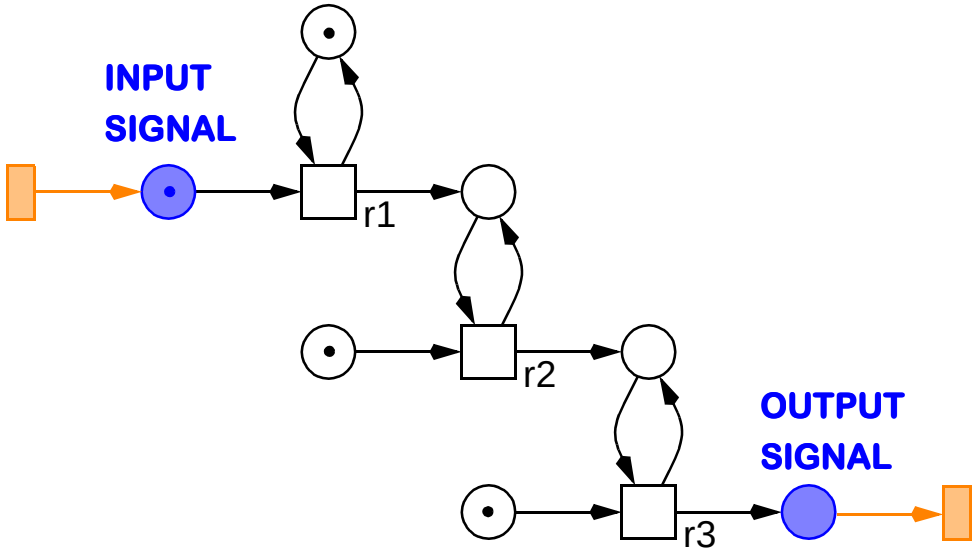


TYPICAL BASIC STRUCTURES III

- **metabolic networks**
  -> *substance flows*



- **signal transduction networks**
  -> *signal flows*

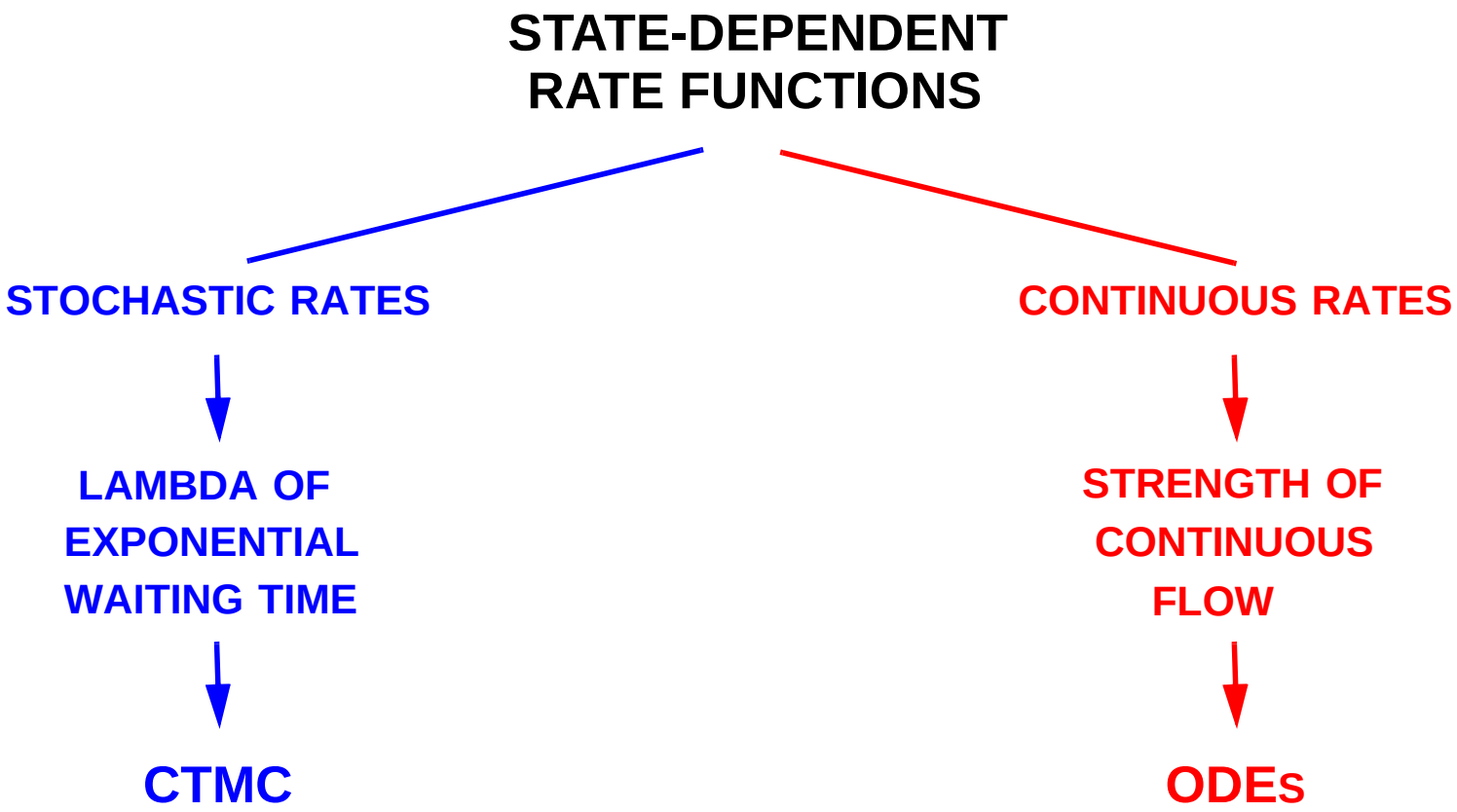


-> OPEN / CLOSED SYSTEMS

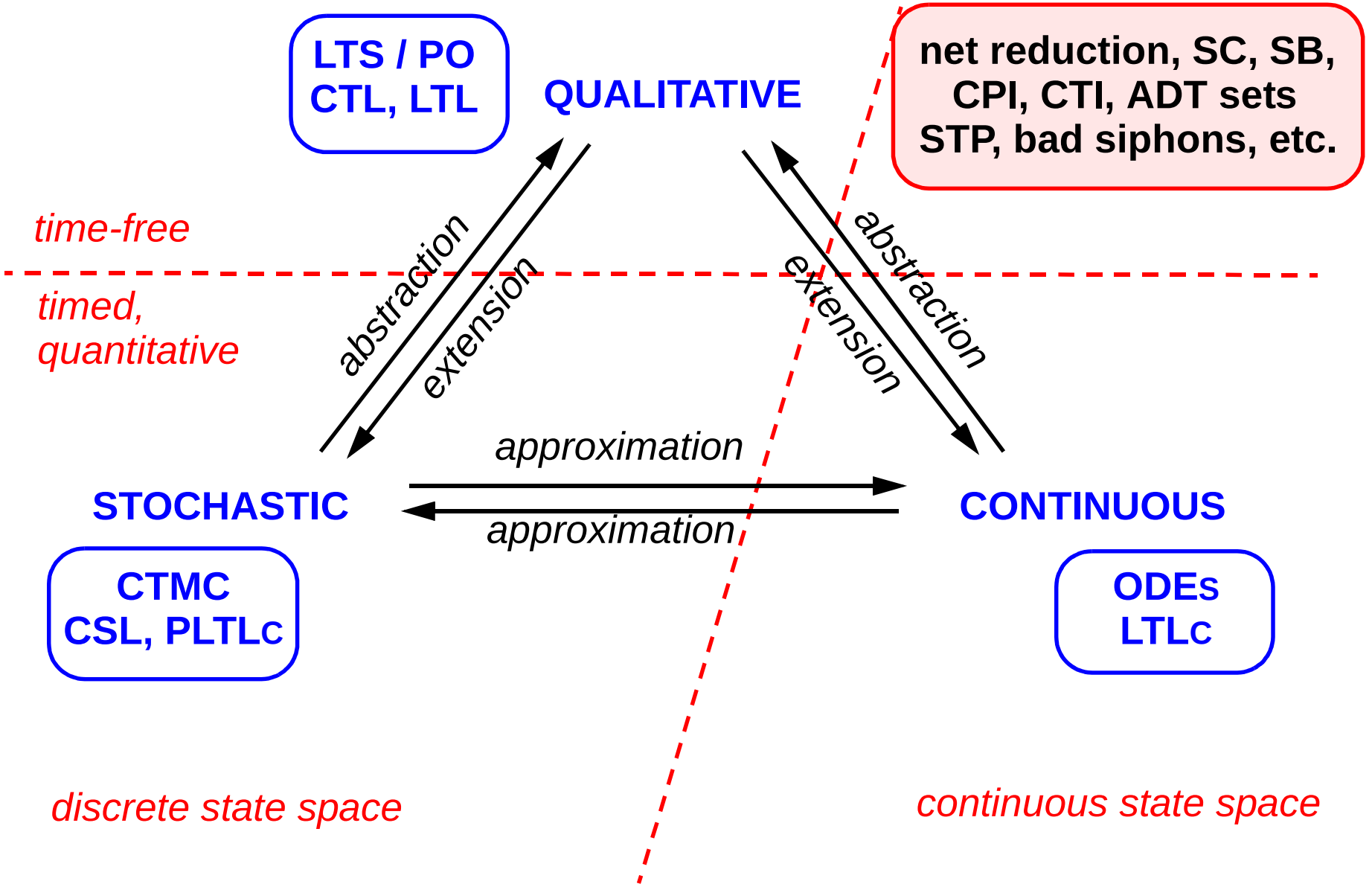
THE PETRI NET FRAMEWORK

monika.heiner@tu-cottbus.de

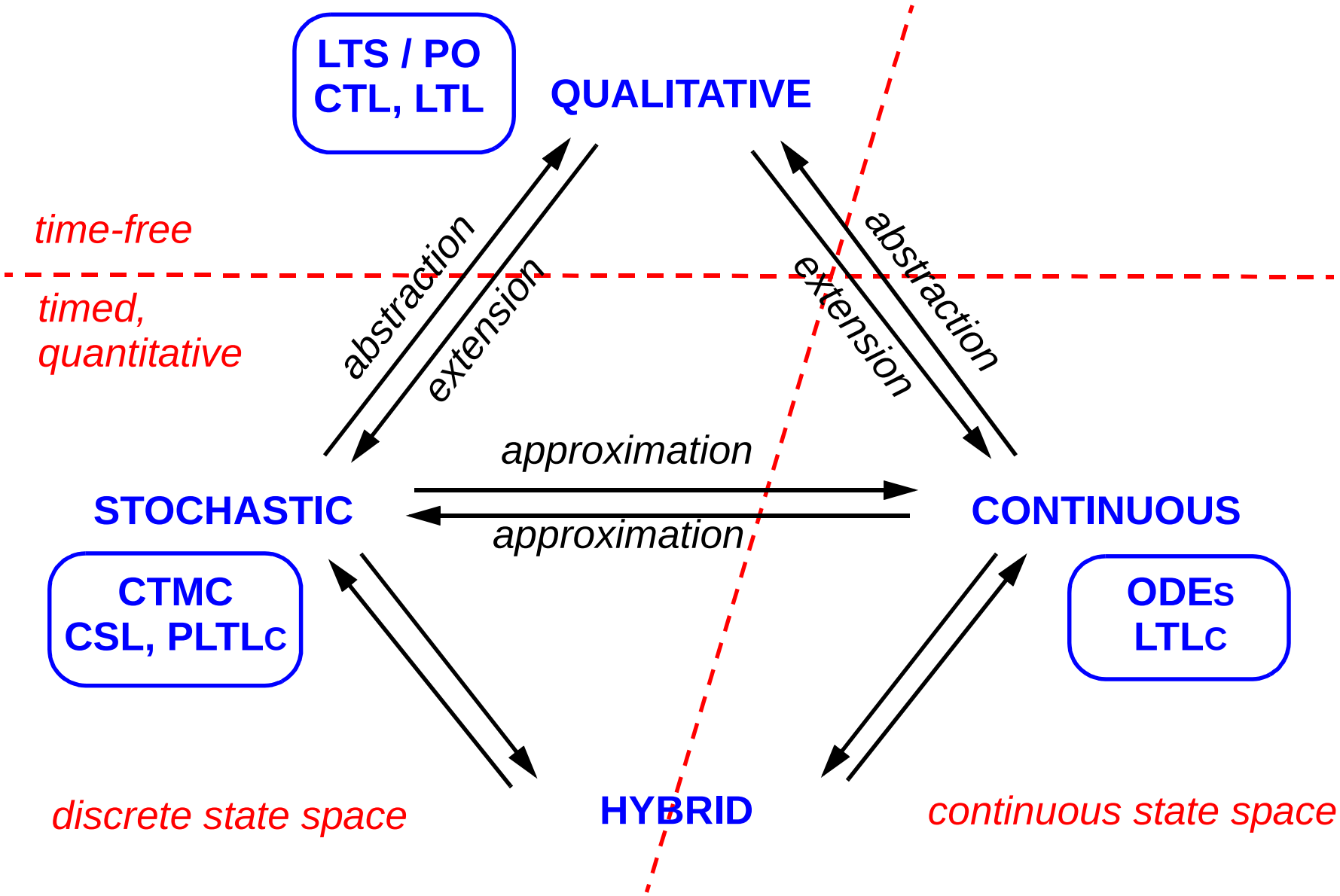
ADDING TIME



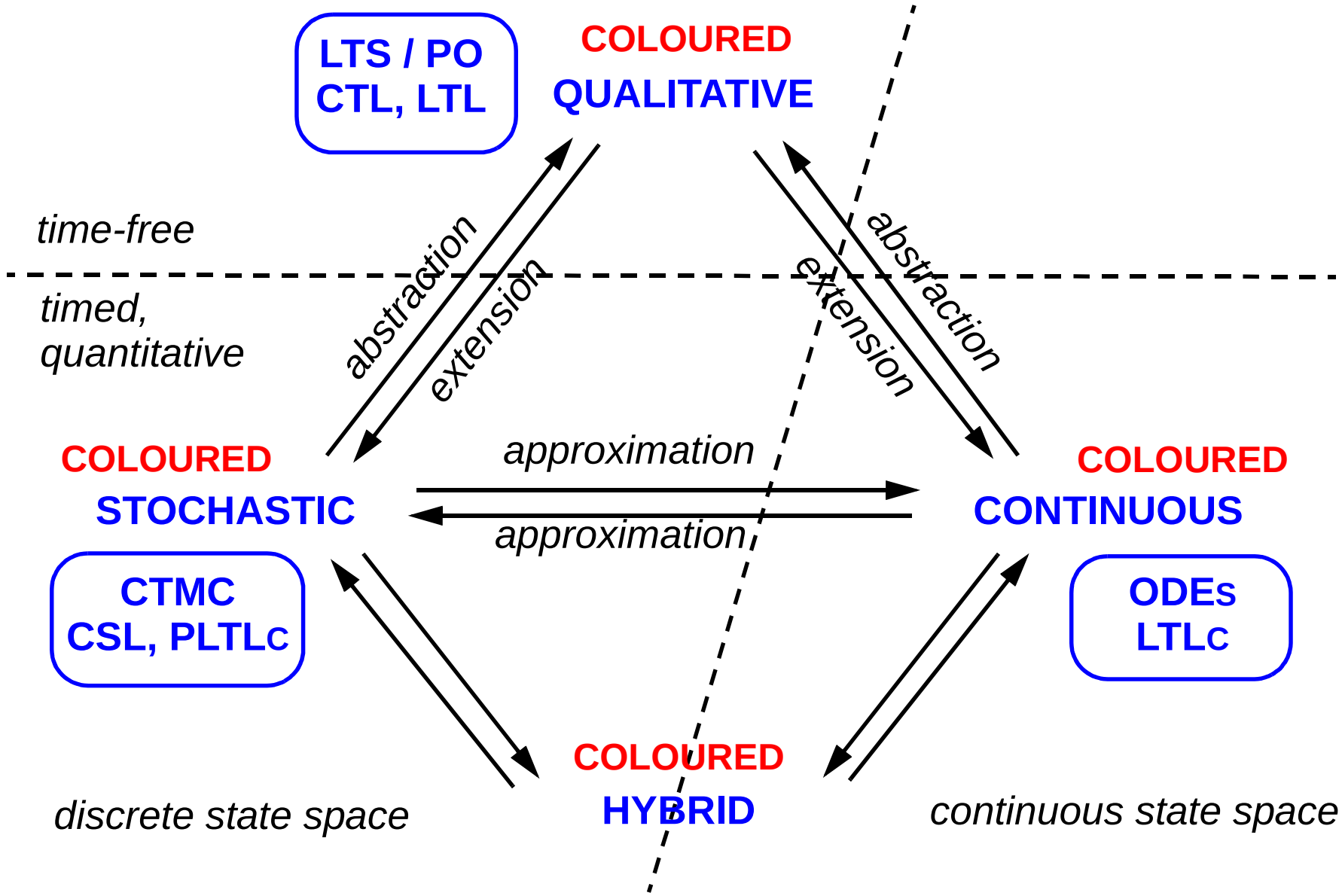
-> supported by, e.g., COPASI, Dizzy, ..., Snoopy


LTS / PO
CTL, LTL
QUALITATIVE
net reduction, SC, SB,
CPI, CTI, ADT sets
STP, bad siphons, etc.
time-free
timed,
quantitative
abstraction
extension
abstraction
extension
approximation
approximation
STOCHASTIC
CONTINUOUS
CTMC
CSL, PLTLc
ODEs
LTLc
discrete state space
continuous state space

FRAMEWORK 2010

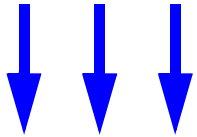


COLOURED FRAMEWORK 2011



4x2

MODELS SHARING STRUCTURE



QUANTITATIVE MODEL = QUALITATIVE MODEL

+

RATE FUNCTIONS (KINETICS)

MODELLING COMFORT

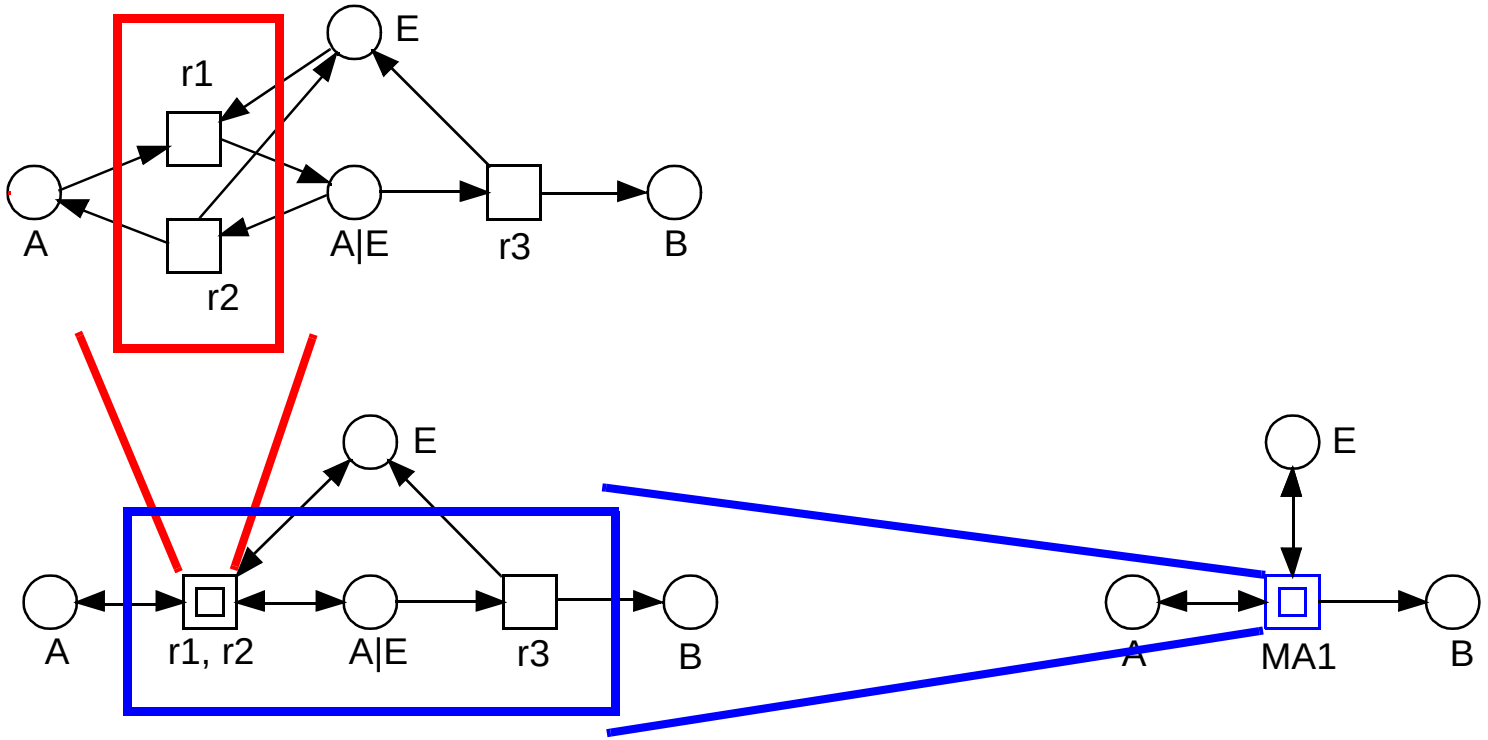
monika.heiner@tu-cottbus.de

HIERARCHICAL STRUCTURING BY MACRO NODES I

MACRO TRANSITION

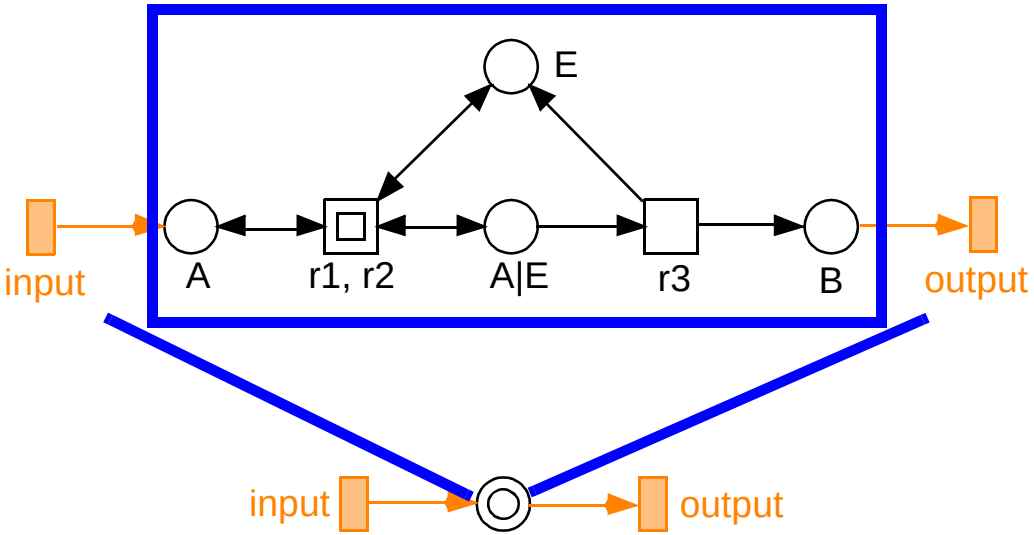
A <E--> A|E --> B

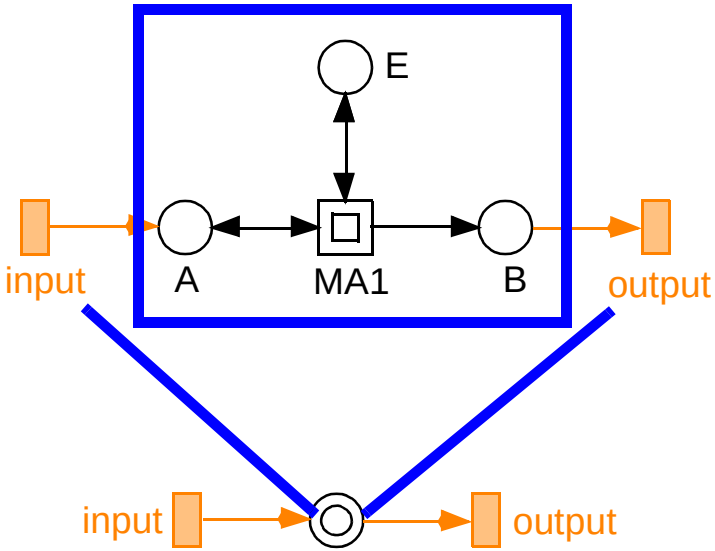
enzymatic reaction,
mass-action kinetics



HIERARCHICAL STRUCTURING BY MACRO NODES II

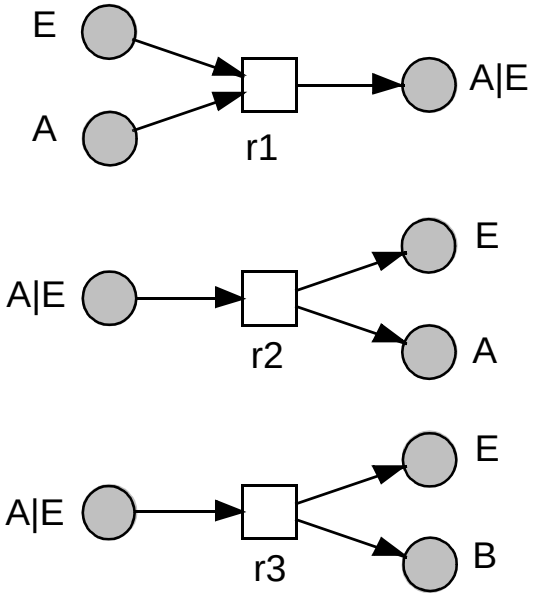
MACRO PLACE



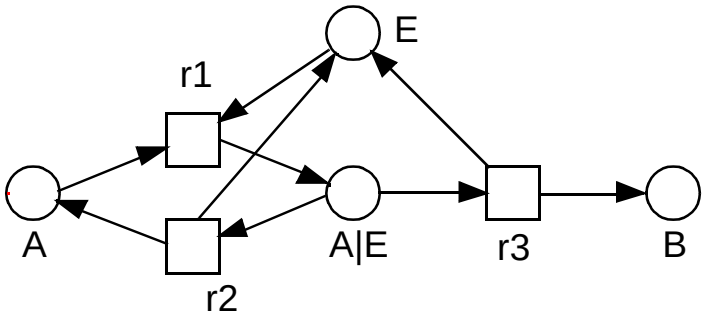


COMPOSITION BY LOGICAL NODES - LAYOUT OPTIONS

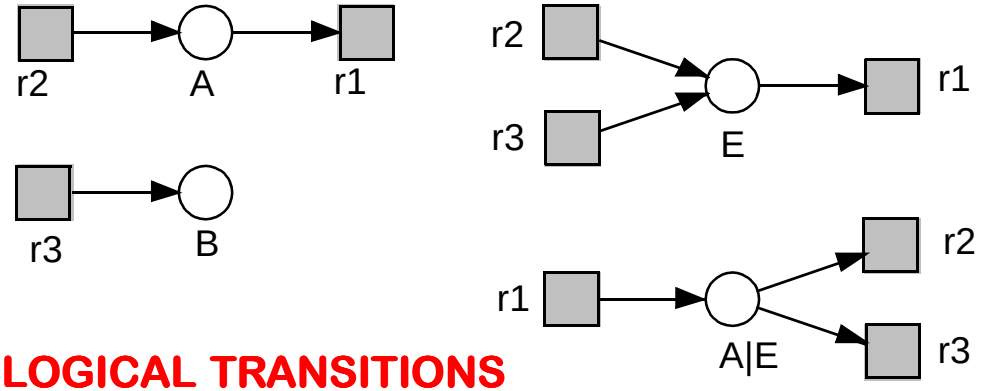
reaction-centred view



process-oriented view



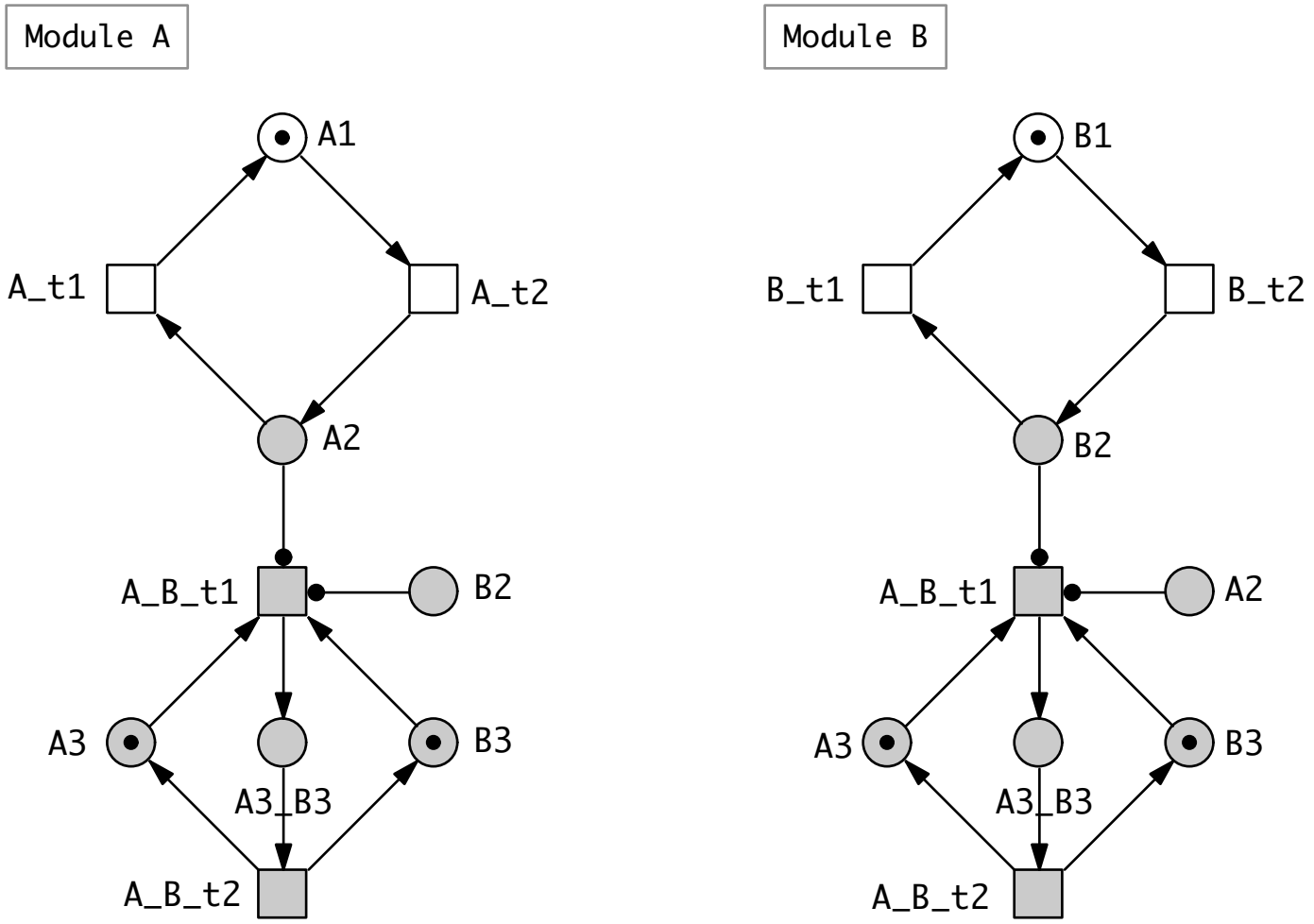
species-centred view



LOGICAL PLACES

LOGICAL TRANSITIONS

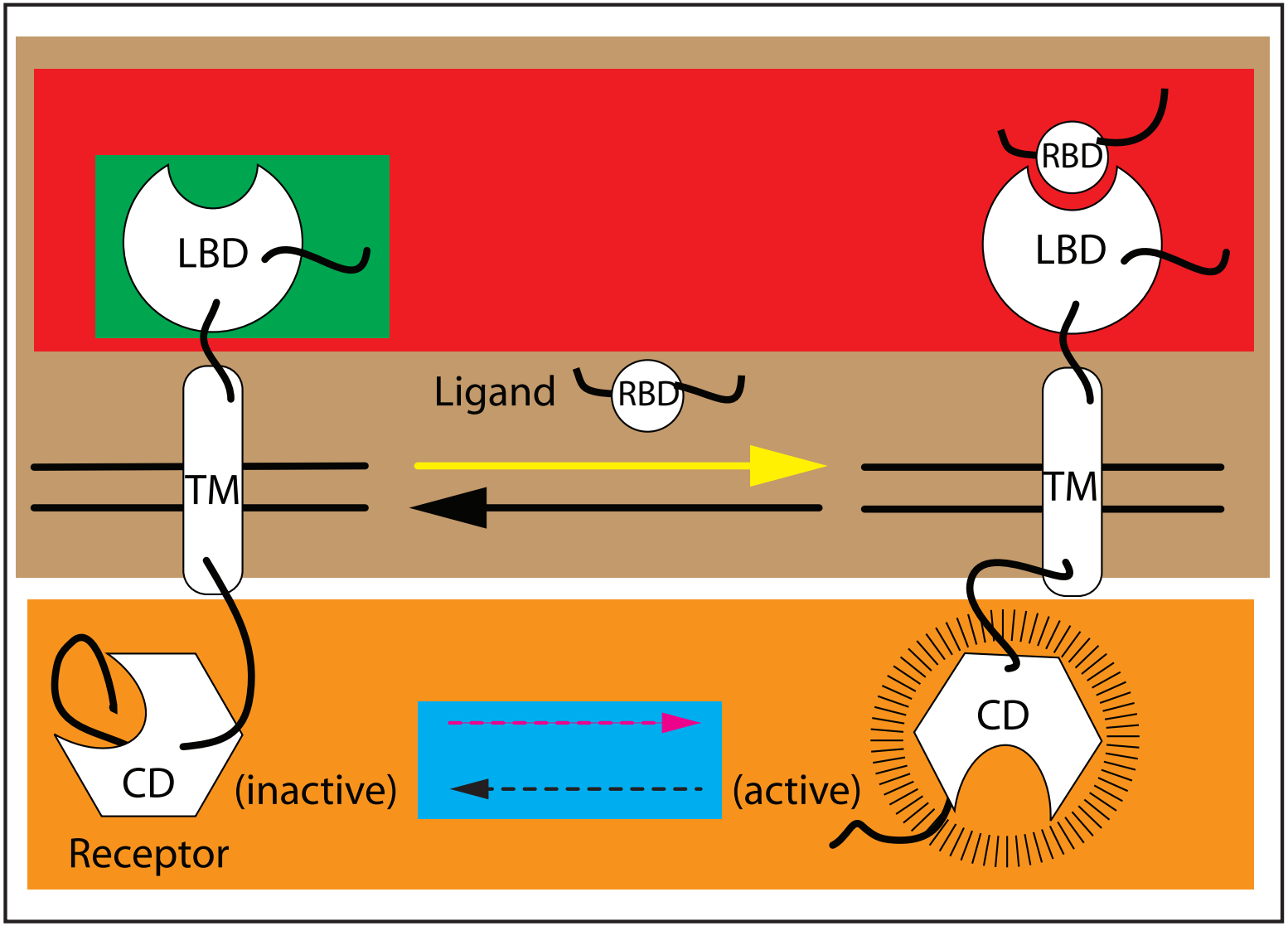
COMPOSITION BY LOGICAL NODES - SUBNETS



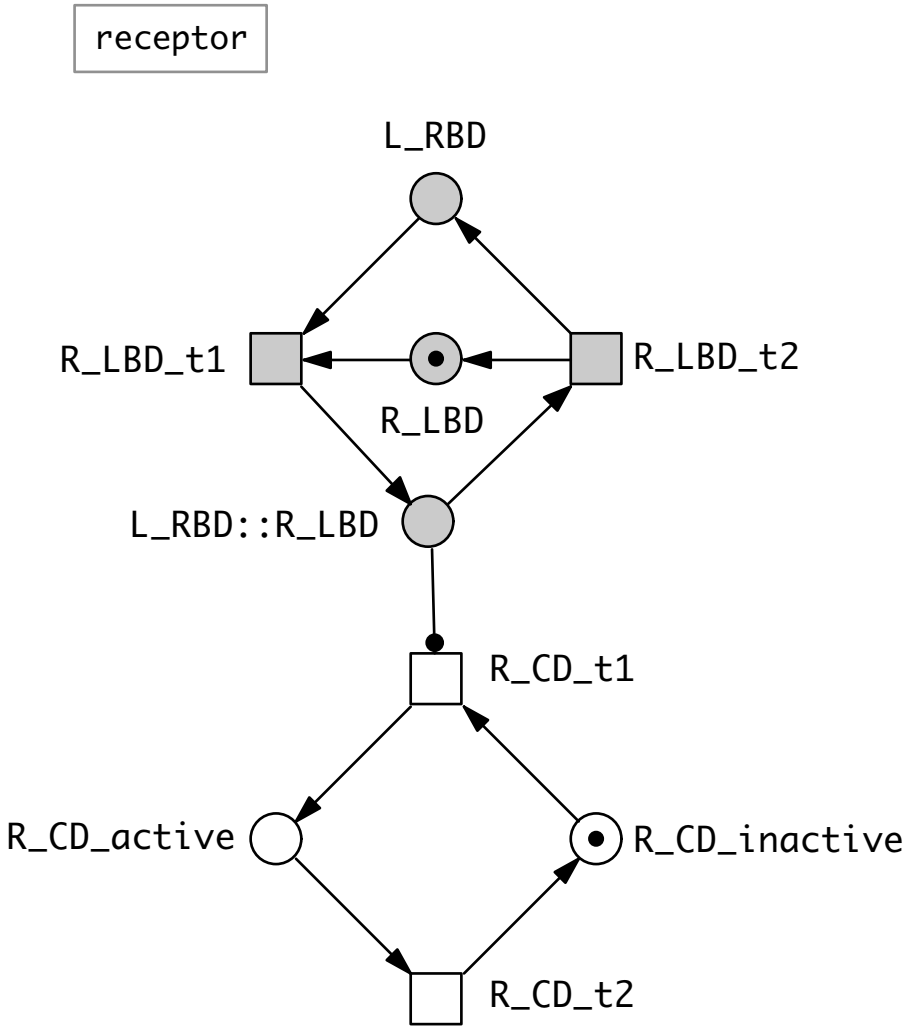
MODULAR MODELLING

monika.heiner@tu-cottbus.de

RECEPTOR - LIGAND BINDING, SCHEME

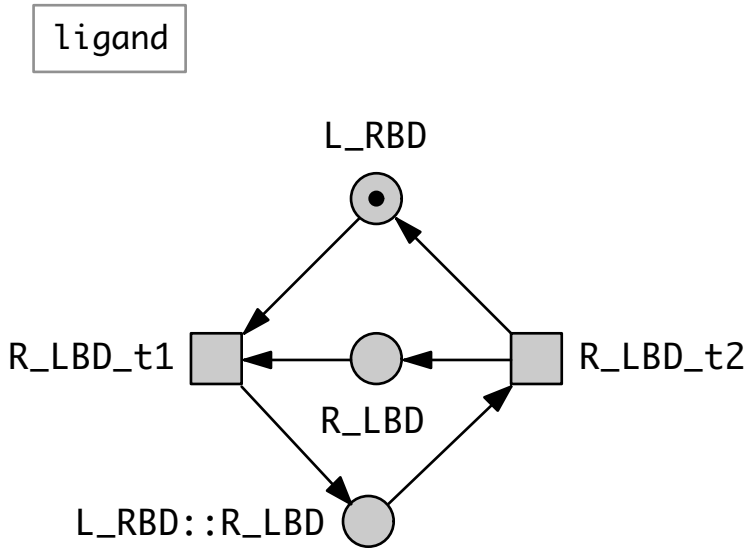


RECEPTOR - LIGAND BINDING, PETRI NET



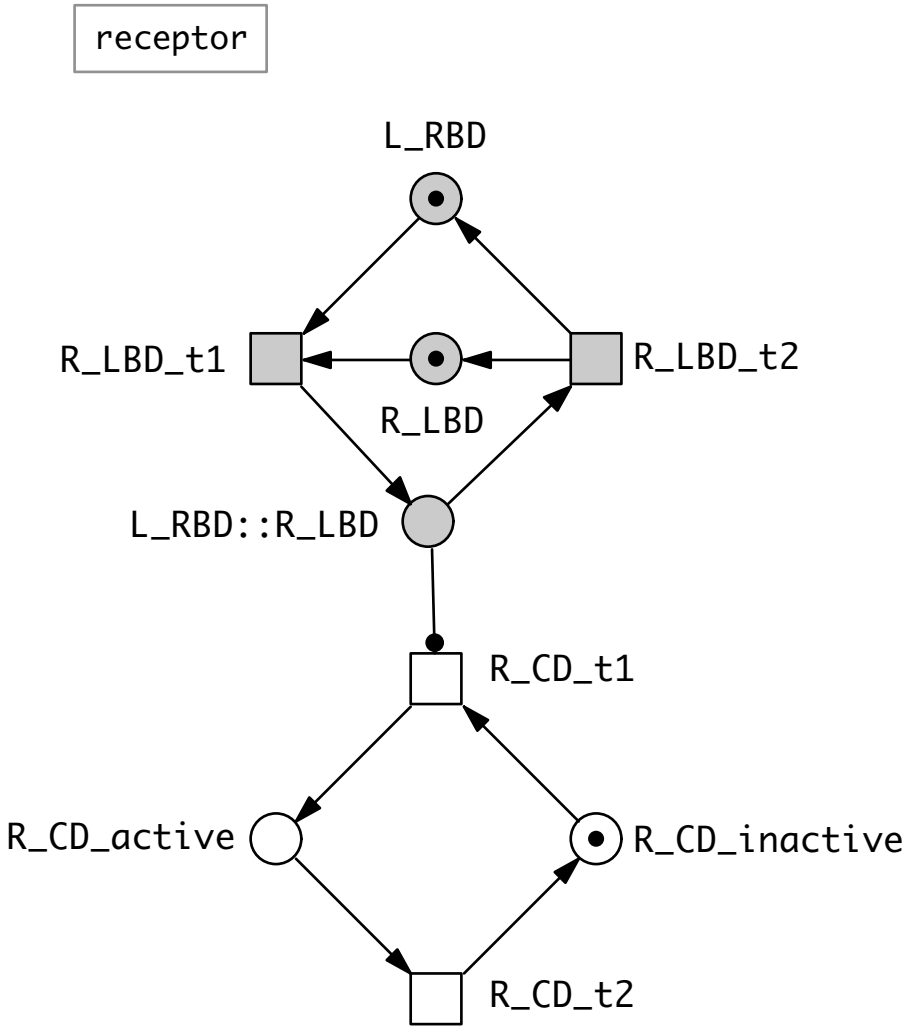
LBD - Ligand Binding Domain
RBD - Receptor Binding Domain
CD - Catalytic Domain

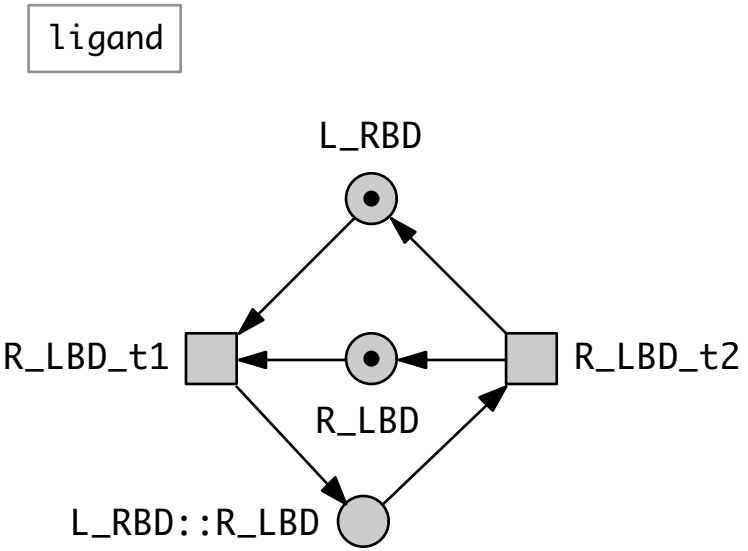
RECEPTOR - LIGAND BINDING, PETRI NET



LBD - Ligand Binding Domain
RBD - Receptor Binding Domain
CD - Catalytic Domain

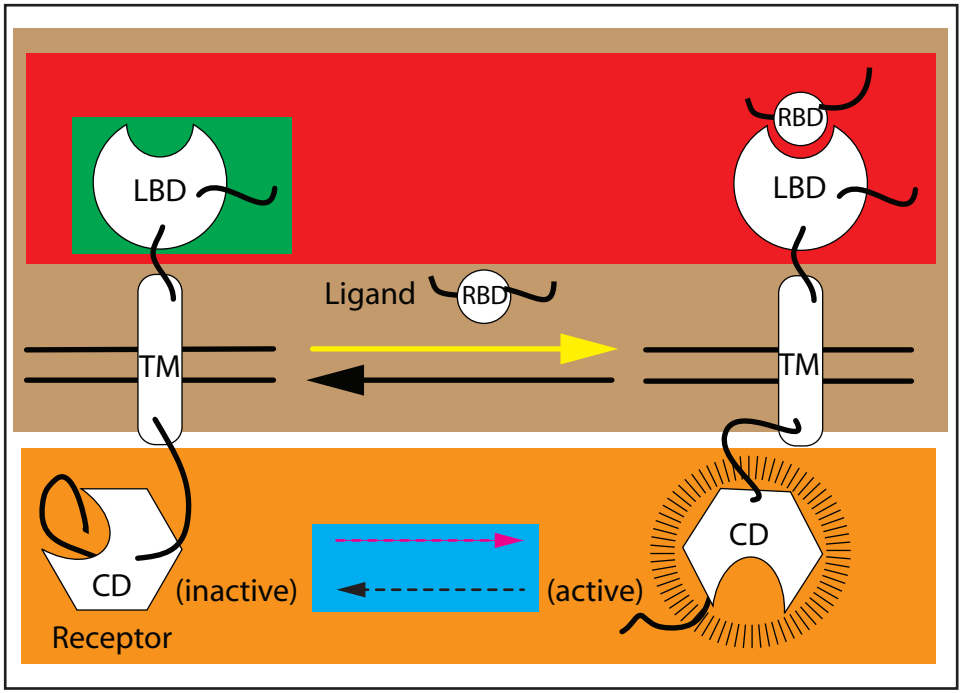
RECEPTOR - LIGAND BINDING, PETRI NET

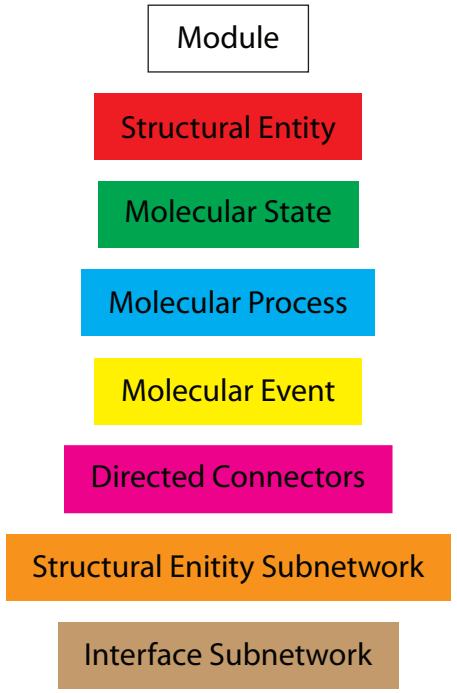


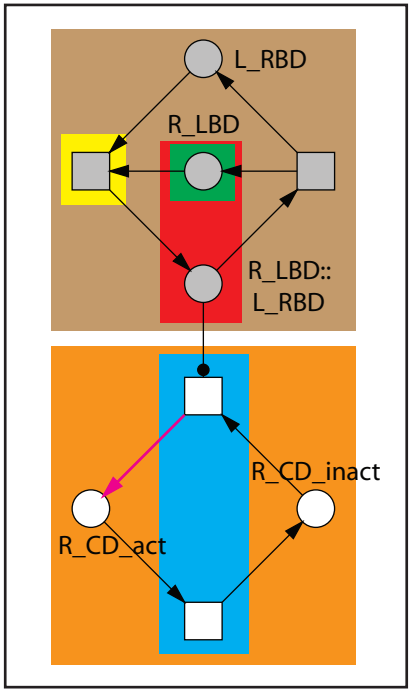


LBD - Ligand Binding Domain
RBD - Receptor Binding Domain
CD - Catalytic Domain

RECEPTOR - LIGAND BINDING, SCHEME - PETRI NET







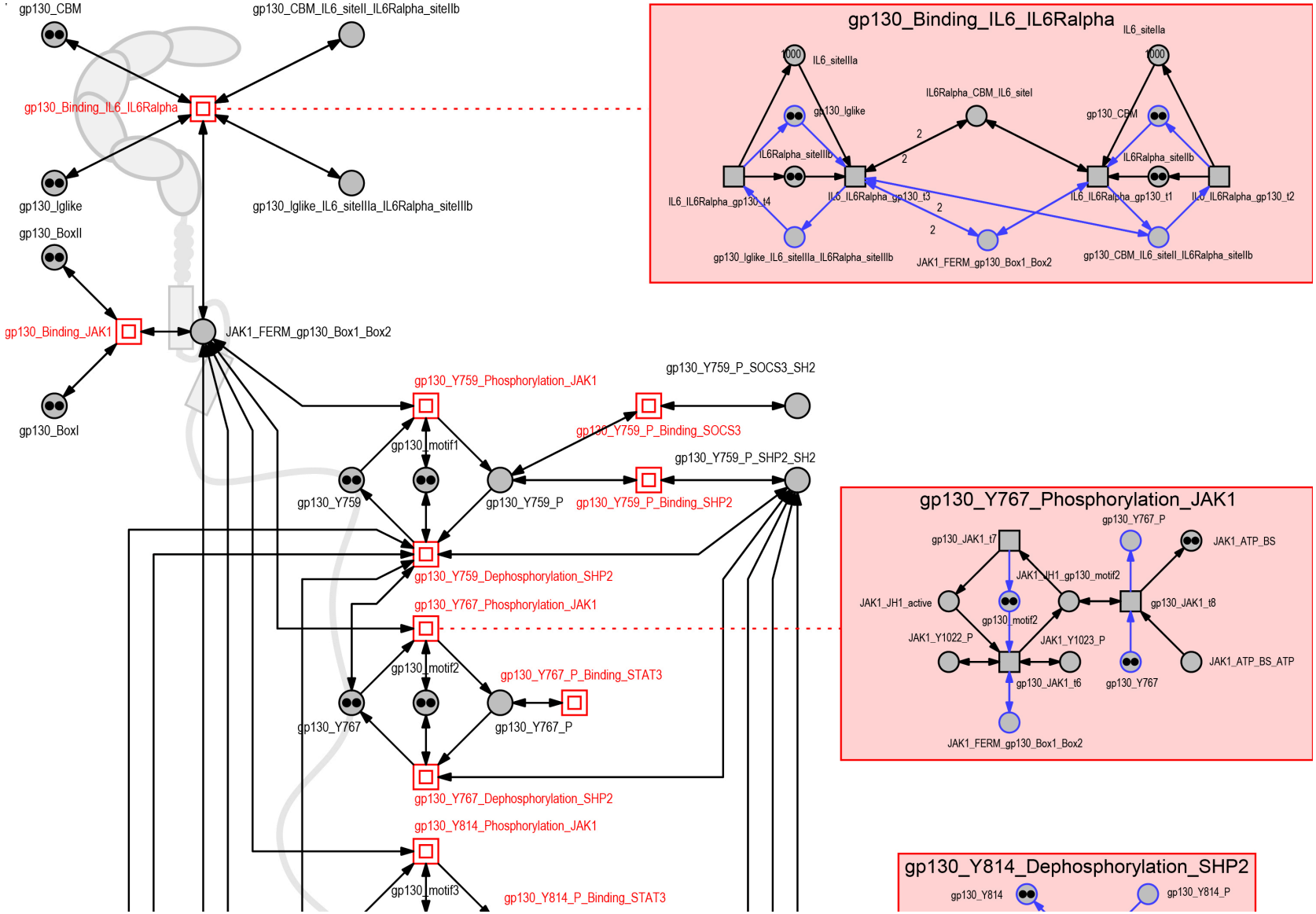
monika.heiner@tu-cottbus.de

- **JAK-STAT pathway in IL-6 signalling**
  - -> *Anna Dietrich, Fred Scharper, OvG University Magdeburg*
  - -> *constraints: induced by IL-6 cytokine, one isoform*
  - -> *7 protein modules: JAK1, STAT3, SOCS3, SHP2, gp130, IL-6, IL-6R*
    + SOCS3 biosynthesis module
  - -> *in total: 92 places, 102 transitions, 58 pages, nesting depth 4*

- **phosphate regulatory network**
  - -> *basics demonstrated in CMSB 2012 paper*

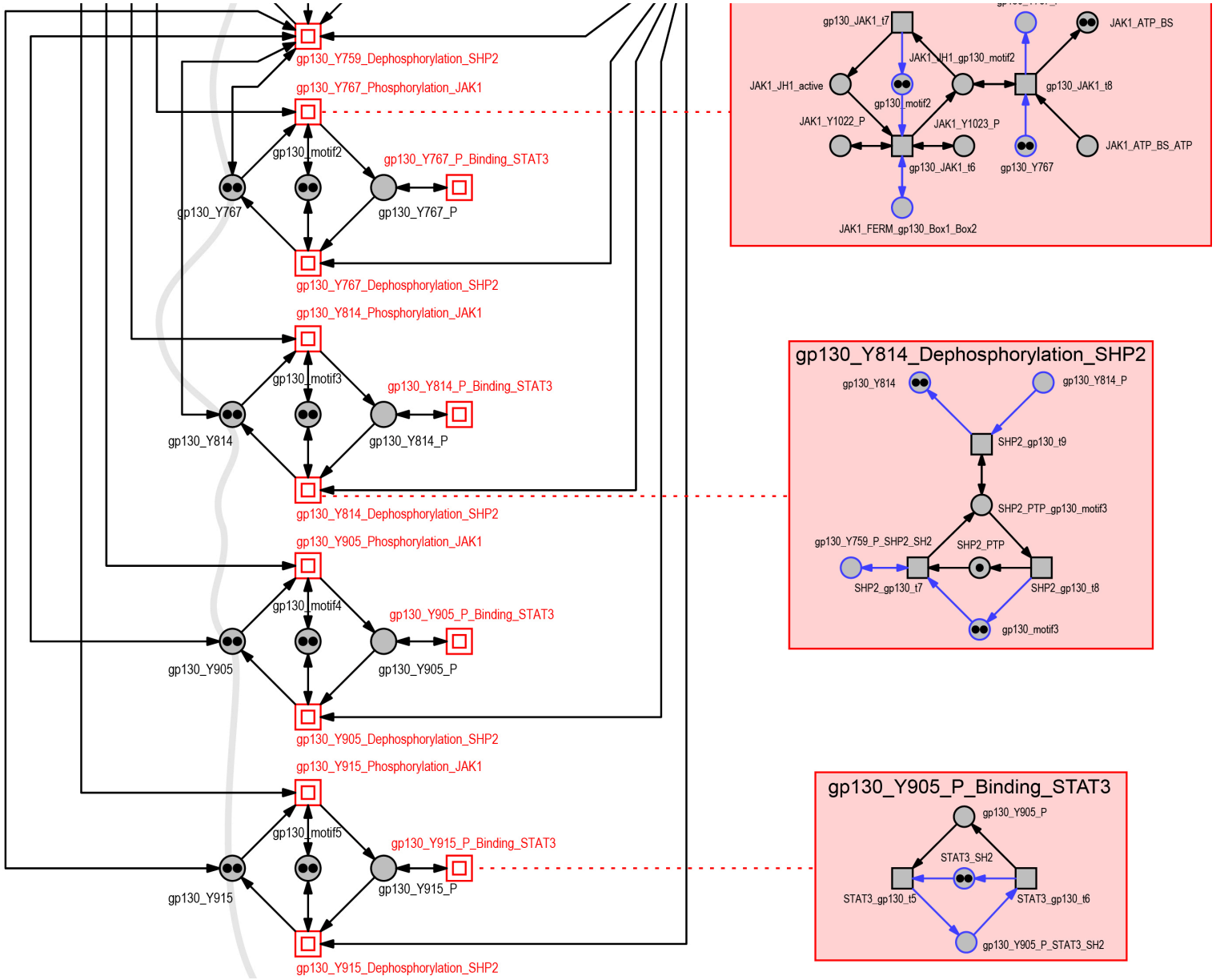
- **nociceptive network in pain signalling**
  - -> *running BMBF project with 7 consortium partners*
  - -> *(so far) 38 protein modules, among them*
    several membrane receptors, kinases, phosphatases and ion channels
  - -> *in total (so far):*
    713 places, 775 transitions, 325 pages, nesting depth 4

MODULE GP130 TRANSMEMBRANE RECEPTOR



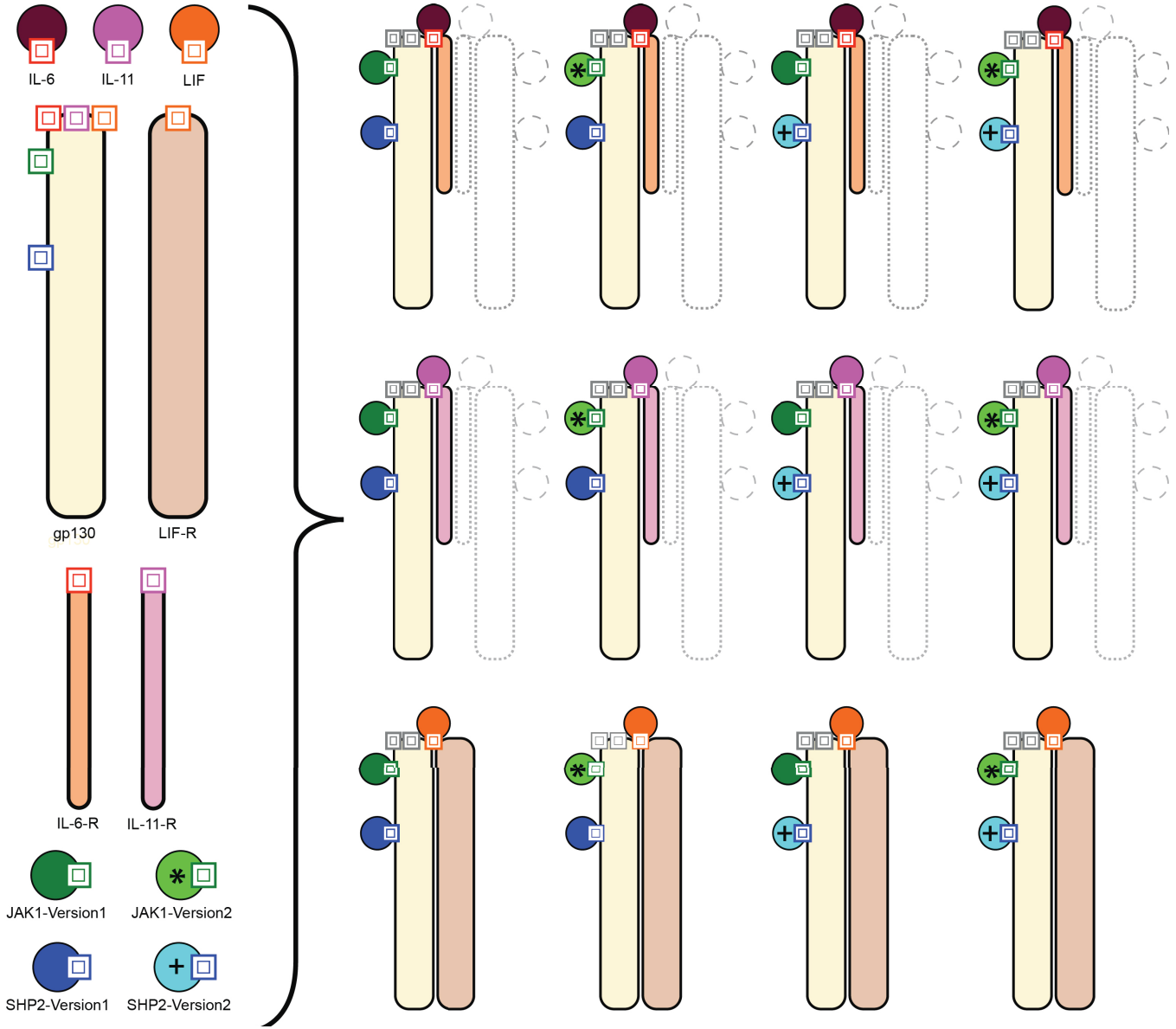
monika.heiner@tu-cottbus.de

MODULE GP130 TRANSMEMBRANE RECEPTOR



MODUL COMPOSITION

- 3 cytokines
  IL-6, IL-11,LIF
- gp130
  common
  receptor chain,
  5 binding cites
- 3 cytokine
  receptors
  LIF-R
  IL-6-R
  IL-11-R
- 2 signalling
  proteins
  JAK1, SHP2
  in 2 versions



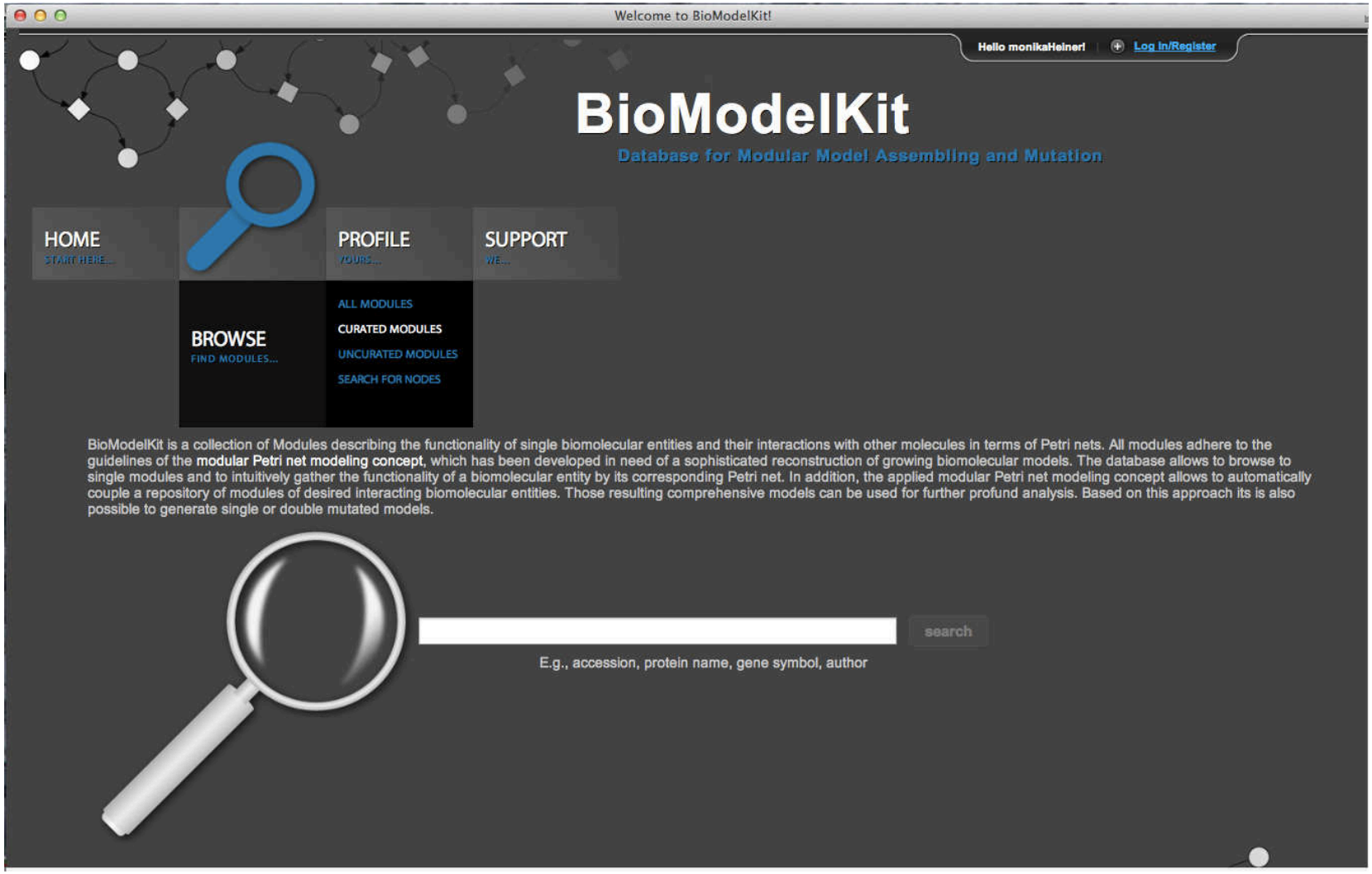
DATABASE WITH WEB INTERFACE

WWW.BIOMODELKIT.ORG

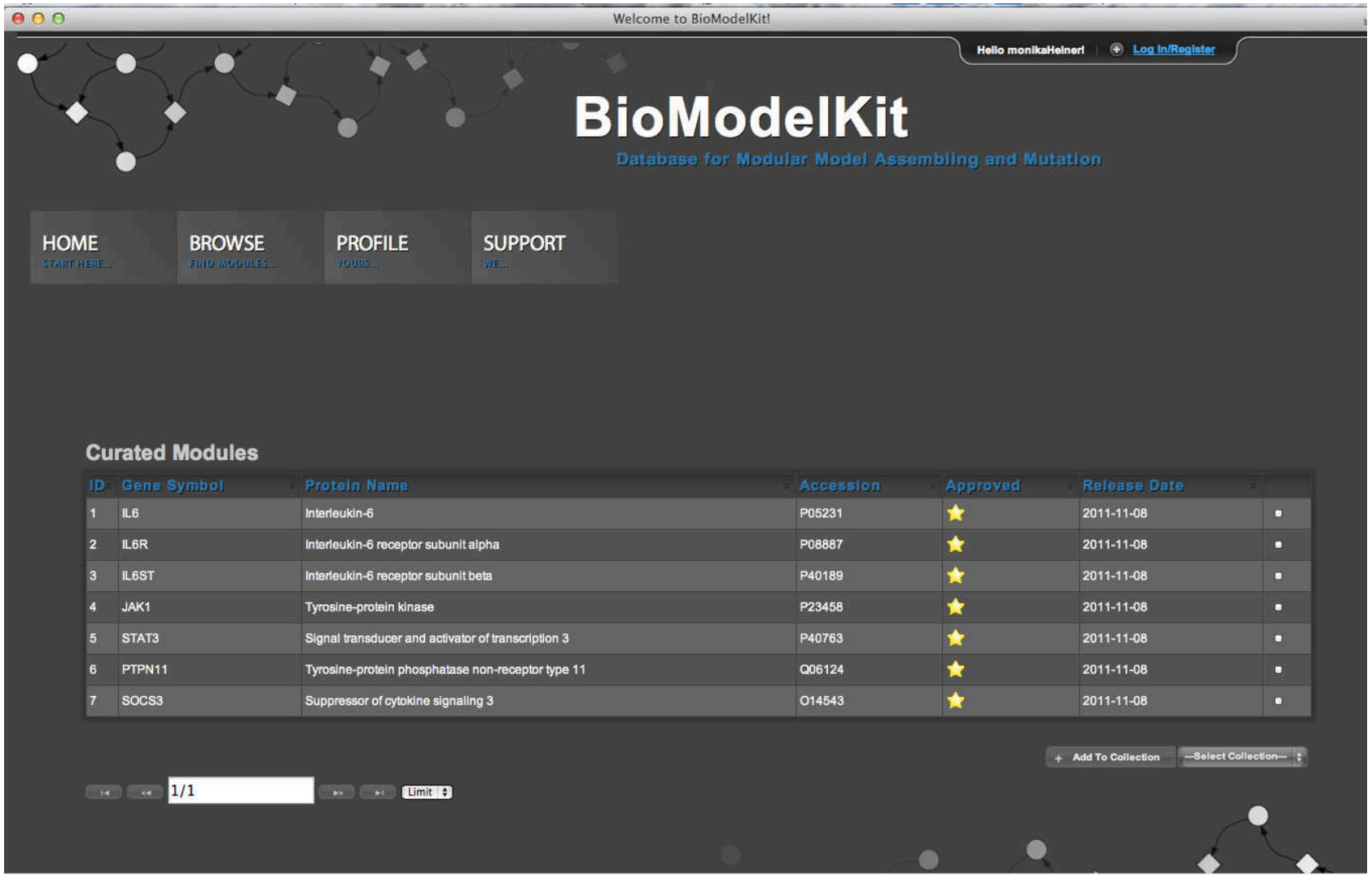
- PROTOTYPE -

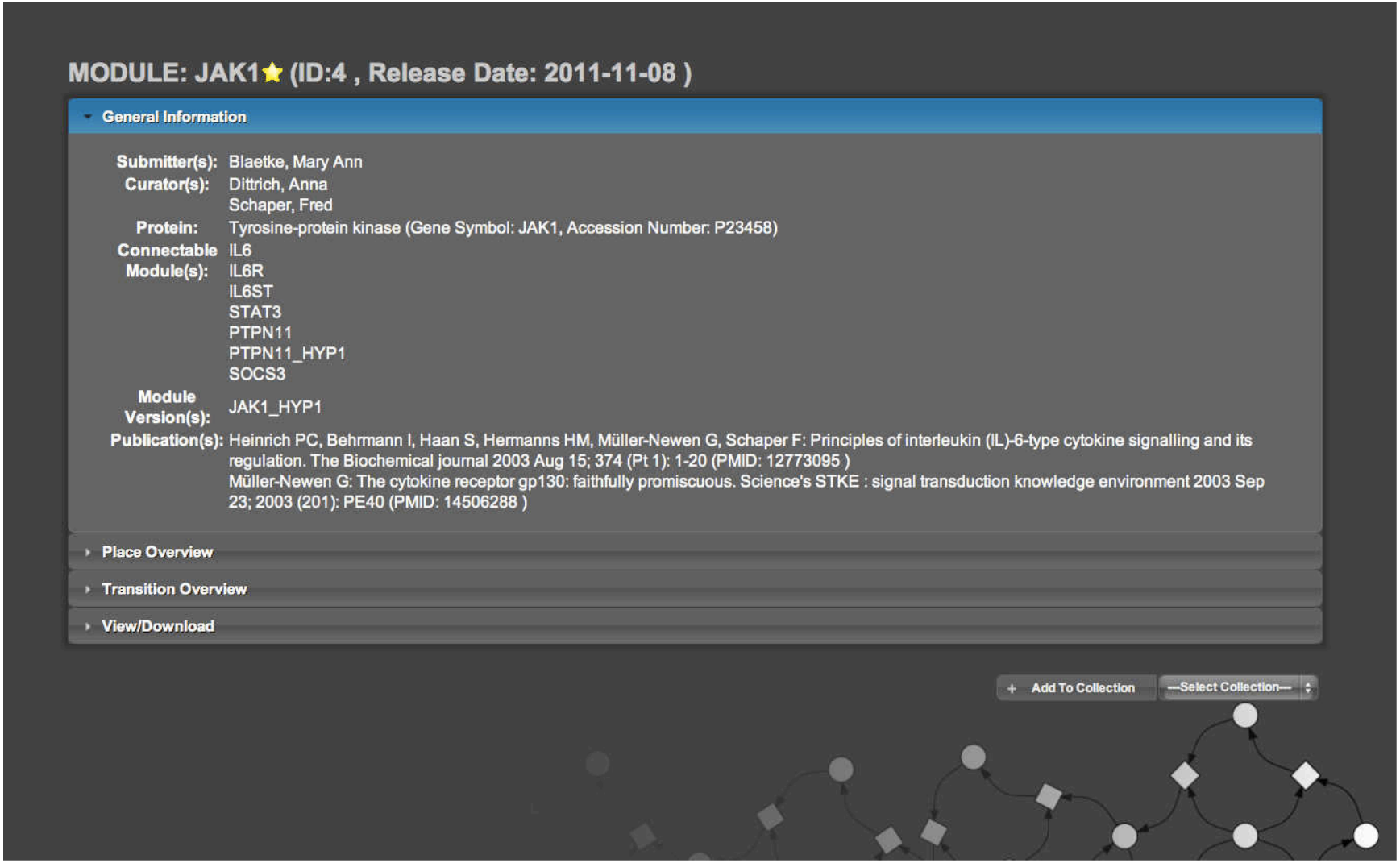
monika.heiner@tu-cottbus.de

DATABASE SUPPORT

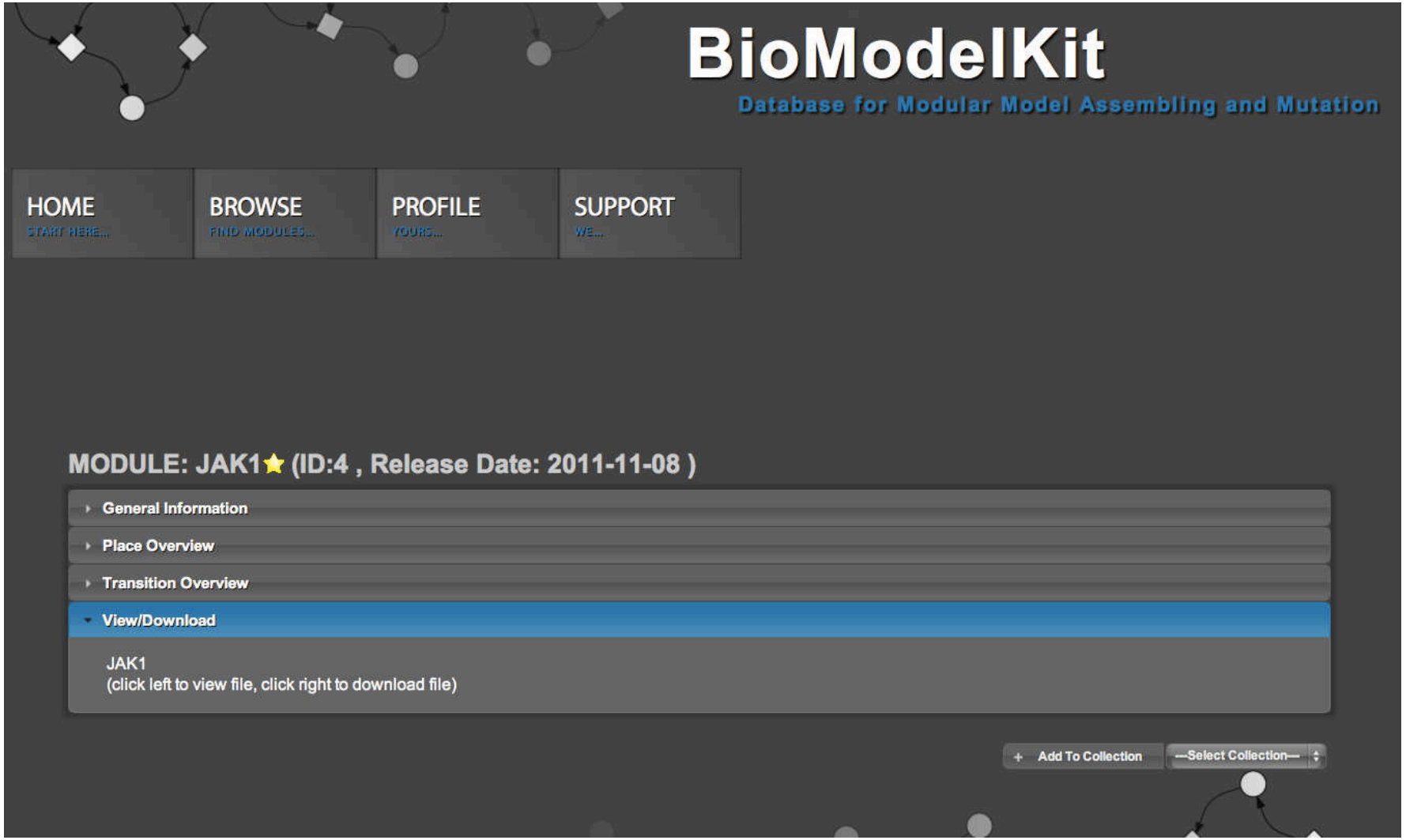


WWW.BIOMODELKIT.ORG

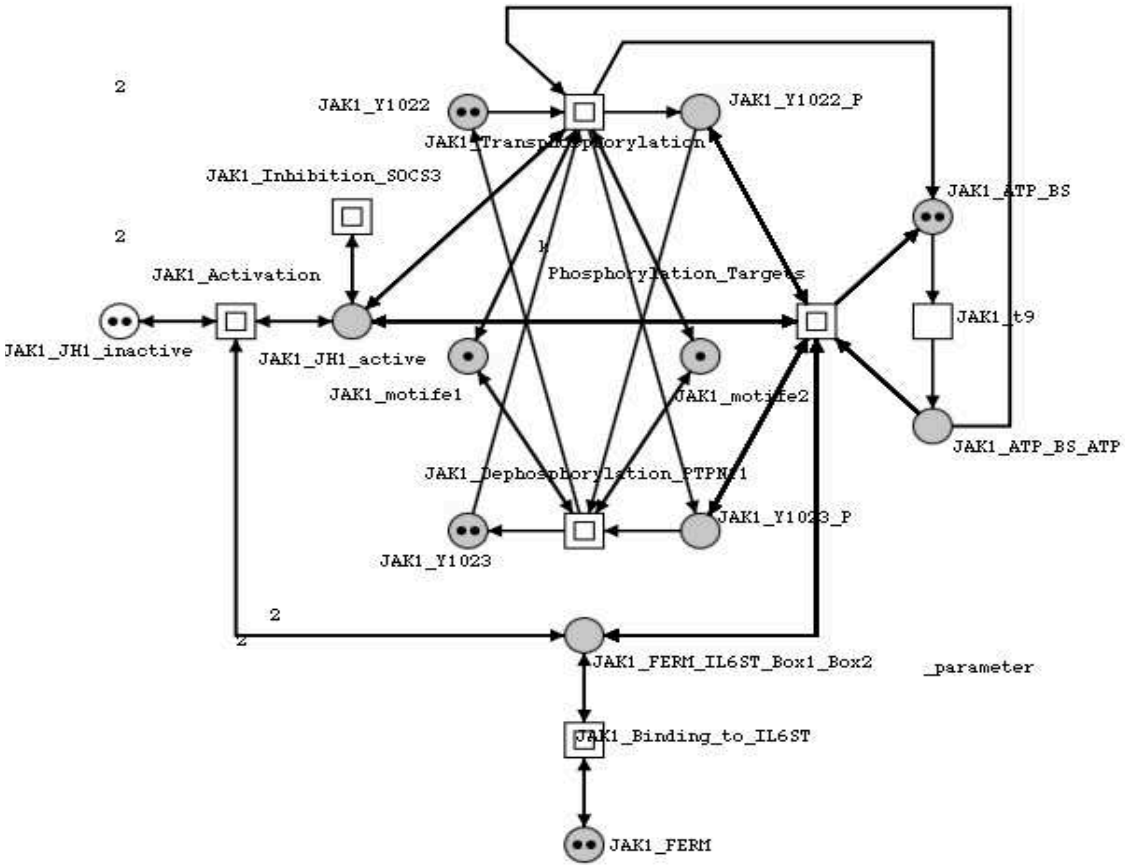

Welcome to BioModelKit!
Hello monikaHeiner!
Log In/Register
BioModelKit
Database for Modular Model Assembling and Mutation
HOME
START HERE...
BROWSE
FIND MODULES...
PROFILE
YOURS...
SUPPORT
WE...
Curated Modules
ID
Gene Symbol
Protein Name
Accession
Approved
Release Date
1 IL6 Interleukin-6 P05231 2011-11-08
2 IL6R Interleukin-6 receptor subunit alpha P08887 2011-11-08
3 IL6ST Interleukin-6 receptor subunit beta P40189 2011-11-08
4 JAK1 Tyrosine-protein kinase P23458 2011-11-08
5 STAT3 Signal transducer and activator of transcription 3 P40763 2011-11-08
6 PTPN11 Tyrosine-protein phosphatase non-receptor type 11 Q06124 2011-11-08
7 SOCS3 Suppressor of cytokine signaling 3 O14543 2011-11-08
Add To Collection
—Select Collection—
1/1
Limit

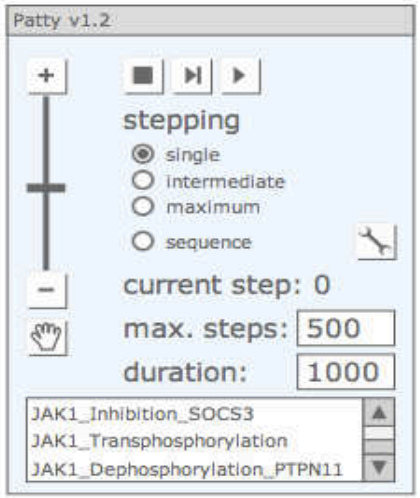

MODULE: JAK1 (ID:4 , Release Date: 2011-11-08)
General Information
Submitter(s): Blaetke, Mary Ann
Curator(s): Dittrich, Anna
Schaper, Fred
Protein: Tyrosine-protein kinase (Gene Symbol: JAK1, Accession Number: P23458)
Connectable Module(s): IL6
IL6R
IL6ST
STAT3
PTPN11
PTPN11_HYP1
SOCS3
Module Version(s): JAK1_HYP1
Publication(s): Heinrich PC, Behrmann I, Haan S, Hermanns HM, Müller-Newen G, Schaper F: Principles of interleukin (IL)-6-type cytokine signalling and its regulation. The Biochemical journal 2003 Aug 15; 374 (Pt 1): 1-20 (PMID: 12773095)
Müller-Newen G: The cytokine receptor gp130: faithfully promiscuous. Science's STKE : signal transduction knowledge environment 2003 Sep 23; 2003 (201): PE40 (PMID: 14506288)
Place Overview
Transition Overview
View/Download
Add To Collection
---Select Collection---

DATABASE SUPPORT



DATABASE SUPPORT





PROTOTYPE

SUMMARY & OUTLOOK

SUMMARY

- **design prinicples**

  monolithic network design - process-oriented view - interacting reactions

  modular network design - object-oriented view - interacting compounds

- **protein-centred modules**

  -> *module curation by protein experts*

  -> *easy reuse / maintenance / versioning of modules*

  -> *automatic composition / mutation of networks*

- **modules in the four paradigms**

  -> *qualitative model* -> *discrete Petri nets*

  -> *discrete quantitative model* -> *stochastic Petri nets*

  -> *continuous quantitative model* -> *continuous Petri nets = ODEs, hybrid Petri nets*

- **database with web interface**

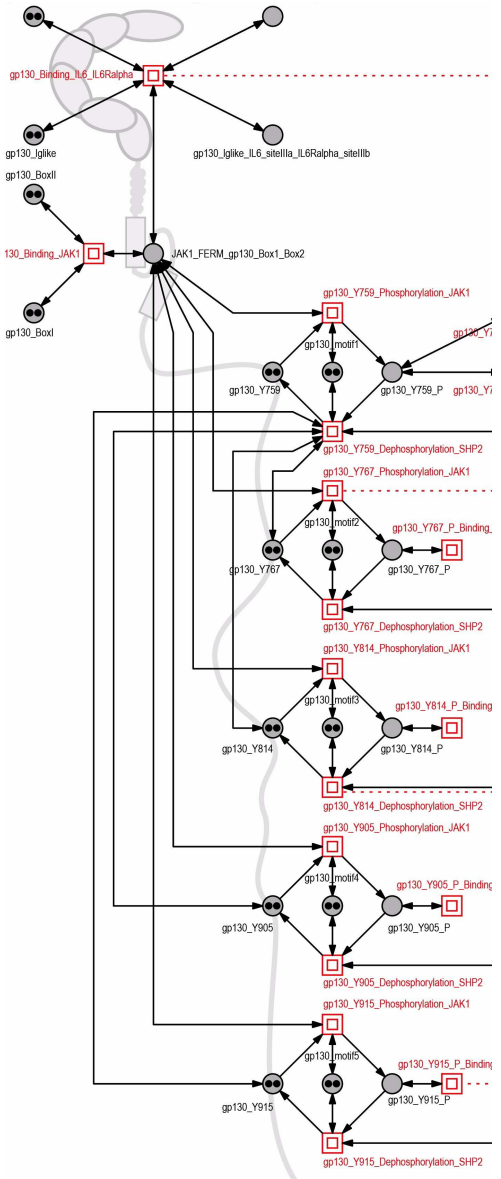
  -> *remote module curation + model composition*

REFERENCES

- MA Blätke, A Dittrich, C Rohr, M Heiner, F Schaper and W Marwan:
  JAK/STAT signalling - an executable model assembled from molecule-centred modules demonstrating a module-oriented database concept for systems and synthetic biology;
  Molecular BioSystem (9) 2013, pp. 1290-1307

- MA Blätke, A Dittrich, M Heiner, F Schaper and W Marwan:
  JAK-STAT Signalling as Example for a Database-Supported Modular Modelling Concept;
  Proc. CMSB 2012, Springer LNCS/LNBI 7605, pp. 362-365, 2012.

- MA Blätke, M Heiner and W Marwan:
  Predicting Phenotype from Genotype Through Automatically Composed Petri Nets;
  Proc. CMSB 2012, Springer LNCS/LNBI 7605, pp. 87-106, 2012.



OUR TOOL BOX

- **SNOOPY**
  - -> *modelling and animation/simulation of hierarchical graphs,*
    e.g. (extended) fault trees,
    various Petri net classes, e.g. QPN, XQPN, SPN, XSPN, CPN, TPN,
    . . . ,
    free style graphs

- **CHARLIE**
  - -> *QPN, XQPN, Time/Timed Petri nets (TPN)*
  - -> *mostly standard analysis techniques of Petri net theory*

- **MARCIE**
  - -> *XQPN, SPN, XSPN, SRN*
  - -> *symbolic and simulative model checking*

- **Patty -> BioModelKit**
  - -> *animation via web browser*

OUR TOOL BOX

- **SNOOPY**
  - -> *modelling and animation/simulation of hierarchical graphs,*
    e.g. (extended) fault trees,
    various Petri net classes, e.g. QPN, XQPN, SPN, XSPN, CPN, TPN,
    . . . ,
    free style graphs
- **CHARLIE**
  - -> *QPN, XQPN, Time/Timed Petri nets (TPN)*
  - -> *mostly standard analysis techniques of Petri net theory*
- **MARCIE**
  - -> *QPN, SPN, XSPN, SRN*
  - -> *symbolic and simulative model checking*
- **Patty -> BioModelKit**
  - -> *animation via web browser*

SBML import/export

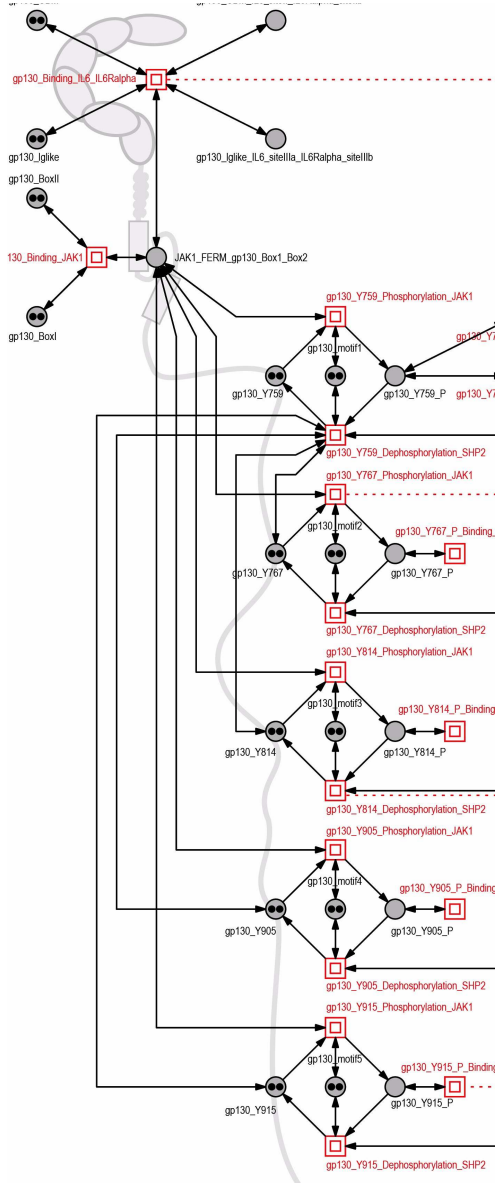
EXPORT TO MATAB AND

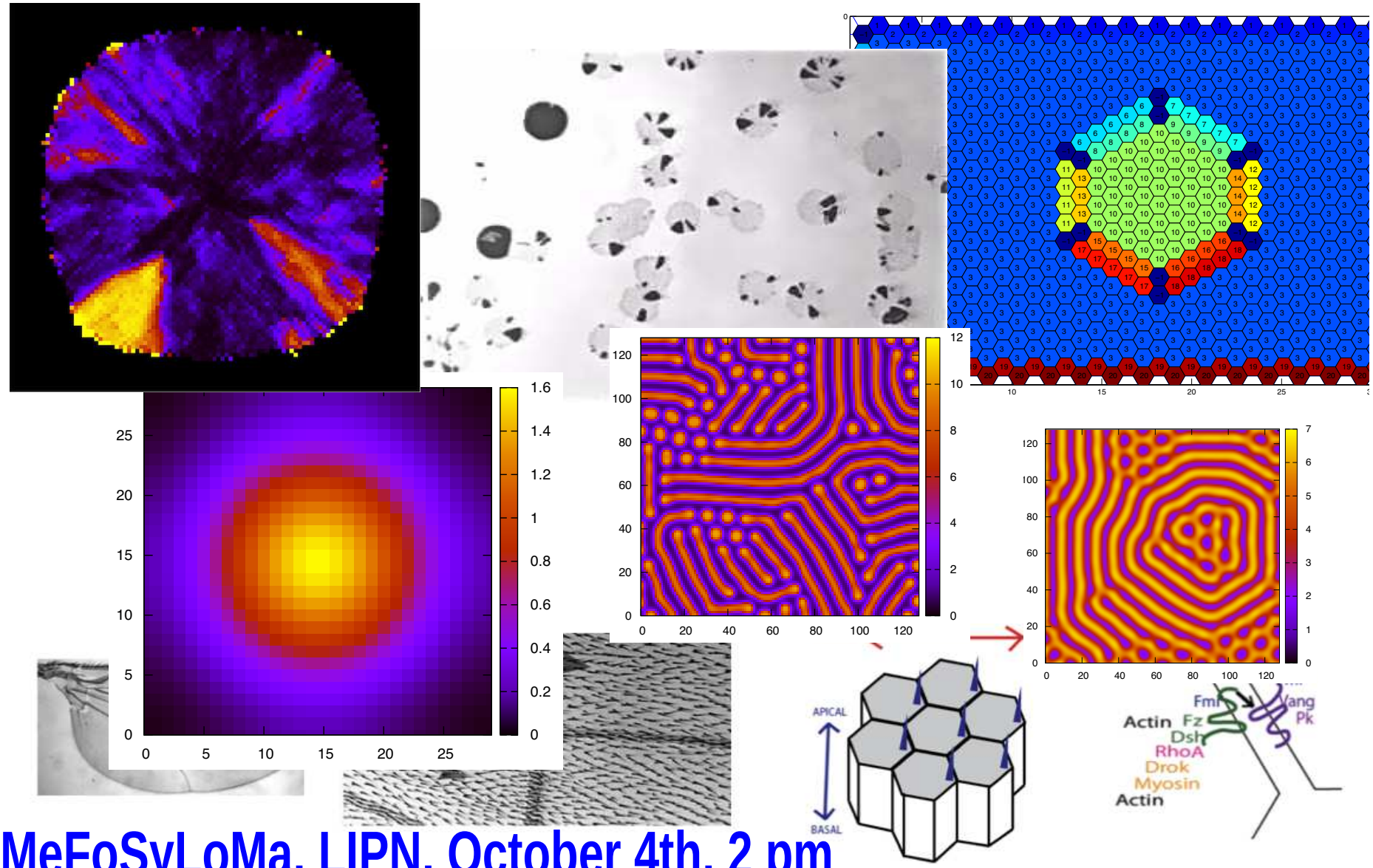
MANY OTHER TOOLS

OUTLOOK

- **database prototype**
- **more views**
  - -> *protein interaction view*
  - -> *process view, e.g. from state A to state B*
  - -> *convenient browsing in net hierarchy*
- **efficient simulation of very large Petri nets**
  - -> *stochastic*
  - -> *continuous*
  - -> *hybrid*
- **(hierarchical) space**
- **biosystem development**

MULTISCALE CHALLENGES

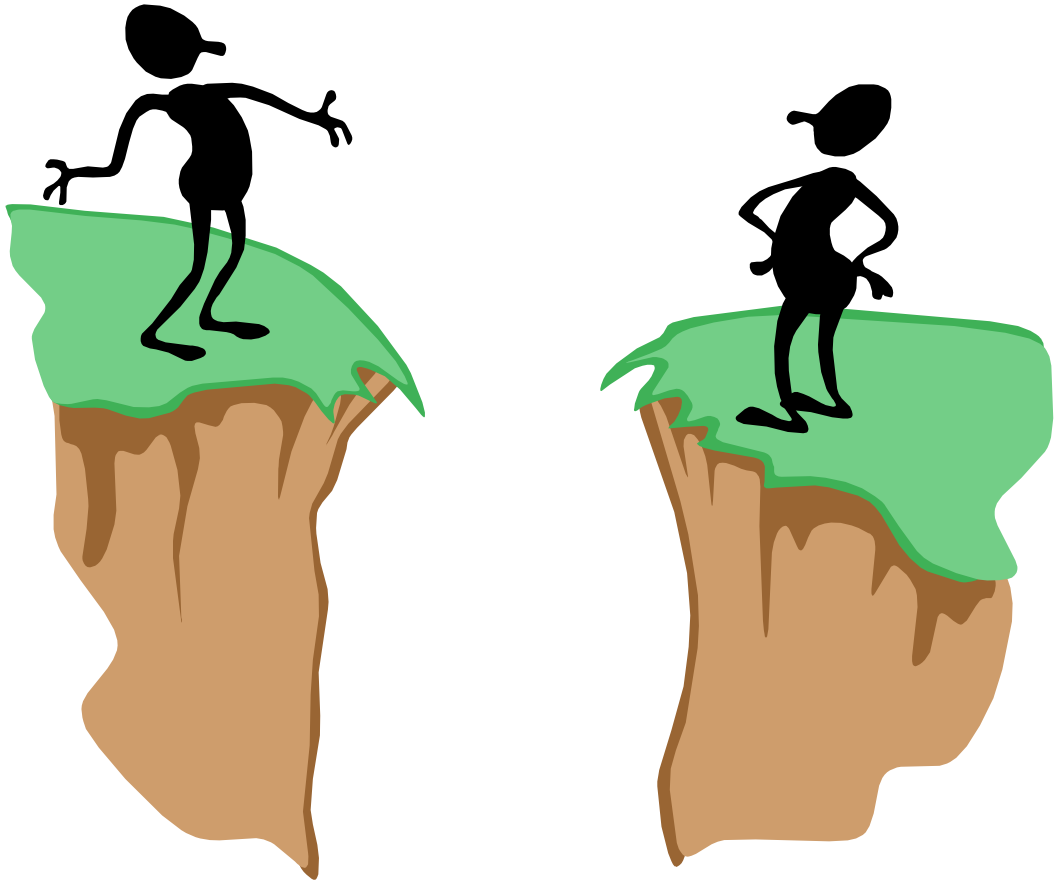




MeFoSyLoMa, LIPN, October 4th, 2 pm

monika.heiner@tu-cottbus.de

OUTLOOK



THANKS !

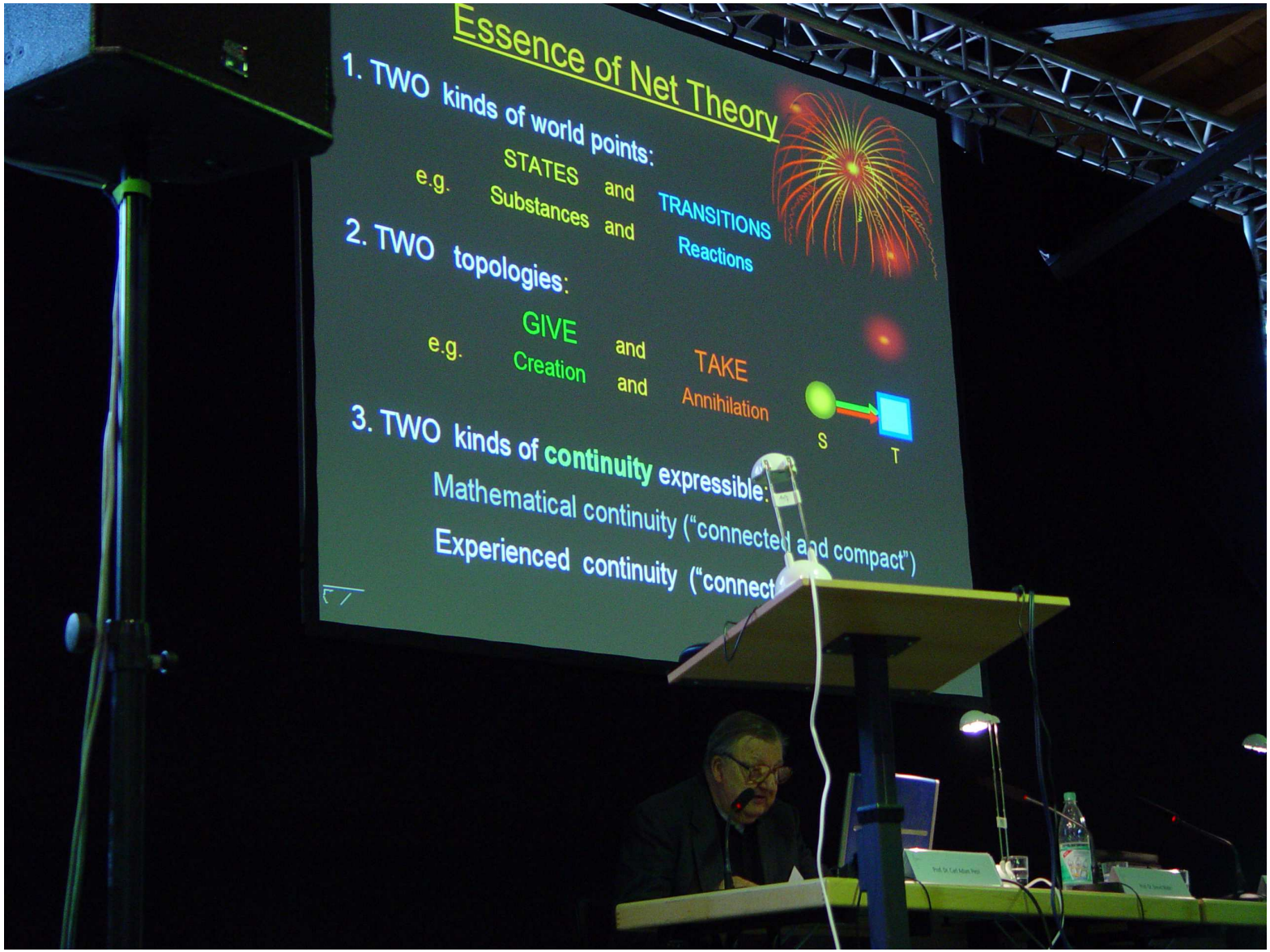
HHTP://WWW-DSSZ.INFORMATIK.TU-COTTBUS.DE

APPENDIX

A BIT OF HISTORY

C. A. PETRI, NOVEMBER 2006

A BIT OF HISTORY



C. A. PETRI
INTERPRETATIONS OF NET THEORY
GMD, INTERNAL REPORT 75-07, 2ND IMPROVED EDITION 1976

places	transitions
state elements	transitional elements
conditions	events/facts
statements	dependencies
model domains	specifications
chemical compounds	chemical reactions
open one-point sets	closed one-point sets
channels	offices
languages	translators
products	poduction activities

[Peterson 1981]

74 Chap. 3 Modeling with Petri Nets

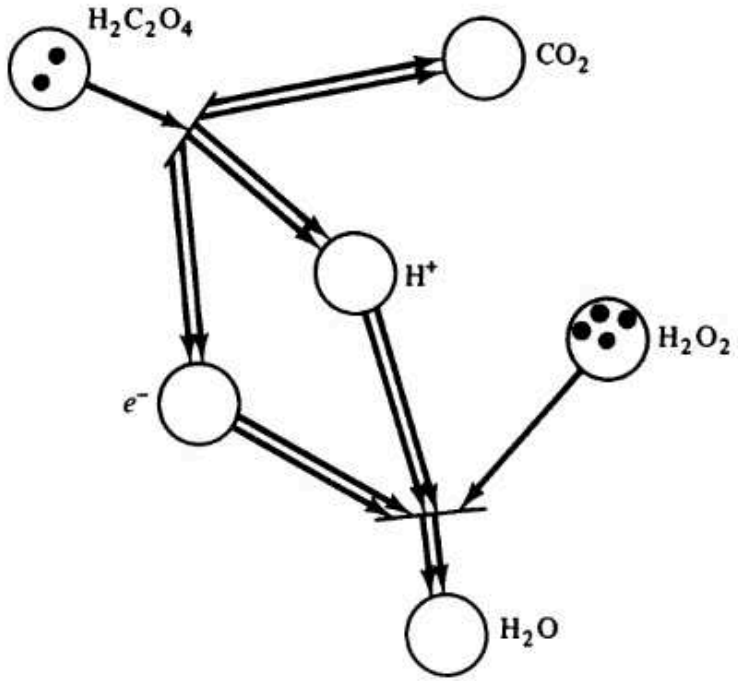


Figure 3.38 A Petri net representing the oxidation-reduction of oxalic acid and hydrogen peroxide into carbon dioxide and water.

$$H_2C_2O_4 \longrightarrow 2CO_2 + 2H^+ + 2e^-$$

$$2e^- + 2H^+ + H_2O_2 \longrightarrow 2H_2O$$

MORE HISTORY 2

[Murata 1989]

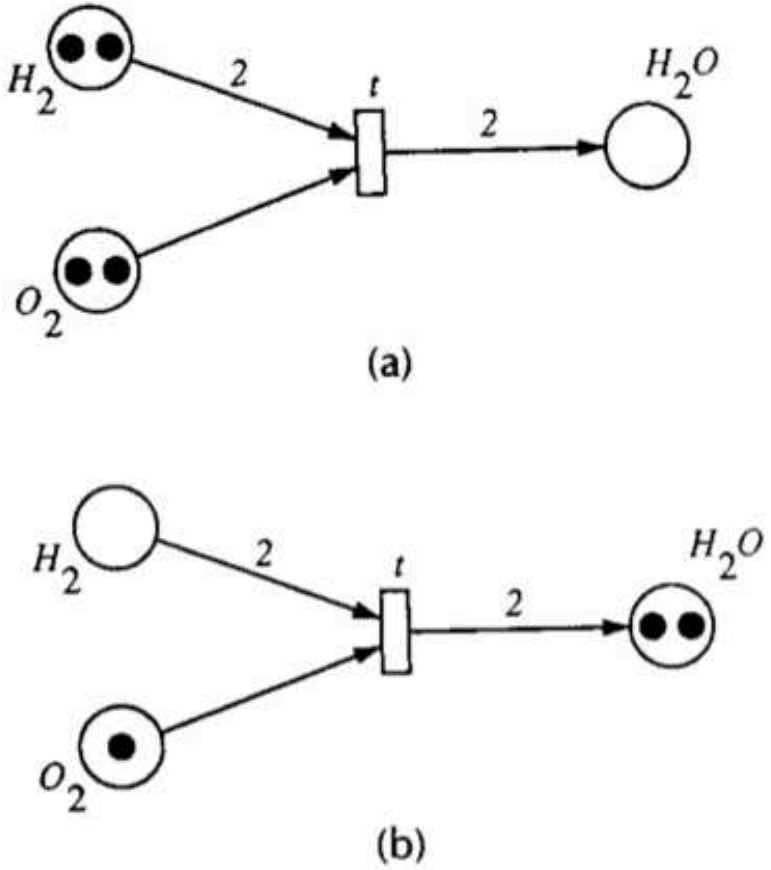


Fig. 1. Example 1: An illustration of a transition (firing) rule: (a) The marking before firing the enabled transition *t*. (b) The marking after firing *t*, where *t* is disabled.

- **transitions r_i get a stochastic waiting time**
  - -> *exponential distribution with parameter lambda*
- **state-dependent lambda defined by rate function $v_i(r_i)$**
  - -> *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
- **semantics: Continuous Time Markov Chain (CTMC)**
  - -> *reachability graph + state transition rates*
- **analysis**
  - -> *standard Markov analysis techniques: transient, steady state*
  - -> *stochastic simulation algorithms (SSA), e.g. Gillespie's SSA*

RATE FUNCTIONS

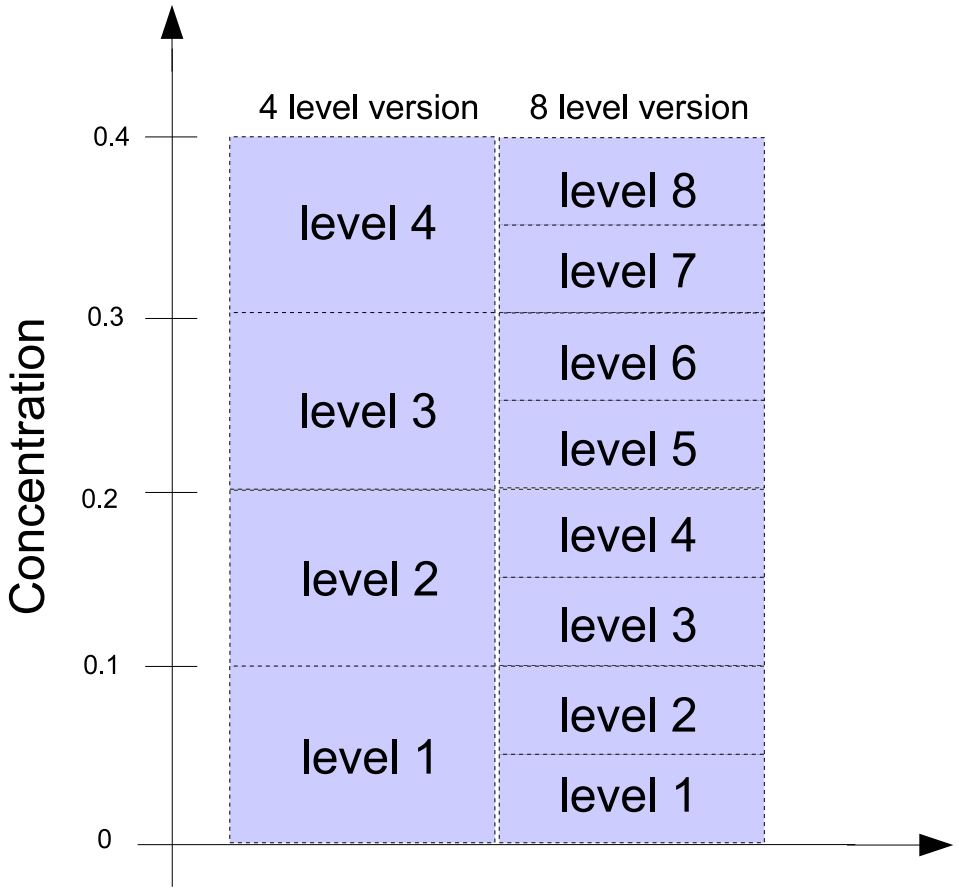
- **mass-action semantics**

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

- **level semantics**

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

LEVEL CONCEPT



- **transitions r_i fire continuously**

- **rate functions $v_i(r_i)$**

  -> *any arithmetic function including*
  the transition's pre-places as real-valued variables and
  user-defined real-valued parameters

- **real-valued tokens**

  -> *concentrations*

- **semantics: set of Ordinary Differential Equations (ODEs)**

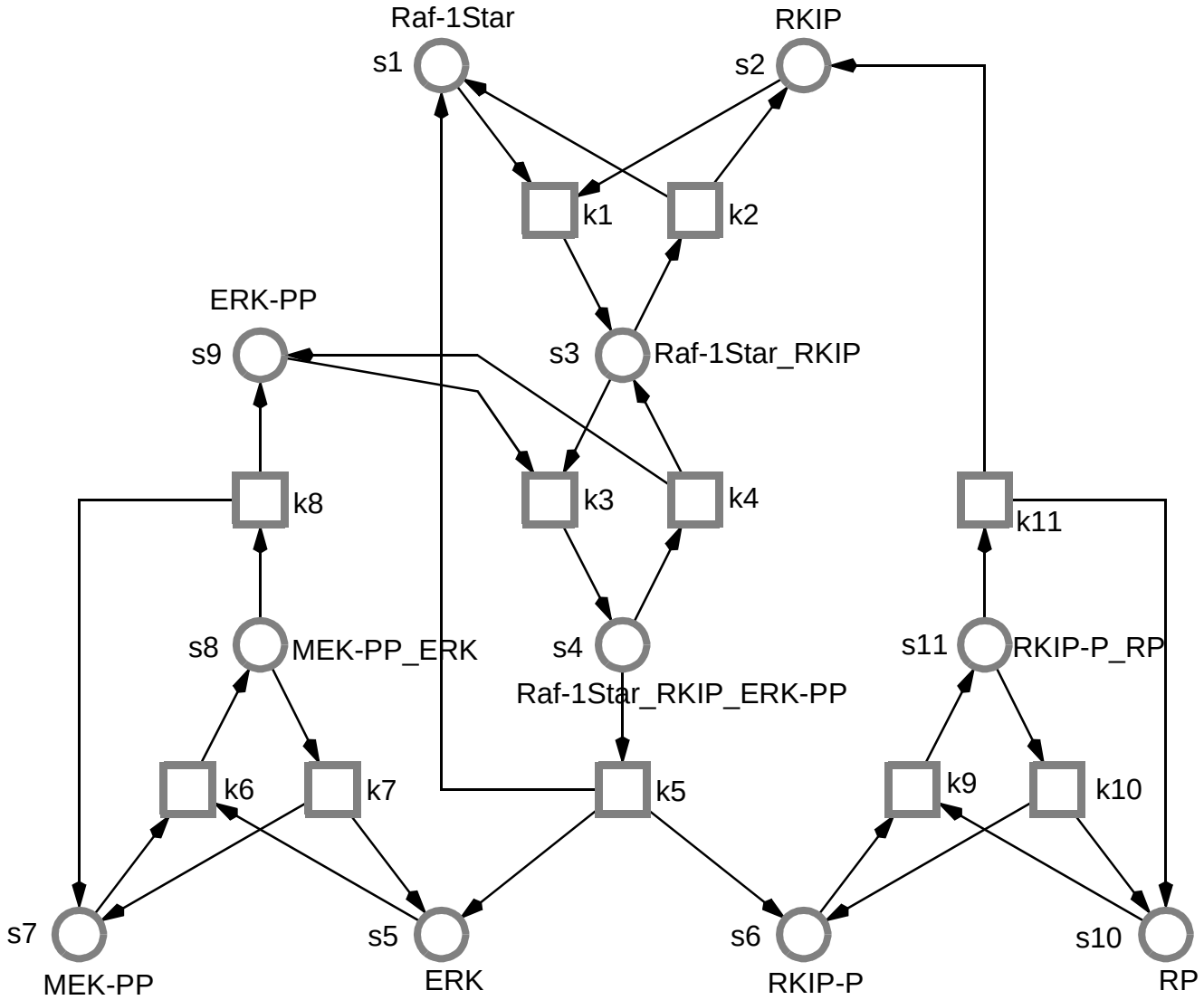
  -> *uniquely defined, but not vice versa* -> [SOLIMAN, HEINER 2010]

  -> *typically non-linear*

- **simulation (numerical integration)**

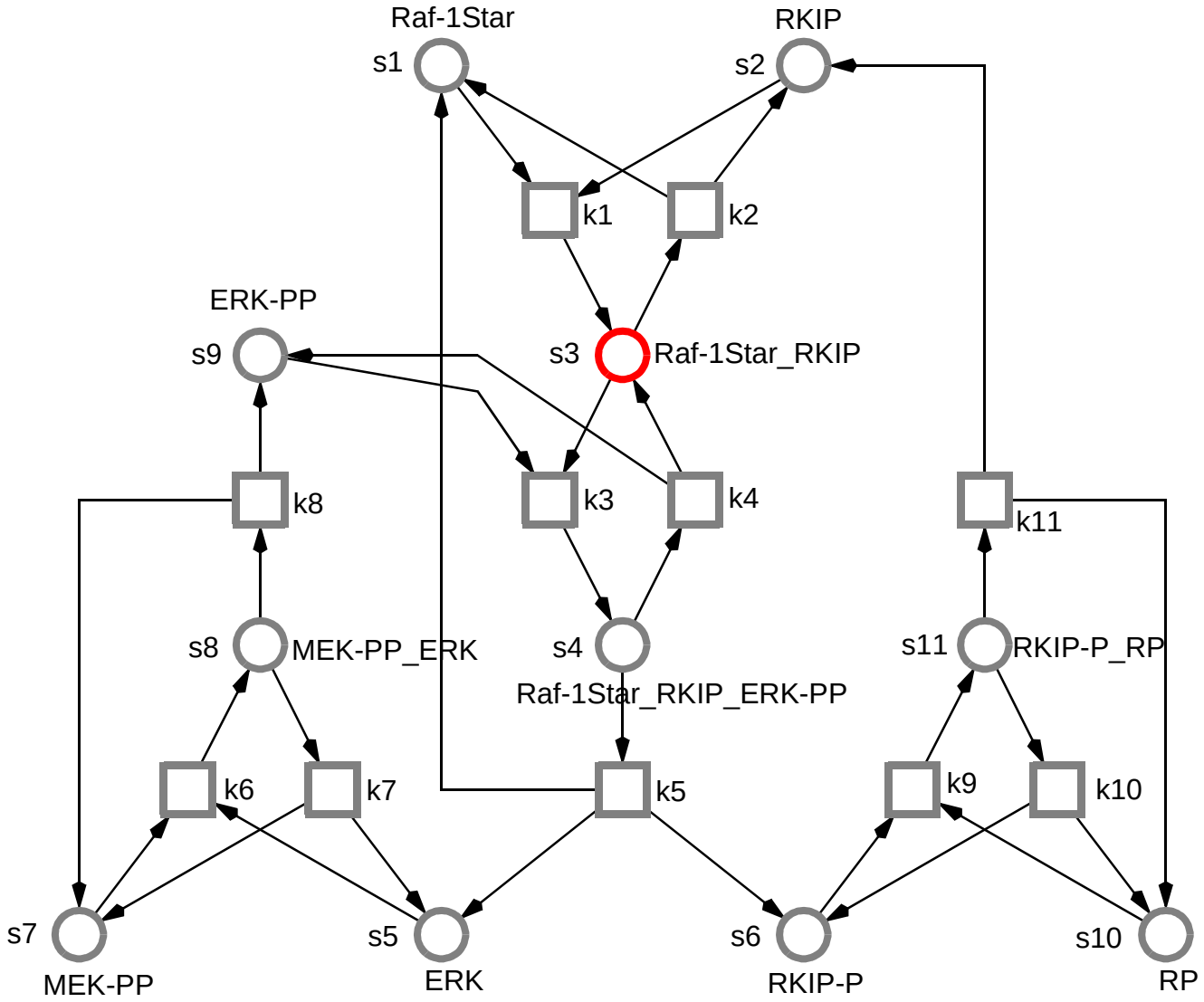
  -> *stiff / unstiff solvers*

CONTINUOUS PETRI NET DEFINES ODES



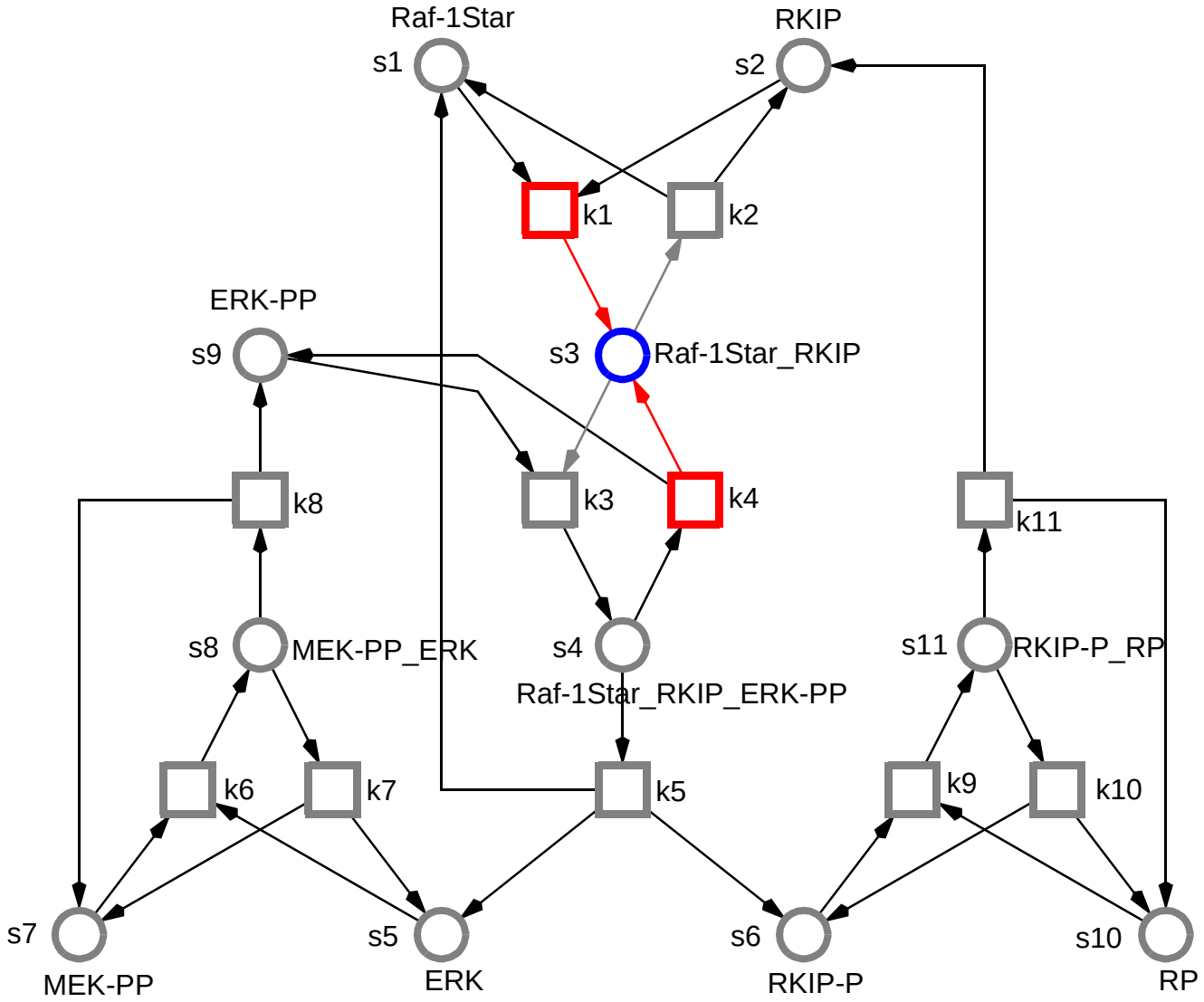
CONTINUOUS PETRI NET DEFINES ODES

$$\frac{ds3}{dt} =$$



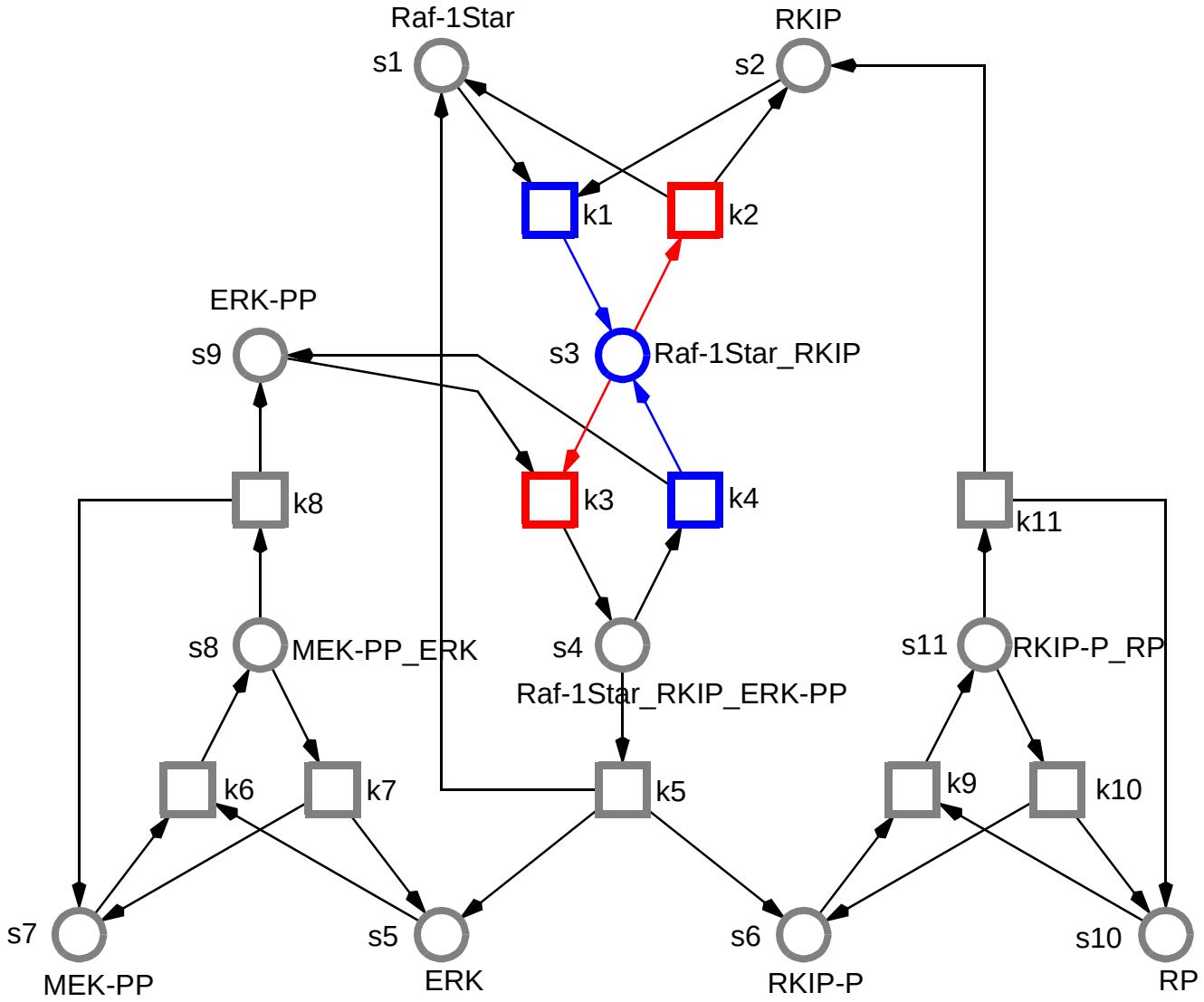
CONTINUOUS PETRI NET DEFINES ODES

$$\frac{ds3}{dt} = + v1 + v4$$



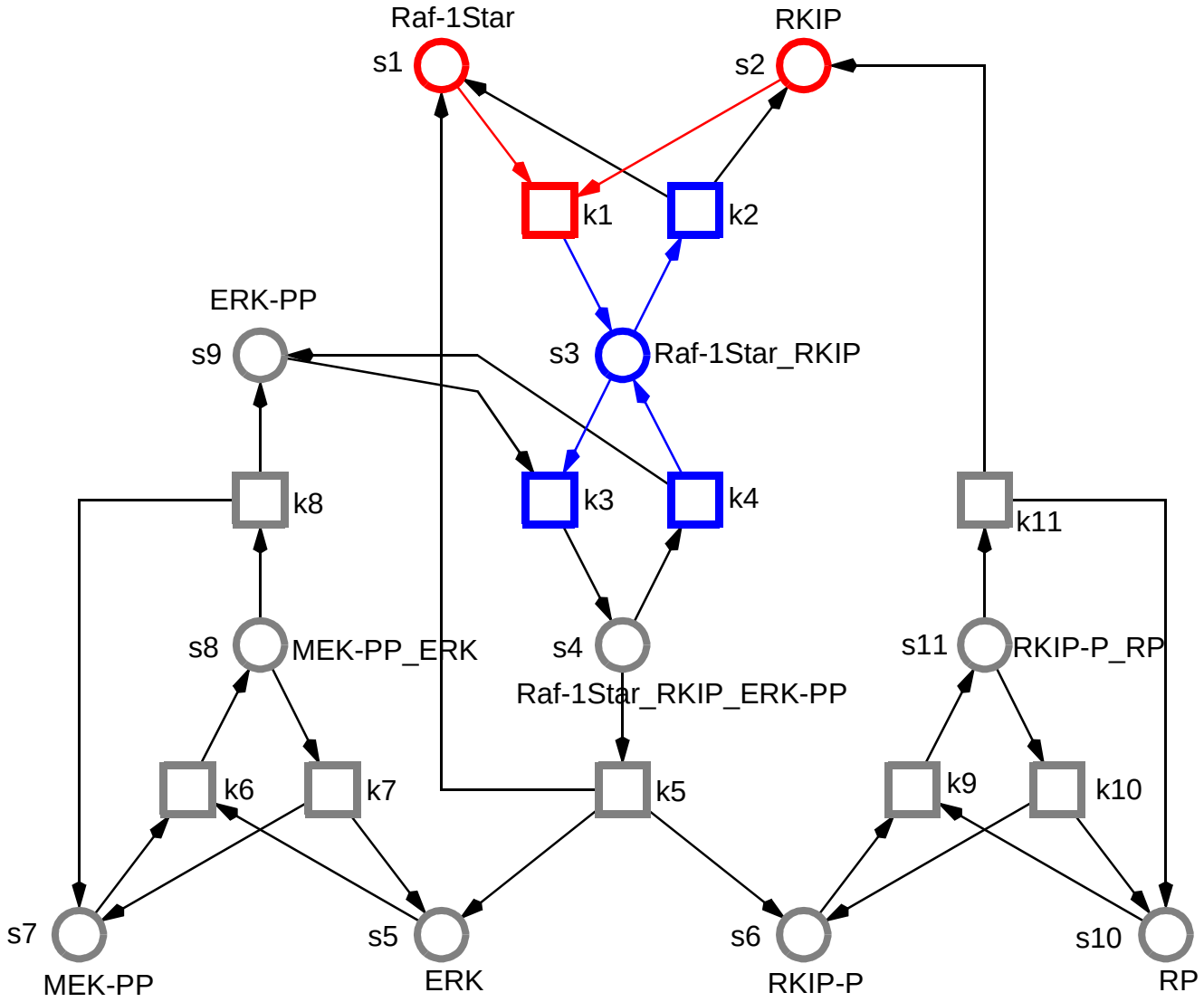
CONTINUOUS PETRI NET DEFINES ODES

$$\frac{ds3}{dt} = +v1 +v4 -v2 -v3$$



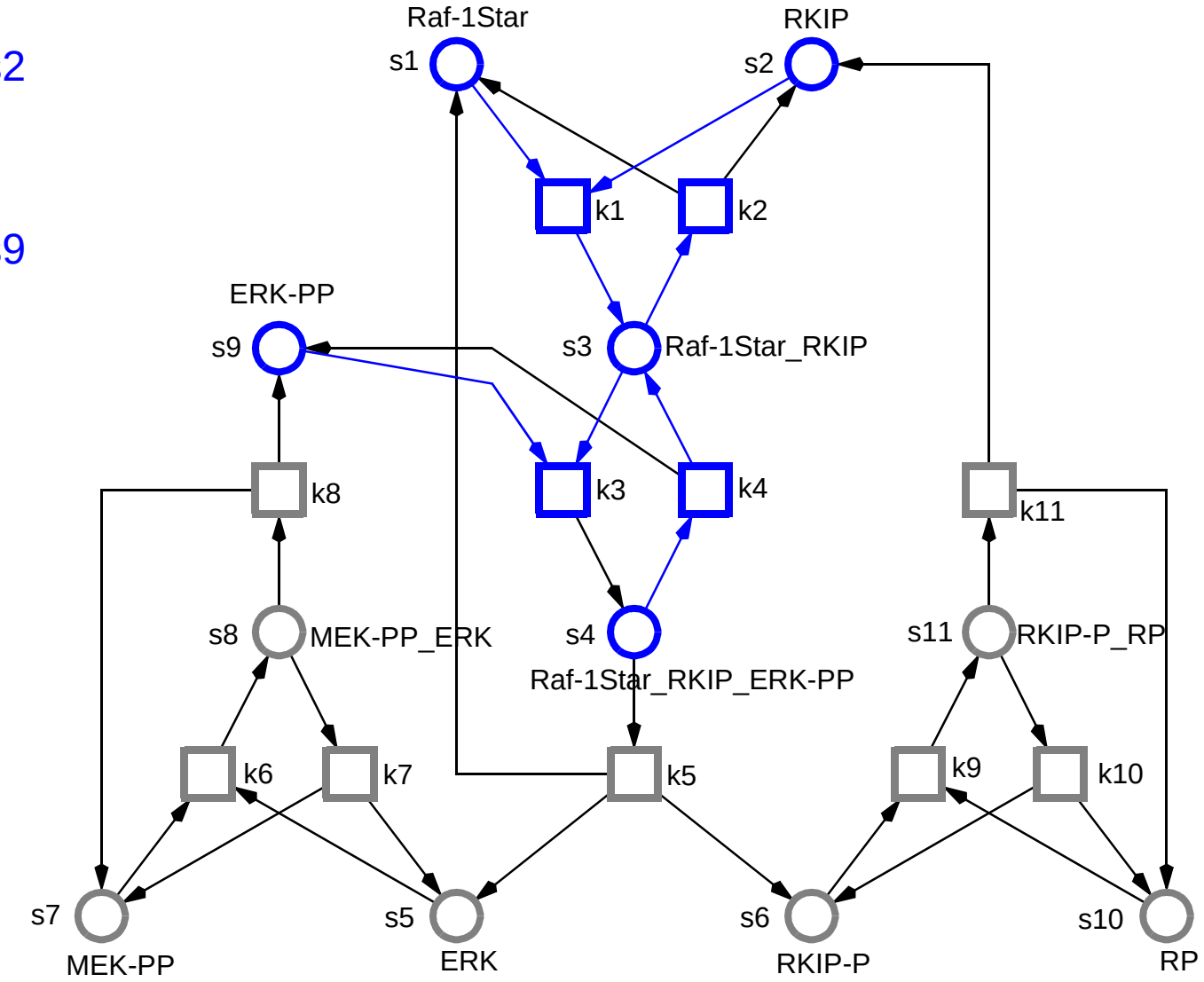
CONTINUOUS PETRI NET DEFINES ODES

$$\frac{ds3}{dt} = + k1 * s1 * s2 + v4 - v2 - v3$$



CONTINUOUS PETRI NET DEFINES ODES

$$\frac{ds3}{dt} = + k1 * s1 * s2 + k4 * s4 - k2 * s3 - k3 * s3 * s9$$



GENERALIZED HYBRID PETRI NETS (GHPN)

- **GHPN = XSPN + CPN**

[HERAJY, HEINER 2010]

- **XSPN - Extended Generalized Stochastic Petri Nets**
  - -> *discrete places*
  - -> *discrete transitions: stochastic, immediate, deterministically delayed, scheduled*
  - -> *special arcs: read, inhibitor, equal, reset*

- **CPN - Continuous Petri Nets**
  - -> *continuous places*
  - -> *continuous transitions*
  - -> *special arcs: read, inhibitor*

- **hybrid simulation engine**
  - -> *static partitioning*
  - -> *dynamic partitioning*