FROM PETRI NETS TO DIFFERENTIAL EQUATIONS

AN INTEGRATIVE APPROACH FOR BIOCHEMICAL NETWORK ANALYSIS

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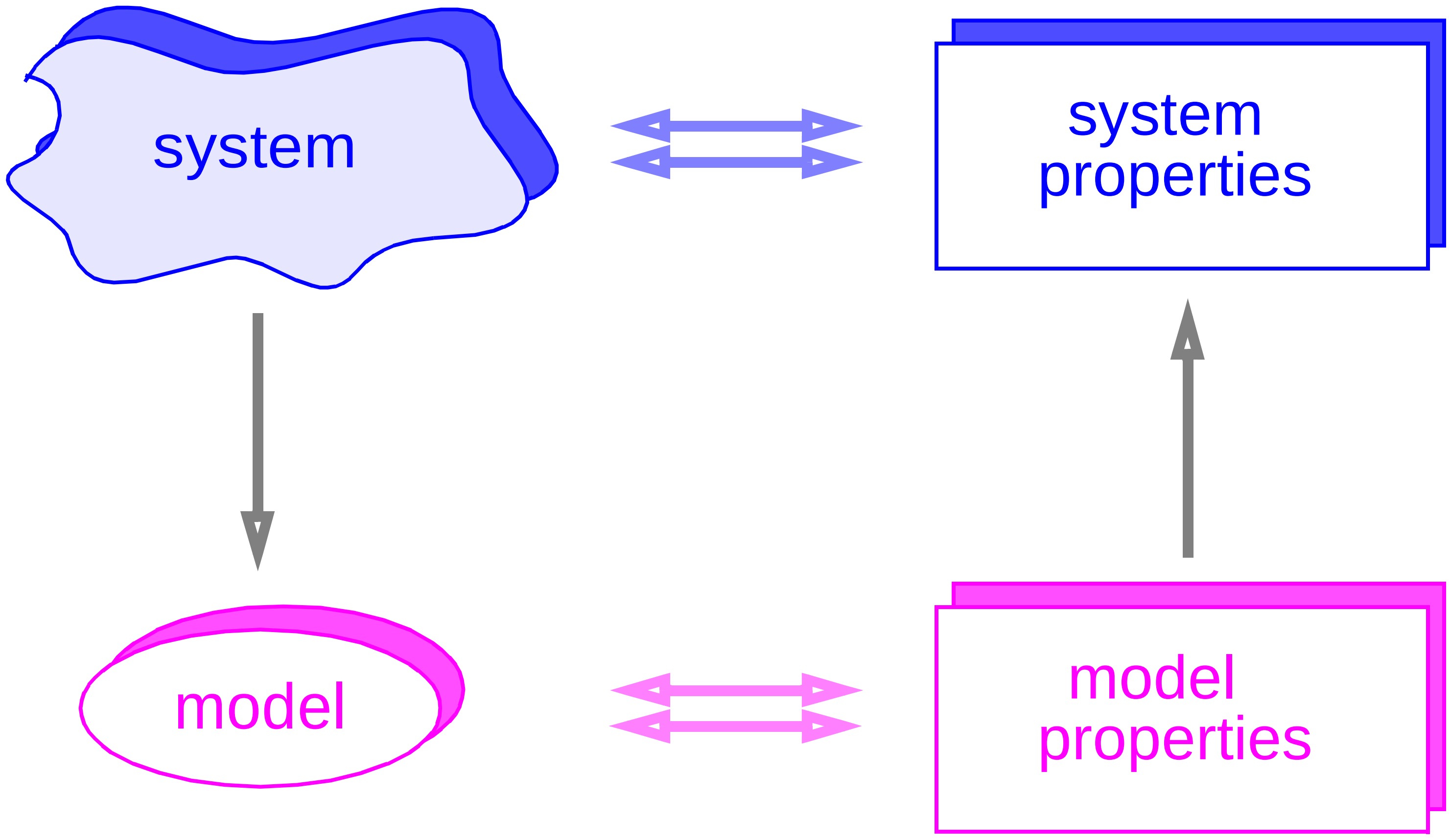
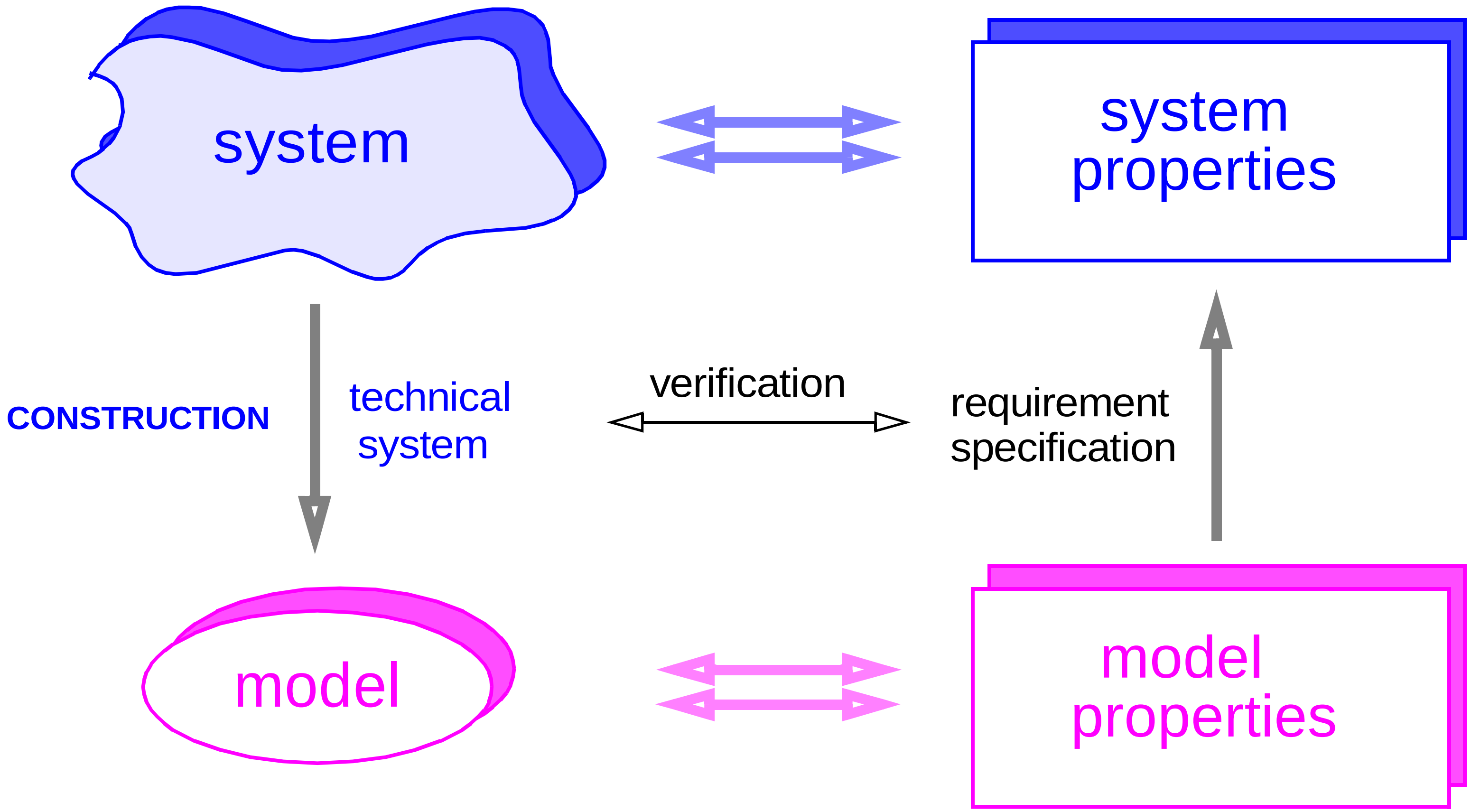
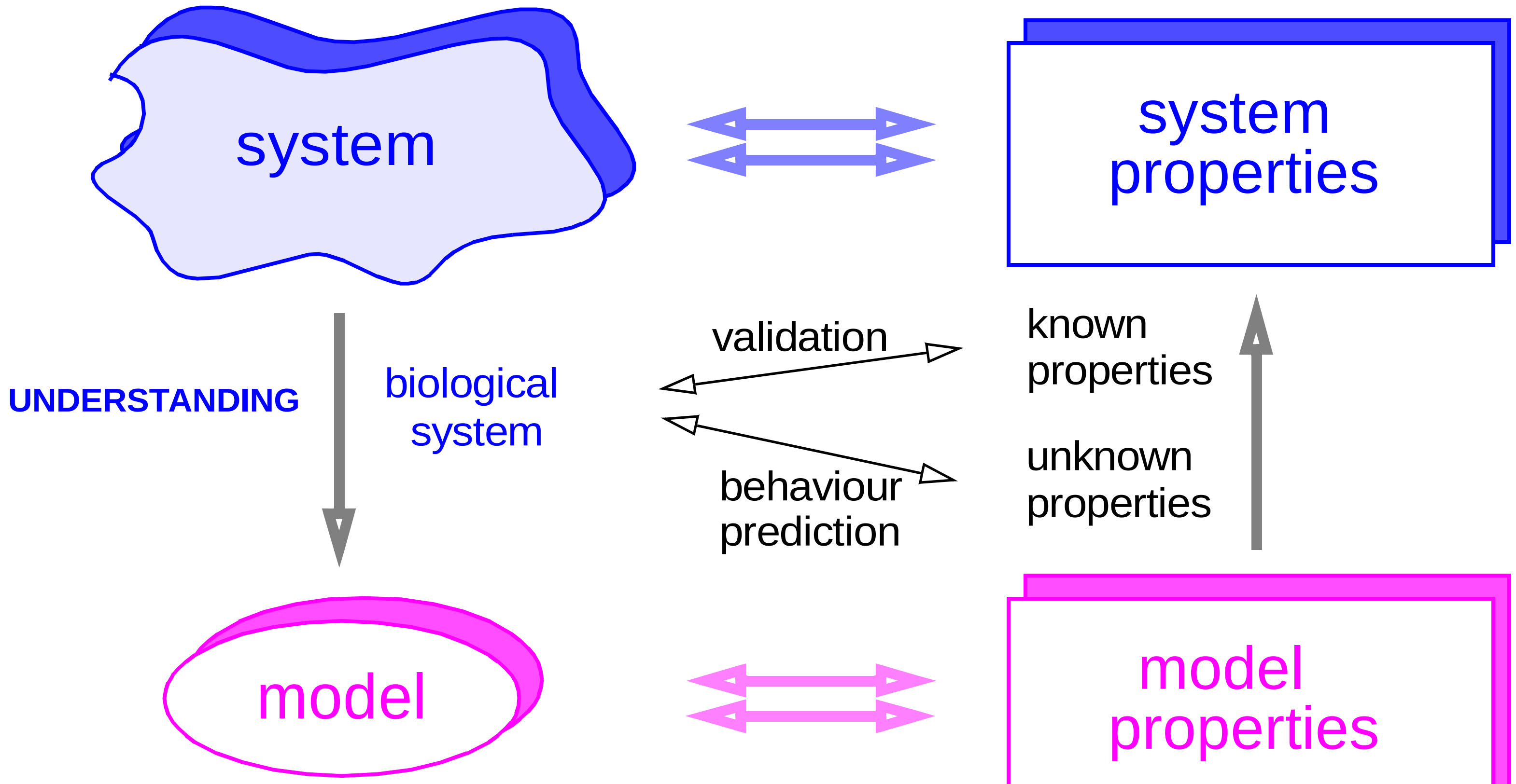

system
system properties
model
model properties

MODEL- BASED SYSTEM ANALYSIS

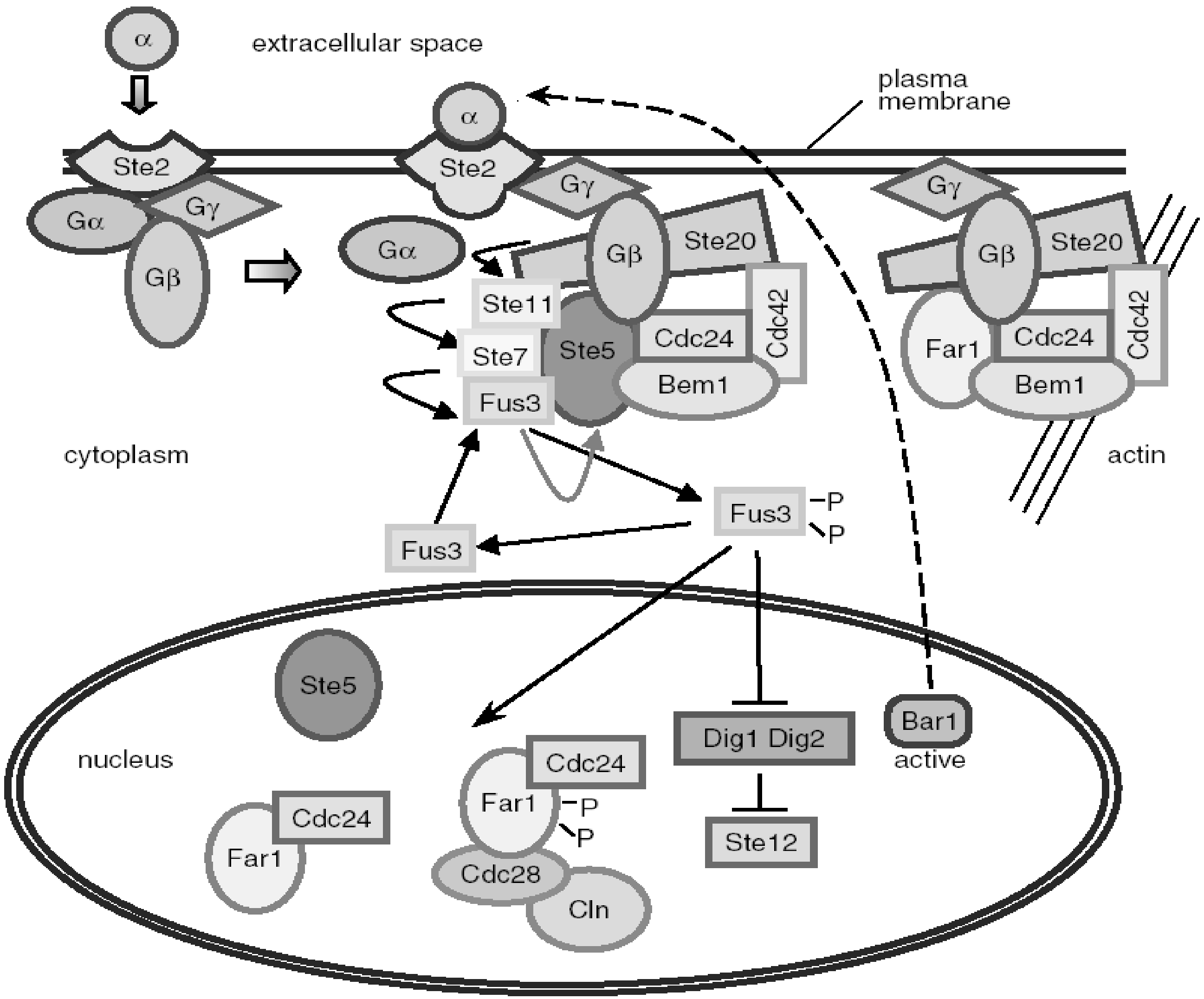




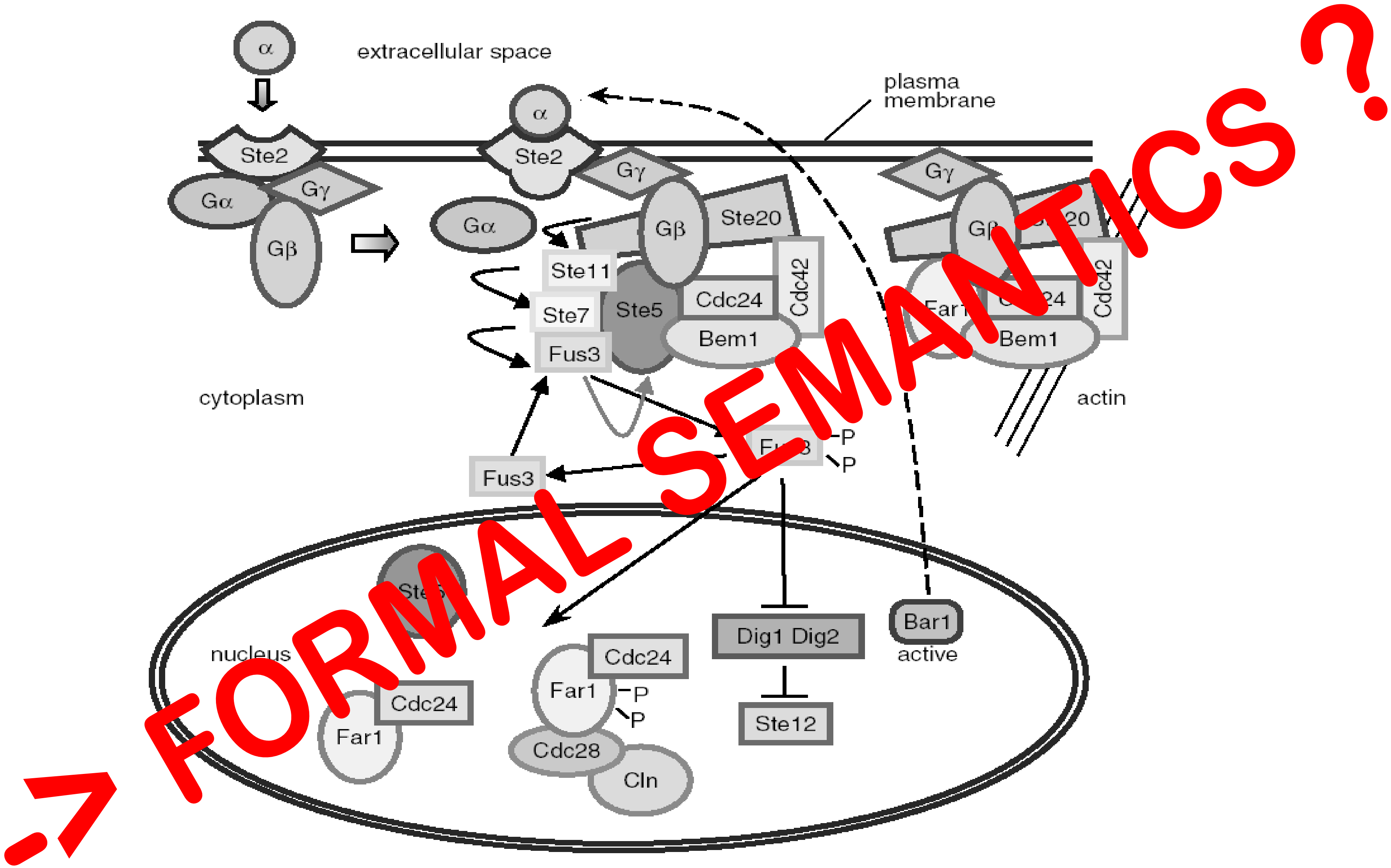
system
system properties
UNDERSTANDING
biological system
validation
behaviour prediction
known properties
unknown properties
model
model properties

WHAT KIND OF MODEL SHOULD BE USED?

NETWORK REPRESENTATIONS, EX1



Network Representations, Ex1



$$\frac{d\alpha}{dt} = -\nu_1$$
$$\frac{dSte2}{dt} = -\nu_2 + \nu_3 - \nu_5$$
$$\frac{dSte2_{active}}{dt} = \nu_2 - \nu_3 - \nu_4$$
$$\frac{dSst2_{active}}{dt} = \nu_{46} - \nu_{47}$$
$$\frac{dG\alpha\beta\gamma}{dt} = -\nu_6 + \nu_9$$
$$\frac{dG\alpha GTP}{dt} = \nu_6 - \nu_7 - \nu_8$$
$$\frac{dG\alpha GDP}{dt} = \nu_7 + \nu_8 - \nu_9$$
$$\frac{dG\beta\gamma}{dt} = \nu_6 - \nu_9 - \nu_{10} + \nu_{11} + \nu_{21} + \nu_{23} + \nu_{25} + \nu_{27} + \nu_{32} - \nu_{42} + \nu_{43}$$
$$\frac{dSte5}{dt} = -\nu_{12} + \nu_{13} + \nu_{17} + \nu_{21} + \nu_{23} + \nu_{25} + \nu_{27} + \nu_{32}$$
$$\frac{dSte11}{dt} = -\nu_{12} + \nu_{13} + \nu_{17} + \nu_{21} + \nu_{23} + \nu_{25} + \nu_{27} + \nu_{32}$$
$$\frac{dSte7}{dt} = -\nu_{14} + \nu_{15} + \nu_{17} + \nu_{21} + \nu_{23} + \nu_{25} + \nu_{27} + \nu_{32}$$
$$\frac{dFus3}{dt} = -\nu_{14} + \nu_{15} + \nu_{17} + \nu_{21} + \nu_{23} + \nu_{25} + \nu_{27} - \nu_{29} + \nu_{30} + \nu_{33}$$
$$\frac{dSte20}{dt} = -\nu_{18} + \nu_{19} + \nu_{21} + \nu_{23} + \nu_{25} + \nu_{27} + \nu_{32}$$

$$\nu_1 = \alpha[t] \cdot Bar1_{active}[t] \cdot k_1$$
$$\nu_2 = Ste2[t] \cdot \alpha[t] \cdot k_2$$
$$\nu_3 = Ste2_{active}[t] \cdot k_3$$
$$\nu_4 = Ste2_{active}[t] \cdot k_4$$
$$\nu_5 = Ste2[t] \cdot k_5$$
$$\nu_6 = Ste2_{active}[t] \cdot G\alpha\beta\gamma[t] \cdot k_6$$
$$\nu_7 = G\alpha GTP[t] \cdot k_7$$
$$\nu_8 = G\alpha GTP[t] \cdot Sst2_{active}[t] \cdot k_8$$
$$\nu_9 = G\alpha GDP[t] \cdot G\beta\gamma[t] \cdot k_9$$
$$\nu_{10} = G\beta\gamma[t] \cdot C[t] \cdot k_{10}$$
$$\nu_{11} = D[t] \cdot k_{11}$$
$$\nu_{12} = Ste5[t] \cdot Ste11[t] \cdot k_{12}$$
$$\nu_{13} = A[t] \cdot k_{13}$$
$$\nu_{14} = Ste7[t] \cdot Fus3[t] \cdot k_{14}$$
$$\nu_{15} = B[t] \cdot k_{15}$$
$$\nu_{16} = A[t] \cdot B[t] \cdot k_{16}$$
$$\nu_{17} = C[t] \cdot k_{17}$$
$$\nu_{18} = D[t] \cdot Ste20[t] \cdot k_{18}$$

NETWORK REPRESENTATIONS, EX2

$$\frac{d\alpha}{dt} = -\nu_1$$
$$\frac{dSte2}{dt} = -\nu_2 + \nu_3 - \nu_5$$
$$\frac{dSte2_{active}}{dt} = \nu_2 - \nu_3 - \nu_4$$
$$\frac{dSst2_{active}}{dt} = \nu_{46} - \nu_{47}$$
$$\frac{dG\alpha\beta\gamma}{dt} = -\nu_6 + \nu_9$$
$$\frac{dG\alpha GTP}{dt} = \nu_6 - \nu_7 - \nu_8$$
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$$\frac{dG\beta\gamma}{dt} = \nu_6 - \nu_9 - \nu_{10} + \nu_{11} + \nu_{21} + \nu_{23} + \nu_{25} + \nu_{27} + \nu_{32} - \nu_{42} + \nu_{43}$$
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$$\frac{dFus3}{dt} = -\nu_{14} + \nu_{15} + \nu_{17} + \nu_{21} + \nu_{23} + \nu_{25} + \nu_{27} - \nu_{29} + \nu_{30} + \nu_{33}$$
$$\frac{dSte20}{dt} = -\nu_{18} + \nu_{19} + \nu_{21} + \nu_{23} + \nu_{25} + \nu_{27} + \nu_{32}$$

$$\nu_1 = \alpha[t] \cdot Bar1_{active}[t] \cdot k_1$$
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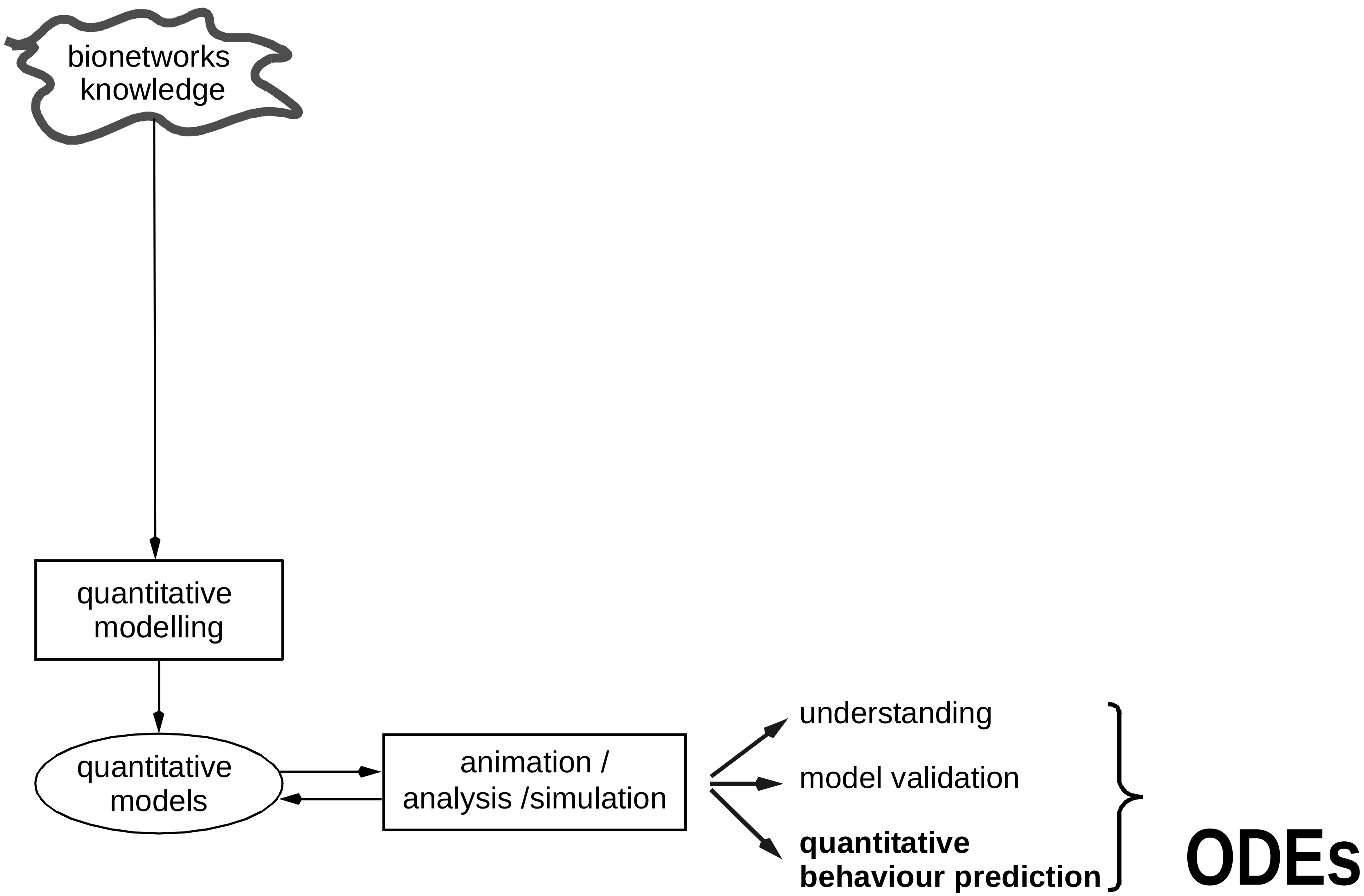
$$\nu_{17} = C[t] \cdot k_{17}$$
$$\nu_{18} = D[t] \cdot Ste20[t] \cdot k_{18}$$

-> READABILITY ?

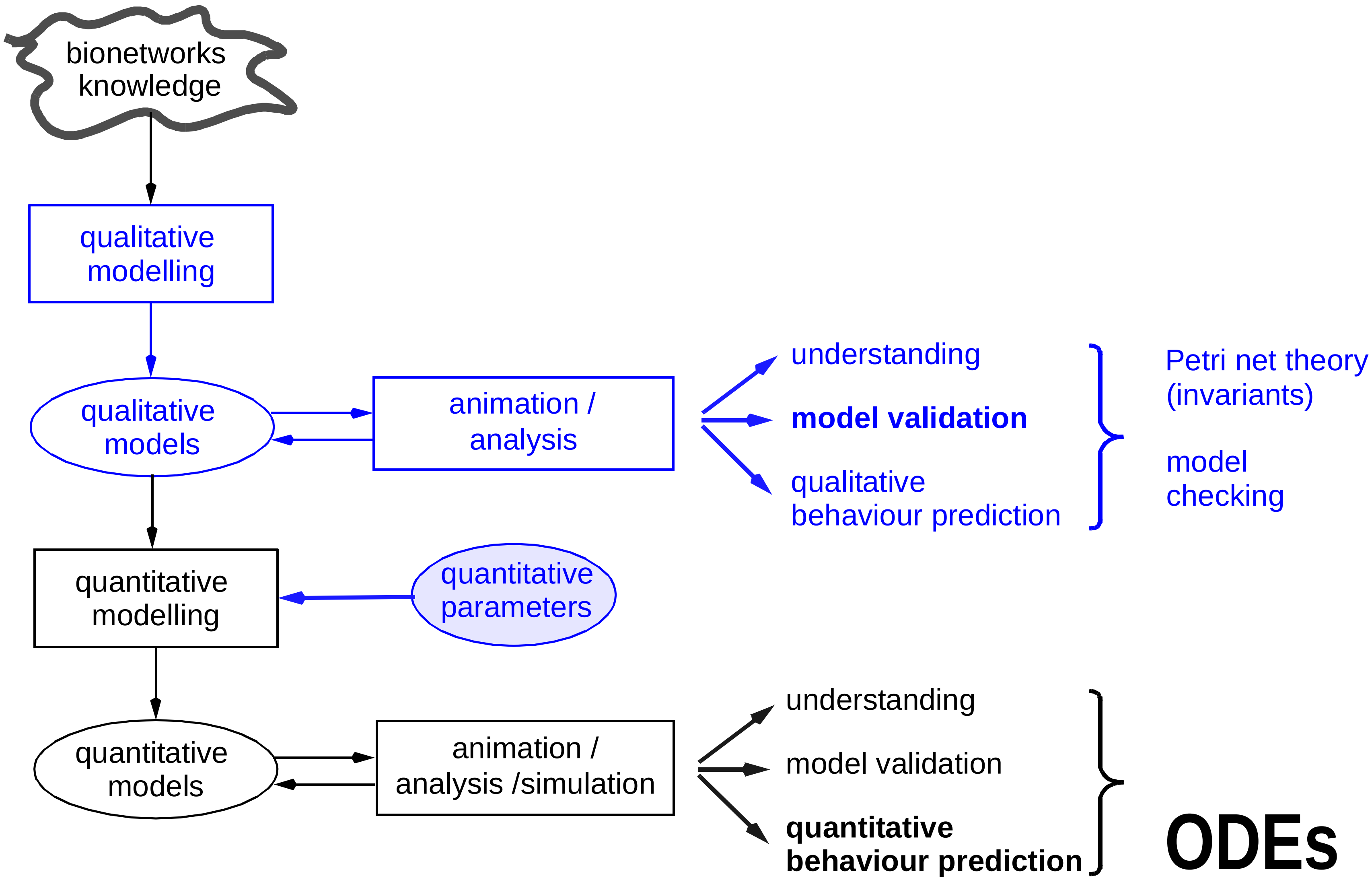
BIONETWORKS, SOME PROBLEMS

- **various, mostly ambiguous representations** *-> PROBLEM 1*
  - -> *verbose descriptions*
  - -> *diverse graphical representations*
  - -> *contradictory and / or fuzzy statements*
- **knowledge** *-> PROBLEM 2*
  - -> *uncertain*
  - -> *growing, changing*
  - -> *distributed over various data bases, papers, journals, . . .*
- **network structures** *-> PROBLEM 3*
  - -> *tend to grow fast*
  - -> *dense, apparently unstructured*
  - -> *hard to read*

- - >> models are full of ASSUMPTIONS << - -


bionetworks knowledge
quantitative modelling
quantitative models
animation / analysis /simulation
understanding
model validation
quantitative behaviour prediction
ODEs

FRAMEWORK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model checking
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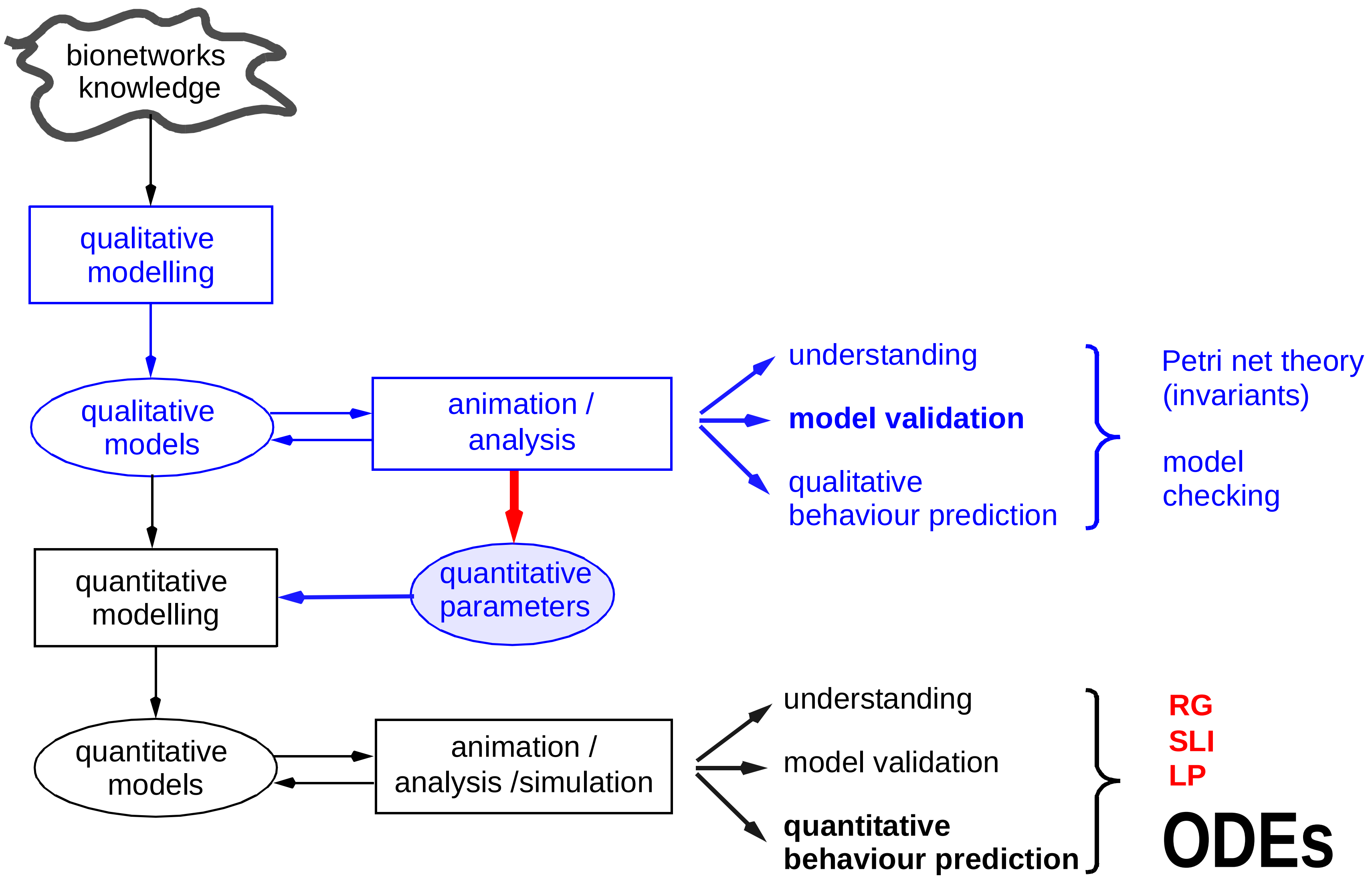
quantitative behaviour prediction
ODEs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animation / analysis /simulation
understanding
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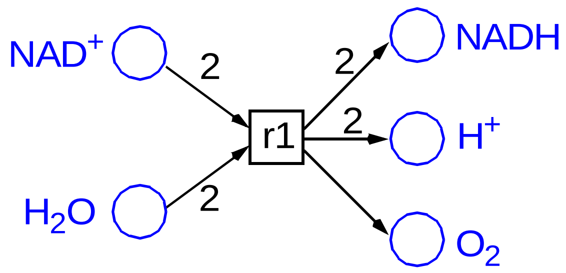
quantitative behaviour prediction
RG
SLI
LP
ODEs

PETRI NETS -
AN INFORMAL CRASH COURSE

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

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

input compounds



output compounds

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

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

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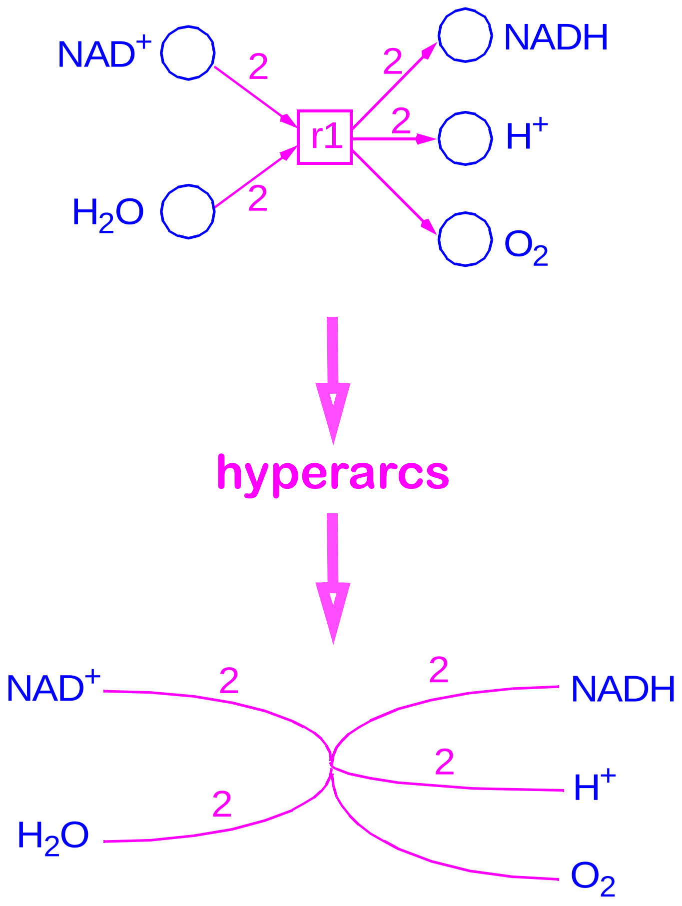
output compounds

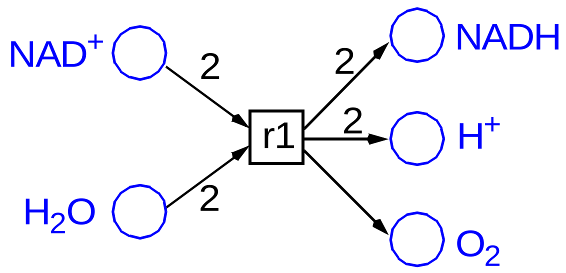


- **atomic actions -> Petri net transitions -> chemical reactions**

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

input compounds

pre-conditions



output compounds

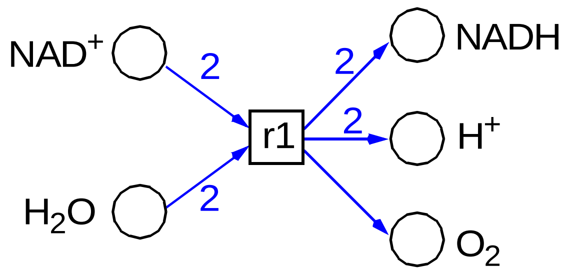
post-conditions

- **local conditions -> Petri net places -> chemical compounds**

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

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

input compounds



output compounds

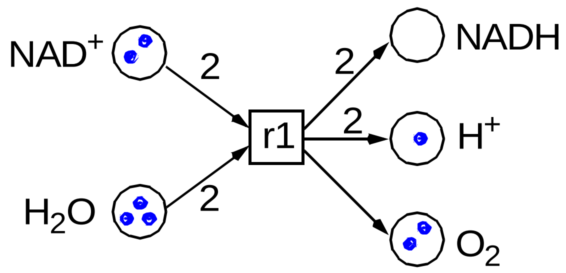
- **local conditions -> Petri net places -> chemical compounds**
- **multiplicities -> Petri net arc weights -> stoichiometric relations**

Petri Nets, Basics - the Structure

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

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

input compounds



output compounds

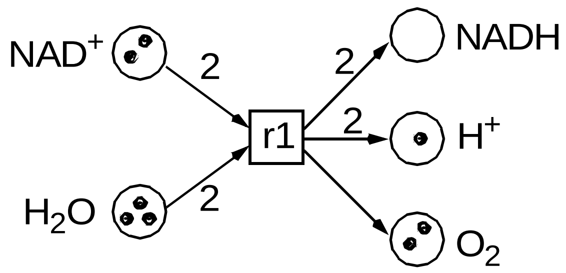
- **local conditions -> Petri net places -> chemical compounds**
- **multiplicities -> Petri net arc weights -> stoichiometric relations**
- **condition's state -> token(s) in its place -> available amount (e.g. mol)**
- **system state -> marking -> compounds distribution**

PETRI NETS, BASICS - THE STRUCTURE

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

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

input compounds



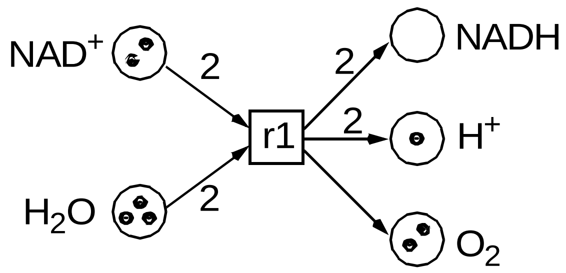
output compounds

- **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**

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

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

input compounds



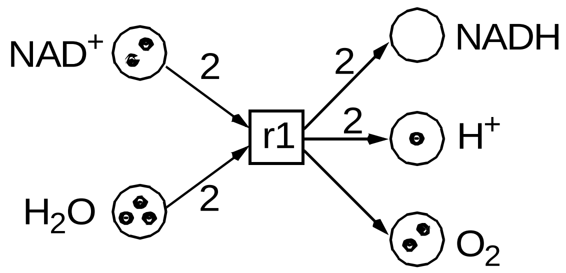
output compounds

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

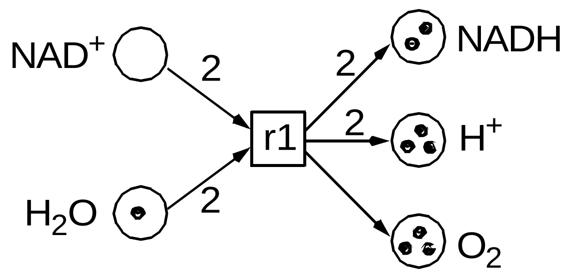
$$2\ NAD^+ + 2\ H_2O \rightarrow 2\ NADH + 2\ H^+ + O_2$$

input compounds

output compounds



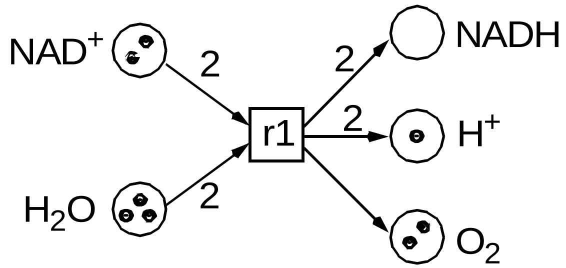
FIRING



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

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

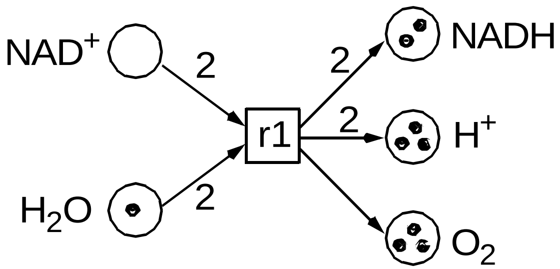
input compounds



output compounds

FIRING

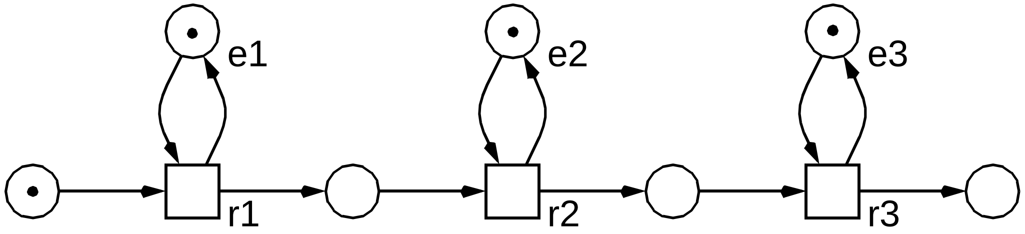
TOKEN GAME



DYNAMIC BEHAVIOUR (substance flow)

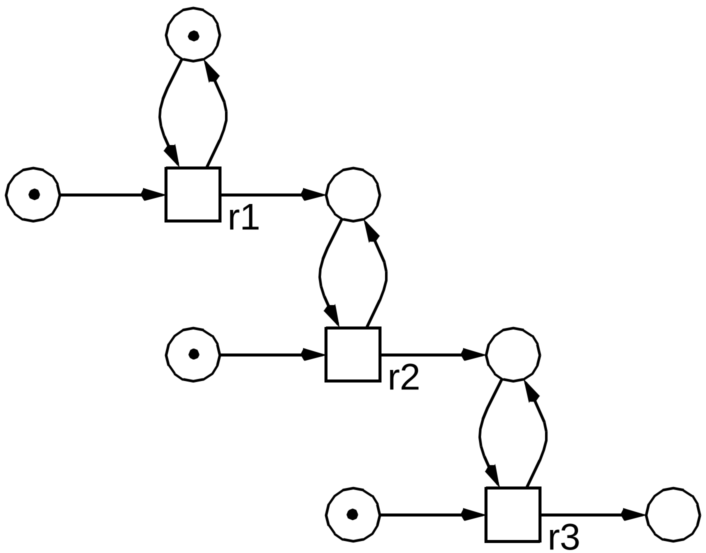
- **metabolic networks**

  -> substance flows

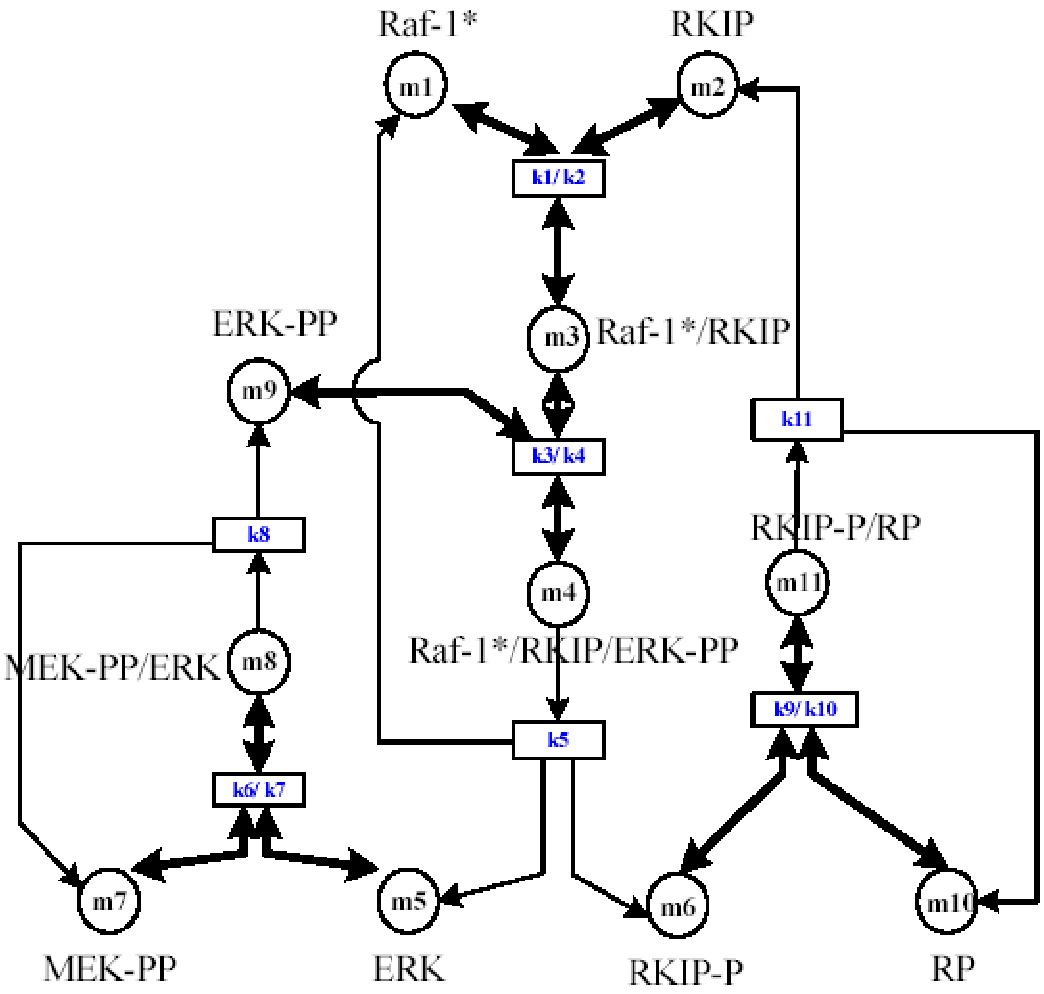


- **signal transduction networks**

  -> signal flows

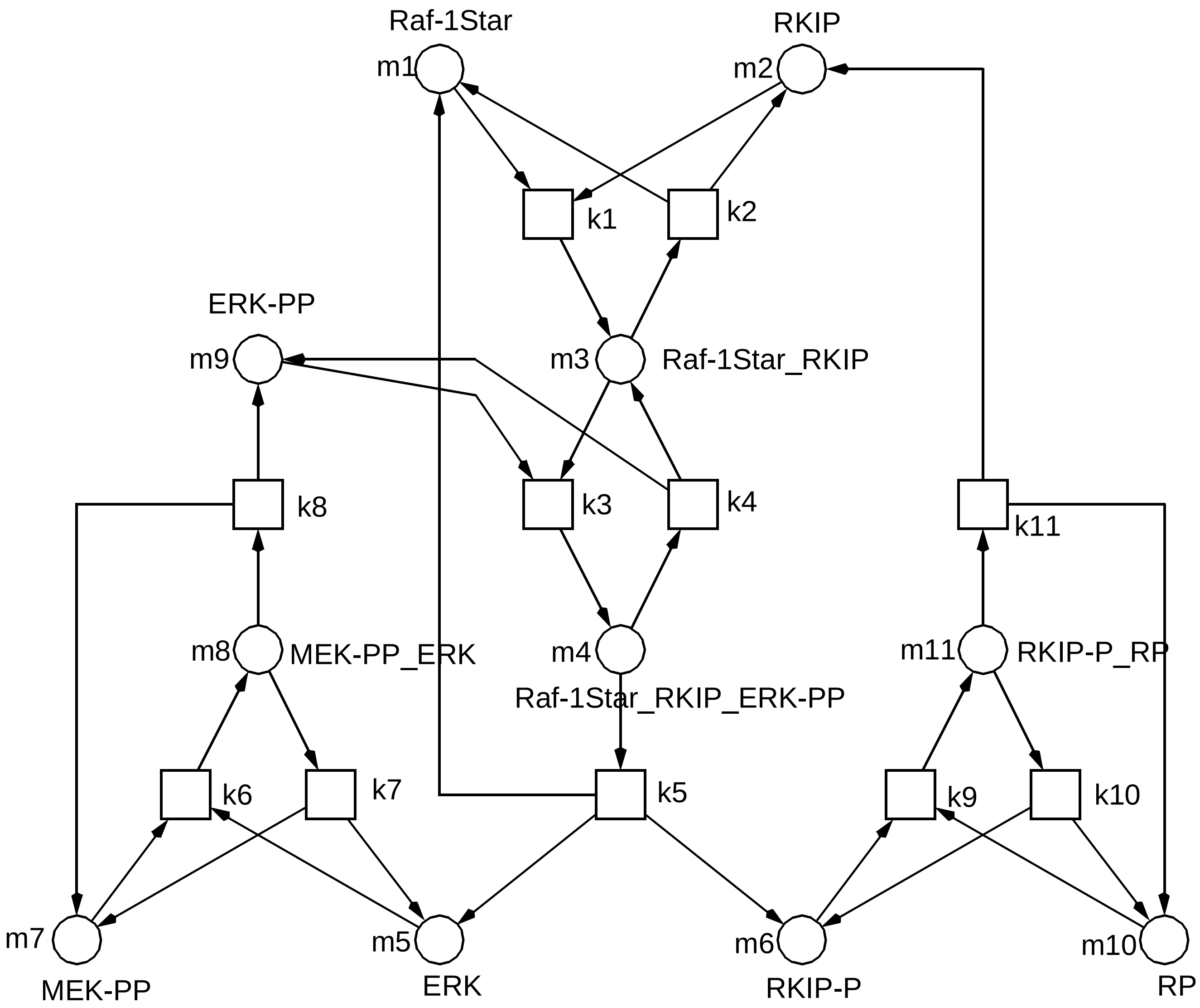


THE RUNNING EXAMPLE - THE RKIP PATHWAY

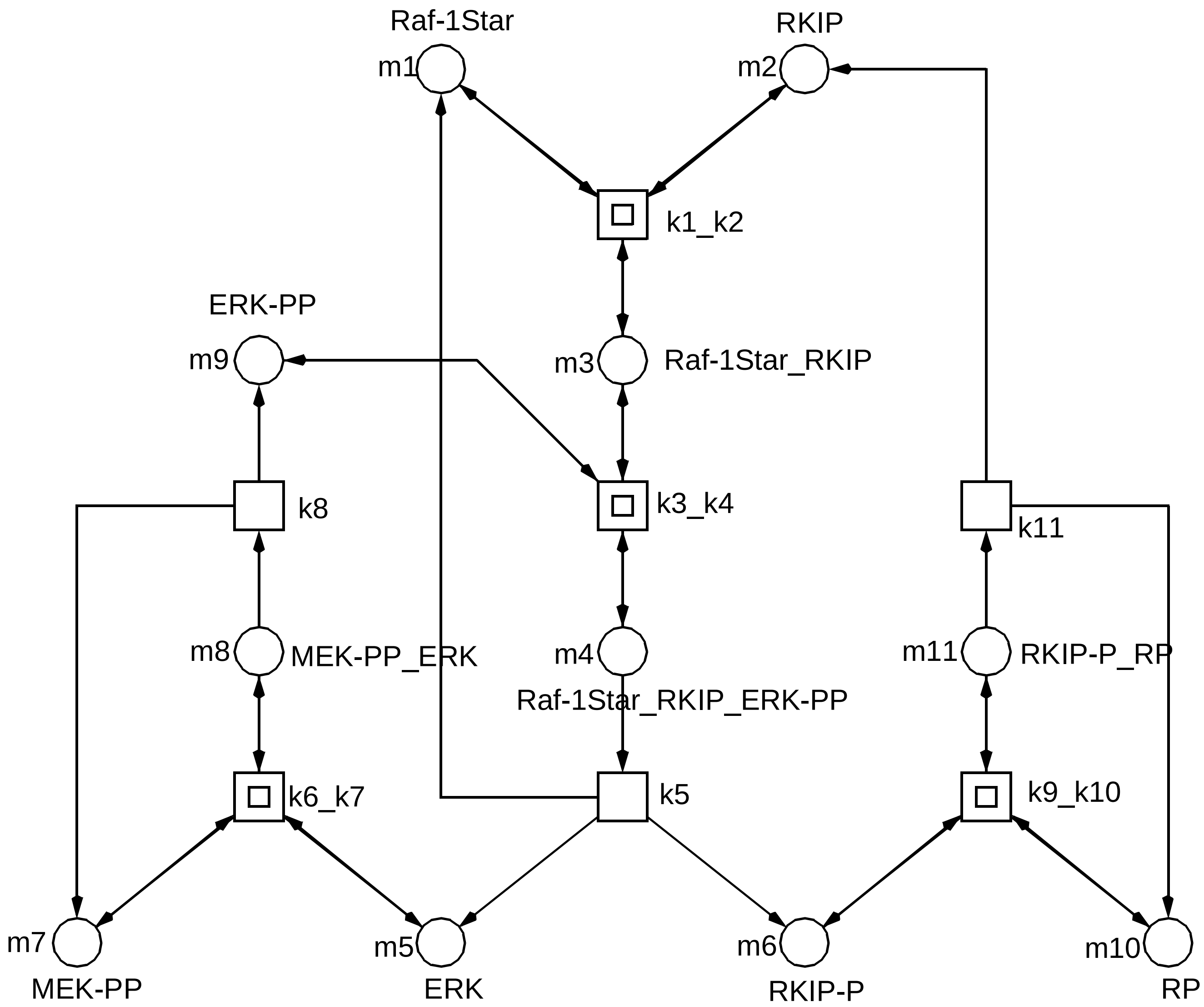


[Cho et al., CMSB 2003]

THE RKIP PATHWAY, PETRI NET

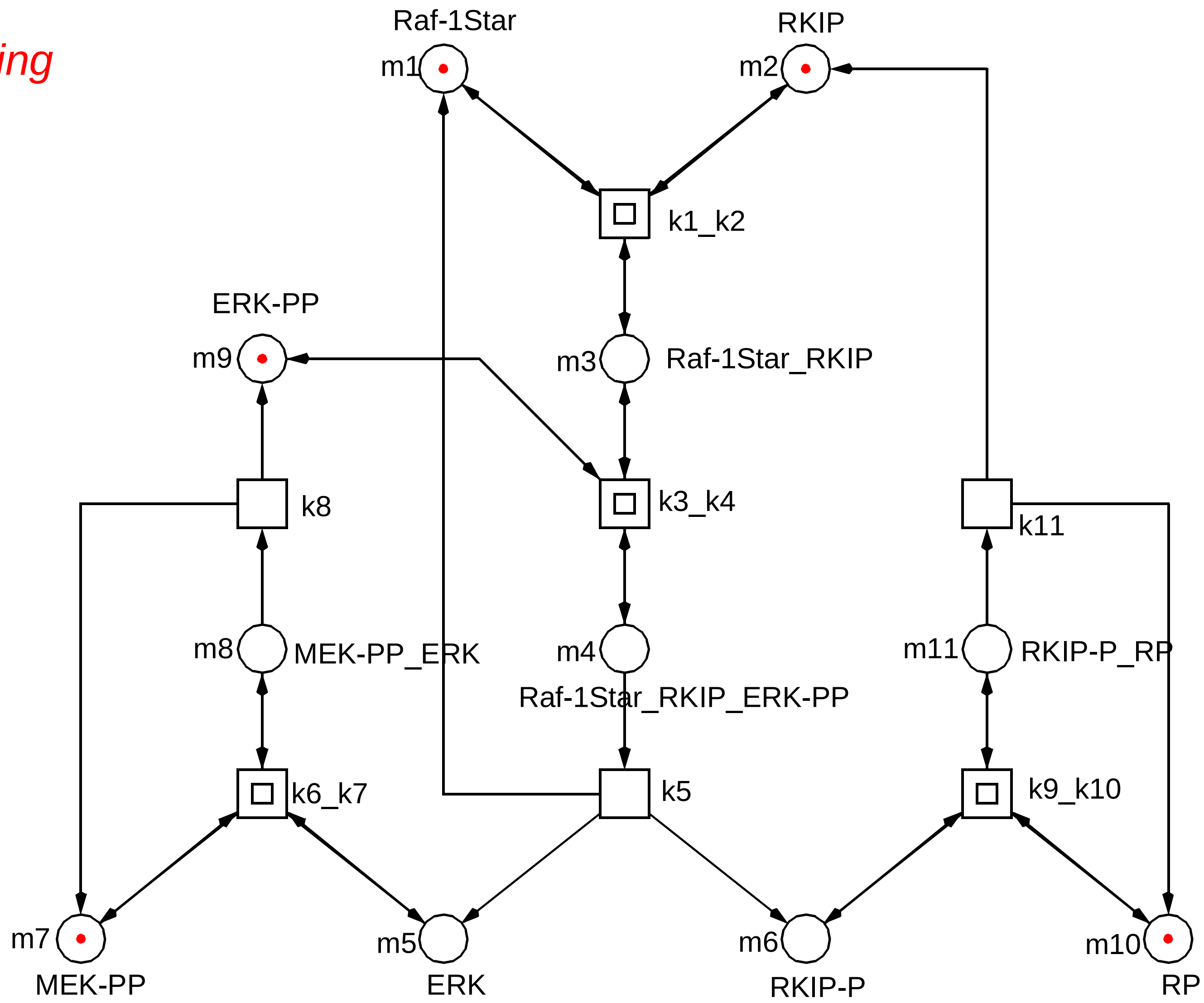


THE RKIP PATHWAY, HIERARCHICAL PETRI NET



The RKIP Pathway, Hierarchical Petri Net

initial marking



BIOCHEMICAL PETRI NETS, SUMMARY

- **biochemical networks**

  -> *networks of (abstract) chemical reactions*

- **biochemically interpreted Petri net**

  -> *partial order sequences of chemical reactions (= elementary actions)*
  transforming input into output compounds / signals
  [respecting the given stoichiometric relations, if any]

  -> *set of all pathways*
  from the input to the output compounds / signals
  [respecting the stoichiometric relations, if any]

- **pathway**

  -> *self-contained partial order sequence of elementary (re-) actions*

- **typical basic assumption**

  -> *steady state behaviour*

QUALITATIVE ANALYSES

ANALYSIS TECHNIQUES, OVERVIEW

- **static analyses** -> **no state space construction**
  - -> *structural properties (graph theory)*
  - -> *P / T - invariants (linear algebra),*

- **dynamic analyses** -> **total/partial state space construction (RG)**

  -> *analysis of general behavioural system properties,*

  e.g. boundedness, liveness, reversibility, . . .

  -> *model checking of special behavioural system properties,*
  e.g. reachability of a given (sub-) system state [with constraints],
  reproducability of a given (sub-) system state [with constraints]

  expressed in temporal logics (CTL / LTL),
  very flexible, powerful querry language

INCIDENCE MATRIX C

- a representation of the net structure **=> stoichiometric matrix**

$C =$

P \ T	t1 . . .	tj	. . . tm
p1			
pi		cij	
: pn		Δtj	

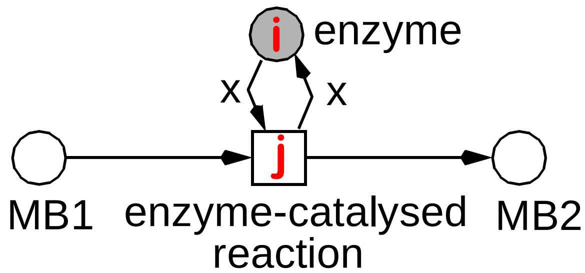
cij = (pi, tj) = F(tj,pi) - F(pi, tj) = Δ tj(pi)

Δtj = Δ tj(*)

- **matrix entry cij:**
  token change in place pi by firing of transition tj

- **matrix column Δtj:**
  vector describing the change of the whole marking by firing of tj

- **side-conditions are neglected**



cij = 0

T-INVARIANTS, BASICS

- **Lautenbach, 1973**

- **T-invariants** -> *multisets of transitions*
  - -> *integer solutions x of* $Cx = 0, x \neq 0, x \geq 0$ -> *Parikh vector*

- **minimal T-invariants**
  - -> *there is no T-invariant with a smaller support* -> *sets of transitions*
  - -> *gcD of all entries is 1*

- **any T-invariant is a non-negative linear combination of minimal ones**
  - -> *multiplication with a positive integer*
  - -> *addition*
  - -> *Division by gcD*

$$kx = \sum_i a_i x_i$$

- **Covered by T-Invariants (CTI)**
  - -> *each transition belongs to a T-invariant*
  - -> *BND & LIVE => CTI (necessary condition)*

T-INVARIANTS, INTERPRETATION

- **T-invariants = (multi-) sets of transitions**
  - -> *zero effect on marking*
  - -> *reproducing a marking / system state*
  - -> *steady state substance flows / reaction rates*
  - -> *elementary modes [Schuster 1993]*

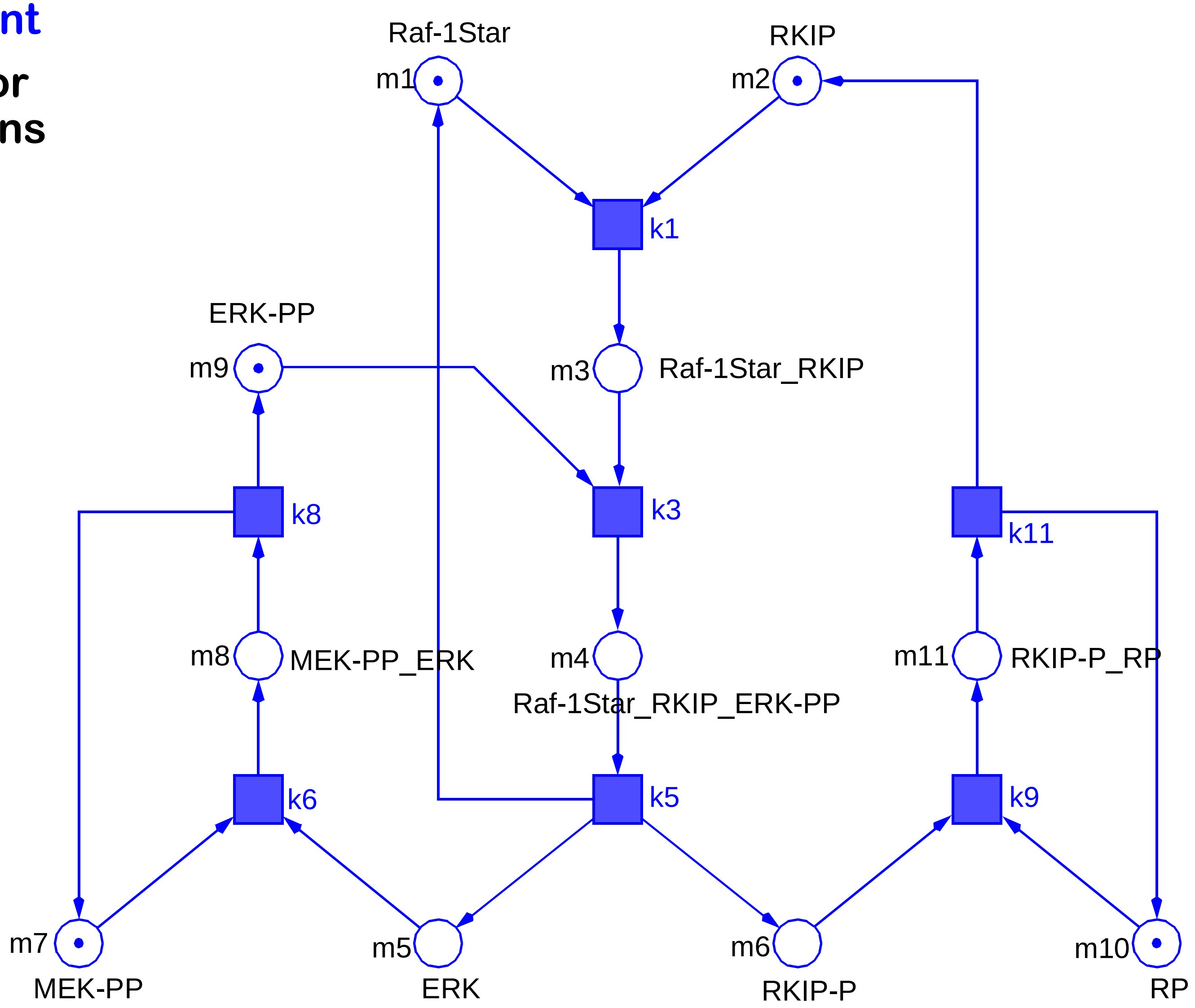
- **realizable T-invariants correspond to cycles in the RG**
  - -> *RG: concurrent transitions -> all transitions' interleaving sequences*
  - -> *if there are concurrent transitions in a realizable T-invariant,*
    then there is a RG cycle for each interleaving sequence
  - -> *analogously for conflicts*

- **a T-invariant defines a subnet** **-> partial order structure**
  - -> *the T-invariant's transitions (the support),*
    + all their pre- and post-places
    + the arcs in between
  - -> *pre-sets of supports = post-sets of supports*

T-INVARIANTS, THE RKIP PATHWAY

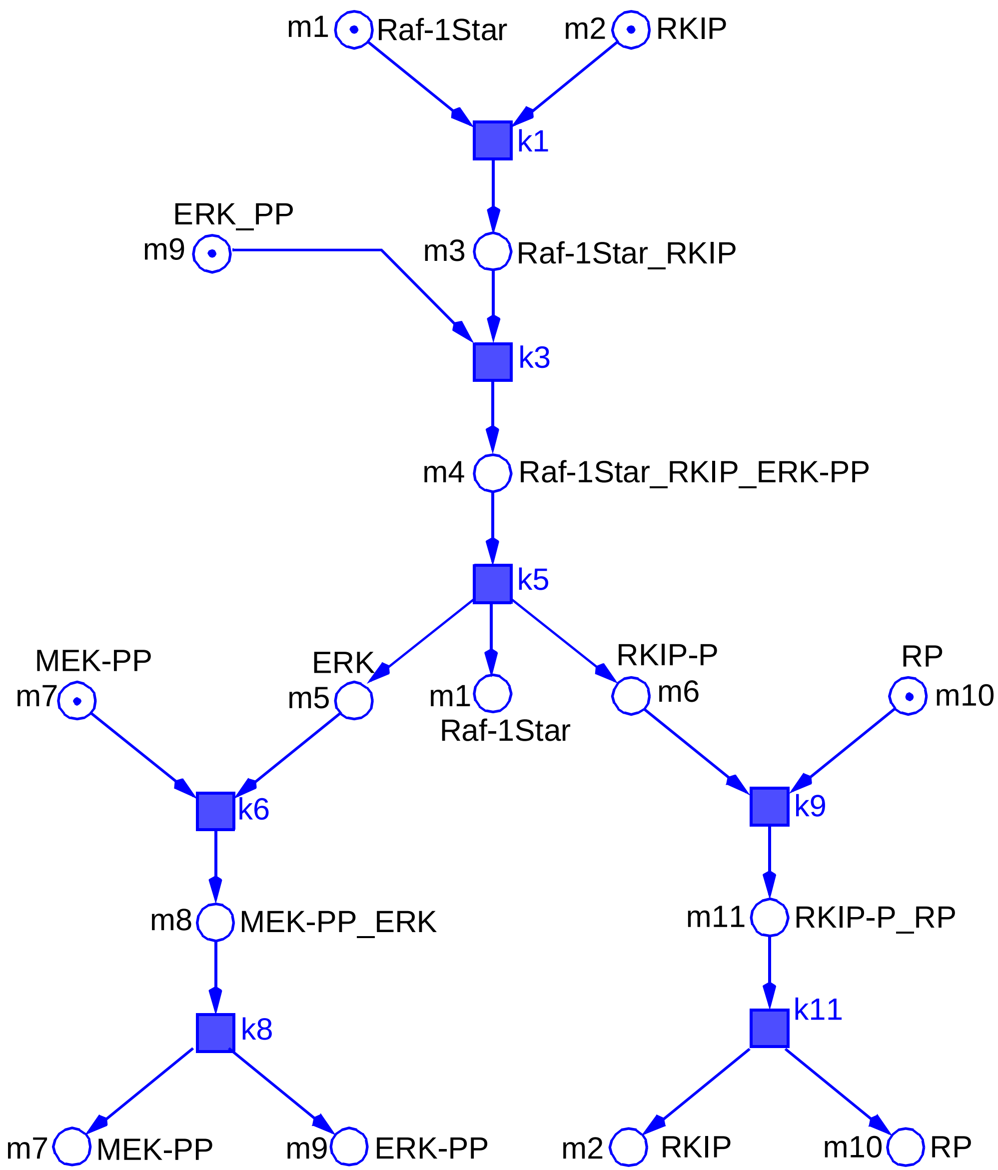
-> non-trivial T-invariant

+ four trivial ones for reversible reactions



Run of the Non-trivial T-invariant

- **partial order structure**
- **T-invariant's unfolding to describe its behaviour**
- **labelled condition / event net**
  - -> *events*
    - transition occurences
  - -> *conditions*
    - input / output compounds
- **partial order semantics**
  - -> *a net's all partial order runs*



- **Lautenbach, 1973**

- **P-invariants** -> *multisets of places*
  - -> *integer solutions y of* $yC = 0, y \neq 0, y \geq 0$

- **minimal P-invariants**
  - -> *there is no P-invariant with a smaller support* -> *sets of places*
  - -> *gcD of all entries is 1*

- **any P-invariant is a non-negative linear combination of minimal ones**
  - -> *multiplication with a positive integer*
  - -> *addition*
  - -> *Division by gcD*

  $$ky = \sum_i a_i y_i$$

- **Covered by P-Invariants (CPI)**
  - -> *each transition belongs to a P-invariant*
  - -> *CPI => BND (sufficient condition)*

- **the firing of any transition has no influence on the weighted sum of tokens on the P-invariant's places**

  -> *for all t: the effect of the arcs, removing tokens from a P-invariant's place is equal to the effect of the arcs, adding tokens to a P-invariant's place*

- **set of places with**

  -> *a constant weighted sum of tokens for all markings m reachable from m_0*

  $$ym = ym_0$$

  -> *token / compound preservation*

- **a place belonging to a P-invariant is bounded**

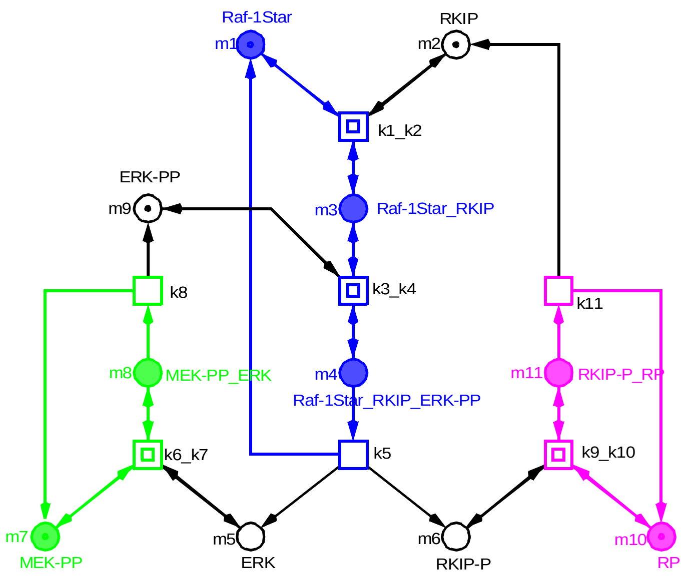
  -> *CPI - sufficient condition for BND*

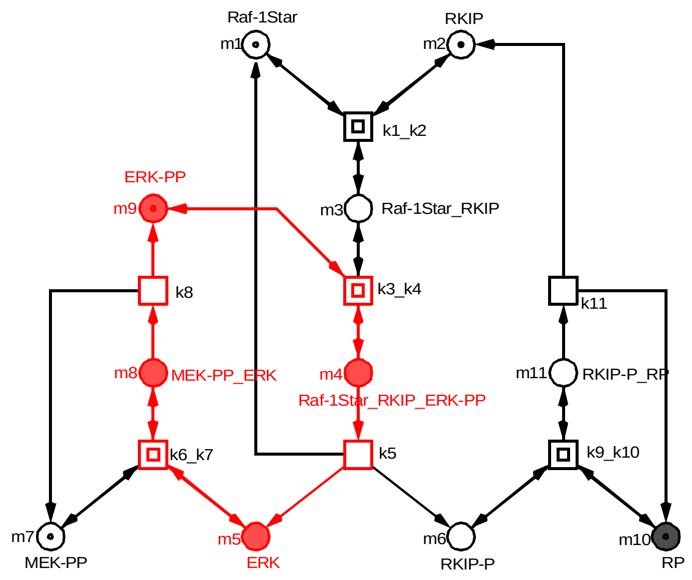
- **a P-invariant defines a subnet**

  -> *the P-invariant's places (the support),*
  + all their pre- and post-transitions
  + the arcs in between

  -> *pre-sets of supports = post-sets of supports*

P-INVARIANTS, THE RKIP PATHWAY





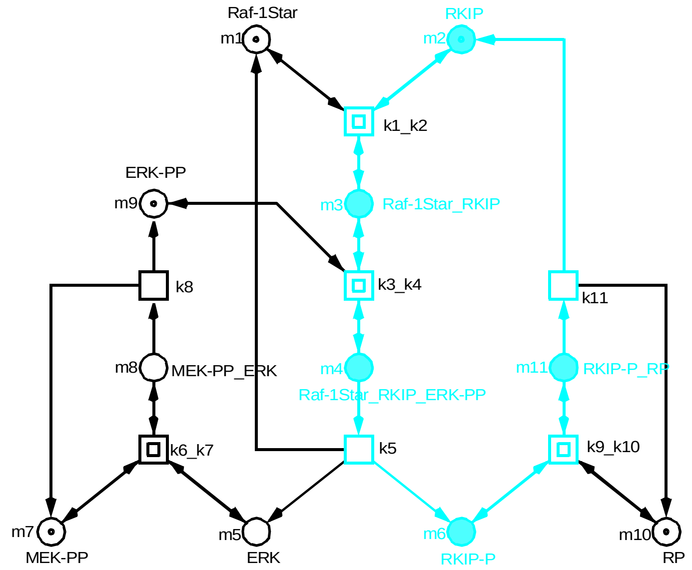
P-INV1: MEK

P-INV2: RAF-1STAR

P-INV3: RP

P-INV4: ERK

P-INV5: RKIP



CONSTRUCTION OF THE INITIAL MARKING

- **each P-invariant gets at least one token**
  -> *P-invariants are structural deadlocks and traps*
- **all (non-trivial) T-invariants get realizable**
  -> *to make the net live*
- **minimal marking**
  -> *minimization of the state space*
- **assumption: top-to-bottom reading of the figure**
  -> *but, all reachable markings are equivalent*
  (= produce same state space)

-> UNIQUE INITIAL MARKING

- **structural properties**

INA

ORD	HOM	NBM	PUR	CSV	SCF	CON	SC	Ft0	tF0	Fp0	pF0	MG	SM	FC	EFC	ES
Y	Y	Y	Y	N	N	Y	Y	N	N	N	N	N	N	N	N	Y

DTP	CPI	CTI	B	SB	REV	DSt	BSt	DTr	DCF	L	LV	L&S
Y	Y	Y	Y	Y	Y	N	?	N	N	Y	Y	Y

- **CPI**
  - -> *structural bounded (SB)*
  - -> *each P-invariant represents a substance conservation subnet (cycle)*

- **CTI**
  - -> *Live & BND -> CTI*
  - -> *4 trivial T-invariants for reversible reactions*
  - -> *1 non-trivial T-invariant describing the essential cyclic behaviour*

- **DTP & ES -> Live**

Dynamic Analysis - Reachability Graph

- **simple construction algorithm**
  - *-> nodes - system states*
  - *-> arcs - the (single) firing transition* *-> single step firing rule*
- **unbounded Petri net -> infinite RG**
  bounded Petri net -> finite RG
- **concurrency**
  - *-> enumeration of all interleaving sequences* *-> interleaving semantics*
- **branching arcs in the RG**
  - *-> conflict* ***OR*** *concurrency*
- **RG tend to be very large**
  - *-> automatic evaluation necessary* *-> model checking*
- **worst case: over-exponential growth**
  - *-> alternative analyses techniques ?*

MODEL CHECKING, EXAMPLES

- **property 1**

  Is a given (sub-) marking (system state) reachable ?

  *EF (ERK * RP);*

- **property 2**

  Liveness of transition k8 ?

  AG EF (MEK-PP_ERK);

- **property 3**

  Is it possible to produce ERK-PP neither creating nor using MEK-PP ?

  E (! MEK-PP U ERK-PP);

- **property 4**

  Is there cyclic behaviour w.r.t. the presence / absence of RKIP ?

  *EG ((RKIP -> EF (! RKIP)) * (! RKIP -> EF (RKIP)));*

QUALITATIVE ANALYSIS RESULTS, SUMMARY

- **structural decisions of behavioural properties** **-> static analysis**
  - -> *CPI* -> *BND*
  - -> *ES & DTP* -> *LIVE*
- **CPI & CTI**
  - -> *all minimal T-invariant / P-invariants enjoy biological interpretation*
  - -> *non-trivial T-invariant -> partial order description of the essential behaviour*
- **reachability graph** **-> dynamic analysis**
  - -> *finite* -> *BND*
  - -> *the only SCC contains all transitions* -> *LIVE*
  - -> *one Strongly Connected Component (SCC)* -> *REV*
- **model checking** **-> requires professional understanding**
  - -> *all expected properties are valid*

Qualitative Analysis Results, Summary

- **structural decisions of behavioural properties** **-> static analysis**

  -> *CPI* -> *BND*

  -> *ES & DTP* -> *LIVE*

- **CPI & CTI**

  -> *all minimal T-invariant / P-invariants enjoy biological interpretation*

  -> *non-trivial T-invariant -> partial order description of the essential behaviour*

- **reachability graph** **-> dynamic analysis**

  -> *finite* -> *BND*

  -> *the only SCC contains all transitions* -> *LIVE*

  -> *one Strongly Connected Component (SCC)* -> *REV*

- **model checking** **-> requires professional understanding**

  -> *all expected properties are valid*

-> VALIDATED QUALITATIVE MODEL

- **validation criterion 0**
  - -> *all expected structural properties hold*
  - -> *all expected general behavioural properties hold*
- **validation criterion 1**
  - -> *CTI*
  - -> *no minimal T-invariant without biological interpretation*
  - -> *no known biological behaviour without corresponding T-invariant*
- **validation criterion 2**
  - -> *CPI*
  - -> *no minimal P-invariant without biological interpretation (?)*
- **validation criterion 3**
  - -> *all expected special behavioural properties hold*
  - -> *temporal-logic properties -> TRUE*

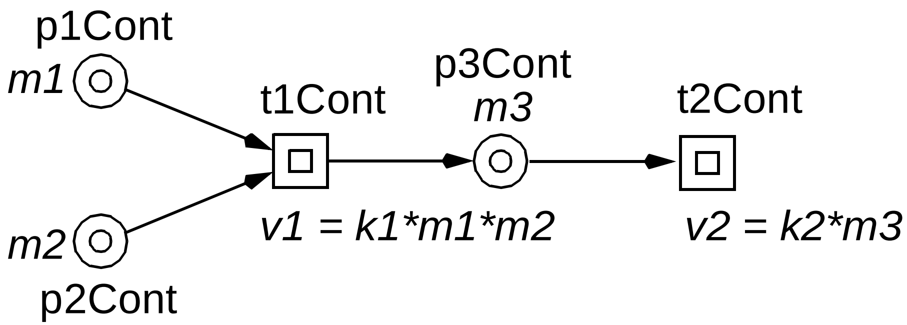
Now we are ready for sophisticated quantitative analyses !

QUANTITATIVE ANALYSIS

- **quantitative model = qualitative model + quantitative parameters**
  -> *BUT: quantitative parameters often unknown*

- **typical quantitative parameters of bionetworks**
  -> *compound concentrations* -> *real numbers*
  -> *reaction rates / fluxes* -> *concentration-dependent*

- **continuous Petri nets**

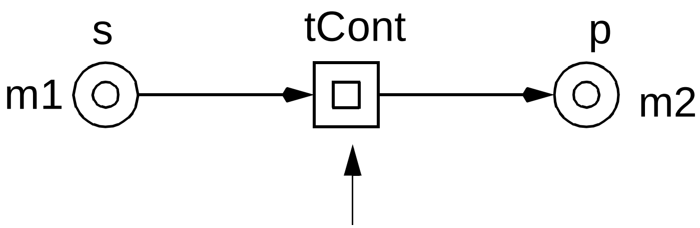


continuous nodes !

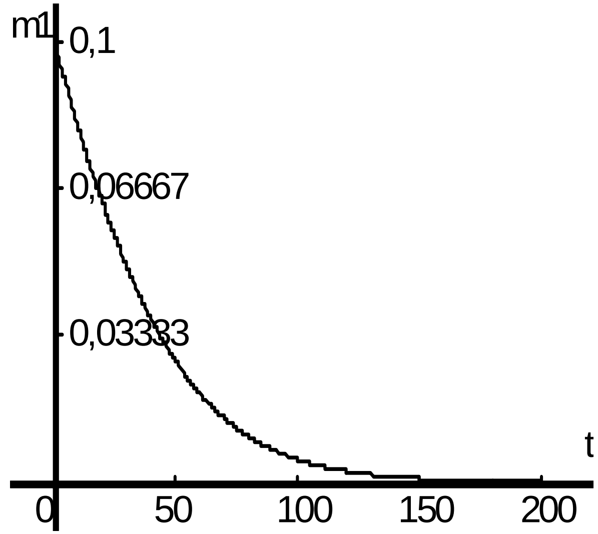
d [p1Cont] / dt = d [p2Cont] / dt = - v1
d [p3Cont] / dt = v1 - v2

ODEs

EXAMPLE - MICHAELIS-MENTEN REACTION

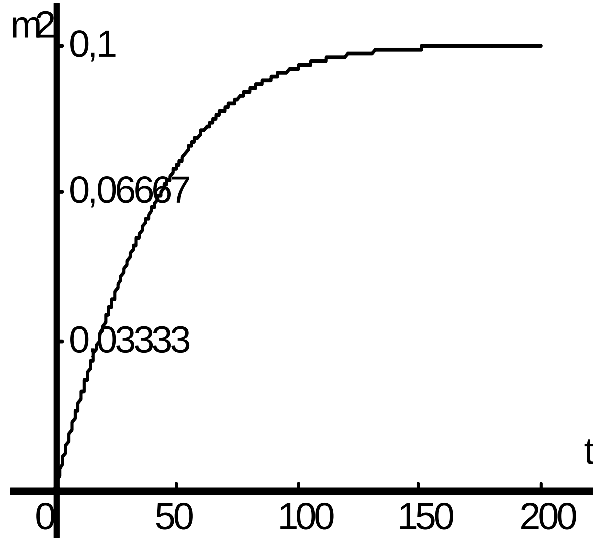


v = 0.005 * m1 / (0.1375 + m1)



Vmax = 0.005 (maximal reaction rate)
Km = 0.1375 (Michaelis constant)

d[s]/dt = d[p]/dt = Vmax*[s]/(Km+[s])
dm1/dt = dm2/dt = Vmax*m1/(Km+m1)



-> Visual Object Nets
-> GON / cell illustrator (?)

THE QUALITATIVE MODEL
BECOMES
THE STRUCTURAL DESCRIPTION
OF THE QUANTITATIVE MODEL !

CHALLENGES

- **extensions**
  - -> *read arcs*
  - -> *inhibitor arcs !?*
  - -> *interleaving / partial order semantics*
  - -> *Turing power !*

- **efficient computation of minimal invariants**
  - -> *exponential complexity*
  - -> *compositional / step-wise refinement approach (under development)*

- **analysis of unbounded nets**
  - -> *besides T-invariant analysis ?*

- **model checking**
  - -> *relevant properties ?*

- **comparision: continuous / hybrid Petri nets <-> ODEs**
  - -> *Petri net simulation versus classical ODEs solver*
  - -> *is there a winner (for certain structures) ?*

SUMMARY

- **representation of bionetworks by Petri nets**
  - -> *partial order representation*
  - -> *formal semantics* -> *various sound analysis techniques*
  - -> *unifying view*
- **purposes**
  - -> *animation* -> *to experience the model*
  - -> *model validation against consistency criteria* -> *to increase confidence*
  - -> *qualitative / quantitative behaviour prediction* -> *new insights*
- **two-step model development**
  - -> *qualitative model* -> *discrete Petri nets*
  - -> *quantitative model* -> *continuous Petri nets = ODEs*
- **many challenging questions for analysis techniques**
  - -> *qualitative as well as quantitative ones*

THANKS !