FROM PETRI NETS TO DIFFERENTIAL EQUATIONS

AN INTEGRATIVE APPROACH FOR BIOCHEMICAL NETWORK ANALYSIS

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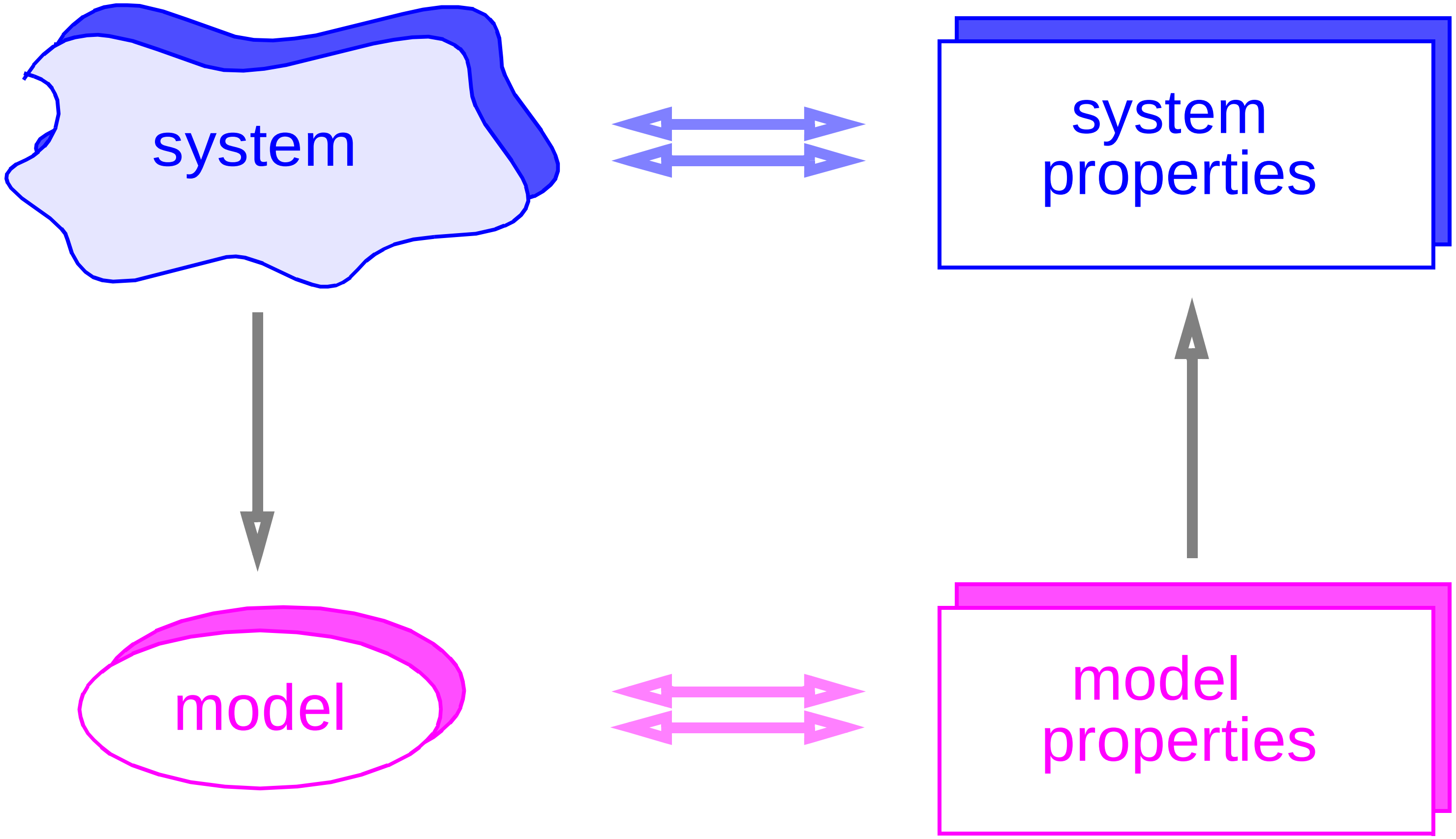
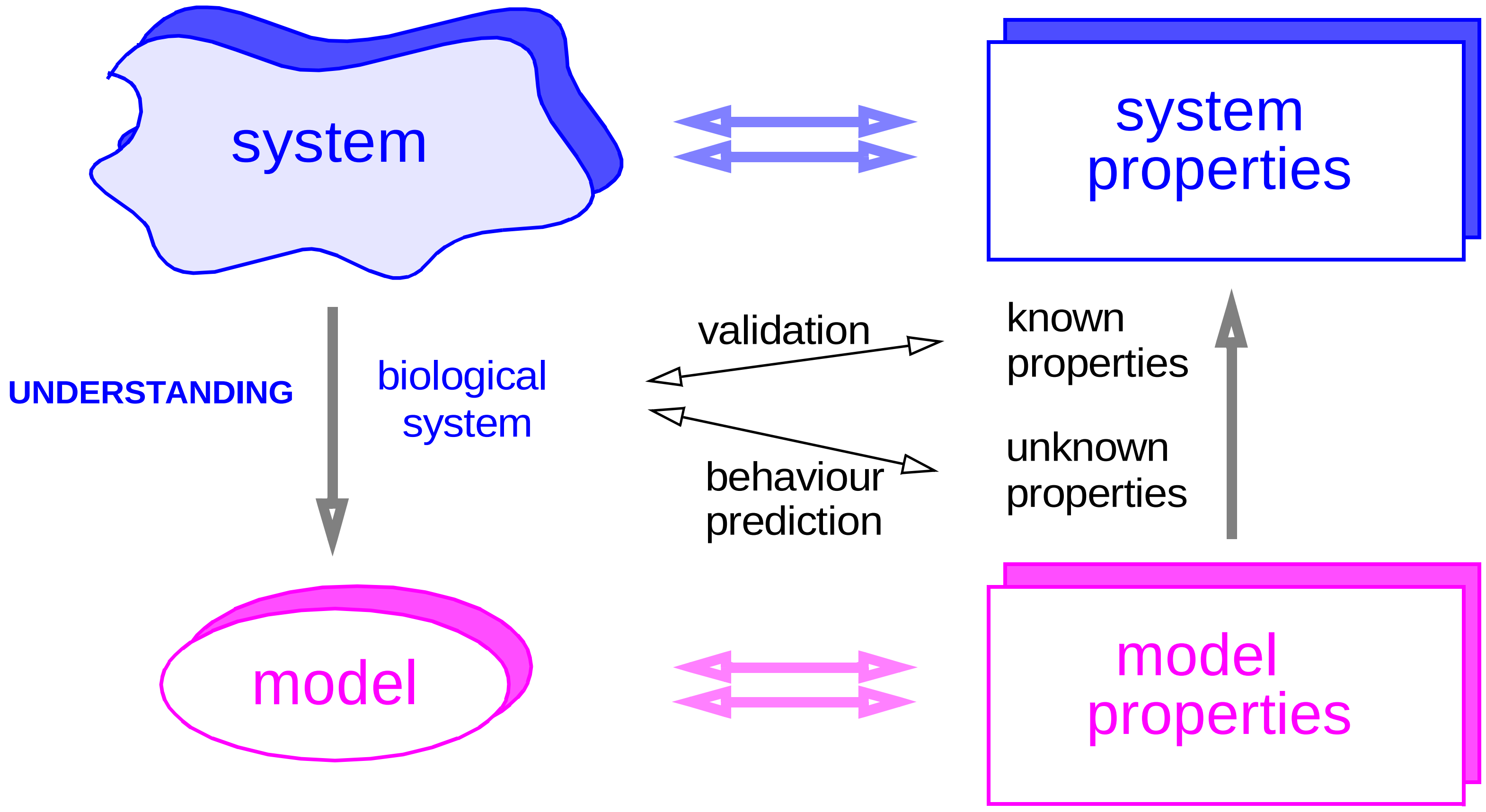
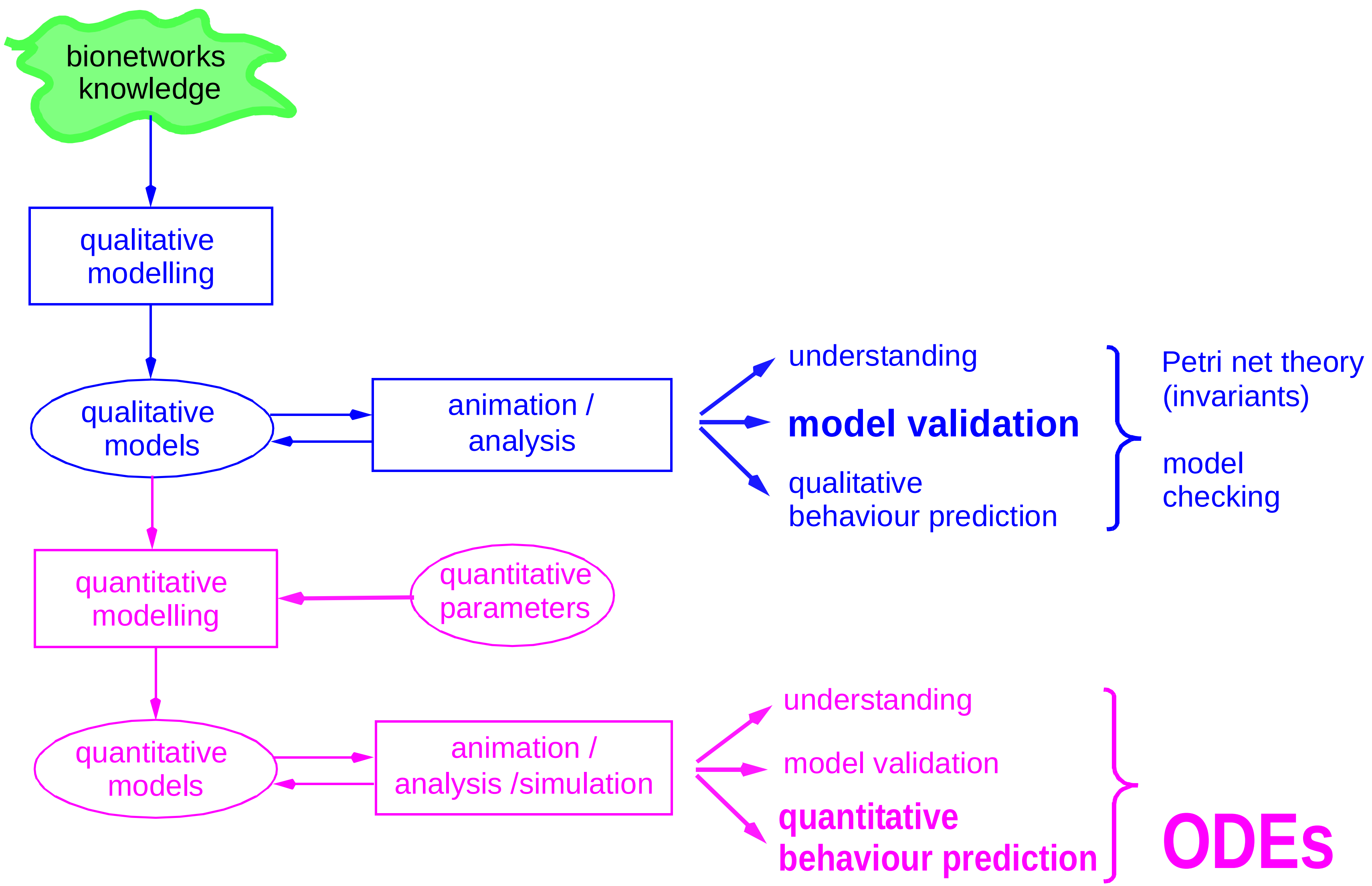

system
system
properties
model
model
properties

MODEL- BASED SYSTEM ANALYSIS



FRAMEWORK


bionetworks knowledge
qualitative modelling
qualitative models
animation / analysis
understanding
model validation
qualitative behaviour prediction
Petri net theory (invariants)
model checking
quantitative modelling
quantitative parameters
quantitative models
animation / analysis /simulation
understanding
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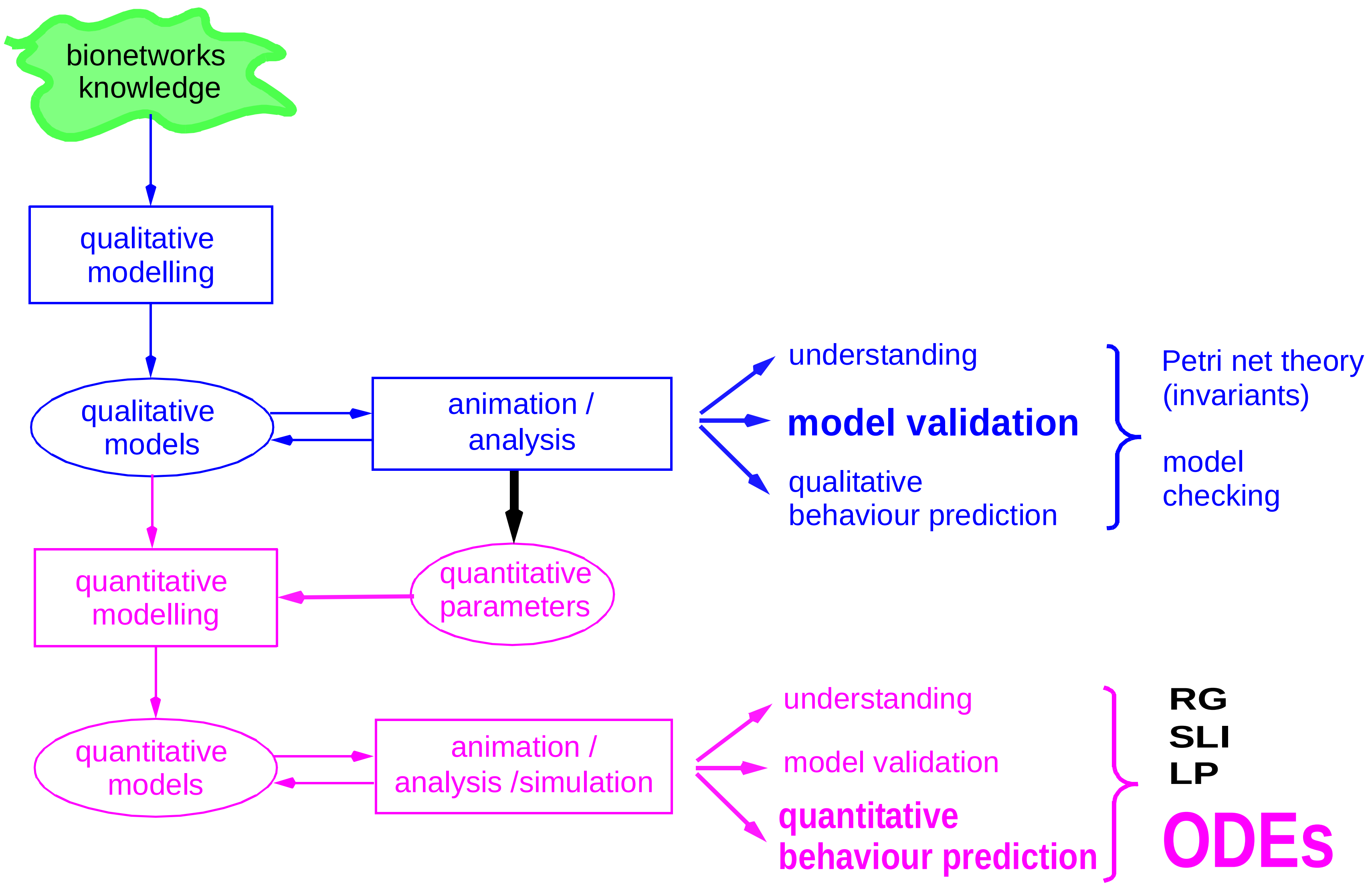
quantitative behaviour prediction
ODEs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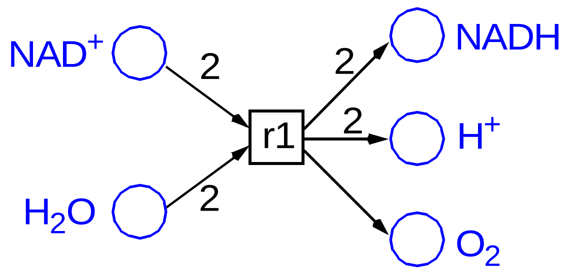
quantitative behaviour prediction
RG
SLI
LP
ODEs

PETRI NETS -
AN INFORMAL CRASH COURSE

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

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

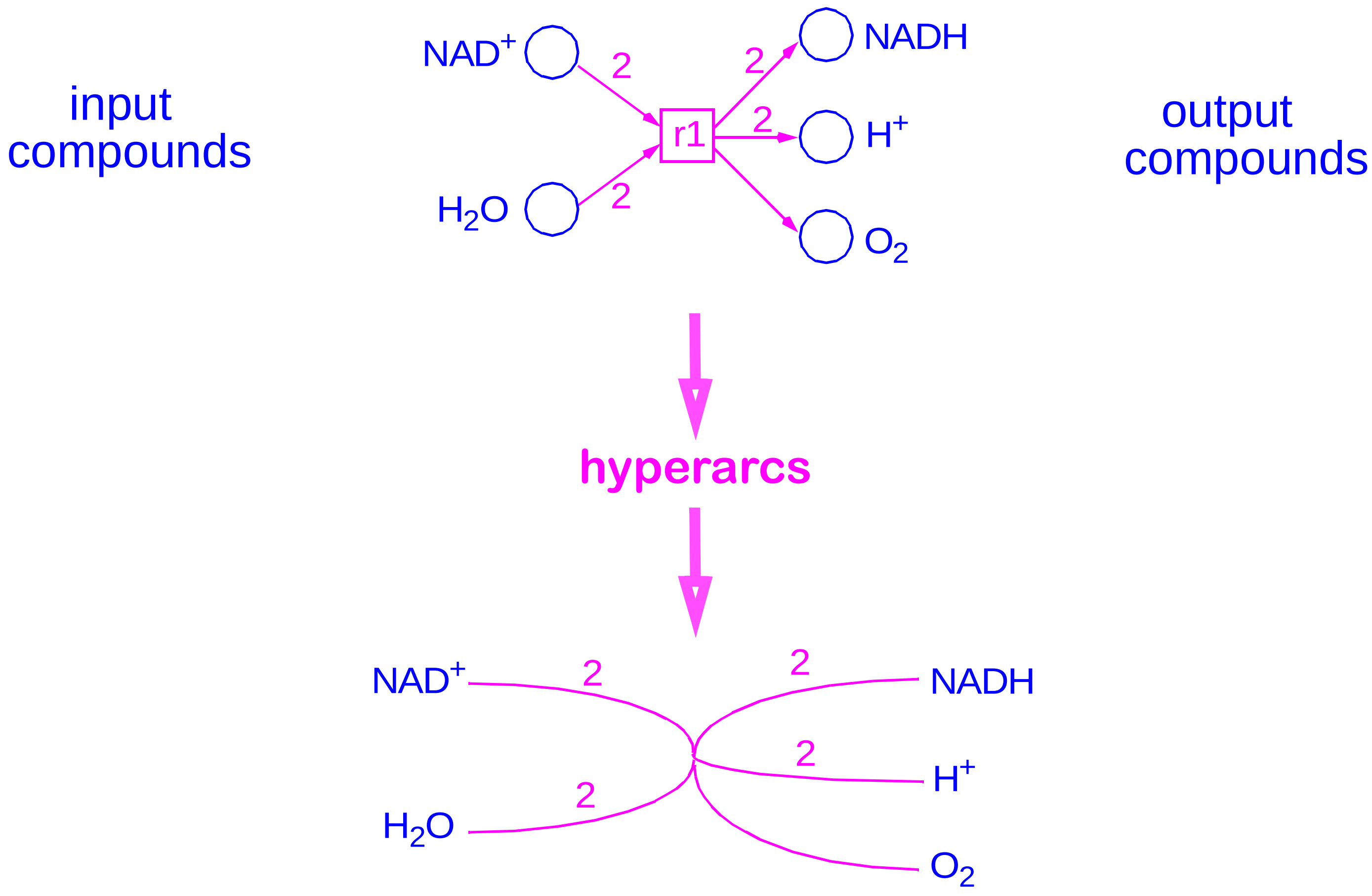
input compounds



output compounds

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

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



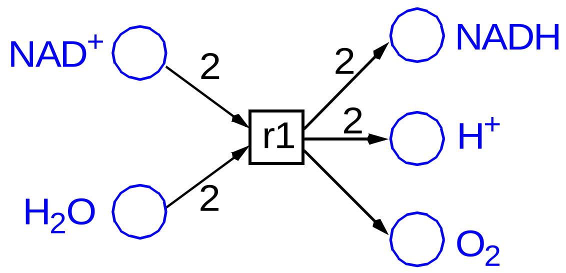
PETRI NETS, BASICS - THE STRUCTURE

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

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

input compounds

pre-conditions



output compounds

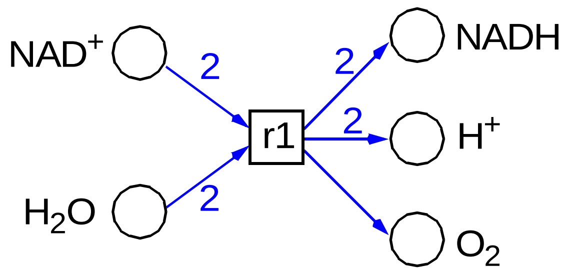
post-conditions

- **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



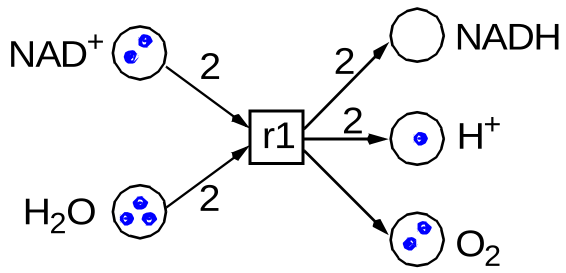
output compounds

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

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

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

input compounds



output compounds

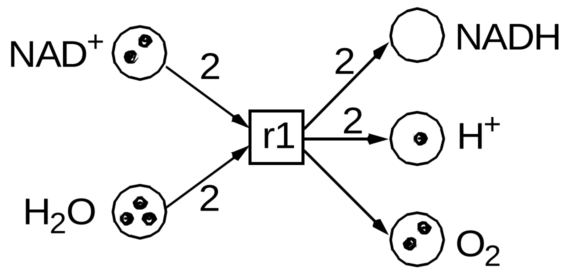
- local conditions -> Petri net places -> chemical compounds
- multiplicities -> Petri net arc weights -> stoichiometric relations
- condition's state -> token(s) in its place -> available amount (e.g. mol)
- system state -> marking -> compounds distribution

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



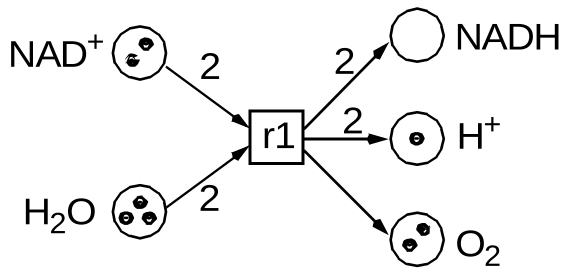
output compounds

- 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
- $PN = (P, T, F, m_0)$, $F: (P \times T) \cup (T \times P) \rightarrow N_0$, $m_0: P \rightarrow N_0$

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

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

input compounds



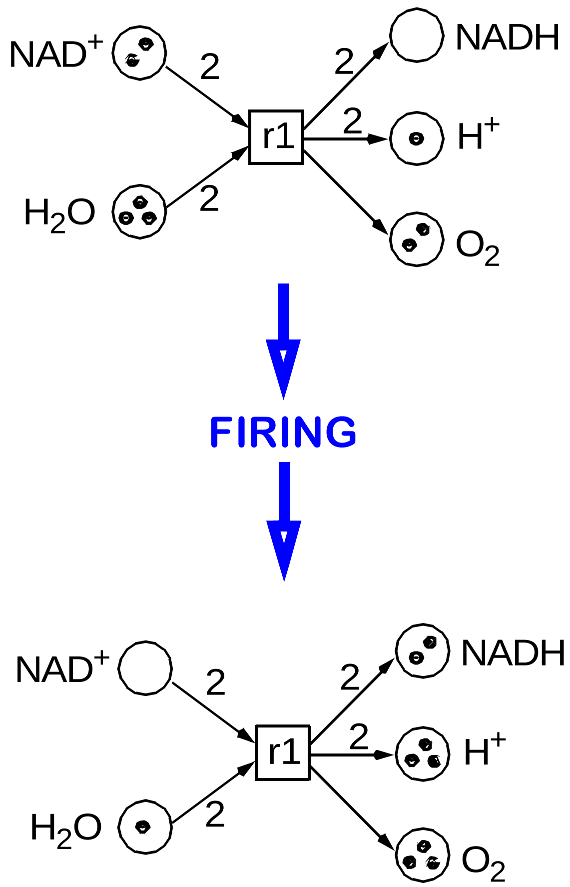
output compounds

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

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

input compounds

output compounds

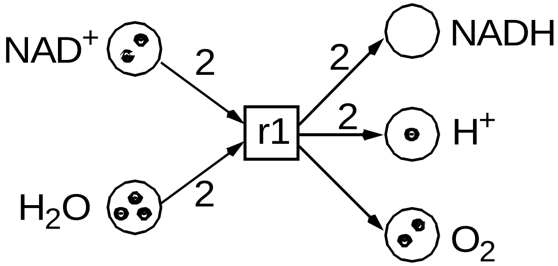


PETRI NETS, BASICS - THE BEHAVIOUR

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

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

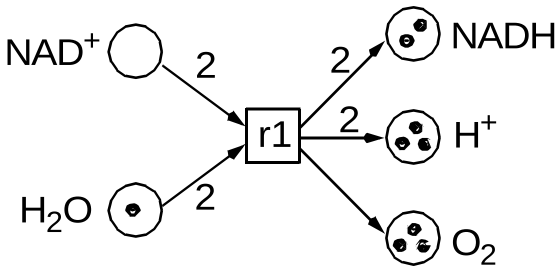
input compounds



output compounds

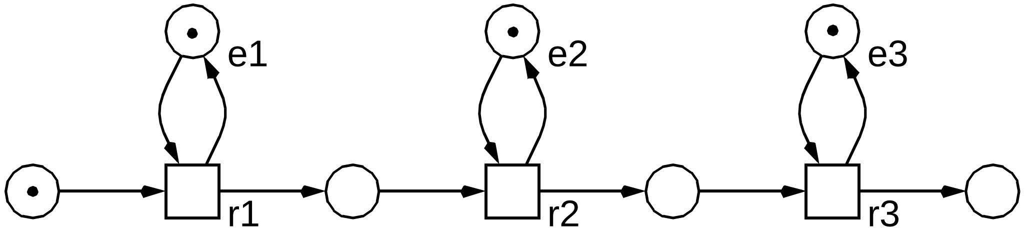
FIRING

TOKEN GAME

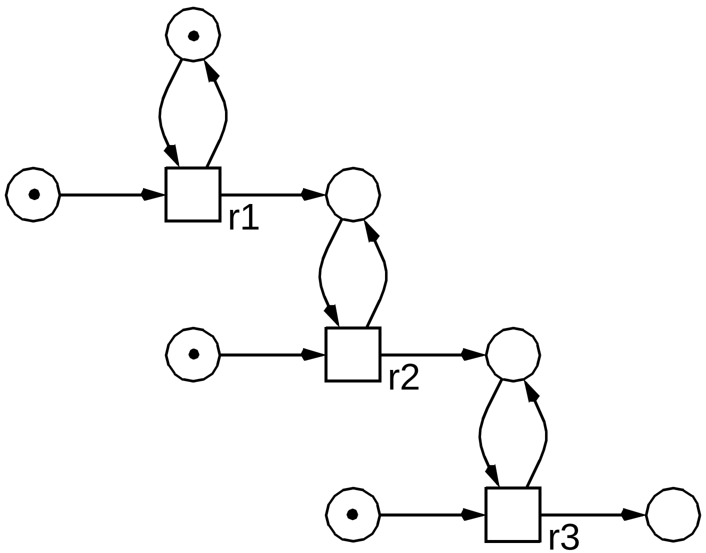


DYNAMIC BEHAVIOUR (substance flow)

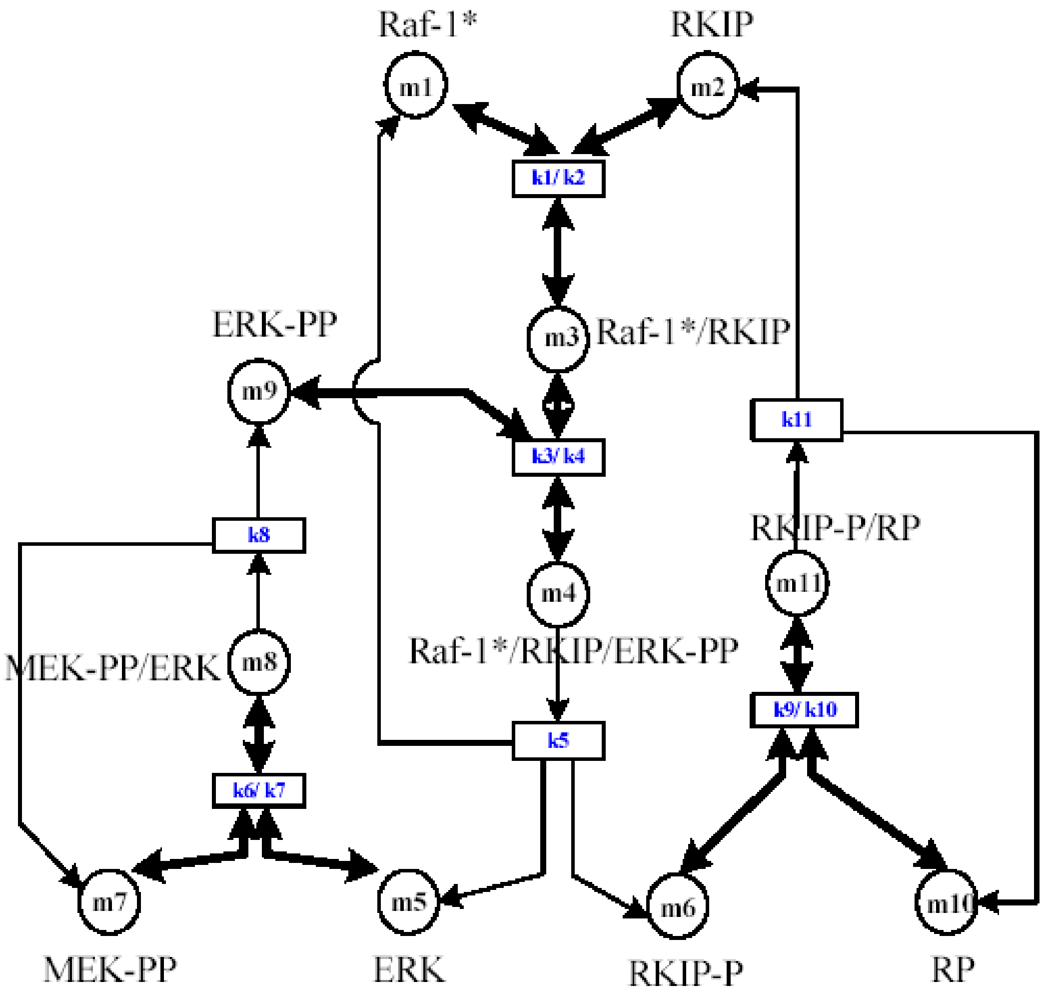
- **metabolic networks**
  -> substance flows



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

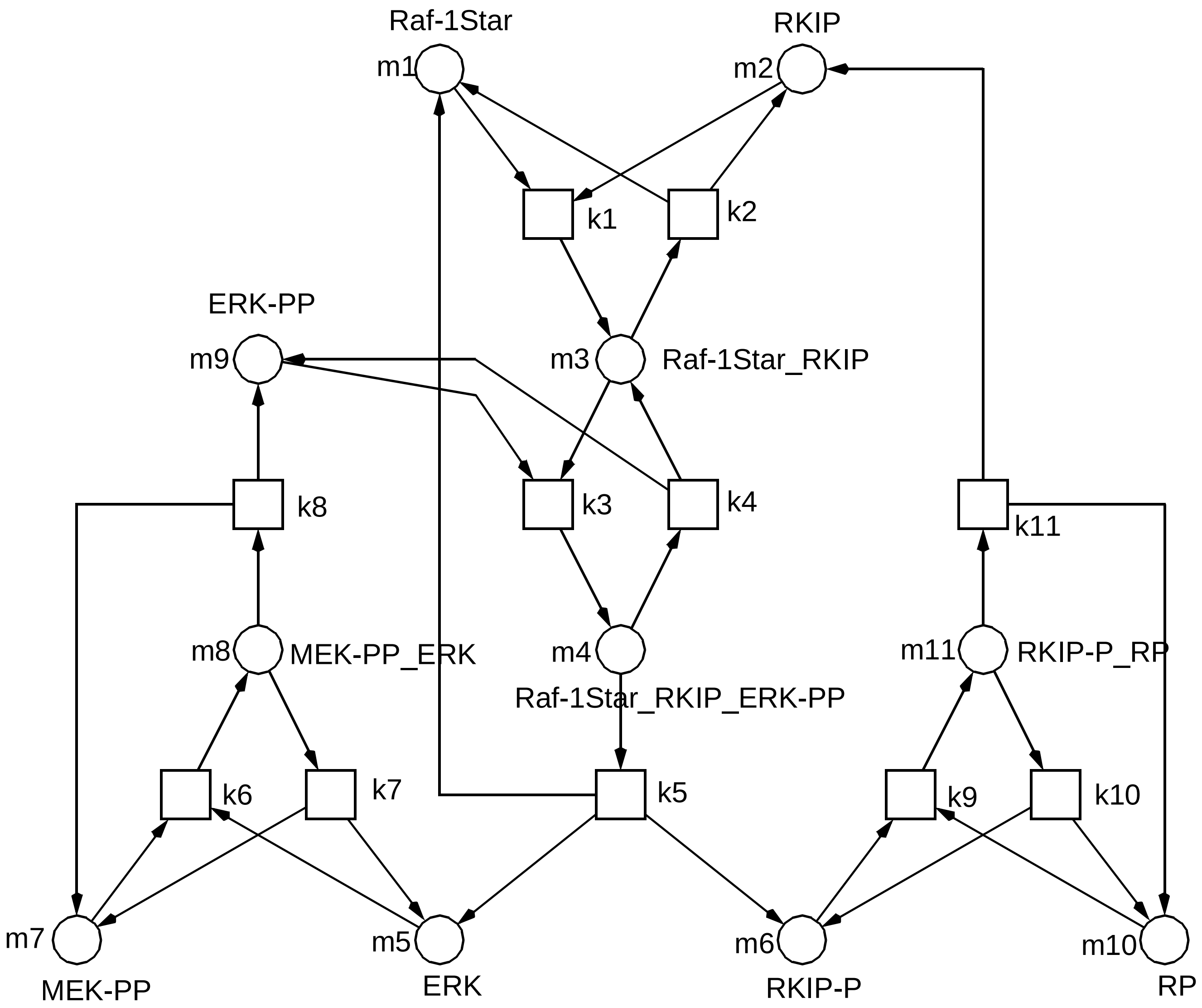


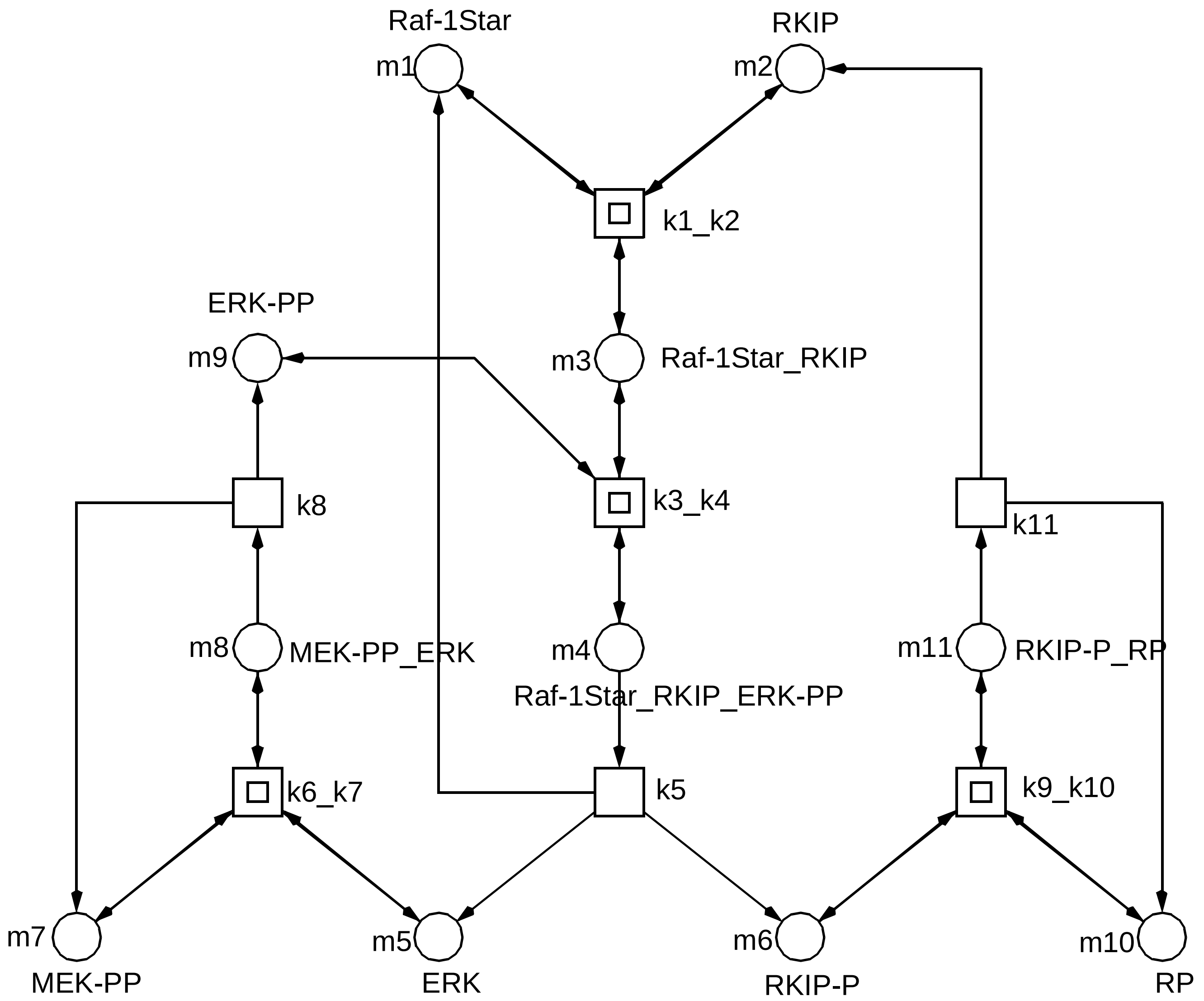
THE RUNNING EXAMPLE - THE RKIP PATHWAY



[Cho et al., CMSB 2003]

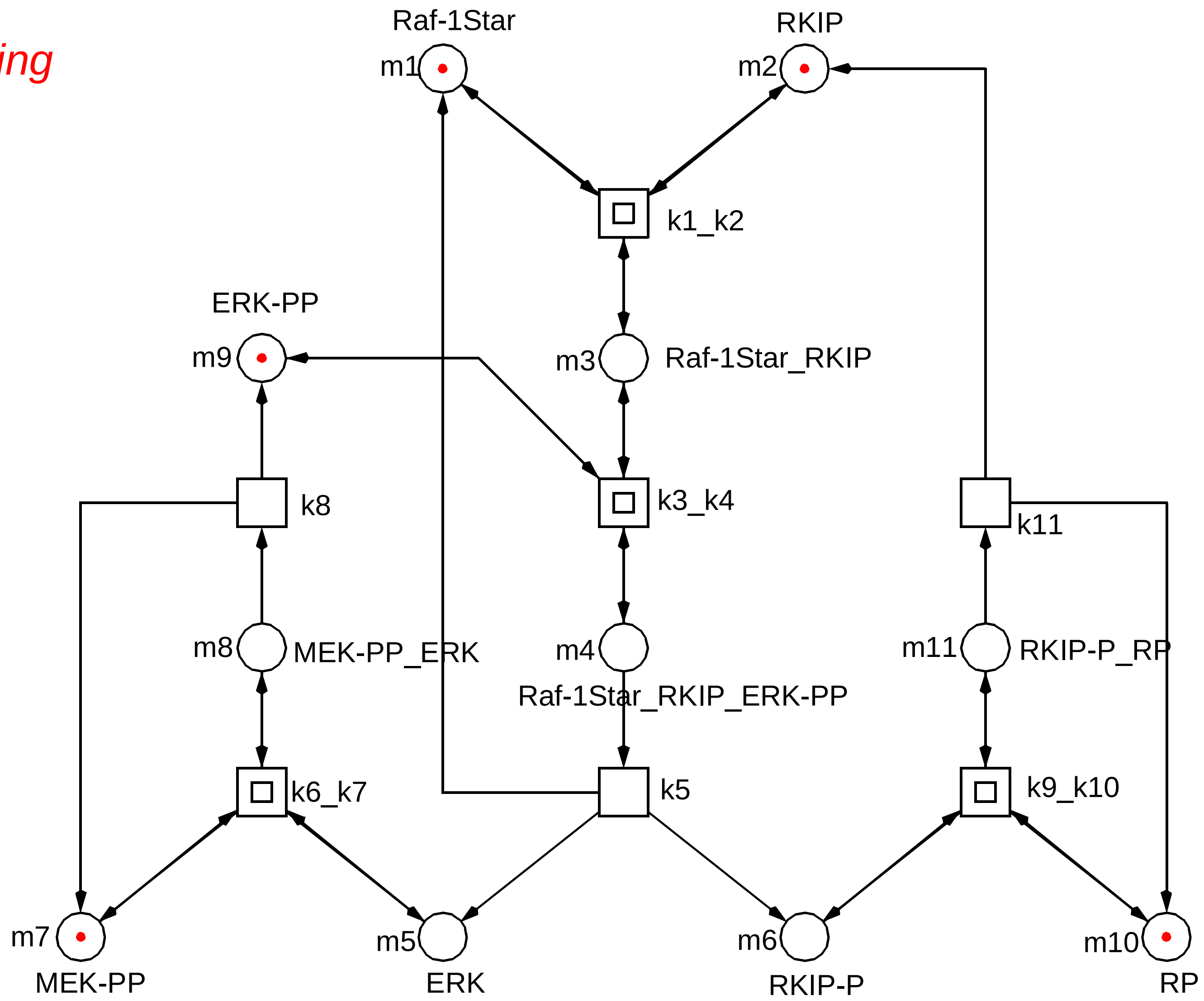
THE RKIP PATHWAY, PETRI NET





Raf-1Star
RKIP
m1
m2
k1_k2
ERK-PP
m9
m3
Raf-1Star_RKIP
k8
k3_k4
k11
m8
MEK-PP_ERK
m4
m11
RKIP-P_RP
Raf-1Star_RKIP_ERK-PP
k6_k7
k5
k9_k10
m7
m5
m6
m10
MEK-PP
ERK
RKIP-P
RP

initial marking



- **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 (for metabolic networks)**

  -> *steady state behaviour*

QUALITATIVE ANALYSES

ANALYSIS TECHNIQUES, OVERVIEW

- **static analyses** -> **no state space construction**
  - -> *structural properties (graph theory, combinatorial algorithms)*
  - -> *P / T - invariants (discrete mathematics),*

- **dynamic analyses** -> **total / partial state space construction**
  - -> *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
  - -> *state space representations: interleaving (RG) / partial order (prefix)*

STATIC ANALYSES

INCIDENCE MATRIX C

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

C =

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

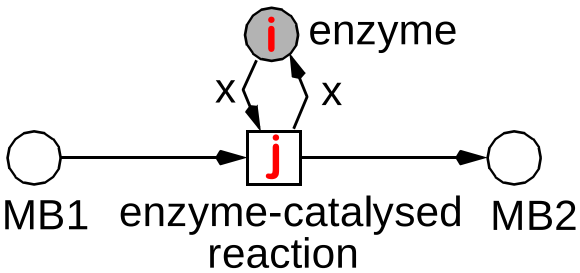
$$cij = (pi, tj) = F(tj,pi) - F(pi, tj) = \Delta\, tj(pi)$$

$$\Delta tj = \Delta\, tj(*)$$

- **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

- **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)*

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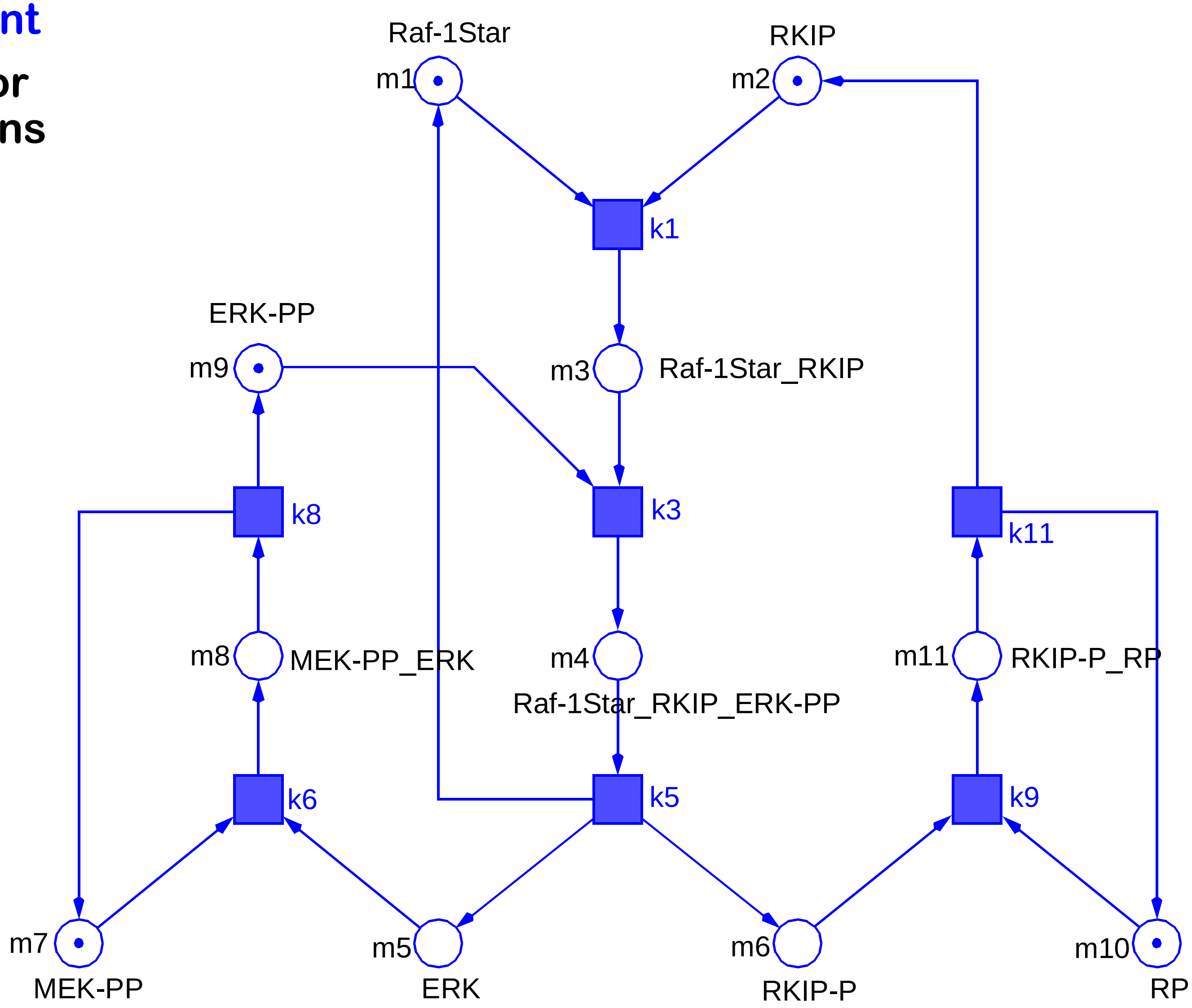
- **T-invariants = (multi-) sets of transitions**
  - -> *zero effect on marking*
  - -> *reproducing a marking / system state*
  - -> *steady state substance flows / reaction rates*
  - -> *elementary modes [Schuster 1993]*
- **realizable T-invariants correspond to cycles in the RG**
  - -> *RG: concurrent 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* -> **self-contained subnet**

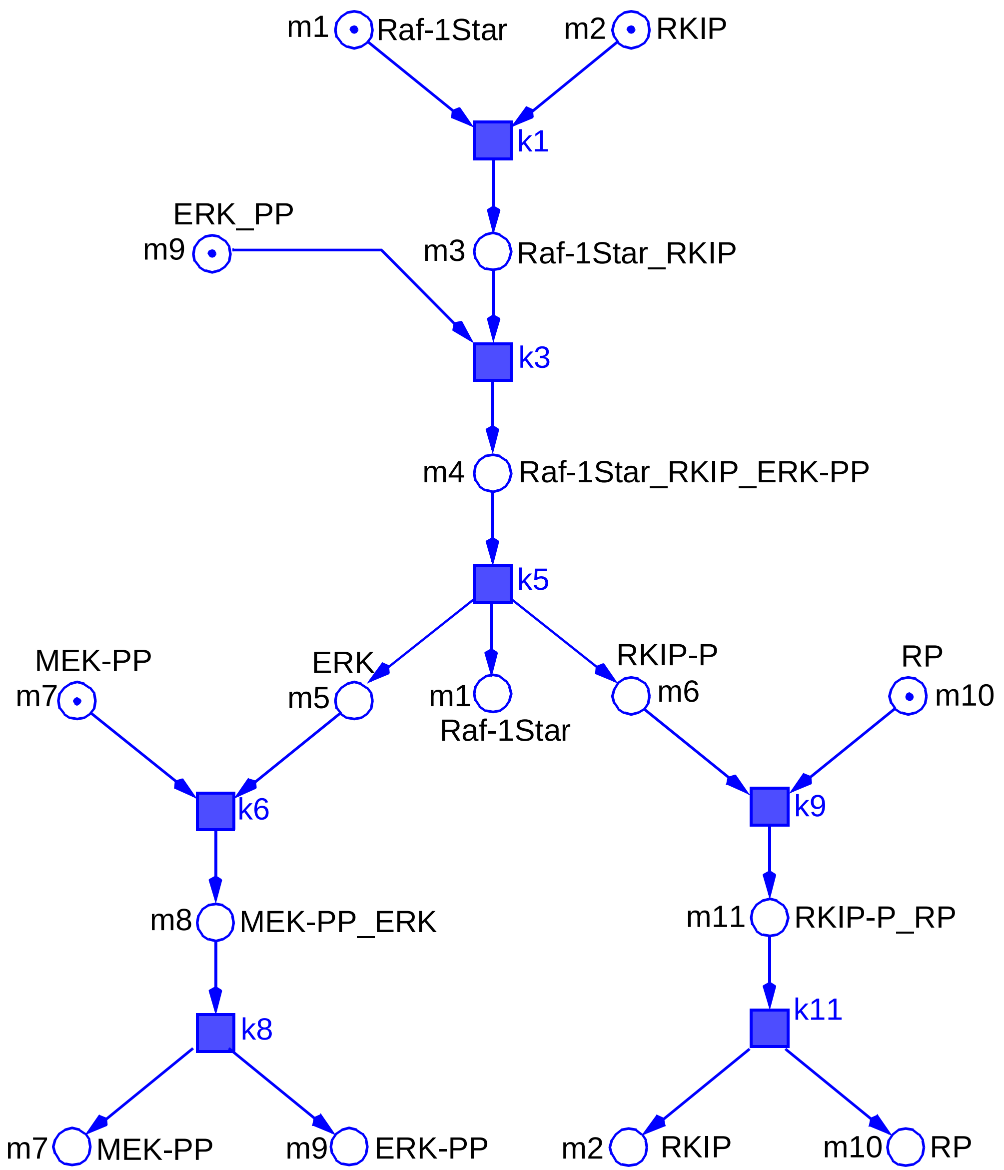
-> non-trivial T-invariant

+ 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*
  - -> *finite prefix*



- **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 place belongs to a P-invariant*
  - -> *CPI => BND (sufficient condition)*

P-INVARIANTS, INTERPRETATION

- **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*

  -> *moieties*

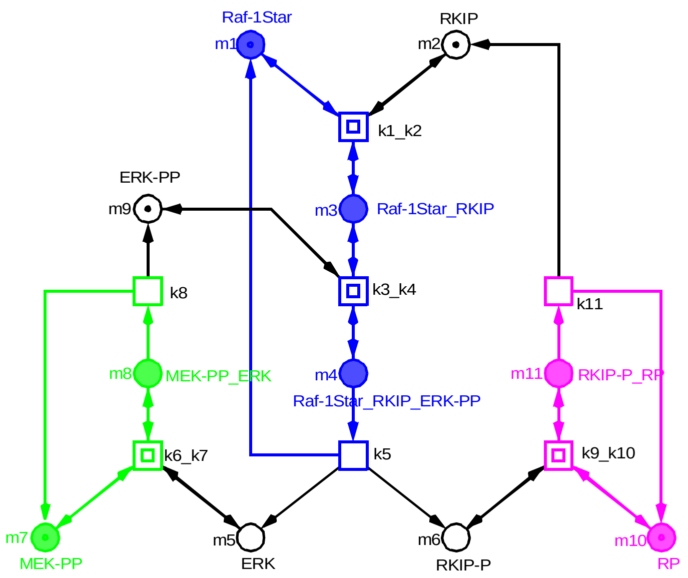
  -> *a place belonging to a P-invariant is bounded*

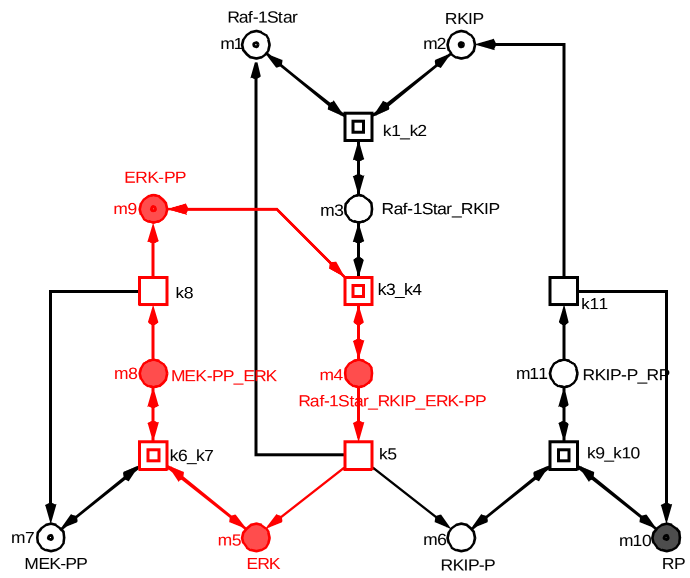
- **a P-invariant defines a subnet**

  -> *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* -> **self-contained, cyclic**

P-INVARIANTS, THE RKIP PATHWAY





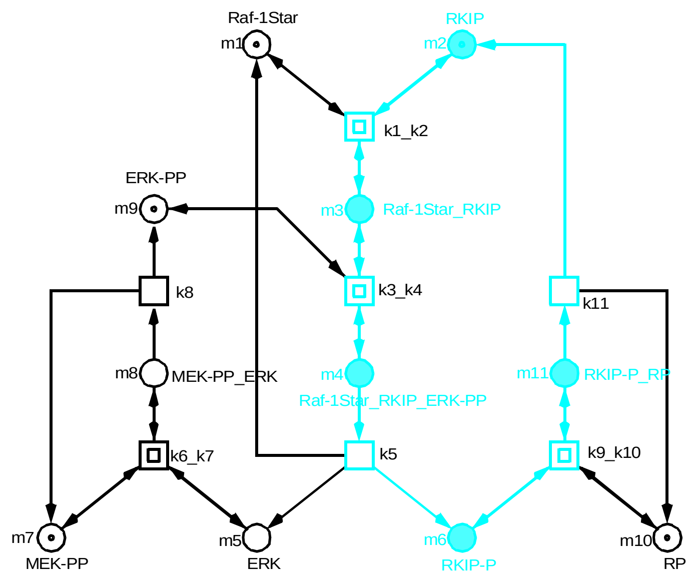
P-INV1: MEK

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

STATIC ANALYSIS, SUMMARY

- **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 ANALYSES

- **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

- ... **is a technique for verifying finite-state concurrent systems against properties specified in temporal logic**

  Clarke, E. M. Jr.; Grumberg, O.; Peled, D. A.:
  Model Checking;
  MIT Press 2001

- **finite state systems = steady state systems = bounded pn**

- **model checking of unbounded systems**
  - -> *CTL* *undecidable*
  - -> *LTL* *decidable, but no tools (not yet ?)*
  - -> *unboundedness + inhibitors = undecidability*

- **how to get bounded model ?**
  - -> *qualitative model - model assumptions of environment behaviour*
  - -> *quantitative model - transition firing rates / durations*

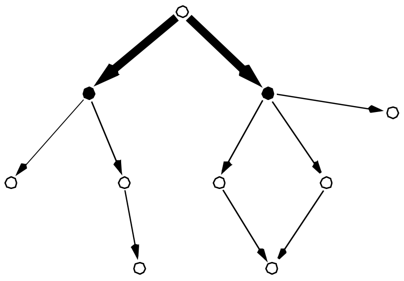
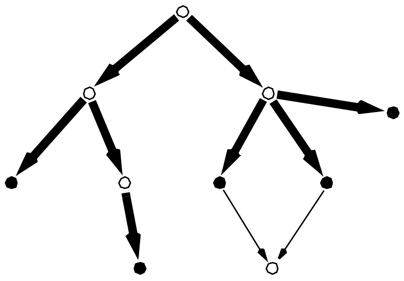
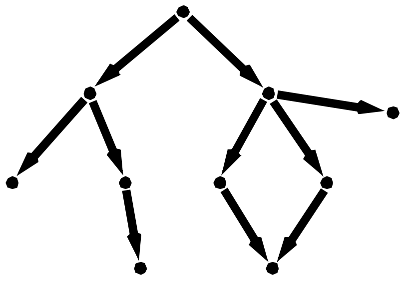
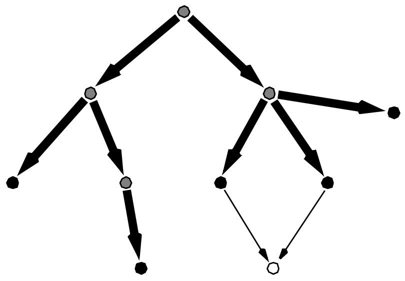
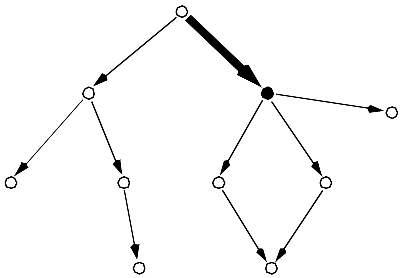
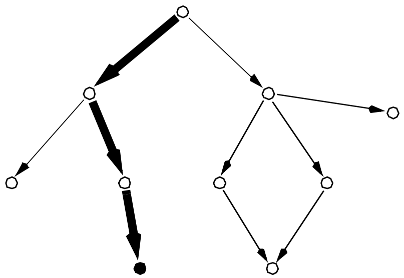
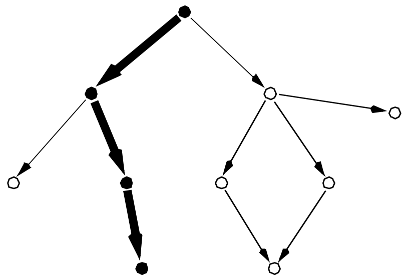
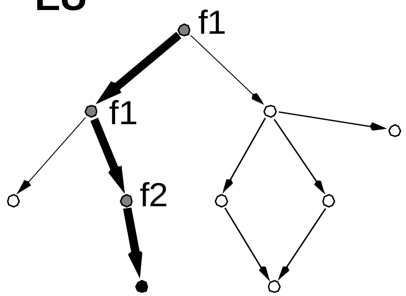
TEMPORAL LOGICS, BASICS

- **extension of classical (propositional) logics by temporal operators**
- **atomic propositions**
  - -> *elementary statements, having - in a given state - a well-defined truth value*
  - -> *e. g. mutex, for 1-bounded pn*
  - -> *e. g. buffer = 2, buffer > 2, else*
- **constants**
  - -> *TRUE, FALSE*
- **classical Boolean operators**

negation	*!*	*conjunction*	*
disjunction	+	*implication*	->

- **temporal operators**
  - -> *to refer to the sequence of states*

CTL Operators, Interleaving Semantics

	next f	finally f	globally f	f1 until f2
on all branches	**AX** 	**AF** 	**AG** 	**AU** 
on some branch	**EX** 	**EF** 	**EG** 	**EU** 

- **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)));*

TECHNIQUES & TOOLS, OVERVIEW

technique	CTL	LTL
reachability graph	INA	PROD, MARIA
stubborn set reduced reachability graph	LoLA	PROD (LTL\X)
symmetrically reduced reachability graph	LoLA (symmetric formulas)	?
BDD, NDD, ..., xDD	DSSZ-CTL, SMART, DSSZ-CTL2	DSSZ-LTL
Kronecker algebra	[Kemper]	?
prefix	PEP (CTL_0)	QQ (LTL\X)
process automata	[pd]	?

QUALITATIVE ANALYSIS, 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*

Quantitative Analyses 1

- Timed Petri Nets

T-INVARIANTS, TWO INTERPRETATIONS

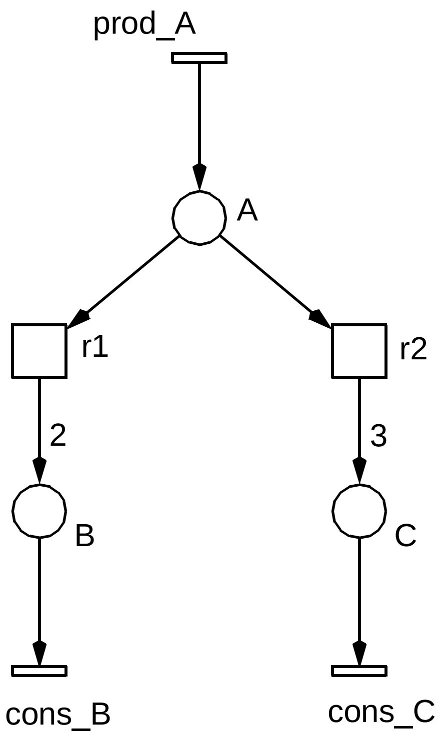
- **Parikh vector**
  - -> *state-reproducing transition sequence (partial order)*
    of transitions occuring one after the other
  - -> *relative transition firing rates*
    of transitions occuring permanently & concurrently

- **relative transition firing rates**
  - -> *may be implemented by transition firing times*
    - *constant*
    - *interval*

- **quantitative modell = qualitative model + quantitative parameters**
  - -> *quantitative parameters - firing times reflecting the firing rates*
  - -> *time-dependent model*

- **claim**
  - -> *transformation preserves all possible behaviour (= minimal T-invariants)*

Transformation, Example



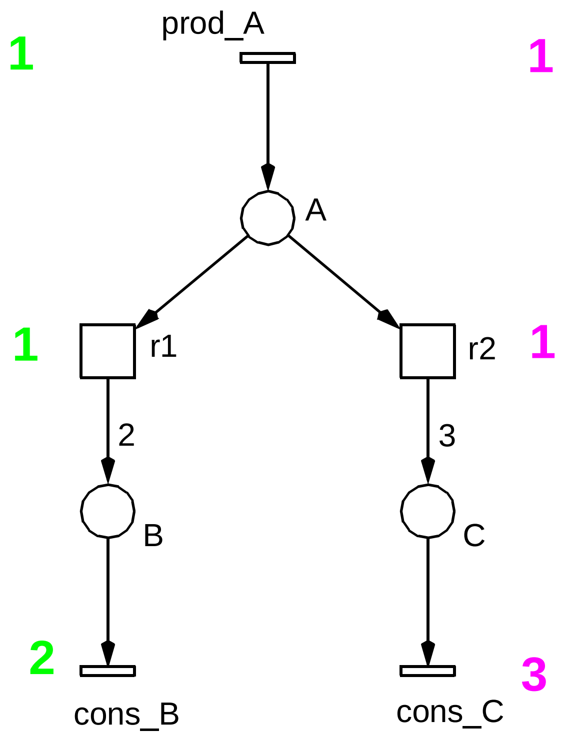
-> properties as time-less net

INA

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

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

TRANSFORMATION, EXAMPLE



T-INVARIANT 1

T-INVARIANT 2

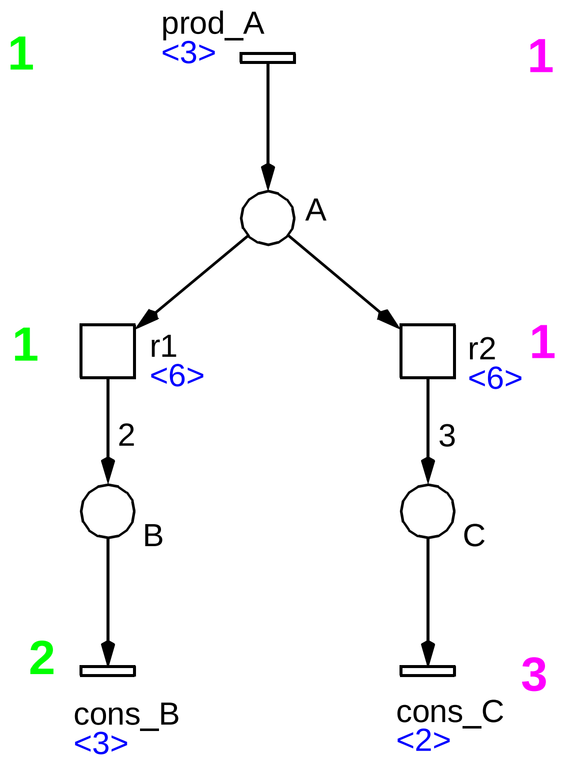
-> properties as time-less net

INA

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

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

TRANSFORMATION, EXAMPLE



T-INVARIANT 1

T-INVARIANT 2

-> properties as time net

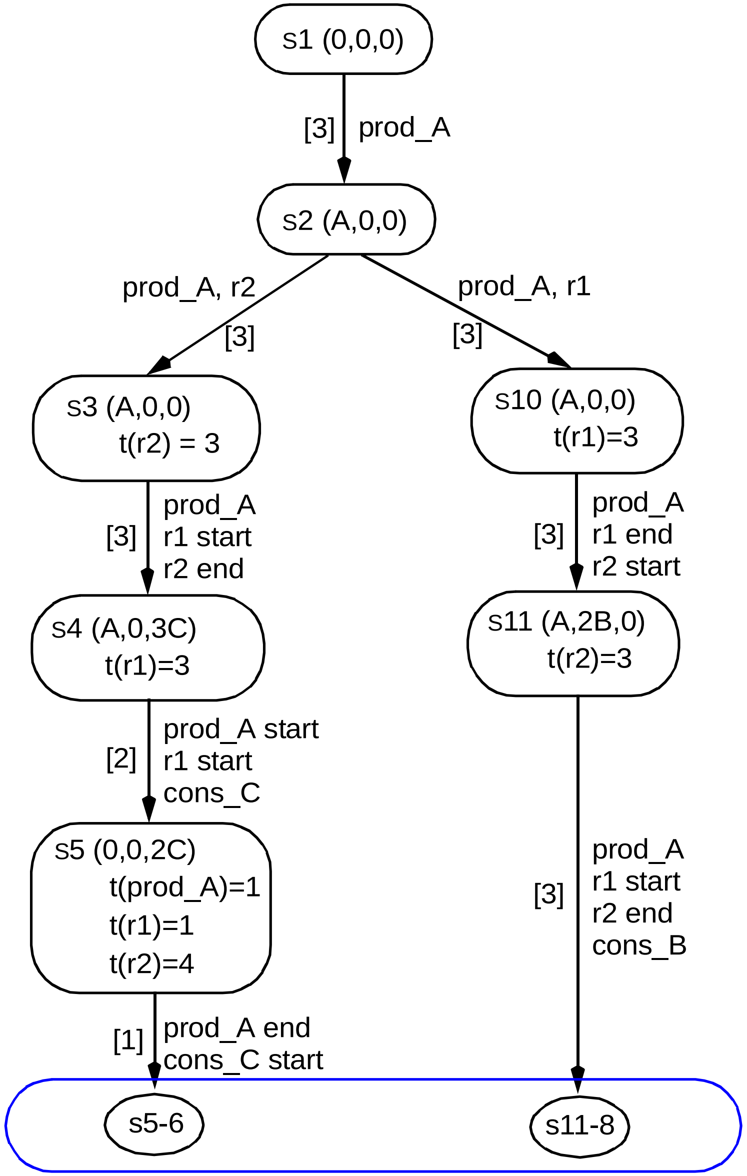
INA

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

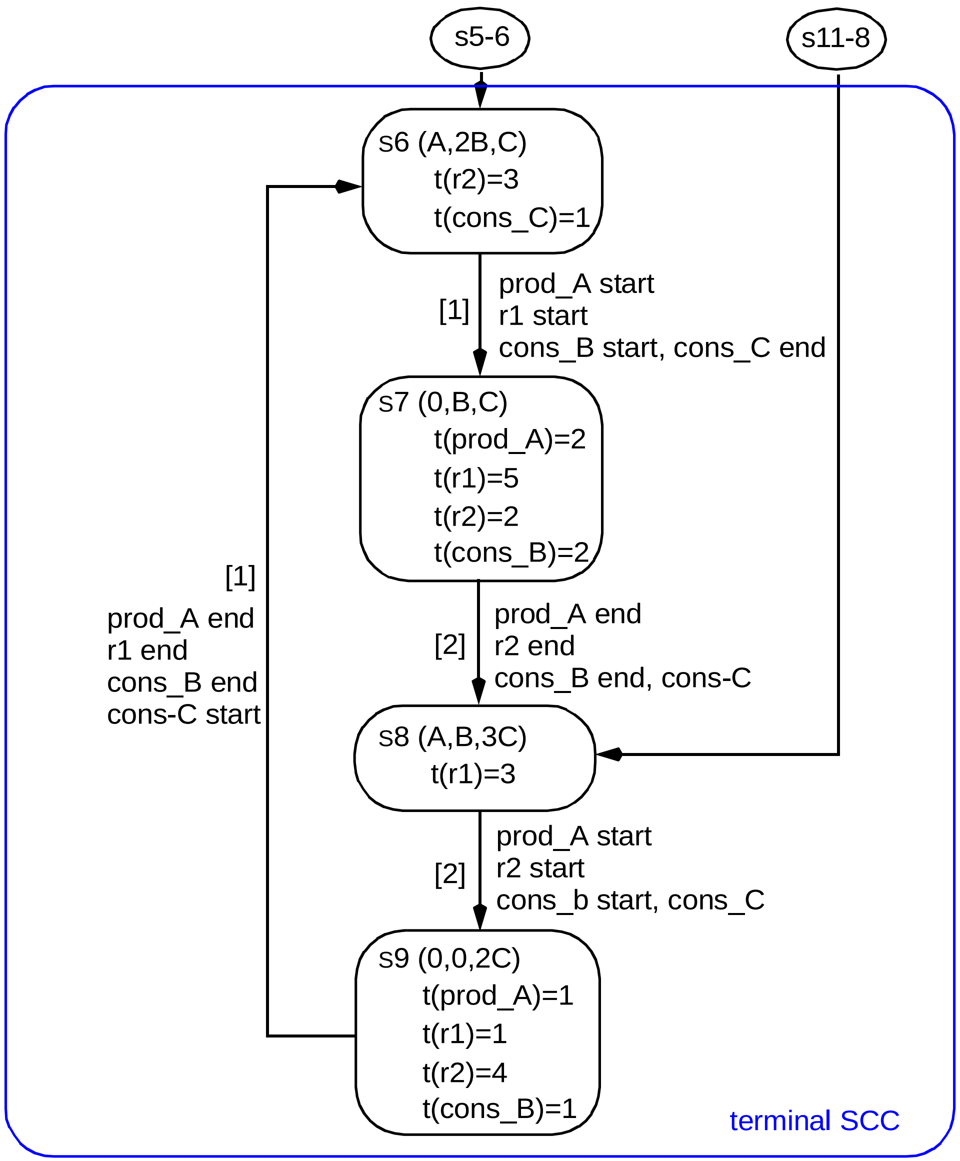
CPI	CTI	B	SB	REV	DSt	BSt	DTr	DCF	L	LV	L&S
N	Y	Y	N	N	N	?	N	Y	Y	Y	N

RG(Example), Part 1

- transient state



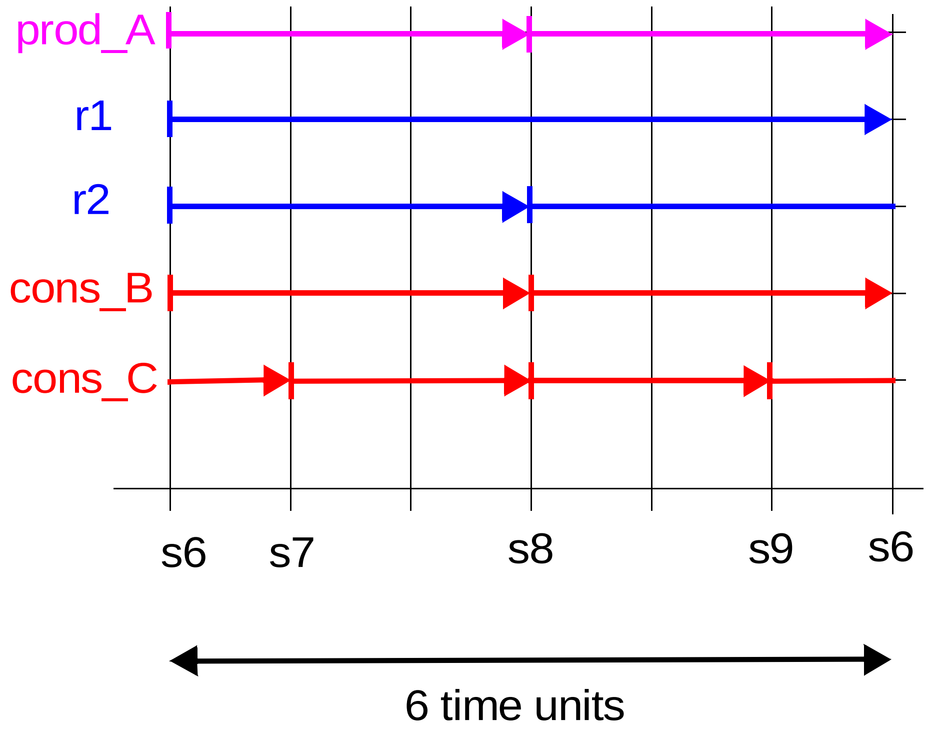
- steady state



RG(EXAMPLE), TERMINAL SCC

- **contains all transitions**
  - -> *always running*
  - -> *start / end at different time points*
- **contains all minimal T-invariants**
- **timing diagram**
- **relative transition firing rates**

prod_A	:	1	+			1
r1	:	1	**r2**		:	1
cons_B	:	2	**cons_C**		:	3

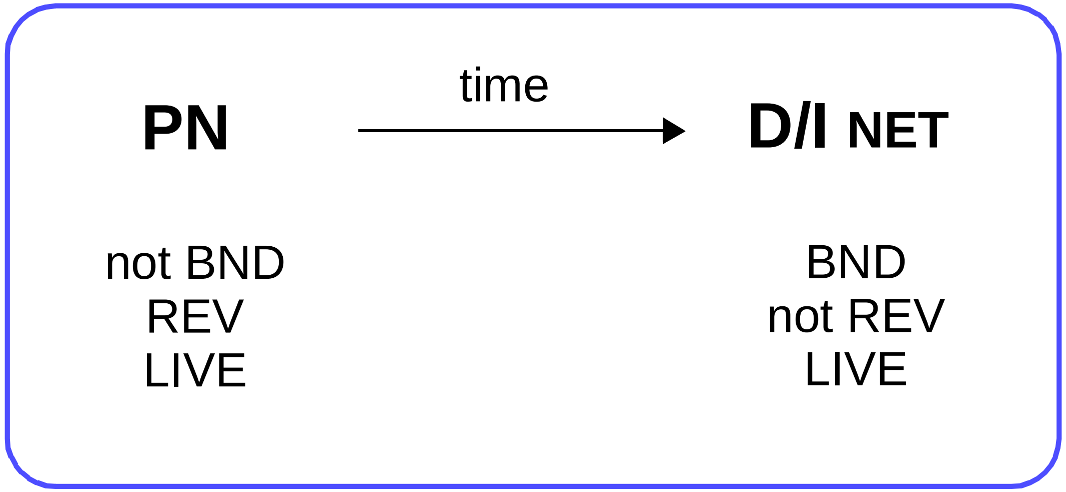


EXAMPLE, SUMMARY

- CTI,
  but not CPI

- transient state
  - -> *initial behaviour to reach steady state*
  - -> *not REV*
  - -> *generally, not DCF*

- steady state behaviour
  - -> *terminal scc*
  - -> *here, BND*
  - -> *here, DCF*



QUANTITATIVE ANALYSIS, METHOD I

interval time Petri net — $I: T \to \mathbf{Q_0}^+ \times \mathbf{Q_0}^+$ and for each $t \in T$ holds $a_t \le b_t$, where $I(t) = (a_t, b_t)$

initial marking / state

finite transition word *w* — $w \in T^*$

(SLI)

$$\begin{cases} b_1 \le a_{11}x_1 + \ldots + a_{1n}x_n \le c_1 \\ \ldots \\ b_m \le a_{m1}x_1 + \ldots + a_{mn}x_n \le c_m \\ a_{ij} \in \{0, 1\},\ b_i \in \mathbf{N},\ c_i \in \mathbf{N} \\ \forall i \forall s \forall k (1 \le i \le n \wedge 1 \le s \le k \le m \wedge \\ a_{is} = a_{ik} = 1 \to \forall j (s \le j \le k \to a_{ij} = 1)) \end{cases}$$

if there is an ***R*** solution,
then there is an ***N*** solution.

w is time-dependent realizable / not realizable

Quantitative Analysis, Method I

interval time Petri net — $I: T \rightarrow \mathbf{Q_0}^+ \times \mathbf{Q_0}^+$ and for each $t \in T$ holds $a_t \leq b_t$, where $I(t) = (a_t, b_t)$

initial marking / state

finite transition word *w* — $w \in T^*$

(SLI)
$$
\begin{cases}
b_1 \leq a_{11}x_1 + \ldots + a_{1n}x_n \leq c_1 \\
\ldots \\
b_m \leq a_{m1}x_1 + \ldots + a_{mn}x_n \leq c_m \\
a_{ij} \in \{0, 1\}, b_i \in \boldsymbol{N}, c_i \in \boldsymbol{N} \\
\forall i \forall s \forall k (1 \leq i \leq n \wedge 1 \leq s \leq k \leq m \wedge \\
a_{is} = a_{ik} = 1 \rightarrow \forall j (s \leq j \leq k \rightarrow a_{ij} = 1))
\end{cases}
$$

w is time-dependent realizable / not realizable

polynomial time ↑

if there is an $\boldsymbol{R}$ solution,
then there is an $\boldsymbol{N}$ solution.

↓ linear time

QUANTITATIVE ANALYSIS, METHOD II

interval time Petri net — $I: T \rightarrow \mathbf{Q_0}^+ \times \mathbf{Q_0}^+$ and for each $t \in T$ holds $a_t \leq b_t$, where $I(t) = (a_t, b_t)$

initial marking / state

finite transition word *w* — $w \in T^*$

(LP)

$$\min / \max\ x_1 + \ldots + x_n$$

$$\begin{cases} b_1 \leq a_{11}x_1 + \ldots + a_{1n}x_n \leq c_1 \\ \ldots \\ b_m \leq a_{m1}x_1 + \ldots + a_{mn}x_n \leq c_m \\ a_{ij} \in \{0, 1\},\ b_i \in \mathbf{N},\ c_i \in \mathbf{N} \\ \forall i \forall s \forall k (1 \leq i \leq n \wedge 1 \leq s \leq k \leq m \wedge \\ a_{is} = a_{ik} = 1 \rightarrow \forall j (s \leq j \leq k \rightarrow a_{ij} = 1)) \end{cases}$$

if there is a solution, then it is an *N* solution.

w is time-dependent realizable / not realizable

min/max time length of *w* (time window of the pathway)

QUANTITATIVE ANALYSIS, METHOD II

interval time Petri net — $I: T \to \mathbf{Q_0}^+ \times \mathbf{Q_0}^+$ and for each $t \in T$ holds $a_t \le b_t$, where $I(t) = (a_t, b_t)$

initial marking / state

finite transition word *w* — $w \in T^*$

(LP)

$$\min / \max\ x_1 + \ldots + x_n$$

$$\begin{cases} b_1 \le a_{11}x_1 + \ldots + a_{1n}x_n \le c_1 \\ \ldots \\ b_m \le a_{m1}x_1 + \ldots + a_{mn}x_n \le c_m \\ a_{ij} \in \{0, 1\},\ b_i \in \mathbf{N},\ c_i \in \mathbf{N} \\ \forall i \forall s \forall k (1 \le i \le n \wedge 1 \le s \le k \le m \wedge \\ a_{is} = a_{ik} = 1 \to \forall j (s \le j \le k \to a_{ij} = 1)) \end{cases}$$

polynomial time

if there is a solution,
then it is an *N* solution.

w is time-dependent realizable / not realizable

min/max time length of *w* (time window of the pathway)

QUANTITATIVE ANALYSIS, SUMMARY

- **Louchka Popova / HUB**
- **transition time**
  -> *continuous intervals*
- **structural technique**
  -> *parametric description*
- **no state space construction**
  -> *works also for infinite systems*
  -> *works also if the reachability graph does not fit into memory*
- **further analysis questions**
  -> *which time windows preserve a transition sequence's realizability*
  -> *which time windows make the net bounded*
  -> *which structures are time-independently live*

QUANTITATIVE ANALYSES 2

- CONTINUOUS PETRI NETS

- **quantitative model = qualitative model + quantitative parameters**

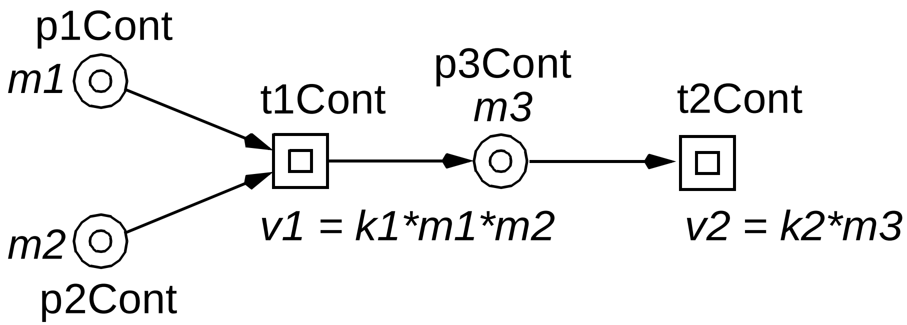
  -> BUT: quantitative parameters often unknown

- **typical quantitative parameters of bionetworks**

  -> compound concentrations -> real numbers

  -> reaction rates / fluxes -> concentration-dependent

- **continuous Petri nets**



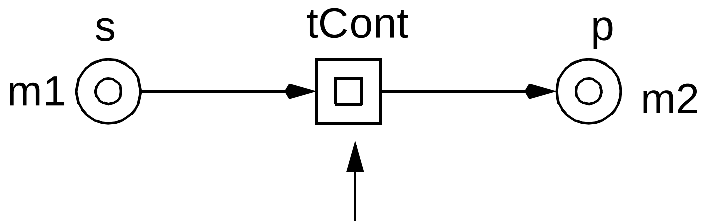
continuous nodes !

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

d [p3Cont] / dt = v1 - v2

ODEs

EXAMPLE - MICHAELIS-MENTEN REACTION



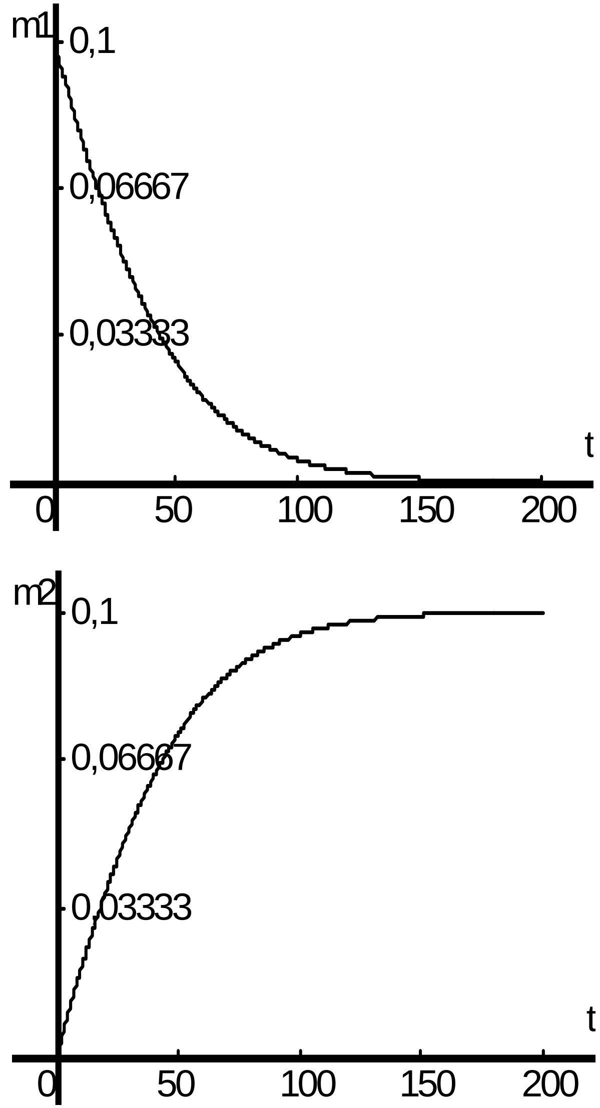
v = 0.005 * m1 / (0.1375 + m1)

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 (?)

-> Snoopy extension in preparation



THE QUALITATIVE MODEL

BECOMES

THE STRUCTURAL DESCRIPTION

OF THE QUANTITATIVE MODEL !

monika.heiner@informatik.tu-cottbus.de

- **extensions**
  - -> *read arcs* -> *interleaving / partial order semantics*
  - -> *inhibitor arcs !?* -> *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**
  - -> *discrete / continuous Petri nets*
  - -> *continuous / hybrid Petri nets <-> ODEs*

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/three-step model development**
  - -> *qualitative model* -> *discrete Petri nets*
  - -> *quantitative model* -> *timed Petri nets, continuous Petri nets (= ODEs)*

- **many challenging questions for analysis techniques**
  - -> *qualitative as well as quantitative ones*

THANKS !