FROM PETRI NETS TO DIFFERENTIAL EQUATIONS (ODES)

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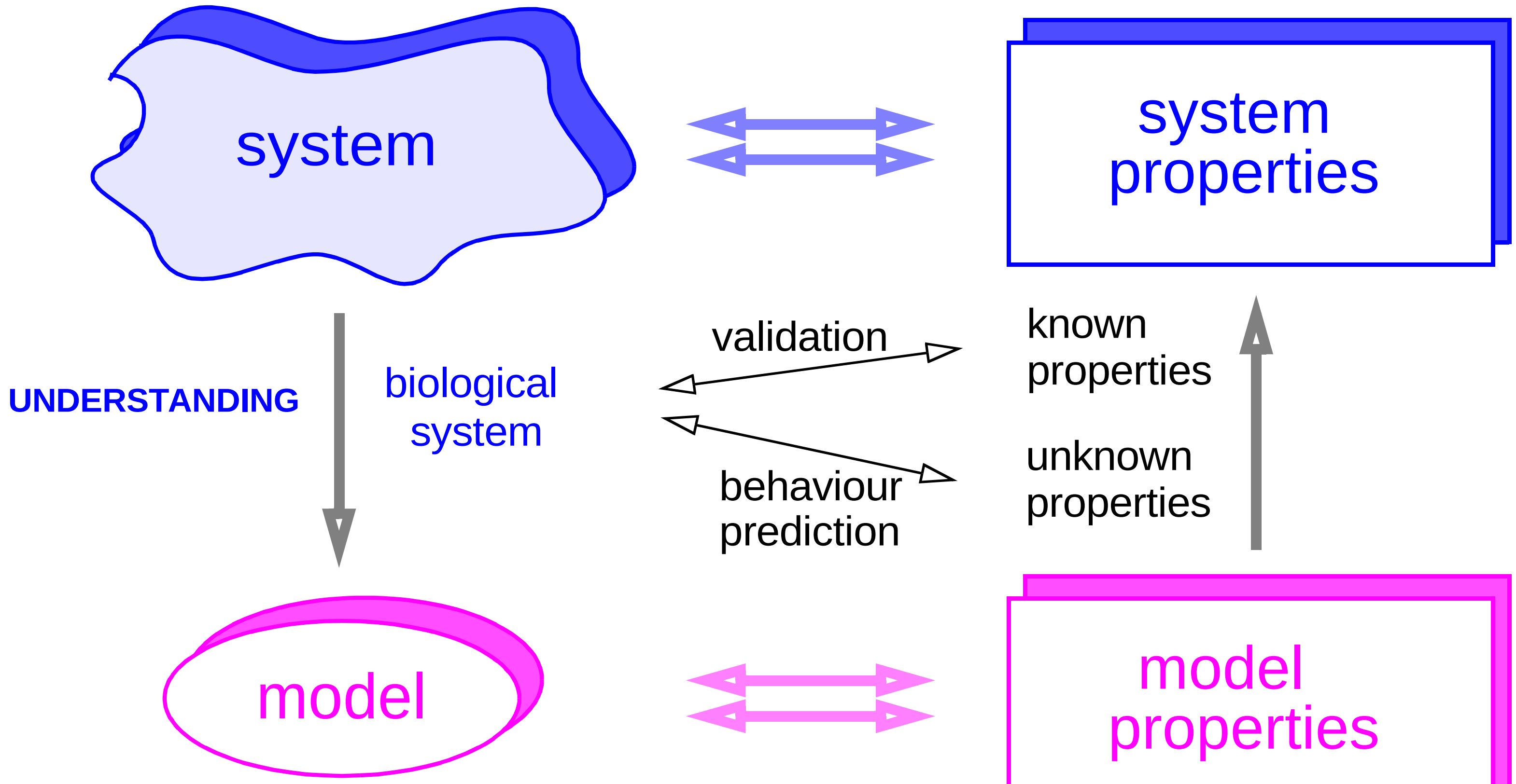
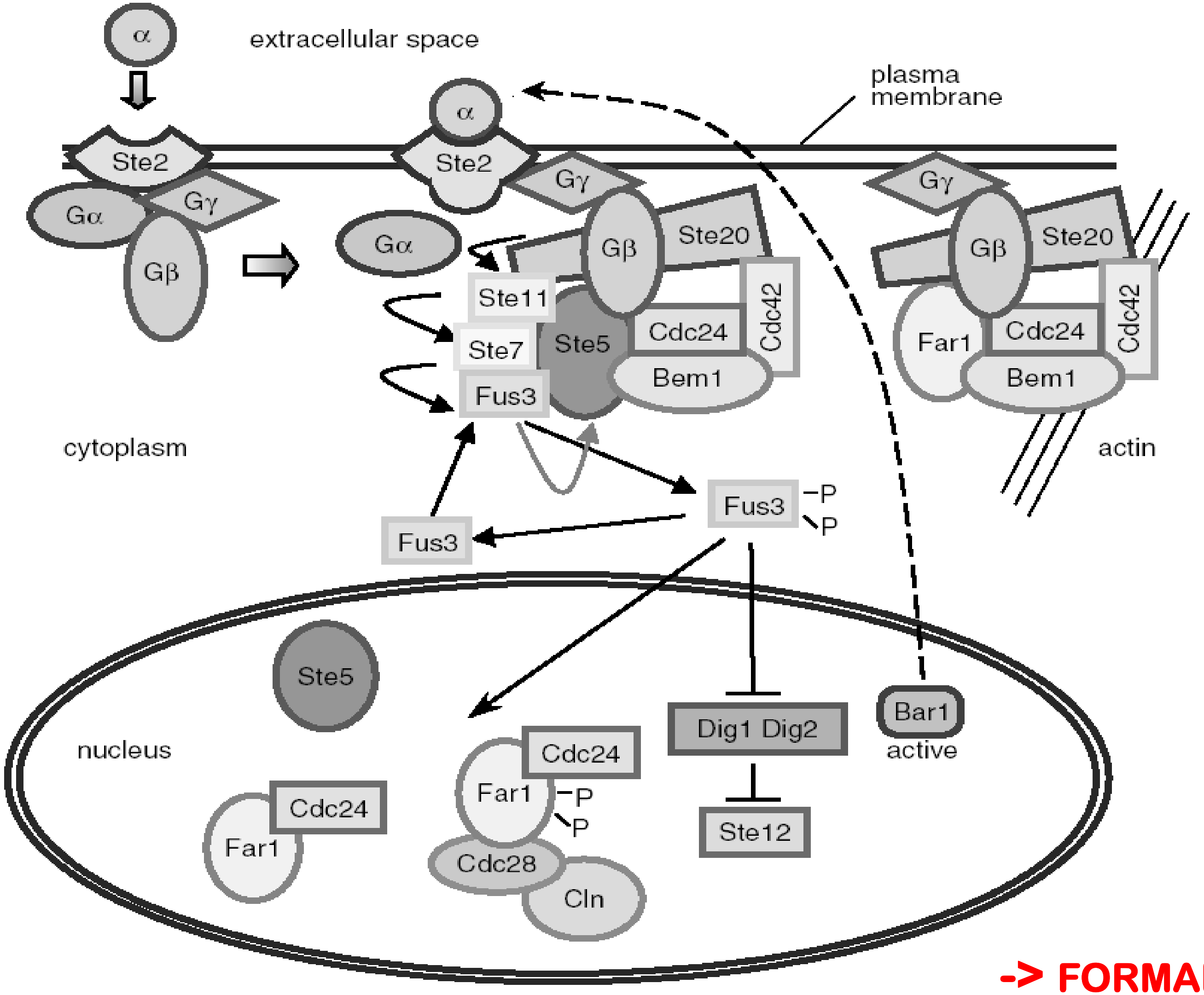
MODEL- BASED SYSTEM ANALYSIS



WHAT KIND OF MODEL SHOULD BE USED?

NETWORK REPRESENTATIONS, EX1



-> FORMAL SEMANTICS ?

NETWORK REPRESENTATIONS, EX2

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

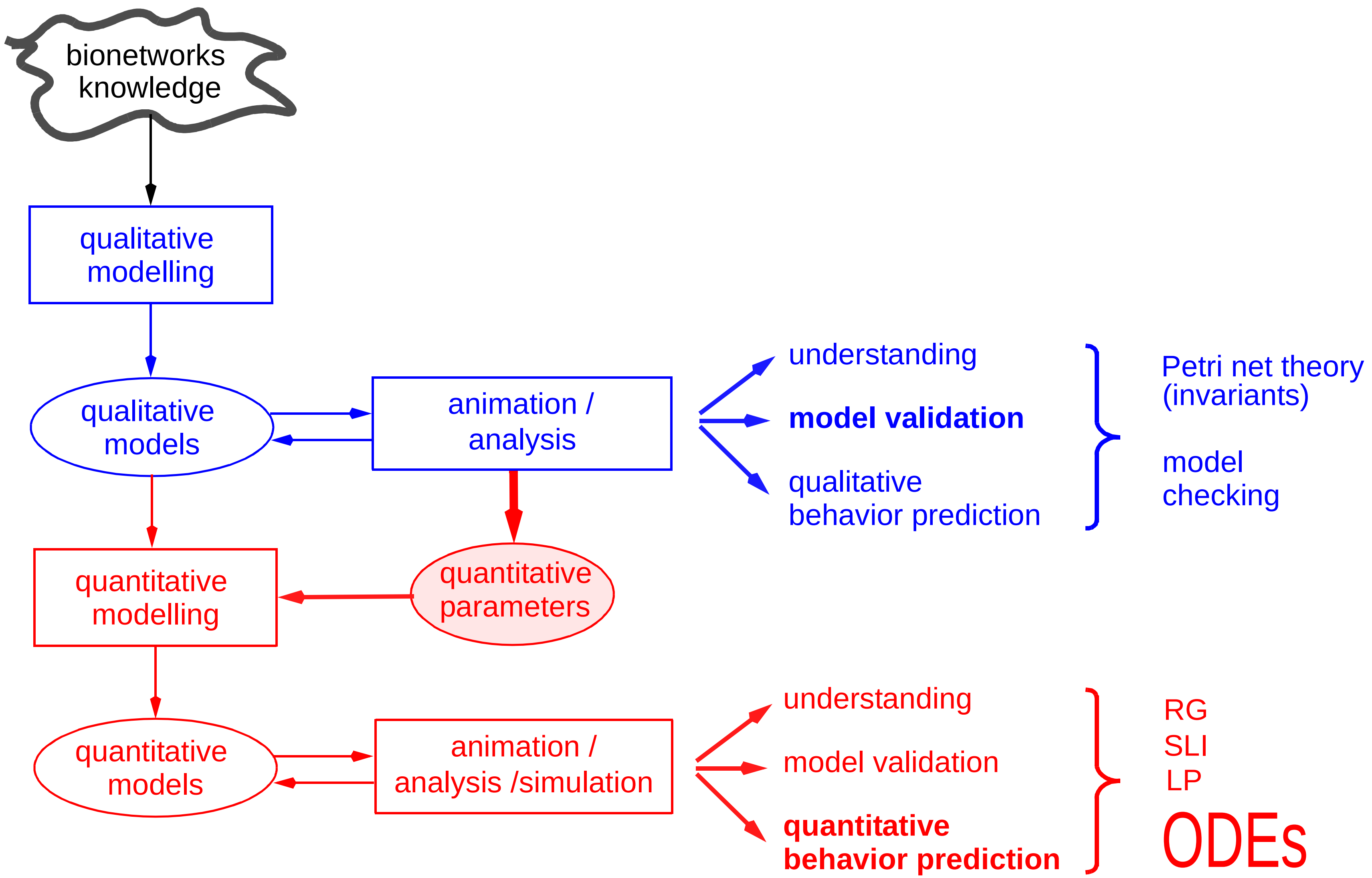
$$\nu_1 = \alpha[t] \cdot Bar1_{active}[t] \cdot k_1$$
$$\nu_2 = Ste2[t] \cdot \alpha[t] \cdot k_2$$
$$\nu_3 = Ste2_{active}[t] \cdot k_3$$
$$\nu_4 = Ste2_{active}[t] \cdot k_4$$
$$\nu_5 = Ste2[t] \cdot k_5$$
$$\nu_6 = Ste2_{active}[t] \cdot G\alpha\beta\gamma[t] \cdot k_6$$
$$\nu_7 = G\alpha GTP[t]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

-> READABILITY ?

BIONETWORKS, SOME PROBLEMS

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

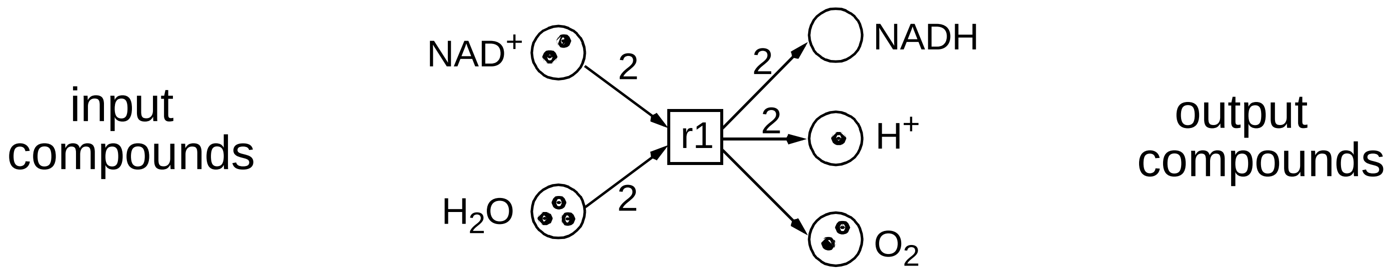
- - >> models are full of ASSUMPTIONS << - -


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

PETRI NETS -
AN INFORMAL CRASH COURSE

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

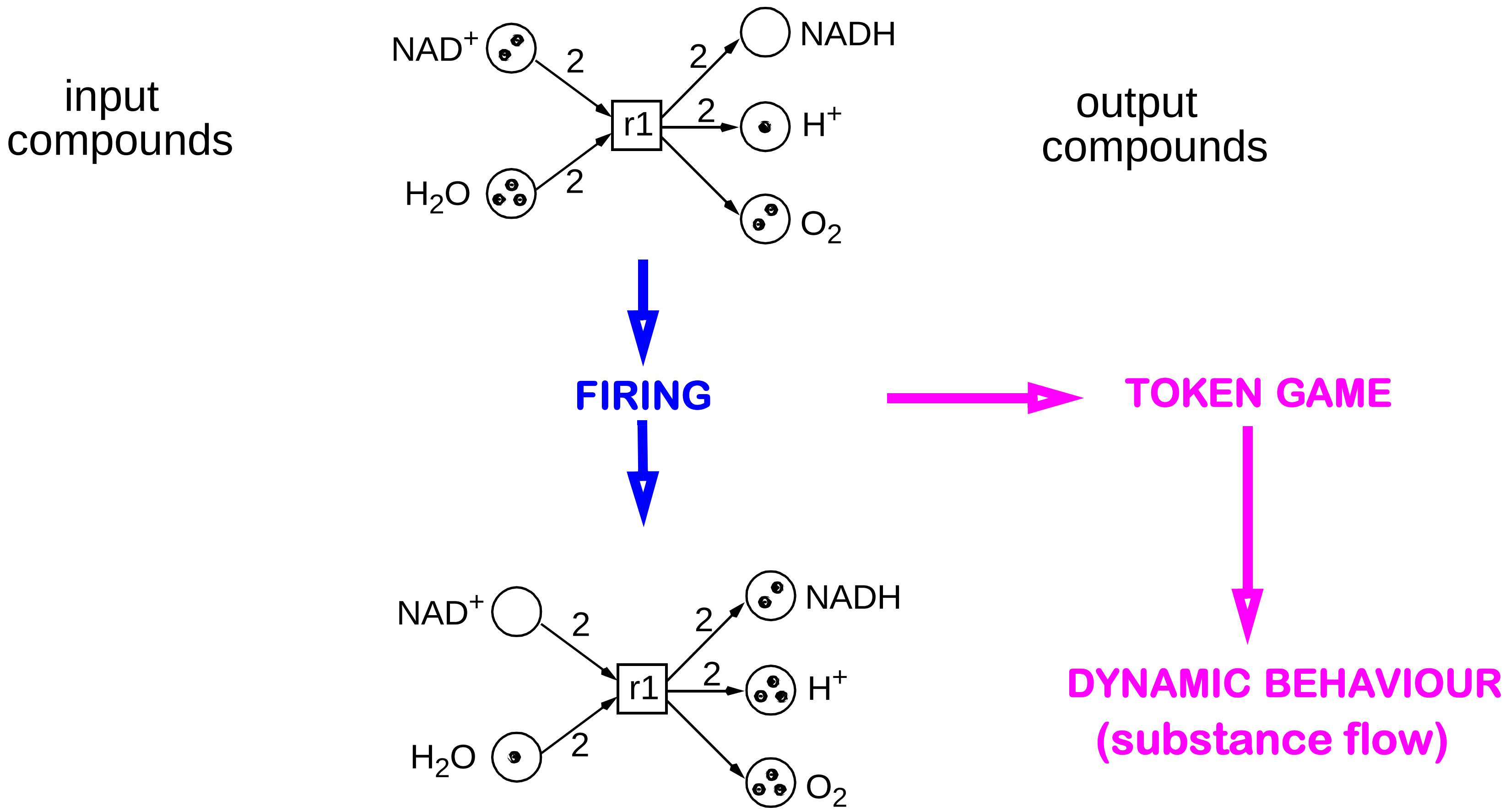
$$2\ NAD^+ + 2\ H_2O \rightarrow 2\ NADH + 2\ H^+ + O_2$$



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

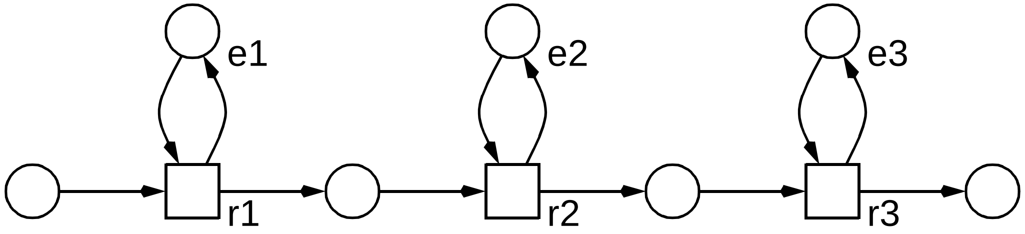
- **atomic actions -> Petri net transitions -> chemical reactions**

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



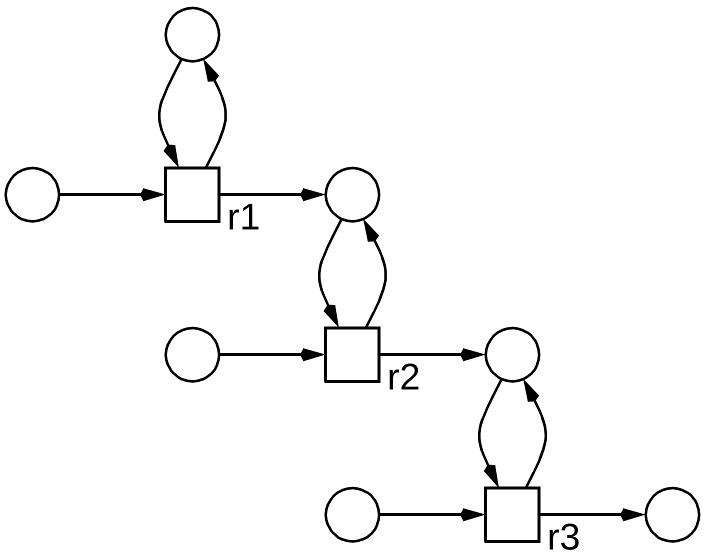
- **metabolic networks**

  -> substance flows

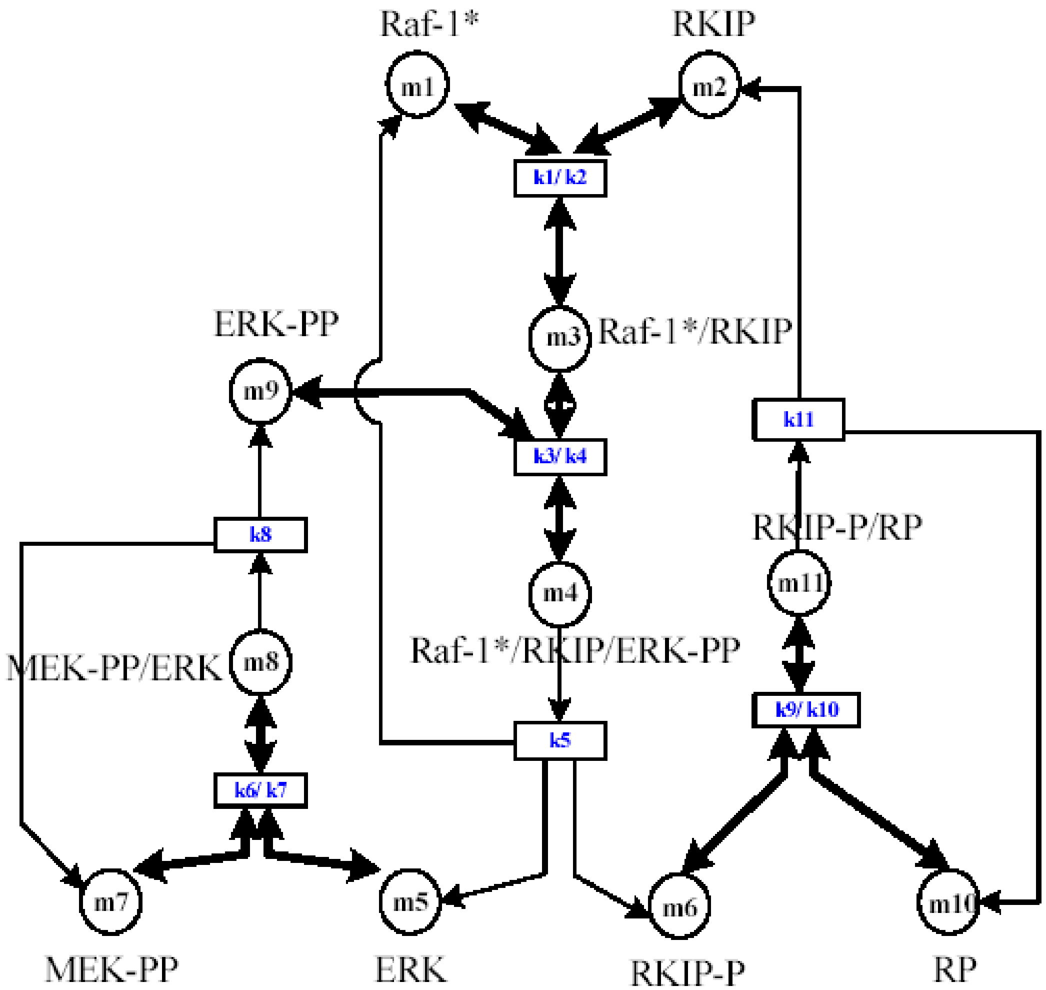


- **signal transduction networks**

  -> signal flows



THE RUNNING EXAMPLE - THE RKIP PATHWAY



[Cho et al., CMSB 2003]

BIOCHEMICAL PETRI NETS, SUMMARY

- **biochemical networks**

  -> *networks of (abstract) chemical reactions*

- **biochemically interpreted Petri net**

  -> *partial order sequences of chemical reactions*
  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*

ANALYSIS TECHNIQUES

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 ?*

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

$C =$

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

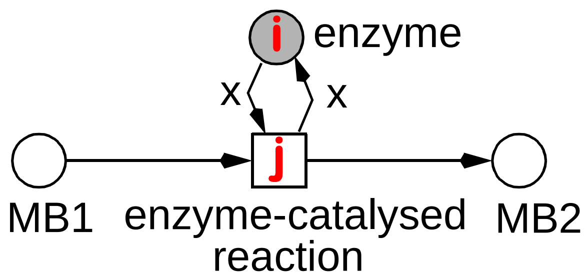
$cij = (pi, tj) = F(tj,pi) - F(pi, tj) = \Delta\ tj(pi)$

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

- **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)*

T-INVARIANTS, INTERPRETATION

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

- **realizable T-invariants correspond to cycles in the RG**
  - -> *RG: concurrency of 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*

P-INVARIANTS

- **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)*

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*

- **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*

semantics / time	interleaving	partial order
linear (LTL)	**traces** (no conflict, no concurrency) Manna & Pnueli, Kröger, jsp 2001 DSSZ/LTL	**runs** (no conflict, but concurrency) Reisig tools: ?
branching (CTL)	**reachability graph** (conflict & concurrency not distinguishable) Emmerson, Clarke PROD/MARIA, INA, DSSZ/CTL	**prefix** (conflicts & concurrency) McMillan, Esparza, pd 2001 PEP

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]	?

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*

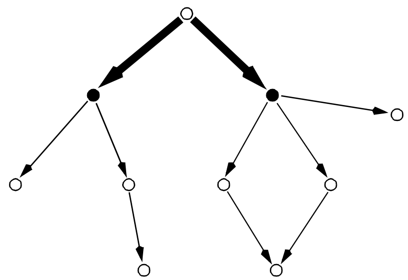
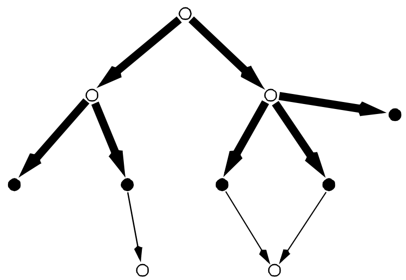
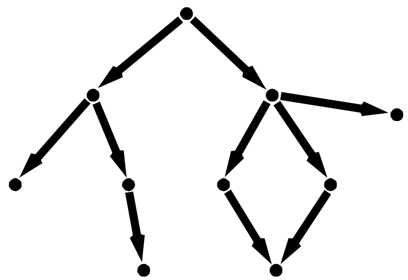
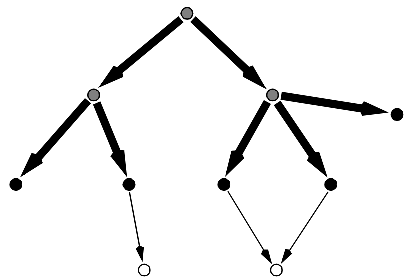
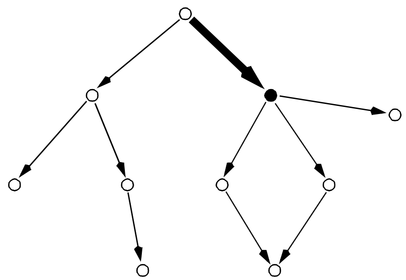
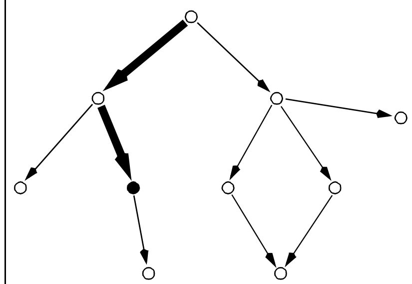
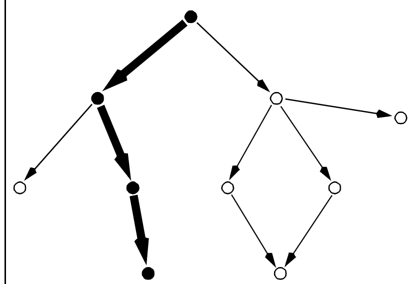
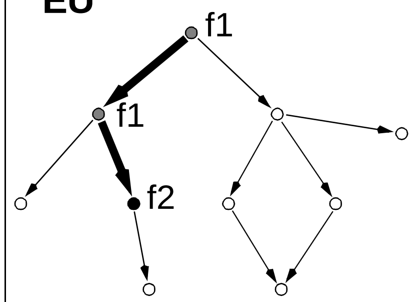
- **constants**
  - -> *TRUE, FALSE*

- **classical Boolean operators**

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

- **temporal operators**
  - -> *to refer to sequences 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** 

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*
  - -> *one Strongly Connected Component (SCC)* -> *REV*
  - -> *the only SCC contains all transitions* -> *LIVE*

- **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 !

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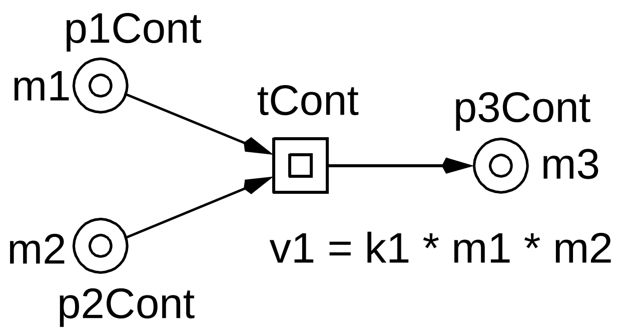
- **quantitative model = qualitative model + quantitative parameters**
  -> BUT: quantitative parameters often unknown

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

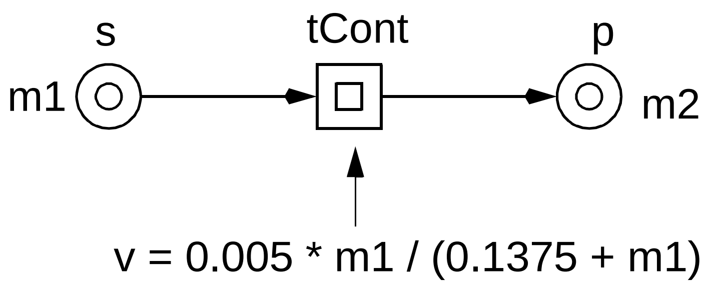
- **continuous Petri nets**

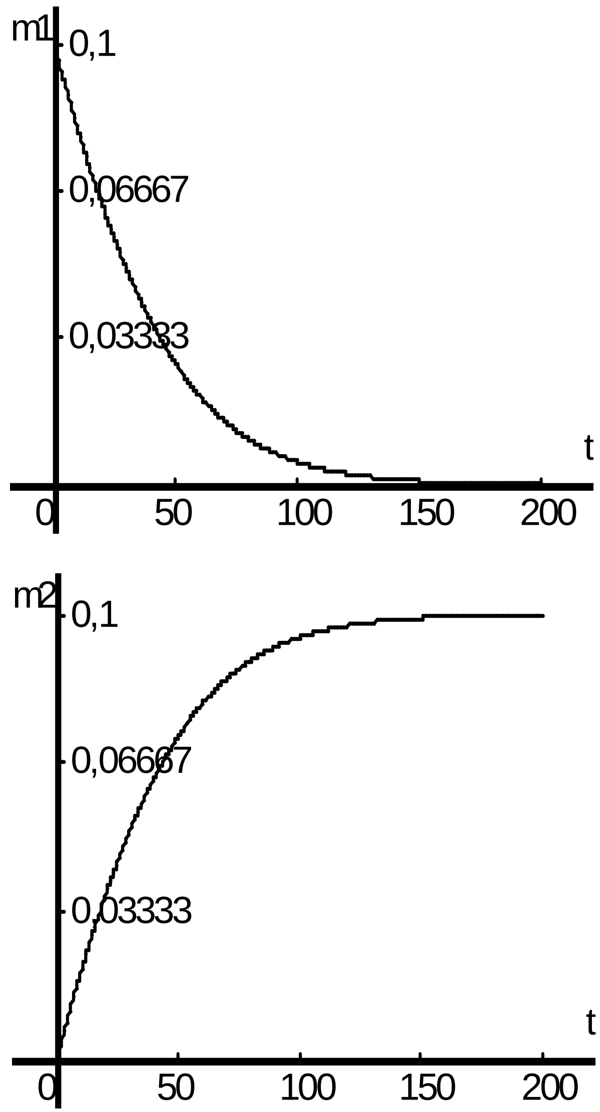


continuous nodes !

$$\left.\begin{aligned} d\,[p1Cont] / dt &= d\,[p2Cont] / dt = -\,v1 \\ d\,[p3Cont] / dt &= v1 - v2 \end{aligned}\right\}$$ **ODEs**

Example - Michaelis-Menten Reaction





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)

-> GON (Genomic Object Nets)
-> 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 ?*
- **comparison: continuous 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 !