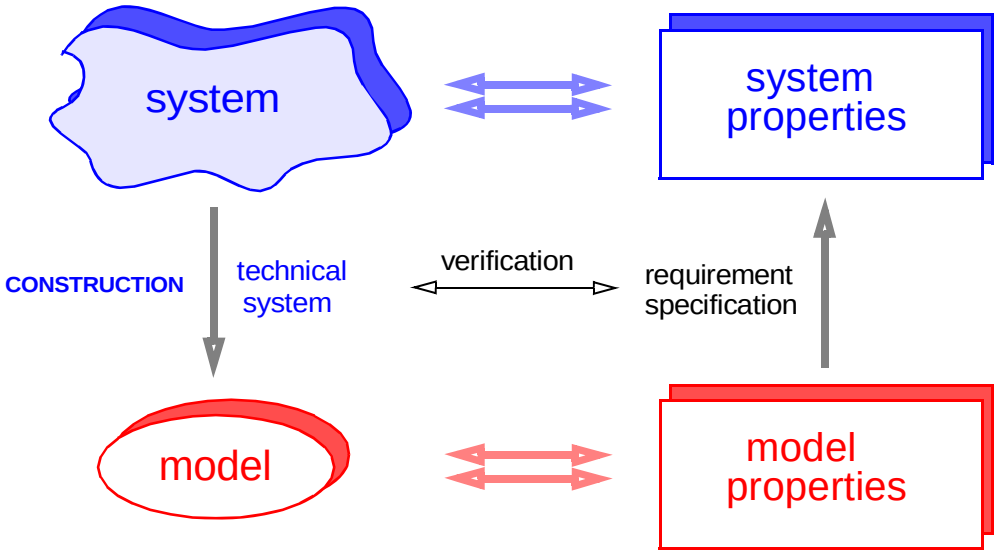
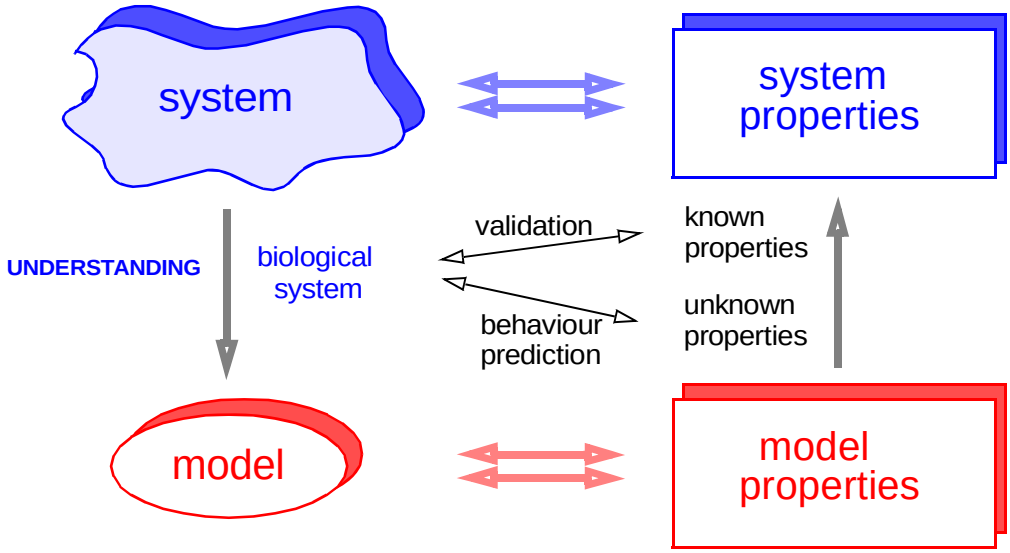
MATHEMATICAL MODELLING OF BIOCHEMICAL NETWORKS WITH PETRI NETS

Monika Heiner

Brandenburg University of Technology Cottbus

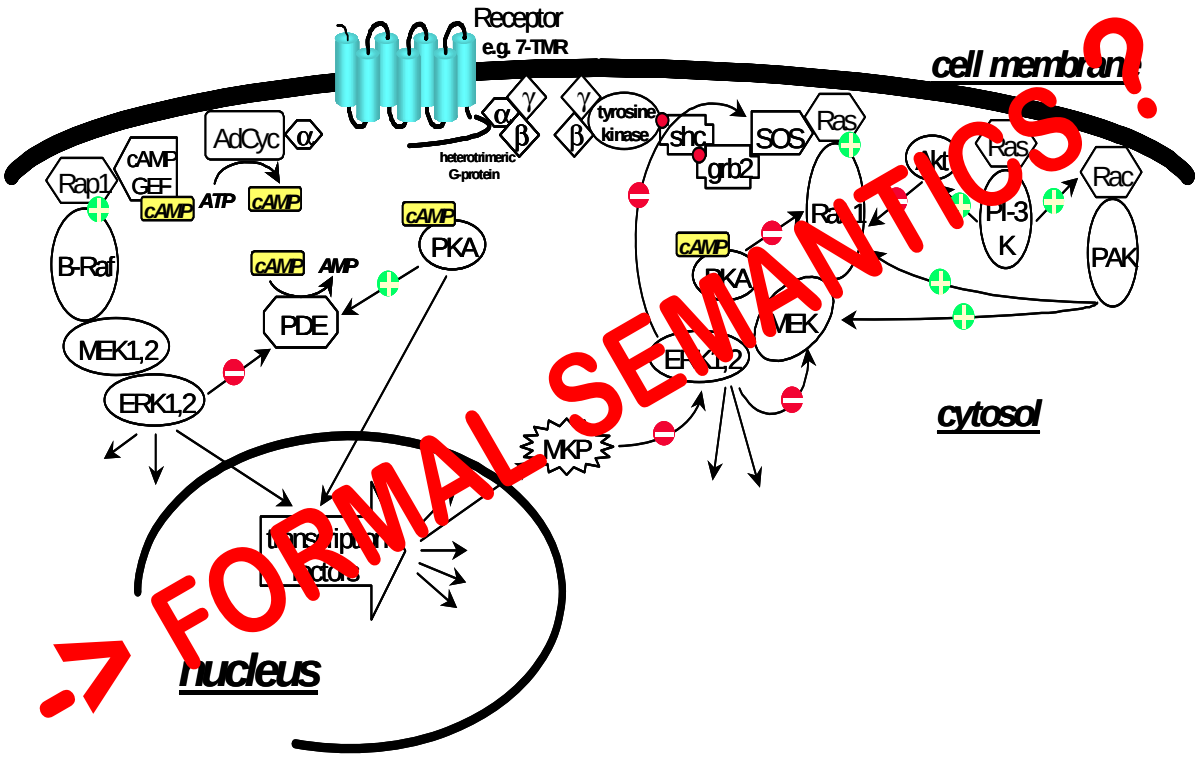
Dept. of CS





WHAT KIND OF MODEL SHOULD BE USED?

NETWORK REPRESENTATIONS, EX1



→ FORMAL SEMANTICS?

monika.heiner@informatik.tu-cottbus.de

NETWORK REPRESENTATIONS, EX2

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

→ READABILITY?

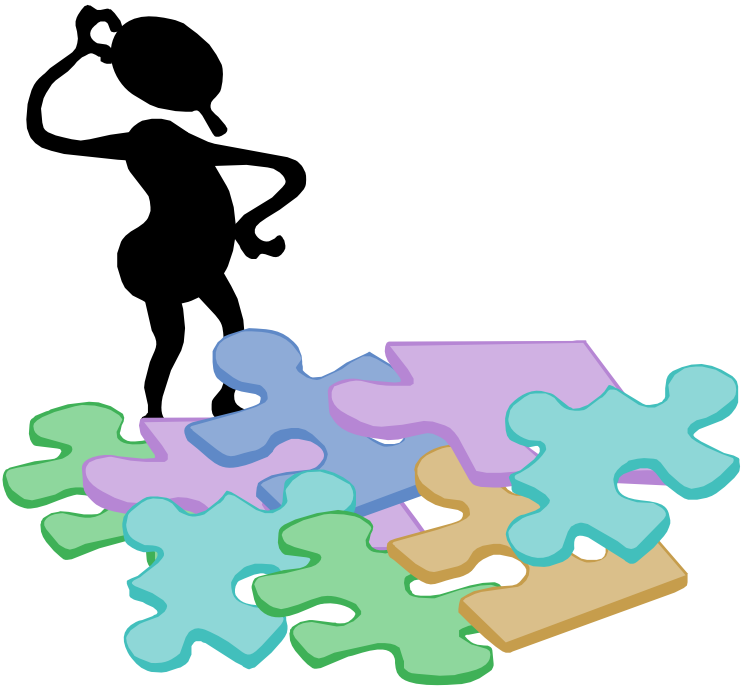
$$v_1 = \alpha[t] \cdot Bar1_{active}[t] \cdot k_1$$
$$v_2 = Ste2[t] \cdot \alpha[t] \cdot k_2$$
$$v_3 = Ste2_{active}[t] \cdot k_3$$
$$v_4 = Ste2_{active}[t] \cdot k_4$$
$$v_5 = Ste2[t] \cdot k_5$$
$$v_6 = Sst2_{active}[t] \cdot G\alpha\beta\gamma[t] \cdot k_6$$
$$v_7 = G\alpha GTP[t] \cdot k_7$$
$$v_8 = G\alpha GTP[t] \cdot Sst2_{active}[t] \cdot k_8$$
$$v_9 = G\alpha GDP[t] \cdot G\beta\gamma[t] \cdot k_9$$
$$v_{10} = G\beta\gamma[t] \cdot C[t] \cdot k_{10}$$
$$v_{11} = D[t] \cdot k_{11}$$
$$v_{12} = Ste5[t] \cdot Ste11[t] \cdot k_{12}$$
$$v_{13} = A[t] \cdot k_{13}$$
$$v_{14} = Ste7[t] \cdot Fus3[t] \cdot k_{14}$$
$$v_{15} = B[t] \cdot k_{15}$$
$$v_{16} = A[t] \cdot B[t] \cdot k_{16}$$
$$v_{17} = C[t] \cdot k_{17}$$
$$v_{18} = D[t] \cdot Ste20[t] \cdot k_{18}$$

monika.heiner@informatik.tu-cottbus.de

- **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 -

BIO NETWORKS, SOME PROBLEMS
PN & Systems Biology



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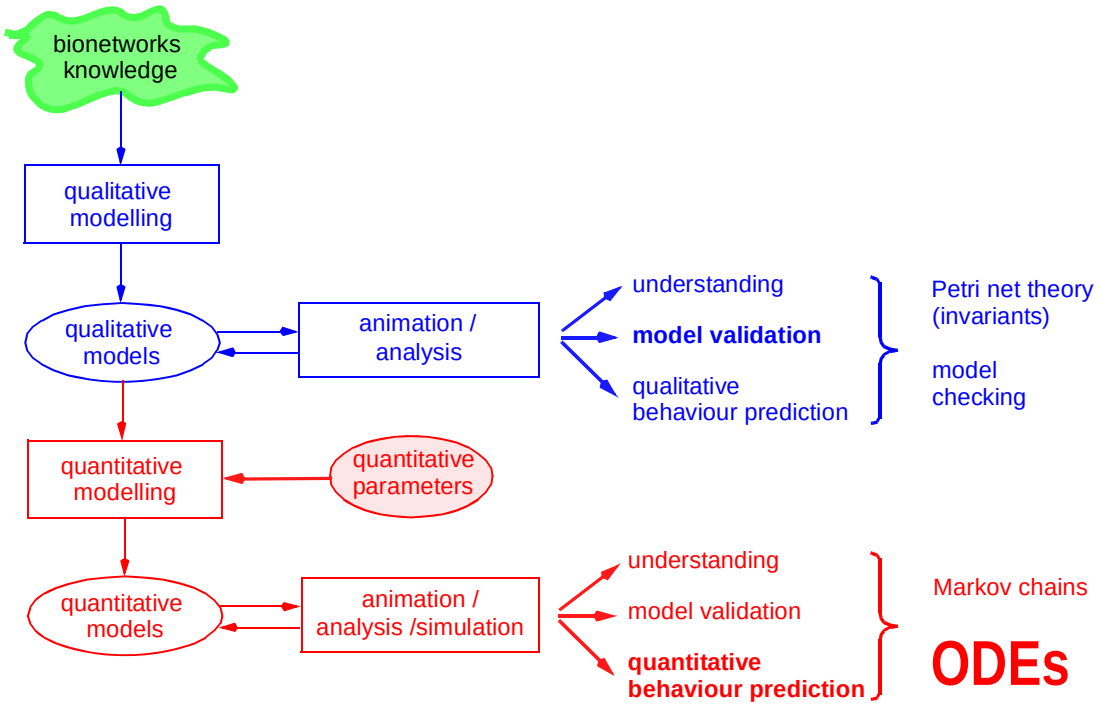
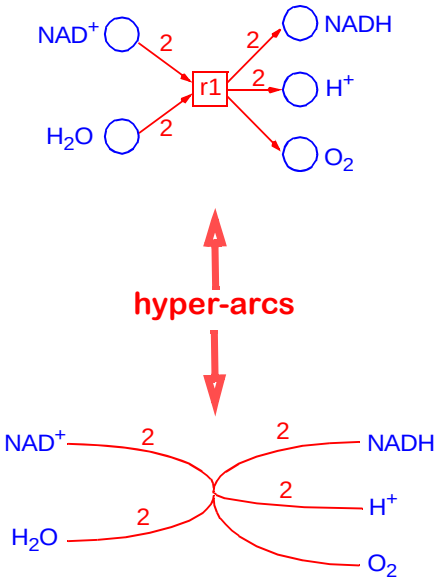


PETRI NETS -
AN INFORMAL CRASH COURSE

❑

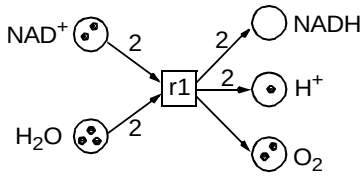
$$2\ NAD^+ + 2\ H_2O \rightarrow 2\ NADH + 2\ H^+ + O_2$$



❑ **atomic actions -> transitions -> chemical reactions**

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

input compounds



output compounds

❑ **local conditions -> places -> chemical compounds**

❑ **multiplicities -> arc weights -> stoichiometric relations**

❑ **condition's state -> token(s) -> available amount (e.g. mol)**

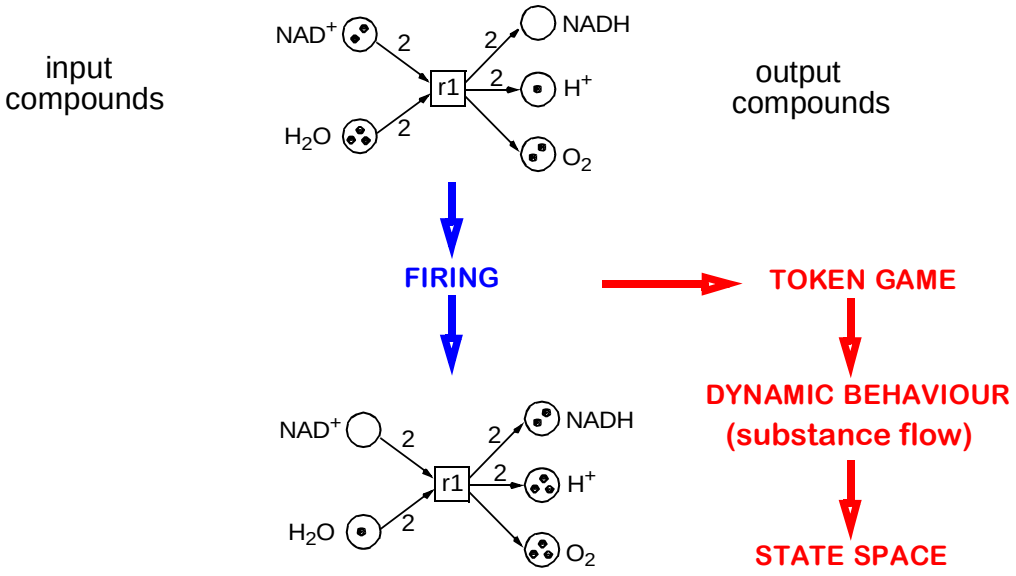
❑ **system state -> marking -> compounds distribution**

❑ **PN = (P, T, F, m_0), F: (P x T) U (T x P) -> N_0, m_0: P -> N_0**

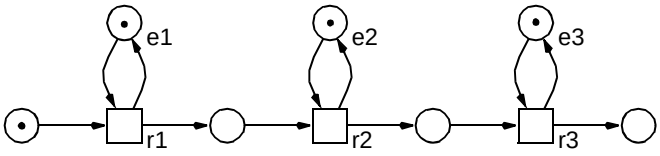
- **an action can happen, if** -> **prerequisite**
  - -> *all preconditions are fulfilled (corresponding to the arc weights);*
- **if an action happens, then** -> **firing behaviour**
  - -> *tokens are removed from all preconditions (corresponding to the arc weights), and*
  - -> *tokens are added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

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

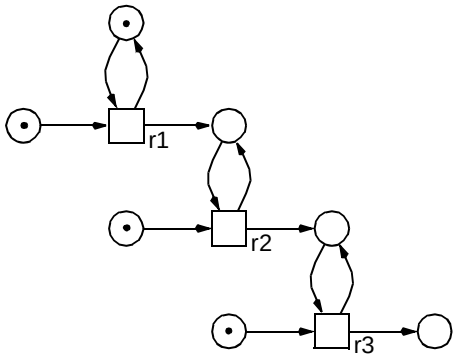
$$2\ NAD^+ + 2\ H_2O \rightarrow 2\ NADH + 2\ H^+ + O_2$$



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



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



- **METABOLIC NETWORKS**
  SIGNAL TRANSDUCTION NETWORKS
  GENE REGULATORY NETWORKS

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

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

- **tokens**
  -> *molecules, moles,*
  -> *concentration levels, gene expression levels, . . .*
  (e.g., high/low = present/not present)

- **biochemical networks**
  -> *networks of (abstract) chemical reactions*

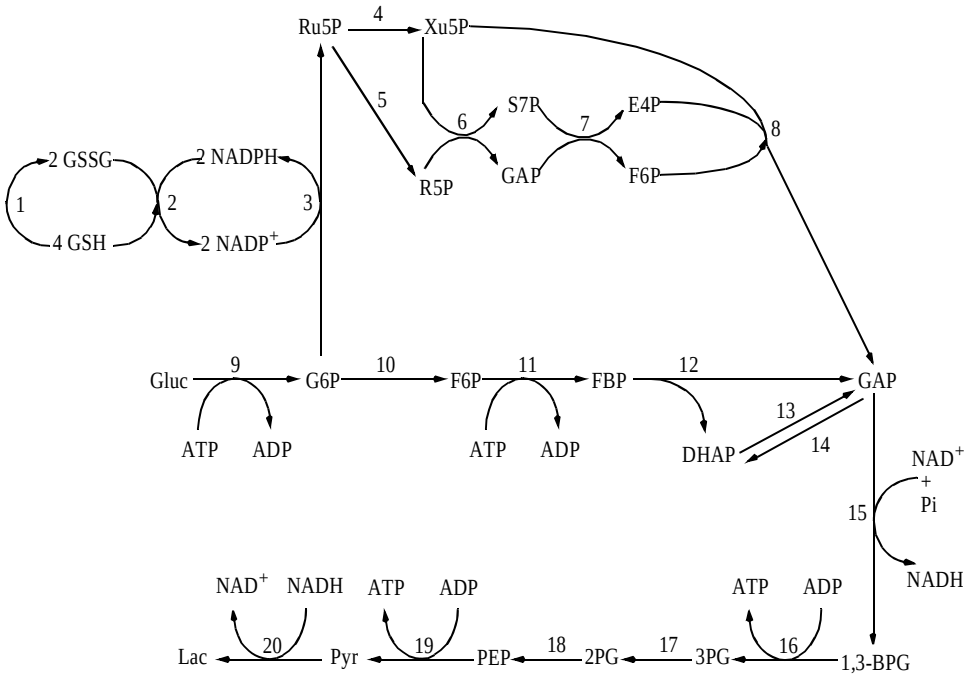
- **biochemically interpreted Petri net**
  -> *partial order sequences of chemical reactions (= elementary actions) transforming input into output compounds / signals [respecting the given stoichiometric relations, if any]*
  -> *set of all pathways from the input to the output compounds / signals [respecting the stoichiometric relations, if any]*

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

BIO PETRI NETS - SOME EXAMPLES

Ex1 - Glycolysis and Pentose Phosphate Pathway

[Reddy 1993]



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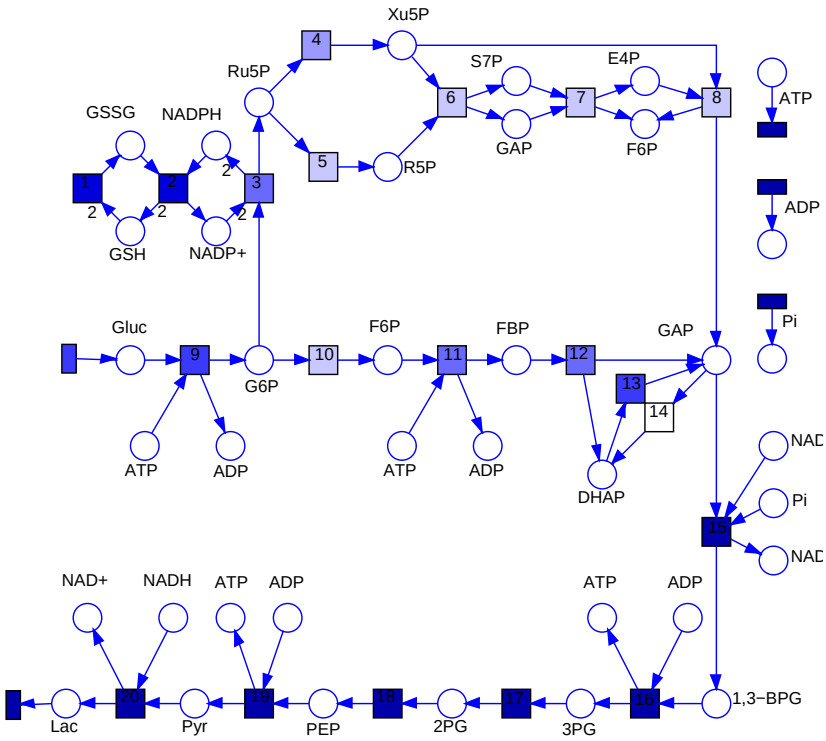
Ex1 - Glycolysis and Pentose Phosphate Pathway

[Reddy 1993]



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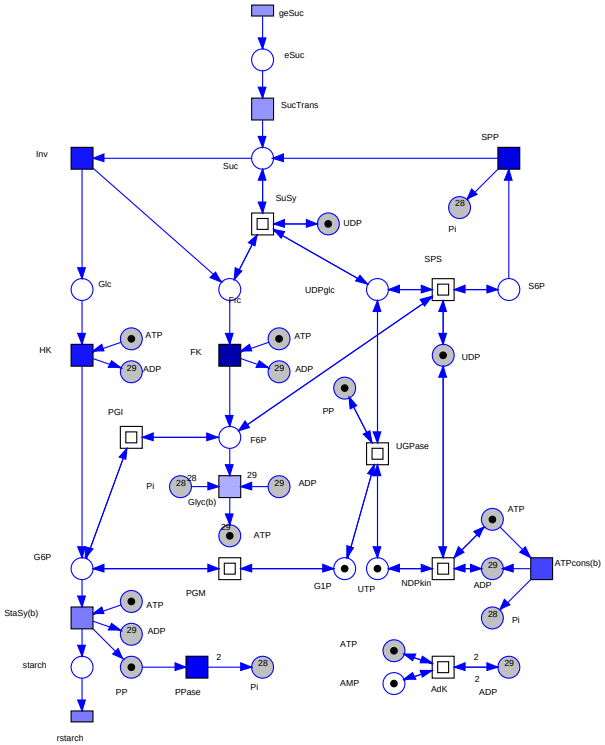
Ex2 - Carbon Metabolism in Potato Tuber

[KOCH; JUNKER; HEINER 2005]



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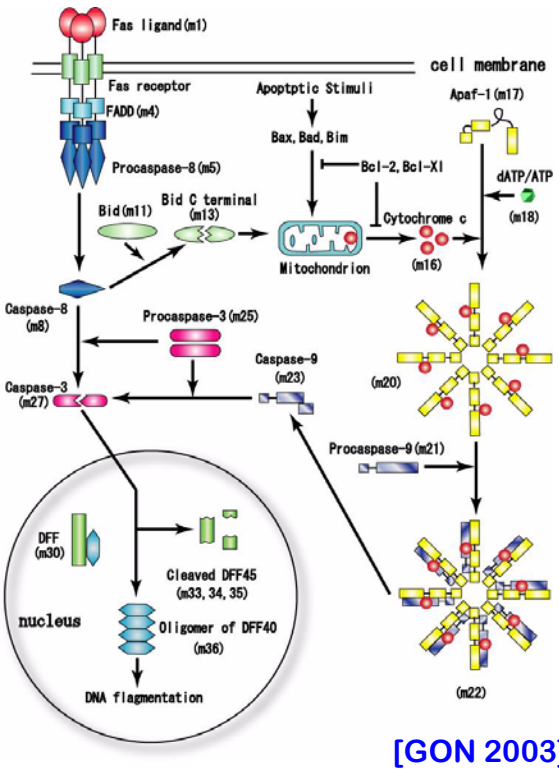
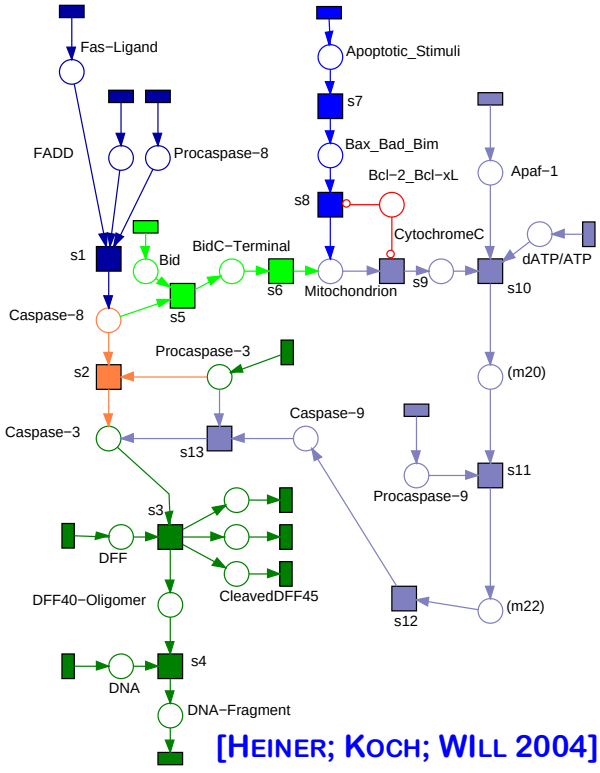
Ex3: Apoptosis in Mammalian Cells



[GON 2003]



[HEINER; KOCH; WILL 2004]

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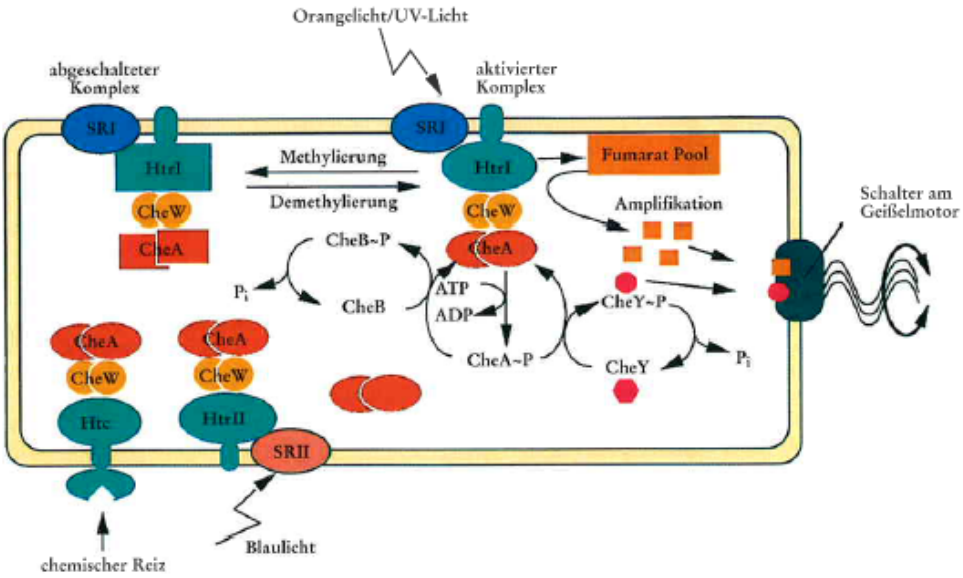
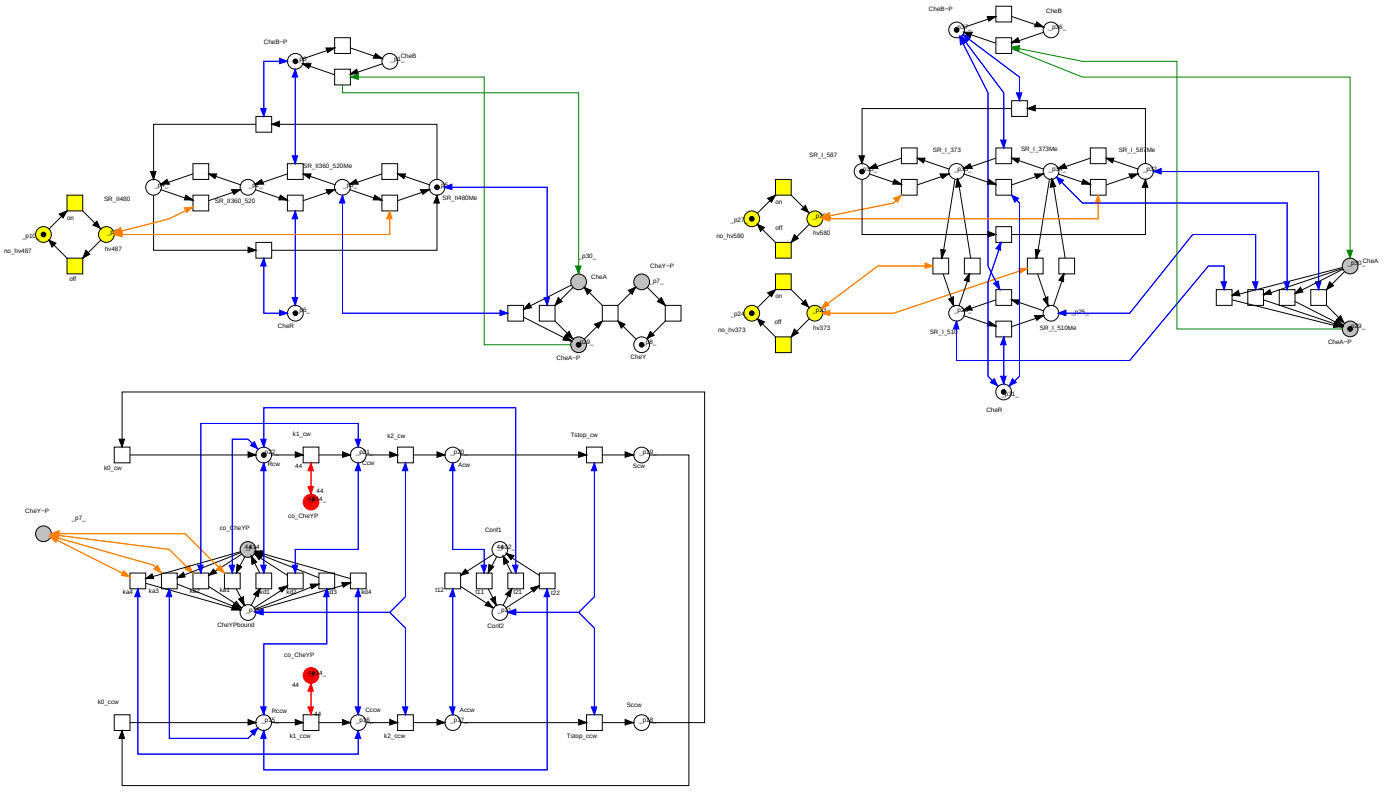


[Marwan; Oesterhelt 1999]

EX4 - SWITCH CYCLE HALOBACTERIUM SALINARUM
PN & Systems Biology



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QUALITATIVE ANALYSES

TYPICAL PETRI NET QUESTIONS

- **How many tokens can reside at most in a given place ?**
  - -> *(0, 1, k, oo)* -> *BOUNDEDNESS*
- **How often can a transition fire ?**
  - -> *(0-times, n-times, oo-times)* -> *LIVENESS*
- **How often can a system state be reached ?**
  - -> *never* -> *UNREACHABLE -> SAFETY PROPERTIES*
  - -> *n-times* -> *REPRODUCIBLE*
  - -> *always reachable again* -> *REVERSIBLE (HOME STATE)*
  - -> *reversible initial state* -> *REVERSIBILITY*
- **Are there behavourally invariant net structures ?**
  - -> *token conservation* -> *P - INVARIANTS*
  - -> *token distribution reproduction* -> *T - INVARIANTS*
- **. . . and many more -> temporal logics**

ANALYSIS TECHNIQUES

- **static analyses** **-> no state space construction**
  - -> *structural properties (graph theory)*
  - -> *P / T - invariants (linear algebra)*
- **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 constaints),
  reproducability of a given (sub-) system state (with constraints)

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

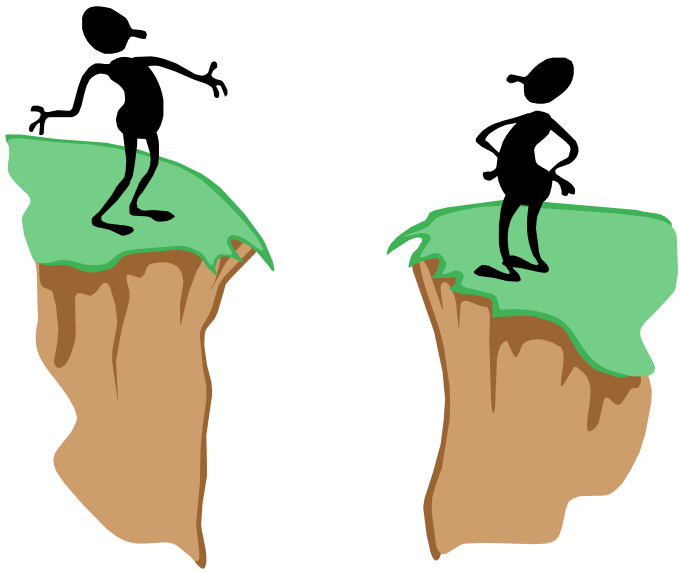
CASE STUDIES -> CREDITS

- **gene regulatory networks**
  - *bacteriophage lambda* -> *C. Chaouiya, D. Thieffry / Univ. Marseille*
- **signal-transduction networks**
  - *RKIP/MEK-ERK signalling pathway* -> *David Gilbert / Univ. Glasgow*
  - *yeast pheromone pathway* -> *Andrea Sackmann, Ina Koch / TFH Berlin*
  - *G1/S - phase in mammalian cells* -> *Thomas Kaunath, Ina Koch / TFH Berlin*
  - *E. coli pathway* -> *Nina Kramer, Ina Koch / TFH Berlin*
  - *lipoprotein metabolism (liver)* -> *Daniel Schrödter / BTU Cottbus*
  - *apoptosis in mammalian cells* -> *Jürgen Will / BTU Cottbus*
  - *blood coagulation, hemostasis* -> *Gerry Neumann / BTU Cottbus*
  - *switch cycle halobacterium salinarum* -> *Wolfgang Marwan / MPI Magdeburg*
- **metabolic networks**
  - *glycolysis in humans* -> *Thomas Runge / BTU Cottbus*
  - *carbon metabolism in potato tuber* -> *Björn Junker / IPK Gatersleben*

SUMMARY

- **representation of bionetworks by Petri nets**
  - -> *partial order representation* -> *better comprehension*
  - -> *formal semantics* -> *sound analysis techniques*
  - -> *unifying view*
- **purposes**
  - -> *animation* -> *to experience the model*
  - -> *model validation against consistency criteria* -> *to increase confidence*
  - -> *qualitative / quantitative behaviour prediction* -> *experiment design, new insights*
- **step-wise model development**
  - -> *qualitative model* -> *discrete Petri nets*
  - -> *discrete quantitative model* -> *stochastic Petri nets*
  - -> *continuous quantitative model* -> *continuous Petri nets = ODEs*

OUTLOOK



THANKS !

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