SYSTEMS BIOLOGY

- A PETRI NET PERSPECTIVE -

WHAT HAVE TECHNICAL AND NATURAL SYSTEMS IN COMMON?

Monika Heiner

Brandenburg University of Technology Cottbus

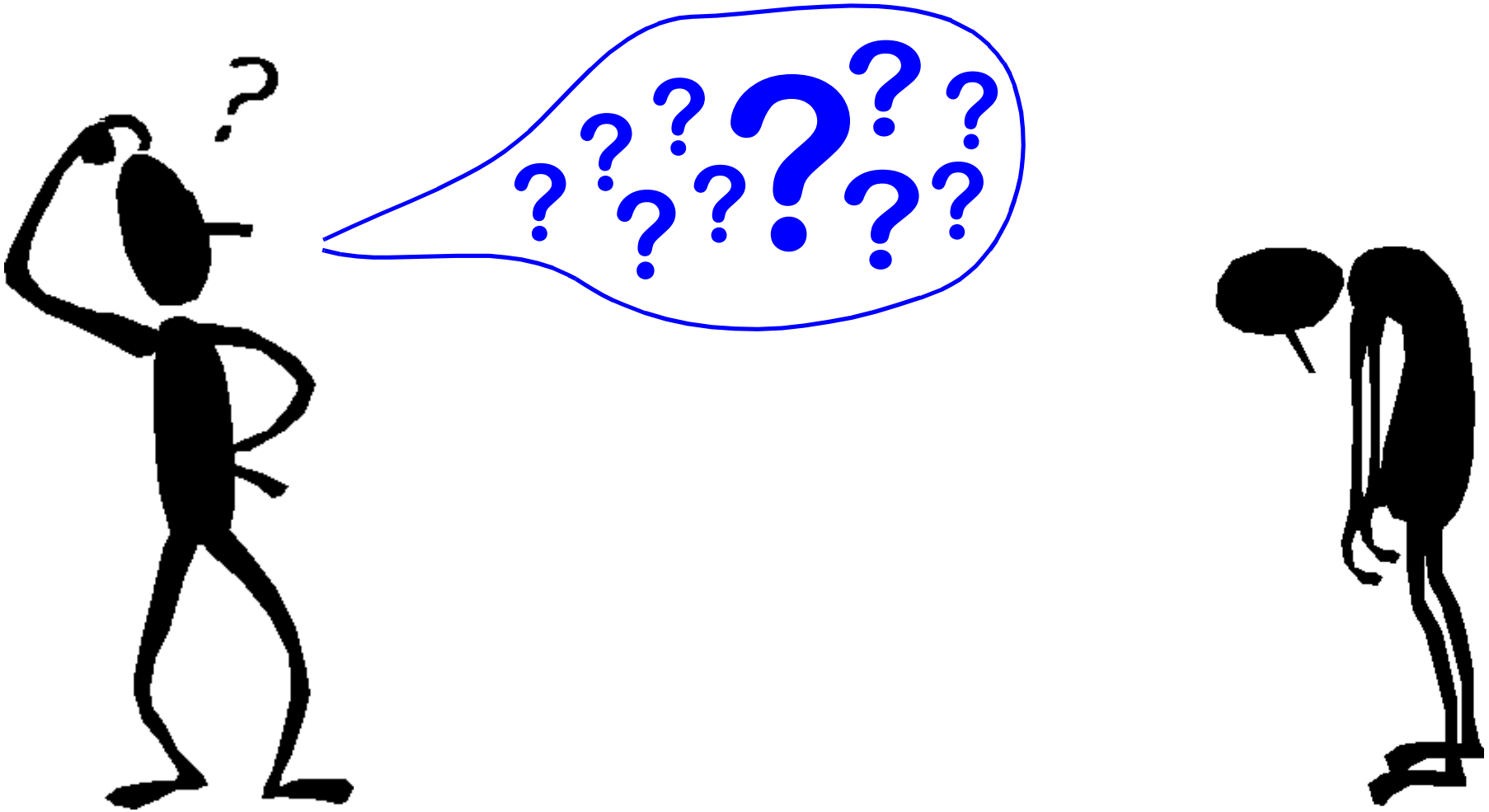
Dept. of CS

LONG-TERM VISION

MEDICAL TREATMENT

LONG-TERM VISION

MEDICAL TREATMENT, APPROACH 1- TRIAL-AND-ERROR DRUG PRESCRIPTION



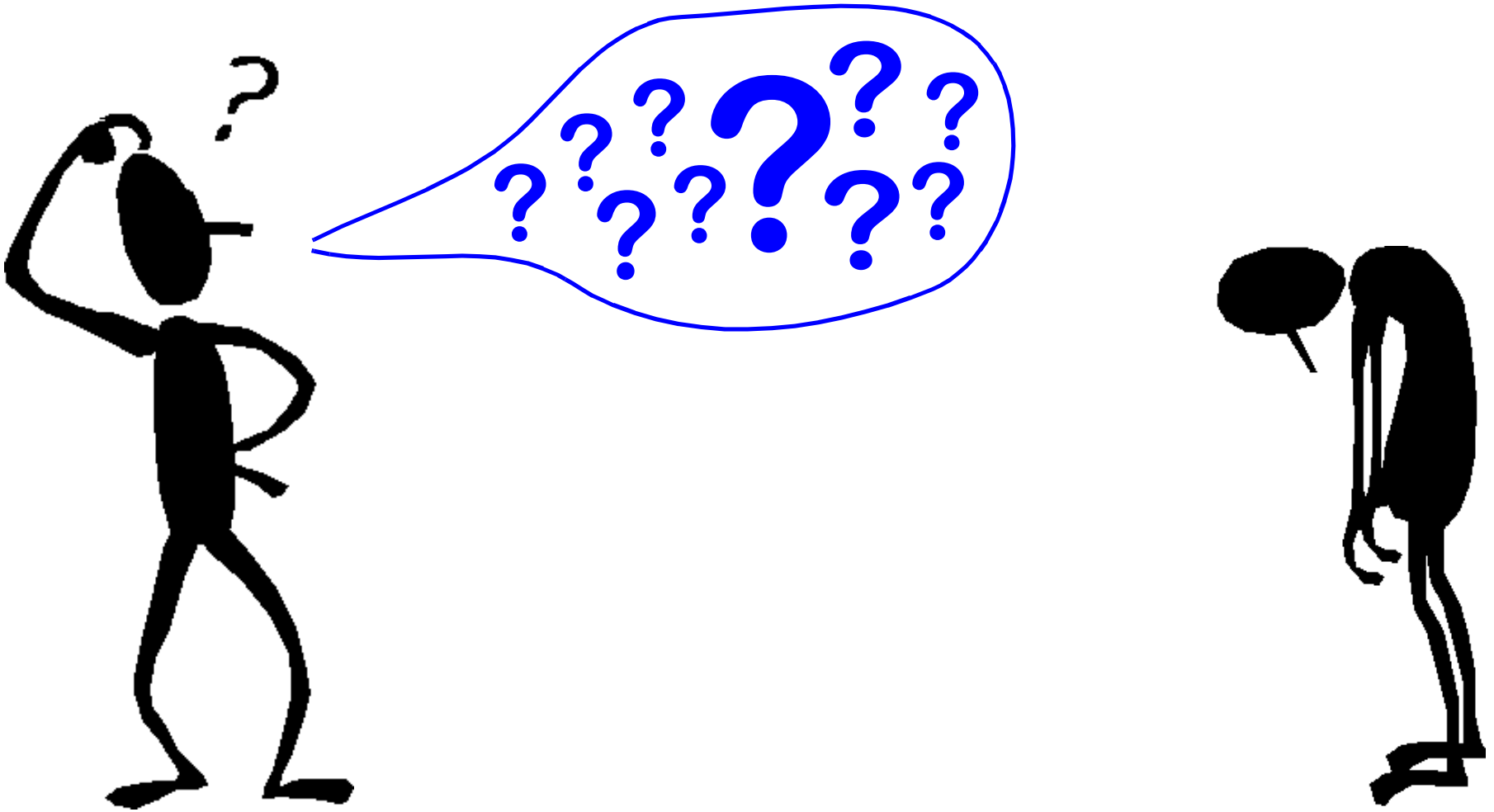
LONG-TERM VISION

MEDICAL TREATMENT, APPROACH 1- TRIAL-AND-ERROR DRUG PRESCRIPTION

LONG-TERM VISION

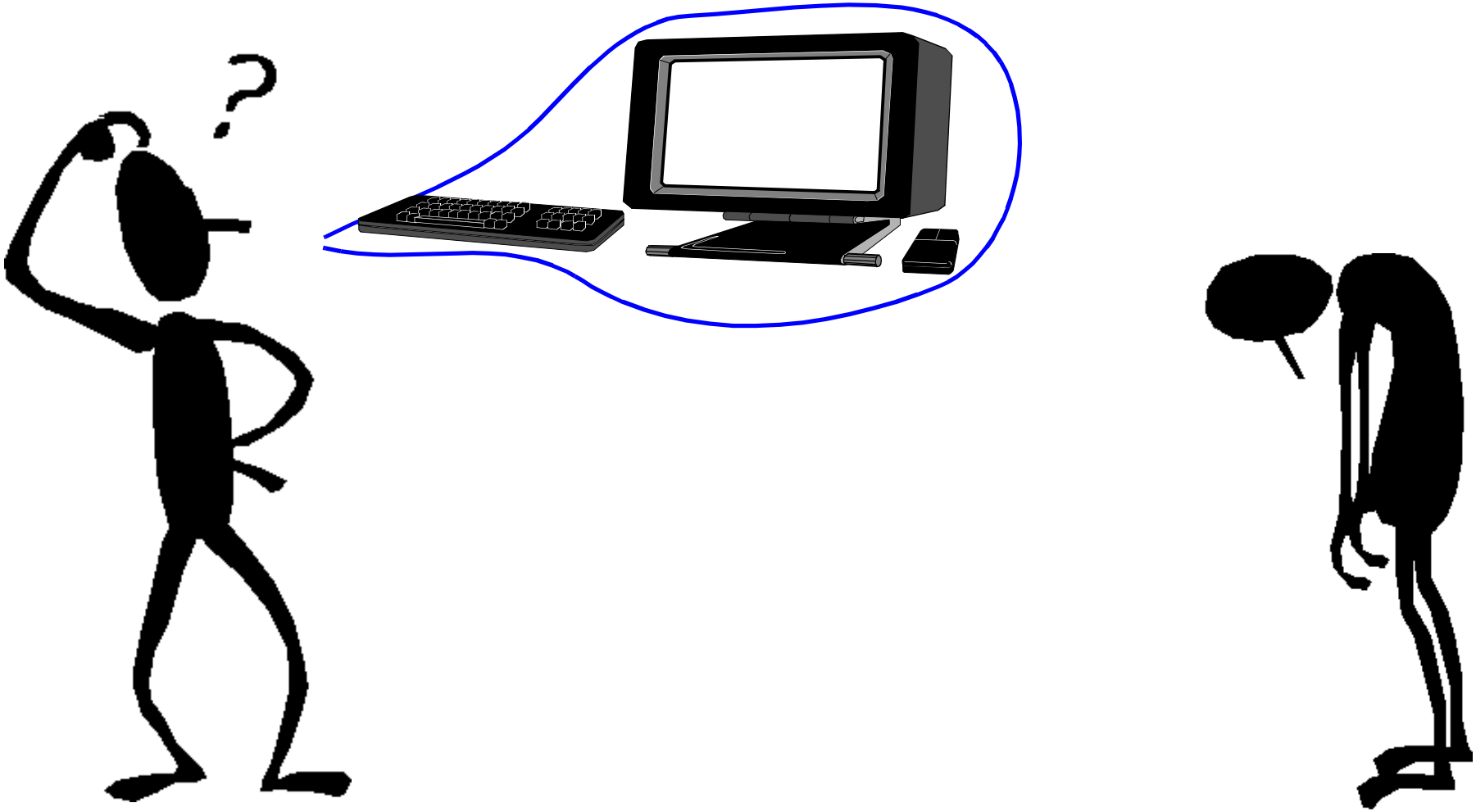
MEDICAL TREATMENT, APPROACH 1- TRIAL-AND-ERROR DRUG PRESCRIPTION

MEDICAL TREATMENT, APPROACH 2



LONG-TERM VISION

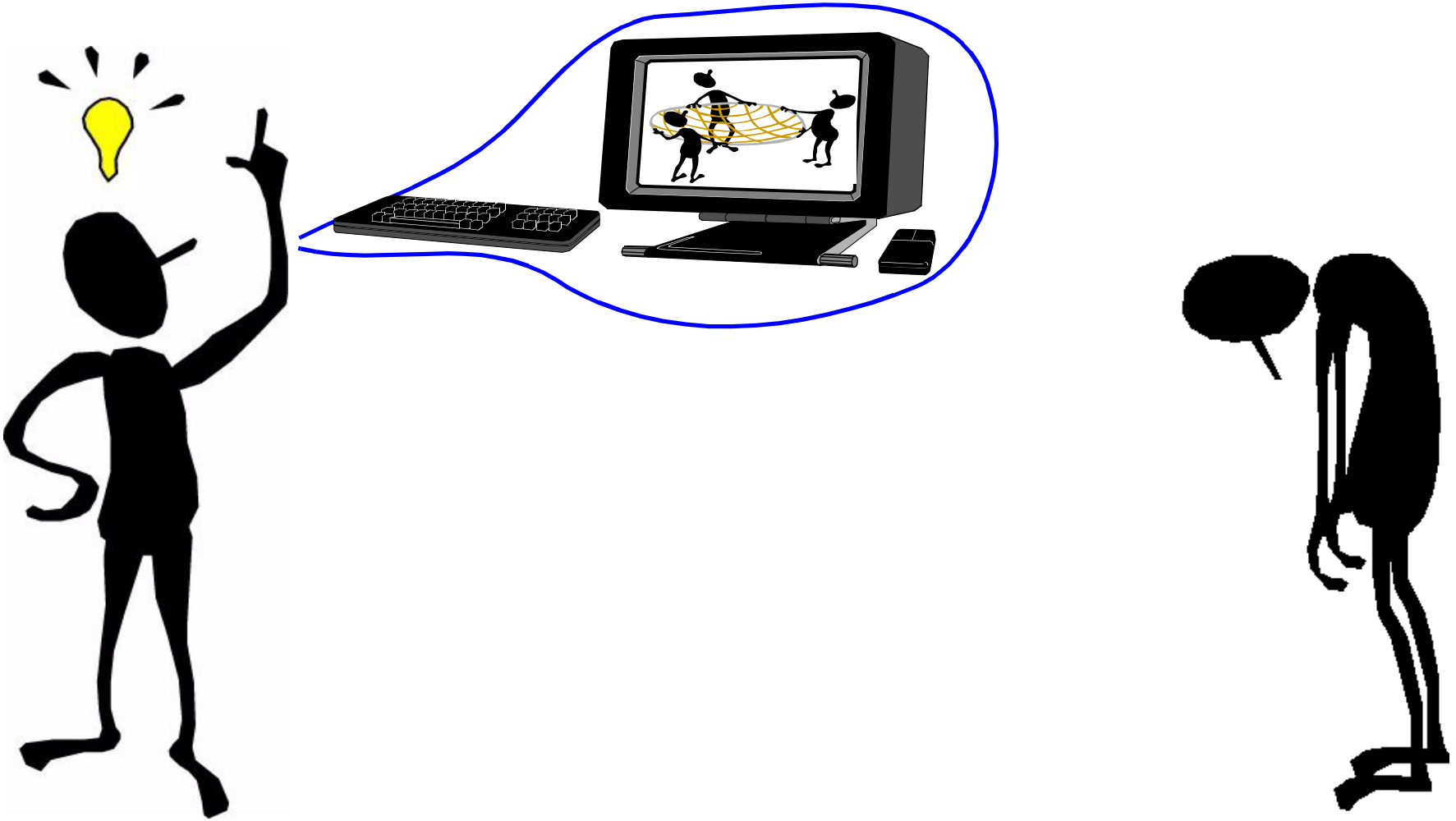
MEDICAL TREATMENT, APPROACH 2 - MODEL-BASED DRUG PRESCRIPTION



monika.heiner@informatik.tu-cottbus.de

LONG-TERM VISION

MEDICAL TREATMENT, APPROACH 2 - MODEL-BASED DRUG PRESCRIPTION

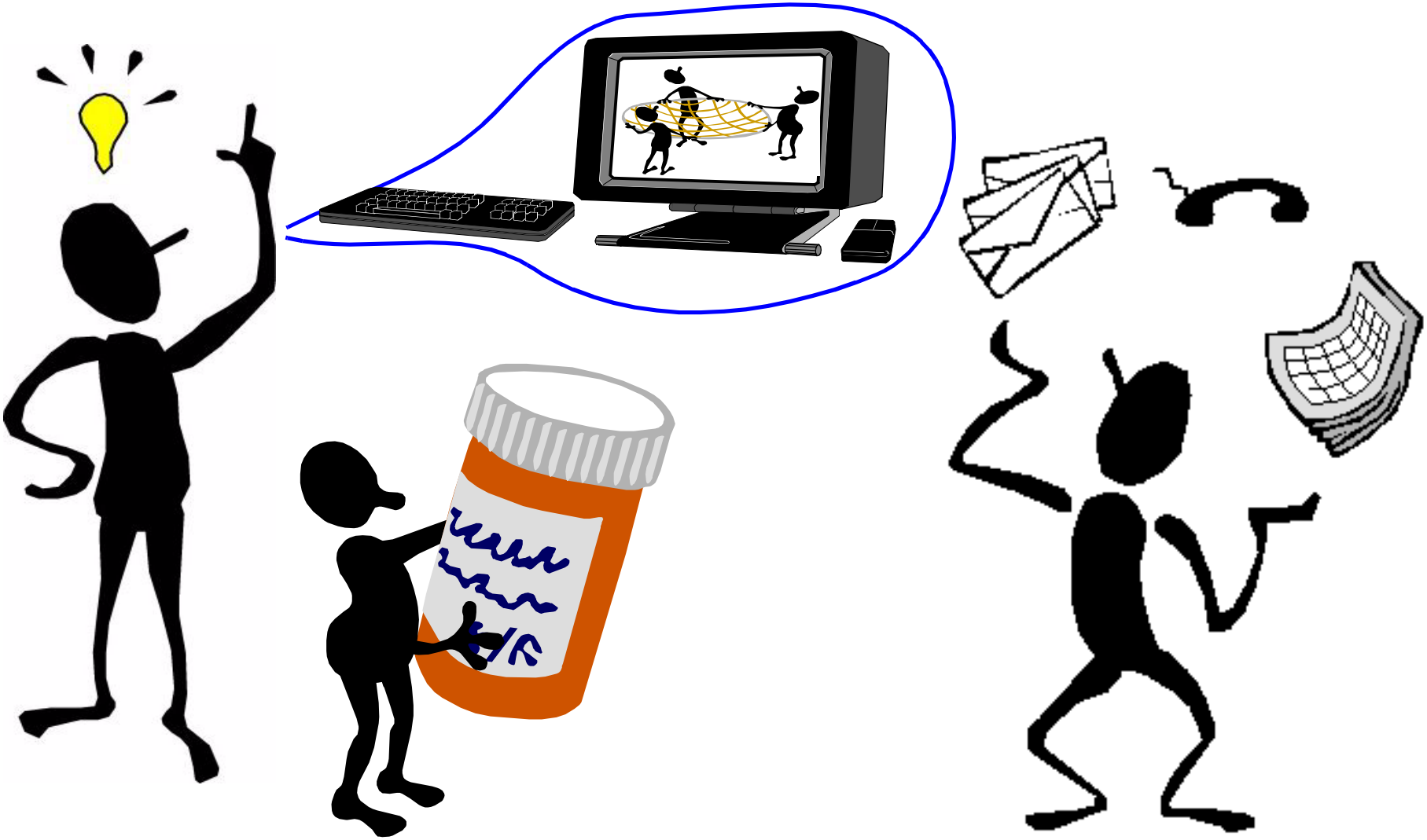


LONG-TERM VISION

MEDICAL TREATMENT, APPROACH 2 - MODEL-BASED DRUG PRESCRIPTION

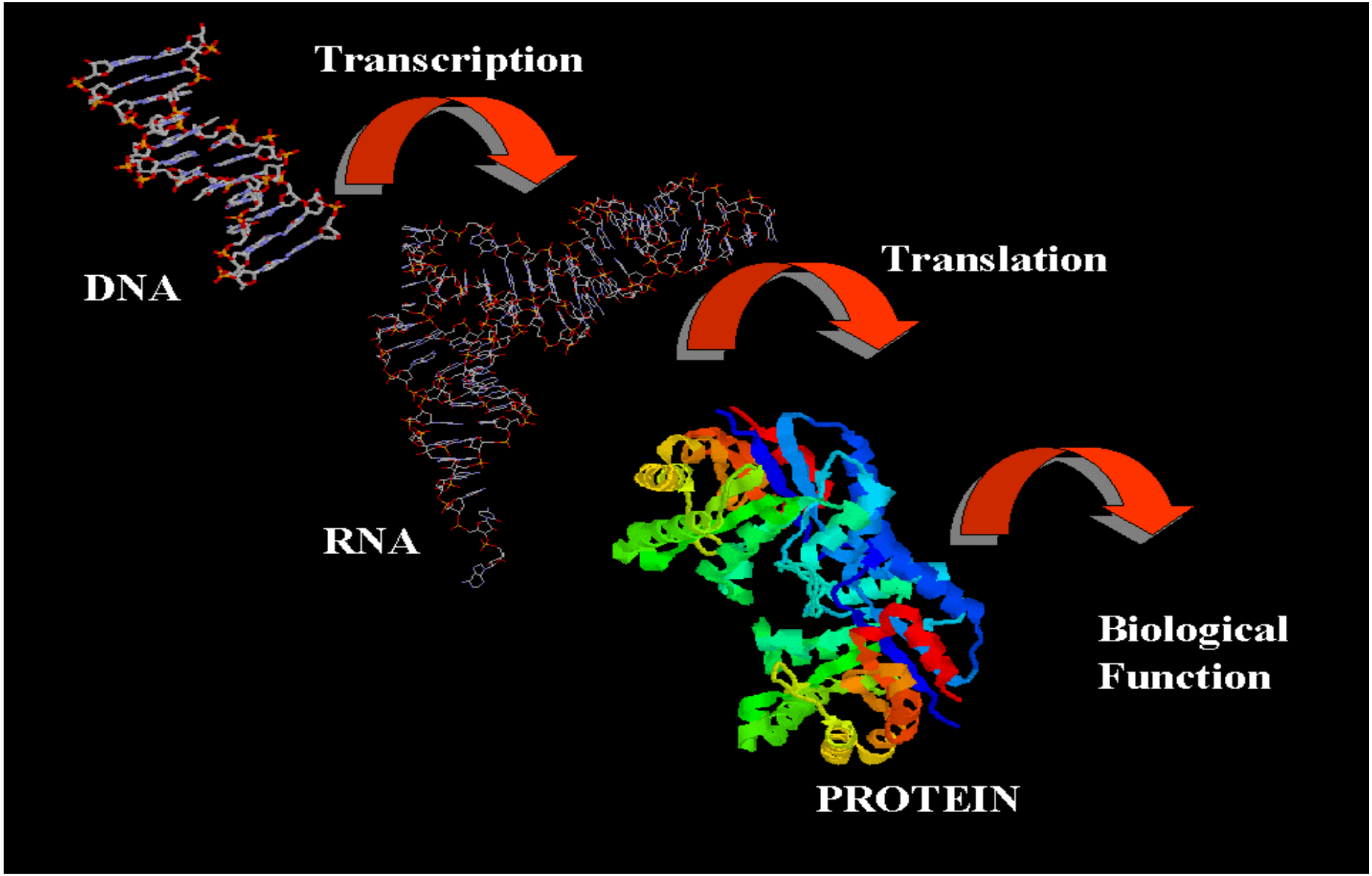
LONG-TERM VISION

MEDICAL TREATMENT, APPROACH 2 - MODEL-BASED DRUG PRESCRIPTION

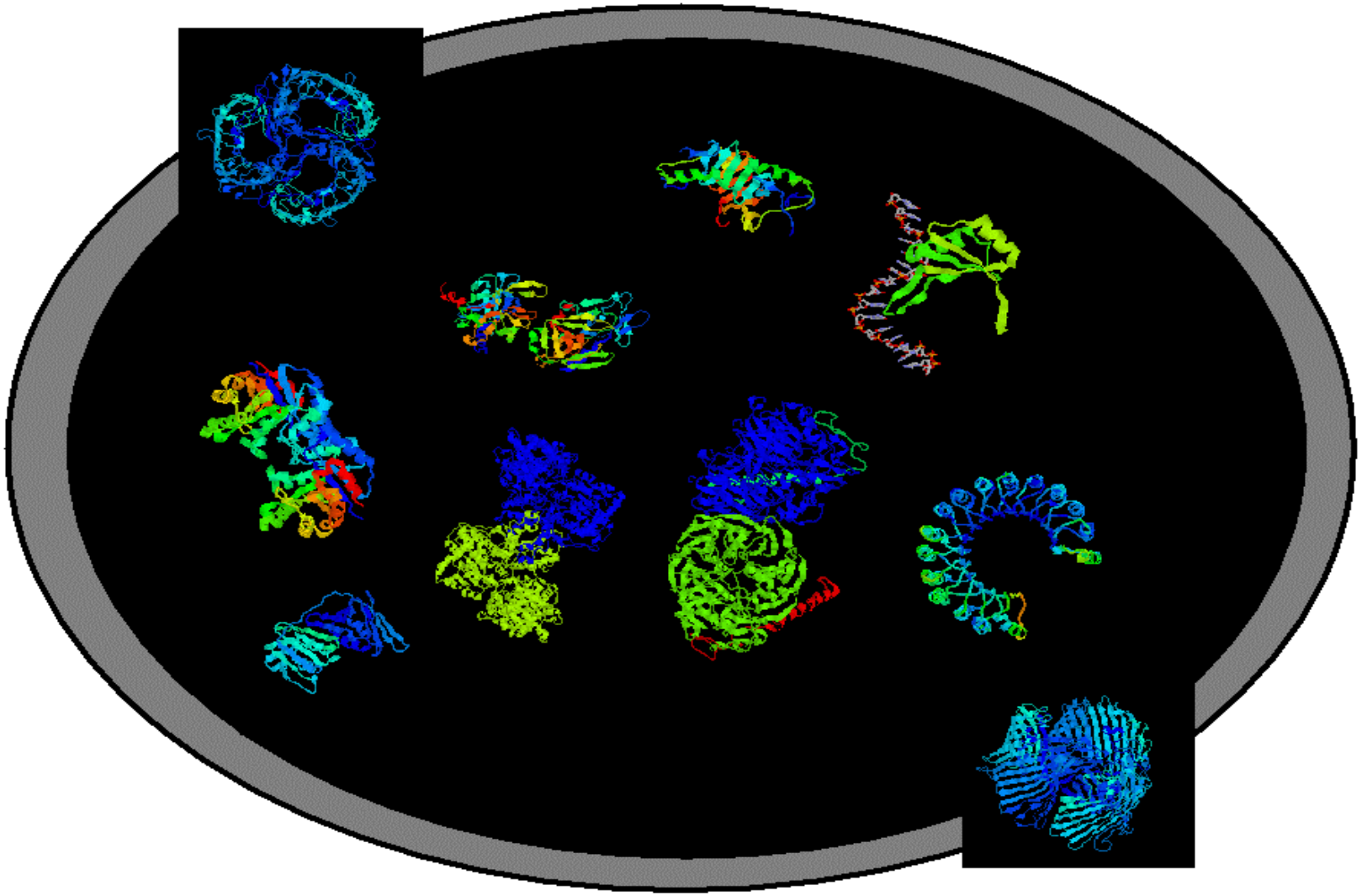


WHAT KIND OF MODEL SHOULD BE USED?

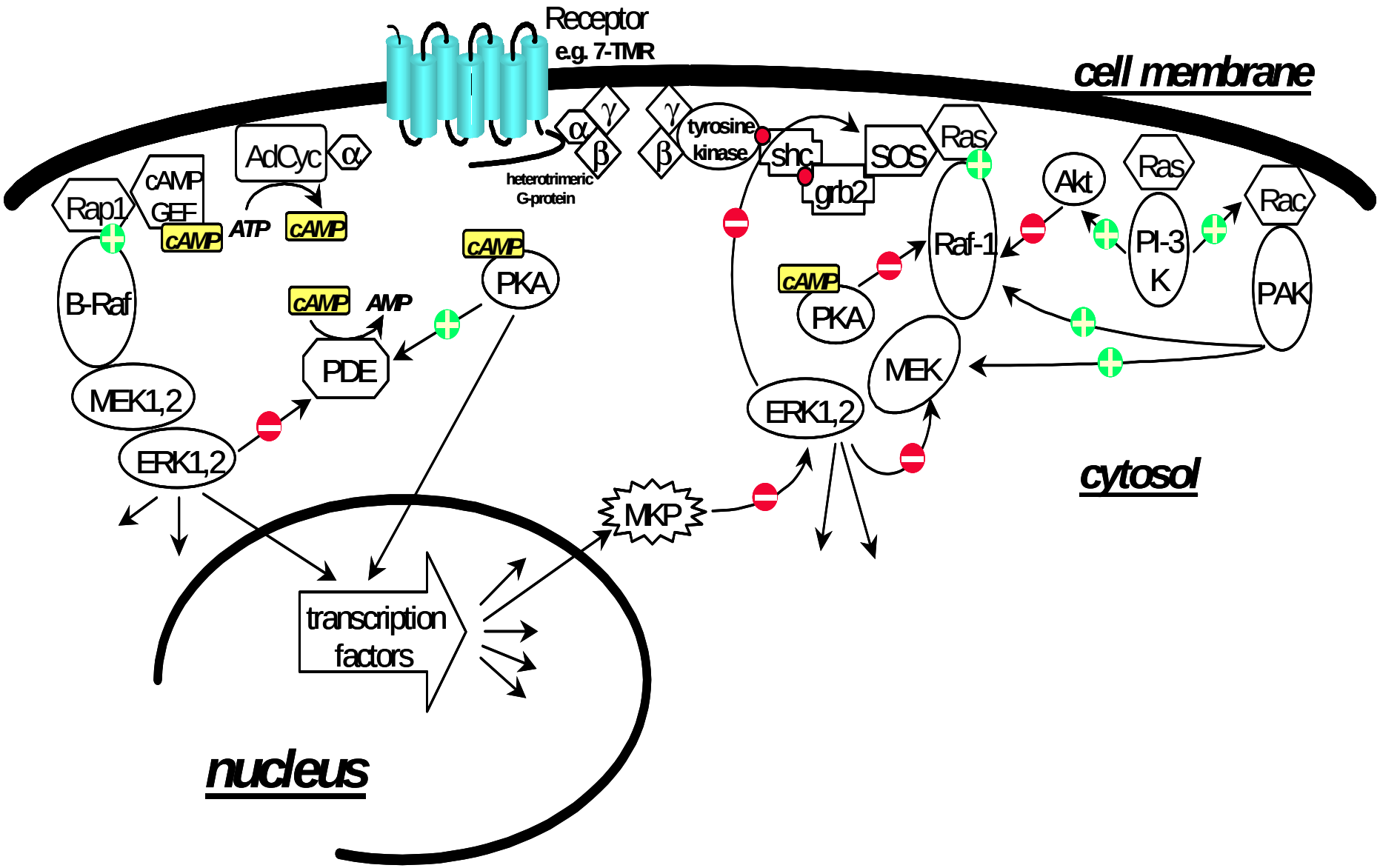
BIOLOGICAL FUNCTION ?



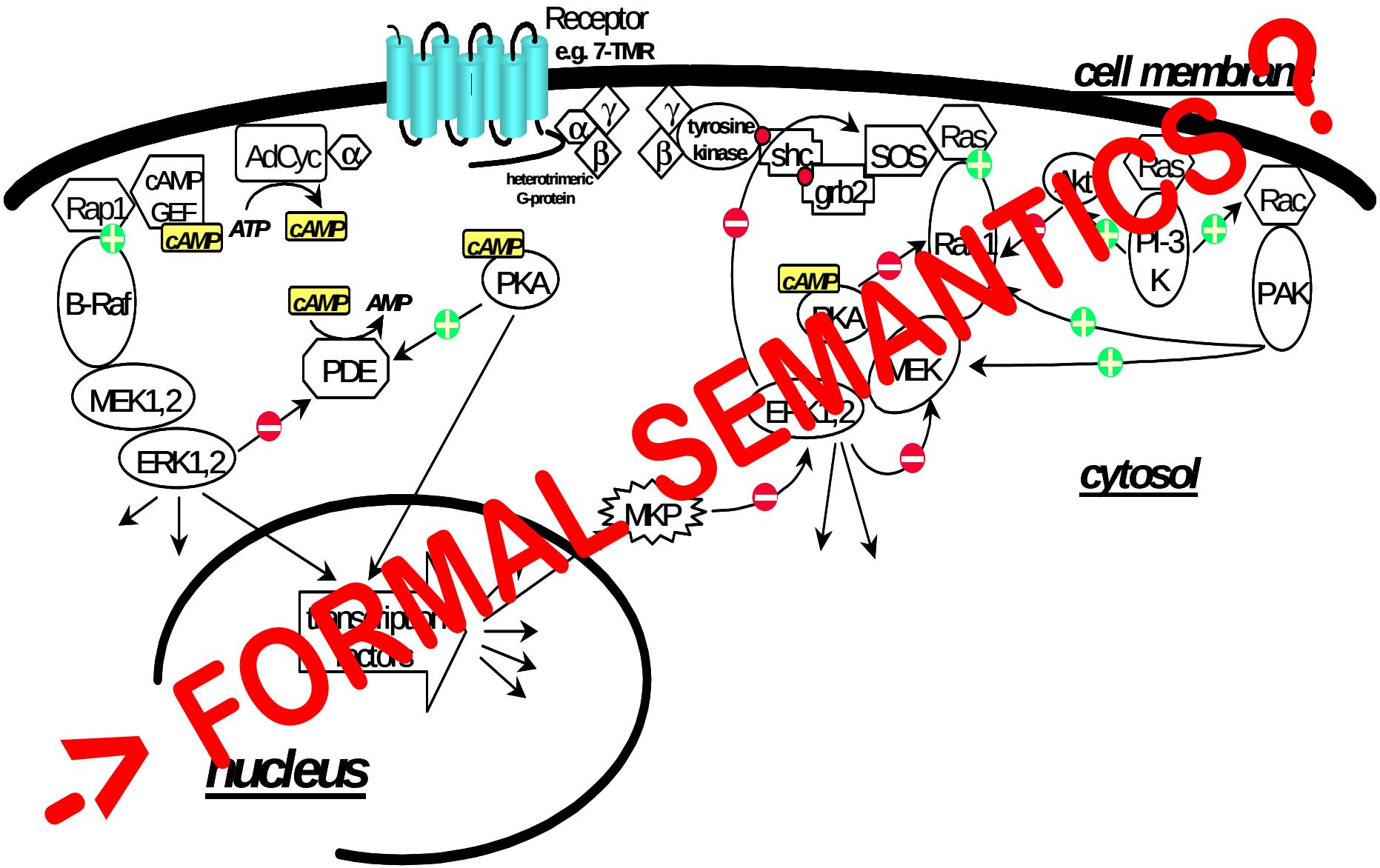
. . . BY INTERACTION IN NETWORKS



NETWORK REPRESENTATIONS, EX1



NETWORK REPRESENTATIONS, EX1



NETWORK REPRESENTATIONS, EX2

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

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

NETWORK REPRESENTATIONS, EX2

$$\frac{d\alpha}{dt} = -\nu_1$$

$$\frac{dSte2}{dt} = -\nu_2 + \nu_3 - \nu_5$$

$$\frac{dSte2_{active}}{dt} = \nu_2 - \nu_3 - \nu_4$$

$$\frac{dSst2_{active}}{dt} = \nu_{46} - \nu_{47}$$

$$\frac{dG\alpha\beta\gamma}{dt} = -\nu_6 + \nu_9$$

$$\frac{dG\alpha GTP}{dt} = \nu_6 - \nu_7 - \nu_8$$

$$\frac{dG\alpha GDP}{dt} = \nu_7 + \nu_8 - \nu_9$$

$$\frac{dG\beta\gamma}{dt} = \nu_6 - \nu_9 - \nu_{10} + \nu_{11} + \nu_{21} + \nu_{23} + \nu_{25} + \nu_{27} + \nu_{32} - \nu_{42} + \nu_{43}$$

$$\frac{dSte5}{dt} = -\nu_{12} + \nu_{13} + \nu_{17} + \nu_{21} + \nu_{23} + \nu_{25} + \nu_{27} + \nu_{32}$$

$$\frac{dSte11}{dt} = -\nu_{12} + \nu_{13} + \nu_{17} + \nu_{21} + \nu_{23} + \nu_{25} + \nu_{27} + \nu_{32}$$

$$\frac{dSte7}{dt} = -\nu_{14} + \nu_{15} + \nu_{17} + \nu_{21} + \nu_{23} + \nu_{25} + \nu_{27} + \nu_{32}$$

$$\frac{dFus3}{dt} = -\nu_{14} + \nu_{15} + \nu_{17} + \nu_{21} + \nu_{23} + \nu_{25} + \nu_{27} - \nu_{29} + \nu_{30} - \nu_{33}$$

$$\frac{dSte20}{dt} = -\nu_{18} + \nu_{19} + \nu_{21} + \nu_{23} + \nu_{25} + \nu_{27} + \nu_{32}$$

$$\nu_1 = \alpha[t] \cdot Bar1_{active}[t] \cdot k_1$$

$$\nu_2 = Ste2[t] \cdot \alpha[t] \cdot k_2$$

$$\nu_3 = Ste2_{active}[t] \cdot k_3$$

$$\nu_4 = Ste2_{active}[t] \cdot k_4$$

$$\nu_5 = Ste2[t] \cdot k_5$$

$$\nu_6 = Ste2_{active}[t] \cdot G\alpha\beta\gamma[t] \cdot k_6$$

$$\nu_7 = G\alpha GTP[t] \cdot k_7$$

$$\nu_8 = G\alpha GTP[t] \cdot Sst2_{active}[t] \cdot k_8$$

$$\nu_9 = G\alpha GDP[t] \cdot G\beta\gamma[t] \cdot k_9$$

$$\nu_{10} = G\beta\gamma[t] \cdot C[t] \cdot k_{10}$$

$$\nu_{11} = D[t] \cdot k_{11}$$

$$\nu_{12} = Ste5[t] \cdot Ste11[t] \cdot k_{12}$$

$$\nu_{13} = A[t] \cdot k_{13}$$

$$\nu_{14} = Ste7[t] \cdot Fus3[t] \cdot k_{14}$$

$$\nu_{15} = B[t] \cdot k_{15}$$

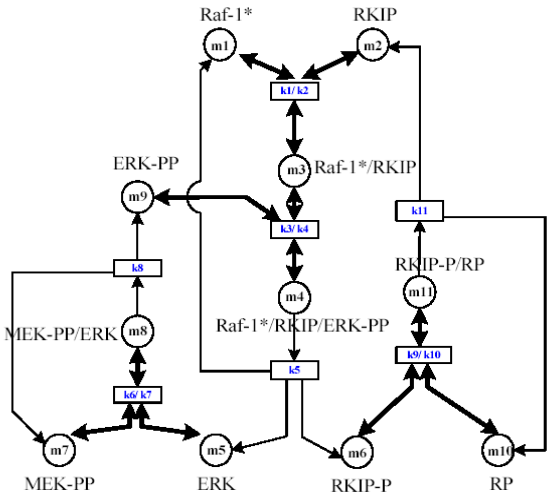
$$\nu_{16} = A[t] \cdot B[t] \cdot k_{16}$$

$$\nu_{17} = C[t] \cdot k_{17}$$

$$\nu_{18} = D[t] \cdot Ste20[t] \cdot k_{18}$$

WHAT IS A BIOCHEMICAL NETWORK MODEL?

- **structure** — graph, QUALITATIVE



- **kinetics, if you can** — reaction rates, QUANTITATIVE

  $d[Raf1^*]/dt = k1*m1*m2 + k2*m3 + k5*k4$

  $k1 = 0.53,\ k2 = 0.0072,\ k5 = 0.0315$

- **initial conditions** — concentrations, marking

  $[Raf1^*]_{t=0} = 2\ \mu Molar$

BIONETWORKS, SOME PROBLEMS

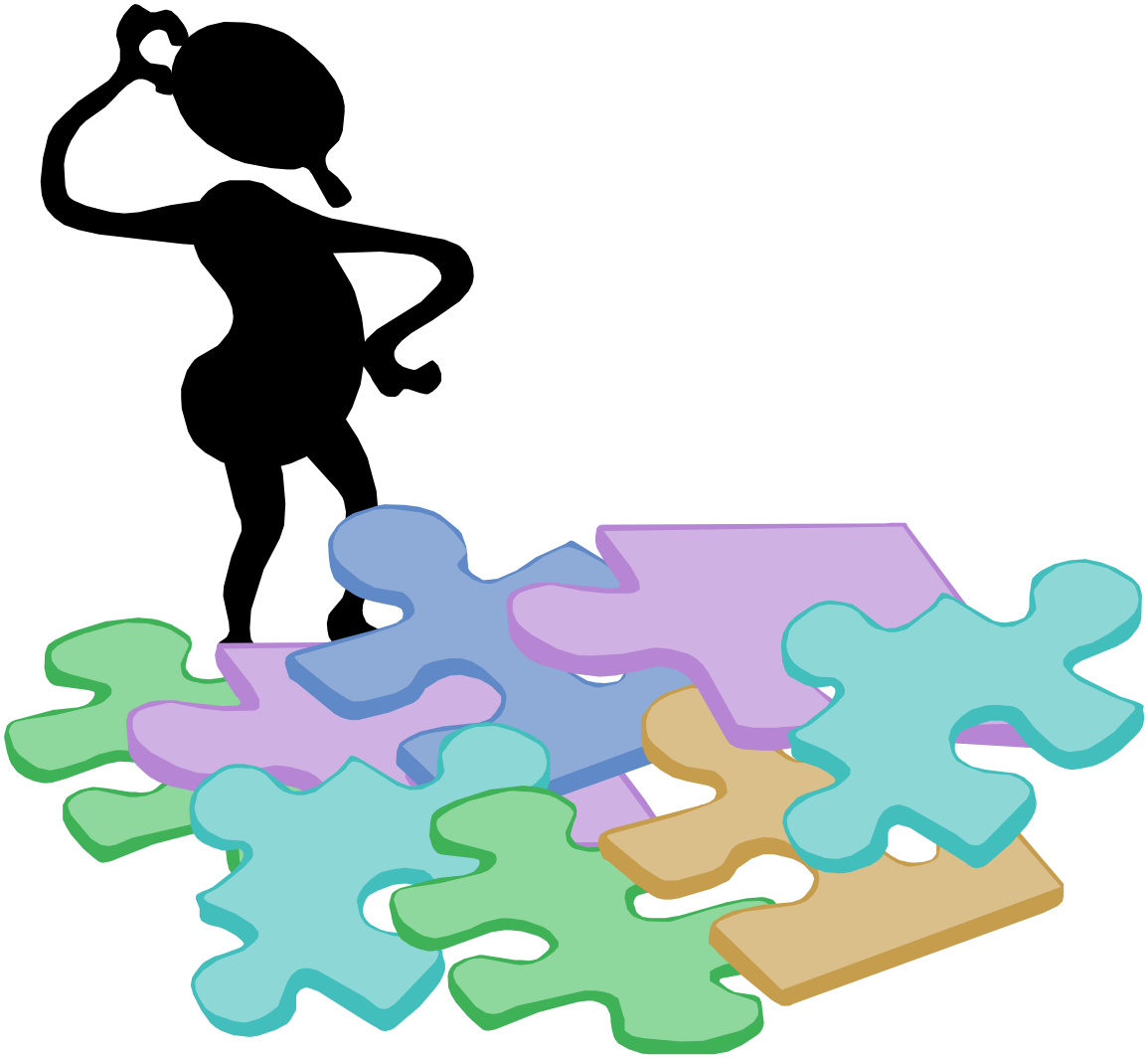
- **knowledge** -> ***PROBLEM 1***
  - -> *uncertain*
  - -> *growing, changing*
  - -> *time-consuming wet-lab experiments*
  - -> *some data estimated*
  - -> *distributed over independent data bases, papers, journals, . . .*
- **various, mostly ambiguous representations** -> ***PROBLEM 2***
  - ->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

BIONETWORKS, SOME PROBLEMS

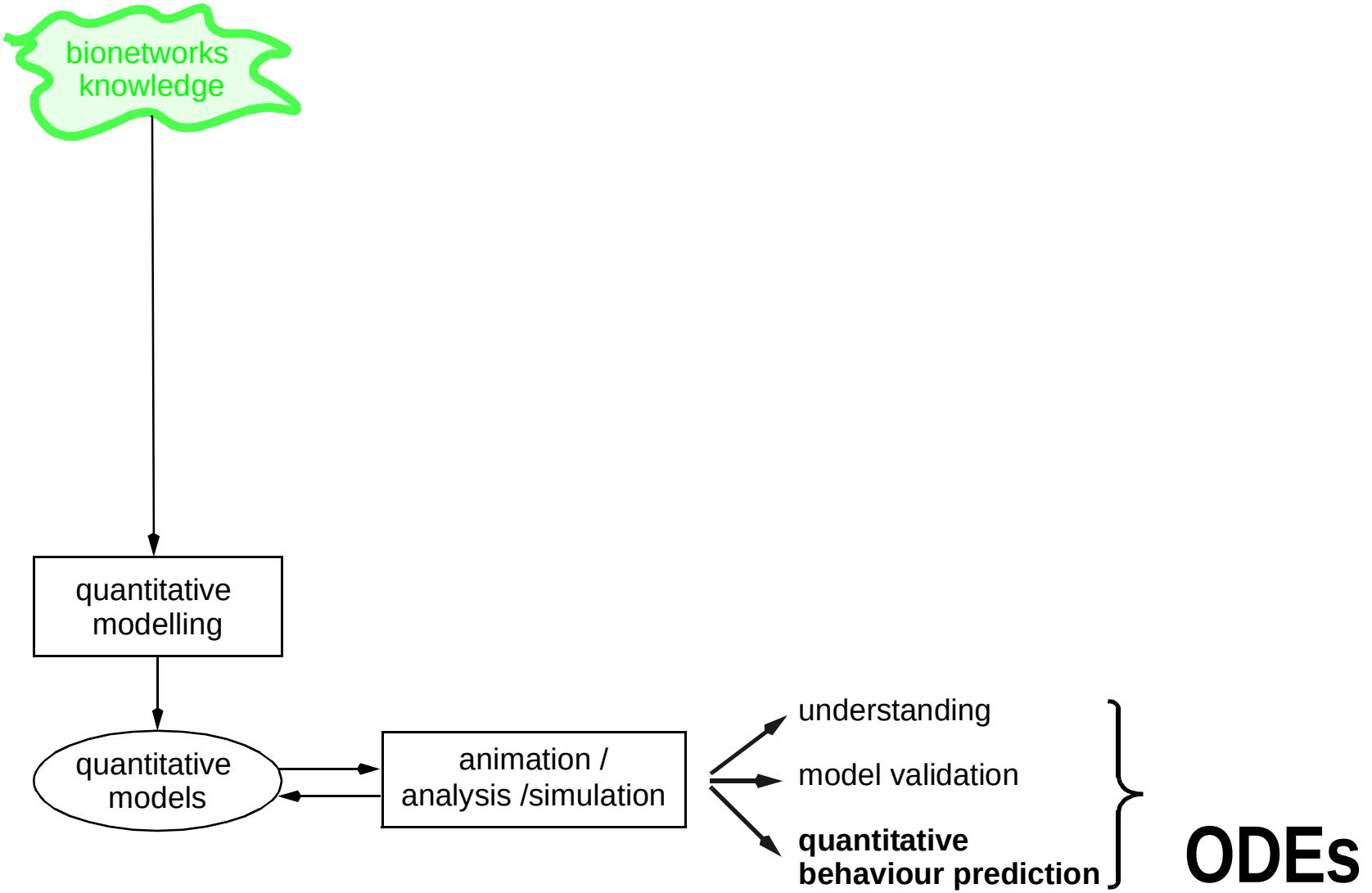
- **knowledge** -> PROBLEM 1
  - -> *uncertain*
  - -> *growing, changing*
  - -> *time-consuming wet-lab experiments*
  - -> *some data estimated*
  - -> *distributed over independent data bases, papers, journals, . . .*
- **various, mostly ambiguous representations** -> PROBLEM 2
  - -> *verbose descriptions*
  - -> *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 -

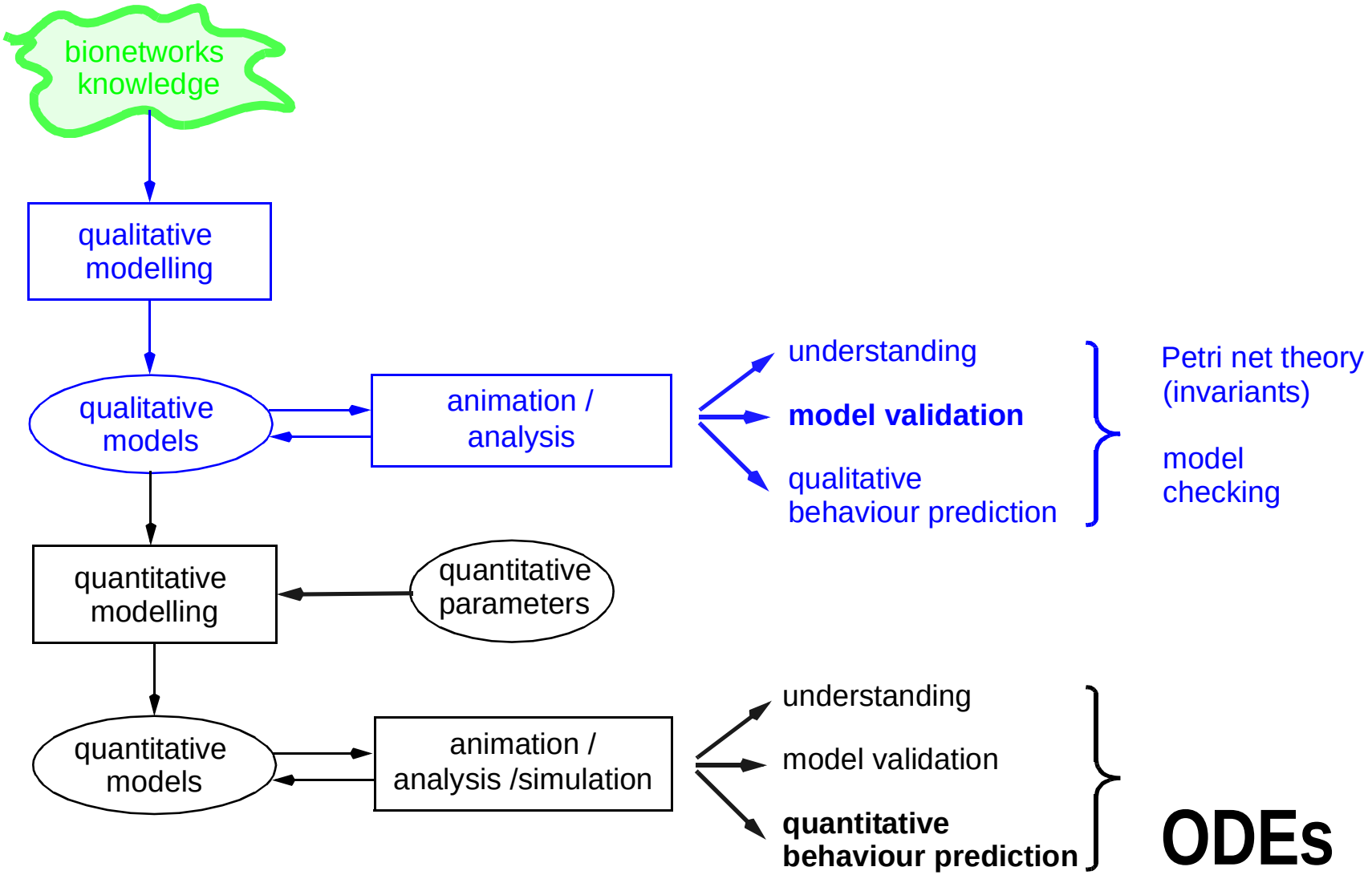
BIONETWORKS, SOME PROBLEMS



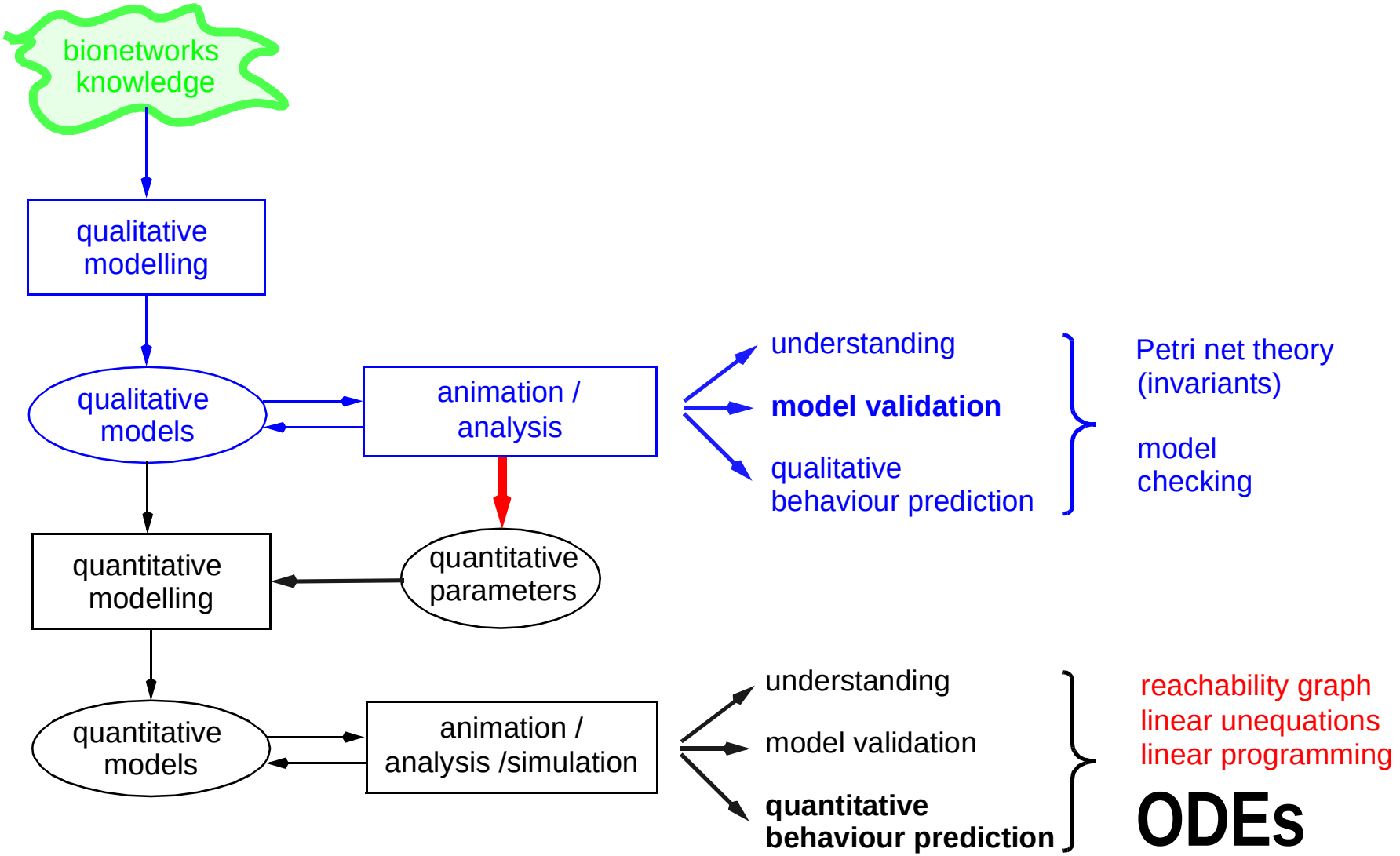
FRAMEWORK


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

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
model validation
quantitative behaviour prediction
ODEs

FRAMEWORK

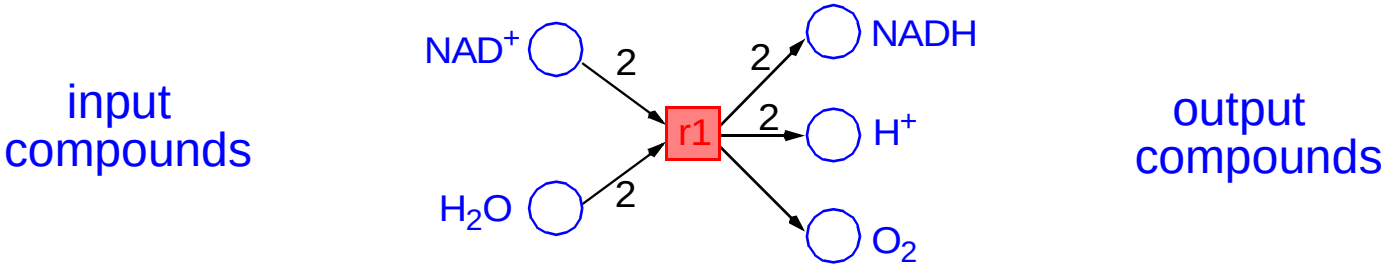

bionetworks knowledge
qualitative modelling
qualitative models
animation / analysis
quantitative modelling
quantitative parameters
quantitative models
animation / analysis /simulation
understanding
model validation
qualitative behaviour prediction
Petri net theory (invariants)
model checking
understanding
model validation
quantitative behaviour prediction
reachability graph
linear unequations
linear programming
ODEs

BIO PETRI NETS - AN INFORMAL CRASH COURSE

monika.heiner@informatik.tu-cottbus.de

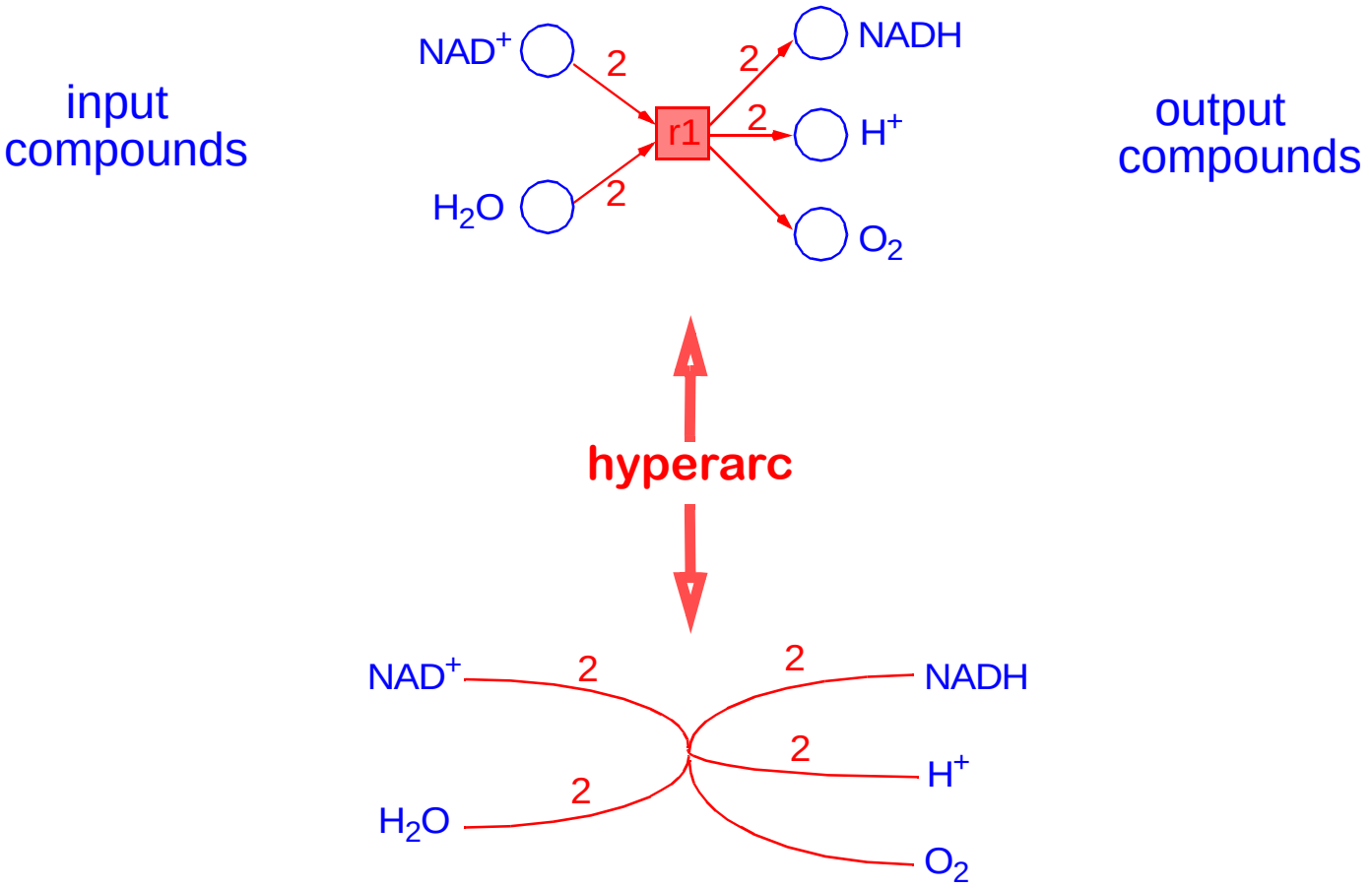
- **atomic actions -> Petri net transitions -> chemical reactions**

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



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

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

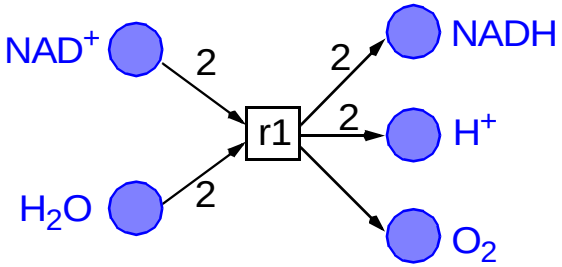


- **atomic actions -> Petri net transitions -> chemical reactions**

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

input compounds

pre-conditions



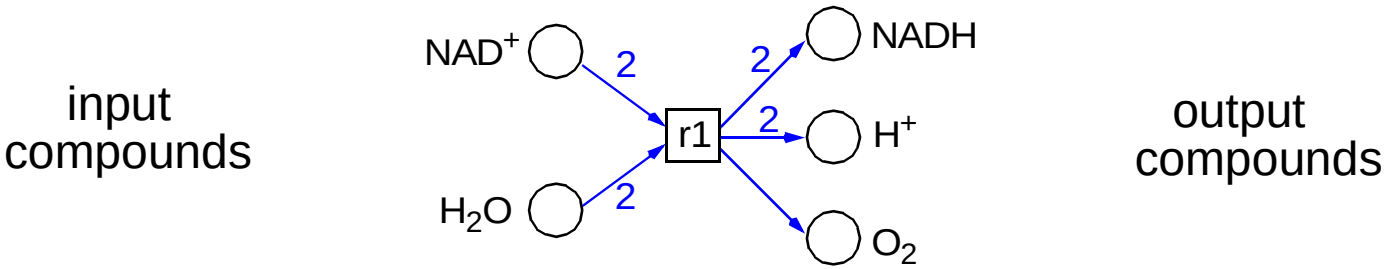
output compounds

post-conditions

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

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

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

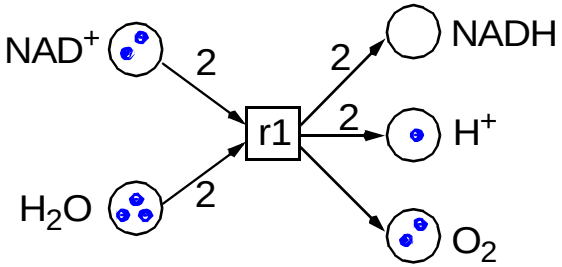


- **local conditions -> Petri net places -> chemical compounds**
- **multiplicities -> Petri net arc weights -> stoichiometric relations**

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

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

input compounds



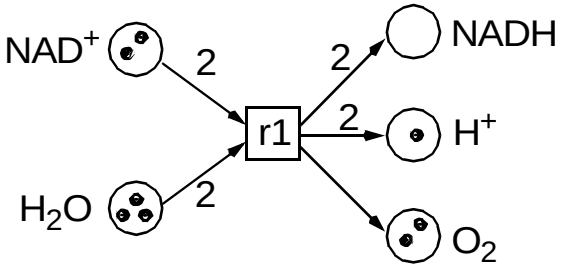
output compounds

- **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**

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

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

input compounds



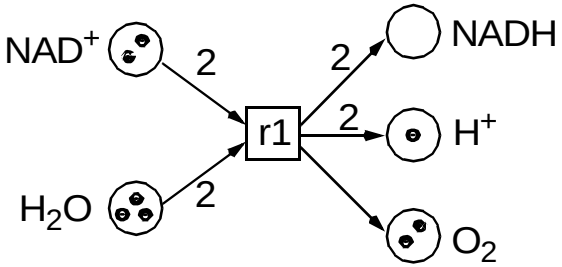
output compounds

- **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

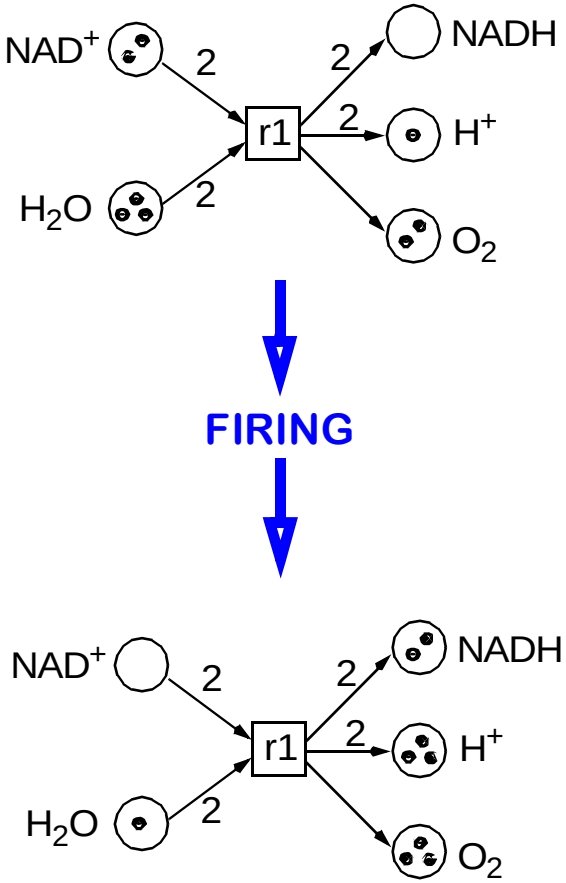


output compounds

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

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

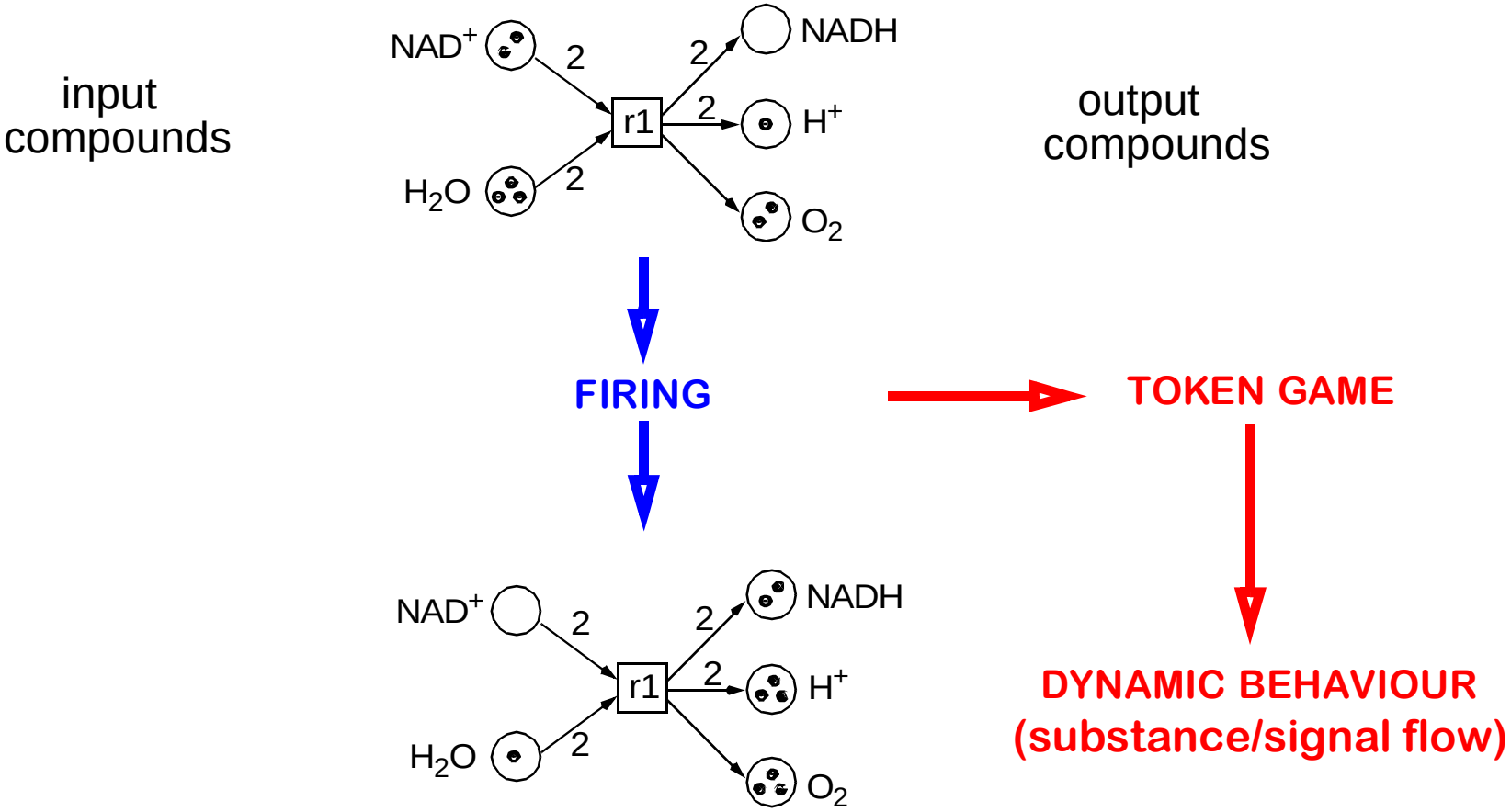
input compounds



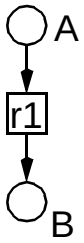
output compounds

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

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



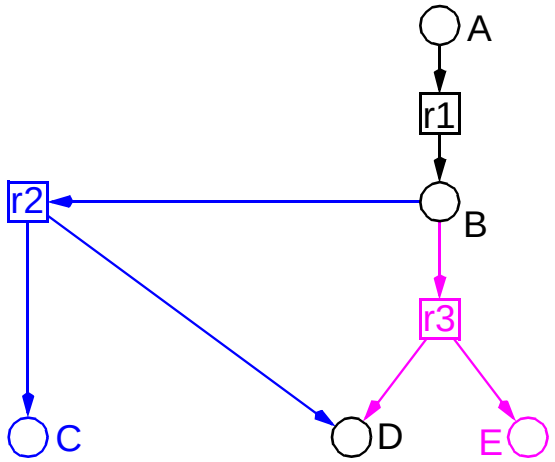
r1: A -> B



r1: A -> B

r2: B -> C + D

r3: B -> D + E



-> alternative reactions

r1: A -> B

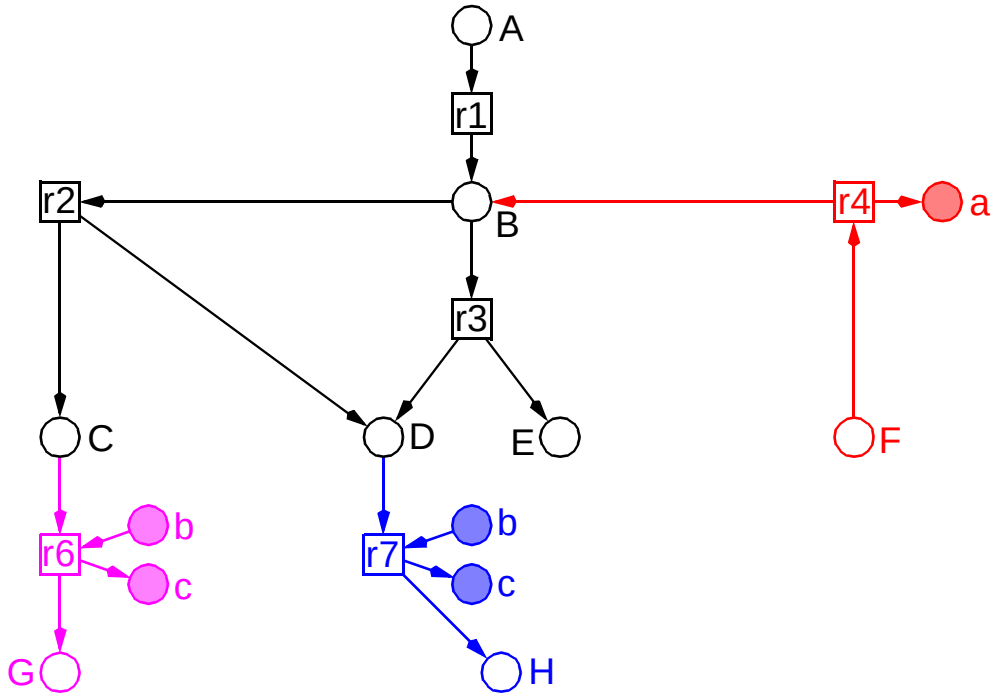
r2: B -> C + D

r3: B -> D + E

r4: F -> B + a

r6: C + b -> G + c

r7: D + b -> H + c



-> concurrent reactions

r1: A -> B

r2: B -> C + D

r3: B -> D + E

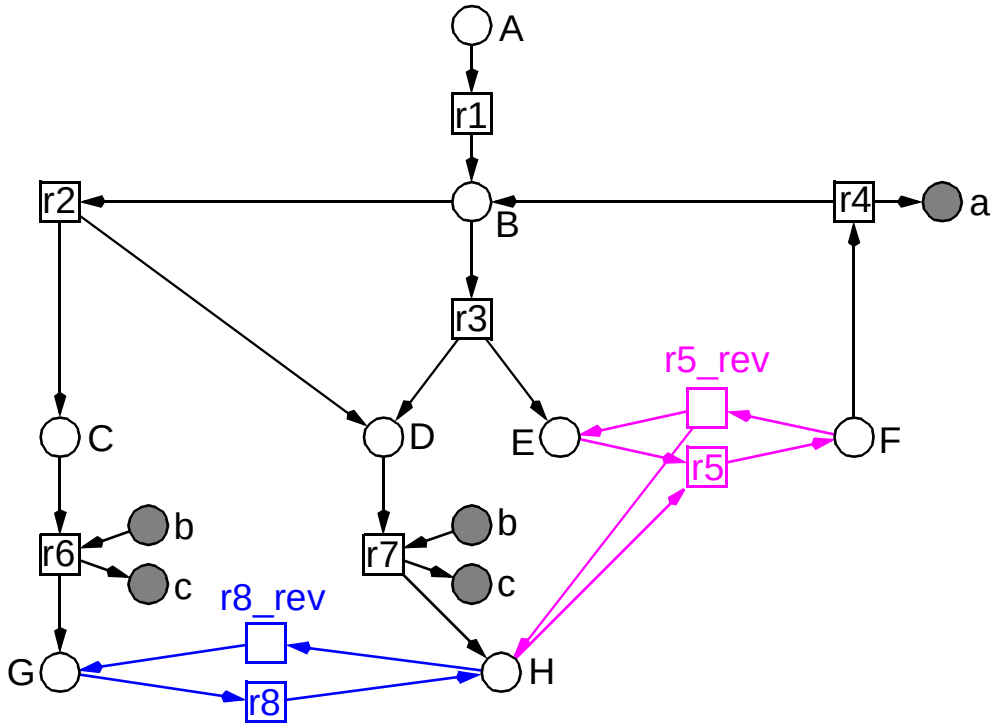
r4: F -> B + a

r5: E + H <-> F

r6: C + b -> G + c

r7: D + b -> H + c

r8: H <-> G



-> reversible reactions

r1: A -> B

r2: B -> C + D

r3: B -> D + E

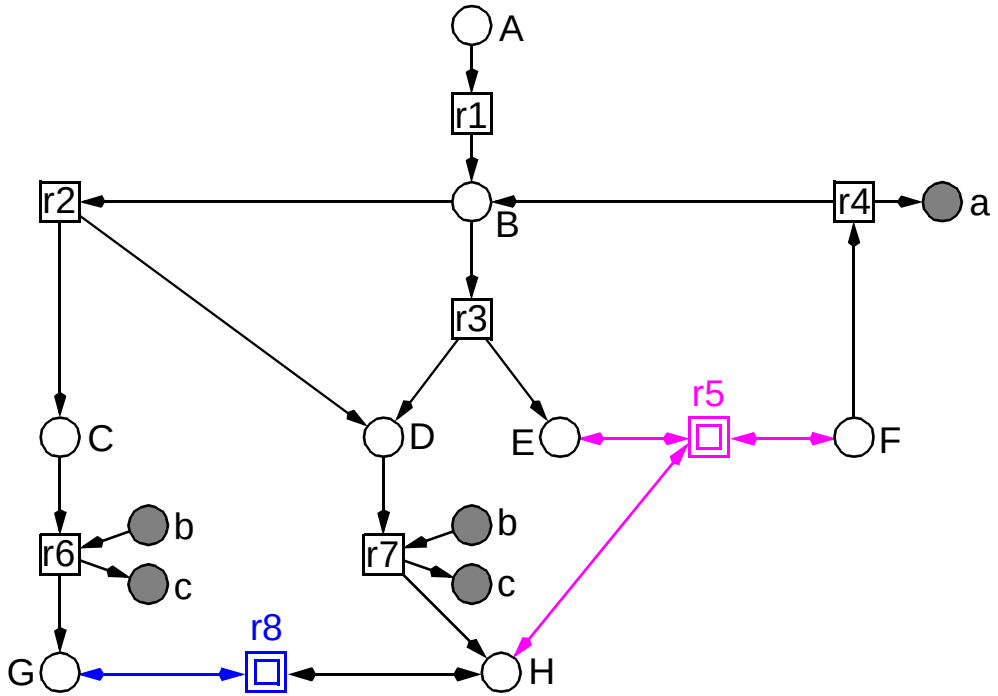
r4: F -> B + a

r5: E + H <-> F

r6: C + b -> G + c

r7: D + b -> H + c

r8: H <-> G



-> reversible reactions

- hierarchical nodes

r1: A -> B

r2: B -> C + D

r3: B -> D + E

r4: F -> B + a

r5: E + H <-> F

r6: C + b -> G + c

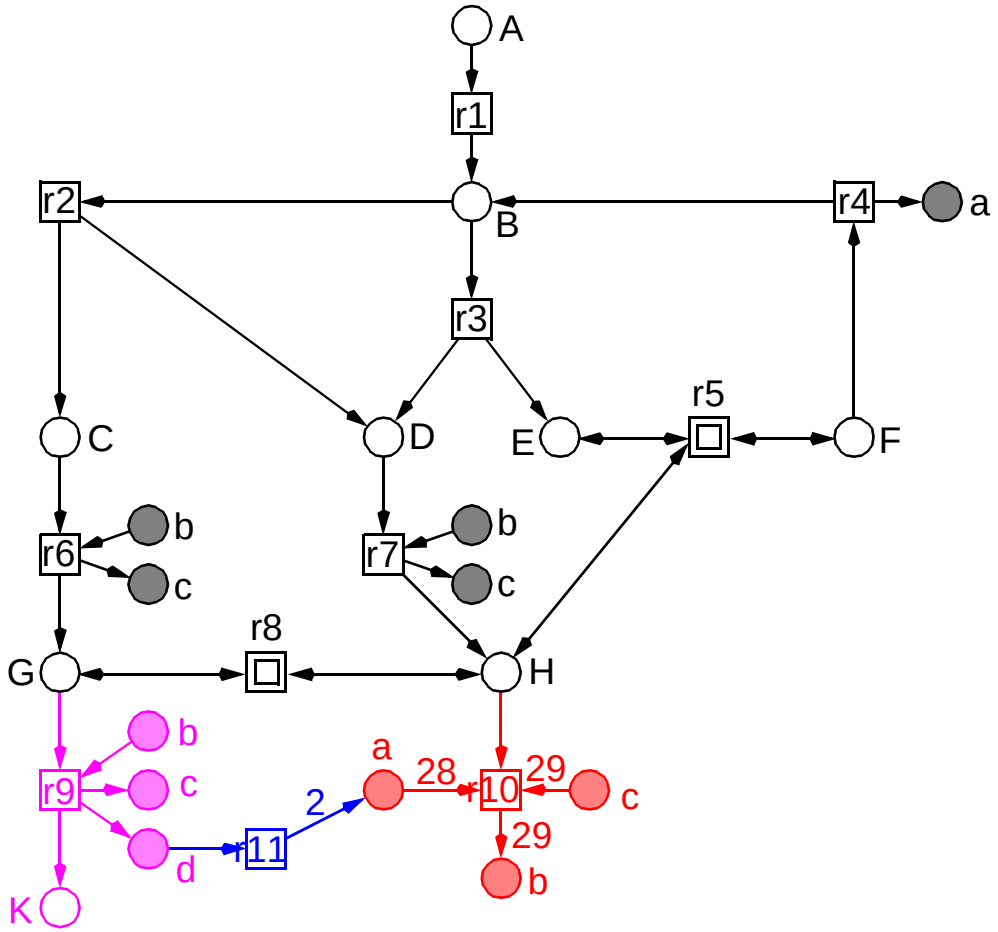
r7: D + b -> H + c

r8: H <-> G

r9: G + b -> K + c + d

r10: H + 28a + 29c -> 29b

r11: d -> 2a



r1: A -> B

r2: B -> C + D

r3: B -> D + E

r4: F -> B + a

r5: E + H <-> F

r6: C + b -> G + c

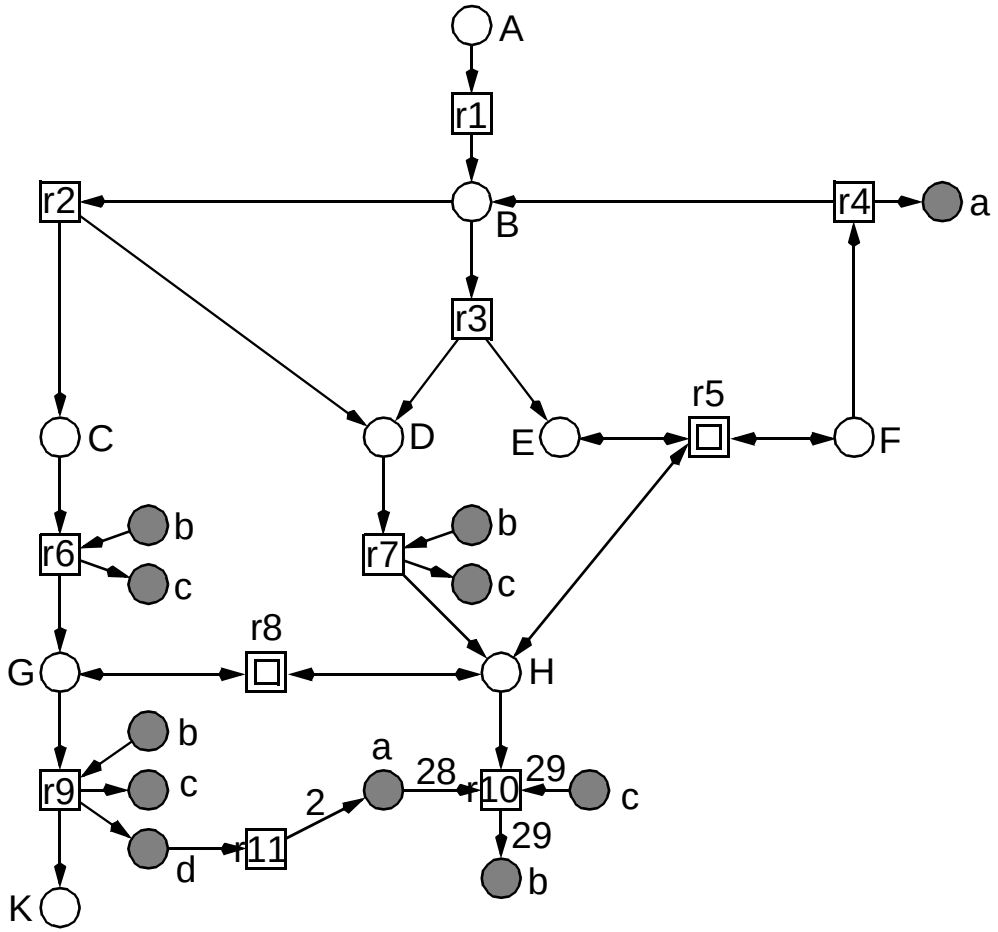
r7: D + b -> H + c

r8: H <-> G

r9: G + b -> K + c + d

r10: H + 28a + 29c -> 29b

r11: d -> 2a



r1: A -> B

r2: B -> C + D

r3: B -> D + E

r4: F -> B + a

r5: E + H <-> F

r6: C + b -> G + c

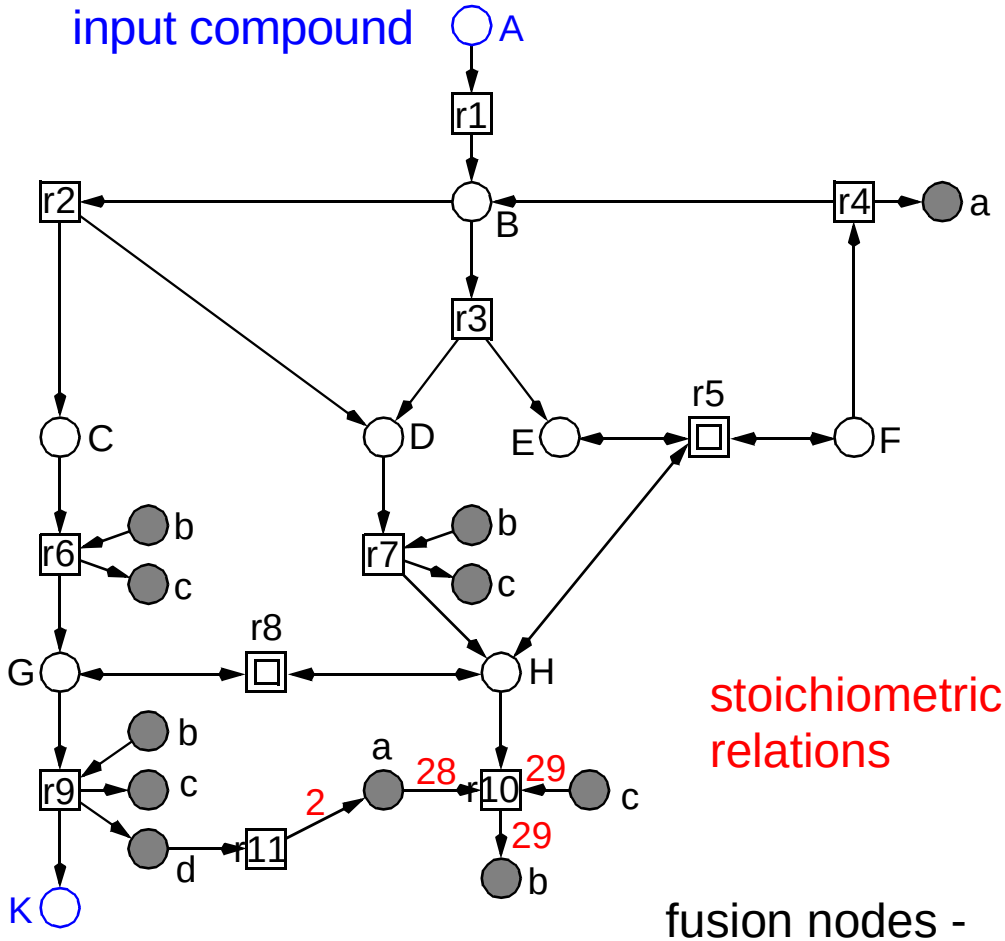
r7: D + b -> H + c

r8: H <-> G

r9: G + b -> K + c + d

r10: H + 28a + 29c -> 29b

r11: d -> 2a



r1: A -> B

r2: B -> C + D

r3: B -> D + E

r4: F -> B + a

r5: E + H <-> F

r6: C + b -> G + c

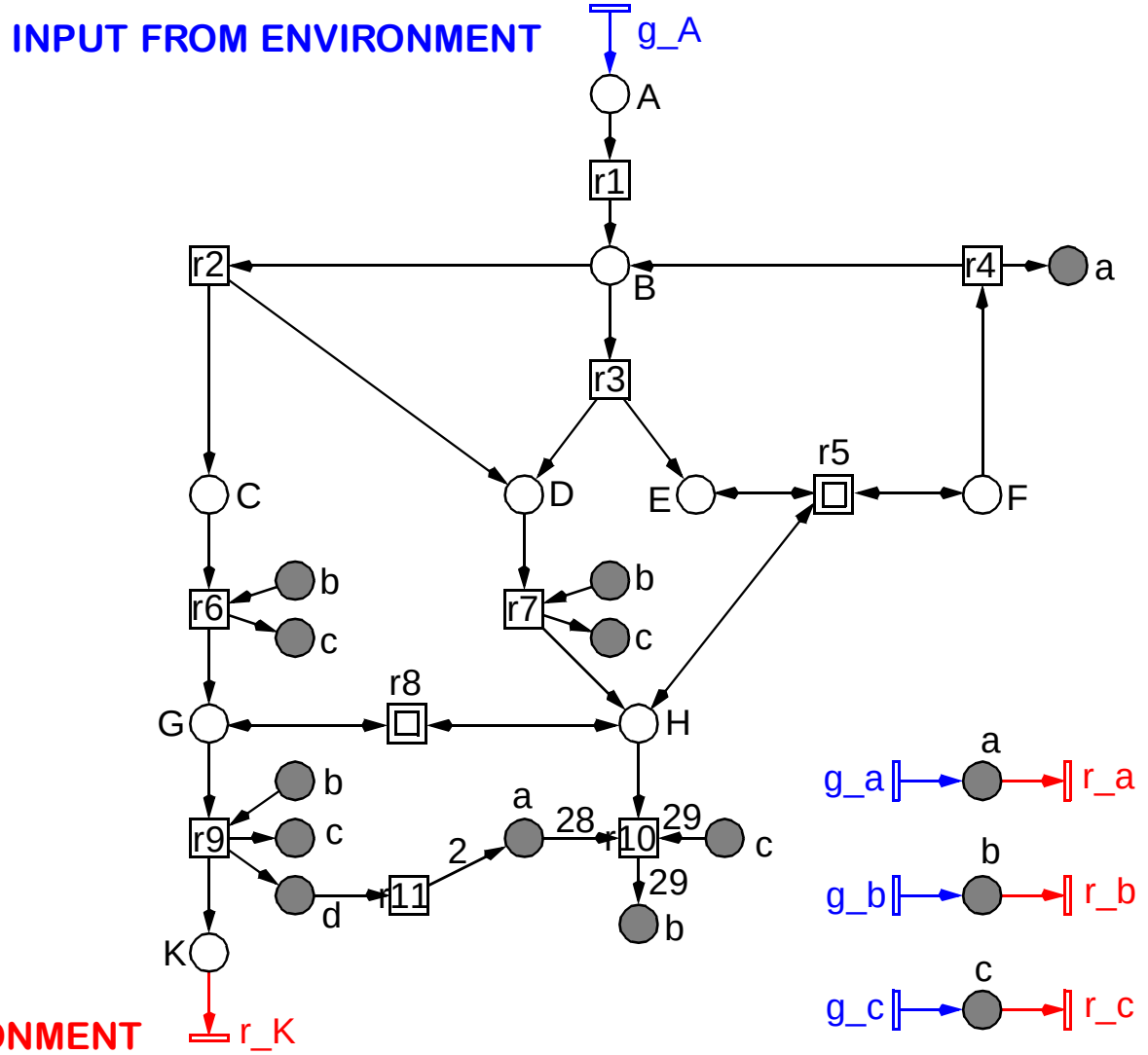
r7: D + b -> H + c

r8: H <-> G

r9: G + b -> K + c + d

r10: H + 28a + 29c -> 29b

r11: d -> 2a



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]*

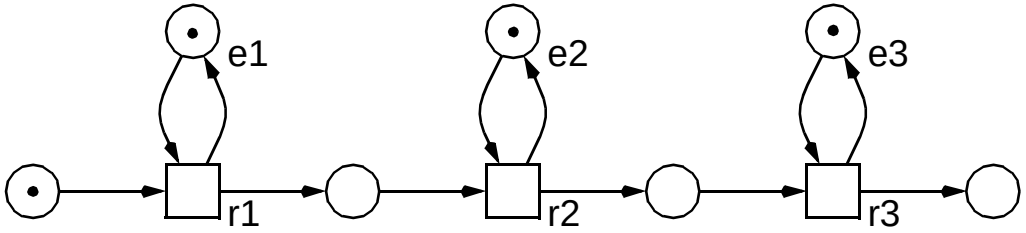
- **pathway**
  -> *self-contained partial order sequence of elementary (re-) actions*

monika.heiner@informatik.tu-cottbus.de

TYPICAL BASIC STRUCTURES

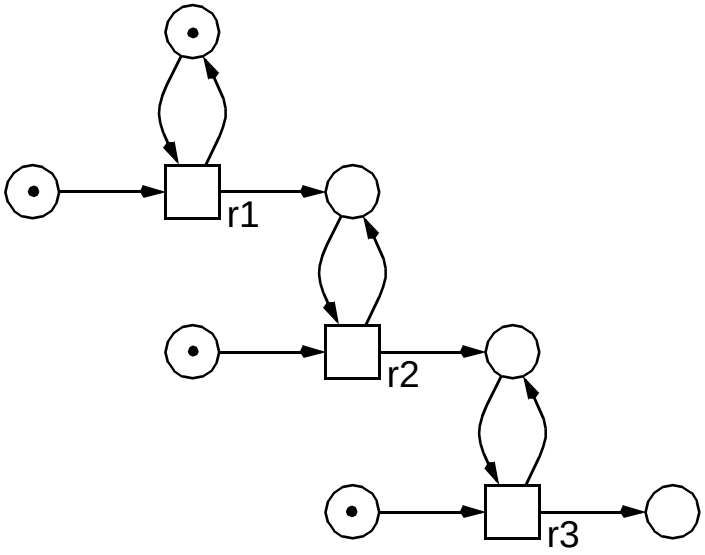
- **metabolic networks**

  -> *substance flows*



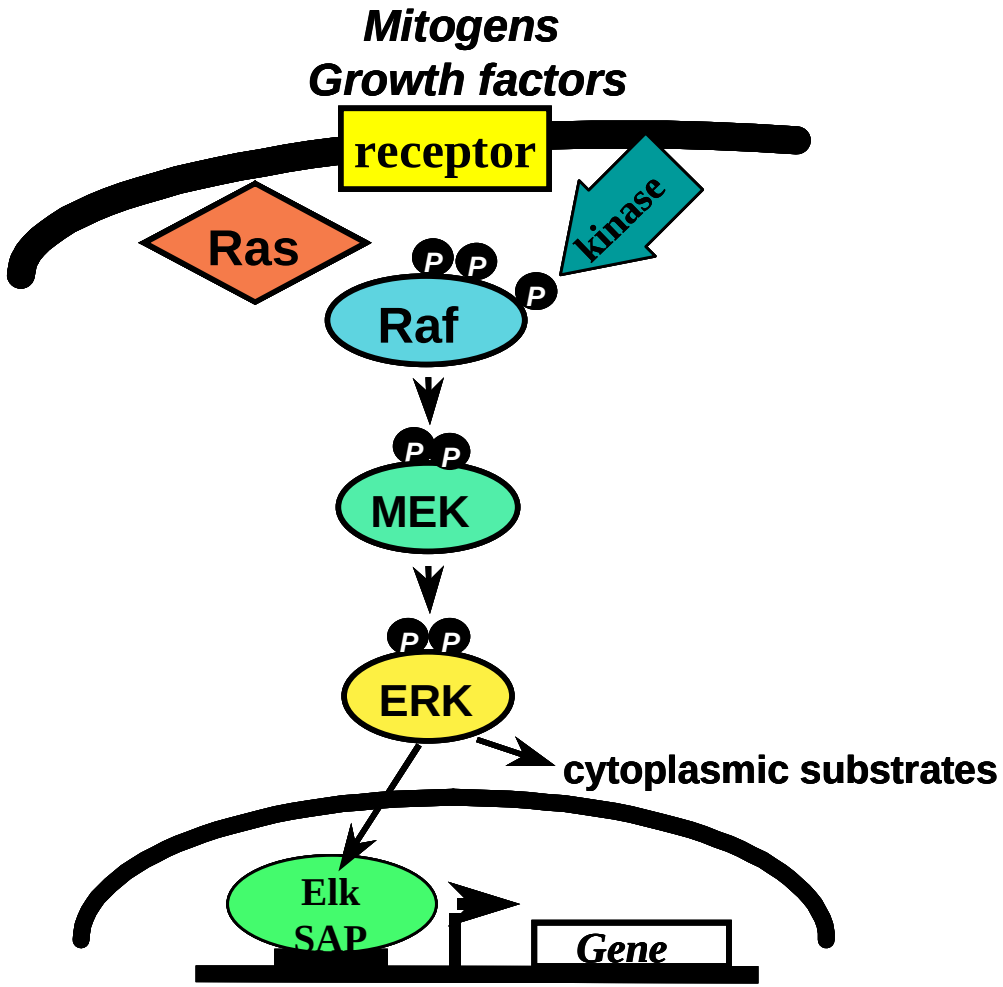
- **signal transduction networks**

  -> *signal flows*

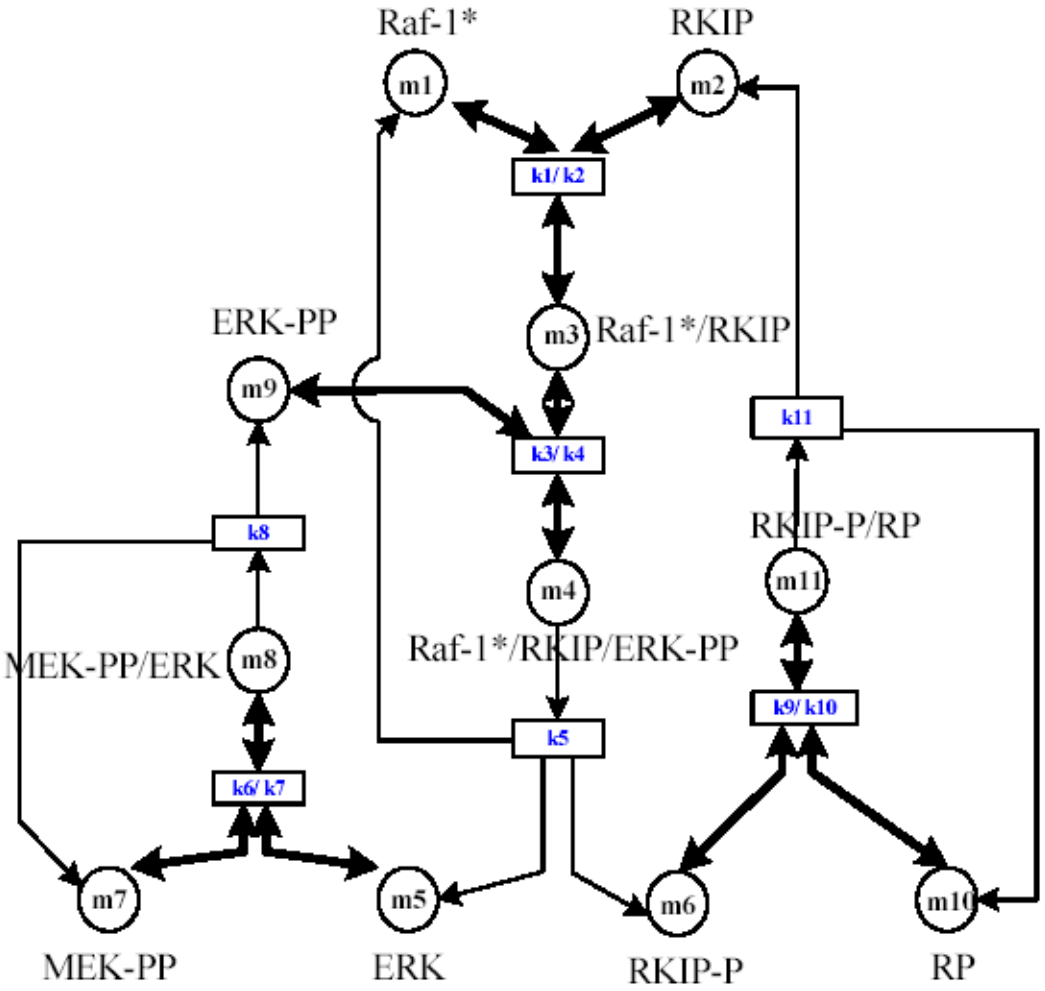


A CASE STUDY

…one pathway…

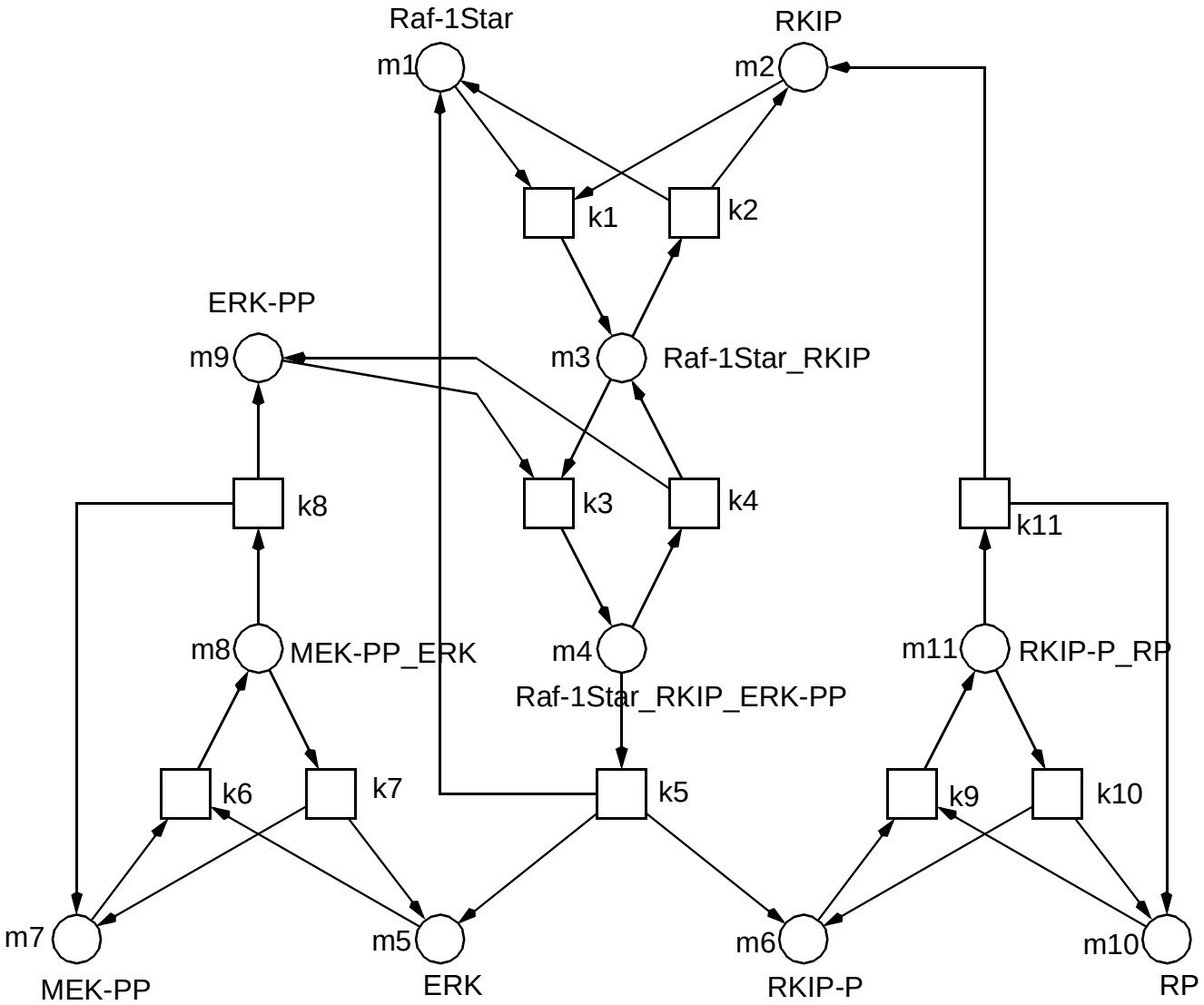

Mitogens
Growth factors
receptor
Ras
kinase
P
P
P
Raf
P
P
MEK
P
P
ERK
cytoplasmic substrates
Elk
SAP
Gene

THE RKIP PATHWAY

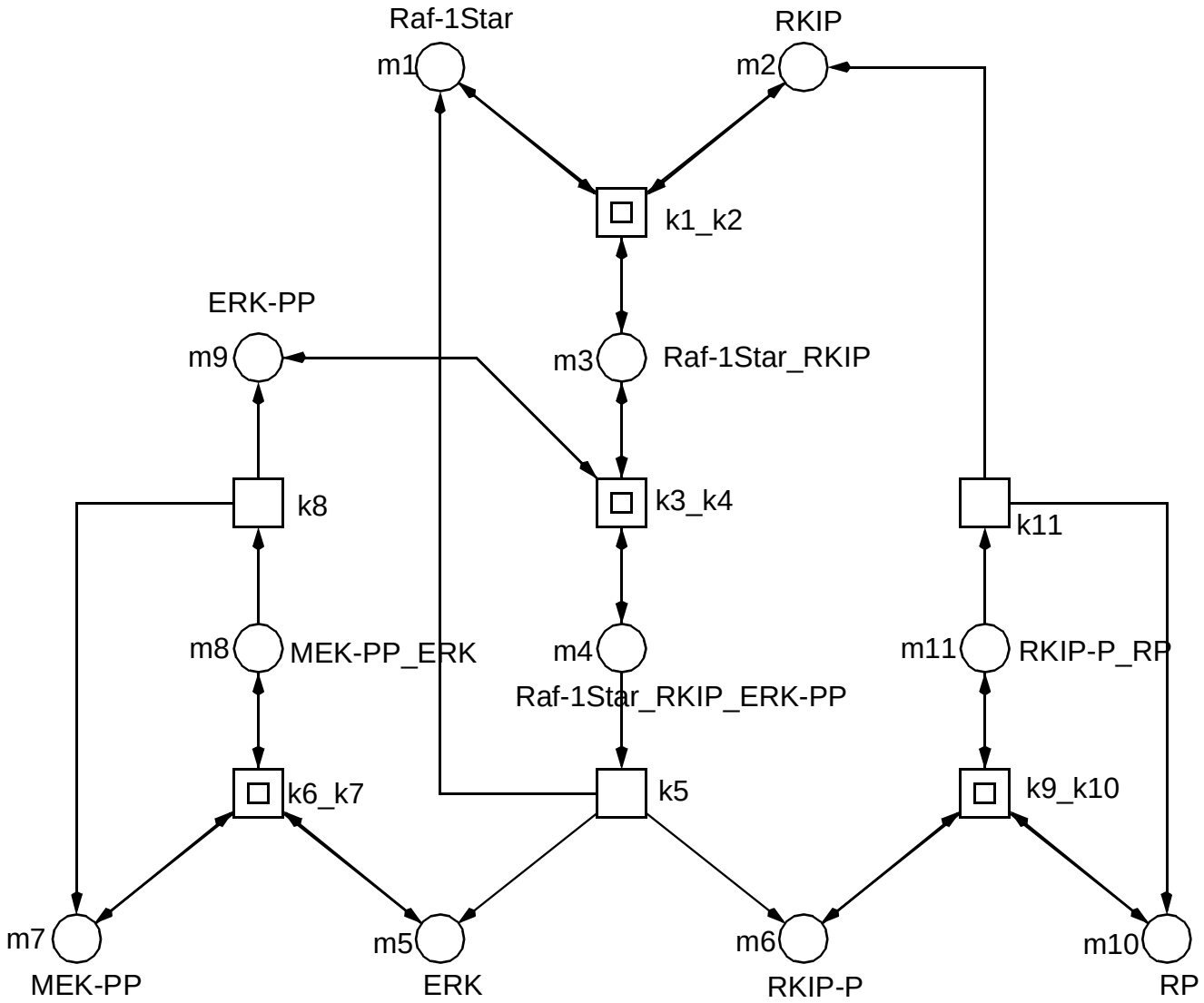


[Cho et al., CMSB 2003]

THE RKIP PATHWAY, PETRI NET

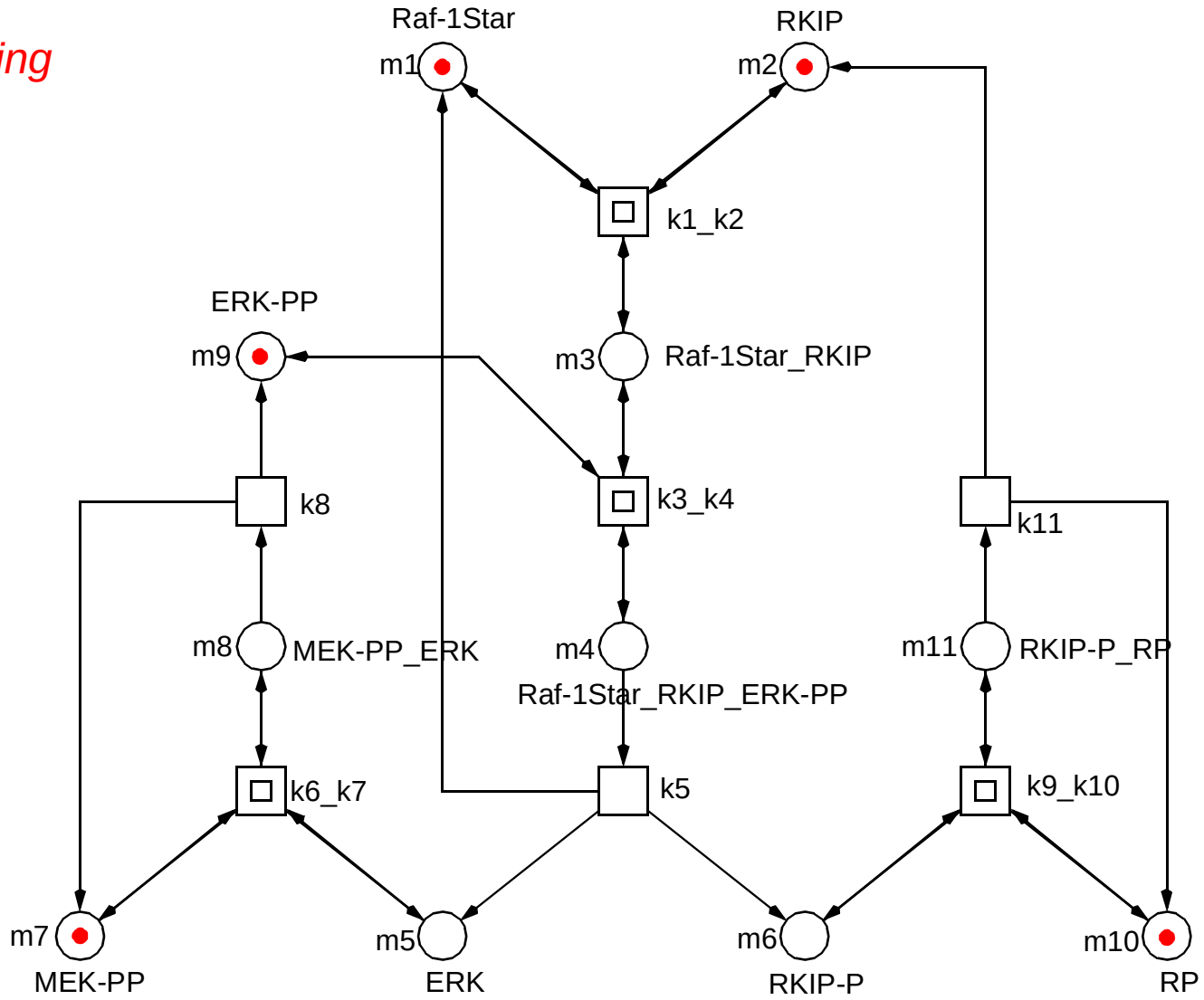


THE RKIP PATHWAY, HIERARCHICAL PETRI NET



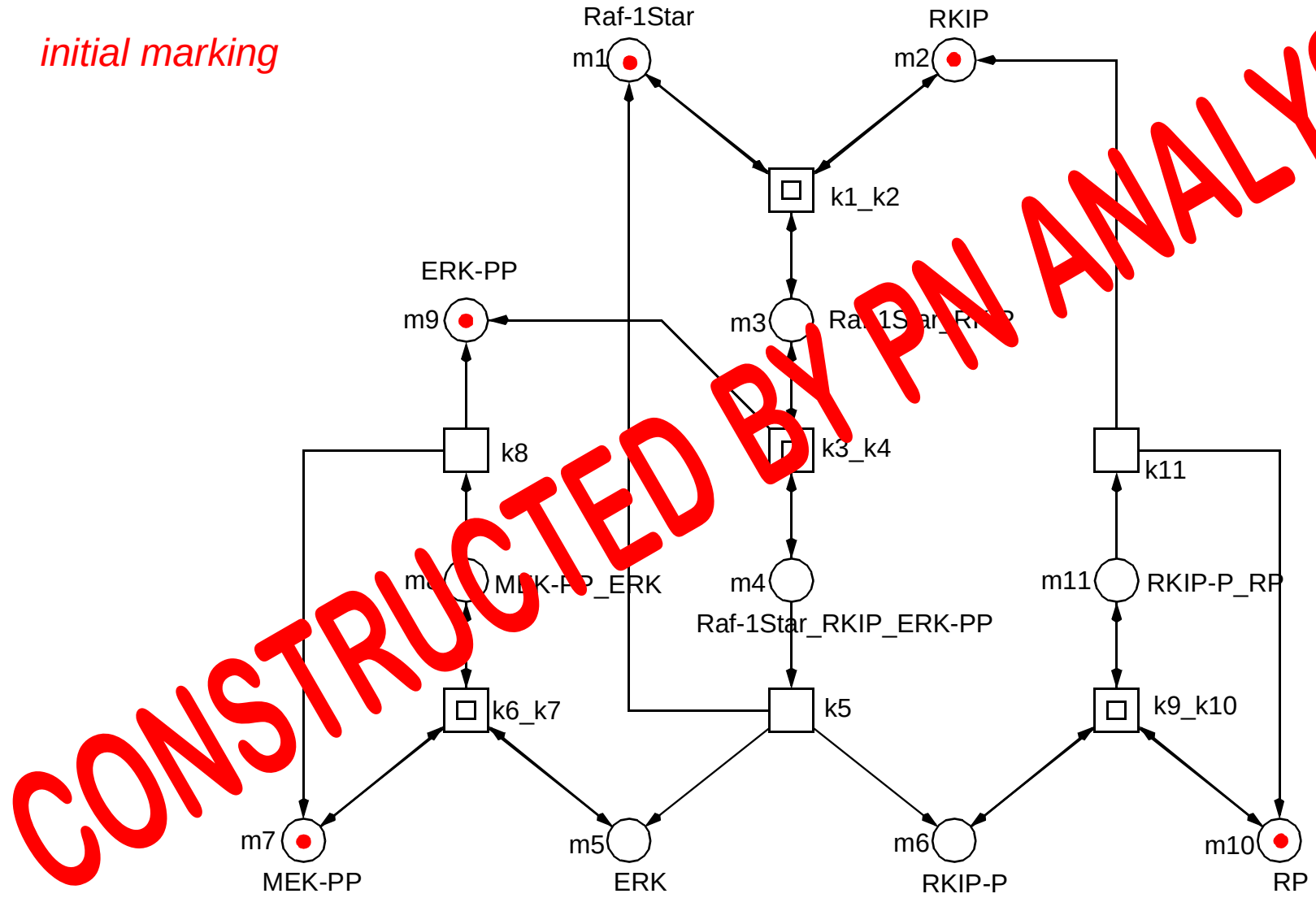
THE RKIP PATHWAY, HIERARCHICAL PETRI NET

initial marking



THE RKIP PATHWAY, HIERARCHICAL PETRI NET

initial marking



CONSTRUCTED BY PN ANALYSIS

QUALITATIVE ANALYSES

ANALYSIS TECHNIQUES, OVERVIEW

- **static analyses** **-> no state space construction**
  - -> *structural properties (graph theory, combinatorial algorithms)*
  - -> *P / T - invariants (discrete computational geometry),*
- **dynamic analyses** **-> total / partial state space construction**
  - -> *state space representations: interleaving (RG) / partial order (prefix)*
  - -> *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

STATIC ANALYSES

INCIDENCE MATRIX C

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

$C =$

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

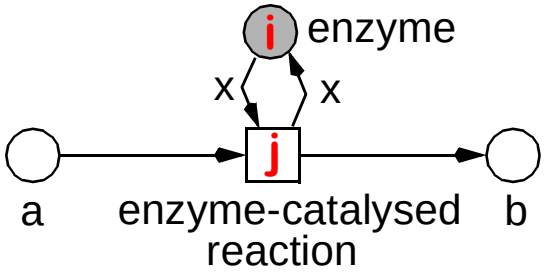
$cij = (pi, tj) = F(tj,pi) - F(pi, tj) = \Delta\, tj(pi)$

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

- 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

P-INVARIANTS, BASICS

- **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)*

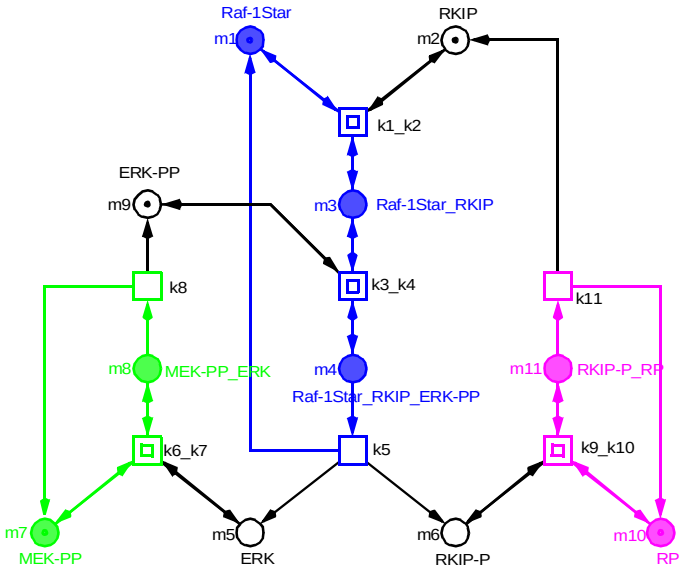
P-INVARIANTS, INTERPRETATION

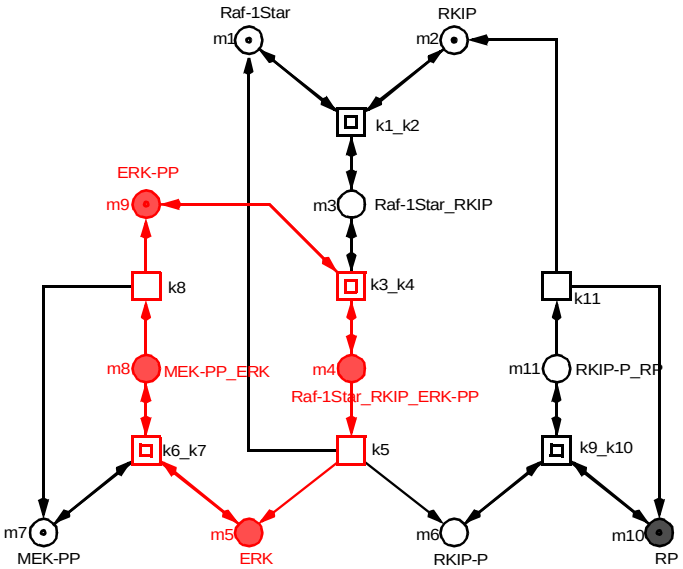
- **the firing of any transition has no influence on the weighted sum of tokens on the P-invariant's places**
  - -> *for all t: the effect of the arcs, removing tokens from a P-invariant's place is equal to the effect of the arcs, adding tokens to a P-invariant's place*

- **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**

THE RKIP PATHWAY, P-INVARIANTS





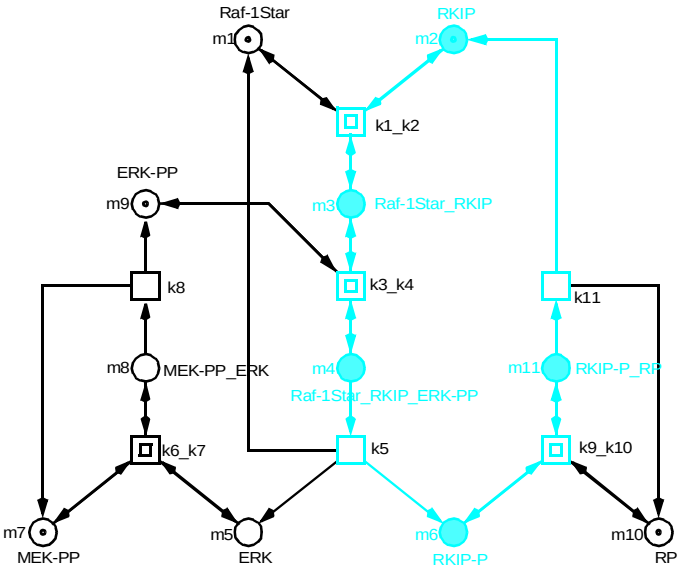
P-INV1: MEK

P-INV2: RAF-1STAR

P-INV3: RP

P-INV4: ERK

P-INV5: RKIP



T-INVARIANTS, BASICS

- **Lautenbach, 1973**
- **T-invariants**
  - -> *integer solutions x of* $Cx = 0, x \neq 0, x \geq 0$
  - -> *multisets of transitions*
  - -> *Parikh vector*
- **minimal T-invariants**
  - -> *there is no T-invariant with a smaller support*
  - -> *gcD of all entries is 1*
  - -> *sets of transitions*
- **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, INTERPRETATIONS

- **T-invariants = (multi-) sets of transitions = Parikh vector**
  - -> *zero effect on marking*
  - -> *reproducing a marking / system state*

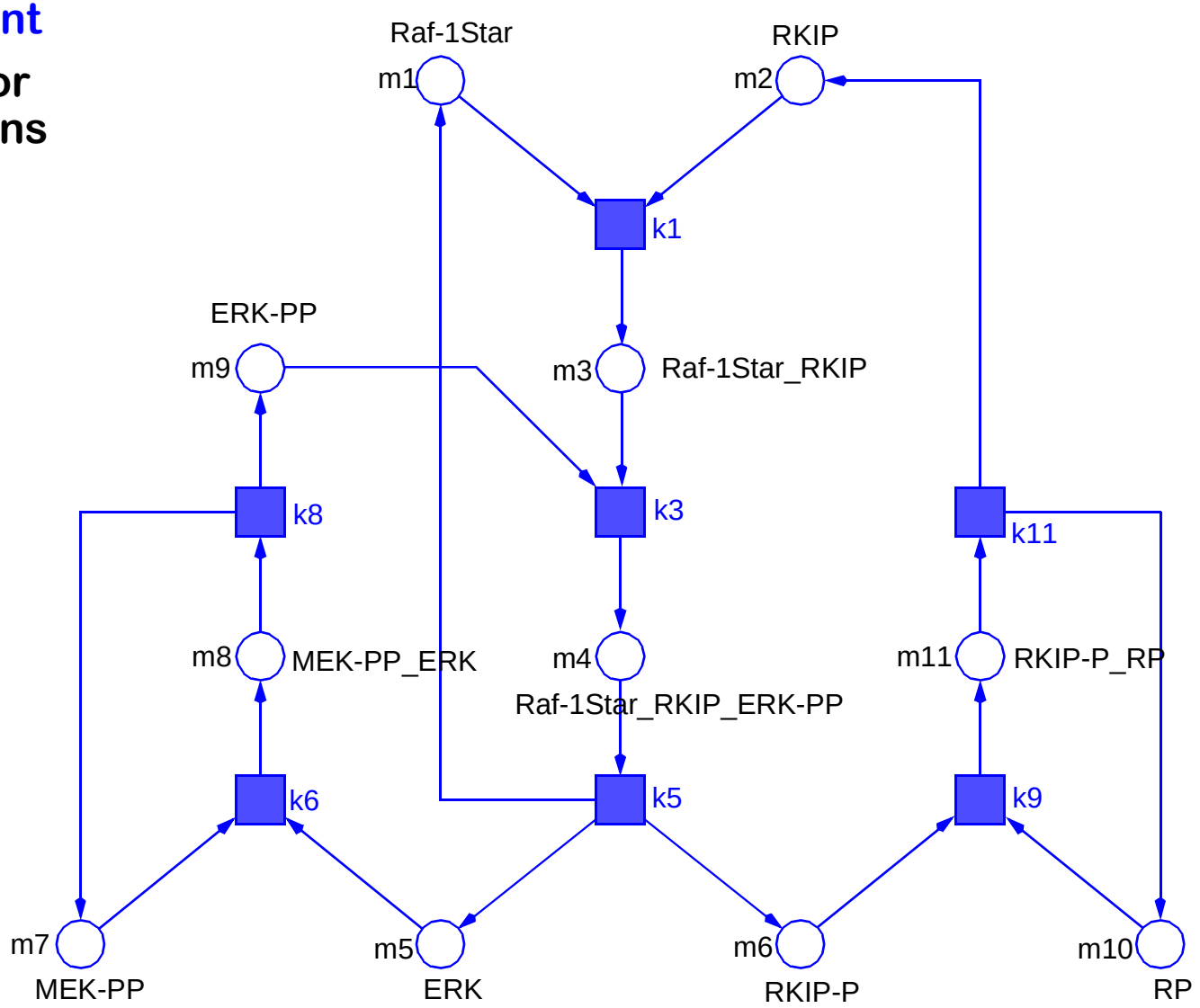
- **two interpretations**
  1. *relative transition firing rates*
     of transitions occuring permanently & concurrently
     -> *steady state behaviour*
  2. *partially ordered transition sequence* **-> behaviour understanding**
     of transitions occuring one after the other
     -> *substance / signal flow*

- **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*

THE RKIP PATHWAY, NON-TRIVIAL T-INVARIANT

-> non-trivial T-invariant

+ four trivial ones for reversible reactions



CONSTRUCTION OF THE INITIAL MARKING

- **each P-invariant gets at least one token**
  -> *P-invariants are structural deadlocks and traps*

- **in signal transduction**
  -> *exactly 1 token, corresponding to species conservation*
  -> *token in least active state*

- **all (non-trivial) T-invariants get realizable**
  -> *to make the net live*

- **minimal marking**
  -> *minimization of the state space*

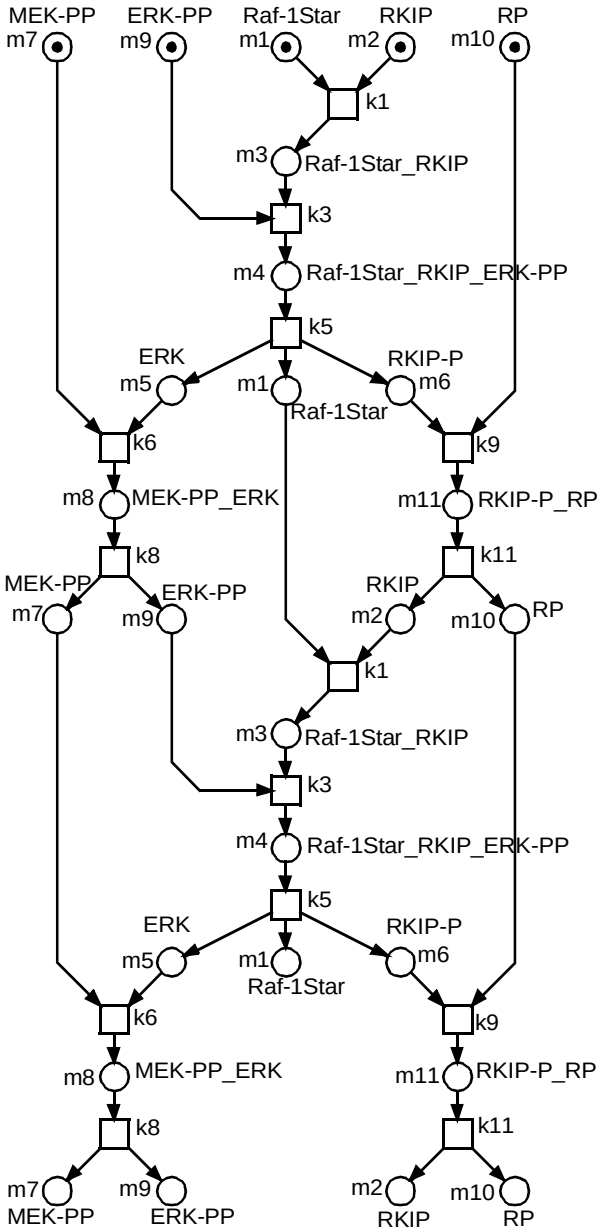
CONSTRUCTION OF THE INITIAL MARKING

- **each P-invariant gets at least one token**
  -> *P-invariants are structural deadlocks and traps*
- **in signal transduction**
  -> *exactly 1 token, corresponding to species conservation*
  -> *token in least active state*
- **all (non-trivial) T-invariants get realizable**
  -> *to make the net live*
- **minimal marking**
  -> *minimization of the state space*

-> UNIQUE INITIAL MARKING <-

NON-TRIVIAL T-INVARIANT, RUN

- realizability check under the constructed marking
- T-invariant's unfolding to describe its behaviour
  -> **partial order structure**
- labelled condition / event net
  -> *events (boxes)*
  - transition occurences
  -> *conditions (circles)*
  - involved compounds
- occurrence net
  -> *acyclic*
  -> *no backward branching conditions*
  -> *infinite*



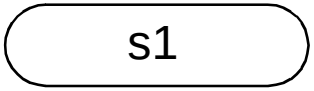
DYNAMIC ANALYSES

DYNAMIC ANALYSIS - REACHABILITY GRAPH

- **simple construction algorithm**
  - -> *nodes* - *system states*
  - -> *arcs* - *the (single) firing transition* -> *single step firing rule*

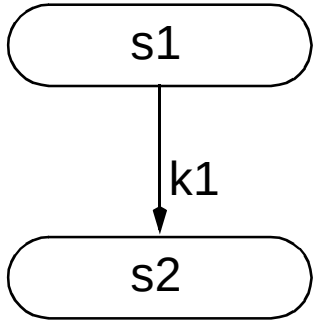
DYNAMIC ANALYSIS - REACHABILITY GRAPH

- **simple construction algorithm**
  - -> *nodes* - *system states*
  - -> *arcs* - *the (single) firing transition* -> *single step firing rule*

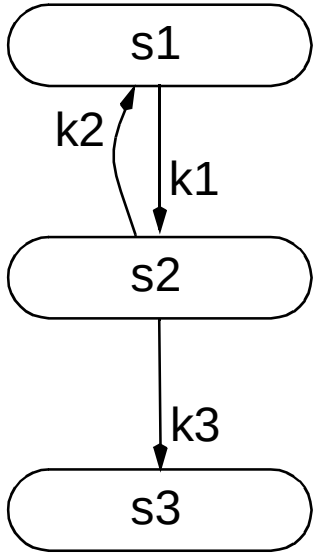


DYNAMIC ANALYSIS - REACHABILITY GRAPH

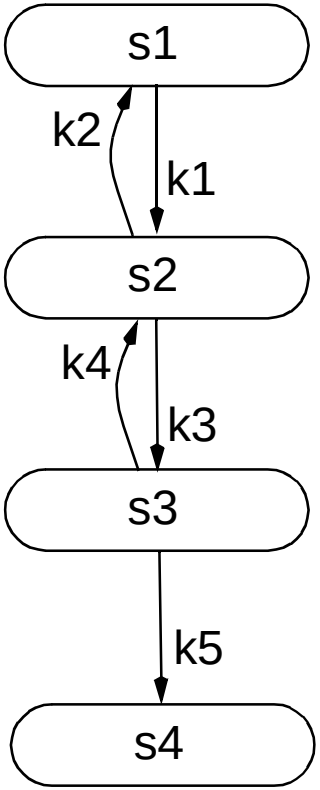
- **simple construction algorithm**
  - -> *nodes* - *system states*
  - -> *arcs* - *the (single) firing transition* -> *single step firing rule*



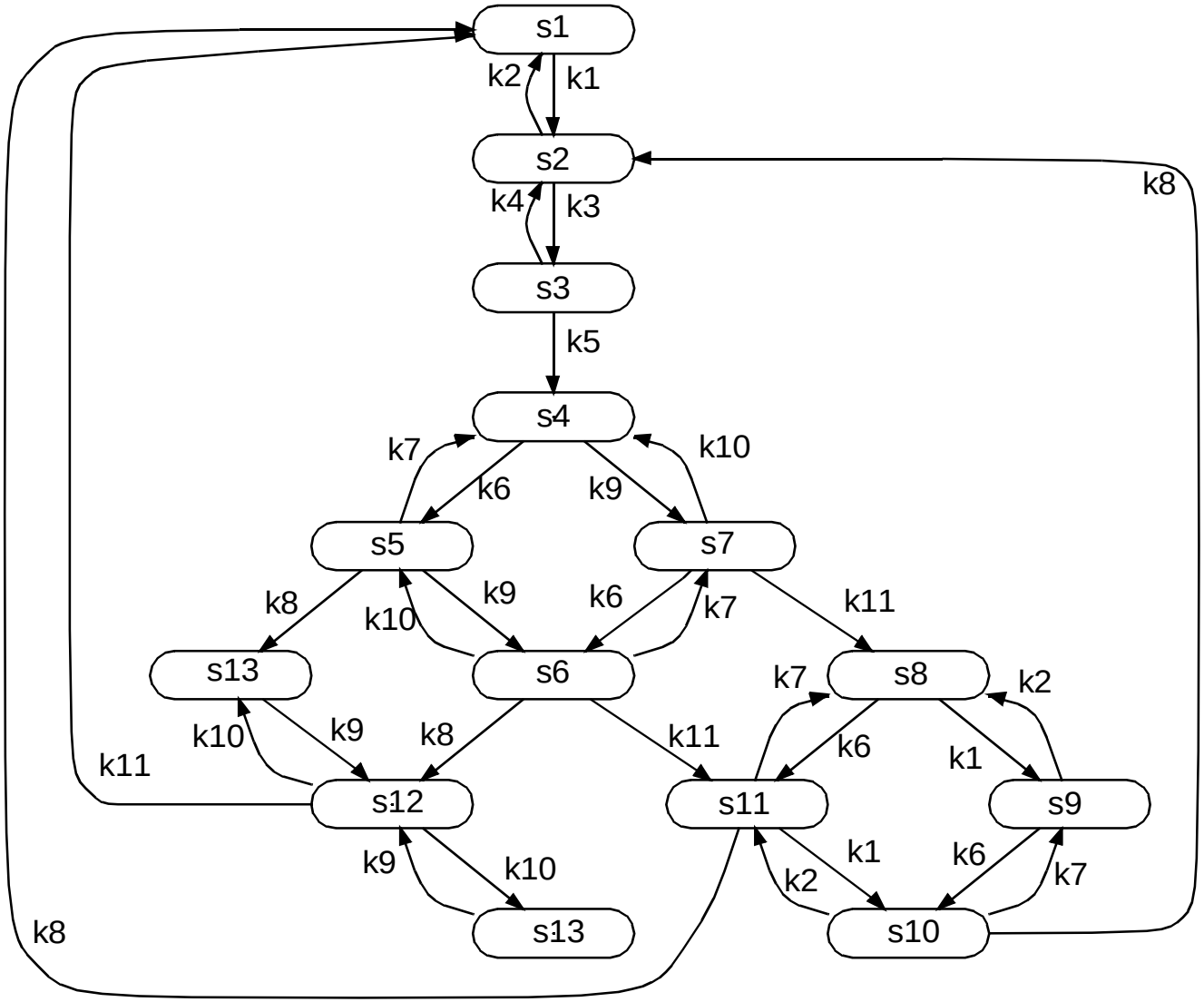
- **simple construction algorithm**
  - -> *nodes* - *system states*
  - -> *arcs* - *the (single) firing transition* -> *single step firing rule*



- **simple construction algorithm**
  - -> *nodes* - *system states*
  - -> *arcs* - *the (single) firing transition* -> *single step firing rule*



RKIP PATHWAY, REACHABILITY GRAPH



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 1**
  - -> *all expected structural properties hold*
  - -> *all expected general behavioural properties hold*
- **validation criterion 2**
  - -> *CTI*
  - -> *no minimal T-invariant without biological interpretation*
  - -> *no known biological behaviour without corresponding T-invariant*
- **validation criterion 3**
  - -> *CPI*
  - -> *no minimal P-invariant without biological interpretation (?)*
- **validation criterion 4**
  - -> *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**

  -> known or estimated quantitative parameters

QUANTITATIVE ANALYSIS

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

  -> known or estimated quantitative parameters

- **typical quantitative parameters of bionetworks**

  -> *compound concentrations* -> *real numbers*

  -> *reaction rates / fluxes* -> *concentration-dependent*

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

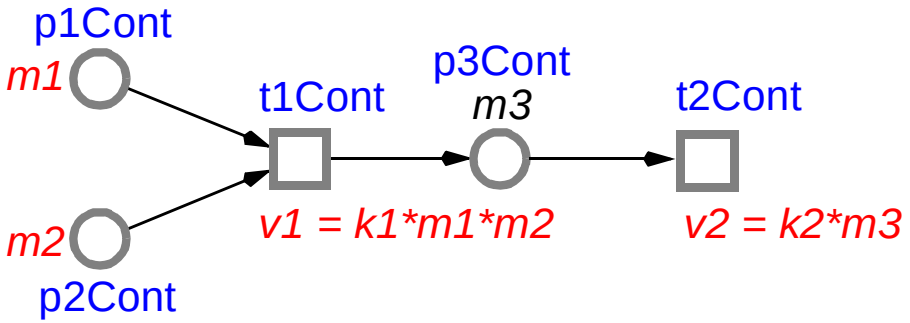
  -> known or estimated quantitative parameters

- **typical quantitative parameters of bionetworks**

  -> *compound concentrations* -> *real numbers*

  -> *reaction rates / fluxes* -> *concentration-dependent*

- **continuous Petri nets**



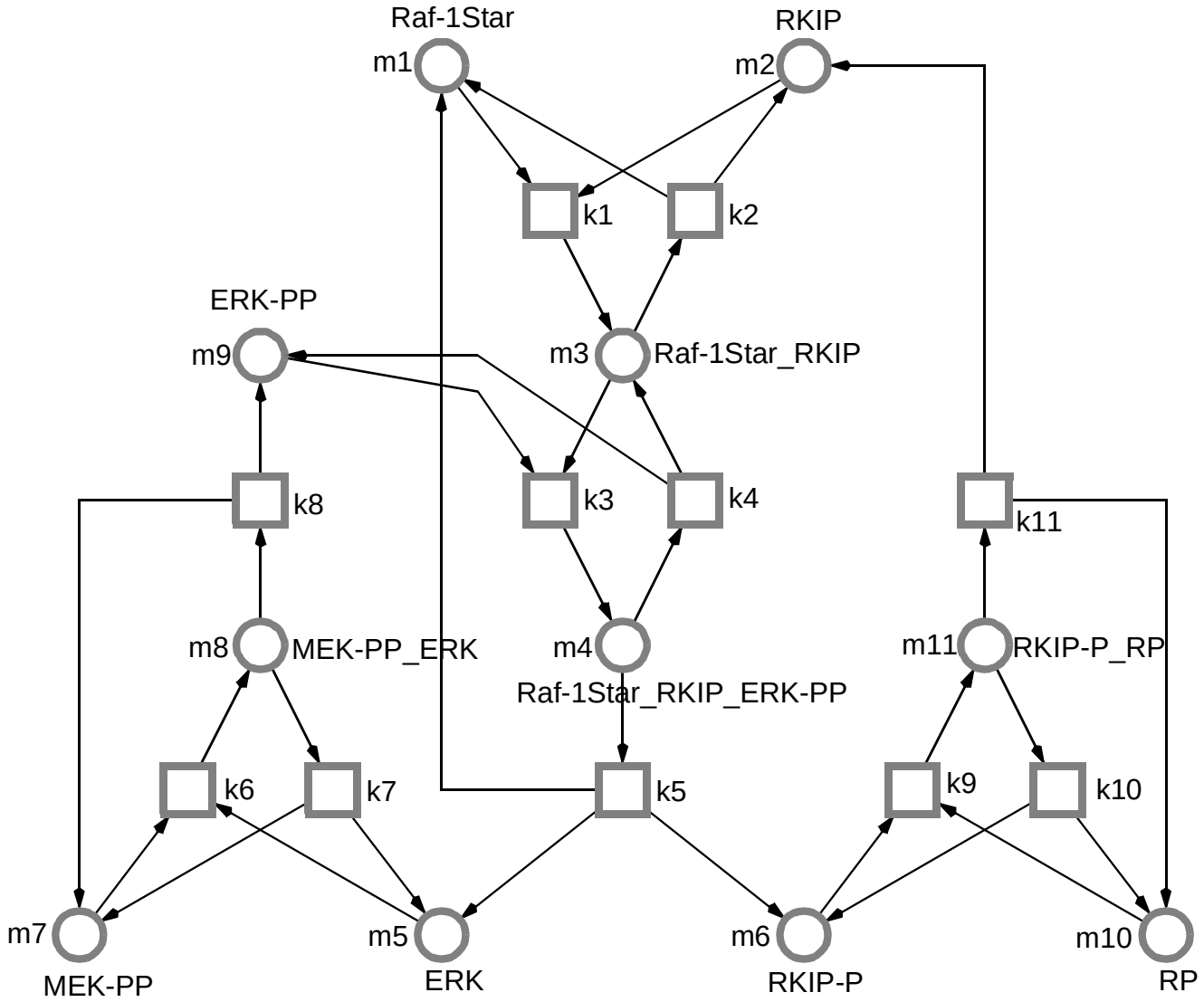
continuous nodes !

dm1 / dt = dm2 / dt = - v1

dm3 / dt = v1 - v2

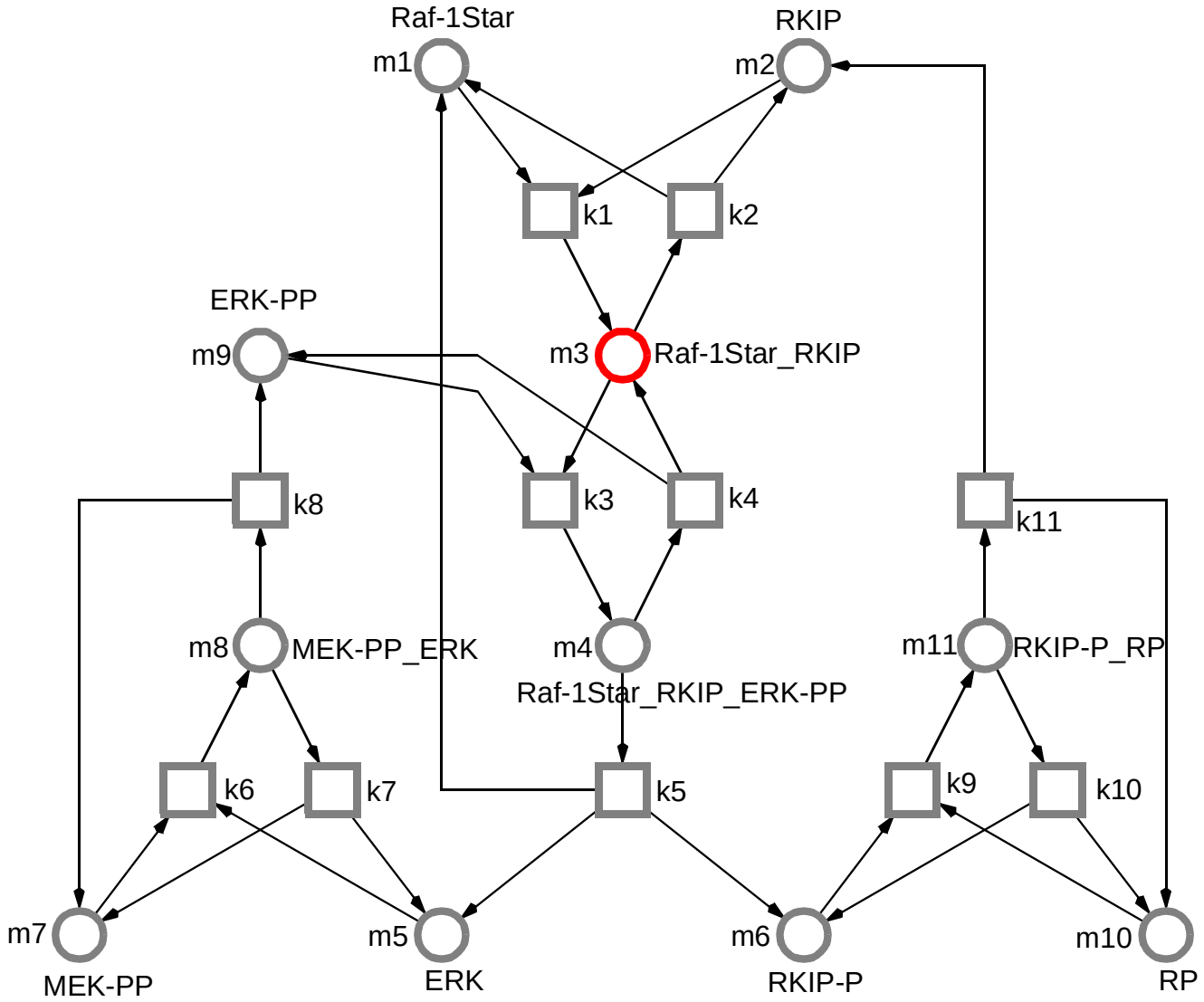
} **ODEs**

THE RKIP PATHWAY, CONTINUOUS PETRI NET



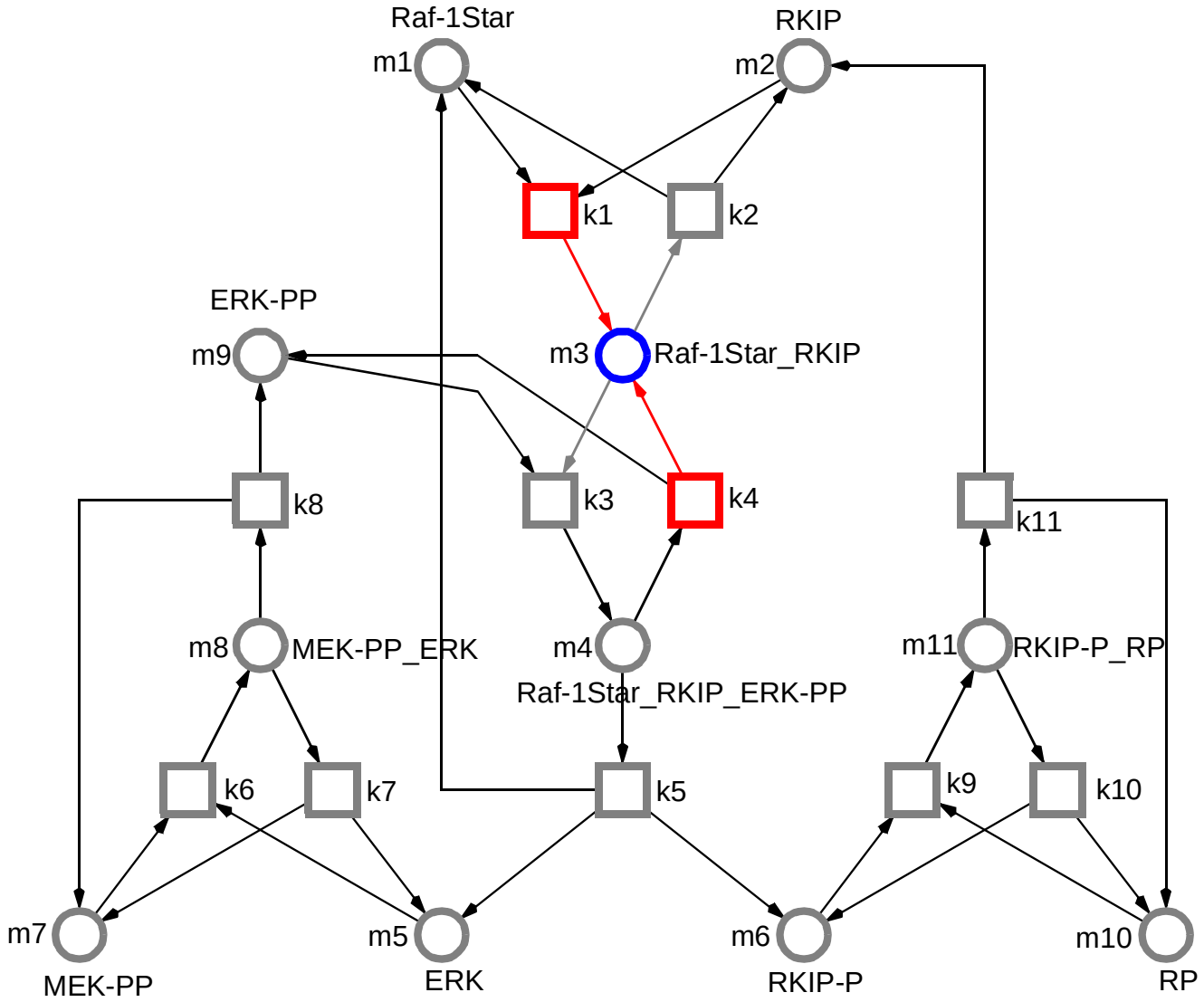
THE RKIP PATHWAY, CONTINUOUS PETRI NET

$$\frac{dm3}{dt} =$$



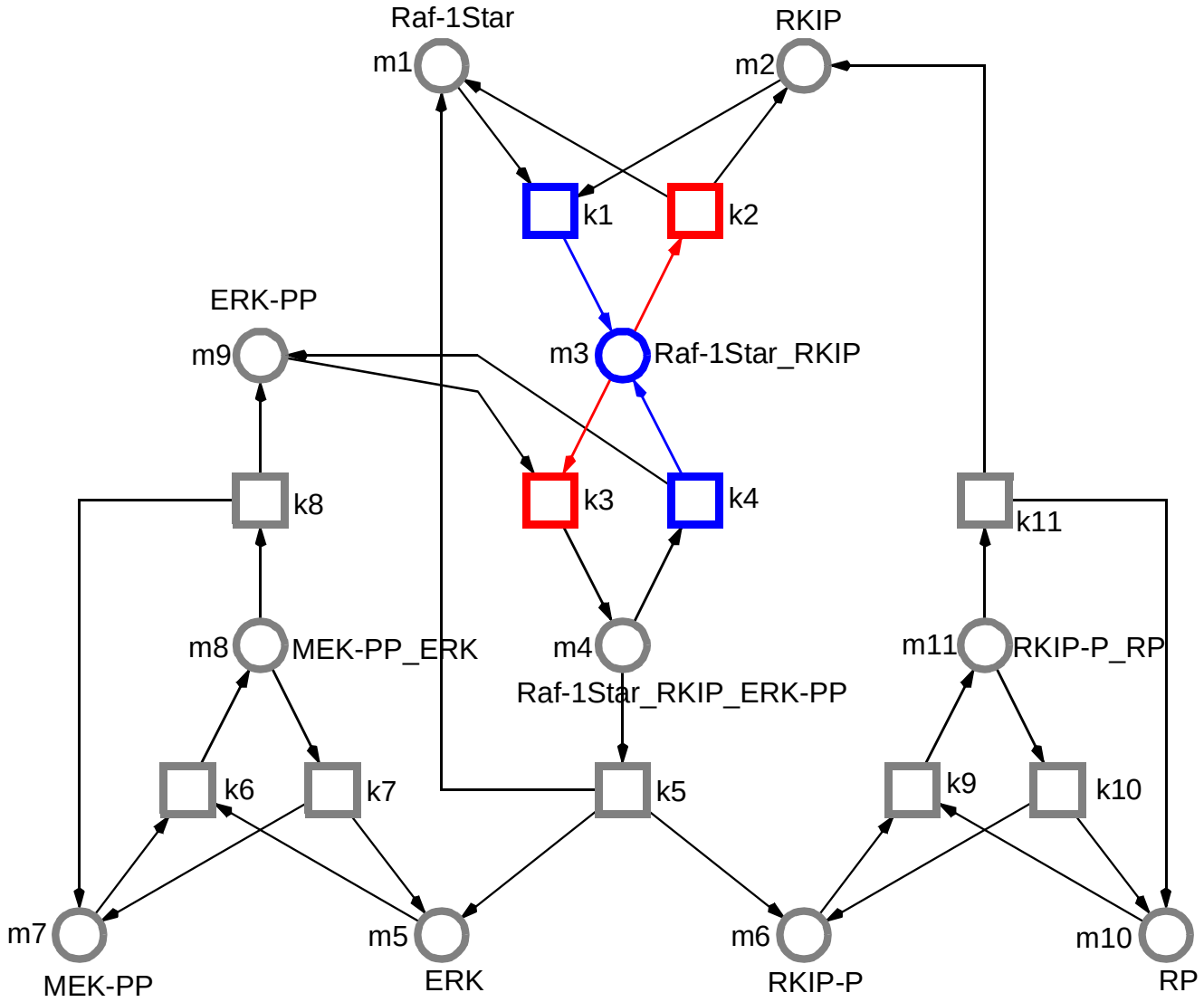
THE RKIP PATHWAY, CONTINUOUS PETRI NET

$$\frac{dm3}{dt} = +r1 + r4$$



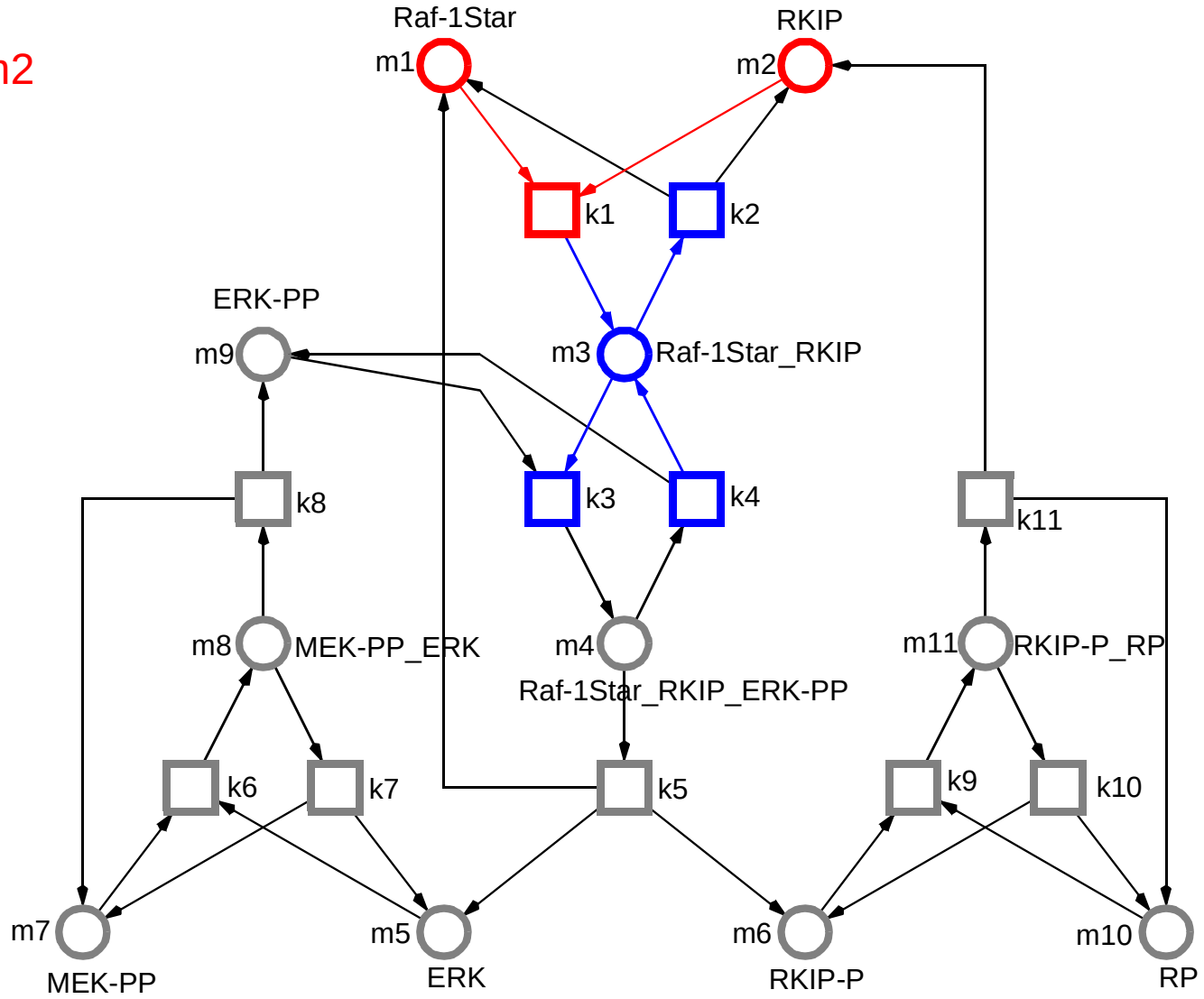
THE RKIP PATHWAY, CONTINUOUS PETRI NET

$$\frac{dm3}{dt} = + r1 + r4 - r2 - r3$$



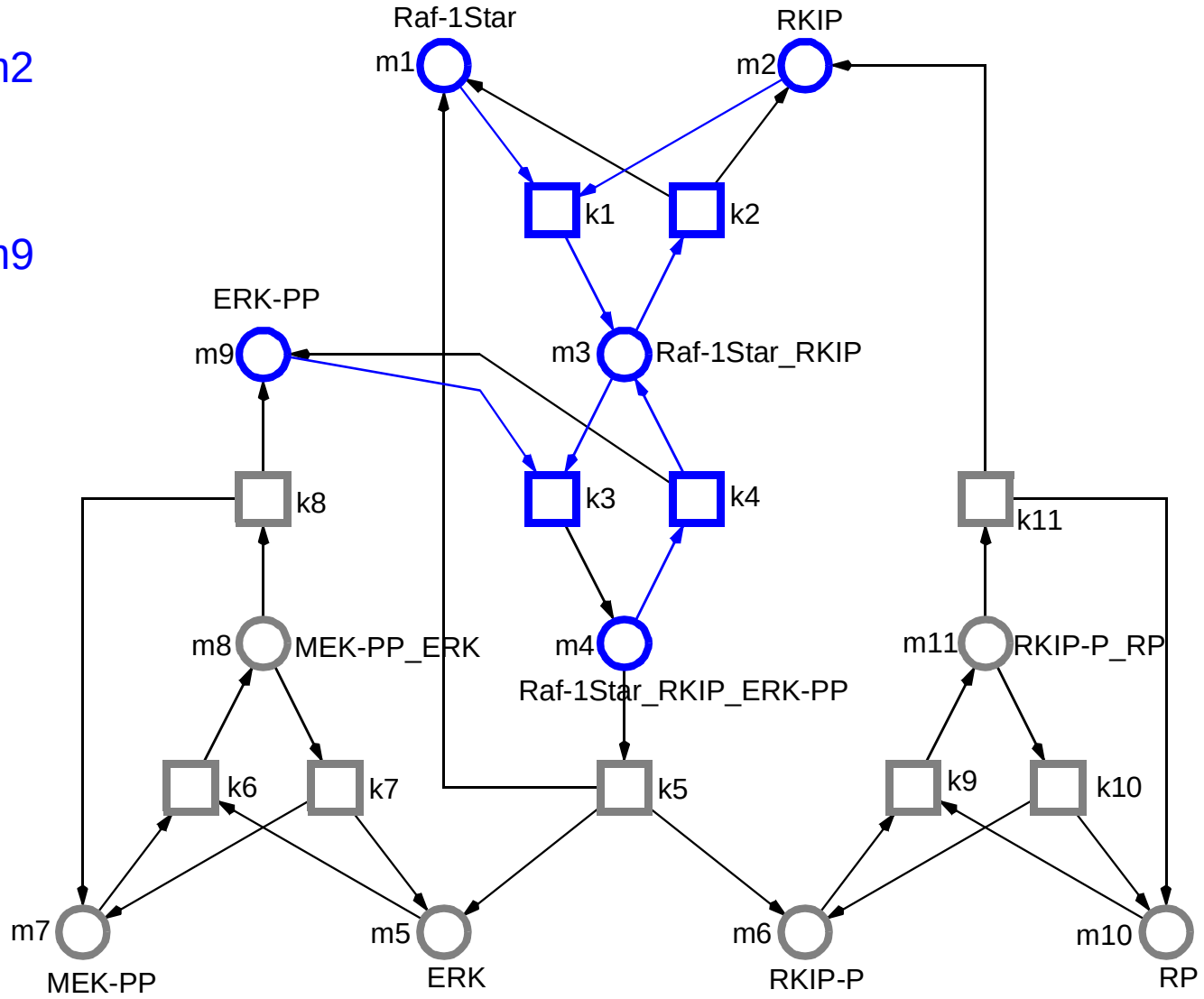
THE RKIP PATHWAY, CONTINUOUS PETRI NET

$$\frac{dm3}{dt} = + k1 * m1 * m2 + r4 - r2 - r3$$



THE RKIP PATHWAY, CONTINUOUS PETRI NET

$$\frac{dm3}{dt} = + k1 * m1 * m2 + k4 * m4 - k2 * m3 - k3 * m3 * m9$$



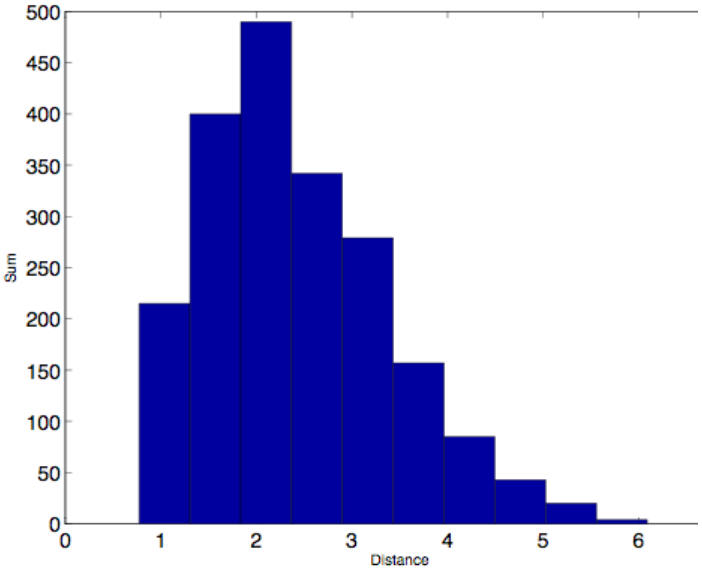
THE QUALITATIVE MODEL BECOMES THE STRUCTURED DESCRIPTION OF THE QUANTITATIVE MODEL !

QUANTITATIVE ANALYSIS

Species	S1	S2	S3	S4	S5	S6	S7	S8	S9	S10	S11	S12	S13
Raf-1*	1	0	0	1	1	1	1	1	0	0	1	1	1
RKIP	1	0	0	0	0	0	0	1	0	0	1	0	0
Raf-1*_RKIP	0	1	0	0	0	0	0	0	1	1	0	0	0
Raf-1*_RKIP_ERK-PP	0	0	1	0	0	0	0	0	0	0	0	0	0
ERK	0	0	0	1	0	0	1	1	1	0	0	0	0
RKIP-P	0	0	0	1	1	0	0	0	0	0	0	0	1
MEK-PP	1	1	1	1	0	0	1	1	1	0	0	1	1
MEK-PP_ERK	0	0	0	0	1	1	0	0	0	1	1	0	0
ERK-PP	1	1	0	0	0	0	0	0	0	0	0	1	1
RP	1	1	1	1	1	0	0	1	1	1	1	0	1
RKIP-P_RP	0	0	0	0	0	1	1	0	0	0	0	1	0

Cho et al

Biochemist

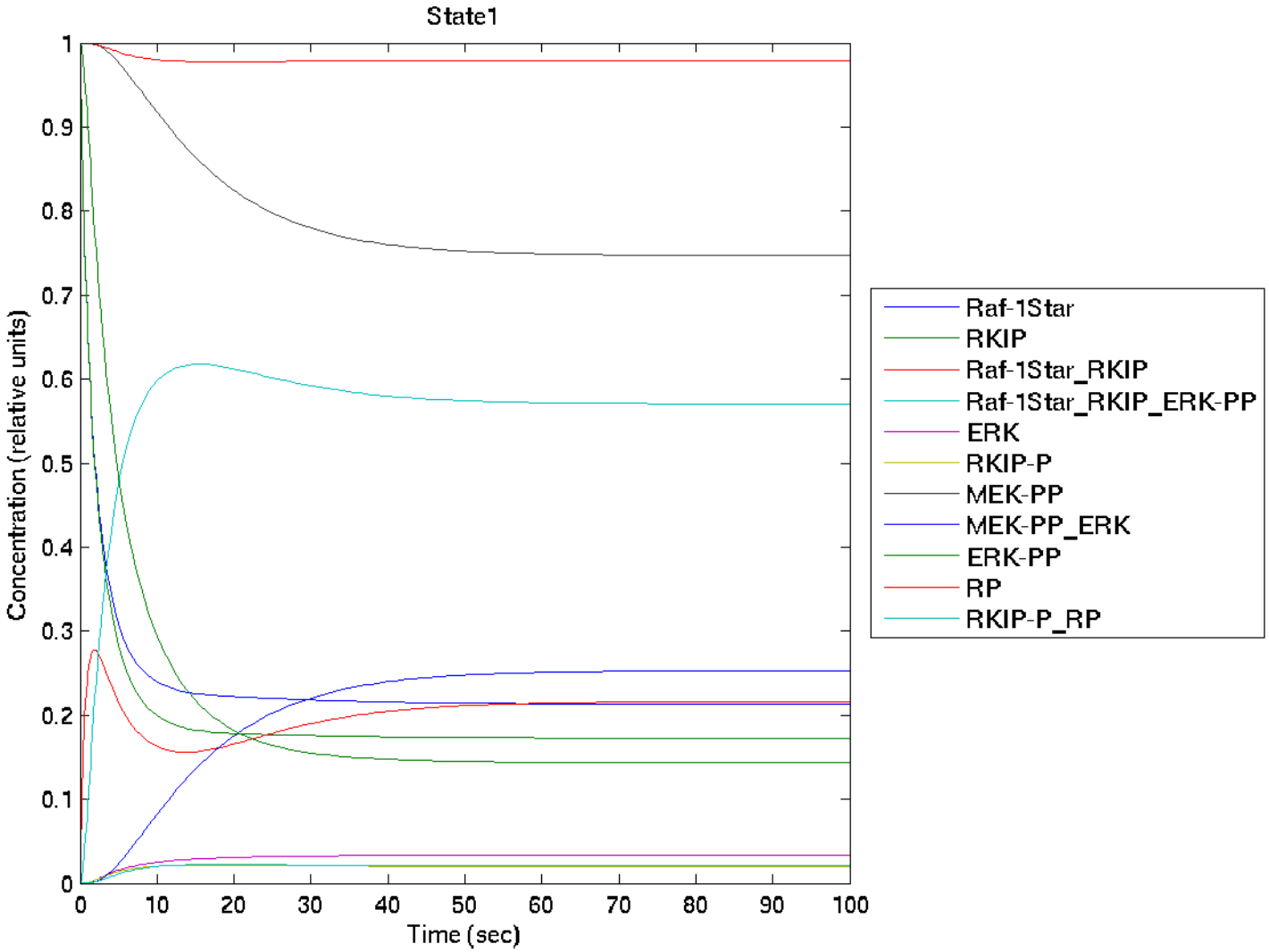


Distribution of `bad' steady states as euclidean distances from the `good' final steady state

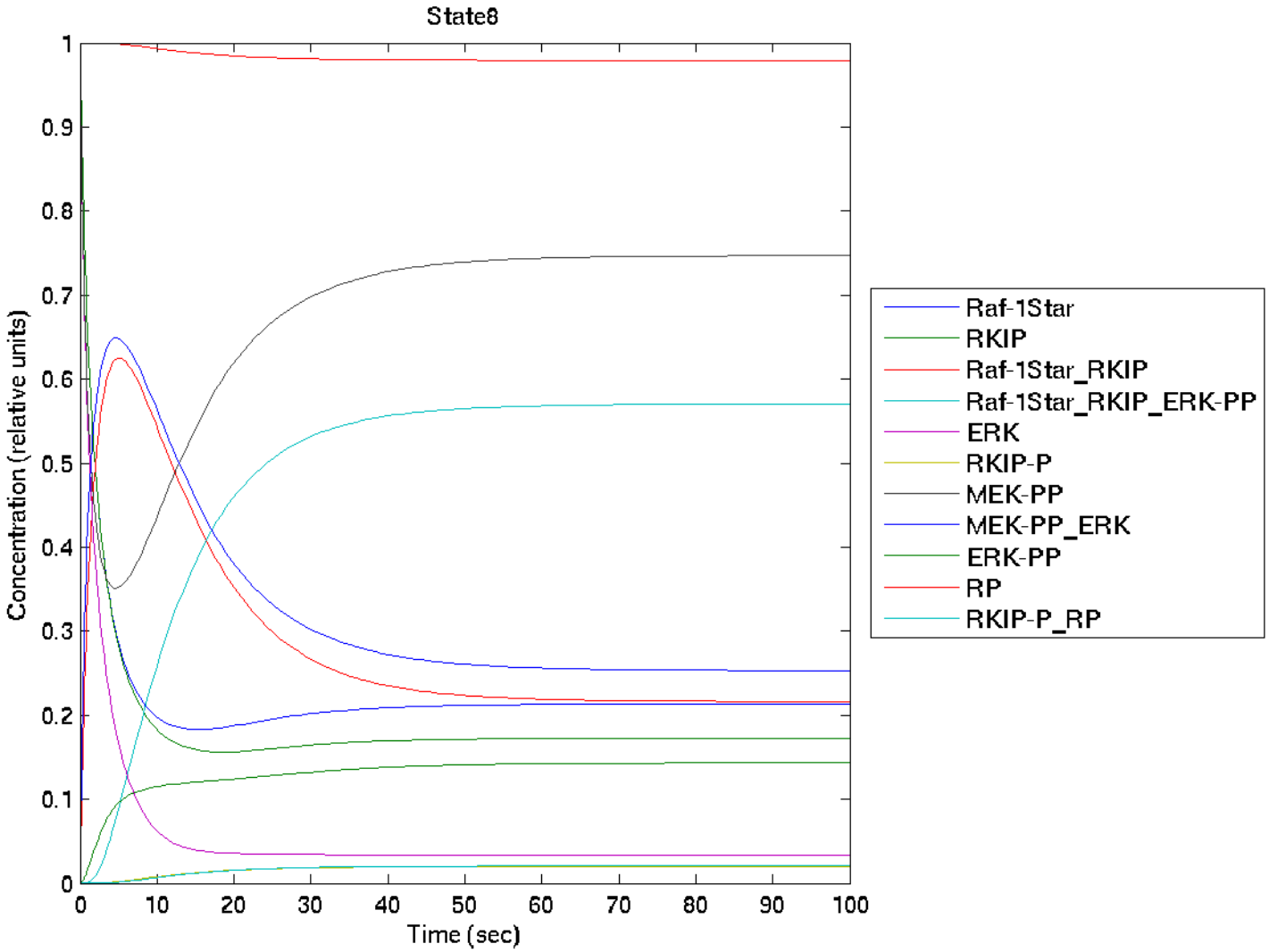
13 “good” state configurations

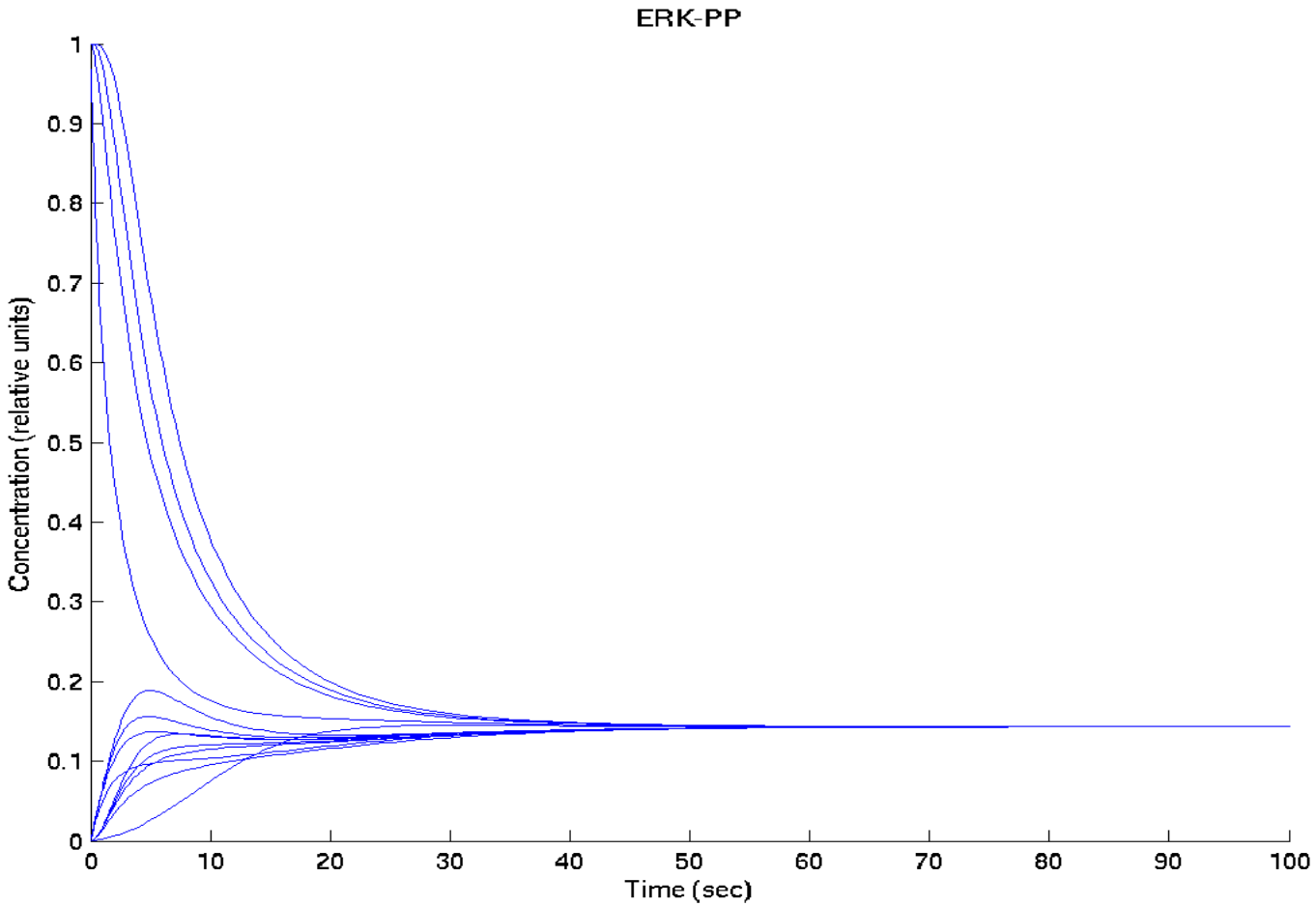
the “bad” ones

QUANTITATIVE ANALYSIS



QUANTITATIVE ANALYSIS




ERK-PP
Concentration (relative units)
Time (sec)
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
0
10
20
30
40
50
60
70
80
90
100

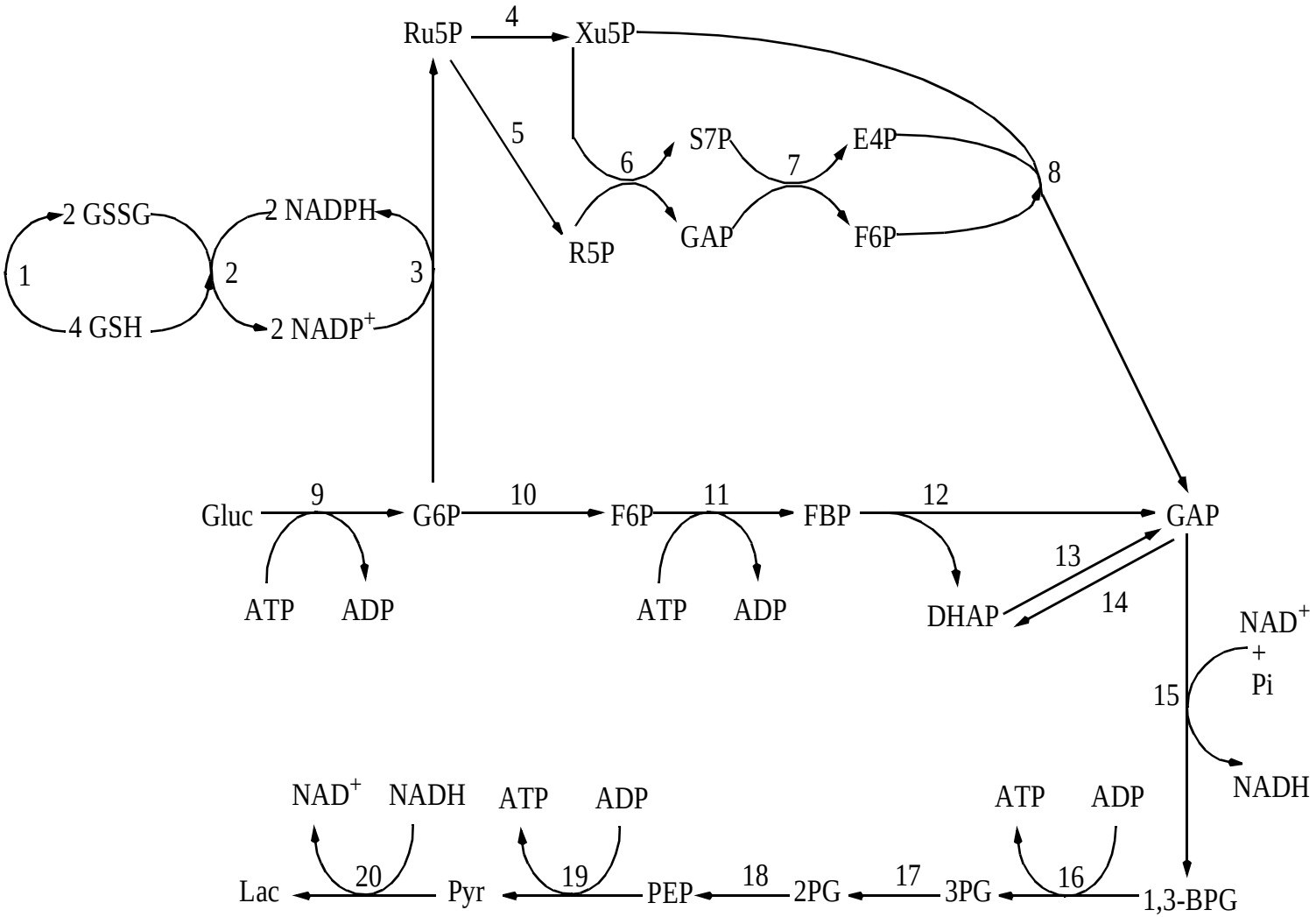
CASE STUDY, SUMMARY

- **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* -> *new insights*
- **two-step model development**
  - -> *qualitative model* -> *discrete Petri nets*
  - -> *quantitative model* -> *continuous Petri nets = ODEs*
- **many challenging open questions**

SOME MORE CASE STUDIES

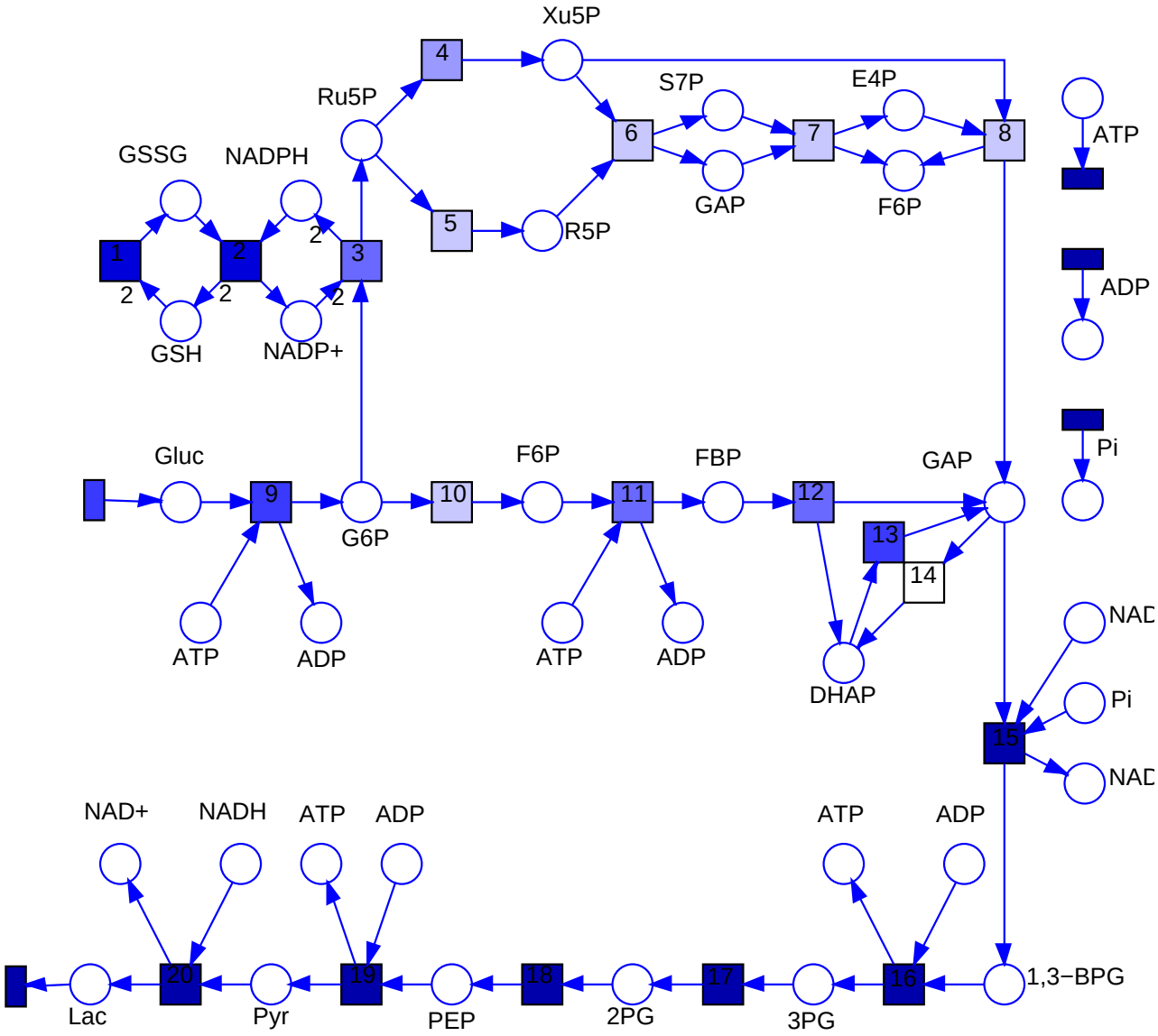
Ex1 - Glycolysis and Pentose Phosphate Pathway

[Reddy 1993]



Ex1 - Glycolysis and Pentose Phosphate Pathway

[Reddy 1993]



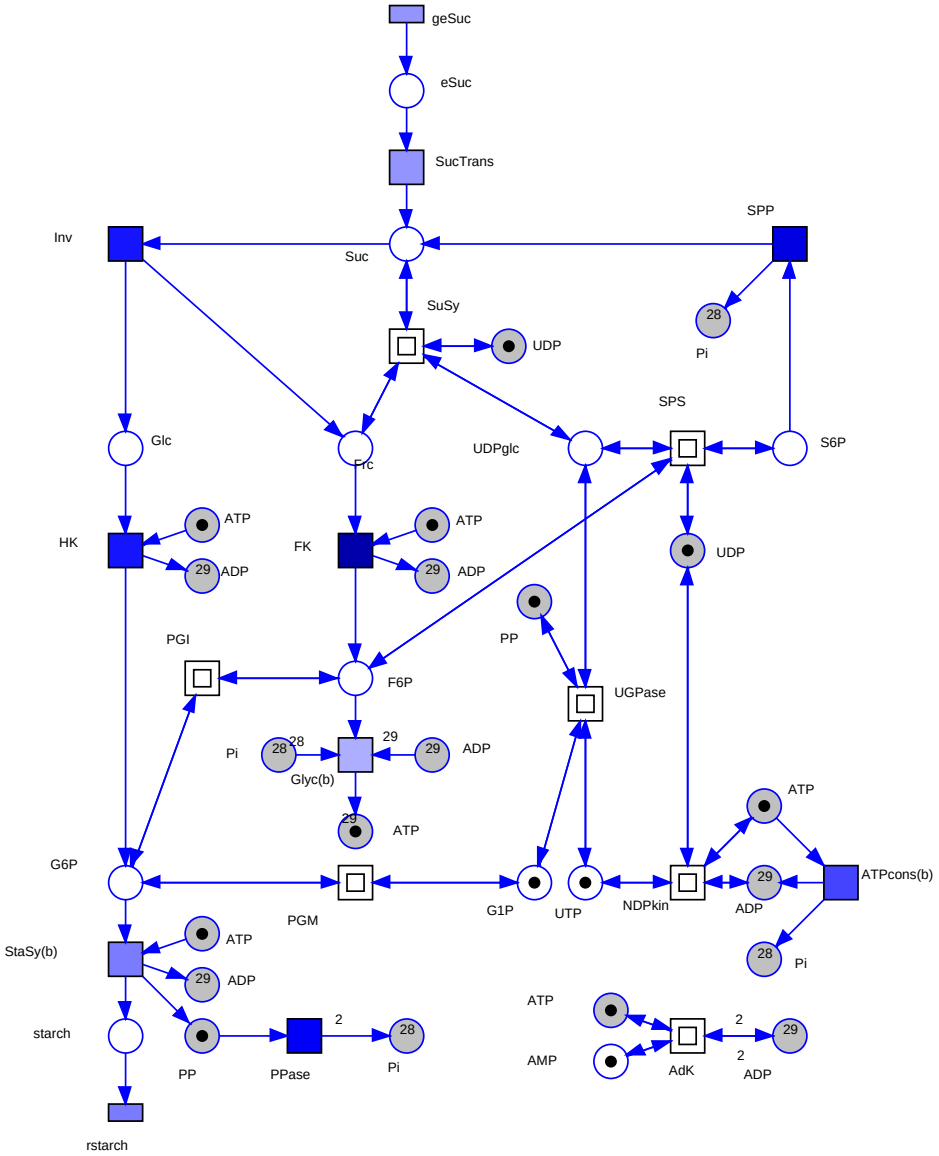
Ex2 - Carbon Metabolism in Potato Tuber

[KOCH; JUNKER; HEINER 2005]

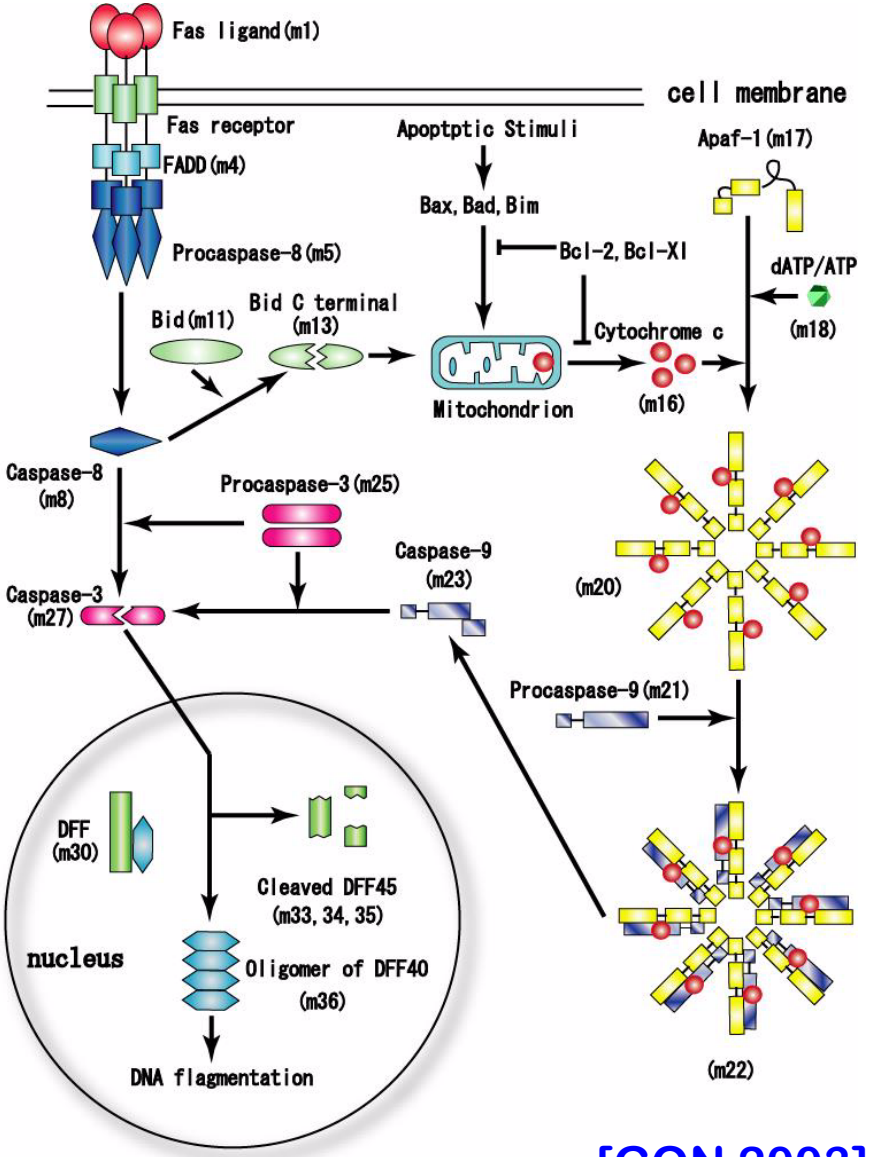
monika.heiner@informatik.tu-cottbus.de

Ex2 - Carbon Metabolism in Potato Tuber

[KOCH; JUNKER; HEINER 2005]

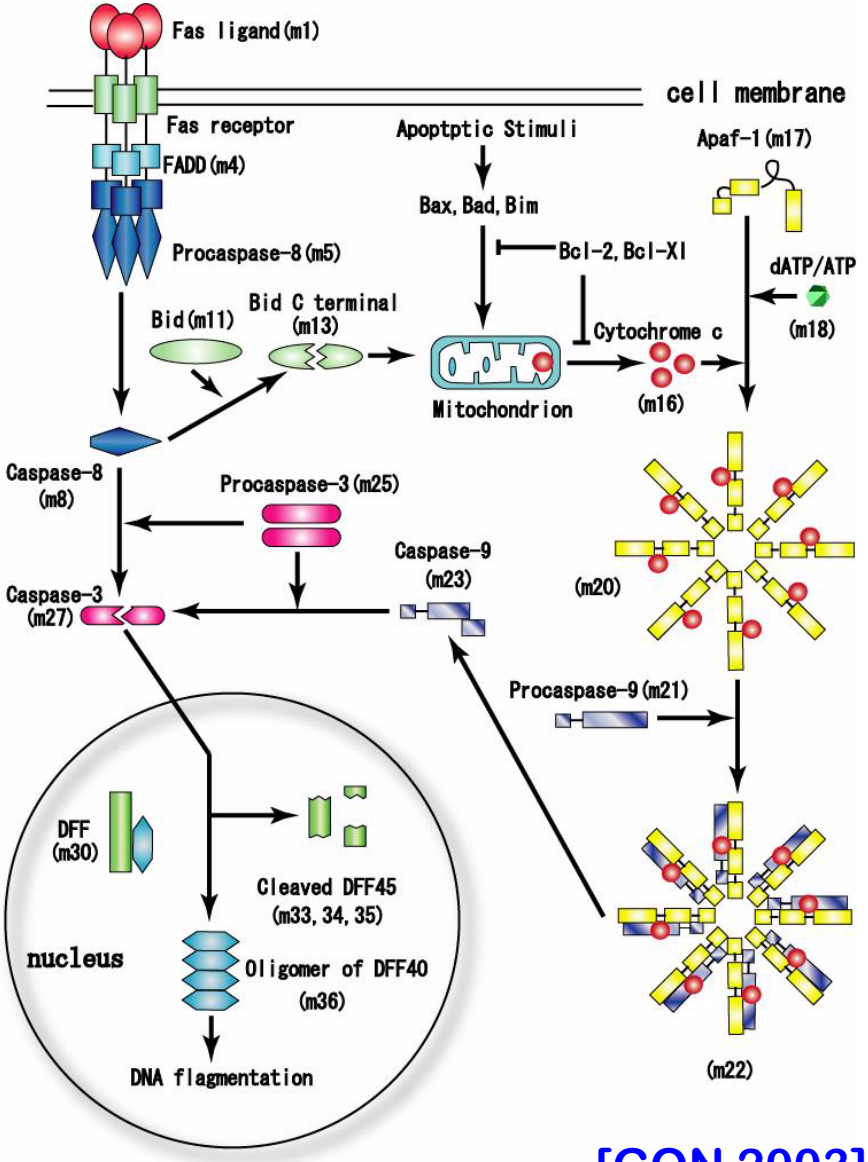


EX3: APOPTOSIS IN MAMMALIAN CELLS

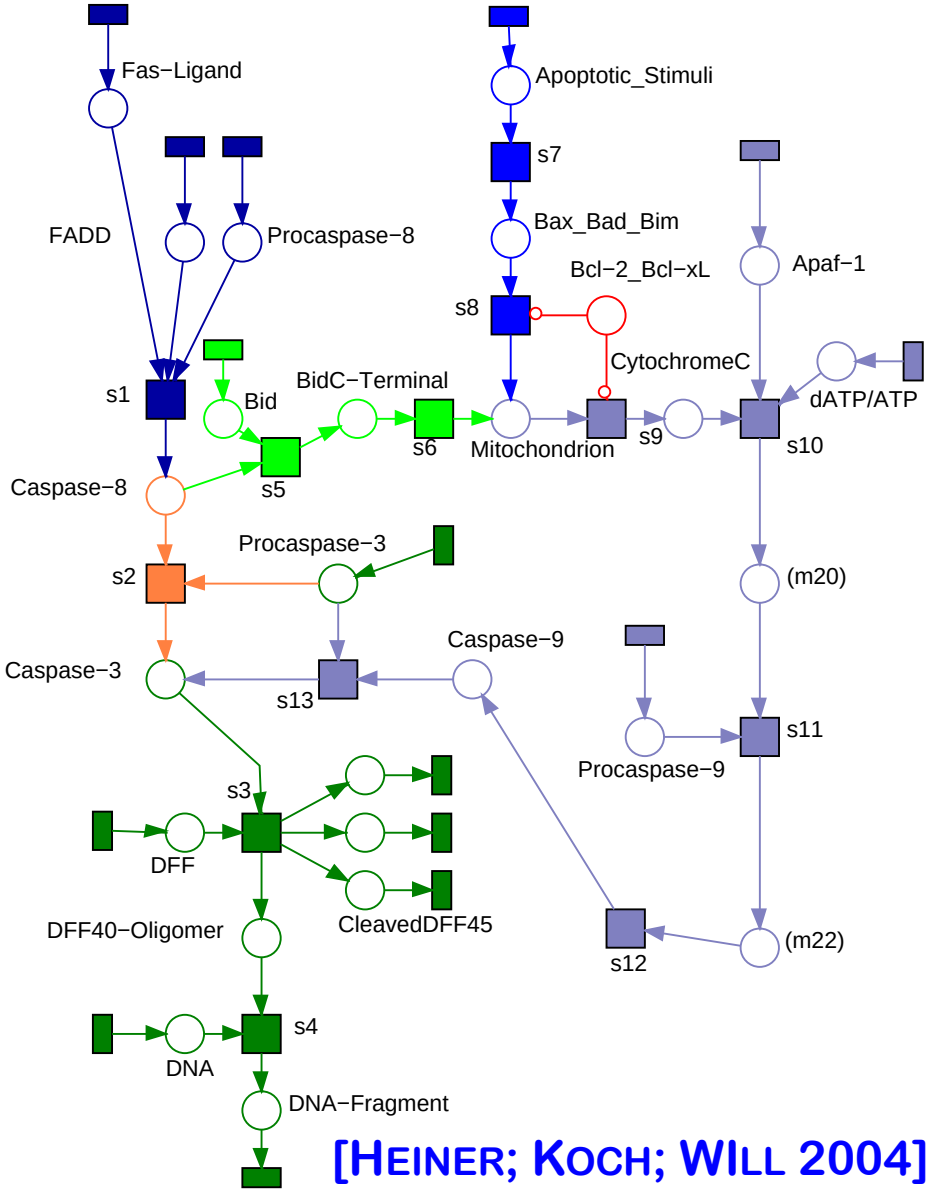


[GON 2003]

EX3: APOPTOSIS IN MAMMALIAN CELLS

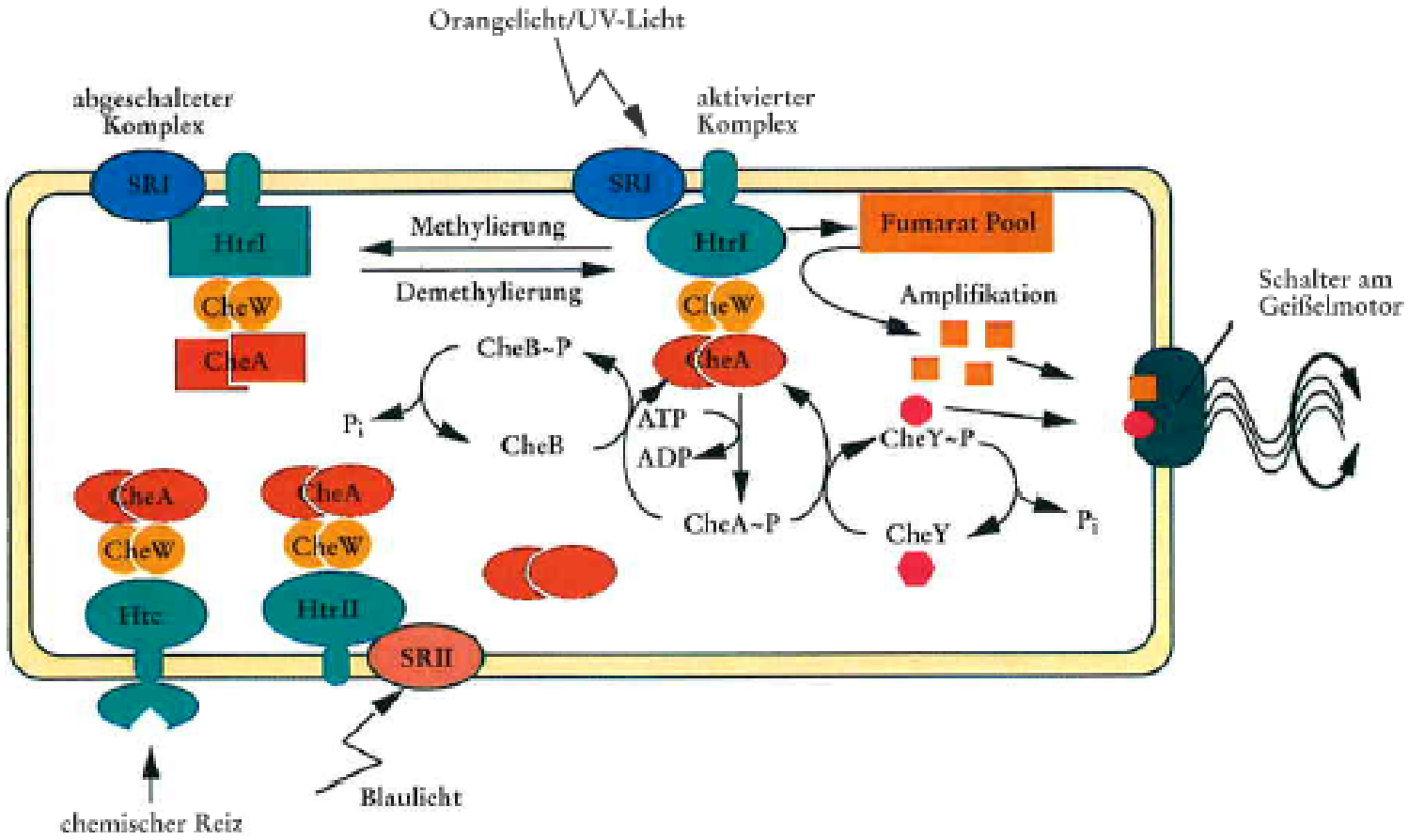


[GON 2003]



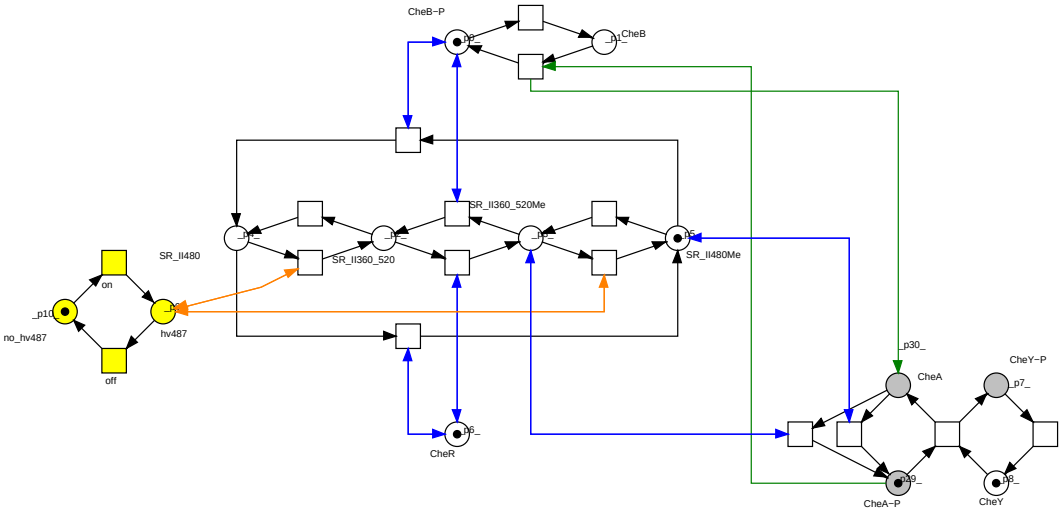
[HEINER; KOCH; WILL 2004]

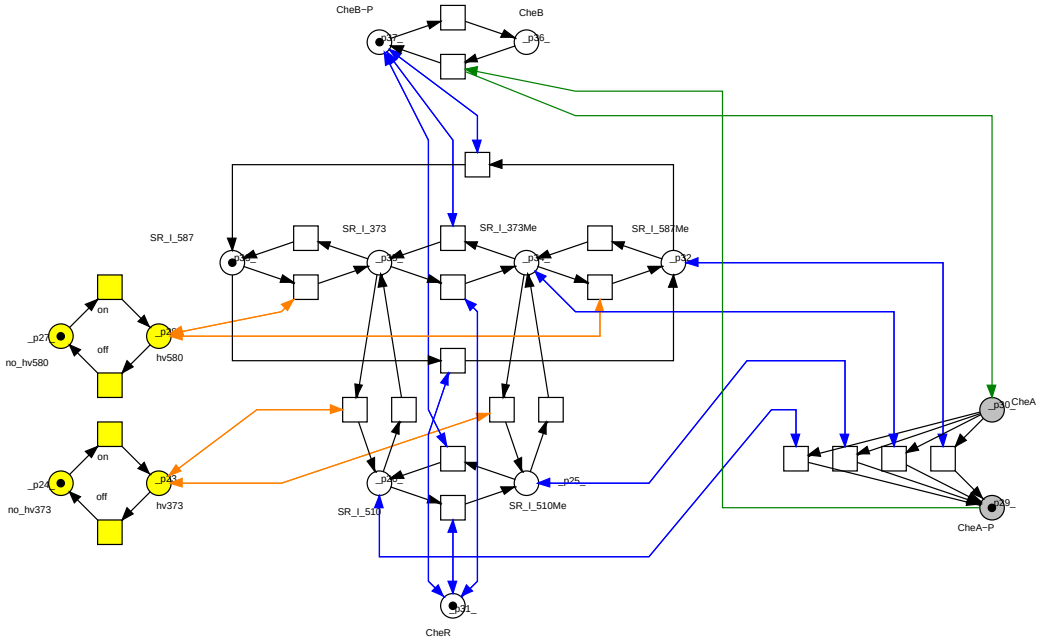
EX4 - SWITCH CYCLE HALOBACTERIUM SALINARUM

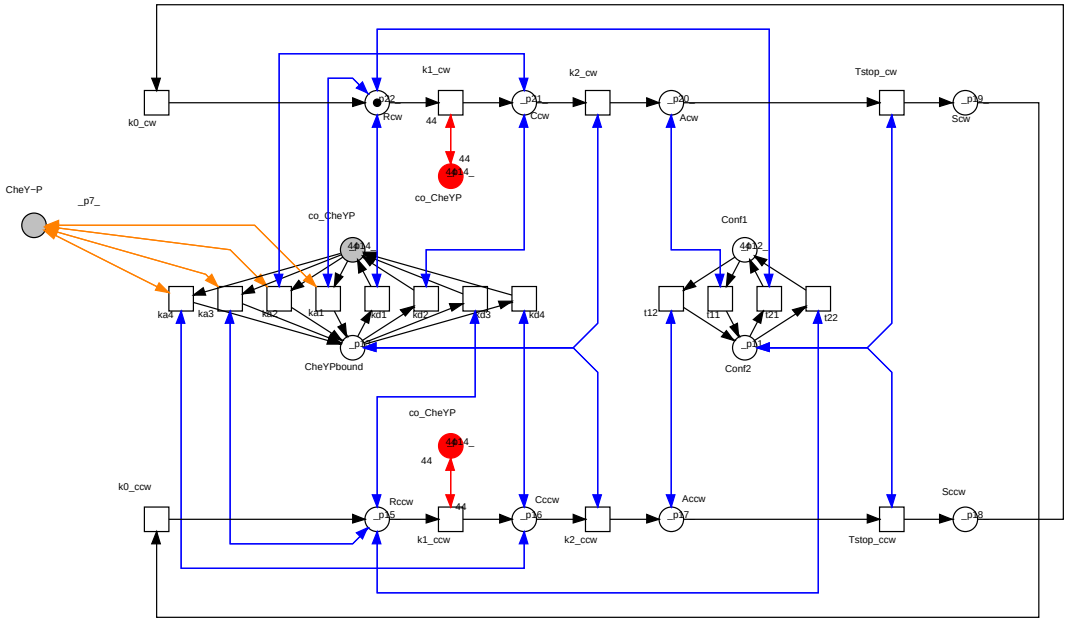


[Marwan; Oesterhelt 1999]

Ex4 - Switch Cycle Halobacterium Salinarum

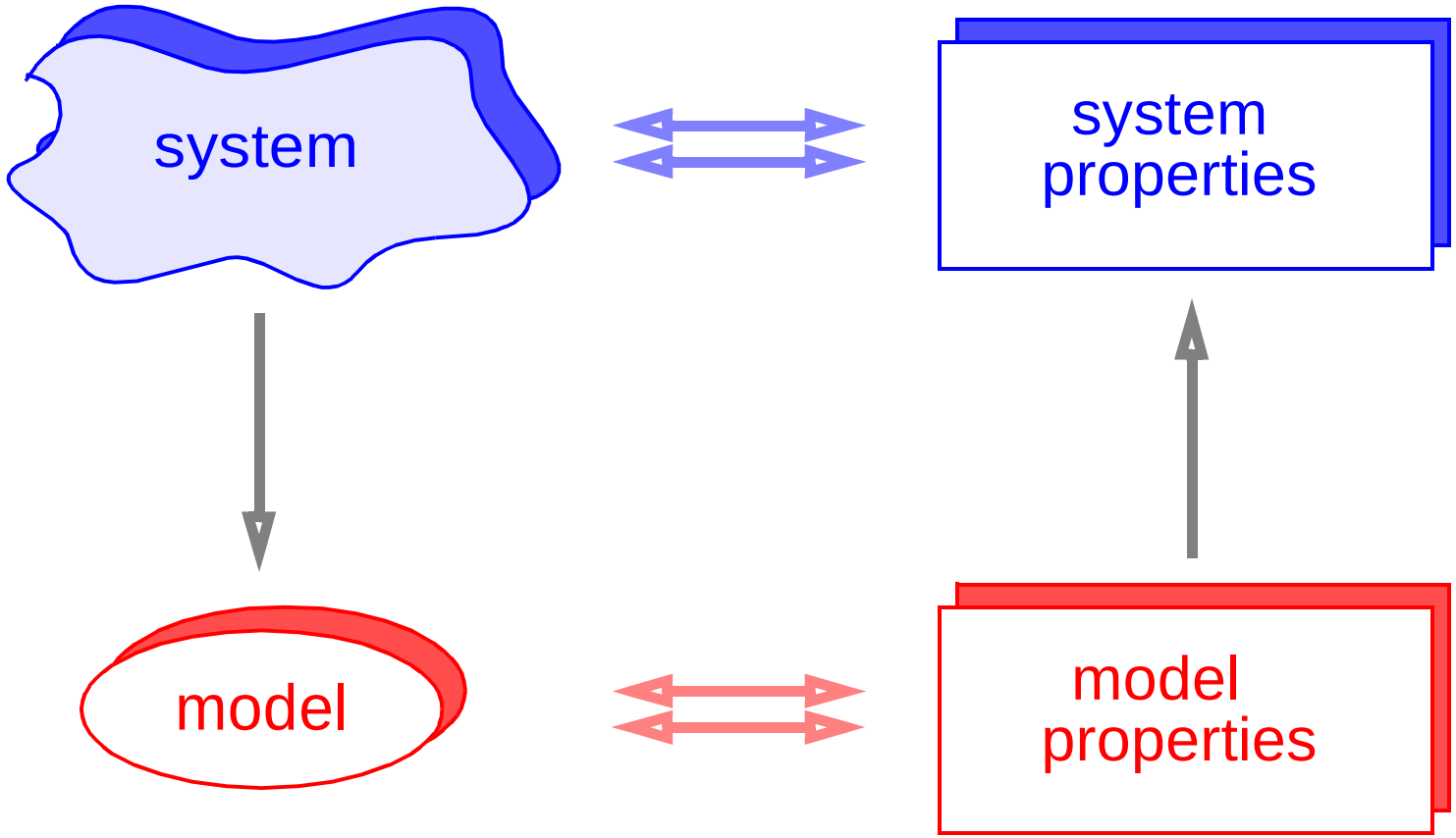


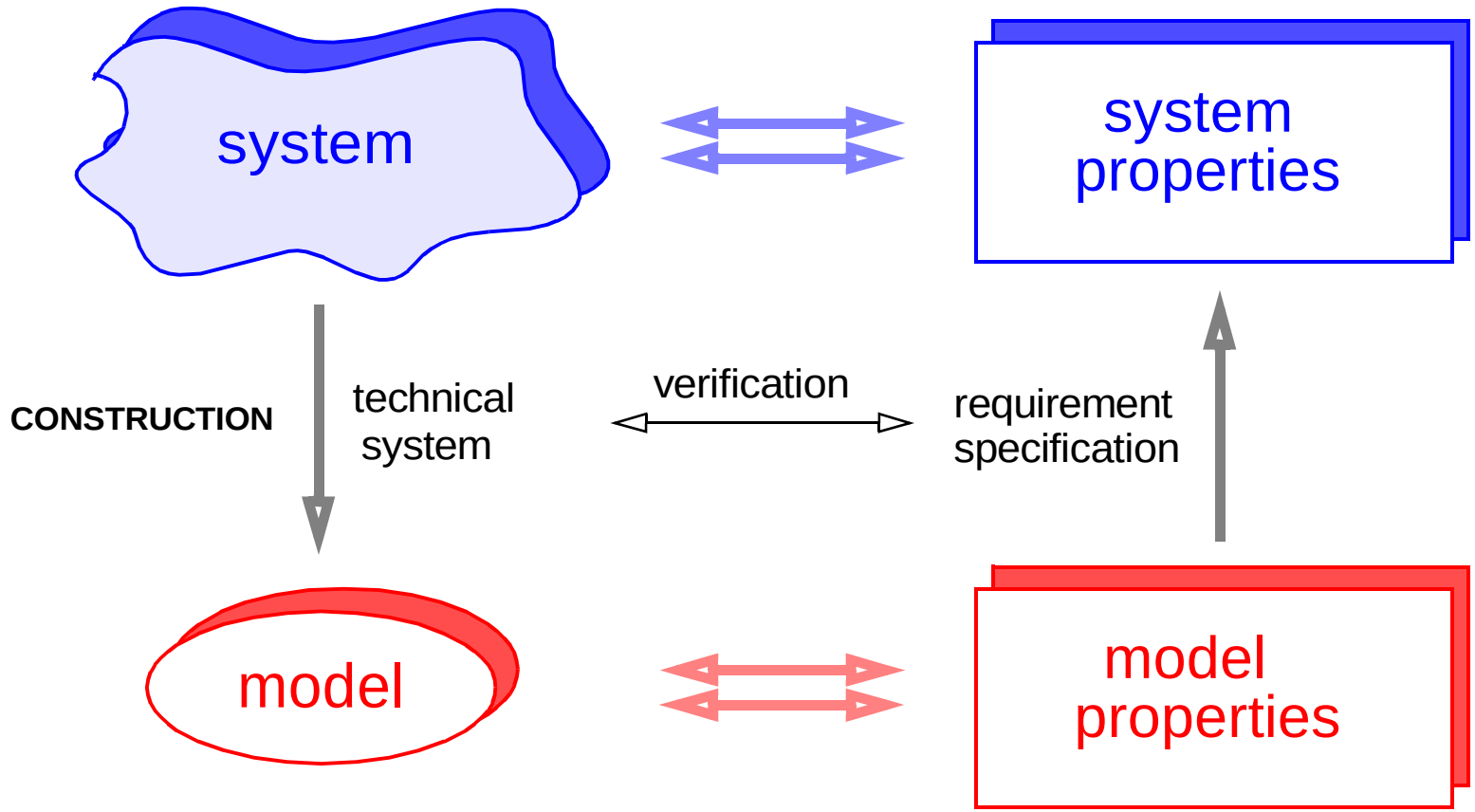




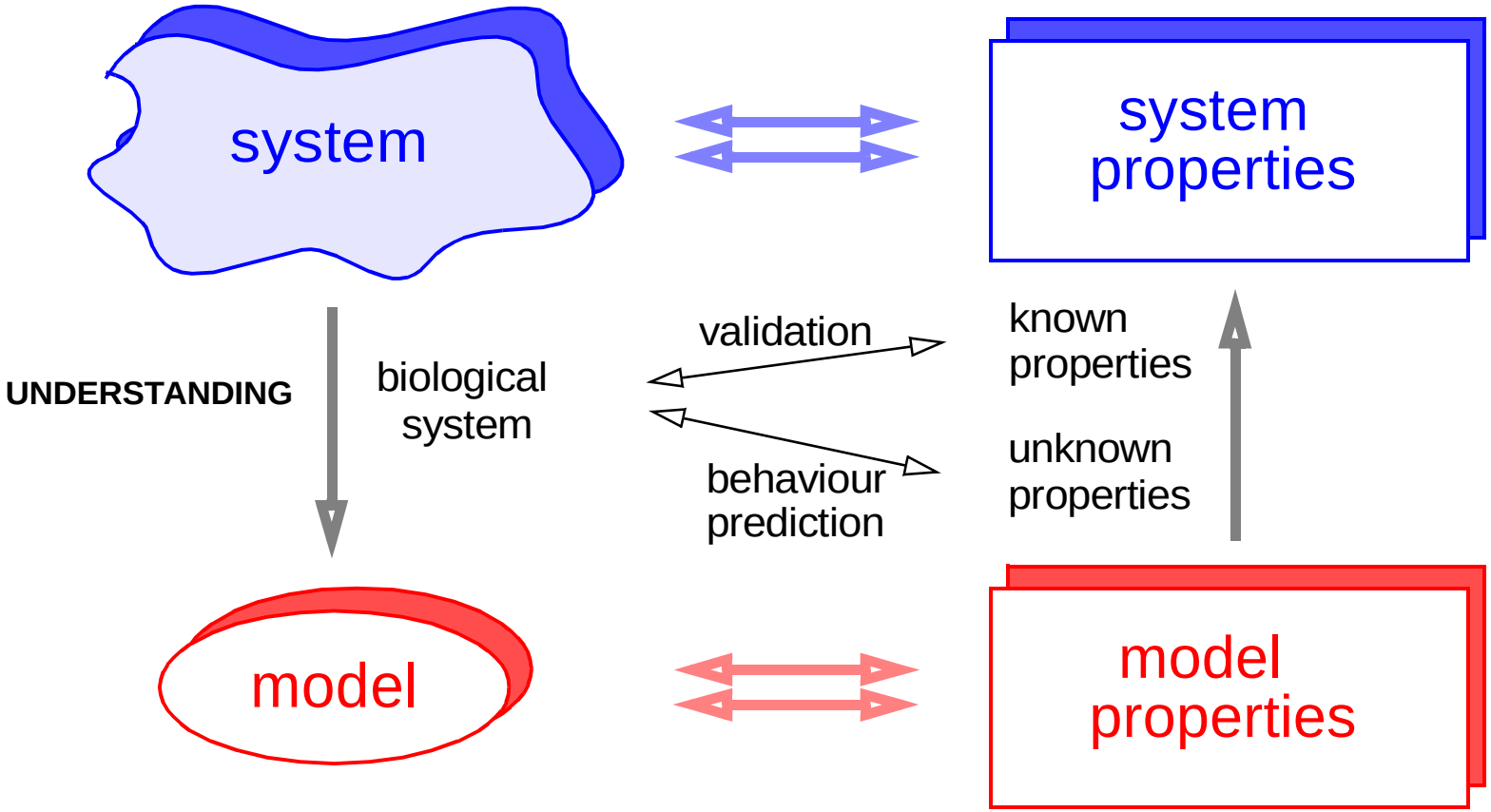
WHAT HAVE TECHNICAL AND NATURAL SYSTEMS IN COMMON?

MODEL-BASED SYSTEM ANALYSIS

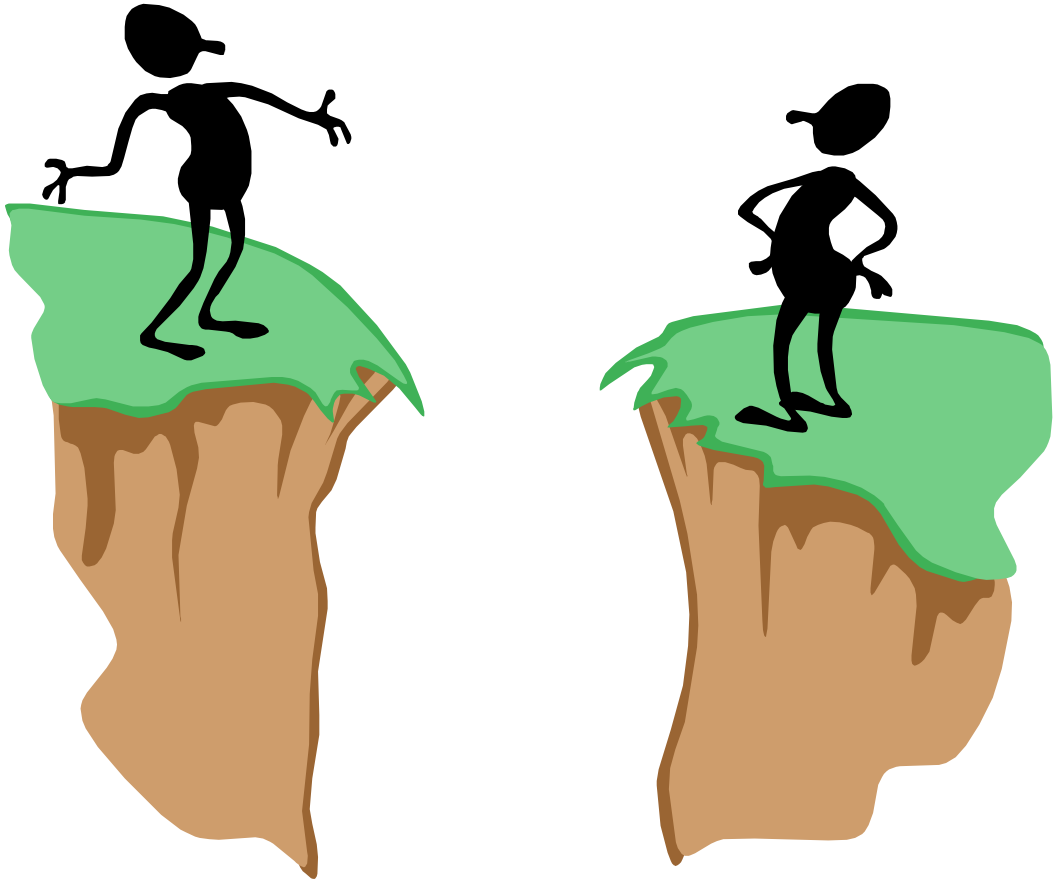



system
system properties
CONSTRUCTION
technical system
verification
requirement specification
model
model properties

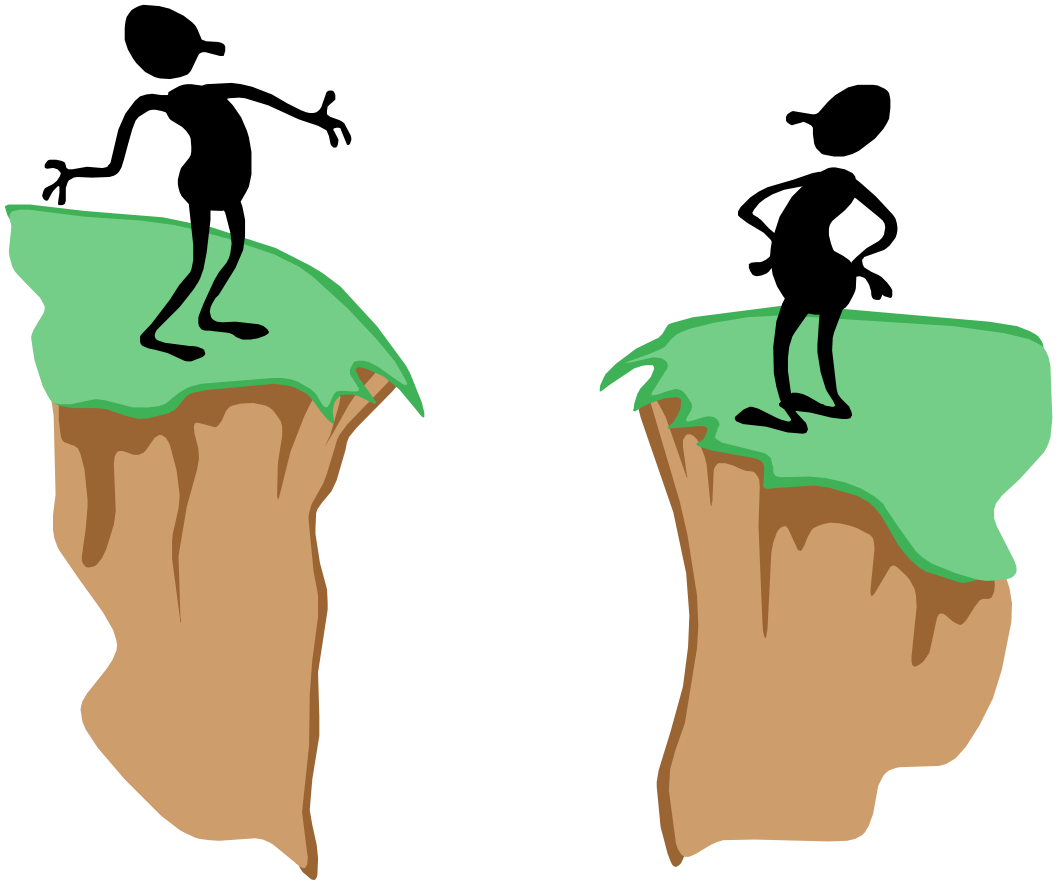
MODEL-BASED SYSTEM ANALYSIS



OUTLOOK



OUTLOOK



THANKS !

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