A STRUCTURED APPROACH . . .
TUTORIAL, PART II

FROM PETRI NETS
TO DIFFERENTIAL EQUATIONS

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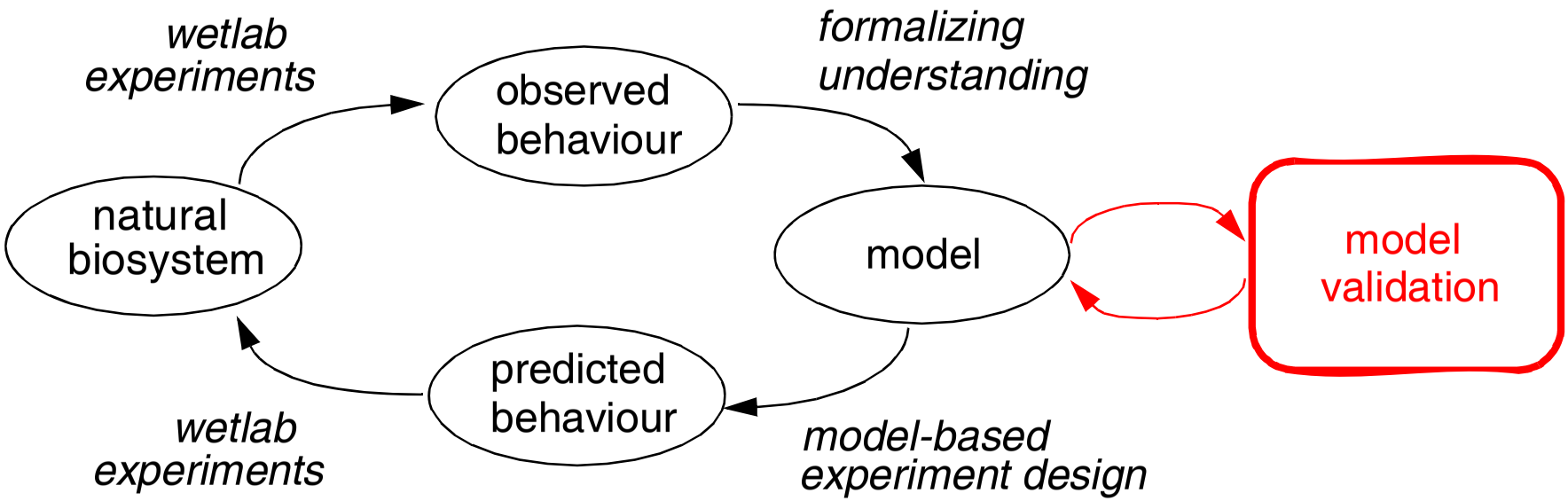
FRAMEWORK: SYSTEMS BIOLOGY

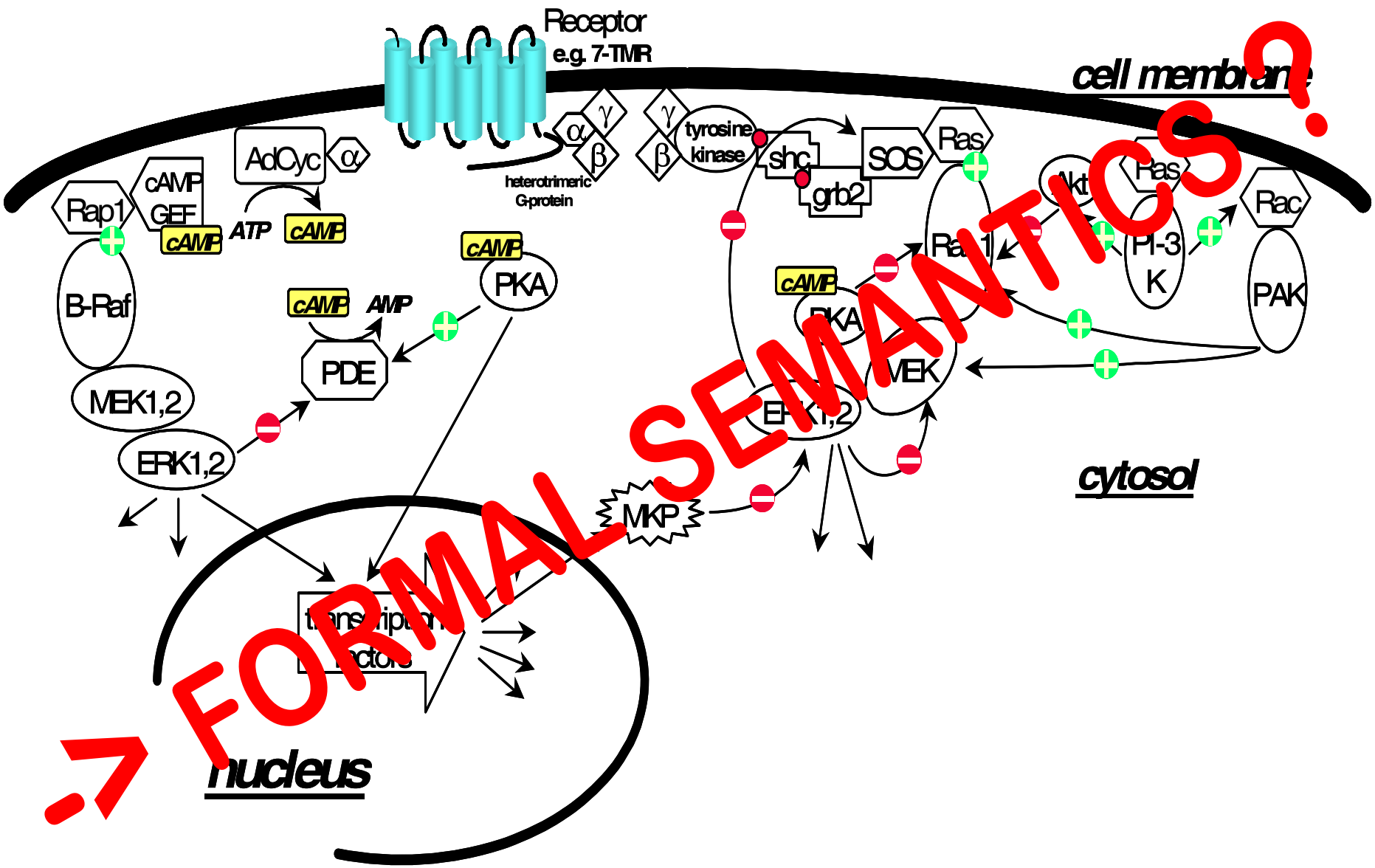
MODELLING = FORMAL KNOWLEDGE REPRESENTATION



MODEL VALIDATION = CONFIDENCE INCREASE

WHAT KIND OF MODEL SHOULD BE USED?

NETWORK REPRESENTATIONS, EX1



NETWORK REPRESENTATIONS, EX2

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

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

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

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

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

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

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

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

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

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

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

$$\frac{dFus3}{dt} = -\nu_{14} + \nu_{[illegible]} + \nu_{17} + \nu_{21} + \nu_{23} + \nu_{25} + \nu_{27} - \nu_{29} + \nu_{30} + \nu_{[illegible]}$$

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

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

$$\nu_2 = Ste2[t] \cdot \alpha[t] \cdot k_{[illegible]}$$

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

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

$$\nu_5 = S[illegible]e2[t] \cdot k_5$$

$$\nu_{[illegible]} = S[illegible]2_{active}[t] \cdot G\alpha\beta\gamma[t] \cdot k_6$$

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

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

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

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

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

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

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

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

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

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

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

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

→ READABILITY?

NETWORK REPRESENTATIONS

- informal cartoon-like representations
  - -> *readability*
  - -> *fault avoidance*
- formal = mathematical representations
  - -> *analysability*

WHY NOT BOTH ?

&

EXECUTABILITY

PETRI NETS - AN INFORMAL CRASH COURSE

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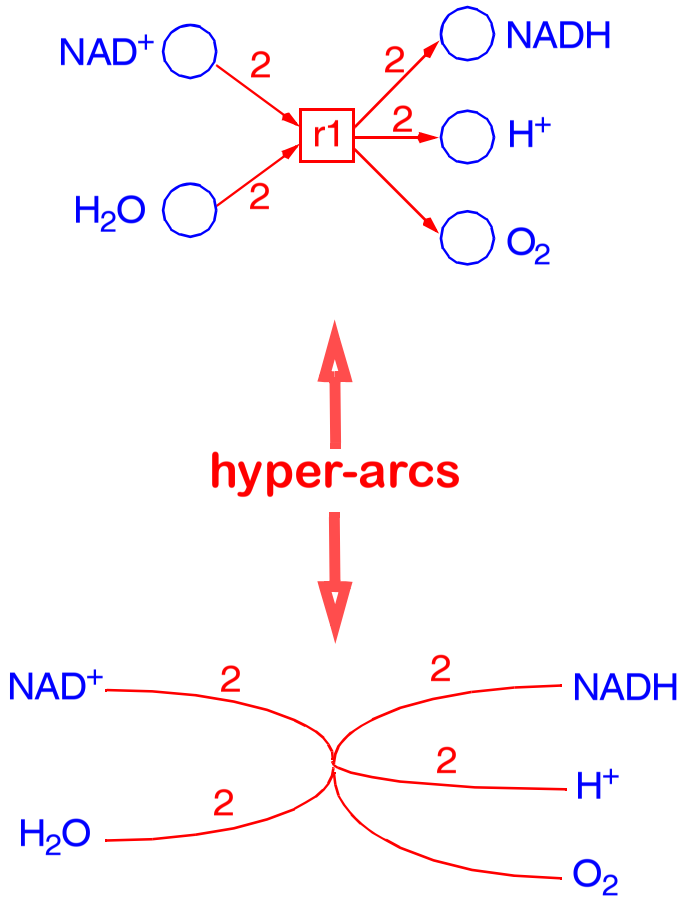
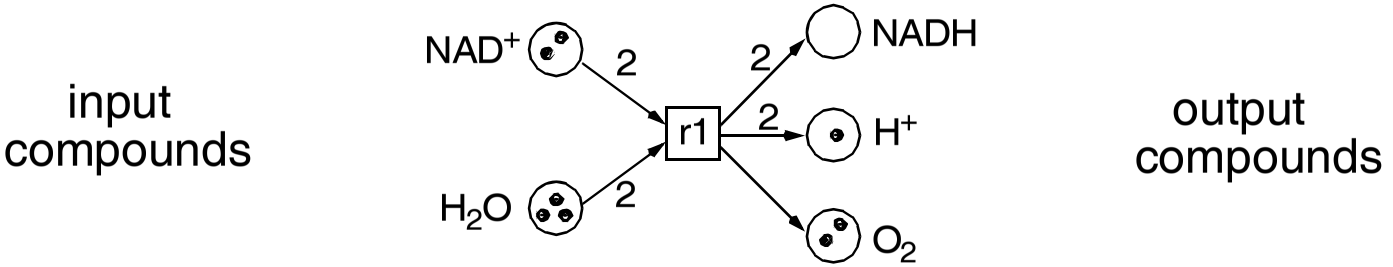
❑

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



- atomic actions -> transitions -> chemical reactions

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

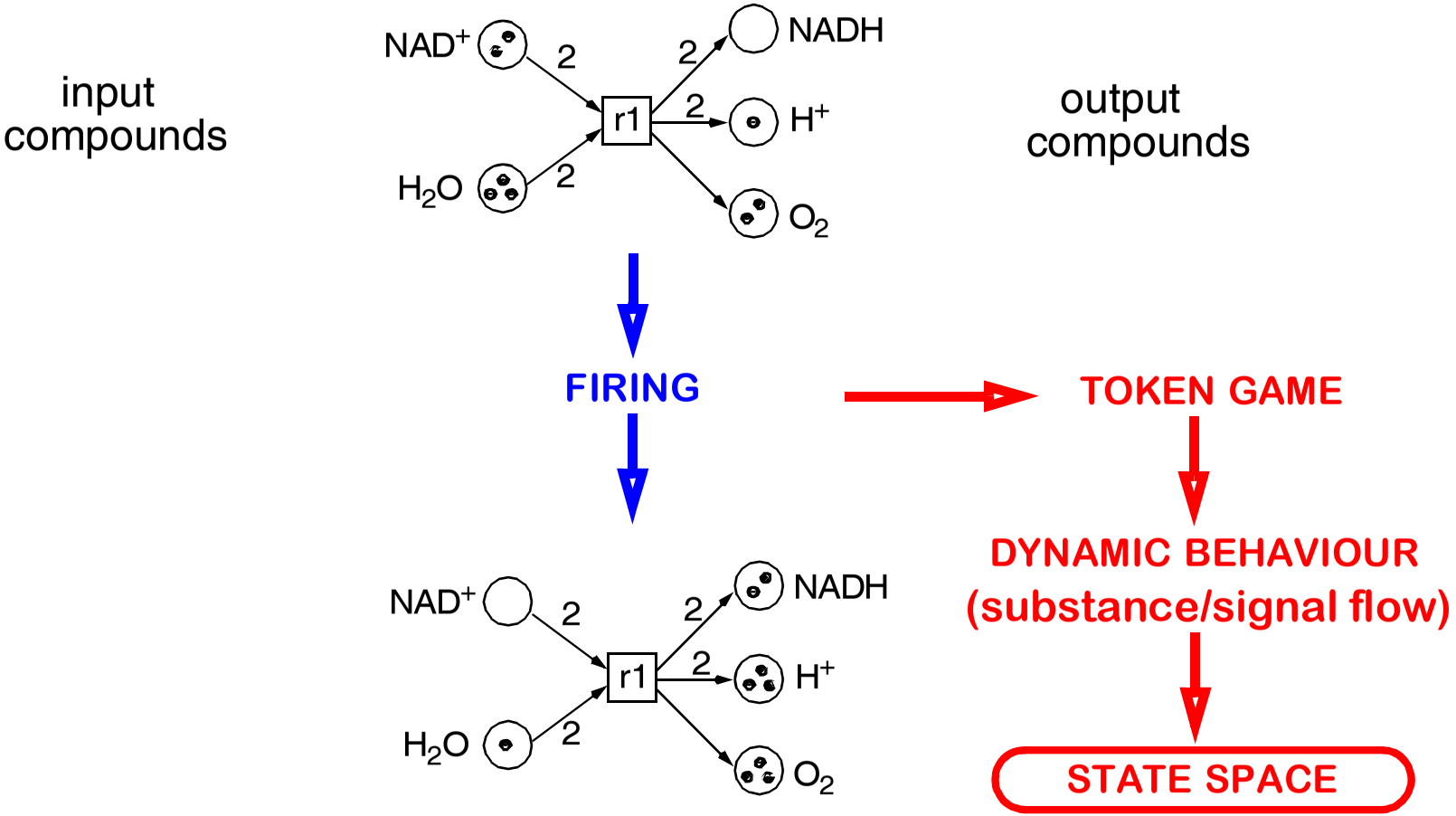


- local conditions -> places -> chemical compounds
- multiplicities -> arc weights -> stoichiometric relations
- condition's state -> token(s) -> available amount (e.g. mol)
- system state -> marking -> compounds distribution
- PN = (P, T, F, m_0), F: (P x T) U (T x P) -> N_0, m_0: P -> N_0

- **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*

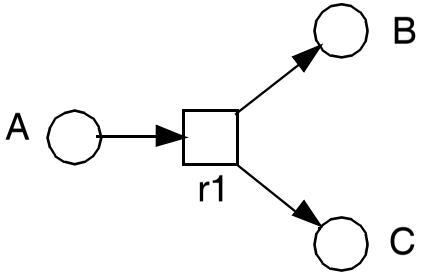
- atomic actions -> transitions -> chemical reactions

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

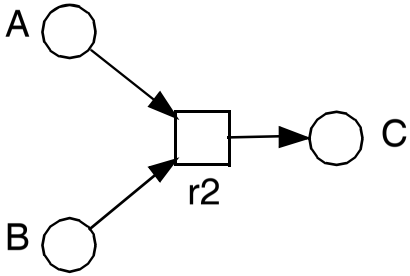


TYPICAL BASIC STRUCTURES I

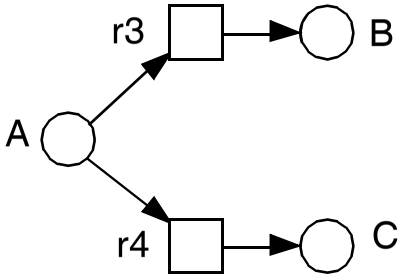
A --> B + C



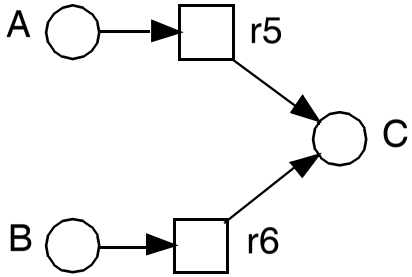
A + B --> C



A --> B,
A --> C

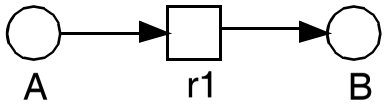


A --> C,
B --> C

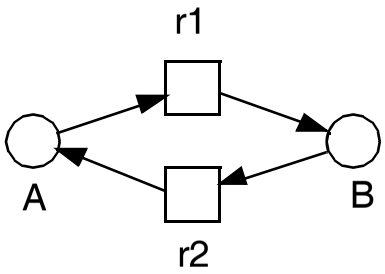


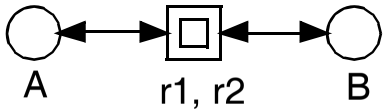
TYPICAL BASIC STRUCTURES II

A --> B

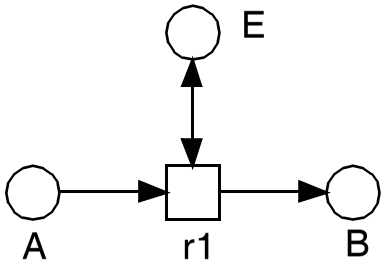


A <--> B

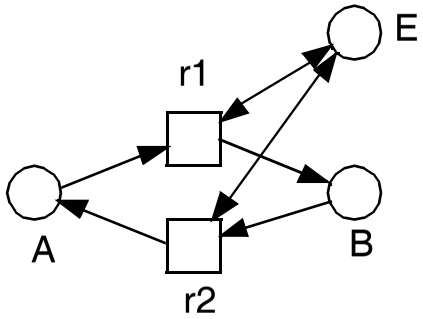


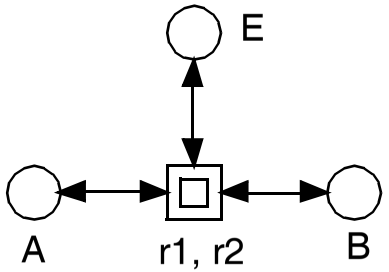


E
A --> B



E
A <--> B

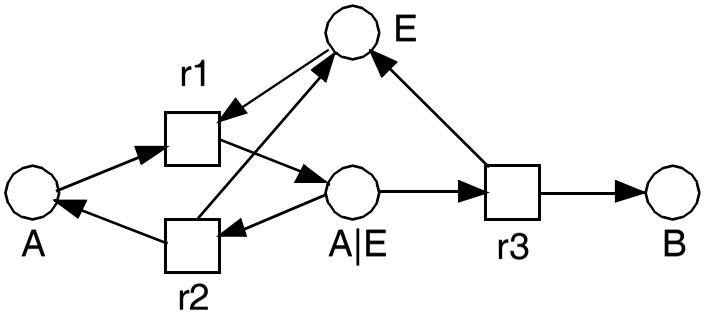


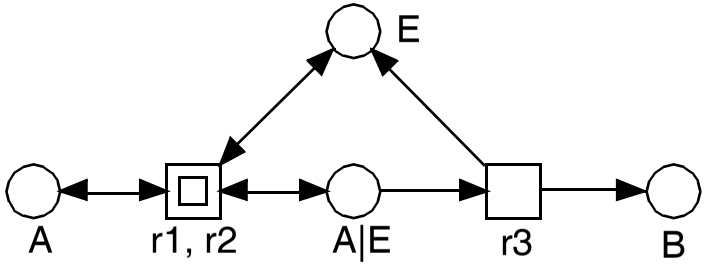


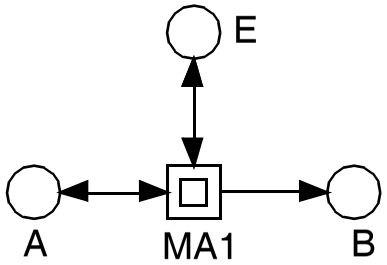
TYPICAL BASIC STRUCTURES III

A <E--> A|E --> B

enzymatic reaction,
mass-action approach 1

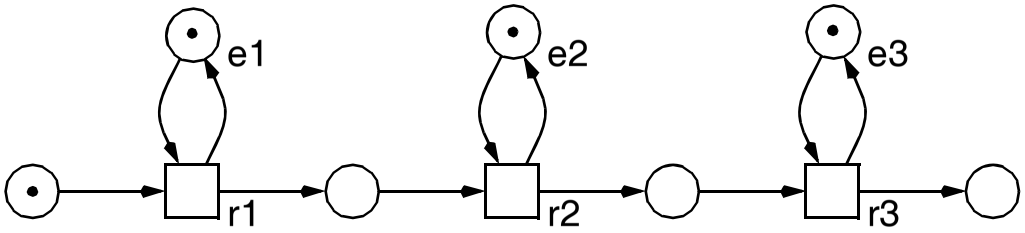




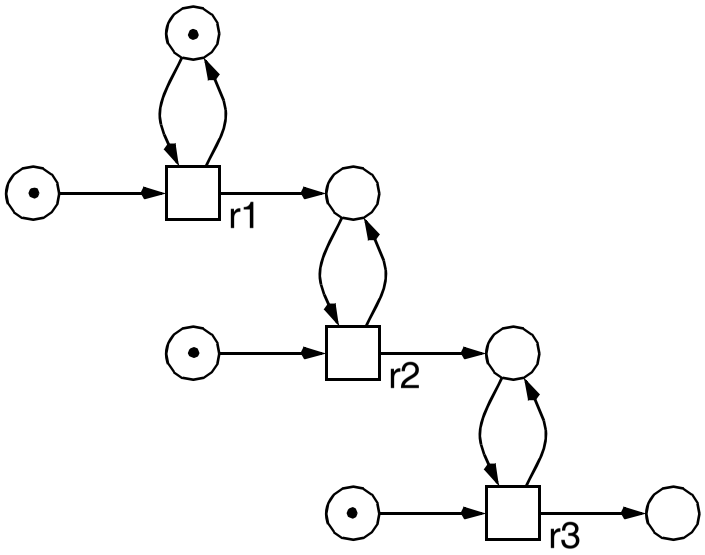


TYPICAL BASIC STRUCTURES IV

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



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



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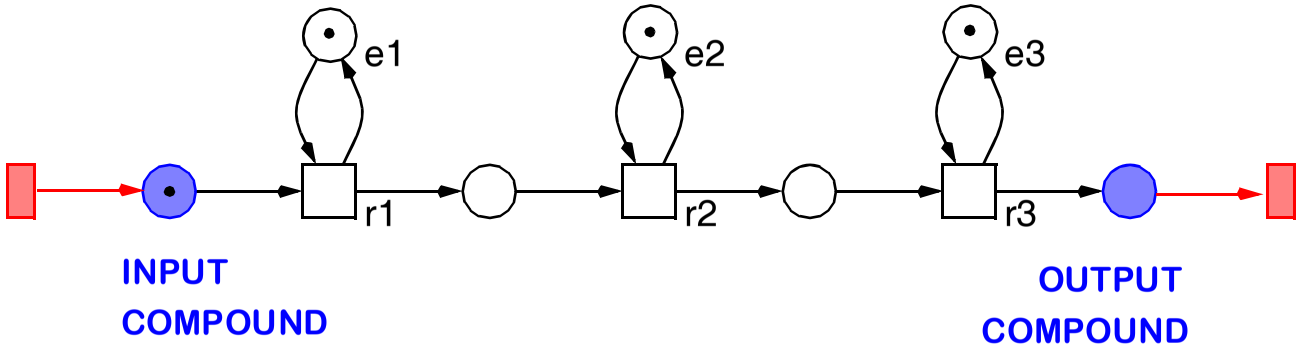

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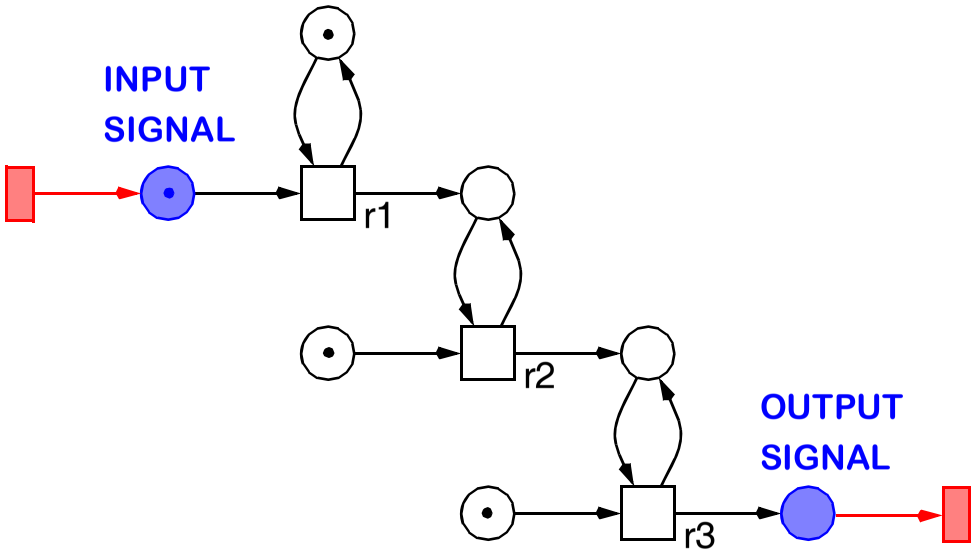

-> OPEN / CLOSED SYSTEMS

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

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

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

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

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*

BIO PETRI NETS - SOME EXAMPLES

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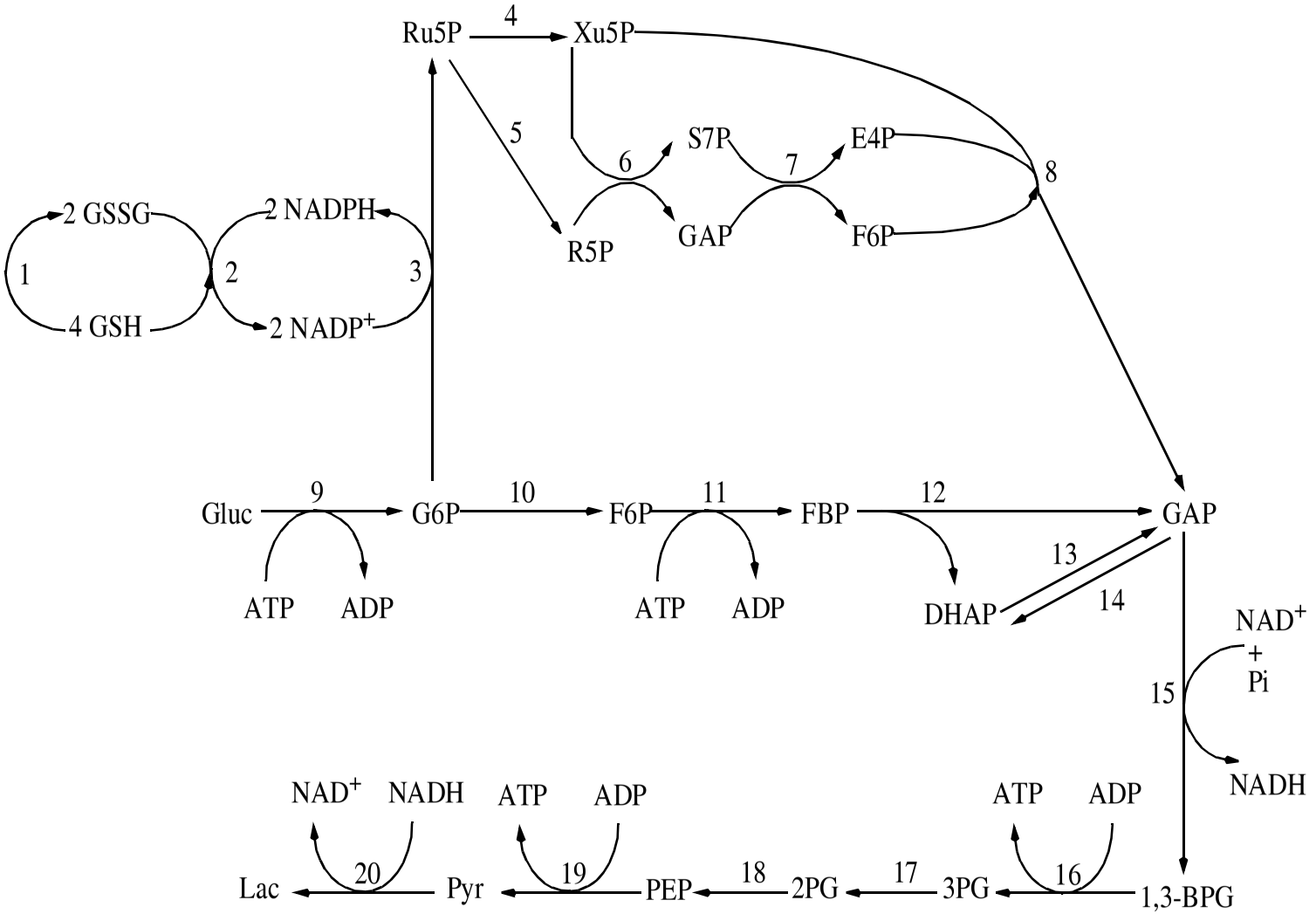
Ex1 - Glycolysis and Pentose Phosphate Pathway

[Reddy 1993]



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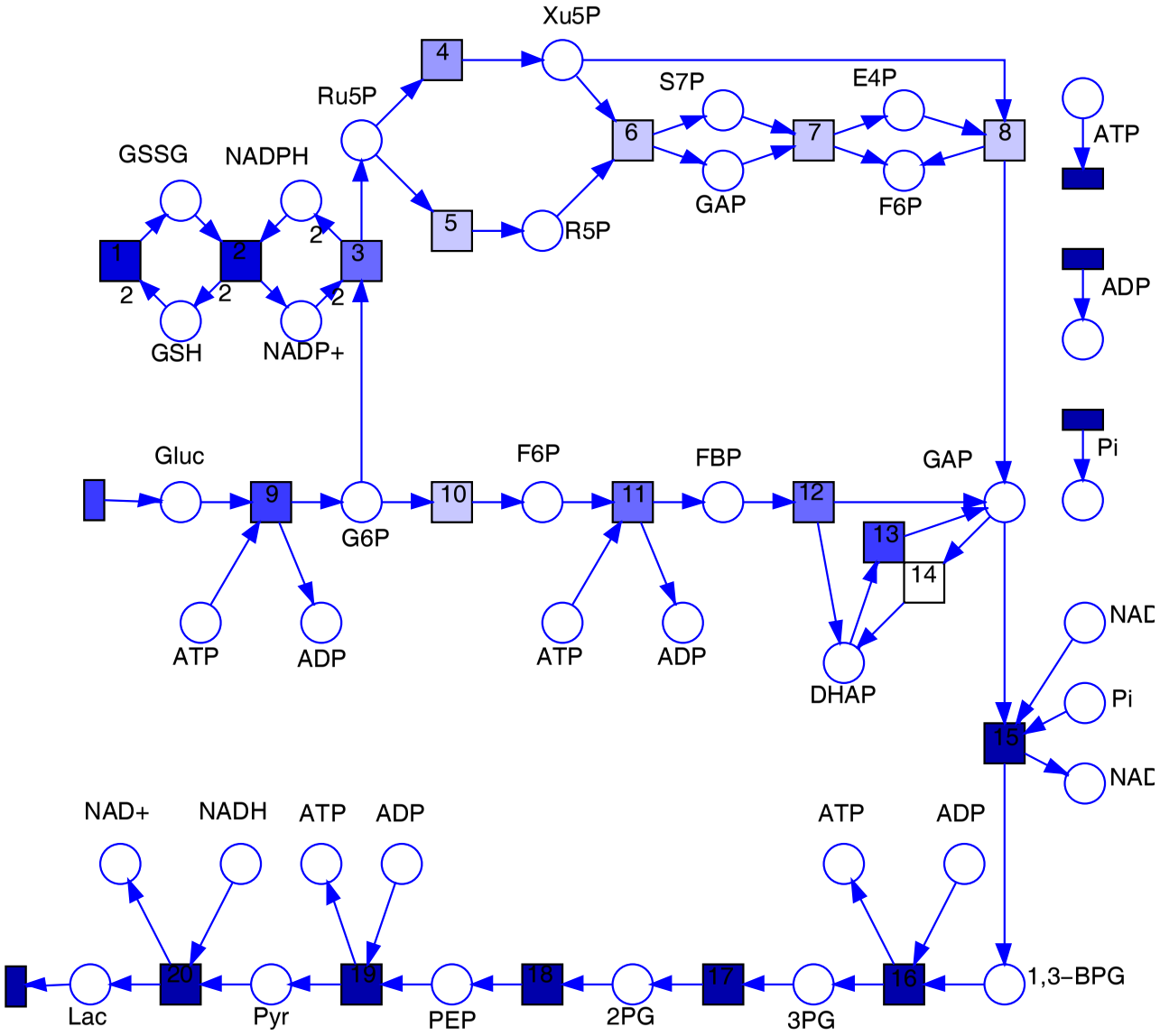
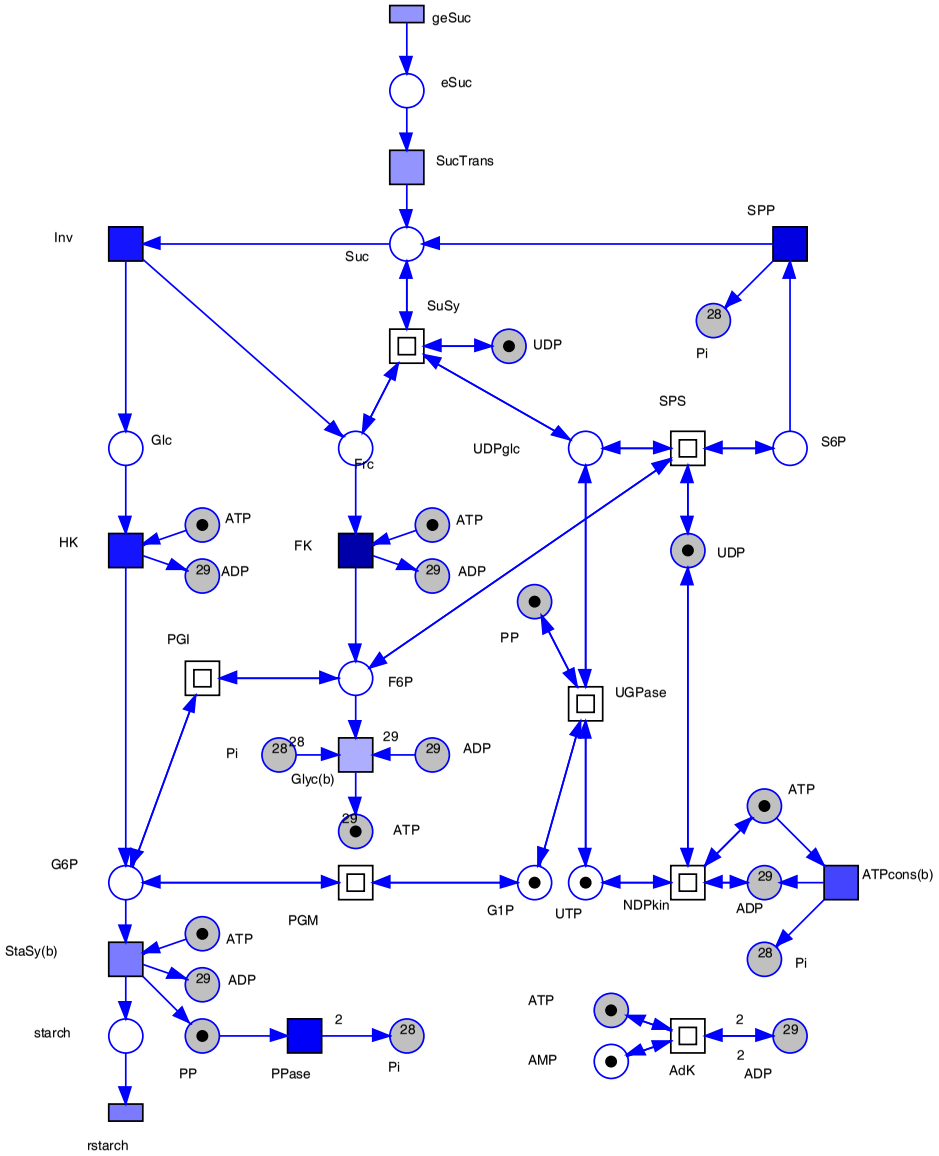
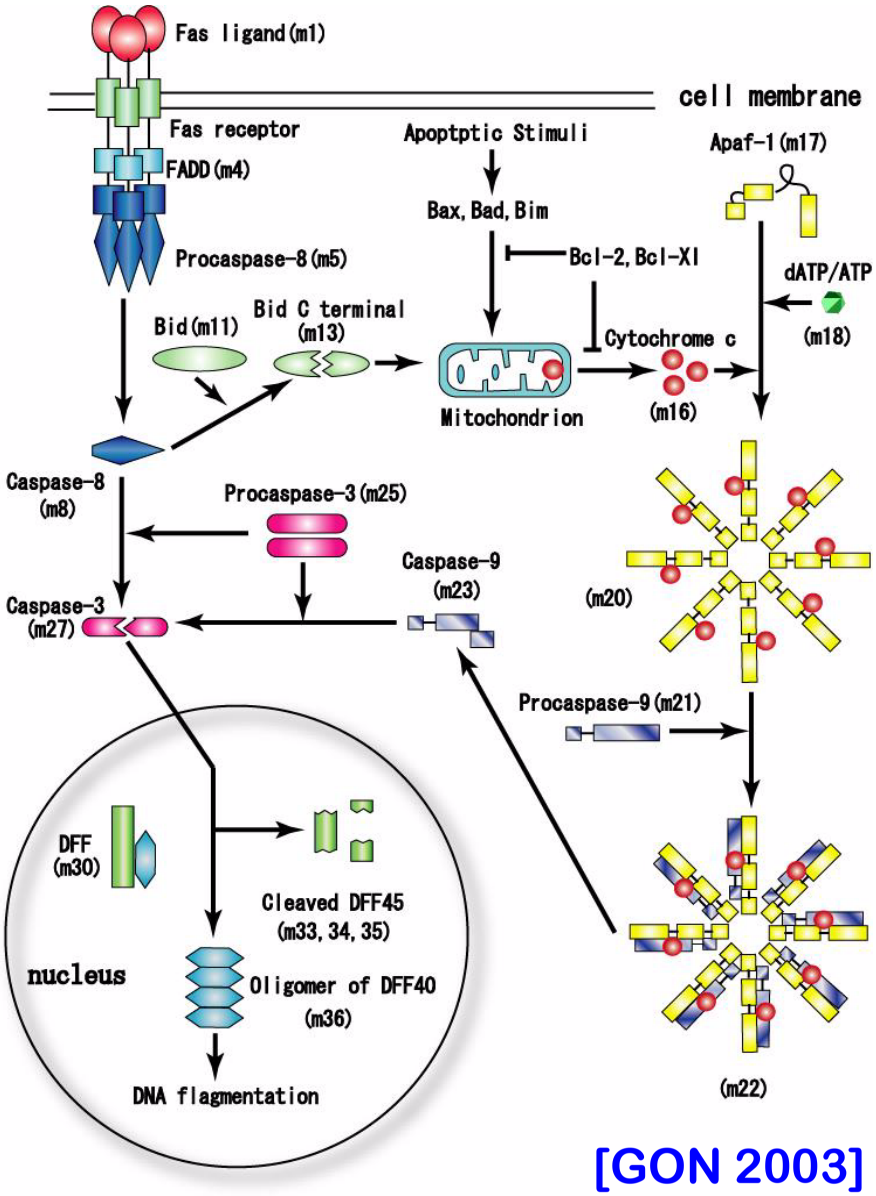


Ex2 - Carbon Metabolism in Potato Tuber

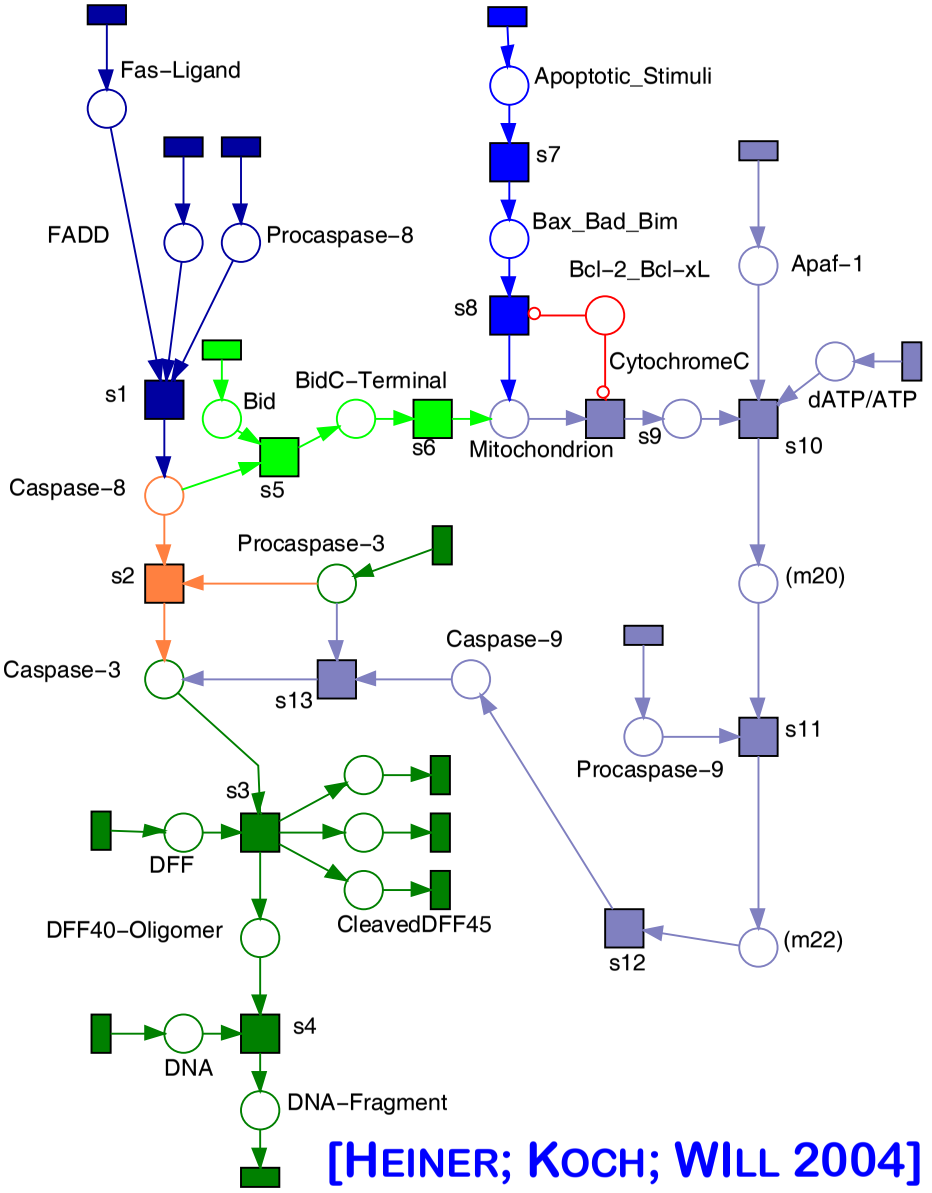
[KOCH; JUNKER; HEINER 2005]



EX3: APOPTOSIS IN MAMMALIAN CELLS

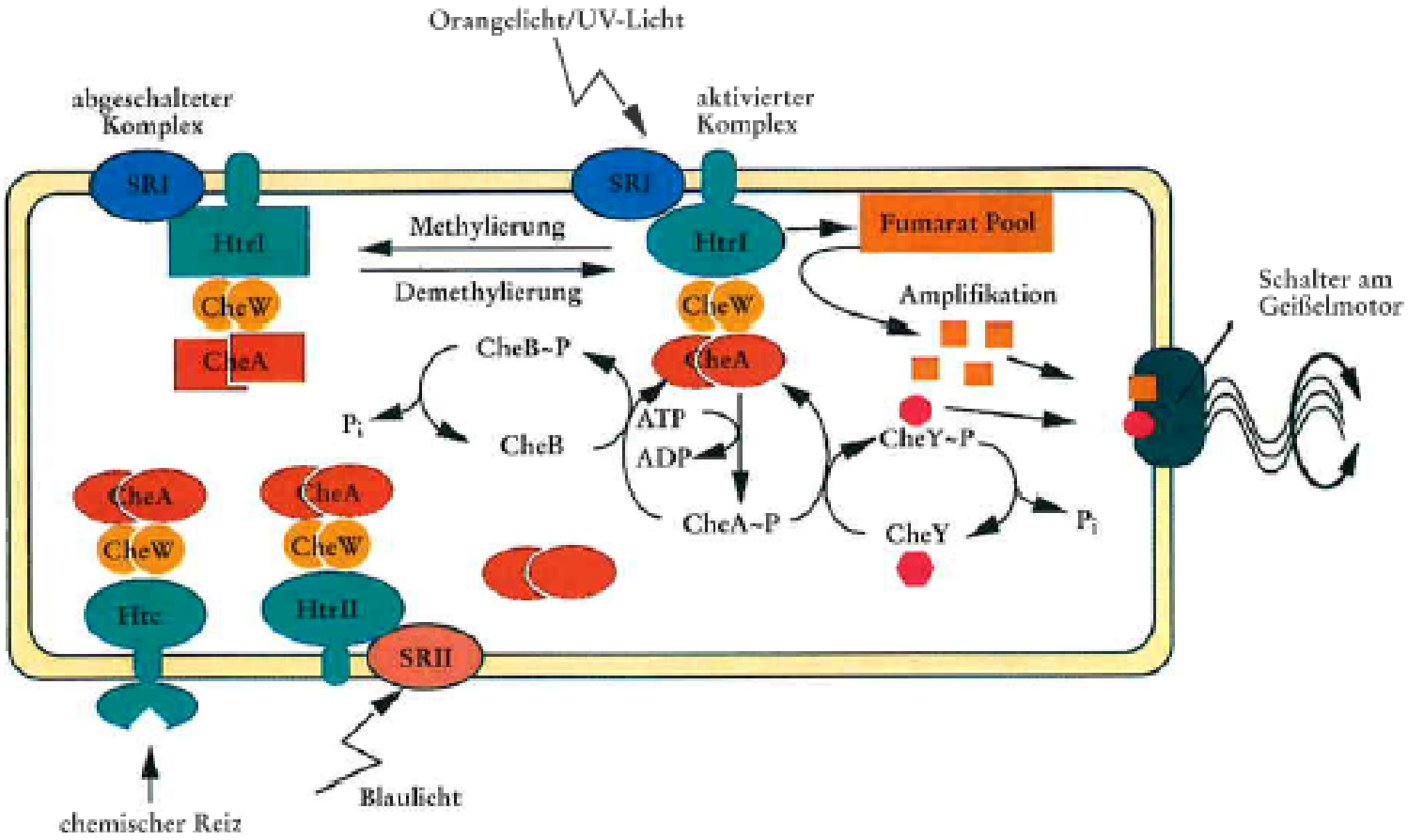


[GON 2003]



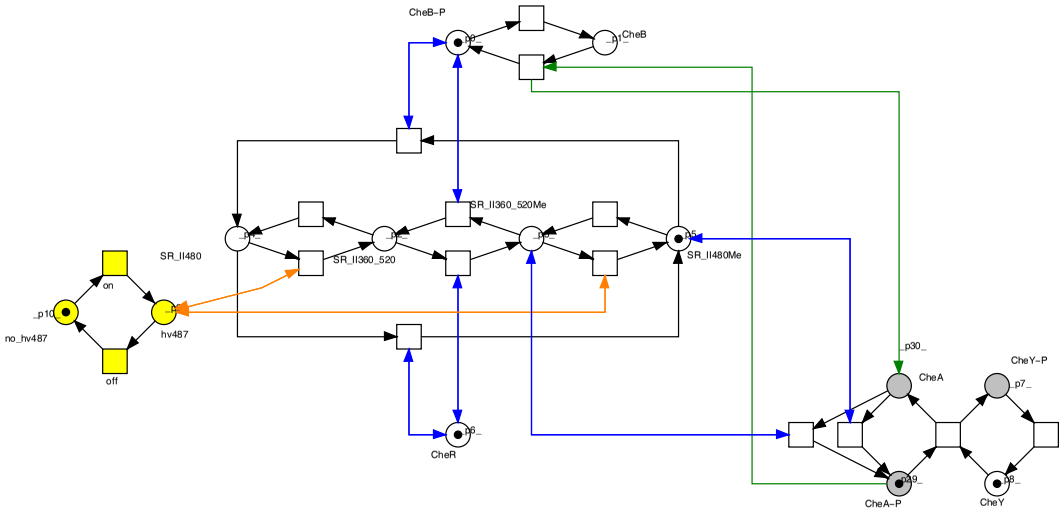
[HEINER; KOCH; WILL 2004]

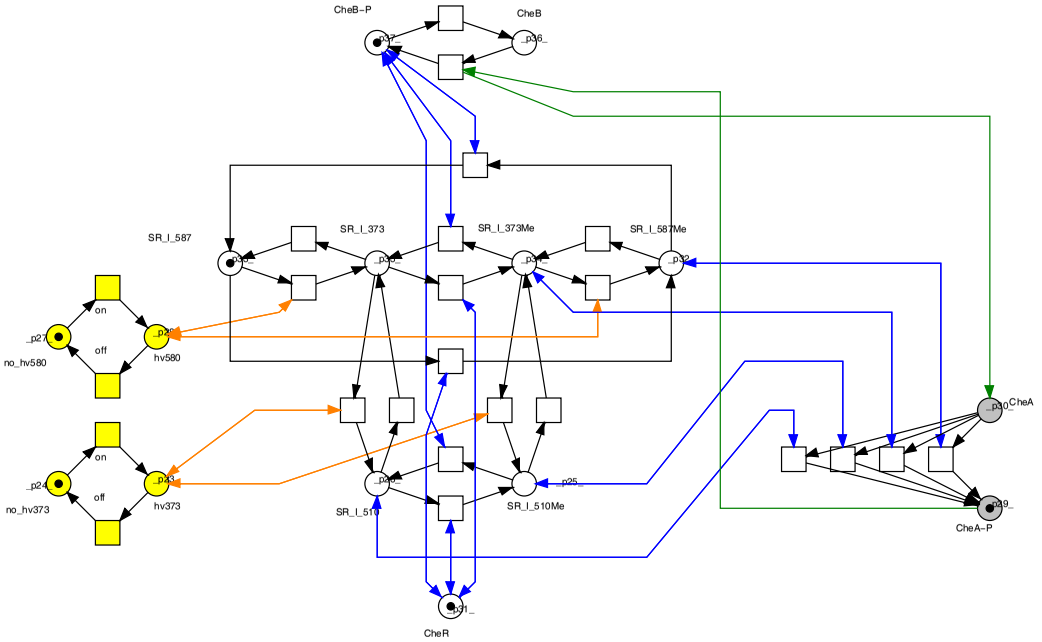
EX4 - SWITCH CYCLE HALOBACTERIUM SALINARUM

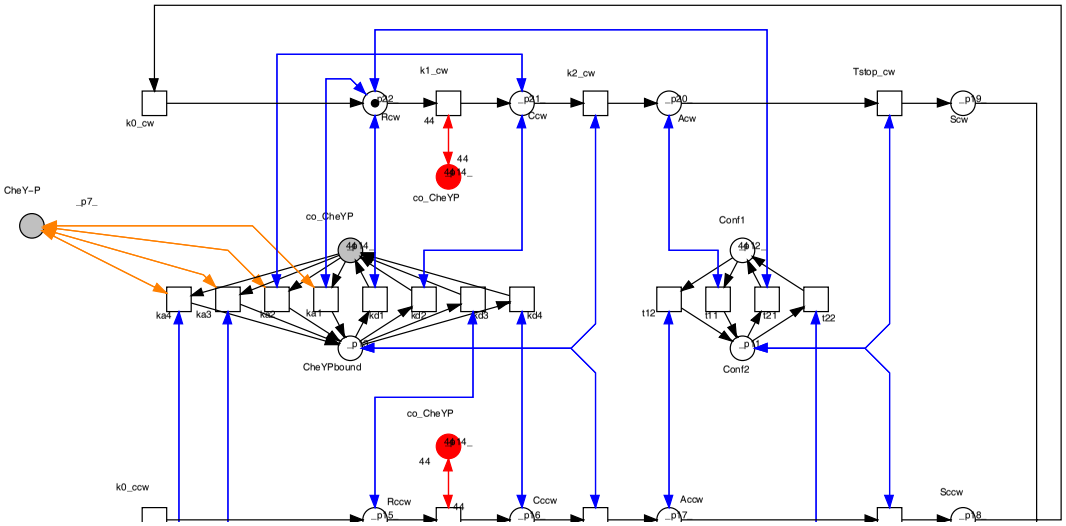


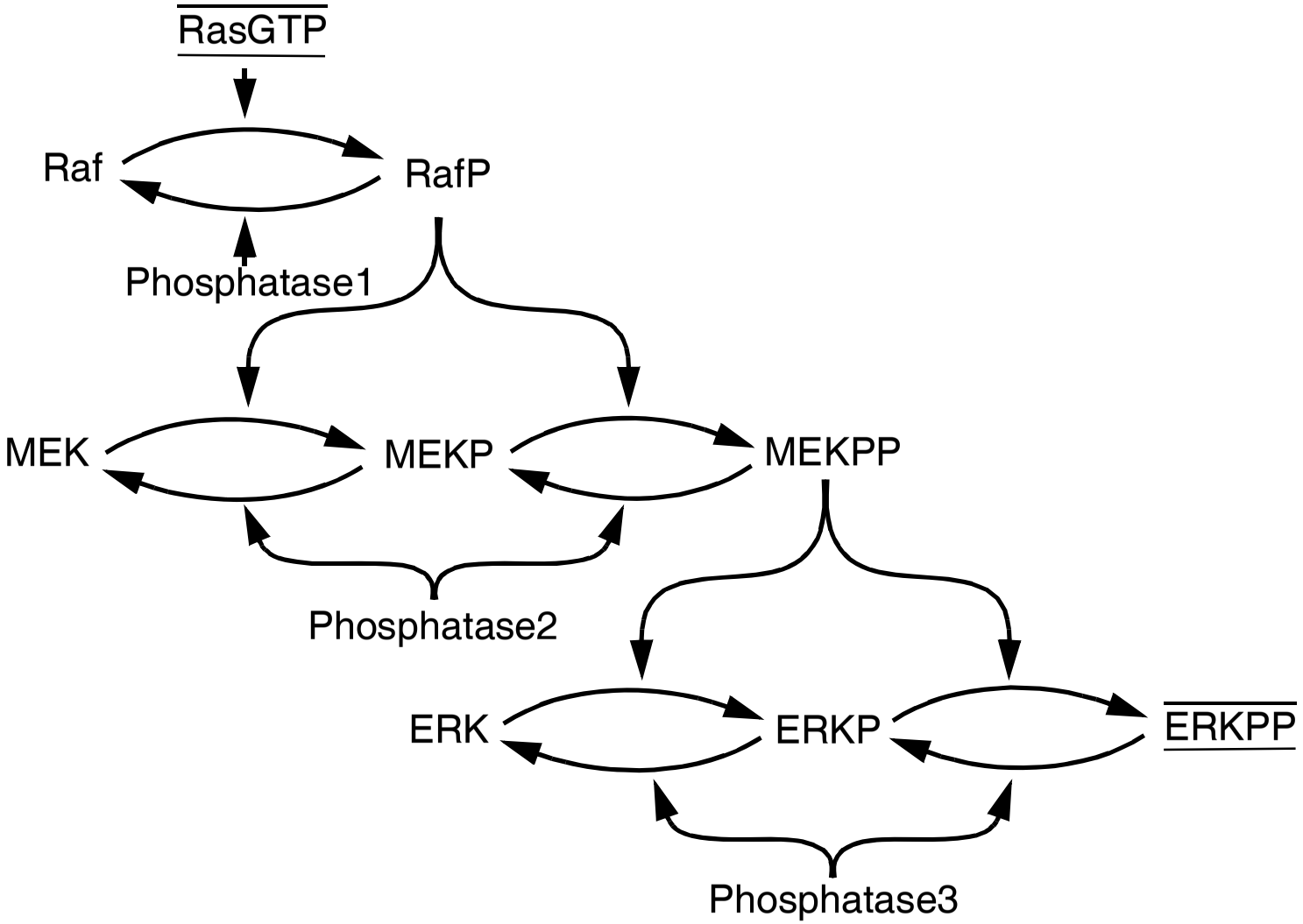
[Marwan; Oesterhelt 1999]

EX4 - SWITCH CYCLE HALOBACTERIUM SALINARUM

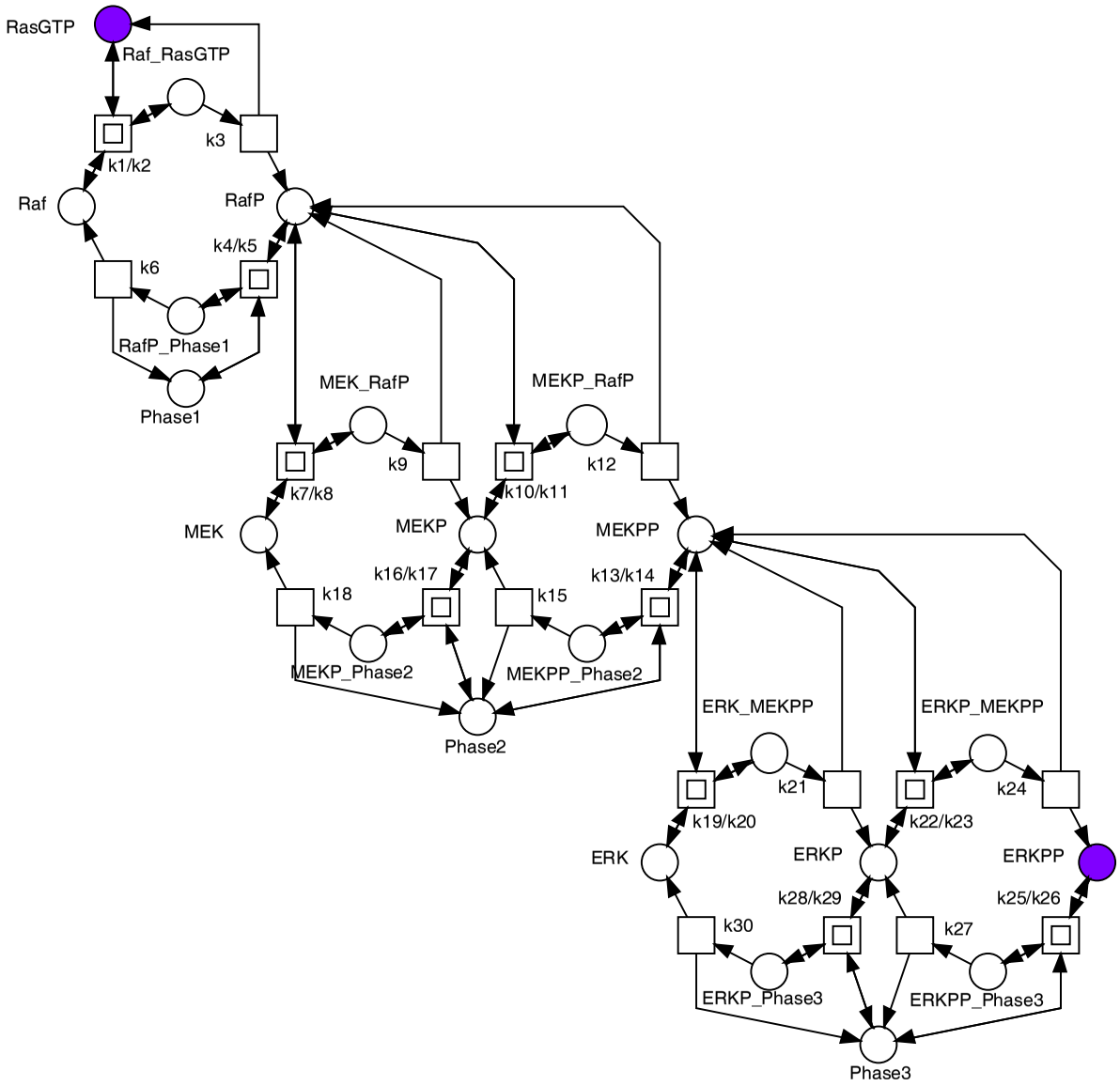







RasGTP
Raf
RafP
Phosphatase1
MEK
MEKP
MEKPP
Phosphatase2
ERK
ERKP
ERKPP
Phosphatase3

EX5 - SIGNALLING CASCADE



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 behaviourally invariant subnet structures ?**
  - -> *token conservation* -> *P - INVARIANTS*
  - -> *token distribution reproduction* -> *T - INVARIANTS*
- **. . . and many more -> temporal logics (CTL, LTL)**

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,*
i.e. boundedness, liveness, reversibility

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

=> expressed in temporal logics (CTL / LTL),
as very flexible & powerful query language

- **validation criterion 1**
  - -> *all expected structural properties hold*
  - -> *all expected general behavioural properties hold*
- **validation criterion 2**
  - -> *initial marking construction*
  - -> *CPI (if closed model)*
  - -> *no minimal P-invariant without biological interpretation*
- **validation criterion 3**
  - -> *CTI*
  - -> *no minimal T-invariant without biological interpretation*
  - -> *no known biological behaviour without corresponding T-invariant*
- **validation criterion 4**
  - -> *all expected special behavioural properties hold*
  - -> *temporal-logic properties -> TRUE*

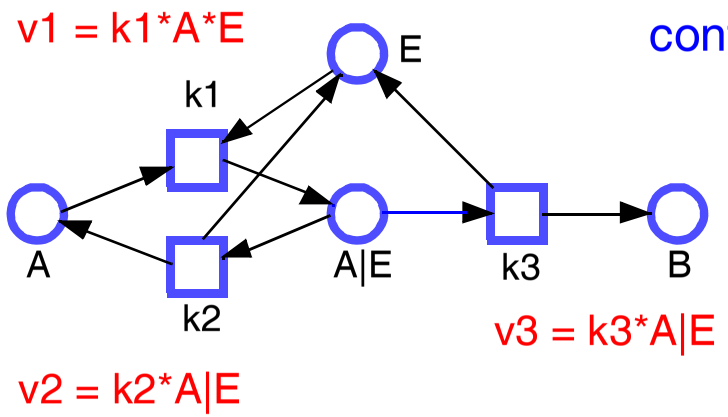
NOW WE ARE READY FOR SOPHISTICATED QUANTITATIVE ANALYSES !

QUANTITATIVE ANALYSIS

- **quantitative model = qualitative model + quantitative parameters**
  -> known or estimated quantitative parameters

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

- **continuous Petri nets = ODEs**



continuous nodes !

dA / dt = -v1 + v2

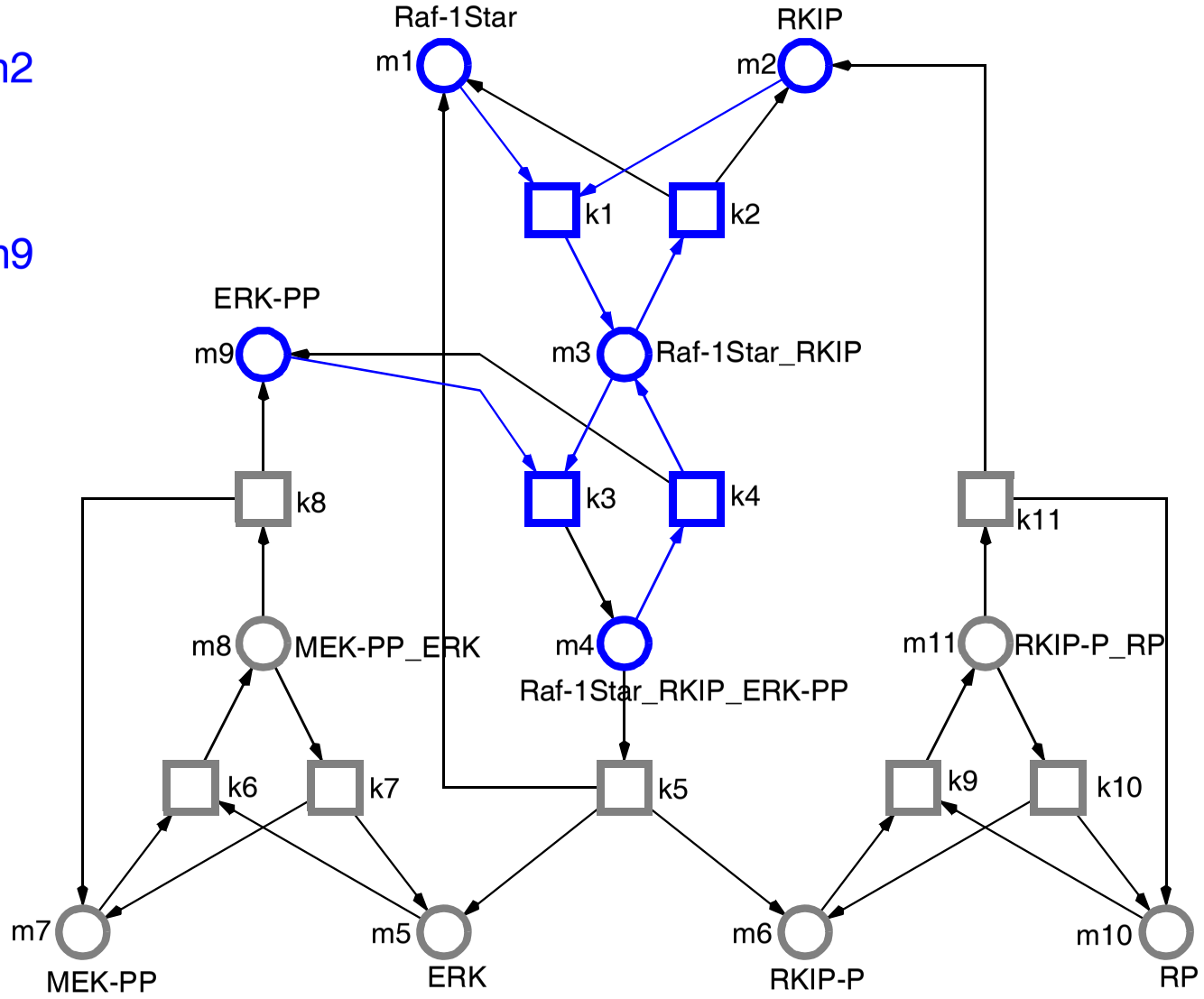
dA|E / dt = v1 - v2 - v3

dB / dt = v3

dE / dt = -v1 + v2 + v3

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 !