MODELLING OF BIOCHEMICAL NETWORKS WITH TIME PETRI NETS

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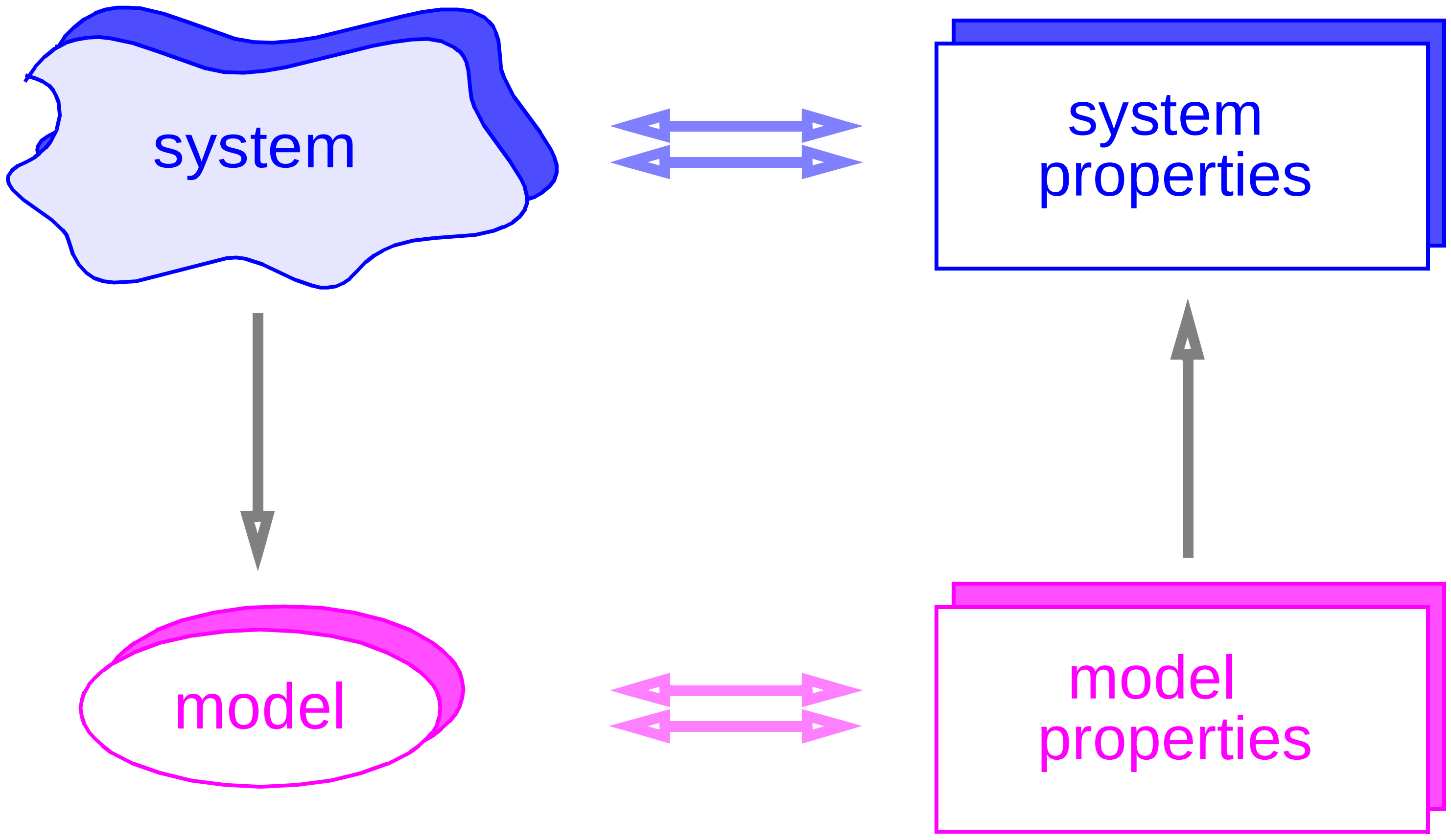
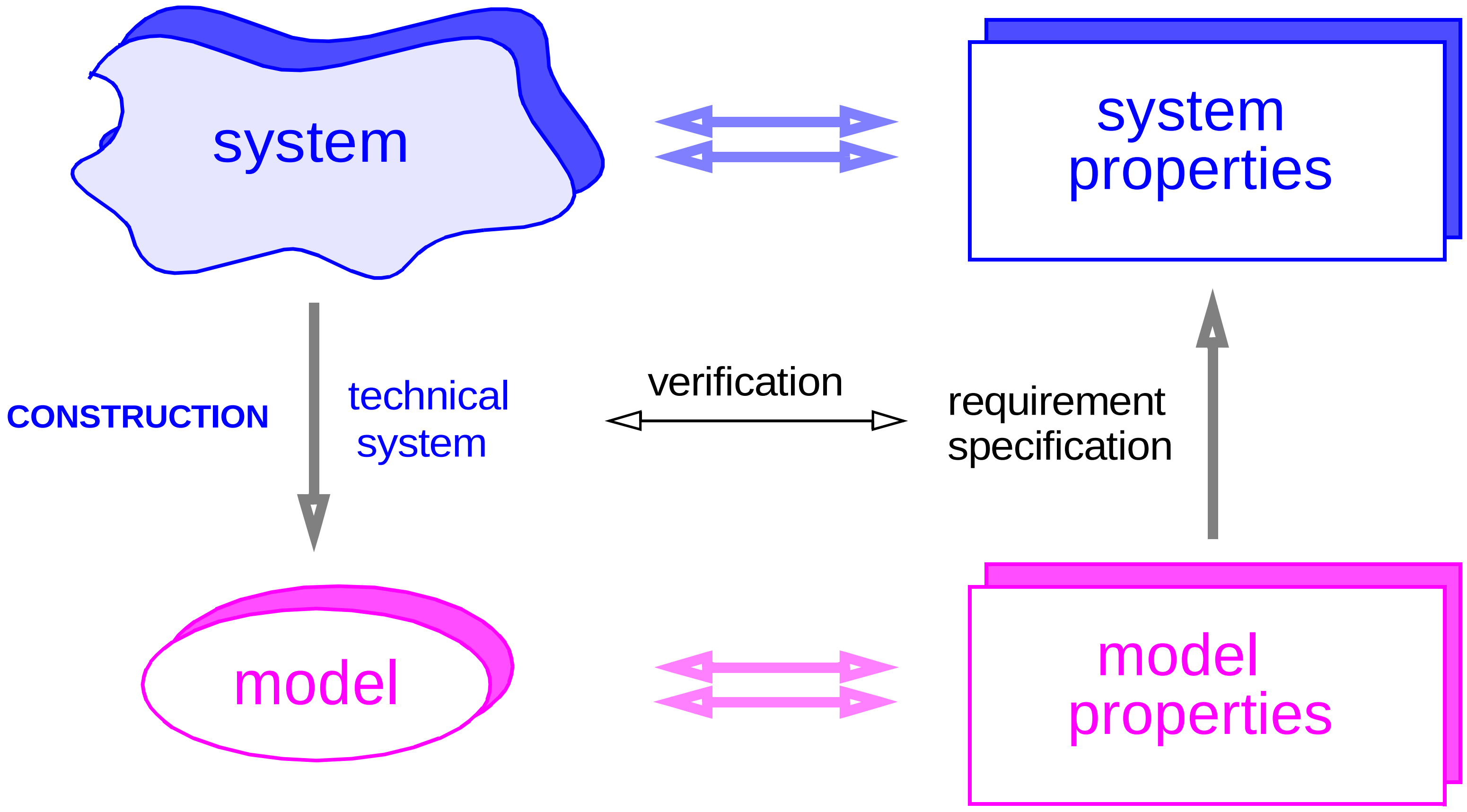
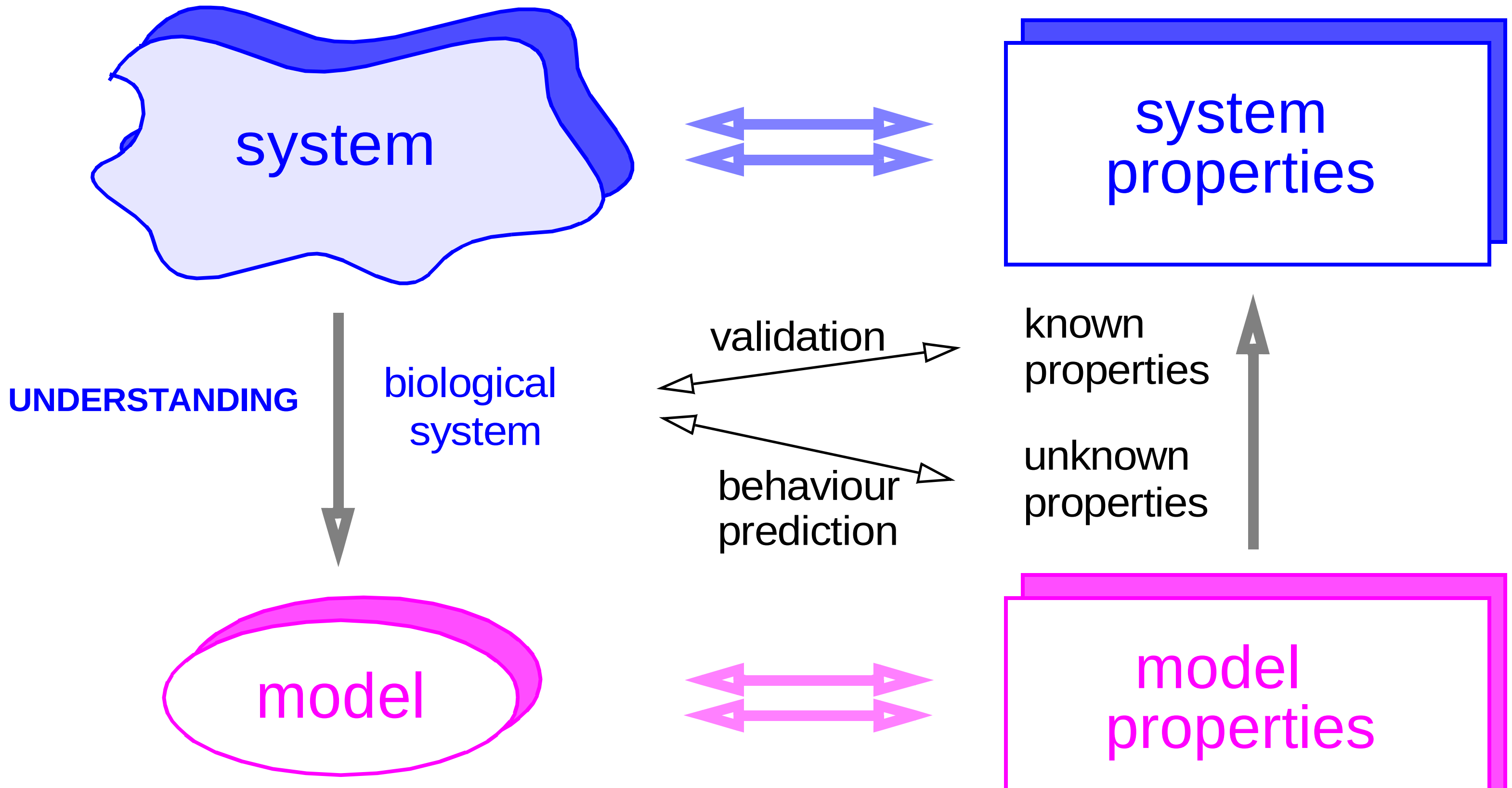
Department of CS

MODEL- BASED SYSTEM ANALYSIS




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

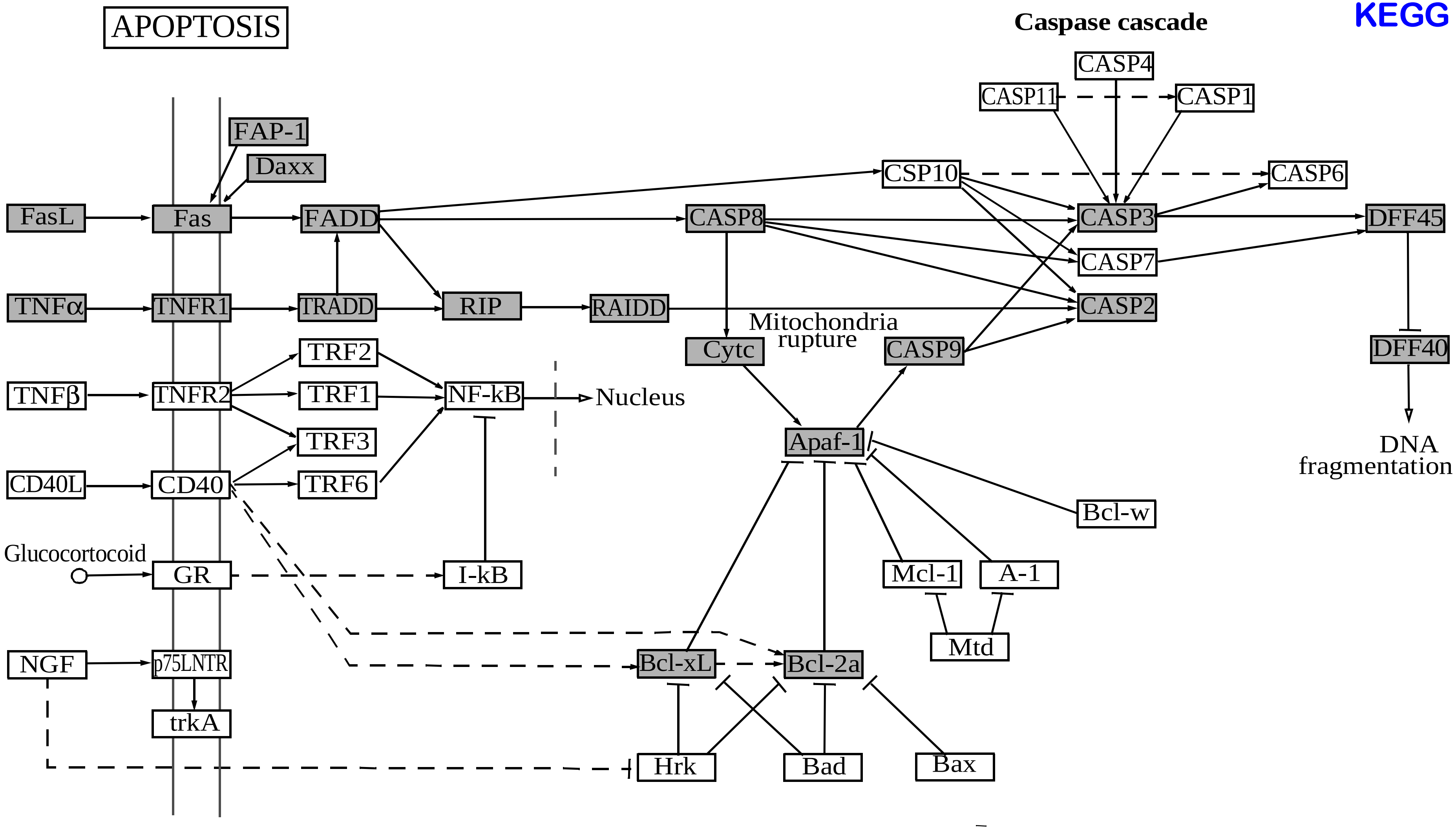
MODEL- BASED SYSTEM ANALYSIS



WHAT KIND OF MODEL SHOULD BE USED ?

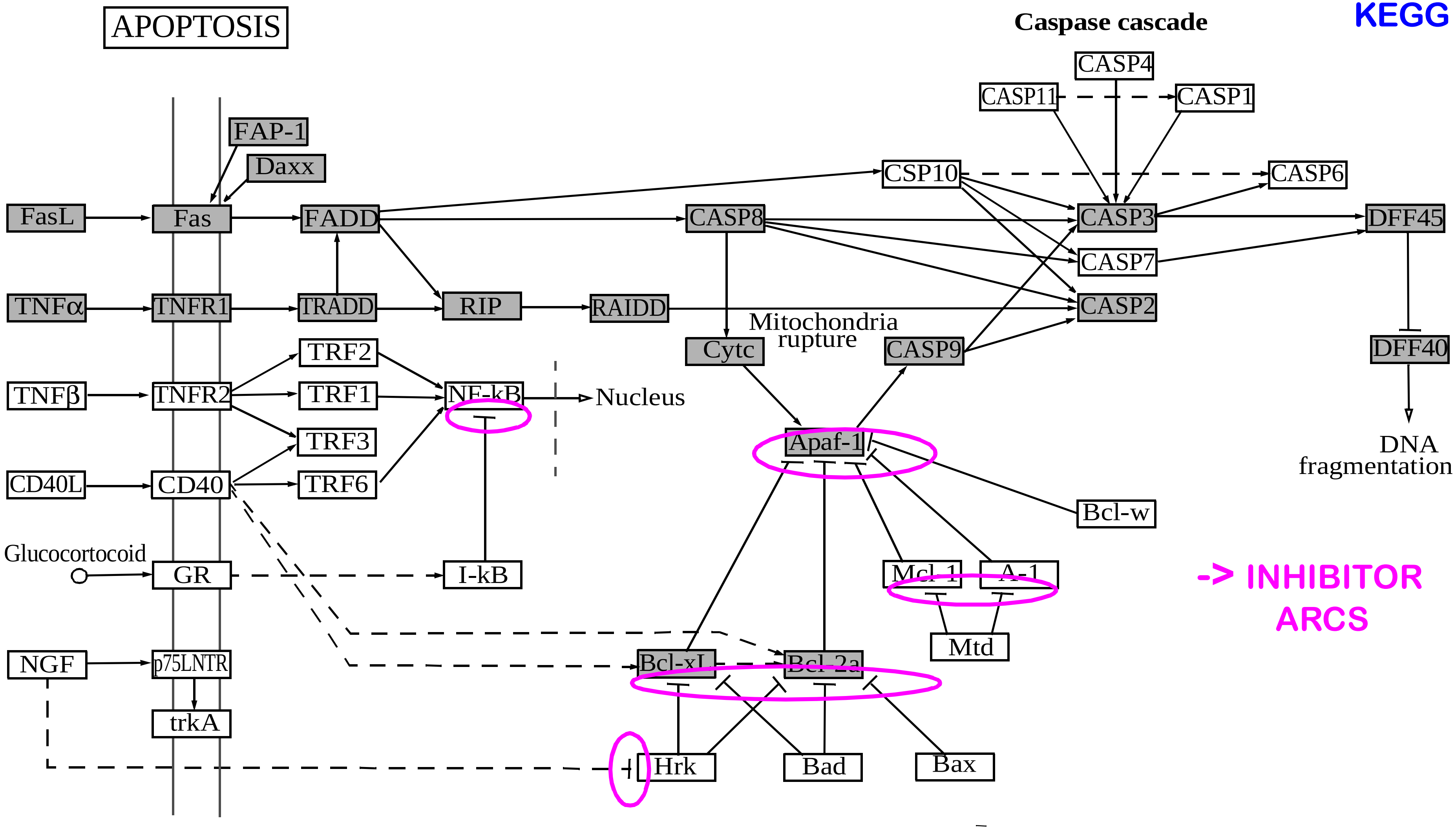
NETWORK REPRESENTATIONS, EX1

KEGG



NETWORK REPRESENTATIONS, EX1

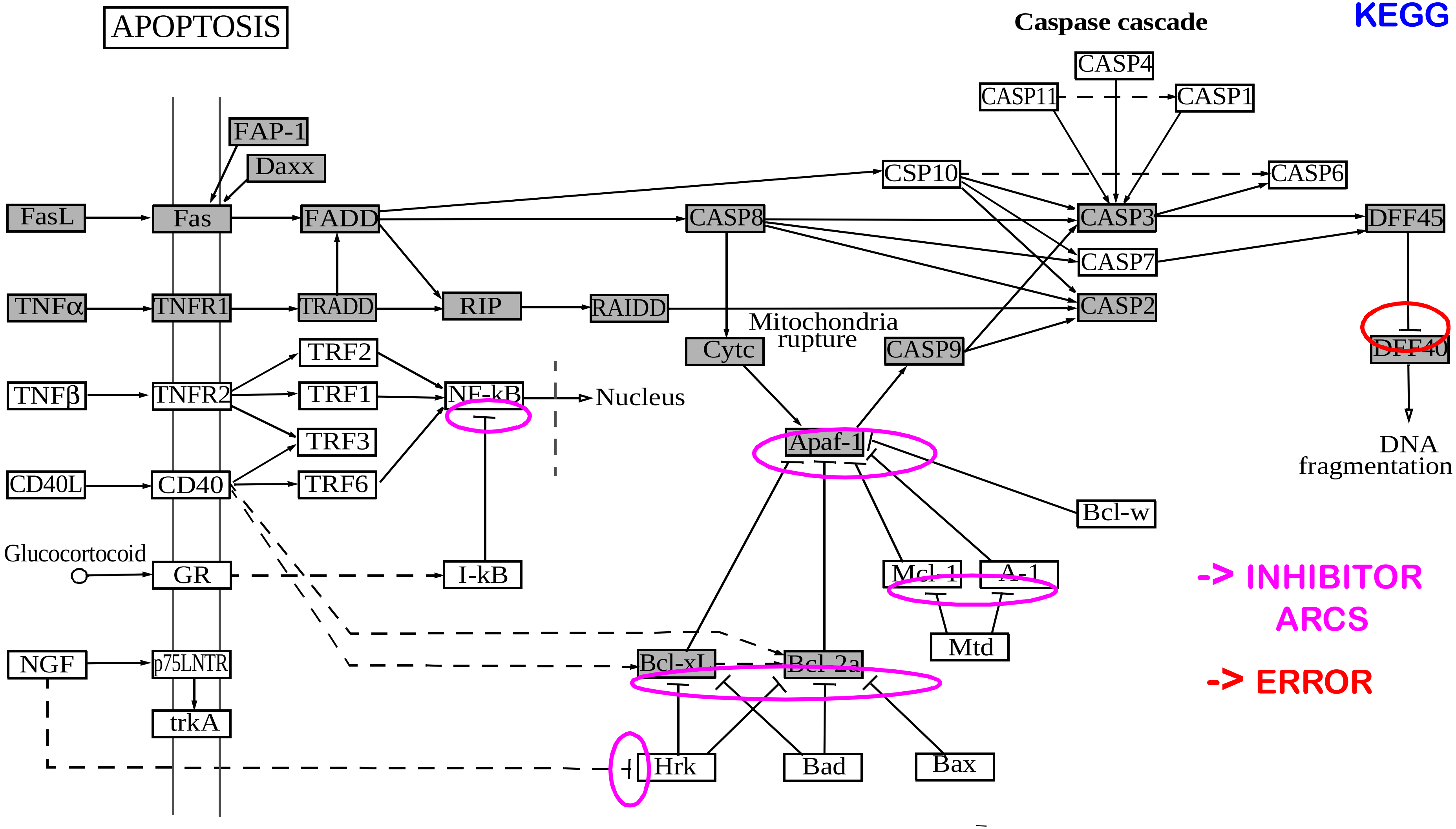
KEGG



-> INHIBITOR ARCS

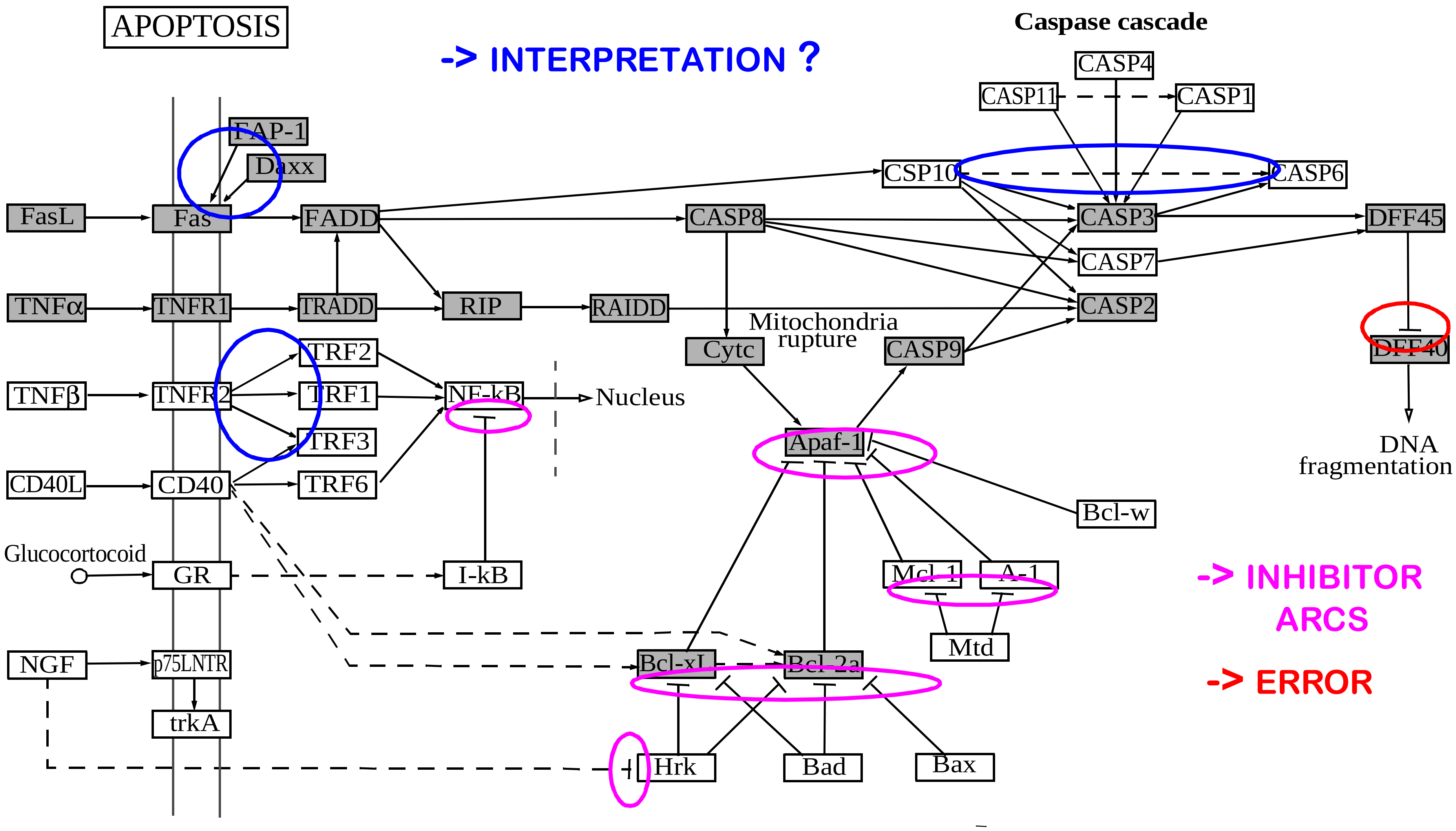
Network Representations, Ex1

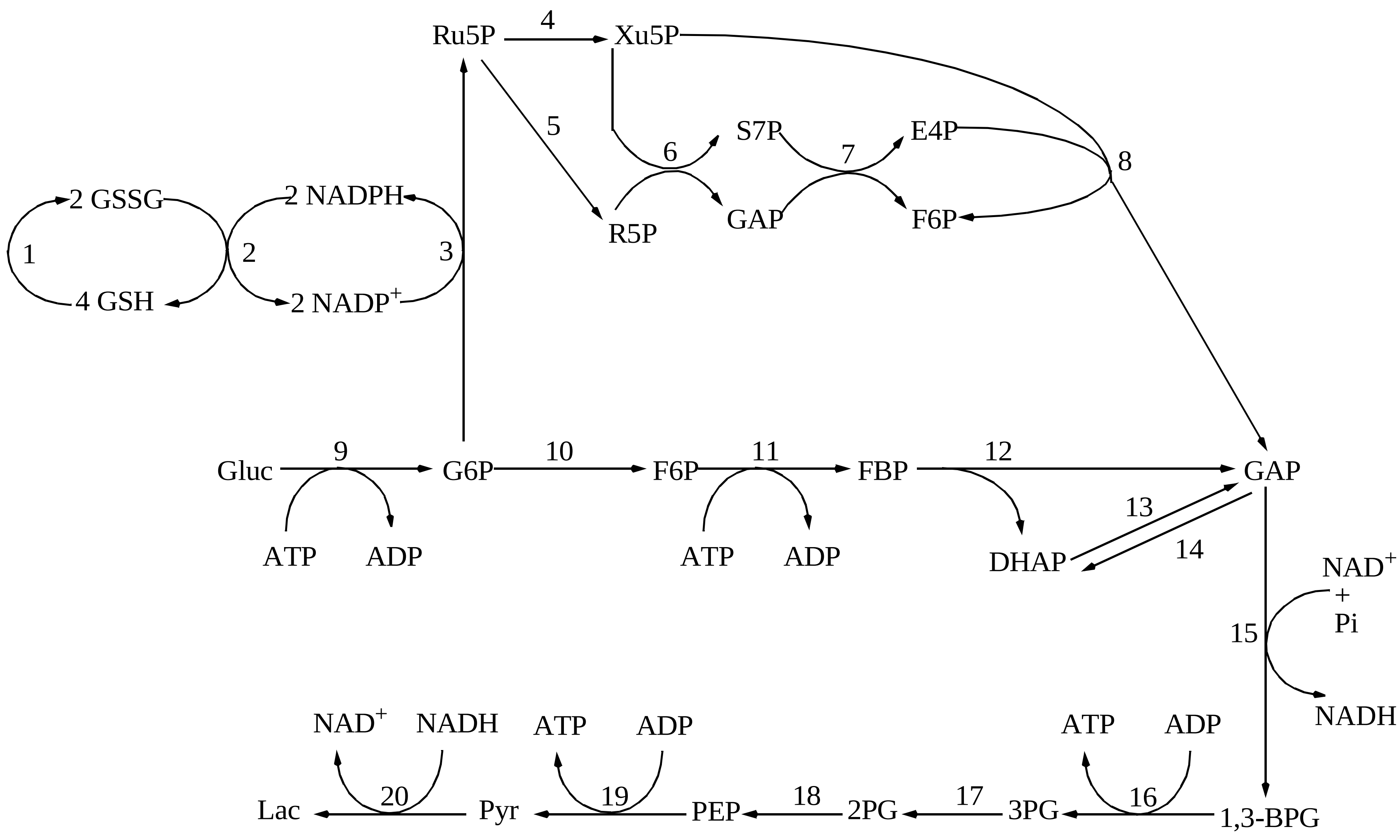
KEGG



-> INHIBITOR ARCS

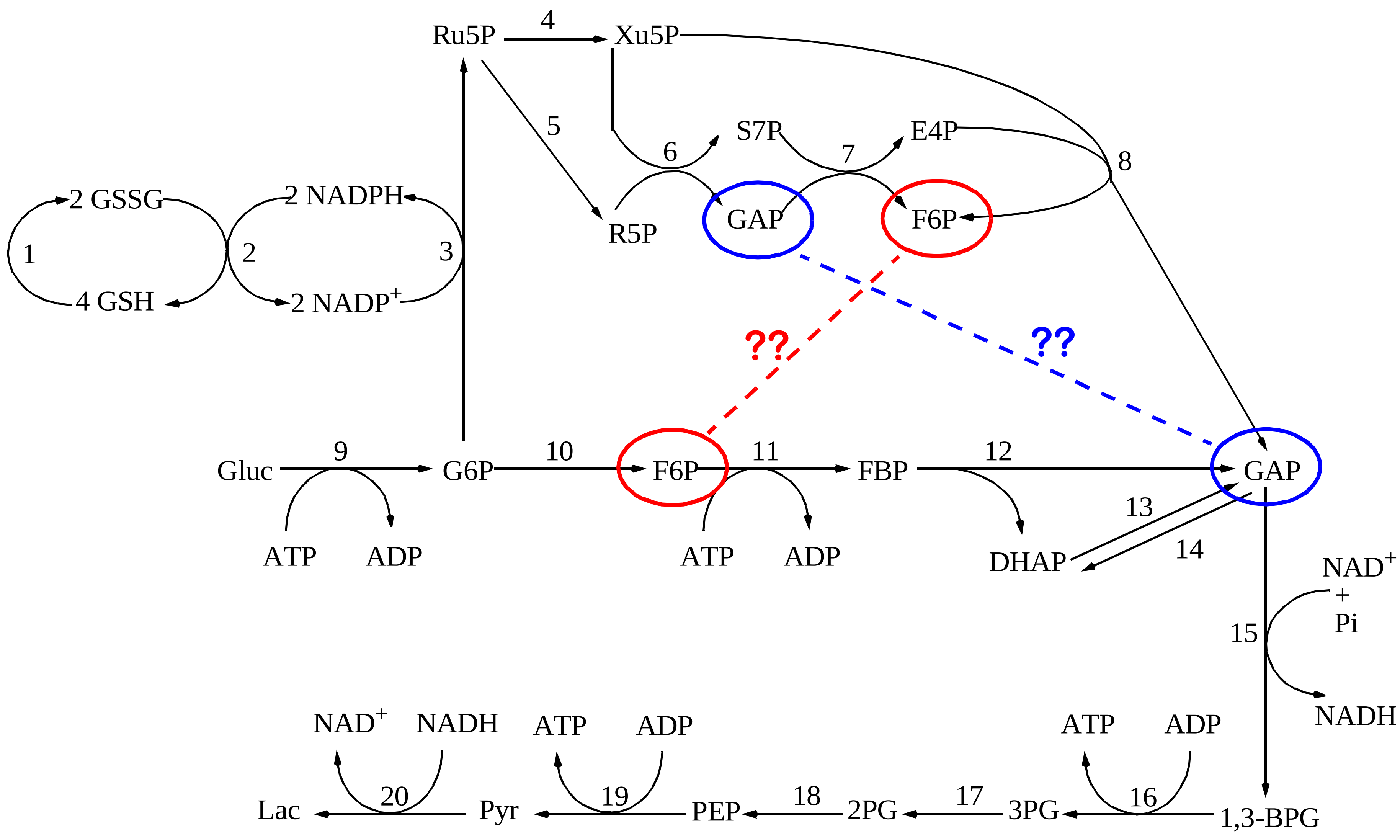
-> ERROR


APOPTOSIS
-> INTERPRETATION ?
Caspase cascade
CASP4
CASP11
CASP1
CSP10
CASP6
FAP-1
Daxx
FasL
Fas
FADD
CASP8
CASP3
DFF45
CASP7
TNFα
TNFR1
TRADD
RIP
RAIDD
CASP2
Mitochondria
rupture
Cytc
CASP9
DFF40
TRF2
TNFβ
TNFR2
TRF1
NF-kB
Nucleus
TRF3
Apaf-1
DNA
fragmentation
CD40L
CD40
TRF6
Bcl-w
Glucocortocoid
GR
I-kB
Mcl-1
A-1
-> INHIBITOR
ARCS
Mtd
NGF
p75LNTR
Bcl-xL
Bcl-2a
-> ERROR
trkA
Hrk
Bad
Bax

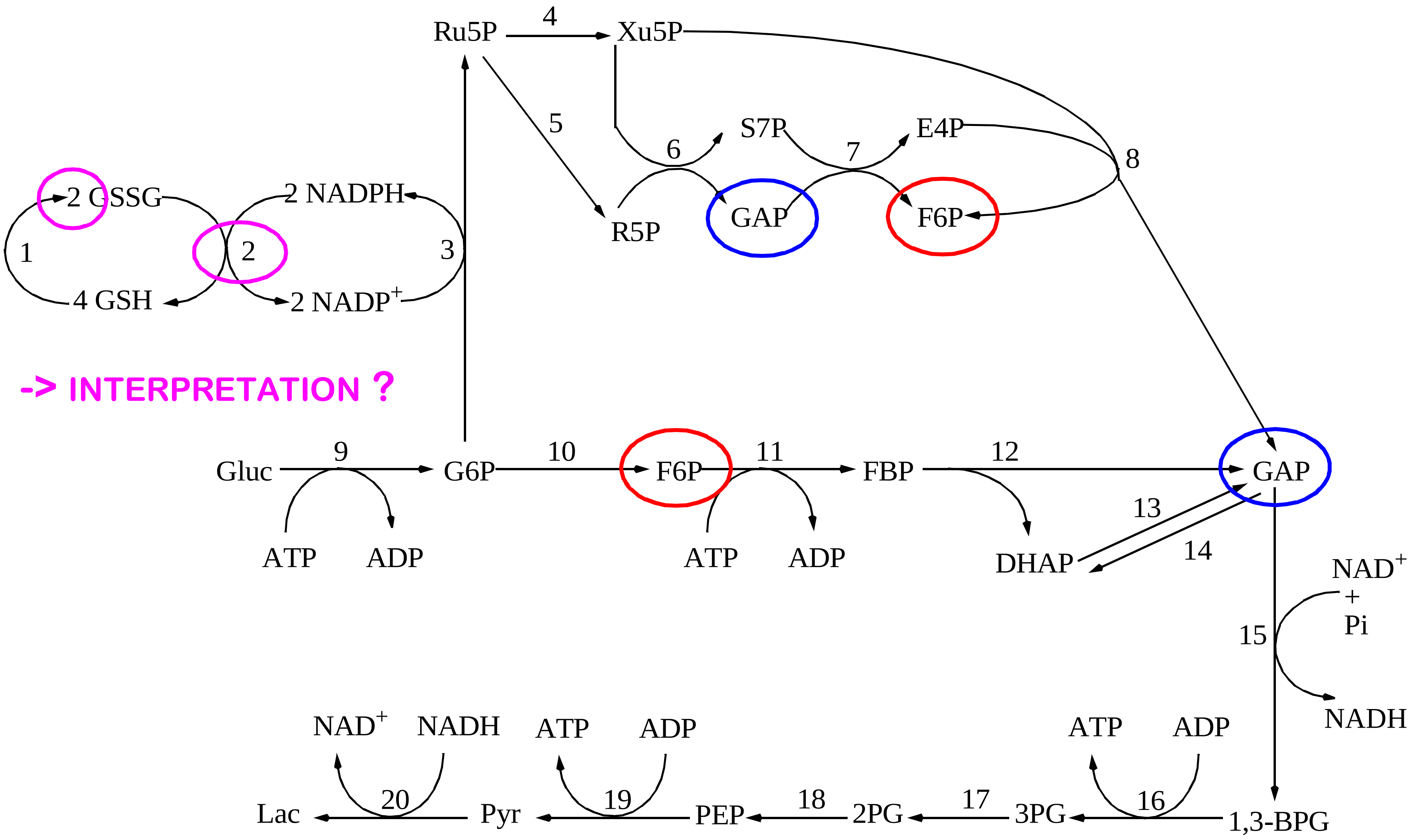


Ru5P
4
Xu5P
5
6
S7P
7
E4P
8
R5P
GAP
F6P
2 GSSG
2 NADPH
1
2
3
4 GSH
2 NADP+
Gluc
9
G6P
10
F6P
11
FBP
12
GAP
13
14
ATP
ADP
ATP
ADP
DHAP
NAD+
+
Pi
15
NADH
NAD+
NADH
ATP
ADP
ATP
ADP
Lac
20
Pyr
19
PEP
18
2PG
17
3PG
16
1,3-BPG

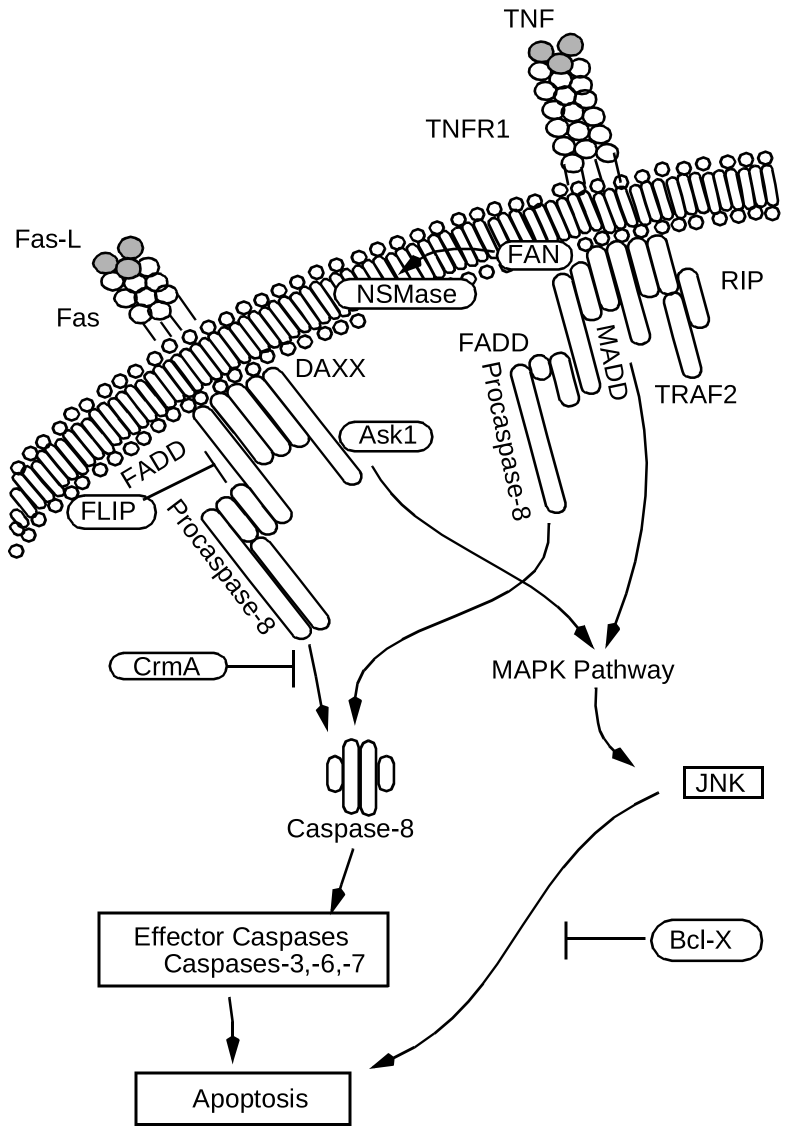
NETWORK REPRESENTATIONS, EX2



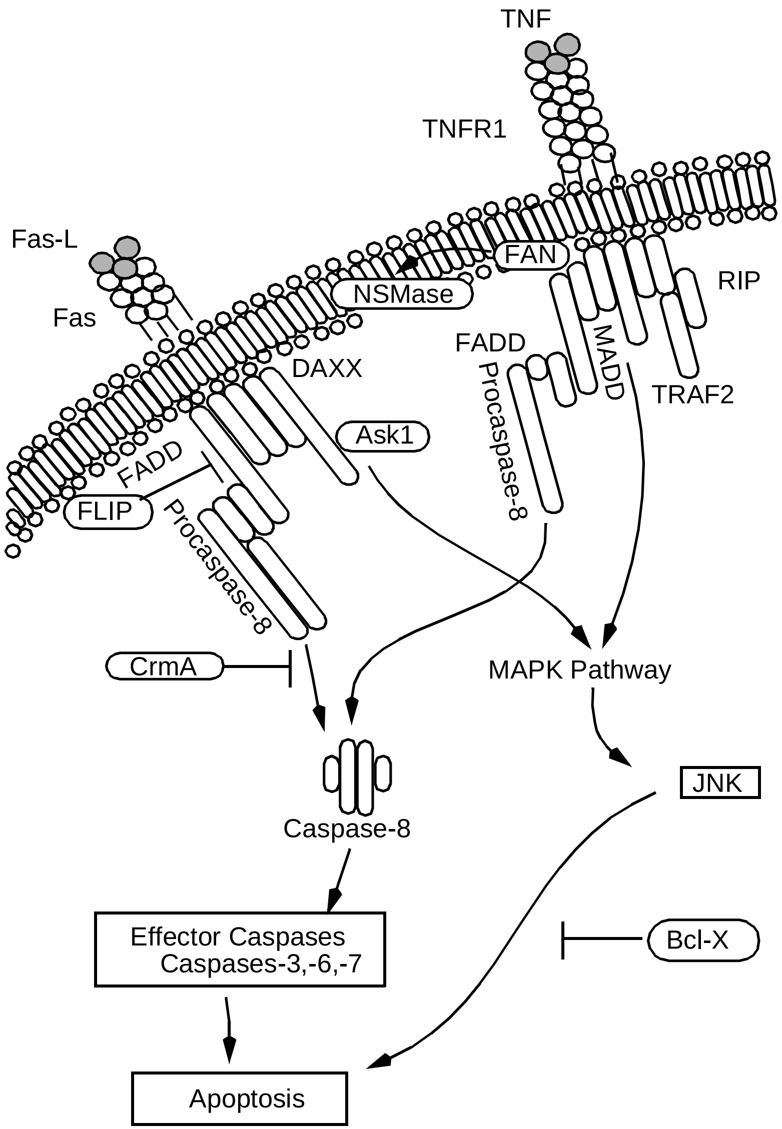
NETWORK REPRESENTATIONS, EX2

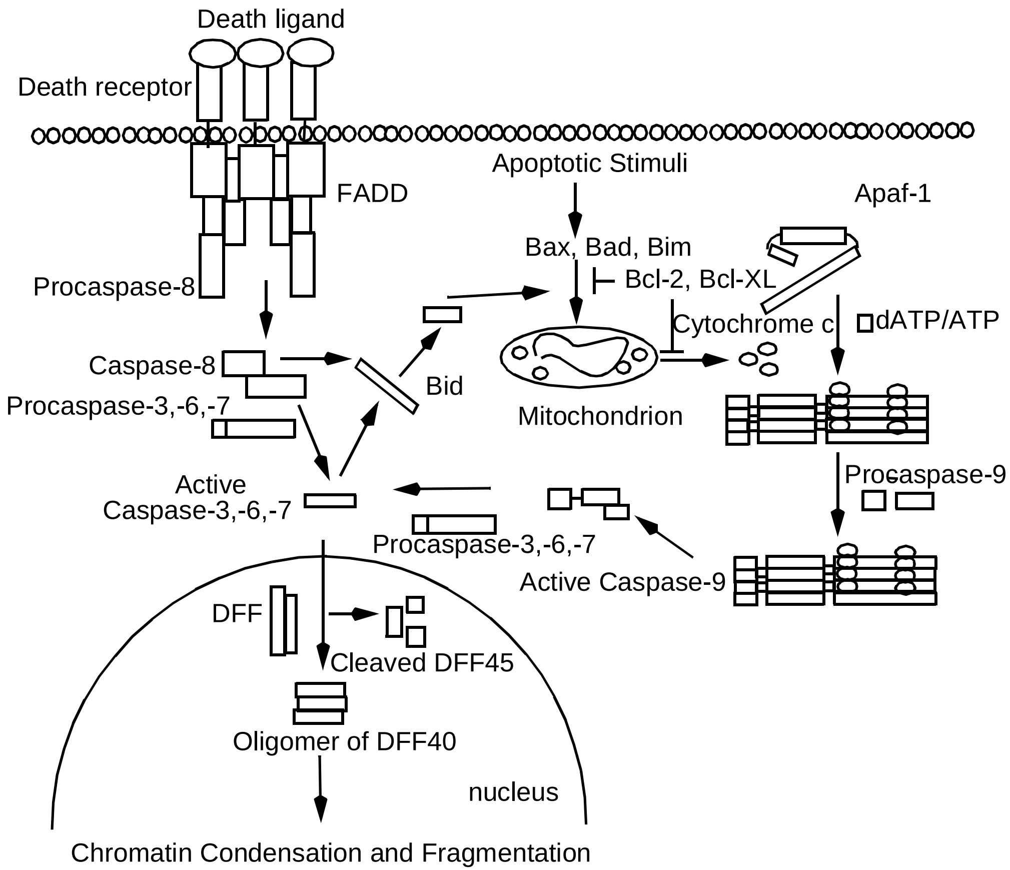


NETWORK REPRESENTATIONS, EX3

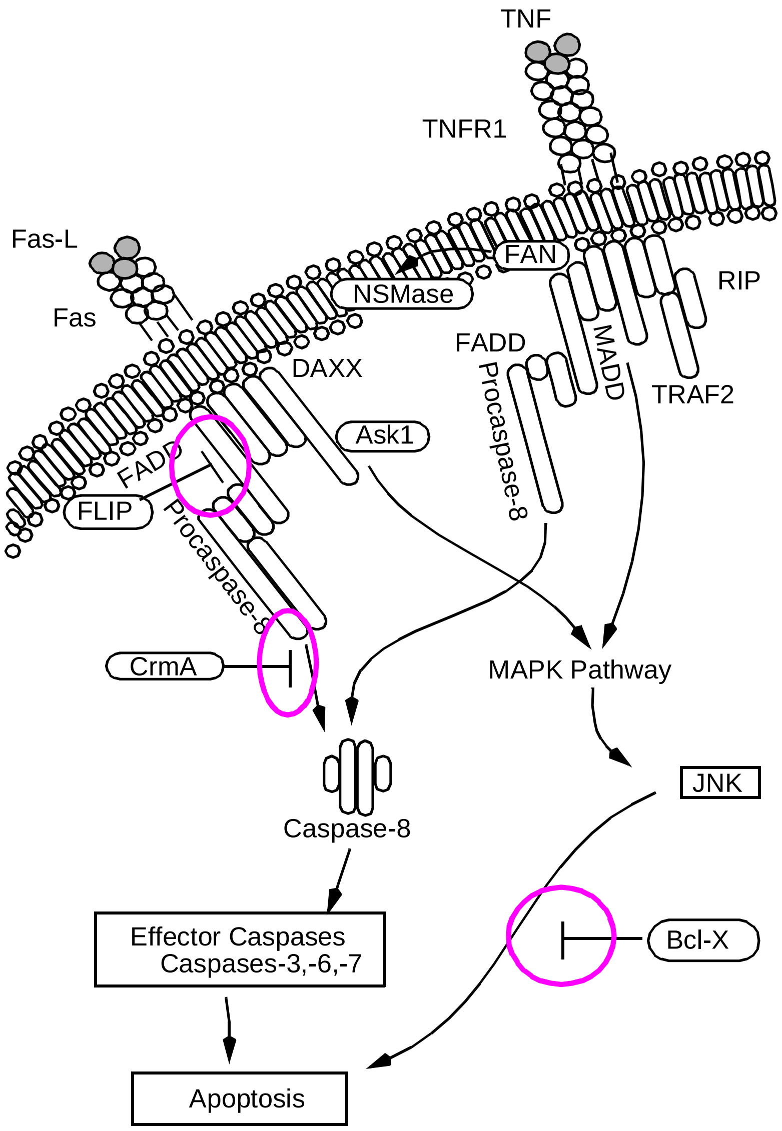


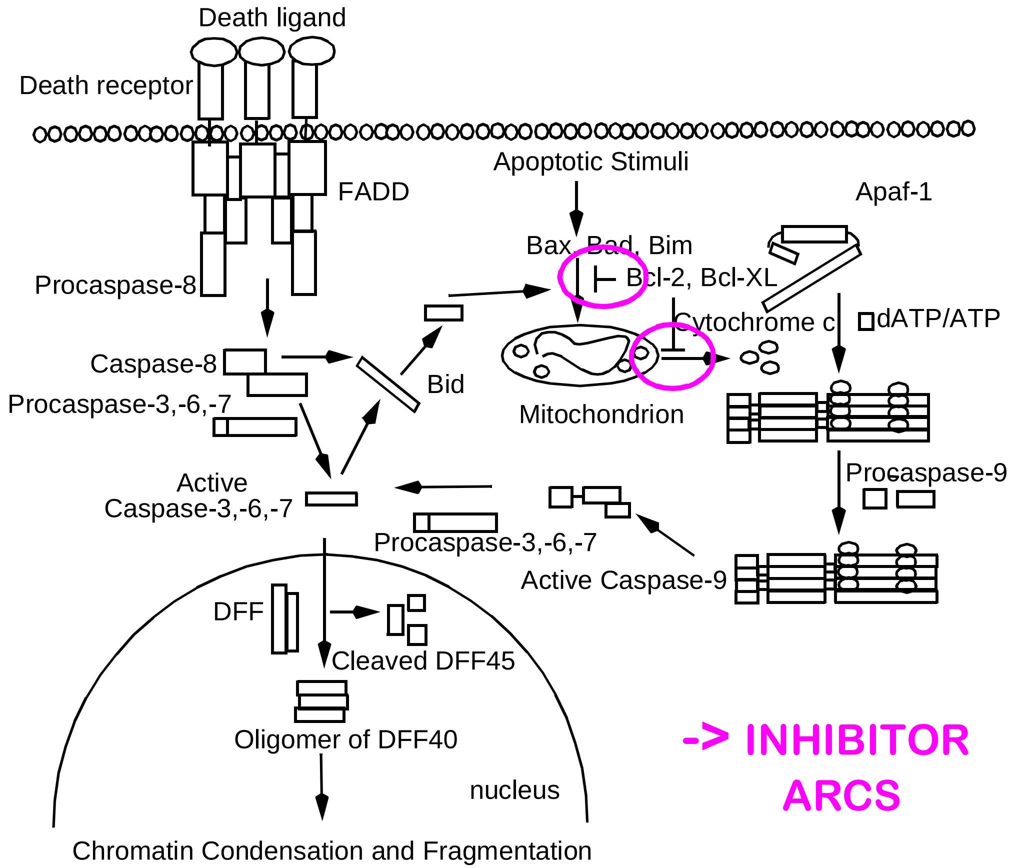
NETWORK REPRESENTATIONS, EX3 + EX4





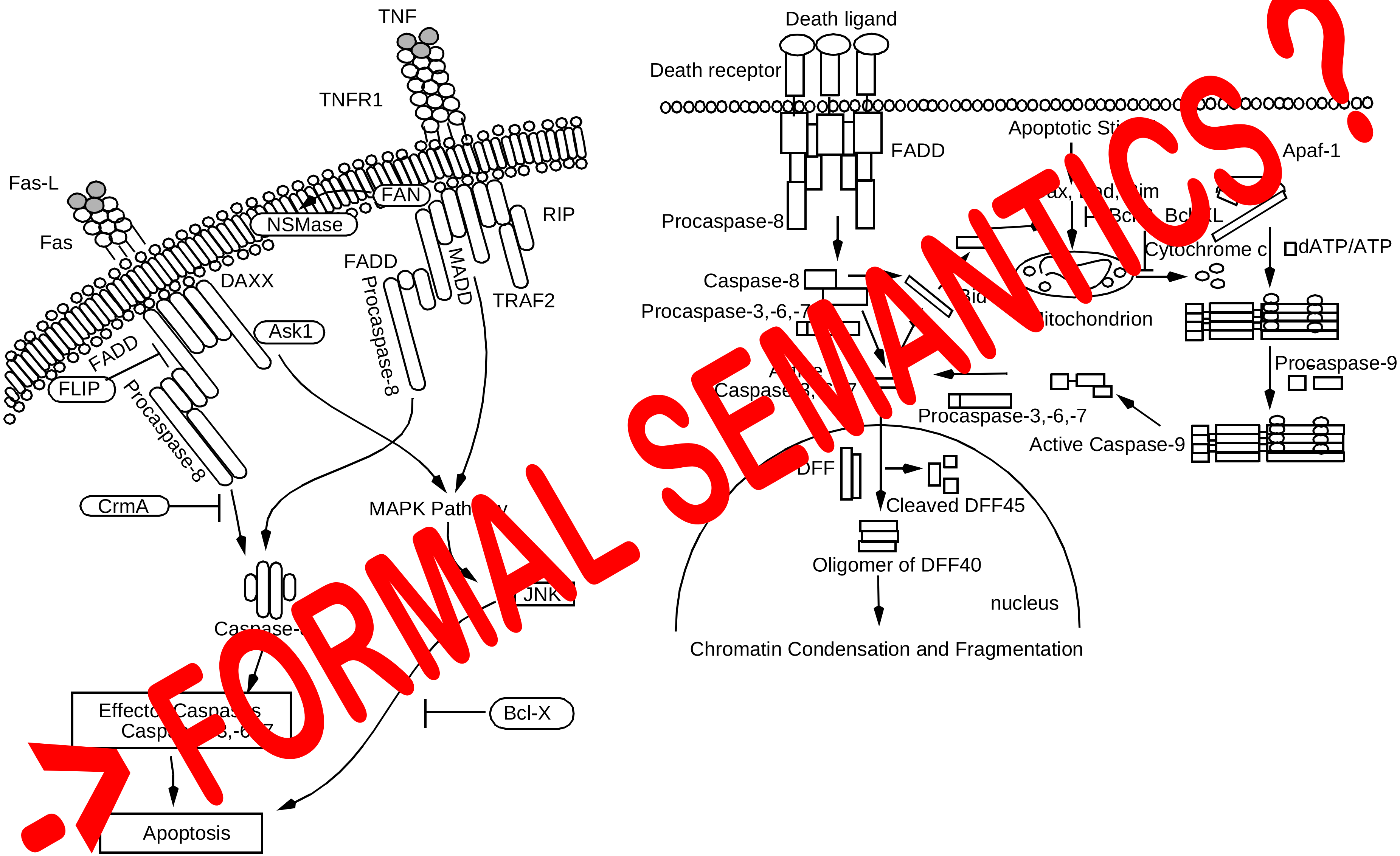
NETWORK REPRESENTATIONS, EX3 + EX4





-> INHIBITOR ARCS

NETWORK REPRESENTATIONS, EX3 + EX4



-> FORMAL SEMANTICS ?

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

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

$$\frac{d\alpha}{dt} = -\nu_1$$
$$\frac{dSte2}{dt} = -\nu_2 + \nu_3 - \nu_5$$
$$\frac{dSte2_{active}}{dt} = \nu_2 - \nu_3 - \nu_4$$
$$\frac{dSst2_{active}}{dt} = \nu_{46} - \nu_{47}$$
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$$\frac{dSte5}{dt} = -\nu_{12} + \nu_{13} + \nu_{17} + \nu_{21} + \nu_{23} + \nu_{25} + \nu_{27} + \nu_{32}$$
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$$\frac{dSte7}{dt} = -\nu_{14} + \nu_{15} + \nu_{16} + \nu_{21} + \nu_{23} + \nu_{25} + \nu_{27} + \nu_{32}$$
$$\frac{dFus3}{dt} = -\nu_{14} + \nu_{15} + \nu_{16} + \nu_{17} + \nu_{21} + \nu_{23} + \nu_{25} + \nu_{27} - \nu_{29} + \nu_{30} + \nu_{33}$$
$$\frac{dSte20}{dt} = -\nu_{18} + \nu_{19} + \nu_{21} + \nu_{23} + \nu_{25} + \nu_{27} + \nu_{32}$$

-> READABILITY?

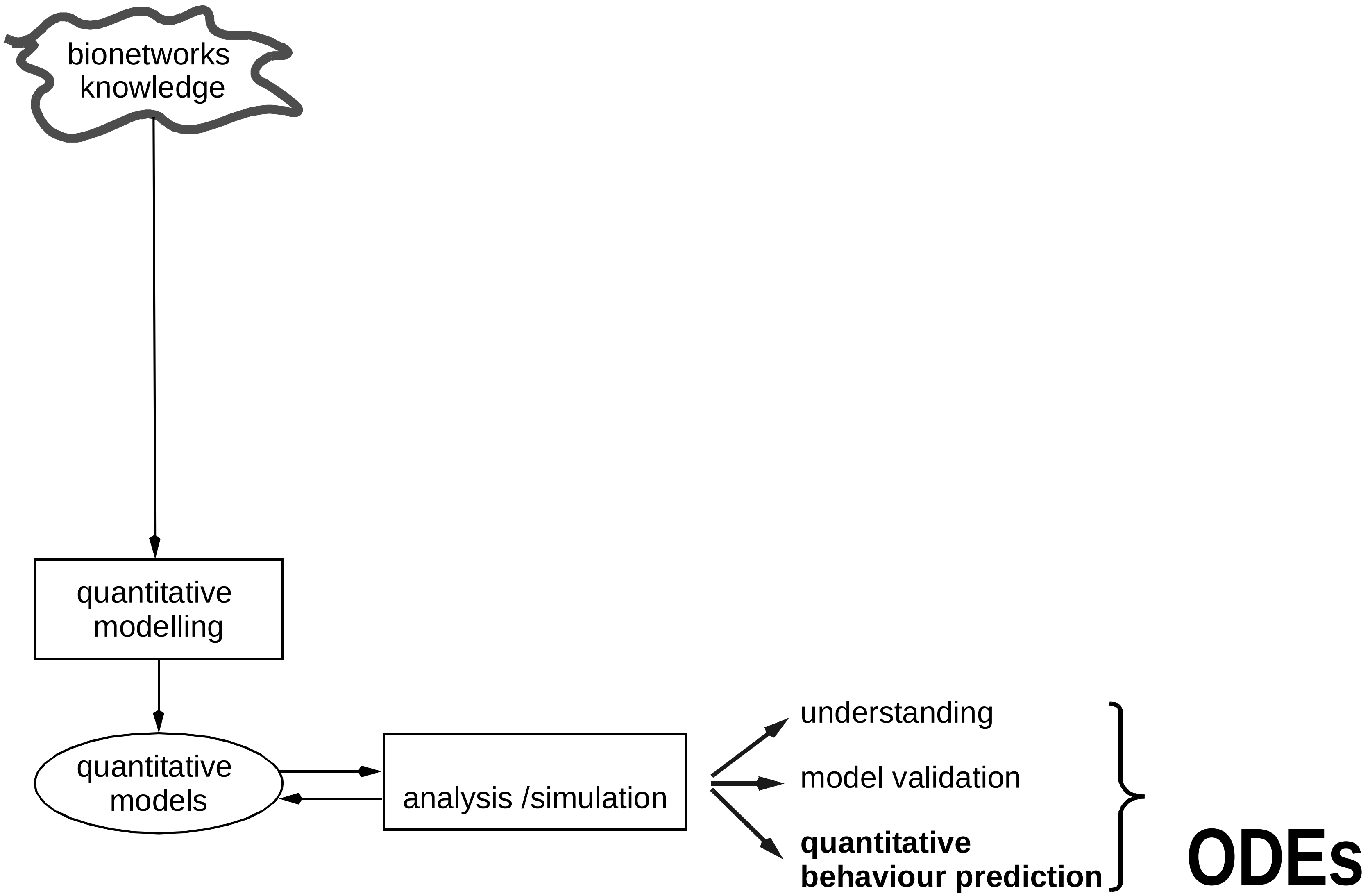
$$\nu_1 = \alpha[t] \cdot Bar1_{active}[t] \cdot k_1$$
$$\nu_2 = Ste2[t] \cdot \alpha[t] \cdot k_2$$
$$\nu_3 = Ste2_{active}[t] \cdot k_3$$
$$\nu_4 = Ste2_{active}[t] \cdot k_4$$
$$\nu_5 = Ste2[t] \cdot k_5$$
$$\nu_6 = Ste2_{active}[t] \cdot G\alpha\beta\gamma[t] \cdot k_6$$
$$\nu_7 = G\alpha GTP[t]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

BIONETWORKS, SOME PROBLEMS

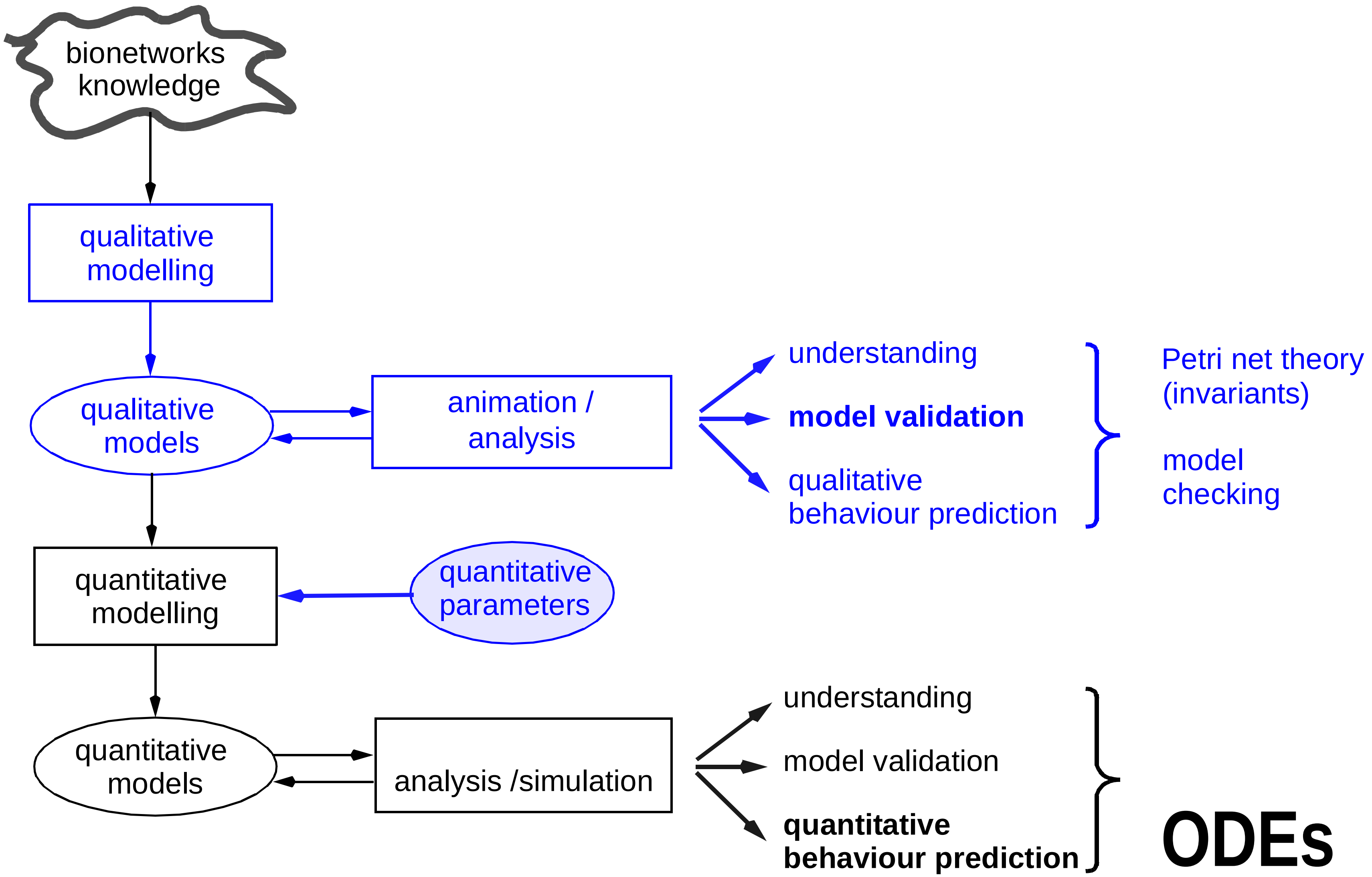
- **various, mostly ambiguous representations** -> ***PROBLEM 1***
  - -> *verbose descriptions*
  - -> *diverse graphical representations*
  - -> *contradictory and / or fuzzy statements*
- **knowledge** -> ***PROBLEM 2***
  - -> *uncertain*
  - -> *growing, changing*
  - -> *distributed over independent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

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

FRAMEWORK


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

FRAMEWORK


bionetworks knowledge
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Petri net theory (invariants)
model checking
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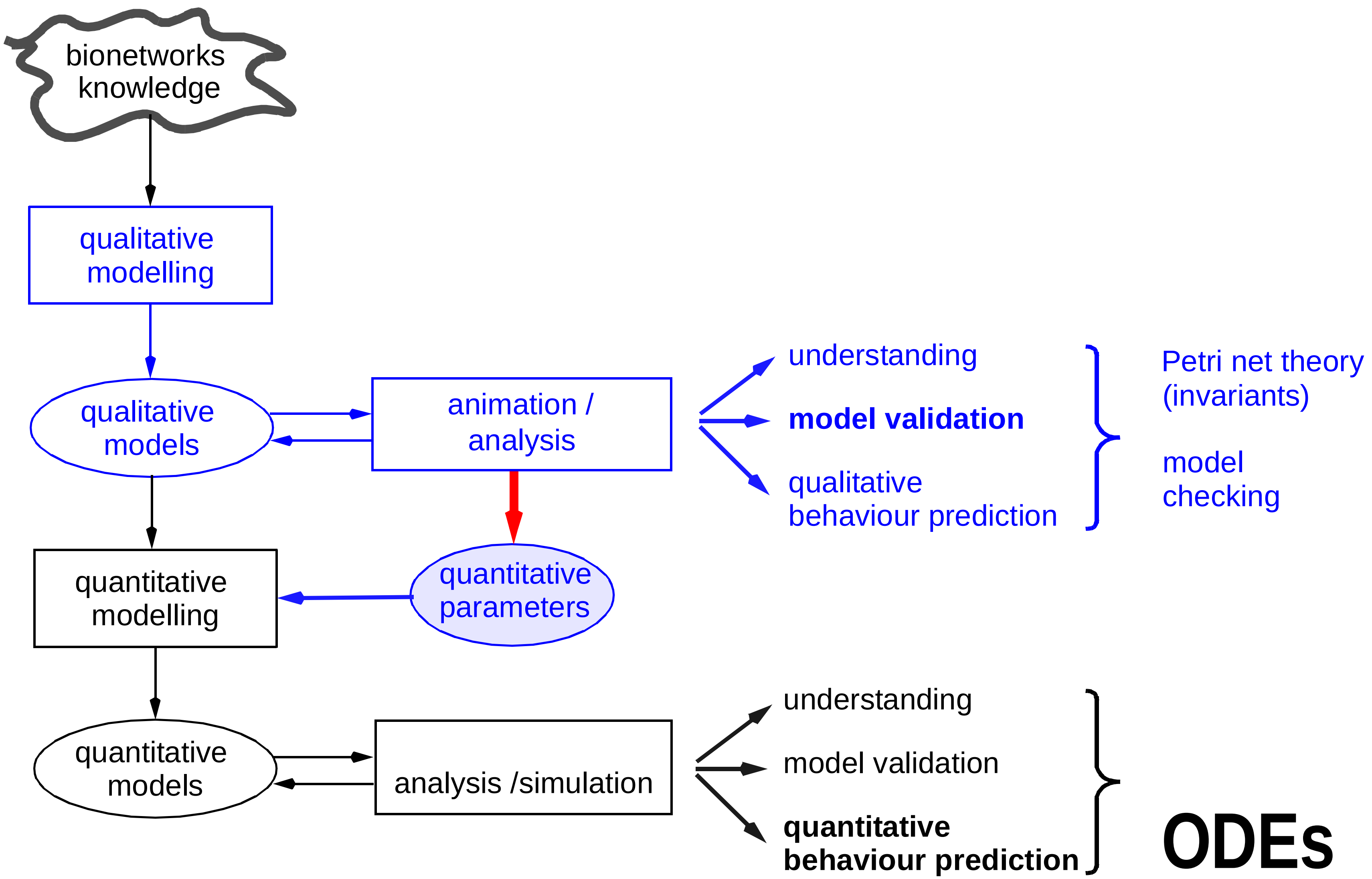
ODEs



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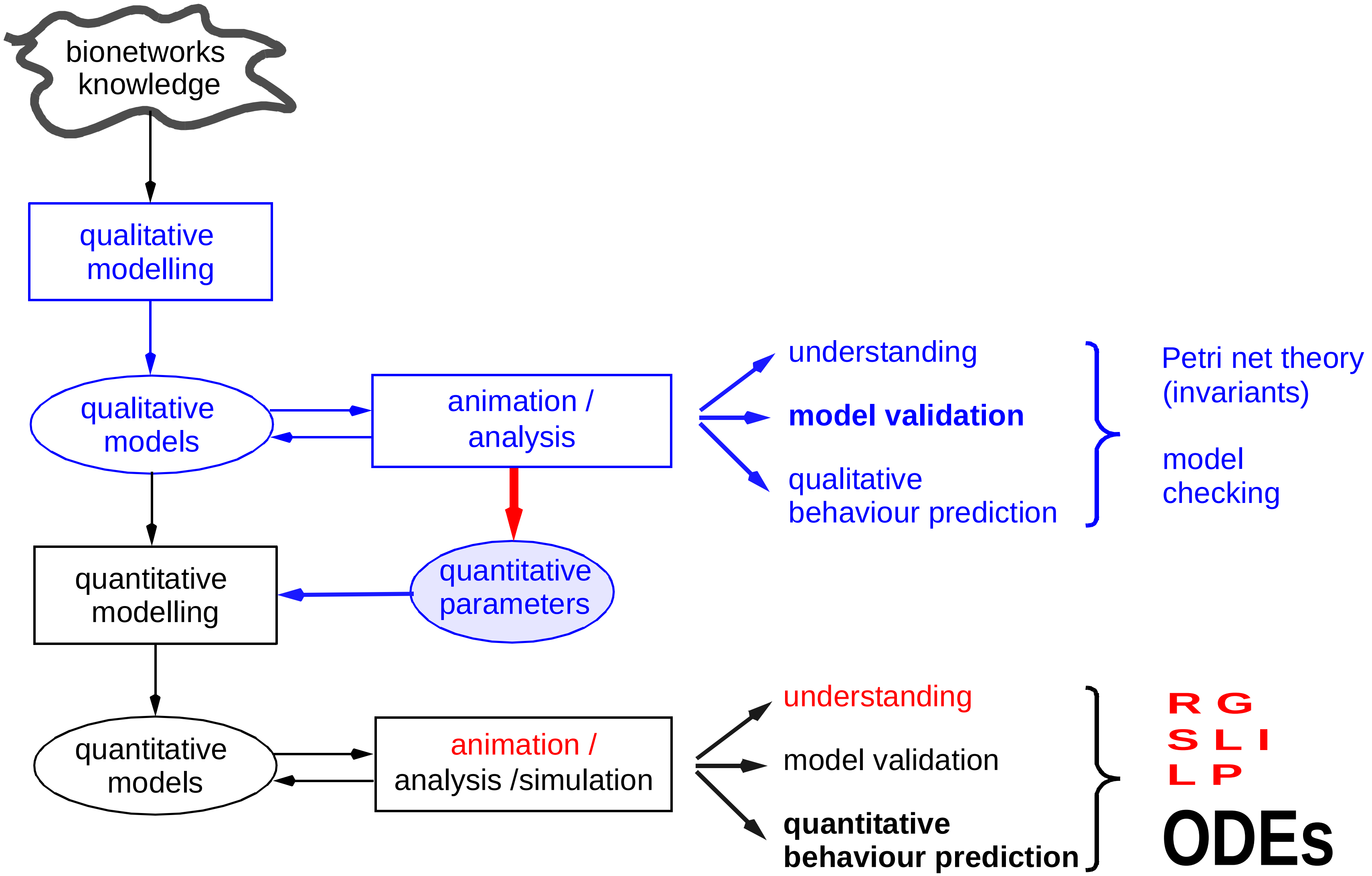
FRAMEWORK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quantitative models
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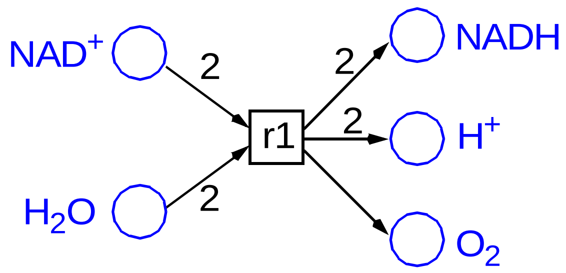
understanding
model validation
quantitative behaviour prediction
R G
S L I
L P
ODEs

PETRI NETS -
AN INFORMAL CRASH COURSE

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

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

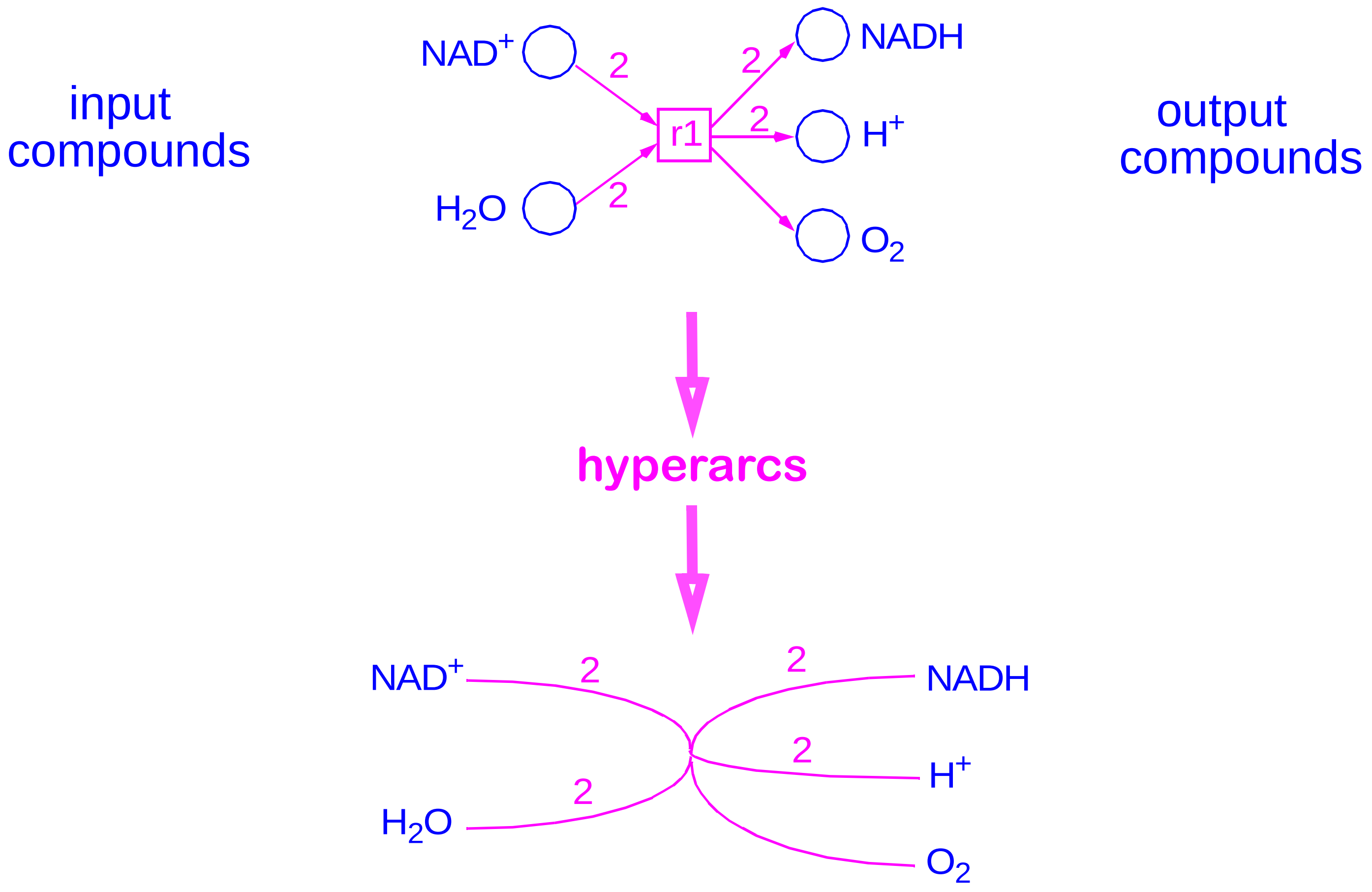
input compounds



output compounds

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

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

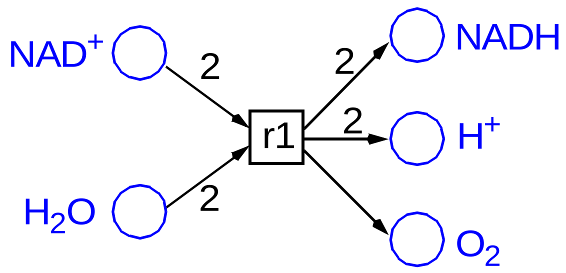


- **atomic actions -> Petri net transitions -> chemical reactions**

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

input compounds

pre-conditions



output compounds

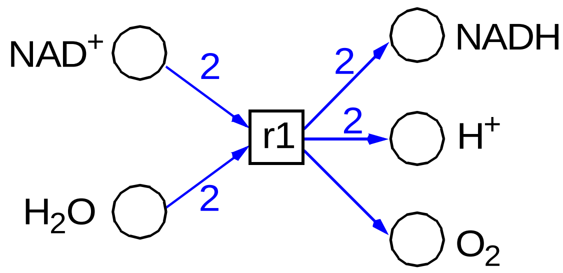
post-conditions

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

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

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

input compounds



output compounds

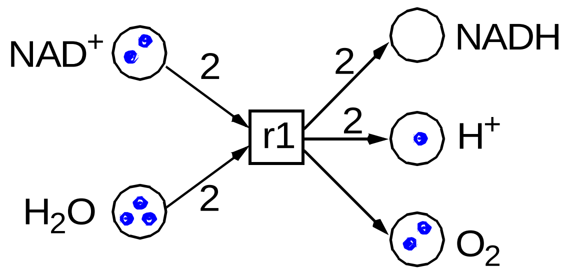
- **local conditions -> Petri net places -> chemical compounds**
- **multiplicities -> Petri net arc weights -> stoichiometric relations**

Petri Nets, Basics - The Structure

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

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

input compounds



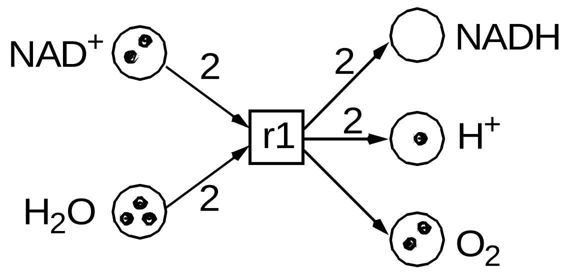
output compounds

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

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

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

input compounds



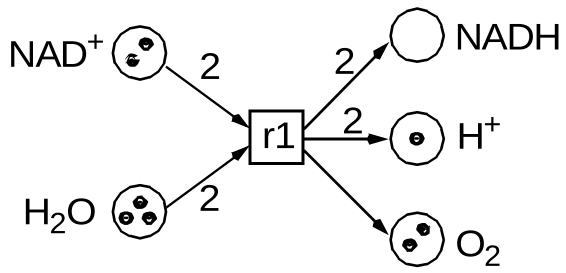
output compounds

- **local conditions -> Petri net places -> chemical compounds**
- **multiplicities -> Petri net arc weights -> stoichiometric relations**
- **condition's state -> token(s) in its place -> available amount (e.g. mol)**
- **system state -> marking -> compounds distribution**
- **$PN = (P, T, F, m_0)$, $F: (P \times T) \cup (T \times P) \rightarrow N_0$, $m_0: P \rightarrow N_0$**

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

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

input compounds



output compounds

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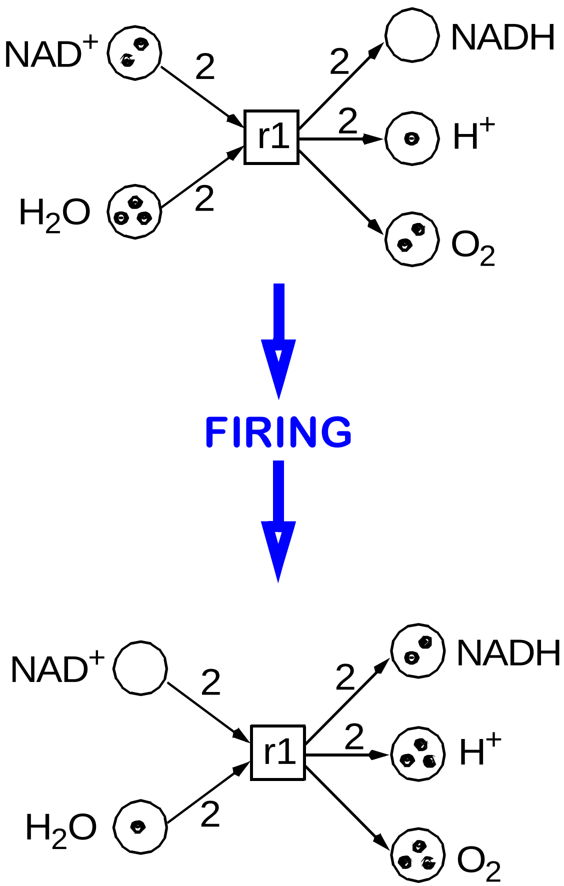
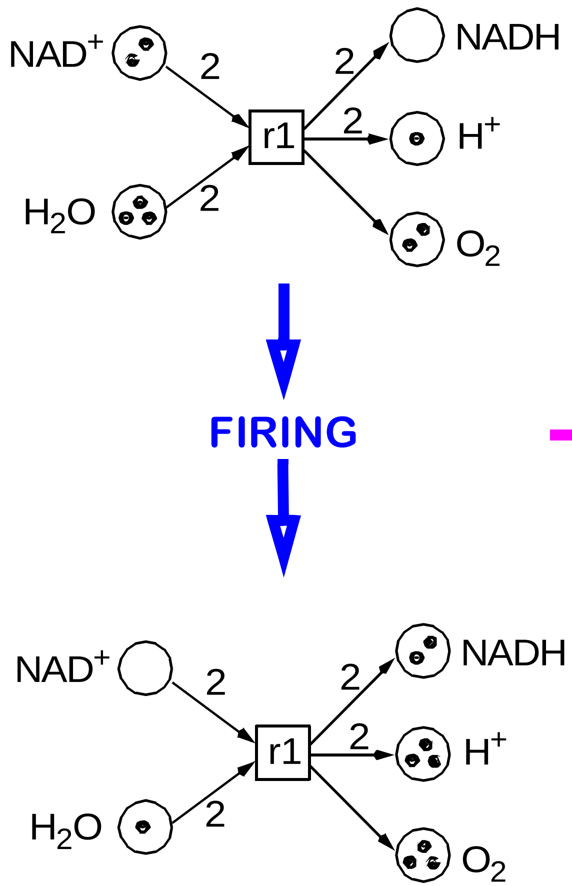


output compounds

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

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

input compounds

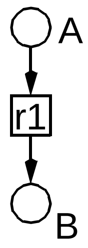


output compounds

TOKEN GAME

DYNAMIC BEHAVIOUR (substance flow)

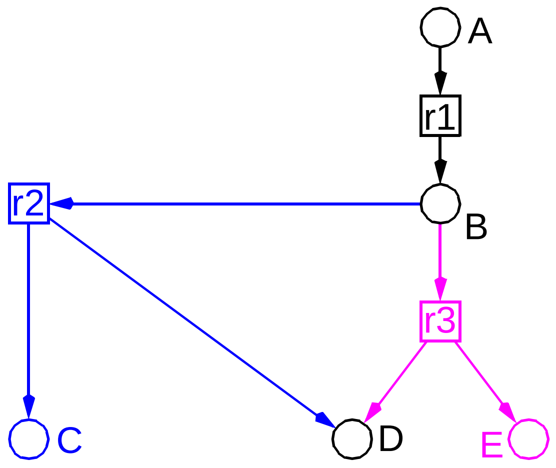
r1: A -> B



r1: A -> B

r2: B -> C + D

r3: B -> D + E



-> alternative reactions

r1: A -> B

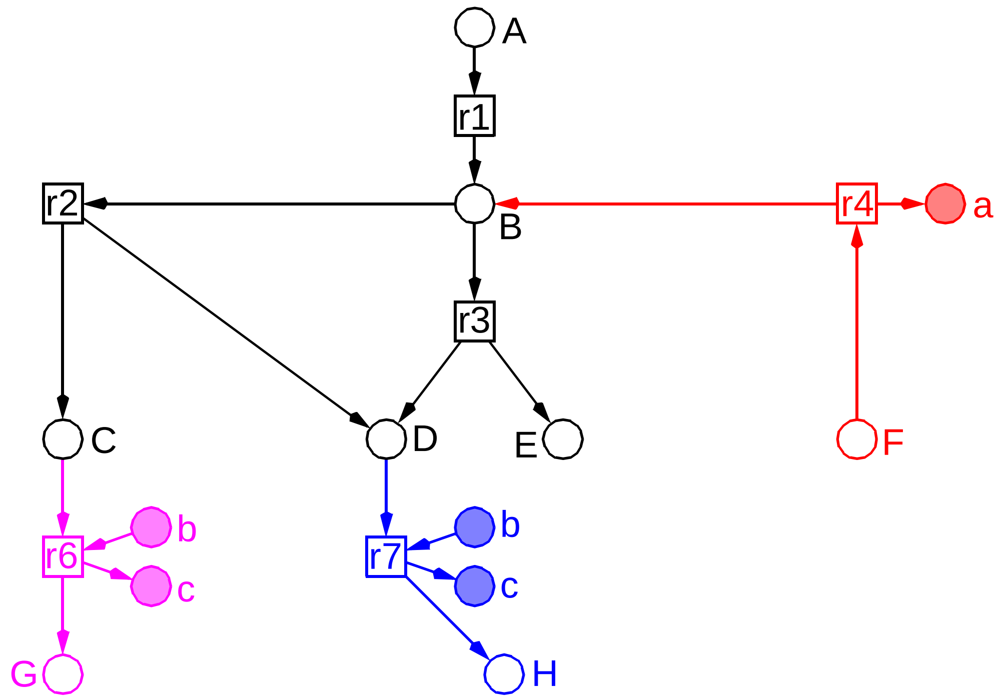
r2: B -> C + D

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

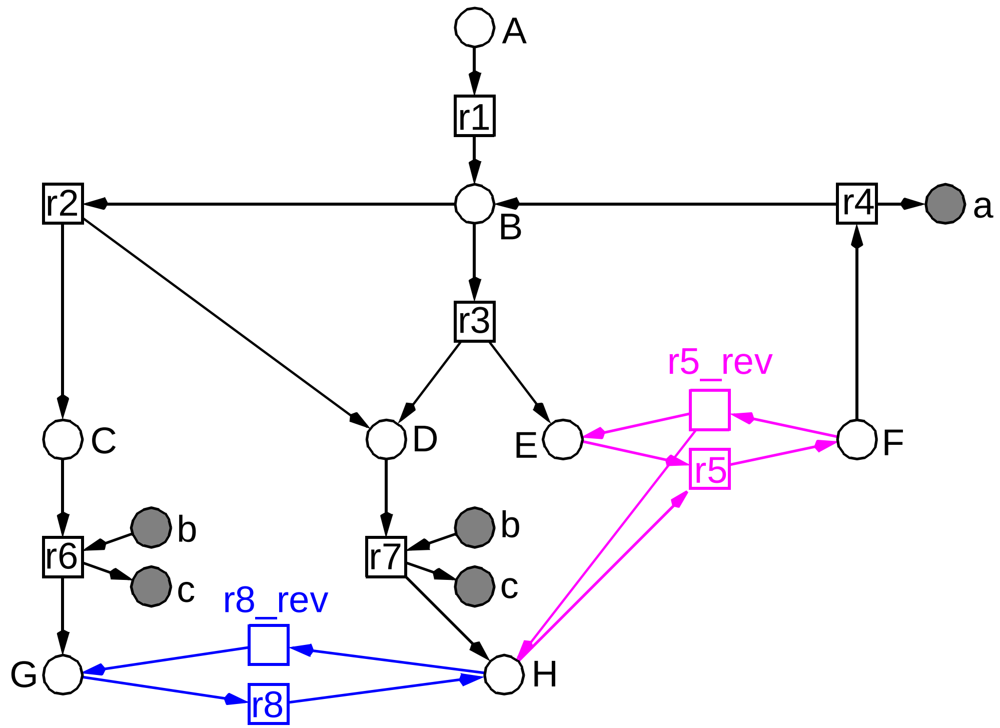
r4: F -> B + a

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

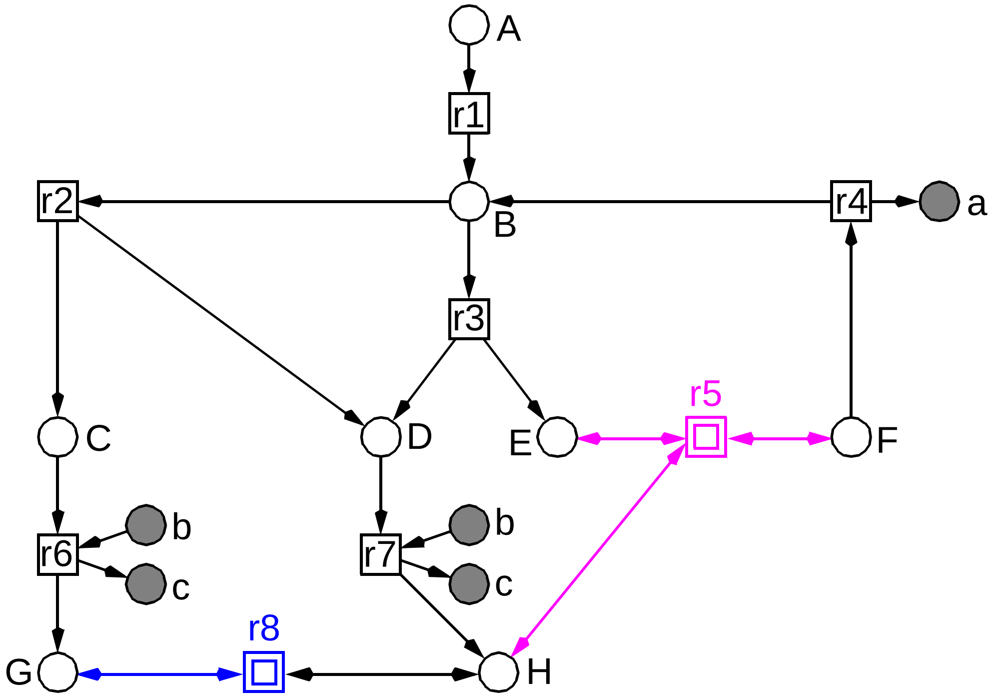
r4: F -> B + a

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

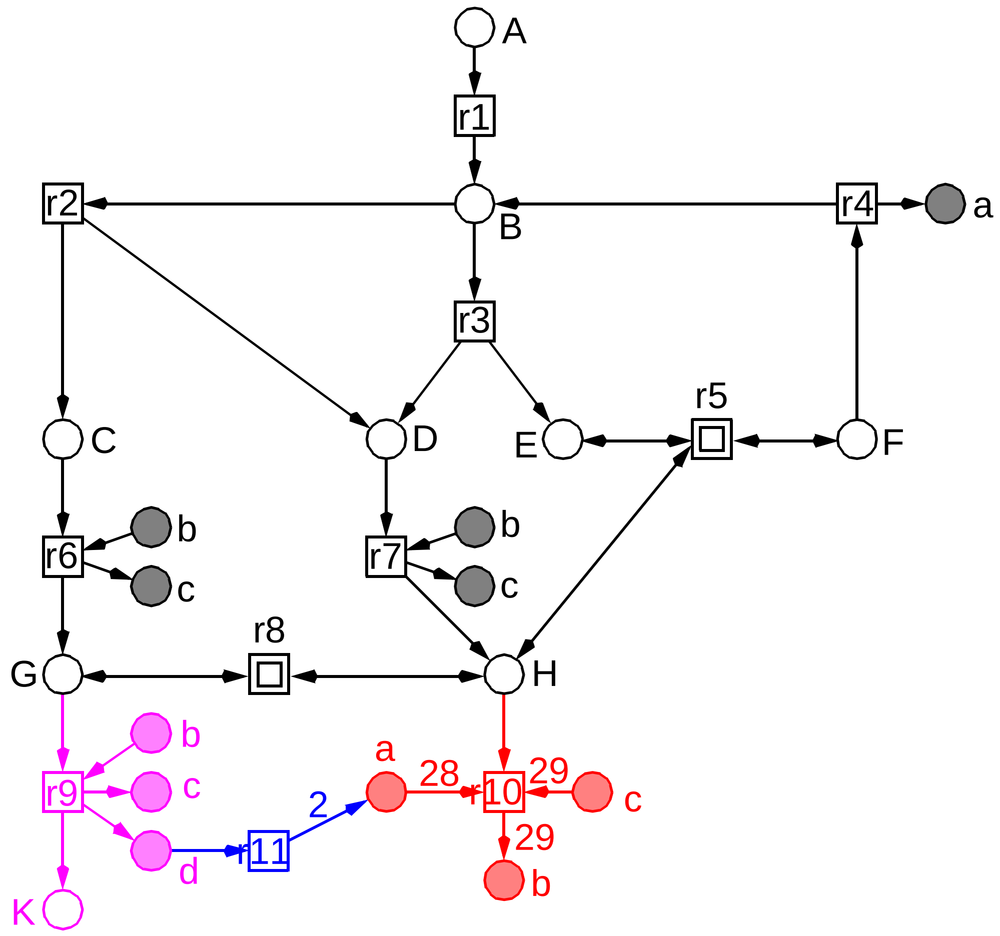
r7: D + b -> H + c

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

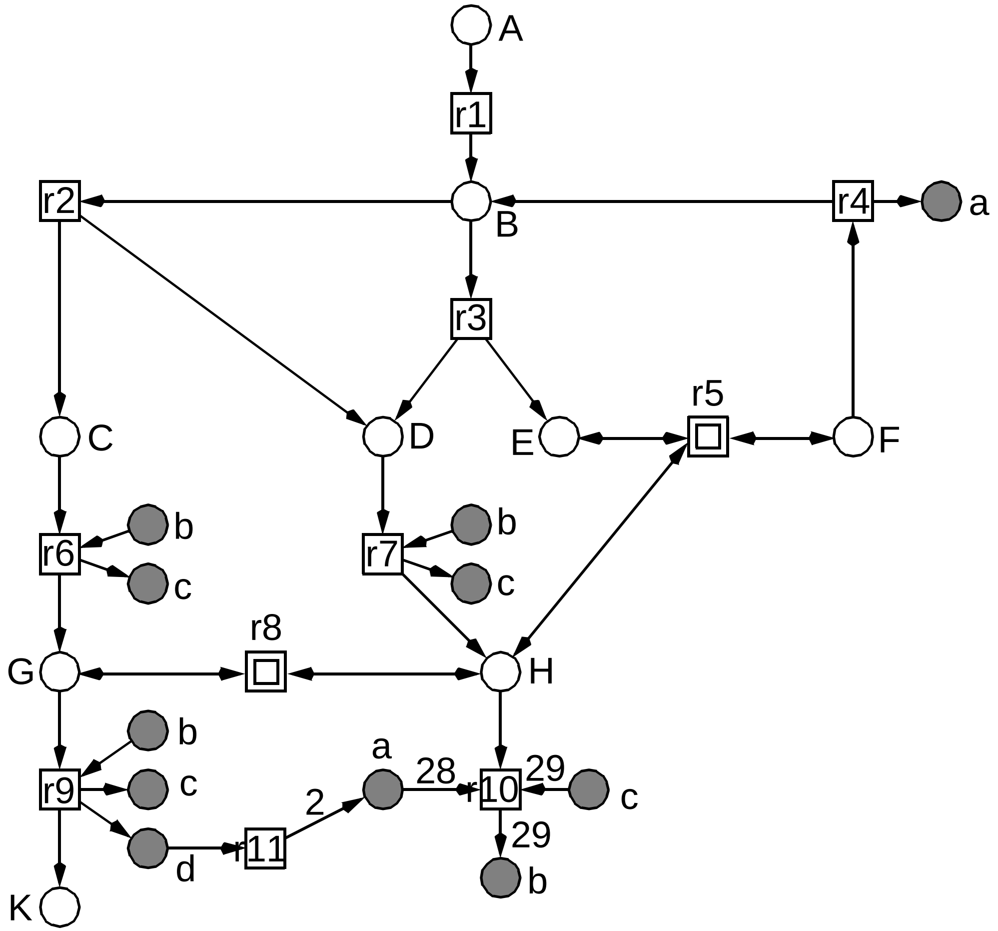
r7: D + b -> H + c

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

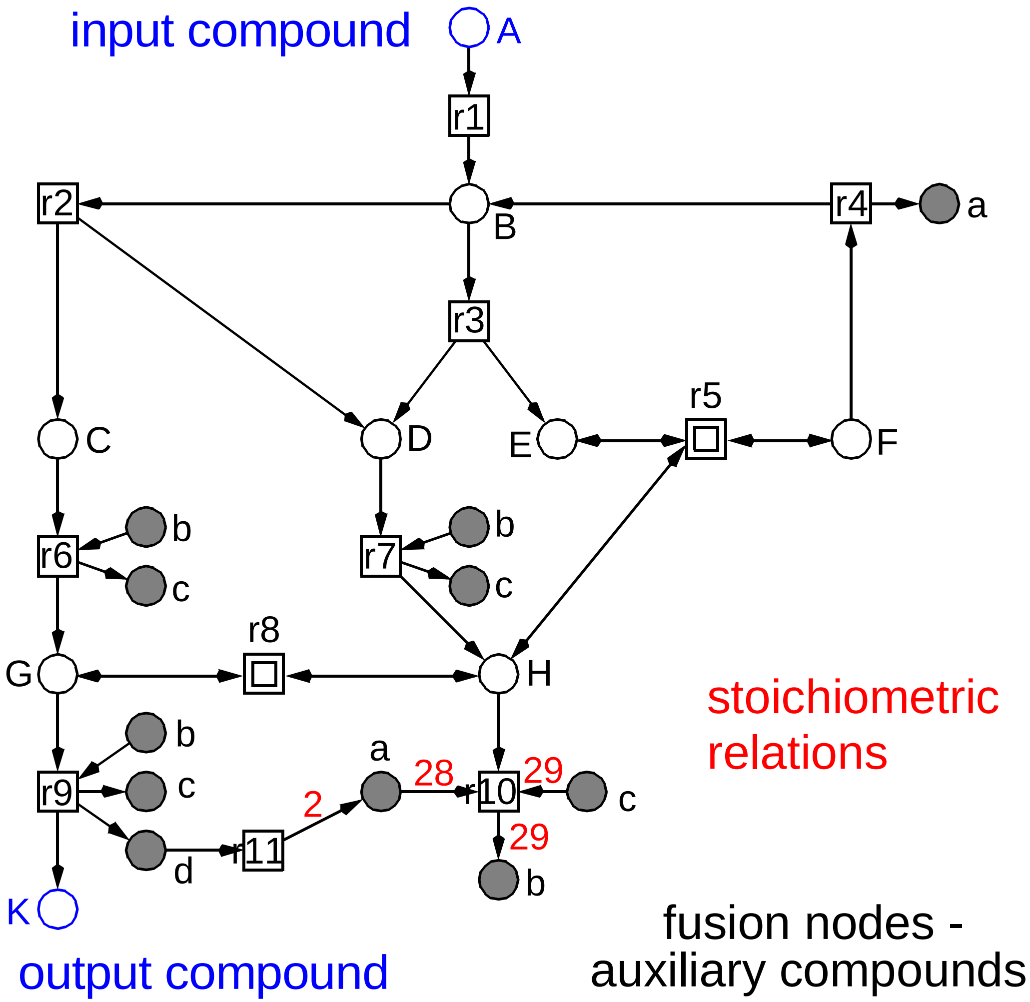
r7: D + b -> H + c

r8: H <-> G

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

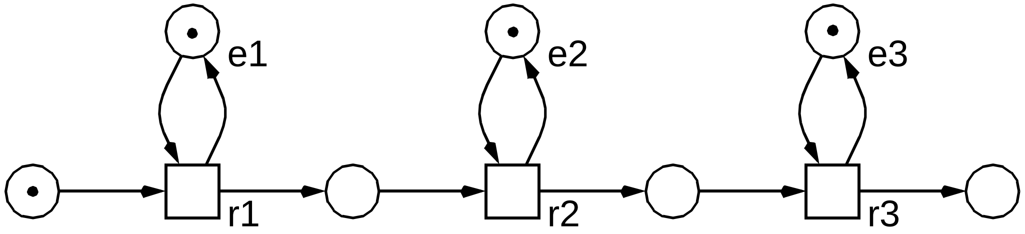
r10: H + 28a + 29c -> 29b

r11: d -> 2a



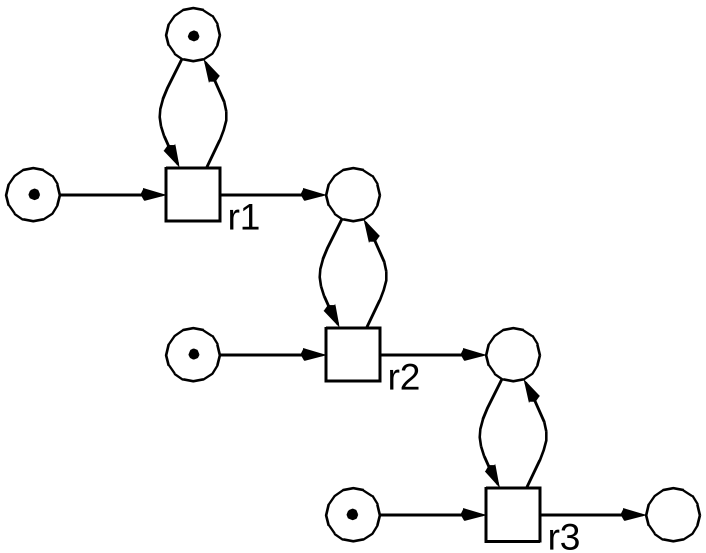
- **metabolic networks**

  -> substance flows



- **signal transduction networks**

  -> signal flows



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

- **biochemically interpreted Petri net**

  -> *partial order sequences of chemical reactions (= elementary actions) transforming input into output compounds / signals [respecting the given stoichiometric relations, if any]*

  -> *set of all pathways from the input to the output compounds / signals [respecting the stoichiometric relations, if any]*

- **pathway**

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

- **typical (structural) properties**

INA

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

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

- **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]

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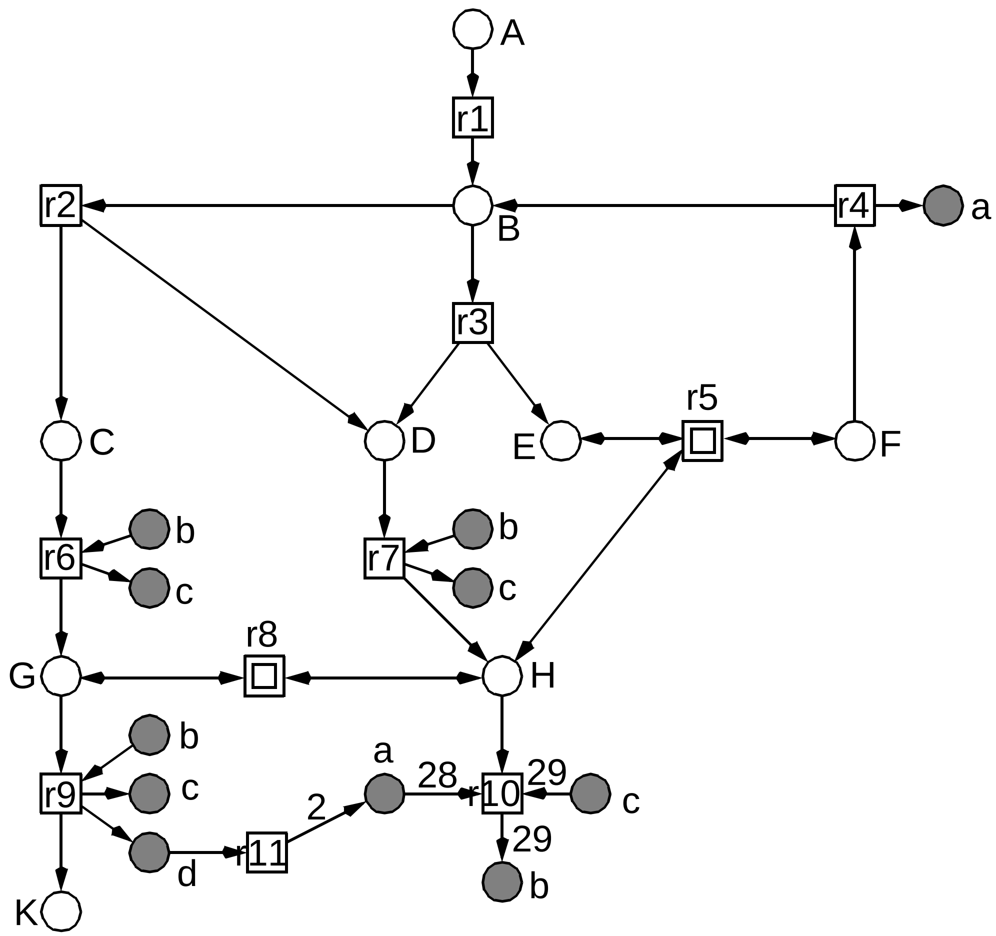
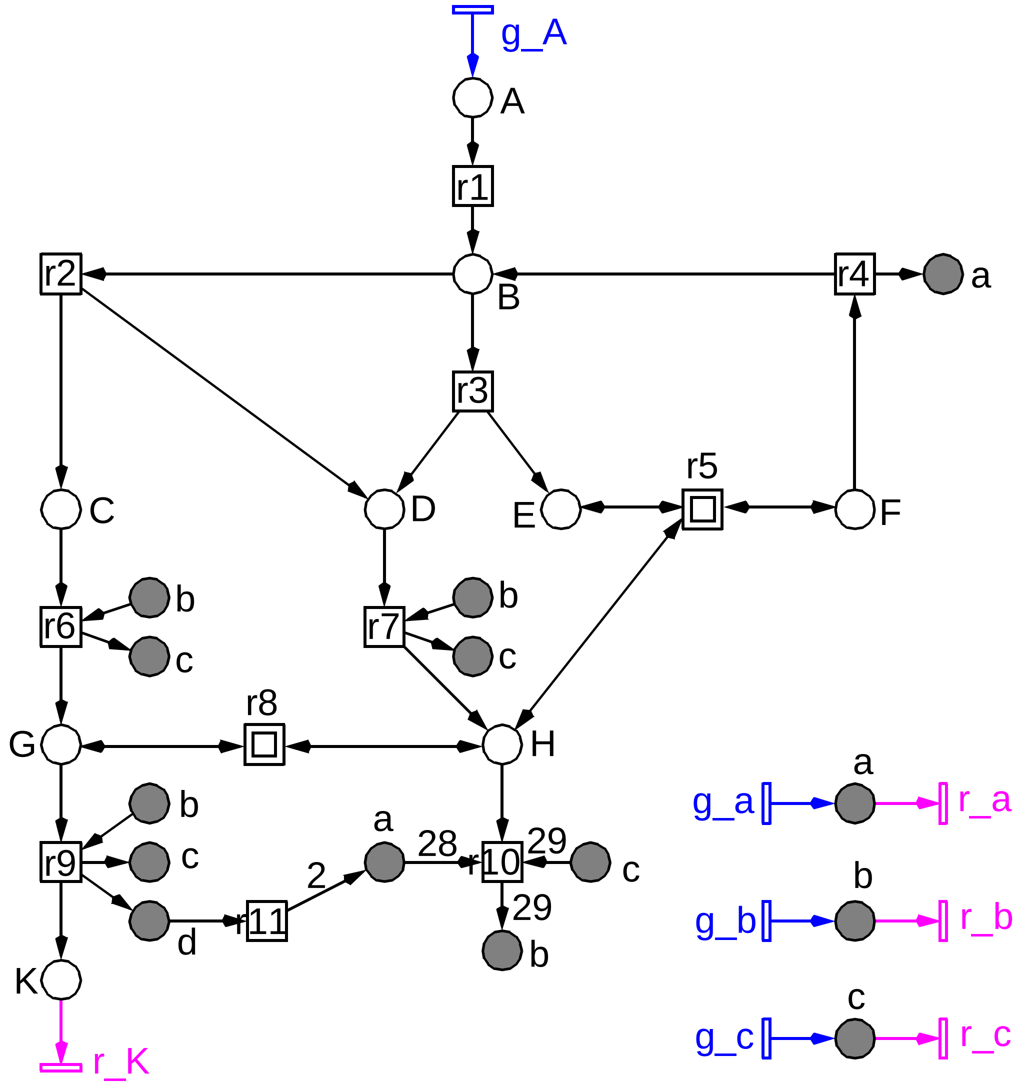
N	N	N	Y	N	N	Y	N	N	N	Y	Y	N	N	N	N	N
DTP	CPI	CTI	B	SB	REV	DSt	BSt	DTr	DCF	L	LV	L&S				
N	N	N	Y	Y	?	?	?	?	?	N	?	N				

BIONETWORKS NEED ENVIRONMENT BEHAVIOUR

- **to animate the model**
  - -> *infinite substance flow*
  - -> *deeper insights*
- **to validate the model**
  - -> *consistency criteria*
- **steady flow**
  - -> *input substances*
  - -> *output substances*
- **auxiliary substances**
  - -> *as much as necessary*
- **minimal assumptions**



- **input substances**
  - *-> generating pre-transitions*
- **output substances**
  - *-> consuming post-transitions*
- **auxiliary substances**
  - *-> both*
- **no boundary places, but boundary transitions**
- **transitions without pre-places**
  - *-> live*
  - *-> all post-places are unbounded*
  - *-> all places simultaneously unbounded (?)*



UNBOUNDEDNESS - WHAT NEXT ?

- **steady state behaviour**
  - -> *all possible flows preserving a given compounds distribution*
  - -> *elementary modes [Schuster 1993] = minimal T-invariants*

- **consistency criteria -> pathways analysis**
  - -> *CTI*
  - -> *no minimal T-invariant without biological interpretation*
  - -> *no known biological behaviour without corresponding T-invariant*

- **typical properties**

INA

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

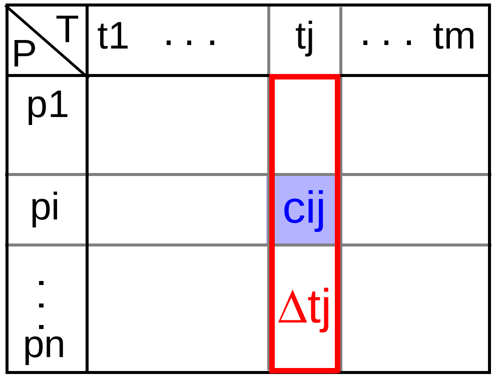
DTP	CPI	CTI	B	SB	REV	DSt	BSt	DTr	DCF	L	LV	L&S
?	N	Y	N	N	?	N	?	n	n	y	y	N

how to prove ?

T-INVARIANTS -
AN INFORMAL CRASH COURSE

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

C =



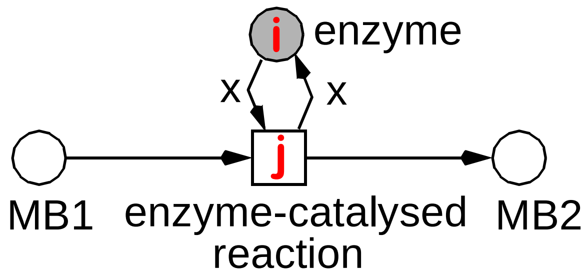
cij = (pi, tj) = F(tj,pi) - F(pi, tj) = Δ tj(pi)

Δtj = Δ 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

T-INVARIANTS, BASICS

- **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 / reaction rates*
  - -> *elementary modes [Schuster 1993]*

- **realizable T-invariants correspond to cycles in the RG**
  - -> *RG: concurrent transitions -> all transitions' interleaving sequences*
  - -> *if there are concurrent transitions in a realizable T-invariant, then there is a RG cycle for each interleaving sequence*
  - -> *analogously for conflicts*

- **a T-invariant defines a subnet** **-> partial order structure**
  - -> *the T-invariant's transitions (the support),*
    + all their pre- and post-places
    + the arcs in between
  - -> *pre-sets of support = post-sets of support*

trivial min. T-invariants (5)

- boundary transitions of auxiliary compounds

  -> (g_a, r_a), (g_b, r_b), (g_c, r_c)

- reversible reactions

  -> (r5, r5_rev), (r8, r8_rev)

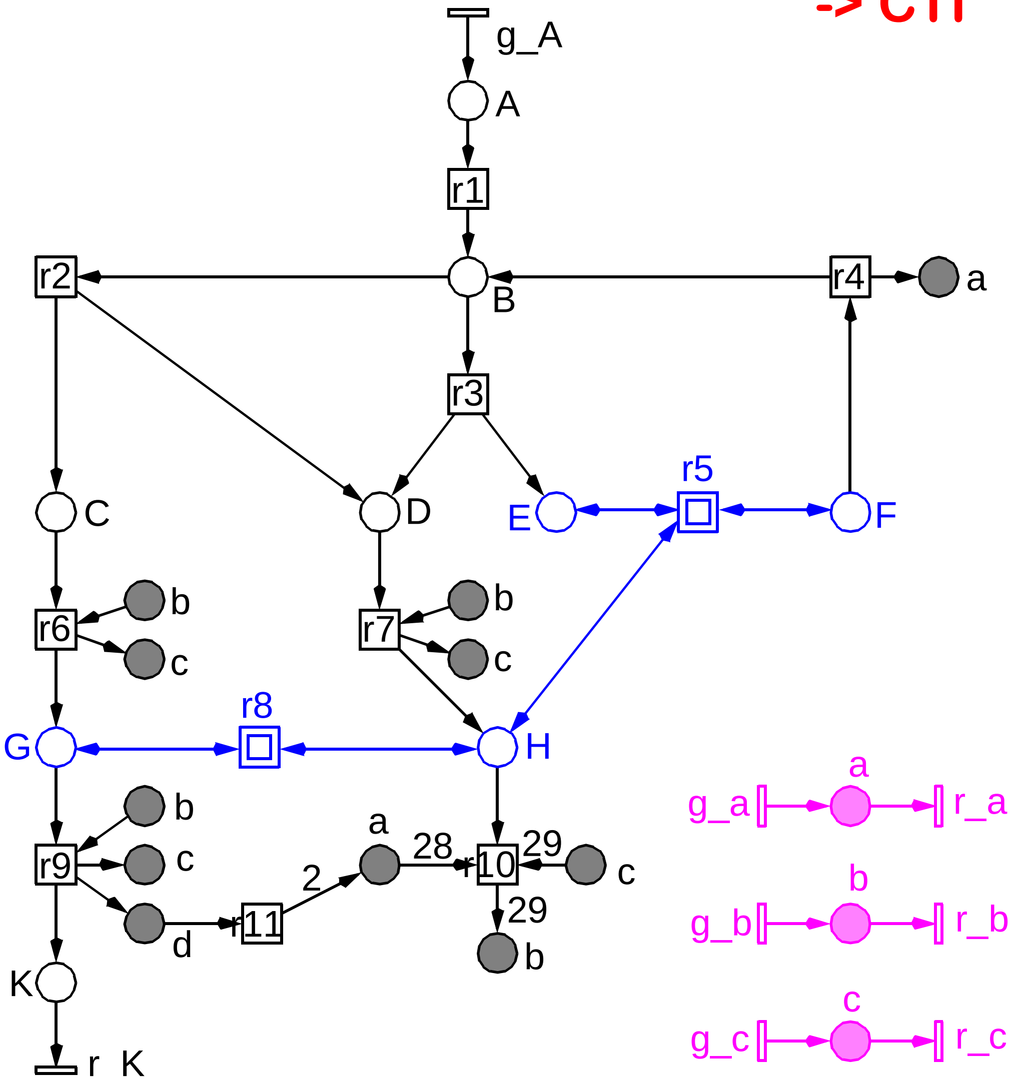
non-trivial min. T-invariants (7)

- covering boundary transitions of input / output compounds

  -> i/o-T-invariants

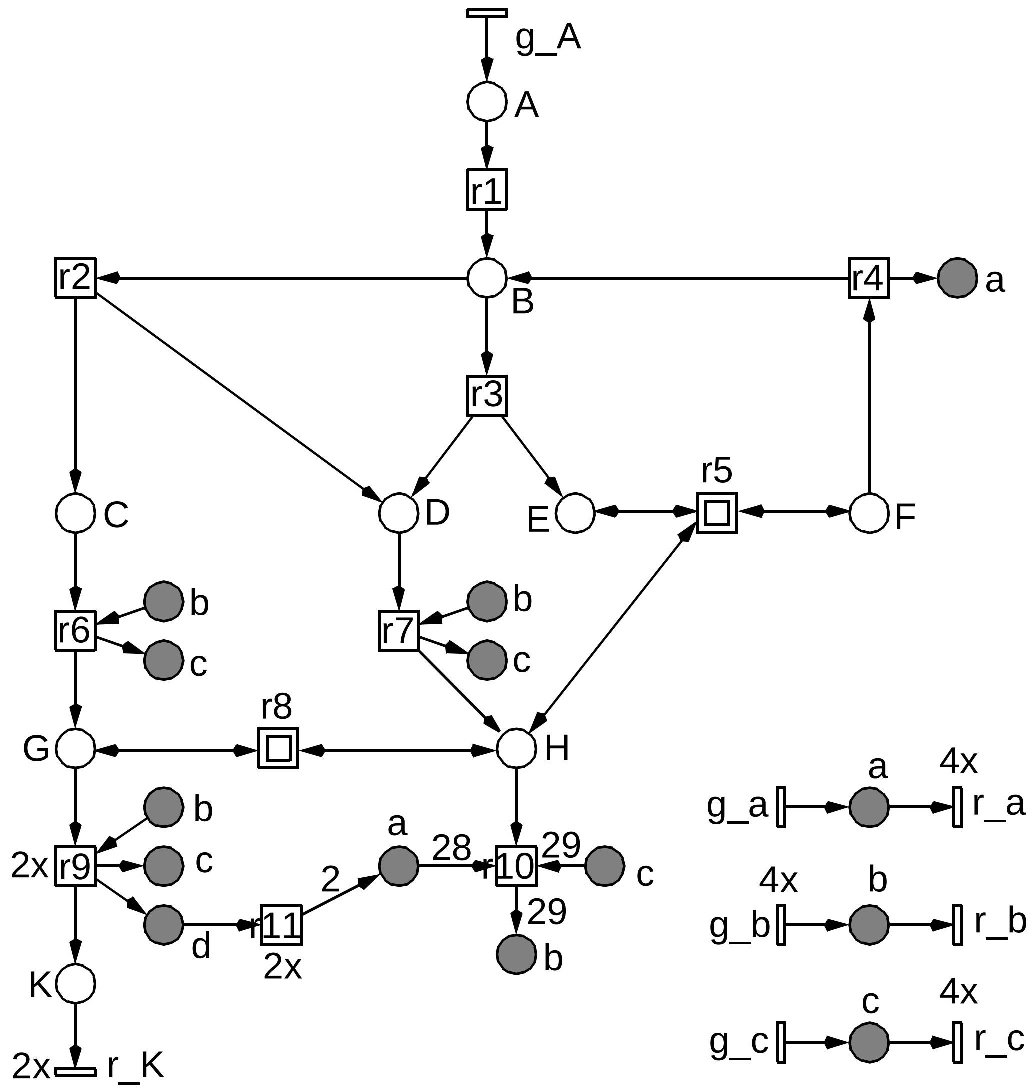
- inner cycles

-> CTI



❑ i/o-T-invariant, example

12	|	*0.r1*	*: 1*
	|	*1.r2*	*: 1,*
	|	*3.r8_rev*	*: 1,*
	|	*4.r6*	*: 1,*
	|	*5.r7*	*: 1,*
	|	*9.r9*	*: 2,*
	|	*12.r11*	*: 2,*
	|	*13.g_A*	*: 1,*
	|	*14.r_K*	*: 2,*
	|	*15.g_b*	*: 4,*
	|	*18.r_c*	*: 4,*
	|	*20.r_a*	*: 4*



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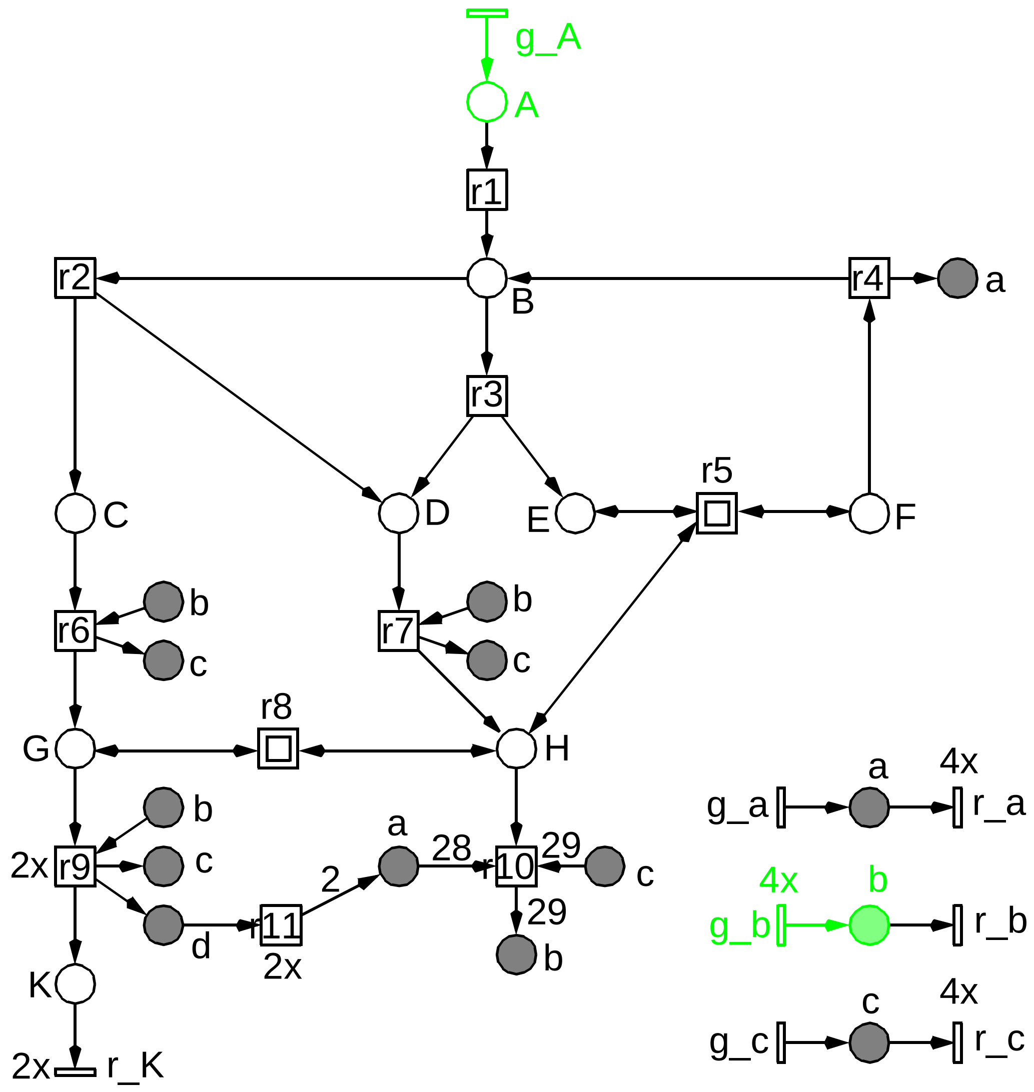

- **i/o-T-invariant, example**

12 | 0.r1 : 1
| 1.r2 : 1,
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| 5.r7 : 1,
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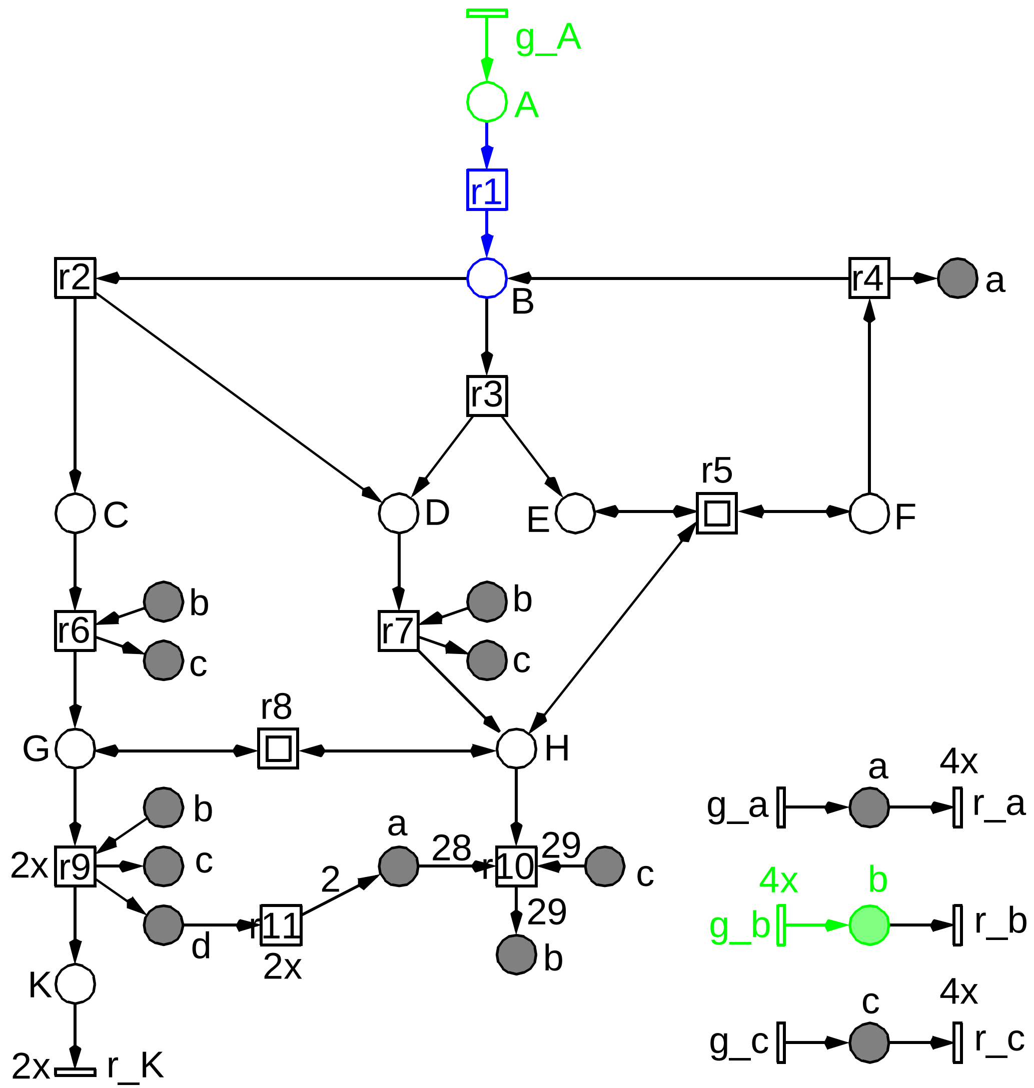

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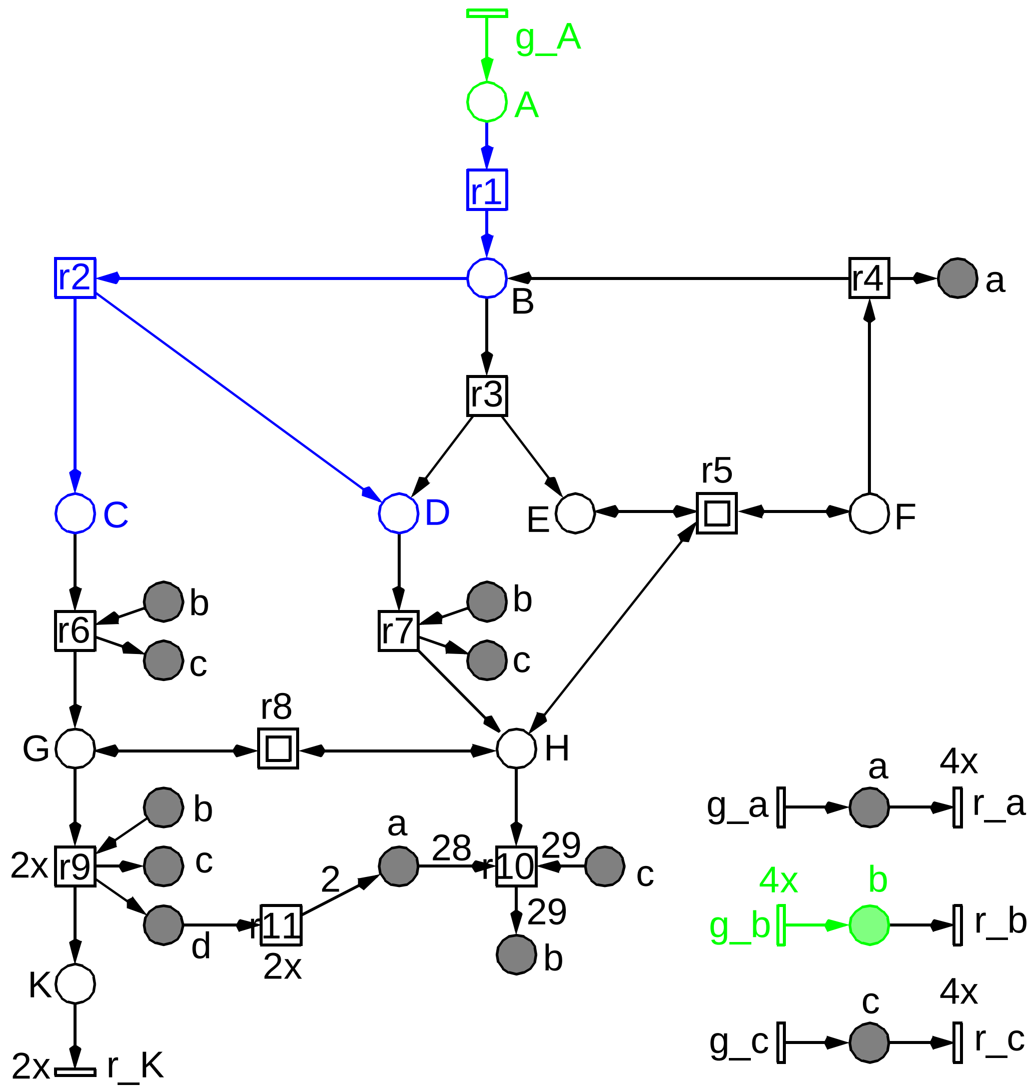

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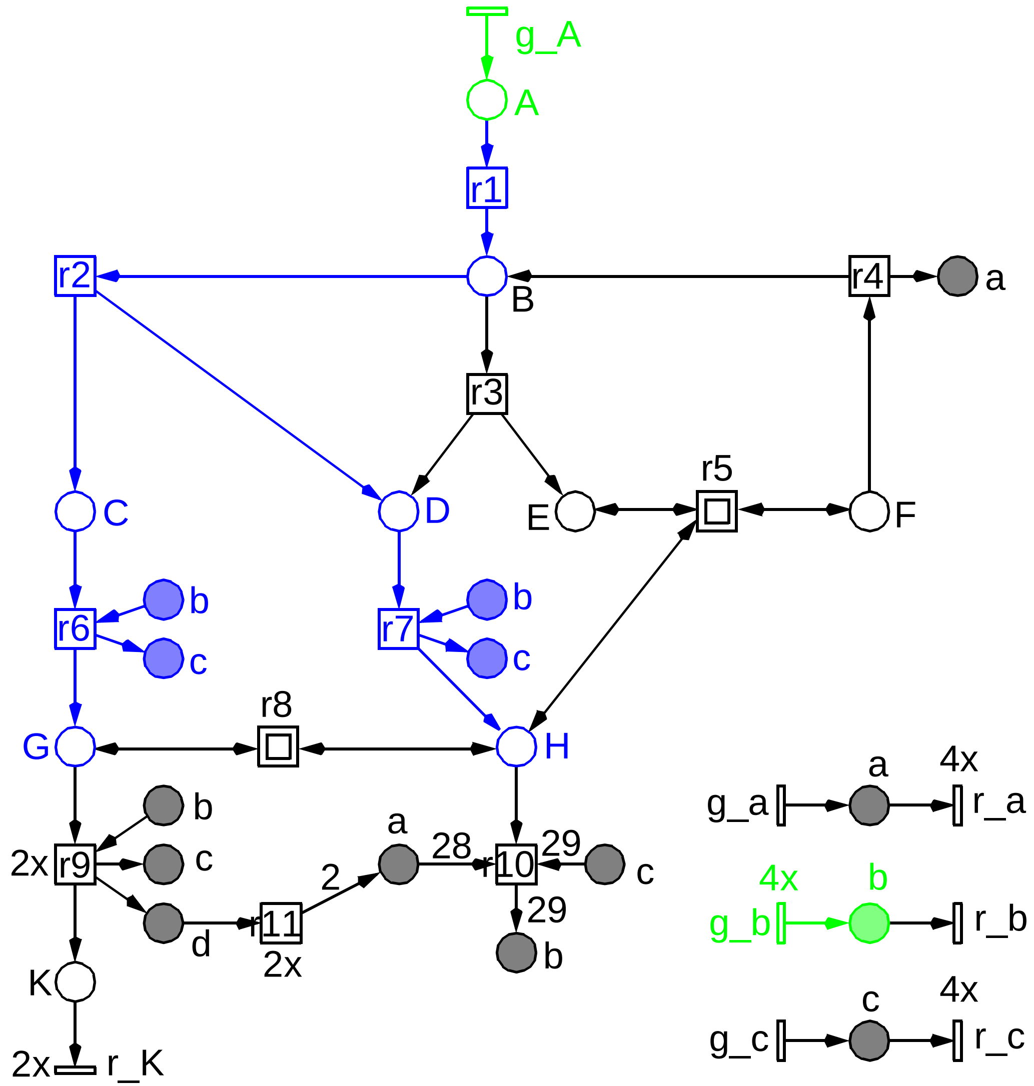

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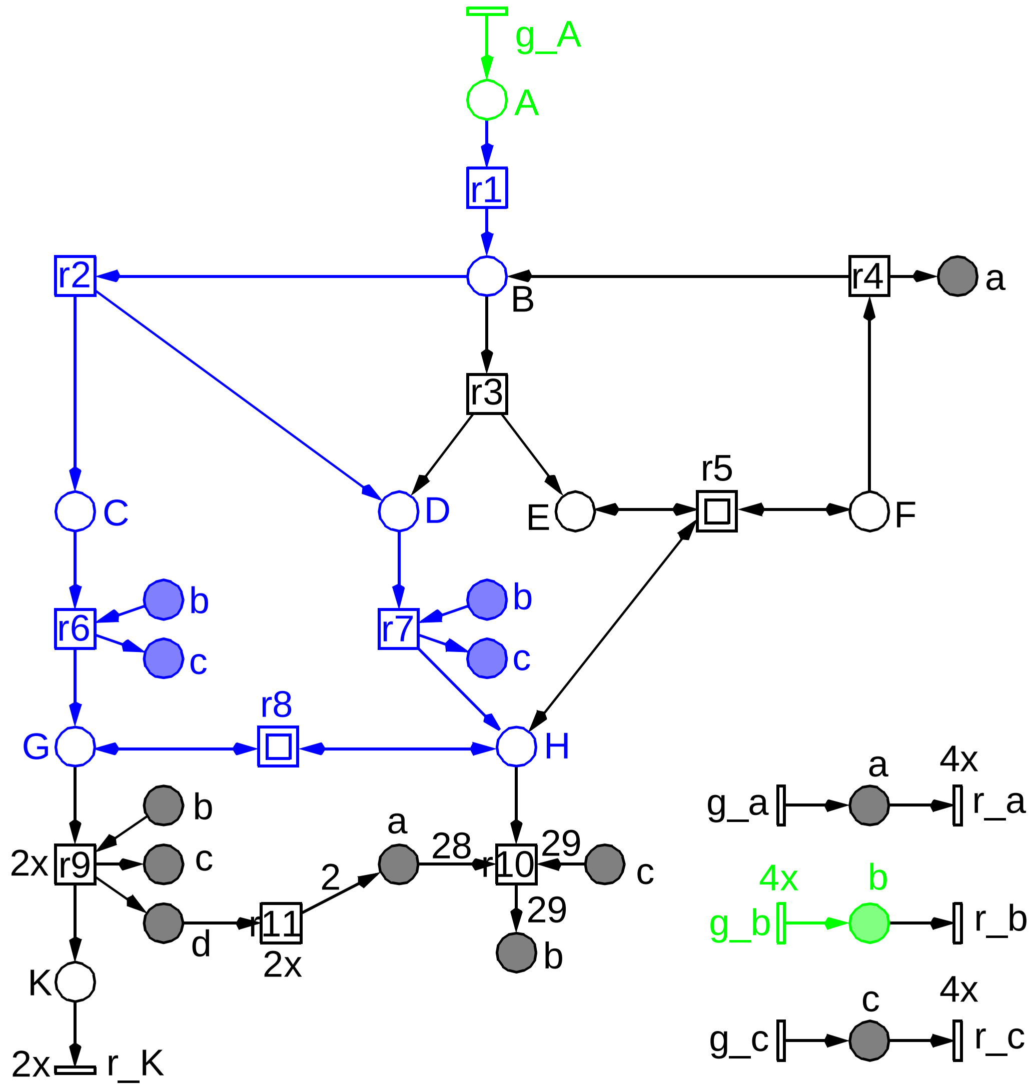

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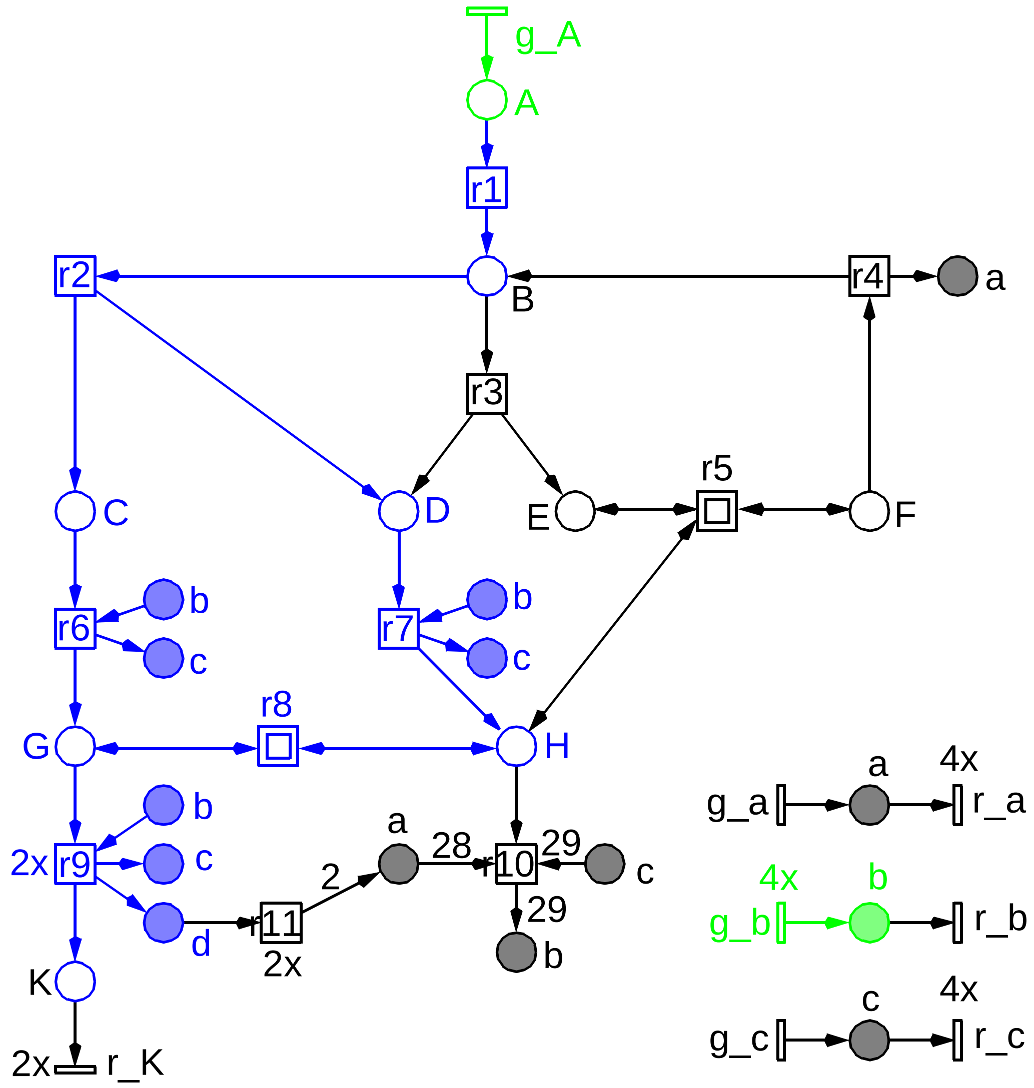

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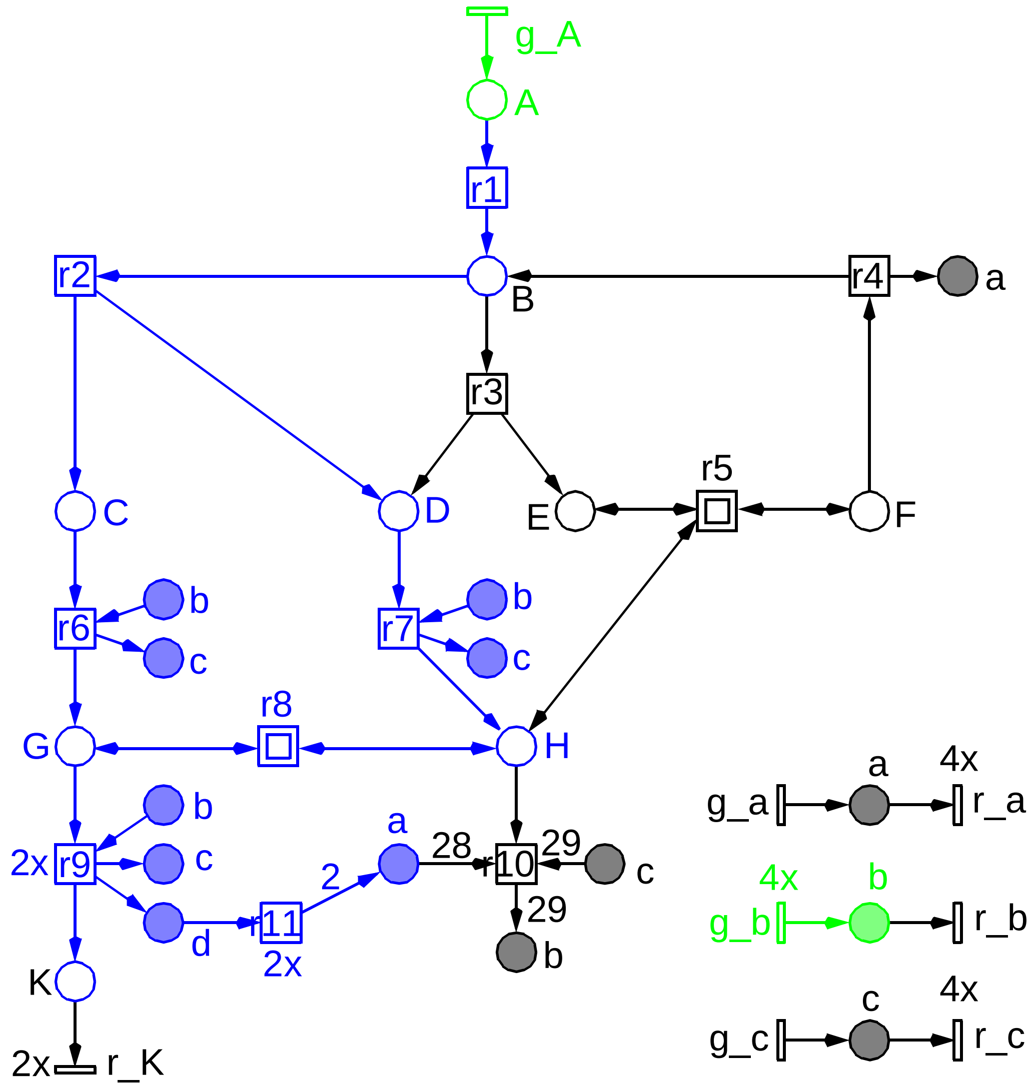

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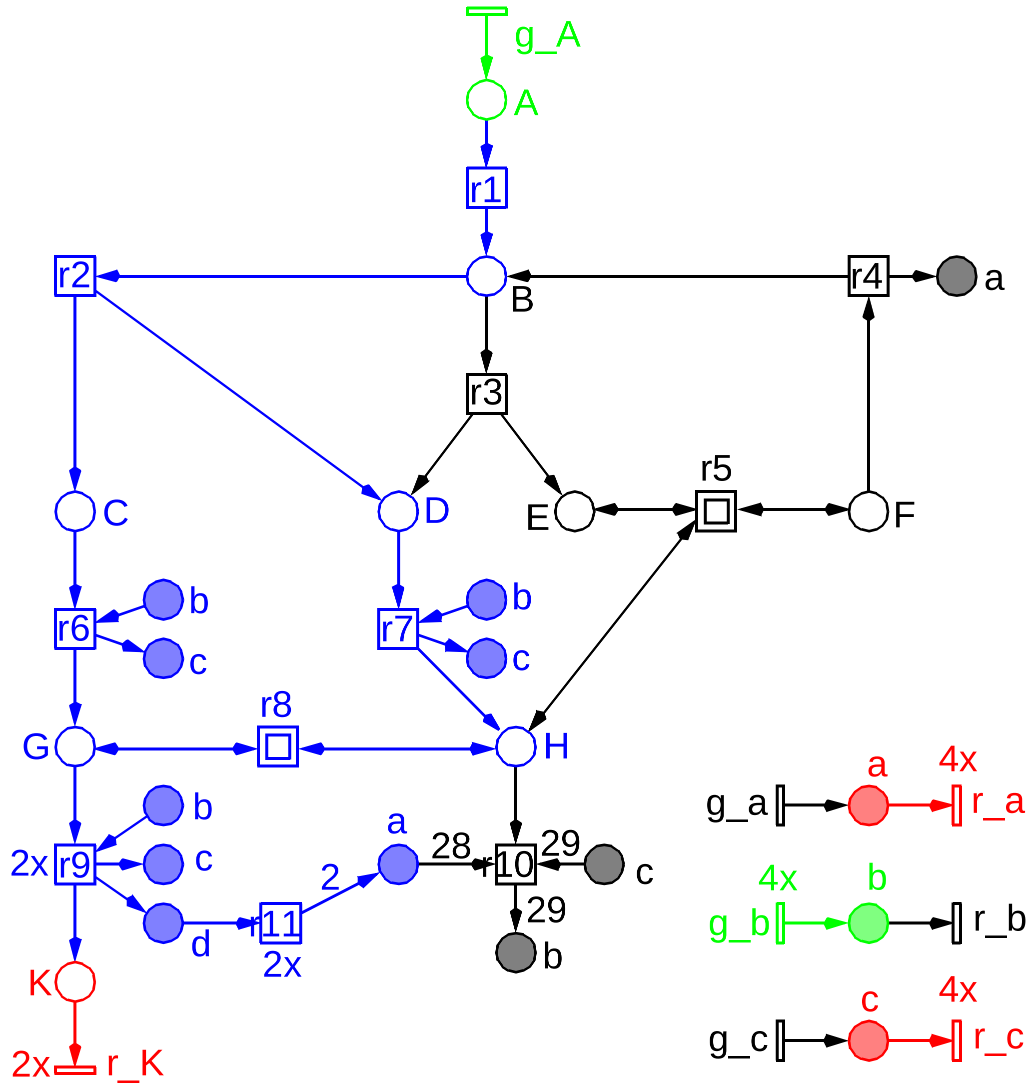

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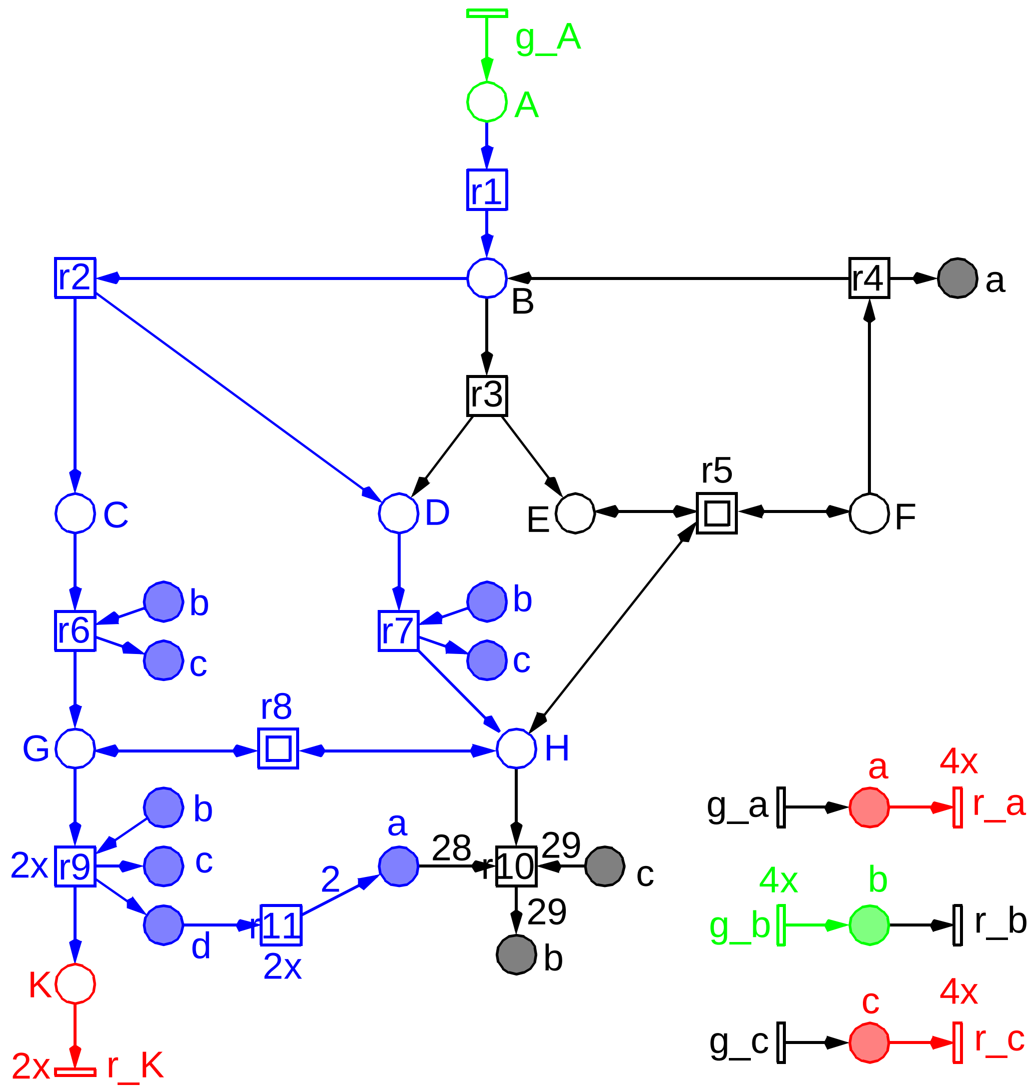

❑ sum equation

A + 4b -> 2K +4a + 4c

T-INVARIANTS, TWO INTERPRETATIONS

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

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

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

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

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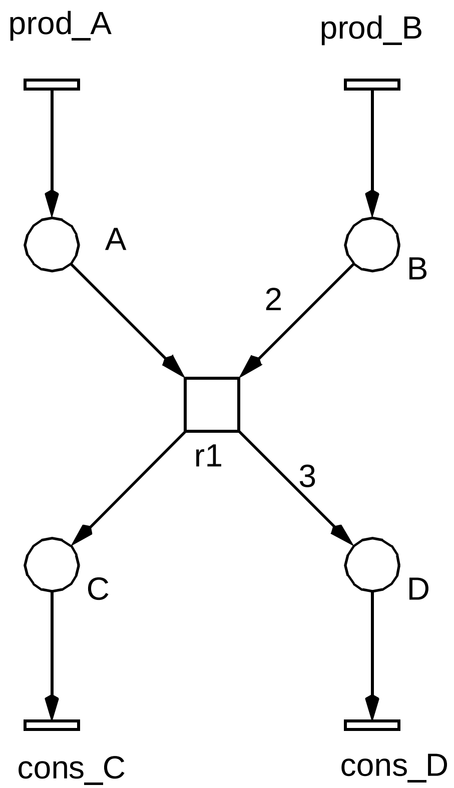
TRANSFORMATION, EX1

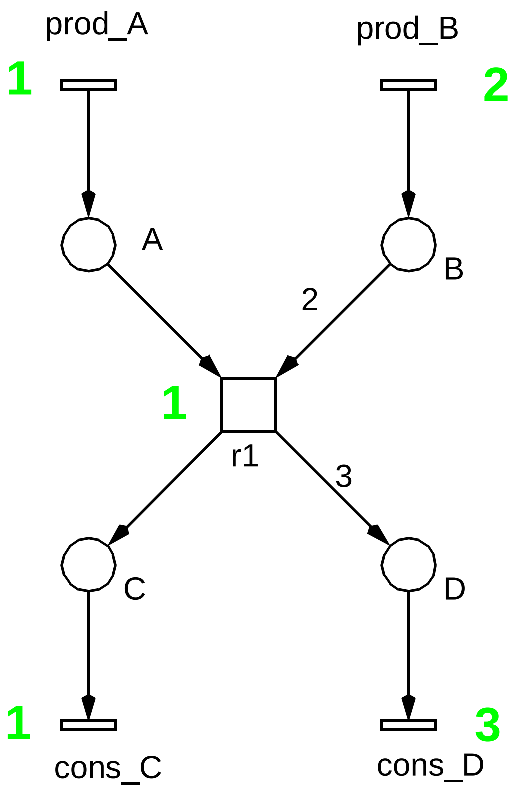


-> properties as time-less net

INA

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

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



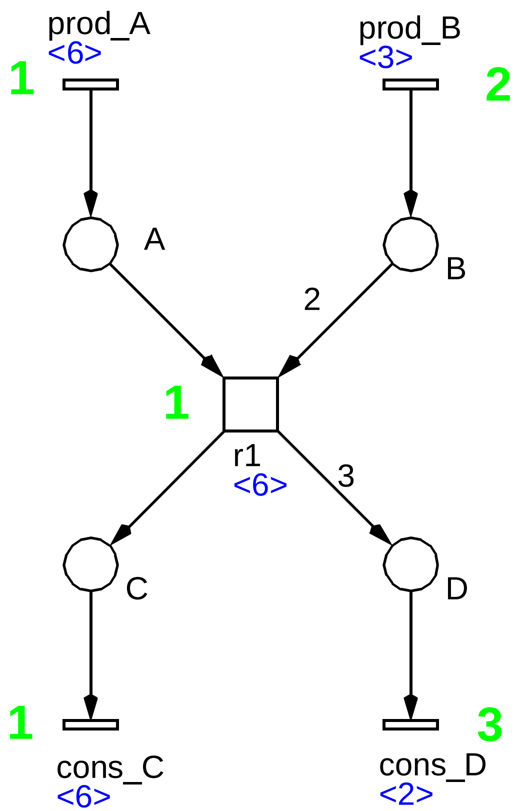
T-INVARIANT

-> properties as time-less net

INA

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

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



T-INVARIANT

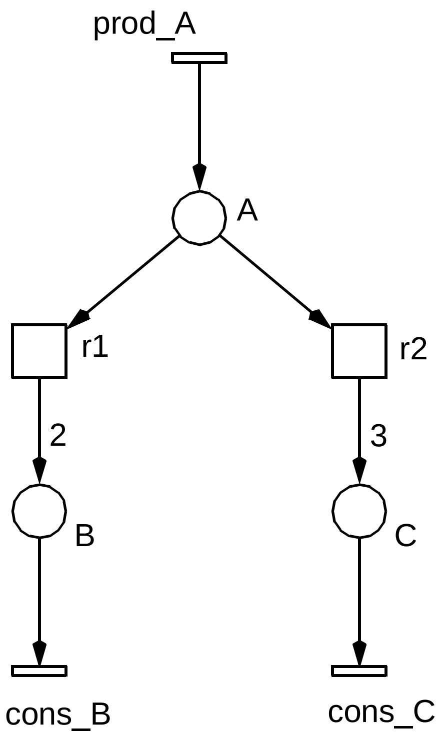
-> properties as time net

INA

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

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

TRANSFORMATION, EX2



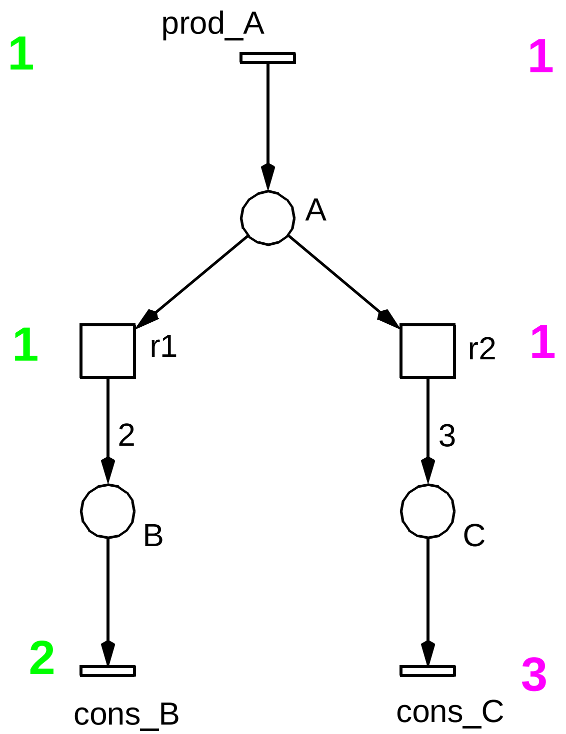
-> properties as time-less net

INA

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

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

TRANSFORMATION, EX2



T-INVARIANT 1

T-INVARIANT 2

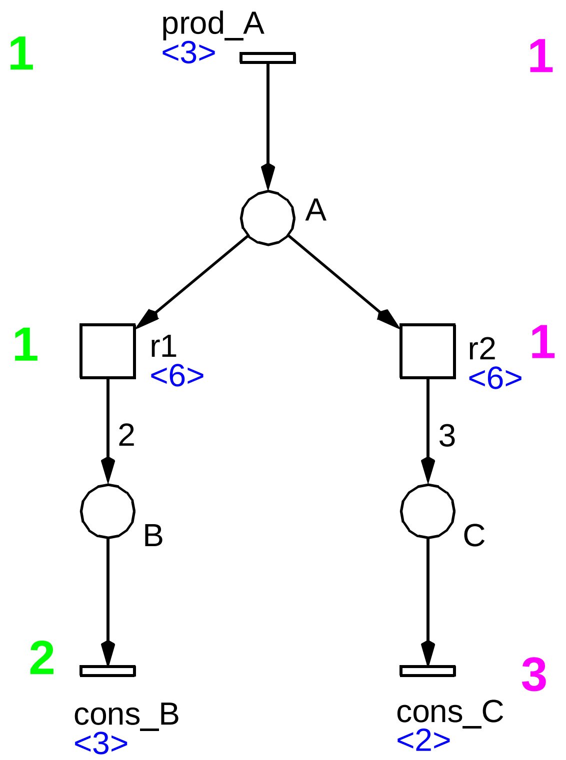
-> properties as time-less net

INA

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

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

TRANSFORMATION, EX2



T-INVARIANT 1

T-INVARIANT 2

-> properties as time net

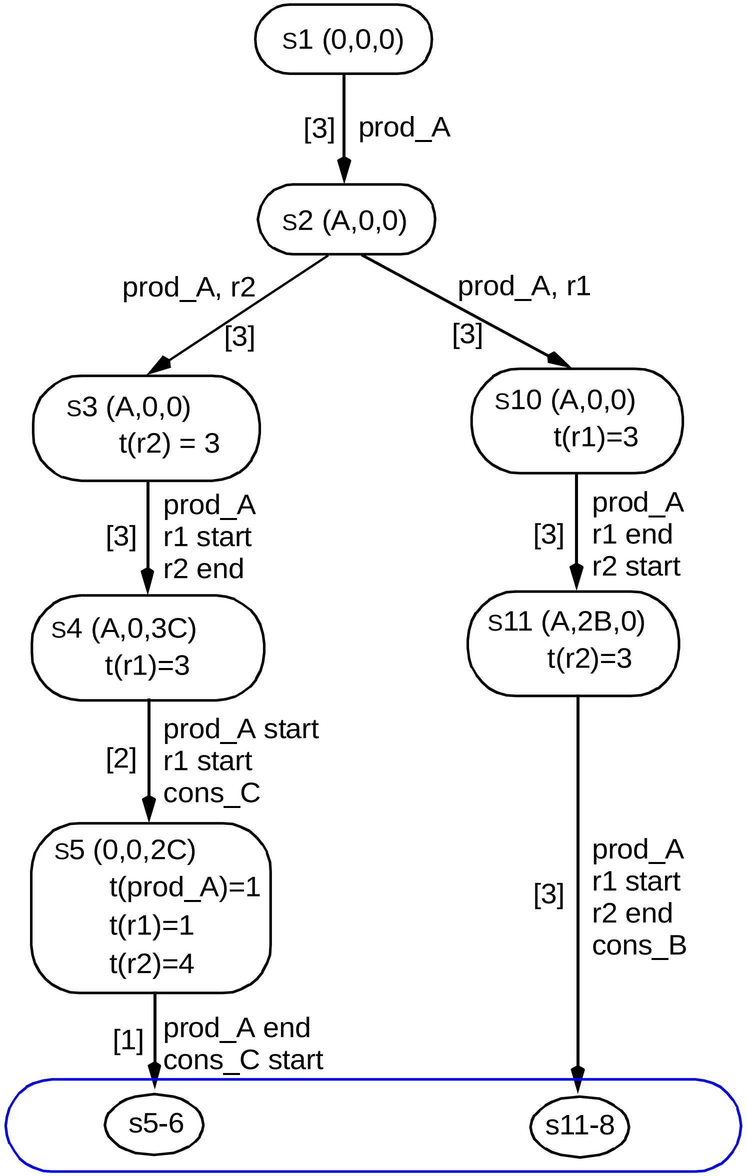
INA

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

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

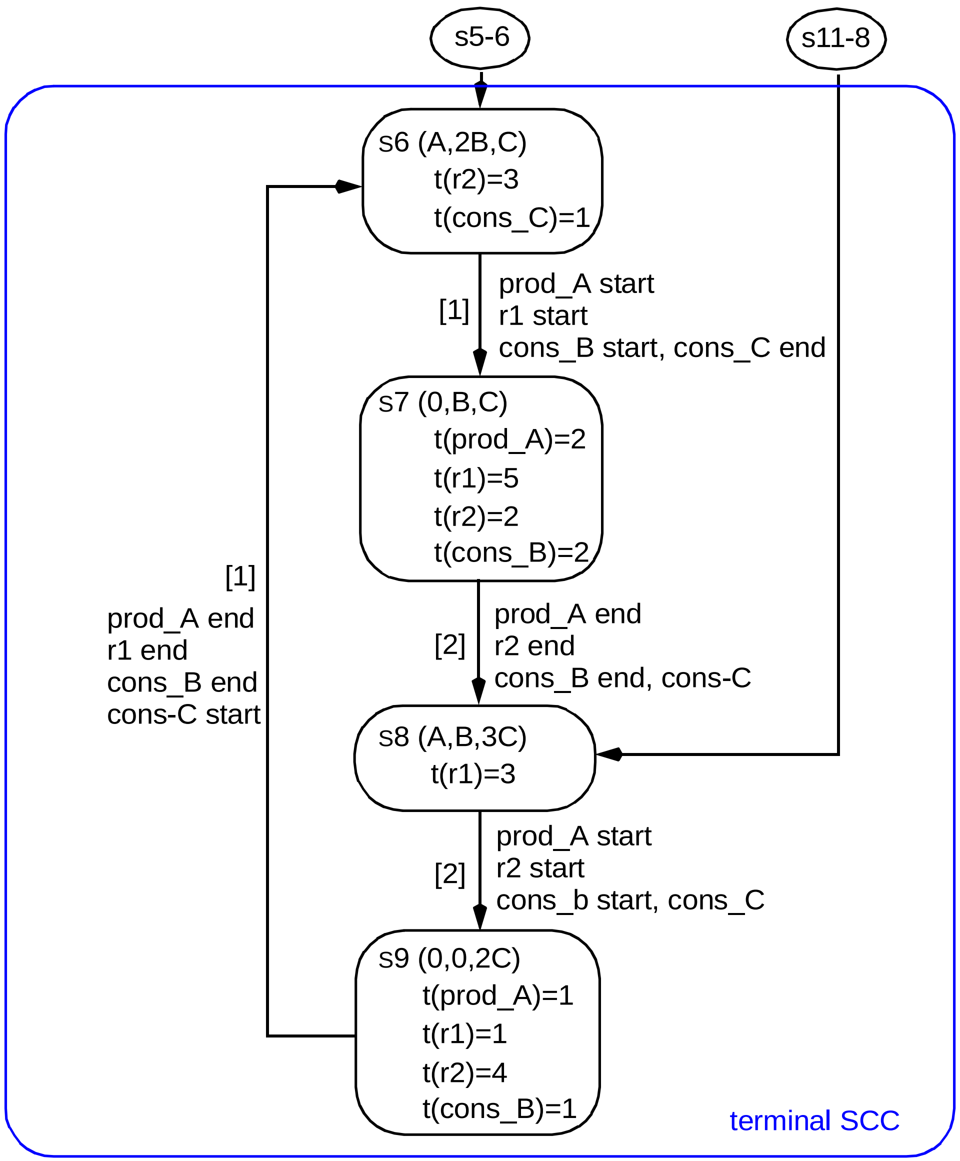
RG(Ex2), Part 1

- transient state



RG(Ex2), Part 2

- steady state



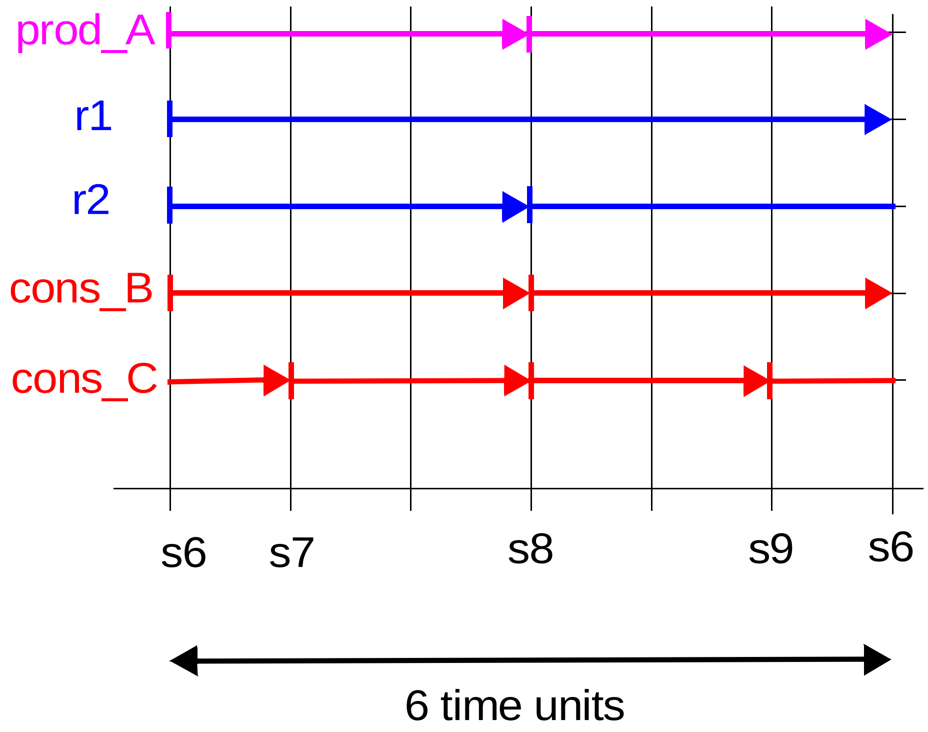
- **contains all transitions**
  - -> *always running*
  - -> *start / end*
    at different time points

- **contains all minimal T-invariants**

- **timing diagram**

- **relative transition firing rates**

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



EX1+ EX2, SUMMARY

- CTI,
  but not CPI

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

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

PN	—— time ——>	**D/I NET**
not BND REV LIVE		BND not REV LIVE

BUT, WHAT DO WE DO

- **if the timed model is bounded,
  but the reachability graph does not fit into memory ?**

- **if the timed model is (still) unbounded ?**

QUANTITATIVE ANALYSIS, QUESTIONS

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

initial marking / state

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

LOUCHKA

w is time-dependent realizable / not realizable

min/max time length of w

which time windows guarantee realizability

QUANTITATIVE ANALYSIS, QUESTIONS

interval time Petri net

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

initial marking / state

finite transition word *w*

$w \in T^*$

(LP)

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

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

w is time-dependent realizable / not realizable

min/max time length of *w*

which time windows guarantee realizability

COOPERATIONS / CASE STUDIES

- **Ina Koch, TFH, Bioinformatics**
  - -> *E. coli pathway*
  - -> *G1/S - phase in mammalian cells*
  - -> *yeast pheromone pathway*
- **Katrin Hafez, HUB**
  - -> *lipoprotein metabolism (liver)*
- **Björn Junker, MPI Golm/IPK Gatersleben**
  - -> *potato tuber*
- **David Gilbert, Univ. Glasgow, Bioinformatics Research Center**
  - -> *signal transduction networks (ERK/RKIP)*
- **Dennis Thieffry, Univ. Marseille, Institute of Developmental Biology**
  - -> *gene regulatory networks*

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* -> *timed Petri nets, continuous Petri nets*

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

THANKS !