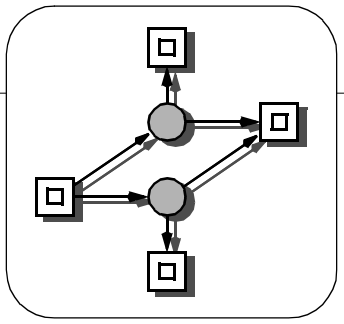


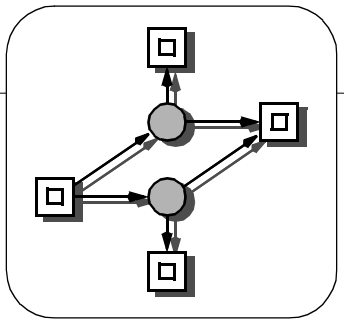
BIOPATHWAYS & PETRI NETS

MONIKA HEINER

BTU COTTBUS
COMPUTER SCIENCE

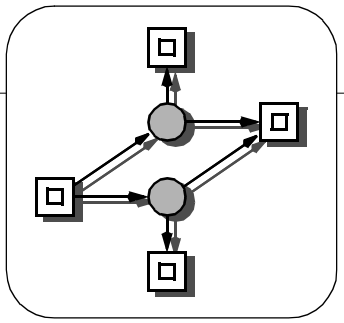
INA KOCH

TFH BERLIN
COMPUTATIONAL BIOLOGY



OUTLINE

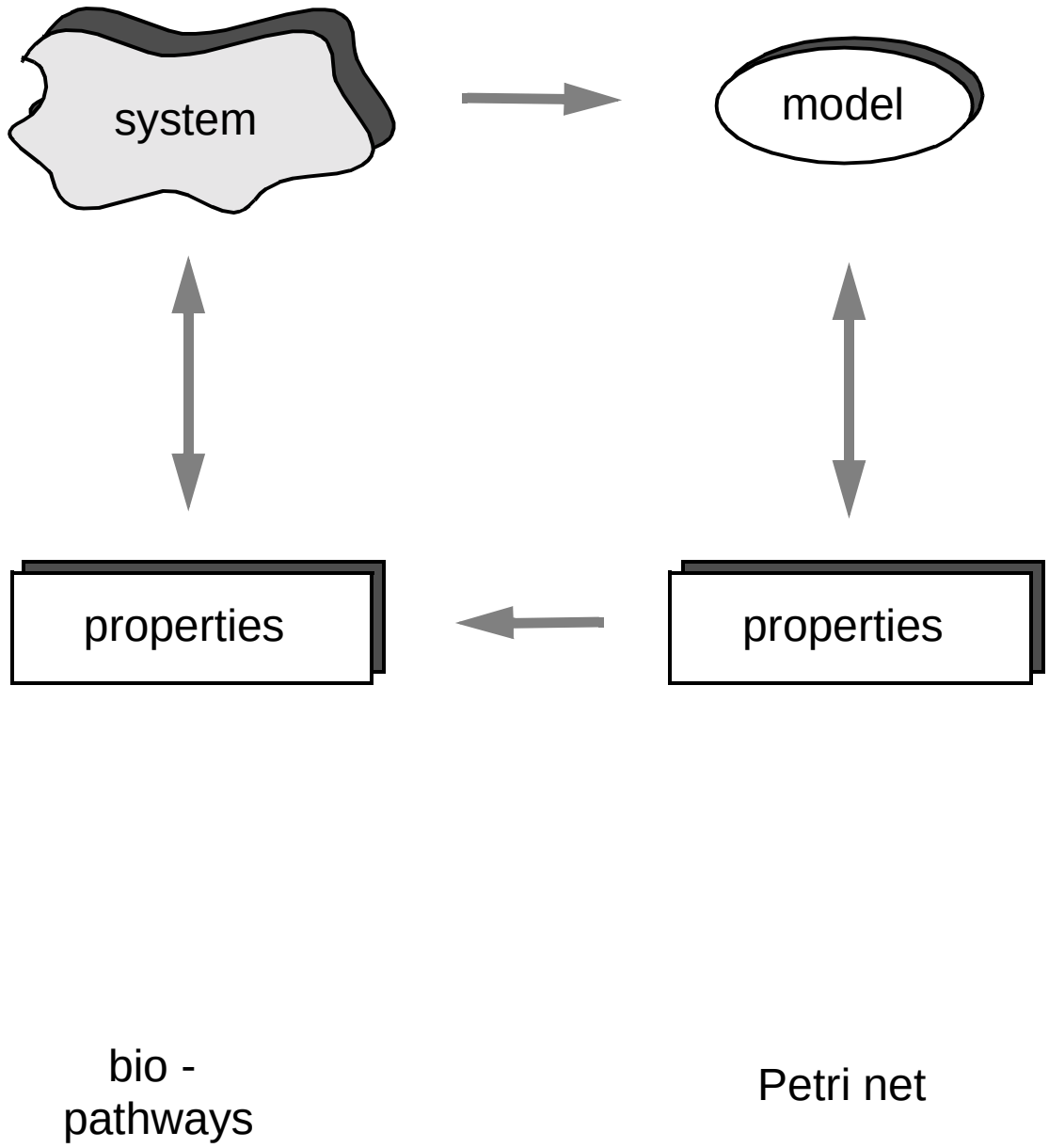
1. MOTIVATION
2. INTRODUCTION INTO (QUALITATIVE) PETRI NETS
3. APPLICATION TO APOPTOTIC PATHWAYS -> MODELLING & ANIMATION
4. MODEL ANALYSIS -> QUALITATIVE & QUANTITATIV
5. SUMMARY
6. OUTLOOK

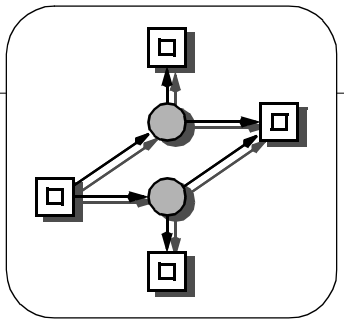


1.

MOTIVATION

MODEL- BASED SYSTEM ENGINEERING





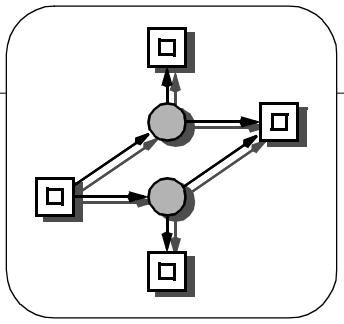
BIOPATHWAYS

EXAMPLES

- metabolic pathways
- signal transduction cascades
- gene regulation
- . . .

BASIC PROPERTIES

- very complex structures
- causal interplay of basic actions (sequence, branching, concurrency)



REPRESENTATIONS, OBJECTIVES

- readability

  -> understanding

- animation

  -> experience

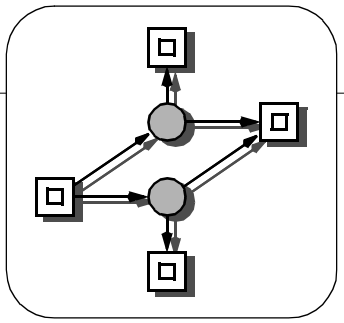
- validation

  -> consistency checks

- analysis

  -> behaviour prediction
  (qualitative / quantitative)

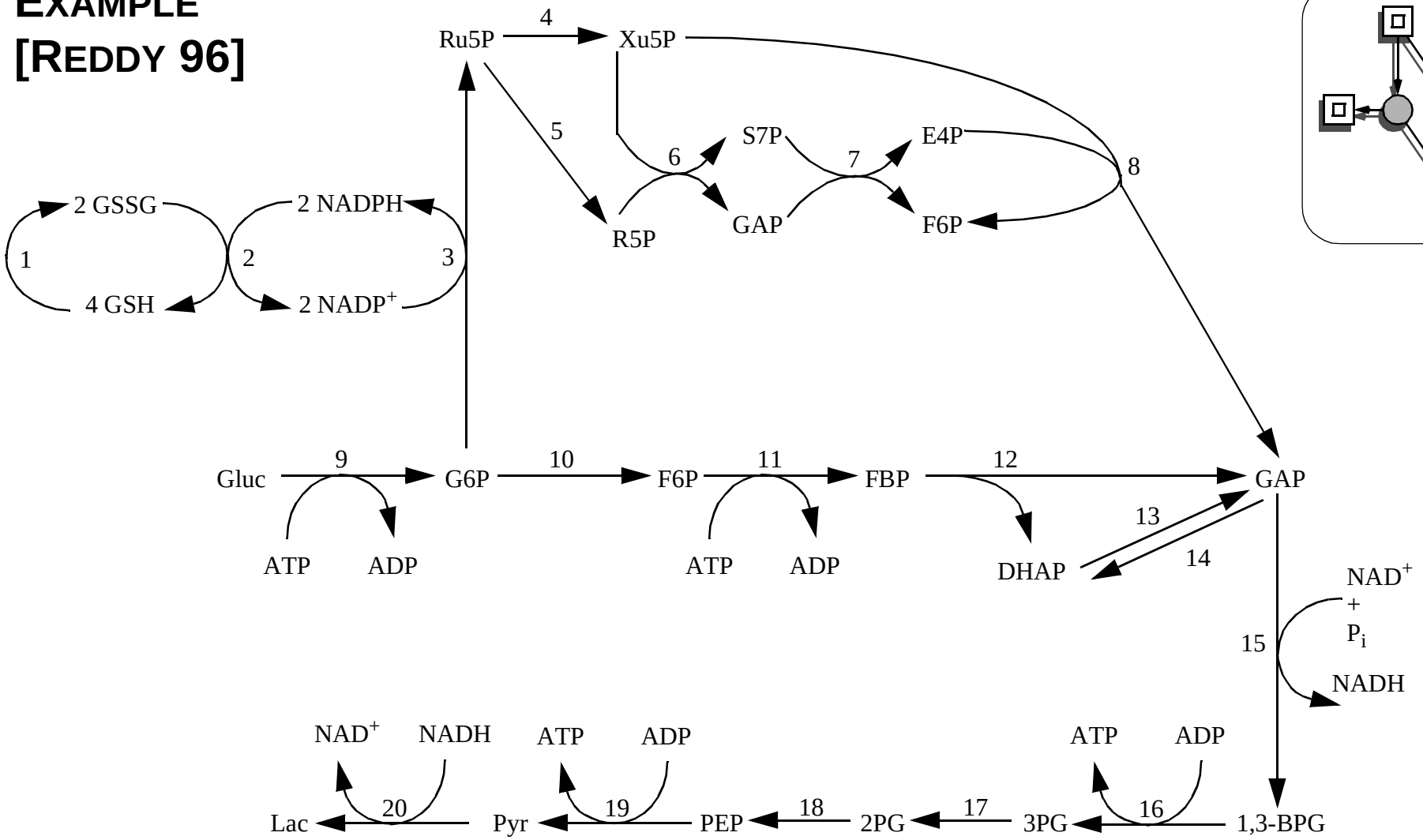
=>> ***How many representations do we really need?***



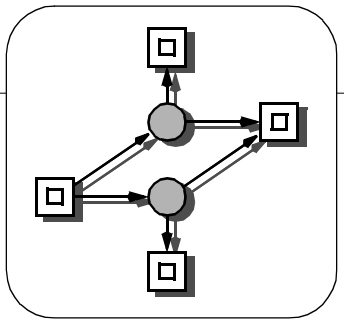
2.

INTRODUCTION INTO (QUALITATIVE) PETRI NETS

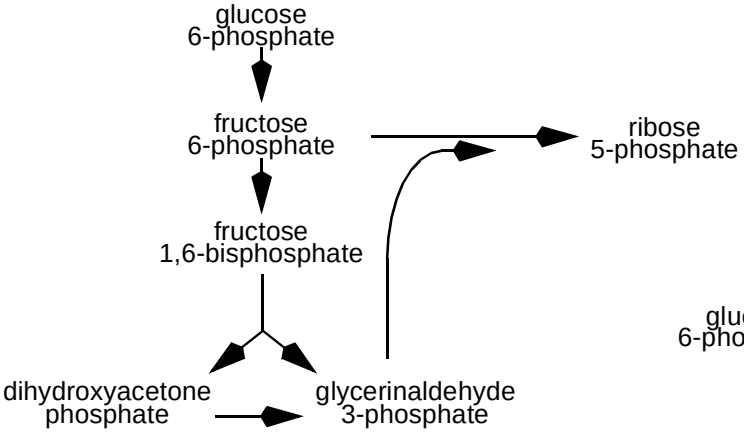
EXAMPLE [REDDY 96]



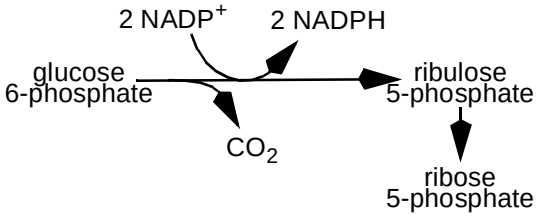
[Reddy 96] Reddy, V. N.; Liebman, M. N.; Mavrovouniotis, M. L.: Qualitative Analysis of Biochemical Reaction Systems; Computers in Biology and Medicine 26(96), 9-24.



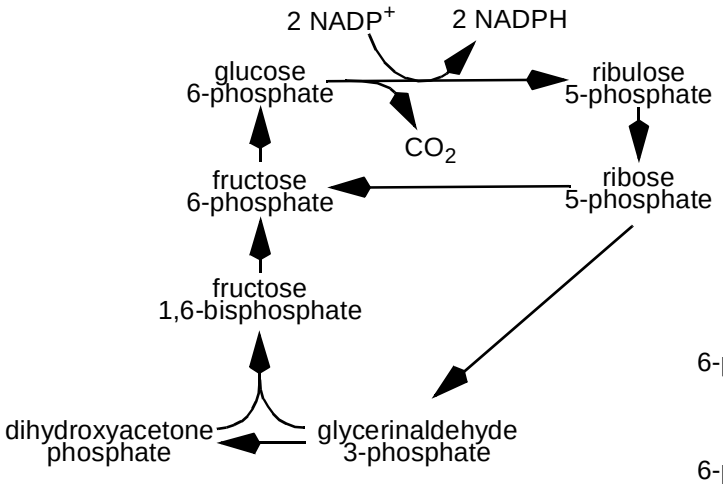
EXAMPLE
PENTOSE PHOSPHATE CYCLE



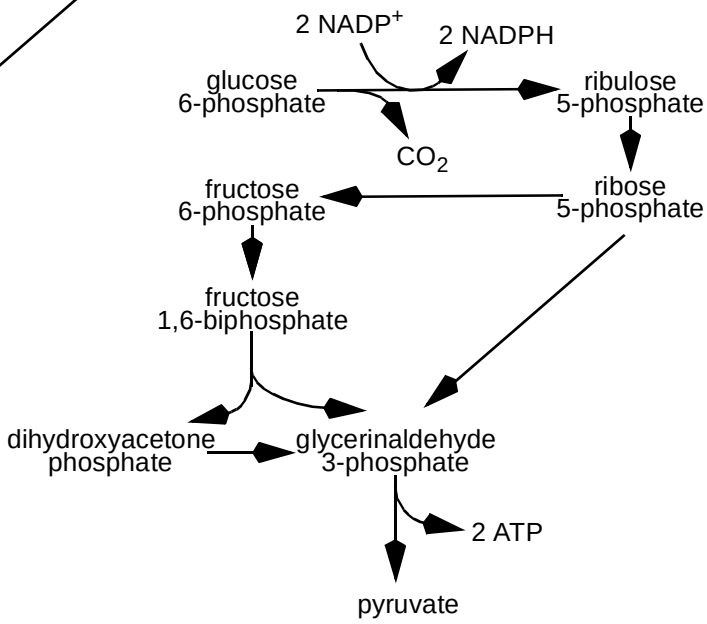
1. possibility



2. possibility

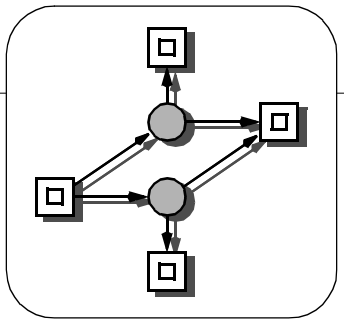


3. possibility



4. possibility

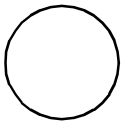
Stryer, L.:
Biochemistry;
Freeman, New York, NY, 1995, p. 450.



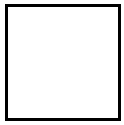
PETRI NETS, BASICS 1

(1) NODES

places



transitions



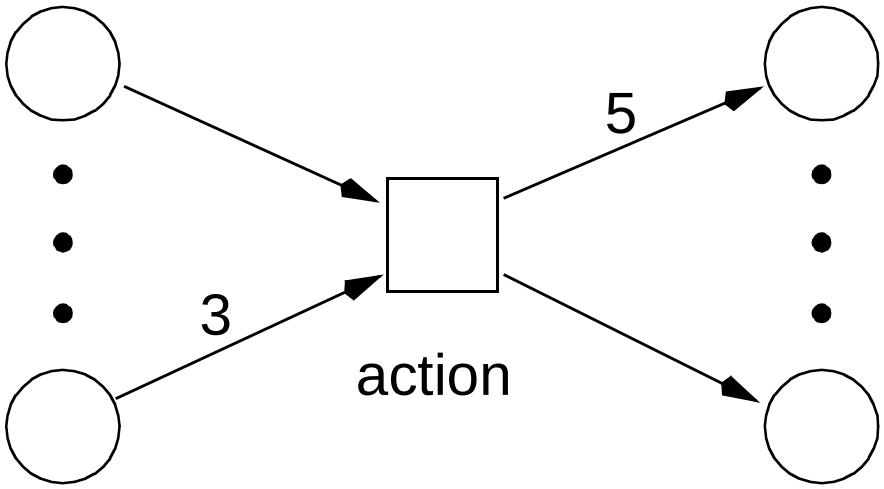
“passive elements”
conditions
states
“*chem. compounds*”

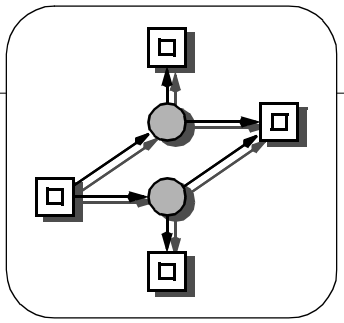
“active elements”
events
actions
“*chem. reactions*”

(2) ARCS

preconditions

postconditions

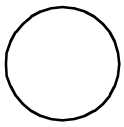




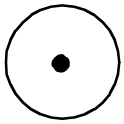
PETRI NETS, BASICS 2

(3) TOKENS

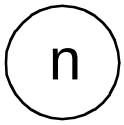
(moving objects,
vehicles, work pieces, control flow pointer,
dates,..., *units of substances (e. g. Mol)*, ...)



condition is not fulfilled



condition is (one times) fulfilled



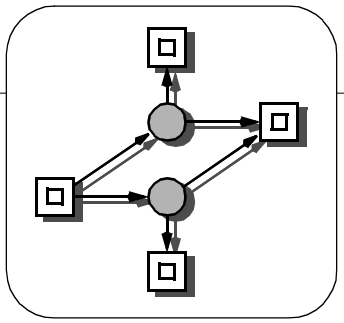
condition is n times fulfilled

(4) MARKING

(system state, *substance distribution*)

How many tokens are on each place?

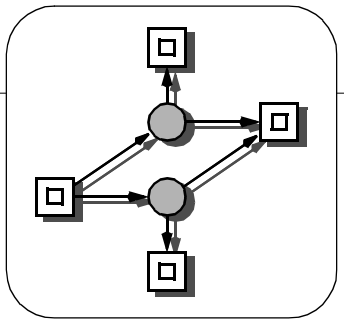
-> initial marking



PETRI NETS, BASICS 3

(5) FLOW OF TOKENS

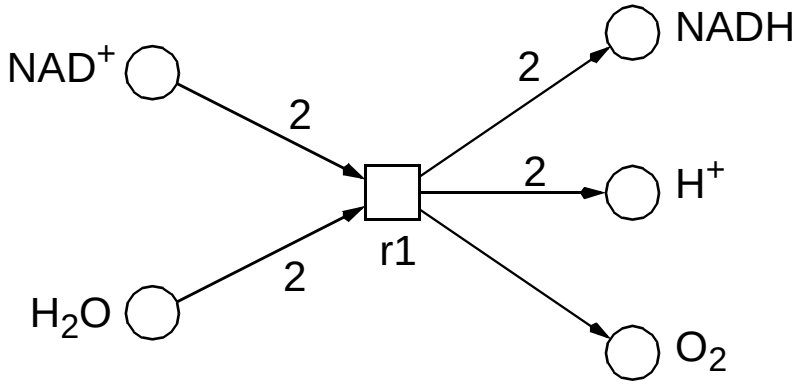
- an action ***may*** happen, if
  - -> all preconditions are fulfilled (corresponding to the arc weights);
- **if** an action happens, **then**
  - -> tokens are removed from all preconditions (corresponding to the arc weights), and
  - -> tokens are added to all postconditions (corresponding to the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



EXAMPLES, REACTION EQUATIONS

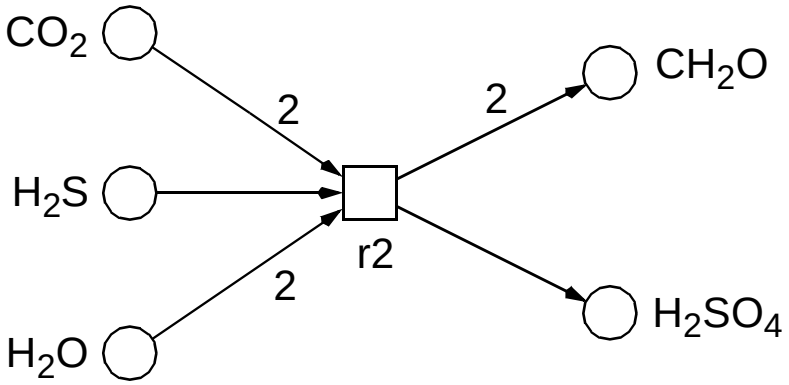
- **FOR LIGHT-INDUCED PHOSPHORYLATION**

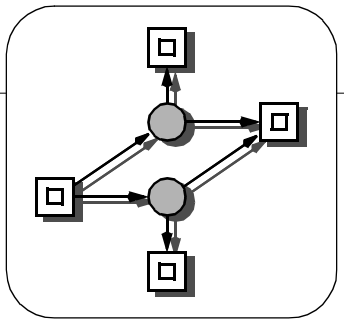
$$2\ NAD^+ + 2\ H_2O \rightarrow 2\ NADH + 2\ H^+ + O_2$$



- **FROM THE PHOTOSYNTHESIS**

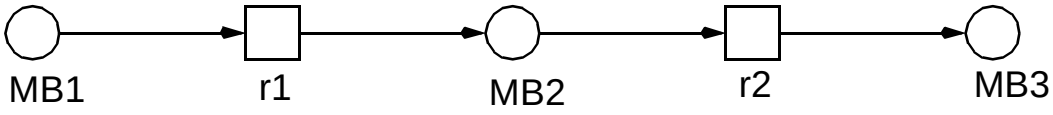
$$2\ CO_2 + H_2S + 2\ H_2O \rightarrow 2\ (CH_2O) + H_2SO_4$$



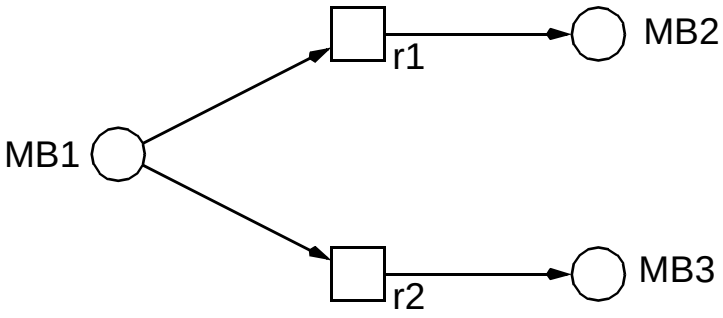


TYPICAL BASIC STRUCTURES 1

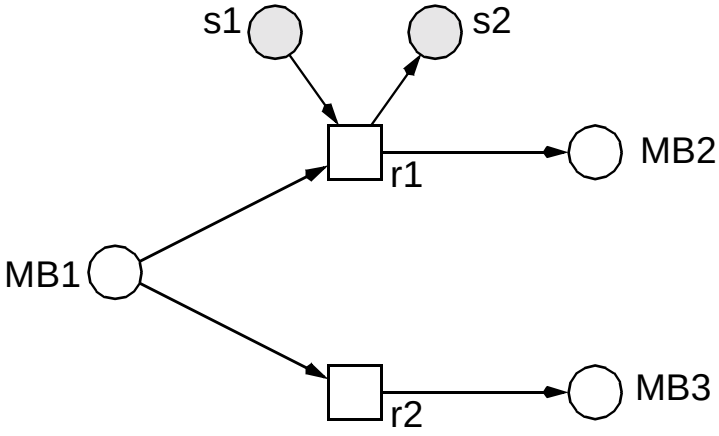
❑ CHAIN OF REACTIONS



❑ (FREE-CHOICE) BRANCHING

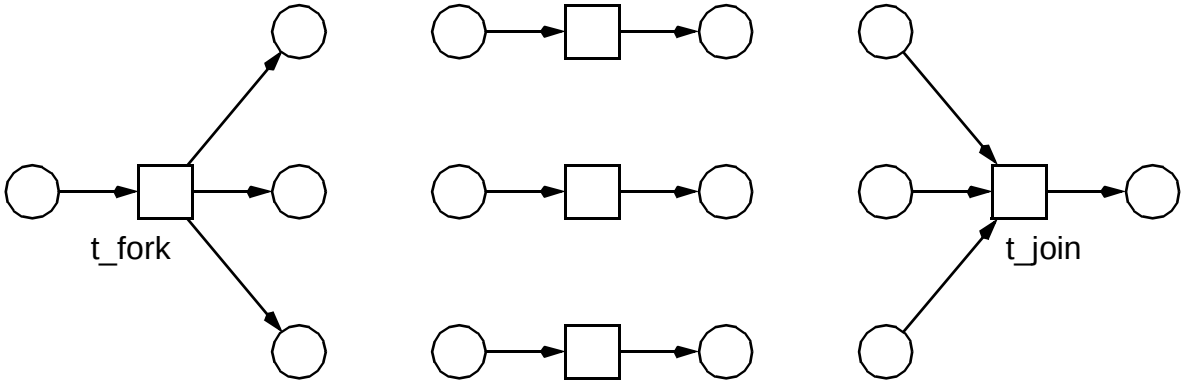


❑ BRANCHING WITH SIDE CONDITION

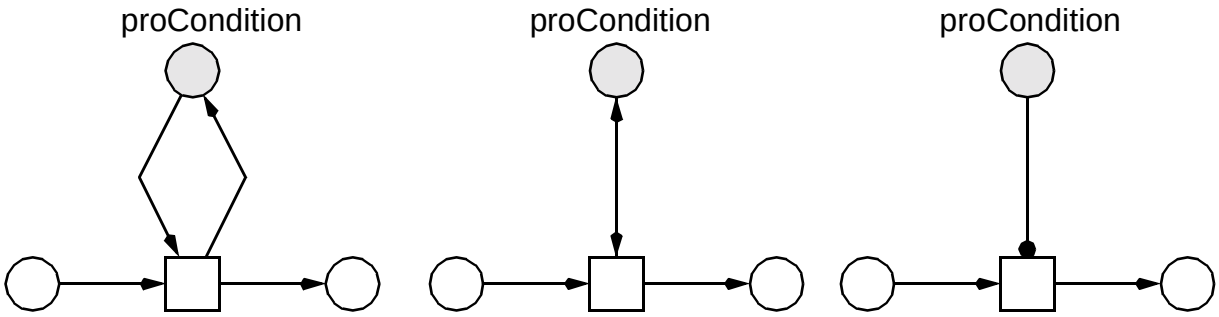


TYPICAL BASIC STRUCTURES 2

❑ CONCURRENCY

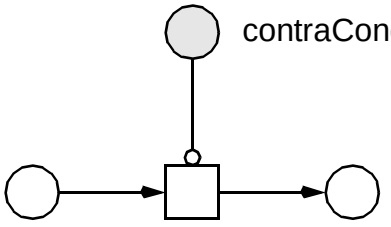


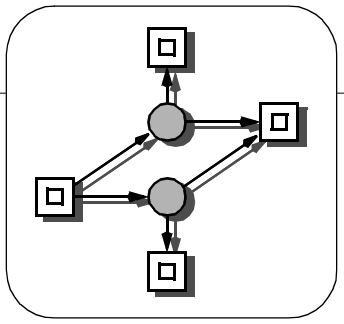
❑ READ ARCS



❑ INHIBITOR ARCS

BUT: CAUTION !





METABOLIC PETRI NETS 1

(1) PLACES

-> involved substances / chem. compounds

- ❑ substrates (boundary places),

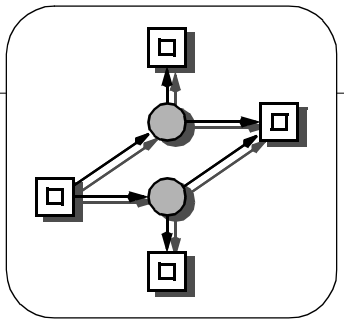
input substrat output substrat

e. g. glucose, lactate;

- ❑ metabolites,
  e. g. glucose 6-phosphate

- ❑ side conditions for reactions,
  e. g. electron carrier,
  phosphate carrier;

- ❑ enzymes, if any

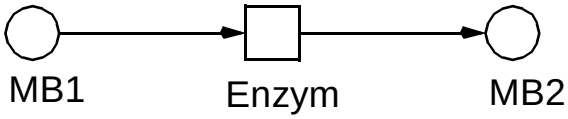


METABOLIC PETRI NETS 2

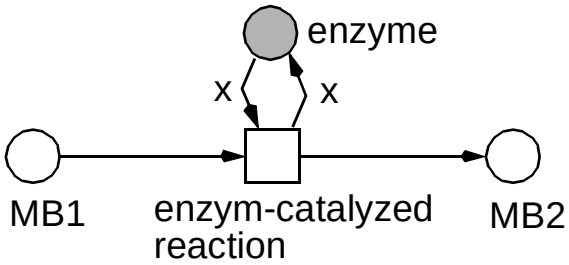
(2) TRANSITIONS

- spontaneous reactions
- enzyme-catalyzed reactions, two ways of modelling:

without enzyme concentration

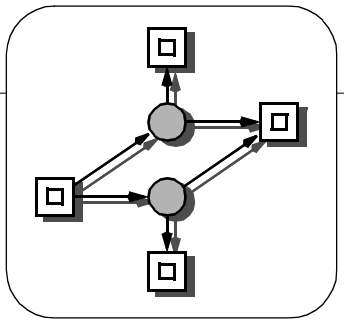


with enzyme concentration x



x - amount of enzyme units required by the reaction

- transport steps, if any -> inhomogeneous substance distribution;



METABOLIC PETRI NETS 3

(3) ARC INSCRIPTIONS

-> amount of units of the substances involved in the reaction

(4) AMOUNT OF TOKENS

-> amount of available units of substances

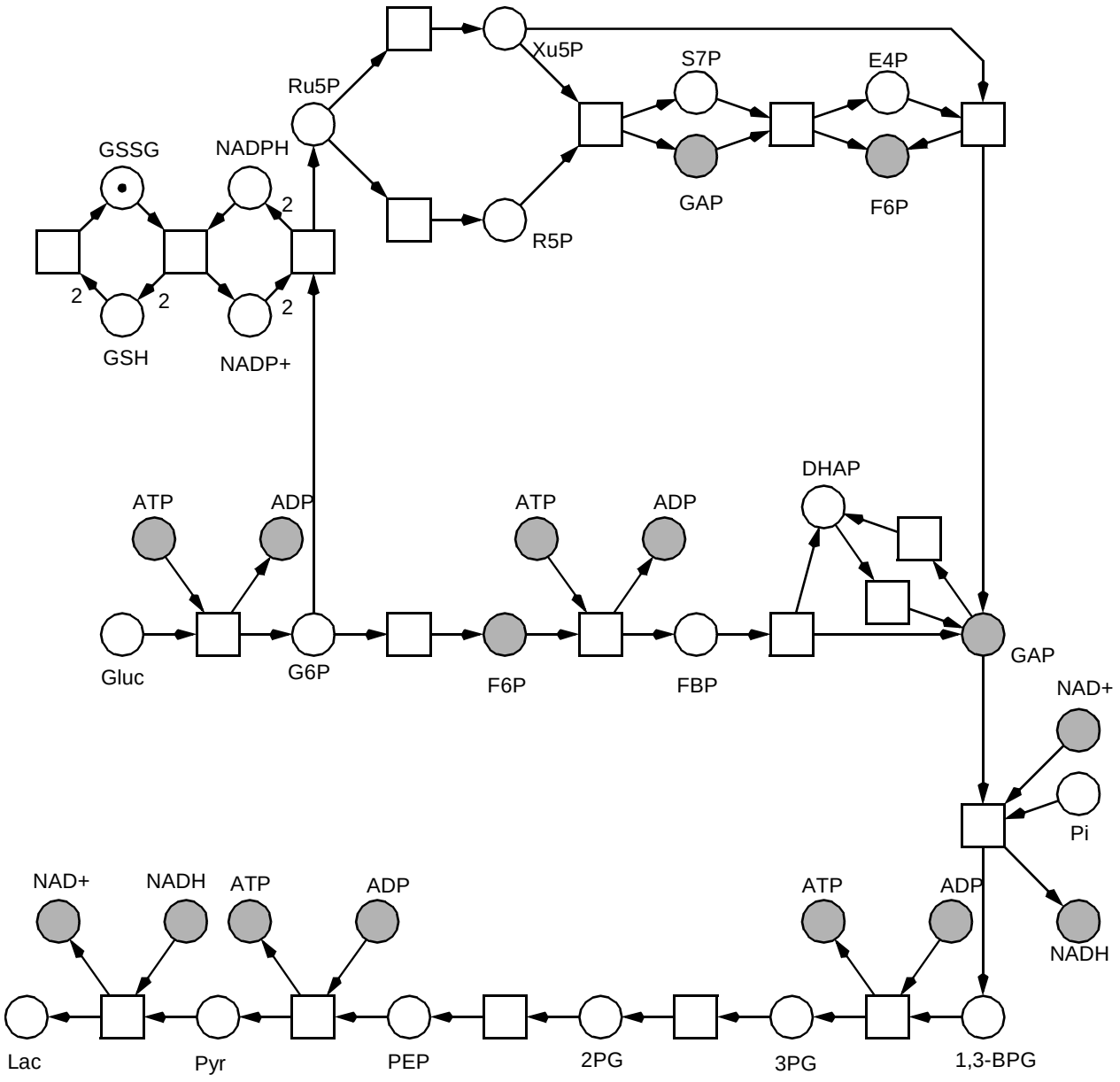
(5) INITIAL MARKING

-> initial substance distribution

Σ METABOLIC PETRI NET (MPN):

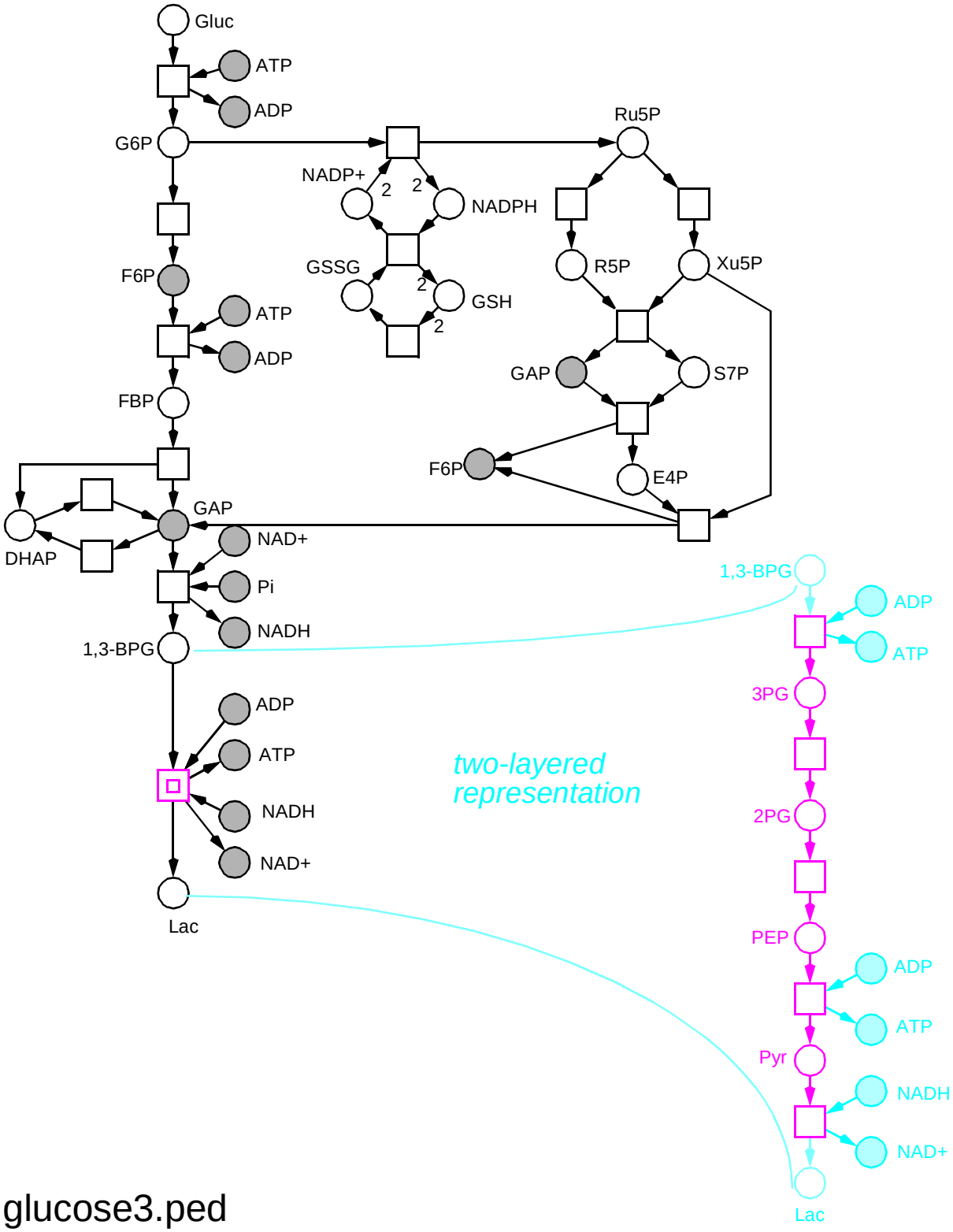
set of all paths
from the input to the output substrates
respecting the stoichiometric relations

EXAMPLE [REDDY 96] AS PETRI NET, VERSION 1

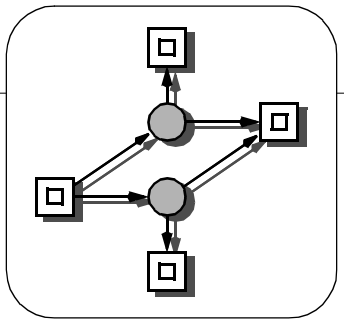


glucose1.ped

EXAMPLE [REDDY 96] AS PETRI NET, VERSION 3



glucose3.ped

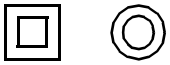


EXTENSIONS, SUMMARY

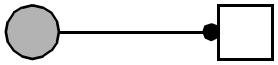
SYNTACTIC SUGAR

- logical nodes
  -> connectors

- hierarchies
  -> different levels of abstraction



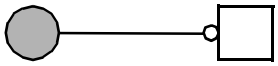
- read arcs
  -> pro-conditions

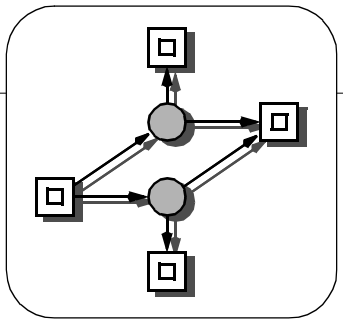


MODELLING POWER

- inhibitor arcs

  -> contra-conditions



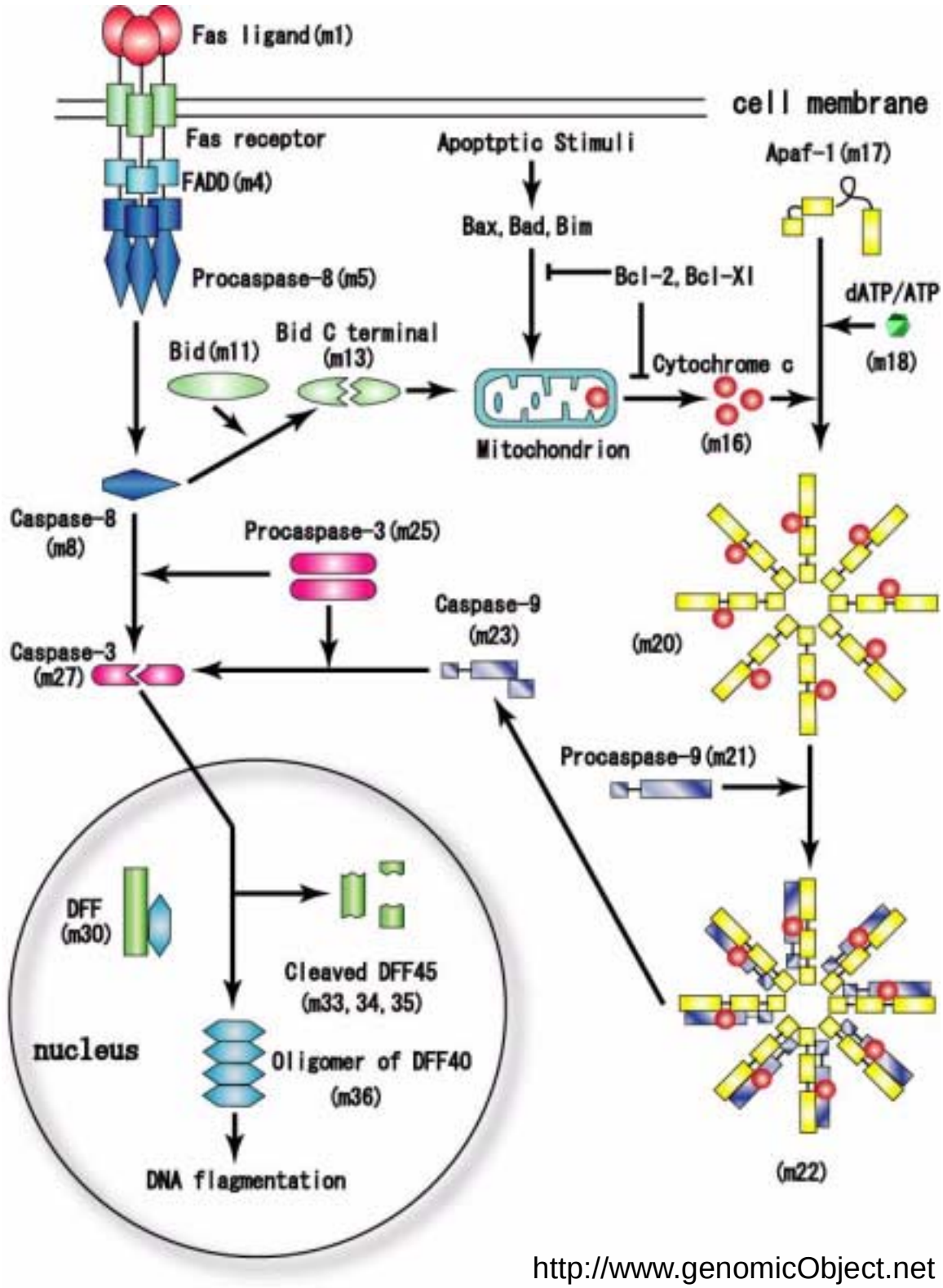


3.

APPLICATION TO APOPTOTIC PATHWAYS

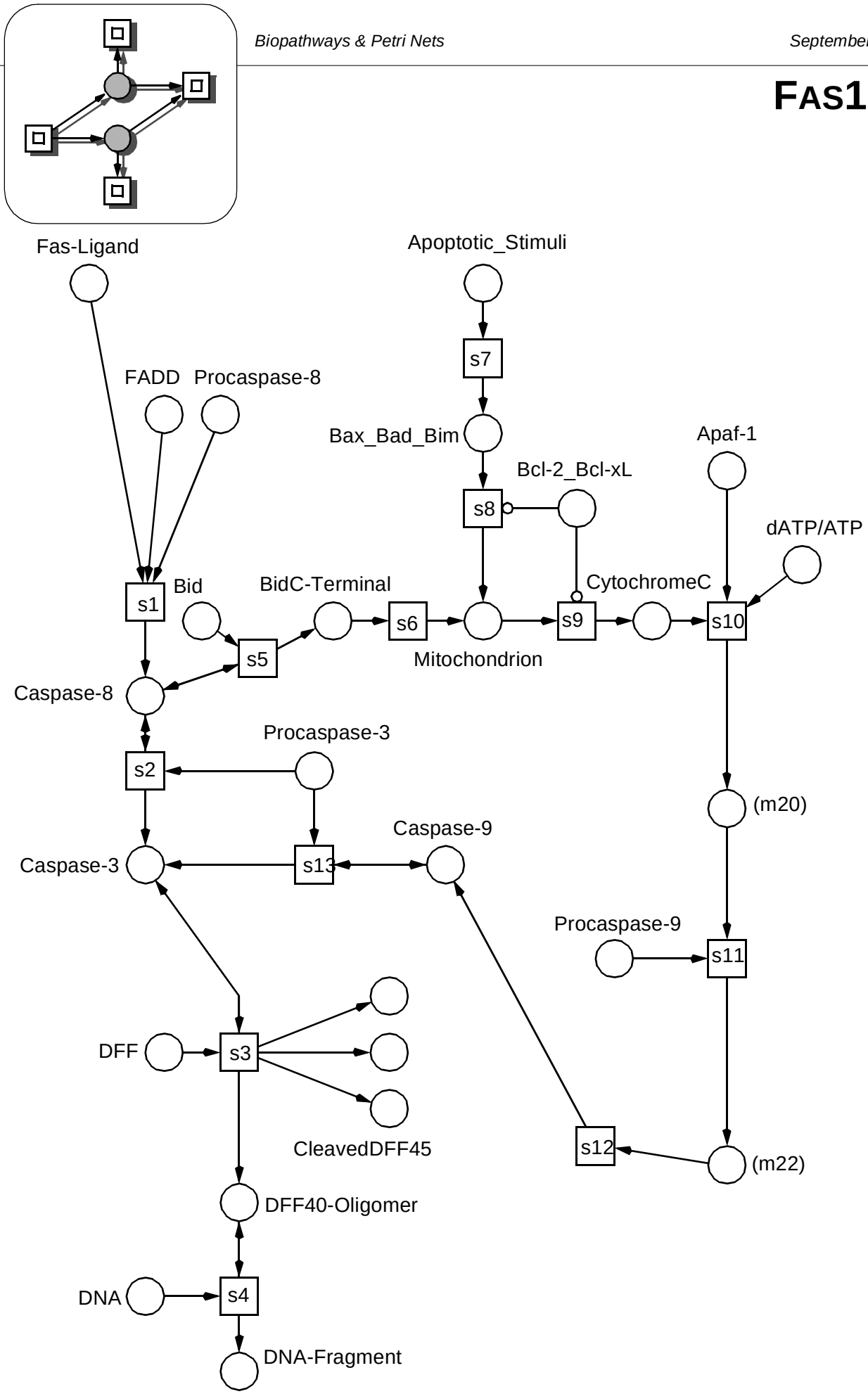
-> MODELLING & ANIMATION

APOPTOSIS, TWO BASIC PATHWAYS

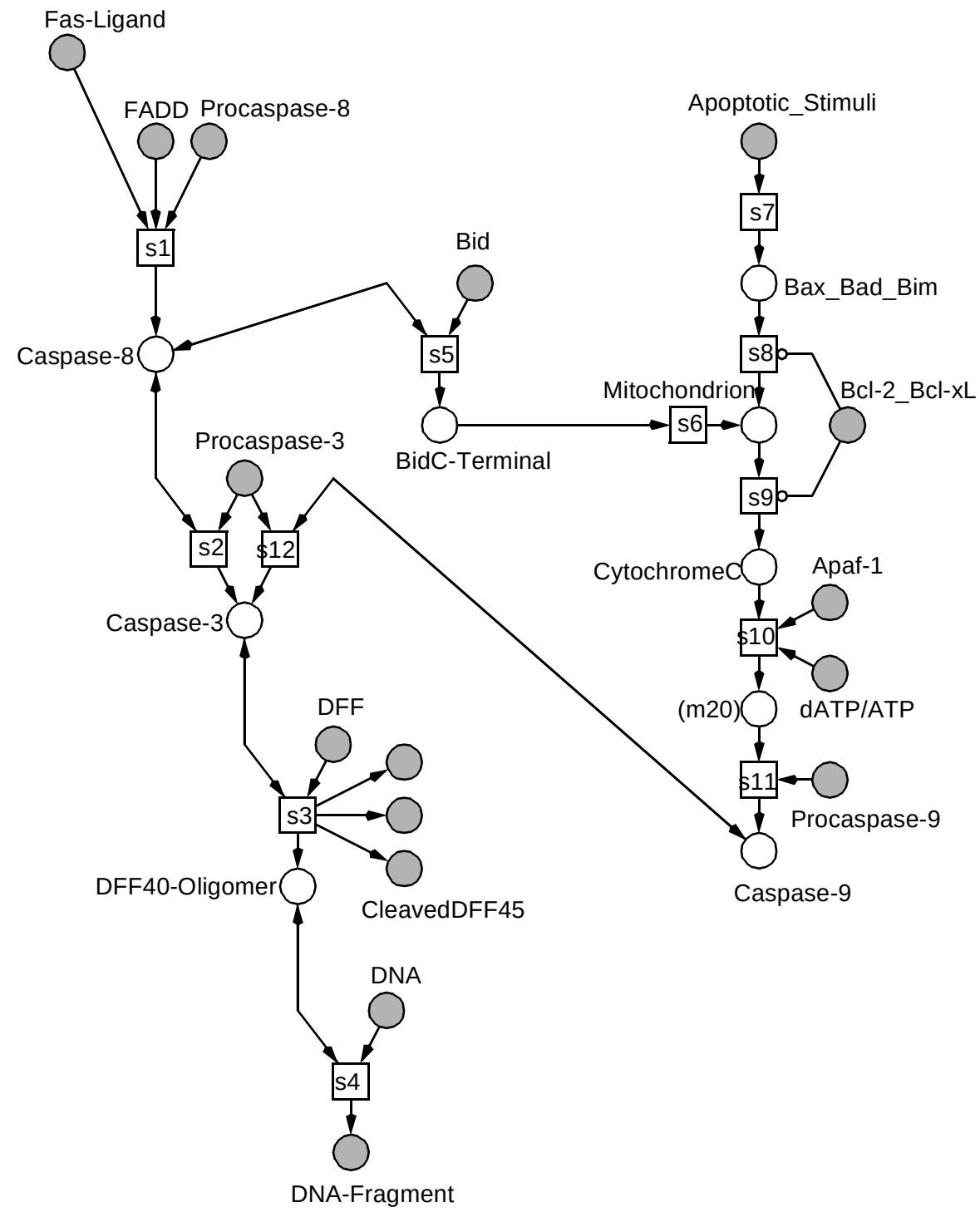


http://www.genomicObject.net

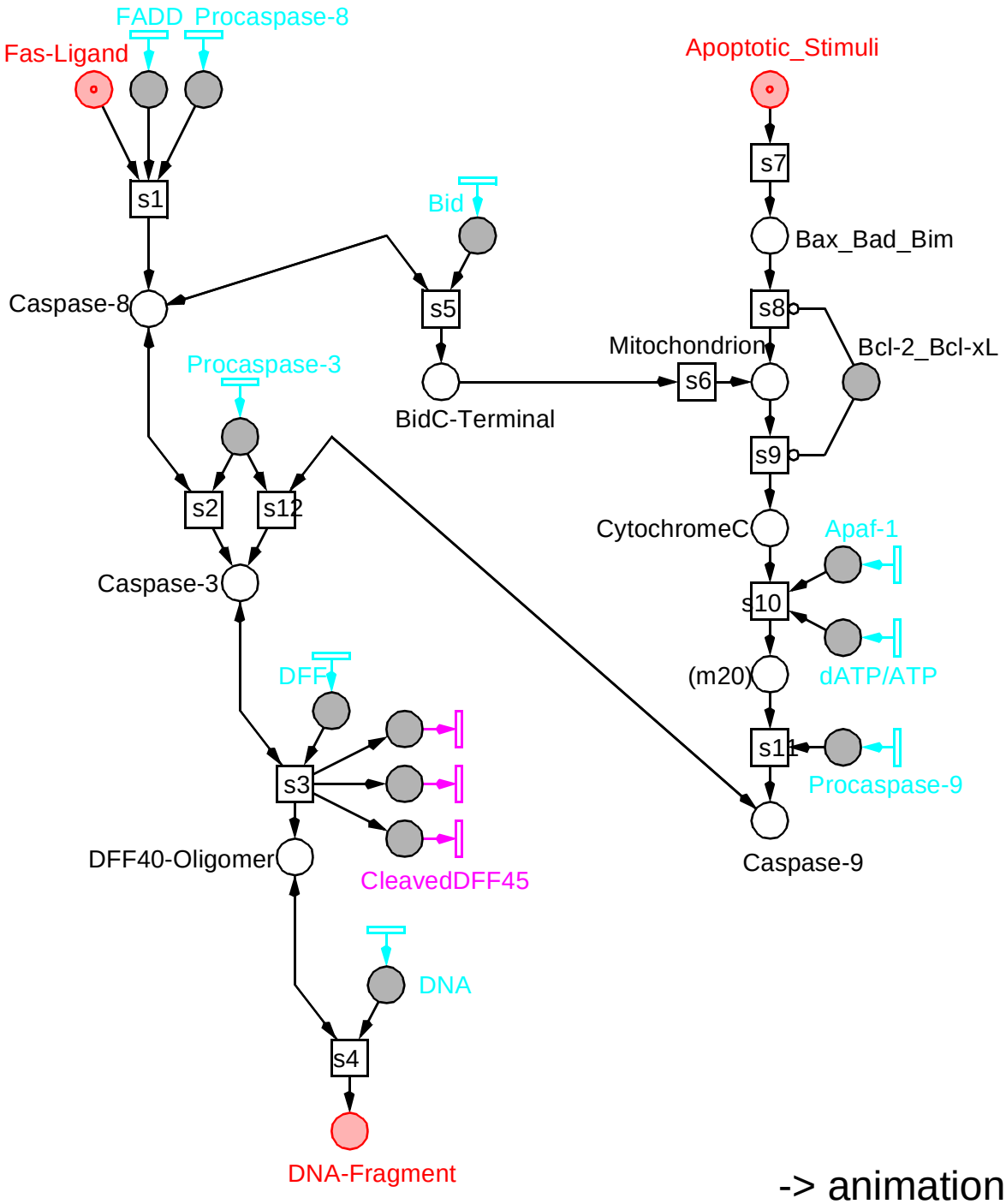
FAS1


Fas-Ligand
Apoptotic_Stimuli
s7
FADD
Procaspase-8
Bax_Bad_Bim
Apaf-1
Bcl-2_Bcl-xL
s8
dATP/ATP
s1
Bid
BidC-Terminal
CytochromeC
s6
s9
s10
s5
Mitochondrion
Caspase-8
Procaspase-3
s2
(m20)
Caspase-9
Caspase-3
s13
Procaspase-9
s11
DFF
s3
CleavedDFF45
s12
(m22)
DFF40-Oligomer
DNA
s4
DNA-Fragment

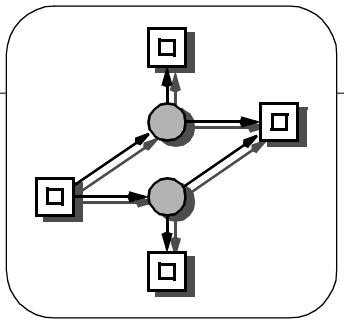
FAS2
= FAS1


Fas-Ligand
FADD
Procaspase-8
s1
Caspase-8
Bid
s5
BidC-Terminal
Apoptotic_Stimuli
s7
Bax_Bad_Bim
s8
Mitochondrion
Bcl-2_Bcl-xL
s6
s9
Procaspase-3
s2
s12
Caspase-3
CytochromeC
Apaf-1
s10
(m20)
dATP/ATP
DFF
s3
s11
Procaspase-9
DFF40-Oligomer
CleavedDFF45
Caspase-9
DNA
s4
DNA-Fragment

FAS3

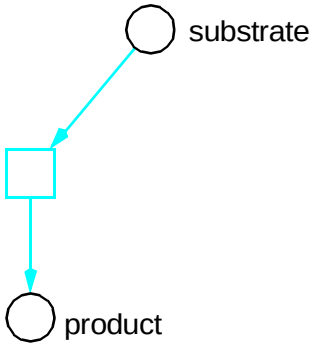


-> animation

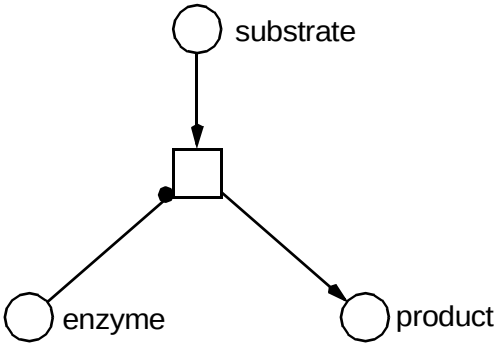


REFINEMENT: AUTOCATALYSIS

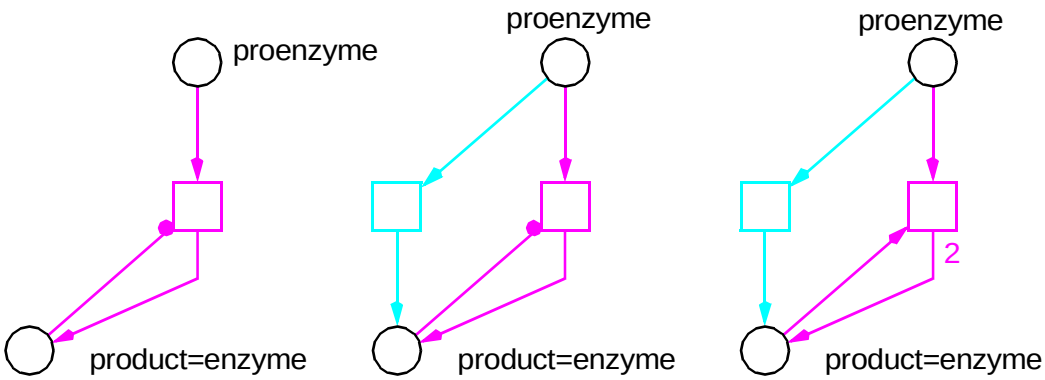
- REACTION



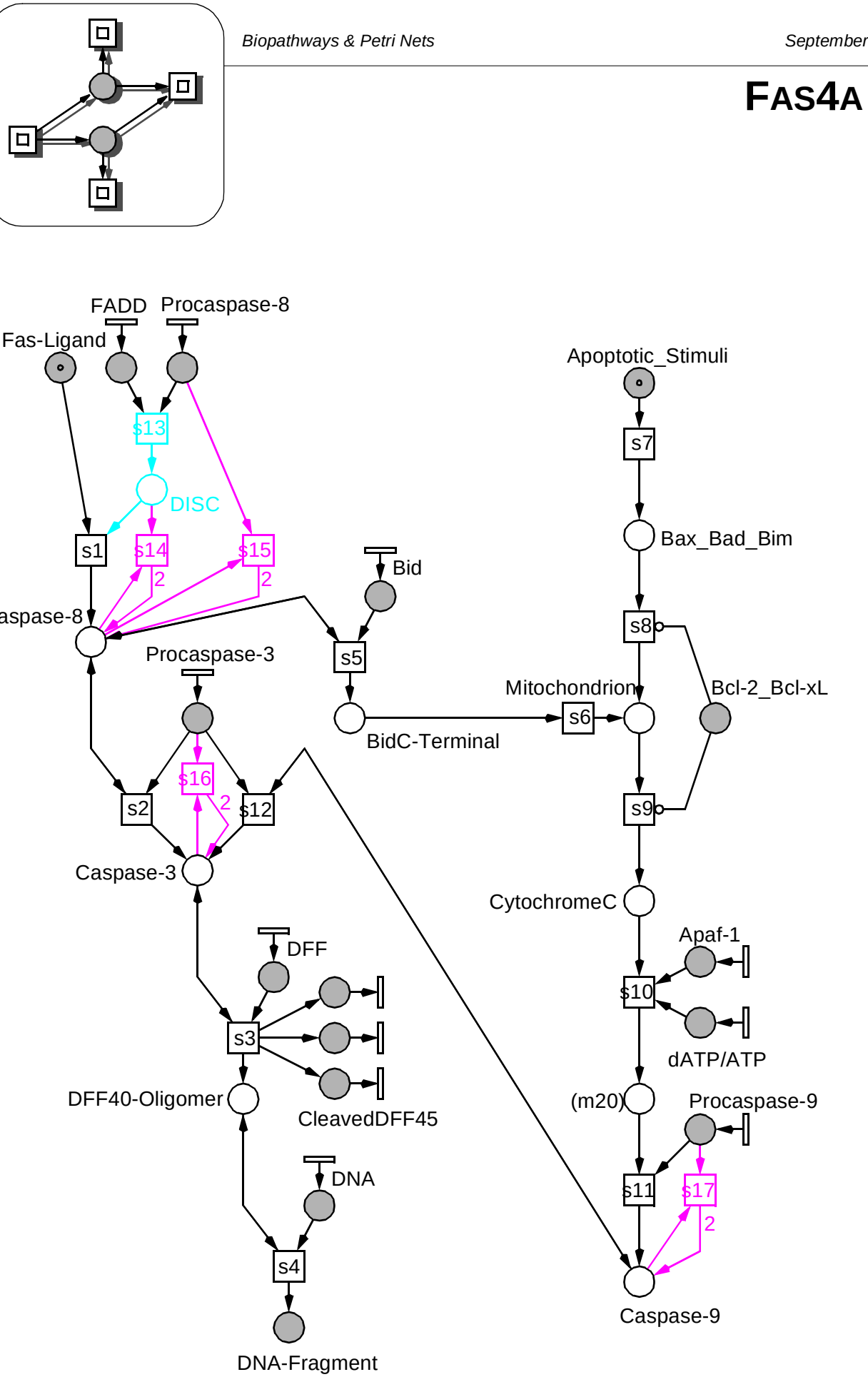
- CATALYSIS



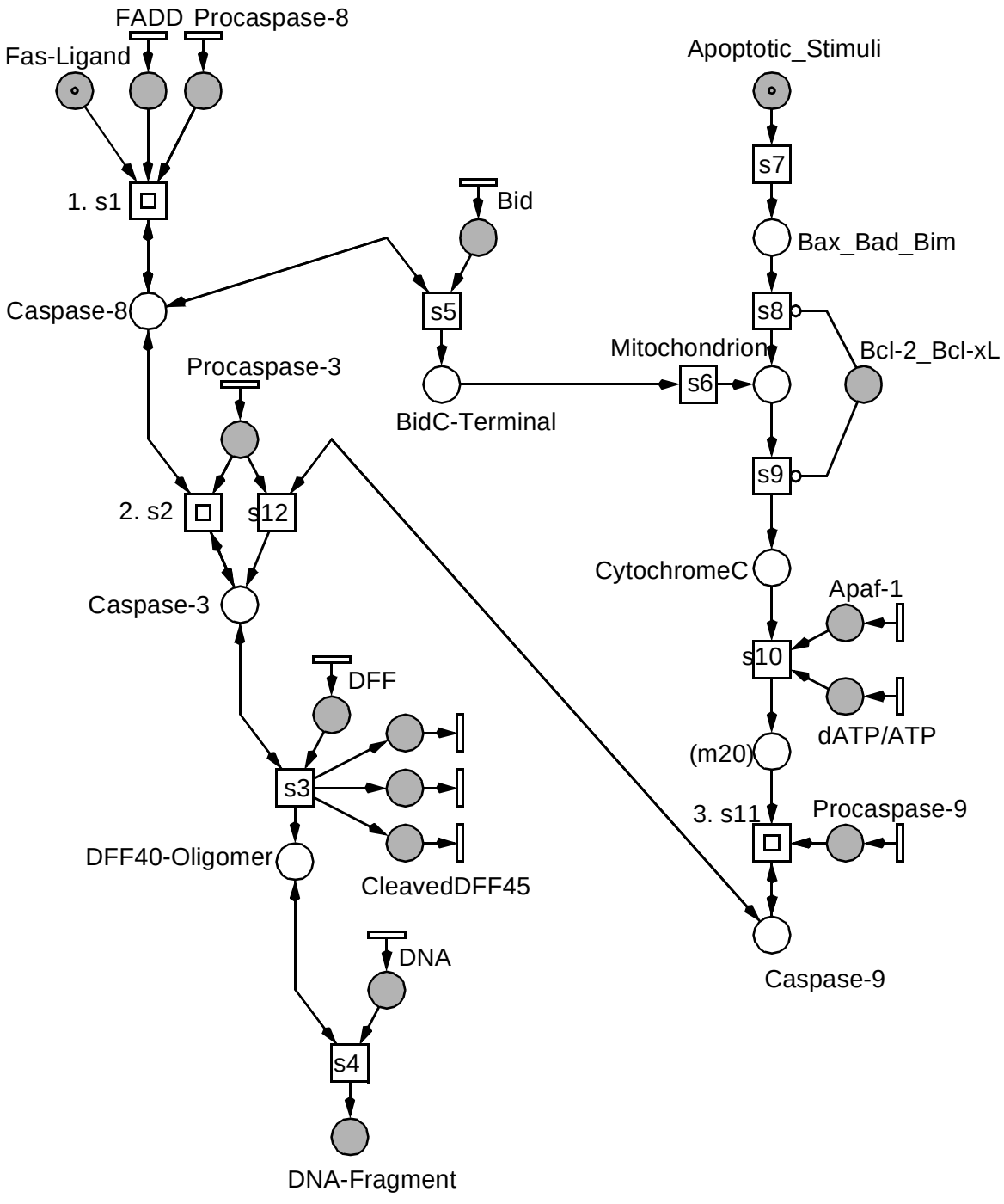
- AUTOCATALYSIS

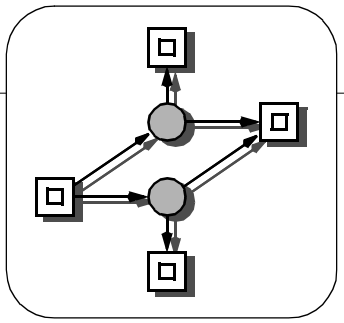


FAS4A

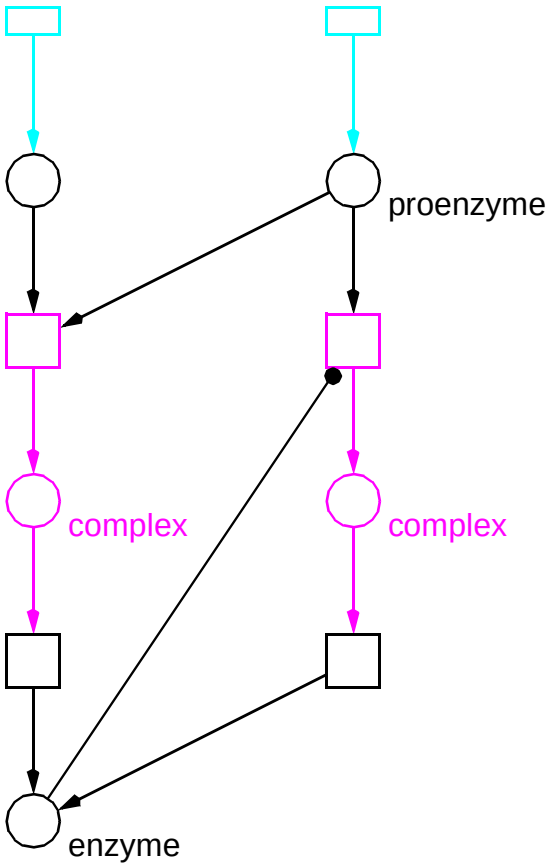

FADD
Procaspase-8
Fas-Ligand
s13
DISC
s1
s14
s15
2
2
Caspase-8
Bid
s5
Procaspase-3
s16
2
s2
s12
Caspase-3
BidC-Terminal
Apoptotic_Stimuli
s7
Bax_Bad_Bim
s8
Mitochondrion
s6
Bcl-2_Bcl-xL
s9
CytochromeC
Apaf-1
s10
dATP/ATP
(m20)
Procaspase-9
s11
s17
2
Caspase-9
DFF
s3
DFF40-Oligomer
CleavedDFF45
DNA
s4
DNA-Fragment

FAS4B
≈ FAS3

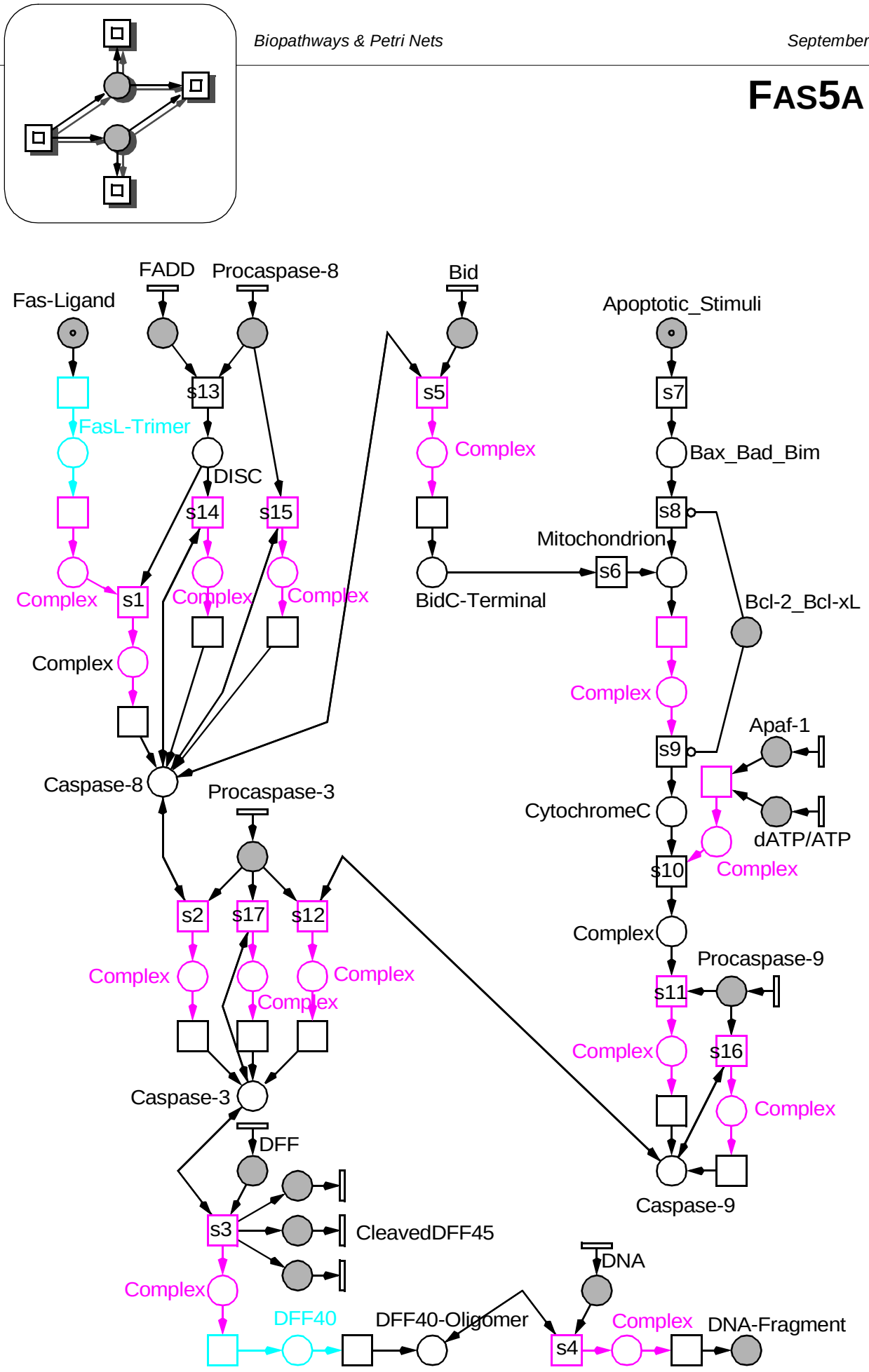

FADD_Procaspase-8
Fas-Ligand
1. s1
Bid
Caspase-8
s5
Procaspase-3
BidC-Terminal
Apoptotic_Stimuli
s7
Bax_Bad_Bim
s8
Mitochondrion
s6
Bcl-2_Bcl-xL
s9
2. s2
s12
CytochromeC
Apaf-1
Caspase-3
s10
DFF
dATP/ATP
(m20)
s3
3. s11
Procaspase-9
DFF40-Oligomer
CleavedDFF45
DNA
Caspase-9
s4
DNA-Fragment



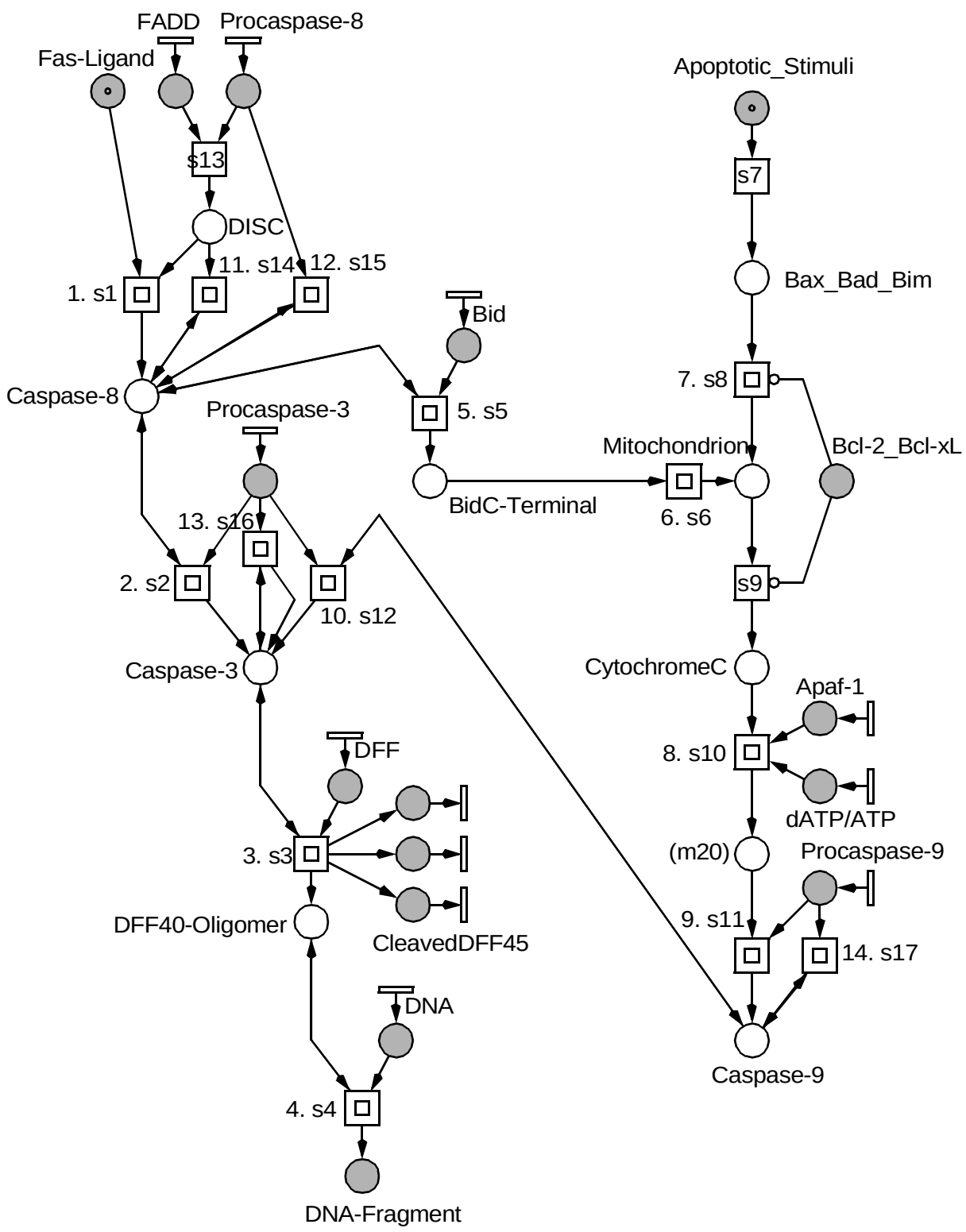
REFINEMENT: INTERMEDIATE COMPLEXES



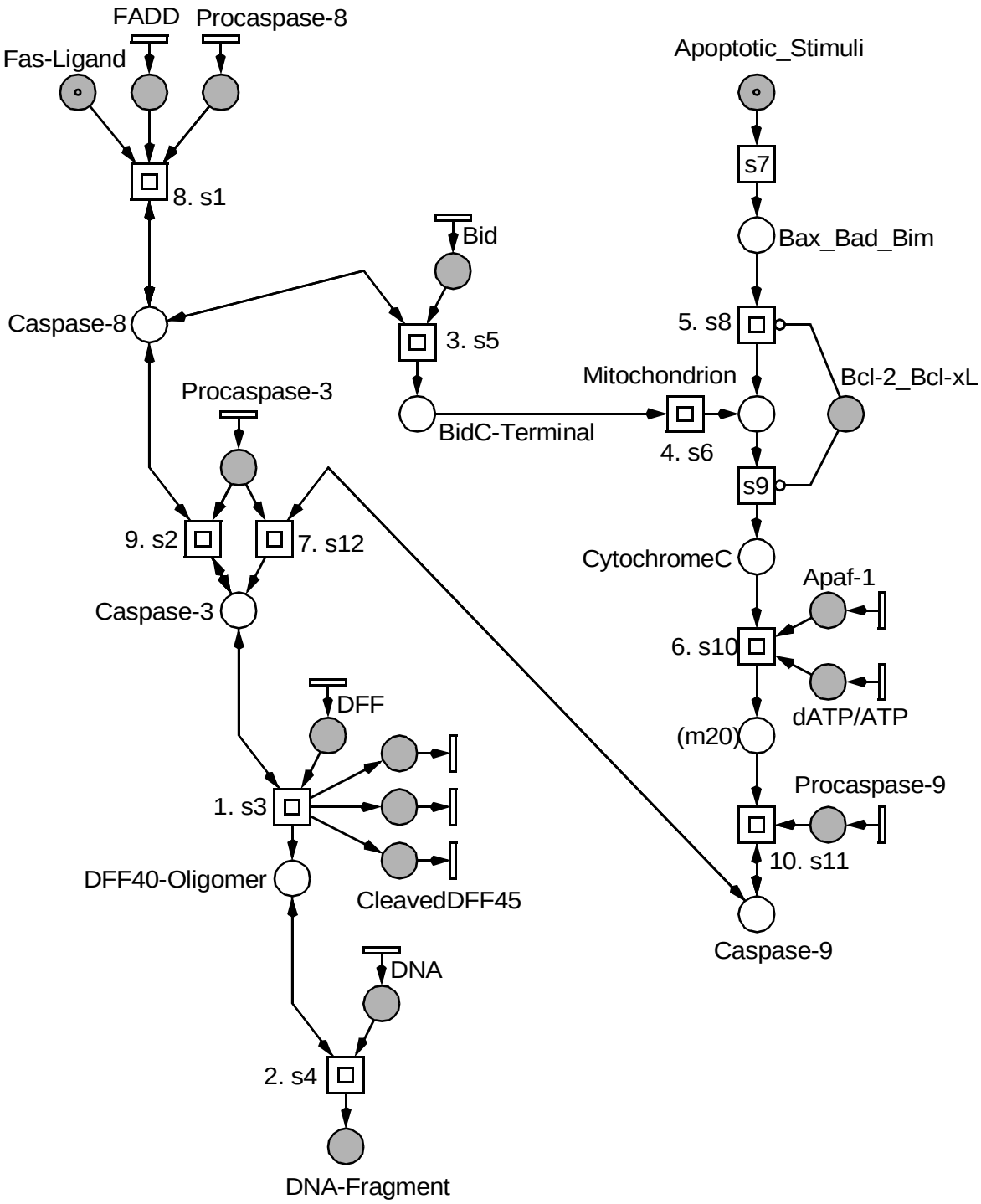
FAS5A


FADD
Procaspase-8
Bid
Fas-Ligand
Apoptotic_Stimuli
s13
s5
s7
FasL-Trimer
Complex
Bax_Bad_Bim
DISC
s14
s15
s8
Mitochondrion
s6
Complex
s1
Complex
Complex
BidC-Terminal
Bcl-2_Bcl-xL
Complex
Complex
Apaf-1
s9
Caspase-8
Procaspase-3
CytochromeC
dATP/ATP
s10
Complex
s2
s17
s12
Complex
Complex
Complex
Complex
Procaspase-9
s11
Complex
s16
Caspase-3
Complex
DFF
Caspase-9
s3
CleavedDFF45
DNA
Complex
DFF40
DFF40-Oligomer
Complex
DNA-Fragment
s4

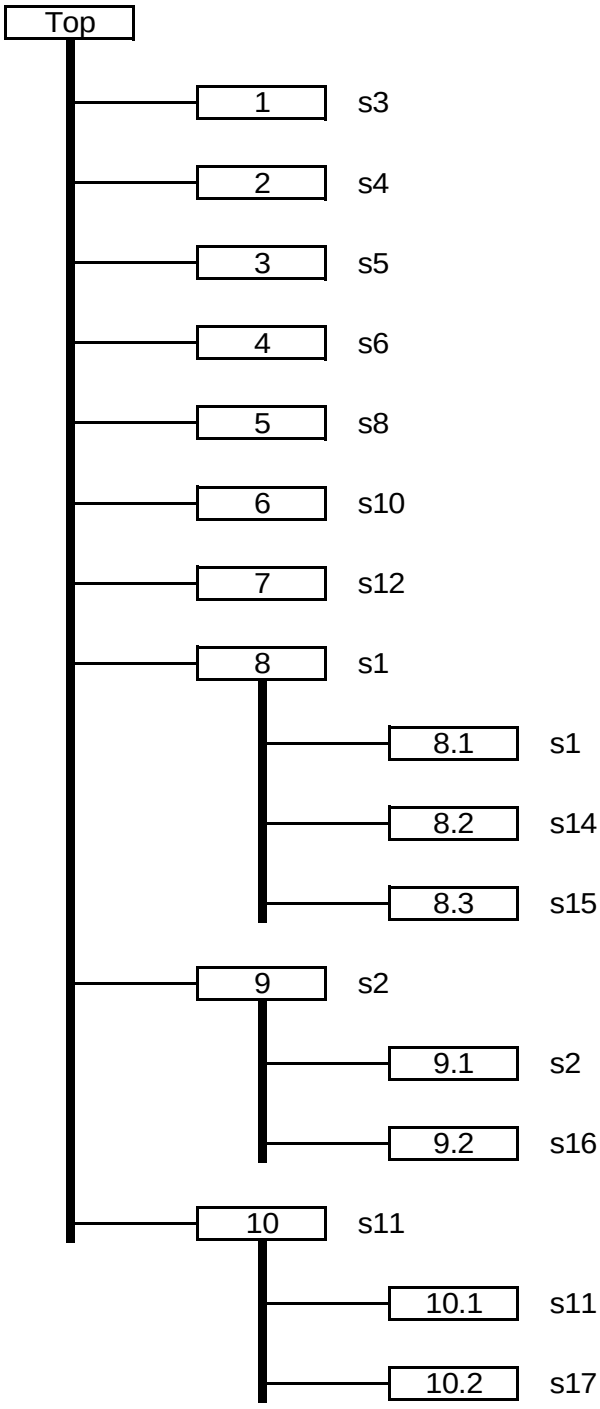
FAS5B
≈ FAS4A

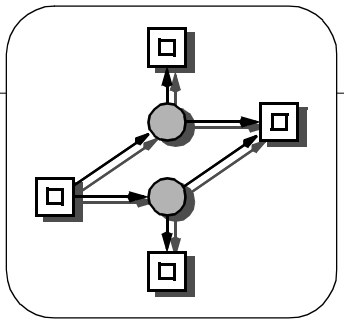

FADD
Procaspase-8
Fas-Ligand
s13
DISC
1. s1
11. s14
12. s15
Bid
Caspase-8
Procaspase-3
5. s5
13. s16
2. s2
10. s12
Caspase-3
DFF
3. s3
DFF40-Oligomer
CleavedDFF45
DNA
4. s4
DNA-Fragment
Apoptotic_Stimuli
s7
Bax_Bad_Bim
7. s8
Mitochondrion
Bcl-2_Bcl-xL
BidC-Terminal
6. s6
s9
CytochromeC
Apaf-1
8. s10
dATP/ATP
(m20)
Procaspase-9
9. s11
14. s17
Caspase-9

FAS5C
≈ FAS3


FADD
Procaspase-8
Fas-Ligand
8. s1
Bid
Caspase-8
3. s5
Procaspase-3
BidC-Terminal
Mitochondrion
4. s6
Bcl-2_Bcl-xL
9. s2
7. s12
Caspase-3
DFF
1. s3
DFF40-Oligomer
CleavedDFF45
DNA
2. s4
DNA-Fragment
Apoptotic_Stimuli
s7
Bax_Bad_Bim
5. s8
s9
CytochromeC
Apaf-1
6. s10
dATP/ATP
(m20)
Procaspase-9
10. s11
Caspase-9

HIERARCHY TREE FAS5C



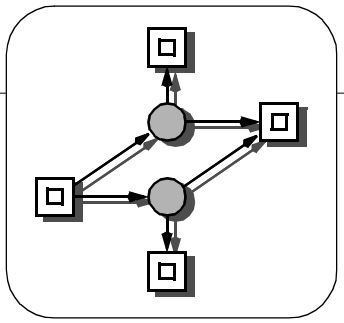


MASTERING COMPLEXITY 1

❑ STEP-WISE MODELLING

1. literal scheme transformation FAS1
2. layout improvement FAS2
   -> use of syntactic sugar
3. adding environment behaviour FAS3
   -> animation
4. adding autocatalysis FAS4A
   -> hierarchic Petri net FAS4B
5. adding intermediate complexes FAS5A
   -> refined hierarchies FAS5B
   FAS5C

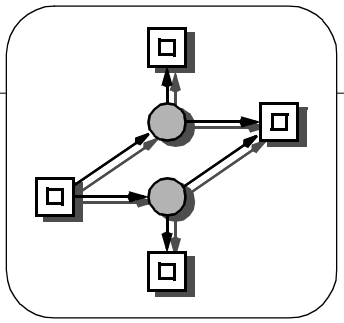
❑ EXPLOIDING SYNTACTIC SUGAR



4.

MODEL ANALYSIS

-> QUALITATIVE & QUANTITATIVE



TYPICAL ANALYSIS TECHNIQUE, EXAMPLE

- T - invariants

  -> set of transitions,
  reproducing a given marking;

  -> metabolic Petri nets:
  set of reactions,
  reproducing a substance distribution;

  -> bio Petri nets:
  set of actions,
  reproducing a system state;

- minimal positive T - invariants

  -> basic behaviour

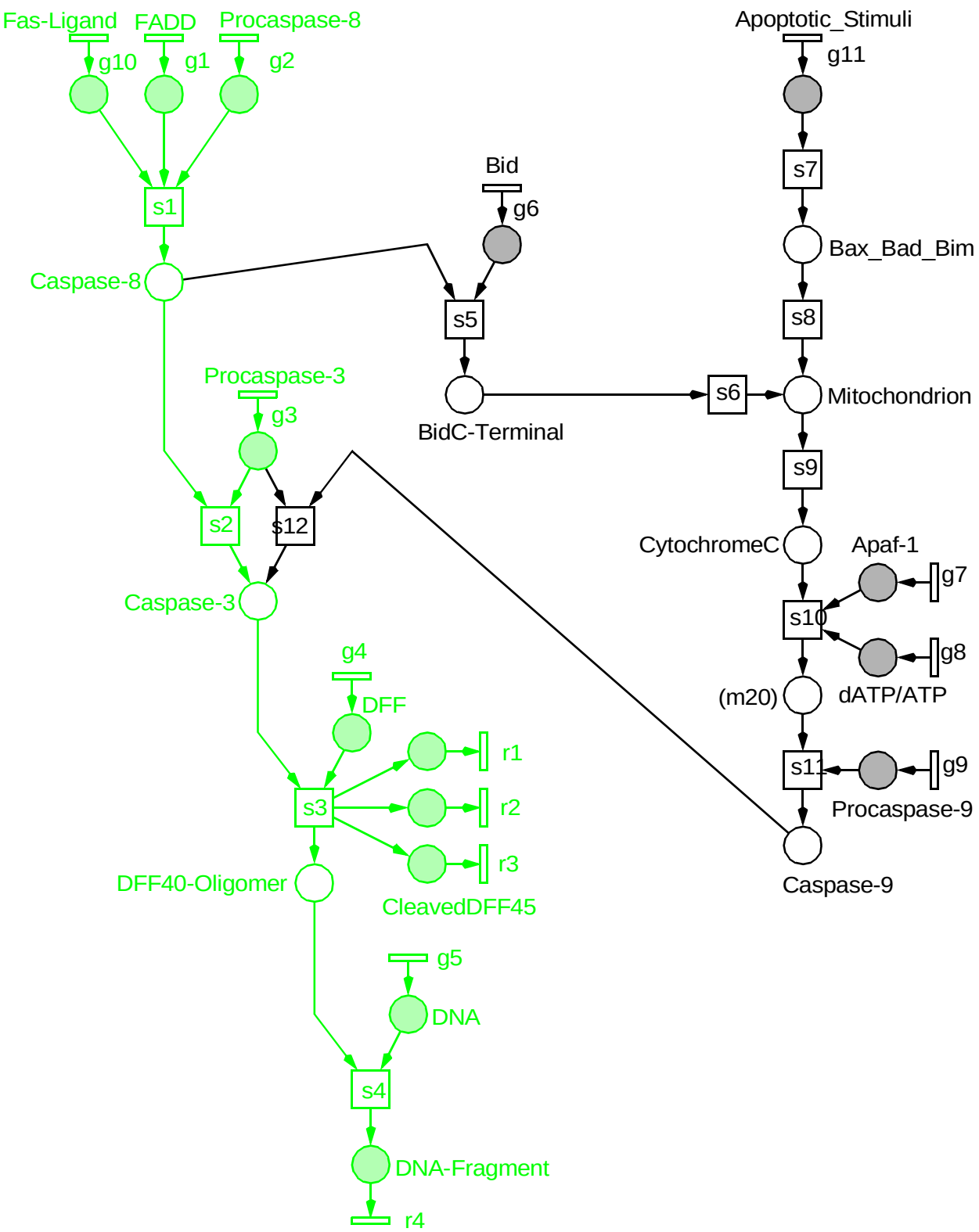
  -> any net behaviour =
  linear combination of them

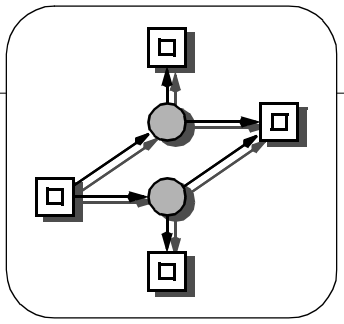
- computation: $[C] \cdot \bar{x} = 0$

  $[C]$ - (P x T) - incidence matrice

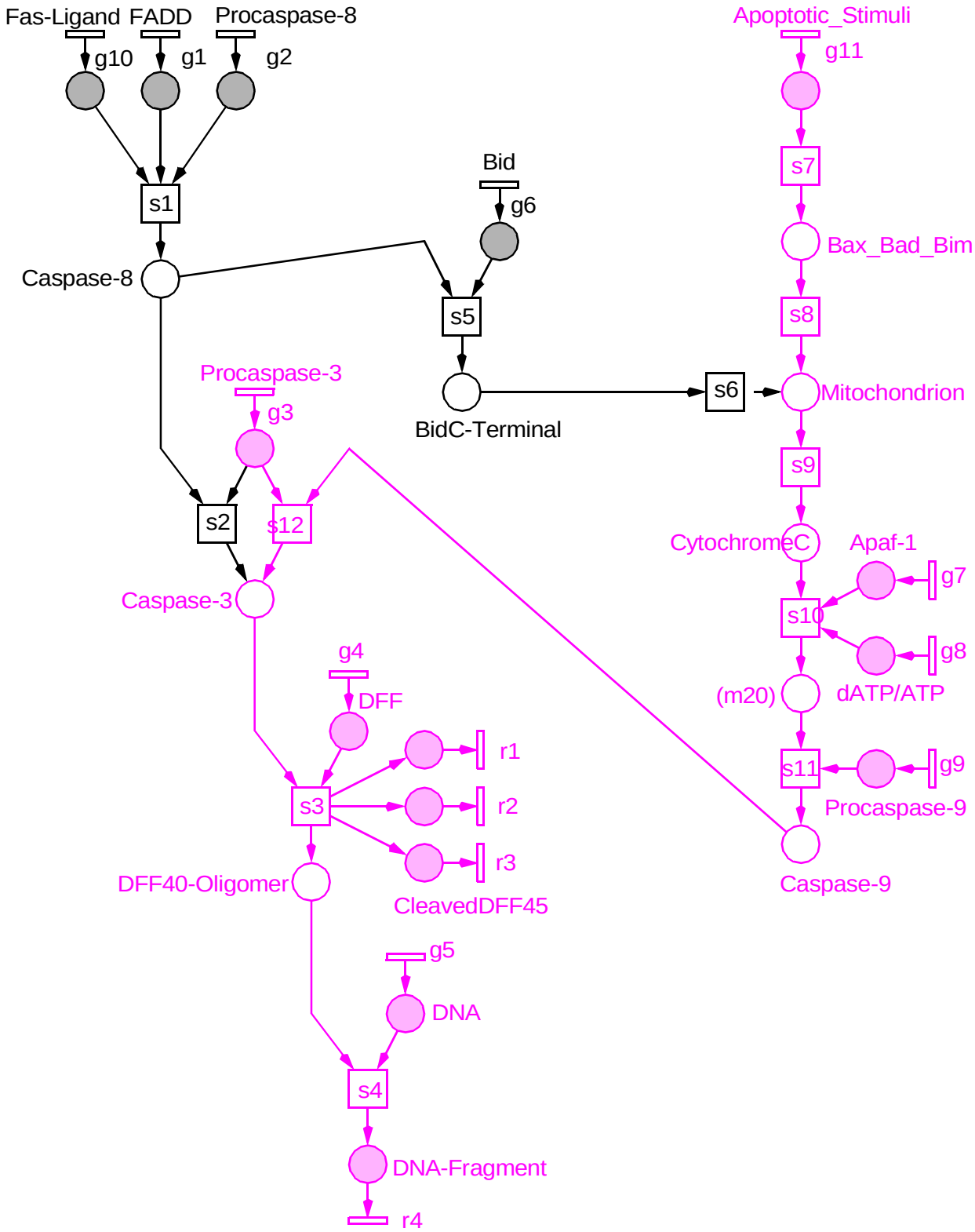
  x - transition vector

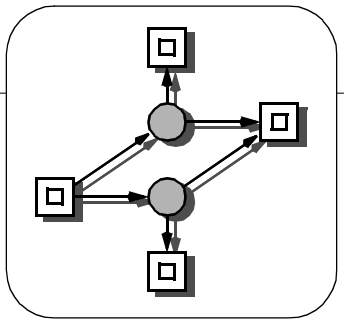
QUALITATIVE ANALYSIS, T - INVARIANT 1: DEATH-RECEPTOR PATHWAY



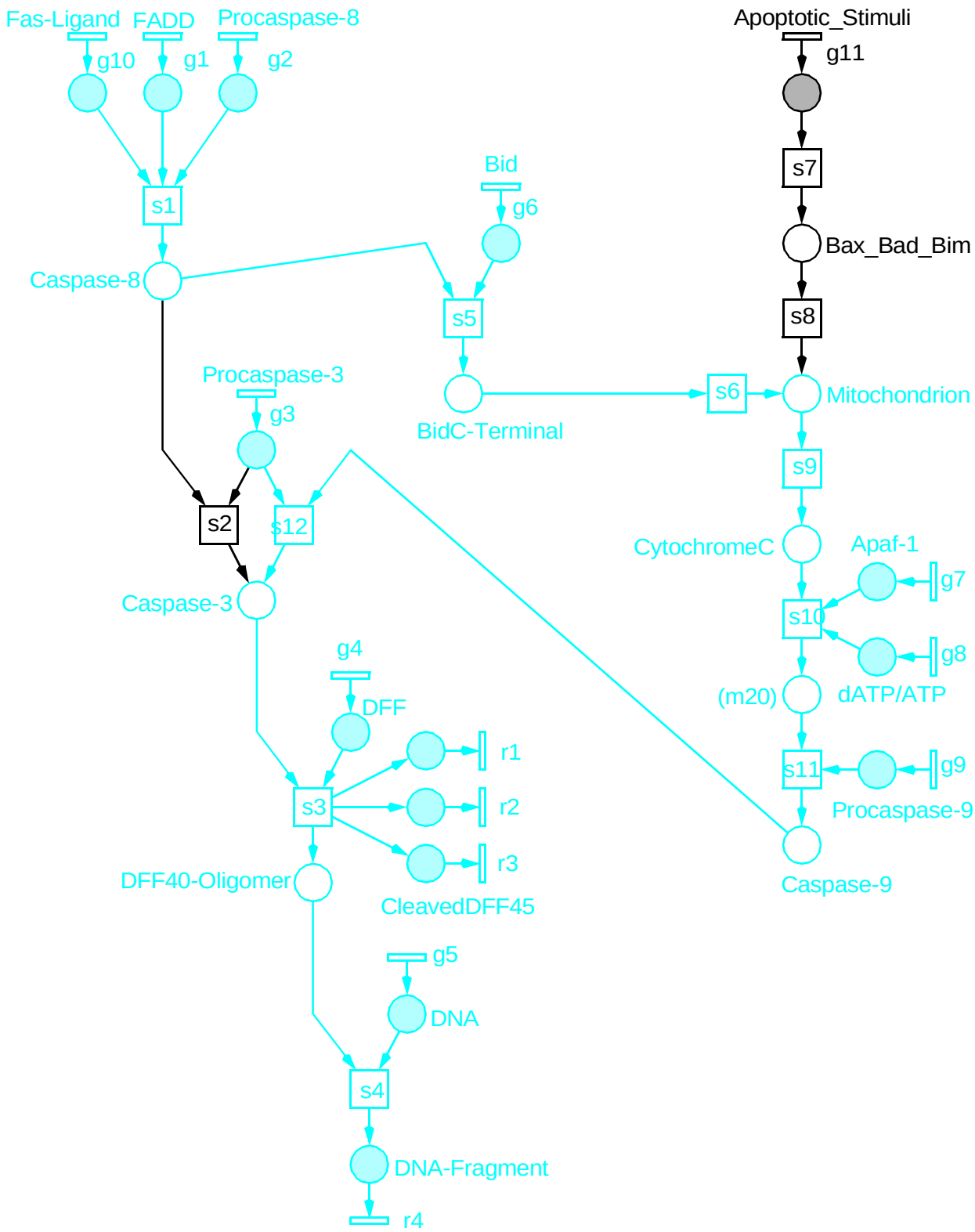


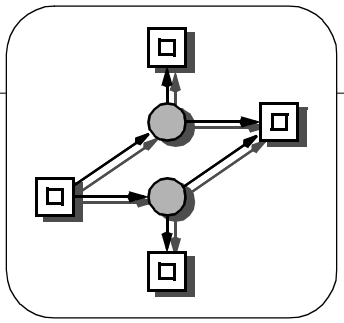
QUALITATIVE ANALYSIS, T - INVARIANT 2: MITOCHONDRIAL PATHWAY





QUALITATIVE ANALYSIS, T - INVARIANT 3: CROSS-TALK BY BID



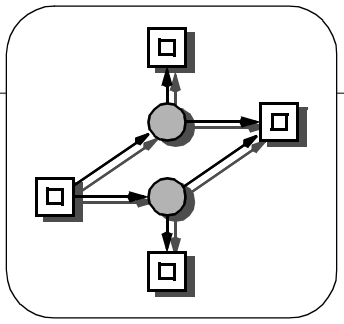


Qualitative Analyses, Summary

- three minimal positive T - invariants
  - -> three basic behaviours ,
  - -> any net behaviour = linear combination of them
- the net is covered by T - invariants
  - -> no idle parts
- reproducible empty marking
  - -> cyclic behaviour possible (reversability)
- coverability graph (Karp - Miller)
  - -> 8121 nodes
  - -> no dead states

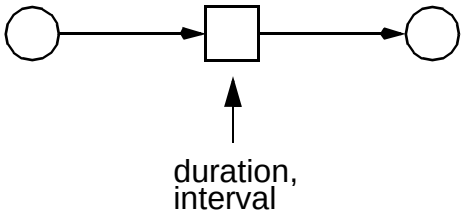
ORD	HOM	NBM	PUR	CSV	SCF	CON	SC	Ft0	tF0	Fp0	pF0	MG	SM	FC	EFC	ES
Y	Y	Y	Y	N	N	Y	N	Y	Y	N	N	N	N	N	N	

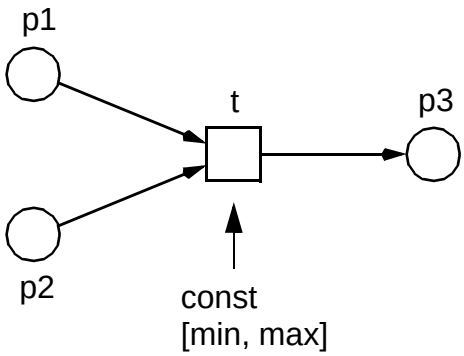
DTP	SMC	SMD	SMA	CPI	CTI	B	SB	REV	DSt	BSt	DTr	DCF	L	LV	L&S
Y	N	N	N	N	Y	N	N	?Y	N	?N	N	?N	Y	Y	N



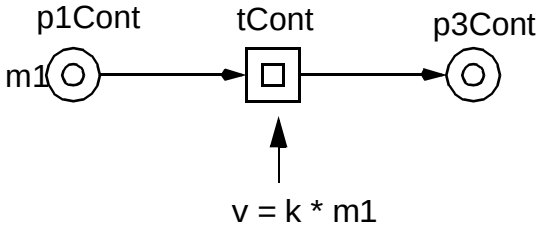
INTEGRATION OF QUANTITATIVE ANALYSES

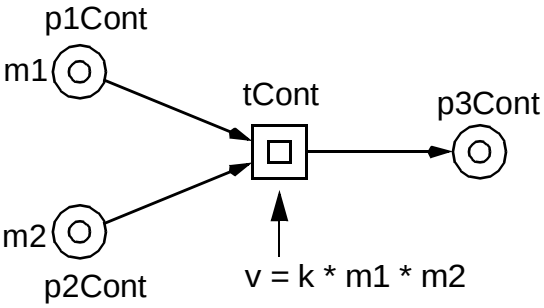
❑ DISCRETE TIME

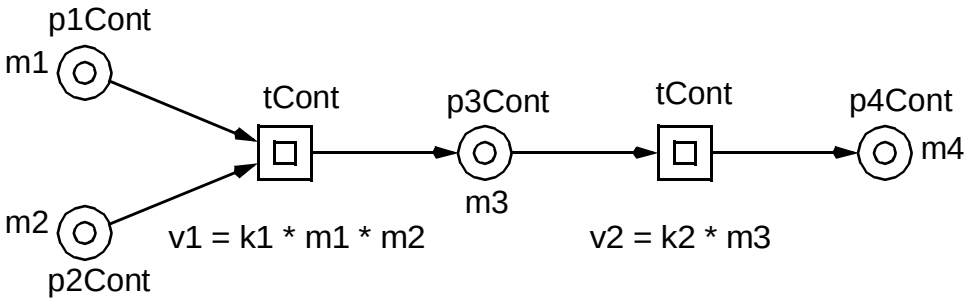




❑ CONTINEOUS TIME



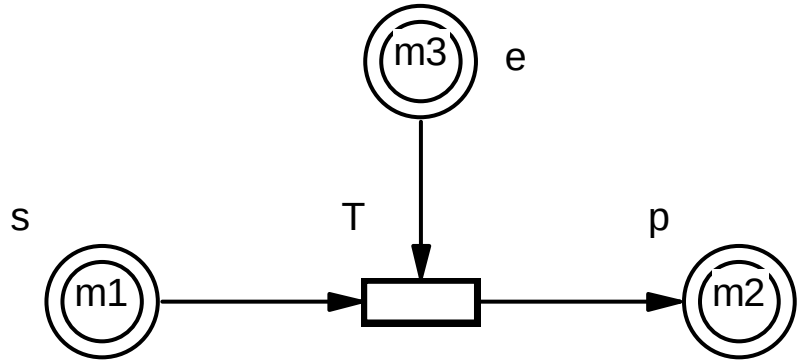




d [p1Cont] / dt = d [p2Cont] / dt = - v1
d [p4Cont] / dt = v2
d [p3Cont] / dt = v1 - v2

-> SELF-MODIFYING PETRI NETS

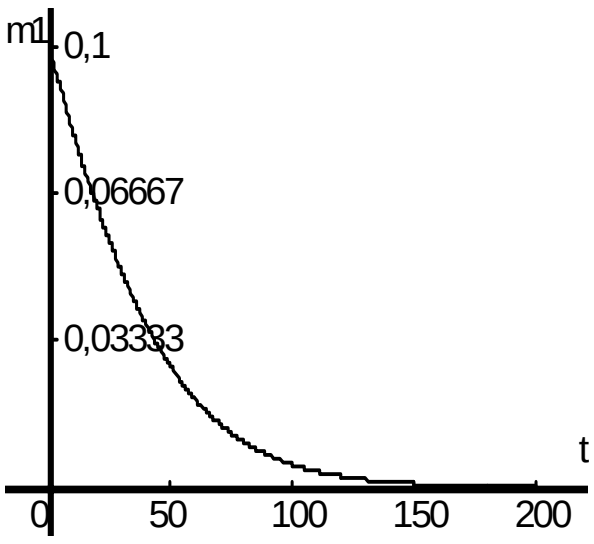
MICHAELIS-MENTEN REACTION
[GENOMIC OBJECT NET]

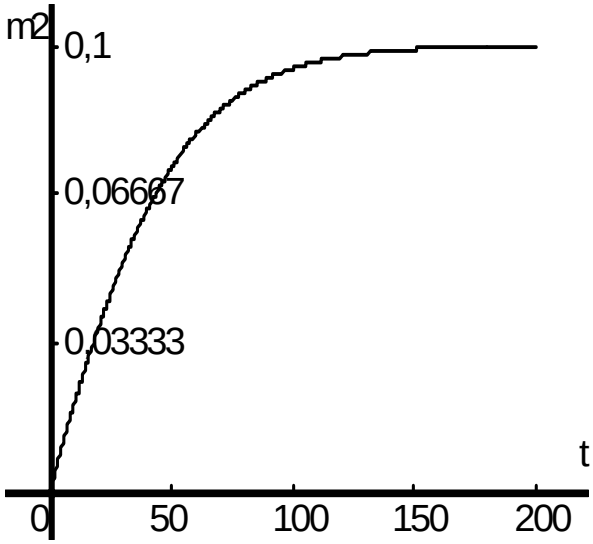


Vmax = 0.005 (maximal reaction rate)

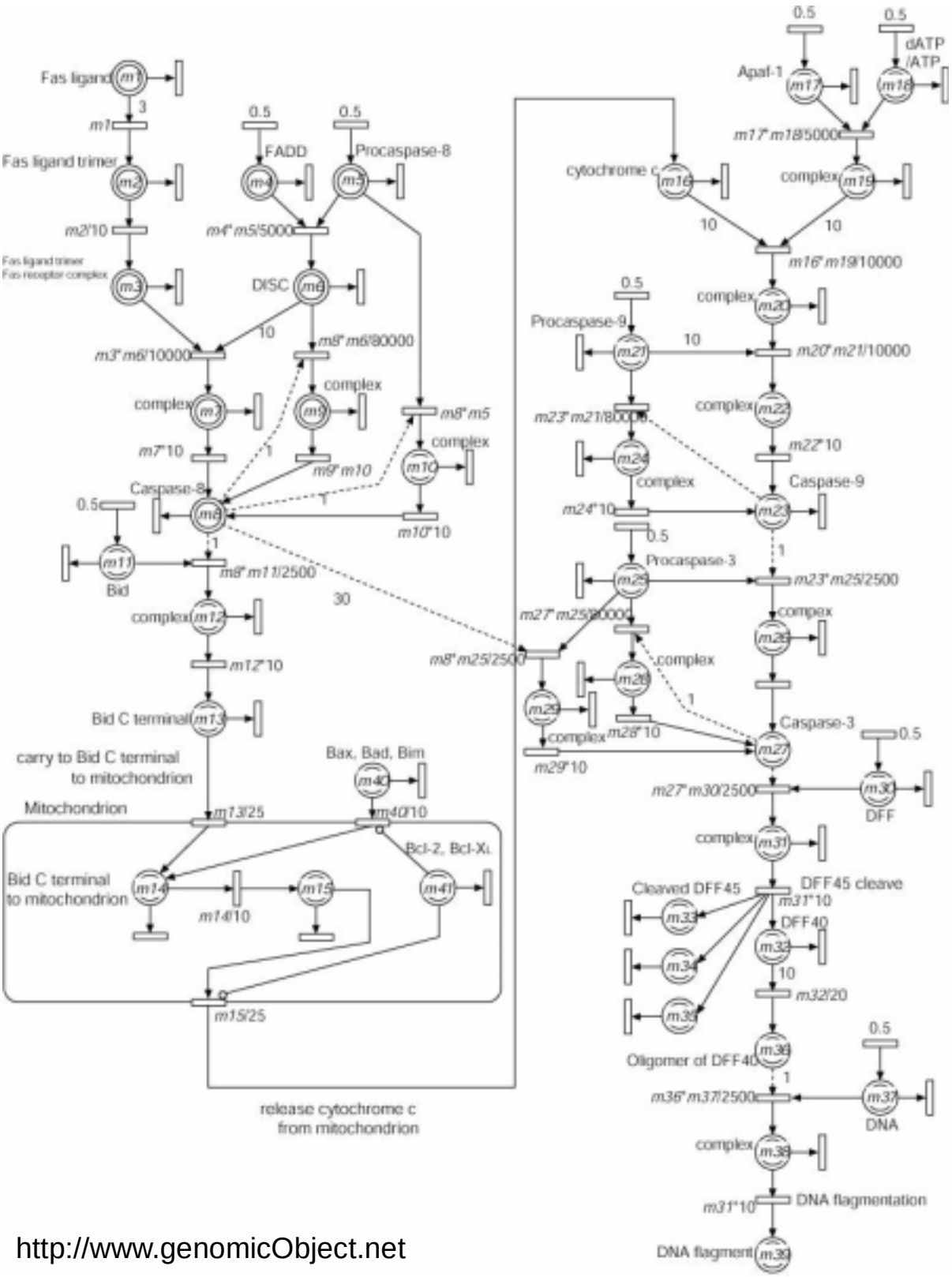
Km = 0.1375 (Michaelis constant)

d[s]/dt = d[p]/dt = Vmax*[s] / (Km+[s])

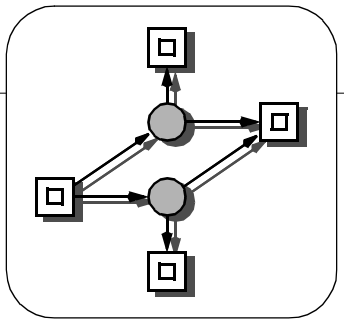




GENOMIC OBJECT NET [MATSUNO ET AL. 200X]

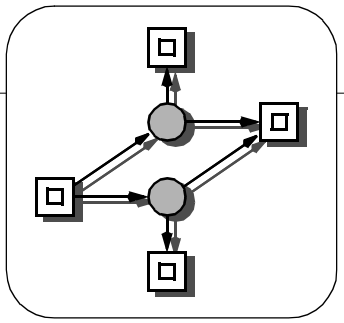


http://www.genomicObject.net



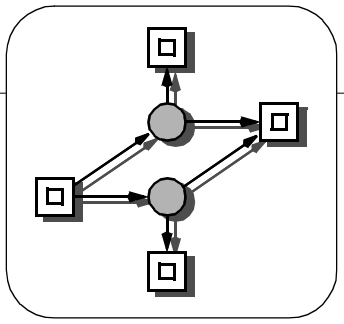
5.

SUMMARY



MASTERING COMPLEXITY 2

- step-wise model development for
  - -> animation
  - -> validation
  - -> (qualitative) analysis
  - -> (quantitative) simulation
- integration of
  - -> model validation
  - -> behaviour prediction
- one all-purpose model
  - -> animation model
  - -> “qualitative model = animation model”
  - -> “quantitative model =
    qualitative model
    + quantitative paramter”



APPLICATIONS OF BIO PETRI NETS, SUMMARY

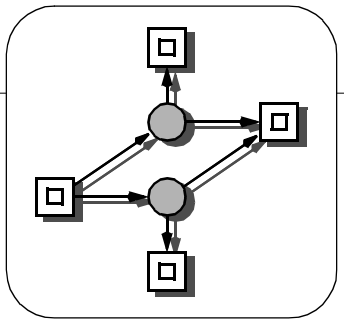
(1) step-wise construction
of graphical (=visual) models

(2) graphical model animation

(3) validation of model integrity

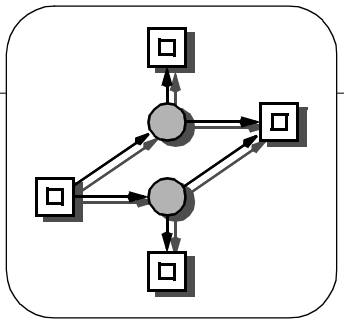
(4) qualitative analyses
of biological / bio-technological questions

(5) quantitative analyses
of biological / bio-technological questions



6.

OUTLOOK



TYPICAL PETRI NET QUESTIONS

- How many tokens may reside at most in a given place ?
  -> (0, 1, k, oo)
  -> BOUNDEDNESS

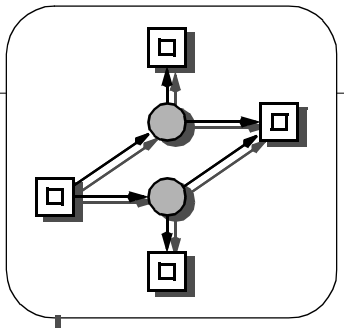
- How often may a transition fire ?
  -> (0-times, n-times, oo-times)
  -> LIVENESS

- Is a given system state . . .
  -> always reachable again?
  -> PROGRESS PROPERTIES

  -> never reachable?
  -> SAFETY PROPERTIES

- Are there behavourally invariant structures?
  -> token conservation
  -> P - INVARIANTS

  -> token distribution reproduction
  -> T - INVARIANTS



QUALITATIVE ANALYSIS TECHNIQUES

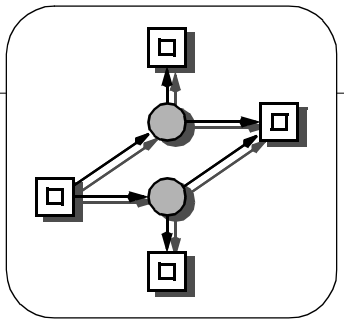
- NET REDUCTION
- STRUCTURAL PROPERTIES
- LINEAR PROGRAMMING
  - place / transition invariants
  - state / trap equation

static analysis

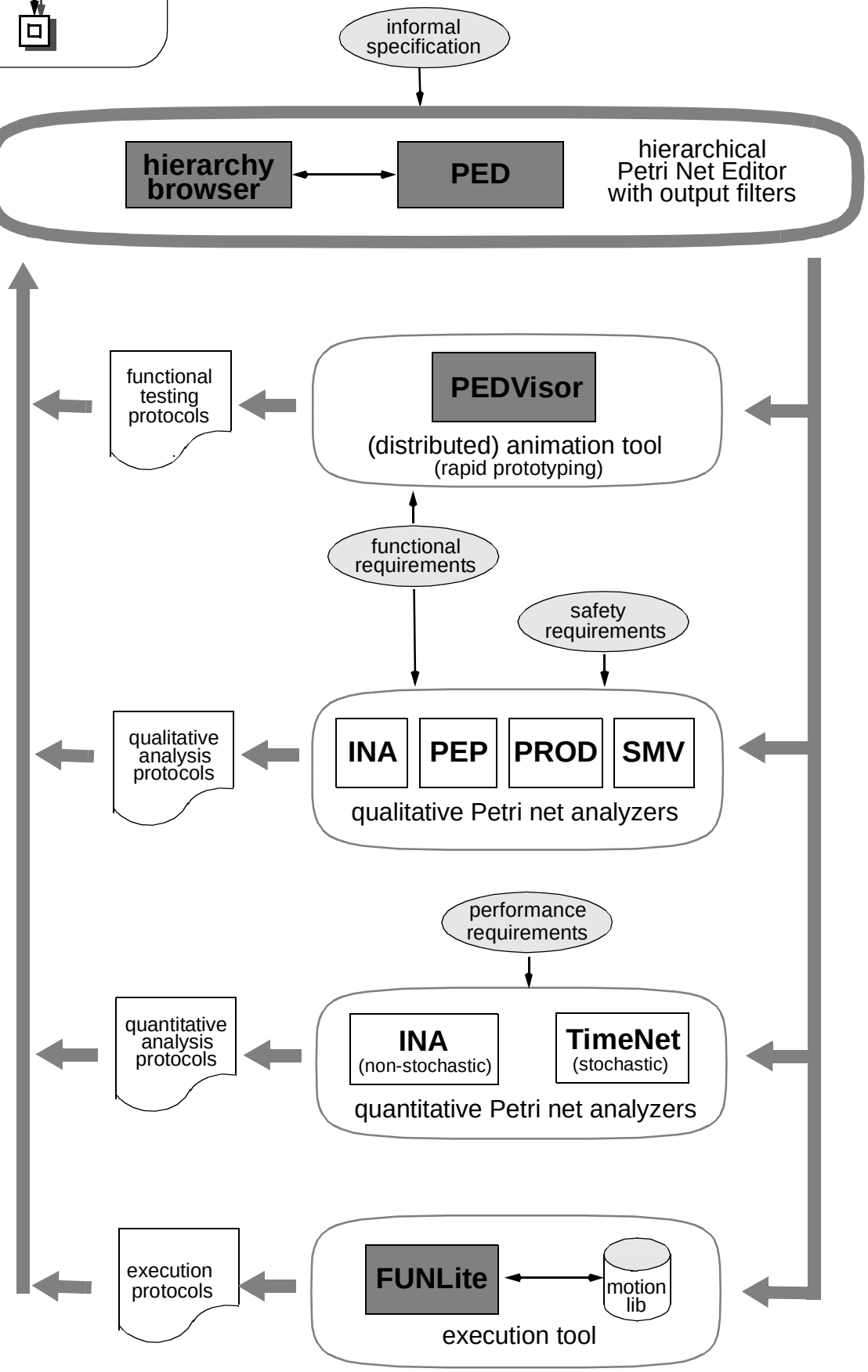
- REACHABILITY ANALYSIS
  - (complete) reachability graph
  - compressed state spaces
    - OBDDs, ONDDS
    - Kronecker products
  - reduced state spaces
    - coverability graph
    - symmetry
    - stubborn / sleep sets
  - branching processes
  - concurrent automaton

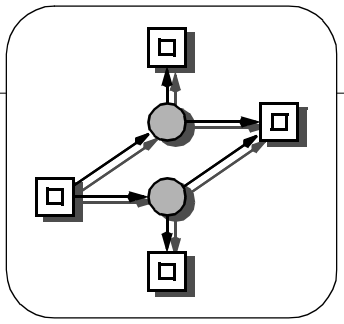
dynamic analysis

(model checking)



TOOL OVERVIEW (UNCOMPLETE)





MODEL CLASSES

PETRI NETS

- PLACE/TRANSITION PETRI NET (COLOURED PN)
  - context checking by Petri net theory
  - verification by temporal logics
- TIME-DEPENDENT PN
  - DISCRETE PETRI NET
    - worst-case evaluation
  - CONTINUOUS PETRI NET
    - performance prediction
  - STOCHASTIC PETRI NET
    - reliability prediction