**BTU COTTBUS**
**COMPUTER SCIENCE**
**INSTITUTE**

# METABOLIC PETRI NETS

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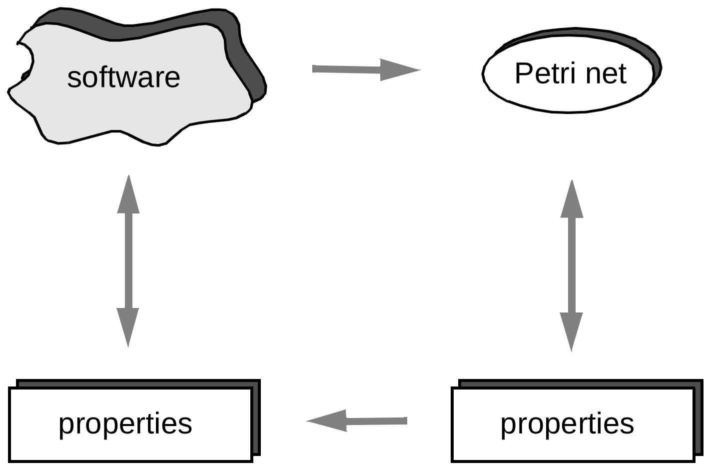
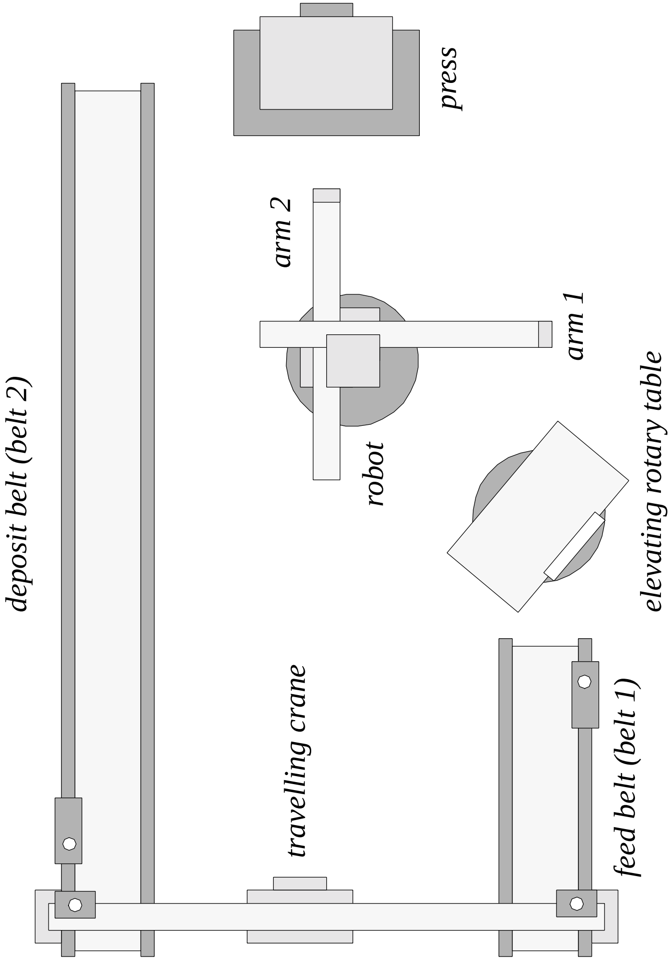
## SOFTWARE ENGINEERING & PETRI NETS




metabolic
networks

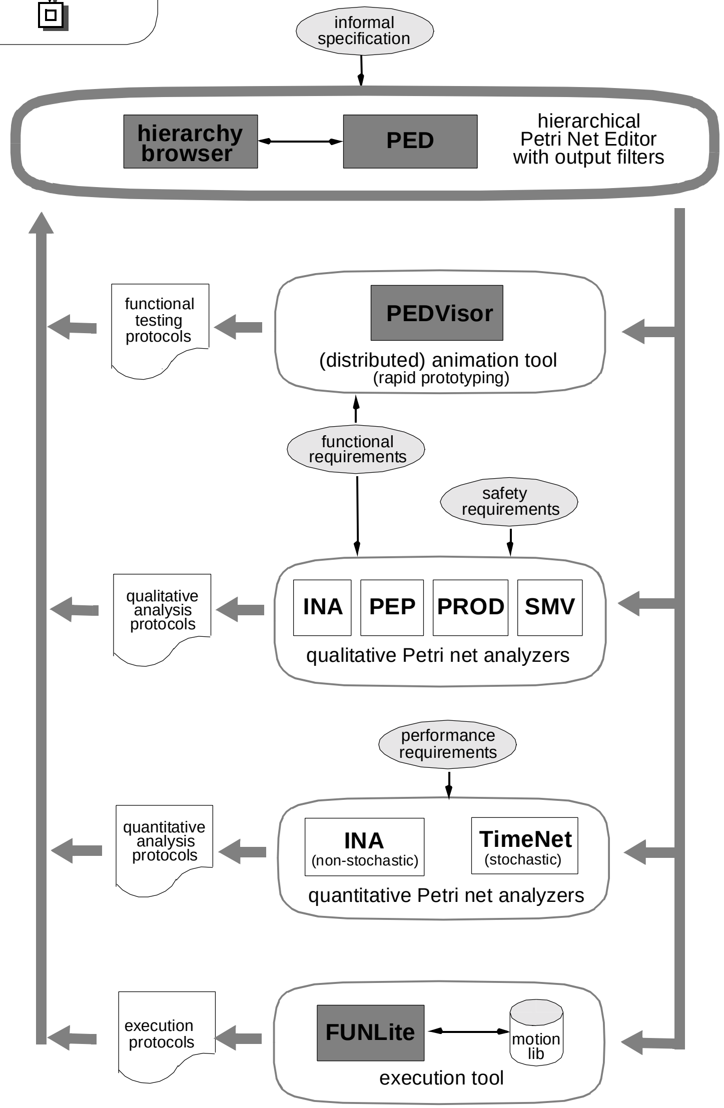
# Production Cell:



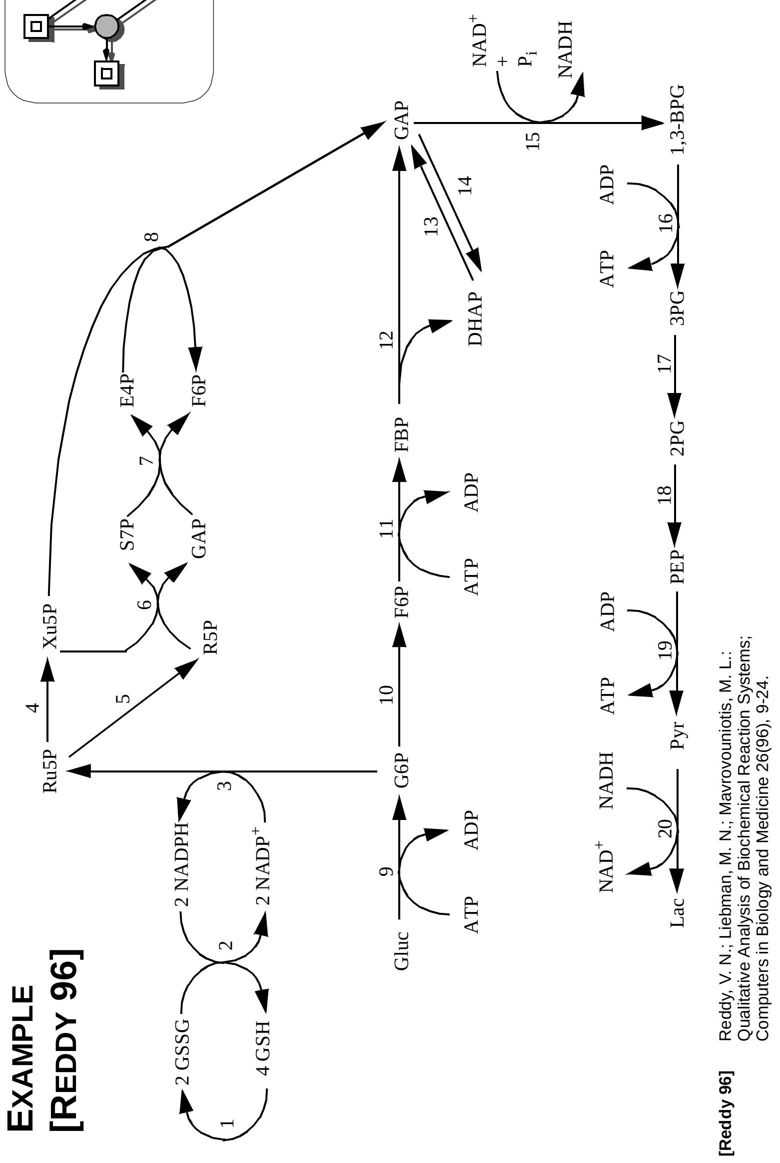





# TOOL OVERVIEW



# EXAMPLE [REDDY 96]

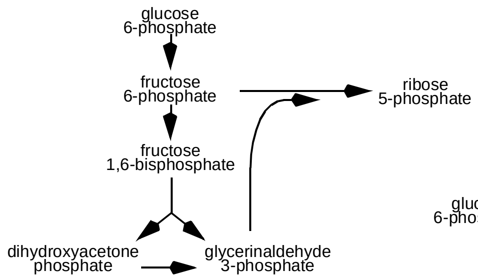



**[Reddy 96]** Reddy, V. N.; Liebman, M. N.; Mavrovouniotis, M. L.: Qualitative Analysis of Biochemical Reaction Systems; Computers in Biology and Medicine 26(96), 9-24.

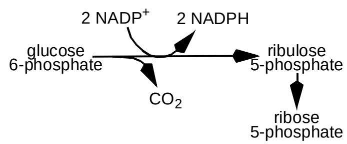




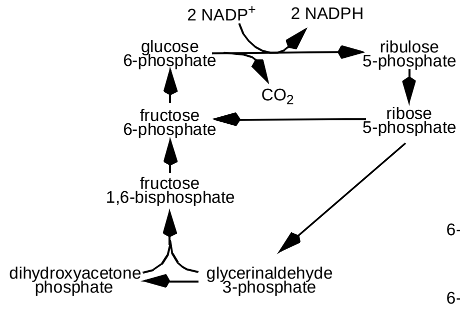
# EXAMPLE PENTOSE PHOSPHATE CYCLE



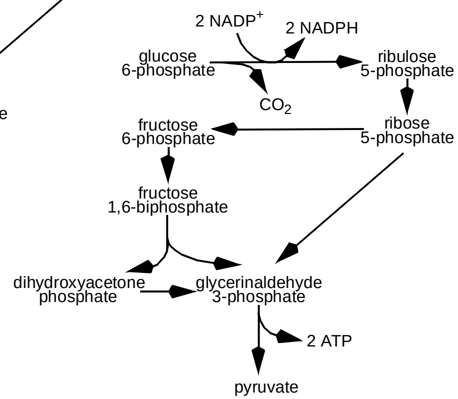

**1. possibility**




**2. possibility**




**3. possibility**



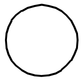

**4. possibility**

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

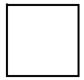
# PETRI NETS, BASICS 1

## (1) NODES

places



transitions



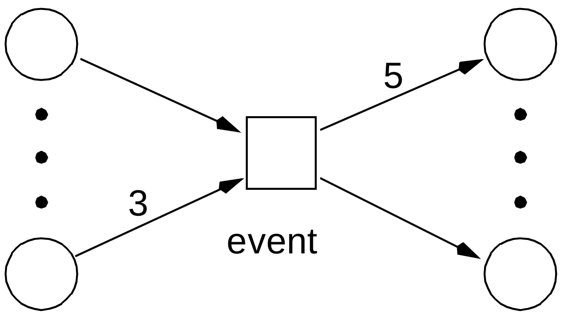
"passive elements"
conditions
states
"*chem. compounds*"

"active elements"
events
actions
"*chem. reactions*"

## (2) ARCS

preconditions

postconditions



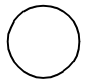




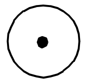

# PETRI NETS, BASICS 2

## (3) TOKENS

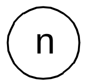
(moving objects,
vehicles, work pieces, dates, control flow pointer, ..., *units of substances (e. g. Mol)*, ...)



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 event ***may*** happen, if

-> all preconditions
are fulfilled
(corresponding to the arc weights);

❑ if an event 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 event happens
(firing of a transition)

-> atomic

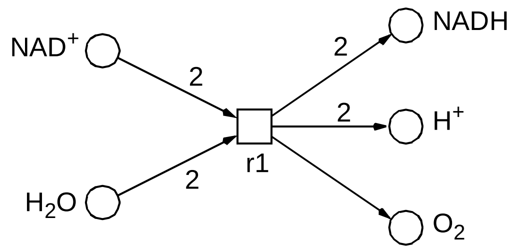
-> time-less



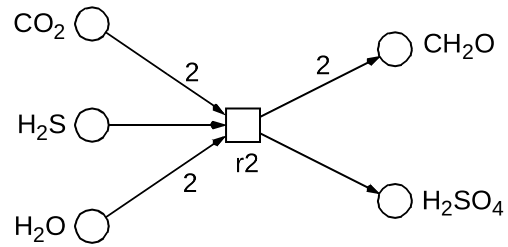


## EXAMPLES, REACTION EQUATIONS

❑ **FOR LIGHT-INDUCED PHOSPHORYLATION**
**$2\ NAD^+ + 2\ H_2O$ -> $2\ NADH + 2\ H^+ + O_2$**

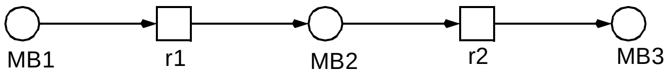



❑ **FROM THE PHOTOSYNTHESIS**
**$2\ CO_2 + H_2S + 2\ H_2O$ -> $2\ (CH_2O) + H_2SO_4$**

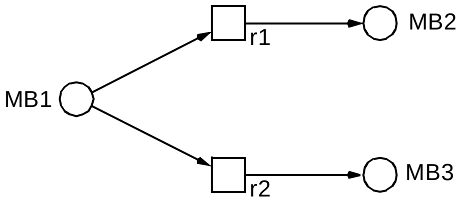


# TYPICAL BASIC STRUCTURES

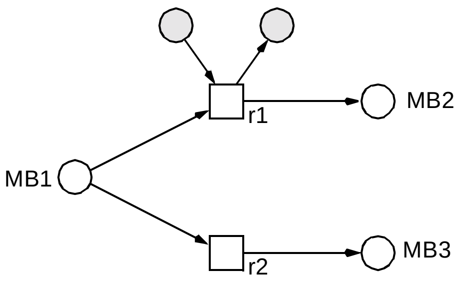
## ❑ CHAIN OF REACTIONS




## ❑ (FREE-CHOICE) BRANCHING




## ❑ BRANCHING WITH SIDE CONDITION





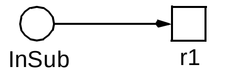



# METABOLIC PETRI NETS

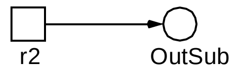
## (1) PLACES

-> 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;

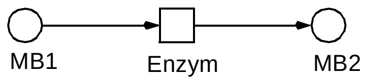
❑ enzymes, if any

## METABOLIC PETRI NETS 2

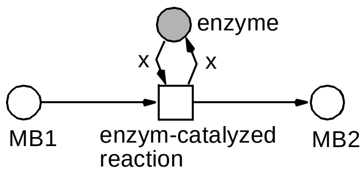
### (2) TRANSITIONS

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

  without the enzyme concentration




  with the enzyme concentration x




  x - amount of units of substances
  required by the reaction

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





## METABOLIC PETRI NETS 3

### (3) ARC INSCRIPTIONS

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

### (4) AMOUNT OF TOKENS

-> amount of available units of substances

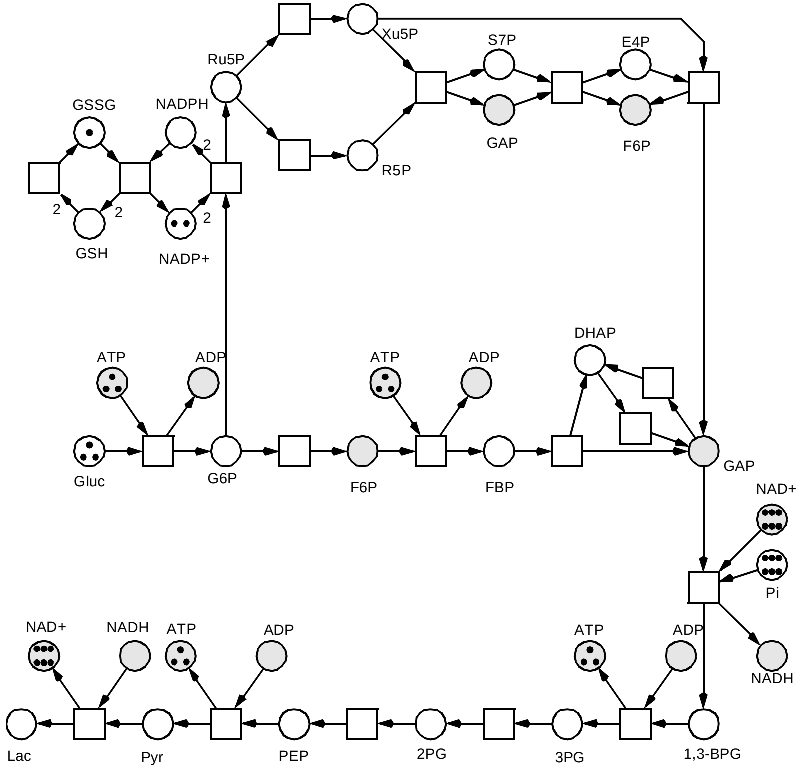
### (5) INITIAL MARKING

-> initial substance distribution

### Σ METABOLIC PETRI NET (MPN):

set of all paths
from the input to the output substrates
taking into consideration the
stoichiometric relations;

# EXAMPLE [REDDY 96] AS PETRI NET, VERSION 1

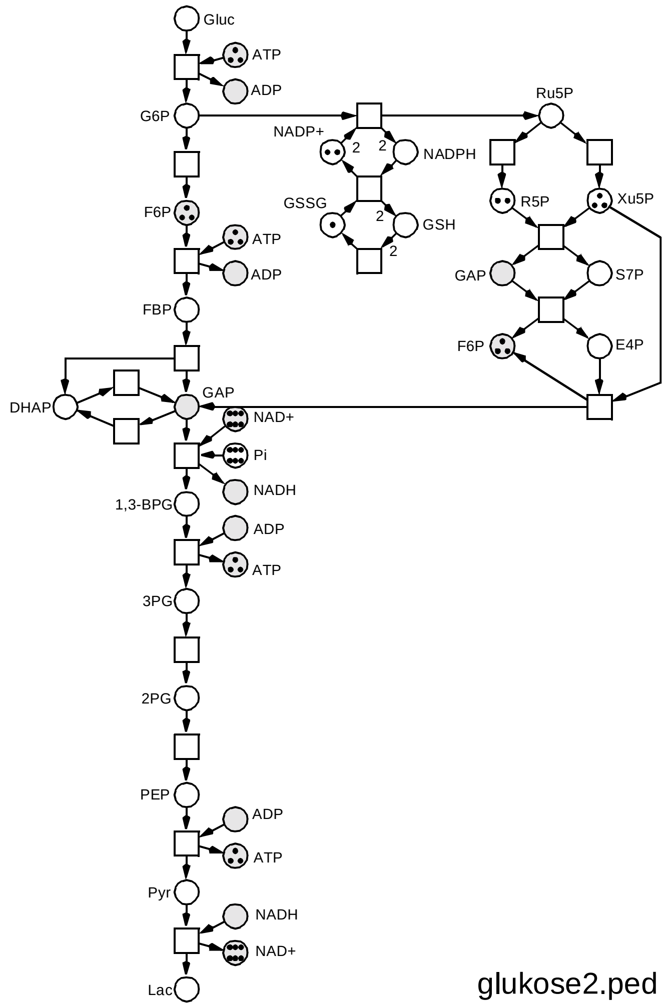



glukose1.ped



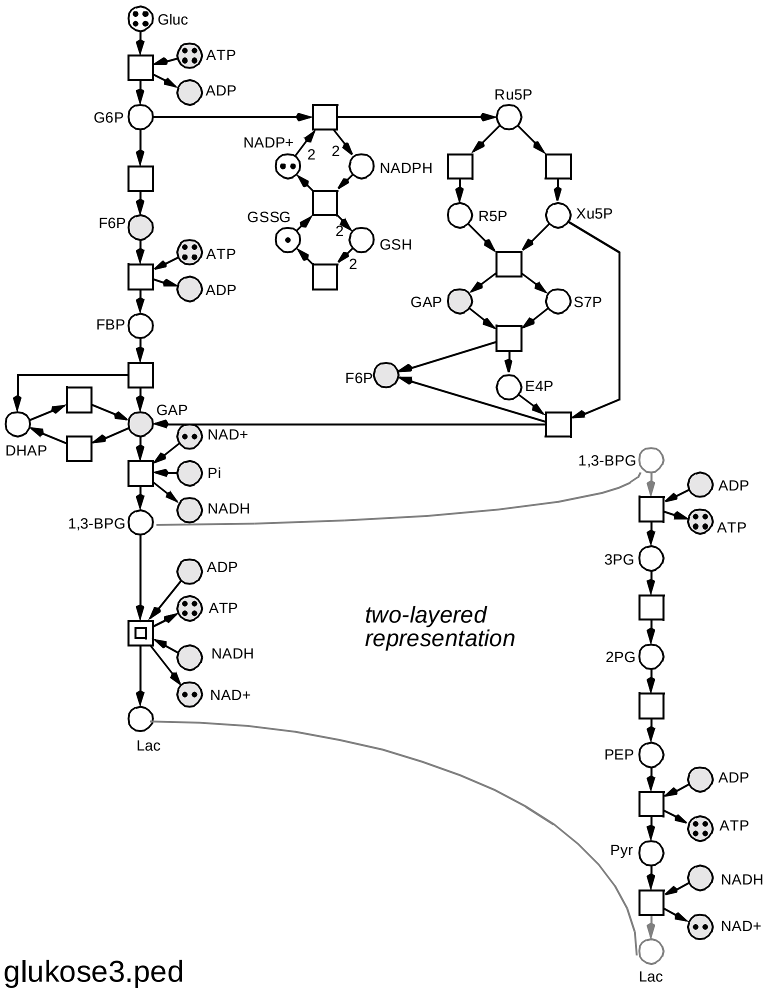


# EXAMPLE [REDDY 96] AS PETRI NET, VERSION 2




glukose2.ped

# EXAMPLE [REDDY 96] AS PETRI NET, VERSION 3

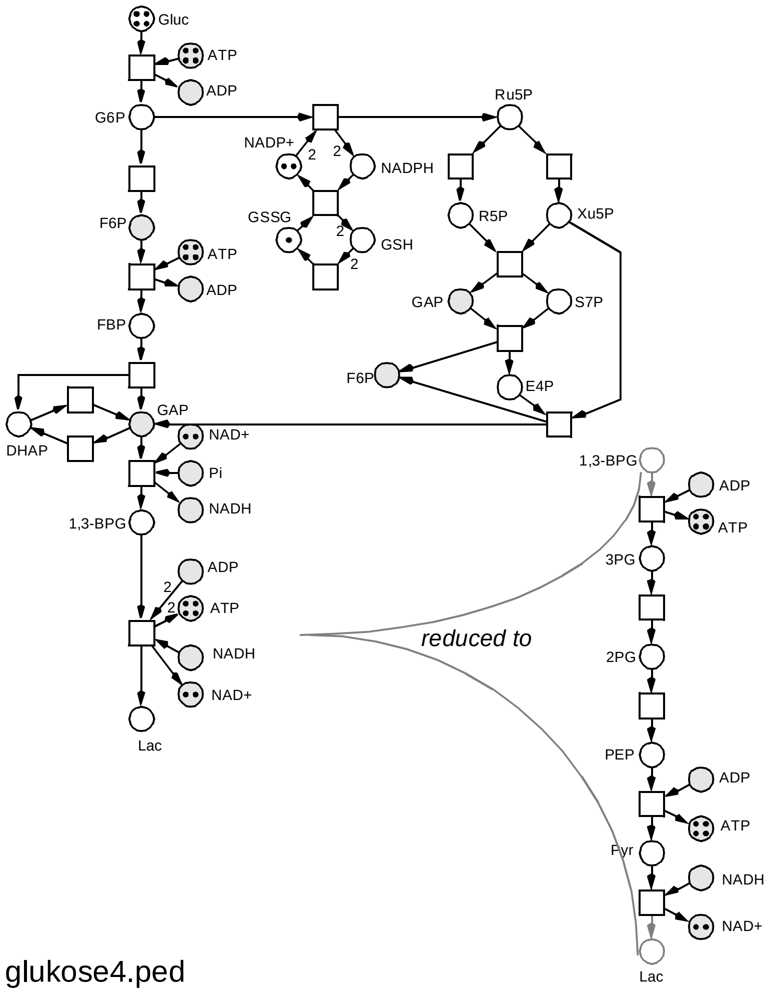



glukose3.ped





# EXAMPLE [REDDY 96] AS PETRI NET, VERSION 4




glukose4.ped

# TYPICAL PETRI NET QUESTIONS

(1) How many tokens may reside at most in a given place?

❑ (0, 1, k, oo)
**-> BOUNDEDNESS**

(2) How often may a transition fire?

❑ (0-times, n-times, oo-times)
**-> LIVENESS**

(3) Is a given system state

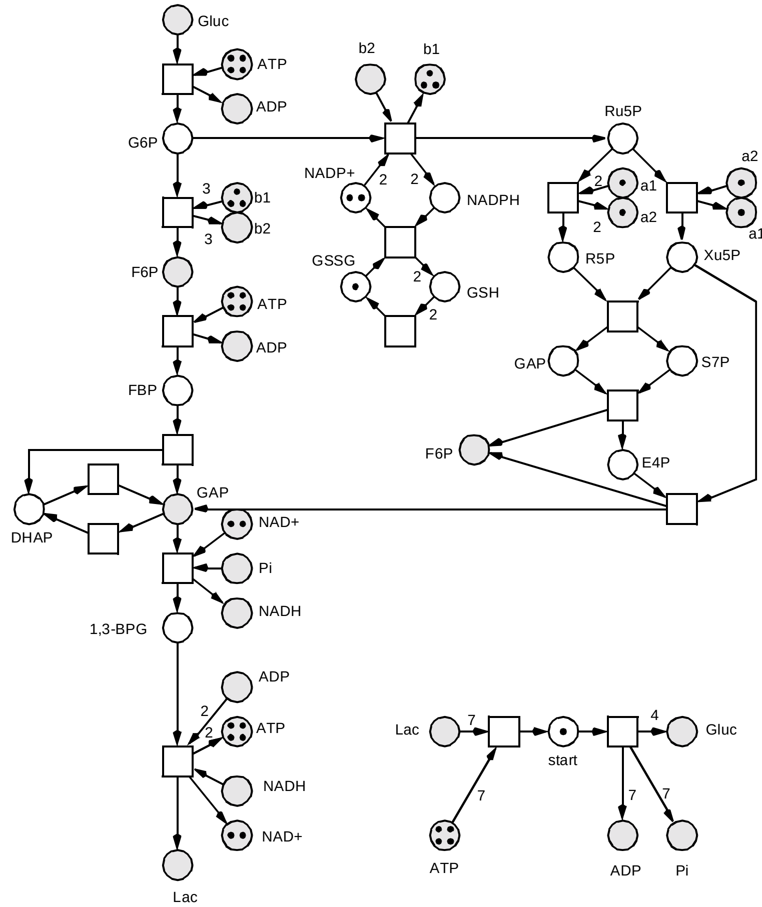
❑ always reachable again?
**-> PROGRESS PROPERTIES**

❑ never reachable?
**-> SAFETY PROPERTIES**





# EXAMPLE [REDDY 96] AS PETRI NET, VERSION 5




glukose4_zyk.ped

## ASSUMPTIONS IN VERSION 5

- the two appearances of GAP can be separated (no logical / fusion nodes)

- the branching probabilities at the conflicts of
  G6P and Ru5P
  are known and
  may be characterized by the relations
  G6P - 3 : 1
  Ru5P - 2 : 1

  -> STEADY STATE:
  all intermediates have to be balanced with respect to inputs and outputs



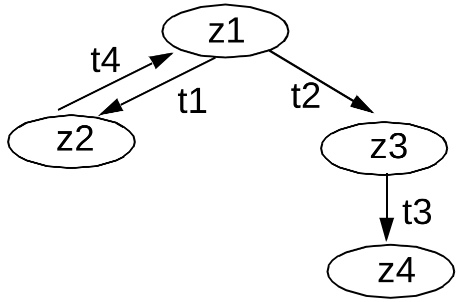


## TYPICAL ANALYSIS TECHNIQUES 1

**(1) TOKEN GAME (?)**

**(2) REACHABILITY GRAPH**

nodes: system states
arcs: the firing transition




**(3) REDUCED REACHABILITY GRAPH**

**(4) STRUCTURAL ANALYSES**

e. g.: conservative -> bounded

# TYPICAL ANALYSIS TECHNIQUES 2

## (5) NET INVARIANTS

- P-INVARIANTS

  -> set of places with (weighted) constant token sum;

  mPn: meta substance preservation rules, all electron carriers

  Ex: P-Invariant (Pi ,..., Lac); i.e. their can be produced only as much lactate as $P_i$ is provided;

- T-INVARIANTS

  -> set of transitions, reproducing a given marking;

  mPn: reaction chains, reproducing a substance distribution;

  BND, LIVE mPn: elementary modes [Schuster 9x]

  Ex: forward / backward reaction of the triose phosphate isomerase





# QUALITATIVE ANALYSIS TECHNIQUES

static analysis:

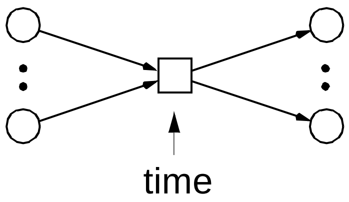
- NET REDUCTION
- STRUCTURAL PROPERTIES
- LINEAR PROGRAMMING
  - place / transition invariants
  - state / trap equation

dynamic analysis *(model checking)*:

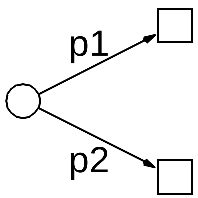
- REACHABILITY ANALYSIS
  - (complete) reachability graph
  - compressed state spaces
    - OBDDs, ONDDS
    - Kronecker products
  - reduced state spaces
    - coverability graph
    - symmetry
    - stubborn / sleep sets
  - branching processes
  - concurrent automaton

# Integration of Qualitative and Quantitative Analyses

- ❑ TIME CONSUMPTION




- ❑ BRANCHING PROBABILITIES




$$p1 + p2 = 1$$





# Model Classes

PETRI NETS

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

## Applications of Metabolic Petri Nets

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

(2) graphical model animation (simulation)
with / without disturbances

(3) validation of metabolic models
-> model integrity

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

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





## Derived Basic Questions

- relation between

  metabolic network properties ⟷ Petri net properties

- relation between

  metabolic control theory ⟷ Petri net theory

  (Heinrich) (Heiner)

-> pros / cons ?
-> strength / weaknesses ?

## Work Packages 1

**(A) Mapping the Terminologies**

- A-1 selection of case studies
- A-2 initial comparison of modelling principles
- A-3 initial comparison concerning typical analysis questions

**(B) Investigation of the A-1 Case Studies**

- B-1 by means of control theory
- B-2 by means of Petri net theory

**(C) Case Studies' Result Comparison**

- C-1 modelling power
- C-2 qualitative analysis
  -> power / efficiency
- C-3 quantitative analysis
  -> power /efficiency





## Work Packages 2

**(D) Integration**

- D-1 definition of selection criteria
- D-2 proposal of a combined methodology

**(E) Petri Net Based Analyses**

- E-1 supplementing model validation
- E-2 realization with available pn techniques
- E-3 dedicated tool kit

**(F) Case Studies**

- -> more sophisticated case studies

**(G) Tutorial & Demo Version**

**(H) Final Report**