PETRI NETS 4
BACTERIAL BIOENGINEERING

Monika Heiner

on sabbatical leave from **Brandenburg Technical University**
Computer Science Institute

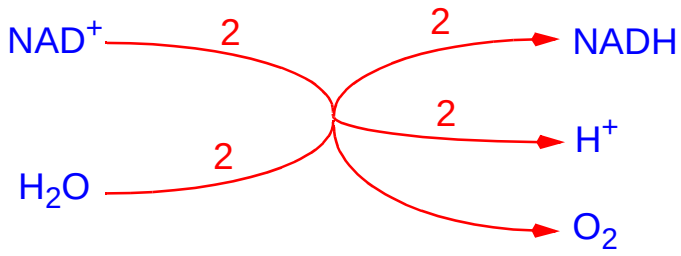
THE PETRI NET FRAMEWORK

monika.heiner@brunel.ac.uk

...

ARE NETWORKS OF BIOCHEMICAL REACTIONS

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



. . .

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NATURALLY EXPRESSIBLE AS PETRI NETS

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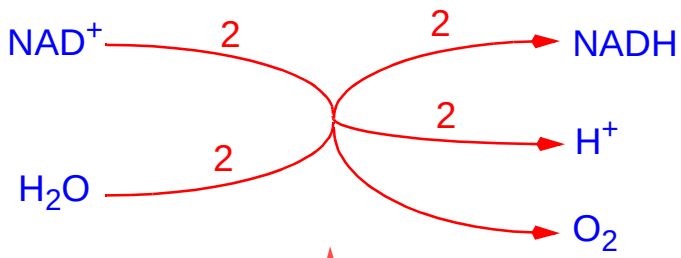
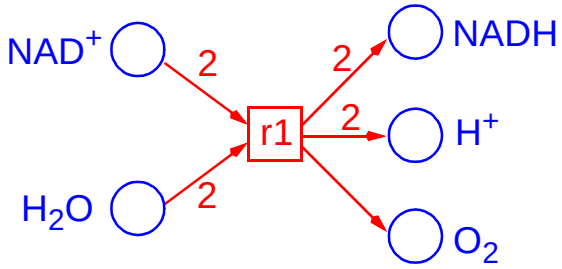


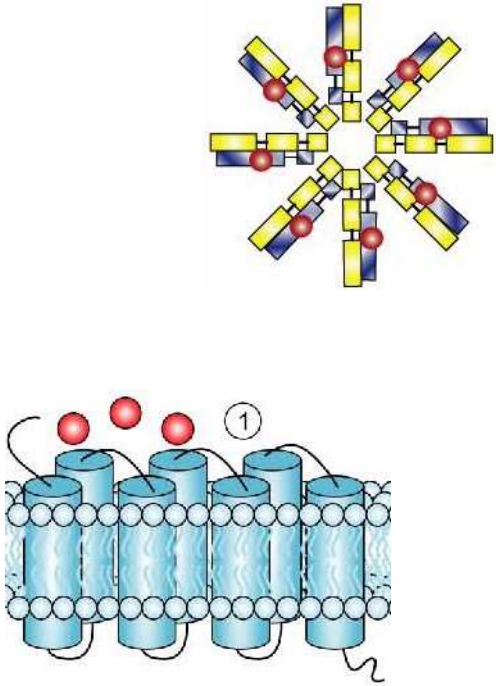
hyper-arcs



PLACES, TRANSITIONS - SOME BIO INTERPRETATIONS

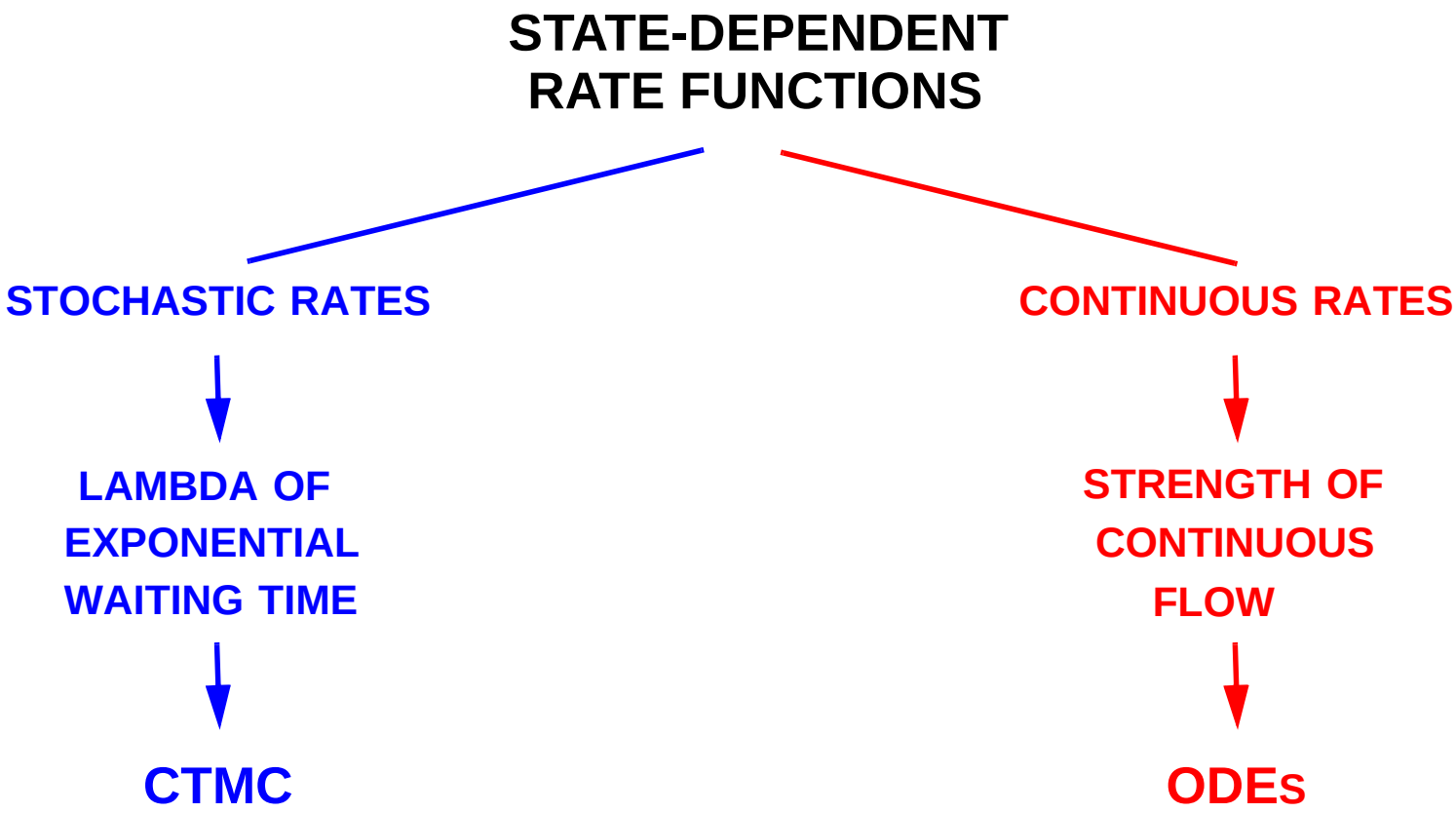
- **places -> model variables**
  - -> *(bio-) chemical compounds*
  - -> *proteins*
  - -> *protein conformations*
  - -> *complexes*
  - -> *genes, . . . , etc.*
  - *. . . in different locations*

- **transitions -> atomic events**
  - -> *(stoichiometric) chemical reaction*
  - -> *complexation / decomplexation*
  - -> *phosphorylation / dephosphorylation*
  - -> *conformational change*
  - -> *transport step, . . . , etc.*
  - *. . . in different locations*



STATE-DEPENDENT RATE FUNCTIONS

ADDING TIME



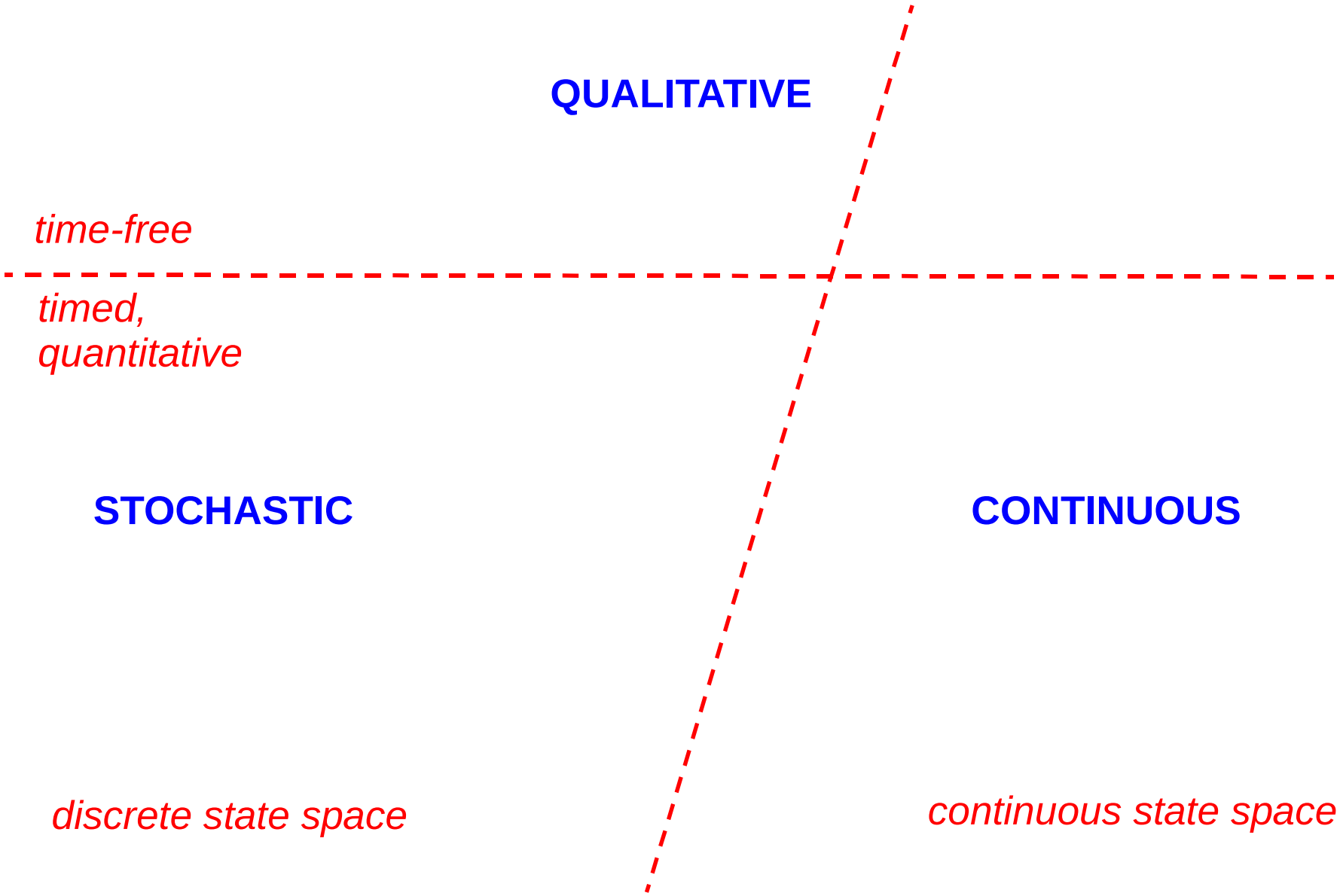
-> supported by, e.g., COPASI, Dizzy, ..., Snoopy

QUALITATIVE

STOCHASTIC

CONTINUOUS

FRAMEWORK 2007



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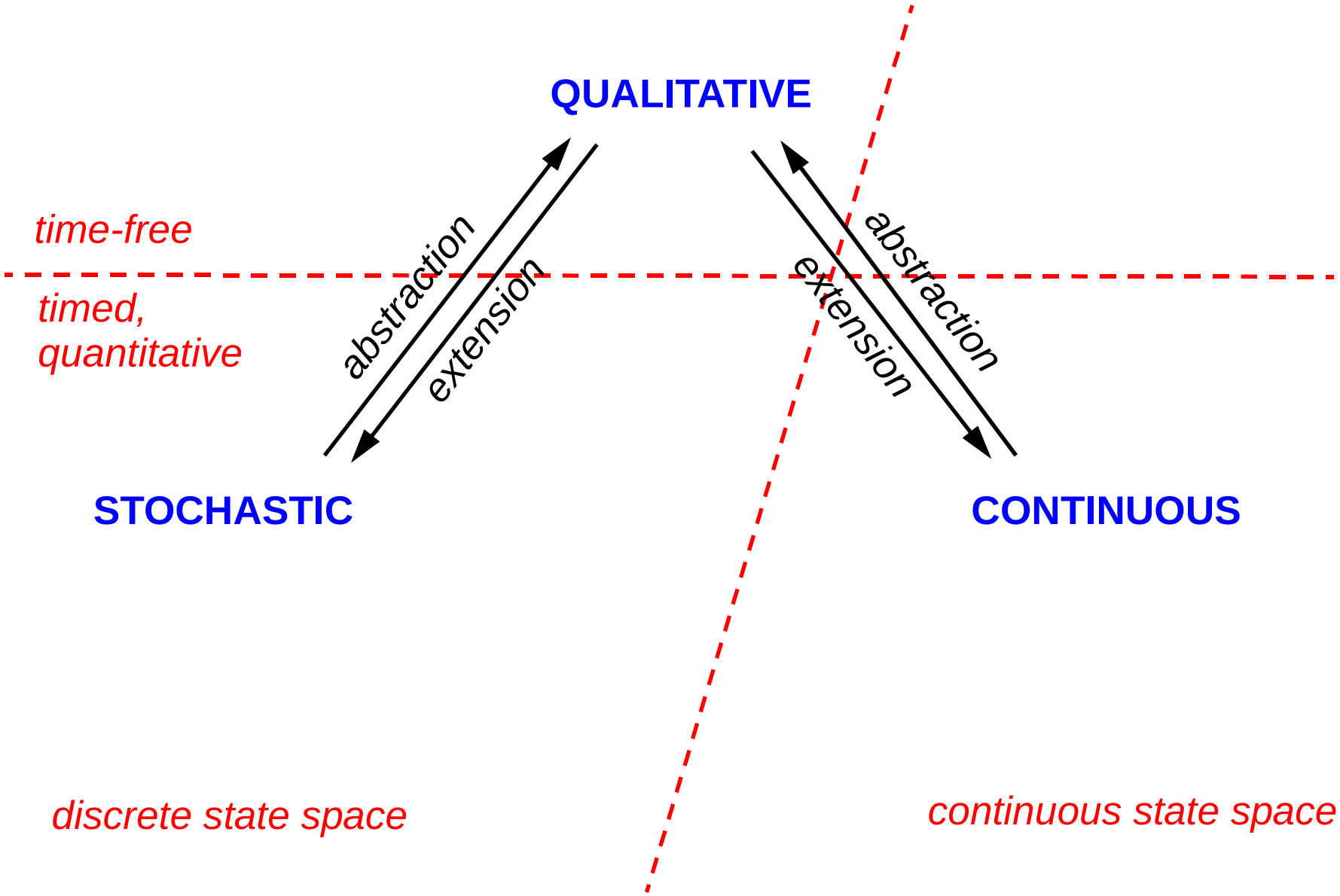

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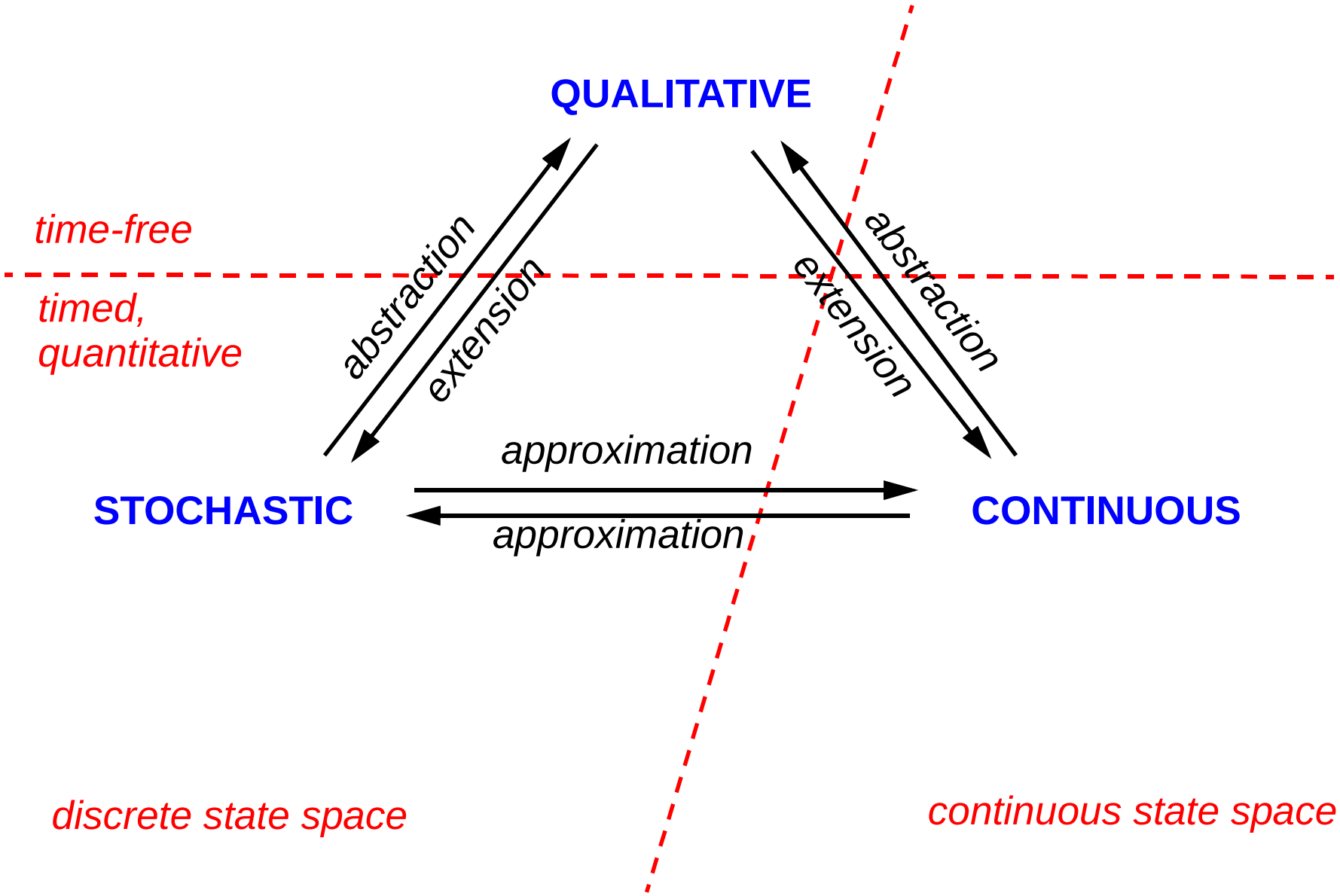
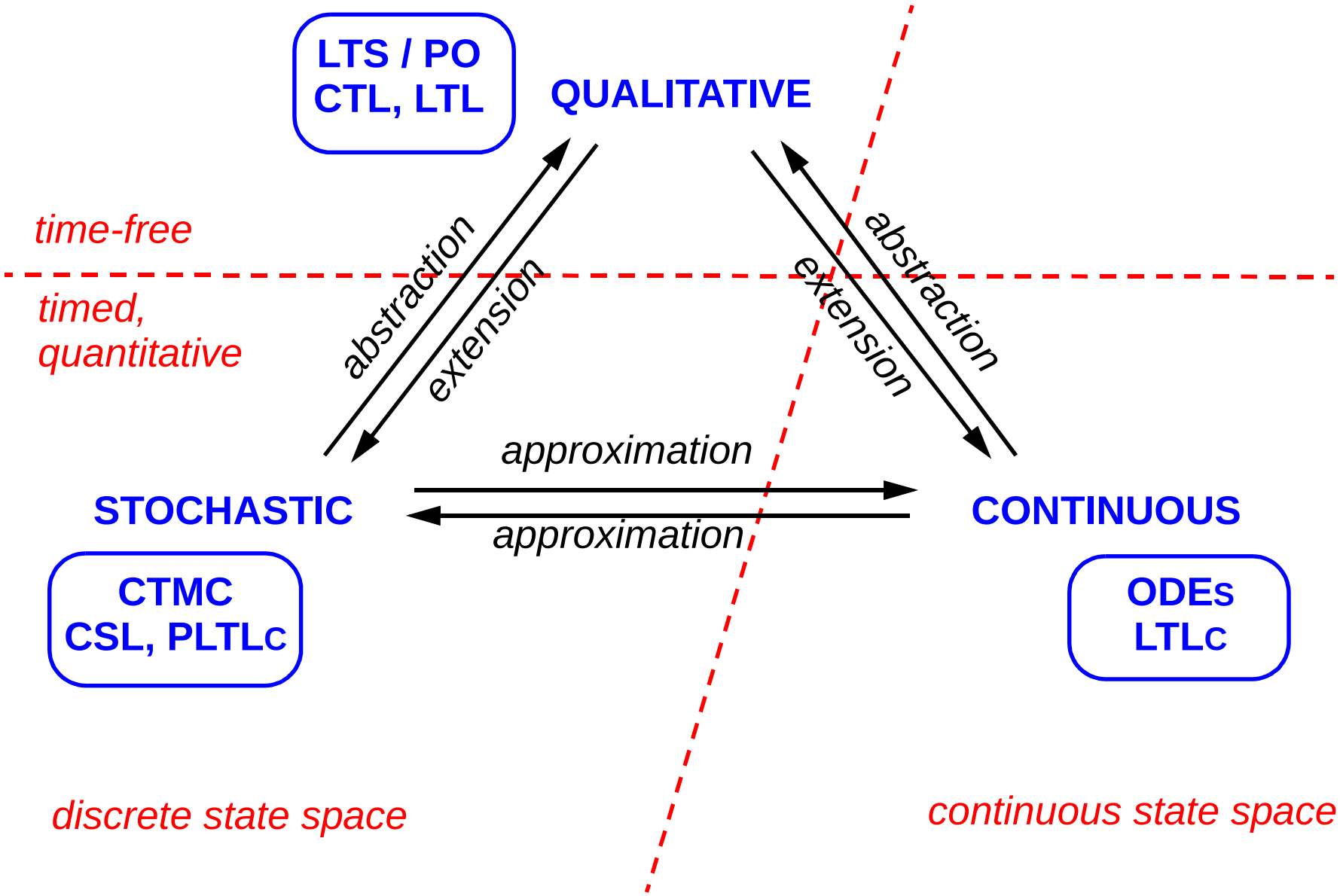

QUALITATIVE
time-free
timed,
quantitative
abstraction
extension
abstraction
extension
approximation
approximation
STOCHASTIC
CONTINUOUS
discrete state space
continuous state space

FRAMEWORK 2007



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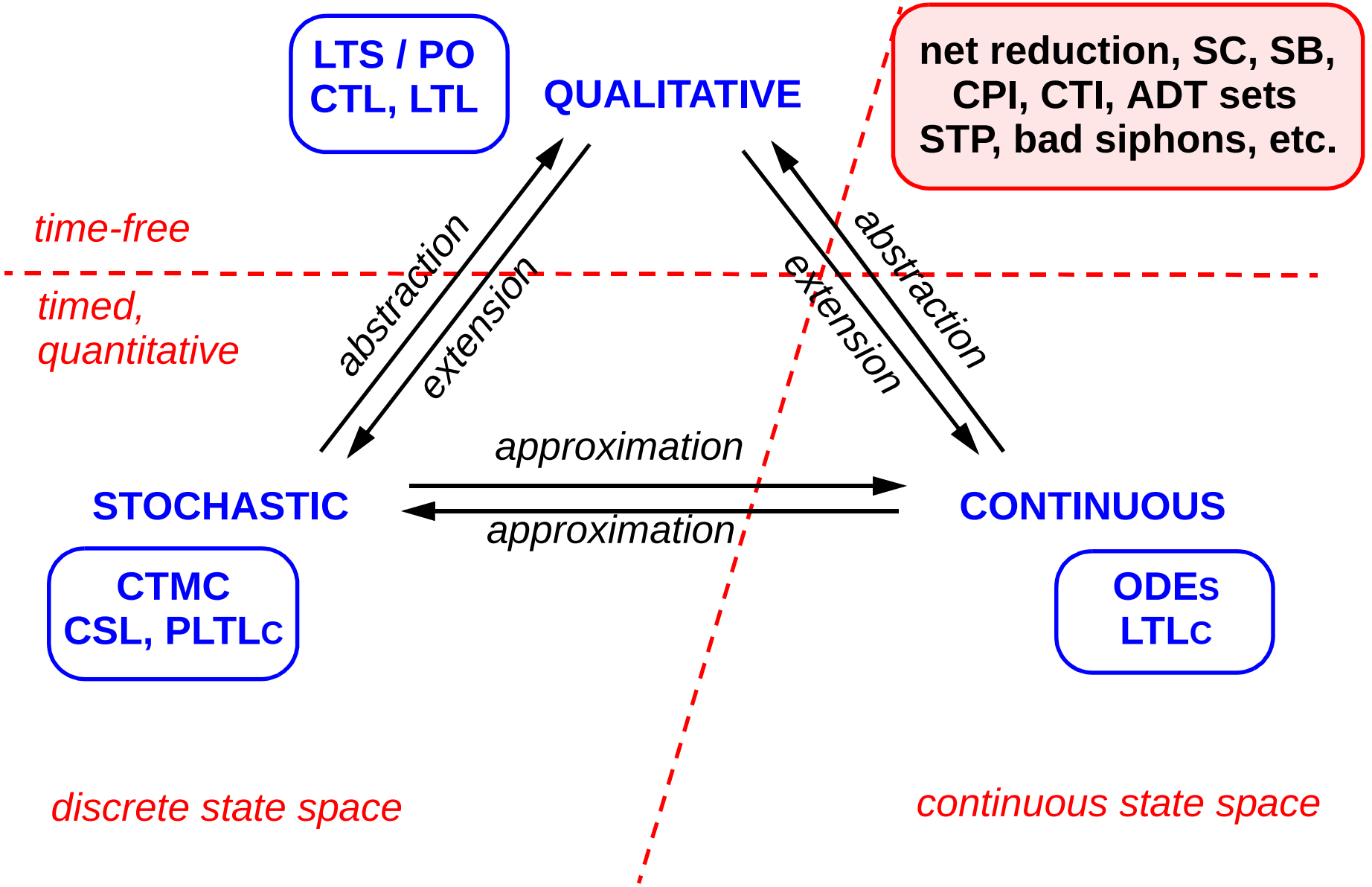
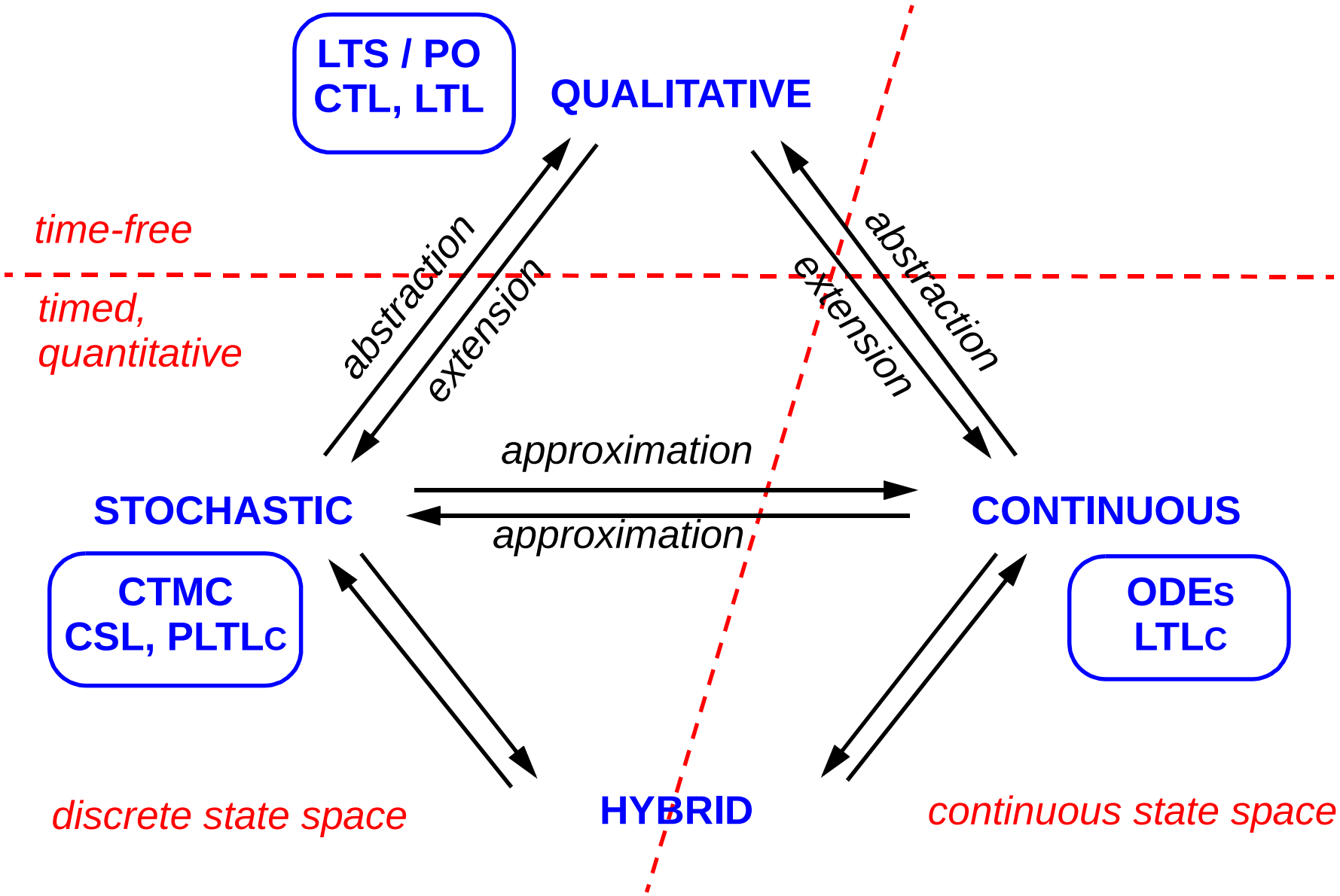
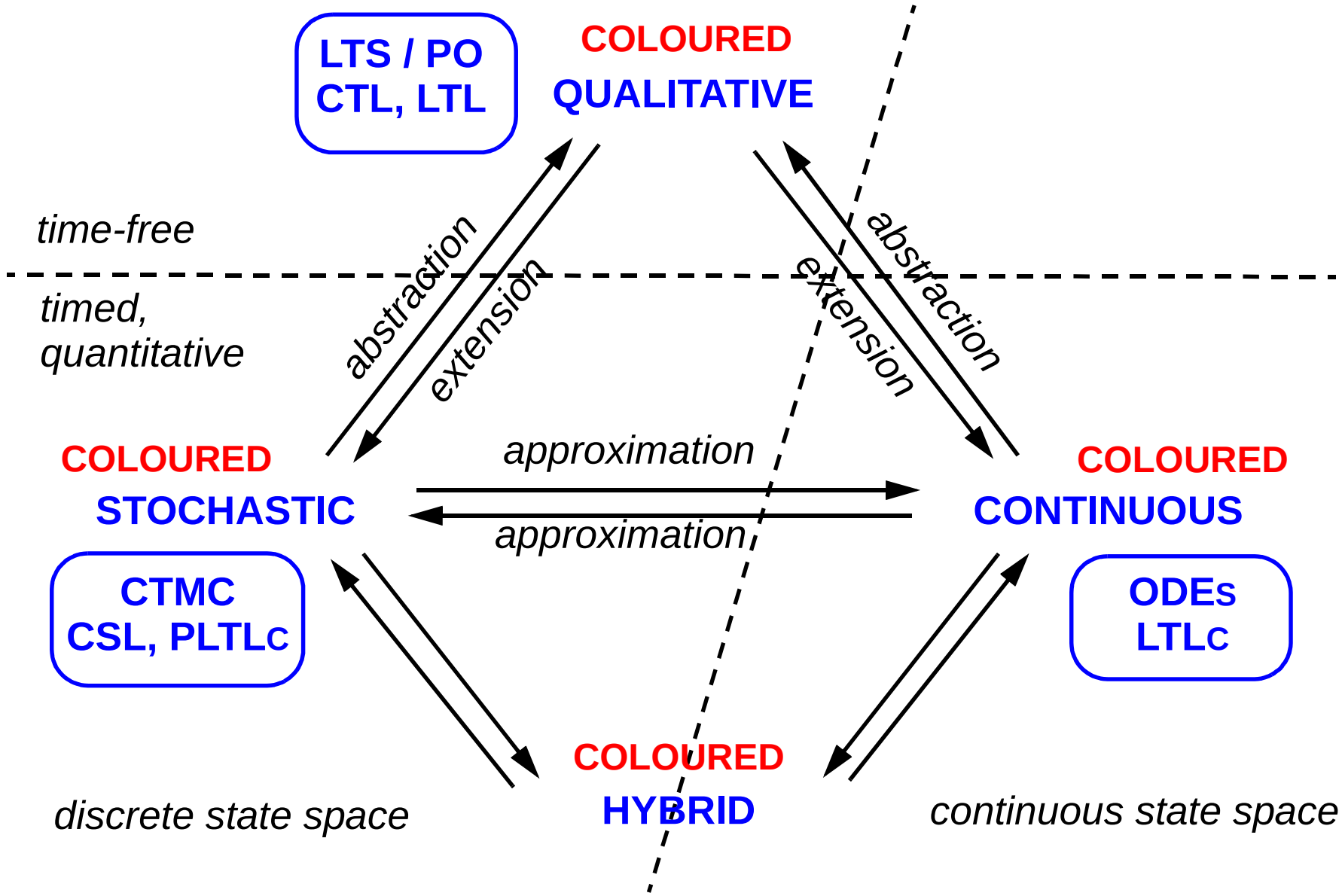


FRAMEWORK 2010



COLOURED FRAMEWORK 2011



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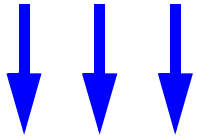
4x2

MODELS SHARING STRUCTURE



QUANTITATIVE MODEL = QUALITATIVE MODEL

+

RATE FUNCTIONS (KINETICS)

Our Toolbox

OUR TOOL BOX

SNOOPY

-> *modelling and animation/simulation of hierarchical graphs,*
e.g. various Petri net classes, e.g. PN, XPN, SPN, XSPN, CPN, ...

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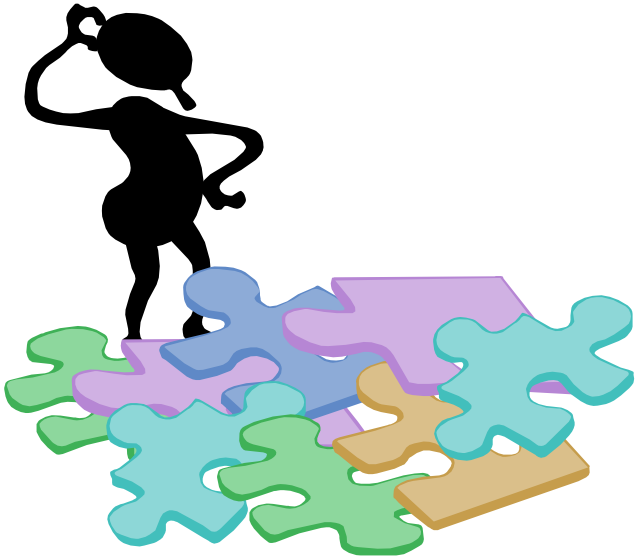
SBML import/export

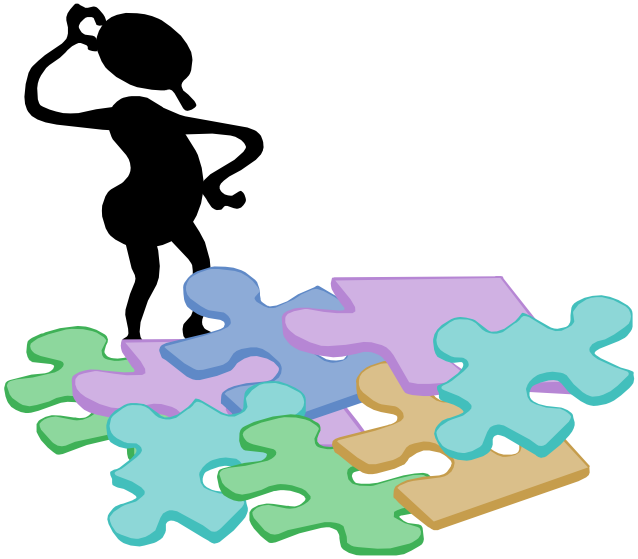
EXPORT TO MATAB AND

MANY OTHER TOOLS

PETRI NETS - THE BIG PROS



PETRI NETS - THE BIG PROS



- **readable & unambigious**
  -> fault avoidant model construction
- **locality - causality - concurrency**
- **compositional, hierarchical notations**
  -> logical and macro nodes
- **executable**
  -> animation, simulation (token game)

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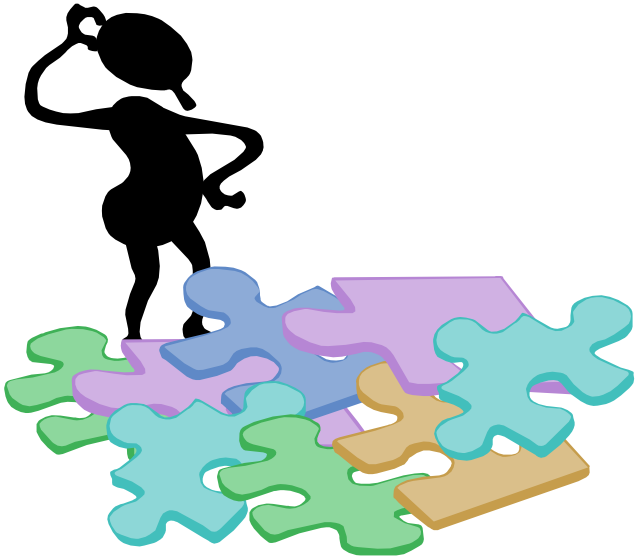

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  - -> *Siphon/Trap Property (STP), reduction rules, . . .*

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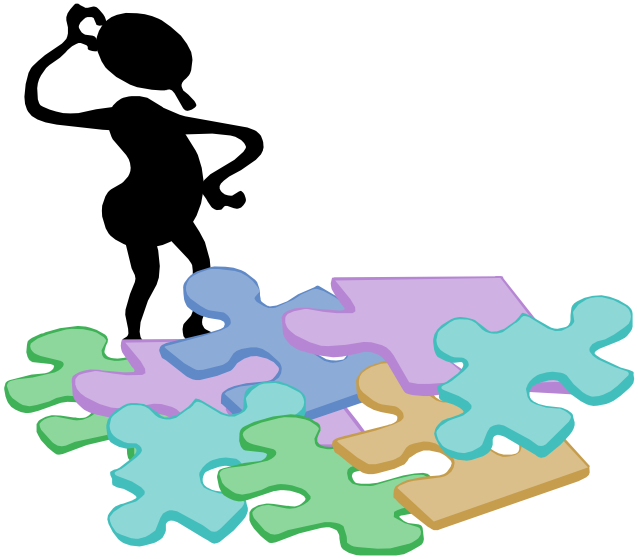

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- **umbrella with unifying power**
  - -> *interpretation in qualitative / stochastic / continuous / hybrid paradigm*

T- INVARIANTS

(ELEMENTARY MODES)

(EXTREME PATHWAYS)

(GENERIC PATHWAYS)

T- INVARIANTS, EX

r1: A -> 2 B
r2: 2 A -> 3 C

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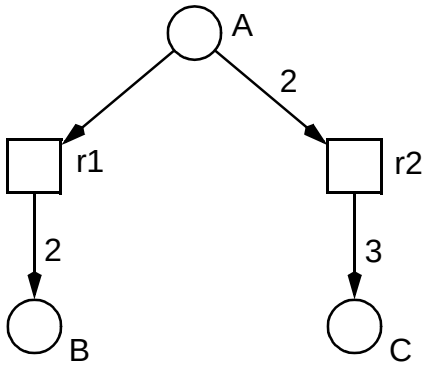

T- INVARIANTS, EX

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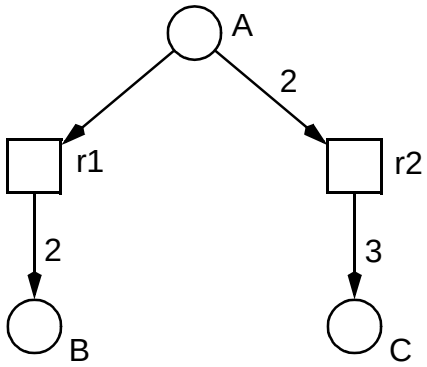

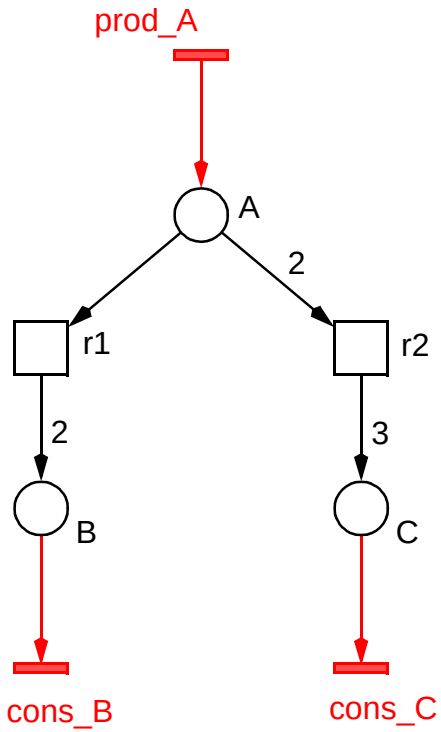

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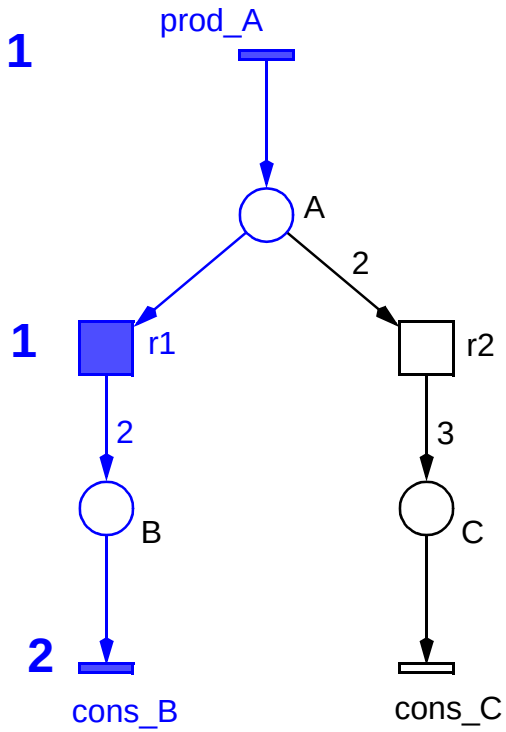
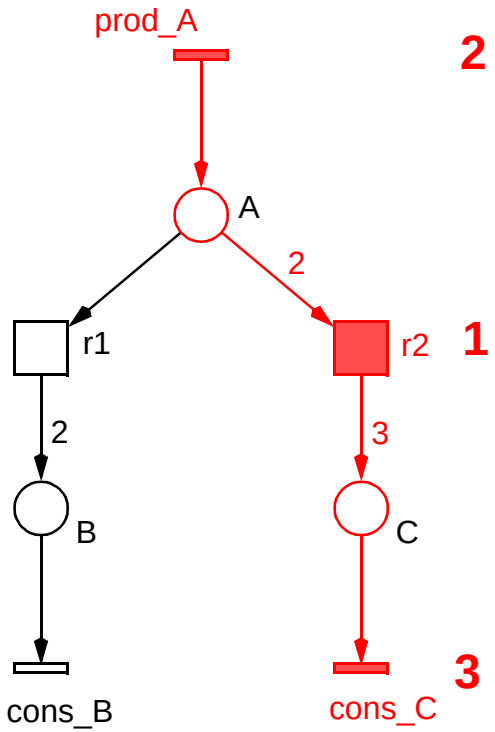


T-INVARIANT 1



T-INVARIANT 2

INCIDENCE MATRIX C

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

$C =$

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

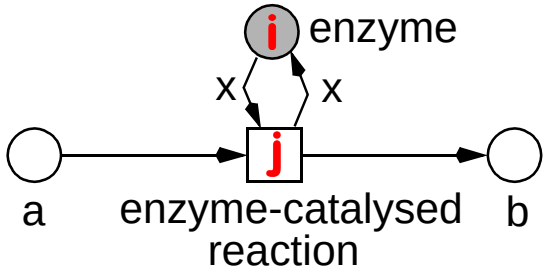
$cij = (pi, tj) = F(tj,pi) - F(pi, tj) = \Delta\, tj(pi)$

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

- **matrix entry cij:**
  token change in place pi by firing of transition tj

- **matrix column Δtj:**
  vector describing the change of the whole marking by firing of tj

- **side-conditions are neglected**



cij = 0

T-INVARIANTS, BASICS

- **Lautenbach, 1973** -> **Schuster, 1993**
- **T-invariant x** -> *multiset of transitions*
  -> *integer solution of* $Cx = 0, x \neq 0, x \geq 0$
- **support of a T-invariant x -> supp(x)** -> *set of transitions*
  -> *set of transitions involved, i.e.* $x(i) \neq 0$
- **minimal T-invariants**
  -> *there is no T-invariant with a smaller support*
  -> *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*

$$kx = \sum_i a_i x_i$$

T-INVARIANTS, INTERPRETATIONS

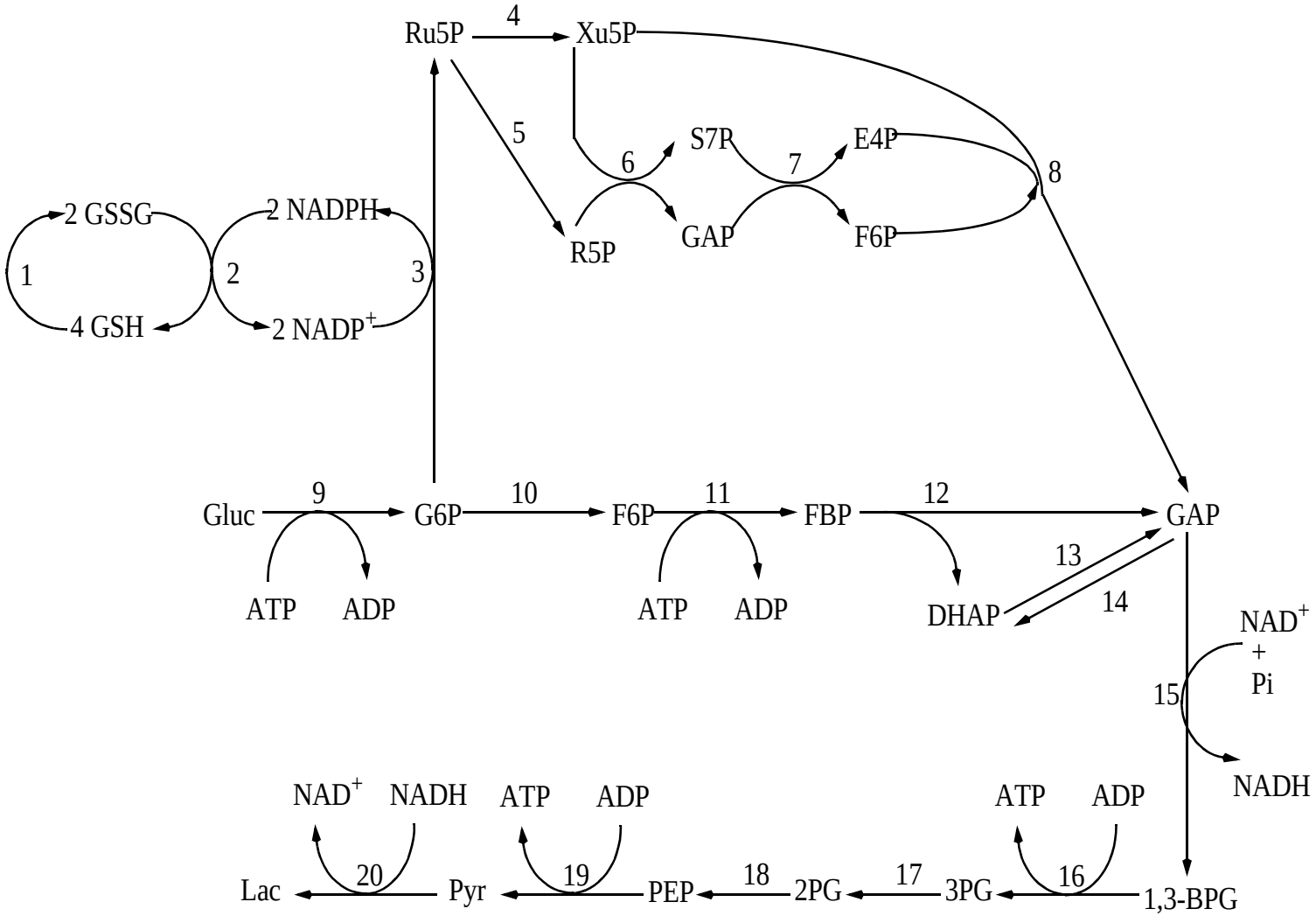
- **T-invariants = (multi-) sets of transitions = Parikh vector**
  - -> *zero effect on marking*
  - -> *reproducing a marking / system state*

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

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

Ex1 - Glycolysis and Pentose Phosphate Pathway

[Reddy 1993]



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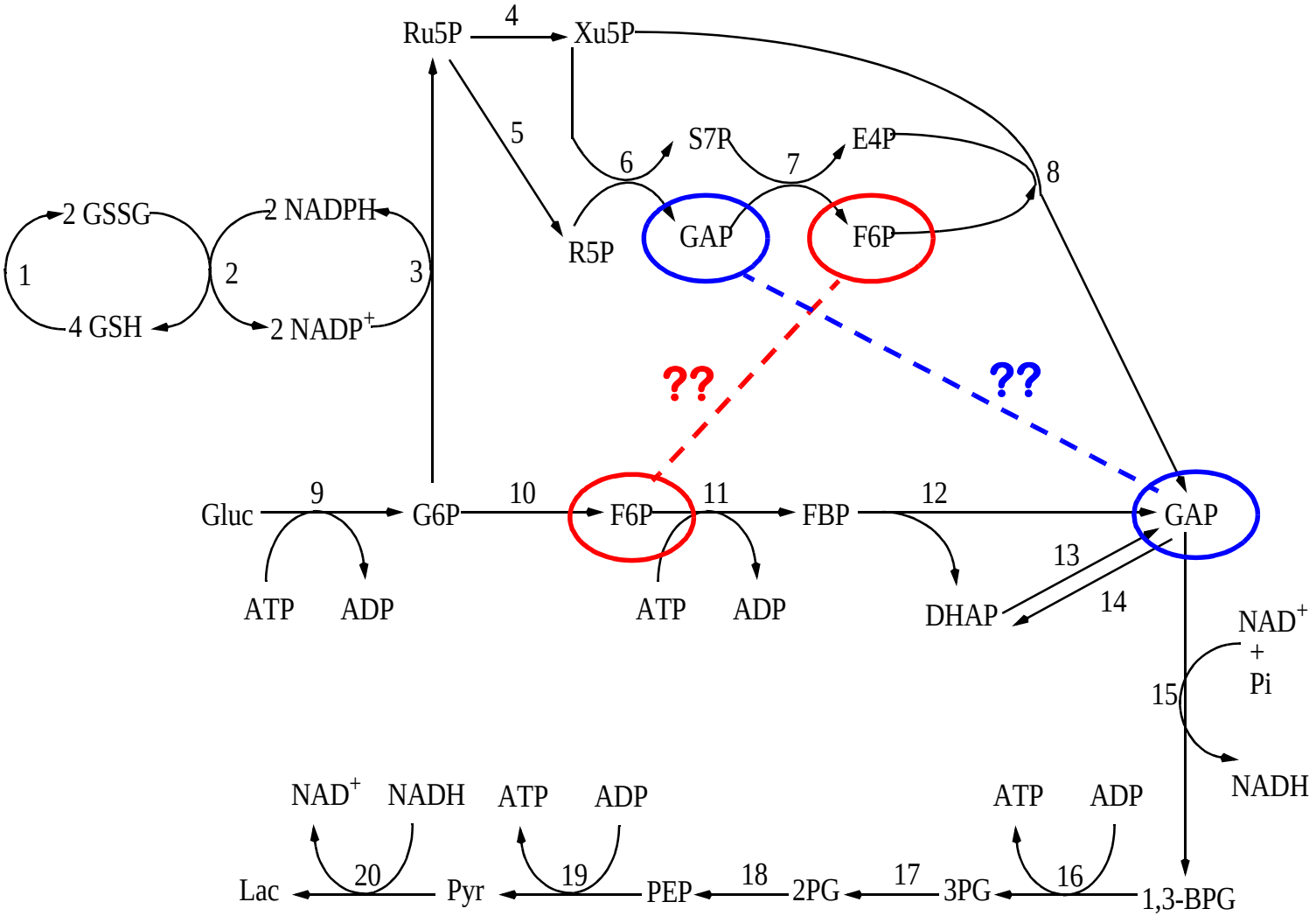

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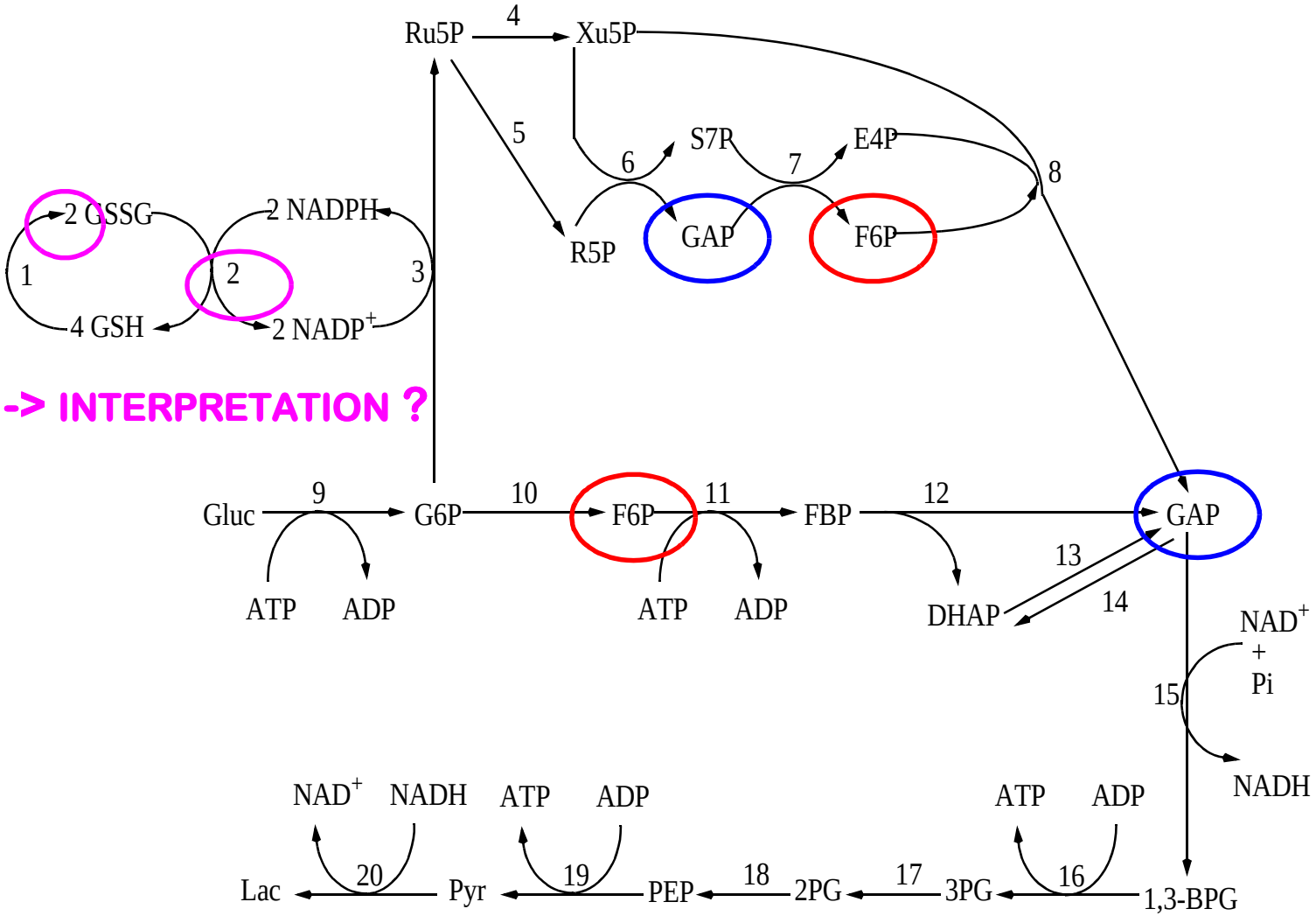

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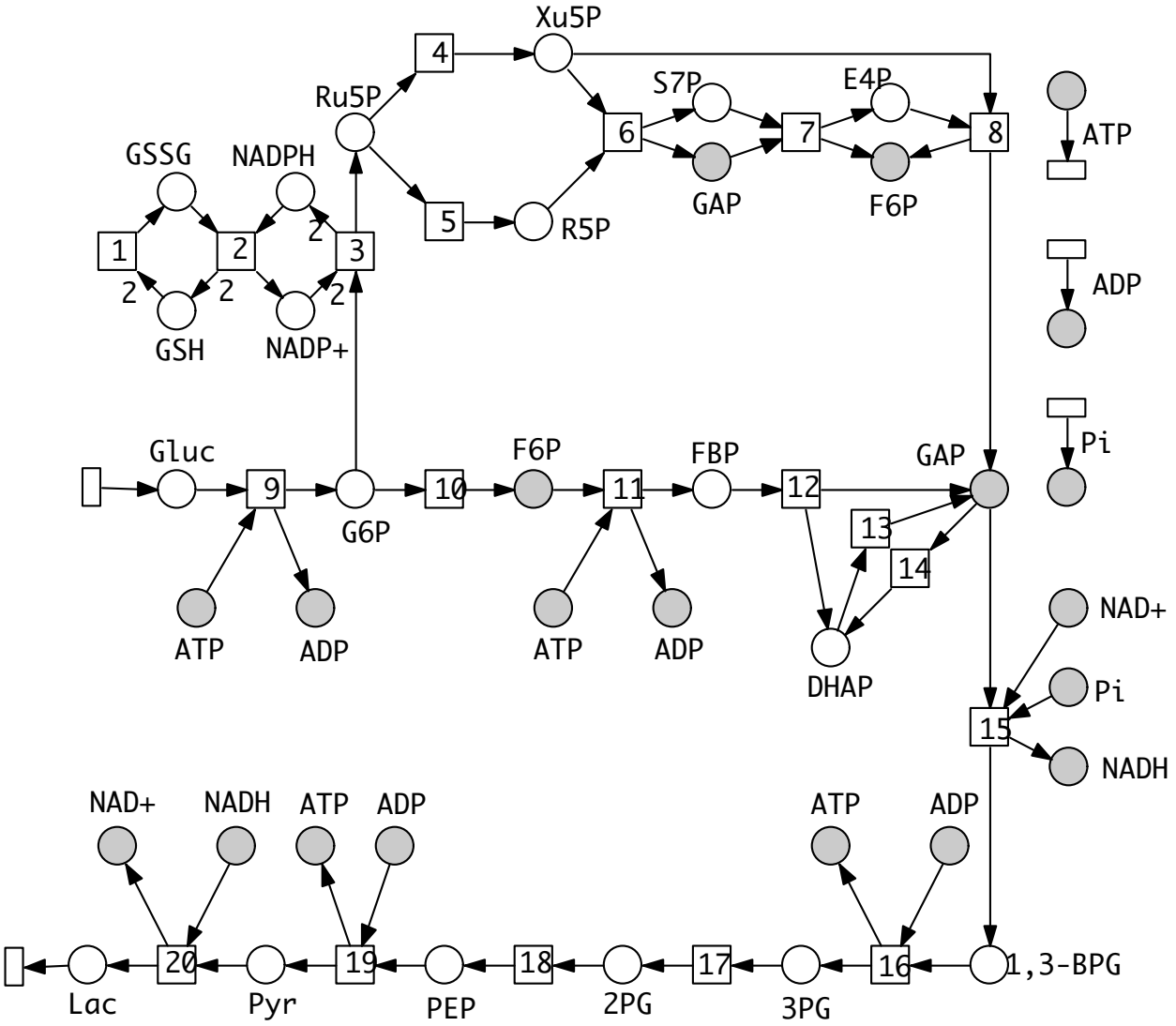

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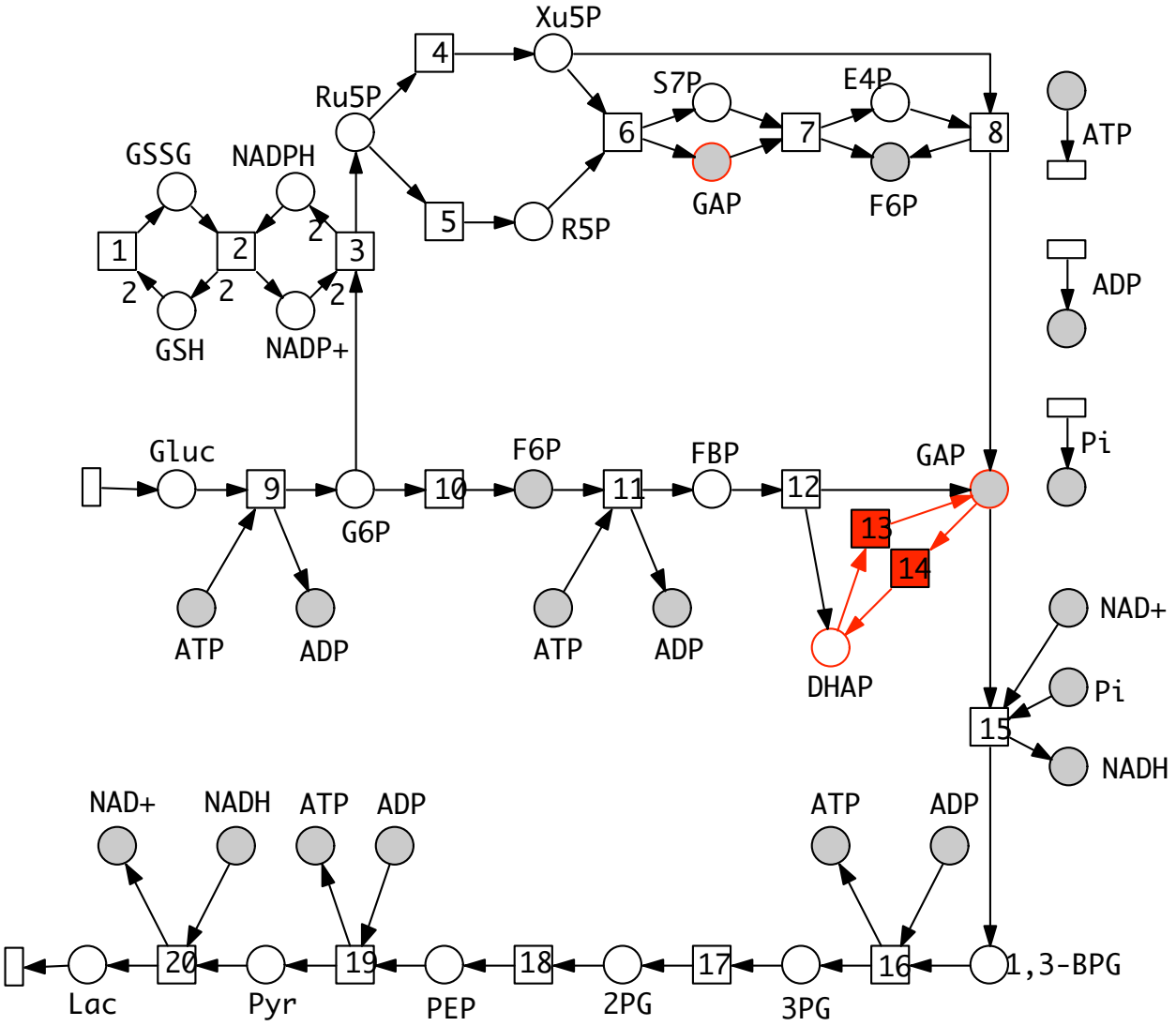

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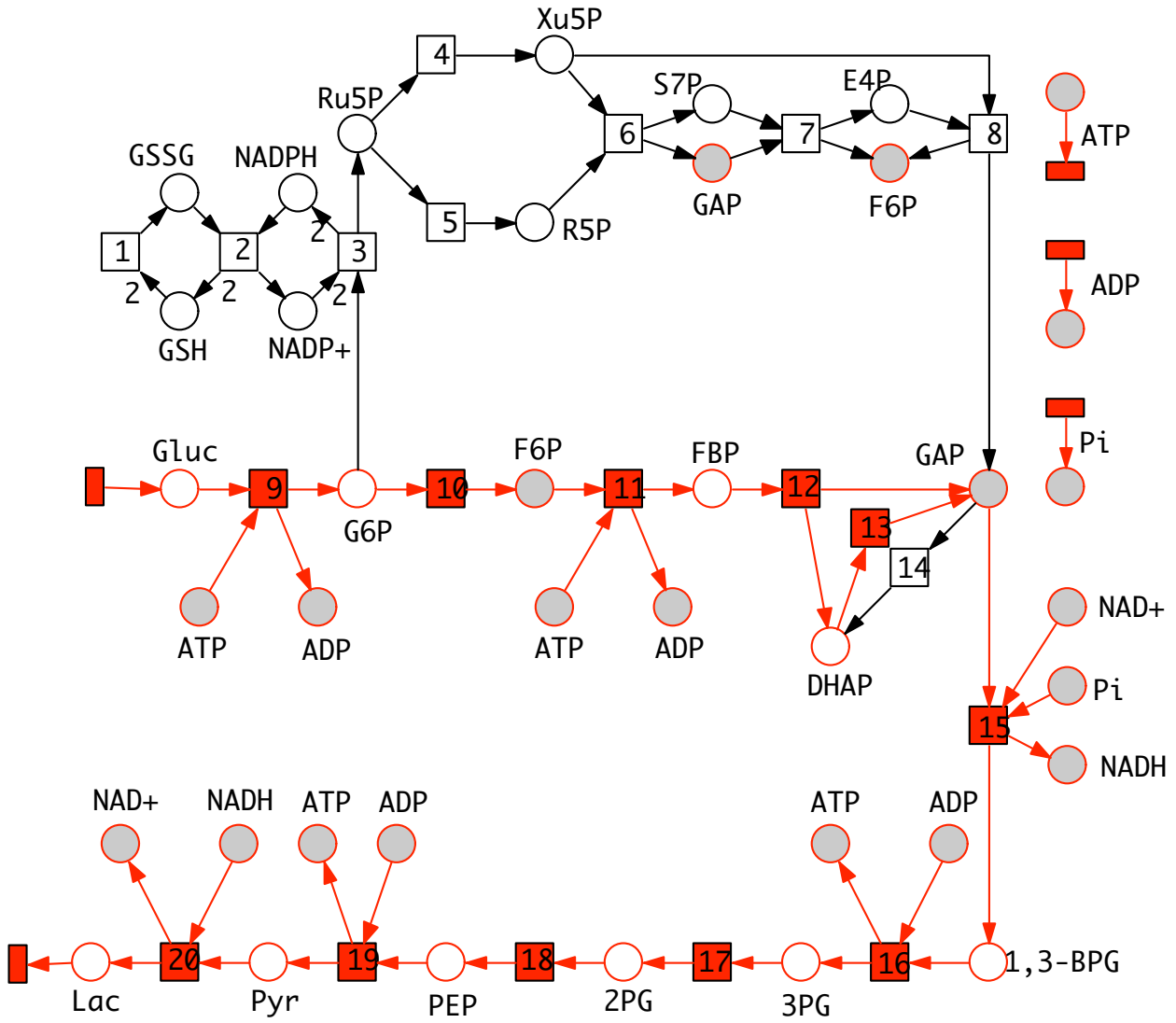

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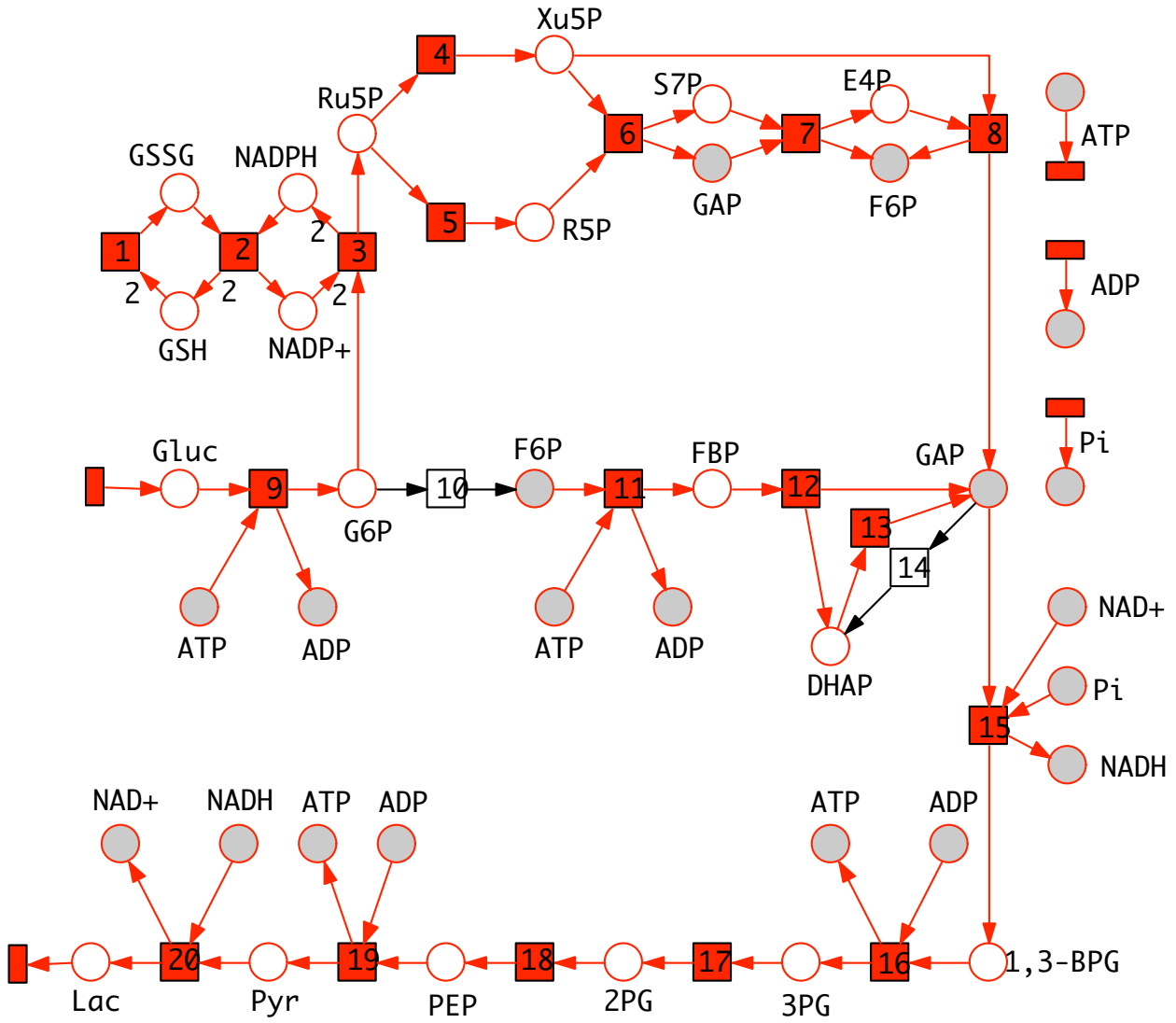

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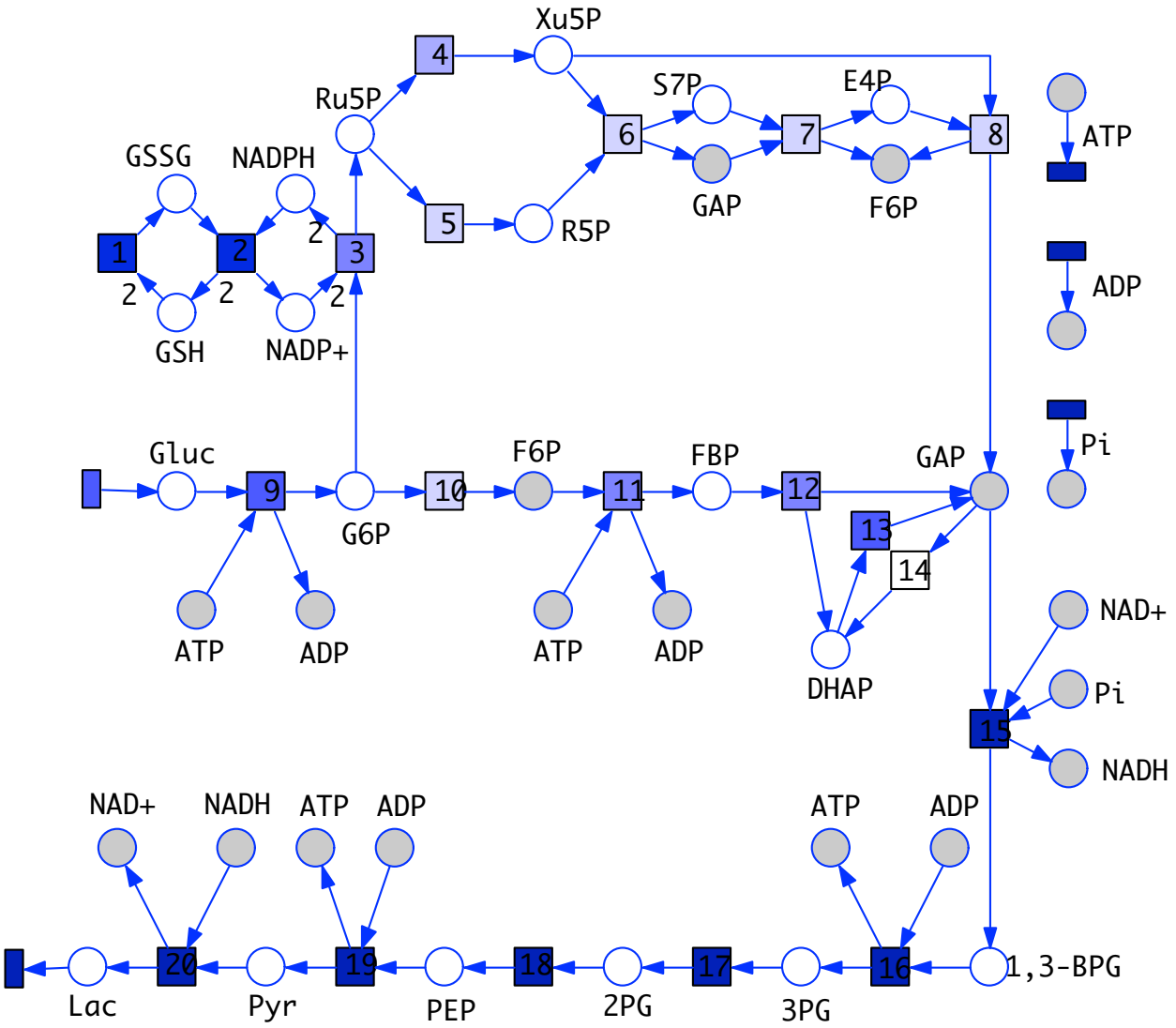

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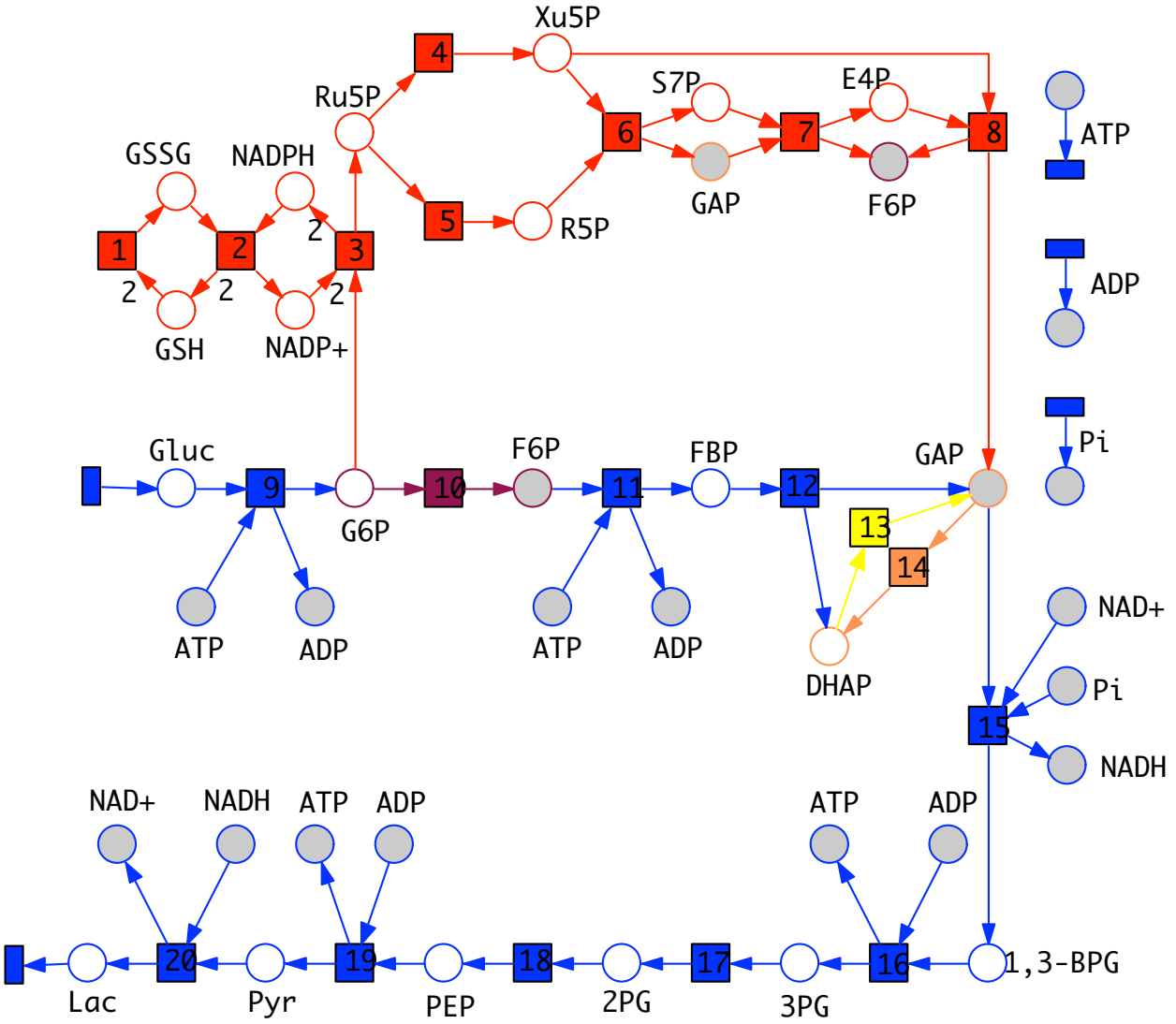

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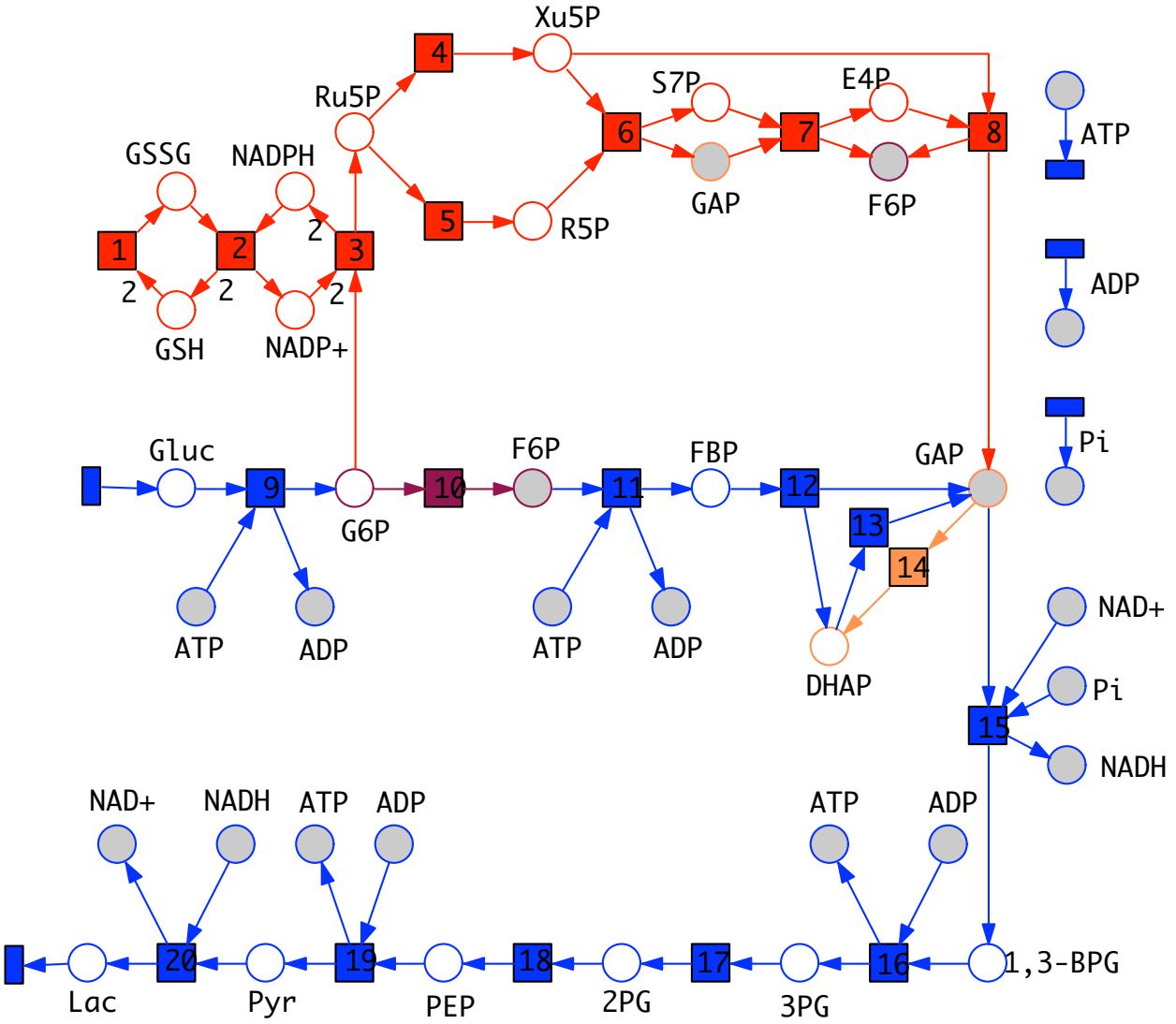

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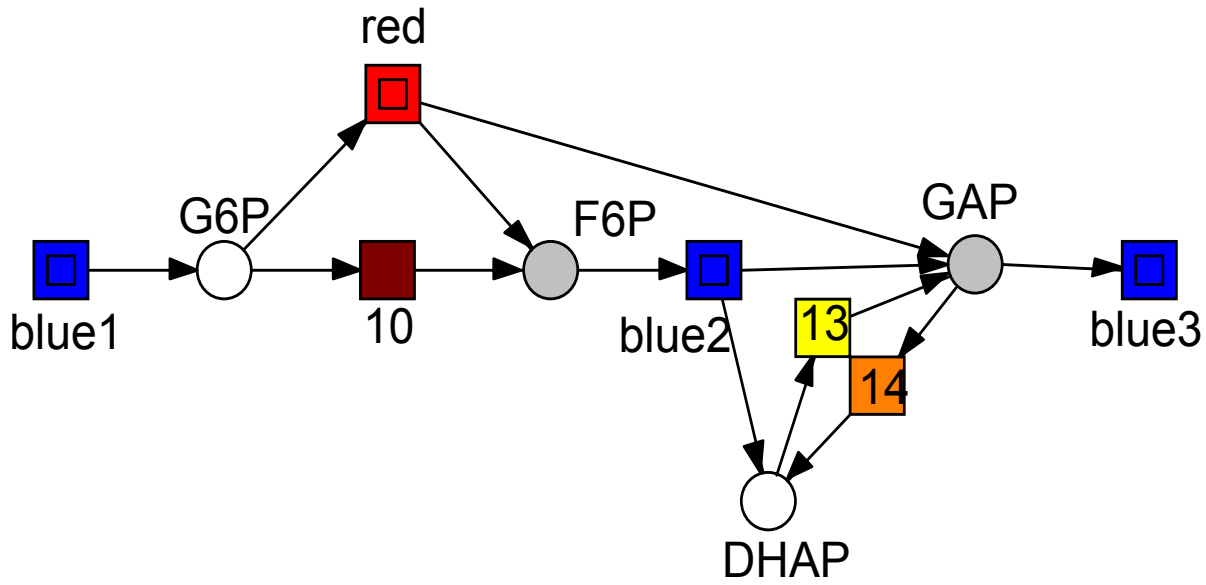

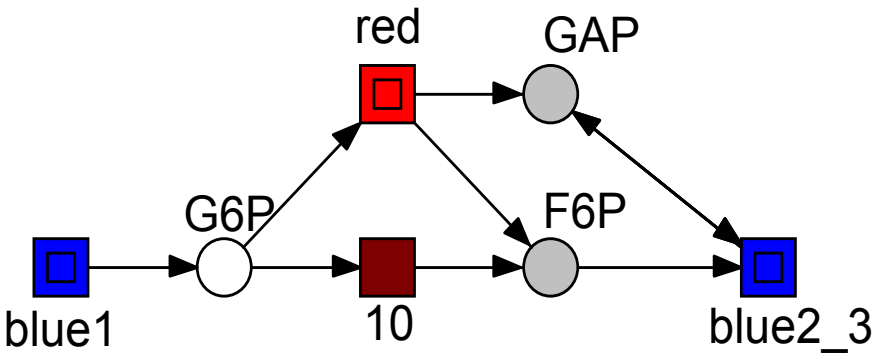

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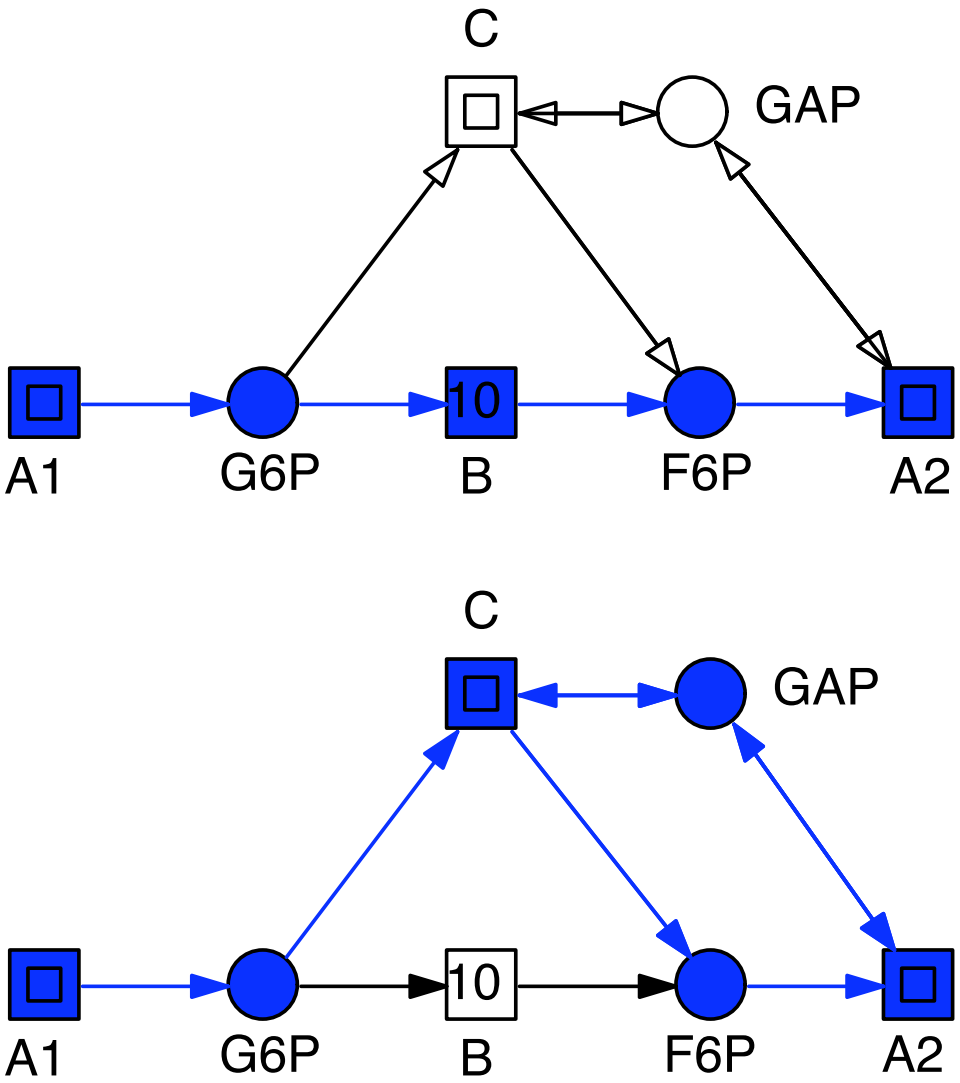

About the Relation Qualitative vs Continuous

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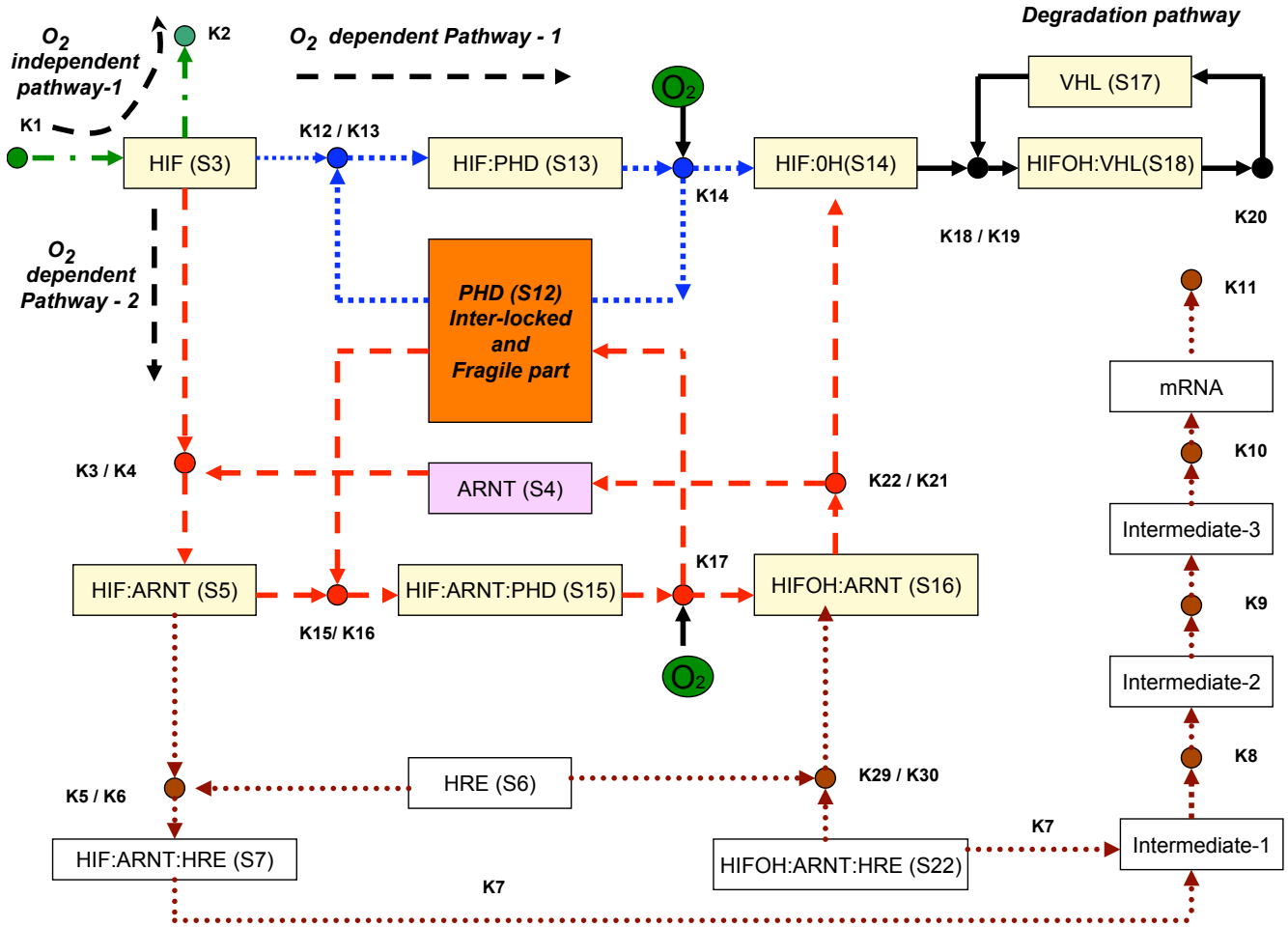
EX4 - HYPOXIA

[YU ET AL. 2007]



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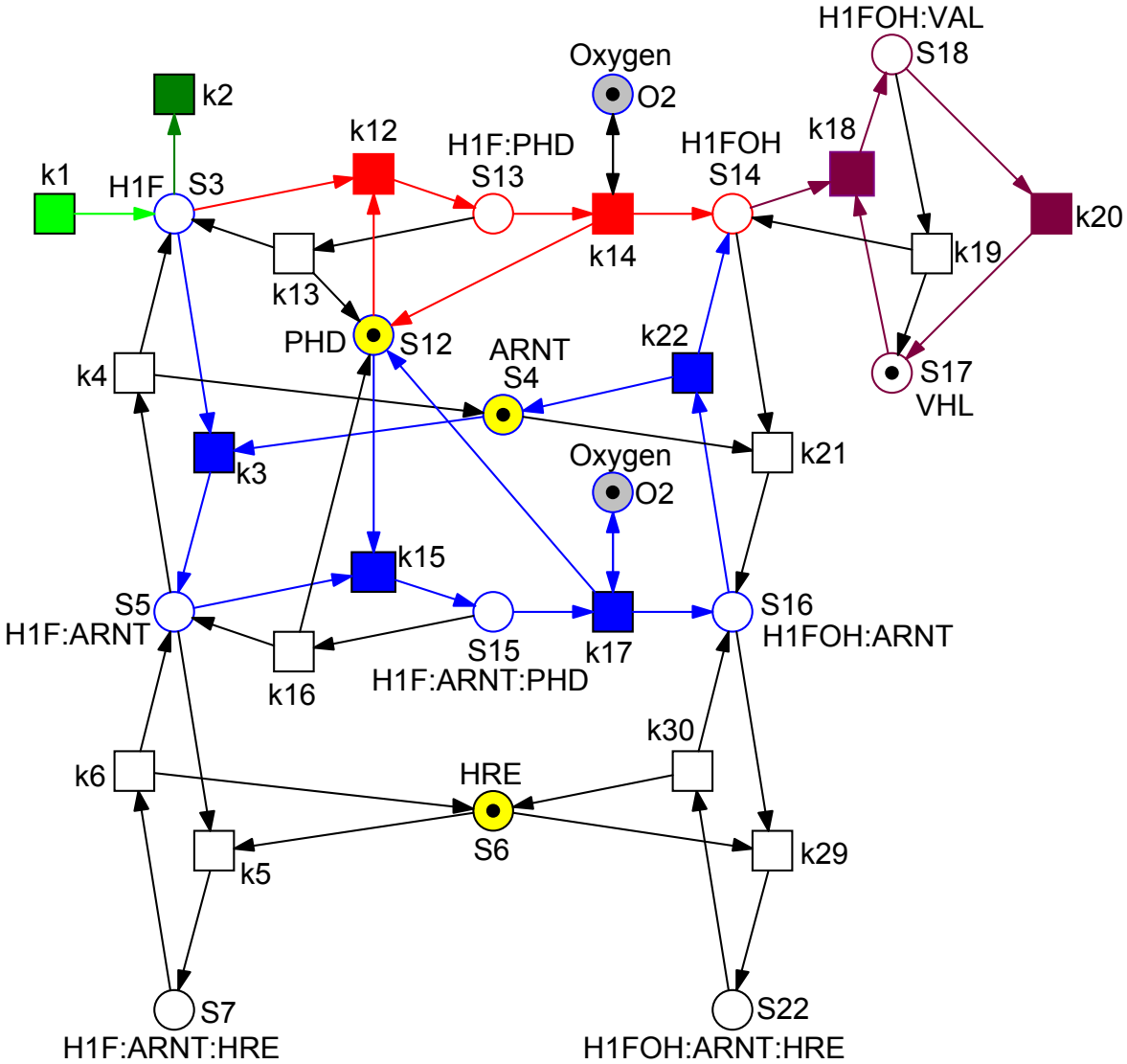
[HEINER, SRIRAM 2010]



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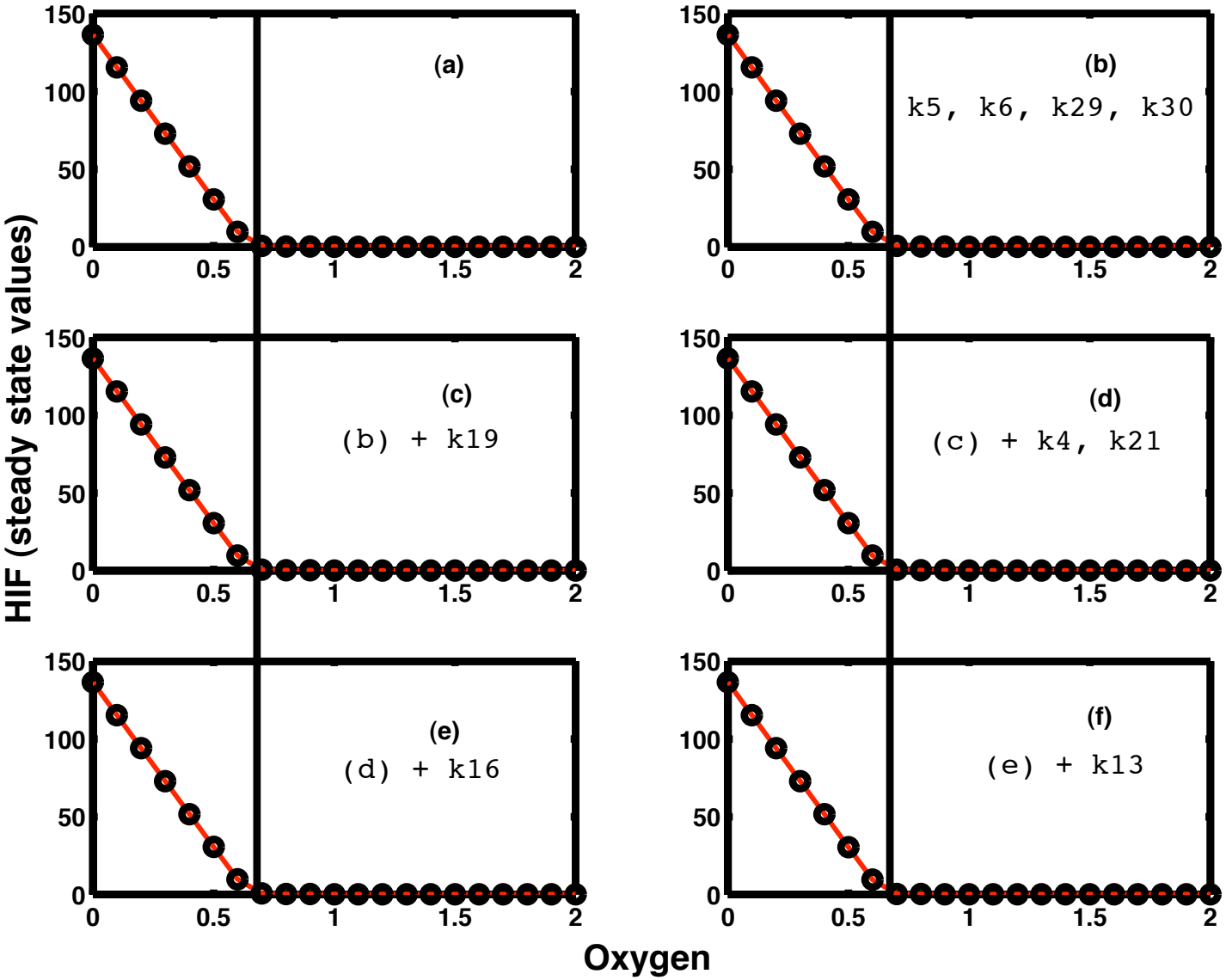
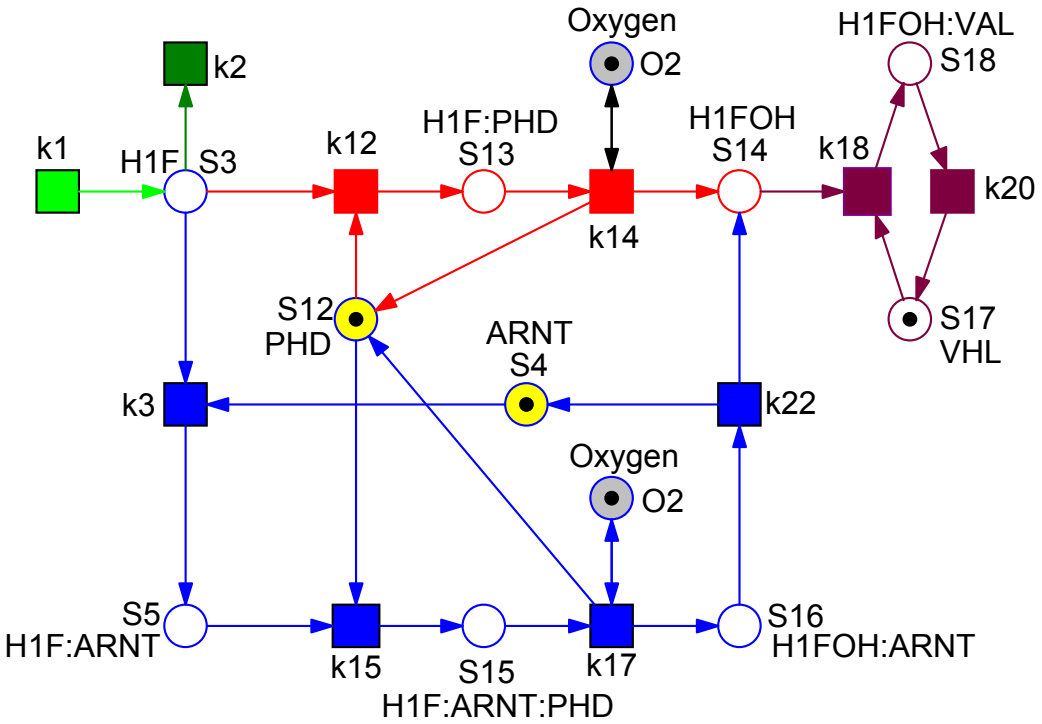
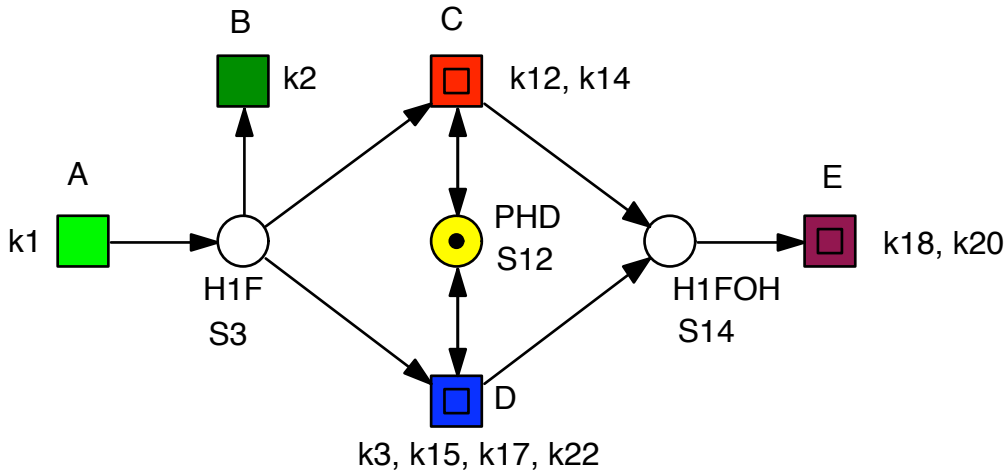
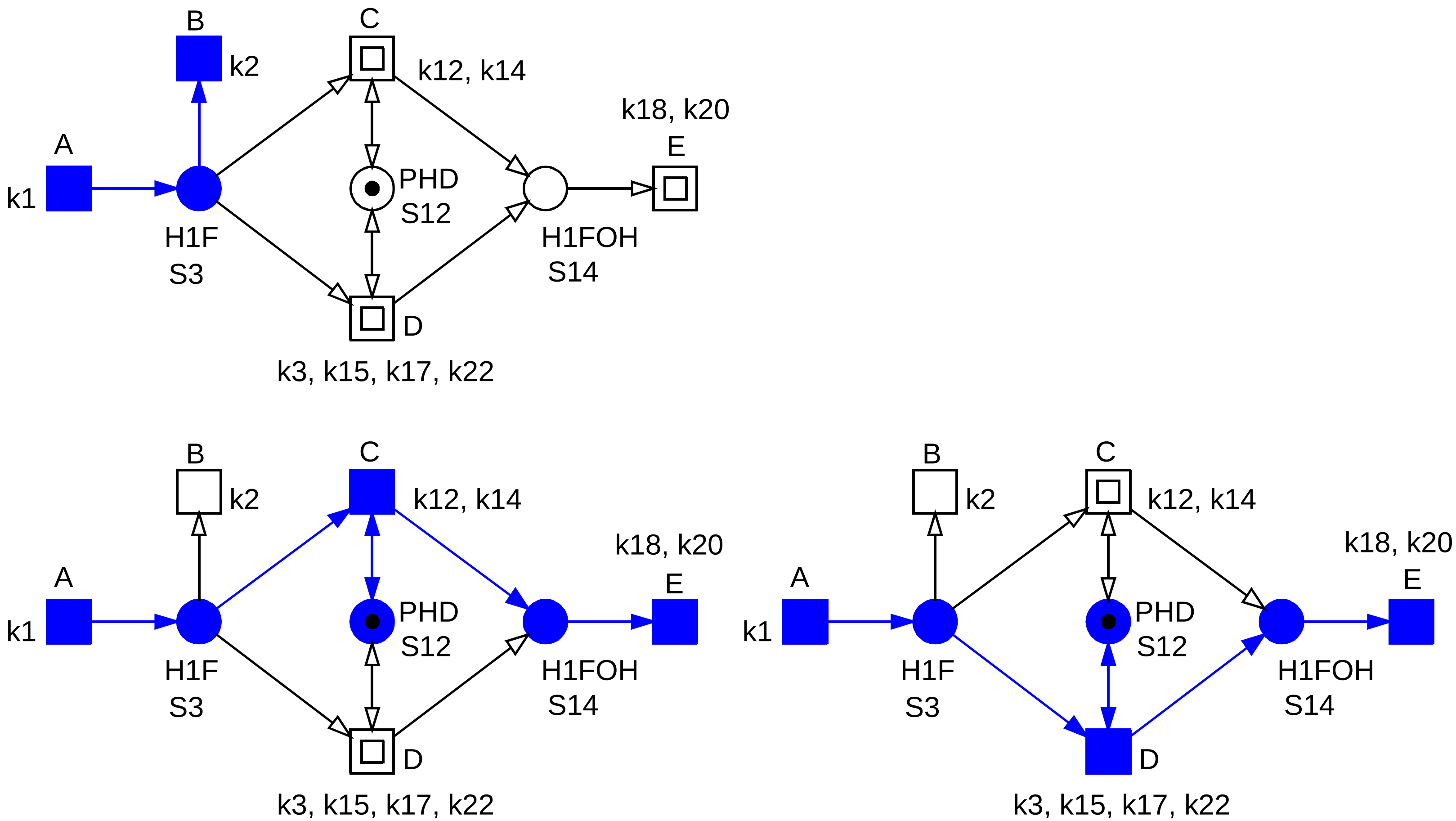

HIF (steady state values)
Oxygen
(a)
(b)
k5, k6, k29, k30
(c)
(b) + k19
(d)
(c) + k4, k21
(e)
(d) + k16
(f)
(e) + k13
150
100
50
0
0
0.5
1
1.5
2

EX4 - HYPOXIA

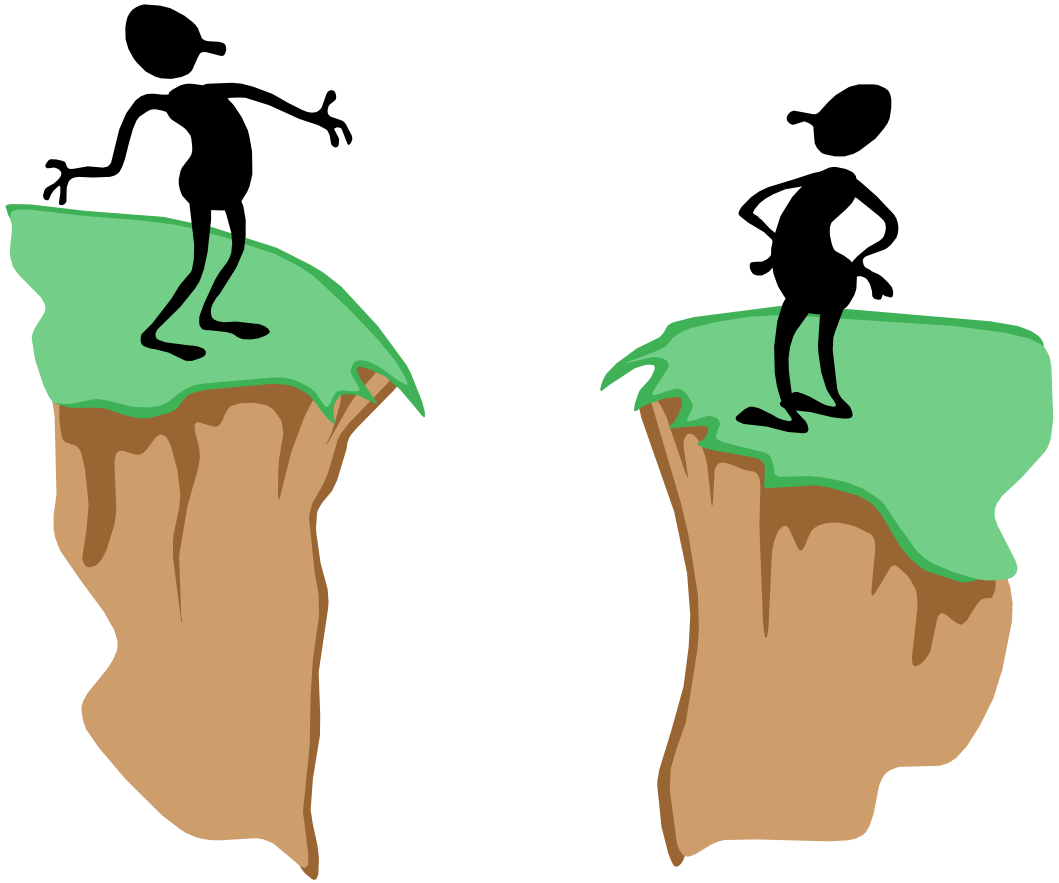

Oxygen
O2
H1FOH:VAL
S18
k2
k1
H1F
S3
k12
H1F:PHD
S13
H1FOH
S14
k18
k20
k14
S12
PHD
S17
VHL
ARNT
S4
k3
k22
Oxygen
O2
S5
H1F:ARNT
S16
H1FOH:ARNT
k15
S15
H1F:ARNT:PHD
k17

EX4 - HYPOXIA


B
C
k2
k12, k14
A
E
k1
PHD
S12
k18, k20
H1F
S3
H1FOH
S14
D
k3, k15, k17, k22


A
k1
B
k2
C
k12, k14
PHD
S12
H1F
S3
D
k3, k15, k17, k22
k18, k20
E
H1FOH
S14
A
k1
B
k2
C
k12, k14
PHD
S12
H1F
S3
D
k3, k15, k17, k22
k18, k20
E
H1FOH
S14
A
k1
B
k2
C
k12, k14
PHD
S12
H1F
S3
D
k3, k15, k17, k22
k18, k20
E
H1FOH
S14

OUTLOOK



THANKS !

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