PETRI NETS 4
BACTERIAL BIOENGINEERING

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THE PETRI NET FRAMEWORK
.. ARE NETWORKS OF BIOCHEMICAL REACTIONS

2 NAD$^+$ + 2 H$_2$O $\rightarrow$ 2 NADH + 2 H$^+$ + O$_2$
BIO NETWORKS

... ARE NETWORKS OF BIOCHEMICAL REACTIONS ...

... NATURALLY EXPRESSIBLE AS PETRI NETS ...

\[ 2 \text{NAD}^+ + 2 \text{H}_2\text{O} \rightarrow 2 \text{NADH} + 2 \text{H}^+ + \text{O}_2 \]
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

STATE-DEPENDENT RATE FUNCTIONS

STOCHASTIC RATES

LAMBDA OF EXPONENTIAL WAITING TIME

CTMC

CONTINUOUS RATES

STRENGTH OF CONTINUOUS FLOW

ODEs

-> supported by, e.g., COPASI, Dizzy, ..., Snoopy
FRAMEWORK 2007

QUALITATIVE

time-free

timed, quantitative

STOCHASTIC

discrete state space

CONTINUOUS

continuous state space
QUALITATIVE

STOCHASTIC

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timed, quantitative

CONTINUOUS

discrete state space

continuous state space

abstraction

extension
FRAMEWORK 2007

QUALITATIVE

time-free

abstracted

extension

approximation

STOCHASTIC

discrete state space

approximation

CONTINUOUS

continuous state space

timed, quantitative
**FRAMEWORK 2007**

- **QUALITATIVE**
  - LTS / PO
  - CTL, LTL

- **STOCHASTIC**
  - CTMC
  - CSL, PLTLc

- **CONTINUOUS**
  - ODEs
  - LTLc

**timed**, **quantitative**

**time-free**

**approximation**

**discrete state space**

**continuous state space**
QUALITATIVE

time-free
timed, quantitative

STOCHASTIC

abstraction
extension

approximation

CTMC
CSL, PLTLc

continuous state space
discrete state space

CONTINUOUS

abstraction
extension

approximation

LTS / PO
CTL, LTL

ODEs
LTLc

net reduction, SC, SB,
CPI, CTI, ADT sets
STP, bad siphons, etc.
FrameworK 2010

LTS / PO
CTL, LTL

QUALITATIVE

time-free

abstraction
extension

extension
abstraction

STOCHASTIC

CTMC
CTMC

approximation
approximation

CTMC
CTMC

continous state space

C
ODEs
C

LTLc

ODEs
LTLc

continuous state space

*/
COLOURED FRAMEWORK 2011

LTS / PO
CTL, LTL

QUALITATIVE

COLOURED

COLOURED

STOCHASTIC

CTMC
CTMC
CSL, PLTLc
CSL, PLTLc

approximation
approximation

HYBRID

continuous state space

COLOURED

CONTINUOUS

ODEs
ODEs
LTLc
LTLc

discrete state space

PN & BioModel Engineering

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KEY IDEA

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, ...
OUR TOOL BOX

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- **S4**
  - standalone, computational steering server
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  - PN, XPN, Time/Timed Petri nets (TPN)
  - mostly standard analysis techniques of Petri net theory
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  - symbolic and simulative model checking
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- **Patty**
  - Animation via web browser
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+ SBML import/export

Export to MATLAB and many other tools
PETRI NETS - THE BIG PROS

- readable & unambiguous
  -> fault avoidant model construction

- locality - causality - concurrency

- compositional, hierarchical notations
  -> logical and macro nodes

- executable
  -> animation, simulation (token game)
- Petri net theory -> model validation
  - P/T-invariants, partial order interpretation of T-invariants,
    conclusions CTI/CPI -> behavioural properties
  - Siphon/Trap Property (STP), reduction rules, . . .
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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

\[ r1: \quad A \rightarrow 2B \]
\[ r2: \quad 2A \rightarrow 3C \]
$r_1: \ A \rightarrow 2 \ B$

$r_2: \ 2 \ A \rightarrow 3 \ C$
r1: A → 2 B  
r2: 2 A → 3 C
**T- INVARIANTS, Ex**

\[ r1: \quad A \rightarrow 2 \, B \]
\[ r2: \quad 2 \, A \rightarrow 3 \, C \]

**T-INVARIANT 1**

**T-INVARIANT 2**
### INCIDENCE MATRIX C

- **a representation of the net structure**

  $$ C = \begin{bmatrix} p_1 & \ldots & t_j & \ldots & t_m \\ p_1 & & & & \\ p_i & c_{ij} & & & \\ \vdots & & \Delta t_j & & \\ p_n & & & & \end{bmatrix} $$

  where $c_{ij} = (pi, tj) = F(tj, pi) - F(pi, tj) = \Delta t_j(pi)$

  $\Delta t_j = \Delta t_j(*)$

- **matrix entry $c_{ij}$:**
  token change in place $pi$ by firing of transition $tj$

- **matrix column $\Delta t_j$:**
  vector describing the change of the whole marking by firing of $tj$

- **side-conditions are neglected**

  ![Diagram of a reaction catalyzed by an enzyme](image)

  - $c_{ij} = 0$
T-INTEGRANTS, BASICS

- Lautenbach, 1973 -> Schuster, 1993

- T-invariant $x$
  -> integer solution of $Cx = 0, x \neq 0, x \geq 0$

- support of a T-invariant $x$ -> supp($x$)
  -> 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
T-invariants = (multi-) sets of transitions = Parikh vector
- zero effect on marking
- reproducing a marking / system state

two interpretations
1. partially ordered transition sequence
   of transitions occurring one after the other
   - substance / signal flow
2. relative transition firing rates
   of transitions occurring 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

[Raddy 1993]
Ex1 - Glycolysis and Pentose Phosphate Pathway

[Reddy 1993]
Ex1 - Glycolysis and Pentose Phosphate Pathway

[Reddy 1993]

- INTERPRETATION?
Ex1 - Glycolysis and Pentose Phosphate Pathway

[Reddy 1993] [Heiner 1998]
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ABOUT THE RELATION
QUALITATIVE VS CONTINUOUS
Ex4 - Hypoxia

[Yu et al. 2007]
Ex4 - HYPOXIA

[HEINER, SRIRAM 2010]
Ex4 - HYPOXIA

![Reaction Network Diagram](Ex4_HYPOXIA.png)
THANKS!
HTTP://WWW-DSSZ.INFORMATIK.TU-COTTBUS.DE