BIOMODEL ENGINEERING
- A PETRI NET PERSPECTIVE -

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Qualitative

Protein A rises, then falls before rising again.
Protein B starts decreasing after the first peak of A until it reaches its steady state.
Protein C peaks between the two peaks of A.

Semi-qualitative

Protein rises then falls to less than 50% of its peak concentration.

Semi-quantitative

Protein rises then falls to less than 50% of its peak concentration at 60 minutes.

Quantitative

Protein rises then falls to less than 100 microMol at 60 minutes.

Models explaining these observations?
MODELLING = FORMAL KNOWLEDGE REPRESENTATION

natural biosystem

wetlab experiments

observed behaviour

formalizing understanding

predicted behaviour

model (knowledge)

model validation

model-based experiment design

analysis simulation

FORMAL KNOWLEDGE REPRESENTATION

CONFIDENCE INCREASE

FORMAL KNOWLEDGE REPRESENTATION

CONFIDENCE INCREASE
MODELLING = FORMAL KNOWLEDGE REPRESENTATION

DESCRPTIVE

PREDICTIVE

MODEL VALIDATION = CONFIDENCE INCREASE
\[
\begin{align*}
\frac{d\alpha}{dt} &= -v_1 \\
\frac{d\text{Ste}2}{dt} &= -v_2 + v_3 - v_5 \\
\frac{d\text{Ste}2_{\text{active}}}{dt} &= v_2 - v_3 - v_4 \\
\frac{d\text{Sst}2_{\text{active}}}{dt} &= v_4 - v_47 \\
\frac{dG\alpha\beta\gamma}{dt} &= -v_6 + v_9 \\
\frac{dG\alpha\text{GTP}}{dt} &= v_6 - v_7 - v_8 \\
\frac{dG\alpha\text{GDP}}{dt} &= v_7 + v_8 - v_9 \\
\frac{d\beta\gamma}{dt} &= v_6 - v_9 - v_{10} + v_{11} + v_{21} + v_{23} + v_{25} + v_{27} + v_{32} - v_{42} + v_{43} \\
\frac{d\text{Ste}5}{dt} &= -v_{12} + v_{13} + v_{17} + v_{21} + v_{23} + v_{25} + v_{27} + v_{32} \\
\frac{d\text{Ste}11}{dt} &= -v_{12} + v_{13} + v_{17} + v_{21} + v_{23} + v_{25} + v_{27} + v_{32} \\
\frac{d\text{Ste}7}{dt} &= -v_{14} + v_{15} + v_{17} + v_{21} + v_{23} + v_{25} + v_{27} + v_{32} \\
\frac{d\text{Fus}3}{dt} &= -v_{14} + v_{15} + v_{17} + v_{21} + v_{23} + v_{25} + v_{27} - v_{29} + v_{30} + v_{33} \\
\frac{d\text{Ste}20}{dt} &= -v_{18} + v_{19} + v_{21} + v_{23} + v_{25} + v_{27} + v_{32} \\

v_1 &= \alpha[t] \cdot \text{Bar} \cdot \text{I}_{\text{active}}[t] \cdot k_1 \\
v_2 &= \text{Ste}2[t] \cdot \alpha[t] \cdot k_2 \\
v_3 &= \text{Ste}2_{\text{active}}[t] \cdot k_3 \\
v_4 &= \text{Ste}2_{\text{active}}[t] \cdot k_4 \\
v_5 &= \text{Ste}2[t] \cdot k_5 \\
v_6 &= \text{Ste}2_{\text{active}}[t] \cdot G\alpha\beta\gamma[t] \cdot k_6 \\
v_7 &= G\alpha\text{GTP}[t] \cdot k_7 \\
v_8 &= G\alpha\text{GTP}[t] \cdot \text{Sst}2_{\text{active}}[t] \cdot k_8 \\
v_9 &= G\alpha\text{GDP}[t] \cdot G\beta\gamma[t] \cdot k_9 \\
v_{10} &= G\beta\gamma[t] \cdot C[t] \cdot k_{10} \\
v_{11} &= D[t] \cdot k_{11} \\
v_{12} &= \text{Ste}5[t] \cdot \text{Ste}11[t] \cdot k_{12} \\
v_{13} &= A[t] \cdot k_{13} \\
v_{14} &= \text{Ste}7[t] \cdot \text{Fus}3[t] \cdot k_{14} \\
v_{15} &= B[t] \cdot k_{15} \\
v_{16} &= A[t] \cdot B[t] \cdot k_{16} \\
v_{17} &= C[t] \cdot k_{17} \\
v_{18} &= D[t] \cdot \text{Ste}20[t] \cdot k_{18}
\end{align*}
\]
\[
\begin{align*}
\frac{d\alpha}{dt} &= -\nu_1 \\
\frac{d\text{Ste2}}{dt} &= -\nu_2 + \nu_3 - \nu_5 \\
\frac{d\text{Ste2}_{\text{active}}}{dt} &= \nu_2 - \nu_3 - \nu_4 \\
\frac{d\text{Sst2}_{\text{active}}}{dt} &= \nu_4 - \nu_47 \\
\frac{d\alpha \beta \gamma}{dt} &= -\nu_6 + \nu_9 \\
\frac{d\alpha \gamma \text{GTP}}{dt} &= \nu_6 - \nu_7 - \nu_8 \\
\frac{d\alpha \gamma \text{GDP}}{dt} &= \nu_7 + \nu_8 - \nu_9 \\
\frac{d\beta \gamma}{dt} &= \nu_6 - \nu_9 - \nu_1 + \nu_21 + \nu_23 + \nu_25 + \nu_27 + \nu_37 - \nu_42 + \nu_43 \\
\frac{d\text{Ste5}}{dt} &= -\nu_1 + \nu_3 + \nu_17 + \nu_21 + \nu_23 + \nu_25 + \nu_17 + \nu_3 \\
\frac{d\text{Ste5}}{dt} &= -\nu_1 + \nu_13 + \nu_17 + \nu_21 + \nu_23 + \nu_25 + \nu_27 + \nu_32 \\
\frac{d\text{Fus3}}{dt} &= -\nu_1 + \nu_13 + \nu_17 + \nu_21 + \nu_23 + \nu_25 + \nu_27 + \nu_32 \\
\frac{d\text{Ste10}}{dt} &= -\nu_1 + \nu_13 + \nu_17 + \nu_21 + \nu_23 + \nu_25 + \nu_27 + \nu_32 \\

\nu_1 &= \alpha[t] \cdot \text{Bar1}_{\text{active}}[t] \cdot k_1 \\
\nu_2 &= \text{Ste2}[t] \cdot \alpha[t] \cdot k_2 \\
\nu_3 &= \text{Ste2}_{\text{active}}[t] \cdot k_3 \\
\nu_4 &= \text{Ste2}_{\text{active}}[t] \cdot k_4 \\
\nu_5 &= \text{Ste2}[t] \cdot k_5 \\
\nu_6 &= \text{Ste2}_{\text{active}}[t] \cdot \alpha \beta \gamma[t] \cdot k_6 \\
\nu_7 &= \alpha \gamma \text{GTP}[t] \cdot k_7 \\
\nu_8 &= \alpha \gamma \text{GTP}[t] \cdot \text{Ste2}_{\text{active}}[t] \cdot k_8 \\
\nu_9 &= \alpha \gamma \text{GDP}[t] \cdot \alpha \beta \gamma[t] \cdot k_9 \\
\nu_{10} &= \beta \gamma[t] \cdot C[t] \cdot k_{10} \\
\nu_{11} &= D[t] \cdot k_{11} \\
\nu_{12} &= \text{Ste5}[t] \cdot \text{Ste11}[t] \cdot k_{12} \\
\nu_{13} &= A[t] \cdot k_{13} \\
\nu_{14} &= \text{Ste7}[t] \cdot \text{Fus3}[t] \cdot k_{14} \\
\nu_{15} &= \text{Ste7}[t] \cdot F[t] \cdot k_{15} \\
\nu_{16} &= \text{Ste20}[t] \cdot E[t] \cdot k_{16} \\
\nu_{17} &= C[t] \cdot k_{17} \\
\nu_{18} &= D[t] \cdot \text{Ste20}[t] \cdot k_{18}
\end{align*}
\]
OUTLINE

- **FRAMEWORK**
  - unifying four paradigms: QPN - SPN - CPN - HPN
  - structural analysis by T-invariants

- **ABSTRACT-DEPENDENT TRANSITION SETS**
  - modularisation
  - hierarchical representation (coarsening)
  - network structuring
  - identification of fragile nodes

- **STEADY STATE INTERPRETATION**
  - core network identification

- **SUMMARY & OUTLOOK**
  - open problem: weakly boundedness
THE PETRI NET FRAMEWORK
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, 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
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
QUALITATIVE

- LTS / PO
- CTL, LTL

STOCHASTIC

- CTMC
- CSL, PLTLc

CONTINUOUS

- ODEs
- LTLc

approximation

- abstraction
- extension

time-free

timed, quantitative

discrete state space

continuous state space

net reduction, SC, SB, CPI, CTI, ADT sets STP, bad siphons, etc.
COLOURED FRAMEWORK 2011

LTS / PO
CTL, LTL

QUALITATIVE

time-free

abstractation

extension

extension

abstractation

approximation

approximation

STOCHASTIC

CTMC
CSL, PLTLc

discrete state space

COLOURED
HYBRID

CONTINUOUS

ODEs
LTLc

continuous state space
**KEY IDEA**

**4x2 MODELS SHARING STRUCTURE**

\[
\text{QUANTITATIVE MODEL} = \text{QUALITATIVE MODEL} + \text{RATE FUNCTIONS (KINETICS)}
\]
MODELLING BIO PETRI NETS
**Approach 1**

signalling cascade as wiring diagram
enzymatic reaction, mass-action kinetics
SINGLE
MASS-ACTION STEP
NET COMPOSITION FROM BUILDING BLOCKS

SINGLE PHOSPHORYLATION / DEPHOSPHORYLATION
DOUBLE PHOSPHOYLATION / DEPHOSPHORYLATION
SIGNALLING CASCADE AS PETRI NET

[Raf_RasGTP, RasGTP]

[Raf, Raf_P, Raf_P_Phase1, MEK, MEK_P, MEK_P_Phase2, MEKPP, MEKPP_Phase2, ERK, ERK_P, ERK_P_Phase3, ERKPP, ERKPP_Phase3]

[k1/k2, k3, k4/k5, k6, k7/k8, k9/k10, k11, k12/k13, k14, k15/k16, k17, k18/k19, k20, k21/k22, k23/k24, k25/k26, k27/k28, k29/k30]

[Gilbert, Heiner, Lehrack 2007]
[Heiner, Gilbert, Donaldson 2008]
APPROACH 2

Literature
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October 2013
Bio Networks, Some Problems

- Knowledge
  - uncertain
  - growing, changing
  - distributed over independent data bases, papers, journals, ...

- Various, mostly ambiguous representations
  - verbose descriptions
  - diverse graphical representations
  - contradictory and/or fuzzy statements

- Network structure
  - tend to grow fast
  - dense, apparently unstructured
  - hard to read

-> Problem 1
-> Problem 2
-> Problem 3
**Bio Networks, Some Problems**

- **Problem 1**: Knowledge is uncertain, growing, and changing. Distributed over independent databases, papers, journals, etc.

- **Problem 2**: Various, mostly ambiguous representations. Verbose descriptions, diverse graphical representations, contradictory and/or fuzzy statements.

- **Problem 3**: Network structure tends to grow fast. Dense, apparently unstructured. Hard to read.

Models are patchworks full of assumptions.
**PETRI NETS - THE BIG PROS**

- **readable & unambiguous**
  -> fault avoidant model construction

- **locality - causality - concurrency**

- **compositional, hierarchical notations**
  -> logical and macro nodes

- **executable**
  -> to experience the model, spec. causality

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

- **Petri net theory -> model validation**
  -> P/T-invariants, partial order interpretation of T-invariants,
  conclusions CTI/CPI -> behavioural properties
  -> STP, reduction rules, ...
T- INVARIANTS
ELEMENTARY MODES
EXTREME PATHWAYS
GENERIC PATHWAYS
INCIDENCE MATRIX \( C \)

- a representation of the net structure
  
  \[
  C = \begin{pmatrix}
  p_1 & \ldots & t_j & \ldots & t_m \\
  \vdots & & \vdots & & \vdots \\
  p_n & & \Delta t_j & &
  \end{pmatrix}
  \]

  \[ c_{ij} = (p_i, t_j) = F(t_j, p_i) - F(p_i, t_j) = \Delta t_j(p_i) \]

  \[ \Delta t_j = \Delta t_j(*) \]

- matrix entry \( c_{ij} \):
  token change in place \( p_i \) by firing of transition \( t_j \)

- matrix column \( \Delta t_j \):
  vector describing the change of the whole marking by firing of \( t_j \)

- side-conditions are neglected

\[
\text{enzyme-catalysed reaction}
\]

\[ c_{ij} = 0 \]
T-invariants, 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

$C x = 0, x \neq 0, x \geq 0$

$k x = \sum_{i} a_i x_i$
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
     - of transitions occurring one after the other
     - substance / signal flow
     -> behaviour understanding
  2. Relative transition firing rates
     - of transitions occurring permanently & concurrently
     - steady state behaviour
     -> 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
T-INVARINTS, 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
     of transitions occurring one after the other
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     of transitions occurring permanently & concurrently
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- 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
T- INVARIANTS, Ex

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

T-INVARIANT 1

T-INVARIANT 2
Ex1 - Glycolysis and Pentose Phosphate Pathway

[Reddy 1993]
Ex1 - Glycolysis and Pentose Phosphate Pathway

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Ex1 - Glycolysis and Pentose Phosphate Pathway

[Reddy 1993] [Heiner 1998]
Ex1 - Glycolysis and Pentose Phosphate Pathway

[Reddy 1993]  
[Heiner 1998]
Ex1 - Glycolysis and Pentose Phosphate Pathway

[Reddy 1993] [Heiner 1998]
Ex1 - Glycolysis and Pentose Phosphate Pathway

[Reddy 1993]
[Heiner 1998]
T-invariants may contain any structure

- minimal T-invariants generally overlap
  -> combinatorial effect brings explosion in the number of min. T-invariants ($2^4$)
MODULARIZATION
BY T-INVARIANTS
ABSTRACT DEPENDENT TRANSITION SETS (ADT-SETS)

- Let $X$ denote the set of all (non-trivial) minimal $t$-invariants $x$ of a given PN.

- **dependency relation**
  Two transitions $i, j$ depend on each other,
  if they always appear together in all minimal $T$-invariants $x$, i.e.
  
  $$\forall (x \in X) : supp(x)(i) = supp(x)(j)$$

- **equivalence relation** in the transition set, leading to a partition of $T$
  - reflexive
  - symmetric
  - transitive

- The **equivalence classes** $A$ represent maximal ADT-sets
  $$\forall (x \in X) : A \subseteq supp(x) \lor A \cap supp(x) = \emptyset$$
ADT-SETS, Ex1

\[ r1: \ A \rightarrow 2 \ B \]
\[ r2: \ 2 \ A \rightarrow 3 \ C \]
r1:  \( A \rightarrow 2\ B \)

r2:  \( 2\ A \rightarrow 3\ C \)
AADT-SETS, Ex2

\[ r1: \quad A \rightarrow 2B \]
\[ r2: \quad 2A \rightarrow 3B \]
ADT-SETS, Ex2

\[ r1: \ A \rightarrow 2 \ B \]
\[ r2: \ 2 \ A \rightarrow 3 \ B \]
ADT-SETS, INTERPRETATION

- **maximal ADT-sets**
  - disjunctive subnets
  - not necessarily connected

- **minimal T-invariants**
  - overlapping subnets
  - connected

- **interpretation**
  - structural decomposition into rather small subnets
  - smallest biologically meaningful functional units
  - building blocks

- **variations**
  - with / without trivial T-invariants
  - whole / partial set of T-invariants

- **classification of all transitions** based on the T-invariants’ support
- maximal ADT-sets
  - not necessarily connected

- further decomposition into connected ADT-sets
  - possibly according to primary compounds, only, i.e. neglecting connections by auxiliary compounds
  - non-maximal ADT-sets

- coarse network structure, definition
  - macro transitions - abstract from connected ADT-sets
  - places - interface between functional units
  - (minimal) path - (minimal) T-invariant

- coarse network structure, what for?
  - set of T-invariants gets structured
  - better understanding of the net behaviour
Ex1 - Glycolysis and Pentose Phosphate Pathway
Ex1 - Glycolysis and Pentose Phosphate Pathway
Ex1 - Glycolysis and Pentose Phosphate Pathway
**Ex2 - Apoptosis in Mammalian Cells**

![Diagram of Apoptosis Pathways](image)

- Fas ligand (m1)
- Fas receptor
- Procaspase-8 (m5)
- Bid (m11)
- Caspase-8 (m8)
- Caspase-3 (m27)
- DFF (m30)
- Cleaved DFF45 (m33, 34, 35)
- Oligomer of DFF40 (m36)
- DNA fragmentation
- Cell membrane
- Apoaptotic Stimuli
- Apaf-1 (m17)
- dATP/ATP
- Bcl-2, Bcl-xL
- Bax, Bad, Bim
- Bcl-2, Bcl-xL
- Bid C terminal (m13)
- Bax/Bad/Bim
- Cytochrome c (m16)
- Mitochondrion
- Cleaved DFF45
- Cleaved DFF45
- DNA fragmentation

[**GON 2003**] [**HEINER, KOCH, WILL 2004**]
EX2: APOPTOSIS IN MAMMALIAN CELLS

Caspase-8 → Procaspase-3 → Mitochondrion

s2 → Procaspase-3 → Caspase-3
EX2: APOPTOSIS IN MAMMALIAN CELLS
Ex3 - Carbon Metabolism in Potato Tuber

[Koch; Junker; Heiner 2005]

ADT-sets without trivial T-invariants
ABOUT THE RELATION QUALITATIVE VS CONTINUOUS
STOCHASTIC SIMULATION

Stochastic Output – 1 Level

Concentration (Levels)

0.0 0.2 0.4 0.6 0.8 1.0

Time (s)

0 20 40 60 80 100
STOCHASTIC SIMULATION

Stochastic Output – 10 Levels

Concentration (Levels)

Time (s)
Stochastic Simulation

Stochastic Output – 100 Levels

Concentration (Levels)

Time (s)
Deterministic Simulation

Deterministic Output

Concentration (μMol)

0.0 0.2 0.4 0.6 0.8 1.0

Time (s)

0 20 40 60 80 100
Ex4 - RKIP Signalling Pathway, Petri Net

\[ \text{[Heiner, Gilbert 2006]} \]

\[ \text{[Heiner, Donaldson, Gilbert 2010]} \]
Ex4 - RKIP, Reachability Graph (STS)

- simple algorithm
- nodes: system states
- arcs: the (single) firing transition
- single step firing rule
### Ex4 - RKIP, Quantitative Analysis

**Species**

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<th>S3</th>
<th>S4</th>
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</tbody>
</table>

**Cho et al**

**Biochemist**

13 good state configurations

the bad ones

Distribution of `bad' steady states as euclidean distances from the `good' final steady state
Ex4 - RKIP, Quantitative Analysis

State1

Concentration (relative units)

Time (sec)

0 10 20 30 40 50 60 70 80 90 100

0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1

Raf-1Star
RKIP
Raf-1Star_RKIP
Raf-1Star_RKIP_ERK_PP
ERK
RKIP-P
MEK-PP
MEK-PP_ERK
ERK-PP
RP
RKIP-P_RP
Ex4 - RKIP, Quantitative Analysis

State8

Time (sec)

Concentration (relative units)

0 10 20 30 40 50 60 70 80 90 100

Raf1Star
RKIP
Raf1Star_RKIP
Raf1Star_RKIP_ERK_PP
ERK
RKIP_P
MEK_PP
MEK_PP_ERK
ERK_PP
RP
RKIP_P_RP
Ex4 - RKIP, QUANTITATIVE ANALYSIS
Ex5 - HYPOXIA
Ex5 - HYPOXIA
OPEN PROBLEM -
TIME-DEPENDENT BOUNDEDNESS
TIME-DEPENDENT BOUNDEDNESS

- **given:** time-free Petri net
  - -> unbounded
  - -> live (supposed to be)

- **wanted:** corresponding time-dependent Petri net
  - -> (weakly) bounded
  - -> (still) live

- relative transition firing rates
  - -> *may be implemented by transition firing duration* (constant / interval)

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

- **guess**
  - -> *transformation reflects the steady state, so the model should become bounded*
However, this does not always work!
COUNTEREXAMPLE 1

1-working time for all transitions;
FC, there are no deadlocks, traps, p-invariants, besides the pseudo-P-invariant (A, co_A);

wBND & LIVE for the given initial marking
COUNTEREXAMPLE 2

[DESEL 2006], WEAKLY BOUNDED PETRI NETS; AWPN ’06
TIME-DEPENDENT BOUNDEDNESS

- **given:** time-free Petri net
  - \( \rightarrow \) unbounded
  - \( \rightarrow \) live (supposed to be)

- **wanted:** corresponding time-dependent Petri net
  - \( \rightarrow \) (weakly) bounded
  - \( \rightarrow \) (still) live

- **questions**
  - \( \rightarrow \) for which structures does it work / does it not work ?
  - \( \rightarrow \) are there sufficient / necessary conditions ?
  - \( \rightarrow \) which time intervals make the net bounded ?
  - \( \rightarrow \) which time intervals preserve a transition sequence’s realizability ?

- **consistency criterion for (steady state) bio networks !?**
SUMMARY
& OUTLOOK
OUR TOOL BOX

- **SNOOPY**
  - modelling and animation/simulation of hierarchical graphs,
  - e.g. (extended) fault trees,
  - various Petri net classes, e.g. QPN, XQPN, SPN, XSPN, CPN, TPN,
  - . . . ,
  - free style graphs

- **CHARLIE**
  - QPN, XQPN, Time/Timed Petri nets (TPN)
  - mostly standard analysis techniques of Petri net theory

- **MARCIE**
  - XQPN, SPN, XSPN, SRN
  - symbolic and simulative model checking

- **Patty**
  - animation via web browser
OUR TOOL BOX

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  - -> animation via web browser

SBML import/export

EXPORT TO MATLAB AND MANY OTHER TOOLS
**SUMMARY**

- **representation of bio networks by Petri nets**
  - partial order representation -> better comprehension
  - formal semantics -> sound analysis techniques
  - unifying view

- **purposes**
  - animation -> to experience the model
  - model validation against consistency criteria -> to increase confidence
  - qualitative / quantitative behaviour prediction -> experiment design, new insights

- **step-wise model development**
  - qualitative model -> discrete Petri nets
  - discrete quantitative model -> stochastic Petri nets
  - continuous quantitative model -> continuous Petri nets = ODEs, hybrid models
  - locality and space -> coloured Petri nets
OUTLOOK

- efficient simulation of very large Petri nets
  - stochastic
  - continuous
  - hybrid

- (hierarchical) space

- shape and volume of components

- hierarchical organisation of components

- observables

- biosystem development

MULTISCALE CHALLENGES
Processes over Time and Space

MeFoSyLoMa, LIPN, October 4th, 2 pm
THANKS!

HTTP://WWW-DSSZ.INFORMATIK.TU-COTTBUS.DE
APPENDIX
T-INVARIENTS, BASIC TYPES IN BIO NETWORKS

- **trivial minimal T-invariants**
  - $\Rightarrow$ reversible reactions
  - $\Rightarrow$ boundary transitions of auxiliary compounds

- **non-trivial minimal T-invariants**
  - $\Rightarrow$ i/o-T-invariants
    - covering boundary transitions of input / output compounds
  - $\Rightarrow$ inner cycles
substances involved
- input substance A
- output substance C
- auxiliary substance B

Example diagram:

- **gA** to **A**
- **ab** to **B**
- **ac** to **C**
- **gb** to **B**
- **rb** to **B**
- **bc** to **C**
- **rc**
**EXAMPLE, T-INVARIANTS**

- substances involved
  - input substance A
  - output substance C
  - auxiliary substance B

```
A
  o  gA  ab  ac  B
  |   |  rB  bc  C  
  |   |   |   |  rC
B
  |  gB  inv5
  |  inv4
  |  inv3
  |  inv2
  |  inv1
```

`papin2003.spped`
Example, Elementary Modes

- substances involved
  - input substance A
  - output substance C
  - auxiliary substance B

inv1  inv2  inv3  inv4  inv5

no elementary mode
Example, Extreme Pathways

- substances involved
  - input substance A
  - output substance C
  - auxiliary substance B

no extreme pathway

inv5

inv4

inv1

inv2

inv3

no elementary mode
EXAMPLE, EXTREME PATHWAYS

- substances involved
  - input substance A
  - output substance C
  - auxiliary substance B

\[
inv5 = inv5 + inv2 - inv3
\]

no extreme pathway

\[
inv4 = inv5 + inv2 - inv3
\]
substances involved
- input substance $A$
- output substance $C$
- auxiliary substance $B$
substances involved
- input substance A
- output substance C
- auxiliary substance B

ELEMENTARY MODES

inv5

inv4

inv1

inv2

papin2003.spped
 EXAMPLE, SUMMARY

- substances involved
  -> input substance A
  -> output substance C
  -> auxiliary substance B

MINIMAL T-INVARINTS

inv5

inv4

inv1

inv2

inv3

substances involved:
- input substance A
- output substance C
- auxiliary substance B

papin2003.spped