SNOOPY -
A UNIFYING PETRI NET FRAMEWORK
TO INVESTIGATE
BIOMOLECULAR NETWORKS

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PRELIMINARIES
A Bit of History

- predecessor: Petri Net Editor PED, 1992 - 2004

- initial implementation concepts

- core implementation
  -> Markus Fieber, Master Thesis, 2004

- Master Theses supervised by staff members
  -> Denny Bayer, Matthias Dube, Anja Kurth, Sebastian Lehrack, Ronny Richter, Christian Rohr, Daniel Scheibler, Krispin Schulz, Marcel Schwarze, Alexey Tovchigrechko, Katja Winder, . . . and many students’ projects

- now about 120,000 lines of code (without running extensions)

- many features influenced by
  -> Wolfgang Marwan,
    Otto von Guericke University & Magdeburg Centre for Systems Biology & MPI
AVAILABILITY

- supported operating systems
  - MAC OS X
  - Windows
  - Linux (selected distributions)

- free of charge for non-commercial use

- reference for acknowledgements
  C Rohr, W Marwan, M Heiner:
  Snoopy - a unifying Petri net framework to investigate biomolecular networks;
  Bioinformatics 2010 26(7): 974-975

- source code available on request
  - close cooperation partners

- further information
  http://www-dssz.informatik.tu-cottbus.de/software/snoopy.html
Basic Properties

- **Platform-independent**
  - implementation in C++
  - wxWidgets (http://www.wxwidgets.org)

- **Extensible**
  
generic design facilitates the addition of new graph classes

- **Adaptive**
  - simultaneous use of several graph types in a homogeneous environment
  - GUI adopts dynamically to graph type in active window

- **Open**
  - export to many foreign (qualitative) analysis tools, among them
    Charlie (http://www-dssz.informatik.tu-cottbus.de/charlie.html)
    METATOOL (http://pinguin.biologie.uni-jena.de/bioinformatik/networks)
  - import of a few formats + automatic layout
  - import / export of SBML, Level 2, Version 3 (http://sbml.org)
Graph Classes

- qualitative Petri nets - QPN
  - Petri net - PN
  - extended Petri net - xPN

- quantitative Petri nets
  - stochastic Petri net - SPN (xSPN)
  - continuous Petri net - CPN
  - timed Petri nets (duration Petri, reaction Petri net)

- other Petri net classes
  - modulo Petri net, music Petri net

- other graph types
  - reachability graph, fault tree, extended fault tree, MTBDD, MTIDD, freestyle net

- outlook
  - coloured Petri nets, hybrid Petri nets
The diagram illustrates the framework of QPN, SPN, CPN, and timed, quantitative models. The framework is divided into two dimensions:

- **Top-to-bottom**: *time-free* vs. *timed, quantitative*
- **Left-to-right**: *discrete state space* vs. *continuous state space*

This framework helps in understanding the relationship between different types of models in systems biology.
time-free

timed, quantitative

SPN

QPN

CPN

discrete state space

continuous state space
THREE MODELS SHARING STRUCTURE

quantitative model = qualitative model

+ quantitative parameters (kinetics)
QUALITATIVE
PETRI NETS
- QPN -
2 \text{NAD}^+ + 2 \text{H}_2\text{O} \rightarrow 2 \text{NADH} + 2 \text{H}^+ + \text{O}_2
2 NAD\(^+\) + 2 H\(_2\)O \rightarrow 2 NADH + 2 H\(^+\) + O\(_2\)
\[ 2 \text{NAD}^+ + 2 \text{H}_2\text{O} \rightarrow 2 \text{NADH} + 2 \text{H}^+ + \text{O}_2 \]
PETRI NET ELEMENTS, INTERPRETATIONS

- **metabolic networks**
  - signal transduction networks
  - gene regulatory networks

- **transitions**
  - (reversible, stoichiometric) chemical reactions,
  - enzyme-catalyzed conversions of metabolites, proteins, . . .
  - complexations/decomplexations, de-/phosphorylations, . . .

- **places**
  - (primary, secondary) chemical compounds,
  - (various states of) proteins, protein complex, genes, . . .

- **tokens**
  - molecules, moles, . . .
  - concentration levels, gene expression levels, . . .
    - e.g., high/lows = present/not present, or any finite integer number
LEVEL CONCEPT

PN & Systems Biology

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enzymatic reaction, mass-action approach 1

$E$

$A \leftrightarrow A|E \rightarrow B$
enzymatic reaction, mass-action approach 1

\[ A \leftrightarrow A|E \rightarrow B \]
**Enzymatic reaction, mass-action approach 1**

A <-> A|E --> B
HOW TO SURVIVE LARGER NETS - LOGICAL NODES

reaction-centred view

process-oriented view

species-centred view

logical places

logical transitions
NET COMPOSITION FROM BUILDING BLOCKS

SINGLE MASS-ACTION STEP
SINGLE PHOSPHORYLATION / DEPHOSPHORYLATION

SINGLE MASS-ACTION STEP
SINGLE PHOSPHORYLATION / DEPHOSPHORYLATION

DOUBLE PHOSPHORYLATION / DEPHOSPHORYLATION
\textbf{xPN = PN + Special Arc Types}

- Read arcs with arc weight \( n \)
  \( \rightarrow \) \textit{enabled, if tested place contains at least} \( n \) \textit{tokens}

- Inhibitor arcs with arc weight \( n \)
  \( \rightarrow \) \textit{enabled, if tested place contains less than} \( n \) \textit{tokens}

- Equal arcs with arc weight \( n \)
  \( \rightarrow \) \textit{enabled, if tested place contains exactly} \( n \) \textit{tokens}

  \textbf{-- no marking change upon firing --}

- Reset arcs
  \( \rightarrow \) \textit{do not restrict enabledness}
  \( \rightarrow \) \textit{upon firing all tokens are removed}
STOCHASTIC PETRI NETS
- SPN \((xSPN)\) -
STOCHASTIC PETRI NETS, BASICS

- stochastic transitions get a stochastic waiting time
  -> exponential distribution with parameter lambda

- state-dependent lambda defined by propensity function
  -> any arithmetic function including the transition’s pre-places as integer variables and user-defined real-valued parameters
  -> modifier arcs
  -> popular kinetics: mass-action semantics, level semantics

- multiple initial markings, parameter sets, and function sets

- deterministically timed transitions
  -> immediate transitions - zero waiting time
  -> deterministic transitions - delay relative to the enabling time
  -> scheduled transitions - scheduled at absolute time points

- stochastic simulation algorithms (SSA), e.g. Gillespie’s SSA
**Rate Functions**

- **molecules semantics**

\[ h_t := c_t \cdot \prod_{p \in \bullet t} \left( \frac{m(p)}{f(p, t)} \right) \]

- **concentration levels semantics**

\[ h_t := k_t \cdot N \cdot \prod_{p \in \bullet t} \left( \frac{m(p)}{N} \right) \]
Stochastic Simulation

Stochastic Output – 10 Levels

Concentration (Levels)

Time (s)

0 2 4 6 8 10

0 20 40 60 80 100
DETERMINISTIC SIMULATION
CONTINUOUS PETRI NETS - CPN -
CONTINUOUS PETRI NETS, BASICS

- transitions fire continuously

- rate functions
  -> any arithmetic function including
     the transition’s pre-places as real-valued variables and
     user-defined real-valued parameters

- real-valued tokens
  -> concentrations

- multiple initial markings, parameter sets, function sets (not yet)

- a CPN defines uniquely a set of ordinary differential equations (ODEs),
  but not vice versa
  -> export of the generated ODEs to LaTeX and ASCII

- simulation (numerical integration)
  -> six stiff and six unstiff solvers
CONTINUOUS PETRI NET DEFINES ODEs
\[
\frac{dm_3}{dt} = \]
\[ \frac{dm_3}{dt} = + r_1 + r_4 \]
\[
d\frac{m3}{dt} = + r1 + r4 - r2 - r3
\]
\[
\frac{\mathrm{d} m_3}{\mathrm{d} t} = + k_1 \cdot m_1 \cdot m_2 \\
+ r_4 \\
- r_2 \\
- r_3
\]
\[
\frac{dm_3}{dt} = + k_1 \cdot m_1 \cdot m_2 \\
+ k_4 \cdot m_4 \\
- k_2 \cdot m_3 \\
- k_3 \cdot m_3 \cdot m_9
\]
SUMMARY
representation of bionetworks by Petri nets

-> partial order representation
-> formal semantics
-> unifying view

-> better comprehension
-> sound analysis techniques
SUMMARY

- **representation of bionetworks 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
SUMMARY

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

- purposes
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- step-wise model development
  - qualitative model -> discrete Petri nets
  - discrete quantitative model -> stochastic Petri nets
  - continuous quantitative model -> continuous Petri nets = ODEs
PRINCIPAL COLLABORATORS

- Rainer Breitling
  University Glasgow, Integrative and Systems Biology &
  University of Groningen, Groningen Bioinformatics Centre

- David Gilbert
  Brunel University London/Uxbridge,
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- Wolfgang Marwan
  Otto von Guericke University & Magdeburg Centre for Systems Biology &
  Max Planck Institute for Dynamics of Complex Technical Systems

- Louchka Popova-Zeugmann
  Humboldt University Berlin, Computer Science Institute
REFERENCES, CASE STUDIES QPN - SPN - CPN


REFERENCES, SNOOPY

- C Rohr, W Marwan, M Heiner: Snoopy - a unifying Petri net framework to investigate biomolecular networks; Bioinformatics 2010 26(7): 974-975


THANKS

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