BIOCHEMICAL NETWORKS
- A PETRI NET PERSPECTIVE -

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MODEL-BASED SYSTEM ANALYSIS
MODEL-BASED SYSTEM ANALYSIS
MODEL-BASED SYSTEM ANALYSIS
MODEL-BASED SYSTEM ANALYSIS

UNDERSTANDING

system

biological system

model

model properties

system properties

validation

behaviour prediction

known properties

unknown properties
WHAT KIND OF MODEL SHOULD BE USED?
<**NETWORK REPRESENTATIONS, Ex1**>

If you have any questions or need further assistance, feel free to ask. monika.heiner@informatik.tu-cottbus.de  
August 2010

- FORMAL SEMANTICS?
**Network Representations, Ex2**

\[
\begin{align*}
\frac{d\alpha}{dt} & = -v_1 \\
\frac{d\text{Ste2}}{dt} & = -v_2 + v_3 - v_5 \\
\frac{d\text{Ste2}_{active}}{dt} & = v_2 - v_3 - v_4 \\
\frac{d\text{Sst2}_{active}}{dt} & = v_46 - v_47 \\
\frac{dG\alpha\beta\gamma}{dt} & = -v_6 + v_9 \\
\frac{dG\alpha\text{GTP}}{dt} & = v_6 - v_7 - v_8 \\
\frac{dG\alpha\text{GDP}}{dt} & = v_7 + v_8 - v_9 \\
\frac{dG\beta\gamma}{dt} & = v_6 - v_9 - v_{10} + v_{11} + v_{21} + v_{23} + v_{25} + v_{27} + v_{32} \\
& \quad - v_{42} + v_{43} \\
\frac{d\text{Ste5}}{dt} & = -v_{12} + v_{13} + v_{17} + v_{21} + v_{23} + v_{25} + v_{27} + v_{32} \\
\frac{d\text{Ste7}}{dt} & = -v_{14} + v_{15} + v_{17} + v_{21} + v_{23} + v_{25} + v_{27} + v_{32} \\
\frac{d\text{Fus3}}{dt} & = -v_{14} + v_{15} + v_{17} + v_{21} + v_{23} + v_{25} + v_{27} - v_{29} \\
& \quad + v_{30} + v_{33} \\
\frac{d\text{Ste20}}{dt} & = -v_{18} + v_{19} + v_{21} + v_{23} + v_{25} + v_{27} + v_{32} \\
\end{align*}
\]

\[
\begin{align*}
v_1 & = \alpha[t] \cdot \text{Bar1}_{active}[t] \cdot k_1 \\
v_2 & = \text{Ste2}[t] \cdot \alpha[t] \cdot k_2 \\
v_3 & = \text{Ste2}_{active}[t] \cdot k_3 \\
v_4 & = \text{Ste2}_{active}[t] \cdot k_4 \\
v_5 & = \text{Ste2}[t] \cdot k_5 \\
v_6 & = \text{Ste2}_{active}[t] \cdot G\alpha\beta\gamma[t] \cdot k_6 \\
v_7 & = G\alpha\text{GTP}[t] \cdot k_7 \\
v_8 & = G\alpha\text{GTP}[t] \cdot \text{Sst2}_{active}[t] \cdot k_8 \\
v_9 & = G\alpha\text{GDP}[t] \cdot G\beta\gamma[t] \cdot k_9 \\
v_{10} & = G\beta\gamma[t] \cdot C[t] \cdot k_{10} \\
v_{11} & = D[t] \cdot k_{11} \\
v_{12} & = \text{Ste5}[t] \cdot \text{Ste11}[t] \cdot k_{12} \\
v_{13} & = A[t] \cdot k_{13} \\
v_{14} & = \text{Ste7}[t] \cdot \text{Fus3}[t] \cdot k_{14} \\
v_{15} & = B[t] \cdot k_{15} \\
v_{16} & = A[t] \cdot B[t] \cdot k_{16} \\
v_{17} & = C[t] \cdot k_{17} \\
v_{18} & = D[t] \cdot \text{Ste20}[t] \cdot k_{18}
\end{align*}
\]
\[
\begin{align*}
\frac{dV_1}{dt} & = v_1 - d \cdot V_1 \\
\frac{dV_2}{dt} & = v_2 + v_3 - v_4 \\
\frac{dV_3}{dt} & = v_5 + v_6 - v_7 - v_8 \\
\frac{dV_4}{dt} & = v_9 - v_10 \\
\frac{dV_5}{dt} & = v_11 - v_12 \\
\frac{dV_6}{dt} & = v_13 - v_14 \\
\frac{dV_7}{dt} & = v_15 - v_16 \\
\frac{dV_8}{dt} & = v_17 - v_18
\end{align*}
\]
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**
  - tends to grow fast
  - dense, apparently unstructured
  - hard to read

%"#&'()*+,-./0123456789:;<=?>@ABCDEFGHIJKLMNOPQRSTUVWXYZ[\]^_`abcdefghijklmnopqrstuvwxyz{|}~
**Bio Networks, Some Problems**

- **knowledge**
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- **network structure**
  - tends to grow fast
  - dense, apparently unstructured
  - hard to read

-> **MODELS ARE FULL OF ASSUMPTIONS <**
FRAMEWORK: SYSTEMS BIOLOGY

MODELLING = FORMAL KNOWLEDGE REPRESENTATION

natural biosystem

wetlab experiments

observed behaviour

formalizing understanding

predicted behaviour

model

model-based experiment design

wetlab experiments
MODELLING = FORMAL KNOWLEDGE REPRESENTATION

natural biosystem

wetlab experiments

observed behaviour

predicted behaviour

model

formalizing understanding

model-based experiment design

wetlab experiments

model validation

MODEL VALIDATION = CONFIDENCE INCREASE
**Bio Network Representations Should Be**

- **Readable**
  - fault avoidance
  - informal = cartoon-like representations?

- **Analysable**
  - formal = mathematical representations

- **Executable**
  - to experience the model

- **Unifying Power**
  - high-level description for various analysis approaches
bionetworks knowledge

quantitative modelling

quantitative models

animation / analysis / simulation

understanding
model validation
quantitative behaviour prediction

ODEs
FRAMEWORK

QPN

SPN

CPN
FRAMEWORK

PN & Systems Biology

QPN

abstraction

extension

time-free

timed, quantitative

SPN

discrete state space

CPN

continuous state space

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FRAMEWORK

PN & Systems Biology

QPN

time-free

timed, quantitative

abstraction

extension

approximation

SPN

discrete state space

CPN

continuous state space

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 FRAMEWORK

PN & Systems Biology

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**FRAMEWORK**

---

**RG**

**CTL, LTL**

**QPN**

---

**time-free**

**abstracted, quantitative**

---

**SPN**

---

**CTMC**

**CSL, PLTLc**

---

**CPN**

---

**ODEs**

**PLTLc**

---

**discrete state space**

**continuous state space**

---

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THREE MODELS SHARING STRUCTURE

QUANTITATIVE MODEL = QUALITATIVE MODEL + QUANTITATIVE PARAMETERS (KINETICS)
QUALITATIVE PETRI NETS - QPN -
. . . ARE

NETWORKS OF

(BIO-) CHEMICAL REACTIONS
\[ 2 \text{H}_2 + \text{O}_2 \rightarrow 2 \text{H}_2\text{O} \]
2 H₂ + O₂ -> 2 H₂O
2 \( \text{H}_2 \) + \( \text{O}_2 \) \( \rightarrow \) 2 \( \text{H}_2\text{O} \)

Diagram:

- **Hyper arcs**: Arrows indicating connections between places and transitions.
- **Places**: Symbols representing \( \text{H}_2 \), \( \text{O}_2 \), and \( \text{H}_2\text{O} \).
- **Transitions**: Process steps indicated by arrows and numbers.
atomic actions $\rightarrow$ Petri net transitions $\rightarrow$ chemical reactions

$$2 \text{H}_2 + \text{O}_2 \rightarrow 2 \text{H}_2\text{O}$$
PETRI NETS, BASICS - THE STRUCTURE

- atomic actions -> Petri net transitions -> chemical reactions
  
  \[2 \text{H}_2 + \text{O}_2 \rightarrow 2 \text{H}_2\text{O}\]

- local conditions -> Petri net places -> chemical compounds
Petri Nets, Basics - The Structure

- **atomic actions** -> **Petri net transitions** -> **chemical reactions**

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

- **local conditions** -> **Petri net places** -> **chemical compounds**

- **multiplicities** -> **Petri net arc weights** -> **stoichiometric relations**

---

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PETRI NETS, BASICS - THE STRUCTURE

- atomic actions -> Petri net transitions -> chemical reactions
  
  \[ 2 \text{H}_2 + \text{O}_2 \rightarrow 2 \text{H}_2\text{O} \]

- local conditions -> Petri net places -> chemical compounds

- multiplicities -> Petri net arc weights -> stoichiometric relations

- condition’s state -> token(s) in its place -> available amount (e.g. mol)

- system state -> marking -> compounds distribution
PETRI NETS, BASICS - THE STRUCTURE

- atomic actions $\rightarrow$ Petri net transitions $\rightarrow$ chemical reactions
  
  $2 \text{H}_2 + \text{O}_2 \rightarrow 2 \text{H}_2\text{O}$

- local conditions $\rightarrow$ Petri net places $\rightarrow$ chemical compounds

- multiplicities $\rightarrow$ Petri net arc weights $\rightarrow$ stoichiometric relations

- condition’s state $\rightarrow$ token(s) in its place $\rightarrow$ available amount (e.g. mol)

- system state $\rightarrow$ marking $\rightarrow$ compounds distribution

$\text{PN} = (P, T, F, m_0), \quad F: (P \times T) \cup (T \times P) \rightarrow N_0, \quad m_0: P \rightarrow N_0$
Petri Nets, Basics - the Firing Rule

- an action may happen, if
  - all preconditions are fulfilled
    (corresponding to the arc weights);

- if an action 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);

- action happens (firing of a transition)
  - atomic
  - time-less

-> prerequisite

-> firing behaviour

-> model assumptions
atomic actions  ->  Petri net transitions  ->  chemical reactions

$$2 \text{H}_2 + \text{O}_2 \rightarrow 2 \text{H}_2\text{O}$$

input compounds

output compounds
atomic actions -> Petri net transitions -> chemical reactions

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

Input compounds

\[ \text{H}_2 \quad (4) \rightarrow 2 \quad \text{r} \rightarrow 2 \quad \text{H}_2\text{O} \]

\[ \text{O}_2 \quad \rightarrow \quad \text{r} \rightarrow 2 \quad \text{H}_2\text{O} \]

Output compounds

FIRING
**PETRI NETS, BASICS - THE BEHAVIOUR**

- **atomic actions**  \rightarrow  **Petri net transitions**  \rightarrow  **chemical reactions**

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

```
input compounds

H_2 (4) \rightarrow 2 \rightarrow r \rightarrow 2 \rightarrow \text{H}_2\text{O}

O_2 \rightarrow r \rightarrow \text{H}_2\text{O}

output compounds

FIRING

TOKEN GAME

DYNAMIC BEHAVIOUR (substance/signal flow)

STATE SPACE
```
Typical Basic Structures

- **metabolic networks**
  -> *substance flows*

- **signal transduction networks**
  -> *signal flows*
petri net elements, interpretations

- metabolic networks
  - signal transduction networks
  - gene regulatory networks

- transitions
  - (reversible, stoichiometric, enzyme-catalyzed) chemical reactions,
  - conversions/transport 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/low = present/not present, or any finite integer number
**Level Concept**

![Diagram showing levels of concentration](image)

- Level 1
  - Level 1
  - Level 2
  - Level 3
  - Level 4
- Level 2
  - Level 2
  - Level 3
  - Level 4
  - Level 7
- Level 3
  - Level 3
  - Level 4
  - Level 6
  - Level 8
- Level 4
  - Level 4
  - Level 5
  - Level 6
  - Level 8

**Concentration**

- 0.0
- 0.1
- 0.2
- 0.3
- 0.4

**4 Level Version**

**8 Level Version**
BIO PETRI NETS - SOME EXAMPLES
Ex1 - Glycolysis and Pentose Phosphate Pathway

[Reddy 1993]
Ex1 - Glycolysis and Pentose Phosphate Pathway

[Reddy 1993]
[Heiner 1998]
**Ex2: Apoptosis in Mammalian Cells**

![Diagram of the apoptotic process in mammalian cells.](image_url)

[**GON 2003**]
Ex2: APOPTOSIS IN MAMMALIAN CELLS

[QON 2003]

[HEINER, KOCH, WILL 2004]
Ex3 - Carbon Metabolism in Potato Tuber

[Koch, Junker, Heiner 2005]
Ex3 - Carbon Metabolism in Potato Tuber

[Koch, Junker, Heiner 2005]
positive feedback

[**GILBERT, HEINER, ROSSER, FULTON, GU, TRYBILIO 2008**]
Ex4 - Biosensor

[Gilbert, Heiner, Rosser, Fulton, Gu, Trybiolo 2008]
RasGTP

Raf → RafP

Phosphatase1

MEK → MEKP → MEKPP

Phosphatase2

ERK → ERKP → ERKPP

Phosphatase3
Ex6 - HYPOXIA

[YU ET AL. 2007]
Ex6 - HYPOXIA

[Heiner, Sriram 2010]
Ex6 - HYPOXIA

[HEINER, SRIRAM 2010]
Ex6 - HYPOXIA

[HEINER, SRIRAM 2010]
Ex7 - Switch Cycle Halobacterium Salinarum

[Marwan, Oesterhelt 1999]
Ex7 - Switch Cycle Halobacterium Salinarum

PN & Systems Biology
QUALITATIVE ANALYSES
Typical Petri Net Questions

- How many tokens can reside at most in a given place?
  - $\Rightarrow (0, 1, k, \infty) \Rightarrow \text{BOUNDEDNESS}$
Typical Petri Net Questions

- How many tokens can reside at most in a given place?
  -> \((0, 1, k, \infty)\) -> BOUNDEDNESS

- How often can a transition fire?
  -> \((0\text{-times, n-times, oo-times})\) -> LIVENESS
Typical Petri Net Questions

- How many tokens can reside at most in a given place?
  - \( (0, 1, k, \infty) \) -> **Boundedness**

- How often can a transition fire?
  - \( (0\text{-times}, n\text{-times}, oo\text{-times}) \) -> **Liveness**

- How often can a system state be reached?
  - **never** -> **Unreachable** -> **Safety Properties**
  - **n-times** -> **Reproducible**
  - **oo-times** -> **Reversibility**
**TYPICAL PETRI NET QUESTIONS**

- **How many tokens can reside at most in a given place?**
  - \( (0, 1, k, \infty) \)  
  - **BOUNDENESS**

- **How often can a transition fire?**
  - \( (0\text{-times}, n\text{-times}, oo\text{-times}) \)  
  - **LIVENESS**

- **How often can a system state be reached?**
  - never  
  - \( n\text{-times} \)  
  - \( oo\text{-times} \)  
  - **UNREACHABLE → SAFETY PROPERTIES**  
  - **REPRODUCIBLE**  
  - **REVERSIBILITY**

- **Are there behaviourally invariant net structures?**
  - **token conservation**  
  - \( P \text{- INVARIANTS} \)
  - **token distribution reproduction**  
  - \( T \text{- INVARIANTS} \)
**Typical Petri Net Questions**

- **How many tokens can reside at most in a given place?**
  -> \((0, 1, k, \infty)\)  -> **BOUND EDNESS**

- **How often can a transition fire?**
  -> \((0\text{-times}, n\text{-times}, oo\text{-times})\)  -> **LIVENESS**

- **How often can a system state be reached?**
  -> never  -> **UNREACHABLE**  -> **SAFETY PROPERTIES**
  -> \(n\text{-times}\)  -> **REPRODUCIBLE**
  -> \(oo\text{-times}\)  -> **REVERSIBILITY**

- **Are there behaviourally invariant net structures?**
  -> **token conservation**  -> **P - INVARIANT S**
  -> **token distribution reproduction**  -> **T - INVARIANTS**

- **... and many more -> temporal logics**  -> **CTL / LTL - CSL / PLTL**
**Typical Petri Net Questions**

- **How many tokens can reside at most in a given place?**
  - \( (0, 1, k, \infty) \)  
  - \( \text{BOUNDENESS} \)

- **How often can a transition fire?**
  - \( (0\text{-times, } n\text{-times, } \infty\text{-times}) \)  
  - \( \text{LIVENESS} \)

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  - \( \text{never} \)  
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  - \( \text{REVERSIBILITY} \)

- **Are there behaviourally invariant net structures?**
  - \( \text{token conservation} \)  
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- **... and many more**
  - \( \text{temporal logics} \)  
  - \( \text{CTL / LTL - CSL / PLTL} \)

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August 2010
ANALYSIS TECHNIQUES

- **static analyses** -> no state space construction

- **dynamic analyses** -> total/ partial state space construction
ANALYSIS TECHNIQUES

- **static analyses**
  - no state space construction
    - structural properties (graph theory, combinatorics), e.g. DTP
    - P / T - invariants (linear algebra)

- **dynamic analyses**
  - total/ partial state space construction
ANALYSIS TECHNIQUES

- static analyses
  -> no state space construction
  -> structural properties (graph theory)
  -> P / T - invariants (linear algebra)

- dynamic analyses
  -> total/ partial state space construction
  -> analysis of general behavioural system properties,
     e.g. boundedness, liveness, reversibility, . . .

  -> model checking of special behavioural system properties,
     e.g. reachability of a given (sub-) system state (with constraints),
     reproducability of a given (sub-) system state (with constraints)

  expressed in temporal logics (CTL / LTL),
  -> very flexible, powerful query language
A CASE STUDY
...one pathway...

Mitogens
Growth factors

receptor

Ras

Raf

MEK

ERK

cytoplasmic substrates

Elk

SAP

Gene
THE RKIP PATHWAY

[Cho et al., CMSB 2003]
THE RKIP PATHWAY

[Cho et al., CMSB 2003]
THE RKIP PATHWAY, PETRI NET

PN & Systems Biology
THE RKIP PATHWAY, HIERARCHICAL PETRI NET
THE RKIP PATHWAY, HIERARCHICAL PETRI NET

*initial marking*
initial marking
**THE RKIP PATHWAY, P-INVARIANTS**

**P-INV1: MEK**
**P-INV2: RAF-1STAR**
**P-INV3: RP**
**P-INV4: ERK**
**P-INV5: RKIP**
CONSTRUCTION OF THE INITIAL MARKING

- each P-invariant gets at least one token
  -> P-invariants are structural deadlocks and traps

- in signal transduction
  -> exactly 1 token, corresponding to species conservation
  -> token in least active state

- all (non-trivial) T-invariants get realizable
  -> to make the net live

- minimal marking
  -> minimization of the state space
CONSTRUCTION OF THE INITIAL MARKING

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- minimal marking
  -> minimization of the state space

  -> UNIQUE INITIAL MARKING
NON-TRIVIAL T-INARIANT, RUN

- realizability check under the constructed marking

- T-invariant’s unfolding to describe its behaviour
  -> partial order structure

- labelled condition / event net
  -> events (boxes)
    - transition occurrences
  -> conditions (circles)
    - involved compounds

- occurrence net
  -> acyclic
  -> no backward branching conditions
  -> infinite
property 1

Is a given (sub-) marking (system state) reachable?

\[ EF ( \text{ERK} \ast \text{RP} ); \]

property 2

Liveness of transition k8?

\[ AG EF ( \text{MEK-PP\_ERK} ); \]

property 3

Is it possible to produce ERK-PP neither creating nor using MEK-PP?

\[ E ( \neg \text{MEK-PP} \ U \text{ERK-PP} ); \]

property 4

Is there cyclic behaviour w.r.t. the presence / absence of RKIP?

\[ EG ( ( \text{RKIP} \rightarrow EF ( \neg \text{RKIP} ) ) \ast ( \neg \text{RKIP} \rightarrow EF ( \text{RKIP} ) ) ); \]
QUALITATIVE ANALYSIS RESULTS, SUMMARY

☐ structural decisions of behavioural properties
   -> CPI  -> BND
   -> ES & DTP  -> LIVE

☐ CPI & CTI
   -> all minimal T-invariant / P-invariants enjoy biological interpretation
   -> non-trivial T-invariant -> partial order description of the essential behaviour

☐ reachability graph
   -> finite  -> BND
   -> the only SCC contains all transitions  -> LIVE
   -> one Strongly Connected Component (SCC)  -> REV

☐ model checking
   -> requires professional understanding
   -> all expected properties are valid
QUALITATIVE ANALYSIS RESULTS, SUMMARY

- structural decisions of behavioural properties
  - CPI -> BND
  - ES & DTP -> LIVE

- CPI & CTI
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- reachability graph
  - finite -> BND
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- model checking
  - all expected properties are valid

-> VALIDATED QUALITATIVE MODEL
**BIONETWORKS, VALIDATION**

- **validation criterion 1**
  - \( \text{all expected structural properties hold} \)
  - \( \text{all expected general behavioural properties hold} \)

- **validation criterion 2**
  - \( \text{CTI} \)
  - \( \text{no minimal T-invariant without biological interpretation} \)
  - \( \text{no known biological behaviour without corresponding T-invariant} \)

- **validation criterion 3**
  - \( \text{CPI} \)
  - \( \text{no minimal P-invariant without biological interpretation (?)} \)

- **validation criterion 4**
  - \( \text{all expected special behavioural properties hold} \)
  - \( \text{temporal-logic properties} \)  \( \text{TRUE} \)
NOW WE ARE READY FOR SOPHISTICATED QUANTITATIVE ANALYSES!
STOCHASTIC
PETRI NETS
- SPN (xSPN) -
STOCHASTIC PETRI NETS, BASICS

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

- state-dependent lambda defined by rate 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

- semantics: Continuous Time Markov Chain (CTMC)
  -> reachability graph + state transition rates

- analysis
  -> standard Markov analysis techniques: transient, steady state
  -> stochastic simulation algorithms (SSA), e.g. Gillespie’s SSA
• *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 – 100 Levels

Concentration (Levels)

Time (s)
DETERMINISTIC SIMULATION

Deterministic Output

Concentration (μMol)

Time (s)
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

- semantics: set of Ordinary Differential Equations (ODEs)
  -> uniquely defined, but not vice versa
  -> typically non-linear

- simulation (numerical integration)
  -> stiff/unstiff solvers
CONTINUOUS PETRI NET DEFINES ODEs

PN & Systems Biology

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August 2010
\[ \frac{dm_3}{dt} = \]
\[
\frac{dm_3}{dt} = + r_1 + r_4
\]
\[
\frac{dm_3}{dt} = + r_1 \\
+ r_4 \\
- r_2 \\
- r_3
\]
\[ \frac{dm_3}{dt} = + k_1 \cdot m_1 \cdot m_2 \\
+ r_4 \\
- r_2 \\
- r_3 \]
\[ \frac{dm_3}{dt} = + k_1 \times m_1 \times m_2 \\
+ k_4 \times m_4 \\
- k_2 \times m_3 \\
- k_3 \times m_3 \times m_9 \]
THE QUALITATIVE MODEL BECOMES THE STRUCTURED DESCRIPTION OF THE QUANTITATIVE MODEL!
### Quantitative Analysis

<table>
<thead>
<tr>
<th>Species</th>
<th>S1</th>
<th>S2</th>
<th>S3</th>
<th>S4</th>
<th>S5</th>
<th>S6</th>
<th>S7</th>
<th>S8</th>
<th>S9</th>
<th>S10</th>
<th>S11</th>
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**Cho et al.**

13 "good" state configurations

**Biochemist**

the "bad" ones
QUANTITATIVE ANALYSIS
SUMMARY
representation of bionetworks by Petri nets

- partial order representation  \rightarrow  better comprehension
- formal semantics  \rightarrow  sound analysis techniques
- unifying view
SUMMARY

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  - partial order representation -> better comprehension
  - formal semantics -> sound analysis techniques
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  - animation -> to experience the model
  - model validation against consistency criteria -> to increase confidence
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SUMMARY

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  - 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
**Toolkit - Snoopy’s Export Features**

- Latex
- MetaTool
- Continuous PN
- Extended PN
- Stochastic PN
- Petri Net
- Music PN
- Modulo PN
- Time PN
- SBML Level 2
- APNN
- INA
- LoLA
- Maria
- PEP
- Prod
- Tina
- INA tim
- INA tmd
- PRISM
- SMART
- IDD-CSL
- EPS; MIF; Xfig
- Charlie

All net classes export to EPS; MIF; Xfig.
All Petri net classes are read by Charlie.

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August 2010
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  *Extended Stochastic Petri Nets for Model-based Design of Wet-lab Experiments*; 

- M Heiner, M Schwarick, A Tovchigrechko: 

- M Schwarick, M Heiner: 
Thanks!

http://www-dssz.informatik.tu-cottbus.de