SYSTEMS BIOLOGY
- A PETRI NET PERSPECTIVE -

WHAT HAVE
TECHNICAL AND NATURAL SYSTEMS
IN COMMON?

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LONG-TERM VISION

MEDICAL TREATMENT
LONG-TERM VISION

MEDICAL TREATMENT, APPROACH 1- TRIAL-AND-ERROR DRUG PRESCRIPTION
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July 2006
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MEDICAL TREATMENT, APPROACH 2
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MEDICAL TREATMENT, APPROACH 2 - MODEL-BASED DRUG PRESCRIPTION

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July 2006
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MEDICAL TREATMENT, APPROACH 2 - MODEL-BASED DRUG PRESCRIPTION
WHAT KIND OF MODEL SHOULD BE USED?
BIOLOGICAL FUNCTION?
BY INTERACTION IN NETWORKS
NETWORK REPRESENTATIONS, Ex2

\[
\begin{align*}
\frac{d\alpha}{dt} &= -v_1 \\
\frac{d\text{Ste2}}{dt} &= -v_2 + v_3 - v_5 \\
\frac{d\text{Ste2}_{\text{active}}}{dt} &= v_2 - v_3 - v_4 \\
\frac{dS\text{st2}_{\text{active}}}{dt} &= v_46 - v_47 \\
\frac{dG\alpha \beta \gamma}{dt} &= -v_6 + v_9 \\
\frac{dG\alpha \text{GTP}}{dt} &= v_6 - v_7 - v_8 \\
\frac{dG\alpha \text{GDP}}{dt} &= v_7 + v_8 - v_9 \\
\frac{dG\beta \gamma}{dt} &= v_6 - v_9 - v_{10} + v_{11} + v_{21} + v_{23} + v_{25} + v_{27} + v_{32} - v_{42} + v_{43} \\
\frac{d\text{Ste5}}{dt} &= -v_{12} + v_{13} + v_{17} + v_{21} + v_{23} + v_{25} + v_{27} + v_{32} \\
\frac{d\text{Ste11}}{dt} &= -v_{12} + v_{13} + v_{17} + v_{21} + v_{23} + v_{25} + v_{27} + v_{32} \\
\frac{d\text{Ste7}}{dt} &= -v_{14} + v_{15} + v_{17} + v_{21} + v_{23} + v_{25} + v_{27} + v_{32} \\
\frac{d\text{Fus3}}{dt} &= -v_{14} + v_{15} + v_{17} + v_{21} + v_{23} + v_{25} + v_{27} - v_{29} + v_{30} + v_{33} \\
\frac{d\text{Ste20}}{dt} &= -v_{18} + v_{19} + v_{21} + v_{23} + v_{25} + v_{27} + v_{32}
\end{align*}
\]

\[
\begin{align*}
v_1 &= \alpha[t] \cdot \text{Bar} I_{\text{active}}[t] \cdot k_1 \\
v_2 &= \text{Ste2}[t] \cdot \alpha[t] \cdot k_2 \\
v_3 &= \text{Ste2}_{\text{active}}[t] \cdot k_3 \\
v_4 &= \text{Ste2}_{\text{active}}[t] \cdot k_4 \\
v_5 &= \text{Ste2}[t] \cdot k_5 \\
v_6 &= \text{Ste2}_{\text{active}}[t] \cdot G\alpha \beta \gamma[t] \cdot k_6 \\
v_7 &= G\alpha \text{GTP}[t] \cdot k_7 \\
v_8 &= G\alpha \text{GTP}[t] \cdot S\text{st2}_{\text{active}}[t] \cdot k_8 \\
v_9 &= G\alpha \text{GDP}[t] \cdot G\beta \gamma[t] \cdot k_9 \\
v_{10} &= G\beta \gamma[t] \cdot C[t] \cdot k_{10} \\
v_{11} &= D[t] \cdot k_{11} \\
v_{12} &= \text{Ste5}[t] \cdot \text{Ste11}[t] \cdot k_{12} \\
v_{13} &= A[t] \cdot k_{13} \\
v_{14} &= \text{Ste7}[t] \cdot \text{Fus3}[t] \cdot k_{14} \\
v_{15} &= B[t] \cdot k_{15} \\
v_{16} &= A[t] \cdot B[t] \cdot k_{16} \\
v_{17} &= C[t] \cdot k_{17} \\
v_{18} &= D[t] \cdot \text{Ste20}[t] \cdot k_{18}
\end{align*}
\]
WHAT IS A BIOCHEMICAL NETWORK MODEL?

- **structure**

- **kinetics**, if you can
  \[
  \frac{d[Raf1^*]}{dt} = k1*m1*m2 + k2*m3 + k5*k4
  \]
  \[k1 = 0.53, k2 = 0.0072, k5 = 0.0315\]

- **initial conditions**
  \[ [Raf1^*]_{t=0} = 2 \mu\text{Molar} \]
BIONETWORKS, SOME PROBLEMS

- knowledge
  -> uncertain
  -> growing, changing
  -> time-consuming wet-lab experiments
  -> some data estimated
  -> 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
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- **network structure**
  - tend to grow fast
  - dense, apparently unstructured
  - hard to read

.models are full of assumptions.
BIONETWORKS, SOME PROBLEMS
FRAMEWORK

bionetworks knowledge

quantitative modelling

quantitative models

animation / analysis / simulation

understanding
model validation
quantitative behaviour prediction

ODEs
FRAMEWORK

bionetworks knowledge

quantitative parameters

qualitative models

qualitative modelling

quantitative modelling

quantitative models

quantitative models

animation / analysis

animation / analysis /simulation

understanding

model validation

qualitative behaviour prediction

model checking

Petri net theory (invariants)

ODEs

model validation

quantitative behaviour prediction

understanding
FRAMEWORK

- bionetworks knowledge
  - qualitative modelling
    - qualitative models
      - animation / analysis
        - quantitative parameters
          - quantitative models
            - animation / analysis /simulation
              - quantitative behaviour prediction
                - model validation
                  - understanding
                    - model checking
                      - Petri net theory
                        (invariants)
                      - reachability graph
                        linear inequalities
                      - linear programming
                        ODEs
BIO PETRI NETS -
AN INFORMAL CRASH COURSE
atomic actions -> Petri net transitions -> chemical reactions

2 $\text{NAD}^+$ + 2 $\text{H}_2\text{O}$ -> 2 $\text{NADH}$ + 2 $\text{H}^+$ + $\text{O}_2$
atomic actions      -> Petri net transitions      -> chemical reactions

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

Diagram: Petri net with transitions and compounds.
PETRI NETS, BASICS - THE STRUCTURE

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

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

- local conditions -> Petri net places -> chemical compounds
PETRI NETS, BASICS - THE STRUCTURE

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

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

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

- **multiplicities** -> Petri net arc weights -> stoichiometric relations
PETRI NETS, BASICS - THE STRUCTURE

- atomic actions -> Petri net transitions -> chemical reactions
  
  2 NAD\(^+\) + 2 H\(_2\)O \rightarrow 2 NADH + 2 H\(^+\) + O\(_2\)

- 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** -> Petri net transitions -> chemical reactions
  
  \[ 2 \text{NAD}^+ + 2 \text{H}_2\text{O} \rightarrow 2 \text{NADH} + 2 \text{H}^+ + \text{O}_2 \]

- **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

- **PN = (P, T, F, m_0)**, \[ F: (P \times T) \cup (T \times P) \rightarrow \mathbb{N}_0, \] \[ m_0: P \rightarrow \mathbb{N}_0 \]
atomic actions -> Petri net transitions -> chemical reactions

2 NAD$^+$ + 2 H$_2$O $\rightarrow$ 2 NADH + 2 H$^+$ + O$_2$
atomic actions -> Petri net transitions -> chemical reactions

2 NAD$^+$ + 2 H$_2$O $\rightarrow$ 2 NADH + 2 H$^+$ + O$_2$
atomic actions -> Petri net transitions -> chemical reactions

2 NAD$^+$ + 2 H$_2$O $\rightarrow$ 2 NADH + 2 H$^+$ + O$_2$
r1: A \rightarrow B
r1: A -> B
r2: B -> C + D
r3: B -> D + E

-> alternative reactions
r1: A → B
r2: B → C + D
r3: B → D + E
r4: F → B + a
r6: C + b → G + c
r7: D + b → H + c

-> concurrent reactions
r1: A -> B
r2: B -> C + D
r3: B -> D + E
r4: F -> B + a
r5: E + H <-> F
r6: C + b -> G + c
r7: D + b -> H + c
r8: H <-> G

-> reversible reactions
r1: A -> B
r2: B -> C + D
r3: B -> D + E
r4: F -> B + a
r5: E + H <-> F
r6: C + b -> G + c
r7: D + b -> H + c
r8: H <-> G

-> reversible reactions
- hierarchical nodes
r1: A -> B
r2: B -> C + D
r3: B -> D + E
r4: F -> B + a
r5: E + H <-> F
r6: C + b -> G + c
r7: D + b -> H + c
r8: H <-> G
r9: G + b -> K + c + d
r10: H + 28a + 29c -> 29b
r11: d -> 2a
r1: A \rightarrow B
r2: B \rightarrow C + D
r3: B \rightarrow D + E
r4: F \rightarrow B + a
r5: E + H \leftrightarrow F
r6: C + b \rightarrow G + c
r7: D + b \rightarrow H + c
r8: H \leftrightarrow G
r9: G + b \rightarrow K + c + d
r10: H + 28a + 29c \rightarrow 29b
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r1: A -> B
r2: B -> C + D
r3: B -> D + E
r4: F -> B + a
r5: E + H <-> F
r6: C + b -> G + c
r7: D + b -> H + c
r8: H <-> G
r9: G + b -> K + c + d
r10: H + 28a + 29c -> 29b
r11: d -> 2a
BIOLOGICAL SYSTEMS, INTRO

r1: A $\rightarrow$ B
r2: B $\rightarrow$ C + D
r3: B $\rightarrow$ D + E
r4: F $\rightarrow$ B + a
r5: E + H $\leftrightarrow$ F
r6: C + b $\rightarrow$ G + c
r7: D + b $\rightarrow$ H + c
r8: H $\leftrightarrow$ G
r9: G + b $\rightarrow$ K + c + d
r10: H + 28a + 29c $\rightarrow$ 29b
r11: d $\rightarrow$ 2a

INPUT FROM ENVIRONMENT

OUTPUT TO ENVIRONMENT
BIOCHEMICAL PETRI NETS, SUMMARY

- **biochemical networks**
  - networks of (abstract) chemical reactions

- **biochemically interpreted Petri net**
  - partial order sequences of chemical reactions (= elementary actions) transforming input into output compounds / signals
  - set of all pathways from the input to the output compounds / signals

- **pathway**
  - self-contained partial order sequence of elementary (re-) actions
TYPICAL BASIC STRUCTURES

- metabolic networks
  -> substance flows

- signal transduction networks
  -> signal flows
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, PETRI NET

K11

K8

K5

K10

K9

K7

K6

K4

K3

K2

K1

RP

M10

RKIP-P

ERK

M5

MEK-PP

M7

MEK-PP

ERK

M6

RKIP-P

M11

RKIP-P_RP

M3

Raf-1Star_RKIP

M4

Raf-1Star_RKIP_ERK-PP

M9

ERK-PP

M8

MEK-PP_ERK

M2

RKIP

M1

Raf-1Star

M1

m1

m2

m3

m4

m5

m6

m7

m8

m9

m10

m11

k1

k2

k3

k4

k5

k6

k7

k8

k9

k10

k11
THE RKIP PATHWAY, HIERARCHICAL PETRI NET

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July 2006
THE RKIP PATHWAY, HIERARCHICAL PETRI NET

initial marking
THE RKIP PATHWAY, HIERARCHICAL PETRI NET

initial marking

CONSTRUCTED BY PN ANALYSIS
QUALITATIVE ANALYSES
ANALYSIS TECHNIQUES, OVERVIEW

- **static analyses**  
  -> no state space construction
  -> structural properties (graph theory, combinatorial algorithms)
  -> $P / T$ - invariants (discrete computational geometry),

- **dynamic analyses**  
  -> total / partial state space construction
  -> state space representations: *interleaving* (RG) / *partial order* (prefix)

- 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
STATIC
ANALYSES
**INCIDENCE MATRIX C**

- **a representation of the net structure**
  
  $C = \begin{array}{c|cccc}
  p & t_1 & \ldots & t_j & \ldots & t_m \\
  \hline
  p_1 & & & & \\
  p_i & & & c_{ij} & \\
  \vdots & & & \Delta t_j & \\
  p_n & & & & \\
  \end{array}$

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

  $\Delta t_j = \Delta t_j(\ast)$

- **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**

  ![Diagram](image)

  $c_{ij} = 0$
P-invariants, Basics

- Lautenbach, 1973

- P-invariants
  - integer solutions $y$ of $yC = 0, y \neq 0, y \geq 0$  
  - minimal P-invariants
    - there is no P-invariant with a smaller support
    - $\text{gcd}$ of all entries is 1

- any P-invariant is a non-negative linear combination of minimal ones
  - multiplication with a positive integer
  - addition
  - Division by $\text{gcd}$

- Covered by P-Invariants (CPI)
  - each place belongs to a P-invariant
  - CPI $\Rightarrow$ BND (sufficient condition)
P-invariants, interpretation

- The firing of any transition has no influence on the weighted sum of tokens on the P-invariant’s places.
  - For all \( t \): the effect of the arcs, removing tokens from a P-invariant’s place is equal to the effect of the arcs, adding tokens to a P-invariant’s place.

- Set of places with:
  - A constant weighted sum of tokens for all markings \( m \) reachable from \( m_0 \):
    \[ y_m = y_{m_0} \]
  - Token/compound preservation
  - Moieties
  - A place belonging to a P-invariant is bounded

- A P-invariant defines a subnet:
  - The P-invariant’s places (the support),
    - All their pre- and post-transitions
    - The arcs in between
  - Pre-sets of supports = post-sets of supports
  - Self-contained, cyclic
**The RKIP Pathway, P-Invariants**

**P-INV1**: MEK  
**P-INV2**: RAF-1STAR  
**P-INV3**: RP  
**P-INV4**: ERK  
**P-INV5**: RKIP
T-INVARIANTS, BASICS

- Lautenbach, 1973

- **T-invariants**
  - integer solutions $x$ of $Cx = 0$, $x \neq 0$, $x \geq 0$ -> multisets of transitions
  - Parikh vector

- **minimal T-invariants**
  - there is no T-invariant with a smaller support -> sets of transitions
  - $\gcd$ 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 $\gcd$

- **Covered by T-Invariants (CTI)**
  - each transition belongs to a T-invariant
  - $BND \& LIVE \Rightarrow CTI$ (necessary condition)
T-INVARIENTS, INTERPRETATIONS

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

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

- a T-invariant defines a subnet
  - the T-invariant’s transitions (the support), + all their pre- and post-places + the arcs in between
  - pre-sets of supports = post-sets of supports

- zero effect on marking
- reproducing a marking / system state
- relative transition firing rates of transitions occurring permanently & concurrently
- steady state behaviour
- partially ordered transition sequence of transitions occurring one after the other
- substance / signal flow
- pre-sets of supports = post-sets of supports
THE RKIP PATHWAY, NON-TRIVIAL T-INARIANT

-> non-trivial T-invariant
+ four trivial ones for reversible reactions
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
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- UNIQUE INITIAL MARKING
NON-TRIVIAL T-IN Variant, 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
DYNAMIC ANALYSES
Dynamic Analysis - Reachability Graph

- simple construction algorithm
  - nodes - system states
  - arcs - the (single) firing transition -> single step firing rule
simple construction algorithm

- nodes - system states
- arcs - the (single) firing transition
  -> single step firing rule

s1
simple construction algorithm

- nodes - system states
- arcs - the (single) firing transition

single step firing rule
simple construction algorithm

- nodes - system states
- arcs - the (single) firing transition

- single step firing rule
simple construction algorithm

- nodes - system states
- arcs - the (single) firing transition -> single step firing rule

Diagram:

- Nodes: s1, s2, s3, s4
- Arrows (arcs):
  - k1 from s1 to s2
  - k2 from s1 to s2
  - k3 from s2 to s3
  - k4 from s2 to s3
  - k5 from s3 to s4
RKIP Pathway, Reachability Graph
property 1

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

\[ EF(ERK \ast RP); \]

property 2

Liveness of transition k8?

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

property 3

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

\[ E(!MEK-PP \ U \ ERK-PP); \]

property 4

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

\[ EG((RKIP \rightarrow EF(!RKIP)) \ast (!RKIP \rightarrow EF(RKIP))); \]
QUALITATIVE ANALYSIS RESULTS, SUMMARY

- structural decisions of behavioural properties  -> static analysis
  - 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  -> dynamic analysis
  - 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 -> static analysis
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- model checking -> requires professional understanding
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-> VALIDATED QUALITATIVE MODEL
BIONETWORKS, VALIDATION

- **validation criterion 1**
  - all expected structural properties hold
  - all expected general behavioural properties hold

- **validation criterion 2**
  - CTI
  - no minimal T-invariant without biological interpretation
  - no known biological behaviour without corresponding T-invariant

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

- **validation criterion 4**
  - all expected special behavioural properties hold
  - temporal-logic properties -> TRUE
NOW WE ARE READY
FOR SOPHISTICATED
QUANTITATIVE ANALYSES!
quantitative model = qualitative model + quantitative parameters

-> known or estimated quantitative parameters
QUANTITATIVE ANALYSIS

- quantitative model = qualitative model + quantitative parameters
  -> known or estimated quantitative parameters

- typical quantitative parameters of bionetworks
  -> compound concentrations -> real numbers
  -> reaction rates / fluxes -> concentration-dependent
QUANTITATIVE ANALYSIS

- quantitative model = qualitative model + quantitative parameters
  -> known or estimated quantitative parameters

- typical quantitative parameters of bionetworks
  -> compound concentrations  -> real numbers
  -> reaction rates / fluxes  -> concentration-dependent

- continuous Petri nets

\[
\begin{align*}
\frac{dm_1}{dt} &= \frac{dm_2}{dt} = -v_1 \\
\frac{dm_3}{dt} &= v_1 - v_2 \\
v_1 &= k_1 m_1 m_2 \\
v_2 &= k_2 m_3
\end{align*}
\]

\{ ODEs \}
THE RKIP PATHWAY, CONTINUOUS PETRI NET

The diagram represents the RKIP pathway using a continuous Petri net model. The model includes states such as MEK-PP, ERK, RKIP, RKIP-P, and RKIP-P_RP, with transitions mediated by parameters k1 to k11. The pathway involves interactions such as RKIP-P_RKIP, Raf-1Star_RKIP, and MEK-PP_ERK. The diagram illustrates the flow of signaling molecules and regulatory interactions within the RKIP pathway.
\[
\frac{dm_3}{dt} =
\]
\[
\frac{dm_3}{dt} = + r_1 + r_4
\]
\[
\frac{dm_3}{dt} = + r_1 + r_4 - r_2 - r_3
\]
\[
\frac{dm_3}{dt} = + k_1 \cdot m_1 \cdot m_2 \\
+ r_4 \\
- r_2 \\
- r_3
\]
\[
\frac{dm_3}{dt} = + k_1 \cdot m_1 \cdot m_2 \\
+ k_4 \cdot m_4 \\
- k_2 \cdot m_3 \\
- k_3 \cdot m_3 \cdot m_9
\]
THE QUALITATIVE MODEL BECOMES THE STRUCTURED DESCRIPTION OF THE QUANTITATIVE MODEL!
QUANTITATIVE ANALYSIS

Species
Raf-1*       1 0 0 1 1 1 1 1 1 0 0 1 1 1
RKIP          1 0 0 0 0 0 0 1 0 0 1 0 0
Raf-1*_RKIP  0 1 0 0 0 0 0 0 1 1 0 0 0
Raf-1*_RKIP_ERK-PP 0 0 1 0 0 0 0 0 0 0 0 0 0
ERK           0 0 0 1 0 0 1 1 1 0 0 0 0
RKIP-P        0 0 0 1 1 0 0 0 0 0 0 0 1
MEK-PP        1 1 1 1 0 0 1 1 1 0 0 1 1
MEK-PP_ERK    0 0 0 0 1 1 0 0 0 1 1 0 0
ERK-PP        1 1 0 0 0 0 0 0 0 0 0 1 1
RP            1 1 1 1 1 0 0 1 1 1 1 0 1
RKIP-P_RP     0 0 0 0 1 1 0 0 0 0 0 1 0

Distribution of `bad' steady states as euclidean distances from the `good' final steady state

13 “good” state configurations    the “bad” ones
QUANTITATIVE ANALYSIS
QUANTITATIVE ANALYSIS

ERK PP

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 1.0

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July 2006
CASE STUDY, 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  -> new insights

❑ two-step model development
  -> qualitative model    -> discrete Petri nets
  -> quantitative model   -> continuous Petri nets = ODEs

❑ many challenging open questions
SOME MORE CASE STUDIES
Ex1 - Glycolysis and Pentose Phosphate Pathway

[Reddy 1993]
Ex1 - Glycolysis and Pentose Phosphate Pathway

[Reddy 1993]
Ex2 - Carbon Metabolism in Potato Tuber

[Koch; Junker; Heiner 2005]
Ex2 - Carbon Metabolism in Potato Tuber

[KOCH; JUNKER; HEINER 2005]
EX3: APOPTOSIS IN MAMMALIAN CELLS

[GON 2003]
EX4 - SWITCH CYCLE HALOBACTERIUM SALINARUM

[Marwan; Oesterhelt 1999]
WHAT HAVE
TECHNICAL AND NATURAL SYSTEMS
IN COMMON?
MODEL-BASED SYSTEM ANALYSIS

Problem system

model

system properties

model properties
MODEL-BASED SYSTEM ANALYSIS

CONSTRUCTION

technical system

verification

requirement specification

model properties

model

system

system properties
MODEL-BASED SYSTEM ANALYSIS

UNDERSTANDING

system

biological system

model

validation

behaviour prediction

system properties

known properties

unknown properties

model properties
OUTLOOK

THANKS!

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