FROM PETRI NETS TO DIFFERENTIAL EQUATIONS

AN INTEGRATIVE APPROACH FOR BIOCHEMICAL NETWORK ANALYSIS

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MODEL-BASED SYSTEM ANALYSIS

system

model

system properties

model properties

Problem system

PN & Systems Biology

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MODEL-BASED SYSTEM ANALYSIS

UNDERSTANDING

system

biological system

model

Model-Properties

system properties

known properties

behaviour prediction

validation

unknown properties

model properties
FRAMEWORK

- bionetworks knowledge
  - qualitative modelling
    - qualitative models
      - animation / analysis
        - quantitative parameters
          - quantitative modelling
            - quantitative models
              - animation / analysis / simulation
                - understanding
                  - model validation
                    - qualitative behaviour prediction
                      - model checking
                        - Petri net theory (invariants)
                          - RG
                            - SLI
                              - LP
                                - ODEs
                                  - understanding
                                    - model validation
                                      - quantitative behaviour prediction
PETRI NETS -
AN INFORMAL CRASH COURSE
PETRI NETS, BASICS - THE STRUCTURE

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

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

Input compounds: NAD\(^+\) and H\(_2\)O

Petri net transition r1:

- Input: 2 NAD\(^+\) and 2 H\(_2\)O
- Output: 2 NADH, 2 H\(^+\), and O\(_2\)

Output compounds: NADH, H\(^+\), and O\(_2\)
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 \( \text{H}^+ \) + \( \text{O}_2 \)

Diagram:
- Input compounds: \( \text{NAD}^+ \), \( \text{H}_2\text{O} \)
- Output compounds: \( \text{NADH} \), \( \text{O}_2 \), \( \text{H}^+ \)
- Hyperarcs: \( \text{NAD}^+ \) to \( \text{NADH} \), \( \text{H}_2\text{O} \) to \( \text{H}^+ \), \( \text{O}_2 \) to \( \text{O}_2 \)
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

input compounds

pre-conditions

NAD\(^+\)

H\(_2\)O

output compounds

post-conditions

NADH

H^+

O\(_2\)
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 → 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

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

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

![Diagram of a Petri net model for the reaction 2 NAD$^+$ + 2 H$_2$O $\rightarrow$ 2 NADH + 2 H$^+$ + O$_2$.]
atomic actions \rightarrow Petri net transitions \rightarrow chemical reactions

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

**FIRING**

**TOKEN GAME**

**DYNAMIC BEHAVIOUR** (substance flow)
TYPICAL BASIC STRUCTURES

- metabolic networks
  - substance flows

- signal transduction networks
  - signal flows
THE RUNNING EXAMPLE - THE RKIP PATHWAY

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

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initial marking
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
     [ respecting the given stoichiometric relations, if any ]
  -> set of all pathways
     from the input to the output compounds / signals
     [ respecting the stoichiometric relations, if any ]

- **pathway**
  -> self-contained partial order sequence of elementary (re-) actions

- **typical basic assumption (for metabolic networks)**
  -> steady state behaviour
QUALITATIVE ANALYSES
ANALYSIS TECHNIQUES, OVERVIEW

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

- **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

  - state space representations: interleaving (RG) / partial order (prefix)
STATIC ANALYSES
**INCIDENCE MATRIX C**

- **a representation of the net structure**

  *C* =

<table>
<thead>
<tr>
<th>P</th>
<th>t1 ... tj ... tm</th>
</tr>
</thead>
<tbody>
<tr>
<td>p1</td>
<td></td>
</tr>
<tr>
<td>pi</td>
<td>c_{ij}</td>
</tr>
<tr>
<td>...</td>
<td></td>
</tr>
<tr>
<td>pn</td>
<td>Δt_j</td>
</tr>
</tbody>
</table>

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

  \( Δt_j = Δt_j(*) \)

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

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

- **side-conditions are neglected**

  \( c_{ij} = 0 \)

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T-INVARIANTS, BASICS

❑ Lautenbach, 1973

❑ T-invariants
  -> integer solutions of \( Cx = 0, x \neq 0, x \geq 0 \)
  -> multisets of transitions

❑ minimal T-invariants
  -> there is no T-invariant with a smaller support
  -> \( \text{gcd} \) 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 \( \text{gcd} \)

❑ Covered by T-Invariants (CTI)
  -> each transition belongs to a T-invariant
  -> \( \text{BND} \) & \( \text{LIVE} \) \( \Rightarrow \) CTI (necessary condition)
**T-INvariants, Interpretation**

- **T-invariants** = (multi-) sets of transitions
  - zero effect on marking
  - reproducing a marking / system state
  - steady state substance flows / reaction rates
  - elementary modes [Schuster 1993]

- **realizable T-invariants** correspond to cycles in the RG
  - RG: concurrent transitions -> all transitions’ interleaving sequences
  - if there are concurrent transitions in a realizable T-invariant, then there is a RG cycle for each interleaving sequence
  - analogously for conflicts

- **a T-invariant defines a subnet** -> partial order structure
  - 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
  - self-contained subnet
T-INVARIENTS, THE RKIP PATHWAY

-> non-trivial T-invariant
+ four trivial ones for reversible reactions
Run of the Non-Trivial T-Invariant

- Partial order structure
- T-invariant’s unfolding to describe its behaviour
- Labelled condition / event net
  - Events
    - Transition occurrences
  - Conditions
    - Input / output compounds
- Partial order semantics
  - A net’s all partial order runs
  - Finite prefix
P-INVARINTS, 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
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

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

- minimal marking
  -> minimization of the state space

- assumption: top-to-bottom reading of the figure
  -> but, all reachable markings are equivalent
    (= produce same state space)

-> UNIQUE INITIAL MARKING
STATIC ANALYSIS, SUMMARY

- **structural properties**

  INA
  
  ORD  HOM  NBM  PUR  CSV  SCF  CON  SC  Ft0  tF0  Fp0  pF0  MG  SM  FC  EFC  ES
  Y    Y    Y    N    N    Y    Y    N    N    N    N    N    N    N    N    Y
  DTP  CPI  CTI  B  SB  REV  DSt  BSt  DTr  DCF  L  LV  L&S
  Y    Y    Y    Y    Y    Y    N    ?    N    N    Y    Y    Y

- **CPI**

  -> *structural bounded (SB)*

  -> *each P-invariant represents a substance conservation subnet (cycle)*

- **CTI**

  -> *Live & BND -> CTI*

  -> *4 trivial T-invariants for reversible reactions*

  -> *1 non-trivial T-invariant describing the essential cyclic behaviour*

- **DTP & ES -> Live**
DYNAMIC ANALYSES
DYNAMIC ANALYSIS - REACHABILITY GRAPH

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

- unbounded Petri net -> infinite RG
  bounded Petri net -> finite RG

- concurrency
  -> enumeration of all interleaving sequences
  -> interleaving semantics

- branching arcs in the RG
  -> conflict OR concurrency

- RG tend to be very large
  -> automatic evaluation necessary
  -> model checking

- worst case: over-exponential growth
  -> alternative analyses techniques?
MODEL CHECKING

- is a technique for verifying finite-state concurrent systems against properties specified in temporal logic

  Clarke, E. M. Jr.; Grumberg, O.; Peled, D. A.:
  Model Checking;
  MIT Press 2001

- finite state systems = steady state systems = bounded pn

- model checking of unbounded systems
  -> CTL undecidable
  -> LTL decidable, but no tools (not yet ?)
  -> unboundedness + inhibitors = undecidability

- how to get bounded model ?
  -> qualitative model - model assumptions of environment behaviour
  -> quantitative model - transition firing rates / durations
TEMPORAL LOGICS, BASICS

- extension of classical (propositional) logics by temporal operators

- atomic propositions
  - elementary statements, having - in a given state - a well-defined truth value
  - e.g. mutex, for 1-bounded pn
  - e.g. buffer = 2, buffer > 2, else

- constants
  - TRUE, FALSE

- classical Boolean operators
  - negation !
  - conjunction *
  - disjunction +
  - implication ->

- temporal operators
  - to refer to the sequence of states
### CTL OPERATORS, INTERLEAVING SEMANTICS

<table>
<thead>
<tr>
<th></th>
<th>next f</th>
<th>finally f</th>
<th>globally f</th>
<th>f1 until f2</th>
</tr>
</thead>
<tbody>
<tr>
<td>on all branches</td>
<td>AX</td>
<td>AF</td>
<td>AG</td>
<td>AU</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="AX" /></td>
<td><img src="image" alt="AF" /></td>
<td><img src="image" alt="AG" /></td>
<td><img src="image" alt="AU" /></td>
</tr>
<tr>
<td><strong>on some branch</strong></td>
<td>EX</td>
<td>EF</td>
<td>EG</td>
<td>EU</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="EX" /></td>
<td><img src="image" alt="EF" /></td>
<td><img src="image" alt="EG" /></td>
<td><img src="image" alt="EU" /></td>
</tr>
</tbody>
</table>
MODEL CHECKING, EXAMPLES

❑ property 1

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

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

❑ property 2

Liveness of transition k8?

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

❑ 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?

\[ EG ( ( \text{RKIP} \rightarrow EF ( \neg \text{RKIP} ) ) \ast ( \neg \text{RKIP} \rightarrow EF ( \text{RKIP} ) ) ); \]
### TECHNIQUES & TOOLS, OVERVIEW

<table>
<thead>
<tr>
<th>technique</th>
<th>CTL</th>
<th>LTL</th>
</tr>
</thead>
<tbody>
<tr>
<td>reachability graph</td>
<td>INA</td>
<td>PROD, MARIA</td>
</tr>
<tr>
<td>stubborn set reduced reachability graph</td>
<td>LoLA</td>
<td>PROD (LTL\X)</td>
</tr>
<tr>
<td>symmetrically reduced reachability graph</td>
<td>LoLA (symmetric formulas)</td>
<td>?</td>
</tr>
<tr>
<td>BDD, NDD, ..., xDD</td>
<td>DSSZ-CTL, SMART, DSSZ-CTL2</td>
<td>DSSZ-LTL</td>
</tr>
<tr>
<td>Kronecker algebra</td>
<td>[Kemper]</td>
<td>?</td>
</tr>
<tr>
<td>prefix</td>
<td>PEP (CTL_0)</td>
<td>QQ (LTL\X)</td>
</tr>
<tr>
<td>process automata</td>
<td>[pd]</td>
<td>?</td>
</tr>
</tbody>
</table>
QUALITATIVE ANALYSIS, 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
  - 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

-> VALIDATED QUALITATIVE MODEL
BIONETWORKS, VALIDATION

- validation criterion 0
  - all expected structural properties hold
  - all expected general behavioural properties hold

- validation criterion 1
  - CTI
  - no minimal T-invariant without biological interpretation
  - no known biological behaviour without corresponding T-invariant

- validation criterion 2
  - CPI
  - no minimal P-invariant without biological interpretation (?)

- validation criterion 3
  - all expected special behavioural properties hold
  - temporal-logic properties -> TRUE
QUANTITATIVE ANALYSES 1

- TIMED PETRI NETS
T-invariants, two interpretations

- **Parikh vector**
  - state-reproducing transition sequence (partial order) of transitions occurring one after the other
  - relative transition firing rates of transitions occurring permanently & concurrently

- **Relative transition firing rates**
  - may be implemented by transition firing times
    - constant
    - interval

- **Quantitative modell = qualitative model + quantitative parameters**
  - quantitative parameters - firing times reflecting the firing rates
  - time-dependent model

- **Claim**
  - transformation preserves all possible behaviour (= minimal T-invariants)
TRANSFORMATION, EXAMPLE

-> properties as time-less net

INA
ORD HOM NBM PUR CSV SCF CON SC Ft0 tF0 Fp0 pF0 MG SM FC EFC ES
N Y N Y Y N Y N Y Y N N Y N Y Y
CPI CTI B SB REV DSt BSt DTr DCF L LV L&S
N Y N N Y N ? N N Y Y N

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TRANSFORMATION, EXAMPLE

T-INARIANT 1

T-INARIANT 2

-> properties as time-less net

prod_A

A

r1

B

r2

C

cons_B

cons_C

IN

ORD HOM NBM PUR CSV SCF CON SC F0 tF0 Fp0 pF0 MG SM FC EFC ES
N Y N Y N Y Y N Y N Y N Y N Y Y
CPI CTI B SB REV DST BST DTR DCF L LV L&S
N Y N N Y N ? N N Y Y N
TRANSFORMATION, EXAMPLE

-> properties as time net

1. prod_A
2. r1<6>
3. cons_B

1. T-IN Variant 1
2. T-IN Variant 2

1. A
2. B
3. C

ORDER HOM NBM PUR CSV SCF CON SC FT0 tF0 Fp0 pF0 MG SM FC EFC ES
N Y N Y Y N Y N Y N Y N Y N Y Y Y
CPI CTI B SB REV DSt BSt DTr DCF L LV L&S
N Y Y N N N ? N Y Y Y Y N
transient state
steady state

![Diagram of steady state transitions]

- **S6 (A,2B,C)**
  - \(t(r2)=3\)
  - \(t(\text{cons}_C)=1\)
- **S7 (0,B,C)**
  - \(t(\text{prod}_A)=2\)
  - \(t(r1)=5\)
  - \(t(r2)=2\)
  - \(t(\text{cons}_B)=2\)
- **S8 (A,B,3C)**
  - \(t(r1)=3\)
- **S9 (0,0,2C)**
  - \(t(\text{prod}_A)=1\)
  - \(t(r1)=1\)
  - \(t(r2)=4\)
  - \(t(\text{cons}_B)=1\)

Terminal SCC:

- **s5-6**
- **s11-8**

Transition labels:

- \([1]\) prod_A start
- \([2]\) prod_A end
- \([1]\) r1 start
- \([2]\) r1 end
- \([1]\) cons_B start, cons_C end
- \([2]\) cons_B start, cons_C end

Transitions:

- \(\text{prod}_A\) start -> \(\text{cons}_B\) start, \(\text{cons}_C\) end
- \(\text{prod}_A\) end -> \(\text{cons}_B\) end, \(\text{cons}_C\) start
- \(\text{r1}\) start -> \(\text{cons}_B\) end, \(\text{cons}_C\) start
RG(Example), Terminal SCC

- contains all transitions
  - always running
  - start / end at different time points
- contains all minimal T-invariants
- timing diagram
- relative transition firing rates

<table>
<thead>
<tr>
<th>Event</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>prod_A</td>
<td>1</td>
</tr>
<tr>
<td>r1</td>
<td>1</td>
</tr>
<tr>
<td>r2</td>
<td>1</td>
</tr>
<tr>
<td>cons_B</td>
<td>2</td>
</tr>
<tr>
<td>cons_C</td>
<td>3</td>
</tr>
</tbody>
</table>

6 time units
EXAMPLE, SUMMARY

- CTI, but not CPI

- transient state
  -> initial behaviour to reach steady state
  -> not REV
  -> generally, not DCF

- steady state behaviour
  -> terminal scc
  -> here, BND
  -> here, DCF
**Quantitative Analysis, Method I**

Interval time Petri net

Initial marking / state

Finite transition word $w$

\[
\begin{align*}
\{ & \quad b_1 \leq a_{11}x_1 + \ldots + a_{1n}x_n \leq c_1 \\
& \quad \ldots \\
& \quad b_m \leq a_{m1}x_1 + \ldots + a_{mn}x_n \leq c_m \\
& \quad a_{ij} \in \{0, 1\}, \quad b_i \in N, \quad c_i \in N \\
& \quad \forall i \forall s \forall k(1 \leq i \leq n \land 1 \leq s \leq k \leq m \land \\
& \quad \forall i \forall s \forall k(1 \leq i \leq n \land 1 \leq s \leq k \leq m \land \\
& \quad a_{is} = a_{ik} = 1 \rightarrow \forall j(s \leq j \leq k \rightarrow a_{ij} = 1))
\end{align*}
\]

(SLI)

$I: T \rightarrow Q_0^+ \times Q_0^+$ and for each $t \in T$ holds $a_t \leq b_t$, where $I(t) = (a_t, b_t)$

$w \in T^*$

If there is an $R$ solution, then there is an $N$ solution.

$w$ is time-dependent realizable / not realizable
**Quantitative Analysis, Method I**

Interval time Petri net
Initial marking / state
Finite transition word $w$

\[
\begin{align*}
  b_1 &\leq a_{11}x_1 + \ldots + a_{1n}x_n \leq c_1 \\
  \vdots \\
  b_m &\leq a_{m1}x_1 + \ldots + a_{mn}x_n \leq c_m \\
  a_{ij} &\in \{0, 1\}, b_i \in \mathbb{N}, c_i \in \mathbb{N} \\
  \forall i \forall s \forall k(1 \leq i \leq n \land 1 \leq s \leq k \leq m \land a_{is} = a_{ik} = 1 \rightarrow \forall j(s \leq j \leq k \rightarrow a_{ij} = 1))
\end{align*}
\]

$I: T \to \mathbb{Q}_0^+ \times \mathbb{Q}_0^+$ and for each $t \in T$ holds
$a_t \leq b_t$, where $I(t) = (a_t, b_t)$

$w \in T^*$

Polynomial time
If there is an $R$ solution, then there is an $N$ solution.

Linear time

$w$ is time-dependent realizable / not realizable
QUANTITATIVE ANALYSIS, METHOD II

interval time Petri net
initial marking / state
finite transition word $w$

If there is a solution, then it is an $N$ solution.

\[ I: T \rightarrow Q_0^+ \times Q_0^+ \text{ and for each } t \in T \text{ holds} \]
\[ a_t \leq b_t, \text{ where } I(t) = (a_t, b_t) \]

\[
\begin{align*}
\min / \max x_1 + \ldots + x_n \\
& b_1 \leq a_{11}x_1 + \ldots + a_{1n}x_n \leq c_1 \\
& \ldots \\
& b_m \leq a_{m1}x_1 + \ldots + a_{mn}x_n \leq c_m \\
& a_{ij} \in \{0, 1\}, b_i \in N, c_i \in N \\
& \forall i \forall s \forall k (1 \leq i \leq n \wedge 1 \leq s \leq k \leq m \wedge \\
& a_{is} = a_{ik} = 1 \rightarrow \forall j (s \leq j \leq k \rightarrow a_{ij} = 1))
\end{align*}
\]

$w$ is time-dependent realizable / not realizable

min/max time length of $w$ (time window of the pathway)
\[ \begin{align*}
\min / \max x_1 + \ldots + x_n \\
&\quad b_1 \leq a_{11}x_1 + \ldots + a_{1n}x_n \leq c_1 \\
&\quad \ldots \\
&\quad b_m \leq a_{m1}x_1 + \ldots + a_{mn}x_n \leq c_m \\
&\quad a_{ij} \in \{0, 1\}, b_i \in \mathbb{N}, c_i \in \mathbb{N} \\
&\quad \forall i \forall s \forall k (1 \leq i \leq n \land 1 \leq s \leq k \leq m \land \ a_{is} = a_{ik} = 1 \rightarrow \forall j (s \leq j \leq k \rightarrow a_{ij} = 1))
\end{align*} \]

\[ I: T \rightarrow Q_0^+ \times Q_0^+ \text{ and for each } t \in T \text{ holds } a_t \leq b_t, \text{ where } I(t) = (a_t, b_t) \]

\[ w \in T^* \]

\text{interval time Petri net}

\text{initial marking / state}

\text{finite transition word } w

\text{if there is a solution, then it is an } N \text{ solution.}

\text{polynomial time}

\text{w is time-dependent realizable / not realizable}

\text{min/max time length of } w \text{ (time window of the pathway)}
Quantitative Analysis, Summary

- Louchka Popova / HUB

- Transition time
  - \(\rightarrow\) continuous intervals

- Structural technique
  - \(\rightarrow\) parametric description

- No state space construction
  - \(\rightarrow\) works also for infinite systems
  - \(\rightarrow\) works also if the reachability graph does not fit into memory

- Further analysis questions
  - \(\rightarrow\) which time windows preserve a transition sequence's realizability
  - \(\rightarrow\) which time windows make the net bounded
  - \(\rightarrow\) which structures are time-independently live
QUANTITATIVE ANALYSES 2
- CONTINUOUS PETRI NETS
QUANTITATIVE ANALYSIS

- quantitative model = qualitative model + quantitative parameters
  - BUT: quantitative parameters often unknown

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

- continuous Petri nets

\[
\begin{align*}
\frac{d [p1\text{Cont}]}{dt} &= \frac{d [p2\text{Cont}]}{dt} = -v1 \\
\frac{d [p3\text{Cont}]}{dt} &= v1 - v2
\end{align*}
\]

\[
\begin{align*}
v1 &= k1 \cdot m1 \cdot m2 \\
v2 &= k2 \cdot m3
\end{align*}
\]

ode nodes!
EXAMPLE - MICHAELIS-MENTEN REACTION

\[ v = 0.005 \times m_1 / (0.1375 + m_1) \]

\[ V_{\text{max}} = 0.005 \text{ (maximal reaction rate)} \]
\[ K_m = 0.1375 \text{ (Michaelis constant)} \]

\[ \frac{d[s]}{dt} = \frac{d[p]}{dt} = V_{\text{max}} \frac{[s]}{(K_m + [s])} \]
\[ \frac{dm_1}{dt} = \frac{dm_2}{dt} = V_{\text{max}} \frac{m_1}{(K_m + m_1)} \]

-> Visual Object Nets
-> GON / cell illustrator (?)
-> Snoopy extension in preparation
THE QUALITATIVE MODEL BECOMES
THE STRUCTURAL DESCRIPTION
OF THE QUANTITATIVE MODEL!
CHALLENGES

❑ extensions
   -> read arcs  -> interleaving / partial order semantics
   -> inhibitor arcs!?  -> Turing power!

❑ efficient computation of minimal invariants
   -> exponential complexity
   -> compositional / step-wise refinement approach (under development)

❑ analysis of unbounded nets
   -> besides T-invariant analysis?

❑ model checking
   -> relevant properties?

❑ comparison
   -> discrete / continuous Petri nets
   -> continuous / hybrid Petri nets <-> ODEs
SUMMARY

❑ representation of bionetworks by Petri nets
  - partial order representation
  - formal semantics
  - unifying view

❑ purposes
  - animation
  - model validation against consistency criteria
  - qualitative / quantitative behaviour prediction

❑ two/three-step model development
  - qualitative model
  - quantitative model

❑ many challenging questions for analysis techniques
  - qualitative as well as quantitative ones
THANKS!