Computational approaches to analyze complex dynamic systems: model-checking and its applications.

Part 3: Model-checking of timed transitions systems: timed extensions of Petri nets

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École Centrale de Nantes - IRCCyN - *MeForBio team*

Lecture Series - Lecture 3 / NII - 2013/04/10

1. Models: from time Petri nets to stopwatch Petri nets
   - From time Petri nets to stopwatch Petri nets
   - Dense-time vs discrete-time
   - State space abstraction dedicated to discrete-time
2. Formalizing specification through timed modal logics
   - TCTL model-checking
   - Introduction to TCTL parametric model-checking
3. Application to biological systems
4. Model-checking tools

Motivations

Objective: formal verification of properties

- Model the system S :
  - Discrete models: finite state automata, Petri nets, ... $\Rightarrow$ Lecture 1
  - Timed models:
    - Timed extensions of finite state automata $\Rightarrow$ Lecture 2
    - **Timed extensions of Petri nets: time/stopwatch Petri nets $\Rightarrow$ Lecture 3**
- Formalize the specification φ :
  - Observers
  - Temporal logics: LTL, CTL, ... $\Rightarrow$ Lecture 1
  - **Timed extensions of temporals logics: TCTL, ... $\Rightarrow$ Lectures 2 & 3**
- Does $S \models \varphi$?

Model-checking algorithms

$\Rightarrow$ State space exploration

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Some major issues

Need for modeling tasks with suspending/resuming features

Expressivity/Decidability compromise to discuss ⇒ Lectures 2 & **3**

State space combinatorial explosion

- Need for symbolic approaches ⇒ Lectures 2 & **3**
- Need for new models and abstracted algorithms ⇒ Lecture 4

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Last week's and today's issue

Tricky question

Coming from France, why do I need an average 3-4 days period not to be jet-lagged anymore in Tōkyō?

Observation

- Discrete models do not encompass sufficient information to get a thorough description of the gene regulation network behind the circadian clock **w.r.t. time**
- Some related issues:
  - Is it possible to determine the lower limit of the day/night period cycle during which the circadian clock continues to stabilize?
  - Why does the body better support backward phase delay than advance phase delay?
- $\rightarrow$ On-going modeling project with **biologists** and **computer scientists** (CNRS PEPII funded project CirClock)

Contribution

Scientific challenge

How can we get information about the **production and degradation rates** of a protein in a biological regulatory network?

Objectives of this talk

- From discrete model to timed model → emphasize on the **progressive enrichment** of a model and its drawbacks
- Focus on the introduction of **quantitative** timing information
- Discuss the most appropriate **time semantics** adapted to the model

Joint work with

- G. Bernot, JP. Comet, A. Richard (methodology and application to biology)
- D. Lime, P. Molinaro and O.H. Roux (Petri nets theory)

Overview

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   - Dense-time vs discrete-time
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Time Petri nets - Reminder

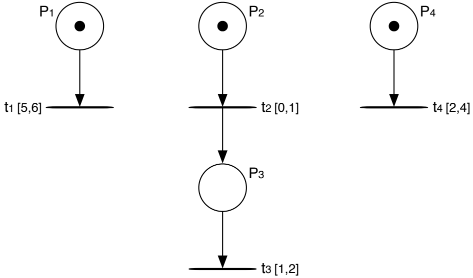

Figure: A dense-time Petri net

$$\begin{array}{lcl} \{P_1, P_2, P_4\} & & \{P_1, P_2, P_4\} \\ \theta(t_1) = 0 & & \theta(t_1) = 0.2 \\ \theta(t_2) = 0 & \xrightarrow{0.2} & \theta(t_2) = 0.2 \\ \theta(t_4) = 0 & & \theta(t_4) = 0.2 \end{array}$$

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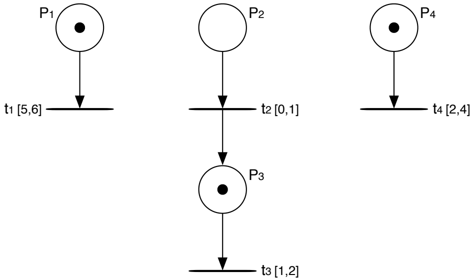

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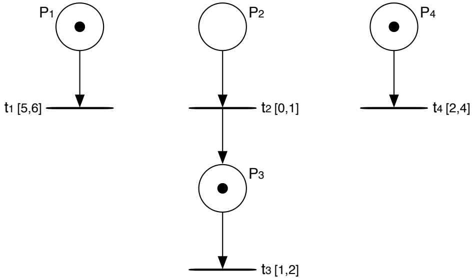

Figure: A discrete-time Petri net

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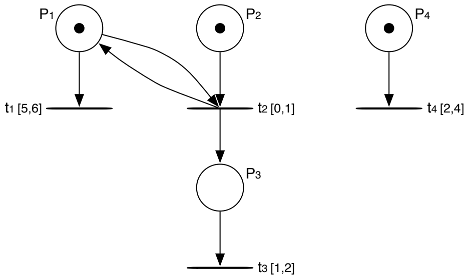
Time Petri nets - About read arcs



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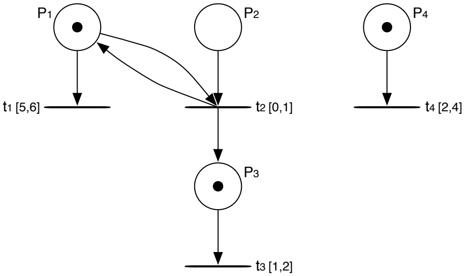

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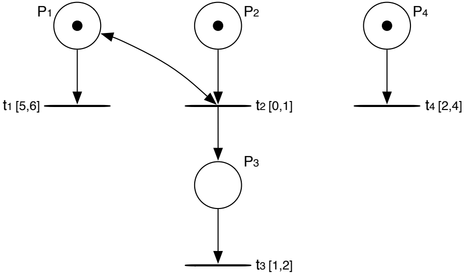

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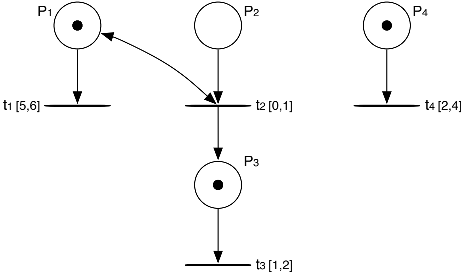

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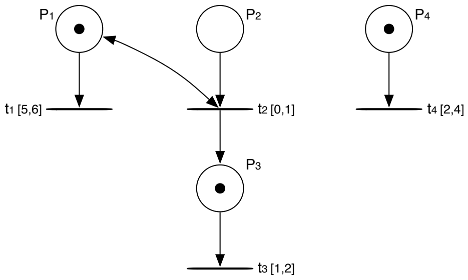

Figure: A Time Petri net with read arcs

Theorem

Time Petri nets with read arcs are more expressive than time Petri nets.

Stopwatch Petri nets - SwPN

Objective

Keep track of the state of a suspended action

Solution

Extend the Time Petri nets with the notion of stopwatches

- Resources and proprieties integrated to the places [RD01] or transitions [BFSV04]
- Activator arcs [BLRV07]
- **Inhibitor hyperarcs** [RL04] :

  If t is enabled by the marking M :
  - t is **inhibited** by $M \Rightarrow \dot{\theta}(t) = 0$
  - t **is not inhibited** by $M \Rightarrow \dot{\theta}(t) = 1$

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Stopwatch Petri nets

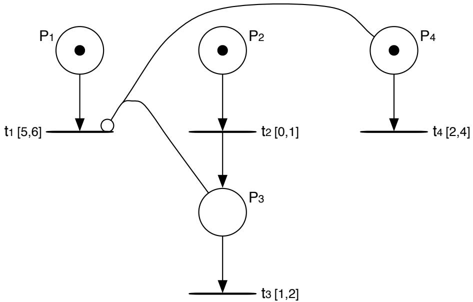

Figure: Stopwatch Petri nets: Petri nets with suspension / resuming features

$$\begin{array}{l} \{P_1, P_2, P_4\} \\ \theta(t_1) = 0 \\ \theta(t_2) = 0 \\ \theta(t_4) = 0 \end{array} \quad \xrightarrow{0.2} \quad \begin{array}{l} \{P_1, P_2, P_4\} \\ \theta(t_1) = 0.2 \\ \theta(t_2) = 0.2 \\ \theta(t_4) = 0.2 \end{array}$$

Stopwatch Petri nets

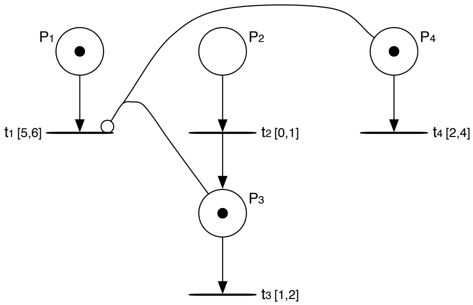

Figure: A SwPN : t_1 inhibited iff $(M(P_3) \geq 1$ **and** $M(P_4) \geq 1)$

$$\begin{array}{l}\{P_1, P_2, P_4\}\\ \theta(t_1)=0\\ \theta(t_2)=0\\ \theta(t_4)=0\end{array} \xrightarrow{0.2} \begin{array}{l}\{P_1, P_2, P_4\}\\ \theta(t_1)=0.2\\ \theta(t_2)=0.2\\ \theta(t_4)=0.2\end{array} \xrightarrow{t_2} \begin{array}{l}\{P_1, P_3, P_4\}\\ \theta(t_1)=0.2\\ \theta(t_3)=0\\ \theta(t_4)=0.2\end{array} \xrightarrow{1} \begin{array}{l}\{P_1, P_3, P_4\}\\ \theta(t_1)=0.2\\ \theta(t_3)=1\\ \theta(t_4)=1.2\end{array}$$

Stopwatch Petri nets

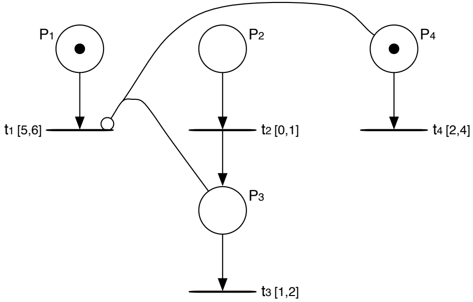

Figure: A SwPN : After the "reactivation" of t_1

$$\begin{array}{l}\{P_1, P_2, P_4\}\\ \theta(t_1) = 0\\ \theta(t_2) = 0\\ \theta(t_4) = 0\end{array} \xrightarrow{0.2} \begin{array}{l}\{P_1, P_2, P_4\}\\ \theta(t_1) = 0.2\\ \theta(t_2) = 0.2\\ \theta(t_4) = 0.2\end{array} \xrightarrow{t_2} \begin{array}{l}\{P_1, P_3, P_4\}\\ \theta(t_1) = 0.2\\ \theta(t_3) = 0\\ \theta(t_4) = 0.2\end{array} \xrightarrow{1} \begin{array}{l}\{P_1, P_3, P_4\}\\ \theta(t_1) = 0.2\\ \theta(t_3) = 1\\ \theta(t_4) = 1.2\end{array} \xrightarrow{t_3} \begin{array}{l}\{P_1, P_4\}\\ \theta(t_1) = 0.2\\ \theta(t_4) = 1.2\end{array}$$

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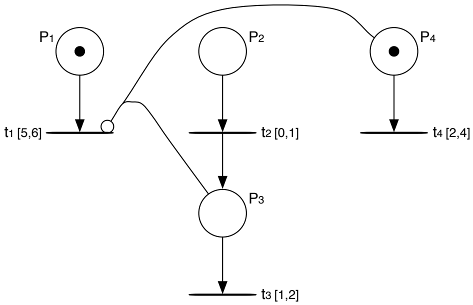

Figure: A discrete-time SwPN

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Stopwatch Petri nets: Definition

Definition

A *Stopwatch Petri Net* (SwPN) is a tuple
$\mathcal{T} = (P, T, {}^\bullet(), ()^\bullet, M_0, a, b, {}^\diamond(.), I)$ where :

- $P = \{p_1, p_2, \ldots, p_m\}$ is a non-empty finite set of *places*;
- $T = \{t_1, t_2, \ldots, t_n\}$ is a non-empty finite set of *transitions* $(T \cap P = \varnothing)$;
- ${}^\bullet() \in (\mathbb{N}^P)^T$ is the *backward incidence function*; $()^\bullet \in (\mathbb{N}^P)^T$ is the *forward incidence function*;
- $M_0 \in \mathbb{N}^P$ is the *initial marking* of the net;
- $a \in (\mathbb{Q}^+)^T$ and $b \in (\mathbb{Q}^+ \cup \{\infty\})^T$ are functions giving for each transition respectively its *earliest* and *latest* firing times $(a \leq b)$;
- ${}^\diamond(.) \in (\mathbb{N}^P)^T$ is the *reset incidence function*;
- $\mathrm{I} = \{(k, t) | k \in \mathbb{N}^P, t \in T\}$ is a finite set of *branch inhibitor hyperarcs*.

Notations

- *enabled*(M) is the set of transitions that are **enabled** by marking M (*i.e.* $t \in enabled(M)$ if $M \geq^{\bullet} t$)
- $\uparrow enabled(M, t')$ is the set of transitions that are **newly enabled** resulting from the fire of t' in marking M
- *inhibited*(M) is the set of transitions that are **inhibited** by marking M (*i.e.* $t \in inhibited(M)$ if $\exists i \leq I(t), {}^{\circ}t^{i} \leq M$)

Semantics

Basic assumptions

- Single-server semantics
- Intermediary semantics
- Strong semantics

Choosing an appropriate time model

- *Dense-time* : continuous evolution of time
- *Discrete-time* : time "jumps" from one integer to the next one at every clock tick

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Dense-time behavioral semantics [MMR09a]

Timed Transition System $\mathcal{S}_{\mathcal{T}} = (Q, q_0, T, \rightarrow)$ where:

- $Q = \mathbb{N}^P \times (\mathbb{R}^+)^T$: set of all states of the system
- $q_0 = (M_0, \overline{0})$: initial state
- $\rightarrow \in Q \times (T \cup \mathbb{R}) \times Q$ defined by:
  - continuous transition: $(M, \theta) \xrightarrow{\epsilon(d)} (M, \theta')$

$$\text{iff } \forall t_i \in T, \begin{cases} \forall t_i \in enabled(M), \theta'(t_i) = \left\| \begin{array}{l} \theta(t_i) \text{ if } t_i \in enabled(M) \\ \text{ and } t_i \in inhibited(M) \\ \theta(t_i) + d \text{ otherwise,} \end{array} \right. \\ M \geq^\bullet t_i \Rightarrow \theta'(t_i) \leq b(t_i) \end{cases}$$

  - discrete transition: $(M, \theta) \xrightarrow{t_i} (M', \theta')$

$$\text{iff } \begin{cases} t_i \in enabled(M) \text{ and } t_i \notin inhibited(M), \\ M' = M - max({}^\diamond t_i \times M^t, {}^\bullet t_i) + t_i^\bullet, \\ a(t_i) \leq \theta(t_i) \leq b(t_i), \\ \forall t_k, \theta'(t_k) = \left\| \begin{array}{l} 0 \text{ if } t_k \in \uparrow enabled(M, t_i), \\ \theta(t_k) \textit{ otherwise} \end{array} \right. \end{cases}$$

Discrete-time behavioral semantics [MMR09b]

Transition System $\mathcal{S}_{\mathcal{T}} = (Q, q_0, T, \rightarrow)$ where:

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Summary about "logic" arcs

Discrete models

- Read arcs do not add expressivity to Petri nets
- Reset arcs add expressivity to Petri nets
- Logic inhibitor arcs add expressivity to Petri nets

Time models

- Read arcs add expressivity to TPN (but not to SwPN)
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Expressiveness/Decidability balance

Problem

With a dense-time semantics, the state reachability problem of a SwPN, even bounded, is undecidable [BLRV07].

From the translation of discrete-time TPN into untimed Petri nets, we proved (see next section):

Theorem

With a discrete-time semantics, the state reachability problem of a **bounded** *SwPN is decidable [MMR09b].*

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Decidability results

	TPN				SwPN			
	Dense-time		Discrete-time		Dense-time		Discrete-time	
	General	Bounded	General	Bounded	General	Bounded	General	Bounded
Boundedness	I	D	I [MMR09b]	D	I	I	I [MMR09b]	D [MMR09b]
k-boundedness	I	D	D	D	I	I	D [MMR09b]	D [MMR09b]
Liveness	I	D	I [MMR09b]	D	I	I	I [MMR09b]	D [MMR09b]
Marking reachability	I	D	I [MMR09b]	D	I	I	I [MMR09b]	D [MMR09b]
State reachability	I	D	I [MMR09b]	D	I	I	I [MMR09b]	D [MMR09b]

Table: Decidability results for TPN and SwPN

Abstractions for discrete-time models: general plan

Problem

The state space of a TPN/SwPN is infinite (in general).

Computation of the state space of dense-time SwPN

Abstractions techniques (semi-algorithms) ⇒ Group states in equivalence classes

Computation of the state space of discrete-time SwPN

- **Enumerate** the set of states
- Adapt the dense-time **symbolic** methods to discrete-time

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From discrete-time to untimed model: the **fictitious clock** model

Principle

- Simulate time elapsing with a dedicated *tick* transition.
- *Clock* classically associated to transitions: viewed as a place whose marking is incremented by one with every *tick* transition.
- Discrete-time SwPNs can then be described as *parallel composition* of PNs with reset arcs and inhibitor hyperarcs (synchronized product of PNs)
- Then follows:
  - Expressivity and decidability results;
  - Practical way to enumerate the state space of discrete-time *bounded* SwPNs

From discrete-time to untimed model: the **fictitious clock** model

Principle

- Simulate time elapsing with a dedicated *tick* transition.
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From discrete-time TPNs to untimed PNs [MMR06]

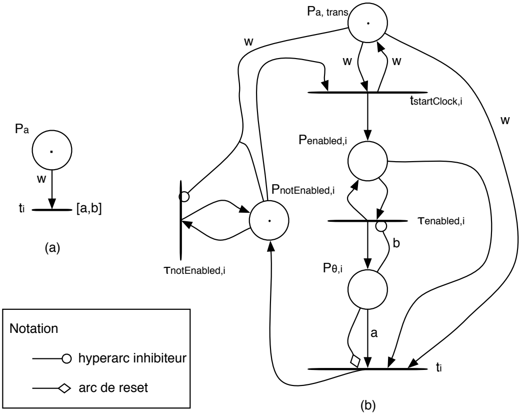

Figure: Translating a discrete-time TPN into an untimed PN with reset arcs and inhibitor hyperarcs

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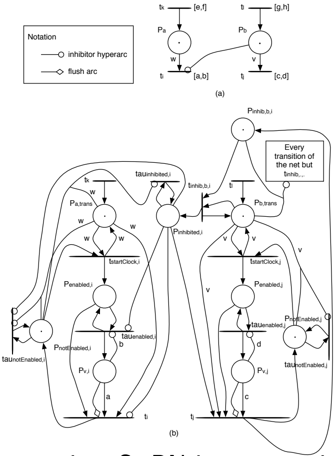

Figure: Translating a discrete-time SwPN into an untimed PN with reset arcs and inhibitor hyperarcs

State space of discrete-time models: enumerative approach

Computation of the state space of discrete-time models

Translation of discrete-time Petri nets towards models that can be analyzed thanks to **efficient data-structures**:

- **BDD**-inspired datastructures for untimed Petri nets : Markg tool [MDR02] (Lecture 1)
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Experimental results [MMR06]

Net	Discrete-time - Markg		Discrete-time - FAST		Discrete-time - LEVER	
	Time	Memory	Time	Memory	Time	Memory
Ex 12	336.15 s	55 040 KB	0.22 s	3 000 KB	0.07 s	1 320 KB
Ex 13	NA	NA	62.04 s	20 196 KB	0.26 s	3 596 KB
Ex 14	612.85 s	55 116 KB	0.65 s	3 404 KB	0.05 s	1 320 KB
Ex 15	NA	NA	NA	NA	NA	NA
Ex 16 (avec ∞)	0.10 s	1 320 KB	0.33 s	2 524KB	NA	NA
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Table: PENTIUM ; 2 GHz; 2Go RAM

Experimental results [MMR06]

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About the experimental results [MMR06]

Discussion

- Computationally speaking:
  - Large firing intervals $[1, 1000] \Rightarrow$ **Combinatorial explosion** of the number of states!
  - Dense-time may be more efficient than discrete-time: then, what is the advantage of discrete-time?
- "Theoretically and practically" speaking:
  - On some models, computation terminates **only for discrete-time semantics**.
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How discrete time and dense-time discretization are connected?

Question

Can we consider the state space of discrete-time nets as the **discretization** of the state space of the corresponding dense-time model?

Problems

- Identify the cases when this assumption is valid
- Design an algorithm to symbolically compute the state space
- Model-check TCTL properties of SwPN using this algorithm

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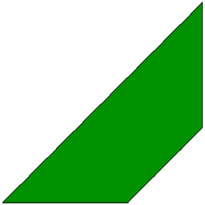
Abstraction of the state space of dense-time SwPN

Problem

Group states in d'equivalence classes (abstraction)

$\Rightarrow$ Use state class graph [BM83]

$$C = \left\{ \begin{pmatrix} 1 \\ 0 \\ 1 \\ 0 \end{pmatrix}, \right.$$



$$\left. \right\}$$

TPN and some sub-classes of SwPN : the firing domain can be encoded by a Difference Bound Matrix (DBM) $[d_{ij}]_{i,j \in [0..n]}$:

$$\begin{cases} -d_{0i} \leq \theta_i - 0 \leq d_{i0}, \\ \theta_i - \theta_j \leq d_{ij} \end{cases}$$

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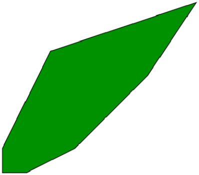

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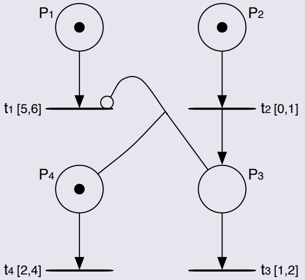
SwPN : polyhedra $A\bar{\theta} \leq B$

State class graph

SwPN



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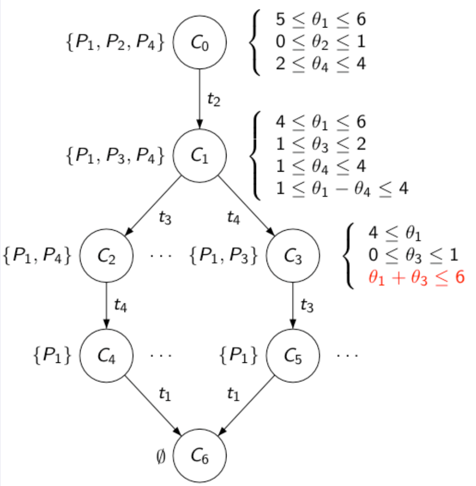
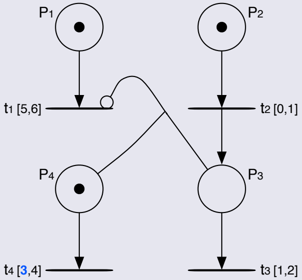


Non-DBM vs DBM polyhedral constraints

SwPN



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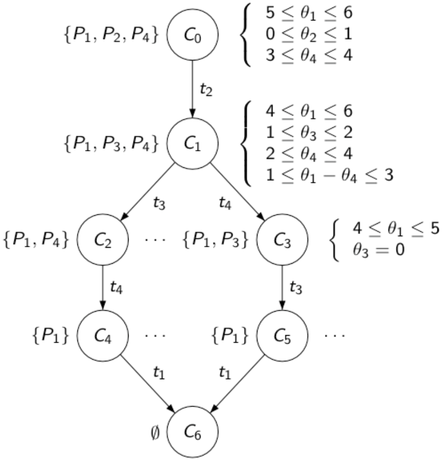

State classes for discrete-time SwPN

Objective

Extend the principle of state classes to discrete-time

State classes for discrete-time SwPN

$$C = \left\{ \begin{pmatrix} 1 \\ 0 \\ 1 \\ 0 \end{pmatrix}, \right.$$

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$\Rightarrow$ Define symbolic state classes

Symbolic state classes for discrete-time SwPN

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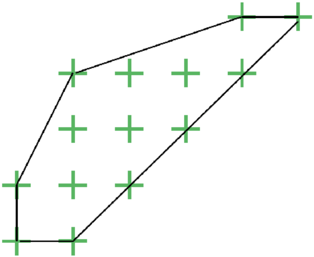

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Problems caused by the discretization of symbolic classes

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Does the successor of a symbolic discrete-time state class $(M, Poly)$ is equal to the discretization of the dense-time successor of this class?

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- And for SwPN ?

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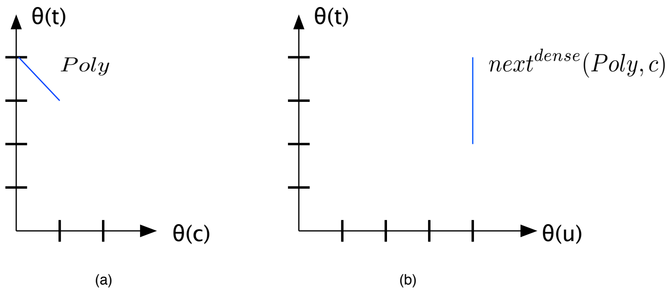

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Do all points resulting from the discretization of $next^{dense}(Poly, c)$ have a predecessor whose all coordinates are integers?
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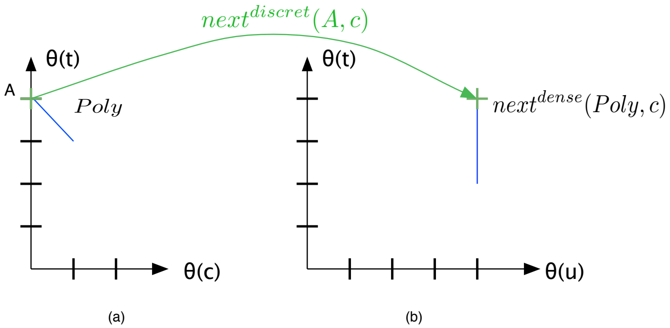

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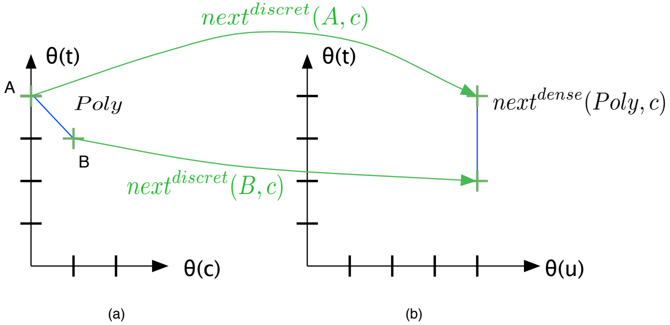

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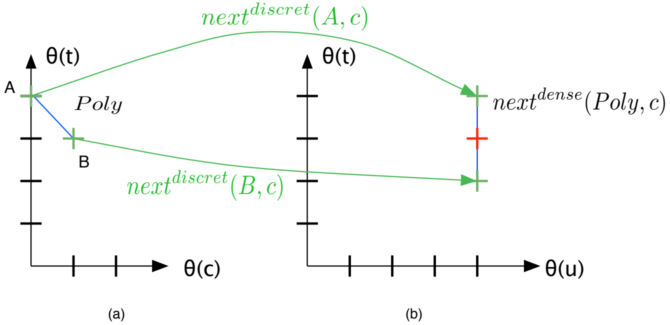

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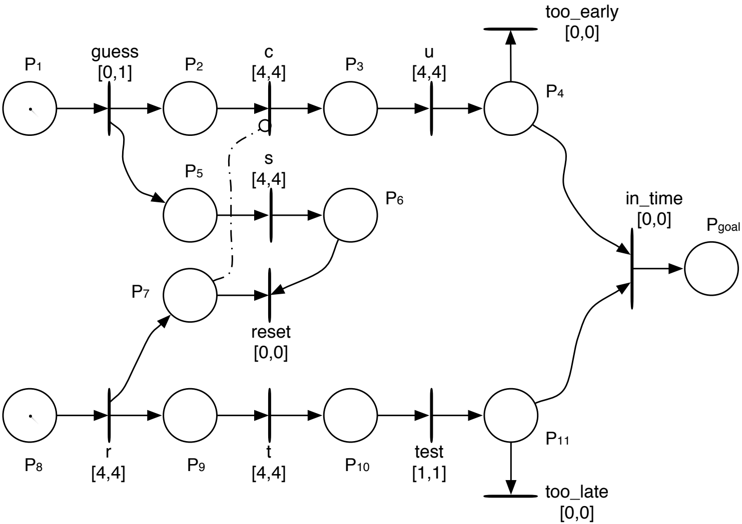
SwPN counter-example: discrete-time ≠ discretization of dense-time



Theorem

The state space of a discrete-time TPN and the discretization of the corresponding dense-time net are equal.

⇒ What for SwPN?

Theorem

The state space of a discrete-time SwPN and the discretization of the corresponding dense-time net are not equal [MMR09b].

Remark about Timed Automata

A similar result exists:

Theorem

For every $k \geq 1$, there exists a digital circuit such that the reachability set of states in dense-time is strictly larger than the one in discrete time (with granularity $\frac{1}{k}$) [BS90].

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Symbolic computation of the state space of discrete time nets

Principles

- Compute the state space of the corresponding dense-time network **as long as a non-DBM polyhedron does not appear** ;
- All non-DBM polyhedron *Poly* is **decomposed into a union of DBM**, $DBM\_split(Poly)$, s.t. $\mathcal{D}isc(Poly) = \mathcal{D}isc(DBM\_split(Poly))$

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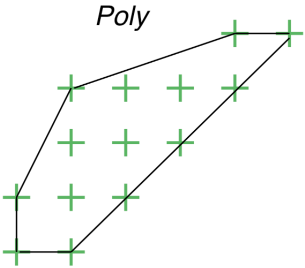

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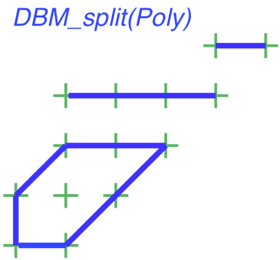

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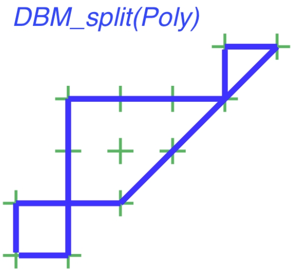

Theorem

For discrete-time SwPN, the algorithm to symbolically compute their state space is correct w.r.t. marking and state reachability and language.

Theorem

The termination of the algorithm is ensured for bounded discrete-time nets.

Benchmark: symbolic vs enumerative

Net	Symbolic algo. - ROMÉO		Enumerative algo. - Markg	
	Time	Memory	Time	Memory
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Table: PENTIUM ; 2 GHz; 2Gb RAM

⇒ Model-checking of timed **quantitative** properties

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$\Rightarrow$ Model-checking of timed **quantitative** properties

Overview

Model-checking formal properties - Reminder

Qualitative properties

- LTL
- CTL
- CTL*

Quantitative timing properties

A TCTL formula:

$$\varphi := ap \mid \neg ap \mid \varphi \wedge \varphi \mid \varphi \vee \varphi \mid A\varphi U_I \varphi \mid E\varphi U_I \varphi$$

with:

- *ap* an atomic assertion
- I an interval from $\mathbb{R}^+$ with integer bounds s.t. $[n, m]$, $[n, m[$, $]n, m]$, $]n, m[$, or $[m, \infty[$, $n, m \in \mathbb{N}$

Model-checking of TCTL properties - Reminder

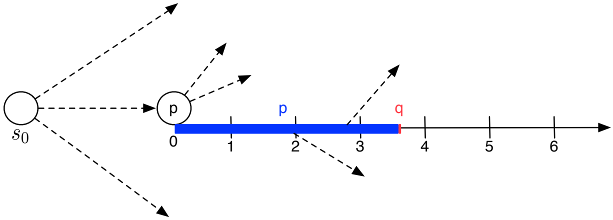

Figure: $s_0 \models E(\mathrm{p}U_{[2;4]}\mathrm{q})$

Some additional TCTL example - Reminder

Bounded liveness/response [DT98]

- "Whenever a property p becomes true, q must be true within n seconds" ($n \in \mathbb{N}$)
- $AG(p \Rightarrow AF_{[0,n]}q)$
- Denoted $p \rightarrow_{[0,n]} q$ in most model-checkers

Model-checking formal properties on TPN and SwPN: TPN-TCTL

Quantitative timing properties

A TPN-TCTL formula:

$$\varphi := \mathrm{GMEC} \mid \neg\varphi \mid \varphi \Rightarrow \psi \mid A\varphi U_I \varphi \mid E\varphi U_I \varphi$$

with:

- GMEC (*Generalized Mutual Exclusion Constraints*) is a **conjunction/disjunction of linear constraints** that limit the weighted sum of tokens in a subset of places (e.g. $(M(P_1) + 4M(P_2) \geq 3) \wedge (M(P_2) + 3M(P_3) \leq 10)$;
- I an interval from $\mathbb{R}^+$ with **integer bounds** s.t. $[n, m]$, $[n, m[$, $]n, m]$, $]n, m[$, or $[m, \infty[$, $n, m \in \mathbb{N}$

A taste of TCTL model-checking thanks to observers

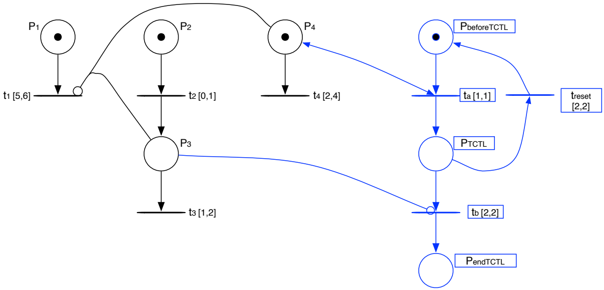

Figure: Addition of an observer to the initial net to model-check
$E((M(P_4) = 1)U_{[1;2]}(M_(P_3) = 0))$

A taste of TCTL model-checking thanks to observers

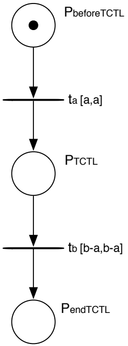

Figure: Generic observer to model-check $\mathrm{E}\varphi U_{[a;b]}\psi$

TPN-TCTL model-checking on time and stopwatch Petri nets

How to verify quantitative time properties

- **Translate TPN into TA** and use available TA model-checking tools (e.g. UPPAAL)
- Build an **observer** (*i.e.* a supervisory net) corresponding to the expected property and model-check the global network
- **On-the-fly** computation of the state space, then checking of the property

Parametric TPN-TCTL model-checking on time and stopwatch Petri nets [TLR09]

Parametric SwPN

A pSwPN is a n-tuple $\mathcal{N} = (P, T, Par, ^{\bullet}(.), (.)^{\bullet}, ^{\circ}(.), a, b, M_0, D_p)$, where:

- $Par = \{\lambda_1, \lambda_2, \ldots, \lambda_l\}$ is a finite set of **parameters** (we denote $\Gamma(Par)$ the set of linear expressions over Par);
- $a : T \to \Gamma(Par)$ is the function that gives the *earliest firing time* of a transition, expressed as a **linear expression over the set of parameters**;
- $b : T \to \Gamma(Par) \cup \{\infty\}$ is the function that gives the *latest firing time* of a transition, that is either a **linear expression over the set of parameters** or equal to ∞;
- $D_p \subseteq \mathbb{N}^{Par}$ is the *domain of the parameters*;

Parametric TCTL for SwPN [TLR09]

Quantitative timing properties

A PTCTL formula:

$$E\varphi\ U_I\psi \mid A\varphi\ U_I\psi \mid EF_I\varphi \mid AF_I\varphi \mid EG_I\varphi \mid AG_I\varphi \mid \varphi \leadsto_{I_r} \psi$$

with:

- φ et ψ are **GMEC** (*Generalized Mutual Exclusion Constraints*);
- I et I_r are **parametric intervals with integer bounds** s.t. $[n, m]$, $[n, m[$, $]n, m]$, $]n, m[$, or $[m, \infty[$, $n, m \in \mathbb{N}$, with the restriction that $I_r = [0, m]$ or $I_r = [0, \infty[$

Parametric TCTL for SwPN: Application [TLR09]

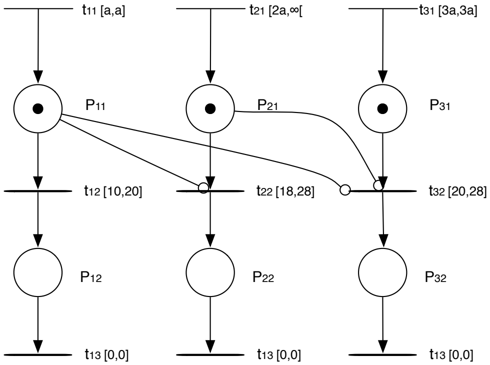

Figure: Example of a parametric SwPN modeling a system of three tasks, two being periodic, one sporadic [BFSV04]

Parametric TCTL for SwPN: Application [TLR09]

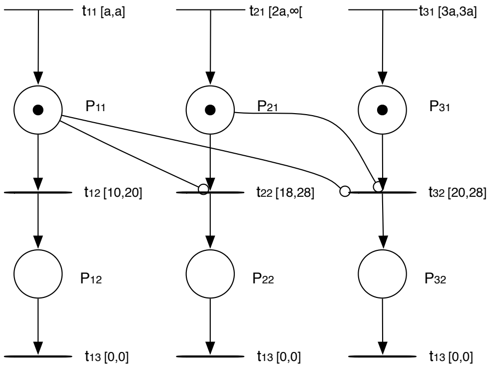

Figure: Verification of the *schedulability* of the tasks (do a task always terminate before an other instance of the same task is created?): $\forall P_i, AG_{[0,\infty[}(M(P_i) \leq 1)$

Parametric TCTL for SwPN: Application [TLR09]

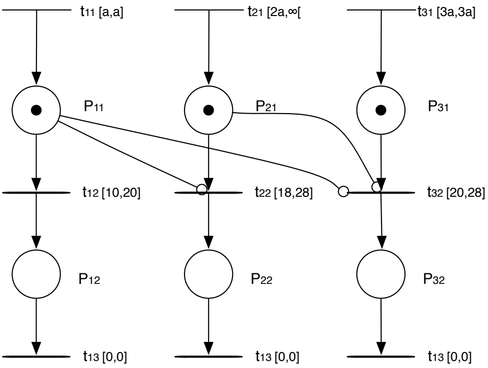

Figure: Verification of the *schedulability* of the tasks (do a task always terminate before an other instance of the same task is created?):
$\forall P_i, AG_{[0,\infty[}(M(P_i) \leq 1), whichleadsto\{a > 48\}$

Parametric TCTL for SwPN: Application [TLR09]

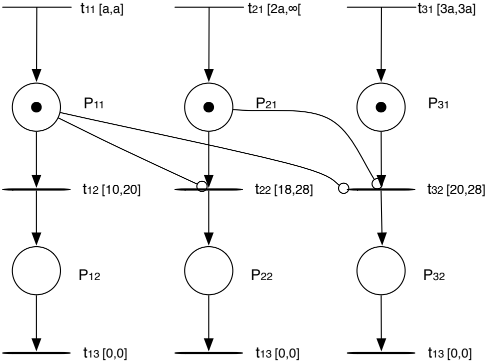

Figure: With the new constraint $\{a > 48\}$, what is the worst case response time of task 3? $M(P_{31}) > 0 \rightsquigarrow_{[0,b]} M(P_{32}) > 0$

Parametric TCTL for SwPN: Application [TLR09]

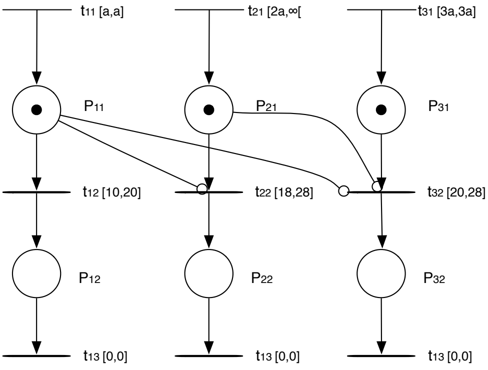

Figure: With the new constraint $\{a > 48\}$, what is the worst case response time of task 3? $M(P_{31}) > 0 \rightsquigarrow_{[0,b]} M(P_{32}) > 0, whichleadsto\{b = 96\}$

Overview

Short insight on the meaning of Petri net components - Reminder

Intuitive meaning

- Marking of a place: **presence/absence** or **quantity** of a component
- Arc : **precedence** or **succession**
- Transition : **event** andor **transformation**
- Weight : necessary **quantity**, consumed and/or produced

Petri nets for modeling biochemical networks - Reminder

Principle of qualitative modeling

- Places : reactants, products, enzymes
- Transitions : reactions, catalysis
- Weight on the arcs: stoichiometry

Application to the modeling of biochemical reactions - Reminder

$$2NAD^+ + 2H_2O \rightarrow 2NADH + 2H^+ + O_2$$

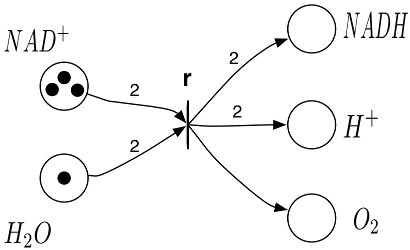

Figure: An example of a very simple translation from a biochemical reaction

Additional modeling features

Critical issues

- How to **test** the number of tokens in a place (e.g. concentration level of a protein) without decrementing it? $\Rightarrow$ Read arcs
- How to **reset the number of tokens** in a place (e.g. reset of a system) whatever was its previous concentration? $\Rightarrow$ Reset arcs
- How to **integrate quantitative information about speed of reactions** that can start, stop or resume, depending on thresholds (e.g. a concentration of a protein)? $\Rightarrow$ Inhibitor (hyper)arcs that allow to model stopwatches

Additional modeling features

TCTL model-checking

- Allows to validate a model
- Can help biologists to **infer discrete parameters** (e.g. tendency of evolution)
- Can help biologists to **infer timing quantitative parameters** (e.g. speed of reactions)

Overview

1. Models: from time Petri nets to stopwatch Petri nets
   - From time Petri nets to stopwatch Petri nets
   - Dense-time vs discrete-time
   - State space abstraction dedicated to discrete-time
2. Formalizing specification through timed modal logics
   - TCTL model-checking
   - Introduction to TCTL parametric model-checking
3. Application to biological systems
4. Model-checking tools

Model-checking tools

Verification of time extensions of Petri nets: Roméo [GLMR05]

- Provides a GUI and command-line tools for editing and verifying not only time Petri nets, but also **stopwatch Petri nets**
- Tool box for *validation* (simulation) and **verification** (model-checking)
- Developed at IRCCyN (Nantes, France)
- Tackles reachability and safety verification, and parametric analysis
- `http://romeo.rts-software.org/`

Model-checking tools

Verification of timed automata: UPPAAL [LPY97]

- Tool box for *validation* (simulation) and **verification** (model-checking)
- Developed by Uppsala University (Sweden) and Aalborg University (Denmark)
- Provides a GUI and command-line tools for editing and verifying TA
- Continuously **kept up-to-date** with new extensions (e.g. games) and improvements
- `http://www.uppaal.org`

Model-checking tools

Verification of linear hybrid automata: HyTech [HHWT95]

- Addresses **linear** hybrid automata
- Tackles reachability and safety verification, and parametric analysis
- http://embedded.eecs.berkeley.edu/research/hytech/
- Not maintained anymore ⇒ the tool has been overtaken by **PHAVer**: http://www-verimag.imag.fr/~frehse/phaver_web/ [Fre05]

Petri nets in the modeling of biological systems

Summary

- Intuitive modeling, easy to adapt to biological systems
- Progressive introduction of time delays and **parametric inference**
- But **combinatorial explosion** of state space, despite symbolic approaches

Further work

- Analysis of **multi-scale networks**
- Application to the circadian clock (on-going project with University of Nice I3S BioInfo and Circadian System Biology teams)
- Take advantage of the potential of **chronometric** information modeling
- New approaches to study **large networks** $\rightarrow$ **Lecture 4: Approaches inspired by pi-calculus and static analysis**

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