Time Petri Nets: Theory, Tools and Applications

Part III

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Outline

1. Application
2. Tools
3. References
4. Appendix
The relationship between cyclin and cdc2 in the cell cycle

\textbf{aa: amino acids}

\textbf{~P: ATP}

\textbf{P_i: inorganic phosphate}

\[\text{cyclin} \rightleftharpoons P \quad \text{cdc2} \quad \text{cyclin} \rightleftharpoons P \quad \text{cdc2}\]

\[\text{cyclin} \rightarrow \text{cdc2} \quad \text{P}_i \quad \text{cyclin} \rightarrow \text{cdc2} \quad \text{P}_i\]

\[\text{cyclin} \rightarrow \text{cdc2} \quad \text{P}_i \quad \text{cyclin} \rightarrow \text{cdc2} \quad \text{P}_i\]

\[\text{aa} \quad \text{aa}\]
The relationship between cyclin and cdc2 in the cell cycle as a DIPN

A PN model of the continuous system:
The relationship between cyclin and cdc2 in the cell cycle as a DIPN

A PN model of the system (a biochemical network) should be **bounded** and **live** in the time.
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For each reaction a minimal and maximal rate is given (described with a differential equation)
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- The outcome of this is a minimal and a maximal duration for each reaction
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- A PN model of the system (a biochemical network) should be **bounded** and **live** in the time.
- For each reaction a minimal and maximal rate is given (described with a differential equation)
- The outcome of this is a minimal and a maximal duration for each reaction
- The time dependent model of the system is a DIPN (Duration Interval Petri Net)
The relationship between cyclin and cdc2 in the cell cycle as a DIPN

A DIPN model as a momentary snapshot of the continuous system:
The relationship between cyclin and cdc2 in the cell cycle as a DIPN

The DIPN model is **bounded** and **live**, because:

- The skeleton is bounded; Proved with INA
- The TPN, derived by the translation of the DIPN is live; Proved with INA
- The minimal time distance between the initial state and an arbitrary state in which $k_4$ is ready to fire is 74; Proved with INA

Thus, the minimal time for starting the dephosphorylation of the cdc2 in order to form active MPF modelled with $k_4$ is not less than 74 minutes.
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Thus, the minimal time for starting the dephosphorylation of the cdc2 in order to form active MPF modelled with $k_4$ is not less than 74 minutes.
Graphical Net Editor

**Snoopy:** a tool to design (and animate timeless) graph-based formalisms for Linux, Windows, Mac

(http://www-dssz.informatik.tu-cottbus.de/software/snoopy.html)

- place/transition Petri net
- extended Petri net (read / inhibitor / reset arcs)
- reachability graph
- time Petri net
- timed Petri net
- . . .
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**Snoopy** can export datas (files) to several tools:

- INA
- TINA
- LoLA
- Maria
- PEP
- …
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Petri Net Analyzer

INA
Integrated Net Analyzer
(http://http://www2.informatik.hu-berlin.de/~starke/ina.html)
Petri Net Analyzer

- **INA** runs on Unix, Linux, Windos.
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   - edit (alphanumerical)
Petri Net Analyzer

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- **INA** can
  - edit (alphanumerical)
  - analyze classical PN, colored PN, Time PN, Timed PN, (PN with timed arcs) for:
    - time length of a run,
    - shortest and longest (time) distance between states/p-markings in bounded (time dependent) PN, etc.
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- **INA** can
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    - qualitative properties: statically and dynamically (s. next slide)
Petri Net Analyzer

- **INA** runs on Unix, Linux, Windows.
- **INA** can:
  - edit (alphanumerical)
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    - qualitative properties: statically and dynamically (s. next slide)
    - some quantitative properties:
      - time length of a run,
      - shortest and longest (time) distance between states/p-markings in bounded (timedependent) PN, etc.
Current net options are:

- token type: black (for Place/Transition nets)
- time option: no times
- firing rule: normal
- priorities: not to be used
- strategy: single transitions
- line length: 80
Current net options are:

- **token type**: black (for Place/Transition nets)
- **time option**: no times
- **firing rule**: normal
- **priorities**: not to be used
- **strategy**: single transitions
- **line length**: 80
Current net options are:

token type: coloured (for Coloured Petri nets)
time option: no times
firing rule: normal
priorities: not to be used
strategy: single transitions
line length: 80
Current net options are:

- **token type**: black  (for Place/Transition nets)
- **time option**: no times
- **firing rule**: normal
- **priorities**: not to be used
- **strategy**: single transitions
- **line length**: 80
Current net options are:

- token type: black (for Place/Transition nets)
- time option: durations
- firing rule: normal
- priorities: not to be used
- strategy: single transitions
- line length: 80
Current net options are:
  token type: black         (for Place/Transition nets)
  time option: intervals
  firing rule: normal
  priorities: not to be used
  strategy: single transitions
  line length: 80
Current net options are:
- token type: black  (for Place/Transition nets)
- time option: no times
- firing rule: normal
- priorities: not to be used
- strategy: single transitions
- line length: 80
INA - A Short Introduction

Current net options are:
- token type: black (for Place/Transition nets)
- time option: no times
- firing rule: normal with capacities
- priorities: not to be used
- strategy: single transitions
- line length: 80
Current net options are:

- token type: black (for Place/Transition nets)
- time option: no times
- firing rule: save
- priorities: not to be used
- strategy: single transitions
- line length: 80
Current net options are:
- token type: black (for Place/Transition nets)
- time option: no times
- firing rule: normal
- priorities: not to be used
- strategy: single transitions
- line length: 80
Current net options are:
  token type: black  (for Place/Transition nets)
  time option: no times
  firing rule: normal
  priorities: to be used
  strategy: single transitions
  line length: 80
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  token type: black  (for Place/Transition nets)
  time option: no times
  firing rule: normal
  priorities: not to be used
  strategy: single transitions
  line length: 80
Current net options are:

- token type: black  
- time option: no times  
- firing rule: normal  
- priorities: not to be used  
- strategy: maximal steps  
- line length: 80
Current net options are:
  token type: black (for Place/Transition nets)
  time option: no times
  firing rule: normal
  priorities: not to be used
  strategy: single transitions
  line length: 80
Do You want to

- edit ? .................................................... E
- fire ? ..................................................... F
- analyse ? ............................................. A
- reduce ? ............................................... R
- read the session report ? ...................... S
- delete the session report ? ................... D
- change options ? ................................. O
- quit ? .................................................... Q
Do You want to

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quit ? ............................................................... Q

Petri net input file > tyson-without-time.pnt
Information on elementary structural properties:

The tyson-without-time PN is:

- The net is not statically conflict-free.
- The net is pure.
- The net is not ordinary.
- The net is not conservative.
- The net is not subconservative.
- The net is not a state machine.
- The net is not free choice.
- The net is not extended free choice.
- The net is not extended simple.
- The net is not safe.
- The net is not live and safe.
- The net is marked.
- The net is not marked with exactly one token.
- The net is not a marked graph.
- The net is not homogenous.
- The net has not a non-blocking multiplicity.
- The net has no nonempty clean trap.
- The net has no transitions without pre-place.
- The net has no transitions without post-place.
- The net has no places without pre-transition.
- The net has no places without post-transition.
- The net is connected.
- The net is strongly connected.
Further Properties

- DTP: deadlock-trap-property
- SMC: state machine coverable
- SMD: state machine decomposable
- SMA: state machine allocatable
- CPI: covered by place invariants
- CTI: covered by transition invariants
- B: bounded
- SB: structurally bounded
- REV: reversible
- DSt: dead state reachable
- BSt: bad state reachable
- DTr: dead transition at initial marking
- DCF: dynamically conflict free
- L: live
- LV: live when ignoring dead transitions
- L&S: live and safe
- Liveness for coloured nets
- WL: weakly live
- CL: collectively live
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INA: Further Analyze

Analysis menu: Decide structural boundedness.................................B
Non-reachability test of a partial marking using the state equation..............N
Compute the symmetries of the net.........................................................Y
Compute a shortest path from the initial state to a target marking..............P
Compute a minimal path from the initial state to satisfy a predicate...........O
Compute a reachability graph.................................................................R
Compute a coverability graph to decide boundedness and coverability.........G
Compute a basis for all P/T-invariants [non-reachability test].....................I
Compute a basis for all semipositive P/T-[sub/sur]-invariants......................S
Format lines written to INVARI.HLP earlier...........................................F
Test place- or transition-vectors for invariant properties...........................T
INA: Further Analyze

Graph analysis menu

- quit analysis of the computed graph ...................... Q
- test the reachability/coverability of a marking .......... R
- convert a set of states to a predicate ...................... C
- define an enabledness predicate ............................. E
- check a CTL-formula .............................................. F
- compute distances ............................................... A
- compute circuits .................................................. K
- check liveness properties ...................................... L
- compute strongly connected components ................ V
- write the computed graph (states and arcs) ............. W
- write all arcs ......................................................... X
- write all states ..................................................... M
- write all states satisfying a predicate ................... P
- write a trace to a state .......................................... T
- write the list of executed steps .............................. I
A Short Part of the Bibliography

Popova-Zeugmann, L. and Schlatter, D.
Analyzing Path in Time Petri Nets.
*Fundamenta Informaticae (FI) 37, IOS Press, Amsterdam*, pages 311–327, 1999.

Popova-Zeugmann, L. and Werner, W. and Richling, J.
Using State-equation to Prove Non-reachability in Timed Petrinets.

Popova-Zeugmann, L.

Popova-Zeugmann, L.
*Time and Petri Nets (in German).*

Popova-Zeugmann, L. .
Quantitative Evaluation of Time Dependent Petri Nets and Applications to Biochemical Networks.

For more see:
http://http://www2.informatik.hu-berlin.de/~starke/ina.html
http://http://www2.informatik.hu-berlin.de/~popova
Thank you!
Thank you!
Thank you!
The relationship between cyclin and cdc2 in the cell cycle

In step 1, cyclin is synthesized *de novo*. Newly synthesized cyclin may be unstable (step 2). Cyclin combines with cdc2-P (step 3) to form pre-maturation promoting factor (preMPF). At some point after heterodimer formation, the cyclin subunit is phosphorylated. ... The cdc2 subunit is then dephosphorylated (step 4) to form active MPF. In principle, the activation of MPF may be opposed by protein kinase (step 5). Assuming that active MPF enhances the catalytic activity of the phosphatase, I arrange that MPF activation is switched on in an autocatalytic fashion. Nuclear division is triggered when a sufficient quantity of MPF has been activated, but concurrently active MPF is destroyed by step 6. Breakdown of the MPF complex releases phosphorylated cyclin, which is subject to rapid proteolysis (step 7). Finally, the cdc2 subunit is phosphorylated (step 8, possibly reversed by step 9), and the cycle repeats itself.
