Modeling and Evaluating the Cdc2 and Cyclin Interactions in the Cell Division Cycle with a Time Dependent Petri Net (Case Study)

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Outline

1. The Task
2. The Model
3. The Evaluation
The Task

Cell Division Cycle

Outer ring:
I = Interphase
M = M-phase

Inner ring:
G<sub>1</sub> = Growth phase 1
S = Synthesis
G<sub>2</sub> = Growth phase 2
M = Mitosis (Karyokinesis)
C = Cytokinesis

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The Task

The relationship between cyclin and cdc2 in the cell cycle

aa: amino acids
~P: ATP
P_i: inorganic phosphate

Diagram:

1. aa → cyclin
2. cyclin → P
3. P → ~P
4. ~P → P_i
5. P_i → ~P
6. ~P → cdc2
7. P_i → cyclin
8. ~P → cdc2
9. P_i → cdc2
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The relationship between cyclin and cdc2 in the cell cycle

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).
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The relationship between cyclin and cdc2 in the cell cycle as a PN

A PN model of the continuous system:
Minimum Conditions a Model has to fulfilled

A PN model of the system (a biochemical network) should be

- **bounded** and
- **live**

in the time.
The Model

Computing a min/max duration from a min/max rate using the mass-action equation:

- Each reversible reaction $A + B \rightleftharpoons A' + B'$ is described by a mass-action equation. It combines the *rate equations* of the both reactions in the equilibrium.
  - For the reaction $A + B \rightarrow A' + B'$ the *simple rate equation* is of the form:
    \[
    \text{affinity} = k[A]^a[B]^b.
    \]
    Writing the dissociated active mass at some point in time as $x$, the rate of reaction is given as
    \[
    \frac{dx}{dt} = k([A] - x)^a([B] - x)^b
    \]
  - *Complicated rate equations* are not of the form above.

- At equilibrium the two rates of reaction and reverse reaction must be equal.
Time Context for the Model

It holds:

- \( \text{min}_{\text{duration}} = \frac{1}{\text{max}_{\text{rate}}} \) and
- \( \text{max}_{\text{duration}} = \frac{1}{\text{min}_{\text{rate}}} \)
Time Context for the Model

It holds:

- $\text{min\_duration} = \frac{1}{\text{max\_rate}}$ and
- $\text{max\_duration} = \frac{1}{\text{min\_rate}}$

Computing the min/max durations for the Tyson-PN:

- Using a simple mass-action equation: for all transitions except $r_4$.
- Using the mass-action equation in a complicated form for $r_4$. 
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- \( \text{min\_duration} = 1/\text{max\_rate} \) and
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Computing the min/max durations for the Tyson-PN:

- using a simple mass-action equation: for all transitions except \( r_4 \).
- using the mass-action equation in a complicated form for \( r_4 \).

The time dependent model of the system is a DIPN (Duration Interval Petri Net)
Min/max durations values for the Tyson-PN:

<table>
<thead>
<tr>
<th>$t_i$</th>
<th>$k_i$</th>
<th>min_rate</th>
<th>max_rate</th>
<th>min_dur.</th>
<th>max_dur.</th>
<th>[ [min_dur.], [max_dur.] ]</th>
</tr>
</thead>
<tbody>
<tr>
<td>$r_1$</td>
<td>0.015</td>
<td>0.015</td>
<td>0.18</td>
<td>$\frac{100}{18}$</td>
<td>$\frac{200}{3}$</td>
<td>[6, 67]</td>
</tr>
<tr>
<td>$r_3$</td>
<td>200</td>
<td>200</td>
<td>28800</td>
<td>$\frac{1}{28800}$</td>
<td>$\frac{1}{200}$</td>
<td>[0, 0]</td>
</tr>
<tr>
<td>$r_4$</td>
<td>10</td>
<td>$\frac{5}{18}$</td>
<td>$\frac{2560}{144}$</td>
<td>$\frac{144}{2560}$</td>
<td>$\frac{18}{5}$</td>
<td>[0, 4]</td>
</tr>
<tr>
<td>$r'_4$</td>
<td>0.018</td>
<td>$\frac{9}{500}$</td>
<td>$\frac{27}{125}$</td>
<td>$\frac{125}{27}$</td>
<td>$\frac{500}{9}$</td>
<td>[5, 56]</td>
</tr>
<tr>
<td>$r_6$</td>
<td>0.1</td>
<td>0.1</td>
<td>1.2</td>
<td>$\frac{5}{6}$</td>
<td>10</td>
<td>[1, 10]</td>
</tr>
<tr>
<td>$r_7$</td>
<td>0.6</td>
<td>0.6</td>
<td>7.2</td>
<td>$\frac{5}{36}$</td>
<td>$\frac{5}{3}$</td>
<td>[1, 2]</td>
</tr>
<tr>
<td>$r_8$</td>
<td>10</td>
<td>10</td>
<td>1200</td>
<td>$\frac{1}{120}$</td>
<td>$\frac{1}{10}$</td>
<td>[0, 1]</td>
</tr>
<tr>
<td>$r_9$</td>
<td>0.1</td>
<td>0.1</td>
<td>1.2</td>
<td>$\frac{5}{6}$</td>
<td>10</td>
<td>[1, 10]</td>
</tr>
</tbody>
</table>
The relationship between cyclin and cdc2 in the cell cycle as a DIPN

A DIPN model:
The relationship between cyclin and cdc2 in the cell cycle as a TPN

Translation of the DIPN model into a TPN model:
The DIPN model is **bounded** and **live**?, because:

1. The skeleton is bounded. Its state space contains 101,840 markings. Proved with INA and proved with tina.
2. The construction of the reachability graph for the TPN failed with "memory exhausted", after computation of 384 millions states in about 41 hours. Proved with tina.
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Quantitative Properties

- The **minimal time distance** between the initial state and an arbitrary state in which $k_4$ is ready to fire is 24 min; Proved with tina.
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- The feasible run which realizes the distance 24 min is
  
  $0, t6, 0, t11, 0, t6, 0, t6, 6, t0, 0, t1, 0, t7, 0, t11, 0, t6, 0, t8, 6, t0, 0, t1, 2, t2, 0, t10, 0, t7, 0, t11, 0, t6, 0, t8, 4, t0, 0, t1, 1, t2, 0, t7, 0, t6, 0, t11, 0, t8, 5, t0, 0, t2, 0, t4, 0, t6, 0, t1, 0, t7, 0, t6, 0, t11, 0, t9$
  
  and it consists of 35 transitions.
The maximal time distance between the initial state and an arbitrary state in which $k_4$ is ready to fire (ignoring loops) cannot be computed at present because of the size of the state space. A lower bound for such a maximal time distance is $10^7$ min. The feasible run which realizes the distance $10^7$ min consists of 61 transitions.
Quantitative Properties

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- A lower bound for such a maximal time distance is 107 min.
Quantitative Properties

- The maximal time distance between the initial state and an arbitrary state in which $k_4$ is ready to fire (ignoring loops) cannot be computed at present because of the size of the state space.

- A lower bound for such a maximal time distance is 107 min.

- The feasible run which realizes the distance 107 min consists of 61 transitions.
A Short Part of the Bibliography

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

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

Tyson, J.J.
Modeling the cell division cycle: cdc2 and cyclin interactions.

For more see:
http://http://www2.informatik.hu-berlin.de/~starke/ina.html
http://www.laas.fr/tina/
Thank you!
Thank you!
Thank you!
Computation the **minimal and maximal durations** for the transition \( r_1 \):

\[
\begin{align*}
    r_1 &= k_1 \cdot [aa] \quad \Rightarrow \\
    r_{1-min} &= 0.015 \cdot 1 = 0.015 \quad \Rightarrow \quad max_{dur}(r_1) = \frac{200}{3} \\
    r_{1-max} &= 0.015 \cdot 12 = 0.18 \quad \Rightarrow \quad min_{dur}(r_1) = \frac{50}{9}
\end{align*}
\]

Computation the **minimal and maximal durations** for the transition \( r_3 \):

\[
\begin{align*}
    r_3 &= k_3 \cdot [Y] \cdot [CP] \quad \Rightarrow \\
    r_{3-min} &= 200 \cdot 1 \cdot 1 = 200 \quad \Rightarrow \quad max_{dur}(r_3) = \frac{1}{200} \\
    r_{3-max} &= 200 \cdot 12 \cdot 12 = 28800 \quad \Rightarrow \quad min_{dur}(r_3) = \frac{1}{28800}
\end{align*}
\]
Computation the minimal and maximal durations for the transition $r_1$:

\[
r_1 = k_1 \cdot [aa] \implies r_{1\text{-}min} = 0.015 \cdot 1 = 0.015 \implies \max_{\text{dur}}(r_1) = \frac{200}{3}
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r_1_{\text{-}max} = 0.015 \cdot 12 = 0.18 \implies \min_{\text{dur}}(r_1) = \frac{50}{9}
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r_{3\text{-}max} = 200 \cdot 12 \cdot 12 = 28800 \implies \min_{\text{dur}}(r_3) = \frac{1}{28800}
\]

Computation the minimal and maximal durations for the transition $r_4$:

\[
r_4 = k_4 \cdot [pM] \cdot (\left[\frac{M}{CT}\right])^2, \text{ and } [CT] = [pM] + [M] + [C2] + [CP] \implies
\]

\[
r_{4\text{-}min} = 10 \cdot 1 \cdot (\frac{2}{12})^2 = \frac{10}{36} \implies \max_{\text{dur}}(r_4) = \frac{18}{5}
\]

\[
r_{4\text{-}max} = 10 \cdot 4 \cdot (\frac{8}{12})^2 = \frac{160}{9} \implies \min_{\text{dur}}(r_4) = \frac{9}{160}
\]