Semi-quantitative modelling of biological systems with Fuzzy Petri nets

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BioPPN’13, Milano, Italy
Synthetic biology

Design and construction

*in vivo implementation*

Desired behaviour

New biological system

Measured data

Verification

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Synthetic biology

Design and construction

Model

Desired behaviour ↔ New biological system

Measured data

Verification

in silico ↔ in vivo

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Modelling approaches

Quantitative

Qualitative
Modelling approaches

Quantitative

Qualitative

Concentration

Time

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Modelling approaches

Quantitative
- Deterministic (ODEs)
- Accurate kinetic rates?!

Qualitative
- Stochastic (CME)

Concentration [X] vs. Time [s]
Modelling approaches

Quantitative
  - Deterministic (ODEs)
  - Stochastic (CME)
   - Accurate kinetic rates?!?

Semi-quantitative

Qualitative
  - Less accurate than quantitative
  - Quantitatively significantly more relevant than qualitative
  - More forgiving when we lack accurate knowledge
Petri nets

<table>
<thead>
<tr>
<th>Qualitative PNs</th>
<th>Fuzzy PNs</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Qualitative description</td>
<td>- Qualitative description</td>
</tr>
<tr>
<td>- Behavioural properties</td>
<td></td>
</tr>
</tbody>
</table>

Time-free

<table>
<thead>
<tr>
<th>Stochastic PNs</th>
<th>Continuous PNs</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Molecules</td>
<td>- Concentrations</td>
</tr>
<tr>
<td>- Stochastic rates</td>
<td>- ODEs</td>
</tr>
<tr>
<td></td>
<td>- Deterministic rates</td>
</tr>
</tbody>
</table>

Timed, Quantitative

Discrete State Space  Continuous State Space

Elowitz repressilator


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Elowitz repressilator

mRNA: \[
\frac{dm_i}{dt} = -k_{dm} m_i + \frac{\alpha}{1 + p_j} + \alpha_0
\]

Protein: \[
\frac{dp_i}{dt} = \beta m_i - k_{dp} p_i
\]

i = lacI, tetR, cl
j = cl, lacI, tetR
Elowitz repressilator
Timed, continuous Petri nets

\[
\frac{dP}{dt} = \sum_{i=1}^{n} r_i - \sum_{j=1}^{m} r_j
\]

Elowitz: \( r_{\text{Translation}} = \beta \times mRNA_P \)
\( r_{\text{Degradation}} = k_d \times P \)

Gilbert et al, From Petri nets to Differential Equations – an Integrative approach for Biochemical Network Analysis, 2006

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Fuzzy logic approach

- Computing with words (IF-THEN rules)
- From an equation to “intuitive description”
Fuzzy logic approach

- Computing with words (IF-THEN rules)
Fuzzy logic approach

- Computing with words (IF-THEN rules)

*IF (ProteinConc) is High THEN (Change) is High*Change
*IF (ProteinConc) is Med THEN (Change) is Med*Change
*IF (ProteinConc) is Low THEN (Change) is Low*Change
Fuzzy logic approach

- Computing with words (IF-THEN rules)
Fuzzy logic approach

- Computing with words (IF-THEN rules)
Fuzzy logic approach

- Computing with words (IF-THEN rules)
- Fuzzification

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Fuzzy logic approach

- Computing with words (IF-THEN rules)
- Fuzzification
  - Defining fuzzification for different abstraction levels
  - Different membership functions to achieve desired description
  - Using the knowledge about the system we have to gain more accurate description
Fuzzy logic approach

• General (Elowitz)
  – The system/cell can contain up to approximately 2000 molecules of each protein
  – One protein molecule equals about 1nM in concentration

• Dynamical
  – Approximate protein, mRNA half-life
  – Approximate binding/disassociation affinity

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Fuzzy logic approach

- Semi-quantitative representation

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Fuzzy logic and Petri nets

Degradation (Fuzzy)
P -> 0

IF (f[P] is High) THEN (f[C] is HighChange)
IF (f[P] is Med) THEN (f[C] is MedChange)
IF (f[P] is Low) THEN (f[C] is LowChange)
Fuzzy logic and Petri nets

Degradation:
P => 0

[Diagram of Petri net showing Degradation (Fuzzy) and P transition]
Results

- Degradation - Elowitz, 2000
- Degradation - FL approach

Protein Concentration

Time [s]
Fuzzy logic and Petri nets

Translation:
mRNAP $\rightarrow$ P

Degradation:
P $\rightarrow$ 0

Constant Translation

$r_{\text{Translation}} = \beta \times mRNA_P$

Degradation (Fuzzy $k^d \times P$)
Results

![Graph showing protein concentration over time with two lines representing Elowitz, 2000 and FL approach.](Image)

- Elowitz, 2000
- FL approach
Conclusions and future work

- Proposed fuzzy Petri net approach can be used to semi-quantitatively model biological processes as demonstrated on degradation
- Can be used to augment existing methods where kinetic data or parameters are missing

- Formal definition of fuzzy Petri nets used for our approach and building more complex FPN models
- Fuzzy description of other basic biological processes
- Simulation result evaluation and verification
- Color for different fuzzy abstractions
- Stochastic fuzzy modelling