Overcoming Unknown Kinetic Data for Quantitative Modelling of Biological Systems Using Fuzzy Logic and Petri Nets

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Synthetic biology

Design and construction

*in vivo implementation*

- Desired behaviour
- Measured data
- Verification
- New biological system

Synthetic biology

Design and construction

Desired behaviour

in silico

Model

in vivo

New biological system

Measured data

Verification

Heiner et al, Petri nets for systems and synthetic biology, 2008
Modelling approaches

Quantitative

Qualitative
Modelling approaches

Quantitative

Qualitative

• Qualitative behavioral properties of the system

• Can be discrete or continuous

• No notion of time and quantity
Modelling approaches

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

Qualitative
Modelling approaches

Quantitative
- Deterministic (ODEs)
- Stochastic (CME)

Accurate kinetic rates?!?

Qualitative
- Parameter estimation only possible when experimental data is available
- Strict limitations in order to get biologically relevant and realistic parameters
- Changing the biological system requires new parameter estimation
- Inconvenient when we want to test multiple GRN topologies (e.g. GRN oscillators)
Modelling approaches

Quantitative

- Deterministic (ODEs)
- Stochastic (CME)

Fuzzy logic as an alternative

Qualitative

- Intuitive qualitative description of system dynamics by using linguistic description
- Can approximate quantitative approaches when kinetic data is known
- More forgiving when we lack accurate kinetic data
- Quantitatively significantly more relevant than qualitative approaches

Accurate kinetic rates?!?
### 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>Timed, Quantitative</th>
<th>Stochastic PNs</th>
<th>Continuous PNs</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Molecules</td>
<td>- ODEs (concentrations, deterministic rates)</td>
<td></td>
</tr>
<tr>
<td>- Stochastic rates</td>
<td>- Fuzzy PNs (function approximation⁵; can be used for quantitative modelling even if kinetic data is unknown)</td>
<td></td>
</tr>
</tbody>
</table>

*Discrete State Space*

*Continuous State Space*

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Transcription-translation system

- Inputs: DNA, transcription resource (TsR), translation resource (TlR)
- Output: Protein concentration
- Processes: transcription, translation, degradation, consumption

Transcription-translation system

- Fuzzy approach for modelling translation
- Other processes are modelled as a system of ODEs

\[ \frac{d[\text{Protein}]}{dt} = \frac{\kappa_{r, b} \cdot [TlR] \cdot [mRNA]}{m_g} + [mRNA] \]

\[ f_0 \]

Modelling translation using Fuzzy logic

Concentration of mRNA and TLR

How concentration of protein changes depending on concentrations of mRNA and TLR?

Protein concentration change
Modelling translation using Fuzzy logic

Knowledge base
- Membership functions
- Fuzzy rule base

Numerical value

Fuzzification

Inference Engine

Defuzzification

Numerical value
Modelling translation using Fuzzy logic

- Fuzzification of mRNA and TIR concentration

![Graph showing mRNA concentration fuzzification with 50% Med and 50% High](image)

![Graph showing TIR concentration fuzzification with 50% Low and 50% Med](image)
Modelling translation using Fuzzy logic
Modelling translation using Fuzzy logic

- Defining IF-THEN rules for protein concentration change
- Rules are very descriptive and intuitive

<table>
<thead>
<tr>
<th>TlR \ mRNA</th>
<th>None</th>
<th>VeryLow</th>
<th>Low</th>
<th>Med</th>
<th>High</th>
<th>VeryHigh</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Low</td>
<td>None</td>
<td><strong>VeryLow</strong></td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
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<td>Med</td>
<td>None</td>
<td>VeryLow</td>
<td>Low</td>
<td>Med</td>
<td>Med</td>
<td>High</td>
</tr>
<tr>
<td>High</td>
<td>None</td>
<td>VeryLow</td>
<td>Low</td>
<td>Med</td>
<td>High</td>
<td><strong>VeryHigh</strong></td>
</tr>
</tbody>
</table>

IF (mRNA) is VeryLow AND (TlR) is Low THEN (ConcentrationChange) is VeryLow

\[
\frac{d[\text{Protein}]}{dt} = k_{tl} \cdot [TlR] \cdot [mRNA] \frac{m_{tl}}{m_{tl} + [mRNA]}
\]
Modelling translation using Fuzzy logic

Knowledge base
- Membership functions
- Fuzzy rule base

Numerical value → Fuzzification → Inference Engine → Defuzzification → Numerical value
Modelling translation using Fuzzy logic

• Defuzzification of protein concentration change (*Center of gravity*)

![Graph showing defuzzification of protein concentration change](image-url)
Modelling translation using Fuzzy logic & Petri nets

• One transition is transformed into fuzzy logic Petri net with corresponding input and output
Modelling translation using Fuzzy logic & Petri Nets

**Fuzzification**
- mRNA concentration
  - VeryHigh: 0.72
  - High: 0.28
  - None: 0
- TIR concentration
  - VeryHigh: 0.63
  - Medium: 0.37
  - Low: 0
  - None: 0

**IF-THEN rules**

**Defuzzification**
- Protein (GFP) concentration change
  - VeryHigh: 0.68
  - High: 0.32
  - Medium: 0
  - None: 0.05
- Protein (GFP) concentration
  - VeryHigh: 23.9
  - High: 314
Simulation

• Building the model
  • Matlab Simulink
  • Fuzzy logic toolbox

• Simulation run
  • Matlab engine
  • Regards fuzzy logic steps as one step
  • Allows an easy way of building fuzzy system
  • Simulation run with ODEs and fuzzy logic in the same model
Simulation
Results

GFP concentration - (Fuzzy translation)
(Insert 3.4nM of DNA at different time points)

GFP concentration - (pure ODE model)
(Insert 3.4nM of DNA at different time points)
Conclusions

• Fuzzy logic can be used to overcome missing kinetic data
• We lose some accuracy, but still get biologically relevant results
• With more knowledge we can reduce the error
• Can be used with existing methods
• Automatic generation of Petri net based on defined fuzzification/defuzzification/IF-THEN rules?
Computational Biology Group

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http://lrss.fri.uni-lj.si/bio/