University *of Ljubljana*
Faculty *of Computer and Information Science*

Semi-quantitative modelling of biological systems with Fuzzy Petri nets

Jure Bordon,
dr. Miha Moškon, prof. Miha Mraz

University of Ljubljana
Faculty of Computer and Information Science

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Synthetic biology

Design and construction

in vivo implementation

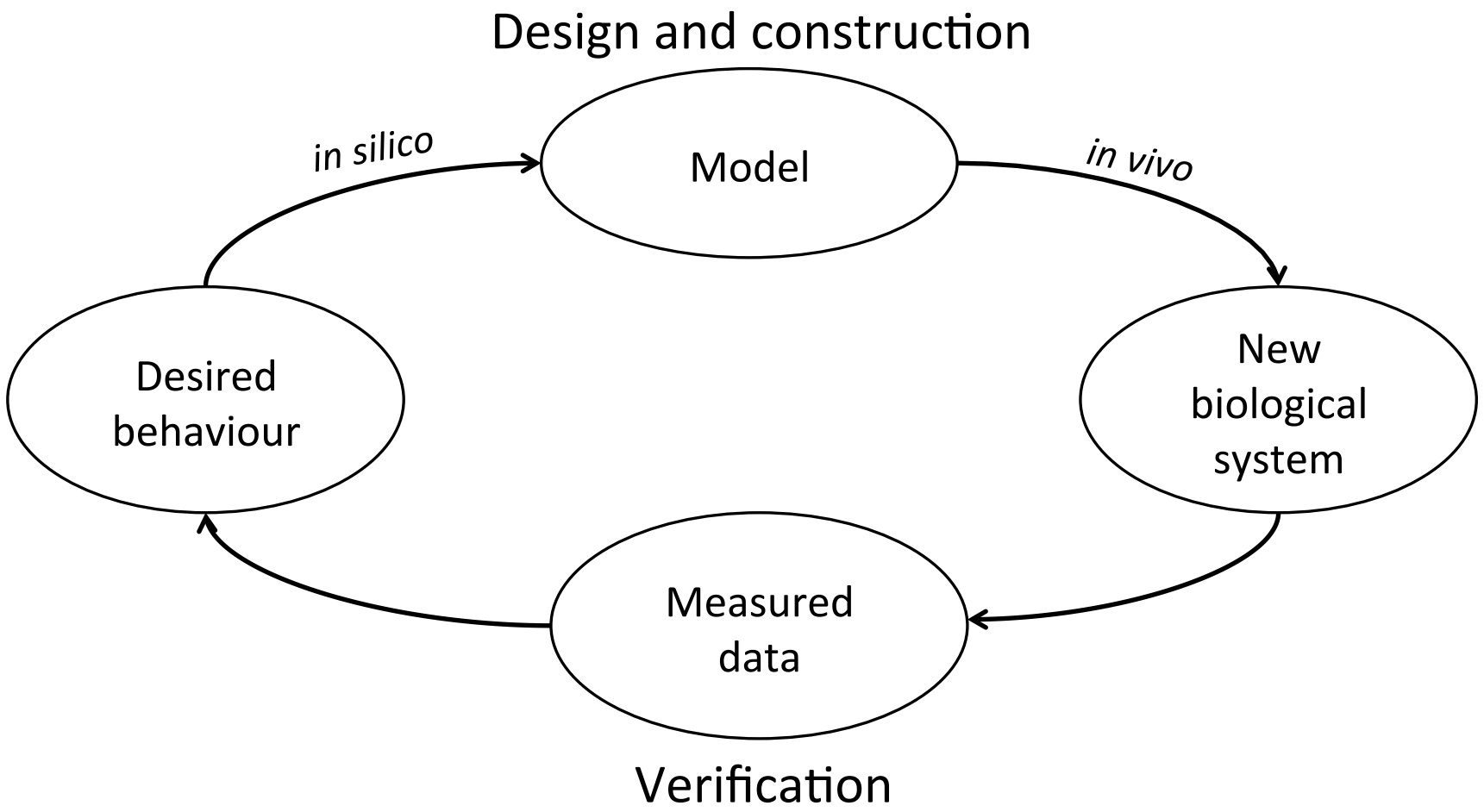
Desired behaviour

New biological system

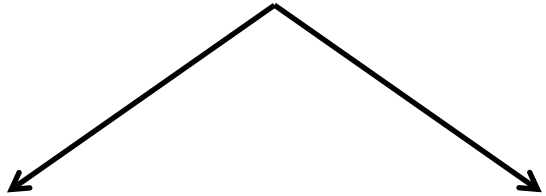
Measured data

Verification

Synthetic biology



Modelling approaches



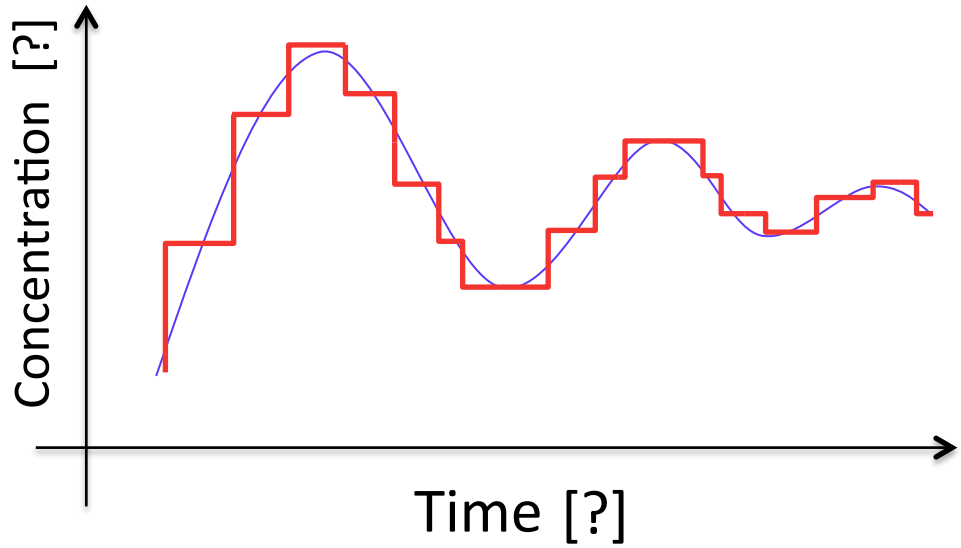
Quantitative

Qualitative

Modelling approaches

Quantitative

Qualitative



Modelling approaches

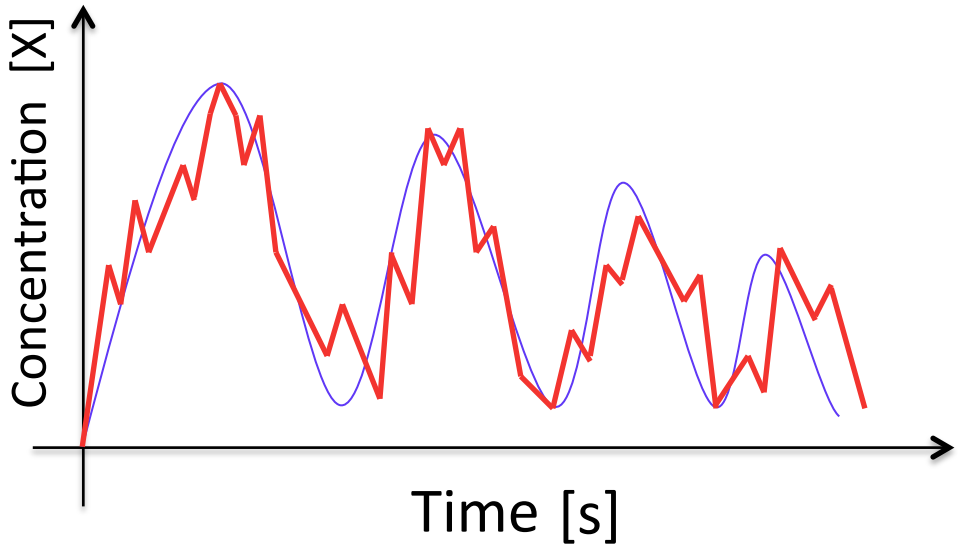
Quantitative

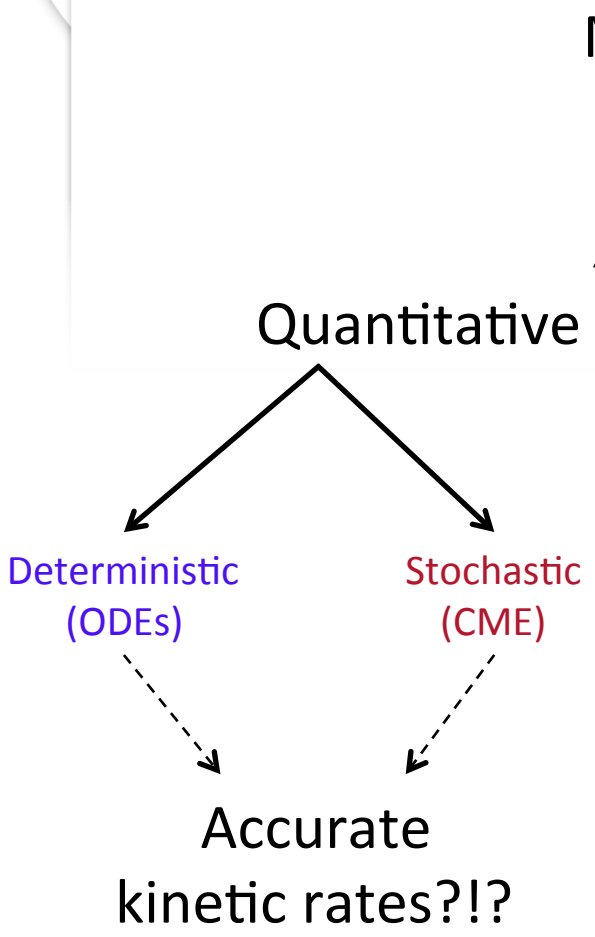
Qualitative

Deterministic (ODEs)

Stochastic (CME)

Accurate kinetic rates?!?





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

Petri nets

Qualitative PNs

-Qualitative description
-Behavioural properties

Time-free

Fuzzy PNs

-Qualitative description

Stochastic PNs

-Molecules
-Stochastic rates

Timed, Quantitative

Discrete State Space

Continuous PNs

-Concentrations
-ODEs
-Deterministic rates

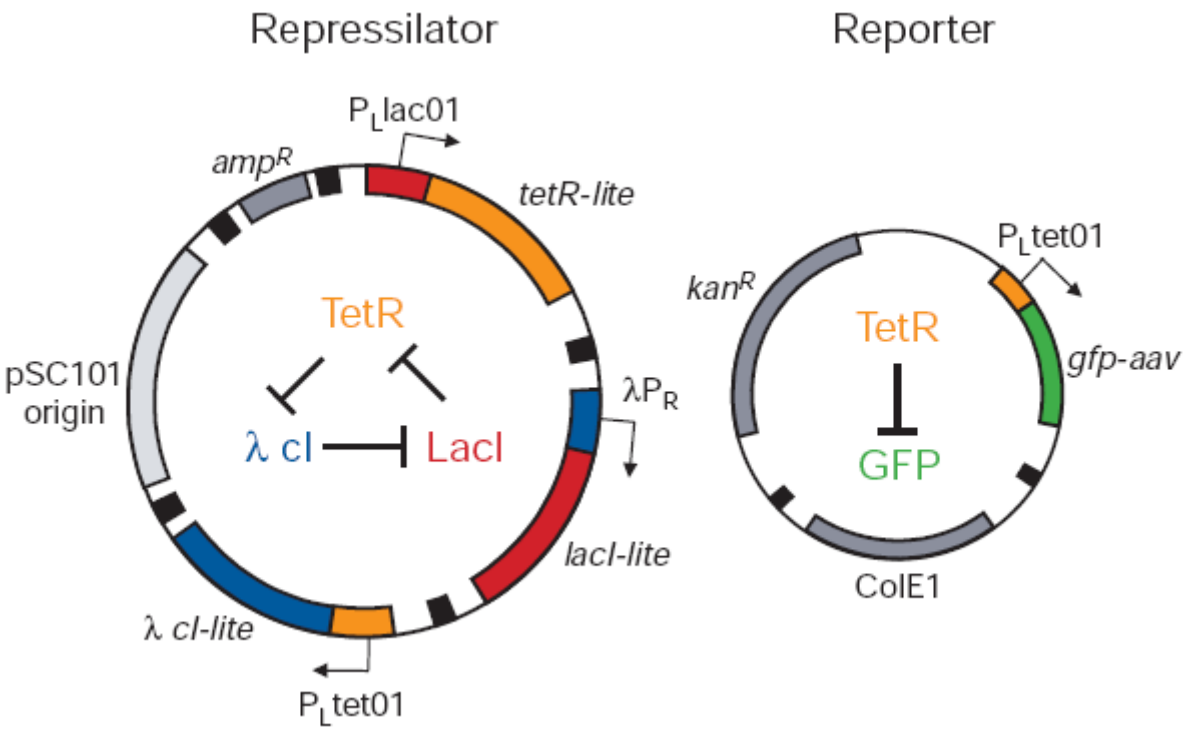
Fuzzy PNs

-Semi-quantitative
-Augment existing methods

Continuous State Space

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

Elowitz repressilator



Elowitz et al, *A synthetic oscillatory network of transcriptional regulators,* 2000

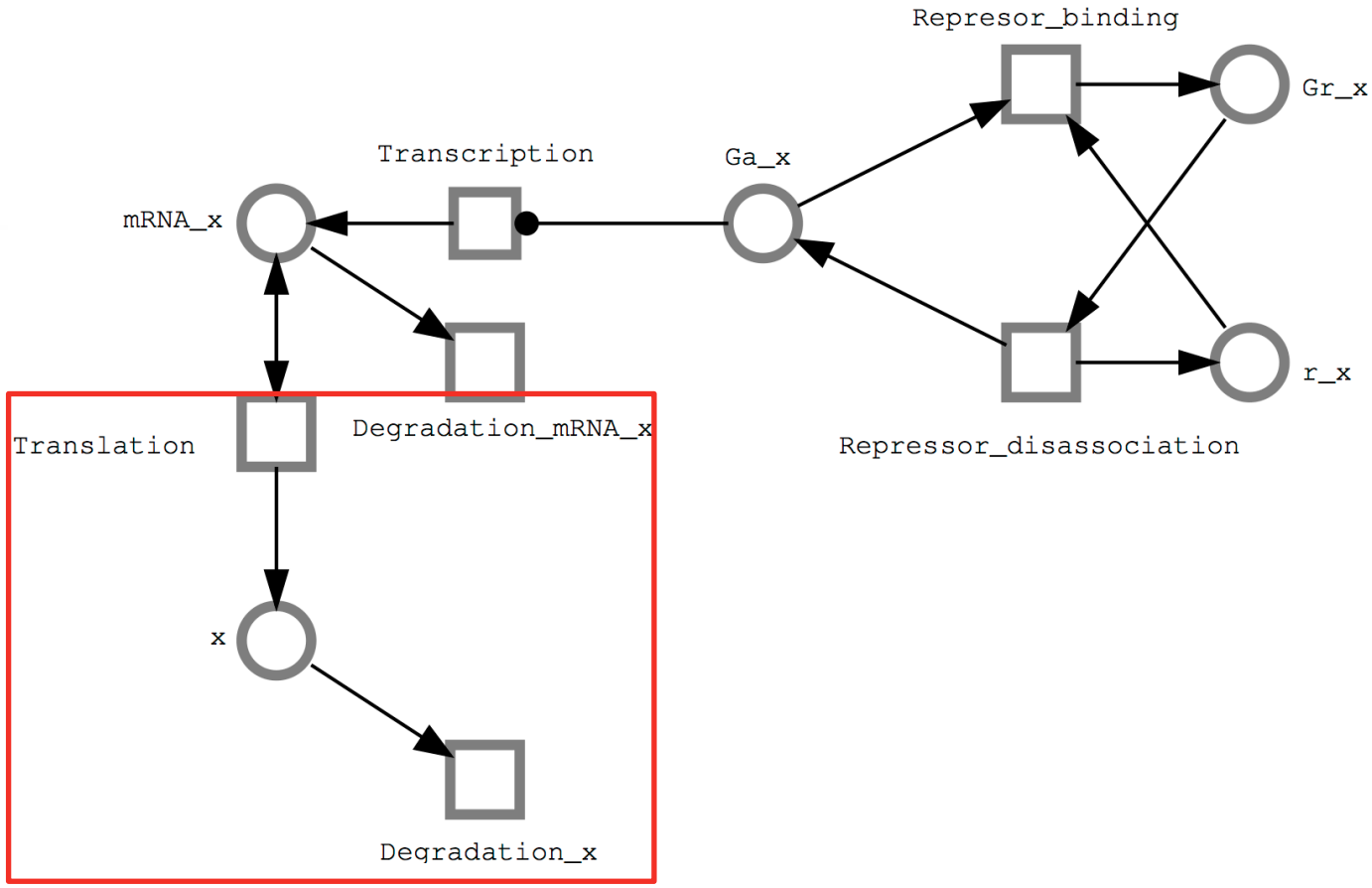
Elowitz repressilator

mRNA: $$\frac{dm_i}{dt} = -k_{d_m} m_i + \frac{\alpha}{(1 + p_j)} + \alpha_0$$

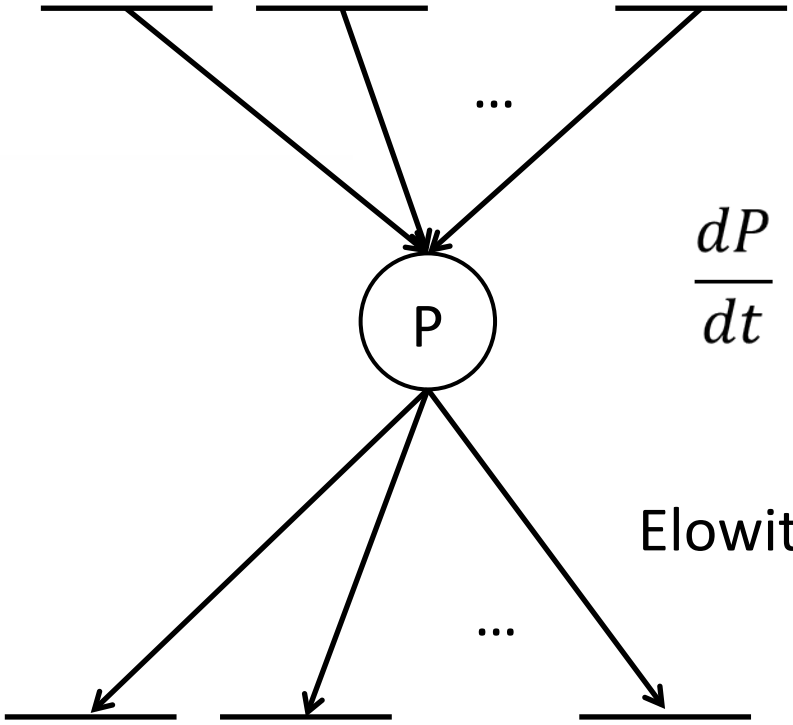
i = lacI, tetR, cI
j = cI, lacI, tetR

Protein: $$\frac{dp_i}{dt} = \beta m_i - k_{d_p} p_i$$

Elowitz repressilator



Timed, continuous Petri nets



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

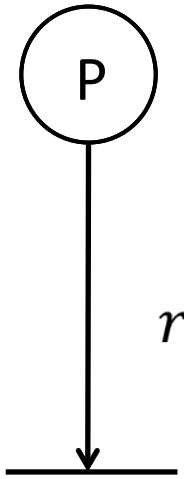
Elowitz: $r_{Translation} = \beta * mRNA_P$

$r_{Degradation} = k_d * P$

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

Fuzzy logic approach

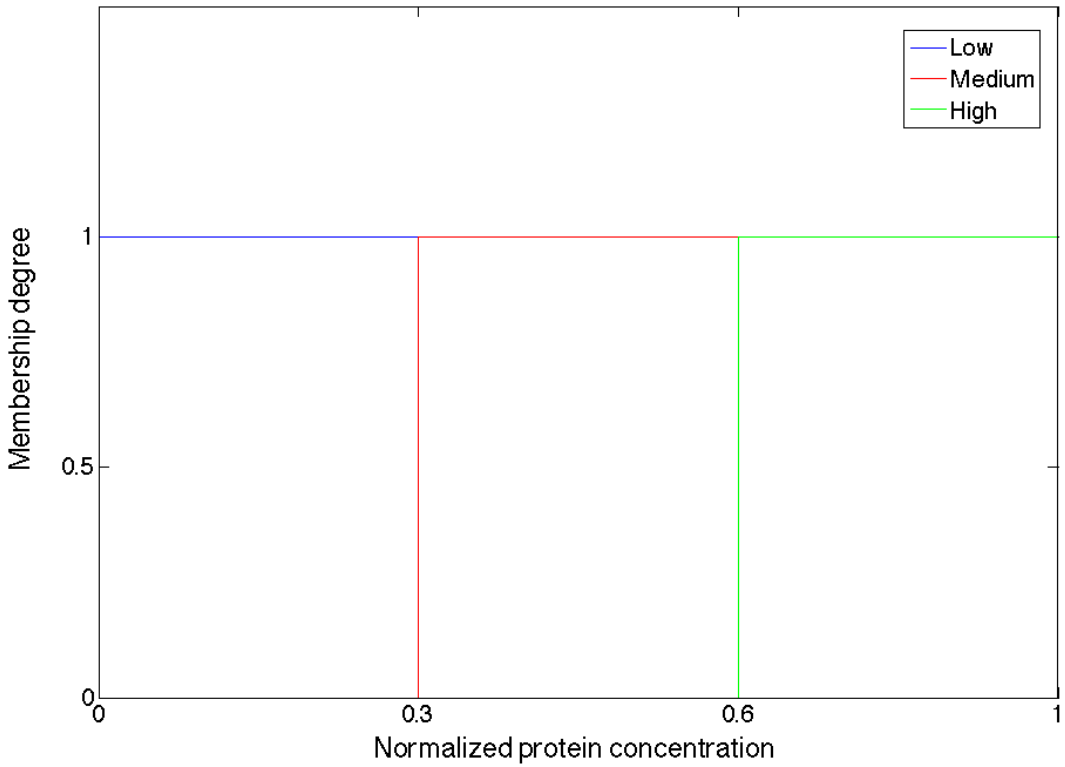
- Computing with words (IF-THEN rules)
- From an equation to “intuitive description”



$$r_{Degradation} = k_d * P \longrightarrow \begin{array}{l} Higher\ concentration = \\ Higher\ contribution\ to\ the \\ change\ in\ concentration \end{array}$$

Fuzzy logic approach

- Computing with words (IF-THEN rules)



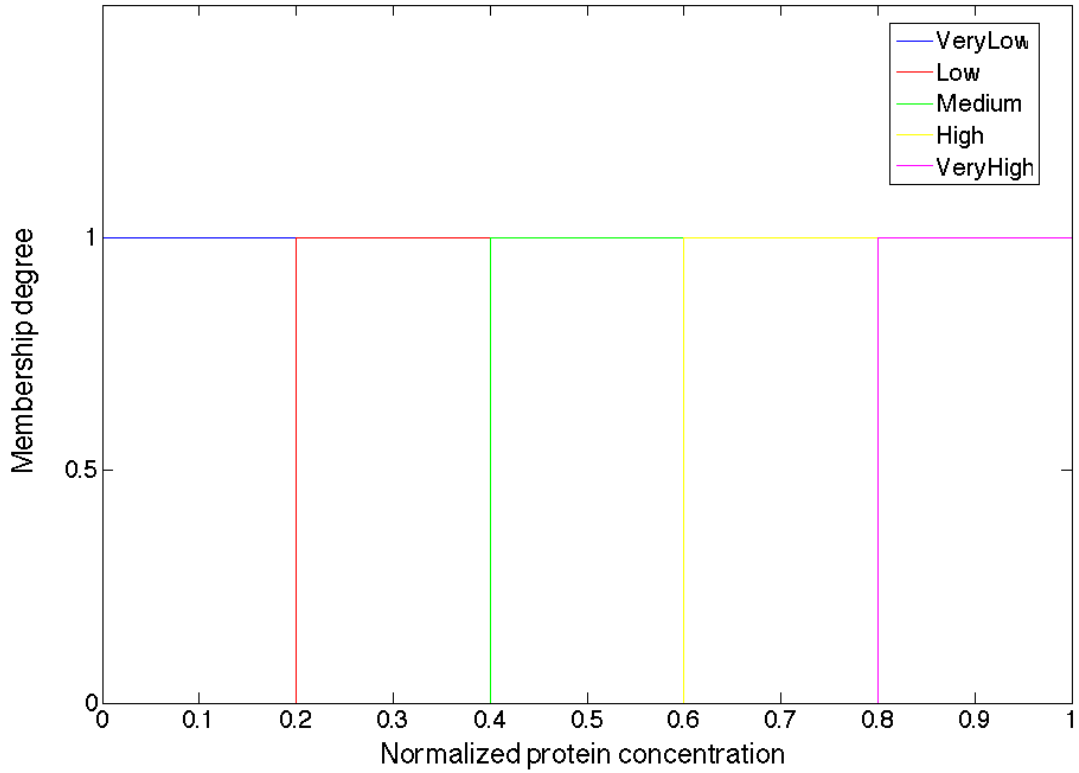
Fuzzy logic approach

- Computing with words (IF-THEN rules)

$$IF\ (ProteinConc)\ is\ High\ THEN\ (Change)\ is\ HighChange$$
$$IF\ (ProteinConc)\ is\ Med\ THEN\ (Change)\ is\ MedChange$$
$$IF\ (ProteinConc)\ is\ Low\ THEN\ (Change)\ is\ LowChange$$

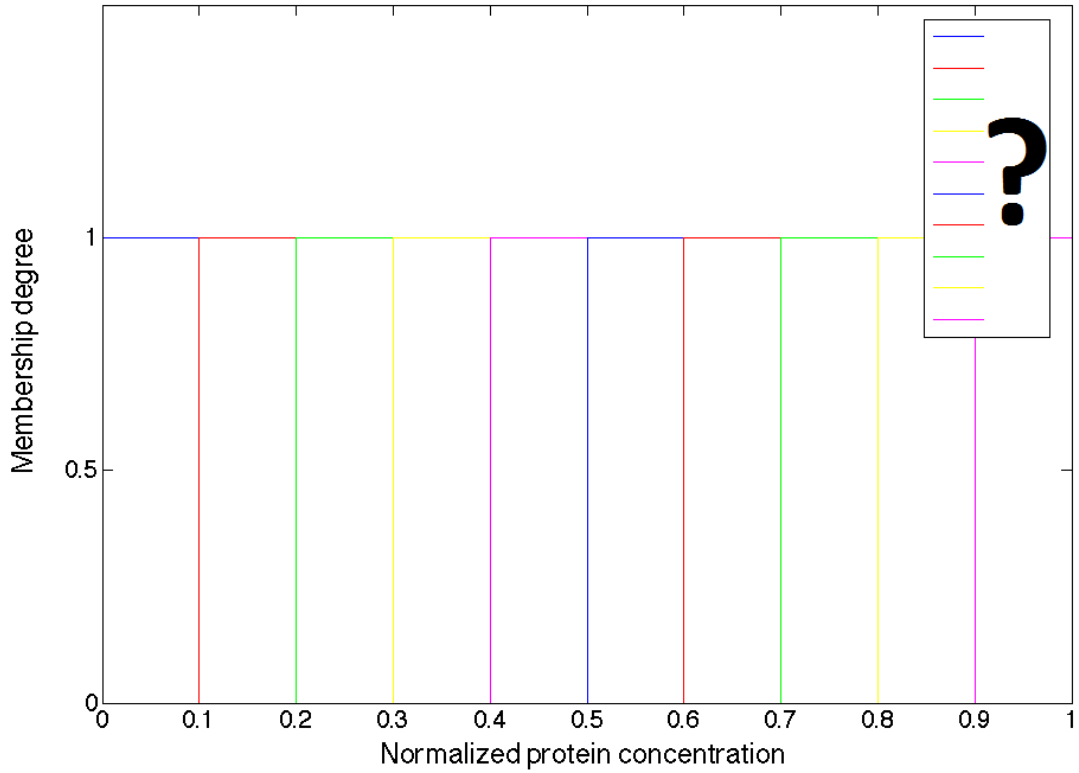
Fuzzy logic approach

- Computing with words (IF-THEN rules)



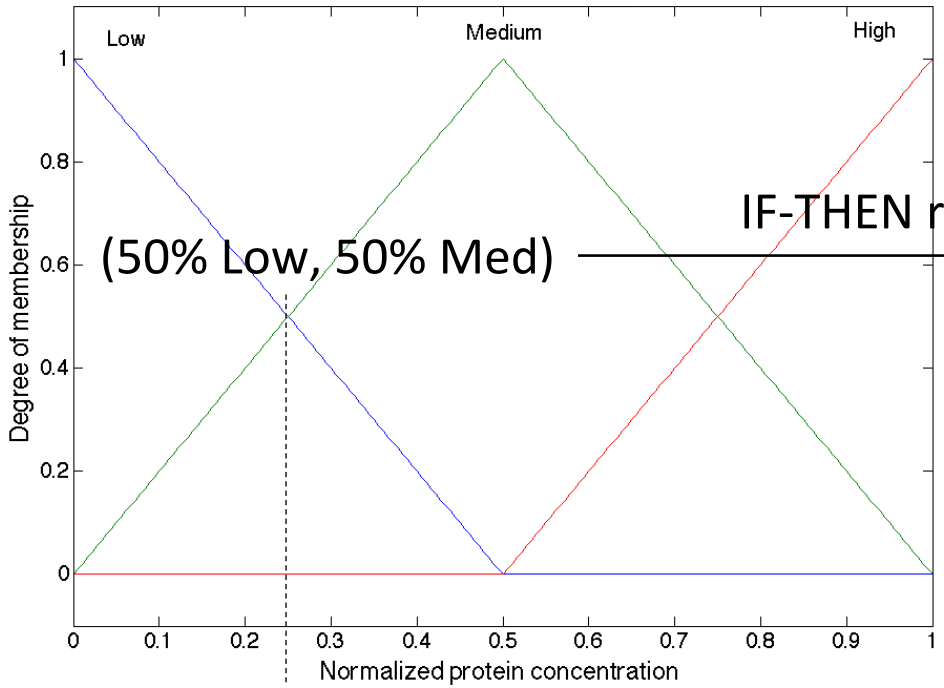
Fuzzy logic approach

- Computing with words (IF-THEN rules)



Fuzzy logic approach

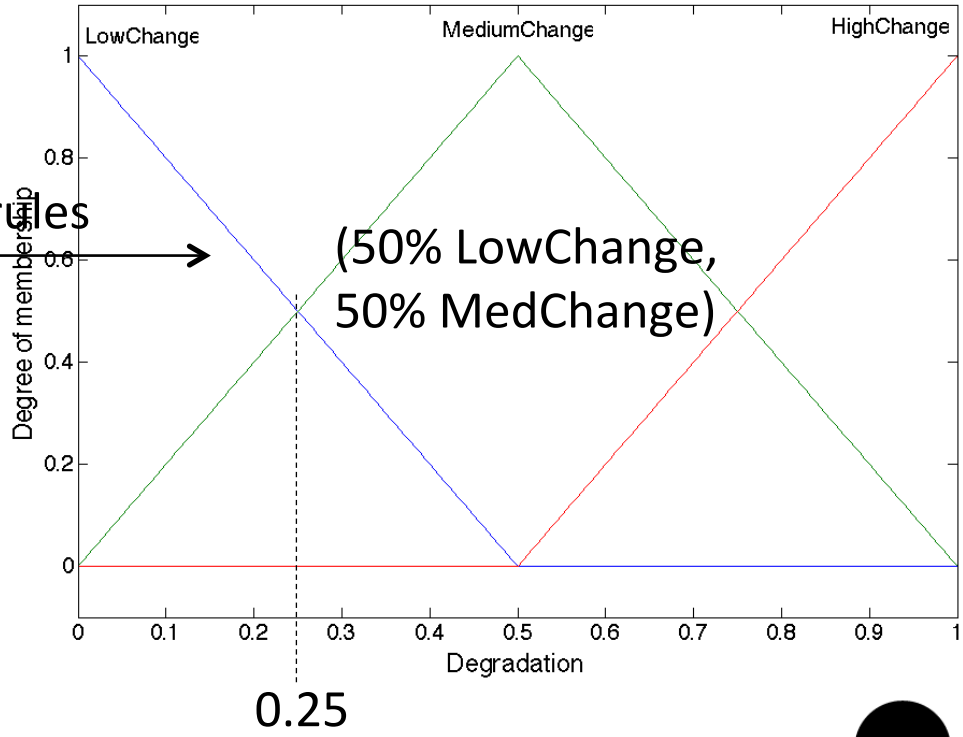
- Computing with words (IF-THEN rules)
- Fuzzification



(50% Low, 50% Med)

IF-THEN rules

(50% LowChange, 50% MedChange)



Fuzzy logic approach

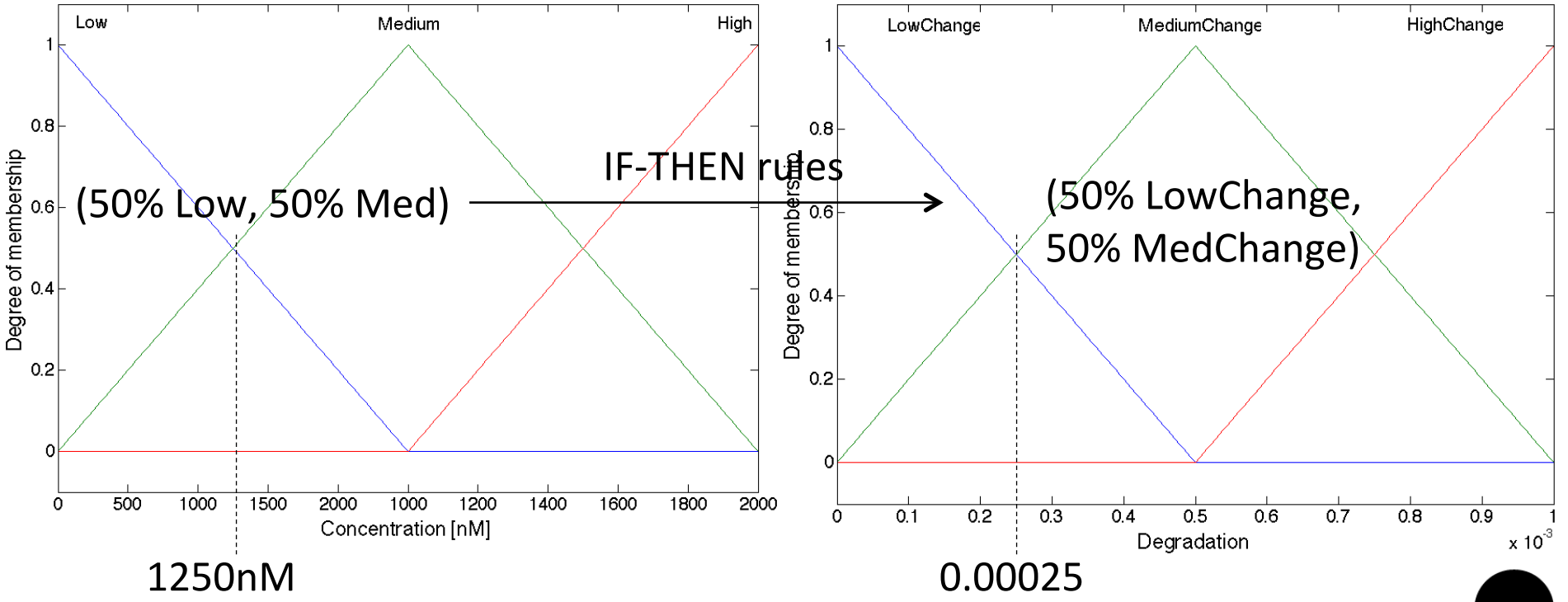
- Computing with words (IF-THEN rules)
- Fuzzification
  - Defining fuzzification for different abstraction levels
  - Different membership functions to achieve desired description
  - Using the knowledge about the system we have to gain more accurate description

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

Fuzzy logic approach

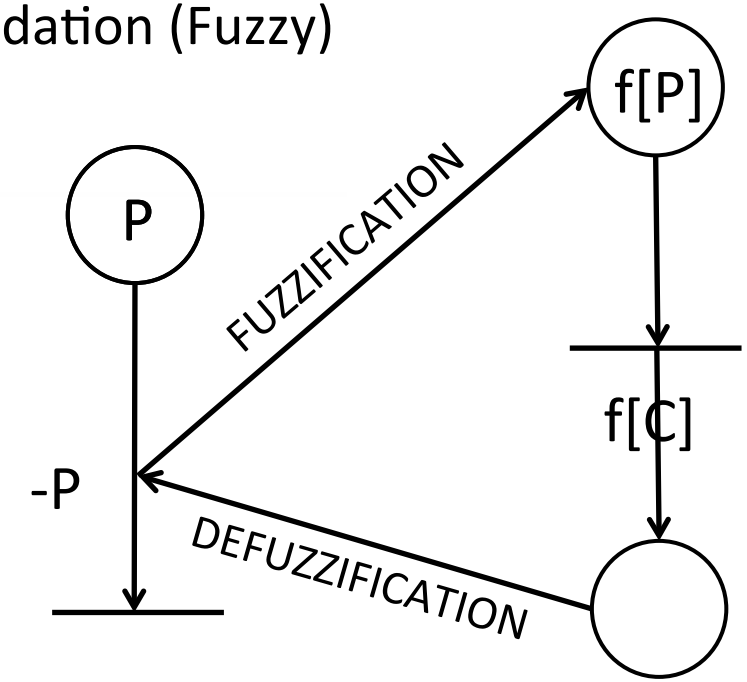
- Semi-quantitative representation



Fuzzy logic and Petri nets

Degradation (Fuzzy)

P -> 0

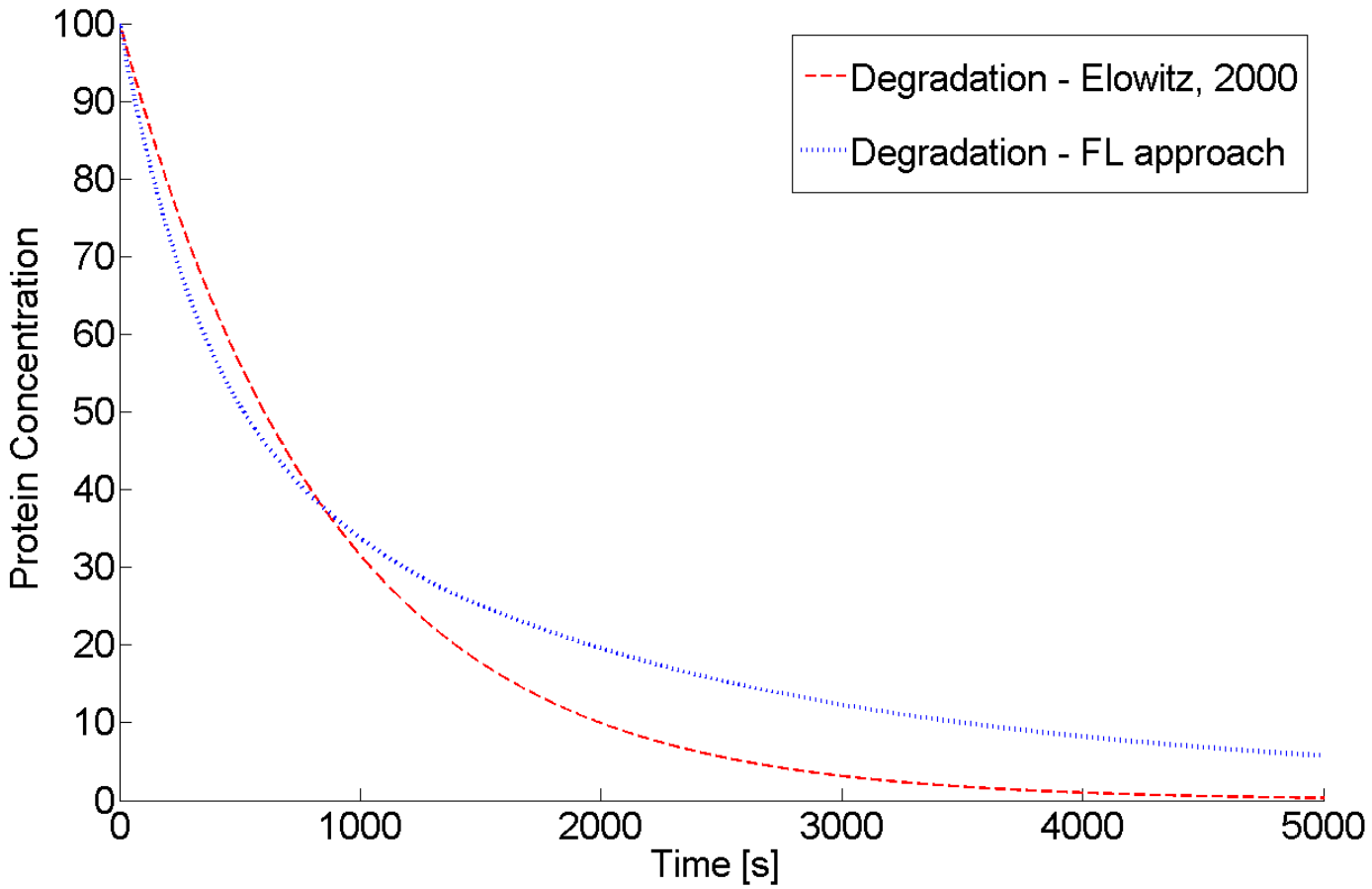


IF (f[P] is *High)* THEN (f[C] is *HighChange)*
IF (f[P] is *Med)* THEN (f[C] is *MedChange)*
IF (f[P] is *Low)* THEN (f[C] is *LowChange)*

Fuzzy logic and Petri nets

Degradation:
P -> 0

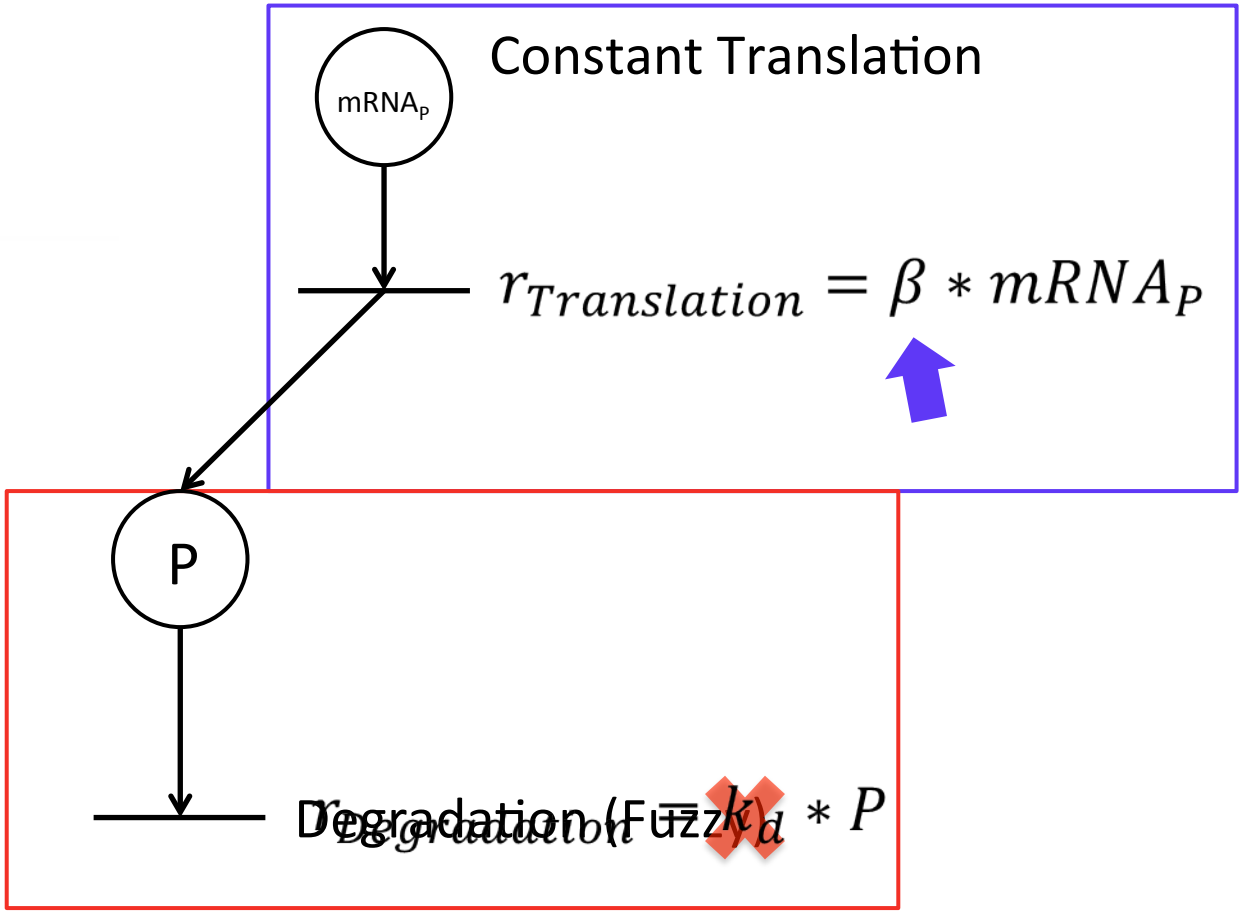
Results


Degradation - Elowitz, 2000
Degradation - FL approach
Protein Concentration
Time [s]
0
10
20
30
40
50
60
70
80
90
100
0
1000
2000
3000
4000
5000

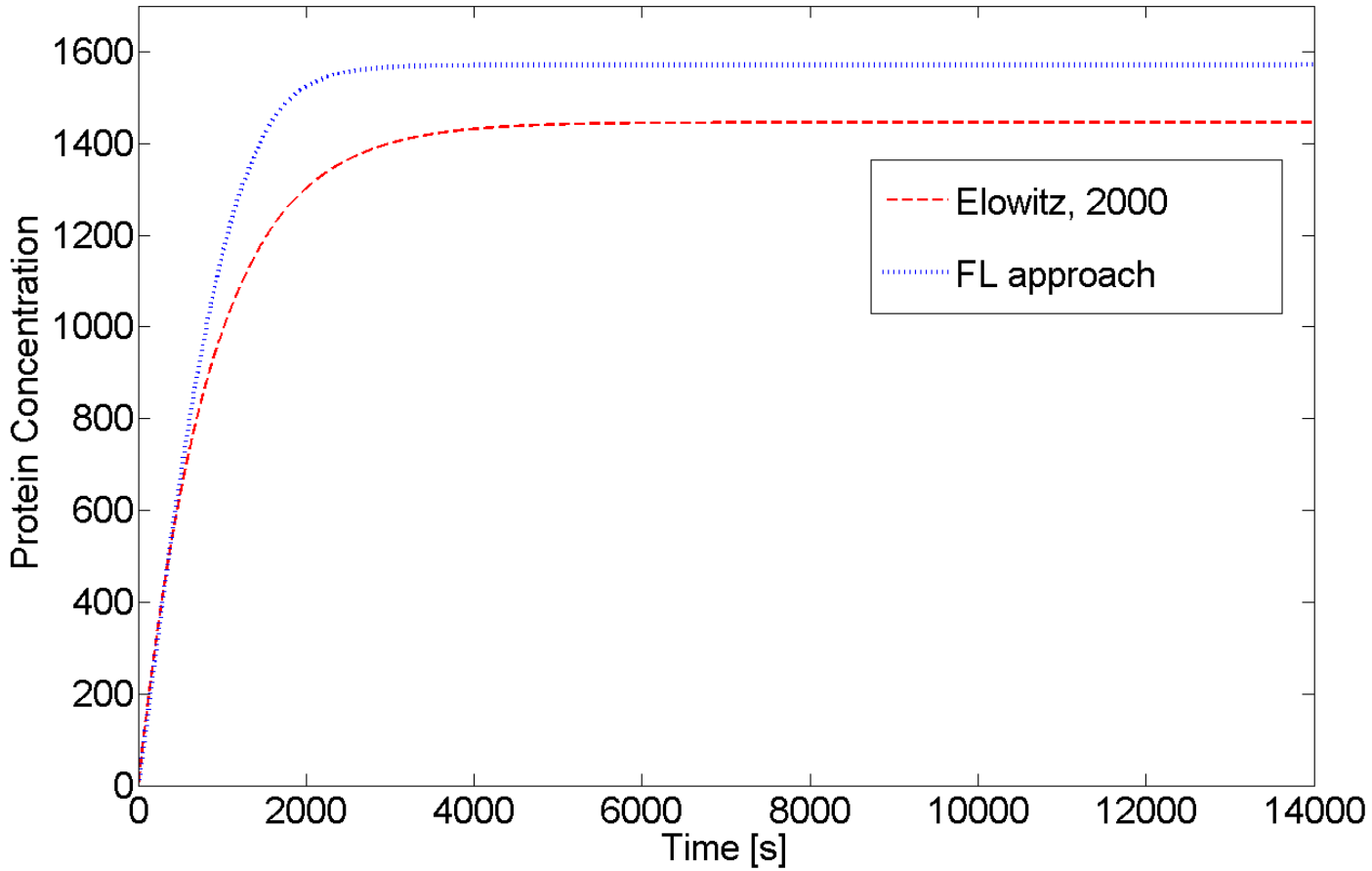
Fuzzy logic and Petri nets

Translation:
mRNAP -> P

Degradation:
P -> 0



Results


Protein Concentration
Time [s]
0
200
400
600
800
1000
1200
1400
1600
0
2000
4000
6000
8000
10000
12000
14000
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