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

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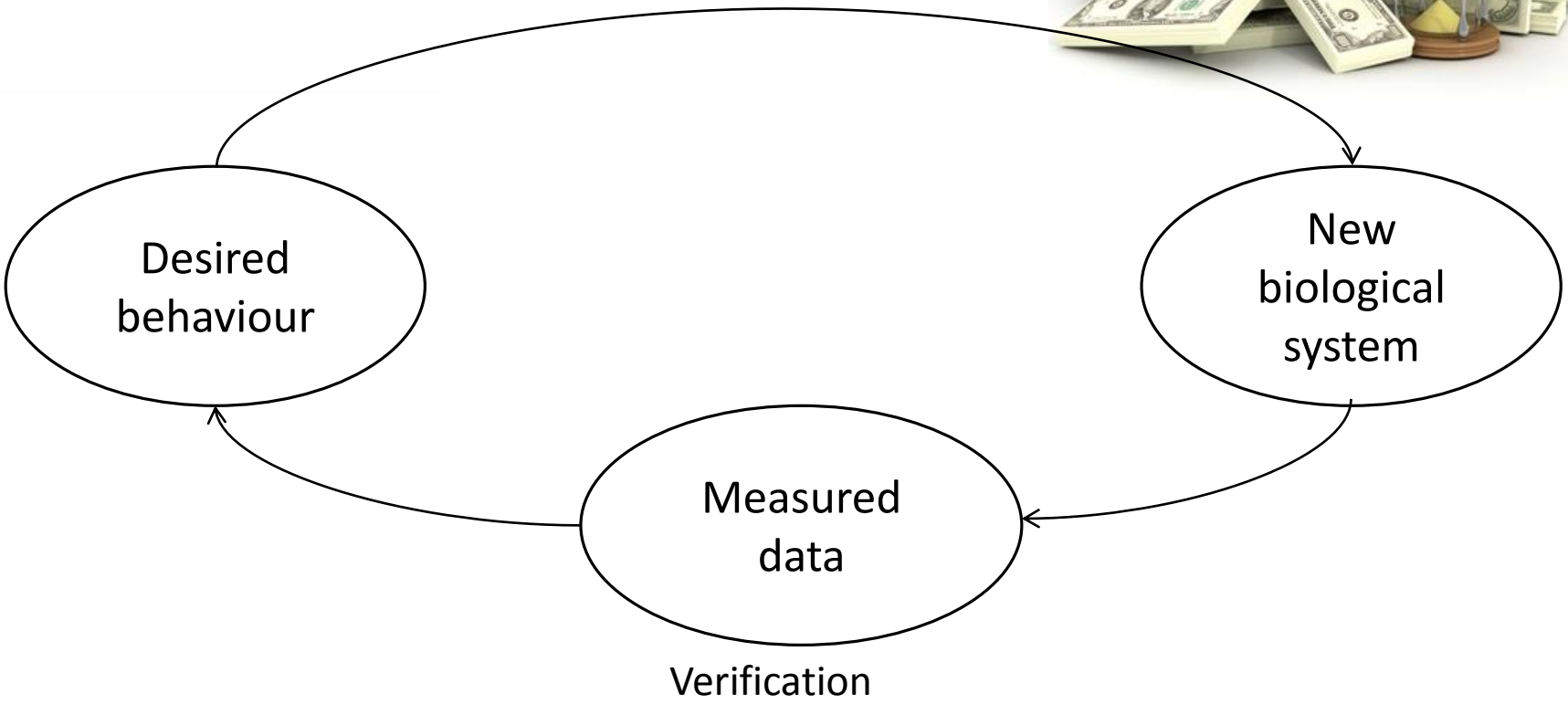
Synthetic biology

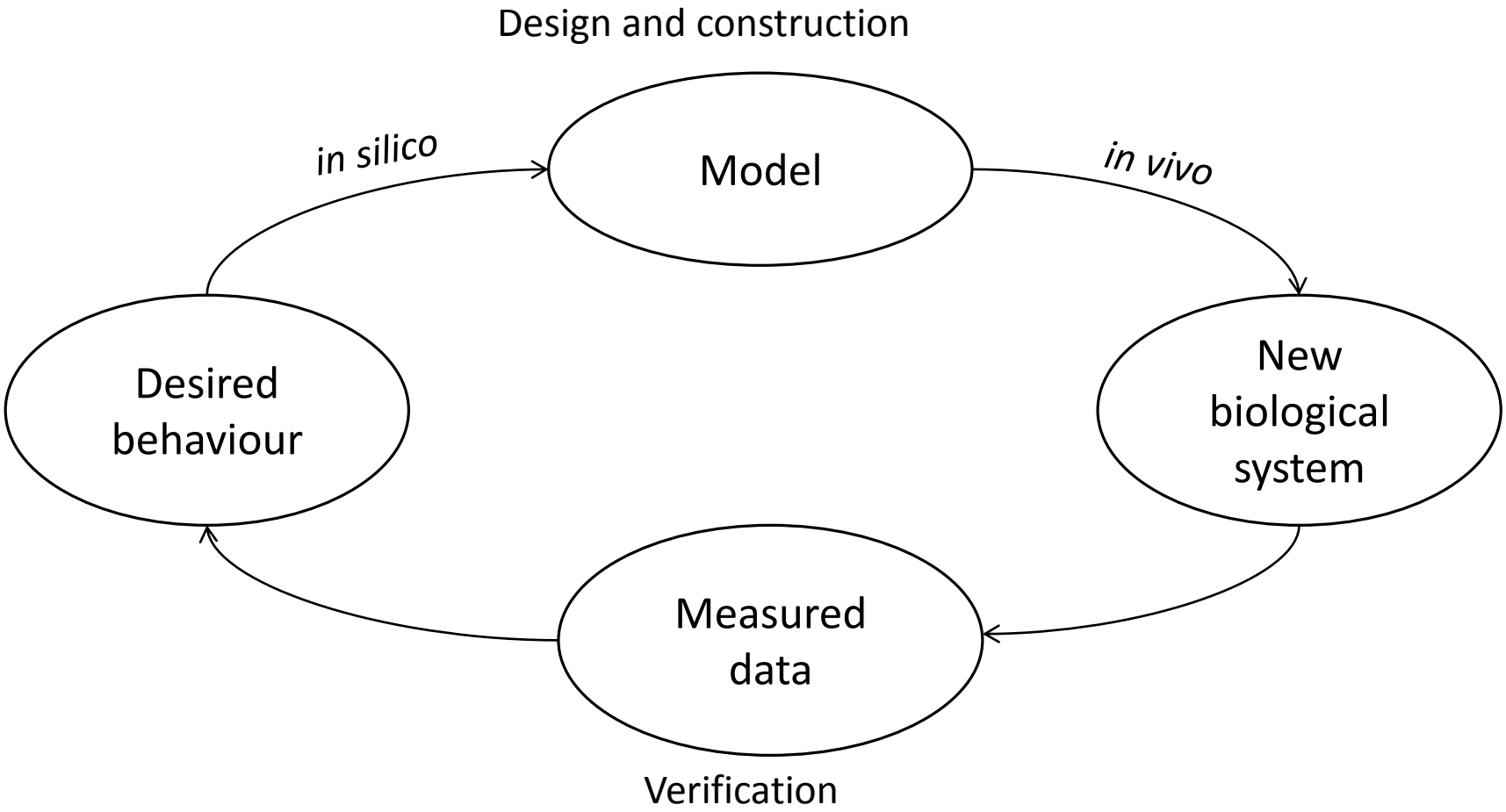
Design and construction

in vivo implementation



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

Synthetic biology



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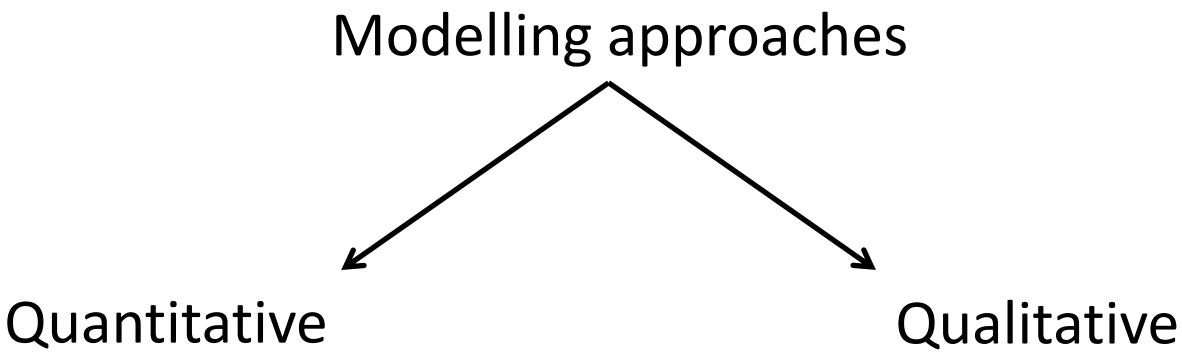
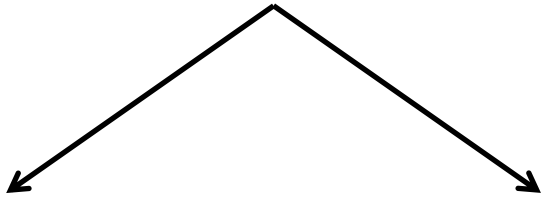

Modelling approaches
Quantitative
Qualitative

Modelling approaches



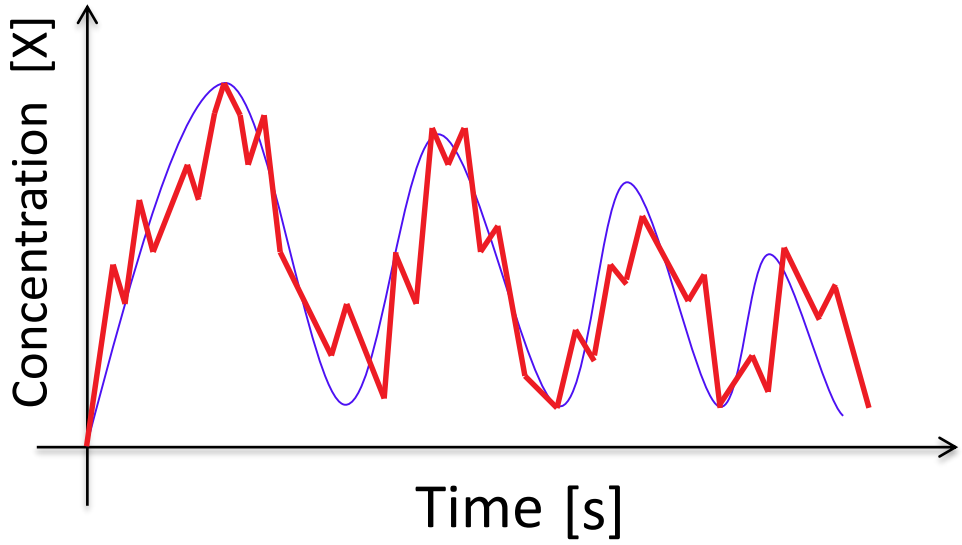
Quantitative

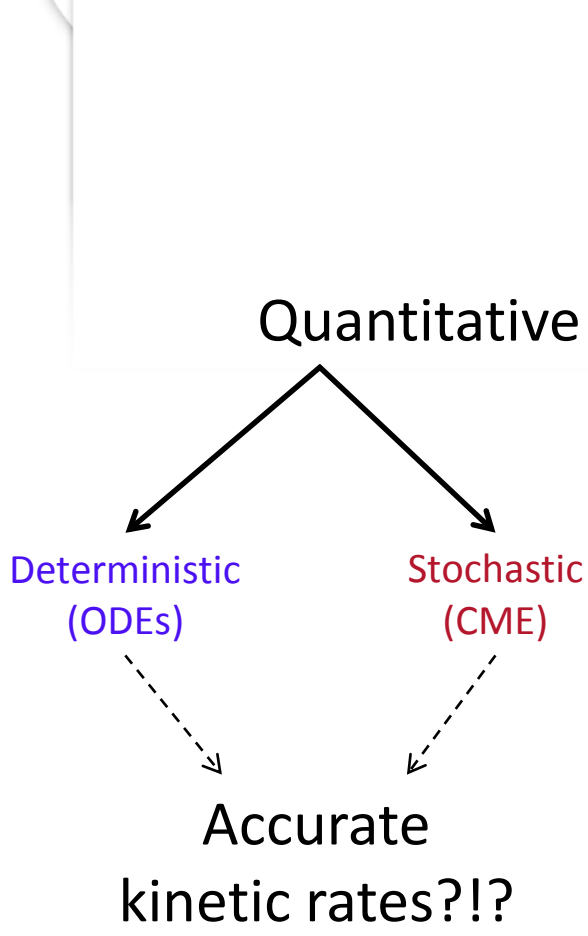
Qualitative

- Qualitative behavioral properties of the system
- Can be discrete or continuous
- No notion of time and quantity

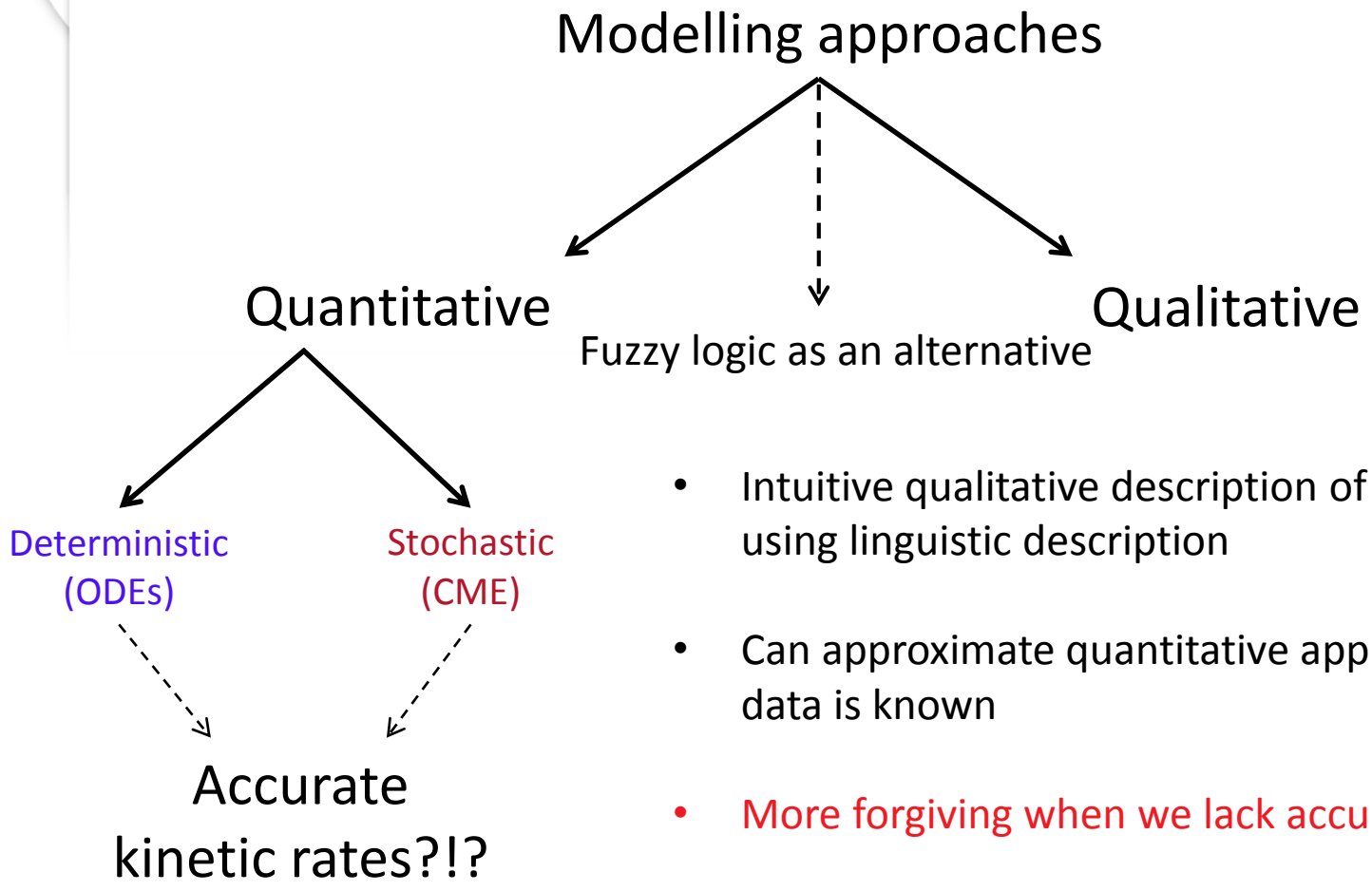
Modelling approaches

- Quantitative
  - Deterministic (ODEs)
  - 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)



- 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

Petri nets[1]

Qualitative PNs

- Qualitative description
- Behavioural properties

Fuzzy PNs

- Qualitative description

Time-free

Timed, Quantitative

Stochastic PNs

- Molecules
- Stochastic rates

Continuous PNs

- ODEs (concentrations, deterministic rates)
- Fuzzy PNs (function approximation[2]; can be used for quantitative modelling even if kinetic data is unknown)

Discrete State Space

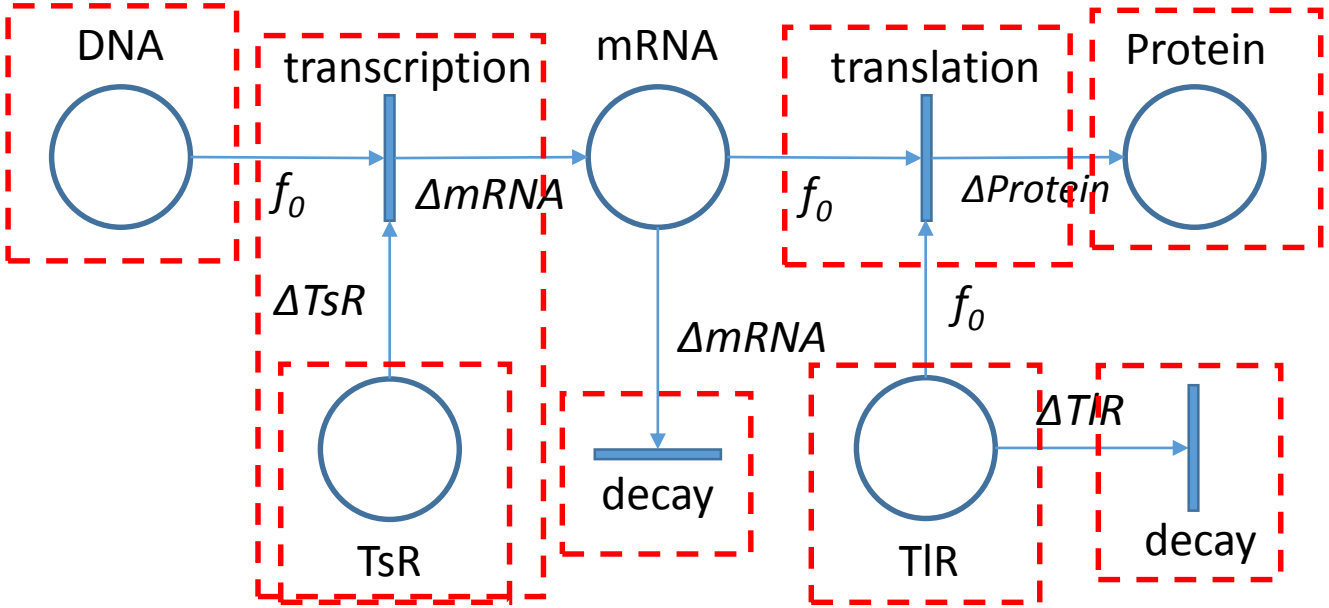
Continuous State Space

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

[2]Windhager, Modeling of Dynamic Systems with Petri nets and Fuzzy Logic, *PhD thesis*, 2013

Transcription-translation system[1]

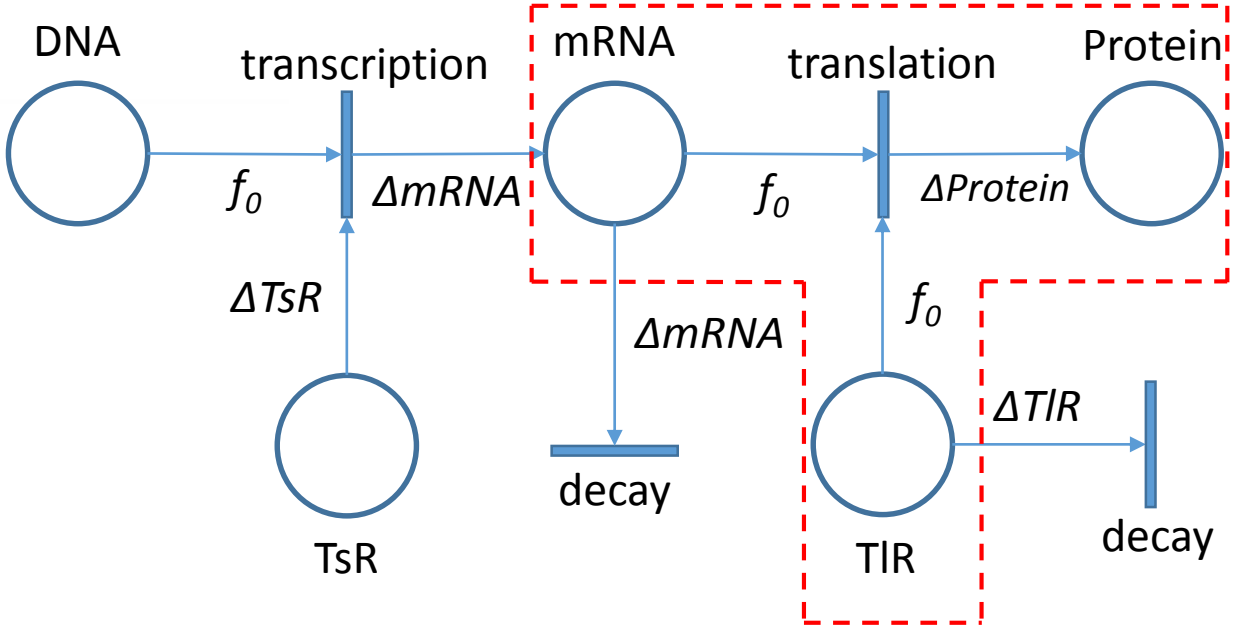
- Inputs: DNA, transcription resource (TsR), translation resource (TlR)
- Output: Protein concentration
- Processes: transcription, translation, degradation, consumption



[1]Windhager, Modeling of Dynamic Systems with Petri nets and Fuzzy Logic, *PhD thesis*, 2013

Transcription-translation system

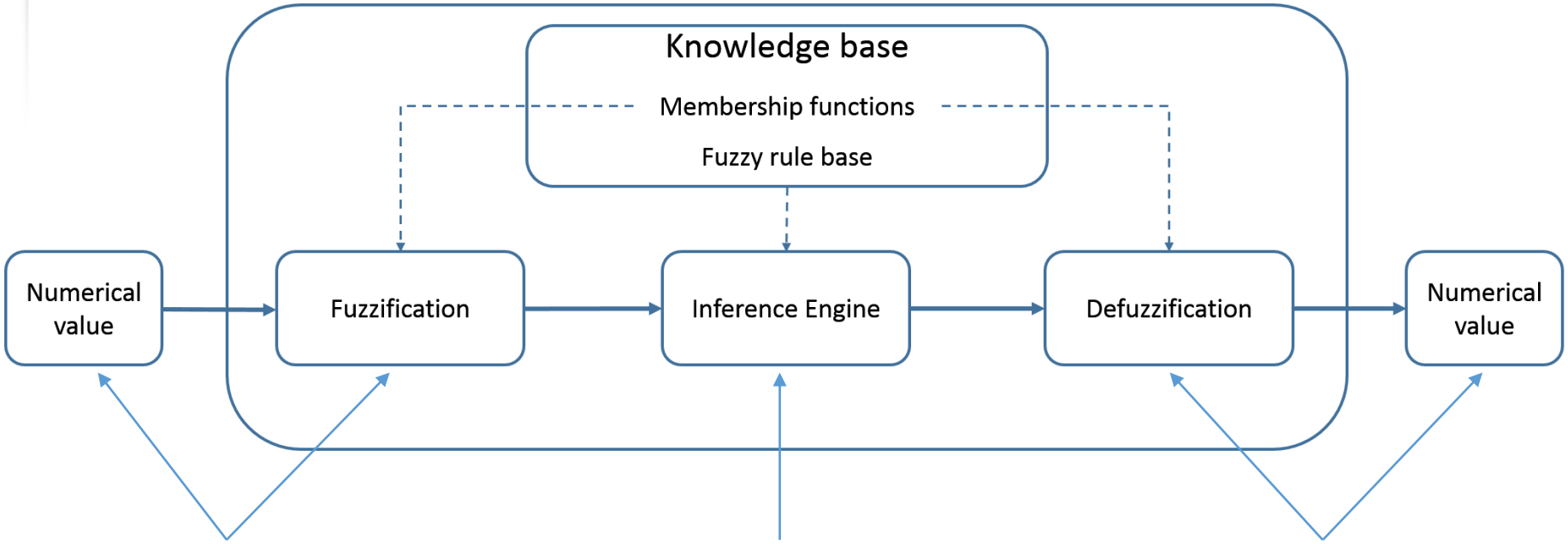
- Fuzzy approach for modelling translation
- Other processes are modelled as a system of ODEs[1]



$$\frac{d[Protein]}{dt} = \frac{k_{tl} \cdot [TlR] \cdot [mRNA]}{m_{tl} + [mRNA]}$$

[1]Windhager, Modeling of Dynamic Systems with Petri nets and Fuzzy Logic, *PhD thesis*, 2013

Modelling translation using Fuzzy logic

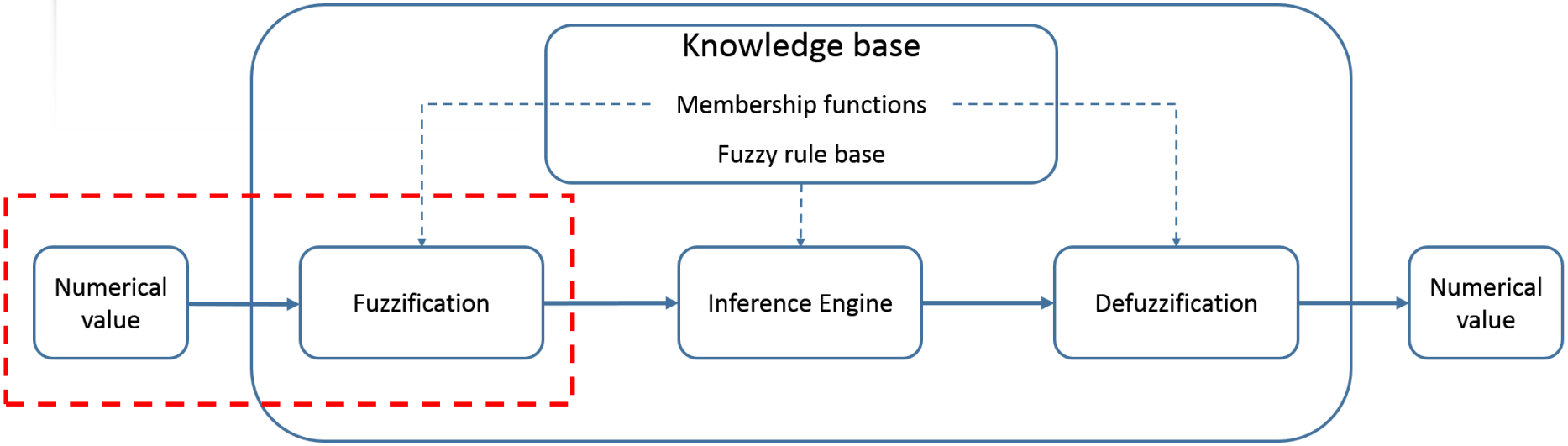


Concentration of mRNA and TlR

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

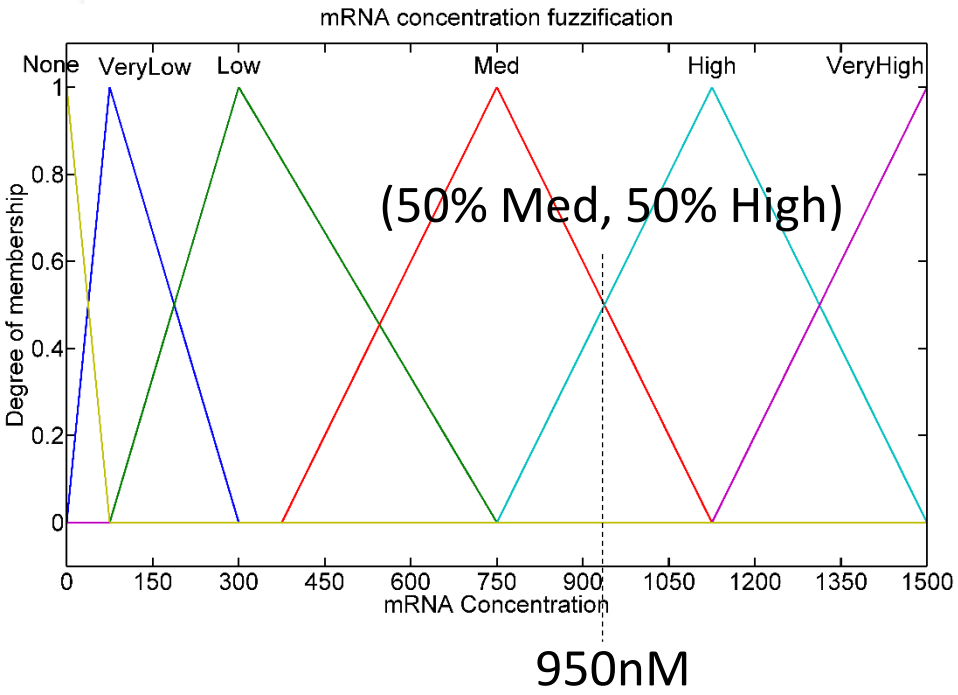
Protein concentration change

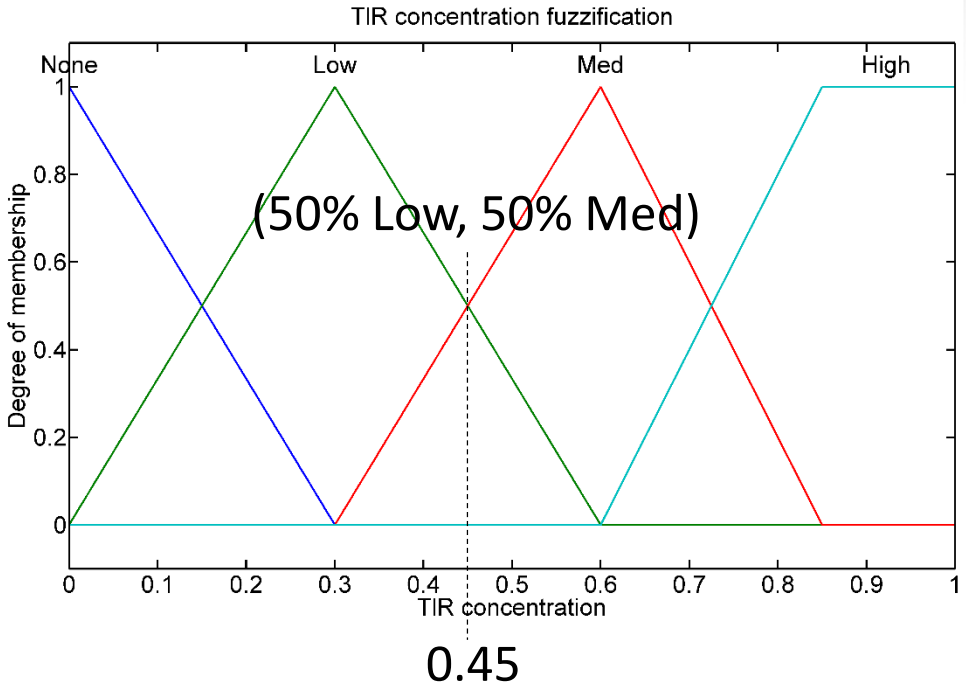
Modelling translation using Fuzzy logic



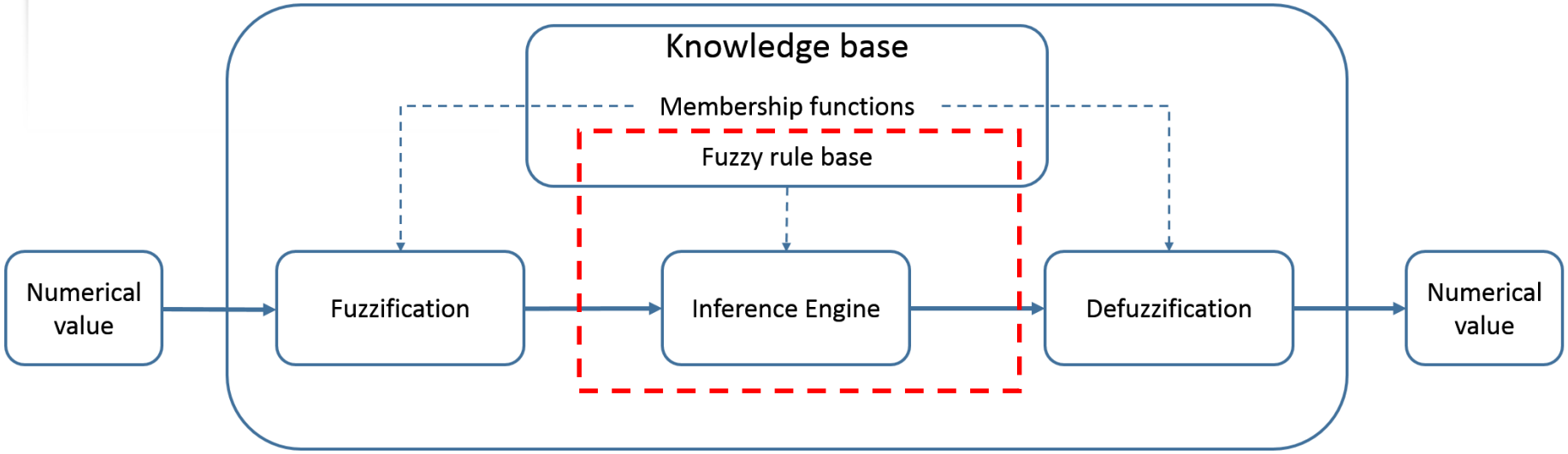
Modelling translation using Fuzzy logic

- Fuzzification of mRNA and TlR concentration





Modelling translation using Fuzzy logic



Modelling translation using Fuzzy logic

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

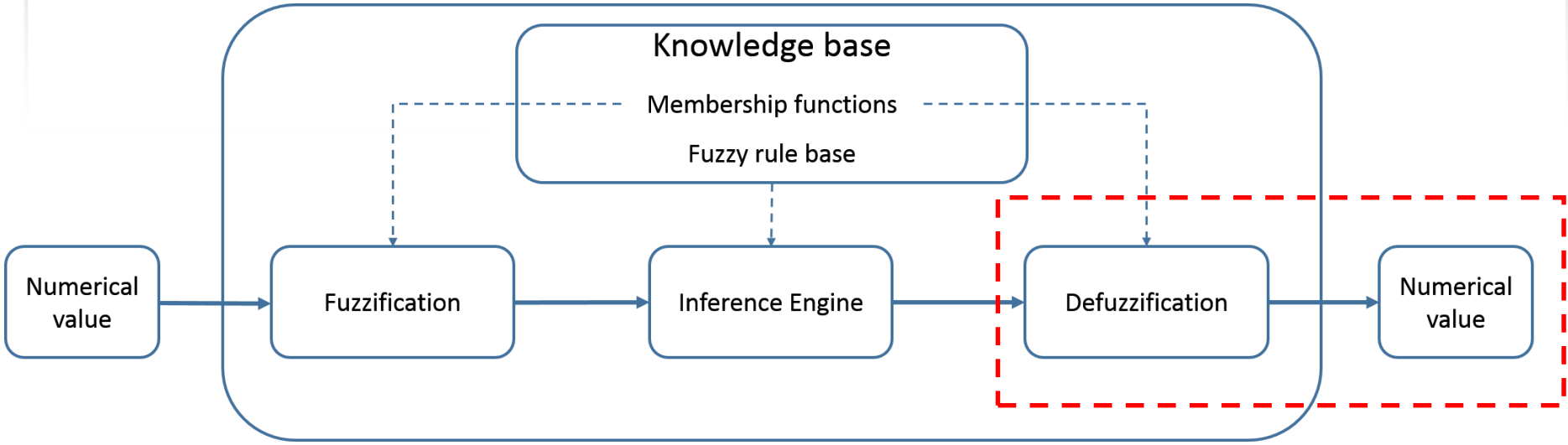
$TlR \setminus mRNA$	None	VeryLow	Low	Med	High	VeryHigh
None	None	None	None	None	None	None
Low	None	VeryLow	Low	Low	Low	Med
Med	None	VeryLow	Low	Med	Med	High
High	None	VeryLow	Low	Med	High	VeryHigh

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

VS.

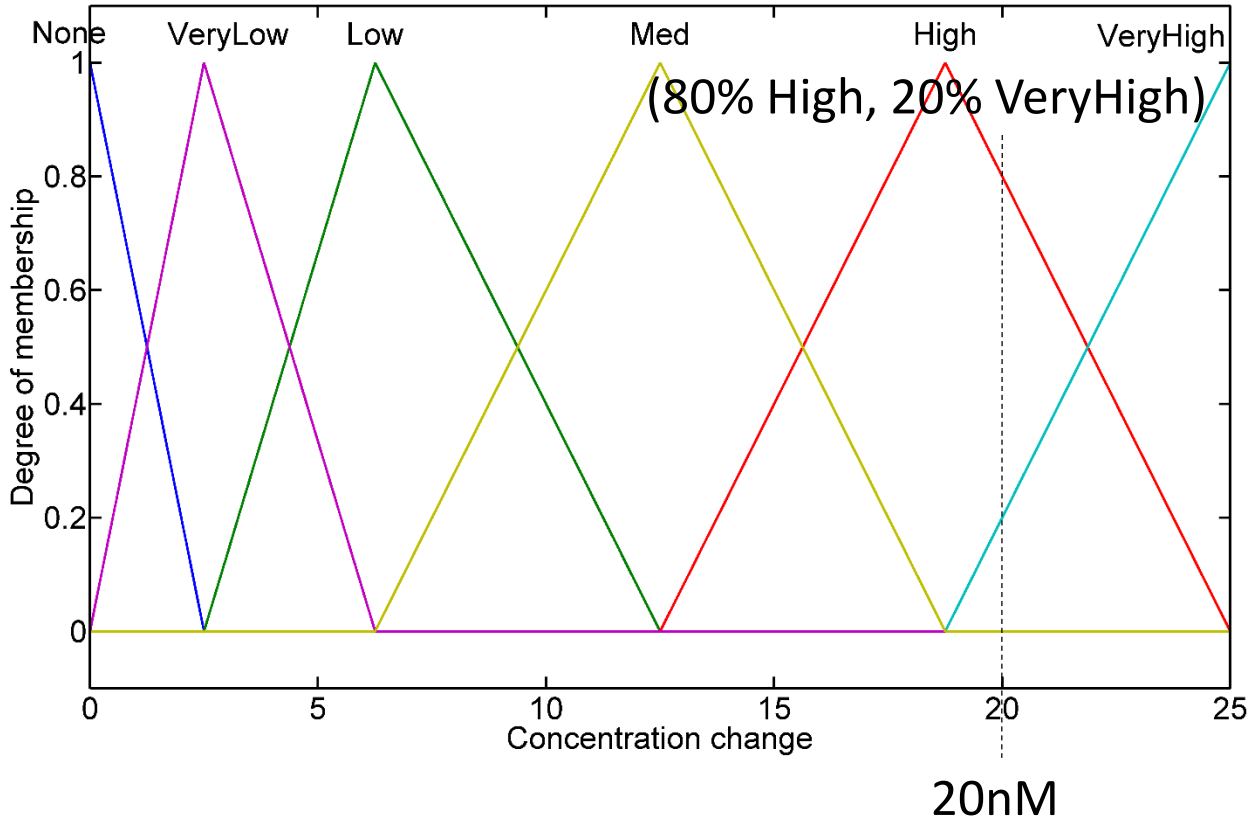
$$\frac{d[Protein]}{dt} = \frac{k_{tl} \cdot [TlR] \cdot [mRNA]}{m_{tl} + [mRNA]}$$

Modelling translation using Fuzzy logic



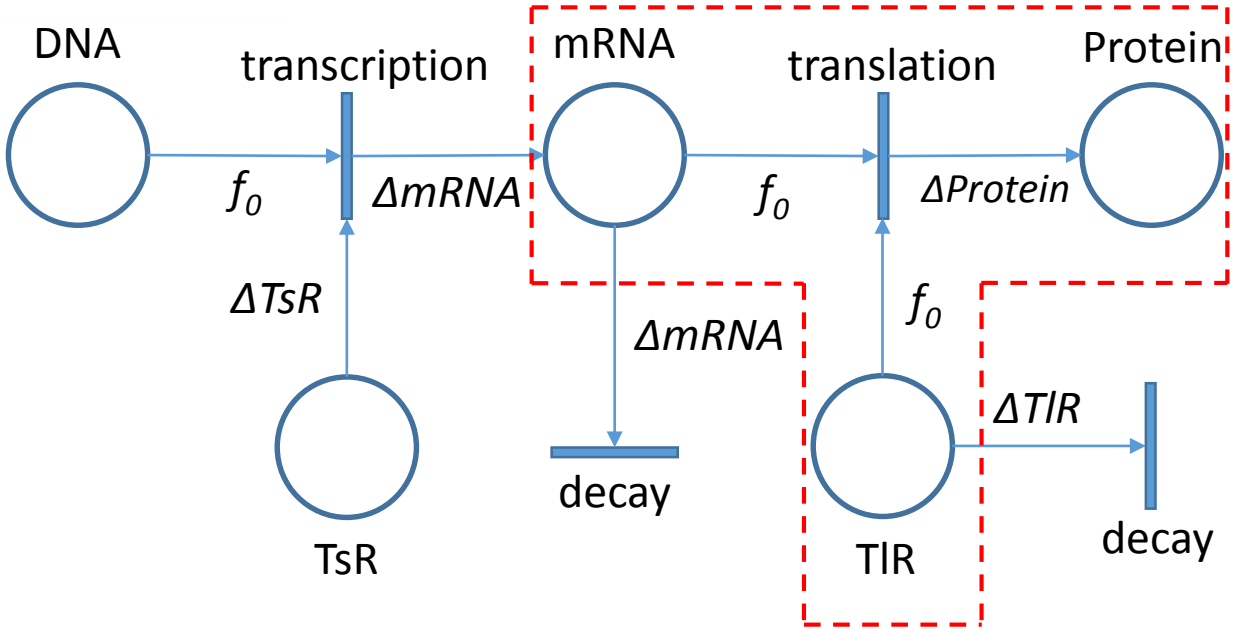
Modelling translation using Fuzzy logic

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

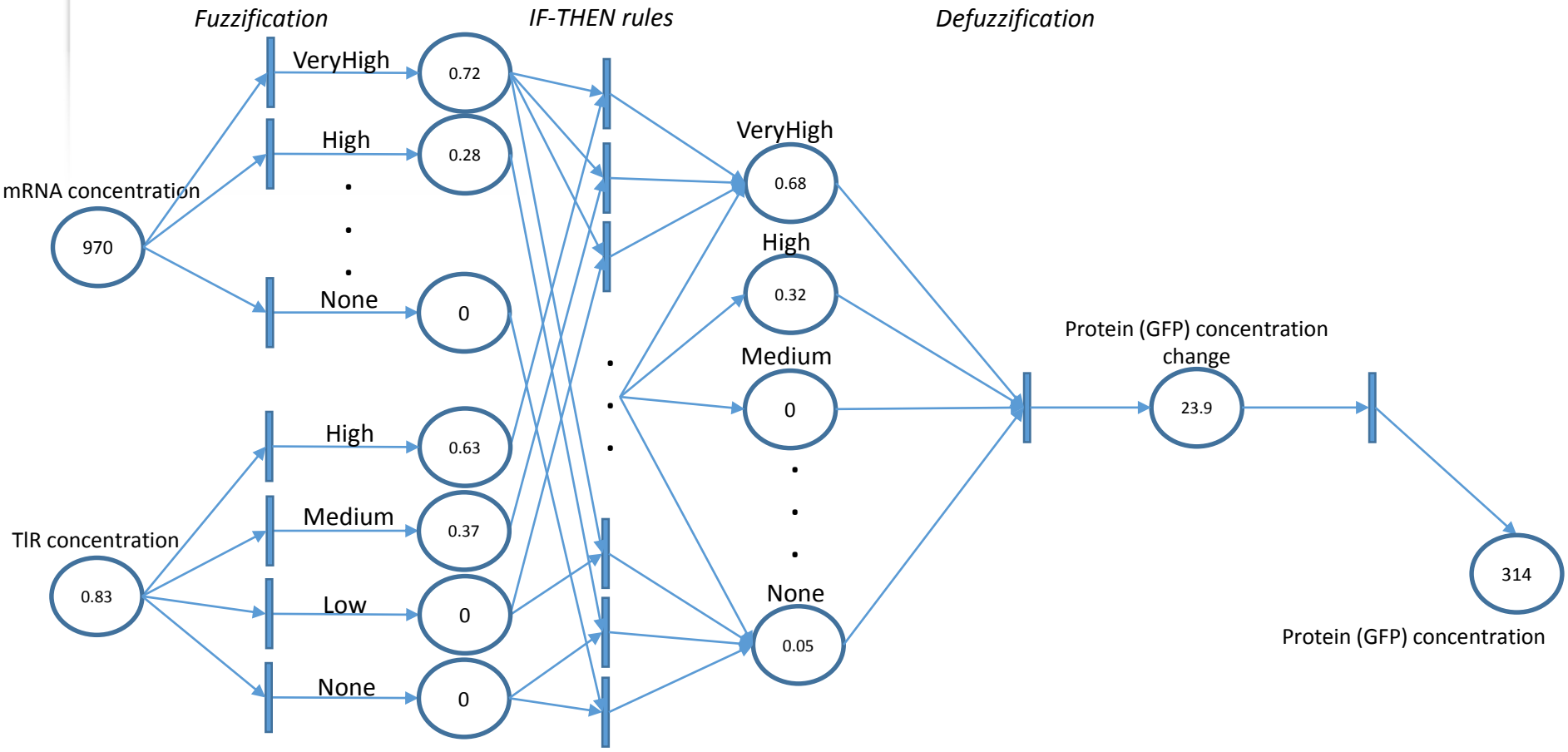


Modelling translation using Fuzzy logic & Petri nets

- One transition is transformed into fuzzy logic Petri net with corresponding input and output



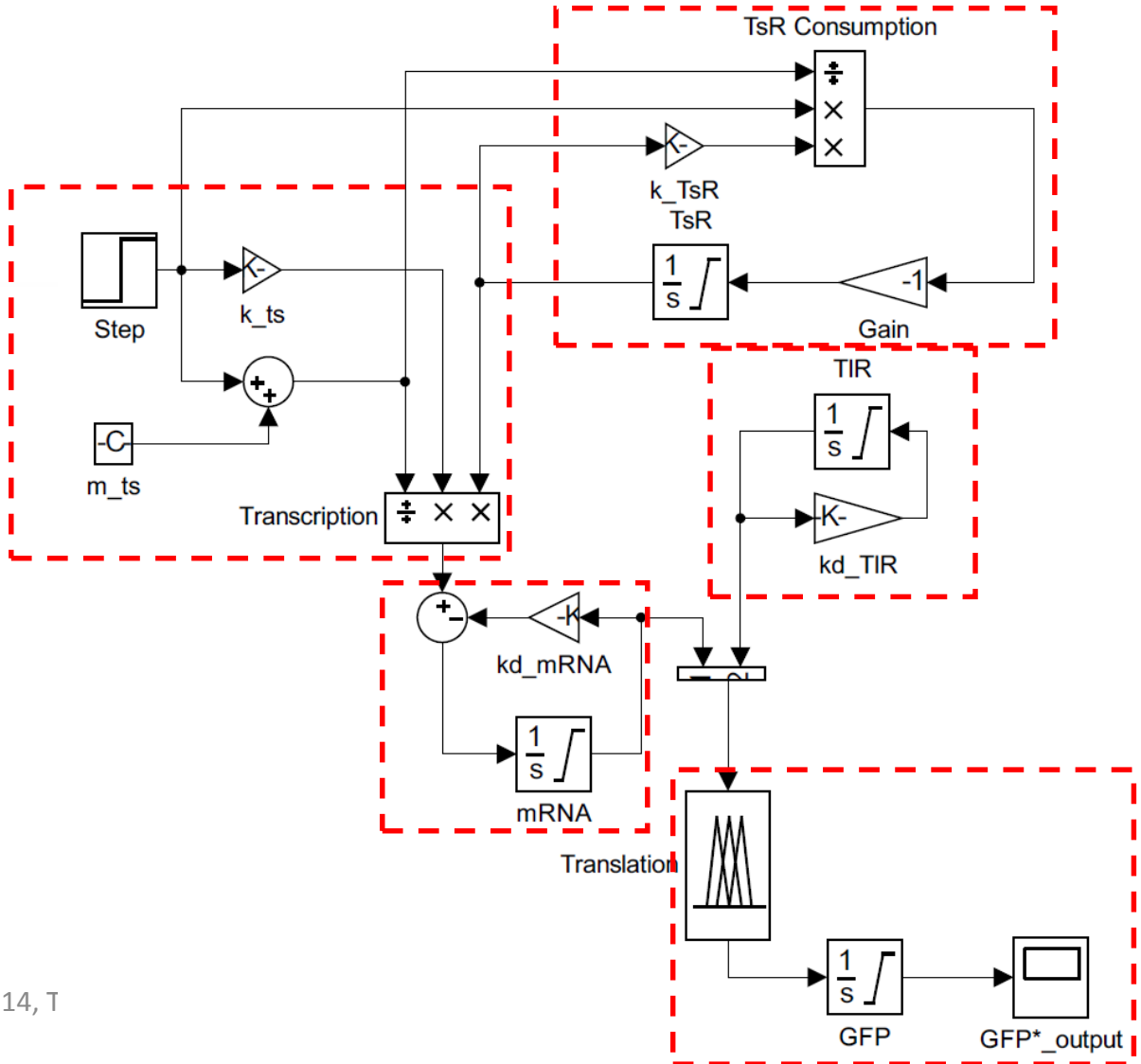
Modelling translation using Fuzzy logic & Petri Nets



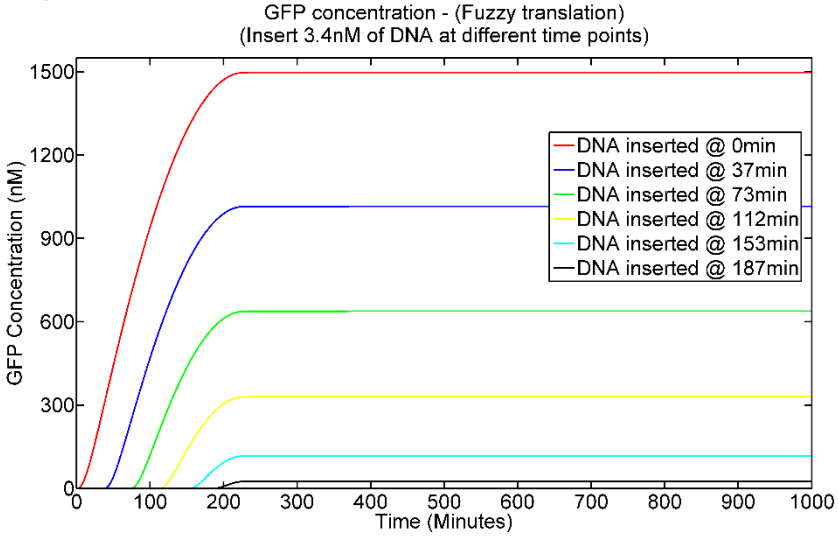
Simulation

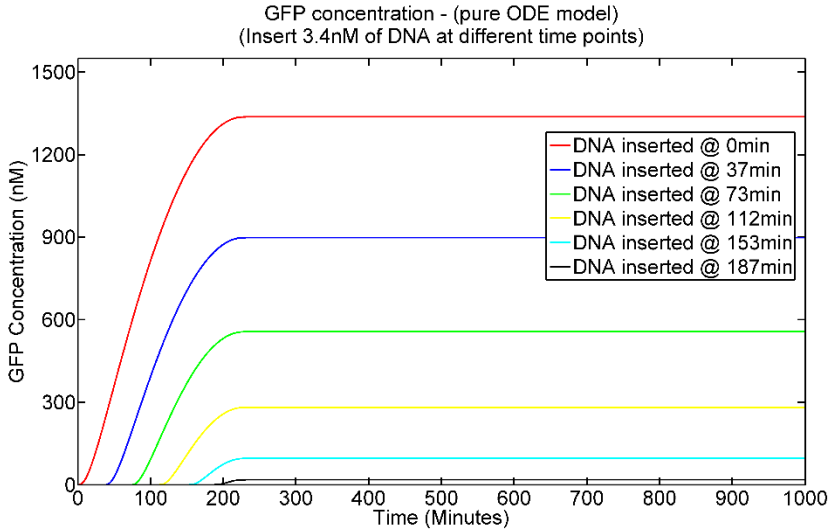
- Building the model
  - Matlab Simulink
  - Fuzzy logic toolbox
- Simulation run
  - Matlab engine
  - Regards fuzzy logic steps as one step
  - Allows an easy way of building fuzzy system
  - Simulation run with ODEs and fuzzy logic in the same model

Simulation


TsR Consumption
k_TsR
TsR
Gain
-1
Step
k_ts
m_ts
-C
Transcription
TIR
kd_TIR
kd_mRNA
mRNA
Translation
GFP
GFP*_output

Results


GFP concentration - (Fuzzy translation)
(Insert 3.4nM of DNA at different time points)
GFP Concentration (nM)
Time (Minutes)
DNA inserted @ 0min
DNA inserted @ 37min
DNA inserted @ 73min
DNA inserted @ 112min
DNA inserted @ 153min
DNA inserted @ 187min


GFP concentration - (pure ODE model)
(Insert 3.4nM of DNA at different time points)
GFP Concentration (nM)
Time (Minutes)
DNA inserted @ 0min
DNA inserted @ 37min
DNA inserted @ 73min
DNA inserted @ 112min
DNA inserted @ 153min
DNA inserted @ 187min

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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