PACS Meeting

Parameters synthesis by using abstract interpretation in Parametric Stochastic Automata Networks

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Joint work with:
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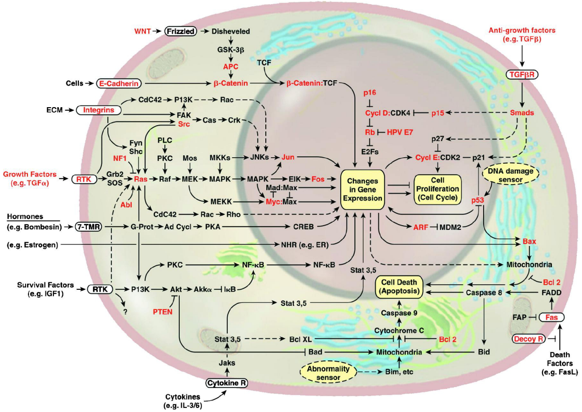
Context



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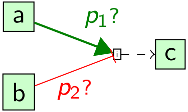
- Cellular processes $\Longrightarrow$ networks of biological interactions.
- Nodes (biological components), edges (interactions).

Motivation

General knowledge
Literature
Hypotheses



Times series data

Genes	1h	...	24h
Gene 1		...	
Gene 2		...	

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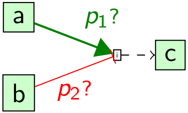
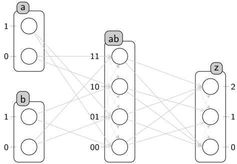


Algebraic Modelling



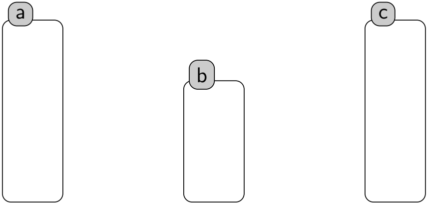
Times series data

Genes	1h	...	24h
Gene 1		...	
Gene 2		...	

Formal inference of the parameters of Biological Networks:

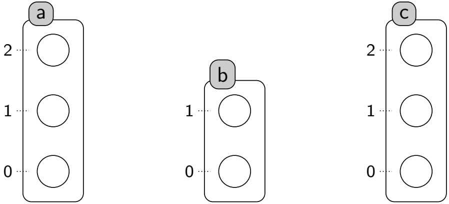
- Avoid critical behaviors.

Parametric Stochastic Automata Networks



Automata: components a, b, c

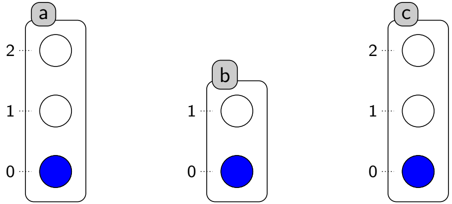
Parametric Stochastic Automata Networks



Automata: components a, b, c

local states: levels of expression c_0, c_1, c_2

Parametric Stochastic Automata Networks



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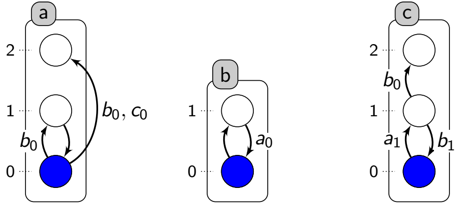
Parametric Stochastic Automata Networks



Automata: components $a,\ b,\ c$

local states: levels of expression $c_0,\ c_1,\ c_2$

States: sets of active local states a_0, b_0, c_0

Transitions: dynamics $t_1 = a_0 a_1 b_0,\ t_2 = a_1 a_0,\ t_3 = a_0 a_2 b_0, c_0,\ t_4 = b_0 b_1$

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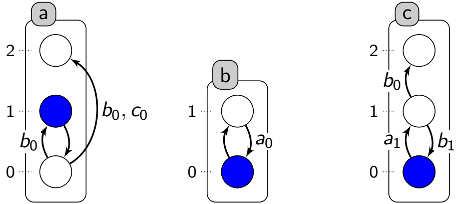

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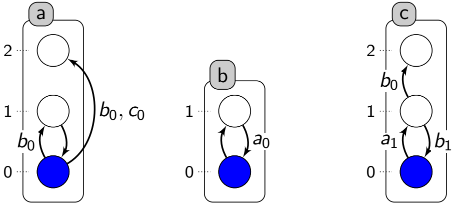

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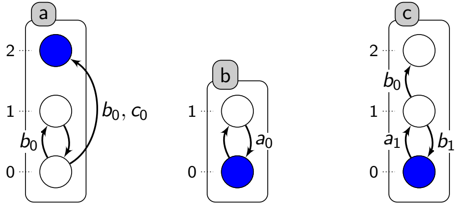

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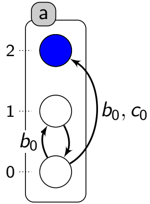

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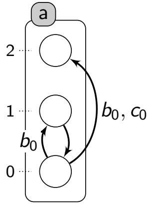
Parametric Stochastic Automata Networks



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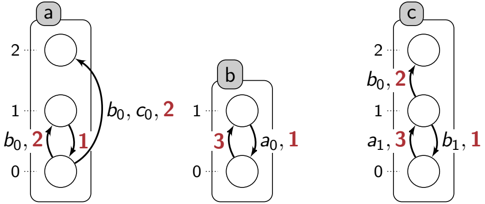

Automata: components $a,\ b,\ c$

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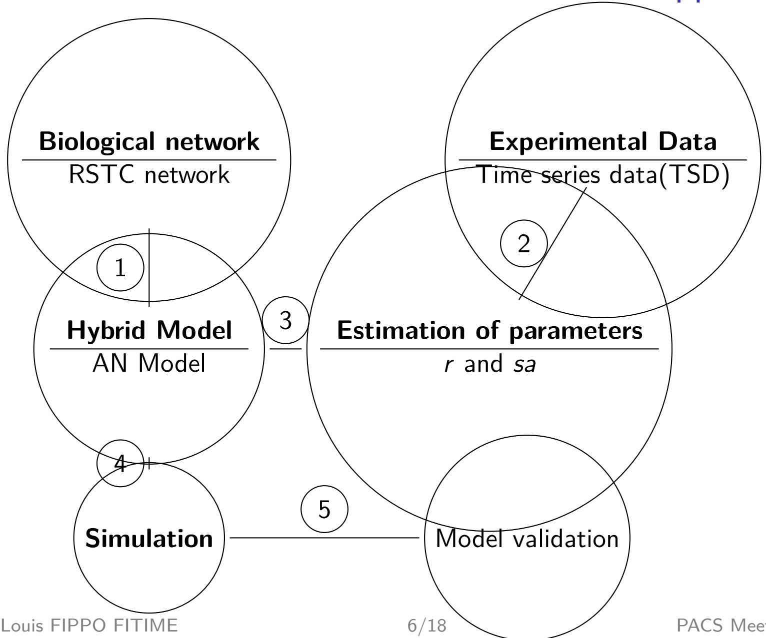
States: sets of active local states a_2, b_1, c_0

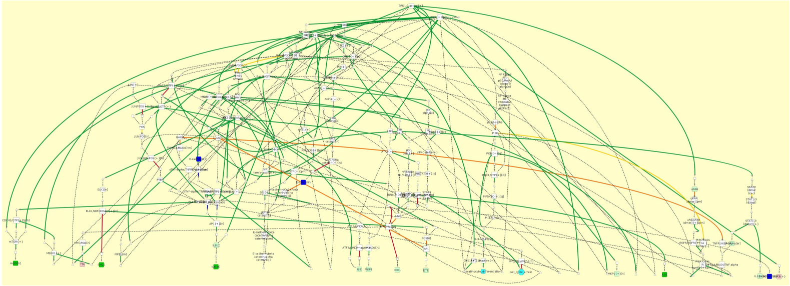
Transitions: dynamics $t_1 = a_0 a_1 b_0, \mathbf{2},\ t_2 = a_1 a_0 \mathbf{1},\ t_3 = a_0 a_2 b_0, c_0, \mathbf{2},\ t_4 = b_0 b_1 \mathbf{3}$

Approach


Biological network
RSTC network
Experimental Data
Time series data(TSD)
1
2
3
Hybrid Model
AN Model
Estimation of parameters
r and sa
4
5
Simulation
Model validation

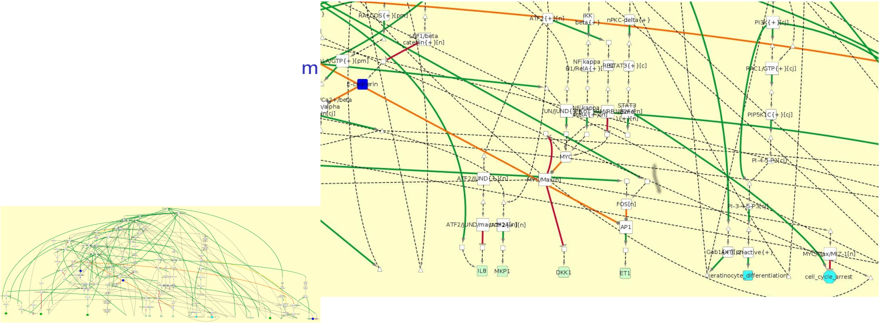
RSTC Network

multi-layer receptor-signaling-transcription-cell state



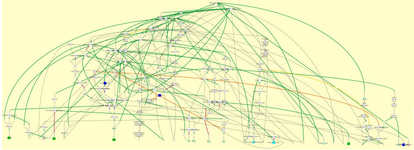
- Pathway Interaction Database
- 293 nodes: signaling proteins, transcription factors, mRNA expressions
- 375 interactions: activations, inhibitions, complexes dissociation

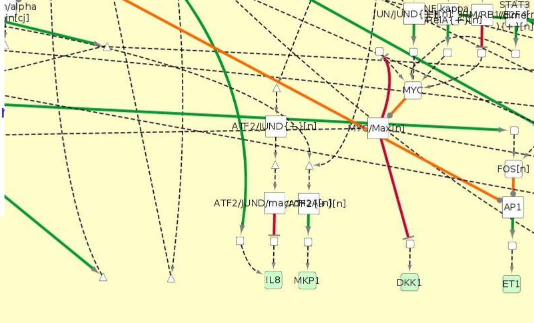
◦ Parameters estimation from time-series data



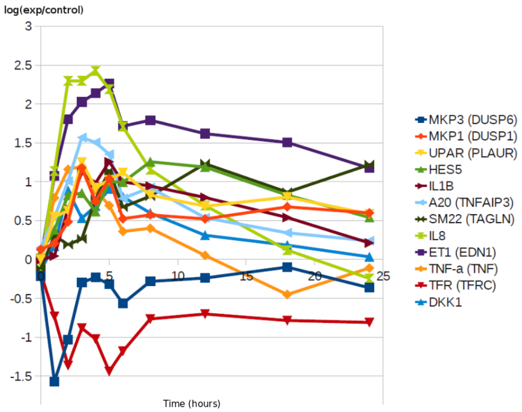
◦ Parameters estimation from time-series data

multi-layer r



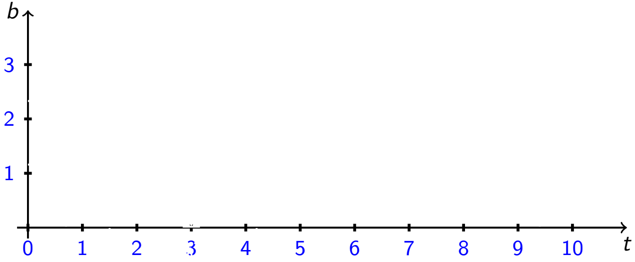


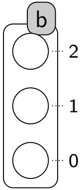
Time series data



- Experiment: calcium stimuli
- Measured at 10 time-points(0-24hrs)
- 200 transcripts selected (dynamic patterns)
- We included in our model a subset of 12 of them

Data estimation from TSD





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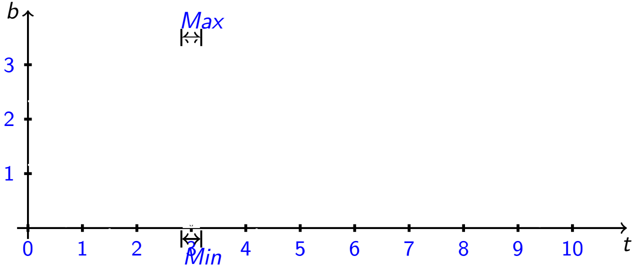

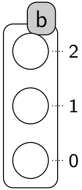

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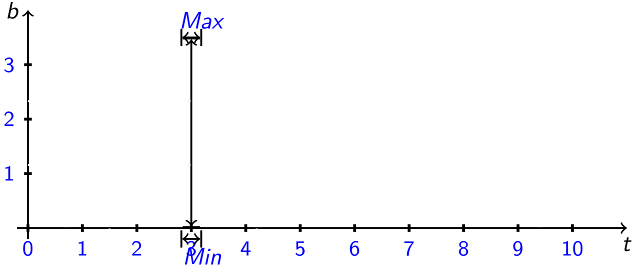

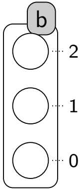

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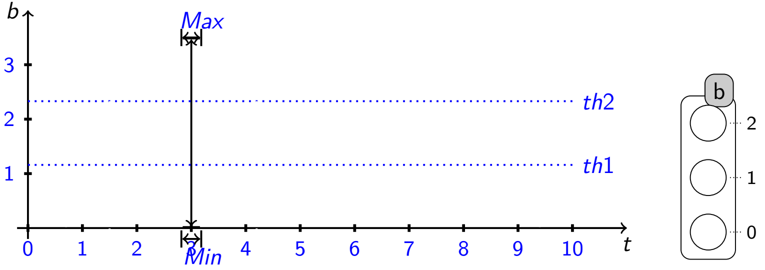

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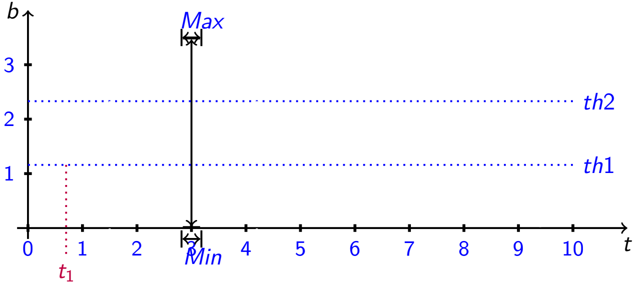
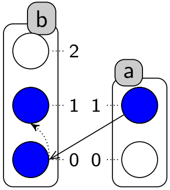
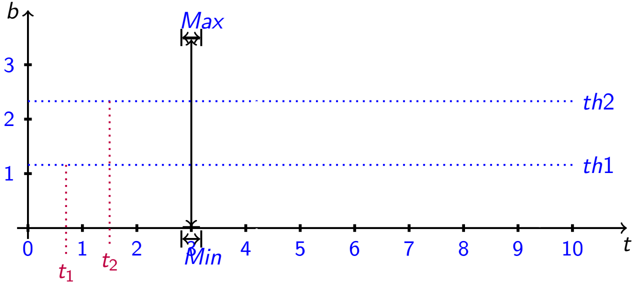
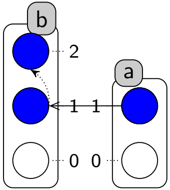




$a_1 b_0 b_1$ with $r_1 = \frac{1}{t_1 - t_0}$

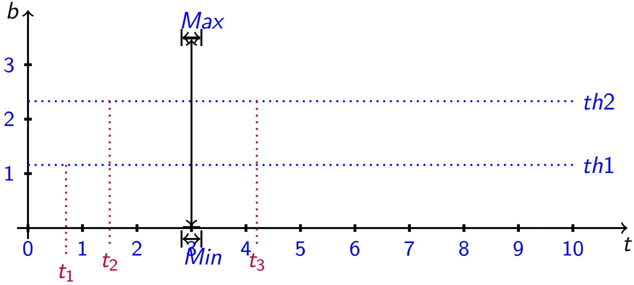
Data estimation from TSD

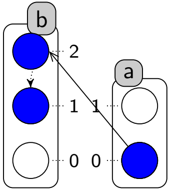




$a_1 b_0 b_1$ with $r_1 = \frac{1}{t_1 - t_0}$
$a_1 b_1 b_2$ with $r_2 = \frac{1}{t_2 - t_1}$

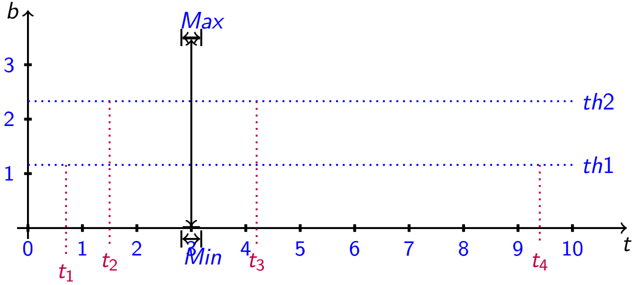
Data estimation from TSD

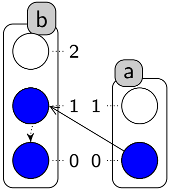




$a_1\,b_0\,b_1$ with $r_1 = \frac{1}{t_1 - t_0}$
$a_1\,b_1\,b_2$ with $r_2 = \frac{1}{t_2 - t_1}$
$a_0\,b_2\,b_1$ with $r_3 = \frac{1}{t_3 - t_2}$

Data estimation from TSD

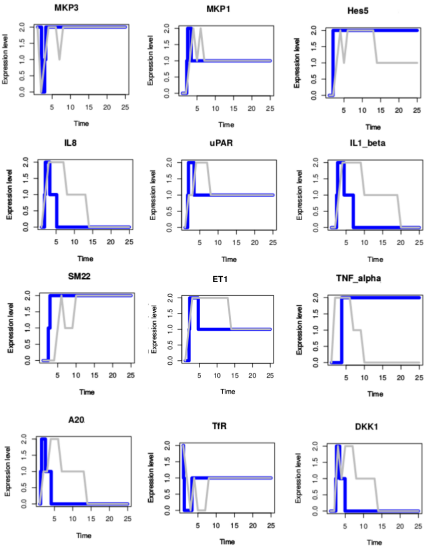




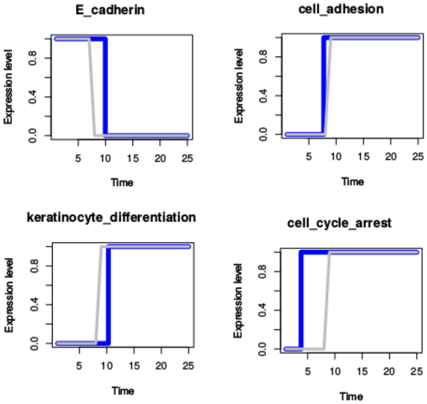
$a_1\, b_0\, b_1$ with $r_1 = \frac{1}{t_1 - t_0}$
$a_1\, b_1\, b_2$ with $r_2 = \frac{1}{t_2 - t_1}$
$a_0\, b_2\, b_1$ with $r_3 = \frac{1}{t_3 - t_2}$
$a_0\, b_1\, b_0$ with $r_4 = \frac{1}{t_4 - t_3}$

The formula to estimate the rate of the dynamics of a component according to it TSD is $r_i = \frac{1}{t_i - t_{i-1}}$

Simulations and analysis



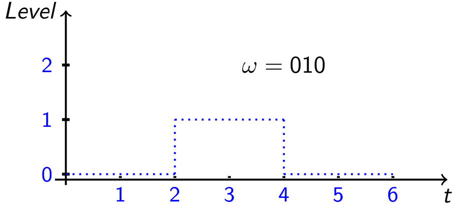
Simulations and analysis

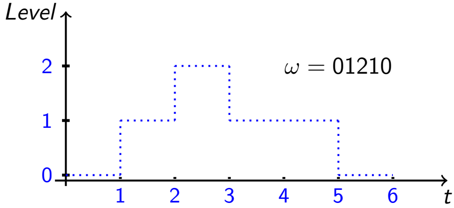


Simulations

- Input node of the system (E_cadherin)
- For biological processes (Cell adhesion, Cell cycle arrest, Keratinocyte differentiation)

Simulation and Trace analysis





for each component C_i, $1 \leq i \leq P$, N simulations will generate $\omega_{i1}, \omega_{i2}, \ldots, \omega_{iN}$ words.

for $1 \leq j \leq N$

$$\omega_{ij} \Rightarrow \boxed{\mathcal{A}_{C_i}} \Rightarrow yes/no$$

$$\%ofAcceptance = \frac{YES}{Simulations}$$

Simulation and Trace analysis

Automate	components	% validation	% of acceptance T_1
$\mathcal{A}_2(01210)$	A20	91	100
$\mathcal{A}_2(01210)$	IL1_beta	81	100
$\mathcal{A}_2(01210)$	IL8	93	100
$\mathcal{A}_2(01210)$	TNF_alpha	0	0
$\mathcal{A}_3(01211)$	uPar	76	99
$\mathcal{A}_3(01211)$	ET1	8	19
$\mathcal{A}_4(0121210)$	DKK1	13	43
$\mathcal{A}_5(0121211)$	Hes5	0	17
$\mathcal{A}_5(0121211)$	MKP1	9	97
$\mathcal{A}_6(0212)$	SM22	11	100
$\mathcal{A}_7(02010)$	MKP3	11	98
$\mathcal{A}_8(02121)$	Tfr	0	94

Formal inference of parameters

Discussion

PACS Meeting

Parameters synthesis by using abstract interpretation in Parametric Stochastic Automata Networks

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Thank you for your attention!!!