Journées Starting Block - CRIStAL — 2020-09-15

BioComputing

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CRIStAL
Centre de Recherche en Informatique, Signal et Automatique de Lille

Université de Lille
cnrs
centralelille

Centrale Nantes PhD thesis	2011 2014	
Univ Kassel postdoc	2014 2015	
Univ Nice ATER	2015 2016	
Univ Nantes ATER	2016 2017	
Univ Rennes postdoc	2017 2018	
CNRS/LS2N postdoc	2018 2019	
Centrale Lille **maître de conférences**	2019 ⋮	

Analysis of the Dynamics

Efficient reachability analysis

Dynamical patterns enumeration

Hepatocellular carcinoma progression

Machine Learning

Constraints on hybrid parameters

Learning models from time series data

Cerebral aneurysms & Myopathy

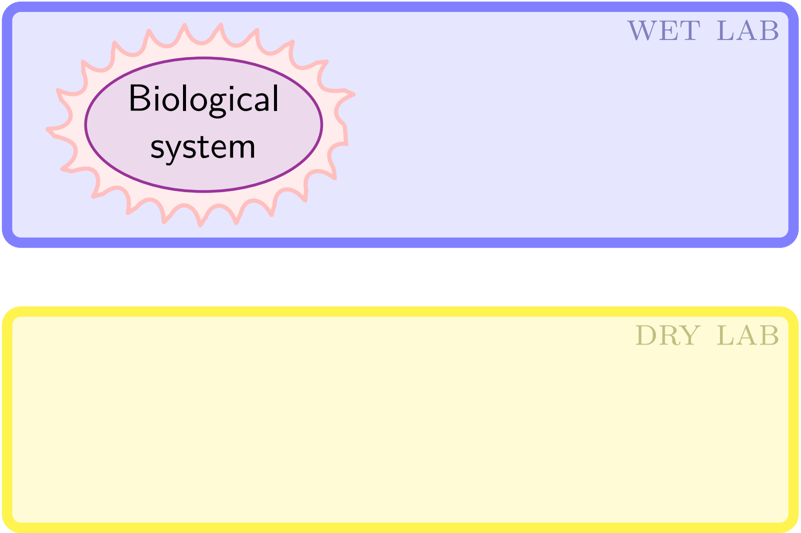
New projects

Diabetes Understanding & Prediction

Marine ecological systems (algae)

The Modeling Problem

Experiments *in silico*



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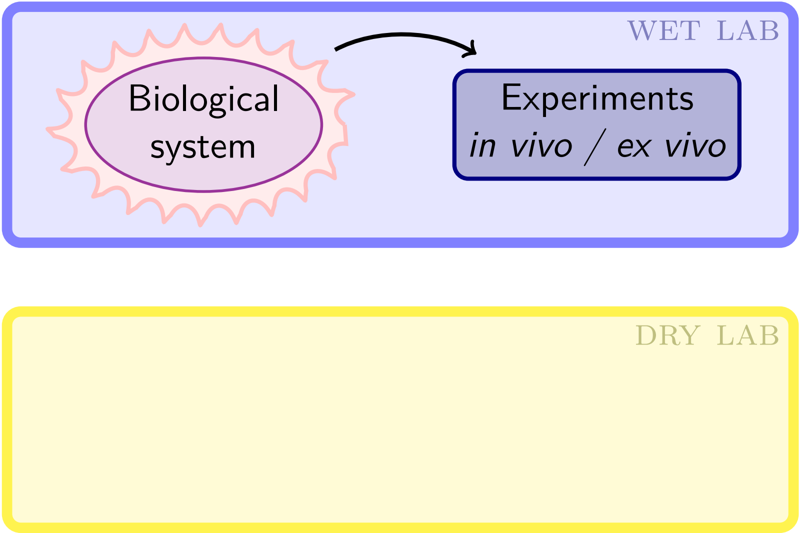

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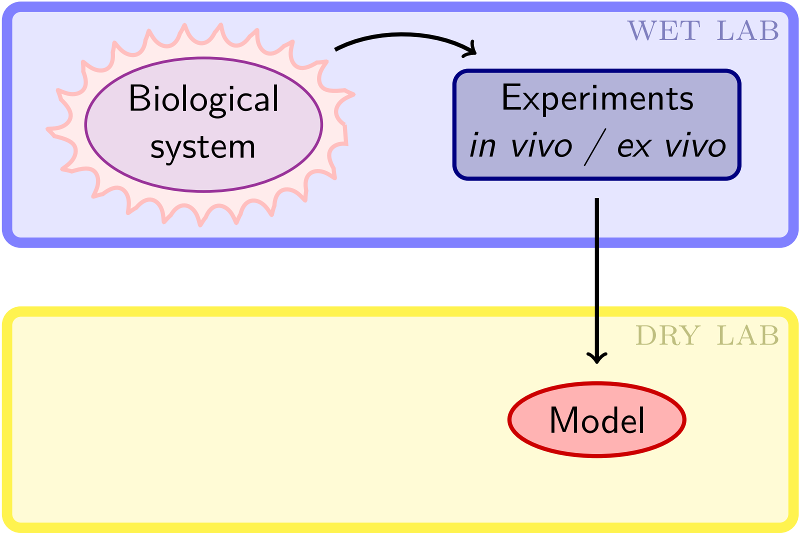

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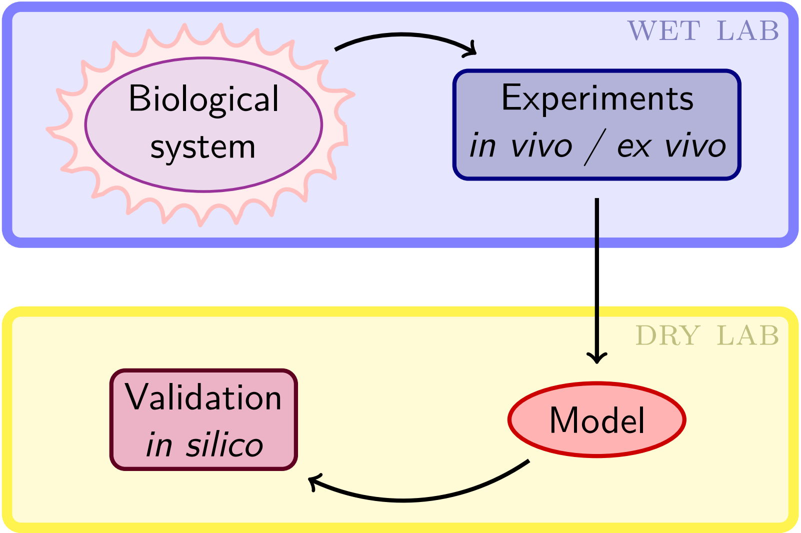

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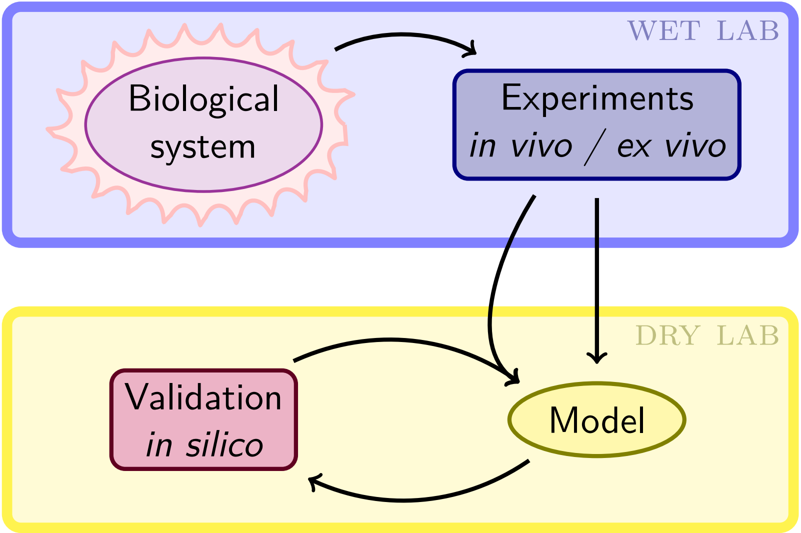

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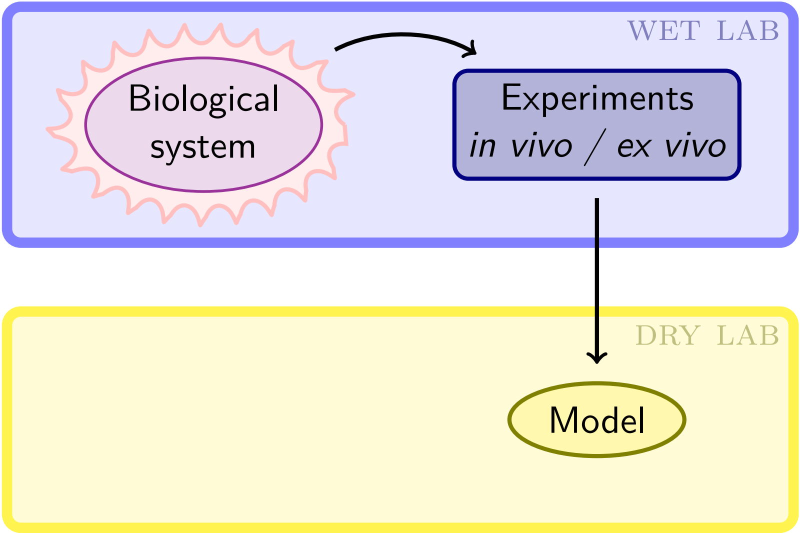

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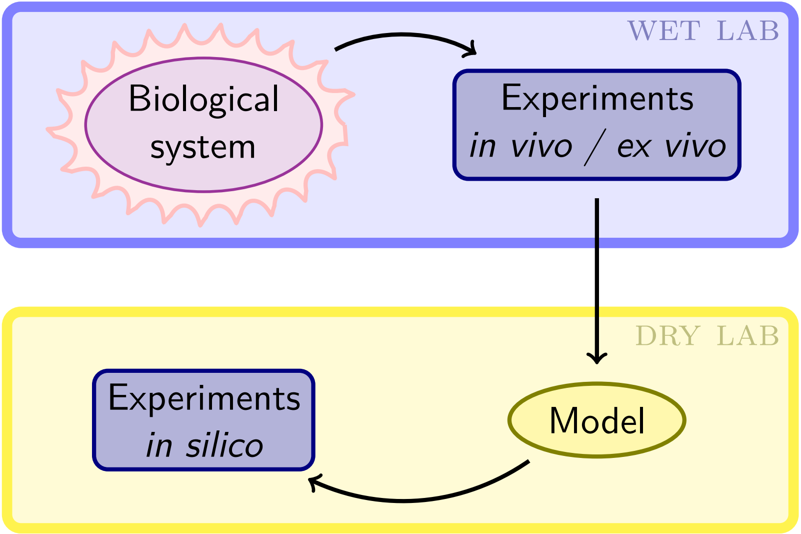

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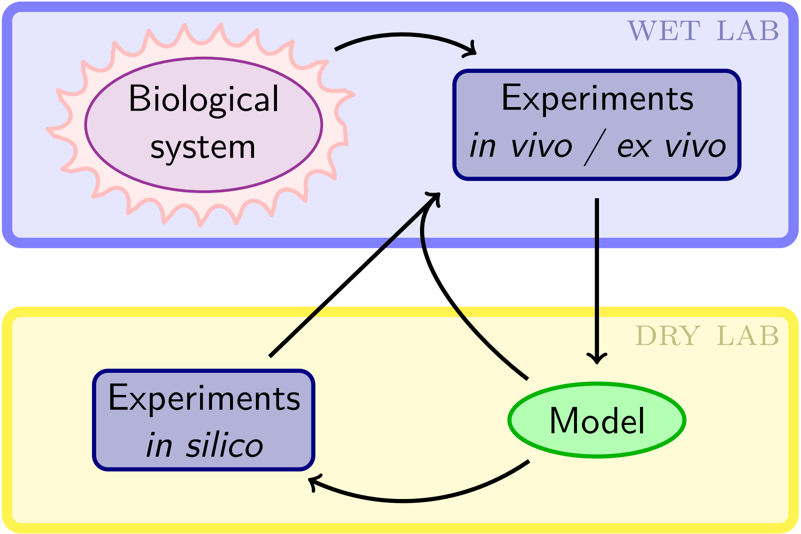

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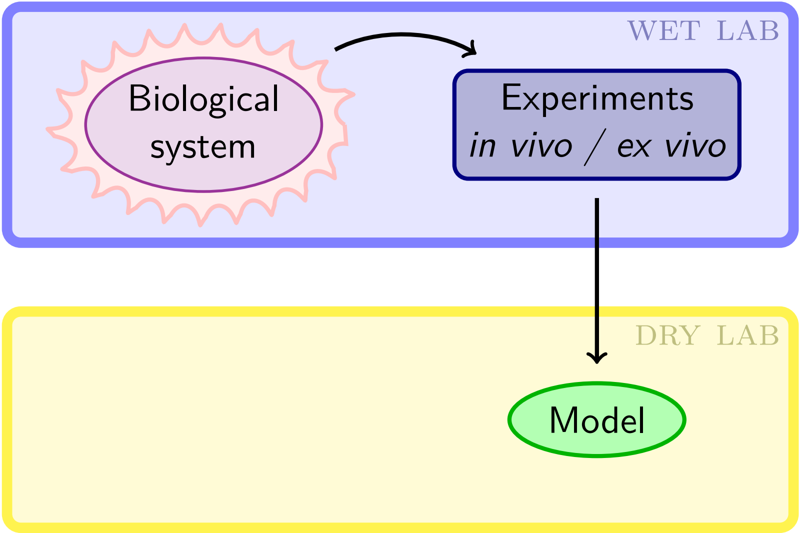

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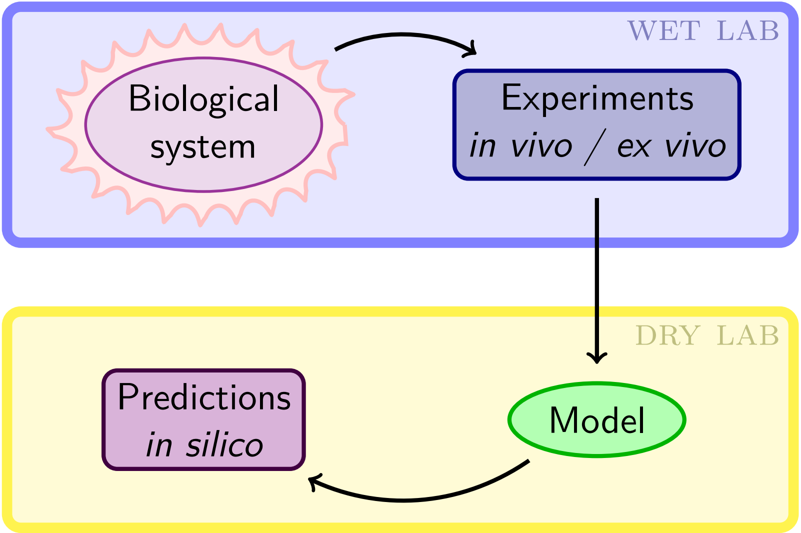

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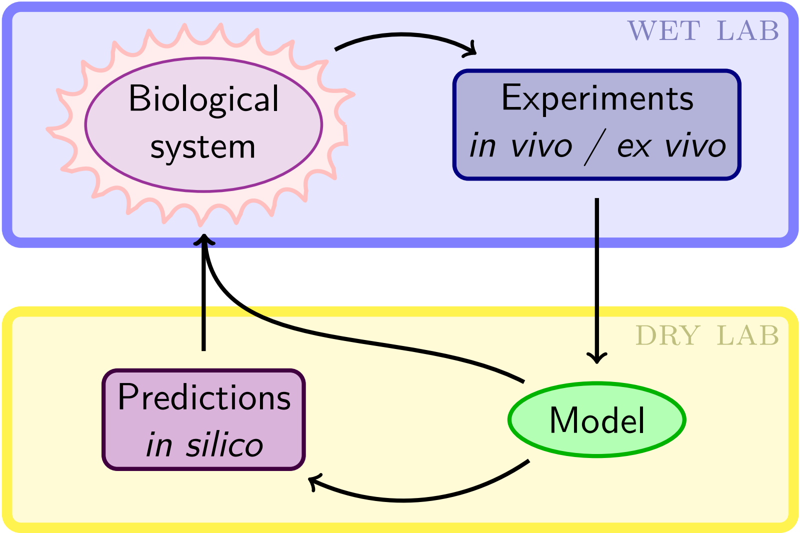
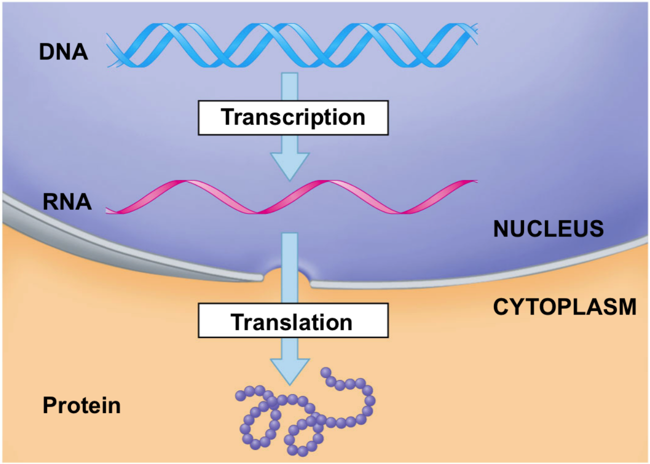


Preliminary Abstraction



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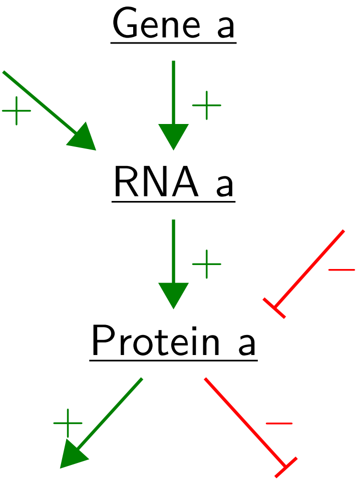

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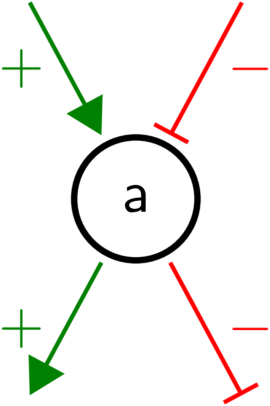
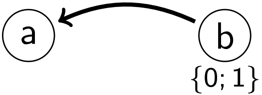
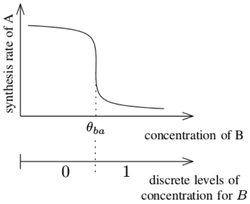


Discretization and Asynchronism

[Richard *et al.*, 2008]





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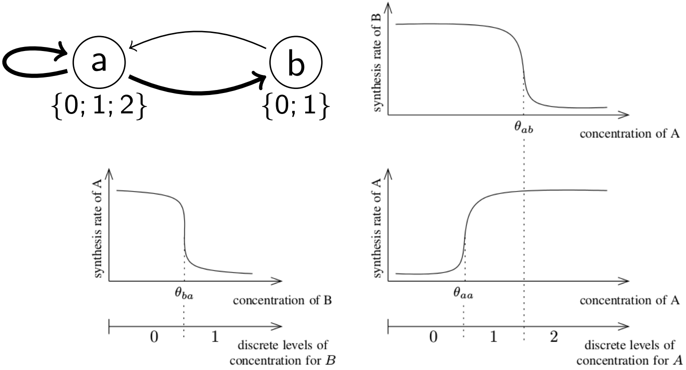
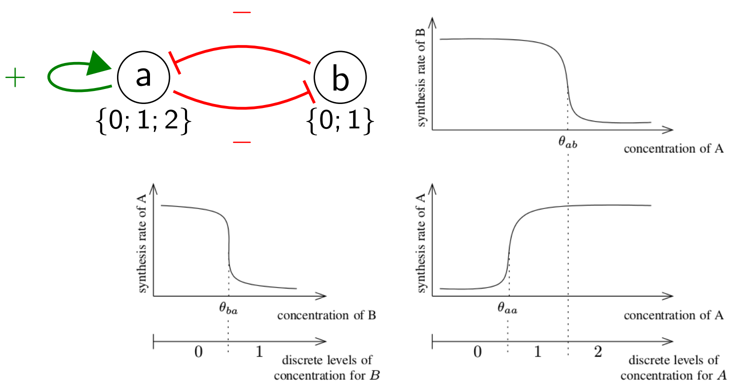


- **Discrete** levels and thresholds

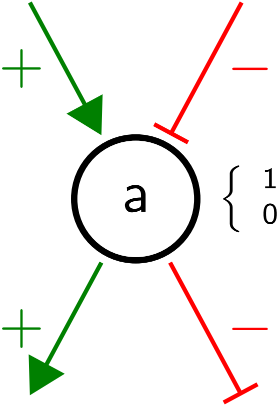
Discretization and Asynchronism

[Richard *et al.*, 2008]



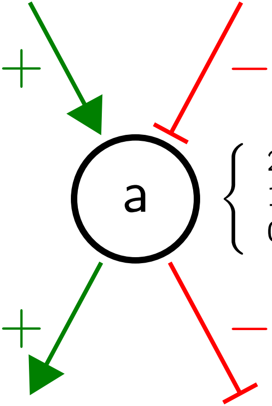
- **Discrete** levels and thresholds
- **Nature** of interactions

Preliminary Abstraction



$$\left\{ \begin{array}{l} 1 = \text{active} \\ 0 = \text{inactive} \end{array} \right\}$$

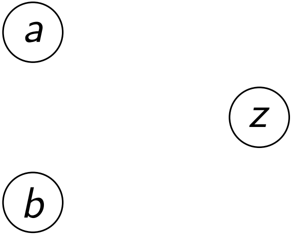
Preliminary Abstraction



$$\left\{ \begin{array}{l} 2 = \text{saturation} \\ 1 = \text{traces} \\ 0 = \text{complete degradation} \end{array} \right\}$$

Discrete Networks / Thomas Modeling

[Kauffman, *Journal of Theoretical Biology*, 1969]
[Thomas, *Journal of Theoretical Biology*, 1973]



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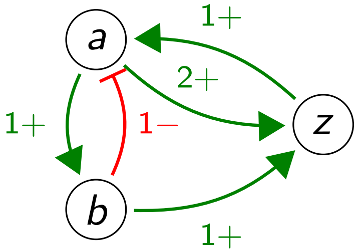


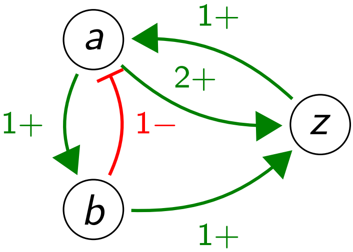
Discrete Networks / Thomas Modeling

[Kauffman, *Journal of Theoretical Biology*, 1969]
[Thomas, *Journal of Theoretical Biology*, 1973]

a	f^b
0	**0**
1	**1**
2	**1**

z	b	f^a
0	0	**1**
0	1	**0**
1	0	**1**
1	1	**2**

a	b	f^z
0	0	**0**
0	1	**0**
1	0	**0**
1	1	**0**
2	0	**0**
2	1	**1**

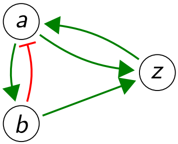


State-graph

The state-graph depicts explicitly the whole dynamics

abz

000	010	001	011
100	110	101	111
200	210	201	211



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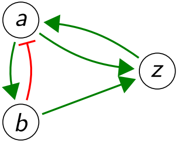
abz			
000	010	001	011
$100 \longrightarrow$	110	101	111
200	210	201	211



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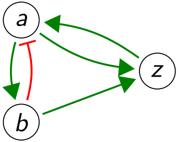
$$\begin{array}{cccc} 000 & 010 & 001 & 011 \\ & \uparrow & & \\ 100 \longrightarrow & 110 & 101 & 111 \\ & & & \\ 200 & 210 & 201 & 211 \end{array}$$



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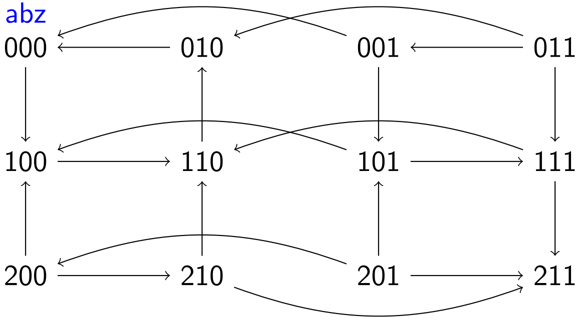

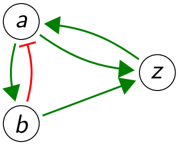

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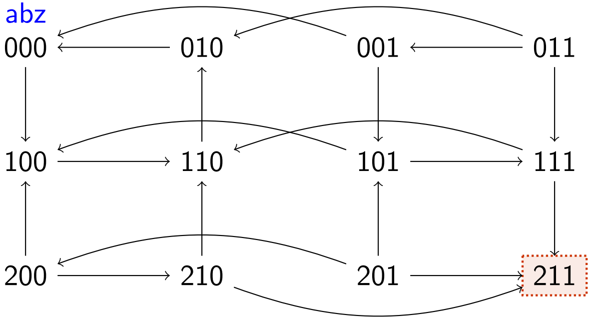
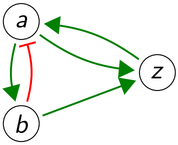
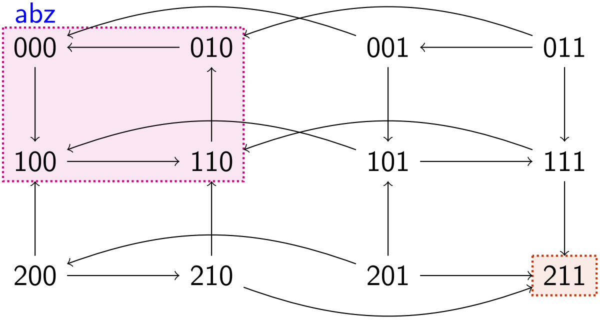


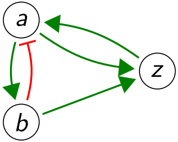


- **Stable state** = state with no successors

State-graph

The state-graph depicts explicitly the whole dynamics





- **Stable state** = state with no successors
- **Complex attractor** = minimal loop or composition of loops from which the dynamics cannot escape

State-graph

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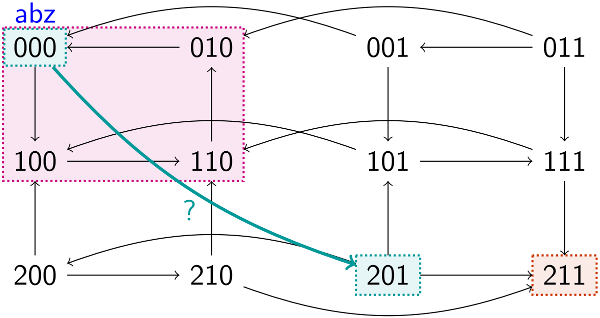
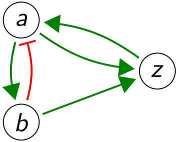
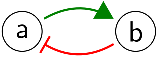




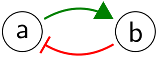
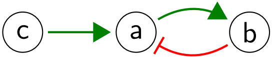
- **Stable state** = state with no successors
- **Complex attractor** = minimal loop or composition of loops from which the dynamics cannot escape
- **Reachability** = from **201**, can I reach **000**?

Analysis of Big Models

Combinatorial explosion

Model	Possible states
	4
	8
	16
⋮	⋮
(10)	1024
(20)	1048576
(100)	1267650600000000000000000000000

Combinatorial explosion

Model	Possible states
	4
	8
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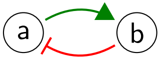
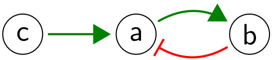
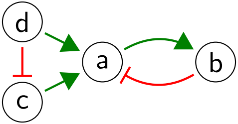
Combinatorial explosion

Model	**Possible states**
	4
	8
	16
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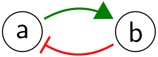
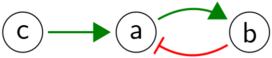
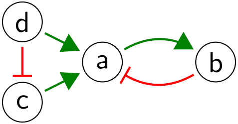
	4
	8
	16
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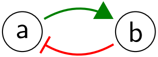
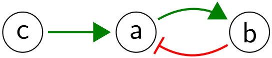
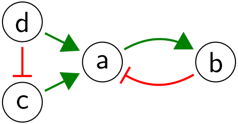
	4
	8
	16
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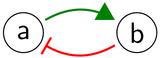
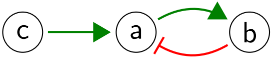
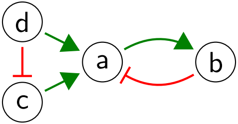
	4
	8
	16
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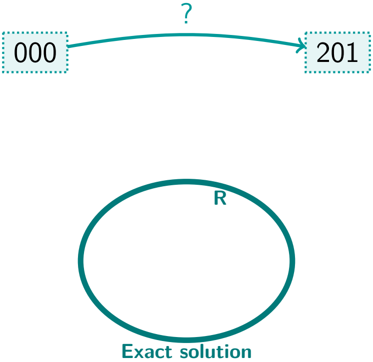
Approximation of the Dynamics

[Paulevé *et al.*, *Mathematical Structures in Computer Science*, 2012]
[Folschette *et al.*, *Theoretical Computer Science*, 2015a]



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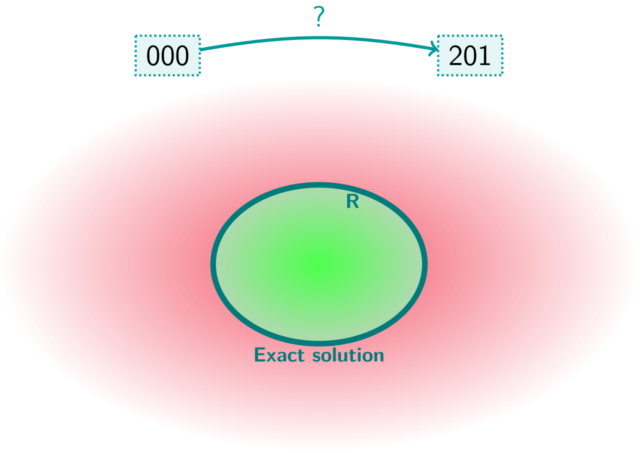

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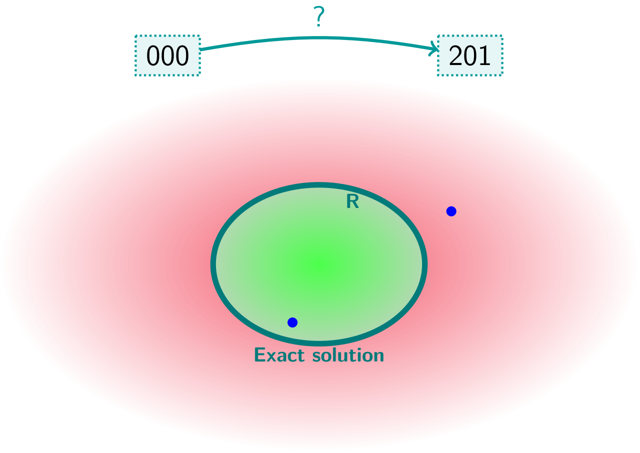

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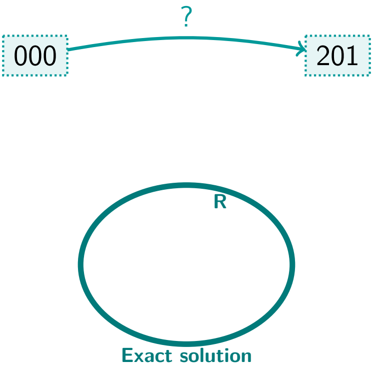

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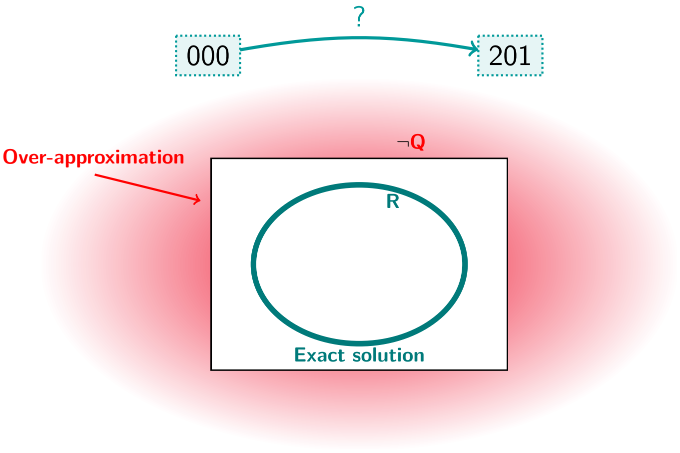

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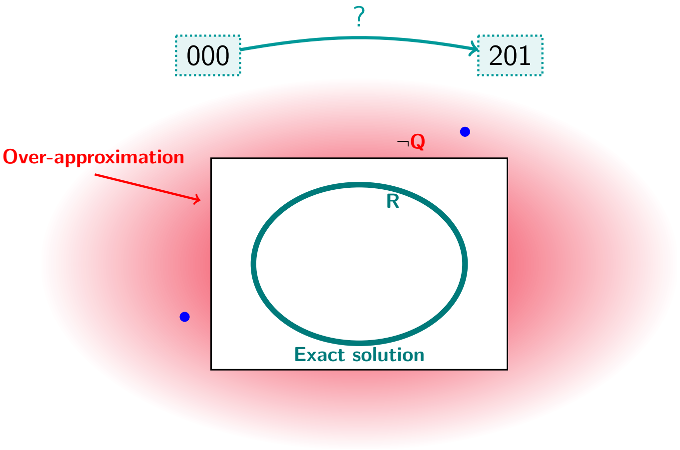

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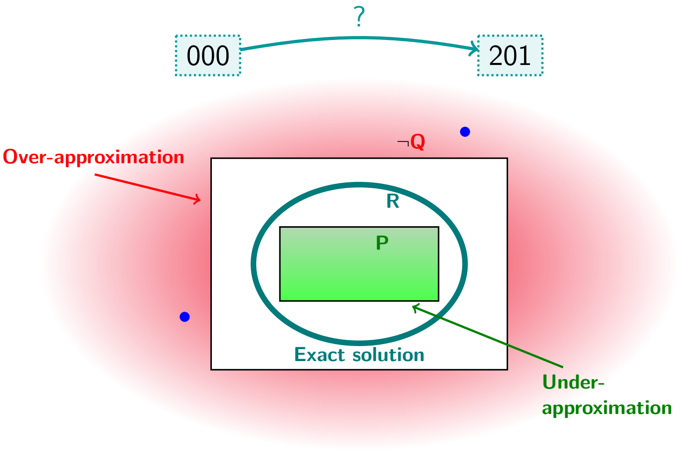

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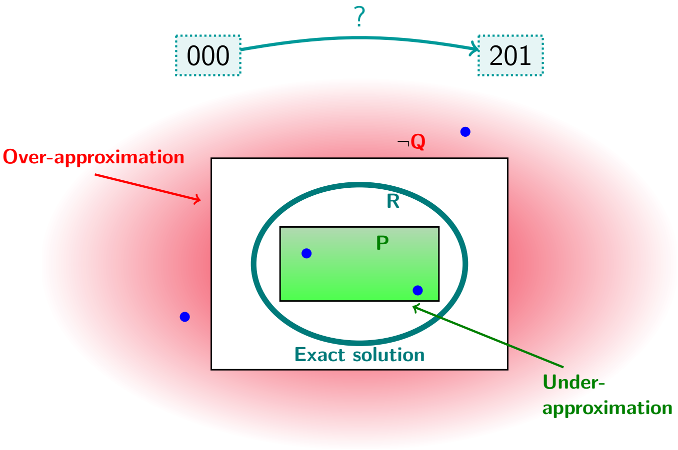

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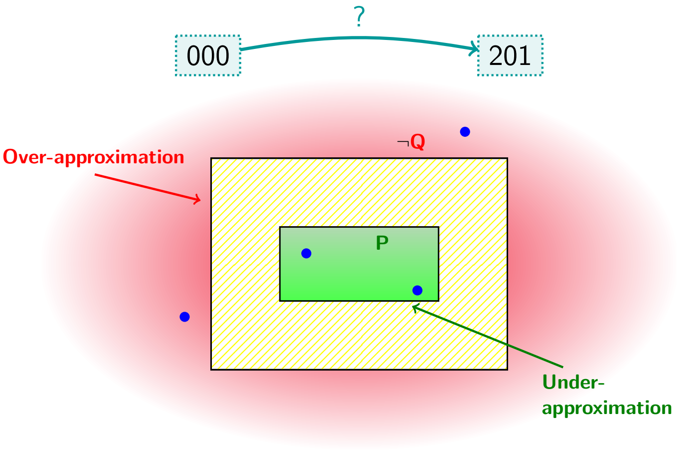

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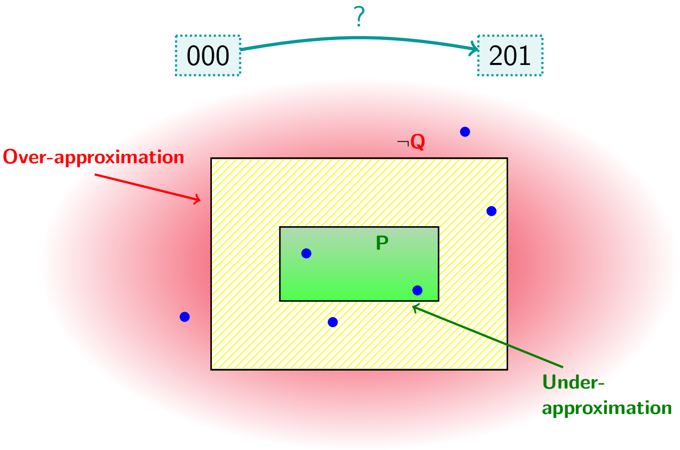
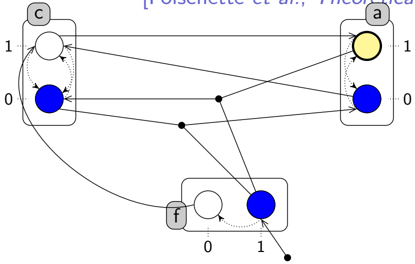


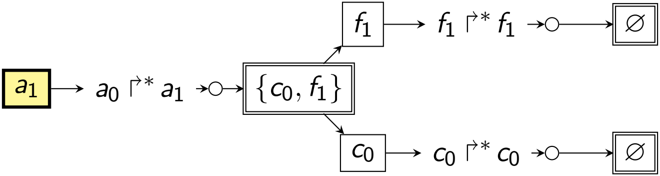
Approximation of the Dynamics

[Folschette *et al.*, *Theoretical Computer Science*, 2015b]



Sufficient condition:

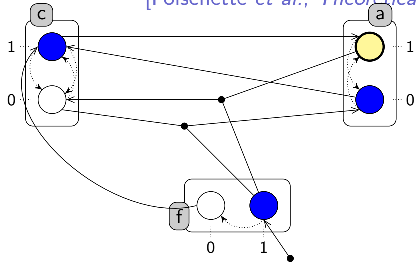
- No cycle
- No conflict
- All leaves are $\boxed{\varnothing}$



P is true $\Rightarrow$ **R** is true

Approximation of the Dynamics

[Folschette *et al.*, *Theoretical Computer Science*, 2015b]



Sufficient condition:

- No cycle
- No conflict
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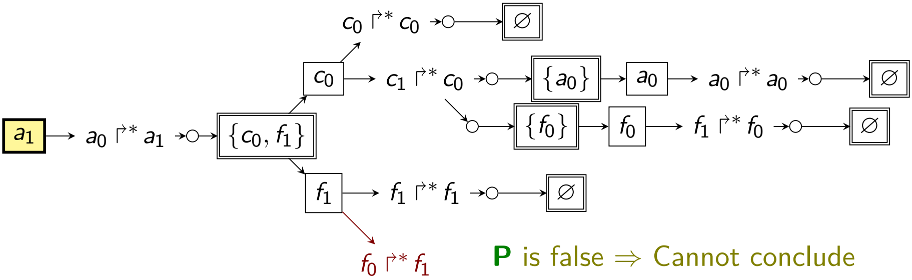
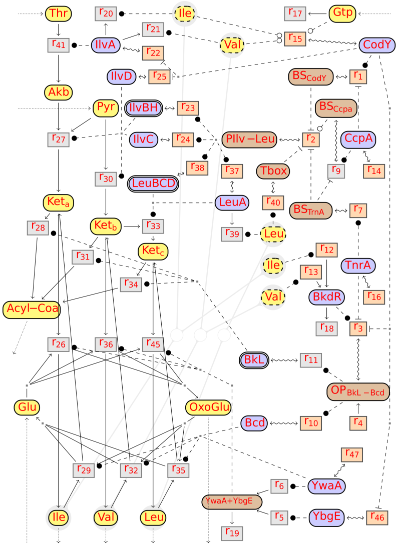


P is false $\Rightarrow$ Cannot conclude

Leucine Reaction Network

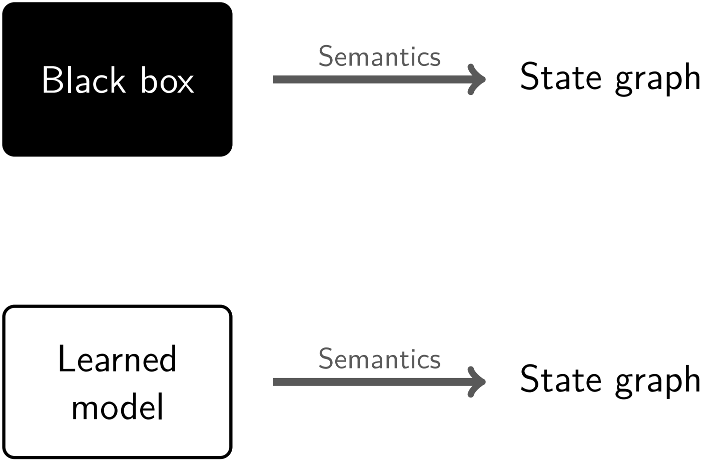
[Allart *et al.*, *Computational Methods in Systems Biology*, 2019]



Machine Learning

Learning Models from Execution Traces

[Ribeiro *et al.*, *Inductive Logic Programming*, 2018] (ACEDIA)
[Ribeiro *et al.*, *Inductive Logic Programming*, 2017] (GULA)



Learning Models from Execution Traces

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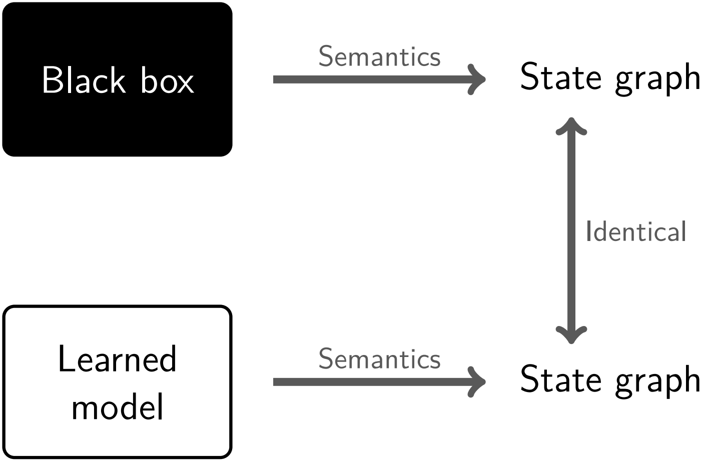

Learning Models from Execution Traces

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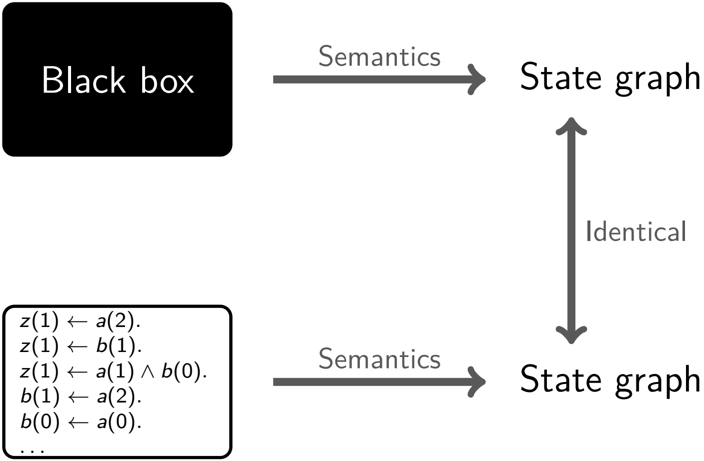
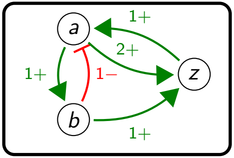


Learning Models from Execution Traces

[Ribeiro *et al.*, *Inductive Logic Programming*, 2018] (ACEDIA)
[Ribeiro *et al.*, *Inductive Logic Programming*, 2017] (GULA)

Black box $\xrightarrow{\text{Semantics}}$ State graph

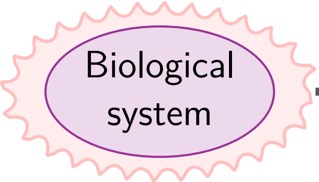
Identical



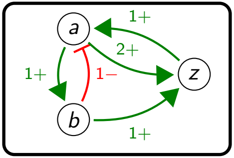
$\xrightarrow{\text{Semantics}}$ State graph

Learning Models from Execution Traces

[Ribeiro *et al.*, *Inductive Logic Programming*, 2018] (ACEDIA)
[Ribeiro *et al.*, *Inductive Logic Programming*, 2017] (GULA)



Semantics → State graph



Semantics → State graph

Learning Models from Execution Traces

[Ribeiro *et al.*, *Inductive Logic Programming*, 2018] (ACEDIA)
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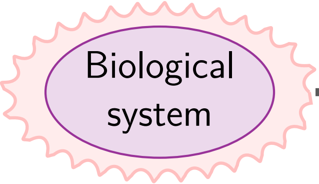
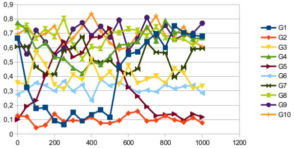
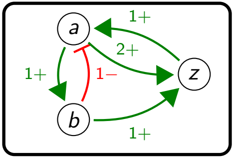


Semantics





Semantics

State graph

Learning Models from Execution Traces

[Ribeiro *et al.*, *Inductive Logic Programming*, 2018] (ACEDIA)
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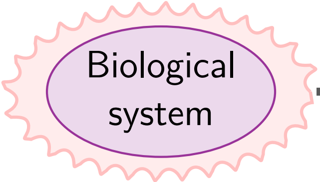
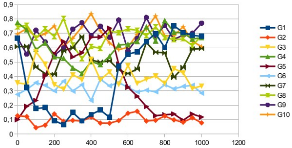
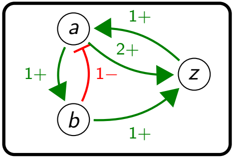


Semantics



Equivalent
(discretization)

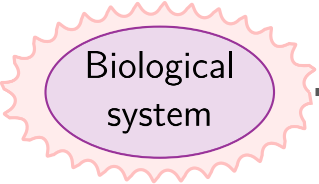


Semantics

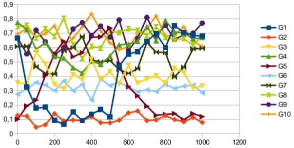
State graph

Learning Models from Execution Traces

[Ribeiro *et al.*, *Inductive Logic Programming*, 2018] (ACEDIA)
[Ribeiro *et al.*, *Inductive Logic Programming*, 2017] (GULA)

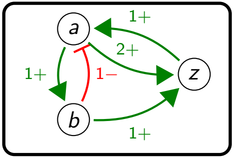


Semantics



No discretization
(ACEDIA)

Equivalent
(discretization)

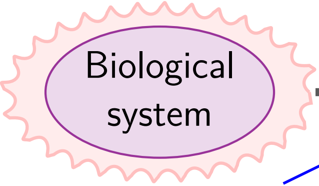


Semantics

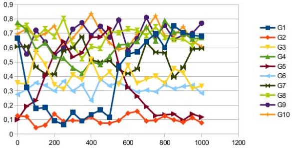
State graph

Learning Models from Execution Traces

[Ribeiro *et al.*, *Inductive Logic Programming*, 2018] (ACEDIA)
[Ribeiro *et al.*, *Inductive Logic Programming*, 2017] (GULA)



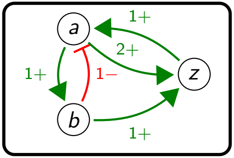
Semantics



Unknown semantics (GULA)

No discretization (ACEDIA)

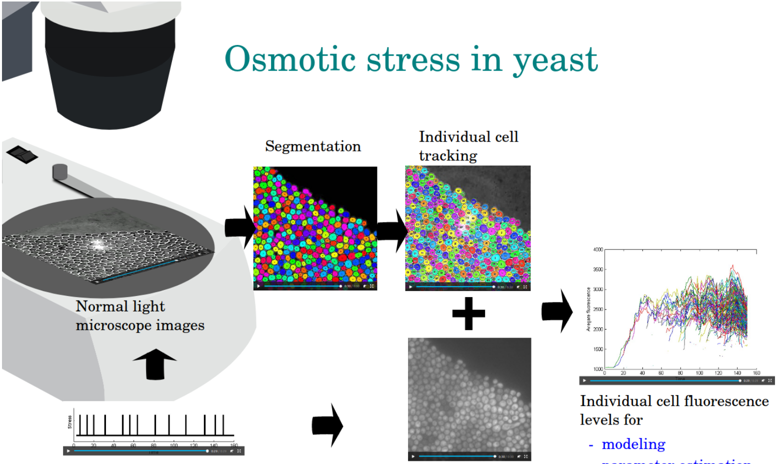
Equivalent (discretization)



Semantics

State graph

Osmotic stress in yeast

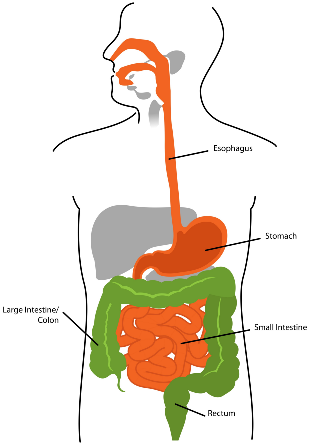


Osmotic stress = temporary addition of salt to solution thanks to microfluidic device

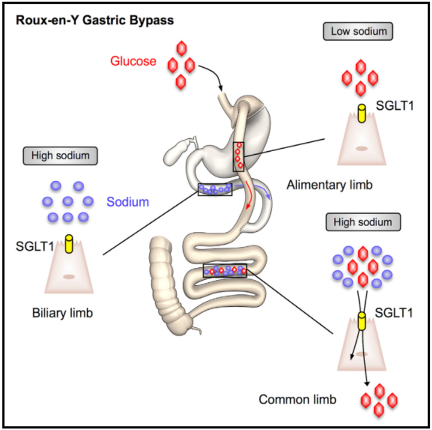
Modeling of Diabetes

Gastro-Intestinal Anatomy

[https://foodandhealth.com/digestive-diseases-awareness/]
[Baud *et al.*, *Cell Metabolism*, 2016]



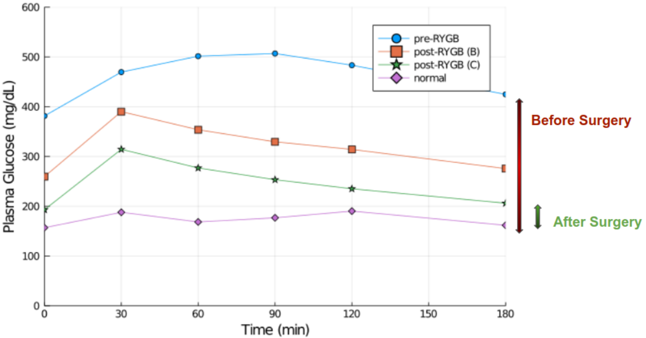
Gastro-intestinal anatomy



Roux-En-Y Gastric Bypass

Effects of Bariatric Surgery

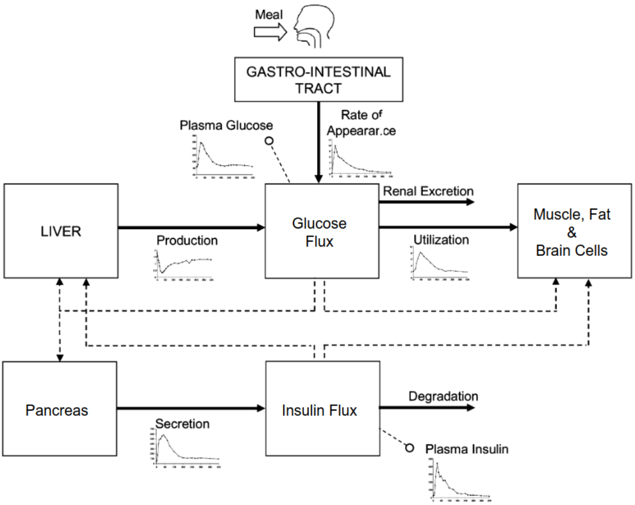
Courtesy of Pattou and coll.



Glucose homeostasis restored by bariatric surgery

Glucose Flux

[Dalla Man *et al.*, *IEEE Transactions on Biomed. Eng.*, 2007]



Discussion