CRIEC 2013

The Process Hitting framework: a qualitative Bio-informatics modelling

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Context and Aims

MeForBio team:
Qualitative modelling to study
complex dynamical biological systems

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   Efficient methods thanks to the **Process Hitting** framework

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3) What for?

   Understanding leads to **solutions**

What is Bio-informatics?

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- Sequencing
- Gene regulations
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- Experiments
- ...

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    - Algebraic/qualitative
    - Hybrid
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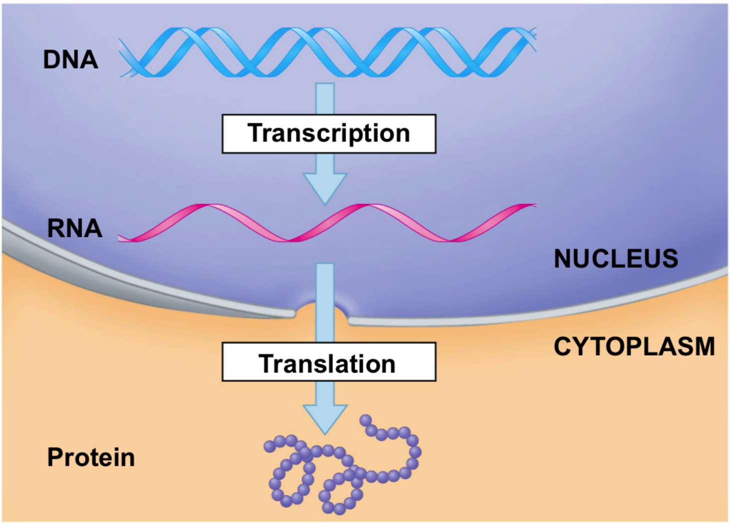
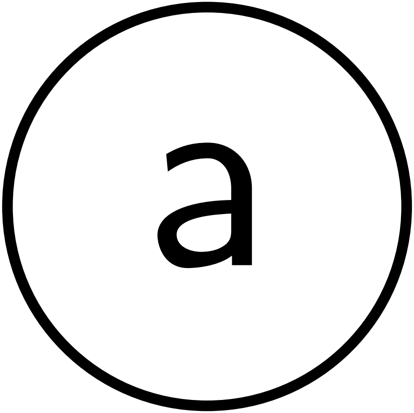
Gene regulations



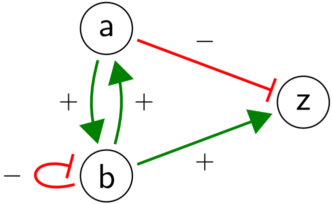
Gene regulations



Usual biological algebraic models

[De Jong, *Journal of Computational Biology*, 2002]

Modelling interacting genes/proteins:



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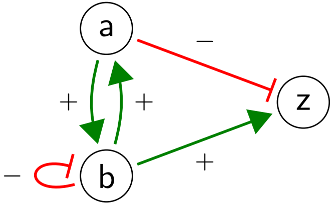
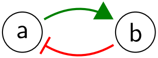


Questions:

- How does ⓩ **behave**?
- Is it **possible** to make ⓐ inactive?
- If I **knock-out** ⓑ, what changes?

What do I do?

→ Problem: easy to understand but hard to study (**exponential**)

Model	**Possible configs**
	4

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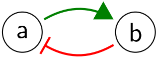
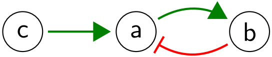
	4
	8

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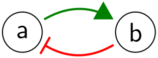
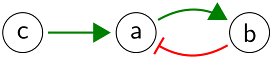
	4
	8
⋮	⋮
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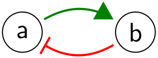
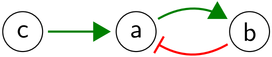
	4
	8
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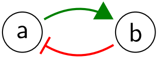
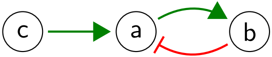
	4
	8
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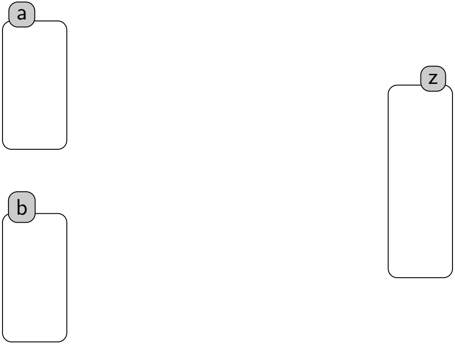
The Process Hitting modelling

[Paulevé *et al.*, *Transactions on Computational Systems Biology*, 2011]



Sorts: components *a*, *b*, *z*

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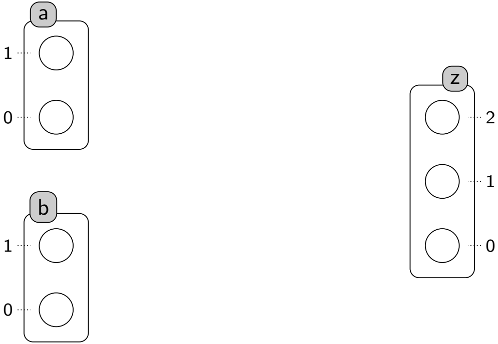

Sorts: components a, b, z

Processes: local states / levels of expression z_0, z_1, z_2

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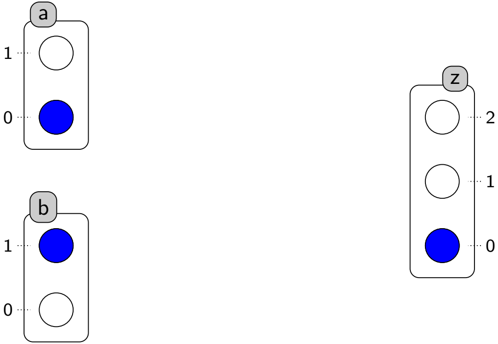

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States: sets of active processes $\langle a_0, b_1, z_0 \rangle$

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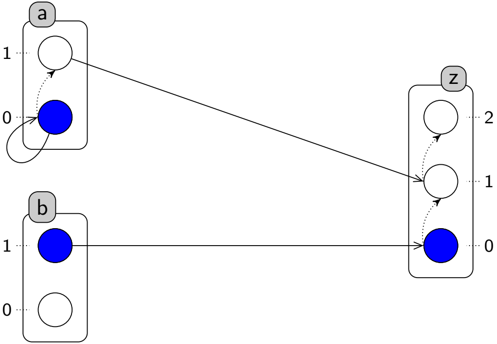

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Actions: dynamics $b_1 \rightarrow z_0 \upharpoonright z_1, a_0 \rightarrow a_0 \upharpoonright a_1, a_1 \rightarrow z_1 \upharpoonright z_2$

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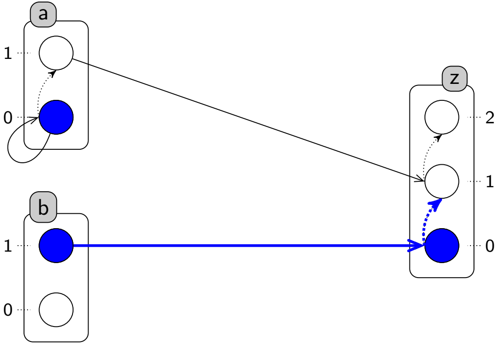

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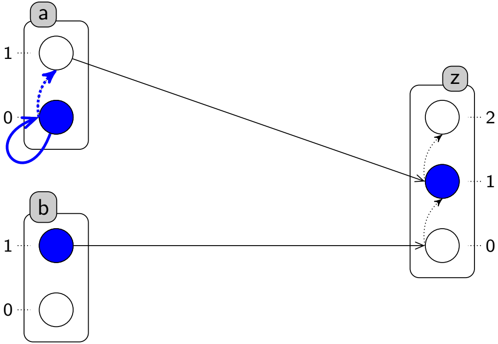

Sorts: components $a,\ b,\ z$

Processes: local states / levels of expression $z_0,\ z_1,\ z_2$

States: sets of active processes $\langle a_0, b_1, z_1 \rangle$

Actions: dynamics $b_1 \rightarrow z_0 \upharpoonright z_1,\ \underline{a_0 \rightarrow a_0 \upharpoonright a_1},\ a_1 \rightarrow z_1 \upharpoonright z_2$

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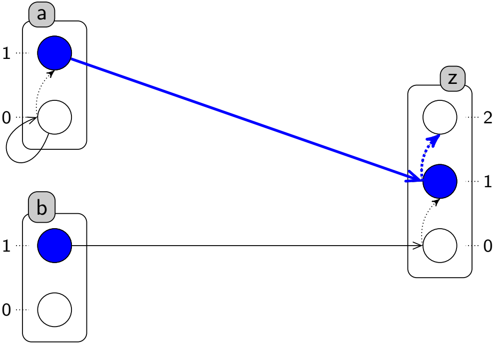

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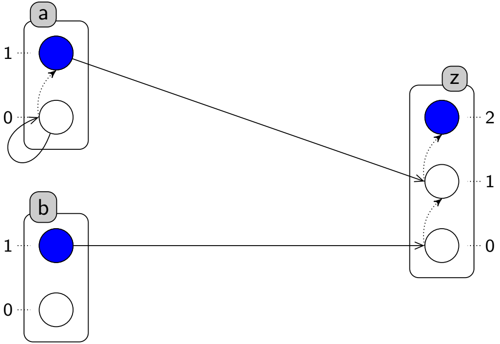

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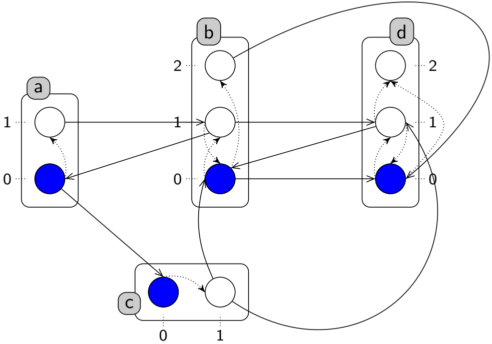
Static analysis: successive reachability

[Paulevé *et al.*, *Mathematical Structures in Computer Science*, 2012]



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$\langle a_1, b_0, c_0, d_0 \rangle$

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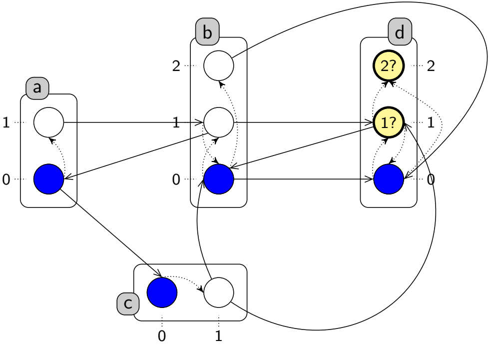

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$$\langle a_1, b_0, c_0, d_0 \rangle$$

- Objectives

$$[\ \Rsh d_1\ :: \Rsh d_2\ ]$$

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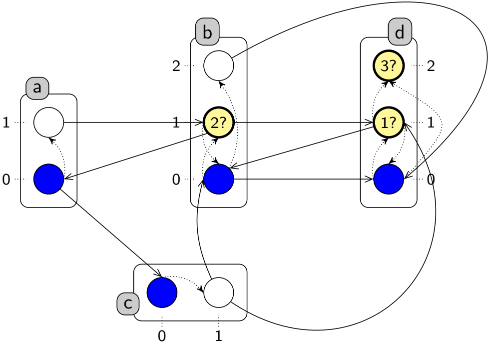

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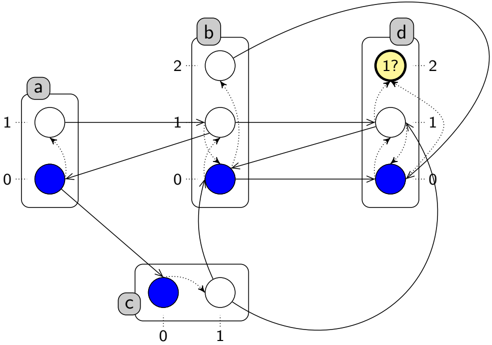

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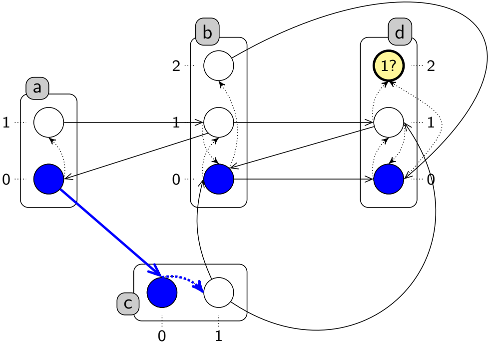

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$$[\ \Rsh d_1\ ::\ \Rsh d_2\ ]$$
$$[\ \Rsh d_1 :: \Rsh b_1 :: \Rsh d_2\ ]$$
$$[\ \Rsh d_2\ ]$$

→ Concretization of the objective = scenario

$$\underline{a_0 \rightarrow c_0 \Rsh c_1} :: b_0 \rightarrow d_0 \Rsh d_1 :: c_1 \rightarrow b_0 \Rsh b_1 :: b_1 \rightarrow d_1 \Rsh d_2$$

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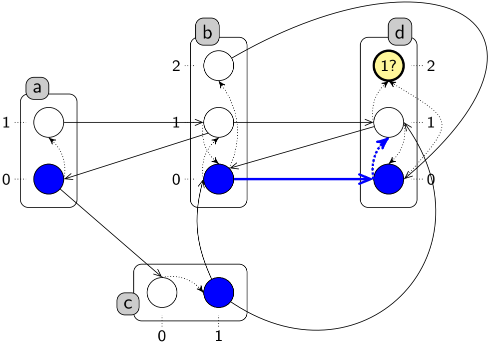

- Initial state

$$\langle a_1, b_0, c_0, d_0 \rangle$$

- Objectives

$$[\ \Rsh d_1\ :: \Rsh d_2\ ]$$
$$[\ \Rsh d_1 :: \Rsh b_1 :: \Rsh d_2\ ]$$
$$[\ \Rsh d_2\ ]$$

$\rightarrow$ Concretization of the objective = scenario

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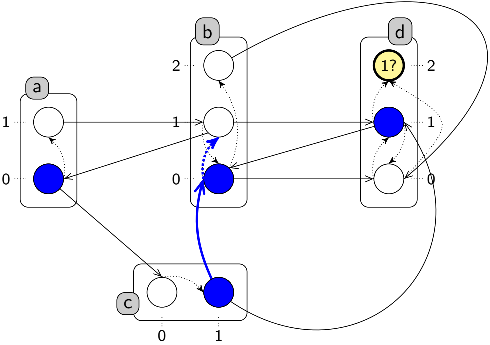

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$[\ \Rsh d_1 :: \Rsh d_2\ ]$

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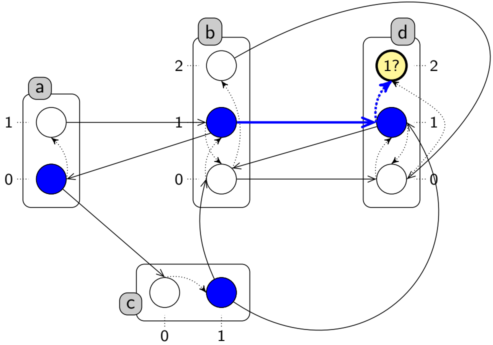

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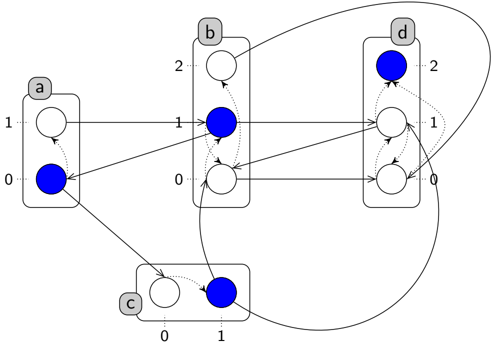

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Over- and Under-approximations

[Paulevé *et al.*, *Mathematical Structures in Computer Science*, 2012]

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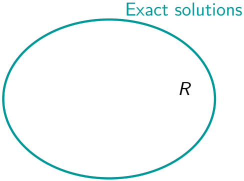
- → Rather check **approximations** P and Q so that: $\underline{P \Rightarrow R \Rightarrow Q}$



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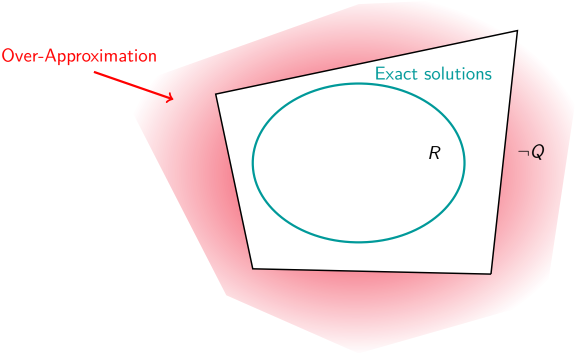

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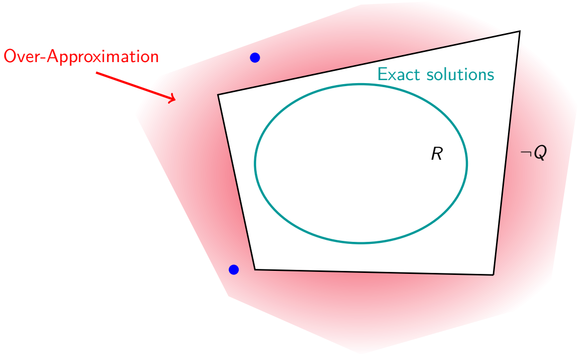

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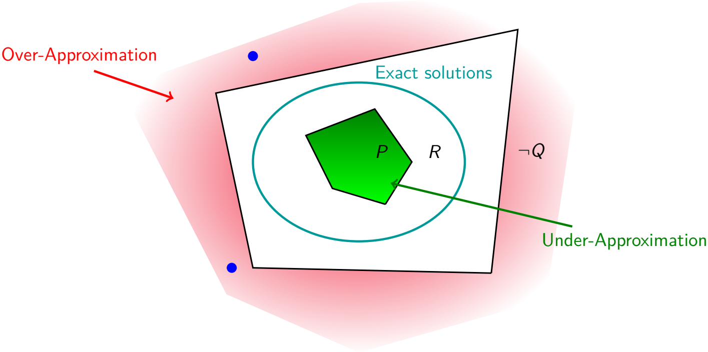

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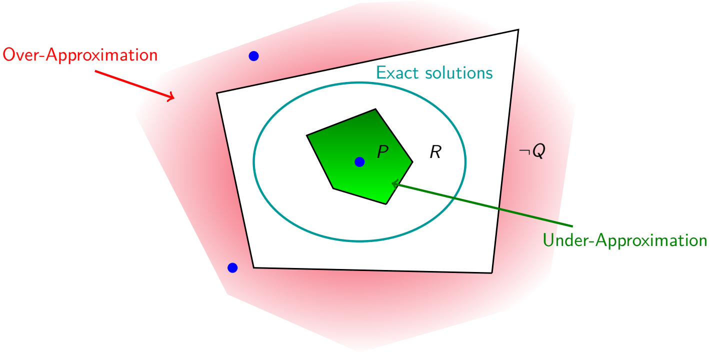

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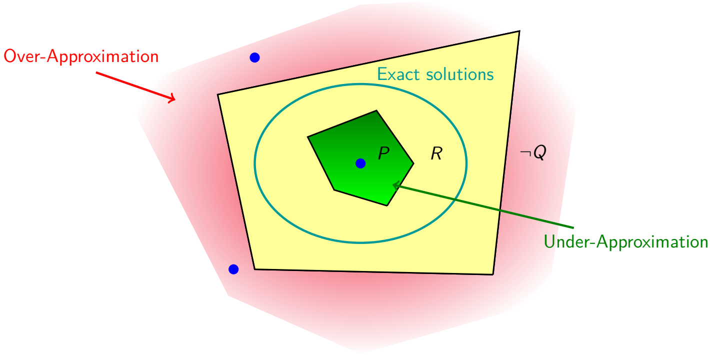

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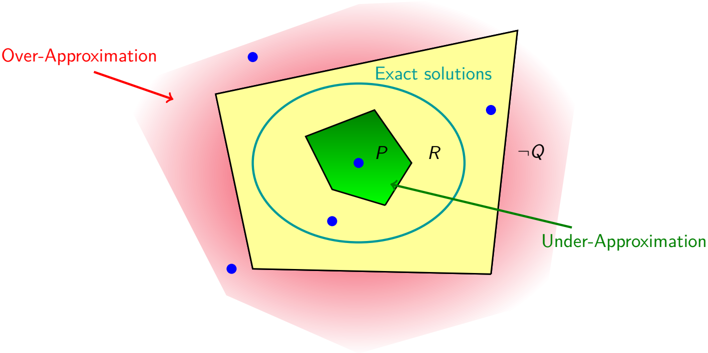

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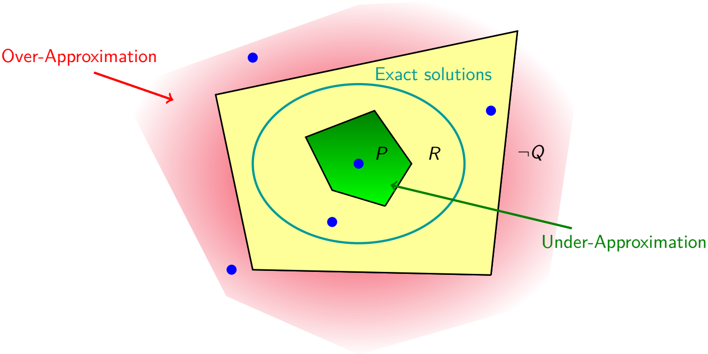
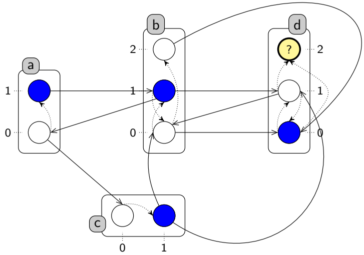
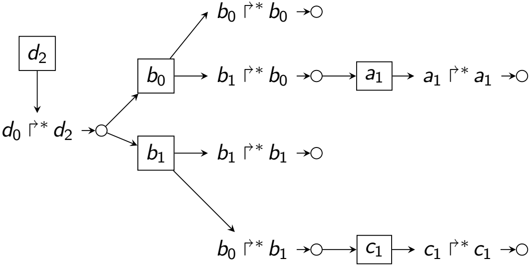


Computing P or Q is much simpler (roughly **polynomial**)

→ Efficient for big models → **Hundredths of seconds**

Under-approximation




$\boxed{d_2}$

$d_0 \Rsh^* d_2 \rightarrow \bigcirc$

$\boxed{b_0}$

$b_0 \Rsh^* b_0 \rightarrow \bigcirc$

$b_1 \Rsh^* b_0 \rightarrow \bigcirc \longrightarrow \boxed{a_1} \longrightarrow a_1 \Rsh^* a_1 \rightarrow \bigcirc$

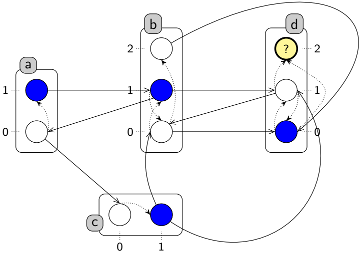
$\boxed{b_1}$

$b_1 \Rsh^* b_1 \rightarrow \bigcirc$

$b_0 \Rsh^* b_1 \rightarrow \bigcirc \longrightarrow \boxed{c_1} \longrightarrow c_1 \Rsh^* c_1 \rightarrow \bigcirc$

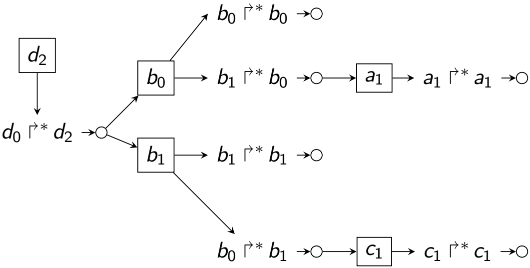
$\boxed{d_2}$	Required process
$d_0 \Rsh^* d_2$	Objective
○	Solution to an objective

Under-approximation



Sufficient condition:

- no cycle
- each objective has a solution



$\boxed{d_2}$

$d_0 \Rsh^* d_2 \rightarrow$ ○

$\boxed{b_0}$

$b_0 \Rsh^* b_0 \rightarrow$ ○

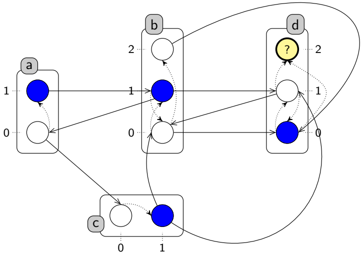
$b_1 \Rsh^* b_0 \rightarrow$ ○ $\rightarrow \boxed{a_1} \rightarrow a_1 \Rsh^* a_1 \rightarrow$ ○

$\boxed{b_1}$

$b_1 \Rsh^* b_1 \rightarrow$ ○

$b_0 \Rsh^* b_1 \rightarrow$ ○ $\rightarrow \boxed{c_1} \rightarrow c_1 \Rsh^* c_1 \rightarrow$ ○

$\boxed{d_2}$	Required process
$d_0 \Rsh^* d_2$	Objective
○	Solution to an objective

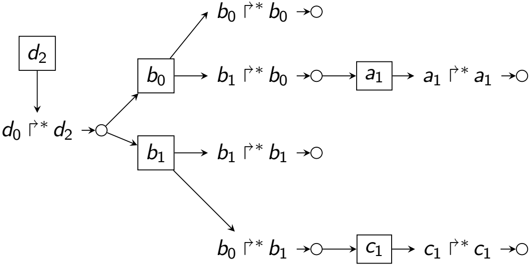


Under-approximation

Sufficient condition:

- no cycle
- each objective has a solution

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



$\boxed{d_2}$

$d_0 \Rsh^* d_2 \rightarrow ○$

$\boxed{b_0}$

$b_0 \Rsh^* b_0 \rightarrow ○$

$b_1 \Rsh^* b_0 \rightarrow ○ \rightarrow \boxed{a_1} \rightarrow a_1 \Rsh^* a_1 \rightarrow ○$

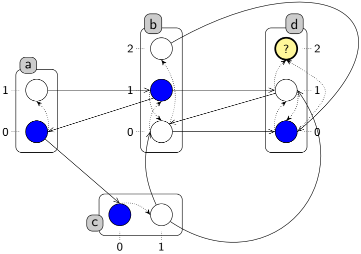
$\boxed{b_1}$

$b_1 \Rsh^* b_1 \rightarrow ○$

$b_0 \Rsh^* b_1 \rightarrow ○ \rightarrow \boxed{c_1} \rightarrow c_1 \Rsh^* c_1 \rightarrow ○$

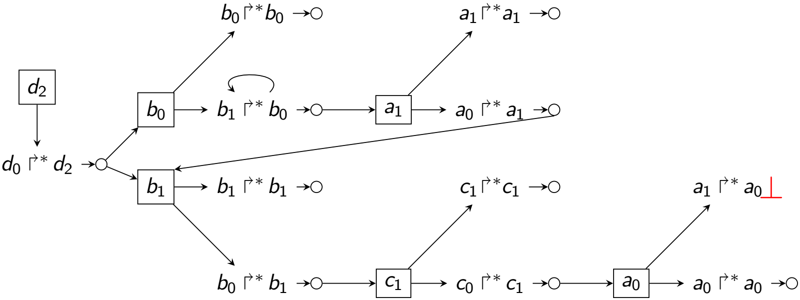
$\boxed{d_2}$	Required process
$d_0 \Rsh^* d_2$	Objective
○	Solution to an objective

Under-approximation



Sufficient condition:

- no cycle
- ~~each objective has a solution~~



d_2

$d_0 \Rsh^* d_2$

b_0

b_1

$b_0 \Rsh^* b_0$

$b_1 \Rsh^* b_0$

$b_1 \Rsh^* b_1$

$b_0 \Rsh^* b_1$

a_1

$a_1 \Rsh^* a_1$

$a_0 \Rsh^* a_1$

c_1

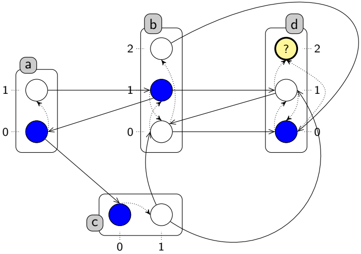
$c_1 \Rsh^* c_1$

$c_0 \Rsh^* c_1$

a_0

$a_1 \Rsh^* a_0 \perp$

$a_0 \Rsh^* a_0$

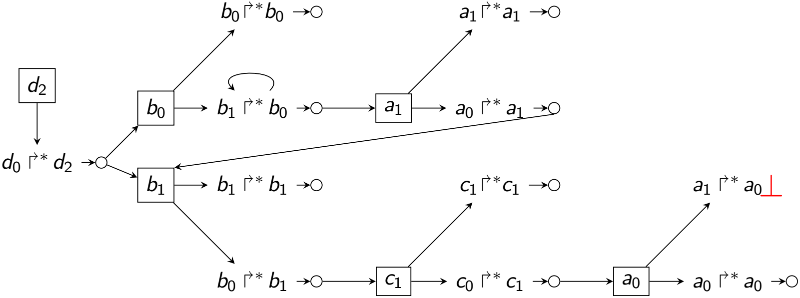


Under-approximation

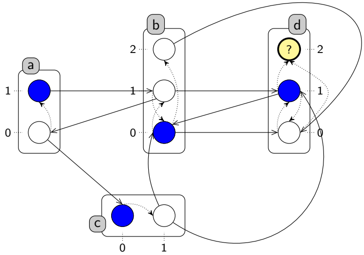
Sufficient condition:

- no cycle
- ~~each objective has a solution~~

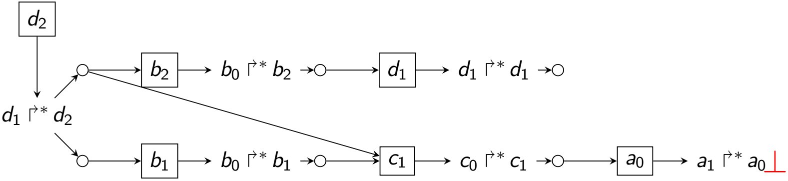
P is false $\Rightarrow$ Inconclusive



Over-approximation



Necessary condition:



d_2

$d_1 \Rsh^* d_2$

b_2

$b_0 \Rsh^* b_2$

d_1

$d_1 \Rsh^* d_1$

b_1

$b_0 \Rsh^* b_1$

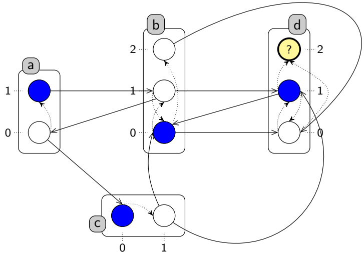
c_1

$c_0 \Rsh^* c_1$

a_0

$a_1 \Rsh^* a_0 \perp$

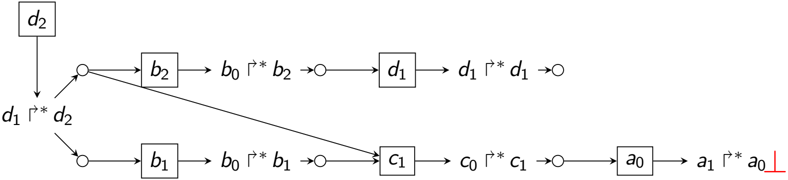
Over-approximation



Necessary condition:

There exists a traversal with no cycle

- objective → follow **one** solution
- solution → follow **all** processes
- process → follow **all** objectives



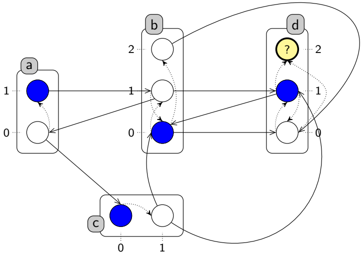
d_2

$d_1 \Rsh^* d_2$

b_2 → $b_0 \Rsh^* b_2$ → d_1 → $d_1 \Rsh^* d_1$

b_1 → $b_0 \Rsh^* b_1$ → c_1 → $c_0 \Rsh^* c_1$ → a_0 → $a_1 \Rsh^* a_0$ $\bot$

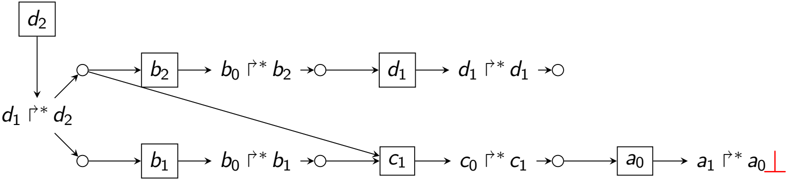
Over-approximation



Necessary condition:

~~There exists a traversal~~ with no cycle

- ~~objective → follow **one** solution~~
- solution → follow **all** processes
- process → follow **all** objectives



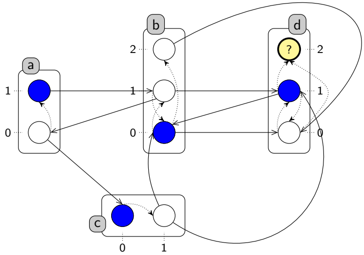
d_2

$d_1 \Rsh^* d_2$

b_2 → $b_0 \Rsh^* b_2$ → d_1 → $d_1 \Rsh^* d_1$

b_1 → $b_0 \Rsh^* b_1$ → c_1 → $c_0 \Rsh^* c_1$ → a_0 → $a_1 \Rsh^* a_0 \bot$

Over-approximation

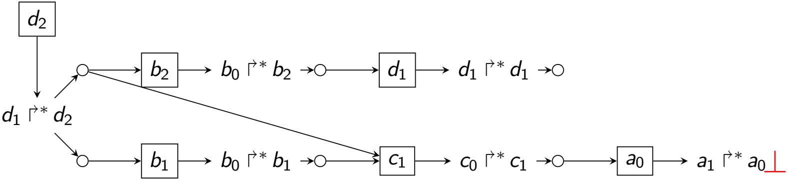


Necessary condition:

~~There exists a traversal~~ with no cycle

- ~~objective → follow **one** solution~~
- solution → follow **all** processes
- process → follow **all** objectives

Q is **false** ⇒ R is **false**

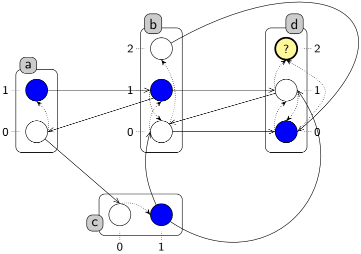


$\boxed{d_2}$

$d_1 \Rsh^* d_2$

$\boxed{b_2}$ $b_0 \Rsh^* b_2$ $\boxed{d_1}$ $d_1 \Rsh^* d_1$

$\boxed{b_1}$ $b_0 \Rsh^* b_1$ $\boxed{c_1}$ $c_0 \Rsh^* c_1$ $\boxed{a_0}$ $a_1 \Rsh^* a_0$ $\bot$



Over-approximation

Necessary condition:

There exists a traversal with no cycle

- objective → follow **one** solution
- solution → follow **all** processes
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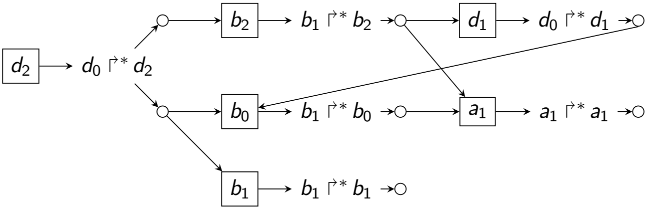


$\boxed{d_2}$ $d_0 \Rsh^* d_2$

$\boxed{b_2}$ $b_1 \Rsh^* b_2$

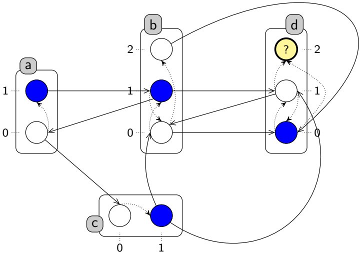
$\boxed{d_1}$ $d_0 \Rsh^* d_1$

$\boxed{b_0}$ $b_1 \Rsh^* b_0$

$\boxed{a_1}$ $a_1 \Rsh^* a_1$

$\boxed{b_1}$ $b_1 \Rsh^* b_1$

Over-approximation

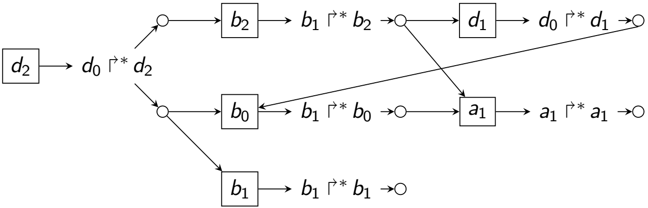


Necessary condition:

There exists a traversal with no cycle

- objective → follow **one** solution
- solution → follow **all** processes
- process → follow **all** objectives

R is true ⇒ Inconclusive



d_2 → $d_0 \Rsh^* d_2$

b_2 → $b_1 \Rsh^* b_2$

d_1 → $d_0 \Rsh^* d_1$

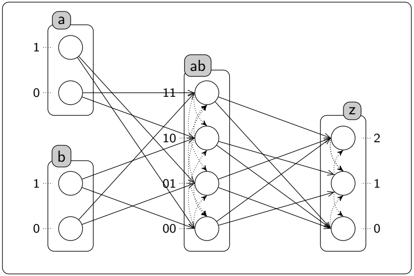
b_0 → $b_1 \Rsh^* b_0$

a_1 → $a_1 \Rsh^* a_1$

b_1 → $b_1 \Rsh^* b_1$

Translation of PH models

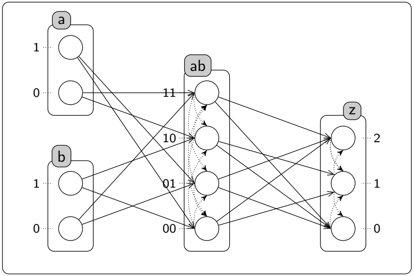
[Folschette *et al.*, *Computational Methods in Systems Biology*, 2012]



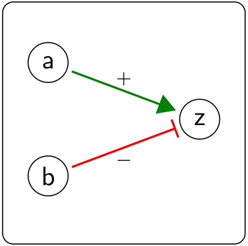
Process Hitting
Efficient but recent

Translation of PH models

[Folschette *et al.*, *Computational Methods in Systems Biology*, 2012]



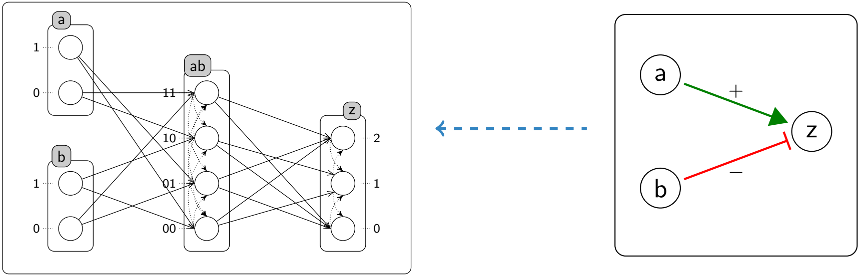
Process Hitting
Efficient but recent



Usual modelling
Widespread & readable

Translation of PH models

[Folschette *et al.*, *Computational Methods in Systems Biology*, 2012]



Process Hitting
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Translation of PH models

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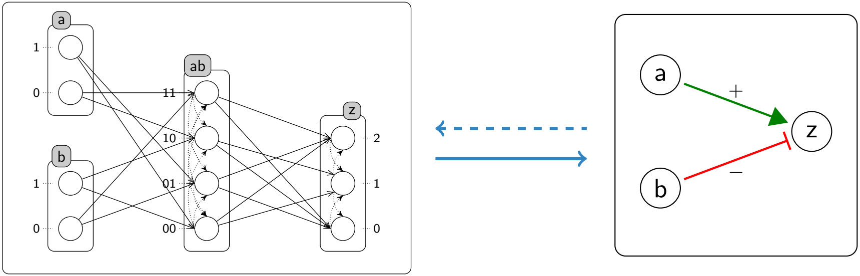
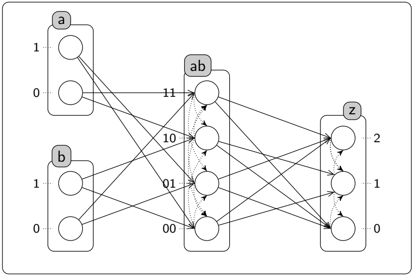


Process Hitting
Efficient but recent

Usual modelling
Widespread & readable

Enrich PH semantics

[Folschette *et al.*, *CS2Bio*, 2013]



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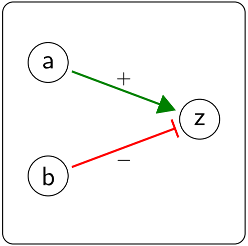
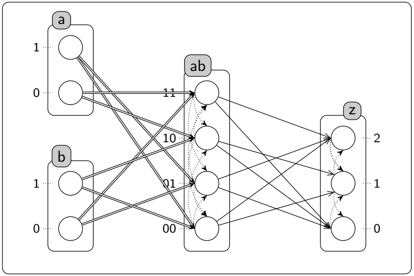


Process Hitting
Loose behaviour

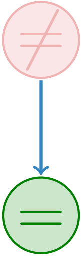
Usual modelling
Accurate behaviour

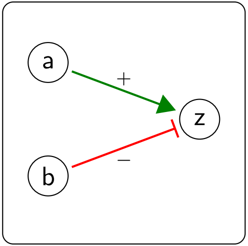
Enrich PH semantics

[Folschette *et al.*, *CS2Bio*, 2013]



Process Hitting
Accurate behaviour





Usual modelling
Accurate behaviour

What for?

Very well, but. . .

What for?

Very well, but. . .

What's the point?

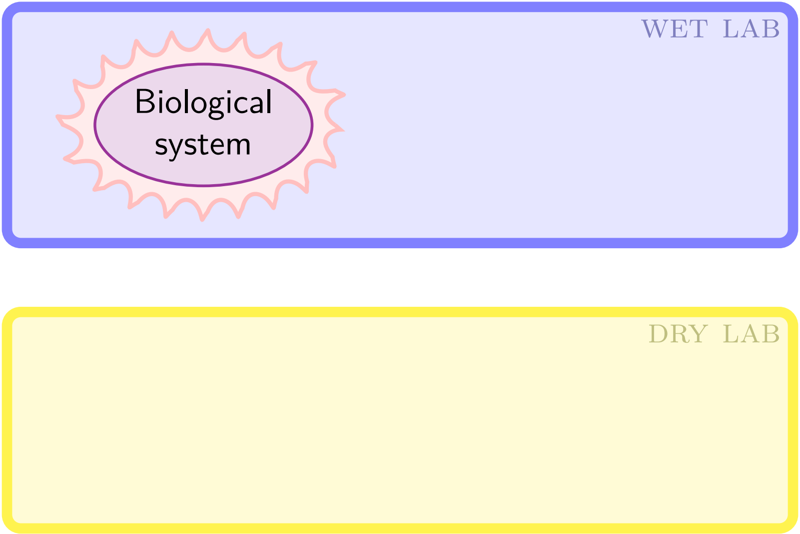
What for?

Very well, but. . .

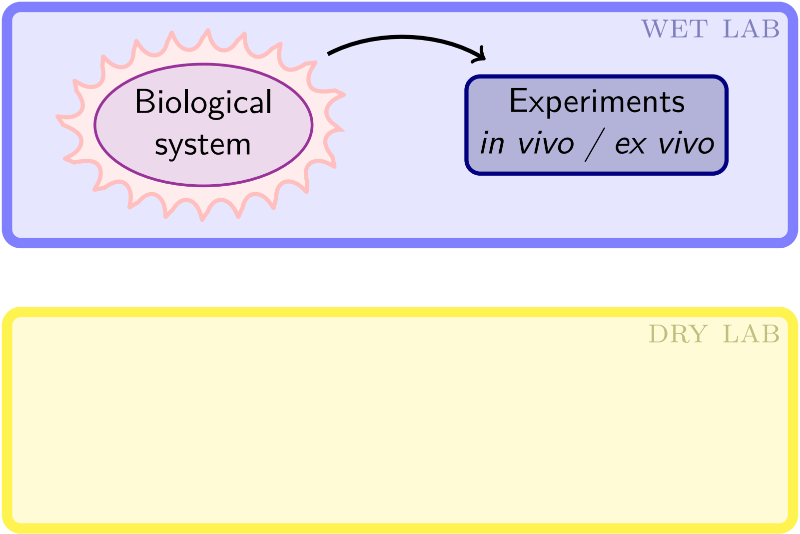
What’s the point?

- Validating the models
- Predicting behaviours
- Finding gene therapies

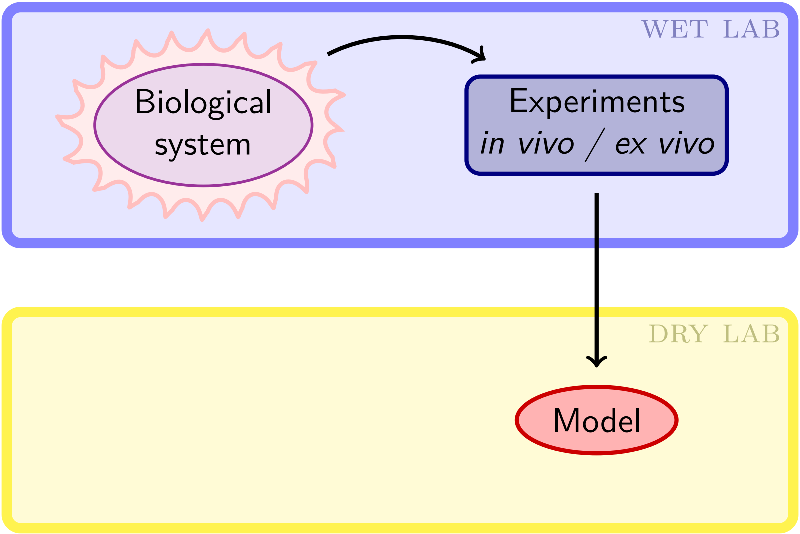
Experiments *in silico*



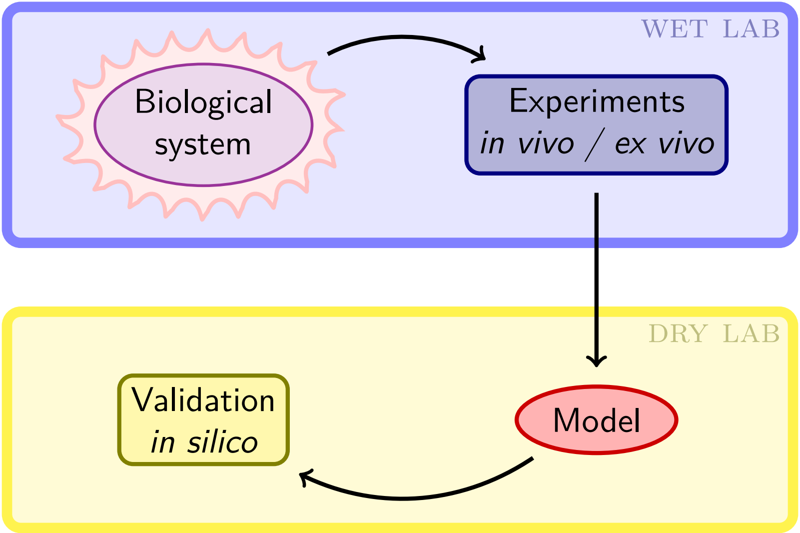
Experiments *in silico*



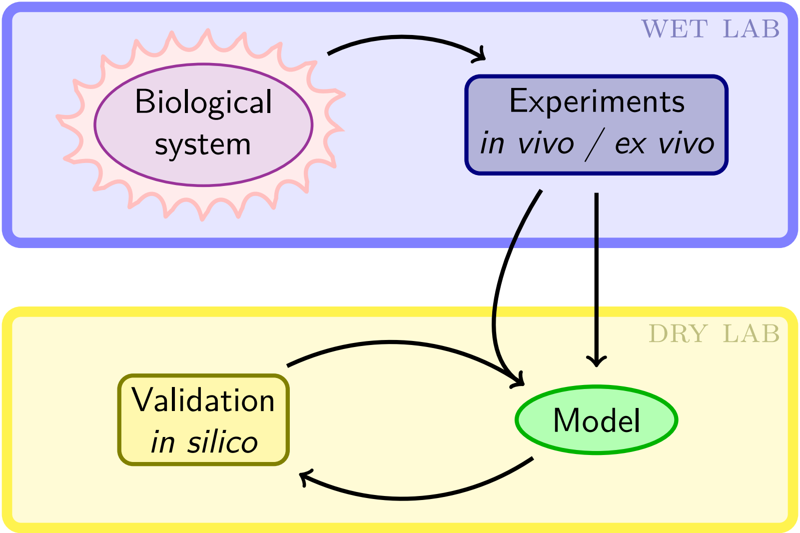
Experiments *in silico*



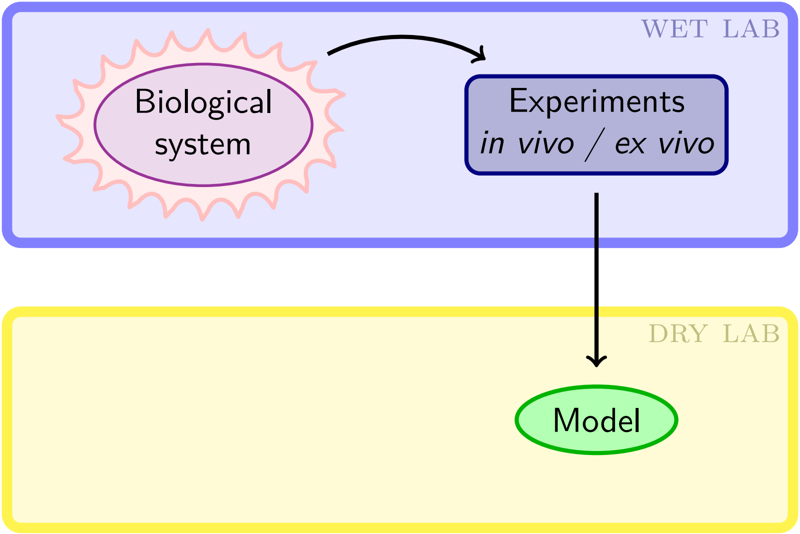
Experiments *in silico*



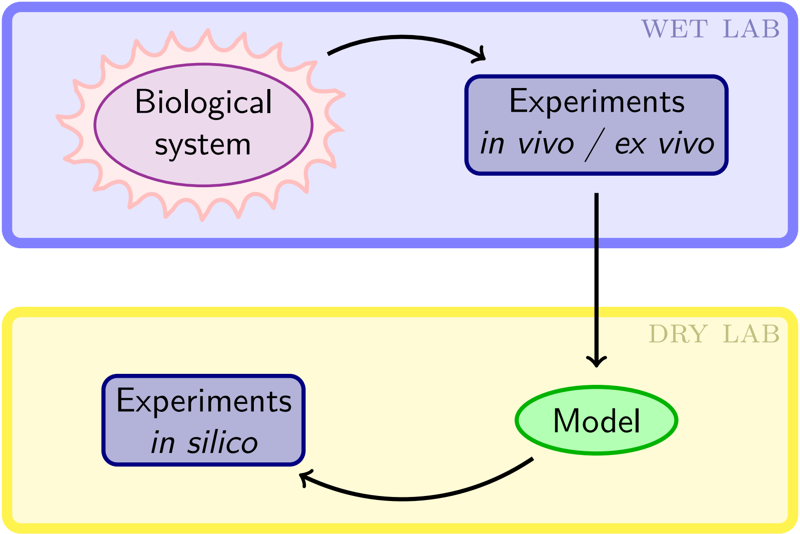
Experiments *in silico*



Experiments *in silico*



Experiments *in silico*



WET LAB

Biological system

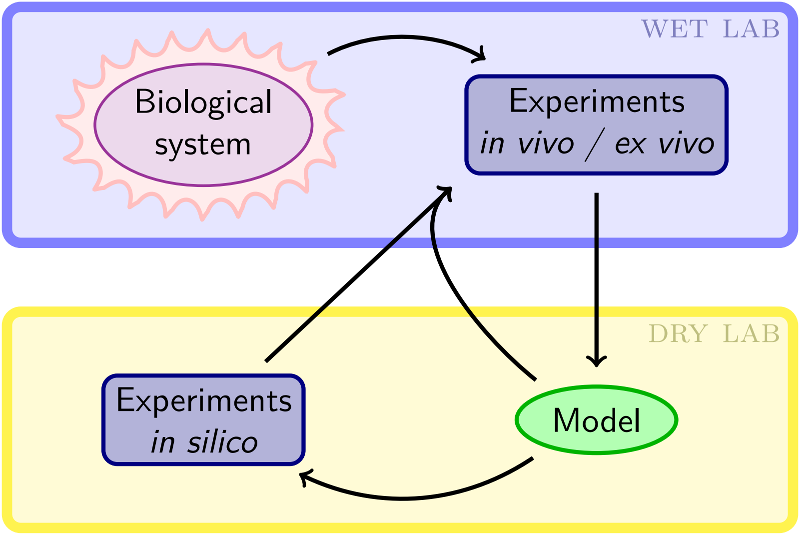
Experiments *in vivo* / *ex vivo*

DRY LAB

Model

Experiments *in silico*

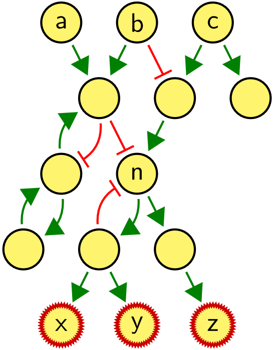
Experiments *in silico*



Gene therapies

Modify DNA to cure a disease

- Replace a mutated gene → remove a **harmful protein**
- Add a new gene → produce a **therapeutic protein**



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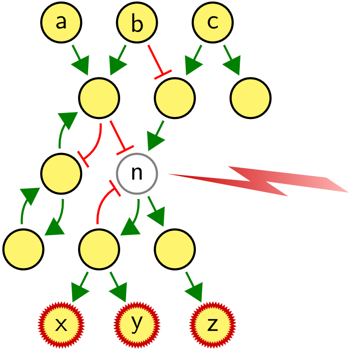

Gene therapies

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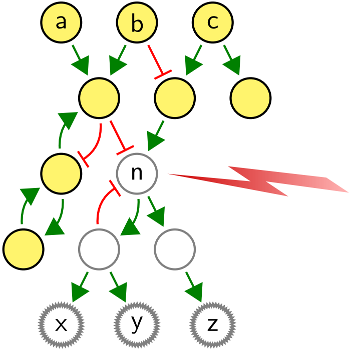
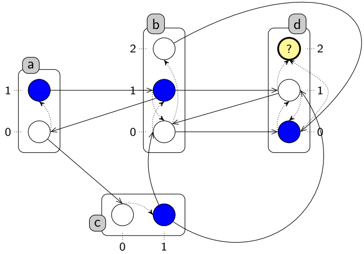


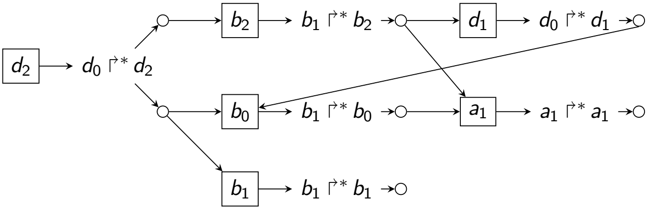
Back to the Over-approximation



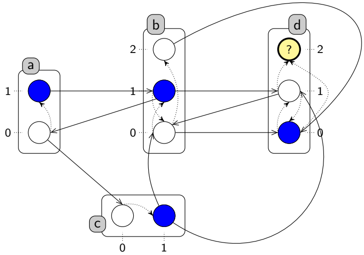
Necessary condition:

There exists a traversal with no cycle

- objective → follow **one** solution
- solution → follow **all** processes
- process → follow **all** objectives



Back to the Over-approximation

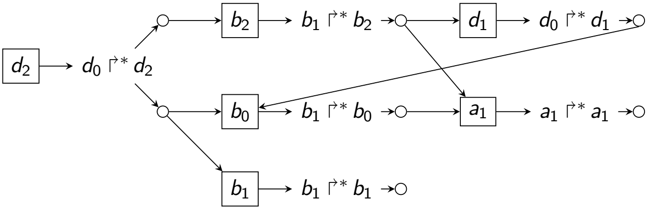


Necessary condition:

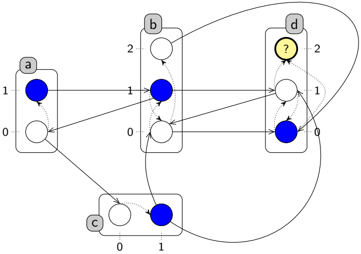
There exists a traversal with no cycle

- objective → follow **one** solution
- solution → follow **all** processes
- process → follow **all** objectives

***R* is true ⇒ Inconclusive**



Back to the Over-approximation



Necessary condition:

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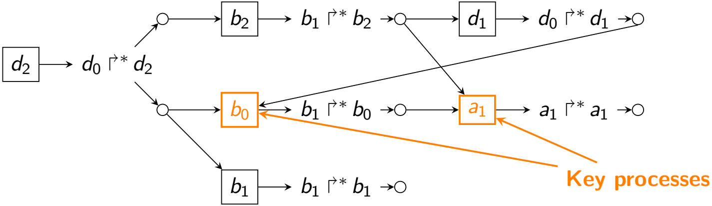


$\boxed{d_2} \rightarrow d_0 \Rsh^* d_2$

$\boxed{b_2} \rightarrow b_1 \Rsh^* b_2$

$\boxed{d_1} \rightarrow d_0 \Rsh^* d_1$

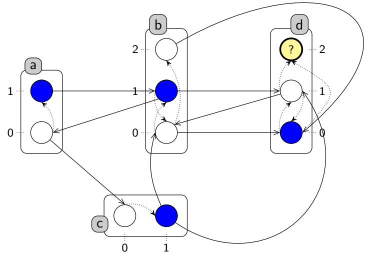
$\boxed{b_0} \rightarrow b_1 \Rsh^* b_0$

$\boxed{a_1} \rightarrow a_1 \Rsh^* a_1$

$\boxed{b_1} \rightarrow b_1 \Rsh^* b_1$

Key processes

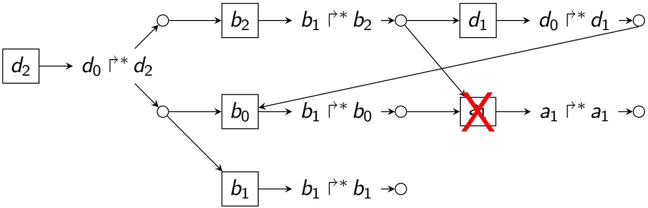
Back to the Over-approximation



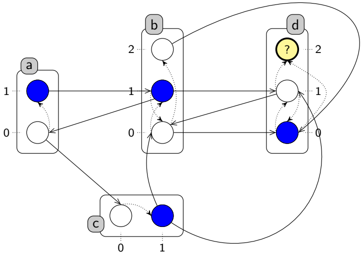
Necessary condition:

There exists a traversal with no cycle

- objective → follow **one** solution
- solution → follow **all** processes
- process → follow **all** objectives



Back to the Over-approximation



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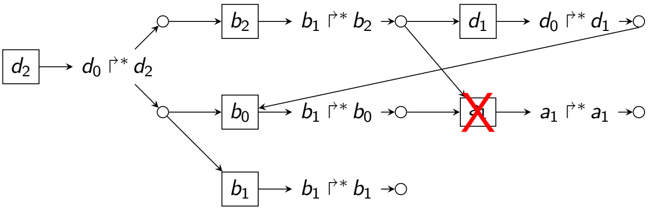
Q is **false** ⇒ R is **false**



d_2 $d_0 \Rsh^* d_2$

b_2 $b_1 \Rsh^* b_2$ d_1 $d_0 \Rsh^* d_1$

b_0 $b_1 \Rsh^* b_0$ $\xcancel{a_1}$ $a_1 \Rsh^* a_1$

b_1 $b_1 \Rsh^* b_1$

Summary & Conclusion

- What is Bio-informatics?
  - → Qualitative modelling of **gene regulations**
  - → Large models are hard to study (**exponential**)
- What do I do?
  - → The **Process Hitting** modelling
  - → Very efficient on large-scale models (**polynomial**)
  - → 2 important contributions
- What for?
  - → **Validating** & **utilizing** biological models
  - → Gene therapies

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Thank you