Formally Bridging Models: A Key Tool to Better Understand Biological Systems

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Journée du GREYC — 2025 Juin 17

Systems biology

Reasoning about biological systems

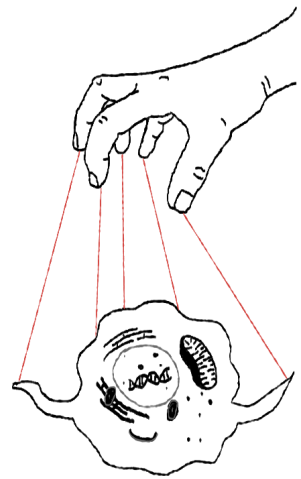
How does the system evolve?

Is the population of some cell type stable over time?

How to control the system?

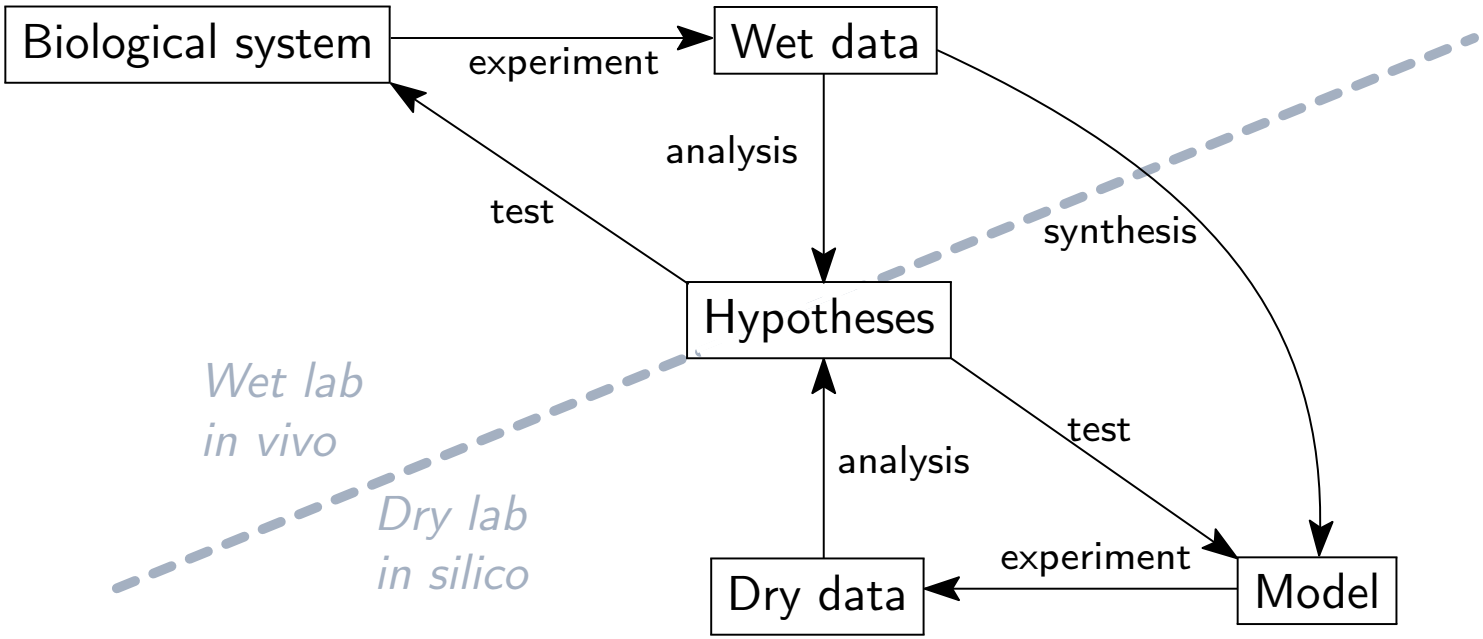
Cure a pathological system

Produce more of some species of interest



A model = an abstract representation (abbreviated and convenient) of the reality (more complex and detailed)

The workflow of system biology [Kohl et al., 2010]



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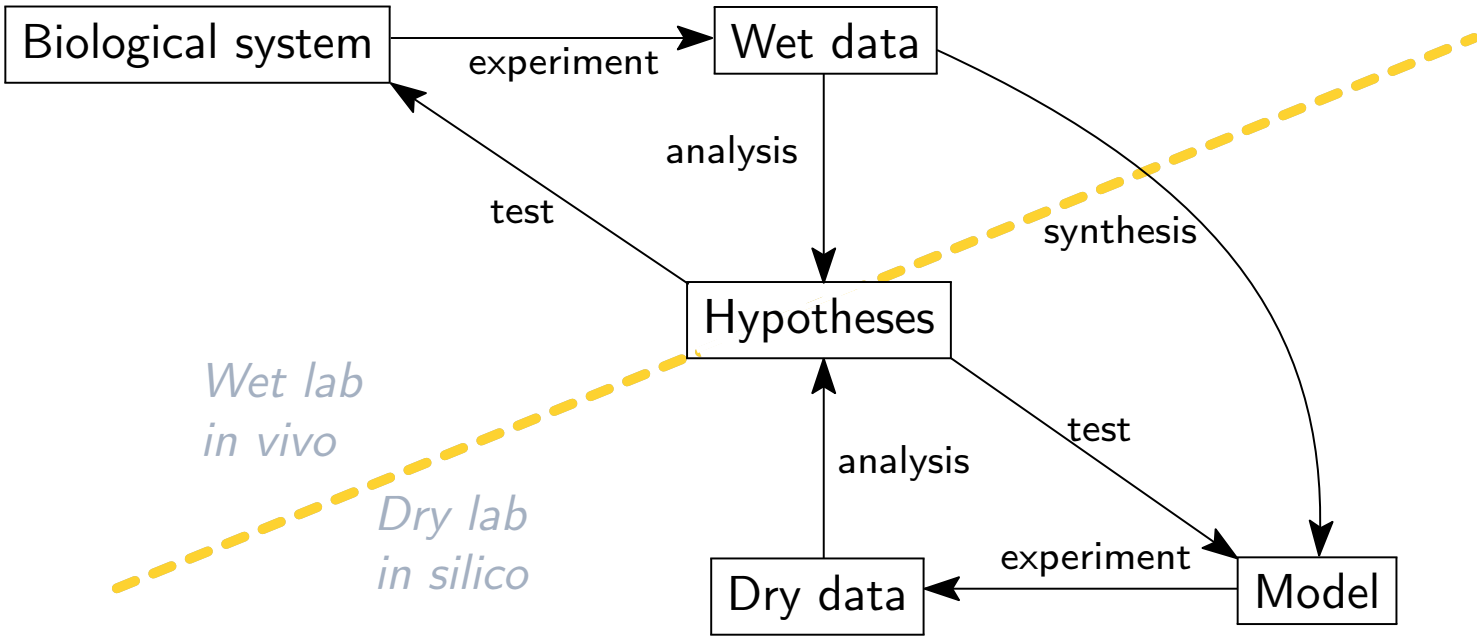

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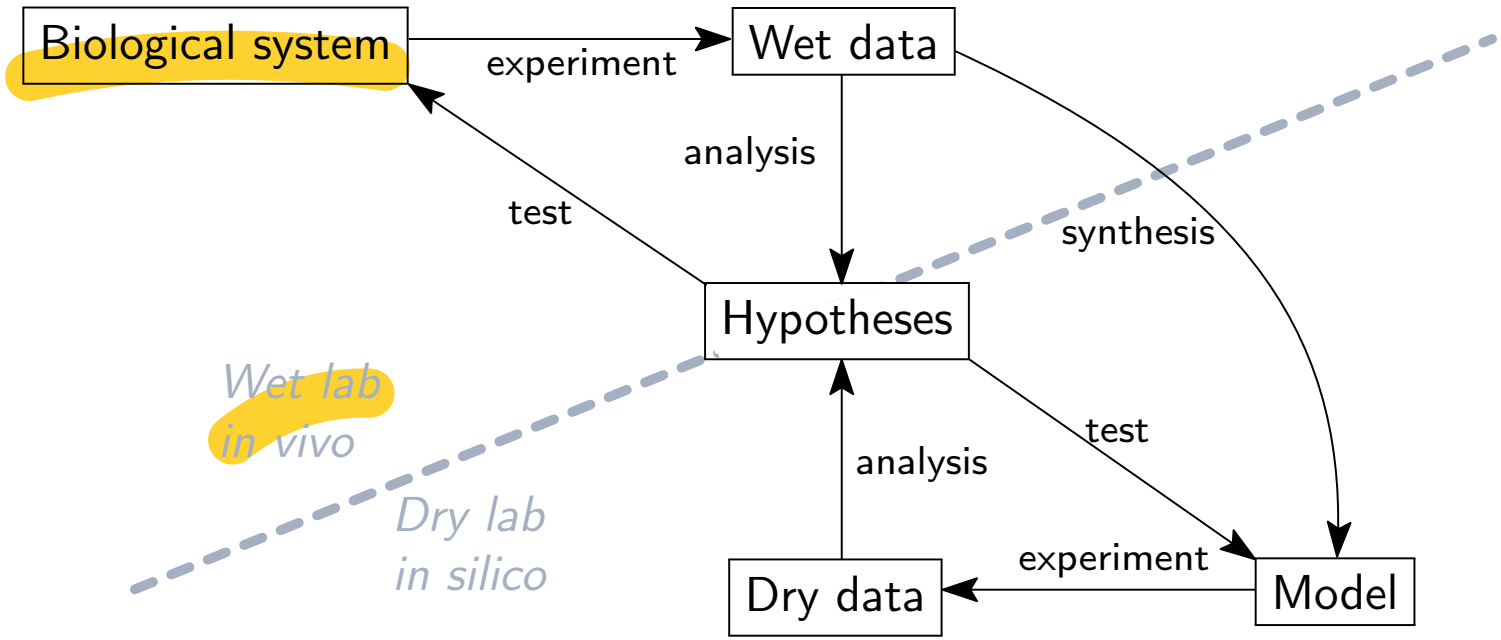

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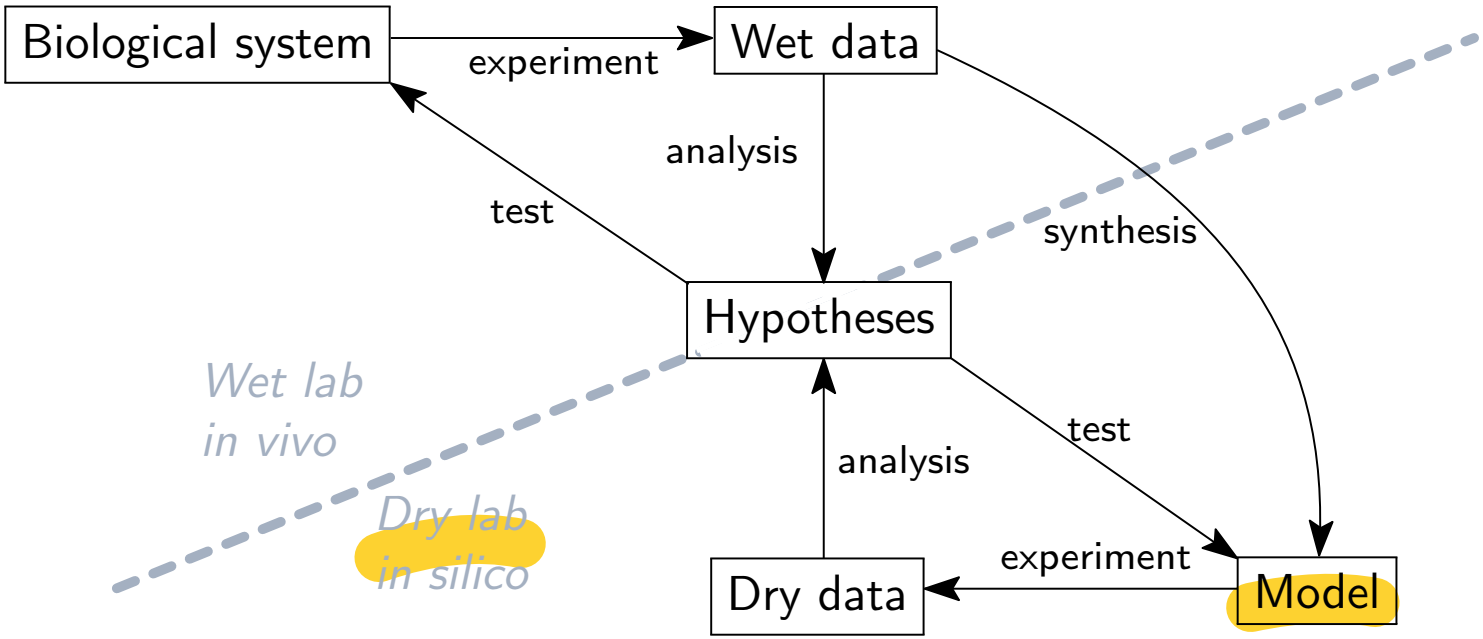

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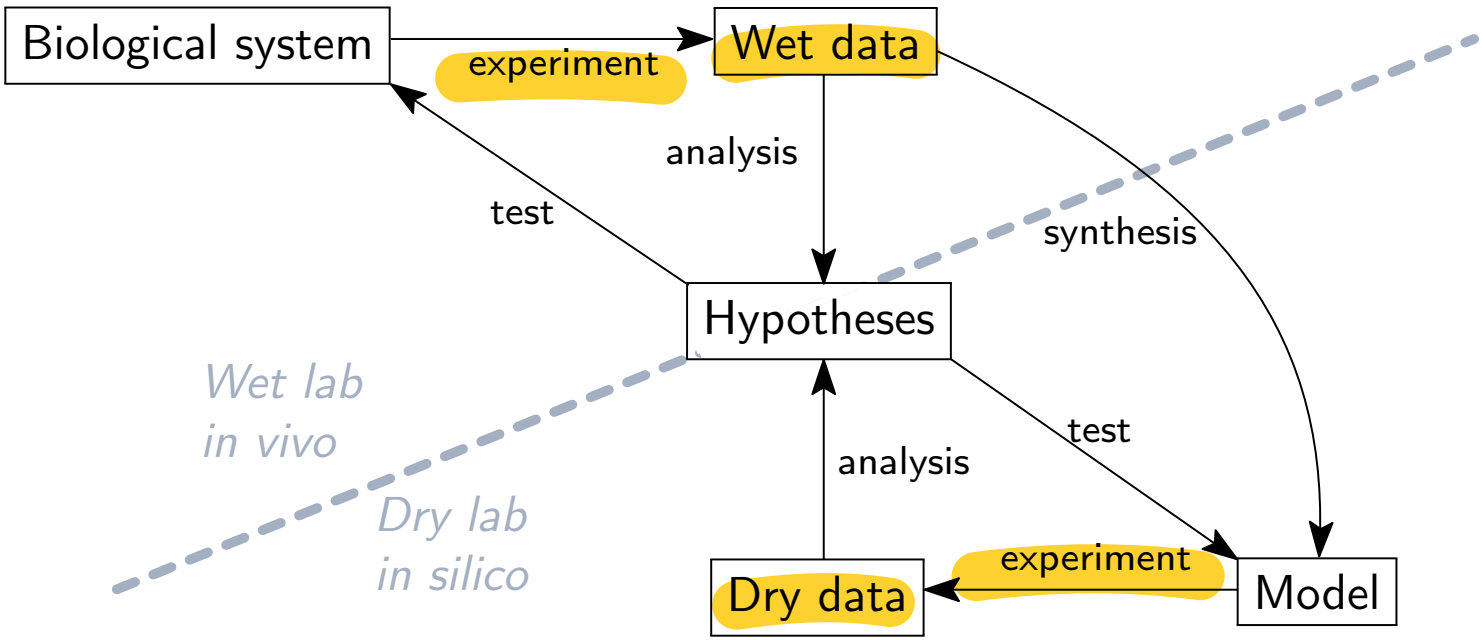

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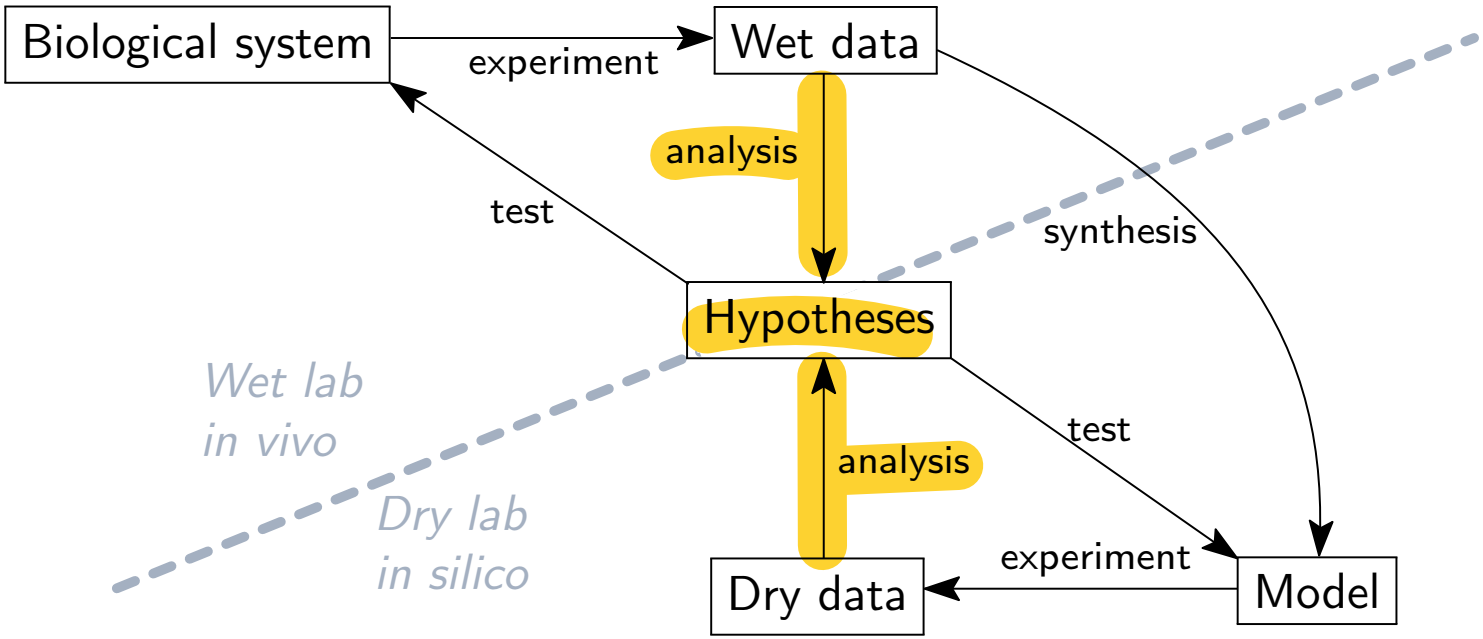

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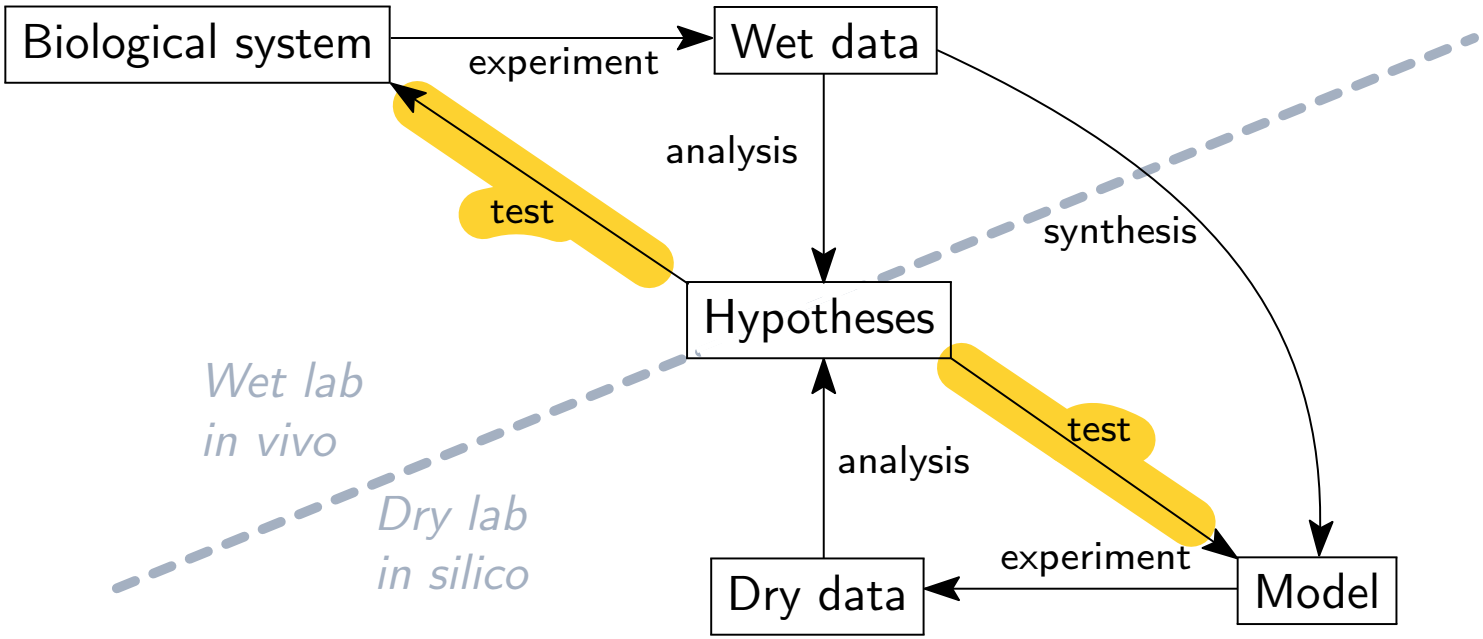

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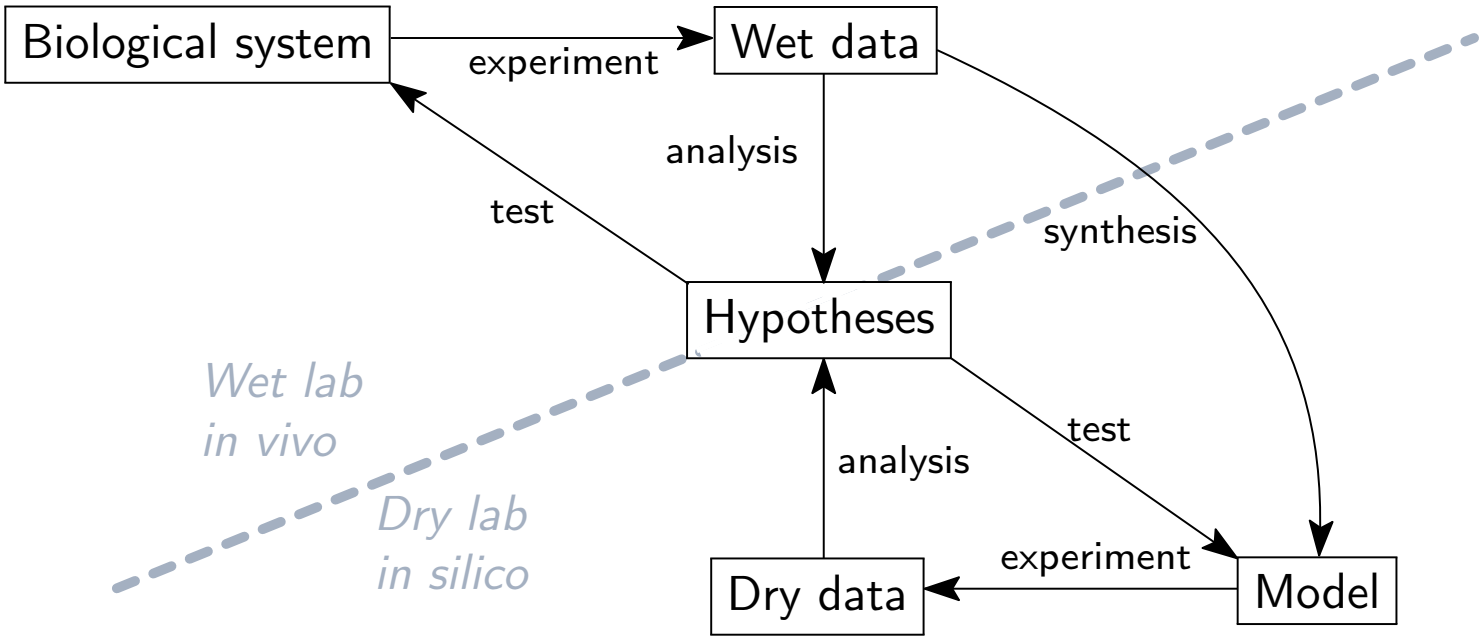


A zoo of modelling approaches

Reaction network

continuous time Markov chain

ODEs

statistical models

Petri net

informal diagrams

Boolean transition system

Boolean automata network

A zoo of modelling approaches

Two opposites views

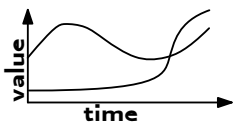
Model = rules $A \rightarrow B$

Reaction networks

Transformation of reactants into products

Differential equations

$\dot{B} = f(A)$



Time series

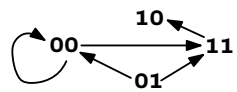
Continuous time and values

Boolean networks

Influence of regulators on regulees

Boolean functions (propositional logics)

$B = f(A)$



Transition graph

Discrete time, boolean values

Where *abstraction* comes into play

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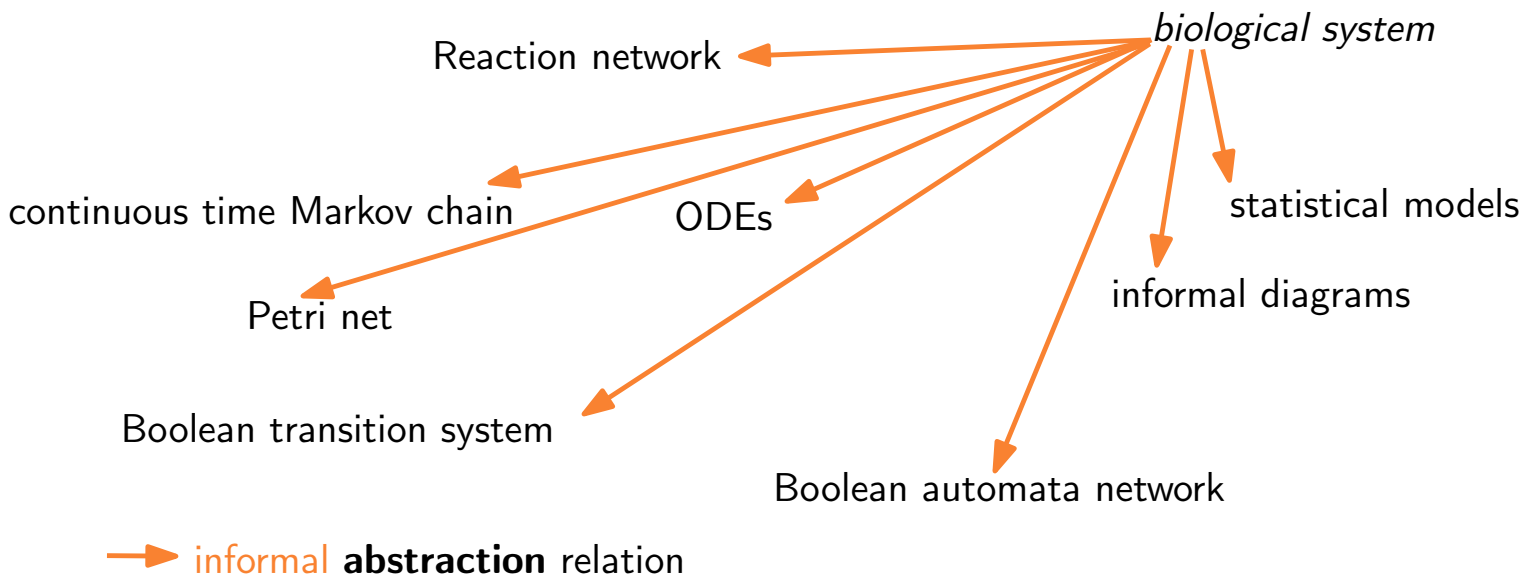
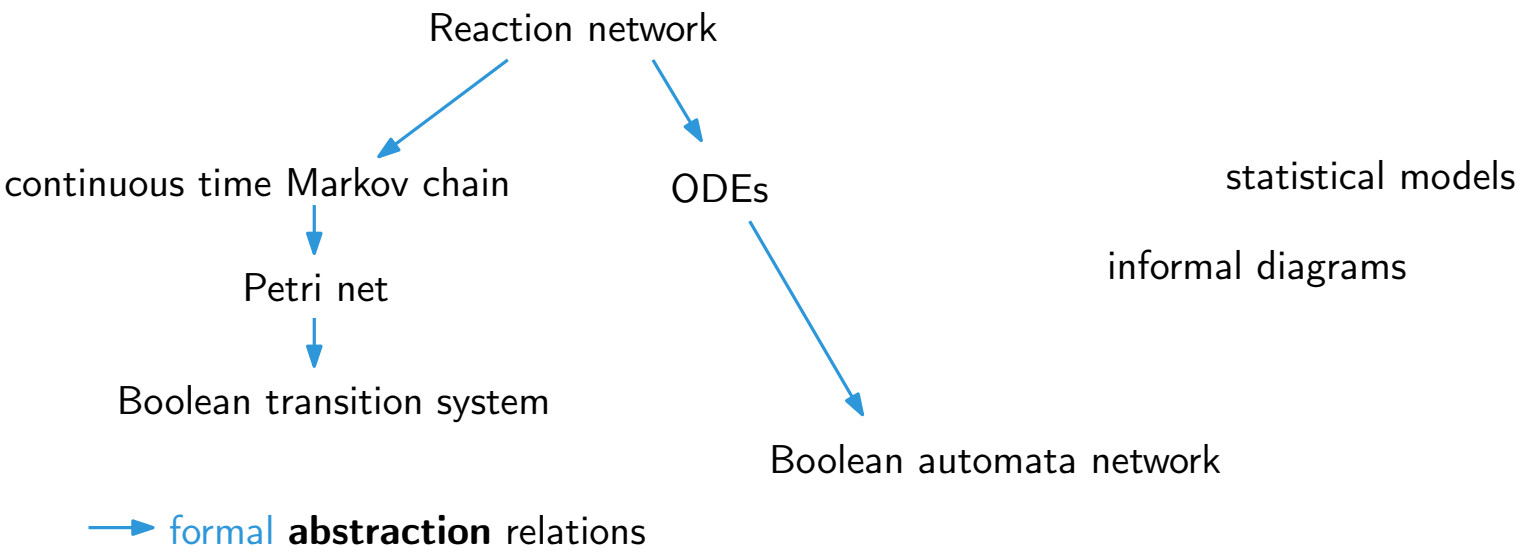
Where *abstraction* comes into play



- A model is an informal abstraction of a biological system

Where *abstraction* comes into play



- A model is an informal abstraction of a biological system
- Goal: understanding the formal relationships of abstraction between modelling approaches
  [Paulevé et al. 2020, Fages, Soliman, 2008a, Vaginay 2023]

The notion of *abstraction*

Definition

Mapping between simulation traces of a **concrete** model and those of an **abstract** model, such that we can derive correct conclusions. [Fages, Soliman, 2008a]

$\Longrightarrow$ Analogy with abstract interpretation [Cousot, Cousot, 1977]

Example

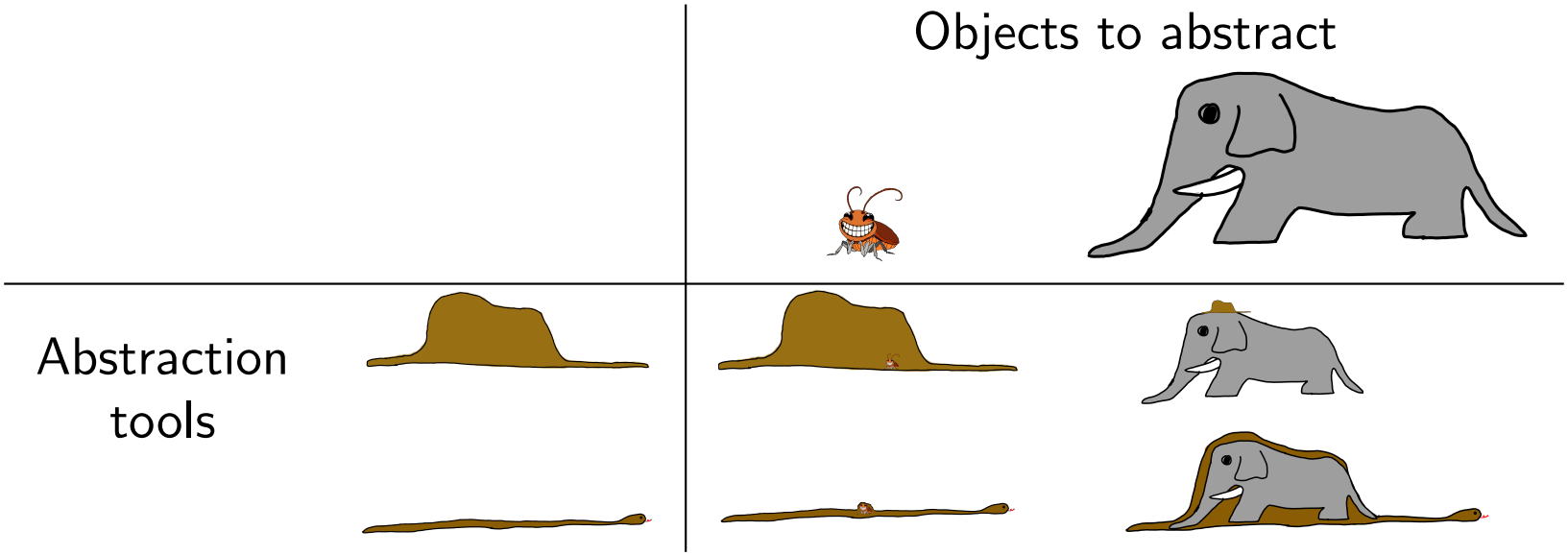
Given $x, y \in \mathbb{R}$, return the sign of $z = x + y$.

- Concrete algo: compute z then check its sign
- Abstract algo: drop the precise values, use the **rule of signs**

$+$	p	n
p	p	?
n	?	n

The notion of *abstraction*

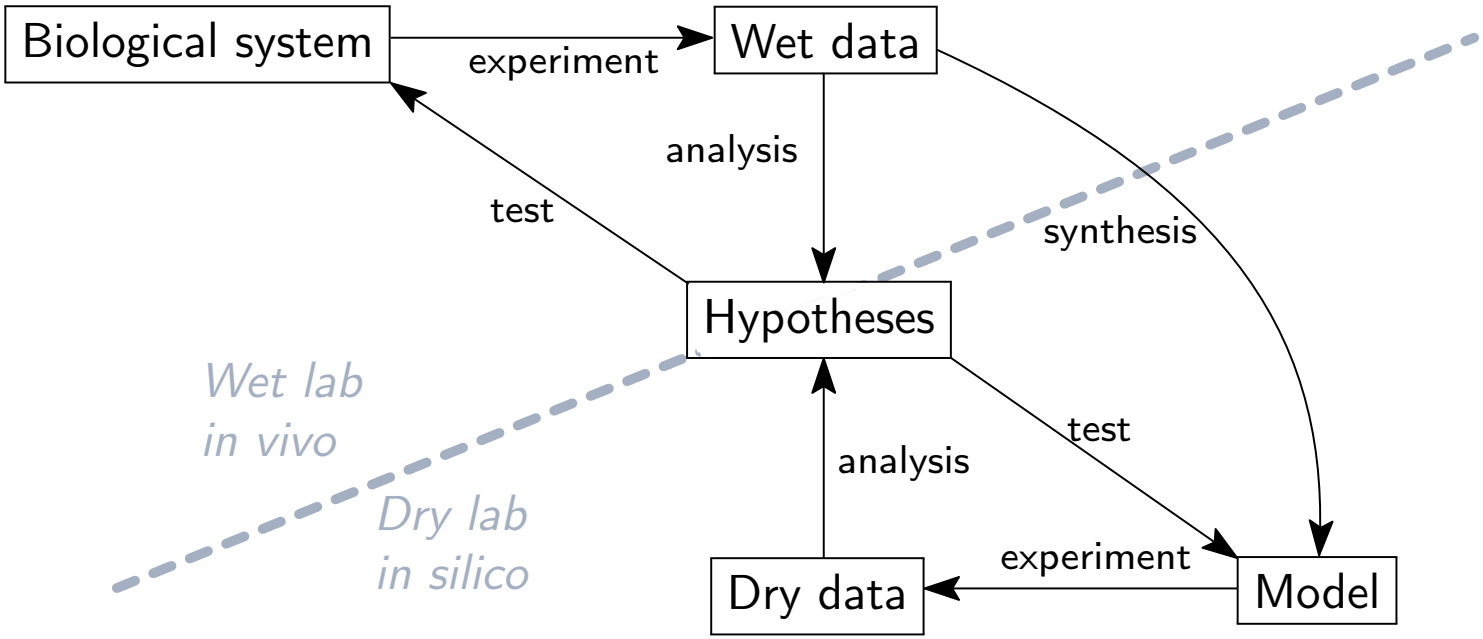
Correctness and tightness, informally



Figures inspired from [Saint-Exupery 1943]

- Hat: not complete nor tight
- Snake: complete and tight

Where I stand



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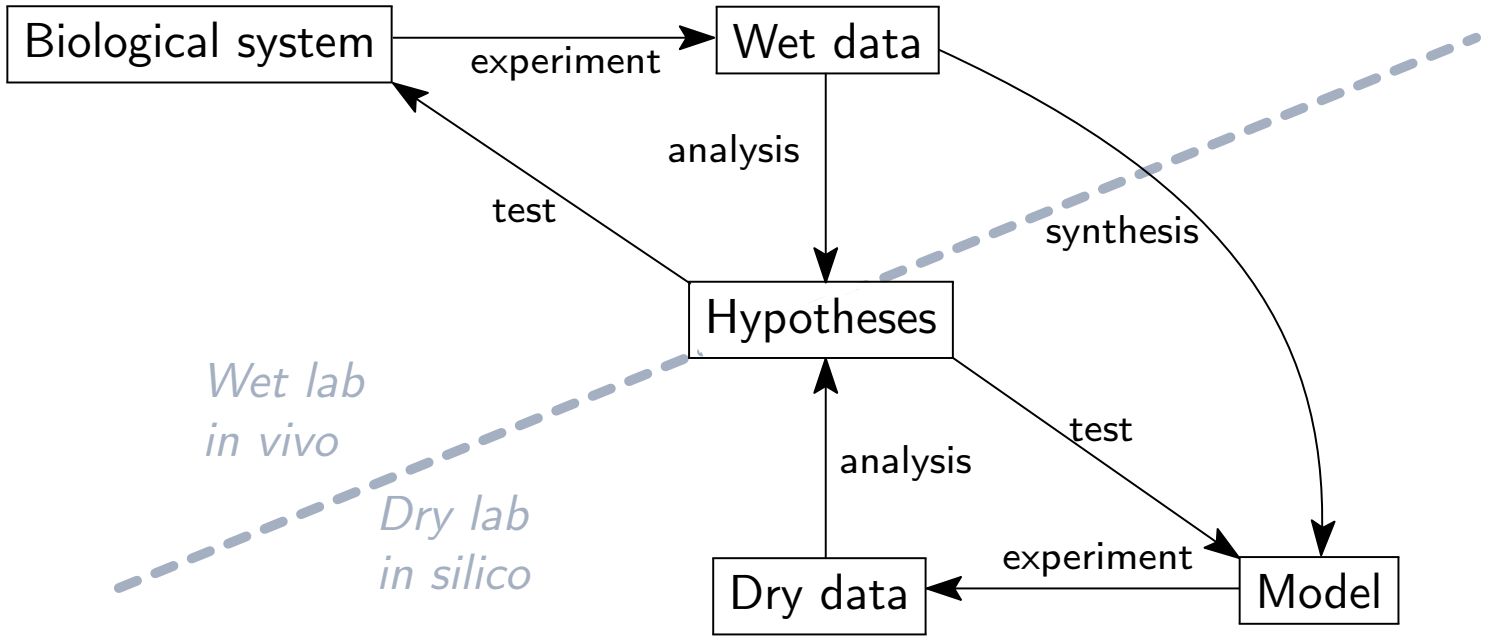

Side effects of understanding the formalisms better:

- Better synthesis of models (application to Boolean networks [Vaginay et al., 2021])
- Simplify the use of models (abstract simulation of reaction networks, [Niehren et al., 2022])

Declarative Logic Programming

$$\text{Facts} + \text{constraints} \rightarrow \text{solver} \rightarrow \text{answers}$$
$$\text{ASP, SAT}$$

- Elegant, focus on the *what* not the *how*
- Modular, easy prototype
- Keep *human in the loop*

"it is false to select a conjunction that uses a literal that is not allowed by the PKN"

```
ig(ParentID, x, V):- conjTaken(ConjID, ParentID, V); V!=0.
:- ig(ParentID, x, V) ; not pkn(ParentID, x, V).
```

Thank you for your attention.

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