Systems Biology approach

Production of a huge amount of data

Challenge : understanding how complex interaction networks control the cell behavior

Topology of the network : knowledge on the involved components

Dynamical modeling : understanding the dynamical properties of the system

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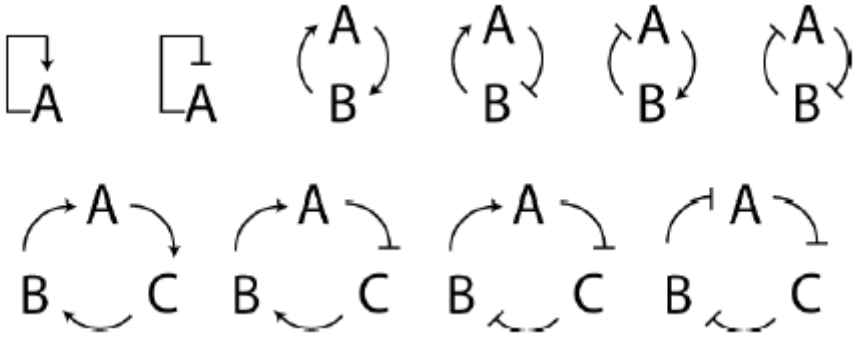
Why the need for modeling ?

Looking at the following very simple networks involving three proteins, could you identify the ones that will lead to the oscillations of the protein concentrations (A, B and C)?



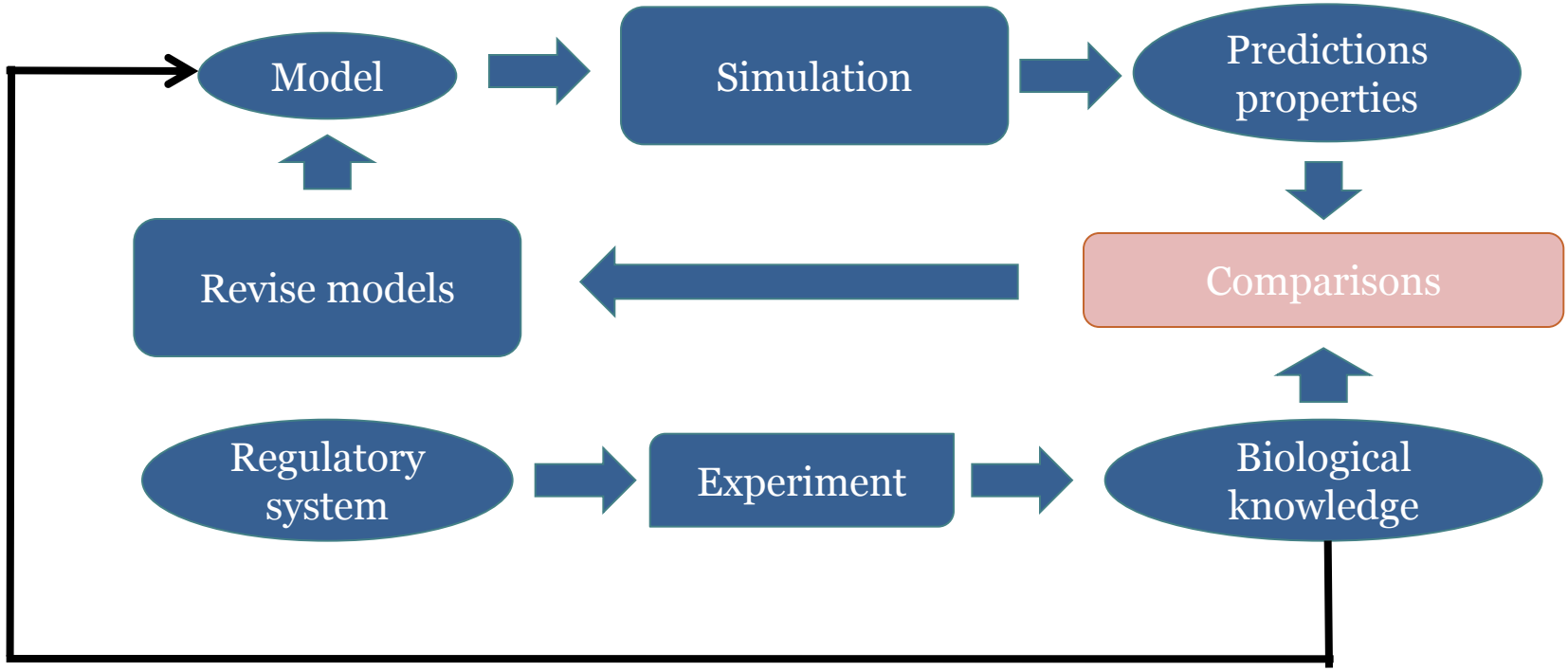
Not so easy!
At least, the last one will and it is known under the name “repressilator”

Systems Biology approach

- Description of the acquired understanding

- Explanatory of biological mechanisms

- Predictive of the behavior of the system when it is perturbed (mutations, chemical intervention, change in the environment…)



Formalizing our understanding

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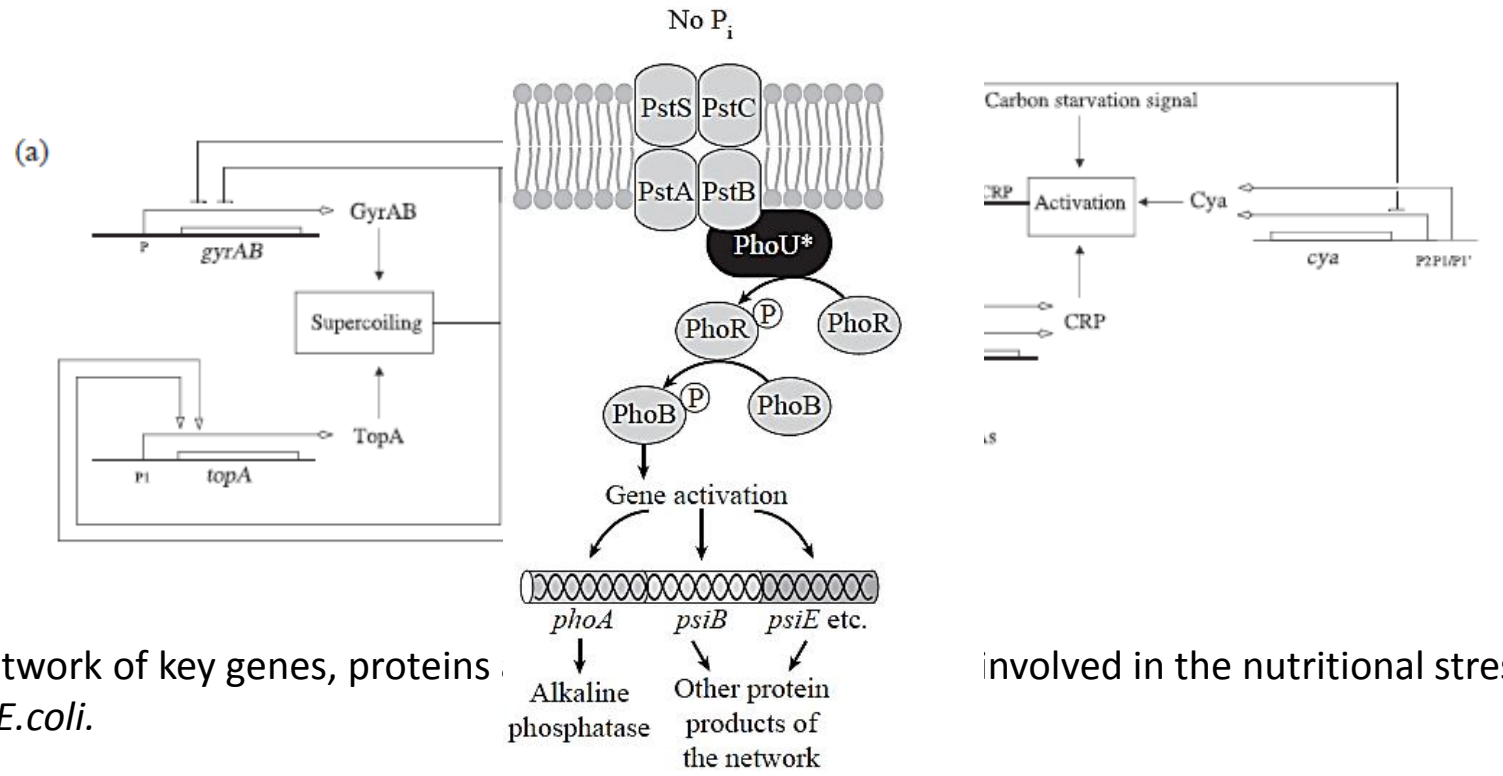
Example of biological knowledge :



Network of key genes, proteins involved in the nutritional stress network in *E.coli.*

Phosphate regulation in enterobacteria

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What is a model?

- a simple abstract representation of reality
- can not explained all the details of a biological system
- but can help to understand the structural relationships and time-dependent dynamic behavior
- can reveal missing components or reactions
- allows to test hypotheses

Biological system analysis:

1. Make assumptions and abstraction to keep the model as simple as possible
2. Set boundaries to limit your model (it should stay reasonable)
3. Identify the involved components and their different states if required
4. Identify all actions and any changes occurring in the system
5. Define the relationships between components and actions
6. Define the stoichiometry
7. Define the initial state

It is recommended to start with a simple model and if necessary to refine the model afterwards by adding information.

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Two main classes of dynamical models:

- quantitative models:
  - ✓detailed representation of the model
  - ✓ produce quantitative results
  - ✓ require accurate kinetic data (often missing)
  - ✓ mainly based on ordinary differential equation (ODE)

- qualitative models:
  - ✓ require only abstract representation of threshold or concentration (example when the protein X is present at a concentration higher than θ_1 it activates the transcription of gene *a* and when it is present at a concentration higher of θ_2 it represses the transcription of gene *b*. With $\theta_1 < \theta_2$)
  - ✓ defined through discrete formalisms or piecewise linear differential equation

Those modeling techniques are complemented by simulation techniques to make predictions on the behavior of the biological process.

Systems Biology approach

Different modeling approaches among them:

model	Qualitative	Quantitative	Deterministic	Stochastic
Ordinary Differential Equations (ODE)		X	X	
Graph theory	X		X	
Bayesian networks		X		X
Piecewise Linear Differential Equations	X		X	
Boolean/Logical models	X		X	
Petri Nets	X	X	X	X