Introduction to Systems Biology: Modelling of regulatory networks

Jean-Paul Comet (projet Bioinfo Formelle)

EPU dept GB - 4ème année
Université Côte d'Azur

September, 12 2025

Teaching organization

- 3 sessions of 3 hours
- 50% lectures + 50% TDs
- teachers :

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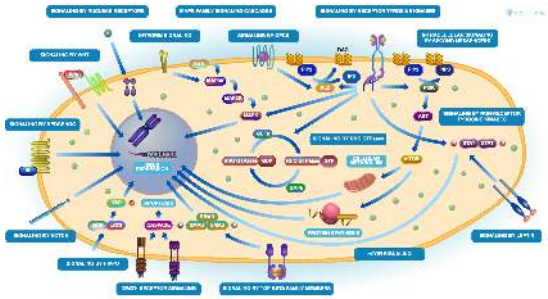
	sessions	hours	teacher
1	5 septembre 2025	13h30-16h30	GB
2	12 septembre 2025	13h30-16h30	JPC
3	19 septembre 2025	13h30-16h30	SD
–	24 septembre 2025	13h30-16h30	Group Project

- Evaluation :
  A mini **group** project : done in 2h (out of 20)
- Supports : https://www.i3s.unice.fr/~comet/SUPPORTS/

The Cell as a Complex System

Cells behave as dynamic and complex systems, capable of :

- Detecting internal or external signals
- Making decisions (proliferation, differentiation, apoptosis)
- Adapting to changing environments



from https://blog.opentargets.org/q-n-a-reactome-visualisations/

https://reactome.org

Regulatory networks involve :

- Genes (information code)
- mRNA (transcription intermediates)
- Proteins (effectors)
- Specific regulators (TFs, microRNAs, metabolites)

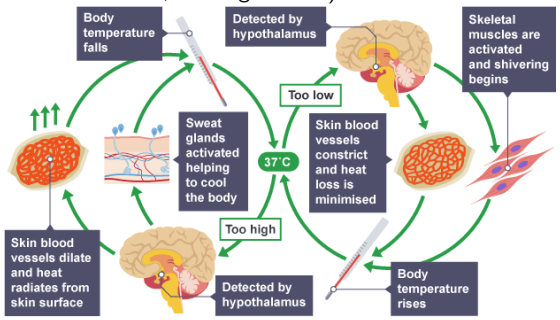
Biological Interaction Networks

- Key Principles :
  - Biological entities act in networks, not in isolation.
  - These networks ensure regulation, coordination, and adaptability.
- Types of Interactions :
  - Gene → Gene : via regulatory proteins
  - microRNA → mRNA : translation inhibition
  - Protein → Enzyme/Ion channel : activation or inhibition of intracellular signals
- Feedback Loops :
  - Positive feedback : amplifies cellular responses
  - Negative feedback : stabilizes and refines responses

These interconnected interactions form regulatory circuits that shape the precision and dynamics of cellular behavior.

Examples of biol. functions piloted by regulation

- Homeostasis : maintenance of stable internal conditions (e.g., temperature, pH, ion concentrations, blood glucose...).



from https://www.bbc.co.uk/bitesize/guides/zqdg7p3/revision/5

- Cell differentiation : commitment to a specific cell fate, often irreversible (e.g., stem cell → neuron).
- Stress response : rapid activation of defense pathways (e.g., oxidative stress → activation of p53).
- Cell cycle : orderly transitions between phases (G1, S, G2, M) through cyclic regulation of cyclins/CDKs.
- Apoptosis : programmed cell death triggered by internal or external signals.

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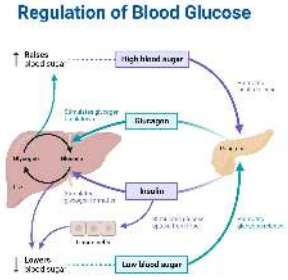

from https://microbenotes.com/homeostasis/

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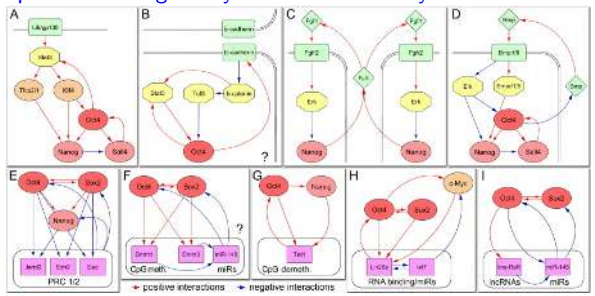
parts of the regulatory networks for Embryonic Stem Cells



from https://doi.org/10.1016/j.scr.2018.02.012

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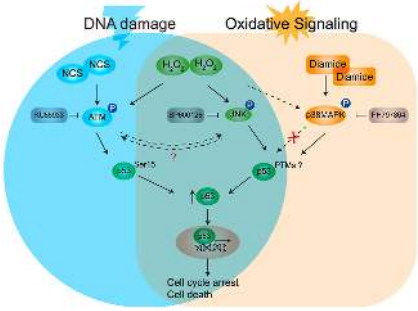

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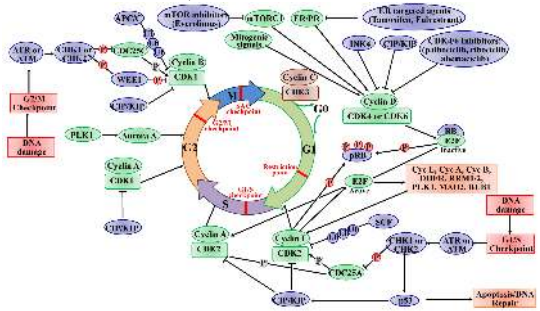

from https://www.creativebiolabs.net/cell-cycle-regulation.htm

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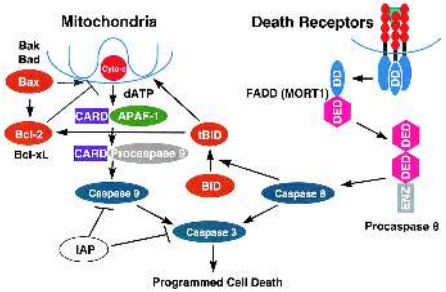

from https://doi.org/10.1016/S0092-8674(00)00119-7

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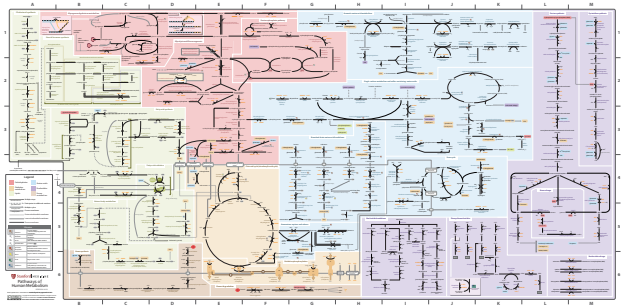
Why is Modeling Necessary ?

- Limits of Human Intuition
  - Thousands of components and interactions (genes, proteins, RNAs...)



from https://metabolicpathways.stanford.edu/

  - Nonlinear dynamics, thresholds, bifurcations
  - Local changes can cause unpredictable global effects

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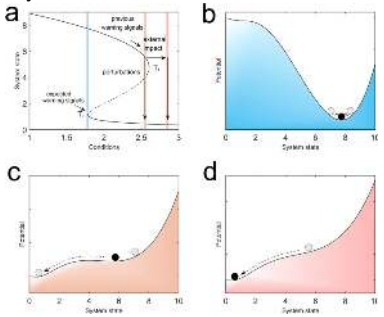

from https://doi.org/10.1038/s42005-023-01210-3

  - Local changes can cause unpredictable global effects

1- Représenter la complexité des systèmes biol.

Les systèmes biologiques comportent :

- des milliers de composants moléculaires,
- un réseau dense d'interactions,
- des régulations non linéaires, souvent multi-échelles,
- des comportements non intuitifs (effets émergents, bifurcations, oscillations...).

La modélisation permet de :

- **Représenter** ces interactions de manière structurée (graphe, équations, logique...),
- **Réduire** cette complexité en focalisant sur les éléments essentiels.

2- Comprendre les dynamiques du système

Un système biologique n'est pas statique :
$\Rightarrow$ il évolue dans le temps.

La modélisation vise à capturer cette dynamique pour :

- **Identifier** les états stables (ou attracteurs) du système, qui peuvent correspondre à des phénotypes cellulaires (par ex. cellule souche vs différenciée).
- **Comprendre** les transitions entre états (e.g. : passage d'un état sain à un état pathologique).
- **Étudier** la stabilité, les oscillations (e.g. : cycle cellulaire, rythmes circadiens), ou les comportements chaotiques.

3- Analyser les rétroactions et les motifs régulateurs

La théorie de *René Thomas* montre l'importance des **boucles de rétroaction** :

- Les rétroactions **positives** peuvent conduire à :
  - des décisions irréversibles (comme une différenciation cellulaire),
  - des changements d'état bistables (commutateurs moléculaires).
- Les rétroactions **négatives** peuvent produire :
  - des oscillations régulées (comme dans le cycle cellulaire),
  - des mécanismes de contrôle homéostatique.

La modélisation permet de repérer ces motifs, les analyser et les tester virtuellement.

4- Tester des hypothèses biologiques

Grâce aux modèles, on peut :

- **Simuler** l'effet de l'activation ou de l'inhibition d'un gène,
- **Prédire** les conséquences d'une mutation ou d'une drogue ciblée,
- **Tester *in silico*** des combinaisons de perturbations, **[combinatoire]**
- **Proposer de nouvelles expériences** à partir des résultats simulés.