

Introduction to Systems Biology: Modelling of regulatory networks



Jean-Paul Comet (projet Bioinfo Formelle)

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

September 18, 2026

Teaching organization

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

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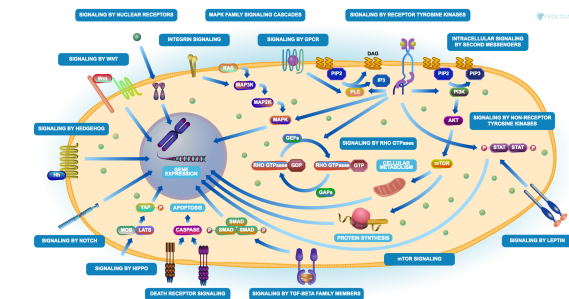
	sessions	hours	teacher
1	4 septembre 2026	13h30-16h30	GB
2	18 septembre 2026	13h30-16h30	JPC
3	25 septembre 2026	13h30-16h30	SD
–	30 septembre 2026	13h30-16h30	Group Project

- ▶ 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.

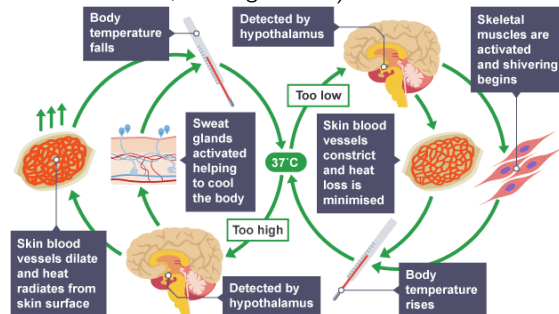
Examples of biol. functions piloted by regulation

Reg.
Networks

J-P Comet

Introduction
Objectives

- ▶ 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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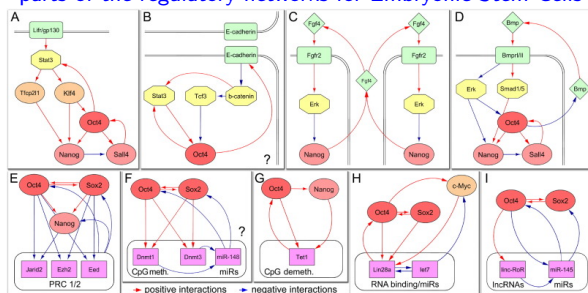
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parts of the regulatory networks for Embryonic Stem Cells



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

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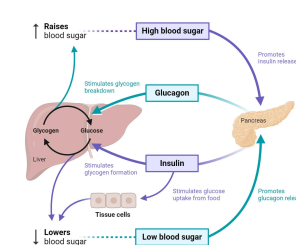
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Regulation of Blood Glucose



from <https://microbenotes.com/homeostasis/>

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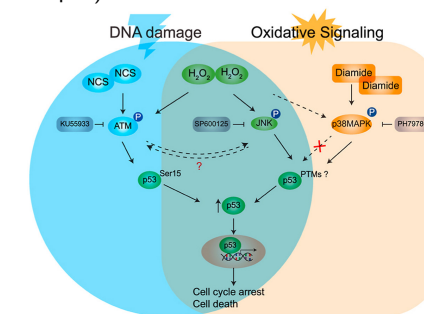
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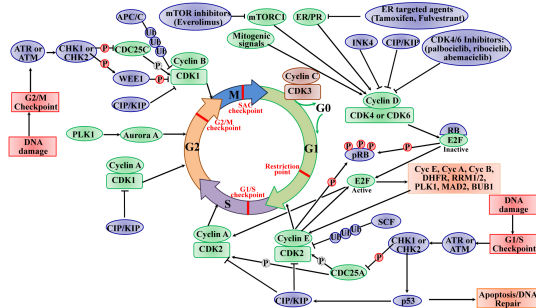
from <https://doi.org/10.1016/j.freeradbiomed.2021.06.013>

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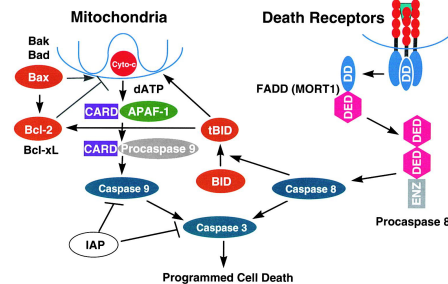


from <https://www.creativebiolabs.net/cell-cycle-regulation.htm>

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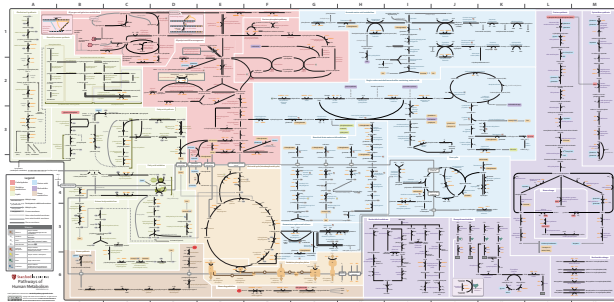
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from
[https://doi.org/10.1016/S0092-8674\(00\)00119-7](https://doi.org/10.1016/S0092-8674(00)00119-7)

Why is Modeling Necessary?

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

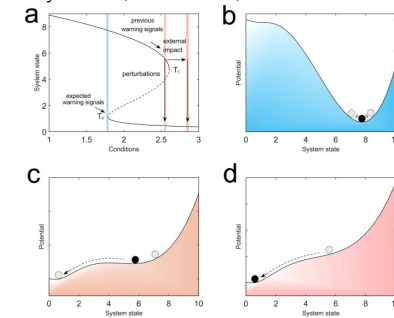


from <https://metabolicpathways.stanford.edu/>

- ▶ 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 :
⇒ 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.