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Introduction

Systems Biology is a recent field that studies how complex biological phenomena emerge from the fundamental building blocks of life. Understanding the mechanisms of the cell is essential in several areas such as drug development, biomedical research and biotechnological production. Current environmental concerns create a demand for sustainable energy sources such as biofuels (Fig. 1). Computational models allow the prediction of cellular behavior under different conditions and facilitate the selection of the optimal manipulations that produce the ideal phenotype for a specific application. These models are built in iterative cycles of experiment and refinement by multidisciplinary research teams that gather biologists, engineers and computer scientists. Although recent high-throughput technologies generate large amounts of (so-called *omics*) data for network reconstruction, we are still far from a whole-cell model that integrates all kinds of biological networks.

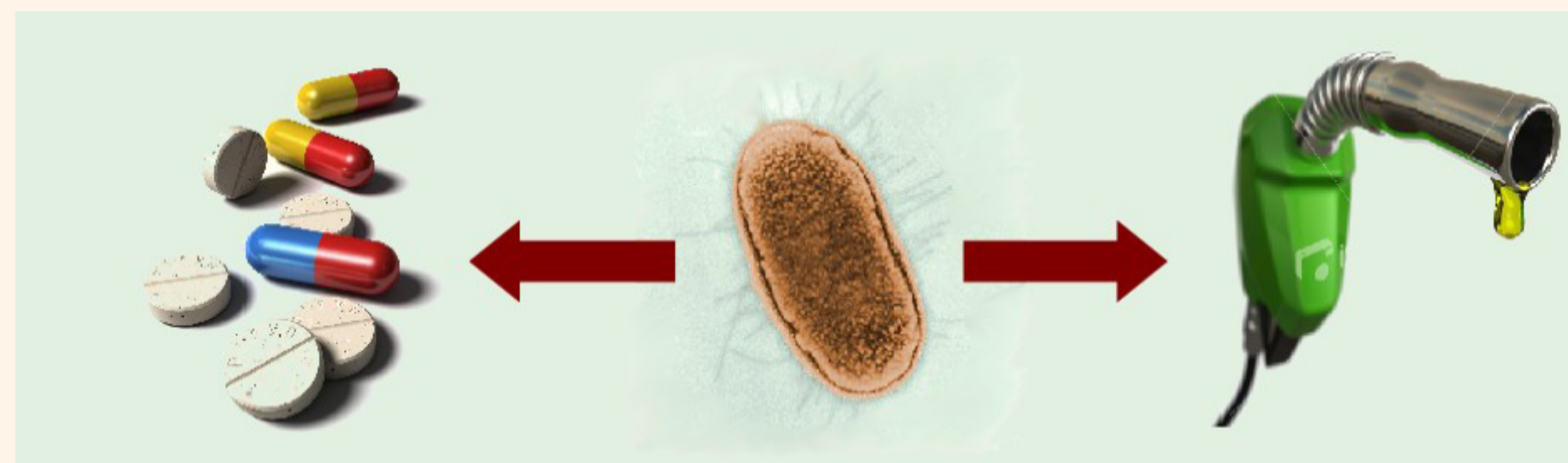
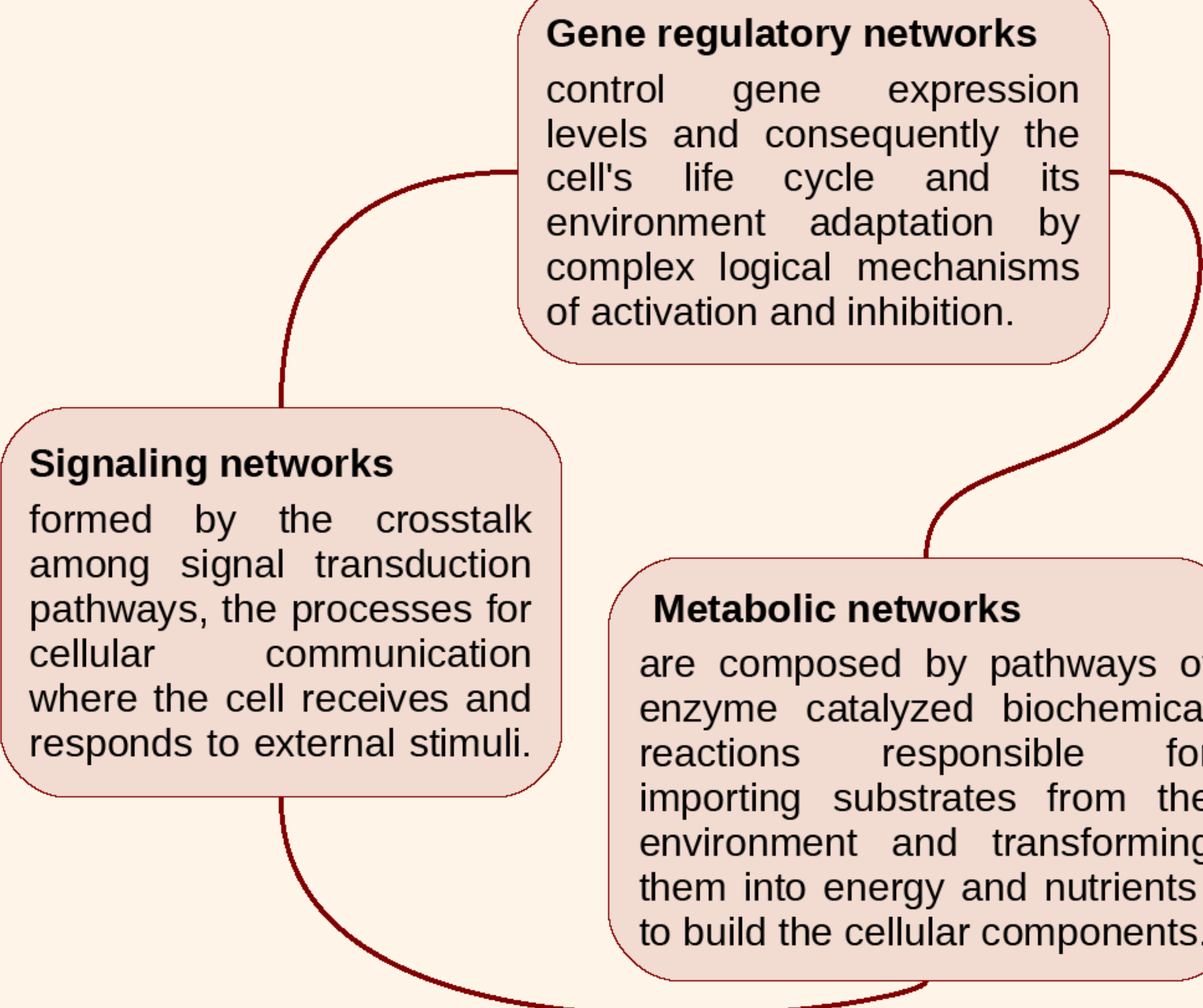


Figure 1: Microbes like *E. coli* can be genetically engineered for production of commodity products such as drugs and biofuels.

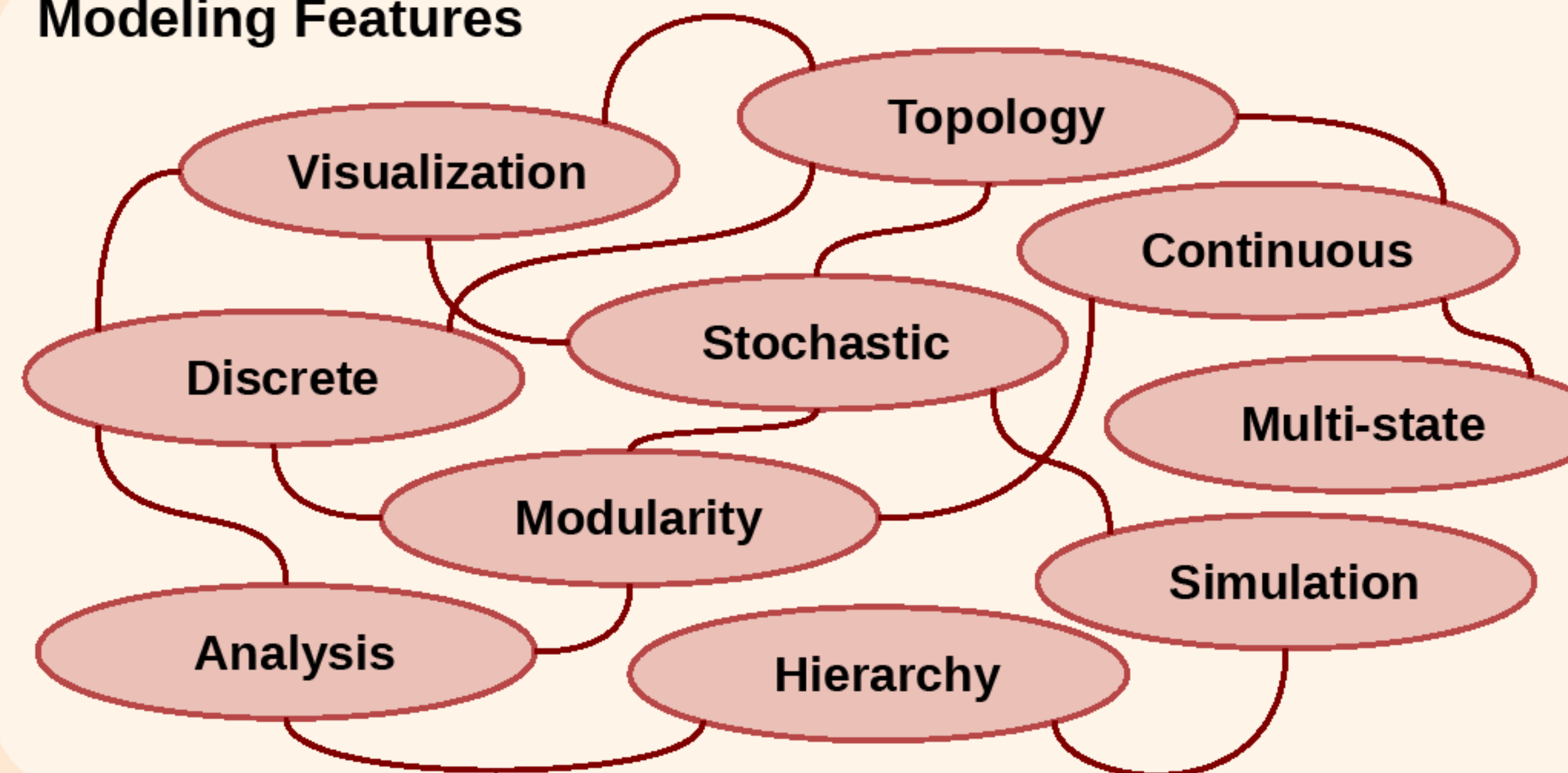
Objectives

- Classify the main types of biological network and understand the relevant modeling features to describe all the biological phenomena.
- Review modeling formalisms currently used in Systems Biology.
- Select a suitable formalism to create a common modeling framework for integrated analysis and simulation of different biological networks.
- Application on an integrated regulatory metabolic model of *E. coli*.

Biological Networks



Modeling Features



Modeling Formalisms

- Boolean networks:** used for modeling gene regulatory networks with boolean variables controlled by logic activation rules [5].
- Petri nets:** bipartite graphical and mathematical representation used for modeling all types of biological networks [6].
- Process algebras:** developed for communication systems, these formalisms are specially suited for modeling signaling networks [7].
- Constraint-based:** models based on imposition of mathematical constraints provide flexibility to handle the lack of kinetic detail [1].
- Differential equations:** accurate modeling framework for all types of biological models when all the kinetic details are known [8].
- Rule-based:** abstract rules for reaction generation that avoid the combinatorial explosion caused by multi-state components [2].
- Interacting state machines:** define relationships between the states of the parts of the system using a modular approach [3].
- Cellular automata:** suited for processes with spatial diffusion, it consists on a grid of components with spatiotemporal evolution [9].
- Multi agent systems:** use populations of autonomous agents with internal state, suited to relate external with intracellular behavior [4].

Conclusions

Although none of the formalisms fits all the required features, Petri nets seem one of the most promising. They use an intuitive graphical notation with sound mathematical basis, with several extensions available, such as, stochastic, continuous, hybrid, colored, and hierarchical. Building a tool for integrated analysis and simulation of all kinds of components is still challenging. As the size of models continues to grow, hierarchical modeling and support for different levels of refinement will become fundamental for understanding and handling the complexity of whole-cell models.

References

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