

From Bio-Inspired to AI-Driven Algorithms: Modeling, Simulation and Optimization of Complex Systems

Leonardo Giannantoni

This thesis investigates how computational intelligence can support the modeling, simulation, and design of complex biological systems. The work spans three inter-related contributions, each addressing a different level of abstraction in synthetic biology and biofabrication workflows.

The first contribution is a design space exploration (DSE) framework for *in silico* biofabrication protocol design. A genetic algorithm drives the optimization of spatiotemporal input sequences, evaluated through a multiscale simulation loop that integrates heterogeneous biological models. The approach is demonstrated in a case study on epithelial monolayer formation. While a supporting co-simulation library (CoSimo) was developed to implement the workflow, the focus of this contribution lies in the formulation and validation of the optimization strategy itself.

The second contribution is the Biology System Description Language (BiSDL), a domain-specific modeling language for synthetic multicellular systems. Designed as a ubiquitous language, BiSDL allows researchers to describe spatial, behavioral, and regulatory features in a structured, biologically meaningful format. These models compile to hierarchical Petri nets and are directly executable using an extended simulation backend. Case studies confirm its expressiveness and its ability to reduce the modeling burden in complex multicellular systems.

The final contribution applies reinforcement learning (RL) to the automated design of synthetic gene circuits. The RL-OvS framework treats simulation as an interactive environment and learns suitable parameters to induce target behaviors without the need for analytical gradients or training data. The method is evaluated on oscillator design tasks and serves as a proof of concept for the conceptual development of bioANN, a framework for biological neural networks.

Together, these methods aim to bridge the gap between abstract modeling and practical implementation. They emphasize modularity, clarity, and reusability, and contribute to a broader computational perspective on the design of programmable biological systems.