This thesis addresses the mathematical modeling of cellular culture processes through a structured progression across three levels of biological complexity: macroscopic dynamics, intracellular metabolism, and gene-level regulation. Each modeling approach is developed with increasing mechanistic detail, reflecting the core objective of better describing and connecting observable culture behavior with the molecular processes that drive cellular function. This stepwise exploration offers a refined and biologically grounded view of cellular systems with direct relevance to the design and optimization of biotechnological applications.

At the macroscopic level, a novel hybrid modeling approach was developed to describe the dynamic behavior of cellular cultures. This method uses elementary flux mode (EFM) analysis to derive a reduced metabolic reaction network capturing key pathways, and combines this inferred reaction scheme with kinetic modeling that integrates mechanistic rate laws and machine learning (artificial neural networks) for improved predictive accuracy. This enables data-driven refinement of kinetics while preserving a biochemical basis for the model structure.

At the microscopic model, a constructive methodology was established for elaborating intermediate-size metabolic networks. This bottom-up approach iteratively integrates fundamental biological knowledge (core pathways, thermodynamic constraints) with constraint-based modeling tools (flux balance, variability, and coupling analyses) to curate a metabolic network of manageable size. The method includes explicit modeling of energy metabolism (e.g., proton motive force) to improve physiological realism. Two case studies on photosynthetic microorganisms (a cyanobacterium and a microalga) illustrate the construction of detailed metabolic models under both steady-state and dynamic (diurnal) conditions.

At the genetic-integration level, a new framework was developed to couple metabolic models with gene expression models in the context of synthetic biology. By incorporating a burden-aware gene expression formulation, the model constrains metabolic fluxes based on enzyme availability and resource allocation within the cell. This integrated approach was applied to *E. coli* engineered with a synthetic pathway, allowing direct simulation of how changes in gene expression (through the promoter and ribosome binding site strengths of introduced genes) affect cellular growth and product formation.

Each modeling level yielded significant findings. The macroscopic hybrid model successfully overcame the combinatorial explosion of EFMs and improved predictive performance in animal cell culture case studies, showing that integrating neural networks can capture complex kinetics where traditional models fall short. The microscopic modeling approach led to validated metabolic networks for *Arthrospira* (yielding accurate flux predictions under various nutrient conditions) and *Tisochrysis* (capturing carbon storage dynamics in day/night cycles), demonstrating that mid-sized models can achieve a realistic balance between detail and tractability. The gene-

integrated model significantly reduced the solution space of feasible flux distributions by enforcing regulatory constraints, and it identifies optimal gene expression strategies for maximizing the biosynthesis of a metabolite of interest (p-coumaric acid) while maintaining cell viability. Collectively, these results form a coherent multi-scale modeling strategy: the higher-level models benefit from mechanistic grounding, and the lower-level models are informed by broader physiological context, all contributing to a more comprehensive understanding of cellular behavior.