# MODEL-BASED PREDICTIVE CONTROL AND STATE ESTIMATION STRATEGIES FOR BIOPROCESS OPTIMIZATION

Bioprocesses, characterized by their inherent complexity and dynamic behavior, present significant challenges in the design of effective control strategies. In particular, hybridoma and microalgae cultures exhibit intricate metabolic and physiological properties, which are difficult to model, predict, and control for optimal performance. This work explores model predictive control and state estimation strategies to address these challenges, providing a framework for optimal bioprocess control.

The research begins with an extensive review of control theory, emphasizing modeling, parameter identification, state estimation, optimization, and control techniques applicable to dynamic systems. Building on this foundation, the application of some of these techniques then proceeds, demonstrating the applicability of control and estimation frameworks with hybridoma and microalgae cultures serving as case studies. Both systems share basic similarities – as bioprocesses; however, their metabolic behaviors are distinctly different, making them particularly interesting as benchmarks for the aforementioned techniques.

Hybridoma cultures, pivotal in monoclonal antibody production, exhibit metabolic shifts that influence productivity, necessitating precise control of substrate and byproduct levels. Considering technical difficulties that arise in measuring the main species for metabolic control – i.e., glucose and glutamine, this work investigates metabolic thresholds and develops a novel observer for estimating alternative critical variables such as lactate and ammonia concentrations. After verifying the system's observability, a novel approach combining algebraic model rearrangement and a version of an Extended Kalman Filter (EKF) observer, which is adapted as an Unknown Input Observer (UIO), is deployed to estimate critical subproduct variables – i.e., lactate and ammonia concentrations, enabling real-time calculation of reaction rates. The integration of this observer with a Nonlinear Model Predictive Control (NMPC) strategy demonstrates enhanced control performance and robustness through computational simulations. The controller-observer scheme is then analyzed in the presence of measurement noise and initial condition error to emulate real conditions.

In the case of Microalgae cultures – which hold promise for sustainable applications in biofuels, food, health, animal feed, wastewater treatment, and environmental protection; the research leverages experimental data to identify and validate a mathematical model. Early in the study, microalgae cultures were observed in an experimental phase with photobioreactors in laboratory facilities, where diverse operational conditions were explored. Particular attention is placed on both the inhibitory effects of light irradiance and the optimization of dilution rates. Parameter correlation and identifiability are addressed systematically. Based on the identified physics-based model, and provided a study on the system's observability, a tailored NMPC strategy is

developed – including an EKF state estimation, manipulating these inputs to maximize biomass production. Moreover, a Receding Horizon Observer (RHO) is also implemented, including an extension into an adaptive control form; i.e., an ARHO. Last, in the face of limitations exhibited by physic-based models when the complexity under consideration is increased, a proposal with a hybrid model using neural networks is built, achieving a better representation of the system – even under adverse simulation conditions, opening the door to future applications.

As a result of theoretical analysis, experimental validation, and computational simulations – using MATMAB/Simulink and Python – this thesis demonstrates the efficacy of advanced control methodologies in managing bioprocess complexity, the versatility of NMPC in handling nonlinear dynamics, and the importance of integrating state estimation to mitigate real-time measurement challenges.