

“Methodology for developing complex kinetic models, structured on multiple levels of detail (hybrid), used in (bio)chemical engineering calculations regarding optimization of industrial biochemical or biological reactors”

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Abstract

The thesis develops a new biochemical engineering calculation methodology aimed at optimizing the operation of industrial synthesis bioreactors in the food or pharmaceutical industries. This novel approach represents a significant improvement compared to the classical ("default") methods. Specifically, the new modular, deterministic, structured, hybrid kinetic models (MCSMD)—which utilize continuous variables and are based on cellular metabolic reaction mechanisms—are highly original, being structured across at least two levels of bioprocess detail. These models link the kinetics of key cellular reactions involved in the studied bioprocess—belonging to the central carbon metabolism (CCM)—to the dynamics of macroscopic species within the bioreactor under analysis. In the case of multi-enzyme reactions, the MCSMD models detail the interactions between enzymatic reaction modules, connecting them to the dynamics of macroscopic state variables in the industrial semi-continuous (fed-batch/FBR) reactor being studied.

In concrete terms, these dynamic MCSMD models are constructed using the concepts, principles, rules, procedures, and computational algorithms specific to the chemical and biochemical engineering [Maria, 2017]. Through two relevant illustrative examples, the thesis aims to demonstrate the superiority of these two-level structured hybrid kinetic models (MCSMD) for the high-precision, *off-line, in silico* optimization of operating regimes for industrial semi-continuous (FBR) bioreactors. The advantages of using MCSMD hybrid kinetic models over classical ones (such as Monod-type models) stem from their increased prediction accuracy and a significantly higher level of detail regarding the number of species included in the model. For the first time, these dynamic hybrid MCSMD models—validated against experimental data from the literature and collaborators—can predict biomass adaptation to fluctuating bioreactor conditions over hundreds of cell cycles, enabling the dynamic adjustment of FBR operating conditions. The two case studies address the optimization of operating regimes for industrial reactors used in: a) the biosynthesis of tryptophan (an essential amino acid) using genetically modified *E. coli* cultures [Maria, 2021; Maria and Renea, 2021], and b) the synthesis of mannitol (a synthetic sweetener) via a complex bi-enzymatic process [Gijiu, Maria and Renea, 2024]. The thesis makes a remarkable contribution—not only theoretically but also practically—by generating substantial economic benefits through increased bioreactor productivity under optimized operating conditions, alongside reduced raw material consumption.