

Mathematical Formulation and Numerical Methods for the Optimization of Novel Biotherapeutics Manufacturing

by

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Abstract

The emergence of multiple classes of novel biotherapeutics, such as nucleic acids, and cell and gene therapies, are enabling the efficacious treatment of many diseases. A key part of unlocking the full potential of these novel therapeutics and delivering these life-saving medications to patients is the development of efficient biomanufacturing processes that are able to ensure product quality at scale. To that end, digitalization is currently seen as one of the key enabling technologies for driving advances in the industry. A vital component of digitalization process is a computational model of the system, which can then be leveraged for various objectives such as accelerating process development and deploying advanced process control strategies.

In the case of novel biotherapeutics, not only are the manufacturing processes less well understood, these processes and the therapeutic itself can be more complex compared to those for conventional biologics or small molecule drugs. Consequently, the development of mechanistic models for these systems is much harder as there is less established process insight and experimental data available. To address this challenges, this thesis applies concepts and methods from process systems engineering to formulate, develop, and deploy mechanistic models for the production of two classes of biotherapeutics: lipid nanoparticles (LNPs) for nucleic acid delivery, and viral particles. In parallel, ancillary work to develop numerical algorithms to enable the efficient and accurate solution of these models is pursued.

This thesis can be broken down into three parts: Part 1 explores the conceptualization and formulation of mechanistic models for LNP and viral particle production. Recognizing the paucity of modeling approaches available in the literature for these systems, the use of first principle concepts such as mass and energy balances and insights from adjacent fields in formulating the models are discussed.

Part 2 outlines the development of numerical algorithms for the solution of two classes of partial differential equation systems that are essential for modeling these systems, namely population balance models (PBMs) and phase-field models (PFMs). The proposed method for PBMs uses a combination of variable transformations, specially constructed meshes, operator splitting, and solving the equation at the limit of

numerical stability to achieve efficient (in some cases, as low as memory reallocation) and accurate (in some cases to machine precision) solution of many classes of PBMs. For the PFM, a spline approximation is used to regularize the logarithmic nonlinearity found in physically-accurate forms of the Cahn–Hilliard equation which enables its solution at model parameter values otherwise inaccessible.

Part 3 showcases the development and deployment of these models with the development of a multi-scale model for LNP production, and the application of advanced process control for a continuous viral bioreactor. The proposed multi-scale model for LNP production adopts incorporates a computational fluid dynamics (CFD) model at the mixer-scale and thermodynamic modeling at the molecular-scale, to yield salient information which is cascaded into a PFM model at the particle-scale. For the control of the continuous viral bioreactor, the use of nonlinear economic model predictive control is demonstrated to be able to achieve a variety of process objectives such as maximizing yield and purity and is also shown to be robust under plant-model mismatch.

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