Process Analytical Technology and Digital Biomanufacturing of Monoclonal Antibodies

Moo Sun Hong, Weike Sun, Amos E. Lu, and Richard D. Braatz*

Department of Chemical Engineering, Massachusetts Institute of Technology, Cambridge, MA
** Corresponding author (braatz@mit.edu)*

Abstract

Biomanufacturing is moving toward digital manufacturing with increased application of process analytical technology (PAT) and continuous manufacturing. This article discusses strategies and components of the digital biomanufacturing approach, including mechanistic models and their validation, automation of the construction of models by data analytics and machine learning to improve efficiency and improve model quality, and real-time feedback control of critical quality attributes (CQAs).

Keywords

Biomanufacturing, Biopharmaceutical manufacturing, Process analytical technology, Continuous manufacturing, Process data analytics

Introduction

Among biologics, monoclonal antibodies (mAbs) are the highest selling class, particularly because of their specific action and reduced immunogenicity.[1] As mAbs facilitate better targeted immunological approaches of treating many diseases including cancer, the market demand is projected to have continual growth for the foreseeable future, except for the temporary reduction in market due to supply and demand failures associated with the COVID-19 outbreak.[2] Much of the market needs will come from mAbs which are currently under regulatory review, which includes drugs for diseases such as Alzheimer's that afflict much larger populations than most current mAbs.[3] As such, biopharmaceutical manufacturing processes will need to be developed to produce new mAbs for this growing market. This article describes methods and strategies being developed to shorten the time required to develop an efficient and reliable biomanufacturing process for mAbs. Although the focus of this article is on mAbs, most of the methods and strategies also apply to other biological drug products, as well as for small-molecule pharmaceuticals.

Process Analytical Technology and Quality by Design

The development of efficient and reliable biopharmaceutical manufacturing processes relies on Process Analytical Technology (PAT) which is "a system for designing, analyzing, and controlling manufacturing through the timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality."[4] Measuring critical quality attributes (CQAs) on-line leads to increased process understanding of multivariable interactions and dynamics and is used to construct process models.[1] The process models range from data-driven to first principles based on the degree of process understanding (Figure 1).[5] Product quality can be consistently improved with advanced control algorithms enabled by real-time process measurements and process models from PAT,[1] which implements Quality by Design (QbD) promoted by regulatory agencies.[6]

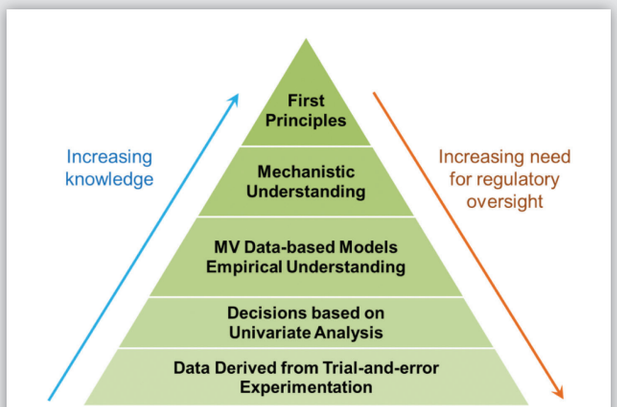

Figure 1. Knowledge pyramid for model-based decision making. Higher layers in the pyramid correspond to greater knowledge, more informed and better reliability of decision making, and lower requirements for regulatory oversight. "First-principles" refers to models involving rather complete mechanistic understanding, e.g., chemical reaction stoichiometry and kinetics; constitutive relationships that define the kinetics of mass, heat, and momentum transfer; and mass, energy, and momentum conservation equations. Adapted from Ref. 5.

Continuous and Digital Manufacturing

In addition to collecting data on-line and constructing models, batch-to-continuous transition of biomanufacturing is increasingly being developed and applied to improve product quality and reduce manufacturing costs (Figure 2).[7-9] Several academic groups and companies have demonstrated the direct connection of all upstream and downstream operations to form a continuous or semi-continuous biopharmaceutical manufacturing facility.[10-12] Continuous biomanufacturing necessitates a plant-wide control strategy to handle the propagation of impurities and other disturbances caused by tight integration of continuous unit operations,[13] which have been demonstrated for small-molecule pharmaceuticals.[14-16]

The above strategies and technologies ultimately lead biomanufacturing to digital manufacturing, which is an integrated approach to manufacturing centered around a computer system. Digital manufacturing is enhanced by using modern system engineering tools.[1,11] Modeling and simulation provide increased mechanistic fidelity, better empirical approaches, and automated decision making. Process optimization enables drug- and patient-specific manufacturing and reduces experimental costs. Process control deals with process variations and enables fully automated systems to minimize operator error. Synergy between these tools enhances the potential benefits to digital biomanufacturing.[1,11] Laboratory-scale continuous biomanufacturing unit operations and facilities are ideal for evaluating and validating the development of digital manufacturing, as well as for associated tools for data analytics, modeling, control, and quality assurance.

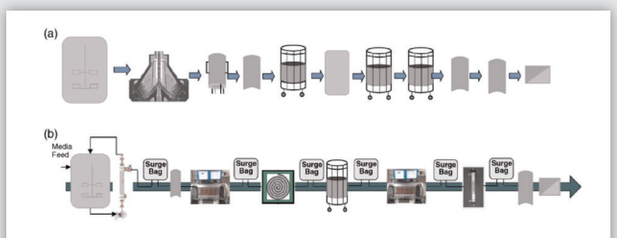

Figure 2. High-level process flow diagrams for (a) batch and (b) continuous manufacturing of monoclonal antibodies. In batch processing, each batch unit operation runs to completion and then has its output sent to the next batch unit operation. Batch operation has hold steps consisting of the entire quantity of material in between each unit operation, with all material generated in the bioreactor staying in the system for a long time before making it through the polishing steps. The continuous operation can potentially include small surge tanks or single-use bags for priming and managing flow between unit operations. Figure courtesy of Wiley-Blackwell.[12]

Process Data Analytics and Machine Learning

Well-validated mathematical models are unavailable for much of the important phenomena and interactions in biopharmaceutical manufacturing, which means that much of the models for design of safe operating regions ("design spaces") require the use of data analytics (DA). The number of available data analytics methods and software packages has grown exponentially over the last decade, which are collectively called machine learning in the data science community. Machine learning methods have been demonstrated to significantly improve both model accuracy and reliability for both identifying and building relationships between critical process parameters and critical

quality attributes for an industrial mAb manufacturing process.[17,18] Experience in the application of surface response methodology, partial least squares, and principal component analysis does not directly translate over to many of the modern machine learning (ML) tools, which typically require a high degree of expertise to apply effectively. One of the challenges today is how to work through the large number of available methods and tools for each specific dataset to figure out how to construct the most accurate and reliable models.

A smart process data analytics software has been developed to assist manufacturers in selecting the best DA/ML tools for a biomanufacturing dataset based on its specific characteristics and on expert domain knowledge.[17-19] The user is able to specify their needs and input special data properties for special handling of the data. For automated model construction, a rigorous nested cross-validation procedure is implemented, which provides accurate estimates of model accuracy. This software is built in Python with a user-friendly interface. The user provides data sets and information asked in the software, and then the final model and model performance are provided from the software.

Looking into more details into how this software works, its first step is to apply tools to automatically interrogate the dataset to ascertain its characteristics such as nonlinearity, dynamics, and multicollinearity. The extent of correlation and nonlinearity is quantified by matrix correlation analysis and nonlinearity quantification. The extent of dynamics is quantified using serial cross-correlation and autocorrelation. Then, based on the degree of characteristics, a best-in-class data analytics tool is selected from the data analytics triangle (Figure 3). The data analytics triangle is constructed based on literature review, theoretical analysis, and case studies and maps modeling techniques to data characteristics. Lastly, the final model is constructed using a fully automated rigorous cross-validation procedure. The cross-validation involves splitting the data into training, validation, and testing. The training and validation datasets are used to fit the model and tune hyperparameters in the modeling procedure, respectively. The test dataset is used to provide an unbiased evaluation of the model accuracy. Model bias is minimized by using a nested cross validation procedure, in which many splits of the original data into the three sets are used in the model construction and evaluation.

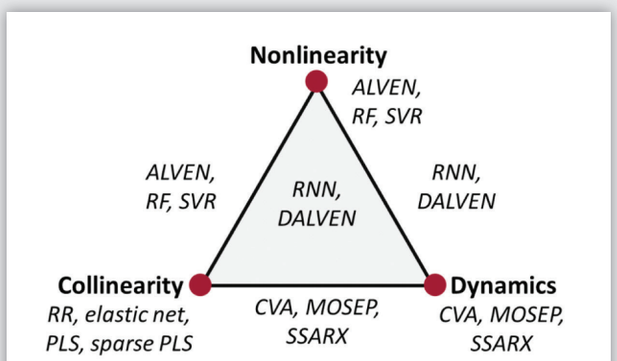

Figure 3. The data analytics triangle for predictive modeling with a single response variable. The modeling techniques are mapped to three major model regression characteristics. ALVEN, algebraic learning via elastic net; CVA, canonical variate analysis; DALVEN, dynamic ALVEN; MOESP, multivariable output error state space; PLS, partial least squares; RF, random forest; RNN, recurrent neural network; RR, ridge regression; SVR, support vector regression. Adapted from Ref. 19, which describes the individual algorithms in the figure in detail.

Nearly all of the DA/ML methods in Figure 3 are well established in the literature, with software implementations available in Python, R, or Matlab. The new methods are algebraic learning via elastic net (ALVEN) and its extension to modeling dynamic relationships (dynamic ALVEN),[20] which combine machine learning with expert knowledge in the form of algebraic relationships that commonly arise in biological and chemical processes. These methods balance model complexity and prediction accuracy through a two-step feature selection procedure, to produce an interpretable model useful for process applications while avoiding overfitting.

Closing

This article describes strategies and technologies for an integrated digital approach for the manufacturing of monoclonal antibodies, which includes process analytical technology and Quality by Design, continuous manufacturing, first-principles modeling, process data analytics and machine learning, and unit operation and plant-wide control. Process measurements from PAT are used for development and validation of first-principles and data-driven models for biopharmaceutical manufacturing processes, to provide insights into impurity rejection and multivariable interactions and dynamics between unit operations. These models enable the design of advanced control algorithms to manufacture the highest quality products.

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Author Biographies

Moo Sun Hong *is a researcher in the group of Prof. Richard D. Braatz at the Massachusetts Institute of Technology (MIT). He received an M.S. in Chemical Engineering Practice from MIT and the Jefferson W. Tester Prize for enthusiasm and leadership in the Practice School. He has constructed mathematical models for multiple bioreactor configurations and does research in the model-based design and control of continuous protein crystallization and viral inactivation.*

Richard D. Braatz *is the Edwin R. Gilliland Professor of Chemical Engineering at the Massachusetts Institute of Technology (MIT). He leads the process analytics, modeling, design, and control activities of many (bio)pharmaceutical manufacturing efforts at MIT, which are primarily in continuous manufacturing. He has consulted or collaborated with more than 20 companies including Novartis, Pfizer, Takeda, Merck, Biogen, and Amgen. He is a member of the U.S. National Academy of Engineering.*