Model Predictive Controller Design For Bioprocesses Based On Machine Learning Algorithms

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Abstract: The optimization of critical quality attributes in biopharmaceutical processes demands the development of a scalable and optimal control scheme to meet the process constraints and objectives. In this paper, we designed a model predictive controller (MPC) to find the optimal feeding strategy to maximize cell growth and metabolite production in fed-batch bioprocesses. Due to high complexity of bioprocesses and lack of high-fidelity first principle models, we evaluated the use of machine learning algorithms in the forecast model to aid in our development. By taking advantage of the bioprocess model, this controller aims to maximize the protein production daily for each batch. The control scheme of the bioprocess is defined as an optimization problem to be solved while all metabolites and cell culture process variables are maintained within the specification. To evaluate the performance of the controller, we designed and implemented MPC with the best model to a bioreactor in a real experiment. The experimental validation confirms more than 2% improvement in final protein production compared to average historical experiments.

1. INTRODUCTION

The biopharmaceutical industry continuously strives to improve productivity while ensuring the process remains reliable and cost-effective. With the advent of Industry 4.0 capabilities such as new digital technologies, higher computational power, better integration flexibility, and artificial intelligence, new avenues have emerged to meet these objectives. One of these is by harnessing process data to improve the way we control the process. Recently, many smart factories have attempted to manage various process scenarios and process automation using adaptive models without human intervention, [Catlin et al. (2017)]. To achieve this successfully, advanced control of the processes in real-time is necessary.

Due to a variety of challenges such as scarcity of measurements and process complexities, the control of biopharmaceutical processes has rarely evolved beyond simple PID control of small sets of variables in practice [Whitby et al. (2019); Sen et al. (2014)]. In such processes, the traditional method of control aims to manipulate the extracellular environment to control the intracellular reactions of the culture [Boudreau and McMillan (2006)]. Model predictive control (MPC) is an advanced multi-step control method that is not only efficient in multivariate process control but can also address the constraints imposed by both the manipulated variables (inputs) and the controlled vari-

ables (outputs) [S.J. Qin (2003)]. The main component of the MPC is the dynamical model of the process which is used to determine the optimal control action leading to an optimized and feasible objective ahead of time.

In the literature, there are a variety of first-principle and data-driven models for bio processes [Craven et al. (2013); Tulsyan et al. (2018)]. The first-principle models are mostly obtained based on Monod kinetics and enzymatic schemes which bring about nonlinear state models with many unknown free parameters [Craven et al. (2014)]. On the other hand, the use of data-driven methods for the purpose of process monitoring and control are intensively studied [Kiran and Jana (2009); Tulsyan et al. (2020)]. The choice of model is important as it affects the computational load as well as the accuracy and reliability of the control policy. Neural network models have been used in many works for the purpose of controller design in fed-batch fermentation processes [Chtourou et al. (1993); Patnaik (2003)]. Unfortunately, due to the time-varying characteristics of the fed-batch fermentation and limited number of training data, the models typically do not have high accuracy.

As stated above, models such as Monod kinetics may result in a large number of unknown parameters. However, the discrete feed stream in fed-batch processes may cause insensitivity of the target variables to the feed strategy.

Furthermore, the complex multilevel reactions in the process, quick adaptability of cells in the process [Sinclair and Kristiansen (1987)], and random variability that occurs during a batch operation, may also decrease the accuracy of these simplified models [Jose et al. (1999)].

The objective of the present study is to perform an analysis on the performance of linear and nonlinear regression models in model predictive control of fed-batch processes. Due to the strong relation between glucose level (GLC) and other cell culture variables, the regression models are designed to capture the correlation between each variable and GLC. Furthermore, the relationship between GLC and glucose feed volume ($feed$) is governed by mass balance of the total glucose in the system. The combination of the mass balance and regression model constitutes a hybrid model that represents the behavior of the fed-batch process. Initially, a linear regression model is developed and then a neural network model with a number of regressors is trained. Next, the MPC is designed based on the best model to determine the optimal $feed$ strategy that can produce maximum viable cell density (VCD) in the culture.

2. BIOPROCESS MODELING

In order to model the bioprocess, we needed data from real experiments. The data set may be used for identification of unknown parameters in physics-based models or used to train supervised learning models based on machine learning algorithms. Although first-principle models cover large ranges of the process operation, the common ones found in the literature are non-structured and non-segregated models which need to be fine-tuned based on the system identification techniques.

2.1 Data sets

The experiments were carried out in an Amgen Process Development laboratory and the process under consideration is a fed-batch process with 35 batches. The data were collected every day and each batch of the experiments was run 12 days. The operating variables of the experiments were *pH, dissolved Oxygen, temperature* and *feed* in the culture. The experiments were designed by controlling the operating variables at predefined set points. Based on process knowledge and post experimental factorial analysis, we confirmed that *feed* is the most effective input for this process. During the experiment, viable cell density (VCD), viability ($VIAB$), and metabolite concentrations such as glucose (GLC), lactate (LAC), Glutamine (GLN), Glutamate (GLU), Ammonium (NH_4), Sodium (Na), Potassium (K), and Osmolality ($OSMO$) were also recorded. We developed models of these variables at each step based on their values of previous steps. All data are collected every day and are cleaned properly to address data quality issues. The cleaning process included outlier removal and missing data imputation.

For this fed-batch process, the *feed* contained a high concentration of glucose and was added in bolus at specific times to the bioreactor. As a result, the recorded data contains many zero values for *feed* in each batch. The sparsity in the *feed* caused problems in process identification and modeling. In the next section we will discuss how this issue is resolved.

The historical data in this work are collected from $2L$ and $3L$ bioreactors. The bioreactor might be fed either with glucose or nutrient feed solutions; in addition, the nutrient feed may increase the bioreactor volume by 25%. The nutrient feeds are added to the bioreactors in the middle of the culture in a rule-based fashion. In order to exclude the impact of the volume change, we converted all the data set to non-volume based format. For instance, the unit of VCD is in number of cells and unit of *feed* is in grams (g).

2.2 Modeling

The first principle models found in the literature show that there is a physical relationship between *feed* and cell culture variables and to model this relationship properly, at each time point, the data of each model parameter needs to be available and identified. In order to identify the model parameters, the parameter data should be collected with uniform time intervals. As discussed in Section 2.1, adding bolus *feed* in the fed-batch bioprocess means that the *feed* level added might be zero at some sample times. This causes the process to have non-uniform *feed* input and as a result the model parameters may not be identified appropriately. In other words, this issue caused by the sparse and non-uniform *feed* addition in the *feed* data set makes the model insensitive to the *feed*, which is not desirable for controller design. However, since glucose is the metabolite of interest and it is a major composition of the *feed*, we can simplify the *feed* complexity and focus on evaluating the mass balance between *feed* and GLC levels as follows:

$$GLC[t+1] = GLC[t] + \Delta t \left[feed[t] - K_s[t] \times \frac{VCD[t+1]}{VCD[t]} \right] \tag{1}$$

where $K_s[t]$ is the glucose consumption rate at time t which will be discussed later. As discussed in the past section, all the quality attributes are in non-volume based format and the last term on the right hand side of (1) updates the consumption rate per cell basis.

Similarly, the data-driven models can also suffer from the sparsity in the *feed* data set if *feed* is used as an input in the model structure. Since GLC level varies over time (i.e. does not suffer from sparsity) and it has a physical relationship with *feed* (1), we can also use GLC as the input in the data-driven model. Thus, to have a comprehensive model of the whole bioprocess, we can combine the data-driven model with the glucose mass balance equation (1) and create a hybrid model.

Machine learning   Since the behavior of every bioprocess is unique, we tried a variety of machine learning models to pick one with high accuracy and low complexity. As described in Section 2.1, the bioprocess under consideration has 11 states. Moreover, it was discussed that the evolution of each state (cell culture variables) over time may depend on the past values of GLC and 10 other variables. As a result, a variety of regressors may be considered in the modeling process.

In order to find the best model, linear regression for multi-regressor models were created. Since the bioprocess is

complex, nonlinear models were also developed and the best fit was found to be a two-layer neural network model. First, a linear model was created where each variable is taken as a function of that variable and the GLC level, that is one-step behind. This two-regressor linear model is defined as,

$$X_i[t+1] = a_i^1 X_i[t] + a_i^2 GLC[t] + a_i^3 \qquad (2)$$

where a_i^j ($j \in \{1, 2, 3\}$) are the model parameters to be identified through model training and $X_i[t]$ is the ith state at time t. Second, to make one-step ahead prediction for each variable, a neural network model of that variable together with GLC from the last 3 time steps were combined to create the model. This model is a six-regressor nonlinear model defined as:

$$X[t+1] = F_{tr}(X[t], X[t-1], X[t-2],$$
$$GLC[t], GLC[t-1], GLC[t-2]) \quad (3)$$

where F_{tr} is a nonlinear six-regressor neural network model.

It should be noted that in both scenarios each state is predicted based on the past values of that state and GLC only. The models could include other quality attributes as regressors, but they do not improve the model performance considerably.

Remark. *The consumption rate, $K_s[t]$ in (1) is an internal process variable that is not easily measured. Hence, it is estimated using (1) and based on past values of GLC and feed as follows:*

$$K_s[t] = \left[feed[t-1] - \frac{GLC[t] - GLC[t-1]}{\Delta t} \right] \frac{VCD[t-1]}{VCD[t]}$$
$$(4)$$

Indeed, we are estimating the consumption rate based on the latest measurement as this property normally has smooth changes over the culture. However, if rapid changes occur, it can be filtered using Monte-Carlo estimation of $K_s[t]$ by taking the average of the estimations from the beginning of the batch until time t.

2.3 Model selection

In order to develop models for the variable of interest, the supervised learning models were trained using 80% of the dataset and then the rest of the dataset was used for testing. These models represent the evolution of each metabolite over time in each batch. In the process of training and testing the models, a mixed data set from all batches was used. Table 1 represents the root mean square error (RMSE) for one-step ahead prediction of the metabolites with linear and nonlinear models. In order to develop a good non-linear model a larger dataset is required compared to developing a linear model. From this table we can observe that the RMSEs based on the linear model structure are almost half of that for nonlinear model. We do expect the non-linear model's RMSEs to improve as we accumulate more data for the model. Due to the lower RMSEs from the linear model, we decided to move forward with the linear model for the MPC design. In addition, from an optimization point of view, simpler structure of the linear model imposes less complexity for the optimal control. These benefits all together led us to select the linear model as the best model for MPC design.

3. CONTROL METHODOLOGY

We cast the model predictive control of the bioprocess as a discrete-time optimization problem to find the optimal *feed* strategy. Each control decision is the amount of *feed* at a specified time point. As the reactions in the bioprocesses are slow, the control action was calculated every day.

3.1 Optimization problem

Our MPC framework strives to minimize the difference between the cell culture variables' quantities and the set points while ensuring that the variables remain within the specification. Hence, a constrained optimization problem over a finite time horizon can be formulated for every batch.

Objective function The main goal in this work is to maximize productivity of the bioprocess while the byproducts are minimized. As a result, desired thresholds were defined for each variable and the objective function was developed as the summation of quadratic errors between the variables and their desired set points over the time horizon,

$$\underset{X_i(i=1,\ldots,11), feed}{\text{minimize}} \qquad J(X_i[t], feed[t]) \qquad (5)$$

where

$$J(X_i[t], feed[t]) = \sum_{k=1}^{T_P} \sum_{i=1}^{11} W_i (X_i[t+k] - X_i^{ref}[t+k])^2$$

$$+ \sum_{j=1}^{T_C} W_{feed} (feed[t+j-1] - feed[t+j-2])^2 \quad (6)$$

In (6), T_P, T_C, W_i, W_{feed}, and $X_i^{ref}[t]$ are prediction horizon, control horizon, weight parameter for state $X_i[t]$, weight parameter for *feed* (input), and set point for state $X_i[t]$, respectively. It should be noted that the parameters in the objective function (6) need to be tuned for the bioprocess.

Constraints As discussed in Section 2.1, every bioprocess is productive when the cell culture variables vary with a predefined specification. If the cell culture variables go beyond the specification, the process would deviate from the norm and the quality of the product may be adversely impacted. Moreover, it does not make sense for the cell culture variables' concentrations to become negative. Consequently, based on the bioprocess expectations, we may consider constraining the normalized value of all

Table 1. Normalized average RMSEs in one-step ahead prediction with linear and nonlinear models

Metabolite	Linear model RMSE	Nonlinear model RMSE
VCD	1.00	1.92
TCD	1.00	2.16
VIAB	1.00	1.71
LAC	1.00	1.32
GLN	1.00	2.02
GLU	1.00	1.58
NH4	1.00	1.74
Na	1.00	2.04
K	1.00	1.31
OSMO	1.00	1.39

bioprocess variables to remain in the boundaries defined as follows:

$$0 \leq VCD, TCD \tag{7a}$$
$$0 \leq LAC, GLN, GLU, NH4, K \leq 1 \tag{7b}$$
$$0.2 \leq GLC \leq 0.8 \tag{7c}$$
$$0.4 \leq VIAB \leq 1 \tag{7d}$$
$$0.18 \leq Na \leq 1 \tag{7e}$$
$$0.33 \leq OSMO \leq 1 \tag{7f}$$

Remark. *The linear and nonlinear models that were proposed in section 2.2 have only one input (feed). If we consider non-zero weights for variables other than VCD in the cost function (6), that would mean that the controller is driving multiple variables toward their set points with only a single input. Moreover, since the main objective is to maximize VCD, a high threshold value can be used while the other variables are constrained so that they remain within the aforementioned ranges.*

Remark. *The LMPC problem is a convex optimization while the nonlinear MPC is non-convex. In order to solve either convex or non-convex problems, at each time step, the optimizer iterates the gradient descent for Lagrangian function to optimize the process input over the prediction horizon [Kiran and Jana (2009)]. For the convex problem, these iterations end up with a global minima at each time step while the non-convex problem has the potential of never converging. Additionally, the optimizer in nonlinear MPC may truncate the iterations if the gradient descent method does not converge to global minima, which could report an incorrect value. Furthermore, it is worth mentioning that the solution to the LMPC is globally optimal when the state constraints are considered as soft constraints. If these constraints are hard constraints, then the solution to the optimization problem might become infeasible. As a result, the global optima obtained by the linear model in LMPC is counted as another advantage over the nonlinear models in MPC problems.*

3.2 Implementation of Linear MPC (LMPC)

In order to find the optimal *feed* strategy for the bioprocess, the optimization problem needs to utilize a process model to predict the optimal behavior over the prediction horizon. In Section 2.2, a two-regressor linear model was selected as the best one with more accuracy and less complexity.

In order to evaluate the performance of LMPC against the rule-based control technique, we considered two bioreactors at Amgen Process Development laboratories. One bioreactor was fed based on the LMPC glucose feed recommendations and the other (Manual) was controlled by the lab operators based on the traditional techniques. As mentioned before, both bioreactors are fed by nutrient feed (glucose excluded) in the middle of the batches. Moreover, as the normalized *GLC* level in the bioreactors was bounded in the range of 0.2 and 0.8, if LMPC recommended higher *feed*, we cut it off to meet the upper bound of *GLC* level. It is important to note that after the experiment was performed, the team realized that the media was not batched properly for the LMPC condition. As a result, the LMPC condition had 2% less nutrients every time the bioreactor was fed compared to the Manual condition.

In the next section, the results of MPC problem will be shown by considering the optimization with the linear model. Since the model, objective function and the bounding constraints are all convex, the linear MPC problem will be convex optimization and its solution will be globally optimal.

Remark. *Due to the process-model mismatch, the state constraints may not be satisfied over the prediction horizon which makes the MPC problem infeasible. In order to maintain the feasibility in the linear MPC problem described above, it is assumed that the state constraints are soft constraints so that the solution is globally optimal.*

4. RESULTS AND DISCUSSION

The following section shows the experimental results of linear MPC with the objective to maximize *VCD*. Note that all trends are in per volume basis and y-axes have been normalized for proprietary reasons. In the design of LMPC a prediction horizon of 30 days and a control horizon of 8 days were considered. Moreover, the weights for all the batches are considered as 1 while the weight of the control move (W_{feed}) is 5. The intention for such a selection is to penalize abrupt changes in the feed pump. Finally, the Desired Targets (as calculated from experimental data) for the variables are shown in Table 2.

Table 2. Desired targets for cell culture variables in LMPC

Metabolite	Value
VCD^{ref}	2
TCD^{ref}	2
$VIAB^{ref}$	85
GLC^{ref}	0.3
LAC^{ref}	0.1
GLN^{ref}	0.16
GLU^{ref}	0.08
$NH4^{ref}$	0.08
Na^{ref}	0.22
K^{ref}	0.26
$OSMO^{ref}$	0.6

Figure 1 represents the cumulative evolution of protein production over the batch. Since little measurable *titer* is produced prior to day 4, the plot shows the measurement from day 4 onward. A closer look at Figure 1 confirms that the *Titer* production trends are very similar in both bioreactors up to day 8; however, their ratio fluctuates from day 9 to 11 and finally the *Titer* produced by LMPC stays a bit higher than the Manual. Table 3 shows the normalized protein production in Manual and LMPC against the average among the past experiments controlled by rule-based techniques. This table confirms 2% increment in productivity of the LMPC bioreactor.

Figures 2-4 show the trajectories of process quality attributes in LMPC bioreactor against the Manual bioreactor. From Figure 2, it is clear that the *VCD* trajectory in the Manual bioreactor travels higher than that of LMPC over the culture, but LMPC produces higher *Titer*. This means that the LMPC's glucose feeding increased the specific productivity of the culture when compared to the manual reactor. Based on these results, the LMPC glucose feeding led to more productive cells instead of more

Table 3. Protein production through average of past offline experiments, Manual, and LMPC normalized to offline data

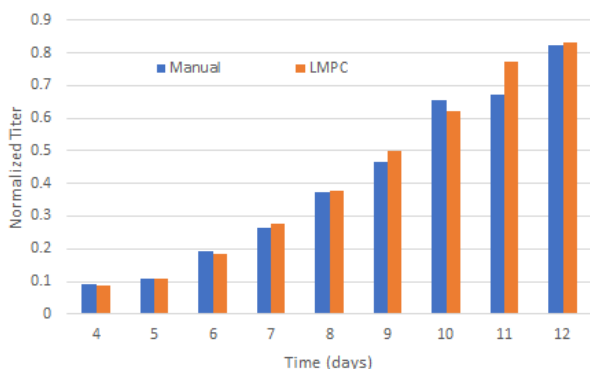| Experiment	Offline data	Manual	LMPC
Produced Titer	1	1.007	1.02

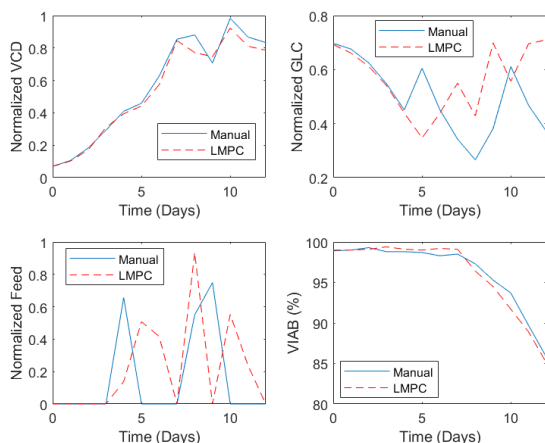Fig. 1. Production of *Titer* over the batch

Fig. 2. Trajectories of *VCD*, *feed*, *GLC*, and *VIAB* in bioreactors

cell production. This is important considering the LMPC reactor was underfed nutrients by approximately 2%. If the proper amount of nutrients was fed to the LMPC reactor, it is believed that the *VCD* and therefore *Titer* production for this reactor would have been higher. The overall trend of the resulting *VCD* fluctuates over time and such fluctuation in *VCD* is expected as the high volume of bolus *feed* and cell growth would cause the cell density to drop or increase in the culture. This figure also shows that LMPC tries to maintain the *GLC* at a higher level by recommending more *feed*. Indeed, The LMPC recommended feeding approximately 35% more glucose than the Manual condition. However, LMPC did not feed glucose until day 5 while the Manual condition fed on day 4. The lack of day 4 *feed* led to LMPC's lower *VCD* on days 5-7. On the other hand, the viability of the cells remains at the same level over the batch which confirms LMPC bioreactor has had a healthy environment for the cell.

Nutrient feed is essential for the bioreactors to be added on days 4 and 8 which includes *K*, *GLN*, and *Na*. Figure 3 illustrates the trajectories of these metabolites in both
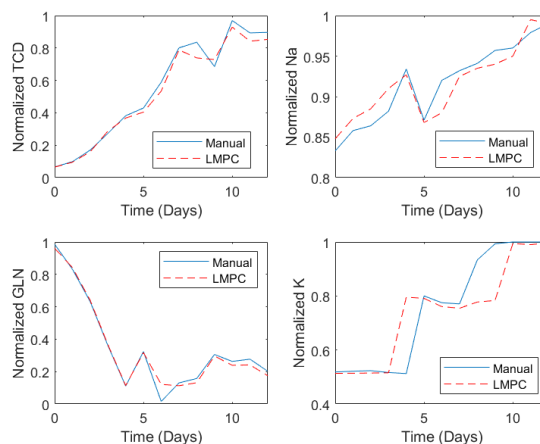

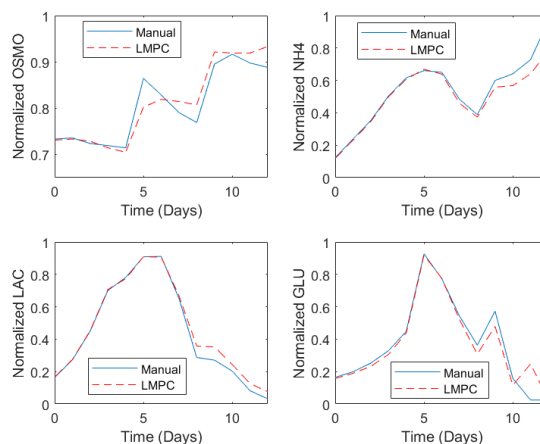Fig. 3. Trajectories of *TCD*, *Na*, *GLN*, and *K* in bioreactors

Fig. 4. Trajectories of *OSMO*, *NH4*, *LAC*, and *GLU* in bioreactors

bioreactors; however, the measured *Na* drops on day 4. Although these measurements are quickly obtained by the offline analyzer in the laboratories, the reason for this drop might be either because of volume change caused by Nutrient feed or the uncertainty of the measuring devices. The plots for *GLN* and *K* show that the corresponding levels have increased with the addition of nutrient feeds. In addition, Figure 3 also shows the trajectory of *TCD* which confirms the similarity with *VCD* trend in Figure 2.

By evaluating Figure 4, it was also observed that the undesirable byproducts of both bioreactors, such as *NH4* and *LAC*, have very similar trajectories over the batch; however, the *NH4* level of the Manual bioreactor stays higher on the last days. As shown in Figure 4, the other variables such as *OSMO* and *GLU* also have similar trajectories in both bioreactors. Since there is no overall benefit from the byproducts perspective, the simpler and more consistent LMPC is more desirable.

We also further analyzed the samples from the culture after harvesting and observed that the protein itself was also purer in LMPC, leading to more favorable Main peak and Basic Peak 3 results from the CEX-HPLC assay.

By combining the *Titer* production and product quality benefits, the LMPC has the potential to reduce costs by 5% or save the equivalent of 1 production batch every 20 batches.

Finally, it should be noted that each of linear and nonlinear MPC may provide a variety of benefits through the control of bioprocesses. Therefore, the authors are currently actively developing and investigating the nonlinear MPC application on a real process.

5. CONCLUSION

The focus of this paper was to demonstrate the application of machine learning and model predictive control on bioprocesses using real data. Bioprocess modeling based on both first-principle techniques and machine learning algorithms were evaluated; however, it was found that a hybrid model combining these two techniques provided the best model for this bioprocess. Based on the machine learning algorithm, we obtained a linear model and a nonlinear model; however, the linear model represented a higher accuracy. We implemented the designed LMPC to a real bioreactor and compared its performance against another bioreactor controlled by the rule-based control technique. The resulting experiments showed that LMPC led to higher protein production with higher protein quality than the Manual while maintaining all the quality attributes and byproducts in a desired range. Finally, we concluded that the simple structure of LMPC produced 2% more product than rule-based control technique on average.

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