Critical Quality Predictive Control of
Fed-Batch Mammalian Cell Bioreactors *

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Abstract: A model predictive control (MPC) formulation for a mammalian cell fed-batch
bioreactor processes is developed. A nonlinear fundamental model for the bioreactor is used
to generate a database of historical runs comprising of the measurement variables and the
manipulated input feed flow rate to the bioreactor. The database is used with subspace
identification methods to develop a state-space model of the process. The identified model is used
to design various MPC formulations with different objective criteria, including the conventional
trajectory-tracking objective function and a novel terminal objective for maximizing the product
yield at completion of a run. Case studies involving the simulated bioreactor process demonstrate
the efficacy of the MPC algorithms subject to unknown disturbances, random variations
in the inlet feed glucose and glutamine concentrations, and measurement noise. Compared
to the traditional proportional-integral control algorithm, the trajectory-tracking predictive
control algorithm is able to better track the reference glucose concentration set-point with
an improvement of 5.1% in the tracking error. The critical quality attribute predictive control
algorithm designed to maximize the product yield results in a 3.9% increase in the product
concentration at the completion of the run.

Keywords: model predictive control, system identification, fed-batch bioreactor process,
mammalian cell culture, critical quality attribute control

1. INTRODUCTION

Batch and fed-batch processes account for a significant
proportion of the production capacity in the pharmaceutical industry due to the flexible nature of their operation (Birol et al., 2002). Most fed-batch processes in the
pharmaceutical industry are run around a constant operating point to maintain ideal conditions for production.
In many cases, the fed-batch pharmaceutical processes
are operated in an open-loop manner, with low yields of
high-valued pharmaceutical products. This operating policy potentially reduces the production yield significantly,
rendering the fed-batch processes inefficient. The high-
value final product makes determination of an optimal
control profile important, especially for product yield maximization (Papathanasiou et al., 2017; Cao et al., 2016; Lu
et al., 2019). Improving the yield of fed-batch processes in
pharmaceutical industry necessitates developing an accurate model of the fed-batch pharmaceutical process and
solving complex constrained mathematical optimization
problems. The determination of optimal feed rate profiles
is an important control problem in many fed-batch pharmaceutical processes. The solution of the optimal control
problem for fed-batch processes is challenging because
of the nonlinear system dynamics and the presence of
state and input constraints. To overcome this issue, the
control problems are formulated and solved using simple
and computationally tractable surrogate models, rather
than the nonlinear fundamental first-principles models of
the processes (Jackson et al., 2018). The development
of simple approximation models of the complex nonlinear mechanistic models enables efficiently capturing the
relationships among the system inputs and outputs to
predict the process operation (Caballero and Grossmann,
2008; Bhosekar and Ierapetritou, 2018; Yoshio and Biegler,
2021). The approximation models mimic the behavior of
the fed-batch process accurately while being computationally efficient to evaluate.

Various approximation methods have been reported in the
literature. This work concentrates on the use of data-
driven, global approximations using system identification
techniques. The readily exploitable linear models are often preferred due to the convenience of identifying linear
state-space models through numerically efficient projection tools emanating from prudent numerical techniques
like singular value decomposition (SVD) or even QR factorization. While parametric methods, such as predictor-
error methods or maximum likelihood estimation techniques, for estimation of state-space models exist, they
often require solving complex nonlinear and possibly non-
convex optimization problems (Rashid et al., 2017, 2019).
In contrast, the subspace identification methods typically
involve projections, which are computationally efficient to
compute and thus directly amenable for development of

computationally tractable models that can be used for the design of predictive controllers. Once such a global approximation is attained, it can be readily leveraged to gain insight into the behavior of the underlying system as the surrogate models are easily queried, optimized, visualized, and seamlessly integrated into optimal control strategies like model predictive control (MPC) (Allgöwer et al., 1999; Rawlings, 2000).

The typical trajectory-tracking predictive control (TTPC) approach is valid for operating continuous processes around an equilibrium point. However, for batch and fed-batch processes that transition through multiple operating modes with transient nonlinear dynamics, the TTPC approach may be suboptimal for the objective of maximizing the yield of the high-value product. In contrast to TTPC, formulations specifically designed for the unique criteria of batch and fed-batch processes are required. One such predictive control formulation tailored to the unique circumstances of the fed-batch processes is the critical quality attribute predictive control (CQAPC) formulation. In the CQAPC approach, the objective of closely tracking a reference trajectory is replaced with the objective of maximizing a desired critical quality attribute, such as the product yield, at the completion of the fed-batch operation. Moreover, constraints can be imposed on the state and input variables throughout the fed-batch operation for process safety or to maintain suitable operating conditions. Such predictive control formulations are generally better suited for the control of fed-batch processes employed in the pharmaceutical industry. One such pharmaceutical fed-batch process that is typically operating in an open-loop manner and stands to benefit from the implementation of novel MPC formulations is the mammalian cell fed-batch bioreactor process for culturing Chinese hamster ovary cells to produce monoclonal antibodies. However, the development of MPC algorithms for fed-batch mammalian cell bioreactor processes is challenging due to lack of predictive, tractable mathematical models representing the underlying bioprocess system.

Motivated by the above consideration, in this work, we demonstrate the use of system identification to develop a model of the fed-batch bioreactor processes and the implementation of model-based control to maximize therapeutic product yields. The proposed algorithms are demonstrated using a test-bed Chinese hamster ovary mammalian cell bioreactor simulator. The test-bed bioreactor simulator is developed from the models proposed in the literature (Craven et al., 2014; Gan et al., 2018). The simulation environment enables the design and evaluation of prototype modeling and control approaches before deploying the algorithms in industrial settings. The system identification approach develops state-space models able to characterize the dynamic future evolution of the fed-batch mammalian cell bioreactor. Besides predicting the entire dynamic evolution of the bioreactor operation, the model facilitates design of predictive control algorithms to achieve the desired closed-loop performance relative to a specified objective. The capabilities of the model are leveraged to design a controller that may, depending on the objective, maintain desired quality attributes and improve the cost effectiveness of the process. The proposed approach will improve the operation of the fed-batch therapeutic protein production process.

2. DESCRIPTION OF THE PROCESS

The fed-batch pharmaceutical process can be compactly expressed as

$$\dot{x}(t) = f\left(x(t), u(t)\right) + w(t) \tag{1}$$
$$y_k = g(x_k) + v_k \tag{2}$$

where $x(t) \in \mathbb{R}^n$ is the vector of system state variables at time t (with $n = 8$), $u(t) \in \mathbb{R}^m$ is the vector of manipulated input variables (in this case, the inlet feed flow rate, $m = 1$) at time t, $f : \mathbb{R}^n \times \mathbb{R}^m \to \mathbb{R}^n$ is a nonlinear function representing the dynamic behavior of the fed-batch process, $w(t) \in \mathbb{R}^n$ is the process noise, k is the discrete time index (i.e., x_k means $x(t_k)$), $y_k \in \mathbb{R}^p$ is the output measurements available at time instant t_k, $g : \mathbb{R}^n \to \mathbb{R}^p$ is the output measurement function and the measurement noise $v_k \sim \mathcal{N}(0, R_k)$ with covariance $R_k > 0$. In this work, we use the fundamental mechanistic model of the mammalian cell bioreactor process as a surrogate for the industrial process. Each run of the mammalian cell fed-batch bioreactor is initialized with state variables drawn from a Gaussian distribution, such that $x(0) \sim \mathcal{N}(x_0, \Pi_0)$, with $\Pi_0 > 0$. We use historical batch runs generated from the simulated fed-batch process to model the process with system identification algorithms, and the identified state-space models are subsequently used to design predictive control algorithms.

3. DATA-DRIVEN BATCH PROCESS MODELING

In this section, we first review the subspace identification approach used to identify linear time-invariant state-space models of batch and fed-batch processes, followed by simulation results demonstrating the efficacy of the modeling approach.

3.1 Subspace Identification Approach for Batch and Fed-Batch Processes

We briefly review the conventional subspace-based state-space system identification approach used to determine the system matrices of a discrete-time state-space model (Moonen et al., 1989; Negiz and Cinar, 1997; Negiz and Ç inar, 1997; Ljung, 1998; Qin, 2006; Liu et al., 2013). A model of the following form is identified:

$$\tilde{x}_{k+1} = A\tilde{x}_k + Bu_k + w_k \tag{3}$$
$$y_k = C\tilde{x}_k + Du_k + v_k \tag{4}$$

where $\tilde{x} \in \mathbb{R}^{\tilde{n}}$ denotes the vector of state variables, $y \in \mathbb{R}^p$ denotes the vector of output measurements, $u \in \mathbb{R}^m$ denotes vector of manipulated inputs, and the system matrices have appropriate dimensions. The process noise $w \in \mathbb{R}^{\tilde{n}}$ and the measurement noise $v \in \mathbb{R}^p$ are assumed to be zero mean, white noise, with covariance matrices:

$$\mathbb{E}\left[\begin{pmatrix} w_p \\ v_q \end{pmatrix} \begin{pmatrix} w_p^T & v_q^T \end{pmatrix}\right] = \begin{pmatrix} Q & S \\ S^T & R \end{pmatrix} \delta_{pq}$$

where $\mathbb{E}[x]$ is the expected value of variable x and δ_{pq} is the Kronecker delta.

The system identification approaches use Hankel matrices constructed from process measurements and manipulated inputs. For an arbitrary batch b in n_b total batches with $n_s^b + 2i - 1$ samples, the 'future' and 'past' output Hankel matrices are developed as follows

$$Y_f^b = \begin{bmatrix} y_{i+1|i} & y_{i+2|i} & \cdots & y_{i+n_s^b|i} \end{bmatrix} \tag{5}$$

$$Y_p^b = \begin{bmatrix} y_{1|i} & y_{2|i} & \cdots & y_{n_s^b|i} \end{bmatrix} \tag{6}$$

where i is a user-specified parameter that is greater than the observability index, or the system order $\tilde{n}$, and $y_{k|i}$ is composed of vectors of stacked output measurements as

$$y_{k|i} = \begin{bmatrix} y_k^T & y_{k+1}^T & \cdots & y_{k+i-1}^T \end{bmatrix}^T$$

The input block Hankel matrices U_f^b and U_p^b are defined similarly. The individual block Hankel matrices of various batches are assembled together as

$$Y_f = \begin{bmatrix} Y_f^1 & Y_f^2 & \dots & Y_f^{n_b} \end{bmatrix} \tag{7}$$

and likewise for Y_p, U_f, and U_p.

The repeated iterative application of the model equations yield

$$Y_f = \Gamma_i X_f + \Phi_i U_f \tag{8}$$

$$Y_p = \Gamma_i X_p + \Phi_i U_p \tag{9}$$

where X_f and X_p are the future and past state sequences, Γ_i is the extended observability matrix, and Φ_i is the lower block Toeplitz matrix, the matrices being as

$$\Gamma_i = \begin{bmatrix} C \\ CA \\ CA^2 \\ \vdots \\ CA^{i-1} \end{bmatrix} \quad \Phi_i = \begin{bmatrix} D & 0 & 0 & \cdots & 0 \\ CB & D & 0 & \cdots & 0 \\ CAB & CB & D & \cdots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ CA^{i-2}B & CA^{i-3}B & CA^{i-4}B & \cdots & D \end{bmatrix}$$

The realization of the unknown system states can be obtained by computing the intersection between the past and future input-output spaces, with the intersecting space readily determined by the application of singular value decomposition (Moonen et al., 1989). Once an estimate of X_f for each of the batches is computed, a system realization is readily obtained by solution of a least-squares problem.

3.2 Data-Driven Modeling Results for Mammalian Cell Bioreactor Process

The precursor to model-based predictive control algorithms is the availability of a reliable and accurate model that is able to describe the transient dynamic evolution of the fed-batch bioreactor process. A high-fidelity model of the batch process is developed in this work for use in predictive control formulations. The model is identified with five output measurement variables ($p = 5$: glucose, glutamine, lactate, ammonia, and product concentrations), and the only manipulated input is the feed flow rate for fed-batch operation. Using trial and error, the order of the identified state-space model is $\tilde{n} = 8$. The greater order of the identified linear state-space model helps to better characterize the nonlinear dynamics of the underlying processes. A total of 20 batches is used to identify the state-space model, with each batch starting from a randomly sampled initial condition for the state variables, and each

batch having a duration of 150 h with output variables sampled every 15 min.

Table 1 provides the root-mean-square error (RMSE) and mean absolute percentage error (MAPE) for predicting the overall batch trajectory from the incipient phase of the batch until the completion of the batch process. Fig. 1 illustrates the prediction results for a select test batch of the mammalian cell bioreactor process. Note that the predictions are conducted in an open-loop manner, with feedback correction of the estimates through an observer only during the first 10 sampling instances, after which the outputs are predicted without correcting for the errors through feedback. Therefore, the prediction results presented here are a true depiction of the predictive capability of the model, as the output variables are predicted through the entire transient evolution of the batch duration and the prediction errors are allowed to accumulate and are not corrected through feedback. This prediction represents the worst-case scenario for the longest duration prediction horizon at the incipient phase of the fed-batch mammalian cell bioreactor process. As the batch process progresses, the prediction of the dynamic trajectory of the process improves owing to the shorter prediction horizons. With the fidelity of the model established, we next discuss the closed-loop predictive control results.

4. MODEL PREDICTIVE CONTROL OF FED-BATCH PROCESS

In this section, we detail the mathematical formulations of the trajectory-tracking predictive control (TTPC) and the critical quality attribute predictive control (CQAPC) algorithms. Then we analyze the results of the proposed predictive controllers.

4.1 Trajectory-Tracking Predictive Control

A predictive controller for tracking reference trajectories of mammalian cell fed-batch bioreactor is presented. The optimal control action at the ith sampling instance is computed by solving the following finite-horizon optimal control problem:

$$\min_{u \in \mathbb{U}} \mathcal{J} = \sum_{k=i}^{n_p} \|\hat{y}_k - \bar{y}_k\|_{Q_w}^2 + \|\Delta u_k\|_{R_v}^2 \tag{10}$$

subject to

$$\hat{x}_{k+1} = A\hat{x}_k + Bu_k, \ k \in \{i, \dots, n_p - 1\} \tag{11}$$

$$\hat{y}_k = C\hat{x}_k + Du_k, \ k \in \{i, \dots, n_p\} \tag{12}$$

$$\hat{x}_k = \bar{x}_k \tag{13}$$

where the objective function is a summation of tracking error and rate of change of inputs from the current sampling instance i to the batch termination n_p, $u \in \mathbb{R}^m$ denotes the vector of constrained input variables, taking values in a nonempty convex set $\mathbb{U} \subseteq \mathbb{R}^m$. A positive semi-definite symmetric matrix Q_w is used to penalize the deviations of the outputs from their nominal values and a strictly positive definite symmetric matrix R_v is used to penalize changes in the manipulated variables. The first term in the objective function (Eq. 10) penalizes discrepancies between the predicted output trajectories $\hat{y}$ and the reference trajectories $\bar{y}$ over the prediction horizon n_p and the second term is a move suppression term that

Table 1. Quantitative comparison of output prediction results for 10 test batches of the mammalian cell bioreactor process

	Glucose Concentration	Glutamine Concentration	Lactate Concentration	Ammonia Concentration	Inhibitor Concentration
RMSE (mM)	0.41	0.037	0.64	0.034	0.40
MAPE (%)	2.38	1.00	13.8	1.01	6.21
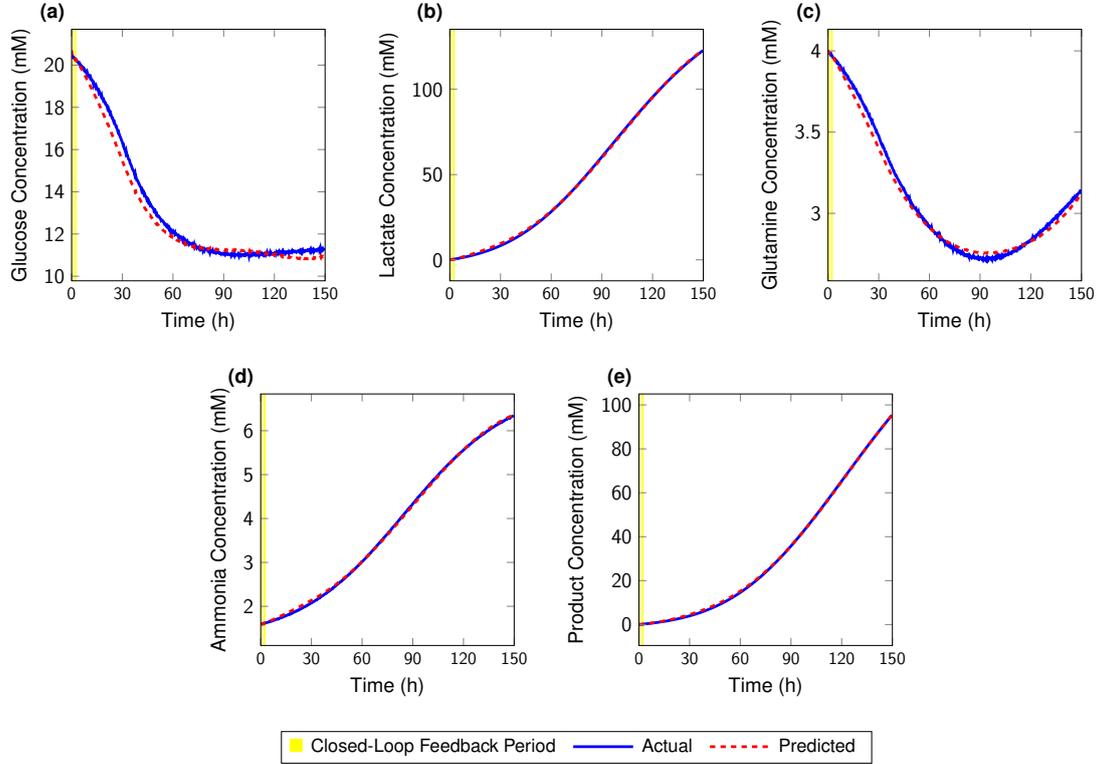
Fig. 1. Prediction results for a select batch of the mammalian cell bioreactor process. The closed-loop feedback period (yellow shaded area) represents the first 10 sampling instances where feedback correction is applied to the state estimates from a Kalman filter algorithm, after which there is no corrective action applied to the predictions and the errors are allowed to accumulate throughout the duration of the batch.

penalizes the magnitude of input changes. The TTPC formulation uses the identified state-space model, Eqs. 11 and 12, to predict the future evolution of the fed-batch bioreactor. Further, $\bar{x}_k$ in Eq. 13 provides the initialization of the state variables at the current sampling instance. The TTPC formulation detailed here can be used to predict the future dynamic trajectory of the bioreactor and solve for the optimal inputs that enable tracking a glucose set-point trajectory profile.

4.2 Maximum Yield Predictive Control

A predictive controller for achieving a maximum end-point critical quality attribute in the mammalian cell fed-batch bioreactor processes is presented. The optimal control action at the ith sampling instance is computed by solving the following finite-horizon optimal control problem:

$$\min_{u \in \mathbb{U}} \ \mathcal{J} = \hat{y}_{n_p}^q \tag{14}$$

subject to

$$\hat{x}_{k+1} = A\hat{x}_k + Bu_k, \ k \in \{i, \ldots, n_p - 1\} \tag{15}$$
$$\hat{y}_k = C\hat{x}_k + Du_k, \ k \in \{i, \ldots, n_p\} \tag{16}$$

$$\hat{y}_{n_p}^q = \beta\hat{x}_{n_p} \tag{17}$$
$$\hat{x}_k = \bar{x}_k \tag{18}$$

where $u \in \mathbb{R}^m$ denotes the vector of constrained input variables, taking values in a nonempty convex set $\mathbb{U} \subseteq \mathbb{R}^m$. The term $\hat{y}_{n_p}^q$ is the prediction of the end-point critical quality attributes as a linear combination of the state variables at the final sampling instant n_p, as shown in Eq. 17. The objective function, Eq. 14, maximizes the predicted end-point critical quality attributes. The predictive controller detailed here can be used to predict the future dynamic trajectory of the bioreactor by employing the identified state-space models, Eqs. 15 and 16, and solve for the optimal inputs that enable maximization of the yield of the bioreactor.

4.3 Predictive Control Results

In this subsection, we compare the proposed MPC algorithms with the proportional-integral-derivative (PID) control algorithm and the open-loop operation with bolus inputs (OLBI) where a amount of feed is occasionally added to the bioreactor, typically once per day.

TTPC Results A trajectory-tracking predictive controller is implemented for the closed-loop control of the fed-batch bioreactor process. The predictive controller tracks the glucose reference set-point value by manipulating the feed flow rate into the bioreactor. Compared to the conventional proportional-integral (PI) control algorithm, the TTPC algorithm better tracks the reference glucose trajectory. A total of 10 closed-loop test batches are simulated with disturbances in the feed composition, specifically including random variations in the glucose and glutamine concentrations of the feed, to demonstrate the disturbance rejection ability of the controllers. We also compare the closed-loop control algorithms with the open-loop operating mode where bolus inputs (OBLI) are added to the fed-batch bioreactor with a 24-hour sampling time, with the quantity of the daily bolus feed calculated as the amount that yields a bioreactor glucose concentration of 20 mM. The average integral of squared error of 10 testing OLBI is found to be 4.83×10^3, while the average integral of squared error of the 10 closed-loop batches for the TTPC algorithm is found to be 1.85×10^3, compared with 1.95×10^3 for the conventional PI controller. The TTPC has , an improvement of 61.7% and 5.1% relative to the OLBI approach and PI control algorithm, respectively. The closed-loop performance of the TTPC and conventional PI control algorithms are is shown in Fig. 2 for a select closed-loop batch of the mammalian cell bioreactor. The glucose concentration reference set-point in the bioreactor is 11 mM in the closed-loop simulation of the TTPC and PI control algorithms to ensure that sufficient glucose is present for the cell growth and proliferation. It is readily observed that the TTPC algorithm tracks the reference set-point closer than the PI control algorithm, resulting in better disturbance rejection performance and a lower tracking error.

CQAPC Results A predictive controller with the objective of maximizing the product yield at the termination of the run is implemented for the closed-loop control of the fed-batch bioreactor process. The CQAPC predicts and maximizes the product yield at the end of the run and mitigates disturbances that reduce the final product concentration. The manipulated variable in the CQAPC is the volumetric feed flow rate into the bioreactor. Compared to the TTPC algorithm, the CQAPC algorithm designed to maximize the bioreactor product yield results in 3.9% higher product concentration. The CQAPC increases the feed flow rate, thus increasing the glucose and glutamine available for cell proliferation and therapeutic protein production. A total of 10 closed-loop test batches are simulated with disturbances in the feed composition, specifically random variations in the feed composition, to demonstrate the disturbance rejection ability of the controllers. The average product concentration of 10 testing closed-loop batches for the CQAPC algorithm is found to be 99.7 mM, compared to 95.7 mM for the TTPC algorithm. The closed-loop performance of the TTPC and CQAPC algorithms is shown in Fig. 2 for a select closed-loop batch of the mammalian cell bioreactor. The OLBI operating mode has poor product yield performance due to lack of feedback and predictive control of the fed-batch process, with 96.1 mM product concentration at the completion of the run. The OLBI operating mode is not suitable for rejecting disturbances and maximizing the product concentration in the fed-batch process.

The product yields across all 10 closed-loop test batches are shown in Fig. 3. It is readily observed that the CQAPC increases the product concentration, resulting in disturbance rejection performance, while the therapeutic protein product yield is maximized. Although the improvement in the therapeutic protein product concentrations is modest, it can have substantial effects on downstream processing (purification and recovery) of the final product. It is noteworthy that the proposed model-based predictive control algorithms are not dependent on a fixed duration of the fed-batch run, and the model and control algorithms do not need to be modified for fed-batch runs of varying durations. Therefore, CQAPC algorithm can be readily implemented for fed-batch runs of varying durations, and the CQAPC will maximize the product concentration at the end of the batch regardless of the run duration.

5. CONCLUSION

The predictive control of the mammalian cell bioreactor process is investigated through the use of a simulation test-bed platform. A system identification approach is used to develop computationally tractable state-space models that are leveraged to design MPC algorithms. A trajectory-tracking predictive control algorithm is formulated and shown to have better disturbance rejection abilities compared to the conventional proportional-integral control algorithm. A critical quality attribute predictive control approach is developed to maximize the product yield at the completion of the bioreactor run. The simulation platform will be a useful tool for the development of the Industry 4.0 software tools and algorithms, facilitating advanced manufacturing in the pharmaceutical industry.

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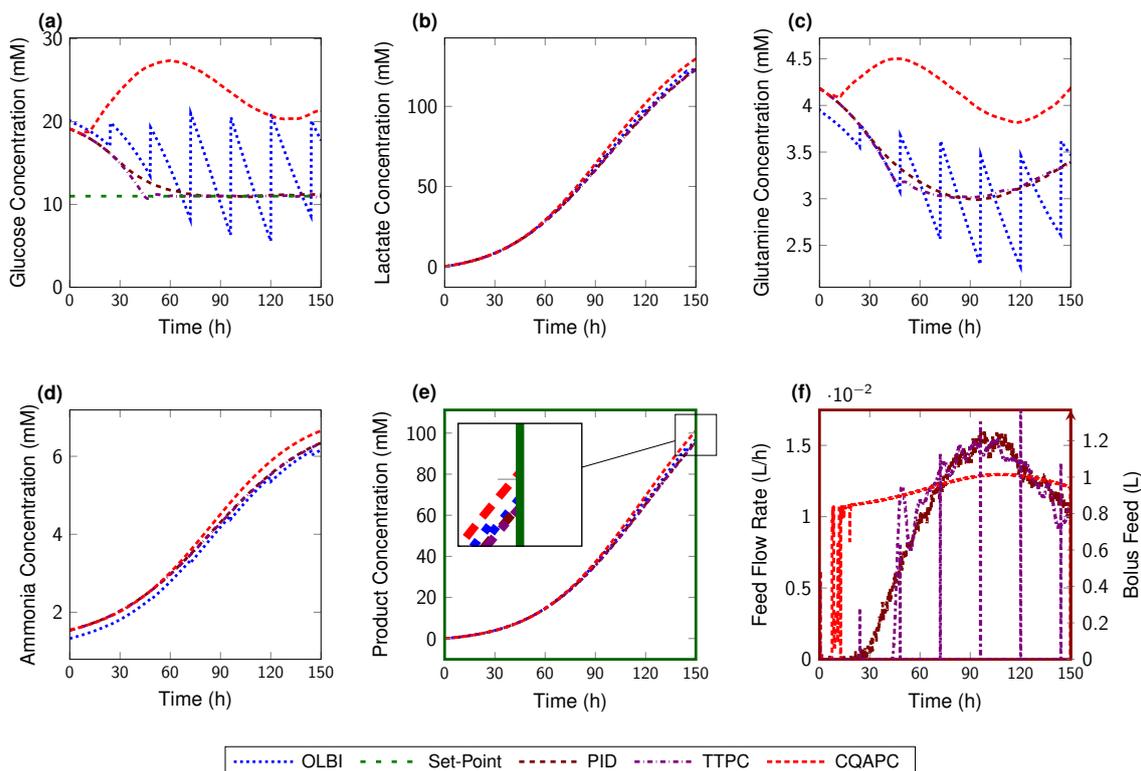
Fig. 2. Comparison of conventional OLBI against the closed-loop control results of TTPC and CQAPC algorithms for a select test run of the mammalian cell fed-batch bioreactor process.
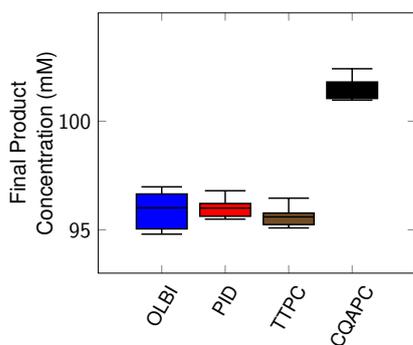
Fig. 3. Comparison of conventional OLBI, TTPC and CQAPC algorithms through product yields at completion of mammalian cell fed-batch bioreactor runs.

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