Model Identification and Model Predictive Control of Biopharmaceutical and Biomedical Systems

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Abstract: This paper demonstrates the use of model predictive control (MPC) formulations for uncertain time-varying biopharmaceutical and biomedical systems implemented using measured data without prior knowledge of an accurate model. Furthermore, we demonstrate how prior knowledge can be incorporated in the identification of the model either through constraints or as regularization of the system identification procedure. We demonstrate the use of system identification to develop a model of the fed-batch Chinese hamster ovary mammalian cell bioreactor process and the implementation of model-based control to maximize therapeutic product yields. We also use a time-varying nonlinear biomedical system to demonstrate improvements due to incorporating prior information in the learning of the models and reidentification of the models when prediction accuracy deteriorates. We propose a new partial least squares algorithm that incorporates regularization from prior knowledge and can handle missing data in the independent covariates. Simulation case studies involving a biopharmaceutical production process and automated drug delivery demonstrate the capabilities of the proposed techniques.

Keywords: model identification, model predictive control, regularized latent variables models, biopharmaceutical process, biomedical systems

1. INTRODUCTION

The digital revolution is fostering innovations in cross-disciplinary fields at the edge of natural sciences and systems engineering, leading to novel approaches in biotechnology and biomedical system control. The biological systems considered are challenging processes to control due to their complex nonlinear dynamics. Their behaviors can be described accurately by fundamental mathematical models that often contain large numbers of uncertain parameters requiring estimation for accurate characterization of the system. The complex nonlinear behavior of the biological systems leads to high levels of uncertainties. This uncertainty is further amplified by the lack of measurements for the outputs of the mathematical models based on first principles knowledge, which obscures the on-line state information. On the other hand, data-driven modeling techniques have gained momentum in recent decades due to their ability to yield simpler, well-posed models from experimental data. The data-driven models can be harnessed to design model predictive control (MPC) formulations that effectively integrate both the identified dynamic system model and the real-time measurements to achieve the desired optimal closed-loop performance.

MPC, with its repeated online solution of an optimization problem over predicted future system trajectories, is well-suited to intrinsically handle complex system dynamics, critical variable constraints, and explicitly take performance criteria into account. A central component in the implementation of MPC is the model of the system. In this work, we demonstrate the advantages of forming dynamic system models from measured data through system identification techniques. We utilize uncertain time-varying biopharmaceutical and biomedical systems to show how an MPC algorithm can be implemented using the measured data, without prior knowledge of an accurate model. Furthermore, we demonstrate how prior knowledge can be incorporated in the identification of the model either through constraints or as regularization of the system identification procedure. Case studies involving a biopharmaceutical production process and automated drug delivery demonstrate the capabilities of the proposed techniques.

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 de-

ploying 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 (Rashid et al., 2017). 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 is shown to improve the operation of the fed-batch therapeutic protein production process.

We also use a time-varying nonlinear biomedical system to demonstrate improvements due to incorporating prior information in the learning of the models and reidentification of the models when prediction accuracy deteriorates. We propose a new partial least squares (PLS) algorithm that incorporates regularization from prior knowledge and can handle missing data in the independent covariates (Pillonetto et al., 2014; Chen, 2018; Sun et al., 2021). The latent variable (LV) based modeling technique first develops a LV-based model using historical time series data, and then the score vectors of the new incomplete observation are estimated using the known data regression method to obtain predictions of the future system trajectory as a linear combination of estimated scores and loadings Zhu et al. (2020); Loehlin and Beaujean (2016); Zhou et al. (2016). We show how different dynamic setpoint trajectories to be specified that are congruent with the natural system behavior. We use the example of automated insulin delivery systems in people with type 1 diabetes to show how better recognizing the current operating conditions of the physiological and metabolic system, and handling missing data in the identification process, can yield better control of complex processes such as glucose control in diabetes despite the presence of unmeasured disturbances and system perturbations.

A case study illustrates the potential of machine learning from historical data to capture the trends of daily behavior of people with Type 1 Diabetes (T1D) and use this information for improving the performance of MPC Rashid et al. (2019). In particular, the daily patterns of meal consumption and physical activities of individuals with T1D are are determined. Then, such personal information are used as future potential disturbances in MPC to improve the accuracy of personalized future glucose predictions and compute more accurate insulin dosing strategies by artificial pancreas systems for automated insulin delivery.

These three case studies illustrate benefits of systems engineering to provide advanced control technologies for complex biological systems by leveraging data-driven techniques in system identification, multivariate statistical analysis and machine learning. The remainder of the paper is structured as follows. Section 2 is devoted to identification and control of fed-batch mammalian cell bioreactor system. Latent variables based modeling to accommodate missing data in is automatic control of blood glucose regulation in people with T1D is presented in Section 3. Conclusions are provided in Section 4.

2. IDENTIFICATION AND CONTROL OF FED-BATCH MAMMALIAN CELL BIOREACTOR SYSTEM

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.

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:

$$\min_{u\in\mathbb{U}} \mathcal{J} = \sum_{k=i}^{n_p} \|\hat{y}_k - \bar{y}_k\|^2_{Q_w} + \|\Delta u_k\|^2_{R_v} \tag{1}$$

subject to

$$\hat{x}_{k+1} = A\hat{x}_k + Bu_k,\ k \in \{i, \ldots, n_p - 1\} \tag{2}$$
$$\hat{y}_k = C\hat{x}_k + Du_k,\ k \in \{i, \ldots, n_p\} \tag{3}$$
$$\hat{x}_k = \bar{x}_k \tag{4}$$

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. 1) 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 penalizes the magnitude of input changes. The TTPC formulation uses an identified state-space model to predict the future evolution of the fed-batch bioreactor. Further, $\bar{x}_k$ in Eq. 4 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.

The typical 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 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. A predictive controller for achieving a maximum end-point critical quality attribute in the mammalian cell fed-batch bioreactor processes is obtained by replacing the cost function (Eq. 1) with the

new objective function $\mathcal{J} = \hat{y}^q_{n_p}$ where $\hat{y}^q_{n_p}$ 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. This objective maximizes the predicted end-point critical quality attributes. 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.

The product yields across all 10 closed-loop test batches are shown in Fig. 1. 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.

3. PERSONALIZED ADAPTIVE MPC ROBUST TO MISSING DATA FROM SENSORS

In this section, we develop a MPC algorithm based on regularized partial least squares (rPLS) method where missing data is readily handled and prior knowledge of exponential stability is integrated to improve the prediction accuracy. For a collection of inputs $\boldsymbol{X}^T = [\boldsymbol{x}_1, \ldots, \boldsymbol{x}_n]$ and outputs $\boldsymbol{Y}^T = [\boldsymbol{y}_1, \ldots, \boldsymbol{y}_n]$, developing a data-driven prediction model entails finding a reasonable representation of

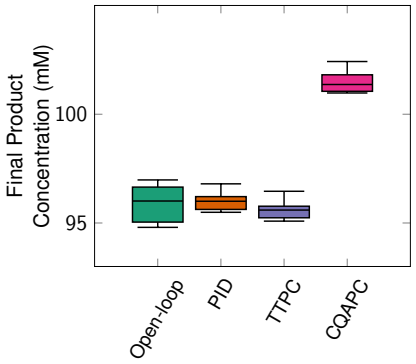

Fig. 1. Comparison of conventional open-loop operating policy, proportional-integral-derivative (PID) control, TTPC and CQAPC algorithms through product yields at completion of mammalian cell fed-batch bioreactor runs.

the relationships between $\boldsymbol{X}$ and $\boldsymbol{Y}$. However, collinearity in the data causes ill-conditioning issues and renders the identification of simple linear regression models sensitive to measurement noise. The redundant information makes multivariate statistical modeling techniques the preferred approach to model the relations between input $\boldsymbol{X}$ and output $\boldsymbol{Y}$ through intermediate latent variables (LV). The estimation of the LVs and incorporation of prior knowledge, a rPLS approach is adopted Sun et al. (2021) as

$$\begin{aligned} \max_{\boldsymbol{t}} J_{rPLS} &= \boldsymbol{u}^T\boldsymbol{t} - \frac{\delta}{2}\boldsymbol{w}^T\boldsymbol{K}\boldsymbol{t} \\ s.t.\ \boldsymbol{t} &= \boldsymbol{X}\boldsymbol{w},\ \|\boldsymbol{w}\| = 1 \\ \boldsymbol{u} &= \boldsymbol{Y}\boldsymbol{q},\ \|\boldsymbol{q}\| = 1 \end{aligned} \tag{5}$$

where $\boldsymbol{t}$ and $\boldsymbol{u}$ are the LVs of the input data $\boldsymbol{X}$ and output data $\boldsymbol{Y}$, respectively, $\boldsymbol{w}$ and $\boldsymbol{q}$ are the weights (or the directions) for the raw data projection, δ is the hyperparameter to balance the trade-off between the terms in the objective function that can be estimated by cross-validation. The regularization term is based on a kernel matrix $\boldsymbol{K}$ that encompasses prior information of the model and improves the numerical properties of the model. To model dynamical systems, a minimum level prior knowledge is that the process model is exponentially stable, which means that the weights corresponding to the variates are expected to decay exponentially. The kernel matrix $\boldsymbol{K}$ can be designed as a first-order stable spline kernel Pillonetto et al. (2014); Chen (2018). For multiple input variables, we assume that the variates are independent of each other. The ijth element of the kernel matrix can be computed as

$$K\left(i,j\right) = \lambda_1{\lambda_2}^{max(i,j)},\ \boldsymbol{\eta} = [\lambda_1, \lambda_2] \tag{6}$$

where λ_1 is a positive value that tunes the magnitude of kernel matrix $\boldsymbol{K}$ and $\lambda_2 \in (0,1)$ account for the exponentially decrease property of model weights $\boldsymbol{w}$. When the magnitude of elements of the kernel matrix are large, the corresponding weights founded by the rPLS method trend to be small. If the weights are sufficiently small, the related input variable is redundant and not considered important in modeling the system behavior as its contribution to the LV is close to zero. Therefore, the problem of tuning model complexity directly is readily translated to tuning the hyperparameters of the kernel matrix, which is relatively straightforward.

The solution of objective (5) can be achieved by the Lagrange multipliers method, which leads to

$$\begin{aligned} \boldsymbol{X}^T\boldsymbol{Y}\boldsymbol{q} &= \delta\boldsymbol{K}\boldsymbol{w} + \lambda_w\boldsymbol{w} \\ \boldsymbol{Y}^T\boldsymbol{X}\boldsymbol{w} &= \lambda_q\boldsymbol{q} \end{aligned} \tag{7}$$

where λ_w and λ_q are the Lagrange coefficients. Sequential LVs can be extracted after deflating $\boldsymbol{X}$ and $\boldsymbol{Y}$ using the LV $\boldsymbol{t}$ and corresponding weight:

$$\begin{aligned} \boldsymbol{p} &= \boldsymbol{X}^T\boldsymbol{t}/\boldsymbol{t}^T\boldsymbol{t} \\ \boldsymbol{X} &= \boldsymbol{X} - \boldsymbol{t}\boldsymbol{p}^T \\ \boldsymbol{Y} &= \boldsymbol{Y} - \boldsymbol{t}\boldsymbol{q}^T \end{aligned} \tag{8}$$

where $\boldsymbol{p}$ is the loading vector of $\boldsymbol{X}$.

The details of rPLS method are summarized in table 3. After extracting the latent variables, the prediction model can be expressed as

$$\begin{aligned} \boldsymbol{T} &= \boldsymbol{X}\boldsymbol{W}\left(\boldsymbol{P}^T\boldsymbol{W}\right)^{-1} \\ \boldsymbol{Y} &= \boldsymbol{T}\boldsymbol{Q}^T \end{aligned} \tag{9}$$

where $\boldsymbol{T} = [\boldsymbol{t}_1, \ldots, \boldsymbol{t}_l] = [\boldsymbol{\tau}_1, \ldots, \boldsymbol{\tau}_n]^T$ is the matrix that containing l latent variables $\boldsymbol{t}$ and $\boldsymbol{\tau}_i$ is the latent variable (also called score) of the ith input sample $\boldsymbol{x}_i$. $\boldsymbol{P} = [\boldsymbol{p}_1, \ldots, \boldsymbol{p}_l]$, $\boldsymbol{W} = [\boldsymbol{w}_1, \ldots, \boldsymbol{w}_l]$, and $\boldsymbol{Q} = [\boldsymbol{q}_1, \ldots, \boldsymbol{q}_l]$ are the weight matrices. For a new input $\boldsymbol{x}$, the output of the model can be estimated as

$$\begin{aligned} \boldsymbol{\tau}^T &= \boldsymbol{x}^T \boldsymbol{W} \Big(\boldsymbol{P}^T \boldsymbol{W} \Big)^{-1} \\ \boldsymbol{y}^T &= \boldsymbol{\tau}^T \boldsymbol{Q}^T \end{aligned} \tag{10}$$

To predict the future trajectory of the output variables, define the unavailable variables in $\boldsymbol{x}$ as $\boldsymbol{x}^{\#}$ and observed variables as $\boldsymbol{x}^*$, then it is possible to estimate $\boldsymbol{y}$ if the score $\boldsymbol{\tau}$ can be calculated using $\boldsymbol{x}^*$. Thus, it is critical to establish the relationship between $\boldsymbol{\tau}$ and $\boldsymbol{x}^*$ where the training input matrix $\boldsymbol{X}$ is first partitioned into two parts $\boldsymbol{X} = \Big[\boldsymbol{X}^*, \boldsymbol{X}^{\#}\Big]$, where $\boldsymbol{X}^*$ contains the same variables as $\boldsymbol{x}^*$ and $\boldsymbol{X}^{\#}$ is consisting of all variables in $\boldsymbol{x}^{\#}$ Nelson et al. (1996); Folch-Fortuny et al. (2015); Arteaga and Ferrer (2002). Then, the regression coefficient $\boldsymbol{\theta}$ is found by minimizing the residual between $\boldsymbol{T}$ and $\boldsymbol{X}^*\boldsymbol{\theta}$, which can be achieved by regularized least squares estimation as collinearity may exist in $\boldsymbol{X}^*$ that can result in ill-conditioned issues:

$$\hat{\boldsymbol{\theta}} = \arg\min_{\theta} J_{rLS} = \big\| \boldsymbol{T} - \boldsymbol{X}^* \boldsymbol{\theta} \big\| + \delta_1 \boldsymbol{I} \tag{11}$$

where δ_1 is the regularization parameter that reduce the influence of ill-conditioned issues by introducing some estimation bias. With known regression coefficient $\boldsymbol{\theta}$, the score vector $\boldsymbol{\tau}$ and corresponding BGC measurements $\boldsymbol{y}$ can be predicted as

$$\begin{aligned} \boldsymbol{\tau}^T &= \boldsymbol{x}^{*T} \boldsymbol{\theta} \\ \boldsymbol{y}^T &= \boldsymbol{\tau}^T \boldsymbol{Q}^T \end{aligned} \tag{12}$$

Note that all variables are normalized to zero mean and unit variance at the beginning of the modeling process and after the model is obtained, it is possible to scale the regression coefficient rather than scale the input $\boldsymbol{x}$ for predicting future output values. Assuming that the regression coefficient $\boldsymbol{Q\theta^T}$ is scaled to estimate the future glucose values $\boldsymbol{y}$ from raw input $\boldsymbol{x}^*$ and the scaled regression coefficient is defined as $\boldsymbol{\Theta}$. Then, the future predicted values can be obtained as

$$\hat{\boldsymbol{y}} = \boldsymbol{\Theta} \boldsymbol{x}^* + \boldsymbol{C}_0 \tag{13}$$

where $\boldsymbol{C}_0$ is a constant vector.

To facilitate the design of MPC strategy, the rPLS model can be readily formulated as a state space model. At each sampling instance, the training data $\boldsymbol{X}$ and $\boldsymbol{Y}$ can be updated and the future trajectory of the output measurements can be predicted after updating the model parameters through the rPLS method using the latest training data.

Table 1. Regularized partial least squares method

1. Normalize $\boldsymbol{X}$ and $\boldsymbol{Y}$ to zeros-mean and unit variance. Determine kernel hyperparameter η and generate kernel matrix $\boldsymbol{K}$. And set $i = 1$.
2. Set $\boldsymbol{X}_i = \boldsymbol{X}$ and $\boldsymbol{Y}_i = \boldsymbol{Y}$.
3. Initialize $\boldsymbol{u}_i$ as the first column of $\boldsymbol{Y}_i$, and iterate the following process until convergence

$$\begin{aligned} \boldsymbol{w}_i &= (\delta \boldsymbol{K} + \boldsymbol{I})^{-1} {\boldsymbol{X}_i}^T \boldsymbol{u}_i \\ \boldsymbol{t}_i &= \boldsymbol{X}_i \boldsymbol{w}_i;\ \boldsymbol{w}_i = \boldsymbol{w}_i / \|\boldsymbol{w}_i\| \\ \boldsymbol{q}_i &= {\boldsymbol{Y}_i}^T \boldsymbol{t}_i \\ \boldsymbol{u}_i &= \boldsymbol{Y}_i \boldsymbol{q}_i \end{aligned}$$

4. Deflate $\boldsymbol{X}$ and $\boldsymbol{Y}$ as

$$\begin{aligned} \boldsymbol{p}_i &= \boldsymbol{X}^T \boldsymbol{t}_i / {\boldsymbol{t}_i}^T \boldsymbol{t}_i \\ \boldsymbol{X} &= \boldsymbol{X} - \boldsymbol{t}_i {\boldsymbol{p}_i}^T \\ \boldsymbol{Y} &= \boldsymbol{Y} - \boldsymbol{t}_i {\boldsymbol{q}_i}^T \end{aligned}$$

5. Set $i = i + 1$, and return to Step 2 until enough latent variables are extracted.

3.1 Adaptive Learning Model Predictive Control

We propose an Adaptive Learning Model Predictive Control (AL-MPC) for use in multivariable artificial pancreas (AP) systems that automate insulin delivery in people with T1D to control the blood glucose concentration levels. The AL-MPC calculates the optimal insulin injection rate by employing adaptive weights that modify the penalty weighting matrices in the MPC objective function Askari et al. (2020). It calculates the optimal insulin injection rate over a finite horizon by using the recursively identified subspace-based dynamic models and three different predictions obtained for the unknown process disturbances by solving the following quadratic programming problem at each sampling time k

$$\begin{aligned} &\Big\{ \mathbf{z}^*_{i,j}, \mathbf{m}^*_i \Big\}_{i=0}^{m_f - s} := \\ &\underset{\substack{\mathbf{z}_j \in \mathcal{Z} \\ \mathbf{m} \in \mathcal{M}}}{\operatorname{argmin}} \mathcal{J}_{\substack{k \\ m_f - s}} (\mathcal{Q}_{j,k}, P_k, \mathcal{R}_k, \{\mathbf{m}_i\}_{i=0}^{m_f - s}, \{\mathbf{z}_{j,i}\}_{i=0}^{m_f - s}) \end{aligned}$$

$$\text{s.t.} \begin{cases} \mathbf{z}_{j,i+1} = A_k \mathbf{z}_{j,i} + B_k \mathbf{m}_i + d_{j,i} \\ \mathbf{q}_{j,i} = C_k \mathbf{z}_{j,i} + D_k \mathbf{m}_i \\ \mathbf{z}_{j,0} = \hat{x}_{j,k} \\ \mathbf{m}_{j,i}^{min} \le \mathbf{m}_i \le \mathbf{m}_{j,i}^{max} \\ \mathbf{z}_{j,i}^{PIC,min} \le \mathbf{z}_{j,i}^{PIC} \le \mathbf{z}_{j,i}^{PIC,max} \\ \mathbf{e}_{j,i}^{PIC} = \mathbf{z}_{j,i}^{PIC} - \mathbf{z}_{j,i}^{PIC,des} \\ \mathbf{z}_{j,i}^{PIC,max} = (\beta_{m,k} + \beta_f) \times (a_{j,i}^{max} \times \mathbf{q}_{j,i} + b_{j,i}^{max}) \\ \mathbf{z}_{j,i}^{PIC,min} = (\beta_{m,k} + \beta_f) \times (a_{j,i}^{min} \times \mathbf{q}_{j,i} + b_{j,i}^{min}) \\ \mathbf{z}_{j,i}^{PIC,des} = (\beta_{m,k} + \beta_f) \times (a_{j,i}^{des} \times \mathbf{q}_{j,i} + b_{j,i}^{des}) \end{cases} \tag{14}$$

incorporated with the objective function

$$\begin{aligned} \mathcal{J}_{\substack{k \\ m_f - s}} := &\sum_{i=0}^{m_f - s} \sum_{j=1}^{3} \Big(\mathbf{q}_{j,i} - \mathbf{r}_{j,i} \Big) \mathcal{Q}_{j,k} \Big(\mathbf{q}_{j,i} - \mathbf{r}_{j,i} \Big) \\ &+ (\mathbf{m}_i - \mathbf{m}_{\substack{basal \\ i}}) \mathcal{R}_k (\mathbf{m}_i - \mathbf{m}_{\substack{basal \\ i}}) + \mathbf{e}_{j,i}^{PIC} P_k \mathbf{e}_{j,i}^{PIC} \end{aligned} \tag{15}$$

where $\mathbf{z}_{j,k} \in \mathbb{R}^{n_x}$ and $\mathbf{q}_{j,k} \in \mathbb{R}$ represent the estimated state variables and the output of the model, respectively, A_k, B_k, C_k and D_k are the state-space system matrices, and $d_{j,i}$ is the disturbance term. The disturbance term is predicted independently based on dynamic regularized latent variable regression (DrLVR), which is useful for disturbance forecasting, uncertainty quantification, and improving the system output predictions by

incorporating historical data. For the prediction/control horizon $m_f - s$, $\mathbf{m}_i \in \mathbb{R}$ represents the constrained input variable, which takes values in a nonempty convex set $\mathcal{M} := \left\{\mathbf{m}_k \in \mathbb{R} : \mathbf{m}_{\mathrm{j,k}}^{min} \leq \mathbf{m}_k \leq \mathbf{m}_{\mathrm{j,k}}^{max}\right\}$ with $\mathbf{m}_{j,k}^{min} \in \mathbb{R}$ and $\mathbf{m}_{j,k}^{max} \in \mathbb{R}$ denote the lower and upper limits on the manipulated variable, respectively. $r_{j,k}$ is the target set-point, and $\mathbf{m}_{\underset{k}{basal}}$ is the patient-specified rate of basal insulin. The nonempty convex set $\mathcal{Z}$ with $\mathcal{Z} := \left\{\mathbf{z}_{j,k} \in \mathbb{R}^{n_x} : \mathbf{z}_{j,k}^{min} \leq \mathbf{z}_k \leq \mathbf{z}_{j,k}^{max}\right\}$, $\mathbf{z}_{j,k}^{min} \in \mathbb{R}^{n_x}$ and $\mathbf{z}_{j,k}^{max} \in \mathbb{R}^{n_x}$ represent the lower and upper bounds on state variables, respectively, with one of the state variables as the estimated plasma insulin concentration (PIC), denoted $\mathbf{z}_{j,k}^{PIC}$ that is constrained by the PIC limits ($\mathbf{z}_{j,k}^{PIC,max}$, $\mathbf{z}_{j,k}^{PIC,min}$, and $\mathbf{z}_{j,k}^{PIC,des}$) where the $\mathbf{z}_{j,k}^{PIC,des}$ is the desired PIC value. $\hat{x}_{j,k}$ provides an initialization of the vector of state variables, $\mathcal{Q}_{j,k} \geq 0$ is a positive semi-definite symmetric matrix utilized to penalize the deviations of the outputs from their desired set-point, and $\mathcal{R}_k$ and P_k are strictly positive definite symmetric matrix to penalize manipulated variables and the PIC errors, respectively. At each iteration, the quadratic programming problem described by (14) is solved, and $u_k := \mathbf{m}_0$ which is the optimal solution implemented to inject insulin over the current control horizon with the MPC computation repeated at next sampling time using new glucose data, updated state variables, and newly computed penalty weights of the objective function.

3.2 Results

In this study, the robustness and efficiency of the proposed personalized MPC (pMPC) and personalized adaptive MPC (paMPC) are further assessed by introducing missing glucose data to the AP system randomly. Specifically, the interval of missed glucose data lasts for 5 minutes to 30 minutes (1 sample to 6 samples).

The average percentage of time in different glycemic ranges and statistical measures of the controlled glucose measurements are summarized in Table 2. For the proposed paMPC strategy, the average percentage of time in safe range improves 8.36%, from 76.52% to 84.88%, in contrast to pMPC strategy. There is a considerable decrease in time in high glucose range of 8.37% obtained by incorporating the adaptive rules into pMPC approach. The average maximum value of glucose measurement drops from 276.5 mg/dL to 250.7 mg/dL, which is slightly higher than the threshold of severe high glucose values (250 mg/dL) and the mean value of average glucose measurements during the closed-loop study decreases 7.06 mg/dL. Even though mild low glucose measurements occurs and lasts for 5 samples, all the 20 subjects are in the clinical sub-optimal region and the minimum value of glucose measurements is 67 mg/dL for the proposed paMPC. In contrast, the minimum value of glucose measurement for pMPC strategy is 70 mg/dL, which is not significantly higher than the minimum value for paMPC approach.

To demonstrate the variation of the controlled glucose measurements under the pMPC and paMPC strategies, the mean continuous glucose monitoring (CGM) measurements, bolus insulin dosages, and basal insulin rates are compared in Fig. 2 along with the areas formed by mean±standard deviation. The glycemic trajectory for both MPC strategies are both in the safe range for large percentage of time, where glycemic trajectory for the proposed paMPC is in the range for longer time as postprandial glucose concentration returns back to the safe range faster. During the period of midnight to 8 AM, tight glycemic regulation is achieved by using both MPC strategies even though some of CGM data missed during the night. The patterns of bolus insulin and basal insulin infusion rate are different for the compared two MPC strategies, where larger bolus dosages can be observed for the proposed paMPC approach and smaller bolus dosages that are delivered for more times are observed for the pMPC strategy. In addition, the basal insulin infusion rate for pMPC method is almost always higher than the basal insulin infusion rate for the proposed paMPC approach.

To evaluate the influence of missing data on the AP system, the detailed glycemic trajectory, insulin trajectory, and hyper-parameter α of the proposed paMPC strategy for subject 19 in the two case studies are compared in Fig. 3 where the missing data interval ranges from 5 minutes to 30 minutes and the missed CGM data are replaced by estimated values. Overall, the differences between two glycemic trajectories, bolus insulin dosages, basal insulin infusion rates, and hyper-parameter α are negligible. Specifically, when CGM data are missed during the night, before meals, and postprandial periods where fluctuation of CGM measurements is not severe, the effects caused by missed CGM data are so small that almost can not be observed. Even though the effects of missed CGM data during the period of carbohydrate absorption where glycemic fluctuation is severe on hyper-parameter α that adaptive tunes the aggressiveness and conservativeness of the proposed paMPC are comparable large, the different of controlled trajectories are relatively small that demonstrates robustness of the proposed paMPC strategy.

4. CONCLUSION

This paper demonstrates the use of MPC formulations for uncertain time-varying biopharmaceutical and biomedical systems implemented using measured data without prior knowledge of an accurate model. Simulation case studies involving a biopharmaceutical fed-batch Chinese hamster overy mammalian cell bioreactor process and automated insulin delivery in T1D for controling blood glucose levels demonstrate the capabilities of the proposed techniques.

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Table 2. Controller performance across 20 virtual subjects for closed-loop glycemic control with pMPC and paMPC strategies (Mean ± STD (standard deviation)).

CGM data missed or not		No		Yes	
MPC strategy		pMPC	paMPC	pMPC	paMPC
Time in range (%)	[40, 55)	0±0	0±0	0±0	0±0
	[55, 70)	0±0	0±0	0±0	0.01±0.06
	[70, 180]	76.48±7.50	84.58±7.65	76.52±7.58	84.88±7.36
	(180, 250]	21.83±5.89	14.84±6.82	21.66±5.82	14.63±6.69
	(250, 400]	1.69±2.08	0.58±0.91	1.81±2.19	0.47±0.81
CGM measurement (mg/dL)	Minimum	74.9±1.48	74±2.58	74.81±1.48	73.42±2.67
	Maximum	277.8±25.62	255.05±31.01	276.5±24.26	250.7±25.48
	Mean	138.46±10.75	131.71±10.56	138.42±10.93	131.36±9.91

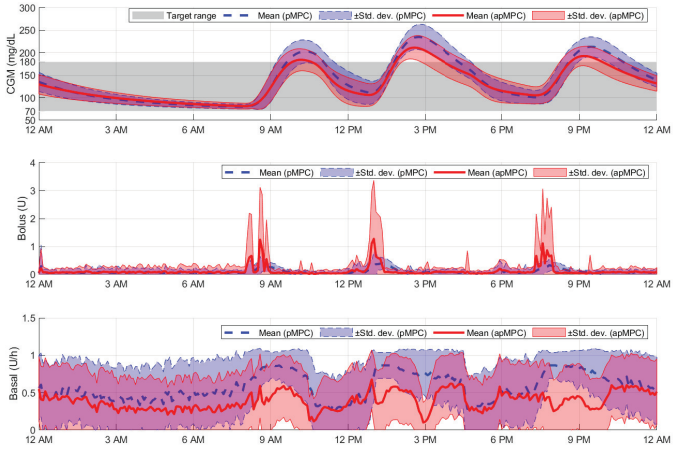

Fig. 2. Glycemic trajectory, bolus, and basal insulin infusion rate across 20 virtual subjects of closed-loop control for pMPC and paMPC strategies with missing CGM measurement.

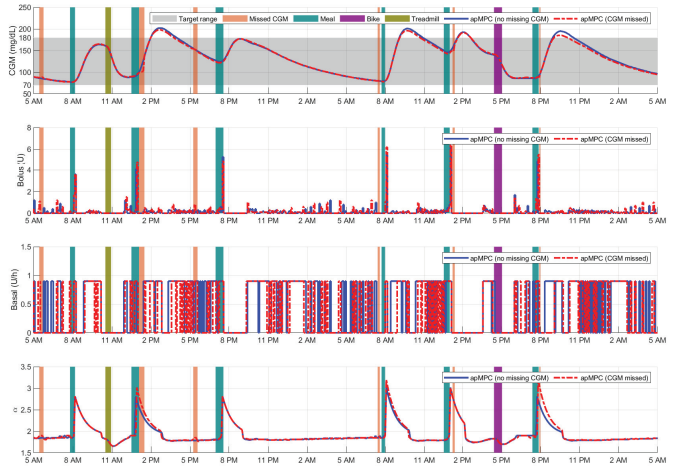

Fig. 3. Comparing glycemic trajectory, bolus insulin dosage, basal insulin infusion rate, and α of subject 19 for closed-loop control with and without missing CGM measurement.

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