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Design of an Artificial Pancreas using Zone Model Predictive Control with a Moving Horizon State Estimator

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Abstract

A zone model predictive control (zone-MPC) algorithm that utilizes the Moving Horizon State Estimator (MHSE) is presented. The control application is an artificial pancreas for treating people with type 1 diabetes mellitus. During the meal challenge, the prediction quality of the zone-MPC algorithm with the MHSE was significantly better than when using the current Luenberger observer to provide the state estimate. Consequently, the controller using the MHSE rejected the meal disturbance faster and without inducing extra hypoglycemia risk (e.g., lower postprandial blood glucose peak by 10 mg/dL and higher postprandial minimum blood glucose by 11 mg/dL). The faster rejection of the meal disturbance led to a longer time in the clinically accepted safe region (70–180 mg/dL) by 13%, and this may reduce the likelihood of the complications related to type 1 diabetes mellitus.

I. INTRODUCTION

Type 1 diabetes mellitus (T1DM) is a metabolic disorder in which an individual loses his/her ability to control blood glucose (BG) levels, due to a lack of insulin secretion and production from the pancreatic β -cells. Thus, an individual with T1DM is required to receive exogenous insulin injection therapy for survival. Otherwise, he or she may experience chronic hyperglycemia (i.e., high level of BG, $BG > 180$ mg/dL) that can result in damage to the eyes, the kidneys, or the nervous system. However, excessive insulin injection is also harmful, as an over-dose of insulin may result in hypoglycemia (i.e., low level of BG, $BG < 70$ mg/dL) that may lead to the acute short-term complications (e.g., confusion, coma, or a death) if not treated [1].

A closed-loop Artificial Pancreas (AP) is an automated system that measures BG and delivers insulin to maintain BG at a safe level (e.g., clinically accepted safe region, 70 mg/dL $< BG < 180$ mg/dL) for people with T1DM. After the introduction of the first glucose regulation system in the 1970s (Biostator[®]) [2], development of an AP has been an active research topic, but several challenges remain. One of the most difficult challenges is overcoming meal disturbances that are unannounced (i.e., the timing and size of which are not informed to the controller). Due to the actuation delay of the subcutaneous insulin delivery, and the feedback delay associated with subcutaneous glucose sensing by a

Continuous Glucose Monitor (CGM), closed-loop control action by an AP often results in prolonged postprandial (i.e., after meal) hyperglycemia and late postprandial hypoglycemia. Thus, it is critical to develop a control algorithm that reacts quickly to the meal disturbance but does not deliver an excessive amount of insulin and induce hypoglycemia [3], [4], [5], [6], [7], [8].

The authors' current zone Model Predictive Control (zone-MPC) algorithm utilizes a Luenberger observer to estimate the state for the MPC initialization, and underwent successful clinical trials [9]. However, it suffered a delayed meal response because of the under-prediction at the beginning of the meal challenge and the over-prediction at the middle of the meal challenge, as demonstrated in Figure 1. These under- and over-predictions occurred at the meal time because of 1) the current model's inability to accommodate meal information and 2) the Luenberger observer's inability to deal with plant/model mismatch or sensor noise [10]. Increasing the gain of Luenberger observer did not resolve this under- and over-prediction problem. Since meal-announcement depends on user-compliance, and furthermore because meal-announcement typically lacks accurate estimation of the size and contents of the meal, it is critical for an AP system to handle unannounced meals (disturbance) via appropriate state estimation and control based on feedback only.

In this work, the Moving Horizon State Estimator (MHSE) was incorporated into the zone-MPC algorithm of an AP. The MHSE calculates the optimal sequence of the uncertainty terms that minimize a cost function [10], [11], [12], [13]. The cost function often consists of 1) the penalty for the deviation of the estimated outputs from the measured outputs, 2) the usage of the uncertainty terms, and 3) the penalty for the deviation of the initial state of the history horizon from the previously estimated state [10], [11], [12], [13]. During meal time, when the plant/model mismatch is the largest, the penalty for the initial state term can be reduced, so that the MHSE would reconstruct the state trajectory relying heavily on the recent measurements and inputs, rather than the model. Given the need to be able to operate without meal information, this approach may results in better state estimation during meal time, and, consequently, the prediction based on the MHSE (Figure 2) would be more accurate than the one based on the Luenberger observer. As can be seen in Figure 2, the zone-MPC prediction based on the MHSE more accurately captured the rise of the BG at the beginning of the meal response, and also the subsequent downturn after the peak. This allowed the controller to be more aggressively tuned, to reject the meal disturbance faster, without delivering an excessive amount of insulin, in summation over the entire meal response.

II. Method

A. Linear System

A single-input single-output Linear Time Invariant (LTI) system is considered:

$$x(k+1) = Ax(k) + Bu(k) \quad (1)$$

$$y(k) = Cx(k),$$

where $x(k) \in \mathbb{R}^n$, $u(k) \in \mathbb{R}^m$, and $y(k) \in \mathbb{R}^q$ are the state, the input, and the output, respectively.

B. Zone Model Predictive Control

Zone-MPC is a type of model predictive control algorithm that calculates the optimal future inputs to maintain the predicted output within a desired zone, rather than a single set-point. Using a zone as a control objective has several benefits. First, zone-MPC is able to deal with sensor noise, and maintain stability in the presence of plant/model mismatch, better than MPC with a set-point [14], [15]. Furthermore, in the AP development, a zone is considered a more suitable objective than a set-point because normoglycemia (i.e., healthy range of BG, $70 \text{ mg/dL} < \text{BG} < 180 \text{ mg/dL}$) itself is defined as a zone [1]. The work by Grosman *et al.* [15] demonstrated that zone-MPC results in reduced control action variability compared to set-point MPC, and this ability of zone-MPC not to react to the small CGM noise would result in a safer glucose regulation [15].

The cost objective employed in the zone-MPC algorithm is presented in (2). The algorithm employs the upper and lower boundaries as soft constraints rather than hard constraint, so that the boundaries can be violated with finite costs. The algorithm calculates the optimal future input trajectory that minimizes the cost function, J_{zone} :

$$J_{\text{zone}}(u) = \sum_{i=1}^P e(k+i|k)^2 + \sum_{j=0}^{M-1} \{ \hat{R} \hat{u}(k+j|k)^2 + \check{R} \check{u}(k+j|k)^2 \} \quad (2)$$

$$e(k+i|k) := \begin{cases} y(k+i|k) - y_{ub} & \text{if } y(k+i|k) \geq y_{ub} \\ y_{lb} - y(k+i|k) & \text{if } y(k+i|k) \leq y_{lb} \\ 0 & \text{otherwise} \end{cases}$$

$$\hat{u}(k+j|k) := \max(u(k+j|k), 0)$$

$$\check{u}(k+j|k) := \min(u(k+j|k), 0)$$

where $y(k+i|k)$, $u(k+j|k)$, y_{ub} , y_{lb} , P , M , and e are the predicted output, the predicted input, the upper boundary (140 mg/dL in this paper), the lower boundary (80 mg/dL in this paper), the prediction horizon, the control horizon, and the error, respectively [14], [15]. In this study the sample period is 5 min, the values of P and M are 8 (40 min) and 5 (25 min) time steps, respectively, and the asymmetric input cost scheme presented in [16] was used. $\hat{u}(k +$

$j(k)$ and $\tilde{u}(k+j|k)$ represent the positive and negative deviations of the input, $u(k+j|k)$, from the basal rate (steady state level), respectively [16].

C. A priori Control Relevant Model

The *a priori* control relevant model that was identified by van Heusden *et al.* [17] was used in this work. The model is given as follows:

$$\frac{G'(z)}{I'(z)} = \frac{FKCz^{-3}}{(1 - 0.98z^{-1})(1 - 0.965z^{-1})^2} \quad (3)$$

where $G'(z)$, $I'(z)$, F , K , and C are the glucose deviation, the insulin injection, the safety factor, the individual gain, and the conversion factor, respectively [17]. Rewriting the model (3) in state-space form results in LTI system (1) with:

$$x(k) = \begin{bmatrix} x_1(k) \\ x_2(k) \\ x_3(k) \end{bmatrix} = \begin{bmatrix} y(k+2) \\ y(k+1) \\ y(k) \end{bmatrix} \quad (4)$$

$$A = \begin{bmatrix} 2.91 & -2.8226 & 0.9126 \\ 1 & 0 & 0 \\ 0 & 1 & 0 \end{bmatrix}$$

$$B = \begin{bmatrix} FKC \\ 0 \\ 0 \end{bmatrix}$$

$$C = \begin{bmatrix} 0 & 0 & 1 \end{bmatrix}.$$

The controller based on this linear model has been evaluated in both simulation studies and extensive clinical trials [9], [17], and both evaluations demonstrated that the linear model captured the dynamics of the non-linear plant (i.e., people with T1DM) accurately enough to yield an effective controller.

D. State Estimation

A state-space model's state characterizes the entire status of the system, and the accurate estimation of the model state from the measured outputs is critical for the model predictive controller's performance. However, output measurements are affected by sensor and process noise [13]. Thus a state estimation strategy that can partially reject the effects of disturbances, and continue to provide an accurate state estimate despite operating in a noisy

environment, is required. The following two sections briefly describe the Luenberger observer (current choice of state estimator for the zone-MPC) and the MHSE (proposed approach) that are used in this work.

1) Luenberger Observer—The Luenberger observer is a linear observer that recursively estimates the current state using the measurement and the system equation, assuming no uncertainty in the dynamics or the measurement. Let $\hat{x} \in \mathbb{R}^n$ denote the state of the state estimator. Then, the estimator is updated according to the following equation (5):

$$\tilde{x}(k) = A\hat{x}(k-1) + Bu(k-1), \tilde{y}(k) = C\tilde{x}, \quad (5)$$

$$\hat{x}(k) = \tilde{x}(k) + L(y(k) - \tilde{y}(k))$$

where $L \in \mathbb{R}^n$ denotes the estimator gain, that is a design parameter [18], [19]. Even though the mechanism of the Luenberger observer exploits or accommodates no explicit noise term, the design of the gain L somewhat permits a strategic tuning in the observers noise rejection properties.

2) Moving Horizon State Estimator—The MHSE is an online optimization-based state estimator that takes both system uncertainties and constraints into account. At the current sampling instant, the MHSE calculates the optimal sequence of the uncertainty terms that account for the process and the measurement noises to minimize a cost function, within a fixed history horizon. From the sequence, the estimator takes the last value as the estimate of the uncertainty for the current state. At the next sampling instant, the MHSE repeats the steps. In this manner, the estimator utilizes the most recent feedback information (i.e., output measurement and command input) [13].

Based on system (1), the MHSE is implemented via a constrained optimization problem as follows:

$$\min_{\hat{v}(k-N+1), \dots, \hat{v}(k), \hat{x}_0} J = \|x_0(k-N) - \hat{x}_0(k-N)\|_{Q_0}^2 + \sum_{j=k-N+1}^k (\|\hat{y}(j) - y(j)\|_Q^2 + \|\hat{v}(j)\|_R^2)$$

(6)

subject to

$$\hat{x}(k+i+1) = A\hat{x}(k+i) + Bu(k+i) + \hat{v}(k+i)$$

$$\hat{y}(k+i) = C\hat{x}(k+i)$$

where $N = 5$, $Q_0 = 10^{-5} I_n$, $Q = 10^{-2}$, and $R = I_n$ are the length of history horizon, the weight for the initial state deviation, the weight for the estimated output deviations, and the weight for the usage of estimated uncertainty terms, respectively [13]. The use of $\hat{v}$ allows a noise term to be considered in the state estimation, which is a key difference between the Luenberger observer and the MHSE.

III. Results

To evaluate the proposed design, a single meal (50 g-carbohydrates) protocol and ten subjects from the UVA/Padova FDA-accepted metabolic simulator [20] were used to challenge the system. In the protocol, the closed-loop control begins two hours after the start of the simulation, and meal time is three hours after closed-loop commences. For this single meal protocol, the fixed meal time (i.e., no variation of meal time among the subjects) is chosen because the baseline (i.e., pre-meal BG) stays the same regardless of meal time. Note that the simulator parameters are time-invariant, thus the time of day of meal ingestion is of no relevance. The following two sections describe the results of the evaluations.

A. Quality of State Estimation

The Square Sum of the state estimation Errors (SSE) is calculated for the MHSE and the Luenberger observer cases (Table I) to compare the quality of the state estimation. The SSE was defined for each dimension j of the state x as follows:

$$SSE_j := \sum_{i=1}^{SL} (\hat{x}_j(i) - x_j(i))^2, \quad (7)$$

where SL is the simulation length. Table I shows that the MHSE estimated the states better than the Luenberger observer. On average SSE values were 100%, 80%, and 55% smaller for x_3 , x_2 , and x_1 , respectively, in the MHSE case compared to the Luenberger observer case. This better estimation of the states would provide a better initial condition for the zone-MPC prediction, and, consequently, the quality of prediction would be improved. Based on the fact that the estimate of x_3 by the MHSE is 0, it should be noted that the MHSE might be more responsive to the noise, compared to the Luenberger observer. The individual example of the state estimation is given in Figure 3 (subject 1 from the UVA/Padova metabolic simulator). The (A), (B), and (C) panels of Figure 3 corresponds to, x_1 , x_2 , and x_3 , respectively, and State Estimation Error (SEE) is defined for each dimension j of the state x as follows:

$$SEE_j := \hat{x}_j(k) - x_j(k). \quad (8)$$

As shown in Figure 3, the SEE are smaller in the MHSE case compared to the Luenberger observer case in all three states. Because $x_1(k)$, $x_2(k)$, and $x_3(k)$ correspond to $y(k+2)$, $y(k+1)$, and $y(k)$ (see (4)), the SEE of x_3 is the smallest, while the SEE of $x_1(k)$ is the largest.

B. In silico Meal Challenge Evaluation

The simulation results that compare the quality of BG regulation by the zone-MPC with the MHSE and by the zone-MPC with the Luenberger observer are summarized in Figure 4 and Table II. As shown in Figure 4, the zone-MPC with the MHSE was able to provide a faster response to the meal (20 min faster to deliver twice of the basal insulin delivery) with a sharper insulin delivery profile (insulin delivery above the basal within 1 hours after the meal was 1.89 U and 0.73 U in the MHSE and Luenberger observer cases, respectively). In addition, the insulin delivery by the zone-MPC with the MHSE returned to the basal insulin delivery rate by 2 hours after the meal, but it took 3.7 hours for zone-MPC with the Luenberger observer to reach the basal insulin delivery rate after the meal. Due to this faster meal response without over-delivery of insulin, the controller with the MHSE achieved significantly tighter BG regulation (lower postprandial BG peak by 10 mg/dL and higher postprandial minimum BG by 11 mg/dL) than the Luenberger case. In addition, the subjects in the MHSE case experienced a longer duration in the desired zone (13% longer time in the clinically accepted safe region (70–180 mg/dL)) compared to the Luenberger observer case (Table II). The statistically significant differences (i.e., p-value from the paired t-test < 0.05) were indicated by the asterisks in the tables. Also, there was one subject (subject 7) who experienced severe hypoglycemia (BG < 50 mg/dL) in the Luenberger observer case.

As can be seen in Figures 1 and 2, the zone-MPC prediction based on the MHSE more accurately captured the rise of the BG at the beginning of the meal response compared to the Luenberger case. The Sum of 30 min Prediction Errors (SPE) within the 30 min (6 sample-periods) postprandial period were −96 mg/dL and −231 mg/dL for the MHSE and the Luenberger cases, respectively, and the SPE is defined as:

$$SPE(k) := \sum_{m=1}^{SH} \{\hat{y}(k+m+6|k) - y(k+m+6)\}, \quad (9)$$

where SH is the length of the summation horizon. In addition, the utilization of the MHSE resulted in better prediction at the downturn, after the peak. The SPE within the 30 min after the peak were 42 mg/dL and 81 mg/dL for the MHSE and the Luenberger cases, respectively. The prediction based on the MHSE reacted to the CGM noise more (the prediction fluctuates more), and resulted in a higher variability in insulin delivery. However, the advantage of the faster meal disturbance rejection, without over-delivery, far outweighs this disadvantage of a slightly elevated insulin variability.

To illustrate the difference between the controller action by the two controllers, an individual plot (subject 7 from the UVA/Padova simulator) is provided in Figure 5. As shown in the figure, the zone-MPC with MHSE responded (i.e., delivered more than twice of the basal) 20 min after the meal, but the controller with Luenberger observer took 40 min to respond. In addition, due to a larger insulin delivery between 1 hour and 2 hours after the meal (2.0 U and 2.6 U in the MHSE and the Luenberger observer cases, respectively), the controller with Luenberger observer induced severe hypoglycemia in the subject.

IV. Discussion

No process or measurement noise is accommodated, or exploited, in the controller setup consisting of a zone-MPC state-feedback controller and the Luenberger observer as the state estimator. In a real-world scenario disturbances and noise exist, but they are difficult to model and to determine bounds for, and it is difficult to characterize their stochastic properties, e.g., means and covariances. Thus, formal robust control and/or robust estimation techniques are not readily applicable. As a step towards including disturbances within the state estimation procedure, instead of using a Kalman filter approach, where the estimates of the noise covariances are required, the MHSE optimization approach, where no assumptions about noise is required, was incorporated into the zone-MPC framework. Specifically, during meal time, when plant/model mismatch is the biggest, the MHSE approach is expected to be a more effective compared to the Luenberger observer.

V. Conclusions

The simulation results suggested that the MHSE would be a better choice of state estimator for the zone-MPC algorithm compared to the Luenberger observer, given the current choice of the model. The quality of the state estimation by the MHSE was superior (i.e., a smaller state estimation error) than the one by the Luenberger observer. Due to the better predictions performed within the zone-MPC algorithm, the zone-MPC using the MHSE rejected a meal disturbance quicker than the zone-MPC using the Luenberger observer without inducing hypoglycemia. This better glucose regulation would reduce the likelihood of the complications that are related to T1DM, and may improve the quality of life of the people with T1DM.

The zone-MPC using the MHSE responded to the meal disturbance faster, but it also responded more to noise. As shown in Figures 1 and 2, the prediction based on the MHSE fluctuated more than the one based on the Luenberger observer. This quick response to the change of the signal is desirable when meal consumptions are expected, but it is not when the system is expected to be near steady-state (e.g., overnight period). Thus, in the future, a MHSE strategy that modulates its tuning appropriately based on time of the day might be desirable.

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Fig. 1.

Closed-loop BG regulation by the zone-MPC using the Luenberger observer (subject 1 from the UVA/Padova simulator). Top panel: CGM, predicted output, the clinically accepted safe region (70–180 mg/dL), the control objective (80–140 mg/dL), and the severe hypoglycemia (50 mg/dL) are presented by the red circles, the blue line and dots, the green shaded region, the yellow shaded region, and the red stars, respectively. Middle panel: 30 min prediction error, defined as the difference between the 30 min prediction and the corresponding measurement. Bottom panel: Insulin delivery by the controller.

Fig. 2.

Closed-loop BG regulation by the zone-MPC using the MHSE (subject 1 from the UVA/Padova simulator). Top panel: CGM, predicted output, the clinically accepted safe region (70–180 mg/dL), the control objective (80–140 mg/dL), and the severe hypoglycemia (50 mg/dL) are presented by the red circles, the blue line and dots, the green shaded region, the yellow shaded region, and the red stars, respectively. Middle panel: 30 min prediction error, defined as the difference between the 30 min prediction and the corresponding measurement. Bottom panel: Insulin delivery by the controller.

Fig. 3. State Estimation Error for each state x_1 , x_2 , and x_3 depicted in subplot (A), (B), and (C), respectively. The State Estimation Error (SEE) was defined as the following: $SEE_j = \hat{x}_j(k) - x_j(k)$.

Fig. 4.

Population summary of the glucose regulation by the zone-MPC with Moving Horizon State Estimator and the zone-MPC with the Luenberger observer. Top panel: The clinically accepted safe region (70–180 mg/dL), the control objective zone (80–140 mg/dL), the average BG trace of the MHSE case, the average BG trace of the Luenberger case, the standard deviation (STDEV) BG envelope of the MHSE case, the STDEV envelope of the Luenberger observer case, and the meal are represented by the yellow shaded region, the green shaded region, the black dashed dot line, the black solid line, the red shaded region, the blue shaded region, and the black bar, respectively. Bottom panel: Insulin delivery by the zone-MPC using the MHSE and the Luenberger observe are represented by the red dashed dot line and the blue solid line, respectively.

Fig. 5.

Individual comparison between the zone-MPC with the Moving Horizon State Estimator (MHSE) and the zone-MPC with the Luenberger observer. Top panel: The BG/CGM trace of the MHSE case, the BG/CGM trace of the Luenberger observer case, the clinically accepted safe region (70–180 mg/dL), the controller objective (80–140 mg/dL), and the meal are presented by the red solid/dashed lines, the blue solid/dashed line, the yellow shaded region, the green shaded region, and the black bar, respectively. Bottom panel: insulin delivery by the zone MPC using the MHSE and the Luenberger observer are represented by the red line and the blue line, respectively.

TABLE I

Square Sum of State Estimation Error of MHSE and Luenberger observer (Luen.)

Subject	$x_3, [(mg/dL)^2]$		$x_2, [(mg/dL)^2]$		$x_1, [(mg/dL)^2]$	
	MHSE	Luen.	MHSE	Luen.	MHSE	Luen.
1	0	273	834	4,740	6,720	17,600
2	0	213	780	3,710	6,130	13,700
3	0	293	1,067	5,090	8,850	18,600
4	0	225	904	3,910	7,220	14,300
5	0	242	1,011	4,170	8,150	15,000
6	0	226	647	3,940	4,920	14,800
7	0	324	1,068	5,640	8,840	21,000
8	0	307	1,166	5,340	9,550	19,700
9	0	163	680	2,790	5,190	10,100
10	0	183	911	3,180	5,330	11,800
Average	0	245	887	4,250	7,090	15,700

TABLE II

Comparison of zone-MPC with MHSE and zone-MPC with Luenberger observer.

	MHSE	Luenberger Observer
Postprandial Peak [mg/dL]	208 ± 24 *	218 ± 26 *
Postprandial Minimum [mg/dL]	108 ± 11 *	97 ± 23 *
Postprandial 3h [mg/dL]	158 ± 23 *	180 ± 27 *
Postprandial 5h [mg/dL]	118 ± 15	114 ± 31
Postprandial time in the target zone (80–140 [mg/dL]), [%]	35 *	23 *
Postprandial time in the clinically accepted safe region (70–180 [mg/dL]), [%]	67 *	54 *
Number of Subjects that Experienced Severe Hypoglycemia Episode, BG < 50 [mg/dL]	0	1

* indicates that the paired t-test comparing the MHSE and the Luenberger observer cases satisfied $p < 0.05$