Using Model Moving Horizon Estimation and Objective Function Optimization for Type 1 Diabetes Mellitus Patient Safety

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ABSTRACT

This study introduces a closed-loop control model which i) incorporates Moving Hoizon Estimation (MHE) for dynamic and unmeasured parameters and ii) implements a safety focused objective function. Results from MHE analysis of patient data indicate the reasonableness of estimating two parameters with a 3-hour horizon. The ”disturbance” variable was estimated as a manipulated variable, and the ”insulin sensitivity” parameter was estimated as a fixed variable for the time horizon. The trends in both disturbance and sensitivity were reasonable for the known trends that could be predicted by our model. The safety focused objective function uses a hyperbolic tangent gradient to reward a blood sugar in the middle of the desired range in addition to severely penalizing time below the acceptable blood sugar threshold. Compared to other objective functions, the modified objective function keeps the patient out of dangerous ranges and keeps the patient near the optimal level of 80 mmol/dL.

Keywords: Moving Horizon Estimation, Model Predictive Control

INTRODUCTION

Diabetes Mellitus is a general term referring to a group of conditions where the body is not able to produce insulin in sufficient quantities and by extension not able to regulate blood glucose levels. These elevated blood glucose levels are associated with ailments such as heart, circulatory, eye, kidney and nerve failure (Organization, 2021). More than 433 million people worldwide are affected by diabetes, with an increasing amount of patients diagnosed each year.

According to Stach (2016), ”Diabetes is a lifelong disease that requires active participation by patients and/or their health care providers in the treatment of the disease.” Self-tracking is currently an essential factor for diabetic patients to accurately assess their insulin needs (Schroeder et al., 2019). In the past, manual control requires sparse measurements and inaccurate, manual administration of insulin. New hardware including Continuous Glucose Monitors (CGM) facilitate automated and accurate control.

1 LITERATURE REVIEW

Closed loop control of blood glucose has established sensors and actuators for control. This review will focus on proposed methods for control. Insulin pumps deliver steady *basal insulin* which regulates glucose outside of meals, and *bolus insulin* which is delivered in a single dose during meal times.

Control of diabetic blood sugar is a complicated task. Control algorithms must account for non-linear dynamics, delays in insulin delivery and volume. In addition to the dynamics of the system, parameters such as basal metabolic rate, and insulin sensitivity vary between individuals and through out the day. Finally, meals cause disturbances which result in a peak of blood glucose absorption. During this time, a brief period of hyperglycemia is acceptable.

1.1 Dynamic Models of Diabetes

Insulin and glucagon work together to regulate blood sugar. Insulin aids in the absorption of blood glucose, lowering the blood glucose, while glucagon signals to the liver to release stored glucose, raising

blood glucose. There are many models which describe the interaction between additional insulin, glucose ingested, and parameters which vary such as insulin effectiveness and basal metabolic rate. The Bergman minimal model was developed in 1979 and benefits from a near linear structure though it does not accurately account for dynamic parameters mentioned before nor delay (Bergman, 1970). Different models include Equilibrium based models and compartment based models, as well as many variations of the Bergman minimum model. This study will use the Bergman model due to its simplicity, with many parameter inaccuracies ideally corrected with MHE.

The Bergman Minimum Model models the following states:

- Blood Glucose (mg/dL) (G)
- Remote Insulin (μ u/ml) (X)
- Plasma Insulin (μ u/ml) (I)
- Gut Glucose (mg/dL) (GG)
- Insulin Added (mU/min) (U)
- Glucose Ingested (mmol/min) (D)

The Bergman Minimum Model also includes the following constant parameters:

- Basal Blood Glucose (bg)
- ($p1$)
- ($p2$)
- Insulin Sensitivity (si)
- Insulin Distribution Volume (vi)
- Glucose Distribution Volume (vg)

The Bergman Minimum Model relates the states and parameters as follows:

$$\frac{dG}{dt} = -p_1 * (G - bg\_s_i * X * G + f * \frac{k_{abs}}{vg} GG + \frac{f}{vg} D \tag{1}$$

$$\frac{dX}{dt} = p_2(I - X) \tag{2}$$

$$\frac{dI}{dt} = -k_e * I * U \tag{3}$$

$$\frac{dS_1}{dt} = U - k_{emp} * S_1 \tag{4}$$

$$\frac{dS_2}{dt} = -k_{emp} * (S_2 - S_1) \tag{5}$$

$$\frac{dGG}{dt} = k_{emp} * S_2 - k_{abs} * GG \tag{6}$$

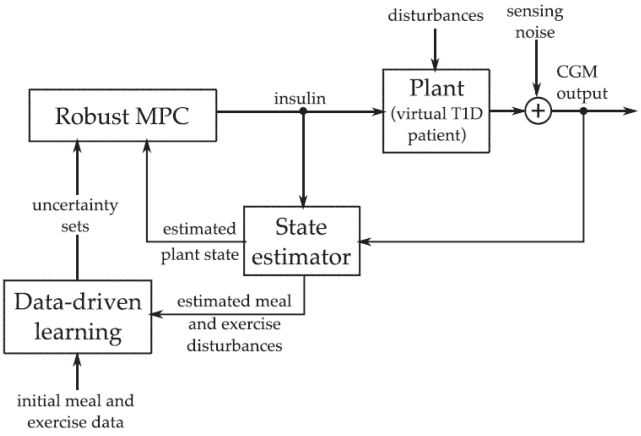

Figure 1. Block Diagram of information flow for dual Moving Horizon Estimation and Model Predictive Control

Meal	Breakfast	Snack 1	Lunch	Snack 2	Dinner	Snack 3
Probability of Occurring	0.8	0.4	0.9	0.2	0.95	0.4
Time (Lower Bound)	5:00	9:00	11:00	14:00	16:00	19:00
Time (Upper Bound)	9:00	11:00	14:00	16:00	19:00	23:00
Average Meal Size (peak mmol/ L min)	2500	1250	2800	1250	2800	1250

Table 1. Data for Meal simulation for a given patient day

1.2 Control Systems

Moving Horizon Estimation (MHE) is ideal for a problem such as blood glucose regulation as measurements within the horizon help estimate the state of parameters which are constantly changing. MHE is ideal as it allows one to estimate both state and disturbances unlike other methods such as Kalman filters (enc, 2020). Chen et al. (2019) use MHE to detect the disturbances of meals. Gondhalekar et al. (2014) simplifies MHE models to a first-order linear model fitted during periodic CGS calibration.

Chen et al. (2019) propose a specialized method of MHE they call *Committed Moving Horizon Estimation* (CMHE) which allows not only for state estimation of current parameters, as well as probabilistic estimation of a future meal disturbance. This meal detection ability allows the control to accurately predict the bolus insulin needed and prevent hyperglycemia.

Current state estimations and reasonably accurate enable Model Predictive Control (MPC). Paoletti et al. (2020) gives an outline of dual MHE and MPC in diabetic blood glucose control in Figure 1. They use this model to control Blood Glucose amid disturbances from both meals and exercise.

2 MATERIALS AND METHODS

Simulation was performed *insilico* rather than with closed loop physical tests. The simulation included two portions: i) a MHE parameter estimation using patient data to observe changes in parameters and ii) control with realistic noise caused by both measurement error, and mismatch between control and the CGM output to test control performance with different objective functions.

MHE simulation is performed with patient gathered between February and April 2021 with a CGM. The CGM relays both blood glucose readings every 5 minutes, as well as the insulin feed rate every minute. Rather than control in a closed loop, the controlled and manipulated variables are measured and the insulin sensitivity and disturbances are estimated using a horizon of three hours. In a closed loop study, these estimations would be fed into the MPC controller for accurate prediction of how the system would perform.

A diabetic patient is simulated with both the Bergman Minimum Model, and a random day. Since disturbances such as eating introduce the largest blood glucose volatility, a random day with meals and snacks is created. Each day may have meals, and snacks, of varying sizes, times, and probabilities that

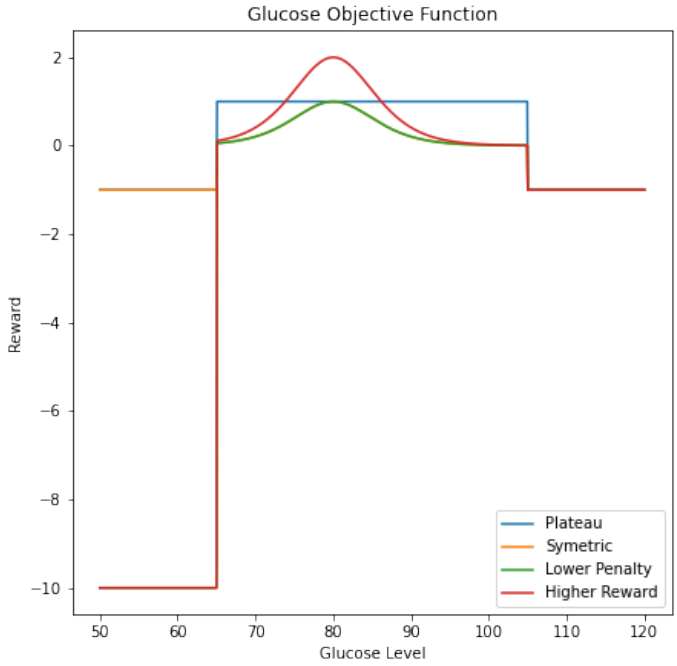

Figure 2. Objective Functions for MPC

they will occur. Information on this information is included in Table 1. With meal disturbance information, and system dynamics, each day is controlled using MPC in Python GEKKO. During the simulation, proper noise is created using Python's numpy.random functions.

The four objective Functions are displayed in Figure 2. Blood Glucose is evaluated by this objective function every 5 minutes with the goal of maximizing the reward. The plateau function has a simple value of -1 for values outside of the acceptable range and +1 for values within the acceptable range. The Symmetric objective function uses a squared hyperbolic tangent function to give an additional reward to values near the target 80 blood sugar level, compared to the plateau function. The lower penalty function modifies the symmetric function by adding a more severe penalty to deviations lower than the lower acceptable blood glucose limit. Finally, the Higher Reward function rewards values closer to the target 80 blood glucose level more severely.

Since a closed-loop test would endanger a human participant, the in-silico simulation introduces realistic noise with measurement error of up to 18% and actuator error of up to 10%. To counteract these inaccuracies, the controller controls based on the last 25 minutes of blood glucose data while the blood glucose level is within safe bounds. As the blood glucose approaches the upper and lower acceptable limits, a single measurement has more weight so that the controller can react and ameliorate the situation.

Each objective function is evaluated with 100 days of independent simulations. Then, results such as time above and below the ideal range, as well as average blood glucose may be studied.

3 RESULTS

3.1 Moving Horizon Estimation

The MHE was performed with real data from a volunteer that uses Continuous Glucose Monitoring (CGM) and an insulin pump with a digital log. The CGM collects measurements every 5 minutes and the pump provides insulin injections rates on a minute basis. There is significant delay and error in the glucose measurements, upwards of 15% overall error when all is accounted for, but the Bergmann model we used does not directly account for this, so our estimator assumes timely measurements and responses. The delays in insulin effectiveness are built into the model and the parameters for these kinetics are

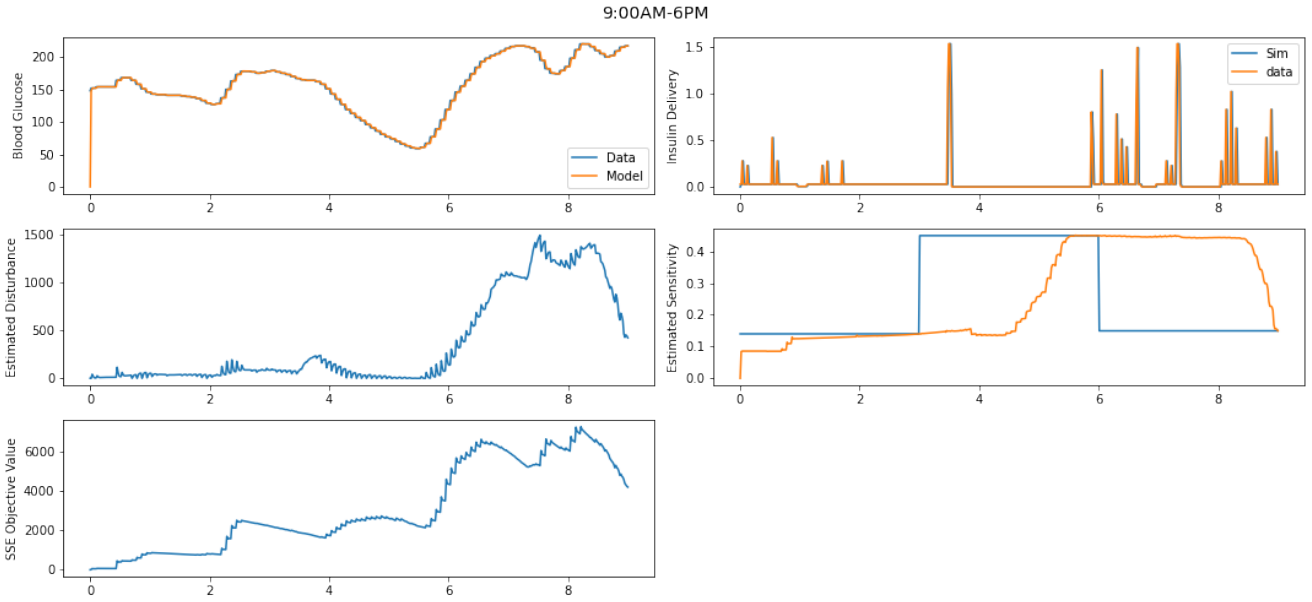

Figure 3. MHE for a nine hour period

Objective Function	Average BG (mmol/dL)	Time above 105 (min)	Time Below 65 (min)
Plateau	87.30	133.05	212.25
Tanh	101.92	187.70	8.85
Tanh + Lower Penalty	86.34	123.70	10.45
2(Tanh) + Lower Penalty	86.42	124.70	8.70

Table 2. Summary Statistics for the Objective Functions Tested

population averages.

Figure 3 illustrates the utility of using a MHE rather than estimating parameters in fixed chunks. The variability of insulin sensitivity with time is significant enough to warrant continuous updates for goodness of fit. The disturbance variable acts as expected, though a more complex model and information about meals etc. would give a more "real-life" depiction of the system. When implemented in conjunction with predictive modelling, it could give an indication that a disturbance is beginning and inject an appropriate amount of insulin to counteract the subsequent rise in blood sugars. The prediction of insulin sensitivity would also decrease the likelihood of overdosing. Disturbance variables are difficult to predict, especially without a fixed eating regiment, but MHE with MPC can help combat these difficulties, especially if time-related trends can be identified.

3.2 Model Predictive Control

The MPC controller controls blood glucose efficiently *in-silico*. Figure 4 shows the system without noise, Figure 5 shows the system with measurement and actuator error, and Figure 6 shows the system with noise as well as control based on the average measurement over the last 25 minutes. Note that the system without noise performs near perfectly as one would expect. When noise is introduced, the insulin input oscillates severely. The magnitude of this oscillation is dampened by taking the average of recent measurements within a safe range and still performs well.

Table 2 shows the summary statistics for the different objective functions. The objective functions which include the hyperbolic tangent peak at 80 mmol/dL maintain blood glucose within acceptable limits better than a flat plateau. Additionally, the objective functions which penalize lower deviations with a penalty multiplier spend on average an hour more per day within the desired bounds.

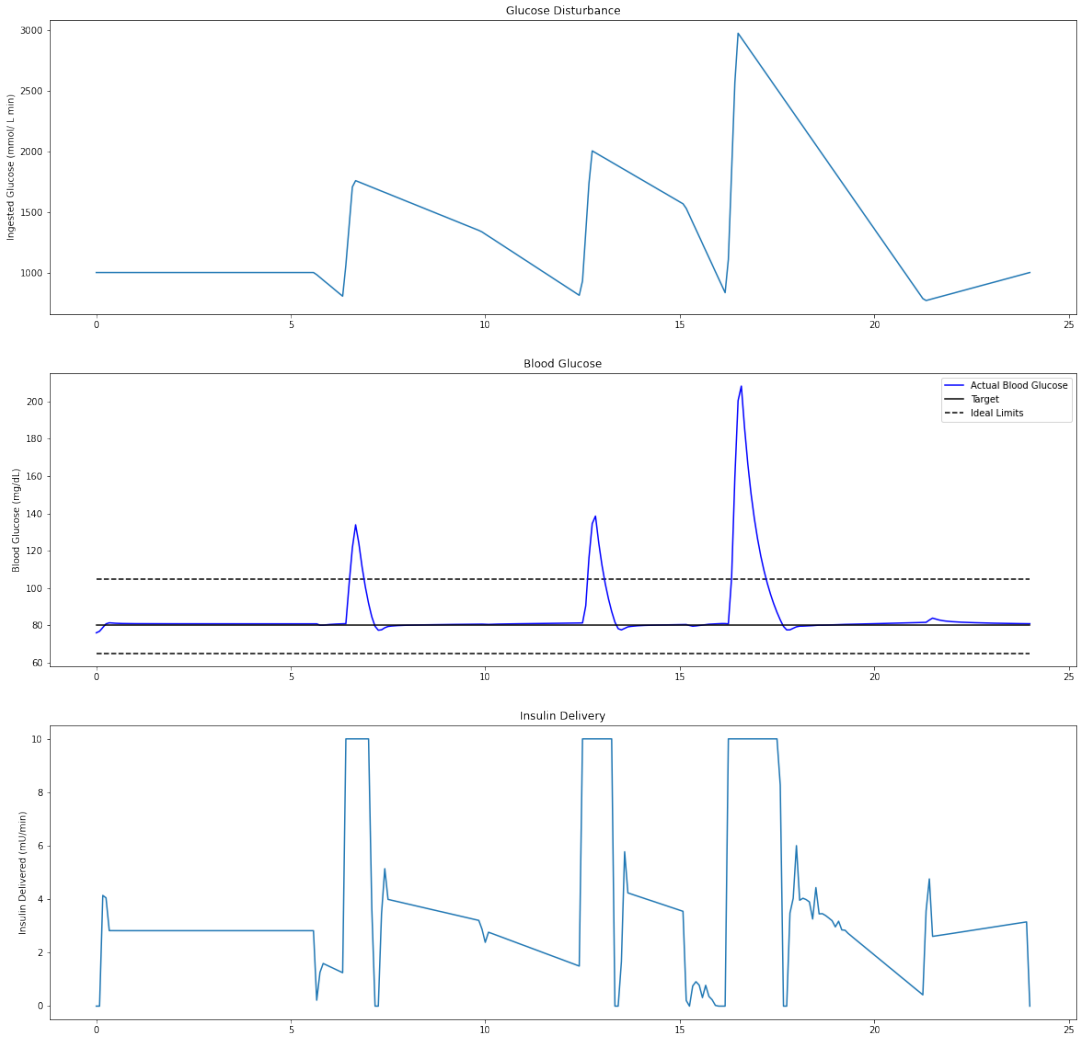

Figure 4. MPC control without noise

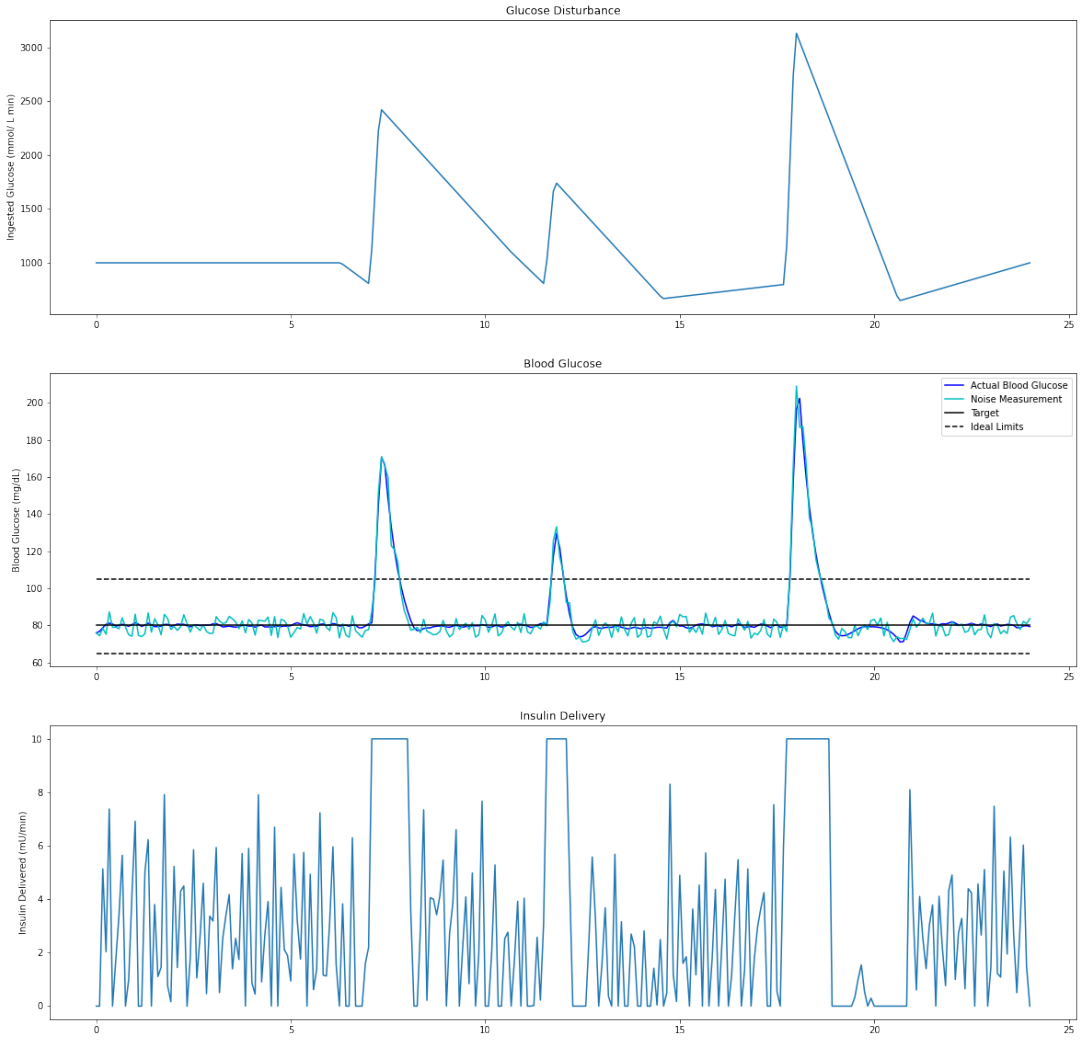

Figure 5. MPC with measurement and actuator error

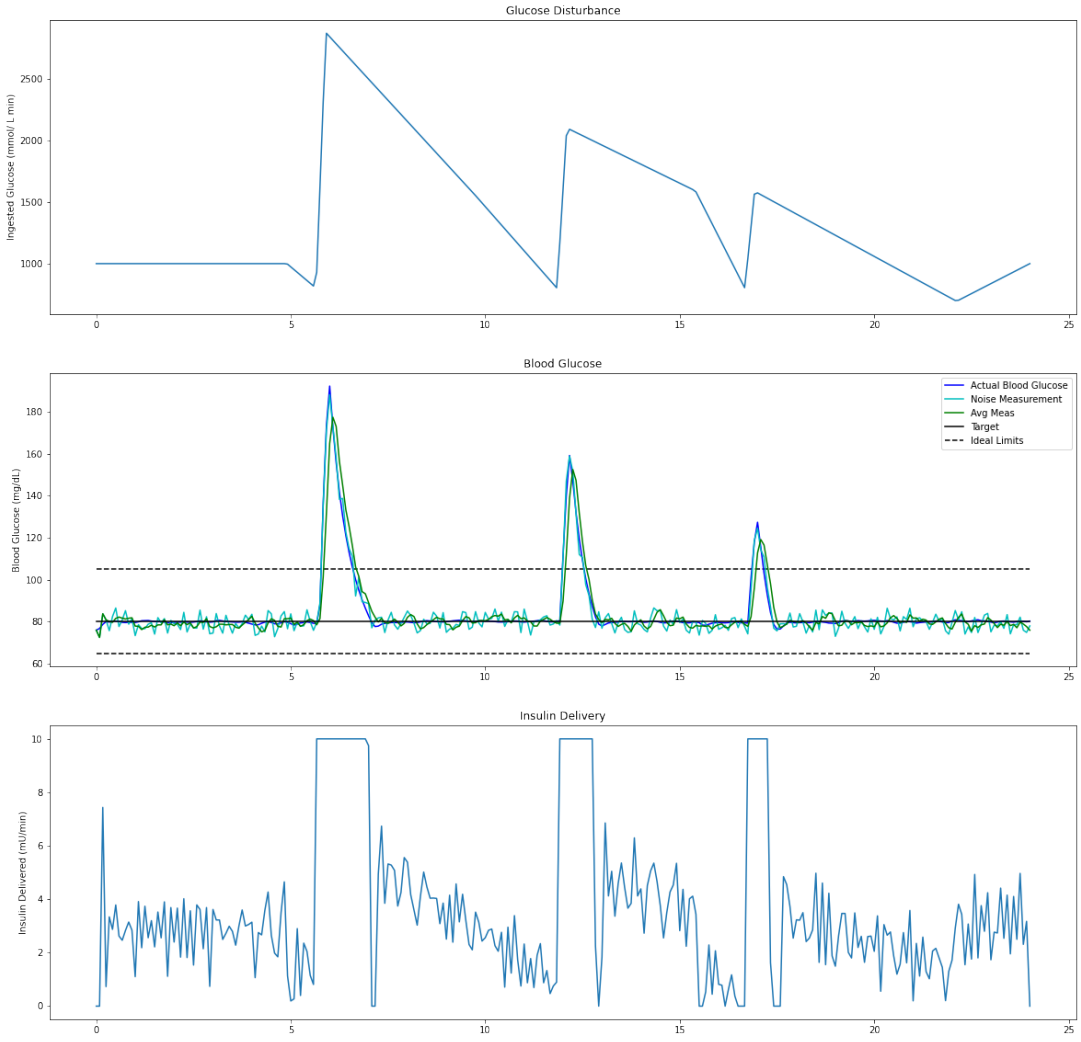

Figure 6. Control based on the last 25 minutes of measurements

4 DISCUSSION

As discussed in the Literature Review, one strength of MHE is the ability to predict behavior with a simple model by fitting parameters to current behavior. The tandem success of the MHE system to predict disturbances and parameter behavior coupled with the ability of the MPC controller to control amid lifelike disturbances indicates the future success of a closed loop system connecting the two.

The three objective functions which have the tanh reward for achieving 80 mmol/dL likely maintain blood glucose within acceptable ranges as the MPC targets the middle of the acceptable range. With the steady state value in the middle of the acceptable bounds, there is more time for the controller to react given a disturbance. Interestingly, there is no remarkable difference between including a severe penalty for low blood glucose deviations, and keeping the penalty symmetrical. While the authors advise to keep this constraint as a safety mechanism, the controller likely already optimizes to keep within acceptable bounds. The absence of any different with the penalty likely indicates that deviations below acceptable ranges of blood sugar will happen regardless of controller tuning.

4.1 Future Work

While MPC performs well in simulation, even with noise, the unpredictability of lifelike errors and parameter drift should be studied. Testing how MPC performs when unaccounted shifts in parameters occur would be helpful to study the robustness of the control. Aside from regressing parameters using MHE, parameters could be predicted based on the time of day, and input from wearable technology such as smart watches or cell phones.

5 CONCLUSION

Living with Diabetes requires lifelong active management of Blood Glucose. In this study, MHE control is able to regress drifting parameters from patient data, which can then be utilized as a more accurate prediction for feed forward control without the need for additional sensors. MPC with an objective function that rewards both staying within an acceptable range, and optimizing an ideal blood glucose level of 80 mmol/dL avoids dangerous hypoglycemic events.

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