Shaping the MPC Cost Function for Superior Automated Glucose Control

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Abstract: The properties of an objective function are fundamental to the functionality of a model predictive controller (MPC). In automated glucose control, avoidance of hypo- and hyperglycemia introduces significant challenges in the design of this cost function. We present a new formulation of the cost function for an MPC based on clinical requirements, and validate the algorithm under in silico and advisory mode assessments. The proposed formulation exhibits significant improvements in avoiding hypoglycemia, compared to clinically validated controllers, and can also mitigate hyperglycemia, across a wide range of in silico scenarios as well as glucose responses seen in actual clinical settings.

Keywords: Model predictive control, biomedical control, medical applications, constraints, model adaptation

1. INTRODUCTION

Over 1.25 million people in the United States are affected by Type 1 Diabetes Mellitus (T1DM), a disease caused by a lack of endogenous insulin production (Daneman 2006). People with T1DM suffer from consistently high blood glucose (BG) concentrations (hyperglycemia), leading to neuropathy, nephropathy, retinopathy, and other chronic complications. These patients need exogenous insulin delivery to survive. Proper dosage of insulin is most often manually calculated, placing a significant burden on patients with the potential to lead to hypo or hyperglycemia due to human errors. In comparison to many over the counter medicines, even a minute overdose of insulin may cause the patients to suffer from low BG concentrations (hypoglycemia), with acute consequences, possibly leading to death in a matter of hours or minutes, if left untreated (The Diabetes Control and Complications Trial Research Group 1993). The average lifespans of T1DM patients lag at least a decade behind the overall population (Miller et al. 2012).

Artificial Pancreas (AP) devices have been in development since the 1980’s to help these people, by automating the insulin delivery. Recent advancements in insulin pump and glucose sensor technologies have accelerated this progress. Over 84 clinical trials of AP devices have been published since 2005 (Doyle III et al. 2014), including more than 12 trials so far in 2015 alone (Doyle III et al. 2015). Significant improvements have been seen in the algorithms that control AP devices. Model predictive control (MPC) algorithms is the most widely utilized algorithm for AP, with more than 50% of published clinical trials of AP incorporating MPC of some form (Dassau et al. 2015, Elleri et al. 2015, Haidar et al. 2015, Kropff et al. 2015, Pinsker et al. 2016).

The flexibility and adaptability afforded by the MPC paradigm allows a wide variety of approaches to overcome the multiple challenges inherent in glucose control. For instance, unlike process control and setpoint tracking in many electronics and machinery applications, there is lack of a well-defined model that relates BG and insulin interactions. Several control-relevant models have been proposed for the design of control algorithms (van Heusden et al. 2012) in AP, but the predictions of these models are not perfect. Moreover, the asymmetry inherent within the BG scale must also be taken into account, given the acute, imminent consequences of hypoglycemia that occur within a very small range of BG, and the chronic, long-term consequences of hyperglycemia that are seen in a wider range (Walsh and Roberts 2006). This is especially important due to the dangerous consequences of excess insulin, and the inability to remove insulin from the body after delivery.

To address the difficulties of obtaining an accurate prediction of the BG values, and the greater severity of clinical risk for hypoglycemia in comparison to hyperglycemia, an MPC with a target zone, instead of a target setpoint, was initially proposed (Grosman et al. 2010) and tested under clinical settings. Although this algorithm performed well, there was not sufficient suspension of insulin delivery when it was clinically required (Harvey et al. 2014). A formulation that modified this algorithm that reduces the penalty on insulin delivery deviations from basal when BG is below the target (Gondhalekar et al. 2014) performed well in prevention of hypoglycemia (Dassau et al. 2015), but exhibited a need for tighter control against hyperglycemia. Another formulation that decreased the buffer back to a setpoint provided a tighter control during in silico (Lee et al. 2013) and clinical studies (Lee et al. 2015), but still showed potential hypoglycemia.

The contribution of this paper is to demonstrate an exponential-quadratic shaping of the cost function utilized within an MPC for artificial pancreas that shows improved performance compared to previous controllers that were validated in clinical settings. This medically inspired formulation of the cost function incorporates an exponential cost to the glucose excursions below the therapeutic target, while maintaining a quadratic penalty to the excursions above the therapeutic target. The proposed controller thus improves attenuation and suspension of insulin delivery during impending hypoglycemia, and more agilely adjusts for...
hyperglycemia (particularly after meal disturbances), completing the two primary objectives for BG control. The advantages of strong asymmetry in penalizing BG deviations above or below the target have been previously reported (Boiroux et al. 2010, Gondhalekar et al. 2014), and the proposed innovation in this paper advances this concept. The performance of an MPC controller with this new shaping of the cost function is compared against clinically validated AP controllers under three conditions: 1) an in silico simulated stress test of edge cases of hypo- and hyperglycemia; 2) an in silico clinical trial that mimics protocols utilized in clinical applications, including challenges such as an unannounced meal; and 3) an advisory mode validation of the controller on clinical subject data.

2. METHODS

2.1 Development of the Model Predictive Control Algorithm

A control-relevant model of BG-insulin interactions previously developed in (van Heusden et al. 2012) was personalized based on a priori available clinical characteristics (Lee et al. 2013). The initial 3rd order model proposed in (van Heusden et al. 2012) is

\[ M_p(z^{-1}) = \frac{g(z^{-1})}{h(z^{-1})} = \frac{Kz^{-3}}{(1-0.98z^{-1})(1-0.956z^{-1})^2}. \]

where \( z^{-1} \) is the discrete-time backwards-shift operator, \( I \) is insulin delivery (pmol/min), and \( G \) is BG concentration (mg/dL), with a sampling time of 5 minutes, both in deviation variables from basal delivery and 110 mg/dL, respectively. The model gain \( K \) can be personalized based on a priori available clinical parameters (total daily insulin (TDI) and basal profile), as in (Lee et al. 2013). This model can then be explicitly implemented in an MPC algorithm, as in (Gondhalekar et al. 2013). For brevity, please refer to the cited literature for details of the personalization of the model gain and the derivation of the controller. The control and prediction horizons were set to \( N=5 \) and \( P=12 \), respectively.

2.2 Shaping of the Cost Function to Improve Response to Hypo- and Hyperglycemia

Development of a proper cost function is a critical component in the operation of any MPC controller. The cost function in the Zone-MPC (ZMPC) controller was implemented as (Gondhalekar et al. 2013)

\[ J^{ZMPC} \left( \{ I(k+j) \}_{j=0}^{N-1} \right) = \sum_{j=0}^{N-1} ||G^\text{zone}(k+j)||^2 + R_+ \sum_{j=0}^{N-1} ||I^+_j(k+j)||^2 + R_- \sum_{j=0}^{N-1} ||I^-_j(k+j)||^2, \]

where \( R_+ = 7,000 \) and \( R_- = 100 \) were design parameters, that weighed the insulin inputs, \( I^+_j(k+j) \) and \( I^-_j(k+j) \), corresponding to the glucose excursions beyond the target zone, defined as

\[ G^\text{zone}(k+j) = \begin{cases} G(k+j) - 140 & \text{if } G(k+j) > 140 \\ 0 & \text{if } G(k+j) < 80 \\ 80 - G(k+j) & \text{otherwise} \end{cases}. \]

and \( k \) and \( j \) representing the actual time step and the prediction step, respectively. Higher values of the design parameters indicated a greater penalty on the corresponding inputs, and thus fewer input deviations away from basal.

In the personalized MPC (pMPC), the gain of the model was personalized, and the cost function was modified as

\[ J^{pMPC} \left( \{ I(k+j) \}_{j=0}^{N-1} \right) = \sum_{j=0}^{N-1} ||G^\text{pMPC}(k+j)||^2 + R_+ \sum_{j=0}^{N-1} ||I^+_j(k+j)||^2 + R_- \sum_{j=0}^{N-1} ||I^-_j(k+j)||^2, \]

with \( R_+ = R_- = 11,000 \), where \( G^\text{pMPC}(k+j) \) represents the glucose excursions above or below the setpoint.

Although the formulation of the cost function for the ZMPC as in equation (2) showed reasonable performance in hypoglycemia prevention, the controller’s response to hyperglycemic incidents was less pronounced due to the presence of a quiescent range of glucose values. In comparison, the formulation of the cost function for the pMPC as in equation (4) improved response to glucose excursions above 110 mg/dL, at the cost of potentially increased hypoglycemic risk. In both cases, the excursions in both directions were penalized by a quadratic function, meaning that only a scalar multiplier determined the differences between the risk of hypo- and hyperglycemia.

From a clinical perspective, hypoglycemia must be addressed with urgency (i.e., immediately, or when possible, predictively), whereas hyperglycemia may be treated more cautiously and with longer-term considerations. Consequently, it is important to incorporate a fundamentally different scaling of the penalties on glucose values above versus below the targets, rather than just a scalar multiplier. Ideally, the advantages of the ZMPC and the pMPC would be combined, maintaining good response to both hyper and hypoglycemia, without increasing susceptibility to minute deviations around the setpoint.

To achieve these objectives, the cost function was reshaped to contain a quadratic penalty on excursions above the setpoint, and an exponential penalty on excursions below setpoint. The resulting cost function \( J \) for which the MPC is optimized is defined as

\[ J \left( \{ I(k+j) \}_{j=0}^{N-1} \right) = \sum_{j=0}^{N-1} ||G^\text{pMPC}(k+j)||^2 + \sum_{j=1}^{p} \exp(\alpha ||G^\text{pMPC}(k+j)||) + R_+ \sum_{j=0}^{N-1} ||I^+_j(k+j)||^2 + R_- \sum_{j=0}^{N-1} ||I^-_j(k+j)||^2, \]

where \( R_+ = 7,700 \), \( R_- = 2,500 \), and \( \alpha = 0.18 \) is a design parameter representing the exponential coefficient. This approach allows an exponentially greater penalty on glucose excursions below the target to compensate aggressively for hypoglycemia, while keeping a quadratic penalty scaling on excursions above the zone to maintain a reasonable, but less aggressive response to hyperglycemia. Moreover, the exponential formulation near the target allows the controller to have a reasonably conservative, but nonzero, response to
fluctuations around the setpoint, without sacrificing the ability to respond quickly to larger excursions.

2.3 Development of other constraints on MPC Optimization

One consequence of the unique physiology of insulin is the need for additional constraints based on prior delivery to take into account insulin that was delivered, but not yet utilized and remaining within the body. These constraints, called Insulin-On-Board (IOB) (Ellingsen et al. 2009) and formulated to estimate the percentage of prior insulin delivery that remains unutilized within the system, were implemented as an additional part of the constraints placed on the MPC; refer to (Lee et al. 2016) for a complete description of these constraints.

2.4 Design of the In Silico Studies

The US FDA-accepted Universities of Virginia/Padova metabolic simulator (Kovatchev et al. 2009) was utilized to evaluate the proposed controller in silico. First, to test the controllers’ robustness against sudden hypo- and hyperglycemic events, the controller was tested in silico with a “secret” (uninformed) 5U bolus, followed by a 30g rescue carbohydrate (CHO) treatment 1h later while undergoing a simulated pump occlusion for 2 hours, on a virtual subject whose settings represented the furthest outlier of glucose-insulin interactions and therefore the greatest susceptibility to anomalous glucose changes. Next, a protocol identical to those tested under other clinical trials, included two announced (feed-forward) meals (65g, 50g CHO), and one unannounced meal (65g CHO), as well as an overnight period, was utilized to validate the controller’s performance in practical conditions.

Finally, the controller was tested under advisory mode of insulin and glucose traces of an actual subject that underwent clinical trials with an AP. An advisory mode validation provides the glucose and insulin values at each data point from the clinical trial to the proposed algorithm (Pinsker et al. 2016), and records the resulting recommendations by the algorithm, at every time step (Gillis et al. 2007). This method gives a means for a qualitative validation of the controller’s performance against clinical outcomes (attenuation of insulin delivery in cases where hypoglycemia was seen in future points, and vice versa for hyperglycemia).

3. RESULTS

3.1 Preliminary Validation of the Asymmetric and Quadratic or Exponential Cost Functions

The design parameters to shape the proposed asymmetric, quadratic and exponential cost function for the MPC, called enhanced MPC (eMPC), were initially developed in reference to the following clinically validated cost functions and penalty indices as their basis:

a) Zone-Asymmetric (ZMPC)

b) Setpoint-Symmetric (pMPC)

c) Low/High BG Index (LBGI/HBGI), a widely used clinical metric to assess BG control performance (Kovatchev et al. 2002)

These design parameters were implemented to maximize the time in BG range of 70-180 mg/dL and minimize time below

3.2 Penalties on Exponential Cost Functions

The design parameters to shape the proposed asymmetric, quadratic and exponential cost functions for the MPC, called enhanced MPC (eMPC), were initially developed in reference to the following clinically validated cost functions and penalty indices as their basis:

a) Zone-Asymmetric (ZMPC)

b) Setpoint-Symmetric (pMPC)

c) Low/High BG Index (LBGI/HBGI), a widely used clinical metric to assess BG control performance (Kovatchev et al. 2002)

These design parameters were implemented to maximize the time in BG range of 70-180 mg/dL and minimize time below

3.3 Comparison of Design Parameters

The design parameters to shape the proposed asymmetric, quadratic and exponential cost functions for the MPC, called enhanced MPC (eMPC), were initially developed in reference to the following clinically validated cost functions and penalty indices as their basis:

a) Zone-Asymmetric (ZMPC)

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c) Low/High BG Index (LBGI/HBGI), a widely used clinical metric to assess BG control performance (Kovatchev et al. 2002)

These design parameters were implemented to maximize the time in BG range of 70-180 mg/dL and minimize time below

3.4 Simulation of Clinical Trials

The design parameters to shape the proposed asymmetric, quadratic and exponential cost functions for the MPC, called enhanced MPC (eMPC), were initially developed in reference to the following clinically validated cost functions and penalty indices as their basis:

a) Zone-Asymmetric (ZMPC)

b) Setpoint-Symmetric (pMPC)

c) Low/High BG Index (LBGI/HBGI), a widely used clinical metric to assess BG control performance (Kovatchev et al. 2002)

These design parameters were implemented to maximize the time in BG range of 70-180 mg/dL and minimize time below

3.5 Validation of the Proposed Controller

The design parameters to shape the proposed asymmetric, quadratic and exponential cost functions for the MPC, called enhanced MPC (eMPC), were initially developed in reference to the following clinically validated cost functions and penalty indices as their basis:

a) Zone-Asymmetric (ZMPC)

b) Setpoint-Symmetric (pMPC)

c) Low/High BG Index (LBGI/HBGI), a widely used clinical metric to assess BG control performance (Kovatchev et al. 2002)

These design parameters were implemented to maximize the time in BG range of 70-180 mg/dL and minimize time below

3.6 Implementation of the Proposed Controller

The design parameters to shape the proposed asymmetric, quadratic and exponential cost functions for the MPC, called enhanced MPC (eMPC), were initially developed in reference to the following clinically validated cost functions and penalty indices as their basis:

a) Zone-Asymmetric (ZMPC)

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c) Low/High BG Index (LBGI/HBGI), a widely used clinical metric to assess BG control performance (Kovatchev et al. 2002)

These design parameters were implemented to maximize the time in BG range of 70-180 mg/dL and minimize time below

3.7 Evaluation of the Proposed Controller

The design parameters to shape the proposed asymmetric, quadratic and exponential cost functions for the MPC, called enhanced MPC (eMPC), were initially developed in reference to the following clinically validated cost functions and penalty indices as their basis:

a) Zone-Asymmetric (ZMPC)

b) Setpoint-Symmetric (pMPC)

c) Low/High BG Index (LBGI/HBGI), a widely used clinical metric to assess BG control performance (Kovatchev et al. 2002)

These design parameters were implemented to maximize the time in BG range of 70-180 mg/dL and minimize time below

3.8 Comparison of Controller Performance

The design parameters to shape the proposed asymmetric, quadratic and exponential cost functions for the MPC, called enhanced MPC (eMPC), were initially developed in reference to the following clinically validated cost functions and penalty indices as their basis:

a) Zone-Asymmetric (ZMPC)

b) Setpoint-Symmetric (pMPC)

c) Low/High BG Index (LBGI/HBGI), a widely used clinical metric to assess BG control performance (Kovatchev et al. 2002)

These design parameters were implemented to maximize the time in BG range of 70-180 mg/dL and minimize time below

3.9 Clinical Validation of the Proposed Controller

The design parameters to shape the proposed asymmetric, quadratic and exponential cost functions for the MPC, called enhanced MPC (eMPC), were initially developed in reference to the following clinically validated cost functions and penalty indices as their basis:

a) Zone-Asymmetric (ZMPC)

b) Setpoint-Symmetric (pMPC)

c) Low/High BG Index (LBGI/HBGI), a widely used clinical metric to assess BG control performance (Kovatchev et al. 2002)

These design parameters were implemented to maximize the time in BG range of 70-180 mg/dL and minimize time below

3.10 Performance of the Proposed Controller

The design parameters to shape the proposed asymmetric, quadratic and exponential cost functions for the MPC, called enhanced MPC (eMPC), were initially developed in reference to the following clinically validated cost functions and penalty indices as their basis:

a) Zone-Asymmetric (ZMPC)

b) Setpoint-Symmetric (pMPC)

c) Low/High BG Index (LBGI/HBGI), a widely used clinical metric to assess BG control performance (Kovatchev et al. 2002)

These design parameters were implemented to maximize the time in BG range of 70-180 mg/dL and minimize time below

3.11 Discussion of Controller Performance

The design parameters to shape the proposed asymmetric, quadratic and exponential cost functions for the MPC, called enhanced MPC (eMPC), were initially developed in reference to the following clinically validated cost functions and penalty indices as their basis:

a) Zone-Asymmetric (ZMPC)

b) Setpoint-Symmetric (pMPC)

c) Low/High BG Index (LBGI/HBGI), a widely used clinical metric to assess BG control performance (Kovatchev et al. 2002)

These design parameters were implemented to maximize the time in BG range of 70-180 mg/dL and minimize time below

3.12 Conclusion

The design parameters to shape the proposed asymmetric, quadratic and exponential cost functions for the MPC, called enhanced MPC (eMPC), were initially developed in reference to the following clinically validated cost functions and penalty indices as their basis:

a) Zone-Asymmetric (ZMPC)

b) Setpoint-Symmetric (pMPC)

c) Low/High BG Index (LBGI/HBGI), a widely used clinical metric to assess BG control performance (Kovatchev et al. 2002)

These design parameters were implemented to maximize the time in BG range of 70-180 mg/dL and minimize time below

Fig. 1. The scaled costs of excursions above or below the target objectives imposed by the cost functions utilized in the clinical trial of the ZMPC and pMPC controllers, the novel controller with asymmetric, quadratic and exponential cost functions (eMPC), and the LBGI/HBGI scale. The green zones represent the 80-140 mg/dL euglycemic zone, and the yellow zones represent the 70-180 mg/dL safe glycemic zone. (A) Penalties for BG between 0 to 250 mg/dL. (B) 10x zoomed view of the penalties near 110 mg/dL. 70 mg/dL. The specific values were selected by modifying the design parameters for the excursions below the target until hypoglycemia was minimized, then adapting the design parameters to also simultaneously minimize excursions above the target, without sacrificing hypoglycemia prevention.

An illustration of the resulting costs against a range of glucose values (scaled to represent the relative weighing based on glucose excursions, rather than input deviations) for the settings used in the ZMPC and pMPC clinical trials, as well as the scaled LBGI/HBGI index and the eMPC cost functions, are shown in Figs. 1a and 1b. The asymmetry introduced by eMPC allows for a significantly more agile response to glucose excursions in either extreme. In comparison, the cost function for the pMPC is necessarily limited to a conservative response to compensate for the symmetric penalty to excursions below the setpoint. Further, although the cost function for the ZMPC incorporates a heavy penalty to glucose excursions below the targeted euglycemic zone and a more aggressive penalty to excursions above the zone (80-140 mg/dL), the width of the control target zone means that the overall system response to excursions above the zone are limited to be even more conservative than the pMPC. LBGI/HBGI indices show a degree of asymmetry similar to the (eMPC) on regions near the zone, but show a significantly decayed response to larger excursions, and has the most conservative penalties at glucose values beyond 200 mg/dL.

The eMPC cost function applies a lower, but nonzero, penalty to excursions within the safe glycemic range (70-180 mg/dL), and places a rapidly rising penalty to excursions below this range. The penalty is also slightly increased for excursions above the range, taking advantage of the increased window of delivery provided by the better defense against hypoglycemia to take more rapid action against hyperglycemia. This formulation enables a rapid response to sustained glucose excursions beyond standard fluctuations above or below the safe glycemic range, maintaining the advantages of the
ZMPC within and below the range and pMPC above the range, without needing a buffer zone. Further, the exponential formulation of the cost function can naturally accommodate negative glucose excursions, unlike LBGI/HBGI indices.

3.2 Edge Case Robustness Validation under an Extreme Stress-Test Scenario

Hyperglycemia and hypoglycemia are challenging events that may occur successively due to the natural response of the glucose-insulin system, especially under closed-loop. For instance, if a subject enters closed-loop while having a significant amount of IOB, the BG values may begin dropping independently from controller action. The AP system may respond by suspending insulin delivery, and recommending rescue carbohydrates. Ingestion of the rescue carbohydrates, especially after insulin suspension, may cause a rapid rise in BG, which may invoke controllers to potentially respond with an overly aggressive insulin delivery, caused partly by a relaxation of the IOB constraints due to the known history of insulin suspension. The end result of this behavior is a repeated series of hyper- and hypoglycemic events, which cannot be adequately addressed by modification of the IOB constraints alone.

This behavior was replicated by initially delivering a 5U intravenous insulin bolus 1h after the initiation of an in silico closed-loop simulation, without informing the controller. This was an unmeasured, unknown stress to the system that would simulate a significant hypoglycemic event. Next, a 30g rescue carbohydrate (CHO) treatment at 2h was paired with a simulated pump occlusion from 1h to 3h to induce an extreme rebound hyperglycemia and further challenge the controllers. The system response was recorded for 8 hours after delivery of the unknown bolus. This procedure was applied to the most sensitive subject available within the 10 in silico adult cohort in the UVA/Padova simulator.

It should be noted that the American Diabetes Association’s recommendation for hypoglycemia treatment is 15g of fast acting CHO with repeated treatment every 15min if needed. A 30g CHO treatment, with a simulated pump occlusion to minimize remaining insulin action during the CHO treatment, was utilized in this study to reproduce the rapid glucose excursions seen in clinical studies during similar situations. Figs. 2a and 2b show the resulting responses of the ZMPC, pMPC, and eMPC. The thin lines of insulin delivery visible between t=1h and t=3h represent each controller’s recommendations during the period of simulated pump occlusion. The proposed controller significantly outperforms either previous clinical controller in managing post rescue CHO rebound hypoglycemia, decreasing the prandial peak (331 mg/dL (eMPC) versus 341 mg/dL (pMPC) and 361 mg/dL (ZMPC)), and increasing the minimum glucose value after the treatment (83 mg/dL (eMPC) versus 59 mg/dL (pMPC) and 42 mg/dL (ZMPC)), largely due to the increased attenuation of insulin delivery starting at t=5h, or 4h after the unknown insulin delivery.

3.3 Closed-Loop Performance Assessments under a Realistic Clinical Protocol

The performance of each controller was also assessed in a clinical protocol identical to those used in clinical trials. This 27.5h protocol mimics a day in the life of a person with T1DM, with three meals of reasonable carbohydrate content, starting from 4:00 PM on the first day and ending at 7:30 PM on the second day. A dinner (65g, 6:30 PM) and breakfast (50g, 6:30 AM) are consumed by the subjects with a bolus (feed-forward insulin delivery) at the time of ingestion. This bolus is calculated according to each subject’s insulin-to-carbohydrate ratio, a common clinical parameter utilized to calculate the grams of carbohydrates that is compensated by one unit of insulin. A lunch (65g, 12:30 PM) during the following day is also consumed by the subjects without a mealtime bolus (unnounced), to stress the design and evaluate the ability of an AP to mitigate the possibility for human error in practical T1DM management.

Figs. 3a, 3b, and 3c depict the mean BG and insulin delivery traces for 10 adult in silico subjects within the UVA/Padova simulator, and a magnified portion of the insulin delivery profiles for the announced meal. The eMPC maintains the glucose control performance seen in the clinical controllers, statistically significantly improving the mean glucose value during the entire trial duration (135.6 mg/dL (pMPC) versus 143.6 mg/dL (ZMPC), p=0.015) and the time within the euglycemic range (66.6% (eMPC) versus 58.3% (ZMPC), p=0.015). The mean glucose during the post prandial period after the announced lunch (174.7 mg/dL (eMPC) versus 188.2 mg/dL (ZMPC) and 178.7 mg/dL (pMPC)) and the time taken to return to the 70-180 mg/dL safe glucose range (210.5min (eMPC) versus 238.5min (ZMPC) and 228min (pMPC)) were also improved, although the differences were not statistically significant due to the small sample sizes.

3.4 Advisory Mode Assessment of eMPC versus Clinical Data

As previously described, an advisory mode assessment provides glucose and insulin histories to the proposed controller at every time point, and records the point-by-point recommendation by the controller to review against actual clinical data. Fig. 4 shows the BG and insulin delivery traces
of a subject that was controlled by the pMPC during a closed-loop clinical trial in an identical protocol to the in silico trials featured in the previous section (Pinsker et al. 2016), and advisory mode recommendations by the eMPC given the same traces. As can be seen in the figures, the rapid glucose rises following the hypoglycemic events during the overnight period caused the pMPC to give at least the basal insulin delivery throughout the period. Not only does this lead to repeated hypoglycemia, but the multiple rescue CHO ingestions before the breakfast lead to oscillatory behavior and continued undesirable post prandial glucose fluctuations. On the other hand, the eMPC advisory mode results show clear reductions in recommended insulin delivery values throughout each hypoglycemic incident (0:00, 2:00 and 4:00 AM), and at relatively high BG values near the setpoint (110 mg/dL) for which the pMPC had not yet responded. This shows promise for hypoglycemia reduction by the eMPC during clinical trials. Furthermore, the controller also shows an increased response for the unannounced meal, potentially signifying a more agile response for such clinical events.

4. CONCLUSIONS

An eMPC for AP applications with a novel reshaping of the cost function was designed and validated under in silico trials and advisory mode of clinical data. Glucose excursions were penalized asymmetrically, with exponential scaling for movements below the target to respond agiley to glucose excursions significantly below the setpoint, and quadratic scaling for movement above the target, to maintain the reasonable responses to unannounced meals seen in clinical settings. This formulation allows the controller to combine the advantages of, and improve upon, the clinically validated ZMPC and pMPC controllers. In silico and advisory mode validations showed improvements in prevention of both post rescue CHO hypoglycemia and overall BG control on several relevant clinical metrics, in comparison to clinically tested controllers.

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