Tackling problem nonlinearities & delays via asymmetric, state-dependent objective costs in MPC of an artificial pancreas

Ravi Gondhalekar*, Eyal Dassau*, and Francis J. Doyle III*
University of California Santa Barbara, Santa Barbara, CA, USA.

Abstract
The design of a Model Predictive Control (MPC) law for an Artificial Pancreas (AP) that automatically delivers insulin to people with type 1 diabetes mellitus is considered. An MPC law was recently proposed that exploits the simplicity of linear dynamical models, but is in two ways a ‘nonlinear’ departure of standard linear MPC, while circumnavigating the complexity of cumbersome, fully nonlinear MPC approaches. The first of two issues focused on is the nonlinearity of the control problem, and it is demonstrated how this can be tackled via asymmetric objective functions. The second issue is controller induced hypoglycemia resulting from the large delay in actuation and sensing. The proposed MPC strategy employs an asymmetric, state-dependent objective function that leads to a nonlinear optimization problem. The result is an AP controller with significantly elevated safety and comparable control performance. The contribution of this paper is a detailed in-silico analysis of the proposed control law, and a clinical demonstration of the benefits of asymmetric objective functions.

Keywords
Model predictive control; asymmetric objective cost; state-dependent objective cost; nonlinear optimization; safety critical control; artificial pancreas; type 1 diabetes

1. INTRODUCTION
Type 1 Diabetes Mellitus (T1DM) is an auto-immune disease that destroys the pancreas’ insulin-producing β-cells, rendering people with T1DM dependent on exogenous insulin to prevent chronic hyperglycemia and its destructive, long-term effects. Research into a so-called Artificial Pancreas (AP), an automatic device that delivers insulin to people with T1DM, has made steady improvements since commencing in the 1970s [Clemens et al. (1977); Cobelli et al. (2011)]. An AP’s control system must be suitably aggressive in commanding insulin delivery to correct hyperglycemia, but must prevent over-insulinization, which may lead to hypoglycemia, the results of which are immediate and include dizziness, unconsciousness, coma, and death. Various control paradigms have been applied to the AP control problem; see the review by Doyle III et al. (2014). The focus in this paper is on Model Predictive Control (MPC) [Maciejowski (2002)], considered by others in an AP context in [Hovorka et al. (2004); Magni et al. (2009); Turksoy et al. (2013)], and by the

gondhalekar@engineering.ucsb.edu, dassau@engineering.ucsb.edu, doyle@engineering.ucsb.edu.
authors in [Parker et al. (1999); Grosman et al. (2010); Gondhalekar et al. (2013)]. In particular a subcutaneous-subcutaneous AP is considered, where insulin delivery (control input) is performed by a Continuous Subcutaneous Insulin Infusion (CSII) pump, and glucose sensing (output measurement for feedback) is based on a Continuous Glucose Monitor (CGM).

Physiological models of insulin-glucose dynamics are typically nonlinear [Colmegna and Sánchez Penña (2014)]. Nevertheless, the AP control strategies typically adopted, and adopted by the authors here, employ a linear model. There seem to be two main reasons for this. First, the control-relevant nonlinearity of the insulin-glucose dynamics is not a major impediment to controller design, as was demonstrated and concluded in Hernjak and Doyle III (2005). The second is that characterizing models, of any class, is difficult due to the large intra- and inter-patient variability, and also the dearth of input-output data, especially at the unsafe glucose output levels. The emphasis is on identifying control-relevant models that lead to effective control and that are suitably simple, and the authors have successfully trialed multiple variations of MPC based on the linear time-invariant (LTI) control-relevant model proposed in van Heusden et al. (2012) (see Section 2.1).

The AP control problem is highly asymmetric and benefits from nonlinear controllers. First, the consequences of hypoglycemia are immediate and more detrimental than those of (temporary) hyperglycemia. Second, an AP controller has only little leeway to attenuate insulin delivery from the basal-rate, the baseline insulin requirement, whereas aggressive insulin infusion above the basal-rate is realizable. Third, in the single-hormone AP considered here there is no antagonistic control action to insulin. This asymmetry is well known and commented on, yet most glucose controllers do not address it. Most MPC schemes use symmetric, quadratic cost functions to penalize both predicted glucose outputs and insulin inputs. The resulting challenge is that a controller tuned to respond conservatively to hyperglycemia has difficulty performing a pump-suspension in the face of hypoglycemia, and a controller tuned to easily perform pump-attenuations tends to over-correct hyperglycemia, resulting in controller-induced hypoglycemia. To tackle this tradeoff, asymmetric input cost functions were proposed and demonstrated in Gondhalekar et al. (2014). These permit the positive and negative portions of the scalar insulin delivery input to be penalized independently, and facilitate the decoupled design of the AP’s response to hyperglycemia and hypoglycemia. Others have considered asymmetric cost functions in MPC of an AP [Hernjak and Doyle III (2005); Magni et al. (2009); Boiroux et al. (2010); Cameron et al. (2011); Boiroux et al. (2012)], but some seem to have mis-identified asymmetry with general nonlinearity. Importantly, the proposed asymmetric input costs, in combination with linear dynamics and linear inequality constraints, lead to a readily solvable, convex, continuous Quadratic Program (QP). In contrast, some other attempts at implementing asymmetric weights have been abandoned due to the excessive complexity of a nonlinear MPC approach. We wish to emphasize here that an asymmetric, linear MPC approach is effective for a nonlinear control problem, and that the resulting MPC optimization problem results in a nonlinear control law. The asymmetric input cost functions were proposed previously in Gondhalekar et al. (2014) and have proved useful in the authors’ most recent clinical trials. A contribution of this paper is a detailed in-silico analysis, and a clinical demonstration, of their use.
Meal ingestion that is unannounced, i.e., the controller is not informed about the meal by the subject, poses a major challenge for an AP controller, in particular one based on CGM feedback and CSII pumps, due to the large delay in subcutaneous sensing and actuation. Meal consumption causes a hyperglycemic excursion, and an AP controller must respond by administering more insulin. Importantly, earlier insulin delivery is more effective, and significant insulin delivery after the glucose peak has been reached may lead to controller induced hypoglycemia, which must be avoided. To yield a controller that is aggressive on the uphill leg of a hyperglycemic excursion, but conservative on the downhill leg, the authors proposed in Gondhalekar et al. (2015) the notion of velocity-weighting, whereby the quadratic MPC cost used to penalize the glucose deviation is velocity-dependent, i.e., the quadratic cost parameter itself is a function of the rate of change of the glucose output. Such state-dependent cost functions, in an otherwise linear MPC framework, lead to an unusual nonlinear optimization problem, that can readily be solved via a sequence of QPs, and results in a nonlinear controller. A contribution of this paper is a detailed in-silico analysis of the use of velocity-weighting.

2. MPC DESIGN

2.1 Model of insulin-glucose dynamics

The control law design is based on the discrete-time LTI system (1) with sample-period $T := 5$ [min]. The step index is denoted by $i \in \mathbb{N}$, the linearized insulin (control) input by $u \in \mathbb{R}$ [U], the linearized blood-glucose output by $y \in \mathbb{R}$ [mg/dL], and an approximation of the rate of change of the linearized blood-glucose output by $v \in \mathbb{R}$ [mg/dL/min]; $v$ is henceforth termed the velocity. The dynamical model of the transfer-characteristics from $u$ to $y$ was derived in van Heusden et al. (2012), where the interested reader may find an explanation of the gain terms $F$, $c$, and $1800$, and a derivation of the poles $p_1$ and $p_2$. The state-space form and velocity output $v$ were introduced and explained in Gondhalekar et al. (2014, 2015).

$$x_{i+1} = Ax_i + Bu_i, \quad y_i = C_y x_i, \quad v_i = C_v x_i \quad (1)$$

$$A := \begin{bmatrix} p_1 + 2p_2 - 2p_1p_2 - p_2^2 & -p_2^2 & 0 \\ 1 & 0 & 0 \\ 0 & 1 & 0 \end{bmatrix} \in \mathbb{R}^{3 \times 3}$$

$$B := \frac{1800Fc}{uTDI} \begin{bmatrix} 1 \\ 0 \\ 0 \end{bmatrix}^T \in \mathbb{R}^3$$

$$C_y := \begin{bmatrix} 0 & 0 & 1 \end{bmatrix} \in \mathbb{R}^{1 \times 3}, \quad C_v := \begin{bmatrix} 0.1 & 0 & -0.1 \end{bmatrix} \in \mathbb{R}^{1 \times 3}$$
\[ c_\ast = -60(1 - p_1)(1 - p_2)^2 \]

\[ p_1 = 0.98 , \quad p_2 = 0.965 , \quad F = 1.5 \]

\( u_{\text{TDI}} > 0: \) Total daily insulin, subject specific [U]

System (1) is linearized about a steady-state achieved by the subject-specific, time-dependent basal input rate \( u_{\text{BASAL,}i} [\text{U/h}] \), that results in the steady-state blood-glucose output \( y_s := 110 [\text{mg/dL}] \). The absolute insulin input administered per sample-period is denoted by \( u_{\text{IN,}i} [\text{U}] \), and the absolute blood-glucose output by \( y_{\text{BG,}i} [\text{mg/dL}] \):

\[ u_{\text{IN,}i} = u_i + \frac{u_{\text{BASAL,}i}}{60 \text{ min/h}} , \quad y_{\text{BG,}i} = y_i + y_s . \]

### 2.2 State-estimation

The model state \( x \) is provided at each step \( i \) by a linear recursive state-estimator (Luenberger observer). Estimator details are omitted for brevity, thus for simplicity we assume the state \( x_i \) is available for all \( i \).

### 2.3 Blood-glucose target zone

The proposed MPC strategy is a zone-MPC strategy, i.e., predicted blood-glucose trajectories are penalized based on their excursion from a target zone [Grosman et al. (2010); van Heusden et al. (2012); Gondhalekar et al. (2013)]. In this work the blood-glucose target zone is the interval \([\zeta^\flat, \zeta^\breve]\), \( \zeta^\flat := 80 \text{ mg/dL}, \zeta^\breve := 140 \text{ mg/dL} \), at all times. The (signed) zone-excursion function \( Z : \mathbb{R} \rightarrow \mathbb{R} \) is defined as:

\[ Z(y) = \arg \min_{\alpha \in \mathbb{R}} \{ \alpha^2 y^2 + y_s - \alpha \in [\zeta^\flat, \zeta^\breve] \} \quad (2) \]

### 2.4 Insulin delivery constraints

Insulin delivery is non-negative, and this is enforced as a constraint within the proposed MPC law:

\[ u_{\text{IN,}i} \geq 0 \iff u_i \geq \frac{u_{\text{BASAL,}i}T}{60 \text{ min/h}} . \quad (3) \]

Insulin delivery is further subject to an Insulin On Board (IOB) constraint – a constraint based on the insulin delivery history, preventing over-delivery when much insulin was recently delivered, e.g., after a meal-bolus. At each time step \( i \) an upper bound \( u_{\text{IOB,}i} \in \mathbb{R} \geq 0 \) is characterized, and enforced according to (4). Note that \( u_{\text{IOB,}i} \geq 0 \) implies
that the lowest IOB constraint limits insulin infusion to the basal-rate in absolute infusion terms. The IOB constraint definition applied in this paper is a slight modification of that described in Gondhalekar et al. (2015) which was successfully employed in the authors’ most recent clinical trials [Dassau et al. (2015)]; details omitted for brevity.

\[ u_i \leq \bar{u}_{\text{IOB},i} \quad (4) \]

**2.5 MPC problem**

We denote by \(\mathbb{Z}_+\) the set of positive integers, by \(\mathbb{Z}_+^b\) the set of consecutive integers \(\{a, \ldots, b\}\), by \(N_y \in \mathbb{Z}_+\) the prediction horizon, by \(N_u \in \mathbb{Z}_+^N\) the control horizon, by \(u, x, y, v\), the predicted input \(u\), state \(x\), glucose output \(y\), and velocity output \(v\), respectively. We denote by \(\hat{R}, \bar{R} \in \mathbb{R}_{>0}\) costs for positive and negative control inputs, and by \(Q: \mathbb{R} \to \mathbb{R}_{>0}\) a velocity-weighting function (see Section 3).

**MPC Problem:** Determine

\[ \{u_0^*, \ldots, u_{N_u - 1}^*\} := \arg \min_{\{u_0, \ldots, u_{N_u - 1}\}} J(x_i, \{u_0, \ldots, u_{N_u - 1}\}) \]

with cost function

\[ J(\cdot) := \sum_{k=1}^{N_y} \left[ z_k^2 + Q(y_k) x_k^2 \right] + \sum_{k=0}^{N_u - 1} R^u_k^2 + \bar{R}_k^2 \quad (5) \]

and subject to

\[ x_0 := x_i \quad (6a) \]

\[ x_{k+1} := Ax_k + Bu_k \quad \forall k \in \mathbb{Z}_0^{N_y} - 1 \quad (6b) \]

\[ y_k := C_y x_k \quad \forall k \in \mathbb{Z}_0^{N_y} \quad (6c) \]

\[ v_k := C_v x_k \quad \forall k \in \mathbb{Z}_0^{N_y} \quad (6d) \]
\[ \hat{u}_{IOB,i} \geq u_k \geq -\frac{u_{BASAL, (i + k)T}}{60 \text{ min/h}} \quad \forall k \in \mathbb{Z}^{N_u - 1}_0 \quad (6e) \]

\[ u_k^* = 0 \quad \forall k \in \mathbb{Z}^{N_u - 1}_0 \quad (6f) \]

\[ \hat{u}_k^* = \max(u_k, 0) \quad \forall k \in \mathbb{Z}^{N_u - 1}_0 \quad (6g) \]

\[ \tilde{u}_k^* = \min(u_k, 0) \quad \forall k \in \mathbb{Z}^{N_u - 1}_0 \quad (6h) \]

\[ z_k^* = \max(Z(y_k), 0) \quad \forall k \in \mathbb{Z}^{N_y}_0 \quad (6i) \]

\[ \tilde{z}_k^* = \min(Z(y_k), 0) \quad \forall k \in \mathbb{Z}^{N_y}_0 \quad (6j) \]

Eqs. (6a)-(6d) enforce the dynamics of model (1), initialized to the current state. Eq. (6e) enforces input constraints (3), (4) across the control horizon. Eq. (6f) implies that beyond the control horizon the basal-rate is delivered. Eqs. (6g)-(6h) provide the positive and negative deviations of input \( u \) from the basal-rate, and facilitate an asymmetric input cost in (5). Eqs. (6i)-(6j) provide positive and negative zone deviations to penalize in (5), and facilitate an asymmetric penalization of the zone deviation.

3. ASYMMETRY & VELOCITY-WEIGHTING

If \( \bar{R} = \bar{R} \) then the quadratic input cost function of (5) is symmetric. If additionally \( Q(v) = 1 \ \forall v \) then the quadratic glucose excursion cost is also symmetric. Such a setup is termed Standard MPC henceforth. An MPC setup with \( \bar{R} \neq \bar{R} \) and \( Q(v) = 1 \ \forall v \) is termed Asymmetric MPC hereafter. The Proposed MPC scheme employs the parameters \( N_y := 9 \), \( N_u := 5 \), \( \bar{R} := 7000 \), \( \bar{R} := 100 \), and
\[ Q(v) := \begin{cases} 1 & \text{if } v \geq 0 \\ \epsilon & \text{if } v \leq -1 \\ \frac{1}{2} \cos(v\pi)(1 - \epsilon) + (1 + \epsilon) & \text{otherwise} \end{cases} \quad \text{(7)} \]

with \( E := 10^{-6} \), depicted in Fig. 1.

The Asymmetric MPC scheme with \( \bar{R} \ll \hat{R} \) has proven useful. The value of \( \hat{R} \) determines the controller’s aggressiveness as to correcting hyperglycemia, and must be chosen large to enforce conservative insulin delivery. However, a large value of \( \bar{R} \) does not permit the controller to easily attenuate the pump, i.e., command a negative input. To facilitate suitable pump-attenuations it is required that \( \bar{R} \) be so small it never pose an obstacle to a negative control input when the predicted glucose trajectory traverses the lower target zone boundary. Additionally, however, \( \bar{R} \) must be large enough that when the predicted glucose trajectory rises into the target zone the control input is ‘pulled’ back to zero, i.e., the basal-rate is commanded; predictive pump-resumption. The asymmetric MPC scheme can be implemented using QP problems by explicitly splitting the scalar control input into non-negative and non-positive components. Note that such a QP cannot be formulated in an unconstrained setting, because at least one constraint of each predicted control input is active.

The velocity-weighting function (7) was chosen to yield the Asymmetric MPC scheme in all situations except when a predicted hyperglycemic state is in the process of converging towards the glucose target zone. First, the weighting function \( Q(\cdot) \) affects only \( \hat{z} \), the hyperglycemic zone excursion. Second, \( Q(v) = 1 \) for non-negative \( v \), implying that when the predicted hyperglycemic glucose values are rising, or steady, then the excursion \( \hat{z} \) is penalized with ‘full weight’, according to the Asymmetric or Standard MPC approaches. The motivation for the velocity-weighting is to reduce control action when predicted glucose values are falling. If \( Q(v) \) is any positive constant the MPC problem can be formulated as a QP. However, the velocity-weighting function of (7) results in a more general nonlinear optimization problem. The authors solve this by solving a sequence of QPs: An initial guess of \( \{u_0, \ldots, u_{N_u-1}\} \), given a current state \( x_i \), leads to \( \{v_0, \ldots, v_{N_u-1}\} \) and \( \{Q(v_0), \ldots, Q(v_{N_u-1})\} \). Based on these costs a QP is formulated and solved, yielding an update of the predicted input sequence \( \{u_0, \ldots, u_{N_u-1}\} \), and, in turn, an updated set of costs and a new QP. This iterative process is continued until there is no significant change in the costs \( \{Q(v_0), \ldots, Q(v_{N_u-1})\} \). If \( v_k \geq 0 \forall k \in N_0^N \) then only one iteration is required. The solution method is similar to sequential quadratic programming, but simpler, because no numerical differentiation is required.

4. IN-SILICO COMPARISON

The Proposed, Asymmetric, and three differently tuned Standard MPC strategies were evaluated via simulations. The five tunings are tabulated in Table 1. Standard-1 MPC uses a

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symmetric input cost function, tuned to provide the analogous response to hyperglycemia as
the Proposed and Asymmetric MPC schemes. The Standard-2 and Standard-3 MPC variants
are increasingly more conservative, i.e., provide less hyperglycemia correction. Simulations
were performed using the University of Virginia (UVA)/Padova metabolic simulator [Dalla
Man et al. (2014)] with its entire adult cohort, consisting of 10-subject and 100-subject
simulator cohorts. The latter contains a 101st subject ‘average’, resulting in a combined
cohort of 111 in-silico subjects. For a demonstration of the effects of asymmetric input costs
and velocity-weighting using individual in-silico subjects the interested reader is referred to
Gondhalekar et al. (2014, 2015). A contribution of this paper is a detailed battery of cohort
level results.

The case study simulations start at 14:00. Closed-loop control commences at 16:00.
Simulations finish at 18:00 the next day. This corresponds to the authors’ most recent
clinical trial protocol, which further stipulates a maximum meal size of 90 gCHO (grams
carbohydrate). Three large, 90 gCHO meals are provided: Dinner at 18:30, breakfast at
07:00 (next day), lunch at 13:00. This scenario represents a challenging stress-test for an AP
controller. Results are tabulated in Table 1. The second set of rows contains time-in-range
percentages for various Blood-Glucose (BG) ranges and thresholds. The third set of rows
contains counts of the number of subjects who experience one or more episodes of BG
beyond the stated thresholds. The fourth set of rows contains counts of the total number of
events of BG beyond the stated thresholds. The fifth set of rows lists the number of pump
suspensions of various lengths. The UCSB Health Monitoring System (HMS) [Harvey et al.
(2012)], which provides predictive hypoglycemia alarms, was run during the simulations.
The fifth set of rows lists the total number of HMS alarms, as well as the number of subjects
that experience one or more alarms. The Low Blood Glucose Index (LBGI) and High Blood
Glucose Index (HBGI) values were computed according to Magni et al. (2009), and the
Control-Variability Grid Analysis (CVGA) analysis is based on Magni et al. (2008).

The motivation for Asymmetric MPC is to safeguard from hypoglycemia by permitting the
controller to more easily attenuate insulin delivery from basal when the need arises.
Progressing from Standard-1 to Asymmetric MPC, there is an evident reduction in
hypoglycemia risk and associated HMS alarms, and a very large increase in the number of
pump suspensions. The penalty for this is a slight increase in hyperglycemia risk. The
Proposed MPC scheme significantly reduces the hypoglycemia risk from that of
Asymmetric MPC. Importantly, it reduces the number of required pump-suspensions also,
because the velocity-weighting reduces controller action when a state of hyperglycemia is
returning to a safe state, leading to a slowed descent. The downside to Proposed MPC is a
slightly elevated hyperglycemia risk. The Standard-2 and Standard-3 MPC schemes are
included to demonstrate that simply de-tuning a standard MPC scheme does not result in an
analogous risk reduction as the Proposed MPC scheme. The Proposed MPC scheme
achieves significantly lower hypoglycemia risk at comparable, and lower, hyperglycemia
risk as Standard-2 and Standard-3 MPC, respectively. It is important to observe the very low
number of pump-suspensions when using Standard MPC, despite the risk of hypoglycemia
and large number of hypoglycemic events.
The CVGA analysis supports the conclusion that Proposed MPC is both effective and safer than the alternatives, with a high count in the desirable B zones, and the lowest count in the undesirable D and E zones. Note that due to the large unannounced meals no controller achieves a result in the most desirable A zone. Fig. 2 shows associated CVGA plots. The prominent shift to the left when using Asymmetric and Proposed MPC is obvious. The Standard-3 achieves a shift to the left compared to Standard-1, but also contains more higher points.

5. ASYMMETRIC MPC: CLINICAL DEMO

The asymmetric input cost functions were deployed in the authors’ most recent clinical trials [Dassau et al. (2015)], and proved very successful in improving the safety of an AP. A contribution of this paper is the first clinical demonstration of Asymmetric MPC. Note that the clinical controllers are slightly different than in the simplified description of this paper: To reduce the risk of nocturnal hypoglycemia the authors’ clinical controllers employ a diurnal (periodically time-dependent based on the time of day) glucose target zone, and also a diurnal upper bound on the insulin infusion [Gondhalekar et al. (2013)].

Plotted in Fig. 3 is a trial portion covering nighttime. The diurnal glucose target zone and insulin constraint are depicted. The CGM trajectory of the top subplot spends a prolonged period (22:55–06:30) below the glucose target zone. The middle subplot shows the insulin delivery trajectory of the Asymmetric MPC law employed during the trial. Interestingly, a pump suspension occurs at 22:20, while the CGM value is within the target zone. This occurs because, given the CGM trend, a glucose excursion to below the target zone is predicted. The prediction horizon is $TN_y = 45$ minutes; the MPC cannot predict zone excursions or hypoglycemia prior to that. The short prediction horizon was chosen due to the difficulty in modeling and performing accurate predictions; it is not possible to predict the nighttime hypoglycemia earlier (e.g., at 21:00) and prevent its occurrence. A predictive pump resumption occurs at 02:10, because based on the CGM trend the glucose trajectory is predicted to enter the target zone, even though in reality it does not. A second prolonged pump-suspension occurs ~03:00–05:50. The short-lived pump-resumption at 06:00 is again due to a predicted entry of the glucose trajectory into the target zone, that does not occur in practice. The CGM dip following breakfast at 07:15 is also accompanied by a pump-suspension.

The lower subplot of Fig. 3 depicts the insulin delivery trajectory the Standard-1 MPC would have given, based on the same CGM trajectory and insulin delivery history. While a slight pump attenuation is evident over the night-time period, the Standard-1 MPC makes no prolonged or significant attempt to suspend the pump despite the hypoglycemia risk and significant depth of the CGM value below the target zone, where this depth is exacerbated by the use of the elevated nighttime target zone. It is not possible to know what would have happened, had the Standard-1 MPC law been employed in the trial.
6. CONCLUSION

An MPC law with two novel features to control glucose levels in people with T1DM was presented. Asymmetric input cost functions improve safety by allowing a controller to attenuate insulin delivery more easily. Velocity-weighting cost functions help prevent controller induced hypoglycemia by strategically reducing the controller’s aggressiveness when a hyperglycemic state is in the process of correction. In combination these two features have been demonstrated, using a detailed in-silico analysis, to greatly reduce the risk of hypoglycemia, while maintaining effective control performance. The asymmetric input cost function was demonstrated using data from a clinical trial. The velocity-weighting has been chosen by the authors for inclusion in the next iteration of clinical controllers. While the MPC framework employs a linear dynamical model, the two presented features are a means to address a nonlinear control problem in a manner simpler than fully nonlinear MPC, and lead to an interesting class of nonlinear optimization problem and nonlinear control law.

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Fig. 1.
Velocity-weighting function $Q(v)$ defined in (7).
Fig. 2.
CVGA plots for the Proposed (\(^\uparrow\)), Asymmetric (\(^\nearrow\)), Standard-1 (\(\swarrow\)), and Standard-3 (\(\searrow\)) MPC strategies. Table 1 lists tuning parameters and performance statistics. The blue dot and the circle radius are, respectively, the mean and standard deviation of the cluster of dots, in the underlying CVGA space.
Fig. 3.
Clinical demonstration. **Top**: CGM data and diurnal glucose target zone. **Middle**: Insulin delivery trajectory of the trial, i.e., using Asymmetric MPC. **Bottom**: Simulation of controller response using Standard-I MPC.
Table 1.
Tunings & statistics of the five MPC laws contrasted: Proposed, Asymmetric, & three increasingly conservative Standard

| MPC style   | Proposed | Asymmetric | Standard-1 | Standard-2 | Standard-3 |
|-------------|----------|------------|------------|------------|------------|
| $\hat{R}$   | 7000     | 7000       | 10000      | 13000      |            |
| $\bar{R}$   | 100      | 100        | 10000      | 13000      |            |
| $Q(v)$      | Eq. (7)  | := 1       | := 1       | := 1       | := 1       |

| BG [mg/dL] % time | | | | | |
|-------------------|---|---|---|---|---|
| $\in [80, 140]$  | 45.12 | 47.67 | 47.83 | 45.08 | 42.82 |
| $\in [70, 180]$  | 57.46 | 59.96 | 60.28 | 57.03 | 54.18 |
| < 80              | 0.62 | 2.21 | 3.21 | 2.01 | 1.04 |
| < 70              | 0.29 | 1.46 | 1.86 | 0.95 | 0.51 |
| < 60              | 0.15 | 0.83 | 1.01 | 0.53 | 0.20 |
| < 50              | 0.06 | 0.45 | 0.55 | 0.23 | 0.08 |
| < 40              | 0.03 | 0.13 | 0.16 | 0.11 | 0.04 |
| > 180             | 42.62 | 38.58 | 37.87 | 42.02 | 45.32 |
| > 250             | 20.30 | 18.50 | 16.98 | 20.59 | 23.66 |
| > 300             | 6.37 | 6.01 | 4.92 | 6.35 | 8.05 |
| > 350             | 1.30 | 1.38 | 1.14 | 1.50 | 1.81 |
| > 400             | 0.54 | 0.53 | 0.45 | 0.55 | 0.72 |

| #Subj. w. BG [mg/dL] | | | | | |
|----------------------|---|---|---|---|---|
| < 80                 | 12 | 33 | 47 | 29 | 16 |
| < 70                 | 8  | 24 | 31 | 18 | 11 |
| < 60                 | 5  | 17 | 19 | 13 | 6  |
| < 50                 | 2  | 14 | 13 | 7  | 2  |
| < 40                 | 1  | 5  | 5  | 3  | 2  |
| > 180                | 111 | 111 | 111 | 111 | 111 |
| > 250                | 103 | 103 | 97  | 99  | 100 |
| > 300                | 52  | 53  | 45  | 49  | 58  |
| > 350                | 13  | 16  | 12  | 13  | 16  |
| > 400                | 5   | 6   | 5   | 5   | 6   |

| #Events BG [mg/dL] | | | | | |
|--------------------|---|---|---|---|---|
| < 80               | 20 | 67 | 93 | 50 | 30 |
| < 70               | 12 | 51 | 58 | 31 | 21 |
| < 60               | 7  | 35 | 38 | 21 | 9  |
| < 50               | 3  | 25 | 25 | 10 | 4  |
| < 40               | 2  | 7  | 10 | 5  | 3  |
| > 180              | 333 | 337 | 335 | 331 | 330 |
| > 250              | 289 | 282 | 262 | 280 | 287 |
| > 300              | 134 | 133 | 111 | 127 | 146 |
| > 350              | 31  | 34  | 27  | 32  | 36  |
| > 400              | 13  | 14  | 11  | 13  | 15  |
| MPC style | Proposed | Asymmetric | Standard-1 | Standard-2 | Standard-3 |
|-----------|----------|------------|------------|------------|------------|
| ≥15 min   | 254      | 365        | 34         | 7          | 2          |
| ≥30 min   | 74       | 157        | 12         | 1          | 0          |
| ≥60 min   | 9        | 44         | 0          | 0          | 0          |
| ≥90 min   | 1        | 19         | 0          | 0          | 0          |
| ≥120 min  | 0        | 3          | 0          | 0          | 0          |
| #HMS alarms | 26       | 116        | 157        | 80         | 47         |
| #Subj. w. alarms | 16       | 37         | 55         | 34         | 24         |
| Mean LBGI | 0.11     | 0.41       | 0.56       | 0.34       | 0.18       |
| Mean HBGI | 10.49    | 9.67       | 9.14       | 10.50      | 11.65      |
| CVGA      |          |            |            |            |            |
| Zone count: A | 0     | 0          | 0          | 0          | 0          |
| Zone count: B | 65    | 59         | 63         | 66         | 59         |
| Zone count: C | 33    | 19         | 11         | 22         | 34         |
| Zone count: D | 8     | 18         | 21         | 11         | 11         |
| Zone count: E | 5     | 15         | 16         | 12         | 7          |
| Fig. 2 subplot | \    | /          | ✓          | N/A        | \          |