Initial titration for people with type 1 diabetes using an artificial pancreas

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Abstract: For people with type 1 diabetes and some with type 2 diabetes, the problem of insulin titration, i.e. finding an adequate basal rate of insulin, is a complex and time-consuming task. This paper proposes a simple model-free algorithm and a procedure for fast initial titration in people with type 1 diabetes (T1D). A modified proportional-integral-derivative (PID) controller (i) updates the estimated insulin basal rate, and (ii) administers micro-boli of insulin every 5 minutes using glucose measurements from a continuous glucose monitor (CGM). A bolus calculator mitigates the effect of meals and reduces postprandial peaks. We evaluate the performance of our system qualitatively and numerically using a virtual clinic of 1,000 T1D patients with a broad inter-patient variability representative of a real population of people with T1D. We let the titration phase run for three consecutive days, followed by a three-day test phase using the newly computed basal insulin infusion rate. The proposed algorithm is able to provide a safe titration and individualized treatment for people with T1D.

Keywords: Control algorithm, PID, Feed-forward control, Run-to-run control, Diabetes, Artificial pancreas.

1. INTRODUCTION

Type 1 diabetes (T1D) accounts for around 10% of the 463 million people living with diabetes worldwide. Due to autoimmune β-cell destruction, people with T1D are unable to produce insulin. Life-long treatment using daily insulin injections is vital to avoid an elevated blood glucose (BG) level (Riddle et al., 2018). Common ways to administer insulin are multiple daily injections (MDI) and continuous subcutaneous insulin infusion (CSII) therapy. MDI therapy uses pens to administer long-acting insulin once daily and rapid-acting insulin several times per day, usually before meals. CSII therapy uses a pump to continuously administer a rapid insulin analogue.

The artificial pancreas (AP) provides closed-loop insulin therapy for T1D, and has even been considered to treat some people with T2D (Bally et al., 2018; Taleb et al., 2019). The AP consists of (i) a continuous glucose monitor (CGM), (ii) a control algorithm and (iii) a CSII pump. The CGM provides frequent glucose measurements, typically every 5 minutes. The control algorithm resides on a smartphone for most prototypes (Cobelli et al., 2012; Kovatchev et al., 2013), but for commercial systems the control algorithm should preferably be embedded on the pump.

Several control technologies have been considered for the AP, such as linear model predictive control (MPC) (Eren-Oruklu et al., 2009; Schmidt et al., 2013; Boiroux et al., 2018), nonlinear MPC (Hovorka et al., 2004; Boiroux and Jørgensen, 2018), fuzzy logic control (Biester et al., 2019), and proportional integral derivative (PID) control (Marchetti et al., 2006, 2008; Ly et al., 2016). Although MPC-based APs showed similar or slightly better performance in clinical studies than PID-based APs (Steil, 2013; Pinsker et al., 2016), PID technology has proven to be successful in currently available hybrid control systems (Laxminarayan et al., 2012; Ly et al., 2017). The PID-controller can easily be implemented using simple tuning rules, does not require any metabolic model of the insulin-glucose dynamics, and mimics the behavior of the pancreas for a healthy patient (Steil et al., 2004).

The initial use of CSII can be challenging considering the need of estimating the insulin basal rate that brings the BG level to a safe range (King et al., 2016). The basal rate needs to be high enough to lower the glucose level. However, too much insulin causes hypoglycemia and in worst case can be fatal. To estimate the initial basal rate for adult patients in todays CSII treatment, the healthcare professionals calculate the initial basal rate. Either based on the total daily dose (TDD) of MDI or on a combination of the TDD with a body-weight-based method (King, 2012; Chow et al., 2016; Bode et al., 2011). A recent study shows that the TDD method underestimated the patients basal rate with a median error of 10.06%, while the body weight-based method overestimates the patient's basal rate with a median error of 11.1% (Chow et al., 2016).

As an approach to find a safe basal rate for CSII treatment when the TDD is unknown, e.g. for insulin naive patients, we present an implementation of a model-free controller

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for initial titration of people with T1D. The proposed controller is a modified PID-controller in the sense that it uses a deadband and contains an anti-windup algorithm. A further modification is that at mealtimes, we suspend the PID-controller for 5.5 hours and give bolus insulin to compensate for the carbohydrates (CHO) intake. To find the estimated basal rate, the patients use an AP with the PID-controller in a three days titration phase. When the estimated basal rate is obtained, we let the study continue with a three days test phase, to test the suggested basal rate. We evaluate the performance of the method by simulating a cohort of 1,000 random generated virtual patients.

The rest of the paper is structured as follows. Section 2 describes the control algorithm. We define the scenario and the simulator used for in silico trials in Section 3. The results are presented in Section 4, the discussion in Section 5, and the conclusion in Section 6.

2. CONTROL ALGORITHM

People with T1D need basal insulin to compensate for the long-term endogenous glucose production, and bolus insulin to control the glucose level after intake of CHO. For each discrete time, t_k, the insulin pump administers the total amount of insulin, $u_{tot}(t_k)$, given by,

$$u_{tot}(t_k) = u_{micro-bolus}(t_k) + u_{bolus}(t_k). \tag{1}$$

$u_{micro-bolus}(t_k)$ is the amount of micro-bolus insulin required to manage the endogenous glucose production, and $u_{bolus}(t_k)$ is the bolus insulin estimated to compensate for the intake of CHO. The micro-bolus insulin basal rate is calculated as,

$$\bar{u}_{micro-bolus}(t_k) = \frac{u_{micro-bolus}(t_k)}{\Delta t_k} = \bar{u}_{basal}(t_k) + \bar{v}(t_k). \tag{2}$$

The nominal basal rate is described by $\bar{u}_{basal}(t_k)$ and $\bar{v}(t_k)$ is the adjustments in the basal rate. $\Delta t_k = T_s$ denotes the time interval the calculated basal rate will be applied for i.e. the sampling time (Jørgensen et al., 2019).

2.1 Filter

The derivative term of the PID-controller is highly sensitive to noise. Though modern CGM systems provide a filtered signal, a first order low-pass filter in discrete time is implemented before computing the basal rate. The filtered CGM-signal $y_F(t_k)$ is calculated as,

$$y_F(t_k) = \alpha y_{CGM}(t_k) + (1-\alpha) y_F(t_{k-1}), \tag{3}$$

where the smoothing factor $\alpha = 0.2$, corresponding to a time constant of approximately 20 minutes, and $y_{CGM}(t_k)$ is the signal provided by the CGM.

2.2 Micro-bolus and basal rate

The basal insulin rate for controlling the glucose level is conducted by a PID-controller using the filtered CGM-signal $y_F(t_k)$. In continuous time, we consider a PID-controller defined by,

$$\bar{v}(t) = K_p(\bar{y}(t) - y_F(t)) + K_i \int_0^t e_i(\tau)d\tau - K_d \frac{dy_F(t)}{dt}, \tag{4}$$

where K_p, K_i, and K_d denote the proportional, integral, and derivative gains. $\bar{y}(t)$ is the glucose target and $e_i(\tau)$ is the error at the integral. The discrete-time PID-controller corresponding to the continuous-time PID-controller is

$$\bar{v}(t_k) = K_p(\bar{y}(t_k) - y_F(t_k)) + I(t_k) - \frac{K_d}{T_s}(y_F(t_k) - y_F(t_{k-1})). \tag{5}$$

The sampling time, T_s, equals the sampling rate of the CGM, commonly 5 minutes. $I(t_k)$ describes the changes in the basal rate and can be expressed as,

$$I(t_k) = I(t_{k-1}) + K_i T_s e_i(t_k). \tag{6}$$

The error term $e_i(t_k)$ has an integral deadband in the range from 4 to 8 mmol/L. The deadband prevents the integrator from integrating when the glucose level is inside the range of the deadband,

$$e_i(t_k) = \begin{cases} l_{low} - y_F(t_k), & y_F(t_k) \le l_{low}, \\ 0, & l_{low} < y_F(t_k) \le l_{up}, \\ l_{up} - y_F(t_k), & y_F(t_k) > l_{up}, \end{cases} \tag{7}$$

where l_{low} and l_{up} are the lower and upper limits of the target range. To avoid integrator windup and negative micro-bolus rate, $\bar{u}_{micro-bolus}(t_k)$ is limited to the interval $[0, U_{\max}]$, where $U_{\max} = 12$ mU/min for the first 12 hours of simulation while the virtual patients are fasting, and afterwards at the time $t = 12$ hours, the limit is set to $U_{\max} = 2I(t_{k-1})$. The micro-bolus rate $\bar{u}_{micro-bolus}(t_k)$ is then,

$$\bar{u}_{micro-bolus}(t_k) = \min(\max(0, \bar{u}_{basal}(t_k) + \bar{v}(t_k)), U_{max}). \tag{8}$$

For patients with low insulin sensitivity the limit on 12 mU/min will in some cases be too insufficient to influence the BG. Therefore, before $U_{\max}$ is changed from 12 mU/min to $2I(t_{k-1})$, we measure the filtered CGM signal $y_{F(t_k)}$. If $y_{F(t_k)}$ is in the hyperglycaemic range above $y_{hyper} = 10$ mmol/L, and the basal rate after 12 hours is limited to U_{max}, then $I(t_{12hours})$ is set to U_{max},

$$I(t_{12hours}) = \begin{cases} U_{max}, & (y_{F(t_k)} > y_{hyper}) \wedge \\ & (u_{basal}(t_k) = U_{max}), \\ I(t_k), & otherwise. \end{cases} \tag{9}$$

The above definition of the micro-bolus rate consists of the estimated basal rate as well as corrections computed by the PD-controller. Hence, the estimated basal insulin rate is

$$\hat{u}_{basal}(t_k) = \bar{u}_{basal}(t_k) + I(t_k) \tag{10}$$

2.3 Bolus calculator

To balance the glucose level after intake of CHO, people with T1D need bolus insulin. The size of the bolus is calculated using a bolus calculator. Common equations for bolus calculation typically exist of three parts 1) meal insulin, 2) correction insulin, and 3) insulin on board (IOB) (Schmidt and Nørgaard, 2014). The equation is given as (Jørgensen et al., 2019)

$$u_{bolus}(t) = \frac{\hat{d}(t)}{carbF} + \alpha_{corr}\frac{y_F(t) - \bar{y}(t)}{corrF} - \alpha_{IOB}IOB(t). \tag{11}$$

For this paper we only use the meal insulin part of the bolus calculator, and assume that the PID-controller used for the basal rate will do the corrections of the error (Jørgensen et al., 2019). The equation for the bolus calculator is given by

$$u_{bolus}(t) = ICR \cdot \hat{d}(t), \tag{12}$$

where $ICR = 1/carbF$ and $\hat{d}(t)$ is the estimated amount of CHO in grams in the meal. ICR $(U/gCHO)$ is the insulin to CHO ratio, i.e. ICR denotes the amount of CHO covered by 1 unit of insulin. Appendix A reports the procedure for computation of the ICR in this paper.

3. SCENARIO

To evaluate the control algorithm, we use a simulator based on the physiological model developed by Hovorka et al. (2004). The Hovorka model describes the metabolic system for people with T1D. It interprets the pharmacokinetic (PK) and pharmacodynamics (PD) response of subcutaneous insulin infusion, CHO absorption, and insulin action.

In the scenario, we simulate a population of 1,000 randomly generated virtual patients. The parameter distribution is stated in Hovorka et al. (2002); Wilinska et al. (2010) and Boiroux et al. (2018). The first three days of the scenario is the titration phase. In this phase, the virtual patients use an AP with the PID-controller to estimate the basal rate. The titration phase is followed by a three-day test phase where we test the estimated basal rate.

We start the study at 18:00 assuming that the patient has not taken any dinner to initiate the titration overnight. For the remaining time of simulation an intake of 60 g, CHO is simulated at 6:00 AM and at 12:00 PM, and an intake of 90 g CHO is simulated at 6:00 PM. The controller gets an announcement at mealtimes, and a bolus is calculated to correct the glucose level after CHO intake. In the titration phase, the PID-controller is suspended for 5.5 hours after a meal, and the basal rate is fixed to the last calculated rate before the meal announcement.

4. RESULTS

Fig. 1 illustrates the glucose concentration, the CHO intake, the bolus insulin administration, the micro-bolus insulin administration and the estimated basal insulin for 10 virtual patients. The first chart shows the glucose concentration, where the postprandial peaks are a response to the CHO intake shown in the second chart. The amplitude of the peaks depends on the amount of CHO and the ratio between the time constants for CHO absorption and subcutaneous (sc) insulin absorption (El Fathi et al., 2018; Boiroux and Jørgensen, 2018). The third chart shows the calculated bolus based on the estimated amount of CHO intake and the virtual patients ICR. After the first 12 hours of simulation, $U_{\max}$ is set to $2I(t_{k-1})$, which is reflected by the adjustments in the micro-bolus rate in the fourth

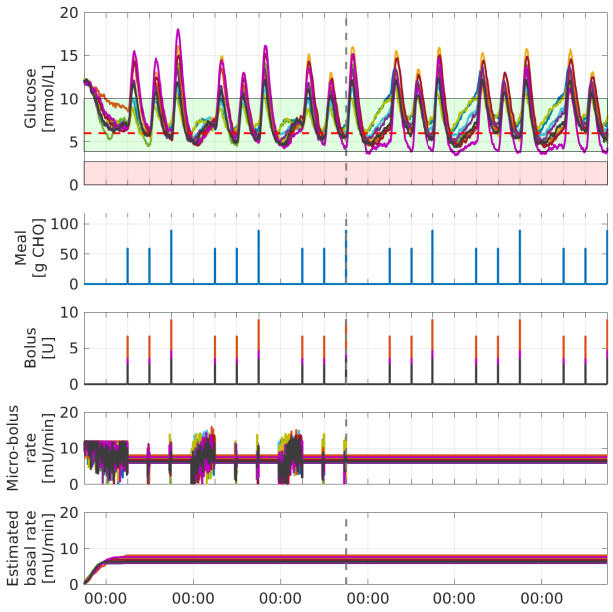

Fig. 1. Simulation of 10 virtual patients. The titration phase runs for three days, followed by a three-day test phase using the estimated basal rate.

Table 1. Distribution of time spend in different glucose concentration ranges during the titration phase for a population of 1,000 virtual patients.

Glucose(mmol/L)	Mean	Q_1	Q_2	Q_3
$0 \leq G < 3$	0.0%	0.0%	0.0%	0.0%
$3 \leq G < 3.9$	0.2%	0.0%	0.0%	0.0%
$3.9 \leq G \leq 10.0$	77.7%	71.9%	77.4%	84.6%
$10.0 < G \leq 13.9$	19.2%	15.0%	19.7%	23.3%
$13.9 < G \leq 26.1$	3.0%	0.0%	0.6%	3.8%

chart. The integrator value emulates the basal rate that we aim to find and is shown in the fifth chart of the figure.

We evaluate the performance of the controller based on the three-day test phase using the estimated basal rate. The mean of the estimated basal rate for the virtual clinic is 8.04 mU/min with a minimum of 5.06 mU/min and a maximum of 29.86 mU/min.

A cumulative distribution was performed on the glucose values of the 1,000 virtual patients in the test phase. Fig. 2 illustrates the result for the cumulative distribution with a mean time in range (TIR) of 78.5%.

Tables 1 and 2 report the population distribution of the time spent in different glucose concentration ranges. Figure 3 illustrates the glucose concentration trajectory for the patient having the worst hypoglycemic episodes (lowest and most time spent in hypo). From these results, it is clear that while the titration is not perfect, it improves current practice and leads to no severe situations.

Recommendations from the International Consensus on TIR (Battelino et al., 2019) states that people living with T1D should spend above 70% time in target range (3.9 -10.0 mmol/L), less than 4% below 3.9 mmol/L, less than

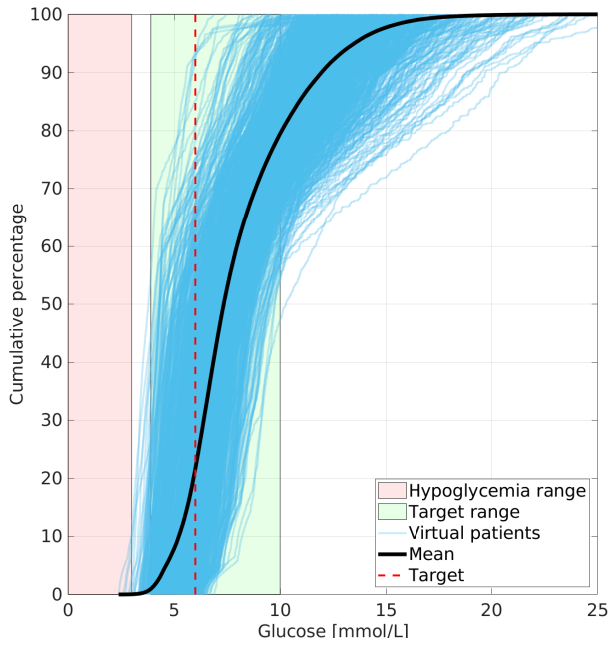

Fig. 2. Cumulative distribution of glucose values, for 1,000 virtual patients in the test phase.

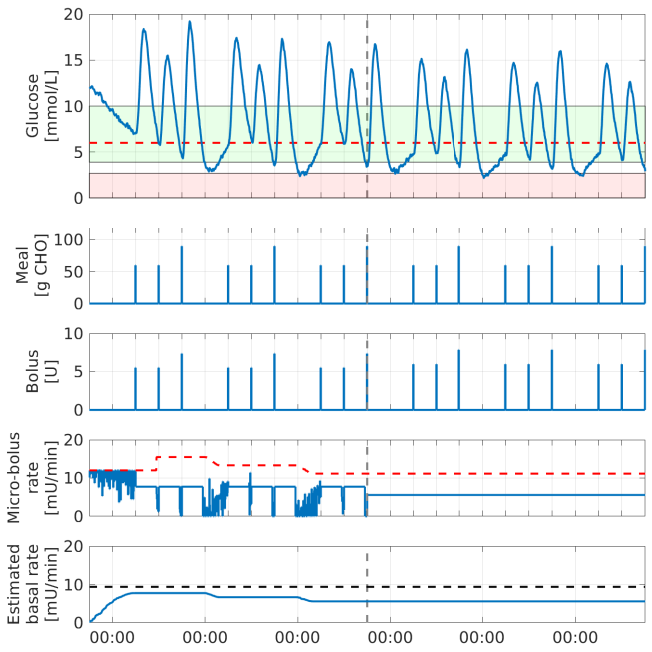

Fig. 3. Profiles for the patient with most time in the glucose concentration range $0 \leq G < 3$. Notice that the time in severe hypoglycemia is very limited and not due to the basal insulin rate being too high. Rather it is due to an overestimated insulin bolus to compensate for the meal.

1% below 3.0 mmol/L, less than 25% above 10.0 mmol/L and less than 5% above 13.9 mmol/L.

In respect to hypoglycemia in our scenario, 2 out of 1,000 virtual patients spend more than 1% below 3.0 mmol/L in the titration phase. In the test phase the number increases to 5 virtual patients, with a minimum of 2.4 mmol/L for both phases. 20 out of 1,000 virtual patients spend more than 4% below 3.9 mmol/L in the titration phase. In test phase the number increases to 59 virtual patients.

Table 2. Distribution of time spend in different glucose concentration ranges during the test phase for a population of 1,000 virtual patients.

Glucose(mmol/L)	Mean	Q_1	Q_2	Q_3
$0 \leq G < 3$	0.0%	0.0%	0.0%	0.0%
$3 \leq G < 3.9$	0.9%	0.0%	0.0%	0.0%
$3.9 \leq G \leq 10.0$	78.5%	72.1%	78.0%	84.6%
$10.0 < G \leq 13.9$	16.5%	13.3%	17.7%	20.8%
$13.9 < G \leq 25.9$	4.1%	0.0%	0.0%	6.8%

200 out of 1,000 virtual patients did not achieve the goal of 70% TIR during the titration phase. In the test phase the number decreases to 183 virtual patients.

Regarding hyperglycemia 161 out of 1,000 virtual patients spend more than 25% above 10.0 mmol/L in the titration phase while the number decreases to 53 in the test phase. 204 out of 1,000 virtual patients spend more than 5% above 13.9 mmol/L in the titration phase, and in the test phase the number increases to 294.

By using the suggested method, we can get 61.9% of the virtual patient to achieve the recommendations within a 6 days study.

5. DISCUSSION

We evaluated the performance of our system on a virtual clinic of 1,000 T1D patients with a broad inter-patient variability representative of a real population of people with T1D.

It is important to note that the implemented model does neither account for patient intraday variability nor changes in ISF and ICR over time. The effect of exercising or inactivity, e.g. during sleep, is not considered in this paper. In real life, T1D patients in CSII treatment will schedule their basal rates throughout the day. In our test phase we do not tailor the basal rate to the time of the day, which will leave room for improvement of the study. Before the method can be implemented in a real life scenario, we need to obtain the ICR for the patient (King, 2012). In this paper, we use the approach described in Appendix A.

By analyzing our simulations, we can tell that the reason some of the virtual patients suffer from hypoglycemia is mainly due to the bolus insulin. Different bolus administration strategies have an impact on glucose regulation for people with T1D. A more sophisticated bolus calculator could therefore be considered as described in Boiroux et al. (2017), but that would require to identify a T1D model for every patient, and is beyond the scope of this paper.

When the patients start the titration phase, the basal rate is unknown. If we should have used an MPC instead of a PID-controller, we would have needed a good guess on the initial basal rate. Though the MPC might perform better in the long run, it is not suited for the goal of this paper. In addition, after the titration phase is over, and the estimated basal rate is found, it could be considered to

initialize a treatment using an AP with an MPC. Due to cost or individual preferences other patients might prefer to continue the treatment using CSII or MDI.

The goal we use for TIR is internationally recommended. However, goal-settings for glucose regulation should be individualized due to achievable goals for the single patient (Battelino et al., 2019). Large real-world data and studies shows that the average T1D patient's TIR usually lies between 50%-60% (Beck et al., 2019). Therefore, a goal at 70% TIR may not be achievable for all patients. In our results, we stated that it was not possible for all 1,000 virtual patients to reach the goals recommended by the International Consensus within the 6 days scenario; but the majority of patients are better off with the the titration method suggested in this paper.

6. CONCLUSION

In this paper we propose a method for initial titration based on a modified PID-controller combined with a simple bolus calculator. We construct a 6 days scenario consisting of a three days titration phase followed by a three days test phase. In the titration phase, we use an AP with the PID-controller. At mealtimes, we calculate a bolus, suspend the controller for 5.5 hours, and set the basal rate to a fixed rate. When the titration phase ends, we switch off the controller and test the estimated basal rate in a three days test phase. The performance of our system is qualitatively and numerically evaluated using a virtual clinic of 1,000 T1D patients.

Goal-settings and treatment of people living with T1D should be individualized. While our method may not be suited for all, we can get 61.9% of the virtual patients to achieve the recommendations from the International Consensus on TIR within a 6 days study.

The results indicate the potential of the method compared to conventional titration. Further studies of the process and clinical studies are required before the titration method can be recommended for clinical practice.

Appendix A. BOLUS CALCULATOR AND INSULIN-TO-CARB RATIO

To estimate the ICR for the virtual patients in the model, we use the penalty function described below to find the bolus size for meals in the range 20 g to 120 g of CHO with an increment of 20 g CHO. When the bolus for the different meal sizes are obtained, linear regression is used to find the insulin to CHO ratio.

As described in Boiroux and Jørgensen (2018) and in Jørgensen et al. (2019), the quadratic glucose penalty function is given by

$$\bar{\rho}(z(t), \bar{z}) = \frac{1}{2}(z(t) - \bar{z})^2, \tag{A.1a}$$

$$\rho_{\min}(z(t), \bar{z}_{\min}) = \frac{1}{2}(\min\{0, z(t) - \bar{z}_{\min}\})^2, \tag{A.1b}$$

$$\rho_{\max}(z(t), \bar{z}_{\max}) = \frac{1}{2}(\max\{0, z(t) - \bar{z}_{\max}\})^2, \tag{A.1c}$$

in which $z(t)$ denotes the predictive BG concentration, and the glucose setpoint $\bar{z}$ is set to 6.0 mmol/L. The lower threshold is $z_{\min} = 5.3$ mmol/L, and the upper threshold is $z_{\max} = 8.3$ mmol/L. The penalty function is defined as

$$\rho(z(t)) = \bar{\rho}(z(t), \bar{z}) + \kappa\rho_{\min}(z(t), \bar{z}_{\min}) + \lambda\rho_{\max}(z(t), \bar{z}_{\max}), \tag{A.2}$$

where κ and λ are weights associated with hypoglycemia and hyperglycemia, respectively. Since we want the bolus calculator to safely mitigate the effects of CHO intake, i.e. to avoid postprandial hypoglycemia, we set $\kappa \gg \lambda$. The optimal bolus size, u_{bolus}, for a given estimated meal size, $\hat{d}$, from a steady state, x_{ss}, and with subsequent administration of the basal insulin rate, u_{basal}, is given by minimizing the area under the glucose penalty function curve, i.e. $u_{bolus} = u_{bolus}(\hat{d}; x_{ss}, u_{basal})$ is obtained by solution of the following univariate optimization problem:

$$\min_{u_{bolus}} \quad \phi = \int_{t_0}^{t_N} \rho(z(t))dt, \tag{A.3a}$$

$$\text{s.t.} \quad x(t_0) = x_{ss} + \Gamma_u u_{bolus} + \Gamma_d \hat{d}, \tag{A.3b}$$

$$\dot{x}(t) = f(x(t), u_{basal}, 0), \qquad t \in [t_0,\, t_N], \tag{A.3c}$$

$$z(t) = g(x(t)), \qquad t \in [t_0,\, t_N], \tag{A.3d}$$

$$0 \le u_{bolus} \le u_{bolus,\max}. \tag{A.3e}$$

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