An artificial pancreas based on simple control algorithms and physiological insight

John Bagterp Jørgensen, **Dimitri Boiroux**, **Zeinab Mahmoudi**

Department of Applied Mathematics and Computer Science,
Technical University of Denmark, DK-2800 Kgs. Lyngby, Denmark

Abstract: We present a simple control algorithm for a single-hormone artificial pancreas (AP). The AP consists of a continuous glucose monitor (CGM) measuring the interstitial glucose concentration, a control algorithm computing the insulin to administer, and an insulin pump dosing the insulin. The control algorithm is based on insights into the underlying dynamics of the glucose-insulin dynamics in people with type 1 diabetes. The main components in this control system are 1) an insulin bolus calculator to compensate for carbohydrates in meals, 2) a run-to-run algorithm for adjusting the basal insulin to long-term metabolic variations, and 3) a micro-bolus correction of the basal insulin to compensate for short-term variations in the endogenous insulin production and insulin sensitivity.

1. INTRODUCTION

The single-hormone artificial pancreas (AP) for people with type 1 diabetes (T1D) consists of a continuous glucose monitor (CGM), a control algorithm and supporting safety algorithms, and a pump for administration of a fast acting insulin analogue. The control algorithm may reside on a smart-phone as in most research prototypes of an artificial pancreas. However, for commercial systems the control algorithms will most likely be embedded on a chip in the pump hardware, even if the pump is a patch pump. The miniaturization of this hardware would benefit from simple easily implementable control algorithms. In this paper, we use insight in the pharmaco-kinetics and pharmaco-dynamics (PK-PD) of meal carbohydrates (CHO) and subcutaneously (SC) injected fast acting insulin to suggest simple high-performing control algorithms for the artificial pancreas.

1.1 Single-hormone artificial pancreas

The research literature has reported single-hormone AP control algorithms based on linear model predictive control (Boiroux et al., 2018; Schmidt et al., 2013; Messori et al., 2014; Magni et al., 2009; Gondhalekar et al., 2016; Grosman et al., 2010), adaptive linear model predictive control (Boiroux et al., 2017; Eren-Oruklu et al., 2009; Turksoy et al., 2014; Turksoy and Cinar, 2014), nonlinear model predictive control (Boiroux et al., 2010a,b, 2016; Boiroux and Jørgensen, 2017), adaptive nonlinear model predictive control (Hovorka et al., 2004), PID control technology (Steil et al., 2004; Marchetti et al., 2008; Palerm, 2011), and fuzzy-logic technology that is branded as MD-logic (medical doctor logic) technology (Atlas et al., 2010). However, the classification of controllers according to the algorithm (MPC, PID, fuzzy logic) does not address the more important question related to the structure and function of the control algorithm. Due to the PK-PD of SC injected fast acting insulin in relation to meal CHO, it is beneficial to structure the control algorithm into a bolus algorithm, a basal algorithm, and a micro bolus correction algorithm.

1.2 Bolus algorithm

The bolus algorithm is a feedforward algorithm that computes the insulin injection based on the estimated and announced CHO in the meal to compensate for the blood glucose (BG) excursion due to the actual CHO in the meal (Walsh et al., 2011; Schmidt and Nørgaard, 2014; Ziegler et al., 2017; Herrero et al., 2017). Since even faster acting subcutaneously injected insulin is absorbed slower than meal CHO, it is nearly optimal to administer the meal compensating insulin as a bolus (Boiroux et al., 2010c). Using an insulin pump and no administration of long acting insulin, the post prandial performance can be improved by suspending the basal insulin for 2-4 hours after the meal and giving the equivalent basal insulin as part of the bolus in a so-called super bolus (Bondia et al., 2009; Boiroux et al., 2010c; Herrero et al., 2015). The bolus algorithm may also provide correction boluses, based on the measured glucose concentration. In that case the correction bolus needs to be adjusted for the insulin that is already on board (Palerm, 2011).

1.3 Basal algorithm

The determination of the correct basal insulin level is called insulin titration. In classical feedback control, the insulin level giving zero offset in the glucose level from its setpoint would be determined by an integral-controller (Franklin et al., 1997; Åström and Murray, 2008; Seborg et al., 2010; Åström and Hägglund, 2005). As large post prandial glucose concentration excursions are unavoidable,

a classical integral controller is not well-suited for determination of the basal insulin level. It would be better to run the integral controller at fasting conditions and determine the basal insulin level such that the glucose setpoint was reached. In everyday daily life, nighttime resembles a fasting period the most. Nighttime could be from say 22:00 - 6:00, where it is assumed that breakfast is consumed at or after 6:00. The run-to-run (R2R) algorithm for iterative learning has been suggested as an alternative to integral control for basal insulin adjustment (Palerm et al., 2008; Wang et al., 2009; Wang and amd Francis J. Doyle, III, 2010; Toffanin et al., 2014, 2017a,b; Tuo et al., 2015). The run-to-run algorithm is motivated by clinical practice. In clinical practice, insulin titration is conducted by adjusting the basal insulin rate (long acting insulin if a pen system is used) according to the pre-prandial glucose concentration measured by a self monitoring blood glucose (SMBG) device (Arnolds et al., 2013). Many clinical approaches to basal insulin titration increases the basal insulin dose by one unit per day if the average of the 3 last morning pre-prandial glucose concentrations exceeds the target range. The basal insulin dose is reduced if any hypoglycemic events occur.

1.4 Micro bolus correction algorithm

Most control algorithms described in the literature are in reality micro bolus correction controllers, but does not directly address the large glucose concentration disturbances associated with meals. In MPC based micro bolus algorithms for an AP, a number of research groups use low order models (van Heusden et al., 2012; Boiroux et al., 2018; Toffanin et al., 2018). As an optimal controller designed using internal model control (IMC) is the inverse of the transfer function, the optimal controllers are also low order transfer functions that are often equivalent to PID-controllers (Rivera et al., 1986; Morari and Zafiriou, 1989). Accordingly, this observation suggests that these micro bolus correction controllers based on MPC technology can equivalently be implemented based on PID technology. In this paper, we use physiological insight to design simple controllers that has approximately the same performance as MPC based controllers. This controller design provides insight into the fundamental principles and limitations of glucose control using subcutaneously (SC) administered fast acting insulin and may also have lower hardware requirements than an MPC.

1.5 Paper organization

This paper is organized as follows. Section 2 describes the hardware configuration and control structure in a single-hormone artificial pancreas for controlling blood glucose by administering insulin. In Section 3, the control algorithm is developed, and Section 4 presents an illustrative simulation using this simple control algorithm. Section 5 summarizes the conclusions of this paper.

2. CONTROL SYSTEM ARCHITECTURE

The insight about the insulin pharmaco-kinetics and pharmaco-dynamics may be used to in several ways to structure the functions of a control algorithm for a single-hormone AP. In this section, we present the hardware configuration for a single-hormone AP and the corresponding structure of a control algorithm. Fig. 1 illustrates a single-hormone AP and the corresponding main functionality of a control system based on simple control algorithms.

2.1 Hardware configurations

Fig. 1a shows a single-hormone AP. The single-hormone AP constists of 1) a CGM that continuously (e.g. every 5 min) provides a filtered signal of the IG concentration, 2) a control algorithm residing on a smart phone computes the dose of fast acting insulin to administer; and 3) an insulin pump that delivers the insulin dose computed by the control algorithm. The control algorithm computes the insulin concentration to deliver every 5 min based on meal information from the user and the IG concentration measured by the CGM. The high-frequency adjustment of the insulin injection allows the single-hormone AP to adjust the basal insulin profile based on feedback from the CGM. Additionally, a self monitoring blood glucose (SMBG) device may be used to calibrate the CGM. In the configuration described in this paper, we assume that the SMBG information is given directly to the CGM and thus only indirectly interfere with the control algorithm. Similarly, the described hardware configuration does not receive physical activity related inputs from accelerometers nor heart rate measurement devices.

2.2 Controller configuration

Fig. 1b shows the key elements in the control algorithm for a single hormone AP that we propose in this paper. The algorithm receives the CGM signal every 5 minutes and filters this signal using a low pass filter. The filtered CGM signal that represents the measured interstitial glucose concentration is used by a) the meal bolus controller, b) the basal R2R controller, and c) the micro bolus proportional-derivative (PD) controller. Switch logic related to among other things a super bolus as well as safety rules are applied to the insulin signal from the controller before the actual insulin delivery command is sent to the insulin pump.

The meal bolus calculator uses an estimate of the meal CHO content, $\hat{d}$, to compute the meal bolus insulin dosage. This meal bolus may be adjusted according to a bolus correction factor and the insulin-on-board as in traditional pen based insulin therapy. In addition, the basal and micro bolus insulin delivery may be switched off for a period after the meal. The basal insulin that would have been administered in that period is administered together with the bolus in a so-called super bolus.

The R2R algorithm uses a weighted average of the glucose concentration during the previous night to adjust the nominal basal insulin injection rate. The primary purpose of the basal insulin algorithm is to compute the average basal insulin requirements by titration. Due to the large unavoidable glucose concentration excursions in association with meals, only the night glucose concentrations until breakfast are included in the titration as these glucose concentrations resemble fasting glucose concentrations the best.

(a) Single hormone (insulin) AP.　　　(b) Single hormone (insulin) AP hardware configuration and control algorithm.
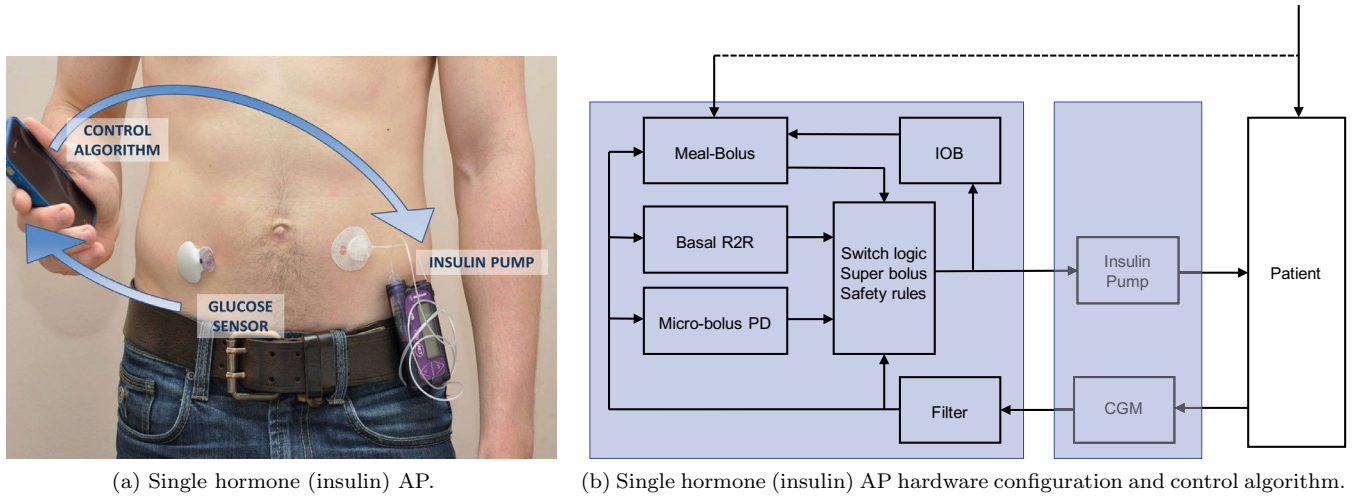
Fig. 1. Diabetes technology for a single-hormone AP. The single-hormone AP use fast acting insulin to compensate for both meals (bolus insulin) and endogenous glucose production (basal insulin). (a) The realization of a single-hormone AP using a glucose sensor (CGM), a smart phone with the control algorithm, and an insulin pump administering fast acting insulin. (b) The structure of the control algorithm in a single-hormone AP. This structure is motivated by the large size of meal disturbances and that meals are absorbed faster than sc injected fast acting insulin.

The micro bolus controller adjusts the micro boluses such that they are adapted to the IG concentration measured continuously by a CGM. This is needed as the basal insulin requirements in a patient during say a night may vary significantly, i.e. the intra patient basal insulin variability is non-negligible and one of the reasons that a feedback system such that an AP is needed for better and safer glucose concentration control in people with T1D. The basal R2R algorithm adjusts the nominal basal insulin infusion rate around which the micro bolus controller varies the insulin infusion rate. In this paper, we suggest a PD controller for the micro bolus correction algorithm, as this is the simplest reasonable algorithm. Other possibilities such as a linear MPC or an IMC algorithm exist.

3. CONTROL ALGORITHM

The *amount* of insulin administered by the insulin pump at each discrete time, t_k, is

$$u(t_k) = u_{bolus}(t_k) + u_{super-bolus}(t_k) + u_{basal}(t_k), \quad (1)$$

where $u_{bolus}(t_k)$ is the bolus, i.e. the amount of insulin administered to compensate for the estimated amount of carbohydrates in a meal, $u_{super-bolus}(t_k)$ is the amount of basal insulin given along with the bolus to compensate for subsequent suspension of the basal insulin, and $u_{basal}(t_k)$ is the amount of insulin in a micro-bolus, i.e. the insulin mimicing basal insulin to compensate for the endogenous glucose production. The basal insulin amount, $u_{basal}(t_k)$, is computed as

$$u_{basal}(t_k) = \Delta t_k \left(\bar{u}_{basal}(t_k) + \bar{u}(t_k) \right), \quad (2)$$

where Δt_k is the time interval for which the dose will be applied (administered either at a constant rate distributed over the interval or in an impulsive way at the beginning of the interval). Typically, $\Delta t_k = T_s$, where $T_s = 5$ min is the sample rate of the CGM and the the sample time of the digital control algorithm. The injection *rate* of basal insulin consists of two parts: 1) a nominal basal injection rate, $\bar{u}_{basal}(t_k)$, that is intended to compensate for an

average long-term endogeneous glucose production; and 2) $\bar{u}(t)$ that denotes the rate of basal insulin that adjusts the basal insulin rate to compensate for short-term metabolic variations.

It should be noted that $u_{bolus}(t_k)$ and $u_{basal}(t_k)$ in our algorithm are complementary in the sense that they are never both non-zero.

3.1 Filter

The signal provided by the CGM is already a filtered signal of the raw measurement signal. However, for the calculation of the basal insulin rate, we filter the meaasured interstitial glucose concentration, $Y(s)$, provided by the CGM using a first-order filter

$$Y_F(s) = F(s)Y(s), \qquad F(s) = \frac{1}{\tau_F s + 1}, \quad (3)$$

in which $Y_F(s)$ is the filtered interstitial glucose concentration. In the time-domain, this filter can be represented by the differential equation

$$\frac{dy_F}{dt}(t) = \frac{1}{\tau_F} \left(y(t) - y_F(t) \right). \quad (4)$$

3.2 Bolus algorithm

The bolus calculator in insulin pumps are typically given as (Walsh et al., 2011; Schmidt and Nørgaard, 2014; Ziegler et al., 2017)

$$u_{bolus}(t) = \frac{\hat{d}(t)}{carbF} + \alpha_{corr} \frac{y_F(t) - \bar{y}(t)}{corrF} - \alpha_{IOB} IOB(t) \quad (5)$$

When administered subcutaneously, even faster-acting insulin has an absorption time that is longer than the meal absorption time. In this case, it is optimal to administer the insulin in advance of the meal. For safety reasons, we only allow the insulin to be administered when the meal is started. In simple bolus calculators, the amount

of bolus insulin, $u_{bolus}(t)$, is proportional to the estimated carbohydrate content, $\hat{d}(t)$, in the meal

$$u_{bolus}(t) = K_{ICR}\hat{d}(t). \tag{6}$$

In this formula, we do not use a correction bolus ($\alpha_{corr} = 0$) and the associated insulin-on-board ($\alpha_{IOB} = 0$), as we assume that the frequent adjustment of the basal insulin using micro-boluses compensates for errors in the estimated bolus insulin. An empirical relation for K_{ICR} is (Walsh et al., 2011)

$$K_{ICR}(U/g\,CHO) = \frac{1}{carbF} = \frac{TDD(U/day)}{5.7 \cdot BW(kg)}. \tag{7}$$

Super bolus: As even fast acting insulin is absorbed slower than meal CHO, the post prandial glucose concentration peak is lowered by giving some of the basal insulin in the post prandial period as bolus insulin (Bondia et al., 2009; Boiroux et al., 2010c; Herrero et al., 2015). This super bolus is

$$u_{super-bolus}(t) = \bar{u}_{basal}(t)T_{sp}, \tag{8}$$

where $\bar{u}_{basal}$ is the nominal basal insulin injection rate and T_{sp} is the suspension period for the basal insulin delivery. The suspension period is meal size dependent and patient dependent. For one patient, we compute it as

$$T_{sp} = \begin{cases} T_{sp,a}, & d \leq d_a, \\ T_{sp,a} + \dfrac{T_{sp,b} - T_{sp,a}}{d_b - d_a}(d - d_a), & d_a < d < d_b, \\ T_{sp,b}, & d \geq d_b, \end{cases} \tag{9}$$

where $T_{sp,a} = 90$ min, $d_a = 20$ g, $T_{sp,b} = 180$ min, and $d_b = 100$ g. In addition we have limits on the maximal allowable total bolus insulin to administer. The micro bolus controller is able to handle small meal disturbances. Therefore, we do not suspend it for small meals, i.e. in this case meals smaller than 20 g CHO.

Insulin on board: The insulin PK-model presented by Hovorka et al. (2004) is

$$\dot{S}_1 = \bar{u} - \frac{S_1}{\tau_S}, \tag{10a}$$

$$\dot{S}_2 = \frac{S_1 - S_2}{\tau_S}, \tag{10b}$$

$$\dot{I}_p = \frac{S_2}{\tau_S V_I} - k_e I_p, \tag{10c}$$

such that the IOB is

$$IOB = S_1 + S_2 + V_I I_p. \tag{11}$$

The corresponding steady-state values are

$$S_{1b} = \tau_S \bar{u}_{basal}, \tag{12a}$$
$$S_{2b} = S_{1b} = \tau_S \bar{u}_{basal}, \tag{12b}$$
$$I_{pb} = \frac{S_{2b}}{k_e \tau_S V_I} = \frac{\bar{u}_{basal}}{k_e V_I}, \tag{12c}$$

and

$$IOB_b = S_{1b} + S_{2b} + V_I I_{pb} = \frac{2\tau_S k_e + 1}{k_e} u_{basal}. \tag{13}$$

The suspension period, T_{sp}, and the amount of super bolus insulin, $u_{super-bolus}$, may be related to the IOB in relation to the basal IOB. Instead of the 3rd order insulin PK model, a 2nd order PK model can also be used (Palerm, 2011).

3.3 Run-to-run algorithm for basal insulin

In conventional insulin therapy, the nominal basal insulin requirement is determined by a process called insulin titration. In this paper, we use a R2R algorithm for insulin titration. The novelty in this R2R algorithm is the penalty function, which penalizes occurrence of hypoglycemia more than occurrence of hyperglycemia. This penalty function is similar to the penalty function used in some MPC algorithms for APs (Boiroux et al., 2018).

Consider the penalty functions

$$\bar{\rho}(y, \bar{y}) = \frac{1}{2}(y - \bar{y})^2, \tag{14a}$$

$$\rho_{\min}(y, \bar{y}_{\min}) = \frac{1}{2}(\min\{0, y - \bar{y}_{\min}\})^2, \tag{14b}$$

$$\rho_{\max}(y, \bar{y}_{\max}) = \frac{1}{2}(\max\{0, y - \bar{y}_{\max}\})^2, \tag{14c}$$

that have the derivatives

$$\frac{\partial}{\partial y}\bar{\rho}(y, \bar{y}) = y - \bar{y} = -(\bar{y} - y), \tag{15a}$$

$$\frac{\partial}{\partial y}\rho_{\min}(y, \bar{y}_{\min}) = \begin{cases} y - \bar{y}_{\min}, & y \leq \bar{y}_{\min}, \\ 0, & y \geq \bar{y}_{\min}, \end{cases} \tag{15b}$$

$$\frac{\partial}{\partial y}\rho_{\max}(y, \bar{y}_{\max}) = \begin{cases} 0, & y \leq \bar{y}_{\max}, \\ y - \bar{y}_{\max}, & y \geq \bar{y}_{\max}. \end{cases} \tag{15c}$$

Then we can define the penalty function

$$\rho(y) = \bar{\rho}(y, \bar{y}) + \kappa\rho_{\min}(y, \bar{y}_{\min}) + \lambda\rho_{\max}(y, \bar{y}_{\max}), \tag{16}$$

which has the derivative

$$\begin{aligned} \frac{\partial}{\partial y}\rho(y) &= \frac{\partial}{\partial y}\bar{\rho}(y, \bar{y}) \\ &+ \kappa\frac{\partial}{\partial y}\bar{\rho}_{\min}(y, \bar{y}_{\min}) + \lambda\frac{\partial}{\partial y}\bar{\rho}_{\max}(y, \bar{y}_{\max}). \end{aligned} \tag{17}$$

Define the integral

$$I_k = \frac{\int_{T_{k-1}}^{T_k} -w(t)\frac{\partial}{\partial y}\rho(y_F(t))dt}{\int_{T_{k-1}}^{T_k} w(t)dt} \tag{18}$$

such that a run-to-run algorithm for the basal insulin can be expressed as

$$\bar{u}_{basal}(T_k) = \bar{u}_{basal}(T_{k-1}) + K_I I_k. \tag{19}$$

Using a PI-control parameterization for K_I, we have that $K_I = K_P/\tau_I$. The integral time, τ_I, can be tuned to determine the rate at which $\bar{u}_{basal}$ is adjusted. T_{k-1} and T_k are specified pre-prandial times in the previous and current day, while $w(t)$ are weights that can used include only nighttime filtered IG concentrations, $y_F(t)$, in the integral (18). Then in the current day, the nominal basal insulin rate is

$$\bar{u}_{basal}(t) = \bar{u}_{basal}(T_k), \qquad T_k \leq t < T_{k+1}. \tag{20}$$

3.4 PD-controller for the micro bolus algorithm

The micro-bolus corrections for fast variations in the glucose concentration are governed by a PD-controller,

$$\begin{aligned} \bar{u}(t) &= K_P(\bar{y}(t) - y_F(t)) - K_D\frac{dy_F(t)}{dt} \\ &= K_P(\bar{y}(t) - y_F(t)) - \frac{K_D}{\tau_F}(y(t) - y_F(t)), \end{aligned} \tag{21}$$

on the filterered interstitial glucose concentration, $y_F(t)$. $\bar{y}(t)$ is the glucose concentration (IG and BG) set point.
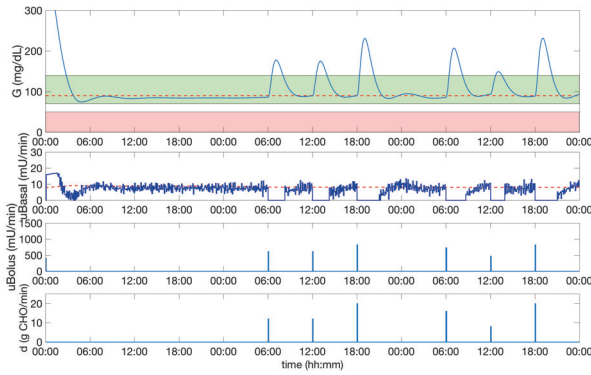
Fig. 2. A closed-loop simulation using the AP for basal titration in the first day and control to meal challenges the next two days.

$K_D = K_P \tau_D$ such that $\frac{K_D}{\tau_F} = K_P \frac{\tau_D}{\tau_F}$. Notice that the proportional term, $\bar{u}_P(t) = K_P(\bar{y}(t) - y_F(t))$, may be regarded as a micro-bolus correction term. Accordingly, an empirical expression for K_P related to the total daily insulin dose is (Walsh et al., 2011)

$$K_P = -corrF = -\frac{109\,\text{mmol/L}}{TDD\,(\text{U/day})}. \qquad (22)$$

IOB modification: As an additional safety measure and to avoid activating the micro bolus correction algorithm when a lot of bolus insulin is still on board, the micro bolus insulin correction is adjusted by the formula (Palerm, 2011)

$$\tilde{u}(t_k) = \bar{u}(t_k) - \gamma \max\left(0, IOB(t_k) - IOB_b\right). \qquad (23)$$

3.5 Parameters

The main adjustable parameters for the single-hormone AP control algorith are: 1) the total daily insulin dosage (TDD) and the body weight (BW); 2) the time constant for the filtering algorithm (τ_F), the R2R algorithm (τ_I), and the micro bolus PD algorithm (τ_D); and 3) the suspension period parameters (T_a, T_b, d_a, d_b). Typically, the following parameters are fixed: 1) The weights (κ and λ) for the penalty function in the R2R algorithm; 2) the insulin micro bolus modification parameter (γ); 3) the parameters for the IOB, i.e. the insulin PK parameters (τ_S, k_e, $V_I = \bar{V}_I \cdot BW$); 4) the parameters α_{corr} and α_{IOB} in the bolus calculator; and 5) the sampling time (T_s). The gains are computed according to $K_{ICR} = TDD/(5.7 \cdot BW)$, $K_P = 109/TDD$, $K_D = K_P \tau_D$, and $K_I = K_P/\tau_I$.

4. ILLUSTRATIVE SIMULATION

Fig. 2 illustrates the performance of the AP based on simple control algorithms presented in this paper.

5. CONCLUSION

A single-hormone AP control system can be divided into a meal bolus compensation algorithm, an R2R basal titration algorithm, and a micro bolus correction algorithm. The control algorithm is based on the following key physiological insights: 1) due to the insulin PK, the micro bolus algorithm should be suspended in period after a meal bolus and a super bolus given at meal time; and 2) the R2R algorithm should be updated based on measured glucose concentrations in the night time. Such an algorithm provides nearly optimal performance and is simple, yet different than standard PID control technology.

REFERENCES

Arnolds, S., Heise, T., Flacke, F., and Sieber, J. (2013). Common standards of basal insulin titration in T2DM. *Journal of Diabetes Science and Technology*, 7(3), 771–788.

Åström, K.J. and Hägglund, T. (2005). *Advanced PID Control*. International Society of Automation.

Åström, K.J. and Murray, R.M. (2008). *Feedback Systems. An Introduction for Scientists and Engineers*. Princeton University Press.

Atlas, E., Nimri, R., Miller, S., Grunberger, E.A., and Phillip, M. (2010). MD-logic artificial pancreas system. *Diabetes Care*, 33(5), 1072–1076.

Boiroux, D., Finan, D.A., Poulsen, N.K., Madsen, H., and Jørgensen, J.B. (2010a). Nonlinear model predictive control for an artificial beta-cell. In *Recent Advances in Optimization and its Applications in Engineering*, 299–308. Springer.

Boiroux, D., Duun-Henriksen, A.K., Schmidt, S., Nørgaard, K., Madsbad, S., Poulsen, N.K., Madsen, H., and Jørgensen, J.B. (2018). Overnight glucose control in people with type 1 diabetes. *Biomedical Signal Processing and Control*, 39, 503 – 512.

Boiroux, D., Duun-Henriksen, A.K., Schmidt, S., Nørgaard, K., Poulsen, N.K., Madsen, H., and Jørgensen, J.B. (2017). Adaptive control in an artificial pancreas for people with type 1 diabetes. *Control Engineering Practice*, 58, 332 – 342.

Boiroux, D., Finan, D.A., Jørgensen, J.B., Poulsen, N.K., and Madsen, H. (2010b). Meal estimation in nonlinear model predictive control for type 1 diabetes. *IFAC Proceedings Volumes*, 43(14), 1052 – 1057. 8th IFAC Symposium on Nonlinear Control Systems.

Boiroux, D., Finan, D.A., Jørgensen, J.B., Poulsen, N.K., and Madsen, H. (2010c). Optimal insulin administration for people with type 1 diabetes. *IFAC Proceedings Volumes*, 43(5), 248 – 253.

Boiroux, D., Hagdrup, M., Mahmoudi, Z., Poulsen, N.K., Madsen, H., and Jørgensen, J.B. (2016). An ensemble nonlinear model predictive control algorithm in an artificial pancreas for people with type 1 diabetes. *2016 European Control Conference (ECC)*, 714–719.

Boiroux, D. and Jørgensen, J.B. (2017). C code generation applied to nonlinear model predictive control for an artificial pancreas. *2017 21st International Conference on Process Control (PC)*, 327–332.

Bondia, J., Dassau, E., Zisser, H., Calm, R., Vehí, J., Jovanovič, L., and Francis J. Doyle, I. (2009). Coordinated basal-bolus infusion for tighter postprandial glucose control in insulin pump therapy. *Journal of Diabetes Science and Technology*, 3(1), 89–97.

Eren-Oruklu, M., Cinar, A., Quinn, L., and Smith, D. (2009). Adaptive control strategy for regulation of blood glucose levels in patients with type 1 diabetes. *Journal of Process Control*, 19(8), 1333 – 1346.

Franklin, G.F., Powell, J.D., and Workman, M.L. (1997). *Digitial Control of Dynamic Systems*. Addison-Wesley, 3rd edition.

Gondhalekar, R., Dassau, E., and Doyle, F.J. (2016). Periodic zone-mpc with asymmetric costs for outpatient-ready safety of an artificial pancreas to treat type 1 diabetes. *Automatica*, 71, 237 – 246.

Grosman, B., Dassau, E., Zisser, H.C., Jovanovič, L., and Doyle III, F.J. (2010). Zone model predictive control: A strategy to minimize hyper- and hypoglycemic events. *Journal of Diabetes Science and Technology*, 4(4), 961–975.

Herrero, P., Bondia, J., Adewuyi, O., Pesl, P., El-Sharkawy, M., Reddy, M., Toumazou, C., Oliver, N., and Georgiou, P. (2017). Enhancing automatic closed-loop glucose control in type 1 diabetes with an adaptive meal bolus calculator - *in silico* evaluation under intra-day variability. *Computer Methods and Programs in Biomedicine*, 146, 125 – 131.

Herrero, P., Pesl, P., Bondia, J., Reddy, M., Oliver, N., Georgiou, P., and Toumazou, C. (2015). Method for automatic adjustment of an insulin bolus calculator: In silico robustness evaluation under intra-day variability. *Computer Methods and Programs in Biomedicine*, 119(1), 1 – 8.

Hovorka, R., Canonico, V., Chassin, L.J., Haueter, U., Massi-Benedetti, M., Federici, M.O., Pieber, T.R., Schaller, H.C., Schaupp, L., Vering, T., and Wilinska, M.E. (2004). Nonlinear model predictive control of glucose concentration in subjects with type 1 diabetes. *Phyiosol. Meas.*, 25, 905–920.

Magni, L., Raimondo, D., Man, C.D., Nicolao, G.D., Kovatchev, B., and Cobelli, C. (2009). Model predictive control of glucose concentration in type i diabetic patients: An in silico trial. *Biomedical Signal Processing and Control*, 4(4), 338 – 346. Special Issue on Biomedical Systems, Signals and Control Extended Selected papers from the IFAC World Congress, Seoul, July 2008.

Marchetti, G., Barolo, M., Jovanovič, L., Zisser, H., and Seborg, D.E. (2008). A feedforward–feedback glucose control strategy for type 1 diabetes mellitus. *Journal of Process Control*, 18(2), 149 – 162.

Messori, M., Fornasiero, E., Toffanin, C., Cobelli, C., and Magni, L. (2014). A constrained model predictive controller for an artificial pancreas. *IFAC Proceedings Volumes*, 47(3), 10144 – 10149. 19th IFAC World Congress.

Morari, M. and Zafiriou, E. (1989). *Robust Process Control*. Prentice Hall.

Palerm, C.C. (2011). Physiologic insulin delivery with insulin feedback: A control systems perspective. *Computer Methods and Programs in Biomedicine*, 102(2), 130 – 137.

Palerm, C.C., Zisser, H., Jovanovič, L., and Doyle III, F.J. (2008). A run-to-run control strategy to adjust basal insulin infusion rates in type 1 diabetes. *Journal of Process Control*, 18(3–4), 258 – 265.

Rivera, D.E., Morari, M., and Skogestad, S. (1986). Internal model control. 4. PID controller design. *Ind. Eng. Chem. Process Des. Dev.*, 25, 252–265.

Schmidt, S., Boiroux, D., Duun-Henriksen, A.K., Frøssing, L., Skyggebjerg, O., Jørgensen, J.B., Poulsen, N.K., Madsen, H., Madsbad, S., and Nørgaard, K. (2013). Model-based closed-loop glucose control in type 1 diabetes: the diacon experience. *Journal of Diabetes Science and Technology*, 7(5), 1255–1264.

Schmidt, S. and Nørgaard, K. (2014). Bolus calculators. *Journal of Diabetes Science and Technology*, 8(5), 1035–1041.

Seborg, D.E., Edgar, T.E., Mellichamp, D.A., and Doyle III, F.J. (2010). *Process Dynamics and Control*. Wiley, 3rd edition.

Steil, G.M., Panteleon, A.E., and Rebrin, K. (2004). Closed-loop insulin delivery - the path to physiological glucose control. *Advanced Drug Delivery Reviews*, 56, 125–144.

Toffanin, C., Del Favero, S., Aiello, E.M., Cobelli, C., and Magni, L. (2018). Glucose-insulin model identified in free-living conditions for hypoglycemia prevention. *Journal of Process Control*, 64, 27–36.

Toffanin, C., Messori, M., Cobelli, C., and Magni, L. (2017a). Automatic adaptation of basal therapy for type 1 diabetic patients: A run-to-run approach. *Biomedical Signal Processing and Control*, 31, 539 – 549.

Toffanin, C., Sandri, A., Messori, M., Cobelli, C., and Magni, L. (2014). Automatic adaptation of basal therapy for type 1 diabetic patients: a run-to-run approach. *IFAC Proceedings Volumes*, 47(3), 2070 – 2075. 19th IFAC World Congress.

Toffanin, C., Visentin, R., Messori, M., Di Palma, F., Magni, L., and Cobelli, C. (2017b). Towards a run-to-run adaptive artificial pancreas: In silico results. *IEEE Transactions on Biomedical Engineering*.

Tuo, J., Sun, H., Shen, D., Wang, H., and Wang, Y. (2015). Optimization of insulin pump therapy based on high order run-to-run control scheme. *Computer Methods and Programs in Biomedicine*, 120(3), 123 – 134.

Turksoy, K. and Cinar, A. (2014). Adaptive control of artificial pancreas systems - a review. *Journal of Healthcare Engineering*, 5(1), 1–22.

Turksoy, K., Quinn, L.T., Littlejohn, E., and Cinar, A. (2014). Artificial pancreas systems: An integrated multivariable adaptive approach. *IFAC Proceedings Volumes*, 47(3), 249 – 254. 19th IFAC World Congress.

van Heusden, K., Dassau, E., Zisser, H.C., Seborg, D.E., and Doyle III, F.J. (2012). Control-relevant models for glucose control using a priori patient characteristics. *IEEE Transactions on Biomedical Engineering*, 59(7), 1839–1849.

Walsh, J., Roberts, R., and Bailey, T. (2011). Guidelines for optimal bolus calculator settings in adults. *Journal of Diabetes Science and Technology*, 5(1), 129–135.

Wang, Y. and amd Francis J. Doyle, III, E.D. (2010). Closed-loop control of artificial pancreatic beta-cell in type 1 diabetes mellitus using model predictive iterative learning control. *IEEE Transactions on Biomedical Engineering*, 57(2), 211–219.

Wang, Y., Gao, F., and Doyle III, F.J. (2009). Survey on iterative learning control, repetitive control, and run-to-run control. *Journal of Process Control*, 19(10), 1589 – 1600.

Ziegler, R., Freckmann, G., and Heinemann, L. (2017). Boluses in insulin therapy. *Journal of Diabetes Science and Technology*, 11(1), 165–171.