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Hypoglycemia Prevention in Closed-Loop Artificial Pancreas for Patients with Type 1 Diabetes

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1. Introduction

The current chapter addresses the problem of hypoglycemia in type 1 diabetes from biomedical and control engineering points of view. It gives a general introduction to the artificial pancreas system, and the risk of hypoglycemia in closed-loop insulin treatment. Then, it provides a review on the state of the art in hypoglycemia control, and the recent approaches in dealing with hypoglycemia in closed-loop artificial pancreas systems. Next, different control techniques that can be used to minimize the risk of hypoglycemia and improve the control outputs are presented.

Since the Diabetes Control and Complications Trial (DCCT), tight glycemic control has been established as the control objective in the treatment of patients with type 1 diabetes mellitus (T1DM) (DCCT Research Group (1993)), except if some contraindication exists. However, there still lacks a universal, efficient and safe system able to normalize the glucose levels of patients. The intensive insulin therapy required to achieve the tight glycemic control, based on the injection of basal and bolus insulin to reproduce its physiological secretion, has as counteraction an increase in the risk of significant and severe hypoglycemia with all their consequences. Therefore, hypoglycemia is considered as one of the major limiting factors in achieving tight glycemic control in T1DM (Cryer (2008)).

With the inability of conventional therapy to achieve satisfactory glycemic control, and the development in continuous glucose monitoring (CGM) systems and the increasing use of insulin pumps, the idea of developing an artificial pancreas is viewed as the ideal solution for glycemic control in T1DM (Bequette (2005); Hovorka et al. (2006); Kumareswaran et al. (2009)). The artificial pancreas is an automated closed-loop system that maintains blood glucose levels within the desired range and prevents hypoglycemia, while minimizing or eliminating the need for patient intervention. The artificial pancreas replaces the β-cells functions in glucose sensing and insulin delivery. It consists of three main components (Figure 1): a glucose sensor to measure glucose concentration, a pump for insulin delivery, and a closed-loop control algorithm to bridge between the glucose measurements and the dose of insulin to be delivered. As other medical devices, the architecture of closed-loop

artificial pancreas should include strict safety measures implemented as safety module or supervision system, to evaluate the performance of the control algorithm and apply fault detection techniques (Doyle III et al. (2007)).

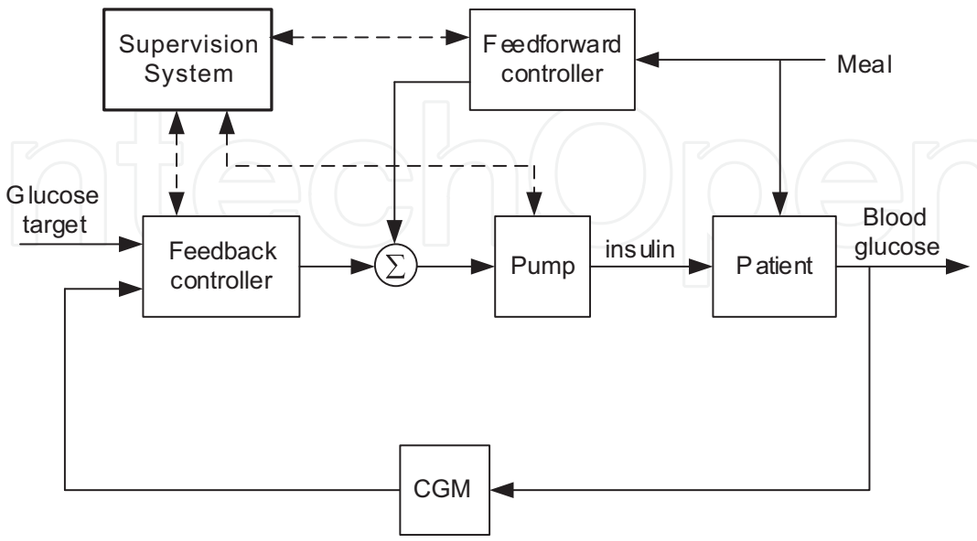


Fig. 1. Artificial pancreas components with patient in the loop. Control algorithm may use feedback or feedforward-feedback control loops

Closed-loop control of blood glucose has been a subject of continuous research for more than 40 years, however, till now no commercially available product does exist. The continuous subcutaneous insulin infusion (CSII) pumps are being widely used, and a number of CGM systems have received regulatory approval (Kumareswaran et al. (2009)). Although the sensors and pumps systems still have some limitations, their use in an open-loop combination resulted in better clinical outcomes over conventional injections therapy (Klonoff (2005); Kumareswaran et al. (2009)). Thus, the primary limitations to develop such an artificial pancreas are the development of reliable closed-loop control algorithms, and the availability of robust and precise glucose sensors. However, recent research in the development of the artificial pancreas suggests that types of the automatic glucose control system are likely to come to market in the near future.

1.1 Patient modeling

The artificial pancreas automatically regulates the blood glucose level based on the glucose measurements, the insulin infusions and in model-based control approaches, on the mathematical insulin-glucose model (diabetic patient model) used to design the controller. Also, these models are essential for testing and validating the artificial pancreas in simulation studies (i.e. *in-silico*) before putting it into clinical use with real patients. Thus, one essential task in the development of artificial pancreas is to obtain a model of T1DM patient, which can help in the development of a closed-loop control system.

Several models with different structures and degrees of complexity are being used to describe the glucoregulatory system - mainly as insulin-glucose and meal-glucose relationships - in T1DM. Most of these are first principle models represented by differential and algebraic equations and based on existing knowledge and hypotheses regarding the underlying physiological system. Among the models that have been frequently used to represent the

diabetic patient in artificial pancreas studies are: the *Meal model* (Dalla Man et al. (2006; 2007)), *Hovorka model* (Hovorka et al. (2004; 2002)), the minimal model (Bergman et al. (1979)), and *Sorensen model* (Sorensen (1985)). Extensive reviews on available models can be found in Chee & Fernando (2007) and Cobelli et al. (2009). Some of these models have been implemented in simulation environments designed to support the development of the closed-loop artificial pancreas (Kovatchev et al. (2009); Wilinska et al. (2010)).

Due to the complex nature of the insulin-glucose system, different empirical models have been proposed to relate insulin input to glucose response (see for example Eren-Oruklu et al. (2009b); Finan et al. (2009)). Empirical models develop a functional relationship between insulin and glucose based on empirical observations (i.e. collected patient data). These models do not describe the physiological model, but they explicitly address inter-patient variability since the data-driven model is specific to individual patient dynamics. Empirical models are more suitable for real-time parameter estimation and updating due to their simple structure in comparison with complex first order models.

1.2 Control problems

The feasibility of closed-loop artificial pancreas systems and their advantage over conventional treatment has been proved in several clinical studies (Atlas et al. (2010); Clarke et al. (2009); Hovorka et al. (2010); Steil et al. (2011; 2006); Weinzimer et al. (2008)), and a wide spectrum of control algorithms has been proposed to close the control loop, including classical and modern control strategies. Many reviews on closed-loop algorithms are available, see for example (Bequette (2005); Chee & Fernando (2007); Doyle III et al. (2007); El-Youssef et al. (2009); Takahashi et al. (2008)).

However, blood glucose control in T1DM is still one of the difficult control problems to be solved in biomedical engineering. In addition to the inherent complexity of glucoregulatory system, which includes the presence of nonlinearities, and time-varying and patient-specific dynamics, there exist other problems, such as noisy measurements, limitations of the models used to develop the control algorithms, as well as the limitations of the subcutaneous route used for glucose sensing and insulin delivery (e.g. technological and physiological delays and subcutaneous tissues dynamics). The aforementioned challenges make it very difficult to find a general and reliable solution to the nonlinear problem of glycemic control. Therefore, the design of a robust closed-loop control algorithm is an essential step for the progress of the artificial pancreas.

For closed-loop artificial pancreas system to be optimal and replicate the normal insulin secretion, the insulin therapy should respect the fact that hypoglycemia is not a naturally occurring episode in T1DM. Also, hypoglycemia is believed to be more dangerous in short term than hyperglycemia. Therefore, in order to achieve tight control while not substituting the problem of hyperglycemia for the life-threatening hypoglycemia, the insulin therapy in T1DM should be optimized so that it reduces the risk of hyperglycemic events in both frequency and magnitude, without provoking significant or severe hypoglycemia as a result of excessive or ill-timed insulin infusion.

2. Hypoglycemia in closed-loop artificial pancreas

Hypoglycemia is the most common complication of insulin therapy in T1DM and continuously limits the efforts to improve glycemic control. Therefore, hypoglycemia prevention should be unavoidably considered among the main objectives in the development of the closed-loop artificial pancreas systems. Severe hypoglycemia episodes are a

well-known cause of death in diabetic patients, and are more commonly seen during the night than during the day. Given that the first generations of the artificial pancreas are not expected to achieve complete regulation of the glucose levels during the 24 hours period, first generations of the artificial pancreas might be focusing on critical aspects like preventing hypoglycemia episodes during night (Hovorka et al. (2010)).

Currently, the vast majority of closed-loop artificial pancreas works focuses on the achievement of tight control during daily life conditions (i.e. 24 hours control), and therefore addresses both hyper- and hypoglycemia in fasting and postprandial conditions. Various strategies are employed in these works to avoid fasting, postprandial and nocturnal hypoglycemia. Mostly, the control algorithms use changes in the target blood glucose to adjust the doses of insulin to prevent hypoglycemia (i.e. higher target glucose level during night and postprandial periods) (Eren-Oruklu et al. (2009a); Marchetti et al. (2008); Weinzimer et al. (2008)). In other works, hypoglycemia prediction algorithms were tested, and short-term suspension of insulin pump was used as safety approach when hypoglycemia is predicted (Lee & Bequette (2009)). Also, variations in insulin sensitivity during the day (due to the 24 hours circadian cycle in insulin sensitivity), have been considered in the design of artificial pancreas control algorithms, and used to adjust the basal insulin requirements during the day (Garcia-Gabin et al. (2009); Steil et al. (2003); Wang et al. (2009)).

Another strategy used to avoid hypoglycemia is the double hormone closed-loop system, which uses glucagon infusion in response to low glucose levels. In T1DM, insulin deficiency is often accompanied by the loss of glucagon secretory response to hypoglycemia. Furthermore, insulin therapy causes even more degradation in the functionality of other counterregulatory hormones (Briscoe & Davis (2006)), and consequently, results in higher possibility for hypoglycemic risk. Different artificial pancreas studies have demonstrated that glucagon infusion significantly reduces the risk of insulin-induced hypoglycemia in T1DM (Castle et al. (2010); El-Khatib et al. (2009; 2010); Ward et al. (2008)).

2.1 Overnight hypoglycemia control

Overnight closed-loop insulin delivery has received great interest because it addresses the critical problem of nocturnal hypoglycemia. Furthermore, prevention of nocturnal hypoglycemia and achieving good control overnight can help in improving the quality of glycemic control during the day (Hovorka et al. (2010)) (e.g. starting the day with acceptable glucose levels). A number of clinical and *in-silico* studies attempts to deal with the hypoglycemia prevention - mainly nocturnal hypoglycemia - as the primary control objective. In (Wilinska et al. (2009)), a manual closed-loop insulin delivery system was employed during night period using model predictive control (MPC) algorithm and CGM measurements (CGM readings were provided to the MPC by medical staff), and aimed at regulating glucose level overnight to avoid nocturnal hypoglycemia. In (Hovorka et al. (2010)), the system was tested in a clinical study with children and adolescents. Earlier version of this MPC algorithm was tested in previous clinical study to evaluate its control and prediction performance during fasting conditions (Shaller et al. (2006)). An automated closed-loop insulin delivery system was tested in a multinational clinical trial (Bruttomesso et al. (2009); Clarke et al. (2009)). The system used a personalized MPC algorithm developed in (Magni et al. (2007)). The system was developed completely *in-silico* and then tested in the clinical trial.

The studies concluded that the MPC algorithm is well suited for glucose control under fasting and overnight conditions in T1DM patients. The studies showed that the artificial pancreas is superior to open-loop control in preventing overnight hypoglycemia where significant

reduction in overnight hypoglycemia episodes was observed with closed-loop control in comparison with standard therapy. Also, during closed-loop period, the blood glucose level was within the target glycemic range for a longer time period, and the frequency of low glucose values was reduced.

2.2 Hypoglycemia alarm systems

Beside control algorithms, several algorithms for hypoglycemia detection and prediction are proposed as alarm systems to avoid hypoglycemia. The progress in CGM systems has made it possible to develop such real-time algorithms to reduce the hypoglycemic risk. These algorithms can be used to detect occurring hypoglycemia or warn about a pending hypoglycemic episode. The algorithms are based mainly on a combination of CGM data and a set of defined threshold of glucose and glucose rate of change. Different estimation and prediction approaches (e.g. linear and statistical prediction, Kalman filter optimal estimation, time series, etc.) have been proposed to develop these algorithms (Buckingham et al. (2009); Cameron et al. (2008); Hughes et al. (2010); Palerm et al. (2005); Sparacino et al. (2007)). Nguyen et al. (2009) used a specialized sensor (*Hypoglycemia monitor*) for nocturnal hypoglycemia detection, based on bayesian neural networks approach. The sensor measures specific physiological parameters continuously trying to detect the hypoglycemic events. In Skladnev et al. (2010), a data fusion approach was used to enhance the hypoglycemia alarm of CGM systems. The CGM information (data and alarms) was fused with autonomic nervous system responses that were detected by the specialized *Hypoglycemia monitor*. The data fusion method was able to improve nocturnal hypoglycemia alarms, and reduced the number of undetected hypoglycemic events.

Hypoglycemia prediction/detection algorithms are usually coupled with specific supporting actions to improve their efficiency in preventing hypoglycemia. Different actions have been proposed, such as gradual insulin attenuation (Hughes et al. (2010)), pump suspension (Buckingham et al. (2009); Lee & Bequette (2009)), glucose infusion (Choleau et al. (2002)), and audible (Buckingham et al. (2009); Weinzimer et al. (2008)) or visual (Hughes et al. (2010)) alarms to alert the patient about actual or impending hypoglycemia. The statistical and linear hypoglycemia predictors with pump suspension algorithm proposed in (Buckingham et al. (2009)) were used in a clinical study, and proved to be effective in preventing hypoglycemia without provoking rebound hyperglycemia after the suspension of the pump.

3. Hypoglycemia prevention by control algorithm improvement

To improve the performance of the closed-loop system, and significantly reduce the risk of hypoglycemia, the control system of the artificial pancreas can be augmented with different control techniques. Such techniques can be introduced either by modifying the controller structure (i.e. internal), or by implementing the additional technique separately (i.e. external component). The increased cost or complexity that could be added to the system by incorporating such techniques can be justified by the improved performance of the system in dealing with life-threatening hypoglycemia. Both external and internal techniques have been tested and proved to provide satisfactory results, and to outperform the stand-alone closed-loop controllers.

3.1 Model predictive control

Several studies have concluded that model predictive control (widely known as MPC) is expected to be the core of closed-loop control algorithm in the near future artificial pancreas.

Therefore, MPC is discussed in some details in this chapter. MPC is a control strategy that has developed considerably over the past few decades. Basically, MPC is based on a model of the system to be controlled. The model is used to predict the future system outputs, based on the past and current values and on the proposed optimal future control actions. These actions are calculated by optimizing a cost function where the future tracking error is considered, as well as the system constraints if any (Maciejowski (2002)). MPC employs a receding horizon strategy; repeated displacement of the time horizon, while only applying the first control signal in the calculated sequence at each time step, with the rest of the sequence being discarded.

MPC has many virtues that make it a competitive candidate for the blood glucose control problem: (1) The prediction nature of MPC allows for anticipatory and careful insulin delivery to avoid large fluctuations in glucose levels. Such feature is important for avoiding overdosing and hypoglycemic risk. (2) The ability of MPC to handle constraints on system inputs and outputs is a major advantage of MPC over other control strategies. These constraints are very critical when dealing with the human body, and allow to satisfy hardware specifications of the insulin pump. (3) The applicability of MPC to systems with time delays can be useful to overcome the physiological and technological delays associated with the subcutaneous route. (4) MPC allows the introduction of feedforward control action to compensate for known sources of disturbance affecting the system, such as meal intake. These advantages of MPC over other control strategies have promoted the use of MPC in the field of insulin delivery. Different MPC schemes are being used in artificial pancreas research, where the applicability of such control strategy has been demonstrated in *in-silico* studies (see for instance (Abu-Rmileh et al., 2010a; Dua et al., 2009; Grosman et al., 2010; Hovorka et al., 2004; Lee & Bequette, 2009; Magni et al., 2007; Parker et al., 1999)), and clinical trials as mentioned earlier.

3.2 Unequal penalization

Closed-loop control schemes can be designed so that unequal penalties are used upon hyperglycemia and hypoglycemia. The reason for such unequal penalties is that in diabetes therapy, the performance requirement of a controller has asymmetric nature, as hypoglycemic events are much less tolerable than hyperglycemia. Since hypoglycemia is believed to be more life-threatening in the short term, the control algorithm should be more aggressive in avoiding hypoglycemic episodes than in correcting hyperglycemic events.

MPC is one control strategy that permits to incorporate this kind of unequal penalization. To achieve such requirements of asymmetrical response, an asymmetric cost function is used in the optimization algorithm in MPC. The asymmetric cost function imposes different weight on hypoglycemia than on hyperglycemia, in contrast to conventional cost functions that impose the same weight on hypoglycemic and hyperglycemic events. As stated before, MPC calculates the insulin control action u_k, by optimizing a quadratic cost function, penalizing predicted output deviations and control signal along some prediction horizons. The asymmetric cost function has the form:

$$\min_{\Delta u} J = \sum_{j=1}^{N_p} \|w^y(\hat{y}(k+j|k) - r(k+j))\|^2 + \sum_{j=1}^{N_u} \|w^{\Delta u}(\Delta u(k+j|k)\|^2 + q\varepsilon^2 \quad (1)$$

Subject to the following constraints:

$$\begin{aligned} u_{min} \leq u_k \leq u_{max} \\ \Delta u_{min} \leq \Delta u_k \leq \Delta u_{max} \\ y_{min} - \varepsilon\Phi_{min} \leq y_k \leq y_{max} + \varepsilon\Phi_{max} \end{aligned} \tag{2}$$

where $\hat{y}(k+j|k)$ is the j-step prediction of the output on data up to instant k, $r(k+j)$ is the target glucose level, Δu is the insulin input increment, N_p and N_u are the prediction and control horizons, and $w^{\Delta u}$, w^y are weights on the insulin increments and the error between $y(k)$ and $r(k)$ respectively, ε is a slack variable used for output constraints softening (to avoid infeasibility problems in the optimization), q is the weight on the slack variable ε, $u_{min/max}$, $\Delta u_{min/max}$ and $y_{min/max}$ are the constraints imposed on the input, input increments, and output respectively, and Φ_{min}, Φ_{max} are the relaxation variables.

The cost function in equation (1) is asymmetric in the sense that the lower and upper output constraints are subjected to unequal relaxation bands and therefore, the constraints have different levels of softness. The unequal softness levels could be achieved by introducing the nonnegative relaxation variables Φ_{min}, Φ_{max} which represent the concern for relaxing the corresponding constraint; the larger Φ, the softer the constraint. MPC with asymmetric cost function was tested with different diabetic patient models, and showed an excellent ability to minimize the hypoglycemic events, especially in postprandial period (Abu-Rmileh & Garcia-Gabin (2010a;b); Kirchsteiger & Del Re (2009)). Kirchsteiger & Del Re (2009) give a comparison between symmetric and asymmetric cost function MPC's, where the latter shows superior performance in avoiding hypoglycemia.

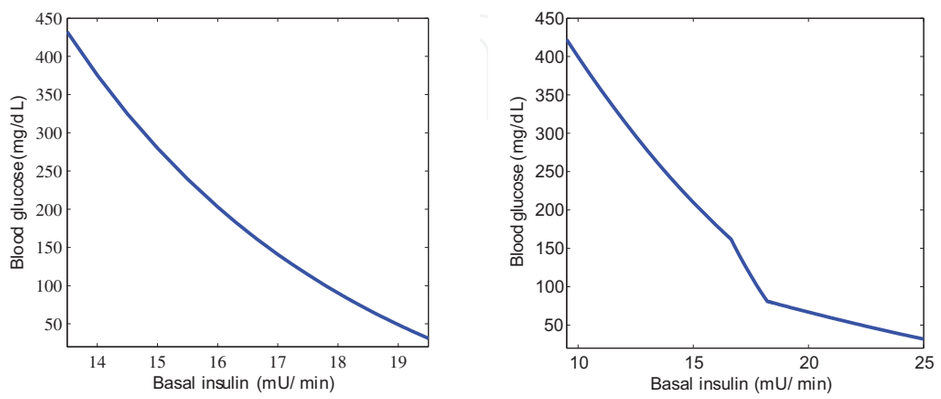
In Dua et al. (2009), a multi-programming MPC is used, and provided with different techniques to avoid hypoglycemia. In the multi-programming approach, the optimization problem in MPC is solved by searching for optimal solution within some valid regions (search regions) defined by the constraints and the parameters of the cost function. The main advantage of the multi-parametric MPC is that it provides the same performance as traditional MPC with lower computational load. The controller is provided with asymmetric cost function, and higher priority is given to the satisfaction of constraints imposed on hypoglycemia. Another type of asymmetric performance is presented in Grosman et al. (2010) to minimize the undesirable hypoglycemic and hyperglycemic events. The proposed MPC uses a glycemic zone rather than a fixed glucose level as a target (Zone-MPC). Three different zones are defined (permitted, lower, and upper zones), where the control objective is adjusting the insulin input to maintain glucose level within the permitted zone.

3.3 Gain scheduling

Gain scheduling (GS) is a well-known technique for controlling nonlinear systems by linear controllers. Briefly, GS is one of the simplest forms of adaptive control that employs different control structures in the different operating ranges of the nonlinear system. In glucose control, GS was inspired from the natural pancreas where the level of insulin activity varies between different glycemic ranges; being dominant in the hyperglycemic range, in balance with glucagon action in normoglycemia, and almost inactive in the hypoglycemic range where glucagon is dominant.

From an engineering perspective, a simple nonlinearity test (e.g. steady state insulin-glucose relationship) can be used to show that insulin has a nonlinear effect on blood glucose in different glycemic ranges (see Figure 2). Linear control algorithms are intended to control

linear systems, and they usually offer poor results when used to control nonlinear systems in regions far from where the linear model used was obtained. Therefore, nonlinear control or multiple linear controllers should be applied to handle each glycemic range separately and mimic the natural pancreas secretions. The use of multiple linear controllers by gain scheduling approach is discussed here, while nonlinear control is addressed later in this chapter.



(a) Smooth nonlinearity (*Meal model*) (b) Strong nonlinearity (*Hovorka model*)

Fig. 2. Nonlinear steady-state insulin-glucose behavior in different models of diabetic patients

The idea behind using the GS strategy in artificial pancreas is to use multiple linear controllers to deal with the system nonlinear behavior and maintain the ability of handling each glycemic range separately according to its dynamics. Since most of the closed-loop control strategies use insulin only, the control algorithm should provide the different levels of insulin activity in different glycemic ranges by employing the GS technique. GS scheme requires the assignation of scheduling parameters that can be used to select the suitable linear controller for each range. The GS strategy overcomes the limitations of the linear control approach which is only valid in the neighborhood of a single operating point, and provides a performance similar to nonlinear controllers with lower complexity.
A simplified diagram of the GS control is shown in Figure 3. As it can be seen in the figure, the measured glucose level is used as a scheduling variable, and also delivered to the controllers box as feedback signal. The controllers receive the desired glucose level (glucose target) to calculate the required insulin based on the difference between target glucose and CGM measurements, and the glycemic range defined by the GS selection. A control approach combining linear MPC with GS was tested in (Abu-Rmileh & Garcia-Gabin (2010a;b)), and proved to enhance the performance of the closed-loop controller in avoiding hypoglycemia.

3.4 Meal announcement

Regulation of blood glucose level after a meal is one of the main challenges for the fully developed artificial pancreas. Meals usually lead to a significant glucose flux into the blood stream. If feedback control is used to eliminate the meal effect, the controller reacts only after a rise in glucose has occurred and been detected by the CGM sensor. Elevated glucose level can lead to insulin overdosing, resulting in postprandial hypoglycemia (Steil et al. (2006)).

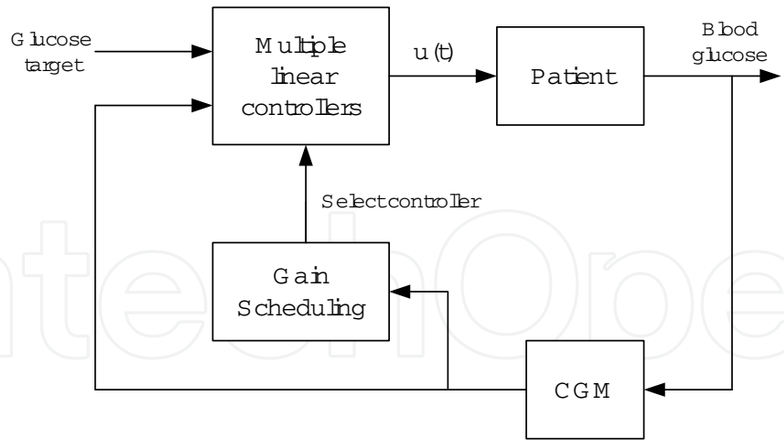


Fig. 3. Gain scheduling control scheme; the CGM output is delivered to the controllers box as a feedback signal, and to GS to select the controller to be used.

To avoid the limitation of purely reactive feedback control action and improve the controller response against meal effect, feedforward control (i.e. meal announcement) can be used. Feedforward is a well-known control technique used to eliminate the disturbance effect when the source of disturbance can be measured. In blood glucose control, the meal intake can be viewed as a known source of disturbance, and feedforward control can be used for meal announcement. In case information is given to the artificial pancreas system about the upcoming meal (size and time), a feedforward scheme may be implemented to deliver additional meal-time insulin bolus (Figure 1).
For the design of the feedforward controller, the effect of meal on blood glucose level should be modeled. The system model (insulin-glucose) in the feedforward element describes or predicts how each change in insulin will affect glucose, while the disturbance model (meal-glucose) is used to describe or predict how each change in meal will affect glucose. Let G_s and G_d be the system and disturbance models respectively, the feedforward control u_{ff} is calculated as:

$$u_{ff} = -\frac{G_d}{G_s} \times Meal \tag{3}$$

Feedforward controllers can range from simple scaling multipliers (static feedforward) to sophisticated differential equations (dynamic feedforward). Dynamic models give a better description of actual system and disturbance behaviors, often achieving improved disturbance rejection performance. However, the dynamic feedforward can be difficult to obtain and implement. In specific control algorithms such as MPC, the feedforward control signal can be calculated by the controller itself rather than using a separate feedforward controller. If the meal effect is included in the prediction model of the MPC, the controller predicts the future glucose levels as a function of insulin-glucose dynamics, CGM measurements, and meal information. Consequently, the meal effect on blood glucose will be considered in calculating the future insulin dose (i.e. predictive feedforward). In this controller configuration, the insulin dose has two parts: feedback insulin delivered in fasting conditions, and feedforward insulin bolus used at meal time to obtain better meal compensation.

The different configurations of feedforward (static, dynamic, and predictive) are being used in the artificial pancreas research, and their feasibility in improving the overall controller performance has been demonstrated in different clinical and simulation studies (Abu-Rmileh & Garcia-Gabin (2010a;b); Abu-Rmileh et al. (2010b); Lee & Bequette (2009); Marchetti et al. (2008); Weinzimer et al. (2008)). Since the feedforward action starts to deliver insulin before the meal effect appears in the CGM feedback loop, lower fluctuations in glucose levels are observed, with higher percentage of time within the acceptable glycemic range. An example of the improved performance achieved with feedforward control is shown in Figure 4. Finally, it should be mentioned that meal announcement must be done carefully, since an excess of insulin or badly-timed bolus may induce undesirable hypoglycemia episodes.

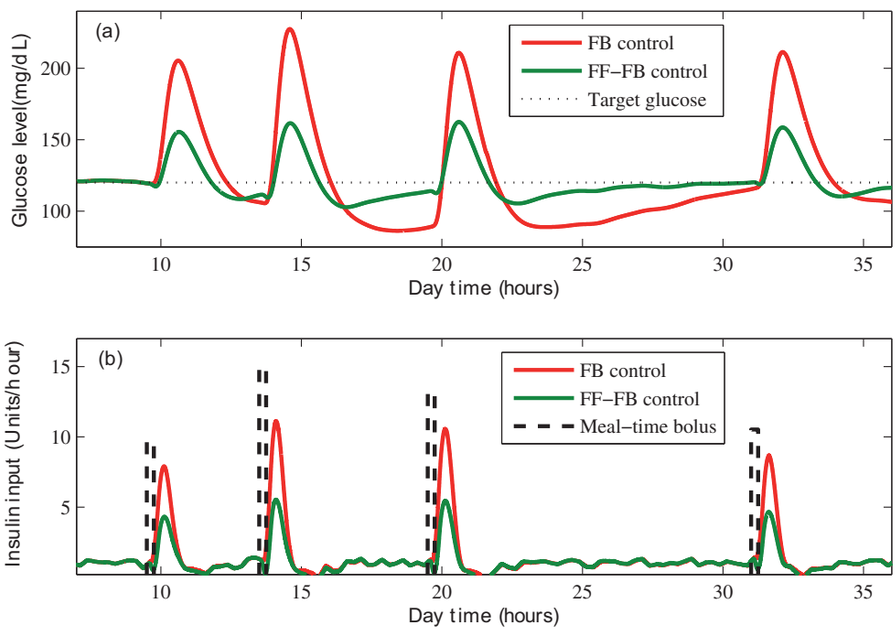


Fig. 4. Feedback (FB) vs. feedforward-feedback (FF-FB) control performance, (a) glucose level (b) insulin input

3.5 Meal detection

Beside feedback and feedforward control, meal detection techniques can be used to deal with meal challenge. Although feedforward-feedback control achieves better results than feedback alone, it is not uncommon that patients forget to announce upcoming meals. Therefore, a system for meal compensation that does not require information from the patient, would be preferable. The CGM measurements along with a set of thresholds on glucose levels and glucose rates of change (i.e. first and second derivative), can be used to build meal detection/compensation algorithms. When a meal is detected, the algorithm can be used to initiate extra meal-time insulin dose, or to activate an alarm for the patient. The meal-time dose can be delivered as insulin bolus or micro boluses, or a gain scheduling scheme can be used to adjust the controller output when a meal is detected. Meal detection and CGM-activated insulin dose remove the need for patient's interventions, and make the closed-loop artificial pancreas fully automatic. Meal detection algorithms also reduce the

hypoglycemic risk produced by erroneous insulin bolus or skipped meal, which may occur in the case of feedforward meal announcement.

Three main types of meal detection algorithms currently exist. A voting scheme is used in (Dassau et al. (2008)) to detect meals based on a combination of four different methods for calculating glucose rates of change. Another algorithm is proposed in (Lee & Bequette (2009); Lee et al. (2009)), where the meal detection algorithm is developed by using a finite impulse response filter and a set of threshold values. The algorithm estimates the meal size at the time of detection. Since the main objective of the development of meal detection algorithms is the application to closed-loop artificial pancreas, Lee & Bequette (2009) tested the design algorithm in combination with a MPC closed-loop controller, and demonstrated that meal detection strategy is efficient and outperforms the stand-alone feedback control scheme. Cameron et al. (2009) presented a probabilistic and evolving algorithm to detect the meal and predict its shape, and to estimate the total appearance of glucose from the meal. The algorithm has proved to enhance the meal-compensation ability of the feedback controller.

3.6 Time delay compensation

It is well-known that the time delay in the subcutaneous route is a major challenge in the development of the artificial pancreas (Hovorka (2006)). Both physiological and technological delays exist in glucose sensing and insulin delivery. Such time delays can result in poorly controlled glucose since hypoglycemia can be induced and remains undetected for a significant time period. In an attempt to eliminate or minimize the effect of time delay, closed-loop control structures with time-delay compensation features can be used to improve the control outputs and reduce the hypoglycemic risk produced by physiological and technological delays.

Smith predictor structure is a control scheme that presents good properties in controlling systems with long time delay. The idea behind Smith predictor is to incorporate the system model within the closed-loop control structure (i.e. the system model becomes an explicit part of the controller). Thus, the design of Smith predictor scheme requires a model of the system dynamics and an estimate of the system time delay t_0. In the Smith predictor scheme, there are two parallel paths for the control signal $u(t)$ (see Figure 5); one passing through the real system (the patient), and one passing through the model of the system G_s. The function of the parallel path containing the model is to generate the difference $e_m(t)$ between the actual system output $y(t)$ and a model-based prediction of the control signal effect on the system output $y_m(t)$. The Smith predictor uses the model to predict the delay-free response of the system $\bar{y_m}(t)$. Then, it compares this prediction to the target glucose level $r(t)$ to decide what control actions are needed. To avoid drifting and reject external disturbances, the Smith predictor also compares the actual system output with a prediction that takes the time delay into account. The error $e_m(t)$ contributes to the overall error signal $e(t)$ delivered to the feedback controller.

The Smith predictor structure has been recently used in artificial pancreas studies (Abu-Rmileh et al. (2010a;b)). With an initial estimation of the time delay, the Smith predictor shows the ability to minimize the effect of time delays and the associated risk of hypoglycemia, and to enhance the controller performance. As mentioned before, the MPC strategy, which has been extensively studied in artificial pancreas applications, is another competitive control algorithm with inherited ability to deal with system time delays (Hovorka (2006)).

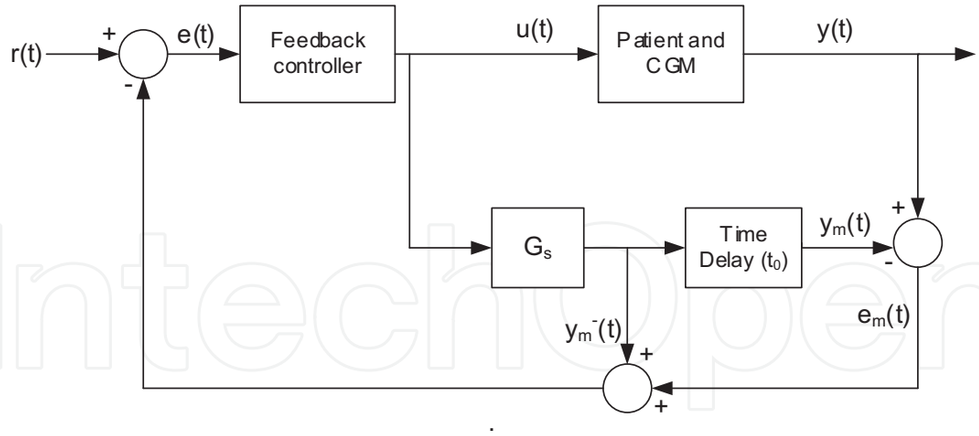


Fig. 5. Smith predictor control structure for time-delay compensation

3.7 Insulin on board and insulin feedback

As discussed previously, the use of subcutaneous route faces a challenging problem represented by the delayed insulin action. The effect of subcutaneous insulin may remain active over an extended time period (3-5 hours) after administration. Insulin on board (IOB) is a term used to describe how much insulin is still active from previous doses. Modern insulin pumps include the IOB option that helps in calculating the next required insulin dose. Therefore, IOB curves (time-action profiles) can be used in the development of artificial pancreas control algorithms to consider the effect of previous insulin, and provide a type of safety measure to avoid the problem of overdosing and the associated hypoglycemia. Ellingsen et al. (2009) developed a MPC scheme with IOB constraints. The IOB was used as dynamic safety constraints with a set of curves, to account for the time profile of delayed insulin action. Lee et al. (2009) used the IOB safety constraints in an integrated control scheme for the artificial pancreas that includes MPC strategy, meal detection algorithm, IOB constraints, and pump suspension option to avoid hypoglycemia.

Another technique used to reduce insulin infusion is the *insulin feedback*, initially introduced by Steil et al. (2004). The algorithm aims at reproducing as close as possible the insulin secretion from the natural pancreas. The idea behind this technique is to consider that a part of previous insulin is still active, and can cause further reduction in glucose level. Based on a pharmacokinetic model (Steil et al. (2006)), the algorithm estimates the plasma insulin level, and reduces the output of a proportional-integration-derivative (PID) controller by using the insulin feedback term, that is proportional to the estimated plasma insulin. Different versions of the algorithm have been used in clinical studies (Steil et al. (2011; 2006); Weinzimer et al. (2008)). In a recent study (Steil et al. (2011)), the insulin feedback has been used to improve the PID controller response in avoiding hypoglycemia after breakfast, and has achieved the desired performance.

3.8 Nonlinear modeling and control

Since the effect of insulin is nonlinear across the different glycemic ranges, the use of nonlinear models able to describe this nonlinear behavior would facilitate the design of more robust nonlinear control strategies, to handle the difference between glycemic ranges and their insulin requirements. Nonlinear models are more flexible in capturing complex behavior than the linear models, and consequently, the nonlinear control strategies are considered to be more suitable for this type of systems than linear control strategies. Therefore, nonlinear

control is believed to be more appropriate for the closed-loop artificial pancreas, and will enhance hypoglycemia prevention features of closed-loop systems due to its ability to provide particular insulin profile for each glycemic region. However, the identification of nonlinear models is still a challenging task in the artificial pancreas research. In order to be used in closed-loop control, such nonlinear model should be sufficiently accurate to capture the main system behavior and nonlinearity, while being relatively simple to be identified from the available data such as CGM measurements, and insulin and meal information.

Nonlinear control strategies like nonlinear MPC (NMPC) and sliding mode control (SMC), have shown superior performance over classical linear controllers in the blood glucose control problem. Most of the available MPC strategies are based on a linear model of the system. For systems that are highly nonlinear, the performance of a linear MPC can be poor. This has motivated the design of the NMPC, where a more accurate nonlinear model of the system is used for prediction and optimization. NMPC has been used in a number of artificial pancreas studies (Hovorka et al. (2010; 2004); Schlotthauer et al. (2005); Trajanoski & Wach (1998)).

SMC is a nonlinear robust procedure to synthesize controllers for linear and nonlinear systems. The design of SMC algorithm includes two main steps. 1) Choosing a switching (sliding) surface, along which the system can slide to its desired final value. The sliding surface is designed so that it describes the desired system dynamics. The sliding surface divides the phase plane into regions where the switching function has different signs. 2) By using appropriate control law: make the system reach the switching surface *(reaching phase)*, and keep it on the surface *(sliding phase)*. The structure of the controller is intentionally altered as its state crosses the surface in accordance with a prescribed control law. SMC exhibits good robustness against parameter variations, modeling errors and disturbances.

SMC algorithms have been employed successfully in different *in-silico* studies of artificial pancreas (Abu-Rmileh et al. (2010a;b); Kaveh & Shtessel (2008)). The combination between SMC and Smith predictor used in (Abu-Rmileh et al. (2010a;b)) is simple in its formulation and implementation, yet has some good features such as accuracy and robustness, insensitivity to internal and external disturbances, time-delay compensation and finite time convergence. These features make the proposed control algorithm suitable for the blood glucose problem which incorporates many sources of uncertainty and disturbances, and imposes some specific time requirements to avoid hypoglycemia and extended hyperglycemia. Other nonlinear control and modeling techniques have been used in the artificial pancreas research. Brief descriptions of frequently used approaches are given here, while comprehensive reviews are provided in Bequette (2005); Chee & Fernando (2007); El-Youssef et al. (2009); Takahashi et al. (2008)).

As mentioned before, the glucoregulatory system is nonlinear and difficult to model mathematically. Therefore, empirically-based and model-free control techniques such as fuzzy and neural network systems would be key components in artificial pancreas control systems. Fuzzy systems are based on the idea that input-output relationships are not crisp, but can change gradually from one state to the next, and partial membership rather than crisp membership can be used to adjust the control action. Fuzzy logic control takes the input variables and maps them into fuzzy levels by sets of membership functions. Each input variable has determined value's degree of membership in a fuzzy set. The process of converting crisp input values to fuzzy values is called *fuzzification*. The fuzzy controller makes decisions for what action to take based on a set of rules. The set of rules are built generally based on expert knowledge. The input signal is processed applying the corresponding rules and generating a result for each, then combining the results of these rules. Finally, the fuzzy

controller output is obtained via *defuzzification* combining result back into a specific crisp control output value. Different fuzzy control schemes have been implemented in artificial pancreas studies (see for example Atlas et al. (2010); Campos-Delgado et al. (2006); Ibbini (2006); Ibbini & Massadeh (2005)). In Atlas et al. (2010), a personalized fuzzy logic controller has been validated clinically, and proved to minimize hyperglycemic peaks while preventing hypoglycemia.

Neural networks are modeling techniques that result in a nonlinear model based on experimental data. It is a black-box model organized in sequential layers containing neurons. The network output is obtained as a weighted sum of inputs through the hidden layers. The weights are found during a training process by minimizing the error between desired and network output. Neural networks show excellent adaptation and learning ability. Neural networks deal with the blood glucose problem without explicit description of the exact model of the insulin-glucose system. Such approach is very useful in irregular situations (e.g. patients have a disease or abnormal conditions) that limit the usability of normal models (Takahashi et al. (2008)). Neural networks have been used to obtain insulin-glucose models for the design of nonlinear closed-loop controllers (El-Jabali (2005); Schlotthauer et al. (2005); Takahashi et al. (2008); Trajanoski & Wach (1998)). A combination between fuzzy logic and neural network (neuro-fuzzy) control strategy was applied by Dazzi et al. (2001) in clinics, and proved to provide superior glycemic control compared to conventional algorithms, with hypoglycemic events reduced to half.

Adaptive control is another approach used for glucose regulation. The complexity of glucose control mechanism highlights the need for an adaptive control algorithm to compensate for variations in patient dynamics (e.g. time-varying insulin sensitivity, stress and physical exercise) or disturbances by adapting the controller and model parameters to the changing patient conditions (Eren-Oruklu et al. (2009a); Hovorka (2005)). Adaptive control includes several configurations that allow not only outputs of the controller to be changed over time, but also the method by which those outputs are generated; the controller continuously monitors its own adaptation through a defined metric, and is capable of altering its own control scheme to better meet the adaptation criterion. For blood glucose control, different adaptation schemes have been employed (Chee & Fernando (2007)), in systems that use the sensor measurements to track the changes in glucose dynamics and update the controller structure to assign the required insulin regime. In model-based adaptive control, patient model is used to predict future glucose levels based on current and past insulin infusions. The model parameters are continuously updated and used in the control algorithm to calculate the required insulin. Adaptive control strategies have the ability to individualize the control scheme and/or patient model to represent the inter- and intra-patient variability. Adaptive schemes have achieved safe control while avoiding hypoglycemia in spite of all the challenges facing the closed-loop artificial pancreas (Eren-Oruklu et al. (2009a); Shaller et al. (2006)).

4. Conclusions

Closed-loop insulin delivery by the artificial pancreas gives hope to achieve tight glycemic control in T1DM by reducing the risk of hypoglycemia while solving the problem of hyperglycemia. The prevention of life-threatening hypoglycemia is considered as a possible goal for the first generation of the artificial pancreas before reaching the fully developed device that mimics the function of natural pancreas in night, fasting and prandial conditions. The closed-loop system can be subjected to different modifications to implement control techniques that reduce the risk of hypoglycemia. The feasibility of some of these techniques

has been tested and proved to improve the performance of the closed-loop control and reduce the hypoglycemia episodes. Other techniques are still under study.

While partial results obtained in different artificial pancreas studies are promising, several aspects regarding the fully developed artificial pancreas are still open, and further improvements are needed. Obtaining models from patient's input-output data using advanced modeling techniques is recommended for blood glucose control. Nonlinear identification of insulin-glucose models for control is desirable. Development of advanced control techniques is needed due to the nonlinear behavior, unmodeled disturbances, delay and inaccuracy in measurements, together with modeling errors and patient variability.

Another required improvement is the modeling of different meal contents, since most of the available models are restricted to carbohydrates effect. Using multiple variable control (i.e. considering insulin, glucagon, exercise, stress, etc.), and incorporating the effect of insulin sensitivity change during the day in the control algorithm design, would increase the reliability of models in representing the real conditions of the diabetic patient, and consequently, improve the overall performance of the designed artificial pancreas.

Although the nonlinearity in the insulin-glucose system is quite obvious, the available hypoglycemia detection and prediction algorithms do not consider the nonlinear nature of the system through the different glycemic ranges (Chan et al. (2010)). Taking into account the nonlinearity of the system would be a possible way to enhance the performance of the algorithms and increase their effectiveness in preventing hypoglycemia (Chan et al. (2010)). The inclusion of IOB effect in predicting future hypoglycemic episodes could be another technique to improve the feasibility of these algorithms (Buckingham et al. (2009)). Finally, improving the accuracy and reliability of CGM systems is an essential task, since both control algorithms and hypoglycemia alarms depend widely on CGM measurements. Poorly functioning sensor increases the risk of system-induced and undetected hypoglycemia, while accurate sensor improves the control quality and reduces the risk.

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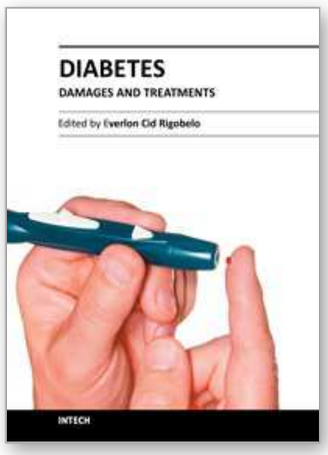

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Over the last few decades the prevalence of diabetes has dramatically grown in most regions of the world. In 2010, 285 million people were diagnosed with diabetes and it is estimated that the number will increase to 438 million in 2030. Hypoglycemia is a disorder where the glucose serum concentration is usually low. The organism usually keeps the serum glucose concentration in a range of 70 to 110 mL/dL of blood. In hypoglycemia the glucose concentration normally remains lower than 50 mL/dL of blood. Hopefully, this book will be of help to many scientists, doctors, pharmacists, chemicals, and other experts in a variety of disciplines, both academic and industrial. In addition to supporting researcher and development, this book should be suitable for teaching.

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