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Blood glucose control algorithms for type 1 diabetic patients: A methodological review

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ABSTRACT

A method for optimal continuous insulin therapy for diabetes patients has been sought since the early 1970s. Although technical and medical advances have been made, a fully automated artificial pancreas to replace the functions of the natural organ is still a research aim. This review compares recent control algorithms for type 1 diabetic patients which automatically connect continuous glucose monitoring and insulin injection, without patient intervention. Black-box model and gray-box model based control strategies are described and their performances are evaluated, with a focus on their feasibility of implementation in a real-life situation. In conclusion, a satisfactory control strategy has not yet been proposed, mainly because most control algorithms rely on continuous blood glucose measurement which is not yet available. Modeling the effect of glucose ingestion as an external disturbance on the time evolution of blood glucose concentration, is now the norm for the control community. In contrast, the effects of physical activity on the metabolic system is not yet fully understood and remain an open issue. Moreover, clinical studies on evaluation of control performance are scarce. Therefore, research on blood glucose control needs to concentrate on advanced patient modeling, control optimization and control performance evaluation under realistic patient-oriented conditions.

Contents

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1. Introduction

Diabetes mellitus is a widespread disease. According to the World Health Organisation (WHO), in 2011 approximately 346 million people suffered from diabetes world-wide. India, China and the USA rank among the top three countries with the largest numbers of diabetic patients [1]. For 2030, an increase up to 552 million patients is prognosed by the International Diabetes Federation (see Diabetes Atlas 2011).

In the human body, the pancreas is responsible for blood glucose control. By producing and releasing the counteracting hormones insulin and glucagon, blood glucose concentration can be decreased or increased, respectively, and stabilized within the physiological range of 70–120 mg/dl.

Diabetes mellitus is characterized by a dysfunction of the pancreas, often in combination with reduced insulin sensitivity. Based on the underlying pathological mechanisms, the disease is classified into three types. Patients suffering from type 1 diabetes are insulin-dependent because the majority of insulin-producing β-cells in the pancreas is destroyed due to an autoimmune reaction. Patients with type 2 diabetes are initially independent of exogenous insulin administration, but will become insulin-dependent over time. These metabolic disturbances are generally caused by reduced insulin sensitivity of the glucose-consuming cells, or deteriorated glucose sensing of the pancreas. Initially, this results in increased insulin production and, finally, in a progressive loss of insulin secretion. Other forms of diabetes which are frequently non-permanent are caused by metabolic stress in critically ill patients, drug-induced hypoglycemia or by pregnancy.

At the moment, insulin-dependent diabetic patients face the daily challenge of manually controlling their blood glucose concentration as shown in Fig. 1. After measuring their blood glucose concentration e.g. with a test strip, they have to determine the appropriate size of the insulin bolus and inject it subcutaneously with an insulin pen or pump. Thus, in the resulting discrete control loop, the patient appears twice: once as the glucose *metabolic system* which has to be controlled and again as the controller itself (*cognitive system*). In the decision-making process, external disturbances and internal system changes have to be taken into account. Since it is difficult to take all effects into consideration, the discrete control method is often accompanied by hypo- or hyperglycemic events. On the one hand, a low blood glucose concentration (<60 mg/dl) may induce an acute medical condition, such as sudden loss of consciousness or even coma, which can be fatal. On the other hand, a high blood glucose concentration (>180 mg/dl) may not be immediately life-threatening but can lead to severe secondary disorders, such as diabetic nephropathy, neuropathy and retinopathy.

To avoid patients having to determine each insulin dose manually, and to limit the large variation in blood glucose concentration, an artificial pancreas needs to be developed as an important scientific research aim. The basic idea is to calculate the required insulin dose using a control algorithm based on continuous glucose measurements, which are obtained via a sensor without human input. For this, a mathematical patient model may support the computation of an appropriate insulin injection. Then, the precise insulin dose is automatically administered via a pump that continuously delivers insulin. Fig. 2 shows a schematic of the resulting closed-loop system in which the patient appears only once, i.e. as the glucose metabolic system to be controlled.

This review evaluates state-of-the-art control algorithms which aim to close the loop for blood glucose control in type 1 diabetic patients. Recent black-box and gray-box model-based control

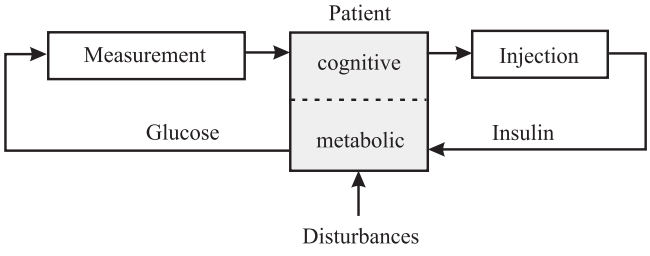

Fig. 1. Schematic of current glucose management process: the patient appears once as the metabolic system to be controlled and again as the controller itself.

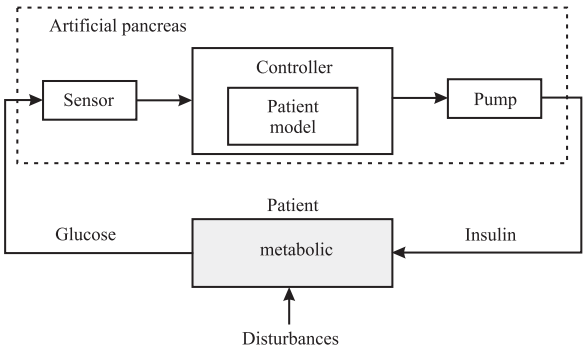

Fig. 2. Schematic of glucose management with an artificial pancreas: here, the patient appears only once as the metabolic system to be controlled.

algorithms are introduced and compared, focusing on application in patients and realization of an implantable closed-loop system. Section 2 deals with the artificial pancreas, highlighting problems related to control design and evaluation. In Section 3, the characteristics of the glucose–insulin metabolic system are described and several mathematical models of the glucose dynamics of a diabetic patient are briefly presented. Sections 4 and 5 introduce black-box and gray-box model-based control strategies followed by a discussion on the remaining technical limitations in Section 6. Finally, Section 7 presents a summary and recommendations for future studies, focusing on implementation of a fully-automated artificial pancreas.

2. Artificial pancreas

2.1. State-of-the-art

Clinical studies by the Diabetes Control and Complication Trial Research Group [2–4] and others [5] show that frequent blood glucose control of diabetes patients results in smaller variations of glucose concentration. A decrease of the incidence of secondary diabetic disorders in turn increases the patient's quality of life and reduces healthcare cost. Thus, successful development of a fully-automated closed-loop system for blood glucose control will benefit both insulin-dependent diabetic patients and the healthcare system.

Since the early 1970s, researchers have aimed to comprehend diabetes and to develop a therapy support system. Until now, however, fundamental methodological and technological problems remain unsolved, such as development of a glucose regulation strategy which accounts for varying insulin sensitivity, effected by physical and psychical stress, and of a continuous glucose sensing method for reliable long-term measurements. Several review articles have focused on the problem of intravenous and subcutaneous control routes for a closed-loop application e.g. [6–10]. The latter paper also focuses on the state of the art in insulin therapy for type 1 diabetic patients and comments on the recently FDA (American Food and Drug Administration) approved proxy for an *in silico* artificial patient, for test and evaluation of controllers.

The state-of-the-art devices include pumps that provide continuous subcutaneous administration of insulin, and sensors that allow continuous subcutaneous measurement of glucose concentration. These devices are commercially available and have tentatively been applied to diabetes patients for open loop [11,12] or initial closed-loop therapy under intense supervision [13–16]. However, for safety reasons, instead of closing the loop, decision-support systems [15] or sensor-augmented insulin-pump therapies [5] are currently preferred in real-life situations. That means that the patient still has to manually control his glucose concentration and is responsible for all related actions. Research on sensors has made considerable progress in recent years [17–21] and tests of implantable insulin pumps are ongoing [22]. Research in the control field for a closed-loop system is also progressing (see below).

2.2. Challenges of control design

2.2.1. Requirements

The design of a control algorithm for blood glucose control is currently challenging due to opposing requirements for control application, i.e.:

- Blood glucose concentration needs to be stabilized in the physiological range of 70–120 mg/dl to reduce the risk of secondary disorders. This aim can be achieved by mimicking the behavior of the natural pancreas injecting both hormones insulin and glucagon.
- The quality of life of diabetes patients should be improved by reducing daily skin penetration. This demand can be satisfied by having as few minimally invasive therapeutic devices as possible, and by requesting as few external patient data as possible e.g. on weight, actual glucose ingestion and muscular activity.

Therefore, an appropriate approach for glucose control should be able to respond to each kind of disturbance, and to rapidly adapt to alternations in the system with as few external system information requirements as possible (see also [7]).

In the control algorithms reviewed here, glucose concentration is measured either in the interstitium or in blood and is defined as controlled variable. The actuating variable is generally the insulin infusion rate, which is applied either subcutaneously or intravenously. As glucagon is not included as a second control variable, it is accepted that the behavior of the natural pancreas cannot be mimicked in a physiological manner. The time delays associated with subcutaneous glucose sensing and insulin injection are a serious problem for control design. Therefore, advanced control algorithms based on patient models are needed which, in turn, require patient information in order to adapt control performance to system changes. Applying a nonlinear assessment technique on the glucose control problem, Hernjak and Doyle concluded that a linear internal model is sufficient for glucose control, but that a simple PD control algorithm is not flexible enough for high performance requirements [23].

2.2.2. Performance evaluation

Evaluation of control performance represents another restriction to control design, as clinical studies cannot be initiated until the safety of the algorithm has been proven. Because an overdose of insulin can be fatal, the step between *in silico* and *in vivo* studies is vulnerable and highly sensitive.

Control performances have recently been evaluated in a Hardware-in-the-loop system in which the patient (Fig. 2) is replaced by mathematical models e.g. by Dassau et al. [24]. However, for reasons of safety, for most of the reviewed control algorithms the subsequent important step from simulation to clinical study has not been made to evaluate the control performance under real conditions.

3. Diabetes patients

3.1. Characteristics

In healthy subjects, blood glucose concentration is regulated by the counter-regulatory hormones: insulin and glucagon which decrease or increase the glucose level, respectively, reacting to external and internal effects. According to [11,25], after ingestion, it takes less than 2 h for blood glucose concentration to return to a normal level. Thereby, pancreatic response to glucose changes can be divided into basal rates and bolus. The natural pancreas releases a basal rate of insulin for general glucose demand. In addition, a sudden uptake of glucose is counteracted by fast release of insulin within approximately 4 min to avoid a hyperglycemic event followed by a slow second phase starting 10 min after the disturbance to achieve normoglycemia. This behavior is called *multiphase insulin response*, see [11,26–29]. Humans also have other sensor modalities like smelling of food or chewing motion which can initiate a fast response of the pancreas transmitted through the autonomous nerve system, a modality which can be labeled as feedforward control. As will be discussed in Section 6.5, the effect of physical stress on blood glucose concentration is not yet fully

understood, and hence, generally neglected when describing the glucose metabolism.

In diabetes patients, when insulin is injected subcutaneously, the time constant of the distribution between interstitium and blood is reported to be 10–20 min [20]. The measurement delay between blood glucose and interstitial glucose concentration is reported to be at least 15 min [8]. Thus, the natural glucose–insulin system is artificially slowed down by up to 40 min in total, caused by the so-called *subcutaneous control route*. Note that in some publications, a total delay of up to 100 min has been assumed [30–32,8].

3.2. Mathematical models

Over the years, researchers modeled the behavior of the glucose–insulin system in diabetes patients by applying either an empirical approach [33,34] or the more attractive compartment modelling technique based on mass balance equations which results in first-principles models, as described in [11,35]. The corresponding glucose–insulin model is referred to here as the *patient model*.

In 1981, Bergman proposed a small nonlinear 3rd-order model [26] followed by Cobelli's more complex proposal in 1984 [36]. The modification of Bergman's model to a type 1 diabetic behavior became generally known as the *minimal model*. The intention of the model is to simulate the response of the blood glucose concentration to an intravenous glucose tolerance test. Consisting of three compartments, the *minimal model* describes the behavior of glucose concentration in plasma $\mathrm{Gluc}_{\mathrm{iv}}(t)$ and insulin concentration in plasma $I_{\mathrm{iv}}(t)$ which are connected by an insulin-effect remote compartment $I_{\mathrm{is}}(t)$

$$\frac{\mathrm{dGluc}_{\mathrm{iv}}(t)}{\mathrm{d}t} = -p_1\mathrm{Gluc}_{\mathrm{iv}}(t) - I_{\mathrm{is}}(t)(\mathrm{Gluc}_{\mathrm{iv}}(t) + \mathrm{Gluc}_{\mathrm{iv,b}}) + d(t) \quad (1)$$

$$\frac{\mathrm{d}I_{\mathrm{is}}(t)}{\mathrm{d}t} = -p_2 I_{\mathrm{is}}(t) + p_3 I_{\mathrm{iv}}(t) \quad (2)$$

$$\frac{\mathrm{d}I_{\mathrm{iv}}(t)}{\mathrm{d}t} = -n(I_{\mathrm{iv}}(t) + I_{\mathrm{iv,b}}) + \frac{\mathrm{IIR}_{\mathrm{iv}}(t)}{V_{\mathrm{I}}}. \quad (3)$$

The concentrations given are related to the basal value of insulin $I_{\mathrm{iv,b}}$ and glucose $\mathrm{Gluc}_{\mathrm{iv,b}}$, intravenous glucose injection is defined as disturbance $d(t)$ and the actuating variable is the intravenous insulin infusion rate $\mathrm{IIR}_{\mathrm{iv}}(t)$. p_1, p_2, p_3 and n are system parameters and V_{I} is an assumed intravenous insulin distribution volume [37,38]. Fig. 3 illustrates a schematic of mass transport according to Eqs. (1)–(3). The dashed line indicates the effect of one concentration on another, and the continuous lines indicate mass transports.

Motivated by these simple glucose–insulin models, other approaches were proposed. In 1985, Sorensen presented a patient model consisting of 19 differential equations including the insulin and glucagon systems. It is often applied as a complex artificial patient for *in silico* control tests [11,30] where it replaces real patient behavior. In 2004, Hovorka et al. introduced a model based on 8 differential equations [39,40] which describes the

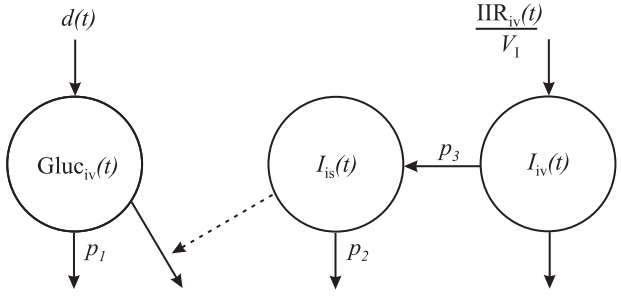

Fig. 3. Scheme of the Bergman's *minimal model*.

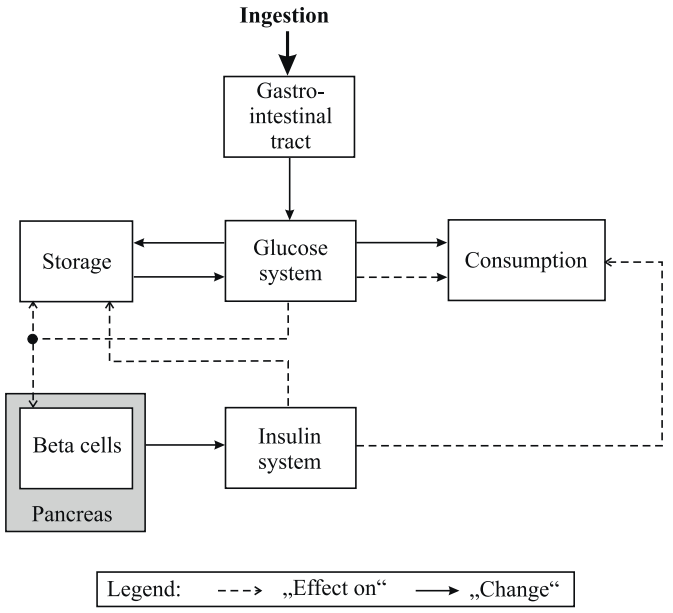

Fig. 4. The model proposed by Dalla Man et al. adapted from [42].

glucose–insulin system behavior in a type 1 diabetic patient with exogenous insulin administration. In parallel, Fabietti et al. presented a 9th-order model which accounts for distinguished food intake of glucose, starch and mixed meals [41]. More recently, in 2007, Dalla Man et al. published a 12th-order mathematical model of healthy humans [42] the schematic of which is shown in Fig. 4. Dashed lines indicate the effects of one system on another, the continuous lines indicate mass transports and the boxes outline the systems or glucose-processing compartments. That model was later extended to diabetic behavior by including subcutaneous insulin administration [43]. In 2008, the FDA approved the use of a computer simulator for *in silico* closed-loop tests,[1] which includes the model proposed by Dalla Man et al. [42,43] as an artificial diabetes patient [44].

Patient models are essential for closed-loop *in silico* (computational) trials, see also Parker and Doyle [45]. Moreover, such patient models are also necessary for *in vivo* trials using model-based closed-loop systems.

4. Black-box model-based control algorithms

4.1. Control idea

The idea behind a black-box model-based control algorithm is to control blood glucose concentration without detailed knowledge of the patient's internal metabolic behavior. This method is deployed if either no internal information about the control system is available, or the behavior of the system is too complex to be described from first principles. In this case, the experimentally acquired input/output behavior of the real patient is the basis for control design. According to [11], black-box based controllers can be broadly categorized as:

- *Curve-fitting:* Measurement data are used as a basis which show the relation between system input and output. By curve fitting, the value of the actuating variable $u(t)$ is chosen depending on the current and aimed value of the control variable, and the approximated input–output relation. For example an adequate algorithm

[1] http://www.artificialpancreasproject.com.

Table 1
Overview of reviewed control algorithms classifying them using the input, output and model type, part I.

Publication	Control algorithm							
	Control strategy	Internal model	Input Gluc(t)	Output IIR(t)	Manual input	Sampling time	Glucose target	Adaptation
Black-box model-based control strategies								
Steil (2006)	PID	–	s.c.	s.c.	–	5 min (CGMS), 20 min BG i.v.	120 mg/dl	√
Dalla Man (2007)	PID	–	s.c.	s.c.	–	continuous	130 mg/dl	–
Gantt (2007)	Adaptive PI	–	s.c.	s.c.	–		81 mg/dl	√
Marchetti (2008)	ext. PID	–	filt.	s.c.	Switch time	5 min	80 mg/dl	√
Palerm (2008)	Run-to-run	–	i.v.	s.c.	–	5 times/day	80 mg/dl	√
Grey-box model-based control strategies								
Parker (1999)	Linear MPC With Kalman filter	Sorensen and Lehman	i.v.	i.v.	*D*, ?	5 min		–
Lynch (2001)	Linear MPC With Kalman filter	*minimal model*, Lehman/Fisher	s.c.	i.v.	?	5 min	81.3 mg/dl	–
Gillis (2007)	Linear MPC With Kalman filter	*minimal model*, Part. Hovorka	s.c.	s.c.	*D*	5 min	80 mg/dl	√
Magni (2007)	Linear MPC	Red. Dalla Man	s.c.	s.c.	*BW*, *D*	30 min	112 mg/dl	√
Magni (2008)	Nonlinear MPC	Dalla Man	s.c.	s.c.	*BW*, *D*	30 min	135 mg/dl	–
Hovorka (2004)	Nonlinear MPC (self-adapting)	Hovorka	i.v.	s.c.	–	15 min	6 mmol/L, Time-variant	√
Marchetti (2008)	Feedforward-feedback Control strategy	ext. Hovorka	i.v.	s.c.	*D*	5 min	Time-variant	√

was applied in the Biostator® as the first bedside glucose control system as described by Clemens et al. [46].

- *Lookup-table control:* Lookup tables can be used as reference to determine the necessary system input for the desired system output. A linearized lookup-table is applied by Furler et al. [47] or the extended control method by Ollerton [48]. For more publications see [11].
- *Rule-based control:* In a clinical situation, nurses assume that a patient has a certain physiological status. Thus, depending on the current and preceding system outputs, the system input is determined. The basis of decision-making is similar to the method used in expert systems. For an adaptive basal therapy, Wang et al. [49] developed a nine zone mosaic to adapt the control gain by prescribing a basal multiplier. Here, the area, spanned by the current glucose value and the rate of change of glucose, is split into several parts which are individually connected to the controller gains.
- *Common control methods:* A more mathematically-based control strategy is dependent on output error and its proportional-integral-derivative (PID) behavior [32,43,50,51]. An alternative method is the repetitive control strategy [52].

Nowadays, for acute diabetes patients, application of a common control method like PID is preferred as it is based on mathematical calculations and no detailed knowledge of the patient's behavior is required. Steil et al. [53] ask the question if the behavior of the β-cells emulate the characteristics of a PID controller since the β-cell include a 3-phase response. Citing studies that state that the β-cell model have used three components: proportional to glucose, rate of change of glucose and a slow increment which corresponds to an integrator, they conclude that the β-cell model is similar to a PID controller. As this method is more likely to be included in an artificial pancreas compared to decision-support systems, the following section focuses on mathematical control strategies. In Tables 1 and 2, the most important control parameters are summarized and will be discussed in Section 6.

Table 2
Overview of reviewed control algorithms classifying them using the input, output and model type, part II.

Publication	Control evaluation				
	Meal	*In silico*	*In vivo*	Settling time	Future adaptation
Black-box model-based control strategies					
Steil (2006)	40–90 g	–	10 type 1		More robust for noise, faster settling time
Dalla Man (2007)	45–70 g, adaptive	Dalla Man	–		Discrete measurement, robust noise response
Gantt (2007)	3–33 mg	mod. *minimal model*	–		Response to meal uptake more aggressively
Marchetti (2008)	60 g	ext. Hovorka	–		Automatic control switch-off, s.c. glucose measurement
Palerm (2008)	Not given	ext. Hovorka	–		Continuous time-dependent insulin infusion
Grey-box model-based control strategies					
Parker (1999)	50 g	yes, Model unknown	–	Approx. 3 h	s.c. glucose measurement Possibly s.c. insulin infusion
Lynch (2001)	50 g	Sorensen	–	Approx. 3 h	s.c. glucose measurement More aggressively performance
Gillis (2007)	50 g	Hovorka +noise, Historical data	Advisory mode	approx. 6 h	Reduction of BG undershoot
Magni (2007)	45–80 g	Dalla Man (full)	–	Approx. 6 h	s.c. glucose measurement
Magni (2008)	45–85 g	Dalla Man	–	Unclear	s.c. glucose measurement
Hovorka (2004)	–	Evaluation Algorithm	10 type 1	–	Meal response s.c. glucose measurement
Marchetti (2008)	60 g ± 50 %	ext. Hovorka	–	min. 5 h	s.c. glucose measurement

4.2. Control strategies

4.2.1. PID control with variable control gain

To mimic the multiphase insulin response in natural blood glucose regulation, Steil et al. applied a time-discrete PID control strategy [27] in preliminary clinical trials using the subcutaneous control route [32]. For reasons of closing the loop virtually, Dalla Man et al. [43] included a continuous extended version of that PID control algorithm in their simulation platform which should be discretised for real-life control application. The realization of the discrete PID control was given by

$$\mathrm{Prop}(k) = K_\mathrm{P} \cdot e(k) \tag{4}$$

$$\mathrm{Int}(k) = \mathrm{Int}(k-1) + \frac{K_\mathrm{P}}{T_\mathrm{I}} \cdot e(k) \tag{5}$$

$$\mathrm{Deriv}(k) = K_\mathrm{P} T_\mathrm{D} \left(\frac{e(k) - e(k-1)}{T_0} \right) \tag{6}$$

$$\mathrm{IIR_{sc}}(k) = \mathrm{Prop}(k) + \mathrm{Int}(k) + \mathrm{Deriv}(k) \tag{7}$$

with $\mathrm{Prop}(k)$ corresponding to the proportional, $\mathrm{Int}(k)$ to integral and $\mathrm{Deriv}(k)$ to derivative behavior of the output error $e(k)$

$$e(k) = \mathrm{Gluc_{meas,sc}}(k) - \mathrm{Gluc_{sp}} \tag{8}$$

at discrete time step k. $\mathrm{IIR_{sc}}(k)$ is the resulting subcutaneous insulin infusion rate as the actuating variable, $\mathrm{Gluc_{meas,sc}}(k)$ indicates the current measured subcutaneous glucose concentration, and $\mathrm{Gluc_{sp}} = 120\,\mathrm{mg/dl}$ denotes the constant glucose setpoint. T_0 is the sampling interval. The parameter T_I and T_D are time constants and the parameter K_P is an amplification factor which is defined to be dependent on the daily insulin requirement of the patient. For dynamic reasons, the time constant T_I was adapted to day and night and T_D to the rise and fall in glucose levels.

In clinical trials by Steil et al. [32], the closed-loop system showed good results with respect to mean glucose concentration and the reduction of hypoglycemic events. However, because participating patients received additional attention from medical staff, the results should only be seen as encouraging waypoint towards feasibility. Concerning hyperglycemia caused by glucose ingestion, it seemed to be infeasible for the PID control algorithm to decrease the blood glucose concentration within the same time as the natural pancreas.

To account for different risks associated with hypo- and hyperglycemic variation, Gantt et al. [50] developed an asymmetric PI control algorithm. Based on subcutaneous glucose measurement and subcutaneous insulin infusion, the proportional gain is adapted as a function of the output error. Negative glucose variations from normal value are treated more aggressively than positive variations. *In silico* performance evaluation based on the modified *minimal model* showed oscillatory response to a single meal uptake such that the glucose setpoint could not be reached until 4 h after glucose ingestion. Assuming a normal day with several meals, the asymmetric PI controller showed superior performance compared to a normal PI strategy. Hypoglycemic events could be reduced but not completely prevented. For the application to a closed-loop scenario, the control algorithm has to be improved to completely impede hypoglycemia and to shorten the time of blood glucose settling to normal state after ingestion.

4.2.2. Switching PID control

Marchetti et al. proposed a switching PID control algorithm with a time-varying intravenous glucose setpoint $\mathrm{Gluc_{iv,sp}}(t)$ (see Eq. (9)) [51] as shown in Fig. 5. Prior to ingestion, the controller was switched off manually. The switching time to restart the controller was determined by a *Decision system* depending on the current blood glucose concentration. The basis of decision-making

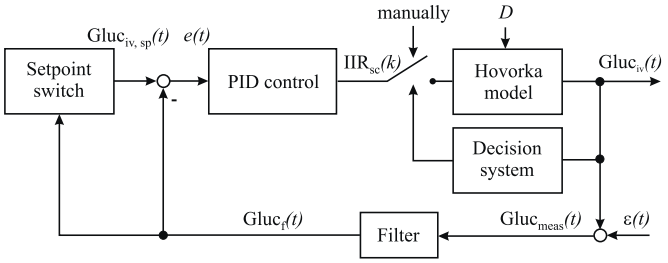

Fig. 5. Switching closed-loop system including the time-varying glucose setpoint $\mathrm{Gluc_{sp}}(t)$ for PID control.

about a controller restart is important as hypoglycemic events may occur when started too early. In addition, the glucose setpoint was changed from time-invariant to time varying in the *Setpoint-switch* according to

$$\mathrm{Gluc_{iv,sp}}(k^*) = \begin{cases} 80\,\mathrm{mg/dl} & \text{if } \mathrm{Gluc_f}(k^*) \le 80\,\mathrm{mg/dl} \\ (\mathrm{Gluc_f}(k^*) - 80) \cdot \exp\left(-\dfrac{k^*}{\tau_\mathrm{sp}}\right) + 80 & \text{else} \end{cases} \tag{9}$$

where k^* is the current sampling time, τ_sp is a tuning parameter and $\mathrm{Gluc_f}(t)$ is the filtered glucose value. The subcutaneous insulin infusion rate $\mathrm{IIR_{sc}}(k)$ was chosen as the control variable.

In silico trials were conducted for a 30-day period using the extended *Hovorka model* to represent an artificial patient [40,54] and applying several daily disturbances of $D = 60\,\mathrm{g}$ glucose. A random noise $\varepsilon(t)$ was added to the closed-loop system to simulate the effect of noise on glucose measurement $\mathrm{Gluc_{meas}}(t)$, and a first-order low-pass *Filter* was included.

The virtual semiclosed-loop trials with manual interruptions showed improved blood glucose concentration behavior compared with a common manual insulin therapy. Here, responses to challenges such as meals of various size and random variations in insulin sensitivity were analyzed. The control performance was also promising with respect to differing patient body weights and initial glucose values. As the switching criteria for the PID controller are dependent on direct blood glucose measurement $\mathrm{Gluc_{iv}}(t)$, the proposed control algorithm needs to be modified before applying it to a subcutaneous control system.

4.2.3. Repetitive control strategy

As an alternative method adapted from the chemical process industry [55], Palerm et al. applied the run-to-run optimization strategy to blood glucose control to find the best-fitting basal insulin injection doses [52]. The idea behind the run-to-run strategy is based on the assumption that one day is similar to the preceding one, including ingestion times and meal sizes. Thus, by dividing the day into four segments as shown in Fig. 6, the basal insulin demand of the preceding day in one segment is similar to the demand during the same segment on the subsequent day including minor changes.

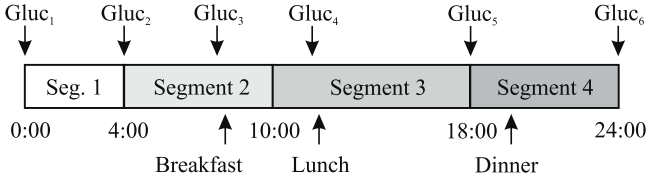

Fig. 6. Nominal basal segments for a day showing blood glucose measurements and ingestion times.

To effectively measure blood glucose concentration, five time points were selected which are indicated by $Gluc_i$, $i = 1, \ldots, 5$, in Fig. 6. For simulation studies over several days, it holds that $Gluc_1 = Gluc_6$. To test the control performance *in silico*, the Hovorka model [40,54] was used as an artificial patient. It was extended with a circadian variation model of insulin sensitivity to mimic the diurnal sensitivity alternation [52]. The control response was compared to manually optimized basal insulin infusion profiles from a group of diabetic subjects. It could be shown that within approximately 6 days, the algorithm converged to a behavior which successfully adjusts the basal infusion rates such that hypoglycemic events do not appear.

The repetitive blood glucose control strategy focuses on the adaptation of the basal insulin infusion rate. It cannot respond to a rapid change in glucose concentration which may cause severe hyperglycemia. Therefore, the control method should be advanced such that it calculates continuous time-dependent insulin infusion doses and counteracts extreme blood glucose variations. The limiting factor for real-life application is the prerequisite, that each day has to pass almost identically to other days.

5. Grey-box model-based control algorithms

5.1. Control idea

Grey-box model-based control strategies involve a model of the control system for two reasons:

- The control algorithm includes a plant model as internal model for prediction properties.
- In the closed-loop system, the plant model is used instead of the real control system for *in silico* control design and control performance evaluation.

With an internal patient model, the control algorithm may predict the blood glucose trajectory and anticipate critical events. Furthermore, the control performance can be safely optimized by using a patient model before the application to a real diabetic patient. Currently, the following control methods are conceivable among others for blood glucose regulation:

- *Feedfoward-feedback control:* By estimating the effect of external disturbances based on a process model, a feedfoward controller preprocesses the control setpoint according to the disturbance long before the disturbance impact can be measured.
- H_∞ *control:* Based on a process model and assumed reasonable state and parameter uncertainties, the control algorithm can be designed for robust control response. Hence, small system variations should not destabilize the controller. H_∞ control methods are advanced robust control strategies which account for worst-case system gains. Several controllers for blood glucose application have already been published like the robust tracking problem by Ruiz-Velázquez et al. [56], a robust controller by Parker et al. [57] which uses linearized system models for the design and the optimal H_∞ insulin injection controller for ICU application by Chee et al. [58].
- *Robust control:* Sliding mode control belongs to the class of robust controllers which include H_∞ control. García-Gabín et al. [59] proposed a two degree of freedom controller. It includes a sliding-mode feedback controller tracking a desired glucose level in conjunction with a feedforward controller which prescribes insulin boli in response to a scheduled meal. Kaveh and Shtessel [60] augmented the system model with an integrator to eliminate the deliterious effects of chattering which is inherent in any sliding-model controller.

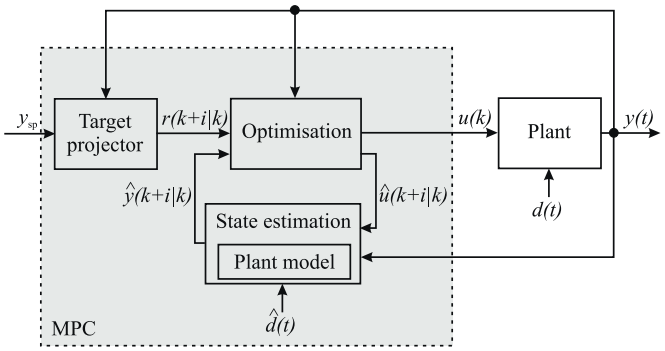

Fig. 7. Scheme of MPC method including optimization algorithm and plant model.

- *Model-predictive control:* One of the strongest motivation for the use of model predictive control (MPC) is the ability to incorporate hard constraints on the state and control variables. Since MPC requires solving an optimization problem repeatedly, computational cost has often been a deterrent for its applications for all but the systems that have very slow dynamics. However, with the development of powerful convex optimization solvers, applying MPC controllers for blood glucose regulation is becoming feasible see [31,37,61]. Dua et al. [62] present a parametric programming approach which generates explicit relationship between the current blood glucose concentration and the constrained optimal control profile.

The following sections are focused on linear model predictive control (LMPC) and nonlinear MPC (NMPC) strategies which include either a linear or a nonlinear internal model, as well as on feedforward control methods.

5.2. Model-predictive control

5.2.1. Strategy

An MPC algorithm is able to synthesize a control action in anticipation of the expected system response. Furthermore, it allows including constraints for the system state and control signals in the design [63]. Therefore, these algorithms are usually applied to systems when it is preferable to operate near constraint bounds specified by physiological limits and when signals are subject to large time delays. Fig. 7 shows a general schematic of a closed-loop system based on MPC. The most important requirement for the application of an MPC algorithm is the knowledge of the entire system state. In biomedical engineering, the first-principles-method is generally applied for plant modeling which results in a state space representation. Transfer function models are rarely used for empirical modeling approaches. Hence, for the case of state space representation, if it is not possible to measure the entire system state, a state estimator has to be included to estimate the unmeasured states.

The strategy of an MPC algorithm is to find the best-fitting process input $u(k)$ with respect to the constraints, such that the future plant output $y(t)$ converges towards the reference trajectory $r(k+i|k)$ to track the setpoint $y_{sp}(t)$. The *Target projector* updates the best-fitting reference trajectory r depending on the setpoint and the current plant output such that y converges as rapidly as possible to y_{sp}. With respect to a priori known disturbances such as periodic disturbances, MPC can compensate for anticipated deviations of the output due to the disturbance. In contrast, unknown (non-periodic) disturbances which have not been approximated by a general disturbance model cannot be anticipated in advance and consequently cannot be accounted for in time.

The strategy can be realized by minimizing an objective function $J(k)$ with respect to Δu over the optimization horizon $H_C \in \mathbb{N}$ depending on the prediction horizon $H_P \in \mathbb{N}$. The objective function is generally given by

$$J(k) = \sum_{i=1}^{H_P} ||r(k+i|k) - \hat{y}(k+i|k)||^2_{Q(i)} + \sum_{i=0}^{H_C-1} ||\Delta\hat{u}(k+i|k)||^2_{R(i)}, \quad (10)$$

where $\hat{y}(k+i|k)$ is the internally predicted plant output and $\Delta\hat{u}(k+i|k)$ is the manipulated actuating variable increment at a future time step, $k+i$, which is predicted at the current time step, k. $Q(i)$ and $R(i)$ are symmetric positive definite matrices in quadratic form, which could be a function of time. The tuning parameters for control adaptation are the horizons $H_P > H_C > 1$, the matrices Q and R and the reference trajectory r. In Fig. 7, $d(t)$ is the real process disturbance and $\hat{d}(t)$ is the estimated counterpart. The simplest assumption in linear models is an additive disturbance.

By minimizing the objective function $J(k)$ with respect to Δu, the convergence of $\hat{y}$ towards r is stated and, thus, the best-fitting process input $\hat{u}(k+i|k)$ for the subsequent discrete time steps i is calculated. Generally, the control output is optimized for the control horizon H_C and the calculated control action is applied for time step k before re-optimizing the control variable after shifting the control horizon by one sampling interval. The prediction horizon H_P and the control horizon H_C remain at the same length which is why the process is called the *receding horizon principle*. For blood glucose application, the process input is optimized after each control step to prevent large deviation between the model and the real system behavior.

5.2.2. Application

The main problem for current closed-loop blood glucose control systems is the delayed system's dynamics caused by the lack of a continuous blood glucose sensor. The aim of applying an MPC algorithm on the trajectory of diabetic glucose concentration is that it can improve control performance by accounting for the time delay. Based on the internal patient model and estimated disturbances, the MPC algorithm can predict critical events and anticipate the impact of the disturbance by adapting the current insulin dose in time [64].

In addition, the control variable $u(t)$ can be bounded by defining constraints with respect to pump mechanism. Hence, the maximal and minimal clinical acceptable insulin injection amount per day, the resulting limited insulin infusion rate and the insulin infusion rate deviation can be considered. Furthermore, blood glucose concentration can be bounded with respect to critical levels.

However, these predictive properties require manual control inputs such as upcoming external disturbances $d(t)$, or individual patient parameters.

5.2.3. State estimation

The most important requirement for the application of an MPC strategy is the need for the complete system state information. If the state is not entirely known, a Kalman filter can be used for the purpose of state estimation.

The idea of the Kalman filter is to calculate the missing individual states based on the known plant inputs, the measured plant outputs, and a linear discrete state-space model of the plant. For each control step, the unknown states are estimated and, depending on the current measurement and a defined Kalman filter gain, the states and the Kalman filter are updated. Details on the Kalman filter are given e.g. in [31,63,61].

With regard to the challenge of blood glucose control, the glucose concentration is generally the sole measured value in order to reduce patient penetration. Thus, all other internal concentrations which are assumed in the linear compartment model are estimated by a Kalman filter, except for the glucose concentration in the compartment at the sensor side. As numerous glucose–insulin models are nonlinear the more complex state estimators such as the extended Kalman filter, unscented Kalman filter or particle filter need to be used to estimate the system states.

5.3. Linear MPC strategies

5.3.1. LMPC based on linear step-response model

Parker et al. [31,64] designed an LMPC algorithm including a self-developed linear step-response model as the internal model. Although the system description is a black-box model and the control approach should be included in Section 4, the authors took the liberty to include it in this section since we gauged the contribution of the paper was more focused on the proposed MPC. Here, arterial blood sampling and intravenous insulin infusion were calculated with a sampling time of $T_0 = 5$ min. To simulate the artificial patient, an extended version of the patient model by Sorensen [30,65] was used. The performance of control response to oral glucose tolerance tests was investigated.

The control algorithm showed satisfactory behavior applying a 50 g glucose meal and including artificial measurement noise. Extended by state estimation with a Kalman filter, the control performance could be improved, meaning that control overshoots were reduced. A limitation of the LMPC algorithm applied in a closed-loop system is the assumption that blood glucose concentration is available instantaneously. The requirement has to be adapted to currently available glucose sensors. To test control performance with assumed subcutaneous glucose measurement, the available glucose concentration was artificially delayed. When a delay of more than 10 min was imposed, the LMPC responded with oscillatory behavior, as demonstrated in [31].

5.3.2. LMPC based on minimal model

Lynch et al. proposed an LMPC method including the 5th-order linearized *minimal model* for blood glucose control application [37,38]. The internal model was extended by a first-order meal disturbance model from either Lehmann et al. [65] or Fisher [66], and a first-order model for glucose transport from plasma to interstitium. The aim was to adjust intravenous insulin injection for type 1 diabetes patients depending on subcutaneous glucose measurements in the presence of several meal ingestions. The control performance was evaluated *in silico* for a 50 g glucose meal including a diabetic version of the Sorensen model [30] as the artificial plant, and measurement and disturbance noise. Compared to other simulated glucose concentration trajectories, the tracking of blood glucose was promising for both meal models. It could be shown, that external glucose impact was completely compensated approximately 3 h after ingestion. For future *in vivo* closed-loop application, the glucose measurement has to be adapted for the subcutaneous control application.

Similarly, Gillis et al. proposed a simple advisory mode LMPC algorithm including the linearized *minimal model* which was extended by submodels of Hovorka et al. [40] to describe the glucose ingestion and subcutaneous insulin infusion [61]. The aim was to adapt the subcutaneous insulin infusion rate based on subcutaneously measured glucose concentration which was disturbed by a 50 g glucose meal. Initial *in silico* tests of the controller performance showed desirable behavior when responding to noisy measurements for small prediction horizons. Furthermore, the prediction mode was extended by adding an unknown disturbance term to the internal model to compensate for subject-model mismatch and the lack of meal information. Without meal announcement, the control advice was not as effective as with ingestion information, but it was

better than a manual insulin therapy. The glucose setpoint could be reached within 6 h following the glucose ingestion.

5.3.3. Discrete LMPC based on Dalla Man's model

Based on the patient model of Dalla Man et al. [43,42], Magni et al. [67,68] proposed a linear discrete MPC algorithm. The aim was to design a control algorithm including a model with input–output representation to avoid state estimation. Hence, the remaining tuning parameters to minimize the resulting quadratic discrete-time objective function $J(k)$ with

$$J(x(k), u(.)) = \sum_{i=0}^{N-1} \left(||y_{sp}(k+i|k) - \hat{y}(k+i|k)||^2_{Q_D} + ||u(k+i|k)||^2_{R_D} \right) + ||y_{sp}(k+N|k) - \hat{y}(k+N|k)||^2_{S_D} \quad (11)$$

with the positive scalars Q_D, R_D and S_D, and the prediction horizon N. Here, $y_{sp}(k+i|k) = 135$ mg/dl are the future setpoints at time $k+i$ which is assumed to be constant, and $\hat{y}(k+i|k)$ is the predicted blood glucose concentration at time $k+i$ which can be calculated by applying a reduced discrete state-space model. For control application, it was assumed that ingestion can be modeled as additive output disturbance and blood glucose trajectory is not far away from the equilibrium point of model linearization. Online-optimization of the controller was renounced and is promised to be a future topic.

To test the control performance *in silico*, the entire glucose–insulin model of Dalla Man et al. [43,42] was used the artificial type 1 diabetic patient. Its behavior was adapted to 100 different patient datasets taken from the FDA approved simulation platform. Comparison with a common PID control method showed improved glucose concentration behavior during 4-day simulations such that the blood glucose concentration was closer to the setpoint and no hypoglycemic event occurred. In future, glucose measurement has to be changed to subcutaneously sensing devices.

5.4. Nonlinear MPC strategies

5.4.1. NMPC with Dalla Man's model

Following the linear and discrete model predictive controller (see Section 5.3), Magni et al. proposed a continuous NMPC algorithm [68] based on the entire nonlinear glucose–insulin model of Dalla Man et al. The objective function in Eq. (11) was changed to the continuous function

$$J(\bar{t}) = \int_{\tau=\bar{t}}^{\bar{t}+H_P} \left[(r(\tau) - \hat{y}(\tau))^T \mathbf{Q} (r(\tau) - \hat{y}(\tau)) + (u(\tau) - u(\bar{t}))^T \mathbf{R} (u(\tau) - u(\bar{t})) \right] d\tau \quad (12)$$

where $\bar{t}$ is the current time when optimization is started and H_P the prediction horizon, $\mathbf{Q}$ and $\mathbf{R}$ are tuning matrices, $r(\tau)$ is the desired blood glucose trajectory, $\hat{y}(\tau)$ denotes the predicted blood glucose concentration, and $u(\bar{t})$ and $u(\tau)$ define the current and future process input, respectively, where the latter has to be piecewise constant. Here, $u(t) = \mathrm{IIR}_{sc}(t)$ denotes the subcutaneous insulin infusion rate. Initial *in silico* trials with Dalla Man's model as the artificial patient showed that the NMPC algorithm has the potential to improve glucose regulation response compared to LMPC application by reducing post-prandial hyperglycemia. However, because NMPC requires increased computational effort compared with LMPC, it needs to be established whether this additional expenditure is worthwhile [68]. As the resulting plots and the given setpoints are not consistent, the settling time of blood glucose concentration after glucose ingestion cannot be clearly determined.

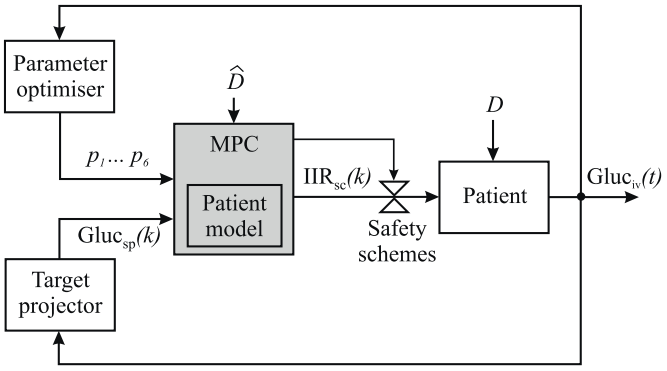

Fig. 8. Block diagram of the adaptive MPC algorithm adapted from [40].

5.4.2. NMPC adaptive to insulin sensitivity

Based on their 8th-order nonlinear glucose–insulin model as the internal model, Hovorka et al. presented the self-adapting NMPC algorithm shown in Fig. 8 [40]. The aim was to control diabetes patients in fasting conditions. Compared to other MPC algorithms, this concept includes the option for self-adaptation of the control algorithm with respect to some insulin sensitivity-dependent parameters. As the insulin sensitivity of glucose-consuming cells changes according to the day time, physical activity, patient age and health status, parameter adaptation may account for system alternation. Thus, the parameters $p_1 \dots p_6$ which describe the insulin sensitivity are re-estimated at each control step depending on the current plasma glucose measurement $\mathrm{Gluc}_{iv}(t)$. Bayesian parameter estimation is applied for this procedure and computes the following objective function $J_p(k)$ to find the best-fitting parameter set in the *Parameter optimizer*-block in Fig. 8

$$J_p(k) = \left\{ \sum_{i=1}^{N_W} w_{k-i} \left[\hat{y}(k-i|p_1 \dots p_6) - \mathrm{Gluc}_{iv}(k-i) \right]^2 + \sum_{i=1}^{6} p_i^2 \right\}. \quad (13)$$

The objective function has to be minimized with respect to the parameter $-2.5 \le p_1 \dots p_6 \le 2.5$ within the retrospective learning window N_W, the length of which is chosen by an internal algorithm. w_{k-i} is a weighting factor which is the reciprocal of the squared measurement error, $\hat{y}(k-i|p_1 \dots p_6)$ is the model predicted blood glucose concentration at time $k-i$ for given parameters $p_1 \dots p_6$, and $\mathrm{Gluc}_{iv}(k-i)$ is the measured blood glucose concentration. The *Target projector*-block determines the reference trajectory for blood glucose concentration depending on the difference from the setpoint of 6 mmol/*l*.

Insulin was injected subcutaneously according to the computed subcutaneous insulin infusion rate $\mathrm{IIR}_{sc}(k)$ and with respect to four *Safety schemes*. Before testing the control performance on real patients, *in silico* tests were performed according to a specialized methodology [69] including life-adapted and system-dynamic adapted variations. The first clinical studies during fasting conditions in 10 type 1 diabetic patients showed promising results, even with simulated glucose measurement delays of 30 min. This procedure was performed to investigate control behavior with subcutaneous glucose sensing. In Fig. 8, D and $\hat{D}$ as the real and estimated glucose ingestion size, respectively, were included for reasons of completeness, but have not yet been used in the control application because fasting conditions were the focus for control validation. In the future, glucose disturbances have to be taken into account for control performance evaluation.

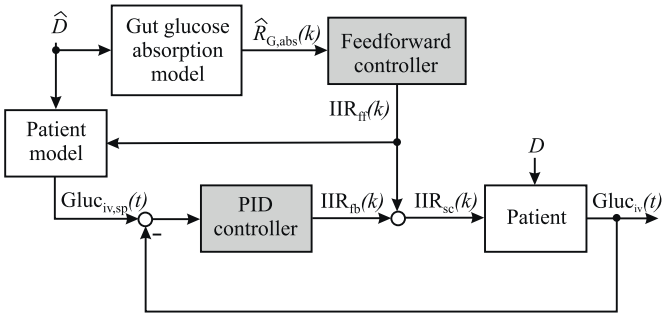

Fig. 9. Block diagram of a feedforward-feedback control strategy for type 1 diabetic patients.

5.5. Feedforward-feedback control

To avoid critical states like hypoglycemia, Marchetti et al. proposed a feedforward-feedback control strategy [51,70]. For it, the PID control algorithm introduced in Section 4 was augmented with a *Feedforward controller*. This modification is intended to enhance the feedback control by online adjustment of the setpoint $\mathrm{Gluc}_{\mathrm{sp}}(t)$ and the actuating variable $\mathrm{IIR}_{\mathrm{sc}}(k)$ through simulated patient behavior. The corresponding schematic is shown in Fig. 9.

Taken from industrial process control, a feedforward control generally consists of a lead-lag approximation of the plant given in Eq. (19). For control design, information is required on

- the effect of subcutaneous insulin infusion rate $\mathrm{IIR}_{\mathrm{sc}}(k) = u(k)$ on blood glucose concentration $\mathrm{Gluc}_{\mathrm{iv}}(t) = y(t)$, and
- the effect of measured glucose disturbance $D = d(k)$ by ingestion on blood glucose concentration $\mathrm{Gluc}_{\mathrm{iv}}(t) = y(t)$.

Thus, the glucose concentration variation induced by step changes of the input variables is approximated by first and second-order transfer functions

$$\frac{\mathrm{Gluc}^{\Delta}_{\mathrm{iv,ff}}(s)}{\hat{R}^{\Delta}_{\mathrm{G,abs}}(s)} = G_{\mathrm{d}}(s) = \frac{K_{\mathrm{d}}}{\tau_{\mathrm{d}} s + 1} \tag{14}$$

$$\frac{\mathrm{Gluc}^{\Delta}_{\mathrm{iv,ff}}(s)}{\mathrm{IIR}_{\mathrm{ff}}(s)} = G_{\mathrm{p}}(s) = \frac{K e^{-\theta s}}{(\tau_1 s + 1)(\tau_2 s + 1)} \tag{15}$$

with $\hat{R}^{\Delta}_{\mathrm{G,abs}}(s)$ defined as the deviated glucose absorption of the gut and $\mathrm{IIR}_{\mathrm{ff}}(s)$ as the deviated insulin infusion rate. The aim of the feedforward control algorithm is to balance the blood glucose concentration effected by external disturbances, i.e. the estimated deviation of blood glucose concentration $\mathrm{Gluc}^{\Delta}_{\mathrm{iv,ff}}(s)$ from steady state has to be reduced. Hence, it holds

$$G_{\mathrm{d}}(s) \cdot \hat{R}^{\Delta}_{\mathrm{G,abs}}(s) + G_{\mathrm{p}}(s) \cdot \mathrm{IIR}_{\mathrm{ff}}(s) = 0 \tag{16}$$

which results in the feedforward control law

$$\mathrm{IIR}_{\mathrm{ff}}(s) = \mathrm{G}_{\mathrm{ff}}(s) \cdot \hat{R}^{\Delta}_{\mathrm{G,abs}}(s) \tag{17}$$

where

$$\mathrm{G}_{\mathrm{ff}}(s) = -\frac{G_{\mathrm{d}}(s)}{G_{\mathrm{p}}(s)} \tag{18}$$

$$\mathrm{G}_{\mathrm{ff}}(s) = -\frac{K_{\mathrm{d}}}{K} \frac{(\tau_1 s + 1)(\tau_2 s + 1) e^{\theta s}}{\tau_{\mathrm{d}} s + 1} \approx -K_{\mathrm{f}} \frac{\tau_3 s + 1}{\tau_4 s + 1} \tag{19}$$

is a lead-lag approximation of the glucose–insulin system which serves as feedforward controller. As glucose uptake has the opposite effect on blood glucose concentration than insulin injection, G_{d} and G_{p} have opposite signs as can be seen in Eq. (18). The remaining parameters τ_3, τ_4 and K_{f} are tuned based on the minimization of the integral absolute value for the control error

$$e(t) = \mathrm{Gluc}_{\mathrm{iv,sp}}(t) - \mathrm{Gluc}_{\mathrm{iv}}(t). \tag{20}$$

The extended glucose–insulin model by Hovorka et al. [40,54] was chosen as the *Patient model* in the feedforward loop as well as the artificial *Patient* for *in silico* trials (see Fig. 9). In addition, its gut absorption submodel was applied separately as *Gut glucose absorption model* to preprocess the input of the feedforward controller. D and $\hat{D}$ denote the real and estimated glucose ingestion amount, respectively, $\hat{R}_{\mathrm{G,abs}}(k)$ is the calculated glucose absorption rate of the gut, and $\mathrm{IIR}_{\mathrm{ff}}(k)$ and $\mathrm{IIR}_{\mathrm{fb}}(k)$ are the prescribed insulin infusion rates dimensioned by the feedforward and feedback control, respectively. Finally, $\mathrm{Gluc}_{\mathrm{iv}}(t)$ denotes blood glucose concentration.

Simulation studies of the closed-loop system showed that the feedforward-feedback control algorithm successfully responds to changes of 50 % of insulin sensitivity and incorrect meal estimates. During simulations, the constraint towards lower glucose concentration, i.e. hypoglycemia, was reported to be violated when insulin boli were over-estimated based on 50 % increased insulin sensitivity. Adaptation of K_{f} according to the current basal insulin infusion rate and upcoming meal size showed reduced hypoglycemic intervals. Hence, setpoint adaptation combined with a feedforward control strategy shows a promising control performance.

This control strategy mainly depends on the accuracy of the patient model, as this influences the actuating variable by a feedforward control. Thus, a more complex dynamic model might be required to improve control performance and to reduce possible subject-model missmatch. In addition, another artificial patient should be applied for *in silico* trials to test robust control performance and for closed-loop application, glucose sensing has to be adopted.

6. Control limitations

6.1. Control overview

Table 1 compares the reviewed control algorithms for blood glucose control with a focus on the most important control parameters. In Table 2, the control performance evaluation is summarized including blood glucose settling time and possible future control adaptations for performance improvement. The first named author and the publication year of the paper indicate the adequate control algorithm which are applied in both tables. Based on the classification used in the present review, the control algorithms are divided into black-box and gray-box model-based strategies. The utilized abbreviations are as follows: *ext. = extended, red. = reduced, mod. = modified* and *part. = partially*, *BW* is the patient's body weight and D the glucose ingestion as external disturbance. Furthermore, glucose concentration $\mathrm{Gluc}(t)$, which represents the controlled variable can be measured subcutaneously (*s.c.*), intravenously (*i.v.*) or is already filtered (*filt.*, Fig. 5). The actuating variable is the insulin infusion rate $\mathrm{IIR}(t)$ which is administered either subcutaneously (*s.c.*) or intravenously (*i.v.*). The control sampling times and the glucose target are also given. Finally, it is important to note whether the control algorithms adapts to intrapersonal changes. Further manual inputs, which are touched but not explicitly named, are marked by question marks.

With regards to the evaluation of the controller, a distinction is made between *in silico* and *in vivo* tests. Table 2 includes information whether or not the control behavior was evaluated with respect to ingestion response, which is simply called a *Meal*, and to the quantity of glucose ingested.

6.2. Performance evaluation

Most of the reviewed control algorithms assume continuous intravenous glucose measurement. However, because no adequate sensor device is available, the algorithms have not yet been applied in clinical studies for closed-loop diabetic insulin therapy.

For those algorithms addressing adequate sensor devices, the step from *in silico* to *in vivo* application did not appear sufficiently safe for the patient. Therefore, the performance of the controllers was generally evaluated by application on simulation platforms only [44,69]. Of the 12 control algorithms discussed here, only 3 algorithms were tested as closed-loop systems in clinical trials which were performed similar to that of Hovorka et al. [40] and Steil et al. [32]. In other clinical trials, the feasibility of closed-loop application was investigated as presented in [22,71,72].

6.3. Time delays

The challenge of mimicking the natural closed-loop behavior with state-of-the-art diabetes therapy devices are the large time delays induced by subcutaneous glucose measurements and the effect of subcutaneously injected insulin on glucose metabolism. Because the response of black-box model-based control algorithms to disturbances is slowed down, a rapid increase in blood glucose cannot be prevented in reasonable time by applying a common PID control algorithm. This control strategy can only be used for initial closed-loop trials.

To stabilize blood glucose concentration at normoglycemia, advanced control algorithms are preferred, such as MPC or feedforward-feedback control. These gray-box model-based strategies include information on the patient's glucose metabolism and, thus, may prevent critical events, depending on the accuracy of the internal model.

6.4. Actuating variables

Due to control simplification and reduced patient penetration, insulin is generally used as the sole system input (cf. Table 1) and the counter hormone glucagon is ignored as an actuating variable.

As insulin is responsible for a decrease in glucose concentration, the controller has to be designed with a slow dynamic behavior in order to avoid hypoglycemic events. This requirement is valid for single-input control algorithm, but is even more important for black-box model-based control strategies than for gray-box model-based ones. Especially the internal patient models in the latter control strategy are modified by supplementary external information such as the patient's body weight. Impending glucose ingestion must be announced in order to adapt the calculations of insulin dose to reduce hyperglycemia and impede hypoglycemic events.

Table 1 shows that almost all gray-box model-based control strategies require supplementary patient information (manual input), which increases the manual effort but improves the control performance. In contrast, the black-box model-based control strategies do not need extra patient information.

6.5. Disturbances

Several external and internal disturbances change the behavior of the diabetic patient:

- Glucose ingestion and physical activity have a considerable impact on the patient's blood glucose concentration. According to patient models reviewed in [11] and summarized in Table 1, glucose uptake through the gastro-intestinal tract is assumed to be well understood. In contrast, the influence of physical activity on glucose metabolism is not yet fully elucidated and is generally ignored. Initial model approaches have been reported by Derouich et al. [73], Breton [74] and Dalla Man et al. [75], and an overview of therapeutic measures is provided by Nagi et al. [76].
- Diurnal variation of insulin sensitivity of the glucose-consuming cells affects the essential amount of plasma insulin. This behavior depends, for example, on eating and sleeping times (see [42]).
- Interpersonal differences also exist: for example, glucose storage and consumption differ between individuals depending on age, health and gender, etc. [77].

Thus, a patient's specific insulin demand depends on external disturbances and intracorporeal metabolic changes, and differs between individuals.

Some of the reviewed control algorithms are able to adapt to the individual patient and minor system changes as indicated with a check in Table 1. Especially black-box model-based control strategies have the advantage that they do not require specific patient information for satisfactory control performance. Hence, PID control seems to be suitable for application to blood glucose control with respect to unknown external disturbances. In contrast, gray-box model-based algorithms are able to control blood glucose concentration in a tighter way, by adapting the internal model to the patient's individual behavior with the information provided. Their performance is based on specifying the time and size of the meal, but, due to missing models, they are not yet able to react to physical activity (e.g. sports).

7. Conclusion

This review compares black-box and gray-box model-based control algorithms, which aim to be applied to a closed-loop blood glucose control in type 1 diabetic patients. Black-box model-based control algorithms have a simple structure, do not require detailed information about the patient's internal behavior, and are easily designed. However, their performance is not optimal due to large time delays, and system changes such as alterations in insulin sensitivity are typically not accounted for except some approaches presented here (see [27,40]).

In contrast, as model-based control algorithms predict the plant behavior they may prevent critical events from occurring. As their response depends on the accuracy of the internal model, control performance degradation is caused by model-induced system simplification and neglected adaptation to the individuals patient's glucose metabolism.

In future studies, the focus should be on the following topics:

- **Control methods:** The focus of control theory should be on control strategies which automatically respond to disturbances without the need of additional patient information, show an optimal performance concerning time delays, and might be extended to include glucagon as a second actuating variable.

  A research group in Boston, MA, investigated control algorithms with insulin and glucagon as actuating variables [78,79], followed by first clinical trials. According to [71], the initial closed-loop trials showed promising behavior, which can be used for further investigations.
- **Performance evaluation:** The proposed control algorithms have to be evaluated *in vivo* to obtain realistic results in relation to consequences for real-life situations. To reduce the step between *in silico* and *in vivo* evaluation see Kovatchev et al. [80,44], preclinical trials could be performed in animals with similar metabolic behavior to humans such as pigs, as proposed by El-Khatib et al. [81]. Also, extension of the patient models by simulating the effect of physical activity will improve *in silico* control evaluation.

- **Therapy devices:** To enhance blood glucose control, a reliable sensor to measure blood glucose on the longer term is required as also stated in [6,8,64]. This will reduce the control problem of large time delays between reaction and measurement. In combination with an implantable insulin pump, an implantable artificial pancreas in a closed-loop system could then be developed.

In conclusion, several problems remain to be solved before an autonomous blood glucose control system becomes a reality. A significant shortcoming of existing sensors is their inability to function for long periods of time without calibration. In addition, the available sensors measure glucose concentration in adipose tissue which is time delayed and dampend compared to blood glucose concentration. Consequently, control strategies have to anticipate disturbances effecting blood glucose concentration. Until such a blood glucose sensor becomes available, control strategies need to be improved by elaborating on the glucose–insulin model so that an optimal insulin therapy for diabetes patients based on subcutaneous devices is possible. For evaluation of control performance, large animal studies should reduce the transition time to clinical trials under real-life conditions.

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