

# Continuous glucose monitoring and closed-loop systems

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## Abstract

**Background** The last two decades have witnessed unprecedented technological progress in the development of continuous glucose sensors, resulting in the first generation of commercial glucose monitors. This has fuelled the development of prototypes of a closed-loop system based on the combination of a continuous monitor, a control algorithm, and an insulin pump.

**Method** A review of electromechanical closed-loop approaches is presented. This is followed by a review of existing prototypes and associated glucose sensors. A literature review was undertaken from 1960 to 2004.

**Results** Two main approaches exist. The extracorporeal s.c.–s.c. approach employs subcutaneous glucose monitoring and subcutaneous insulin delivery. The implantable i.v.–i.p. approach adopts intravenous sampling and intraperitoneal insulin delivery. Feasibility of both solutions has been demonstrated in small-scale laboratory studies using either the classical proportional–integral–derivative controller or a model predictive controller. Performance in the home setting has yet to be demonstrated.

**Conclusions** The glucose monitor remains the main limiting factor in the development of a commercially viable closed-loop system, as presently available monitors fail to demonstrate satisfactory characteristics in terms of reliability and/or accuracy. Regulatory issues are the second limiting factor. Closed-loop systems are likely to be used first by health-care professionals in controlled environments such as intensive care units.

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**Keywords** artificial pancreas, automated insulin delivery, continuous glucose sensing, control algorithm, insulin pump

**Abbreviations** Adicol, advanced insulin infusion using a control loop; CGMS, continuous glucose monitoring system; CSII, continuous subcutaneous insulin infusion; ePID, external physiological insulin delivery; CHO, carbohydrate; IRR, insulin infusion rate; i.p., intraperitoneal; iPID, implantable physiological insulin delivery; i.v., intravenous; LTSS, long-term sensor system; MPC, model predictive control; OGGT, oral glucose tolerance test; PD, proportional–derivative; PID, proportional–integral–derivative; s.c., subcutaneous; SMBG, self-monitoring of blood glucose

## Introduction

Following the first reported use of continuous *ex vivo* glucose measurement in humans by Weller *et al.* in 1960 [1], who deter-

mined glucose excursions after an oral glucose tolerance test (OGTT), Kadish [2] used continuous real-time glucose monitoring to close the loop with an ‘on–off system’ using an intravenous (i.v.) infusion of insulin and glucose (or glucagon) in a subject with diabetes in 1964. The performance of Kadish’s system was hampered by the absence of any meaningful computational aid to titrate insulin/glucose delivery but it should nevertheless be recognized as the first approach to closed-loop glucose control.

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Ten years later, in 1974, two groups independently developed a true ‘artificial endocrine pancreas’. Albisser *et al.* [3,4] in Toronto and Pfeiffer *et al.* [5] in Ulm have combined continuous glucose monitors with algorithms implemented on a micro-computer to automate insulin delivery. The potential to achieve near-normal glucose homeostasis in subjects with Type 1 diabetes was established. The commercial device, the Biostator [6] (Miles Laboratory Inc., Michawaka, IN, USA) was put into production in 1977 and is still used by research laboratories.

Whilst being a pioneering device, the Biostator suffers from serious limitations. It needs constant supervision. It is a bulky device, withdrawing and discarding continuously venous blood to measure glucose levels *ex vivo* using an oxidase-containing membrane. The original insulin titrating algorithm was linked to the rate of glucose change by Albisser *et al.* [3] with modifications by Botz [7], Marliss *et al.* [8], and Kraegen *et al.* [9] to reduce postprandial hyperglycaemia and hyperinsulinaemia. These were reviewed by Broekhuysen *et al.* [10], who concluded that none of the algorithms was superior and that further work was required to achieve normalization of the glucose concentration.

In the last two decades, considerable technological progress has been made. Three continuous or semicontinuous monitors have received regulatory approval. Since the introduction of continuous subcutaneous insulin infusion (CSII) [11], insulin pumps have been miniaturized and their reliability improved. Novel titrating algorithms have been postulated, adopting new control paradigms. All these factors have advanced the progress towards a truly personal wearable treatment system. Several prototypes have been developed and tested in clinical settings. However, the lack of availability of a glucose monitor with adequate properties hinders further progress and the development of a commercially viable system.

The present review describes the development of closed-loop systems and their testing with continuous glucose monitors and presents a review of various types of electromechanical closed-loop solutions. This is followed by the description of existing prototypes and associated glucose sensors. A literature review of English articles was undertaken from 1960 to 2004 using PubMed, Web of Science, and author’s private databases. Some German articles were also considered if they were deemed to contain essential information.

## Types of closed-loop system based on meal dosing

An important feature of a closed-loop system is the way it handles mealtime insulin delivery.

First, the glucose controller delivers insulin without information about the time of the meal or its size. Insulin is administered purely by evaluating the rise in (postprandial) glucose in a way similar to glucose responsive insulin secretion from the  $\beta$ -cell cell. This approach can be termed a ‘fully closed-loop’ to signify the nature of its autonomous function.

At the other end of the spectrum, the glucose controller is provided with the information about the time and size of the

meal. This information is normally used by the controller to generate advice, in an open-loop manner, on prandial insulin bolus. This is termed ‘closed-loop with meal announcement’ or ‘semiclosed-loop’ control.

The third approach provides the controller with information about the time but not size of the meal. This information is used by the controller to switch into a more aggressive mode of insulin delivery to counteract postprandial glucose rise. This can be termed ‘closed-loop with qualitative meal announcement’.

Most closed-loop systems adopt the former two approaches. Only one system, recently described, has adopted the solution with qualitative meal announcement [12].

## Types of closed-loop systems based on body interface

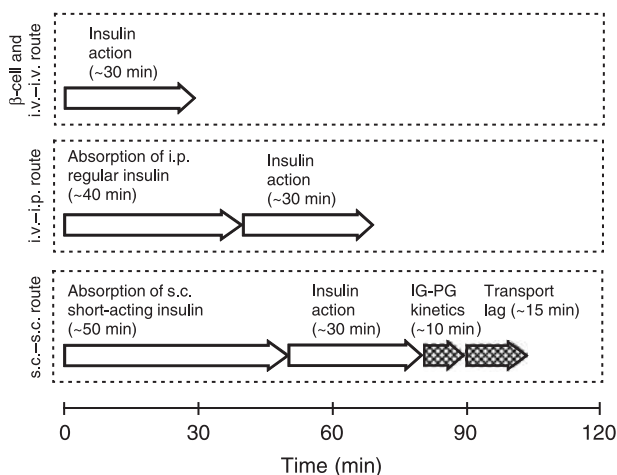
Two major practical solutions of a closed-loop system based on the body interface exist. The s.c.–s.c. approach adopts the s.c. route for both glucose monitoring and insulin delivery. The i.v.–i.p. approach relies on intravenous glucose monitoring and intraperitoneal insulin delivery.

### Subcutaneous–subcutaneous closed-loop system

A minimally invasive solution, the s.c.–s.c. approach has arguably the greatest potential to achieve widespread application. It can benefit from the experience of over 200 000 external insulin pump users [13]. The s.c.–s.c. approach is unlikely to be compatible with a fully closed-loop system although opposite claims have been made [14]. The main reason is the presence of delays, see Fig. 1, disallowing effective compensation of large disturbances such as meals.

The delay because of insulin absorption (50 min with short-acting insulin analogues [15]), insulin action (30 min and more [16]), interstitial glucose kinetics (10 min [17]), and the transport time for *ex vivo*-based monitoring systems such as those based on the microdialysis technique (10–30 min [18]) results in an overall 100 min or more time lag from the time of insulin delivery to the peak of its detectable glucose-lowering effect. Thus, once administered, insulin will continue to increase its measurable effect for nearly 2 h, complicating effective lowering of glucose concentration following meal ingestion using a fully closed-loop approach. First, a glucose increase has to be detected but this can happen only after at least a 10–40 min lag. Based on the analysis of a short section of the s.c. glucose profile, the system must determine that a meal has been digested and administer an appropriate insulin dose. The ability of the system to compensate subsequently for a ‘misjudged’ insulin dose is compromised by long delays and the inability to ‘withdraw’ insulin once administered.

It is likely that users of the s.c.–s.c. approach will have to enter nutritional information to assist in the delivery of the prandial insulin dose. Information about exercise activity may also be needed.



**Figure 1** Delays associated with the i.v.–i.v., i.v.–i.p., and s.c.–s.c. closed-loop control routes. The top block shows that the total delay in an i.v.–i.v. system (and also the native  $\beta$ -cell) is about 30 min, representing the delay in insulin action. The middle block shows that the i.v.–i.p. route has two delays totalling 70 min, representing the time-to-peak of the plasma insulin concentration following intraperitoneal administration of regular insulin (40 min) and the time it takes insulin to cross from the plasma to the interstitial fluid, to be bound to the insulin receptor, and to activate the glucose transporter system (30 min). The bottom block indicates the four delays associated with the s.c.–s.c. route. The time-to-peak of the plasma insulin concentration for short-acting insulin analogues such as lispro and aspart is 40–50 min. It is followed by the delay in the insulin action. The two sensing delays are denoted by crosshatched arrows. The delay associated with glucose diffusion from the plasma to the interstitial fluid is about 10 min. This is optionally followed by a device-dependent lag for *ex vivo* measurement systems representing the transport of the interstitial fluid from the s.c. tissue to the sensing unit. This transport lag is present in microdialysis or microperfusion-based systems.

### Intravenous–intraperitoneal closed-loop systems

The i.v.–i.p. approach has a marginally greater potential to enable a fully close-loop system. The delays in the system are slightly shorter (about 70 min), see Fig. 1, although still longer than physiological delays (30 min). This may reduce the quality of glucose control as reported in an earlier study comparing closed-loop with intravenous and intraperitoneal insulin delivery [19]. With implantable pumps, insulin is normally infused intraperitoneally, achieving a more physiological insulin delivery with the portal extraction/peripheral gradient, which has been perceived as a major advantage of the approach.

There is limited experience with the use of implantable pumps. Worldwide, only a little over 1000 pumps have been implanted to date [20]. The pumps are more expensive and need surgical implantation. The major complications leading to premature pump removal include ‘pump-pocket’ infections and device failures [21]. The pumps use highly concentrated U400 insulin and are refilled every 40 days. Surprisingly, the delay in insulin absorption is similar to that experienced with subcutaneous administration of short-acting insulin with a

40 min time-to-peak of plasma insulin [22]. No data exist about intraperitoneal administration of short-acting insulin. Stability of insulin is a concern because of insulin aggregation [21].

Several major hurdles must be overcome before a fully implanted closed-loop system for long-term glucose control is widely available [23].

### Other approaches

The i.v.–i.v. approach employing intravenous glucose sampling and intravenous insulin delivery has, at present, a place in special situations, such as in critically ill patients. Subject to s.c. monitoring being suitable for the critically ill, an open question currently being investigated [24], s.c. sensing can be combined with i.v. insulin delivery. This is explored by the EC funded project Closed Loop Insulin Infusion for Critically Ill Patients (Clinicip; <http://www.clinicip.org>).

### Control algorithms

A wide spectrum of control algorithms has been proposed to titrate insulin in a closed-loop fashion, see a review by Parker *et al.* [25]. For a clinical evaluation, two main categories have been employed, classical feedback control embodied in the proportional–integral–derivative (PID) controller [3,26,27], and model predictive control (MPC).

### Feedback control

The principles of feedback control can be exemplified using the PID controller. The controller continuously adjusts the insulin infusion rate (IIR) by assessing glucose excursions from three viewpoints, the departure from the target glucose (the proportional component), the area-under-curve between ambient and target glucose (the integral component), and the change in ambient glucose (the derivative component). IIR is computed as

$$IIR = K_p(G - G_t) + K_I \int (G - G_t) + K_D \frac{dG}{dt} \quad (1)$$

where  $K_p$ ,  $K_I$ , and  $K_D$  represent weights (gains) given to the proportional, integral, and derivative components, and  $G$  and  $G_t$  represent ambient and target glucose levels, respectively. A high proportional gain  $K_p$  makes the control unstable. The integral component is added to avoid offset, i.e. a deviation of ambient and target glucose at equilibrium. The derivative component is critical for control when glucose changes rapidly. Some controllers include a subset of components, for example, a proportional–derivative (PD) controller includes the proportional and derivative components to improve robustness.

Tuning of the controller corresponds to the determination of constants  $K_p$ ,  $K_I$ , and  $K_D$ . This can be achieved by an offline assessment using, for example, pharmacokinetic modelling [14]. The constants can also be estimated from the subject’s daily dose.

### Model predictive control

Model predictive control is at the forefront of the recent research with contributions, for example, by Parker *et al.* [28], Lynch and Bequette [29], Trajanoski *et al.* [30], and Hovorka *et al.* [31]. The MPC approach is most suitable for systems with long delays and open-loop characteristics [32] and therefore well suited for the s.c.–s.c. approach with meal announcement.

The vital ingredient of model predictive control is a model linking insulin infusion and meal ingestion to glucose excursions. This can be a physiological model representing fundamental gluoregulatory processes [31] or a ‘black-box’ model disregarding the physiological insights but learning the insulin–glucose relationships using pattern recognition techniques [30]. Both approaches can benefit from a wide range of models of the gluoregulatory system [33–36].

The model representation enables simulation of ‘what if’ scenarios, in particular the prediction of future glucose excursions resulting from projected insulin infusion rates. These prediction capabilities enable the construction of insulin infusion rates leading to a predefined ‘target’ glucose excursion. The insulin infusion rate is obtained by minimizing the difference between the model-predicted glucose concentration and the target glucose trajectory over, say, a 4-h prediction window corresponding to the duration of action of short-acting insulin. The minimization is carried at each control step, normally every 10–15 min.

The development of the MPC controller consists of selecting a suitable model, obtaining model parameters, and deciding on other elements, such as the length of the prediction window and the form of the target trajectory. Adaptive techniques allow model parameters to be individualized either off- or online.

### Performance assessment

In this section, criteria for the assessment of closed-loop systems are discussed.

#### Closed-loop control

No widely accepted measures exist to assess specifically the performance of closed-loop systems. As a measure of efficacy, the mean glucose over 24 h, the mean overnight glucose, the pre-meal glucose concentration and postprandial glucose (2 h) have all been reported. Glycated haemoglobin is not relevant as prototypes are used only for several days. The number of hypoglycaemic events provides a measure of safety. Occasionally, the per cent of time spent in clinically relevant glucose ranges is reported.

Measures based on ‘averaging’ glucose values disregard information about fluctuations. The existing measures taking this information into consideration, such as the mean amplitude of glucose excursions (MAGE) [37], Schlichtkrull’s *M*-value [38], and *J*-index [39], might not be appropriate given the continuous nature of glucose measurement during closed-loop control.

Recently, a grading system specifically designed to assess closed-loop systems from the clinical viewpoint has been suggested [40]. The system introduces six grades according to the level of control and the therapeutic intervention outside-meal and postprandial conditions. The outcome of grading is the quantification of time spent in each grade.

### Prototype systems

In this section, a review of reported prototypes of the closed-loop system is presented. Table 1 lists clinical trials of the prototypes in subjects with Type 1 diabetes.

#### Shichiri’s group

The group led by Professor Shichiri, based in Kumamoto, Japan, has contributed extensively in the field. The achievements of the group are summarized in an edited monograph [41]. As early as 1975, the group developed a prototype of an artificial endocrine pancreas [41], which was later made into a compact bedside version, STG-22 (Nikkiso Co. Ltd, Tokyo, Japan) [42]. The group presented enviable results but these failed to be confirmed by others.

The group developed a prototype wearable artificial pancreas using the s.c.–s.c. route with unmodified short-acting insulin [43,44] and a short-acting insulin analogue [14], and most recently the s.c.–i.p. route [45]. The latest versions of the closed-loop system use a microdialysis-type [46] or a ferrocene-mediated needle-type [45] glucose sensor. The group claim that both work over a period of 7 days without any *in vivo* calibration, followed by 14 days with one point calibration [47].

The authors do not describe the performance of the sensors using the Clarke error grid [48,49]. They report a correlation coefficient of 0.95 between the sensor and a reference blood glucose measurement for the first 4 days of sensor deployment [46].

The fully s.c.–s.c. closed-loop system with insulin lispro also showed impressive results, achieving near ‘perfect’ glucose normalization over 24 h [14,47]. In five lean, well-controlled ( $HbA_{1c}$  6.7–8.2%) subjects with Type 1 diabetes, the post-meal glucose was 9.5 mmol/l and postprandial glucose was normalized within 3 h to 4.0–5.5 mmol/l without hypoglycaemia. The standard deviation of between-subject glucose variability was approximately 1 mmol/l.

These results are remarkable given that a non-adaptive PD controller was used

$$IIR(t) = K_p G(t) + K_D \frac{dG(t)}{dt} + K_C \quad (2)$$

where  $IIR(t)$  is the insulin infusion rate,  $G(t)$  is the monitored glucose concentration, and  $K_p$ ,  $K_D$ , and  $K_C$  are constants which are dependent on the type of insulin delivery, subcutaneous vs. intravenous, and also on the type of insulin, unmodified short-acting vs. short-acting analogue insulin lispro [14,47].

The author’s research group have tested this controller on a glucose simulator with the intention to carry out clinical

**Table 1** Clinical studies with s.c.–s.c. or i.v.–i.p. closed-loop control in subjects with Type 1 diabetes

<i>n</i>	Duration of control (h)	Number of meals	Sensing/infusion	Sensor	Insulin	Algorithm	Control interval (min)	Type of control ††	Glucose control (plasma glucose unless stated otherwise) (mean ± SD)	Ref.
6	72	6	s.c.–s.c.	Needle-type [44]	Regular	§PD	††1	f-cl	Hypo not reported; <i>M</i> -value 15 ± 4; mean glucose 6.1 ± 0.5 mmol/l; MAGE 73 ± 14 mg/dl	[44]
5	5	1 (OGTT)	s.c.–s.c.	Needle-type [46]	Regular	§PD	††1	f-cl	Hypo not reported; postprandial(1.5 h) 10.6 ± 0.9 mmol/l; late postprandial (5 h) 2.8 ± 0.4 mmol/l	[14, 47]
5	5	1 (OGTT)	s.c.–s.c.	Needle-type [46]	Lispro	§PD	††1	f-cl	No hypo (< 2.8 mmol/l); postprandial (1 h) 8.5 ± 0.5 mmol/l;	[14, 47]
5	24	3	s.c.–s.c.	Needle-type [46]	Regular	§PD	††1	f-cl	Hypos observed; glucose between peak (b'fast postprandial) 12.5 ± 1.0 mmol/l and nadir (before dinner) 2.7 ± 0.3 mmol/l	[14, 47]
5	24	3	s.c.–s.c.	Needle-type [46]	Lispro	§PD	††1	f-cl	No hypo; near normal control	[14, 47]
9	8	No meals	i.v.–s.c.	*Offline	Lispro	MPC	15	cl-ma	†No hypo (< 3.3 mmol/l); ‡ 6.1 ± 0.6 mmol/l	[52]
6	8	No meals	**Simulated s.c.–s.c.	*Offline	Lispro	MPC	15	cl-ma	†No hypo (< 3.3 mmol/l); ‡6.6 ± 0.8 mmol/l	[53, 54]
6	14	1	**Simulated s.c.–s.c.	*Offline	Lispro	MPC	15	cl-ma	†No hypo (< 3.0 mmol/l); preprandial 7.0 ± 1.1 mmol/l; ¶6.3 ± 1.6 mmol/l	[105]
11	26.5	3	**Simulated s.c.–s.c.	*Offline	Lispro	MPC	15	cl-ma	1 hypo (< 3.3 mmol/l); 84% glucose values between 3.5 and 9.5 mmol/l	[55]
5	24	3	s.c.–s.c.	Viscometric [56]	Lispro	MPC	15	cl-ma	No hypo (< 3.3 mmol/l); 87% sensor values between 3.5 and 9.5 mmol/l	[57]
6	27.5	5	s.c.–s.c.	CGMS/Guardian [58, 106]	Lispro	PID	††1–5	f-cl	Hypo not reported; preprandial 5.8 ± 1.2 mmol/l; postprandial (2 h) 9.8 ± 1.6 mmol/l	[82]
4	48	6	i.v.–i.p.	LTSS [83, 84]	U400	PID	††1–5	f-cl	Hypo not reported; 84% glucose values between 4.4 and 13.3 mmol/l	[88]
12	32	4	s.c.–s.c.	SCGM1 [89]	Lispro	Empirical	10	cl-ma	1.1 hypo per day per subject; 56% glucose values between 5.0 and 8.3 mmol/l	[90]
12	7	1	s.c.–s.c.	Comparative microdialysis [94]	Lispro	MPC	12	cl-ma	Hypo not reported; mean glucose 8.0 ± 2.3 mmol/l; postprandial increase 3.0 ± 1.6 mmol/l	[95]
8	24	3	s.c.–s.c.	Comparative microdialysis [94]	Lispro	MPC	12 (day) 36 (night)	cl-ma	One hypo (< 3.3 mmol/l) mean glucose 7.8 ± 0.7 mmol/l; postprandial increase 2.9 ± 1.3 mmol/l	[93, 96]

\*Beckman Glucose Analyzer 2.

\*\*i.v. glucose measurements delayed by 30 min.

†Number of hypos as a result of the controller throughout the study.

‡Mean ± SD in the last 2 h of control.

§Proportional–derivative controller.

¶Over 4 h following meal.

††Not reported, an estimate from plot(s).

†††f-cl, fully closed-loop; cl-ma, closed-loop with meal announcement.

testing. However, even within the simulator it was not possible to reproduce the reported results. Hypoglycaemia and hyperglycaemia were observed as the basal need for the simulated subjects was between 80 and 430  $\mu\text{U}/\text{kg}/\text{min}$ , whereas the formula is tuned for subjects with a basal rate of 225  $\mu\text{U}/\text{kg}/\text{min}$ . A possible explanation is that Japanese subjects are more homogeneous in terms of insulin needs and in the absorption rate of food from the intestine, with the latter possibly attributable to the Japanese diet.

#### Advanced insulin infusion using a control loop (Adicol) project

In 2000, a consortium of academic, clinical and industrial partners commenced work on a 3-year EC-funded project Adicol [50]. The modular concept of the Adicol's extracorporeal s.c.–s.c. artificial pancreas consisted of a minimally invasive subcutaneous glucose system, a handheld PocketPC computer, and an insulin pump (Disetronic D-Tron, Burgdorf, Switzerland) delivering subcutaneously insulin lispro.

By the end of the project, significant progress had been made in the development of the glucose monitor, which utilized open-flow microperfusion [51] and an enzymatic glucose sensor. However, loss of sensitivity prevented the use of the monitor in the clinical evaluation of the glucose controller. To overcome this limitation, throughout the Adicol project the intravenous glucose measurement was used, delayed by 30 min to simulate the lag associated with s.c. glucose sampling, which includes a physiological 10–15-min lag [51] and a 10–15 min transport and sensing lag with the set-up envisaged for the Adicol glucose monitor.

Adicol adopted a non-linear MPC, which included a model based on a two-compartment representation of glucose kinetics with three insulin actions, the stimulation of glucose distribution/transport, the stimulation of glucose kinetics, and the suppression of endogenous glucose kinetics [16] extended by submodels representing the absorption of short-acting insulin lispro, the insulin kinetics, the renal clearance of glucose, and food absorption from the intestine.

The MPC approach was combined with an adaptive Bayesian technique to individualize the glucoregulatory model to represent the inter- and intrasubject variability [31]. The individualization was integrated within the control algorithm and was executed at each 15-min control cycle. This facilitated fast deployment of the algorithm without the need for a 'separate' experiment or procedure to determine individual parameters. The control commenced once glucose was measured for 90–180 min.

Clinical evaluation of the MPC controller started with a feasibility study followed by efficacy studies. The feasibility study assessed the ability of the MPC controller to achieve normoglycaemia during fasting [52]. Glucose was measured intravenously to simplify the control problem; insulin lispro was infused subcutaneously (the so-called i.v.–s.c. route), see Table 1. Nine subjects with Type 1 diabetes treated by CSII ate a standardized breakfast at 08.00 h and their glucose levels were controlled by the MPC from 11.30 h for 8 h without

further meal ingestion. No hypoglycaemia event ( $< 3.3$  mmol/l) occurred as a result of the insulin infusion by the MPC. At the end of the study, the plasma glucose concentration was 6.1 mmol/l with a target of 6.0 mmol/l. A reduction of the standard deviation of plasma glucose from 3.3 mmol/l at the beginning to 0.6 mmol/l at the end of the control period demonstrated the ability to achieve the target in all subjects.

The second study evaluated the efficacy of the MPC controller during fasting conditions with 'simulated' (i.e. delayed) s.c. glucose sensing [53,54]. Plasma glucose was delayed by 30 min. Six subjects with Type 1 diabetes treated by CSII were studied using an experimental design as in the first study. No hypoglycaemia event was observed as a result of the MPC control. At the end of the study, the mean plasma glucose was 6.6 mmol/l (target 6.0 mmol/l). From the start to the end of the control period, the standard deviation reduced from 2.4 to 0.8 mmol/l. The delay in i.v. glucose values by 30 min did not influence the quality of control [54].

The next study evaluated feasibility of the prandial bolus advice generated by the MPC algorithm with simulated s.c. sensing. Blood glucose in six subjects with Type 1 diabetes treated by CSII was controlled from 22.00 until 12.00 h the following day. The MPC generated a prandial bolus for the standardized breakfast of 40 g carbohydrate (CHO) at 08.00 hours. No hypoglycaemia event ( $< 3.0$  mmol/l; this slightly different limit was set by the clinical investigator) as a result of the MPC control was observed. The glucose concentration before breakfast was at 7.0 mmol/l (target 6.0 mmol/l), i.e. slightly higher than in previous studies. The standard deviation was reduced from 4.6 mmol/l at the start to 1.1 mmol/l before breakfast. The bolus controlled the post-prandial glucose well with a glucose concentration of  $6.3 \pm 1.6$  mmol/l between 08.00 and 12.00 h.

The next study assessed the efficacy of the MPC controller with 30-min delayed glucose sampling over 24 h in 11 subjects with Type 1 diabetes [55]. Pretreatment involved glucose normalization, followed by dinner with an individually determined prandial bolus at 18.00 h, and control by the MPC from 19.30 to 22.00 h the following day. The controller determined prandial boluses for breakfast at 07.00 h, lunch at 12.00 h, and dinner at 18.00 h (all day 2).

One hypoglycaemia event (nadir at 3.3 mmol/l) as a result of the MPC control was recorded. The highest glucose concentration was 13.3 mmol/l following breakfast; 84% of glucose measurements were between 3.5 and 9.5 mmol/l.

The Adicol project was unable to assess the controller with a working s.c. monitor. This was achieved after the completion of the Adicol project using the viscometric glucose sensor [56]. Five subjects with Type 1 diabetes treated by CSII were studied for 24 h [57]. The control period commenced after a 90-min monitoring period at 13.00 h on day 1, lasted until 13.00 h on day 2, and included the determination of prandial boluses for lunch at 14.00 h, dinner at 19.00 h (day 1), breakfast at 07.00 h, and lunch at 11.00 h (day 2). No hypoglycaemia event ( $< 3.3$  mmol/l) as a result of the MPC control was

observed. Overall, 87% of sensor values were between 3.5 and 9.5 mmol/l. Outside the 3 h post-meal periods, 74% of sensor measurements were in the range 3.5–7.5 mmol/l. The study demonstrated the feasibility of closed-loop control with meal announcement using the MPC controller.

### Medtronic MiniMed closed-loop project

In 1999, the Continuous Glucose Monitoring System (CGMS; Medtronic MiniMed, Northridge CA, USA) [58] became the first commercially available continuous glucose monitor. The system adopts Holter style monitoring to store up to 3 day's data for retrospective analysis. CGMS is the most studied monitoring system.

CGMS employs an electrochemical sensor inserted into the subcutaneous tissue connected by a lead to a pager-sized unit for data preprocessing and storage. The sensing adopts the hydrogen peroxide-based enzyme electrode [59]. A signal is sent to the unit every 10 s, a digitally filtered value is stored every 5 min. The system is calibrated using self-monitoring of blood glucose (SMBG) using commercially available meters. At least four calibrations are recommended per day.

In a recent study by Sachedina and Pickup in subjects with Type 1 diabetes [60], CGMS gave 95% values in zone A and B of the Clarke error grid and 97% in the consensus grid. The correlation between the sensor and SMBG data was 0.85. The mean absolute deviation was 15%. The sensor failure rate was 28% of the total inserted sensors. The failures were primarily because of rapid fluctuations of the current signal. Similar results have been observed by others [61,62]. The new 'gold' sensor introduced in November 2002 is more accurate than the original sensor (the mean absolute deviation 15 vs. 20% [63]).

The major issue with CGMS is the failure of sensors and overestimation of hypoglycaemia and, to a lesser degree, hyperglycaemia episodes [64,65]. Reproducibility of the measurement using two sensors was also questioned [66]. Some authors have discussed the utility of the sensed glucose profiles for insulin titration and concluded that it cannot replace but can complement conventional glucose meters [67], confirming the intended use of the CGMS [68]. Others suggest potential for education, increased motivation, and treatment adjustment to reduce hypoglycaemia events, provided the limitations are understood [69–72].

Recently, a new system, the Guardian Continuous Monitoring System (Medtronic MiniMed), has been introduced with real-time hypo- and hyperglycaemia alerts [73]. In a two-period, randomized, multicentre study in 71 subjects with diabetes, the system detected hypoglycaemia (< 3.9 mmol/l) with 67% sensitivity, 90% specificity, and 47% false alerts. Hyperglycaemia (> 13.9 mmol/l) was detected with similar characteristics but with a lower (19%) false alert rate.

In combination with the CGMS/Guardian sensor, an external physiological insulin delivery (ePID) has been developed. The paradigm adopted in the design of a controller is to emulate the characteristics of the  $\beta$ -cell, in particular the first and second

phase insulin secretion as observed during the hyperglycaemic glucose clamp [74,75]. This expresses the authors' belief that these two phases are necessary and possibly sufficient to achieve euglycaemia in a fully closed-loop setting [26]. However, the classical first phase does not exist under physiological conditions. The meal-stimulated insulin response to glucose is enhanced by the concomitant action of incretins and neural responses to nutrient ingestion [76].

A suitable solution was found by adopting a PID controller [77] which can be considered to reproduce the first phase insulin secretion by linking insulin administration to the rate of change in glucose concentration (the proportional component of the controller) and the second phase by linking insulin administration to the difference between the ambient and target glucose (the integrative component of the controller). The s.c.–s.c. approach encounters significantly longer delays than the  $\beta$ -cell in healthy subjects (100 vs. 30 min) and thus the controller works under different, less favourable conditions, see Fig. 1. There are other important factors determining meal-related insulin secretion in healthy subjects, such as the incretin effect [78], amino acids without or in combination with incretin hormones [79] and cephalic insulin release [80].

The first studies, with a fully closed-loop, were carried out in dogs [81] starting from induced hyperglycaemia (25 mmol/l) with the aim of achieving 6.7 mmol/l. Two meals were administered over 2 days, a lunch on day 1 and a breakfast on day 2. The example presented in [26] shows peak post-meal glucose of 15 mmol/l. The set point was reached in approximately 11 h.

The individualization of the PID controller was achieved by assigning the proportional gain  $K_p$  a value resulting in a normal daily insulin dose of the dog at euglycaemia. The remaining parameters were also individualized whilst the ratios  $K_D/K_p$  and  $K_p/K_I$  were assigned values of 66 min and 150 min, respectively. In a follow-up study, the proportional constant  $K_p$  was increased as the earlier results suggested that it was underestimated, but the ratios  $K_D/K_p$  and  $K_p/K_I$  were kept unchanged [81].

Another approach to control glucose with a closed-loop with qualitative meal announcement employs switching between a meal mode and fasting mode [12]. During the meal mode, the proportion  $K_D/K_I$  is increased when glucose is increasing, thus reducing the peak post-meal value from 13.9 to 10.3 mmol/l in four depancreatized dogs.

A recent evaluation of the ePID system was carried out in six subjects with Type 1 diabetes over 27.5 h with four meals: breakfast, lunch, dinner and snack [82]. The sensor was calibrated before the start of closed-loop control and checked regularly. The target glucose level was 6.7 mmol/l. Preprandial and postprandial (2 h) glucose levels were  $5.8 \pm 1.2$  and  $9.8 \pm 1.6$  mmol/l (mean  $\pm$  SD). Morning glucose after overnight control was  $6.8 \pm 1.0$  mmol/l.

### Renard's group (using Minimed Medtronic monitor)

Renard's group is developing the i.v.–i.p. approach. This approach is based on a long-term sensor system (LTSS) [83,84]

evaluating the implantable physiological insulin delivery (iPID) system.

The invasiveness of the approach is exemplified by the device set-up. LTSS contains an intravenous enzymatic oxygen-based sensor developed by Medtronic MiniMed. The sensor is implanted by direct jugular access in the superior vena cava under general anaesthesia. It is connected by a subcutaneous lead to an implanted insulin pump delivering insulin intraperitoneally.

The sensor induces a time delay (8 min) and a transport delay (8 min) attributable to the large glucose oxidase pad required to guarantee a sensor life of over 1 year [26].

The system has been investigated in 10 subjects with Type 1 diabetes with collected data per sensor of about 280 days [85]. At present, most investigations with LTSS have adopted the open-loop approach. The accuracy of the system has been tested by comparing sensor data with self-monitored glucose concentration. The authors document a relative mean absolute deviation of 18 and 96% of sensor data in zone A and B of the Clarke error grid.

The fully closed-loop system was tested over 48 h, reducing the per cent time spent at  $< 3.9$  mmol/l from 18 to 6%, and the time spent at  $> 13.3$  mmol/l from 17 to 2%. With the addition of an insulin bolus at mealtime (information how this was achieved was not provided), the time outside the range 3.9–13.3 mmol/l was eliminated completely [85]. It appears that control is achieved using a PD controller [86,87].

Recently, the iPID system was evaluated in four elderly lean subjects with Type 1 diabetes over 48 h [88]. Breakfast (40 g CHO), lunch (80 g CHO), and dinner (80 g CHO) were given. During the second 24-h control period following empirical tuning of the algorithm, 4 and 7% of time was spent below 4.4 mmol/l in the postprandial (0–2 h) period and outside meal conditions, respectively, 12 and 32% was spent in the region 4.4–6.7 mmol/l, 63 and 60% was spent in the region 6.7–13.3 mmol/l, and 20 and 2% was spent above 13.3 mmol/l.

### Roche Diagnostics closed-loop project

The subcutaneous continuous glucose monitor (SCGM1; Roche Diagnostics GmbH, Mannheim, Germany) is a prototype system which has been designed to monitor glucose in the subcutaneous interstitial fluid for up to 4–5 days [89]. It has been tested with an s.c.–s.c. closed-loop system with meal announcement [90,91].

SCGM1 employs the microdialysis technique with an *ex vivo* glucose measurement based on an electrochemical flow-through sensor and produces a signal every second. This is reduced to one glucose measurement every 5 min. Recalibration is required once every 24 h [18,89].

SCGM1 has a very low flow rate (0.3  $\mu$ l/min), achieving nearly a 100% recovery of the subcutaneous glucose in the dialysate but resulting in an approximately 30-min technical lag. The system requires a 12-h run-in-time. *In vitro* performance was impressive with a mean absolute difference of 0.2–3.8% in 10 sensor units [89].

In combination with an empirical algorithm [90], the SCGM1 was used in an s.c.–s.c. closed-loop approach with meal announcement. The term ‘empirical algorithm’ reflects a set of rules, derived from empirical observations related to insulin dosing, which are adopted by the algorithm to determine the insulin microbolus administered every 10 min. The empirical algorithm has been converted into a model predictive framework [91,92].

The closed-loop system was evaluated in 12 well-controlled ( $HbA_{1c} < 8.5\%$ ) subjects with Type 1 diabetes treated by CSII [90]. The parameters of the algorithm were derived individually from self-monitored blood glucose data and other information included in the subject’s log-book. Each subject was studied on two occasions, once when glucose was controlled by the algorithm and once with their standard self-directed therapy. Control on each occasion lasted over 32 h with the ingestion of breakfast, lunch, dinner and a snack. The target glucose concentration was 6.7 mmol/l. The prandial bolus dose was calculated from the carbohydrate content of the meal.

After sensor qualification, the Clarke error grid showed 90 and 10% of SCGM1 glucose values in zones A and B, respectively, out of 320 readings. The algorithm achieved a near-target monitored glucose concentration (6.9 vs. 6.2 mmol/l; mean, algorithm vs. self-directed therapy). It reduced the number of hypoglycaemia interventions from 3.2 to 1.1 per day per subject, exemplifying the considerable number of hypoglycaemia events in well-controlled subjects on self-directed therapy. It reduced the carbohydrate intake need to treat hypoglycaemia from 55 to 14 g/day. During the algorithm therapy, 56% of SCGM1 values were within the 5.0–8.3 mmol/l range compared with 33% with the self-directed therapy.

The results of the study demonstrated the feasibility of closed-loop control with meal announcement with a technical delay in glucose sensing of over 40 min.

### Ulm group

The work initiated by Professor Pfeiffer in the early 1970s continues. Most recently, Freckmann *et al.* have summarized the progress which has been made [93].

This work has concentrated on the development of glucose sensors for the measurement of s.c. glucose concentration and on the development of s.c.–s.c. closed-loop approach with meal announcement. The sensor system is based on the amperometric–enzymatic approach in combination with the microdialysis technique.

The continuous flow method uses a slow continuous flow through the tubing, achieving nearly 100% recovery. This causes, however, almost a 30-min lag, corresponding to the time it takes the perfusate to be transported from the probe to the extracorporeal sensor. The system needs to be re-calibrated as a result of an inherent drift in the electrochemical system [93].

The comparative method does not require calibration [94]. Saline with glucose (5.5 mmol/l) is pumped through the probe in a stop-flow mode. During the stop mode, nearly 100%

equilibrium between the interstitial plasma glucose and the perfusate is achieved. The technique facilitates sensor internal calibration for each measuring cycle and yields five glucose measurements per hour. It has a 9-min technical lag because of the measurement process.

The comparative method was tested in six non-diabetic and six Type 1 diabetes subjects over 24 h. Comparisons with capillary (control) and venous (Type 1 diabetes) blood glucose measurements gave a relative mean absolute error of 11–18%. Clarke error grid analysis gave 99% measurements in zone A and B [94]. The continuous flow technique has also been evaluated for up to 72 h against self-monitored blood (free living conditions), venous blood and capillary blood (hospital setting) glucose, returning 96% measurements in zone A and B [93].

The group developed and tested a model predictive controller to titrate s.c. lispro insulin infusion to test an s.c.–s.c. closed-loop approach with meal announcement [95,96]. The algorithm discriminates between the basal insulin requirement, determined from one individual rate, and a postprandial insulin requirement, expressed as an insulin-to-carbohydrate ratio. A model of insulin action utilizes these values to make predictions of future glucose excursions and determines the amount of insulin needed to achieve the target glucose level of 6.7 mmol/l. The algorithm was tested in eight subjects with Type 1 diabetes over a period of 24 h. The subjects digested three meals, with a maximum of 60 g of CHO in each meal. The average glucose value was  $7.8 \pm 0.7$  mmol/l (mean  $\pm$  SD). The authors report stable glucose concentration during the night (SD of 0.4–1.2 mmol/l in an experiment). The postprandial increases were  $2.9 \pm 1.3$  mmol/l with the largest excursions recorded after breakfast. One hypoglycaemic event ( $< 3.3$  mmol/l) was observed [96]. The algorithm was also successfully tested during moderate exercise [93].

### Glucose control in intensive care units

Glucose control in intensive care units is under review following the findings by Van den Berghe *et al.* [97], who demonstrated that normalizing glucose levels to the target range of 4.4–6.1 mmol/l in critically ill patients in the surgical intensive care unit (ICU), using aggressive insulin dosing, significantly decreased mortality, morbidity as a result of sepsis, sepsis-related organ failure, transfusion requirements, and polyneuropathies. The earlier Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study demonstrated that intensive insulin treatment significantly decreased long-term mortality relative to control subjects with diabetes with acute myocardial infarction [98].

In the critically ill, Chee *et al.* [99] have explored the use of the CGMS sensor to control glucose in a fully closed-loop setting with the s.c.–i.v. approach. A proportional–integral controller based on a sliding scale algorithm was used. The target region was between 6 and 10 mmol/l, well above the glucose level of 6.1 mmol/l recommended by Van den Berghe *et al.* [97].

Despite reports about improvements of glucose control using simple paper-based guidelines, glucose control particularly in the surgical ICU requires substantial expert input, training, and supervision. Often, such guidelines require empirically acquired modifications, limiting their transferability among staff and units. In surgical patients, Zimmerman *et al.* [100] achieved 60% glucose values in the target range of 4.4–8.3 mmol/l while over 15% were below the hypoglycaemia threshold of 3.6 mmol/l. Better results were obtained in a medical ICU in 62 critically ill subjects by Goldberg *et al.* [101], who achieved 52% glucose values in the target range between 4.4 and 6.1 mmol/l and only 0.3% values below 3.3 mmol/l after the target level was achieved. The nurse-implemented algorithm by Goldberg *et al.* also utilized the trend in glucose excursions to calculate the insulin infusion rate.

Recently, the algorithm of Golberg *et al.* was tested in the surgical ICU in 118 subjects [102]. The median time to reach target was 5 h. The target range was slightly higher from 5.6 to 7.8 mmol/l with 58% values in the range and 0.2% values below 3.3 mmol/l.

### Other glucose monitors

Other glucose monitors have received regulatory approval and others are under development, see reviews by Chia and Saudek [103] and Koschinsky and Heinemann [104].

### Conclusions

The glucose monitor remains the limiting problem in the development of a commercially viable closed-loop solution. The presently available monitors fail to display satisfactory properties in terms of reliability and accuracy. However, minimum requirements have yet to be determined.

Experience to date suggests that it is not compulsory to achieve minute-to-minute glucose measurements, but that measurements every 10–15 min are sufficient. In terms of accuracy, the glucose monitor should have at least a 15%, but more likely a 10%, mean absolute deviation. Hypoglycaemia is the major concern and therefore higher accuracy is preferable at the lower range between 4 and 6 mmol/l. Ideally, the sensor should be free of bias but this might not be possible because of true physiological differences between s.c. and i.v. glucose. Thus, extended periods of overestimation or underestimation may occur. The latter is preferable from the safety viewpoint of hypoglycaemia.

The closed-loop system will require diagnostic capability to monitor performance and to increase reliability. In case of sensor failure, the system can switch into an open mode using the predefined insulin delivery stored in the insulin pump.

Regulatory issues are the second limiting factor. Few medical devices exist which operate in a closed-loop fashion, in the home environment, and whose failure can cause serious health complications. Risk-benefit analysis will be instrumental in assisting the decision-making process. It is unlikely that the

first generation of closed-loop systems will achieve complete normalization of the glucose profile. However, it should at least improve or maintain the level of glycated haemoglobin while reducing the frequency of hypoglycaemia particularly in well-motivated subjects, who, at present, may achieve good control but at the expense of frequent hypoglycaemia. The achievement of 'true' physiological homeostasis in a closed-loop system is likely to require at least two hormones with opposing action, i.e. insulin and glucagon.

Methodological advancements are required to allow direct comparisons among closed-loop solutions. The plethora of clinical measures prevents clearer understanding of drawbacks and advantages of various approaches. The comparisons must include dimensions related to glucose control, and algorithm initialization and tuning.

Closed-loop solutions may find their first widespread use in controlled environments, such as in the intensive care unit, where the benefits of tight glucose control have been demonstrated. From this application area, spin-off to other areas should be possible.

## Competing interests

R.H. is a paid consultant of Disetronic A/G.

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