Expert Opinion

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Closed-loop insulin delivery – what lies between where we are and where we are going?

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Closed-loop insulin delivery in individuals with diabetes can potentially lead to near-normal glucose profiles. To this end, existing subcutaneous glucose sensors and external insulin pumps can be linked with an insulin delivery algorithm to create a completely automated closed-loop system. This paper reviews current research into the development of such a system, with particular emphasis on creating a system emulating the physiological properties of the β-cell. Issues related to using subcutaneous interstitial fluid for glucose sensing and insulin delivery are reviewed. Criteria for optimising the system are discussed using historical data. Existing strategies for open-loop pump therapy are presented with the objective of defining a path to advance from the existing physician/patient determined insulin therapy to a completely automated system.

Keywords: continous glucose monitoring, continuous glucose monitoring system, continuous subcutaneous insulin infusion, insulin secretion, minimal model

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1. Introduction

No treatment has been shown to prevent Type 1 diabetes in humans [1]. Devoid of a means to prevent the disease, islet [2] or pancreas/kidney transplantation [3] are thought to be possible cures. Neither option is widely available as there are insufficient organ donors. Engineered cell lines [4], use of stem cells [5], or xenotransplantation [6], may overcome the islet shortage, but the timeline is unclear and the recipient may still require immunosuppressive therapy, which can have significant associated risks [7]. Without a means to prevent or cure the disease, the focus is on improving therapy. Benefits of intensive insulin therapy were clearly established in the Diabetes Control and Complications Trial (DCCT) [8] and continue to be observed [9,10]. Nonetheless, somewhere between improved therapy and prevention/cure, lies the completely automated, artificial, closed-loop insulin delivery system.

There is general agreement that such a system should be implanted with minimal surgery and, thereafter, restore normal blood glucose profiles for the life of the recipient. This may be unrealistic and opinions as to how a realistic system should look and how best to achieve it vary widely. Closed-loop insulin delivery requires a sensor for measuring glucose, an algorithm for determining the insulin delivery rate and a pump. Glucose-sensing technology, for which a recent comprehensive review is available [11], comes in noninvasive and minimally invasive forms, the latter being on the market today in the form of subcutaneous interstitial fluid glucose sensors. The suitability of the subcutaneous site for glucose sensing has been extensively studied, but no clear consensus regarding the delay or response during hypoglycaemia has emerged. The primary means for delivering insulin, aside from a simple injection, is the external insulin pump with subcutaneous insulin delivery. Implantable pumps utilising intraperitoneal delivery result in a more rapid appearance of insulin into plasma with some of the insulin likely to appear first in the portal vein; however, these require surgery to implant and are not fully released in the US. As for the algorithm, opinions

are diverse. This is probably due to the divergent backgrounds of clinicians who treat Type 1 diabetes mellitus (T1DM) and engineers who apply control theory.

A completely automated closed-loop insulin delivery system is unlikely to be realised in one step from where we are today. At present, multiple daily insulin injection therapy remains common, continuous subcutaneous insulin infusion shows benefit in reducing haemoglobin A1c in some [12,13], but not all, [14] studies, and continuous glucose monitoring data are only available retrospectively [15]. Pump therapy is largely determined by trial and error with the help of a few empirical rules. The most advanced form of insulin delivery consists of meter blood glucose (BG) values that can be automatically transmitted to a pump (Medtronic MiniMed Paradigm® 512 pump), which can provide a bolus recommendation. Recommendations are based on a carbohydrate to insulin ration (CIR) and a correction factor (CF) that are entered by the user (g carbohydrate and mg/dl drop in blood glucose, expected for 1 unit of insulin). A time profile specifying the fraction of insulin yet to act is defined and has been termed insulin on board (IOB). The recommended bolus (U) is subsequently calculated from a meter BG entry as in Equation 1. Variations of the algorithm exist in pumps manufactured by several companies.

$$Bolus = \left(\frac{BG - Setpoint}{CF}\right) + \frac{Carbohydrate}{CIR} - IOB(t) \quad (1)$$

Where t is time.

Empirical rules exist for estimating CF and CIR, based on reciprocal relations with total daily insulin (TDI) [16]:

$$CF = \frac{ISI}{TDI} \qquad CIR = \frac{CSI}{TDI} \quad (2)$$

Where ISI is an insulin sensitivity index and CSI is a carbohydrate sensitivity index.

ISIs of 1500 – 1800 have been proposed by P Davidson [17], and are commonly referred to as the '1500 rule' and '1800 rule', respectively. A value of 500 is common for the CSI. Basal rate recommendations involving a fixed percentage of the TDI delivered over 24 h also exist (50% in adults, 40% in adolescents [18]). Collectively, these rules (ISI = 1500; CSI = 500, and basal rate = 50% TDI/24 h) were used as an initial guide by Demeglio *et al.* [19] in a study characterising pump use in toddlers and adolescents. Variations in the number of basal rates [19] and the time at which the maximal basal rate occurs, can be expected [20].

The need to establish multiple basal rates, a CIR and CF, estimate meal carbohydrate content (g), and possibly make adjustments based on stress, exercise and numerous other factors, is far from straight forward. Can the process be circumvented by a closed-loop insulin delivery system? Undoubtedly there are obstacles, both real and perceived, in achieving such a solution.

2. The subcutaneous glucose sensing site

It is unlikely that any one area related to subcutaneous glucose sensing has captured the attention of more researchers than the putative differences between plasma and ISF glucose. These differences are thought to include insulin-induced changes in the plasma to ISF glucose gradient [21,22], different response times for falling and rising glucose signals [23], protracted recovery times following hypoglycaemia [24,25], and suggestions that ISF glucose can fall in advance of plasma glucose [26,27]. These issues have been assessed in studies using lymph as a surrogate for ISF fluid, and by modelling the subcutaneous glucose sensor current. From the kinetics of glucose in lymph (canine model) we have shown the delay in ISF glucose to be $\leq 5 - 12$ min and that neither it nor the gradient are affected by the prevailing plasma insulin level [28]; conclusions that are supported by sensor modelling studies in dogs [29]. In humans, we have found the delay to be only 6 – 8 min during hyper- [30] and hypoglycemic clamps [31], with no difference in delay during falling or rising glucose. These estimates are consistent with those recently reported in individuals with T1DM by Boyne *et al.* [32]. Delays of this magnitude introduce only minor errors in the glucose signal [28], and signal processing routines have been proposed to correct them [29,33]. Thus the authors believe the use of subcutaneous interstitial fluid for glucose sensing is unlikely to pose a substantial barrier in the development of a closed-loop insulin delivery system.

3. The subcutaneous insulin delivery site

The applicability of the subcutaneous site for insulin delivery has been greatly enhanced by the development of rapidly absorbing insulin analogues. However, the kinetics are still substantially delayed. Following a subcutaneous bolus, plasma insulin concentration does not achieve a peak level for 40 – 60 min, and subsequently takes 3 – 6 h to fully dissipate (**Figure 1**, closed circles).

While the insulin kinetics are substantially delayed, they are reasonably well approximated by mathematical models. For the response shown in **Figure 1**, a mathematical construct (Equation 3) characterising two delays (τ_1 and τ_2 in min) provides a reasonable description of the profile (**Figure 1**, line).

$$Ip(t) = A\left[e^{\frac{-t}{\tau 1}} - e^{\frac{-t}{\tau 2}}\right] \quad (3)$$

The response is scaled by a factor (A) to normalise the area under the curve (AUC) to the subject's insulin clearance (insulin clearance = insulin dose/AUC), and all parameters ($\tau 1, \tau 2$, A) can be obtained by standard mathematical

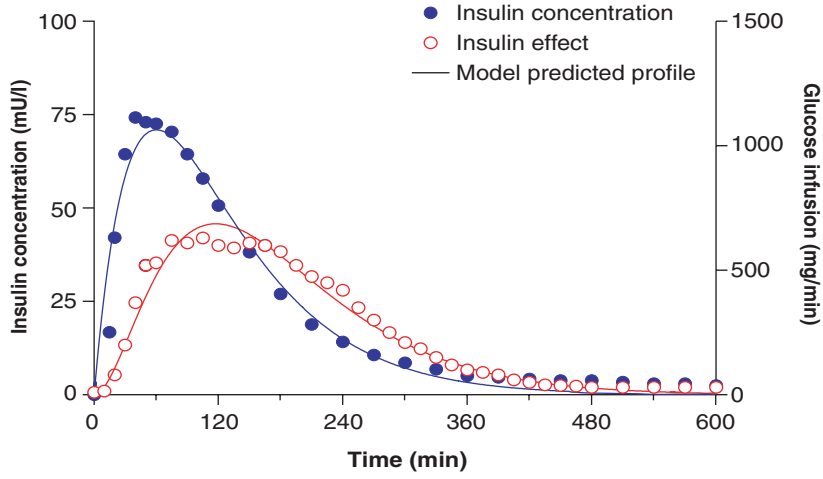

Figure 1. Plasma insulin concentration following a subcutaneous bolus of insulin aspart (solid circles; left axis) together with a model predicted profile (solid line). Required glucose infusion rate to maintain plasma glucose at basal (open circles; right axis) and model fit. Data adapted from MUDALIAR SR, LINDBERG FA, JOYCE M *et al.*: Insulin aspart (B28 asp-insulin): a fast-acting analog of human insulin: absorption kinetics and action profile compared with regular human insulin in healthy nondiabetic subjects. *Diabetes Care* (1999) **22**:1501-1506; see text for model equations.

techniques (model fits in **Figure 1** were obtained using non-linear least squares routines available in Mlab, Civilized Software, Bethesda, MD, USA). This characterisation is only one of numerous models for describing plasma insulin as a function of subcutaneous insulin delivery with alternate, more complex models available [35]. However, Equation 3 can describe plasma insulin concentrations obtained with arbitrary pump profiles using a mathematical process known as convolution [36] (summing individual boluses). Although delays in subcutaneous insulin absorption pose a substantial challenge to closing the loop, the fact that the response is well characterised by a model can be used to benefit closed-loop insulin delivery immensely.

Insulin action does not occur simultaneously with changes in insulin concentration. The delay can be characterised by the glucose infusion rate required to maintain euglycaemia (**Figure 1**, open circles), and can be described by mathematical models. The simplest such model is to assume that all action occurs in a compartment remote from plasma (i.e., interstitial fluid bathing insulin-sensitive tissue). This, of course, is the same assumption used by the well known minimal model of glucose kinetics [37], and leads to a predicted glucose infusion rate of:

$$\frac{dG_{inf}}{dt} = -p_2 G_{inf} + K\langle I - I_b \rangle \qquad (4)$$

In this form, the rate-of-change of glucose infusion (dG_{inf}/dt) is proportional (K) to the plasma insulin concentration above basal ($I - I_B$) and the delay is defined by p_2 (time for half-maximal action proportional to $1/p_2$). Although Equation 2 may look, at first, to be complex, it nonetheless provides a simple means to model the insulin-effect time course and effectively describes data obtained by Mudaliar (**Figure 1**) [34]. As with the insulin kinetic description, the model prediction can be used to great benefit in a closed-loop insulin delivery algorithm.

4. Closed-loop insulin delivery algorithms

Two recent articles have reviewed closed-loop insulin delivery algorithms using either intravenous [38] or subcutaneous delivery [39] sites. Although this review focuses on the ambulatory closed-loop system (subcutaneous delivery), the review of intravenous insulin delivery [38] is valuable as it presents a more detailed historical perspective of closed-loop insulin delivery and the model predictive control strategy. The review on subcutaneous insulin delivery [39] includes a section on emerging information technology and telemedicine approaches for adjusting open-loop therapies, which is of interest in assessing what lies between where we are and we are going. Both review articles require some background in the mathematics of control theory.

Although the use of control theory will undoubtedly aid in the development of an insulin delivery algorithm, the same can be said for understanding and modeling how the β-cell maintains glucose homeostasis. This latter course has been reviewed [40]. Briefly, the main arguments are that the β-cell adjusts the ratio of first-to-second-phase insulin release to compensate for the delay in insulin action [41], and that it adapts the magnitude of its response to keep the product of insulin sensitivity (S_I) and the AUC of the first-phase insulin response constant: the constant being the 'disposition index' originally proposed by R Bergman [42,43] and demonstrated in humans by S Kahn [44].

Insulin secreted by the β-cell appears directly in the portal vein, whereas the objective in creating an ambulatory system is to have the insulin delivered by subcutaneous or intraperitoneal

routes. Portal insulin appearance is thought to have a rapid direct effect to suppress hepatic glucose output [45-47] and alter other metabolites [48]. However, these effects are also thought to be mediated by an indirect action of insulin in peripheral interstitial fluid: the 'single gateway' hypothesis [49-55]. The existence of a direct effect of portal insulin to suppress hepatic glucose output (mg/min) suggests that, in individuals with T1DM, peripheral insulin delivery would require an elevation in insulin concentration to normalise fasting glucose turnover (glucose turnover approximately equals hepatic glucose output under fasting conditions). However, Chiasson *et al.* have shown that glucose turnover can be normalised in individuals with T1DM [56], compared with age- and weight-matched controls, without an elevation in either fasting insulin or fasting glucose (experiments performed in women during and following pregnancy). Thus, the higher portal insulin concentration that would have been present in the normal controls did not affect the steady-state endogenous glucose production rate. This observation is consistent with the hypothesis that the indirect effect of insulin is dominant [51,57].

In any case, if β-cell dynamics are to become the underlying basis for a closed-loop insulin delivery algorithm, a mathematical model must be developed to describe its secretory response to glucose. Numerous models exist [58-66], all of which follow the work of G Grodsky [67-69]. These models [58-66] all include terms that describe glucose-induced insulin secretion as components that react proportionally to changes in glucose, have a delayed reaction to glucose and/or react to the rate-of-change of glucose. The ability of one model [58,59] to describe hyperglycemic clamps and meal profiles in healthy subjects has recently been evaluated [70]. In this study, the model estimate of second-phase insulin release obtained from the clamp was inconsistent with the estimate obtained from a meal. Although this may have been due to an insufficient number of samples taken during the meal (C Cobelli, pers. commun.), it has also been shown that the predicted secretion rate does not compensate for changes in basal insulin requirement [71]. Changes in basal insulin can occur following changes in S_I or endogenous glucose appearance.

In light of these observations, a three-phase model of insulin secretion was proposed and consisted of the slow component suggested in [58,59,63,65], the proportional component suggested in [60-62,64,65] and the rate of change component in [58-62,65]. Although it remains to be determined whether the three-phase model can provide consistent estimates of second-phase insulin release during meals and clamps, it has been shown with simulations that it can maintain normoglycaemia in the presence of changes in S_I or glucose production [71]. This three-phase model has become the basis for a closed-loop insulin delivery algorithm using systems based on both subcutaneous glucose sensing with subcutaneous insulin delivery [72], and intravenous glucose sensing with intraperitoneal insulin delivery [73]. Preliminary results from clinical trials using this model/algorithm are promising [72,73]. This β-cell based control algorithm has been termed physiologic insulin delivery (PID) [71,72].

Two points regarding the β-cell algorithm seem particularly relevant in the context of the present review. The first is that although the algorithm was derived from a model of glucose-induced insulin secretion (the β-cell), it is not structurally different from a classical proportional-integral-derivative controller [36] used throughout the engineering world for many decades. The second point is that as the β-cell delivers insulin into the portal vein and the algorithm is intended for subcutaneous delivery, a modification or adjustment is required. Ideally, modifications and adjustments would be made in an effort to achieve optimal results. There is, however, no consensus as to what the optimal glucose profile should look like.

Closed-loop algorithms with intravenous insulin delivery can achieve lower glucose excursions than those observed in healthy animals with normal β-cell function. This was originally shown in dogs using an insulin delivery (ID) algorithm consisting of a fixed (constant) basal rate (a_0), and components that responded proportionally to glucose above setpoint (a_1 x [G-setpoint]) and to the rate of change of glucose (a_2 x dG/dt):

$$ID\langle t\rangle = a_0 + a_1\langle G - setpoint\rangle + a_2\frac{dG}{dt} \qquad (5)$$

This algorithm contains two of the three components of the PID β-cell model, lacking only the component necessary to generate a slow rise in second-phase insulin release. With subcutaneous glucose sensing, the algorithm was shown to be able to achieve glucose profiles during oral glucose tolerance tests (OGTTs) that were lower than those achieved by normal control animals (**Figure 2A** triangles versus closed circles). The lower glucose response was, however, accompanied by a higher than normal plasma insulin response (**Figure 2B** triangles versus closed circles), a characteristic that may not be desirable. As basal glucose was well matched in the two groups (determined by a_0) it can be argued that lower values for a_1 and a_2 (Equation 5) would have achieved glucose profiles more closely matching the healthy animal.

Although lowering a_1 and a_2 can be expected to lead to a glucose profile more closely approximating the normal animal, it does not address the issue of how to choose the relative ratio between the two. Apart from purely empirical approaches to adjust a_1 and a_2, most engineering approaches require a model of the system being controlled. In this context, the model is not of insulin secretion, but rather insulin action. Similiar to insulin secretion, numerous models of insulin action also exist [76], but no single model is universally accepted. Three of the more common models (Bergman's minimal model [77], AIDA [78] and Sorensen [79]) were recently compared and significant differences were found among them [80].

Although differences exist among these models, the simplest of the three (minimal model) can describe the data of **Figure 2** provided mathematical descriptions of the plasma insulin

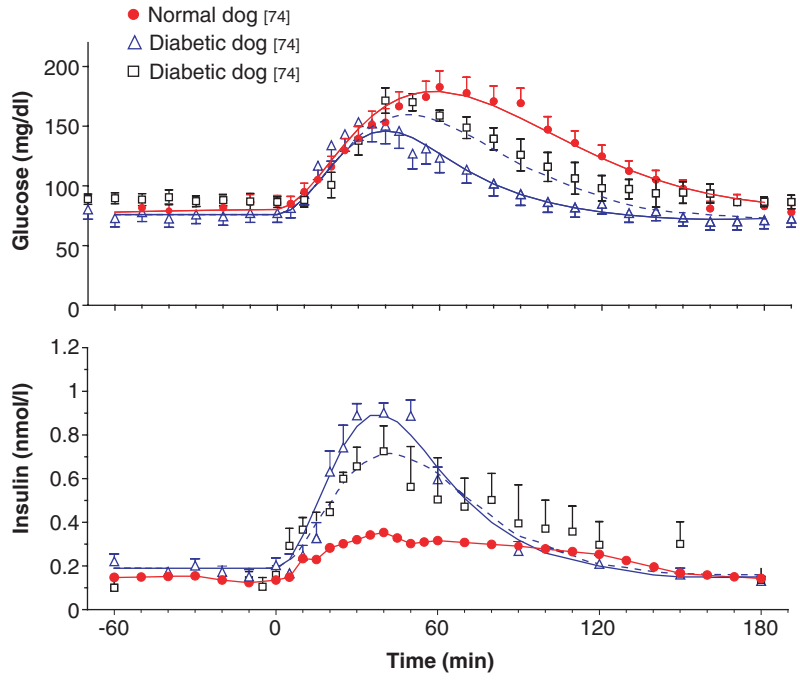

Figure 2. Glucose and insulin responses in normal (closed circles) and diabetic dogs under proportional derivative control (open triangles) together with the fit of Equation 6 (solid lines). Adapted from REBRIN K, FISCHER U, VON WOEDTKE T, ABEL P, BRUNSTEIN E: Automated feedback control of subcutaneous glucose concentration in diabetic dogs. *Diabetologia* (1989) **32**:573-576. Simulated profiles with closed-loop gains reduced by 50% (dashed lines) together with experimental data (open squares) adapted from FISCHER U, FREYSE EJ, SALZSIEDER E, REBRIN K: Artificial connection between glucose sensing and insulin delivery: Implications of peritoneal administration. *Artif. Org.* (1992) **16**:151-162.

concentration ($I_p[t]$), and rate of glucose appearance ($R_a[t]$) during an OGTT, are available. **Figure 1** provides such a description for $I_p(t)$ following a subcutaneous bolus, but not for the kinetics following an intravenous bolus, and no model exists to describe the rate of glucose appearance following OGTT (the AIDA model is a possible exception as it has a piecewise linear model to describe a standard meal [78]). Glucose tracer methods are emerging for estimating the rate [81,82] and this will likely aid in further developments. Here, the rate of glucose appearance following an oral glucose load is approximated as having two rate constants (rate constants $1/p_4$ and $1/p_5$), and the concentration of insulin following an intravenous insulin bolus as having a single rate parameter ($1/p_6$):

$$\begin{aligned} \frac{dG}{dt} &= -\langle p_1 + X\rangle G + R_{a\langle BASAL\rangle} + R_{a\langle OGTT\rangle}\langle t\rangle \\ \frac{dX}{dt} &= -p_2 X + p_3\langle I - I_B\rangle \\ \frac{dI_p}{dt} &= -p_6 I_p + p_7 ID\langle t\rangle \\ R_{a\langle OGTT\rangle} &= Ae^{-p4t} - Ae^{-p5t} \end{aligned} \qquad (6)$$

Parameters of the first two equations are defined by the minimal model (p_1 characterises the effect of glucose *per se* to increase glucose disposal and decrease glucose production; p_2 characterises the delay in insulin action; p_3/p_2 is S_I) and the third equation characterises insulin clearance (p_7/p_6 in ml/min) and plasma insulin half-life (proportional to $1/p_6$). The final equation characterises the rise and fall in glucose appearance following the oral glucose load (rate parameters, $1/p_4$ and $1/p_5$ in min; parameter A is in units of mg/min/dl and reflects the total g of carbohydrate in the OGTT normalised to the distribution volume of glucose).

Although this formulation is clearly based on many simplified assumptions, it serves to describe the glucose profiles in both the healthy and diabetic animals (**Figure 2A**, solid lines through healthy [closed circle] and diabetic [open triangle] glucose profiles). Minimal model (p_1, p_2, p_3) and glucose appearance (p_4, p_5 and A) parameters were assumed to be identical in the diabetic and normal animals and the final fitted curves obtained with standard mathematical routines (Mlab, Civilized Software Bethesda, MD, USA). Once the model was fit to the data (using nonlinear least squares) [74], simulations using lower values of a_1 and a_2 were performed (dashed line), and the simulated profiles compared with data obtained by the same authors in a later study [75] (open squares). This last step, which validates that the model is

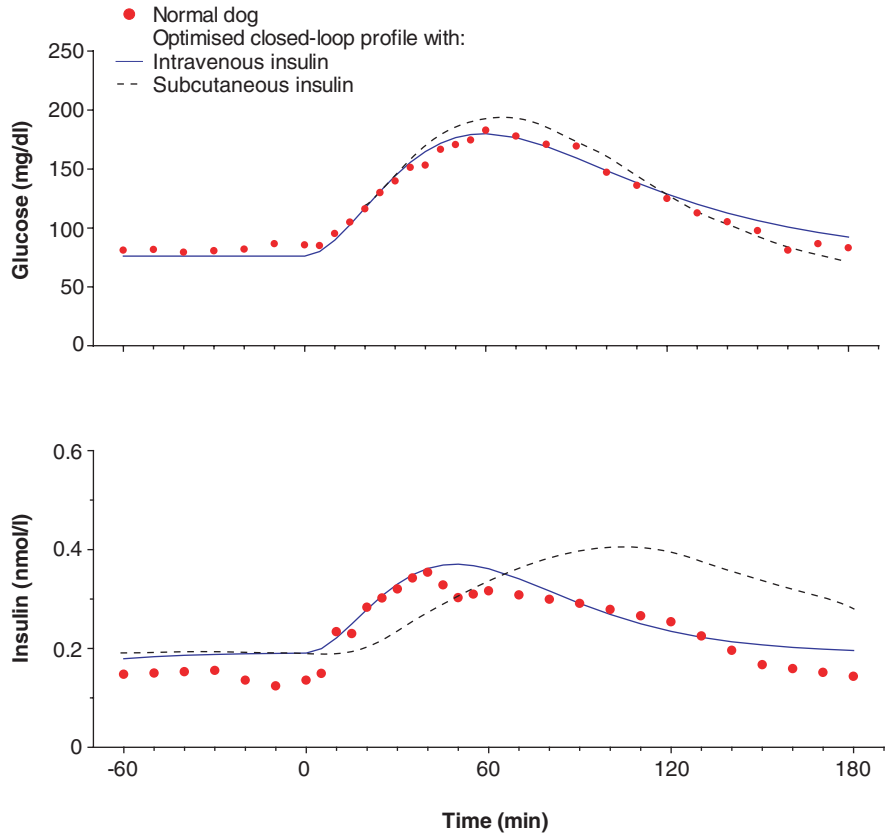

Figure 3. Glucose and insulin profiles obtained in the normal dog (solid circles), together with simulated closed-loop response using proportional derivative control with intravenous insulin delivery (solid line; optimised to fit both the glucose and insulin response in the normal dog) and subcutaneous insulin delivery (dashed line; optimised to fit the glucose profile).
Data adapted from REBRIN K, FISCHER U, VON WOEDTKE T, ABEL P, BRUNSTEIN E: Automated feedback control of subcutaneous glucose concentration in diabetic dogs. *Diabetologia* (1989) **32**:573-576.

predictive for changes in controller tuning, provides a basis for optimising the closed-loop parameters a_1 and a_2 (Equation 5).

Although virtually any optimisation criteria can be specified in this process, the optimal glucose profile is that which would be achieved by the β-cell [40]. To this end, values of a_1 and a_2 can be chosen to minimise the difference (least squares) in the glucose profile predicted by the model under closed-loop conditions and the profile in the healthy control group (**Figure 3**, solid lines). For subcutaneous insulin delivery, the relationship between insulin delivery and insulin concentration in Equation 6 can be replaced with the relationship in **Figure 1** (and Equation 3) and new values of a_1 and a_2 obtained. This last step leads to slightly higher glucose levels with a delay in the insulin profile (**Figure 3**, dashed line).

The model-based optimisation strategy highlighted in **Figure 3** provides insight into how algorithm parameters can be rationally determined. However, the control equation (Equation 5) used is unable to adjust for changes in insulin demand. If an insulin delivery rate greater than a_0 is required during stable fasting conditions (stable fasting implies dG/dt = 0), glucose (G) must be greater than setpoint for ID to be greater than a_0. Furthermore, the metabolic model used in the optimisation process (Equation 6) does not explicitly describe the underlying mechanisms leading to a diurnal or interday variation in insulin need. Although we have shown the PID model, viewed either as a model of the β-cell or as a classical control algorithm, to compensate for changes in insulin requirement [71], it is not clear that existing models of insulin action characterised the changes in insulin requirement typically seen in an individual with T1DM [80].

A metabolic model that could fully characterise the glucose dynamics in an individual with T1DM during day-to-day activities, can aid in developing a closed-loop algorithm. Such a model could also optimise open-loop bolus estimation algorithms (e.g., Equation 1) and help determine diurnal patterns of basal insulin delivery. Finally, the same model could monitor food intake, exercise and insulin delivery and predict an occurrence of hypoglycaemia in time for corrective measures to be taken. Ultimately, a perfect model could simply allow a computer to adjust insulin delivery without any feedback. However, the authors of this review do not believe such a model exists (see Section 5).

5. Expert opinion and conclusion

Models are imperfect. In the present report, the simple equations used to describe the OGTT performed well; however, OGTT conditions are far less complicated than the daily profiles seen in individuals with T1DM. Even for the simple model used here (Equation 5), addition of diurnal variation adds significantly to the complexity. Consider the putative dawn phenomenon. Does blood glucose rise because endogenous glucose production ($R_{a[BASAL]}$) increases or because S_I decreases? If S_I decreases, is it due to a decrease in the ability of insulin to increase glucose uptake into cells once it binds to the insulin receptor, or is it due to a decrease in the ability of insulin to reach the cell (these affect p_2 and p_3 differently)? Could the increase in glucose be related to changes in the effect of glucose *per se* (p_1 in Equation 5)? Does insulin clearance vary during the day? The list goes on.

Existing models do not address many of these issues. However, new data are rapidly emerging. Glucose sensors provide multiple days of continuous glucose data, insulin pumps accurately track insulin delivery and many subjects are well trained in calculating carbohydrate content, meal type, and duration and intensity of exercise. This wealth of new data will allow more comprehensive models to be developed and validated.

Improved metabolic models can benefit open-loop insulin treatment as well as aiding the development of closed-loop algorithms, potentially answering the question 'what lies between where we are and where we are going?' Model-based optimisation of open-loop therapy is likely to precede any full closed-loop system. Such therapy can be implemented either in an insulin pump, or combined with a telemedicine approach. A model may be able to serve a monitoring role for open-loop insulin delivery and early forms of closed-loop delivery, thus allowing failures in any system components (catheter, sensor, pump) to be diagnosed in advance of any potential problem.

Although significant research remains to be conducted, a completely closed-loop system is attainable. Although the system may not be achievable in a single step from where we are today, steps to automate open-loop pump therapy can occur simultaneously with research on a fully closed-loop insulin delivery system. Both open- and closed-loop therapy can be expected to benefit from metabolic modelling. For closed-loop systems, algorithms emulating the β-cell response can be optimised to compensate for delays in glucose sensing and insulin delivery. Optimisation that falls short of achieving perfect β-cell-like control, but requires minimal patient interaction, will, nonetheless, improve the lives of many individuals.

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