Published in final edited form as:

Endocrinol Metab Clin North Am. 2012 March ; 41(1): 105–117. doi:10.1016/j.ecl.2011.12.003.

Closed-loop Insulin Delivery in Type 1 Diabetes

Hood Thabit, MD^a and Roman Hovorka, PhD^b

^aClinical Research Fellow, Institute of Metabolic Science, University of Cambridge, Addenbrookes Hospital, Cambridge, United Kingdom

^bPrincipal Research Associate, Institute of Metabolic Science, University of Cambridge, Addenbrookes Hospital, Cambridge, United Kingdom

Keywords

Closed-loop; continuous glucose sensor; insulin pump; algorithm1

Introduction

Advances in diabetes technology have led to significant improvements in the quality of life and care received by subjects with diabetes. In spite of this, achieving tight glycemic control through intensive insulin therapy and modern insulin regimens is challenging due to the barrier of hypoglycemia¹, the most feared complication of insulin therapy as reported by patients, carers, and physicians².

Recent research in the field of therapeutic devices for type 1 diabetes has been geared towards improving glucose monitoring and insulin delivery devices with the view of integrating these into an artificial pancreas, a closed-loop insulin delivery system³. Coupling subcutaneous continuous glucose monitoring⁴ and subcutaneous insulin pump delivery⁵, closed-loop systems deliver insulin in continually glucose-responsive fashion (Figure 1). This novel approach differs from conventional pump therapy through the use of a control algorithm which directs insulin delivery according to real-time sensor glucose levels⁶. The artificial pancreas may transform the management of type 1 diabetes and improve the quality of life acting as a bridge to cure until the stem cell therapy or islet cell transplantation become available.

The first effort to develop components of the artificial pancreas started with studies on semi-continuous glucose monitoring by Weller in 1960⁷. The first “portable” insulin pump was designed by Kadish in 1964⁸. Prototypes of the artificial pancreas adopting intravascular

© 2011 Elsevier Inc. All rights reserved.

^bCorresponding author for proof and reprints: Roman Hovorka, PhD, Institute of Metabolic Science, University of Cambridge, Box 289, Level 4, Addenbrooke's Hospital, Cambridge, CB2 0QQ United Kingdom, Phone: +44 1223 762 862, Fax: +44 1223 336 996, rh347@cam.ac.uk.

^aCoauthor address: Hood Thabit, MD, Institute of Metabolic Science, University of Cambridge, Box 289, Level 4, Addenbrooke's Hospital, Cambridge, CB2 0QQ United Kingdom, Phone: +44 1223 769 074, Fax: +44 1223 336 996, ht312@medschl.cam.ac.uk

Competing Interest

RH reports having received speaker honoraria from Minimed Medtronic, Lifescan, and Novo Nordisk, serving on advisory panel for Animas and Minimed Medtronic, receiving license fees from BBraun and Beckton Dickinson; and having served as a consultant to Beckton Dickinson, BBraun and Profil. HT has nothing to declare.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

sensing and delivery in 1970's by Albisser and Pfeiffer^{9, 10} then paved the way for the first commercial closed-loop bedside device in 1974, the Biostator (Miles Laboratories, Elkhart, IN, USA). Attempts to miniaturize the Biostator concept followed¹¹ but given the infection risk and lack of commercially available devices supporting the intravascular route, focus turned in late 1990's to alternative body access ports.

Prototypes that are currently in use adopt the subcutaneous route for measurement of interstitial glucose and insulin delivery¹². Other means of insulin delivery and glucose sensing have been studied. The delivery of insulin intraperitoneally has been demonstrated to be feasible by Renard et al¹³ but focus firmly remains on the subcutaneous route.

This chapter outlines the individual components of the closed-loop system together with existing clinical evidence. The artificial pancreas prototypes currently used in clinical studies are reviewed as well as obstacles and limitations facing the technology. Additional information can be found elsewhere^{3, 14, 15}.

Components of the closed-loop systems

Continuous Glucose Monitoring

The advent of real-time glucose sensing has been a crucial step in the glucose monitoring technology⁴. In contrast to older devices that provided Holter-type retrospective data¹⁶, real-time glucose monitoring allows the patient to make immediate adjustments to their insulin doses, food intake and physical activity by inspecting glucose values and trends, and by responding to low and high glucose alarms.

The present generation of continuous glucose monitors provides a minimally invasive method to measure glycemic variations and report glucose trends¹⁷. Most widely used devices utilize a subcutaneously implanted needle-type amperometric enzyme electrode, which measures interstitial glucose concentration by detecting changes in the electric current caused by the enzymatic catalysation of glucose by glucose oxidase into hydrogen peroxide¹⁸. Examples include Enlite® (Medtronic MiniMed, Northridge, CA, USA), Dexcom™ SEVEN® PLUS (DexCom Inc, San Diego, CA, USA) and Freestyle Navigator® (Abbot Laboratories, Alameda, CA, USA) continuous glucose monitors (Figure 2). The devices display a new glucose reading every 1 to 5 minutes for up to seven days of continuous wear per sensor insertion.

Reverse iontophoresis was utilised by GlucoWatch (Cygnus, Redwood City, CA, USA) to measure interstitial glucose *ex vivo*¹⁹- the device is no longer available. Microdialysis²⁰ with *ex vivo* glucose-oxidase sensing is used by the GlucoMen® device (Menarini Diagnostics, Firenze, Italy) employing a fine hollow dialysis fibre implanted in the subcutaneous tissue and perfused with isotonic fluid, which then carries glucose to an *ex vivo* placed glucose-oxidase sensor²¹.

The main value of continuous glucose monitoring in clinical practice is in identifying trends of glucose values and reducing the frequency and severity of hypoglycemia events. A meta-analysis²² of randomized controlled trials evaluating continuous glucose monitoring in the adults and youth documented a significant reduction in HbA1c particularly in those with the highest HbA1c at baseline and frequent users of continuous glucose monitoring. Exposure to hypoglycemia is also reduced during continuous glucose monitoring. Criticisms has been leveled at the need to use the sensors 80% of the time to achieve benefits²³ but continuous glucose monitoring in combination with intensive insulin therapy appears to be cost-effective relative to self-monitoring of blood glucose²⁴.

Insulin Pump

Insulin pump therapy uses a portable electromechanical pump to mimic nondiabetic insulin delivery. The pump infuses insulin at preselected rates—normally a slow basal rate with patient-activated boosts at mealtime⁵. The use of insulin pump therapy is growing but is varied across developed countries; an estimated 20–25% of subjects with type 1 diabetes use insulin pump in the US, 10% in Sweden and Germany and <1% in Denmark²⁵.

Most modern insulin pumps are around the size of a pager. They comprise an insulin reservoir, a small battery-operated motor that is linked to a computerized control mechanism, and a subcutaneous infusion set (cannula and tubing system). Sensor-augmented insulin pumps, such as the MiniMed Paradigm Veo® (Medtronic MiniMed, Northridge, CA, USA) (Figure 3) or Vibe™ (Animas, West Chester, PA, USA) feature integration with a continuous glucose monitor with documented benefits on HbA1c reduction²⁶. A recent innovation in pump design has been the introduction of the patch pump (the Omnipod, Insulet, MA, USA), which has a reservoir unit that adheres directly to the patient's skin and houses an integrated infusion set and automated inserter, thus making it “tubing-free”²⁷.

Insulin pump normally deliver rapid-acting insulin analogues²⁸. Modern “smart” pumps have a built-in customizable bolus calculator and monitor “insulin on board” to reduce the risk of insulin stacking²⁹.

Control Algorithm

Two main families of control algorithm have been employed in closed-loop clinical studies⁶, the classic feedback proportional-integral-derivative (PID) controller^{30–34} and the model predictive controller (MPC)^{35–38}. The PID controller adjusts insulin delivery by assessing glucose excursions from three viewpoints; the departure from target glucose (the proportional component), the area-under-curve between ambient and target glucose (the integral component), and the rate of change in ambient glucose (the derivative component)³². PID controllers have been used with intravascular and subcutaneous glucose sensing and insulin delivery^{11, 39, 40}, as well as during intraperitoneal insulin delivery¹³.

Most recent research focuses on the MPC approach⁴¹ as it can more easily accommodate delays associated with insulin absorption and also account for meal intake and prandial insulin boluses. The vital ingredient of the MPC is a mathematical model that links insulin delivery and meal ingestion to glucose excursions³⁶. The MPC approach works by comparing the model predicted glucose levels with the actual glucose levels, updating the model, and calculating future insulin infusion rates to minimize the difference between the model predicted glucose concentration and target glucose concentration. Other clinically evaluated control approaches include fuzzy logic⁴² which modulate insulin delivery on the basis of approximate rules and may be suitable to express empirical knowledge acquired by diabetes practitioners. Algorithms may include a safety module to constrain insulin delivery⁴³ limiting the amount of insulin on board⁴⁴, or the maximum rate of insulin delivery, or suspending insulin delivery when glucose levels are low or decreasing⁴⁵.

Artificial Pancreas Prototypes

Research prototypes of the artificial pancreas adopting the subcutaneous route include the Artificial Pancreas Software (APS), a modular system⁴⁶ supporting wireless connection to a range of glucose sensors and insulin pumps. The physiologic insulin delivery (ePID) system comprises Medtronic's glucose sensor and pump and uses the proportional-integral-derivative algorithm with recent modification for insulin feedback⁴⁷. The Florence platform expands on the manual Cambridge system⁴⁸ and uses Navigator continuous glucose

monitor, the Aviator insulin pump and an MPC controller, see Figure 4. The Boston prototype for dual hormone delivery uses manual closed-loop control adopting venous blood glucose measurement (GlucoScout, International Biomedical), and an MPC algorithm for insulin delivery and a PID controller for glucagon delivery³⁷. The Oregon prototype for dual hormone delivery uses manual closed-loop control with a fading memory proportional derivative controller³³.

Closed Loop Approaches

Overview

It is anticipated that closed-loop systems will evolve with increasing technology sophistication and more comprehensive treatment objectives⁴⁹. Early generations are likely to provide benefits in terms of reduced incidence of hypoglycemia. Follow-up closed-loop applications may address hyperglycemia, postprandial control and life style activities including exercise. Meals and exercise can be “announced” to the control algorithm and prandial insulin boluses can be delivered by the patient simplifying the closed-loop operation. In a more challenging “fully closed-loop” configuration, the control algorithm is not aware of meals and exercise and delivers insulin solely on sensor glucose levels. Glucagon co-administration can be used to counteract peripheral overinsulinisation following insulin boluses or delayed insulin absorption. Table 1 lists closed-loop approaches and associated results.

Low Glucose Suspend

The low glucose suspend function is the first example of a commercial application of closed-loop insulin delivery. An insulin pump with an integrated continuous glucose monitoring (Paradigm® Veo, Medtronic Diabetes, Northridge, CA, USA) automatically suspends insulin delivery for up to two hours when hypoglycemia is detected and hypoglycemia alarm is not acknowledged by the patient. Low glucose suspend aims to reduce severity of hypoglycemia as prolonged low sensor glucose levels may lead to seizures⁵⁰.

Post-marketing studies with low glucose suspend in adults and children documented significant reductions in the frequency and duration of nocturnal hypoglycemia particularly in those with greatest risk^{51, 52}. In spite of occasional suboptimal sensor accuracy, no adverse events such as severe hyperglycemia, ketosis or other safety issues were noted. Patients found the low glucose suspend function useful and were in favor of its regular use⁵¹.

Hypoglycemia Prevention

Low glucose suspend function aims to reduce severity but does not prevent hypoglycemia which is an objective of work by Buckingham *et al* who tested an algorithm to discontinue insulin delivery when pending hypoglycemia was predicted⁵³. The approach prevented hypoglycemia on 75% of nights (84% events) without hyperglycemia rebound. Up to four hour and rarely longer suspension of insulin delivery are also present during overnight closed-loop. Assessment of safety and efficacy has been made for PID⁵⁴ and MPC⁴⁵ controllers in children and adolescents indicating that prolonged suspension is safe and useful.

Overnight Closed-Loop Studies

Most severe hypoglycemic events occur after midnight⁵⁵. Young children are vulnerable to the adverse effects of neuroglycopenia such as seizures, which are related to hypoglycemia when they sleep⁵⁶. Thus, overnight closed-loop delivery to reduce the risk of hypoglycemia

may provide a solution to an important clinical problem of concern to many parents and caregivers⁵⁷.

Randomized cross-over studies in young patients demonstrated that overnight closed-loop control was able to significantly increase the time spent in target glucose range and reduce the time spent in hypoglycemia³⁸. No nocturnal hypoglycemic episodes were documented and rescue carbohydrates were not required during closed-loop. This was an important step towards realizing the clinical potential of the closed-loop system. Randomized closed-loop studies in adults have shown similar promising results. Closed-loop delivery increased the overnight time spent within target glucose levels and reduced overnight time in hypoglycemia⁴⁸. Similar to studies in children, overnight hypoglycemia below 55mg/dl (3.0 mmol/l) was eliminated by closed-loop insulin delivery in adults.

Risk analysis using extensive *in-silico* testing to assess the impact of calibration errors and sensor artefacts suggested that overnight closed-loop may reduce substantially incidence of nocturnal hypoglycemia⁵⁸. These improvements encourage the progress to ambulatory testing.

Day and Night Closed-Loop Studies

Waking hours present a unique set of challenges including variable dietary and exercise patterns. The postprandial period is particularly challenging due to delays associated with absorption of subcutaneously delivered insulin and variable appearance of glucose from the meal. This can lead to late postprandial hypoglycemia as closed-loop systems may deliver too much insulin in an attempt to correct high postprandial glucose levels. During conventional pump therapy, the delayed action of insulin may lead to “insulin stacking” increasing the risk of hypoglycemia and similar concerns apply to closed-loop.

A practical solution is to combine closed-loop operation with conventional manual delivery of prandial boluses. A PID algorithm with meal announcement (a hybrid closed-loop system) gave significantly better postprandial glucose levels compared to a fully closed-loop system³⁴ using small prandial boluses given 10–15 minutes before meals. A multinational study evaluating an MPC controller documented reduced frequency of nocturnal hypoglycemia events and after breakfast, the closed-loop controlled glucose levels as effectively as patient-directed conventional insulin pump therapy. A sample glucose profile from a closed-loop study with an MPC controller during adolescence⁵⁹ is shown in Figure 5.

The feasibility and efficacy of MPC-based closed-loop insulin delivery was demonstrated in women throughout different stages of pregnancy⁶⁰. Randomized study of a well controlled cohort of pregnant women suggested a reduced risk of very low glucose levels with closed-loop insulin delivery but otherwise similar glucose outcomes⁶¹.

Dual-hormone or bi-hormonal delivery systems incorporate the delivery of insulin with counter-regulatory hormones such as glucagon. The advantage of using glucagon is that it acts rapidly mimicking the physiological response to hypoglycemia without the need for fast-acting oral glucose. Glucagon co-administration has been investigated with the fully closed-loop approach^{33, 37} and although effective, glucagon could not fully counteract insulin overdelivery and on occasions hypoglycemia presented³⁷.

Limitations and Obstacles

Accuracy of Continuous Glucose Monitors

Suboptimal accuracy and reliability remains one of the biggest obstacle for closed-loop systems^{12, 14}. Commercially available CGM devices can achieve a median relative absolute

difference between sensor and reference glucose measurements of 15% or less which should be commensurate with closed-loop glucose control. However, transient and persistent deviations of greater magnitude occur. Transient deviations relate to temporal loss or increase of sensor sensitivity, or mechanical perturbation including temporal sensor dislodgment⁶². Persistent deviations are caused by erroneous calibration, an inappropriate calibration algorithm or by a slow drift of sensor sensitivity. When sensor over-reads blood glucose levels, the persistent deviations pose the greatest challenge to safe closed-loop insulin delivery, as insulin overdelivery may occur increasing the risk of hypoglycemia.

A 5 to 15minute time lag between glucose levels in the interstitial fluid and blood glucose values contributes to the sensor deviations and reflects the transport of glucose from blood to the interstitial fluid^{63, 6465, 66}.

Insulin Absorption

Even with modern rapid-acting insulin analogues it takes approximately 90–120 minutes for subcutaneously delivered insulin analogues to reach its maximum glucose-lowering capacity, and its action can continue well beyond this peak. The administration of several correction boluses in close sequence will cause “insulin stacking” and a high risk of hypoglycemia. This issue, if not accounted for by the control algorithm, can pose a safety hazard for closed-loop systems⁴⁴ and high glucose levels may have to be normalized slowly even during closed-loop delivery complicating postprandial glucose control. Control during and after exercise may require pre-emptive carbohydrate intake or dual hormone treatment to eliminate the risk of hypoglycemia⁶⁷.

Individual Variability

Insulin absorption and insulin action vary substantially between and within subjects⁶⁸. Inter-subject variability is due to factors influencing insulin sensitivity such as body mass, age, gender, physical activity and smoking. Intra-subject variability reflects the day-to-day and also hour-to-hour variations related to circadian and diurnal cycles, dawn phenomenon⁶⁹, acute illness, stress⁷⁰ as well as the delayed effects of exercise and alcohol⁷¹. These variations in insulin requirements need to be compensated for by closed-loop operations and adaptive systems may be required to compensate fully for these variations.

Future Directions

The next research priority is to test the artificial pancreas outside the confines of a controlled laboratory environment and ultimately in the patient’s home. Artificial pancreas studies at home may involve short-term testing, possibly at transitional hotel-like facility, followed by long-term testing to compare closed-loop control against conventional insulin therapy.

The introduction of the artificial pancreas into clinical practice will likely be a staged process focusing initially on hypoglycemia prevention followed by tightening of glucose control. It is important to set realistic goals as clinically meaningful improvement of glycemic control expressed by HbA1c may occur gradually. Wider use may depend upon the establishment of appropriate infrastructures that can provide support, both technical and clinical, to patients and clinical practitioners who will be using the artificial pancreas.

References

1. Cryer PE. The barrier of hypoglycemia in diabetes. *Diabetes*. 2008; 57(12):3169–3176. [PubMed: 19033403]
2. Unger J, Parkin C. Hypoglycemia in insulin-treated diabetes: a case for increased vigilance. *Postgrad Med*. 2011; 123(4):81–91. [PubMed: 21680992]

3. Hovorka R. Closed-loop insulin delivery: from bench to clinical practice. *Nat Rev Endocrinol*. 2011; 7(7):385–395. [PubMed: 21343892]
4. Klonoff DC. Continuous glucose monitoring: roadmap for 21st century diabetes therapy. *Diabetes Care*. 2005; 28(5):1231–1239. [PubMed: 15855600]
5. Pickup J, Keen H. Continuous subcutaneous insulin infusion at 25 years: evidence base for the expanding use of insulin pump therapy in type 1 diabetes. *Diabetes Care*. 2002; 25(3):593–598. [PubMed: 11874953]
6. Bequette BW. A critical assessment of algorithms and challenges in the development of a closed-loop artificial pancreas. *Diabetes Technol Ther*. 2005; 7(1):28–47. [PubMed: 15738702]
7. Weller C, Linder M, Macaulay A, et al. Continuous in vivo determination of blood glucose in human subjects. *Ann N Y Acad Sci*. 1960; 87:658–668. [PubMed: 13784216]
8. Kadish A. Automation control of blood sugar. I. A servomechanism for glucose monitoring and control. *Am J Med Electron*. 1964; 3:82–86. [PubMed: 14150660]
9. Albisser AM, Leibel BS, Ewart TG, et al. An artificial endocrine pancreas. *Diabetes*. 1974; 23(5):389–396. [PubMed: 4598089]
10. Pfeiffer EF, Thum C, Clemens AH. The artificial beta cell--a continuous control of blood sugar by external regulation of insulin infusion (glucose controlled insulin infusion system). *Horm Metab Res*. 1974; 6(5):339–342. [PubMed: 4607598]
11. Renard E, Costalat G, Chevassus H, et al. Closed loop insulin delivery using implanted insulin pumps and sensors in type 1 diabetic patients. *Diabetes Res Clin Pract*. 2006; (Suppl 2):S173–S177.
12. Hovorka R. Continuous glucose monitoring and closed-loop systems. *Diabet Med*. 2006; 23(1):1–12. [PubMed: 16409558]
13. Renard E, Place J, Cantwell M, et al. Closed-loop insulin delivery using a subcutaneous glucose sensor and intraperitoneal insulin delivery: feasibility study testing a new model for the artificial pancreas. *Diabetes Care*. 2010; 33(1):121–127. [PubMed: 19846796]
14. Steil GM, Rebrin K. Closed-loop insulin delivery - what lies between where we are and where we are going? *Expert Opin Drug Deliv*. 2005; 2(2):353–362. [PubMed: 16296759]
15. Renard E, Costalat G, Chevassus H, et al. Artificial beta-cell: clinical experience toward an implantable closed-loop insulin delivery system. *Diabetes Metab*. 2006; 32(5 Pt 2):497–502. [PubMed: 17130808]
16. Mastrototaro J. The MiniMed Continuous Glucose Monitoring System (CGMS). *J Pediatr Endocrinol Metab*. 1999; 12 (Suppl 3):751–758. [PubMed: 10626266]
17. Oliver NS, Toumazou C, Cass AE, et al. Glucose sensors: a review of current and emerging technology. *Diabet Med*. 2009; 26(3):197–210. [PubMed: 19317813]
18. Feldman B, Brazg R, Schwartz S, et al. A continuous glucose sensor based on wired enzyme technology -- results from a 3-day trial in patients with type 1 diabetes. *Diabetes Technol Ther*. 2003; 5(5):769–779. [PubMed: 14633342]
19. Tamada JA, Garg S, Jovanovic L, et al. Noninvasive glucose monitoring: comprehensive clinical results. *Cygnus Research Team JAMA*. 1999; 282(19):1839–1844.
20. Bolinder J, Ungerstedt U, Arner P. Microdialysis measurement of the absolute glucose concentration in subcutaneous adipose tissue allowing glucose monitoring in diabetic patients. *Diabetologia*. 1992; 35(12):1177–1180. [PubMed: 1478372]
21. Valgimigli F, Lucarelli F, Scuffi C, et al. Evaluating the clinical accuracy of GlucoMen®Day: a novel microdialysis-based continuous glucose monitor. *J Diabetes Sci Technol*. 2010; 4(5):1182–1192. [PubMed: 20920438]
22. Pickup JC, Freeman SC, Sutton AJ. Glycaemic control in type 1 diabetes during real time continuous glucose monitoring compared with self monitoring of blood glucose: meta-analysis of randomised controlled trials using individual patient data. *BMJ*. 2011; 343:d3805. [PubMed: 21737469]
23. Peters A. Do we really need continuous glucose monitoring? *Diabetes Technol Ther*. 2009; 11 (Suppl 1):S128–130. [PubMed: 19469672]

24. McQueen R, Ellis S, Campbell J, et al. Cost-effectiveness of continuous glucose monitoring and intensive insulin therapy for type 1 diabetes. *Cost Eff Resour Alloc.* 2011 Sep.14(9):13. [PubMed: 21917132]
25. Selam S. CSII in Europe: where are we, where are we going? An analysis of articles published in Infusystems International. *Diabetes Res Clin Pract.* 2006; 74(Suppl 2):S23–126.
26. Bergenstal RM, Tamborlane WV, Ahmann A, et al. Effectiveness of sensor-augmented insulin-pump therapy in type 1 diabetes. *N Engl J Med.* 2010; 363(4):311–320. [PubMed: 20587585]
27. Zisser H, Jovanovic L. OmniPod Insulin Management System: patient perceptions, preference, and glycemic control. *Diabetes Care.* 2006; 29(9):2175. [PubMed: 16936173]
28. Bode BW. Comparison of pharmacokinetic properties, physicochemical stability, and pump compatibility of 3 rapid-acting insulin analogues-aspart, lispro, and glulisine. *Endocr Pract.* 2011; 17(2):271–280. [PubMed: 21134878]
29. Zisser H, Wagner R, Pleus S, et al. Clinical performance of three bolus calculators in subjects with type 1 diabetes mellitus: a head-to-head-to-head comparison. *Diabetes Technol Ther.* 2010; 12(12):955–961. [PubMed: 21128842]
30. Clemens AH. Feedback control dynamics for glucose controlled insulin infusion system. *Med Prog Technol.* 1979; 6(3):91–98. [PubMed: 481365]
31. Marchetti G, Barolo M, Jovanovic L, et al. An improved PID switching control strategy for type 1 diabetes. *IEEE Trans Biomed Eng.* 2008; 55(3):857–865. [PubMed: 18334377]
32. Steil GM, Rebrin K, Darwin C, et al. Feasibility of automating insulin delivery for the treatment of type 1 diabetes. *Diabetes.* 2006; 55(12):3344–3350. [PubMed: 17130478]
33. Castle JR, Engle JM, El Youssef J, et al. Novel use of glucagon in a closed-loop system for prevention of hypoglycemia in type 1 diabetes. *Diabetes Care.* 2010; 33(6):1282–1287. [PubMed: 20332355]
34. Weinzierl SA, Steil GM, Swan KL, et al. Fully automated closed-loop insulin delivery versus semiautomated hybrid control in pediatric patients with type 1 diabetes using an artificial pancreas. *Diabetes Care.* 2008; 31(5):934–939. [PubMed: 18252903]
35. Magni L, Raimondo DM, Bossi L, et al. Model predictive control of type 1 diabetes: an in silico trial. *J Diabetes Sci Technol.* 2007; 1(6):804–812. [PubMed: 19885152]
36. Hovorka R, Canonico V, Chassin LJ, et al. Nonlinear model predictive control of glucose concentration in subjects with type 1 diabetes. *Physiol Meas.* 2004; 25(4):905–920. [PubMed: 15382830]
37. El-Khatib FH, Russell SJ, Nathan DM, et al. A bihormonal closed-loop artificial pancreas for type 1 diabetes. *Sci Transl Med.* 2010; 2(27):27ra27.
38. Hovorka R, Allen JM, Elleri D, et al. Manual closed-loop insulin delivery in children and adolescents with type 1 diabetes: a phase 2 randomised crossover trial. *Lancet.* 2010; 375(9716): 743–751. [PubMed: 20138357]
39. Steil GM, Panteleon AE, Rebrin K. Closed-loop insulin delivery-the path to physiological glucose control. *Adv Drug Deliv Rev.* 2004; 56(2):125–144. [PubMed: 14741112]
40. Shimoda S, Nishida K, Sakakida M, et al. Closed-loop subcutaneous insulin infusion algorithm with a short-acting insulin analog for long-term clinical application of a wearable artificial endocrine pancreas. *Front Med Biol Eng.* 1997; 8(3):197–211. [PubMed: 9444512]
41. Camacho, EF.; Bordons, C. *Model Predictive Control.* Springer-Verlag; 1999.
42. Atlas E, Nimri R, Miller S, et al. MD-logic artificial pancreas system: a pilot study in adults with type 1 diabetes. *Diabetes Care.* 2010; 33(5):1072–1076. [PubMed: 20150292]
43. Kovatchev B, Patek S, Dassau E, et al. Control to range for diabetes: functionality and modular architecture. *J Diabetes Sci Technol.* 2009; 3(5):1058–1065. [PubMed: 20144419]
44. Ellingsen C, Dassau E, Zisser H, et al. Safety constraints in an artificial pancreatic beta cell: an implementation of model predictive control with insulin on board. *J Diabetes Sci Technol.* 2009; 3(3):536–544. [PubMed: 20144293]
45. Elleri D, Allen JM, Nodale M, et al. Suspended insulin infusion during overnight closed-loop glucose control in children and adolescents with Type 1 diabetes. *Diabet Med.* 2010; 27(4):480–484. [PubMed: 20536523]

46. Dassau E, Zisser H, Palerm C, et al. Modular artificial beta-cell system: a prototype for clinical research. *J Diabetes Sci Technol*. 2008; 2(5):863–872. [PubMed: 19885271]
47. Steil GM, Palerm CC, Kurtz N, et al. The effect of insulin feedback on closed loop glucose control. *J Clin Endocrinol Metab*. 2011; 96(5):1402–1408. [PubMed: 21367930]
48. Hovorka R, Kumareswaran K, Harris J, et al. Overnight closed loop insulin delivery (artificial pancreas) in adults with type 1 diabetes: crossover randomised controlled studies. *BMJ*. 2011; 342:d1855. [PubMed: 21493665]
49. Kowalski AJ. Can we really close the loop and how soon? Accelerating the availability of an artificial pancreas: a roadmap to better diabetes outcomes. *Diabetes Technol Ther*. 2009; 11 (Suppl 1):S113–119. [PubMed: 19621478]
50. Buckingham B, Wilson DM, Lecher T, et al. Duration of nocturnal hypoglycemia before seizures. *Diabetes Care*. 2008; 31(11):2110–2112. [PubMed: 18694975]
51. Choudhary P, Shin J, Wang Y, et al. Insulin pump therapy with automated insulin suspension in response to hypoglycemia: reduction in nocturnal hypoglycemia in those at greatest risk. *Diabetes Care*. 2011; 34(9):2023–2025. [PubMed: 21868778]
52. Danne T, Kordonouri O, Holder M, et al. Prevention of hypoglycemia by using Low Glucose Suspend function in sensor-augmented pump therapy. *Diabetes Technol Ther*. 2011
53. Buckingham B, Chase HP, Dassau E, et al. Prevention of nocturnal hypoglycemia using predictive alarm algorithms and insulin pump suspension. *Diabetes Care*. 2010; 33(5):1013–1017. [PubMed: 20200307]
54. Cengiz E, Swan KL, Tamborlane WV, et al. Is an automatic pump suspension feature safe for children with type 1 diabetes? An exploratory analysis with a closed-loop system. *Diabetes Technol Ther*. 2009; 11(4):207–210. [PubMed: 19344194]
55. Epidemiology of severe hypoglycemia in the diabetes control and complications trial. The DCCT Research Group. *Am J Med*. 1991; 90(4):450–459. [PubMed: 2012085]
56. Davis EA, Keating B, Byrne GC, et al. Hypoglycemia: incidence and clinical predictors in a large population-based sample of children and adolescents with IDDM. *Diabetes Care*. 1997; 20(1):22–25. [PubMed: 9028688]
57. Elleri D, Acerini CL, Allen JM, et al. Parental attitudes towards overnight closed-loop glucose control in children with type 1 diabetes. *Diabetes Technol Ther*. 2010; 12(1):35–39. [PubMed: 20082583]
58. Wilinska ME, Budiman ES, Taub MB, et al. Overnight closed-loop insulin delivery with model predictive control: assessment of hypoglycemia and hyperglycemia risk using simulation studies. *J Diabetes Sci Technol*. 2009; 3(5):1109–1120. [PubMed: 20144424]
59. Elleri D, Allen JM, Kumareswaran K, et al. Day-and-night closed loop (CL) glucose control in adolescents with type 1 diabetes (T1D). *Diabetes*. 2011; 60 (Suppl 1):A41.
60. Murphy HR, Elleri D, Allen JM, et al. Closed-loop insulin delivery during pregnancy complicated by type 1 diabetes. *Diabetes Care*. 2011; 34(2):406–411. [PubMed: 21216859]
61. Murphy HR, Kumareswaran K, Elleri D, et al. Safety and efficacy of 24-h closed-loop insulin delivery in well-controlled pregnant women with type 1 diabetes: A randomized crossover case series. *Diabetes Care*. 2011; 34(10):2337–2340. [PubMed: 22111430]
62. McGarraugh G, Bergenstal R. Detection of hypoglycemia with continuous interstitial and traditional blood glucose monitoring using the FreeStyle Navigator Continuous Glucose Monitoring System. *Diabetes Technol Ther*. 2009; 11(3):145–150. [PubMed: 19216686]
63. Garg SK, Voelml M, Gottlieb PA. Time lag characterization of two continuous glucose monitoring systems. *Diabetes Res Clin Pract*. 2010; 87(3):348–353. [PubMed: 20022127]
64. Weinstein RL, Schwartz SL, Brazg RL, et al. Accuracy of the 5-day FreeStyle Navigator Continuous Glucose Monitoring System: comparison with frequent laboratory reference measurements. *Diabetes Care*. 2007; 30(5):1125–1130. [PubMed: 17337488]
65. Keenan DB, Mastrototaro JJ, Voskanyan G, et al. Delays in minimally invasive continuous glucose monitoring devices: a review of current technology. *J Diabetes Sci Technol*. 2009; 3(5):1207–1214. [PubMed: 20144438]
66. Wei C, Lunn DJ, Acerini CL, et al. Measurement delay associated with the Guardian RT continuous glucose monitoring system. *Diabet Med*. 2010; 27(1):117–122. [PubMed: 20121899]

67. Tsalikian E, Kollman C, Tamborlane WB, et al. Prevention of hypoglycemia during exercise in children with type 1 diabetes by suspending basal insulin. *Diabetes Care*. 2006; 29(10):2200–2204. [PubMed: 17003293]
68. Heinemann L. Variability of insulin absorption and insulin action. *Diabetes Technol Ther*. 2002; 4(5):673–682. [PubMed: 12450450]
69. Carroll MF, Schade DS. The dawn phenomenon revisited: implications for diabetes therapy. *Endocr Pract*. 2005; 11(1):55–64. [PubMed: 16033737]
70. Riazi A, Pickup J, Bradley C. Daily stress and glycaemic control in Type 1 diabetes: individual differences in magnitude, direction, and timing of stress-reactivity. *Diabetes Res Clin Pract*. 2004; 66(3):237–244. [PubMed: 15536020]
71. Turner BC, Jenkins E, Kerr D, et al. The effect of evening alcohol consumption on next-morning glucose control in type 1 diabetes. *Diabetes Care*. 2001; 24(11):1888–1893. [PubMed: 11679452]
72. Buckingham B, Cobry E, Clinton P, et al. Preventing hypoglycemia using predictive alarm algorithms and insulin pump suspension. *Diabetes Technol Ther*. 2009; 11(2):93–97. [PubMed: 19848575]
73. Kovatchev B, Cobelli C, Renard E, et al. Multinational study of subcutaneous model-predictive closed-loop control in type 1 diabetes mellitus: summary of the results. *J Diabetes Sci Technol*. 2010; 4(6):1374–1381. [PubMed: 21129332]

Figure 1.

Illustration of a closed-loop system comprising of a glucose sensor (rectangle on the left-hand side of the abdomen), an insulin pump (device in the pocket connected to patient via an infusion-set) and a mobile sized device containing the control algorithm (in patient's hand). Each component communicates with each other wirelessly. (From Hovorka R. Closed-loop insulin delivery: from bench to clinical practise. Nat. Rev.Endocrinol 2011; 7: 385–395)

Figure 2. Examples of continuous glucose monitoring devices; the Dexcom™ SEVEN® PLUS (above), and the Freestyle Navigator® (below).

Figure 3.
A sensor augmented insulin pump; the MiniMed Paradigm Veo® integrated with the Enlite® continuous glucose sensor.

Figure 4.

A study participant displaying the Florence closed-loop insulin delivery system, consisting of a handheld device (Companion) which receives and displays glucose value data from the Freestyle Navigator Transmitter, communicating with the Control Algorithm Device (CAD) and controlling the subcutaneous insulin pump.

Figure 5.

The three panels illustrate glucose levels and insulin delivery profiles observed during a 36 hour closed-loop study in a young subject. The bold line shows the continuous subcutaneous glucose trace and the black square indicate reference plasma glucose values (not used to determine the insulin delivery but shown to demonstrate deviation between sensor and plasma glucose levels). Insulin infusion rates during closed-loop delivery are denoted by the grey line. Vertical arrows indicate meals and snacks (light grey arrow) and insulin boluses (dark grey arrow). Carbohydrate contents of the meal/snack and insulin doses are also shown. Horizontal dashed lines illustrate the target range of 90 to 180 mg/dl (3.9 to 10mmol/L).

Table 1

Summary of achieved results with various closed-loop delivery approaches.

Objective/approach	Status	Results	Ref
Low glucose suspend	Postmarketing studies	Reduced nocturnal hypoglycemia in those with greatest risk; well accepted by patients	51, 52
Suspend to prevent low glucose	Laboratory studies; home studies planned	Nocturnal hypoglycemia prevention of 80 % events; effective as part of overnight closed-loop	53, 72
Treat to range	Laboratory testing underway	---	--
Overnight	Laboratory studies; home studies planned	Increased time spent in target glucose range by 20% in adolescents and adults; reduced risk of nocturnal hypoglycemia	38, 48
Meal announcement	Laboratory studies	Feasibility documented in children, adults, pregnant women using various control algorithms; preferred option by most investigators	59, 60, 73
Fully closed-loop	Laboratory studies	Feasibility documented in children and adults; addition of small prandial bolus improves control; delayed insulin absorption/action remains a challenge	13, 32, 34, 42, 47
Fully closed-loop with glucagon co-administration	Laboratory studies	Feasibility documented in adults; glucagon helpful but cannot always overcome insulin overdosage	33, 37