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Closed loop insulin delivery systems

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Introduction

Type 1 diabetes affects 90,000 children in Europe, and its incidence has doubled over the last 10 years.[1] It leads to lifelong dependency on insulin injections. Insulin therapy targets both basal and prandial insulin requirement with the aim of achieving overall glucose control (assessed by glycated haemoglobin HbA1c) sufficient to prevent long term complications.[2] However, reductions in HbA1c are often associated with an increasing risk of hypoglycaemia; the most feared complication for children and their parents.[3] On standard insulin regimens 45-60% of subjects may have profound, severe, prolonged, generally asymptomatic, hypoglycaemia overnight.[4,5] Fear of hypoglycaemia may be a major impediment to achieving glycaemic targets and the Hvidore study and recent data from Germany[6,7] indicate that HbA1c levels are still too high, particularly during adolescence.

The standard therapy of type 1 diabetes is based on multiple insulin injections using a combination of short and long acting insulin analogues supported by blood glucose self monitoring.[8] Treatment using a continuous subcutaneous insulin infusion (CSII) and an insulin pump is increasing.[9] Diabetes technology is continually improving and in the last decade, at least five continuous glucose monitors (CGM) have received regulatory approval although some did not live up to expectations.[10] These devices have demonstrated the extent of the challenges posed by our attempts to mimic normal pancreatic insulin secretion using injections or infusions. They demonstrate the extreme variability in insulin response relating to short term changes in diet or exercise and long term variation related to puberty and gender.[11]

Islet cell or pancreatic transplant remains on the horizon but in the interim a technological solution to the problem of targeting insulin therapy may be available. The combination of the available CGM and insulin pump technology has prompted research into closed-loop systems[12-16,] which could deliver insulin according to 'real-time' changes in glucose levels. A closed-loop approach has the potential to revolutionise the management of glucose control. A closed-loop system, also called the artificial pancreas consists of three components, a continuous glucose monitor to measure glucose concentration, a titrating algorithm to compute the amount of insulin to be delivered, and an insulin pump delivering computed insulin

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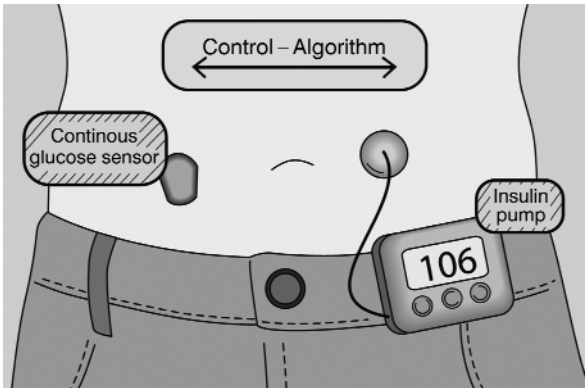

Fig. 1. *The Artificial Pancreas (reprinted with permission from www.jdrf.org/artificialpancreas).*

doses, see figure 1. So far, only few prototypes have been developed and testing has been limited to clinical settings. However, an aggressive concerted effort promises an accelerated progress towards home testing of closed-loop systems and beyond.

Closed-loop systems can be divided according to the way prandial insulin delivery is handled and according to the body interface.

Meal-associated glucose excursions pose greatest challenge to closed-loop control. In a "fully closed-loop" mode, insulin is delivered in a fully automated fashion without information about the time or size of the meal or other inputs such as exercise. Insulin delivery is based solely on the evaluation of glucose excursions.[17] In a less ambitious configuration, so called "closed-loop with meal announcement" or "semi-closed-loop" system is informed about a meal and its size and may generate an advice on prandial insulin, which is delivered in an open-loop mode.[18] A "hybrid" approach is characterised by administering up to 50% of prandial bolus and allowing the remaining insulin to be delivered through the feedback control.[19,20]

Depending on body interface, three major types of closed-loop systems can be defined, (i) the subcutaneous (sc) glucose sensing and sc insulin delivery (sc-sc) system, (ii) the iv sensing and intraperitoneal (ip) delivery (iv-ip) system, and (iii) the iv sensing and iv delivery (iv-iv) system. As a minimally invasive solution and given the relatively widespread use of external insulin pumps,[9] the sc-sc approach has the greatest potential to achieve a widespread application and is the focus of the present article. However, it may not be compatible with a fully closed-loop system due to system delays disallowing safe and timely control of large or rapidly absorbed meals. The iv-ip can utilise the existing intraperitoneal insulin pump technology.[21] The iv-iv approach is usable at special situations such as in the critically ill, surgical operations, or for research investigations.

Underpinning technologies

Closed-loop systems utilise four underpinning technologies, a continuous glucose monitor, an insulin pump, wireless communication, and a control algorithm.

Continuous glucose monitors. Limited accuracy of CGMs has long limited the development of closed-loop systems. However, recent data look promising. The Freestyle Navigator (Abbott Diabetes Care, Alameda, CA, US) achieves 14% median relative absolute difference (MRAD),[22] which is commensurate with closed-loop control according to computer simulations conducted in the author's laboratory. A higher MRAD values have been reported with the Guardian RT (Med-tronic Minimed, Northridge, CA, US)[23] but the gap is narrowing[24] The lowest MRAD of 11% has been reported for the DexCom Seven STS (Dex Com, San Diego, Ca, US).[25] Whilst accuracy improved, CGM reliability remains an issue and it is now important to narrow the spread of MRAD, i.e. reduce the percentage of measurements with high MRAD. Despite these issues, the FreeStyle Navigator, the Guardian RT, and the DexCom CGMs are all being used to develop closed-loop systems within the Juvenile Diabetes Research Foundation's Artificial Pancreas project.[26]

Insulin pumps. Technological improvements over 30 years of continuous subcutaneous infusion9 have facilitated the development of insulin pumps ready to be used in closed-loop systems. The insulin pumps are small, can be remotely controlled, have alarms for cannula blockage, low battery, empty syringe, internal electronic failure etc. They have a resolution up to 0.05 U/h suitable for toddlers receiving small insulin amounts. However, insulin pumps do not alarm against leakage or dislodgement of the infusion cannula, which can complicate closed-loop control.

Wireless communication. Most of the approved CGMs and some insulin pumps implement a wireless communication for data transmission and device control facilitating at least in principle an easy assembly of closed-loop prototypes. The wireless communication is normally based on a proprietary radio-frequency protocol, details of which are not

publicly available and development of closed-loop prototypes requires collaboration among industrial and/or academic partners.

Control algorithms. Two main families of control algorithms have been employed clinically,[27] the classical feedback control embodied in the proportional-integral-derivative (PID) controller,[28-30] and the model predictive control (MPC).[18]

The PID controller adjusts the insulin infusion rate according to 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). The integral component is added to avoid long-term 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 PD controller includes the proportional and derivative components to improve robustness.

The model predictive control is at the focus of the recent research.[18,31-33] The vital ingredient of the model predictive control is a glucoregulatory model linking insulin infusion and meal ingestion to glucose excursions. This can be a physiological model representing fundamental glucoregulatory processes[18] or a "black-box" model disregarding the physiological insights but learning the insulin-glucose relationships using pattern recognition.[33]

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 minimising the difference between the model-predicted glucose concentration and the target glucose trajectory over, say, a four-hour prediction window corresponding to the duration of action of short acting insulin.

Clinical testing

So far, testing of closed-loop systems has been confined to laboratory settings. A major milestone, home testing needs to be tackled in the near future. Details of laboratory testing have been described in detail elsewhere.[12] Here, we focus on recent achievements.

Employing the Guardian RT (Medtronic Mini Med, Northridge CA, US) and the Medtronic 511 Paradigm Pump, an external physiologic insulin delivery (ePID) has been developed by Minimed – Medronic.[17] The system uses a PID controller.[34] An evaluation of the ePID system using the fully closed-loop in 10 subjects with type 1 diabetes over 28 h gave preprandial and postprandial (2 h) glucose levels at 5.6 ± 1.6 and 10.8 ± 2.6 mmol/L (mean ± SD).[17] In total, 17 hypoglycaemia events were observed mainly in the late postbreakfast period indicating postprandial hyperinsulinaemia with the fully closed-loop approach. A similar number of hypoglycaemia events were observed during open-loop control. Glucose was within the range 3.9–10.0 mmol/l 75% of the time under closed-loop versus 63% for open-loop treatment.

The group at Yale University carried out an exciting study and evaluated the ePID system in 17 well controlled (HbA1c 7.1 ± 0.8%) adolescents with type 1 diabetes over 34 hours of closed-loop control.[20] The fully closed-loop approach was tested against the meal announcement approach delivering up to 50% prandial insulin bolus 10-15 min before the meal. The latter approach markedly improved postprandial (peak 10.8 ± 2.6 vs. 12.6 ± 2.8 mmol/l) and mean (7.8 ± 2.6 vs. 8.3 ± 3.2 mmol/l) glucose levels. The overall night glucose levels and the associated standard deviations were excellent (6.2 ± 1.5 mmol/l). In the last 24 hours of the closed-loop control three nocturnal hypoglycaemia events (<3.3 mmol/l) were observed. The studies strongly support a further development of the ePID system with preference for the delivery of part of the usual meal bolus in the meal announcement mode.

The project Advanced Insulin Infusion using a Control Loop (Adicol)[35] was an EC funded project completed in 2002. The Adicol's sc-sc closed loop with meal announcement consisted of a minimally invasive subcutaneous glucose system, a handheld PocketPC computer, and an insulin pump (Disetronic D-Tron).

Adicol adopted an adaptive nonlinear model predictive controller (MPC).[18] The largest clinical study performed in the Adicol project assessed the efficacy of the MPC controller with 30min delayed iv glucose sampling over 26 h in 11 subjects with type 1 diabetes. One hypoglycaemia event (touchdown at 3.3 mmol/L) due to the MPC control was observed. The highest glucose concentration was 13.3mmol/L following breakfast; 84% of glucose measurements were between 3.5 – 9.5mmol/L.[36]

Building on the work by "Evaluation dans le

Diabete du Traitement par Implants Actifs" (EVADIAC) group, the work by Renard et al is at the forefront of the fully closed-loop iv-ip approach. The group has developed the implantable physiologic insulin delivery (iPID) system, which uses a long-term sensor system (LTSS).[37,38]

LTSS, an intravenous enzymatic oxygen-based sensor developed by Medtronic MiniMed (Northridge CA, US), is implanted by direct jugular access in the superior vena cava. It is connected by a subcutaneous lead to an insulin pump delivering insulin intraperitoneally and implanted in the abdominal wall. The pump implements a PD controller similar to that used by the ePID system.

The iPID system was evaluated in four elderly lean subjects with type 1 diabetes over 48 h.[39] Glucose was within 4.4-13.3 mmol/l 84.1% of the time. Following retuning of the algorithm after 24hours, the percentage of time within 4.4-6.7 mmol/l increased during the final 24 hours. Excluding meals, glucose was <13.3 mmol/l for 98% of the time. In a recent review, Renard at al concluded that the benefits of more physiological insulin kinetics with the LTSS due to intra-peritoneal delivery were hampered by the slow response time of intravenous sensors and that improvements are needed to increase sensor longevity and reduce sensor delay.[15]

In 2006, the Juvenile Diabetes Research Foundation (JDRF) initiated the Artificial Pancreas Project[26] funding seven research teams based in the US, the UK, Italy, and France. While collaborating on various underpinning aspects, the teams approach the closed-loop control from different perspectives. The common thread is the use of existing regulatory-approved or under-approval CGMs and insulin pumps for the sc-sc route while focusing on algorithm development and clinical testing. The groups develop closed-loop glucose control for children and adolescents with type 1 diabetes, for fasting and postmeal closed-loop glucose control in adults, and to prevent severe nocturnal hypoglycaemia. An approach utilising subcutaneous delivery of glucagon to prevent ensuing hypoglycaemia during closed-loop control is also being developed.[40]

Outlook

Historically, the artificial pancreas has been expected to lead to near-normal glucose levels in "one big step", without the need for perfection while being fully autonomous. Indeed, at the first glance, the term "artificial pancreas" may imply a full replacement of beta-cell function. Considerable energy has been expended to achieve this goal with an accompanying media interest.

These expectations need to be tempered to reflect the realistic gradual introduction of the closed-loop approach into the clinical practice Each AP generation will need to provide a clinically meaningful improvement of glucose control expressed as the reduction of HbA_{1C}, the risk of hy-poglycaemia, or both. Waiting for perfection is counterproductive. The first AP generation may switch off insulin pump at low glucose levels to prevent severe hypoglycaemia or may close the loop overnight when meal intake and exercise do not confound glucose control. The second generation may address glucose control around meals with user-triggered delivery of at least part of the prandial dose as advocated by the Yale group.[20] The next generation may consider a fully closed-loop control around meals and possibly during exercise. The fully implantable systems or systems with dual control utilising glucagon or glucagon-like effect may be the next generation

The most important question is what can be achieved with the existing technologies and when the first generation of closed-loop systems will see the daylight. Only the future will tell but the first generation, however simple but necessary to open the door for more complex approaches, is getting close.

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