Closing the loop, squaring the circle: Studies on insulin delivery, glucose monitoring and the artificial pancreas
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This thesis focuses on the steps necessary to create a functional closed loop system. In PART I of this thesis we investigated how the body reacts on a glucose load. We especially focused on ingestion of meals. In PART II of this thesis we investigated the nuances and variability of insulin infusion, focussing on the differences in insulin infusion materials on insulin administration. In PART III we investigated the accuracy of continuous glucose monitors (CGM), with a special focus on comparing CGM systems for use in a closed loop system. In PART IV we investigated a closed loop prototype to provide glycaemic control using two different control algorithms.

PART I

Chapter 2 investigates the optimal timing of administration of a rapid-acting insulin analogue before the meal to diminish postprandial glucose excursions. Although it is standard practice to give a bolus of these rapid acting insulins directly at the start of the meal, we showed that when comparing administration directly at the meal, 15 minutes before the meal and 30 minutes before the meal, administration 15 minutes before the meal provided the most favourable postprandial glycaemic profile. This knowledge was incorporated in our closed loop control algorithms which incorporate meal announcement and infuse a bolus of insulin 15 minutes before the meal commences.

Chapter 3 discusses the use of the Oral Glucose Tolerance Test (OGTT) in an age where HbA1c measurement is becoming of increasing importance not only to assess glycaemic control but also as a diagnostic tool. We discuss the advantages of the OGTT which directly reflects disturbances in the handling of a glucose load by the body analogous to the ingestion of a meal. We discuss its ability to detect stages of pre-diabetes more accurately than HbA1c and the ability to investigate postprandial glucose levels in a physiological way. We postulate that OGTT will remain one of the hallmark tests in the field of diabetology.
The previous studies show that the mealtime is one of the most challenging aspects of glucose control. A better understanding of the insulinaemic response of the human body on ingestion of meal could contribute to better functioning and near-physiological control of blood glucose levels by means of a closed loop system.

**PART II**

A plethora of equipment is at the disposal of diabetes professionals and patients to administer insulin. This equipment ranges from simple syringes to electronically controlled high-tech insulin infusion pumps.

**Chapter 4** investigates the differences in dosing accuracy between administration by insulin pens or conventional insulin syringes. The study shows that especially when concerning delivery of relatively small boluses, the insulin pens display superior accuracy. This chapter illustrates the importance of an accurate way of insulin administration since most modern closed loop systems employ the administration of micro-boluses. Of course in a closed loop system insulin infusion pumps are used.

**Chapter 5** investigates the differences in dosing accuracy between two different types of insulin infusion pumps. The conventional catheter based pump employs a lengthy catheter (in this study 60 cm) for the administration of insulin, while the patch-pump is worn directly on the abdomen and uses virtually no catheter. In this study we showed that catheter length had no significant effect on insulin absorption or postprandial glucose levels. We also showed that absorption of insulin was altered in both insulin infusion pumps with the ageing of the catheter insertion site, with significantly faster insulin absorption and lower postprandial glucose levels on the third day of use versus the first day of use. This was the first study to show no difference between patch pumps and catheter based pumps and the study corroborated earlier findings that the age of the catheter insertion site influences insulin absorption. In addition we showed that this difference also results in clinically important changes in postprandial glucose systems. These finding could be incorporated in closed loop systems, adjusting for these differences in insulin absorption by means of algorithm adjustment after a catheter has been changed.
PART III

One of the key components of a closed loop system is the glucose sensor. In the past years CGM has grown from a novelty to acquiring a growing role in the management of diabetes.

Chapter 6 provides knowledge on the usefulness of CGM in certain patient groups. This comes from an extensive review of literature and meta-analysis. This meta-analysis showed limited evidence for the effectiveness of real-time CGM use in children, adults and patients with poorly controlled diabetes. We also showed that the largest improvements in glycaemic control were seen for sensor-augmented insulin pump therapy in patients with poorly controlled diabetes who had not used an insulin pump before.

In Chapter 7 the optimal way to assess a glucose sensor in terms of accuracy was studied. We found that assessment at home versus assessment at the clinical research centre (CRC) resulted in different findings of sensor accuracy. The study illustrates the importance of the setting used when assessing CGMS accuracy. CGMS accuracy at home appeared better than at the CRC. This is probably due to the higher sampling rate of reference measurements feasible only in the CRC. Testing CGMS accuracy in the CRC provides valuable information over and above home testing. We incorporated this knowledge into designing the study described in Chapter 8 in which we assessed accuracy and longevity of the three most used CGM systems. We assessed the accuracy of these systems both at home and at the CRC and we also went on to assess the accuracy beyond manufacturer specified lifetime, including longevity of the sensor. We showed that when assessed at the CRC the sensor manufactured by Dexcom was less accurate than those manufactured by Abbott and Medtronic, which seemed comparable. While at home, the sensor manufactured by Medtronic was less accurate than those manufactured by Abbott and Dexcom. Moreover, CGM systems often showed sufficient accuracy to be used beyond manufacturer specified lifetime. However, the importance of this study lies in the fact that it proposes a standardized method of assessment for all new-to-market
CGM systems which incorporates both tightly controlled CRC phases and real-life at home phases, allowing for a more complete sensor assessment. This, in turn, is essential for selecting CGM systems to be used in closed loop control.

PART IV

The knowledge gathered in the previous parts come together in Chapter 9 in which we describe a study in which patients with type 1 diabetes underwent closed loop control in the CRC for a near full-day, 23 hour period. Patients were fitted with a study CGM system and insulin pump and were connected to the prototype closed loop system. The prototype closed loop was controlled by an algorithm from the University of Cambridge or the algorithm of the collaboration between the universities of Padova, Pavia and Virginia. We showed that closed loop decreased time spent in hypoglycaemia and we showed that glucose control was comparable to self-management of patients. Furthermore this study showed that the closed loop algorithms were safe and can be used in an outpatient setting.

The future for the closed loop is exciting; we showed that closed loop control is feasible and safe. Future studies will be performed at home, allowing for prolonged closed loop interventions. It will be in these settings that closed loop therapy will be able to prove its value reducing hypo- and hyperglycaemia and ultimately in reducing HbA1c. Moreover, from a patient perspective, it will be able to prove its usefulness in reducing the burden on quality of life by reducing the time needed for self-management of diabetes. However, there are some hurdles which still need to be taken to allow for the dream of a fully automated closed loop. More research needs to be done towards understanding and reacting to postprandial glucose peaks. Currently announcement of mealtime to the closed loop system can be used to deal with this problem, but in its elimination lays a challenge with a promise for even more patient freedom. More research is also needed towards developing an even more accurate CGM sensor. Currently, initiatives are underway to develop multimodality sensors which do not only rely on one detection method but combine chemo-electrical and chemo-illumination methods to provide more
accurate glucose readings. The availability of even better CGM systems will herald an essential improvement in closed loop systems. Improvement could also come from the development of more accurate and reliable administration of insulin, in particular gains could be made from diminishing the effect of catheter wear time and the development of ultra-fast-acting insulin analogues. With the promise of improvements in the aforementioned areas and continued research, we might yet be able to square the circle which is closed loop insulin therapy.