Challenges and Opportunities in Design of Control Algorithm for Artificial Pancreas

Mahboobeh Ghorbani and Paul Bogdan

University of Southern California
Electrical Engineering Department
{mahboobg,pbogdan}@usc.edu

Abstract

With discovery of the insulin, Type-1 diabetes converted from a fatal and acute to a chronic disease which includes micro-vascular complications which range from Kidney disease to stroke and micro-vascular complications such as retinopathy, nephropathy and neuropathy. Artificial pancreas is a solution to improve the quality of life for people with this very fast growing disease in the world and to reduce the costs. Despite technological advances e.g., in subcutaneous sensors and actuators for insulin injection, modeling of blood glucose dynamics and control algorithms still need significant improvement. In this paper, we investigate challenges and opportunities for development of efficient algorithm for designing robust artificial pancreas. We discuss the state of the art and summarize clinical and in silico assessment results. We contrast conventional integer order system approach with a newly proposed fractal control and summarize its benefits.

1998 ACM Subject Classification G.1 [Mathematics of Computing]: Numerical Analysus, J.3 [Computer Application]: Life and Medical Science-Health

Keywords and phrases Cyber-Physical Systems, Artificial Pancreas, Optimal and Model Predictive Control, Fractal Model Predictive

Digital Object Identifier 10.4230/OASIcs.MCPS.2014.49

1 Introduction

In healthy individuals, the alpha and beta cells of the pancreas regulate the blood glucose concentration to around 80 mg/dl. For people suffering from Type-1 diabetes mellitus (T1DM), which is one of the fastest growing diseases globally, there is little or no endogenous insulin production, leaving the body unable to lower blood glucose without exogenous insulin. The impact of the intensive insulin therapy was not revealed up until the publication of results of Diabetes Control and Complication Trial (DCCT) in 1993 [26]. The CDDT involved a comparison of conventional therapy (one or two daily insulin injections and a daily monitoring of blood glucose or urine) and intensive insulin therapy and concluded that intensive therapy resulted in lower mean blood glucose values and significantly reduced complications (retinopathy, nephropathy and macro-vascular disease). The risk of complication is directly related to glycated hemoglobin known as HbA1c. OGrady et al. find that tighter blood glucose levels achievable with a closed-loop artificial pancreas (AP) results in Medicare savings of 1.9 billion over 25 years with improved quality of life (QOL) [24]. A schematic view of a closed-loop artificial pancreas is shown in Fig. 1, which is mainly composed of three parts:

Continuous time blood glucose measurement (CGM): The knowledge of glucose concentration in blood is a key aspect in the quantitative understanding of the glucose-insulin system and in diagnosis and treatment of diabetes. By the ability of CGM devices to provide glucose readings in real time, engineers can exploit signal processing and control theory to

Medical Cyber Physical Systems – Medical Device Interoperability, Safety, and Security Assurance (MCPS'14).
Editors: Volker Turau, Marta Kwiatkowska, Rahul Mangharam, and Christoph Weyer; pp. 49–57

OpenAccess Series in Informatics
Schloss Dagstuhl – Leibniz-Zentrum für Informatik, Dagstuhl Publishing, Germany

be used in designing efficient artificial pancreas. Besides the improvement of hardware part of CGM devices, a vast amount of research has devoted to address denoising, prediction and alert generation [13, 1, 5, 22, 17, 3, 6].

Control algorithm and safety layer: The main component of AP is the control algorithm that determines the right insulin injection rate based on CGM data to prevent hyperglycemia and hypoglycemia. Design of a QOL-aware AP is a challenging task since it requires building accurate mathematical model of glucose-insulin kinetics. Algorithms often include a safety layer as a supervisory module that constraints insulin delivery. This layer may monitor and limit insulin on board (the insulin delivered but yet to exert its action) or maximum insulin rate or may suspend insulin delivery at low glucose levels or when glucose is decreasing rapidly. In this paper, we overview these challenges and control strategies employed so far.

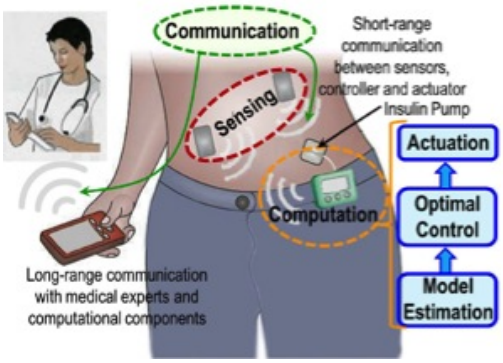

Figure 1 Systematic view of artificial pancreas [23].

Insulin injection device: The essential function of AP is the Insulin delivery. Insulin pumps, if inserted in a proper closed-loop system allow automatic insulin delivery. There are several technologies that can perform this task: an intra-venous route, subcutaneous insulin infusion (SCII) or intaperitoneal insulin delivery. Continuous subcutaneous insulin infusion (CSII) uses a portable electromechanical pump to mimic nondiabetic insulin delivery as it infuses at preselected rates normally a slow basal rate with patient-activated boosts at mealtime.

2 Control related challenges and constraints

Blood glucose (BG) regulation requires control algorithm to determine the best insulin injection over time. They have been tested in-silico and clinically over time and improved over the years. In this section, we first address the main challenges and constraints in designing efficient control algorithm. Next, we explain different control algorithms proposed so far and compare their performance.

Non-negligible delay in glucose measurement and between insulin injection and absorption: After administration of a subcutaneous bolus of rapid acting insulin analogues, the maximum BG lowering effect may occur after up to 90–120 min. This time lag is often not accounted for design of control algorithm. Patients treated with insulin pump are warned against stacking caused by the administration of a series of correction boluses. The same principle applies to closed-loop systems. In order to prevent hypoglycemia, high glucose levels have to be brought within normal range slowly during closed-loop delivery. Methods to assess the impact of injecting insulin (e.g. the one proposed in [7]) are highly needed in order to protect against insulin overdosing. Two alternative insulin delivery routes, intraperitoneal (IP) and technosphere insulin (TI) showed faster pharmacokinetic characteristics that can improve the design of future AP systems. Design of the AP using these fast acting alternative routes may enhance BG regulation by reducing actuation delays, especially during mealtime.

Asymmetric risk for low and high BG levels: The ultimate objective of any AP is to improve QOL and minimize complications resulting from poor blood glucose control. Toward this end, one should note to the asymmetric risk associated to high BG levels. Low BG levels are acutely risky as they can result in altered mental state, seizures and coma. Meanwhile, high BG levels increase the risk of chronic complications such as retinopathy, nephropathy and cardiovascular disease.

Irreversible action of insulin: Only positive amount of the injected insulin is possible and it cannot be collected back from the patients blood. An alternative to deal with this problem is to use bihormonal treatment [12] consisting of injecting glucagon and insulin. However, this also increases the problem space and complexity.

Meal detection/estimation: Meal dynamics can have a significant disturbance effect on BG level. In a fully closed-loop mode, insulin is delivered on the basis of glucose excursions only, without information about timing or meal size. In a less ambitious configuration that uses meal announcement, the closed-loop system is informed about meal size, and may generate advice on prandial insulin bolus.

Alternatively, control algorithms can automatically increase insulin delivery based on the carbohydrate content of the meal. A hybrid approach is characterized by administration of a small pre-meal priming bolus or administration of a fixed bolus and delivering the remaining insulin through the closed-loop operation [9].

Time dependency of control requirements: An important challenge in development of artificial pancreas is that overnight treatment requires slow acting insulin injection while post-prandial control requires rapid and aggressive insulin delivery to control BG.

On the other hand, exercise of moderate intensity increases the risk of hypoglycemia [32]. Exercise announcement or heart rate monitoring to suspend insulin during closed-loop delivery may be another effective method to control glucose levels during exercise. Pre-emptive carbohydrate intake or dual hormone treatment with glucagon might be needed to fully eliminate the risk of exercise-related hypoglycemia as responses to exercise are highly variable. To sum up, BG control is a time dependent process and this should be taken into account in order to have a safe and efficient AP.

Variability of model parameters: Up to 4 times inter-subject variability in rapid-acting insulin analogue pharmacokinetics has suggested with occasionally as much as 50 % intra-subject variability [12]. Within subject variability of insulin needs includes both day-to-day and hour-to-hour variations in insulin sensitivity owning to circadian and diurnal cycles, dawn phenomenon (an abnormal early morning increase in BG concentration), acute illness, stress and a delayed effect of alcohol intake. Basal insulin needs are generally lower in young individuals compared with older ones. Also, since overnight control requires regulation based on mild control actions while postprandial regulation is characterized by prompt and energetic correction, timely control effect should take place.

3 Control algorithms for BG level regulation

In this section we present two main groups of controller for BG level regulation namely proportional-integral-derivative and model predictive controller.

3.1 Proportional-Integral-Derivative (PID) controller

PID controller is a generic control loop feedback mechanism widely used in industrial control. The PID control algorithm for artificial pancreas adjusts the insulin delivery rate by assessing glucose excursions from three viewpoints: the departure from the target glucose level (the proportional component), the area under the curve between measured and target glucose levels (the integral component) and the rate of change in measured glucose levels (the derivative component). Some controllers include only a subset of the components (e.g. a proportional-derivative [27]).

To better understand the intuition behind using PID controller in the control algorithm for artificial pancreas, one should note that dose of insulin is directly related to the proportional error (P) (current glucose minus target glucose) since a patient with higher glucose level needs more insulin rather than one with lower glucose level. Moreover, in two patients with the same glucose level but with different rate of glucose increase, the one with higher increase rate should get a higher dose of insulin and this justifies the derivative element (D). To understand the role of Integral element (I), it should be noted that for two patients with the same current glucose level and no change in the very recent minutes, the one with more hours spending in high BG level (thus, having more integral error) needs more insulin due to the fact that this is a sign on insulin resistivity. Steil et al. have shown the normal healthy pancreas displays proportional, derivative and integral dynamics [14]. They argue that the abrupt step increase in glucose causes a rapid rise in pancreatic insulin release, which is called first phase response and is related primarily to the derivative component. Slower rise in insulin is called the second phase response, which corresponds to proportional term and persists as long as glucose is elevated. There is also an integral component employed in the second phase since insulin secretion after 3 hours of elevated glucose at a fixed level is greater than insulin secretion after only 1 hour at the same glucose level.

Equation 1 shows the the components of control signal ($u(t)$) that is the amount of insulin injection rate as a function of $e(t)$ which is the difference between BG level and the reference value. The K_p, K_i and K_d parameters can be assigned by learning algorithms that have been discussed in control related textbooks. Optimizing using PID controller needs tuning of the controller by some methods, like the ones proposed in [16] and [2].

$$u(t) = K_p e(t) + K_i \int_0^t e(\tau)d\tau + K_d \frac{de(t)}{dt} \tag{1}$$

PID approach has inherent limitations due to time lags in glucose sensing and insulin action. Several studies have investigated this approach and achieved some improvement over conventional PID approach. For example, Weinzimer et al. in [29] have tested PID algorithm for insulin injection in 17 adolescences. They have tested both fully closed-loop and hybrid closed-loop (with pre-meal priming bolus) and show the addition of small manual priming bolus doses of insulin given 15 min before meals improves glycemic excursions. A different study by Renard et al. in [10] proved the feasibility of intraperitoneal insulin delivery for artificial beta cell and supported the need for further study since subcutaneous insulin delivery from a portable pump encountered delays and variability in insulin absorption. They evaluated their proposed method in a clinical study on eight T1DM patients while the time spent in 4.4–6.6 mmol/l was the primary end point. Another study in [12] uses both insulin and glucagon to prevent hypoglycemia encountered in PID algorithm with only insulin as the treatment.

3.2 Model Predictive Controller

Model Predictive Control (MPC) is a general optimization framework that can involve many different types of models and objective functions. The MPC approach is at the front of current research into closed-loop systems. It acceptably accommodates delays associated with insulin absorption and can also easily account for meal intake and prandial insulin boluses by the patient. The other advantage of model predictive control paradigm is the fact that it can account for variability since the model parameters can be personalized. The main advantage of MPC is the fact that it allows the current timeslot to be optimized, while keeping future timeslots into account. This is achieved by optimizing a finite time-horizon, but only implementing the current timeslot. MPC has the ability to anticipate future events and can take control actions accordingly.

The vital ingredient of MPC is a model that links insulin delivery and meal ingestion to glucose excursions. This model can be physiological and account for fundamental processes regulating glucose levels or a black box model that disregards insights but learns the insulin glucose relationship via formal pattern recognition technique. They both can benefit from a wide range of mathematical models of glucoregulatory system. It is therefore clear that proper models of glucose and insulin kinetics as well as models that can be used to predict near-future metabolic behavior are mandatory. Minimal models (describing the key components of system functionality) and maximal models (nonlinear, high order models) are reviewed by Cobelli in [6].

A general MPC problem formulation, which includes optimization objective (Equation 2), glucose-insulin dynamical model (Equation 3) and initial value, glucose state and insulin control constraints (Equation 4) can be written as follows.

$$min_{u(t)} \int_0^{t_f} F(g(t), u(t))\, dt \tag{2}$$

$$\frac{dg(t)}{dt} = a_G\, g(t) + b_G\, u(t) \tag{3}$$

$$g(t=0) = g_0, u_{min} \leq u(t) \leq u_{max}, g_{min} \leq g(t) \leq g_{max} \tag{4}$$

where $g(t)$ denotes the BG level and $u(t)$ denotes the amount of insulin injected at time t which should be determined by solving the optimization problem; a_G and b_G are coefficients representing the impact of injected insulin on the BG dynamics. Also, t_f represents the finite horizon of the control problem which is usually 2h to 4h prediction window that corresponds to the bulk duration of action of a rapid acting insulin analogue such as aspart, lispro and glulisine. $g_{ref}(t)$ is the time dependent glucose reference value that can be chosen depending on the current state to avoid hypoglycemia or hyperglycemia. Initial condition is addressed by including g_0 which is the initial glucose level. Finally, u_{min} and u_{max} are the minimum and maximum allowed insulin amounts to be injected and g_{min} and g_{max} are the lower and upper bounds on the glucose level. $F(g(t)$ is a generic form for all possible cost functions. But, it is usually desired to minimize a summation form including both the distance to the reference glucose value and insulin injection effort. MPC has shown to be suitable for multivariate nonlinear systems such as the human body and it significantly gives better performance than PID control with patient-specific tuning. Several variations of MPC have been proposed in the literature. We briefly categorize them as follows:

Linear model predictive control (LMPC): There are several research studies that use linear model predictive controller. The work presented in [21] was the first in silico trial for

linear model predictive approach which also showed better performance of MPC rather than PID controller in terms of limiting the oscillation of glucose levels. Research efforts presented in [31] and [9] were the first clinical investigations of linear model predictive algorithms in artificial pancreas that reported the superiority of using this approach over PID controller. in [21] Magni et al. in present an unconstrained MPC where the model is a linearization of a nonlinear parameters.

Researchers extend the MPC by defining new types of objective function and additional features to the problem formulation. Heusden et al. proposed using a priori patient characterization and fitting a linear control relevant model around the control point [20]. They also defined a new cost function named zone model predictive in contrast to previous studies in which only the distance to a target reference point is considered as the cost function. They consider a range for the BG level as the objective of the optimization and define the cost function as the minimum distant to the preferred zone. They have verified the robustness of the algorithm in silico and showed that the hypoglycemia is completely avoided even after meal disturbance. Lee et al. in [15] use new meal size estimation algorithm to the integrated AP and show how its performance is better than MPC-only case.

Non-linear model predictive (NMPC): Hovorka et al. in [28] present a nonlinear model and Bayesian techniques to estimate parameters in simulation studies. Clinical studies were performed under fasting conditions based on measurements that were delayed by 30 min to mimic the time lag associated with a sensor. The authors performed overnight studies using an algorithm and transferring results to a pump at 15 min intervals. The major result was a reduction in nocturnal hypoglycemia compared to standard pump treatment. Zarkogianni et al. also use a nonlinear model-predictive control for prediction of BG and control algorithm [19]. They have shown the usefulness of using this nonlinear MPC in silico for different meal profiles, fasting conditions, inter-patient variability and intraday variation.

Fractal model predictive control (FMPC): In spite of significant amount of work in PID and MPC, the complexity of BG dynamics has not been fully addressed. For instance BG is time dependent process that is influenced by various factors (meal size, exercise, psychological state, etc.). This has prompted a comprehensive multifractal investigation of BG dynamics [23] from publicly available data set [33]. The authors have shown how using fractional order controller leads more robust control over conventional integer order model predictive controller. They formulate the BG dynamics as a time dependent fractional order control problem and report the feasibility of implementation of fractional controller in hardware and report their results in terms of area and speed in field programmable gate array (FPGA). We compare the impact of applying fractional order controller to the conventional first order derivative controller. Fig 2 shows the outcome of applying both types of controllers to bring to some reference value which is $100mg/dL$ in this case. Unlike the expectation of integer order controller the final glucose value at the end of control horizon is much lower than the one expected.

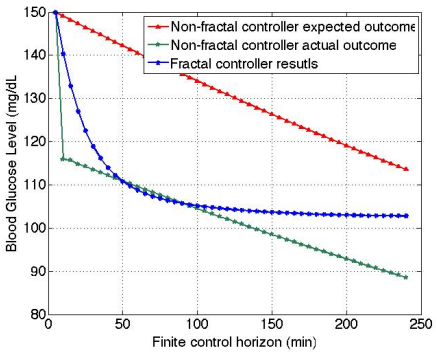

Figure 2 Performance of fractal and non-fractal MPC.

3.3 Assessment of Control performance

The ultimate goal of any closed-loop artificial pancreas controller is to minimize the complications resulting from poor BG control. Research studies that have evaluated closed-loop systems lasted at most several days. In these studies, *time when glucose is in the target range* is the most widely used metric to assess closed-loop performance. On the other hand, target glucose range differs in overnight and fasting condition (3.9–8.0 mmol/l) versus post-prandial condition (up to 10 mmol/l). The low BG index can be helpful in quantifying the duration and extent of hypoglycemia and other measures to assess severity of hypoglycemia and hyperglycemia have been proposed such as Grade score [25]. To sum up, in spite of existence of some FDA approved simulation environments ([4] and [8]), there is still significant need for establishing unified simulation sequences and defining precise criteria to compare different control algorithms. The same problem exists with the clinical studies in which there are no unified clinical conditions to be able to compare performance of different control algorithm.

4 Conclusions and future work

The ultimate goal of any medical cyber physical system is to use technology to increase the QOL for people. In type-1 diabetes mellitus, which is one of the fastest growing diseases globally, the patient's pancreas is not able to release insulin endogenously. As a result, the patient needs exogenous insulin in order to control BG to reduce acute and chronic complications. Recent technological advances have led to a paradigmatic shift in diabetes treatment by offering automatic and semi-automatic systems to replace traditional procedures to improve the QOL for diabetic people and let them forget about their disease.

Despite very advanced technologies in sensing and actuation technology, there is still a huge gap to fill for designing a robust AP, which comes from lack of accurate mathematical models and robust control algorithm. In this paper, we present main challenges and problems to be addressed in design of AP. Then, we present the state of the art control algorithms for closed-loop AP, which is mainly, composed of PID and model predictive control groups. As discussed in the paper, even with application of model predictive controller, which is proved to perform better than PID controller, clinical tests only prove simple situations e.g. over night or after meal conditions and more sophisticated glycemic control during meals and exercise is still challenging.

Future directions in research for developing more accurate mathematical models and control algorithm include investigation and application of the recently investigated time dependent fractional model for BG on more comprehensive data set for control purpose and also investigating this state of the art model for hormone levels e.g. insulin and glucagon. This is especially valuable for dual hormone closed-loop system [12, 11, 18], which is proven to be effective only when the predictions of the hormone levels are accurate [30]. More importantly, incorporating this mathematical model in state of the art software simulations, which are reference for evaluation of several control algorithms.

References

1 DB. Keenan at al. Continuous glucose monitoring considerations for the development of a closed-loop artificial pancreas system. *Journal of diabetes science and technology*, 5(6):1327–1336, 2011.

2 A. Ali et al. Pid controller tuning for integrating processes. *ISA transactions*, 49(1):70–78, 2010.

3 A. Ouattara et al. Blood glucose variability: a new paradigm in critical care? *Anesthesiology*, 105(2):233–234, 2006.

4 BP. Kovatchev et al. In silico preclinical trials: a proof of concept in closed-loop control of type 1 diabetes. *Journal of diabetes science and technology*, 3(1):44–55, 2009.

5 C. Chen et al. Recent advances in electrochemical glucose biosensors: a review. *RSC Advances*, 3(14):4473–4491, 2013.

6 C. Cobelli et al. Diabetes: models, signals, and control. *IEEE Reviews in Biomedical Engineering*, 2:54–96, 2009.

7 C. Ellingsen et al. Safety constraints in an artificial pancreatic β cell: An implementation of model predictive control with insulin on board. *Journal of diabetes science and technology*, 3(3):536–544, 2009.

8 CD. Man et al. Meal simulation model of the glucose-insulin system. *IEEE Trans on Biomedical Engineering*, 54(10):1740–1749, 2007.

9 D. Bruttomesso et al. Closed-loop artificial pancreas using subcutaneous glucose sensing and insulin delivery and a model predictive control algorithm: preliminary studies in padova and montpellier. *Journal of diabetes science and technology*, 3(5):1014–1021, 2009.

10 E. Renard 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*, 33(1):121–127, 2010.

11 FH. El-Khatib et al. Adaptive closed-loop control provides blood-glucose regulation using dual subcutaneous insulin and glucagon infusion in diabetic swine. *Journal of Diabetes Science and Technology*, 1(2):181–192, 2007.

12 FH. El-Khatib et al. A bihormonal closed-loop artificial pancreas for type 1 diabetes. *Science Translational Medicine*, 2(27):27ra27–27ra27, 2010.

13 G. Sparacino et al. "smart" continuous glucose monitoring sensors: On-line signal processing issues. *Sensors*, 10(7):6751–6772, 2010.

14 GM. Steil et al. Modeling β-cell insulin secretion-implications for closed-loop glucose homeostasis. *Diabetes technology & therapeutics*, 5(6):953–964, 2003.

15 H. Lee et al. A closed-loop artificial pancreas using model predictive control and a sliding meal size estimator. *Journal of diabetes science and technology*, 3(5):1082–1090, 2009.

16 J. Cho et al. Cascade control strategy for external carbon dosage in predenitrifying process. *Water Science & Technology*, 45(4-5):53–60, 2002.

17 J. Kildegaard et al. Sources of glycemic variability—what type of technology is needed? *Journal of diabetes science and technology*, 3(4):986–991, 2009.

18 JR. Castle et al. Novel use of glucagon in a closed-loop system for prevention of hypoglycemia in type 1 diabetes. *Diabetes Care*, 33(6):1282–1287, 2010.

19 K. Zarkogianni et al. An insulin infusion advisory system based on autotuning nonlinear model-predictive control. *IEEE Transactions on Biomedical Engineering*, 58(9):2467–2477, 2011.

20 KV. Heusden et al. Control-relevant models for glucose control using a priori patient characteristics. *IEEE Transactions on Biomedical Engineering*, 59(7):1839–1849, 2012.

21 L. Magni et al. Model predictive control of type 1 diabetes: an in silico trial. *Journal of diabetes science and technology*, 1(6):804–812, 2007.

22 LBEA. Hoeks et al. Real-time continuous glucose monitoring system for treatment of diabetes: a systematic review. *Diabetic Medicine*, 28(4):386–394, 2011.

23 M. Ghorbani et al. A cyber-physical system approach to artificial pancreas design. In *Proc of IEEE/ACM/IFIP CODES*, page 17, 2013.

24 MJ. O'Grady et al. Changes in medicare spending for type 1 diabetes with the introduction of the artificial pancreas. *New York (NY): JDRF*, 2011.

25 NR. Hill et al. A method for assessing quality of control from glucose profiles. *Diabetic medicine*, 24(7):753–758, 2007.

26 P. Reichard et al. The effect of long-term intensified insulin treatment on the development of microvascular complications of diabetes mellitus. *New England Journal of Medicine*, 329(5):304–309, 1993.

27 PG. Jacobs et al. Development of a fully automated closed loop artificial pancreas control system with dual pump delivery of insulin and glucagon. In *Proc of IEEE EMBC*, pages 397–400, 2011.

28 R. Hovorka et al. Five-compartment model of insulin kinetics and its use to investigate action of chloroquine in niddm. *American Journal of Physiology-Endocrinology And Metabolism*, 265(1):E162–E175, 1993.

29 SA. Weinzimer 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*, 31(5):934–939, 2008.

30 SJ. Russell et al. Efficacy determinants of subcutaneous microdose glucagon during closed-loop control. *Journal of diabetes science and technology*, 4(6):1288–1304, 2010.

31 WL. Clarke et al. Closed-loop artificial pancreas using subcutaneous glucose sensing and insulin delivery and a model predictive control algorithm: the virginia experience. *Journal of diabetes science and technology*, 3(5):1031–1038, 2009.

32 DCCT Research Group et al. Epidemiology of severe hypoglycemia in the diabetes control and complications trial. *The American journal of medicine*, 90(4):450–459, 1991.

33 Diabetes Research in Children Network (DirecNet) Study Group et al. Accuracy of the glucowatch g2 biographer and the continuous glucose monitoring system during hypoglycemia. experience of the diabetes research in children network (direcnet). *Diabetes Care*, 27(3):722, 2004.