Medical Informatics Group

Continuous Glucose Monitoring Algorithm: Accuracy Improvement and Evaluation in Type 1 Diabetes

PhD thesis by
Zeinab Mahmoudi

River Publishers

Continuous Glucose Monitoring Algorithm: Accuracy Improvement and Evaluation in Type 1 Diabetes

Continuous Glucose Monitoring Algorithm: Accuracy Improvement and Evaluation in Type 1 Diabetes

PhD Thesis by

Zeinab Mahmoudi

Medical Informatics Group,
Department of Health Science and Technology,
Aalborg University, Denmark

River Publishers

ISBN 978-87-93237-36-0 (Paperback)
ISBN 978-87-93237-37-7 (Ebook)

Published, sold and distributed by:
River Publishers
Niels Jernes Vej 10
9220 Aalborg Ø
Denmark

Tel.: +45369953197
www.riverpublishers.com

Contents

Preface

The present thesis is submitted to Aalborg University, May 2014, in order to fulfil the requirements for the degree of Doctor of Philosophy in Biomedical Science and Engineering. The thesis includes my work as a PhD student employed at the Medical Informatics Group, Department of Health Science and Technology, Aalborg University, Denmark, and it presents algorithmical methods to improve the accuracy of continuous glucose monitoring and explores approaches to evaluate the methods. The PhD study was supervised by Professor Ole Hejlesen and co-supervised by Associate Professor Mette Dencker Johansen.

Acknowledgments

First and foremost, I would like to express my gratitude to my supervisor, Professor Ole K. Hejlesen, for the patient guidance, and encouraging supervision he has provided throughout my time as his student. Certainly I would like to express sincere thanks to my co-supervisor, Associate Professor Mette Dencker Johansen, for her enthusiastic and motivating supervision.

My special thanks go to my colleagues at the Medical Informatics Group, for their hospitality and the positive work atmosphere they made for me, especially my officemates Anne Sofie Korsager, and Ask Schou Jensen for their friendship and invaluable discussions about everything from personal to scientific issues. I would also like to thank my friends at Aalborg University, who empowered me when challenges seemed difficult to deal with.

Finally, I express my deep appreciation to my beloved mother Fatemeh, and my dearest brothers Vahid, Farid, and Abolfazl, for their splendid love and unlimited support, for those I am in great debt.

Abstract

The biggest challenge in management of type 1 diabetes is lowering high blood glucose (BG) into normal glucose range by means of intensive insulin therapy, without increasing the risk of hypoglycemia. Therefore, it is of crucial importance that BG be monitored continuously for detection of hypoglycemia and subsequent treatment. The isolated self-monitoring of BG (SMBG) is unable to detect hypoglycemic episodes sufficiently. Continuous glucose monitoring (CGM) provides frequent and time-ordered information about BG through sampling of interstitial glucose (IG), which can facilitate detection of hypoglycemia. The main obstacle facing CGM systems is the large deviation of CGM readings from reference BG or plasma glucose (PG) levels that can cause substantial failure in detection of hypoglycemia, and consequently may result in incorrect recommendations for treatment adjustments. In order to have adequate accuracy, sophisticated signal processing algorithms-mainly consisting of filtering and calibration- must be applied to CGM data. Although considerable advances have been achieved in the CGM technology, improving CGM algorithms is still a challenging issue in terms of reducing the filtering delay and increasing calibration sufficiency. In addition, it is of great importance to evaluate the enhanced CGM algorithms not only by measuring the proximity of the CGM reading to the concurrent BG values but also by investigating the effect of the improved accuracy on the quality of clinical decision making in diabetes. Hence, this PhD aimed at developing a sophisticated signal processing algorithm to enhance CGM accuracy, and explored novel methodologies to evaluate the algorithm.

The first aim of the PhD project was to develop a CGM algorithm with an enhanced accuracy. This goal was achieved in study 1 and study 2. In study 1, a two-step CGM algorithm was presented. In the first step, a new method of filtering which is focused on minimizing the filtering delay was developed. In the second step, a calibration approach with several novel features targeting at reducing hypoglycemia inaccuracy was introduced. In study 2, the calibration part of the algorithm in study 1 was further enhanced by using a one-point

calibration instead of a two-point calibration. The results of study 2 indicate further accuracy improvement compared to study 1.

The second aim of the thesis was evaluating the accuracy of the new CGM algorithm from different aspects. The two main evaluation perspectives are assessing the numerical accuracy (study 3), and the clinical accuracy (study 4) of the algorithm. In study 3, the algorithm in study 1 was compared with the commercial algorithm used in the Guardian® REAL-Time (Medtronic Diabetes, Northridge, CA) CGM system, by using numerical performance metrics. The new CGM algorithm reduced PG-CGM deviation and increased hypoglycemia sensitivity, but it also slightly (not significantly) reduced the hypoglycemia specificity. In study 4, the impact of the improved numerical accuracy on the precision of the clinicians' decision making was tested. Precision is an indicative of the CGM-based clinical decision making reliability. Precision was defined in terms of the inter-clinician agreement and intra-clinician reproducibility of the clinicians' decisions to adjust the insulin dosage with the aim of avoiding glycemic excursions. The results indicate the potential of the new algorithm to increase the precision of the treatment adjustment.

Based on the results of the studies performed in the thesis, a new signal processing algorithm for filtering and calibration of CGM data is presented. The numerical evaluation of the algorithm indicates that the algorithm is able to reduce the deviation of CGM readings from BG and PG levels, and has an improved performance over the compared state-of-the-art CGM algorithms. The clinical evaluation of the algorithm suggests that the higher numerical accuracy of CGM data achieved by the new algorithm can be translated into higher clinical reliability of the CGM-based decision making, which is the ultimate goal for the CGM accuracy improvement efforts.

Dansk resumé

Den væsentligste udfordring ved behandling af type 1-diabetes er at sænke det forhøjede blodglukose (BG)-niveau gennem intensiv insulinbehandling, så det falder inden for målintervallet uden samtidig at forøge risikoen for hypoglykæmi. Det er derfor af afgørende betydning, at BG monitoreres konstant med henblik på at påvise hypoglykæmi og sikre behandling heraf. Egenmåling af BG (SMBG) giver, medmindre det kombineres med andre monitoreringsmetoder, ikke grundlag for adækvat monitorering af hypoglykæmiske episoder. Kontinuerlig glukosemonitorering giver derimod frekvente tidsseriemålinger baseret på interstitiel glukose (IG), som skaber grundlag for påvisning af hypoglykæmi. Den største hindring for udbredelsen af systemer til kontinuerlig glukosemonitorering (Continous Glucose Monitoring, CGM) er, at CGM-målinger kan afvige betydeligt fra reference-BG- eller plasmaglukoseniveauerne, hvilket kan medføre en væsentlig forringelse af systemernes evne til at detektere hypoglykæmi og derfor også bevirke, at de leverer forkerte anbefalinger til ændring af behandlingen. Sofistikerede signalprocesseringsalgoritmer, der primært filtrerer og kalibrerer CGM-data, er nødvendige for at opnå en tilstrækkelig nøjagtighed. Selv om CGM-teknologien har gjort betydelige fremskridt, så udgør udviklingen af CGM-algoritmer fortsat en udfordring, og herunder især en mindskelse af filtreringsforsinkelsen og en forøgelse af kalibreringens tilstrækkelighed. Endvidere er det afgørende at evaluere de forbedrede CGM-algoritmer, ikke alene ved at måle hvor tæt CGM-målingerne er på samtidige BG-værdier, men også ved at undersøge effekten af den styrkede nøjagtighed på kvaliteten af de kliniske beslutninger, der tages i forhold til patientens diabetes. Målet med denne ph.d.-afhandling var derfor at udvikle en sofistikeret signalprocesseringsalgoritme, der kunne forøge nøjagtigheden af CGM, og at udforske nye metoder til evaluering af algoritmen.

Ph.d.-projektets første målsætning var udviklingen af en CGM-algoritme, der havde en højere nøjagtighed end eksisterende algoritmer. Denne målsætning opnåedes i studie 1 og studie 2. I studie 1 præsenteres en totrins-CGM-algoritme. I det første trin udvikles en ny filtreringsmetode, der er

fokuseret på at minimere filtreringsforsinkelsen. I det andet trin introduceres en kalibreringsmetode, som målrettet reducerer unøjagtighed i forhold til påvisning af hypoglykæmi. I studie 2 forbedres kalibreringsalgoritmen fra studie 1 yderligere gennem anvendelse af etpunktskalibrering i stedet for topunktskalibrering. Resultaterne af studie 2 indikerer, at der er opnået yderligere forbedringer sammenholdt med studie 1.

Afhandlingens anden målsætning var at evaluere den nye CGM-algoritmes nøjagtighed med udgangspunkt i forskellige parametre. Der fokuseres primært på to evalueringsperspektiver; dels algoritmens numeriske nøjagtighed (studie 3), dels dens kliniske nøjagtighed (studie 4). I studie 3 sammenlignes algoritmen fra studie 1 med den kommercielle algoritme, som anvendes i Guardian® REAL-Time (Medtronic Diabetes, Northridge, CA) CGM-systemet. Sammenligningen gennemføres ved hjælp af numeriske performansmetrikker. Den nye CGM-algoritme reducerer PG-CGM afvigelse og forøger hypoglykæmi-sensitiviteten, men den reducerer også hypoglykæmi-specificiteten en smule (ikke-signifikant). I studie 4 testes effekten af den forbedrede numeriske nøjagtighed på præcisionen i klinikernes beslutninger. Præcision giver således en indikation af reliabiliteten af CGM-baserede kliniske beslutninger. Præcision defineres på grundlag af interkliniker-overensstemmelse og intrakliniker-reproducerbarhed af klinikernes beslutninger om at ændre insulindosis for at undgå glykæmiske udsving. Resultaterne viser algoritmens potentiale med hensyn til at forøge præcisionen i behandlingstilpasningerne.

På grundlag af resultaterne fra de studier, der indgår i afhandlingen, præsenteres en ny signalprocesseringsalgoritme til filtrering og kalibrering af CGM data. Den numeriske evaluering af algoritmen indikerer, at algoritmen kan reducere afvigelserne mellem CGM-målinger på den ene side, og BG- og PG-niveauerne på den anden, og viser, at algoritmen muliggør bedre resultater end de førende CGM-algoritmer, som den sammenlignes med. Den kliniske evaluering af algoritmen peger på, at den højere numeriske nøjagtighed af CGM-data, som opnås med algoritmen, kan omsættes i en højere klinisk reliabilitet i CGM-baserede beslutninger, hvilket er det endelige mål for enhver indsats for at forøge CGM-nøjagtigheden.

List of Publications and Related Work

The PhD thesis is based on the four papers, resulted from the four studies of the thesis:

Paper 1 Mahmoudi Z, Johansen MD, Christiansen JS, Hejlesen OK. A multi-step algorithm for processing and calibration of micro-dialysis continuous glucose monitoring data. *Diabetes Technol Ther.* 2013; 15(10): 825–835.

Paper 2 Mahmoudi Z, Johansen MD, Christiansen JS, Hejlesen OK. Comparison between one-point calibration and two-point calibration approaches in a continuous glucose monitoring algorithm. *Diabetes Sci Technol. Published online before print April 21, 2014; DOI: 10.1177/1932296814531356.*

Paper 3 Mahmoudi Z, Jensen M, Johansen MD, Tarnow L, Christensen TF, Christiansen JS, Hejlesen OK. Accuracy evaluation of a new real-time continuous glucose monitoring algorithm in hypoglycemia. *Diabetes Technol Ther. In press, 2014; DOI: 10.1089/dia.2014.0043.*

Paper 4 Mahmoudi Z, Johansen MD, Nørgaard HH, Andersen S, Pedersen-Bjergaard U, Tarnow L, Christiansen JS, Hejlesen OK. Effect of continuous glucose monitoring accuracy on clinicians' decision making in diabetes. *Diabetes Technol Ther. Submitted*; 2014.

In addition the author has contributed to the following scientific work during the PhD:

Paper Jensen MH, Mahmoudi Z, Christensen TF, Tarnow L, Seto E, Johansen MD, Hejlesen OK. Evaluation of an algorithm for retrospective hypoglycemia detection using professional continuous glucose monitoring data. *Diabetes Sci Technol* 2014; 8 (1) 117–122.

Paper	Jensen M, Christensen T, Tarnow L, Mahmoudi Z, Johansen MD, Hejlesen OK. Professional continuous glucose monitoring in subjects with type 1 diabetes: Retrospective hypoglycemia detection. *Diabetes Sci Technol.* 2013; 7(1):135–143.
Conference Abstract In journal	Mahmoudi Z, Jensen MH, Christensen TF, Johansen MD, Tarnow L, Christiansen JS, Hejlesen OK. Performance Assessment of a Continuous Glucose Monitoring Calibration Algorithm in Hypoglycemia. 7th International Conference on Advanced Technologies & Treatments for Diabetes, 8–10 February 2014, Vienna, Austria. *Diabetes Technol Ther*, Vol. 16, No. Suppl. 1, 2014, p. A-75, No. P-194.
Conference Abstract In proceeding	Mahmoudi Z, Johansen MD, Christiansen JS, Hejlesen OK. A Novel Algorithm for Processing and Calibration of Continuous Glucose Monitoring Data. Conference abstract in proceeding: 12th Annual Diabetes Technology Meeting, Diabetes Technology Society, 8–10 November 2012, Bethesda, USA, p. A84.

1

Introduction

1.1 Diabetes Mellitus

Diabetes mellitus is a metabolic disease, which is defined by high blood glucose (BG) levels (hyperglycemia)[1], and is featured by halted insulin production in type 1 diabetes and insufficient insulin production and insulin resistance in type 2 diabetes.[2] Diabetes is a major chronic disease with a rapidly-growing global prevalence and loading excessive cost, morbidity, and mortality.[3,4] It is estimated that by 2050, one third of adults in the United States will be influenced by diabetes.[5] The morbidity and mortality of diabetes are connected with long-term diabetes complications associated with high BG level. Being the main cause of blindness due to retinopathy, the main cause of renal failure due to nephropathy, responsible for 60% of non-traumatic lower limb amputation due to neuropathy, and causing 2- to 4- times higher risk of stroke, diabetes is a leading factor reducing quality of life.[2,5,6] The scope of the current PhD thesis is within type 1 diabetes mellitus.

1.2 Diabetes Complications

1.2.1 Long-Term Diabetes Complications

Long-term diabetes complications are health conditions, caused by inappropriately high BG levels, developing with the course of time, in diabetes patients with poor glycemic control. The complications mainly include eye problems, chronic kidney disease, foot disease, autonomic neuropathy, cardiovascular problems, musculoskeletal complications, and skin problems.[3,5,7–9]

Eye problems: Of people with diabetes (both type 1 and type 2) in the UK, 2% are registered blind caused by diabetes, and 87%-98% of patients with type 1 diabetes will suffer from retinopathy after 30 years of disease.[7]

Diabetes kidney disease (nephropathy): Nephropathy is one of the most severe complication associated with diabetes.[7,10] Around 30% of patients

with type 1 and 10% to 40% of those with type 2 diabetes will eventually have nephropathy.[11]

Diabetic foot: The peripheral nerve damage caused by diabetes may lead to reducing heat and pain sensation, which make the diabetic foot vulnerable to ulceration. In addition, impaired blood supply in diabetic foot slows ulcer healing process, which exacerbates the condition.[7]

Neuropathy: Diabetes neuropathy affects up to 50% of diabetes patients, and is vital to be detected.[7,12] Nerve damage is caused by the decreased blood flow, and high blood sugar levels in the capillaries supplying oxygen and nutrients to the nerves. Diabetic neuropathy has several manifestation including pain or loss of sensation, weakness, paralysis, loss of reflexes, muscle atrophy, and impaired glucose counter-regulatory responses.

Cardiovascular complications: Cardiovascular complications are the main causes of mortality in both type 1 and type 2 diabetes patients, which affect the heart and large vessels, and can cause atherosclerosis of the coronary arteries, hypertrophy of the myocardium, systolic hypertension, and stroke.[7,13]

Musculoskeletal complications: Musculoskeletal complications are often observed complication in patients with type 1 diabetes; however, they are also seen in patients with type 2 diabetes. The frequently affected sites are hands, shoulders, feet, and skeleton.[14]

Skin problems: Skin problems, which precede the onset of diabetes in 15% of patients, are the first indications of poor glycemic control, and can be indicative of other diabetes complications including nephropathy, retinopathy, and neuropathy.[7,15]

1.2.2 Hypoglycemia

Hypoglycemia is not a direct complication of diabetes, but is a complication of diabetes therapy. Hypoglycemia is the main side effect of insulin therapy in insulin-dependent diabetes patients, particularly in patients with type 1 diabetes.[16−18] Around 2–4% of deaths in patients with type 1 diabetes are related to hypoglycemia.[19] American Diabetes Association (ADA) suggests the BG level below 70 mg/dl (3.9 mmol/L) is the start of hypoglycemia.[20] Activation of glucose counter-regulatory system starts at glucose level of 65–70 mg/dl (3.6–3.9 mmol/L), and symptoms of hypoglycemia ranging from mild to severe including tremors, sweating, dizziness, pale skin color, cognitive dysfunction, seizure, and coma start at 50–55 mg/dl (2.8–3.1mmol/L).[16,21] However, the threshold of symptomatic hypoglycemia seems to depend on factors such as age, history of diabetes, frequency of hypoglycemia incidence, insulin sensitivity and lifestyle.[22,23] Up to 50% of the hypoglycemic events

was reported to be nocturnal hypoglycemia when patients with type 1 diabetes were monitored.[24] The probable reasons might be stopped glucose intake and reduced sympatho-adrenal response at night.[17] Severe hypoglycemia (hypoglycemia resulting in stupor, seizure, or unconsciousness, during which someone else's help is required) most often occurs in type 1 diabetes patients with long history of diabetes. The premise behind that relies in the link between severe hypoglycemia and neuropathy. Severe hypoglycemia is not only the result of insulin overdoses, but also is a side effect of autonomic neuropathy. Autonomic neuropathy impairs autonomous nervous system to start and control glucose counter-regulation (mainly the activation of three hormones: glucagon, epinephrine and cortisol), and therefore, it impairs the main defense against hypoglycemia and leads to hypoglycemia unawareness, and finally severe hypoglycemia.[25–27]

1.3 Challenge of Glycemic Control in Type 1 Diabetes

According to ADA, diabetes mellitus is identified by glycosylated hemoglobin (HbA1c) greater than 6.5%.[1] HbA1c $< 7\%$ is associated with reduction in the risk of macrovascular and microvascular complications, suggesting that lowering HbA1c to the safe range is the main key to diabetes management.[1,8,28–31] The main treatment to reduce HbA1c in type 1 diabetes is intensive glycemic control by means of multiple-dose insulin (MDI) injections (three to four injections per day of basal and prandial insulin) or continuous subcutaneous insulin infusion (CSII).[1] Glycemic control (maintaining blood glucose in the normal range) for type 1 diabetes patients essentially concerns striking a balance between insulin, meal, and exercise.[32] Ill-timed insulin administration with respect to the meal timing, wrong insulin type and/or improper insulin dosage in relation to the content of meal, and also unadjusted insulin dosage/type/timing to exercise profile can result in significant glycemic variations.[33–35] Other factors challenging glycemic control include stress, reduction in endogenous glucose production following alcohol ingestion, increased sensitivity to insulin due to weight loss, decrease in insulin clearance caused by kidney disease (renal failure), disease such as hepatic failure, adrenocortical failure, and certain heart or high blood pressure medicine.[7,23]

Being insulin the main glucose lowering agent, patients under intensive insulin therapy are likely to have hypoglycemia by 2–3-times,[36,37] associating with excess mortality rate.[19] Furthermore, hypoglycemia-related symptoms instill fear of hypoglycemia and anxiety. Patients with hypoglycemia may respond to such fear by non-adherence to the intensive insulin regimen, which

subsequently results in hyperglycemia.[38,39] Hypoglycemia can therefore indirectly result in diabetes complications associated with high blood glucose level.

Although, patient education[40–42] and the use of insulin with more reproducible and predictable profiles [17,43] can reduce the incidence of hypoglycemia in patients with type 1 diabetes under intensive glycemic control, hypoglycemia is still the main barrier of intensive insulin therapy. Therefore, intensive insulin therapy without inappropriately lowering BG level is the main challenge of glycemic control. [8,29,44]

1.4 Glucose Monitoring in Type 1 Diabetes

Glucose monitoring is a necessary component and cornerstone of glycemic control for patients and healthcare providers to assess progression in achieving glycemic targets, adjusting medications, and detecting hypoglycemic and hyperglycemic excursions of BG.[1,45–47] The three methods of glycemic monitoring which are currently used by health care providers and patients are HbA1c, Self-monitoring of blood glucose (SMBG), and continuous glucose monitoring (CGM).

1.4.1 HbA1c

HbA1c describes a series of stable hemoglobin components formed gradually from glucose and hemoglobin. The rate of HbA1c formation is directly proportional to the glucose concentration. The HbA1c level - presented as percentage- provides an accurate glycemic history of the previous 120 days.[48] HbA1c reflects the long-term average plasma glucose (PG), hence serves as a strong predictive of long-term diabetes complications.[9,30] HbA1c is widely used by clinicians to assess patient glycemic control over time.[49] HbA1c should be performed routinely in all diabetes patients, at the time of diabetes diagnostics, and afterwards as a part of diabetes management. The frequency of HbA1c testing is individualized depending on the treatment regimen and the clinician's decision, and should be performed at least two times a year for patients who meet glycemic goals and more frequently for patients who has changed diabetes therapy or who do not meet glycemic target.[48]

1.4.2 Self-Monitoring of Blood Glucose Measurement

SMBG is the measurement of glucose from capillary blood using blood glucose meters and glucose test strips, by patient. In order to have optimal benefit in glycemic control, SMBG should be performed with appropriate

timing and frequency. Generally, patients with type 1 diabetes and those with a history of severe hypoglycemia regardless of HbA1c level and insulin regimen should perform SMBG at least three times per day.[47] However, it is recommended that patients with intensive insulin therapy do SMBG prior to meals, postprandially, at bedtime, prior to exercise, when feeling hypoglycemia and after treating it, and prior to tasks that require high attention such as driving.[1,47] This will result in testing of BG 6–8 times per day. Testing $>$ 10 times daily is advised for patients with frequent incidence of hyper- and hypoglycemia, hypoglycemia unawareness, and when self-adjustment of insulin dosage is required.[47] This implies the improvement of glycemic control by increasing the frequency of glucose sampling.

The Inadequacy of HbA1c and SMBG for glycemic control

Although HbA1c is an inseparable part of diabetes management as a means of glycemic monitoring in order to predict and avoid long-term diabetes complications, it merely provides an averaged glucose level, which cannot reflect daily glycemic variation. In addition, although frequent SMBG seems to make glycemic goals more approachable, and enhances the quality of diabetes management, the inability of SMBG measurements to provide patients with a broad picture of glycemic variation together with the pain associated with frequent finger pricking render SMBG to be insufficient for glycemic control.[50,51] Therefore, there is the need for a glucose monitoring method which is able to reveal fluctuations and excursions of blood glucose more completely and more conventionally than SMBG and HbA1c. This is achieved by frequent subcutaneous measurement of glucose by means of CGM. The scope of the current PhD thesis is within the field of CGM in patients with type 1 diabetes.

1.4.3 Continuous Glucose Monitoring

Continuous glucose monitoring (CGM) allows for continuous measurement of glucose concentrations from interstitial fluid (ISF), and therefore, produces a detailed series of successive observations of interstitial glucose (IG) concentration.[52,53] Because of the large glycemic variation in type 1 diabetes patients due to insulin, and therefore the necessity of continuous glycemic monitoring, CGM is mainly used in type 1 diabetes patients.

A CGM device with enzyme-based electrochemical amperiometric glucose sensor typically consists of (i) a glucose sensor that continuously measures interstitial glucose levels, (ii) an electronic processing unit that is in

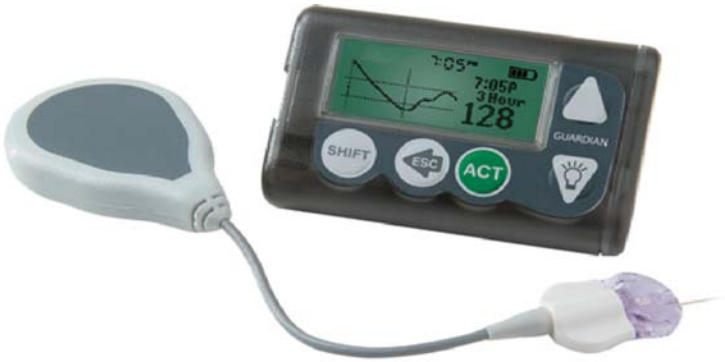


Figure 1.1 Guardian ® REAL-Time (medtronic diabetes, Northridge, CA) CGM system

communication (usually wireless using radiofrequency) with glucose sensor, and (iii) a data display unit,[54,55] as illustrated in Figure 1.1.

To date, direct measurement of IG is the only technique used in the commercial CGM devices. Devices using this technique are referred to as minimally invasive, and operate with either a subcutaneous needle-type sensor or microdialysis technique.[51] Both techniques use electrochemical glucose sensors which rely on glucose-oxidase enzyme-based technology for sensing glucose. Electrochemical sensors are the only sensors used in the currently available commercial CGMs due to their better sensitivity, reproducibility, and their low cost compared to other types of glucose sensors.[55]

Subcutaneous sensor-based CGM and microdialysis-based CGM differ only in the way that IG is sampled.[56] In a CGM with subcutaneous glucose sensor, the amperiometric enzyme-based glucose sensor is inserted subcutaneously and the sensor is in direct contact with ISF. In a microdialysis-based CGM, a small hollow catheter is inserted in subcutaneous tissue. The circulation of a glucose-free isotonic solution through the catheter results in the diffusion of glucose from ISF through the semipermeable membrane into the catheter. The glucose level in the solution is measured outside the body by means of an external amperiometric enzyme-based glucose sensor.[55,57–59]

Food and Drug Administration (FDA)-approved and commercially available CGMs have been introduced over the last decade. The first one on the marked was the MiniMed (Medtronic Diabetes, Northridge, CA) Continuous Glucose Monitoring System (CGMS®) which stores glucose readings every 5 min up to 3 days, and sensor glucose values were available only retrospectively and could be downloaded in a physician's office.[55,58] The GlucoWatch®

Table 1.1 Commercially available CGM systems

Device	Manufacturer	Sensor	Real-Time	Associated with Insulin Pump
CGMS iPro	Medtronic	subcutaneous	No	No
Guardian REAL-Time	Medtronic	subcutaneous	Yes	No
Paradigm REAL-Time	Medtronic	subcutaneous	Yes	Yes
Paradigm Veo	Medtronic	subcutaneous	Yes	Yes
SEVEN	Dexcom Inc.	subcutaneous	Yes	No
SEVEN Plus	Dexcom Inc.	subcutaneous	Yes	No
G4 Platinum	Dexcom Inc.	subcutaneous	Yes	No
G4AP	Dexcom Inc.	subcutaneous	Yes	No
Freestyle Navigator	Abbott Inc.	subcutaneous	Yes	No
GlucoDay S	Menarini Inc.	Microdialysis	Yes	Yes

2 Biographer (Cygnus Inc., Redwood City, CA) was the first CGM with real-time glucose values. However, because of inaccurate readings, false alarms, and local irritation on the insertion site, the GlucoWatch CGM systems are not in use anymore.[58] CGM devices produce a glucose measurement every one to five minutes. The disposable sensor can be used for three to seven days.[55] The majority of commercially available CGM systems have subcutaneous sensors. The only microdialysis-based CGM on the marked is GlucoDay (A. Menarini Diagnostics, Florence, Italy).[60] SCGM1 (Roche Diagnostics GmbH, Mannheim, Germany) is also a microdialysis-based CGM system, which is under development.[59] The current FDA-approved CGM devices on the marked are listed in Table 1.1.

1.5 Electrochemical Sensing of Glucose in Minimally Invasive CGM

In the amperiometric electrochemical CGM sensor, a current which is generated by means of oxidation-reduction reactions, flows from a working electrode to a counter electrode. [55,61] To this purpose, a potential is applied between the working electrode and a reference electrode. The enzyme GOx is immobilized at the working electrode and catalyses the oxidation of glucose to gluconolactone. Flavin Adenine Dinucleotide (FAD) is required to act as an electron acceptor reducing to $FADH_2$, according to the following reaction[56,62]

$$\text{Glucose} + \text{GOx(FAD)} \longrightarrow \text{Gluconolactone} + \text{GOx}(\text{FADH}_2) \qquad (1.1)$$

The flavin is re-oxidized in the presence of oxygen, producing hydrogen peroxide[56,63]

$$\mathrm{GOx\ (FADH_2)} + \mathrm{O_2} \longrightarrow \mathrm{GOx\ (FAD)} + \mathrm{H_2O_2} \tag{1.2}$$

By applying a potential (around + 0.6 V) between the working electrode and a reference electrode, an electrochemical current (nA) which is proportional to the glucose concentration is produced by releasing electron according to Eq. 1.3[56]

$$\mathrm{H_2O_2} \longrightarrow 2\mathrm{H^+} + \mathrm{O_2} + 2\mathrm{e^-} \tag{1.3}$$

The electrochemical signal is radiofrequency- transmitted to a receiver, where it is denoised, and converted to a glucose value through calibration.[52]

1.6 Relationship between Blood Glucose and Interstitial Glucose

Minimally invasive CGMs sample IG in ISF, hence reflect BG variations through ISF. The two-compartmental model illustrated in Figure 1.2B has been used to describe glucose diffusion from capillary blood to ISF.[54,56,58,64–66] In Figure 1.2B, G_1 is BG, G_2 is IG, k_{02} is the rate of glucose uptake from ISF, V_1 and V_2 are the volumes of blood and ISF and k_{12} and k_{21} are the fractional diffusion rates between blood and ISF.[67]

A mass transport equation describes the dynamic relationship between BG and IG

$$\frac{dV_2IG}{dt} = -\left(k_{02} + k_{12}\right)V_2IG + k_{12}V_1BG \tag{1.4}$$

Eq. 1.1 has the Laplace transfer function

$$\frac{IG(s)}{BG(s)} = \frac{K}{\tau s + 1} \tag{1.5}$$

Here, the static gain K and the time constant τ are defined by

$$K = \frac{k_{21}V_1/V_2}{k_{02} + k_{12}}, \tau = \frac{1}{k_{02} + k_{12}} \tag{1.6}$$

The static gain K can be considered equal to 1. [65] τ causes the time-lag between BG and IG and varies between individuals, but it is usually considered in the range of 3–15 minutes for human.[56,68,69]

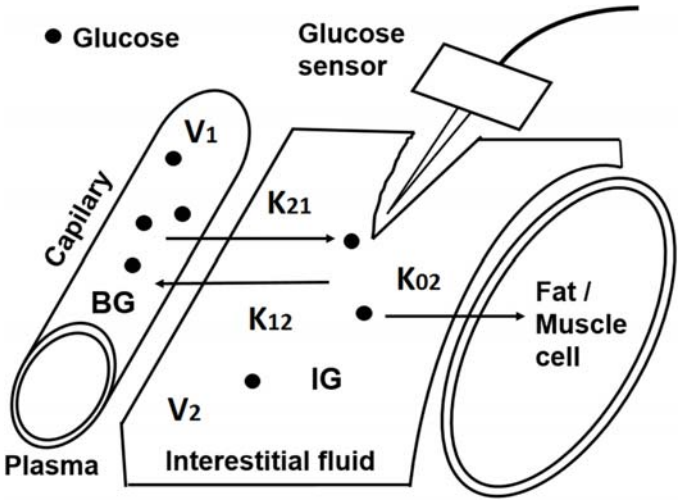


Figure 1.2 Placement of subcutaneous glucose sensor in the subcutaneous tissue, and diffusion of glucose from capillary blood to interstitial fluid

1.7 Glycemic Control with CGM

CGM has been shown promising in diabetes management by providing patients and clinicians with a wider view and continuous awareness to glucose variations through real-time detection of hyperglycemia and hypoglycemia, and through professional retrospective reviewing of CGM data.[32,34,35,70−79]CGM is expected to improve diabetes management by providing three features[34]:

- Medication adjustment in response to real-time data
- Proactive action based on glucose trends
- Medication adjustment based on retrospective data review (professional CGM)

CGM is recommended by ADA to be used in lowering HbA1c in adults aged $\geq$ 25 years using intensive insulin regimen. Tamborlane et al.[80] studied a 26-week randomized trial of 322 patients with type 1 diabetes and showed that adults aged $\geq$ 25 years using intensive insulin therapy and CGM had 0.5% lower HbA1c (HbA1c of 7.1%) compared with patients using intensive insulin therapy with SMBG (HbA1c of 7.6%). However CGM in children, teens and adults up to age 24 did not result in significant reduction of HbA1c, as they were not adherent to the use of CGM as adults were in the study. [80] A 5-week pilot study by Bode et al. demonstrated that adjusting diabetes therapy by

the use of professional CGM (CGMS, Medtronic Diabetes, Northridge, CA) reduced HbA1c significantly from $9.9\% \pm 1\%$ at baseline to $8.8\% \pm 1\%$ at week 5 without changing daily insulin dosage. [77] Deiss et al. studied 156 patients with type 1 diabetes adherent to intensive insulin therapy. It was reported that patients who used CGM (Guardian REAL-Time, Medtronic Diabetes, Northridge, CA) for three months had a larger reduction in HbA1c that patients who used only SMBG ($1.0\% \pm 1.1\%$ vs $0.4\% \pm 1.0\%$).[81]

The larger reduction in HbA1c achieved with CGM compared to with only SMBG, besides the increased awareness to inappropriately high BG levels and subsequent medication adjustment, may arise from the ability of CGM to detect unrecognized hypoglycemia by real-time alarms or by retrospective screening of CGM data by clinicians. Having access to this facility provided by CGM, it is possible to follow a safer intensive insulin therapy aiming at reducing HbA1c towards the targeted range, without the risk of hypoglycemia. This is hard to achieve when SMBG is the only means of glucose monitoring, and that explains to avoid low HbA1c caused by undetected hypoglycemic events, healthcare providers set higher HbA1c target than the goal HbA1c $<$ 6.5% for patients under intensive insulin therapy.[1]

The ability of CGM to lower HbA1c, while reducing the risk of hypoglycemia is reported by several researchers. *Hirsch et al.*[82] evaluated the clinical effectiveness of an insulin pump in two groups of type 1 diabetic patients. The first group used the pump with real-time CGM and the second group (control group) used the pump with standards SMBG regimen. HbA1c decreased from baseline in both groups ($-0.71 \pm 0.71\%$ in the first group and $-0.56 \pm 0.072\%$ in the second group). However, the mean hypoglycemia area under the curve (AUC) and the number of hypoglycemic events increased for the group with insulin pump and SMBG; while, there was no increase in AUC, and hypoglycemic events for the group with insulin pump and CGM. In a study by Juvenile Diabetes Research Foundation,[83] it was demonstrated that the group with CGM had lower HbA1c than the group with SMBG. In addition, the CGM group had less frequent hypoglycemia ($\leq$ 70 mg/dl) and less frequent events with glucose $\leq$ 60 mg/dl.

In real-time application of CGM for glycemic control, the issue of insulin 'over-bolus' in hyperglycemia treatment should be considered into account. Having access to frequent glucose measurement brought by CGM, patients may overcompensate high BG levels by frequent bolusing of insulin, which consequently increases the risk of hypoglycemia.[34,84] This, however, is in contrast to the merit of CGM in lowering the risk of hypoglycemia by detection of unrecognized hypoglycemia. To avoid such pitfalls in CGM use, patient

education by giving thorough practical advice is required. Particularly, it is important that patients be aware not to rely only on CGM readings for therapeutic interventions or corrective actions without confirmation of the values by SMBG.[34,81]

1.8 Use of Professional CGM in Clinical Decision-Making

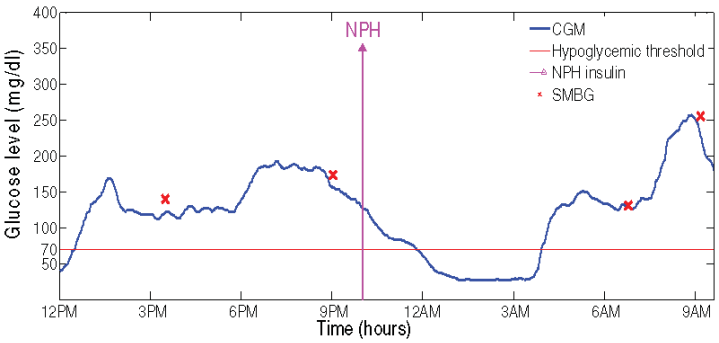
CGM as an adjunctive tool is recommended by ADA for patients with hypoglycemia unawareness and/or frequent hypoglycemic events.[1] By the use of CGM, it is possible to identify more number of hypoglycemic events compared to standard SMBG regimen.[85−88] Jungheim et al. [85] demonstrated that four daily SMBG measurements could miss up to 71% of the hypoglycemic events that CGM can detect. Identifying hypoglycemic episodes and treating them by modifying diabetes medications is therefore a particular use of CGM.[74] The role of insulin as the main hypoglycemia-inducing agent and its relation to carbohydrate intake appears to be of great importance in clinical recommendation for avoidance of hypoglycemia.

In Table 1.2, a list of therapy adjustments and recommendations to avoid hypoglycemia is given.[33,76,77,79] The adjustments are mainly in insulin and diet.

Figure 1.3 indicates an example of a nocturnal hypoglycemic episode (CGM $\leq$ 70 mg/dl), starting around 12 a.m. and ending around 4 a.m., detected by CGM but unrecognized by SMBG. The hypoglycemia may be caused by NPH insulin that is injected at bedtime as basal insulin. The treatment adjustment to avoid incidence of nocturnal hypoglycemia could be reducing dosage or changing the type of basal insulin.[33−35]

Table 1.2 List of therapy adjustment for hypoglycemia prevention

Change in one or more prandial insulin dosage and timing
Change in one or more basal insulin dosage and timing
Change in type of basal insulin
Change in type of prandial insulin
Change in insulin-to-carbohydrate ratio
Adding extra carbohydrate
Use glucose tablets instead of food for rapid treatment of hypoglycemia
Avoidance of simple sugar
Changing from insulin injection to insulin pump therapy to allow more flexible basal insulin rate
Change in early morning basal rate for patients with insulin pump
Alteration in approach to exercise if exercise is followed by hypoglycemia



insulin.[33-35]

Figure 1.3 Sample CGM graph with nocturnal hypoglycemia

1.9 The Importance of CGM Accuracy

It is evident that the use of CGM can benefit patients in controlling diabetes and achieving the goal HbA1c, while reducing the risk of hypoglycemia. However, achieving a good glycemic control through CGM requires CGM of adequate accuracy particularly in hypoglycemia. Due to substantial CGM inaccuracy, CGM profiles may differ significantly from BG profiles, and that can cause critical circumstances in several CGM applications, for example, hypo- and hyperglycemic alarms[58,89], treatment adjustment by retrospective reviewing of CGM data[90], and artificial pancreas which relies on CGM output[91,92]. The inaccuracy of CGM systems is particularly higher in hypoglycemia,[66,93–95] and CGM shows a substantial rate of false negatives in hypoglycemia.[93] In addition, CGM glucose readings overestimate BG levels when BG is falling, and underestimate BG, when BG is rising.[53,96] Overestimation and underestimation of BG by CGM can result in misinterpretation of CGM measurements by patients and clinicians, with severe consequences.

Therefore, accuracy is the most important requirement of a CGM device, and lack of accuracy reduces confidence among patients and clinicians.[51] The present thesis contributes to solving the problem of inaccurate CGM for glucose monitoring of type 1 diabetes patients.

1.10 Sources of CGM Inaccuracy

The accuracy of CGM glucose readings are affected by the presence of several sources of error, e.g, BG-to-IG kinetics, random noise and spike, problems caused by biochemistry of glucose sensors such as biofouling and

electrochemical interferences, device physics, improper calibration, and signal processing limitations.[53,60,97–99] The BG-to-IG kinetics according to Eq. 1.5 is a first order linear low-pass filter; therefore, glucose concentrations in blood and ISF are expected to be different because of the low-pass filtering distortion (attenuation in amplitude and distortion in phase).[64,65,98–100] It is reported that values of IG levels can vary between 50% and 100% of the BG levels due to the BG-to-IG kinetics.[101] Considering this discrepancy and adding the errors due to the sensors' physics and biochemistry, calibration and signal processing insufficiencies, the resulted deviation of CGM readings from BG levels becomes so large that makes CGM systems unreliable to replace finger stick measurements of BG for glycemic control. In the following, the three sources of CGM inaccuracy which are the main areas of focus in the CGM signal processing algorithms are introduced, and the mechanisms with which they contribute to CGM inaccuracy are discussed.

1.10.1 Time-Lag between BG and CGM

There are three main sources of time-lags between BG and CGM glucose readings: physiological time-lag, instrumental time-lag, and filtering time-lag. The physiological time-lag as specified in Eq. 1.6 indicates that there is a limited transcapillary exchange of glucose between blood and ISF, and therefore, any variation in the capillary BG concentration cannot be transported to ISF immediately.[54,56,68,69,102] This physiological time-lag may vary depending on the absolute glucose levels, and the rate and direction of variation.[54,58,103] In addition, in diabetic patients the altered capillary wall structure may increase the diffusion barrier and thereby prolong the physiological time-lag.[54] Also, the inter- and intra-individual variability of the time-lag between glucose changes in blood and in ISF remains to be clarified.[54]

The instrumental lag is the time that an amperometric electrochemical sensor requires to respond to glucose changes in ISF, and is reported to be between 1–2 minutes.[68,69,89] In addition to the sensor lag, in microdialysis-based CGM, there is often a significant response delay due to the time until the dialysate is transferred from the microdialysis catheter to the site of glucose sensing.[59] This instrumental transport delay is reported to vary between 5 and 45 min.[104]

The sensor signals are noisy and require filtering. Filtering introduces additional time-lag to the CGM signal which is proportional to the amount of smoothing.[69,89,105] Keenen et al.[69] reported the delays associated with

filtering per se in three CGM devices: these manufacturer-reported delays are 8.25 min for Guardian REAL-Time (RT), three min for *CGMS*® *Gold*™ (Medtronic Diabetes, Northridge, CA) and ten min for GlucoWatch (Cygnus Inc. Redwood City, CA). In the study done by Wei et al.,[106] the delay due to data processing was suggested to be five to ten min for Guardian RT.

The summation of the three sources of time-lags causes a substantial overall time-lag between BG levels and CGM readings, and consequently, results in a large deviation of CGM glucose readings from concurrent BG concentrations. The deviation is particularly magnified when BG concentration is changing rapidly.[78,94,107]. The time-lag causes that CGM readings overestimate BG levels when BG is decreasing rapidly (e.g., dropping BG to hypoglycemia), and underestimate BG levels when BG is rising rapidly (e.g., after a meal).[53,96] A consequent of the over- and under-estimation can be an erroneous real-time corrective action. For example, patients may attempt to correct for a hypoglycemic value of glucose read from CGM, which does not have a concurrent true hypoglycemic BG level. This may occur when BG is recovering from hypoglycemia (BG with positive rate of change). Due to the lag between BG and CGM, the recovered BG is not yet read by CGM sensor. It is reported that in this case, patients may reduce their basal insulin in order to avoid hypoglycemia. This may lead to overtreating hypoglycemia, and as a result, patients may end up having a cycle of significant glycemic variability.[76,84]

The most important effect of the time-lag is inducing error to calibration, where in the presence of a time-lag, a linear calibration is insufficient to convert the current measured by the sensor to a true BG concentration.[108] Figure 1.4 depicts the time-lag between BG and CGM data.

The delay between BG values and CGM readings is detectable from by comparison between the peak (or nadir) time points of the BG values and the CGM readings.

1.10.2 Signal Artifacts

The electric current measured by CGM sensor is affected by artifacts such as electric noise, movement artifacts, sensor drift, and loss of glucose sensor sensitivity.[65,69,97,100,109−114] It is frequently reported that CGM time series are corrupted by a random noise component likely originated from electronics.[69,97,110,111] Movement artifact may also cause occasional spikes in the CGM profile.[97] For example, particular movement of patient can occlude the microdialysis tube, in the microdialysis-based CGM, inserted into the

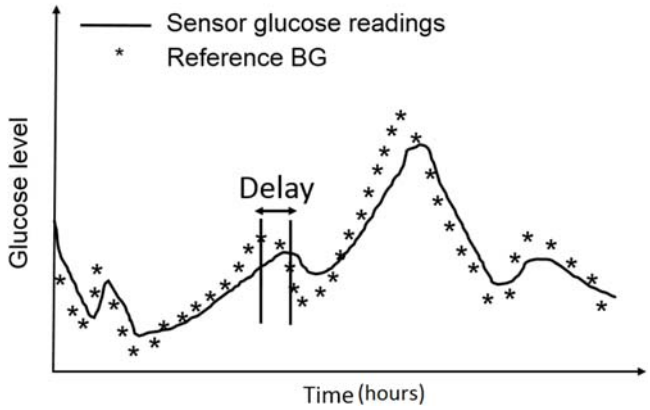


Figure 1.4 BG reference samples (stars) versus CGM profiles (line)

abdominal wall, and consequently cause spike in the CGM readings.[112] The electric current drop caused by the pressure on the subcutaneous sensor is another effect of movement artifact.[107] The roughness and irregularities in the CGM signal, caused by noise and spikes, increases the signal uncertainty and imprecision, and consequently complicate the CGM interpretation and limit its practical use, in particular, may significantly raise the rate of false alerts in hypo- and hyperglycemic CGM alarms.[100,113,114] Figure 1.5 illustrates a CGM profile corrupted with random noise and spikes.

CGMs exhibit 'drift' in their sensor signal in *in-vivo* applications, which changes the sensor function over time.[54,58,115] It is reported that commercial glucose electrodes show a considerable signal drift within 3 days.[54] The main cause of drift is the biocompatibility problem such as covering

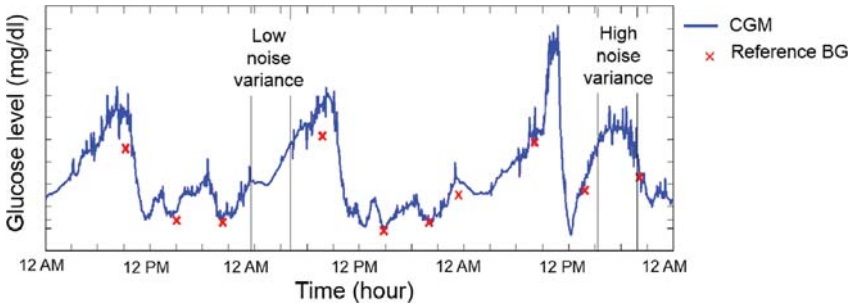


Figure 1.5 CGM profile from a patient with type 1 diabetes wearing SCGM1 which is a microdialysis-based CGM

of the electrode surface by cells and other substances as the result of foreign body reaction, and consequently reduction of the glucose influx to the electrodes.[54,58,60,115] Other sources of sensor drift are inflammatory reaction and wound healing. Inflammatory cells consume glucose around the subcutaneous sensor[116]. Therefore, a lower glucose concentration will be measured in the present of an inflammation reaction.[116] In addition, after inserting subcutaneous sensor and during the wound healing process, more capillaries supply glucose to the area which may cause higher glucose concentration readings.[58] Sensor drift can result in a complete loss of correlation between changes in the sensor signal and glucose levels. Updating calibration at fixed intervals can address the problem related to the signal drift, at least for a limited time.[54,58] Improving glucose sensors biocompatibility would mitigate the problem of sensor drift during the sensor lifetime.[117]

Reduction in the sensor conductivity and also inactivation of the enzyme degrade the sensor and reduce the sensor sensitivity.[54,58,115] According to Eq. 1.2, the electric current generated by sensor is proportional not only to the glucose concentration, but also to the oxygen concentration; therefore, ample oxygen concentration is required for the proper electrochemical measurement of glucose.[57] Oxygen limitation reduces the sensitivity of the glucose sensor and the glucose readings are lower than the actual IG concentrations when oxygen level is not sufficient.[56,60,63,118] The reduction in sensor sensitivity may be compensated for by updating calibration for a limited time.[57]

1.10.3 Calibration

The transformation of the electrical signal (in nA) generated by the glucose sensor into an estimation of the concurrent glucose concentration (in mg/dl or mmol/l) by exploiting one, or more reference BG measurements is referred to as a calibration, and is one of the key issues for development of CGM systems.[65,119] During calibration process, BG levels (measured by SMBG) are related to the glucose sensor signal through a linear regression[120]

$$y = mx + b \tag{1.7}$$

where x is the independent variable (reference BG) and y is the dependent variable (the current measured by the sensor). m is the sensor sensitivity and b is the background current which is the current generated by the sensor in the absence of glucose concentration.[66,121] Because the sensor glucose samples IG levels, calibration of the sensor signal versus BG levels necessitates that BG concentration is directly related to IG concentration,

and it requires the assumption that the BG-to-IG gradient remains relatively constant.[58,89,122] All the subsequent glucose sensor values are then adjusted according to the regression parameters and are converted into meaningful CGM readings.[54,123]

$$CGM = \frac{(y - b)}{m} \tag{1.8}$$

Based on Eq. 1.7, two calibration approaches have been introduced for CGM systems.[51,89,119,124] The first approach is a one-point calibration, in which the background current of the sensor is known and remains constant or it is zero ($b = 0$). In a one-point calibration, only one pair of sensor signal- BG readings is required. The second approach is a two-point calibration, in which the sensor background current is not considered fixed and it is estimated by fitting m and b in Eq. 1.7 to at least two pairs of sensor signal-BG readings. The linear regression analysis in Eq. 1.7 assumes that the independent variable (BG measurements) is known and that the dependent variable (the current measured by the glucose sensor) is uncertain. This may be a good assumption if BG measurements are of high quality; however standard reference glucose test meters have error. Panteleon *et al*[125] obtained better calibration results (lower mean average deviation of CGM readings from BG) when the raw glucose current signal is used as the independent variable in the linear regression analysis of Eq. 1.7.

In real-time calibration, calibration coefficients (m and b) are re-estimated, when new BG measurements are available, to adjust to the changes in the sensor sensitivity and the sensor drift during the lifespan of the glucose sensor.[56] In retrospective calibration, after collecting all the data corresponding to all days of operation, m and b are estimated by minimization of the absolute relative error of the estimated BG with respect to the BG measurements in the calibration points.[56]

The accuracy of CGM readings depends, among the other factors, on the calibration algorithm, and a substantial part of CGM inaccuracy originates in the calibration insufficincy.[51,126] Because of the foreign body response, and the time-varying gradient between BG and IG caused by varying user physiology (exercise, diet, medication, anoxia, or hypoxia), the *in-vitro* calibration of CGM sensor does not satisfy the *in-vivo* time-varying changes in the sensor sensitivity and background current, and therefore, for real-time *in-vivo* application of CGM, calibration should be repeated during the sensor lifetime.[51,119] Three main factors affect the validity of real-time calibration: the time-lag between BG and IG[51,65,98], the incorrect estimation

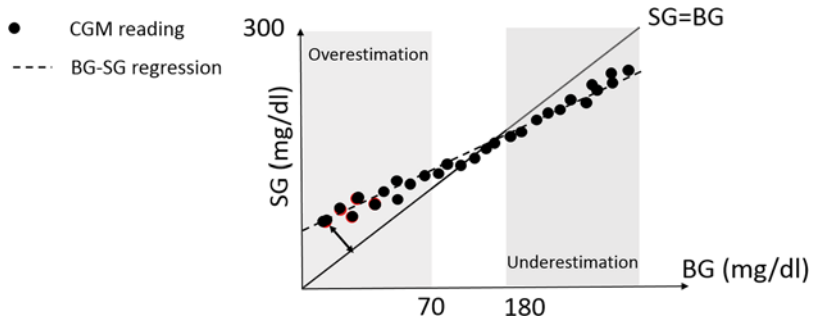


Figure 1.6 Effect of sensor background current on the BG-SG regression

of the sensor background current[51,66,119,121,123], and the error of the test strips for SMBG measurements[51,127]. These factors are discussed in the following paragraphs.

CGM sensor measures IG levels. Due to the presence of the physiological time-lag, the gradient between BG and IG is variable and has large values when BG is changing rapidly (e.g., BG can be 20mg/dL higher than IG).[51,65,98] The linear calibration in Eq. 1.7 with fixed parameters cannot compensate for the variable discrepancy between BG and IG.[103]

Incorrect estimation of the background current increases the deviation of sensor readings from reference BG measurements so that BG levels below the calibration point are over-read and BG values above the calibration point are under-read.[53,56,66,120,121] This consequently results in failure to detection of hypoglycemia, and causes underestimation of hyperglycemia.[66,123] Figure 1.6 indicates the systematic over- and under-reading of BG by CGM.

The imprecision of the BG measurements, which are used for calibration, affects the CGM accuracy.[127] For example, the glucose strips used for SMBG measurements induces approximately 5% error in CGM readings.[51]

The complexity of the relation between the above mentioned interconnected factors affecting the accuracy of calibration contrasts with the rather simplified methodologies used in the calibration algorithms of the current commercial CGM devices.[128]

1.11 CGM Accuracy Improvement

Enhancing of the CGM accuracy appears to be the most important challenge in the development and broadening the application of CGM systems. It should be noted that although the observed deviation of an isolated CGM data point

from a concurrent reference BG level is indeed large, the extra information provided by the frequently time-sampled CGM readings allows the application of error reduction methods, by means of delay reduction, artifact correction and calibration improvement, which makes it possible to mitigate the CGM deviation from reference BG values.[53]

1.11.1 Delay Reduction

Several attempts have been made to deal with the delay between BG and CGM., which can be divided into correction for the physiological time-lag between BG and IG, and reduction of the filtering-induced delay. The latter will be discussed in the Denoising section. Correction of the physiological time-lag have been addressed both mechanically [129], and algorithmically[65−67,107,130−133].

Stout et al.[129] developed a modulated pressure application technique to mitigate the BG-to-IG time-lag by elevating blood perfusion at the measurement site. The technique reduces the time-lag for glucose to diffuse across the capillary wall into the interstitial space, and consequently increases the CGM accuracy by lowering the BG-to-IG time-lag. The algorithmic correction of the physiological time-lag is based on the physiological kinetic model between BG and IG. The parameters of the kinetic model are either estimated through model identification or are borrowed from the population studies in literature. The basis of the model-based time-lag correction approaches is re-gaining BG from calibrated CGM. Several methods have been developed for this purpose, which are mainly based on deconvolution, the Wiener filter, and the Kalman filter.

Rebrin et al.[133] estimated the gradient and the time-lag of the BG-to-IG kinetic model using BG values and the current measured by the sensor. By rearranging the input (BG) and output (IG) of the model, BG values were calculated as output of the model based on the sensor glucose measurements as input. Although this method corrected for delay, the approximation of the BG was very sensitive to noise, which was partially corrected by averaging the sensor glucose derivative term in the finite difference equations of the model. Guerra et al.[107] developed a real-time deconvolution-based approach for estimating BG from CGM. The basis of this approach was considering IG(t) as the product of convolving BG(t) by the linear impulse response g(t) of the BG-to-IG kinetics. A population value for the physiological time-lag was used in the model.

Keenan et al.[67] corrected for the physiological time-lag by identification of the inverse of BG-to-IG impulse response using Wiener filtering approach, with population parameters for the IG-to-BG kinetic model. The authors

suggested that a BG sample rate of at least every 30 min is necessary to update the Wiener filter coefficients. In a Medtronic patent [134], Steil and Rebrin cited the use of a Wiener filter for lag compensation, without providing more technical details.

Bequette[131] adopted a three-state Kalman filter for correction of the BG-to-IG time-lag, in the presence of substantial sensor noise. Knobbe and Buckingham developed an extended Kalman filter for real-time estimation of BG. The Kalman filter model employed IG, BG, BG-to-IG time-lag, and the BG rate of change as the states to be estimated. The median absolute relative deviation (MARD) of the lag-compensated sensor signal from the reference BG values was relatively small. Facchinetti et al.[65] performed time-lag correction using BG-to-IG kinetic model with population parameters in an extended Kalman filter, with utilizing the routine four reference BG values per day for calibration. The accuracy improved compared to the algorithm of Knobbe and Buckingham.[130]

1.11.2 Denoising

The raw signal of all CGM sensors has noise and needs filtering, before further signal processing algorithms is applied to the signal. Analog filters smooth the electric current measured by the sensor before analog-to-digital (A to D) conversion, but the signal requires further digital denoising.[89] Filtering can also be applied to the derivatives of the current measured by CGM sensor.[134] This section focuses on the digital filters that have been used for CGM denoising.

Finite and infinite impulse response filters

The most often filtering approaches in commercial CGM systems are finite impulse response (FIR) and infinite impulse response (IIR) filters. A widely used FIR filter is moving average (MA)[135−137], which is used in the Medtronic CGMS Gold,[69] and also in the Medtronic Guardian RT system.[69] Abbott reports a FIR filter that can switch between two different filter orders depending on the glucose rate-of-change.[66] Dexcom reports the use of an IIR filter for raw CGM signal.[138] Because the signal and the noise spectra often overlap, the low-pass filtering by FIR and IIR filters introduces distortion to the signal.[139] When the high-frequency content in the signal is because of the rapid physiological changes and not caused by the noise, the filtering distortion creates delay in the signal, proportional to the amount of smoothing, which affects the estimation of the true sensor signal[69].

Nonlinear filtering

One of the simple and effective methods for removing spike and unphysiological high-frequency noise from CGM is median filtering[103,140], which may respond better than FIR and IIR filters in the presence of spikes and outliers.[67] The use of a five-point median filtering for CGM is suggested by Poitout et al.[141] Mueller et al. [135] in a Medtronic patent describe a nonlinear filtering approach which is similar to median filtering. Mueller et al. [135] also present a nonlinear filtering method for hard limiting of the signal rate-of-change. In several CGM filtering approaches, a combination of linear filtering with nonlinear elements is applied to the sensor signal. For example, Goode et al.[109] in a Dexcom patent describe a method for replacing transient artifacts in the CGM signal, which comprises detecting the signal artifacts through monitoring the signal frequency content, and replacing the detected artifact by trimmed averaging, IIR filtering, or linear/nonlinear regression. Applying nonlinear filtering distorts the assumption of the linear relation between BG(t) and the filtered signal. This may affect the estimation of BG(t) by deconvolving the filtered signal[107] which is proportional to IG (t), and also affects the estimation of BG(t) by inverse filtering (Wiener filtering) of the filtered signal[67], where in both methods, the assumption of linearity between BG(t) and the filtered sensor signal is necessary.

Model-based filtering approaches

The two CGM filtering methodologies based on the BG-to-IG kinetic model are the Wiener filtering and the Kalman filtering, both using the optimal estimation of glucose values. Keenan et al.[64] indicated that the CGM accuracy obtained with the Wiener filtering is higher than that achieved with the FIR filtering. Medtronic has patented a Wiener filter that estimates BG from sensor glucose values.[132] The Kalman filters with tunable parameters have been introduced to cope with the interindividual and intraindividual variability of the signal to noise (SNR) ratio.[97,110] These modified Kalman filters have smaller filtering delay compared to MA and have greater smoothness than the conventional Kalman filters. Facchinetti et al.[114] developed a three-module 'Smart' algorithm, which consists of denoising, accuracy enhancement, and prediction. The Smart algorithm is implemented in the G4AP (Dexcom Inc) CGM system and is reported to have higher accuracy compared to the older product G4 Platnium (Dexcom Inc).[142] Generally, the model-based filtering approaches can be expected to estimate the true BG levels if the model describing the BG-to-IG is of sufficient accuracy, and also if the sensor glucose values are adequately calibrated and do not overestimate or underestimate

BG.[66] Therefore, a Wiener filter may require frequent reference BG per day to adopt the filter coefficients to cope with the calibration insufficiency.[67] In the case of insufficient sensor calibration, a Kalman filter may adequately smooth the sensor glucose, but may not necessarily have a good estimation of the true BG values.[66] In addition, Kalman filters require a burn-in interval for tuning the parameters. The advantage of the Wiener filter and the Kalman filter over conventional FIR and IIR filter is that they can smooth the signal and at the same time can correct for the physiological time-lag by estimation of BG from CGM readings.[66]

1.11.3 Calibration Improvement

A verity of methods have been used for estimation of the sensor sensitivity and the sensor background current, including the Kalman filter and Wiener filter approaches[65,130,143], polynomial modeling of the sensor sensitivity and sensor background current[144], and using a fixed value for the background current[145].

The base of almost all calibration approaches used by the CGM manufacturers is linear regression. Medtronics uses a one-point calibration exploiting four sensor-BG pairs.[135,137] In Dexcom CGM systems a two-point calibration is used, with an auxiliary electrode for detection of the sensor sensitivity changes.[138] In an Abbott patent[146], a weighted averaged sensor sensitivity is suggested for calibration. In another patent by Abbott[147], an automated method for measuring sensor sensitivity is presented, which reduces the need for multiple SMBG.

In order to have high accuracy calibration, several conditions should be considered into account. Calibration should be performed in the periods of glucose stability. In addition, the difference between the two BG values in a two-point calibration should be larger than a certain value. The reference BG levels and the BG measurement error also play an important role in the quality of calibration.[94,98,120,148–151]

A more detailed description of the state-of-the-art CGM calibration improvement can be found in the paper 3[152] of this thesis.

1.12 CGM Accuracy Evaluation

Evaluation of CGM accuracy is a necessity, both in real-time and also in professional CGM applications.[65] It is of crucial importance though to provide a broad picture to the CGM accuracy by evaluating the CGM algorithms from

different accuracy perspectives. A complete view to CGM accuracy can be achieved not only by evaluating the CGM numerical accuracy but also by assessing the impact of the improved numerical accuracy on the CGM clinical reliability which is the end-point expectation from a CGM algorithm or a CGM system in general.

1.12.1 Numerical Evaluation of CGM Accuracy

The first goal of enhancing CGM algorithms is reducing the deviation of CGM measurements from BG or PG levels, or on the other hand, increasing the numerical accuracy of the CGM data. For the numerical assessment of CGM accuracy, CGM readings are evaluated with respect to their concurrent reference BG or PG concentrations.[115] The often used CGM numerical evaluation metrics based on such assessment approach are introduced in Table 1.3, which reflect the numerical proximity of the CGM readings to their time-paired reference BG or PG values.

The assessment of CGM numerical accuracy is a challenging task to deal with for two main reasons. 1) CGMs measure IG levels, while they are exploited by patients and clinicians to assess BG levels and variations. This means that comparing CGM readings with BG values, which is the principle of all CGM numerical evaluation metrics, seems to be fundamentally challenging. 2) CGM readings are time-ordered interdependent data points, while the reference BG or PG values, which are used for comparison with CGM readings, are isolated points in time. Pairing the isolated reference glucose values with the concurrent CGM readings for accuracy evaluation makes no use of the abundant temporal information provided by CGM.

1.12.2 Clinical Evaluation of CGM Accuracy

The evaluation metrics in Table 1.3 do not give a clinical view to the quality of diabetes control affected by CGM accuracy. Although the two latter metrics (ISO and Clarke EGA) assess the clinical risk of a CGM system associated with any discrepancies between CGM readings and BG values[114,119,155,156], these two metrics do not yet go beyond a point-to-point evaluation of the CGM data. Therefore, the numerical evaluation of CGM accuracy gives an incomplete view to the CGM performance.

The end-point use of CGM is to adjust treatment decisions such as insulin dosage modification by healthcare providers in order to avoid glycemic excursions. Therefore, the purpose of all efforts to improve CGM accuracy should be finally directed towards improving the quality of clinical decision making

Table 1.3 The commonly used CGM numerical accuracy metrics

Numerical evaluation metric	Definition
Absolute deviation (AD) [105]	Deviation of CGM readings from the concurrent reference glucose measurements
Absolute relative deviation (ARD)[105]	AD divided by the reference glucose measurements
Correlation coefficient[138]	correlation between CGM glucose readings and reference glucose values
R-squared[153]	R-squared of the regression analysis between CGM readings and reference glucose measurements
Hypoglycemia /hyperglycemia sensitivity[154]	The percentage of hypoglycemic/hyperglycemic reference values which are detected as hypoglycemic/hyperglycemic by CGM readings
Hypoglycemia /hyperglycemia specificity[154]	The percentage of non-hypoglycemic/non-hyperglycemic reference values which are detected as non-hypoglycemic/ non-hyperglycemic by CGM readings
Delay[69,96,103,108,110]	The delay between CGM readings and reference glucose measurements
International Organization for Standardization (ISO) criteria[155]	The percentage of CGM readings within $\pm$ 15 mg/dl from reference when the reference glucose value is $\leq$ 75 mg/dl and within $\pm$20% from reference when the reference glucose value is $>$ 75 mg/dl
Clarke error grid analysis[156] (EGA)	Classification of reference glucose-CGM readings pairs into five clinically-interpretable categories

for diabetes treatment adjustment. Without screening the impact of CGM numerical accuracy improvement on the quality of clinical decision making, the route to the improved CGM-based treatment adjustment, which starts from developing mathematical approaches for CGM accuracy enhancement, remains incomplete.

The clinical reliability of CGM depends on its ability to provide sufficiently accurate information to clinicians for making reliable and precise decisions on diabetes treatment adjustment.[98] Lack of CGM accuracy may result in incorrect clinicians' recommendations to the patients about modifications of their treatment including changing insulin type and dose level, modifying diet, and adjusting exercise approach[90]. The incorrect advice can consequently cause unreliable clinicians' decisions for treating/prevention of glycemic excursions.

The premise behind the clinical evaluation of CGM accuracy is to assess the effect of accuracy enhancement in CGM algorithms on CGM-based treatment decisions.[95] For this purpose, it is important to design measurable

metrics and create an approach to quantify the impact of CGM numerical accuracy on the quality and reliability of diabetes treatment adjustments. The effect of CGM accuracy on the reliability of clinical decision making can be investigated not only by screening the level of success of the CGM-based decisions to achieve glycemic goals over time,[32,35,74,77,79] but also by studying the effect of CGM accuracy improvement on the precision of the decisions. Precision is the necessity of all clinical decision making which are based on subjective reviewing of visual data such as radiographs, and computed tomography images.[157−159]

The literature about the effect of CGM accuracy improvement on the precision of clinical recommendations for diabetes treatment modifications is missing, which indicates this issue demands further investigation.

2

Aims of the PhD Thesis

The first objective of this PhD thesis was developing an algorithm for improving the CGM accuracy through two main steps: 1) presenting an effective method of artifact and noise removal for the CGM data, with reduced filtering delay between BG and CGM, and 2) improving CGM calibration to mitigate calibration insufficiencies, with particular focus on enhancing hypoglycemia accuracy. The second objective of the thesis was evaluating the accuracy of the proposed CGM algorithm, from different perspectives including numerical and clinical assessments of the algorithm performance.

2.1 PhD Studies

Based on the objectives of the thesis, four studies were employed in the PhD project. Study 1 and Study 2 of the thesis dealt with the first objective. Study 3 and study 4 of the thesis contributed to the second objective of the thesis. The diagram in Figure 2.1 indicates the relation between the studies in the thesis.

2.1.1 Study 1

A Multi-Step Algorithm for Processing and Calibration of Micro-Dialysis Continuous Glucose Monitoring Data [105]

In Study 1, a CGM algorithm which comprises filtering and calibration was developed. The purpose of the study was to enhance the CGM accuracy by presenting a CGM filtering approach with small delay and a robust calibration method with special focus on hypoglycemia accuracy improvement.

2.1.2 Study 2

Comparison between One-Point Calibration and Two-Point Calibration Approaches in a Continuous Glucose Monitoring Algorithm[160]

In Study 2, the CGM algorithm developed in the first study was improved by exploiting a one-point calibration instead of a two-point calibration. Then,

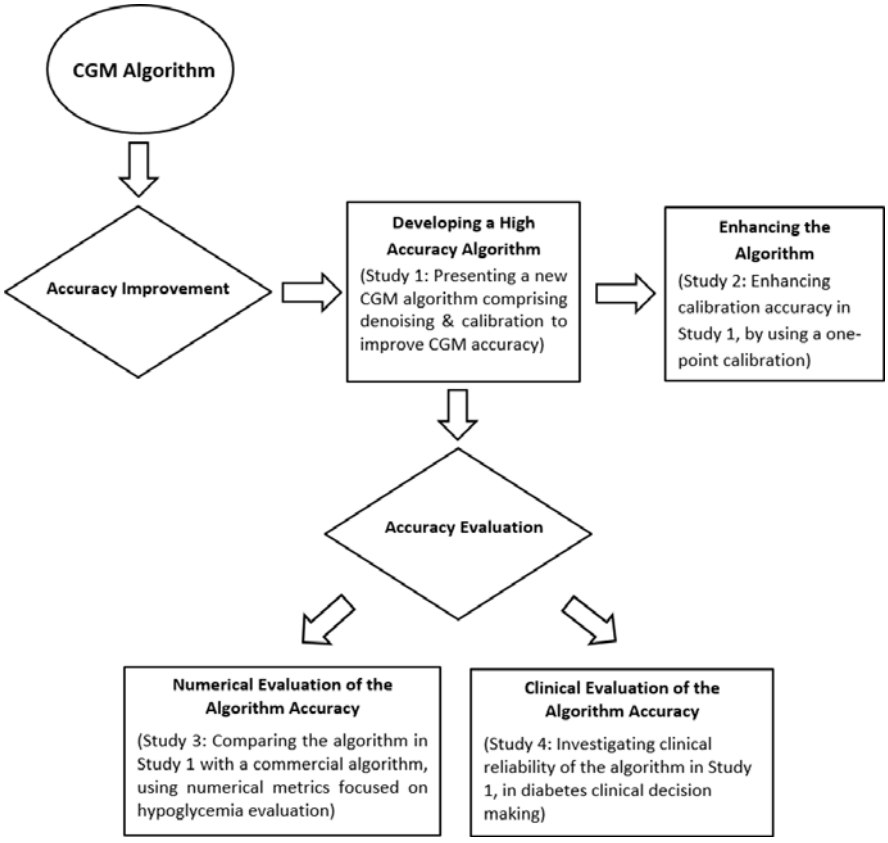


Figure 2.1 The composition of the present PhD thesis

the performance of the enhanced algorithm was compared with algorithm in Study 1, across the whole range of BG in a large dataset.

2.1.3 Study 3

Accuracy Evaluation of a New Real-Rime Continuous Glucose Monitoring Algorithm in Hypoglycemia.[152]

In Study 3, the accuracy of the CGM algorithm developed in the Study 1 was numerically evaluated in hypoglycemic range of plasma glucose using insulin-induced hypoglycemia data. The accuracy of the new algorithm was then compared with that of the routine algorithm in the Guardian RT CGM system, using several numerical evaluation metrics.

2.1.4 Study 4

The Effect of Continuous Glucose Monitoring Accuracy on Clinicians' Decision Making in Diabetes.

In Study 4, the CGM algorithm in Study 1 was clinically evaluated and compared with the algorithm in the SCGM1 system. The purpose of the study is to assess whether the increased numerical accuracy of the CGM data can be translated into higher inter-clinician and intra-clinician precision of the CGM-based clinical decision making.

Study 1 (Paper 1)

A Multi-Step Algorithm for Processing and Calibration of Micro-Dialysis Continuous Glucose Monitoring Data[105]

Zeinab Mahmoudi, Mette Dencker Johansen, Jens Sandahl Christiansen, Ole Hejlesen

Journal of Diabetes Technology and Therapeutics, 2013; 15 (10):825–835.

Study 2 (Paper 2)

Comparison between One-Point Calibration and Two-Point Calibration Approaches in a Continuous Glucose Monitoring Algorithm[160]

Zeinab Mahmoudi, Mette Dencker Johansen, Jens Sandahl Christiansen, Ole Hejlesen

Journal of Diabetes Science and Technology, 2014; 8: 709–719;
DOI: 10.1177/1932296814531356.

Study 3 (Paper 3)

Accuracy Evaluation of a New Real-Time Continuous Glucose Monitoring Algorithm in Hypoglycemia[152]

Zeinab Mahmoudi, Morten Hasselstrøm Jensen, Mette Dencker Johansen, Toke Folke Christensen, Lise Tarnow, Jens Sandahl Christiansen, Ole Hejlesen

Journal of Diabetes Technology and Therapeutics, 2014; 16(10):667–678; DOI: 10.1089/dia.2014.0043.

Study 4 (Paper 4)

Effect of Continuous Glucose Monitoring Accuracy on Clinicians' Retrospective Decision Making in Diabetes- a pilot study

Zeinab Mahmoudi, Mette Dencker Johansen, Hanne Holdflod Nørgaard, Steen Andersen, Ulrik Pedersen-Bjergaard, Lise Tarnow, Jens Sandahl Christiansen, Ole Hejlesen

Submitted to the journal of Computer Methods and Programs in Biomedicine, 2014

3

Discussions and Conclusion

3.1 Discussions

Tight glycemic regulation by means of intensive insulin therapy is the key to diabetes management in type 1 diabetes patients. However, intensive insulin therapy increases the incidence of hypoglycemia, as insulin is the main glucose lowering agent. Hypoglycemia as the main complication of diabetes treatment reduces quality of life for type 1 diabetes patients; therefore hypoglycemic episodes of BG should be detected and treated subsequently by real-time corrective actions or through retrospective treatment adjustments. Detection of hypoglycemia requires frequent monitoring of BG, which cannot be provided by sparse SMBG measurements. Continuous glucose monitoring (CGM) facilitates detection of hypoglycemia by frequent subcutaneous glucose sampling. However, CGM data deviate substantially from blood/plasma glucose levels due to several interacting reasons including BG-to-IG kinetics, signal artifacts such as noise and spikes, limitations of glucose sensor technology, signal processing shortcomings, and calibration insufficiencies.[53,60,64,65,97–100] The particularly large inaccuracy of CGM in hypoglycemia – caused by the time-lag and the calibration insufficiencies- renders the CGM systems unreliable for detection of hypoglycemia.[66,71,93–95] Due to the time-lag between BG and CGM, caused by the BG-to-IG kinetics and the filtering delay, the inaccuracy of CGM worsens when BG is changing rapidly, for example, after meal and after insulin administration.[53,96] Furthermore, inadequate noise removal from CGM reduces the precision of CGM data, which can further affect the accuracy of CGM clinical interpretation of and may consequently result in lack of confidence and precision of the CGM-based clinical decision making for diabetes treatment adjustment.[90,100,113,114]

The two main areas that the present thesis deals with are improving the CGM accuracy, and then evaluating the improved accuracy. A route was built to relate the two main scopes of the thesis. The start-point of this route

is algorithmically enhancing the accuracy of CGM, and the end-point is investigating the effect of this accuracy improvement on reliability of the clinical decision making for diabetes treatment adjustments. The focus of the first area of the thesis was reducing filtering delay and enhancing CGM calibration sufficiency in order to mitigate the discrepancy between CGM readings and reference glucose levels. The second area of the thesis further aimed to assess the performance of the new CGM algorithm both numerically and clinically, in order to provide a broad picture of the CGM accuracy evaluation.

In paper 1[105], an algorithm for denoising and calibration of continuous subcutaneous glucose monitoring data is presented. The denoising part in the algorithm was designed to have short filtering delay, which was achieved through a selective filtering approach. In addition, the calibration part was focused to have high accuracy particularly in hypoglycemia, and this was realized by incorporating a series of modifications in the calibration pairs and also in the calibration conversion function. The algorithm was evaluated on CGM data from SCGM1 system (Roche Diagnostics, Mannheim, Germany) in 16 patients with type 1 diabetes, and was compared with an alternative CGM algorithm which has a Kalman filter as the denoising part and a Medtronic calibration method as the calibration part.[135]

The results of paper 1 shows that the new CGM algorithm shows promise to enhance CGM accuracy by having lower mean and median ARD especially in hypoglycemia, and also by introducing shorter delay compared to the alternative algorithm. The average filtering delay of 2.1 min across the patients appears to compare well with the filtering delay of the Guardian RT algorithm (reported to be 8.25 min)[69], and the CGM Gold algorithm (reported to be 3 min) [69]. The new algorithm with the mean and median ARD values of 14.7% and 10.3% is comparable with Guardian RT CGM system (mean and median ARD of 19.9% and 16.9%)[161], and Dexcom STS CGM system (mean and median ARD of 16.7% and 14.2%)[161]. In addition, the improved hypoglycemia accuracy achieved in Study 1 (mean and median ARD of 22.6% and 14.8%) seems to outperform the FreeStyle Navigator (mean and median ARD of 35.7% and 26.4% in hypoglycemia).[162]

In paper 2[160], the algorithm in study 1 was modified by replacing the two-point calibration approach with a one-point calibration approach. Of special interest in paper 2 was estimating the sensor background current both real-time, and retrospectively. CGM data from SCGM1 system in 132 patients with type 1 diabetes was used to evaluate the performance of the modified algorithm and compare it with the older version in Study 1.

Results of paper 2 indicates that using a one-point calibration is superior to a two-point calibration approach, which is observable in the lower ARD and higher percentage of the sensor readings in clinically acceptable Clarke EGA zones (zone A+B) for the one-point calibration algorithm. A higher accuracy observed by the one-point calibration compared to the two-point calibration approach is also reported by Choleau et al.[119] The real-time and retrospectively estimated sensor background current are zero suggesting that the background current can be considered zero for the SCGM1 sensor.

In paper 3[152], the calibration algorithm in study 1 was particularly evaluated in hypoglycemia by applying the algorithm to the data of the Guardian RT CGM in 10 patients with type 1 diabetes. The data contain insulin-induced hypoglycemic episodes, which maked it possible to perform a hypoglycemia-focused evaluation. The algorithm was compared with the routine calibration algorithm implemented in the Medtronic Guardian RT CGM on the same data, by using several numerical evaluation metrics.

The results of paper 3 indicate that the new calibration algorithm has significantly higher hypoglycemia accuracy than the Guardian RT algorithm, which is manifested in the 29% lower mean ARD, 256% higher sample-based hypoglycemia sensitivity, 46% higher event-based hypoglycemia sensitivity, and 34% lower overestimation of the hypoglycemic plasma glucose levels of the new algorithm. However, the new calibration algorithm slightly but not significantly reduces the hypoglycemia specificity and has one false positive event in the data, while the Guardian RT does not have any false positive. The new calibration algorithm (presented in paper 1) appears to outperform not only the Guardian RT calibration algorithm, but also the new calibration algorithm used in the Paradigm Veo CGM system, because to the contrary of the Veo calibration algorithm, the new calibration algorithm (which was first presented in paper 1) increases hypoglycemia sensitivity without reducing the accuracy of the higher glucose range.[154,163]

In paper 4, the impact of the improved CGM accuracy on the precision of clinical decisions for diabetes treatment adjustments was evaluated. Precision was defined in terms of the inter-clinician agreement and intra-clinician reproducibility of the clinicians' recommendations for modifications of the basal and prandial insulin dosage. The SCGM1 data from 12 patients with type 1 diabetes were processed by two CGM algorithms: the original manufacturer algorithm (Roche Diagnostics, Mannheim, Germany) and the new CGM algorithm in study 1, with the new algorithm having higher numerical accuracy (lower mean ARD) for each patient. Three clinicians reviewed the

processed data by the two algorithms, and advised the necessary modifications of the insulin dosage in order to avoid glycemic excursion.

The results of paper 4 indicate that a higher inter-clinician agreement and a higher intra-clinician reproducibility can be achieved, by processing the CGM data with the higher accuracy algorithm (the new algorithm). However, due to the limited number of clinicians and patients, the results cannot be generalizable.

Relation between the findings

The algorithmical steps used in the calibration algorithm in study 1, including modification of the calibration set (BG-CGM signal pairs) for low SD of the BG values, and for low correlation between BG values and their paired CGM signal measurement, and also inclusion of a corrective intercept in the calibration to mitigate the effect of time lag in hypoglycemia, resulted in the reduced deviation of calibrated CGM values from concurrent reference glucose levels. This manifested itself in study 3, where the new algorithm showed a significantly lower ARD and lower hypoglycemia overestimation compared to the Guardian RT algorithm. The particularly higher hypoglycemia accuracy of the new algorithm leaded to the significantly larger hypoglycemia sensitivity compared to the Guardian RT algorithm. The lower noise and smaller irregularities in the CGM data processed by the new CGM algorithm in the current thesis, compared to the CGM data processed by the manufacturer's algorithm, improved the precision of the data, which eased the interpretation of CGM profiles, and may have consequently contributed to making more reproducible treatment adjustments by clinicians.

3.2 Limitations

One limitation of the present thesis is using data from microdialysis-based CGM for development of the CGM algorithm in study 1 and study 2, while almost all CGM systems in the market are subcutaneous sensor-based, and the only microdialys-based CGM which is commercially available, is GlucoDay. Although in paper 3, the algorithm was tested on data from a subcutaneous sensor-based CGM (Guardian RT), the evaluation of the algorithm remained incomplete, because of the two reasons. First, in paper 3 the number of subjects (10 subjects) included in the study were too small to conclude the performance of the new algorithm on the subcutaneous sensor-based CGM data. Second, manufacturers usually do not give access to the very raw and unfiltered sensor

data; therefore, we could not test the denoising part of the algorithm on the subcutaneous sensor-based CGM data, and only the calibration part was tested on this type of CGM systems. Therefore, the numerical evaluation of the whole algorithm was not possible using the existing data from Guardian RT.

In addition, an incomplete clinical evaluation of the algorithm is also observed in paper 4, where only three clinicians and 12 type 1 diabetes patients were included in the study. Therefore, although the results of paper 4 can be an indicative of higher clinical reliability of the new CGM algorithm, due to the small number of clinicians and patients in paper 4, the algorithm still lacks a more complete clinical evaluation.

3.3 Future Directions

Although the CGM algorithm presented in paper 1 can be used for prospective applications, in all studies of the thesis the algorithm was applied retrospectively. A more complete evaluation of the algorithm- both numerically and clinically-can be achieved by implementing the algorithm in real-time CGM systems and testing the algorithm prospectively and on larger datasets.

Because the patterns of glycemic variations and excursions may be different in type 2 diabetes patients from that of type 1 diabetes patients, evaluation of the algorithm on patients with type 2 diabetes could give a broader view to the algorithm performance. This may be a perspective of the algorithm evaluation in future.

It is of interest also to broaden the clinical evaluation of the algorithm by categorizing the clinicians into 'nurse' and 'doctors', and in each category evaluating the algorithm in subgroups of 'less experienced', 'experienced', and 'well experienced' clinicians. In addition, in order to more precisely investigate the effect of CGM accuracy per se on the precision of the CGM-based clinical decision making, it seems necessary to perform the study in paper 4 on CGM profiles which are divided into 'profiles with only CGM', 'profiles with CGM and SMBG', and 'profiles with CGM, SMBG, and HbA1c'. In this case, the effect of CGM accuracy can be studied alone and also in relation to SMBG, and HbA1c.

Finally, it is of interest to compare the CGM algorithm, which is developed and evaluated numerically and clinically in this thesis, with other commercial CGM algorithms rather than only with Guardian RT. This can be achieved by applying the new algorithm in parallel with commercial algorithms to the same datasets, collected under the same experimental set up, and comparing the performance of the algorithms.

3.4 Conclusion

This PhD thesis describes two main areas concerning the accuracy of CGM data: 1) improving the CGM accuracy, and 2) evaluating the improved accuracy. The first two studies of the thesis contribute to the first area. In study 1, a new CGM algorithm with a reduced filtering delay and improved calibration accuracy is presented. In study 2 an enhanced calibration approach is introduced, and compared with the algorithm in study 1. The enhanced calibration has higher accuracy than the calibration algorithm in study 1.

Study 3 and study 4 deal with the second area of the thesis, and they describe two different methodologies of evaluating the improved accuracy achieved in the first area of the thesis. In study 3, the numerical accuracy of the CGM algorithm in study 1 was evaluated by comparing the performance of the new algorithm with the routine CGM algorithm in the Medtronic Guardian RT CGM system. The results indicate a higher numerical accuracy for the new algorithm compared to the Guardian RT algorithm. In study 4, the accuracy of the algorithm in study 1 was clinically evaluated. For this purpose, the precision of the clinical decision making in diabetes was assessed in two scenarios: decision making using CGM data which was processed with the lower accuracy algorithm (the SCGM1 manufacturer algorithm), and decision making using CGM data which was processed with the higher accuracy algorithm (the algorithm in study 1). The results can be indicative of the precision improvement made by the new algorithm.

Bibliography

[1] American Diabetes Association. Standards of medical care in Diabetes—2013. Diabetes Care. 2013;36(1):S11–S66.

[2] Alberti KGMM, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications Part 1: Diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabetes Medicine. 1998;15:539–553.

[3] Bos M, Agyemang C. Prevalence and complications of diabetes mellitus in northern africa, a systematic review. BMC Public Health. 2013;13:387–2458–13–387.

[4] Guariguata L, Whiting D, Weil C, Unwin N. The international diabetes federation diabetes atlas methodology for estimating global and national prevalence of diabetes in adults. Diabetes Res Clin Pract. 2011;94(3):322–332.

[5] Kent D, D'Eramo Melkus G, Stuart PM, et al. Reducing the risks of diabetes complications through diabetes self-management education and support. Popul Health Manag. 2013;16(2):74–81.

[6] LeCaire TJ, Palta M, Klein R, Klein BE, Cruickshanks KJ. Assessing progress in retinopathy outcomes in type 1 diabetes: Comparing findings from the wisconsin diabetes registry study and the wisconsin epidemiologic study of diabetic retinopathy. Diabetes Care. 2013;36(3):631–637.

[7] Shaw K, Cummings M, eds. Diabetes chronic complications. 3rd ed. Hoboken, NJ, USA: Wiley-Blackwell; 2012.

[8] Wang PH, Lau J, Chalmers TC. Meta-analysis of effects of intensive blood-glucose control on late complications of type I diabetes. The Lancet. 2009;341(8856):1306–1309.

[9] Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): Prospective observational study. BMJ. 2000;321(7258):405–412.

[10] Liu Y, Zhu X, Zhang L, et al. Up-regulation of glyoxalase 1 by mangiferin prevents diabetic nephropathy progression in streptozotocin-induced diabetic rats. Eur J Pharmacol. 2013;721 (1–3):355–364.

[11] National Kidney Foundation. Diabetes and kidney disease. http:// www.kidney.org/atoz/content/diabetes.cfm. Updated 2014.

[12] Tesfaye S, Boulton AJM. Diabetic neuropathy/edited by Solomon Tesfaye, Andrew Boulton. Elektronisk udgave ed. Oxford : Oxford University Press; 2009.

[13] Caprio S, Wong S, Alberti K, King G. Cardiovascular complications of diabetes. Diabetologia. 1997;40(3):B78–B82.

[14] Kim RP. The musculoskeletal complications of diabetes. Current diabetes reports. 2002;2(1):49.

[15] Kildegaard J, Christensen T, Dencker Johansen M, Randlov J, Hejlesen K. Modelling the effect of blood glucose and physical exercise on plasma adrenaline in people with type 1 diabetes. Diabetes Technol Ther. 2007;9(6):501–507.

[16] Vander A, Sherman J, Luciano D, eds. Human physiology. Eighth ed. New York: McGraw-Hill; 2001.

[17] Brunton SA. Nocturnal hypoglycemia: Answering the challenge with long-acting insulin analogs. MedGenMed. 2007; 9(2):38.

[18] Cryer PE. Glucose counterregulation: Prevention and correction of hypoglycemia in humans. Am J Physiol. 1993; 264(2 Pt 1):E149–55.

[19] Cryer P. Hypoglycemia, pathophysiology, diagnosis and treatment. New York: Oxford Univ Press; 1997.

[20] Workgroup on Hypoglycemia, American Diabetes Association. Defining and reporting hypoglycemia in diabetes: A report from the american diabetes association workgroup on hypoglycemia. Diabetes Care. 2005;28(5):1245–1249.

[21] Cryer PE. Preventing hypoglycaemia: What is the appropriate glucose alert value? Diabetologia. 2009;52(1):35–37.

[22] Amiel SA, Sherwin RS, Simonson DC, Tamborlane WV. Effect of intensive insulin therapy on glycemic thresholds for counterregulatory hormone release. Diabetes. 1988;37(7):901–907.

[23] Borghouts L, Keizer H. Exercise and insulin sensitivity: A review. . Int J Sports Med. 2000; 21(1):1–12.

[24] Schultes B, Jauch-Chara K, Gais S, et al. Defective awakening response to nocturnal hypoglycemia in patients with type 1 diabetes mellitus. PLoS Med. 2007;4(2):e69.

[25] Cryer PE. Mechanisms of hypoglycemia- associated autonomic failure and its component syndromes in diabetes. Diabetes. 2005;54(12):3592–3601.

[26] Hoeldtke RD, Boden G. Epinephrine secretion, hypoglycemia unawareness, and diabetic autonomic neuropathy. Ann Intern Med. 1994; 120(6):512–517.

[27] Hepburn DA, Patrick AW, Eadington DW, Ewing DJ, Frier BM. Unawareness of hypoglycaemia in insulin-treated diabetic patients: Prevalence and relationship to autonomic neuropathy. Diabet Med. 1990;7(8):711–717.

[28] Barnard K, Parkin C, Young A, Ashraf M. Use of an automated bolus calculator reduces fear of hypoglycemia and improves confidence in dosage accuracy in patients with type 1 Diabetes mellitus treated with multiple daily insulin injections. J Diabetes Sci Technol. 2012;6(1):144–149.

[29] Cryer PE. The barrier of hypoglycemia in diabetes. Diabetes. 2008;57(12):3169–3176.

[30] The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993;329(14):977–86.

[31] Turner RC. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. Lancet. 1998; 352: 837–853.

[32] Rodbard D. Interpretation of continuous glucose monitoring data: Glycemic variability and quality of glycemic control. Diabetes Technol Ther. 2009;11 Suppl 1:S55–67.

[33] Kaufman FR, Gibson LC, Halvorson M, Carpenter S, Fisher LK, Pitukcheewanont P. A pilot study of the continuous glucose monitoring system. Diabetes Care. 2001;24:2030–2034.

[34] Hirsch IB, Armstrong D, Bergenstal RM, et al. Clinical application of emerging sensor technologies in diabetes management: Consensus guidelines for continuous glucose monitoring (CGM). Diabetes Technol Ther. 2008;10(4):232–44; quiz 245–6.

[35] Yogev Y, Haroush AB, Chen R, Kaplan B, Phillip.M., Hod M. Continuous glucose monitoring for treatment adjustment in diabetic pregnancies- a pilot study. Diabet. Med. 2003;20:558–562.

[36] Jensen M, Christensen T, Tarnow L, Mahmoudi Z, Johansen MD, Hejlesen OK. Professional continuous glucose monitoring in subjects with type 1 diabetes: Retrospective hypoglycemia detection. J Diabetes Sci Technol. 2013;7(1):135–143.

[37] Leahy JL, William TC, LeRoith D, eds. Insulin therapy, an issue of endocrinology and metabolism clinics of north america. USA: W B Saunders; 2012; No. 41.

[38] Barnard K, Parkin C, Young A, Ashraf M. Use of an automated bolus calculator reduces fear of hypoglycemia and improves confidence in dosage accuracy in patients with type 1 diabetes mellitus treated with multiple daily insulin injections. J Diabetes Sci Technol. 2012;6(1):144–149.

[39] Schwartz FL, Guo A, Marling CR, Shubrook JH. Analysis of use of an automated bolus calculator reduces fear of hypoglycemia and improves confidence in dosage accuracy in type 1 diabetes mellitus patients treated with multiple daily insulin injections. J Diabetes Sci Technol. 2012;6(1):150–152.

[40] Pieber TR, Brunner GA, Schnedl WJ, Schattenberg S, Kaufmann P, Krejs GJ. Evaluation of a structured outpatient group education program for intensive insulin therapy. Diabetes Care. 1995;18: 625–630.

[41] Lowe J, Linjawi S, Mensch M, James K, Attia J. Flexible eating and flexible insulin dosing in patients with diabetes: Results of an intensive self-management course. Diabetes Res Clin Pract. 2008;80(3): 439–443.

[42] DAFNE Study Group. Training in flexible, intensive insulin management to enable dietary freedom in people with type 1 diabetes: Dose adjustment for normal eating (DAFNE) randomized controlled trial. Diabet Med. 2003;20 Suppl 3:4–5.

[43] Danne T, Datz N, Endahl L, et al. Insulin detemir is characterized by a more reproducible pharmacokinetic profile than insulin glargine in children and adolescents with type 1 diabetes: Results from a randomized, double-blind, controlled trial. Pediatr Diabetes. 2008;9(6):554–560.

[44] Ridderstråle M, Jensen MM, Gjesing RP, Niskanen L. Cost-effectiveness of insulin detemir compared with NPH insulin in people with type 2 diabetes in denmark, finland, norway, and sweden. Lancet. 2013;16(4):468–478.

[45] Monnier L, Colette C, Lapinski H, Boniface H. Self-monitoring of blood glucose in diabetic patients: From the least common

denominator to the greatest common multiple. Diabetes metabolism. 2004;30(2):113–119.

[46] Danne T. Self-monitoring of blood glucose (SMBG): From theory to clinical practice. http://www.medscape.org/viewarticle/709187, updated 2009.

[47] Hirsch IB, Bode BW, Childs BP, et al. Self-monitoring of blood glucose (SMBG) in insulin- and non-insulin-using adults with diabetes: Consensus recommendations for improving SMBG accuracy, utilization, and research. Diabetes Technol Ther. 2008;10(6):419–439.

[48] Kempe K, Price D, Ellison J, Marhoul J, Morrow L, Win K, Kuschma K, Hompesch M.et al. Capillary and venous blood glucose concentrations measured during intravenous insulin and glucose infusion: A comparison of steady and dynamic states. Diabetes Technol Ther. 2009; 11(10):669–674.

[49] Mitka M. Monitoring glycemic control in diabetes. The journal of American Medical Association. 2007;298(19):2252.

[50] Jensen MH, Christensen TF, Tarnow L, Seto E, Dencker Johansen M, Hejlesen OK. Real-time hypoglycemia detection from continuous glucose monitoring data of subjects with type 1 diabetes. Diabetes Technol Ther. 2013; 15(7): 538–543.

[51] Vaddiraju S, Burgess DJ, Tomazos I, Jain FC, Papadimitrakopoulos F. Technologies for continuous glucose monitoring: Current problems and future promises. J Diabetes Sci Technol. 2010;4(6):1540–1562.

[52] Ramchandani N, Heptulla RA. New technologies for diabetes: A review of the present and the future. International Journal of Pediatric Endocrinology. 2012; 28:1–10.

[53] Breton M, Kovatchev B. Analysis, modeling, and simulation of the accuracy of continuous glucose sensors. Journal of Diabetes Science and Technology. 2008;2(5):853–862.

[54] Koschinsky T, Heinemann L. Sensors for glucose monitoring: Technical and clinical aspects. Diabetes Metab Res Rev. 2001;17(2): 113–123.

[55] Yoo EH, Lee SY. Glucose biosensors: An overview of use in clinical practice. Sensors (Basel). 2010;10(5):4558–4576.

[56] Rossetti P, Bondia J, Vehi J, Fanelli CG. Estimating plasma glucose from interstitial glucose: The issue of calibration algorithms in commercial continuous glucose monitoring devices. Sensors (Basel). 2010;10(12):10936–10952.

[57] Gough DA, Armour.J.C. Development of the implantable glucose sensor, what are the prospects and why is it taking so long. Diabetes. 1995; 44:1005–1009.

[58] Cengiz E, Tamborlane WV. A tale of two compartments: Interstitial versus blood glucose monitoring. Diabetes Technol Ther. 2009; 11: s-11–s-15.

[59] Heinemann L, Glucose Monitoring Study Group. Continuous glucose monitoring by means of the microdialysis technique: Underlying fundamental aspects. Diabetes Technol Ther. 2003;5(4): 545–561.

[60] Ricci F, Moscone D, Palleschi G. Ex vivo continuous glucose monitoring with microdialysis technique: The example of GlucoDay. IEEE sensors journal. 2008;8(1):63–69.

[61] McGarraugh G. The chemistry of commercial continuous glucose monitors. Diabetes Technol Ther. 2009; 11 Suppl 1:S17–24.

[62] Wang J. Electrochemical glucose biosensors. Chem. Rev. 2008; 108:814–825.

[63] Collier BB, McShane M. Enzymatic glucose sensor compensation for variations in ambient oxygen concentration. 2013. Proc. SPIE 8591, Optical Diagnostics and Sensing XIII: Toward Point-of-Care Diagnostics; doi:10.1117/12.2001840

[64] Barry Keenan D. Interstitial fluid glucose time-lag correction for real-time continuous glucose monitoring. Biomedical signal processing and control. 2013;8(1):81–89.

[65] Facchinetti A, Sparacino G, Cobelli C. Enhanced accuracy of continuous glucose monitoring by online extended kalman filtering. Diabetes Technol Ther. 2010;12(5):353–363.

[66] Rebrin K, Sheppard NF, Steil GM. Use of subcutaneous interstitial fluid glucose to estimate blood glucose: Revisiting delay and sensor offset. J Diabetes Sci Technol. 2010;4(5):1087–1098.

[67] Keenan DB, Mastrototaro JJ, Weinzimer SA, Steil GM. Interstitial fluid glucose time-lag correction for real-time continuous glucose monitoring. Biomedical signal processing and control. 2013;8(1): 81–89.

[68] Voskanyan G, Barry Keenan D, Mastrototaro JJ, Steil GM. Putative delays in interstitial fluid (ISF) glucose kinetics can be attributed to the glucose sensing systems used to measure them rather than the delay in ISF glucose itself. J Diabetes Sci Technol. 2007;1(5): 639–644.

[69] Keenan DB, Mastrototaro JJ, Voskanyan G, Steil GM. Delays in minimally invasive continuous glucose monitoring devices: A review of current technology. J Diabetes Sci Technol. 2009;3(5): 1207–1214.

[70] Davey RJ, Stevens K, Jones TW, Fournier PA. The effect of short-term use of the guardian RT continuous glucose monitoring system on fear of hypoglycaemia in patients with type 1 diabetes mellitus. Prim Care Diabetes. 2012;6(1):35–39.

[71] Harvey RA, Dassau E, Zisser HC, Dassau E, Zisser HC, Bevier W, Seborg DE, Jovanovič L, Francis J. Doyle III. Clinically relevant hypoglycemia prediction metrics for event mitigation. Diabetes Technol Ther. 2012; 14(8): 719–727.

[72] Iscoe KE, Davey RJ, Fournier PA. Increasing the low-glucose alarm of a continuous glucose monitoring system prevents exercise-induced hypoglycemia without triggering any false alarms. Diabetes Care. 2011;34(6):e109.

[73] Buckingham B. Continuous glucose monitoring in children with type 1 diabetes. J Pediatr. 2007; 151(4): 388–393.e2.

[74] McLachlan K, Jenkins A, O'Neal D. The role of continuous glucose monitoring in clinical decision-making in diabetes in pregnancy. Aust N Z J Obstet Gynaecol. 2007;47(3):186–190.

[75] Kaufman FR, Gibson LC, Halvorson M, Carpenter S, Fisher LK, Pitukcheewanont P. A pilot study of the continuous glucose monitoring system: Clinical decisions and glycemic control after its use in pediatric type 1 diabetic subjects. Diabetes Care. 2001;24(12): 2030–2034.

[76] Hammond P. Continuous glucose monitoring : The clinical picture. how to interpret and use the data. Practical Diabetes. 2012;29(9): 364–368.

[77] Bode BW, Gross TM, Thornton KR, Mastrototaro JJ. Continuous glucose monitoring used to adjust diabetes therapy improves glycosylated hemoglobin: A pilot study. Diabetes Res Clin Pract. 1999;46(3):183–190.

[78] Klonoff DC. Buckingham B, Christiansen JS, Montori VM, Tamborlane WV, Vigersky RA, Wolpert H. Continuous glucose monitoring: An endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2011;96(10):2968–2979.

[79] Schaepelynck-Belicar P, Vague P, Simonin G, Lassmann-Vague V. Improved metabolic control in diabetic adolescents using the

continuous glucose monitoring system (CGMS). Diabetes Metab. 2003;29(6):608–612.

[80] Tamborlane WV, Beck RW, Bode BW. Continuous glucose monitoring and intensive treatment of type 1 diabetes. N Engl J Med. 2008;359:1464–1476.

[81] Deiss D, Bolinder J, Riveline J, et al. Improved glycemic control in poorly controlled patients with type 1 diabetes using real-time continuous glucose monitoring. Diabetes Care. 2006;29(12): 2730–2732.

[82] Hirsch IB, Abelseth J, Bode BW, et al. Sensor-augmented insulin pump therapy: Results of the first randomized treat-to-target study. Diabetes Technol Ther. 2008;10(5):377–383.

[83] Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group, Beck RW, Hirsch IB, et al. The effect of continuous glucose monitoring in well-controlled type 1 diabetes. Diabetes Care. 2009;32(8):1378–1383.

[84] Wolpert HA. Use of continuous glucose monitoring in the detection and prevention of hypoglycemia. J Diabetes Sci Technol. 2007;1(1): 146–150.

[85] Jungheim K, Wientjes KJ, Heinemann L, Lodwig V, Koschinsky T, Schoonen AJ. Subcutaneous continuous glucose monitoring: Feasibility of a new microdialysis-based glucose sensor system. Diabetes Care. 2001;24(9):1696–1697.

[86] Chico A, Vidal-Rios P, Subira M, Novials A. The continuous glucose monitoring system is useful for detecting unrecognized hypoglycemias in patients with type 1 and type 2 diabetes but is not better than frequent capillary glucose measurements for improving metabolic control. Diabetes Care. 2003;26(4):1153–1157.

[87] Weber KK, Lohmann T, Busch K, Donati-Hirsch I, Riel R. High frequency of unrecognized hypoglycaemias in patients with type 2 diabetes is discovered by continuous glucose monitoring. Exp Clin Endocrinol Diabetes. 2007; 115(8):491–494.

[88] Wojciechowski P, Rys P, Lipowska A, Gaweska M, Malecki MT. Efficacy and safety comparison of continuous glucose monitoring and self-monitoring of blood glucose in type 1 diabetes: Systematic review and meta-analysis. Pol Arch Med Wewn. 2011; 121(10):333–343.

[89] Bequette BW. Continuous glucose monitoring: Real-time algorithms for calibration, filtering, and alarms. J Diabetes Sci Technol. 2010; 4(2):404–418.

[90] Metzger M, Leibowitz G, Wainstein J, Glaser B, Raz I. Reproducibility of glucose measurements using the glucose sensor. Diabetes Care. 2002; 25(7):1185–1191.

[91] Magni L, Raimondo DM, Bossi L, Dalla Man C, De Nicolao G, Kovatchev B, Cobelli C. Model predictive control of type 1 diabetes: An in silico trial. Diabetes Sci Technol. 2007; 1:804–812.

[92] Kovatchev BP, Breton M, Dalla Man C, Cobelli C. In silico preclinical trials: A proof of concept in closed-loop control of type 1 diabetes. Diabetes Sci Technol. 2009; 3:44–55.

[93] Bode B, Gross K, Rikalo N, et al. Alarms based on real-time sensor glucose values alert patients to hypo- and hyperglycemia: The guardian continuous monitoring system. Diabetes Technol Ther. 2004; 6(2):105–113.

[94] Iscoe KE, Davey RJ, Fournier PA. Do different glucose levels at calibration influence accuracy of continuous glucose monitoring readings in vitro? J Diabetes Sci Technol. 2012; 6(2):477–478.

[95] Kovatchev B, Anderson S, Heinemann L, Clarke W. Comparison of the numerical and clinical accuracy of four continuous glucose monitors. Diabetes Care. 2008; 31(6):1160–1164.

[96] Kulcu E. Physiological differences between interstitial glucose and blood glucose measured in human subjects. Diabetes Care. 2003; 26(8):2405.

[97] Facchinetti A, Sparacino G, Cobelli C. Online denoising method to handle intraindividual variability of signal-to-noise ratio in continuous glucose monitoring. IEEE Trans Biomed Eng. 2011; 58(9): 2664–2671.

[98] Kovatchev BP, King C, Breton M, Anderson S, Clarke W. Clinical assessment and mathematical modeling of the accuracy of continuous glucose sensors (CGS). Conf Proc IEEE Eng Med Biol Soc. 2006; 1:71–74.

[99] Facchinetti A, Sparacino G, Cobelli C. Modeling the error of continuous glucose monitoring sensor data: Critical aspects discussed through simulation studies. J Diabetes Sci Technol. 2010; 4(1):4–14.

[100] Sparacino G, Facchinetti A, Cobelli C. "Smart" continuous glucose monitoring sensors: On-line signal processing issues. Sensors (Basel). 2010; 10(7):6751–6772.

[101] Roe JN, Smoller BR. Bloodless glucose measurements. Crit Rev Ther Drug Carrier Syst. 1998; 15(3):199–241.

[102] Penfornis A, Personeni E, Borot S. Evolution of devices in diabetes management. Diabetes Technol Ther. 2011; 13 Suppl 1:S93–102.

[103] Kovatchev BP. Graphical and numerical evaluation of continuous glucose sensing time lag. Diabetes technology therapeutics. 2009; 11(3):139.

[104] Summers L, Clark M, Humphreys S, Bugler J, Frayn K. The use of microdialysis to monitor rapid changes in glucose concentration. Horm Metab Res. 1999; 31:424–428.

[105] Mahmoudi Z, Johansen MD, Christiansen JS, Hejlesen OK. A multi-step algorithm for processing and calibration of micro-dialysis continuous glucose monitoring data. Diabetes Technol.Ther. 2013; 15(10):825–835.

[106] 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.

[107] Guerra S, Facchinetti A, Sparacino G, Nicolao GD, Cobelli C. Enhancing the accuracy of subcutaneous glucose sensors: A real-time deconvolution-based approach. IEEE Trans Biomed Eng. 2012; 59(6):1658–1569.

[108] Garg SK. Time lag characterization of two continuous glucose monitoring systems. Diabetes Res Clin Pract. 2010; 87(3):348.

[109] Goode J,P.V., Brauker JH, Kamath AU, Thrower JP, Carr-Brendel V, inventorsSystems and Methods for Replacing Signal Artifacts in a Glucose Sensor Data Stream. 2011.

[110] Facchinetti A, Sparacino G, Cobelli C. An online self-tunable method to denoise CGM sensor data. IEEE Trans Biomed Eng. 2010; 57(3):634–641.

[111] Chase JG, Hann CE, Jackson M, et al. Integral-based filtering of continuous glucose sensor measurements for glycaemic control in critical care. Comput Methods Programs Biomed. 2006; 82(3): 238–247.

[112] Vriesendorp TM, DeVries JH, Holleman F, Dzoljic M, Hoekstra JB. The use of two continuous glucose sensors during and after surgery. Diabetes Technol Ther. 2005; 7(2):315–322.

[113] Sparacino G, Facchinetti A, Maran A, Cobelli C. Continuous glucose monitoring time series and hypo/hyperglycemia prevention: Requirements, methods, open problems. Curr Diabetes Rev. 2008; 4(3):181–192.

[114] Facchinetti A, Sparacino G, Guerra S, et al. Real-time improvement of continuous glucose monitoring accuracy: The smart sensor concept. Diabetes Care. 2013; 36(4):793–800.

[115] Valgimigli F, Lucarelli F, Scuffi C, Morandi S, Sposato I. Evaluating the clinical accuracy of GlucoMen® Day: A novel microdialysis-based continuous glucose monitor. Diabetes Sci Technol. 2010; 4(5): 1182–1192.

[116] Schoonen A, Wientjes K. A model for transport of glucose in adipose tissue to a microdialysis probe. Diabetes Technol Ther. 2003; 5(4):589–597.

[117] Onuki Y, Bhardwaj U, Papadimitrakopoulos F, Burgess DJ. A review of the biocompatibility of implantable devices: Current challenges to overcome foreign body response. J Diabetes Sci Technol. 2008; 2(6):1003–1015.

[118] Gilligan BC, Shults M, Rhodes RK, et al. Feasibility of continuous long-term glucose monitoring from a subcutaneous glucose sensor in humans. Diabetes Technol Ther. 2004; 6(3):378–386.

[119] Choleau C, Klein J, Reach G, et al. Calibration of a subcutaneous amperometric glucose sensor implanted for 7 days in diabetic patients. part 2. superiority of the one-point calibration method. Biosensors & bioelectronics. 2002; 17:647–654.

[120] King C, Anderson SM, Breton M, Clarke WL, Kovatchev BP. Modeling of calibration effectiveness and blood-to-interstitial glucose dynamics as potential confounders of the accuracy of continuous glucose sensors during hyperinsulinemic clamp. J Diabetes Sci Technol. 2007;1(3):317–322.

[121] El Youssef J, Castle JR, Engle JM, Massoud RG, Ward WK. Continuous glucose monitoring in subjects with type 1 diabetes: Improvement in accuracy by correcting for background current. Diabetes Technol Ther. 2010;12(11):921–928.

[122] Rebrin K, Steil GM. Can interstitial glucose assessment replace blood glucose measurements? Diabetes Technol Ther. 2000;2(3):461–472.

[123] Signal M, Le Compte A, Harris DL, et al. Impact of retrospective calibration algorithms on hypoglycemia detection in newborn infants using continuous glucose monitoring. Diabetes Technol Ther. 2012; 14(10):883–890.

[124] Heller A. Implanted electrochemical glucose sensors. Annu Rev Biomed Eng. 1999; 1:153–75.

[125] Panteleon AE, Rebrin K, Steil GM. The role of the independent variable to glucose sensor calibration. Diabetes Technol Ther. 2003;5(3):401–410.

[126] Barceló Rico F. A multiple local models approach to accuracy improvement in continuous glucose monitoring. Diabetes Technol Ther. 2012; 14(1):74–82.

[127] Schoemaker M, Andreis E, Roper J, et al. The SCGM1 system: Subcutaneous continuous glucose monitoring based on microdialysis technique. Diabetes Technol Ther. 2003; 5(4):599–608.

[128] Girardin CM, Huot C, Gonthier M, Delvin E. Continuous glucose monitoring: A review of biochemical perspectives and clinical use in type 1 diabetes. Clin Biochem. 2009;42(3):136–142.

[129] Stout PJ, Racchini JR, Hilgers ME. A novel approach to mitigating the physiological lag between blood and interstitial fluid glucose measurements. Diabetes Technol Ther. 2004; 6(5):635–644.

[130] Knobbe EJ, Buckingham B. The extended kalman filter for continuous glucose monitoring. Diabetes Technol Ther. 2005; 7(1):15–27.

[131] Wayne Bequette B. Optimal estimation application to continuous glucose monitoring. 2004. 2004:958–962.

[132] Kanderian SS, Steil GM, inventors: Apparatus and method for controlling insulin infusion with state variable feedback. U.S. Patent 2010/0305545. Dec. 2, 2010

[133] Rebrin K, Steil GM, van Antwerp WP, Mastrototaro JJ. Subcutaneous glucose predicts plasma glucose independent of insulin: Implications for continuous monitoring. Am J Physiol. 1999;277(3 Pt 1): E561–71.

[134] Steil GM, Rebrin K, inventors: Closed loop system for controlling insulin infusion. U.S. Patent 7,354,420. April 8, 2008.

[135] Mueller JC, Keenan DB, Wang L, Mastrototaro JJ, inventors: Systems and methods for calibrating physiological characteristic sensors. U.S. Patent 7,783,442. August 24, 2010.

[136] Mastrototaro JJ, Gross TM, Shin JJ, inventors: Glucose monitor calibration methods. U.S. Patent 6,424,847. July 23, 2002.

[137] Shin J, Holtzclaw KR, Dangui ND, Kanderian S Jr, Mastrototaro JJ, Hong PI, inventors: Real time self-adjusting calibration algorithm. U.S. Patent 6,895,263. May 17, 2005.

[138] Goode PV, Brauker JH, Kamath AU, inventors: System and methods for processing analyte sensor data. U.S. Patent 8,560,037. October 15, 2013.

[139] Shanthi S, Kumar D. Neural network based filter for continuous glucose monitoring: Online tuning with extended kalman filter algorithm. WSEAS transaction on information science and applications. 2012;9(7):199–209.

[140] Pretty CG, Chase JG, Le Compte A, Shaw GM, Signal M. Hypoglycemia detection in critical care using continuous glucose monitors: An in silico proof of concept analysis. J Diabetes Sci Technol. 2010;4(1):15–24.

[141] Poitout V, Moatti Sirat D, Reach G, et al. A glucose monitoring system for online estimation in man of blood glucose concentration using a miniaturized glucose sensor implanted in the subcutaneous tissue and a wearable control unit. Diabetologia. 1993; 36(7):658–63.

[142] Garcia A, Rack-Gomer AL, Bhavaraju NC, et al. Dexcom G4AP: An advanced continuous glucose monitor for the artificial pancreas. J Diabetes Sci Technol. 2013; 7(6):1436–1445.

[143] Kuure-Kinsey M, Palerm CC, Bequette BW. A dual- rate kalman filter for continuous glucose monitoring. 2006 International Conference of the IEEE Engineering in Medicine and Biology Society. 2006:63–66.

[144] Facchinetti A, Favero SD, Sparacino G, Castle JR, Ward.W.K., Cobelli C. Modeling the glucose sensor error. IEEE Trans Biomed Eng. 2014;61(3):620–629.

[145] Youssef JE. Continuous glucose monitoring in subjects with type 1 diabetes: Improvement in accuracy by correcting for background current. Diabetes Technol Ther. 2010;12(11):921–928.

[146] Feldman B, McGarraugh G, inventors: Method of calibrating an analyte measurement device, and associated methods, devices and systems. U.S. Patent 8,219,174. July 10, 2012.

[147] Hayter G, Doniger K, Budiman E, Zhang S, Mazza J, inventors: Method and system for providing calibration of an analyte sensor in an analyte monitoring system. U.S. Patent Application 2014/0046155 A1. February 13, 2014.

[148] Leelarathna L, English SW, Thabit H, et al. Accuracy of subcutaneous continuous glucose monitoring in critically ill adults: Improved sensor performance with enhanced calibrations. Diabetes Technol Ther. 2014;16(2):97–101.

[149] Zueger T, Diem P, Mougiakakou S, Stettler C. Influence of time point of calibration on accuracy of continuous glucose monitoring in individuals with type 1 diabetes. Diabetes Technol Ther. 2012;14(7):583–588.

[150] Aussedat B, Thome-Duret V, Reach G, et al. A user-friendly method for calibrating a subcutaneous glucose sensor-based hypoglycemic alarm. Biosensors & bioelectronics. 1997;12(11):1061–71.

[151] Diabetes Research In Children Network (Direcnet) Study Group, Buckingham BA, Kollman C, et al. Evaluation of factors affecting CGMS calibration. Diabetes Technol Ther. 2006;8(3):318–325.

[152] Mahmoudi Z, Jensen M, Johansen MD, et al. Accuracy evaluation of a new real-time continuous glucose monitoring algorithm in hypoglycemia. Diabetes Technol Ther. 2014; 16(10):667–678.

[153] Chen ET, Nichols JH, Duh S, Hortin G. Performance evaluation of blood glucose monitoring devices. Diabetes Technol Ther. 2003;5(5):749–768.

[154] Keenan DB, Cartaya R, Mastrototaro JJ. Accuracy of a new real-time continuous glucose monitoring algorithm. J Diabetes Sci Technol. 2010;4(1):111–118.

[155] International organization for standarization: In vitro diagnostic test systems: Requirements for blood-glucose monitoring systems for self-testing in managing diabetes mellitus. ISO 15197:2013.

[156] Clarke WL. Cox D, Gonder-Frederick LA,Carter W, Pohl SL, Evaluating clinical accuracy of systems for self-monitoring of blood glucose. Diabetes Care. 1987; 10(5):622–628.

[157] Smith SW, Meyer RA, Connor PM, Smith SE, Hanley EN, Jr. Interobserver reliability and intraobserver reproducibility of the modified ficat classification system of osteonecrosis of the femoral head. J Bone Joint Surg Am. 1996;78(11):1702–1706.

[158] Tanna AP, Bandi JR, Budenz DL, et al. Interobserver agreement and intraobserver reproducibility of the subjective determination of glaucomatous visual field progression. Ophthalmology. 2011;118(1): 60–65.

[159] Martin JS, Marsh JL, Bonar SK, DeCoster TA, Found EM, Brandser EA. Assessment of the AO/ASIF fracture classification for the distal tibia. J Orthop Trauma. 1997;11(7):477–483.

[160] Mahmoudi Z, Dencker Johansen M, Christiansen JS, Hejlesen OK. Comparison between one-point calibration and two-point calibration approaches in a continuous glucose monitoring algorithm. J Diabetes Sci Technol. 2014; 8: 709–719.

[161] Mazze RS. Strock E, Borgman S, Wesley D, Stout P, Racchini J. Evaluating the accuracy, reliability, and clinical applicability of

continuous glucose monitoring (CGM): Is CGM ready for real time? Diabetes technology therapeutics. 2009;11(1):11–18.

[162] Weinstein RL, Schwartz SL, Brazg RL, Bugler JR, Peyser TA, McGarraugh GV. Accuracy of the 5–day FreeStyle navigator continuous glucose monitoring system comparison with frequent laboratory reference measurements. Diabetes Care. 2007; 30(5):1125–1130.

[163] Keenan DB, Mastrototaro JJ, Zisser H, et al. Accuracy of the enlite 6–day glucose sensor with guardian and veo calibration algorithms. Diabetes Technol Ther. 2012;14(3):225–231.