Impact of Continuous Glucose Monitoring System on Model Based Glucose Control

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Table of Contents

List of Figures

List of Tables

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Abstract

Critically ill patients are known to experience stress-induced hyperglycemia. Inhibiting the physiological response to increased glycaemic levels in these patients are factors such as increased insulin resistance, increased dextrose input, absolute or relative insulin deficiency, and drug therapy. Although hyperglycemia can be a marker for severity of illness, it can also worsen outcomes, leading to an increased risk of further complications.

Recent studies have shown that tight control can reduce mortality up to 43%. Metabolic modelling has been used to study physiological behaviour and/or to control glycaemia for a long time and many successful approximate system models have been developed. Due to the malfunction of medical equipments, clinical measurements obtained usually come with noise. In addition, the few such systems currently available can have errors in excess of 20-30%. Therefore, to fully simulate the clinical data, the system model also needs to couple with a successful noise model. This research has developed a new noise model that better fits the current available statistical description of the noise profile and therefore can be applied to achieve better simulation results. The research also designed a filter algorithm that is capable of reducing the sensor measurement error down to an acceptable value. Achieving such a goal is a significant step towards fully automated adaptive control of hyperglycaemia in critically ill patients and would therefore reduce mortality.

Introduction and Overview

1.1 Summary

This chapter provides a general background and overview of the world-challenging issue of diabetes. The causes of stress related hyperglycemia as often found in critical care and its current treatment are also described. A brief summary on the broad range of blood glucose monitoring and control technologies is included.

1.2 Overview of the Diabetes Problem

Diabetes has become one of the most challenging public health problems around the world. Research shows that there are up to 65% of adults in the US who are either overweight or obese, and perhaps another 16% of them may be similarly categorised [Hedley AA 1999 - 2000]. These conditions have stemmed from increasingly sedentary lifestyles and have led to growing rates of diabetes. Furthermore, the United States is not the only country facing this issue. Obesity, overweight and related metabolic dysfunction problems have been growing rapidly in both developed and developing economies all over the world [M Chopra 2002; Day 2006].

Despite public awareness of the problem and its consequences, traditional methods for diabetes control have been generally unsuccessful at reducing incidence or complications. Scientific research has been broadly undertaken around the world and has shown great promise of controlling this worrying situation.

However, to date none have had significant impact on patent outcomes. More specifically, currently at least seven types of continuous glucose sensors [Klonoff 2005], three types of insulin delivery systems [M. Shichiri 1998; B. Kalatz 1999; E. Renard 2004], four general types of control algorithms [R.S. Parker 1999; B. Gopakumaran 2005; G.M. Steil 2005; X.W. Wong and I. Singh-Levett a 2006] have been reported. All are under investigation for eventual use in an artificial pancreas system. The goal of an insulin infusing artificial pancreas is to automate glucose monitoring and insulin delivery mimicking normal human function control.

1.3 Introduction of Diabetes

Diabetes is defined as a disorder of metabolism, which is the way that human body utilizes digested food for growth and energy. Most of the food is carbohydrate that is broken down into glucose, which is then passed into the bloodstream to be used by cells for their energy and growth. For glucose to transport into cells, the right amount of insulin, which is a hormone produced by the pancreas, has to be present. If the delivered insulin is less than is required or no insulin is produced at all, glucose will accumulate in the blood and overflow into the urine. As a result, the human body loses

its main fuel source, in addition to which the excess blood glucose is toxic to several organ tissues. This concentration of insufficient or no insulin is known as diabetes. In normal individuals the pancreas provides the correct amount of insulin (virtually) in all normal situations [W. Gareth; P. John, (2004)].

There are two main types of clinically defined diabetes: Type 1 diabetes and Type 2 diabetes [W. Gareth; P. John, (2004)].

- **Type 1 diabetes** is caused by failure of the autoimmune system. With this type of diabetes, the immune system attacks and destroys the insulin-producing beta cells in the pancreas. Thus, for type 1 diabetes patients to maintain a normal life, they must take exogenous insulin injections or infusion daily.

- **Type 2 diabetes** is the far more common form of diabetes. However, this form of the disease is usually related to older age, obesity and/or a family history of diabetes. People who are diagnosed in this category produce insulin, but their bodies are resistant to absorb and use the insulin leading to and effective shortage of the hormone. In addition, they may not produce enough insulin on their own. The symptoms of Type 2 diabetes are usually developed gradually and it is much harder to diagnose early than the sudden more extreme onset of Type 1 diabetes.

Complications of Diabetes:

Lack of insulin results in high and dangerous blood glucose levels, which if untreated over time, would in turn lead to expensive complications. The risks of complications increase proportional to the duration of the disease and exposure to elevated blood glucose levels. Diabetic individuals are more likely to develop other severe complications than non-diabetic individuals, such as retinopathy, cataracts, ulcers, kidney failure, and skin infections. In addition, diabetic individuals also have an increasing risk of heart disease, peripheral vascular (out blood vessel) disease and stroke, as well as other nervous system or sensory loss or diseases.

Current Treatment of Diabetes:

Currently, treatment of Type 1 and severe (often) insulin-dependent Type 2 diabetes involves constant monitoring of the plasma glucose level and injecting insulin into the subcutaneous tissue as required. A measure of best practice was laid out by the Diabetes Control and Complications Trial (CDCCT) Research Group in 1993. Currently, control is done using a glucose monitoring system and an insulin pump or syringe injections. All current treatments are performed manually by the patients or, in a hospital setting, under professional care. Thus, diabetic individuals are usually required to monitor food intake and daily activity to maintain blood glucose levels at an acceptable level.

For ease of management, subjects are encouraged to stick to strict routines and diets to keep manual monitoring and injections to a minimum, reducing intervention and invasiveness. However, this regime can lead to severe limitation of the subjects' lifestyle and is prone to error. As a result, many diabetic individuals do not, or are not able to, maintain tight blood glucose control. The result of this loss of control is regular and continuous exposure to elevated blood glucose levels, which leads to increased complications. Therefore, one primary problem with current treatment is that there is no interface between the monitoring system and insulin pump to automate the treatment with stability and robustness.

1.4 Stress Induced Hyperglycemia

Severe medical illness and surgery can also cause a state of high level of mental stress, which accordingly results in increased insulin resistance and consequently decreased insulin sensitivity. It can occur regardless of history in both diabetic and non-diabetic patients [S. E. Capes 2000; S.E. Capes 2000; Christensen 2001; Bloomgarden 2003; Murray 2003].

This form of hyperglycaemia is typically encountered in critical care units in hospital. Given this stress-induced insulin resistance, hyperglycemia in critical care is exacerbated by the administration of intravenous fluids containing dextrose and in particular by high carbohydrate nutritional regimes [J. A. Krishnan 2003; Krinsley 2003].

Its primary treatment is typically the administration of intravenous insulin[Weissman 1999; K. C. McCowen 2001; Mizock 2001]. Physiologically, increased counter-regulatory hormone secretion stimulates endogenous glucose production and increases effective insulin resistance [KC McCowen 2001; Mizock 2001]. This dynamic elevates equilibrium glucose levels and decreases the amount of glucose that the body can use when a certain amount of insulin is produced. Nutritional regimes with high glucose content further exacerbate hyperglycemia and outcomes [JF Patino 1999; J. A. Krishnan 2003].

Hyperglycemia also has many other adverse effects. It increases the risk of further complications and other severe infections [Bistrian 2001], myocardial infarction [SE Capes 2000], critically illness polynerropathy. However, recent research shows that with tight control of glucose level, the mortality can be reduced 18% to 45% [Van den Berghe 2001; JS 2003; Krinsley 2003].

Current Treatment of Hyperglycemia in ICU

The most common management of blood glucose level in hospital is to use a 'sliding-scale' protocol to administer insulin [Albisser 1974; Woolfson 1980; F. Chee 2002]. An example of this method is shown in Table 1-1. However, this method is often modified by medical staff, or used only as a guide, with changes based on medical staff intuition and experience the art of medicine. There are also many problems with the

sliding scale approach. In particular, it is reactive only to blood glucose level, which can result in large swings between hypoglycaemia and hyperglycemia for some patients due to the lag in measurement response. It also has received a number of measurable amount of resistance by physicians and researchers that have considered the sliding scale and found the method to be unsatisfactory [Radack 1997; Sawin 1997; W. S. Queale 1997; Kletter 1998].

Blood Glucose (mmol/L)	Sliding Scale Insulin Infusion (U/hr)
< 8	0
8 – 10	1
10 – 12	2
12 – 14	3
>15	6

Table 1-1: Example of a Sliding Scale Insulin Protocol

In all cases, blood glucose is monitored leading to a control decision. This control decision results in a change in input insulin. All these steps are subject to measurement error, control algorithm error, input error and/or patient compliance.

1.5 Glucose Control Technologies

1.5.1 Glucose Monitoring Instruments

The fundamental aspect of ongoing treatment regimes for diabetes involves self-monitoring of blood glucose levels. The standard for obtaining a blood sample is the

finger prick method. The blood sample is applied manually to a test strip and, in conjunction with a portable meter; the blood glucose measurement is then produced. The subject must then use their prior knowledge and experience, along with a prediction of the exercise and glucose intake they expect to experience in the next few hours, to interpret the glucose measurement and provide the insulin necessary to control their Glycemic level.

Frequent monitoring of blood glucose concentration is highly important to avoid hypoglycemic and hyperglycemic incidents. However, due to the pain, inconvenience and expense of testing, a number of diabetic individuals do not monitor their glucose levels as often as would be preferred by health professionals [B. L. G. Nyomba 2003; L. Monnier 2004; Karter 2005]. In addition, this approach is subject to error due to poor device ergonomics resulting in misuse by the diabetic individual [W. Rogers 2001].

Alternative sites for blood glucose sampling have been proposed in less sensitive areas of the body and devices have been developed to take these measurements. Health and industrial workers are among the groups who have found the finger as a site for blood extraction less than desirable. The AtLast meter developed by Amira Medical in early 2000 can be used in alternative test sites in either the forearm or the thigh. In contrast, the Freestyle meter developed by TheraSense Inc in mid 2000 produces a “pin-head” size blood sample painlessly from forearm [L. R. Reynolds 2002]. Lifescan and Abott Laboratories have also introduced a number of options for alternative site testing [K.

Johnson 2001]. It should be noted that alternative site testing may result in bruising, and that the fingertip is preferable over the forearm or thigh for detecting rapid changes in glucose levels, and hence is suggested for confirmation if the subject is concerned [K. Johnson 2001].

Beyond these choices, technological advances have led to many options for sensing glucose levels with less invasiveness and inconvenience. The main options available on the market are the glucoseWatch Biographer from Cygnus and the Medtronic MiniMed Continuous Glucose Monitoring System (CGMS) [Muir 2003]. There are also emerging non-invasive technologies on the market, such as infra-red sensing [Anscombe 2003].

However, these Continuous Glucose Monitors (CGM) all have errors in the range of 20-30%. In contrast, typical bedside testing kits have errors of approximately 7-10% or less. Thus, despite the greater measurement frequency of CGM, there is a significant increase in the amount of noise, which if it is not successfully filtered, may severely limit the ability of the controller to consistently regulate blood glucose. Initial work has had some success in reducing the effect of noise in the CGM on glucose prediction using integral-based parameter identification [JG Chase 2004]. However further improvements to the filtering of the noise are required to more accurately extract the true signal in real-time and thus much better enable tight glucose control.

The GlucoWatch Biographer developed by Cygnus is one of the forerunners in the field of emerging semi-invasive glucose sensors, providing frequent, automatic and semi-invasive glucose measurements. It works by extracting glucose through the skin using a low level current passed between a cathode and an anode in a method known as reverse iontophoresis. Uncharged glucose molecules are carried in the stream of charged sodium ions heading for the cathode, and the amount of glucose extracted is correlated to the blood glucose levels. Glucose measurement is performed using an electrochemical biosensor which detects H_2O_2 produced in the glucose/glucose oxidise reaction.

The GlucoWatch has limitations, with data accuracy compromised in the presence of noise, open or short circuits, and excessive perspiration. More importantly, GlucoWatch applies high electrical currents at the electrodes, which would also increase the system's ability to pick up external interference. Incorporated in the GlucoWatch are skin temperature and conductance sensors to detect where perspiration may have affected the reading. The predetermined Criterion on the temperature and conductance sensors and the glucose measurement causes nonconforming readings to be skipped. A study of 13,573 biographer readings resulted in only 3.1% of skipped reading in semi-controlled use [K. R. Pitzer 2001].

The Medtronic Minimed CGMS is currently seen to be more useful as a diagnostic tool than a day-to-day monitoring device, but can fulfil either role. The key components are

an abdominal subcutaneous glucose sensor, and a small pager-type monitor, for diagnosis and analysis. The sensor can be worn for up to 72 hours, and the battery operated monitor averages the 10 second samples to display a glucose output every 5 minutes. The limitations found so far include premature sensor failure, a high level of noise produced by the system, some failures to accurately detect glucose changes, sensor calibration drift/bias and the risk of infections at the injection site.

1.5.2 Insulin Infusion Technology

Insulin pump therapy, also known as Continuous Subcutaneous Insulin Infusion (CSII), uses a portable electromechanical pump to help mimic non-diabetic insulin delivery. It acts by infusing short-acting insulin into the subcutaneous tissue at pre-selected rates, which is usually set by a clinician or nurse according to patient's historical glucose readings, knowledge of feed details, experience and intuition. The technology is now used by more than 200,000 people in the United States, and its use is growing world wide [Nadeau 2003] as it allows greater flexibility in delivery than infrequent Multiple Daily Injections (MDI).

Advantages of CSII

Most studies have shown that CSII provides as good and often better glycemic control than does intensive diabetes management with Multiple Daily Injection (MDI). However, most studies suggest that the improvement is modest. For example, one study

of 107 patients with type 1 diabetes treated with MDI that were switched to CSII had a decline in the mean HbA1c from 7.6 to 7.1% [J. W. Rudolph 2002].

The improvement in lifestyle may be the most important reason for the patient who chooses CSII. The ability to increase flexibility in moment-to-moment living is the reason most frequently cited by individuals who have chosen CSII. The increased flexibility in controlling insulin delivery and thus glucose control that CSII enables may be fuelling the upsurge in patient demand for CSII more than any other factor.

Disadvantages of CSII

There is no subcutaneous depot of long-acting insulin with CSII as there is with injection. If the flow of the regular, short-acting insulin is interrupted, ketonemia and diabetic ketoacidosis can develop more rapidly and more frequently with CSII. This interruption can occur to needle blockage or any other form of pump failure. In contrast, MDI patients have a more “sure” form of delivery.

Although hypoglycemia is generally less common with CSII than with MDI, proper use of the insulin pump requires the user to monitor glucose frequently and to work with the diabetes team to program the appropriate basal infusion rates. Without patient cooperation and active patient oversight, hypoglycemia may occur. In particular, if basal infusion rates are not set properly, hypoplycemica and weight-gain may occur. New technologies have been investigated and currently a sensor system with closed-loop function is considered to be one of the most viable technologies that are able to solve the described clinical hypoplycemica problem effectively [C. David 2007].

1.6 The Need for Model Based Analysis

Metabolic modelling has been used to study physiological behaviour and/or to control glycaemia for a long time and has been extensively published in the literature[R.N. Bergman 1985; K. Turnheim 1988; R. Hovorka 2003; JG Chase 2005]. The primary use of metabolic models has been the development of model-based measures to assess metabolic parameters, with particular focus on measuring insulin sensitivity.

The system model used in this research has evolved over the past three years from the original 3 compartment minimal model [R. N. Bergman 1985]. It now comprises two non-linear differential equations which can be decomposed into three more linear equations. Two different insulin kinetics models including Michaelis-Menten saturation are also added to these equations. The evolution of the model based analysis has been an iterative process, which aims to capture all essential dynamics while complexity is minimized. This means that the approach remains minimal in computational effort, which in turn offers the model more opportunity to be applied in real-time control systems, where patient condition and patient specific parameters are often highly variable and must be regularly re-identified [C.E. Hann 2005].

However, the above described system model ignores the noise profile that normally comes with the clinical measurements. There have been many studies conducted on the noise profile [WL Clarke 1998; P Goldberg 2004], but the actual noise profile presented has not been determined. To further analyse the noise profile, model-based

approach is also preferred as it offers the flexibility of using statistical results to fully investigate the nature of the noise profile. The ultimate successful determination of the noise profile will enable other technologies to be applied to the real clinical measurements. Thus less noisy glucose measurements are able to be obtained, which will provide clinical professionals more confidence to control glycaemia.

1.7 Research Objectives

The overall objective of this research is to investigate alternative signal processing techniques that can be used for continuous CGM sensor data filtering. The outcome of this research is to improve the accuracy of CGM so that automating insulin infusion technology can deliver better results in critically ill patients as well as (eventually) ambulatory type 1 diabetes. To reach this goal, a number of avenues are considered. The research presented focuses on:

1. Developing a standardized CGM noise model that can replicate clinical results
2. Research into and design of signal processing techniques for CGM noise
3. Investigate sensor calibration drift and account for it in filtering with a drift compensation algorithm
4. Design drift-compensating algorithm

These 3 goals can create a platform for improved sensor output from typical CGM systems of all types.

System and Noise Model

2.1 Summary

This chapter provides a review of model based analysis of the glucose-insulin system and outlines the key aspects of the integral-based parameter and identification approach. Two different noise models for CGM are introduced and verified. Their performances in terms of correlation coefficients matching those reported for similar systems in the literature are then used to determine the best noise model to use in this research.

2.2 Physiology and Metabolic System Model

The basis for the glucose-insulin system model presented is the minimal model by Bergnam at al [R.N. Bergman 1985]. An addition to this model is required that accounts for unutilised insulin in the plasma or insulin that had bound and then unbound to cell walls, tissues or insulin receptors. This addition has a similar effect to splitting the insulin compartment into a slow path and a fast path, which indicates the existence of fast and slow absorption channels and the presence of local insulin degradation [K. Turnheim 1988; C. Cobelli 1999; R. Hovorka 2003].

Turnheim and Waldhausl [K. Turnheim 1988] studied the pharmacokinetic modelling of intravenous insulin injection, and concluded that the concentration of plasma insulin following a bolus injection declines with at least two exponentials or two different rates. The first is a rapidly disappearing component of insulin representing elimination from the intravascular space, and the second is a more slowly disappearing component that reflects elimination from the interstitial fluid and the tissues that utilize insulin. These two components have half-lives of approximately 2.4 and 50 - 30 minutes, respectively.

Between the 1970s and 1980s, several papers were published regarding the plasma insulin disappearance kinetics in humans. Many found flaws in the first order assumptions of insulin disappearance that had been predominantly used in previous models (e.g.[C. Cobelli 1999]). These flaws were assumed and based on the narrow range of insulin levels studied, which shows non-proportionality between plasma concentration and plasma disappearance rate published by Sonksen et al. [P.H. Sonksen 1973]. More complete experimental studies were undertaken considering the concentrations resulting from a series of intravenous insulin infusions at different rates in both normal and diabetic subjects, as reviewed in [Thorsteinsson 1990]. These studies concluded that insulin disappearance is often governed by Michaelis-Menten saturation dynamics.

In addition, insulin mediated glucose clearance, once insulin has reached the interstitial space, is controlled primarily by insulin sensitivity, which links insulin concentration

and glucose levels. However, as the dose of exogenous insulin is increased in controlled hyperglycemic clamp studies, insulin sensitivity decreased [R.L. Prigeon 1996]. Therefore, there is a need to account for a saturable mechanism on insulin action. Natali et al.[R.L. Prigeon 1996] added Michaelis-Menten saturation of insulin action on fractional glucose extraction in a circulatory model, and obtained good fits to clinical data with limitations only occurring in the first 60 minutes, which were attributed to the irregular onset of insulin action during this initial phase of the clamp studies they used. Finally, to reduce model complexity and better match known physiological response, a term must be included to suppress endogenous insulin secretion during high exogenous insulin infusion periods [R.A. Defronzo 1979], which are similar to the high infusion rates that are often encountered in critical care (e.g.[C.V. Doran 2004]).

A recent modelling and control algorithm has been developed and clinically validated in several studies including Chase et al. [JG Chase 2005], and uses an integral based identification method developed in Hann et al. [CE Hann 2004]. The model is defined:

$$\dot{G}(t) = -p_G G(t) - S_I\left(G(t) + G_E\right)\frac{Q(t)}{1+\alpha_G Q(t)} + P(t) \tag{2-1}$$

$$Q(t) = k\int_0^t I(\tau)e^{-k(t-\tau)}d\tau \tag{2-2}$$

$$\dot{I}(t) = -\frac{nI(t)}{1+\alpha_I I(t)} + \frac{u(t)}{V_I} \tag{2-3}$$

where G(t) = Plasma Glucose Concentration above GE (mmol/L), GE = Glucose Equilibrium Concentration (mmol/L), I(t) = concentration of the plasma insulin

(mU/L), P(t) = Exogenous Glucose Infusion Rate (mmol/(L·min)), u(t) = Insulin Infusion Rate (mU/min), Q(t) = interstitial insulin concentration (mU/L), I(t) = plasma insulin concentration (mU/L), V_I = Assumed Insulin Distribution Volume (L), n = Insulin Interstitial Delay (min^{-1}), p_G = Clearance of Glucose at Basal Insulin (min^{-1}), S_I = time-varying insulin sensitivity (L/mU·min), k = Determines half-life (min^{-1}), α_I = Insulin Saturation Parameter, α_G = Glucose Saturation Clearance.

The model has been developed to account for non-linear saturation of exogenous insulin disappearance rate from plasma (in Equation (2-3)) and its saturable utilization to reduce blood glucose levels (in Equation (2-1)). The addition of transient insulin kinetics through interstitial boundaries via a convolution integral accounts for the dynamics seen in clinical trials [JG Chase 2005]. Overall, this approach and model matches physiological knowledge better. This model also effectively splits the glucose compartment into fast and slow compartments over a continuum rather than discrete states (e.g. [P Vicini 1997]). Finally, significant exogenous insulin infusions, as typically encountered in hyperglycaemic critical care patients, effectively suppress endogenous insulin production [RA DeFronzo 1979]. Any remaining endogenous insulin action is captured here in part by the term p_G for simplicity [JG Chase 2005; Doran 2004].

2.3 Parameter fitting and Identification

The parameters (V_I = 12L, n = 0.16 min^{-1}, k = 0.0099min^{-1}, α_G = 0.04L/mU, α_I = 0.0017L/mU) were found through an extensive literature search [Doran 2004], and

assumed to be constant and set to mean population values. The exogenous feed details, P(t), are known for each patient in this study. The equilibrium glucose level, G_E, can be estimated by averaging the glucose readings across the prior 8 to 12 hours. The reported parameter ranges are: $0.0005 \leq \alpha_I \leq 0.0043$, $0.0053 \leq k \leq 0.0139$, $0.02 \leq n \leq 0.3$ (the majority have $0.02 \leq n \leq 0.16$) and $0.001 \leq \alpha_G \leq 0.04$ [Doran 2004].

The overall approach is to fix k, n, α_G and α_I at average population values for all patients then identify the dominant variables S_I and p_G as time-varying values [CE Hann 2004]. This approach can be thought of as a minimal approach where the major dynamics are identified first, before secondary parameters are modified (as needed) to better fit the data if required. Therefore, it is important to ensure the fitting method for identifying time-varying, patient specific parameters is as low in computation as possible, as it allows other parameters to be varied without significantly affecting the overall computation time. Computational time is a significant factor to consider in real-time control. Fast parameter identification can also streamline the process of refining and testing the model on large numbers of patients.

Integrating both sides of Eq. (2-1) and defining $\overline{Q} = Q/(1+\alpha_G Q))$, the following expression holds for any segment of time from t_0 to t:

$$\int_{t0}^{t} \dot{G} dt = \int_{t0}^{t} (-p_G G - S_I (G + G_E)\overline{Q} + p) dt))$$

$$\Rightarrow G(t) - G(t_0) = -\int_{t0}^{t} p_G G dt - \int_{t0}^{t} S_I (G + G_E)\overline{Q} dt + \int_{t0}^{t} p dt \qquad (2\text{-}4)$$

Substituting the total glucose level $G_T = G + G_E$ into Eq. (2-4) results in an equivalent expression that is easy to compute given measured total glucose levels:

$$G(t) - G(\mathrm{t}_0) = -\int_{\mathrm{t}0}^{t} \mathrm{p}_\mathrm{G}(\mathrm{G}_\mathrm{T} - \mathrm{G}_\mathrm{E})\mathrm{dt} - \int_{\mathrm{t}0}^{\mathrm{t}} \mathrm{S}_\mathrm{I}\mathrm{G}_\mathrm{T}\overline{\mathrm{Q}}dt + \int_{t0}^{t} pdt \qquad (2\text{-}5)$$

To reduce computational complexity and account for a variation over time, the total time interval is divided into equal segments during which p_G and S_I are defined as piecewise constant:

$$p_G = \sum_{i=1}^{N} P_{Gi}(H(t - t_{i-1}) - H(t - t_i)) \qquad (2\text{-}6)$$

$$S_I = \sum_{i=1}^{N} S_{Ii}(H(t - t_{i-1}) - H(t - t_i)) \qquad (2\text{-}7)$$

where $H(t - t_0)$ is the Heaviside function, which defines that $H(t - t_0) = 0$ when t is less than t_0, and $H(t - t_0) = 1$ when t is equal t_0 or greater than t_0. Note that N in Eqs. (2-6) and (2-7) may be different depending on the number of hours used per segment. During this research, the glucose effectiveness – p_G is held constant over the period of two hours while the insulin sensitivity – S_I varies hourly.

The only unknown parameters in Eq. (2-5) are p_{Gi} and S_{Ii} when Eqs. (2-6) and (2-7) are used. However, these are constant parameters such that after numerically integrating the data, Eq. (2-5) can be written as a simple linear system in terms of these unknown values:

$$A\begin{Bmatrix} p_{Gi} \\ S_{Ii} \end{Bmatrix} = b \qquad (2\text{-}8)$$

where the number of equations for each time segment can be arbitrarily selected by integrating over different time segments. To ensure that the values obtained for and are within physiologically valid range, weighted constraints can be readily and easily placed on both parameters when solving Eq. (2-8).

The convex least squares solution of Equation (2-8) defines the time-varying profile of S_I for that time period by solving for the S_{Ii} values. Using integrals, instead of derivative based fitting methods, has the advantage of being robust to noise in the measured glucose data, effectively providing a low-pass filter in the summations involved in numerically integrating the data. A full error analysis is contained in Hann et al [C.E. Hann 2005] along with further details.

2.4 Monte-Carlo Analysis

Monte Carlo methods are one of the most widely used computational algorithms for simulating the behaviour of various physical and mathematical systems [Bernd 2004]. It is usually considered as a stochastic approach because the result of this simulation is a non-deterministic range of outcomes that can be quantified using statistical distribution and methods. The algorithm is also repetitive and usually involves a large number of calculations.

Monte Carlo simulation methods are especially useful in investigating systems with a large number of coupled degrees of freedom, such as liquids, disordered materials and

nano-structures. More broadly, Monte Carlo methods are useful for modelling phenomena with significant uncertainty in inputs. These features of the Monte Carlo method enable its use in evaluating the effectiveness of model-based simulations subject to sensor or other error.

2.5 CGMS Sensor Noise Modelling

2.5.1 Gaussian Noise Model

According to the literature, an implanted continuous sensor may malfunction due to calibration drift, a lag between concentrations of arterial blood glucose and interstitial fluid glucose during rapid fluctuation, sensor fouling, and local inflammatory complications [C. David 2007]. The malfunction from an implanted sensor has a direct impact on the accuracy of the measurements that the sensor delivers and therefore generates noise. However, the exact distribution of CGM noise profiles has not been reported in the literature to date. Specifically, no study has reported a histogram of CGM error or values versus gold standard measures. However, an approximate model can be created using the available literature and data. Presently, the accuracy and error of CGM measurements are referenced to laboratory standard measurements using a Clarke Error Grid.

The Minimed CGMS system is the most widely available and widely used system. Hence it is studied throughout the rest of this thesis. However, all methods of models are readily generalized to any CGM sensor. According to the literature, in critical care

condition, there are 78% of the CGMS measurements are within 20% of the actual value, which defines the A Range on the Clarke Error Grid [WL Clarke 1998]. The correlation between gold standard and CGMS approximated blood glucose values is r = 0.88 [P Goldberg 2004]. In addition, the maximum error is no greater than approximately 40% based on observation of the results presented. These reported noise values are reasonably consistent or slightly smaller throughout the literature on these sensors [F. Chee 2002; D.R. Tavris 2004; G.M. Steil 2005; Nicholls 2005; Raskin 2005; T.M. Vreisendorp 2005; Wolpert 2005]. Hence, there is enough data to create an overall picture suitable for a simple, approximate model of CGMS sensor noise.

The error profile can be simply and approximately modelled using a normal distribution with 17% (0.17) standard deviation. This standard deviation and distribution allows 78% of the measurements to be within 20%, matching the reported values of [P Goldberg 2004]. In addition, a limit of 40% (~2.5 standard deviations) was put in place to limit the peak error to match the reported data as observed in [F. Chee 2002; D.R. Tavris 2004; G.M. Steil 2005; Nicholls 2005; Raskin 2005; T.M. Vreisendorp 2005; Wolpert 2005]. Thus, this model is simply a normal distributed random noise added to a simulated glucose profile used as the “true” glucose value. Overall, it represents the possible initial model.

Note that none of the references [F. Chee 2002; D.R. Tavris 2004; G.M. Steil 2005; Nicholls 2005; Raskin 2005; T.M. Vreisendorp 2005; Wolpert 2005] provide a specific statistical distribution or histogram of the noise profile to provide further insight, as all

errors are primarily reported for this and similar sensors in terms of Clarke Error Grid performance. In addition, the Clarke Error Grid is the current gold standard for reporting such sensor performance. However it does not show the resulting error distribution, which is critical for effective filtering. Figure 2-1 shows a segment of a simulated patient glucose profile with "x" denoting the value with added CGMS error.

Bands are shown for 20% and 40% error to show the size of the error that can occur using the resulting model.

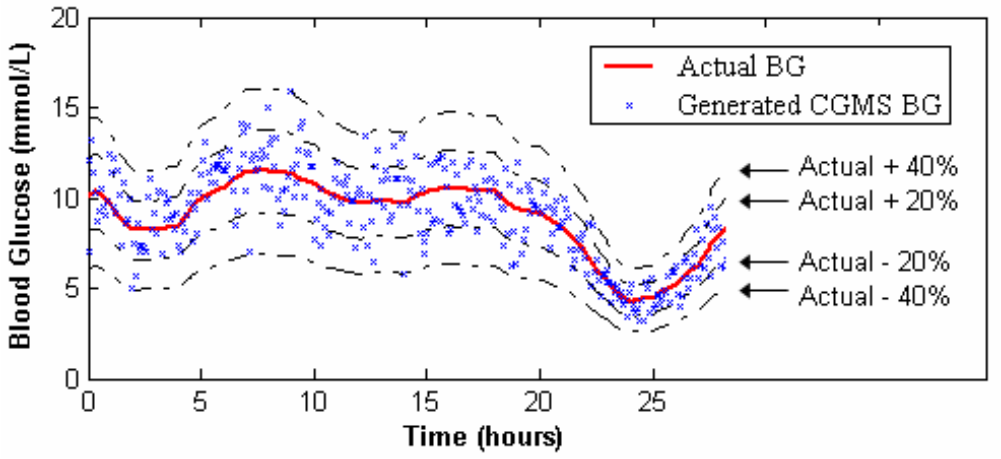

Figure 2-1: Example of approximated CGMS error to a simulated glucose profile. Dashed lines show 20% and 40% bounds to estimate the magnitude of any error [JG Chase 2005].

2.5.2 Patient Data Selection for Testing

To test this model, a random selection of 10 patients from a 201 patient data audit at Christchurch Hospital were used [Doran 2004]. Each patient record had a period of greater than one day with intervals between measured data points of about three hours. The data density of three hours was selected to ensure enough measurements to enable a good model evaluation. The entire length of stay was not always considered, as many

patients only had a shorter period of data that fitted these criteria. This subset broadly represents the cross-section of patients seen in the ICU, regarding medical condition, age, sex, APACHE II scores and mortality, which is summarized in Table 2-1. Type 1 and Type 2 diabetes are somewhat over-represented because these patients are often more frequently measured. Note that BMI is not typically recorded in most ICU's and was therefore not retrospectively available. Patients with serious head injury, morbid obesity, or who were moribund, were excluded [Doran 2004]. Ethical consent was obtained from the Canterbury Ethics Committee for this retrospective data analysis and research.

Patient Number	Medical Subgroup	APACHE II Score	Age	Sex	Mortality	Diabetes
24	Other Medical	25	47	M	Y	Type 1
87	Other Medical	26	62	F		
130	Trauma	11	21	M		Type 1
289	Cardiac	18	70	M		
484	Other Medical	34	30	F		
519	General Surgical	29	69	M		Type 2
554	Other Medical	26	20	F		Type 1
666	Cardiac	8	44	F		Type 2
1016	General Surgical	20	37	F		Type 2
1025	Pulmonary	36	48	M		Type 2

Table 2-1: Retrospective Patient Cohort and Data

2.5.3 Method Validation and Testing

Each patient data set was fitted using the method described in section 2.2.1. Therefore, a time varying $S_I(t)$ profile and approximated trajectory for G_E were obtained. This data creates a virtual patient from which a glucose profile can be obtained using the

retrospective feed and insulin infusion details, or other inputs as desired. Normally distributed CGMS sensor noise is added to the resulting glucose trajectory, *G(t)*, as depicted in Figure 2-1, to the resulting virtual patient glucose profiles to create noisy data.

Each patient profile was simulated n = 20 times to test the algorithm and generate statistics on performance. Such repeated Monte-Carlo style simulation allows appropriate performance statistics to be generated. Thus, there are 10 * 20=200 simulations in total where each is different due to the use of random added noise given to each simulated glucose measurement.

The outcome performance measurement is a comparison of the predicted blood glucose over the next hour and the simulated noise-free "true" value. Low mean absolute prediction error indicates successful filtering of the measurement error that will result in accurate identification of the model-based insulin sensitivity at that point in time from the noisy data [JG Chase 2005]. The overall goal of those simulated analysis was an analytical proof of concept test of the methods developed prior to clinical testing.

2.5.4 Model Validation and Results

The Clarke Error Grid for a simulation of one of the10 patients is shown in Figure 2-2 and the mean of the correlation coefficients over the 20 simulations is equal to 0.8684. The results are visually comparable to those found in the literature and the correlation

coefficient is only slightly lower than reported values for critical care evaluation of 0.88 [P. Goldberg 2004]. Finally, each individual patient simulation yielded 500 – 2000 simulated measurements. Thus, the error grids as shown in Figure 2-2 are primarily useful qualitatively due to the extreme large number of points compared to clinical studies.

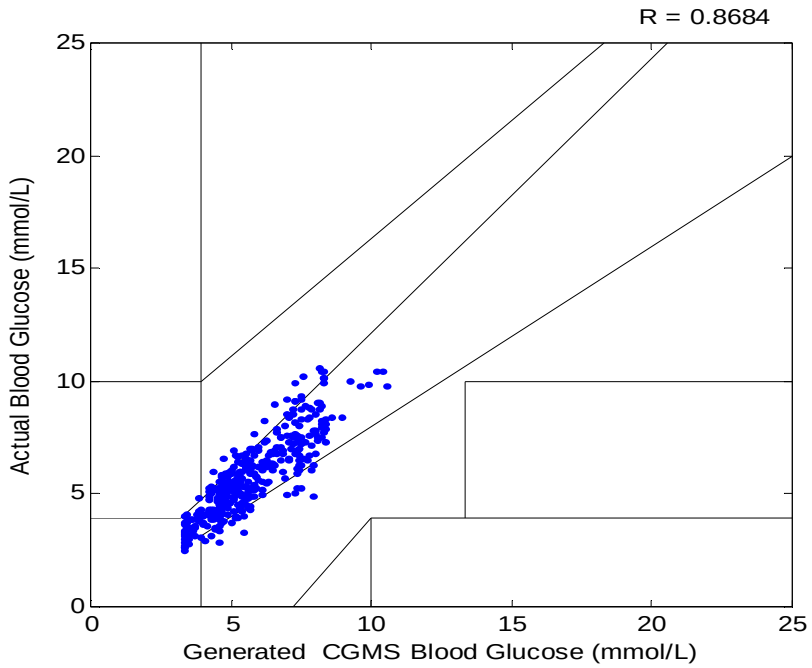

Figure 2-2: Clarke Error Grid for 1 of the 10 patient simulations with Gaussian Noise Model

Patient Number	Correlation Coefficients (MPRD)
24	0.8434
87	0.8567
130	0.8681
289	0.8966
484	0.8784
519	0.8552
554	0.8827
666	0.8385
1016	0.7697
1025	0.8526

Table 2-2: Mean Correlation Coefficients for Ten Patients – Noisy Glucose Data

All the ten patients were used to evaluate the noise model to validate the fundamental assumptions. Table 2-2 shows that the mean correlation coefficients obtained from ten patient profiles over n=20 simulations. The range of the mean correlation coefficients for these ten patients' simulations is 0.7697 to 0.8966, which brackets the result in the literature.

The results in Figure 2-2 and Table 2-2 show that the simple approximate Gaussian noise model is slightly conservative. More specifically, the correlation coefficients are about 8.6% lower than those reported in the literature. These differences are likely due to the actual CGMS error distribution possibly being slightly tighter than a true normal distribution, but the actual quantitative amount has not been determined due to the random distribution nature of the error profile. The assumed actual noise distribution model is shown in Figure 2-4. Thus, more of the errors in the ±20% A- band would be distributed closer to the mean value than the normal distribution allows. This result is further confirmed by the mean absolute relative difference (MARD) reported in CGMS trials of 13% [Buckingham 2005] being slightly lower than the 17% standard deviation value used in this initial model.

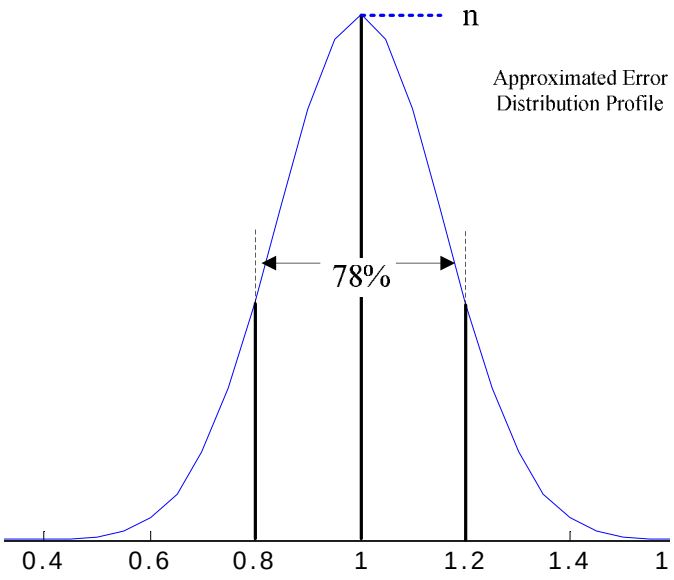

Figure 2-3: Approximated Normal Distributed Noise Model

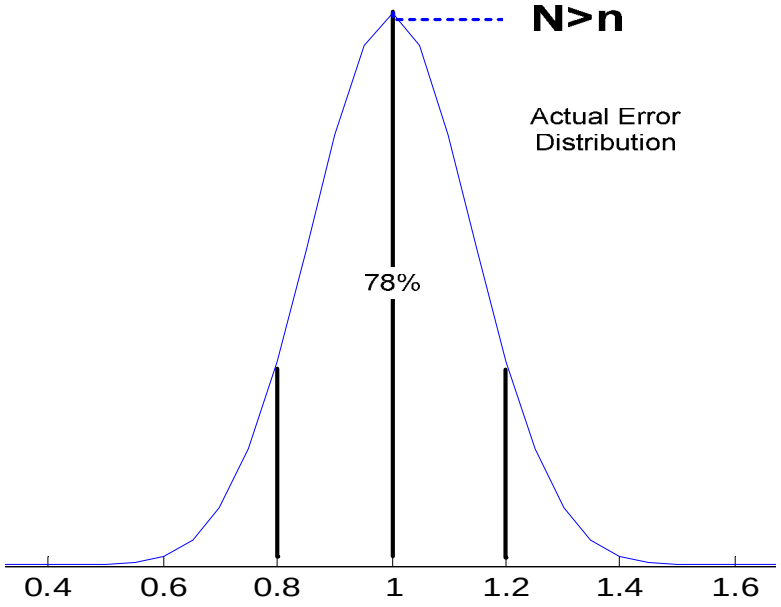

Figure 2-4: Actual Noise Distribution Profile

2.6 Two Sided Laplace Noise Model

2.6.1 Laplace Distribution

The Laplace distribution is also called the double exponential distribution. It is a distribution of the differences between two independent variates with identical exponential distribution [M. Abramowitz 1972] . A random variable has a Laplace distribution if its probability density function satisfies:

$$f(x) \mid \mu, b) = \frac{1}{2b} \exp(-\frac{| x - \mu |}{b}) \tag{2-9}$$

Where μ is a location parameter and b is a scale parameter

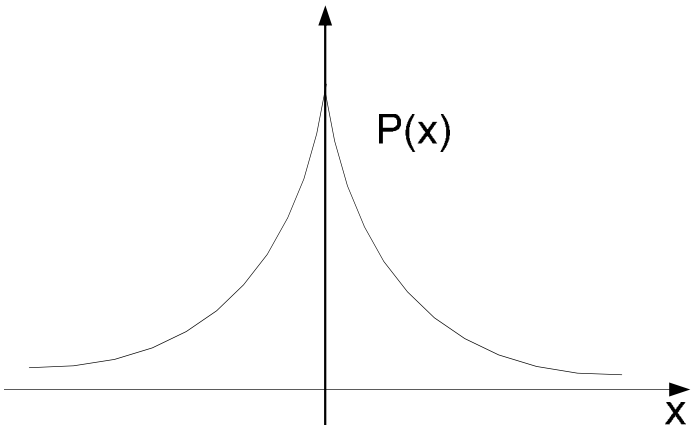

Figure 2-5: Laplace Distribution Example

The Laplace distribution sets more values closer to the (zero) mean. Thus, the $\pm$20% error range will have more values closer to zero. Hence, it may better represent CGMS noise reported in the literature.

2.6.2 Double Laplace Distribution

The simple normally distributed error model proposed is a fairly close approximation to the limited clinical data reported. As shown in Table 2-2, the correlation coefficients vary from patient to patient and there are cases that the values are lower than reported. Therefore, the model is not perfectly reliable for any patient data set.

For a third noise model, a double Laplace noise model is proposed. This model contains two double exponential distributions as shown in Figure 2-6. The inlier of the distribution is defined using the data reported to lie within ±20% A- range and the region from ±20% to ±40% is defined as outliers. The double Laplace Distribution is generated separately with a two different pairs of standard deviation and mean. These two different processes are completed isolated from each other, therefore the percentage of data within the inlier and outlier varies can be fixed to match the reported data. As a result, less patient-dependant and stable correlation coefficients will be produced.

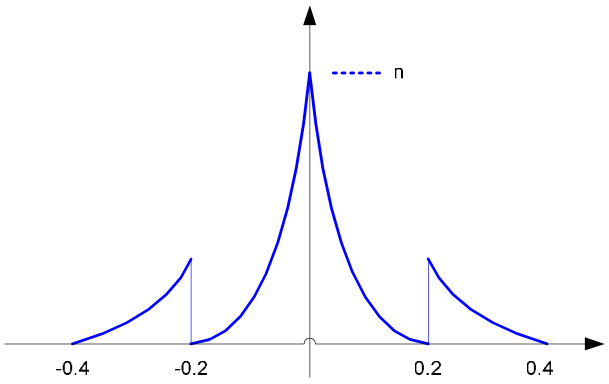

Figure 2-6: Approximated Double Laplace Distribution

2.6.3 Model Validation and Results

The same patient data sets are used for validating the double Laplace noise model. The Clarke Error Grid for a simulation of 1 of the 10 patients is shown in Figure 2-7. The mean of the correlation coefficients over the 20 simulations is equal to 0.8848 and the variance is 0.0876. This correlation coefficient value is almost the same as that reported in the literature [P Goldberg 2004].

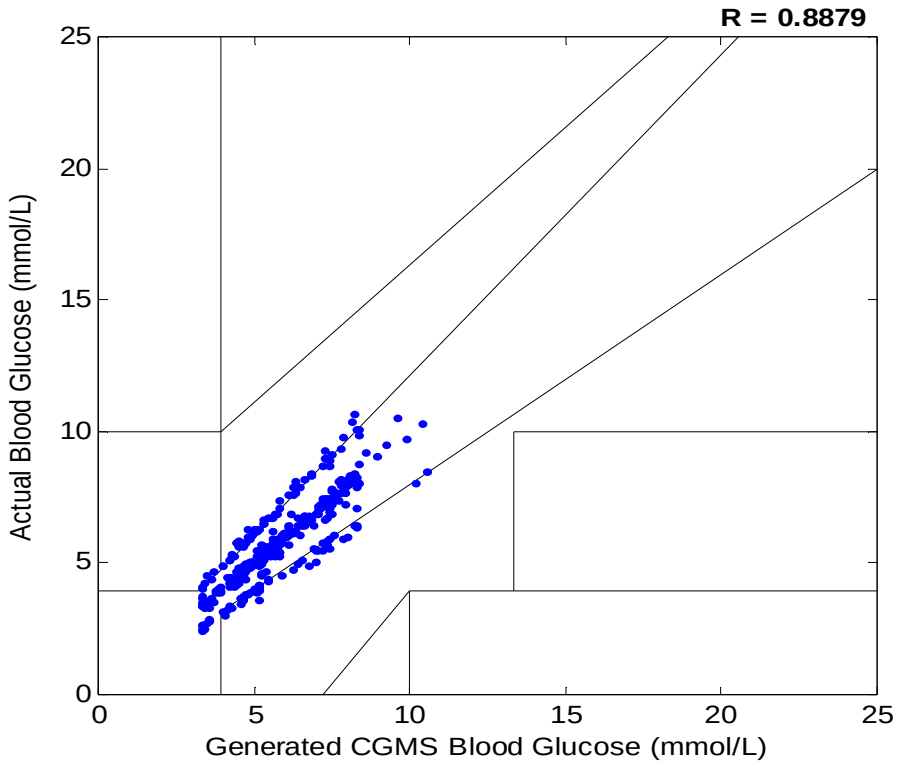

Figure 2-7: Clarke Error Grid for 1 of the 10 patient simulations with Double Laplace Noise Model

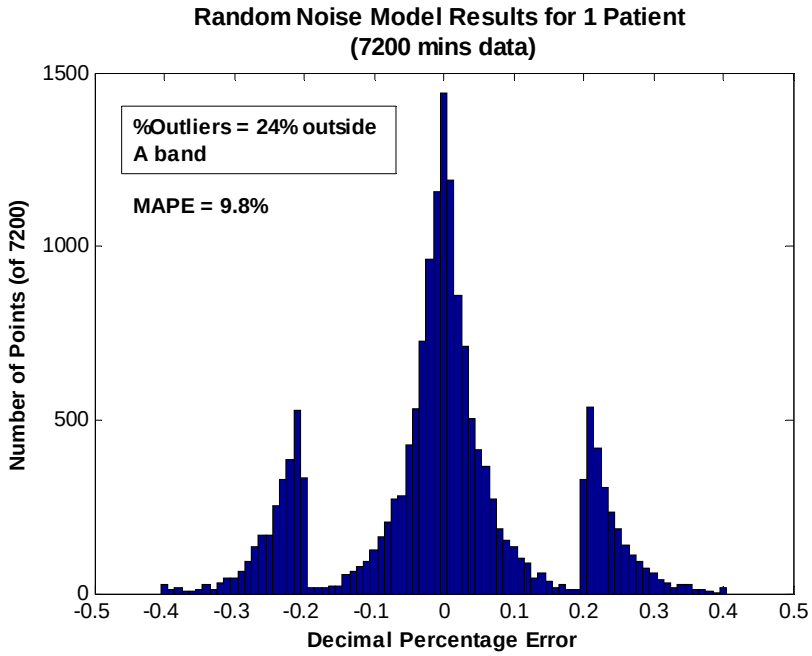

Figure 2-8: Double Laplace Noise Model Plot from the Simulation

Table 2-3 shows that the mean correlation coefficients obtained from ten patient profiles over n=20 simulations. The range of the mean correlation coefficients for these ten patients' simulations is 0.8295 to 0.9277, which is also higher than the result from normal distribution model. It also contains effectively all reported CGMS results in the literature.

Patient Number	Correlation Coefficients (MPRD)
24	0.8848
87	0.8948
130	0.9034
289	0.9277
484	0.9115
519	0.8946
554	0.9149
666	0.879
1016	0.8295
1025	0.8964

Table 2-3: Mean Correlation Coefficients for Ten Patients

2.7 Comparison of the Two Models

By comparing the correlation coefficients in Table 2-2 and Table 2-3, it is obvious that the correlation coefficients from the double Laplace noise model are generally slightly higher than those produced from the normal distribution noise model and are much closer to those found in the literature. The double Laplace noise model also provides more realistic MARD error values. Finally, the double Laplace model provides greater flexibility to represent the (reported) noise/error values for any CGM sensor and not just the CGMS system, enabling the approach to be better generalized in the absence of actual error histograms to create a model. Those factors provide a much higher level of confidence of using model based simulation. Therefore we chose the double Laplace noise model in this research.

Filtering Techniques

3.1 Summary

This chapter addresses the need for filtering techniques on CGM data and describes three different types of filters that can be applied, namely, Median Filter, Least Square Fitting and Spline Fitting. Finally, a filter array processing diagram is also proposed.

3.2 Filtering Techniques

CGM sensors have been initially developed as complementary measurement systems, rather than replacements for current glucose pin-stick methods [Raskin 2005]. Because of their high measurement frequency, they are very effective at capturing trends and the impact of any therapy changes. It should be noted that if the noise level in CGM measurements could be improved, it would give them more potential to be used in automated blood glucose regulating systems. Therefore, it is important to undertake research on possible filtering techniques and propose an effective filtering scheme that is specifically designed in this case for Minimed CGMS data as it is tested on a CGMS noise model.

It is also important that any filtering or estimation based on a noisy measurement does not have a significant time lag due to the method used as time is one of the most important issues for treating ICU patients and type 1 diabetics alike. Minimizing lag in the filtered/estimated glucose levels used in model-based control is also critical in ensuring that subsequent glucose predictions are accurate. Without minimizing lag, the modelled state for determining a control action might not fully represent the actual state, leading to potentially dangerous clinical control actions, poor control and poor outcomes.

Therefore, this research has looked into many possible solutions and developed the following filter array combination to reduce the impact of large errors and noise from these sensors. This filter array has produced a minimum of lag with good accuracy.

3.3 Filter Types

Several possible filters have been investigated here and elsewhere. In particular, a wide variety of Kalman-based approaches have been considered [Buckingham 2005; M. Kurre-Kinsey 2006]. These were discarded due to lack of a good linear model for the sensor or the system. Maximum Likelihood Approach [L. R. Shenton 1977] was also considered. This section, however, presents only the filter elements seriously considered and used in this thesis.

3.3.1 Median Filter

The median value function is a non-linear operation that can be used to remove noise from images or other signals, particularly outliers. Median filters are extremely useful when there is impulsive noise, which appears randomly either in a small or large scale in a true signal. The CGMS noise is modelled as random distributed noise and 78% of it lies within ±20% with a maximum of ±40%. In addition, the sensor is assumed to provide a reading every five minutes and the noise will only occur when the reading is taken place. Therefore, the error profile can be conceptualised as a collection of impulses that have different amplitude levels. Since median filter is capable of handling this type of noise, it is very likely the median filter could be able to reshape the noise and improve the signal to noise ratio. The following example demonstrates how this concept can be visualised.

a) ***An example of a unit step true blood glucose status every 5 minutes. This is achieved by using impulses with same amplitude***

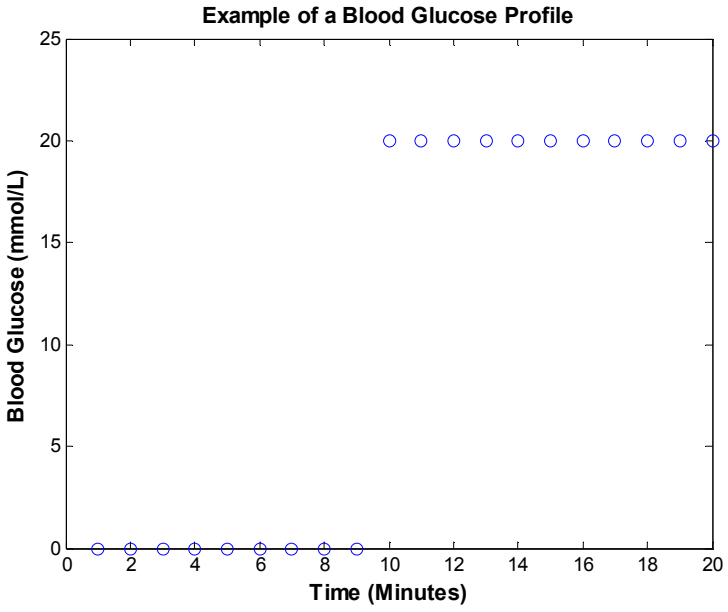

Figure 3-1: True Blood Glucose in Impulse Example

b) ***If the blood glucose is to be measured every 5 minutes, then random noise will occur when the measurements are taken. An example of this type of random noise is shown in Figure3-2. The noise profile therefore can be considered as a collection of impulses with different amplitude levels***

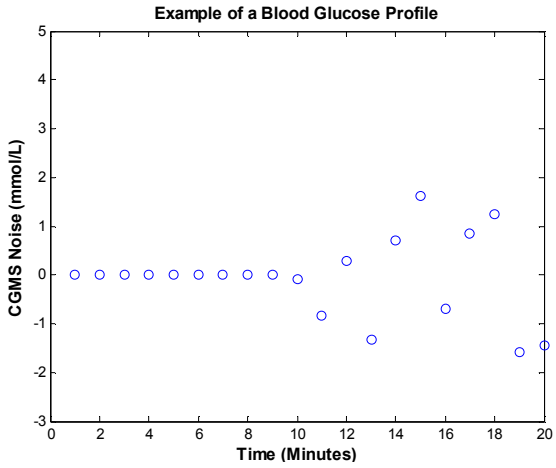

Figure 3-2: Example of True CGMS Noise to be Applied to step Change in Step (a) after t = 9min

c) ***By Adding (b) to (a), it will result in the blood glucose that clinically measured. The result is shown in Figure3-3 and still seen as a collection of impulses.***

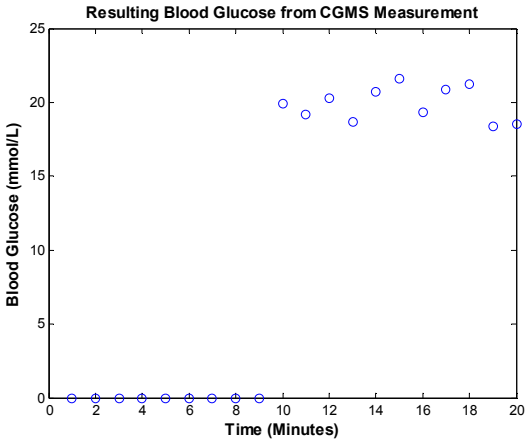

Figure 3-3: Example of the Resulting Noisy Blood Glucose Measurement

d) ***The Resulting Blood Glucose from Step (c) is then applied with 3-point median filter. The output from the median filter shown in Figure3-4 is close to the true blood glucose in Figure3-1.***

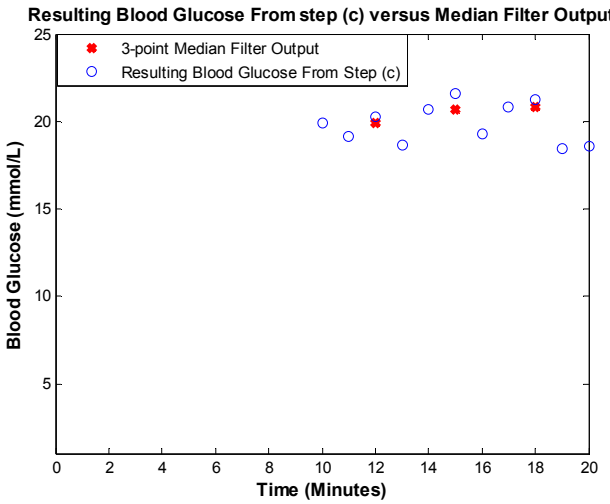

Figure 3-4: Example of a 3-Point Median Filter Performance

3.3.2 Least Squares Fitting - Polynomial

Least Square Fitting (LSF) is a mathematical procedure for finding the best-fitting curve of a fixed order to a given set of data points by minimizing the sum of the squares of the offsets or "residuals" of the points from the curve [Weisstein]. The sum of the squares of the offsets is used instead of the offset absolute values because it allows the residuals to be treated as a continuous differentiable quantity.

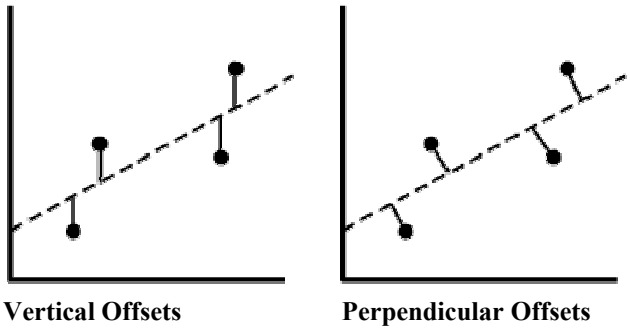

Figure 3-5: Vertical and Perpendicular offsets

In practice, there are two types of offsets, vertical offsets and perpendicular offsets, as shown in Figure 3-4. The vertical offsets from a line are almost always minimized instead of the perpendicular offsets. This provides a fitting function for the independent variable x that estimates y for a given x. It also allows uncertainties of the data points along the x and y axes to be incorporated simply. Finally, it provides a much simpler analytic form for the fitting parameters than would be obtained using a method based on perpendicular offsets, which involve both the input variable x and the output variable y. In addition, the fitting technique can be easily generalized from a best-fit higher-order line to a best-fit polynomial when sums of vertical distances are used.

Generalizing from a straight line (i.e. first degree polynomial) to a *k*th degree polynomial

$$y = a_0 + a_1 x + \cdots + a_k x^k \tag{3-1}$$

Vertical least squares fitting is proceeded by finding the sum of the squares of the vertical deviations R^2 of a given set of data.

$$R^2 = \sum_{i=1}^{n} [y_i - (a_0 + a_1 x_i + \cdots + a_k x^k)]^2 \tag{3-2}$$

Therefore, the partial derivatives are defined:

$$\frac{\partial(R^2)}{\partial(a_0)} = -2\sum_{i=1}^{n} [y - (a_0 + a_1 x + \cdots + a_k x^k)] = 0 \tag{3-3}$$

$$\frac{\partial(R^2)}{\partial(a_1)} = -2\sum_{i=1}^{n} [y - (a_0 + a_1 x + \cdots + a_k x^k)]x = 0 \tag{3-4}$$

$$\vdots$$

$$\frac{\partial(R^2)}{\partial(a_k)} = -2\sum_{i=1}^{n}[y-(a_0+a_1x+\cdots+a_kx^k)]x^k = 0 \tag{3-5}$$

These lead to the following equations:

$$a_0 n + a_1\sum_{i=1}^{n}x_i + \cdots + a_k\sum_{i=1}^{n}x_i{}^k = \sum_{i=1}^{n}y_i \tag{3-6}$$

$$a_0\sum_{i=1}^{n}x_i + a_1\sum_{i=1}^{n}x_i{}^2 + \cdots + a_k\sum_{i=1}^{n}x_i{}^{k+1} = \sum_{i=1}^{n}x_iy_i \tag{3-7}$$

$$\vdots$$

$$a_0\sum_{i=1}^{n}x_i{}^k + a_1\sum_{i=1}^{n}x_i{}^{k+1} + \cdots + a_k\sum_{i=1}^{n}x_i{}^{2k} = \sum_{i=1}^{n}x_i{}^k y_i \tag{3-8}$$

And this result can be written in matrix form:

$$\begin{bmatrix} n & \sum_{i=1}^{n}x_i & \cdots & \sum_{i=1}^{n}x_i^k \\ \sum_{i=1}^{n}x_i & \sum_{i=1}^{n}x_i^2 & \cdots & \sum_{i=1}^{n}x_i^{k+1} \\ \vdots & \vdots & \ddots & \vdots \\ \sum_{i=1}^{n}x_i^k & \sum_{i=1}^{n}x_i^{k+1} & \cdots & \sum_{i=1}^{n}x_i^{2k} \end{bmatrix} \begin{bmatrix} a_0 \\ a_1 \\ \vdots \\ a_k \end{bmatrix} = \begin{bmatrix} \sum_{i=1}^{n}y_i \\ \sum_{i=1}^{n}x_iy_i \\ \vdots \\ \sum_{i=1}^{n}x_i^k y_i \end{bmatrix} \tag{3-9}$$

This is a Vandermonde matrix. To obtain a least squares fit, the above matrix can also be written as the following

$$\begin{bmatrix} 1 & x_1 & \cdots & x_1^k \\ 1 & x_2 & \cdots & x_2^k \\ \vdots & \vdots & \ddots & \vdots \\ 1 & x_n & \cdots & x_n^k \end{bmatrix} \begin{bmatrix} a_0 \\ a_1 \\ \vdots \\ a_k \end{bmatrix} = \begin{bmatrix} y_1 \\ y_2 \\ \vdots \\ y_n \end{bmatrix} \tag{3-10}$$

Thus, the equation for a polynomial fit is given by

$$y = \mathrm{X}a \tag{3-11}$$

3.3.3 Spline Fitting

Spline fitting techniques utilize a wide range of functions over various applications. Typically, they are used for data interpolation and/or smoothing. Spline interpolation functions are usually determined as the minimizers of suitable measures of roughness subject to interpolation constraints [H. Ahlberg 1967]. A spline is a special function that is defined piecewise with polynomials. In its most general form, a polynomial spline S: $[a,b] \in R$ consists of polynomial pieces $P_i[t_i, t_{i+1}) \in R$, where

$$a = t_0 < t_1 < \cdots < t_{k-2} < t_{k-1} = b \tag{3-12}$$

That is,

$$S_0(t) = P_0(t),\ t_0 \le t \le t_1$$

$$S_1(t) = P_1(t),\ t_1 \le t \le t_2$$

$$\vdots$$

$$S_{k-2} = P_{k-2}(t),\ t_{k-2} \le t \le t_{k-1} \tag{3-13}$$

The given k points t_i are called knots. The vector $t = (t_0, \ldots, t_{k-1})$ is called a knot vector for the spline. If the knots are equally distributed in the interval $[a, b]$, the spline is said to be uniform, otherwise it is non-uniform.

Spline can be fitted to any rough data series to create a smooth, continuous function. These functions are also differentiable to the polynomial order used. Hence, when noise levels are relatively low they can be and effective form of multi-point interpolation.

3.4 Proposed Filter Array Diagram

Using the above identified filters, one of the objectives of this research is to undertake the parametric analysis of these filters and then come up the best combination of them. Figure 3-5 shows the possible combination. In this instance, the median filter is used to remove outliers and reduce overall noise levels. Least Squares or Splines are used to interpolate these median filtered values. In between, other filters may be required to further smooth the data.

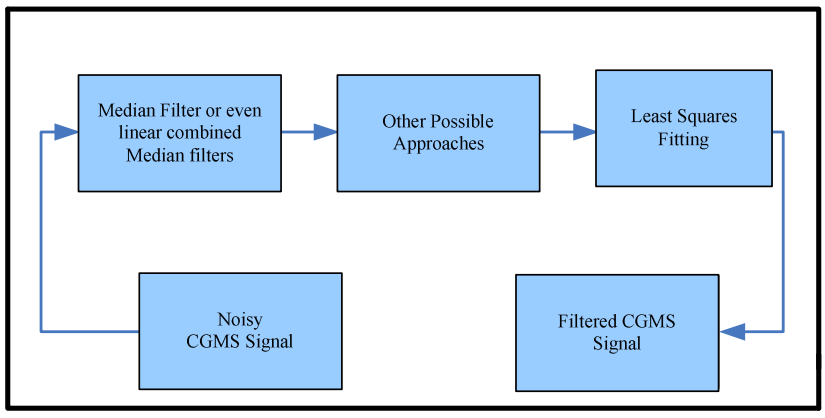

Figure 3-6: Proposed Possible Filter Array Block Diagram

Patient Cohort Summary and Filter Parametric Analysis

4.1 Summary

This chapter summarises the patient cohort used for model validation in this research and presents the detailed parametric analysis on median filters and least squares filters.

4.2 Summary of Patient Cohort

A wide range of data have been used for testing and validating the models, these data come mainly from clinical research and can be summarized as follows.

4.2.1 Retrospective Patient Data

The detailed description of retrospective patient data is contained in section 2.5.2 and Table 2-1. Throughout this research project, these data were used not only for testing and validating the noise model, but also for investigating and evaluating potential digital filters.

However, for completeness, patients who had undergone other glucose therapy protocols were included to add more clinical data for comparison.

4.2.2 SPRINT Patient Data

A computerized protocol that determines optimal feed and insulin inputs to achieve tight glucose control was effective in 10 to 24 hour clinical trials [X.W. Wong 2005]. However, its complexity makes it difficult to implement in some ICUs that do not already possess bedside computing power and trained computer support personnel. The Specialized Relative Insulin and Nutrition Tables (SPRINT) protocol was designed to provide an easy-to-use equivalent and achieve equal overall glycemic control to the computerized protocol [T. Lonergan 2006].

The SPRINT protocol is a simplified paper-based implementation of a computerized protocol developed by Chase et al [J. G. Chase 2005; J. G. Chase 2005]. It automatically determines the required hourly external nutrition rate and insulin bolus to minimize hyperglycemia. The computerized AIC4 protocol optimizes Eqs. 2-3 to regulate both nutritional and insulin inputs for each hour of patient care. The paper-based SPRINT protocol was developed from the results of simulated patient trials based on the same mathematical model [T. Lonergan 2006]. A detailed description of the SPRINT protocol and analysis may be found in Lonergan et al [T. Lonergan 2005; T. Lonergan 2006].

4.2.3 Other Data Used

Experimental glucose data retrieved from the paper by Kurre-Kinsey et al [M. Kurre-Kinsey 2006] were also used for analysis. The data originally comes from testing of an experimental subcutaneous glucose sensor error rates and were provided by Bequette et al [M. Kurre-Kinsey 2006].

4.3 Parametric Analysis on filters

4.3.1 Median Filter

The major parameter that affects the performance of a median filter is the number of points that the filter will be applied to. For the median filter to work, a minimum of three points are required and this is used a baseline for comparison. The filter performance of a typical median filter with three input points of data is simulated using the blood glucose profile from one of the Retrospective patients with the results shown in Figure 4-1.

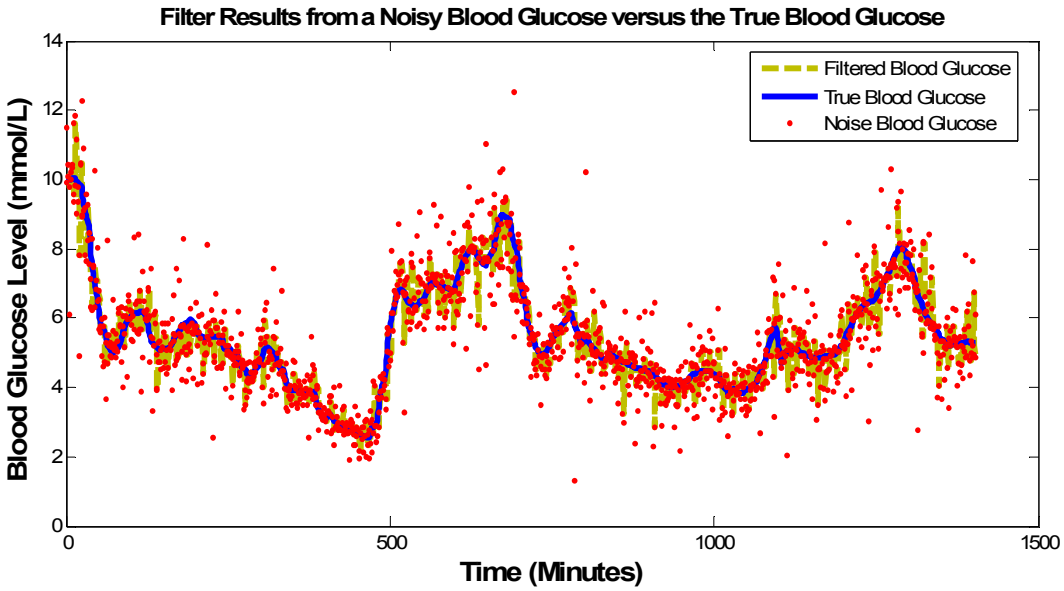

Figure 4-1: Typical Filter Results from a 3-Point Median Filter

To numerically measure the degree of the filtering performance, the Mean Absolute Percentage Error (MAPE) between the filtered glucose and true glucose is calculated. The value for this base model is 6.17%±5%. Note that the original noisy measurement has a MAPE value of 10.7%±3%. The value has been almost halved for a single median filtering pass.

The number of intake data points is then incremented one by one to a maximum of 8. This maximum represents 40 minutes of CGMS data above which the median may fail as significant physiological changes in blood glucose level can easily occur in that time frame. Hence, shorter filters are more responsive, and larger ones may take longer to see (sudden) changes. The same simulation procedure is applied to each case and their performance in terms of MAPE is summarised in Table 4-1 for all Retrospective patients.

Num of Input Points Used	Mean of MAPE	Std of MAPE
4	5.32	4.77
5	4.40	3.87
6	3.77	3.15
7	3.53	3.33
8	3.56	3.33

Table 4-1: Summary of Filter Performance with Different Number of Input Data points for Retrospective Patients

It is obvious that generally the value of MAPE decreases when the number of intake data points increases. However, when the number of intake data points increases, the filter also has to require more future data, which means the filter lag between the filtered glucose and true glucose will significantly increase if a centred median is used. This situation is not applicable in the real ICU situation as timing is a critical issue for glucose therapy protocols. Alternatively, a non-centred median could be used, examining only the current and N-1 prior points of data. Figure 4-2 shows the result for the 8-point median filter.

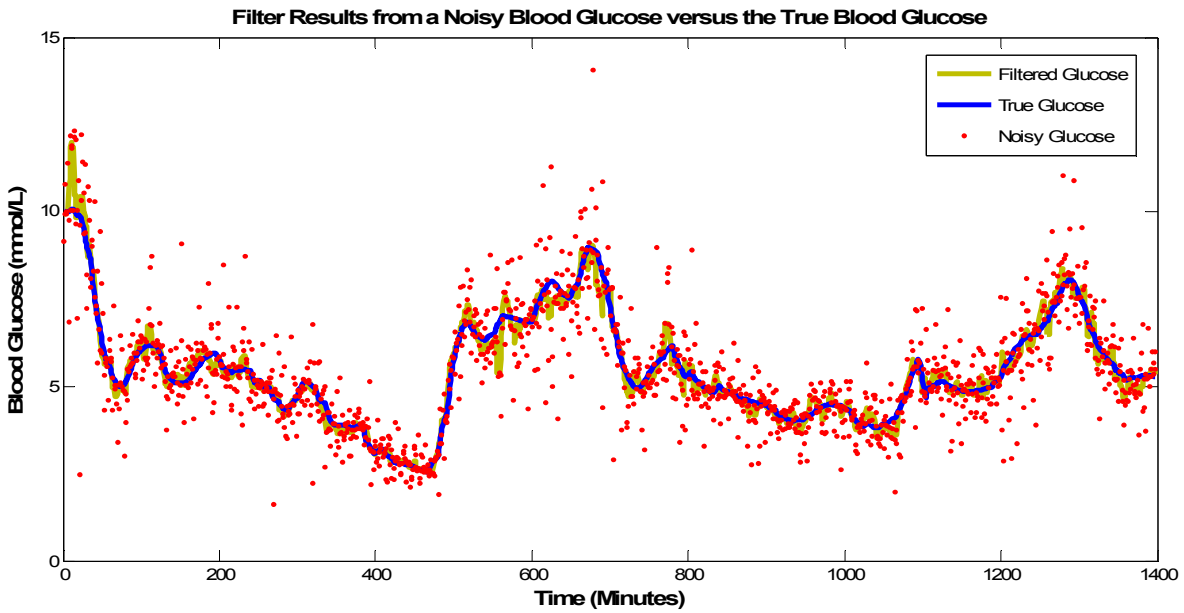

Figure 4-2: Typical Filter Results from an 8_Points Median Filter

A low order median filter which uses a reasonable, small number of input data points usually gives a good approximate representation of the true value, while a high order median filter, which takes a great number of future data points, offers a good description of the trend that will happen to the true data in the future. Therefore, one might come up with a combination of a filter that applies both a low order filter and a high order filter, which gives the filter results the feature of not only providing the good approximation of the true value, but also capturing some of the future trend of the true value by adding lag.

To analyze the performance of combined median filters of different lengths, the base median filter model with 3 input data is combined with a range of relatively higher order median filters. The same patient glucose data is then applied to the combined filter block. The performance results are summarised in Table 4-2.

Num of Input Points Used	Mean of MAPE	Max of MAPE	Min of MAPE
3 + 4	5.2974	6.0582	4.7812
3 + 5	4.6919	5.086	4.1883
3 + 6	4.3604	5.0182	4.0199
3 + 7	4.139	4.4545	3.5903
3 + 8	4.0974	4.4993	3.6862

Table 4-2: Summary of Filter Performance from Combined Median Filters

Overall, the filter combination of a 3 data input median filter and an 8 data input median filter gives the best performance, but it has filtering delay of up to 35 minutes, which exceeds the limit required for model based simulation. Therefore, a combination of a 3 data input median filter and a 7 data input median filter is selected for this research project introducing a 30 minutes lag unless a prior-points only filter is utilized. Finally, note that the values in Table 4-2 are still large enough to cause some error in fitting and prediction for control.

4.3.2 Least Squares Fitting

One of the main concerns of using Least Square Fitting is that fitted polynomial curves tend to positive or negative infinity at the edges. This behaviour implies that the fitting results at the edges might incur a wide range of fluctuation and increase the inaccuracy of the filtering system. Figure 4-3 shows one example this problem caused from using a polynomial fitting method. However, the example also shows that the fitting results

between the two edges are a very good approximation of the original signal. Therefore, the negative effect of edge problem can be potentially reduced if only the fitting results between edges are used in creating the filtering output results.

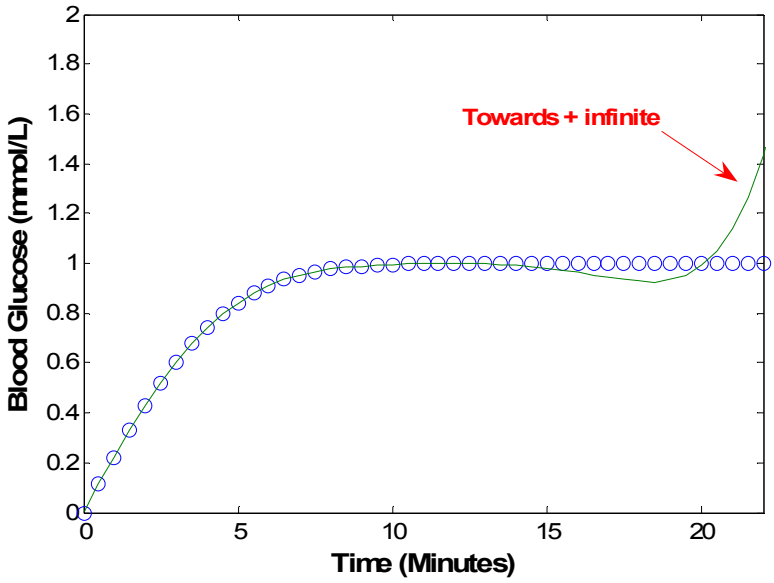

Figure 4-3: Example of Fitting Results Tend to Infinite

In addition, the filter or fitting window for this application has to be less than 30 minutes, as any delay that takes processing time longer than that would be regarded as inappropriate and add lag. In the case of a maximum fitting length of 30 minutes, there are 6 CGMS sensor measurements and by using the truncating method, the first and last two fitting outputs are cut off and only the remaining three results are valid as fitting outputs. The effect of this processing technique is demonstrated in Figures 4-4 and 4-5.

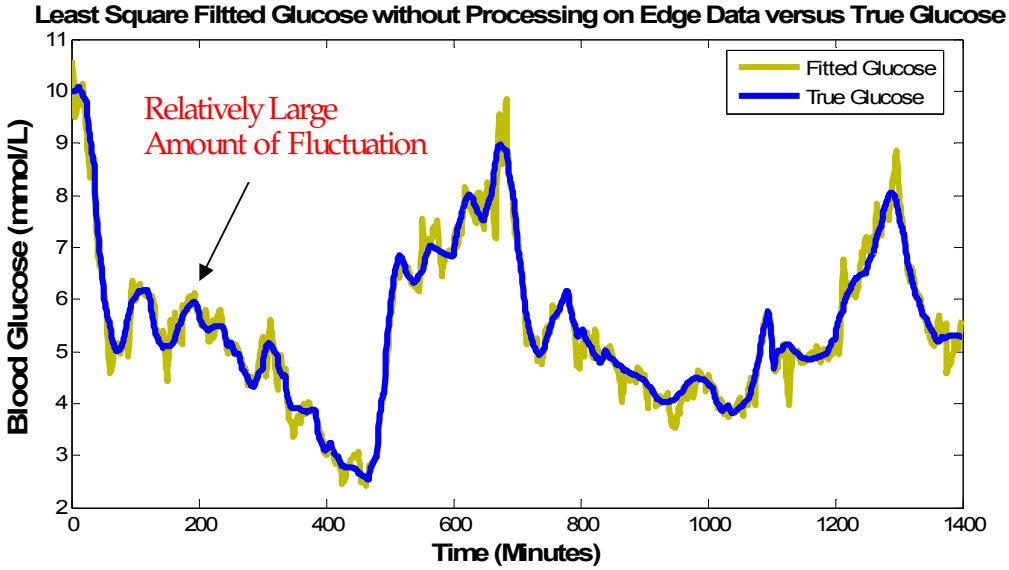

Figure 4-4: An Example of Least Square Fitting Result after Median filtering without Edge Processing

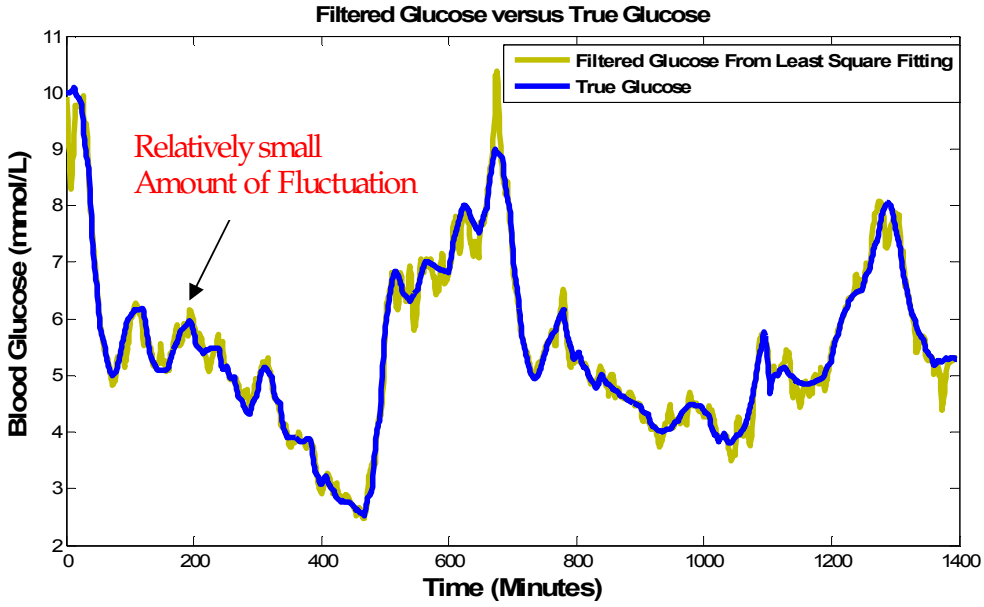

Figure 4-5: An Example of Least Square Fitting Result after Median Filtering with Edge Data Further Processed

To evaluate the performance of the Least Square Fitting approach, this method is applied to the filter results of combined median filter block. A Monte Carlo analysis is performed for the same patient and the final result shows that the mean MAPE for the 20 simulations is reduced to 3.13%±4%. This is almost a further reduction of 24% compared to the mean MAPE value from combined median filtering and a total drop of 71%±2% from the original of the noisy data.

4.4 S_I Fitting Comparison as a Surrogate for Prediction

In the model based simulation system that typically combines Eq 2-1, 2-2 and 2-3, the ultimate purpose of system is to apply filtering algorithms to current available noisy CGMS measurements and use the system equations to uncover the appropriate hidden S_I profile during this period. This fitted S_I profile can then be used to estimate the glucose trend in the short future based on any intervention. This approach is extremely useful as the glucose trend is unveiled and ICU staff can use other software and tools to monitor and control a patient's glucose levels. Therefore, maintaining of a high accuracy of the S_I fitting is one of the most important priorities for the filter.

Another aspect of evaluating the current designed filtering algorithm is to compare fitted S_I from the system model and filtering algorithm with the true S_I profile. The procedure for this experiment is outlined in Figure 4-6.

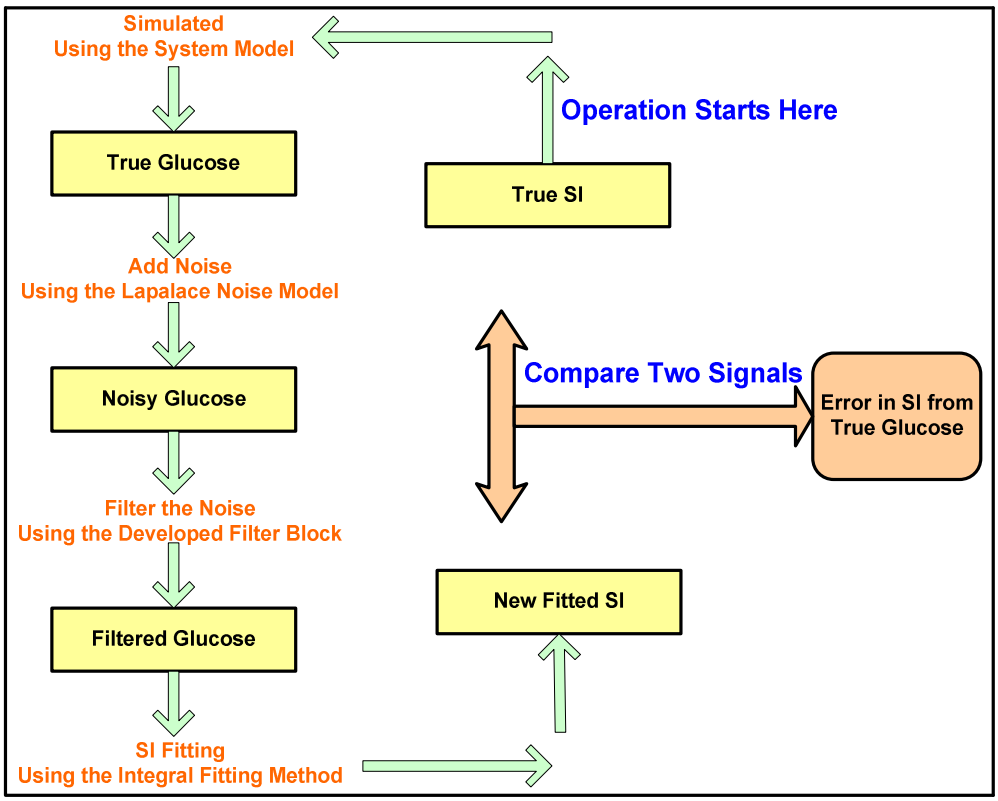

Figure 4-6: S_I Comparison Operation Diagram

Prior to comparing the fitted S_I from the filtered glucose data with the true S_I, the performance of the filtering algorithm in terms of improving MAPE in glucose is analysed. This task is achieved by first fitting the noisy CGMS glucose from one of the patients and its fitted S_I. Figure 4-7 shows both true and fitted S_I where the latter was fit to the noisy glucose data. It has a MAPE value of 21.4%. In the next step, this patient's filtered glucose is used to find the S_I and the result is shown in Figure 4-8. However, the MAPE value is reduced in this case to 8%. This means that by using the filtering algorithm the estimation of SI can be improved by 63%. This result shows the efficiency of the approach which is now tested on the full cohort.

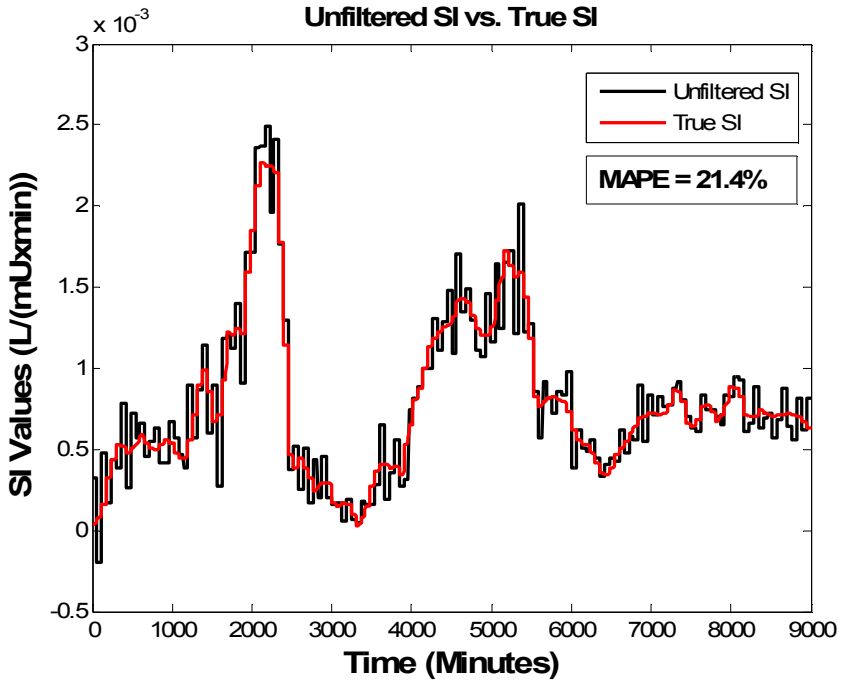

Figure 4-7: Fitted S_I Using Noisy Glucose versus True S_I

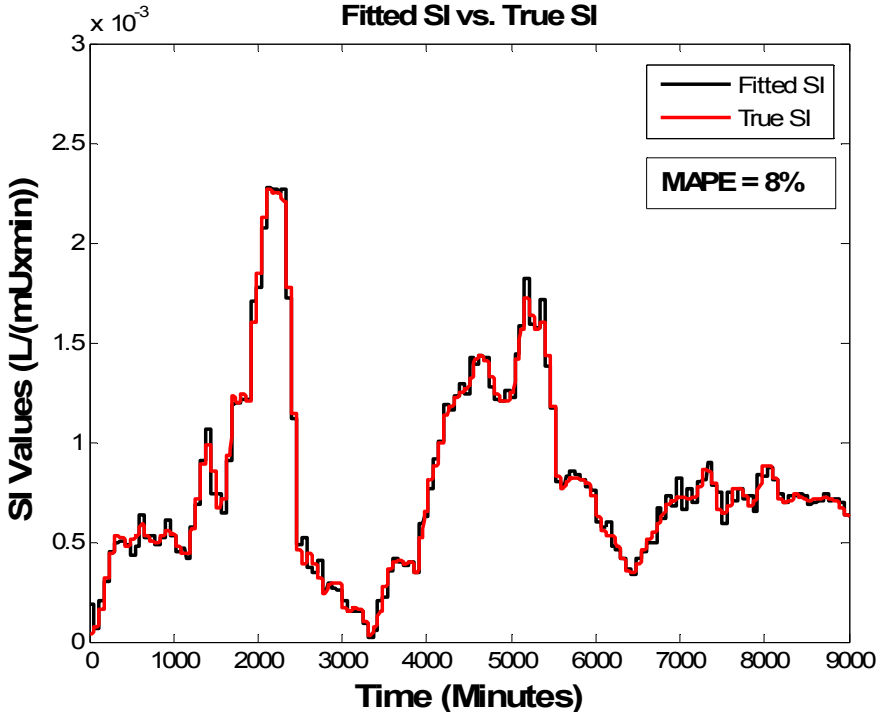

Figure 4-6: Fitted S_I from Filtered Glucose data versus True S_I

The experiment was then progressed using the 10 Retrospective patients and 10 SPRINT patients. The results for these two different category patients are shown in Tables 4-3 and 4-4. Due to the reason that the actual noise profile is still uncertain, the model is valued from the worst case with noise standard deviation of 0.2 to the best case with a noise standard deviation of 0.1. It is expected that simulation with these ranges of standard deviation would capture any unknown noise and error profile. The simulation results show the filtering algorithms produced a solid MAPE values amongst 3 different noise levels and the overall MAPE from these 20 patients are ranging from 4.45% to 6.8%.

	Patient	Noise Level	MAPE (%)	[5% 95%] MAPE (%)
Retrospective	24	Small	3.83	[0.19 9.75]
		Medium	4.26	[0.25 15.70]
		Large	5.60	[0.33 17.40]
	87	Small	5.44	[0.20 16.12]
		Medium	7.05	[0.27 21.55]
		Large	8.09	[0.37 23.58]
	130	Small	6.56	[0.44 15.76]
		Medium	7.00	[0.53 18.61]
		Large	8.12	[0.57 22.53]
	289	Small	2.86	[0.35 8.97]
		Medium	3.64	[0.29 9.56]
		Large	4.10	[0.42 11.73]
	484	Small	2.67	[0.29 7.84]
		Medium	3.13	[0.35 9.81]
		Large	3.98	[0.39 11.45]
	519	Small	5.08	[0.18 17.82]
		Medium	6.87	[0.26 24.26]
		Large	8.08	[0.32 26.55]
	554	Small	3.13	[0.30 9.87]
		Medium	3.85	[0.36 11.80]
		Large	4.51	[0.38 12.36]
	666	Small	8.52	[0.49 33.85]
		Medium	11.51	[0.65 38.87]
		Large	13.92	[0.66 56.47]
	1016	Small	4.89	[0.24 15.24]
		Medium	6.00	[0.31 18.62]
		Large	6.74	[0.47 21.33]
	1025	Small	3.03	[0.17 9.24]
		Medium	3.99	[0.28 9.74]
		Large	4.88	[0.26 13.19]
	Overall_ MAPE	Small	4.60	[0.29 14.45]
		Medium	5.73	[0.36 17.44]
		Large	6.80	[0.42 19.34]

Table 4-3: MAPE between True S_I and Fitting S_I using Filtered Glucose of 10 Retrospective Patients

	Patient	Noise Level	MAPE (%)	[5% 95%] MAPE (%)
SPRINT	AIC5006	Small	2.91	[0.22 8.68]
		Medium	3.02	[0.21 9.78]
		Large	3.56	[0.21 11.67]
	AIC5008	Small	4.03	[0.30 11.74]
		Medium	4.74	[0.35 13.04]
		Large	5.17	[0.44 13.48]
	AIC5011	Small	6.35	[0.26 30.12]
		Medium	6.51	[0.40 25.58]
		Large	7.76	[0.47 28.70]
	AIC5019	Small	6.11	[0.53 16.04]
		Medium	6.67	[0.44 17.46]
		Large	7.00	[0.44 18.49]
	AIC5020	Small	3.94	[0.32 13.04]
		Medium	4.30	[0.28 12.79]
		Large	4.76	[0.43 13.39]
	AIC5026	Small	3.30	[0.25 9.03]
		Medium	3.90	[0.31 10.61]
		Large	4.20	[0.38 12.09]
	AIC5028	Small	6.19	[0.34 21.48]
		Medium	7.33	[0.47 27.97]
		Large	9.18	[0.44 28.56]
	AIC5032	Small	3.17	[0.28 9.40]
		Medium	3.41	[0.28 9.68]
		Large	3.58	[0.23 10.99]
	AIC5040	Small	6.13	[0.27 12.53]
		Medium	7.74	[0.32 12.93]
		Large	8.68	[0.30 18.26]
	AIC5049	Small	2.33	[0.14 7.07]
		Medium	2.65	[0.22 7.19]
		Large	3.00	[0.24 8.01]
	Overall_ MAPE	Small	4.446	[0.29 13.91]
		Medium	5.027	[0.33 14.70]
		Large	5.689	[0.35 15.05]

Table 4-4: MAPE between True S_I and Fitting S_I using Filtered Glucose of 10 SPRINT Patients

Evaluation of the Filter Design

5.1 Summary

This chapter presents the ultimate design of the filter block. The performance of this filter block is evaluated using the blood glucose data from Retrospective and SPRINT patients as well as the experiment data. The results obtained from true glucose profiles are comparable to the reported data, which was simulated using other filtering techniques.

5.2 The Ultimate Design of the Filter Block

After an in-depth analysis of the filter parameters, the final design of the filtering block has been concluded, as shown in Figure 5-1. The first stage of the filtering consists of two median filters, one with 10 minutes delay and the other with 30 minutes delay. The results from these two parallel moving median filters are then averaged and fed into the moving Least Square Fitting Stage, which applies edge data processing technique.

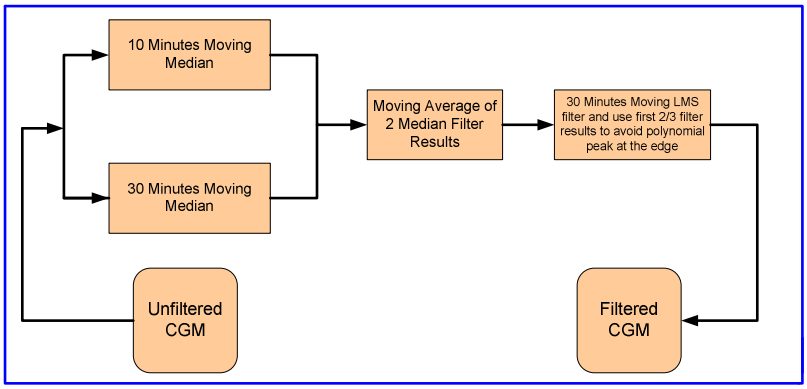

Figure 5-1: The Ultimate Design of the Filtering Block

5.3 Trial Results and Discussion

The designed filtering block is then applied to Retrospective and SPRINT patient data. Examples of actual performance graphs are shown in Figures 5-2 and 5-3. The Monte Carlo analysis results for all 20 patients are summarized in Table 5-1.

It is noted that average MAPE values for SPRINT patients are generally smaller than those for Retrospective patients. SPRINT patients have undergone a much tighter protocol and result in much more stable true blood glucose values, resulting in fewer changes and thus fewer errors due to lag. There is also only a small variation of the filter results for each category of patients, which means the filter performance for this type of application is still very robust. In addition, the overall MAPE value for SPRINT and Retrospective patients are 1.4% and 2.6%, respectively. These processed data have errors less than 7 - 10%, which is the standard laboratory testing error. This last result indicates that the developed signal processing technique is effective in terms of noise reduction during the trial.

Therefore the technique is possibly a valid tool to deal with the CGMS noise. Hence if this technique is applied to CGMS data in practice, the filtered data could be potentially used for a model-based tight blood glucose control system.

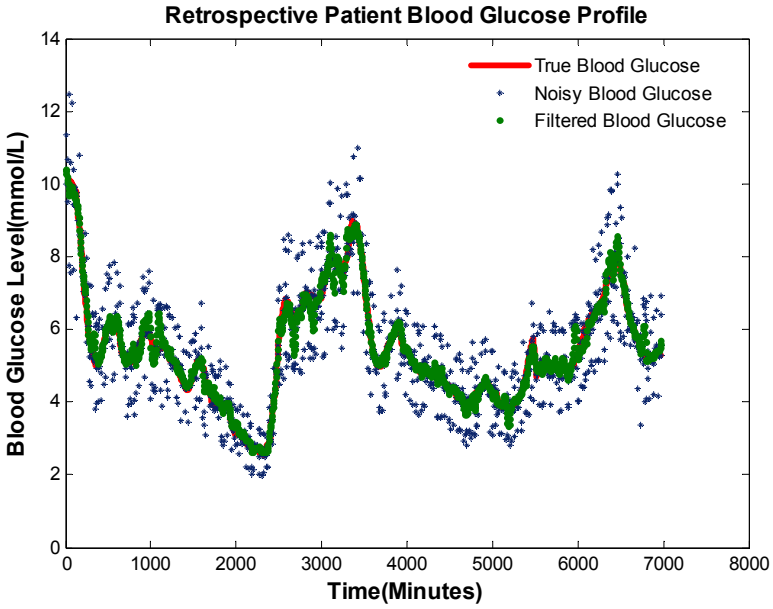

Figure 5-2: Example of Filtering Demonstration on Retrospective Patient

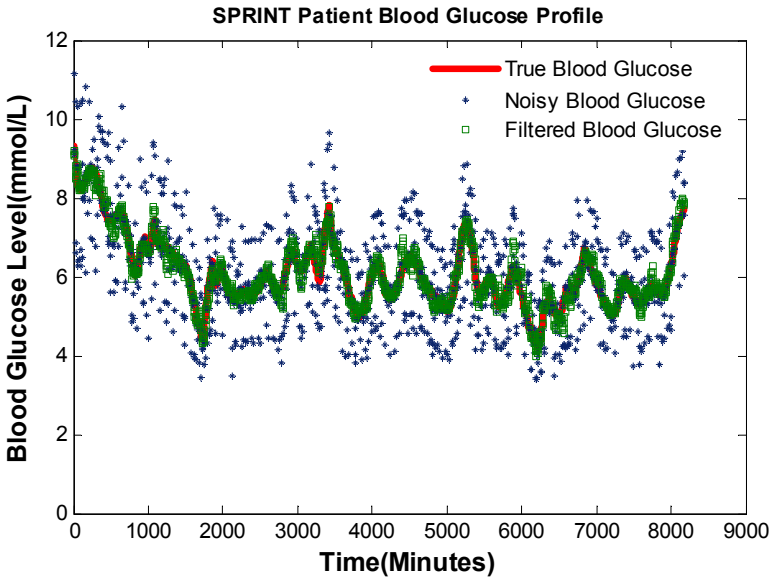

Figure 5-3: Example of Filtering Demonstration on Sprint Patient

	PATIENT	Mean Absolute % Error (MAPE)	5% ~ 95% MAPE
SPRINT Patients	24	1.6	[0.1 3.7]
	87	1.4	[0.1 3.4]
	130	1.3	[0.1 3.4]
	289	1.4	[0.1 3.7]
	484	1.4	[0.1 3.7]
	519	1.4	[0.1 3.7]
	554	1.4	[0.1 3.6]
	666	1.3	[0.1 3.7]
	1016	1.5	[0.1 3.9]
	1025	1.5	[0.1 4.0]
Overall A		**1.4**	**[0.1 3.7]**
Retrospective Patients			
	24	2.8	[0.2 8.3]
	87	3.4	[0.2 9.3]
	130	3.4	[0.2 8.4]
	289	3.2	[0.2 8.8]
	484	2.8	[0.2 8.9]
	519	3	[0.2 7.8]
	554	3.2	[0.2 9.4]
	666	3.1	[0.2 7.7]
	1016	2.9	[0.2 8.9]
	1025	2.6	[0.2 8.7]
Overall B		**2.6**	**[0.2 8.4]**
Overall of A & B		**1.8**	**[0.13 5.4]**

Table 5-1: Table of Summarized Filter Performance on Retrospective and Sprint Patients

5.4 Real Data Testing and Comparison with Reported Data

To evaluate the performance of the designed filter block in real situations, two sets of rat blood glucose data using CGMS were used for analysis [M. Kurre-Kinsey 2006]. Each data set hold double Lapalace noise added with standard deviation of 15% and also features 78% of data within 20% of the true glucose values. The filtered glucose data were plotted along with the true glucose in Figures 5-4 and 5-6. The results show that the filtered data are a very good approximation of the original true glucose value. The reported filtering results using dual Kalman Filters on the same set of the rat data are also shown in Figures 5-5 and 5-7 for comparison [M. Kurre-Kinsey 2006]. The comparison between the results of these two different approaches indicates that the filtering method developed from this research is comparable with the Kalman filter performance. Furthermore, the developed technique has less complexity in design, uses less computational effort, and requires less input data or modelling that may not be accurate in all cases.

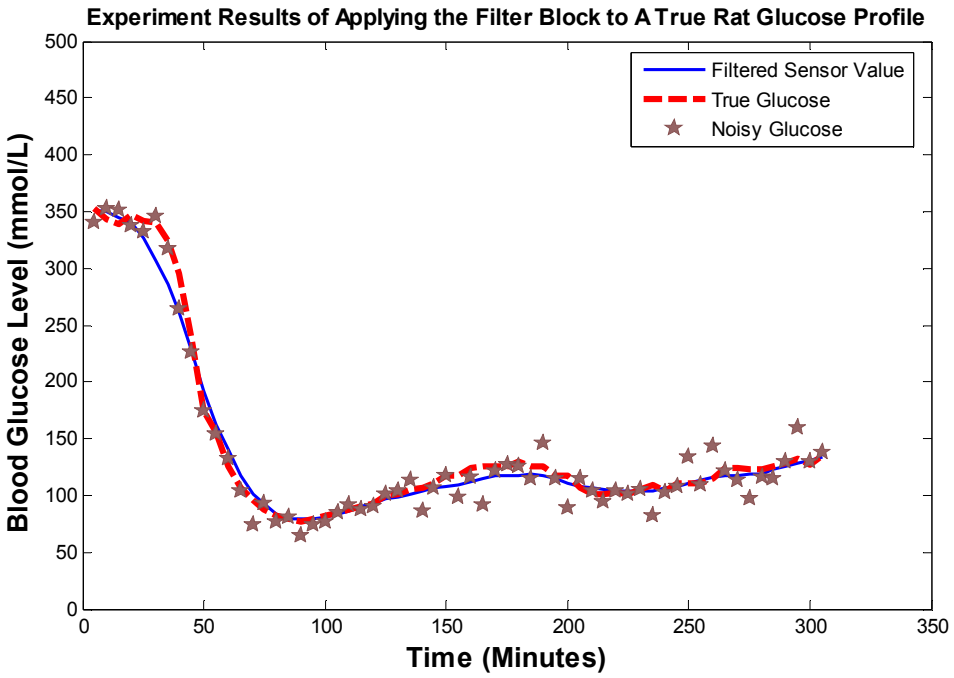

Figure 5-4: Filter Results of a Rat Glucose Profile in Bequette et al [M. Kurre-Kinsey 2006]

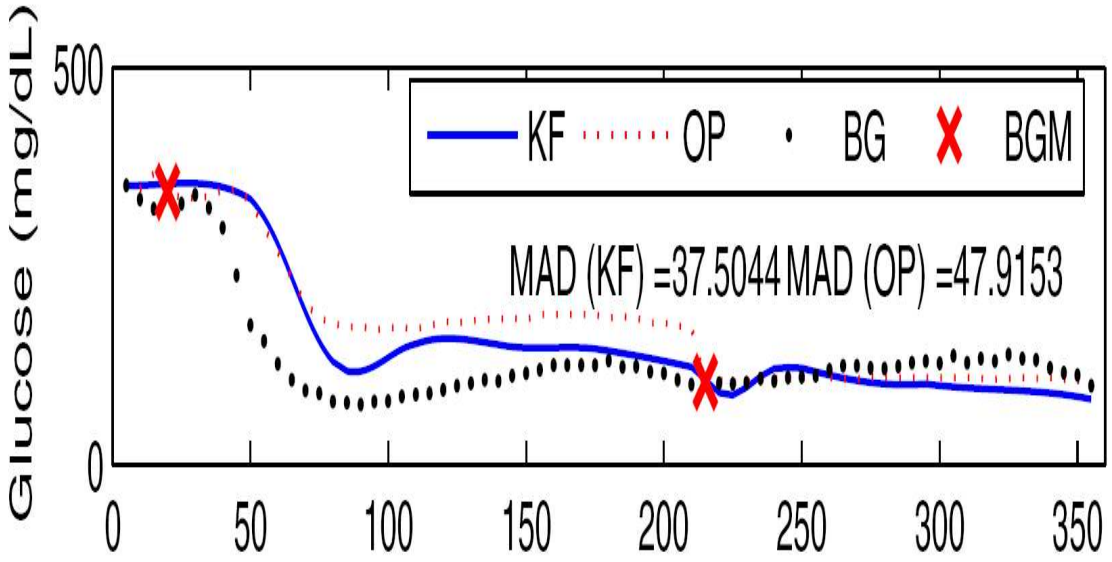

Figure 5-5: Reported Dual Kalman Filter Results of the Same Rat Glucose Profile in Bequette et al [M. Kurre-Kinsey 2006]

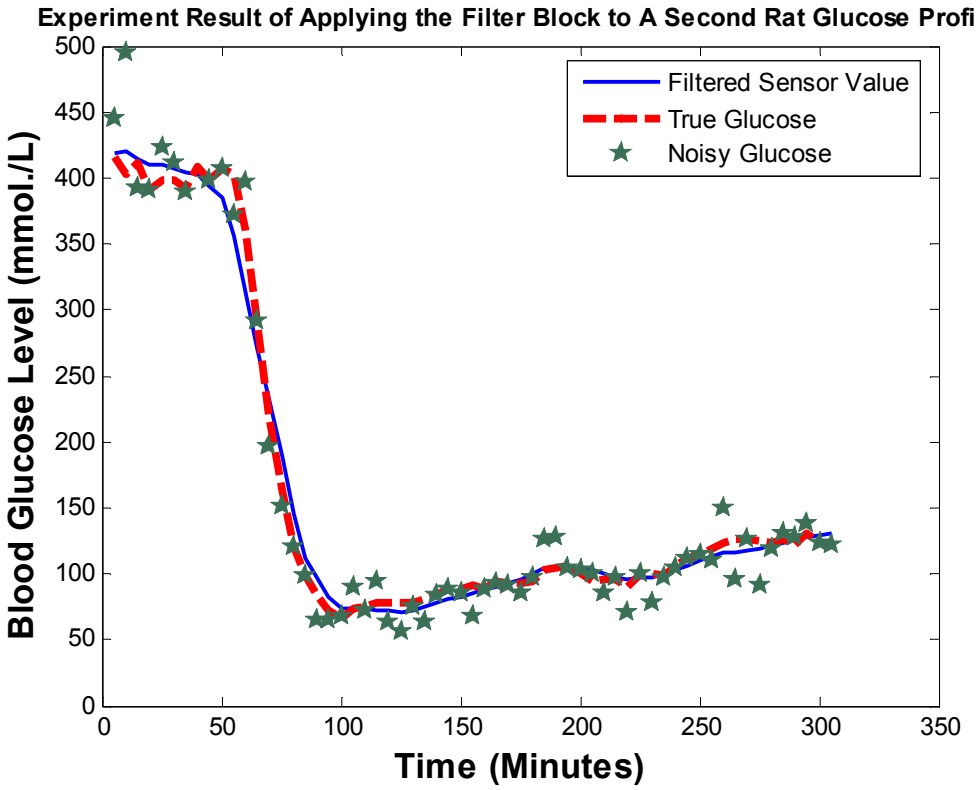

Figure 5-6: Filter Results of a Second Rat Glucose Profile in Bequette et al [M. Kurre-Kinsey 2006]

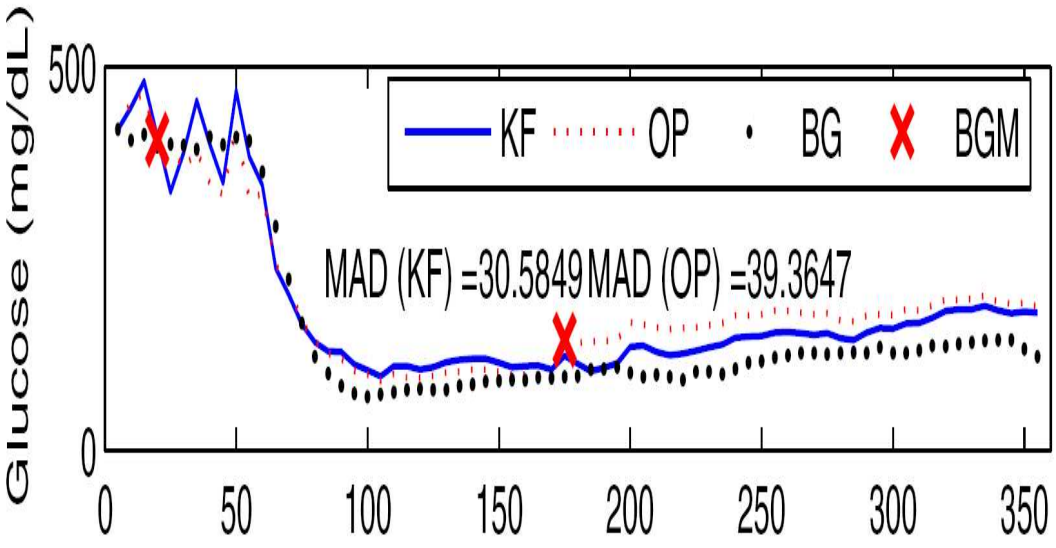

Figure 5-7: Reported Dual Kalman Filter Results of the Same Rat Glucose Profile in Bequette et al [M. Kurre-Kinsey 2006]

Sensor Drift and Calibration

6.1 Summary

Continuous sensors require regular re-calibration, as it can change over time, a drift, due to a variety of factors [C. David 2007]. This chapter therefore describes the need for drift calibration in the sensor system and propose a new method. Results are compared to other calibration methods from the literature.

6.2 Drift Calibration

An implanted continuous sensor may malfunction for many reasons [C. David 2007]. These include: 1) calibration drift; 2) a lag between concentrations of arterial blood glucose and interstitial fluid glucose during rapid fluctuations; 3) sensor fouling; 4) rejection and fibrosis; and 5) local inflammatory complications.

The measurement from an implanted sensor can be allowed to drift according to Federal Regulations [40]. Almost all continuous glucose sensors that are available in the market or under new development require regular blood glucose checks to maintain proper calibration. Calibration is required because these sensors are subcutaneous, which means they measure glucose concentration in the tissue, not directly from blood plasma. This difference could result in a lag between rapidly fluctuation blood glucose levels and interstitial fluid glucose levels. The magnitude of the lag may be no more than approximately five minutes [K. Rebrin 1999; G. M. Steil 2005] with a freshly inserted subcutaneous glucose sensor. However, after prolonged implantation, the sensor surface may become increasingly fouled with fibrotic material and the lag time can progressively increase. Even though the new sensor systems have improved since the first generation appeared in the market, there is still plenty of room for further improvement [Klonoff 2005]. Through an extensive literature search, the degradation of a continuous glucose sensor is modelled using exponential decay with a half life of 72 hours [M. Kurre-Kinsey 2006] shown in Figure 6-1.

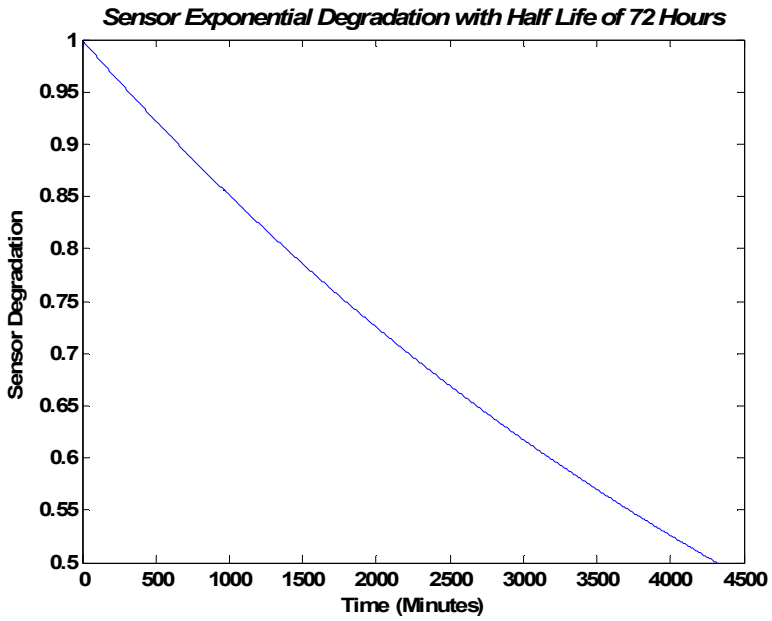

Figure 6-1: Example of Sensor Degradation

Traditionally, blood glucose levels are calibrated using a one-point method [C. Choleau 2002] to calibrate a sensor reading against a reference assay, which is usually a pin-stick measurement. This method is not sufficient as the sensor degrades over time. Therefore, the sensor gain drifts, which introduces errors in the blood glucose estimation from the sensor itself.

The following example shown in Figure 6-2 simulates the sensor drifting problem, where it is calibrated using standard one-point method. This example assumes that sensor noise is neglected and constant blood glucose is detected by the CGMS sensor. However, due to the calibration drift which is caused by other factors, the sensor reading is reporting biased values. Although the sensor is calibrated every 6 hours (420 min) and a compensation gain

is calculated to improve future data, the values it produces after calibration will still be moving away from true glucose value as the gain is stationary and not able to compensate the continuous drift loss shown in Figure 6-1.

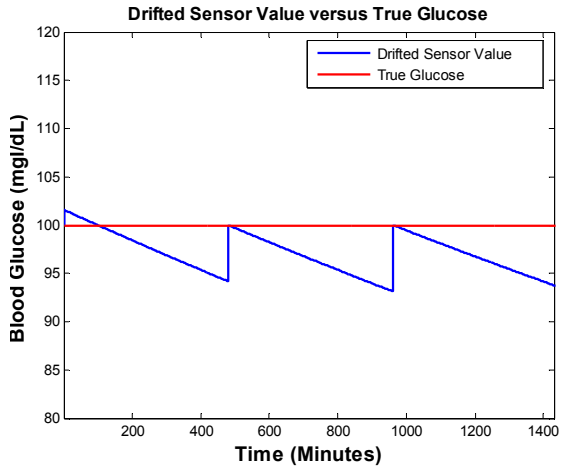

Figure 6-2: Example of Drift Sensor Measurement vs. True Glucose

Retrospective calibration methods were also introduced by Medtronic Minimed [MiniMed 2003], but are deterministic in nature and therefore also dynamic in terms of compensating the sensor drift. There are also recent studies using Kalman filters for gain estimation and noise filtering [M. Kurre-Kinsey 2006], and it shows great promise of using such a technique. However, this type of filtering technique strictly requires a continuous matching reference signal, in this application, the true glucose signal that is not available. The Kalman filter is applicable in the model based simulation since the true glucose is known. However, in the real clinical situation, the true glucose is hidden. Therefore whether Kalman filtering is a good candidate for solving the calibration drift problem is still under consideration and further investigation is required.

6.3 The Proposed Method for Calibration

The issues in section 6.2 motivate the use of other methods, which could be used to compensate for the drift while requiring fewer conditions, complexity or assumptions. This goal inspires designing a stochastic estimation technique based on retrospective calibration methods that predicts variable calibration gains to compensate for the drift.

6.3.1 Overview of Traditional Retrospective Calibration Method

The traditional retrospective calibration method is started by comparing the current sensor measurement against the measurement from pin-stick readings. A gain is determined by the difference of these two values. The sensor then uses this gain to adjust this measurement before preceding to the next calibration. This process is illustrated in Figures 6-3 and 6-4. Despite of using this method, Figure 6-4 still shows a biased value of 7mg/dL in 8 hours. Note that Figures 6-3 and 6-4 show relatively small drifts from the examples in [M. Kurre-Kinsey 2006].

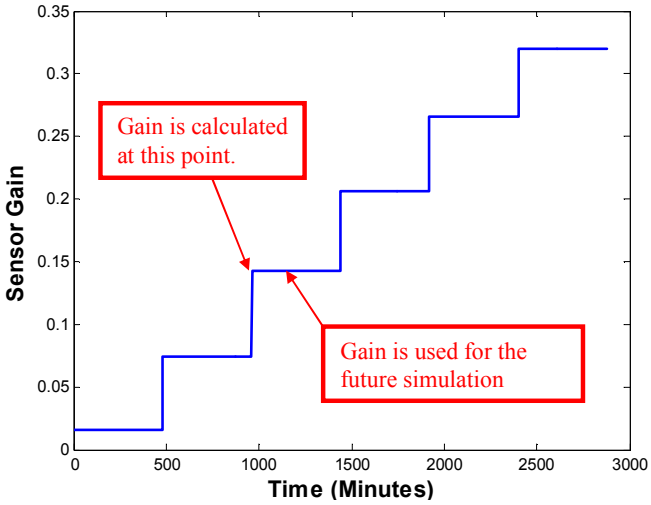

Figure 6-3: Sensor Gain versus Time from Traditional Calibration Method

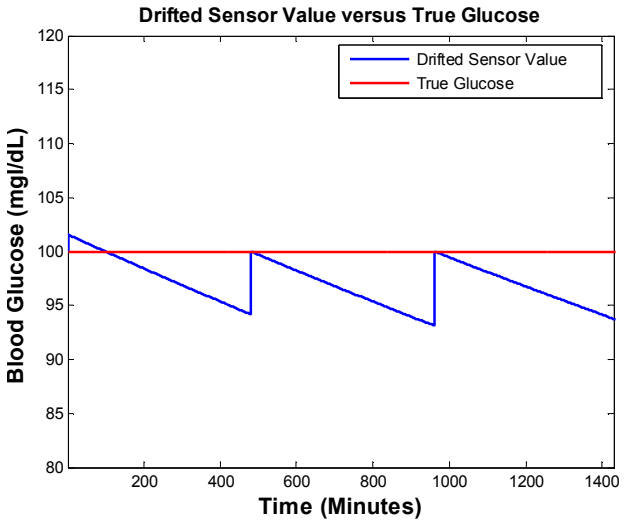

Figure 6-4: Calibrated Sensor Measurement vs. True Glucose

It should be noted that current CGMS systems are calibrated 4 times every 24 hours [M. Kurre-Kinsey 2006]. However, the calibration remains static. In addition, these calibrations can produce errors or difficulty with same patients [C. David 2007].

6.3.2 Spline and Polynomial Fitting Gain Prediction

In the traditional calibration method, although the sensor is calibrated and the gain is used to adjust the measurement, the fast that the gain is fixed means it is still not able to compensate the largely exponentially decaying degradation effect. Therefore, a valuable approach would allow the sensor to identify and use changeable time-varying gains to compensate the dynamic drift effect.

One of the stochastic gain estimation methods investigated is to use two or three of the previous determined gain values and perform a fitting based on these values. Because the fitted function is a time-dependent function, the values from this function will be changing continuously over the time. The fitting method presented here applies both spline fitting approach and polynomial fitting approach. The overall approach is described:

1. Because pin-stick testing causes patient discomfort, it is usually taken infrequently, typically 4 – 5 times daily. Therefore, if the fitting method involves processing these data, the infrequent pin-stick testing could increase the complexity of the approach. In addition, if there are delays during the daily pin-stick testing routine, this could further result in inaccuracy. Hence, spline fitting methods are used to fit the previous 2 or 3 pin-stick measurements in the first stage.

2. When the spline fitted result is available, a middle point of the spline fitted result between every 2 physical gain values is selected. This value is used as an actual gain value for future processing.

3. Polynomial fitting is applied to the gain values and the result is used to predict the gain values for the next period of simulation.

The graphical simulation result of the sensor gain is demonstrated in Figure 6-5 using the drift of Figure 6-1. In this case, only tow points are used a time. Hence, the result is a series of changing linear calibration lines.

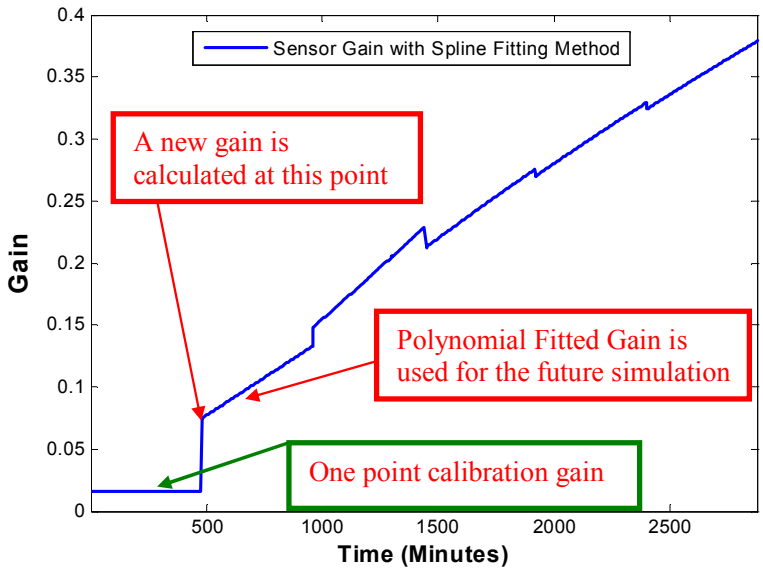

Figure 6-5: Sensor Gain versus Time from Two-Point Stochastic Calibration Method

The blood glucose simulation result is displayed in Figure 6-6. The first 8 hours is calibrated using the one-point calibration method due to insufficient data points. As a

result, the blood glucose value from sensor is moving away from the true glucose. In the next 8 hours, because there are two physical sensor gain values available, the model uses spline and polynomial calibration methods, whose effect keeps the sensor measurements from drifting away from true glucose. Although the blood glucose measurement still drifts away, the amount of drift has been greatly decreased compared to the results in one-point calibration in Figure 6-4.

A similar procedure is carried out for the rest of the experiment and the model started to provide the sensor larger than expected gains. Therefore, the sensor reading started to exceed the true glucose value. Overall, the error between the true glucose and the sensor measurements calibrated using two-point method is reasonably small and the new method is shown to be effective.

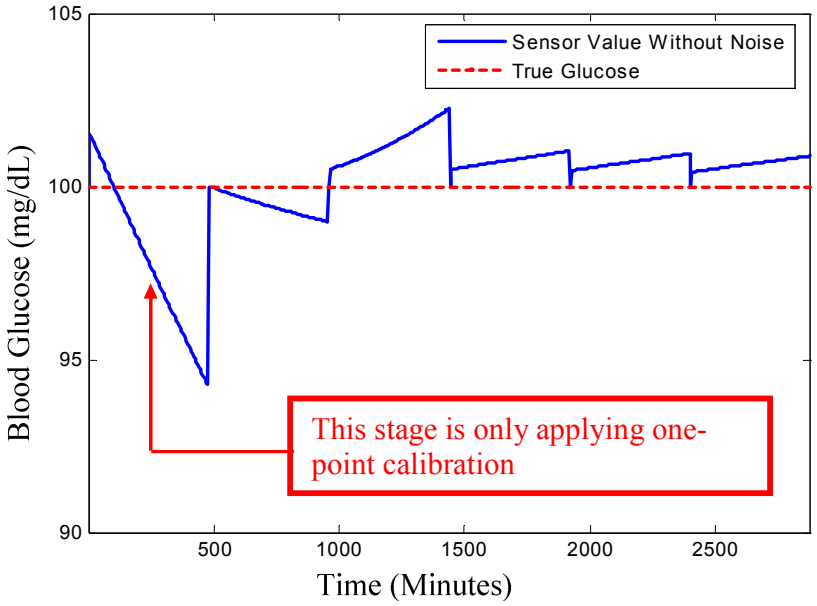

Figure 6-6: Calibrated Sensor Measurement vs. True Glucose

6.3.3 Noise Model for Bedside Testing

The pin-stick measurements in the previous simulations are assumed to be noise-free. However, the real pin-stick data are reported to have errors approximately 7 – 10%. To qualify the real pin-stick model, a pin-stick noise model with standard deviation of 5% and maximum error of 12% is added.

6.3.4 Filter for Bedside Testing Measurements

To attenuate the noise in bedside testing measurements, a special median filter is designed. The filter takes the current bedside testing value as input and also refers to previous measurements. If there are 2 previous measurements available, the filter will apply the median filter algorithm, otherwise it uses a linear combination algorithm to calculate the effective value.

6.3.5 Further Testing and Validation

The following steps are taken in this validation:

a) A simulation using the newly designed pin-stick noise model is simulated and result is shown in Figure 6–7. After introducing the pin-stick noise, the simulation result shows that the fitting method still produced good sensor blood glucose estimation.

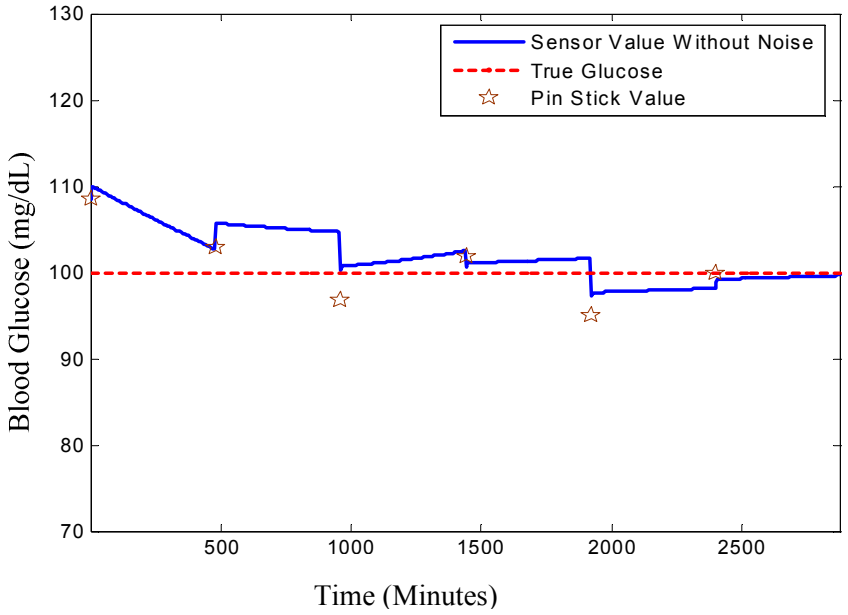

Figure 6-7: Calibrated Sensor Measurement vs. True Glucose

b) In all the previous experiments, a constant true blood glucose profile is used for simulation. This assumption is practically unrealistic, as there will always be variations in the glucose. Therefore, to further observe the model's behaviour on a fast changing glucose, especially in the case of hyperglycemia, a sinusoidal glucose with mean value of 100mg/dL and peak-to-peak amplitude of 60mgl/dL is utilized. The simulation result of using this glucose profile is shown in Figure 6-8. It shows that the main errors occurred at the peaks. The MAPE between the sensor value and the true glucose is 9.1%.

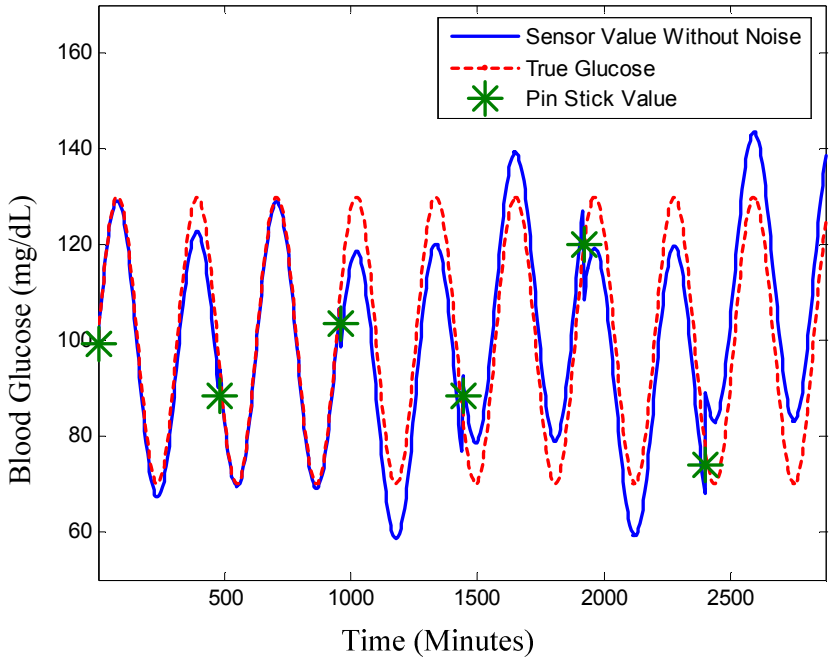

Figure 6-8: True Blood Glucose vs. Sensor Measurements Simulated using Sine

c) A more complicated experiment is to fully adapt all the models into the system. Specifically, the pin-stick noise model, sensor noise model and calibration model, and use all the filtering techniques to process the glucose data and verify the final result. Based on the previous results, the double Laplace noise model was used with r = 0.88±0.06. The resultant noisy sensor glucose measurement is shown in blue in Figure 6-9. The measurement data were then filtered by the filter block of Figure 5-1. The result in Figure 6-10 shows that the signature of the calibrated sine glucose was preserved very well by the filter, while a large amount of noise has been eliminated. The MAPE value is 10.27%, which is close to the result obtained in section b). Despite using the median filter, the peak errors were still very large.

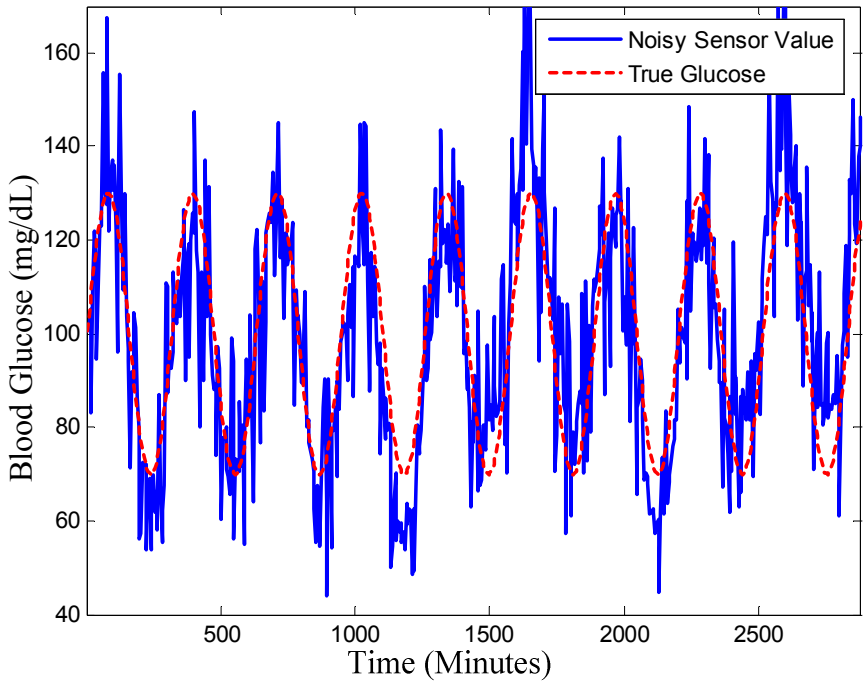

Figure 6-9: True Blood Glucose vs. Noisy Sensor Measurements Simulated using Sine

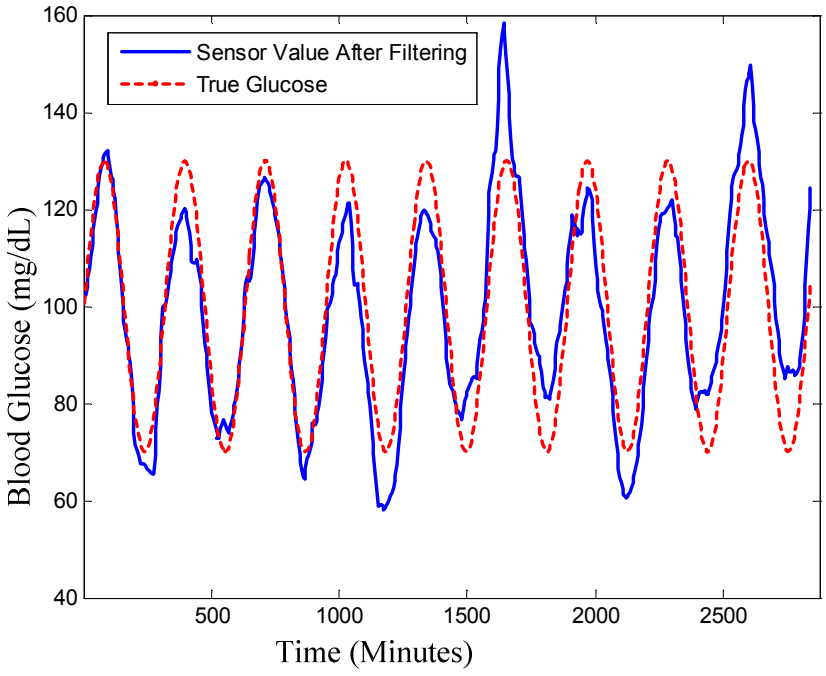

Figure 6-10: True Blood Glucose vs. Filtered Noisy Sensor Measurements Simulated using Sine

d) The Monte Carlo simulation approach for the full model was then carried out. The MAPE values of 20 simulations vary between 6.7% and 10.4%, and 13% of the simulations also produced results slightly better than the one obtained without adding the sensor noise. These latter cases possibly benefited from using the median filters due to its averaging nature and the random nature of the noise models.

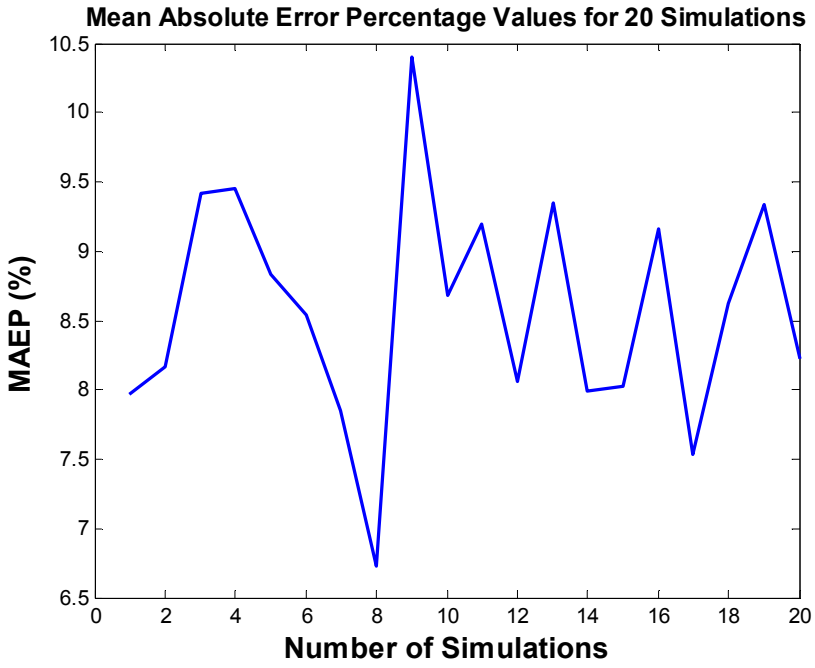

Figure 6-11: MAPE Values of the 20 Simulations

6.4 Comparison with Reported Kalman Filtering Results

The reported dual Kalman filtering results from Kurre Kinsey et al [M. Kurre-Kinsey 2006], which simulated constant and sinusoidal glucose cases, are shown in Figures 6-12 and 6-13. These results are slightly better than the ones produced from the filtering

algorithm presented and shown in Figures 6-7 and 6-8. However, the dual Kalman filter is very specific. Therefore, if any internal parameter is not tuned properly, the results might become terribly wrong. In contrast, the filter block designed is a general filtering approach, which doesn't require tuning any parameters to adapt to a particular glucose profile in order to perform well and therefore could be more generally applicable. In addition, the current CGMS noise is still undetermined. Therefore, a more general approach would be more attractive in the research.

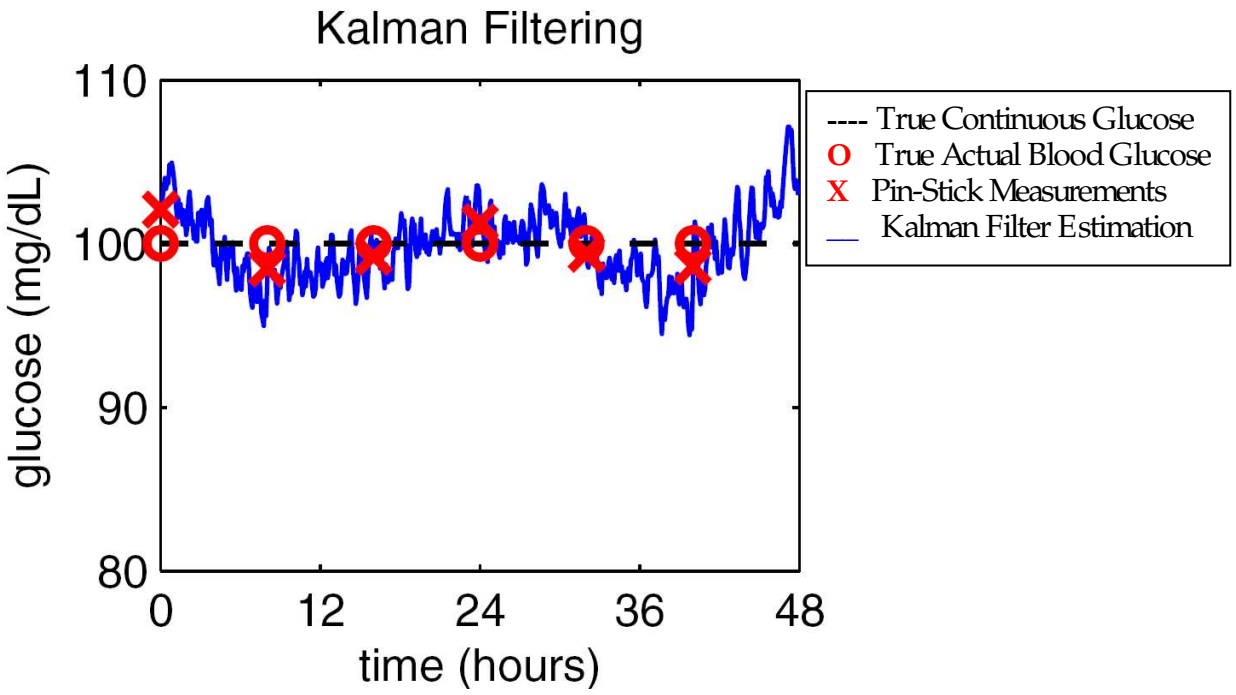

Figure 6-12: Reported Kalman Filter Results of a Constant Blood Glucose Profile

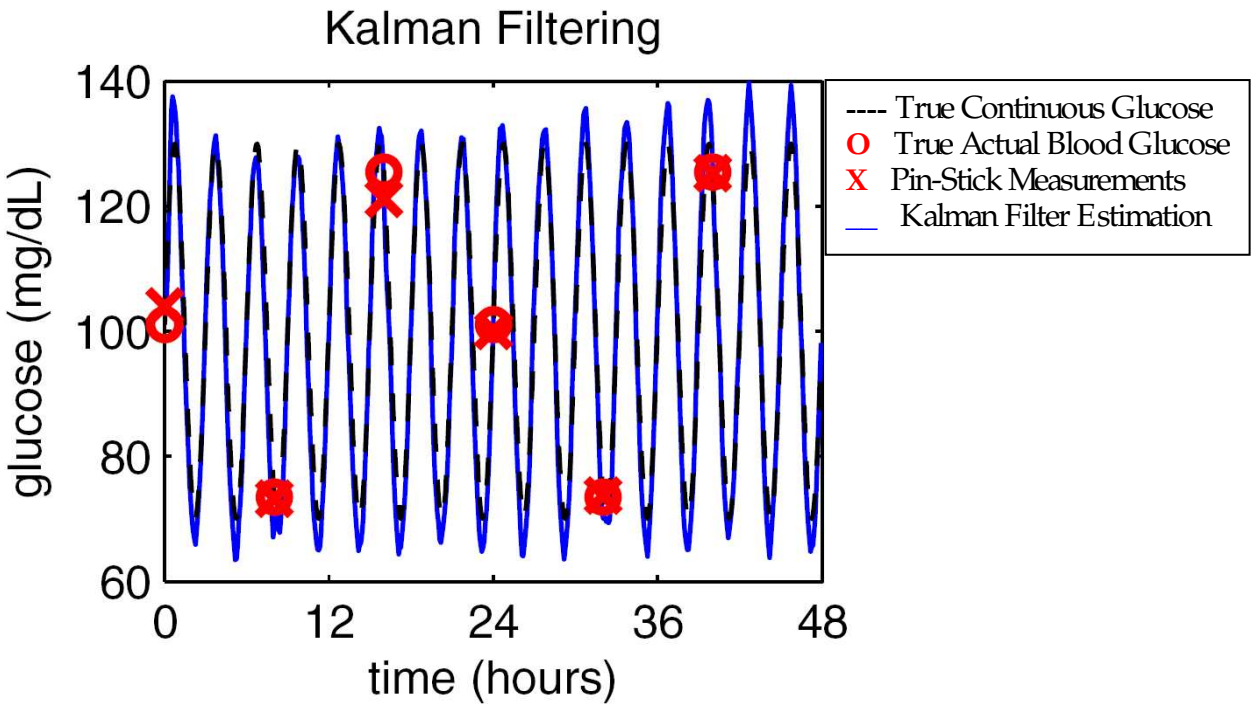

Figure 6-13: Reported Kalman Filter Results of a Sine Blood Glucose Profile

Conclusion

7.1 Summary

This research has successfully derived a better-qualified noise model for model-based simulation and analysis of CGM data. The filtering algorithm developed is general and therefore can be used for broader applications with any similar type of data stream. The outcome from drift calibration analysis also proposed useful calibration algorithms, which if optimised, can further increase the accuracy of CGM sensor measurements.

Overall, the author believes that the research presented is a significant step towards fully automated control of hyperglycaemia in critically ill patients.

7.2 New Noise Model Development

The normally distributed noise model is slightly conservative as correlation coefficients from its simulation are generally 8.6% lower than the reported value. A double Lapalace

noise model was derived in section 2.6.2 from analysing the normal distributed noise model and other possible noise models. The double Lapalace noise model increased the accuracy of correlation coefficients values by increasing the number of data points close to ±20% of signal level. This result is achieved by using a single Lapalace distribution for inliers, which has more than 78% noise within ±20%, and another separated smaller Lapalace distribution profile used for outliers, which pushes this distribution of noise levels towards ±30%. Overall, the simulation results from the double Lapalace noise model indicates that this newly developed model better matches the reported nature of CGMS noise and could be very useful in the model based simulation.

7.3 Filtering Algorithm Design

The filtering algorithm designed in this project comprises median filters and least square fitting. The trial results show a large amount noise truncation using the algorithm. The overall MAPE value for the simulations based on Retrospective and SPRINT patients is 1.8%, which is far lower than the value that standard testing kits produce. The algorithm also shows an important property. Specifically, it provides a universal approach to filtering this type of CGM error. Therefore, the algorithm has a broader capability, which matches the goal of “one size fits all”.

7.4 Drift Calibration Analysis

The ultimate calibration method developed also shows great promise for possible areas that can be tackled to further reduce all the noise levels in CGM data. The calibration approach is also simple and general. It involves a minimal amount of calibration and does not require an initial estimation of the glucose or any knowledge of the true glucose or sensor dynamics or drift dynamics. The simulation results obtained from this approach are also comparable to reported results from highly mathematical methods based on a specific invalidated sensor model.

Future Work

8.1 Introduction

Although the thesis presented has covered a wide range of modelling, literature reviews, new model creation, filtering algorithm development and data analysis, it has not been extensive enough to address a number of questions and objectives proposed. The ultimate objective of the research at the Bio-engineering group is to develop a medical control system that is capable at accurately predicting future blood glucose levels in clinical situations and ambulatory diabetic patients. More importantly, the system would thus be better able to control the glycemic levels. To achieve this goal, extensive modelling and testing is required, justifying the models and filtering algorithms, as well as control methods.

8.2 Noise Model Development

The simulation results using the newly developed noise model have shown a significant improvement in accurately capturing reported results, and when compared with a normal

distribution noise model. However, because the nature of true CGMS sensor noise has not been reported, the double Laplace is still unproven, although perhaps a better approximation. Therefore, there might be a better model that could better capture the nature of the CGMS sensor noise. In addition, clinical studies need to be carried out to validate the Laplace, or any other, noise model. The ultimate research goal would be to fully understand the behaviour of this noise and define a model to simulate that noise, but this step requires better clinical data.

8.3 Filtering Algorithm Development

The filtering algorithm developed from this research has already been able to produce a good result regardless of the noise model used. However, due to the time frame of the research, only a limited number of possible filtering approaches were investigated. There might be more optimal filtering methods available that could be applied to this noise problem.

The present filter algorithm used in this research combines two median filters, one of which requires data in the future 30 minutes or introduces a lag. Although this time delay is within a clinically acceptable level, it is still a long period for patients in ICU and makes control more difficult in highly dynamic cases. Thus, a goal of future research in this area would be to create filters with minimal time delay of less than 30 minutes.

8.4 Clinical Trials

Although the developed filtering algorithm has produced good results, they were only from simulation. There are not yet actual clinical trial results available, as the filter has just been designed. The next step would be physically adapting the filtering algorithm into a CGMS system and testing the results of this research. Actual clinical trials would provide significant insights into both the sensor noise and the filtering efficiency.

The calibration algorithm developed in the research is still very specific as it assumes procedures would happen in certain sequences. Future work for this research requires clinical testing and quantification of this drift beyond the limited data reported in the literature. Once available, this calibration issue can be more fully and properly addressed.

8.5 Contribution of the Research

By analysing the available statistical data, this research has successfully developed a new noise model. By comparing to the traditional normal distributed noise model, the simulation results of using such noise model are closer to the one described in the literature. Therefore it has the potential to be incorporated with proven system models to fully mimic the clinical CGMS measurements, based on which, true glucose values are able to be recovered.

By using the filtering algorithm from this research, the simulation results have indicated its solid performance on the data which is generated using the system model and different types of noise model. Since all the noise models used have a similar property that is randomly distributed, it indicates that the filtering algorithm is effective for processing the data coupled with random noise. This means that the filtering algorithm has the potential to be commercially applied to the clinical data for processing CGMS measurements and benefits many lives.

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