A Multiple Hypothesis Approach to Estimating Meal Times in Individuals with Type 1 Diabetes

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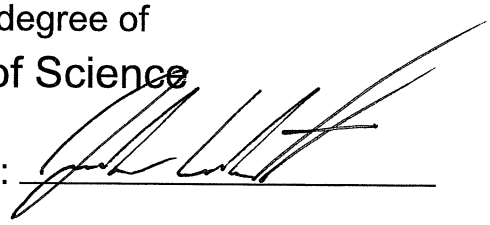
Author Signature: 

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"I never let my schooling get in the way of my education."

Mark Twain

UNIVERSITY OF VIRGINIA

Abstract

Department of Systems and Information Engineering

Master of Science

A Multiple Hypothesis Approach to Estimating Meal Times in Individuals with Type 1 Diabetes

by John CORBETT

In order to properly titrate insulin dosages for individuals with type 1 diabetes (T1D), it is essential to have accurate information regarding when they have eaten and taken insulin to reconcile those events with their blood glucose levels throughout the day. A verifiable record of when insulin was taken can be obtained by downloading data from the patient's insulin pump. While this record shows exactly when insulin was injected, it remains unclear when that person actually ate. Although information about consumed carbohydrates is often logged at the time of an insulin bolus, it has been shown that individuals with T1D often dose insulin long after they have eaten. This practice is not advised and has been linked to an increased risk of developing complications. This project demonstrates a method to estimate the times of meals using a multiple hypothesis approach. When an insulin dose is recorded multiple hypotheses are spawned describing different variations of when the meal in question occurred. As postprandial glucose values further inform the model, the posterior probability of the truth of each hypothesis is evaluated, and from these posterior probabilities an expected meal time is found. This technique could be used to help advise physicians about the mealtime insulin dosing behaviors of their patients and potentially influence changes in their treatment strategy.

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...and as always to my family and friends.

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AP	**A**rtificial **P**ancreas
BG	**B**lood **G**lucose
BMI	**B**ody **M**ass **I**ndex
Carb	**C**arbohydrate
CGM	**C**ontinuous **G**lucose **M**onitor
DAMON	**D**ata **A**uthenticity **MON**itoring
EGG	**E**lectro **G**lotto**G**raphy
EMG	**E**lectro **M**yo **G**raphy
GV2a	**G**lucose **V**ariability **2** Part **a**
HbA1c	**H**emaglobin **A1c**
MAE	**M**ean **A**bsolute **E**rror
MDI	**M**ultiple **D**aily **I**njections
ME	**M**ean **E**rror
PAIN	**PA**rameter **IN**variant
SE	**S**tandard **E**rror
SOGMM	**S**ubcutaneous **O**ral **G**lucose **M**inimal **M**odel
T1D	**T**ype **1** **D**iabetes

Dedicated to…

Nicole Perrot Foster
August 18, 1985 - December 17, 2010

Chapter 1

Motivation

1.1 Introduction

Type 1 diabetes (T1D) is a chronic disease caused by an autoimmune reaction that destroys the insulin producing beta cells in the pancreas. Insulin is a naturally produced hormone that helps regulate the amount of glucose in the blood (*Type 1 Diabetes | Basics | Diabetes | CDC*).

Although numbers vary, it is estimated that 1.25 million people in the United States have T1D (*Type 1 Diabetes Facts - JDRF*). 200,000 of whom are under the age of 20. Roughly 40,000 people are diagnosed with T1D each year. By the year 2050, it is expected that 5 million people in the U.S. will have T1D.

People with T1D monitor their BG values and take insulin to maintain acceptable glycemic levels. Traditionally, individuals with T1D were able to check BG levels through self-monitoring of blood glucose (SMBG), where the person pricks his or her finger, draws blood, and deposits it on an oxidizing strip in a glucometer. In recent years, continuous blood glucose monitors (CGMs) have become more accurate, available, and affordable which has significantly increased the amount of use within the U.S. These devices consist of a sensor placed beneath the skin in the interstitial fluid and a transmitter that sends BG information every 5 minutes to either a standalone receiver or a smart-phone. The frequency at which this information is collected allows the person using it to notice trends and potentially prevent low or high BG from occurring (Bode and Battelino, 2010).

In addition to monitoring glycemia, those with T1D take synthetic insulin to

maintain euglycemic levels. Insulin therapy is administered through either multiple daily injections (MDI) or with an insulin pump. In each case, the person with T1D takes insulin at meal times. These doses are called meal boluses. They also take supplemental insulin doses to correct for hyperglycemia, known as correction boluses. People using MDI inject long-acting insulin once or multiple times a day. Insulin pumps on the other hand do not use long-acting insulin and instead deliver micro-doses of insulin every few minutes, producing a basal insulin rate ("Continuous Subcutaneous Insulin Infusion at 25 Years" 2002).

Physical activity also factors largely into BG control for those with T1D. Exercise increases insulin sensitivity which can cause BG to significantly drop during periods of activity (Zisser et al., 2011). Conversely, some forms of exercise such as anaerobic exercise or intense aerobic exercise may actually cause BG to increase. This is due to stress hormones signaling for stored glucose to be released into the blood stream. In essence, physical activity and exercise have a significant effect on BG and are often a source of uncertainty for those with T1D.

Less than one third of individuals with T1D are achieving target BG control levels (Wood et al., 2013). Complication of uncontrolled BG levels are severe. Extremely low BG can cause short and long-term complications such as myocardial infarction, neurocognitive dysfunction, cerebrovascular disease, retinal cell death, and loss of vision (Kalra et al., 2013). This may lead the individual to be severely impaired and may even cause death.

Prolonged hyperglycemia also has dangerous short and long-term effects. Complications that cause micro-vascular damage may lead to organ failure, loss of limb, and even death (Kalra et al., 2013). The complications of hypo and hyperglycemia can largely be avoided through good management practices (Group, Diabetes Interventions, and Research, 2000).

In order to reduce the burden of managing as well as mitigate complications, researchers have been developing methods to better treat diabetes using data. These technologies fall under two main categories; open and closed-loop. Closed-loop technologies implement a feedback system where meal, insulin, and BG information is regularly collected and a controller decides a strategy for dosing insulin based on

BG predictions. These systems are often referred to as artificial pancreas (AP) systems. Open-loop technologies encompass a broader range of new developments. These innovations leverage data to analyze risk, optimize dosing parameters, calculate insulin doses in a more sophisticated manor, and provide decision support to the patient. There are advantages and disadvantages to both approaches, but a commonality between the two is that they use data and the accuracy and validity of that data is paramount in the decision-making process.

1.2 Problem Statement

1.2.1 Challenges with Self-Reported Type 1 Diabetes Data

Self-reported data is still a cornerstone of the latest technology used to manage T1D. Because there are no sensors readily available to measure when someone is eating and how much, it is up to the user of the system to acknowledge when he or she has eaten. Additionally, insulin records for those without insulin pumps and who use multiple daily injections (MDI), still a majority of the T1D population, are recorded manually if at all. This may change when connected pens become more prolific in the United States. Self-reported information, especially of meals, can be very subjective.

The amount of insulin required for a person living with T1D is periodically shifting. There are long and short-term factors that cause insulin sensitivity to fluctuate. Because of this, people with T1D meet with their endocrinologists on a frequent basis to adjust their various basal and mealtime insulin doses. In order to effectively titrate insulin, physicians use information about the number of grams of carbohydrates in meals and insulin injection amounts to reconcile BG values recorded throughout the day. Doctors ask patients keep a record of their carbohydrate and insulin amounts leading up to their visits in order to provide information that may help them appropriately change treatment.

For those with insulin pumps, the information about when they dose insulin and how much is stored automatically, which allows pump users to have a more accurate record of insulin than those using MDI. When a person with an insulin pump eats, they usually enter a SMBG done through a finger prick or a CGM value and the amount of carbohydrates in their meal into a bolus calculator. This program then

calculates the amount of insulin needed to correct their current glucose level and account for the consumed carbs. Lastly, the user is asked to adjust the bolus as they deem necessary and confirm the delivery. In addition to mealtime boluses, insulin is also delivered in small doses throughout the day on a schedule and the user is also capable of giving insulin doses at times when they are not eating to correct for hyperglycemia. This gives clinicians the opportunity to download a verbatim record of all the delivered insulin for a particular individual from their insulin pump.

1.2.2 Dissonance Between Meals and Insulin Dosing

Whereas the timing and amounts of insulin injections are known with a great deal of certainty, what is not is when food was actually consumed. It is possible and oftentimes likely that the user of the pump ate and then gave themselves a corresponding bolus sometime afterwards. To the clinicians and for purposes of analysis, it is impossible to tell when these meals are actually occurring.

This occurs frequently and is usually a consistent behavioral trend. A study done to gauge the prevalence of pre versus post-meal bolusing behavior showed that 32% of the 21,533 participants surveyed regularly bolused after or during meals (Peters et al., 2017). This practice is not recommended and those who gave insulin after meals reported higher hemoglobin A1c (HbA1c) values. HbA1c is a measure of average BG. Higher values can be predictive of developing diabetes related complications such as damage to the small blood vessels in the eyes, organs, and extremities (Lind et al., 2009).

Although this practice is neither recommended nor ideal, it does happen and there are many real-life examples of why this might be the case. Anyone with small children knows that just because you make them an amount of food does not mean that they will eat it. Dosing insulin in this scenario could be very dangerous if the child does not his or her full meal. This does not just apply to despondent children, adults are just as guilty of not taking insulin in sync with when they eat.

Imagine a situation where you are at a birthday party. It's your birthday and for dinner you eat 2 slices of pizza, dutifully you give yourself a bolus before you eat. Now it's time for cake. Everyone sings, you blow out the candles, and someone handing out cake gives you a piece. As you are walking to your table, grandma

approaches. She begins a long story about what you were like as a little kid and as you listen you start taking bites of cake. The story ends, you hug grandma, and then sit down. At this moment, you realize that you forgot to bolus before you ate and your BG is already sharply rising. Clinical guidelines are in place for a reason, but sometimes life gets in the way. It's not always grandma, but it's is always something.

1.3 Objectives

The purpose of this work is to begin an exploration into how to characterize insulin dosing behavior. The aim of this is to provide tools to clinicians so they can determine if their patients are being adherent to clinical recommendations and address a problem if there is one. Say for instance a person regularly forgets to bolus until 20 minutes after he or she eats. This tool would make that apparent to their doctor who might be able to offer interventional help, either by demonstrating to the patient how important it is to take insulin on time or to tailor treatment to this ingrained behavioral inclination.

The first step in the development of algorithmic tools like those developed in this thesis. Past methods of meal detection were only able to establish that a meal occurred, but not when or how many carbs it consisted of. This work proposes a framework for taking unverified data streams and making meal time estimates using bolus times as a starting off point. The multiple hypothesis framework delivers statistical insight into how events may have occurred in terms of their timing and magnitude. Other attempts have focused strictly on detection and have not proposed a way to amend the record of events recorded by the patient based on a probabilistic representation of potential events.

The major objective of this exploration is to define a methodology to estimate when meals have occurred based on pump records. This could be implemented to make statements about the dissonance between when food was ingested and when insulin was subsequently taken to account for it. It is often the case that people with T1D, particularly children, will inject insulin long after meals leading to higher HbA1c levels (Peters et al., 2017). This practice can cause postprandial hyperglycemia and disturb the glycemic balance potentially causing more hyper or

hypoglycemic events if insulin and meals are not aligned properly (Cobry et al., 2010). Because it is not apparent from the meal and insulin record alone, a method needs to be developed to highlight instances where these events may not happen concurrently.

1.4 Contributions

The contributions of this work are as follows:

1. A methodology for calculating and comparing the posterior probability of multiple hypotheses regarding meal timing
2. A procedure for estimating meal times with regards to when insulin was dosed
3. Demonstration of this method on both real and simulated data
4. Insight into how this tool could be used in practice and the implications it might have on individuals with T1D

Chapter 2

Literature Review

2.1 Meal Detection

Meal detection has long been a focus of the diabetes technology community. This body of work serves to create solutions to a number of diabetes management problems related to meal time insulin dosing. Many of the papers in this field aim to incorporate meal detection into a closed-loop insulin dosing system.

The purpose of meal detection is to eliminate the need for patients to acknowledge meals manually. In most, if not all systems, insulin is taken at the time of meals. In order to initiate this process, the user of the system estimates the carbohydrate content of the meal and then doses insulin accordingly. Carbohydrate content is usually measured in grams of carbohydrates. This is sometimes referred to as "carb counting." For those with insulin pumps, this information is entered into a bolus calculator that, based on carb ratios and correction factors, calculates an appropriate amount of insulin to deliver. There are many reasons why a user might not want to do this. It is a burdensome process, especially if someone eats many small meals throughout the day and also it presents an opportunity for a lapse in focus to create a significant problem. If someone forgets to take insulin at the time of a meal on accident, BG levels following the meal can reach dangerously high levels (Randløv and Poulsen, 2008). If there was a way to detect meals automatically as well as determine when that person ate and how much, there would be a huge reduction in the amount of work required of people with T1D to manage their disease and also the potential of eliminating forgotten insulin injections.

2.1.1 CGM-only Meal Detection

Seminal work using CGM was done by Dassau and colleagues (Dassau et al., 2008), where meals were detected based on a voting algorithm with rules defined by different evaluations of glucose rate of change.

The detection algorithm works as follows:

1. The most recent CGM reading is fed into the algorithm. The monitor is able to read BG every 5 minutes, so the algorithm is iterated on a 5-minute basis. The CGM readings are processed in parallel by a rate of change component and a Kalman filter estimation algorithm.

2. A rate of change calculation is conducted on the CGM signal using 4 different methods 1.) backward difference rate of change from the raw signal 2.) backward difference rate of change from the Kalman filtered glucose estimation 3.) Kalman Filter estimation of glucose and the rate of change 4.) the Kalman estimate of the rate of change of the rate of change of BG.

3. Each of these rules are evaluated against their respective thresholds.

4. Voting algorithm is then implemented and a meal is only detected if two of three rules or three of four rules are triggered within the same 5-minute interval.

5. The controller receives a meal flag if the voting algorithms determines that there is significant evidence to detect a meal and the system acknowledges the meal.

The Glucose Rate of Increase (GRID) method was able to detect meals, where the associated bolus was withheld for an hour, with a great deal of certainty. For this specific instance where glucose rose rapidly following a meal, GRID was able to detect greater than 90% of meals within 30 minutes of the onset of eating.

This method was refined in a later work by Harvey et al. (Harvey et al., 2014) in 2014. The GRID+ method eliminated the voting algorithm and used only a filtered glucose rate of change to detect meals. This new formulation of the algorithm was able to detect 87.5% of meals in a training data set of real and virtual patients where

insulin was given at the time of the meal. The mean time to detection using GRID+ was 42 minutes.

2.1.2 Model-based Meal Detection

Where some meal detection algorithms operate on knowledge of CGM values alone, some others have attempted to use insulin-glucose models to determine when and if meals occurred using insulin and meal records as well as CGM values.

In a more recent work, Turksoy used CGM measurements as well as a formulation of the Bergman minimal model with the addition of an unscented Kalman Filter for state estimation (Turksoy et al., 2016). From this the estimated rate of appearance of glucose is used for meal detection. This algorithm was evaluated on 9 subjects and the results indicate that the method works with high accuracy. On average glucose only changed by 16 ($\pm$9.42) mg/dL between the meal and the time of detection for 61 detected meals and snacks. This was developed for the purpose of integrating it into an AP controller to dose insulin for meals automatically.

Weimer has proposed a method of detecting meals that is agnostic to certain patient specific parameters usually incorporated in other model schemes (Weimer et al., 2016). The physiological parameter-invariant (PAIN) detector is based on a minimal insulin-glucose model and is by design not subject to some of the patient-specific customization required in other models. This algorithm was able to achieve a near constant false alarm rate across all subjects and was compared to three existing meal detection algorithms using a clinical T1D data set.

The PAIN-based detector achieved 86.9% sensitivity and two false alarms on average per day. It also outperformed all three of the other algorithms across all false alarm rates. This method has the unique characteristic of maintaining low variance in detection and false alarms for all subjects in the data set without patient specific tuning or training.

2.1.3 Meal Detection with Non-Glucose Sensors

Many methods other than those involving measurements of BG or insulin-glucose models have been used to detect when people eat across a plethora of domains.

Some of these methods were created with the aim of improving or understanding diabetes management, but others were generalized to contexts outside of T1D. Instead of an approach strictly based on sensor streams generally related to T1D, many methodologies use other passive sensing techniques to glean information about people's eating habits. The following works focus solely on wearable food intake monitoring technologies that use passive sensors.

The Automatic Approach There are a number of methods that have been attempted that are classified under the epithet of Automatic Approaches. These include attempts to monitor food intake using force sensors in either a plate or as part of a table. The so-called "Diet-Aware Dining Table" achieved 80% accuracy in determining the amount of food transferred from each part of the table and the amount consumed by each person seated at it (Chang et al., 2006). A smart surface was developed that rests on top of a dining table and was able to detect eating movements, but could not classify what type of food was being shift around or how much (Zhou et al., 2015).

Others have tried to create methods for detecting when people eat by using surveillance-video. These methods employ a stationary camera that observes individuals and classifies their behavior using image processing. A method by Cadavid et al. used an active appearance model system to detect chewing motions when the camera was able to collect images of people's faces (Cadavid, Abdel-Mottaleb, and Helal, 2012).

A third automatic approach implements Doppler sensing to detect meals. These methods use microwave Doppler motion sensors to determine if an individual is eating or not. Tanigawa et al. explored the use of the Doppler effect caused by mastication to detect if someone was eating (Tanigawa et al., 2008). This was determined from the relationship between jaw movement, Doppler frequency and moving speed.

The Wearable-Based Approach Since it has been thoroughly established that manual meal records are not accurate and clunky stationary devices are required for most automatic approaches, wearables provide the unique benefit of being able to collect information on a semi-continuous basis and also monitor their users in a minimally

invasive fashion (Burke et al., 2005), (Westerterp and Goris, 2002). There are many different sensor types that have been used to try to detect meals such as, acoustic sensors, visual sensors, inertia sensors, EMG/EGG-based sensors, Piezoelectric sensors, and sensors that combine multiple sources of information.

The acoustic methods characterize eating by the sounds that people make when they chew or swallow. Saznov et al. used support vector machines to differentiate eating specific sounds from ambient noise (Sazonov et al., 2010).

The visual approach to eating detection, uses image processing to recognize food and people's motions related to eating. In an on-going work, initially conceptualized by Sun et al., the eButton is button sized camera that can be worn by an individual and is capable of determining the amount of food in a portion, what it is, and then relate it to nutritional values stored in the USDA Food and Nutrient Database (Sun et al., 2014). This work has been further improved upon by a number of other researchers (Zhu et al., 2010), (Zhu et al., 2011), (Fengqing Zhu et al., 2010), (Sun et al., 2014), (Chen et al., 2013), (Wenyan Jia et al., 2012).

The inertial approach uses the motion of the eating process to detect meals. Gyroscopes have been used to detect wrist motion that is indicative of eating. The most renowned work using this method was initially created and improved upon by Dong et al. to track wrist motion when the user takes a bite and was able to detect meals with 80% accuracy under laboratory conditions for certain foods ("Detecting Periods of Eating During Free-Living by Tracking Wrist Motion"). Additional studies have been done where accelerometers were used embedded in a smart watch or band to detect eating activities (Thomaz, Essa, and Abowd, 2015), (Mendi et al., 2013).

The physiological approach employs electroglottography (EEG) and electromyography (EMG) sensors to determine whether or not a person is eating. EEG senses motion-induced impedance changes between two electrodes placed across the larynx. By using an EEG sensor Farooq was able to detect 89.7% of meal events in females and 90.3% in males (Farooq, Fontana, and Sazonov, 2014).

EMG sensors have been widely used to monitor food intake. This sensor is efficient in detecting both chewing and swallowing. Its primary function is to assess bite size and hardness of food being eaten. Woda et al, used EMG to determine the

effect of food hardness, bite size, chewing cycles and sequence duration for various foods and subject behaviors (WODA, MISHELLANY, and PEYRON, 2006), (Woda et al., 2006).

Other researchers have delved into whether or not piezoelectric materials are a viable way to detect food consumption. Farooq and Sazonoz utilized piezoelectric film sensors to identify jaw movements during chewing (Farooq and Sazonov, 2016). By placing two sensors below one ear they were able to detect chewing with and error rate of 8.09%.

Kalantarian et al., used piezoelectric materials to detect movement in the throat during swallowing (Kalantarian, Alshurafa, and Sarrafzadeh, 2014). The authors of this work embedded piezoelectric materials in a necklace to detect changes in the movement of the throat of a person. This method was able to recognize swallowing with 86% accuracy when it was tested on 10 subjects in a laboratory setting.

Other food intake monitoring technologies employ a combination of sensors to detect eating. These methods are known as fusion eating monitoring methods. An example of this is a combination acoustic-visual approach. Liu et al. described a method for using both a camera and a microphone to detect eating (Liu et al., 2012). This system utilizes a microphone to detect chewing. Then a camera is triggered to that collect video in order to classify the type and amount of food being consumed.

Sen et al. developed a fusion method that used both visual and inertial sensors to monitor food intake (Sen et al., 2015). This is similar to the Liu method in that it uses one sensor to trigger a camera that can provide more detailed information about eating. The accelerometer and gyroscope built into a smart-watch trigger a camera when eating occurs and then information is relayed to a server via a smart phone.

Fontana et al. proposed a method called the Automatic Ingestion Monitor that uses piezoelectric, accelerometer, and proximity sensors to monitor food intake (Fontana, Farooq, and Sazonov, 2014). By using this sensor set, their algorithm detects eating by using a combination of signals that collect information regarding jaw movement, body motion, and hand gestures. This method was 89.8% accurate in a laboratory setting when it was tested on 12 subjects.

2.1.4 Multiple Hypothesis Methods

The foundation of the work described in this thesis comes from a paper written by Patek (Patek, 2010). In this paper, the author describes a linear, time-invariant system subject to non-zero mean disturbance processes. These disturbance processes are described with a finite set of hypotheses that are differentiated from one another by the magnitude and timing of these disturbance processes. Zero-mean Gaussian noise and sensor noise also affects the measurement of the output of the system.

By decomposing the state estimation problem with respect to the spawned hypotheses, optimal filtering equations and Bayesian update rules used to find the posterior probabilities of each hypothesis. From this Bayesian method the hypotheses can be compared to one another and hypothesis that most aptly determines what is affecting the system. This process can also be used to determine the stage-by-stage optimal open-loop feedback control action.

The methodology described in this work provided the framework for evaluating multiple hypotheses against one another. Each hypothesis holds within it a different sequence of events and through Bayesian methods the posterior probabilities of each are found. Those probabilities are then compared to each other. The residual difference between the known sequence of events and what is described in each hypothesis creates a profile of the disturbances that caused the response of the system as a function of time.

The Patek paper presents how this could be applied to any linear time-invariant system subjected to this particular type of disturbances. For this application the linear system is the Bergman Subcutaneous Oral Glucose Minimal Model and the disturbance processes are the insulin and ingested glucose signals that are used as inputs for this model ("Quantitative estimation of insulin sensitivity").

In work closely related to this proposal, Cameron developed a method for detecting meals using multiple hypotheses (Cameron, Niemeyer, and Buckingham, 2009). In this work, Cameron evaluated the probability of no meal happening at a given time and compared that to the hypothesis that a meal had occurred. As time progresses, the model becomes more informed and the probability of each hypothesis updated. If a meal is detected, actions are taken to deliver insulin automatically in a

simulated closed-loop system. Evaluations of this technique reduced post-meal BG from 137 to 132 mg/dL over 1.5 without any increase in incidences of hypoglycemia.

2.2 Prior Work Using Multiple Hypotheses

In previous work, a multiple hypothesis method was implemented to assess the authenticity of events in a data stream. Figure 2.1 shows 12 hours of BG and meal data for a clinical trial participant. The posterior probability calculation for two hypotheses, that a meal occurred as recorded and that no meal occurred at that time, are displayed in the center subplot. When no meal has been announced for at least 6 hours this probability is set to a prior value, but once a meal is announced the algorithm begins to evaluate the probability of each hypothesis. If the probability of no meal occurring reaches a threshold of 0.9, then a rule is violated triggering a detection of the fake meal. A Boolean evaluation of this rule is shown in the bottom subplot.

It can be seen in the plot that a "spoofed" meal event was added to the data log at 3 a.m. Following the fake meal, the algorithm begins to evaluate the probability of a meal or no meal happening at that time. Shortly after 3 a.m., the probability of the no meal hypothesis exceeds the allowable threshold and the rule in place is violated triggering a detection of the fake meal. At 7:45 a.m. the subject eats breakfast and the algorithm correctly classifies the meal as having actually occurred.

In this method whether or not a meal happened is being assessed, a similar method was used in the previously described O.L.F.C. paper by Patek to evaluate the timing of recorded meals (Patek, 2010). The foundational knowledge of the multiple hypothesis evaluation processes is already understood from prior investigation, which provided an advantage in developing this methodology. Additionally, the code base for multi-hypothesis evaluation existed in large and was expanded on for the purpose of this thesis.

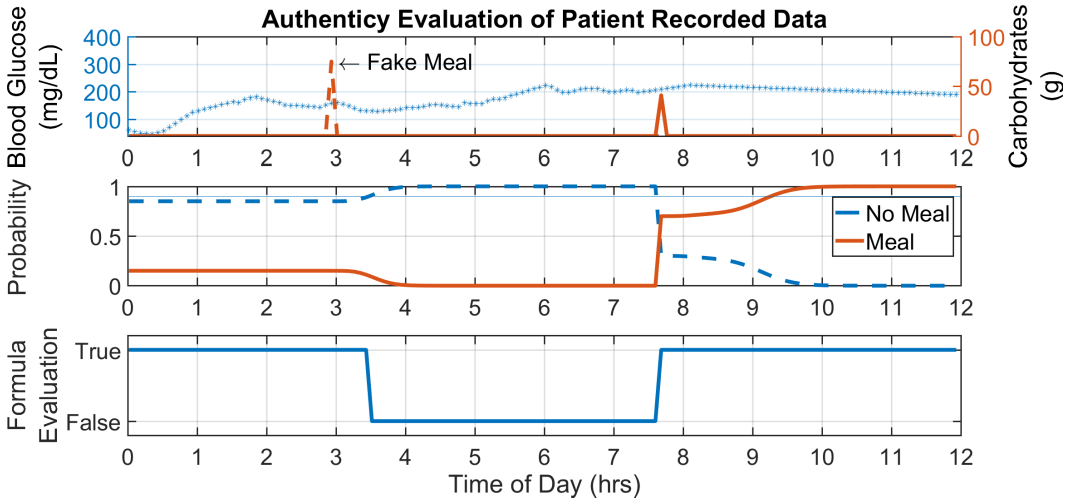

FIGURE 2.1: Multiple hypothesis Classifier for Real and Fake Meal Events.

2.3 Literature Reflection

All of the works described previously in this section describe methods where eating or meals are detected. Some involve passive sensing techniques with wearable sensors and other use physiological signals such as BG and signal processing techniques to determine when people are eating. Some of these methods are distinct from this work, because they require the additional use of hardware, others just determine that a meal happened without giving more information about it that might be necessary for treatment purposes. Additionally, many of these methods if not all do not pinpoint the exact moment at which the meal occurred. The goal of the method proposed in this work is to precisely estimate meal times based on data reported by the patient without additional hardware or user input.

Chapter 3

Approach

3.1 Data

Actual patient data collected in a clinical setting as well as simulated data engineered to recreate certain events was used to test this meal time estimation method. Both kinds of data were used so that a multitude of situations could be tried out within the context of the system. These datasets were used to evaluate the performance of this methodology when meals and boluses occurred simultaneously and when they were misaligned.

3.1.1 Clinical Data

Any data related to meal and insulin events collected outside of a strictly controlled, clinical environment is likely to be flawed. For this reason, the data used to evaluate the proposed method is actual, patient data, but was collected during part A of the Glucose Variability study (GV2a) at UVA where participants acted freely except their meal and insulin information was recorded meticulously under the supervision of the study team. This study was funded through the R01 DK051562 grant awarded to UVA from the NIH and has been approved by the IRB (#18348). This data includes physiological measures such as height and body weight which affect parameters in the insulin-glucose model, as well as diabetes management related information such as delivered insulin, meals, basal profiles, CGM measurements, SMBG measurements, carbohydrate to insulin ratios, and BG correction factors. Because this was collected in the Clinical Research Unit of the UVA Hospital under a strict protocol, it is know that meals and insulin happened exactly when they were recorded.

TABLE 3.1: GV2a study demographics.

	Age	Gender	Race	Height	Weight	BMI	HbA1c	Control Period
40101	26	M	W	182.2	89.9	27.1	7	1/28-30/16
40103	34	F	W	155.2	53.3	22.1	8.4	10/16-18/15
40105	53	F	W	170.1	88.1	30.4	7.4	12/11-13/15
40106	33	M	W	185.2	106.9	31.2	7.1	10/20-22/15
40108	50	F	W	163	70.3	26.5	9.7	12/15-17/15
40109	26	F	W	159.3	84.8	33.4	7.6	12/15-17/15
40110	39	F	W	173	74.2	24.8	7.1	11/17-19/15
40112	54	F	W	170	57.1	19.8	7.4	11/20-22/15
40115	45	F	W	162	76.7	29.2	8.3	12/18-20/15
40122	57	F	W	158	61.8	24.8	7.3	2/19-21/16
40123	33	M	W	183.1	97	28.9	7.5	1/28-30/16

This provides the opportunity to use it as a testbed, which is unique considering many of the recent trials have been at home and meal times cannot be verified.

The admission portion of the GV2a study was conducted in Fall of 2015 through Winter of 2016 at the UVA Hospital. During the two day admission, participants were monitored by the study team as they acted freely and managed their T1D as they would in their everyday lives. A subset of 11 patients were selected from the GV2a data, because they were pump users and had complete data for the admission. On average the participants were 41 years old. 8 of the participants were female and 3 male. All participants were Caucasian. Average height, weight, and BMI were 169 cm, 78 kg, and 27 kg/m^2 respectively. The participants had an HbA1c of 7.7 on average. More details about the participant's demographics are shown in Table 3.1.

3.1.2 Simulated Data

In order to recreate situations where meals and insulin doses were misaligned, simulated data was created using the FDA-accepted UVA-Padova Simulator. In this data, 100 adult subjects were simulated over the course of a day where they ate breakfast at 6:00 a.m., lunch at 12:00 p.m., and dinner at 6:00 p.m. Each meal was proportional to their body weight. At breakfast each subject ate 0.5 grams of carbs per kilogram of body weight, at lunch it was 1 g/kg, and for dinner they had 0.8 g/kg. Insulin doses were randomly distributed for each meal from an hour preceding when the person ate until an hour after. It was necessary to create these events insilico, because even

though it is highly likely insulin is not always taken at meal times it is difficult to find examples of this due to the method that the data normally collected. The clinical data set used was selected becasue meal times are verified and as a result of the conditions it was collected in there are few instances where meal time insulin doses were taken a long time before or after a participant ate. For this particular reason, these events were created artificial in the simulation data.

3.2 Algorithm Description

The aim of this work is to characterize the timing of meals using a multiple hypothesis approach. The following sections describe the methodology of how the hypotheses were structured, what they described, the model in which they were fed into, how the posterior probability of each was calculated, how an estimated meal time was found from those posterior probability values, and how the results were evaluated.

3.2.1 Preprocessing

For both the clinical and simulated data, a number of preprocessing techniques were used to clean and curate the data. Raw CGM signals often have large unexplained, jumps in the measured glucose values that are not physiologically possible and are caused by signal interference. Because this is a known issue with the raw signal, the CGM measurements were smoothed and this transformed signal was used in the algorithm. Additionally if there were gaps in the CGM readings greater than 5 minutes, the missing entries were interpolated. Because the actual data was collected in a controlled environment and technicians were on hand to prevent issues such as signal loss between receiver and transmitter, these gaps are small or nonexistent in the clinical data. Most CGM readings are collected on a 5-minute basis and because of this all events were snapped to the closest 5-minute interval. Although many of these issues were not present in the simulated data the same process was done on both data sets.

3.2.2 Hypothesis Formulation

At each meal event, a number of hypotheses representing different descriptions of how the meal may have occurred were spawned. Initially, the time of the insulin bolus was considered to be the time of the meal. This could be thought as the null hypothesis in this context. The amount carbs in the meal was said to be what was recorded in the original record. Keeping the bolus at the time that it was known to have been taken, the meal record was altered for each hypothesis. 25 different versions of the meal record were written. Each had a different time for when the meal occurred with the time of the insulin dose held constant. These hypothesized meals ranged from one hour before the insulin dose was taken to an hour after, each one altered by an increment 5 minutes. The times of these hypotheses were -60, -55, -50, -45, -35, -30, -25, -20, -15, -10, -5, 0, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, and 60 minutes all relative to the time of the insulin injection. The initial probability of each hypothesis was the reciprocal of the number of hypotheses spawned, in this case 1/25.

Figure 3.1, shows how the hypotheses were structured. This example only shows 9 hypotheses with hypothesized meal times ranging from 60 minutes before the meal to 60 minutes after. Each of the hypothesis' meal time differed from the others by 15 minutes. This illustration only used 9 hypotheses versus the normal 25 to make the structure clearer and so all of the traces could distinctly be shown in one plot.

In the top subplot, the probability of each hypothesis is shown as a function of time. Below that, there is a graph of the CGM trace during this period of time. In the plot that is second to the bottom, the structure of the hypothesis set is shown. Each peak represents a different hypothesis' meal time. The apex of these peaks are at the time that this hypothesized meal was recorded in the log. The magnitude of these peaks correspond to the meal amount in grams of carbohydrates. This demonstrates that each hypothesis, maintained the original meal size, but offset the time of that meal from when the bolus was administered. The bottom subplot shows the amount of insulin given at the time of the meal and when that dose occurred. For each of the hypotheses, the insulin record was kept the same. The amount of insulin and timing of the meal time bolus was consistent for each due to the fact that it is known to be

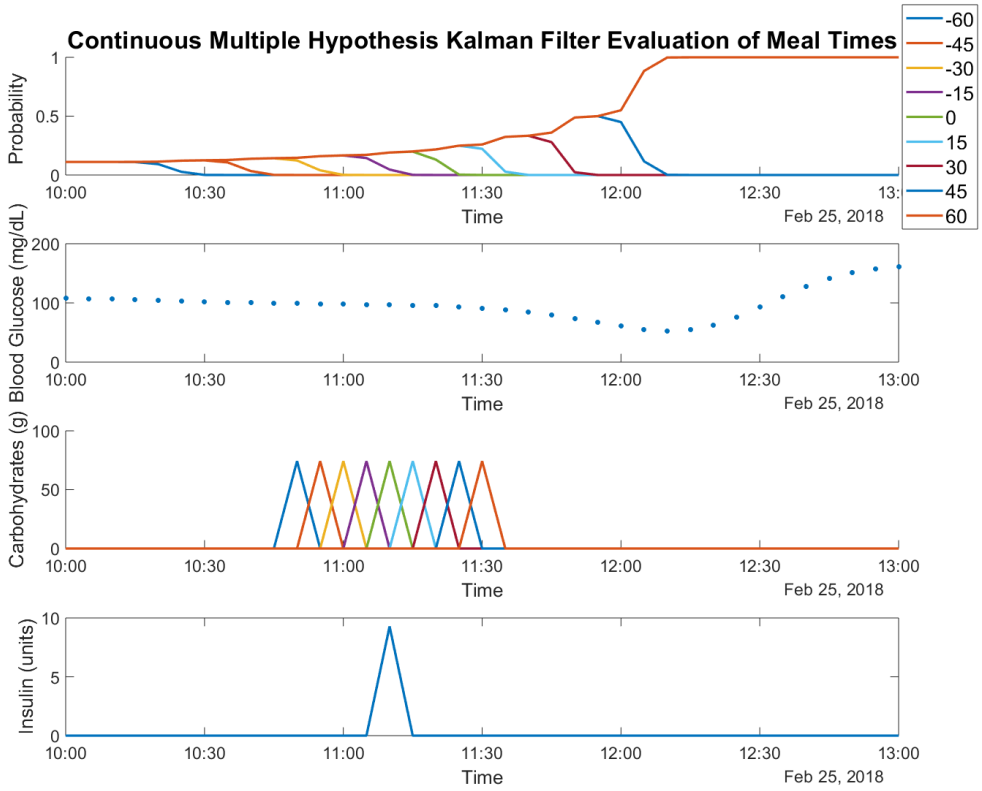

FIGURE 3.1: Hypothesis probabilities, CGM trace, meal timing for each hypothesis, and time of the actual bolus.

true based on pump records.

3.2.3 Model Description

For this analysis, there were 25 competing accounts of what may have happened. In each the CGM values, insulin record, and ingested carbohydrate amounts remained the same, only the time at which those carbs were consumed differentiated the hypotheses. These 25 hypothesized scenarios were the inputs that were fed into the physiological model used to explain the insulin-glucose dynamic for individuals with T1D. In this evaluation, the Subcutaneous Oral Glucose Minimal Model was used. The core of this model was initially developed by Bergman et al. in the late 1970's ("Quantitative estimation of insulin sensitivity"). Patek and colleagues added the oral and subcutaneous compartments, so ingested carbohydrates and injected insulin could be used as inputs ("Empirical Representation of Blood Glucose Variability in a Compartmental Model *"). This model describes the insulin-glucose relationship as a linear time-invariant system where,

$$x(k+1) = Ax(k) + Bu(k) + Gd(k) + Hw(k)$$
$$k = 0, 1, ..., N-1$$

describes the state. Insulin injections $u(k)$, relative to the basal rate of the particular individual, serve as an input and disturbances $d(k)$ represent meal events recorded that could explain the response of BG over time. These noisy measurements representing BG, subject to zero-mean white Gaussian process, can be represented discreetly as,

$$y(k) = Cx(k) + v(k)$$

Figure 3.2 is a visual interpretation of the SOGMM, which is a type of compartmental model. The inputs of the model, shown entering the compartments from the left and top of the diagram are insulin in either short or long-acting form and carbs ingested either at meals or as a treatment for hypoglycemia. It should be noted that because the subjects used in the aforementioned data set are either actual or virtual pump users, long-acting insulin was not use and instead a constant basal dose of short-term insulin was administered. This input enters the model through the

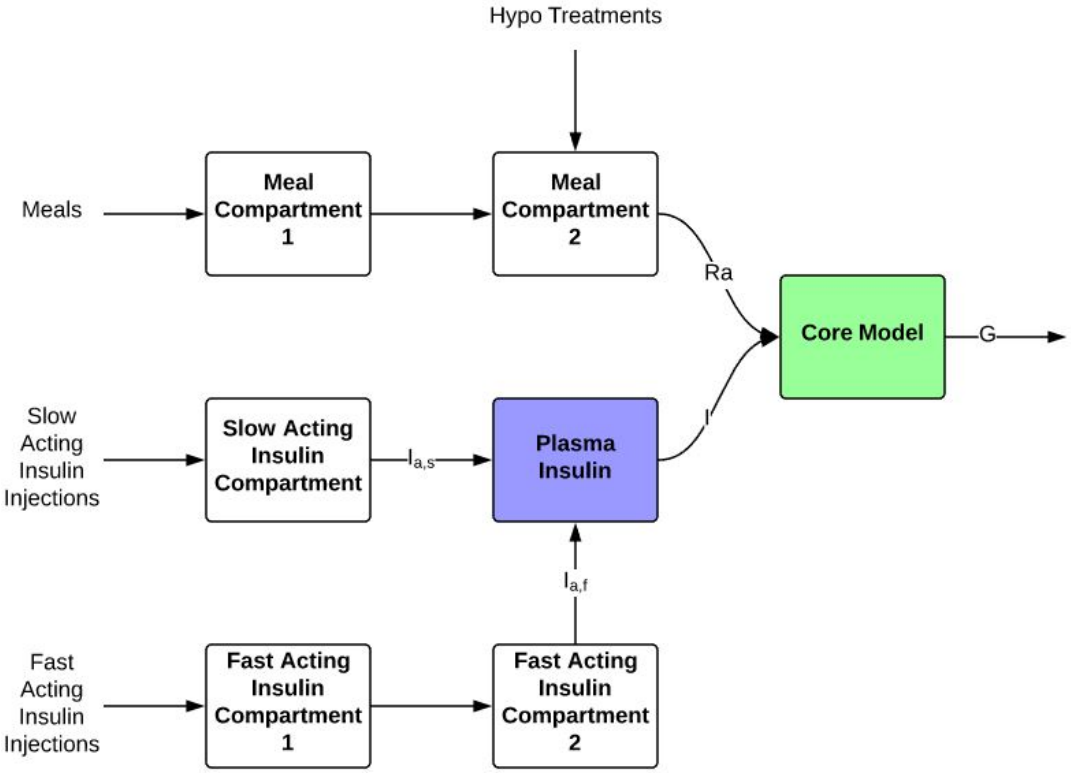

FIGURE 3.2: Visual representation of Subcutaneous Oral Glucose Minimal Model.

fast-acting insulin compartment just as correction and meal boluses would. Additionally, hypoglycemia treatments are analogously represented as meal time carbs. These inputs take the form of insulin or glucose and enter the core compartment through their respective intermediary compartments. The state of the system, as well as current expected BG are described mathematically in the core compartment of the model. This was previously described by the state space equations listed above. The output of the model is an anticipated value for BG at each discrete time step.

3.2.4 Posterior Probability Calculation

At each step in time, the optimal least-squared estimate of glucose was calculated using a discrete-time Kalman filter for each hypothesis. This prediction was then compared to the measured glucose and the posterior probability of each hypothesis was calculated using a formulation of Bayes' Rule. As the model predictions are evaluated, the hypothesis with the highest probability should be associated with the true description of the events that occurred.

The following method is largely described in Patek's paper, Open-Loop Feedback Control under Multiple Disturbance Function Hypothesis (Patek, 2010). Much of the method and description of the method is paraphrased from that work.

Setting The equation used to describe the state space of the SOGMM model,

$$x(k+1) = Ax(k) + Bu(k) + Gd(k) + Hw(k)$$

was used as the underlying governing equation for the LTI system for the posterior probability calculation. This was observed during a finite horizon $k = 0, 1, ..., N-1$, where A, B, G, and H are appropriately dimensioned state-space matrices. It was assumed that,

1. $x(0)$ was normal with a mean of $\bar{x_0}$ and a covariance matrix of X_0.
2. $\{w(k)\}_{k=0}^{N-1}$ was a zero-mean, white Gaussian process with a covariance matrix W

3. $\{d(k)\}_{k=0}^{N-1}$ was another disturbance process that could take one of n_h different forms:

$$d(k) = d^h(k),$$
$$k = 0, 1, ..., N-1;$$
$$h = 1, 2, ...n_h$$

the prior probabilities for each were denoted as $\pi^1(0)$, $\pi^2(0)$,...,$\pi^{n_h}(0)$

4. $u(k)$ at each stage $k = 0, ...N-1$ was determined historically by past measurements and inputs $I(k) = \{y(k), u(k-1); I(k-1)\}$

Additionally, this system produced noisy measurements,

$$y(k) = Cx(k) + v(k)$$

for the purposes of this evaluation individual CGM values were used for $y(k)$ with C as an appropriately dimensioned matrix and $\{v(k)\}_{k=0}^{N-1}$ as a zero-mean, white Gaussian process with covariance matrix V.

Optimal Filtering This section describes the decomposition of the problem of estimating $x(k)$ as one of maintaining a conditional estimate $\hat{x}^h(k)$ for each hypothesis.

The optimal least squares estimate of $x(k)$ at any stage $k = 0, ..., N$ was given by the conditional expectation $\hat{x}(k) = \mathbb{E}\{x(k)|I(k)\}$. Conditioned on the event E_h, meaning that the $h-th$ disturbance process is driving the system. From this it can be seen that,

$$\hat{x}(k) = \sum_{h=1}^{n_h} \pi^h(k)\hat{x}^h(k)$$

where $\hat{x}^h(k) = \mathbb{E}\{x(k)|I(k), E_h\}$ and $\pi^h(k) = P(E_h)|I(k))$, $k = 0, ..., N$

The following section describes how $\hat{x}(k)$ and $\pi^h(K)$ are found.

Optimal State Estimation under the h-th Disturbance Process Given the event, E_h, the state, $x(k)$, changes according to,

$$x(k+1) = Ax(k) + Bu(k) + Gd^h(k) + Hw(k)$$

The optimal estimate pertaining to that particular event, E^h, was found though a discrete-time Kalman filter:

$$\check{x}^h(k) = A\hat{x}^h(k-1) + Bu(k-1) + Gd^h(k-1)$$
$$\hat{x}^h(k) = \check{x}^h(k) + L_k[y(k) - C\check{x}^h(k)]$$

with $\hat{x}^h = \hat{x}(0)$. The Kalman Filter gain matrix L_k and error covariance matrix P_k were found recursively. These are independent of the hypotheses and can be shown as:

$$\check{P}_k = AP_{k-1}A' + HWH'$$
$$P_k = I - L_kC\check{P}_k$$
$$L_k = \check{P}_kC'[C\check{P}_kC' + V]^{-1}$$

with $P_0 = X_0$. Given $I(k)$ and E_h, $x(k)$ is conditionally normal with mean $\hat{x}^h(h)$ and a covariance matrix P_k. Therefore, $x(k)$ has a conditional density $N(\cdot; \hat{x}^h(h), P_k)$. Additionally, given $(k-1)$, $u(k-1)$, and E_h, $y(k)$ is conditionally normal with mean,

$$\check{y}^h(k) = C\check{x}^h(k)$$

and covariance matrix,

$$Y_k = C\check{P}_kC' + V$$

Thus, $y(k)$ has a conditional density $N(\cdot; \check{y}^h(k), Y_k)$.

Posterior Probability of the h-th Disturbance Process From the observations described in the last section, the posterior probability that d^h was disturbing the system was found recursively.

$$\pi^h(k) = \frac{N(y(k); \check{y}^h(k), Y_k)\pi^h(k-1)}{\sum_{a=1}^{n_h} N(y(k); \check{y}^a(k), Y_k)\pi^a(k-1)}$$

The posterior probability of each hypothesis can be found this way, because it is effectively an application of Bayes' rule. In this case, $y(k)$ is conditionally normal with a mean of $\check{y}^h(k)$ and covariance matrix Y_k, given $I(k-1)$, $u(k-1)$, and E_h. The terms in the numerator and denominator represent the conditional likelihood of making the observation $y(k)$ given that the the corresponding hypothesis is true, weighted by the conditional probability $P(E_A|u(k-1), I(k-1))$.

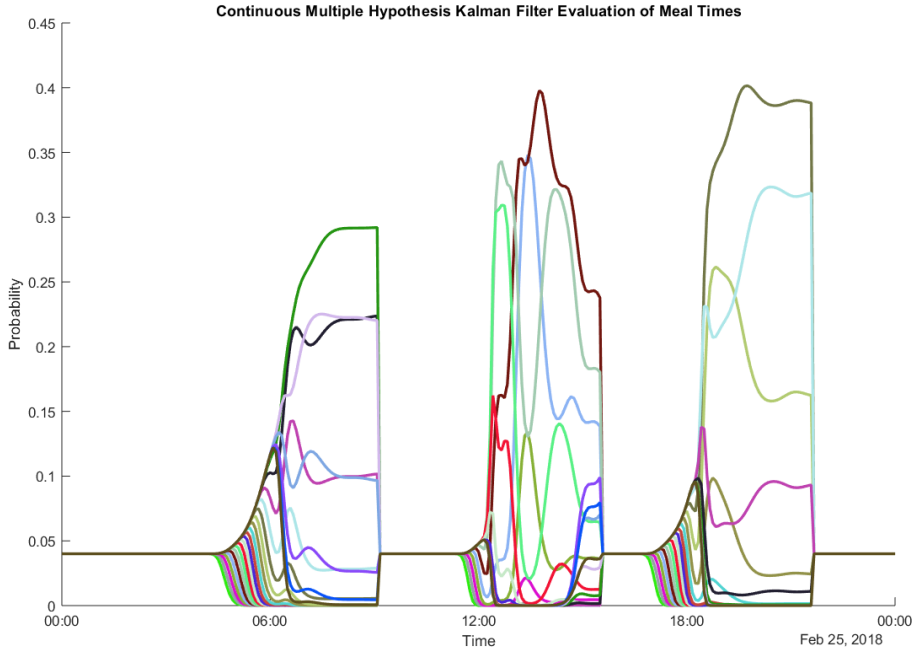

FIGURE 3.3: Posterior probability of each hypothesis throughout the day.

Implementation This technique was used to recognize if a subject ate at a time other than when the insulin dose was recorded. The set of disturbance functions mentioned previously, d_h, were ingrained in the hypotheses that were evaluated. The framework of this methodology dictated that the size of the perturbation was the same for each hypothesis and was in the form of ingested carbs, but the time where that disturbance occurred was different. The probability of a disturbance or hypothesis being correct was denoted as π_h. This is the probability of the meal occurring at the time described by the disturbance function relative to the other disturbance functions in the hypothesis set.

Figure 3.3 shows how the probability of each hypothesis evolves and shifts throughout the day for one given subject. As meal and insulin events occur and as BG changes, the likelihood of a given hypothesis changes. Each hypothesis has the same probability at the beginning of each meal evaluation and as time goes on the model becomes more informed, distinguishing what is possible from what is predicted by the model.

There are three distinct meals shown in Figure 3.3. This representation of how the

probability of each hypothesis changed was taken from one insilico subject used in the data set. The first meal occurred at 6:00 a.m. and it can be seen that the algorithm started sometime before this. The evaluation of the various hypotheses began when the first hypothesis' meal took place. Based on when the bolus for this particular subject occurred, this could have been as early as 5:00 a.m. if the bolus was given an hour before the meal or 7:00 a.m. if the bolus was delivered an hour after. Shortly after the evaluation began, the probability of certain hypotheses quickly dropped to near zero values. Simultaneously, others rose just as dramatically upwards. All of the hypotheses' probabilities summed to one at all times. This caused the various posterior probabilities to behave in a manner that was proportional to one another. The lunchtime meal occurred at noon and dinner took place at 6:00 p.m. In each case the hypotheses' probabilities changed as a function of how BG was behaving and what the predicted BG was for that particular hypothesis. Hypotheses with large residual differences between the predicted BG and the actual BG at a given time had low probabilities. A hypothesis that was close in value to the actual BG would have had a higher or equal posterior probability to the other hypotheses with similar predicted BG values.

3.3 Meal Time Estimation

At the end of the evaluation period, the posterior probabilities of each hypotheses were compared to each other. Ideally, the hypothesis closest to the actual sequence of event would have had the largest probability and each of the probabilities summed to one.

If a patient is a pump user, it can be assumed that the times of boluses are recorded exactly as they occurred. This is due to the fact that they are automatically logged as they are administered if they are given through an insulin pump or connected insulin pen. Because this is assumed to be true in the actual data and there is much more uncertainty around when meals may have taken place, this evaluation was centered around the bolus times. For the admission data used, most of the insulin doses happened within a short period of time of the meals they were associated with. This is generally advisable and even though is not always what is done in free

living conditions per the requirements of the study, boluses were taken right when or before the participant ate. In the simulation data generated, boluses are randomly distributed anywhere from an hour before until an hour after each meal. This may be more representative of how people actually behave considering there is evidence to suggest that delayed bolusing happens frequently with some individuals (Peters et al., 2017).

Each meal was evaluated from two hours preceding when the meal time bolus was administered until, 4 hours after. This means that for the simulated data, the meal could have occurred anywhere from one hour before to one hour after that bolus. The evaluation window was chosen so no matter when the meal occurred there was enough time for the Kalman Filter to "warm up" to a reasonable state before evaluating any of the hypotheses and run long enough to take into account the full effect of the meal on BG. Throughout that evaluation window the posterior probability of each hypothesis in relation to the others was calculated at each 5-minute iteration. By the end of the 6-hour period, each hypothesis had an associated vector of probability values describing the likelihood of that description of events at each moment in time. There could have been one hypothesis that had dominance over all others or a number of hypotheses may have shared the probability mass. Ideally, the hypothesis that actually describes the events that took place would have a probability of one by the end of the evaluation window. This would in turn associate to an error,

$$error = t_{estimate} - t_{actual} \tag{3.1}$$

of zero.

Figure 3.4, shows a distribution of what the final posterior probabilities of each of the 25 hypotheses may look like. In this case, the hypothesis that described the meal occurring zero minutes before the bolus was given was the most likely. The hypotheses that described the meal happening 5 and 10 minutes before or after the bolus also had nontrivial probabilities in comparison to some of the others. The

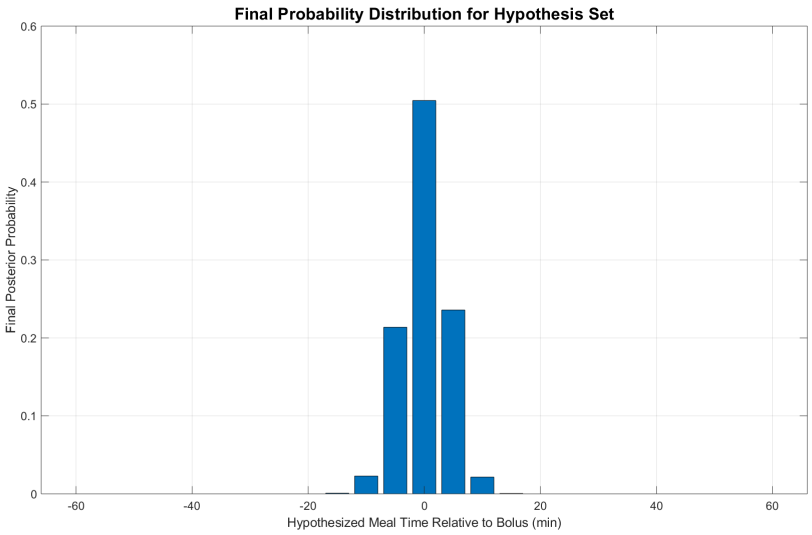

FIGURE 3.4: Final posterior probabilities associated with each hypothesis. In this example the meal occurred at the time of the insulin bolus.

other hypotheses either had zero probability of having happened or negligible values. This demonstrates that the algorithm was able to deem one hypothesis the most likely, in this case the correct one, and also state that there was still some chance that the meal occurred shortly before or after the estimated meal time. The probability mass was centered on the correct hypothesis, but there was some uncertainty. As long as this uncertainty was centered on the correct hypothesis the final meal time estimate should be close to when the meal actually took place.

In both simulation and actual clinical data, there were issues involving the posterior calculation of each descriptive scenario. The correct hypothesis was not always deemed the most probable. This can be attributed to a number of factors. Primarily, the issue was in how the underlying SOGMM relates glucose rate of appearance or the dynamics of how insulin affects BG levels after it is administered. Additionally, unaccounted for inputs such as physical activity, stress, and sickness may affect BG in the actual patients. After a meal, BG does not rise instantaneously. It begins to go up some time after the meal, dependent on the fat, protein, carb balance, and then increases at a rate related to that meal's nutritional composition as well as the individual's metabolic processes. Because of the complicated mechanism that causes glucose to be absorbed into the blood stream, the models created to describe this

process are highly subjective to an individual's physiology as well as the content of the meal, their sensitivity to insulin at the time which may be related to activity levels, and numerous other factors. Thus, the existing SOGMM serves as a reference point for how the insulin-glucose relationship should behave in a given situation, but is far from perfect.

Because it was often the case that more than one hypothesis had a posterior probability greater than zero, the expected meal time was found by taking a weighted average of all of the hypotheses' meal times based on their final posterior probability.

$$t_{estimate} = \sum_{h=1}^{n_h} \pi^h(N) * \Delta d^h, \tag{3.2}$$

where π^h is the final posterior probability of a particular hypothesis and Δd^h was the time difference between the hypothesized meal time and the time of the insulin bolus.

3.4 Parameter Tuning

In order to produce more accurate results, a number of parameters were tuned within the SOGMM. Prior to tuning there was an issue with how the model used for the posterior probability calculation expected BG to react and how it was behaving in the clinical and insilico data. This problem was caused by a number of parameters in the SOGMM, all related to the appearance and clearance of glucose to and from the blood stream, not being representative of the data set.

From observation it was clear that in some situations, particularly when insulin doses were taken long after a meal occurred, the correct hypothesis did not have the highest probability. Take for instance when a meal occurred one hour before insulin was administered, for certain subjects the algorithm would actually conclude that the person ate an hour after they took their insulin.

This can be clearly seen in Figure 3.5. For this particular simulation subject, all three meals were eaten and then an insulin dose was delivered sometime after. At lunch there was only a small gap between the meal time and the bolus time, but

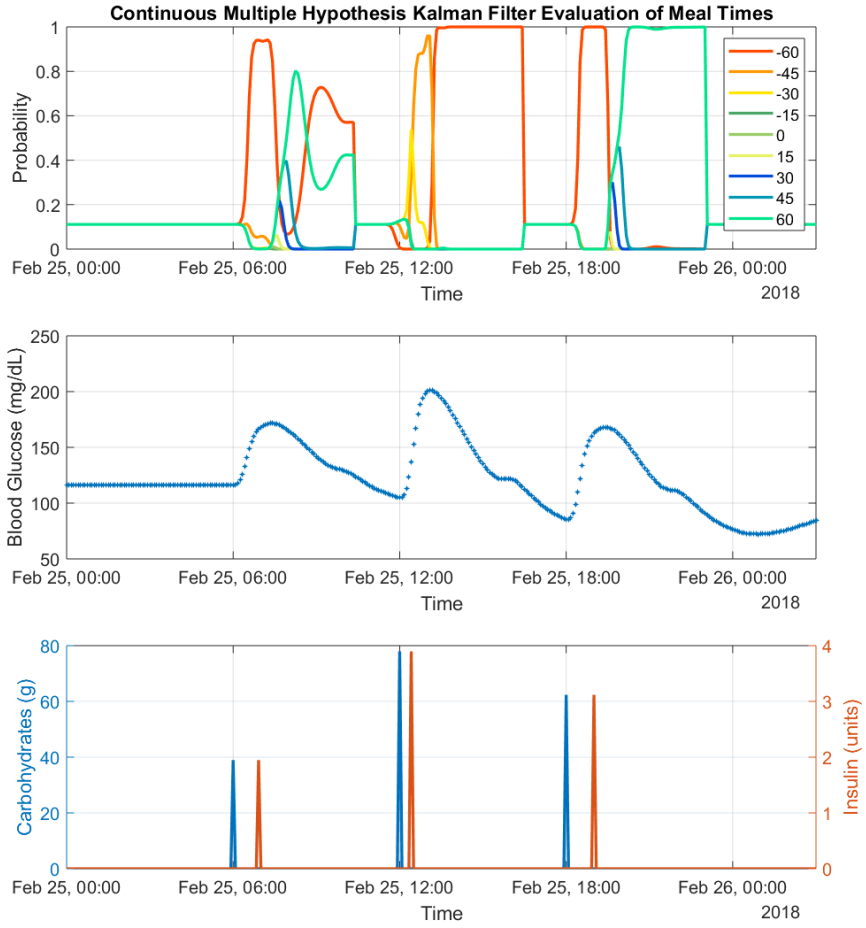

FIGURE 3.5: Visualization of meal evaluation process. Top subplot shows the posterior probability of each hypothesis at each point in time throughout the evaluation. The middle subplot shows CGM values throughout the day. The bottom subplot shows meals in blue and the associated boluses in orange.

at dinner and breakfast the time delay in insulin dosing was much larger. Shortly after the insilico subject ate breakfast the probability of the hypothesis where the meal occurred 60 minutes prior to the bolus increased dramatically and the other hypotheses' probabilities are reduced to nearly zero. Then as BG began to rapidly decline, so did that probability of that hypotheses.

In this evaluation, the correct hypothesis, stating that the bolus was after the meal was initially picked, then as the model became more informed another was chosen in its place. Why did this happen? It can be seen in the middle subplot that the correct hypothesis' probability began to decline when BG peaked and started to drop. This also correlated to when the insulin dose was taken, which is indicated by the orange spike in the lower subplot.

From observing the data, it appeared that confusion in the model occurred primarily when boluses followed long after meals occurred. These "early meal" instances provided a source of disparity between what the predicted glucose value was given the hypothesized version of events and what actually happened. Often it was the case, as was shown in Figure 3.5, that when a meal took place and then insulin was taken long after that, the hypothesis correctly describing what happened would be most likely until BG reached its postprandial peak and began to descend.

This is indicative of parameters describing how insulin and glucose should interact with one another being maladjusted within the SOGMM. In order to test if this was the case, a small set of parameters were selected and incrementally changed to see if a better set of values could be chosen. Due to the nature of the error and consistency in how this was occurring, the parameters that describe how oral glucose is absorbed (k_{abs}), physiological and sensor lag (k_{sc}), oral glucose transport (k_{tau}), and subcutaneous insulin transport (k_{cl}) were selected to be the hyperparameters that were altered.

In order to minimize absolute error, a grid search was conducted using the 4 relevant parameters. Each parameter was multiplied by an individual constant that ranged from 200%-400% of the original value in increments of 25%. For each set of parameters in the grid search, the algorithm was run on all 100 simulation subjects. The absolute error,

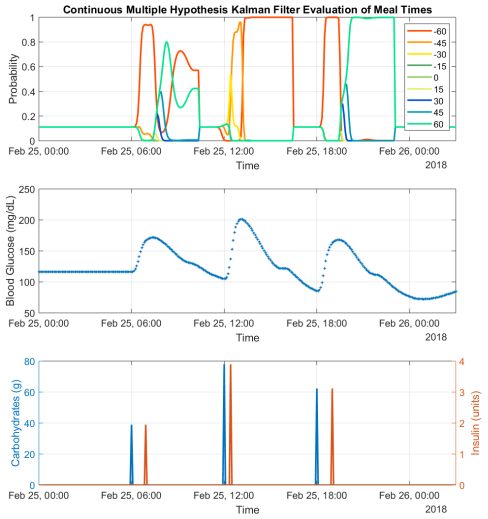

FIGURE 3.6: Normal Parameters.

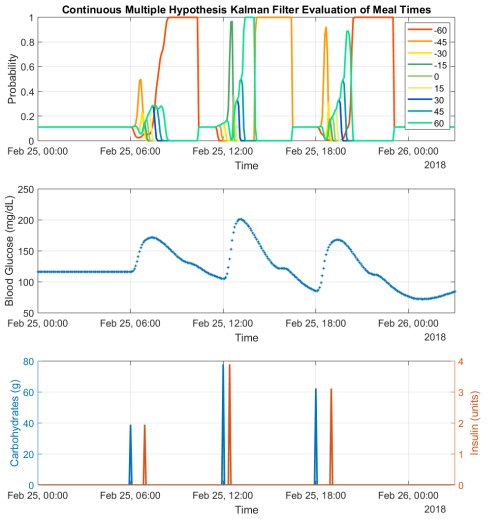

FIGURE 3.7: Optimized Parameters.

$$\text{absolute error} = \sqrt{(t_{actual} - t_{estimated})^2}$$

for the sample data was reported for each evaluated meal. Population parameters were chosen based on which parameter values yielded the lowest mean absolute error for all subjects.

It can be seen in Figure 3.7 how the issue described before was corrected by adjusting the model parameters. In this case, instead of the wrong hypotheses being selected ones that more closely described what actually happened were determined to be the most likely. In all three cases, the expected meal time was within 5 minutes of the actual meal times when the optimal parameters were used.

3.5 Algorithm Evaluation

The performance of these algorithms was evaluated using a number of different metrics. To understand how each was performing in an overall sense the error for each meal was calculated by taking the difference between the estimated meal time and the actual meal time.

$$error = t_{estimate} - t_{actual} \tag{3.3}$$

The mean was then taken to get a sense if the algorithm was consistently biased towards over or underestimated when a meal happened. The formula for mean error (ME) is intuitively,

$$\text{ME} = \frac{1}{n}\sum_{i=1}^{n}(t_{estimate} - t_{actual}) \tag{3.4}$$

To determine the performance of the algorithm in a way that would not be affected by balanced under and overestimation error of equal magnitude, mean absolute error (MAE) was also measured for each data set.

$$\text{MAE} = \frac{1}{n}\sum_{i=1}^{n}\sqrt{(t_{estimate} - t_{actual})^2} \tag{3.5}$$

Additionally, sample standard deviation, and sample standard error were calculated for each parameter set's results. These results were further segmented for the simulation data into when the meal occurred. "Early meals" were instances when the meal happened more than 20 minutes prior to when insulin was administered. "On-time meals" were any eating events that happened 20 minutes or less from the respective insulin dose and "late meals" were when insulin was taken at least 20 minutes before the subject ate. These results and a visualization of each of he meal categories distributions are presented in Section 4.

These metrics were conducted on two sets of results. The first set is for when the algorithm was run using the SOGMM and its original parameters. The second set used the SOGMM with the parameters selected based on which set yielded the lowest mean absolute error in the simulation data. The same metrics were reported for both sets of parameters on both the clinical admission and simulated data.

Chapter 4

Results

The performance of the algorithm was evaluated for both the standard SOGMM parameters as well as the parameters that were optimized to minimize absolute estimation error in the simulation data set. In the following section the ME, MAE, sample standard deviation, SE, and distribution of error is presented for both parameter sets. This result is broken down further for the simulation data set into when the meals occurred. The three subsets are when the bolus followed the meal by 25 minutes or more this group is referred to as "early meals." If the meal occurred 20 minutes or less from the time of the bolus this was considered to be an "on-time" meal. If the bolus was greater than 20 minutes before the meal this was deemed a "late meal." All of the instances described are focused on when the meal happened with reference to the bolus, but could also be framed based on when the bolus happened. This may be more customary to how insulin doses are normally talked about and the subsets of the meals would then be late boluses, on-time boluses, and early boluses.

4.1 Clinical Data

4.1.1 Clinical Data Performance Evaluation

The evaluation results for the clinical data set are presented in Table 4.1. The parameters optimized on the simulation data as well as standard parameters were evaluated. The standard parameters produced a mean error of -2.88 minutes and an MAE of 29.89 minutes. The algorithm returned a sample standard deviation of 36.05 minutes and an SE of 0.61. The optimized parameters had a mean error of 1.34

TABLE 4.1: The mean error, mean absolute error, sample standard deviation, and standard error for the algorithm run with the original parameter values and the optimized parameters evaluated on clinical data.

		Original Parameters	Optimized Parameters
Overall	ME	-2.88	1.34
	MAE	29.89	24.88
	Sample St.Dev	36.05	32.35
	SE	0.61	0.55

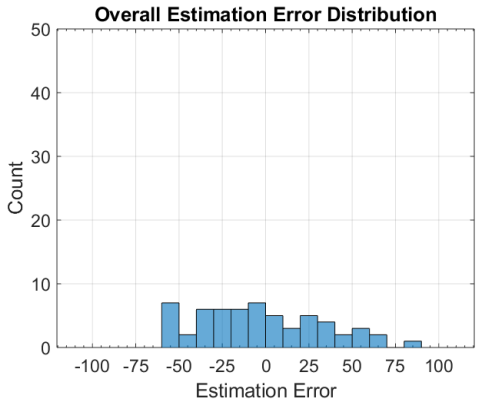

FIGURE 4.1: Overall distribution of error for clinical data when original parameters are used.

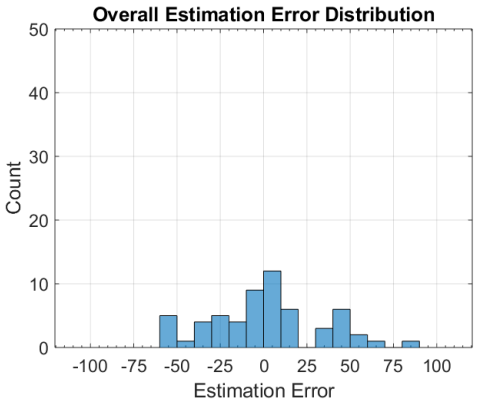

FIGURE 4.2: Overall distribution of error for clinical data when optimized parameters are used.

minutes and an MAE of 24.88 minutes. The sample standard deviation and SE when the optimized parameters were used in the algorithm were 32.35 minutes and 0.55 minutes respectively.

4.1.2 Clinical Data Error Distribution

Figures 4.1 and 4.2 show the distribution of error for the clinical admission data. The independent variable of these histograms indicates the time difference between the estimated meal time and the actual meal time. Each of the bins represent 10 minute windows of time ranging from -120 minutes to 120 minutes from the insulin dose. An error of -70 minutes would correspond to an estimated meal time 10 minutes before the bolus when the meal actually occurred one hour after the insulin dose was taken. Figure 4.1 shows the distribution of error for the meal estimation algorithm when the original SOGMM parameters were used. Figure 4.2 presents the results

TABLE 4.2: The mean error, average absolute error, sample standard deviation, and standard error for the algorithm run with the original parameter values and the optimized parameters evaluated on clinical data.

		Original Parameters	Optimized Parameters
Overall	ME	0.87	-0.01
	MAE	22.78	3.54
	Sample St.Dev	33.99	4.56
	SE	0.11	0.02
Early	ME	28.17	-0.57
	MAE	44.88	3.36
	Sample St.Dev	50.30	4.53
	SE	0.57	0.05
On-time	ME	-6.78	-0.26
	MAE	12.19	4.29
	Sample St.Dev	14.43	5.33
	SE	0.13	0.05
Late	ME	-14.85	0.75
	MAE	14.85	2.87
	Sample St.Dev	4.83	3.49
	SE	0.05	0.03

when the parameters optimized on the simulation data were used in the SOGMM and the algorithm was applied to the clinical data set. The error ranged from -60 to 90 for the results of the algorithm, regardless of which set of parameters were used in the SOGMM.

4.2 Simulation

4.2.1 Simulation Data Performance Evaluation

Table 4.2, shows the ME, MAE, sample standard deviation, and SE calculated for the meal time estimates of the algorithm using both standard and optimized parameters for the simulation data set. The results presented are for the overall evaluation of the meals as well as a break down of early, on-time, and late meals.

For the data set as a whole, the ME for the algorithm using the original SOGMM parameters was 0.87 minutes. The MAE using this parameter set was 22.78 minutes. The sample standard deviation was 33.99 minutes and the SE was 0.11 when the standard parameters were used. When the optimized parameters were applied to the SOGMM an ME of -0.01 minutes and an MAE of 3.54 minutes were achieved. The

sample standard deviation and SE for this subset of the data set were 4.56 minutes and 0.02 minutes respectively.

For the early meals, that is those that occurred more than 20 minutes before a meal bolus was delivered, the ME was 28.17 minutes for the normal parameters and -0.57 minutes for the optimized parameters. The MAE for the standard parameters was 44.88 minutes. When the optimized parameters were used, the MAE fell to 3.36 minutes. The sample standard deviation was 50.30 and 4.53 for the regular and optimized parameters respectively. The SE when the regular parameter values were used was 0.57. It was 0.05 minutes when the optimized parameters were inputted into the model.

When meals occurred 20 minutes or less from their associated insulin dose, the ME was -6.78 and -0.26 minutes for algorithms when normal and optimized parameters were used. The MAE was 12.19 minutes for the normal parameters and 4.29 minutes for the optimized values. The SE's were 0.13 minutes and 0.05 minutes for the original and optimized parameter values.

For the late meals, the ME for the standard model parameters was -14.85 minutes. Comparatively, the ME was 0.75 minutes when the optimized values were used in the SOGMM. The original parameters yielded an MAE of 14.85 minutes, a sample standard deviation of 4.83 minutes, and a SE of 0.05 minutes. The optimized model parameters had an MAE of 2.87 minutes, a sample standard deviation of 3.49 minutes and an SE of 0.03 minutes.

4.2.2 Simulation Data Error Distribution

Figures 4.3 and 4.4, show the overall distribution of estimation error for both parameter sets. The error values for the original parameter values fall into bins ranging from 40 minutes before the true meal time to 100 minutes after. This bin with the largest frequency is 10 to 20 minutes before the actual meal time. The range of error when the optimized parameters are used is $\pm$ 10 minutes the actual meal time with the bin 0 to 10 having the most number of entries.

The distribution of error for the early meals can be seen in Figures 4.5 and 4.6. These meals occurred 20 minutes before to 20 minutes after the insulin dose. The

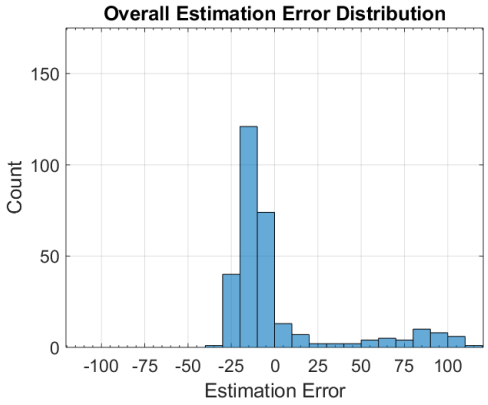

FIGURE 4.3: Overall distribution of error for simulated data when original parameters are used.

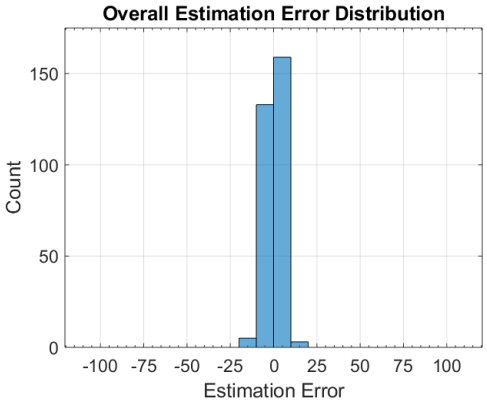

FIGURE 4.4: Overall distribution of error for simulated data when optimized parameters are used.

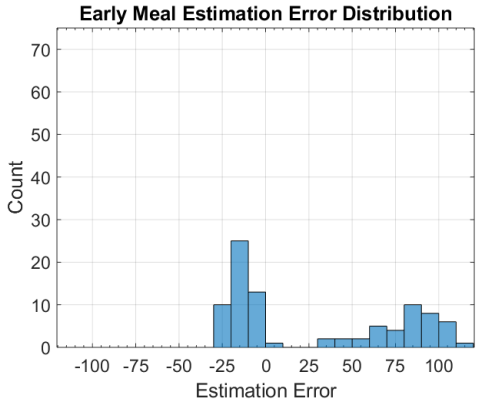

FIGURE 4.5: Distribution of error for simulated data for early meals when original parameters are used.

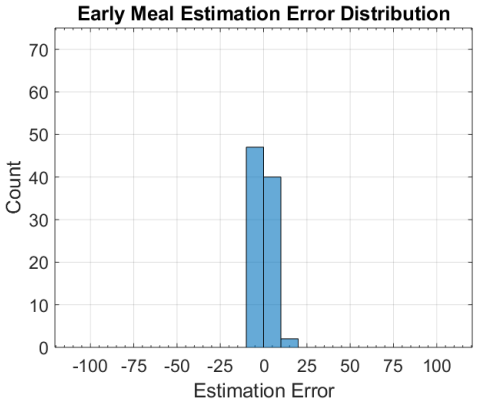

FIGURE 4.6: Distribution of error for simulated data for early meals when optimized parameters are used.

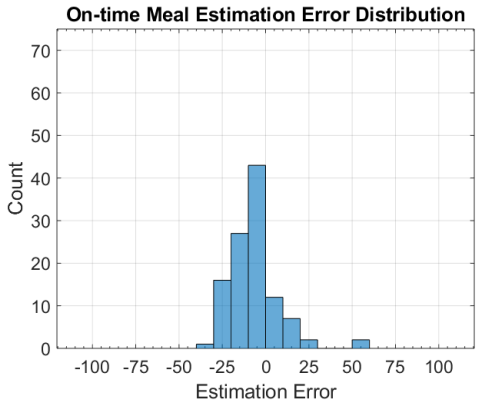

FIGURE 4.7: Distribution of error for simulated data for on-time meals when original parameters are used.

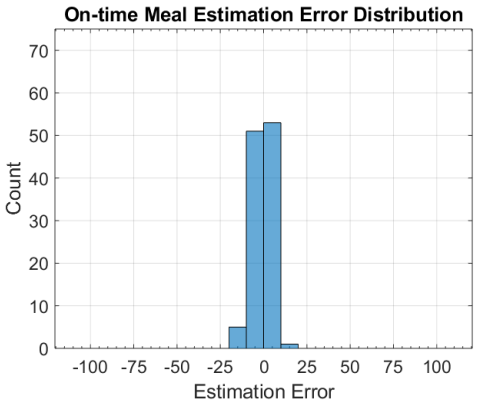

FIGURE 4.8: Distribution of error for simulated data for on-time meals when optimized parameters are used.

spread of error for the original SOGMM parameters is from -40 minutes to 60 minutes. The range of the algorithmic error ranges from -20 to 20 from the meal time when optimized parameters were used. The bins with the highest frequency represent -10 to 0 and 0 to 10 minute errors for the original parameters and the optimized parameters respectively.

Figures 4.7 and 4.8 show the distribution of the difference between the estimated meal times and the actual meal times for the simulated data set for on-time meals. Figure 4.7 shows the error when the original parameters were used ranging from -30 to 0. The bin with the highest frequency represents error values from -10 to -20 minutes. It can be seen in Figure 4.4 that the error values range from -10 to 10 minutes with respect to the actual meal time. The bin with the highest frequency is for an error value of 0 to 10 minutes after the meal.

Similarly, Figures 4.9 and 4.10 present the distribution of error for the late meals. The distribution of error ranges from -30 to 0 minutes for the original parameter values and from -10 to 10 minutes when the optimized parameters are used. The bins where most of the error fell was -10 to -20 and 0 to 10 minutes for the original and optimized parameters respectively.

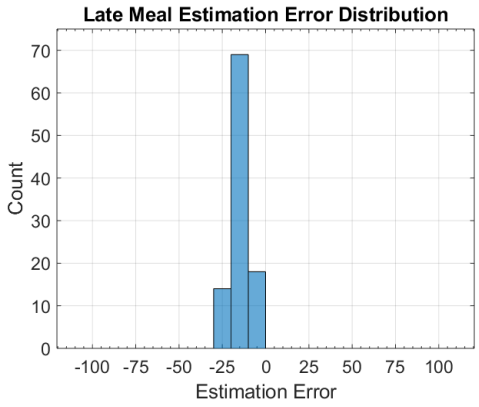

FIGURE 4.9: Distribution of error for simulated data for late meals when original parameters are used.

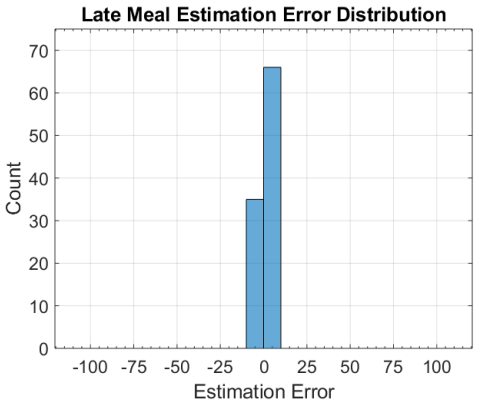

FIGURE 4.10: Distribution of error for simulated data for late meals when optimized parameters are used.

Chapter 5

Discussion

5.1 Clinical Data

5.1.1 Accuracy Metrics

For the clinical data the algorithm performed better when the optimized parameter set was used. It is evident that the original parameters tended to cause the algorithm to estimate a meal time that was slightly before when the meal occurred on average. When the parameters were changed to values found by optimizing on the simulation data, the opposite happened, meals were estimated to have happened a little over a minute after they actually happened on average. By taking the metrics regarding variance, namely sample standard deviation and SE, into account, it is apparent that there was a large spread in the results when either parameter set was used. For some meals, the algorithm estimated a meal time that was long before the actual meal time. For others the opposite was true and the meal time was estimated long after it actually happened. This in turn led to the average error being close to zero. Creating a near zero mean distribution of error.

Although there was a large spread in the error values, there is a significant benefit of having this kind of error distribution. Because the ultimate goal of this work is develop a method that could be refined so that general behavior patterns could be determined, having error that is evenly distributed around zero would lead to more acceptable results. This would allow for an aggregate assessment of behavior to be close to the truth instead of having a distinct skew in one direction or another. Ideally, the variance would be as small as possible.

A more telling statistic related to general algorithm performance is the mean absolute error. This metric effectively represents how much error there is in the meal time estimation algorithm in an absolute sense. The mean error can wash out certain inaccuracies because of a large spread in the error of the algorithm. The mean absolute error does not provide this ability to negate balanced error. For the clinical data set the mean absolute error was nearly 30 minutes when the original SOGMM parameters were used and appropriately 25 minutes when the optimized parameters were used. This can be considered a notable reduction in error.

There are a number of possible caused of this inaccuracy. The better set of parameters used offers an improvement in estimation ability, but still had relatively large error. These parameters were selected based on what minimized error for the insilico data set. The optimization was done in this manner, because the insilico data set was nearly 5 times larger than the clinical data set with 300 meals and 100 patients versus 11 patients and 59 meals. Some of the patients in the clinical data set only had two or three usable meals. Additionally, the subjects in the clinical data set are inherently more heterogeneous than those in the simulated population. There may be a large range of physiological disparities between the individuals that participated in this study.

It should also be taken into account that some individual's treatment parameters such as carb ratio, correct factors, and basal rates may not be properly tuned. Their insulin sensitivity may be different from what was calculated in the algorithm. Additionally, there is still not an established method for precisely estimating this due to its nature to change on an inter and inter-day basis.

An additional factor that may lead to some confusion in the model is that the SOGMM does not incorporate physical activity. If a person exercised before or after a meal their insulin sensitivity is increased and BG would behave differently than if they had not. Insilico subjects are not affected by the kind of BG variability caused by physical activity whereas actual patients are very much affected by this. This could lead to differences in predicted and actual BG values when the algorithm is applied to the clinical data set. These are not excuses for errors in the methodology, but they should be acknowledged as limitations. Ideally, a this method would be robust enough to withstand this kind of immeasurable uncertainty.

5.1.2 Distribution

The distribution of error for the clinical data was widespread for both sets of parameters. In both cases, it spanned from -60 to 90 minutes. When the original model parameters were used in the algorithm the error is right tailed and often times meant that the meal was predicted to have happened before it actually did. When the optimized parameters were used the distribution of error is more centered towards zero. There are still error values far from zero were meals were estimated long before or after the actual meal time, but with this parameter set there is some semblance of a centralized error distribution.

There are additional, deeper questions in the clinical data. When were the meals recorded? Did this happen at the beginning of the meal, throughout or at the end and did it depend on who was recording it? Other non-controlled for variables may have also had an impact on gylcemia. For instance, what was the composition of the meals? If a person had a high fat, high carb meal like pizza it would affect glucose in an entirely different way than if they just drank a glass of juice. It may also be the case that certain sized meals are easier to classify than ones with lower carb content. Further evaluation may elucidate how these factors affect estimation accuracy.

5.2 Simulation Data

5.2.1 Accuracy

There was a dramatic improvement in accuracy between the original SOGMM parameter values and the optimized parameters when the algorithm is used to estimate the meal times of the simulated subjects. The optimized parameter performed better than the original parameter set in every metric for every sample subset. This has to be partially attributed to the fact that the parameters were optimized to minimize error in this data set. Nonetheless, the performance of the algorithm significantly improved when these values were used in the BG prediction model.

For the data set as a whole, the ME was -0.01 minutes and the MAE was 3.54 minutes when the optimized parameters were used. This is a huge improvement compared to the standard model which had an ME of 0.87 which seems respectable, but

an egregious amount of absolute error on average, 22.78 minutes. The variance in the results also dramatically decreased when the optimized parameters were used. For the algorithm using the optimized parameters the sample standard deviation dropped from 33.99 minutes to 4.56 minutes.

The early meals provided a great deal of difficulty for the original parameter set. As was explained when the motivation for the parameter optimization was described, these meals caused the probability calculation of the correct hypothesis to initially have a high probability that quickly descended as BG began to drop after the meal. By adjusting the parameters describing the insulin-glucose dynamic, the residual between the expected BG for these hypotheses and what was observed was reduced greatly. This led to a reduction in MAE of more than 41 minutes. The sample standard deviation for this subset of meal also decreased from 50.30 minutes to 4.53 minutes.

The improvement between the two parameter sets was the smallest for the meals that happened within relative proximity of the insulin dose, but the improvement is still notable. The ME decreased from -6.78 to -0.26 minutes and the MAE went from 12.19 minutes to 4.29 minutes. As was the case with the other meal classifications the deviation in the results for the parameters sets also decreased when they were optimized.

For the late meals the ME was reduced from -14.85 minutes to 0.75 minutes when the optimized parameters were used in the insulin-glucose model. The MAE also decreased from 14.85 minutes to 0.75. The standard deviation and SE of the optimized group were reduced to acceptably accurate amounts.

Overall, there was a large reduction in error and deviation when the optimized parameters were used in the SOGMM. This held true for all subsets of the data sets. Even though certain BG values following meals were more difficult to match to predicted values the overall error is comfortably within an acceptable range for the simulation data. It was possible to estimate meal times within 4 minutes of when they occurred for the data set as a whole as well as for early, on-time, and late meals.

5.2.2 Distribution

Figures 4.3 and 4.4 of Section 4 clearly demonstrate how the optimized parameters eliminate large errors and dramatically tighten the distribution of errors centering it at zero. The original parameters caused certain meals to yield very large error values. This tended to happen when the meal time was significantly before or after the bolus. Early meals provided a great deal of disparity between the predicted glucose and the observed values. With the optimized parameters all of the error values were equal to or less than 30 minutes, without some meal had an error in the estimated meal time of up to 120 minutes.

It can be seen in Figure 4.5, that the original SOGMM parameters produced error values for the early meals that resembled a bimodal distribution. Much of the error was centered around zero, but a notable portion of meals had an estimated time that was greatly after when the meal happened. This second modality ranged from 30 to 120 minutes from the time of the meal. When the optimized parameters were used in the SOGMM within the algorithm the error was kept to between -10 and 20 minutes with a large portion of the errors being between -10 and 0.

For the on-time meals, shown in Figures 4.7 and 4.8, it is apparent how the optimized parameters affected the distribution of error for the meal estimation algorithm. The optimized parameters greatly reduced the span of the errors and made it so most meals were estimated within 10 minutes of the time of their occurrence. The spread was dramatically reduced so that no meal had an absolute error of more than 20 minutes.

The late meals were most accurately estimated with the original parameter values. Optimization did provide some improvement in the spread of the error, reducing it from -30 to 0 to $\pm$ 10 minutes. In the optimized case, the majority of the errors were between 0 and 10 minutes whereas with the normal parameter values, most of the meals were estimated 10 to 20 minutes before they actually happened.

Chapter 6

Conclusions and Future Work

6.1 Conclusions

It is imperative that meal information is known precisely when analyzing BG data. The timing of these meals has a significant impact on glycemia and based on how this information is usually collected in clinical trials insulin doses and times are known with accuracy, but it is often unclear about when meals happened. This exploration has shown how a multiple hypothesis method could be used to estimate meal times. The accuracy of this method could be improved on through additional signal processing techniques as well as a refinement of the underlying model. The impact of this work is to serve a foundation that can be built upon to create accurate meal time estimation tools. These tools when tuned properly could then be used so that clinicians can work with their patients to demonstrate to them how BG may improve if insulin was delivered properly at meal times. guidelines were followed more closely.

6.2 Future Work

Only something that worthwhile is worth improving upon. This exploration asks an important question, "How can we find out precisely when people eat with as little burden on the subject as possible?" Data collection used in diabetes research is burdensome on behalf of the participants and is a source of frustration for the researchers analyzing it because of its faults. The patient should not be held accountable for this, because what they are being asked to do, meticulously categorize

every morsel of food entering their mouths, is an unreasonable request. It is simply not sustainable over an extended period of time and it is the responsibility of the researchers to find ways to collected data in a less invasive manner or create technology that can work with imperfect data.

The methodology developed in this thesis is the first step of exploration in a potentially fruitful way of estimating meal times messy patient data collected passively through an action that they already do regularly. The proliferation of insulin pumps has made insulin records verbatim and gotten us much closer to having complete meal records for individuals who use them. There a number of ways that this method can be improved on or implemented that are discussed in this section, but are by no means exclusive.

6.2.1 Parameter Tuning

Based on the current SOGMM, BG can be estimated roughly from insulin and meal information. Its short coming is that not all patients are the same and the inherent customization does not tailor predictions perfectly to all people. A further parameter optimization could be done for this particular data set as well as different meal compositions (high fat and high carb, carb only, etc.). Based on how the posterior probability of the correct hypothesis behaves at times, it is evident that some constants pertaining to insulin sensitivity, glucose rate of appearance, or insulin clearance could be tuned more precisely. Additionally, patient customization of model parameters may create more accurate predictions of BG. Further exploration could serve to enhance the performance of a multiple hypothesis method for meal time estimation.

6.2.2 Behavioral Profiling

From this information, clinicians could potential create a profile for patients based on their insulin dosing behavior. By observing estimations of meal times, one could make an inference about how a patient was regularly taking insulin with regard to meals. If it was estimated that most insulin dosages are happening significantly before or after meals, then it could be more strongly supported that there needed to

be a behavioral intervention by the medical team. This would have to be in a done in a way that was not accusatory of the patient and used as a teaching experience to explain that by regularly doing this they may have negative effects on postprandial glucose values. Dosing insulin may lead to higher overall glucose values and could cause the person to develop complications.

6.2.3 Behaviorally Dependent Control

Behavioral models have been introduced into a number of control schemes for T1D (Patek, 2010), (Cameron, Niemeyer, and Buckingham, 2009). These methods use behavior and past events to control BG. The proliferation of machine-learning techniques presents an opportunity to personalize technology. For instance, if an algorithm such as the one described in this work was to determine that an individual regularly announced meals sometime after consuming them, maybe it could take that into account and suggest different insulin doses than usual. This could potentially create a system where behavior would not be influenced by a system, but rather the system would adapt to the user's behavior.

6.2.4 Plant-Model Deviation Analysis

The SOGMM has been in existence for decades. Although there are some significant blind spots in its form, it does an incredibly good job of modeling glucose considering its simplicity. The kind of analysis done in this work, compares model predictions with actual or simulation generated events. Through Bayesian methods there is an inherent commentary on the performance of the underlying model in terms of predicting glucose. It provides a comparison between individual's actual insulin-glucose dynamic and how a well-established model says that this interaction should be. It shows that for some and in certain situations this model performs very well and in others it fails somewhat dramatically.

The question is, why does this happen? There are many reasons why this might occur. First, there is a significant part of reality that the SOGMM does not take into account. Physical activity is not an input. To anyone familiar with T1D, this is an evident flaw. Physical activity has a significant impact on glycemia and is a large

contributor to variations in BG (Zisser et al., 2011), (Riddell and Perkins, 2009). The SOGMM uses insulin and consumed food as an input, but noticeably neglects physical activity.

This was not done as the result of an oversight. It has been common knowledge that physical activity makes BG decline long before the creation of this model. The reason for its absence as an input is that the relationship between physical activity is largely still unclear. Light and moderate activity drops BG, whereas intense activity will raise it (Riddell and Perkins, 2009). Lots of ongoing work is trying to reconcile BG, insulin, consumed carbs, and physical activity (Dalla Man, Breton, and Cobelli, 2009), (Ding and Schumacher, 2016), (Breton et al., 2014).

Apart from the SOGMM not including physical activity, there are some other reasons why it may fail to accurately recreate BG for a particular subject. There are a number of conditions that may cause an individual's BG to act in a way that would not be considered normal for someone with T1D.

Take for instance, diabetic gastroparesis. This condition that affects 40% of patients with T1D causes chronic delayed gastric emptying without mechanical obstruction (Parkman, Fass, and Foxx-Orenstein, 2010). If a patient were to have this condition how they process glucose would differ significantly from someone without diabetic gastroparesis. This in turn would cause a large divergence from model predictions and actual glucose given the inputs. One can envision using this divergence to draw attention to its potential causes and maybe creating a framework for diagnosing conditions that are known to affect the insulin-glucose dynamic in specific ways.

6.2.5 Profile Based Priors

Were this methodology to be implemented in an actual patient population there would be a number of distinct advantages. The data set used, for both real and generated subjects only provided a small number of meals for each patient. In the clinical data set collected over the course of two days, there were 4-7 meals. The in silico subjects there were three meals per patient. The goal in developing this method was to create an overarching profile to describe behavior and given that dataset that was not possible. It would be however if there was a large amount of data for each

subject. This would provide a broader perspective on their behavior and hopefully the algorithms, although not perfect, could see the general trends. This would allow for some anomalous meals to go grossly misclassified and still show a general profile for a subject. If a person always bolused either late or early, this would be apparent. When they actually ate in relation to an insulin dose would become less significant when compared to the aggregate and ultimately give a sense of what that person did regularly.

Additionally, a greater amount and more consistent information could allow for some machine learning techniques to be implemented. For instance, if someone always ate 20 minutes before their insulin was delivered, a system could recognize this and adjust the priors of each hypothesis to match previous behavior moving the starting point just a little closer to what is likely to have happened.

6.2.6 Data Robustness Analysis

There is a distinct need to conduct a sensitivity analysis on this method in order to determine how it performs under certain criteria. What if there are sensor gaps? What if there is sensor noise? How does meal size affect the ability of the algorithm to estimate meal time? These are all very valid questions that warrant further exploration. In order for this to be feasible testing needs to be conducted on messy data streams subjected to a plethora of unideal modeling situations. Further expansion of this method so that it is robust enough to handle many of these occasions would make it more feasible to employ in an online system.

6.2.7 Meal Amount Estimation

Future work could improve upon the idea of meal time estimation to also include meal amounts. One can envision another level of variables being added to the hypothesis set, where not only are meal times changed variably, but meal amounts are changed from the operating point of what the person logged.

People are often inaccurate when counting carbs and this could provide a better account of when and how much they ate (Kawamura et al., 2015), (Meade and Rushton, 2016). This tool if it was accurate enough could then be used by medical

professionals to diagnose habitual misestimation of carbs. It could also be implemented in a system to automatically compensate for this kind of behavior if there was a strong enough pattern of it happening.

6.3 Impact on Patients

The end goal of this work is to create a tool that clinicians could use to diagnose meal time insulin dosing behavior that could be improved upon in their patients. It is important not to forget how this may impact patients. If used improperly this could be a method for doctors to technologically point the finger at bad behavior and scold. That is not my intention. This is tool to provide information to clinicians so that they can help their patients, not chastise them.

At this stage of development there is nothing in place for that to really be enforced, but moving forward should be a consideration. Diabetes is a work intensive disease that does not halt for life's unexpected events.

The control of BG in T1D is as much a human problem as it is a physiological one and by understanding people's behavior there is an opportunity to find room for improvement or to change treatment practice to fit what is effective for them. What makes it a unique disease is that often medical professionals have little to do with the dosing and administration of treatment. Doctors may suggest what they think are best practices, but it is entirely up to the patient to be compliant. Some are diligently compliant others are not and that is their right to do so. That being said, tools like this could be used as a source of encouragement or a push further away.

BG is affected by many different things and often times the source of a particular effect on BG is unidentifiable. The mechanisms that govern it are sophisticated and the models that describe it are mathematical quagmire. People with T1D are often faced with the question, "Why is this happening to me?" Not in a profound existential way, but more simply that their BG is not what they expected and there is seemingly no explanation why. This tool could provide some insight. Particularly because the effects of misaligned insulin and meal events are not usually apparent.

The usefulness of this is based entirely on how it is received by those who it is supposed to be helping. It is also very possible that it is not providing them with

anything that they did not already know. Few people are going to be surprised that they regularly dose insulin sometime other than when they are supposed to, but this is not evident to the endocrinologists who are not with the patient and cannot witness this behavior. Not many people would willingly tell their doctor that they are not doing what he or she told them to do, but this might give physicians the opportunity to know that this behavior is happening. Hopefully, this can provide fodder for a conversation that may inform or gently nudge the patient into being more adherent to best practices and not create an opportunity for additional conflict.

Furthermore, if a person was regularly bolusing long after a meal and having postprandial hyperglycemia as a result of this other technologies could provide insight into how this was affecting BG and how it could be improved. A technologically capable medical team could show simulations that demonstrated how BG behaved after a late bolus and how it would have been better if insulin was taken before or at the time of a meal. Some may like the additional information and others would just be lost in the numbers.

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