Intelligent Diabetes Assistant

A Telemedicine System for Modeling and Managing Blood Glucose

David L. Duke

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Submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Robotics

The Robotics Institute
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Thesis

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ACCEPTED:

Chuck Thorpe — Thesis Committee Chair — 20 Jan 2010 — Date

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Abstract

The creation of a diabetes management assistant that can remotely collect data, increase communication between patient and care provider, and automatically analyze all available information could improve the health of many diabetics. Individual models, taking into account nutrition, medication, and exercise, with appropriate mathematical modeling, can learn accurate representations of specific patients suitable for providing therapy advice.

The fundamental goal of effective diabetes management is for the patient to select behaviors that maintain glycemic homeostasis. Thus the goal of an intelligent diabetes assistant is to help the patient select optimal behaviors. To do this the assistant must be able to learn how a patient's choices will affect blood glucose. From the care providers perspective a system should be able to provide detailed and accurate data about the patient, increase interaction between patient and expert, and be efficient. This thesis describes an intelligent diabetes assistant (IDA) designed to meet these goals.

IDA uses a mobile phone application and other devices to measure the three primary components that affect blood glucose: meals, medication, and exercise. The data are used to learn models for predicting how behaviors around meal times affect postprandial blood glucose, and to create a new continuous physiological model that includes exercise. These models can then be used in a variety of ways to generate therapy advice for the patient and health care provider. The complete system is presented in this thesis.

Acknowledgments

My journey through graduate school took an unexpended turn when I was diagnosed as a diabetic. Not only did this completely change my life, but it also changed my research focus from autonomous vehicles to diabetes. My wife, Lanny, has loved and supported me through this whirlwind of change in ways that I will never be able to adequately repay. I also want to thank my two sons, Elijah and Caleb, for providing unimaginable joy when the research and writing was frustrating. Thanks also go to my father, mother, brother, and sisters for their encouragement and support.

This thesis would have never happened if my advisor, Chuck Thorpe, had not given me the opportunity to explore this research topic and to go with him to Qatar, so thank you Chuck and Leslie for your friendship and the grand adventure we shared in Doha. I also want to thank everyone at Carnegie Mellon Qatar for helping me with this research project, and Jeff Schneider and Fernando De la Torre for all the video conferences. Beyond Carnegie Mellon, I want to thank Hamad Medical Corporation and specifically Dr. Mahmoud Zirie and Mazahir Mahmoud for their support for the project. The Qatar Diabetes Association, and specifically Karie Nahas and Nedaa El-Khatib, were an integral partner in this research as well. I also want to thank Bill Greer and Lars Hedin for all the great conversations over coffee, and the Qatar National Science Fund for supporting this project.

Finally, I want to dedicate this thesis to my two grandfathers: Johnnie Duke and Cliff Ganus. Johnnie has had type 1 diabetes for almost 70 years and is an amazing example of how to manage the disease. He is now 94 and going strong. Cliff has type 2 diabetes, but he does not let the disease control his adventurous life. So thank you Papa Duke and Pawpaw for demonstrating to me how to live life to its fullest as a diabetic.

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The best way to escape from a problem is to solve it.

Alan Saporta

Chapter 1

Introduction

The creation of a diabetes management assistant that can remotely collect data, increase communication between patient and care provider, and automatically analyze all available information could improve the health of many diabetics. Individual models, taking into account nutrition, medication, and exercise, with appropriate mathematical modeling, can learn accurate representations of specific patients suitable for providing therapy advice.

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The specific goals that were presented when this research project was initiated are listed below. The methods IDA uses to address these goals are described in the following chapters.

- Demonstrated a functioning system that can

  Collect data.

  Share data.

  Analyze data.

- Demonstrate an improvement over previous methods of prediction.
- Demonstrated policy search to suggest behavior modifications.

IDA uses a unique mobile phone based telemedicine system for collecting and sharing data. The data is used to train individualized models using Gaussian Process regression to predict the effect that medication, exercise, and nutrition has on postprandial blood glucose. These models are able to predict postprandial blood glucose with better accuracy than previous systems. A new physiological model that includes exercise was implemented as an Extended Kalman Filter to continuously model glucose dynamics and the uncertainty in the system. This model was compared with a model without exercise and auto-regressive models to determine the best method for modeling glucose dynamics. These models are used to generate useful therapy advice for the patient and analysis for the health care provider.

1.1 Motivation

In the United States there are approximately 20 million diabetics which is a prevalence rate of approximately 6% [8]. In Qatar, where this research took place, the prevalence rate of diabetes is approximately 15%. In the US the disease and its related complications are the 6th leading cause of death [41, 7, 83], but with proper management the risks of complications can be reduced [101, 102, 103, 104, 105, 106, 45]. However, many diabetics have a difficult time managing the disease on their own; a intelligent assistant could help such individuals. IDA is a system that links data from patients to care providers while processing patient behaviors. This work contributes to robotics in three areas: the construction of the diabetes assistant, the creation of a rich diabetes database, and the development of data modeling algorithms to process the data.

The overall goal of IDA is to provide physicians with the tools to improve the health of diabetics. It does this through the innovative combination of remote patient monitoring with feedback produced by a physician and intelligent system. IDA utilizes technologies that have emerged on the market in the last few years to collect high quality datasets *in situ*. Figure 1.1 represents the difference between the traditional diabetes self-management loop and our new proposed system.

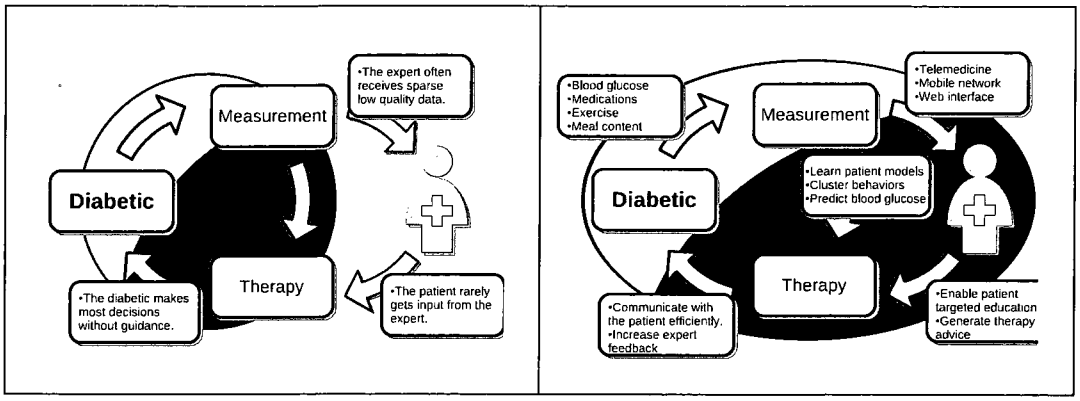


Figure 1.1: Adjustments to the diabetes management loop. On the left, the typical pattern for diabetes management rarely involves the care team. The diabetic is responsible for self-measurement and therapy decisions. The right image describes how the Intelligent Diabetes Assistant provides the care team with better information and more contact with the patient.

This research project uses this data to learn individually tuned models for the glucose regulatory system. The goal is to create a system that simplifies both the data collection process for the patient and the data analysis process for the care provider without compromising quality. Our success of the first goal will be measured by comparing predicted blood glucose values to the measured value.

The fundamental task in diabetes management is to select behaviors that maintain optimal levels of blood glucose. Thus the primary goal of modeling diabetes is to help the diabetic with this task. Before a decision support system can be developed, the system needs to be able to predict the outcome of a given behavior. The model can then be used to suggest a therapy adjustment which will move the system towards optimal levels of blood glucose.

1.2 Background

This project is multidisciplinary and may interest readers from a wide range of backgrounds. This section includes a detailed introduction to the physiology of diabetes and its treatment, as well as an introduction to machine learning.

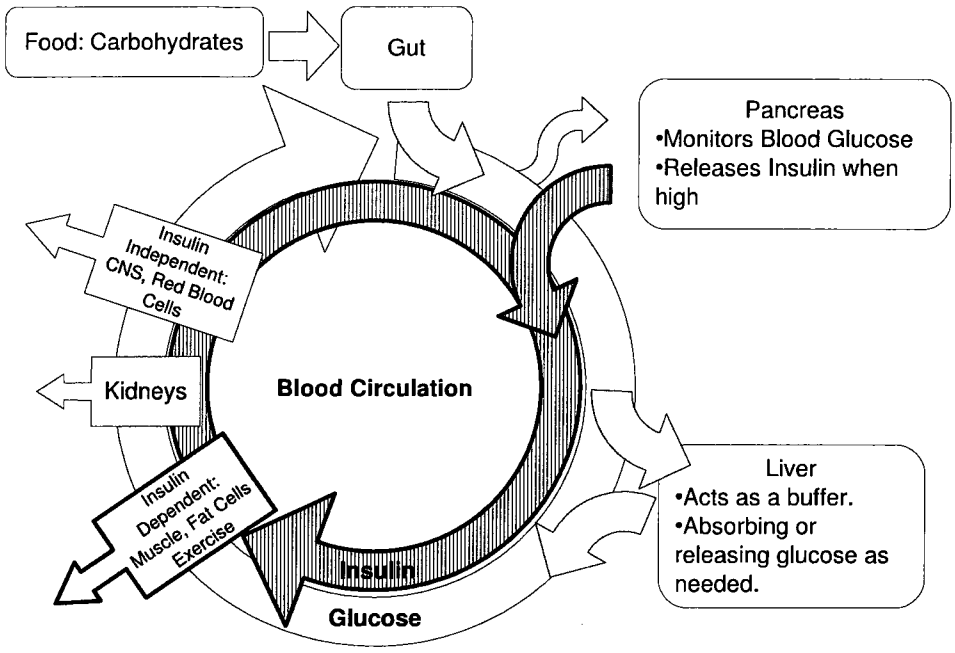


Figure 1.2: Normal blood glucose regulatory cycle. Glucose is introduced to the system by food intake, and removed by insulin independent organs, the kidney, and insulin dependent organs. The pancreas monitors glucose levels and releases insulin to regulate glucose.

1.2.1 Physiology of Diabetes

Diabetes is a chronic condition that occurs when a person's body does not properly regulate blood glucose levels. In a healthy person the concentration of glucose is maintained between 70-110 mg/dl with a biological control loop. Figure 1.2 shows the transfer of glucose from ingestion to removal in a normal individual. If the glucose level rises, the pancreas releases insulin to increase the transfer of glucose from the blood to muscle and fat and to increase the uptake of glucose into the liver. When the blood glucose level decreases, the insulin level drops as well and a person's liver increases glucose production to bring the glucose level back to normal. In a diabetic, this biological control loop fails, and an artificial correction must take place to correct the problem.

The type of diabetes present depends on the location of the failure in the control loop. Type 1 diabetes (T1DM) occurs when the pancreas does not produce insulin, so rising glucose levels

cannot be controlled. Figure 1.3 shows how the glucose regulatory cycle changes for a person with T1DM. Type 2 diabetes (T2DM) occurs when the insulin sensitivity of cells is decreased. Even though insulin is present to promote the transfer of glucose from blood to muscle and fat cells, the decrease in insulin sensitivity causes blood glucose to remain high. The glucose regulatory cycle for T2DM is diagrammed in Figure 1.4.

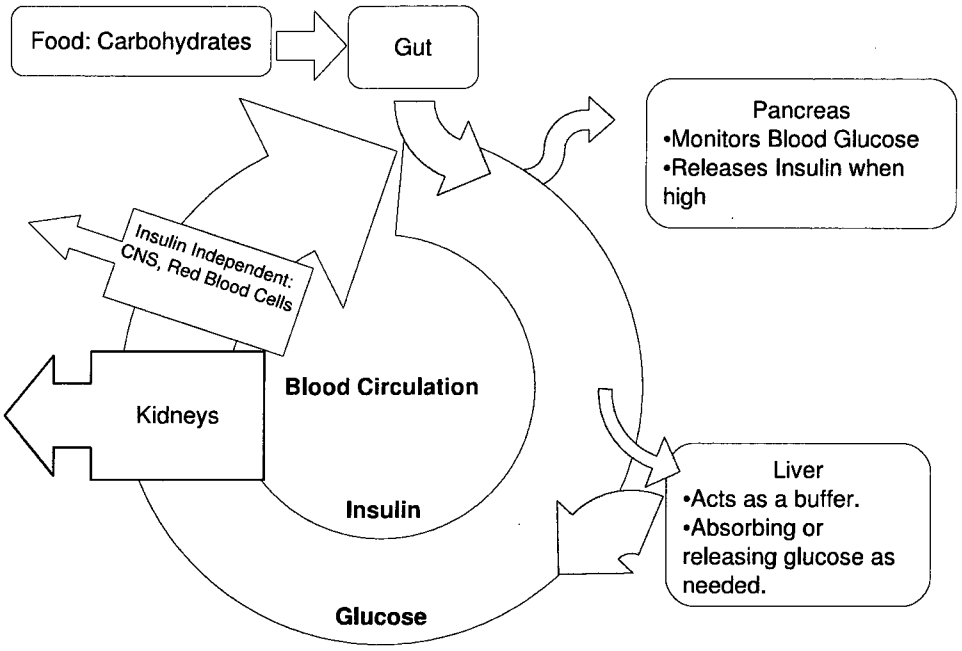


Figure 1.3: Blood glucose regulatory cycle in a patient with Type 1 diabetes. The pancreas is no longer capable of producing insulin, so glucose cannot be controlled.

Diabetes Therapy

When diabetes occurs the primary treatment goal is to maintain the optimal level of blood glucose by adjusting the inputs into the system. Many factors can influence blood glucose levels, but the most significant three are diet, exercise, and medication. These inputs are all controllable by the patient. Other factors that affect blood glucose, like stress and hormone changes, cannot be controlled by the patient, so the goal of a diabetic is to adjust the amounts and timing of diet,

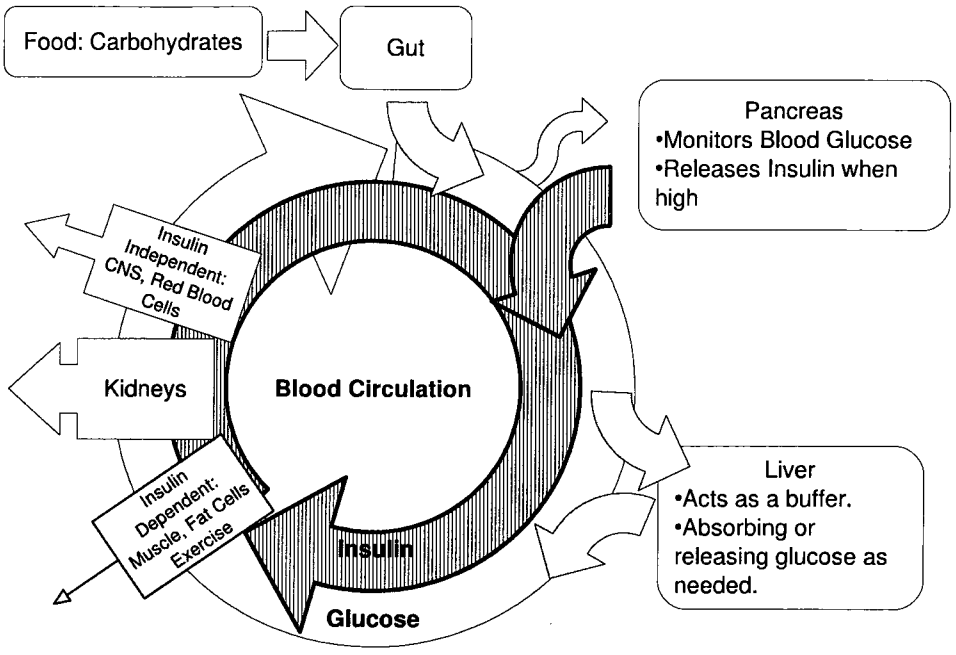


Figure 1.4: Blood glucose regulatory cycle in a patient with Type 2 diabetes. Decreased insulin sensitivity causes elevated levels of blood glucose.

exercise, and medication to control blood glucose levels.

If blood glucose is not controlled then hyperglycemia or hypoglycemia may occur. Hyperglycemia means that the blood glucose level is too high. It is often defined as having a fasting blood glucose greater than 140 mg/dl or greater than 180 mg/dl if measured postprandial, within two hours after a meal. It typically does not result in immediate danger, but it is strongly associated with long term complications [101]. Hypoglycemia is the result of low levels of blood glucose when it falls below 60 mg/dl. If immediate action is not taken and glucose levels continue to fall it can result in unconsciousness and death. Hypoglycemia is a major limiting factor blocking the development of an artificial pancreas [33, 34, 67].

Behaviors that cause one patient to become hypoglycemic may not have the same effect on other patients because each diabetic is different. When treating diabetics it is important for the care team to treat each patient as an individual.

In an ideal setting, the treatment plan for managing diabetes involves a support team. In the *Standards of Medical Care for Patients with Diabetes Mellitus* published by the American Diabetes Association [6] the ideal management plan is described as follows.

> The management plan [for diabetes] should be formulated as an individualized therapeutic alliance among the patient and family, the physician, and other members of the health care team.

In contrast to this quote describing the ideal plan, the department report from the endocrinology department at Hamad Medical Center in Doha, Qatar describes the common state of diabetes care in many clinics around the world.

> Diabetes and Endocrine disorders are quite common in Qatar, the patient load per staff in Endocrine and diabetes is high, therefore the time allocated per patient is short, in spite of adding more and more clinics,...

The physicians and care providers in Qatar, as in many hospitals worldwide, work hard to care for their patients, but they are constrained by time. This limits their ability to form an ideal "individualized therapeutic alliance." The adjustments to the diabetes management loop implemented in IDA, Figure 1.1, incorporate tools that shift the typical management pattern towards the ideal alliance. While IDA was not tested on a large patient population, the practical management of large numbers of diabetics might be improved with the data collection and communication tools implemented in IDA. It is designed to do the following.

- Measure all the primary inputs for diabetes.
- Simplify data collection for the patient.
- Share data between the care team and patient.
- Assist both patient and care team with data analysis.

This system implements these goals by collecting nutrition, medication, and exercise data to represent the primary inputs. The devices used to collect the data are simple for the diabetic to use.

Patient and care team share data using a cellular network and the Internet. And individual models of the patients' physiology are created to assist with data analysis and blood glucose optimization.

To achieve widespread use a system must be cost-effective, safe, and effective. This project addresses the effectiveness of the machine learning components of IDA and discusses possible ways it can improve cost-effectiveness and safety.

1.2.2 Diabetes and Machine Learning

Supervised learning is the process of identifying a function to represent a system based on a set of sample data. Sample data usually includes input data, X, and output data, g, that is to be predicted. There are many methods used to select the function that minimizes some error metric. The primary method discussed in this work is Gaussian Process regression. Rasmussen and Williams provide a detailed reference for Gaussian Process regression in [90]. This learning method is both flexible and robust.

There is a long history of using computer technology to assist in the management and understanding of diabetes. General guidelines for diabetes information systems and diabetes modeling have been presented by Young *et al.*[112] and the American Diabetes Association [88]. Below is a summary of previous work that has led to this project.

Initial information systems for diabetes were limited to blood glucose databases. In the early 1990's work began to make the databases more useful by adding telemedicine, modeling blood glucose, and incorporating decision support.

A study done by Montori *et al.* [82] determined that treatment of diabetes using telemedicine to transmit glucose values and receive feedback significantly improves glycemic control compared to telemedicine without feedback.

Farmer *et al.* [39] built a similar telemedicine system to test the benefit of having real time feedback about blood glucose results. They found an improvement in blood glucose with the telemedicine system, but believe that real-time decision support for medication therapy and lifestyle choices is needed to see significantly improved glycemic control.

Diabetes education by telemedicine was found to be as effective as in-person education by

Izquierdo [56]. In this study one group received in-person education, and the other education by telemedicine, and both groups experienced similar improvement.

The first noted physiological model for blood glucose was created by Bergman [15, 14] in order to determine insulin sensitivity during a glucose tolerance test. This model, commonly referred to as Bergman's minimal model, is strictly tailored for this test and therefore is not applicable to everyday use. From this starting point many other groups developed variants of the Bergman minimal model. One version [1] used a Bayesian approach to fitting the model to data. Other groups added parameters to model β-cell mass and insulin receptor dynamics [51] . A summary of other versions of this model can be found in [76].

The dynamics of blood glucose are complicated and non-linear, so an ideal model should include the major input and output variables. The primary inputs into the glucose regulatory system are carbohydrate intake, medication, and exercise. Many models have been developed to simulate the influence of carbohydrates and insulin on blood glucose[76], but these models usually ignore exercise. Autoregressive models were used by Bremer [22] to try to predict future blood glucose values based only on previous blood glucose measurements.

The influence of exercise on blood glucose is difficult to model. In order to maintain adequate blood glucose levels during exercise the liver releases glucose into the blood. Muscles, on the other hand absorb and utilize glucose if insulin is present. Therefore, depending on the patient's current blood glucose and insulin levels, exercise can cause hyperglycemia or hypoglycemia [31, 85, 84]. This is one reason why exercise is often left out of physiological models. Another reason is the challenge of measuring exercise accurately in everyday life.

The most successful method for modeling diabetics has been through the use of compartmental models. Compartmental models are commonly used to model the flow of material between different containers[57, 79]. Many groups have developed physiological models based in part on a compartmental system. The diabetes educational software package AIDA [1] developed by Lehmann [72, 71, 73] uses compartmental models to simulate the glucose kinetics for type 1 diabetics. He lists reasons why simulating blood glucose is difficult, and one of his first observations is that the

[1] http://www.2aida.net

quality of data collected is lacking in quantity and accuracy. He also says that the effects of exercise and stress are not well understood.

Tresp and Briegel [108, 23] have created a model that combines a compartmental model with a neural network. This model is unique because it includes a binary variable for exercise. Other groups have also used neural networks [107]. Tresp and Briegel used this model within a Monte Carlo framework to estimate uncertainty information.

The ability to estimate the uncertainty in a measurement is vital towards modeling any noisy system [92]. This idea has been pursued by Hovorka and Andreassen in their development if DIAS[2]. In this system they use Causal Probabilistic Networks or Dynamic Hidden Markov Models[10, 52, 53]. These models benefit from the ability to give an estimate for the probability of having a blood glucose measurement at a given time. Other groups have also investigated the use of Bayesian belief networks to understand diabetes [89].

More recent models have built on previous models and have focused on refining the components. Chen [27] created a model that is a mixture of Bergman's minimal model and AIDA. Man [78, 77] has focused on improving the models simulation of glucose production by the liver and the absorption of mixed meals (meals with varying composition of carbohydrate, fat and protein).

Many of these models have been used to try to optimize insulin dosage. Lehman and Deutsh used heuristic rules to generate therapeutic advice[100]. McCausland and Mareels also use rule-based control to give advice on insulin therapy [80]. DIAS has also been used for optimization[50].

One of the key problems in the field of diabetes modeling has been the lack of quality data that represent the major inputs to the system. Our system aims to overcome this problem by the use of new monitoring equipment and custom software to simplify data collection.

At a recent meeting of world leading glucose modeling researchers they identified three primary challenges facing future research [99]. The primary challenge they identified was the physiological variance in the glucose regulatory system. They also discussed the lack of openness within this research community; researchers rarely make models or data available for evaluation by outside sources. IDA addresses these challenges by collecting a rich database that can be shared with

[2]http://www.miba.auc.dk/ spp

outside researchers.

1.3 Introduction to IDA

The glucose regulatory system can be modeled to allow patient data to automatically be analyzed. Otherwise the health care team would face the burden of processing additional data, and the efficiency of diabetes management would decrease. There are two modeling problems that this thesis focuses on: predicting postprandial blood glucose, and continuously modeling blood glucose.

The first step of modeling is monitoring. Chapter 2 describes the data collection devices and software in detail along with a discussion on the design choices made to improve patient usability and system efficiency.

Data is a basic requirement for learning models. The clinical data collection protocol and descriptive statistics are in Chapter 3. The data is used to train and test the models. The two broad modeling problems discussed are the prediction of postprandial blood glucose and the continuous dynamic modeling of glucose.

1.3.1 Predicting Postprandial Glucose

Chapter 4 describes the modeling methods used to predict postprandial blood glucose. Postprandial blood glucose is typically measured two hours after a meal. This measurement is used to evaluate the management decisions made just before a meal; diabetics make most therapy decisions before eating a meal. They decide when and how much medication to take and how much food to eat. Predicting the outcome of these decisions would cover most therapy decisions made to improve blood glucose. Also, continuous glucose measurements are not required to learn or evaluate this predictor.

This problem can be viewed as optimizing an open loop control system for meals. The data set becomes the set of inputs immediately prior to a meal, X_{t-}, and the estimated inputs for the meal, x_t. The output becomes the blood glucose reading 2 hours after the meal, $g_{t+2hours}$.

This model is applicable to both type 1 and type 2 diabetics. It could be used to help select

an insulin dose, meal portion, or exercise to optimize glucose levels.

1.3.2 Continuously Modeling Blood Glucose

Chapter 5 details a new physiological model for continuously modeling blood glucose that incorporates energy expenditure. This new model is compared to a physiological model without exercise, an autoregressive (AR) model, and an autoregressive model with exogenous inputs (ARX). For the continuous modeling problem the system should predict the immediate change in blood glucose based on recent inputs to the system. The inputs to the system include X_{t-}, where the delay is chosen based on the length of influence of the system inputs. For example, fast acting insulin has an impact for about 4 hours after injection, so the lag time should be at least 4 hours. The output is the next value of blood glucose, g_{t+1}.

Machine Learning Approach to Prediction

There are two different prediction methods that can be used to solve the continuous modeling problem. One method is to use a parametrized physiological model. The second method is to use a black-box statistical method such as an AR or ARX model.

These problems are usually approached using physiological models, though no model currently exists that incorporates continuous energy expenditure. A modified physiological model that incorporates energy expenditure is presented in Chapter 5. Physiological models are useful because they can cover the entire space of patient behavior while giving an prediction that is justified by physiology. The biggest challenge to physiological modeling is the complexity of human physiology and impossibility of accurately modeling every component of the system.

Physiological models can also be used to generate advice that is optimal according to the model. For example if the patient wants to determine the best meal for a certain dose of insulin, the model could find the nutritional content that optimizes the predicted blood glucose. It can do this even if the patient has never recorded data from a similar event.

Additionally the problems have been set up to fit into many black-box statistical learning algorithms for regression or classification, and from a machine learning point of view these problems

poses many challenges. First, physiological data is noisy because the system is complex and direct measurement is difficult. Also, the size of the training sets is limited. Fortunately humans have habits, so their behaviors are not dispersed throughtout the space of possible actions. Instead, behaviors tend to repeat.

The repetition of behaviors means that the patient will have data recorded that represents their common actions and states. In these cases the data can be the model, as it inherently captures the complexity of the biological system.

Generating therapy advice using a strictly statistical regressor is limited by the inability to predict effects for behaviors that have never been seen. This is the exploration/risk problem seen in policy search. Since, in this case, the risk is death, the best approach is to gradually adjust therapy.

1.3.3 Therapy Advice

Chapter 6 describes some methods for generating therapy advice from the postprandial and continuous glucose models. Learning to simulate the system is useful for education purposes, therapy advice, and closing the blood glucose control loop. An educator could let a patient manipulate inputs to a simulator to learn how the inputs affect blood glucose. Because the simulator would be trained on the patient's data, the education would better reflect the patient's individual system. A simulator could also be used to find appropriate inputs to optimize blood glucose levels. It could suggest an insulin dose or food portion that would result in better control. Finally, it could be used with an insulin pump and continuous monitoring system to develop a personalized feed-forward control strategy that could function as an artificial pancreas.

The problem of optimizing future blood glucose levels for diabetics is often reduced to finding the needed insulin intake to optimize future blood glucose. This leads directly to the artificial pancreas control problem. In general a blood glucose simulator is more applicable for patients with type 1 diabetes.

1.3.4 Other interesting results

Diabetes management is such a large problem that other interesting results came about while collecting this data and studying this problem. Chapter 7 describes some of these initial results related to calculating meal portions and recognizing meals. These are very preliminary, but they may lead to future research projects.

1.3.5 Conclusions and Future Directions

Chapter 8 contains a summary of the conclusions from this thesis and a discussion on the future of robotics in chronic care management. As the prevalence of chronic conditions such as diabetes continue to grow more opportunities will arise for developing intelligent assistants to help patients and health care providers manage the diseases.

To linger in the observation of things other than the self implies a profound conviction of their worth.

Charles-Damian Boulogne

Chapter 2

IDA Measurement System

The first step toward predicting blood glucose and optimizing therapy is the system of devices that interacts with the patient and health care provider. The Intelligent Diabetes Assistant's data collection system, described in the chapter, was designed to be simple to use, efficient for the patient and health care provider, and complete in its measurements of the behaviors that affect glucose. This chapter describes the data collection system in detail and the system for interacting with the health care team.

2.1 Introduction

In order to learn to model how a patient's behaviors impact blood glucose, an intelligent diabetes assistant must first be able to accurately measure data that capture the input and output of the system. This requires a balance between the accuracy of a measurement method and simplicity of use. If a collection method is too complex or time consuming for a patient then one ends up with less data because of the extra burden placed on patients. Also, the patients must be able to go places and live life without being burdened by the data collecting equipment. This chapter describes IDA's data collection methods.

When learning models for prediction from patient data, the prediction performance is limited by the uncertainty in measurements. To model diabetes a system should collect measurements of

meal consumption, exercise, medications, and blood glucose. While there are other factors that affect blood glucose, these are the inputs to the system that are controllable by the patient. Stress can elevate blood glucose, but it is difficult to both measure and control.

There have been numerous diabetes telemedicine studies, but IDA uses a unique set of data collection equipment. Most studies include measurements of medications, carbohydrates, and blood glucose. IDA augments this data by also collecting exercise data and images of meals. These two data provide insight into the behaviors of the patient and place blood glucose measurements into the context of the patient's life.

In addition to the type of measurements, it is important to collect data that accurately reflect the patients typical lifestyles. To do this, the equipment must be mobile and convenient to use. In some cases this requirement causes the gold standard of data collection methods to be infeasible because of the impracticality of daily using the method.

IDA primarily uses a mobile phone based data collection system because it is very common, portable, and networked. This allows patients to have the data collection equipment with them at all times without requiring additional devices. It also provides a mechanism for providing feedback to the patient. While this study did not specifically look at health outcomes when providing feedback to the patient, IDA was designed with these features.

The data collected by this study are unique, so one of the goals is to determine the feasibility of collecting this data. If collection is feasible, a second goal would be to determine a minimal set of data necessary to model the glucose dynamic system in order to optimize blood glucose. Measurements that do not provide benefit would not need to be collected so that the collection would be more efficient.

The mobile phone platform selected for this study was the Nokia N70 seen in Figure 2.1. This was selected based on its implementation of J2ME APIs. Originally the mobile application was written as one monolithic piece of software; but after testing, it was divided into a modular design that could easily be customized for each patient. Diabetes management can vary greatly among patients, and diabetes management software needs to be flexible. This phone also allowed individually customized shortcuts to be placed on the home screen to make entering data more

efficient.

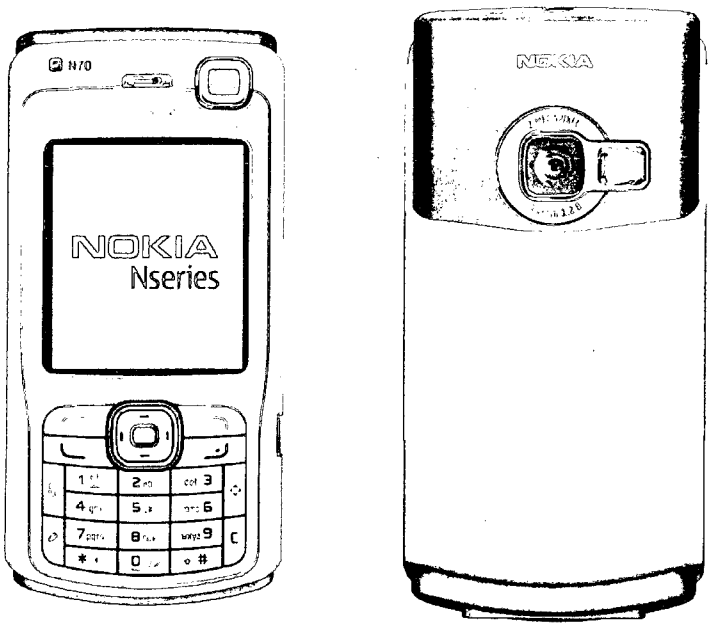


Figure 2.1: IDA was implemented using Java on a Nokia N70 Mobile phone.

To summarize the requirements of the data collection system before going into specific detail, it is important for the data collection equipment to be:

- **In situ** - measuring a patient's typical behavior in real life
- **Accurate** - minimizing the uncertainty of the measurement
- **Efficient** - minimizing patient time and effort
- **Complete** - measuring all controllable inputs to the system
- **Networked** - capable of telemedicine

2.1.1 Blood Glucose

Blood glucose was measured by the patient with a OneTouch Ultra-Mini glucose meter, displayed in Figure 2.2, provided to each patient for the study. The gold standard for measuring blood

glucose is the venous glucose concentration, but this cannot be practically used to measure glucose concentrations in a patient's everyday life. Capillary glucose concentrations measured by the patient using a glucose meter are a reasonable substitute for this standard. However, this does add error to the system. glucose meter measurements taken by an expert following the correct protocol have an uncertainty of ±6% mg/dl, but measurements take by patients have an uncertainty of ±15% mg/dl because patients often do not follow the correct protocol [97].

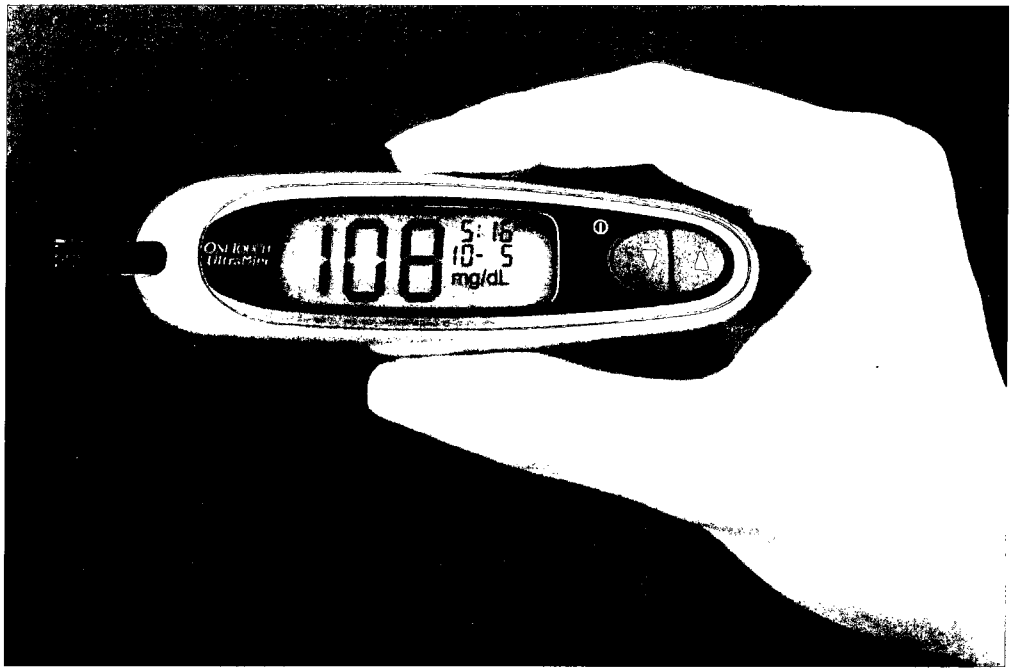


Figure 2.2: OneTouch Ultra-mini glucose meter

In an ideal system the glucose meter should be built into or linked wirelessly to the mobile phone, but in its current stage of development IDA requires the user to input the measurement into the mobile phone application displayed in Figure 2.3. This introduces another source of error as the patient might enter the wrong number. To minimize this effect on the outcomes of the study, measurements that were outside of the physiological possible range of blood glucose were omitted from analysis: glucose concentrations greater than 1000 were omitted from the study.

Blood glucose measurements taken with a glucose meter are fairly accurate but very sparse. Continuous glucose measurements (CGM) can be collected once every five minutes, but their

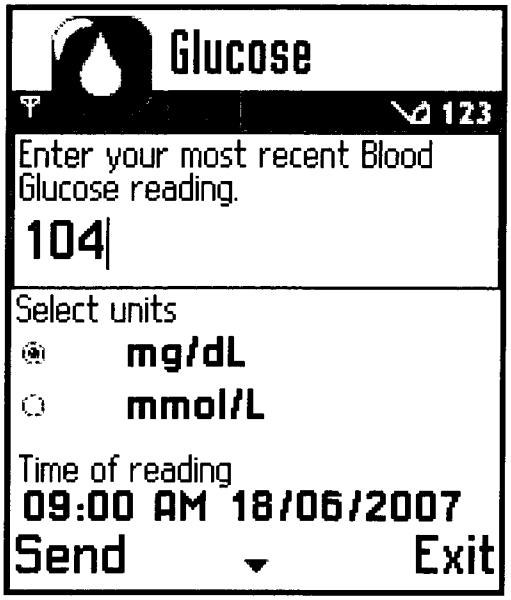


Figure 2.3: IDA blood glucose data entry application.

accuracy is significantly lower than blood glucose measurements. CGM are collected by measuring the concentration of glucose in the interstitial fluid. This quantity is closely related to blood glucose, but it has been shown to be less accurate during times of rapid increase or decrease of blood glucose. The CGM value tends to lag behind the blood glucose concentration. Figure 2.4 compares CGM measurements and BG measurements taken using IDA at identical times. The average error between CGM and BG measurements is $\pm 20\%$ and only 67 percent of the points are in region A of the Clarke Error grid.

2.1.2 Food Intake

Determining the nutritional content of a meal outside of a lab is the most challenging measurement to make. The primary value to estimate is the amount of carbohydrates in a meal because carbohydrates are quickly absorbed as glucose into the blood, but blood glucose is also affected by the type of carbohydrate and overall composition of the food. Generally, patients are asked to perform carb counting: which is estimating the amount of carbohydrates they are about to eat. Even with training, patients estimate carbohydrates with an error of $\pm 30\%$ [63]. Meal consumption

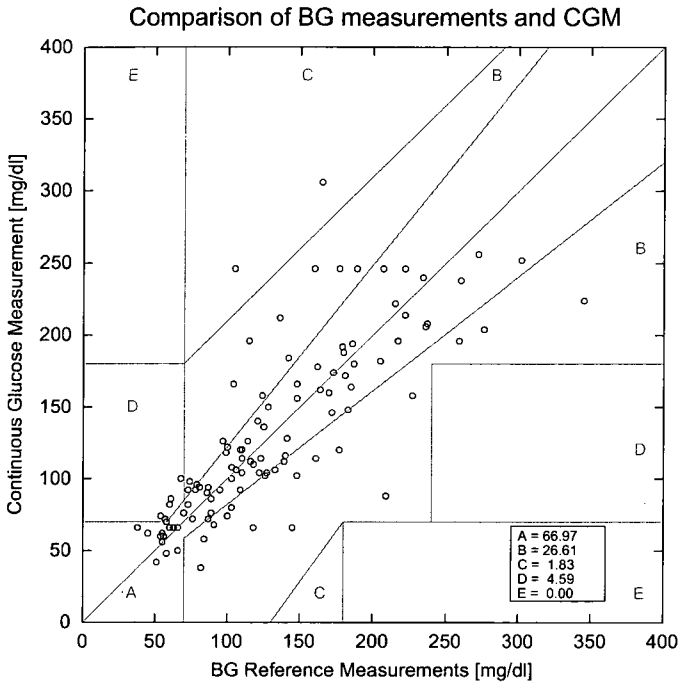


Figure 2.4: Comparison of CGM and BG measurements. The average error is ±20%.

is the input with the largest amount of uncertainty while also causing the largest disturbance to the system.

Meal consumption is also a large source of patient individuality. This study includes a wide variety of meals eaten by patients from Qatar, Egypt, India, Philippines, Australia, and other cultures. However, most carbohydrate counting educational material comes from Western sources and does not directly apply to many of the common meals in other cultures. This is one reason why it is important to collect more than a patient's estimation of carbohydrates.

In addition to estimated carbohydrates, IDA lets patients photograph each meal. Figure 2.5 displays the mobile application used to collect meal images. An image provides important additional information that a single carbohydrate estimation omits. It allows a dietitian to evaluate a patient's ability to estimate carbs. It can be used to estimate the amounts of fat, protein, and other nutrients. An image can be used to estimate the portion size of food items. The values derived from an image have a high degree of uncertainty, but the extra information is valuable.

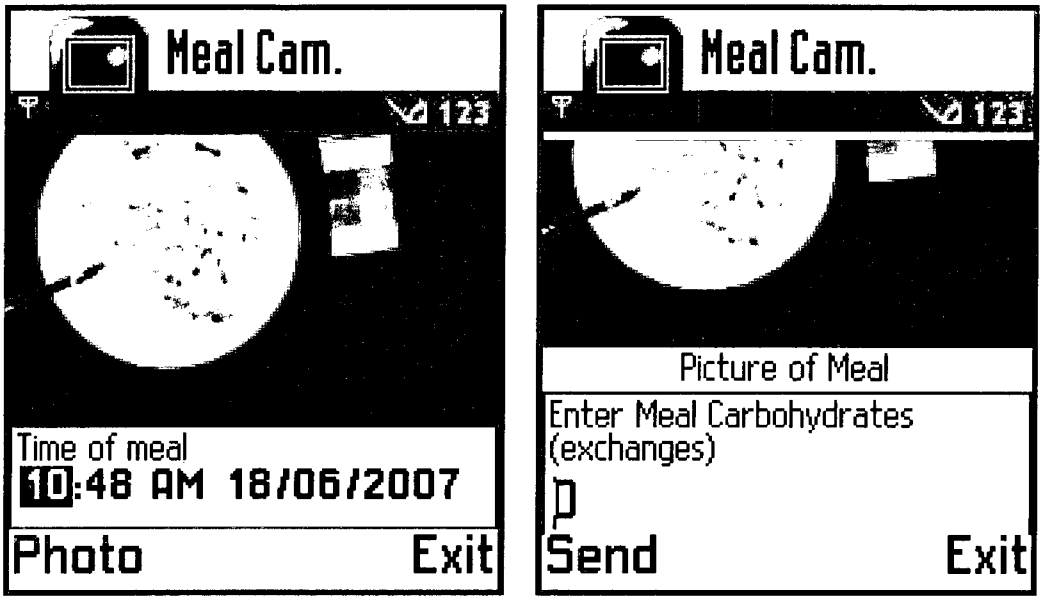


Figure 2.5: Meal image collection application

Another advantage to collecting images of meals is its simplicity. Most modern mobile phones include a camera, so patients do not need to carry additional equipment or log books. A photograph can be taken in seconds compared to hand writing each food included in a meal in a log book.

The nutrition data contains the following measurements for a meal:

Nutrition Data	Units
Carbohydrates	*grams*
Protein	*grams*
Fat	*grams*
Total Calories	*Kcal*
Additional nutritional values are also available	

Most data collection systems only record a patient's estimate for the carbohydrates in a meal. By also estimating the protein, fat, and total calories, IDA can capture mixed meals as well.

2.1.3 Medications and Insulin

Patients with diabetes may use many different types of therapy plans that require different medications. The medications can be grouped into three main therapy strategies. The first group

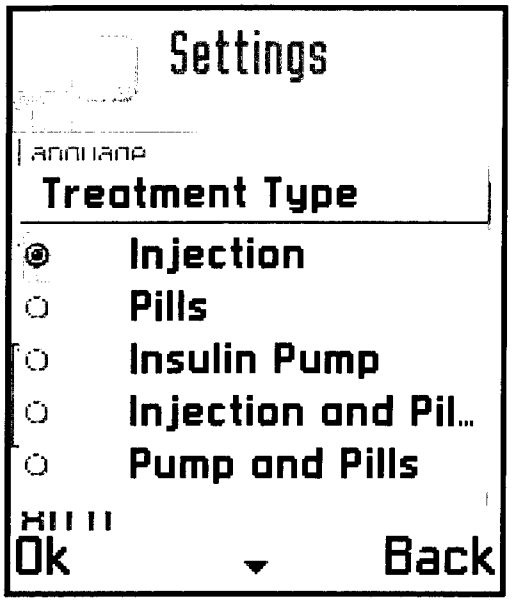


Figure 2.6: Medication settings

is oral medication. This primarily applies to patients with type 2 diabetes. The second group includes patients with both type 1 and 2 diabetes who require insulin injections. Sometimes these patients also take oral medications. The final group is patients using an insulin pump. IDA can be customized for any combination of these three therapy groups.

Figure 2.6 is a screen-shot of the options for patient therapy. Selecting one of these options customizes other interfaces to simplify data entry for the patient in order to make the process more efficient.

In an ideal system, medication types and doses would be collected automatically using smart pill dispensers and injectors. Because networked versions of these products are not readily available, patients were required to enter doses manually into the mobile phone.

Medications

Most patients with T2DM are started on a therapy regimen of oral diabetes medications, diet, and exercise. For some of these medications the timing is important, so IDA contains a simple application for recording timestamped medication data. The medication data contains the following

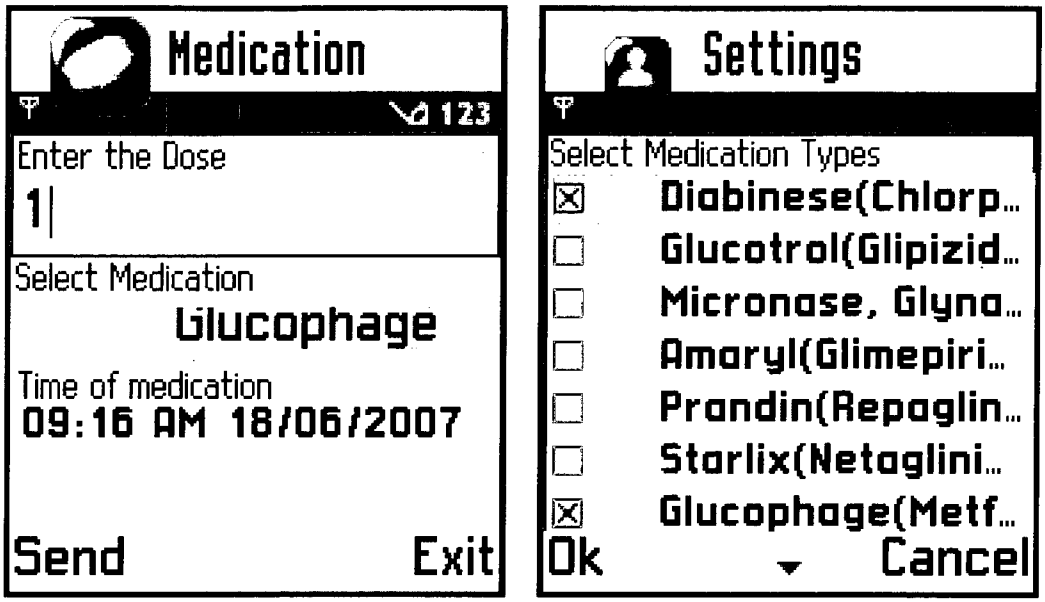


Figure 2.7: The medication application is customized for the patient so that data entry is efficient.

measurements:

Medication Data	Notes
Medication type	
Dose	*Dependent on type*
⋮	*Additional medication if necessary*

Figure 2.7 displays two screen shots of the medication entry application. The application is customized based on the types of medications selected in the settings application. Most patients take a consistent dose so the default dose can be remembered as well.

Insulin

All patients with type 1 diabetes, and many with type 2, are required to take insulin. There are many types of insulin classified by their time to peak action. The most common types of insulin are listed below.

- **Rapid Insulin** - This insulin reaches peak activity after 45 minutes. The most common types are Humalog and Novalog.

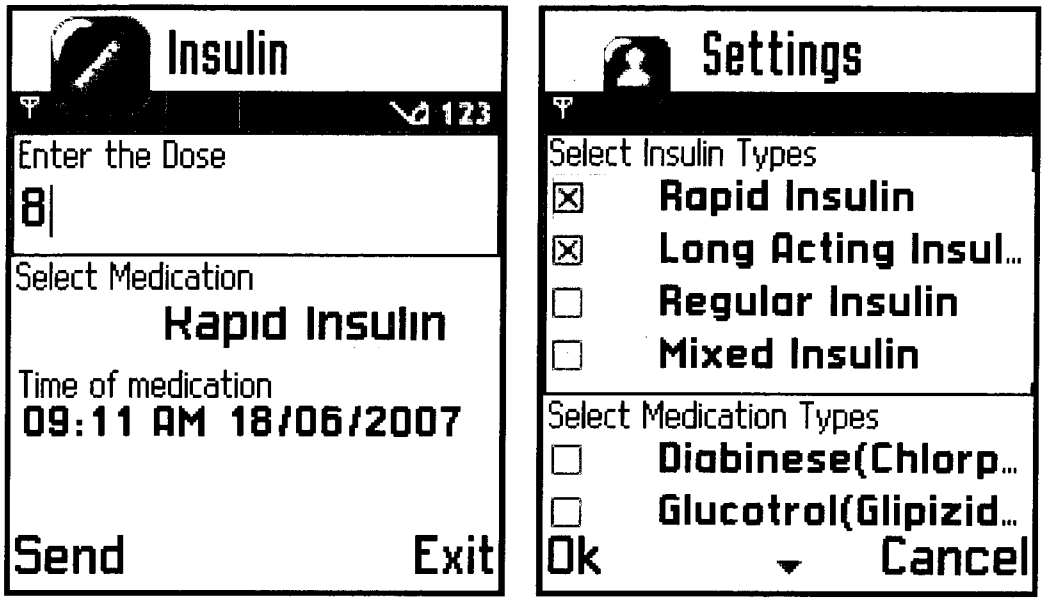


Figure 2.8: Insulin injection application

- **Long Acting Insulin** - There is no peak in this insulin as the absorption rate is fairly constant. The most common commercial type is Lantus.
- **Regular Insulin** - This is also referred to as human insulin. The time to peak activity is closer to two hours.
- **Mixed Insulin** - Mixed insulin contains a mix of regular or rapid acting insulin and a longer acting insulin. The most common type is a 70/30 mix of long acting and regular insulin.

IDA also allows the insulin application to be customized for each patient. The types of insulin used by the patient can be selected so that data entry is quick. Figure 2.8 displays screen shots of the insulin injection data entry application and the settings options.

This application is only for patients using insulin injections. Patients using an insulin pump require a more complex application to capture the additional capabilities of insulin pumps.

Insulin Pump

There are two components to insulin pump therapy: the basal insulin profile and bolus doses for meals. The basal profile specifies an insulin dose rate for each 30 minute time window in the day.

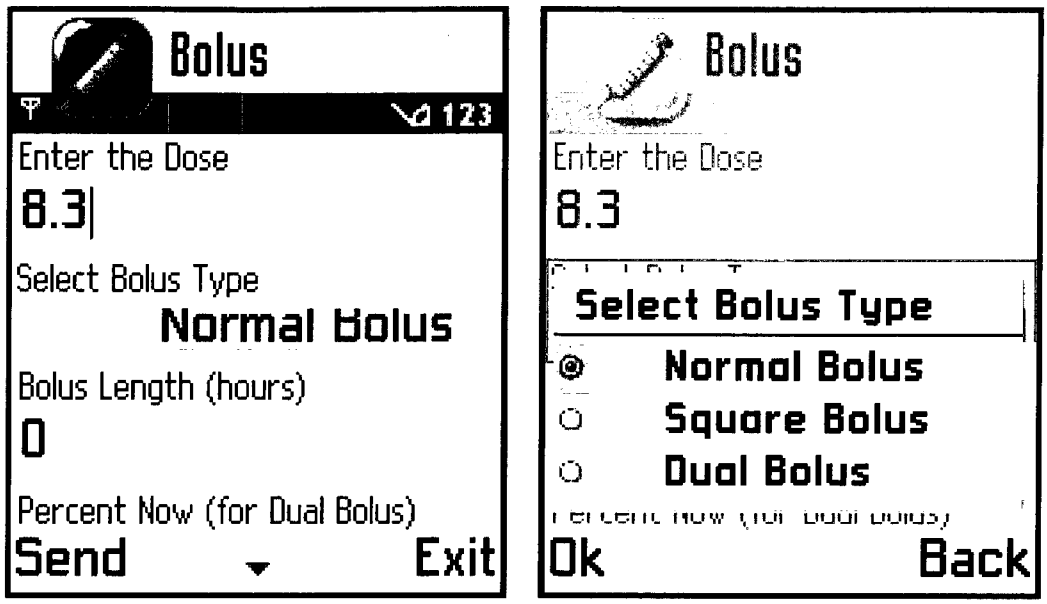


Figure 2.9: Insulin bolus application

Most pumps allow the user to define and save multiple basal profiles. IDA mimics this functionality by allowing users to save multiple basal profiles.

Most insulin pumps can also give different types of bolus insulin patterns. The three most common types of bolus patterns are listed below.

- **Normal Bolus** - All the insulin is infused at once.
- **Square Bolus** - The insulin is infused at a constant rate over a period of time.
- **Dual Bolus** - This is a combination of a normal and square bolus defined by a percentage of insulin to give as a normal bolus.

Figure 2.9 displays a screen shot of the bolus application and the bolus type selection. Figure 2.10 displays the basal profile editor. In future systems the bolus and basal entry procedures could be simplified if an insulin pump could be wirelessly interfaced to a mobile phone.

2.1.4 Meal Wizard

Around meal times patients often measure their blood glucose, inject a dose of insulin, and estimate meal carbohydrates. To make data entry around meals more efficient, a meal wizard application

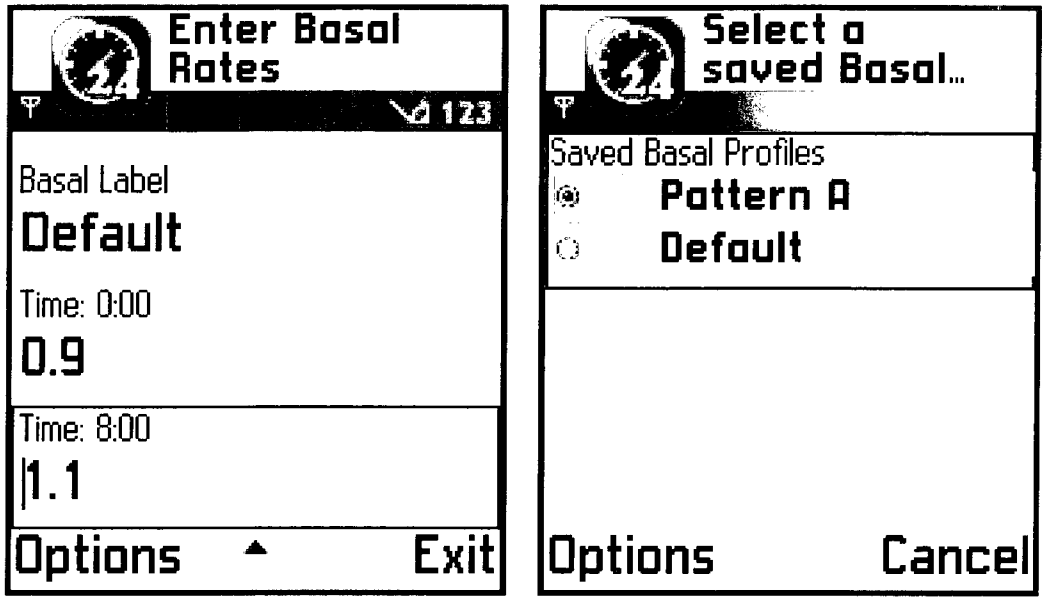


Figure 2.10: Basal Profile Application

was developed that combines the blood glucose, bolus, and meal image applications to step the patient through the process.

2.1.5 Data Collection Alerts

To help patients adhere to data collection protocols IDA notifies the patient if a blood glucose measurement was not taken before a meal or two hours after a meal. It will also notify patients on insulin injection or insulin pump therapy if no insulin dose is recorded before a meal. Other measurement protocols can also be programmed into IDA to improve patient adherence.

2.1.6 Exercise

The three controllable inputs that affect blood glucose are meals, medication, and exercise, but most diabetes management systems overlook physical activity. Exercise can have a significant impact on blood glucose, and it should be included in a complete diabetes management system.

Like meals, exercise can be difficult to measure. There is debate over the most useful metric for quantifying exercise for diabetes research. The main three forms of exercise data collection

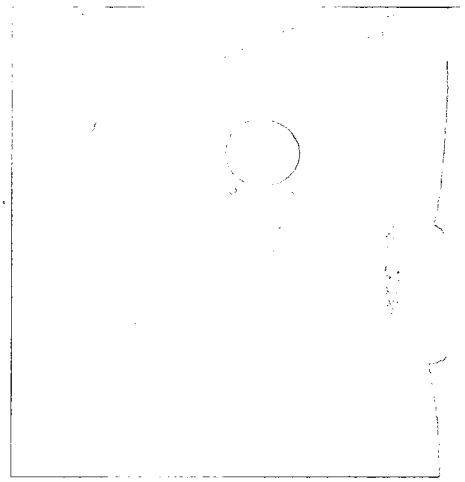


Figure 2.11: The Bodymedia Sensewear armband is used to estimate energy expenditure.

are exercise logs, measuring the heart rate, and accelerometers to measure movement. The device selected for exercise measurement for IDA is the Bodymedia Sensewear Armband. It uses a combination of thermometers to measure skin temperature, accelerometers to measure movement, and sensors to measure galvanic skin response to estimate the amount of calories burned per minute.

The Bodymedia Armband, displayed in Figure 2.11, is worn on the upper arm. The exercise data measured and calculated by the armband contains the measurements in Table 2.1 taken every minute.

The data collected by the armband can potentially be used in many other ways beyond estimating exercise. For example, the estimate for sleep could be used to adjust the device behavior to minimize patient annoyance.

The Armband has wireless capabilities, but it currently cannot be interfaced wirelessly to a mobile phone. Ideally the data would be available in real-time. Currently IDA only uses the exercise data in retrospective analysis.

2.1.7 Additional System Capabilities

In addition to the data collection capabilities, IDA can also record text messages, audio messages, and hemoglobin A1c. It can also receive text messages from a health care provider. These specific

Exercise Data	Units
Energy expenditure	$Kcal/min$
Physical activity	Binary
Sleeping	Binary
Lying down	Binary
Galvanic skin response	$\mu Siemens$
Number of steps	steps
MAD acceleration lateral	g
MAD acceleration transverse	g
Average acceleration lateral	g
Average acceleration transverse	g
Peak acceleration lateral	g
Peak acceleration transverse	g
Cover temperature	$°C$
Skin temperature	$°C$
Heat flux	W/m^2

Table 2.1: Measurements recorded by the Bodymedia armband

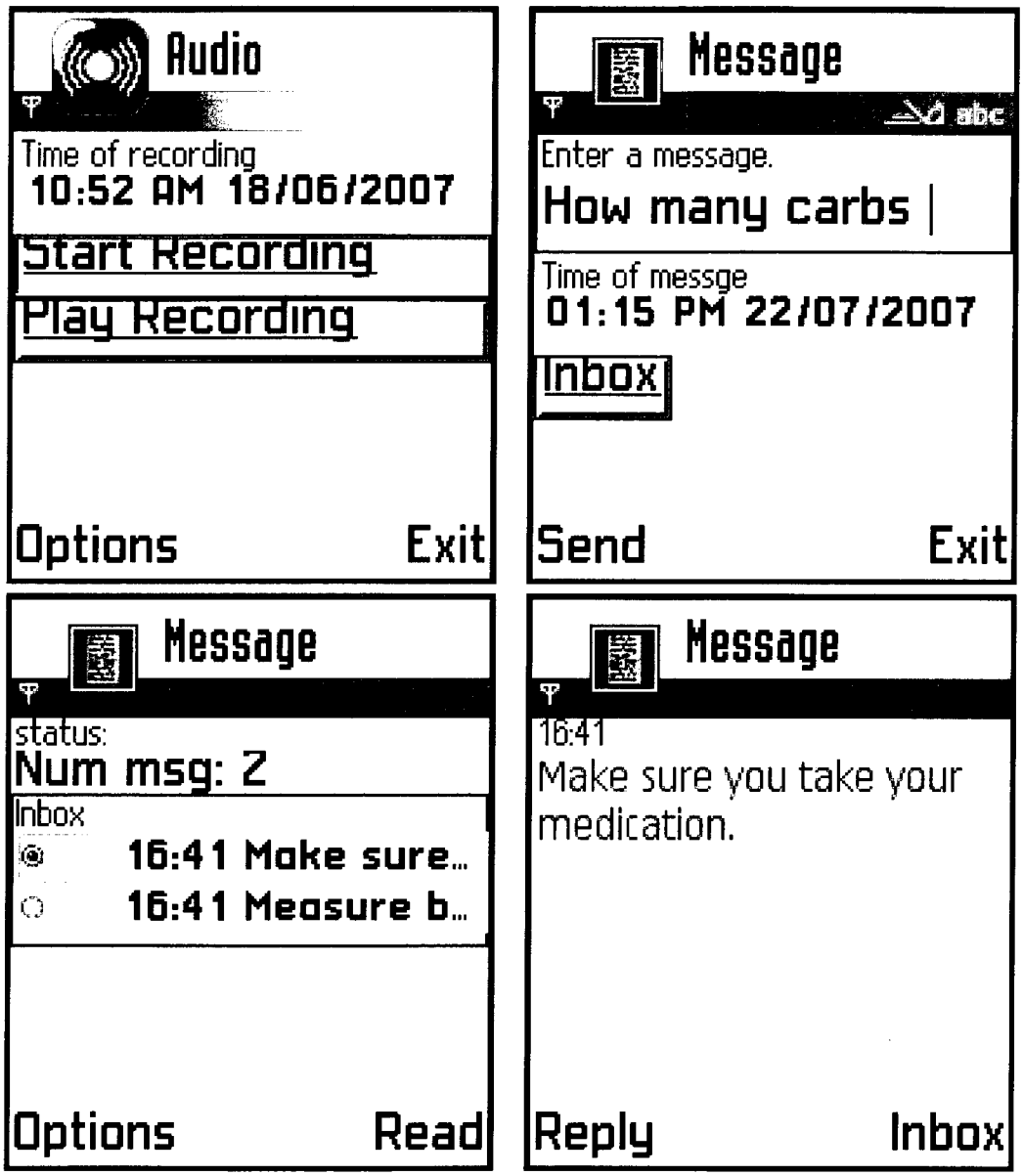


Figure 2.12: Other IDA capabilities include recording audio and text messages and receiving text messages from a health care provider.

capabilities were not used in the clinical study, but they could be used in future studies. Figure 2.12 contains screen shots of IDA's additional applications.

2.2 Conclusions

The design goals for the data collection devices and applications used by IDA along with how IDA addresses each goal are listed below.

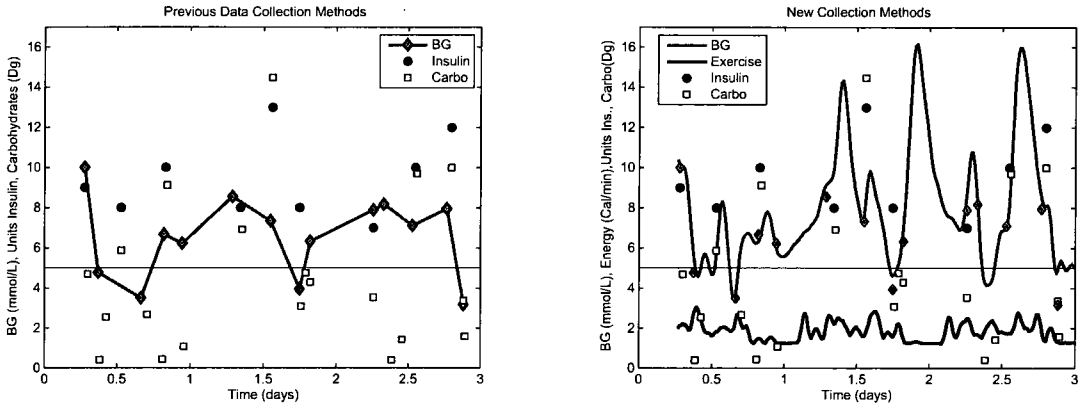


Figure 2.13: Data collected with a CGMS, glucose meter, Bodymedia armband, along with user recorded food and medication intake.

- **In situ** - Patients can easily take the mobile phone and armband with them to collect data that represents their real-life behavior.
- **Accurate** - The devices selected provide the best balance of accuracy and portability.
- **Efficient** - The mobile phone application was designed to minimize the number of key presses necessary to enter data. Whenever possible the application is customized to simplify data collection.
- **Complete** - IDA measures meal intake, medications, and exercise along with blood glucose.
- **Networked** - The mobile phone provides network access for the patient.

The devices and software created for IDA achieve the design goals for a useful telemedicine diabetes management system. With this proposed system all the data necessary can be collected to evaluate the diabetes models. Figure 2.13 demonstrates the quality of data from previous

measurement techniques. The data is sparse and lacks a measure of exercise. It is placed next to a plot containing the detailed data that has been collected using IDA.

As we acquire more knowledge, things do not become more comprehensible, but more mysterious.

Albert Schweitzer

Chapter 3

Telemedicine and Clinical Protocol

3.1 Introduction

A clinical study was designed to evaluate IDA as a means of remotely collecting diabetes lifestyle data and to develop algorithms for automatically analyzing the data. Chapter 2 described the devices and applications that IDA uses to interact with patients, and this chapter describes IDA from the health care providers point of view. Unfortunately no company currently has a system available to collect all the data necessary for this project, so part of this project was to develop a system that is flexible enough to include data from different sources and combine it into a single usable source. Figure 3.1 diagrams the flow of data from the devices used in IDA by the patient, to the database and analysis system, and then passed through the care provider back to the patient.

This chapter will present the web-based interface the health care team uses to view data, process meals, and communicate with the patient. Then the clinical data collection protocol used to collect patient data will be presented followed by descriptive statistics of the patients included in the study.

3.2 Telemedicine System

To make the data useful for physicians a web-based graphical front-end to the database was created. The interface allows the user to view and interact with the data and communicate with the patient.

After the data are collected they are transmitted instantly to a secure MySQL database server.

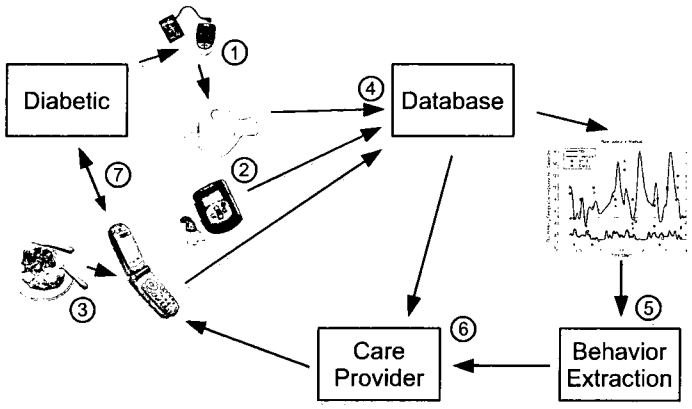


Figure 3.1: IDA data flow from patient to database where therapy advice is generated and returned back to the patient through the care provider.

A custom web interface has been developed to allow the patient or care provider to access, interact with, and process the data. The web application has three primary interfaces that allow the patient or care provider to view and analyze data. The first is a data plot that displays all the collected data on a time-line. This lets the user visually identify patterns in the diabetics management in order to improve therapy. For example a dietitian could view an image of the patients meal with a plot of the effect the meal had on the patients blood glucose. Figure 3.2 displays a screen capture of the data plot interface.

The second interface is designed to allow a dietitian to evaluate the nutritional content of a meal based on an image of the meal. The interface displays an image of the meal and an text box to search a food database. Foods are identified and the total nutritional content of the meal is calculated. For the study the dietitian hand labeled the outline for each food in the meal. Figure 3.3 displays this interface. In this example the meal selected is high in carbohydrates and results in postprandial hyperglycemia.

The final interface allows the user and care provider to send text messages between the web interface and the mobile phone. This facilitates instant feedback from the care provider. Combined, these three interfaces provide the care team with better information and tools to monitor the patients health and the means to communicate advice. Figure 3.4 contains a screen-shot of the messaging interface. This interface lists both text messages and audio messages from the patient.

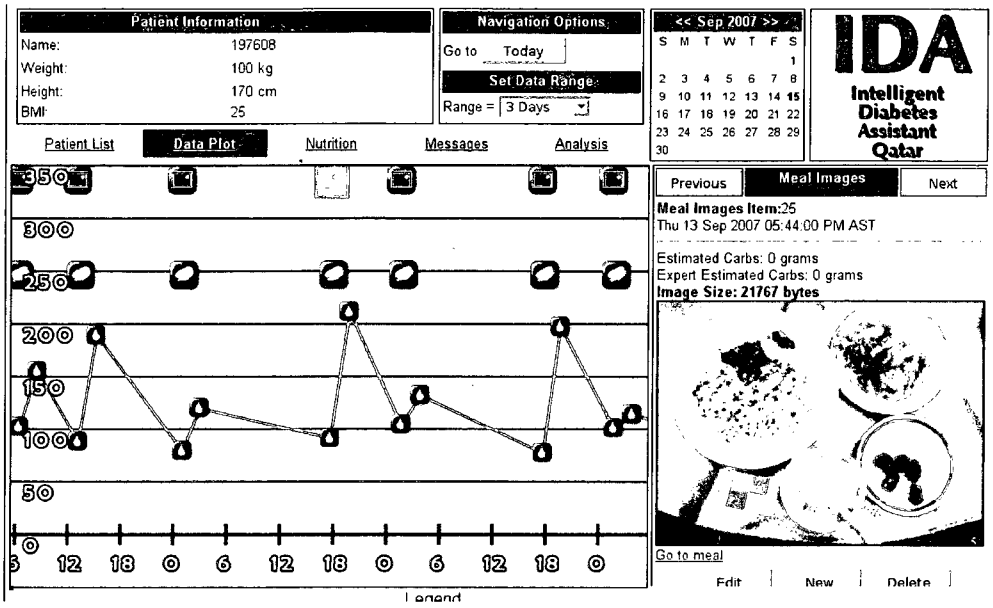


Figure 3.2: The time-line interface combines all data on one time-line and allows the health care provider and patient to explore the impact that behaviors have on blood glucose.

During the data collection, the web interface allowed the research team to monitor patients participating in the study. The study did not use the communication features to measure the impact of the system on patient health. It was designed primarily as a data collection.

3.3 Data Collection Protocol

Prior to the data collection phase each subject was taught how to use the data-collection devices, answered a questionnaire, and had standard blood-work done. The subjects were informed in detail about the project, including the potential benefits and risks, and required to sign a consent form. This experiment was conducted under the review of the Hamad Medical Corporation Research Committee (#7017/07) and the Carnegie Mellon University Institutional Review Board (HS08-139) in compliance with the Helsinki Declaration.

The patient questionnaire was used by a collaborating dietitian to evaluate the subject's knowledge of diabetes, nutrition, and other lifestyle factors that can affect blood glucose. Blood was drawn by a medical practitioner and used to assess each subjects health status. The sample was

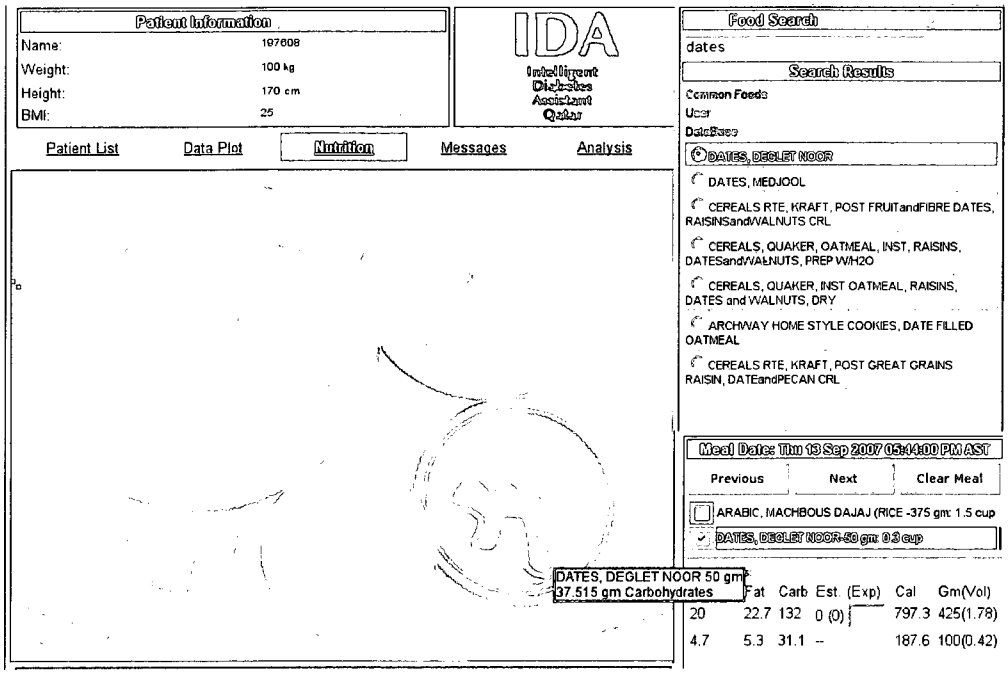


Figure 3.3: The meal analysis interface lets the dietitian search a food database to label foods contained in the meal image. The interface calculates the total fat, protein, carbohydrates, and calories for the meal.

be used to measure lipids, blood glucose, and HbA1c. If the subject had blood work done in the past month then it would be used.

Subjects who were younger than eighteen, pregnant, or experiencing diabetes related complications were excluded from the study. The study also required that patients be able to understand basic English.

During the data collection phase the subjects used IDA's mobile phone application to enter medication information, blood glucose readings, audio and text messages, and meal images. The data entered on the phone was transmitted wirelessly to a secure database. The software is written to work on most modern mobile phones. If a subject had a compatible phone and wished to install the software on it, they were allowed; otherwise a phone was provided. Costs incurred by the subject for data transmission related to this project were covered by providing the patients with enough prepaid minutes to complete the study. The patients were financially responsible for any additional charges.

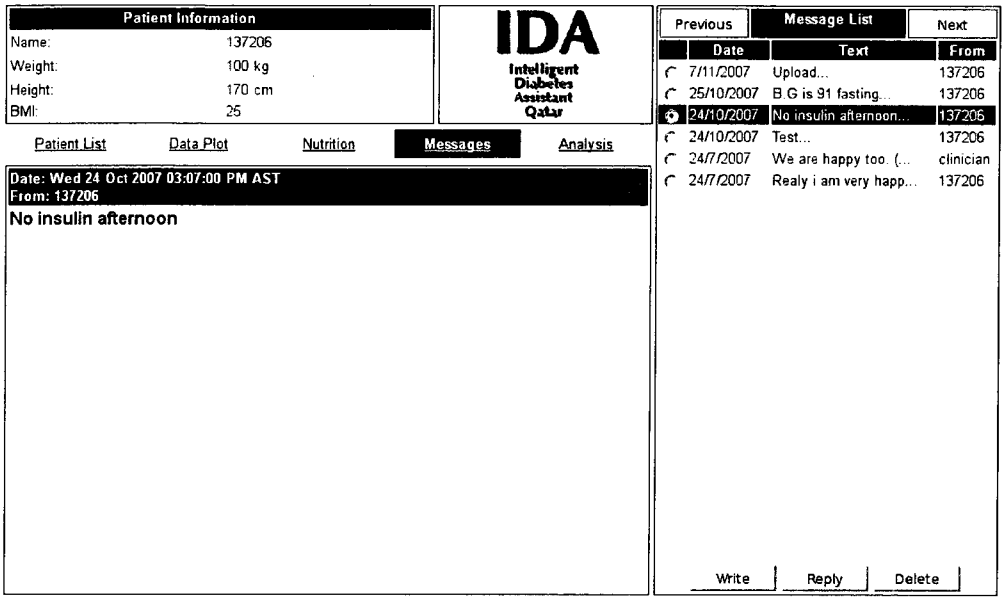


Figure 3.4: The messaging interface is designed to be similar to an email Inbox with both the sent and received messages listed on the right side in order to track the time-line of a conversation.

The subjects also used a Bodymedia Sensewear Armband and to monitor their energy expenditure. The subjects were instructed to wear the armband continuously, except for during showers or swimming. Exceptions were made for subjects who experienced discomfort when wearing the armband at night. After the study the data were downloaded from the armband and uploaded into the database. Detailed instructions for each device were provided to each subject along with a phone number where they could call for additional help.

The data-collection lasted for two weeks and included two weekends. Each day the subject was instructed to follow their normal self-management routine as prescribed by their care-providers while recording the specified data. The subjects measured blood glucose before and two hours after each meal, recorded all diabetes related medications, and photographed each meal. Figure 3.5 contains a diagram of the data collection protocol.

This data-collection is designed to capture data that reflects the subject's lifestyle patterns, so therapeutic advice was not be given until after the collection was complete. However, a physician monitor the data, and if at any time the physician noticed a harmful pattern in the data, they were to contact the subject. All patient data was stored securely and anonymously by a random

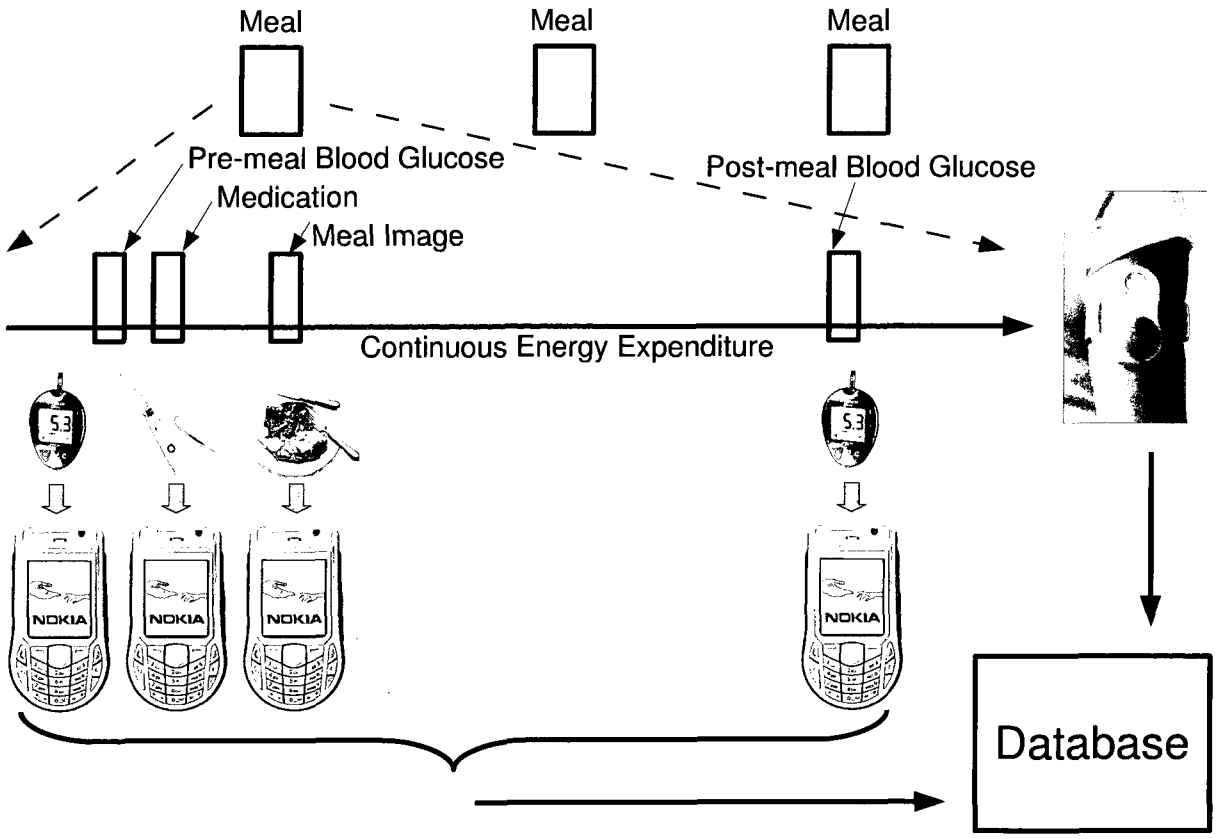


Figure 3.5: During a day each subject was instructed to measure blood glucose before each meal and two hours after each meal.

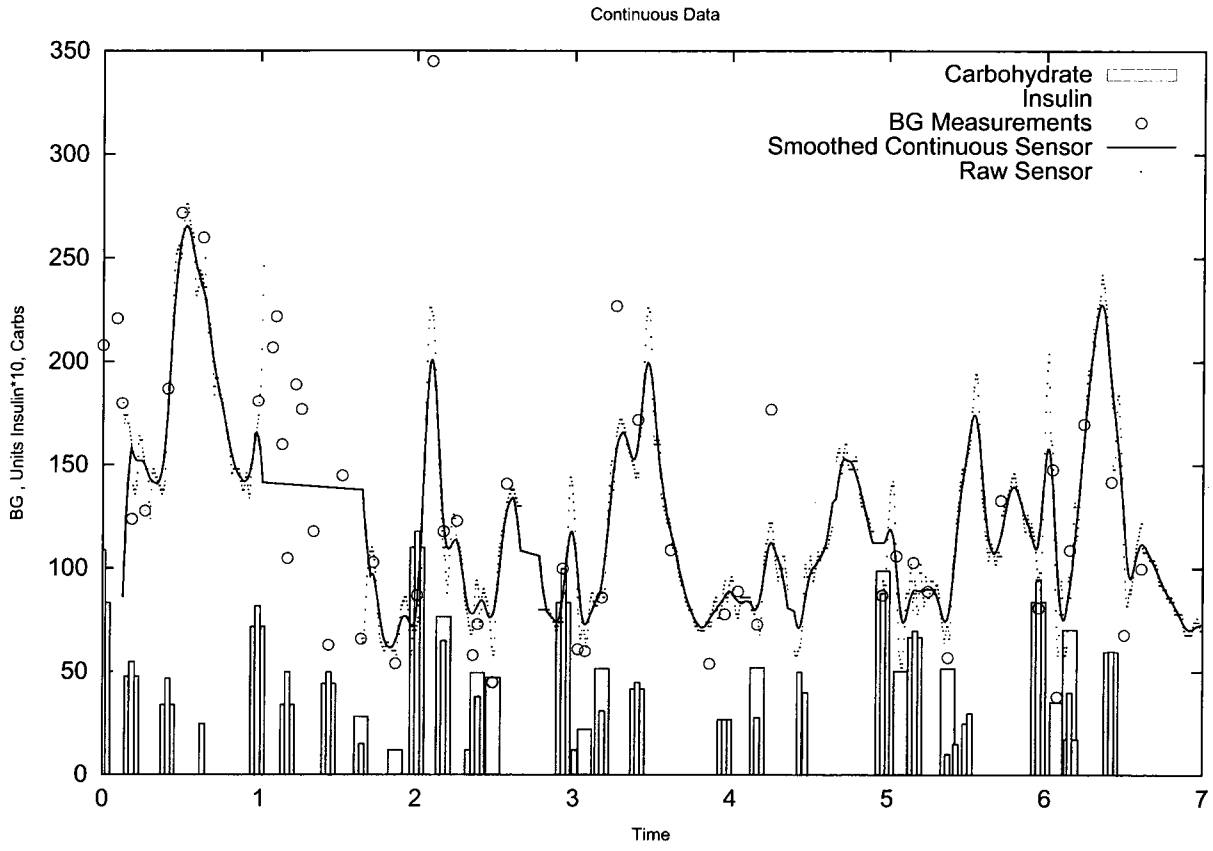


Figure 3.6: Sample data collected using the protocol described

patient id. Only the primary physician will have access to the patient identification.

Following the data collection the subjects returned the devices and had the opportunity to discuss the data with care-providers. All subjects also received a printed report containing detailed data that they could keep for reference. After successfully completing the study the subjects were given a glucose meter, kitchen scale, and a small gift of appreciation.

3.3.1 Sample Data

Some sample data measured over the first week of a data collection is plotted in Figure 3.6. Ideally if the patient followed the protocol then they would have data from about three meals a day for a total of about 52 meals over the two weeks. Each meal should have two associated blood glucose

Parameter	Min	Mean	Max
Age (yrs)	19	46	56
BMI	21	29	43
Weight (lbs)	121	170	232
Mean BG (mg/dl)	108	147	229
Std BG (mg/dl)	15	55	83
Mean Carb (gm)	35	66	116
Std Carb (gm)	17	35	68
Mean Exercise (cal/m)	1.25	1.74	2.73
Std Exercise (cal/m)	0.40	0.92	1.76
Number BG measurements	18	60	115

Table 3.1: Descriptive Statistics for the Study Population

measurements, so each patient should have about 104 recorded glucose measurements. In the sample data most of the meals have an associated insulin bolus. The error in CGM data can also be seen in this figure.

3.3.2 Descriptive Statistics

In all, the study recruited 16 subjects to take part in the data collection. Two subjects failed to collect enough useful data by not following the protocol. These two subjects were omitted from the data analysis. All subjects were able to use the devices and software, so IDA achieved one goal of being simple to use.

The subjects were selected to represent a broad range of diabetes. There were seven subjects with type 1 diabetes and nine with type 2. Seven of the subjects are male and nine are female. Among the subjects there were some with tightly controlled diabetes while others were not very controlled.

Table 3.1 lists the descriptive statistics of the subject population. The population included both young and old subjects ranging in age from 19 to 56 years. Subject BMI ranged from the normal range, 21, to obese, 43. One of the subjects had tightly controlled diabetes with a mean blood glucose of 108 mg/dl while the subject with the most uncontrolled blood glucose had a mean of 229 mg/dl. Some subjects rarely exercised while others exercised regularly. On average subjects recorded 60 blood glucose measurements representing an average of thirty meals.

3.4 Conclusions

The goal of the clinical study was to collect data from a diverse set of people with diabetes representing a wide range of behaviors. Based on the descriptive statistics, the study achieved this goal. IDA was designed to have practical uses for all types of patients with diabetes, so it was important for the study to sample across the spectrum of the disease. This allows models to be tested on a wide range of real-life scenarios.

The first law of dietetics seems to be if it tastes good, its bad for you.

Isaac Asimov

Chapter 4

Postprandial Prediction

Managing diabetes is a control problem; patients try to choose combinations of behaviors that they believe will optimize their future blood glucose. Patients make many of these choices just before meals, but in general they are not able to correctly predict the outcome of their behaviors. Gaussian process regression provides a significant improvement over human prediction and, with a Gaussian kernel, is able to represent nonlinearities in the system. The nonlinearities are important, so the Gaussian kernel performs significantly better than a linear kernel. Additionally the physiology of each patient is unique, so models that are trained specifically for an individual patient predict outcomes better than a generic model trained from a joint dataset. The model performance improves enough after being trained with about three days of data, representing nine meal events, to use for making predictions on similar meals. The glucose regulatory system is very complex and any data collected in a patient's real life setting will be very noisy.

4.1 Introduction

The largest disturbance to glucose homeostasis occurs after meals, so the decisions patients make surrounding their meals are very important for controlling blood glucose. The challenge of optimizing postprandial blood glucose could be aided by creating models that learn to predict how patient behaviors around meal times will affect their glucose. Meals are when diabetics make most of their

decisions. They decide how much to eat and an appropriate amount of medication to correct the glucose excursion.

Modeling the behaviors and outcomes at meal times is useful for both type 1 and type 2 diabetics. Optimizing therapy to correct meal excursions would provide significant health benefits for diabetics, and potentially lead to better heal outcomes. This is a very challenging problem, but it is a necessary one to solve. Patients will be attempting to predict the results of their choices, so any system that outperforms humans is an improvement.

Learning models to predict postprandial glucose values poses many difficult problems. The first is the noise in the system and the uncertainty of measurements. Additional noise comes from patient error and unmodeled factors. Besides all the sources of uncertainty, diabetes datasets often have few measurements for training and evaluating models. Finally, patients are all unique and may have different outcomes after the same input. Predicting postprandial glucose values can be expressed as learning a noisy function from sparse input data.

Methods for predicting postprandial blood glucose values are well represented in literature. IDA adds to these studies by incorporating energy expenditure and nutrition estimates based on IDA's unique meal image analysis. The inclusion of exercise and meal images helps capture the behavior of the patients: it places blood glucose readings into the context of daily life.

In this chapter the postprandial prediction problem will be explored in five experiments. The first experiment is designed to identify the most important input measurements and establish an order for including measurements into a model. The second experiment will compare modeling methods ranging from basic linear regression to nonlinear kernel based methods. The third experiment will compare models trained with an individual's data to models trained with data from a mixture of patients. The fourth experiment compares the performance of models on a new patient as more measurements become available for training the model. Finally, the quality of prediction will be compared to patient descriptive statistics to determine whether it is possible to identify ideal candidates for this method.

4.2 Problem Formulation

To train the model the system is given a set of recent past measurements, X_t, and anticipated inputs in the near future, X_{t+}, associated with a meal at time t. The anticipated measurements typically include planned exercise and estimated meal content. The output of the model is the predicted glucose measurement, g_{t+2}, taken two hours after a meal. The inputs to this system are energy expenditure, nutrition, medication, time-of-day, and the blood glucose measurement taken just prior to the meal. The clinical study was designed to prompt patients to collect data in this format. The primary problem is to learn a function of X_t and X_{t+} to predict g_{t+2}.

$$f\left(X_t, X_{t+}\right) \rightarrow g_{t+2} \tag{4.1}$$

While this is the ultimate goal, many other problems need to be addressed. One problem is that the raw input set is probably not the best set of input measurements. The best set of input variables will minimize the error while also minimizing the burden on the patient. Thus measurements that are not correlated with postprandial glucose would not be necessary to collect on a regular basis.

The best modeling method also needs to be determined. The data collected is sparse, noisy, and nonlinear. A model needs to be able to robustly represent the underlying function without over-fitting.

Another challenge is the initial learning phase for a diabetic. Incremental learning can be used to update the model when new data is available. It is important to understand how a model will perform as the input data set grows and when the model can be used to make predictions with confidence.

Similarly, a patient's model might be improved by using input data from other patients. Particularly in the cases where the patient has few training data and in cases where the patient is trying new behaviors, using training data from other patients may help. The data from patient p, out of P patients, will be labeled as X_T^p. Similarly the postprandial glucose measurements for a patient will be referred to as g_{T+2}^p. The complete set of input data from all patients will be labeled

as X_T^P. In this case a model learned from an individual's data will be compared to models learned from the joint data set.

$$f^p\left(X_t^p, X_{t+}^p\right) \rightarrow g_{t+2}^p \tag{4.2}$$

Finally, these models might perform better for certain classes of patients. In the study patients were recruited that represent a broad range of diabetics. Correlations may exist between the descriptive statistics of a patient and the performance of the models.

4.2.1 Data Preparation

To prepare the raw data for analysis, it is processed to identify meals that meet certain criteria. A meal is included if the patient collected pre-meal and 2 hour postprandial glucose measurements. Postprandial glucose measurements are considered valid if they are taken between 1.5 and 2.5 hours after a meal. The energy expenditure measurements are averaged into four samples, each lasting one hour, ranging from two hours before the meal to two hours after. The resulting input data set contains the variables listed in Table 4.1.

In addition to pre-meal glucose, medications, meals, and exercise, the input data set includes the time of day of the meal. This is included to allow for the dawn phenomena [95] and other time related glucose patterns. After identifying data that meets the requirements, the data are centered and normalized.

4.2.2 Error Metrics

Two metrics will be used to evaluate the quality of predictions. The first is the R^2 coefficient. This metric reflects the amount of variance explained by the model and is a standard measure of regression performance. All results are listed using the R^2 statistic defined as follows:

$$R^2 = 1 - \frac{\sum_{i=1}^{N}(g_i - \hat{g}_i)^2}{\sum_{i=1}^{N}(g_i - \bar{g})^2} = 1 - \frac{ESS}{TSS} \tag{4.3}$$

In this equation g_i is the reference value, $\hat{g}_i$ is the estimate from the model, and $\bar{g}$ is the mean

X_t	Description	Units
1	Pre-meal blood glucose	mg/dl
2	Postprandial time of BG measurement	min
3	Average exercise from 2-1 hr before meal	cal/min
4	Average exercise from 1-0 hr before meal	cal/min
5	Average exercise from 0-1 hr after meal	cal/min
6	Average exercise from 1-2 hr after meal	cal/min
7	Time of Day	hrs
8	Patient estimated carbs	gm
9	Expert estimated carbs	gm
10	IDA calculated carbs	gm
11	IDA calculated fat	gm
12	IDA calculated protein	gm
13	IDA calculated calories	gm
14	recent calculated carbs	gm
15	recent calculated fat	gm
16	recent calculated protein	gm
17	recent calculated calories	gm
18	Rapid Insulin	units
19	Regular Insulin	units
20	Recent Mixed Insulin	units
21	Earlier Mixed Insulin	units
23	Sulfonylureas	
24	Meglitinides	
25	Netaglinide	
26	Biguanides	
27	Thiazolidinediones	
28	Alpha-Glucosidase Inhibitors	
g_t	Output Variables	
1	2 hr Postprandial blood glucose	mg/dl

Table 4.1: Input data and output data for postprandial glucose prediction

glucose value. This can be summarized as one minus the residual sum of squares error, ESS, divided by the total sum of squares, TSS. This metric can be thought of as the amount of variance explained by the model. A perfect value for R^2 is one and a value of zero signifies no correlation.

The second error metric is the Clarke Error grid developed by Clarke in [28]. This plot is designed specifically for the diabetes blood glucose domain by identifying the clinically significant types of errors between predictions and reference values. The Clarke error grid labels five clinically significant areas in a regression plot between the prediction and reference data. Figure 4.1 is an example of a Clarke error grid.

The areas are typically labeled alphabetically A, B, C, D, and E. Region A contains data where the predictions are within $\pm 15\%$ of the reference values. Region B contains data that have significant quantitiative error, but would still be labeled identically as hypoglycemic, normal, or hyperglycemic. Region C contains data that are in the normal glucose range but labeled incorrectly as hypoglycemic or hyperglycemic. Region D contains points that are falsely labeled as normal when they are actually hypoglycemic or hyperglycemic. Finally, region E contains data that are dangerously mislabled. In region E hypoglycemic data is labeled as hyperglycemic, and hyperglycemic data is labeled as hypoglycemic. This type of error could lead a patient to choose a dangerous therapy.

In two studies, patients were able to predict their postprandial glucose values with 28.5 percent in region A [96] and 41.5 percent in region A [47]. Other computational prediction systems have achieved results with 34 percent and 51 percent in region A [3, 4]. Finally in a simulation study the theoretical bound for prediction performance was estimated at 43.6% when using typical data collection methods [63]. These are the baselines that IDA needs to improve upon for predicting postprandial blood glucose.

4.3 Statistical Models

There are many potential models to evaluate for predicting postprandial glucose. An ideal model for a problem should match the nature of the data it is intended to represent, so the ideal model for

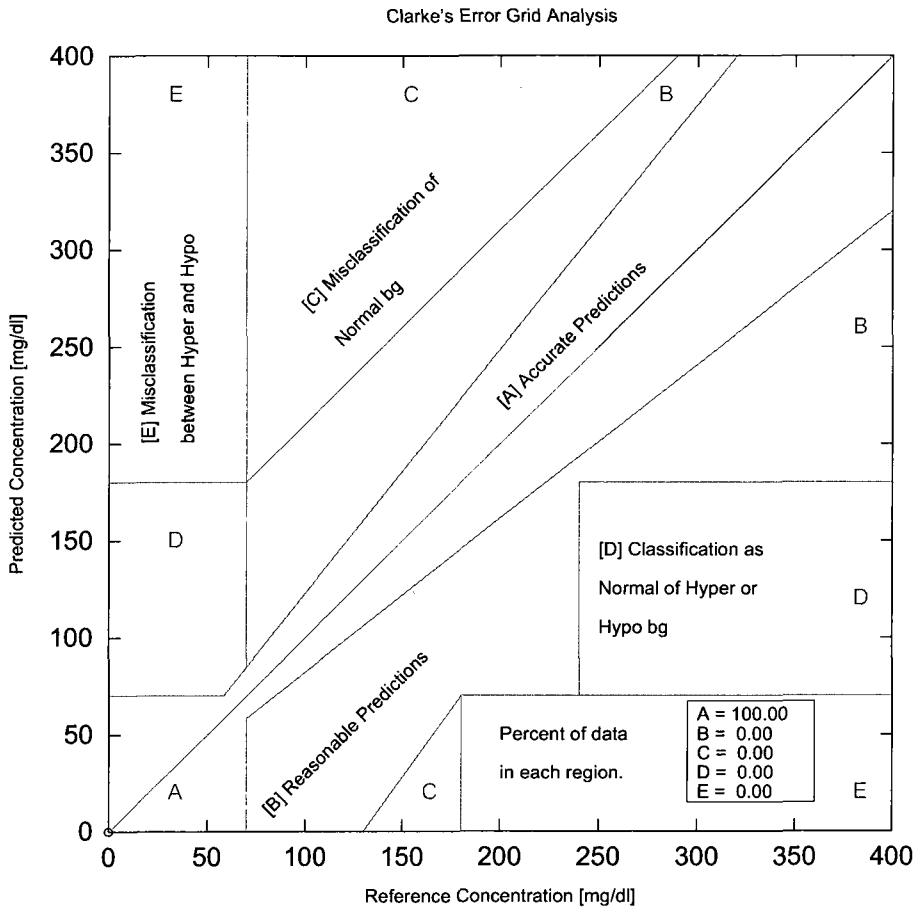


Figure 4.1: Example Clarke Error grid: The labeled regions identify clinically significant errors in predictions.

this problem should be robust, nonlinear, and able to learn from small datasets. The ideal model should also be transparent. A physician needs to be able to understand the process that created the prediction. Both patients and physicians are hesitant to trust a black box.

Postprandial Glucose Prediction Models
Gaussian process regression with a linear kernel using individual data.
Gaussian process regression with a linear kernel using joint data.
Gaussian process regression with a linear kernel using weighted data.
Gaussian process regression with a Gaussian kernel using individual data.
Gaussian process regression with a Gaussian kernel using joint data.
Gaussian process regression with a Gaussian kernel using weighted data.
Reduced rank regression using Mixture data.

Table 4.2: Postprandial prediction models

The models listed in Table 4.2 will be described in detail in this chapter and used to address specific aspects of postprandial glucose prediction. They will be used to determine whether the system can be approximated by a linear function or whether a nonlinear function is necessary. The models will also be used to test how individualized a model needs to be for a patient. Each model will be described in detail in the following sections.

4.3.1 Gaussian Process Regression

Gaussian Process regression applies a probability distribution across an infinite function-space to identify underlying functions that are consistent with the training data. The method does not require an explicit parameterization of all possible models, but instead bases predictions on the likelihood of functions given a prior distribution in function-space and the training data. It differs from regression methods, such as linear regression, that estimate coefficients of a parameterized model. The predictions are in the form of a full predictive distribution, providing both the mean and variance of the predictions. This difference makes Gaussian Process regression an appealing choice when the system being modeled is complex and difficult to parameterize.

In this type of complex system the best model is often the training data. Gaussian Process

regression is a data driven method which allows it to model unknown interactions. The downside is that it is only as good as the training data. If a variable has no variation in the training set then Gaussian Process regression cannot identify any correlation with the output variable. A model built on expert information might be able to account for such variables.

The key to Gaussian Process regression is the covariance function. It governs the properties of the resulting functions; it can be changed to produce linear or nonlinear results. The covariance function can be thought of as a kernel function similar to those used in support vector machines and other kernel based learning algorithms. For this research project two covariance functions are used: a linear function and a Gaussian radial basis function. These two functions will be used to determine the complexity of model needed to predict postprandial glucose. If a linear function works, the the more complex nonlinear is unnecessary.

Derivation

The solution for Gaussian process regression is often presented as finding the maximum of a predictive probability distribution in function-space. For realistic modeling scenarios it is assumed that the training function values, g, are noisy representations of the true output. Assuming additive input, the covariance of g can be expressed as the following.

$$cov(g) = K(X, X) + \mu I \tag{4.4}$$

With this noise term, the joint distribution of the observed glucose values and predicted glucose values for test input under the prior can be written as the following.

$$\begin{bmatrix} g \\ g^* \end{bmatrix} \sim \mathcal{N}\left(0, \begin{bmatrix} K(X,X) + \mu I & K(X,X^*) \\ K(X^*,X) & K(X^*,X^*) \end{bmatrix}\right) \tag{4.5}$$

The joint distribution can be used to derive the predictive distribution for Gaussian process regression by conditioning on the training glucose values, g.

$$p(g^*|X, g, x^*) \sim \mathcal{N}(\bar{g}^*, cov(g^*)) \tag{4.6}$$

Where the mean of the predictive distribution are calculated with the following equation.

$$\bar{g}^* \triangleq \mathbb{E}[g^*|X, g, x^*] = K(X^*, X)[K(X, X) + \mu I]^{-1} g \tag{4.7}$$

And the covariance is calculated with

$$cov(g^*) = K(X^*, X^*) - K(X^*, X)[K(X, X) + \mu I]^{-1} K(X, X^*). \tag{4.8}$$

A key benefit of Gaussian process regression is that it provides a full predictive distribution. For diabetes applications, automated decision support can benefit from using both the predicted value and the uncertainty of the prediction.

The mean of the solution can also be expressed as a minimization of least squares problem. The least squares method is presented here. Given a set of training data, (X, g), containing input data, X, and postprandial glucose, g, least squares minimization is used to find the coefficients that will minimize the error of the following regression equation.

$$g = K(X, X)\beta \tag{4.9}$$

Where $K(X, X)$ is the covariance function evaluated on the training set and β a set of coefficients to estimate. The solution for β is found by minimizing the following error function.

$$E(\beta) = \|g - K(X, X)\beta\|^2 \tag{4.10}$$

The solution is found by inverting the covariance function .

$$\beta = K(X, X)^{-1} g \tag{4.11}$$

This solution, however, assumes that there is no noise in the training data and that the kernel

matrix is invertible. Left this way, it will tend to over-fit noisy data, and diabetes data is noisy. This can be fixed by adding a regularization parameter to the error function. This is similar to ridge regression. The specific error function that includes the regularization parameter is below.

$$E(\beta) = \frac{1}{2\mu} \|g - K(X,X)\beta\|^2 + \frac{1}{2} \|K(\cdot,X)\beta\|^2 \tag{4.12}$$

This can be minimized by taking the partial with respect to β, setting it to zero, and solving for β.

$$\frac{\partial E(\beta)}{\partial \beta} = -\frac{1}{\mu} K(X,X)^T g + \frac{1}{\mu} K(X,X)^T K(X,X)\beta + \mu\beta K(X,X) \tag{4.13}$$

The solution for β that minimizes equation 4.12 is the well known solution for Gaussian Process regression.

$$\beta = [K(X,X) + \mu I]^{-1} g \tag{4.14}$$

This can be inserted into equation 4.9 to make predictions at new test points, X^*.

$$g^* = K(X^*,X) [K(X,X) + \mu I]^{-1} g \tag{4.15}$$

All that remains to complete the regression method is a definition of the covariance function.

Linear Covariance Function

Gaussian process regression with a linear covariance function is very similar to basic linear regression. More accurately, it mimics ridge regression. The linear covariance function is given in equation 4.16.

$$K_L(X_i, X_j) = X_i^T X_j \tag{4.16}$$

When this covariance function is inserted into equation 4.17 the solution for new data becomes the following.

$$g^* = X^{*T}\left[X^T X + \mu I\right]^{-1} X^T g \tag{4.17}$$

This solution is identical to ridge regression or Tikhonov regularization. It should be noted that the Gaussian Process regression framework can be used to mimic other regression techniques, in this case ridge regression, by the choice of covariance function.

This model will form a baseline for comparison with more complex nonlinear models. It will also identify correlations between input data and postprandial glucose values. Finally, it will be used to compare models learned from a single individual to models learned from the combined data from all patients.

Gaussian Covariance Function

A Gaussian kernel function will be used in Gaussian Process regression as a covariance function to account for nonlinearities in the system. The glucose regulatory system is complex so the best modeling method may be to use a data driven method. The Gaussian kernel captures the similarity between data and is not constrained by a rigid parameterization. It can model unknown interactions that are not explicitly included in a physiological model; however, it can also easily over fit the noise in the data.

The Gaussian covariance function is given in equation 4.18. The width of the kernel, Σ, is used to balance between over-fitting and, in a sense, over-smoothing: losing the fine detail in the system.

$$K_G(X_i, X_j) = \alpha e^{\left(-\frac{1}{2}(X_i - X_j)^T \Sigma^{-2} (X_i - X_j)^T\right)} \tag{4.18}$$

Prior to processing, the data collected by IDA were centered and normalized. The data were normalized using the standard deviation calculated with the data from all the patients in order to have a uniform kernel width for all patients. A kernel width of 0.5σ was found to work well for modeling when comparing experiments done with different kernel widths. Because the data were normalized, the same width was applied to all variables.

There is a significant amount of noise in diabetes data, so smaller kernel widths suffered from

over-fitting. Larger kernel widths caused the model to fail to capture the detail in the system. This effect was particularly noticeable in patients with reduced behavior variability. The change in performance when changing kernel width, however, was not extremely volatile, and performance was statistically similar for a range of widths.

Other Covariance Functions

In addition to the linear kernel and Gaussian kernel, other covariance functions can be used in Gaussian Process Regression. Periodic functions could be used to model time-based glucose changes like the dawn-phenomena. These effects were roughly handled by using the time-of-day as an input variable with the Gaussian kernel.

4.3.2 Interpatient Model Variability

A single patient with diabetes may not have enough data to adequately model how new behaviors will affect his glucose, so this research project also investigates using data from multiple patients to improve the model for a single diabetic. Three types of models were compared to see whether predictions improve when using training data from additional patients. The first is the joint model that generates predictions using the data from all the patients equally. The second is the individual model that only uses data from a single patient, ignoring data from all other patients. The third is a weighted mixture model that weights data more heavily from similar patients when making predictions.

Joint

The joint model includes data from all patients and assumes that there is no variability between patients. This model is not expected to be the best, but it acts as the baseline for comparison with the individual and mixture models. The benefits of the joint model are that it covers the largest range of input space in the training data, so that it is more likely that a new patient behavior is represented by the training data.

In the joint model the covariance function is calculated using all available data.

$$g^* = K(X^*, X^P)\left[K(X^P, X^P) + \mu I\right]^{-1} g^P \tag{4.19}$$

The main fault in this approach is that it is not able to represent the individuality of patients.

Individual

The individual model only uses the training data from the individual patient. Unlike the joint model it ignores all information from other patients, so it may suffer from having limited training data. Testing the individual model will establish the other endpoint of the spectrum from the joint to individual. The Gaussian Process regression model for patient j will only use X^j as training data.

$$g^* = K(X^*, X^j)\left[K(X^j, X^j) + \mu I\right]^{-1} g^j \tag{4.20}$$

The glucose regulatory process for every patient with diabetes is different, so this method will treat every patient as an individual. However, because of the limited training data, the model will be forced to extrapolate more as new behaviors will not be represented in the training set.

Weighted Mixtures

The weighted mixture model lies somewhere between the individual and joint model. It was designed to maintain the strengths of each method while reducing the weaknesses. The weighted mixture model uses the training data from all patients to make predictions, but weights the data according to the similarity between the patients. The similarity is calculated based on the correlation between the training data of two patients. The assumption is that if two patients have similar outcomes associated with known similar behaviors, then they will also have similar outcomes when other new behaviors occur. For example, if a patient has never consumed 100 grams of carbohydrates without insulin, but a similar patient has, then the data from the similar patient is useful for predicting what will happen to the first patient.

The mixture model will cover the full range of input data for all patients while modeling each

patient as an individual. Theoretically, this can be added to the derivation of Gaussian Process regression by modifying the initial probability optimization. For an individual the model selects the output that is most likely produced by the input. Given a test point x_*^j from patient j the training data from all patients (X^P, g^P) is used to find the glucose value that maximizes the predictive distribution below.

$$p(g_*^j|x_*^j, X^P, g^P) = \int p(g_*^j|x_*^j, w^j)p(w|X^j, g^j) + \int p(g_*^j|x_*^j, w^j)p(w^j = w^p)p(w^p|X^{p\neq j}, g^{p\neq j}) \quad (4.21)$$

The inclusion of data from other patients adds the patient similarity term to the equation, $p(w^j = w^p)$. The similarity term, $s_{j,p}$, estimates the probability that the data from two patients was generated from the same model.

$$s_{j,p} = p(w^j = w^p) \quad (4.22)$$

The value for $s_{j,j}$ is one. The similarity term can be included in the covariance function calculation.

$$K(x^j, x^p)_s = K(x^j, x^p)s_{j,p} \quad (4.23)$$

This modified covariance function can be included in the least squares formulation for Gaussian Process regression given in equation 4.12 using the

$$E(\beta) = \frac{1}{2\mu}\left\|g^P - K(X^P, X^P)_s\beta\right\|^2 + \frac{1}{2}\left\|K(\cdot, X)\beta\right\|^2 \quad (4.24)$$

Minimizing this error function results in the solution below.

$$g^* = K(X^*, X^P)_s\left[K(X^P, X^P)_s + \mu I\right]^{-1} g \quad (4.25)$$

The similarity function $s_{j,p}$ was implemented by calculating the correlation between the output

of two patient models. Thus the similarity measure for a patient $s_{i,i}$ is equal to one, and his similarity to other patients will range from zero to one. It can be interpreted as the probability that the two patient models are the same.

To calculate $s_{j,p}$ the individual models for the two patients are used to predict the output for both patients sets of training data. If g^j is the prediction for the input set $[X^j X^p]$ based on the the individual model of patient j, and similarly, g^p is the predictions for patient p, then the similarity can be calculated using equation 4.26.

$$s_{j,p} = \frac{1/T \sum_{k=1}^{T} (g_k^j - \overline{g}^j)(g_k^p - \overline{g}^p)}{\sigma_g^j \sigma_g^p} \tag{4.26}$$

Other similarity metrics were considered, but this one was chosen because it is easily interpreted. This model was designed to maintain the benefits of an individual model when interpolating near training data, while using data from other patients to improve performance when extrapolating to new behaviors.

Simple Example

To demonstrate the weighted mixture model a simplified problem was first considered. In the Figure 4.2, twenty random linear models were created and a dataset was randomly sampled from each. The portion of the range that was sampled was randomly selected so that some datasets would overlap. Then normally distributed noise was added to the data. The similarity between the models was calculated and Gaussian Process regression with a Gaussian kernel using a weighted mixture of data from the different sources was used to model the data.

The subset being modeled is plotted with large blue diamonds. The probability that other datasets are from the selected subset is represented by the size of the red diamonds. Small black diamonds mean that the two sets are not similar. The red curve is the GP regression learned from only the blue data points. The black curve includes the influence of the red data points. The two methods are very similar when interpolating within the range of blue input data, but the weighted mixture method tends to extend the quality of prediction when extrapolating at the edges of the

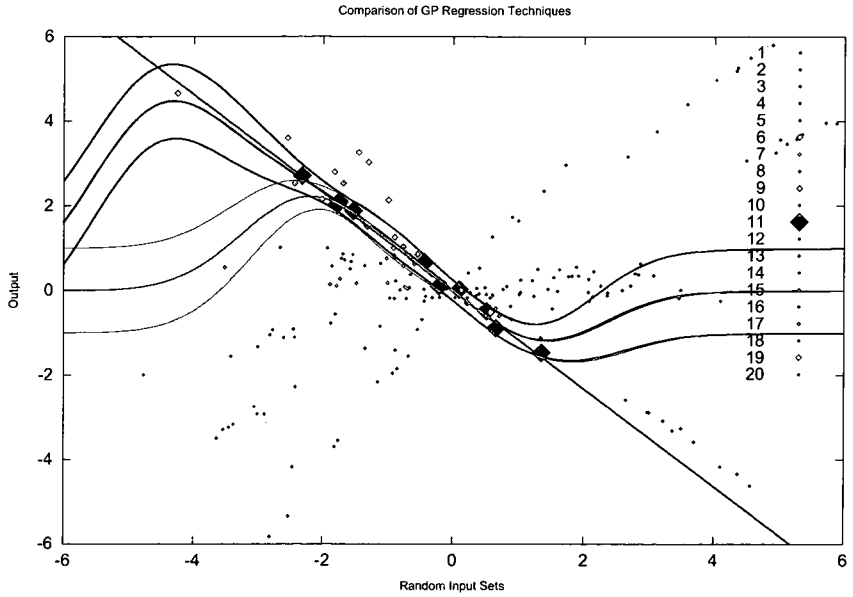


Figure 4.2: Example of the interpolation and extrapolation behavior of the weighted mixture model.

input range. Note that the improved extrapolation only occurs when data from different sources both overlaps and extends beyond the range of the current individual.

4.3.3 Reduced Rank Regression with a Generic Basis

The weighted mixture model balances between the joint model and individual model in order to test the theory that using data from multiple patients will improve performance compared to using data from a single patient. To further test this theory the Reduced Rank Regression with a Generic Basis (RRR) model was developed. This model uses least squares error minimization to simultaneously identify a reduced rank basis for all patients and a patient specific set of coefficients to adjust the basis for the individual.

Noise is a significant problem with glucose modeling, so the model may be improved by using a reduced rank approximation to the noisy data. The variables and parameters for the derivation are defined below.

- N - Number of training points
- V - Number of variables

- k - Size of reduced rank
- P - Number of patients.
- g_m - 1 x N: Output from model m
- X_m - V x N: Input data from model m
- B - V x k: Uniform transformation matrix from $V \Rightarrow k$.
- a_m - 1 x k: specific coefficients for model m.
- o - 1 x k: vector of 1's.
- μ - penalizes when $a_{(i)} \neq 1$
- γ - penalizes when $a_{(i)} \neq 1$

The general equation for evaluating test data using the generic basis and patient specific coefficients is below.

$$g_m^* = a_m B^T X_m^* \tag{4.27}$$

Training data is used to find the best values for a_m and B by minimizing this error function. The matrix B is a transformation matrix to the reduced rank space, and the vector a_m converts the generic basis into a patient specific answer. The reasoning behind this approach is that similarities should exist between diabetics that could be captured by the reduced rank basis. A regularization term is added to the error function to place some constraints on a and B. The value of B is constrained to be close to zero.

$$E_B(a, B) = \gamma \mathrm{Tr} \|B\|^2 \tag{4.28}$$

The combined error function with the regularization term becomes equation 4.29.

$$E(a, B) = \sum_{m=1}^{M} \left\|g_m - a_m B^T X_m\right\|^2 + \gamma \|B\|^2 \tag{4.29}$$

This error metric can be minimized using Alternating Least Squares (ALS) by iterating between first solving for B then solving for a. The first step is to take the partial derivative with respect to B.

$$\frac{\partial E}{\partial B} = \frac{\partial}{\partial B}\left(\sum_{m=1}^{M}\left\|g_m - a_m B^T X_m\right\|^2 + \gamma \mathrm{Tr}\left\|B\right\|^2\right) \tag{4.30}$$

$$= \frac{\partial}{\partial B}\left(\sum_{m=1}^{M}\left\|g_m - a_m B^T X_m\right\|^2\right) + \frac{\partial}{\partial B}\left(\gamma \mathrm{Tr}\left\|B\right\|^2\right) \tag{4.31}$$

$$= 2\sum_{m=1}^{M}\left(X_m X_m^T B a_m^T a_m\right) - 2\sum_{m=1}^{M}\left(X_m g_m^T a_m\right) + 2\gamma B \tag{4.32}$$

The partial is set to zero and a solution can be found for B.

$$0 = 2\sum_{m=1}^{M}\left(X_m X_m^T B a_m^T a_m\right) - \ldots \tag{4.33}$$

$$2\sum_{m=1}^{M}\left(X_m g_m^T a_m\right) + 2\gamma B \tag{4.34}$$

$$\sum_{m=1}^{M}\left(X_m g_m^T a_m\right) = \sum_{m=1}^{M}\left(X_m X_m^T B a_m^T a_m\right) + \gamma B \tag{4.35}$$

$$\mathrm{vec}\left(\sum_{m=1}^{M}\left(X_m g_m^T a_m\right)\right) = \left[\sum_{m=1}^{M}\left(\left(a_m^T a_m\right) \otimes \left(X_m X_m^T\right)\right) + \gamma I\right] \mathrm{vec}(B) \tag{4.36}$$

After solving for $\mathrm{vec}(B)$ it can be reshaped.

$$\mathrm{vec}(B) = \left[\sum_{m=1}^{M}\left(\left(a_m^T a_m\right) \otimes \left(X_m X_m^T\right)\right) + \gamma I\right]^{-1} \mathrm{vec}\left(\sum_{m=1}^{M}\left(X_m g_m^T a_m\right)\right) \tag{4.37}$$

Once a solution is found for B then ALS is used to find the solution for a_m for each patient. Again, the partial of equation 4.29 is calculated, this time with respect to a_m.

$$\frac{\partial E}{\partial a_i} = \frac{\partial}{\partial a_i}\left(\sum_{m=1}^{M}\left\|g_m - a_m B^T X_m\right\|^2 + \gamma \mathrm{Tr}\left\|B\right\|^2\right) \tag{4.38}$$

$$= \frac{\partial}{\partial a_i}\left(\sum_{m=1}^{M}\left\|g_m - a_m B^T X_m\right\|^2\right) + 0 \tag{4.39}$$

$$= \frac{\partial}{\partial a_i}\left(\sum_{m=1}^{M}\left(g_m^T g_m - 2g_m^T a_m B^T X_m + X_m^T B a_m^T a_m B^T X_m\right)\right) \tag{4.40}$$

$$= -2g_i D_i^T B + 2a_i B^T D_i D_i^T B \tag{4.41}$$

Then the partial is set equal to zero and a solution can be found for each coefficient vector, a_m.

$$0 = -2g_i D_i^T B + 2a_i B^T D_i D_i^T B \tag{4.42}$$

$$2a_i B^T D_i D_i^T B = 2p_i D_i^T B \tag{4.43}$$

$$a_i\left(B^T D_i D_i^T B\right) = p_i D_i^T B \tag{4.44}$$

$$a_i = \left(p_i D_i^T B\right)\left(B^T D_i D_i^T B\right)^{-1} \tag{4.45}$$

The process of solving for B and a_m is then repeated until the prediction error on the training set begins to converge. This method consistently minimizes the prediction error for the training set. However, it suffers from over-fitting due to the number of parameters being estimated compared to the amount of training data. Figure 4.3 plots the error as a function of the ALS iteration for the training data and test data for models with a reduced rank ranging from one to four.

4.4 Sample Gaussian Process results

The results for the Gaussian Process regression models using the individual data and joint data are plotted on Clarke error grids in Figure 4.4. This plot shows the levels of noise faced in the predictions and the difference in performance between the individual model and joint model.

The model learned from joint data is not as focused about the diagonal as the predictions using

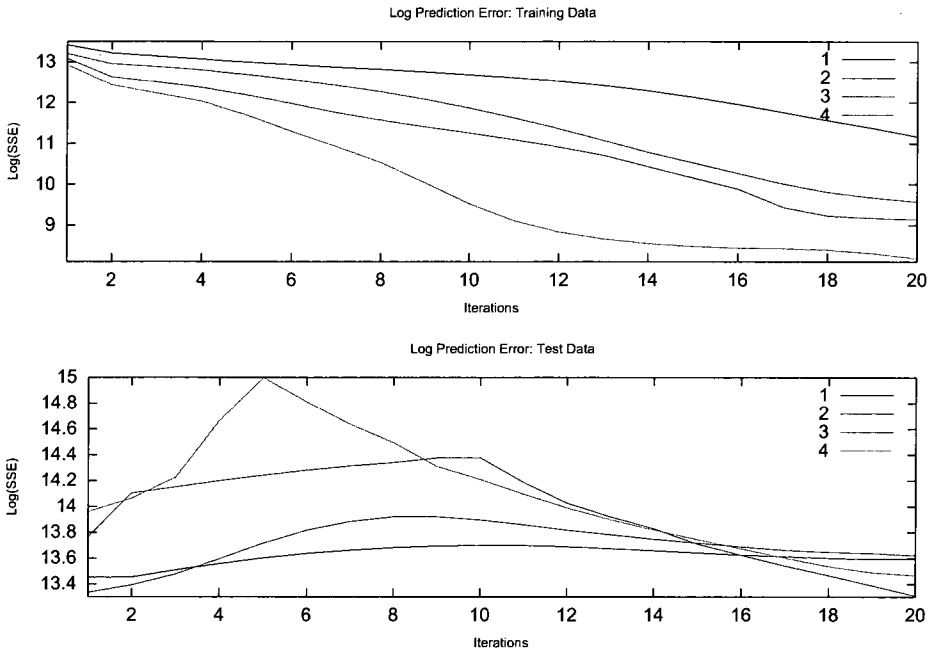


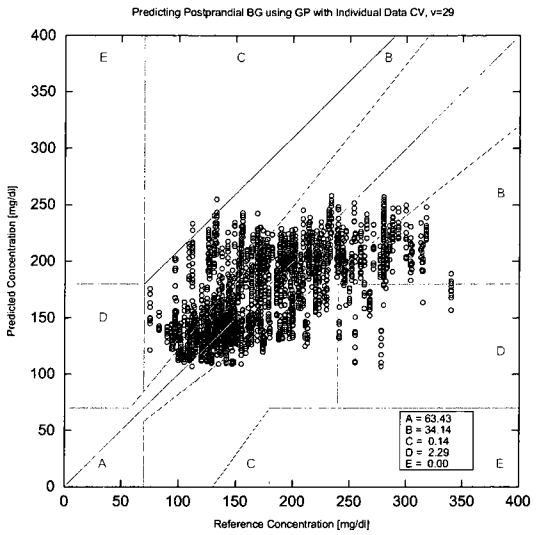
Figure 4.3: The error on the training set goes down as ALS iterates. The model with a reduced rank of three performs the best on the test data.

individual data. A key result is that diabetics need to be treated as individuals and any attempt at a universal model not tuned to the individual will fail.

4.5 Variable Selection

IDA as a system collects many data that may be useful for predicting blood glucose values, but many may be of little value. The first experiment is designed to identify the importance of collected measurements for predicting postprandial glucose. Because of the limited quantity of data the experiment was performed 10 times using random training and test sets. For each experiment the data was split equally into a training set and a test set, and a covariance function for the Gaussian Process regression model was selected. A greedy algorithm was then used to iteratively add the variable to the model that maximized the chosen evaluation metric, either R^2 or the percentage of points in region A of the Clarke Error Grid. A single model was trained on the joint dataset as opposed to training individual models.

(a) Individual Data



(b) Joint Data

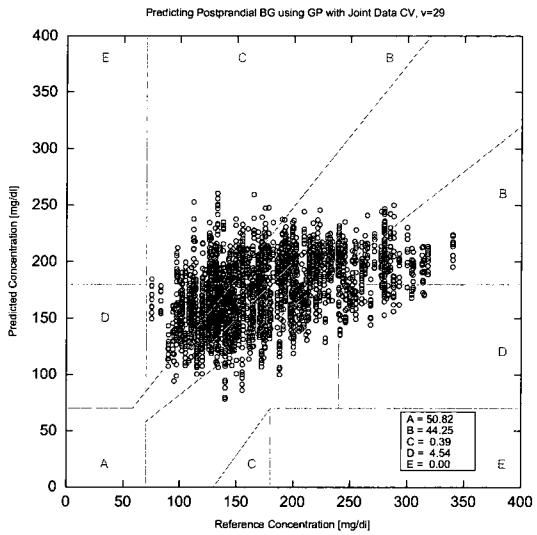


Figure 4.4: Comparison between the models trained on individual data and the joint model using the Clarke Error Grid.

In all there were four possible combinations of covariance function and evaluation metric. For each random training set a variable order was generated. The 10 variable orders obtained from the randomly sampled sets for a given covariance function and evaluation metric were combined using a voting method where the first of the N variable received N votes, the second N-1, with the last receiving one vote. The variables were then reordered according to their combined votes.

Table 4.3 contains the resulting variable orders obtained from this voting method for the four models. While there are many differences between the lists, there are some clear patterns. The pre-meal blood glucose is consistently near the top of the list along with the estimated meal carbohydrates. Another interesting observation is that most of the lists include some measure of blood glucose, insulin, nutrition, and exercise near the top. This suggests the importance of the impact that all four of these inputs have on the glucose regulatory system.

The following experiments in this chapter use the variable order in Table 4.3 that maximizes the percentage of points in region A of the Clarke Error Grid. This metric was selected because the clinical performance of a model is more important than its statistical performance.

Because of the noise in the system, the variable orders depended upon the specific training

	Clarke		R^2	
Order	Linear	Gaussian	Linear	Gaussian
1	Calc Carb	Previous BG	Previous BG	Previous BG
2	Previous BG	Regular Insulin	Time of Day	Regular Insulin
3	Next Exer 1-2	Time of Day	Calc Carb	Earlier Mixed Insulin
4	Calc Cal	Calc Cal	Prev Exer 1-0	N
5	Calc Fat	Prev Exer 2-1	Recent Mixed Insulin	Sulf
6	Time of Day	Rapid Insulin	M	M
7	Recent Carb	Calc Carb	Rapid Insulin	Bigu
8	Time PP BG	Earlier Mixed Insulin	Next Exer 1-2	Th
9	Calc Prot	Time PP BG	Regular Insulin	Recent Prot
10	Next Exer 0-1	Sulf	N	Alph
11	Recent Mixed Insulin	Recent Carb	Bigu	Recent Mixed Insulin
12	Prev Exer 2-1	N	Th	Calc Carb
13	Sulf	Calc Fat	Earlier Mixed Insulin	Recent Fat
14	Prev Exer 1-0	Calc Prot	Alph	Calc Cal
15	Recent Fat	Recent Fat	Recent Carb	Prev Exer 2-1
16	Recent Prot	M	Sulf	Time of Day
17	Earlier Mixed Insulin	Recent Prot	Next Exer 0-1	Rapid Insulin
18	Rapid Insulin	Recent Cal	Time PP BG	Next Exer 1-2
19	Recent Cal	Bigu	Calc Cal	Calc Fat
20	Regular Insulin	Recent Mixed Insulin	Calc Prot	Next Exer 0-1
21	M	Prev Exer 1-0	Prev Exer 2-1	Recent Cal
22	N	Th	Recent Prot	Time PP BG
23	Bigu	Next Exer 1-2	Calc Fat	Recent Carb
24	Th	Alph	Recent Fat	Calc Prot
25	Alph	Next Exer 0-1	Recent Cal	Prev Exer 1-0

Table 4.3: Variable orders determined using the linear and Gaussian kernels and the two error metrics.

points selected. Figure 4.5 compares six of the input data to either the change in blood glucose, or the actual postprandial glucose concentration for a single patient. It displays some of the correlations between data and also displays the noise in the system. The glucose regulatory system is complex, so the goal of modeling the system is to identify the trends that lie beneath the noise. This figure clearly displays the challenge of predicting future glucose values.

For this patient the estimated meal carbohydrates tends to be associated with an increase in postprandial blood glucose, and postprandial exercise seems to cause a decrease in blood glucose. The pre-meal glucose reading has a negative correlation with the change in blood glucose. Finally, the time-of-day demonstrates more volatility around the dinner meal.

4.6 Model Performance

In this chapter a number of modeling methods have been proposed for predicting postprandial glucose values. These models were evaluated with the two metrics, R^2 and percentage in region A, at each level in the variable inclusion order. Because of the limited quantity of data each experiment was performed 10 times using randomly selected training and test sets. The mean value of the performance metrics are presented.

The models evaluated are Gaussian Process regression with the Gaussian kernel using the individual, joint, and weighted mixture models; Gaussian Process regression with the linear kernel using the individual, joint, and weighted mixture models; and the RRGP model. Each model was evaluated at each step of the variable inclusion order as selected in the previous section. Both the variable order determined from the Gaussian kernel and linear kernel were used.

The model performance results for all of these experiments are displayed in Figure 4.6. The top two graphs display the results of the percentage of points in region A, and the lower two graphs use the R^2 metric to compare the models. The left graphs use the variable inclusion order determined using the Gaussian kernel, and the right graphs use the variable inclusion order determined with the linear kernel.

The variable inclusion order determined with the Gaussian kernel significantly outperforms the

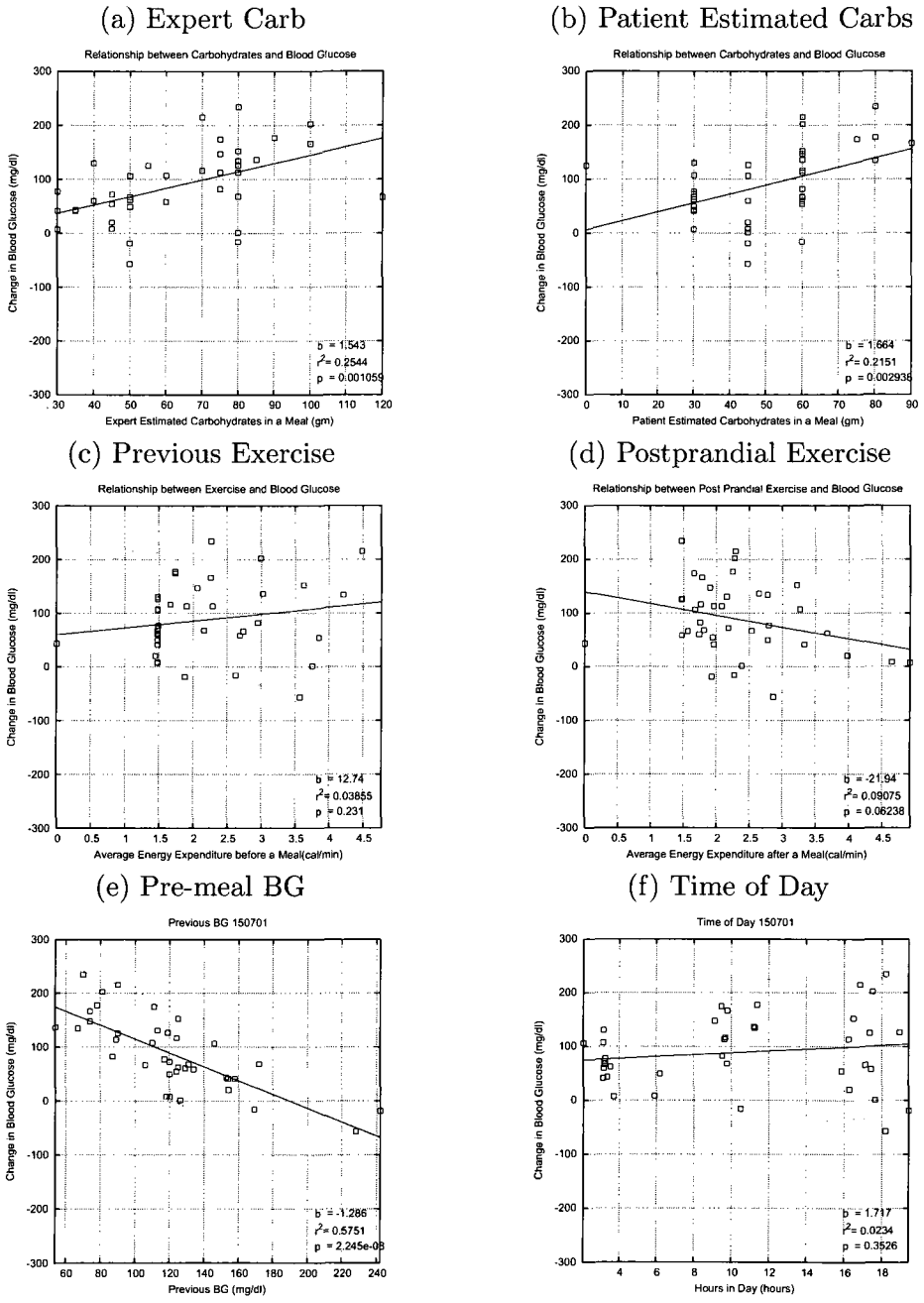
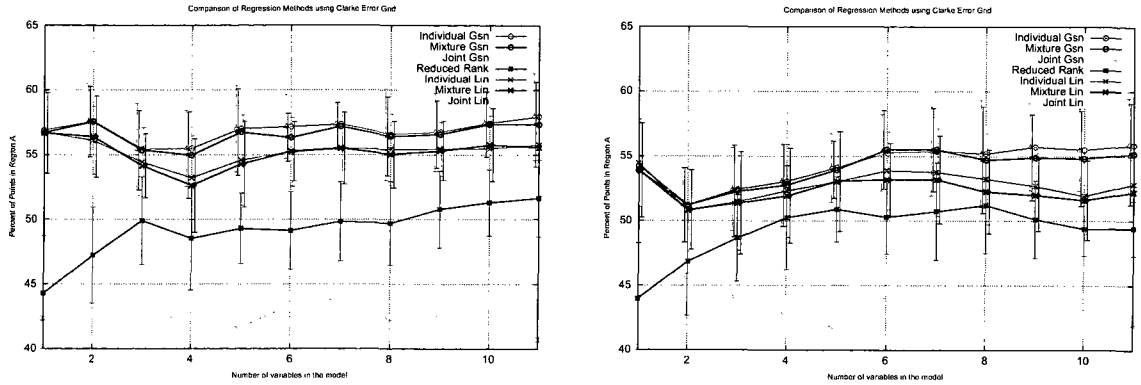


Figure 4.5: Comparison between measurements and the change in postprandial glucose.

(a) Region A: Gsn Var Order

(b) Region A: Lin Var Order



(c) R^2: Gsn Var Order

(d) R^2: Lin Var Order

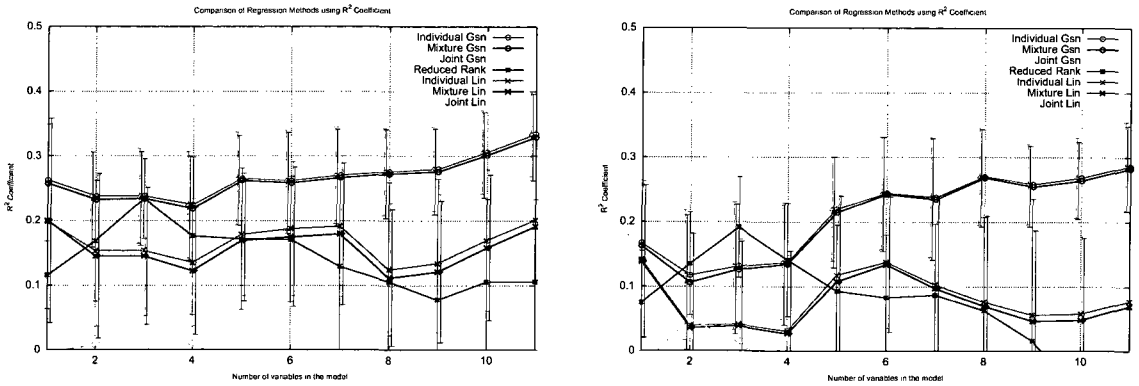


Figure 4.6: The percent of points in region A of the Clarke error grid as a function of the number of variables used in the model. Gaussian Process Regression is the best performing method. The variable order was obtained using a greedy algorithm and Gaussian kernel.

variable inclusion order determined using the linear kernel. The best model is the Gaussian Process regression model with a Gaussian kernel. It captures the non-linearities in the system; and because of the choice of kernel width, it does not suffer too much from over-fitting.

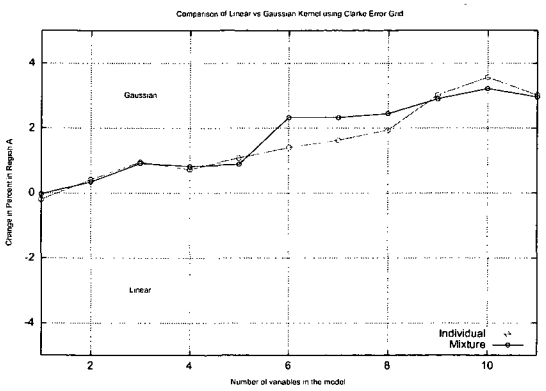
One interesting point to note from these results is that the performance, as measured using the Clarke Error Grid, initially decreases after additional variables are added to pre-meal blood glucose. One explanation for the drop is that the other variables related to medications, meals, and exercise are interrelated. Knowing the dose of insulin provides little help predicting postprandial blood glucose without knowing the carbohydrate content in the meal. After variables representing these three inputs are added the prediction performance starts to improve. The R^2 metric continues to improve even after the percentage of points in region A levels off.

To compare the Gaussian kernel and linear kernel the difference in performance for the two models is plotted in figure 4.7. The Gaussian kernel performs significantly better than the linear kernel due to its ability to capture the non-linearities in the glucose regulatory system.

The Reduced Rank model peaks when the reduced rank is set to three. Including additional dimensions decreases the models performance. In this problem the model does not perform as well as the Gaussian Process regression models, but that could be due to the number of parameters that must be estimated for the RRGP model. This dataset may not contain enough examples to estimate all the parameters.

Compared to many prediction problems, these results do not seem very promising. The models only explain a limited amount of the variance in the output and in the best case only about 57% of the predictions are within $\pm 20\%$ of the reference value in region A. However, it is important to remember that diabetics are going to be making these predictions, so a system can be considered successful if it outperforms humans at the task. Attempting to predict blood glucose and optimize therapy is not an optional task. Thus a system that performs better than the current state-of-the-art is significant. Compared to the ability of humans to estimate postprandial blood glucose, 41.5%, and other published results, 51%, this data collection system and modeling procedure compares very favorably.

(a) Clarke Error Grid



(b) R^2 coefficient

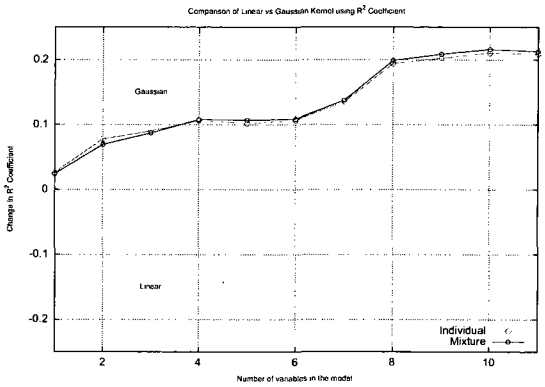


Figure 4.7: The difference in performance between the Gaussian kernel and linear kernel using (a) the percent of points in Region A and (b) the R^2 coefficient as a function of the number of variables in the model. The Gaussian kernel performs significantly better according to both metrics.

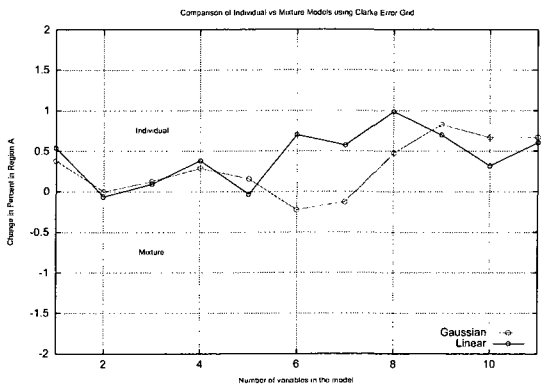
4.7 Interpatient Model Variability Results

One of the goals of this research project is to determine whether a patient's model is improved by using training data from other patients. To test this, three model types were trained that used the individual's data, the joint dataset, and a weighted mixture of data. The joint model performs significantly worse than the individual and weighted mixture models as is clearly evident in Figures 4.6 and 4.4. The RRGP model that creates a reduced-rank basis for all patients and an individualized set of coefficients for each patient also performs worse than the Gaussian Process regression models. Therefore, the competing models are the individual model and weighted mixture model.

The difference between the mean performance over the 10 randomized training and test sets of the individual model and mixed model are plotted in Figure 4.8. The same randomized training and test sets were used for both models, so the differences between them are only due to the modeling method, not the data selected. The individual and weighted mixture models are compared for both the Gaussian kernel and linear kernel.

For both kernels the model trained only using the individual's data improves the percentage of points in region A compared to the weighted mixture model by less than one percent. Compared

(a) Clarke Error Grid



(b) R^2 coefficient

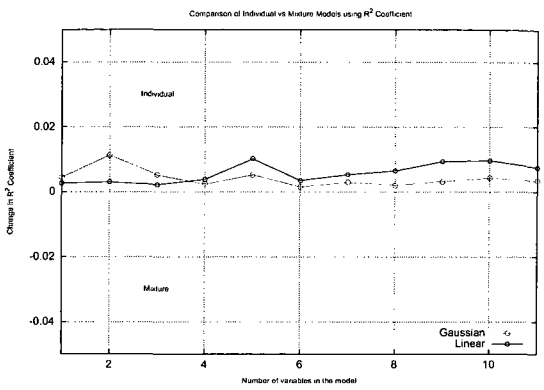


Figure 4.8: The difference in performance between the Individually trained and Mixed patient models using (a) the percent of points in Region A and (b) the R^2 coefficient as a function of the number of variables in the model. There is no significant difference between the two methods.

to the standard deviation for the performance over the 10 randomized training and test sets, this improvement is not significant. Similarly, the performance improvement when using only the individuals data measured by the R^2 metric is not significant.

One reason for the similarity between these two models is that the weighted mixture model was designed to improve the ability of the model to extrapolate to new behaviors not represented in the individuals training set. The lack of improvement could be explained by the repetitive nature of patient behaviors. Figure 4.9 displays the difference between the individual and mixture models as a function of the maximum similarity between the test point and the points in the individual's training set. There is a shift toward the mixture model as the test point becomes less like the training set, but most of the test points do not fall in this category. This is one reason why the individual model performs slightly better.

4.8 Model Performance for a New Patient

After determining the best model, an experiment was done to estimate the number of training examples needed before making predictions. For this experiment data was only used from patients with at least 30 recorded meals. The meals were divided into equal training and test sets. First a

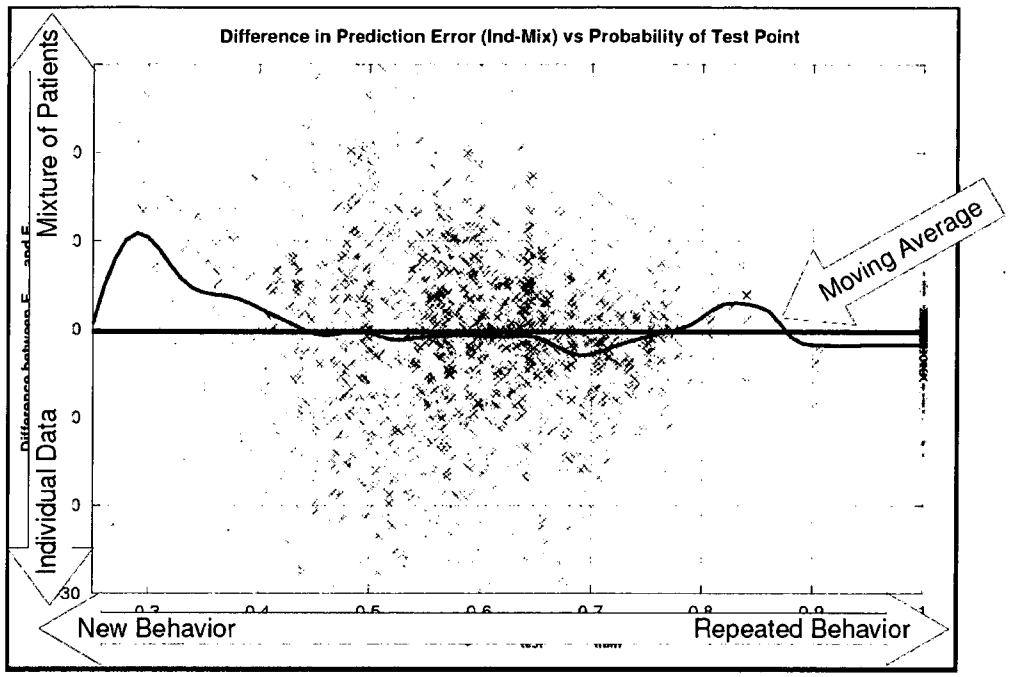


Figure 4.9: Comparison of mixture and individual models as a function of the similarity of the test point to the patient's training set.

model was trained and evaluated using only one of the training points, and then this process was repeated with an additional training point added from two to twenty training points. This entire process was repeated for 10 randomly selected training and test sets for each patient.

Figure 4.10 displays the Clarke error grid results for this experiment as the number of training points is increased. The prediction performance begins to level off after about nine meals, or three days, of data. This is likely due to the repetitive nature of patient behaviors. For example, many people have very similar meals for breakfast every day, so three training points could be sufficient to begin making predictions.

4.9 Predicting modeling performance

The prediction performance for Gaussian Process regression varies significantly between patients with percentages in region A ranging from 27% to 85%. Table 4.4 lists the Clarke error grid results for all patients. The final experiment in this chapter was to determine if model performance is

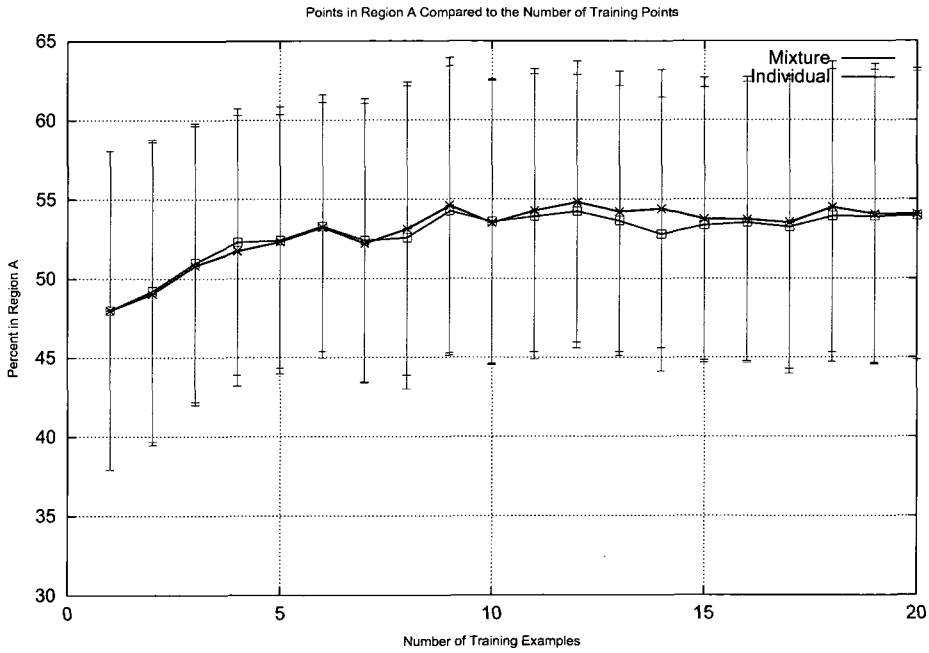


Figure 4.10: Improvement of the percent of points in Region A as a function of the number of training points used. Only patients with sufficient training data were used in this experiment. Performance starts to level after about 10 training points.

correlated to any of the descriptive statistics listed in Table 3.1.

Patient #	A	B	C	D	E
1	65	28	3	4	0
2	75	25	0	0	0
3	60	39	0	1	0
4	77	23	0	0	0
5	32	51	5	12	0
6'	43	43	2	12	0
7	51	49	0	0	0
8	85	15	0	0	0
9	51	35	4	10	0
10	27	42	0	31	0
11	85	15	0	0	0
12	38	42	0	20	0
13	70	25	0	5	0
14	58	37	2	3	0

Table 4.4: Clarke Error grid results for each patient using the individual Gaussian Process model with a Gaussian kernel.

Each pair of descriptive statistics were compared to the performance quality to determine which two dimensions best discriminated between performance quality. After processing all pairs of descriptive statistics the two which best predict performance are the standard deviation of the patients carbohydrate intake and standard deviation of the patients energy expenditure. These values are plotted in Figure 4.11 with the color and size of the plot representing the quality of performance.

Performance improves for patients with greater variability in both carbohydrate intake and energy expenditure. These patients have more signal to help overcome the noise in the system. The predictions perform worse for patients with less variation in their behaviors because the models learn to fit the noise. This is one of the negative aspects of learning models from patient data without prior expert information. If variation does not exist for a behavior then no relationship can be learned between that behavior and blood glucose.

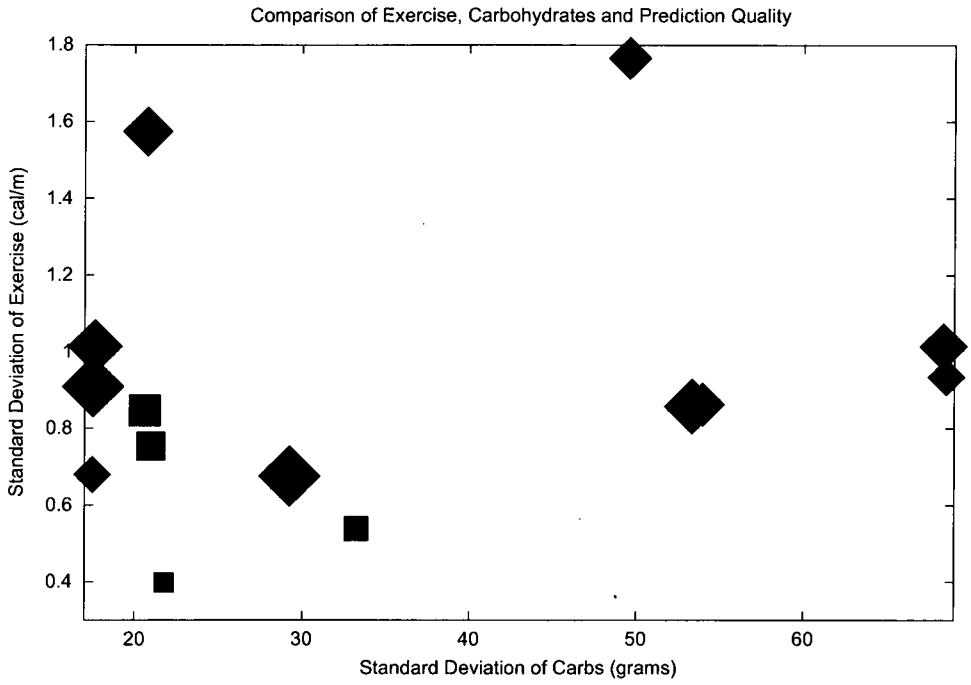


Figure 4.11: Comparing the patients' exercise standard deviation and carbohydrate standard deviation with the quality of prediction. The red squares represent patients where the model placed less than 50 percent of the data points in region A.

4.10 Conclusions

The decisions a patient makes around meals have a significant impact on blood glucose, so predicting postprandial blood glucose is an important challenge for diabetics. Gaussian Process regression with a Gaussian kernel provides the best prediction performance because it can capture the non-linear relationships between the input parameters and blood glucose. This method performs better than humans and other published results. No benefit was seen when including data from other patients in the training set in the weighted mixture model. Finally this modeling method requires about three days of data before predictions can be used. Chapter 6 demonstrates some methods for generating therapy advice using these models.

Whenever I feel like exercise I lie down until the feeling passes.

Robert M Hutchins

Chapter 5

Continuous Dynamic Modeling

There are two competing methods for the dynamic modeling of glucose: physiological models and autoregressive models (ARX). This chapter compares the two methods and presents a new method for including energy expenditure in both models. The ARX model performs better for prediction times less than 45 minutes and the physiological model with exercise performs better for predictions times beyond 45 minutes. The physiological model with exercise also performs better at estimating the real-time value of blood glucose between finger-stick measurements.

5.1 Introduction

The continuous dynamic modeling of glucose is needed to provide optimal therapy at times other than meals. The previous chapter focused specifically on the choices at mealtimes, but patients make many other therapy decisions that are not associated with meals. Also, continuous dynamic models could be beneficial toward developing an artificial pancreas, predicting hypoglycemia, and explaining glucose excursions.

Much work has been done toward developing dynamic glucose models. Many groups have developed sets of differential equations that can be solved numerically to closely approximate a true continuous function. However, for therapy choices this fine resolution is not necessary. In this chapter *continuous* is used to refer to a discrete system model with a time step of five minutes

or less. This scale is equivalent to the sample rate of the Minimed CGMS system, and it is fine enough so that insulin injections made at five minute intervals can adequately approximate a true continuous delivery. Therefore therapy derived at this time scale would be almost identical to that derived from the differential equations.

There are two main categories of continuous models used to simulate the glucose regulatory system. The most common are physiological models that seek to capture the internal dynamics within the systems of the body. This type of model tracks carbohydrate intake as it is converted to blood glucose which then interacts with the kidneys, liver, muscles, and other body systems. The main advantage of these models is that the components are based on data from known interactions. The challenge is that most of the model parameters are hidden and therefore difficult to estimate for a specific patient. Furthermore, physiological models have no way of representing unknown physiological processes that affect glucose.

The second category is autoregressive models with exogenous inputs, ARX models, that use a window of the time series data as input to a regression model. This category of models can learn correlations that exist in a patient's data, but might not exist in a physiological model. However, because the structure of these models is not based on reality they can produce predictions that are wildly wrong potentially having a negative impact on a patient's health.

Optimizing insulin doses for a patient is a challenging problem because of the delay between insulin injection, absorption, and activity. The time to peak action for rapid acting insulins most frequently used for meal boluses and in insulin pumps is around 45 minutes. Injections decisions are made based on what the system state will be in the future. The most common use of dynamic models is for addressing this problem.

One of the missing components of most physiological models is exercise. There is no universally accepted method for incorporating energy expenditure into glucose dynamic models. This chapter presents one possible method; though more data is needed to adequately validate this model. This model will be compared to a model that does not include exercise and to an autoregressive model. The models will be used to predict blood glucose concentrations at multiple times in the future.

5.1.1 Problem Statement

This chapter addresses the challenge of developing an approximately continuous glucose dynamic model that can capture the affects that all the measurable inputs have on blood glucose. In general the model will predict the value of glucose, g, at the next time step based on the current system state, X, and inputs to the system, U.

$$X_{t+1} = f(X_t, U_t) + \varepsilon_t \tag{5.1}$$

$$g_{t+1} = h(X_{t+1}) + \mu_t \tag{5.2}$$

The representation of f and h depend on the modeling method. Four candidate methods - traditional physiological modeling, physiological modeling with exercise, AR, and ARX - will be compared. The implementation details of each method are presented in detail in the following sections.

The models will be used to predict glucose dynamics at a number of future time intervals ranging from five minutes to 45 minutes. Predictions at 45 minutes could be used for insulin dosing as this is the approximate absorption delay from injection to peak insulin action. The predictions will be compared to continuous glucose measurements recorded by a Minimed CGMS. The CGMS measures glucose concentration in interstitial fluid, and is therefore a noisier estimate of blood glucose than a reading from a spot monitor.

Two error metrics will be used to evaluate the prediction performance: the R^2 coefficient and the Clarke error grid. These are the same metrics used when evaluating the prediction of postprandial glucose values. A discussion on these two metrics and their applicability to the glucose prediction problem can be found in Chapter 4.

5.1.2 Data Collection and Preparation

The data collection protocol is identical to the protocol used for postprandial glucose prediction with the addition of continuous glucose measurements, CGM. The protocol is described in detail

Input Measurements		
Var Name	Description	Units
U^{cg}	Continuous Glucose Reading	mg/dl
U^{g}	Blood Glucose Reading	mg/dl
U^{C}	Ingested Carbohydrate	mg
U^{F}	Ingested Fat	mg
U^{P}	Ingested Protein	mg
U^{E}	Current Exercise Rate	cal/min
U^{I}_{f}	Injected Rapid Insulin	units
U^{I}_{r}	Injected Regular Insulin	units
U^{I}_{m}	Injected Mixed Insulin	units
U^{I}_{s}	Injected Long Acting Insulin	units

Table 5.1: System input data for continuous modeling

in Chapter 3. The CGM, while noisier, provide a reference point for evaluating the performance of the modeling methods. Unfortunately, CGM were only collected on a small subset of the cohort and only represent patients with type 1 diabetes using insulin pump therapy. Because of the small data set, evidence is not available to reach strong conclusions. As a result, the conclusions in this chapter are best expressed as observations that require additional verification.

5.1.3 Variable Definitions

The variables used to define the data collected as input into the three models will use the nomenclature shown in Table 5.1. The list does not include any medications other than insulin because CGM data was not collected from any patients on these medications.

The complete set of input data will be referred to as U and input at a specific time as U_t. The input will be zero for many of these variables at a specific time due to their infrequency.

5.2 ARX model

The Auto-Regressive with eXogenous input model uses autoregressive terms and other input measurements to model the dynamics in the system. This is a standard model for time series analysis, so it will be used as a point of comparison for the physiological models. The ARX model is simpler

Input Vector: ARX Model		
Var Name	Description	Units
$\bar{U}^{cg}_{t-\Delta t...t}$	Mean Continuous Glucose Reading	mg/dl
$\bar{U}^{g}_{t-\Delta t...t}$	Mean Blood Glucose Reading	mg/dl
$\sum_{t-\Delta t...t} U^C$	Sum of Ingested Carbohydrate	mg
$\sum_{t-\Delta t...t} U^F$	Sum of Ingested Fat	mg
$\sum_{t-\Delta t...t} U^P$	Sum of Ingested Protein	mg
$\bar{U}^{E}_{t-\Delta t...t}$	Mean Current Exercise Rate	cal/min
$\sum_{t-\Delta t...t} U^I_f$	Sum of Injected Rapid Insulin	units
$\sum_{t-\Delta t...t} U^I_r$	Sum of Injected Regular Insulin	units
$\sum_{t-\Delta t...t} U^I_m$	Sum of Injected Mixed Insulin	units
$\sum_{t-\Delta t...t} U^I_s$	Sum of Injected Long Acting Insulin	units

Table 5.2: Input data for the ARX model

to implement, so if it performs better than physiological models, then it is preferable. Equation 5.3 is the ARX model where the autoregressive terms are the previous continuous glucose measurements, g, and the exogenous input data, X, are the measurements of meals, medication, and exercise.

$$g_{t+1} = \sum_{i=0}^{\infty} \alpha_i g_{t-i} + \sum_{i=0}^{\infty} \beta_i X_{t-i} \tag{5.3}$$

To prepare the raw data for use in an ARX model it is sampled at a uniform rate and placed in a matrix, X. Each column in this matrix, X_t, contains a vector of measurements and input data sampled at that time. Data are sampled by placing the measurement into the nearest time bin that is greater than or equal to the measurements time stamp. This prevents the model from using future data to aid in making a prediction. In cases where the measurement frequency exceeds the time step, the measurements are combined in an appropriate way into the bin. For exercise and continuous glucose, the measurements are averaged when sampling. For nutrition components and medications, the data are summed.

The resulting input vector for the ARX model is described in Table 5.2. After sampling the data, it is divided equally into a training set and a test set. Patients collect data for two weeks, so the first week is used to train the model and the second week is used to test it. After splitting into sets, the training input data is centered and normalized. The test set is then centered and

normalized using the mean and standard deviation of the training set.

To solve for the coefficients a time window is defined, $[t-\tau, t]$, over which measurements will be used in the prediction. The input vectors are then reshaped to solve for the coefficients using least squares.

$$g_{t+1} = \sum_{i=0}^{\tau} \alpha_i g_{t-i} + \sum_{i=0}^{\tau} \beta_i X_{t-i} \tag{5.4}$$

Convert equation 5.4 into matrix form.

$$\begin{bmatrix} g_1 \\ \vdots \\ g_{T+1} \end{bmatrix} = \begin{bmatrix} (g_0 \dots g_{0-\tau}) \\ \vdots \\ (g_T \dots g_{T-\tau}) \end{bmatrix} \begin{bmatrix} \alpha_0 \\ \dots \\ \alpha_\tau \end{bmatrix} + \begin{bmatrix} (X_0 \dots X_{0-\tau}) \\ \vdots \\ (X_T \dots X_{T-\tau}) \end{bmatrix} \begin{bmatrix} \beta_0 \\ \vdots \\ \beta_\tau \end{bmatrix} \tag{5.5}$$

Then augment the input matrices and stack the coefficient matrices to get the final matrix equation.

$$\begin{bmatrix} g_1 \\ \vdots \\ g_{T+1} \end{bmatrix} = \begin{bmatrix} (g_0 \dots g_{0-\tau}) & (X_0 \dots X_{0-\tau}) \\ \vdots & \vdots \\ (g_T \dots g_{T-\tau}) & (X_T \dots X_{T-\tau}) \end{bmatrix} \begin{bmatrix} \alpha_0 \\ \dots \\ \alpha_\tau \\ \beta_0 \\ \vdots \\ \beta_\tau \end{bmatrix} \tag{5.6}$$

Finally, solve for the coefficients using least squares by way of the pseudoinverse. Results from the ARX model will be labeled with "ARX." For comparison purposes an auto-regressive model that excludes the exogenous input was also created. The AR model only uses the continuous glucose measurements as input.

5.3 Physiological model

Physiological models are useful because they are based on known interactions. Previous models of the glucose regulatory system share many common features. Almost all models incorporate carbohydrate intake, renal clearance, hepatic glucose uptake and production, and both insulin-dependent and insulin independent glucose utilization, but most do not incorporate energy expenditure. Furthermore, no previous model has used a continuous measurement of energy expenditure.

Previous equations used to model these processes are almost identical [23, 10, 100]. The functions for the individual components of the body for these models are based on the same data. The components are combined to form the system model.

The overall dynamics of the physiological model can be compartmentalized at the highest level into insulin dynamics, glucose dynamics, and meal absorption dynamics. Insulin dynamics includes the absorption, secretion, and clearance of plasma insulin. Meal absorption dynamics models the digestion of carbohydrates and other nutritional components in the gut, and their absorption as glucose into the blood. Finally glucose dynamics includes the interactions of blood glucose with all the systems in a patients body.

$$\begin{aligned} g_{t+1} = \; & g_t + \ldots && \text{current blood glucose} \\ & \Delta g^{gut} + \ldots && \text{carbohydrate absorption} \\ & \Delta g^{dep} + \ldots && \text{insulin dependent uptake} \\ & \Delta g^{ind} + \ldots && \text{insulin independent uptake} \\ & \Delta g^{egp} + \ldots && \text{hepatic glucose production} \\ & \Delta g^{clr} && \text{renal clearance} \end{aligned} \tag{5.7}$$

5.3.1 Insulin Dynamics

There are two sources of insulin for diabetics: secretion from the pancreas and injection by either a syringe or an infusion device. For patients with type 1 diabetes the amount of insulin secreted is close to zero. When patients initially get the disease they typically have some remaining beta

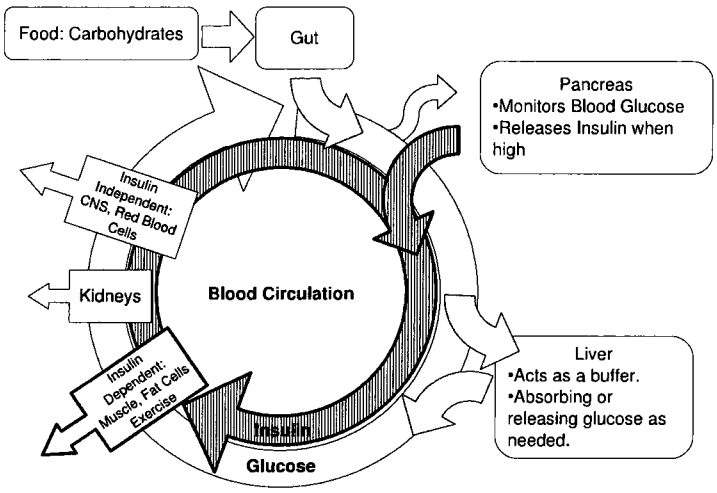


Figure 5.1: Graphic of the components of the physiological model

cells in their pancreas that secrete a residual amount of insulin, but as the disease progresses these remaining cells die. Though the model will only be validated with data from patients with type 1 diabetes, an insulin secretion model is included for completeness.

At a high level the dynamics of insulin in blood can be expressed with the equations in Table 5.3. The three components that need to be modeled are insulin absorption from injections ΔI^{abs}, insulin secretion ΔI^{sec}, and insulin clearance ΔI^{clr}.

Δ Insulin	=	Absorbed Insulin	+	Secreted Insulin	-	Cleared Insulin
ΔI_t	=	ΔI_t^{abs}	+	ΔI_t^{sec}	-	ΔI_t^{clr}

Table 5.3: Model for insulin utilization.

The second source of insulin is from subcutaneous injections. The rate at which this insulin becomes active depends on the patient, the type of insulin, and the injection site. The most common types of insulins currently used are rapid insulin analogues and slow-acting insulin glargine. Other insulins exist including regular insulin, NPH, and premixed insulin. The model can accept input from four types of insulin.

Input Measurements		
Var Name	Description	Units
U_f^I	Injected Rapid Insulin	units
U_r^I	Injected Regular Insulin	units
U_m^I	Injected Mixed Insulin	units
U_s^I	Injected Long Acting Insulin	units

Table 5.4: Input data for insulin injections.

Insulin Absorption

The most frequent location for insulin injections is into subcutaneous fatty tissue. After the injection there is a delay as the insulin is gradually absorbed into the bloodstream. The rate of absorption can be approximated as a constant percentage of the injected insulin remaining in the subcutaneous compartment. The value of this constant is a function of the patient and the type of insulin. Therefore it is important to distinguish between the types of insulin injected. The exception is insulin glargine which is absorbed at a constant rate proportional to the original dose over a 24 hour period. Mixed insulin is made by combining a faster acting insulin analogue with a slow acting insulin in a specific ratio. One of the most common forms is a 70/30 Mix which contains 70% long acting insulin and 30% fast acting insulin. Injections of a mixed insulin are treated as simultaneous injections of rapid insulin and long acting insulin in the appropriate proportions.

$$\begin{aligned} \Delta I_t^{abs} &= \alpha_{f,r,m}^I I_t^{sub} && \text{rapid, regular, mixed} \\ \Delta I_t^{abs} &= \alpha_s^I \textstyle\sum_{24hours} U_s^I && \text{insulin glargine} \\ I_{t+1}^{sub} &= I_t^{sub} - \Delta I_t^{abs} + U_t^I \end{aligned} \tag{5.8}$$

The amount of insulin absorbed into the blood is the sum over all types of insulin injected. The absorption rate parameters used for the types of insulins are below. These values can vary with different patients and with different injection sites. However, for this project they are assumed to be constant, and the variation is attributed to noise.

An example graph of the absorption curves for each type of insulin given equivalent 10 unit injections is displayed in Figure 5.2. The differences in the rate of appearance in the blood can

Parameters	
Var Name	Value
α_f^I	0.015
α_r^I	0.008
α_m^I	0.002
α_s^I	0.001

Table 5.5: Parameter values for insulin absorption

clearly be seen.

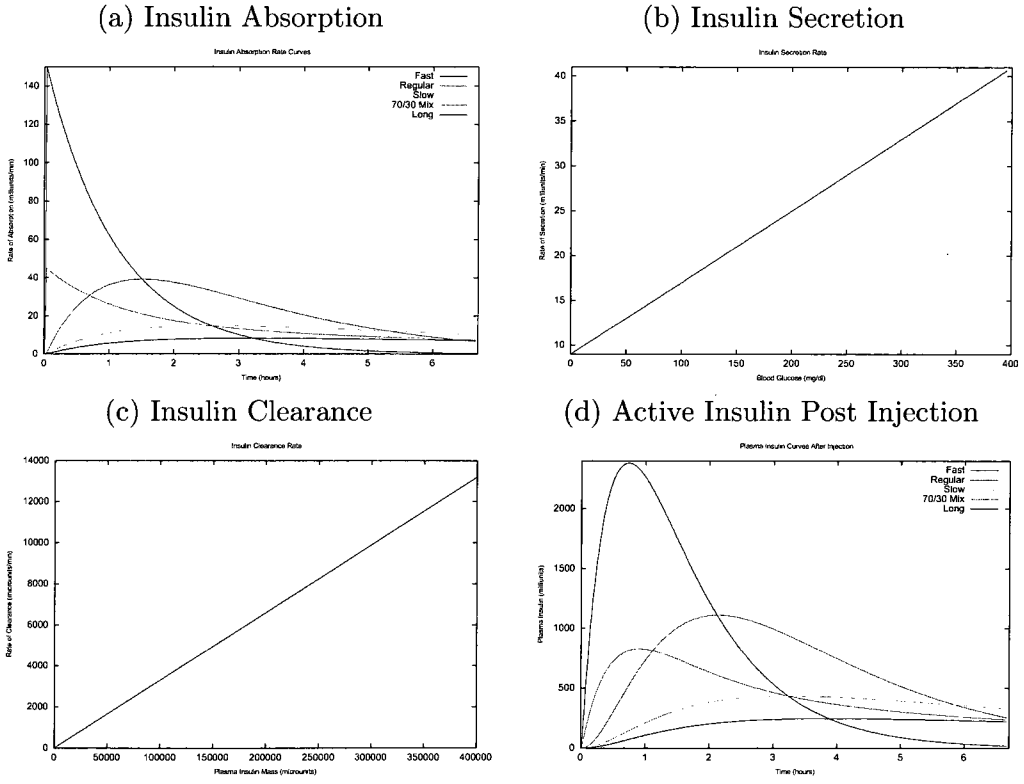


Figure 5.2: The dynamics of insulin from injection and secretion to clearance. (a) contains the absorption rate for different types of insulins after injections. (b) contains the secreted insulin as a function of blood glucose. (c) relates insulin clearance to blood glucose. (d) displays the active plasma insulin profile for different types of insulin after injection.

Parameters	
Var Name	Value
α_1^I	1000
α_2^I	1.2
α_3^I	0.17

Table 5.6: Parameter values for insulin secretion

Insulin Secretion

Increased insulin secretion by the pancreas is triggered when blood glucose deviates from normal, and insulin is also secreted at a basal level during normoglycemia, g_0. Equation 5.9 models the increased secretion of insulin with elevated glucose as well as the basal secretion. The amount secreted is bounded by the maximal rate of secretion, ΔI_{max}^{sec}.

$$\begin{aligned} \Delta I_t^{sec} &= \min\left[\alpha_1^I(\alpha_2^I(g_t - g_0) + \alpha_3^I g_0), \Delta I_{max}^{sec}\right] \quad \text{Type2} \\ \Delta I_t^{sec} &= 0 \qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad \text{Type1} \end{aligned} \tag{5.9}$$

The parameter values can vary between patients. For this project they are assumed to be constant and the variation is attributed to noise. For type 1 patients, insulin secretion is set to zero. If a patient had reduced pancreas functionality it could be modeled by decreasing α_1^I. The parameter values are listed in Table 5.6.

Figure 5.2 plots the insulin secretion rate as a function of blood glucose value. In healthy individuals the amount of insulin secreted decreases as blood glucose drops toward hypoglycemia. When patients on insulin injections approach hypoglycemia their insulin levels remain constant resulting in an increased risk.

Insulin Clearance

Once insulin has been absorbed into the blood it is then removed at a rate proportional to its concentration.

$$\Delta I_t^{clr} = \alpha_c^I I_t \tag{5.10}$$

Parameters	
Var Name	Value
α_c^I	0.033

Table 5.7: Parameter values for insulin clearance

Again, for this process the parameters are considered constant and the variation is attributed to noise.

Figure 5.2 is a plot of the concentration of insulin in the blood for the four types of insulin after a 10 unit injection, similar to the absorption plot, when also using insulin clearance. The difference in time to peak action for each type of insulin can be seen.

Insulin Sensitivity

The insulin sensitivity of a patient is a metric that characterizes how efficiently a patient can utilize insulin to in insulin-dependent glucose uptake. For the following models it is represented as a percentage where a value of 1 represents a patient with normal insulin sensitivity. Patients with reduced insulin sensitivity will have a value less than one. The insulin sensitivity of a patient will affect the amount of insulin necessary to reduce high glucose values to the normal range.

Active Insulin

Active insulin refers to insulin that has interacted with muscle and fat cells to initiate the uptake of blood glucose. This value is different from the concentration of plasma insulin in the blood. The amount of active insulin can also be written as a function of patients' insulin sensitivity as a way to model patients with type 2 diabetes.

$$\begin{aligned} I_t^{active} &= S^I I_t / V_I \\ I_t^{plasma} &= I_t / V_I \end{aligned} \tag{5.11}$$

The value for insulin sensitivity is estimated to minimize the error between the model and blood glucose measurements.

5.3.2 Meal Absorption

The process of consuming meals and their absorption as glucose from the gut to the blood is a very complex process to model. The amount of glucose absorbed and the rate of absorption depend on the nutritional content of the meal. The main three sources of energy in a meal are protein, fat, and carbohydrates. While protein and fat can eventually be converted to glucose, the amount and type of carbohydrate consumed has the most significant immediate affect on blood glucose. Most models of meal absorption only consider the quantity of carbohydrates in the meal, and most consider all carbohydrates identically. Carbohydrates, however, can be classified using the glycemic index. Simple carbohydrates have a high glycemic index and are absorbed quickly, and more complex carbohydrates have a lower glycemic index and a longer absorption curve [69].

Meal consumption causes the largest disturbance to glucose homeostasis and is the largest source of uncertainty in the system. The combination of high impact and high uncertainty makes modeling this component difficult. Patients consume a wide variety of meals, and accurately measuring the carbohydrate content in those meals is difficult. Chapter 2 discusses the data collection methods used by IDA to attempt to reduce the uncertainty in carbohydrate estimation.

After carbohydrates are consumed they are moved through the digestive system and gradually absorbed into the blood. This process can be modeled using two compartments. Alternative, more complex models can be found in [78, 77]. However the proposed model strikes a balance between parameter identification and model representation.

$$\begin{aligned} \Delta C_t^{gut1} &= -\alpha_1^C C_t^{gut1} + U_t^c && \text{Consumption} \\ \Delta C_t^{gut2} &= \alpha_1^C C_t^{gut1} - \alpha_2^C C_t^{gut2} && \text{Digestion} \\ g_t^{gut} &= \alpha_3^C \alpha_2^C C_t^{gut2} && \text{Absorption} \end{aligned} \tag{5.12}$$

The default parameters used for this submodel are listed in Table 5.8.

Figure 5.3 displays the modeled absorption rate of carbohydrate to blood glucose in a typical patient after a meal of 50 grams of carbohydrates. This is one of the components of the blood glucose dynamic model.

Carbohydrate absorption is complex and is the input with the largest uncertainty in its mea-

Carbohydrate Parameters	
Var Name	Value
α_1^C	0.95
α_2^C	0.09167
α_3^C	250

Table 5.8: Parameter values for carbohydrate absorption

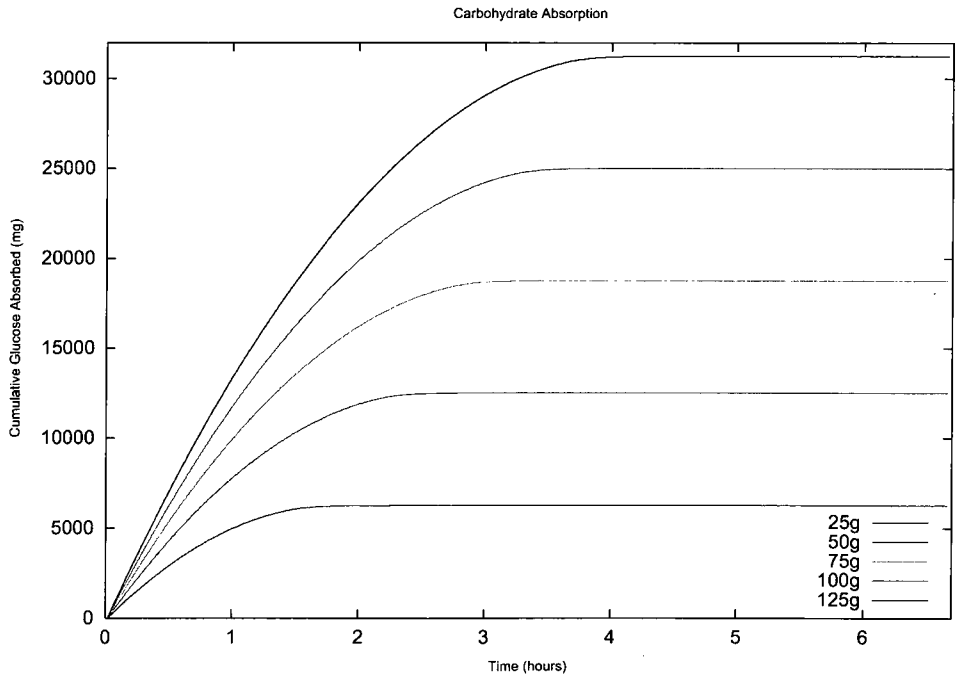


Figure 5.3: Carbohydrate absorption into the blood after a meal of 50 grams of carbohydrates

Glucose Model Compartments

Variable	Abrv.	Description
Δg_t^{egp}	EGP	Endogenous Glucose Production (Liver)
Δg_t^{gut}	GUT	Glucose Rate of Appearance (Carb Absorption)
Δg_t^{ind}	IND	Insulin Independent Utilization (CNS)
Δg_t^{dep}	DEP	Insulin Dependent Utilization (Muscle,Fat)
Δg_t^{clr}	CLR	Renal Clearance (Kidneys)

Table 5.9: Interactions with blood glucose

surement. The two main sources of uncertainty in the model are the estimated quantity of the consumed carbohydrate and the absorption rate of the carbohydrate. In the mathematical model these are represented by the values of U_t^c and α_2^C respectively. The type of carbohydrates in a meal will affect the absorption rate.

5.3.3 Blood Glucose Dynamics

Blood glucose dynamics models the changes in glucose concentration in the blood due to interactions with other body systems. Glucose is used for energy, so its dynamics are affected by almost every cell in the body. When modeling this system the primary compartments modeled are the introduction of glucose to the system from the gut, glucose utilization by insulin-dependent and independent compartments, removal of glucose by the kidneys, and buffering of glucose by the liver.

Table 5.9 lists the main compartments in the glucose physiological model. The three letter abbreviation listed will be used to identify parameters and variables associated with the compartments.

The actual combination of these compartments to determine the change in blood glucose is simple. The total change is blood glucose is equal to the sum of the sources and sinks.

$$\Delta g_t = \Delta g_t^{egp} + \Delta g_t^{gut} - \Delta g_t^{ind} - \Delta g_t^{dep} - \Delta g_t^{clr} \tag{5.13}$$

The models for insulin dynamics and carbohydrate absorption have already been presented. It is important to define these first as the models for the liver and insulin dependent utilization both

Parameters	
Var Name	Value
α_1^{dep}	0.0002
α_2^{dep}	90

Table 5.10: Parameter values for insulin dependent utilization

are a function of the current plasma insulin level. In the following section models for the remaining compartments will be presented.

5.3.4 Insulin Dependent Utilization

Insulin acts as a key allowing muscle cells and fat cells to absorb glucose. When insulin is present the glucose transporter GLUT-4 moves to the cell wall to facilitate the transport of glucose across the membrane. The rate of transport is a function of the amount of insulin, blood glucose concentration, and exercise. However most models do not include exercise in the dynamics of this compartment. Because IDA collects a continuous estimate for energy expenditure, exercise can be included in this model. First, the traditional model is presented below in equation 5.14 followed by a modified version that includes exercise.

$$\Delta g_t^{dep} = \alpha_1^{dep} I_t (g_t + \alpha_2^{dep}) \quad \text{without exercise} \tag{5.14}$$

Values for the parameters in equation 5.14 are listed in Table 5.10. This equation models the increase in glucose uptake associated with increases in insulin and blood glucose.

Figure 5.4 displays a plot of the uptake of glucose as a function of glucose concentration for different levels of insulin.

5.3.5 Insulin Dependent Utilization with Exercise

Exercise needs to be included so that at rest the insulin dependent model is identical to equation 5.14, but when exercise increases, the rate of glucose uptake needs to increase as well. The effect of exercise can also last after the patient has stopped exercising while cells replenish their glucose

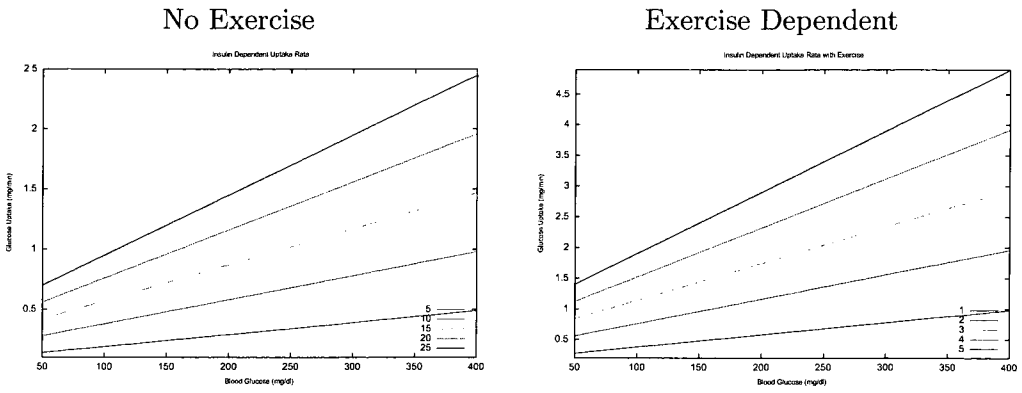


Figure 5.4: (a) Blood glucose uptake as a function of glucose concentration for different levels of plasma insulin, and (b) insulin dependent uptake for different levels of exercise.

stores. Both of these dynamics need to be added to this model. Exercise, or energy expenditure, is measured as the number of calories burned per minute.

The extended effect of exercise can be included by first calculating an exercise effect variable, E_t. The exercise effect is a linear combination of exercise over the past time window. This extends and smooths the effects on insulin.

$$E_t = \sum_{i=0}^{\tau} \alpha_i^{ex} U_{t-i}^{E} \quad \text{exercise effect} \tag{5.15}$$

The exercise effect variable is added to the compartment model as a ratio with the basal level of energy expenditure. When a patient is at basal levels of energy expenditure this function is the same as equation 5.14.

$$\Delta g_t^{dep+e} = \alpha_1^{dep+e} \frac{E_t}{E_0} I_t(g_t + \alpha_2^{dep+e}) \quad \text{with exercise} \tag{5.16}$$

The parameter values for equation 5.16 are identical to those in Table 5.10. These are identical to the parameters in the model without exercise, so when the patient is in a state of basal energy expenditure the two models converge.

Graphs of the uptake rate of glucose due to insulin dependent utilization compared to blood glucose for different levels of exercise with a fixed concentration of insulin are plotted in Figure 5.4.

Parameters	
Var Name	Value
α_1^{ind}	1.2

Table 5.11: Parameter values for insulin independent utilization

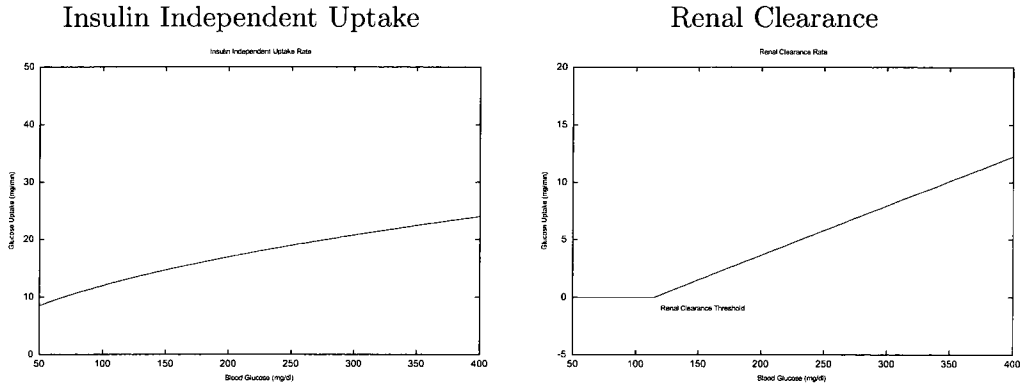


Figure 5.5: Blood glucose uptake as a function of glucose concentration for insulin independent uptake, and renal clearance of blood glucose.

5.3.6 Insulin Independent Utilization

Unlike muscle cells, the central nervous system and red blood cells do not require insulin to activate glucose transport across their cell wall. Therefore their utilization of glucose is independent of insulin. This is very fortunate for patients as it keeps a loss of insulin from being immediately life threatening. The uptake of glucose to this compartment is only a function of the blood glucose concentration.

$$\Delta g_t^{ind} = \alpha_1^{ind} \sqrt{g_t} \tag{5.17}$$

The value for the parameter in equation 5.17 is listed in Table 5.11.

Figure 5.5 displays a plot of the uptake of glucose by the central nervous system and red blood cells as a function of the current blood glucose concentration.

Parameters	
Var Name	Value
α_1^{clr}	0.043
$g_{threshold}^{renal}$	115

Table 5.12: Parameter values for renal clearance

5.3.7 Renal Glucose Clearance

When blood glucose concentrations exceed the renal clearance threshold, $g_{threshold}^{renal}$, the kidneys begin to remove excess glucose from the blood. Unfortunately the clearance rate is not sufficient enough to reduce glucose to normal levels, and the process stresses the kidneys. This process is modeled with equation 5.18.

$$\Delta g_t^{clr} = \begin{cases} \alpha_1^{clr}(g_t - g_{threshold}^{renal}) & \text{if } g_t \geq g_{threshold}^{renal} \\ 0 & \text{else} \end{cases} \tag{5.18}$$

The value for the renal clearance threshold and other parameters in equation 5.18 are listed in Table 5.11.

Figure 5.5 displays a plot of the removal of glucose by the kidneys as a function of the current blood glucose concentration. If a patient were to have reduced renal function, it could be modeled by reducing parameter α_1^{clr}. In this study the model was only used for patients with normal renal function.

5.3.8 Endogenous Glucose Production

Endogenous glucose production refers to the release of glucose by the liver. In a normal individual this occurs when blood glucose levels drop. The liver functions as a buffer to correct for deviations glucose homeostasis. This process depends on the current blood glucose concentration and level of plasma insulin.

$$\Delta g_t^{egp} = \alpha_1^{egp} g_t + \alpha_2^{egp} * e^{\frac{-I_t}{\alpha_3^{egp}}} - \alpha_4^{egp} \tag{5.19}$$

Parameters	
Var Name	Value
α_1^{egp}	-0.0333
α_2^{egp}	45
α_3^{egp}	15
α_4^{egp}	0

Table 5.13: Parameter values for endogenous glucose production

The parameters in equation 5.19 were adjusted to fit the equation to published data [72]. The parameters are listed in Table 5.13 and a plot of the model compared to the published data is given in Figure 5.6.

These models are combined to form the blood glucose physiological model. There are other hormones and factors that can affect glucose, but these are the main compartments. Additional factors are treated as noise in the system.

5.3.9 Other Useful Functions

Other useful functions for calculating blood volume and converting between units are listed in Appendix A. It also includes the molecular weight of insulins and energy conversions for protein, fat, and carbohydrate.

5.4 EKF Implementation Details

The physiological model was implemented as an Extended Kalman Filter to account for the non-linearities in the model. The details of the EKF are in Appendix B. The Extended Kalman Filter was also used to track the propagation of uncertainty in the system from the uncertainty in measurements to that of blood glucose. There is a significant amount of noise in this system that makes accurate modeling almost impossible, but if the uncertainty is modeled correctly then therapy optimization algorithms can still use the model. When the uncertainty is too high, algorithms should act accordingly when suggesting therapy adjustments.

The assumptions made by a Kalman filter include linearity and Gaussian noise. The glucose

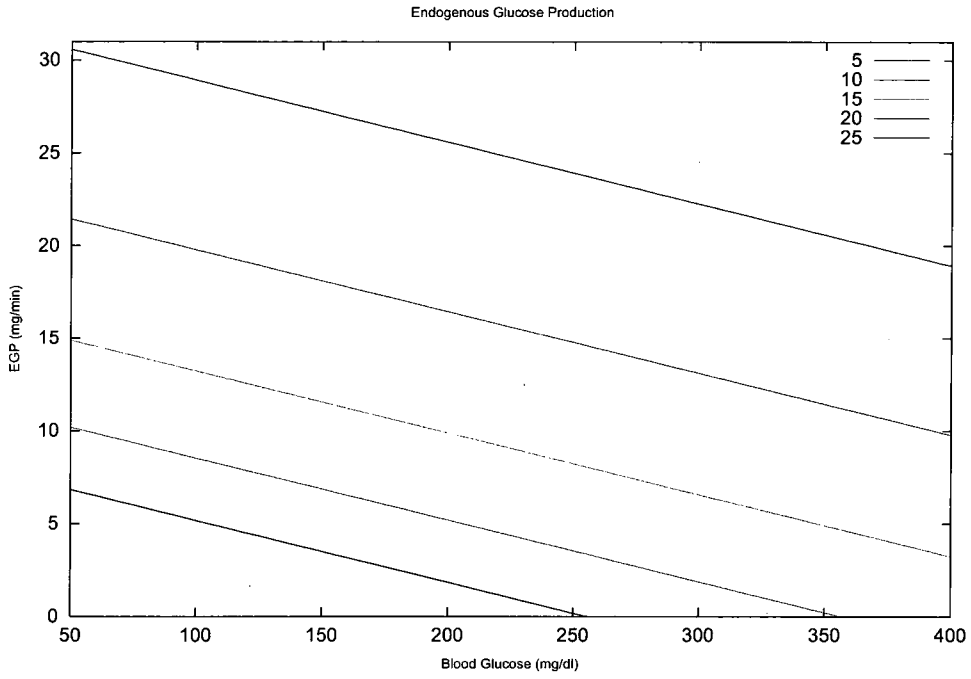


Figure 5.6: Endogenous glucose production as a function of glucose concentration for different levels of plasma insulin.

dynamic model contains nonlinear components and the sources of noise are poorly understood. Extended Kalman filters have demonstrated good performance in other systems with nonlinear components, so the EKF was chosen for the physiological model.

The physiological model is made of many subcompartments such as the kidney function or insulin dependent glucose uptake. To capture this in the EKF each subcompartment was implemented as a separate model. Separating the EKF update into components allowed different models for a compartment to be interchanged quickly to evaluate each. It also allowed each component to function independently to allow investigation into the response of the component to specific input. This design lets each compartment be tested separately, and it made evaluating different models for compartments simpler. One of the primary goals of creating the physiological model was to create a new model that incorporated energy expenditure.

To evaluate the model with exercise, an exercise dependent insulin dependent uptake compartment was created. Experiments were done to compare the effect of replacing the traditional insulin dependent compartment with this new model. The modular design of the EKF facilitated making this comparison by simplifying the process of changing subcompartment models.

5.4.1 EKF Update Equations

The EKF equations assume the model can be expressed in the form given in equation 5.21.

$$X_t = f(X_{t-1}, U_{t-1}) + q_{t-1} \tag{5.20}$$

$$g_t = h(X_t) + r_t \tag{5.21}$$

In this system f is the nonlinear physiological blood glucose model that updates the system state vector X_t at each time-step. The function h describes the measurement of blood glucose as a function of the state vector. The noise parameters q and r represent the uncertainty in the state update and measurement, respectively. The unmodeled factors that affect glucose are treated as a part of q.

The update equations begin with the prediction step. This step updates the state of the system and its covariance without incorporating new information from measurements.

$$X_t^- = f(X_{t-1}, U_{t-1}) \tag{5.22}$$

$$P_t^- = F_{t-1}P_{t-1}F_{t-1}^T + Q_{t-1} \tag{5.23}$$

The matrix F_{t-1} is the derivative of the function $f(X)$ with respect to the state vector evaluated at the current system state and update state.

$$F_{t-1} = \frac{\delta f}{\delta X}(X_{t-1}, U_{t-1}) \tag{5.24}$$

After the prediction step is the correction step where new information or measurements are combined with the prediction.

$$K_t = P_t^- H_t^T (H_t P_t^- H_t^T + R_t)^{-1} \tag{5.25}$$

$$X_t = X_t^- + K_t(g_t - H_t X_t^-) \tag{5.26}$$

$$P_t = P_t^- - K_t(H_t P_t^- H_t^T + R_t)K_t^T \tag{5.27}$$

In the measurement update step the matrix H_t is the Jacobian of the function h with respect the the state vector X evaluated at the current system state.

$$H_t = \frac{\delta h}{\delta X}(X_t) \tag{5.28}$$

Examples

As an example, Figure 5.7 plots the output of the physiological model calculated for a patient with type 2 diabetes. The model is updated at each blood glucose measurement. This patient has mild diabetes, so his insulin sensitivity is almost normal. The insulin sensitivity is the primary

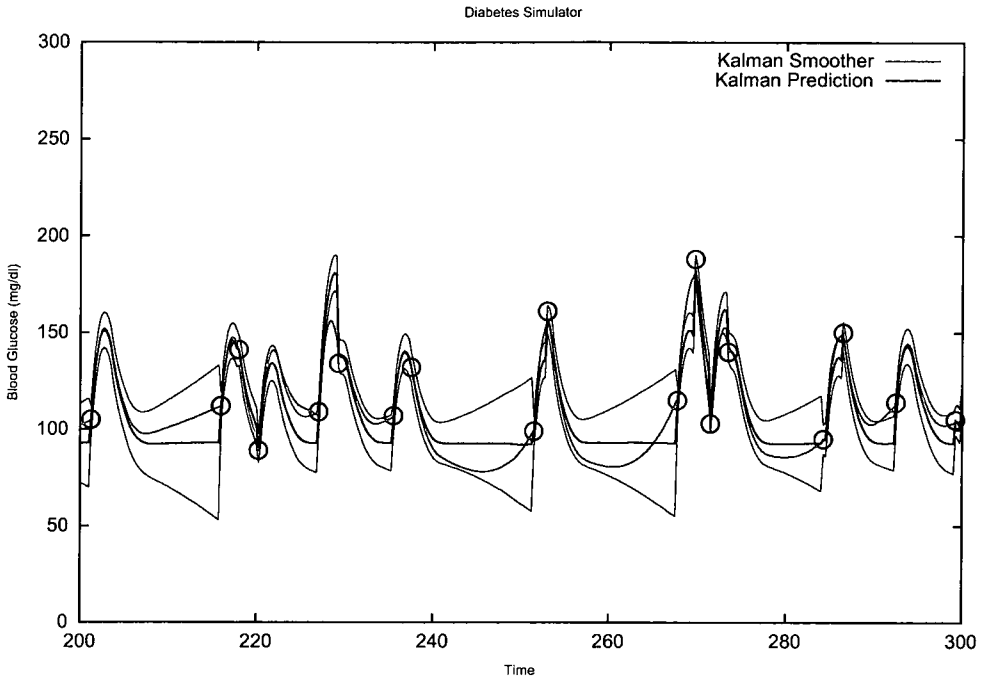


Figure 5.7: Results from the physiological model on a patient with well controlled type 2 diabetes.

parameter to estimate to fit the model to a patient. This parameter adjusts how effectively the patient can use insulin to remove glucose from the blood.

Insulin Sensitivity can range from 0 to 1. A normal person without diabetes would have an insulin sensitivity of 1, and similarly a patient with type 1 diabetes will usually have an insulin sensitivity near 1. The primary difference between these two cases is that the insulin secretion compartment of the physiological model is turned off for the patient with type 1 diabetes.

Estimating Insulin Sensitivity

The possible values for insulin sensitivity are bounded so it can be estimated by trial-and-error. The error between the predicted blood glucose and measured blood glucose is evaluated over the range of possible values for insulin sensitivity. The value that minimizes the error is used as the best estimate for the parameter. Figure 5.8 shows the error as a function of insulin sensitivity for a patient. The optimal estimate is the value that minimizes the error.

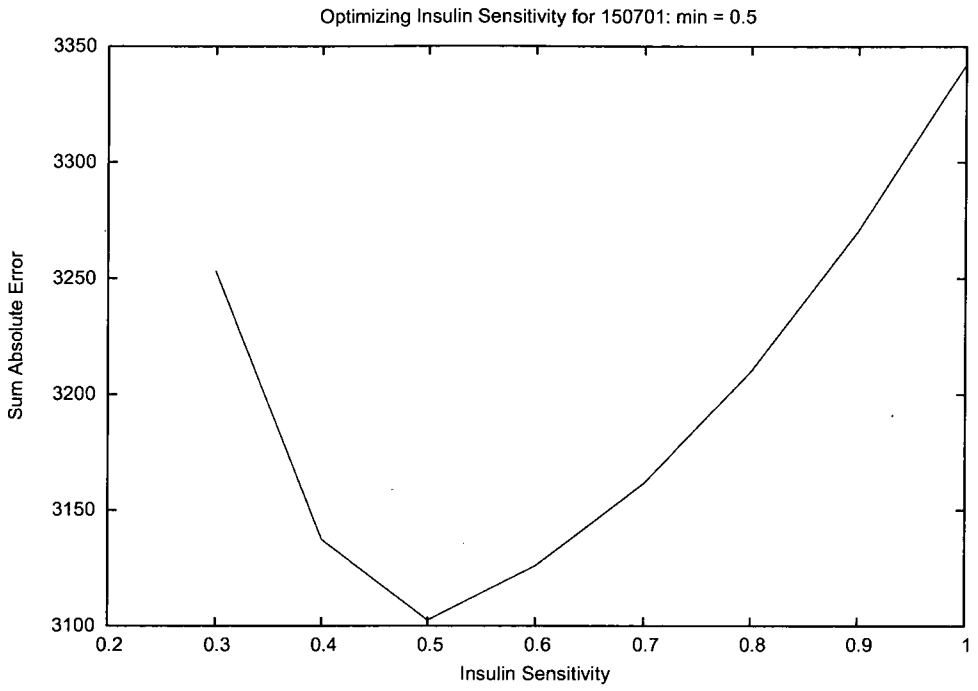


Figure 5.8: Estimating the optimal value for insulin sensitivity for a patient.

5.5 Results

The continuous models were evaluated on patients that had measured continuous glucose when collecting data. Unfortunately, this study only collected about 14 days of data that included continuous glucose measurements, thus the results presented are preliminary and will need to be further evaluated. Despite this, the initial results demonstrate the promise in the approach and the need to invest the time to collect more data for evaluation.

In all, four models were evaluated at different prediction times ranging from 15 minutes to 120 minutes at an increment of 15 minutes. The four models are listed below.

- **AR**: The autoregressive model using recent past CGM data.
- **ARX**: The autoregressive model with exogenous variables including insulin, carbohydrates, and exercise.
- **PM**: The traditional physiological model without exercise.

- **PM+Exercise**: The new physiological model that includes exercise.

The four models were evaluated using the Clarke Error grid. This set of models addressed the difference between statistical models (AR, ARX) and physiological models (PM, PM+Exercise). It also allowed comparisons between the AR and AREX models to determine whether collecting the additional variables is necessary. Finally, the two physiological models were compared to see if including exercise improves the performance.

In the evaluation, specific prediction times were be highlighted for their clinical significance. These prediction times were 15, 45, and 120 minutes. To produce these results with the EKF the model was updated using the most recent continuous glucose measurement and then allowed to make predictions without updates for the next 120 minute window. The model was allowed to use the values for future meals, insulin, and exercise, but not future glucose measurements.

5.5.1 15 Minutes

The prediction time of 15 minutes was highlighted to evaluate how each model makes predictions in the near future. This is useful for predicting hypoglycemia or detecting meals. An alarm for hypoglycemia could be given 15 minutes in advance to provide the patient with enough time to intervene and prevent low blood glucose.

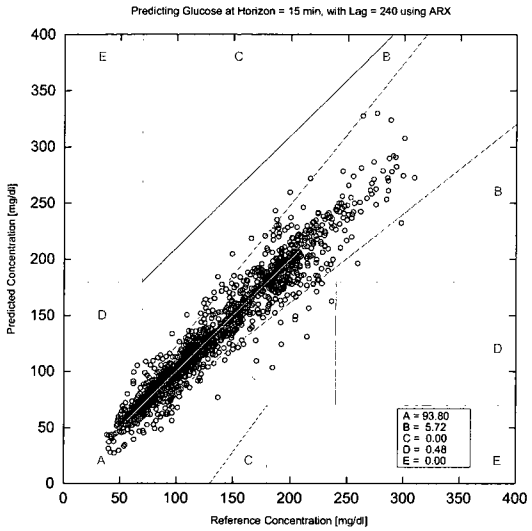
Figure 5.9 displays the Clarke error grids for the four models at a prediction time of 15 minutes. The ARX model performed the best at this time scale followed by the AR model and the two physiological models. For predictions in the near future the autoregressive models perform better because of the limited impact of the non-linearities at this time scale.

5.5.2 45 Minutes

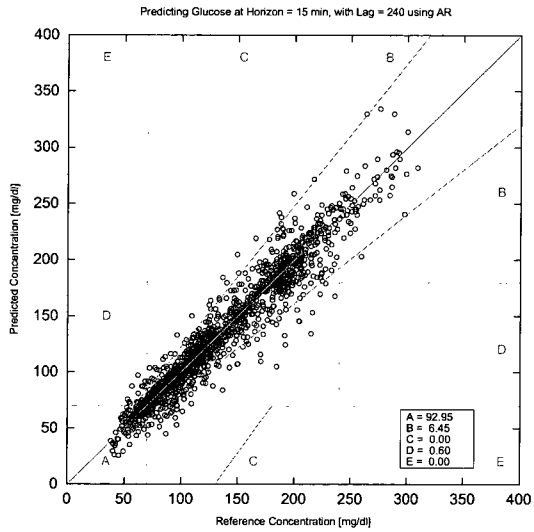
Rapid acting insulin reaches its peak action after about 45 minutes, so this prediction time was highlighted because of its potential impact on closed-loop systems. A closed-loop system would be making insulin adjustments that will impact the patient after 45 minutes.

At this prediction time the ARX model performed slightly better when using the percentage of points in region A of the Clarke error grid. Figure 5.10 displays the results for the four models

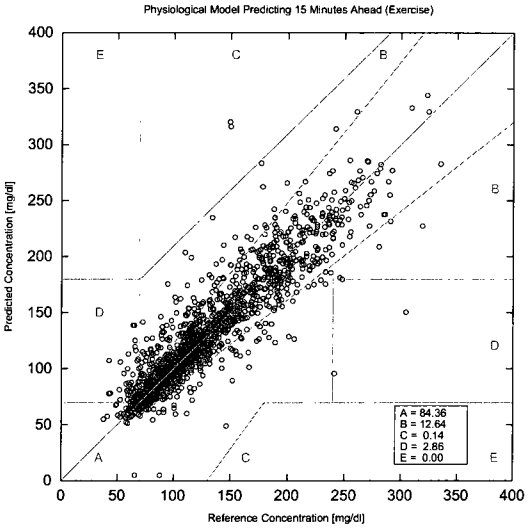
(a) ARX Model



(b) AR Model



(c) Phy. Model Exercise



(d) Phy. Model No Exercise

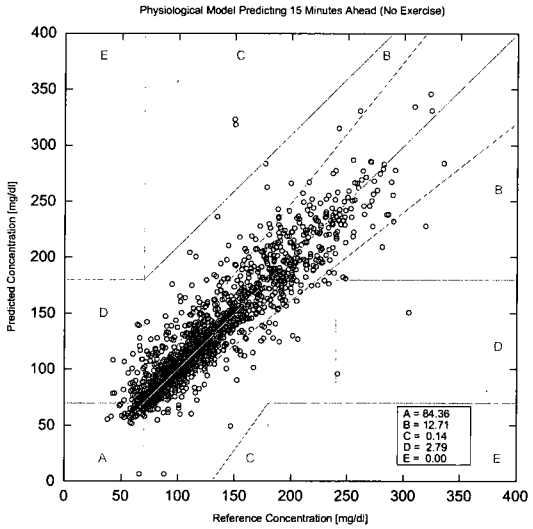
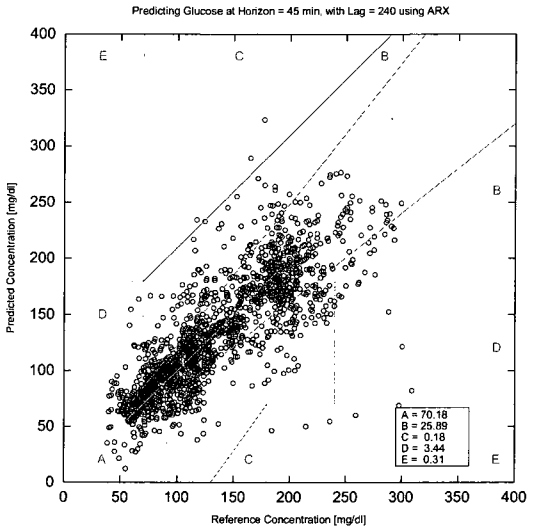


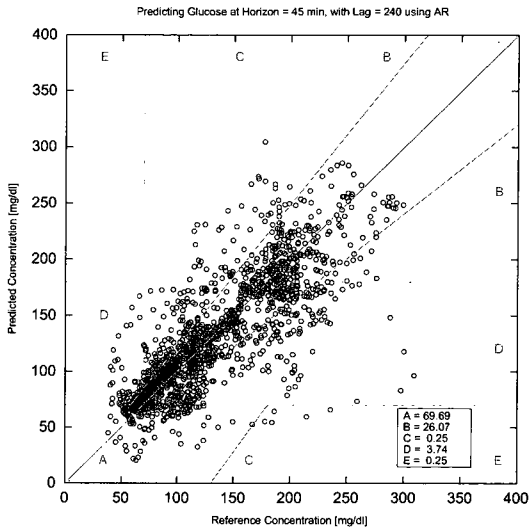
Figure 5.9: Clarke error plots for each model when predicting ahead 15 minutes.

at this prediction time. Both physiological models performed slightly better when comparing the number of points in region E. This is the region where the indicated therapy is the opposite of the optimal therapy, and it is the most dangerous region.

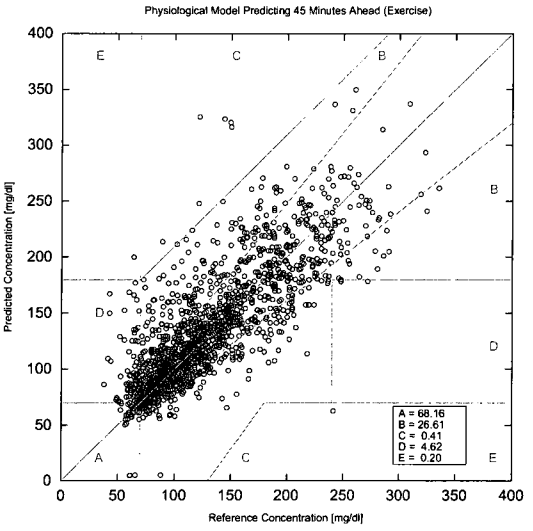
(a) ARX Model



(b) AR Model



(c) Phy. Model Exercise



(d) Phy. Model No Exercise

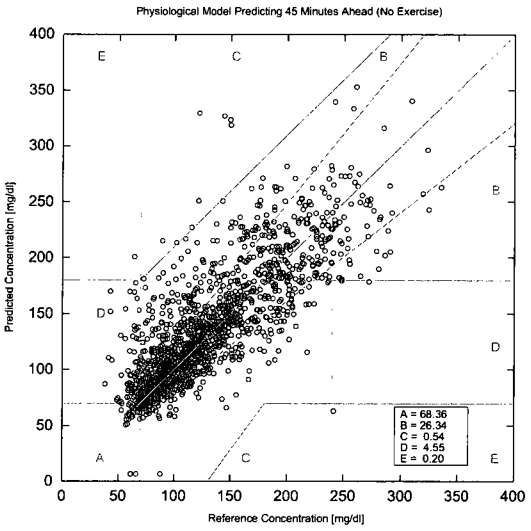
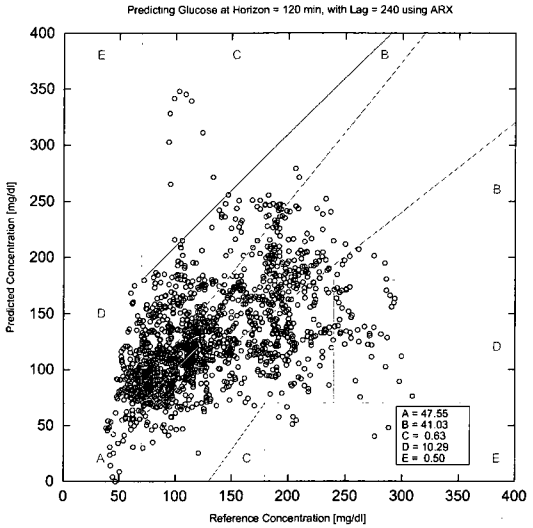


Figure 5.10: Clarke error plots for each model when predicting ahead 45 minutes.

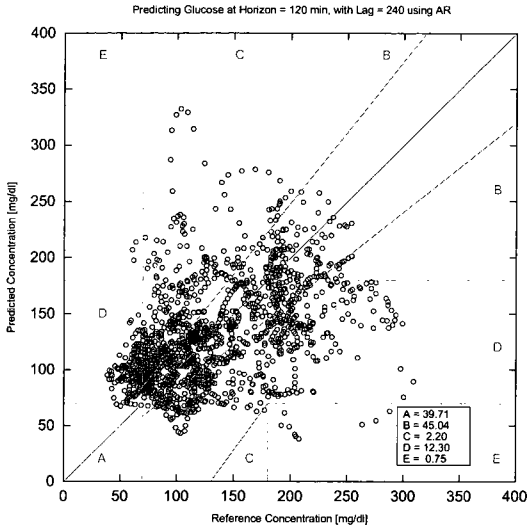
5.5.3 120 Minutes

The prediction time of 120 minutes was useful for evaluating the longer term impact of a therapy adjustment. It also provided a comparison point to the Gaussian Process regression model presented in the previous chapter. The comparison is not perfect because the continuous model must make predictions for all possible behaviors and the postprandial prediction models are specifically

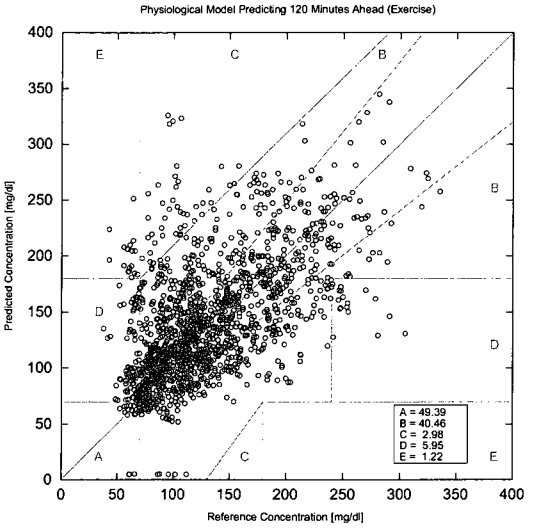
(a) ARX Model



(b) AR Model



(c) Phy. Model Exercise



(d) Phy. Model No Exercise

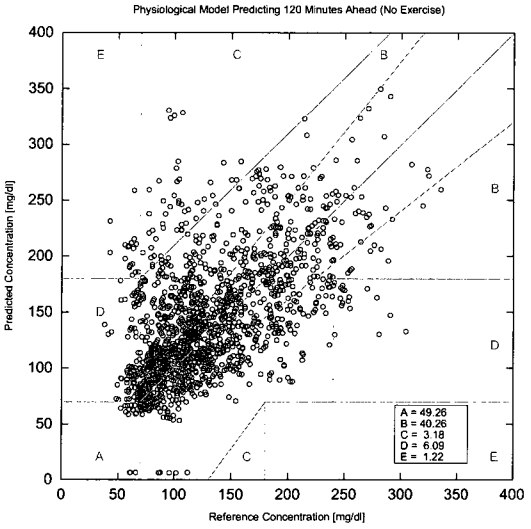


Figure 5.11: Clarke error plots for each model when predicting ahead 120 minutes.

targeted toward meals.

After two hours the physiological models performed better than both autoregressive models, and the ARX model was significantly better than the AR model. The physiological models have built in constraints that help limit them to physiologically possible predictions while the AR and ARX models do not contain these constraints. Also, the three models that include information

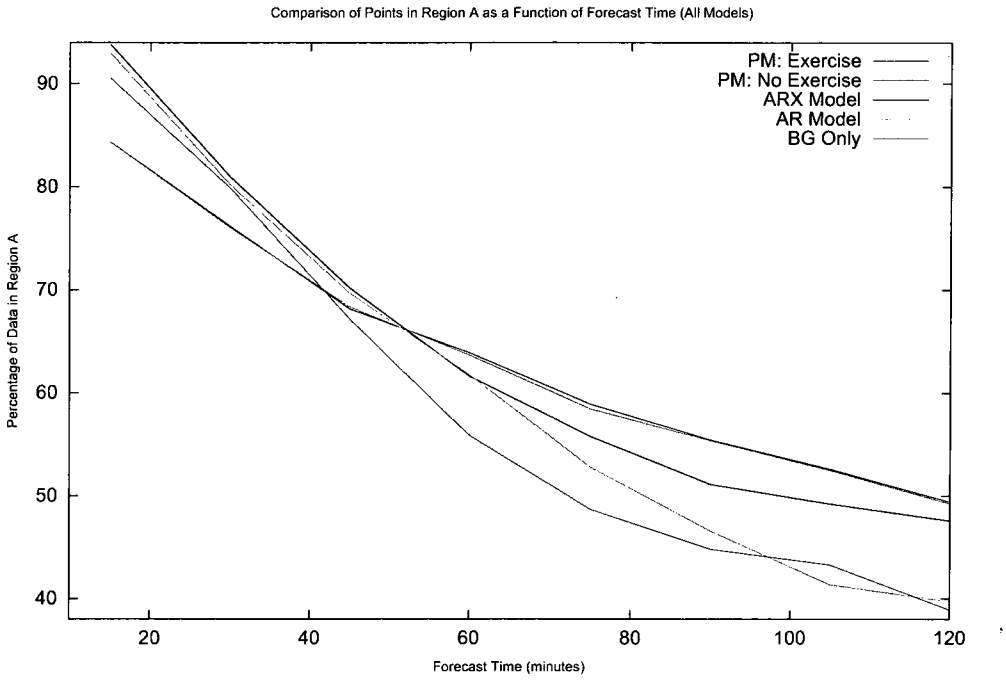


Figure 5.12: Comparison of the percentage of points in Region A for all models as a function of forecast time. The AR and ARX models perform better for near term predictions while the physiological model is better for longer forecast times.

about insulin and carbohydrates perform significantly better at longer prediction times than the simple AR model that only uses continuous glucose measurements.

5.6 Percents in Region

To compare the four models Figure 5.12 plots the percentage of points in region A as a function of the prediction time. For predictions times between 15 and 45 minutes the ARX model performs the best followed by the AR model. At these prediction times the impact of insulin and carbohydrates has not had enough time to influence the blood glucose so the ARX, and AR models that are trained on the continuous measurements perform better.

When making predictions at times further in the future from 45 to 120 minutes the physiological models perform better because they include the delayed influences of insulin and carbohydrates. For this same reason the ARX model performs better than the AR model after about 60 minutes.

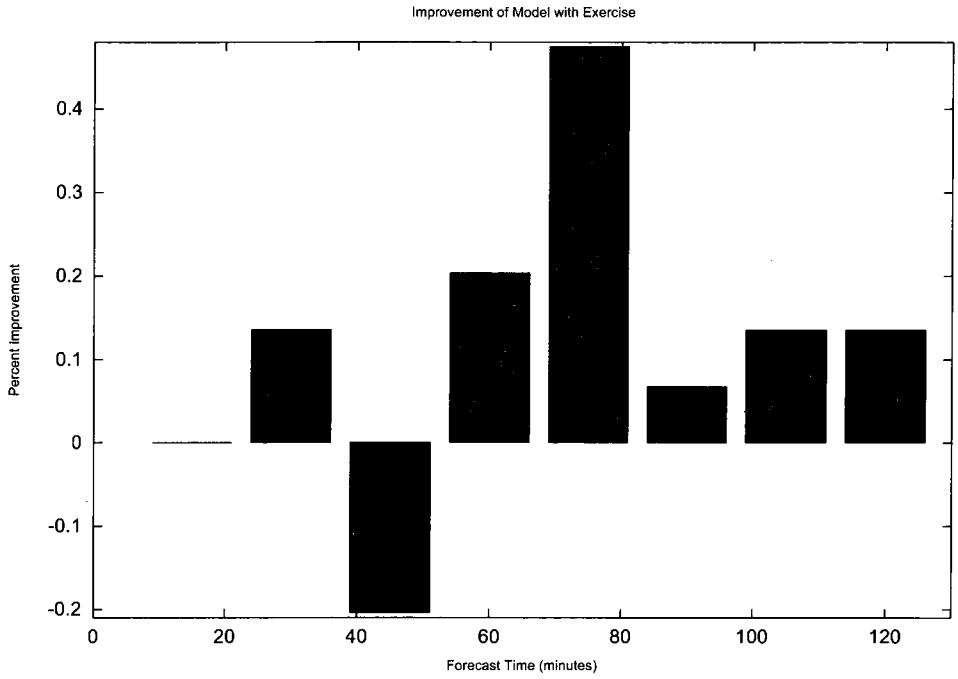


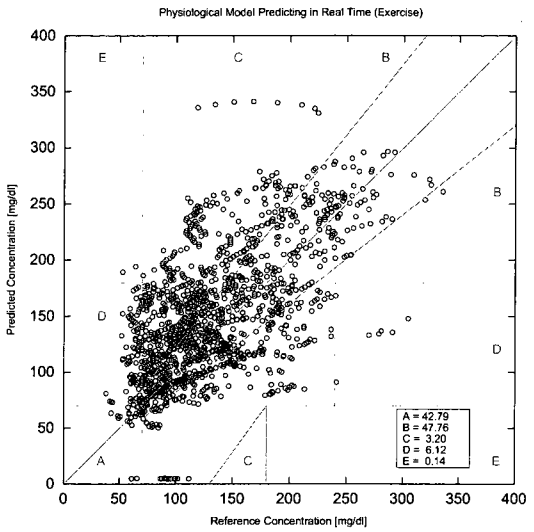
Figure 5.13: Percent change in the points in Region A when adding exercise to the physiological model as a function of forecast time.

The best model can then be selected depending on the purpose of the continuous glucose model. For predicting hypoglycemia an AR model would be sufficient, but for estimating the long-term impact of applying an insulin bolus the physiological model should be selected.

As can be seen from Figure 5.12 there is not much difference between the physiological models with and without exercise. When a patient does not exercise the physiological model that includes physical activity converges to the traditional model, so the difference between the models only occurs during exercise.

Figure 5.13 displays the percent improvement between the physiological models when exercise is added as a function of prediction time. At 15 minutes there is no improvement primarily due to the delayed impact of exercise. Beyond that the physiological model improves the percentage of points in region A by about 0.2%. This value seems insignificant, but if a person exercises three times a week for 30 minutes that equals only 0.9% of the week. Since the models only differ when the patient exercises, the small improvement is actually significant.

(a) Phy. Model Exercise



(b) Phy. Model No Exercise

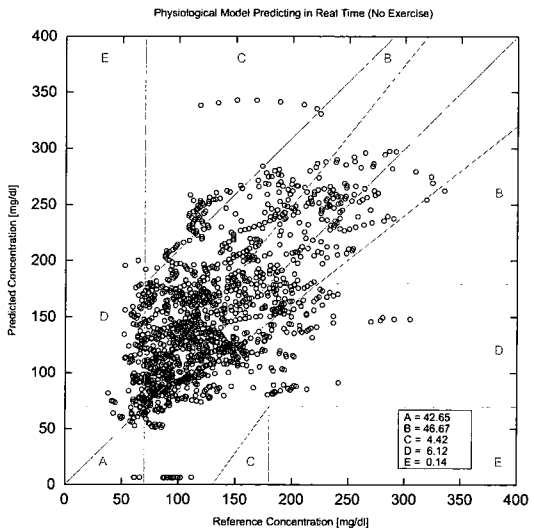


Figure 5.14: Estimating the current continuous glucose concentration using the physiological model with exercise (a) and without exercise (b).

5.7 Real Time Exercise vs No Exercise

Another potential use of the physiological model is to estimate the current blood glucose as a replacement to a continuous glucose monitor. When the EKF is used in this manner it is only updated at BG measurements and the continuous glucose measurements are only used to evaluate the models predictions. In this scenario a patient could use the physiological model to estimate blood glucose in real-time.

This differs from the previous experiment because the prediction time is not fixed. The prediction time for a point is equal to the time since the last blood glucose measurement, so these results include prediction times ranging from 5 minutes to 8 hours. The two physiological models were used for this experiment to compare evaluate if adding exercise to the model improves its capability to estimate blood glucose in real-time.

Figure 5.14 displays the Clarke Error grids for this experiment. The results from the two models are visually very similar with the model with exercise performing slightly better.

The difference between the percentages of points in each Clarke region are displayed as a histogram in Figure 5.15. As can be seen from this figure there is a shift in points from region C

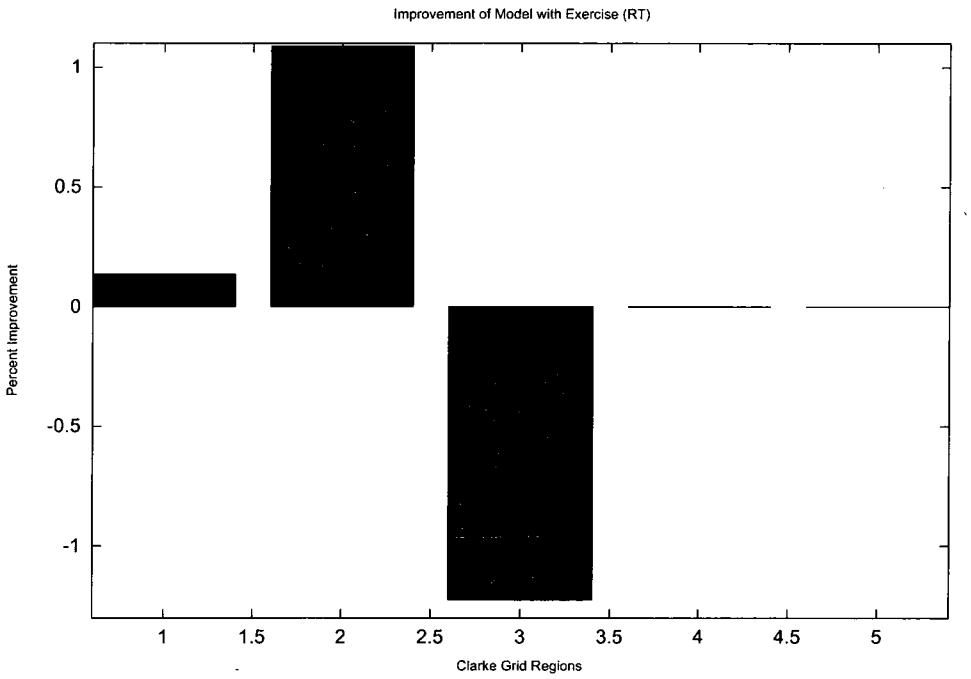


Figure 5.15: Percent change in each region of the Clarke error grid with the addition of exercise. There is a shift of points from region C to regions A and B showing an improvement with the inclusion of exercise.

to regions A and B when exercise is included. As in the previous experiment, the percent change in region A is small, but the shift from regions C to B is significant. For points in region B, the therapy selected would be in the correct general category.

5.8 Conclusions

In this chapter a new physiological model was presented that includes exercise in the insulin dependent glucose utilization compartment. This model was compared to AR and ARX models to evaluate the best method for predicting continuous glucose values. The methods could be evaluated using more data to conclusively prove their value, but even with limited data the physiological model showed promise as a method of improving the performance of modeling for patients that exercise.

For predictions in the near-future up to 45 minutes, the AR and ARX models could be used. They avoided the complexity of the physiological model and performed well at this time scale. For prediction times beyond 45 minutes, the physiological model with exercise was the best way to estimate the influence that insulin, meals, and exercise have on a patient's blood glucose.

The physiological model with exercise was also the best method for estimating a patient's blood glucose in real-time without the aid of a continuous monitor. However, this type of real-time modeling was not accurate enough to make therapy decisions without the aid of supporting blood glucose measurements. There was too much variation in the system to trust any model's accuracy over long periods of time.

An ounce of prevention is worth a pound of cure.[Ancient proverb]

Henry de Bracton, De Legibus, 1240

Chapter 6

Generating Therapy Advice

Modeling postprandial blood glucose or continuous glucose dynamics provides no practical value unless it can be used to provide therapy advice for a patient. The data and models in IDA can be used to generate real-time therapy advice and retrospective advice. It can help adjust insulin doses, provide alerts, and help give individualized education for patients.

6.1 Introduction

Modeling glucose dynamics is useful if it can be used to improve a patient's health. The two categories of modeling addressed in this research, postprandial and continuous, were specifically chosen for their ability to produce practical therapy advice. There are two categories of advice that can be generated using these models: real-time and retrospective. Real-time advice is advice that the patient will use now, and retrospective advice refers to the analysis of a previous dataset to generate useful information. This chapter will demonstrate the practical application of this research toward improving health outcomes. Measuring the actual impact on the health of patients is beyond the scope of this thesis.

There are many possible types of advice that could be given to a patient, including warnings of hypoglycemia, suggesting insulin injection doses, and generating educational advice. The key to automatically generating advice is having quality data representing the patient's normal behaviors

along with blood glucose measurements. A list of glucose measurements without the context of behaviors only provides generic information about the patient's health, so a health care provider or automated system can only provide generic advice.

IDA has the potential to improve the quality of advice from human and automated sources because of its emphasis on capturing lifestyle data. Though not quantitatively measured, the dietitians on the research team found the information available in IDA very helpful for providing patient targeted nutrition education. Automated advice algorithms can also use the detailed lifestyle data to provide more specific advice along with justification for the suggestions.

The advice generated by IDA can also be used to help patients with both type 1 and type 2 diabetes. The lifestyle data collected can be used to give behavior related advice to patients. Many diabetes management systems only focus on insulin dosing so they are not useful for patients whose primary therapy is lifestyle.

One challenge facing all decision support software is that physicians and patients are hesitant to believe a black box, so providing justification for the suggestions is an important part of advice. Both the Gaussian Process Regression method and Physiological model can provide the reasoning behind a decision.

6.2 Real Time Advice

The most helpful real time advice for a diabetic would be suggesting an insulin dose or in the case of an artificial pancreas, selecting an optimal dose. Another type of useful real-time advice is warnings of possible hypoglycemia.

6.2.1 Insulin Injection Dosing

Insulin doses for a meal are usually calculated as a function of the current blood glucose and the quantity of carbohydrates in the meal. The two parameters that are used to calculate the dose are the insulin-to-carb ratio, α_c, and the insulin sensitivity, α_g. The insulin-to-carb ratio adjusts the insulin dose to account for the amount of carbohydrates in the meal, and the insulin sensitivity

adjusts the dose to correct for elevated blood glucose. They are used in the following equation to calculate the dose.

$$I_t = \alpha_g(g_t - g_0) + \alpha_c c_t \tag{6.1}$$

This equation is designed to maximize the probability of glucose reaching normal glucose after a meal. In general this equation works well but may need to be adjusted for specific meals. The data collected by IDA can be used to calculate an insulin dose for a meal by finding the dose that maximizes the probability of leading to normal glycemia. The learned model can be used to find the ideal dose. This can easily be done by an exhaustive search because of the limited range of possible insulin doses.

$$\max_i p(g_{t+2} = \text{good} | I_t = i) \tag{6.2}$$

Where the probability is calculated using the Gaussian Process model with a Gaussian kernel using equation 4.8.

$$p(g_{t+2} = \text{good} | I_t = i)_{ida} = k(x^*, x^*) - k(x^*, X)(K(X, X) + \mu I)^{-1} k(X, x^*) \tag{6.3}$$

This result can be combined with the traditionally calculated insulin as a way to shift insulin doses.

$$p(g_{t+2} = \text{good} | I_t = i) = p(g_{t+2} = \text{good} | I_t = i)_{trad} p(g_{t+2} = \text{good} | I_t = i)_{ida} \tag{6.4}$$

6.2.2 Example

To demonstrate this process an individual Gaussian Process regression model was created for one of the patients with type 1 diabetes. The insulin dose calculation parameters for this patient were known prior to the start of the study. For each meal the equation 6.1 was used to calculate the dose of insulin that would most likely result in normal postprandial blood glucose. A normal probability

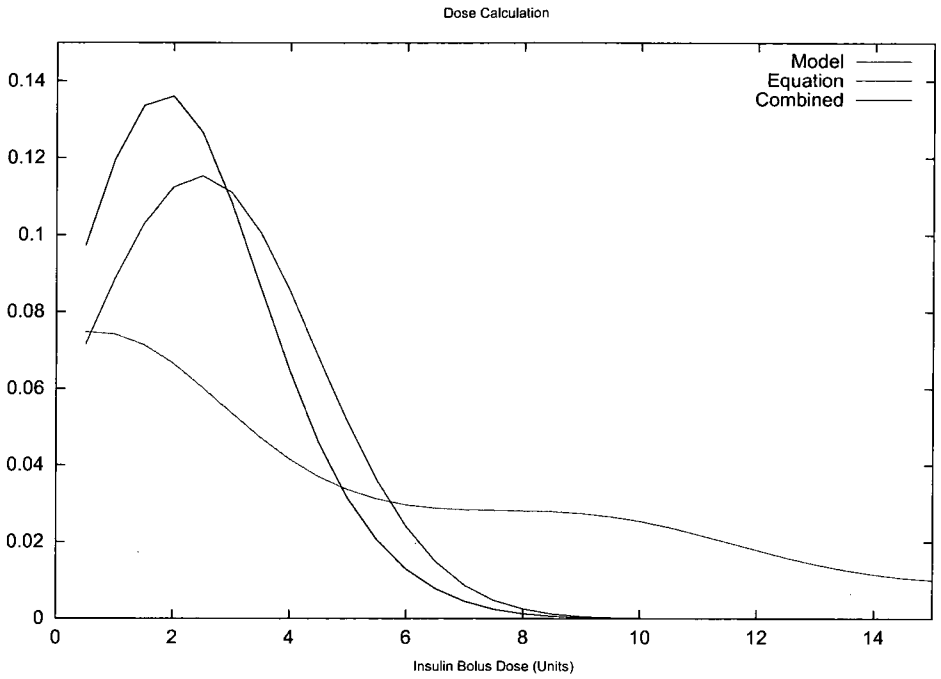


Figure 6.1: Determining the optimal insulin dose based on a combination of the model-based suggestion with traditionally calculated dose. In this specific case the calculated dose resulted in hypoglycemia so a reduced dose would have been better.

distribution was placed around the calculated dose to represent the prior probability of being the correct dose for the meal. Then the model was used to determine the dose of insulin most likely to achieve normal postprandial glucose levels. The two probability distributions for a meal are plotted in Figure 6.1 along with the combined probability distribution.

For this meal the recommended insulin dose is lower than the dose calculated using only the equation. In this case the meal resulted in hypoglycemia, so the recommendation would have improved the outcome.

6.2.3 Providing Justification

The suggestions generated by an automated system should be accompanied by the reasoning for the decisions. Physicians and patients can be hesitant to trust the mysterious suggestions from a black box, so some form of justification can help them accept the system. IDA can provide such

	BG	Carbs	Ins.	Prediction
Query	115	56	5	113
Similar past meals and their outcomes				
meal1	124	47	5	128
meal2	97	47	5	79
meal3	118	76	6	123

Table 6.1: Similar meals from the training set can provide justification for therapy advice.

justification because the data it collects is strongly linked to the patient's lifestyle.

To justify a suggested insulin dose IDA can identify situations in the past where the patient encountered a similar choice. The outcomes of those situations can function as justification for the current advice.

Identifying similar past scenarios is simple when using Gaussian process regression with a Gaussian kernel. The kernel matrix functions as a similarity measure between data. The similarity can be calculated using all available measurements or specific variables. For example, to provide justification for the previous example the system can present the closest three past examples. Figure presents the three most similar past examples for the patient.

The system could also provide examples using specific variables. Table 6.1 presents the patients three most similar behaviors using specific variables. The ability to display meal images makes the justification more understandable to the patient. The patient probably remembers the meals and can clearly see the impact of the choices made then and how the current suggestion compares.

6.2.4 Predicting Hypoglycemia

Another important form of real-time advice is warning of possible hypoglycemia when using a continuous glucose monitor. The continuous glucose model is ideal for this problem, and the ARX model works well because prediction times for hypoglycemia are typically less than an hour. Figure 6.2 contains the ROC curves for hypoglycemia prediction times of 15, 30, 45, and 60 minutes. A true positive occurs when hypoglycemia is correctly predicted for the given prediction time. For this example a hypoglycemic event was defined as occurring when the CGM data was less than 70 mg/dl.

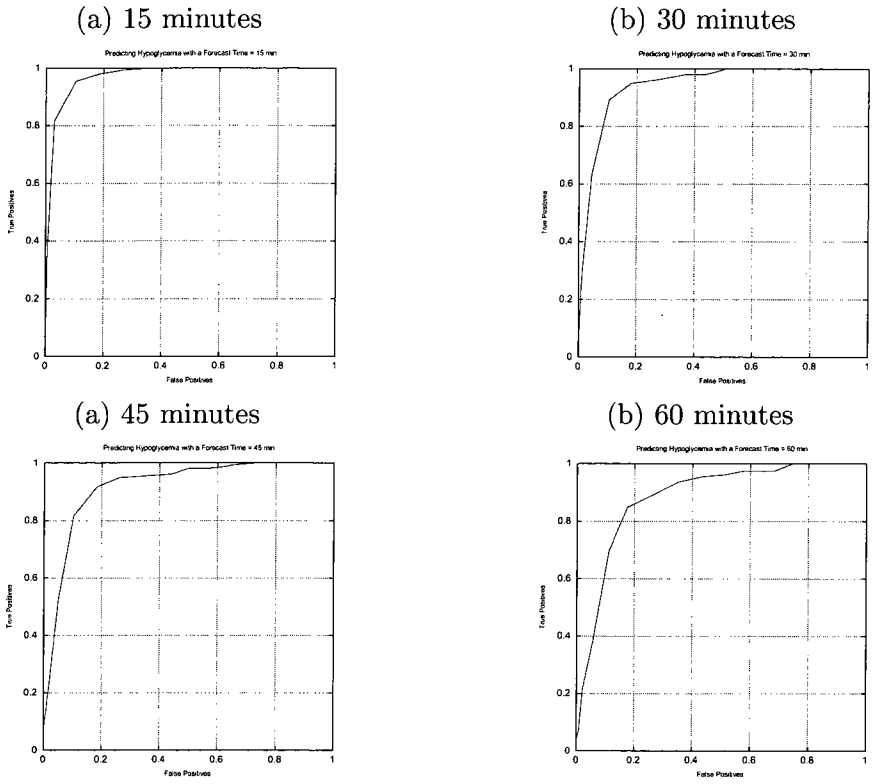


Figure 6.2: ROC Curves for hypoglycemia prediction at four different prediction times.

The ROC curve is generated by varying the threshold at which the model prediction is considered an alert. The value for an alarm threshold can be personalized depending on the level of control a patient is trying to achieve and how aware the patient is of hypoglycemia. If hypoglycemia is likely then the system could send a warning to the patient.

These results are promising, and the ARX model allows better long-term predictions of hypoglycemia than an AR model. The hypoglycemia alarms systems on current CGM systems suffer from false positives because they do not include exogenous input variables.

6.2.5 Artificial Pancreas

The future of diabetes management for people with type 1 diabetes is in closed-loop control systems that mimic the normal glucose regulatory system. The artificial pancreas is an ideal goal, but there are many challenges facing its development. The measurement noise of current CGM systems, delay

in insulin absorption, and physiological variability make closing the loop very difficult.

The most common method being explored for implementing an artificial pancreas is model-predictive control (MPC). In MPC the controller selects the insulin dose that, according to the model, will optimize future blood glucose values. The key to this control strategy is having a model that can predict the outcome for a set of behaviors. The physiological and ARX models that include exercise, presented in Chapter 5, could be used in such a system.

In a recent meeting of leading glucose modeling diabetes researchers from around the world, the key challenge identified that limits the implementation of an artificial pancreas is the variability in the system [99]. The EKF implementation of the physiological model addresses this problem by incorporation exercise, which is one of the sources of variability frequently overlooked, and estimating the uncertainty of the system state. As in may areas of robotics, systems that must operate within an uncertain environment can perform significantly better if they know their uncertainty. This implementation can lead to a system that better understands its uncertainty, and therefore can make better decisions.

Another key topic discussed in this meeting was the need to have systems that can remotely monitor the patient and closed-loop controller. Currently, clinical tests of artificial pancreas systems have occurred in a hospital or controlled laboratory environment, but eventually these systems need to be tested in real-life. IDA's unique combination of telemedicine and modeling can help address this problem.

6.3 Retrospective Advice

In addition to real-time advice the system can be used to retrospectively generate advice. Such advice can be provided when a patient visits their care provider. It can also help the care provider give more specific advice efficiently. Doctors have limited time to interact with patients, so a system that can make that time more efficient can be very useful.

In this chapter IDA is used retrospectively to estimate the blood glucose value between sparse measurements, create behavior advice, and perform parameter estimation for an insulin dose cal-

culation algorithm.

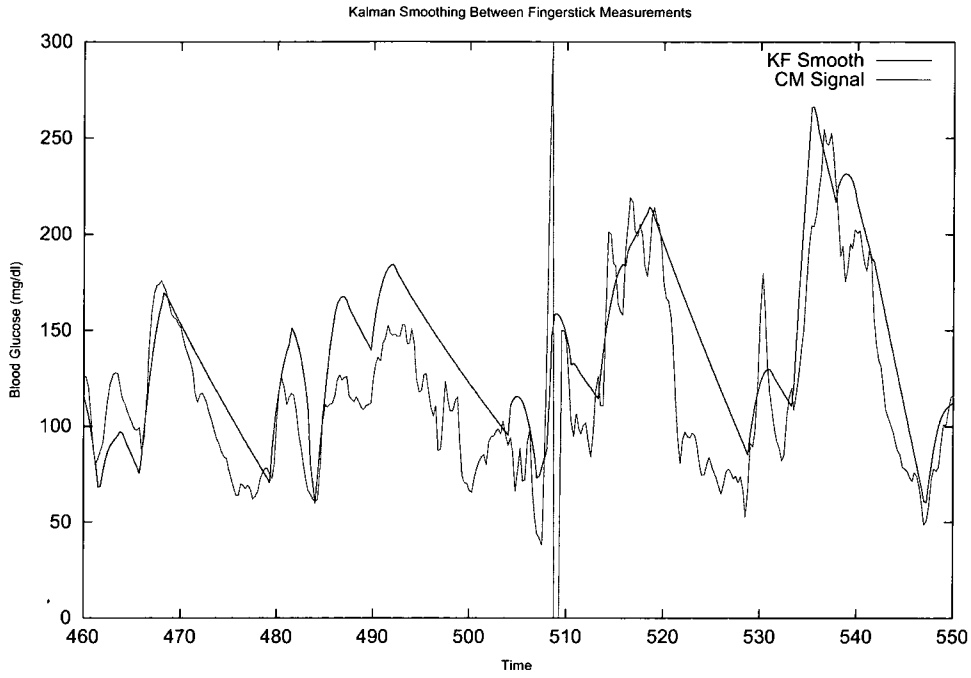


Figure 6.3: Kalman Smoother estimating the most likely value of blood glucose between sparse measurements.

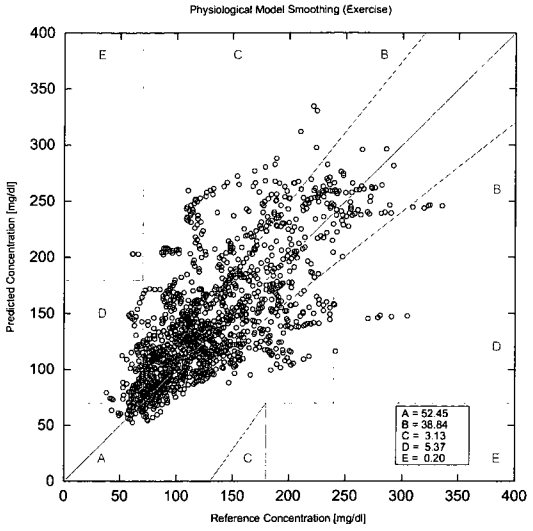
6.3.1 Estimating CGM Between Sparse Measurements

Devices are available to continuously measure glucose but they are infrequently used; so patients typically provide the doctor with sparse blood glucose measurements. The physiological model can be used to determine the most likely blood glucose value between these sparse measurements.

In chapter 5 the extended Kalman filter was used to estimate the system state in real-time, but it can also be used retrospectively to calculate the most probable glucose value between measurements. This is done using forward-backward smoothing.

The forward-backward smoothing equations are from equation 6.5 to equation 6.9. After performing the normal forward Kalman Filter algorithm these equations are applied backward, from $k = T \ldots 0$.

(a) Phy. Model Exercise



(b) Phy. Model No Exercise

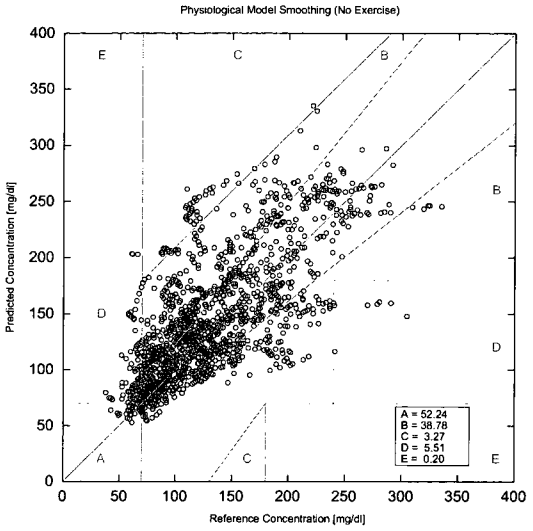


Figure 6.4: A comparison between the physiological model without exercise and with exercise when the EKF is used as a smoother.

$$P_{k+1}^{-} = A_k P_k A_k^T + Q_k \tag{6.5}$$

$$C_k = P_k A_k^T [P_{k+1}^{-}]^{-1} \tag{6.6}$$

$$x_k^s = x_k + C_k[x_{k+1}^s - A_k x_k] \tag{6.7}$$

$$x_k^s = x_k + C_k[x_{k+1}^s - x_{k+1}^{-}] \tag{6.8}$$

$$P_k^s = P_k + C_k[P_{k+1}^s - P_{k+1}^{-}]C_k^T \tag{6.9}$$

An example of data produced by the Kalman smoother is in Figure 6.3. The smoothed estimate is plotted over the CGM data for comparison.

Figure 6.4 displays the clarke error grid comparing the results generated by the traditional physiological model to the estimates generated by the model with exercise.

When compared to the real-time estimates for blood glucose, the estimates from the EKF smoother are much better. Table 6.2 compares the estimates from the smoother with the real-time estimates.

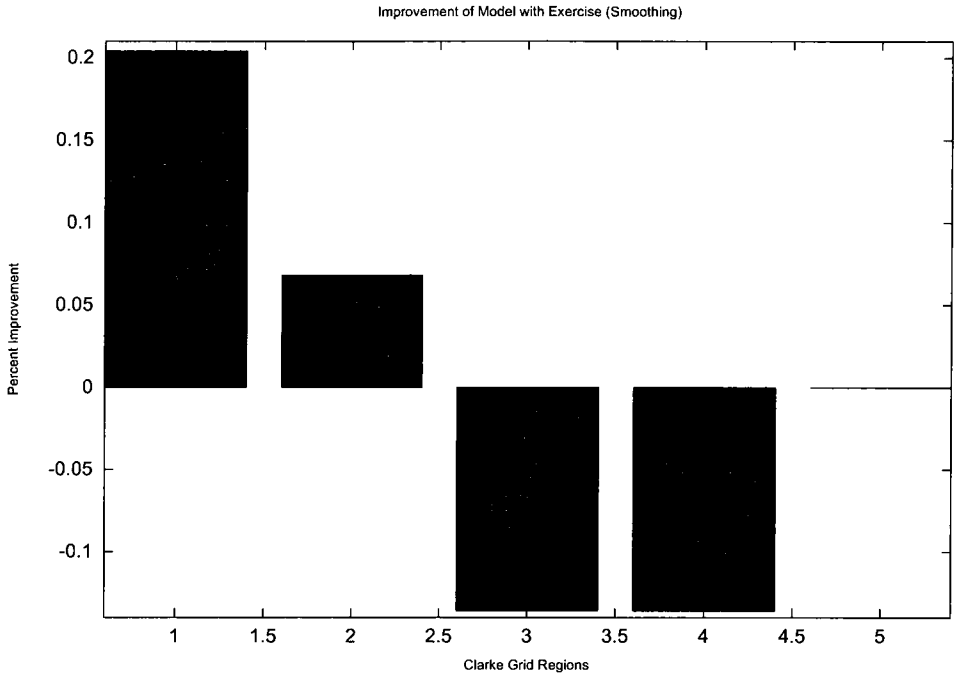


Figure 6.5: The change in the percentage of points in each region of the Clarke Error Grid between the physiological model with exercise and without exercise when used retrospectively to estimate the blood glucose value between sparse measurements.

Region	Smoother	Real-time
A	52.45	42.29
B	38.84	47.76
C	3.13	3.20
D	5.37	6.12
E	0.20	0.14

Table 6.2: Retrospective blood glucose estimation using the EKF smoother is significantly better at estimating the value of blood glucose between finger-stick measurements when compared using the Clarke error grid.

6.3.2 Behaviors Analysis for Education

The data could also be used to give behavior advice for a patient. As an example a patient was selected and a linear Gaussian Process model was trained on the first week and a half of patient data. For the last 9 meals every input was held constant except for the quantity of carbohydrates and pre-meal exercise. Then the model was used to determine the space along these two dimensions that would result in a postprandial blood glucose greater than 160 mg/dl. Figure 6.6 displays four of the test meals and their results. The blue side of the plot is the area that should result in blood glucose less than 160 mg/dl and the red should result in values greater than 160 mg/dl. The circle color indicates the location of the actual action chosen by the patient and is color-coded based on the actual outcome (Red circle = bg $>$ 160, Blue circle = bg $<$ 160). The separation line varies based on the value of the other inputs such as pre-meal blood glucose. The shape of the separating surface confirms that higher carbohydrate intake and less exercise can both lead to high blood glucose.

Out of the nine test meals, the model predicts the actual outcome correctly eight times. Figure 6.6 contains three of the correct classifications and the incorrect classification as well. This suggests that even a simple model can be used to generate useful suggestions to the patient. One direction to which this could lead is training a binary classifier to predict hyperglycemia instead of trying to predict the actual value of postprandial blood glucose.

6.3.3 Parameter Estimation

The data from IDA can be used to give real time suggestions for insulin doses and it can also be used to calculate optimal values for the insulin-to-carb ratio and insulin sensitivity retrospectively to update the traditional method of calculating insulin doses given in equation 6.1.

$$I_t = \alpha_g(g_t - g_0) + \alpha_c c_t \tag{6.10}$$

Using the patient data that resulted in good postprandial blood glucose results, linear regression can be used to find the optimal values for the parameters. Table 6.3 contains the result after

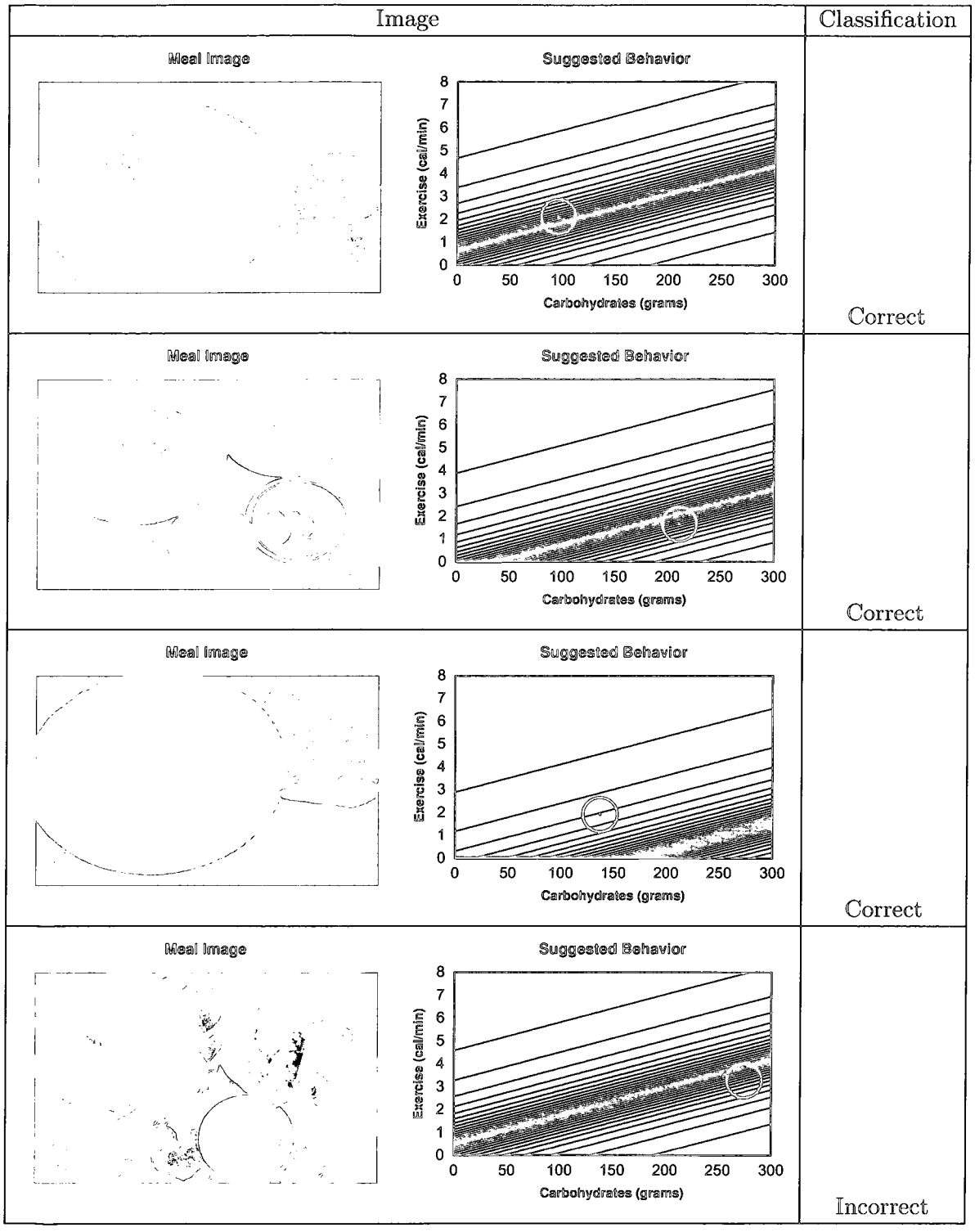


Figure 6.6: A simple linear model was used to identify the boundary in carbohydrate intake and pre-meal exercise space between behaviors that result in postprandial glucose being greater than or less than 160 mg/dl. The red shaded side is for BG > 160 mg/dl.

applying this process to one of the patients with type 1 diabetes. The patient started with an initial insulin-to-carb ratio of 10 carbs/unit, but after the study, it was determined that an insulin-to-carb ratio of 11.2 carbs/unit would result in better postprandial results.

Parameter Estimation	Sensitivity	Insulin-to-Carb
Initial Prescribed Parameters	50	10
Parameter Adjustment	68	11.2

Table 6.3: Insulin dose calculation parameter estimation

6.4 Conclusions

IDA is a very versatile system because of the quality of the data it collects and the models that can be created. It can be used to implement real-time therapy advice such as meal specific insulin dose adjustments, hypoglycemia alerts, and has many potential uses in a closed-loop system. The suggestions can be supported by referencing the past events used to make the suggestion.

The system can also be used retrospectively to provide therapy adjustment advice and educational support. The data collected by IDA uniquely captures the behaviors of patients, so it can be used to generate advice target toward patients that manage their diabetes using only lifestyle and diet. Finally the system can retrospectively calculated parameter adjustments used for insulin dose calculation.

There are many other potential ways for generating therapy advice with IDA. The selection of methods highlighted in this chapter were chosen for the way they highlighted the previous models discussed in Chapters 4 and 5, and they were also chosen because they demonstrated methods for utilizing the unique data collected with IDA. The meal images and exercise allow IDA to be used to explore therapy monitoring and optimizing solutions that previous systems cannot address.

It's a dangerous business, Frodo, going out your door. You step onto the road, and if you don't keep your feet, there's no knowing where you might be swept off to.

J. R. R. Tolkien

Chapter 7

Other Interesting Results

In the course of this project other areas were briefly investigated. Findings from these areas are preliminary, but merit consideration. For example, more could be done with the meal images to automatically process the images to recognize food and estimate the nutritional content of a meal.

7.1 Introduction

This research project generated other ancillary findings. Diabetes is a complex disease with many challenges to address. The results presented in this chapter are preliminary and are not directly related to the focus of the project; however, they may lead to further research projects. The three results presented in this chapter are a method for estimating food portions from meal images, recognizing similar meal images, and remotely monitoring a patient during the Muslim fasting month of Ramadan.

7.2 Automatic Meal Image Processing

One of the unique aspects of IDA is the use of meal images. These provide more detailed information about the nutritional content of a meal than a single estimate of carbohydrates. The food in the images were hand labeled by a dietitian. One reason for collecting meal images was to investigate automated meal recognition. This research was outside of the scope of this project, but initial

results were generated regarding meal portion estimation and meal recognition.

7.2.1 Portion Estimation

A small project was done to determine the feasibility of estimating the portion of a food based on the area of the food in an image. The method assumed there is a way to estimate the conversion from area of pixels to area of food. In this project patients placed a credit card sized color reference card beside their food to calculate this conversion, but many modern mobile phone cameras now contain auto focus lenses that can provide the focal length. The project was designed to compare the food portion estimates by two dietitians and the portion estimates based on the image area to the actual measured portion of the meal.

For the project, twenty images of measured portions of rice were taken using a mobile phone. Rice was chosen because of its high carbohydrate content and common consumption. Two different plates were used. One large plate that allowed the rice to spread out and another smaller plate that limited the spread of the rice. Two dietitians trained in carbohydrate counting were shown the images and asked to estimate the portion size of the rice. Their estimates were compared to estimates generated based on the pixel area of the food.

The portion size was calculated based on the following equation.

$$S = \beta A_{pixels} \tag{7.1}$$

The first 10 images were used to learn the coefficients for the large and small plates. Similarly the first 10 images were used to learn a correction factor for the dietitians' estimates. A representative example of one of the meal images is in Figure 7.1 along with plots comparing the estimates of portion size.

Table 7.1 contains the results comparing the carbohydrate estimates from the dietitians and image pixel area to the actual amount for the meals. These results are plotted in Figure 7.2. There is significantly less noise in the portion estimates calculated from the image pixel area.

The image analysis method for calculating portion size works better on the larger plate that

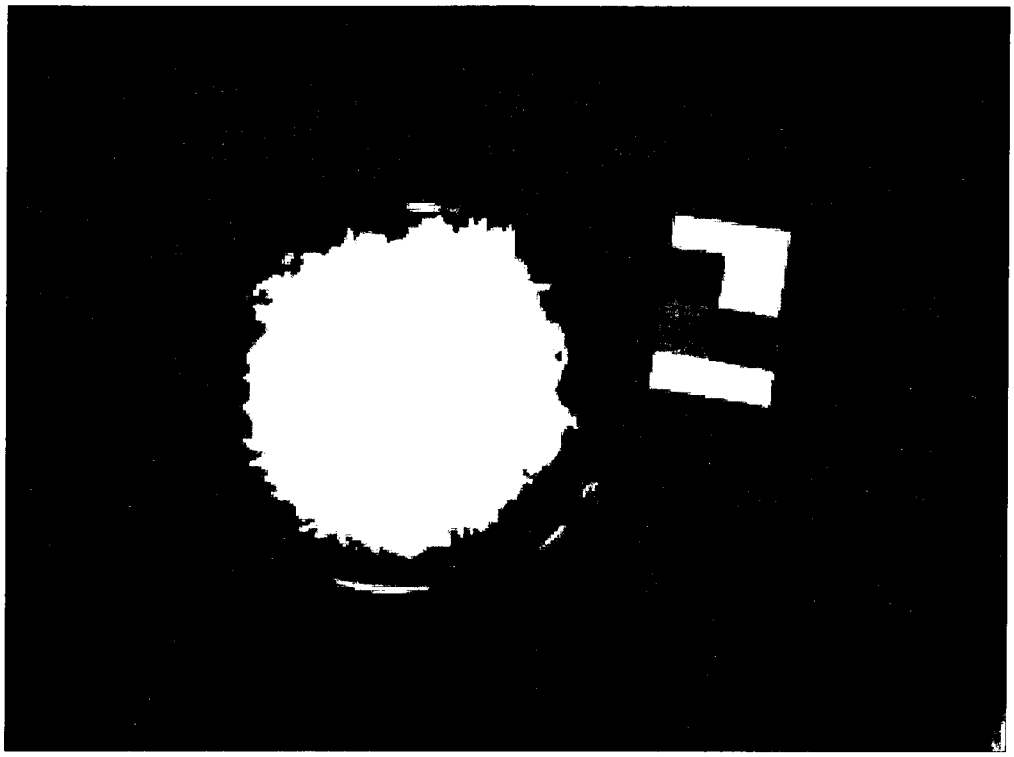


Figure 7.1: Sample meal image for portion estimation experiment.

Carb Estimation Method	MAD
Dietitian 1	8.0441
Dietitian 2	12.980
Image Analysis	5.2274

Table 7.1: Comparison of estimation methods using the mean absolute difference.

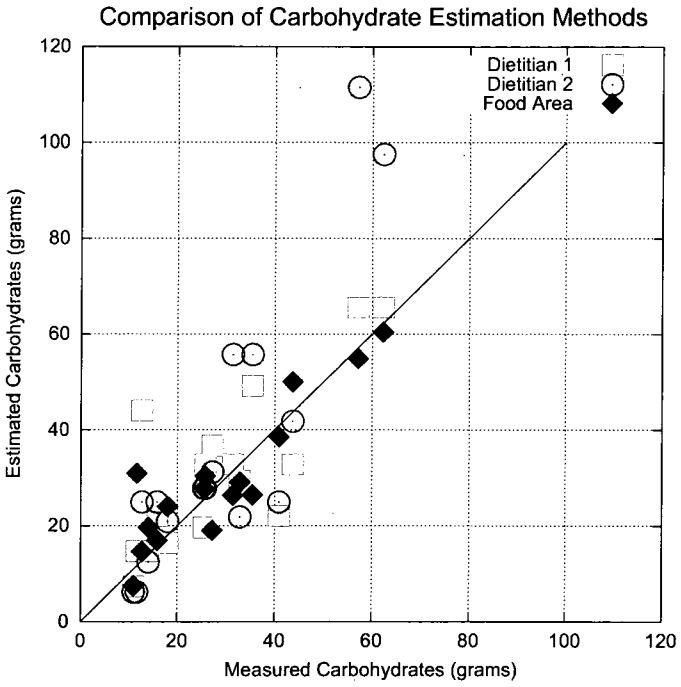


Figure 7.2: Regression plot for portion estimation for dietitian 1, dietitian 2, and the image pixel area.

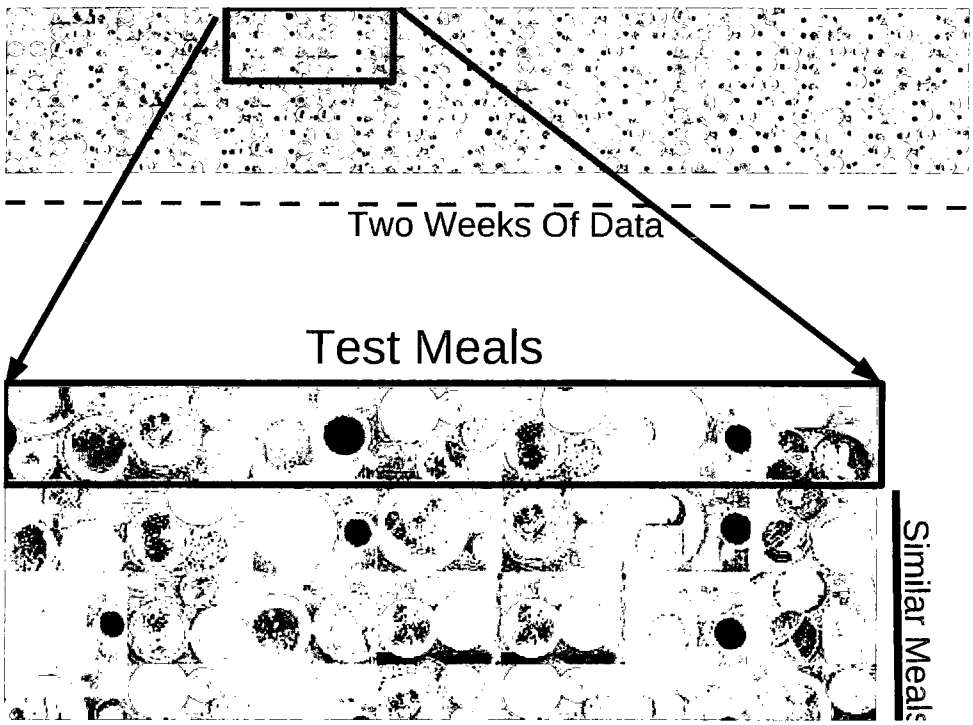


Figure 7.3: Meal image comparison. The top row is the actual meal and the next 10 rows are the images with the closest color histogram.

did not constrain the size of the food, but in both cases it performed better than the dietitians. These results, while preliminary, demonstrate the feasibility of using meal images to estimate the portion size of food.

7.2.2 Meal Image Matching

In addition to estimating meal portion size the meal images could also be used to automatically recognize food. The food recognition problem sounds very difficult, but in reality it is made simpler by the repetition of patient behaviors. People like to eat certain foods, so the problem is not one of recognizing a specific food out of all the possible meals available in the world. The task is to identify similar meals in the patients past because the therapy advice would also be similar.

As an initial project along these lines, a patients meals were analyzed to find the most similar images based on the KL divergence between the color histograms of the images. This is a very

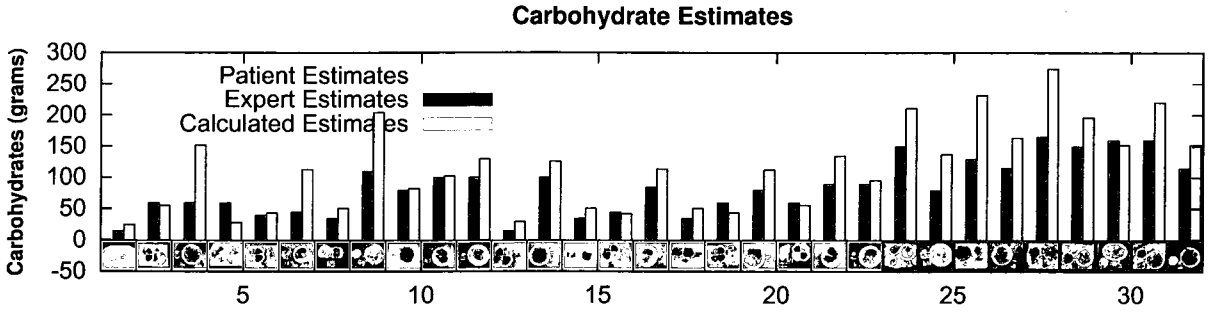


Figure 7.4: Monitoring a patient with type 2 diabetes during Ramadan

basic method, but its results are promising. More advanced image matching algorithms could be investigated.

Touch screens would also allow for a simple and efficient method of seeding a segmentation algorithm to locate areas of food. In this example the matching used every pixel in the image. The results should improve if only pixels representing food are used.

7.3 Monitoring a Patient During Ramadan

As a final diversion from the main focus of this thesis, IDA was used to monitor a patient as he began the fasting during the Islamic month of Ramadan. Many diabetics participate in Ramadan, and the changes in lifestyle pattern cause many to experience increased numbers of hyper and hypoglycemic events. After fasting during the day, diabetics often experience hypoglycemia, and following the large meal after sunset they often have extreme hyperglycemia due to the carbohydrate rich traditional foods consumed. IDA was used to help the patient monitor his transition from normal to fasting behavior.

Figure 7.4 displays the meals consumed one week prior to Ramadan and the first week during Ramadan (starting at meal number 23) and the estimated carbohydrates for each meal. The chart shows how the quantity of carbohydrates increases for this patient after Ramadan begins. At this point, the telemedicine features of IDA could be used to help the patient with meal choices so that he could continue participating without experiencing additional health risks. The increased communication capabilities could allow the patient to make adjustments more quickly.

7.4 Conclusions

The clinical study conducted for this project was focused on predicting glucose, but IDA as a system can be used to explore other research areas. In particular, the meal image capabilities open opportunities to apply computer vision technologies toward meal image segmentation, food recognition, and portion calculation. These applications would not only benefit diabetics, but any person interested in tracking nutrition.

The telemedicine capabilities of IDA can also be explored. During this research project the patients and physicians did not interact with IDA unless absolutely necessary, but the combination of automated analysis and telemedicine can facilitate efficient beneficial communication.

I may not have gone where I intended to go, but
I think I have ended up where I intended to be.

Douglas Adams

Chapter 8

Conclusions and Future

8.1 Key Results

The challenges caused by diabetes range from the global level down to the molecular level. There are enough unanswered diabetes research questions to fill a lifetime. When IDA was initiated the following goals were proposed.

- Demonstrated a functioning system that can

  Collect data.

  Share data.

  Analyze data.

- Demonstrate an improvement over previous methods of prediction.
- Demonstrated policy search to suggest behavior modifications.

These goals have been addressed in the previous chapters, and though IDA does not claim to be the final solution for diabetes it is a step in the right direction. The following sections will address each of the goals and how IDA specifically achieves each.

Collect Data

The system for collecting data was discussed in Chapter 2 and Chapter 3, and it was demonstrated by 16 patients using the system to collect data for two weeks each. All patients, regardless of

experience with mobile phones, were able to use the system to collect data. The applications were designed to be simple to use and efficient for the patient, and the patients were able to collect representative lifestyle data because the system is portable.

Share Data

After data is remotely collected it can be shared with the health care team. The telemedicine system is described in Chapter 3. It is capable of sharing data, text messages, and audio messages from the patient to the health care team, and sending replies back to the patient.

Analyze Data

The data collected has been used to create models to predict postprandial blood glucose and to continuously model glucose dynamics as presented in Chapters 4 and 5 respectively. Many other methods for analyzing the data and using the models were presented in Chapters 6 and 7. These include generating insulin dose adjustments, calculating parameter estimates, predicting hypoglycemia, and suggesting behaviors.

Demonstrate an improvement over previous methods of prediction

Two modeling method have been presented. The first uses Gaussian Process regression with a Gaussian kernel to predict postprandial blood glucose. The model presented here achieves an average percentage of 57 percent in region A of the Clarke Error Grid. Competing results for predicting postprandial blood glucose range from 28.5% and 41.5% for humans making the same prediction, and 34% and 51% for other computational prediction approaches. The improved data collected by IDA and the model used combine to demonstrate an improvement over previous methods.

The second model presented is a new method for including exercise into a physiological model for continuously modeling glucose dynamics. The model with exercise improves the performance of the physiological model without exercise in all three experiments. It improved when making predictions when used with a CGM device, and was also better than the ARX model when predicting beyond

45 minutes. The new model is also better at estimating the real-time blood glucose concentration between finger stick measurements. Finally, it was better when used to retrospectively estimate the blood glucose profile between finger sticks using Kalman smoothing. Comparing models is very difficult due to the closed nature of this research community. However, the method for including exercise could be used in most models, and it should achieve similar improvements.

In addition to the physiological model, a new ARX model was presented that used exercise data. This model significantly outperforms the AR model when making predictions beyond 30 minutes. In each case the modeling methods presented are improved by incorporating energy expenditure. Thus IDA has demonstrated improved methods for modeling this challenging problem.

This thesis has demonstrated the creation of a diabetes management assistant that can remotely collect data, increase communication between patient and care provider, and automatically analyze all available information. It has also demonstrated that individual models, taking into account nutrition, medication, and exercise, with appropriate mathematical modeling, can learn accurate representations of specific patients suitable for providing therapy advice.

Demonstrate policy search to suggest behavior modifications

Methods for estimating insulin dose adjustments and other behavior adjustment suggestions were presented in chapter 6. For insulin dose adjustment the algorithm searched over all possible doses to find the meal specific dosing policy that would most likely results in normal blood glucose levels. The result is combined with the result from a standard insulin dose calculation to shift the dose toward a better result. The data was also used to create behavior recommendations in carbohydrate-exercise space. Other methods were presented for helping patients and the health care team by suggesting behavior or therapy adjustments.

8.2 Future Directions for Robotics in Chronic Care

In the next decade robot health care technology has the potential to inspire a paradigm shift in chronic disease management. As the population ages more people are faced with managing a

chronic disease. Frequently the treatment of these diseases is complicated and difficult. Managing chronic diseases like diabetes, high blood pressure, and sleep apnea requires a combination of education, motivation, lifestyle monitoring, and behavior adjustment. The ideal management plan for diabetes, one of the most common chronic diseases, is described by the American Diabetes Association as an "individualized therapeutic alliance among the patient and family, the physician, and other members of the health care team." Typical management patterns fall short of this goal. Robotics can improve management by monitoring the factors that influence the disease, providing the patient with a personalized education, and assisting the care team with analysis.

One of the most common chronic diseases, diabetes is the sixth leading cause of death in the United States. There are many products today that can collect data and share data. The next step in research is to create agents that understand the patients, their disease, and how their lifestyle impacts their health. In my experience the broad research goal for health care robots working with chronic disease is to create a robot or agent that becomes a contributing member, if not the hub of treatment, in the ideal therapeutic alliance,

8.2.1 Robotics in Chronic Care

Managing a chronic disease poses problems at many levels. At the lowest level the patient and care team must work together to monitor and control a specific biological problem, and at the societal level the epidemic nature of chronic diseases requires a care team to manage large numbers of patients while treating them as individuals. Robot research should address challenges across this spectrum, from assisting a patient with a small task to large scale intelligent patient management systems.

To address the societal challenge of managing large numbers of patients with chronic diseases, health care robotics can be used to provide house calls for patients. Research should address using the connectivity and intelligence of health care robots to improve the efficiency of physicians by directing the doctors expert knowledge and time where it is most needed.

Education and lifestyle intervention are key components to treating chronic conditions. Patients must learn about their disease and how lifestyle choices affect their health. This includes behaviors

involving diet, exercise, and medication. A goal of health care robots should be to work with the patient to monitor these behaviors and identify relevant personalized advice to educate the patient. Research should seek to identify the best methods for integrating into the patient's life in order to be able to monitor the necessary data without feeling intrusive. There are many other angles to the human computer interaction subgoal. Chronic health care robotic research should address issues of patient acceptance, adaptive education, patient and physician trust, and patient motivation.

One approach to integrating robots into chronic care involves the presence of a physical robot or device interacting with patient and care team, and another option is for health care robots to disappear and function in the background. This involves research into context aware computing, smart homes, intelligent networked sensing devices, and wearable computing.

Health care robotics can also play a role in answering fundamental questions about complex biological interactions that affect chronic diseases. Human biology is a complicated system with many unknown interactions between inputs. Many of these interactions are not well known, and they vary between patients. Robots can help illuminate theses interactions by closely monitoring patients in real life settings. Artificial intelligence research can pursue methods for augmenting current medical knowledge of biological systems with machine learning to discover and explore unidentified interactions. It is a key goal to incorporate personalized decision support systems into health care robotics.

Research related to chronic care health care robotics has the potential to impact hundreds of millions of people. The key goal is to create an agent that is the hub of treatment through research into patient-robot interaction, patient-doctor interaction, intelligent networked biological monitoring, and machine learning in a decision support context. Someday soon, I believe that the tedium of daily diabetes management will be replaced by the worry free interaction between patient, doctor, and robot.

Appendix A

Appendix A

A.1 Conversions Between Units

Useful Conversions		
1 mg carb	$\Leftrightarrow$	1 mg glucose
1 mol glucose	$\Leftrightarrow$	180.16 grams
1 mol human insulin	$\Leftrightarrow$	5808 grams
1 mol insulin lispro	$\Leftrightarrow$	5813.63 grams
1 mol insulin aspart	$\Leftrightarrow$	5831.6 grams
1 mol insulin glargine	$\Leftrightarrow$	6063 grams
1 mol insulin detemir	$\Leftrightarrow$	5913 grams
1 gram insulin	$\Leftrightarrow$	22 units
18.016 mg/dl glucose	$\Leftrightarrow$	1 mmol/l
1 μU/dl insulin	$\Leftrightarrow$	7.8262 pmol/l

Appendix B

Appendix B

B.1 EKF Equations for Glucose Kinetics

The EKF state vector used for the physiological model of glucose dynamics is described in Table B.1. The variables included were selected so that it could function as a generic framework for plugging in competing models for the various compartments. For example, some models separate insulin mass into two compartments, so the state vector includes parameters to handle these models.

Separate EKF models were developed for each subcompartment based on the equations presented in the previous section. These models may depend on parameters in the state vector and update vector.

The vector of system inputs is listed in Table B.2. These are the raw timestamped data collected by the patients.

The nonlinear state update functions $f(X, U)$ for each item in the state vector are summarized in Table B.3.

The jacobian of the vector of state update equations with respect to the state vector is in equation B.4.

This Jacobian does not include the dynamics within each subcompartment because they are evaluated individually.

State Vector: X

#	Var Name	Description	Units
1	Δt	Change in Time between estimates	minutes
2	t	Time	minutes
3	g	Blood Glucose Concentration	mg/dl
4	g^m	Blood Glucose Mass	mg
5	g^v	Blood Volume	dl
6	I^v	Insulin Compartment Volume	ml
7	bm	Body Mass	kg
8	g^{m2}	Compartment Glucose Mass	mg
9	I	Active Insulin Concentration	μu/ml
10	I^p	Plasma Insulin Concentration	μu/ml
11	I^m	Insulin Mass	μu
12	I^{m2}	Insulin Compartment Mass	μu
13	S^I	Insulin Sensitivity	unitless
		Subcompartment Rate Variables	
14	Δg^{egp}	Endogenous Glucose Production	mg
15	Δg^{gut}	Glucose Rate of Appearance	mg
16	Δg^{ind}	Insulin Independent Utilization	mg
17	Δg^{dep}	Insulin Dependent Utilization	mg
18	Δg^{ren}	Renal Clearance	mg
19	ΔI^{abs}	Absorbed Injected Insulin	μu
20	ΔI^{sec}	Secreted Insulin	μu
21	ΔI^{clr}	Cleared Insulin	μu

Table B.1: Table caption

Input Vector: U

Var Name	Description	Units
U^t	Time	minutes
U^{cg}	Continuous Glucose Measurement	mg/dl
U^g	Blood Glucose Reading	mg/dl
U^C	Ingested Carbohydrate	mg
U^F	Ingested Fat	mg
U^P	Ingested Protein	mg
U^E	Current Exercise Rate	cal/min
U^I_f	Injected Rapid Insulin	units
U^I_r	Injected Regular Insulin	units
U^I_m	Injected Mixed Insulin	units
U^I_s	Injected Long Acting Insulin	units

Table B.2: Input vector

			Update Equations
1	Δt_{t+1}	=	Δt_t
2	t_{t+1}	=	$t_t + \Delta t_t$
3	g_{t+1}	=	$[g_t^m + \Delta g_t^{egp} + \Delta g_t^{gut} - \Delta g_t^{ind} - \Delta g_t^{dep} - \Delta g_t^{ren}]/g_t^v$
4	g_{t+1}^m	=	$g_t^m + \Delta g_t^{egp} + \Delta g_t^{gut} - \Delta g_t^{ind} - \Delta g_t^{dep} - \Delta g_t^{rem}$
5	g_{t+1}^v	=	$0.22 * bm_t * 10$
6	I_{t+1}^v	=	$0.142 * bm_t * 1000$
7	bm_{t+1}	=	bm_t
8	g_{t+1}^{m2}	=	(only used with dual glucose compartment models)
9	I_{t+1}	=	$S^I * Ip$
10	I_{t+1}^p	=	$[I_t^m + \Delta I_t^{abs} + \Delta I_t^{sec} - \Delta I_t^{clr}]/Iv_t$
11	I_{t+1}^m	=	$I_t^m + \Delta I_t^{abs} + \Delta I_t^{sec} - \Delta I_t^{clr}$
12	I_{t+1}^{m2}	=	(only used with dual insulin compartment models)
13	S^I	=	S^I
			Independent Subcompartments
14	Δg^{egp}	=	$f(g_t, I_t)$
15	Δg^{gut}	=	$f(U^C)$
16	Δg^{ind}	=	$f(g_t, U^E)$
17	Δg^{dep}	=	$f(g_t, I_t, U^E)$
18	Δg^{ren}	=	$f(g_t)$
19	ΔI^{abs}	=	$f(U^I_{(f,r,m,s)})$
20	ΔI^{sec}	=	$f(g_t)$
21	ΔI^{clr}	=	$f(I_t)$

Table B.3: Update equations for each state variable

$$\frac{\delta}{\delta X}\begin{bmatrix} \Delta t \\ t \\ g \\ g^m \\ g^v \\ I^v \\ bm \\ g^{m2} \\ I \\ I^p \\ I^m \\ I^{m2} \\ S^I \\ \Delta g^{egp} \\ \Delta g^{gut} \\ \Delta g^{ind} \\ \Delta g^{dep} \\ \Delta g^{ren} \\ \Delta I^{abs} \\ \Delta I^{sec} \\ \Delta I^{clr} \end{bmatrix} = \begin{bmatrix} 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \frac{1}{g^v} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{1}{g^v} & \frac{1}{g^v} & \frac{-1}{g^v} & \frac{-1}{g^v} & \frac{-1}{g^v} & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 1 & -1 & -1 & -1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 2.2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0.142 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{1}{I^v} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{1}{I^v} & \frac{1}{I^v} & \frac{-1}{I^v} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 1 & -1 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix} \quad \text{(B.1)}$$

Table B.4: Jacobian for the state update vector.

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