PROBLEM DETECTION FOR SITUATION ASSESSMENT IN CASE-BASED REASONING FOR DIABETES MANAGEMENT

A thesis presented to

the faculty of

the Russ College of Engineering and Technology

In partial fulfillment

of the requirements for the degree

Master of Science

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June 2009
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This thesis entitled

PROBLEM DETECTION FOR SITUATION ASSESSMENT IN CASE-BASED

REASONING FOR DIABETES MANAGEMENT

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This thesis presents work in problem detection for situation assessment in Case-Based Reasoning (CBR) for diabetes management. Diabetes is a disease in which the body does not produce, or does not properly make use of, the hormone insulin. Management of diabetes requires insulin therapy, a controlled lifestyle and close monitoring of the disease by both patient and physician. Poor management of diabetes can result in many serious long-term health complications. CBR is an artificial intelligence (AI) approach that makes use of past experiences and knowledge to reason about new situations. CBR has been applied successfully in the medical field, but never as the primary reasoning mode for diabetes management. Situation assessment is the process by which large amounts of patient data are analyzed and problems that may require therapy adjustments are detected. Situation assessment is a critical component of the complete CBR system for diabetes management. In addition, the situation assessment routines may be used directly by physicians to assist in the identification of problems that require changes in therapy. The contributions of this thesis are: the design and implementation of twelve situation assessment routines, the design and implementation of two data aggregation and visualization programs,
and knowledge acquisition for the construction of cases for a Case-Based Reasoning
decision support system for diabetes management.

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Acknowledgments

I would like to thank my family, friends and professors for their support throughout my thesis work. Thanks to Dr. Cynthia Marling for her guidance throughout this process. Thanks also to Dr. Frank Schwartz, Dr. Jay Shubrook and fellow student Tony Maimone. Without their efforts this thesis would never have been possible. Finally, my lovely wife Julia who has supported me throughout this endeavor. She has shown great patience as I took time out of my evenings and weekends to finish writing this paper.
# Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abstract</td>
<td>4</td>
</tr>
<tr>
<td>Acknowledgments</td>
<td>6</td>
</tr>
<tr>
<td>List of Figures</td>
<td>9</td>
</tr>
<tr>
<td>List of Tables</td>
<td>10</td>
</tr>
<tr>
<td>1 Introduction</td>
<td>11</td>
</tr>
<tr>
<td>2 Background</td>
<td>15</td>
</tr>
<tr>
<td>2.1 Diabetes Mellitus</td>
<td>15</td>
</tr>
<tr>
<td>2.2 The Problem of Data Overload</td>
<td>17</td>
</tr>
<tr>
<td>2.3 Case-Based Reasoning</td>
<td>18</td>
</tr>
<tr>
<td>2.4 Case-Based Reasoning for Intelligent Decision Support in Diabetes</td>
<td>21</td>
</tr>
<tr>
<td>2.5 Pattern Recognition</td>
<td>23</td>
</tr>
<tr>
<td>3 Data Visualization for Knowledge Acquisition</td>
<td>26</td>
</tr>
<tr>
<td>3.1 Knowledge Acquisition</td>
<td>26</td>
</tr>
<tr>
<td>3.2 Data Visualization</td>
<td>28</td>
</tr>
<tr>
<td>4 Situation Assessment</td>
<td>33</td>
</tr>
<tr>
<td>4.1 Problem 1: Over-correction for Hypoglycemia</td>
<td>34</td>
</tr>
<tr>
<td>4.2 Problem 2: Hypoglycemia after Exercise</td>
<td>35</td>
</tr>
<tr>
<td>4.3 Problem 3: Possible Pump Problems</td>
<td>36</td>
</tr>
<tr>
<td>4.4 Problem 4: Over-Correction for Hyperglycemia</td>
<td>37</td>
</tr>
<tr>
<td>4.5 Problem 5: Pre-waking CGMS Lows</td>
<td>38</td>
</tr>
<tr>
<td>4.6 Problem 6: Over-bolus for a Meal</td>
<td>39</td>
</tr>
<tr>
<td>4.7 Problem 7: Pre-meal Hyperglycemia</td>
<td>41</td>
</tr>
<tr>
<td>4.8 Problem 8: Pre-meal Hypoglycemia</td>
<td>41</td>
</tr>
<tr>
<td>4.9 Problem 9: Post-meal Hyperglycemia</td>
<td>42</td>
</tr>
<tr>
<td>4.10 Problem 10: Post-meal Hypoglycemia</td>
<td>43</td>
</tr>
<tr>
<td>4.11 Problem 11: Hyperglycemia upon Waking</td>
<td>43</td>
</tr>
<tr>
<td>4.12 Problem 12: Hypoglycemia upon Waking</td>
<td>44</td>
</tr>
<tr>
<td>4.13 Development and Application of Situation Assessment Routines</td>
<td>45</td>
</tr>
<tr>
<td>5 Evaluation and Future Work</td>
<td>47</td>
</tr>
<tr>
<td>5.1 Problems Detected</td>
<td>47</td>
</tr>
</tbody>
</table>
List of Figures

3.1 DataGraph Program .................................................. 30
4.1 Pseudo-code for Detecting Over-correction for Hypoglycemia .... 34
4.2 Pseudo-code for Detecting Hypoglycemia after Exercise .......... 35
4.3 Pseudo-code for Detecting Possible Pump Problems .............. 36
4.4 Pseudo-code for Detecting Over-correction for Hyperglycemia .... 37
4.5 Pseudo-code for Detecting Pre-waking CGMS Lows ............... 38
4.6 Pseudo-code for Detecting Over-bolus for a Meal .................. 40
4.7 Pseudo-code for Detecting Pre-meal Hyperglycemia ............... 41
4.8 Pseudo-code for Detecting Pre-meal Hypoglycemia ............... 42
4.9 Pseudo-code for Detecting Post-meal Hyperglycemia .............. 43
4.10 Pseudo-code for Detecting Post-meal Hypoglycemia ............. 43
4.11 Pseudo-code for Detecting Hyperglycemia upon Waking .......... 44
4.12 Pseudo-code for Detecting Hypoglycemia upon Waking .......... 45
5.1 Statements Regarding the System Overall and Open Ended Questions 53
List of Tables

5.1 Summary of Problems Detected ........................................ 48
5.2 Summary of Feedback for Patterns ................................. 50
5.2 Summary of Feedback for Patterns ................................. 51
5.3 Summary of Feedback for the Overall System .................... 54
CHAPTER 1

Introduction

This thesis presents work in problem detection for situation assessment in Case-Based Reasoning (CBR) for diabetes management. Diabetes is a disease in which the body does not produce (Type I diabetes) or does not properly use (Type II diabetes) insulin. Insulin is a hormone that is needed to convert sugar, starches and other food into energy for life. Diabetes is a disease that affects 20.8 million Americans or 7% of the population (Wray, 2006).

Diabetes can have many adverse long term health complications if patients fail to maintain good glycemic control. These complications include heart disease, strokes, high blood pressure, blindness, kidney disease, neuropathy and amputation. Good glycemic control is typically accomplished through maintaining a strictly controlled diet and lifestyle and insulin therapy.

Patients generally meet with physicians every 3-4 months. Several months worth of data is a lot to analyze. Often this data consist of only blood glucose and meal information, omitting other information such as exercise, stress, illness and many other factors. This leads to a situation in which physicians suffer from data overload, yet often do not have enough information to fully diagnose problems in their patients’ glucose control.
Using computers to assist physicians with diabetes management has been attempted in a variety of ways. Artificial Intelligence (AI) and control theory have been applied to problem detection and management, while various forms of telemedicine have been employed to collect a wider breadth of data and/or increase communication between patients and physicians (Parker et al., 2001; Popow et al., 2003; Bellazzi et al., 2002).

The purpose of this thesis work was to develop a situation assessment component for a CBR decision support system for the management of diabetes. CBR is an approach to AI that is intended to mimic an approach used by people to solve problems by capitalizing upon past experiences to reason about new situations. These past experiences are stored as cases in the system’s case base. A typical case is structured as follows: Problem/Situation, Solution, Outcome. The Problem/Situation contains the description of the problem that the case represents. The Solution describes the action that was recommended to correct the problem. The outcome describes to what degree the solution was followed and what level of success (or failure) was achieved.

Situation assessment is used in CBR systems to categorize/abstract raw data into structured descriptions of problem situations. These situations can then be compared to the Problem/Situation portions of the cases in the system’s case base. If similar cases are found in the case base the Solution and Outcome information can be used to determine an appropriate course of action for the current situation.
CBR has been applied successfully in many branches of medicine (Holt et al., 2005; Bichindaritz and Marling, 2006). This may be because it mimics the reasoning process used by many physicians, namely, recalling similar past cases and applying the knowledge gained from those cases to the current case. To the best knowledge of the author, CBR has never been used as the primary reasoning method in an AI system for the purpose of diabetes management. In addition to being a module in a larger system, the situation assessment routines have been shown to be useful to physicians as a stand alone system.

The primary contributions of this thesis are:

1. Design and implementation of 12 situation assessment routines to detect various problems in glycemic control
2. Design and implementation of textual and graphical applications to display large volumes of diverse patient data
3. Knowledge acquisition from physicians as they adjust patient therapy, in collaboration with other graduate students

This thesis is organized as follows. Chapter 2 contains background information and gives more detailed descriptions of diabetes and CBR. Chapter 3, Data Visualization, describes the two programs developed by the author to present the data submitted by patients. Chapter 4 details the situation assessment routines themselves and the problems they detect. Chapter 5 presents the evaluation of work to
date and discusses future work. Chapter 6 presents a research review including AI applications in medicine, CBR applications in medicine and other non-AI computer based approaches to diabetes management. Chapter 7 contains a short summary and the conclusions of this thesis.
CHAPTER 2

Background

2.1 Diabetes Mellitus

Diabetes mellitus is a common chronic disease around the world. In America there are 20.8 million people, or 7% of the population, who have diabetes (Wray, 2006). Type I diabetes is caused when pancreatic beta-cells are destroyed by autoimmune mechanisms. The pancreas ceases insulin production entirely. Insulin is required by the body to convert sugar, starches and other food into energy. Without insulin a person’s blood glucose levels will rise to a dangerous level, known as hyperglycemia. Type I diabetic patients require an outside source of insulin to control their blood glucose (American Diabetes Association, 2006). However, introducing an outside source of insulin controlled by the patient also introduces the possibility of insulin over-dose which can cause the patient’s blood glucose levels to drop dangerously low. This is known as hypoglycemia. Extended periods of hyper/hypoglycemia can cause secondary health complications that can reduce quality of life and life expectancy. Intensive insulin therapy combined with a strict diet and a regimented lifestyle is often required to achieve glycemic control and therefore avoid chronic complications. Typical complications of diabetes caused by poor glycemic control are: blindness, kidney
failure, heart disease, neuropathy and amputation (American Diabetes Association, 2006).

For years diabetic patients were dependent upon multiple daily injections of insulin (MDII) to control their blood sugars. Two types of injections were common. The first is Basal Insulin which would be an injection of long-term slow release insulin to cover the average insulin needs throughout the day. The second is a short-term acting insulin, called a Bolus, that is taken with every meal (Schwartz, 2005).

With the invention of the insulin pump, many diabetic patients have an alternative to MDII. Insulin pump therapy involves the constant subcutaneous delivery of insulin to the patient through a catheter. The pump delivers a constant level of Basal insulin throughout the day, and provides an interface to allow the patient to choose how large of a Bolus dose they wish to receive before a meal (Davis, 2008).

Whether using MDII or pump therapy to treat their diabetes, patients must monitor their blood glucose levels very closely and confer with their physicians often. Patients are taught to track blood glucose levels and associated daily activities and then adjust insulin dosages based on their past experiences. When physicians meet with their patients they go over the patient’s diary and make recommendations about insulin therapy, diet and daily lifestyle. Proper glycemic control can only be maintained through constant vigilance and frequent communication between doctor and patient.
2.2 The Problem of Data Overload

Dr. Frank Schwartz, M.D., is the director of the Endocrine/Diabetes Center in the Ohio University College of Osteopathic Medicine. Dr. Schwartz has over 700 diabetic patients on insulin pump therapy. Each patient is instructed to keep a daily log of blood glucose data. A patient typically records 4-6 blood glucose readings per day. Historically, physicians would meet each patient every 3-4 months to review the journal, analyze the data and recommend changes to the insulin therapy and diet. With advancements in technology, the amount of data submitted to the doctor and the number of times the doctor must analyze it have increased dramatically. Patients can now email their physicians as often as they like with questions and data. Most insulin pumps record data and generate reports, as do blood glucose monitoring systems. With no automated method to analyze this data, physicians may experience data overload.

An important paradox to note is that despite suffering from data overload, physicians often have insufficient information to interpret the data and develop advice and corrections. This is due to the fact that even if a patient is using an insulin pump and a continuous glucose monitoring sensor (CGMS), the doctor is still only receiving data on very few variables: blood glucose level, basal insulin, bolus insulin, time of meals and estimated carbohydrates (or carbs) contained in meals. There are numerous variables that can affect a patient’s blood glucose level beyond these five.
For example, the data may show that a patient was at an acceptable level, ate a meal, generated a reasonable estimate of the carbs in the meal, and appropriately calculated and delivered their bolus dose. In general you would expect the patient’s blood glucose levels to remain within the normal range (typically 70-180) but in this instance the patient’s blood glucose dropped dangerously low. The data presented to the physician seems to indicate that the patient took appropriate actions at each step.

In order to properly interpret and explain this hypoglycemic event the doctor requires more data. Perhaps the patient exercised after the meal. Perhaps they had a fight with their spouse or children. Any number of events could have an effect on blood glucose that meal and insulin data alone cannot explain. Current systems do not allow documentation of life events, nor do they keep any memory of past experiences of how a particular patient responded to specific situations. It is up to the patient and the physician to document and/or remember this important data.

### 2.3 Case-Based Reasoning

Case-based reasoning (CBR) is an approach to Artificial Intelligence that is intended to mimic an approach that people typically use to solve problems. This is, the use of past experiences to reason about new situations. CBR is used “to solve new similar problems, explain new situations, critique new solutions, or to create an equitable solution” (Kolodner, 1993). The intent of CBR is to encapsulate all the
relevant data about a situation into a “case” that can be retrieved later to provide insight into a similar situation. Kolodner’s definition of a case is: “a contextualized piece of knowledge representing an experience that teaches a lesson fundamental to achieving the goals of the reasoner” (Kolodner, 1993).

The basic format of a Case is: Situation, Response, Outcome. The situation describes the state of the problem and any constraints. The response contains the action taken to correct the problem. And the outcome holds the information that describes the level of success or failure that was achieved when the response was applied to the problem.

A classic example of CBR in medicine in CASEY. CASEY diagnosed heart failure patients. It was an extension of an existing model-based system which diagnosed heart failures based on the physiological model of the heart. CASEY received renown because it was able to come up with diagnoses comparable to the MBR system, but was much faster (Koton, 1988).

In CASEY the situation would consist of all the relevant data from a heart failure patient. It might include data such as weight, age, sex, symptoms, pulse-rate, temperature, pulse and blood pressure.

Case retrieval and indexes are the final critical component to a CBR system. Indexes are essentially the “keywords” tied to a case that the system finds when it searches. The indexes should describe why the case is useful, or what knowledge it contains. The indexes could also represent that the case successfully accounted for
specific constraints. Design choices about what to use as indexes are critical because they control what cases are retrieved and why, which is the heart of CBR.

Many of CASEY’s indexes were qualitative abstractions of quantitative measurements. This was done so that cases could be matched on “high blood pressure” for example, without the patients needing to have precisely the same blood pressure reading. Once CASEY had retrieved the best matching case from the case base, it began a justification algorithm. This algorithm analyzed the difference between the retrieved case and the current patient. It was required to justify that every difference that existed, would not invalidate the treatment that had been issued in the past case. If the retrieved case passed the justification stage, its solution was then adapted for and issued to the current patient.

One of the strengths of CBR is its capacity for expansion of knowledge. After the initial case base has been built, every situation the system is presented with can be incorporated into the case base, assuming of course that there is some mechanism for deciding the outcome. This allows CBR systems to have a great capacity for learning. In CASEY, each patient that the system diagnosed could be added to the case base whenever the case added some new knowledge not already in the case base.


2.4 Case-Based Reasoning for Intelligent Decision Support in Diabetes Management

The Case-Based Reasoning for Intelligent Decision Support in Diabetes Management system is being developed by a team of graduate students at Ohio University, who work closely with physicians from the Diabetes and Endocrinology clinic on campus. The purpose of the overall project is two-fold, both practical and research oriented. The practical goal is to develop a CBR system that would assist physicians with data overload and reduce the time required to issue therapy changes to patients. The research goal is to show that CBR is a feasible approach for creating an intelligent decision support system for the management of diabetes, and other chronic conditions.

A six week pilot study was conducted in which 20 Type 1 diabetic patients on insulin pump therapy submitted detailed logs of their daily life (Marling et al., 2007a; Marling et al., 2007b). These logs included: self-glucose monitoring data, insulin dosages, work schedules, sleep patterns, exercise, meals, stress, illness, menstrual cycles, infusion set changes, pump problems, hypoglycemic episodes, and other events thought to impact glucose levels. It is noteworthy that this level of detail is well beyond the typical level of detail recorded by the average diabetic patient. In addition, each patient wore a continuous glucose monitoring sensor (CGMS) for three different
72 hour periods over the course of the study. CGMS provides a blood glucose value every five minutes.

The purpose of the situation assessment module is to automatically detect problems in the patient data. This module finds the problems in a patient’s currently submitted data and then notifies the case-based reasoning module. The CBR module then compares the current problem to past problems and attempts to generate a solution to propose. In the short term, this module is also intended to be useful to the physicians as a data pre-processor. It could find problems in the patient data and call them to the attention of the physician.

The problem detection routines for the situation assessment module of the system were implemented over the course of the pilot study. The author and other AI researchers met weekly with the physicians, endocrinologist Dr. Schwartz and diabetologist Dr. Jay Shubrook, to analyze the patient data. The physicians identified problems in the patient data and generalized the problems to the best of their ability. The author took the generalized descriptions and implemented routines to automatically detect the problems. In addition, a list of “typical” problems of diabetic patients was provided by Dr. Schwartz. The algorithms to detect these problems make up the bulk of the situation assessment module.
2.5 Pattern Recognition

Situation assessment requires pattern recognition. Pattern recognition is the attempt to classify data into patterns. Most pattern recognition approaches include extracting features (either symbolic or numeric) from the data and then using those features to classify the data based on either a priori knowledge or upon statistical information. There are many approaches to pattern recognition, including: expert systems, belief networks, probabilistic networks, syntactic pattern recognition, structural pattern recognition, neural networks, grammatical inference and statistical pattern recognition (Duin, 2001).

One popular approach to pattern recognition is the use of artificial neural networks (ANN). The idea behind neural networks is to mimic the structure of the neurons and synapses in the brain. Specifically, a neural network is: “an interconnected assembly of simple processing elements. The processing ability of the network is stored in the interunit connection strengths, or weights, obtained by a process of adaption to, or learning from, a set of training patterns” (Gurney, 1997).

A basic neural network consists of a series of inputs that are connected to a series of outputs through one or more layers of “hidden nodes”. Each connection in the network has a corresponding weight. The goal is to configure the weights of the network in such a manner that they can correctly identify a desired pattern in the input data. There are a variety of “training” algorithms to accomplish this goal. Typically, a set of training data, for which the correct result is already known, is
passed through the neural network. Any error between the neural network’s output and the desired output is then used to adjust the weights of the system.

The major advantages of this approach are:

1. Adaptive Learning: learning based on training or experience

2. Self-Organization: creating its own organization or representation of information

3. Real-Time Operation: neural networks typically lend themselves to a parallel computing implementation

Neural network approaches have been successfully applied to many problems, including problems in the medical domain. However, there is a significant disadvantage to neural network approaches: verifiability. When a neural network has been successfully trained, it is relatively easy to collect statistical data on how often it acts correctly on a given dataset. However, it is often much more difficult to explain why and how it achieves its accuracy. The answer is that the network has encoded/abstracted the characteristics necessary to evaluate input into its systems of weights. In the end, a neural network is essentially a large complex mathematical formula/algorithm, and the answer to why this formula works is often difficult to describe. Many physicians prefer an approach with results that are more easily explained.

This is one reason that the author chose to undertake an expert system approach to pattern recognition. This approach involves human experts supplying a priori
knowledge of the patterns that are important to detect and how to detect them. An expert system approach can be verified more easily through pseudo-code. Another reason is related to the amount of data that is available. Neural network approaches typically require large volumes of data for their training sets, and it was not known at the outset if the data obtained during the pilot study would be sufficient. The author chose to develop a separate algorithm for each problem to be detected. The algorithms were developed through interviews and discussions with physicians at the Ohio University College of Osteopathic Medicine.

There are disadvantages to an expert system approach as well. One disadvantage is that an expert system approach is not as flexible as neural networks and is not capable of learning. If the algorithm is found to be lacking in some way, the code must be manually edited. Also, because the knowledge encoded into the algorithms comes from only a few physicians the final product may contain opinions or biases, and other physicians may disagree with the outputs of the system.
CHAPTER 3

Data Visualization for Knowledge Acquisition

3.1 Knowledge Acquisition

Knowledge acquisition is formally defined as “the transfer and transformation of problem solving expertise from some knowledge source to a computer program” (Byrd et al., 1992). The process of knowledge acquisition typically involves a knowledge engineer gaining “procedural and declarative knowledge” from a human expert in the subject domain (Byrd et al., 1992). Facts about classifications and relationships are included in declarative knowledge. Procedural knowledge defines how declarative knowledge is incorporated and manipulated. A general sequence of events for knowledge acquisition for AI is as follows: (adapted from (Byrd et al., 1992))

1. Knowledge Engineer elicits data and information from the domain expert

2. Knowledge Engineer interprets the data and information and draws conclusions about the expert’s underlying knowledge and reasoning processes

3. Knowledge Engineer uses the conclusions to construct a model which describes the expert’s knowledge and processes
4. Repeat steps 1-3 as the expert system evolves into a functional system

The knowledge acquisition process for CBR is essentially the same. Most differences are primarily terminology differences. For example, according to (Cunningham and Bonzano, 1999), knowledge acquisition fulfills two tasks in CBR: Problem analysis and development of the inference mechanism. Problem analysis involves transforming the information taken from the domain expert into the problem and solution fields in the case based data structure. The inference mechanism is the algorithm used for similarity assessment during the case retrieval process. These two tasks can be accomplished by knowledge engineers using essentially the same procedure described above.

The knowledge acquisition process for this project occurred during weekly meetings between the engineers (the author, fellow student Tony Maimone and advisor Dr. Cynthia Marling) and the physicians (Dr. Frank Schwartz and Dr. Jay Shubrook). Each week, the newly submitted data from the patients was reviewed by the patient’s physician. The physician would point out problems he saw in the patient data and the engineers would ask questions in order to better understand the physician’s thought process, the problem and the potential solution(s). This weekly dialog facilitated knowledge acquisition in three ways. First, it provided the engineers insight into how the physician converted large amounts of raw data into problems. Second, it allowed the author and the physicians to decide which problems it would be most useful to automatically detect. Third, collaboration between the engineers and physicians
allowed the engineers to codify the problems found and solutions recommended into proper data structures for use in the case base.

The evolution of situation assessment algorithms #4 Over-Correction for Hyperglycemia and #6 Over-bolus for a Meal (described in detail in chapter 4) are an excellent example of the iterative nature of the knowledge acquisition process during this project. One of the problems Dr. Schwartz recommended for automatic detection was “Hypoglycemia due to over-bolus”. Dr. Schwartz identified hypoglycemia due to over-bolus problems in the patient data reviewed in the weekly meetings, as described above. However, as the iterations continued the author began to have difficulty reconciling the various feedback. This prompted the knowledge engineers to request an in depth re-evaluation of each instance of “Hypoglycemia due to over-bolus” with the domain experts. During the re-evaluation it became clear that hypoglycemia due to over-bolus was better represented as two separate problems: Over-correction for Hyperglycemia and Over-bolus for a meal.

3.2 Data Visualization

The sources of the data for this project were patients from the Endocrine/Diabetes Center in the Ohio Universtiy College of Osteopathic Medicine. Patients submitted, through a webpage, detailed descriptions of their daily lives each day for 6 weeks. An Oracle database was designed, implemented and populated with the patient data. For more details on the webpage, database and data collection please see (Maimone,
The daily data collected during the pilot study was greater in both breadth and quantity than the typical daily journals of the average diabetic patient. In addition to the reports generated by the situation assessment routines, described in the next chapter, the author developed two programs to present the raw data submitted by the patients. These programs helped the physicians to interpret the large volume of data.

The first program was a textual daily report. This program was very basic and consisted of a brief summary of the patient’s “static” information (age, sex, insulin sensitivity, basal rates, blood glucose target levels, carb ratios, and typical daily schedule), followed by a chronological list of all the data the patient entered for a given day. The daily reports were very detailed but it was difficult to quickly get an overall picture of the patient’s day. An example report is included in Appendix A. This program was written in Java making use of the JDBC (Java Database Connectivity) API (Application Programming Interface) to interface with the Oracle database where the patient data was stored.

The second program, called the Datagraph, was developed by the author in order to visually display all the patient data for a given day. An example of the DataGraph display is shown in Figure 3.1. The DataGraph display contains two different scales: one for blood glucose values and one for basal rates. Fingerstick and CGMS data are displayed on a scale from 0-350. Basal rates are displayed on a scale from 0-1, representing units of basal insulin per/hour. Across the top of the DataGraph display
all the events (meals, boluses, exercise, stress etc.) of the patient’s day are displayed.

A key is provided along the bottom of the datagraph which relates each type of event to a specific color.

Figure 3.1: DataGraph Program

Figure 3.1 displays all the data submitted by Patient #1 for the date 02-17-2006. The blue line shows the patient’s blood glucose level as it was recorded every five minutes by the CGMS sensor, while the red boxes represent finger stick measurements taken by the patient. This allows the user to see at a glance that the patient was
higher than his target level of 150 from approximately 5 A.M. to 11 A.M. and dropped below his target level of 70 at approximately 1 P.M. and 10 P.M. The user can also see that the patient ate three meals, exercised once, administered a bolus seven times, changed his infusion set and reported one hypoglycemic episode. The data depicted in Figure 3.1 is identical to the data in the textual daily report included in Appendix A.

The DataGraph program provides a check box for each type of data collected from the patient. These boxes toggle whether or not that type of data is displayed, allowing the user to customize the display with as much or as little data as desired. Previous and Next Day buttons are provided to allow convenient navigation from day to day. Two text boxes are provided. The first is populated with a brief summary of which days have data for the current patient. This alleviates any need for the user to remember which six weeks of the year the given patient participated in the pilot study. The second text box is initially blank. The user can click on any piece of data displayed on the DataGraph and the details (identical to what is shown on the textual report) are displayed in the text box. In Figure 3.1 this box is displaying the information submitted that describes the meal the patient ate at 11:20 AM. The DataGraph program was written in Microsoft Visual C# using Microsoft Visual Studio for the .Net Framework. The .Net Framework is free and can be installed on any Windows computer.
The DataGraph program was used extensively in the weekly meetings with Dr. Schwartz and Dr. Shubrook as the primary method for presenting the patient data. As stated in (Marling et al., 2007a), “the graphic presentation of integrated lifestyle and glucose data developed for this program allows participating physicians to identify trends more readily and adjust therapy more effectively, resulting in improved glucose control”. The DataGraph program also facilitated knowledge acquisition by helping physicians find problems which were then structured into cases for the CBR system (Marling et al., 2007b). Insights gained from this manual problem detection helped in defining procedures for automated problem detection. Automated problem detection is discussed in the next chapter.
Chapter 4

Situation Assessment

Situation assessment is used in CBR systems to catagorize/abstract raw data into problems/situations. During the pilot study 12 problems were identified that would be useful for the situation assessment module to automatically detect. The problems identified by the situation assessment module can be used directly by physicians to assist them with interpreting patient data, and can also be passed to the CBR diabetes decision support system which will retrieve similar cases from the case base. The CBR decision support system can then use the past knowledge stored in the similar cases to recommend a solution to the current problem.

The development of the situation assessment algorithms and code was a highly iterative process. The process began by taking Dr. Schwartz’s descriptions and implementing them based on the author’s interpretation. Next, the problems detected by the software were presented to Dr. Schwartz for review. He would evaluate and point out any that were incorrect and further refine the criteria for disqualifying and/or accepting matches. After several months of revisions, ten procedures were developed and deemed ready for formal evaluation by diabetes specialists. An additional two procedures were developed, but they could be validated numerically and therefore formal evaluation by diabetes specialists was not deemed necessary. A description
of each problem and the pseudo-code for the algorithm that detects the problem are presented below.

### 4.1 Problem 1: Over-correction for Hypoglycemia

Over-correction for hypoglycemia is a common problem for diabetic patients. This problem occurs when the patient realizes that they are having a hypoglycemic episode, either from symptoms or from testing their blood glucose levels, and then consumes too many carbs in an attempt to correct the problem. Typically patients are instructed to eat a snack consisting of 30 carbs to correct for hypoglycemia.

The pseudo-code for the algorithm to detect this problem is as follows:

```plaintext
For each low fingerstick (below patient's low target or below 70) and reported hypo event
   If they corrected¹
      If they went high (fingerstick or CGMS above patient's high target) within 3 hours of
         the initial low fingerstick
         If we do NOT find a Carb_Intake² between correction and the high fingerstick.
            We have a match.

¹Correction is defined as:
   Result of Carb_Intake* calculation is greater than 30 carbs for the 30 minutes after the
   low fingerstick. Or the Patient told us they corrected (entry in the Hypo_Action table)

²Carb_Intake calculation:
   The carb intake function sums all carbs eaten and all boluses taken in time period
   specified. It then computes the amount of carbs eaten that were not accounted for
   by boluses (if any).

Result = Carbs - (Bolus * Carb_Ratio)
```

Figure 4.1: Pseudo-code for Detecting Over-correction for Hypoglycemia
4.2 Problem 2: Hypoglycemia after Exercise

Hypoglycemia after exercise is another common problem. Exercise causes the effectiveness of insulin to increase. In a non-diabetic person the body compensates for this by lowering the production of insulin. If a diabetic patient does not lower their rate of insulin infusion (or compensate for the problem in some other way) they are likely to experience hypoglycemia after exercising.

The pseudo-code for the algorithm to detect this problem is as follows:

For each time the patient exercised
   If there was NOT a low\textsuperscript{1} fingerstick or CGMS reading within 30 minutes before they started exercising
      If they went low within 4 hours of the exercise
         We have a match.
         If an Intervening\_Bolus\textsuperscript{2} is found between the exercise and the low
            Note that the low may be caused by a combination of bolus and exercise.

\textsuperscript{1}Low fingerstick or CGMS reading below patient's low target or below 70, or self-reported hypo event

\textsuperscript{2}Intervening\_Bolus calculation

This function determines if there was any bolus insulin taken during the given time period that cannot be accounted for by carb intake. The Intervening\_Bolus calculation sums all carbs eaten(if any) and all boluses taken(if any) in time period specified. It then computes the amount of bolus insulin taken in excess of what would be needed to cover the carbs.

If: Bolus - (Carbs / Carb\_Ratio)
   is greater than 0 then an intervening bolus was found.
   is less than or equal to 0 no intervening bolus was found.

Figure 4.2: Pseudo-code for Detecting Hypoglycemia after Exercise
4.3 Problem 3: Possible Pump Problems

“Pump Problems” is not really a single problem but a category of problems. These problems are typically characterized by excessively high (much higher than the patient’s normal high readings) blood glucose readings. Often these readings are accompanied by apparently ineffective boluses (or other corrections), and sometimes occur after the patient has changed their infusion set or insulin vial. Typical explanations are: insulin not reaching the body (infusion set change was bad, infusion site resisting the infusion set, kink in the catheter), insulin itself is not viable (this can occur if the insulin was stored at too high a temperature) or hardware failure of the pump itself.

The pseudo-code for the algorithm to detect this problem is as follows:

For each day of the study
    Find the average of the highest daily fingerstick the patient had for the last 7 days.
    If there are at least 2 fingersticks or CGMS readings on this day that exceed the average max by a threshold value (currently 50)
    AND
    If there is no stress within 3 hours before the first excessively high fingerstick
    THEN
        This is a match.
        If the excessively high interval is a strictly increasing trend
            Report a pump failure/total occlusions.
        If excessively high interval is not a strictly increasing trend
            Report a partial occlusion.

Figure 4.3: Pseudo-code for Detecting Possible Pump Problems
4.4 Problem 4: Over-Correction for Hyperglycemia

Over-correction for hyperglycemia occurs when the patient realizes that they are having a hyperglycemic episode, either from symptoms or from testing their blood glucose levels, and then over-corrects for the problem. These over-corrections are typically boluses of too much insulin, but exercise can also lower blood sugar and can contribute to over-corrections.

The pseudo-code for the algorithm to detect this problem is as follows:

For each high (above the patient’s high target) fingerstick
  If they bolused without accompanying meal within 15 minutes before or 30 minutes after the high fingerstick
    Compute Bolus_Effect1.
    If Bolus_Effect < patient’s low target (or 70)
      If patient went low2 within 3 hours of initial high fingerstick
        We have a match
        If there is an intervening_exercise
          Note combined effect

NOTE: This function only checks for corrections in the absence of a meal. If a meal was present within 30 minutes of the high fingerstick this pattern will disqualify it. Pattern 6: OverBolus for meal should find those problems.

1Bolus_Effect calculation
   This function calculates the resulting blood glucose level the at which the patient should be after a given bolus dose.

   Result = Current_FingerStick - (Bolus * Insulin_Sensitivity)

2Low
   fingerstick or CGMS reading below patient’s low target or below 70, or self-reported hypo event

Figure 4.4: Pseudo-code for Detecting Over-correction for Hyperglycemia
4.5 Problem 5: Pre-waking CGMS Lows

Nocturnal hypoglycemia is one of the most dangerous problems diabetic patients face. A single prolonged period of hypoglycemia can result in permanent brain damage, coma and death. This problem is compounded by the fact that some patients are asymptomatic during hypoglycemia and therefore may not wake up in the middle of the night to correct the problem. This algorithm was specifically designed to detect significant periods of low readings in the hours before the patient wakes. Because periods and not individual readings were to be detected, this algorithm operates on CGMS data only, not fingersticks.

The pseudo-code for the algorithm to detect this problem is as follows:

```
For each day in the study
    If the patient told us when they woke up
        Set WAKETIME to when they woke
    else
        Set WAKETIME to when they typically wake up on this day of the week
    If CGMS data exists in the 3 hours before WAKETIME
        Count how many times in that 3 hours they were low and how many times they were not low, Lows that occur in the hour before waking are counted twice (to weight the hour before waking heavier than the previous 2 hours).
        If the lows outnumber the not lows
            Then we consider it "a consistently low trend"
    If at least 2 of 3 days for a given CGMS sensor period have a consistently low trends then they are reported as a match.
```

Figure 4.5: Pseudo-code for Detecting Pre-waking CGMS Lows
4.6 Problem 6: Over-bolus for a Meal

An over-bolus for a meal occurs when a patient administers bolus insulin in excess of what is necessary to account for current blood glucose level and the carbs in the meal. This problem can also occur due to bad “carb-counting”, when a patient incorrectly estimates the number of carbs in a meal. This algorithm takes existing hyperglycemia into account and only reports problems if the bolus exceeds the amount necessary to account for both the carbs in the meal and any existing hyperglycemia. However, at this time it is unable to detect bad carb-counting.

The pseudo-code for the algorithm to detect this problem is as follows:
For each Meal
   Check Blood Glucose within 30 minutes before the meal
   If low
      Return no match
   If there is another meal within 30 minutes of this meal
      Sum the carbs of the meals together.
      Sum all boluses within 30 minutes of the meal.
      Calculate the amount of bolus insulin that is needed to cover the carbs

\[
\text{Expected\_Bolus\_For\_Carbs} = \frac{\text{Carbs}}{\text{Carb\_Ratio}}
\]

Calculate any difference in actual bolus vs. expected bolus for carbs.

\[
\text{Bolus\_Difference} = \text{Sum\_of\_Actual\_Boluses} - \text{Expected\_Bolus\_For\_Carbs}
\]

If the bolus difference is negative
   Return with no match
Calculate how much the bolus difference should lower their blood glucose:

\[
\text{Predicted\_Future\_Blood\_Sugar} = \text{Current\_Blood\_Sugar} - (\text{Bolus\_Difference} \times \text{Insulin\_Sensitivity})
\]

If the predicted future blood sugar is below the patient's low target or below 70
   If they actually went low\(^1\) within 3 hours after the initial meal
      If there are no Intervening\_Bolus\(^2\) between the initial bolus for the meal and the low reading
         We have a match.

\(^1\)Low
fingerstick or CGMS reading below patient's low target or below 70, or self-reported hypo event

\(^2\)Intervening\_Bolus calculation

This function determines if there was any bolus insulin taken during the given time period that cannot be accounted for by carb intake. The Intervening\_Bolus calculation sums all carbs eaten (if any) and all boluses taken (if any) in time period specified. It then computes the amount of bolus insulin taken in excess of what would be needed to cover the carbs.

If: \(\text{Bolus} - \left(\frac{\text{Carbs}}{\text{Carb\_Ratio}}\right)\)
   is greater than 0 then an intervening bolus was found.
   is less than or equal to 0 no intervening bolus was found.

Figure 4.6: Pseudo-code for Detecting Over-bolus for a Meal
4.7 Problem 7: Pre-meal Hyperglycemia

Pre-meal hyperglycemia is characterized by a hyperglycemic fingerstick reading within 30 minutes prior to a meal. Single instances of pre-meal hyperglycemia are not necessarily significant problems. However, when consistent patterns of pre-meal hyperglycemia are found, it is sometimes possible to identify events or habits in the patient’s routine that cause the hyperglycemia. This algorithm, therefore, only reports problems if pre-meal hyperglycemia is found for a given meal (breakfast, lunch or dinner) three days in a row, three days in the same week, or on the same day of the week three weeks in a row.

The pseudo-code for the algorithm to detect this problem is as follows:

```
For each meal of the day (breakfast, lunch and dinner)
  If there is a fingerstick above the patient's high limit, within 30 minutes prior to the meal
    Record a potential match
  For the list of potential matches, report matches if they are found 3 days in a row, 3 days in the same week, or on the same day of the week 3 weeks in a row.
```

Figure 4.7: Pseudo-code for Detecting Pre-meal Hyperglycemia

4.8 Problem 8: Pre-meal Hypoglycemia

Pre-meal hypoglycemia is characterized by a hypoglycemic event within 30 minutes prior to a meal. Unlike hyperglycemia, single events of hypoglycemia are con-
sidered significant problems. Therefore, all occurrence of pre-meal hypoglycemia are reported by the algorithm.

The pseudo-code for the algorithm to detect this problem is as follows:

```
For each meal of the day (breakfast, lunch and dinner)
    If there is a low (below patient's low target or below 70) fingerstick or CGMS, within 30 minutes prior to the meal
        We have a match
```

Figure 4.8: Pseudo-code for Detecting Pre-meal Hypoglycemia

### 4.9 Problem 9: Post-meal Hyperglycemia

Post-meal hyperglycemia is characterized by a hyperglycemic fingerstick reading after a meal. Single instances of post-meal hyperglycemia are not necessarily significant problems. However, when consistent patterns of post-meal hyperglycemia are found, it is sometimes possible to identify events or habits in the patient’s routine that cause the hyperglycemia. This algorithm, therefore, only reports problems if post-meal hyperglycemia is found for a given meal (breakfast, lunch or dinner) three days in a row, three days in the same week, or on the same day of the week three weeks in a row.

The pseudo-code for the algorithm to detect this problem is as follows:
For each meal of the day (breakfast, lunch and dinner)  
  If the patient was above their high limit within 30 minutes before the meal  
      Note that they were already high.  
  If there is a fingerstick above the patient's high limit, between 90 minutes after, and 120 minutes after the meal  
      Record a potential match  
For the list of potential matches, report matches if they are found 3 days in a row, 3 days in the same week, or on the same day of the week 3 weeks in a row. Any potential matches that have an “already high” note attached to them are removed from consideration unless the post meal high exceeds the pre meal high by a given threshold.
of problems. The patient could have been hyperglycemic all night, or it could be the result of either dawn phenomena or Somogyi phenomena. This problem was considered a simple mathematical check on the first fingerstick of the day. Therefore, formal evaluation was not deemed necessary.

The pseudo-code for the algorithm to detect this problem is as follows:

Check the first fingerstick\(^1\) of the day for each day of the study. Every time the patient has 3 (or more) days in a row where their first fingerstick is above their high limit we have a match.

\(^1\)first fingerstick of the day is defined as the first fingerstick after the patient wakes up. If the patient did not specify when they woke up on a given day we use the time they "normally" wake up as specified in their typical daily schedule. Only fingersticks taken within 2 hours of the wake up time and before the patient eats are considered valid for this purpose.

4.12 Problem 12: Hypoglycemia upon Waking

Hypoglycemia upon waking is reported when the patient’s first fasting (must be before breakfast) fingerstick of the day is low. This may indicate a period of nocturnal hypoglycemia, which can be very dangerous, as described in problem 5 above.

The pseudo-code for the algorithm to detect this problem is as follows:
Check the first fingerstick\textsuperscript{1} of the day for each day of the study
If it is below their low limit or 70 we have a match

\textsuperscript{1}first fingerstick of the day is defined as the first fingerstick after the patient wakes up. If the patient did not specify when they woke up on a given day we use the time they "normally" wake up as specified in their typical daily schedule. Only fingersticks taken within 2 hours of the wake up time and before the patient eats are considered valid for this purpose.

Figure 4.12: Pseudo-code for Detecting Hypoglycemia upon Waking

4.13 Development and Application of Situation Assessment Routines

All of the situation assessment routines were written in Java. The data submitted by the patients was stored in an Oracle database, and accessed through the JDBC (Java Database Connectivity) API. JDBC is database independent, which should allow the situation assessment code to be easily portable to other systems, provided that the database design matches the current one. The code and database currently reside on the Ace server at Ohio University.

Throughout the pilot study, the author met weekly with domain experts Dr. Schwartz and Dr Shubrook and presented the week’s worth of matches detected by the situation assessment routines. The physician reviewed the matches detected by the system while reviewing all the data submitted by the patient. They also provided feedback on both the accuracy of the matches as well as the usefulness of calling the matches to the attention of a physician. This feedback was invaluable for the continuing development of the routines themselves and also for generating ideas for
more problems to detect. When both the pilot study and the development of the situation assessment routines were complete, a formal evaluation of the system was conducted by four domain experts. This evaluation is covered in the next chapter.

These routines are intended to be integrated into a CBR decision support system. However, throughout the development process it was also an important goal that the situation assessment routines be useful in and of themselves to physicians. In their current state the routines are well suited to act as a “data preprocessor” for the physicians. These routines could be run prior to the patient’s visit and the physician would be provided with a concise summary of problems detected. These summaries can help the physician to get a quick idea of the patient’s overall status and may help the doctor decide where to start a more detailed review of the patient data.
Chapter 5

Evaluation and Future Work

5.1 Problems Detected

The situation assessment module was able to successfully detect all 12 problems in the data submitted by the patients who completed the pilot study. The problems the system detected are:

1. Over-correction for hypoglycemia

2. Hypoglycemia after exercise

3. Possible pump problems

4. Over-correction for hyperglycemia

5. Pre-waking CGMS lows

6. Over-bolus for a meal

7. Pre-meal hyperglycemia

8. Pre-meal hypoglycemia

9. Post-meal hyperglycemia

10. Post-meal hypoglycemia
Table 5.1. Summary of Problems Detected

<table>
<thead>
<tr>
<th>Problem</th>
<th>Total # of detections</th>
<th># of different patients</th>
</tr>
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<tbody>
<tr>
<td>Problem 1</td>
<td>16</td>
<td>9</td>
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<tr>
<td>Problem 2</td>
<td>52</td>
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<td>11</td>
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<td>Problem 9</td>
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<td>5</td>
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<tr>
<td>Problem 10</td>
<td>37</td>
<td>9</td>
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<td>5</td>
</tr>
<tr>
<td>Problem 12</td>
<td>33</td>
<td>8</td>
</tr>
</tbody>
</table>

11. Hyperglycemia upon waking

12. Hypoglycemia upon waking

The system detected a total of 352 problems for 12 patients, each of whom submitted data for six weeks. Table 5.1 shows the number of times each problem was detected and the number of different patients that were found to have the problem.
5.2 Evaluation

The formal evaluation of the situation assessment module was held on April 13th, 2007. A total of four diabetes specialists evaluated one match each for patterns 1 through 10. These patterns, which were fully described in Chapter 4, are listed in Section 5.1. Patterns 11 and 12, hyperglycemia upon waking and hypoglycemia upon waking, could be verified by checking numeric values; therefore, formal evaluation by diabetes specialists was not deemed to be necessary. The evaluators, three physicians and one advance practice nurse, were presented with a short description of the problem the algorithm was intended to find and a summary of the data the system used to detect the problem. In addition, the Datagraph program described in Chapter 3 was used to present all of the data the system had for the given patient on the given day. When the evaluators felt that they had all the information they needed to evaluate the match, they were asked to rate their agreement with the following three statements:

S1. This is a correct identification of a problem

S2. It would be useful to call this problem to the attention of the patient

S3. It would be useful to call this problem to the attention of the physician

An overview of the responses is given in Table 5.2
Table 5.2. Summary of Feedback for Patterns

<table>
<thead>
<tr>
<th></th>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Mixed Feelings</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
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Table 5.2 (continued)

<table>
<thead>
<tr>
<th>Problem</th>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Mixed Feelings</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
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<tr>
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</table>

As can be seen in Table 5.2, the evaluation of the problem detection software was quite positive. Overall, the evaluators felt that the system was correctly identifying problems. In addition, the responses to statements 2 and 3 regarding the usefulness of bringing these matches to the attention of the patient or doctor indicate that the evaluators felt that the problem identification were valuable.

In response to statement 1, “This is a correct identification of a problem” the system received 12 “Strongly Agree”, 19 “Agree”, 6 “Mixed Feelings”, and only 3 “Disagree” responses. This breaks down to 77.5% (31/40) positive responses, 15% (6/40) neutral responses and 7.5% (3/40) negative responses.

Responses to statement 2, “It would be useful to call this problem to the attention of the patient”, were even more positive. The system received 22 “Strongly Agree”, 13 “Agree”, 4 “Mixed Feelings”, and 1 “Disagree”, resulting in 87.5% (35/40) positive responses, 10% neutral responses and 2.5% (1/40) negative responses.
Responses to statement 3, “It would be useful to call this problem to the attention of the physician” were slightly more positive still. The system received 22 “Strongly Agree”, 14 “Agree”, 3 “Mixed Feelings”, 1 “Disagree”, resulting in 90% (36/40) positive responses, 7.5% (3/40) neutral responses, and 2.5% (1/40) negative responses.

Problem 1 received one “Mixed Feelings” for statement 1 and one “Mixed Feelings” for statement 2, both from the same evaluator. The evaluator made no notes regarding the reasons for the mixed feelings.

Problem 4 received one “Mixed Feelings” and one “Disagree” for statement 1. Both evaluators noted that they felt “Inappropriate meal bolus and correction bolus” would be a better description of the problem than simply over correction bolus. This is because the patient used a dual wave bolus with the preceding meal that could have contributed to the patient’s going low.

Problem 6 received one “Mixed Feelings” for statement 1. The evaluator made no notes regarding the reasons for the mixed feelings.

Problem 7 received two “Mixed Feelings” for statement 1 and one “Mixed Feelings” for statement 2 and statement 3. This pattern detects high blood glucose before meals in various three day patterns. The meals in question were breakfast. Comments by the evaluators indicate that because the meals were breakfast, it is possible that the patient was high throughout the night before.

Problem 8 received one “Disagree” for statement 1 and one “Mixed Feelings” for both statement 2 and statement 3. The evaluator stated that hypoglycemia episodes
Figure 5.1: Statements Regarding the System Overall and Open Ended Questions

should be reported in patterns, as for hyperglycemia, rather than individually. The
domain expert disagreed, due to the criticality of treating every hypoglycemic episode.

Problem 9 received one “Mixed Feelings” and one “Disagree” each for all three
statements. This problem is post-meal hyperglycemia. One evaluator thought the
problem could be caused by a bad vial of insulin. The other evaluator objected
because there was a stressor compounding the problem.

The evaluators were asked to rate their level of agreement with an additional seven
statements regarding the system as a whole. These statements are shown in Figure
5.1.

The evaluator’s responses to statements 1 through 7 are summarized in Table 5.3.

<table>
<thead>
<tr>
<th>Statement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1.</td>
<td>The problems and patterns of glucose detected by this system are important in attaining and maintaining good blood glucose control.</td>
</tr>
<tr>
<td>S2.</td>
<td>The problems detected by this system are important for the safety of the patient in preventing hypo or hyperglycemia.</td>
</tr>
<tr>
<td>S3.</td>
<td>The problems detected by this system might otherwise not be detected by health care professionals.</td>
</tr>
<tr>
<td>S4.</td>
<td>This system enhances a health care professional’s ability to detect these problems.</td>
</tr>
<tr>
<td>S5.</td>
<td>The problems detected by this system might otherwise not be detected by patients.</td>
</tr>
<tr>
<td>S6.</td>
<td>I would feel comfortable using this system’s output to help patients maintain good blood glucose control.</td>
</tr>
<tr>
<td>S7.</td>
<td>I would feel comfortable allowing this system to directly inform a patient when it detects a problem.</td>
</tr>
<tr>
<td>Q8.</td>
<td>What does this system tell us that the CGMS sensor doesn’t already tell us?</td>
</tr>
<tr>
<td>Q9.</td>
<td>What other problems in blood glucose control would it be useful to automatically detect?</td>
</tr>
</tbody>
</table>
Table 5.3. Summary of Feedback for the Overall System

<table>
<thead>
<tr>
<th>Statement</th>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Mixed Feelings</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
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<tr>
<td>Statement 1</td>
<td>3</td>
<td>1</td>
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<tr>
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<td>4</td>
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</tr>
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<td>3</td>
<td>...</td>
<td>1</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
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<td>3</td>
<td>1</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
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<td>2</td>
<td>2</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

The responses to the final statements involving the system as a whole were almost entirely positive. No negative responses were given, and only two “Mixed Feelings” responses were given, one for statement 3 and one for statement 5. These two responses indicate that one of the evaluators had mixed feelings regarding whether or not the problems detected by the system might otherwise be overlooked by doctors and patients. Overall the positive responses of the evaluators to these statements indicate that the problems detected by the system are both important to detect and useful to the patients and doctors.

The final two questions were open ended. Responses to “What does this system tell us that the CGMS sensor doesn’t already tell us?” included:

1. Additional bolus information/Insulin use
2. Diet
3. Activity/Exercise

4. Stress

5. Explains corrective actions

6. Infusion set changes

7. Times meals were consumed

Responses to “What other problems in blood glucose control would it be useful to automatically detect?” included:

1. Combining isolated problems together to develop patterns

2. Prioritize multiple problems

3. Exactly what food they ate and how many carbs were included

4. Baseline data

5. Date of starting a new vial of insulin

5.3 Future Work

Enhancements to the situation assessment module will consist primarily of adding new problems to be detected. Some additional problems identified by Dr. Schwartz are:
1. Dawn Phenomena

2. Somogyi Phenomena

3. Menstrual cycle effects

4. Stress effects

Dawn phenomena and Somogyi phenomena are potential causes of hyperglycemia upon waking. Both are caused by the body releasing counter regulatory hormones in the middle of the night. These hormones oppose the action of insulin, typically causing blood glucose to rise between the hours of 4 and 8 AM. Dawn phenomena is a natural release of these hormones to get the body ready to start the day. Somogyi phenomena is the effect of the body rebounding from overnight hypoglycemia. The same counter regulatory hormones act as the body’s defense system against overnight hypoglycemia. The only way to differentiate the two is to check blood glucose in the middle of the night. A high reading indicates dawn phenomena, a low indicates Somogyi phenomena rebound.

Some women experience changes in their insulin sensitivity during their menstrual cycle. The hormone estrogen typically increases insulin sensitivity and proestrogen typically decreases it. Some women do not experience changes during their cycle but those who do are most likely to notice the effects during the third week when hormone levels are the highest.
Stress can be both mental and physical; anything from a fight with the family to a broken leg can trigger the body’s “fight or flight” hormones. These hormones typically cause an increase in blood glucose. However, a minority of people experience the opposite, a marked drop in blood glucose. Due to this paradox the effects of stress must be dealt with on a patient by patient basis.

These are excellent candidates for the future expansion of the situation assessment module. In addition, 50 cases for the CBR system were defined during the pilot study. Any of these cases that are not covered by the existing situation assessment routines will need to be added as well.

One weakness of the situation assessment module is the fact that it must rely on the patient’s estimations of the number of carbs they consumed with a given meal. This particular piece of data is critical in many of the current situation assessment routines. It would be useful for the system to be able to access a nutritional database to compute/verify the number of carbs based on the food the patient ate. In addition to ensuring the accuracy of the data, this would allow the system to detect another important problem: patient miscounting carbs.

Another source of future work for the situation assessment module could involve formally evaluating its performance in relation to other known problem detection or pattern recognition techniques. It would be useful to know how the situation assessment routines compare to other established methods in regards to accuracy, robustness, flexibility, extendability, and execution time.
The prototype CBR system is currently in use by physicians at the Ohio University College of Osteopathic Medicine (Schwartz et al., 2008). Currently the system scans clinical data collected from a patient and uses the situation assessment module to detect problems. The list of problems and the frequency of each problem are displayed. The physician can then use the datagraph program to view all the data available on the day of any given problem. Next, the physician may select any detected problem and request automated analysis from the CBR system. The system displays the most similar problems from the case base and recommends their solutions as decision support. The physician then decides what advice to give to the patient.

A second clinical research study is currently underway at Ohio University (Marling et al., 2008). There are three major goals of this study. First, grow the case base. This should increase system knowledge and competence. Second, develop patient specific case bases. These should enable the system to learn how an individual patient responds to changes in therapy. Third, develop addition similarity metrics to compare how similar patients are to each other. This will help account for the fact that some patients may have a very similar problem, yet the patients themselves may differ in ways that would necessitate a different solution.
Chapter 6

Related Research

AI has been applied in the medical field for several decades (Altman, 1999). Applications include: decision support, diagnosis, data interpretation, data visualization information management, data mining and classification. Approaches range from Rule-Based, Model-Based and Case-Based reasoning to Neural Networks. Artificial Intelligence is applicable within the medical field for many reasons. Many physicians suffer from data overload, either in the sheer amount of data to be examined, or in the time required to thoroughly examine it. Medicine is also a field of specializations. No one doctor can possibly be a jack of all trades. If a system can be developed that sufficiently models the problem solving or data analysis of one field of study, then that system can act as a decision support tool for general practitioners and other doctors.

The following research review illustrates the advancements that the applications of computers and artificial intelligence have contributed to the medical sciences in general and to the management of diabetes specifically. In addition, some CBR systems are presented that demonstrate the usefulness of the CBR approach in the medical field. CBR has been applied to the diabetes domain before, but only as an addition to Model-Based reasoning (MBR) or Rule-Based reasoning (RBR) systems.
(Montani et al., 2000). CBR has not been directly applied to diabetes as the primary reasoning method to the best knowledge of the author.

6.1 AI in Medicine

The medical field is an ideal research area for Artificial Intelligence mainly because it is so large and varied. Early AI research in medicine (1950’s-1980’s) was focused primarily on diagnosis. Many systems were developed to analyze clinical data and determine what was wrong with the patient. There have been many successful systems, but few of them were put into mainstream use by medical professionals. This is generally attributed to the fact that medical data rarely exists in a digital, semantically clean form. Therefore, doctors are required to enter data that they already have into the system through tedious user-interfaces. As mentioned previously, many doctors already suffer from data-overload. So a system that increases the amount of time a doctor has to spend entering data he already has in another format, is generally not well accepted by the medical community. In addition, it has been noted that “Diagnosis is a relatively rare event, probably accounting for less than 5 percent of physician time. What physicians really need is help following chronic and slowly evolving disease in patients that are seen in brief episodes but require expert interventions” (Altman, 1999).

This statement reflects the more modern trend in AI research in medicine. Beginning in the 1990’s AI research saw a growth in systems designed for decision support
(Altman, 1999). Like diagnosis systems, decision support systems attempt to analyze clinical data, recognize problems, and generate potential solutions. Where diagnosis systems often only had to analyze the current state of the patient, such as symptoms, decision support usually requires the analysis of large amounts of time series data, reflecting the patient’s long term history.

6.2 CBR in Medicine

Case-Based Reasoning is an Artificial Intelligence approach that reasons based on past experiences with known outcomes. This approach is especially useful when a problem domain is not fully understood, or when it cannot be fully modeled, which is often the case in the medical domain. In their overview of CBR systems in medicine, Nilsson and Sollenborn (Nilsson and Sollenborn, 2004) point out the following traits of CBR that are particularly suited for the medical domain.

1. CBR is essentially the way doctors reason about patients and diseases

2. CBR’s adaptive abilities allow it to be tailored to the requirements of an individual physician

3. CBR’s reliance on existing cases (even if those cases are not understood) eliminates the need to rely on subjective knowledge (a problem typical of rule-based reasoners)
4. CBR can gain specific knowledge through adding new cases to the case base as well as gaining abstract knowledge by generalizing cases.

CBR is not always used as the primary reasoning module in AI systems. It is often used as an addition to Model Based and/or Rule Based reasoning. Combining other reasoning approaches with CBR in this way allows past cases to be used to modify the model parameters or rules, and improve the primary reasoning module (Montani et al., 2000).

6.2.1 CBR Breast Biopsy Classifier

Researchers at Duke University (Bilska-Wolak and Floyd, 2002) developed a CBR system to predict biopsy results. Their case base consisted of 1433 past biopsy results. Each case contained the BI-RADS description of the mammogram information that existed pre-biopsy. Of the original 1433 cases, 931 (65%) had turned out to be benign after the biopsy. After adopting a round-robin testing strategy their CBR system was able to reduce the number of misclassified benign lesions by 27%-41%, while only misclassifying 2%-5% of the malignant lesions. This improvement would have saved 186-372 women from having to undergo surgery. Clearly this system can provide assistance to doctors in classification of breast biopsy candidates.
6.2.2 Wellworks/HeartWorks

Researchers at Ohio University developed The Wellworks/Heartworks Adviser/Trainer (WHAT). (Evans-Romaine and Marling, 2003). Staff members of Wellworks/Heartworks are responsible for prescribing physical rehabilitation programs for patients with cardiac or pulmonary disorders. The Wellworks/Heartworks program had a set of rules that were used to train new staff members. These rules were highly conservative and were often disregarded by more experienced staff members. WHAT was developed to determine if a CBR system could prescribe exercise programs as the experienced staff did, without relying on the conservative rules. In testing, WHAT’s CBR system succeeded in prescribing exercise programs much closer to that of the experienced staff than the basic RBR system. This illustrates a well known problem of RBR. This is that rule-based reasoning alone often has difficulty performing at the same level of human beings due to the static nature of rules. CBR is often able to overcome this shortcoming.

6.2.3 INRECA

The INRECA project, funded by the European Union and developed by researchers throughout Europe (Altoff et al., 1998), was dedicated to the development of CBR. INRECA+ was a follow up project focusing on CBR applications to the medical field. One system developed under INRECA+ was dedicated to diagnosing poison victims. This system was intended for use within ambulances and as a sup-
plement to poison emergency phone operators. System response time was therefore a critical issue. One known issue with CBR is that case retrieval can potentially take a long time as the size of the case base grows. To address this issue, the INRECA+ researchers developed the INRECA Tree (Altoff et al., 1998). The INRECA tree is a data-structure based upon a K-D Tree. Essentially, an interior node of the tree represents an attribute of a case, and the transitions to child nodes represent value ranges for that attribute. For example, an interior node may represent a patient’s breathing rate. Four transitions to child nodes may represent breath rate less than X, equal to X, greater than X or unknown. Leaf nodes in the INRECA tree hold all the cases that match the series of decisions made to reach the leaf node from the root. This data structure is an alternative to computing a similarity value for each case in the case base. It allows for faster retrieval by pre-sorting similar cases into the same bin, so that only a small subset of the case base needs to be processed at run time.

6.2.4 The Auguste Project

The Auguste Project is a CBR system for decision support and long term planning, regarding the care and treatment of patients suffering from Alzheimer’s disease (Marling and Whitehouse, 2001). Alzheimer’s patients who visit comprehensive Alzheimer’s disease centers have an interdisciplinary team of specialists that manage their care. The purpose of the Auguste Project is to develop an AI system capable of becoming a member of that team. The first step along that path was the development
of a CBR module to aid in deciding whether or not a patient should be prescribed neuroleptic drugs. A case-base of 28 patients was created and eight additional patients were used for testing purposes. The cases were matched based on nine features. All eight of the test cases were diagnosed correctly by the Auguste system. If the CBR module determined that neuroleptic drugs were needed, a RBR module was then invoked to determine which neuroleptic to prescribe. In testing, three of the eight test cases were prescribed neuroleptics. The RBR module only assigned one of these patients the same neuroleptic drug as the physician had prescribed, although the physician believed the system recommendations to be reasonable. This work is an important first step toward realizing the goals of Auguste Project.

6.3 Computers in Diabetes

6.3.1 Control Theory

One major school of thought attributes the difficulty of glycemic control to the open loop nature of insulin delivery. A major branch of diabetes management research has been dedicated to the development of a closed-loop control algorithm that would be capable of managing insulin delivery. (Parker et al., 2001) compiled an overview of the history of control theory approaches to this problem. A subset of the systems described in this paper are summarized below.
One early control theory approach was the “Biostator” algorithm designed by Clemens in the mid 1970’s. Biostator used continuous-flow blood glucose sampling with a dual infusion system. The control algorithm was a non-linear proportional-derivative type. It performed tolerably in tests but “Patient specificity was an issue, as the algorithm would require individualization prior to its use” (Parker et al., 2001).

“Biostator” was improved upon by Bellomo, et al. in the early 1980’s. They added a patient model update algorithm that updated estimated parameters within the main control algorithm. The model updating was based upon minimizing the sum squared error between predicted and actual blood glucose levels. It was an improvement but still required “other patient-specific coefficients” (Parker et al., 2001).

In the late 80’s and early 90’s, both Ollerton and Fisher attempted to use an integral-squared error (ISE) cost function based on the deviation from a desired blood glucose value. Ollerton’s work was found to “result in physiologically unrealistic insulin profiles”, while Fisher’s work was “not robust to patient uncertainty” (Parker et al., 2001). Both of these controllers also suffered from a long sampling time of 180 minutes and could therefore miss important variations in blood glucose levels.

Garcia et. al., as well as Zafiriou and Chiou, attempted to replace feedback-only control approach with a Model-Based Predictive approach. The intent was to be able to predict, and compensate in advance, for hyper and hypoglycemic episodes. Their work showed acceptable performance but they found that “uncertainty in the model... can lead to significant performance degradation” (Parker et al., 2001).
Nearly 30 years of control theory approaches to glycemic control all seem to struggle with the same basic problem: The model used to describe the patient and their reactions to insulin and meals, requires individualization in some way to the given patient. It is known that there is great variability between patients. For instance, most patients’ glucose levels rise during a stressful event, but some patients have the opposite reaction. Examples such as this make defining a generic patient model difficult.

6.3.2 Telemedicine and Decision Support

Two of the major issues related to good control of diabetes are communication between patient and physician and patient compliance. Diabetic patients typically see their doctors every three or four months and have limited, if any, contact between visits. An uncorrected problem that persists for four months can have life altering effects for the patient. Problems with patient compliance are difficult for the physician to overcome. Some patients will not always do as they are instructed. Telemedicine approaches attempt to account for both these issues. By increasing the frequency of patient-physician communication, both patient compliance and problem correction are often improved. Decision support can also help with patient compliance by giving advice on the various therapy choices a patient must make.
Telemedicine is a term used to describe long distance communication between patients and physicians. Telemedicine typically refers to Internet communication, such as email, but can also be used in reference to telephone calls.

Computer aided decision support for the determination of both basal rates and bolus doses has been the subject of many researchers. Decision support has been attempted through algorithmic methods, artificial intelligence and control theory among others.

6.3.3 VIE-DIAB

VIE-DIAB, developed by researchers at the University of Vienna (Popow et al., 2003), is a Telemedicine support program intended to increase the rate at which doctors respond to their patients. VIE-DIAB collects basic data from patients through mobile phone services. The data collected are: glucose measurements, carbohydrate intake, and insulin dosage. VIE-DIAB has a very basic rule based reasoner that classifies the weekly data into four categories: (1) Not enough data, (2) Good glycemic control, no changes needed, (3) Control needs improvement, (4) Control is poor, contact health center. The above classification is presented to the physician along with the data. VIE-DIAB presents the weekly data in a series of daily bar charts representing the amount of time the patients spent with High, Low or Good blood sugars. The researchers believe that these charts are preferable to the
more conventional scatter plot charts used by most doctors. Once the physician has reviewed the data, his recommendations, if any, are relayed to the patient.

VIE-DIAB succeeded in “intensifying the communication between patients and diabetologists” (Popow et al., 2003). However, it also caused an “increased workload for physicians” (Popow et al., 2003). While it is generally accepted that increasing communication will increase the likelihood of good glycemic control, it is the workload of the physician that is the core of the problem to begin with. Increasing physician workload is a significant disadvantage. In addition, VIE-DIAB’s data presentation is useful for a fast high level diagnosis. But many of the problems and conditions faced by diabetic patients require a more thorough analysis than can be achieved by simply noting how often a patient is high or low.

6.3.4 Telematic Management of Insulin-Dependent Diabetes Mellitus

The Telematic Management of Insulin-Dependent Diabetes Mellitus (T-IDDM) project was another telemedicine system that also incorporated AI (Bellazzi et al., 2002). T-IDDM was comprised of two modules: the Medical Unit (MU), to be used by doctors at the hospital; and the Patient Unit (PU), to be used by patients on their home PC’s. The two units communicate with each other and support communication between doctor and patient through what is essentially an email system.
The PU collects the patient’s insulin and meal data and relays it to the MU. The MU will in turn relay any therapy changes the physician makes back to the PU. The MU also contains a RBR system to provide decision support to the physician. The RBR system was found to have difficulty with very poorly controlled patients and a CBR module was added. The CBR module is not used to provide direct decision support. Instead, it modifies the rules and constraints of the RBR system in an attempt to improve its performance.

T-IDDM underwent an 18 month feasibility study at various hospitals in Europe and the results were encouraging. Communication between doctors and patients was greatly increased and the number of therapy changes doubled.

Montani et al. developed a Multi-Modal Reasoning system for decision support of the treatment of diabetes for use within the T-IDDM project (Montani et al., 2000). The core of their system was a rule-based reasoner dedicated to suggesting changes to treatment. The RBR was enhanced by both a Model-Based component and a Case-Based component. The MBR they used is a statistical method that attempts to derive a “modal-day” for each patient based upon several weeks of past data. This MBR only takes into account blood glucose readings and insulin dosages. If it is able to generate a modal day, then it draws conclusions about the patient’s reaction to insulin. These conclusions are then used to tailor the RBR to the specific patient. If the MBR is unable to generate a modal-day from the patient information, the CBR module comes into play and attempts to tailor the RBR to
the specific patient based on past cases. The MMR system was tested on a diabetic patient simulator and the results were encouraging. This work is valuable because it demonstrates the feasibility of combining multiple reasoning paradigms into one system for the treatment of diabetes.

6.3.5 Computer Assisted Meal Related Insulin Therapy

Researchers at the Institute of Physiology and Biochemistry and Nutrition in Kiel Germany developed the Computer Assisted Meal Related Insulin Therapy (CAMIT) system (Schrezenmeir et al., 2002). The CAMIT algorithms took as input: insulin sensitivity, blood glucose level, and carbohydrates. Bolus doses are calculated before each meal based upon the time of day, estimated carbs to be consumed, intended level of physical activity and current glucose level (Schrezenmeir et al., 2002). The basal rate is calculated based on the late night and next morning blood glucose levels (Schrezenmeir et al., 2002).

The CAMIT algorithms were implemented on pocket computers, and a study was done to verify that the advice provided by the algorithms could be useful to diabetic patients. When compared with the control group, the CAMIT group showed significant improvement in glycemic control over the course of the 6 month study. However, glycemic control still varied greatly and hypoglycemic episodes still occurred. This study did demonstrate that computer aided decision support can be an asset to diabetic patients. However, given the variability from patient to patient regarding how
their blood glucose levels are affected by daily events, such as stress and exercise, it is unlikely that a purely algorithmic solution can be found that will work universally for diabetic patients.
Chapter 7

Summary and Conclusions

This thesis has presented work in problem detection for situation assessment in Case-Based Reasoning for diabetes management. Twelve situation assessment routines were developed. These routines have been incorporated into a prototype Case-Based Reasoning decision support system. This CBR system is important because CBR has never been applied as the primary reasoning module for the purpose of diabetes management. Demonstrating success in this area may motivate others to attempt a CBR based approach to the management of other chronic diseases. In addition to research value, successful development of a CBR decision support system would have practical value to physicians and diabetic patients.

The situation assessment module alone as well as the complete CBR system have many potential applications. The routines have already been demonstrated to be of use to physicians as a method of analyzing large volumes of blood glucose and life-event data provided by diabetic patients. In addition to assisting diabetes specialists, the system could be used by primary care physicians who are not diabetes specialists but still have diabetic patients. The situation assessment module could automatically detect problems in the patient data, while the CBR system could assist the physician by recommending therapy adjustments. This work could also be incorporated into
future generations of insulin pump devices, allowing the pump to detect problems as they occur and generate advice on how to handle them.

Contributions of this thesis include:

1. Design and implementation of twelve situation assessment routines for automatic problem detection

2. Design and implementation of text-based daily reports and the DataGraph visualization tool to assist physicians with manual problem detection

3. Knowledge acquisition from physicians as they adjust patient therapy, in collaboration with other graduate students

The text-based daily report aggregated and displayed the extensive amount of data collected from the patients in the pilot study. The DataGraph program allowed physicians to review the patient data quickly and easily in a graphical format. Upon its completion, the DataGraph program became the primary method of displaying the patient data, and the textual reports were used as a supplement. Both tools enabled knowledge acquisition from physicians about diabetes management. Throughout the pilot study, both the DataGraph program and the textual reports were used in weekly knowledge acquisition meetings. Physicians Frank Schwartz and Jay Shubrook analyzed their patients’ data, identified problems and recommended therapy changes. Outcomes of therapy changes were noted in subsequent meetings. These problems, solutions and outcomes became the cases for the CBR system.
Many of the problems noted during knowledge acquisition became the basis for situation assessment routines. Twelve situation assessment routines were developed, tested and evaluated. The routines were evaluated by a panel of four diabetes specialists. Evaluators were shown actual system outputs and asked to provide feedback via a structured questionnaire. Responses regarding whether or not the system was correctly identifying problem were primarily positive (77.5% positive, 7.5% negative, 15.0% neutral). Responses also indicated that the evaluators felt that the system would be useful to both patients (87.5% positive, 2.5% negative), and physicians (90% positive, 2.5% negative) for the management of diabetes. The situation assessment module represents an important component of the final CBR decision support system for diabetes management. Future work for the situation assessment module will include the development of new situation assessment routines to detect additional problems and the incorporation of a nutritional database to provide additional information to the situation assessment module.

Results of the preliminary clinical study to determine the feasibility of providing case-based decision support for diabetes management have been reported in (Marling et al., 2008). A U.S. patent application, “System and Method for Managing Diabetes” has been filed. A second clinical research study is currently underway at the Ohio University College of Osteopathic Medicine. During this study, additional work on the prototype CBR system will be undertaken, seeking to increase system knowledge and competence.
Bibliography


Appendix A

Example Daily Report

Report for Patient #1
Date of Birth:  1949-12-13
Gender:       M
Height:       68
Age of Onset: 17
Pump Start:   2003-11-01

Blood glucose Targets for Patient#1
Targets assigned on: 2003-11-01
HighTarget: 150
LowTarget: 70

Carb Ratios for Patient#1
Carb Ratios assigned on: 2006-02-16
Starting at 00:00 carb ratio is 13

Basal information
Basal Rate of .35 was assigned on 2006-02-16 00:00:00
Basal Rate of .55 was assigned on 2006-02-16 06:00:00
Basal Rate of .5 was assigned on 2006-02-16 20:00:00
Basal Rate of .35 was assigned on 2006-02-16 21:30:00

Basal Rate of .35 was assigned on 2006-03-09 00:00:00
Basal Rate of .55 was assigned on 2006-03-09 06:00:00
Basal Rate of .5 was assigned on 2006-03-09 20:00:00
Basal Rate of .3 was assigned on 2006-03-09 21:30:00

Insulin Sensitivity for Patient#1
Value: 120
Assigned on: 2006-02-22

Insulin Sensitivity for Patient#1
Value: 100
Assigned on: 2006-02-16
HbA1c for Patient#1
Value: 6.3
Taken On: 2006-03-30

HbA1c for Patient#1
Value: 6.1
Taken On: 2006-01-05

Insulin_Type for Patient#1
Insulin Type: Humalog
Started on: 1111-01-01

Occupation for Patient#1
Intensity: 4
Title: Social Worker

Pump Information Patient#1
Started this pump on: 2003-11-01
Manufacturer: Medtronic
Model: Paradigm512

Relatives of Patient#1 with diabetes
Relation: Brother
Diabetes Type: 1
Age of Onset: 16
Side of Family: null
Complications: No Complications

Weight of Patient#1
Weighed 151 on 2006-02-15

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12:10  TWork  TWork
16:00  FWork  FWork  FWork  FWork  FWork  FWork  FWork
16:10  Exer  Exer  Exer  Exer  Exer  
18:00  Din  Din  Din  Din  Din  
18:30  
23:30  Bed  Bed  Bed  Bed  Bed  

Daily Exercise Table

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<tr>
<th>Int</th>
<th>Type</th>
<th>Desc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mon</td>
<td>5   Aerobic/ Resistance</td>
<td>Walk, jog, cybex machines</td>
</tr>
<tr>
<td>Tue</td>
<td>5   Aerobic/ Resistance</td>
<td>Walk, jog, cybex machines</td>
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<tr>
<td>Wed</td>
<td>5   Aerobic/ Resistance</td>
<td>Walk, jog, cybex machines</td>
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<td>Thr</td>
<td>5   Aerobic/ Resistance</td>
<td>Walk, jog, cybex machines</td>
</tr>
<tr>
<td>Fri</td>
<td>5   Aerobic/ Resistance</td>
<td>Walk, jog, cybex machines</td>
</tr>
<tr>
<td>Sat</td>
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<td>none</td>
</tr>
<tr>
<td>Sun</td>
<td>none</td>
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</tr>
</tbody>
</table>

Report for patient 1 for Friday 2006-02-17 00:00:00

Total Bolus Insulin for the day was 14.7
Total Basal Insulin for the day was 11.425
Total Insulin for the day was 26.125

Bolus was 56.26794 percent of the daily insulin intake
Basal was 43.73206 percent of the daily insulin intake

Fingerstick information
At 2006-02-17 05:00:00.0 fingerstick reading was 131
At 2006-02-17 07:45:00.0 fingerstick reading was 194
At 2006-02-17 08:35:00.0 fingerstick reading was 132
At 2006-02-17 11:20:00.0 fingerstick reading was 132
At 2006-02-17 12:00:00.0 fingerstick reading was 92
At 2006-02-17 14:00:00.0 fingerstick reading was 79
At 2006-02-17 14:40:00.0 fingerstick reading was 88
At 2006-02-17 16:20:00.0 fingerstick reading was 95
At 2006-02-17 17:32:00.0 fingerstick reading was 121
At 2006-02-17 18:00:00.0 fingerstick reading was 126
At 2006-02-17 20:30:00.0 fingerstick reading was 144
At 2006-02-17 22:00:00.0 fingerstick reading was 49
At 2006-02-17 22:45:00.0 fingerstick reading was 165
At 2006-02-17 22:47:00.0 fingerstick reading was 165

Meal information
Patient had Breakfast at 2006-02-17 08:30:00.0
Estimated Carbs 38
Breakfast included:
2 tablespoon(s) Peanut Butter
2 cup(s) Coffee with milk
1 slice(s) whole wheat toast

Patient had Lunch at 2006-02-17 11:20:00.0
Estimated Carbs 46
Lunch included:
5 whole Hersheys Kisses
1 cup(s) beef and veggies
1 whole subway wheat wrap

Patient had Dinner at 2006-02-17 18:10:00.0
Estimated Carbs 58

Bolus information
normal with dose 1.9 administered at 2006-02-17 07:45:00.0
dual with dose 2.7 administered at 2006-02-17 08:40:00.0
dual with dose 2.2 administered at 2006-02-17 11:20:00.0
normal with dose 1.4 administered at 2006-02-17 12:00:00.0
dual with dose 4.5 administered at 2006-02-17 18:10:00.0
normal with dose .5 administered at 2006-02-17 20:30:00.0
dual with dose 1.5 administered at 2006-02-17 22:50:00.0

Work information
Went to work at 2006-02-17 08:20:00.0
and came home at: 2006-02-17 15:45:00.0
at intensity 4

Exercise information
Exercised at 16:00
description: Power Walk and Racquestball
at intensity 6
for null minutes

Sleep information
Went to bed at: 2006-02-17 00:00:00.0
and woke up at 2006-02-17 05:00:00.0

Hypo Event Information
Hypo event began at 2006-02-17 22:00:00.0
Symptoms were weak sleepy irritable
During the event the following action was taken: banana, orange juice
Infusion set was changed at 2006-02-17 07:40:00.0
New set was placed at right side abdomen