

**A NOVEL BLOOD GLUCOSE
CHARACTERISATION SYSTEM FOR TYPE 1
DIABETES**

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Abstract

Title: A novel blood glucose characterisation system for type 1 diabetes.

Key Terms: Basal insulin; blood glucose control; insulin calculation; bolus insulin; equivalent teaspoons sugar; ets; glycaemic control; insulin regime; insulin recommendations; type 1 diabetes; glucose characterisation.

The correct administration of insulin is a constant challenge for type 1 diabetics. The correct insulin regime leads to fewer complications and an easier way of life. The amount of insulin administered must take into account the meals eaten, previous administered insulin, exercise etc.

A rapid process for determining insulin regimes that is accessible to type 1 diabetics will greatly reduce diabetic complications later in life. This study researches such a process. Software is developed to use the ets-concept to simulate blood glucose levels. From these simulations blood glucose characterisation can be done to propose insulin regimes.

Data gathered in previous studies is used to verify the results of this process. These results are compared to factors that describe the accuracy of a person's blood glucose control. The effects the new regimes will have are used to make recommendations to the end-user.

Accurate characterisation leads to insulin regimes that will improve the control performance of type 1 diabetes.

Samevatting

Titel: A novel blood glucose characterisation system for type 1 diabetes.

Sleutel terme: Basale-insulien; bloedsuikerbeheer; insulien bepaling; bolus-insulien; ekwivalente teelepels suiker; ets; insulien skedule; insulien voorstelle; tipe 1 diabetes; glukose karakterisering.

Die korrekte toediening van insulien is 'n konstante geveg vir tipe 1 diabete. Die regte insulien skedule het minder komplikasies tot gevolg en sorg vir 'n makliker lewe. Die hoeveelheid insulien wat toegedien word moet die etes wat geneem is, vorige insulien toedienings, oefening ens. in berekening neem.

'n Vinninge proses waarmee insulien schedules bepaal word en wat toeganklik is vir tipe 1 diabetes sal die risiko van diabetese komplikasies later drasties verminder. Hierdie studie ondersoek so 'n proses. Sagteware wat die ets-konsep gebruik om bloedsuiker vlakke te simuleer is ontwikkel. Vanuit hierdie simulaties kan bloedsuiker gekarakteriseer word om nuwe insulien skedules voor te stel.

Vorige studies se data is gebruik om die resultate te verifieer. Die resultate is vergelyk met faktore wat die akkuraatheid van bloedsuikerbeheer bepaal. Die uitwerking van die nuwe skedule is gebruik om voorstelle te maak vir die eindgebruiker.

Akkurate karakterisering het insulien skedules wat beheer vir tipe 1 diabete verbeter tot gevolg.

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Also thanks to my parents, brothers, my sister and my wife. Their support and encouragement made this study possible.

Abbreviations

WHO: World Health Organisation

ADA: American Diabetes Association

BMI: Body Mass Index

CGM: Continuous Glucose Monitor

ETS: Equivalent Teaspoons Sugar

CSV: Comma Separated Value

BGCP: Blood Glucose Control Performance

AUC: Area Under Curve

ABCM: Area Between Curve and Mean

CHO: Carbohydrates

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1. Introduction

Diabetes is one of the fastest growing diseases in the world with over 240 million diabetics worldwide. Diabetics struggle with insulin dosages to control blood glucose levels daily.

1.1. Background

1.1.1. Diabetes

Genetics and lifestyle are the two major risk factors for the development of Diabetes Mellitus. There are three types of diabetes namely type 1, type 2 and gestational diabetes. Although the symptoms are similar, their cause and physiology are different.

Type 1 diabetes is also known as insulin-dependent diabetes. This disease causes the pancreas to produce very little or no insulin, therefore not enough to sustain the patient. Insulin is essential for storing glucose in the blood as glycogen in the liver and muscle tissue, but also to later utilise it for energy. Previously type 1 diabetes was called Youth-Onset diabetes because it was so often diagnosed in children. Type 1 diabetes can however be diagnosed at any age [1].

Although type 1 diabetes is a manageable condition, it is life-threatening. The cessation of insulin production in the body causes blood sugar levels to increase rapidly. If carbohydrates are ingested without insulin to remove the excess sugar from the blood, blood glucose levels could increase to dangerous levels, leading to complications. These include the possibility of a hyperglycaemic coma or even death.

The most common type of diabetes is type 2 diabetes. It is a condition where the body becomes insulin resistant. Reduced insulin production often also plays a role. The pancreas of type 2 diabetics still produces the hormone insulin. Many factors contribute to the development of diabetes. These include a sedentary lifestyle (lack of exercise), incorrect diet and prolonged emotional stress.

Type 2 diabetes is managed through lifestyle interventions such as correct diet, exercise and stress reduction. Medication to lower blood glucose levels, such as Metformin, is also used. If these interventions fail to achieve acceptable glycaemic control, insulin administration is usually prescribed.

Finally, the least common form, gestational diabetes, is usually a temporary condition experienced during pregnancy. However, gestational diabetes carries a risk factor for

the development of type 2 diabetes later on in life for women. Between 5 - 9% of pregnant women are affected.

In many developed countries diabetes has reached epidemic proportions. New legislation and intervention programs are coming to light to help reduce the progression of diabetes. Only time will tell if these intervention programs will be successful.

Diabetes is also an increasing problem in the rest of the world. It is the fastest growing disease in the world [2]. This can be ascribed to many factors. One of the main causes is obesity which would explain the steep rise of diabetes in the world today [3],[4],[5]. Because of the fast food industry and the so-called “Playstation generation”, obesity in the youth is increasing at alarming rates. This could also lead to an increase in prevalence of diabetes among the youth [6], [7].

According to the WHO (World Health Organisation) there were 171 million people with diabetes in 2000 [2]. This is estimated to increase to 300 million by 2030. This figure was determined assuming obesity prevalence doesn't increase. At the rates that obesity is increasing, this can be seen as an underestimation.

Prevalence in developing countries is estimated to increase much faster than in developed countries. Shown in Figure 1 is the estimated growth of diabetes in developed countries. Figure 2 paints a much bleaker picture for developing countries as the largest increase is shown to occur there.

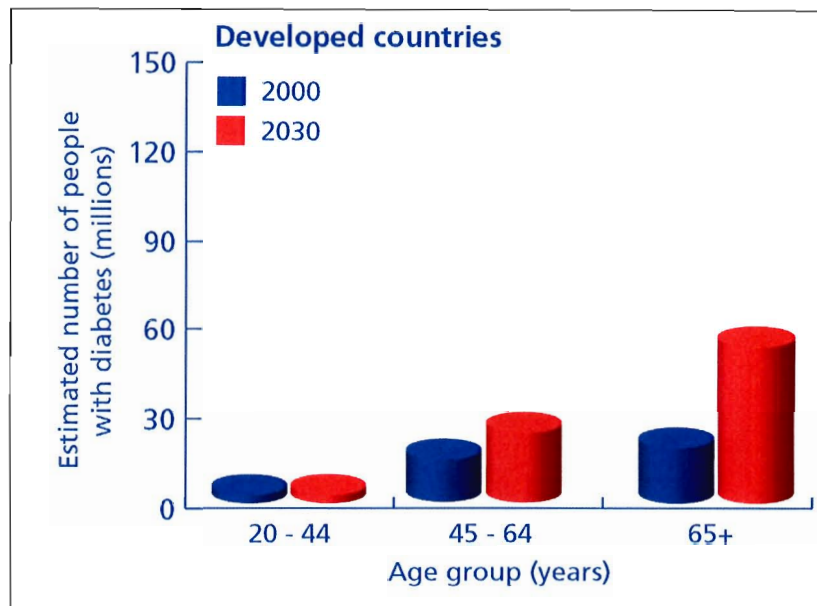


Figure 1: Estimated growth of diabetes in developed countries [2]

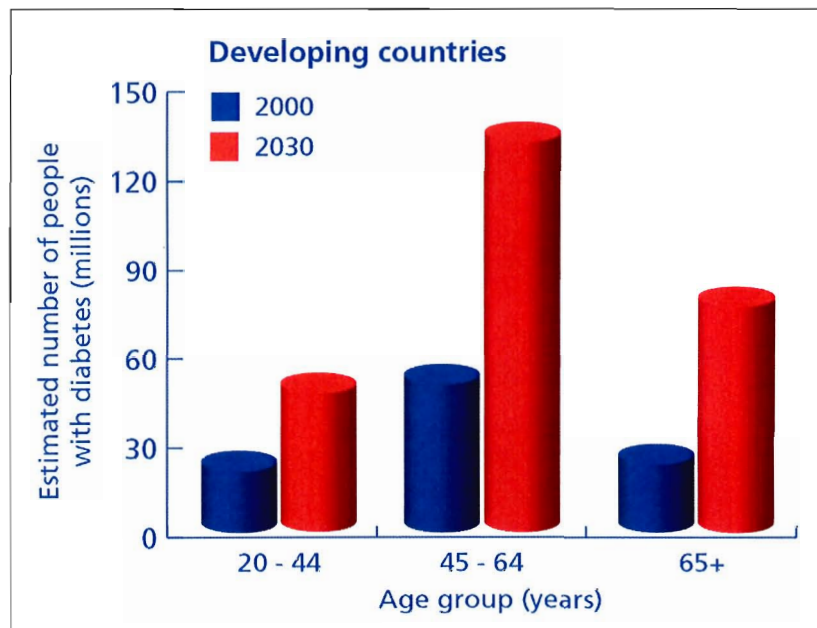


Figure 2: Estimated growth of diabetes in developing countries [2]

When comparing Figure 1 and Figure 2 with the graph in Figure 3, it is easy to see that the growth in developing countries will form the biggest part of the growth across the world. According to Wild et al, this can mostly be attributed to the effect of urbanisation [2].

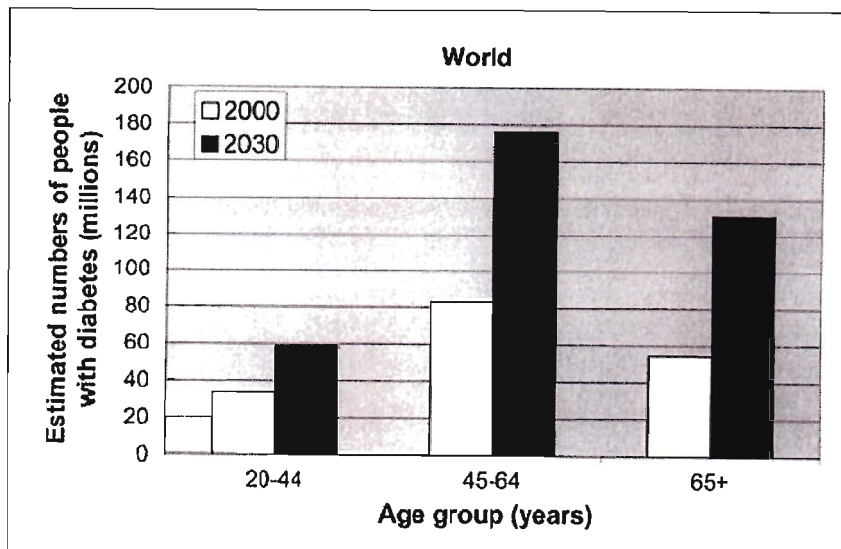


Figure 3: Estimated growth of diabetes in the world

More alarming than the growth rate of diabetes is the mortality rate it incurs. According to Gorelic et al, mortality caused directly by diabetes in 2000 was 2.9 million deaths [8]. This is 5.2% of all-cause mortality in the year 2000. It is comparable to the mortality rate of HIV/ AIDS in 2000.

It is not widely known that the mortality rate of diabetes is this high. The fact that the cause of death is usually ascribed to one of the many complications of diabetes and not diabetes itself also contributes to this.

Diabetes is regarded by most as a disease that is easily lived with. In contrast, it can actually be a frustrating and life threatening disease. It is a disease that causes a great many people to struggle through life each day.

1.1.2. Impact of diabetes

Diabetes causes several short- and long-term complications. The risk for these complications can be reduced by managing blood glucose levels. This is mainly done through medication, exercise, healthier diet and stress reduction.

The complications of type 2 diabetes usually develop over prolonged time periods. Therefore type 2 diabetics are often diagnosed long after their blood glucose control characterised that of diabetes. In that time irreversible damage can be done that may lead to complications later in life.

For most people with type-2 diabetes, routinely taking their medicine is all that is required to keep diabetes complications at bay. It is also required to follow a healthy diet and make sure that the body stays healthy. Generally, if medication is prescribed and used correctly, diabetes may have little effect on a diabetic's life.

Type 1 diabetics find it more difficult and stressful to deal with diabetes. Insulin has to be administered regularly. Dosages should be matched to account for various factors including current blood glucose levels, food intake (portion sizes, macronutrient composition), physical activities, emotional stress or illness.

Blood glucose control for the type 1 diabetic is therefore a difficult and time consuming task. A lot of trial-and-error work is needed to establish good glycaemic control. The patient and medical care provider have to first figure out how the individual's body responds to these factors and then fine tune treatment programs.

A non-diabetic's blood glucose level is usually controlled within a tight range, between 4 and 8mmol/l (millimole per litre). The body acts as an engineering control system to keep levels as steady as possible. Typical blood sugar levels for a healthy person are shown in Figure 4 [9]. When the blood glucose levels rise, insulin is secreted by the pancreas to store the glucose as glycogen.

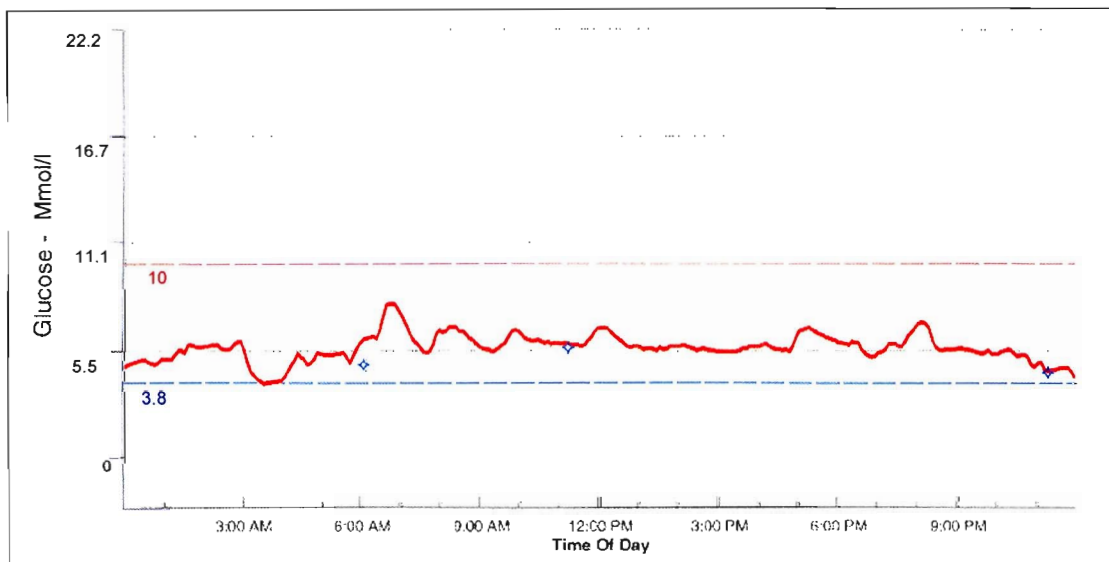


Figure 4: Example of healthy person's blood glucose levels

There are also several counter-regulation hormones including glucagon, cortisol, adrenalin and growth hormone. These hormones promote the release of glucose from

glycogen stores (liver) into the blood when blood glucose levels fall too low or when more energy is needed.

For a person with type-1 diabetes, these levels could vary between two and 25 mmol/l. Blood glucose levels close to these extreme levels are very dangerous. Below two mmol/l, the person falls into a hypoglycaemic coma. It could also result in death in severe cases [10]. At the high extreme, hyperglycaemia causes long term problems that may only surface months or even years later.

Events where blood sugar falls too low are called hypoglycaemic events. Many literature sources define the hypoglycaemic threshold as 3mmol/l [11]. If it falls too low beneath this threshold to a level of 2.2mmol/l [12], the body could go into a coma in order to protect itself. Different sources however, publish different threshold values.

Awareness to hypoglycaemia is characterised by feeling faint, light headed and without energy. With time many diabetics lose their ability to sense hypoglycaemic excursions in time. Consuming carbohydrate-rich foods such as glucose can counteract such an event. Glucagon injections are also used in severe cases of hypoglycaemia.

Events where blood sugar rises too high are called hyperglycaemic events. These are also very dangerous as the damage they cause is mostly not immediately apparent. These are the long term effects of diabetes. These effects may only manifest years later and could cause considerable discomfort in life.

These effects include complications such as retinopathy [13] , hypertension [14] and many more. One of the most common complications is diabetic retinopathy, which could eventually lead to blindness. Nearly all patients with type-1 diabetes develop this condition during some stage in their life [15]. Nearly 77% of type-2 patients who survive more than 20 years with diabetes develop this condition.

Some of the long term effects are (mostly due to hyperglycaemia):

- Retinopathy
- Hypertension [16]

- Diabetic nephropathy [17]
- Diabetic foot [18]

Some of the short term effects are (mostly related to extreme hyperglycaemia or hypoglycaemia):

- Central nervous system symptoms.
- Confusion
- Aberrant behaviour
- Hypoglycaemic coma

1.1.3. The diagnoses of diabetes

The body's natural responses to ingesting glucose can be used to diagnose diabetes in a person. A person's blood sugar levels are expected to be at certain levels at certain times after consuming glucose. If it is higher than expected, the person may be classified after further testing.

The diabetes community is divided over the question of what those levels are [19]. The two main societies that have proposed diagnosis criteria are the WHO and the ADA. Their criteria differed and even went as far as to suggest that different tests be used [20]. This made it difficult for countries and doctors to decide on the criteria for diabetes diagnosis.

In 1999 the WHO published new criteria that promised to predict the onset of diabetes more accurately [21]. A study by Gabir et al has shown that more people with high risk are identified [22]. These criteria increase the prevalence of diabetes. Still many countries are in doubt as to which criteria they should adopt [22].

This illustrates that even diagnosing diabetes is a difficult and arduous task. After diagnosis has occurred, neither the doctor nor the patient knows how intensive treatment should be. An insulin regime must be compiled for the patient. The cornerstone for successfully surviving diabetes is accurate blood glucose control. The person's insulin regime determines how successful that person's blood glucose control is.

1.1.4. Insulin regimes for type 1 diabetics

There are two main types of insulin available to type-1 diabetes patients, long acting insulin (basal) and rapid or short acting (bolus). Mixes are combinations of basal and bolus. Recently inhaled insulin was launched and is a form of short acting insulin [23].

Bolus insulin is only active in the system for a few hours. This is typically taken before a meal. The main goal of bolus insulin is to store glucose present in the blood as glycogen in the liver and muscles [24]. This action is only required after a meal. Insulin's response is usually slower than the absorption of carbohydrates from a meal therefore it is usually administered prior to a meal.

Basal insulin is active in the system for up to 20 to 36 hours [25]. It also depends on the make of the insulin as each one is different. This is typically taken once a day. The goal of this is to allow cells to utilise glucose for energy. Glucose is slowly released throughout the day into the blood from the glycogen stores [24]. As such, there has to be basal insulin in the person's body at all times.

It can be seen how the two types complement each other. The typical day of any type-1 diabetic consists of taking their basal insulin once a day and their bolus a few times before each meal. If the correct dosages are taken, the person's glycaemic control should be tight and he should live a relatively normal life.

In the event of a hypoglycaemic event, the body has emergency stores to normalise blood glucose levels [26]. Organs like the liver have ways to stabilise blood glucose levels. Glycogen stored can be released as glucose into the blood in response to counter regulation hormones such as glucagon, cortisol and adrenalin. The problem with this is that these stores are limited and the efficiency of the regulation ability can decrease over time.

If the counter regulation system is overused, its efficiency will decrease. If it is required later in a real emergency (e.g. insulin overdose) it may not be effective enough to avoid disaster. Basal insulin forms the basis of each patient's regime. It becomes easier to control the absorption of glucose with bolus if the glucose is efficiently being utilised for energy at the correct rate, controlled with basal insulin [27]. As such it is vitally important that the correct basal dosage be determined early.

The current method for determining insulin dosages is inaccurate at best. Most commonly the patient's weight is divided by four. This then equals the units of basal insulin that forms the basis of the patient's daily regime. The daily bolus dosage should also be equal to this amount.

In a follow-up visit weeks later it is determined whether the average blood glucose level was too high or too low. The dosages are then adjusted according to this. The same happens again and again until an acceptable level is reached. So the regime is determined by trial-and-error, taking a long time and causing the patient discomfort.

1.2. Defining the problem

1.2.1. Problems with current methods for determining insulin regimes

As discussed in the previous section, currently insulin regimes are determined using trial-and-error methods. The problem this presents is that it doesn't take the individual's body characteristics into account. Each person differs in weight, height, BMI (body mass index), daily activity level etc.

Furthermore, the rate and effectiveness in which the body absorbs glucose, the resistance to insulin and energy expenditure rates also differs from person to person. This means for one person the current method may work, and another may never find the correct dosage using this.

The first and most obvious problem with this is the time it could take. It can take months or even years to determine a suitable regime. And even then it may not be optimal, but at least passable. During this time hyperglycaemic and hypoglycaemic events could and almost certainly will occur.

In this time the patient will want to keep the hypoglycaemic events as few as possible, thus he will rather keep his blood sugar levels too high. This is because of the fear most patients have of hypoglycaemia that is seen as far worse as hyperglycaemia. This leads to the long-term hyperglycaemic complications of diabetes that may only surface years later.

Another problem that often occurs especially during the first few years of diabetes is insulin over dosage. Patients use too much insulin causing blood glucose levels to fall too low. The counter regulation system then secretes hormones such as glucagon and cortisol to increase the blood glucose level again to prevent hypoglycaemia. Therefore the storage (insulin) and release (glucagon) hormones counteract each other.

This puts stress on the counter regulation system and will gradually decrease the counter regulation system's efficiency. This result in a gradual decline of maximum hepatic glucose output, increasing the risk that hypoglycaemia will occur more often and unexpectedly.

Secondly, the cost involved in such a procedure should be considered as this could grow very rapidly. If the patient has to repeatedly visit the doctor, it could become very expensive. Because blood glucose control is poor, the patient may end up in hospital a few times with complications that are costly to treat.

1.2.2. Inadequacies of new technologies available for diabetes

There are a few technologies available that could make this whole process easier. A few of them can be used constantly and others are used during the trial-and-error process.

CGM

The CGM (Continuous Glucose Monitor) is a very useful invention that takes a blood glucose reading every five minutes. It has memory capacity to store data for up to seven days of data. Most of the CGM's come with software bundled that produce graphs of the patient's blood glucose levels. Such a graph is shown in Figure 5.

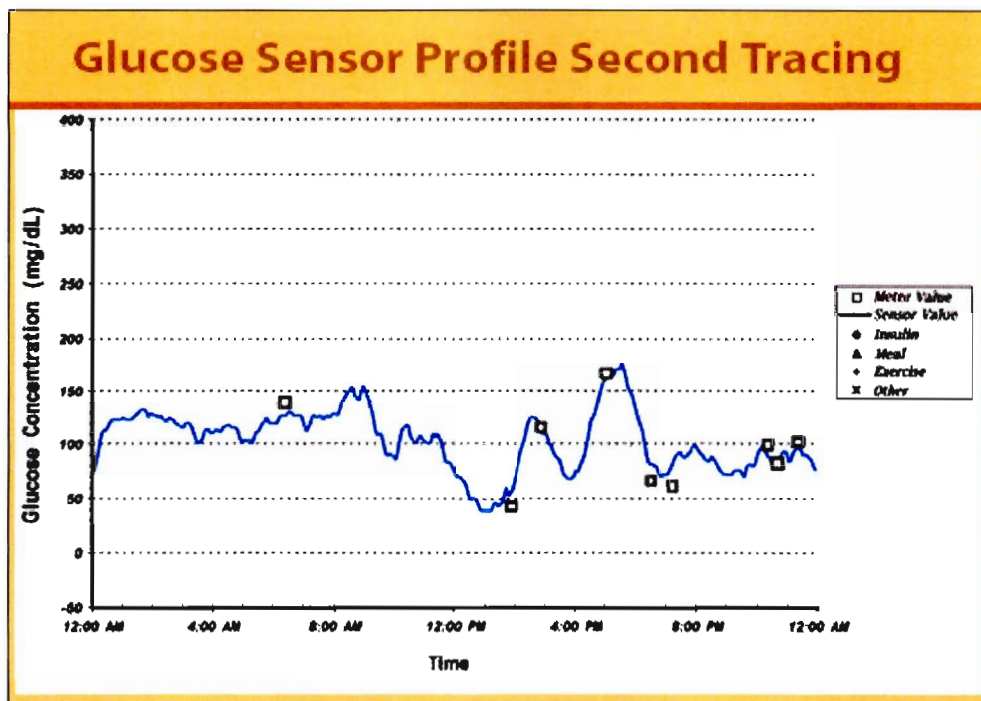


Figure 5: Example of graph produced by CGM software

Pros

- Grants access to information not previously accessible. Trends and full profiles can be seen unlike finger prick monitors used that only give a few isolated measurements.
- Precise history of glucose levels.

Cons

- Expensive.
- Only a limited time period (3 – 7 days) worth of data is recorded with an expensive sensor that can only be used once.
- Graphs are difficult to decipher. Differential concepts are difficult to understand especially in the medical world where mathematics does not play a very important role.
- The graph alone gives little insight into the person's food intake and insulin administration.
- Software provided is not user-friendly and more suitable for laboratory applications.

- The glucose sensors are very expensive and should be replaced frequently.

From the points above it is obvious that the CGM is currently not a long term solution in itself. Permanent use of current systems will be too expensive. The current software bundled with it is of little use in the determining the dosage for the patient. Knowledge of engineering control systems is needed to analyse and use the graphs.

Insulin pump

Insulin pump or continuous subcutaneous insulin infusion (CSII) technology administers insulin on demand. The patient enters a dosage value. Some pumps have simple calculators that take the current BG (blood glucose) level and mass of carbohydrates into account to predict a bolus insulin dosage value. Only rapid acting insulin is used in this sort of therapy [28]. Basal insulin is administered by using rapid insulin that is secreted gradually over a 24 hour period. Figure 6 shows an example of such technology.

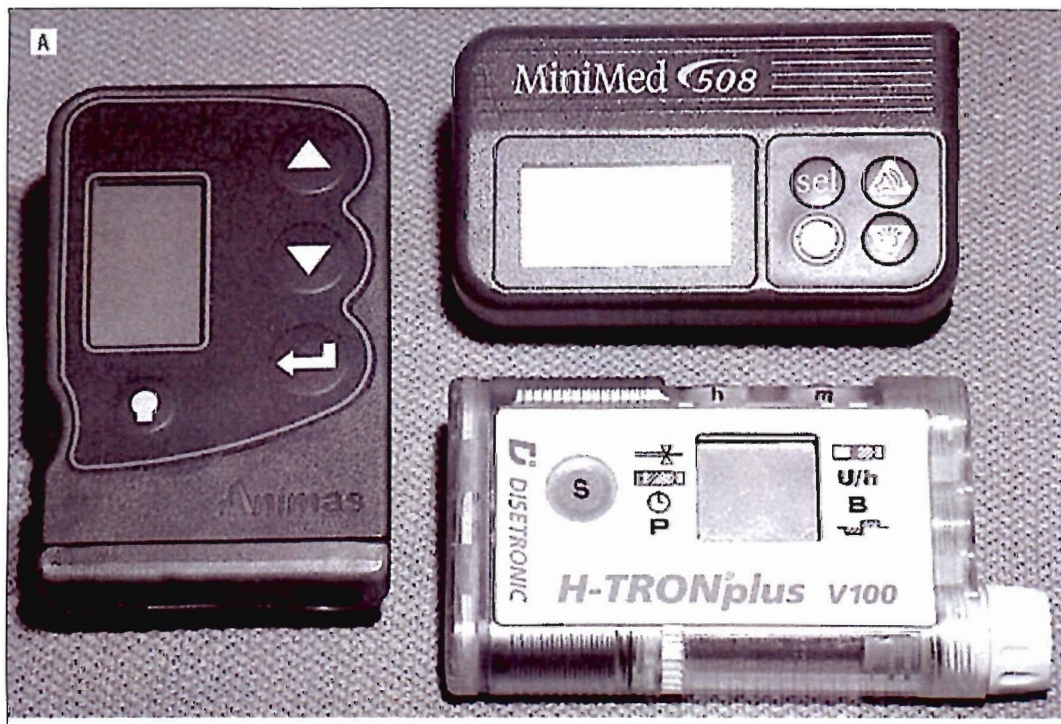


Figure 6: Example of insulin pumps

A study by Bode et al has shown the possible benefits from a treatment like this [28]. On the other hand a study by Chen et al has shown little difference in pregnant woman with diabetes between CSII and normal injection therapy [29]. In this case the persons on CSII actually fared slightly worse.

Pros:

- Insulin data is recorded by the devices for later analysis.
- Less intervention required by patient.
- Lower HbA1c levels.
- Better glycaemic control [30].
- Greater flexibility in lifestyle for patients.
- Reduces the number of hyper- and hypoglycaemic events.

Cons:

- Cost.
- Inconvenience caused by permanently wearing pump.

The biggest problem with this technology is the cost involved. It is not affordable to all patients. This limits its use as a long term solution. As technology advances, it may become cheaper and more reliable, but another solution is needed that can be made available to all patients.

1.2.3. Identifying a new and unique need

The need to establish accurate insulin regimes for type 1 diabetics that result in acceptable glycaemic control has been identified. Furthermore an easy to use procedure is needed to determine how the individual's body responds to various factors that play a role in glycaemic levels. The procedure should reduce the time, cost and inconvenience for finding an acceptable insulin regime.

CGM is a technology that could contribute to this end, but it is not a comprehensive solution in itself. Another technology is needed that augments the CGM technology in the previous section to solve the problems identified. Therefore a new technology is proposed that utilises CGM technology to address this need.

1.3. Contributions of this study

The aim of the study is to achieve the following outcomes:

- Develop a new understanding of blood glucose characterisation of type 1 diabetics
- Utilising CGM technology to calculate, by means of data analysis and simulation, an individual type 1 diabetic's blood glucose response sensitivities to insulin and carbohydrates.
- Calculating a proposed insulin regime for a diabetic based on the insulin and carbohydrate sensitivities calculated.
- Developing a user-friendly practical application for use by the medical doctor to help establish insulin regimes for type 1 diabetics.
- Reduce the overall time taken to establish an acceptable insulin regime
- Verify the results provided by the developed system

1.4. Outline of this document

This study consists of 5 chapters. References and an appendix are also included.

Chapter 2 explores the concept of blood glucose characterisation. The factors that are taken into account in this characterisation are also discussed. The requirements of a characterisation system are defined as well.

Chapter 3 discusses the design and implementation of a characterisation system. The full life cycle of the software is explored.

Chapter 4 verifies the results of the characterisation system in terms of blood glucose control performance.

Chapter 5 serves as the conclusion and closure for this study. Recommendations for further study are also made.

2. Researching a blood glucose characterisation system for type 1 diabetics

This chapter explores what blood glucose characterisation is and also the different factors that should be considered.

2.1. Prelude

This chapter explores what blood glucose characterisation is as well as the different elements that should be taken into account when characterisation is performed. The glycaemic effect of meals, insulin, energy expenditure and counter regulation hormones will be investigated.

The characterisation device is based on the ets-concept, initially developed by Mathews and Botha [31]. It was shown that ets is a better predictor of glycaemic response than the mass of carbohydrates currently being used by most conventional blood glucose simulation technologies.

It is further shown how the basal insulin regime for a type 1 diabetic can be established by using the blood glucose characterisation results. A new measure of rating blood glucose control performance was developed by Mathews and Townsend [32].

2.2. Defining a characterisation system

2.2.1. Definition of blood glucose characterisation

For the purpose and scope of this study, blood glucose characterisation is the process of determining the patient's blood glucose response characteristics. This is done especially for ets ingestion (from carbohydrates in meals), insulin administration and energy expenditure. This study focuses exclusively on type 1 diabetes patients.

These characteristics are defined as sensitivity values expressing the amplitude blood glucose response per unit factor, measured in isolation of the other major factors. Therefore the ets-, insulin- and energy expenditure sensitivities can be determined for a specific patient. By knowing what the patient's sensitivity values are, a better treatment program can be developed to improve blood glucose control of the diabetic patient.

2.2.2. Analysing operational needs and environment

Doctors have limited time when dealing with patients. They are often swamped with patients and therefore try to see as many patients a day as possible. Because of this, doctors don't have time to run through complex and time consuming processes to diagnose or treat a patient.

Doctors need simplified solutions to aid them in treating patients. Results must be obtained in a short time. A better solution would entail that the doctor does not have to do any preliminary work. If an assistant could do that, it would free up the doctor's time. The doctor only needs the results such a system produces.

This would mean a short consultation with the patient is all that the doctor needs to do. More patients can therefore be accommodated. The solution to this study needs to be easy to use and understand. An assistant can do all the input into the system without an extensive medical background or formal computer training.

Time isn't the only or even the most important factor for the system. Another important factor to consider in such a system is accuracy. The doctor and the patient want the best treatment possible.

The goal is to improve glycaemic control and make control easier. To this end the system needs to be more accurate than current methods. It also needs to give the solution faster. Current methods of determining insulin regimes can take months as described in section 1.2.1.

The time-frame to determine a proposed calculated regime is a few days. This starts with the patient's first consultation. It ends with an insulin regime prescribed that will promote improved glycaemic control. This means fewer hyper- and hypoglycaemic events occurring and tighter blood glucose control.

Most doctors' consultation rooms don't have the most up-to-date computer systems installed. Any solution would need to run on basic computer systems that may be a few years old. It has to be compatible with the most commonly used systems used in houses and small businesses.

A prerequisite is real-time blood glucose information. Such technologies have become available and are referred to as Continuous Glucose Monitoring (CGM). There are a few models available in the market.

The CGM stores a glucose reading every five minutes for three days. It supplies the required data in order to reach an accurate solution. Unfortunately it is an expensive piece of equipment.

It is too costly for permanent use for the average diabetic. Therefore CGM use should be limited to reduce costs. The first CGM test will be used to characterise the patient's body and suggest a basal dosage. The second time will be a few months later to verify glycaemic control.

Ideally a company that manufactures and distributes the CGM devices will distribute the solution to this study. A company like Medtronic, Abbot or Dexcom could easily package this solution with their CGM devices. This will enhance the solution's distribution network.

The benefit to these corporations lies in the fact that more of their hardware systems and consumable sensors will be sold. The current software systems distributed with the CGM are difficult to use. The results are also difficult to interpret as they require an understanding of engineering control systems and statistics.

The package should be able to compete with other software in aesthetical aspects. It should also be "bug-free". A high amount of testing is required to ensure that the package is up to standard. Testing procedures have to be determined and done. This will be discussed in chapter 3

The proposed solution should address the needs of the medical doctor, the patient and the system's manufacturer. The requirements of the solution can be summarised as follows:

- Patient related:
 - It must be accurate. The regime should be determined accurately in order to enhance the patient's life.

- The solution must not cost the patient too much.
- It must not inconvenience the patient for too long a period.
- Doctor related:
 - Easy to use. The doctor's assistant must be able to use the system.
 - It must give him the opportunity to offer enhanced services to his patient.
 - It should enable him to see more patients and increase his revenue.
- Manufacturer related:
 - Promote CGM technology by increasing sales of hardware and consumable.
 - Enhance awareness of the CGM technology and its use.
 - Must be enticing in order to attract the attention of companies like Medtronic, Abbot and Dexcom.

2.2.3. Identifying obstacles

Obstacles have been categorised under the following headings:

- Financial obstacles: These include medical aid coverage, initial hardware costs for doctor, consumable costs per patient, etc.
- Technical obstacles: Infrastructure available in typical consulting rooms, clinics, etc.
- Legal aspects: Current malpractice laws make the doctors liable for any wrong dosages prescribed, FDA approval, etc.

Financial obstacles

The hardware (monitor and docking station) and glucose sensors required for this study are very expensive. A normal person would not be able to afford these types of

systems. As such, the solution would have to be sold in conjunction with CGM's to medical institutions.

This would make it a financially viable solution to medical practitioners and hospitals. The treatment would still be expensive, as the patient would have to hire the CGMS. The sensors used also cost approximately R500/sensor and can only be used once. This would still make it an expensive option if any patient had to pay for it himself.

The alternative is much more expensive. Short term diabetic complications can cause a patient to be hospitalised. Long term complications will definitely end up in the patient being hospitalised and expensive procedures being performed. Newly diagnosed patients have to visit a medical practitioner often to have their regime adjusted. These consultation fees are also very high.

It would seem that a solution that could give a more accurate regime could end up saving money in the long run – not to mention lives. The medical-aid schemes could benefit greatly if they covered the cost of these first tests running a few days. It could cut out hospitalisation costs right after diagnoses as well as later in the patient's life. It would also mean a lower risk for diabetic complications which a medical scheme would have to cover.

Technical obstacles

The solution must be able to handle a great deal of data very quickly. The data must also be easy to read and manipulate later. The only viable solution to this obstacle is using databases.

Making the software intuitive and easy-to-use is another obstacle that could prove difficult to overcome. Software must minimise any chance on an incorrect input, as well as handle any incorrect inputs that occur.

The final user may be an untrained person with little or no technical background. People with little or no training tend to give up quickly if the software doesn't react exactly as they expect it to. To this end, the software must communicate any error it detects in the simplest terms. It must guide users as to what is required and expected from them.

As a great amount of data needs to be entered, it must take as little time as possible. The software must look at previous inputs and predict what the next date or type of food may be for example. This will save a lot of time for the user when entering data.

The interface of the CGM systems is unknown and may be difficult to decipher. Most systems on the market use a RS-232 interface. This standard of communication is becoming outdated and is being replaced by the USB standard. Development of a system may prove difficult if compatible hardware to develop with becomes scarce.

Another problem is the protocol used by the CGM systems. At the time of this study an agreement with the providers had not been reached. Because of this it may be possible that the protocol will need to be reverse-engineered. A problem like that falls outside the scope of this study and is recommended for another study.

A possible solution for this study is to use the CGMS software to retrieve the data. The CGMS software has the functionality to export CGMS data in comma separated values (CSV). These can easily be imported into the solution.

In order to achieve this and to still make it an easy-to-use system, the solution will need to do this automatically. The interface of the CGM software must be understood in all aspects. Using simulated key-strokes may then have the desired effect.

This will simulate a user making the inputs into the program. After data has been downloaded and exported to a CSV file, it can be imported into the solution. The data must still be interpreted and used in a database system.

Legal aspects

The legal ramifications of prescribing wrong insulin dosages could damage a doctor's credibility and damage him financially. It is therefore imperative that he is as accurate as possible in the treatment insulin dosage.

Poor glucose control resulting from a non suitable insulin regime will lead to the long-term effects of diabetes quicker. If it can then be proven that the wrong dosage was administered, the doctor might be prosecuted. This places the doctors in a very difficult position and under pressure when treatment is decided.

As it can take a few months to get to the correct dosage, a window may exist in which damage is done. If it can be proven that an incorrect dosage was the cause, the doctor may be held liable. If, however, the correct dosage is determined earlier rather than later, this will not be the cause of any damage and the doctor will not be held responsible.

Of course, like any medical application, the process must first be approved by health authorities before any trials can begin. If any trials are to be done in the USA it must first be approved by the FDA (Food and Drug Administration). Because of these limitations no tests will be done on patients during this study. The simulations will be used to predict a better basal dosage and verified with known parameters.

2.2.4. Novel solution - a unique characterisation system

Considering all the requirements and the fact that every human being is unique, a “one-size-fits-all” solution will not be adequate for this study. The solution will have to take each person’s body into account.

The system will have to use the history of a person to determine the person’s insulin usage with glucose consumed. It will have to characterise the person in terms of a few variables. These variables will be referred to as the person’s insulin- and ets sensitivity.

Using these variables and previous research done, the person’s required basal dosage will be determined. A complete algorithm has to be developed that starts by using the person’s blood glucose information and finishes with the final basal dosage.

2.3. Designing a solution algorithm for the characterisation system

Ideally, the blood glucose characterisation system should be able to determine ets-, insulin- and exercise sensitivities of a diabetic patient accurately. This section explores how each sensitivity factor can be determined and whether it is practically possible to measure each factor independent of the others.

2.3.1. Glycaemic response of meals and ets sensitivity

Mathews showed that ets is a more accurate predictor of glycaemic response than mass of carbohydrates [33], [34], [34]. Unlike carbohydrates, ets also takes the metabolic efficiency of the specific foodstuff into account to produce a more accurate measure of the effective energy available for conversion to glucose released into the blood.

$$\Delta BS_{meal} = f_{BS/ets\ food} \cdot ets_{meal} \quad 2.3.1.1$$

Where:

- $f_{BS/ets\ food}$ is the ets sensitivity factor
- ets_{meal} is the amount of ets in the meal
- ΔBS_{meal} is the increase in blood glucose levels due to the meal

This represents the increase in blood glucose level per unit ets ingested. Both the blood volume and efficiency of the person's digestive system are accounted for in this value [36].

This equation can be used within a broad linear range. At extreme high glucose levels, however, the body's absorption of carbohydrates starts to decline. Therefore equation 2.3.1.1 cannot be used at these extreme glucose levels.

Similarly, when glucose levels fall below 3.8 mmol/l, several counter regulation hormones such as glucagon and cortisol starts converting glycogen to glucose released into the blood. Therefore it becomes difficult to isolate the ets-effect and makes it difficult to measure the ets-sensitivity at very low blood glucose levels.

To obtain the ets quantity of a specific foodstuff, equation 2.3.1.3 can be used. Both the mass of carbohydrates and glycaemic index of the foodstuff are taken into account. When several foodstuffs are combined in a single meal, the combined glycaemic index is dependant on the indexes of the different foodstuffs. Therefore the mixed meal effect should be taken into account [31], [36].

Mathews derived the following equation to determine the ets in a specific foodstuff:

$$ets_{CHO} = \frac{E_{CHO}}{E_{Teaspoon\ Sugar}} = \frac{\eta_{CHO} m_{CHO} \times 4[kCal / g]}{\eta_{Sugar} m_{Teaspoon} \times 4[kCal / g]} = \frac{\eta_{CHO}}{\eta_{Sugar}} \frac{m_{CHO}}{5} \quad 2.3.1.2$$

Where:

- ets_{CHO} = the equivalent teaspoons of sugar in the CHO
- E_{CHO} = the energy in the carbohydrates (kCal)
- $E_{TeaspoonSugar}$ = the amount of energy in one teaspoon of sugar
- η_{CHO} = the metabolic efficiency of the CHO
- m_{CHO} = the mass of the CHO
- η_{sugar} = the metabolic efficiency of sugar
- $m_{teaspoon}$ = the mass of one teaspoon of sugar

Mathews proved that the metabolic efficiency (η_{CHO}) is dependant on the Glycaemic Index (GI) of a specific carbohydrate ($\eta_{CHO} = GI/100$) [37]. The GI for most CHO is available. As such, the η_{CHO} can be determined for most CHO. It is known that the GI of sugar is approximately 65 so $\eta_{sugar} = 0.65$. All that is required is the mass of CHO and the amount of ets that can be determined.

$$ets_{CHO} = \frac{\eta_{CHO} m_{CHO}}{3.25} = \frac{GI_{CHO} m_{CHO}}{325} \quad 2.3.1.3$$

Where:

- η_{CHO} = metabolic efficiency of specific carbohydrate
- GI_{CHO} = glycaemic index of specific carbohydrate

Protein and fats also influence the blood glucose level of diabetics but the effect thereof is negligible compared to carbohydrates. Therefore, this study assumes the effect to be negligible. The macronutrient composition of a meal influences the metabolic efficiency of a meal. This is accounted for by GI .

Ets sensitivity is defined as the increase in a person's blood sugar level due to the intake of food. The ets in different foods can be determined from equation 2.3.1.3 [36]. Ets sensitivity is measured in mmol/l.ets. The effect of consuming food on blood glucose levels is shown by the rising gradient of the graph in Figure 7. It is also displayed by formula 2.3.1.4 [36].

$$\Delta BS = f_{BS/ets, food} \cdot ets_{absorbed} = f_{BS/ets, food} \cdot f_{CHO} \cdot ets_{meal} \quad 2.3.1.4$$

Where:

- $f_{BS/ets, food}$ is the ets sensitivity
- $ets_{absorbed}$ is the amount of ets that was absorbed into the blood stream.

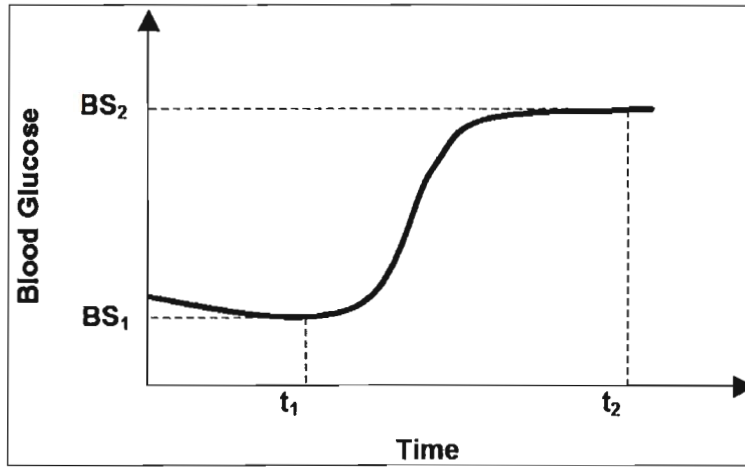


Figure 7: Example of the effects of CHO on blood glucose levels

The problem with determining ets sensitivity is that active insulin in the blood stream decreases blood glucose levels at the same time. As such, a person has to wait till most of the insulin is out of his system before these tests can be done. Typical times that current insulin on the market is active in the blood stream are shown in section 2.3.2.

To determine ets sensitivity manually, the BS level before intake of food and after intake of food should be measured. The amount of ets in the meal must be known. Formula 2.3.1.5 can be used to determine the ets sensitivity.

$$f_{BS/ets} = \frac{BS_2 - BS_1}{ets_{meal}} \quad 2.3.1.5$$

As there is no insulin administered with the test meal at first, this could be a risky undertaking. As such, it is preferable that the person's BS is below 5.5mmol/l before he takes the test meal. Hyperglycaemic excursions higher than 10mmol/l are not desirable. Therefore the amount of ets consumed should be limited and should not elevate the patient's BG higher than 10mmol/l.

Food can take between two and nine hours to digest fully. It is safe to assume that the most glucose will be absorbed by the body within two to three hours for carbohydrate rich meals with little or no fats or proteins. The second measurement has to be taken after this time has passed to insure that the results are as accurate as possible.

The solution must work around the problems mentioned to accurately determine ets sensitivity without disrupting the person's daily routine too much, or even endangering his life.

2.3.2. Insulin, its Glycaemic response and Insulin sensitivity

Insulin is a hormone normally secreted by the pancreas of a healthy person. This hormone plays an important role in the energy cycle as it is used to either store glucose from the blood as glycogen or to allow living cells to receive glucose for energy metabolism.

The pancreas of type 1 diabetics does not secrete insulin. Therefore this hormone should be administered by the diabetic. Balancing insulin with the effect of meals, exercise, stress and other hormones can be a tricky act. Insulin is administered subcutaneously or by inhalation. In order to find an insulin regime that works, it is important to characterise the individual's glucose response to insulin.

Except for the method of administration, insulin is characterised according to its timing properties. The onset-, peak- and duration-times of different insulin define the action profile of insulin. Insulin is usually classified as long acting (basal) or short acting (bolus or rapid) insulin.

Basal insulin (e.g. Lantus) is active for up to 24 hours [25]. The slow and continuous release rate enables cells to utilise glucose for metabolism. Bolus insulin is usually active between one and three hours and is used to store glucose released into the blood

from digestion of meals. The timing properties of different insulin are shown in Table 1. Figure 8 shows the different profiles of insulin.

Type	Description	Onset	Peak concentration time	Duration	Example of commercial products
Bolus	Rapid acting	20-30min	30-90min	60-150min	Apidra
Basal	Long acting	60-90min	None	24hrs	Lantus
Mixes	Mixed action	30min	2-5hrs	18-24hrs	Humalin 50/50
Inhalers	Short acting	20-30min	77 min [38]	240 min [38]	Exubera

Table 1: Examples of different types of insulin and typical timeframes

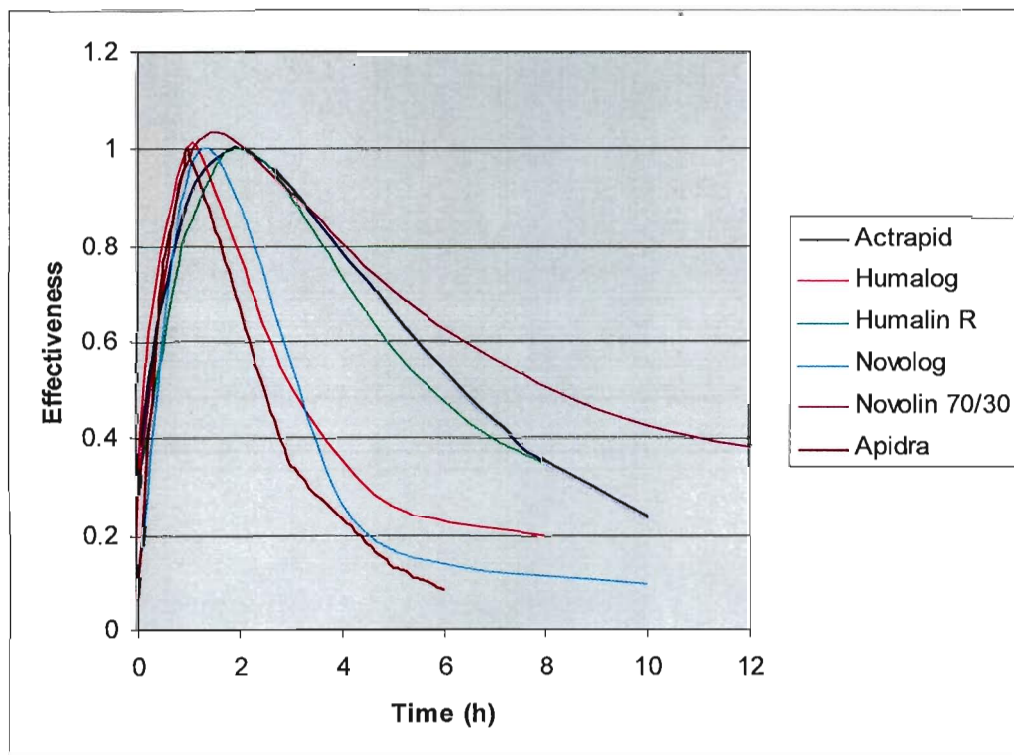


Figure 8: Graph comparing action profiles of different insulin to each other

Insulin sensitivity is defined as the decrease in blood sugar levels per unit insulin injected into the blood stream. Insulin sensitivity is measured in mmol/l.Unit. Insulin takes time to act in the blood stream. This must be remembered when determining the effect of insulin on glucose levels. The effect of insulin is shown by the falling gradient of the graph in Figure 9. It is also displayed by formula 2.3.2.1 [36].

$$\Delta BS_{\text{insulin}} = -f_{BS/\text{insulin}} \cdot I$$

2.3.2.1

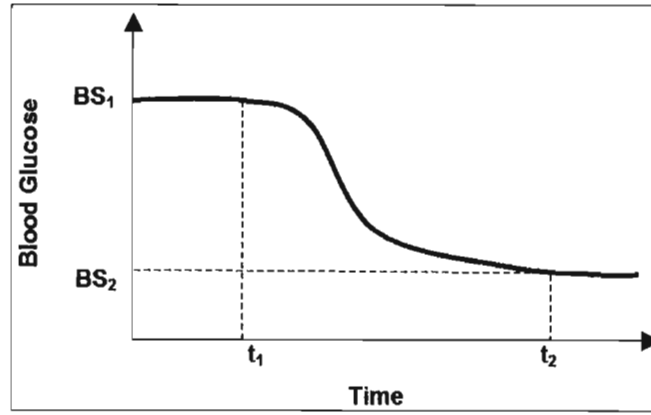


Figure 9: Example of the effect of insulin on blood glucose

Again it should be remembered that food still has an effect on the glucose levels even if insulin is injected. As such, it could make any calculations inaccurate. Blood glucose levels should be stable and no food consumed before a test like this is done.

$$f_{BS/ins} = \frac{BS_2 - BS_1}{Units_{ins}} \quad 2.3.2.2$$

Formula 2.3.2.2 can be used to determine insulin sensitivity. The second reading should only be taken after enough time is allowed for the insulin to be more than 90% effective. This is different for all insulin on the market and the specific insulin's data should be used.

For the safety of the patient, the blood glucose level should be elevated prior to administering insulin. Furthermore the dosage should be appropriate to reduce the glucose level back to normal. The blood glucose level should be monitored to prevent the patient from entering hypoglycaemia. If the final glucose level is below the hypoglycaemic threshold, the sensitivity value cannot be measured accurately because of the prevalence of counter regulation hormones released.

The solution of this study should work around the time problems involved in determining both ets- and insulin sensitivity. The person should also not have to endanger his life by not eating or not taking his insulin to get results.

2.3.3. Exercise and its effect on glucose levels

Pelzer developed the following equation to characterise the effect on energy expenditure on the blood glucose level of the diabetic patient [36]. To accurately

obtain the glycaemic response of a diabetic patient to energy expenditure is a very difficult and time consuming experiment.

$$\Delta BS_{\text{ets removed}} = \frac{27.8}{0.07(m_{\text{patient}})/1.06} \left(\frac{m_{\text{patient}}}{m_{\text{reference}}} \cdot \frac{t_{\text{period exercised}}}{t_{\text{period reference}}} \right) \frac{E_{\text{Expended table}}}{55} \quad 2.3.3.1$$

Pelzer suggested using an average sensitivity value based on the weight of the patient, time duration of the exercise and the intensity of the exercise accounted for energy tables from literature sources on the subject.

Energy, in the form of glucose, is therefore removed from the blood during exercise. There should however be enough basal insulin to promote the energy utilisation during exercise. If not, the glucose level might rise as a result of the counter regulation system releasing glucose into the blood. Counter regulation system will be signaled as if there is not enough energy available to cells, but in reality there is not sufficient insulin.

2.3.4. Blood glucose response to stress or illness

Stress and illness play a major role in the overall glycaemic control of diabetics. During prolonged periods of emotional stress or illness, the counter regulation hormone cortisol is secreted. This hormone causes a continuous elevated blood glucose level. This should be rectified by increasing the long acting (basal) insulin dosage.

Short term stress on the other hand might cause other counter regulation hormones (e.g. adrenalin) to rapidly increase blood glucose levels. Unfortunately these events are not avoidable. When patients' blood glucose data are analysed these manifest as unexplained elevations in glucose.

The characterisation procedure should therefore be performed during a period of normal routine (normal workday) and avoid short term or additional stress (such as writing an exam) or while something stressful is happening in the patient's life.

2.3.5. Simulating the blood glucose levels

The characterisation of a person's blood glucose levels will be determined with a process of simulation. This section will explain the simulation process as well as its deliverables.

Mathews and Botha developed a blood glucose simulation model based on the ets-concept [31]. Using the blood glucose information as well as all meal and insulin event data, a person's blood sugar levels may be simulated. It may be possible to determine what the level would be after a set amount of time.

The amount and timing of food, insulin and exercise have to be accounted for. These individual factors were discussed in the previous sections. A steady state summary of these factors is given by equation 2.3.5.1.

$$BS_{predicted} = BS_{pre-prandial} + \Delta BS_{meal} + \Delta BS_{exercise} + \Delta BS_{insulin\ bolus} + \Delta BS_{counter\ regulation} \quad 2.3.5.1$$

Where:

- $BS_{predicted}$ is the level of blood glucose the next point is predicted to be.
- $BS_{pre-prandial}$ is the previous predicted blood glucose level.
- ΔBS_{meal} is the change in blood glucose due to meal events that influence this point in time.
- $\Delta BS_{exercise}$ is the change in blood glucose due to exercise at this point in time.
- $\Delta BS_{insulinbolus}$ is the decrease in blood glucose due to blood glucose taken before this point in time.
- $\Delta BS_{counter-regulation}$ is the change in blood glucose due to the body's natural response to extreme blood glucose levels.

A starting off point is required from which further simulation will characterise a person. Basic sensitivity values must be determined using a simple process. Gradients of the blood sugar graph are used in this process.

The effect of each meal- and insulin event can be determined, but only if enough time has passed before the next event. If the sensitivity determined falls within acceptable limits, it will be added to the total. The sensitivity will then be determined by dividing this total by the amount of valid values.

Formulas 2.3.1.3 and 2.3.2.2 explained in 2.3.1 and 2.3.2 can be used for such a calculation. As explained in these sections, they don't take each other into account. That is why a further simulation is required, but these values give a good starting off point for such a simulation.

The simulation will follow an iterative process. It will run through the simulation once and determine an error for that simulation. It will change variables in the simulation and run through again. It will continue this process until the smallest possible error is found.

Because of the complexity of the human body, this error will never be zero or very small. The goal is to determine the best possible solution that is achievable by data analysis. This will already serve as a better treatment tool than systems currently employed.

Only one variable will change with an iteration of the simulation. It will change in steps and the new error will be determined. Each variable has a maximum and a minimum. These variable boundaries were determined by running the simulation and only changing one variable. An error graph was then determined for each variable. The variable boundaries were set where the errors were at its lowest points.

The margin by which the variables are changed in a simulation is determined as a percentage of the difference between the current value and the high or low boundary. If the error isn't better for any of these steps, the current value is decided and the next variable is changed.

The basic formula developed is formula 2.3.5.2. This does not take other factors in consideration and if the human body was completely predictable this would give an accurate simulation of blood glucose levels. The formula that has some built in changes for the unpredictable nature is given in 2.3.5.3.

$$SIM_{now} = SIM_{prev} + (Sens_{ets} * ETS_{prev}) - (Sens_{ins} * INS_{prev}) - (Sens_{exercise} * Exer_{now})$$

2.3.5.2

The SIM values are blood glucose values; *now* is the value being simulated and *prev* is the previous simulated values. The variable ETS_{prev} is the total ets contribution between the last entry and this one, whereas INS_{prev} is the total contribution of insulin during this time. The exercise sensitivity is a default value.

$$Sim_{now} = Sim_{prev} + F1 * (Sens_{ets} * ETS_{prev}) - F2 * (Sens_{ins} * INS_{prev}) - Exer_{default}$$

2.3.5.3

F1 and F2 can only vary between 0.9 and 1.1 to either increase or decrease the gradient of the rise and fall in blood glucose levels. This was found to have a profound impact on the minimum error and simulation results. These variables account for some of the unpredictability in the human body, but not completely.

The simulation process is displayed in Figure 10. Each time a smaller error is found, the whole simulation process must be run again to see if a change in another variable won't also lead to a smaller error. If all of the variables have been checked and a smaller error was not found, the best possible solution to the simulation was found.

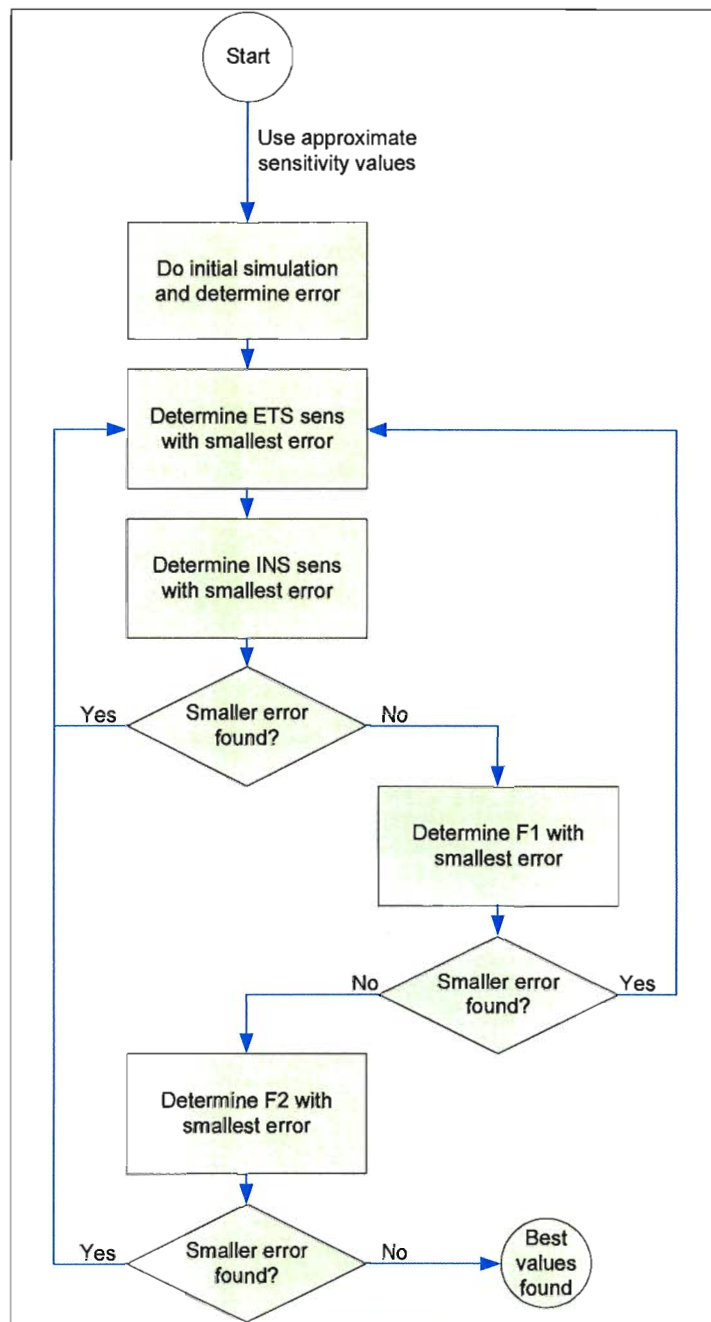


Figure 10: Simulation flow diagram

2.3.6. Determining the patient's basal and bolus insulin regime

In determining the basal dosage required for enhanced glycaemic control, only ets- and insulin sensitivity are important. These are the major factors contributing to the tightness of glycaemic control that will be measured. If they are accurate enough, the other factors will not be brought into the fold by the body.

Pelzer developed a process by which basal dosage can be determined from the sensitivities [36]. It uses a person's recommended daily allowance of calories and

converts it to recommended daily allowance for ets. Using a formula, it then determines the necessary dosage of basal insulin.

To determine the RDA calories of a person, a process developed by the USDA/ARS Nutrition Research Centre at Baylor College of Medicine [39] is used. The variables used in 2.3.6.1 are explained in Table 2.

$$RDA_{Calories} = fa_{gender} + fa_{age} + fa_{activity}(fa_{weight} + fa_{height}) \quad 2.3.6.1$$

Variable	Male	Female
fa_{gender}	662	354
fa_{age}	Figure 11	Figure 11
$fa_{activity}$	1.0 (low activity level) 1.11 (moderate activity level) 1.25 (high activity level) 1.48 (very high activity level)	1.0 (low activity level) 1.12 (moderate activity level) 1.27 (high activity level) 1.45 (very high activity level)
fa_{weight}	Figure 12	Figure 12
fa_{height}	Figure 13	Figure 13

Table 2 : Table with variables for determining $RDA_{calories}$

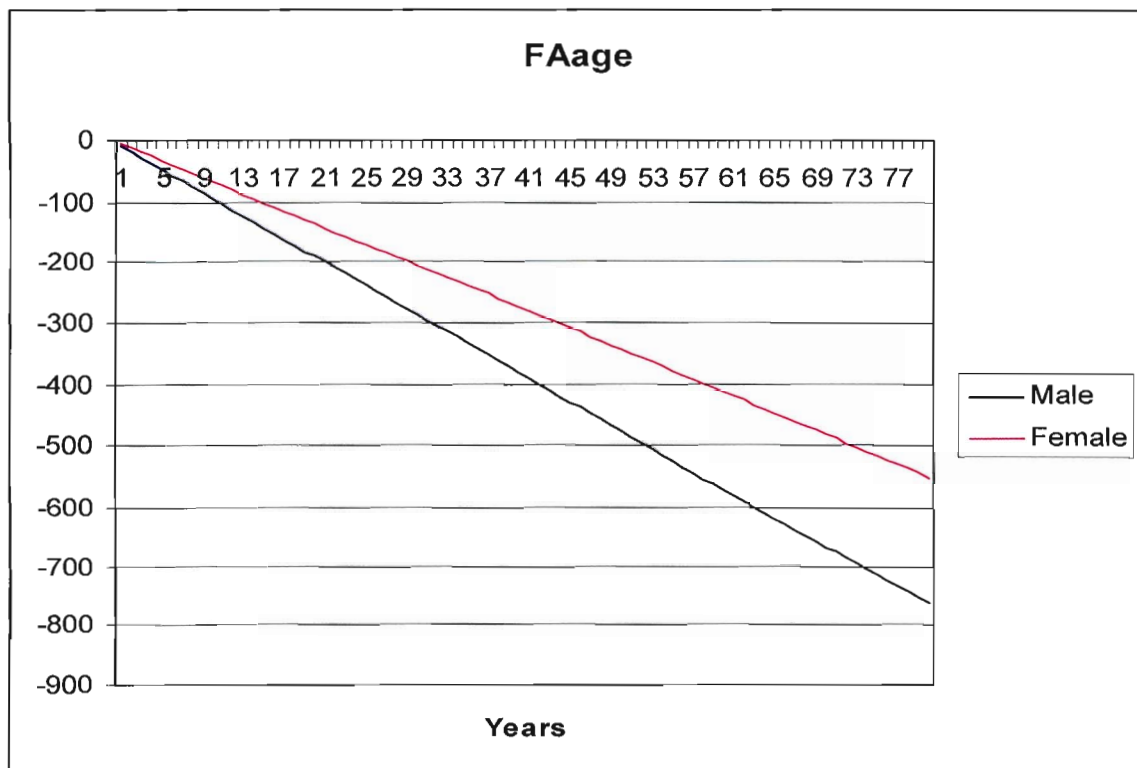


Figure 11: A graph to determine FAage

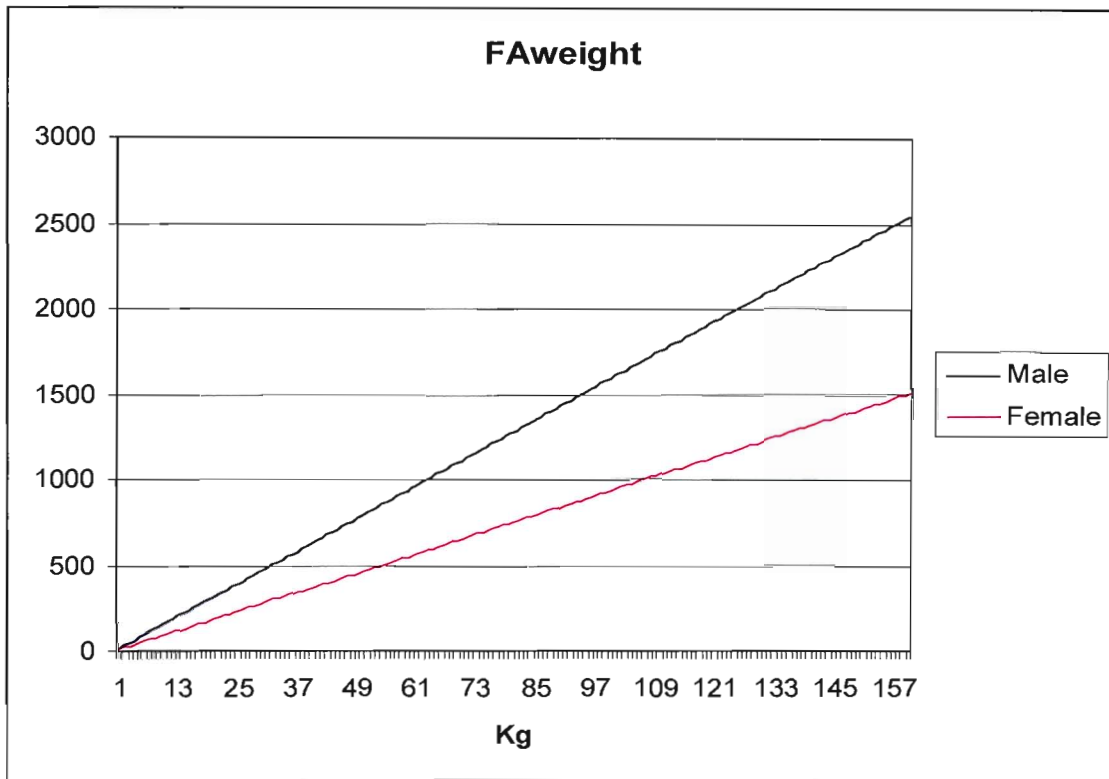


Figure 12: Graph used to determine FAweight

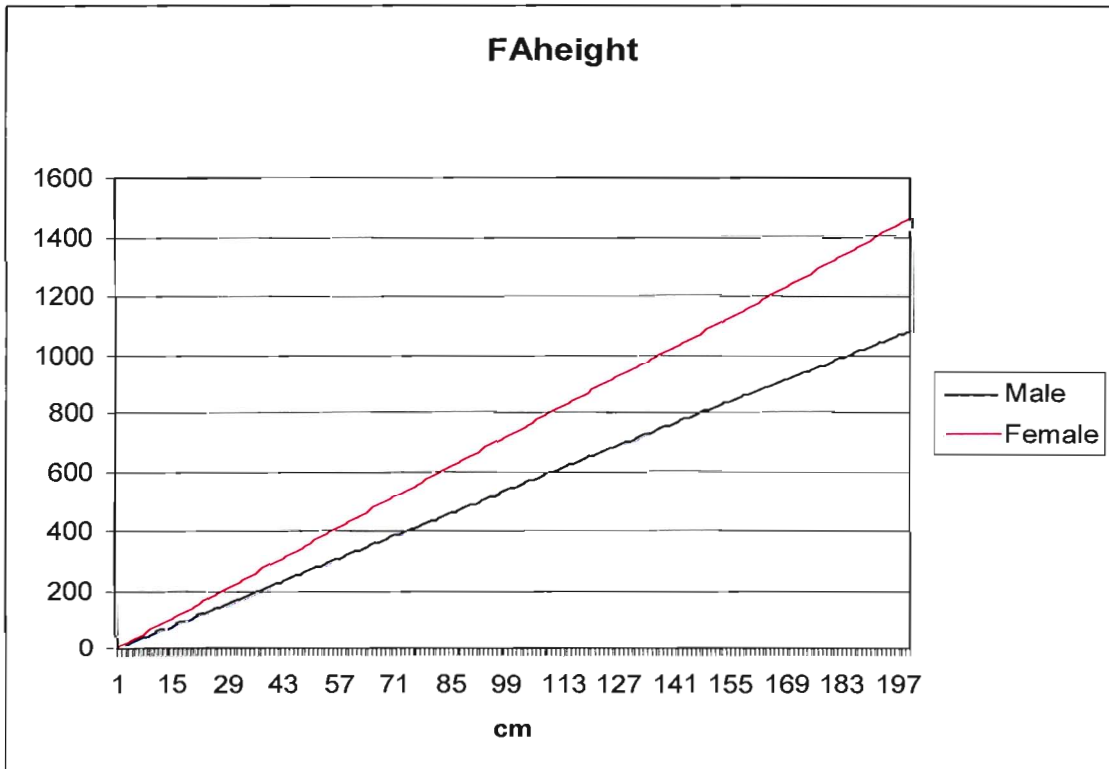


Figure 13: Graph used to determine FAheight

According to Pelzer $RDA_{calories}$ can then be converted to RDA_{ETS} using equation 2.3.6.2 [36]. The bolus dosage is then determined with equation 2.3.6.3, where the

sensitivities are used in conjunction with the person's RDA. The final dosage as determined can be used to achieve better glycaemic control.

$$RDA_{ets} = \frac{RDA_{calories}}{65} \quad 2.3.6.2$$

$$Dosage = RDA_{ets} \times \frac{f_{BS/ets}}{f_{BS/ins}} \quad 2.3.6.3$$

Therefore the sensitivity values can practically be used to determine the recommended basal insulin dosage for the patient. Conventionally only the patient's weight is taken into account for initial basal recommendations. The new proposed method takes the patient's weight, activity level, age, gender, insulin and ets-sensitivities into account.

Establishing a good basal insulin regime lays the foundation of glycaemic control. The insulin and ets sensitivities can be used to determine the amount of bolus insulin required for a specific meal. The following equations can be used.

$$BS_{control} = BS_{pre-prandial} + \Delta BS_{meal} + \Delta BS_{exercise} + \Delta BS_{insulin bolus} \quad 2.3.6.4$$

Where:

- $BS_{control}$ = the desired blood glucose level.
- $BS_{pre-prandial}$ = the previous blood glucose level.
- ΔBS_{meal} = the change in blood glucose due to meals taken.
- $\Delta BS_{exercise}$ = the change in blood glucose due to exercise done.
- $\Delta BS_{insulin bolus}$ = the change in blood glucose due to bolus insulin.

Equation 2.3.6.4 can also be written as:

$$\Delta BS_{insulin bolus} = BS_{control} - BS_{pre-prandial} - \Delta BS_{meal} - \Delta BS_{exercise} \quad 2.3.6.5$$

To calculate the insulin bolus, equation 2.3.6.5 should be divided by the insulin sensitivity factor to obtain Equation 2.3.6.6.

$$I_{bolus} = (BS_{control} - BS_{pre-prandial} - f_{BS/ets food} \cdot ets_{meal}$$

$$-\frac{27.8}{0.07(m_{patient})1.06}\left(\frac{m_{patient}}{m_{reference}}\cdot\frac{t_{period\ exercised}}{t_{period\ reference}}\right)\frac{E_{Expend\ table}}{55}) / f_{BS / insulin}$$

2.3.6.6

These equations are however not practical to use without a calculation device. Pelzer has developed an insulin bolus calculator that resulted in a reduction in HbA1c levels of type 1 diabetics by 0.5 from 8.6% to 8.1%. Townsend further verified the blood glucose control performance of this device and found an average improvement in the blood glucose control performance of diabetics by a factor 1.44. BGCP takes tightness of glycaemic control, frequency of hyper- and hypoglycaemic events into account and also the average blood glucose levels. This concept is explored further in chapter 4.

2.4. Integrating components into a feasible solution

The only option available as a solution to this study is computer software that integrates all the simulation into an easy-to-use interface. This software has to strictly adhere to the specifications set forth in section 2.2.2.

Simulation times will also have to be as short as possible, as the solution will not be usable if a simulation takes more than 10 minutes to achieve. If the simulation takes longer than this it will tie up valuable time of resources, the patient and the doctor.

Software will have to be designed and implemented with the following in mind:

- Easy-to-use intuitive graphical user interface.
- Short simulation times.
- Automatic database integration.
- Easy to understand results must be produced.
- Database encryption to protect intellectual property.
- Accurate simulation.

The next chapter will discuss the design and implementation of the computer software.

3. Developing a practical easy-to-use blood glucose characterisation system

This chapter focuses on the implementation of the blood glucose characterisation system as a practical software package.

3.1. *Prelude*

This chapter describes the process that was followed to use the information given in chapter 1 and 2 to come up with a practical software solution. The stages that development followed are explained.

Specifications are drawn up based on the problem and requirements given in the first two chapters. The final developed solution is explained and measured against the derived specification.

3.2. *The implementation procedure*

3.2.1. *User specification statement*

In the previous section, the specifications of the solution were identified. These must be written as they pertain to software so that the final software solution can be measured against these criteria.

- The system should be intuitive. It should minimise the time needed for input of all the data. Values should be filled in as much as possible.
- The software should have a professional, nice to look at, finish. It should have the same look as current Windows software to make it more marketable.
- It should minimise possible input errors. This is limited as certain inputs cannot be tested for validity. Tests that can be performed, such as making sure all necessary data has been entered, should be performed.
- It must use data gathered by a CGM to determine the blood glucose levels of the patient. It must present this data in a professional, understandable way.
- Any third-party software it uses must be free to use in commercial applications or included with the CGM package.
- It should not need too powerful a computer in order to run.

- The software must be broken down to functional blocks or objects. This will enable it to be used in other software as an API (application programming interface).

3.2.2. System design

The final software system should be modular. This means that objects will have to be used to make it possible to turn it into an API. An object-orientated language should be used when implementing the design to ensure that this is possible. This will also give the desired software re-usability.

For the sake of this dissertation a complete GUI will also be designed and implemented for testing purposes of all software objects. This design will be such that it can be marketed and used as a final product. So both the option of acquiring a final software solution or functional blocks to use in other software will be available.

As a great deal of data will have to be stored, a database system will be needed. It will serve both the purpose of storing patient data as well as being a read-only database for insulin types and effective values. The latter should be distributed with any software using these functional blocks.

The decision was made to use Firebird as the software solution. There were two options, Firebird and MySQL. MySQL is free for personal use, but must be purchased for commercial use. Firebird is free for commercial use as well. There are also many free tools for use with this database system.

Any data change in the software should be updated in the database immediately. This will ensure that no data is lost in case of a power failure or computer failure. This is imperative for user satisfaction as searching for the last time data was saved will cause unhappiness with the product.

The following tables are needed in the database:

- CGM data of all patients – read and write
- Meal data of all patients – read and write
- Exercise data of all patients – read and write

- Table with patients details – read and write
- Insulin types and effective times – read only
- Food types and ets values – read only

A big advantage of stand-alone database software is that the database containing the tables can be sent for support. The manufacturer of the software can load the database and debug the error at their premises. This will cut down immensely on support time in the product lifecycle.

The design done here will reflect the design for the GUI and the objects it interfaces with. The complete design of each object will be given as well as flowcharts and interfaces to the objects. The way the GUI interfaces with the objects will also be given to illustrate how other software may also do this.

The implementation of these objects will be discussed based on how the GUI uses them. Screenshots will be provided to explain the flow of the data input as well as the flow of how the objects should be used.

The main objects are depicted in Figure 14. These blocks form the main functional part of the software. The GUI interfaces with these blocks to pass data to and extract data from the database. Some of these blocks also have other functionality such as drawing a table with all the data and drawing a graph of the data that is stored.

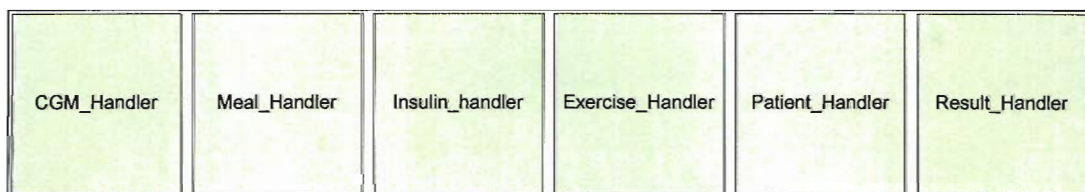


Figure 14: Main structural blocks

The patient_handler class

The patient_handler provides all the tools necessary to manipulate and store patient information. It forms the primary unit of the program as all other records are connected to patients by the number assigned in the Patient_Handler.

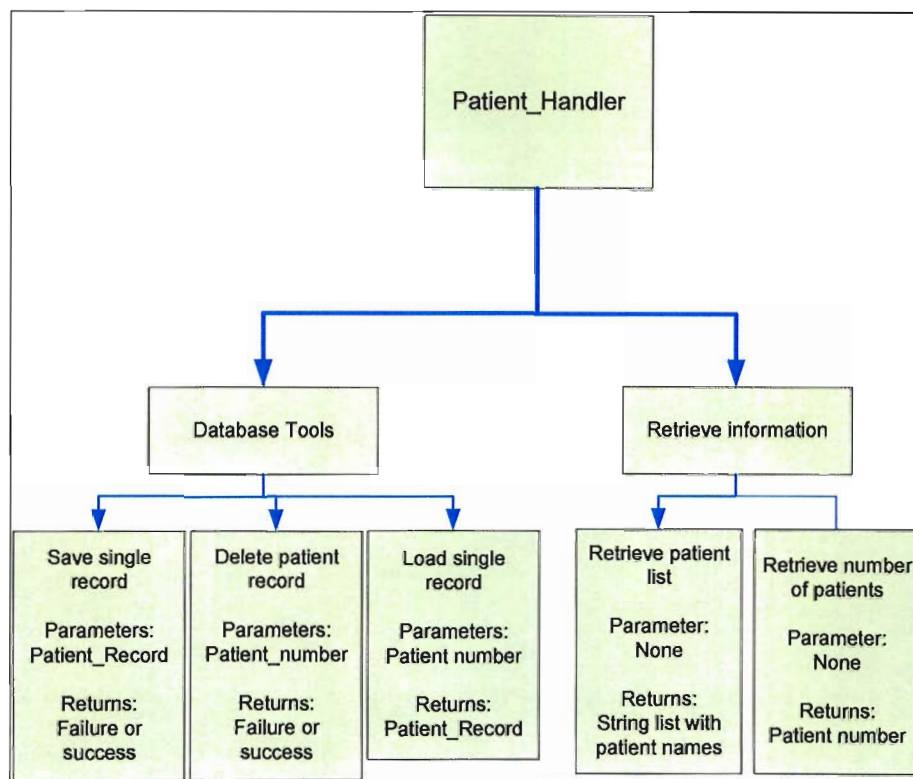


Figure 15: Block diagram of Patient_Handler

Figure 15 displays the functional layout of the Patient_Handler object. It provides functionality to the owner of the object to load patient information and store any updates. It also provides functionality to display all patient names and the number of patients in the system. There are no graphical tools associated with patient information.

The Patient_Record is a structure that holds all the information that is stored in a single entry in the database. It is a type that any other object may use to access a patient's information. It contains the following info:

- ID: System number of the patient.
- Name
- Surname
- Number: The patient's number in the doctor's records.
- Gender
- Height
- Weight

- Age
- ActivityLevel: There is a choice of three for this option. Either high, medium or low.
- BasalType: The type of basal insulin used by the patient.
- BolusType: The type of basal insulin used by the patient.
- BasalDailyDosage
- BolusDailyDosage
- YearsDiagnosed: The number of years the patient since the patient was diagnosed with diabetes.

The CGM_handler class

The CGM_Handler consists mainly of functionality to save data to the database, load it from the database. It also has the functionality to display a graph of and a table with all the data. The tools to interface with the CGM are contained in this class. Functions should be available to import data from the CGM and save it to the database.

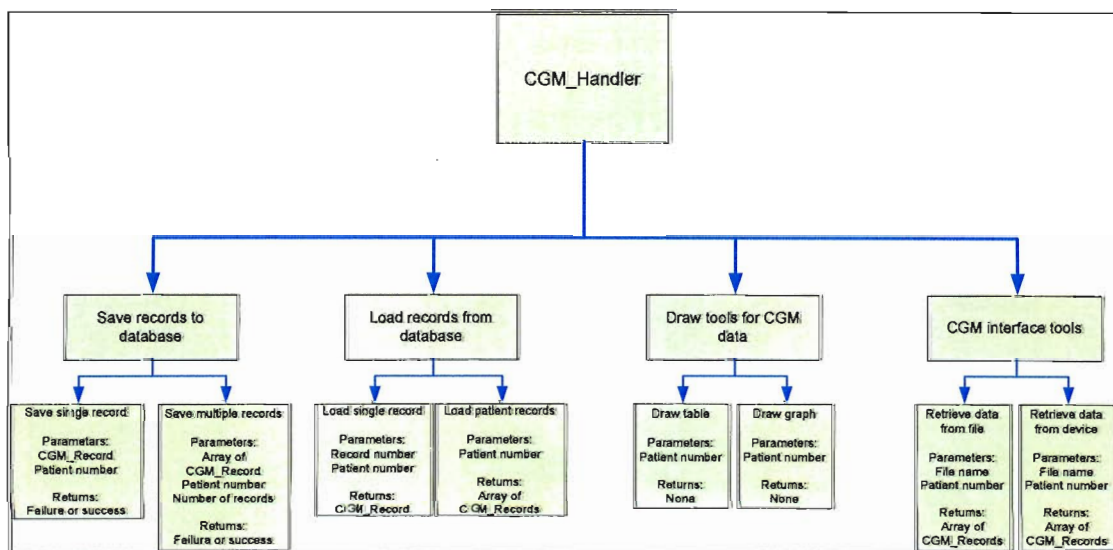


Figure 16: Block diagram of CGM object

Figure 16 is a block diagram displaying the functionality of the CGM object. The blocks in the last row are the functions accessible by the owner of this object. These functions are loading and saving data, displaying data and importing data from CGM

tools. The functions used to retrieve data from the CGM will be discussed in detail in the next section.

The CGM_Record is a type declared in the object. It is usable by any other object. It is necessary if any interaction is required with CGM data. It contains the following data:

- Date of reading
- Time of reading
- Blood glucose level

The meal_handler class

The Meal_Handler will contain all information required to determine ets usage for each intake of foodstuff. The tools required of this object are displaying all the data in table form and saving and loading data from the database. It also handles the data stored in the ets database. Functions should be provided to load this data in their categories.

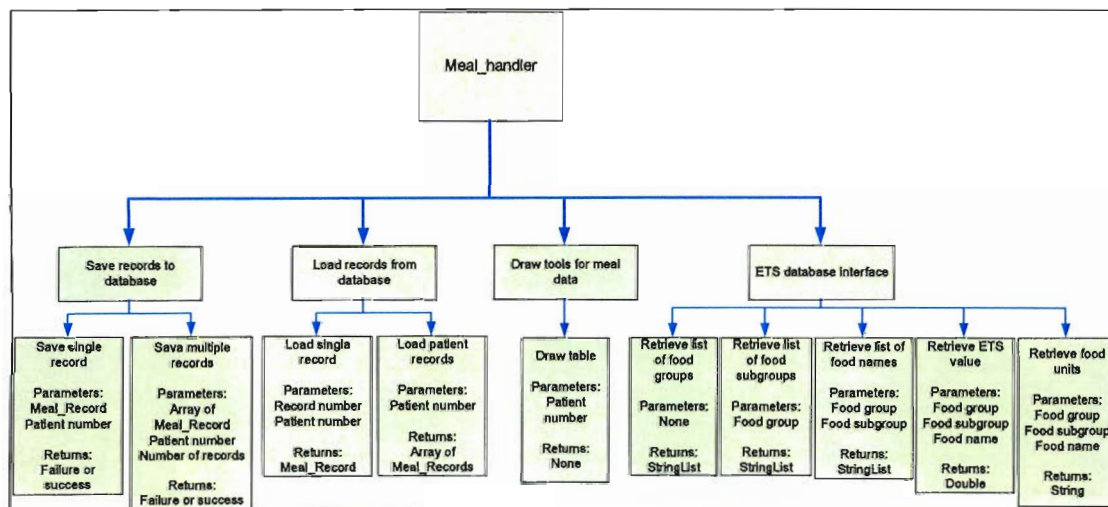


Figure 17: Block diagram of meal object

Figure 17 illustrates the functions available in the meal object. The data can be saved to and loaded from the database. The only draw tool in this object is a table; a graph will not be of any value. The tools to interface with the ets database are also provided in this object.

There are two ways in which to use the interface to the ets database. All food names can be given as a choice to the user, or it can be made easier with a sequence. A choice of food groups is given, then a choice of subgroups and only then does the user choose the food name from a much shorter list. The ets value as well as the amount of the food that contains this much ets is then available.

Keeping this ets database separate has the added advantage of easy updating. If more food values are added to the database through research all that is required is an update of the database. No software update will be required.

The Meal_Record is a type available with the object. Any object or other software can use this type. It has the following data:

- Date
- Time
- Food named consumed
- Amount of units consumed
- Total ets consumed

Accessing a database can take a few seconds. Storing the ets values with the meal data will save time later if it doesn't have to be loaded from the ets database each time. As there can be a lot of data, this can easily save up to a minute later when the data is loaded.

The insulin_handler class

The Insulin_Handler object contains tools for extracting and storing all insulin related data to and from the database. This information will be used to determine the patient's sensitivity to insulin. It also contains the tools to determine how much insulin is still effective in the blood. The read only insulin database is accessed using this object.

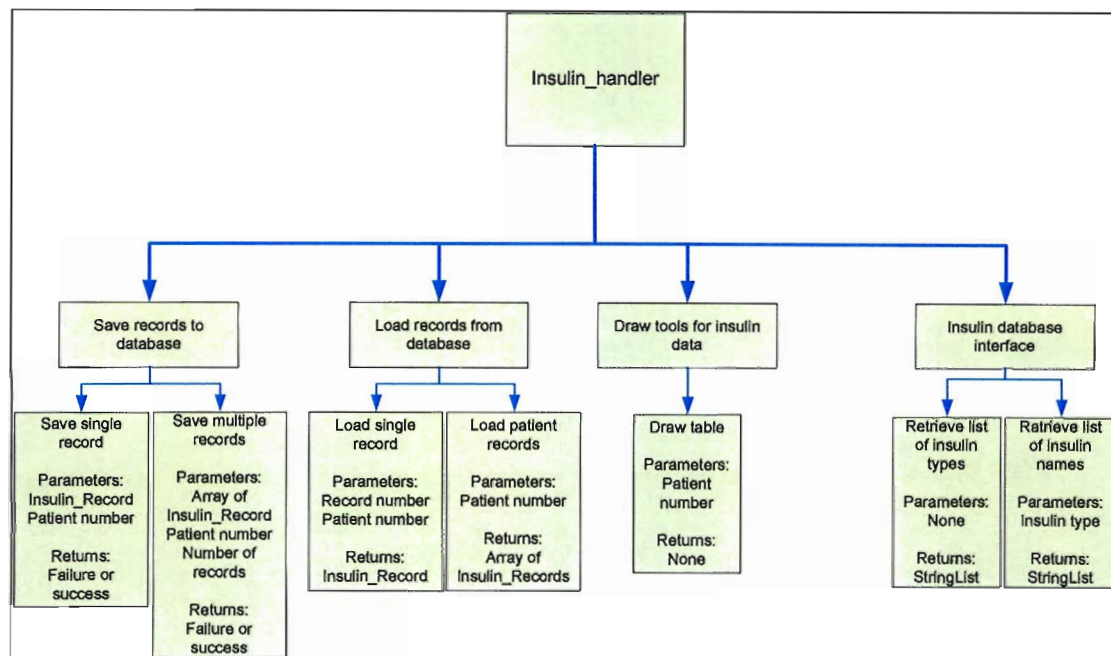


Figure 18: Block diagram of insulin object

Figure 18 shows the block diagram for the Insulin_Handler. This object contains all the tools for loading data from the patient insulin database as well as saving data to the patient insulin database. It also contains a draw function for showing all related patient insulin information in a table format. The tools for loading data from the insulin type database are also in this object.

The Insulin_Record is a structure type defined in the object. It is available to other objects using the object. It is composed of the following:

- Date
- Time
- Type of insulin
- Name of insulin
- Units of insulin administered

The insulin database is stand-alone database to enable easy update with the release of new types of insulin. It contains values for how much insulin is still available in the blood after a certain amount of time. These values are not freely available to the end-user and are only accessible through the software as it contains intellectual property.

The result_handler class

The Result_Handler does all the calculations and simulations explained in this thesis. All data is extracted from the other objects and made into a single record in this object. The simulation is done in this object and the sensitivities and basal dosage are the final results from this object.

There is only one function available to other objects. As the only goal of this object is to determine the final dosage, only a function to do so is available. Other functions are used in this object, but only as a means to return the result. The flow diagram of the function to determine the final result is shown in Figure 19.

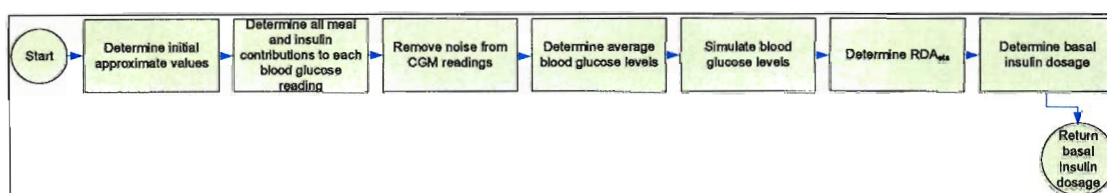


Figure 19: Flow diagram for determining results

All the record types defined in the other objects are passed to this one function where all the data is brought into consideration to determine the final result. The meal and insulin entries are used to determine the ets and insulin contribution to each blood glucose point.

After every point's ets and insulin contributions have been determined, the simulation process described in section 2.3.5 can start. Determining the best result can take numerous runs. Computers can do mathematical calculations extremely fast and this won't take longer than a few seconds.

From the best sensitivities results determined in the simulation the new basal dosage can be determined. Using the equations in 2.3.6 the best insulin dosage will be determined. The dosage, average blood glucose levels, sensitivities and average ets and insulin usage are made available to the owner of this object.

These objects were used in a GUI that can be used as a stand-alone package. This GUI will be explained in the next section by using screenshots from the software application. The interaction that occurs with the objects will also be explained.

3.2.3. System implementation

A stand-alone package was implemented using the objects designed in the previous section. It has an intuitive user interface that strives to always explain what the next step is or if any error in input has occurred.

Patient information

The package starts at the screen shown in Figure 20. The user has the choice to revisit an old patient's details to either add a new study or to view previous studies. The user can also choose to create a new user at this screen.

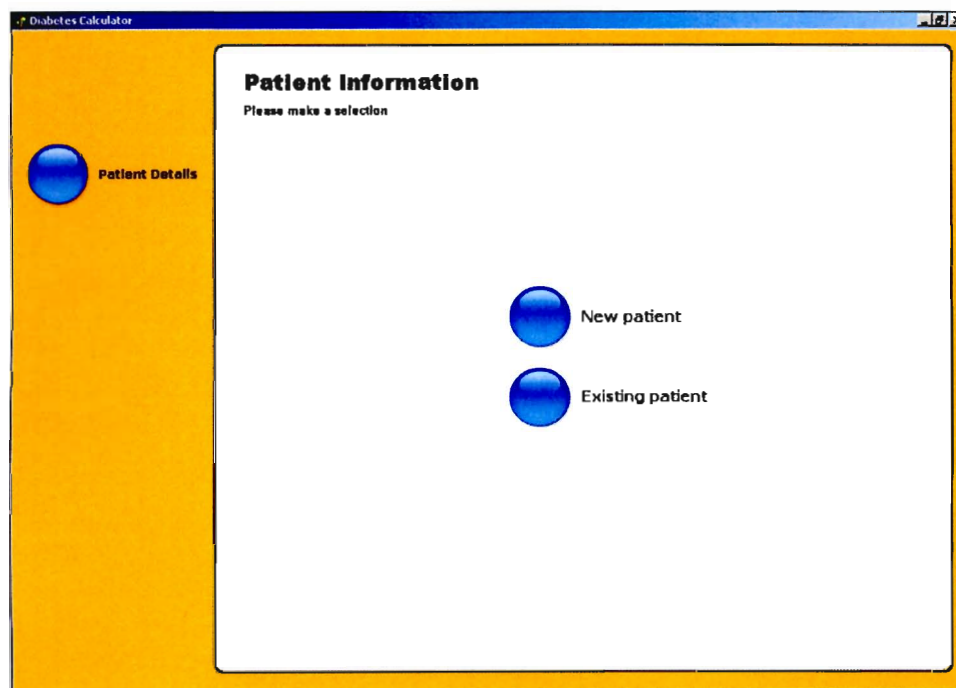


Figure 20: Screenshot of initial page of package

When choosing to create a new patient, the user will be taken to a screen to enter all the details of the patient. The second option will send the user to a screen to choose a previous patient. All the previous patients will be listed in alphabetical order in a box. There is also a choice to create a new patient. This screen is shown in Figure 21.

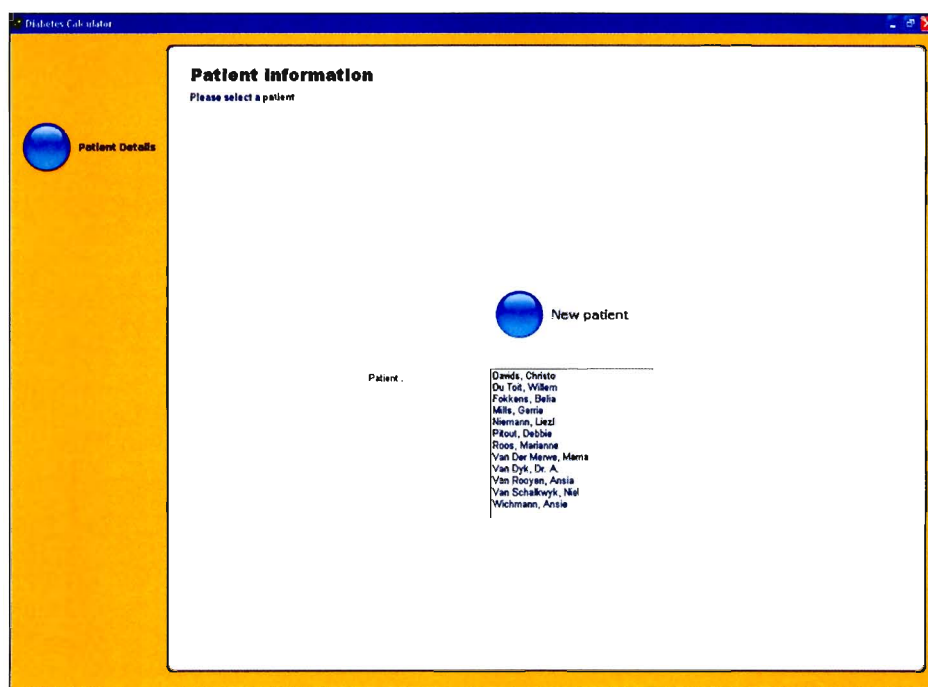


Figure 21: Screenshot of patient selection screen

Both of these choices will result in the patient information screen. Here all the details of the patient are entered. Some of these are necessary for the algorithm; others can be used for later reference. This screen is displayed in Figure 22. The required fields are indicated with an asterisk next to the edit box.

Patient information * Please complete all fields

Please complete the following patient details

First name : Patient *

Last name : TestA *

File/Reference number : ETS no 11 *

Gender : Female *

Age : 44 *

Weight : 93 kg *

Height : 1.6 m *

Daily activity level : Low *

Years diagnosed : *

Insulin pump : ☐ Yes ☒ No

Basal/Mong acting type : Ultratard Total daily Basal dosage : 40

Bolus/rapid acting type : Apidre Total daily Bolus dosage : 30

Required glucose levels : 7 mmol/l

Next step Select other patient Delete

Figure 22: Screenshot of patient information screen

This screen will use the Patient_Handler object. It can load data from the database in the case of a previous patient. It can also save data to the database in case of a new patient or update of a previous patient. This screen also determines the patient number in the database which is essential for the other objects to interface with their respective databases.

As in section 2.3.6 the weight, height, gender, age and activity level are required in order to determine the patient's insulin dosage. The program will not let the user continue if these values have not been entered. As they are essential, it is also imperative that they are as accurate as possible.

The option is also given to delete a previous patient in this screen. All data in all databases of this patient will then be deleted. This is to ensure that databases don't contain old information that is not used any more.

The user can also choose another patient from this screen. This is one of only two screens where this is possible. The user can return to this screen at any time and choose another patient, but he cannot do it from other screens. When the user returns to this screen, all current data is saved and no data will be lost.

When the necessary information has been completed in the patient information screen, a button appears that allows the user to go on to the next screen. This is the CGM data screen.

CGM data input window

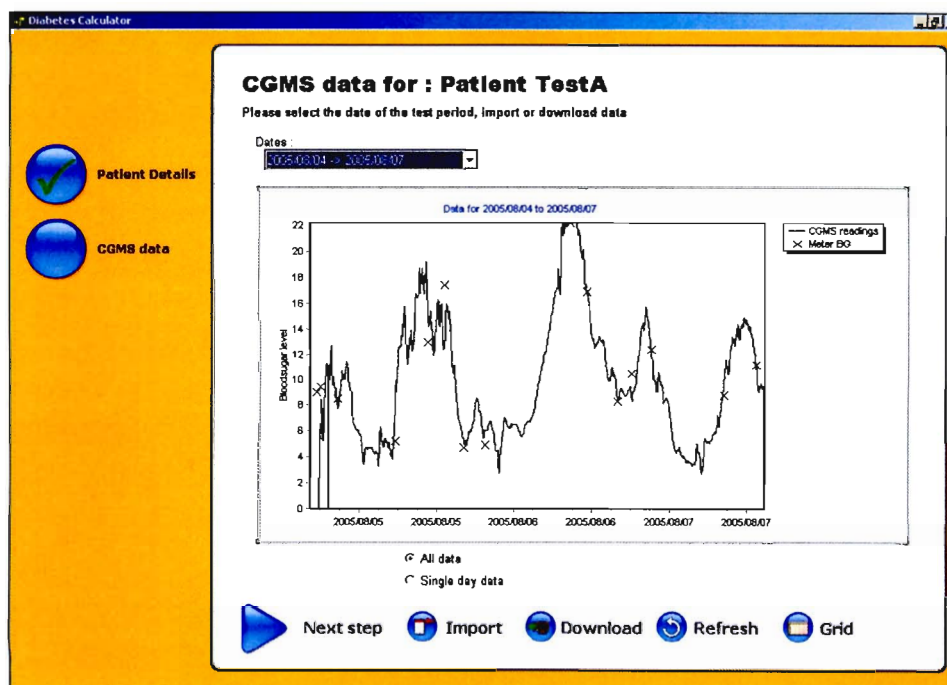


Figure 23: Screenshot of CGM data page

When the user enters the CGM data screen shown in Figure 23, no data is shown. The data will be shown in one of three ways. The user either has to import the data from a file, download the data from the device or choose the previous data's date in case of a previous patient. This will then show the graph of the patient's blood glucose levels over the recorded time period.

Only once valid CGM data is showing will the user be able to go to the next screen. This is to ensure that valid data is selected when it comes to determining a solution. The dates of the data are also used in the next few steps to enter the meal and the insulin data.

The user also has the choice to look at one day of data at a time. This ranges from 00:00 the morning to 24:00 that night. All data can also be shown in table format with the "Grid" button. This will bring up a window showing all the data in the form of a table. This is done using the function call in the CGM object.

The download button will call the object function to interface with the CGM software. During this download the user must have no interaction with the computer. If any interaction occurs and the data is corrupted the process will be voided and will have to

be redone. Only once the download is finished and the software informs the user of this may the user resume interaction.

The import button uses files exported by the CGM software. This file is in a CSV format that is readable by any text reader. This file must not be edited before import, as this could cause the data to be corrupted. Once this has happened the dates of the data imported will be available for selection.

Insulin data input windows

The next screen is available as soon as a valid date selection has taken place. This screen is the insulin data screen. The user will be able to view a summary of all the insulin administrations entered for this patient between the dates selected in the previous screen. This screen is illustrated in Figure 24.

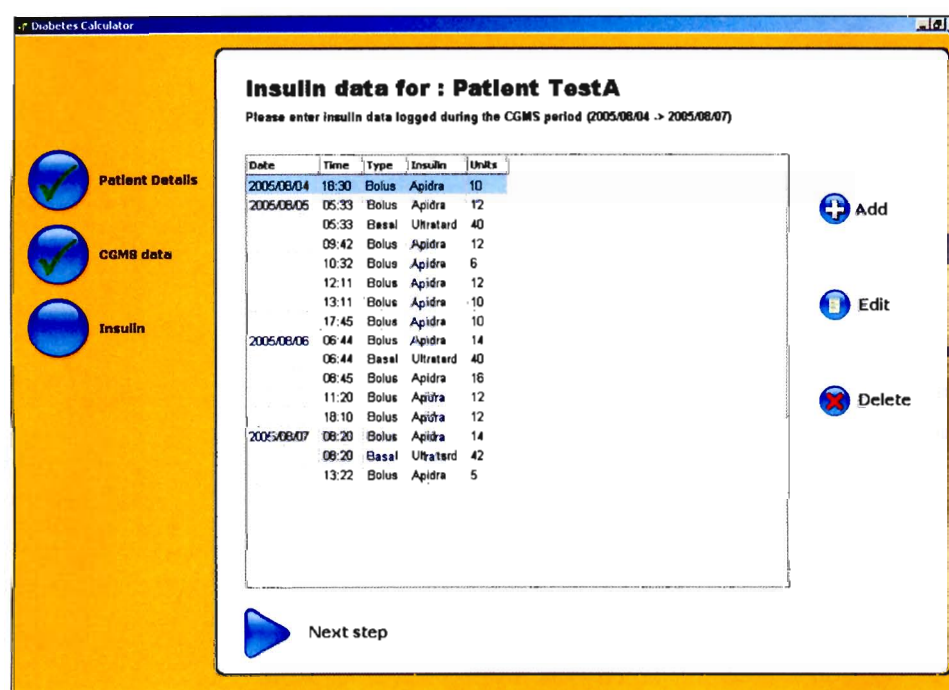


Figure 24: Screenshot of insulin summary screen

The “Next step” button will only appear once a valid entry has been made. As it is unknown how many administrations happened during the recording period it is not possible to hide this button until all entries has been made. If the user leaves out an entry, the results will be inaccurate.

The table display function in the object will only display data in the recording period for the selected patient. The input stage also does not allow data to be entered for

another date. The user has the option of changing an existing entry with the “Edit” screen. He can also delete the data by selecting the entry. Any of these changes will cause permanent changes in the database.

The “Add” and “Edit” button will go to the insulin event screen in Figure 25. In edit mode, all the data will be filled in and ready to be edited. In the new mode, all the fields will either be empty or the default will be selected.

The new mode will select default values and the selections that need others will not show. The “OK” button will also not be showing until valid selections have been made. The date and time of the previous entry will be selected. This is to make selections faster.

Only the insulin type box will show. On selecting a type, the insulin name box will appear. Only once a valid selection is made from that will the user be able to enter the units of insulin. Once a non-zero value has been entered there, the “OK” button will appear.

The screenshot shows the 'Insulin event' window of the 'Diabetes Calculator' application. The window has a yellow sidebar on the left with three buttons: 'Patient Details' (with a green checkmark), 'CGMS data' (with a green checkmark), and 'Insulin' (with a blue circle). The main white area is titled 'Insulin event' and contains the text 'Please enter the information for the insulin event'. It features several input fields: 'Select date:' with radio buttons for 'Thu 04 Aug 2005' (selected), 'Fri 05 Aug 2005', 'Sat 06 Aug 2005', and 'Sun 07 Aug 2005'; 'Select time:' with a digital clock showing '18:30'; 'Select insulin:' with two dropdown menus, the first showing 'Basal' and the second showing 'Lisins'; and 'Units of insulin:' with a text box containing '10.0'. At the bottom are 'OK' and 'Cancel' buttons.

Figure 25: Screenshot of insulin event screen

On clicking “OK” the user will be returned to the insulin summary page. The new entry will either be added or the previous entry edited with the new values. The

“Cancel” button will also return the user to that window, but no entry will be added and all previous entries will retain their original values.

Once all the insulin administrations have been entered, the user can click the “Next step” button in Figure 24. It is very important that all the insulin entries are correct. The user must ensure that this is the case before continuing.

Meal data input windows

The next screen is the meal summary screen which interfaces with the meal object. This screen only uses the part of the meal object to interface to the patient meal database. The ets database is not accessed at this point.

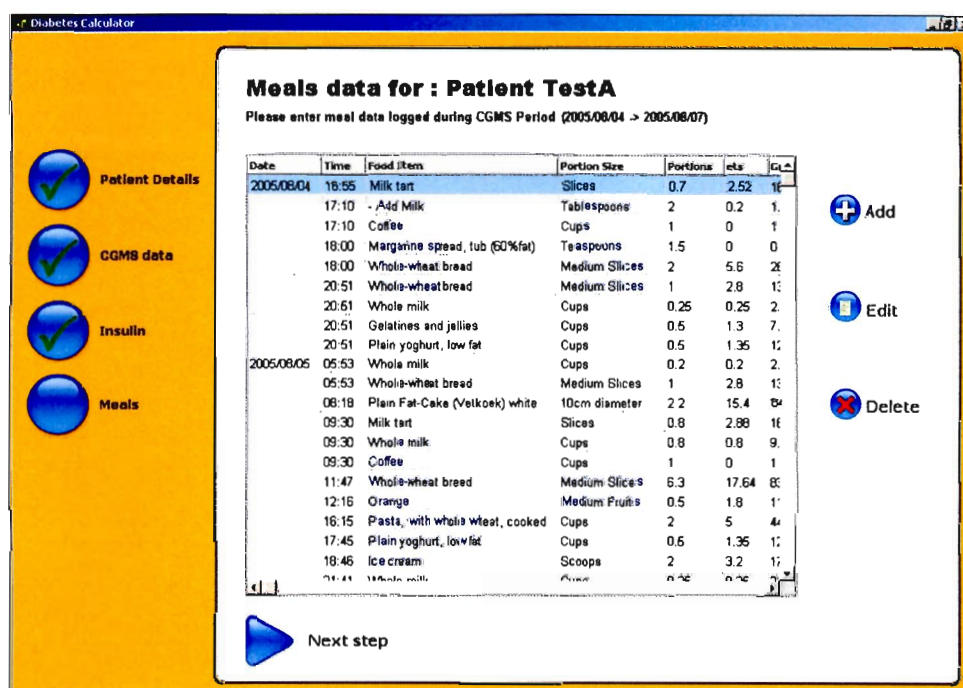


Figure 26: Screenshot of the patient meal summary screen

The function to draw a table of patient data in the meal object is called at this point. It displays all the data in a Meal_Record. The GI value is also displayed as this is used in the result object.

The user is again offered the choice to add a record, edit a current record or delete a current entry. The “Next step” button will only appear if a valid entry has been made. The user can also return to the patient data screen at this point and choose another patient. All data entered up to this point will be saved in the database.

The “Add” or “Edit” buttons result in the same screen. The meal event screen displayed in Figure 27 will appear. Once again that which is displayed will depend on whether it is a new entry or a previous one. With a new entry default values based on previous entries and empty blocks will be displayed. The edit mode will show the details of the selected entry.

Figure 27: Screenshot of the meal entry screen

The new mode will display values for date and time based on the last entry. Only the food groups' box will be shown. Once a choice has been made for the food group, the food subgroups will be displayed. The food names will follow a valid choice in that box.

The user will then be asked the amount of portions the person consumed. This portion name will be extracted from the ets database. The ets value is based on this portion. As an example, if a burger is chosen, the question will be for the amount of burgers where cereal will be measured in cups.

Once a valid number of portions larger than zero have been entered, the ets amount consumed will be displayed. Only then will the “OK” button appear. The values will be saved to the database if “OK” is chosen and the user will return to the meal summary screen. “Cancel” will disregard the entered values and return to the meal summary screen.

Once all the meal entries have been entered and confirmed as correct, the user can continue with the “Next step” button in the screen in Figure 26. The user will be directed to the exercise screen next.

Exercise input windows

The patient exercise screen is shown in Figure 28. This displays all the exercise events that occurred during the recording time. This screen interfaces with the patient object. Only the patient exercise database will be accessed from this screen.

The user has the choice on this screen to add an entry, edit or delete a previous entry. The “Next step” button will be displayed even if no entry is entered as there may have been no exercise during the recording period.

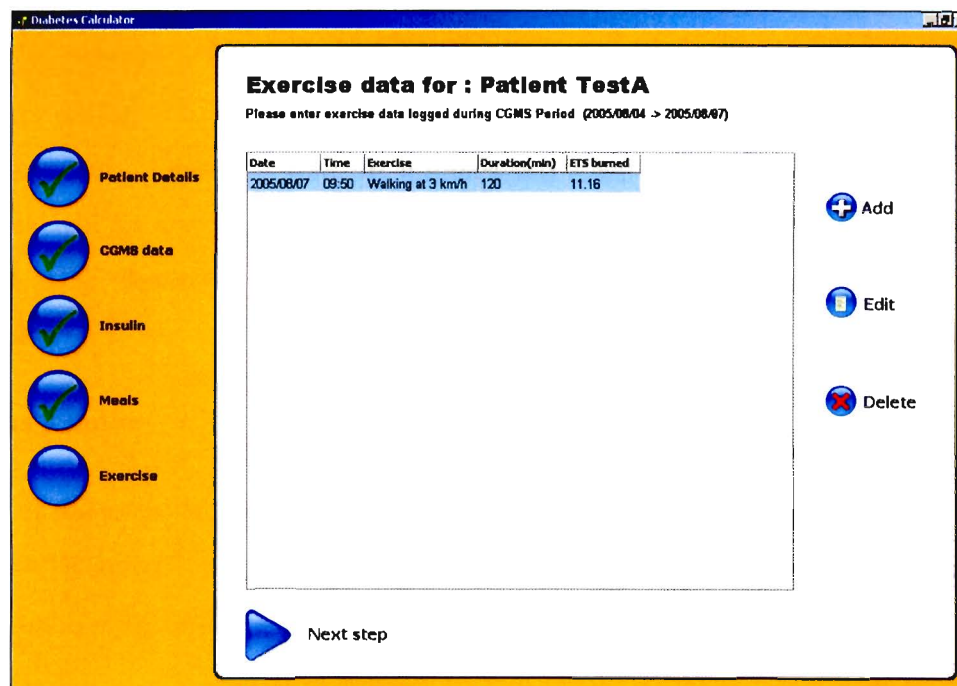


Figure 28: Screenshot of exercise summary screen

The “Add” and “Edit” buttons will both result in the exercise event screen displayed in Figure 29. When the “Edit” is selected, the data of the selected entry will be displayed. “New” will use the date and time of the previous entry and only display the exercise selection box upon entry.

Diabetes Calculator

Diagnostic report

Patient details

Name :	Patient	Surname :	TestA
Gender :	Female	Age :	44 years
Height :	1.6 m	Weight :	93 kg
Daily activity level :	Low	BG control level :	7.00 mmol/l

Blood glucose diagnostic values

Recommended daily basal dosage :	34.80	units
Insulin sensitivity :	0.54	mmol/l/units
ETS sensitivity :	0.59	mmol/l/ets
ETS / insulin :	1.09	ets/unit
Average daily insulin usage :	46.7	units
Average daily ETS consumption :	36.6	ets
Average blood glucose :	9.8	mmol/l

Determine Results

Figure 30: Screenshot of results page

For reference values, the patient's average daily insulin usage over the recorded period is shown. The patient's ets consumption and average blood glucose levels are also shown. This can be used to explain to the patient why it is necessary to change the dosage levels.

The user can now choose "Select other patient" to start with a new patient. If the doctor needs to revisit these results, they will be available upon request. The correct dates need to be chosen at the CGM screen to show these exact results again. No other data will have to be entered.

3.2.4. Interfacing with current monitoring systems

Initially it was planned that the protocol used to communicate with the CGM would be used to extract data. The manufacturer of the device would have to divulge this information. As it was doubtful that they would freely give this information, another solution had to be found.

The CGM software could be used as an interface to the CGM. It has a function that enables it to export data as a CSV (comma separated values) file that can be read by any software.

This presented two choices:

1. It would have to be done manually by the user of the solution.
2. Using simulated keystrokes, it is possible to manipulate the program to download and export the data as a CSV file.

As ease-of-use is one of the main specifications, the second option was decided on. User verification would still be required to ensure that the data transferred correctly. The user would have to tell the solution whether the process went smoothly. The CGM software would not return any information about the success of the process.

The data in the CSV file is very difficult to use if specific values are needed as some string manipulation is required. The best option would be to extract data from the CSV file and store it in records in memory for use. It would then be a relatively easy step to store it in a database. In this database, any blood glucose information of the person will be easily accessible.

Microsoft released the Windows API to enable programmers to use Windows native functions. This can be used for functions such as explorer functions, command line tools etc. This has always been a part of Windows, but the API's help is required to interface with Windows.

Included in the API is the ability to simulate keystrokes from software. Using this it is possible to give commands to other software from code, i.e. one can simulate a person pressing keys. Also included is the ability to switch focus to another window.

Combining these two functions gives the capability that is needed to interface with the CGM software. First, the focus would be changed to the CGM software. A series of keystrokes will then be simulated. The two series of keystrokes will be explained later in this section.

Suitable waiting periods are also required to allow the software to finish what it was doing. As the time required by the software to finish these commands differs from computer to computer, a pre-determined waiting period cannot be used. A dynamic method of determining if the program is finished is required.

Windows keeps a list of all the processes that are currently running. Included in this list is the processor time used by the process. Tools exist that allows you to access this list from software. You can then determine if another program is busy or not.

This ability of Windows can be used to determine if the CGM software is still busy. After each simulated keystroke, the developed software goes into a state of waiting for the CGM software to use 0% of processor resources which indicates that it is in a state of waiting. If this occurs, the next key can be simulated to continue with the process.

There are two sequences that can be simulated to extract data from CGM data. The first is to export a current data file. The second is to download data from the CGM and then to export that data. Both these sequences use a common sequence to export the data.

The sequence of the first is as follows:

1. Change focus to the CGM software
2. Select the “File” menu
3. Select the “Open” option
4. Paste the name of the data file as selected by the user
5. Press “Enter”
6. Go to the common section

The sequence for the second is:

1. Change focus to the CGM software
2. Select the “File” menu
3. Select the “New” option
4. Fill in the patient data as entered in the developed software in the patient detail screen

5. Select the “CGM” menu
6. Select the “download” option
7. Go to the common section

The common section does the following:

1. Select the “File” menu
2. Select the “Export” option
3. Press enter
4. Change focus back to the developed software

After this common section, a test is performed to verify the exported data. As there is no way for the software to verify the procedure in the CGM software, the only way to test it is to see if a CSV file was successfully created. If this is not the case, the user is asked to either retry the procedure or determine why it failed.

If this test passed, the data needs to be imported from the readable CSV file to the database. This is done by using the CGM functions explained in the previous section. After this, the data can be used by the algorithm to determine the patient’s insulin regime.

3.2.5. Testing the final solution

This section explains the testing done to ensure good software quality. The testing and results for the algorithm are not discussed in this section. This is discussed in chapter 4.

The following testing procedures will be done to ensure the quality:

- Vigorous testing by the developer
- Testing by another software developer for obvious flaws
- Testing by another engineer who is given training in using the software

All these steps are necessary as they will each expose different bugs to be fixed or improvements to be made. The first two points should expose most of the bugs. The last two will result in suggestions for improvements as well as minor bugs.

Testing by the developer alone is not enough to expose bugs. The software was developed with his testing methods and it is probable that something will be missed. In order to expose more bugs, another software developer must also test it. Because it is a developer, he will know what to look for in software quality. As he did not write the software, he will not be testing the same functions as the developer.

The other engineer will test the software from a computer expert point of view in terms of usage. He can make suggestions to improve the speed of the software. The flow of the software will also be tested and suggestions as to how it can be made smoother can also result.

3.3. *The solution for the end-user*

3.3.1. Installation of software

The setup of the solution should be easy and painless for the end-user. A single setup run from a CD will be required to set up all necessary software and tools. This includes the developed solution, the database tools and the CGM software.

As the software is intended to be bundled with CGM software, the install for the CGM software will not be included at first. Only after a CGM manufacturer has bought the technology, will it be bundled with their software, either in API form or complete package form.

To set up the database software manually is quite an involved process. It is crucial that this is done automatically. The components that need to be installed are the Firebird database server, the database manager to manually manipulate the data if required and the interface between the code and the database server.

There are also steps required such as setting up usernames and passwords for the database server. The software comes with a default, but as some of the information

stored in the databases is intellectual property, this data must be protected more carefully. This can also be done automatically.

The software must interface with the CGM software and at this stage it is not feasible to install the software automatically. Safeguards must be put in place to ensure that the software does not attempt to extract data if the software is not installed. This was put in the start-up sequence of the software. The software will not start up if the CGM software is not installed. The user will be warned of this.

The setup process at this stage is as follows:

- Install the CGM software bundled with the monitor
- Install the solution (the database and software will be installed)

3.3.2. Setup of necessary hardware

Before commencing in the usage of the software, the necessary hardware must be installed and ready. This means that the interface with the CGM monitor must be complete and functional.

The CGM uses a serial interface to communicate with the PC. This means that an empty COM port is required. These ports are mostly not available in newer PC's, but can be added as an extension. Most laptops don't have this port and USB-to-RS232 expanders are required.

Problems have surfaced when interfacing to the monitor using the USB-to-RS232 technology. Communications are intermittent and sometimes extensive debugging is required to determine the problem with the communication. This is definitely not recommended as a solution, but can be done if absolutely required.

If this software is ever sold to a CGM manufacturer, pure USB communications should be recommended as that is the industry standard these days for interfacing with peripherals.

3.3.3. Training medical staff

When the solution is bundled with the CGM, training will be necessary in the use of the software. The entering of data as well as proper troubleshooting techniques will

have to be taught to all the staff that will be in contact with the software. This includes the doctor and any person that will enter the data if he doesn't do it himself.

If the manufacturers decide to stay with the easy to use interface, the training won't have to be intensive as it was designed to be as easy to use as possible. If, however, they decide to use the API and design their own interface, more intensive training may be required.

If the solution isn't bundled with the CGM and is distributed as a stand-alone package, a manual will be sufficient to explain the usage of the software. A manual together with the on-screen instructions will be able to guide any end-user to using the software correctly. Because the software does not except any erroneous inputs, the chances of using it incorrectly are very remote.

3.4. Overview of the characterisation system

This section sums up all the processes and components discussed in this chapter. The solution is broken down into its main components and the development process is also discussed.

The components are the following:

- The CGM system and it's hardware interface
- The CGM software
- The developed software
 - Patient info
 - CGM info
 - Insulin info
 - Meal info
 - Exercise info
 - Results generator
 - Characterisation algorithm

The software development procedure was as follows:

- Determining and writing the specification
- Designing the solution
- Implementing the solution in code
- Testing of the final solution
- After sales support and training

The result is a complete characterisation system that can be used to determine type 1 diabetics' insulin regimes as written out in the specifications set forth in Chapter 2. In the next section the results generated by this solution will be verified.

4. Verifying the new characterisation system

In this chapter the results achieved are discussed. They are verified against factors describing the patients' blood glucose control.

4.1. Prelude

The results achieved are given and discussed in this chapter. This includes the basal and bolus regimes suggested as well as the calculated insulin and its sensitivity values. These results were determined with the software solution implemented in the previous chapter.

In order to verify these results, they are evaluated as to their effect on a number of factors discussed in the next section. The resulting dosages should lead to better control in these factors. There is also the possibility that the program could not find a suitable solution. In these cases the software should warn the user.

4.2. Criteria for success

4.2.1. Average blood glucose levels

A diabetic's average blood glucose level gives an indication of blood glucose control. It wasn't possible to determine a person's average blood glucose levels until CGM technology, so no definitive values have been determined.

HbA1c values give an indication of the average blood glucose levels in the 2-3 months leading up to measurement [40]. HbA1c can be translated to average blood glucose levels. Table 3 gives the blood glucose levels for HbA1c levels.

HbA1c	BG
6%	7.5
7%	9.4
8%	11.4
9%	13.3

Table 3: HbA1c against blood glucose levels

The ADA recommends that HbA1c levels should be kept below 7% [41]. This translates to a level of 9.4mmol/l. The ADA also states that it is preferred if this level is nearer to 6.5% which translates to about 8.5mmol/l as this is safer and will result in less complications.

Using the CGM, it is possible to very accurately determine a patient's average blood glucose levels. This can be used to determine the effectiveness of a patient's current insulin regime. The results can also be verified by the effect the new dosage will have on a patient's blood glucose levels.

Basal insulin allows cells to utilise glucose for energy, thereby removing glucose from the blood. A higher basal dosage will cause lower blood glucose levels measured over a period of time. A lower dosage will increase blood glucose levels.

The tools for determining these levels have already been programmed into the software solution. The patient's average blood glucose levels are given in the results page.

Unfortunately, average blood glucose levels aren't the only or even most important aspect of a diabetic's blood glucose control. Other factors such as hyper- and hypoglycaemic events also need to be considered. Townsend and Matthews developed a concept to determine how good a diabetic's blood glucose control is [32]. This will be discussed next.

4.2.2. Accuracy of blood glucose control

Even though a diabetic's average blood glucose could give an indication of the blood glucose control, this may not always be the case. The average between very high and very low levels could still be quite good, but these extremes are not factored in. This is displayed in Figure 31 [32]. The average is in the accepted zone, but hyper- and hypoglycaemic events occurred.

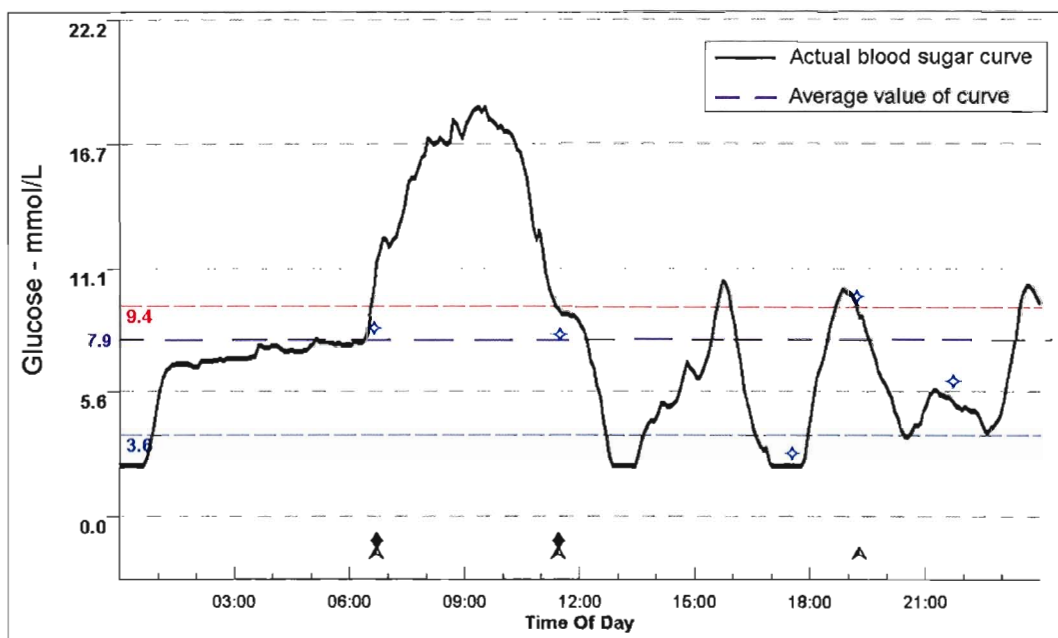


Figure 31: Example of how average alone is not adequate

Mathews and Townsend [32] proposed a new method of defining blood glucose control. It was suggested that the areas that can be determined using the CGM technology would be an effective way to determine blood glucose control. Figure 32 displays the area between curve and mean. This can be used to determine the accuracy of blood glucose control.

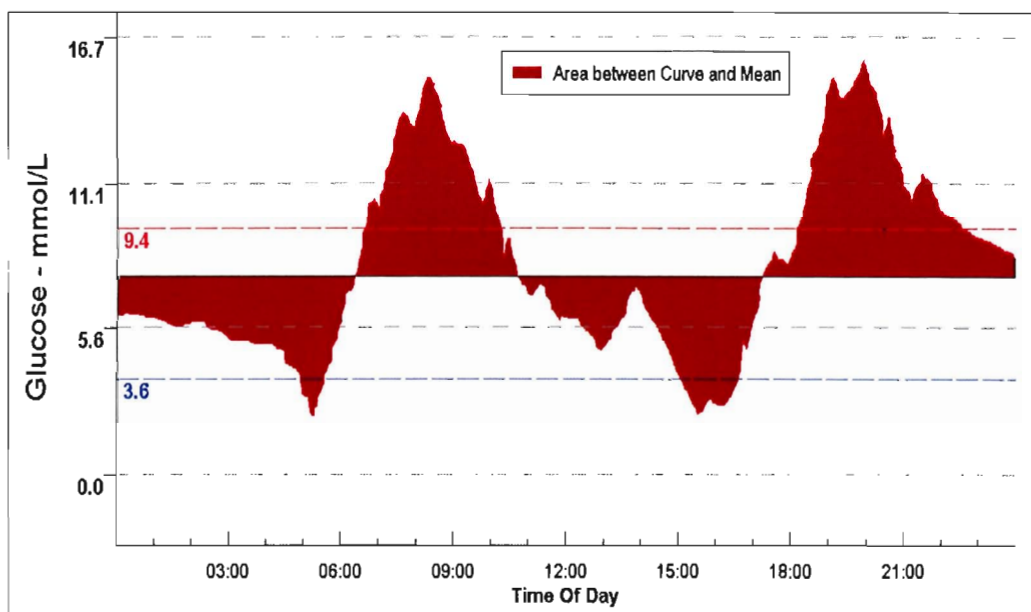


Figure 32: Illustration of the area between curve and mean

Area under curve

The area under the curve (AUC) can be used to calculate the average blood glucose level by dividing the area with the time of the area. This average blood glucose value therefore also gives an indication of HbA1c [42] level of the patient. As diabetics tend to control their blood sugar level too high, it is desirable to lower the area under the curve. The lower it is, the lower the average blood glucose levels will be. It can be determined as in formula 4.2.2.2. This will translate into the area between two readings under the curve.

$$AUC = \sum (BS(t) \times 5) \quad 4.2.2.2$$

Where:

- $BS(t)$ = each reading of the CGM system.
- The variable is multiplied by 5 as the time between glucose readings is 5 minutes.

The events known as hyper- and hypoglycaemic events are characterised by blood glucose levels above 9.4mmol/L and below 3.6mmol/L respectively. It is possible that BG levels could fall into those categories for a very short period. As such, it is only viewed as an event if the levels stay in those categories for more than thirty minutes.

Hyperglycaemic and hypoglycaemic events area

The areas for hyperglycaemic and hypoglycaemic events are determined as the area in which this occurred. Figure 33 illustrates such events. To determine the area for the hyperglycaemic events the areas should be calculated for the green parts above the hyperglycaemic limit for longer than thirty minutes. To determine the hypoglycaemic area, green areas under the hypoglycaemic limit for longer than thirty minutes should be used.

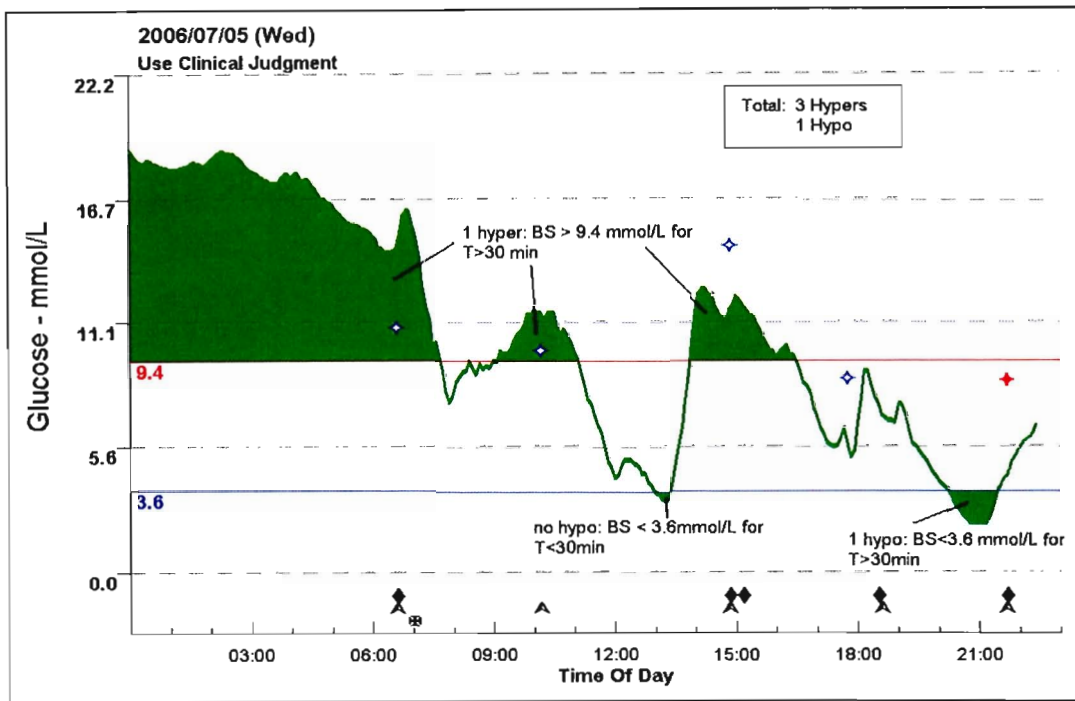


Figure 33: Areas determined for hypo's and hypers

Area between curve and mean

The area used in tightness of control is the area between the curve and the mean (ABCM). The less this is, the tighter the BG control is as this translates to less variation. Figure 32 illustrates the concept of ABCM. By comparing this to a healthy person's ABCM the diabetic's tightness of control can be determined. Formula 4.2.2.3 calculates ABCM.

$$ABCM = \sum |(BS(t) - M) \times 5| \quad 4.2.2.3$$

Where:

- $BS(t)$ = Blood glucose value as a function of the time
- M = Mean value of the blood glucose curve.
- To determine the area the multiplication by 5 is used as this is the time between glucose readings.

4.3. Case studies

These case studies will be entered into the software to generate results. The results as they are presented by the system will be included. In some of the graphs it is evident that the CGM took no readings as the level is 0 for an extended period of time. These periods were left out of any calculations.

It was possible to study 11 patients. For a more detailed and complete study clinical trials will have to be performed. Trials such as these fall outside the scope of this study for the following reasons:

- The ethical committee that decides if a prospective intervention study is acceptable takes too long to approve a study. The risk and possible benefits should be weighed before a decision can be made. Risks in insulin intervention trials are considerable.
- This committee is very strict and it may be necessary to perform this study in phases to satisfy their requirements.
- To make sure that the study is accurate and to give power to the results, the study will have to be conducted on a large group of patients. This is expensive and time-consuming.

For these reasons a study like this will have to be conducted in collaboration with a manufacturer of a CGM system. For the reasons above retrospective data sets for a few case studies were used. It is not possible at this stage to compare actual blood glucose control as a result of the intervention. At this stage, the proposed intervention can only be logically analysed.

4.3.1. Case study A



Type 1 diabetes blood glucose characterisation report

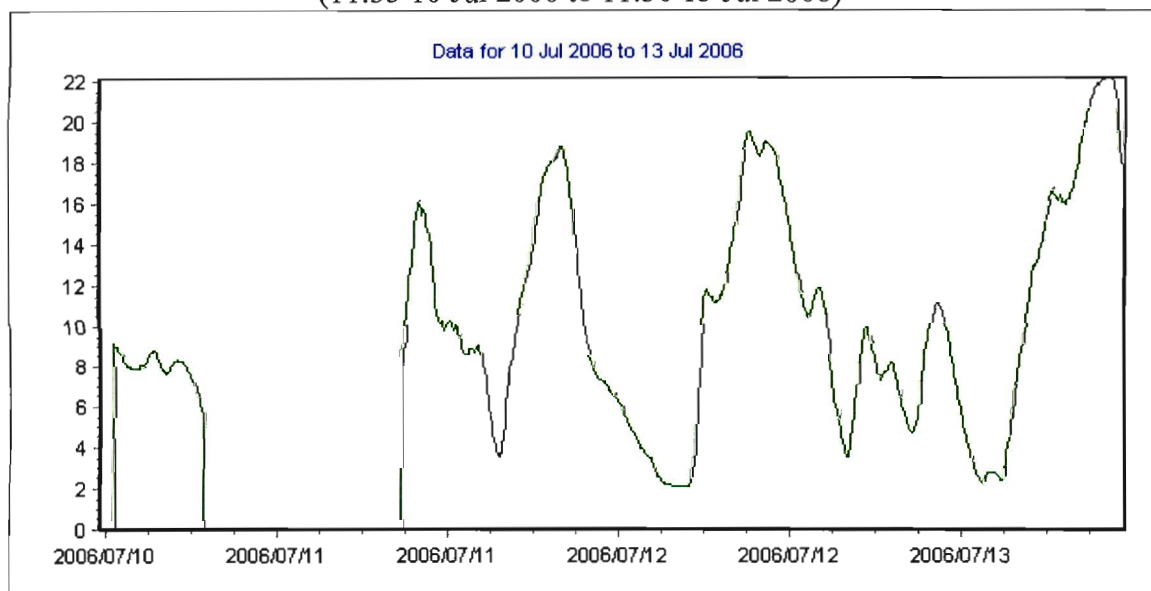
Generated on 12 Dec 2007

Patient details

Patient ID:	01/10072006
Patient name:	Case Study A
Age:	18
Gender:	Female
Height:	1.66 m
Weight:	75.00 kg
BMI:	27.22
Classification:	Overweight
Activity level:	Medium

Blood glucose profile

(11:35 10 Jul 2006 to 11:30 13 Jul 2006)



Regime

	Basal dosage	Bolus dosage	ets Intake
Current	22 U	41 U	32.3 ets
Suggested	26 U	27 U	31.6 ets

Average blood glucose level:	10.22 mmol/l
ets Sensitivity:	0.67 mmol/l.ets
Insulin sensitivity:	0.80 mmol/l.U

Comments

The patient consumes approximately the same amount of ets as the RDA. Therefore expect the bolus dosage to be equal to the basal dosage.

This patient suffers from frequent hyperglycaemia and should try to lower blood glucose levels.

This patient has experienced some hypoglycaemic events.

An increase in basal dosage from 22 units to 26 units is suggested to decrease the patient's average blood glucose levels.

A decrease in bolus dosage from 41 units to 27 units is suggested to raise the patient's post prandial blood glucose levels.

Using the correct insulin and ets sensitivities to calculate insulin bolus dosages should improve the tightness of glycaemic control.

Doctor's recommendations

4.3.2. Case study B



Type 1 diabetes blood glucose characterisation report

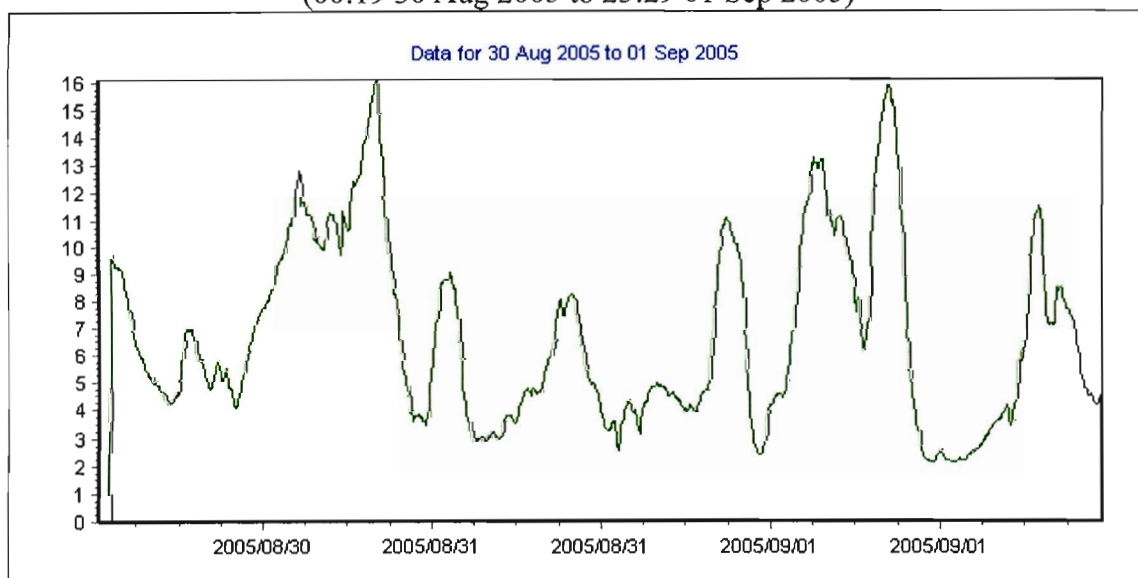
Generated on 12 Dec 2007

Patient details

Patient ID: 01/30082005
 Patient name: Case Study B
 Age: 53
 Gender: Male
 Height: 1.80 m
 Weight: 75.00 kg
 BMI: 23.15
 Classification: Normal weight
 Activity level: Medium

Blood glucose profile

(00:19 30 Aug 2005 to 23:29 01 Sep 2005)



Regime

	Basal dosage	Bolus dosage	ets Intake
Current	24 U	25 U	34.7 ets
Suggested	25 U	25 U	34.2 ets

Average blood glucose level: 6.77 mmol/l
 ets Sensitivity: 0.87 mmol/l.ets
 Insulin sensitivity: 1.20 mmol/l.U

Comments

The patient consumes approximately the same amount of ets as the RDA. Therefore expect the bolus dosage to be equal to the basal dosage.

This patient has experienced some hypoglycaemic events. Please adjust bolus accordingly.

An increase in basal dosage from 24 units to 25 units is suggested to decrease the patient's average blood glucose levels.

No change in bolus dosage is suggested at this time.

Doctor's recommendations

4.3.3. Case study C



Type 1 diabetes blood glucose characterisation report

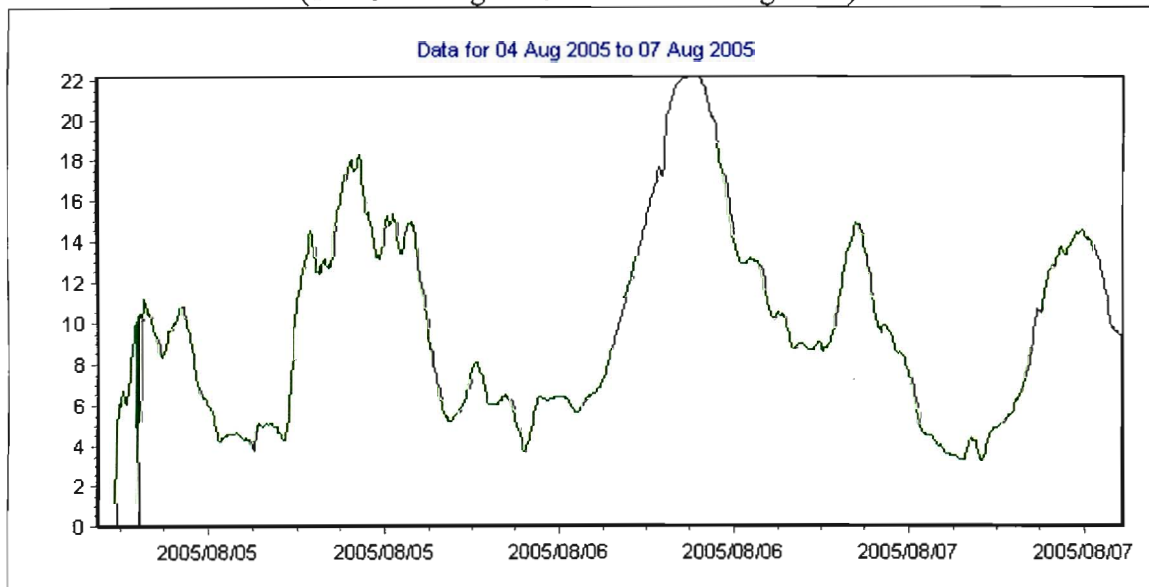
Generated on 12 Dec 2007

Patient details

Patient ID: 01/04082005
 Patient name: Case Study C
 Age: 44
 Gender: Female
 Height: 1.60 m
 Weight: 93.00 kg
 BMI: 36.33
 Classification: Obese
 Activity level: Medium

Blood glucose profile

(16:26 04 Aug 2005 to 14:40 07 Aug 2005)



Regime

	Basal dosage	Bolus dosage	ets Intake
Current	40 U	58 U	53.3 ets
Suggested	37 U	63 U	31.1 ets

Average blood glucose level: 10.02 mmol/l
 ets Sensitivity: 1.28 mmol/l.ets
 Insulin sensitivity: 1.09 mmol/l.U

Comments

The patient consumes more ets than the RDA. Therefore expect the bolus dosage to be more than the basal dosage.

The patient will likely gain weight in the long run as he/she eats much more than his/her RDA

This patient suffers from frequent hyperglycaemia and should try to lower blood glucose levels.

A decrease in basal dosage from 40 units to 37 units is suggested. This will increase the average blood glucose levels, but the increase in bolus will lower the average.

An increase in bolus dosage from 58 units to 63 units is suggested to lower the patient's post prandial blood glucose levels.

Doctor's recommendations

4.3.4. Case study D



Type 1 diabetes blood glucose characterisation report

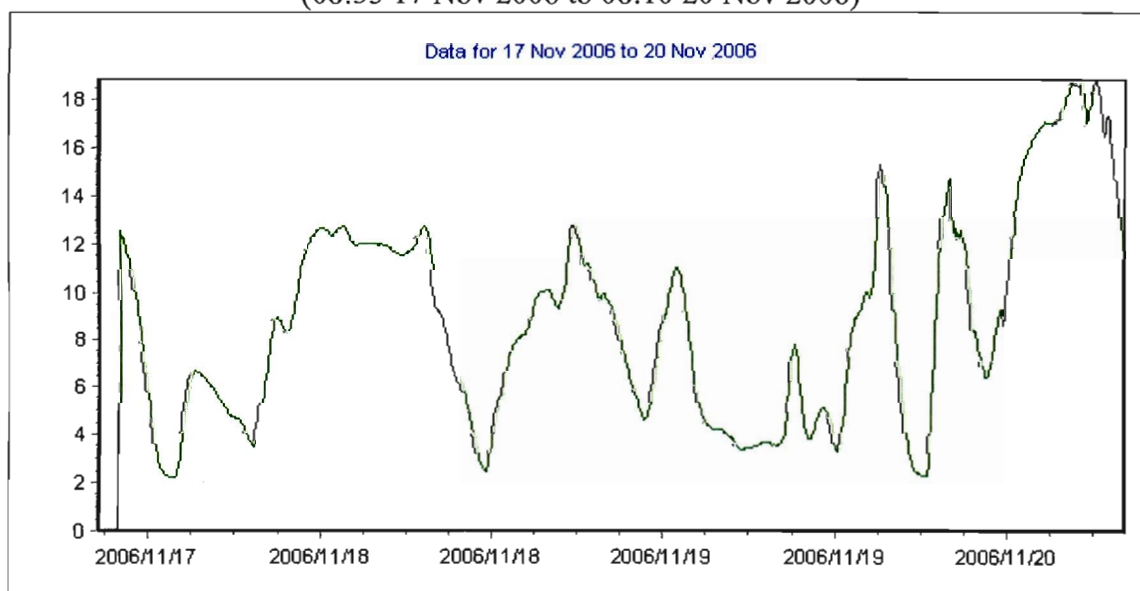
Generated on 12 Dec 2007

Patient details

Patient ID: 01-17112006
 Patient name: Case Study D
 Age: 40
 Gender: Female
 Height: 1.63 m
 Weight: 55.00 kg
 BMI: 20.70
 Classification: Normal weight
 Activity level: Low

Blood glucose profile

(08:35 17 Nov 2006 to 08:10 20 Nov 2006)



Regime

	Basal dosage	Bolus dosage	ets Intake
Current	18 U	22 U	17.7 ets
Suggested	24 U	18 U	23.8 ets

Average blood glucose level: 8.76 mmol/l
 ets Sensitivity: 1.24 mmol/l.ets
 Insulin sensitivity: 1.20 mmol/l.U

Comments

The patient consumes less ets than the RDA. Therefore expect the bolus dosage to be less than the basal dosage.

This patient suffers from infrequent hyperglycaemia.

This patient has experienced some hypoglycaemic events. Please adjust bolus accordingly.

An increase in basal dosage from 18 units to 24 units is suggested to decrease the patient's average blood glucose levels.

A decrease in bolus dosage from 22 units to 18 units is suggested to raise the patient's post prandial blood glucose levels.

Using the correct insulin and ets sensitivities to calculate insulin bolus dosages should improve the tightness of glycaemic control.

Doctor's recommendations

4.3.5. Case study E



Type 1 diabetes blood glucose characterisation report

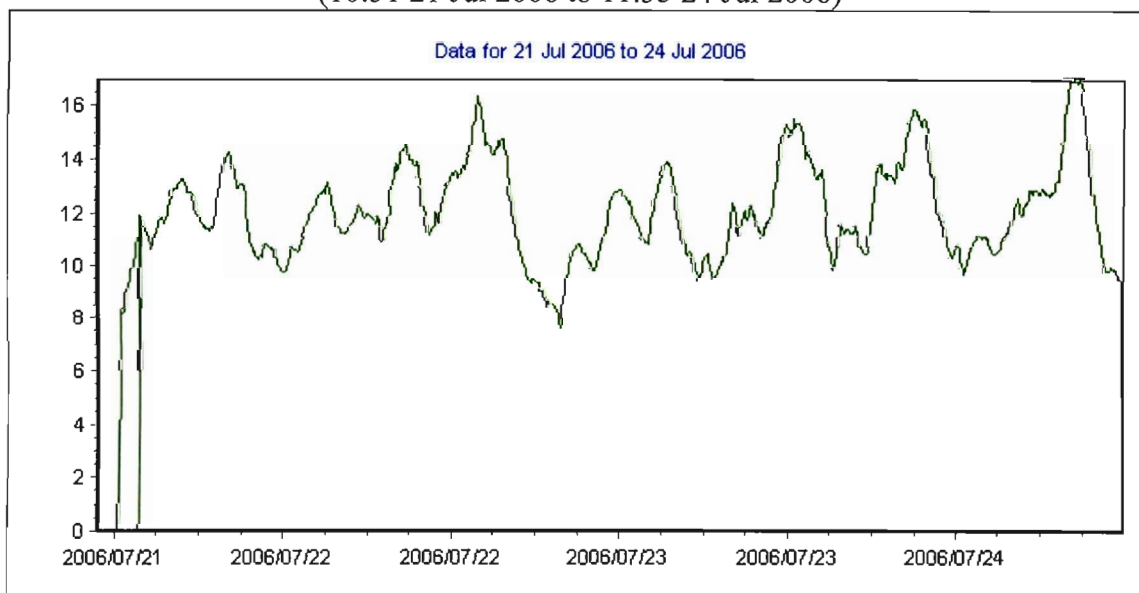
Generated on 12 Dec 2007

Patient details

Patient ID: 01/21072006
 Patient name: Case Study E
 Age: 26
 Gender: Female
 Height: 1.70 m
 Weight: 74.00 kg
 BMI: 25.61
 Classification: Overweight
 Activity level: Medium

Blood glucose profile

(10:51 21 Jul 2006 to 11:55 24 Jul 2006)



Regime

	Basal dosage	Bolus dosage	ets Intake
Current	24 U	27 U	31.0 ets
Suggested	33 U	33 U	31.2 ets

Average blood glucose level: 12.01 mmol/l
 ets Sensitivity: 1.18 mmol/l.ets
 Insulin sensitivity: 1.11 mmol/l.U

Comments

The patient consumes approximately the same amount of ets as the RDA. Therefore expect the bolus dosage to be equal to the basal dosage.

This patient suffers from frequent hyperglycaemia and should try to lower blood glucose levels.

An increase in basal dosage from 24 units to 33 units is suggested to decrease the patient's average blood glucose levels.

An increase in bolus dosage from 27 units to 33 units is suggested to lower the patient's post prandial blood glucose levels.

Doctor's recommendations

4.3.6. Case study F



Type 1 diabetes blood glucose characterisation report

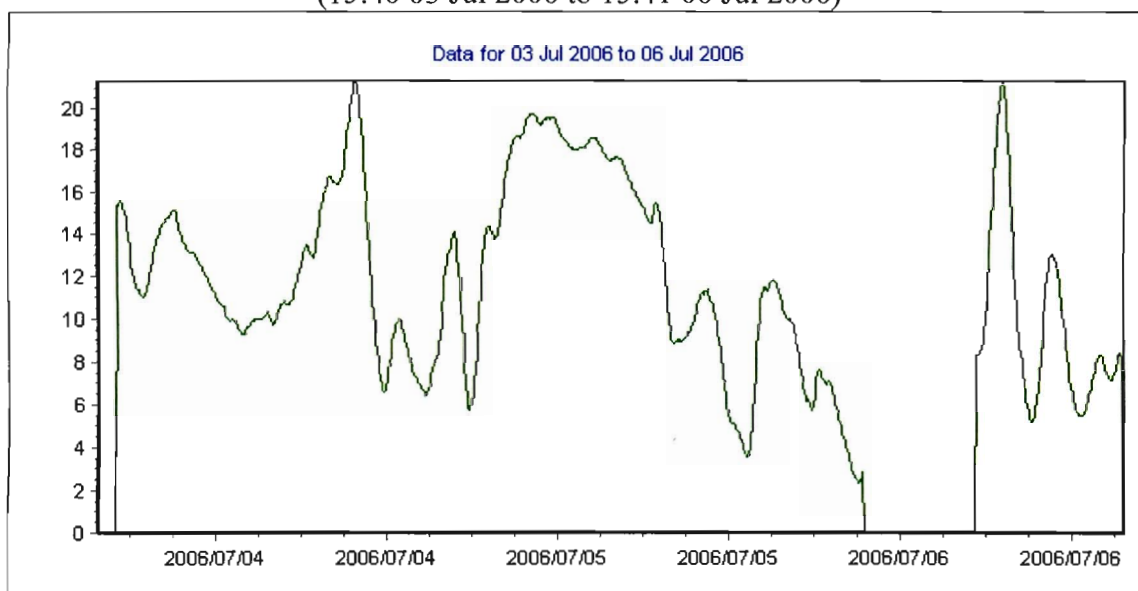
Generated on 12 Dec 2007

Patient details

Patient ID: 01-03072006
 Patient name: Case Study F
 Age: 34
 Gender: Female
 Height: 1.60 m
 Weight: 52.00 kg
 BMI: 20.31
 Classification: Normal weight
 Activity level: Medium

Blood glucose profile

(15:46 03 Jul 2006 to 15:41 06 Jul 2006)



Regime

	Basal dosage	Bolus dosage	ets Intake
Current	16 U	17 U	34.6 ets
Suggested	19 U	25 U	26.3 ets

Average blood glucose level: 11.76 mmol/l
 ets Sensitivity: 0.88 mmol/l.ets
 Insulin sensitivity: 1.20 mmol/l.U

Comments

The patient consumes more ets than the RDA. Therefore expect the bolus dosage to be more than the basal dosage.

The patient will likely gain weight in the long run as he/she eats much more than his/her RDA

This patient suffers from frequent hyperglycaemia and should try to lower blood glucose levels.

An increase in basal dosage from 16 units to 19 units is suggested to decrease the patient's average blood glucose levels.

An increase in bolus dosage from 17 units to 25 units is suggested to lower the patient's post prandial blood glucose levels.

Doctor's recommendations

4.3.7. Case study G



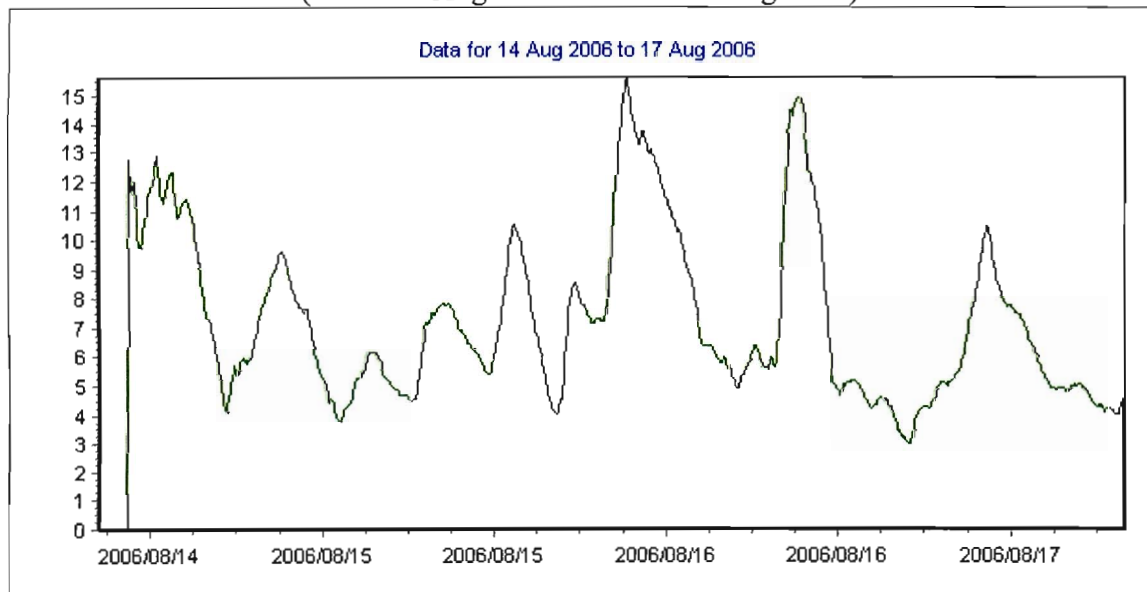
Type 1 diabetes blood glucose characterisation report

Generated on 12 Dec 2007

Patient details

Patient ID: 01-14082006
Patient name: Case Study G
Age: 51
Gender: Male
Height: 1.80 m
Weight: 86.50 kg
BMI: 26.70
Classification: Overweight
Activity level: Low

Blood glucose profile (06:10 14 Aug 2006 to 10:10 17 Aug 2006)



Regime

	Basal dosage	Bolus dosage	ets Intake
Current	24 U	23 U	30.7 ets
Suggested	26 U	24 U	33.8 ets

Average blood glucose level: 7.28 mmol/l
ets Sensitivity: 0.94 mmol/l.ets
Insulin sensitivity: 1.20 mmol/l.U

Comments

The patient consumes less ets than the RDA. Therefore expect the bolus dosage to be less than the basal dosage.

An increase in basal dosage from 24 units to 26 units is suggested to decrease the patient's average blood glucose levels.

An increase in bolus dosage from 23 units to 24 units is suggested to lower the patient's post prandial blood glucose levels.

Doctor's recommendations

4.3.8. Case study H



Type 1 diabetes blood glucose characterisation report

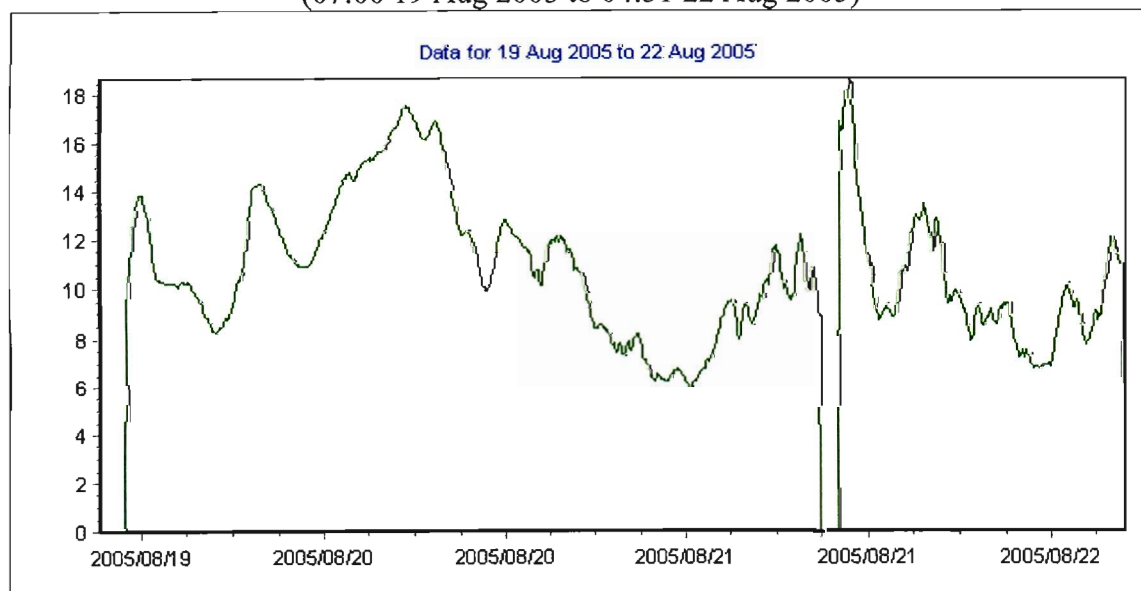
Generated on 12 Dec 2007

Patient details

Patient ID: 01/19082005
 Patient name: Case Study H
 Age: 22
 Gender: Male
 Height: 1.68 m
 Weight: 61.00 kg
 BMI: 21.61
 Classification: Normal weight
 Activity level: High

Blood glucose profile

(07:00 19 Aug 2005 to 04:51 22 Aug 2005)



Regime

	Basal dosage	Bolus dosage	ets Intake
Current	34 U	56 U	45.2 ets
Suggested	34 U	41 U	37.4 ets

Average blood glucose level: 10.86 mmol/l
 ets Sensitivity: 0.45 mmol/l.ets
 Insulin sensitivity: 0.50 mmol/l.U

Comments

The patient consumes more ets than the RDA. Therefore expect the bolus dosage to be more than the basal dosage.

The patient will likely gain weight in the long run as he/she eats much more than his/her RDA

This patient suffers from frequent hyperglycaemia and should try to lower blood glucose levels.

The suggestions for this patient are not accurate enough. The patient will have to redo the study period.

Please make sure that the patient follows these guidelines to ensure more accurate suggestions:

- The test should be repeated during a normal week.
- The patient must not be sick in the period of testing.
- The testing period should not be a stressful period.

The doctor should take extra care during the second test.

Doctor's recommendations

4.3.9. Case study I



Type 1 diabetes blood glucose characterisation report

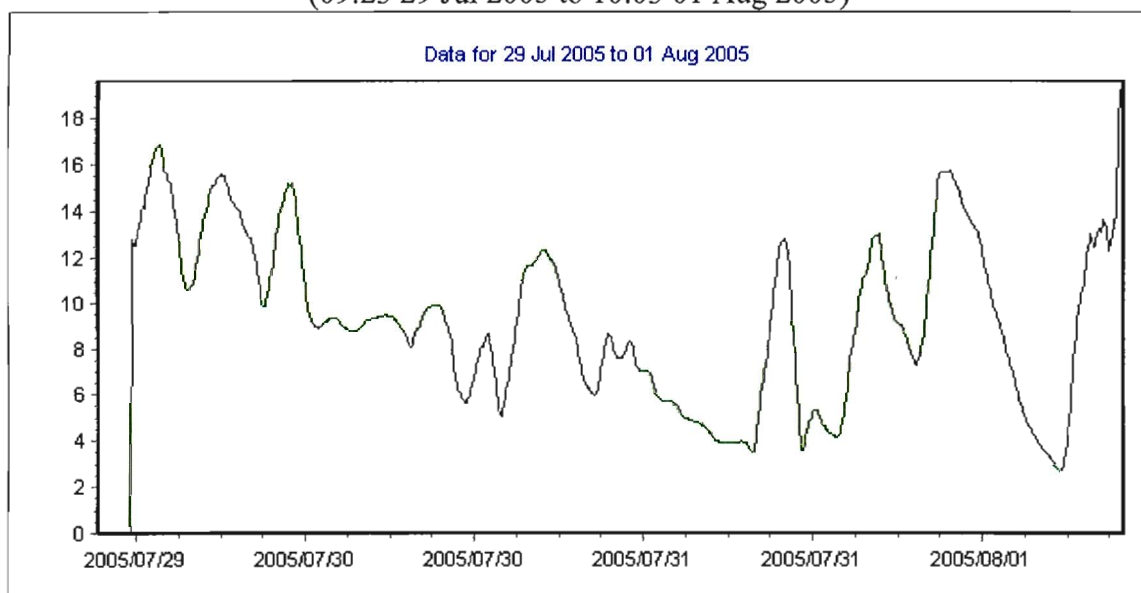
Generated on 12 Dec 2007

Patient details

Patient ID: 01/29072005
 Patient name: Case Study I
 Age: 49
 Gender: Female
 Height: 1.75 m
 Weight: 66.00 kg
 BMI: 21.55
 Classification: Normal weight
 Activity level: Medium

Blood glucose profile

(09:23 29 Jul 2005 to 10:03 01 Aug 2005)



Regime

	Basal dosage	Bolus dosage	ets Intake
Current	16 U	8 U	25.5 ets
Suggested	17 U	15 U	28.5 ets

Average blood glucose level: 9.27 mmol/l
 ets Sensitivity: 1.05 mmol/l.ets
 Insulin sensitivity: 1.81 mmol/l.U

Comments

The patient consumes less ets than the RDA. Therefore expect the bolus dosage to be less than the basal dosage.

This patient suffers from infrequent hyperglycaemia.

An increase in basal dosage from 16 units to 17 units is suggested to decrease the patient's average blood glucose levels.

An increase in bolus dosage from 8 units to 15 units is suggested to lower the patient's post prandial blood glucose levels.

Doctor's recommendations

4.3.10. Case study J



Type 1 diabetes blood glucose characterisation report

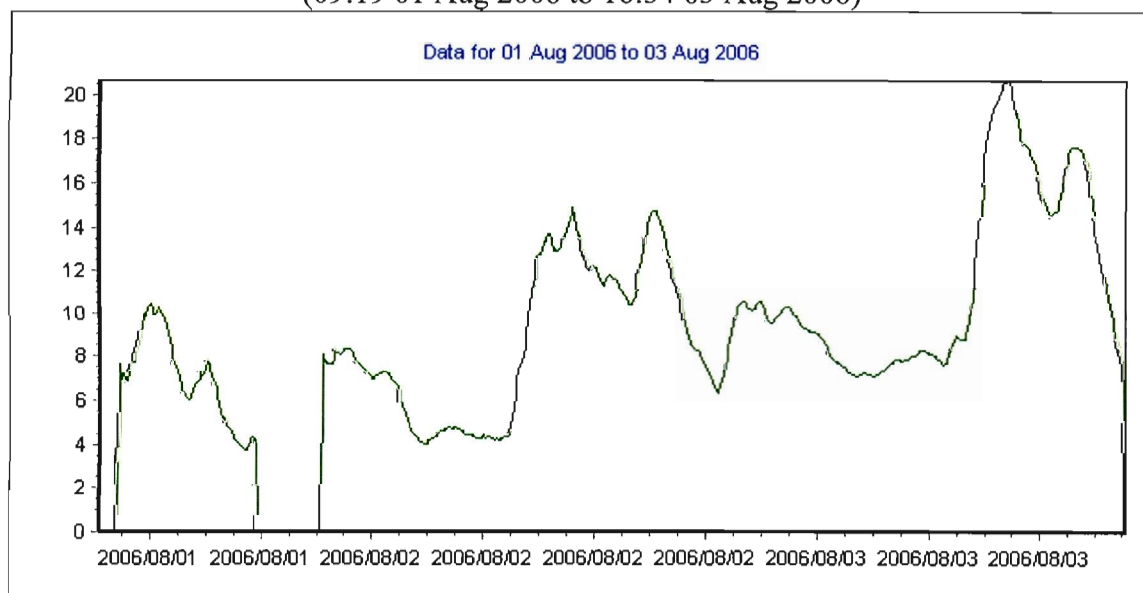
Generated on 12 Dec 2007

Patient details

Patient ID: 01-07082006
 Patient name: Case Study J
 Age: 53
 Gender: Female
 Height: 1.68 m
 Weight: 69.00 kg
 BMI: 24.45
 Classification: Normal weight
 Activity level: Medium

Blood glucose profile

(09:19 01 Aug 2006 to 16:34 03 Aug 2006)



Regime

	Basal dosage	Bolus dosage	ets Intake
Current	19 U	8 U	27.7 ets
Suggested	19 U	19 U	27.8 ets

Average blood glucose level: 9.46 mmol/l
 ets Sensitivity: 1.04 mmol/l.ets
 Insulin sensitivity: 1.49 mmol/l.U

Comments

The patient consumes approximately the same amount of ets as the RDA. Therefore expect the bolus dosage to be equal to the basal dosage.

This patient suffers from infrequent hyperglycaemia.

No change in basal dosage is suggested at this time.

An increase in bolus dosage from 8 units to 19 units is suggested to lower the patient's post prandial blood glucose levels.

Doctor's recommendations

4.3.11. Case study K



Type 1 diabetes blood glucose characterisation report

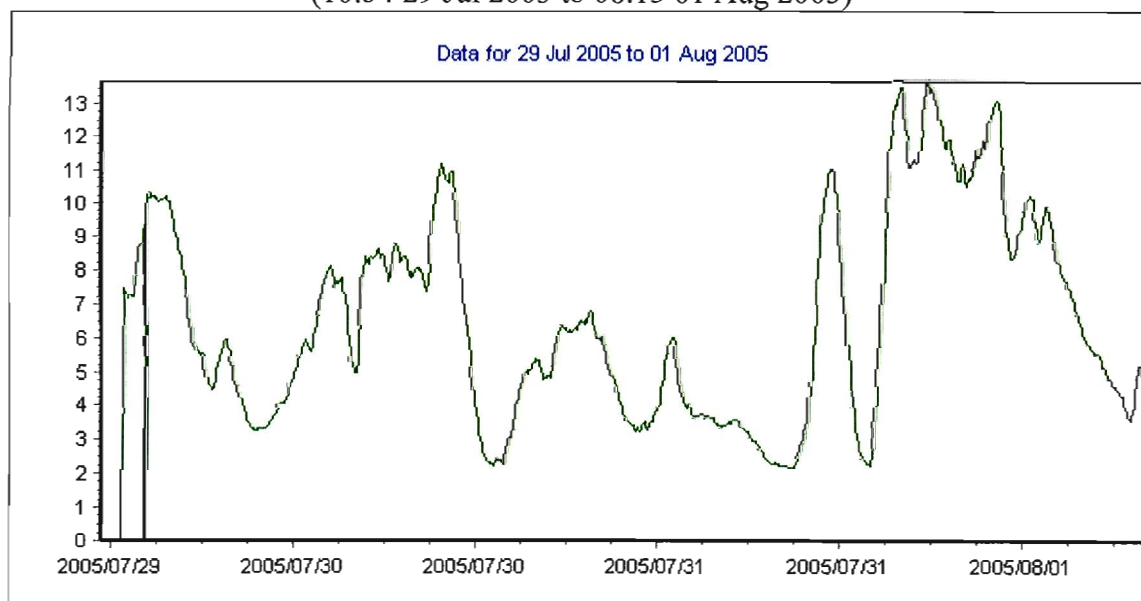
Generated on 12 Dec 2007

Patient details

Patient ID: 01/29072005
 Patient name: Case Study K
 Age: 52
 Gender: Male
 Height: 1.80 m
 Weight: 67.00 kg
 BMI: 20.68
 Classification: Normal weight
 Activity level: Medium

Blood glucose profile

(10:54 29 Jul 2005 to 08:13 01 Aug 2005)



Regime

	Basal dosage	Bolus dosage	ets Intake
Current	18 U	29 U	36.3 ets
Suggested	30 U	34 U	32.5 ets

Average blood glucose level: 6.54 mmol/l
 ets Sensitivity: 1.17 mmol/l.ets
 Insulin sensitivity: 1.25 mmol/l.U

Comments

The patient consumes more ets than the RDA. Therefore expect the bolus dosage to be more than the basal dosage.

The patient will likely gain weight in the long run as he/she eats much more than his/her RDA

This patient has experienced some hypoglycaemic events. Please adjust bolus accordingly.

The suggestions for this patient are not accurate enough. The patient will have to redo the study period.

Please make sure that the patient follows these guidelines to ensure more accurate suggestions:

- The test should be repeated during a normal week.
- The patient must not be sick in the period of testing.
- The testing period should not be a stressful period.

The doctor should take extra care during the second test.

Doctor's recommendations

4.4. Result summary

In all case studies current regimes were changed. The amount of change was determined using the process in chapter 2. These changes are verified against a number of factors that describes a person's blood glucose control accuracy. Further suggestions were made as to how the doctor must proceed.

For most case studies new regimes were suggested that would increase the accuracy of their blood glucose control. It should be noted from the results that a perfect solution was not provided, merely a suggestion that would enhance the blood glucose control, if only by a little. The results for this study are given in Table 4.

Single test patients					
Case study	Current basal dosage	Suggested basal dosage	Current bolus dosage	Suggested bolus dosage	Average Blood glucose levels
A	22	26	41	27	10.22
B	24	25	25	25	6.77
C	40	37	58	63	10.02
D	18	24	22	18	8.76
E	24	33	27	33	12.01
F	16	19	17	25	11.76
G	24	26	23	24	7.28
H*	34	33	56	38	10.86
I	16	16	8	14	9.27
J	19	19	8	19	9.46
K*	18	30	29	34	6.54

Table 4: Results of this study

The results show that 9 out of 11 case studies would show some improvement. The other 2, represented with a asterisk, were not successful, but the solution points this out to the user. Thus, the solution will provide a warning if suggested regimes may cause harm.

The final suggestion as to change in regime is left up to the doctor. The results to some of the cases may fall outside the doctor's margin of safety for a specific patient.

A patient and doctor spend years together trying to come up with the best regime, so they may be hesitant to try new regimes that may seem like a risk.

For this reason the solution is better suited to patients that have not had years to become comfortable with their control levels. The solution to this study will be better utilised as an initial treatment tool rather than a tool to be used by a person experienced in controlling their blood glucose levels. Patients who struggle with control are also recommended to use it, but if a person is comfortable with his control levels this solution should not be used.

It may be that more study will lead to refinement of the simulation model. Suggestions are made in the final chapter as to how future studies can be used to enhance this solution. Clinical trials are needed to verify the intervention results. The feedback from these trials can then be used to further improve the suggestion algorithms and also to improve the safety aspects of the system.

5. Conclusion

This chapter summarises the study. A conclusion is reached in terms of the objective and the developed solution. The results are summarised and further work is proposed.

5.1. Summary

The summary will start with the objective of this study: Design and implement an easy-to-use, accurate solution that will characterise the blood glucose levels in a type 1 diabetic and use this characterisation to determine an optimal insulin regime. Characterisation should be in terms of insulin administration and meals taken.

This solution was then used on data previously gathered for 11 patients to propose a new insulin regime. The characterisation is done using simulation of the blood glucose levels and the basal insulin dosage is determined from the RDA_{ets} and the characterisation variables.

These results were verified against a number of factors including average blood glucose levels, area between mean and curve, area under curve, hyperglycaemic events and hypoglycaemic events. In 9 of the patients a better solution to the one they currently use was proposed. In 2 of them the results would not have resulted in more accurate control, but the developed solution informed the user of this.

The conclusion of this study was that by characterising the patients' blood glucose levels accurately a better insulin regime could be suggested. Each patient's results are individually verified to ensure that better control will result in the suggestions made. The software has automatic verification and comments are made on the change in regime.

It was noted in the previous chapter that more comprehensive prospective clinical trials are needed to truly verify intervention results. The results in this study are based on retrospective datasets of case studies. Actual suggestions were not tried and tested on patients due to several constraints as discussed. The data obtained from these trials can be used to improve accuracy and safety of algorithms being used.

5.2. Recommendations for further work

From this study the following opportunities for future work were identified:

- Combine the solution of this study with the EIBC developed by Pelzer [36] to reach better levels of control.
- It is recommended that the results generated by this study be used in a long term study to determine the exact increase in blood glucose control performance.
- Intervention suggestions should be implemented while closely monitoring patients. The outcomes can be used to improve the accuracy and safety of the algorithms being used to make insulin recommendations.
- A broader clinical trial will have to be conducted. This will have to be done in collaboration with a CGM manufacturer.

5.3. Closure

Through accurate and successful characterisation of blood sugar a more accurate basal insulin dosage can be determined much quicker than current trial-and-error methods. This dosage will lead to tighter blood glucose control which will, in turn, lower the patient's average blood glucose values (HbA1c). It will also lead to less long term complications suffered by diabetes patients.

Recommendations were made for clinical trials to commence and further study to be done in furthering the characterisation process. This study has proven the benefit of combining modern engineering technology (computers) and engineering techniques (simulation) with medical science to enhance patients' lives. The scope for this combination is endless and can solve many problems in the medical field.

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7.1. Appendix A – Business plan for developed solution

Human~Sim



BUSINESS OPPORTUNITY FOR INCREASING CGMS RELATED REVENUE

EXECUTIVE SUMMARY

Finding insulin regimes that result in good glycaemic control is still a difficult and time consuming task for medical doctors. CGMS technology has become available but still many doctors do not know how to interpret these results.

Human-Sim has developed a system that analyses patients' CGMS, food and insulin data to calculate accurate insulin regime parameters. It uses advanced simulation technology to automatically calculate values. Two patents are pending on the advanced technologies used by the system.

The benefits of good glycaemic control for diabetics are obvious. Furthermore, this system makes the life of the medical doctor easier and will increase the revenue of the medical practice. Doctors and patients will be motivated to use the system.

CGMS technology is a core component of the system, therefore it will stimulate CGMS hardware and consumable sales and open the door further for other diabetes care products such as insulin pumps. Our market analysis using very conservative estimations has indicated a potential US\$175 million nett profit in additional CGMS related sales. It will also give the owner of the technology a competitive advantage in a market where new competition is emerging.

IT TAKES TIME TO CONTROL

It is a difficult and time-consuming task for medical doctors to achieve good glycaemic control in Type 1 diabetics. This can only be achieved by a good insulin regime. Feedback from patients has indicated that it took very long for them to find insulin regimes that work, even with the help of a doctor. Many are still struggling.

Most doctors calculate initial insulin dosages by only considering patients' weight. Thereafter insulin is routinely adjusted at each visit. This approach takes very long and causes discomfort to the patient. More recently technology such as CGMS has made treatment decisions easier. Unfortunately most medical doctors either do not use this technology or know how to interpret these results.

Accurate patient characterisation is almost impossible without technology such as CGMS. Furthermore an in-depth analysis of this data in consideration of food, medication and exercise is necessary to truly understand how a patient's blood glucose responds. At this stage, this complete technology is still lacking. This was however developed by Human-Sim and patented. A short summary of the technology is given in the next two sections.

AUTOMATED INDIVIDUAL PATIENT CHARACTERISATION

The advanced blood glucose analysis algorithm characterises patients in terms of insulin and carbohydrate sensitivity. It utilises blood glucose (CGMS) data, food and insulin data to analyse the patient's blood glucose response. The algorithms also uses extensive food and insulin databases in their calculations.

The nurse or assistant of the medical doctor can be used to gather data from the patient and enter it into the software program. Data is then downloaded directly from the CGMS system. A

comprehensive integrated analysis can then be performed. A patient report is generated for the medical doctor.

The patient report includes:

- **Current blood glucose control performance (BGCP).** This factor takes hypo- and hyperglycaemic frequency, tightness of control and average blood glucose levels into account. The doctor can therefore track blood glucose control progress at each visit to see whether progress has been made or not since the last visit.
- **Calculated insulin and carbohydrate sensitivities.** These values give an indication of how much bolus insulin is needed for different meals. The insulin sensitivity value can also be used to determine correction factors for the patient.
- **Proposed total daily basal insulin.** This value is calculated by taking insulin sensitivity, activity level and other body characteristics of the patient into account.

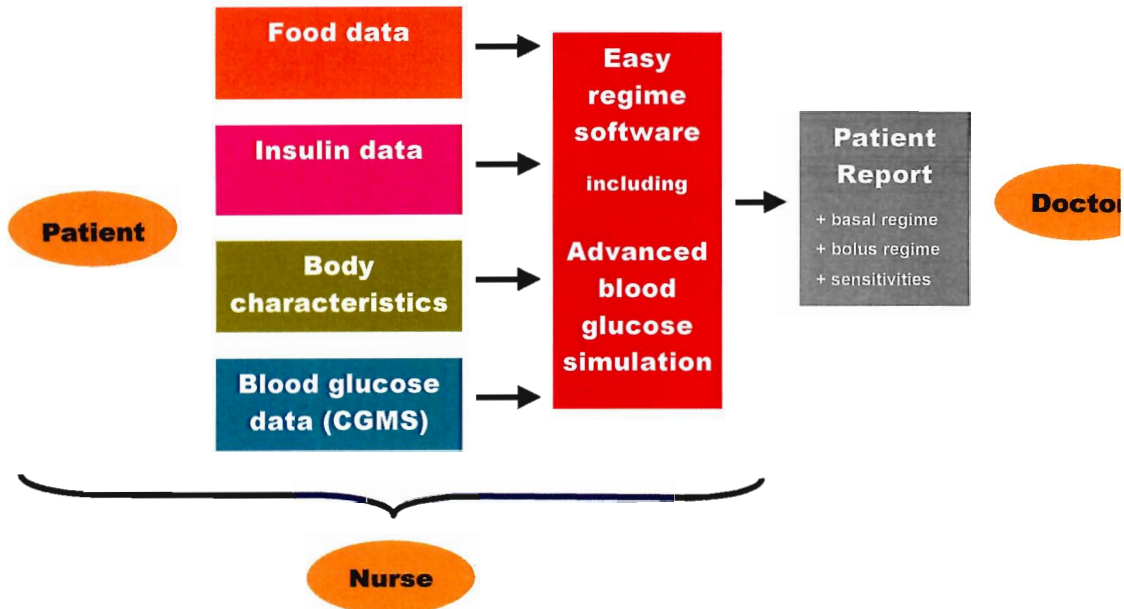


Figure 1: Overview of patient blood glucose characterisation system for diabetics

UNDERLYING TECHNOLOGY

A blood glucose simulation model which was developed by Human-Sim (Pty) Ltd is used in this application. An overview of this simulation model is shown in Figure 2 and 3. This model takes numerous interactions into account in reaction to diabetics' food intake, exercise and insulin administration. This simulation model is based on engineering energy balance equations, similar to those used in award winning industrial applications by Human-Sim's sister company.

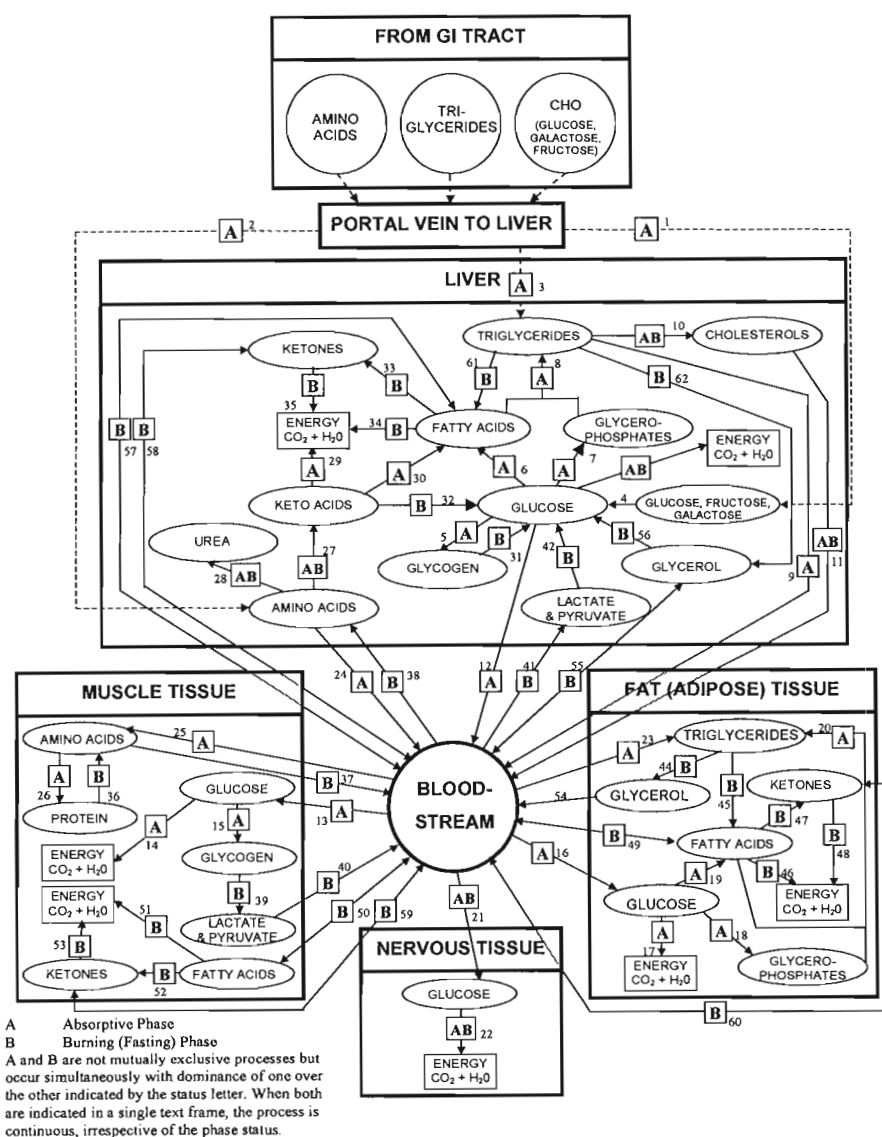


Figure 2: Overview of blood glucose simulation model

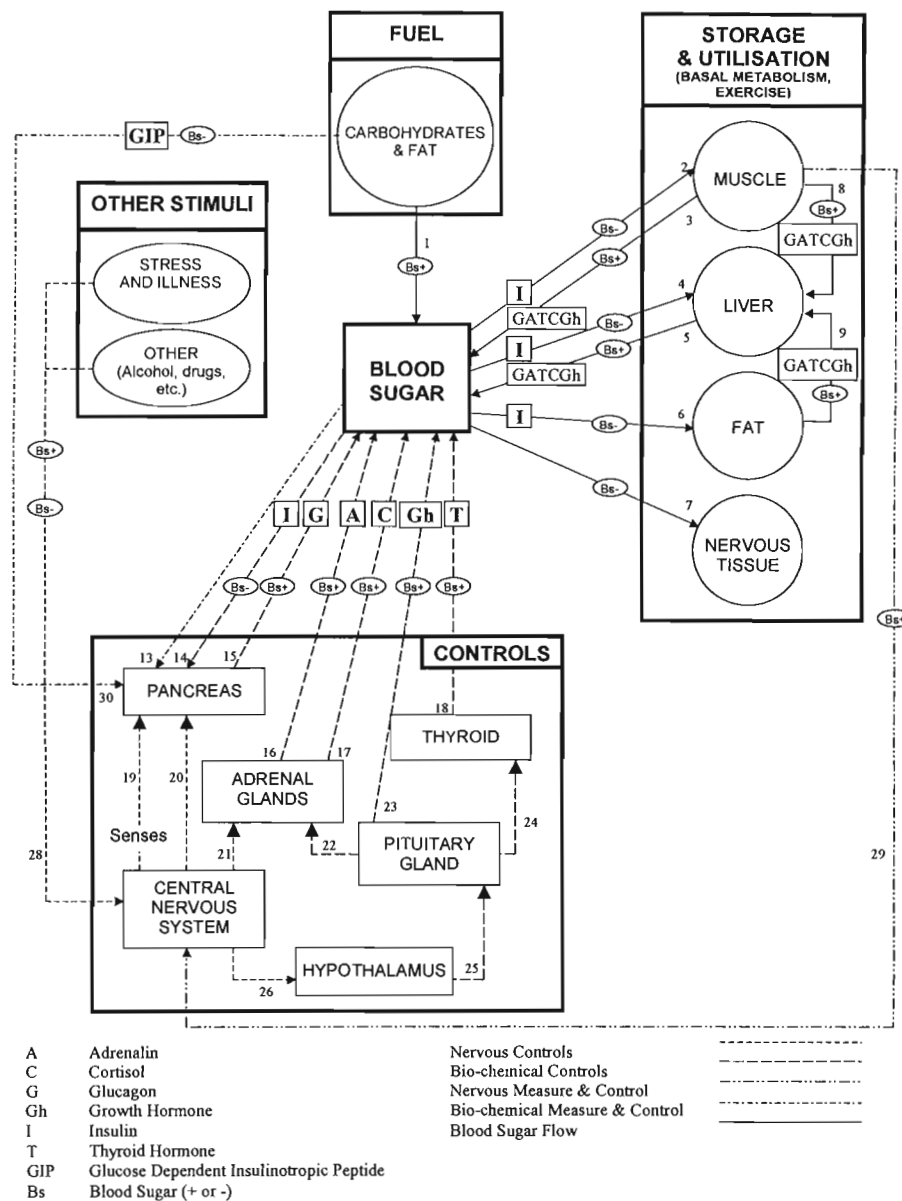


Figure 3: Schematic layout of the blood glucose control system in the human energy system.

The simulation model can be used to predict blood glucose profiles for both diabetics and non-diabetics. Figure 4 illustrates the accuracy of the blood glucose simulation model.

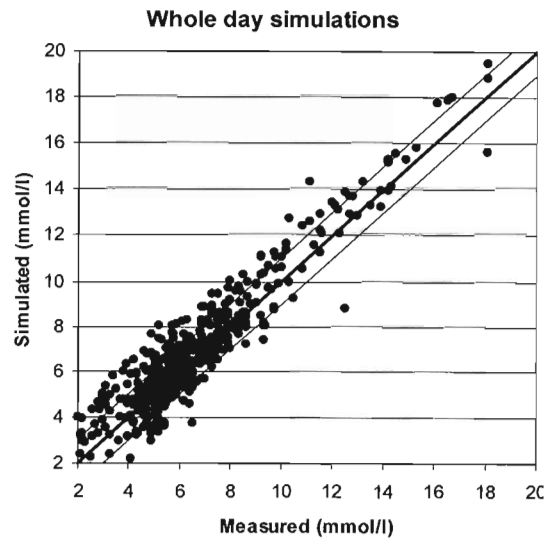


Figure 4: Simulated vs. measured values for a full day simulation using the blood glucose simulation model.

Blood glucose characterisation for diabetics comprises an analysis of blood glucose data in response to food, exercise and medication to determine how the individual's blood glucose responds to these factors. This analysis is made complicated by the fact that these factors simultaneously alter blood glucose response, which makes it difficult to isolate each factor.

Human-Sim developed, using the simulation model, an automated blood glucose characterisation system for Type 1 diabetics. The layout of this system is shown in Figure 1. The patient is connected to a continuous blood glucose monitor. During this monitoring period the patient is required to log food intake, exercise activities and insulin administration. This data can be logged on paper or entered into a mobile phone application with extensive databases designed for this purpose.

At the end of the monitoring period the characterisation system uploads the blood glucose data. A nurse can then enter the food, exercise and insulin data from the log sheets or upload the relevant data directly from the mobile phone application. The characterisation device has extensive databases from which data for the analysis can be accessed. All the relevant patient specific parameters such as daily activity level and body characteristics should also be entered into the system.

An analysis of the blood glucose profiles is then performed. The parameters for the specific patient are first estimated. The blood glucose simulation model uses these estimated parameters to simulate the profile using the entered data. The error between the actual blood glucose data and simulated data is then calculated. The parameter set is then iteratively adjusted, thousands of times, to reduce this error until minimal. This indicates that the parameter set is optimised for the specific patient.

The parameter set includes: insulin sensitivity, carbohydrate sensitivity, carbohydrate-to-insulin ratio and also the proposed basal insulin regime based on the patient's insulin sensitivity and calculated daily energy requirements. These optimised values will greatly aid in establishing good glycaemic control seeing that they form the basis of the basal- and bolus insulin regime. Several data validation techniques are used to eliminate non-relevant and incorrect data to make sure values calculated are accurate.

Another addition to the system is the Blood Glucose Control Performance (BGCP) defined by Human-Sim. It is a common fact that HbA_{1c} is now longer sufficient when evaluating patients' blood glucose control. Therefore BGCP rates the current control performance of patients in terms of hypoglycaemic and hyperglycaemic frequency, average blood glucose level (relating to HbA_{1c}) and also tightness of glycaemic control.

Blood Glucose Control Performance (BGCP)

$$BGCP = 0.25(ABCM_{fac}) + 0.25(AUC_{fac}) + 0.35(HYPO_{fac}) + 0.15(HYPER_{fac})$$

where $ABCM_{fac}$ is a rating factor for the area between the curve and the mean of the blood glucose profile,

AUC_{fac} is a rating factor for the area under the blood glucose curve,

$HYPO_{fac}$ is a rating factor for the frequency of hypoglycaemic excursions experienced and

$HYPER_{fac}$ is a rating factor for the frequency of hyperglycaemic excursions experienced,

The BGCP is calculated by the system for each patient by using the CGMS data. This helps the medical doctor to quickly see whether progress is being made in controlling the patient's blood glucose or not by comparing this value to previous ones.

BENEFITS

PATIENT BENEFITS

Our clinical trials have shown that by doing individual patient blood glucose characterization the following results can be achieved:

- ✓ a relative short time to achieve good glycaemic control,
- ✓ a reduction in frequency of hyperglycaemic events by a factor of 1.5,
- ✓ a reduction in frequency of hypoglycaemic events by a factor of 1.9,
- ✓ a reduction in HbA1c of 0.5% (31% closer to ADA target in three months), and
- ✓ an improvement in tightness of blood glucose control by a factor of 1.14.

In other words glycaemic control can be improved considerably thereby reducing the risk of diabetic complications. Furthermore the time taken to achieve good glycaemic control can be reduced to only a few days.

A retrospective analysis conducted by the North-West University have shown diabetics with insulin regimes close to those calculated by the new system have considerably better glycaemic control as measured by the BGCP factor. The results are shown in Table 1.

Patients with...	Number of patients	Average control performance*	Average % error in basal insulin**
Control performances $\geq 50\%$	11	60%	22%
Control performances $< 50\%$	8	33%	47%

* Blood glucose control performance is a rating system where 100% indicates ideal glycaemic control and 0% worst possible control. It takes hypoglycaemic and hyperglycaemic frequency, average glucose level and tightness of control into account.

** Percentage difference in basal insulin is calculated as the absolute percentage difference between the actual basal insulin dosage being administered and the more correct basal dosage calculated with the new automatic system

Table 1: Retrospective data analysis of 19 Type 1 diabetic patients

DOCTOR BENEFITS

There are several benefits for the medical doctor using the system:

- ✓ Value added service that can be charged for in practice
- ✓ Latest technology means competitive advantage for the medical practice

- ✓ All these mentioned benefits contribute to increased revenue for doctor's practice
- ✓ Reduced time spent per patient, nurse can assist the doctor as insulin regimes are calculated automatically
- ✓ Useful patient reports that help doctor make the best decisions

CGMS MANUFACTURER'S BENEFITS

See the next section for the business opportunity.

- ✓ Increased awareness of CGMS technology and other company products (e.g. insulin pumps) amongst patients and doctors.
- ✓ Competitive advantage in the CGMS market where new competition is emerging.
- ✓ Increased hardware sales.
- ✓ Increased consumables (sensors) sales.

BUSINESS OPPORTUNITY

Human-Sim has identified an opportunity for the manufacturers of CGMS related hardware and consumables.

Our market survey has indicated that:

- diabetic patients in general take a long time to find an insulin regime that provides good glycaemic control,
- medical doctors in general find it difficult to find a good regime for their patients and
- although CGMS technology are available, medical doctors are still not sure how exactly their patients, practice or medical institution would benefit from this.

The easy-to-use characterisation system utilises CGMS technology to calculate sensitivity values to establish a regime. Because this system is intuitive, easy-to-use and provides accurate results, medical doctors will be motivated to start using the system. This means that for each characterisation done, a CGMS sensor will be used. The more institutions using this technology, the more CGMS hardware will be sold. Furthermore the in-depth analysis that the system provides adds tremendous value to the CGMS profiles. It interprets the CGMS data for the medical doctor.

The algorithms used are further expanded to the Type 2 diabetic market. A BGCP factor was also defined for Type 2 diabetics. Diabetes diagnosis and monitoring can effectively be done by using CGMS technology with the diabetes regime software, even if the patient is not administering insulin.

Our market analysis has estimated that the release of the insulin regime software would result in additional US\$175 million CGMS hardware and consumable sales. This estimation is based on the following conservative predictions:

- Extra market penetration to medical doctors of 1%,
- Extra market penetration of 5% to patients buying hardware from doctors (1% doctor penetration) offering service resulting in a total market penetration of 0.05%,
- Market penetration period of 3 years and
- 20% nett profit for CGMS hardware and consumables.

Such a system would not only boost CGMS related sales but also give the sourcing company a competitive advantage in a market where new CGMS systems are launched. Having a software platform on the desktop of its users, the medical doctors and nurses will help create more commercialisation opportunities for other diabetes products such as insulin pumps.

Two preliminary patents have already been registered on the blood glucose simulation and characterisation technology.

CONCLUSION

The concept of computational analysis of patient data makes sense. Blood glucose simulation technology makes it possible to determine patient sensitivities to insulin, carbohydrates and other related factors. This makes it possible to prescribe customized insulin regimes that work. This technology holds benefits for the patient, doctor and manufacturer of CGMS technology.

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