MASTER THESIS
IN
COMPUTER SCIENCE

CONTROLLING DIABETES

Automating self-regulation of insulin-dependent diabetics by using fuzzy logic

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Abstract

The consequences of diabetes mellitus, a metabolic disease, put the society to great expenses. A diabetic himself, especially with respect to the type-I variant (insulin dependent diabetes mellitus), is for the main part responsible for the seriousness of these consequences. With adequate regulation it is even possible to reduce the likelihood of future complications to that of a non-diabetic. The research described in this thesis aims at two different approaches of regulating diabetes by predicting and advising control actions to be employed by a type-I diabetic. The first, modelling the patient specific diabetes mellitus system and deriving a control action is shown to be much too premature to be used sensible and safe. Next, modelling the decision behaviour of a skilled diabetic by means of Fuzzy Logic theory is proposed and implemented in a specific case. Such systems can be used to enlighten discussion between doctor and patient on the one hand, and to support diabetics in determining adequate control actions on the other hand.

Content

1 Introduction

Diabetes mellitus is a metabolic disease. In Europe about 30 million people suffer from diabetes; 20% of them require exogenous insulin administration to survive (insulin-dependent patients). Recent medical evidences show that a better metabolic control achieved through Intensive Insulin Therapy can delay or prevent the development of long-term complications. It requires frequent insulin injections, accurate blood glucose monitoring and strict surveillance by health care professionals. This patient management procedure is expensive and time-consuming. It is calculated that 7% of the total European health care expenditures is absorbed by diabetes care. This thesis aims toward *controlling* insulin dependent diabetes.

After a brief description of the disease in the first chapter, a vast investigation of literature is discussed with regard to the technology in diabetes care. Research in literature about controlling diabetes is done in two directions, model based and non-model based. The first is about constructing a model of the metabolic processes w.r.t. diabetes in the body. With the help of these models predictions about the course of the blood glucose level are done on behalf of deriving adequate compensatory control actions. Because the first idea was to investigate (c.q. eventually improve) these models, much effort is devoted to this subject. Although a small proposal is done in section 3.3.6, the conclusions are that these models are far too premature. Information in literature about the non-model based approach of controlling diabetes is very scarce. Some – rather random selected – approaches are discussed and further research in this direction is substantiated. The investigated approaches of both directions in literature are evaluated by the measure they incorporate or take into account the factors that are of influence on the blood glucose level. These are discussed in the beginning of the chapter about the present days technology in diabetes care.

The remainder of this thesis is about the author's own project about modelling the self-regulating insulin dependent diabetes mellitus patient. It starts with defining the structure and explaining the concept idea. The author developed three subsystems that reproduce and sometimes even improve his reasoning about adequate control actions. Actually, the author's way of reasoning is implemented using Fuzzy Logic theory. These systems are lifestyle-specific improvements on the way of reasoning that is provided to patients starting self-regulation nowadays. The systematically derivative of the model structure according to the characteristics of the DM-system is discussed before dealing with the event related model structure implementation in FuzzyTech.

After discussing the implementation, testing the systems is discussed with regard to two scenarios. The internal working of one of the systems is discussed with the help of a test case and a day out of the author's logbook. All fuzzy logic controller implementations are subjected to an evaluation. After drawing some intermediate conclusions, the safety of Fuzzy Logic controllers is discussed. Before concluding this thesis with a chapter about the (eventual) (near) future work in this research, the final conclusions are drawn.

1.1 Abbreviations

The abbreviations that are listed below are used in this thesis.

BG	Blood Glucose
IDDM	Insulin Dependent Diabetes Mellitus
NIDDM	Non Insulin Dependent Diabetes Mellitus

2 Diabetes Mellitus

Although controlling type I diabetes is central in this research project, this chapter first gives a global impression of the disease. The most important historical facts and properties of the disease, including the role of the hormone insulin and the origin of blood sugar, are discussed. The knowledge about the causes of diabetes is also discussed and some introducing comment is made on its controlling. The chapter ends with a description of two important phenomenons that affect the regulation of the disease. Unless otherwise specified, the information in this chapter is taken from [w31], a web page produced by the university of Massachusetts Medical School, however some sentences are rephrased and some pictures are changed slightly, and a subscript is added. We comment that the impression

2.1 Origins

The medical name for diabetes, *diabetes mellitus*, comes words with Greek and Latin roots.

Diabetes comes from a Greek word that means to siphon. The most obvious sign of diabetes is excessive urination. Water passes through the body of a person with diabetes as if it were being siphoned from the mouth through the urinary system out of the body.

Mellitus comes from a Latin word that means sweet like honey. The urine of a person with diabetes contains extra sugar (glucose). In 1679, a physician tasted the urine of a person with diabetes and described it as sweet like honey.

Anyone can get diabetes. According to [w30] approximately 17 million people in the United States, or 6.2% of the population, have diabetes. While an estimated 11.1 million have been diagnosed, unfortunately, 5.9 million people (or one-third) are unaware that they have the disease.

In the table below some important dates related to the origin of diabetes are summed up. It concerns merely a small part of a more detailed table from [w32].

1552 B.C.	Earliest known record of diabetes mentioned on 3rd Dynasty Egyptian papyrus by physician Hesy-Ra; mentions polyuria (frequent urination) as a symptom.
Up to 11th Century	Diabetes commonly diagnosed by 'water tasters,' who drank the urine of those suspected of having diabetes; the urine of people with diabetes was thought to be sweet-tasting. The Latin word for honey (referring to its sweetness), 'mellitus', is added to the term diabetes as a result.
Early 19th Century	First chemical tests developed to indicate and measure the presence of sugar in the urine.
late 1850s	French physician, Priorry, advises diabetes patients to eat extra large quantities of sugar as a treatment.
1869	Paul Langerhans, a German medical student, announces in a dissertation that the pancreas contains contains two systems of cells. One set secretes the normal pancreatic juice, the function of the other was unknown. Several years later, these cells are identified as the 'islets of Langerhans.'
1908	German scientist, Georg Zuelzer develops the first injectible pancreatic extract to suppress glycosuria; however, there are extreme side effects to the treatment.
May 21, 1922	James Havens becomes the first American successfully treated with insulin.
1959	Two major types of diabetes are recognized: type 1 (insulin-dependent) diabetes and type 2 (non-insulin-dependent) diabetes.

Table 2-1 Summarized history of diabetes.

2.2 The role of insulin

Insulin is a hormone produced in the pancreas to regulate the amount of sugar in the blood. In persons with diabetes, the pancreas produces no insulin, too little insulin to control blood sugar, or defective insulin. To understand how this affects a diabetic, more of the insulin's working needs to be understood. Think of each of the billions of cells in a body as a tiny machine. Like all machines, cells need fuel. The foods one eats are made up of carbohydrates, proteins, and fats, which are broken down to provide fuel for the cells. The main fuel used by the cells is called glucose, a simple sugar. Glucose enters the cells through receptors. Receptors are sites on cells that accept insulin and allow glucose to enter. Once inside, glucose can be used as fuel. But glucose has difficulty entering the cells without insulin. Think of insulin as the funnel that allows glucose (sugar) to pass through the receptors into the cells.

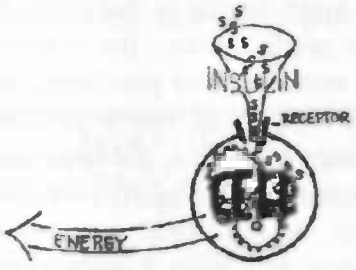


Figure 2-1 Insulin can be seen as a funnel that allows glucose to pass through the receptors into the cells.

Excess glucose is stored in the liver and muscles in a form called glycogen. Between meals, when blood sugar is low and the cells need fuel, the liver glycogen is released to form glucose.

2.3 The pancreas, islets of Langerhans, and beta cells

The pancreas is located in the abdomen, behind the stomach. It is attached to the small intestine and the spleen. Inside the pancreas are small clusters of cells called Islets of Langerhans. Within the islets are beta cells, which produce insulin. Insulin induces a drop in the glucose concentration of the blood, while the alpha cells, which are also contained in the islets, can induce a small increase in the glucose concentration.

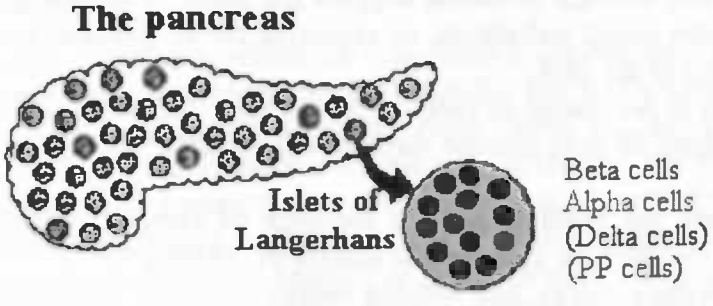


Figure 2-2 The islets of Langerhans contain alpha and beta cells.

In people who do not have diabetes, glucose in the blood stimulates production of insulin in the beta cells. Beta cells "measure" blood glucose levels constantly and deliver the required amount of insulin to funnel glucose into cells. They keep blood sugar (glucose) in the normal range of 4,0 mmol/L to 6,8 mmol/L. This normal concentration of glucose in the blood is called *normoglycemia* or high blood sugar.

When there is little or no insulin in the body, or when insulin is not working properly, glucose has difficulty entering the cells. Also, when there is not enough insulin, excess glucose cannot be stored in the liver and muscle tissue. Instead, glucose accumulates in the blood. This high concentration of glucose in the blood is called *hyperglycemia* or high blood sugar. A normal concentration of glucose in the blood is called *normoglycemia.*

2.4 Where blood sugar comes from

The carbohydrates in consumed food are converted into sugar (glucose) and are next absorbed in the blood circuit from the gut. Not all the sugar in the blood comes from sugar that one eats. Because sugar in the blood is so important to the body, it has a backup source of sugar to

use when one is not eating. The main source is the liver. The liver is like a big factory that makes many of the things that one needs to live. One of those things is blood sugar.

During the day, when one eats, the liver puts some sugar into storage. Doctors call this stored sugar *glycogen*. During the night when one is asleep and not eating, the liver puts that sugar into the blood. And if one skips breakfast, the liver may actually make new sugar to use. It makes this new sugar from proteins that are taken away from our muscles.

The sugar that comes from the liver (and to a smaller degree from the kidneys, too) explains why persons with diabetes can have a high blood sugar even when they are not eating.

2.5 The kidney dam

When blood glucose rises above a certain level, it is removed from the body in urine. Picture the kidney as a dam: when there is too much glucose in the blood, the excess "spill" out. The maximum blood glucose level reached before sugar spills out is called the kidney threshold (usually about 10 mmol/L). Some people with long-term diabetes or kidney disease can have a very high kidney threshold. Sugar will not "spill" into the urine until the blood sugar is very high.

Glucose cannot be passed out of the body alone. Sugar sucks up water so that it can "flow" from the body. The result is *polyuria* or *excessive urination*. People with excess glucose in their blood, as in uncontrolled diabetes, make frequent trips to the bathroom. These people also have sugar in their urine; the medical term for sugar in the urine is *glycosuria*.

Loss of water through urination triggers the brain to send a message of thirst. This results in a condition called *polydipsia*, or *excessive thirst*. Excessive urination can result in *dehydration*, leading to dry skin.

When there is no insulin to funnel glucose into the body's cells, or when the insulin funnel is not working to pass glucose through the receptors, the cells get no fuel and they starve.

This triggers the brain to send a message of hunger, resulting in *polyphagia* or excessive hunger. Because the glucose that should be fuelling the cells is flowing out in urine, the cells cannot produce energy, and without energy, one may feel weak or tired. Weight loss may occur in people whose bodies produce no insulin because without insulin, no fuel enters their cells.

Insulin also works to keep fuels inside the cells. When insulin is low, the body breaks down the fuels, and rapid weight loss results. The breakdown of fat cells forms fatty acids which pass through the liver to form *ketones*. Ketones are excreted in the urine. The medical term for ketones in the urine is *ketonuria*.

2.6 Types of Diabetes

Almost all people with diabetes have one of two major types. About 10% have Type I or insulin dependent diabetes mellitus (IDDM). Their bodies produce no insulin. When diagnosed, most people with Type I diabetes are under 40 and usually thin. Symptoms are often pronounced and come on suddenly. Because their bodies produce no insulin, people with Type I diabetes must obtain it through injection.

About 90% of persons with diabetes have Type II or non-insulin dependent diabetes mellitus (NIDDM). Their bodies produce some insulin, but it is not enough or it doesn't work properly to funnel glucose through the receptors into their cells. When diagnosed, most people with Type II diabetes are over 40 and usually are overweight. Symptoms are usually not pronounced and appear over a long period of time. Type II diabetes can sometimes be controlled with a carefully planned diet and exercise, but oral medications or insulin

injections may be necessary. The following table highlights some of the differences between Type I and Type II diabetes.

	Type I (IDDM)	Type II (NIDDM)
Age at onset	Usually under 40	Usually over 40
Body weight	Thin	Usually overweight
Symptoms	Appear suddenly	Appear slowly
Insulin produced	None	Too little, or it is ineffective
Insulin required	Must take insulin	May require insulin
Other names	Juvenile diabetes	Adult onset diabetes

Table 2-2 A comparison of the major two types of diabetes.

People whose blood contains more glucose than normal, but less than occurs in diabetes, may be diagnosed with a condition called impaired glucose tolerance (IGT).

Some women experience a rise in their blood glucose level during pregnancy. These women have a condition called gestational diabetes mellitus (GDM). Their blood glucose levels usually return to normal after their babies are born.

Other types of diabetes may occur as a result of diseases of the pancreas or the endocrine (gland) system, genetic disorders, or exposure to chemical agents.

2.7 Causes of diabetes

In this section the causes of diabetes, which are type-related, are discussed according to [11].

Probably there is not one evident cause for IDDM, but is it a combination of several factors. Firstly a heritable tendency is assumed. Next, after, e.g. by a viral infection an inflammation in the islands of Langerhans is developed, the disease can come into existence. Here antibodies against the own pancreas are formed causing almost all the beta cells to be destroyed. Because the production of insulin stops, the diabetes originates.

If one has a parent, grandparent, brother, or sister, or even a cousin who has diabetes, he is more likely to develop diabetes himself. There is about a 5% risk of developing Type II diabetes if the mother, father, or sibling has diabetes. There is a higher risk (up to 50%) of developing Type II diabetes if the parent or siblings have Type II diabetes and one is overweight. Eighty percent of people with Type II diabetes are overweight when diagnosed. Diabetes symptoms disappear in many of these obese patients when they lose weight.

2.8 Controlling diabetes

There are no easy cures for most cases of diabetes. Some persons with diabetes can be cured by a transplant of insulin producing cells, but there are significant risks associated with the surgery and with the immunosuppression-type drugs that need to be taken.

But even if diabetes cannot usually be cured, it can be controlled. Control of diabetes means balancing the amounts of glucose and insulin in the blood. To achieve this balance, the diabetes nurse educator or doctor will prescribe a regimen of diet, exercise, and possibly insulin injections or oral medications, dependent on the type. Sticking to the regimen helps keep one healthy and greatly reduces the likelihood of developing diabetes complications.

People with diabetes are vulnerable to a variety of complications over time. Health-care providers all agree that strict control of blood sugar makes complications less likely. This was shown clearly by the Diabetes Control and Complications Trial ([28]). Control of blood sugar is the best way to minimize the risk of complications.

Measures that can be used to evaluate level of control are Blood Glucose (BG) (ca. four daily) and percentage of glycated (simplistically speaking "glucose coated") hemoglobin, HbA_{1c}. This HbA_{1c} percentage is a loose indication of BG average over a period of approximately two months (the average life time of red blood cells), and is measured in that frequency. Percentage of HbA_{1c} has been found to have a good correlation to development of complications [23], and is used clinically as measure of diabetes control in preference to time series data of BG levels.

The difficulty of using HbA_{1c} to measure control performance is the fact that there is only one data point every two months. In [24] an average measure based on magnitude of glucose excursion from normoglycemia, known as the Mean Amplitude Glucose Excursion (MAGE) and is computed by taking an average of a penalty function on blood glucose (BG), *J(BG)*, named the *M-value*. So $MAGE = \frac{1}{N}\sum_{k=1}^{N} J(BG_k)$, where $J(BG) = 10.|\log_{10}(\frac{BG}{s})|^3$. This penalty function is shown in the figure below. According to [24], s = 4.4 mmol/L was reported to have differentiated between brittle and stable diabetics best.

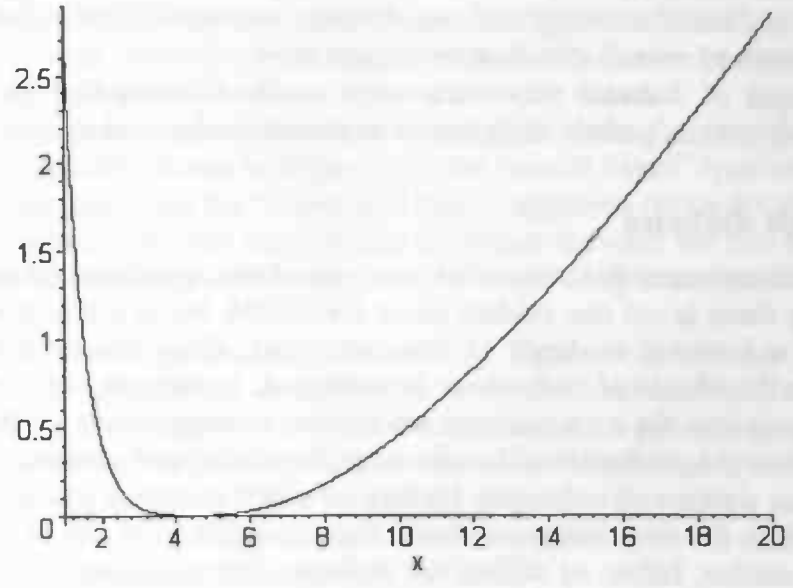


Figure 2-3 The M-value curve: $10.|\log_{10}(x/s)|^3$, for s = 4.4 mmol/L.

2.9 Important phenomenon's

In this section two important phenomenon's that can occur in a diabetic body, the *Somogyi effect* and the *Dawn Phenomenon*, are discussed because they are relevant in controlling IDDM. The definitions are taken from [w29].

The Somogyi effect is a swing to a high level of glucose (sugar) in the blood from an extremely low level, usually occurring after an untreated insulin reaction during the night. The swing is caused by the release of stress hormones to counter low glucose levels. People who experience high levels of blood glucose in the morning may need to test their blood glucose levels in the middle of the night. If blood glucose levels are falling or low, adjustments in evening snacks or insulin doses may be recommended. This condition is named after Dr. Michael Somogyi, the man who first wrote about it. Also called "rebound."

The dawn phenomenon is a sudden rise in blood glucose levels in the early morning hours. This condition sometimes occurs in people with insulin-dependent diabetes and (rarely) in people with NIDDM. Unlike the Somogyi effect, it is not a result of an insulin reaction. People who have high levels of blood glucose in the mornings before eating may need to monitor their blood glucose during the night. If blood glucose levels are rising, adjustments in evening snacks or insulin dosages may be recommended.

3 Technology in diabetes care

3.1 Introduction

A vast investigation of literature is done with the eye on getting home in the technical jargon, and getting a good picture of the current state of art. In this way an overview is created of what has been done already and what hasn't been done. This chapter presents a survey of control algorithms aimed tot stabilize diabetes mellitus, with discussion on the approaches taken and the challenges faced. The information from [1] is used as outline for the impression about the compartmental, minimal and dynamical models.

Many works have been directed into developing some sort of control algorithm for IDDM, ranging from continuous control for insulin infusion – aiming towards a fully automatic "artificial pancreas", "insulin advisors" – for patients taking the multiple daily injection therapy, and various simulation-models, used for educational or parameter calculation purposes. The discussion is focused on the "insulin advisor" type, as this is what this thesis aims towards. The various blood glucose models will also be discussed, since some insulin advising algorithms use models to derive the insulin dose.

This problem can be approached from two angles: model the glucose system or model the control rules, typically known as respectively the "model based" approach (since a model of the plant is constructed) and the "non-model based" approach (since the plant is considered as a black box), respectively. The fundamental difference between the two approaches lies in where the parameters belong, and in the case of adaptive systems, which parameters are updated.

In a model based system, as illustrated in Figure 3-1, a model of the plant is constructed, and the parameters describe the plant behaviour. The controller receives information from the model and executes a control action to the plant. If the plant output does not meet the requirement, it is possibly because the model does not adequately represent plant behaviour, and may be updated. These parameters belong to the model, and it is the model that is updated. The resulting difference in control action is due to the different model – the control algorithm itself remains the same.

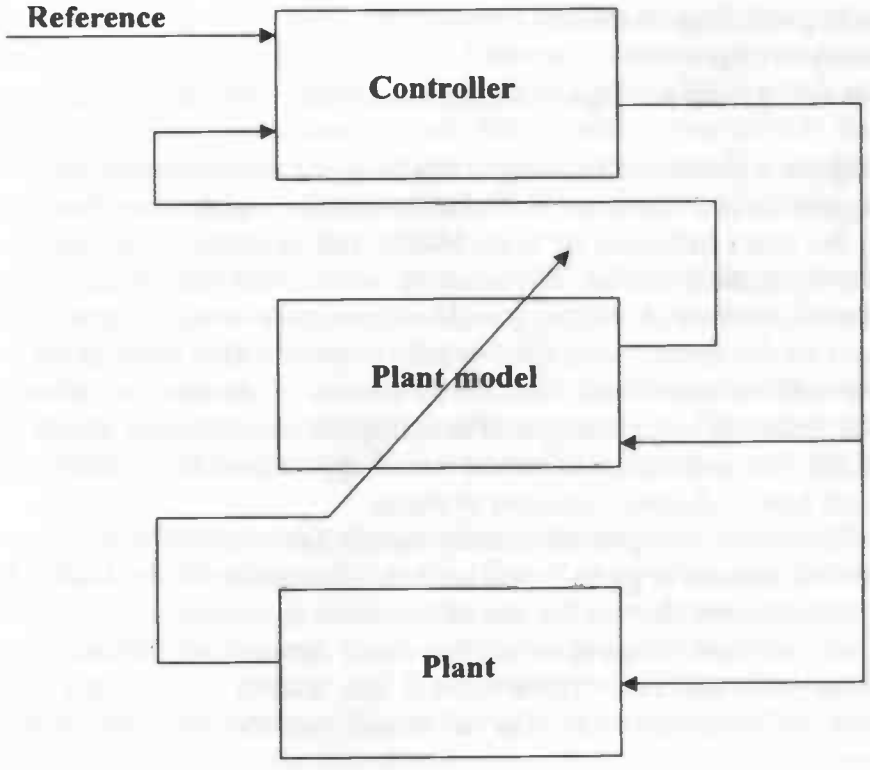


Figure 3-1 Diagram of a model based adaptive system.

On the other hand, non-model based systems are not concerned with full knowledge of the plant. As shown in Figure 4-2, the controller takes output of the plant, and executes a control action to the plant. If the result does not meet the requirement, then parameters of the controller are updated. Since the focus of such systems is on the control rules, they are also called rule based systems.

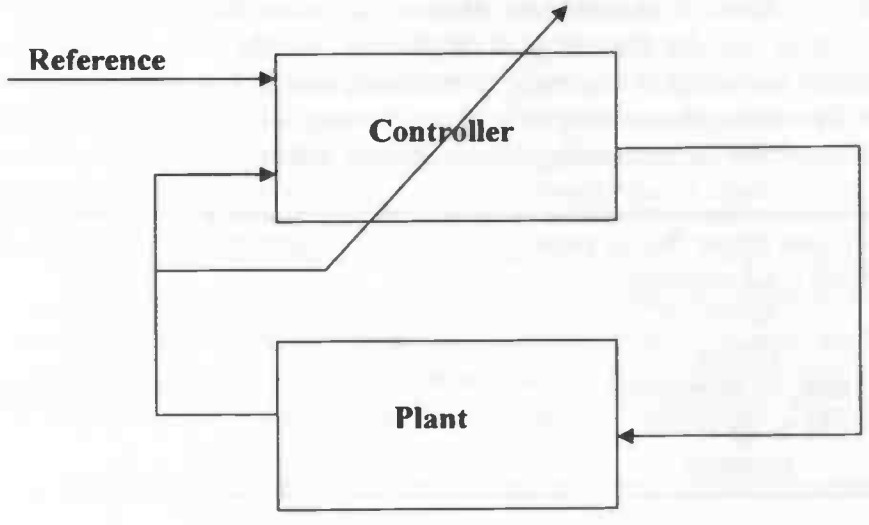


Figure 3-2 Diagram of a non model based adaptive system.

If we compare the two approaches, we can say the following. If eventually the same controller is developed, then a model based approach deserves priority above a non model based approach, because of the following reasons:

- intuitively much clearer;
- tighter to physiological reality;
- more easy to improve;
- one can easily chance things in a model and then calculate the outcome.

When choosing for a construction, using a model based approach, the following things have to be investigated in our opinion. The glucose-insulin metabolism has to be understood, together with the exact influence of food, insulin and exercise on the system. The minimal model and the dynamical model, discussed in one of the following sections, model the glucose-insulin metabolism in healthy people with respect to only glucose and insulin. Here other influences on the system were tried to keep constant. Also some of the formal problems of the models will be mentioned. One small section is devoted to subcutaneous injected insulin profiles, followed to an example of coupling the subcutaneous injected insulin kinetics to such a model. The section about model based approaches is concluded with the models used in two well-known diabetes advisory systems.

After discussing the glucose-insulin metabolism and their models, an abstracting summary with conclusions is given in the section "Evaluation Model Based Approach". This section also provides a preview on the non model based approach.

However, we start with a short section about factors that influence the blood glucose level of people with diabetes. These factors are among the criteria for assessing the appropriateness of a model; the way a model incorporates this factors, decides its appropriateness.

3.2 Factors of influence on blood glucose level

For all clarity, with blood glucose (BG) level, we mean the amount of glucose per litre blood plasma. As mentioned in the chapter about the disease IDDM, there are many factors which influence the BG. Some are measurable, some are difficult to measure, and for some it is almost impossible to measure them (precisely). One of the main factors, which influence BG, is the carbohydrates in food, which end up in the blood stream after digestion by absorption as glucose from the gut. Obviously this raises the BG. The amount of carbohydrate in food is nowadays easy to measure or calculate. One of the main factors causing a drop in BG is insulin, which takes care for the transport of glucose into the cells that need it for 'fuel'. The amount of insulin one takes is also easy to measure, and is simply expressed in a number of standard units. However, the activity of a person is very difficult to measure exactly. In Table 3-1, the most important factors raising BG or causing a drop in BG are mentioned.

Factors that cause BG to raise	Factors that cause BG to drop
Food (carbohydrates)	Insulin
Stress	Exercise
Illness	Alcohol
Dawn phenomenon	(Temperature outside)
Somogy effect	
Exercise	

Table 3-1 Factors of influence on BG.

The factors will briefly be discussed.
We have to comment that BG influences itself. A high BG level will cause the liver to store more glucose. Also, when BG becomes a little bit too low, the liver releases glucose.

The *glycemic index* (the *GI Factor*) is simply a ranking of foods based on their immediate effect on blood glucose levels. It measures how much your blood glucose increases over a period of two or three hours after a meal. Generally, foods high in fat and protein have lower glycemic indexes than foods high in carbohydrate. The problem is that even among the complex carbohydrate not all are created equal. Some break down quickly during digestion and can raise BG to dangerous levels. These are the foods that have higher glycemic indexes. Other carbohydrates break down more slowly, releasing glucose gradually into our blood streams and are said to have lower glycemic indexes.

The body responds to stress with a chain reaction of biological events that result in an increase in blood sugars, faster heart rate, and a rise in blood pressure. These physiological responses were designed to help us survive, choosing "fight or flight".

Illness causes a certain amount of stress on the body. While not the same as emotional stress, physical stress can cause your body to release hormones. These hormones can cause the level of glucose in your blood to rise. This is probably to give the body the energy it needs to heal itself.

The way BG reacts to exercise is dependent of the value of the BG when the exercise is started. If the BG is above about 18 mmol/L, then it is possible that it raises further, but normally it will drop down. Not only during exercise, but even for several hours afterward the BG can drop. Some possible reasons for this are that the glucose transport to the cells by diffusion is increased, that the hepatic and tissue insulin sensitivity is increased so that they store more glucose with less insulin, and that there flows more blood through the tissue that contains remainders of earlier insulin injections.

The dawn phenomenon occurs in the morning when people get up. It is a natural reaction of the body to make the person ready for the day and to take care of energy supply.

The Somogy effect is a counter regulatory action of the liver, when BG levels are too low during the night. When this effect appears, the liver releases a boost of glucose which results in hyperglycaemia.

Insulin takes care of transport of glucose from the blood plasma to the cells, and so it causes a drop in the BG.

Alcohol increases the ability of the liver to store the glucose that circulates in the blood plasma, and so consumption of it will result in a drop of the BG.

Also small other effects as the temperature outside can affect BG; when it is warmer outside, the insulin is absorbed faster. The factor 'temperature outside' is only mentioned for example of other less relevant factors of influence. The site where insulin is injected is also of influence on the absorption rate of the insulin. Sometimes, e.g. because of a bad blood flow through the tissue where the injection took place, the absorption is much less than normally. Also, an injection in the abdomen results in a faster absorption of insulin than an injection in the upper leg.

In the following section the model based approach of controlling the diabetes is discussed and evaluated. With these models a prediction of the time course of BG can be made. The factors, mentioned in this section, are the most important factors that influence this course, so they can be used in the evaluation of a model. Models should incorporate these factors in high measures.

3.3 Model based approach

The principles of non-linear dynamics theory may improve our understanding of the difficult blood glucose control in diabetes, may lead to alternative control strategies in selected

individuals, and might even enlighten the issues involved in automated glucose control for the future, according to [17].

Difficulties in understanding blood glucose (G) behaviour may be the result of a tendency to assume linear relationships between its numerous determinants. Under conditions of constant or zero exercise, a simplified model representing the traditional linear view might be:

$$G(\text{post-prandial}) = G(\text{preprandial}) + a(C - I)$$

where C and I are the amount of carbohydrate eaten at the last meal and the insulin injected beforehand or secreted since, respectively, and 'a' is a constant determined by patient-specific parameters such as body mass index and insulin sensitivity. This is the model on which the traditional 'weighing scales' metaphor of diabetes control is based: correcting for different units, if C 'balances' I at each meal, the glucose level should remain stable.

Clearly, if 'a' is in fact a variable, the equation becomes non-linear. The tendency to mistake variables for constants has been identified as a basis for the inadequacy of linear models more generally in patho-physiology. Such models are appropriate in only a minority of real-life situations.

The model might be better described by a differential equation that includes dG/dt, the rate of change of glucose with respect to time. Such an equation might then do justice to the dynamics through which the numerous determinants of blood glucose are related.

It is natural to think of the glucose regulatory system as a system of compartments; in this case, the glucose compartment and insulin compartment. In essence, the two compartments are separate, but can affect each other. Within each of the two compartments, there could be more compartments, where contents are exchanged. This model framework, known as compartmental modelling, is very commonly used in modelling glucose metabolism.

A brief overview of compartmental modelling will be presented, prior to an exposition of various models and model based systems. The glucose regulatory system is in itself a continuous time system. This philosophy has been adopted by some. Others take a discrete time stance due to the nature of available data.

3.3.1 Compartmental models

Compartmental modelling is a framework where the system is considered as a composition of subsystems, called compartments, where there is exchange/transport of contents with each other and with the environment [2].

Each compartment can be described in this way. For an N-compartmental system in continuous time, consider compartment i, with content m_i. The material transports are: between compartments i and j, denoted F_{ji} and F_{ij}, and with the environment I_i and F_{0i}, as illustrated in Figure 4-3.

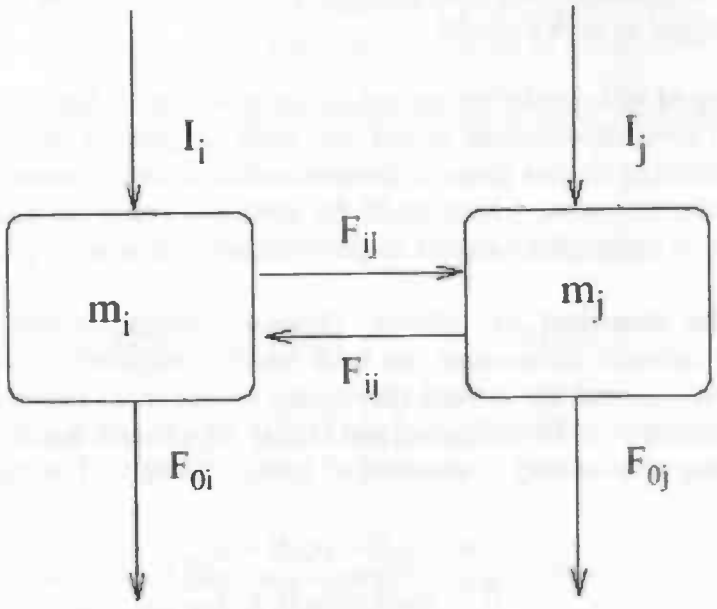


Figure 3-3 Material flow in a compartmental model.

Compartments obey the conservation of mass. Let the flows $F_{ij} = f_{ij}m_i$ be expressed, where in general f_{ij} can be functions of m and t. The balance equation can be expressed by:

$$m_i' = \sum_{j \neq i} (-f_{ij}m_i + f_{ji}m_j) + I_i - F_{0i}$$

Compartmental modeling is used anywhere in the model based approach. In the following, some of the models are going to be investigated, with the purpose to enhance our insights in the glucose-insulin metabolism. The next section is about a test, performed in healthy people. The subjects are in rest, and their blood and insulin plasma concentrations are stable. Only the glucose and blood plasma concentrations are monitored after an injection of glucose in their veins, while trying to keep other influences constant.

3.3.2 Intravenous Glucose Tolerance Test (IVGTT)

Here a standard IVGTT is described, derived from [5].
Ten healthy volunteers (5 males and 5 females) participated in the study. They had maintained a constant body weight for the six months preceding the study. For the three days preceding to the study each subject followed a standard composition diet. Each study was performed at 8:00 AM, after an overnight fast, with the subject supine in a quiet room with constant temperature of 22 – 24 °C.
At time 0 (0') a 33% glucose solution (0.33g Glucose / kg body weight) was rapidly injected (less than 3 minutes) in a vein of one arm. Blood samples were obtained at -30', -15', 0', 2', 4', 6', 8', 10', 12', 15', 20', 25', 30', 35', 40', 50', 60', 70', 80', 100', 120', 140', 160 and 180' the contra lateral arm vein.
The plasma levels of glucose and insulin obtained at -30', -15' and 0' were averaged to yield the baseline values referred to 0'.

3.3.3 Modelling the IVGTT

We think it is important to study models that describe the IVGTT, because in our opinion this is the foundation of the glucose-insulin metabolism. From this foundation it should be possible to extend it to a larger model that incorporates more factors. For example if the

relation of the consumption of food with the absorption rate of glucose from the gut is known, this can be incorporated in such a model.

Works in modelling of BG regulation started in the mid-1960s, due to Ackerman, et al. [3]. They developed a two-compartmental model, one each for glucose and insulin in blood, with the view of understanding further glucose dynamics after an oral glucose input and to explore parameters of insulin response, which could be used as criteria to distinguish normal and diabetic individuals. It assumed a damped sinusoid response to a large glucose input.

The model can be described as follows. Glucose moves from/to the blood glucose compartment. The outward movements are both insulin independent (denoted by G_{out}) and insulin dependent (G_{ins}), and the inward movement comes from external source (G_{ext}). The kinetics of G_{out} is assumed to be diffusive, and G_{ins} to be a linear function of blood hormone level, H. A mirroring relationship is assumed of insulin kinetics. The transport equations are expressed as:

$$G' = -p_{11}G - p_{12}H + G_{ext}$$
$$H' = p_{21}G - p_{22}H + H_{ext}$$

This model could be fitted to glucose measurements up to four hours after an ingestion of glucose tablets, taken at 25 minute intervals.

The Ackerman model simulates glucose and insulin response after a stimulus, until steady state is reached. It was observed that curves from diabetics were mostly underdamped, characterised by lower values of p_{11} and p_{22}. The authors commented that even with the 15 – 30 minute measurement interval, barely enough data was obtained to fit the parameters of the model.

3.3.3.1 Minimal model

The minimal model [4, 6], which is the model currently mostly used in physiological research on the metabolism of glucose, was proposed in the early eighties for the interpretation of the glucose and insulin plasma concentrations following the IVGTT. It is a "set-up" to the simple two-compartment model. It was developed by Bergman et al. [4], by considering an array of compartmental framework and selecting the one whose parameters fitted the data best. The model, as originally proposed by the authors, is to be regarded as composed of two separate parts. The first part [4] uses equation *(t.1)* and *(t.2)* to describe the time course of plasma glucose concentration, accounting for the dynamics of glucose uptake dependent on and independent of circulating insulin; for this first part plasma insulin concentration is to be regarded as a known forcing function. The second part [6] consists of equation *(t.3)* and describes the time course of plasma insulin concentration, accounting for the dynamics of pancreatic insulin release in response to the glucose stimulus; for this second part plasma glucose concentration is to be regarded as a known forcing function. The proposing authors specifically stated [7] that the model parameter fitting has to be conducted in two steps: first, using the recorded insulin concentration as input data in order to derive the parameters in the first two equations, then using the recorded glucose as input data to derive the parameters in the third equation.

As seen above, the physiologic experiment consists in injecting into the bloodstream of the experimental subject a bolus of glucose, thus inducing an (impulsive) increase in the plasma glucose concentration G(t) and a corresponding increase of the plasma concentration of insulin I(t), secreted by the pancreas. These concentrations are measured during a three-hour time interval beginning at injection, after which time interval it is found that the

perturbed concentrations G(t) and I(t) have essentially returned to normal. In order to describe the time course of these concentrations, the Minimal Model of the glucose-insulin kinetics has been proposed.

The standard formulation of the Minimal Model is used, renaming some parameters for ease of notation:

(t.1) $$\frac{dG(t)}{dt} = -[p_1 + X(t)]\,G(t) + p_1 G_b \;, \qquad G(0) = p_0$$

(t.2) $$\frac{dX(t)}{dt} = -p_2 X(t) + p_3[I(t) - I_b] \;, \qquad X(0) = 0$$

(t.3) $$\frac{dI(t)}{dt} = p_4[G(t) - p_5]^{+} t - p_6[I(t) - I_b] \;, \qquad I(0) = p_7 + I_b$$

where

$G(t)$	[mg/dl]	is the blood glucose concentration at time *t* [min];
$I(t)$	[μUI/ml]	is the blood insulin concentration;
$X(t)$	[min^{-1}]	is an auxiliary function representing insulin-excitable tissue glucose uptake activity, proportional to insulin concentration in a "distant" compartment;
G_b	[mg/dl]	is the subject's baseline glycemia;
I_b	[μUI/ml]	is the subject's baseline insulinemia;
p_0	[mg/dl]	is the theoretical glycemia at time 0 after the instantaneous glucose bolus;
p_1	[min^{-1}]	is the glucose "mass action" rate constant, i.e. the insulin-independent rate constant of tissue glucose uptake, "glucose effectiveness";
p_2	[min^{-1}]	is the rate constant expressing the spontaneous decrease of tissue glucose uptake ability;
p_3	[min^{-2} (μUI/ml)$^{-1}$]	is the insulin-dependent increase in tissue glucose uptake ability, per unit of insulin concentration excess over baseline insulin;
p_4	[(μUI/ml) (mg/dl)$^{-1}$ min^{-1}]	is the rate of pancreatic release of insulin after the bolus, per minute and per mg/dl of glucose concentration above the "target" glycemia;
p_5	[mg/dl]	is the pancreatic "target glycemia";
p_6	[min^{-1}]	is the first order decay rate constant for Insulin in plasma;
p_7	[μUI/ml]	is the theoretical plasma insulin concentration at time 0, above basal insulinemia, immediately after the glucose bolus.

In Equation 3, only the positive part of the term $[G(t) - p_5]$ is taken, i.e. when G(t) is greater than p_5 the value is taken to be $[G(t) - p_5]$, otherwise the term's value is taken to be zero. Also in Equation 3, the multiplication by t is introduced by the authors to express, as a first approximation, the hypothesis that the effect of circulating hyperglycemia on the rate of pancreatic secretion of insulin is proportional both to the hyperglycemia attained and to the time elapsed from the glucose stimulus [8]. Multiplying by t in this way introduces the necessity of establishing an origin for time, binding this model to the IVGTT experimental procedure.

Parameters p_0, p_1, p_4, p_5, p_6 and p_7 are usually referred to in the literature as G_0, S_G, γ, *h*, *n* en I_0 respectively, while the Insulin sensitivity index S_I is computed as p_3/p_2.

3.3.3.1.1 Mathematical evaluation of the minimal model

The model parameter fitting has to be conducted in two steps. From a dynamical point of view, the pancreas and tissues form an integrated system with feedback regulations and it would seem desirable to have a model explicitly representing the whole system, which could be fitted in a single pass to both glucose and insulin data, rather than splitting the model into two subsystems and fitting separately each one. In fact, for a model fitting simultaneously the two arms of the control mechanism, the error variance would be a more appropriate expression of the effective applicability of the assumptions underlying both subsystems to the experimental situation. By splitting the system an impression of success is obtained because the error looks smaller, but in fact an internal coherency check is omitted.

So, in order to study glucose-insulin homeostasis as a single dynamical system, a unified model would be desirable. To this end, according to [5], the simple coupling of the original two parts of the minimal model is not appropriate, since it can be shown that, for commonly observed combinations of parameter values, the coupled model would not admit an equilibrium and the concentration of active insulin in the "distant" compartment would be predicted to increase without bounds. Recall that p_5 is the target glycemia which the pancreatic secretion of insulin attempts to attain (i.e. above which the pancreas is assumed to secrete the glycemia-lowering hormone insulin), whereas G_b is the measured baseline glycemia, which results from the equilibrium between the pancreatic action to lower glycemia down to p_5 and the endogenous (liver) glucose production which tends to raise glycemia. In general, G_b may be greater than p_5, and this is in fact the case in the paper where the program to estimate the parameters of the minimal model is described [7]: in the reported series G_b = 92 mg/dl, p_5=89.5 mg/dl.

It must be noted that the Minimal Model incorporates some basic ideas that should be kept under consideration in any further work. First of all, the action of the pancreas on peripheral tissue utilization of glucose is not immediate. In the Minimal Model, it has been chosen to represent it as the progressive accumulation of the active hormone in an intermediate compartment (X), and while other formalizations may be preferred, the idea itself is important and should be retained. Secondarily, a delay is also introduced, via the nonautonomous term t in the third equation, on the actual insulin incretion. That a delay is present is apparent from the classically biphasic shape of the insulin concentration curve after a glucose bolus: while first-phase insulin response occurs immediately (indicating the availability of readily released hormone), second-phase insulin response appears over several tens of minutes, indicating either the slow release of the hormone from previously stored reserves (different from those responsible for first-phase insulin release) or the necessity of de-novo synthesis. However, while it is easy to improve on the description of the pancreatic response to glucose, it is difficult to do so without introducing additional parameters, which will lead to a major experimental cost which is better to avoid, if possible.

3.3.3.2 Dynamical model

In order to overcome the perceived difficulties of the coupled minimal model, another model for the glucose-insulin system is proposed [5]. The physiological hypotheses underlying equation *(t.1)* in the minimal model above have been retained, i.e. that disappearance of glucose from plasma may be described as a first-order process, of rate partly dependent on insulin concentration and partly independent of it. The questionable physiological assumption that the pancreas is able to linearly increase its rate of insulin secretion with time, and the related necessity of establishing an initial time point with respect to which all

biochemical events take place, are both avoided in the proposed formulation. In this way an attempt is made to write a model embodying the underlying physiological mechanism, without associating it by necessity to the IVGTT experiment. The dynamical model of the glucose-insulin system to be studied is therefore:

$$(t.4)\quad \frac{dG(t)}{dt} = -b_1 G(t) - b_4 I(t) G(t) + b_7, \quad G(t) \equiv G_b \ \forall t \in [-b_5, 0), \quad G(0) = G_b + b_0$$

$$(t.5)\quad \frac{dI(t)}{dt} = -b_2 I(t) + \frac{b_6}{b_5} \int_{-b_5} G(s)ds, \quad I(0) = I_b + b_3 b_0$$

where

t	[min]	is time;
G	[mg/dl]	is the glucose plasma concentration;
Gb	[mg/dl]	is the basal (preinjection) plasma glucose concentration;
I	[pM]	is the insulin plasma concentration;
Ib	[pM]	is the basal (preinjection) insulin plasma concentration;
*b*0	[mg/dl]	is the theoretical increase in plasma concentration over basal glucose concentration at time zero after instantaneous administration and redistribution of the I.V. glucose bolus;
*b*1	[min^{-1}]	is the spontaneous glucose first order disappearance rate constant;
*b*2	[min^{-1}]	is the apparent first-order disappearance rate constant for insulin;
*b*3	[pM/(mg/dl)]	is the first-phase insulin concentration increase per (mg/dl) increase in the concentration of glucose at time zero due to the injected bolus;
*b*4	[min^{-1} pM^{-1}]	is the constant amount of insulin-dependent glucose disappearance rate constant per pM of plasma insulin concentration;
*b*5	[min]	is the length of the past period whose plasma glucose concentrations influence the current pancreatic insulin secretion;
*b*6	[min^{-1} pM/(mg/dl)]	is the constant amount of second-phase insulin release rate per (mg/dl) of average plasma glucose concentration throughout the previous *b*5 minutes;
*b*7	[(mg/dl) min^{-1}]	is the constant increase in plasma glucose concentration due to constant baseline liver glucose release.

The above model describes glucose concentration changes in blood as depending on spontaneous, insulin-independent net glucose tissue uptake, on insulin-dependent net glucose tissue uptake and on constant baseline liver glucose production. The term "net glucose uptake" indicates that changes in tissue glucose uptake and in liver glucose delivery are considered together.

Insulin plasma concentration changes are considered to depend on a spontaneous constant-rate decay, due to insulin catabolism, and on pancreatic insulin secretion. The delay term refers to the pancreatic secretion of insulin: effective pancreatic secretion (after the liver first-pass effect) at time t is considered to be proportional to the average value of glucose concentration in the b_5 minutes preceding time t.

Due to the delay, initial conditions for the problem have to be specified including not only the level of glucose at time zero, but also its value at each time from $-b_5$ to 0.

The term $(1/b_5)$ in front of the integral in (eq. *t.5*) has been introduced so as to make the integral equal one for constant unit glucose concentration, thus making b_6 , pancreatic responsiveness, independent of b_5 , the time period of pancreatic sensitivity to plasma glucose concentrations.

The free parameters are only six (b_0 through b_5). In fact, assuming the subject is at equilibrium at (G_b, I_b) for a sufficiently long time ($> b_5$) prior to the administration of the bolus, then

$$0 = -b_1 G_b - b_4 I_b G_b + b_7 \quad \text{and} \quad 0 = -b_2 I_b + b_6 G_b$$

together imply

$$b_7 = b_1 G_b + b_4 I_b G_b, \qquad b_6 = b_2 \frac{I_b}{G_b}.$$

3.3.3.2.1 Stability of the dynamical model

About their dynamical model, [5] stated the following. It depends on six free parameters overall and may exhibit a secondary insulin peak. In contrast to the minimal model, the dynamical model admits only one positive, bounded equilibrium point, which is the couple of resting, basal glucose and insulin values for the subject.

3.3.4 Minimal model and dynamical model versus reality

The two parts of the minimal model are to be estimated separately on the recorded data. In order to study glucose-insulin homeostasis as a single dynamical system, a unifying model would be desirable. The simple coupling of the original two parts of this model would not be appropriate, because it would not admit an equilibrium for commonly observed combinations of parameter values. This in contrast to the dynamical model, which assures a fitting for all possible combinations of parameter values. Moreover, the dynamical model uses less free parameters, and should be easier to fit. The latter seems to be a better model to us.

If these models, once fit on the data of a patient, are used as predictive models, we give the following evaluation, with regard to their approximation of reality.

- **Food**. Only glucose that is injected straight into veins of a subject is considered as external input of glucose. When a subject eats (different combinations of) food, the reaction of the subjects BG is less direct.
- **Exercise**. Exercise induces a higher sensitivity to insulin, and a higher insulin-independent rate constant of tissue glucose uptake. For each process there exists a corresponding parameter in the models. However, the relation between a perturbation in the exercise level and the corresponding parameters has to be found.
- **Insulin**. The models are able to fit the behaviour of the pancreas as reaction on the glucose bolus. In IDDM-subjects, this effect has to be eliminated from the model, and the effect of an injection of insulin has to be inserted in stead of it.
- **Dawn phenomenon / Somogy effect / Illness / Stress (/ Alcohol)**. We don't know if the models are able to fit data of this phenomenon's. Especially for the dawn phenomenon and the Somogy effect we have great doubts, because this kind of reaction/behaviour of the human-system is strongly deviating from normal behaviour.

We conclude that if these models are going to be used for prediction of the glucose level, a lot of investigation with respect to the effect off food, exercise and insulin has to be done yet. Also, such predictive models should be able to cope with the dawn phenomenon, the Somogy effect, illness, and stress.

3.3.5 Subcutaneous insulin kinetics

Subcutaneous insulin kinetics is a complex process whose quantitation is needed for a reliable glycaemic control in the conventional therapy of insulin-dependent diabetes [14]. The major difficulties in modeling include accounting for the distribution in the subcutaneous depot and transport to plasma. A single model describing in detail the various processes for all the commercially available insulin preparations is not available. Several models however have been proposed which vary in the degree of complexity. Virtually all of them handle the regular insulin preparation while a few handle the intermediate acting and the novel insulin analogues.

An important component of a simulation model of an IDDM patient in a conventional therapeutic regimen is the description of how insulin is absorbed and enters plasma after a sc injection. Since the landmark work of Binder (1969), it is a well accepted notion that sc insulin absorption is a complex process influenced by many factors including the associated state of insulin, i.e. concentration, injected volume, injection site/depth and tissue blood flow. In particular, the absorption rate of subcutaneous injected insulin decreases with increasing insulin concentrations as well as with increasing volumes, and this explains the well-known inverse relation between the rate of absorption and the size of injected dose. The quantitative description of insulin absorption is thus a difficult task.

A single model describing in detail the various processes of subcutaneous absorption for all the commercially available insulin preparations is not available, but several more macroscopic models of sc insulin absorption have been proposed which handle one or more preparations. All the models described in [14] handle soluble (regular) insulin while monomer insulin is only analyzed in two of them, and intermediate acting insulin (NPH or lente) is only considered in the model of Berger et al. [15]. It is worth noting that the model of Berger et al. predictions are simulations, while 4 of the 5 other models predictions are best fit to experimental data.

The various models differ essentially in the sc insulin absorption description, since plasma insulin kinetics is, in all cases, assumed to be single compartment. The single pool description, while not adequate in presence of highly dynamic perturbations, is a reasonable approximation when insulin concentration varies with relatively slow dynamics such as after a sc injection.

3.3.5.1 Berger et al.'s model

This model allows the kinetic description of different insulin preparations (regular, NPH, lente and ultralente) based on a logistic equation of insulin absorption which was empirically derived from previous studies. The percent amount of absorbed insulin from the sc space, $A_{\%}$, is given by:

$$A_{\%} = 100A(t) = 100 - \frac{100t^s}{T_{50}^s + t^s}$$

where s characterizes the absorption rate of the various insulin preparations and T_{50} is the time interval to reach a 50% absorption of the injected insulin. T_{50} was described as:

$$T_{50} = aD + b$$

where D is the insulin dose and a and b assume different values for each insulin preparation. Absorption velocity, i.e. the time derivative of $A(t)$ multiplied by the injected dose, is then the insulin input flux into plasma. Thus plasma insulin concentration is:

$$i'(t) = -k_e i(t) + \frac{A'(t)}{V_d} = -k_e i(t) + \frac{t^{s-1} s T_{50}^s D}{V_d (T_{50}^s + t^s)^2}$$

where k_e is the rate constant for insulin degradation and V_d is the plasma insulin distribution volume. The parameter values proposed by the authors for regular and NPH insulin are reported in Table 3-2.

soluble	s	-	2
	a	min U^{-1}	3
	b	min	102
	k_e	min^{-1}	9×10^{-1}
	V_d	ml	12×10^{-3}
NPH	s	-	2
	a	min U^{-1}	10.8
	b	min	294

Table 3-2 Model parameters.

Only two of the proposed models (in [14]), including the described model of Berger et al., account for the inverse relationship between dose and absorption time (Figure 3-4).

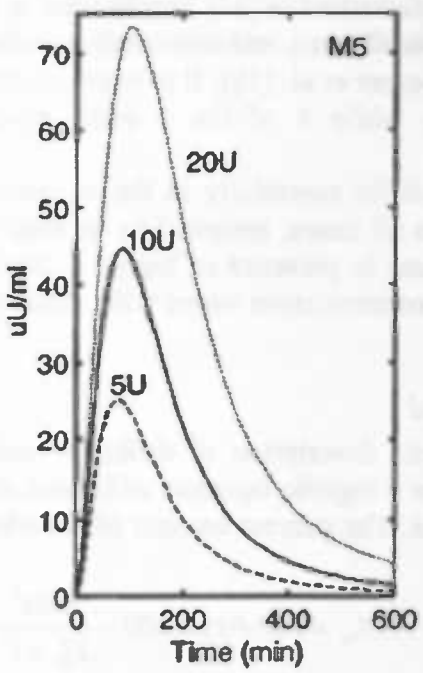


Figure 3-4 Dose dependency of plasma insulin concentration, predicted by the Berger model for a 5U (dashed), 10U (solid) and 20U (dotted) sc injection.

Due to the authors of [14], this is the only available model for the NPH absorption kinetics.

3.3.5.2 Woodworth et al.'s model

However, [16] reported in their article about the short acting insulin [Lys(B28), Pro(B29)]-human insulin, *lispro*, that their previous studies of insulin lispro, regular insulin, and NPH insulin have shown that the one-compartment pharmacokinetic model of Woodworth et al. best fits the subcutaneous administration of these insulins. Two differential equations were used to describe this equation:

$$\frac{dX_1}{dt} = -k_a X_1$$

and

$$\frac{dX_2}{dt} = k_a X_1 - KX_2$$

in which X_1 represents the amount of drug in a depot compartment, X_2 is the amount of drug in the body, k_a is the absorption rate constant, and K is the elimination rate constant. The amount of drug in the body was then related to the concentration (C) with use of the following relationship:

$$C = \frac{X_2}{V/F}$$

in which V/F represents the apparent volume of distribution adjusted for bioavailability (F).

3.3.6 Dynamical model and subcutaneously injected insulin

Here an example is given of the coupling of the dynamical model and a model that describes the kinetic of the insulin which is subcutaneously injected.

With the eye on a model based description of glucose metabolism in IDDM-patients, an idea would be to take the dynamical model, and replace the insulin secretion of the pancreas by the insulin absorption due to a subcutaneous injection. Maybe with this coupling it is possible to do a prediction on the behaviour of the glucose-insulin metabolism in subjects with IDDM, which are in rest just like the healthy subjects in the IVGTT. However, we have to comment that the dynamical and minimal model were originally developed for fitting on known glucose and insulin data, with the purpose of deriving parameters e.g. for the insulin sensitivity of a subject. Anyway, this coupling must create the possibility of deriving such parameters for IDDM patients. After this, it could be used as a predictive model.

The dynamical model (the parameters are commented elsewhere), without begin conditions (derived from t.4 and t.5):

$$(1)\ \frac{dG(t)}{dt} = -b_1 G(t) - b_4 I(t) G(t) + b_7$$

$$(2)\ \frac{dI(t)}{dt} = -b_2 I(t) + \frac{b_6}{b_5} \int_{-b_5} G(s) ds\,.$$

The differential equation used in Berger et al.'s model (described in a previous section) for the plasma insulin concentration:

$$(3)\ \frac{dI(t)}{dt} = -k_e i(t) + \frac{t^{s-1} s T_{50}^s D}{V_d (T_{50}^s + t^s)^2}$$

Now, if we use the dynamical model, but substitute (2) by (3), we get a system that would (if the parameters are chosen well) describe the glucose-insulin kinetics for patients with IDDM being in the same conditions as the healthy subjects in the IVGTT. Because the parameters in equation (3) are all known constants, the only free parameters that remain are b_1, b_4 and b_7 of equation (1). Due to [14] are the constants in (3) derivable from other experiments. The constant b_4 is the constant amount of insulin-dependent glucose disappearance rate per pM of plasma insulin concentration. An idea is to make a variable of this constant, so that the influence on hepatic and tissue insulin sensitivity induced by performing exercise is possible.

Also, when the relation of eating food with its effect on the glucose level, $\frac{dG(t)}{dt}$, is known, the model can be applicable on real life situations. However, we don't know the effect of such a coupling and for our best knowledge there is no literature recorded about it. We can say that the comparison of this adapted dynamical model is the same as the evaluation above, except that it is adapted for insulin injections.

In the next section two well-known insulin advisor simulators are reviewed with respect to the model they use to simulate the glucose-insulin metabolism.

3.3.7 Models used in existing simulators

3.3.7.1 The Automated Insulin Dosage Advisor (AIDA)

Guyton et al. developed a detailed multi-compartmental model, with the focus on the glucose compartment subdivided into smaller compartments based on the organs of major glucose uptake [9]. The authors have expressed that this model was constructed to explore the critical points for experimental design purposes, and not intended for fitting individual curves of data, thus does not include parameters pertaining to the individual. The model described glucose flow from a central compartment to various organs and peripheral tissues, as shown in Figure 3-5.

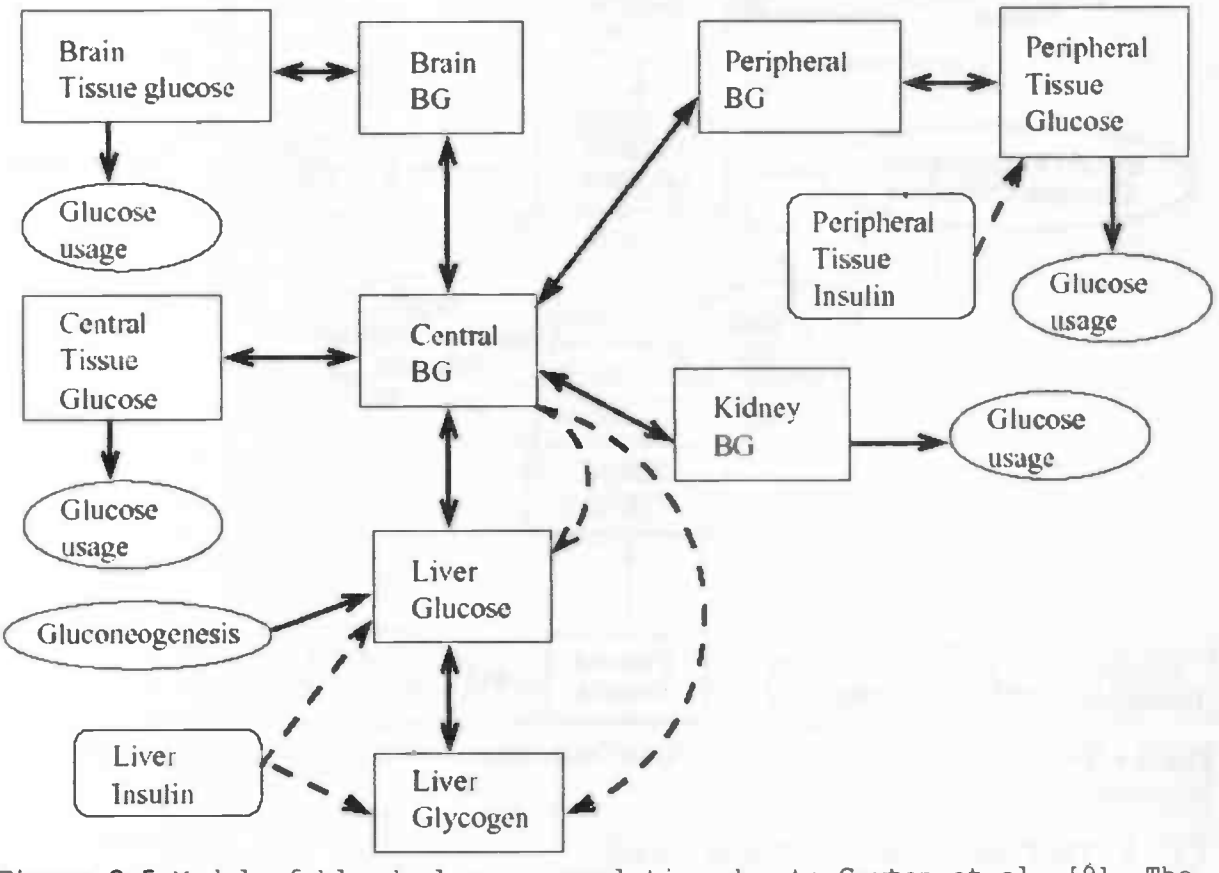


Figure 3-5 Model of blood glucose regulation due to Guyton et al. [9]. The solid lines represent material flow, and the broken lines mean that the material quantity affect flow from the other compartment, without actual exchange of material.

The authors reported that the simulation followed experimental data closely for glucose levels and for insulin rise immediately after glucose infusion, but the two curves deviated towards insulin steady state.

A compartmental model similar in nature to that of Guyton's, is used by Lehmann and Deutsch to base their insulin advisory system, known as AIDA (Automated Insulin Dosage Advisor) [10]. There are three main compartments in AIDA, of glucose, insulin and active insulin, in the same vein as Bergman's minimal model. The glucose and insulin compartments do not exchange contents, but the amount of material effect each other's flow. It is a model of a diabetic person, thus the source of insulin is assumed to be external. As Guyton has done, the glucose compartment is also subdivided to smaller compartments, however the subdivision is based more on the process (e.g. insulin independent glucose uptake) rather than the location/organ in which glucose uptake occur (e.g. brain glucose, renal glucose), as shown in Figure 3-6. This manner of subdivision yields less a number of subcompartments within the glucose compartment, making it a slightly simpler model from the glucose point of view.

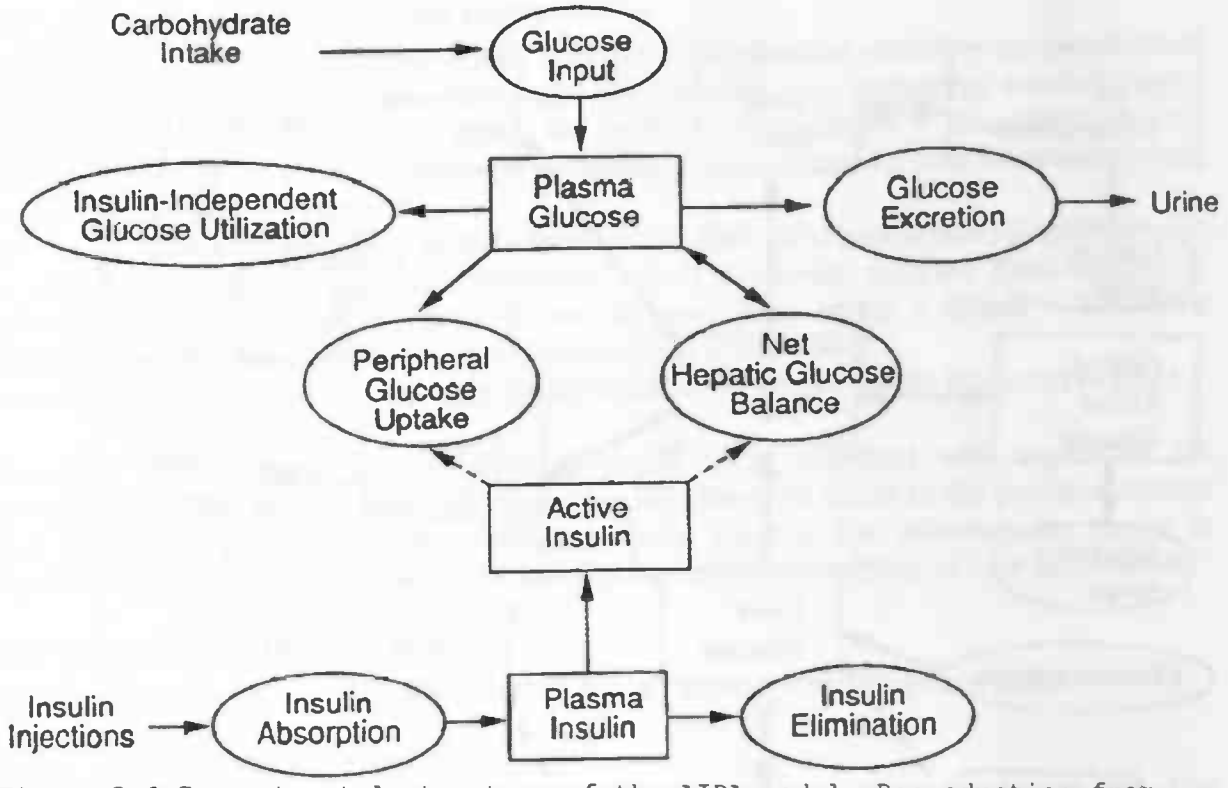


Figure 3-6 Compartmental structure of the AIDA model. Reproduction from Lehmann et al. [19].

3.3.7.2 The Diabetes Advisory System (DIAS)

Contrary to the preciously described continuous time systems, the DIAS system [13] is based on a discrete-time, probabilistic compartmental model, shown in Figure 3-7. It takes this stance on the grounds that glucose levels are discretely sampled, and that it would not be wise to attempt to fit a continuous model to the data. DIAS incorporates a model of the human carbohydrate metabolism implemented in a Bayesian network (causal probabilistic network or CPN), which gives it the ability to handle the uncertainty, for example, in blood glucose measurements or physiological variations in glucose metabolism. Two adjustable parameters are included in the model, the insulin sensitivity and time-to-peak of NPH-type insulin absorption.

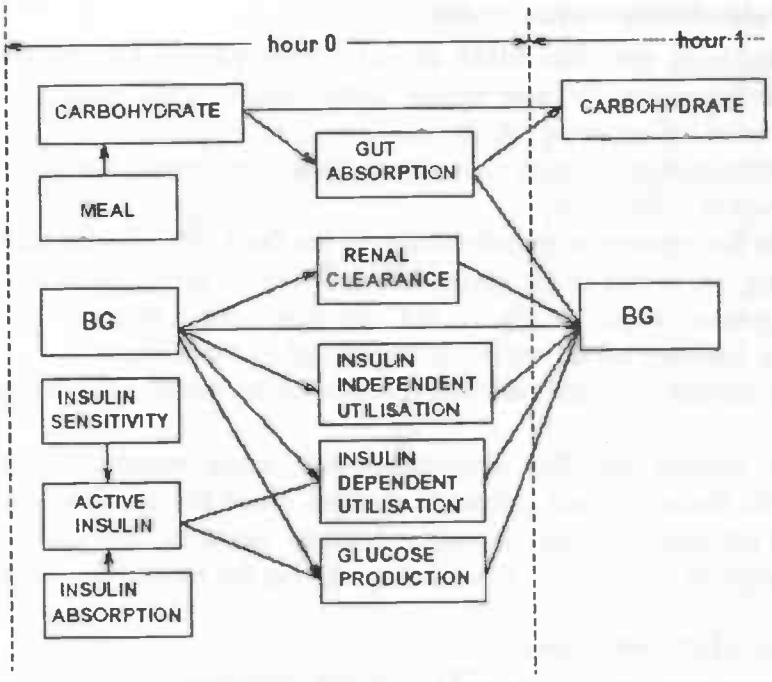


Figure 3-7 DIAS - an advisory system based on a compartmental glucose model. The figure is derived from [13]. A 1h time slice for the difference model in DIAS. The unabsorbed carbohydrate in the gut (CARBOHYDRATE)) and the blood glucose (BG) in the leftmost column can be seen as state variables, determining uniquely the current status. The variables in the second column can be seen as process variables, responsible for the change in CARBOHYDRATE and blood glucose over the next hour. The 24h model in DIAS consists of 24 of these 1h time slices.

The structure of the model is focused on glucose flow, as in Guytons's model, however instead of expressing the dynamics in terms of transport equations, glucose level at the next step is expressed as a conditional probability distribution. Glucose changes are expressed in terms of processes, as in the AIDA model, i.e. insulin dependent and independent usage, glucose inflow (from gut), glucose production in the liver, and glucose excretion through kidneys.

3.3.7.3 E-mail of a member of the DIAS-team

The author was interested in the current state of art of the DIAS-system, and asked the following question to *Ole K. Hejlesen*, a prominent member of the *DIAS-team*.

"Is my conclusion right that you don't look to the patient's physical activity in any way?"

His answer was this (23 – 1 – 2003).

"Martijn, knowing that physical activity influence glucose metabolism, we would very much like to have this explicitly in our model. However, there are not sufficient hard data in the literature to do this, and we therefore have to do it implicitly - i.e. manually or outside the model. We have plans to do some research on how exercise affects the metabolism, but unfortunately this is not an easy task - for example, it looks as if the effect of exercise lasts for several days. More work in this area would be very much welcome...!"

3.3.8 Models in simulators versus reality

There are a few problems with this AIDA model. Firstly **physical activities** are not factored into the insulin independent glucose usage compartment, thus assuming constant usage regardless of the level of exercise. Also, the model is not adaptive – the patient specific parameters are determined at the start, and not updated. This assumes a time-invariant system, which a diabetic person is far from.
AIDA only regards the amount of carbohydrates in the **food**. This means that BG prediction is the same for eating white rise (high glycaemic index) and bread, with the same amount of carbohydrate in grams, which surely is not the case. Also **stress / illness / the dawn syndrome and the Somogy effect** are not incorporated in the model.
On the other hand, insulin injections are incorporated in the model, which is a positive point.

About the DIAS system we can give about the same comment with regard to the incorporation of the factors, which influence the BG. Read the email in the previous section about DIAS and physical activity. Another dubious point is that although the model is adaptive, the parameters are updated at a rate higher than the availability of new information.

3.3.9 Simulators AIDA and DIAS

Here the two advisory systems, AIDA and DIAS, are reviewed as simulation tools.

3.3.9.1 AIDA as simulation tool

This model is incorporated into the advisory system as shown in Figure 3-8. The system operates as follows: simulate a 24-hour period worth of glucose and insulin dynamics, identify problem area – where control goal is not met, consult the rules, 'implement the advice' and resimulate, repeat the above steps until goal is reached.

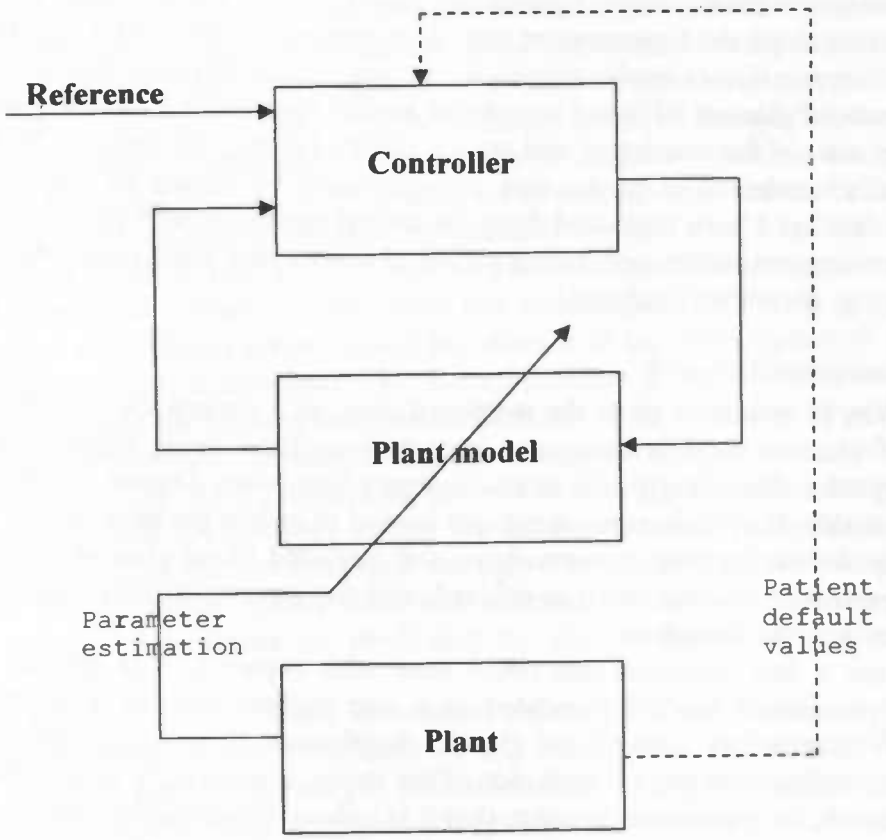


Figure 3-8 AIDA - an advisory system based on a compartmental glucose model, with a set of static rules as controllers.

The controller consists of qualitative static if-then rules combined with patient specific information, to produce a quantitative advice. Some examples of these rules are as follows:

```
advise_for_a_problem (PROBLEM, CONTROL)
      if is_feasible(CONTROL)
      and is_indicated_for (CONTROL, PROBLEM)
      and not (aggravates (CONTROL, OTHER_PROBLEM))
      and not (may_cause_hypo (CONTROL))


is_indicated_for ((decrease_dose, before, MEAL, INSULIN_TYPE),
                  (('-',hypo),PERIOD))
      if (has_stron_effect ((before, MEAL), INSULIN_TYPE,PERIOD)
```

The **advise_for_a_problem** rule generates a control action for a particular problem, and the **is_indicated_for** rule is an example of one of the indication pertaining to the former rule. That particular indication means that the dose of **INSULIN_TYPE** should be reduced if hypoglycaemia occurs during that time period. These qualitative pieces of advice are transformed to quantitative ones using the system's patient database, which include the regular insulin doses, insulin types, meal sizes (in grams of carbohydrate) and times of meals and injections. The control goals are defined as blood glucose ranges during particular time periods, such as

```
blood_glucose_target (breakfast, (4,6))
```

AIDA was developed with the view of predicting blood glucose values, given a set of insulin doses, thus patient dependent parameters are incorporated in the model equations. These parameters are: hepatic (liver) insulin sensitivity S_h, glomerular filtration rate (of the kidneys) GFR, renal threshold glucose *RTG* and peripheral insulin sensitivity S_p. These parameters are initialised at the start of the simulation and are not updated during simulations. When building a patient specific model these parameters are estimated by means of matching the BG concentrations that have been estimated from the model equations with measured BG levels. The renal parameters are determined during a clinical assessment, and given default values for each category (e.g. normal and reduced).

3.3.9.2 DIAS as simulation tool

Insulin sensitivity is estimated to fit the measured data, as a patient specific parameter. The distribution of glucose level is computed in one hour time steps, during which insulin sensitivity is updated. Data is typically available every four hours. During the period when no new data is available, the previous measurement is used to update the parameters.
Insulin is computed on the base of normalizing the predicted blood glucose value. A penalty curve on the predicted glucose level, is utilized, and the optimal insulin value is computed using a steepest descent algorithm.

There are a few questions one could pose with regard to this system. It is rather dubious how parameters could be updated at a rate higher than the availability of new information. With regard to the predicted glucose distribution, the range of allowed values (of one standard deviation wide around each side of the mean) is seemingly greater than the range of normoglycaemia. It is such a wide range that it is indeed questionable whether a data point falling in that range of predicted values justifies as a means to evaluate the predictive performance of this model. Furthermore, it was not clearly reported what the predicted glucose value on which a penalty value is determined should be – whether it is the mean, or otherwise. The authors have reported success in detecting nocturnal hypoglycaemia – a significant clinical issue on it own right. It seems that this capacity is about as much as this system is able to perform, as a safety mechanism for patients with particular problems. To achieve their original aim of an insulin advisor for day-to-day use, there is much room to move with regard to model accuracy.

3.3.10 Evaluation Model Based Approach

In this section we give a short summary and an evaluation about, our research regarding to the model based approach to develop an insulin advisory system to stabilize IDDM. We critically assess the discussed compartmental models with regard to the factors that influence BG. Unresolved issues raised for model-based techniques include the relative lack of input data necessary for generating reasonable blood glucose predictions, and the high level of uncertainty associated with such predictions, which limit their use as guides for therapeutic insulin-dosage adjustments.

Our first point of interest was the pure glucose-insulin metabolism, eliminating as many other influences as possible. In the discussed Intravenous Glucose Tolerance Test (IVGTT), glucose and insulin blood plasma concentrations were measured in healthy subjects who were at rest. The minimal model and the dynamical model are models that describe the glucose-insulin metabolism when the glucose is injected directly into the blood of a subject in rest. To attain our goal, the development of an insulin advisory system, a predictive model is needed. The minimal and dynamical model are for parameter estimation. But if the parameters are estimated, they can be used for predictive purposes. The mathematical problems with the

minimal model, and the smaller number of parameters that are used in the dynamical model brought us to the conclusion that the dynamical model is preferable to the minimal model.

We came with the idea of replacing the pancreatic insulin secretion in the dynamical model by the insulin absorption due to a subcutaneous injection. Except that this reduced the number of free parameters dramatically, we are able to determine the relevant parameters in IDDM subjects now, and next use it for prediction of glucose-insulin metabolism. The most important factors that influence the BG are summed up in Table 3-1. When we put the adapted dynamical model to the light of Table 3-1, we saw the following problems. To enable this adapted dynamical model to cope with the consumption of food, will be a severe problem, because very little is known about the relation of the consumption of food, and the absorption of glucose due to this food. The second problem is that of incorporating exercise into the model, because the relation between an increase in physical activity and the increase in the insulin-independent disappearance of glucose together with the increased sensitivity to insulin, is unknown. The third problem is that we expect great troubles especially for the dawn phenomenon and the Somogy effect we have great doubts, because this kind of reaction/behaviour of the human-system is strongly deviating from normal behaviour. The idea of using the dynamical model, that was adapted to insulin injections, is no longer regarded as a potential candidate for predicting the glucose-insulin metabolism in real life situations.

About the models used in the simulation tools AIDA and DIAS, we concluded the following with regard to the factors influencing BG. Again, only the amount of carbohydrate is regarded, which is surely not enough. Different levels of physical activity are neglected. Other factors, like the dawn phenomenon and the Somogy effect are not incorporated in the model.

Below the accuracy of model based glycaemic predictions is discussed, followed by a concluding section about the unresolved issues of the model based approach. Out of this we finally conclude that we have to examine literature about the non-model based approach.

3.3.10.1 Accuracy of model based glycaemic predictions

Every clinician is aware that a diabetic patient on the same insulin regimen, resting in bed, eating at the same time each day a dietician-prescribed standard diet can have quite different BG readings from day to day. For example Table 3-3 contains the BG data from an 18 year old type 1 diabetic patient resting in bed on the same insulin regimen for 6 consecutive days.

Day	Breakfast		Lunch		Supper		Bedtime	
	Time	Value	Time	Value	Time	Value	Time	Value
Wednesday	08:40	4.4			18:18	11.0		
Thursday	08:45	6.5	13:25	9.0	17:39	8.0	00:09	11.0
Friday	08:35	2.0	12:40	11.0	18:57	8.0		
Saturday	08:31	2.0					00:12	4.0
Sunday	08:34	4.5	12:38	9.0	18:04	9.0	00:11	11.0
Monday	07:46	5.0	12:33	9.0	18:03	10.0	23:53	9.0

Table 3-3 Blood glucose data from an 18 years old insulin-dependent (type 1) diabetic patient resting in bed on the same insulin regimen for 6 consecutive days. Data from Lehmann et al. [19]. Blood glucose values are given in mmol/L.

Clearly the patient's glucose metabolism is not very regular or consistent. From the modeling perspective endocrine processes must be taking place which are not, at present, fully understood and/or which cannot be explicitly modeled. Given this, BG predictions generated by quantitative models cannot be better than the natural variability which exists in the BG data.

To say something about the accuracy of model based glycaemic predictions we consider predictions from the AIDA simulation, because we think this is one of the most successful simulations of glycaemic predictions. Figure 3-9 shows a simple regression graph of observed (measured) BG versus predicted BG derived from a study of 24 patients, followed over a 4-5 day period, referred to in [12]. Predicted BG data were obtained from the AIDA model [10]. As can be seen there is considerable scatter in the data. For individual measurements (or patients) the BG predictions may be a considerable way of the line off identity. However, it needs to be recognized that such plots are relative simplifications of complex associations. For example the predictive capability of such models will also vary with time [19].

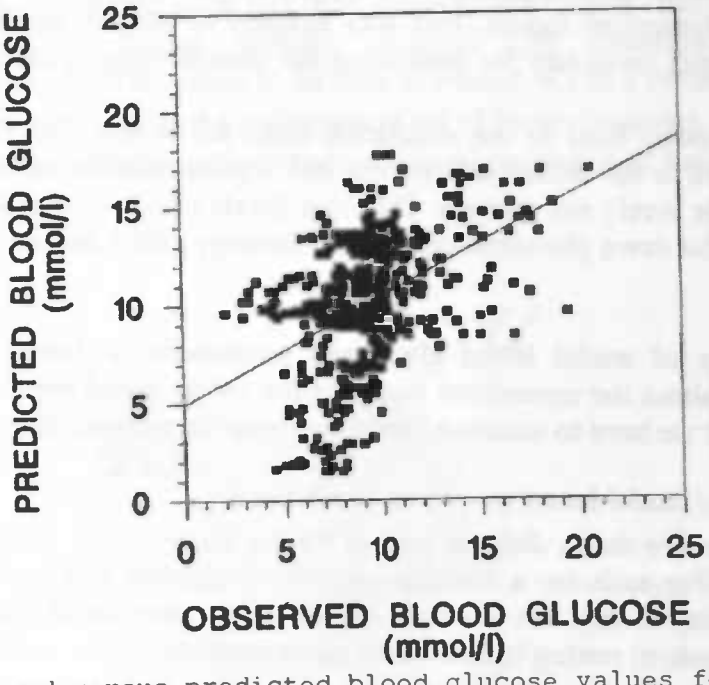


Figure 3-9 Observed versus predicted blood glucose values for a compartmental model of glucose-insulin interaction in diabetes. Data from Lehmann et al. [12], from 24 insulin-dependent (type 1) diabetic patients followed up for 4-5 days. Regression line equation: $y = 4.9 + 0.55x$ ($R = 0.45$).

Nevertheless data such as these –simply expressed as a mean root mean square deviation between observed and predicted BG data of 1.9 mmol/L– led the authors of [10] to realize that such quantitative compartmental models were not reliable enough for making glycaemic predictions or thereby deriving clinical therapeutic decisions for individual patients. It is noted, even through the original data were for the most part derived from a highly selected group of patients [20], that best fit curve exhibited qualitatively different patterns with respect to observed data in six out of 30 patients (20% of the group) [12].

3.3.10.2 Unresolved issues model based approach

In this section the drawbacks of the model based approach are summarized.

Apart from uncertainties over predictive accuracies – there are several concerns regarding modeling approaches. Problems may arise from

- the lack of relevant medical knowledge that would be needed to describe all important factors and processes affecting glucose metabolism,
- methodological difficulties that appear when dealing with complex metabolic systems, and
- quality of data patients report as raw material for state assessment and control.

Clearly the models don't describe the glucose-insulin metabolism deep enough, because there exist more processes that affect glucose dynamics substantially. Current modeling knowledge of the glycaemic effect of food is very limited. Basing the entire assessment of food on the overall carbohydrate content of the meal is a well recognized simplification of a very complex physiological process. However, data are simply not available in the literature about the glycaemic indices and absorption times to peak of a wide variety of foods.

Similarly the effect of exercise, stress, glucose-counter regulatory effect or dawn phenomenon on the BG profile can be complex and counter-intuitive making reliance on compartmental models for individual therapy planning once again unrealistic. Furthermore, such caveats are raised before one considers the difficulties of actually quantifying, for example, the amount of exercise undertaken or the intensity of stress that might result in fast elevation of the BG level.

Even if each unit process is described with sufficient precision a methodological problem would still persist. Hedbrant et al. [21] have suggested that in a fairly complicated system one has to accept a weak description of the whole system despite sharp descriptions of the individual components. The components (e.g. liver, pancreas, muscle or β-cells) are handled separately and described within certain confidence intervals. When these descriptions of the components are put together, the description of the overall performance turns out to be very weak, due to the merging of the confidence intervals.

The major limitations of such model-based approaches come from the data collection process. Both artificially stable and hectic but unrecorded lifestyle conditions make model-based control rather illusory. To generate data for such models, in an attempt to control the clinical test environment, the volunteers or patients are often subjected to somewhat artificial conditions, such as fixed meal times and contents and limited exercise. Also, most patients are reluctant (or unable) to record all relevant lifestyle events (stress, exercise, food intake, etc.) with a consistency and precision that would be needed to build an adequate patient specific model (PSM).

In this respect the glucoregulatory system involves a great number of variables most of which are non-observable and as such, beyond the physician's control. These perturbations are not random, therefore, their effect on the BG level cannot be seen as a white noise affecting observed values. As a result, it is easy to argue against the selection of a small number of parameters within a model and to 'blame' them for the large variability seen in home monitoring BG data.

By placing all this deficiencies of the model based approach on record, we are able to draw our conclusions. The next section shows that these conclusions lead us to take a closer look at the non model based approach.

3.3.11 Conclusions Model Based Approach

We perceived the following drawbacks of the model based approach.

- The lack of relevant medical knowledge that would be needed to describe all important factors and processes affecting glucose metabolism.
- The differences in the insulin's action profile from time to time.

- Errors in measurements.
- The immeasurability of some significant interior processes (e.g. the influence of the central nerve system), so a complete model is almost impossible.
- Because of the many parameters that will be needed for an adequate model, such a model must be very complicated.
- The paucity of data (very much data is needed to tune all the parameters).
- The probably bad quality of the relevant data that patients should report.
- The existence of very complicated non linear relations in metabolism.
- Methodological difficulties that appear when dealing with complex metabolic systems.
- The predictive accuracies are bad, even in the subjects who were the easiest to predict.

We conclude that the models that are currently available only deal with very few real life situations. Even in these situations the predictive accuracies are bad. Suppose that there are N factors that influence the blood glucose regulation. Let the universe $\mathcal{U}$ be an N-dimensional space, with one dimension for each factor. The universe $\mathcal{U}$ consists of all different combinations of factors that influence BG, and includes a subspace $\mathcal{RL}$ that consists of all possible combinations of factors possible in *R*eal *L*ife situations. The developed *C*ompartmental *M*odels of IDDM claim to be able to predict BG in a certain number of cases that occur in real life. Let $\mathcal{CM}$ be the collection of all of these situations. In the Figure 3-10 below a representative reproduction of a two-dimensional projection of these spaces is given.

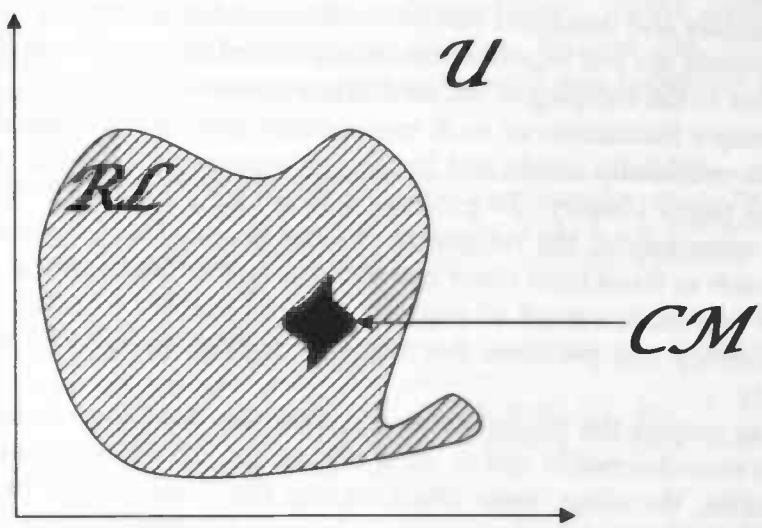


Figure 3-10 In the figure a two-dimensional projection of the universe, $\mathcal{U}$, containing all the different combination of factors that influence BG. $\mathcal{RL}$ is the set of all combinations that could occur in real life situations, and $\mathcal{CM}$ is the set of all real life situations that are claimed to be predictable by compartmental models.

Even the predictions of the compartmental models in the relatively small subspace $\mathcal{CM}$ are according to the authors their self too bad to use for personal predictions.

As in the following sections will appear, the development of a non model / rule based system is preferred. Because of the fact that there are much less articles in scientific libraries to find about this approach than there are about the model based approach, we suspect that there is

less investigation done in this branch of science. Moreover, adding exercise to the inputs doesn't complicate a non model based system very much. This in contrast to the mathematical models which cope with great troubles when one is trying to add the influence of exercise to the system, due to the difficulties in measuring the amount and intensity of the relevant exercise. They can be published and easily reviewed by both clinicians and patients. Such peer review allows their appropriateness and generalizablility to be established. Custom tailored rules are also suitable for adaptive control. Furthermore by their very nature safety features can be incorporated into algorithms (provided of course the algorithms are followed), therefore offering reassurance to clinicians and patients alike.

We hope, by taking the non-model based approach of developing an (artificial intelligent) insulin advisory system, to develop a controller that is able to cope with more situations than those of $\mathcal{CM}$. Such a system certainly can be trained in, or developed for all $\mathcal{RL}$ situations. Here the IDDM-system of human is considered more or less as a black box.

3.4 Non-model based approach

At the end of the previous section we concluded that the models, that are currently available, are only capable of making predictions in a severe limited number of IDDM real life situations. Moreover, these predictions are so erroneous that they sometimes yield perilous advices. These advices were deducted from a model that is constructed from the "IDDM-body". We know, however, that some IDDM patients are adequate controllers to their own IDDM-body in almost all $\mathcal{RL}$ (real life) situations. These patients work with own extensions of the simple IF-THEN rules they learned from medical experts when they started with self-regulation.

Generally rule/non-model based systems are believed to be typically much simpler to develop than their model based counterparts. Curiously enough, this approach is less taken, as literature on non-model based algorithms is scare.

3.4.1 Introduction

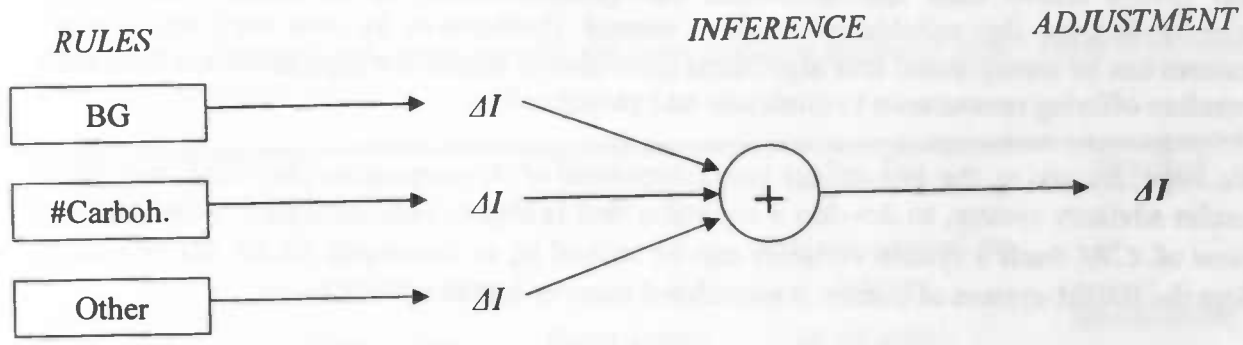
In the non-model based approach, stabilizing IDDM is tried, without modelling the IDDM-system explicitly. The IDDM-system is regarded more or less as a black box, and a controller is developed to control this black box, regarding only the input and output of the box. In this section we discuss a couple of different methods for the construction of an advising system for diabetes management.

The discussed advising systems diverge from advising systems for individuals to cope with different situations, to a system that advises for adequate insulin regimens. These advisory systems stand at a higher level than the individual level. In fact the advice of medical specialists is modelled. Further the construction of a diagram is discussed. This diagram gives advice on adjustments in the rate of insulin infusion on the base of the last two BG measurements on behalf of diabetes management in critical patients. We start with discussing algorithms that contain direct instructions of what to do for the individual patient in different therapeutic situations.

3.4.2 Algorithms for individual patients

Actually, optimal decisions can be selected according to some guidelines (algorithms) that contain direct instructions of what to do in different therapeutic situations. Clinical algorithms encapsulated as production rules or mathematical formulas, reflect the heuristics of the routine therapeutic strategy which attempts to lead the patient to progressively better control by suggesting stepwise changes to the dose or distribution of insulin in response to the

observed patterns/problems of glycaemic control. The inference engine operates in a backward and/or forward chaining mode controlling the invocation of rules that lead to the selection of the control action(s) required. Such systems are composed of mostly static rules, and advices on the amount of insulin adjustment form the prescribed dose. Let this be denoted by ΔI.



Clinical algorithms may recommend changes to the basic insulin dosage regimen as well as to the anticipatory/supplementary insulin adjustments which may be required. For instance, increases in the basal insulin dose may be made to counteract high BG levels which exceed the target range. To help obviate adjustments being made for random variations in BG, hyperglycaemia should be evident for at least 2 days before an incremental adjustment is made, and the patient should be sure that alterations in food intake or activity cannot explain such out-of-range BG findings [22]. Simple algorithms by their very nature cannot cope with situations not explicitly stated. It follows that such guidelines would contain built-in safeguards such as referral to a specialist if the situation became too complex or if unanticipated events arose. The first set of such production rules was published by Skyler et al. in 1981 [22] (Table 3-4).

1. Prevent insulin reactions by eating meals and snacks on time.
2. If fasting BG on arising is < 3.3 mmol/L, or there is evidence of hypoglycaemic reactions occurring overnight, reduce evening intermediate-acting insulin by 1-2 units.
3. If BG after breakfast or before lunch is < 3.3 mmol/L, or if there is a hypoglycaemic reaction between breakfast and lunch, reduce morning regular (short-acting) insulin by 1-2 units.
4. If BG after lunch or before supper is < 3.3 mmol/L, or if there is a hypoglycaemic reaction between lunch and supper, reduce morning intermediate-acting insulin by 1-2 units.
5. If BG after supper or at bedtime is < 3.3 mmol/L, or if there is a hypoglycaemic reaction between supper and bedtime, reduce evening regular (short-acting) insulin by 1-2 units.

Table 3-4 Algorithms for adjusting insulin dosage using a 'split-and-mixed' insulin dosage regimen with patient home monitoring of BG levels. Derived from Skyler et al. [22]. Scenario: hypoglycaemia not explained by unusual diet/exercise/insulin.

This is an early version of such an algorithm and comprises simply a set of IF-THEN rules for each injection time, mainly to guard the patient against (prolonged) hypoglycaemia [22]. These rules take into account BG-information only.

Information on glucose, carbohydrate and/or exercise is taken into account in the algorithm of a handheld device, the Insulin Dosage Computer (IDC) [23]. This algorithm, as the previous, advises users on insulin adjustment. The rules are simple, static rules, expressed as bounded

piecewise linear functions of the various variables, examples of which are shown in Figure 3-11 below.

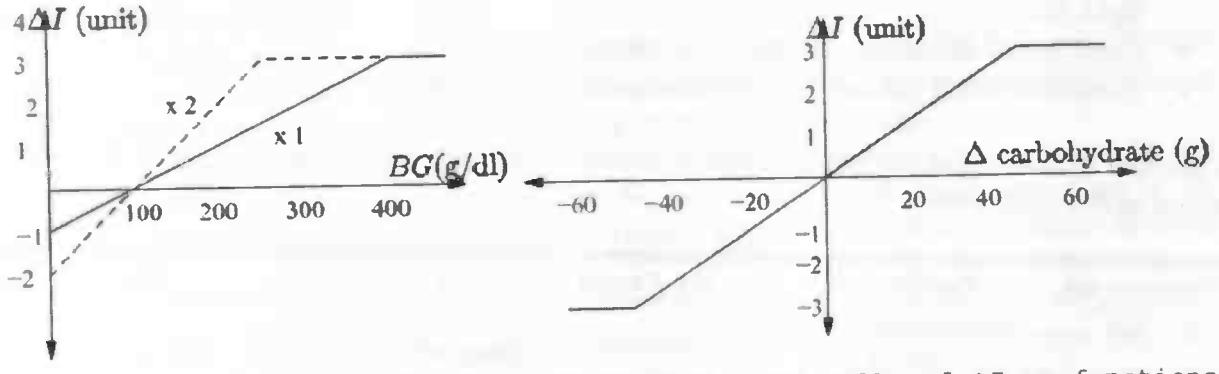


Figure 3-11 Examples of the rules used in the IDC [23], of ΔI as functions of BG and meal deviation from normal (in terms of grams of carbohydrate).

This system regards the effects of BG, carbohydrate, and exercise when applicable, as independent variables to the ΔI functions. The overall effect is regarded to be the superposition of all components. The algorithm is modified, quantitatively as a function of current BG only, and qualitatively in terms of various factors, including hypoglycaemia, carbohydrates, levels of activity, stress, and general health condition such as fever and nausea, in three categories (e.g. mild/less, typical/regular, more/strong).

The IDC-system is implemented in a telephone advisory system, where patients enter their BG reading and injection time (e.g. pre-breakfast, etc.), and then are advised on insulin dose [24]. This telephone advisory system computes adjustments from insulin doses prescribed by physicians, and its use is strictly operated from a clinic. The system stored patient information, and can be used as a database system by the physician.

The authors claim success in the form of reduction in incidence of hypoglycaemia and hyperglycaemia, and report that user friendliness to be a feature which encourages patients to use it, and that there are patient-dependent parameters incorporated to the rules. However, there is no report available about how the rules are parameterised. About the IDC, the authors of [19] report that this device could not explain or justify its reasoning – either to patients or health-care professionals, which may account for its relative lack of widespread use. However, a similar conceptual approach, integrated via a telemedicine system, forms the basis of the newer HumaLink prototype [24].

3.4.3 Advices on insulin regimen

When a diabetic patient starts with self regulation, he is advised by a medical expert for an adequate insulin regimen. Table 3-5 gives examples of possible regimens. As there is very little information in medical literature concerning practical aspects of this issue, medical experts adopt their own rules for insulin regimen specification and dose adjustment. In [25] the application of a neural network approach for the development of a prototype system for knowledge classification in this domain is discussed. The system facilitates decision making for diabetic patient management by insulin administration. The prototype system classifies clinicians' knowledge in the domain of insulin administration. Some main factors participating in the decision making by doctors for insulin prescription are:

- Patient age
- Special condition (pregnancy, surgery, infection)
- Unstable diabetes (yes, no)

- Glucose profile (morning, afternoon, evening, night/unknown, normal, hyperglycemia, hypoglycemia).
- Physical activity (morning-noon, afternoon-evening, night/none-unknown, sedentary, light, heavy)
- Food intake (breakfast, lunch, tea, dinner)
- Desirable blood glucose control (fair, good, very good).

A number of diabetologists came up with the most common regimens used (Table 3-5), which served as the output set.

Regimen no.	Pre-Breakfast	Pre-Lunch	Pre-Tea	Pre-Bed
1	Intermediate acting	-	-	-
2	Short + intermediate acting	-	Short + intermediate acting	-
3	Short acting	Short acting	Short acting	Intermediate acting
4	Short acting	Short acting	Short acting	Short acting

Table 3-5 Most Common Regimens.

The resulting system proved to be applicable to this particular problem, classifying correctly 92% of the testing cases.

It is well recognized that insulin regimen selection is a problem that has more than one scientifically acceptable solution. We think that generalization of the prescription of an adequate insulin regimen is a good point because in such way patients more easily can be exchanged between different medical specialists. Every specialist is accustomed to his own working-method. If every specialist would use such a tool for insulin regimen prescription, we think a more universal way of thinking will emerge, with the effect that the development of general algorithmic prescriptions is easier, and literature can be extended in this field.

3.4.4 Neuro-fuzzy controlling

When a critical patient cannot meet his energy requirements, the parental administration of nutrients is needed. When the same patient is also diabetic, a good glycaemic control is mandatory to avoid energy waste and optimize insulin treatment. To allow an efficient utilization of administered nutrients, BG should be maintained near normal values. Several algorithms to adjust insulin infusion rates have been proposed. These algorithms operate through a feedback regulation (Westenskow, 1997) that follows the logic of an open-loop control system and adjust insulin administration rates according to a time schedule of BG measurements (unmodified insulin infusion rates for BG values between 6.7 and 10.0 mM; + 0.5 U/h for every BG value > 10M; - 0.5 U/h for every value < 6.7 mM). Since these conventional algorithms do not allow reaching and maintaining near normal BG levels without increasing the frequency of BG measurements or the risk of hyper- or hypoglycaemic events, target BG values are higher than desirable (between 8 and 11 mmol/L). To improve glycaemic control, without increasing the number of BG determinations or the risk of hyper- or hypoglycaemic events, the last two BG determinations are considered in [26], where a neuro-fuzzy control method of blood glucose in critical diabetes patients is described.

In this way, taking into account the degree and the direction of the glycaemic variation, the rate of insulin infusion can be more accurately adjusted. They used a neural

network to apply fuzzy logic theoretical principles and to extrapolate rules to be used to elaborate a nomogram for insulin infusion rates (neuro-fuzzy system). A nomogram is nothing else than a table resulting an adaptation in the insulin infusion rate, given the current and the preceding BG value.

Since fuzzy systems do not have the ability of adaptively adjusting their membership functions, a neural network is employed, which can find by itself the relationships between variables, to find the right rules and the adjusting membership functions.

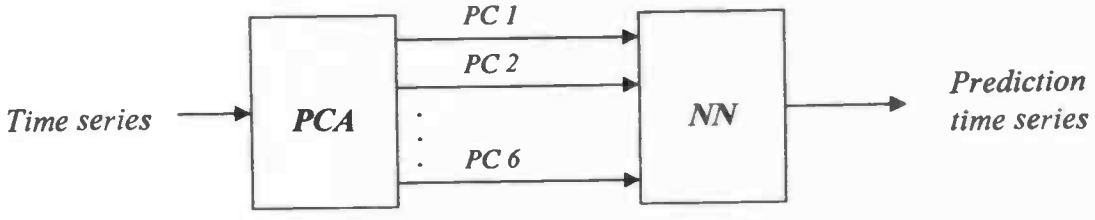
The results pointed out that the neuro-fuzzy method allowed a faster decrease of BG levels, when starting the experiment, and that the BG levels settled down very close to the target value of 6.7 mmol/l, in contrast to the classical approach which settled down at about 10 mmol/L.

One may assume that the fact that (when eliminating other factors that influence BG, like physical activity) the same nomogram is applicable to a large group (20 patients) means that BG behaviour has generic features. [26] convinced us from the fact that neuro-fuzzy methods can help by deducting features from the BG-behaviour of IDDM.

3.4.5 Prediction of morning blood glucose levels

In chaotic systems, deterministic processes readily lead to unpredictable but non-random behaviour, even when the dimension (number of variables in the system) is low. Variation in blood glucose measurements of non-diabetics has been shown to include a chaotic component, but the normal range is narrow compared with that compatible with life, and so it is useful to draw a contrast between the point attractor representing the normal range in a non-diabetic (a homeostatic equilibrium state in which negative feedback dominates), and the much broader attractor of the diabetic state, which includes a component of positive feedback [17].

Liszka-Hackzell [18] has studied a 2-year profile with regard to morning and evening BG values from a single diabetic individual. The resulting model he made, based on six principal components and a neural network, produced a correlation coefficient of 0.76 between observed and predicted glucose values during the first 15 days of the prediction of the morning BG values.



Beyond 15 days the predictability was lost, and the model needed to be reconstructed. This presumably corresponded to movement of the underlying attractor, and highlights the limitations of advice given in out-patient clinics based on historical glucose profiles more than 2 weeks old. Adaptive algorithms translate in the diabetic clinical setting to patient education regarding their own attractor's behaviour, in preference to specific advice from the clinician over dose adjustment, advice that may be soon out of date.

3.4.6 Conclusions Non Model Based Approach

Many patients are a successful regulator of their own IDDM-body. They elaborate a generic prescription, learned from a medical specialist. The IDDM-system isn't stationary or time invariant and changes in about two weeks so much that the current available models are

invalid then. Neuro-fuzzy approaches are capable of learning some of the behaviour of the IDDM-system, at least with regard to the appropriate adaptation in the insulin infusion rate connected to BG values.
We think that the use of computer tools in prescribing insulin regimens can bring physicians to the same train of thought. The outcome of such a tool will be the same with respects to patients in about the same situation, visiting different doctors. This would admit an unified way of reasoning.

3.5 Conclusions Technology in Diabetes Care

The best models constructed with the model based approach of developing an insulin advisory system are only applicable in very few real life situations. The predictions done in these situations have limited use for the construction of patient specific models.

Very much investigation in the model based approach is done, where a model of the IDDM-system is tried to construct on behalf of deducting an adequate control action. On the other hand, little investigation in the non model based approach is done, where a model of an adequate controller is tried to construct. These adequate, already existing controllers are controllers that are able to function in all real life situations, so if an appropriate model of such a controller is made, it can be used to control IDDM in real life situations too.

We think new research into the non model based approach is probably more useful than deepen research into the model based approach.

4 Modelling the self-regulating IDDM-patient

4.1 Defining the structure

This section gives an idea about the scope of interest in this project by defining the structure of the control process. A short introduction into control theory is given in order to clarify the context we are working in and to classify the control system we try to develop. Definitions of *italic* terms are taken from [27].

In mathematical control theory, the mathematical model describing the physical system that we want to behave according to the specification is called *the control system*, *the system to be controlled*, or *the plant*, and the mathematical model of the controller device that is aimed at achieving these specifications is called *the controller*. In our situation the physical system to be controlled is the body of a diabetic with regard to the time course of its BG. Here we call this system, the **DM-system**, where DM = Diabetes Mellitus. This DM-system consists of all sorts of complex non-linear physiological processes that influence BG. However, some diabetics are in fairly full control of their own DM-system in most situations, obviously, without knowing the behaviour of most processes, or even without knowing from the existence of most processes. A diabetic doesn't know the action profile of the insulin he uses, the absorption profile of glucose from the gut induced by food intake, the renal threshold value above which glucose is filtrated out of the blood at a certain rate and other BG determining processes. The average diabetic regards the DM-system more or less as a black box. This is an interesting fact. We conclude that if a model can be derived of the diabetic's decision making, this model can be used for stabilizing the DM-system. No suitable model is developed for the DM-system yet, and thus from now on it is regarded as a black box. In Figure 4-1 the diabetics ignorance of the complicated processes in the DM-system, is illustrated.

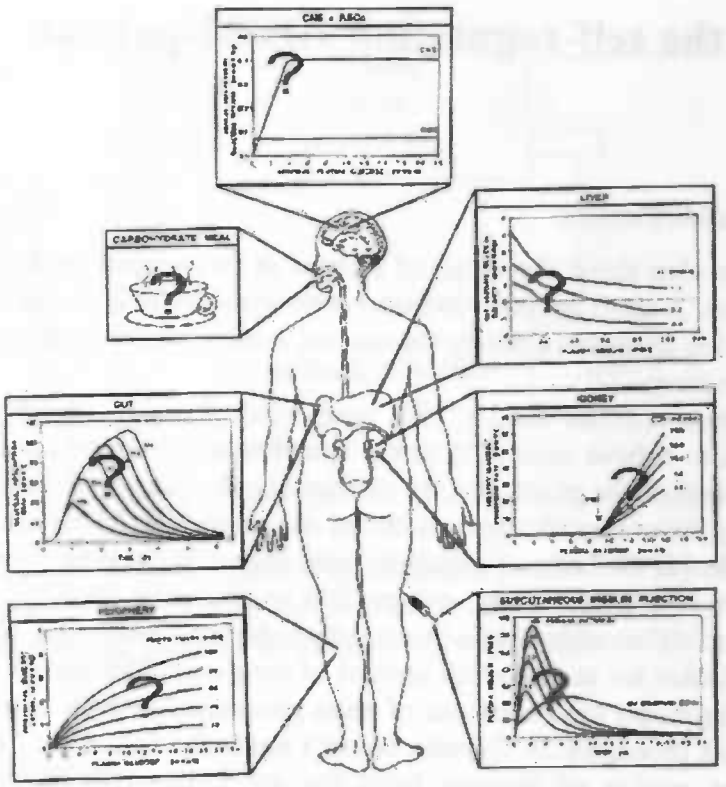


Figure 4-1 The DM-system. Examples of complicated non-linear physiologic processes influencing BG. The ?'s denote the ignorance of the practicing diabetic. The DM-system is hence regarded as a **black box**.

The question mark in the box of a carbohydrate meal indicates the ignorance of the exact amount of carbohydrate and its further composition. Different combinations of carbohydrates and fat have different effects on the eventually carbohydrate absorption from the gut.

The specifications according to which we want the DM-system to behave are the under bound and upper bound of the BG-values with respect to the situation the diabetic is in, sloppy said. We come back to this later, and discuss reasonable values for under and upper bound of BG w.r.t. different situations then. The controller is the diabetic patient who takes control decisions in order to manage his BG. The mathematical description of the system to be controlled, together with the controller is called the *controlled system*. The controlled system here, is a successful or skilled self-regulating diabetic patient, because he is a controller and a DM-system in one. This is shown in Figure 4-2.

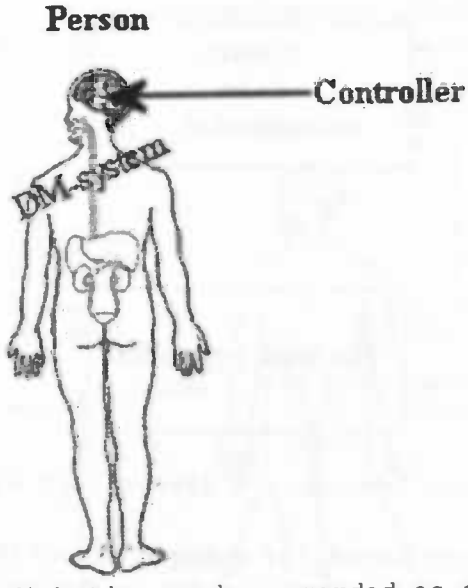


Figure 4-2 The skilled diabetic can be regarded as a controlled system, because he is both the system as the controller.

In order to give a more detailed structure definition, it is useful to give a clear separation of person, system and controller. The system is the collection of all physiologic processes influencing BG. The controller, here a part of the human brain, generates an adequate control advice to stabilize the DM-system with regard to the situation on it's input canal. The person is all what remains when removing the DM-system and the controller from a diabetic (Figure 4-4). The person can execute other control actions than the controller advices him. For example, a diabetic person can ignore an advice for an insulin injection because he is in public transport, e.g. a train, and doesn't like people watching him to open his trousers.

An important paradigm in control systems design, and in mathematical control theory, is *feedback*. The idea of feedback is to let the action of the physical controlling device at any moment in time depend on the actual behaviour of the physical system that is being controlled. This idea imposes a certain 'smart' structure on the controlling device: it 'looks' at the system that it is influencing, and decides on the basis of what it 'sees' how it will influence the system the next moment. In our situations, the person is a kind of interface between system and controller. Obviously we have to cope with feedback, because a self-regulating diabetic monitors his own DM-system all the time; the systems behaviour is never exactly predictable.

Any physical controller "device" that has this *feedback structure* is called a *feedback controller*. In terms of its mathematical model, the feedback structure of a controller is often represented by certain variables (representing what the controller 'sees') being mapped to other variables (representing the influence that the controller exerts on the system). The first kind of variables are called *measured outputs* of the system, the second kind of variables are called *control inputs* to the system.

Typically, the input variables are considered to be *caused* by the measured outputs. Mathematically, the relation between the measured outputs and the control inputs can be described by a *map*. Often, designing a controller for a given system can be formulated as the problem of finding a suitable map between measured outputs and control inputs. The control system corresponding to the combination of a control system and a feedback controller is often called *the closed-loop system*, and one often speaks about *the interconnection* of the control system and the feedback controller. The principle of feedback is illustrated pictorially in the diagram in Figure 4-3.

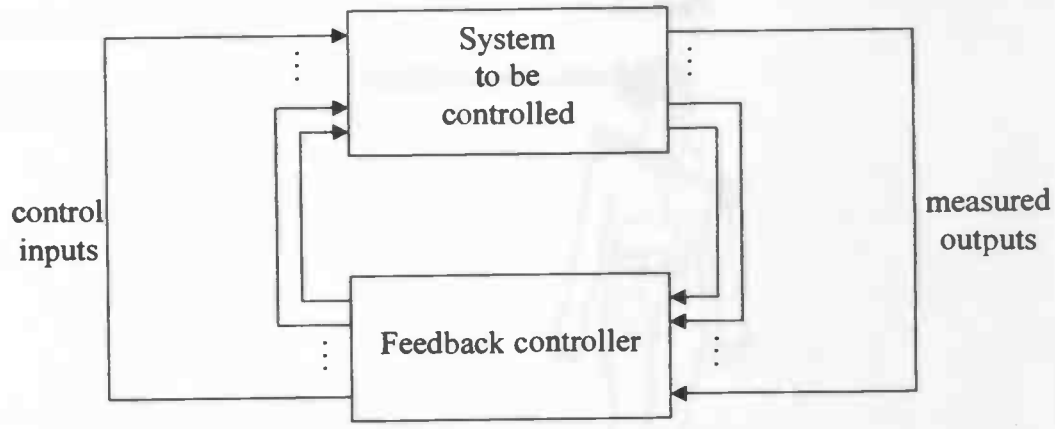


Figure 4-3 The principle of feedback. A closed-loop system.

Our situation is a bit more complicated. For example, not all the inputs of the system are known to the controller. Furthermore there is noise on the measured outputs. In the next section we try to explain the structure in more detail, referring to the following figure (Figure 4-4).

4.2 The concept idea

On behalf of the development of an adequate controller for diabetes, we are interested in the process of taking appropriate control actions by skilled diabetics. A model, taking the same decision in the same situation as a skilled diabetic would do, can be useful for less skilled diabetics with (about) the same DM-system. To submit the diabetics decision making to a closer look, we have to get a better idea of the information flow in this process. The most important output of the DM-system is, of course, that with information on BG. Other outputs such as general health condition are also important, as long as they influence BG, and are quantifiable in some way. Only the output that is used by the controller to establish the necessary control action in some situation is relevant and has to be regarded. This output is (in most situations a part or subset of) the input of the controller. Sometimes the controller derives important effects from the input, that serve as input for a second step in the controller. An example is the trend in BG that is concluded from different BG measurements. The trend in BG is used as input for the controller, but isn't the actual output of the DM-system. The internal structure of the controller is discussed later on.

A skilled diabetic is a person who is able to live his life with a controlled DM-system. The person develops the planning with regard to when (and what) he wants to eat and when he wants to take his exercise. Because the execution of this planning influences the DM-system, the diabetic therefore invokes the controller at some discrete (*math.*) or isolated moments. The controller then delivers an advice about adequate compensating control actions. Also, the controller is able to advice adaptations c.q. postponements in the planning. For example, if physical exercise is planned, and the BG measurement taken before the start is considered to be too low to commence the exercise, the controller will prevent the physical exercise being executed according to the planning, by advising a postponement.

In Figure 4-4, the diabetics integrated controller and DM-system are separated. The global information flow is depicted with arrows. The activities the person planned which can possibly influence the DM-system, together with the information on BG and his physical state coming from the DM-system, are provided to the controller. The controller on his turn advices the person about the execution or postponement of the planning, where needed together with

adequate compensating control actions. Beside this, there are other inputs to the DM-system which are not visible to the controller.

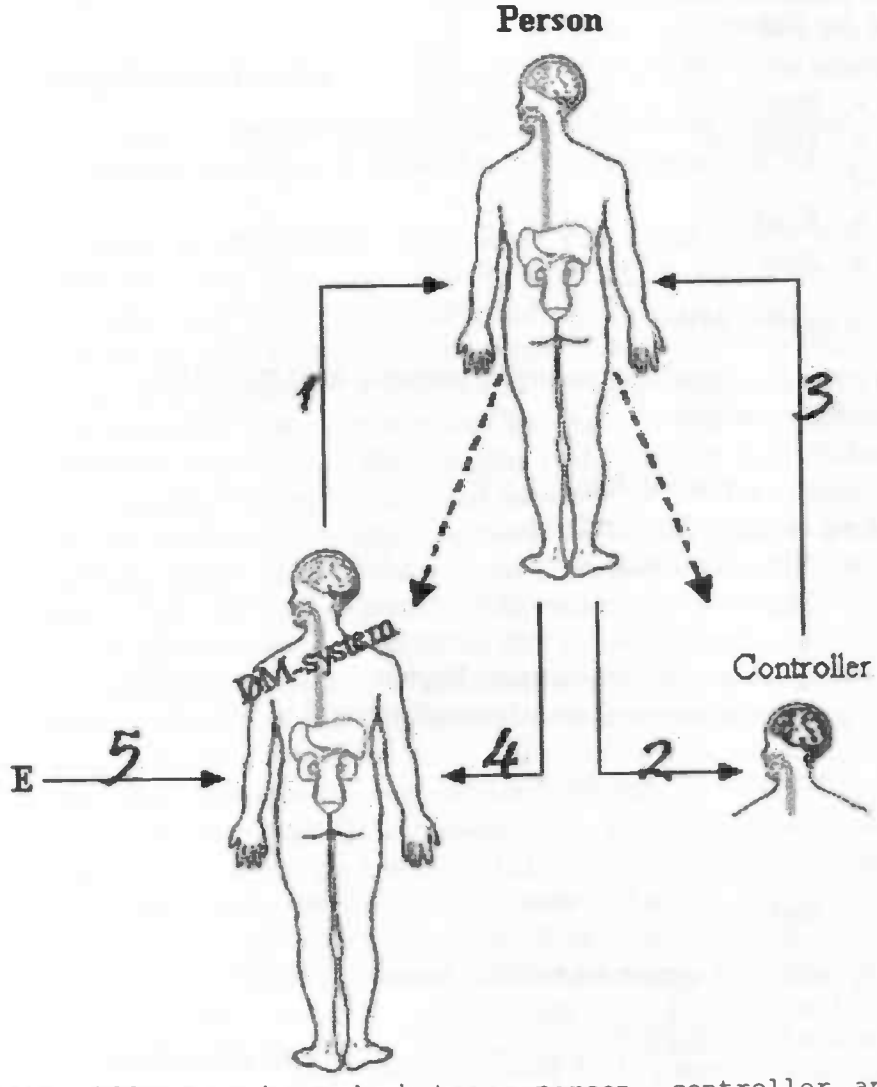


Figure 4-4 Difference is made between person, controller and system. The observations from the DM-system (1), the input provided to the controller (2), the controllers advice (3), executed activities and compensating control actions (4), and other influences on the system (5) are discussed in the text.

The arrows in Figure 4-4 represent a flow of information as status indication, planned BG influencing activities, advice and control action. The arrows are discussed according to their labels.

1 **Derivable information about the state of the DM-system that the person considers to be useful for controller**

Information on BG

- Current BG value
- "Feeling low" / "Feeling high"

➢ Physical state with regard to

- Illness (influenza)
- Stress

2 **Input of the controller**

- Information collected from the DM-system (label 1)
- Planning of the diabetic
  - Physical activities
    - Intensity
    - Duration
  - Food
    - Kind
    - Amount

3 **Advice for a control action**

- Advice for execution or postponement of planning with regard to
  - Physical activities
  - Food
- Advice for control actions about
  - Taking insulin with regard to
    - Kind of insulin
    - Dose
    - Moment
  - Taking food to prevent or remedy hypo's
  - Taking food to compensate a descending trend in BG

4 Execution of activities and control actions

- Food
- Insulin
- Physical activities

5 External inputs to DM-system (not visible to controller)

- A virus starting to cause illness
- A deviation in the contents of the food with regard to the estimation

Of course more examples of external inputs to the DM-system can be nominated as indirect influences on the course of BG. For example a warm surrounding which was not noticed by the diabetic and causes a (small) drop in BG.

Other important disturbances are in the DM-system itself. Sometimes insulin isn't absorbed properly, or unexplainable raises in BG appear. We refer to Table 3-3 that shows different BG values on six consecutive days in a diabetic, keeping external influences constant. This inexplicable internal variance in the DM-system is called **internal noise**. Further, the output, labelled with 1, is polluted by noise. The sensor, which measures the BG values, can give erroneous results (accurateness depends on range; values in normoglycemia are more precise measured; max. 10% deviation), and other things like the different effect physical exercise of the same intensity can have on the system.

Consider the labels in Figure 4-4. We are interested in the way skilled diabetics, in the person of controller, make the mapping of the output of the system (arrow with label 1) together with the planned BG influencing activities, bundled in the arrow with label 2, on the corresponding advice that is generated by the controller (arrow with label 3). We propose to submit the diabetic's decision making to a closer look. We mentioned before that the DM-system is

regarded as a black box. In fact the controller, the human brain, is a black box too; some information goes in, and some control actions go out of it. In spite of this, a lot of structure can be brought in the process a control decision is made.

4.3 Designing the controller

In contrast to the nature of the DM-system being continuous, the controller is discrete (*math.*) in nature. In general the controller is invoked only at discrete events, say a couple of times a day.

The DM-system is time-variant. This means that it can behave different in the same situation at different times. The controller in contrast, is time-invariant. The controller consists of rules about how to cope with different situations. Although one could argue that the diabetic changes his rules when the DM-system changes, the rules that induce other rules to be changed, can also be considered as a part of the controller, so that the controller can be considered to remain static. The essence is that the alternation in some rules isn't induced by time, but by other rules that consider the changing DM-system in time. Of course, the rules of the controller can be refined by new insights of the diabetic.

Although the controller actually is a black box, some structure in it can be derived. Time is an important aspect and is divided in *past*, *present* and *future*. The state of the DM-system in present is here the most important, followed by the near past and future. Eventually it is BG that has to be managed, and therefore BG in present, or the current BG, is the most important state variable. Other factors of influence on BG, discussed yet in chapter 3.2, have to be taken under consideration. Further, where relevant, these factors have to be assigned to the different categories time is divided in. The time categories, present, past and future, are discussed in this order with respect to the relevant influences.

The observable state variables in present firstly are the information about BG, denoted as **BG_current**, and the feeling one has about his BG being all right, denoted as **BG_feeling**. Secondly, the person's activities currently executed. Thirdly, the control actions. These comprise consuming food that is rich in carbohydrates, and injecting insulin. Short working carbohydrates can elevate BG for a moment, and long working carbohydrates can compensate a descending trend in BG. Important aspects with regard to an insulin injection are the moment of the injection and the amount, or dose of injected insulin.

5 Present-day self-regulation

In this chapter the state of art in present-day self-regulation with respect to the insulin injection for a meal is discussed. First the process of starting self-regulation is discussed according to a general document for people starting self-regulation that is provided by a hospital. Next this reasoning is converted into a Fuzzy Logic implementation. The section ends with an evaluation of this approach.

5.1 Starting self-regulation taking 4 shots per day

Patients not deploying self-regulation are restricted to a predefined insulin schedule, drawn up by a physician. Meals ought to be consumed at fixed times and with fixed amounts of carbohydrates. A dietician computes these fixed amounts of carbohydrates. The physician couples these amounts of carbohydrates per meal type to a standard amount of insulin for each meal.

The "Martini Ziekenhuis" in Groningen provide patients starting with self-regulation the following generic advice for adaptations in the standard amount of insulin injected before meals and adaptations in the injected amount of intermediate working insulin. Table 5-1 consists of the BG values that have to be obtained on different moments of the day.

Moment	BG range (mmol/L)
awaking	4 – 7
during daytime	4 – 10
before go to sleep	6 – 8
during the night	> 4

Table 5-1 BG values to obtain.

In the following sections adaptations to the standard insulin regime are discussed. First the intermediate working insulin has to be fine-tuned, to attain a stable basic BG pattern, followed by adaptations in the short working insulin, which is taken before meals.

Only the injection of short working insulin is discussed. Because our research focuses on the correct dealing with breakfast, only this part is of interest here; of course *self-regulation* involves much more.

Adaptation in short working insulin

The dose of short working insulin is given before a meal and can be adapted for each new injection. The dose is checked by BG measurements at the following moments.

1. Before the meal.
2. 1½ h. after the meal.
3. Before the next meal.

Adaptations in short working insulin are influenced by two factors here, BG and the amount of carbohydrates eaten more than the standard prescribed amount. There are big differences in the effectiveness of insulin between different patients. Use the following rules for guidelines in adaptations and adapt them to yourself.

Table 5-2 consists of the adaptations in short working insulin with respect to preprandial BG. The amount of insulin is given in units (U).

BG (mmol/L)	ΔI_{BG} (U)
< 4	If standard amount < 16U then – 2; If standard amount ≥ 16U then – 4.
10 – 15	+ 2
15 – 20	+ 4
> 20	+ 6

Table 5-2 Adaptation in short working insulin due to preprandial BG.

Adaptations in the amount of injected short working insulin, ΔI_{carbo}, due to the consumption of carbohydrates more than in a normal meal are processed as follows. Let k be the extra amount of carbohydrates (gram), and k' = k – 15. Then

$\Delta I_{carbo} = 0$ if k' < 0, and
$\Delta I_{carbo} = k' / 15$ if k' ≥ 0.

The one and only adaptation with respect to the insulin doses that have to be injected the day after physical exercise, is a decrease in the insulin dose taken for breakfast. It concerns only a qualitative advice (the quantitative deviation is patient specific). Let this adaptation be called $\Delta I_{exercise}$.

The total adaptation $\Delta I = \Delta I_{BG} + \Delta I_{carbo} + \Delta I_{exercise}$.

In the following section, the implementation of this reasoning about establishing the correct dose is implemented according to the author's insight.

5.2 Conversion to Fuzzy Logic

In this project the self-regulation advice of the Martini hospital with regard to the adaptations in short working insulin is discussed according to the reasoning above.

The input consists of:

1. the choice for the kind of breakfast;
2. the preprandial blood sugar level;
3. the desired amount of extra carbohydrates to consume.

The output is an advice for the amount of insulin to inject.

The following figure shows the whole structure of this fuzzy system including input interfaces, rule blocks and output interfaces. The connecting lines symbolize the data flow.

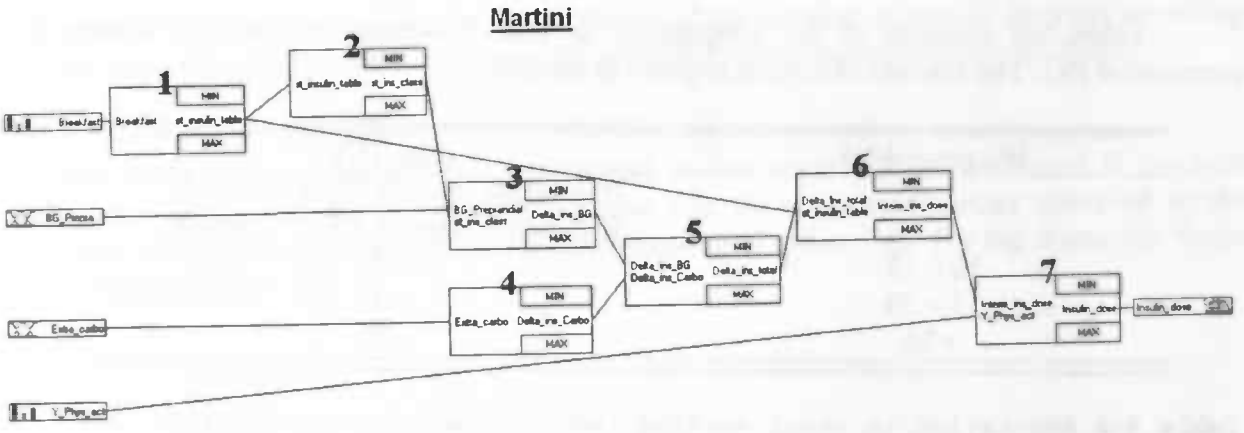


Figure 5-1 The structure of the system according to "self-regulation, Martini". Left the input variables, in the middle the enumerated rule blocks. Right the output variables that form the advice.

The structure is discussed with the help of the enumerated rule blocks.

5.2.1 1 The kind of breakfast

We assume the patient to have a choice for two different kinds of breakfast. For these different kinds of breakfasts the dietician determines the respective insulin dose. The following two choices are implemented:

1. two slices of bread with cheese, and
2. two soft rolls with pudding.

In rule block 1 the coupling of these kinds of breakfast is made with the corresponding amount of insulin.

5.2.2 2 Classification of insulin dose

In rule block 2, simply the check is done whether the result of the former rule block is more or less than 16 U.

5.2.3 3 Insulin due to BG

Here the difference in the insulin injection due to the preprandial BG level is determined according to table 5-2. For example, if 10 mM < BG < 15 mM, then 2 U more are injected, and if 15 mM < BG < 20 mM, 4 U more are injected. Of course, it isn't sensible to have a crisp transition between 2 U and 4 U, if BG is 14.9 mM, respectively 15.1 mM. The author chose for the following relaxing transitions.

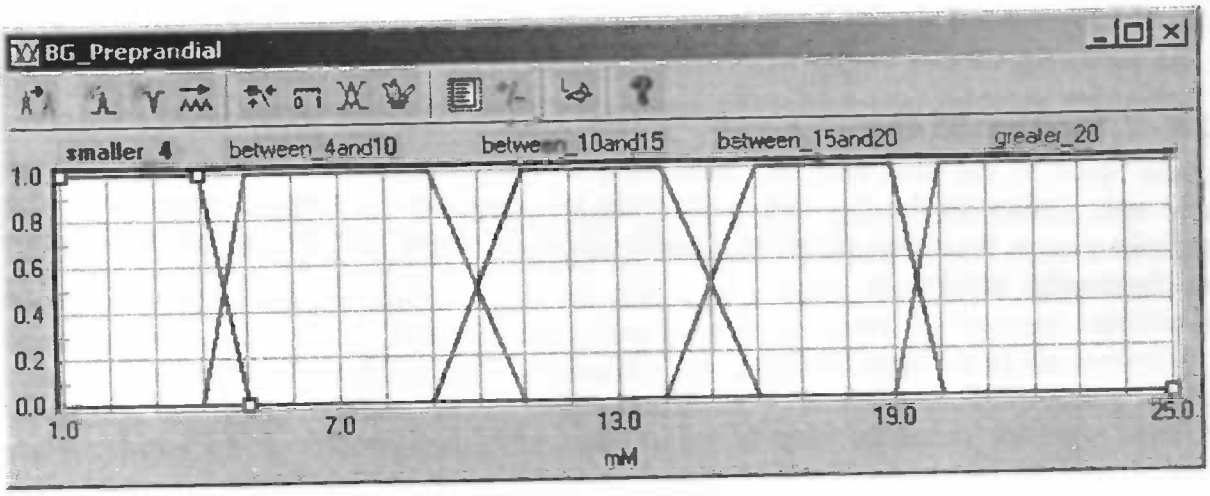


Figure 5-2 The membership functions that classify the preprandial BG.

BG is on the horizontal axis. For example, the BG value 15 mM is for half a part member of the interval "between 10 mM and 15 mM", and the interval "between 15 mM and 20 mM". Thus if BG = 15 mM, the average of 2 U and 4 U is taken.

If BG is smaller than 4 mM, the insulin adaptation depends on the injected amount of insulin. Therefore final adaptation is determined on the base of the classification of BG at the input variable and the outcome of rule block 2.

5.2.4 4 Extra carbohydrates

It seems if the insulin that has to be injected due to an increased amount of carbohydrates, increases linear with the amount of extra carbohydrates, starting with 15 gram. Only the diabetic dependent factor has to be chosen. Here a factor of 2 is chosen. The classification at the input variable is straight forward, and depicted in the figure below.

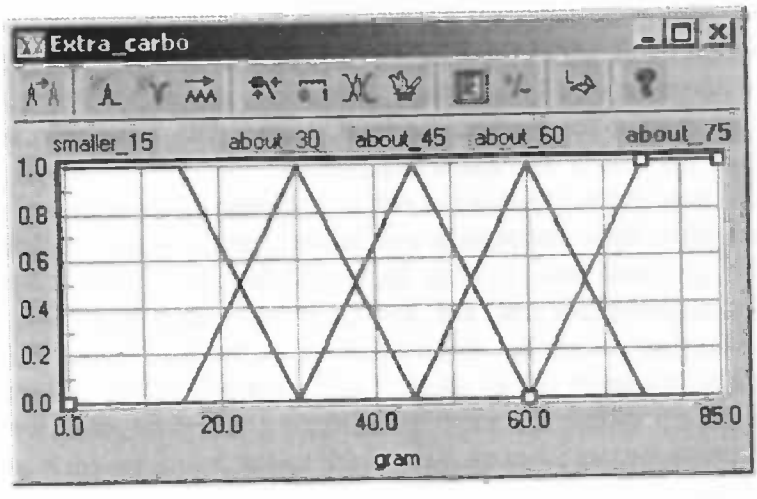


Figure 5-3 The membership functions that classify the amount of extra carbohydrates in breakfast.

5.2.5 5, 6 Intermediate insulin dose

In rule block 5, the adaptation in the insulin dose due to BG and the extra amount of carbohydrates is summed. Eventually, in rule block 6, the standard amount of insulin for the chosen amount of breakfast is summed with the total adaptation due to BG and the amount of

extra carbohydrates. This yields the total amount of insulin that should be injected according to this reasoning. On this amount of insulin, eventually a last adaptation can be done.

5.2.6 7 Total insulin dose

In rule block 7, the total amount, determined in the preceding, is decreased if physical exercise is performed the day before. Because this decrease isn't further specified in the hospital's papers, the author chose for a multiplication of about $^4/_5$th. For big doses, the factor was chosen a bit smaller.

6 Data extraction

In this chapter, the derivation of the controller model with respect to the patient's decision taking is discussed. Not the process of taking decisions, but which decisions and the basis on which these decisions are made, are in the centre of interest. First some definitions and linguistic terms are defined. The data extraction in order to derive the relevant variables is done by means of a logbook. In the following chapter the global structure of the controller – translating the input variables to the output variables – is determined according to the characteristics of the DM-system. The consecutive chapter discusses the case specific structure implementation.

6.1 Definitions, linguistic terms and data extraction

In this and the following section the data extraction out of the "decision taking part" of the life of an educated self regulating IDDM-patient is discussed with an eye on the model construction. On behalf of the data extraction, one needs to define the linguistic terms. Some concepts (**printed bold**) are defined to enlighten further discussion.

The set of **events** is formed by grouping real-life situations that are considered as equivalent with regard to the process of decision taking. Examples of events are waking up, breakfast, and practicing sports. **Control actions** are actions a diabetic can take to manage his BG. Actually the control action is the **output** of the advice system. Examples of control actions are the moment and amount of injected insulin, and postponement of a meal.

At each event there exist a number of factors or variables that significantly influence the required control action. Each variable has a name and, strictly spoken, a set of possible values. The set of these variables is called the **situation**. Actually the situation is the **input** of the advice system. Examples of input variables at (event =) *breakfast* are the BG value (measured at breakfast) and the amount of carbohydrates in the breakfast. A **state** is a situation with one value chosen for each variable. For example, if a situation is *{Current_BG_value, Previous_BG_value}*, then an example of a state is *{10.0 mmol/L, 6.3 mmol/L}*. For each event the situation is different: when one wakes up, studies or practices a sport, different factors have to be regarded in the consideration process which determines an adequate control action. Also, some factors are concerned with different events, but are weighted on different ways. For both physical activity and studying the BG level is an important factor of influence at the control actions, but their weighting depends on the event.

Which control actions are taken, is based on the diabetics experiences with regard to the state from where this action is taken. The diabetic in the person of controller can be seen as a mathematical function, mapping a situation to a control action. The idea is to imitate this function by deriving a model that exhibits the same behaviour as the diabetic.

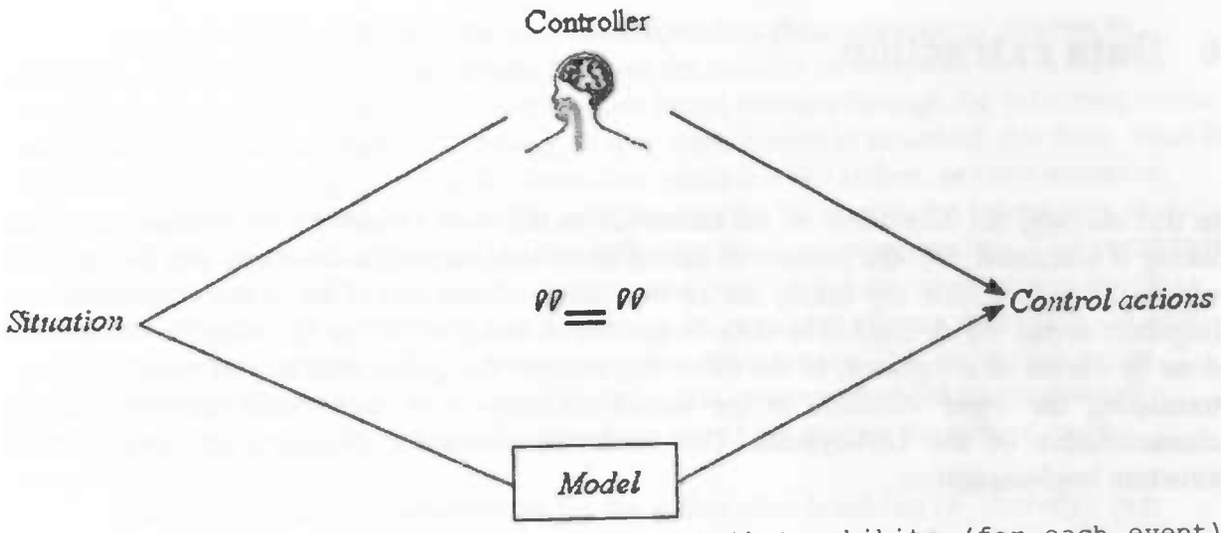


Figure 6-1 The purpose is to derive a model that exhibits (for each event) the same behaviour as the skilled self-regulating diabetic in the person of controller does; the same 'translation' from situation to control action.

For different events the situation is different. To gain insights in which factors are important at which events, a logbook is kept up to date by the author, for some events. A **logbook** is a set of recorded combinations of states that occurred in the diabetic's life and the control actions taken. A logbook is event bound.

The amount of carbohydrates will be expressed in **bread units, BU,** where 1 BU is defined as 15 grams of carbohydrates. The amount of carbohydrates in an average slice of bread equals about 1 BU.

The data extraction out of the skilled diabetics life, in order to get insight in his process of decision taking is done by keeping logbooks up to date for the different relevant events. In the following section four event related logbooks are discussed. Some explanation is given for the choice of the variables yet, but the generation of the control actions out of the input variables is discussed in the next chapter.

6.2 The logbook

For about two weeks the author kept logbooks up to date for the events

1. Wake up,
2. Breakfast – injection at wake up,
3. Breakfast – injection at breakfast, and
4. Supper.

These are the most basic events, always needing a clear control action. *The purpose of keeping logbooks up to date firstly was the deduction and denomination of sensible input and output parameters*. Secondly, the content of the logbook shows a little of the relation between situation and quantity of the concerning control actions. In this section these four logbooks are discussed w.r.t. the significant factors that are used in the consideration about an adequate control action. For some logbooks a little content is included. The first idea was to assume the existence of one all-embracing controller, because the DM-system should not be able to distinguish between different events. This resulted in keeping eventless logbooks up to date, recording each consideration to perform a control action or not. After the discussion of the logbooks about the four events mentioned above, the eventless logbook is discussed w.r.t. its problems and difficulties.

Of course, lifestyle is of major importance in the determination of the correct control action. For example the period between waking up and commencing breakfast. If this period is too big, it will be impossible to inject the insulin for breakfast when one wakes up because of the insulin's premature working. The intuitive reasoning behind the taken control actions, integrated with the author's lifestyle and the arising problems for the different events, are described below.
All observances can be clearly divided in three groups with relation to time:

1. Future,
2. Current, and
3. Past.

6.2.1 Wake up

When the author wakes up, he measures his BG, called *BG_wake-up*. A rough subdivision of *BG_wake-up* is:

		BG_wake-up	< 4	→	too low,
4	<	*BG_wake-up*	< 7	→	good, and
7	<	*BG_wake-up*		→	(too) high.

Roughly said, *BG_wake-up* determines the moment of the injection. If *BG_wake-up* is too high then immediately an increased dose insulin is injected. If *BG_wake-up* isn't too high, then the injection is taken some moments before commencing the breakfast. If *BG_wake-up* is too low, first a bit of fast- and short-working food is consumed before arising. The elapsed time between waking up and commencing breakfast normally is about half an hour. Sometimes, when the injection is taken immediately after measuring *BG_wake-up* (being much too high), a bigger postponement than half an hour of commencing breakfast is wishful.

Except the moment of the injection, *BG_wake-up* also partly determines the insulin dose. The higher *BG_wake-up*, the more insulin is needed.

BG_wake-up being high can have different plausible reasons. On the one hand we have

- eating too much before going to sleep or an extreme high BG before going to sleep,
- injecting too less long-working insulin before going to sleep,
- reduced absorption of the long-working insulin, or
- the *dawn phenomenon*.

The first three are quite trivial. The latter is a metabolic effect that occurs sometimes, and causes release of excess hormones, and especially the liver to release a certain amount of glucose that prepares the body for getting up. This phenomenon manifests itself in a high *BG_wake-up* value, or an increase of BG between *BG_wake-up* and *BG_breakfast*, which is measured when commencing breakfast. If the dawn phenomenon is clearly perceived the moment of commencing breakfast can be postponed for example by another ½ h.

On the other hand it is possible that too much long-working insulin was injected before going to sleep, or that the effectiveness of the long-working insulin was enhanced by great physical activity the day before. This causes BG to drop during the night. When BG reaches a certain (low) value, alpha-cells in pancreas cause a counter regulating action which results in a release of a big amount glucose by the liver that raises BG dramatically (for example to a value of 14 mM when waking up. This effect is called the *Somogy-effect*. In both cases, the amount of glucose has to be removed from the blood by injecting extra short-working insulin.

Of course the amount of *carbohydrates* intended to consume at breakfast positively influence a raise in BG. The amount of carbohydrates is expressed in bread units, BU.

Physical activity enhances the insulin independent disappearance of glucose by diffusion and the effectiveness of insulin because the number of receptors on the cells is increased. Also when exercise is practiced, more blood streams through the subcutane tissue containing the insulin of earlier injections, so that more insulin is absorbed. All three result in a BG drop. So, deploying physical activities like sports the day before, or (less intensive) riding a bike after breakfast, diminish the need for insulin. Of course, the longer ago, or the less intensive, a physical activity is, the less influence it has on dropping BG. This variable is called *Last_time_sported*. Of course the intension of practicing a physical activity is very important. The kind of sport has great influence on the resulting effects, described just now. For example, running takes more effort than playing table tennis. This variable is called *Sport_kind*. On behalf of simplicity and insight in first instance the bold assumption of *Sport_kind* = running is done. In further development of the system the system can be extended.

Mainly there are two possibilities for the author after breakfast (*F_Activity*): ¼ h. bicycling followed by studying or directly studying. Above was roughly said that the value of *BG_wake-up* was the criterion that determined the moment of injection. For certain boundary values, the activity after breakfast can influence this choice by a postponement of the injection.

The result of the former considerations should lead to an intermediate insulin dose. Because the DM-system is time-variant in nature, the local behaviour in time is important to include in the considerations that lead to this final control action. Therefore the standard dose of yesterday (*Y_Ins_st*) is compared to the real injected dose of yesterday (*Y_Ins_Real*), to determine the difference in the need for insulin in that local period of time. Of course, the difference in need can change. So an assessment (*Y_Ins_assess*) of yesterdays real injected dose has to be given. This can vary between good and [(much | little)] too less/much. The former denotation equals the set {much too less, too less, little too less, good, little too much, too much, much too much}.

Concluding, the relevant, and thus in the logbook recorded factors in the situation of waking up, with respect to the time, and the relevant control actions together with their dimensions, are summarized in the following two tables.

Time	Factor	Dimension or range
Future	F_activity	¼ h. bicycling, none
Current	BG_wake-up	mmol/L
Current	Carbohydrates	BU
Past	Last_time_sported	Days
Past	Sport_kind	Running, swimming
Past	Y_Ins _st	U
Past	Y_Ins _real	U
Past	Y_Ins_assess	Good, [(much | little)] too less/much

Table 6-1 Event = Wake up. Dimension or range of the relevant factors w.r.t. their place in time.

Control action	Dimension or range
Take_glucose	Yes, No
Moment_injection	Now, at breakfast
Insulin_dose	U

Table 6-2 Event = Wake up. Dimension or range of the relevant control actions w.r.t. their place in time.

Later on the relation between input and output is discussed. The content of the logbook gives an indication about how this relation is. In the following table some examples of the logbook of waking up are illustrated.

The situation:

Y_Ins_st	Y_Ins_real	Y_Ins_assess	BG_wake-up	Carbohydr.	Last_time_sported	F_activity
7.5 U	8 U	Much too less	13.0 mM	3 BU	1 day	studying
7 U	7 U	Good	13,4 mM	2,5 BU	4 days	¼ h. bic.
8,5 U	9,5 U	Good	11,3 mM	2 BU	1 days	¼ h. bic.

The corresponding control actions:

Take_glucose	Moment_injection	Insulin_dose
No	Wake-up	10,0 U
No	Wake-up	9,5 U
No	Wake-up	6,5 U

At the moment of waking up there are two possible conclusions to be drawn; the injection is taken at that moment, or the injection is taken at the moment of the breakfast. The following two sections are about the decisions that have to be made when the breakfast is commenced. In the first, the injection is already taken at waking up, in the second no injection is taken yet.

6.2.2 Breakfast – injection at wake up

From now on the main interest is in arguing the inclusion of input and output (resp. situation and control action) variables in the process of determination of the right control actions.

About half an hour after taking the injection usually the breakfast commences. In some situations there is a reason to postpone breakfast for the benefit of BG stabilization; if BG was very high at wake up, it takes more time than ½ h. for BG to drop far enough. That BG isn't decreasing as much as expected at the injection can for example be because the insulin isn't absorbed as well as normally. If a postponement of the breakfast (*PostponementMeal*) is sensible depends on

1. The BG value at waking up and the current BG value. If the current BG value is still very high, it would be better to postpone the meal, giving BG more time to drop. On the other hand, the BG course has to be included in the consideration, because if there is a strong decrease of BG (BG at wake up minus current BG is big), a postponement can be dangerous and insensible.
2. The period since the injection is also important; a drop of 5 mM in half an hour is much more dangerous than the same drop in two hours.

If, the postponement is more than an hour since the injection and BG is still high, or even higher than *BG_wake-up*, a second dose of insulin can be decided to give (*Ins_2th_dose*). Important is the willingness of the patient to eat extra carbohydrates (*WnessExtraCarb*) in case the second insulin dose is estimated accidentally a little too big. If not, the best guess is diminished somewhat. The amount of insulin in the first dose (*Ins_wake-up*) is most

important for the determination of the second dose. The relative need for insulin is incorporated in the determination of the first insulin dose. For the determination of an eventual second dose the amount of the first dose is of much more importance than the relative need for insulin (which will be negligible here).

If no further postponement of commencing breakfast, and no second insulin dose are wished, then the determination of the composition of the meal is an important control action to consider. If a hypo is expected, some extra glucose will be needed. Also, if future activity is wished, in some cases extra sugar drink is needed. If BG is descending very quick, an increased amount of carbohydrates (*Carbo_amount*) is whished. Contrary, if BG is descending too less, or even ascending, fewer carbohydrates are wishful.

Concluding, the relevant, and thus in the logbook recorded factors in the situation of waking up, with respect to the time, and the relevant control actions together with their dimensions, are summarized in the following two tables.

Time	Factor	Dimension or range
Future	F_activity	¼ h. bicycling, none
Current	BG_Now	mmol/L
Current	WnessExtraCarb	Yes, no
Past	Ins_when	Minutes
Past	BG_wake-up	mmol/L
Past	Ins_wake-up	U

Table 6-3 Event = Breakfast – injection at Wake up. Dimension or range of the relevant factors w.r.t. the time.

Control action	Dimension or range
Composition_meal	Extra_glucose, Extra_sugarDrink, MoreShortWorking, Normal
Hypo_expected	Glucose_needed, yes, probably_no, absolutely_no
PostponementMeal	No, ½ h, indefinite
Carbo_amount	Same, [(little | much)] more/less
Ins_2th_dose	U

Table 6-4 Event = Breakfast – injection at Wake up. Dimension or range of the relevant control actions.

6.2.3 Breakfast – injection at breakfast

The first comment is that this event resembles parts of the other two events. This one will be discussed more briefly than the other.

If *BG_wake-up* isn't too high, then the injection is taken at the moment of commencing breakfast. This is the most wishful situation. Also, sometimes, when *BG_wake-up* is (too) high, other, non-diabetes circumstances, force to take an injection at the moment of commencing breakfast.

The most important control action is the insulin dose. Also, if *BG_breakfast* is low, or a little low and there is physical activity after breakfast (*F_Activity*), one needs something like drinks with sugar. In some exceptional cases a postponement of breakfast is wishful; e.g. if in first instance *BG_wake-up* was good and *BG_breakfast* is much bigger than *BG_wake-up*. This refers to performance of the dawn phenomenon (section 6.2.1). In fact, the difference between *BG_breakfast* and *BG_wake-up* is of much more importance than the actual value of *BG_wake-up*. Of course the desirable amount of carbohydrates to consume are of major importance for the insulin dose.

Sometimes BG will be decreasing between waking up and commencing breakfast. In some of these cases the BG value at breakfast is about 4.0 or smaller which can emerge in hypoglycaemia.

Just like the reasoning given for the determination of the dose when waking up, the relative need for insulin has to be included in the reasoning about this dose. This concerns again

1. the standard dose that was advised yesterday,
2. the real advised dose yesterday, and
3. the assessment of that the real injected dose.

Again, the last time sported (*Last_time_sported*) has its influence on the effectiveness and thus the dose insulin.

Concluding, the relevant factors in the situation of the injection at breakfast, with respect to the time, and the relevant control actions together with their dimensions, are summarized in the following two tables.

Time	Factor	Dimension or range
Future	F_activity	¼ h. bicycling, none
Current	BG_Breakfast	mmol/L
Current	Carbohydrates	BU
Past	Last_time_sported	Days
Past	BG_wake-up	mmol/L
Past	Y_Ins _st	U
Past	Y_Ins _real	U
Past	Y_Ins_assess	Good, [(much | little)] too less/much

Table 6-5 Event = Breakfast - injection at breakfast. Dimension or range of the relevant factors w.r.t. the time.

Control action	Dimension or range
Composition_meal	Extra_glucose, Extra_sugarDrink, MoreShortWorking, Normal
Hypo_expected	Glucose_needed, yes, probably_no, absolutely_no
PostponementMeal	No, ½ h, indefinite
Insulin_dose	U

Table 6-6 Event = Breakfast - injection at breakfast. Dimension or range of the relevant control actions.

6.2.4 Supper

For a long time the author tried to discover what the relevant influences are on the control actions at supper. The denomination of the linguistic variables, that are necessary for the deduction of the control actions at this event, appeared to be more complex in comparison with the denomination at breakfast. Below the most important variables are discussed together with the raising problems. It is the author's opinion that a controller for supper is possible to develop but that more profound research is needed.

In the first place, the amount of carbohydrate is of major importance for the insulin dose. The main point that determines the amount of carbohydrates is the kind of food (*Food_Kind*). For example, white rice contains very many carbohydrates with respect to mass percentage, potatoes much less. The standard dose for a meal with rice is about 10 U; the standard dose for a meal with potato's is about 6 U. Contrary to the procedure at breakfast,

where the amount is measured in bread units (BU), here an estimation is made in comparison to the standard amount of food (*Food_Amount*). It can be normal, or [(much | little)] more/less. This is the second influence on the dose. These two influences have a fuzzy nature; this requires a good assessment capacity of the relevant patient.

Secondly the presence or absence of a dessert, its kind (e.g. yogurt or quark) (*Dessert_Kind*), and the amount (*Dessert_Amount*) determine the added amount to the dose. The latter can easily be expressed in bread units (BU) by reading on the dessert's packing. The dose has to be compensated by the period that the last physical exercise was ago (*Last_time_sported*).

Further, high values of *BG_supper* need to be compensated by an increment of the dose. If BG is raising quickly (*BG_Local_Delta*), this raise has to be compensated to. On the other hand, if BG is dropping quickly, a little decrease of the dose is wishful. The moment of injection (*Moment_injection*) is both dependent on the height of BG and the average glycaemic index of the food; the higher BG, the earlier the injection, the faster food is absorbed from gut, the earlier the injection, and vice versa. When great physical activity is expected after supper, the amount of short working carbohydrates (*Composition_meal*) should be more than if no physical activity is expected. These things are relatively easy realizable. More difficult is the implementation of the effect of control actions from the near past, like an insulin dose (*Injected_Ins_time* and *Injected_Ins_dose*) or consumption of some food (*Consumed_Food_when*, *Consumed_Food_Kind* and *Consumed_Food_amount*). Or worse, the combination of an injection and several consumptions.

The major problem is the inclusion of physical activity straight after supper (*Activity_after_Supper*), or direct before (*Activity_before_Supper*) and its duration (*Activity_before_Supper_Duration*). The effects are very various. The dose depends very much on the intensity and duration (*Activity_after_Supper_duration*) of the physical activity after supper. If the author is going to run for an hour the (total) injected dose can be 2½ U, contrary to 12 U in case of physical inactivity.

Other problems like a strongly reduced absorption of long-working insulin (*Long_working_Insulin_absorption*) or a temporary in-/decreased need for insulin, by coincidence, are not minor influences on the optimal insulin dose. Also the opposite can happen, an increased absorption of the long-working insulin or an 'over'-dose have negative influence on the amount of injected insulin. The local behaviour with respect to the relative need for insulin can be deducted from the effect of the injections earlier that day. For example the injection at the lunch can be taken. The standard advice (*L_Ins_st*), eventual advice and its assessment (*L_Ins_assessment*) are an indication for the relative need for insulin.

Further, the willingness (*WnessExtraCarb*) to eat a little more to compensate a possible small over-estimated insulin dose (which is the best guess/advice), influences the eventual injected dose. If there is no willingness, little less insulin (than the best guess) has to be injected.

The relevant influences and control actions are summarized with respect to the time, in the following tables.

Time	Factor	Dimension or range
Future	Activity_after_Supper	Running, bicycling, none
Future	Activity_after_Supper_duration	Minutes
Current	BG_supper	mmol/L
Current	BG_Local_Delta	mmol/L
Current	Food_Kind	Rice, potato's, …
Current	Food_Amount	normal, or [(much | little)] more/less
Current	Dessert_Kind	Quark, yogurt
Current	Dessert_Amount	Less, normal, more
Current	WnessExtraCarb	Yes, no
Past	Last_time_sported	Days
Past	Injected_Ins_time (*)	Minutes
Past	Injected_Ins_dose (*)	U
Past	Consumed_Food_when (*)	Minutes
Past	Consumed_Food_Kind (*)	Short working, long working
Past	Consumed_Food_amount (*)	BU
Past	Activity_before_Supper	Running, bicycling, none
Past	Activity_before_Supper_Duration	Minutes
Past	Long_working_Insulin_absorption	Better, normal, worse
Past	L_Ins_st	U
Past	L_Ins_real	U
Past	L_Ins_assessment	Good, [(much | little)] too less/much

Table 6-7 Event = Supper. Dimension or range of the relevant factors w.r.t. the time. (*) More than one occurrences possible.

Control action	Dimension or range
Composition_meal	Extra_glucose, Extra_sugarDrink, MoreShortWorking, Normal
PostponementMeal	No, ½ h, indefinite
Moment_injection	Now, at supper
Ins_dose	U

Table 6-8 Event = Supper. Dimension or range of the relevant control actions.

From this section the conclusion can be drawn that estimating the optimal dose for supper is more complex than at breakfast. The size of the table and the less crisp (more fuzzy) values of the variables give yet a slight impression of the expected size of the model that has to be generated to produce a prediction for the optimal control action. Although the system would become complex, it would probably be possible to derive a good system because the author is also capable of dealing with all this information and able to derive the necessary control actions.

6.2.5 The all-embracing controller

This section is about an all-embracing controller that should be applicable under all circumstances.

Actually, the kind of factors that are monitored by the controller for supper, resemble the kind of factors that would be needed for an all-embracing controller. Of course, some weightings should be completely different, for some events (or activities).

The most remarkable fact is that what good values for BG are, strongly depends on the activity that is performed. The author's perception of the characterization of appropriate BG values for different activities is summarized in the following table.

Activity	BG (mM)				
	Too low	*Low*	*Good*	*High*	*Too high*
Awaking	< 4	4 – 5	5 – 7	7 – 9	> 9
Going to sleep	< 6	6 – 7	7 – 8	8 – 10	> 10
Studying	< 4	4 – 4,5	4,5 – 7	7 – 8	> 8
Cycling	< 5,5	5,5 – 6,5	6,5 – 7,5	7,5 – 8,5	> 8,5
Swimming	< 6	6 – 7,5	7,5 – 10	10 – 12	> 12
Running	< 7,5	7,5 – 9	9 – 12	12 – 15	> 15
Default	< 4	4 – 5	5 – 8	8 – 9	> 9

Table 6-9 The author's perception of the characterization of appropriate BG values for different activities.

This table has to be taken a bit more subtle despite its crispness. For example, when there isn't injected insulin in the past two hours, the values for running and swimming can be a little lower. And the values of going to sleep have to be increased a little, when there was much physical activity that day. But, one can say that in general this are the guidelines.

The development of an all-embracing controller that should be employable under all circumstances is very complex. Consider the complexity of an adequate controller that only deals with supper, and realise that this controller would merely be a subset of an all-embracing controller.

The first ambition of this research was to develop such an all-embracing controller. Starting with the implementation of some initial structure and defining some basic linguistic variables with their terms the upper bound of the number of terms (= 256 in fuzzyTECH 5.30a Professional edition) was easily reached. Anyhow, the subdivision was sensible, considering the expected complexity of an all-embracing system. For each event another subsystem can be developed. With the assemblage of the subsystems an all-embracing system can be acquired. The drawback is the originating redundancy for resembling events with the assemblage.

The author decided not to show a piece of the logbook that was kept up to date on behalf of the development of an all-embracing system because of the size and its probably insignificant value for this report.

7 Model structure according characteristics DM-system

In the former chapter for a couple of events the relevant input and output variables are derived. A structured approach will be needed in order to translate the inputs to the matching outputs or control action advices.

In this chapter, different kinds of control advice and of input variables are distinguished. On the base of the differences in the control advices, advice specific structures are derived. These are discussed in the successive sections. In the next chapter these advice specific structures are implemented with respect to the relevant event.

7.1 Subdividing the control advices

The output variables are the control actions a diabetic can take to manage his BG, given a certain event. The output variables are divided in two categories:

- Insulin related, and
- Non-insulin related advices.

The first are advices about the amount of insulin that has to be injected in a certain situation, and the second are advices that don't deal with the determination of an insulin dose. Examples of the latter are the postponement of a meal and the composition of a meal.

The insulin related advices could be divided in two subcategories:

- Insulin determining,
- Insulin correcting advices.

If BG level is too high, or expected to become too high, for example due to the consumption of a lot of carbohydrates, an insulin dose is necessary. On the other hand it is possible that the former insulin injection was too small, and a correcting dose is necessary to achieve the result that was aimed in first instance. The first kind of advice, the insulin determining advices, is due to non-insulin related reasons, the second kind of advice, the insulin correcting advices, is always a correction on a former insulin injection, in order to achieve the result that was aimed in first instance.

The subdivision is shown in the following diagram.

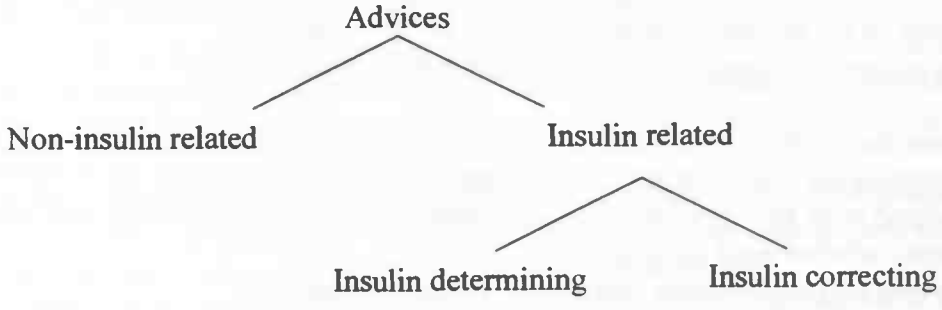


Figure 7-1 A subdivision of sorts of advices.

The main issue in stabilizing DM is taking care of an appropriate insulin level all the time. The DM-system is time variant. This means that it's behaviour changes in course of time with regard to the BG level, even if the external situation remains the same. So, we can conclude that the need for insulin changes in time, even if the external situation remains the same. Because the DM-system is time variant, it will be important to involve the local behaviour of the system in the controller for insulin related advices. With local behaviour, the local behaviour in time is meant. Some input variables will be used for the determination of the concerning situation. These variables are called **the situation determining input variables**. Other input variables will be used for the determination of the local need for insulin.

In the next section the advice specific structures are derived.

7.2 Advice specific structures

The distinguished kinds of advices will be discussed, starting with the non-insulin related advices. Every advice is determined on the base of the situation determining input variables. The only case where a correction on this advice is made, is where an advice for a non-insulin related insulin dose is generated.

7.2.1 Non-insulin related advices

This structure is about static. It is just on the base of the situation determining input variables. For example the threat of an approaching hypoglycaemia can be derived out of the comparison of two BG measurements, the time between them, the amount of injected insulin and the period since that injection. The local behaviour of the system, i.e. the relative need for insulin, isn't influencing the non-insulin related advices, because only the eventual overall effects are studied.

7.2.2 Insulin determining advices

As indicated above, this section is about insulin advices that follow directly from the situation, and are not a correction on an earlier, too small injected insulin dose.

The situation determining input variables, like the last time sported and the height of BG, will determine an amount of insulin to inject. Let this amount be called the standard insulin dose (I_standard). The values for I_standard have to be deduced from the logbook as a sort of average injected dose, all the time in (about) the same situation, thus, with the same external influences. The value I_standard is the starting point in the eventual prediction of the optimal dose. I_standard is believed to be stable within a space of time of about half a year. It can change due to the following reasons:

- A change in the patient's lifestyle (more or less active, for example), and due to this a change in his personal characteristics, as fat percentage;
- The patient (becomes older and) his metabolism changes.

Now, a correction with the local need for insulin is important. Other input variables have to be used to determine the relative need. Once determined this relative need, the standard dose can be compensated with this relative need. The input variables that determine the best guess for the momentary relative need for insulin are:

- The standard insulin dose injected for breakfast yesterday;
- The real injected insulin dose for breakfast yesterday;
- The assessment of the real injected insulin dose for breakfast yesterday.

Their use is explained below. From section x.4.6 (Conclusions Non Model Based Approach) is quoted that the DM-system is time variant. So, if all the influences are kept constant, even then the system's behaviour changes. After about two weeks, much of the predictability is lost by the current available (non model based) systems. From table x.3 (Accuracy of model based glycaemic predictions), slight differences are noticeable in BG values from day to day, while all the external (external) influences are kept constant. This has leaded to the following idea. If there is a temporal need for more insulin in the recent past, it plausible that there is also a need for more insulin in the present. Therefore, we can compare the real injected insulin dose (Y_I_real) of yesterday with the standard dose that was advised yesterday. If yesterday's real need was much bigger than the standard need, this will be the case today.

The problem is that the structure is static now. Because the DM-system's relative need for insulin can change from day to day, an adaptation in the relative need for insulin in a certain situation has to be made from day to day, if necessary. The best way to do this is by making an assessment (Y_I_assessment) of the real injected insulin with regard to its quantity in retrospect, by considering the eventual correcting control action. In this way the relative need for insulin can be corrected day by day. The following figure shows the eventual general structure of a controller.

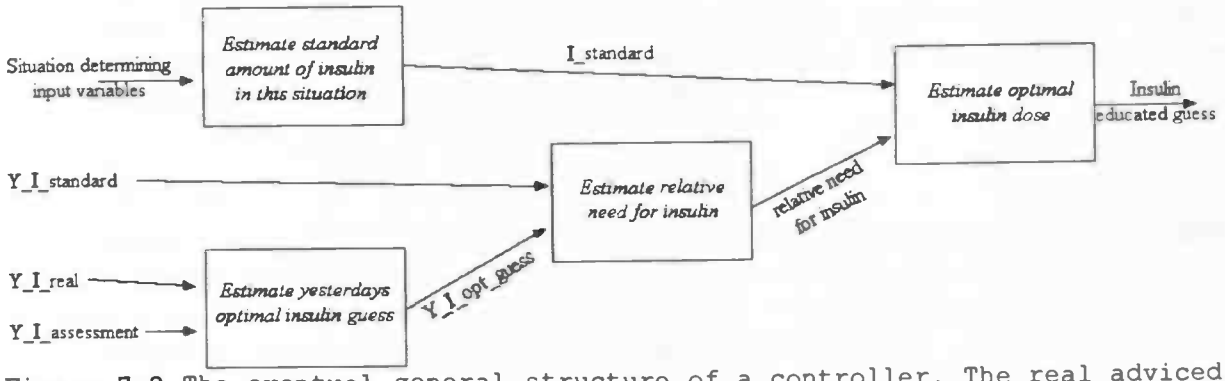


Figure 7-2 The eventual general structure of a controller. The real adviced insulin dose yesterday with its assessment in retrospect lead to the optimal guess for the present need for insulin.

Because of the fact that in this research only a controller is developed for waking up and breakfast, the reference point of the relative need for insulin is yesterday, because no more recent data is available. For controllers at supper for example, more recent data can be processed. We have to distinguish between two different cases, which influence the dose of short working insulin injections.

1. A difference in relative need for insulin due to a change in metabolism, which means that a multiplication of I_standard is necessary, and
2. a difference in the action profile of the injected long working insulin, which means that no multiplication is needed, but a sum of I_standard and a bit less/extra insulin to compensate for the difference in the long working insulin's action profile.

At waking up, it is not possible to make a difference between 1 and 2. The successful control actions of the author at waking up, which often lead to a stable DM-system, imply that it is not necessary to know the cause of elevated BG values at wake-up.
The assessment of the insulin doses typically changes from day to day. The value for the relative need for insulin is typically believed to change significantly within less than two weeks. After half a year the average (recent) values for the relative need for insulin can be computed. The standard advised values could be updated to this average.

7.2.3 Insulin correcting advices

Here already an insulin dose is injected. Anyway, sometimes the injected insulin dose was too small. This is perceived by a BG value that is much higher than expected. If BG is a little too high, most often the choice is made not to inject a second dose. If BG is very much too high, the choice for a second injection is made almost always. In the first case a little insulin is needed, in the second case very much insulin is needed. The average dose is in between.

Of course the amount of insulin in the second dose very much depends on the first amount of insulin in the second, correcting, injection. The influence of the relative need is negligible.

In the following chapter the event related model structure implementation with regard to the advices distinguished above are discussed.

8 Event related model structure implementation

In the former sections the event related inputs and outputs are determined. The following step is the definition of the structure – viewed as a mathematical function – that translates the input to the correct output. In this research, this is done for the following events.

1 Wake up;
2a Breakfast – injection at wake up;
2b Breakfast – injection at breakfast.

The structure actually is made up of a set of rule blocks. Per system these rule blocks are enumerated. The intuitive idea behind these rule blocks is described with an eye on the implementation in FuzzyTech 5.30a Professional Edition. On behalf of the time, only system 1 and 2a are implemented.

The system structure identifies the fuzzy logic inference flow from the input variables to the output variables. The fuzzification in the input interfaces translates analog inputs into fuzzy values. The fuzzy inference takes place in rule blocks that contain the linguistic control rules. The outputs of these rule blocks are linguistic variables. The defuzzification in the output interfaces translates them into analog variables.

8.1 Wake up

In this project, a controller is modelled for the event of waking up. On the basis of seven input variables (one is not in use yet), a control advice is brought out. The advice is about the necessity of glucose, the moment of the injection, and the eventual insulin dose. With the help of the structure discussed below, the advice generation is discussed.

8.1.1 System structure

The following figure shows the whole structure of this fuzzy system including input interfaces, rule blocks and output interfaces. The connecting lines symbolize the data flow.

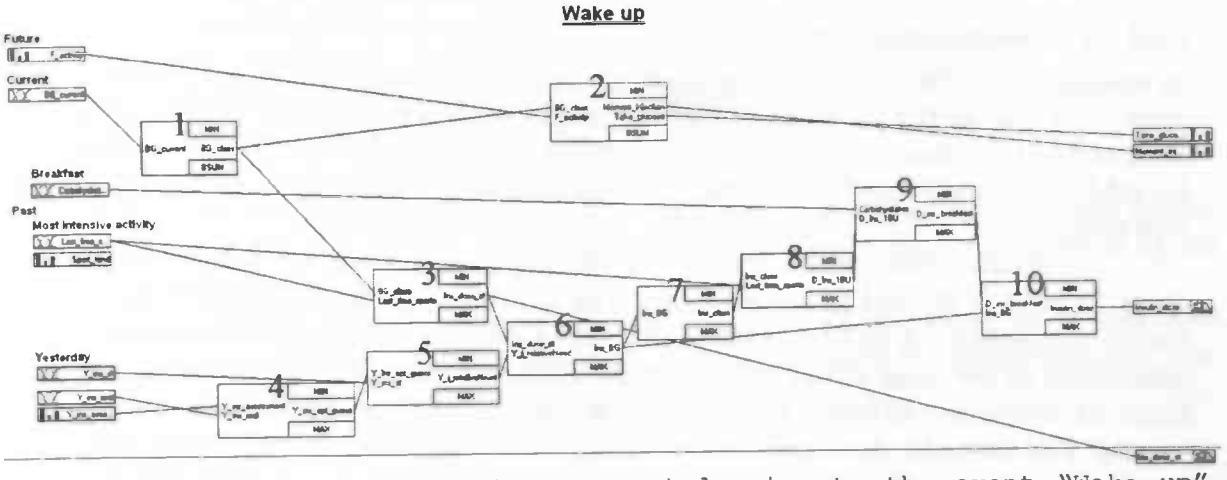


Figure 8-1 The structure of the system belonging to the event "Wake up". Left the input variables, in the middle the enumerated rule blocks. Right the output variables which form the advice (except the variable below the horizontal line).

The precise system structure is discussed according to the global structure that is derived in a previous section. This means that situation determining input variables determine the standard insulin dose that would be injected under certain circumstances, which is compensated with the relative need for insulin. The variables are clearly ordered with respect to time; future, current and past.

The variables that determine the situation here are:
Future:
- activity in future.

Current:
- the current BG value;
- the desired amount of carbohydrates in breakfast.

Past:
- the last time sported.

The variables that determine the local relative need for insulin are:
Past:
- the advised standard amount of insulin;
- the real advised insulin;
- the assessment of the real advised insulin.

In the consecutive sections, first the determination of the advice for the moment of injection and the need for glucose are discussed, followed by the determination of the advice for the insulin dose. The latter is a bit more complicated. It starts with deriving a standard dose out of the variables that determine the situation, which is combined with the best guess for the relative need for insulin. The resulting dose is classified, and according to this classification, the difference in insulin dose due to a difference of one bread unit (1 BU) in breakfast is determined. Remark. The standard amount of carbohydrates in breakfast is 2 BU. The insulin dose is adapted to the possibly present difference in breakfast, resulting in the eventual insulin dose.

All the rule blocks in the structure above are enumerated with red numbers. This enumeration is used in the following discussion.

8.1.2 1 Classification of BG value

At waking up, the BG value is determined. Some decisions are more or less dependent on this value. The precise BG value is not that important, that for every slight difference, decisions are completely different. The decisions a diabetic takes if his BG is 8.1 mM, or if his BG is 8.2 mM, actually will not be different. Sometimes it doesn't even matter if BG is 8.0 or BG is 10.0 mM.

To abstract from the exact value, the BG value range, which runs from about 1 mM to about 25 mM, is divided in a few classes. The number of different classes in the system, is exactly the number of different classes the author globally distinguish. The size of a class is determined by the range of BG values that all lead to the same decision. Because, for different kinds of decisions, different kinds of classes are used, some of the defined classes will overlap. For example, the classification of BG values for studying is different from that for running. A value of BG = 5.0 mM falls in the category 'good' for studying and in 'too low' for running (compare section 6.2.5 about the all-embracing controller). In this system, a classification is used for the determination of the moment of injection, while another

classification is used for the amount of extra insulin that has to be injected due to high BG values.

From now on, only classifications of BG values – made in rule block 1 – are used for decisions.

8.1.3 2 Determination of the moment of injection and the need for glucose

In rule block 2, an indication is given for the best moment of injection and the need for glucose. There is only a need for glucose if BG is smaller than 4 mM. A very simple control action. The moment of injection depends on both the BG value and the activity after breakfast.

The principle idea: if BG is very high, it is not advisable to eat instantaneously, because further increase of BG is not wishful. If the injection is taken instantaneously, and breakfast is commenced after taking a shower; BG has time to drop.

If BG is 7.5 mM or higher, the author takes the injection immediately. If BG is lower, then he will take his injection on a later moment, for example at commencing breakfast. If BG is about 7.5 mM, and the injection is taken at waking up, it is possible that BG dropped so much, that physical activity after breakfast (1/4 h. biking), is not safe. So, if future activity is planned, the minimum BG value at which an instantaneous injection is advised should be a bit higher. The author chose for about 9.0 mM.

8.1.4 3, 4, ..., 10 The determination of the insulin dose

The determination of the insulin dose is the most important and difficult control action. The derivation is done according to the structure defined in the former chapter; the variables that determine the situation determine the standard insulin dose, which is corrected then with the relative need for insulin.

A minor exception on this idea is that the amount of extra injected insulin due to extra carbohydrates is in few cases slightly dependent on the relative need for insulin. It will be discussed below, where the insulin dose is adjusted to a possibly diverging amount of carbohydrates, from the standard amount of 2 BU.

8.1.4.1 The standard insulin dose

When one wakes up, the situation determining variables are

- the (yet classified) BG value;
- the last time sported;
- the planned amount of carbohydrates in breakfast;
- the planned future activity.

Only the first two are used to determine the standard insulin dose. The are discussed below, but first a reason for disregarding the latter two with respect to the determination of the standard insulin dose is given.

It is the author's lifestyle to ignore the future activity, i.e. bicycling for ¼ hour after breakfast, in the determination of the insulin dose. Namely, there are two possibilities, to cope with this future activity:

- decrease the amount of insulin, or
- eat a little more.

The latter is chosen. The relation between future activity and the meal's content is discussed in the advice system that can be used when breakfast is actually started. The other option was to choose for a decrease in the amount of insulin if future activity is planned. This is also a

sensible reaction, but if an approaching hypo is expected, the composition of the meal has to be changed always, so that the total amount of carbohydrates remains the same. The total amount of carbohydrates has to remain the same because the amount of insulin is adapted to this amount. As announced, the meal's content is discussed with the next advice system.

Another important influence on the insulin dose is the amount of carbohydrates. Mostly two slices of bread are consumed at breakfast. As announced above, in first instance, this variable is ignored.

The other two situation determining variables, the classification of the BG value, and the last time sported determine the standard amount of insulin. Two clear qualitative relations between the standard amount of injected insulin and these influences are

- the amount increases with an increased BG level, and
- the amount increases with an increase of the time ago intensive physical activity (like running) was deployed.

Assuming a default situation with regard to all the other variables, the author filled in the following table, to acquire the basic point of departure for the insulin dose.

		Standard insulin dose (U)		
		BG-range (mM)		
		7.5, ..., 10	11, ..., 13	≥ 14
Last time sported (days)	1	5	6	8
	2	6	7	10
	4	8	8	10
	≥ 7	8	10	12

Table 8-1 This table shows the author's choice for the standard insulin dose on the basis of two variables, the last time sported and the range which contains the BG level at waking up.

Injections at wake up are taken only if BG values are not below 7.5 mM, so this range is not included in the table.

The DM-system is a time variant system with respect to its need for insulin. The standard dose ought to be the average injected dose over time. Sometimes more insulin is needed, and sometimes less. The next section explains the deduction of the relative need for insulin.

8.1.4.2 Determination relative need for insulin

The best guess for the current relative need for insulin is to be deducted from the recent past. There will be a major resemblance between the relative need of about 24 hours ago, and the current relative need. To determine this relative need, a comparison is made between the advised standard amount of insulin at yesterday's breakfast and the real amount of injected insulin. For example, if the standard amount would be 8 U yesterday, and the real (and best) amount of injected insulin is 10 U, certainly there is an increased need for insulin. If the standard advice would be 6 U today, then the best guess would be something like 7,5 U.

Globally, on the basis of the standard and the real advice yesterday, the relative need for insulin is determined. This two values are compared in rule block 5. Until now, the assumption was made that the real advised dose, really was the best advisable dose. This isn't always the case. In the first place the DM-system is dynamically with regard to the need for insulin, so the need can change in course of time. In the second place, the real injected dose can be erroneous due to different external influence like mistakes in estimating or filling in the input variables. To make adaptations possible in the relative need for insulin, an assessment is made in retrospect, about the real injected dose yesterday. If this was (little) too much/less, this knowledge is used to deduce the best guess for the real amount of insulin. This assessment is done in retrospect, considering the extent of the control action that was necessary to compensate for the erroneous estimation. The user is responsible for the estimation of the extent of dose that was injected too much or too less. The possible automation of this process is discussed in a later chapter about the artificial intelligent learning patient specific neural networks. In rule block 4, the optimal guess is derived from the real injected dose and its assessment.

In the next section, the coupling of the relative need for insulin with the standard advised amount of insulin is discussed.

8.1.4.3 Intermediate estimation insulin dose

The standard amount can now be compensated in rule block 6 with the best guess for the relative need for insulin. Actually, this is about the inverse of the rule block (5) described above, where the relative need for insulin is determined. If, in rule block 5, the standard amount is 8 U, the optimal guess for the best dose is (9 U) 10 U, and the corresponding relative need is said to be (little stronger) stronger, then, in rule block 6, if the standard amount of insulin would be 8 U and the need for insulin is (little stronger) stronger, the corresponding advised insulin dose has to be (9 U) 10 U.

The conclusion of rule block 6 is an intermediate estimation for the insulin dose. Only if the amount of carbohydrates – wished to consume at breakfast – deviates from 2 BU, the following rule blocks can change this dose.

8.1.4.4 The influence of breakfast on the intermediate estimation for the insulin dose

In rule block 7, 8, 9 and 10, the possible deviation in the insulin dose is determined for possible deviating breakfasts. As commented before, the intermediate estimation for the insulin dose is also the eventual advised insulin dose if a breakfast with a standard amount of carbohydrates of 2 BU is wished.

If more or less than two bread units are wished to be consumed, first an estimation has to be made of the correction that is needed in the dose if there is consumed one bread unit more or less. The factors that determine this number are believed to be

- the last time sported, and
- the intermediate estimation for the insulin dose so far.

First, in rule block 7, the intermediate estimation for the insulin dose is classified. Examples of ranges are: up to 4.5 U, and between 5 U and 8 U. Consecutively the two factors mentioned before are used in rule block 8 to determine the deviation of the insulin dose due to the deviation of 1 BU in breakfast. This value is believed to increase for

- an increase in the time ago that physical activity was deployed;
- an decrease in the total amount of injected insulin,

and it varies between 0.5 U (if the patient sported intensively yesterday, and the intermediate estimation for the insulin dose is about 10 U) and 2.5 U (if the patients last time sported is a week ago, and the intermediate estimation is about 5 U).

In the next rule block (9) a kind of multiplication is done; the total deviation equals the amount of deviating bread units (with respect to the standard amount of 2 BU) times the difference in the dose due to a deviation of 1 BU. And, eventually in rule block 10 a summation of the intermediate estimation (rule block 6's result) with the correction (rule block 9's result) is done. This yields the eventual dose.

8.2 Breakfast – injection at waking up

In this project a controller for breakfast is developed. Assumed is an injection at waking up. On the basis of six input variables, a control advice is brought out for breakfast. The input variables include the BG-course, the amount of and period since the insulin injection. Examples of the advices are revision of the amount of carbohydrates to consume, the composition of the meal, a further postponement of the meal, and a second injection. With the help of the structure discussed in the following section, the advice generation is discussed.

8.2.1 The structure

The following figure shows the whole structure of this fuzzy system including input interfaces, rule blocks and output interfaces. The connecting lines symbolize the data flow.

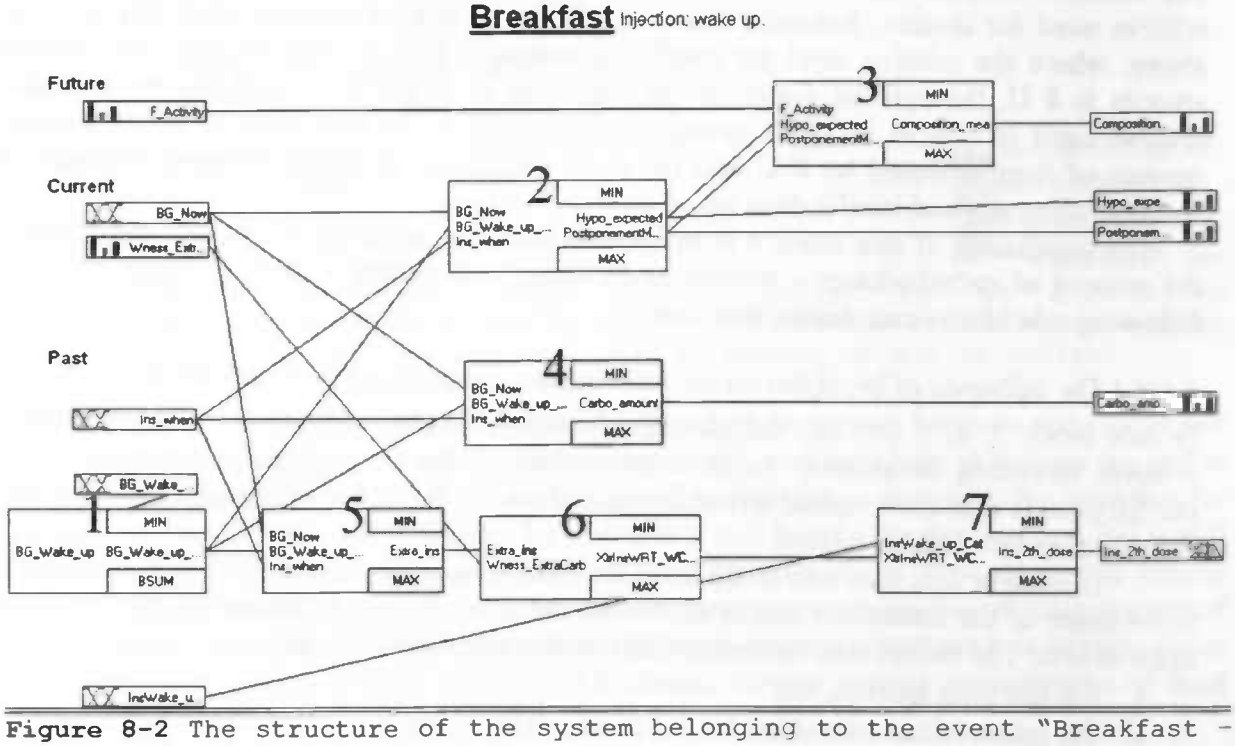


Figure 8-2 The structure of the system belonging to the event "Breakfast - injection at wake up". Left the input variables, the rule blocks are enumerated. Right the output variables which form the advice.

In the following table the input variables are listed with respect their place in time, together with the system's output variables c.q. its advices.

Time	Input variable	Output variable
Future	Activity after breakfast	Composition meal
Current	BG now	Hypo expected
Current	Willingness to eat extra carbohydrates	Postponement meal
Past	Time ago until injection	Amount of carb's to consume
Past	BG at waking up	Second insulin dose
Past	Injection dose at waking up	

Table 8-2 In this table the input and output variables of the system are listed. The input variables are categorized with respect to their place in time.

How the advices are generated out of the input variables, is discussed in the next sections, with the help of the enumerated rule blocks in the figure above. First the estimation for the danger of a hypo is discussed together with the possible advice to postpone the meal. This is followed by the discussion about an advice on the composition of breakfast. Sometimes a reduced or increased amount of carbohydrates is advised, and sometimes even a second insulin dose. The latter two sections are devoted to these subjects.

8.2.2 1, 2 Hypo alarm and advices on the postponement of breakfast

The insulin injection is taken at waking up. The global action profile of the short working insulin used by the author is as follows. The insulin's effects are measurable for about 2 hours. Within a quarter after the moment of the injection and after about two hours, not so much can be expected of the effects of the insulin. After a small half an hour the first effects of the insulin are most often noticeable, and about an hour after the injection, the insulin's effects are the best noticeable in general. The four relevant distinguished periods since the injection are

- ½ hour,
- 1 hour,
- 1 ½ hour, and
- 2 hours.

Given the period since the injection, the BG course – the BG value at waking up, and the BG value now – determines the measure of expecting a hypo in the (near) future, say about the first ½ hour. First in rule block (1) a classification is made of the BG value at waking up; values which yield the same control action are in the same range. Next, this classification is compared with the current BG value. Dependent on the period since the injection, the danger for an approaching hypo is estimated by the author's knowledge. In the figure below, the danger for an approaching hypo is depicted for different values of current BG, the range in which the BG value at waking up fells, and the period since the injection. It reflects the working of rule block 2.

The different stages in the danger for an approaching hypo are

- absolutely yes,
- probably yes,
- probably no, and
- absolutely no.

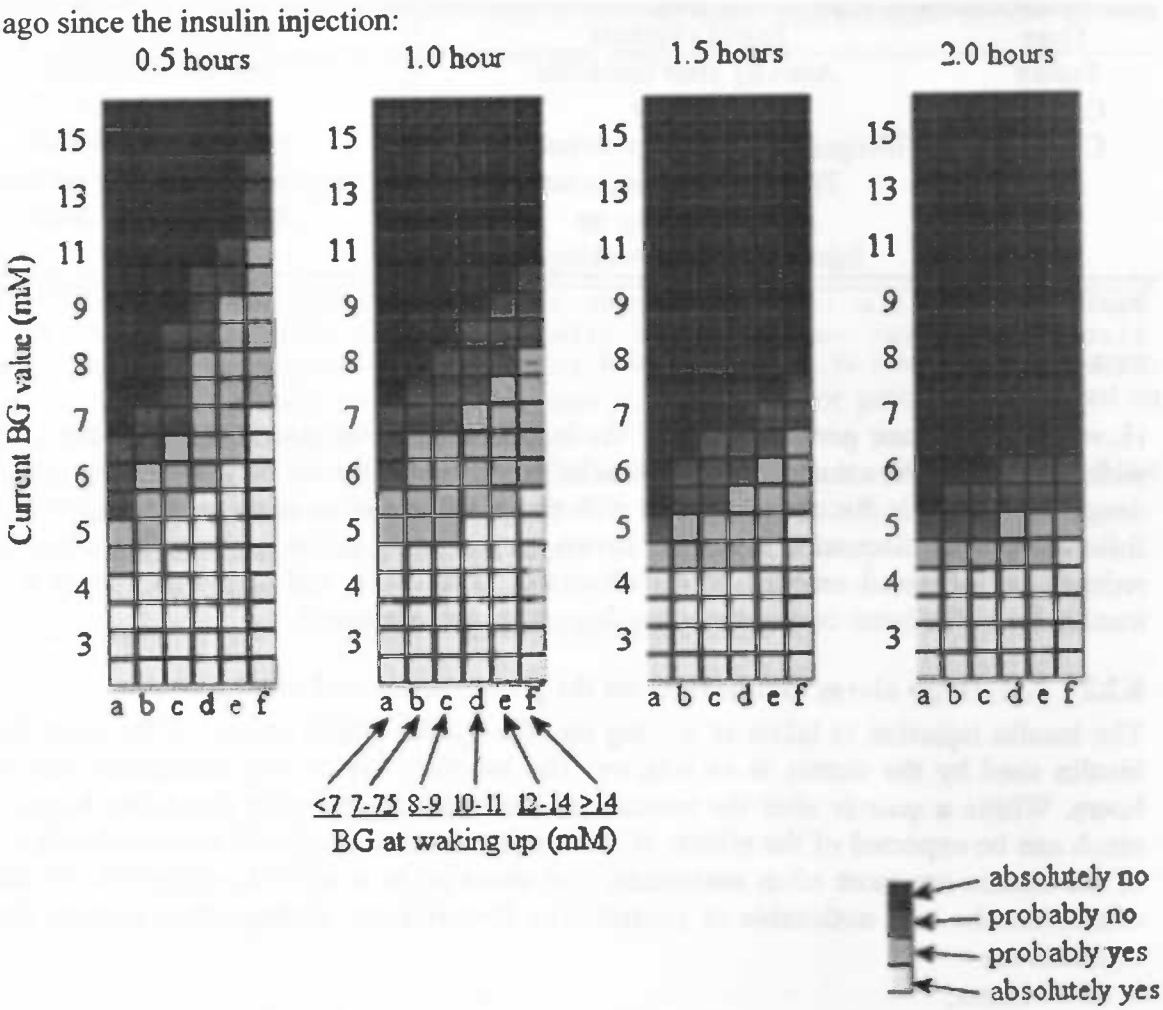


Figure 8-3 The different stages in the danger for an approaching hypoglycaemia in the first ½ hour from now. This danger depends on the time since the injection and the two BG levels at waking up and in current.

Most wishful is the situation that BG dropped so much in the period between waking up and now that breakfast can be commenced. Sometimes, if BG was very high at waking up, and at the current moment it is still high, it can be a sensible decision to postpone the breakfast for e.g. half an hour. It might even happen, for example if two hours after the injection BG is still not dropped enough, to commence breakfast. Because after about two hours, the insulin (almost) worked out, so that it isn't even possible anymore to consume the original amount of carbohydrates without an immense increase in BG level. In such situations it is advised to eat much less up to almost nothing anymore. Of course, for the normal consumption of food another injection is needed now.

The postponement advices can be

- no postponement; commence breakfast now,
- a postponement of half an hour, and
- an "indefinitely postponement" which means skipping the consumption of the food planned to consume when taking the injection.

The postponement is also based on the period since the injection and the BG course, just like the hypo alarm.

In the following section the advice that is brought out on the composition of the meal is discussed.

8.2.3 3 Composition of breakfast

The content of an average breakfast is two slices of bread with cheese. The carbohydrates in sugar drink and glucose are more short working than those in bread. Sometimes it is advisable to change the meal's content, to eat some extra glucose or to drink with sugar – leaving the total amount of carbohydrates assumed taking the initial injection, unaffected. Rule block 3 brings out some advice on the content of the meal, with regard to the ratio of short and long working carbohydrates. Also, a possible advice can be the consumption of some extra glucose or some extra drink with sugar.

The injection at waking up is taken considering the amount of carbohydrates the patient wants to consume at breakfast. Most often, this amount can be consumed without problems, but sometimes it is advisable to eat some more short working carbohydrates instead of the same amount of long working carbohydrates. For example changing the consumption of one slice of bread by the consumption of some drink with sugar as drinking chocolate.

The drop in BG due to the activity is compensated with some extra sugar drink. Also, if an approaching hypo is expected, the composition of the meal is changed, leaving the total amount of carbohydrates unchanged. Now some short working carbohydrates are consumed in stead one slice of bread. The total amount of carbohydrates has to remain the same because the amount of insulin is adapted to this amount.

In situations where *probably no* hypo or *absolutely no* hypo is expected, the content is advised to remain normal. Except, if no postponement is advised and there is planned physical activity after breakfast, then some more short working carbohydrates are advised. On the other hand, if the expectation for a hypo is *absolutely sure*, the consumption of some extra glucose is advised. If there is physical activity after breakfast, and no postponement of the meal is advised, then some extra sugar drink is advised either. Also, if the expectation for a hypo is *probably sure*, in general some extra sugar drink is advised.

Concluding, the information about the content of the meal is derived from

- the activity after breakfast,
- the expectation of a hypo, and
- the eventual postponement of the meal.

The possible advices are

- consume some extra glucose,
- consume some extra sugar drink,
- consume more short working carbohydrates, keeping the total amount constant, and
- no need to change the meal's content.

This section was about the meal's content, the next is about the amount of carbohydrates in a meal.

8.2.4 4 The amount of carbohydrates in breakfast

As discussed in earlier sections (on multiple places), due to the dawn phenomenon, sometimes enormous increases in BG can occur after waking up. Because this is unknown at the moment of the injection at waking up, it cannot be taken into account then. A solution for a compensation of this arise in BG is to diminish the amount of carbohydrates intended to consume. On the other hand, sometimes the drop in BG is much faster than expected and wished, due to an overestimation of the insulin dose or a coincidental increased working of

the insulin. In these cases, it is advisable to eat something more than intended to. The advices about the amount of carbohydrates in breakfast are, consume

- more,
- little more,
- same,
- little less,
- less, and
- much less.

Remark. There are three graduations for eating less, in contrast to two for eating more, because the first occurs more often than the latter and so the author probably developed an increased capability to distinguish these cases.

The advice is brought out on the basis of the same variables as the hypo advice and the advice for the postponement of the meal, namely

- the period between the injection and now,
- the BG value now, and
- the range that included the BG value at waking up.

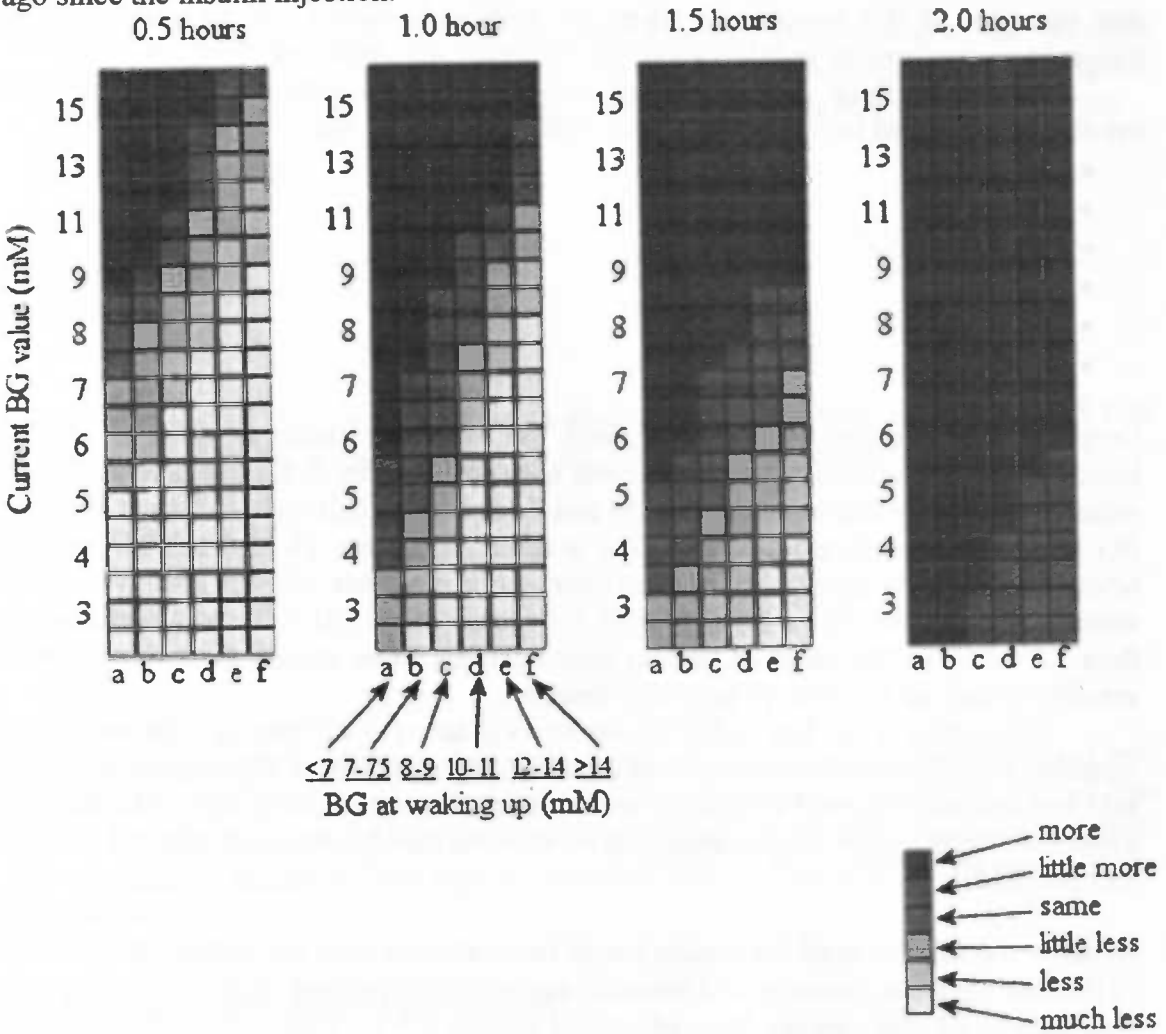


Figure 8-4 The advised amount of carbohydrates in comparison with the amount that is wished to eat at waking up. This advice depends on the time since the injection and the two BG levels at waking up and in current.

The author filled the rule blocks (like all rule blocks) on the basis of this intuition.

The output of this rule block (4) about the amount of carbohydrates to consume is only valid if there isn't taken a second injection; sometimes the situation is so bad that BG doesn't drop enough and a second insulin dose is necessary. The following section is about the latter. This automatically implies that the same amount of carbohydrates can be consumed as originally preferred at the first injection.

8.2.5 5, 6, 7 The second insulin dose

The fact if a second insulin dose is necessary, is (again) derived, in rule block 5, from the three variables

- the period between the injection and now,
- the BG value now, and
- the range that included the BG value at waking up.

The global structure of this process is described in the former section. If there is decided to take a second insulin injection, the amount of this dose mainly depends on the first dose,

which was injected at waking up. It is a correction that is aimed at the intended result at the first injection. If this injection is taken the original breakfast can be consumed (after the indicated postponement) as intended when taking the first injection.

Out of the three variables, mentioned above, the 'relative amount' of extra needed insulin is determined in rule block 5. The 'relative amounts' are:

- None,
- Very little,
- Little,
- Average,
- Much, and
- Very much.

Only the major choices here, are discussed. An important choice is when to take a second injection and when not. The advice to inject *very little* insulin, is for example given, if the BG value at waking up was between 7.0 mM and 7.5 mM, and half an hour later it was 10 mM. If BG is smaller than 10 mM, no injection is taken. If it were 14 mM half an hour later, the advice would be to inject *very much*. Other, more moderate advices are given if the latter value lies in between 10 mM and 14 mM. Of course, if the BG value at waking up was more than 7.5 mM, the BG value of half an hour later has to be greater than 10 mM, to make it sensible to take an injection of *very little* insulin.

Interesting is the fact that if the injection is taken two hours ago, the need for another injection is independent on the BG value at waking up. Only if the current BG value is 8.5 mM or more, there is need for a little extra insulin. For values below 8.5 mM a further drop is expected which makes the consumption of the decreased amount of advised carbohydrates still possible.

Actually the relative need for insulin has to be compared with the injected amount of insulin in the first injection, which would form the amount of the second injection. For example if the first dose is 8 U the average injected second dose is 3.5 U. This is done in rule block 7, but first another operation is executed, discussed in the next section.

8.2.6 6 The diabetic's health is put first

For people with diabetes it is difficult to weigh up the contras of a high BG level and the contras of eating more than wished. The effects of an injection are never exactly predictable. If little less than the best guess is injected, less often a hypo will be caused. The drawback of injecting less is that higher BG levels are reached on average. On the other hand, the drawback of very often eating more than wished, is that people become fat. Moreover, the fatter a person is, the more difficult it is to stabilize his BG level.

This is the reason that an unusual input variable is added to specify the willingness to eat extra carbohydrates in case the dose was little overestimated. The terms present at this input are:

- No, and
- Eventual yes.

If there is willingness to eat some extra carbohydrates if the dose was little overestimated, the best guess for the dose is done on the basis of the output of rule block 5, described in the former section. If there is no willingness, then the output of rule block 5 is decreased with one category.

8.2.7 7 The eventual second insulin dose

The only action performed in rule block 7 is the definition of the meaning of the concepts *very little*, *little*, *average*, ..., in the context of the insulin dose which is injected at waking up. First a classification is made at the input variable of the dose that was injected at waking up:

- 0 U,
- 4 U,
- 6 U,
- 8 U,
- 10 U, and
- 12 U or more

The insulin injection of 10 U at waking up is given as an example of the working of rule block 7, which would be the author's choice for the eventual second insulin dose:

- None: 0 U
- Very little: 2.5 U
- Little: 3 U
- Average: 3.5 U
- Much: 4 U
- Very much: 5 U

Two of the three possible events that can occur with regard to breakfast are discussed yet. First the advice when the diabetic wakes up; which is discussed in the beginning of this section. This leaves two possibilities, the patient immediately takes an injection, or the patient takes the injection at breakfast. The first is discussed above. The latter is discussed in the following section.

8.3 Breakfast – injection at breakfast

In this project the second controller for breakfast will be developed. This time, no injection at waking up is assumed. Actually this is the most ideal situation; the BG value at waking up was all right, so the injection can be taken at breakfast.

The input of this system much resembles the input of the system that is used for the *waking up* event. One more variable is added here, namely the BG value at waking up. Thus, the "power" of this controller should be greater than the controller at waking up. The output, on the other hand, much resembles the output of the system that is used for breakfast, if the injection is taken at waking up yet. The clear difference is that in the latter a second dose is possible, and here an injection is a must. Also, no advice is brought out on the amount of carbohydrates to consume here.

8.3.1 The structure

The following figure shows the whole structure of this fuzzy system including input interfaces, rule blocks and output interfaces. The connecting lines symbolize the data flow. The rule blocks again are enumerated. The rule blocks that are rectangles, are just normal rule blocks. The rule blocks that are round, have a '+' or a 'x' in their center. A plus means that the operation performed is kind of summation, and a cross means a kind of multiplication.

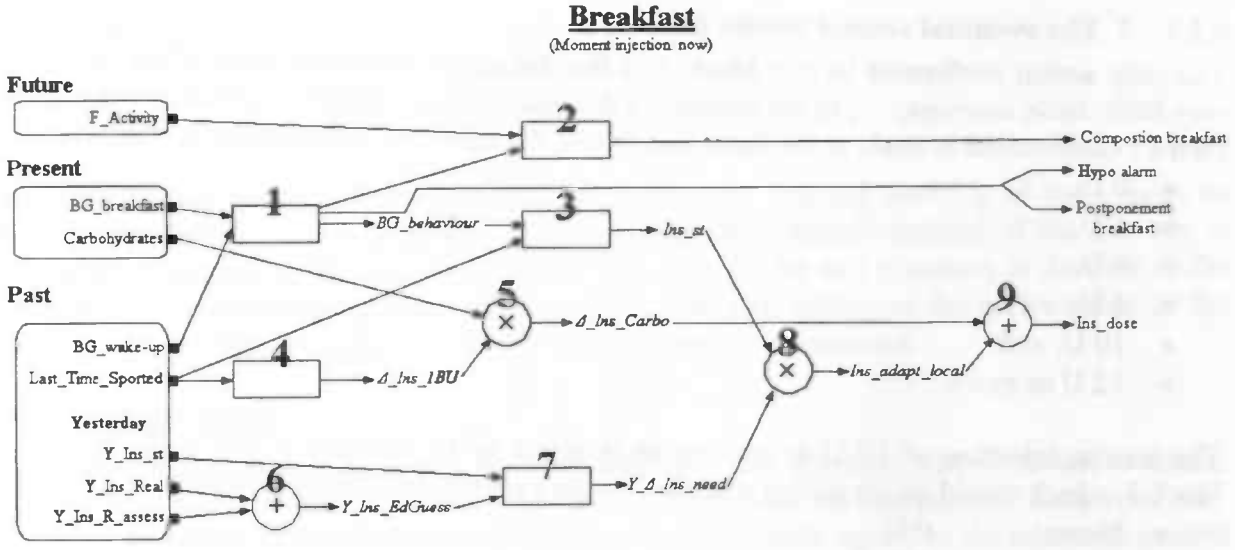


Figure 8-5 The structure of the system belonging to the event "Breakfast - injection at breakfast". Left the input variables, the rule blocks are enumerated. Right the output variables which form the advice. (The system structure isn't implemented yet.)

The first important comment here is that the system isn't implemented yet, so only a draw of the structure – which is the most important part – can be given.

In the following table the input variables are listed with respect their place in time, together with the system's output variables c.q. its advices.

Time	Input variable	Output variable
Future	Activity after breakfast	Composition breakfast
Present	BG breakfast	Hypo alarm
Present	Carbohydrates	Postponement breakfast
Past	BG at waking up	Insulin dose
Past	Last time sported	
Past	Standard dose advised yesterday	
Past	Real injected dose yesterday	
Past	Assessment injected dose yesterday	

Table 8-3 In this table the input and output variables of the system are listed. The input variables are categorized with respect to their place in time.

How the advices are generated out of the input variables, is discussed in the next sections, with the help of the enumerated rule blocks in the figure above. To emphasise the resemblance with the former discussed systems, this one will be discussed with the help of references to the other systems where possible.

8.3.2 1, 2 Composition meal, hypo alarm and postponement meal

The reasoning behind the advice about the composition of the meal (rule block 2) is mainly corresponding to that in rule block 3 in the system about "breakfast – injection at wake up". The major difference is the danger of an approaching hypoglycaemia being much less, because there is no injection taken at waking up, and thus a big drop in BG level isn't the general expectation. The hypo alarm (result of rule block 1) takes care of advising glucose in case of a predicted approaching hypo. The further intuitive idea behind the reasoning in rule

block 2 is about this. If there is planned future activity, there will be advised to eat more short working carbohydrates, assuming that the BG level at breakfast isn't (become) high (e.g. 8.5 mM). This is to avoid a hypo when practicing the activity. In other cases just a normal breakfast is advised.

The BG level at breakfast can be compared with that of waking up. If there is a strong drop, and the current value is also low, then a warning for approaching hypoglycaemia is given (rule block 2). Also, assuming a reasonable BG level (i.e. not above e.g. 7.5 mM, otherwise an injection would have been taken at waking up), the measure of increase or decrease is an important fact in the determination of the standard dose that has to be injected. If there is an ascending trend in BG, of course this has to be compensated with insulin. The BG behaviour is another output of rule block 1.

8.3.3 3, 6, 7, 8 Intermediate estimation insulin dose

The method to derive an appropriate insulin dose mainly resembles the first system's method. The standard dose is determined by the combination of the BG behaviour and the last time sported (rule block 3). This again is like the determination of the standard dose in the first system. The major difference is that at the dose determination at waking up is only on the basis of one BG value, and here – knowing this BG value at waking up being all right (what means not too high) – one more value (the current BG value), and thus the trend in BG, can be included in the evaluation of the standard dose. This will yield a better guess for the insulin dose, because more information is available.

For the output of rule block 3, the standard insulin dose, yields that it is based on the amount of carbohydrates of two slices of bread in breakfast. This is the same assumption as in the first system, and is because of the fact that such a breakfast is quite standard for the author.

The relative need for insulin is derived on the basis of the same method as in the first system; the rule blocks 6, 7 and 8 here, are the same as the rule blocks 4, 5 and 6 respectively in the first system. Their work is already described before. Rule block 8 yields the intermediate insulin dose.

8.3.4 4, 5, 9 Breakfast's influence on intermediate estimation for insulin dose

The standard amount, which is already compensated with the relative need for insulin is based on the standard amount of carbohydrates of 2 BU. Only if the amount of carbohydrates diverges from standard, this dose has to be adapted. The insulin that has to be injected due to 1 BU more or less carbohydrates in breakfast (thus in total 3 BU, or 1 BU), is called **Δ_Ins_1BU**. An eventually diverging amount of carbohydrates it isn't often more than 1 or 1.5 BU. The only significant influence is thought to be the period until the last time intensive physical exercise is performed. In the first system, the insulin dose – determined on the base of the last time sported and BG behaviour – (for a standard meal of 2 BU) is believed to influence Δ_Ins_1BU. Yet, this influence is considered to be minor enough to ignore. It is a minor influence, because the advised doses until now are not influenced that much by BG behaviour, in contrast to the dose that is computed at waking up which strongly depends on the BG level.

Once determined Δ_Ins_1BU (the output variable of rule block 4), it can be multiplied by the difference in breakfast, compared to the standard meal of 2 BU. This multiplication is rule block 5's output, and is summed in rule block 9 with the insulin dose computed so far. This summation yields the eventual insulin dose.

9 Testing

With the testing of a system, we mean both testing the internal working of the system as testing the performance of a system. In this chapter the internal working of the systems is discussed according to the analysis of a real test case. In the end a section is devoted to the evaluation of the testing discussed in this section. But first testing of the performance of the Fuzzy Logic IDDM-controllers as described in this work, is discussed.

9.1 Performance

With the performance of a system, its predictability of the adequate control action is meant. Testing of control advices is a difficult question. In fact, there are two possible scenarios:

1. The system is tested in a set of familiar situations with regard to the adequate control action.
2. The system is tested in practice with regard to the executed advice.

If the performance of the system is tested as in the first case, a set of combinations of situations and corresponding control actions has to be known. This set can be extracted out of real life situations that are assessed in retrospect as controlled adequately. For every situation in the test set, the advice of the system has to be compared with the corresponding advice from the test set. We state that its performance is (almost) as bad as its worst advice. An advice is considered to be worse than another advice if it bears more danger.

For example, a system can yield an advice that is very close to the most adequate advice hundred times, and one time be completely beside the mark, to be bad in comparison with a system that always is a bit faulty, but never makes big mistakes.

The proposal of an adequate control action is a complex question. The author asked two medical doctors that couldn't tell him an appropriate error measure. The following can be stated. If d (> 0) is the adequate insulin dose, and c (> 1) is a number, then

$c*d$ is a worse advice than d/c.

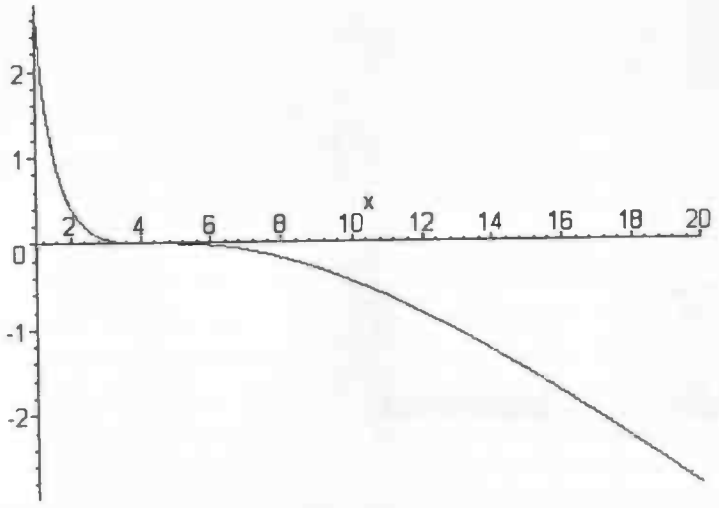
Maybe an adequate error measure uses a square or x^3 because the more an advice diverges, the worse it (relatively) is. More research has to be done to determine an appropriate error measure.

The second case in testing the performance of a system concerns the effect of an executed control action. The only possibility now is considering the effects of the insulin dose with respect to the corresponding BG values. Take a BG sample, for example two hours after the injection and compare its error to the error of the aimed value. The cost function, described earlier in this work, could function here as an error function if the absolute signs are removed and the result is inverted (with adding a minus sign):

$$\text{error}(BG) := -10*(\log_{10}(BG/4.4))^3,$$

An error value above zero means that too much insulin is injected and an error value below zero means that too little insulin is injected.

The function error(x) is plot in the figure below.



More research has to be done with regard to the coupling of this error to an appropriate adaptation in the insulin dose.

9.2 Internal working according to test case

The content of the logbook on February 3 and 4 is:

Input:

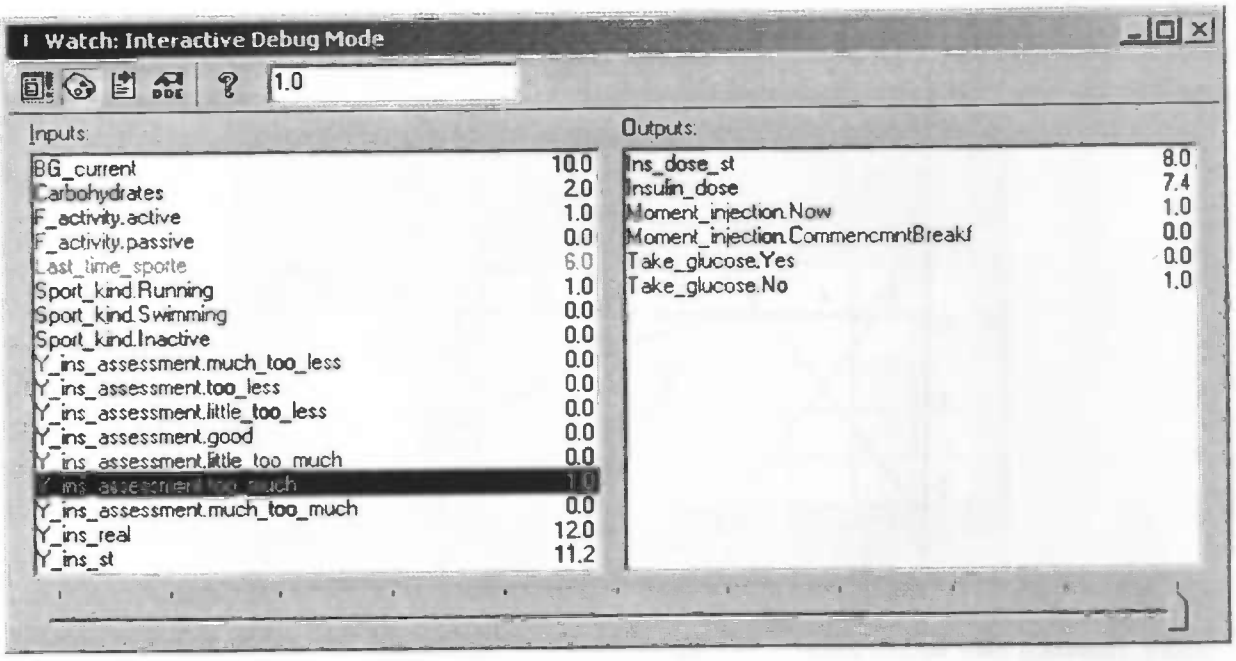
Date	Y_ins_st	Y_ins_real	Y_ins_assess	Carbohydrates	BG_current	F_activity	Last_time_sported
Feb. 3	8,0 U	8,0 U	Good	2,5 BU	15,1 mM	Passive	5,0 days
Feb. 4	11,2 U	12 U	Too much	2,0 BU	10,0 mM	Active	6,0 days

Output:

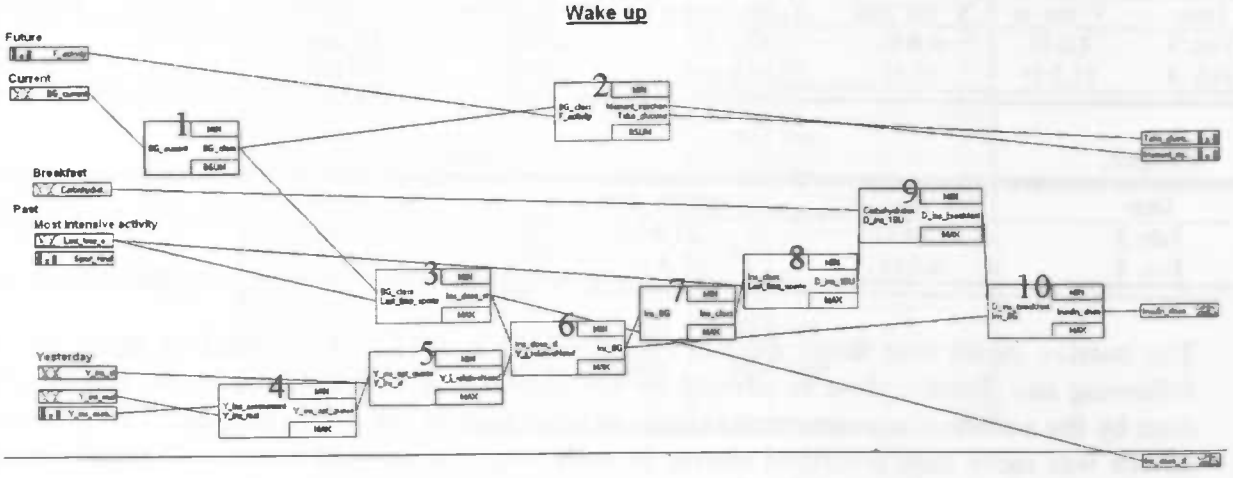
Date	Ins_dose_st	Insulin_dose	Facts: Injected dose	Assessment
Feb. 3	11,2 U	11,8 U	12,0 U	Too much
Feb. 4	8,0 U	7,4 U	7,5 U	Good

The cursive items (the facts) are not output of the system, but are used as input for the following day. Insulin_dose is advised by the system, but *Injected dose* is the real injected dose by the author. The assessment is done in retrospect by the author himself. The generated advice was more than described above; in both cases the advised moment of injection was instantaneously, and the need for glucose was (of course) none.

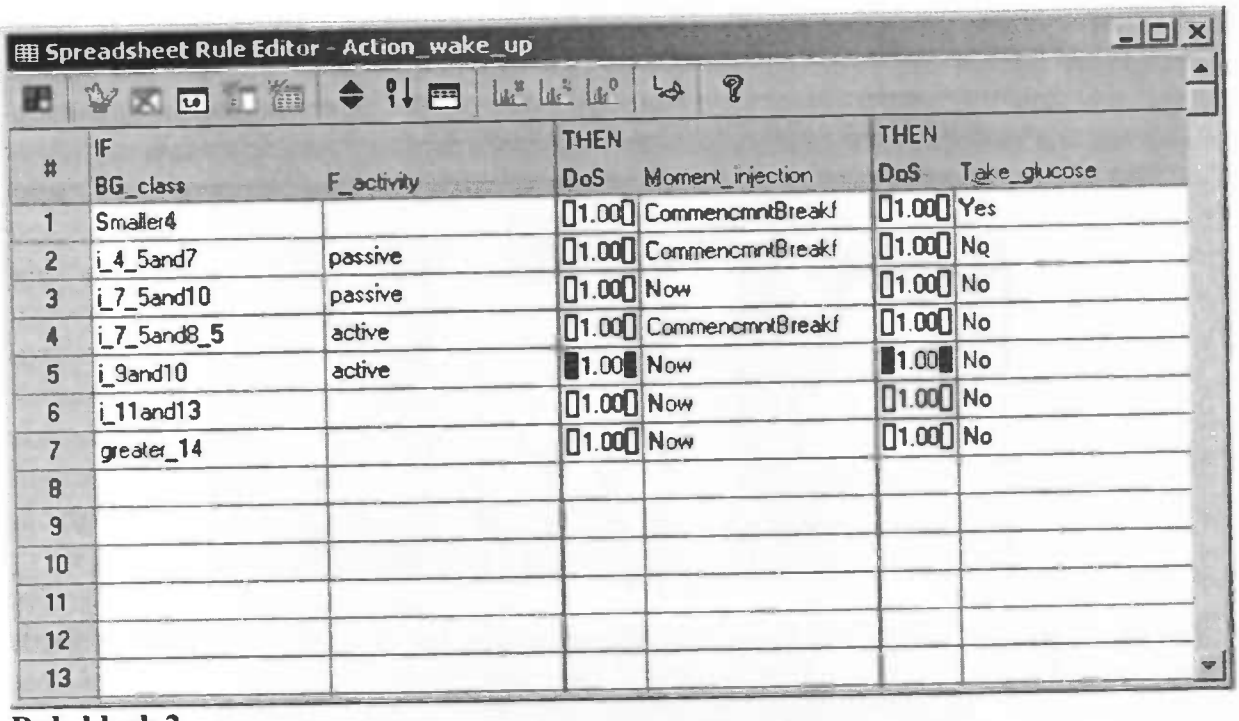
In the following figure, the input and generated output on February 4 are depicted, generated with the system "Wake-up".



For the analog inputs and outputs (BG_current (U), Carbohydrates (BU), Last_time_sported (Days), Y_ins_real (U), Y_ins_st (U), Insulin_dose (U)) the input or output is in their own units. For the terms like Y_ins_assessment.good or Moment_injection.Now, a value of 0.0 means completely false, and a value of 1.0 means completely true. The generation of this advices are described with the help of the structure of the system, treated per (relevant) rule block.



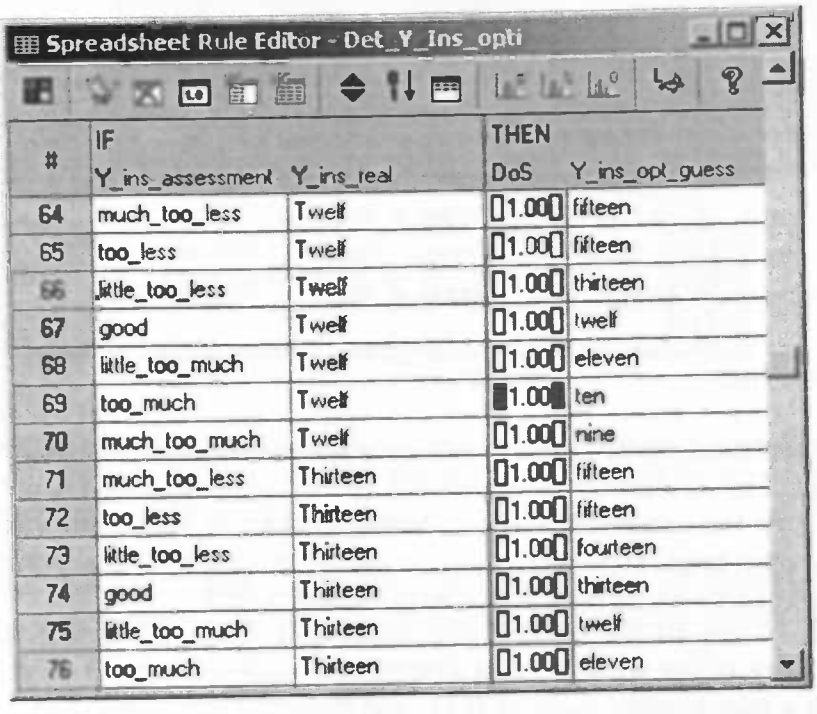
The choices for the actions that have to be taken are trivial and thus not discussed in detail. In the following figure, it is clear that with BG = 10,0 mM, (both the terms i_9and10, and i_7_5and10 have a membership value of 1), together with F_activity = *active*, the only rule activated is rule 5. This means the injection is needed instantaneously and no glucose (of course) has to be taken.



#	IF BG_class	F_activity	THEN DoS	Moment_injection	THEN DoS	Take_glucose
1	Smaller4		1.00	CommencmntBreakf	1.00	Yes
2	i_4_5and7	passive	1.00	CommencmntBreakf	1.00	No
3	i_7_5and10	passive	1.00	Now	1.00	No
4	i_7_5and8_5	active	1.00	CommencmntBreakf	1.00	No
5	i_9and10	active	1.00	Now	1.00	No
6	i_11and13		1.00	Now	1.00	No
7	greater_14		1.00	Now	1.00	No
8						
9						
10						
11						
12						
13						

Rule block 2

Next, the best guess in retrospect of the insulin dose yesterday is done with the actual injected dose, Y_ins_real, and its assessment, in retrospect, Y_ins_assessment. The term *twelve* for Y_ins_real was the only nonzero term, with a membership value of 1. The same yields for the assessment term *too_much*. Because this, only one rule (rule 69) is activated (compare next figure). This results in the fact that the term *ten* gets a membership value of 1. So, in retrospect, the best guess for the dose yesterday, is believed to be 10 U.

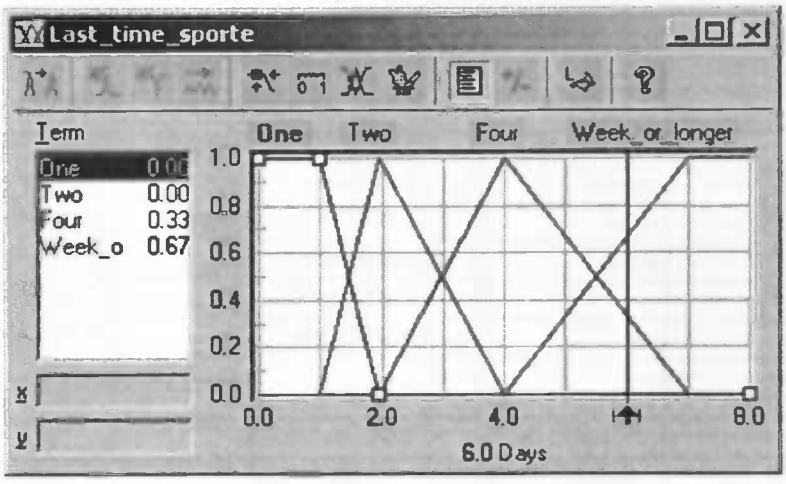


#	IF Y_ins_assessment	Y_ins_real	THEN DoS	Y_ins_opt_guess
64	much_too_less	Twelf	1.00	fifteen
65	too_less	Twelf	1.00	fifteen
66	little_too_less	Twelf	1.00	thirteen
67	good	Twelf	1.00	twelf
68	little_too_much	Twelf	1.00	eleven
69	too_much	Twelf	1.00	ten
70	much_too_much	Twelf	1.00	nine
71	much_too_less	Thirteen	1.00	fifteen
72	too_less	Thirteen	1.00	fifteen
73	little_too_less	Thirteen	1.00	fourteen
74	good	Thirteen	1.00	thirteen
75	little_too_much	Thirteen	1.00	twelf
76	too_much	Thirteen	1.00	eleven

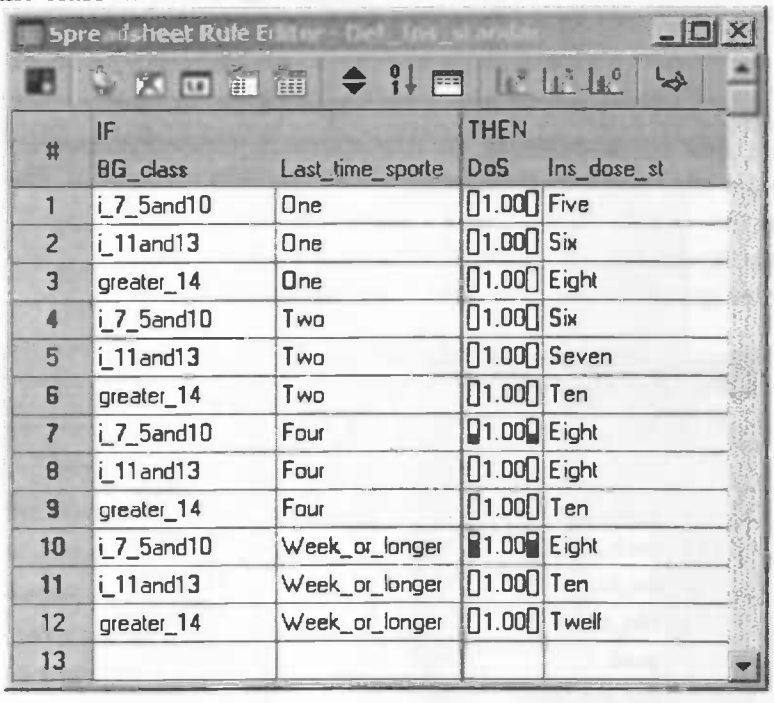
Rule block 4

The determination of the standard injected dose, where only the class where BG falls in, and the period not sported, are regarded, is computed as follows. The membership value of

i_7_5and10 is one (discussed above). The membership values of *Four* and *Week_or_longer* are 0.33 and 0.67, respectively (compare figure below).



The next figure shows the rule block that determines the Ins_st_dose on the basis of the last time sported and the class in which the current BG value falls.



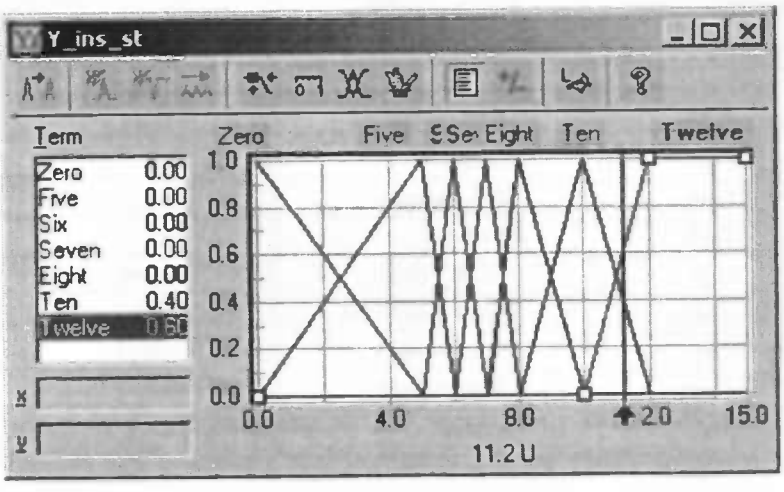
#	IF		THEN	
	BG_class	Last_time_sporte	DoS	Ins_dose_st
1	i_7_5and10	One	1.00	Five
2	i_11and13	One	1.00	Six
3	greater_14	One	1.00	Eight
4	i_7_5and10	Two	1.00	Six
5	i_11and13	Two	1.00	Seven
6	greater_14	Two	1.00	Ten
7	i_7_5and10	Four	1.00	Eight
8	i_11and13	Four	1.00	Eight
9	greater_14	Four	1.00	Ten
10	i_7_5and10	Week_or_longer	1.00	Eight
11	i_11and13	Week_or_longer	1.00	Ten
12	greater_14	Week_or_longer	1.00	Twelf
13				

Rule block 3

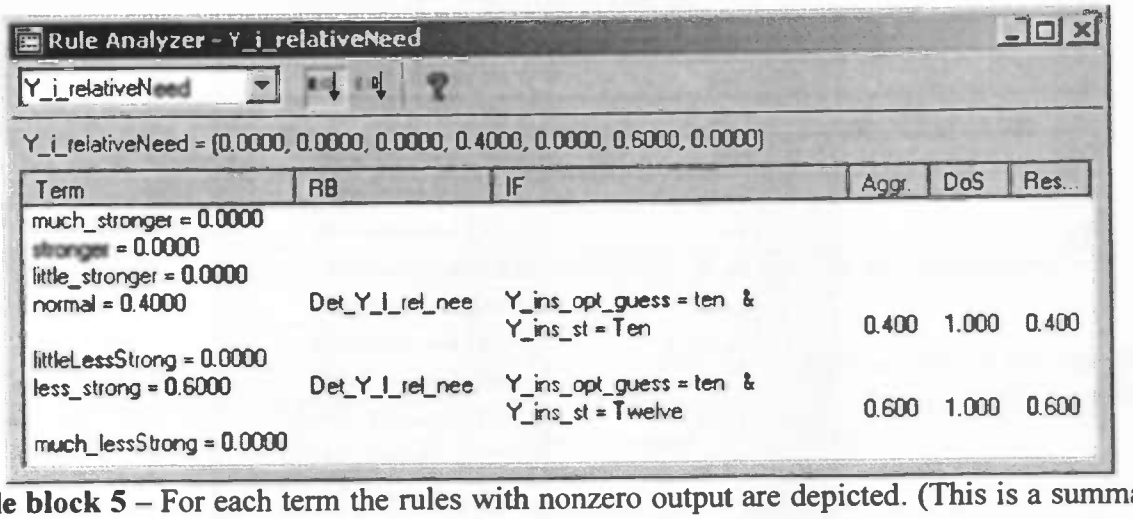
Rule 7 and rule 10 are the only rules with nonzero output. Both rules affect the membership value of *Eight*. The operator used in this rule block, is the MIN-MAX operator. This means that for each rule the minimum of the IF-terms is taken as the output value, or membership value of the output term. The membership value of the concerning output term is equal to the maximum value of all the rules with that term as output term.

In rule 7 and 10 the membership value of I_7_5and10 is one, thus the minimum membership value of the input terms is determined by the other term. In rule 7 the other term is *Four*, with a membership value of 0.33, and therefore the output term, *Eight*, in that rule gets a value of 0.33. In rule 10 the other term is *Week_or_longer*, with a membership value of 0.67 . Now, the eventual membership value of *Eight* is the maximum of 0.33 and 0.67, which is 0.67 .

In rule block 5, out of the yesterdays standard advice and the guess for the best dose in retrospect, yesterday, the relative need for insulin is determined. The standard advice yesterday was 11,2 U. It appears from the following figure that both terms *ten* and *twelve* have a nonzero membership value.



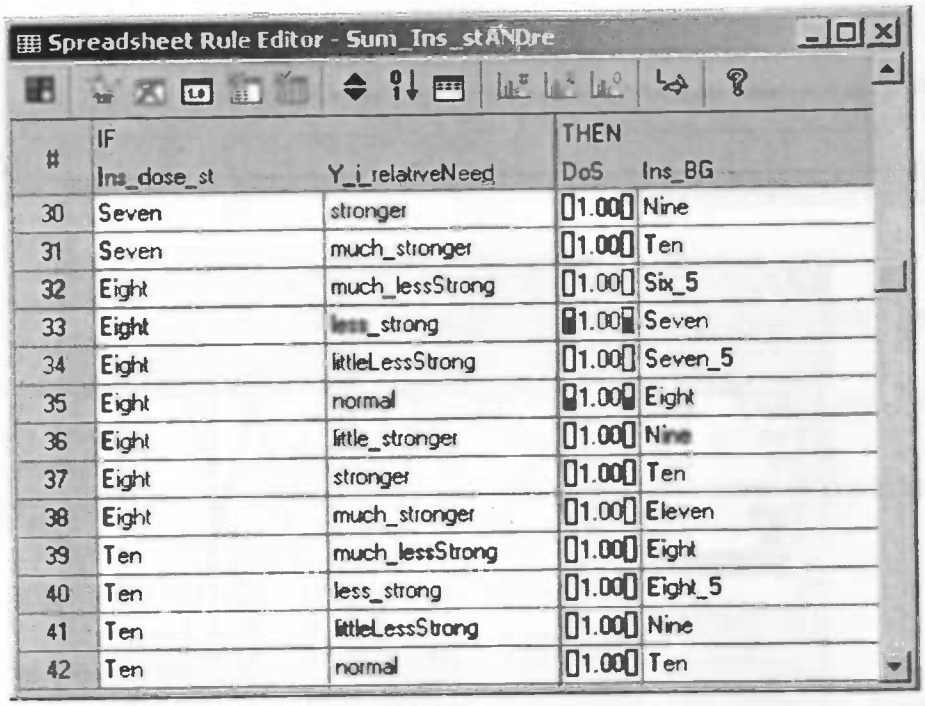
Ten has a membership value of 0.4, and *twelve* of 0.6 . (Compare: 0.4 * 10 + 0.6 * 12 = 11.2 .) Now, at the following rule block, rule block 5, two rules have nonzero output. Because Y_ins_st has 7 terms and Y_ins_opt_guess has 23 terms, the rule block (5) that defines the relative need of insulin yesterday by comparing the two variables, has 7 times 23 = 161 rules. Only two rules are activated. The membership values of the terms of Y_i_relativeNeed, together with the rules that activated the terms are illustrated in the following figure.



Rule block 5 – For each term the rules with nonzero output are depicted. (This is a summary of the relevant part of this rule block.)

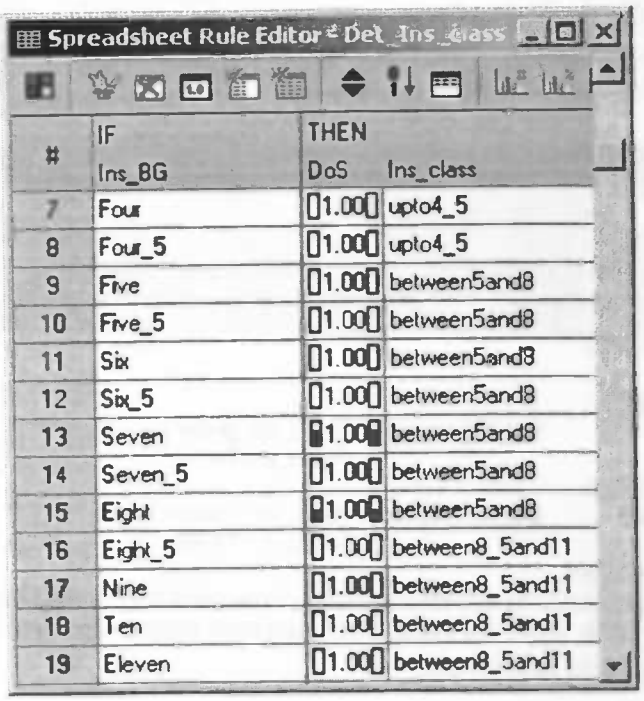
The result of this rule block, that determines the relative need for insulin is, that the term *less_strong* has a membership value of 0.6, and *normal* of 0.4, again computed with the MIN-MAX strategy.

The standard advised insulin dose in this case, *Ins_dose_st*, is eight, with a membership value of 1. As shown above, with regard to the relative need for insulin (yesterday), two terms have nonzero membership value, *less_strong* and *normal*. In rule block 6, which determines the insulin dose so far, Ins_BG, two rules are activated.



Rule block 6

Again according to the MIN-MAX strategy, *Eight* gets a membership value of 0.4, and *Seven* of 0.6. The next step is the classification of the insulin dose, Ins_BG, computed for so far.

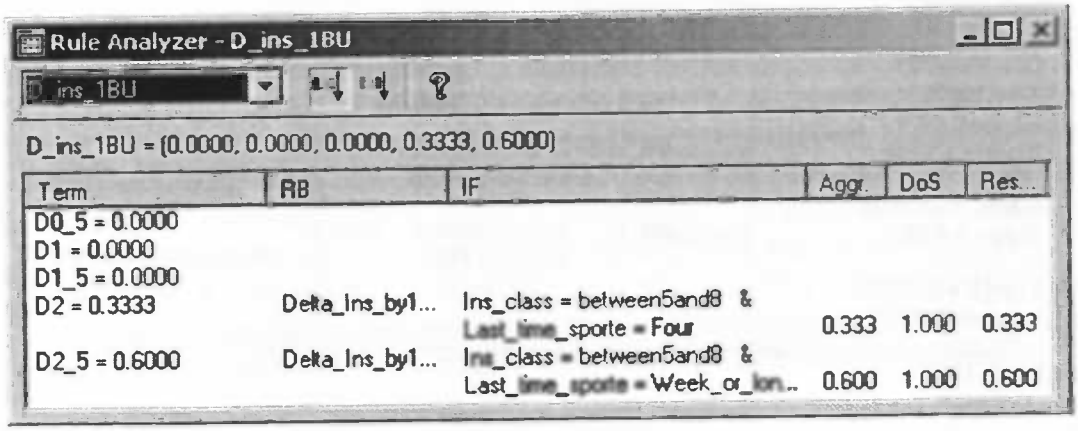


Rule block 7

The only nonzero term is *between5and8*, has a membership value that equals the maximum of the membership values of *Seven* and *Eight*, which is MAX{0.6,0.4} = 0.6 .

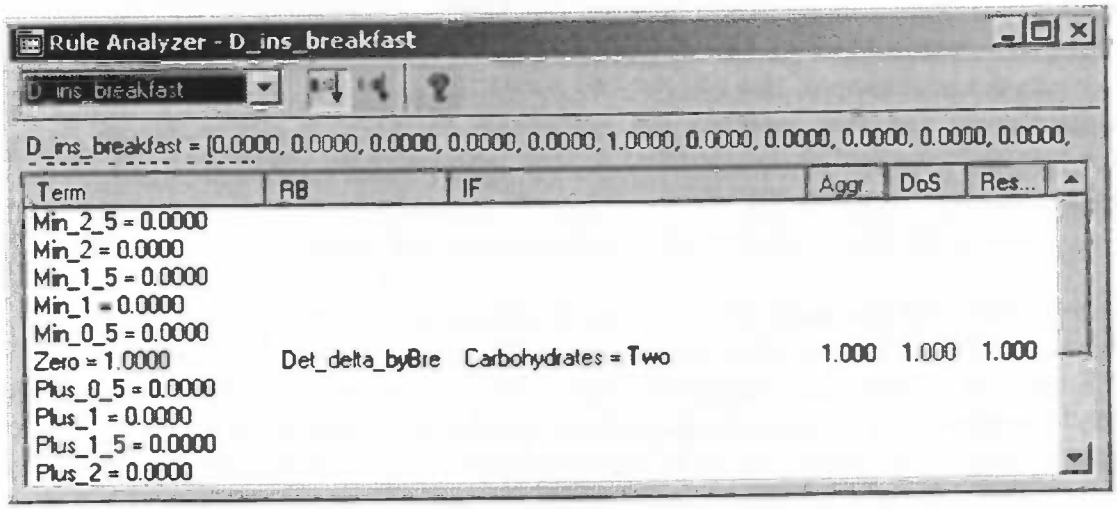
Yet the difference in the insulin dose, D_ins_1BU, due to 1 BU difference in the amount of carbohydrates is to be determined. This is done on the basis of the last time sported and the insulin class. The term D2 and D2_5 get a membership value of 0.3333 and 0.6 respectively. The computation is done in the same way as above. The intuitive meaning of D2

and D2_5 are that the insulin dose increases (decreases) with 2 U, respectively 2.5 U, if the amount of carbohydrates increases (decreases) with the amount of 1 BU. For all clarity, the standard amount of carbohydrates at breakfast is 2.0 BU.



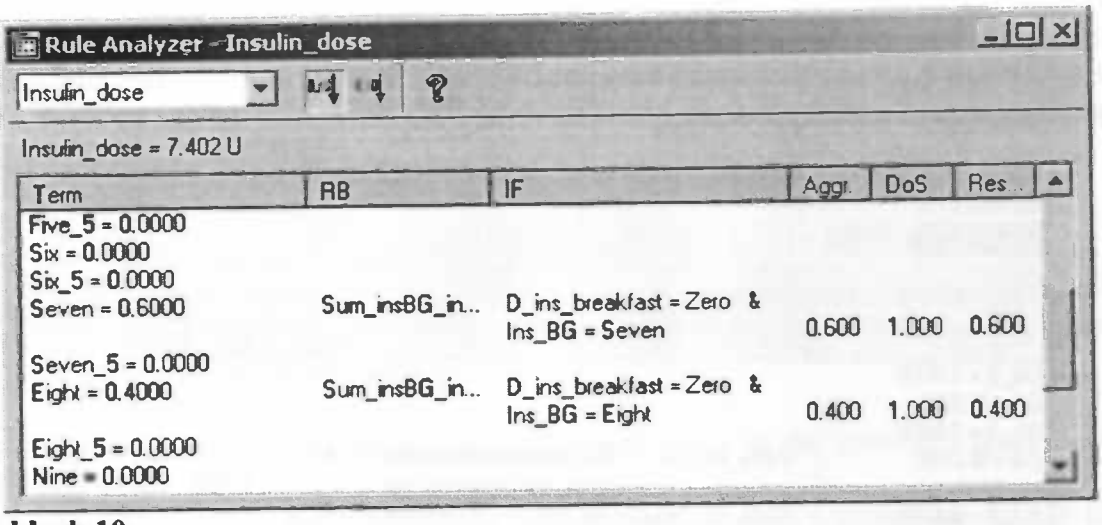
Rule block 8

Yet the total increase is computed due to the amount of carbohydrates in the breakfast. Because at February 4, the standard amount of 2 BU is consumed, the increase is zero. Compare following figure.



Rule block 9

Now the eventual insulin dose is the sum of the insulin dose determined for so far, Ins_BG, and the increase due to an eventual different breakfast. Because the influence of the breakfast is zero here, the dose, computed for so far, is the eventual insulin dose.



Rule block 10

Insulin_dose has a value of 0.6 * 7 + 0.4 * 8 = 7,4 U.

9.3 Evaluation

In the section before the internal working of one of the systems is shown. Situations with a known control action can be explicitly programmed in the Fuzzy structure. Fuzzy provides (eventual non-)linear interpolation between this known situations in a sensible way, as stated in many articles.

In the beginning of this chapter two scenarios in testing the performance of a system are discussed. The first supposes the knowledge of an ideal dose; the second supposes knowledge of the effect of the executed advice. Both cases are described to be realizable, but more research is necessary anyway.

10 Evaluation Fuzzy Logic controller implementations

Every diabetic starting with self-regulation is explained the reasoning described in the chapter about *Present-day self-regulation*. In this chapter the Fuzzy Logic implementation of this way of reasoning is evaluated with regard to the "manual way". The diabetic is expected to refine this reasoning according to his lifestyle and the behaviour of his own DM-system. In the later sections the author's refinements with regard to dealing with the determination of the insulin dose for breakfast and other control actions are discussed. Next, the use of Fuzzy Logic at the implementation of a controller for diabetes is evaluated. The chapter will end with conclusions on the Fuzzy Logic implementation of the different systems. In a next chapter the possible approach of a continuation on patient specific controller models is discussed.

10.1 Present-day starting with self-regulation

The reasoning presented in the chapter about present-day starting with self-regulation is the most basic one possible. The reasons for simplicity are that

1. it has to be applicable on every diabetic as point of departure, and
2. it has to be simple enough to understand for most diabetics.

The first is because a patient-specific implementation is very lifestyle-dependent (this appeared from the author's refined systems).

The Fuzzy Logic implementation yields an exact representation of the reasoning. The advantage in comparison with the normal "manual way", is the predefined gradual transition from one BG category to another. The big advantage is the automation of the process.

Both the relation between BG and an adaptation in the insulin dose, and the relation between the consumption of extra carbohydrates and an adaptation in the insulin dose, are assumed to be non-linear in literature. However, in the hospital's paper, each relation is defined as a linear one; probably on behalf of simplicity. Even (patient-specific) non-linear relations as these can be implemented very easy with the means of Fuzzy Logic. For a patient-specific implementation, the patient-specific quantitative relations can be implemented.

Factors other, that really are important influences on the course of BG, which are not included in this reasoning, are assumed to be invariant. For example, if the activity after breakfast differs from day to day, it is worth it to include it in the contemplations about the correct insulin dose. But, if the activity after breakfast is the same each day, it hasn't to be included in the contemplations about the correct insulin dose every day, because it hasn't any influence.

This restricts the patient in his freedom of movement and requires a regular life. The more alternative ways of living a patient has, the more complicated his control system is.

A drawback of this system's structure is the absence of the theoretical present automated correction mechanism for structural erroneous insulin doses. If there is injected a structural too small or too big dose, and the patient cannot allocate the cause in food, physical activity, stress or illness, the dose has to be adapted by 1 or 2 units. This dose has to be used for at least three days.

In the following three sections the author's extensions (i.e. refinements) of the above reasoning with regard to dealing with breakfast are discussed. More advices than only the insulin dose are included in these systems. The Fuzzy Logic structure implementations are discussed in preceding chapters.

10.2 Waking up

The advices determined here concern the moment of injection, the insulin dose, and the eventual need for glucose. If this system is compared with the point of departure, described above, the following things are striking.

- The extended kinds of advices.
- The automated determination for the optimal guess of the current relative need for insulin.
- The difference in the insulin dose that corresponds with a difference of one BU in breakfast is dependent on the amount of injected insulin and the last time sported.
- The evaluation of the period that no physical activity is performed.

The moment of injection is a useful advice. Because it is totally dependent on the BG value at waking up and the presence of future activity, the determination of this advice is straightforward.

As in section "10.4 breakfast – injection at breakfast", the most remarkable fact is the automated determination for the optimal guess of the current relative need for insulin, in case of an injection. This kind of structure provides adaptations in the insulin dose in course of time. Every day there is a possibility for a correction. However, the author doesn't use this possibility daily. Only if the insulin dose of the past day really wasn't appropriate, this can be registered in the system. Then a correction is made according to the estimated extent of the error in the past day.

One can have his doubts about the fact that such an opportunity has to be offered from day to day for a general diabetic. Considering the importance of the time ago since the last physical exercise in the insulin dose determination, the author's expectation is the following. The system's equilibrium points with respect to the relative need for insulin change in course of time. The actual need for insulin decreases rapidly for an increasing period since the last time sported. This rapid change in the actual need for insulin is expected to cause the relative need for insulin to differ more than if there is no change in the actual need for insulin. Moreover physical activity changes the nature of the DM-system. Diabetics (like the author) with an irregular life with respect to the performance of physical activity are expected more often dealing with a rapid change in the actual need for insulin. Probably this is the reason that the author developed the possibility of a correction on a smaller time scale.

Moreover, if the rapid change in the actual need for insulin is not estimated correct, due to any reason, the next day this can be corrected, so internal faulty configurations of the system are automatically adjusted. So, this automated correction system, is able to correct every deviation in the insulin need.

Of course, for a more moderate effect, the correction mechanism can be used as follows. Let the assessment (in retrospect) of yesterday morning's insulin dose be a sort of average assessment of the insulin doses in the mornings of the past two, three or more days. If the assessments (at least qualitatively) resemble each other, a correction can be made.

The third remarkable fact in the beginning of this section was this. The amount of injected insulin depends on the amount of carbohydrates in breakfast. On a certain moment, the amount that would be injected for a standard meal is known. The deviation in the insulin dose due to a deviation of one BU in the amount of carbohydrates is believed to be dependent on

1. the period not sported, and
2. the amount of injected insulin without a deviation in the amount of carbohydrates.

The exact relation between this two variables and the adaptation in the insulin dose is disputable. Although maybe some improvements can be made here, it is anyhow an improvement in comparison with the system above, because there the two above factors are ignored completely.

The period not sported is very important. The standard insulin dose can be 1.5 times bigger if the last time sported is more than 6 days ago, compared to 1 day ago. In the "hospital's reasoning", only the first insulin dose on the very next day is decreased. For different (groups of) patients this effect will behave different. Also the intensity, kind and duration of the sport are important influences.

Dependent on the height of BG it must be possible to do a (safe) guess for the best period to wait for consuming meal. Further research is necessary.

10.3 Breakfast – injection at waking up

This system provides the patient of a broad advice. The advices are about the composition of the meal, the postponement of breakfast, the amount of carbohydrates in breakfast, the eventual second insulin dose, and a measure for the expectation of hypoglycaemia. This is an advantage in comparison with the hospital's system, because there the patient has to estimate everything by his own.

The willingness for extra carbohydrates in case the insulin dose – that is the best estimation for the average case – appears, in retrospect, to be little overestimated, is believed to be useful in every case an insulin dose is generated.

One could argue that future activity enhances the danger for a hypo, but that is not true because this is compensated with the advice about the meal's content.

The eventual postponement should yield an exact number of minutes (or quarters), and can be extended from the current three categories, *now*, *½ hour*, *infinite*.

10.4 Breakfast – injection at breakfast

The most important difference of this system, in comparison with the former two systems, is the power. This system is believed to be more powerful than the other two, which means that it's predictions are believed to be more sure. The reasons for this are

1. the insight on the course of BG is based on two measurements (and the time in between), and
2. the behaviour of the DM-system is yet stable; BG at waking up is expected to be stable, because no injection is taken at waking up, if this system is used.

Taking up the second reason, the possibilities for the advice for the insulin dose don't vary much in this system. As explained earlier, this is the reason that the intermediate estimated amount of insulin isn't included in the determination for the difference in the injection due to a difference in the amount of carbohydrates by 1 BU.

10.5 Evaluation of the use of Fuzzy Logic and FuzzyTech

The implementation of both the general advice, developed by the "Martini hospital" was straightforward. Determining the structure of the control system, according to the way the author controls his own DM-system appeared to be a very complex. It lasted very long and the structure is redesigned a couple of times. For all systems yield that if the structure is defined properly, the implementation in Fuzzy Logic was straightforward. Every input factor (e.g. the willingness to eat eventual some extra carbohydrates) and output advice (for example the hypo-alarm) comprising fuzzy concepts are easy to implement with the help of fuzzy input variables, if appropriate linguistic terms are chosen. Crisp input and output variables are also easy to implement with the "compute membership" variables. The intelligent part, the choice of the linguistic terms and the interconnections between the rule blocks, which forms the internal structure c.q. the translation from input to output, are drawn from an expert, here the author.

About the reasoning behind a correct control action for diabetes in general, the following can be said. If a diabetic is asked why he takes a certain control decision, he perfectly is able to give a foundation in words. Also, the patients control behaviour is discussed in words between a doctor and his patient; sometimes even on the telephone. Every body is ought to have an idea about the intuitive meaning of the concepts *little less*, *average* or *more*, in case of the advised amount of food. Fuzzy logic probably is an appropriate mean to model the process of control action decision taking.

The Fuzzy Logic structure is implemented with the help of FuzzyTech. The great drawback of FuzzyTech is the absence of an easy implementation of linear summations and multiplications. If the system was implemented in a real advice program, there are easy workarounds to cope this problem.

Anyway, the reasoning in the realised implementations is uttermost transparent and can be adapted where necessary. In fact, this is what happens on a regular doctor consult. Normally, the doctor cannot be absolutely sure if his patient fully understands what he is saying. With the availability of such a system, the doctor can directly implement his advices in the patient-specific system. Errors in communication between doctor and patient, and misunderstandings are not an issue anymore, using such systems.

Using such systems, the patient gets his personal advice, tuned exactly to his situation. For some patients this will provide an easier way to live, because they are not able to give an appropriate estimation of the situation their selves.

10.6 Conclusions

The conclusions about the Fuzzy Logic implementation of the different systems, drawn in this and the preceding chapters, are summed up here.

- It is shown to be possible to realise a Fuzzy Logic implementation by means of FuzzyTech of the most basic ways up to refined ways of reasoning about appropriate control actions.
- Patient specific quantitative relations can be implemented. Complicated non-linear relations between different variables are no problem anymore.
- Interpolation between situations that are familiar to the expert with respect to the corresponding control action is an advantage of a Fuzzy Logic implementation.
- Deriving the structure can be difficult for patients. It should be easier for doctors or expert-patients.
- The patient-specific implementation is lifestyle-dependent. A more extended lifestyle – offering the patient more choices in his life, maintaining the same control goals – requires a more complex model.
- These Fuzzy Logic implementations are uttermost transparent for both doctors as patients, and easy to adapt, if the patient's lifestyle changes or the patient's DM-system's characteristics changed.
- An example of a drawback of using FuzzyTech is the roundabout way of implementing primitive operations as the linear summation of two variables.
- The author's refined system illustrates a possibility for automated insulin corrections in course of time.

11 Safety of Fuzzy Logic controllers

This chapter deals with the safety for IDDM-patients, using control advice systems that are developed on the base of Fuzzy Logic, by means of FuzzyTech here. If the systems are properly used, they are considered to be safe. This is made plausible in the following.

The user may not make any mistake in choosing the right event, because this determines the choice of the subsystem. Also, the values for the respective input variables should be inserted correctly. Obviously the developed event related systems only could be used when the relevant event occurs. The system that brings out advice when one wakes up, cannot be used properly, for example, if about 2 hours before waking up, a small dose insulin is injected due to a high BG.

This, and other practical reasons, for example the absence of the computer (system), contributed to a relatively small test set (9 cases in one month). In these tests, a comparison between the author's own control action, and the advice of the system, is made. The author's and the system's results (almost!) completely resembled. For all clarity, the system is ought to work properly if, for (about) every situation, it resembles the control advices that the author would have given in the same situation.

Though, there aren't much experiments needed to conclude that the system works properly, because it is totally based on the author's knowledge. The author is seen as expert with the full knowledge of his way of controlling his DM-system. For some situations the author is rather sure about the desired control action. These cases are literally implemented in the system and the advices cannot even theoretically differ from the author's control actions. Some small difference in the outcome can be explained by

- different interpolation between known situations, and
- small nuance differences in the situation.

If the situation is somewhere in between other known situations, the author isn't able to perform an appropriate interpolation between the corresponding control actions. The Fuzzy Logic, eventual non-linear interpolation between two states is more confidential. On the other hand, the author is somewhat in advantage, because of the perception of small nuance differences in the situation what for no corresponding input variable exists. But, if the nuance is that influential, an input variable should be added to the model.

The system is fully transparent with regard to the way of reasoning and the contents of the rule blocks. The controllers structure corresponds to the patients reasoning, so if the model is correctly built, no dramatically mistake can be made in it's advices. Moreover, doctors can add or remove factors of influence at own insight, or change the rule block's contents. So, the doctor can construct a patient specific model that corresponds exactly with how he wants the patient to behave. If doctors are assumed to give safe advices, the Fuzzy Logic system that is constructed or validated by a doctor, are also safe.

The final conclusion with regard to the safety for the patients c.q. users is the following. **A doctor is ought to be able to construct a Fuzzy Logic controller. Fuzzy Logic patient specific controllers that are constructed or validated by a doctor are safe.**

12 Final conclusions

This master thesis in computer science aims at controlling insulin-dependent diabetes mellitus (IDDM). Controlling diabetes can be done in two directions:

1. model based, and
2. non-model based.

In the first case (1) the diabetes mellitus (DM-)system is modelled and appropriate control actions are derived out of this models. This approach is preferable to the latter because of its intuitive clearness, its physiological foundation and other reasons mentioned in section 3.1. In section 3.2 the author defined some factors of influence on the blood glucose (BG) level that have to be incorporated in a model, as measure to evaluate the appropriateness of the models currently available and described in literature.

A big problem in this area is the paucity of useful data. (So, the time course of a lot of BG, food, exercise and other relevant factors were kept up to date by the author (a diabetic himself) because it could eventually be of use.) Data merely about the course of BG was published yet when the author completed this thesis; indicating the premature progress in this branch of science. In section 3.3.6 coupling of a simple metabolic model (dynamical model) with a model of the action profile of subcutaneous injected insulin is proposed. Later on in the investigation of literature it appeared that research on this kind of models is far too premature to be useful for glycemic predictions or control actions. The predictive accuracies are very bad, even in the subjects that are the easiest to predict. Because of this and the limited time for this research, the other direction in this research is investigated.

In the second case (2) the DM-system considered more or less as a black box and is tried to construct a model of a feedback controller with the help of a human expert. Very little research is done in this direction.

Diabetics who are starting with self-regulation get minimal advices from the hospital and have to elaborate them eventually, with the help of a medical doctor, according to their lifestyle. Diabetics are ought to take their own decisions with regard to the determination and adaptation of the insulin dose for every injection.

This research showed that this way of reasoning about the correct control action could be modelled with Fuzzy Logic theory. The patient-specific implementation is lifestyle-dependent. A more extended lifestyle – offering the patient more choices in his life, maintaining the same control goals – requires a more complex model. The control actions that have to be taken according to the information of a hospital are implemented in Fuzzy Tech. Also the refined structure of a system (divided in three subsystems), which represents the author's reasoning at breakfast, is implemented (in two of the three cases). It appeared that more control actions than merely the insulin dose could be implemented. Examples are: postponement of meal and the amount of carbohydrates to consume. After the development of the breakfast controller it seems plausible that it is possible to develop an all-embracing controller that can be used during the whole day.

The author proposed an automated insulin dose correction mechanism that takes the non-stationary behaviour of the DM-system with regard to the relative need for insulin into account.

In chapter 7 the structure of the control system is derived out of the characteristics of the DM-system.

The author stated that the determination of the structure of the controller is a complex task; on the other hand, the FL-implementation is quite straightforward.

Although no other controllers using Fuzzy Logic theory are discovered in literature, it is the author's opinion that user-specific Fuzzy Logic IDDM controllers are a useful advice mechanism due to the following reasons.

- It could provide more insight in and support for the determination of adequate control actions to patients who are starting with self-regulation and to less capable patients.
- The communication between a doctor and a patient can be improved by a clear unambiguous way of communicating.

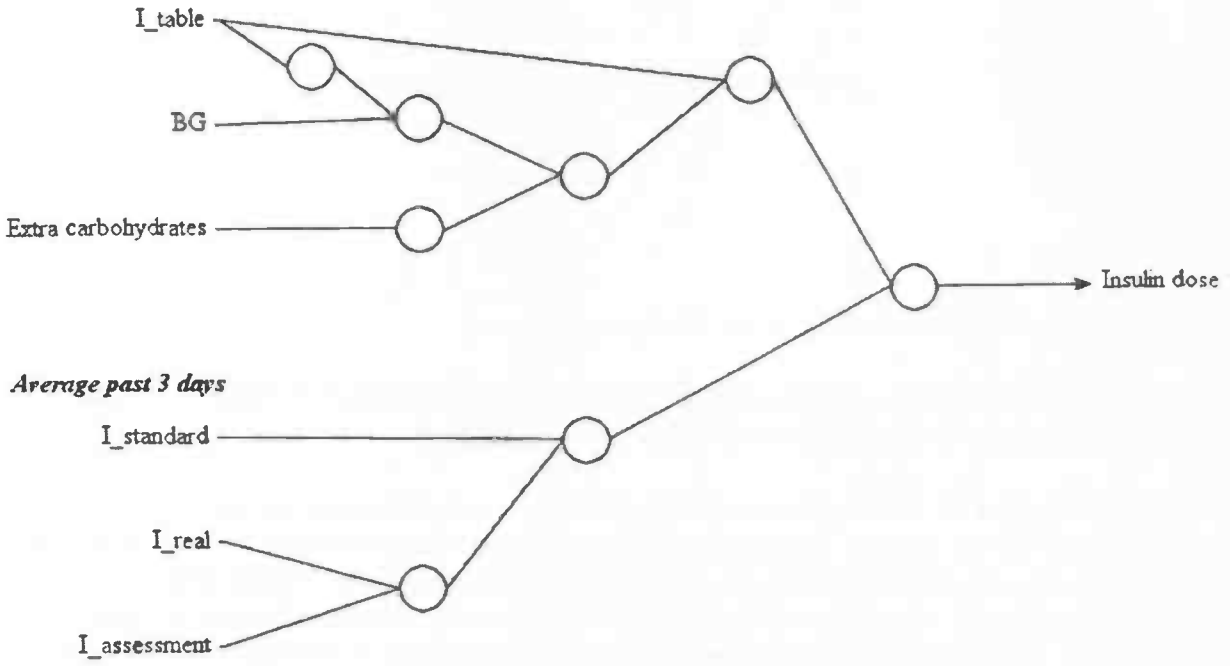
Moreover the implemented systems provide an (eventually non-linear) interpolation between known states, probably better than patients can.

About the safety of the controllers the following is concluded. A doctor is ought to be able to construct a Fuzzy Logic controller. Fuzzy Logic patient specific controllers that are constructed or validated by a doctor are considered to be safe or as safe as possible.

13 Future work

The continuation of this research would be the development of a type-I diabetic control advice-supporting tool. In first instance, this tool would produce a most basic system according to the patient specific parameters. Later on, this basis can be elaborated according to the patient's lifestyle. Although different kinds of control actions exist, the most important one is the determination of the insulin dose for an injection at a meal. Once established the structure for this advice, even more advices can be added, like the author did in the former chapters.

The first step would be the coupling of the most basic advice structure with the correction mechanism that provides a continual update of the relative need for insulin – where necessary (figure below).



Dependent on the patient's characteristics with regard to its DM-system, a first guess about the system's calibration can be done by the computer program. Examples of these characteristics are the patient's total daily amount of insulin, age, weight and body mass index. For an automated initialisation of the correction mechanism the author proposes the following.

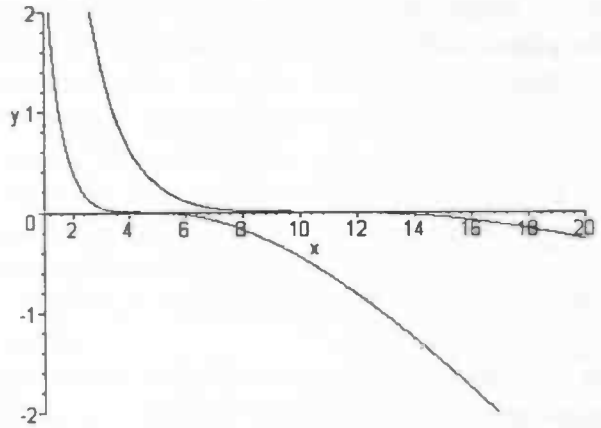
Proposal automated correction mechanism

Until now, the assessment of the insulin dose in the past three days is a subjective matter. In order to determine the assessment, and with this the dose compensation due to this assessment, in an unambiguous and sensible way, the following proposal for an automated initialisation of the correction mechanism is done. If necessary in the individual case, the values can be adapted according to the doctor's insight into the patient-specific characteristics.

For example, take one (or two) BG measurement(s), for example (1 and) 2 (or more) hours after the injection. This value(s) can be compared with the corresponding target BG level according to the following formula. It is derived of the *M-value* that was proposed by [24], discussed earlier in the chapter about the testing of the systems. The use of the formula is explained after showing the graph.

$$f(x, s) := -10 \frac{\ln\left(\frac{x}{s}\right)^3}{\ln(10)^3}$$, where x is a BG value and s is the aimed value.

Below $f(x, 4.4)$ and $f(x, 10.0)$ are plotted.



With $y = f(x, 4.4)$, in red, and $y = f(x, 10.0)$, in blue.

One could argue that $f(x, s)$ is the relative deviation of x in comparison with the target value s. This is an intuitive feeling; further research can be done here.

The initialisation of the insulin correction mechanism can be computed as follows. Let A be the average of the relative deviations on (for example) three successive days. Suppose the total daily amount of insulin to be D. The idea is that the maximum insulin adaptation upward is between 2% and 5% of D, and the maximum insulin adaptation downward between 5% and 10% of D. The maximum percentage depends on the amount of the injection that should be reduced. The greater this dose, the greater the maximum adaptation.

For example, if the dose that should be corrected is greater than 16 U (this value is also used in such a way in the Martini Hospital's starting-self-regulation advices), then an adaptation upward is 5% of D, and an adaptation downward is 10% of D. If the dose is smaller than 8 U, the respective values can be 2% and 5%.

Maybe a value of $A = 1.76$ or greater, is an appropriate value for a maximum adaptation of the insulin dose. To give an impression, if the target value is $s = 4.4$, and $1.76 = f(x_0, 4.4) = -f(x_1, 4.4)$ then the lower and higher values x_0 and x_1 are $x_0 = 1.21$ and $x_1 = 16.0$. In this way, the correction is done in a sensible, structured way.

Elaboration according to the patient's lifestyle

For every patient, a basic structure is defined according to the patient-specific parameters. The outline of the structure is shown in the figure above. With the help of insight in the patient's lifestyle, this structure can be elaborated. The reasoning about occurrences that happen just

sometimes or often (in contrast to "always" or "never"), and exert influence on the control action that has to be taken, have to be included in the structure.

In the former chapters, the outline of the structure if physical exercise and future activity were included, is described. Probably the outline and interconnection of the internal structure is the same for every diabetic, but the content of the rule blocks is expected to differ much between different kinds of persons. This structure can be used.

It is the expectation that the main structure (presence/absence of physical activity and future activity in patient's lifestyle) is easy to generate by asking the patient a couple of simple questions. A medical doctor or a trained diabetes nurse can do further patient-specific implementation.

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