DIAS
- the Diabetes Advisory System:

technical and physiological aspects of the system
and evaluation results obtained so far.

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Department of Medical Informatics and Image Analysis
& Virtual Centre of Health Informatics,
Aalborg University, 1998.
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1. Introduction.

Diabetes mellitus is one of the major chronic diseases and a growing public health problem in both developed and developing countries. A recent WHO expert group estimated that more than 100 million people will suffer from diabetes by the end of this century - 10-15% with the insulin dependent form. In Europe the prevalence of diabetes is 2-5 per cent of the adult population [WHO95]. Diabetes' direct costs in the U.S.A. in 1992 is estimated to represent 5.8 % of total personal health-care expenditures, which again represented over 14% of the GDP, and the indirect costs were even higher [ADA93, Blac93]. In Europe diabetes is estimated to consume about 10% of the total health care budget [Diab97]. The substantial loss of quality of life associated with diabetes is mainly due to the so-called late complications: blindness, kidney failure, amputations and circulatory diseases. Although recent studies [DCCT93, DCCT94] have shown that intensive diabetes treatment with the goal of maintaining blood glucose concentrations close to the normal range lead to a substantial reduction of the rate of the complications, this can be difficult to achieve using conventional means. These studies also showed that intensive treatment also leads to an increase in the frequency of severe hypoglycaemia. It is recognised that a number of patients may have poor control despite specialist care, and this along with devolution of care to non-specialists suggests that alternative interventions should be developed [Bind95].

Decision support systems provide a possible answer to this problem, and many solutions have been proposed over the years. Some of these are based on rules or algorithms for insulin dose adjustment based on expert knowledge [Sky181, Chan85, Schr85, Harv86, Chao89, Deut89, Deut90], and some have used predictions of blood glucose levels based on mathematical models of the carbohydrate metabolism [Swan82, Shim88, Berg89, Salz90, Lean91]. Other systems are based on a combination of the two approaches [Schn88, Berg90, Lehm91]. Despite the many lessons learned from this substantial work, none of the systems has gained widespread use or acceptance.

There may be several reasons for this apparent lack of success. One reason might be the difficulty in handling the interpatient and intrapatient variability, and other reasons might be the uncertainties in the data involved and the fact that the glucose metabolism is influenced by many factors, e.g. stress, fever, exercise and hormonal reactions to low blood glucose. Still other reasons for the evident lack of success might be the problems associated with evaluation of the safety and efficacy of the systems, which several authors have dealt with [Lund87, Mill88, Wyat90, Wyat94].

The present thesis is a review of the technical and physiological aspects of the Diabetes Advisory System (DIAS) and the evaluation results obtained so far. Each of the following sections is based on one particular paper: Sections 2 [Hejl97b] and 3 [Hejl98] outline the underlying metabolic model in DIAS and the general use of the system. Sections 4 [Hejl95a] and 5 [Hejl93] describe how theories were developed and implemented in order to reduce calculation time and enable the system to estimate parameters based on data from multiple days. Sections 6 [Hejl95b] and 7 [Hejl96a] give a description of how the system was optimised and evaluated on retrospective data and how this led to a new perception of the temporal relation between episodes of hypoglycaemia and periods with hyperglycaemia. Sections 8 [Cava96], 9 [Hejl98], 10 [Cava98] and 11 [Hejl97a] give a brief outline of 4 small clinical studies on prediction of unrecognised hypoglycaemia in out-patients in the UK, and on insulin dose advice in in-patients in Denmark, in out-patients in the UK, and in adolescent out-patients in Denmark. Since the hypothesis of the temporal relation between hypoglycaemia and hyperglycaemia is a major theme in the thesis (especially in Section 7, but also in Sections 9, 10, and 11), Section 12 gives a small review of the literature on the subject.
2. The metabolic model.

This section is based on Hejlesen et al. 1997 [Hejl97b], *DIAS - the Diabetes Advisory System: An outline of the system and the evaluation results obtained so far*. It gives an overview of the metabolic model, and how the relations in the model was derived from physiological studies reported in the literature.

The core of DIAS is a compartment model of the human carbohydrate metabolism, and Figure 2.1 shows the two compartments with the arrows indicating flow of carbohydrate in and out of the compartments. The model has two associated state variables: One state variable keeps track of the amount of carbohydrate in the gut compartment (CHO), and another keeps track of the amount of glucose in the blood compartment (BG).

In DIAS the differential equations, describing the flow in the compartment model, have been transformed into difference equations, and Figure 2.2 shows a one hour time slice for the difference model in DIAS:

Besides the two state variables, CHO and BG, the model also contains process variables: Glucose can leave the gut compartment by absorption from the gut, represented by the GUT-ABS process variable. The graph reveals the structure of the difference equations: Each process variable (a child variable), that receive an arrow from one or more (parent) variables, appears on the left side of one of the difference equations. The parent variables, from where the arrows come, appear on the right hand side of the same equation. For example, the GUT-ABS ($\frac{\Delta \text{CHO}}{\Delta t}$) is a function of the carbohydrate content in the gastrointestinal tract: $\frac{\Delta \text{CHO}}{\Delta t} = f(\text{CHO})$, which is shown in Figure 2.3 and which, at least partly, can be found in the literature [Boro87, Boro88, Benn89].

The rest of the glucose transport in and out of the blood compartment is represented by the four process variables below GUT-ABS. The division of the transport in these four components can largely be identified with different organ systems. The main motivation is however that with this division quantitative estimates can be found in the literature for clearance of glucose (RENAL-CL) [Gano83, Benn90], for insulin independent utilisation of glucose (INS-INDEP-UTIL) [Gott83], for insulin dependent utilisation of glucose (INS-DEP-UTIL) [Rizz81, Best81, Gott82, Gott84, Bell86], and for hepatic production of glucose (GLU-PROD) [Rizz81, Best81, Gott82, Gott84, Bell86].

In addition to state variables and process variables the model also contains input variables: The MEAL input variable illustrates how carbohydrate can enter the gastrointestinal tract (gut compartment) by ingestion of sugars, and it represents the amount of carbohydrate ingested at a given time. The INS-INJ input variable illustrates the injected insulin.

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**Figure 2.1** The flow of carbohydrate in the compartment model: Carbohydrate in the meals is added to the contents in the gut compartment, gut absorption adds to the contents in the blood compartment, and glucose utilisation removes carbohydrate from the blood compartment. From Hejl97b.
A one hour time slice for the difference model in DIAS. The unabsorbed carbohydrate in the gut (CHO) 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 CHO and blood glucose over the next hour. The 24 hour model in DIAS consists of 24 of these one hour time slices. From Hejl97b.

As indicated by ‘+’ or ‘−’, the equations used to calculate the state variables are also revealed by the graph in Figure 2.2. For example, the carbohydrate content in the gastrointestinal tract is a function of the 3 parent variables: \( \text{CHO} \text{ (HOUR 1)} = \text{CHO} \text{ (HOUR 0)} - \text{GUT-ABS} \text{ (HOUR 0)} + \text{MEAL} \text{ (HOUR 1)}. \)

The physiological variations between patients is expressed through the two parameters INS-SENS and NPH-MAX: The insulin sensitivity (INS-SENS) is a scaling factor that modifies the biological activity of the injected insulin (INS-INJ), thereby determining the amount of active insulin (ACT-INS). The NPH-MAX parameter is a factor that determines the time from an injection of intermediate type of insulin (NPH) to the maximum of the insulin absorption curve. Absorption curves for different types of insulin was constructed from curves found in the literature [Bind69, Köle78, Laur82, Krae84, Bind84, Hild84, Owen86, Vaag90a, Vaag90b].

The difference model in DIAS is implemented as a causal probabilistic network (CPN or Bayesian network), which gives it the ability to handle the uncertainty, for example, in blood glucose measurements or physiological variations in glucose metabolism. Whereas the arrows in Figure 2.1 shows the flow of carbohydrate in the physiological model, the arrows in Figure 2.2 reflect the presumed causalities: In the CPN language these causalities are specified as
tables of conditional probabilities: e.g. the gut absorption conditional on the carbohydrate content in the gastrointestinal tract, \( P(\text{GUT-ABS} \mid \text{CHO}) \). A more comprehensive exposition of the model can be found elsewhere [Hovo92, Hejl93, Andr94, Hejl95a].

![Figure 2.3](image)

**Figure 2.3** The absorption from the gut, GUT ABS, as a function of the carbohydrate content in the gastrointestinal tract, CHO. From Hejl97b.

### 3. General use of the system.

This section is based on Hejlesen et al. 1998 [Hejl98], *Using a double blind controlled clinical trial to evaluate the Diabetes Advisory System: A feasible approach?* It gives an overview of how the system is operated in three different modes.

The decision support system is operated in three modes: the learning mode, the prediction mode, and the advisory mode. In the learning mode standard data on blood glucose concentration, insulin injections and carbohydrate intake from one or more days are used to estimate the two parameters, INS-SENS and NPH-MAX.

In the prediction mode the estimated parameters for insulin sensitivity and time-to-peak of NPH-type insulin are used to make predictions of the blood glucose concentration, given the carbohydrate intake and insulin regimen of the subject. This mode can be used to predict unrecognised hypoglycaemia or to predict the effect of suggested changes in the insulin regimen or meals on the blood glucose concentration. In Figure 3.1A the blood glucose prediction for the patient on two daily doses, mixed insulin in the morning and NPH insulin before dinner, is shown together with the measured blood glucose. It can be seen that the prediction shows a high risk of hypoglycaemia before lunch and possibly also around 5 a.m. The tendency to hypoglycaemia before lunch was confirmed by the patient reporting symptoms of hypoglycaemia at that time, and Figure 3.1B shows how a different mixture of insulin in the morning (only 20%, instead of 30%, rapid-acting insulin), suggested by the doctor, seems to improve the situation.
Figure 3.1 Blood glucose measurements are shown as black squares connected by straight lines, rapid-acting insulin, Actrapid, as white bars, intermediate-acting insulin, NPH, as black bars, and the carbohydrate content of meals as hatched bars. 4 and 10 mmol/l blood glucose concentration is indicated by the dashed horizontal lines: the blood glucose should ideally remain between these values. A) The bold black curve is the blood glucose prediction, which shows a high risk of hypoglycaemia before lunch and possibly also around 5 a.m. B) Due to the risk of hypoglycaemia before lunch the patient is manually switched to a different mixture of insulin in the morning (20% instead of 30% rapid-acting insulin), and this seems to improve the situation. C) The result of an automatic adjustment procedure performed by the system, suggesting a reduction in the NPH insulin before dinner, from 10 units to 6 units, which seems to reduce the risk of nocturnal hypoglycaemia. From Hejl98.

In the advisory mode, a utility measure is minimised to find the insulin therapy which gives the least overall (predicted) risk of too low or too high blood glucose concentrations. This mode can be regarded as a special version of the prediction mode where the manually suggested changes in the insulin regimen are replaced with an automatic adjustment procedure performed by the system. In the present version of the system the automatic adjustment is allowed to change only the size of the insulin doses; but is not allowed to change the number of doses, their timing or the ratio in the mixtures. In Figure 3.1C data from the same patient as in Figure 3.1A and 3.1B are shown together with the result of an adjustment of the insulin dose, and it can be seen how the system, in addition to the manually suggested change in the ratio of the morning mixture, suggests some reduction in the NPH insulin before dinner, from 10 to 6 units, in order to avoid the predicted risk of nocturnal hypoglycaemia.

The outline of the general use of the system given above does not include a description of how the probabilistic aspects of the system are utilised and a more comprehensive exposition is given in the following sections.
4. Dynamic propagation.

This section is based on Hejlesen et al. 1995 [Hejl95a], Dynamic propagation in causal probabilistic networks with instantiated variables. It gives a description of how it was possible to combine a dynamically defined network, implemented without the use of Hugin, with a static network implemented in Hugin, thereby reducing the calculation time by several orders of magnitude compared to using Hugin alone.

Causal probabilistic networks (CPNs), also called Bayesian networks, have been used to build models of the physiology and pathophysiology of biological systems. These models can be used for diagnosis or for planning of therapy. For example, the MUNIN system diagnoses neuromuscular disorders, performing “at the level of an experienced clinical neurophysiologist” [Andr89]. As another example, the study of temporal aspects in medical reasoning led to the construction of DIAS.

In CPNs all variables are stochastic variables, linked by conditional probabilities, which, in DIAS, can be seen as a translation of the differential equations describing the physiological relations. Therefore, inference in the CPN is not made by solving differential equations, but rather by making a Bayesian updating of the probability distributions associated with the stochastic variables. If we assume that all variables are discrete stochastic variables, then the updating is in principle very simple. In an algebraic notation [Jens90] the initialisation and the stochastic inference is determined by two equations, that specify apparently simple matrix operations. Unfortunately the number of elements in the matrices, the state space, is equal to the product of the number of states of all nodes in the CPN, which makes direct application of these equations impractical in CPNs with more than a few tens of nodes.

The Hugin tool [Ande89] has been developed to make Bayesian inference in CPNs computationally practical. This tool is based on the development of methods for local belief updating in CPNs [Pear86, Laur88]. Roughly speaking, Hugin divides the set of variables in the CPN into a number of subsets, called cliques. The equations for initialisation and updating can then conveniently be applied to the cliques, supplemented by procedures that propagate evidence between the cliques. The size of the cliques depends on the topology of the CPN, and in some cases the cliques generated by Hugin are so large that the computations remain impractical.

The basic ideas.

When CPNs representing full scale medical problems are constructed the cliques generated are often too large to be practical. To reduce the computational effort in DIAS, two new ideas were used to model the insulin injections in DIAS. Together, the two ideas reduced the requirements for storage space for the cliques' state space in the DIAS CPN from an estimated size of $10^{55}$ elements to $10^7$ elements, which is within reach of current computer technology.

The first idea exploits the fact that when a stochastic variable in the network is instantiated, meaning that its current value is known, for example because it has been measured, then the CPN effectively changes topology: The d-separation properties of the CPN are modified [Pear88]. Under some circumstances, the CPN with some instantiated variables will generate smaller cliques.

The other idea is to allow a dynamic construction of CPNs. Instead of constructing one CPN that has to be able to deal with all possible relevant clinical situations, the CPN is divided into a static and a dynamic part. In DIAS the static part (built by using Hugin) represents a model of the patient's glucose metabolism and the dynamic part (built without using Hugin)
represents the patient's insulin injections, which may not only be different in timing and type of insulin for different patients, but may also differ from day to day for the same patient. It turns out, that when a suitable set of variables has been instantiated, it becomes particularly simple to construct a part of the CPN dynamically.

Static versus dynamic compilation.

Relative to Figure 2.2, Figure 4.1 shows a simplified version of the DIAS model only containing the elements required to illustrate the principle and with three time slices, each separated by one hour. The model arrows go from “parent” variables to “child” variables. The arrows indicate that for example the probability distribution for the state variable CHO (carbohydrate content in the guts) at time 1 (CHO-1) can be determined, conditional on the variable's parents: the carbohydrate content one hour earlier (CHO-0) and on the carbohydrate content of the meal eaten at time 1 (MEAL-1).

As described in Section 2 the other state variable, BG, represents the concentration of glucose in the blood. The arrows impinging on for example BG-1 state that the probability distribution for the blood glucose concentration at time 1 (BG-1) can be determined, conditional on four variables, CHO-0, BG-0, INS-SENS, and INS-ABS-0. INS-SENS represents the patient's sensitivity to insulin, and INS-ABS-0 represents the average rate of insulin absorption during

![Diagram](Diagram.png)

**Figure 4.1** Three time slices in the DIAS CPN. The dashed line divides the CPN into the upper "static" part that describes the metabolism of glucose, and the lower "dynamic" part that describes the injection and absorption of insulin. Pale arrows indicate that, as described in the previous section (Figure 2.2), DIAS consists of 24 of these one hour time slices. From Hejl95a.
the first time slice. The insulin is absorbed from the subcutaneous reservoirs created by the insulin injections, INS-INJ. Each injection creates a reservoir, and the arrows in the model state that the insulin absorption during a time slice depends on the absorption from the reservoirs created by all previous injections.

The DIAS CPN, of which one time slice is shown in Figure 2.2 and 3 time slices are shown in Figure 4.1 (both “static” and “dynamic” part), has about 500 nodes with an average of about 10 states each. The state space of DIAS thus has a size of about $10^{500}$, a number that dwarfs the number of elementary particles in the universe. If Hugin is used to compile this CPN, i.e. to form and initialise the cliques, this gives cliques with a total state space of about $10^{55}$ elements. Although this is a remarkable reduction, compared to the original $10^{500}$, the problem is that it is still beyond current computer technology to store a state space of this size. This is in contrast to the $10^7$ elements required to store the cliques from the part of the CPN above the dashed line, in the following referred to as the static part of the CPN. Adding the insulin injection variables, in the following referred to as the dynamic part of the CPN, creates many “cycles” [Jens90] which greatly increases the size of the cliques.

As mentioned, instantiation of variables may simplify a CPN, and in DIAS the insulin injection variables in Figure 4.1 in the dynamic part are instantiated. This is reasonable in the

Figure 4.2 Instantiation of the INS-INJ variables makes it possible to restructure the DIAS CPN, achieving a reduction of total state space to about $10^{50}$. Each INS-INJ variable has been duplicated, once for each of its children. From Hejl95a.
sense that if we for example wish to use the CPN for simulating blood glucose, then it can be assumed that meals and insulin injections are known. Instantiation of the INS-INJ variables modifies the d-separations in the CPN [Pearl 1988]. All d-connections going through the INS-INJ variables are eliminated. The CPN in Figure 4.2 is constructed from the CPN in Figure 4.1 by making additional copies of the INS-INJ variables, one extra copy for each INS-ABS variable that receives an arrow. Inspection of the two CPNs reveals that they have the same d-separation properties, and if all copies of a given INS-INJ variable are instantiated to the same value, then the CPNs in Figure 4.1 and Figure 4.2 have identical properties. If Hugin is used to compile the CPN in Figure 4.2, instead of the CPN in Figure 4.1, this leads to a reduction of total state space by a factor of $10^5$ to about $10^{50}$. Unfortunately it is still not possible to handle a state space of this size.

Implementation of the dynamic propagation in DIAS.

The calculations in the dynamic part and on the border between the static and the dynamic part can, without using Hugin, be simplified to 3 steps given that all INS-INJ variables in the dynamic part are instantiated:

1) The specification of the insulin absorption, given the insulin injections, is such that the probability distributions, $P(INS-ABS \mid INS-INJ)$, can very easily be calculated by adding 10 - 20 normally distributed variables. These variables are obtained by sampling the absorption curves for the insulin injections in a 4-day period prior to the actual time for the insulin absorption.

2) The INS-ABS variables in the static part of the model are multiplied by these probability distributions and

3) divided by the a priori probability distributions of the INS-ABS variables.

Hugin can then be used to calculate the probabilities in the static part of the model, which means that only a state space of $10^7$ has to stored. A more comprehensive exposition of the principles and a full proof of correctness can be found elsewhere [Hejl95a].

In DIAS the assumption that the variables, representing insulin injections, are instantiated has proven very useful. The assumption is valid when the CPN is used to estimate e.g. insulin sensitivity parameters or to predict the time course of blood glucose. It is also true when the CPN is used to adjust the doses of the injected insulin. In that situation the insulin injections are considered to be decision variables, i.e. variables whose value can be determined by a decision. In the traditional influence diagram approach to therapy planning, the decision variables are not considered to be instantiated [Howa84], but in an alternative approach to planning [Andr92b] it is possible to assume that the decision variables are instantiated. As described in the following this makes it possible to use the CPN also for planning of insulin therapy.
5. A learning procedure for multiple observations.

This section is based on Hejlesen et al. 1993 [Hej93], Implementation of a learning procedure for multiple observations in a Diabetes Advisory System based on causal probabilistic networks. It describes the importance of preserving information on both the patient specific means and standard deviations of the parameters, and how this was obtained by implementing a hierarchical model of the parameters.

The outline of the general use of the system given in Section 3, did not include a description of how the probabilistic quality of the system is utilised. Some of the important aspects are connected to estimating the standard deviation of the insulin sensitivity, and thereby estimating the probability distribution of the predicted blood glucose, which again should be discussed in combination with the automatic adjustment procedure for the insulin doses.

A probabilistic approach to decision theory.

The penalty function shown in Figure 5.1 describes the suggested relation between the blood glucose level and the expected loss of life or quality of life, and it has a resemblance to the M-value [Schl65]. The function represents a subjective opinion on the detrimental effect of different blood glucose concentrations. Given the penalty function and a predicted probability distribution for the blood glucose in a 24 hour period, the penalty score, also called the risk, for the period can be calculated. This is done by integrating the product of the penalty function and the predicted blood glucose distribution for each time slice and then adding the risk for each time slice to give the total 24 hour expected risk or penalty score. The automatic adjustment of the insulin doses is then implemented as an iterative procedure of repeated simulations with different insulin doses to identify the insulin doses, which minimises the total risk.

It should be noted that the penalty function rises more steeply for lower blood glucose than for higher, and that the system therefore in the adjusting procedure for smaller standard deviations of the blood glucose would aim at higher insulin doses, i.e. lower predicted blood glucose, than it would for larger standard deviations. This behaviour seems to be in accordance with good medical practice. The reason for this behaviour can be understood from a simple example with only one time slice, and assuming a normal distribution of the blood glucose. With a standard deviation of zero, it can be seen that the system in advisory mode would aim at a mean of 6 mmol/l bringing the penalty down to zero (A in Figure 5.1). If the standard deviation is larger, for example 3 mmol/l, the penalty would be larger too, and the minimal penalty is obtained with a mean blood glucose of approximately 7.5 mmol/l (B in Figure 5.1). The mean is shifted up to keep a respectful distance to the steep left hand side of the penalty curve. Since a large standard deviation in the insulin

![Figure 5.1](from Hej93)
sensitivity gives a large standard deviation in the predicted blood glucose, then a large standard deviation in the insulin sensitivity makes it advantageous to aim for a relatively high blood glucose.

Figure 5.2A shows the result of an automatic adjustment of insulin doses. Running the system in the advisory mode was performed with a priori mean (i.e. equal to the diabetic population average) and a standard deviation of 34% on the insulin sensitivity. The average predicted blood glucose resulting from these "optimal" insulin doses is 9.74 mmol/l with a total insulin dose of 32.3 U. If the insulin sensitivity were known with certainty, i.e. a standard deviation of zero, then the optimal doses would give an average blood glucose of 8.3 mmol/l with a total insulin dose of 35.5 U, as shown in Figure 5.2B. This illustrates that, when the insulin sensitivity is known better, then the system "dares" to be more aggressive in the insulin therapy, or in other words that a reliable estimation of the standard deviation is important.

Implementation of a hierarchical model of the parameters.

Often, measured blood glucose values (and data for meals and insulin regimen) from more than one day are available. A typical example is an ambulatory patient, seeing the doctor and bringing measured blood glucose for four days in the last month.

In order to preserve information on both the means and standard deviations of the parameters, a hierarchical model of the parameters was implemented. Others have built hierarchical models, where they use the different levels to model the population distribution in relation to the patient specific parameters [Bell91]. The example with the insulin sensitivity will be used to illustrate the approach. Using a simplified CPN, Figure 5.3 shows the relations between the a priori knowledge, the

![CPN diagram](Figure 5.3 A CPN estimating insulin sensitivity from one day. From Hejl93.)
insulin sensitivity parameter and the observed blood glucose measurements in the case with only learning from one day. It can be seen that the estimated insulin sensitivity to be used for simulations and adjustments are directly derived from the insulin sensitivity on this one day. In probabilistic terms, the estimated insulin sensitivity is the product of the a priori distribution of the insulin sensitivity and the likelihood of the insulin sensitivity, given the data. Assuming a normal distribution of the insulin sensitivity, leads to the model, shown simplified in Figure 5.4, which has the desired property of preserving information on both mean and standard deviation. Here, the estimated insulin sensitivity is derived from the patient specific parameters, describing the mean and day to day standard deviation of the insulin sensitivity. The estimated insulin sensitivity to be used for simulations and adjustments are derived from the parameters, describing the mean and the day to day standard deviation. The price to pay for this approach is that, in contrast to the situation in Figure 5.3, the estimated insulin sensitivity on Figure 5.4 is forced to have a normal distribution. It should be noted that any parametric description could be used instead of the normal distribution.

As shown in Figure 2.2, the present version of DIAS has two adjustable parameters: the insulin sensitivity and the absorption speed of the NPH insulin. In order to handle more than one parameter without assuming independence between the parameters, the model has to handle the joint distributions of the parameters, i.e. to model the correlation between the individual parameters. The two-dimensional normally distributed parameters, implemented in DIAS, are shown simplified in the CPN formalism in Figure 5.5.

**Figure 5.4** A CPN estimating the insulin sensitivity from multiple days. The patient mean and standard deviation (sd) are included. From Hejl93.
6. Optimisation and retrospective evaluation.

This section is based on Hejlesen et al. 1995 [Hejl95b], Optimization and evaluation of a probabilistic computer model of the glucose metabolism. It describes how the model was optimised by fitting it to collected data, and how it was evaluated by comparing the prediction errors to the intrapatient variability. It is suggested that the model, when compared to the intrapatient variability, does not seem to have systematic errors, large enough to be significant.

In order to judge the value of the metabolic model in the Diabetes Advisory System as an aid to adjust the insulin regimen for a patient with diabetes, it is important to know the quality of the predictions: If the blood glucose predictions, given known data on meals and insulin injections, are good, then it is likely that the simulations, given suggested meals and insulin doses, will be good too. As described in Section 3, the basic idea is then to use the system in an adaptive process adjusting the insulin doses or the meals for the given patient in order to obtain a desirable predicted blood glucose profile.

![Figure 6.1 Mean of the physiologically based endogenous glucose balance in the initial model. From Hejl95b.](image-url)
**Optimisation of the endogenous balance.**

Based on the input data: the type, timing and amount of insulin injections, and the timing and amount of carbohydrate intake, the model for each 1 hour time step calculates the change in the probability distribution of the blood glucose concentration and thereby predicts the resulting blood glucose profile for the 24 hour period. This hourly change in the blood glucose concentration is depending on the blood glucose concentration itself and on the insulin concentration in the body.

As described in Section 2 the initial model was based on quantitative estimates of the physiological relations found in the literature. However, the information available from these sources is quite sparse, and therefore had to be inter- and extrapolated in order to get the information needed for building the model. Figure 6.1 shows the relationship between the concentrations of glucose and insulin in the blood and the endogenous balance of blood glucose in the initial model. The endogenous balance is the balance of blood glucose given no carbohydrate absorption from the gut, and is given by the variables RENAL-CL, INS-INDEP-UTIL, INS-DEP-UTIL and GLU-PROD in Figure 2.2.

Using ‘representative’ data from patients with insulin dependent diabetes admitted to hospital for regulation of their diabetes, the endogenous balance was optimised. The term ‘representative’ reflects that the data was selected in order to make it equally reflect the whole data material from all patients. It should be noted that since the system does not (yet) model the reactions to hypoglycaemia (i.e. an elevated blood glucose level lasting several hours and caused by a hormonal reaction to an incidence of a very low blood glucose level), pronounced hypoglycaemic counter-regulations were excluded from the material. These hypoglycaemic reactions are discussed more thoroughly in the next section.

The ‘predictive power’ of the model was described by fitting the model to the data from one 24 hour period, and then comparing the mean of the predicted probability distribution from the model for the following 24 hour period to the measured blood glucose values. When describing the prediction error of the model, three different methods of measurement were used.

1) The root mean square difference between the mean of the predicted blood glucose concentration and the blood glucose measurements - the *RMS error* ($\sigma_m$).

2) The average of the numeric difference between the mean of the predicted blood glucose concentration and the blood glucose measurements - the *error*.
3) The average of the difference between the mean of the predicted blood glucose concentration and the blood glucose measurements - the offset.

Table 6.1 gives a summary of the results obtained before and after optimising the model, and the optimal endogenous balance is shown in Figure 6.2.

Retrospective evaluation of the metabolic model.

Using ‘periodic’ data from the same 24 patients the system was evaluated by comparing prediction errors to the patient variability. The term ‘periodic’ reflects that the data was selected from periods where the meals and the insulin doses were the same for two or more consecutive days, i.e. the regimen was periodic with a 24 hour period length. Again it should be noted that pronounced hypoglycaemic counter-regulations were excluded from the material, and that they will be discussed more thoroughly in the next section.

To describe the variability of the blood glucose measurements the intrapatient variability, $\sigma_{ip}$, was calculated as the RMS deviations of the blood glucose measurements, over several days (i), relative to the mean blood glucose $x_j$ at the same time (j):

$$\sigma_{ip}^2 = \frac{1}{N} \sum_{ij} (x_{ij} - x_j)^2$$

The intrapatient variability, $\sigma_{ip}$, was then compared with the prediction error of the metabolic model, $\sigma_m$, for the days with periodic regimen (Table 6.2). It can be shown [Hejl95b] that if there had been a significant error in the metabolic model this would have increased the RMS error ($\sigma_m$) making it significantly larger than $\sigma_{ip}$.

Table 6.2 The intrapatient variability compared to the predictive power of the final model using periodic data. All figures in mmol/l. From Hejl95b.

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<thead>
<tr>
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<th>RMS error</th>
<th>error</th>
<th>offset</th>
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<tbody>
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<td>2.07</td>
<td>-0.81</td>
</tr>
<tr>
<td>intrapatient variability</td>
<td>2.89</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
7. The hypoglycaemic counter-regulation.

This section is based on Hejlgesen et al. 1996 [Hejl96a], Analysing the hypoglycaemic counter-regulation: A clinically relevant phenomenon? It contains an analysis of the temporal relation between episodes of hypoglycaemia and counter-regulations, i.e. episodes of hyperglycaemia. The relation was assessed by statistical methods based on the metabolic model in DIAS. It was found that a typical hypoglycaemic counter-regulation begins 6 to 8 hours after the hypoglycaemia, that it lasts 16 to 18 hours, giving a total duration of 24 hours, and that it elevates the blood glucose by 4 to 10 mmol/l.

In the data material selected for optimisation and evaluation of the model, data with pronounced hypoglycaemic episodes were, as described in the previous section, excluded. These data were later used to analyse the temporal relation between hypoglycaemic episodes and counter-regulations, i.e. episodes of hyperglycaemia.

Somogyi reported in his classic paper published more than 30 years ago [Somo59], how insulin over-treatment could be the direct cause of hyperglycaemia in insulin dependent diabetes. This observation has been interpreted as a counter-regulatory mechanism that is triggered by a hypoglycaemic episode. Most physiological studies have focused on the 6 to 12 hours following an induced hypoglycaemia, and a number of hormones and mechanisms have been identified that have this hyperglycaemic effect [Boll83, Boll84a, Laur85, DeFe86, Amie93].

Although Somogyi’s conclusions were general, i.e. that the hyperglycaemia could be caused by hypoglycaemia taking place any time of the day, the concept of the ‘Somogyi effect’ or the ‘rebound hyperglycaemia’ has been attached to one particular concept: that over-treatment with insulin can result in unrecognised nocturnal hypoglycaemia, which in turn can generate a counter-regulatory response leading to fasting hyperglycaemia in the early morning. Most clinical studies have focused on this particular relation, and taken together they do not support a significant role for rebound hyperglycaemia [Tord87, Pram85, Lerm88, Hirs90, Boll92].

A prominent example, where the present study suggests that the hypoglycaemic counter-regulation does play a very significant role, can be seen in Figure 7.1 for a hospitalised patient, NVH. The data illustrates how the patient had very stable blood glucose measurements until February 14, and that the blood glucose started to oscillate on February 15. On February 19 the regimen was changed a little, but, although the phase of the

![Figure 7.1](image)

Figure 7.1 Data for NVH from February 13 to 22, showing blood glucose measurements as black squares connected by straight lines, rapid acting insulin, Actrapid, as white rectangles and intermediate acting insulin, NPH, as black rectangles. 4 and 10 mmol/l is indicated by horizontal lines. It can be seen that the blood glucose on February 15 suddenly starts to oscillate. From Hejl96a.
oscillations was shifted, it did not solve the problem, and the patient was discharged from hospital on February 22.

The clinical importance of avoiding both hyper- and hypoglycaemia has been demonstrated in recent studies: there is a clear correlation between high levels of blood glucose and complications such as blindness, renal failure, amputations and heart disease [DCCT93], and it is shown that recurrent hypoglycaemia may lead to loss of the ability to recognise impending hypoglycaemia, which may, for example, have tragic consequences while driving [Cran94].

Methods.

From patients with pronounced hypoglycaemic counter-regulations, like NVH, the hypothesis was formulated that a typical counter-regulation begins 6 to 8 hours after the hypoglycaemia, that it lasts 16 to 18 hours, giving a total duration of 24 hours, and that it elevates the blood glucose by 4 to 10 mmol/l. This hypothesis was tested by statistical methods based on the predictions from DIAS. Usually the parameters in the DIAS model are adjusted to fit each individual patient, but in order to put as much emphasis on the physiological background knowledge as possible, the parameters were fixed to the mean of the a priori probabilities. For each hypoglycaemic attack, the blood glucose deviations, i.e. the difference between the measured data and the simulated blood glucose profile, were calculated for the following 30 hour period, and two-sided t-tests were made on the blood glucose deviations comparing data from a 6 hour interval, starting at the hypoglycaemic attack, with data from an interval from 10 to 20 hours after the attack. Figure 7.2 shows data and simulation for NVH: The hypoglycaemia is measured at 7 a.m., and the two intervals are indicated at the bottom of the figure.

Data on measured blood glucose, insulin injections, and meals from 20 Danish patients with insulin dependent diabetes mellitus, IDDM, consecutively admitted to hospital for regulation of their diabetes were collected. The patients selected were kept in one out of three types of insulin regimens. The first type of regimen consisted of approximately 8 doses of Actrapid per day (x8 or intensive regimen), the second type consisted of 3 doses of Actrapid given during the daytime and 1 dose of NPH given just before bedtime (x4 or basal bolus regimen), and the third type of regimen consisted of various combinations of 2 or 3 doses of Actrapid, NPH and mixed insulin (x2/x3 or conventional regimen). Most of the patients were on the x8 regimen at the start of admission and then transferred from the x8 regimen to the x4 regimen.

### Table 7.1 Characteristics for the 8 sets of data, showing insulin regimen and time of hypoglycaemic attacks.

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>EKR</th>
<th>GJ</th>
<th>HJ</th>
<th>HTS</th>
<th>MC</th>
<th>NVH</th>
<th>SDO</th>
<th>SS</th>
</tr>
</thead>
<tbody>
<tr>
<td>days in x8 regimen</td>
<td>-</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>-</td>
<td>4</td>
</tr>
<tr>
<td>days in x4 regimen</td>
<td>14</td>
<td>5</td>
<td>9</td>
<td>6</td>
<td>7</td>
<td>-</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>days in x2/x3 regimen</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>9</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>time of hypoglycaemic attacks</td>
<td>12 a.m. 1 p.m. 1 p.m.</td>
<td>7 a.m.</td>
<td>3 a.m. 11 a.m. 7 a.m.</td>
<td>3 p.m. 10 a.m. 10 a.m.</td>
<td>6 a.m.</td>
<td>11 a.m. 11 a.m. 3 a.m. 7 a.m.</td>
<td>4 a.m.</td>
<td>3 a.m. 7 p.m.</td>
</tr>
</tbody>
</table>
or, for a few patients, to the x2/x3 regimen. Some patients were kept on the x4 or x2/x3 regimen during the whole stay, and all patients left the hospital with the x4 or x2/x3 regimen.

The data were examined in order to find patients on the x4 or x2/x3 regimen for 2 or more days with one or more measured hypoglycaemic episodes, defined as measured blood glucose below 3.5 mmol/l. In the material eight patients were found to comply with these criteria, each showing 1 to 4 hypoglycaemic attacks. In order to simplify the analysis, 2 or more measured blood glucose values below 3.5 mmol/l, in an interval of less than 8 hours, were regarded as one attack taking place at the time of the lowest value. The characteristics for the 8 sets of patient data are shown in table 7.1.

Results.

As seen in table 7.2, a t-test on all the data from all eight patients was very significant, p < 0.000001, only 6 out of 18 individual attacks were significant (t-test, p < 0.05), and the t-test values for four out of eight patients were significant. Two more patients seemed to have obvious but not statistically significant counter-regulations (due to sparse data). The average deviation profile for all the attacks from all the patients is shown in Figure 7.3, and visual inspection of these data and the 4th order polynomial regression curve seems to confirm the t-test analysis (r = 0.72, p < 0.001). Comparing day-time and nocturnal hypoglycaemia showed no difference in the resulting counter-regulations.

Even though the results clearly supported the hypothesis regarding the timing of the event - that an average counter-

![Figure 7.2 Data and the simulation, a thick black curve, for NVH at February 21, the data showing a hypo at 7 a.m. The 0-6 and 10-20 hour intervals are indicated at the bottom of the figure: 7 a.m. to 1 p.m. and 5 p.m. to 3 a.m. From Hejl96a.](image1)

![Figure 7.3 The deviation data for 30 hours following the hypoglycaemia is averaged and a 4th order polynomial regression curve is fitted. Hours relative to the hypo is on the x-axis, and the blood glucose deviation, measured minus predicted, in mmol/l is on the y-axis. Adapted from Hejl96a.](image2)
Table 7.2 The first column lists the patient IDs for the 18 attacks in the study, and the next 5 columns give the calculated deviations, data minus predicted blood glucose, for the measurements in the interval from 0 to 6 hours after the hypoglycaemia, i.e. the first figure in each row is the deviation for the hypoglycaemia. The next two columns list the mean deviation for each attack and for each patient for the 0 to 6 hour interval. The following columns list the same deviations for the interval from 10 to 20 hours after the attack. The last three columns list the t-test values for each attack (if available), for each patient, and for all the patients. The significance level has been set to $p < 0.05$, and significant values are marked with a ‘V’. The four rows at the bottom list the mean and the RMS of the deviations for the two intervals, and the mean and the RMS of the deviations at the time of the hypoglycaemic episodes. All figures on data, means, and RMS are in mmol/l.

<table>
<thead>
<tr>
<th>patient ID</th>
<th>deviations 0 - 6 hours</th>
<th>deviations 10 - 20 hours</th>
<th>2-sided t-tests</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean 1.2</td>
<td>0.6</td>
<td>6.3</td>
</tr>
<tr>
<td>EKR</td>
<td>2.0</td>
<td>0.3</td>
<td>1.2</td>
</tr>
<tr>
<td>GJ</td>
<td>-3.0</td>
<td>3.0</td>
<td>3.2</td>
</tr>
<tr>
<td>HJ</td>
<td>-1.6</td>
<td>-2.1</td>
<td>0.0</td>
</tr>
<tr>
<td>HTS</td>
<td>0.8</td>
<td>1.3</td>
<td>-0.25</td>
</tr>
<tr>
<td></td>
<td>-0.4</td>
<td>2.5</td>
<td>1.2</td>
</tr>
<tr>
<td></td>
<td>-1.2</td>
<td>1.3</td>
<td>0.4</td>
</tr>
<tr>
<td>MC</td>
<td>-3.8</td>
<td>-0.5</td>
<td>3.3</td>
</tr>
<tr>
<td>NVH</td>
<td>-2.8</td>
<td>-5.7</td>
<td>-4.3</td>
</tr>
<tr>
<td></td>
<td>-1.4</td>
<td>-6.4</td>
<td>-3.9</td>
</tr>
<tr>
<td></td>
<td>-2.8</td>
<td>-2.6</td>
<td>-3.8</td>
</tr>
<tr>
<td></td>
<td>-3.0</td>
<td>-3.6</td>
<td>-3.2</td>
</tr>
<tr>
<td>SDO</td>
<td>-0.4</td>
<td>1.4</td>
<td>0.5</td>
</tr>
<tr>
<td>SS</td>
<td>-3.2</td>
<td>-1.6</td>
<td>-0.9</td>
</tr>
<tr>
<td></td>
<td>-1.0</td>
<td>-2.6</td>
<td>0.5</td>
</tr>
</tbody>
</table>

| mean deviations | 0.2 | 5.0 | |
| RMS deviations | 3.0 | 6.2 | |
| mean deviations | -1.4 | 2.5 | |

regulation begins 6 to 8 hours after the hypoglycaemic episode and that it lasts 16 to 18 hours - the magnitude of the reactions differed from patient to patient: For the six patients, who had obvious hypoglycaemic counter-regulations, the magnitude of the average counter-regulation for a given patient was between 4 mmol/l and 10 mmol/l above expected blood glucose levels. Two patients seemed to have no or infrequent counter-regulations.
Data for SS on February 12 to 17, showing a relatively stable blood glucose in the regimen consisting of 100% rapid acting insulin February 12 and 13. The daily insulin dosage is then increased, from approximately 46 units to 60 units, when shifted to the regimen consisting of both rapid and intermediate acting insulin, and the blood glucose starts to oscillate. From Hejl96a.

Modelling the hypoglycaemic counter-regulation.

Since there are only a limited number of blood glucose measurements per day, it was also tried to use the metabolic model to estimate the exact time of the hypoglycaemic attacks and to model the following hypoglycaemic counter-regulation. Data from the patient SS was used to illustrate these two points:

1) Figure 7.4 shows the data from SS, and it can be seen how the shift from the regimen consisting of 100% rapid acting insulin to a regimen consisting of both rapid and intermediate acting insulin (by mistake ?!) led to an increase in the total daily insulin dose from approximately 46 units to 60 units. According to a visual inspection, the hypoglycaemia, at 3 a.m. on February 14, leading to a counter-regulation starting some time late in the evening, is not in accordance with the 6-8 hour delay of the hypothesis. The simulation for February 14 and 15 is shown in Figure 7.5A, and it can be seen that the measured hypoglycaemia, at 3 a.m. on February 14, is not confirmed by the model. On the other hand the model predicts a severe hypo around 2 p.m., and the blood glucose data on February 15 are much higher than predicted. The simulation assuming the hypo around 2 p.m. and modelling the counter-regulation hypothesis by adding glucose, a 1.2 mmol/kg/h 'metabolic irregularity', in an 18 hour interval starting 8 p.m. February 14 and ending 2 p.m. February 15, as indicated by the thick black trapezoid graph. From Hejl96a.
very severe hypoglycaemia half a day later, around 2 p.m., and this hypoglycaemia is in good accordance with the hypothesis:

2) Given the hypoglycaemia at 2 p.m. on February 14, Figure 7.5B shows a prediction including the hypothesis in the model: that a typical counter-regulation begins 6 to 8 hours after the hypoglycaemic attack and that it lasts 16 to 18 hours. The counter-regulation was simply modelled by adding glucose, 1.2 mmol/kg/h, to the blood compartment, and it can be seen that the implementation of the hypothesis dramatically improves the prediction.


This section is based on Cavan et al. 1996 [Cava96], Use of the DIAS model to predict unrecognised hypoglycaemia in patients with insulin-dependent diabetes. It describes how DIAS was used to predict blood glucose profiles in eight patients with well-controlled IDDM. DIAS predicted nocturnal hypoglycaemia in six patients and daytime hypoglycaemia in one out of the eight patients. The occurrence of nocturnal hypoglycaemia was not recognised by the patient or suspected by their doctor but was subsequently confirmed by blood testing in five out of six patients. The ability of DIAS to identify such periods of hypoglycaemia with reasonable accuracy illustrates how the system may provide reliable decision support to clinicians.

Methods.

Eight patients with insulin-dependent diabetes mellitus with HbA1 < 10% (representing good glycaemic control, reference range 5.4 to 7.6%) were recruited from the diabetic clinic at St Thomas’ Hospital, London. On recruitment they were asked to collect the following data for four consecutive weekdays: four blood glucose measurements per day (before meals and before bed) and full details of meals and insulin injections. They were asked to record any hypoglycaemic attacks.

Patients were seen within a week following the data collection period. Recorded blood glucose values, insulin injections and carbohydrate intake, assessed by a dietician, were entered into DIAS and a simulation of the blood glucose profile over the four day study period was generated.

Patients for whom the model predicted hypoglycaemia (blood glucose below 3 mmol/l) which was not documented by blood glucose measurement were asked to record four daily blood tests for a further four day period and, in addition, to test their blood at the time hypoglycaemia was predicted. In order to avoid introducing expectation of hypoglycaemia, patients were not advised of the reason for the tests at these times, but only that they would assist in verifying the model.

Results.

DIAS predicted unrecognised hypoglycaemia in seven of the eight patients: In one patient around midday and in six patients at night, at times ranging between 0200 to 0500 hrs. None had been aware of nocturnal hypoglycaemia and only four had reported any hypoglycaemia during the study period. In only one patient was no hypoglycaemia predicted by DIAS or recorded by the patient. Study of previous records showed that four patients in whom recurrent hypoglycaemia was predicted had reported loss of symptoms and one had reported nocturnal hypoglycaemia. All data regarding reported and unrecognised hypoglycaemia are summarised in Table 8.1.
The six patients in whom nocturnal hypoglycaemia was predicted by DIAS proceeded to further study. When asked to set an alarm clock and measure their blood glucose concentration at the exact time hypoglycaemia was predicted by DIAS, all did so on at least one night. Table 8.2 summarises the results. On at least one occasion in five of the six patients, the tests confirmed the hypoglycaemia predicted by DIAS.

**Table 8.1** Relationship between reported hypoglycaemia, unrecognised hypoglycaemia and history of hypoglycaemia unawareness or nocturnal hypoglycaemia in each subject. From Cava96.

<table>
<thead>
<tr>
<th>PATIENT</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>no of reported hypoglycaemic episodes over 4 days</td>
<td>3</td>
<td>0</td>
<td>4</td>
<td>4</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>unrecognised hypoglycaemia predicted by DIAS</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>previously reported hypoglycaemia unawareness (HU) or nocturnal hypoglycaemia (NH)</td>
<td>HU</td>
<td>HU</td>
<td>HU</td>
<td>NH</td>
<td>nil</td>
<td>nil</td>
<td>nil</td>
<td>HU</td>
</tr>
</tbody>
</table>

**Table 8.2** Mean early morning and late evening blood glucose measurements of the six patients in whom unrecognised nocturnal hypoglycaemia was predicted, together with the predicted time of hypoglycaemia. The number of night-time tests performed is shown together with their values. From Cavan et al. 1996.

<table>
<thead>
<tr>
<th>PATIENT</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>late evening blood glucose (mmol/l)</td>
<td>7.6</td>
<td>7.8</td>
<td>11.3</td>
<td>4.3</td>
<td>6.8</td>
<td>8.3</td>
</tr>
<tr>
<td>early morning blood glucose (mmol/l)</td>
<td>6.1</td>
<td>6.1</td>
<td>5.2</td>
<td>10.3</td>
<td>8.4</td>
<td>11.6</td>
</tr>
<tr>
<td>predicted time of hypoglycaemia</td>
<td>0400</td>
<td>0200</td>
<td>0500</td>
<td>0200</td>
<td>0200</td>
<td>0300</td>
</tr>
<tr>
<td>measured values on further study for up to four nights at time hypoglycaemia predicted (mmol/l)</td>
<td>&lt;2</td>
<td>5.1, 4.3, 5.9, 6.3</td>
<td>&lt;2, &lt;2, &lt;2, 4.1</td>
<td>&lt;2, 3.8, &lt;2</td>
<td>4.2, 12.3, 2.6, 5.0</td>
<td>&lt;2</td>
</tr>
<tr>
<td>hypoglycaemia confirmed</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
</tr>
</tbody>
</table>

**9. A double blind controlled study on Danish in-patients.**

This section is based on Hejlesen et al. 1998 [Hejl98], *Using a double blind controlled clinical trial to evaluate the Diabetes Advisory System: A feasible approach?* It assesses the feasibility of using a double blind controlled clinical trial to evaluate a decision support system by applying such a design to an evaluation of DIAS. It indicates that if the results can be confirmed on a larger data set, then it appears that use of the system, at least in the treatment of patients with poor metabolic control, may lead to significant improvements in the blood glucose control. It is concluded that a double blind controlled trial was a suitable evaluation method for this system and that it is doubtless a prerequisite to clinical application for any decision support system.

**Methods.**

When setting up the protocol for the double blind controlled clinical trial, it was concluded that only the non-interactive part, i.e. the advisory mode, of DIAS could be evaluated in the study, and in order to obtain a high degree of patient safety it was decided to study 20 patients with poor metabolic control consecutively admitted to Sønderborg Hospital, Denmark. It was not found feasible to match patients in the control group with patients in the DIAS group.
On admission the patients were maintained on an intensive regimen, with 8 daily blood glucose measurements and 8 doses of rapid-acting insulin, for approximately 4 days. They were then switched to a basal bolus regimen with 3 doses of rapid-acting and 1 dose of intermediate-acting insulin per day. They were discharged on this regimen after a further 4 days, and the regimen was unchanged for at least 2 months. During hospitalisation the patients were maintained on a very regular diet and insulin regimen: rapid-acting insulin injections were given 45 minutes before the 3 main meals, and intermediate-acting insulin was given just before bedtime.

When patients were switched from the intensive regimen to the basal bolus regimen a coordinator situated at another hospital, Odense University Hospital, Denmark, randomly assigned the patients to either the DIAS group or the control group. For four days, at 10 a.m. each day, data (on meals, insulin, and blood glucose) on the patients were faxed to the coordinator, and insulin dose advice was faxed back to Sønderborg. This advice either came from DIAS or an experienced diabetologist at Odense University Hospital. The advised dose was then given to the patients, if their doctor considered it safe. Since the timing and type of the insulin were given by the protocol, only advice on the size of the doses was provided.

The HbA1c was used to assess the improvements in blood glucose control and was measured just prior to admission and 2 months after discharge.

Results.

Table 9.1 summarises the results, and it can be seen that even though the mean improvement in HbA1c is 1.9% for the DIAS group compared to 0.9% for the control group, there are large differences from patient to patient, and a t-test shows no significant difference (p = 0.23) between the two groups. It can also be seen that only 12 patients entered the study. This was due to insufficient resources to fund further admissions.

<table>
<thead>
<tr>
<th>control patient ID</th>
<th>admitted</th>
<th>HbA1c</th>
<th>DIAS patient ID</th>
<th>admitted</th>
<th>HbA1c</th>
</tr>
</thead>
<tbody>
<tr>
<td>JM</td>
<td>10/6 93</td>
<td>10.3</td>
<td>10.3</td>
<td>18/8 93</td>
<td>10.3</td>
</tr>
<tr>
<td>LK</td>
<td>17/8 93</td>
<td>6.6</td>
<td>6.1</td>
<td>8/9 93</td>
<td>13.1</td>
</tr>
<tr>
<td>BSS</td>
<td>29/10 93</td>
<td>6.9</td>
<td>6.7</td>
<td>8/10 93</td>
<td>8.5</td>
</tr>
<tr>
<td>AL</td>
<td>5/11 93</td>
<td>8.7</td>
<td>7.7</td>
<td>15/10 93</td>
<td>10.0</td>
</tr>
<tr>
<td>ELL</td>
<td>3/12 93</td>
<td>8.5</td>
<td>8.4</td>
<td>26/11 93</td>
<td>7.4</td>
</tr>
<tr>
<td>AMS</td>
<td>25/2 94</td>
<td>7.7</td>
<td>7.7</td>
<td>4/3 94</td>
<td>7.2</td>
</tr>
<tr>
<td>mean ±sd</td>
<td>8.1 ±1.4</td>
<td>7.2 ±0.9</td>
<td>9.4 ±2.2</td>
<td>7.5 ±1.0</td>
<td>1.9 ±2.9</td>
</tr>
</tbody>
</table>

Two cases demonstrated how single errors can have dramatic consequences for blood glucose control: (1) Two days after the switch from the intensive regimen to the basal bolus regimen the patient ALK was given an injection of rapid-acting insulin at 8.30 a.m. instead of 10.45 a.m. and (2) because of hyperglycaemia on the day following the switch to the basal bolus regimen, Patient GLF was given 16U instead of 12U as advised by DIAS. In both these cases the result was a serious hypoglycaemic attack followed by a strong hyperglycaemic counter-regulation with a duration of more than 24 hours in the case of ALK and 36 hours in the case
of GLF. These powerful hypoglycaemic counter-regulations, described more detailed in Section 7, made it very difficult to use DIAS properly on these two patients.

10. A double blind controlled study on UK out-patients.

This section is based on Cavan et al. 1998 [Cava98], Preliminary experience of the DIAS computer model in providing insulin dose advice to patients with insulin dependent diabetes. It describes how data from 20 well-controlled IDDM out-patients were used to generate insulin dose advice by both DIAS and a diabetes specialist nurse, and how they were randomly allocated to follow either DIAS or nurse advice. DIAS predicted unrecognised recurrent hypoglycaemia in 12 subjects and generated significantly lower insulin dose advice than the nurse. It is concluded that, in the patients studied, DIAS provided insulin dose advice which maintained good control of diabetes, despite a significant reduction in average insulin dose.

Methods.

Twenty patients with insulin-dependent diabetes mellitus with HbA1 < 10% (representing good glycaemic control, reference range 5.4 to 7.6%) were recruited from the diabetic clinic at St Thomas' Hospital, London. Patient characteristics are shown in Table 10.1. On recruitment they were asked to collect the following data for four consecutive weekdays: four blood glucose measurements per day (before meals and before bed), and full details of insulin injections and food intake.

Patients were seen within a week following the data collection period. Their food diary was reviewed by the dietitian who assessed the carbohydrate content of each meal. These data and data on blood glucose and insulin were entered into DIAS and advice on insulin dose adjustment obtained. The same data were reviewed by an experienced diabetes specialist nurse who provided her recommendation for insulin dose adjustment.

Patients were then randomised, double-blind to receive either the advice from DIAS or that from the specialist nurse (10 in each group). The revised insulin dose was conveyed to the patients the day following the return visit to the clinic and they were asked to take this dose for four consecutive days during which they collected the same data as previously. The data were returned to the clinic at the end of the second data collection period. Comparisons were made using the Mann Whitney U test and Wilcoxon test.

Results.

There was no significant difference between the groups, and table 10.2 shows the effect of insulin dose adjustment. Initial median insulin doses were lower in the DIAS group than the nurse group (41 (30-75) v 54 (37-78) units respectively (NS)). The median insulin dose recommended by DIAS was 39.5 (26-43) units (p<0.01 compared to initial dose); the nurse advice was 55 (38-80) units. Thus patients randomised to receive DIAS advice saw a reduction in

<table>
<thead>
<tr>
<th>TREATMENT RANDOMISATION</th>
<th>DIAS n=10</th>
<th>NURSE n=10</th>
</tr>
</thead>
<tbody>
<tr>
<td>age (yrs)</td>
<td>38.6 (10.4)</td>
<td>37.3 (12.0)</td>
</tr>
<tr>
<td>duration of diabetes (yrs)</td>
<td>16.9 (8.7)</td>
<td>16.7 (9.8)</td>
</tr>
<tr>
<td>BMI</td>
<td>24.7 (2.5)</td>
<td>24.8 (2.8)</td>
</tr>
<tr>
<td>HbA1 (%) (n.r. &lt;7.6%)</td>
<td>8.7 (0.9)</td>
<td>8.9 (0.8)</td>
</tr>
</tbody>
</table>
insulin dose of 13.3 (-25 to +11.6)%, significantly greater than the 0 (-8.7 to +2.5)% change in insulin dose suggested to patients in the nurse group (p<0.05).

Table 10.2 Comparison of patient data before and after DIAS or nurse intervention. From Cava98.

<table>
<thead>
<tr>
<th>TREATMENT RANDOMISATION</th>
<th>DIAS (COMPUTER) n=10</th>
<th>NURSE n=10</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BEFORE</td>
<td>AFTER</td>
</tr>
<tr>
<td>median (range) insulin dose (units/day) % change</td>
<td>41 (30-75)</td>
<td>39.5 (26-43)</td>
</tr>
<tr>
<td>mean (sd) carbohydrate intake (g/day)</td>
<td>189 (62)</td>
<td>177 (59)</td>
</tr>
<tr>
<td>mean (sd) frequency of symptomatic hypoglycaemia (episodes/day)</td>
<td>0.2 (0.4)</td>
<td>0.2 (0.4)</td>
</tr>
<tr>
<td>mean (sd) % of measured blood glucose values below 3mmol/l (% of measurements over 4 days)</td>
<td>5.7 (8.2)</td>
<td>6.9 (11.4)</td>
</tr>
<tr>
<td>mean (sd) blood glucose (mmol/l)</td>
<td>8.3 (1.4)</td>
<td>7.9 (1.8)</td>
</tr>
</tbody>
</table>

11. A controlled study on Danish adolescent out-patients.

This section is based on Hejlesen et al. 1997 [Hejl97a], A controlled trial of insulin dose adjustment in adolescents by DIAS, a model based decision support system: A safe and acceptable clinical tool? It is described how data from 19 adolescent IDDM out-patients were randomly allocated to either a group here DIAS provide advise on insulin dose, or a control group where the advise was provided by an experienced paediatrician. It is suggested that DIAS is a safe and useful tool in insulin dose adjustment in adolescents obtaining at least as good a result as the traditional setting. The study also suggests that acceptance of the advise is conditioned on a thorough understanding of the system and its ability to advise marked reductions in insulin dose.

Methods.

19 adolescents, age 12-16 years, were recruited from the out-patient clinic of the Department of Paediatrics, Aalborg Hospital. They were randomised into two groups, matched according to sex, age and HbA1c levels. There was no significant difference between the groups.

The study period was 3 months, divided into a first month with intensive contact and a follow up period of two months. Apart from the source of the insulin advice, the programme was identical for the two groups: For the DIAS group insulin adjustment was during the first 4 weeks exclusively based on advise from the system, while adjustment in the control group was based on routine principles by the paediatrician.
Table 11.1 The results for HbA1c, insulin dosage and hypoglycaemic attacks per day. From Hejl97a.

<table>
<thead>
<tr>
<th></th>
<th>DIAS group</th>
<th>control group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>D2</td>
<td>D3</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>week 1</td>
<td>11.3</td>
</tr>
<tr>
<td></td>
<td>week 6</td>
<td>11.0</td>
</tr>
<tr>
<td></td>
<td>week 12</td>
<td>10.4</td>
</tr>
<tr>
<td>Insulin dosage (U/kg)</td>
<td>week 1</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>week 2</td>
<td>0.83</td>
</tr>
<tr>
<td></td>
<td>week 4</td>
<td>0.91</td>
</tr>
<tr>
<td></td>
<td>week 12</td>
<td>0.82</td>
</tr>
<tr>
<td>No. of bg &lt;3.5 mmol/l pr. day</td>
<td>week 1</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>week 2</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>week 4</td>
<td>0.0</td>
</tr>
</tbody>
</table>

In the first, second and fourth week the patients collected data on meals, insulin injections and blood glucose measurements for three consecutive days (Monday - Wednesday or Tuesday - Thursday). Thursday or Friday in the first and fourth week the patients visited the outpatient clinic, where they were seen by their usual doctor. In the second week insulin adjustment was based on telephone contact to the patients. In the DIAS group all data were entered into the system, and if acceptable by both the doctor and the patient, the DIAS advise for insulin adjustment was used - if not, the patient was excluded from the study.

During the study DIAS appeared to advise relatively large changes in insulin dose, especially reductions. 6 patients were excluded in the DIAS group and the control group:

Three patients in the DIAS group were excluded because either the doctor (2 patients) or the patient (1 patient) did not accept the DIAS advise on marked changes in insulin dose.

Three patients, two in the DIAS group and one in the control group, were excluded for various other reasons. One patient had, due to an accident in week 3, got his teeth wired together, and was therefore on a fluid diet forcing him to change meal pattern significantly. An other patient came to the outpatient clinic without her parents, and the doctor did not consider it safe to advise significant changes in insulin dose without thoroughly informing the parents. A third patient spontaneously confessed that she, during the whole study, daily had been taking significantly more insulin than recorded.

There was no statistically significant mean reduction in HbA1c comparing week 1 with week 12 in neither the DIAS group (p=0.16) nor the control group (p=0.21).

A relatively large, but not significant (p=0.06), mean reduction in insulin dose from week 1 to week 12 was seen in the DIAS group (12%) but not in the control group (1%).

The 12% reduction of insulin dose in the DIAS group was reflected in a large reduction from week 1 to week 2 and week 4 in the mean frequency of hypoglycaemia (< 3.5 mmol/l) from 0.32 to 0.03 attacks per day (p = 0.09). The reduction in the frequency of hypoglycaemia in the control group was from 0.20 to 0.13 attacks per day (p = 0.35). The results are shown in Table 11.1.
The development in insulin dose (i.u. per kg per day) and HbA1c from week 1 to week 12 for both groups is shown in Figure 11.1. In 3 patients in the DIAS group a marked reduction in insulin dose (D2:18%, D7:15%, D9:18%) was followed by a marked reduction in HbA1c (D2: 0.9%, D7: 1.4%, D9: 1.6%).

12. The clinical relevance of the hypoglycaemic counter-regulation – pro et con.

Since the hypothesis of the hypoglycaemic counter-regulation has become a major theme in the thesis (especially in Section 7, but also in Sections 9, 10, and 11), a small review of the literature on the subject seems to be appropriate.

The model-based approach in Section 7 leading to the relatively precise description of the time course and magnitude of a typical hypoglycaemic counter-regulation is new:

- The counter-regulation begins 6 to 8 hours after the hypoglycaemia, i.e. it has a 6-8 hour lag with no significant effect on the blood glucose.
- After the initial lag, it lasts 16 to 18 hours, giving a total duration of 24 hours.
- It elevates the blood glucose by 4 to 10 mmol/l above expected blood glucose levels.

However, the concept that insulin over-treatment leading to hypoglycaemia can be the cause of hyperglycaemia in insulin dependent diabetes is not new, but was introduced half a century ago: In 1938 Michael Somogyi presented the idea to the St. Louis Medical Society, U.S.A. [Somo38], and in 1959 his observations were described in detail [Somo59]. He proposed that ‘excessive glycosuria is an aftermath of hypoglycaemia’, and that ‘a mild state of diabetes can be readily shifted into a severe state under the influence of excessive insulin action and that the process is reversible’. The concept of the ‘Somogyi phenomenon’ was appealing and gained widespread acceptance. However, in the 80ies a keen debate on the existence of the phenomenon and its clinical relevance took place: Even though a number of studies under experimental conditions [Attv87, Boll83, Boll84a, Boll84b, Clor87, DeFe86, Fowe89, Fowe90, Koll87, Koll88] confirmed Somogyi’s ideas and demonstrated various mechanisms for the counter-regulations, most studies on patients in more clinically relevant circumstances [Havl87, Hirs90, Lerm88, Pram85, Step89, Tord87] were, apparently, not able to show the effect, and the most recent editions of diabetes textbooks clearly state that the Somogyi phenomenon has no clinical significance [Albe97, Hair96, Lero96, Natt96, Pick96, Port96].
However, it seems that, at least partly, the contradicting findings can be explained by different definitions or interpretations of the phenomenon. The discussion of this logically falls into four steps:

1) Blood glucose versus counter-regulatory hormones and insulin.

Most studies under experimental conditions [Attv87, Clor87, DeFe86, Fowe89, Fowe90, Koll87, Koll88] do not report the effect on the blood glucose level *per se*. They mostly focus on hormones and either do not report on blood glucose or report on, for example, glucose infusion rates. Some studies [Clor87, Fowe89, Fowe90, Gale80, Koll87, Koll88, Laur85] explain elevated blood glucose levels by insulin deficiency or insulin resistance, and by some authors [Albe97, Frie93, Havl87, Step89, Tord87] this is, apparently, seen as evidence against the clinical relevance of the hypoglycaemic counter-regulation. However, insulin resistance, relative insulin deficiency, or reduced insulin absorption could be seen as an intermediate mechanism (e.g. hypoglycaemia leading to increased levels of counter-regulatory hormones, leading to insulin resistance or reduced insulin absorption, again leading to hyperglycaemia) and does therefore not contradict the hypothesis of the Somogyi phenomenon.

In the following discussion, the term ‘hypoglycaemic counter-regulation’ will be interpreted as the effect of hypoglycaemia on the blood glucose level *per se*, and the mechanisms will be seen as less important.

2) Comparison of blood glucose levels.

Apparently, there are also different views on how blood glucose levels should be compared. The term ‘hypoglycaemic counter-regulation’ implies that the blood glucose levels after a hypoglycaemic episode in a given patient should be compared with blood glucose levels in the same patient (or, at least, a comparable patient), given no preceding hypoglycaemia, but, otherwise, given the same conditions. Most studies have, explicitly or implicitly, used this definition [Attv87, Boll83, Boll84a, Boll84b, Clor87, DeFe86, Fowe89, Fowe90, Havl87 (only partially), Hirs90, Koll87, Lerm88 (only partially), Perr88, Tord87], and most of these studies, except Havl87, Hirs90, Lerm88, Tord87, which are discussed separately below, support the occurrence of the Somogyi phenomenon.

However, some other studies have compared blood glucose levels in groups which, apparently, were not comparable. For example, some studies [Havl87, Lerm88, Pram85, Step89] have compared pre-breakfast blood glucose levels in two different groups of patients; one group in which nocturnal hypoglycaemia occurred and an other group in which it did not occur – yet, the papers do not demonstrate that the groups were comparable regarding, for example, insulin regimen and carbohydrate intake, and they all suggest that the Somogyi phenomenon does not exist or has no clinical relevance.

3) One or two patient populations?

Most studies, apparently, assume that the hypoglycaemic counter-regulation either exists in all patients or does not exist; i.e. that diabetic patients constitute one population that either can have or can not have counter-regulations – in contrast to, for example, two populations: one that can have counter-regulations, and one that can not.
As described in Section 7, two types of patients were identified: 6 patients seemed to have hypoglycaemic counter-regulations and 2 patients seemed to have no or infrequent counter-regulations, and Hirs90, who found no significant counter-regulations, suggested that the level of control may play a role: As opposed to Hirs90, who studied ‘more representative moderately well controlled patients’, Perr88, who found a significant daytime blood glucose elevation following nocturnal hypoglycaemia, studied ‘very tightly controlled patients’ [Hirs90]. In light of the results from the DCCT study [DCCT93], showing that intensive therapy effectively delays the onset and slows the progression of diabetic complications, the importance of such a difference, if proven, seems to be obvious. Other factors influencing the number of populations might, for example, be insulin regimen, diet composition, or genetic factors.

4) Timing of the hypoglycaemia and the counter-regulation.

Although Somogyi did not restrict his theory to nocturnal hypoglycaemia leading to pre-breakfast counter-regulation, the concept of the ‘Somogyi phenomenon’ has been attached to this particular case. Most papers on patients in more clinically relevant circumstances have focused on this special relation [Gale80, Havl87, Lerm88, Perr88, Pram85, Step89, Tord87], and none of these report large and significant counter-regulations in the early morning. In contrast to this, the results in Section 7, based on clinical data, suggest that the phenomenon is not restricted to nocturnal hypoglycaemia. Furthermore, the results in Section 7 suggest that there is a 6-8 hour lag between the hypoglycaemia and the counter-regulation. Interestingly, this 6-8 hour delay is supported by Boll84a, Boll84b, and Perr88. Furthermore, Koll88 reports an insulin resistance occurring after a lag period of approximately 4 hours after the hypoglycaemia, which is in good accordance with a significant elevation in blood glucose a couple of hours later.

This suggested 6-8 hour lag in the appearance of the counter-regulation, gives one good explanation to why the clinically based studies in general did not find any significant early morning fasting hyperglycaemia following nocturnal hypoglycaemia: Only a very early nocturnal hypoglycaemic episode, during a normal 7-8 hour sleep, seems to be able to cause a reaction in the early morning.

Focus on longer-term counter-regulations.

Given the 6-8 hour lag of the counter-regulation found in Section 7 and supported by Boll84a, Boll84b, Koll90, and Perr88, it seems appropriate here to focus more specifically on the studies reporting data from a period of at least 8 hours following the hypoglycaemia:

*In favour of the Somogyi phenomenon and supporting the results in Section 7 are a series of relatively small studies, most under experimental conditions:*

1) Boll84a, Boll84b, and Perr88 reporting data from a 12 hour period showing a 4-10 mmol/l elevation starting 6-8 hours after the hypoglycaemia and lasting the rest of the study period, and which suggest that epinephrine, growth hormone and cortisol should play an important role. The patients in Perr88 were on their usual regimens of continuous subcutaneous insulin infusion.

2) Clor87, Fowe89, Fowe90, Koll87, and Koll88 reporting data from approximately 8 hours, which suggest that insulin resistance should play an important role,
3) DeFe86 reporting data from 8 hours, which suggest that increased glucose production should play an important role,

4) Gale80, Laur85 reporting data from 4-8 and 8 hours, respectively, which suggest that relative insulin deficiency or reduced insulin absorption should play an important role, which again is supported by Boll84a.

Against the Somogyi phenomenon are often cited [Albe97, Frie93, Hair96, Lero96, Natt96, Pick96, Port96] five clinical studies: Three studies [Havl87, Lerm88, Step89] ‘of large numbers of diabetic patients in more clinically relevant circumstances’ [Frie93], and one smaller study [Hirs90]; all reporting data from a period of 24 hours following the hypoglycaemia. The fifth study [Tord87], not finding significant hypoglycaemic counter-regulations, described the reaction in only a 4-6 hour period following the hypoglycaemia, and therefore support the results in section 7. Three of the studies had overlapping authorship [Havl87, Tord87, Hirs90], and the design of the two first studies [Havl87, Lerm88] was largely identical.:

1) In Havl87, 216 overnight blood glucose profiles (samples at 2100, 0300, and 0700 h) in 75 patients with diabetes were analysed (43 patients with IDDM and 32 with NIDDM, and of the latter 25 treated with insulin). The focus was on morning hyperglycaemia following nocturnal hypoglycaemia (0300 hour), and 0700 hour blood glucose was analysed by grouping the patients according to blood glucose levels at 0300 hour. Although the study found significant differences in the 0700 hour blood glucose in the groups with 0300 hour blood glucose less than 50 mg/dl (2.8 mmol/l) and between 50 and 100 mg/dl (2.8 and 5.6 mmol/l), the effect was, in accordance with the results in Section 7, not found to be very large.

Moreover, as mentioned above, the comparison between the groups with different 0300 hour blood glucose levels was seriously hampered by the groups not being comparable: For example, 17% of the patients in the group with 0300 hour blood glucose less than 50 mg/dl had NIDDM compared with 40% in the group with 0300 hour blood glucose above 100 mg/dl. Furthermore, other important characteristics, like insulin dosage and carbohydrate intake in the groups, were not documented in the study.

More interestingly, the study, for the group with 0300 hour blood glucose less than 50 mg/dl, report that no difference was found in daytime blood glucose concentrations on the day before compared with the day after the nocturnal hypoglycaemia. Even though the study in this analysis only included 12 profiles in 11 patients, and it therefore, in this aspect, was relatively small, other factors are worth considering: First, there was no documentation that there was no hypoglycaemia on the night before, and therefore the blood glucose in some of the profiles on the day before also might be elevated due to counter-regulations. Second, hypoglycaemia on the study night was treated by feeding the patients with carbohydrate, and the effect of a hypoglycaemia, in terms of provoking a counter-regulation, might therefore be less serious than on the night before. Both these aspects of the study design would tend to hamper the demonstration of potentially significant hypoglycaemic counter-regulations. It should be noticed that all patients were in conventional insulin therapy; i.e. used 1 or 2 daily doses of insulin.

2) Lerm88 analysed 281 overnight blood glucose profiles in 66 patients. As mentioned, the design of the study was in general identical to the one in Havl87, described in the previous paragraph. One betterment in Lerm88, compared with Havl87, was that the material was more homogenous: Only patients with IDDM were included, and the two groups, with and without nocturnal hypoglycaemia, had comparable total insulin dose. However, insulin regimen (injections per day) was not comparable, and the paper does not demonstrate that, for
example, carbohydrate intake was comparable in the two groups. Furthermore, when analysing daytime blood glucose levels, the same serious criticism can be raised regarding proper controls as in Havl87.

Regarding results, Lerm88 was also largely identical to Havl87: No significant difference in daytime blood glucose was found when comparing the day before the nocturnal hypoglycaemia with the day after. It should be noted that, in addition to the problems in the study design as already pointed out, the study material, when comparing the day before with the day after the hypoglycaemia, was reduced to 36 blood glucose profiles in 27 patients.

3) In Step89, the third large study in ‘more clinically relevant circumstances’, a different approach was followed. The clinical relevance of a rise in fasting blood glucose between 0300 and 0600 was analysed in 231 24-hour profiles in 97 patients with IDDM, and they found that the patients showing a rise > 100 mg/dl (5.6 mmol/l) compared with patients showing a rise < 50 mg/dl (2.8 mmol/l) had significantly higher daytime blood glucose levels (approximately 3 mmol/l).

However, this study also suffered from the problem that the groups were not comparable: For example, the group with the highest rise in fasting blood glucose and highest daytime blood glucose levels had breakfast insulin doses (units per gram carbohydrate) approximately twice the size of the doses in the groups with lower rise in fasting blood glucose and lower day-time blood glucose levels.

The study also compared daytime blood glucose in the 57 profiles (number of patients not stated) showing nocturnal hypoglycaemia with the profiles not showing nocturnal hypoglycaemia and no significant difference in daytime blood glucose was found – but again, demonstration that the groups were comparable is missing.

4) In Hirs90 10 moderately well controlled patients with IDDM on their usual therapeutic regimen, and including proper controls, were studied on three occasions from 2000 to 2000: On a control day without intervention, on a day with induced nocturnal hypoglycaemia, and on a day where nocturnal hypoglycaemia was prevented. No significant difference between the groups was found in daytime blood glucose levels. However, looking into the detailed results reveals that blood glucose levels on the day with induced nocturnal hypoglycaemia on average were 1-2 mmol/l higher than on the control day without intervention. Even though this was not confirmed when comparing blood glucose levels on the day with induced nocturnal hypoglycaemia with blood glucose levels on the day where nocturnal hypoglycaemia was prevented by intravenous infusion of glucose, a 1-2 mmol/l elevation could, for example, be explained by one out of four diabetic patients having counter-regulations with 5-6 mmol/l elevations of their blood glucose. Unfortunately, the data do not show the individual blood glucose measurements relative to individual patients.

Summing up, the amount of scientifically solid evidence from studies under more clinically relevant circumstances seems to be quite sparse: Under the assumption that ‘more clinically relevant’ means studies on diabetic patients on their usual therapeutic regimen for a period of more than 8 hours following hypoglycaemia and including proper controls, only three studies [Havl87, Lerm88, Hirs90] on 58 24-hour blood glucose profiles with nocturnal hypoglycaemia from 48 patients speak against the Somogyi phenomenon. Furthermore, serious criticism can be raised regarding proper controls in the two first studies [Havl87, Lerm88] on 48 profiles from 38 patients, and some of the results in the third study on 10 profiles from 10 patients [Hirs90] are compatible with a hypothesis that some patients, for example one out of four, have counter-regulations. However, the evidence, from studies under more clinically relevant circumstances, in favour of the Somogyi phenomenon is even sparser: One 12-hour study on 10 profiles from 10 patients [Perr88] have shown significant
counter-regulations in accordance with the results in section 7. However, these patients were on continuous subcutaneous insulin infusion, and even though this was their usual regimen, it is not representative for most patients.

*In conclusion,* the evidence discussed in this section, and the findings in Section 7, are, at least partially, compatible with the hypothesis that nocturnal hypoglycaemia commonly do not lead to early morning fasting hyperglycaemia, but that it is possible that (daytime or nocturnal) hypoglycaemia, at least in a considerable fraction of patients with diabetes (for example one out of four), can lead to longer-term counter-regulations starting 6-8 hour following the hypoglycaemia and elevating the blood glucose by 4-6 mmol/l relative to expected blood glucose levels. Given the, apparently, sparse amount of scientifically solid evidence from studies under more clinically relevant circumstances and the considerable impact the phenomenon, if proven, would have on patients with diabetes, further studies are clearly required to assess the hypothesis.

### 13. Discussion.

The Diabetes Advisory System (DIAS) incorporates a model of the human carbohydrate metabolism, which has elements describing the carbohydrate content in two compartments, the blood and the gut, as functions of processes in various organ systems (Section 2).

The model is implemented in a causal probabilistic network, which gives it the ability to handle the uncertainty, for example, in blood glucose measurements or physiological variations in glucose metabolism. The implementation combines a dynamically defined network, implemented without the use of Hugin, with a static network implemented in Hugin, thereby reducing the calculation time by several orders of magnitude compared to using Hugin alone. It should be emphasised that, apart from substantially reducing calculation time, implementation in this way does not influence the performance of the model (Section 4).

Two adjustable parameters are included in the model, the insulin sensitivity and time-to-peak of NPH-type insulin absorption, and they can be estimated to fit the model to a specific patient. After estimating the parameters, the system can, for example, be used to identify periods with higher risks of hypoglycaemia and to see the effect of changing the type of insulin or of adding extra snacks in these high risk periods. The system also features an automatic insulin adjustment procedure (Sections 3 and 5).

Every model is a subset, or simplification, of the real world. Unlike insulin sensitivity or NPH insulin absorption speed, which are explicitly modelled in DIAS, factors like exercise and differences in meal composition and in rates of gastric emptying are not explicitly modelled. One reason for this is the lack of sufficiently detailed scientific evidence of how these factors influence metabolism; furthermore, to date, other factors have not been considered as important for the model as, for example, insulin sensitivity. However, it should be noted that, although differences in meal composition and in rates of gastric emptying are not explicitly included in the model, they are, due to the probabilistic property, implicitly a part of the model, i.e. although there are no parameters which can be adjusted to each individual patient or meal type, the uncertainties of the absorption are modelled. The sampling interval has been set to one hour, and this seems appropriate for the relatively slowly working metabolic processes in the present version of DIAS. However, in the next version of DIAS, which has been implemented as a prototype, and which implements the new (ultra) short-acting insulin
analogues and modelling of hypoglycaemic counter-regulation, the sampling interval will be shorter.

Even though the metabolic model in DIAS is based on quantitative estimates of the physiological relations found in the literature, the information available from these sources is quite sparse, and the model therefore had to be optimised by fitting it to collected data. After the optimisation of the model, the system was evaluated by comparing the prediction errors to the intrapatient variability. It is suggested that the model, when compared to the intrapatient variability and excluding data with hypoglycaemic episodes, does not seem to have systematic errors, large enough to be significant (Section 6).

The data with hypoglycaemic episodes led to formulation of the hypothesis that a large fraction of IDDM patients respond to hypoglycaemia by a prolonged counter-regulation: A typical hypoglycaemic counter-regulation

- begins 6 to 8 hours after the hypoglycaemia,
- it lasts 16 to 18 hours, giving a total duration of 24 hours, and
- it elevates the blood glucose by 4 to 10 mmol/l.

If the hypothesis holds, then it appears that the hypoglycaemic counter-regulation is a frequently occurring phenomenon, and that it is of clinical interest, not only because it gives rise to substantial and prolonged elevation of blood glucose, but also because it may start a vicious circle: the high blood glucose concentrations caused by the counter-regulations may persuade either the clinician or the patient to increase insulin doses, which in turn increases the probability of a new hypoglycaemic attack at the end of the 24 hour counter-regulation. Although the analysis of the data is strongly suggestive of the occurrence of counter-regulations, the data in the study are from poorly controlled hospitalised patients, in whom there could be an increased frequency of hypoglycaemic counter-regulation. The hypothesis is discussed in Section 12, and as described, there is only a sparse amount of scientifically solid evidence from studies under more clinically relevant circumstances available, and further studies are clearly required to verify the hypothesis (Section 7).

The system has been evaluated, both retrospectively and prospectively. Wyatt et al. [Wyat94] have proposed to divide the evaluation of a medical decision support system into evaluation of design and structure, of function, and of impact: Evaluation of design and structure includes evaluation of embedded knowledge, algorithms, and inference methods. They propose that the function, i.e. performance, safety, and usability, of a decision support system should be evaluated by comparing the ‘output’, i.e. the advise, from the system with the decisions from the current decision makers and with ‘judges´ verdict’ obtained from specialists. They argue that evaluation of the impact on patients and health care system can only take place in a true clinical setting, whereas the impact on clinicians also may be evaluated in simulated settings.

For the evaluation of DIAS, the approach proposed by Wyatt et al. was adopted, but the evaluation of function was modified by replacing comparison with ‘judges´ verdict’ by controlled trials. The reason for this was that ‘individual patients may have poor control despite specialist care’ [Bind95]. This may be due to the often relatively large discrepancies between advice from different specialists, which again may be due to different views on the importance of the hypoglycaemic counter-regulation, described in Section 7.

Regarding the design and structure, the metabolic model of the glucose metabolism in DIAS is, as described in Section 2, based on data found in the physiological literature, and the inference methods is based on the Hugin approach to Bayesian inference. While the Hugin
approach is well documented, the ability of the model to accurately predict blood glucose had to be tested, as described in Section 6. Furthermore, DIAS was used to predict blood glucose profiles in eight patients with well-controlled insulin-dependent diabetes. The system predicted nocturnal hypoglycaemia in six, and daytime hypoglycaemia in one, of the eight patients. The occurrence of nocturnal hypoglycaemia was not recognised by the patient or suspected by their doctor but was subsequently confirmed by blood testing in five out of six patients, when asked to test their blood at the time hypoglycaemia was predicted by DIAS. However, it should be realised that many patients are hypoglycaemic at night, and that proper controlled studies therefore are needed before this facility can be used in clinical practice (Section 8).

The function of DIAS has been tested in three small studies. Both blinded and unblinded controlled studies have been applied:

In a double blind study 12 Danish IDDM patients, hospitalised because of poor regulation, were randomly assigned to either a group, where insulin advice was provided by DIAS, or a control group, where advice was provided by an experienced diabetologist. In both groups HbA1c was measured just prior to admission and 2 months after discharge. The mean improvement in HbA1c was 1.9% (n.s.) for the DIAS group compared to 0.9% (n.s.) for the control group (Section 9).

In another double blind controlled study on out-patients in the UK, insulin dose advice was provided by both DIAS and a diabetes specialist nurse. DIAS predicted unrecognised recurrent hypoglycaemia in more than half of the patients, and it was concluded that DIAS provided insulin dose advice which maintained good control of diabetes, as expressed by the HbA1 level, despite a significant (12%) reduction in average insulin dose (Section 10).

In an unblinded controlled study on Danish adolescents, applying a more realistic, i.e. interactive, study design, it was shown that using the system as an interactive clinical tool had at least as good an effect as using the advice of an experienced paediatrician in maintaining good glycaemic control, as expressed by the HbA1c level. It was also shown that using the system led to reductions in average insulin dose (12%, n.s.), and that the system may be able to contribute to reductions in the frequency of hypoglycaemia (n.s.) (Section 11).

Seen from a medical perspective, the three studies may be compared with phase I and phase II clinical drug trials. Like phase I trials, the studies have evaluated the safety of DIAS, but unlike phase I trials, they have used diabetic patients instead of healthy volunteers. Just as phase II trials evaluate the best dosage of a new drug, the studies also illustrate the importance of the right balance between advice and support: should the system be used as a non-interactive advisory system, as in the trials in Sections 9 and 10, or should it, as in the trial in Section 11, be used as an interactive clinical tool? Even though informal reactions from the participants in the studies, not surprisingly, support the latter, formal studies on this aspect still remain to be carried out. Due to the lack of experience of testing systems like DIAS, there was little previous knowledge of the spread of expected results, and the number of patients in the studies could not be determined by power calculations as would be the case in a drug trial. Studies have been further limited by resource constraints, both with respect to man-power and to patients eligible for the studies. As described in Section 9, where it was planned to study 20 patients, the number of patients had to be reduced to 12, due to practical constraints. Likewise, the number of patients in the study in Section 11 was limited by the number of adolescent patients available in the outpatient clinic. However, since the probability that a paired one-sided t-test for a study on 10 patients, given a 2% mean decrease in HbA1c with sd of 2% (or 1% decrease with sd of 1%), will give a significant (p < 0.05)
result is 0.9, i.e. that the power is 0.9, the number of patients in the studies was deemed to be sufficient.

Regarded separately, none of the clinical studies show scientifically robust evidence of clear clinical benefits from using DIAS. However, taken together they support the hypothesis that the advice from DIAS is, at least, comparable to advice given in clinical practice, and may lead to either reduced HbA1c or reduced frequency of hypoglycaemia.

Even though the study on Danish adolescents might be regarded as a very small study of the impact on patients, full size impact studies (comparable with phase III drug trials) still remain to be carried out.

The future of DIAS is not easy to foresee. If DIAS has a future, this might be anything from a role as a relatively inoffensive warning system to placing the system in the hands of the patient. The former role could be e.g. providing a critique of the inexperienced doctors insulin prescription or detecting patients with a high probability of having hypoglycaemic counter-regulations. Given current trends towards ‘patient centred’ care, the latter role might also one day become reality, leading to a freer lifestyle by helping the patient to adapt to day-to-day changes in, for example meal size or physical activity. However, in addition to the clinical and technical problems that have to be dealt with, legal issues may also have to be resolved before this can happen. It should be emphasised that, even though it may be suggested that DIAS might achieve glycaemic control similar to that obtained by experienced clinicians, this should never lead to poorer contact between patients and clinicians. In fact, DIAS might help to improve understanding and communication between clinicians and patients, and using DIAS as a tool to speed up data analysis, might lead to improved quality of care by allowing more time for other, and perhaps more important, aspects of patient care.

14. Conclusion.

The present status of the Diabetes Advisory System (DIAS) system can be summarised as follows. A system has been constructed that can analyse patient data, perform simulations of blood glucose profiles and if required propose adjustments of insulin doses.

The metabolic model in DIAS has been evaluated, and it has been demonstrated that it can accurately predict blood glucose in patients without hypoglycaemic episodes. Furthermore the discrepancy between predicted and measured blood glucose in patients with hypoglycaemic episodes has been used to develop a description of the amplitude and time course of hypoglycaemic counter-regulations.

The clinical function of DIAS has been evaluated in four small studies, which support the hypothesis that DIAS can generate advice that is safe and of a quality at least comparable to what is available from experienced clinicians.
15. Dansk sammenfatning (summary in Danish).

Diabetes mellitus, sukkersyge, er en af de hyppigste kroniske sygdomme i Vesteuropa. Ca. 2-6% af befolkningen har sygdommen, og det er anslået at omkostningerne ved diabetes svarer til 10% af sundhedsbudgettet [DiabCa]. 15% af patienterne har den insulinkrævende form af sygdommen. Det betydelige tab af livskvalitet i forbindelse med diabetes skyldes en væsentligt øget risiko for udvikling af de såkaldte senkomplikationer: blindhed, nyresvigt, hjerte-kredsløbsygdom, koldbrand mv.

Nyere undersøgelser [DCCT93, DCCT94] har vist at intensiv diabetesbehandling, med det mål at opretholde normale blodsukkerniveauer, fører til en betydelig reduktion af komplikationshyppigheden. De samme undersøgelser har dog også vist at hyppigheden af alvorlige tilfælde af hypoglykæmi, for lavt blodsukker, samtidig øges væsentligt. Da det er erkendt at en del patienter, på trods af behandling varetaget af specialister, har dårlig blodsukkerkontrol, og da der yderligere er en tendens til at mere og mere behandling overgår til ikke-specialister, er det blevet foreslået at alternative initiativer bør forsøges [Bind95]. Denne afhandling beskriver et af disse initiativer.

Afhandlingen giver en oversigt over de tekniske og fysiologiske aspekter af ‘the Diabetes Advisory System’ (DIAS), og over de evalueringresultater som er opnået til dato. Hver sektion i afhandlingen er baseret på en bestemt artikel:

DIAS bygger på en model af menneskets sukkerstoffskift, der beskriver kulhydratindholdet i to fysiologiske rum, blodet og mave-tarmsystemet, som en funktion af processer i forskellige orgaensystemer (sektion 2 [Hejl97b]).

Modellen er opbygget som et kausalt probabilistisk netværk, hvilket betyder at usikkerhed i f.eks. blodsukkermålinger og fysiologiske variationer i stofskiftet kan håndteres. Modellen kombinerer et dynamisk defineret netværk, opbygget uden brug af Hugin¹, med et statisk defineret netværk, der er opbygget ved hjælp af Hugin. Herved reduceres beregningstiden med adskillige størrelsesordener i forhold til at opbygge hele netværket ved brug af Hugin (sektion 4 [Hejl95a]).

Der findes to justerbare parametre i modellen, ‘insulinfølsomheden’ og ‘tiden fra injektion til maksimumvirkning af langsamtvirkende insulin’, og systemet kan justere disse parametre så modellen tilpasses den enkelte patient. Efter at parametrene er justeret kan systemet bruges til f.eks. at udpege tidspunkter med risiko for hypoglykæmi og til at se hvordan ændringer i insulinindoserne påvirker blodsukkerniveauet. Systemet inkluderer også en funktion der automatisk kan foreslå hensigtsmæssige insulinindos (sektion 3 [Hejl98] og sektion 5 [Hejl93]).

De fysiologiske relationer i systemet er baseret på litteraturkilder; men da den eksisterende informationen fra litteraturen har vist sig at være utilstrækkelig, blev modellen optimeret ved hjælp af indsamlade patientdata. Derefter blev fejlen i systemets forudsigelser af blodsukkerkoncentrationen sammenlignet med den tilfældige blodsukkervariation hos den enkelte patient fra dag til dag. Det blev konkludert, at systemets forudsigelser af blodsukkerkoncentrationen, såfremt der blev anvendt data uden hypoglykæmier, ikke har fejl af betydning (sektion 6 [Hejl95b]).

¹ Hugin er et kommercielt tilgengeligt computer-program til opbygning og håndtering af kausale probabilistiske netværk (causal probabilistic networks, CPNs, Bayesian networks). Mere information om Hugin kan findes på http://www.hugin.dk/.
Data indeholdende hypoglykæmier førte til opstillingen af den hypotese, at en stor del af diabetespatienterne reagerer på en hypoglykæmi med et længerevarende modregulering, dvs. et forhøjet blodsukker. En typisk hypoglykæmisk modregulering

- begynder 6-8 timer efter hypoglykæmien,
- varer 16-18 timer, d.v.s. slutter 24 timer efter hypoglykæmien, og
- forhøjer blodsukkeret med 4-10 mmol/l.

Det ser ud til at den hypoglykæmiske modregulering er hyppigt forekommande, og at den fortjener opmærksomhed - ikke kun fordi den resulterer i en længerevarende betydelig forhøjelse af blodsukkeret, men også fordi den kan starte en ond cirkel: Forhøjelse af blodsukkeret kan få enten lægen eller patienten til at øge insulindoseringen, hvilket igen øger risikoen for en ny hypoglykæmi 24 timer efter den hypoglykæmi der udløste det forhøjede blodsukker (sektion 7 [Hejl96a]).

DIAS er blevet afprøvet i 4 små kliniske undersøgelser:

Systemet blev brugt til at forudsige blodsukkerprofilerne for 8 velregulerede diabetespatienter, og det forudsagde gentagne natlige hypoglykæmier hos 6 patienter og hypoglykæmi i dagtimerne hos 1 patient. Hverken læge eller patient var klar over disse hypoglykæmier, og ved efterfølgende blodsukkermålinger blev hypoglykæmierne bekræftet i 5 ud af de 6 patienter som ønskede at deltage (sektion 8 [Cava96]).

I en dobbelt-blind kontrolleret undersøgelse2 blev 12 danske patienter inddraget på sygehus med en dårligt reguleret diabetes. De blev opdelt i en DIAS-gruppe som fik insulindosersingsråd fra systemet, og en kontrolgruppe som fik råd fra en erfaren diabetesspecialist. HbA1c3 blev i begge grupper målt lige før indlæggelsen og 2 måneder efter. Den gennemsnitlige forbedring i HbA1c var 1.9% i DIAS-gruppen og 0.9% i kontrolgruppen (sektion 9 [Hejl98]).

I en anden dobbelt-blind kontrolleret undersøgelse, omfattende 20 ambulante patienter i England, fik halvdelen insulindosersingsråd fra DIAS, og en kontrolgruppe råd fra de diabetes-sygeplejersker som også normalt står for rådgivningen. Det blev konkluderet at rådene fra DIAS, uden at forringe kontrollen undtykt ved HbA1, var i stand til at reducere den gennemsnitlige insulindosering med 12% (sektion 10 [Cava98]).

I en ikke-blind kontrolleret undersøgelse, omfattende 19 danske børn i alderen 12-16 år, blev det vist at anvendelsen af rådene fra systemet havde mindst lige så god effekt, udtrykt ved forbedringen i HbA1c koncentrationen, som hvis rådene kom fra erfarne børnelæger. Det blev også vist at brugen af systemet førte til en reduktion af den gennemsnitlige insulindosering med 12% og til et betydeligt fald i hyppigheden af hypoglykæmi (sektion 11 [Hejl97a]).

Analysen er enkeltvis viser ingen af de kliniske undersøgelser videnskabeligt sikre beviser for klare fordele ved at anvende DIAS. Betragtes undersøgelserne derimod samlet, ser det ud til at DIAS er i stand til at kunne bidrage til reduktion af HbA1c, reduktion af insulindoseringen og/eller til reduktion af hyppigheden af hypoglykæmi.

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2 Ved en kontrolleret undersøgelse forstås i denne sammenhæng en undersøgelse hvor patienterne ved lodtrækning er opdelt i en gruppe, hvor DIAS giver råd, og i en kontrolgruppe hvor lægen giver råd. At undersøgelsen er dobbelt-blind betyder, at hverken patienten eller lægen har kontakt med patienten ved om insulindosersingsrådene kommer fra DIAS eller fra en diabetesspecialist.

3 HbA1c (eller i nogle tilfælde HbA1), sukkerhæmoglobin, er almindeligt anerkendt som en god indikator for hvor velregulert en patient er. HbA1c koncentrationen på et givet tidspunkt afspjeler det gennemsnitlige blodsukkerniveau i en periode på 2-3 måneder inden målingen, dvs. at en lav HbA1c koncentration indikerer et lavt gennemsnitligt blodsukkerniveau.
Only some of the references, from the papers on which the thesis is based, are included in the reference list below. For each section a more comprehensive reference list can be found in the corresponding paper.


[Havr87] C.E. Havlin, and P.E. Cryer, Nocturnal hypoglycemia does not commonly result in major morning hyperglycemia in patients with diabetes mellitus, Diabetes Care, 10 (1987) 141-147.


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