A DECISION SUPPORT SYSTEM FOR INSULIN-DOSE ADJUSTMENT IN INSULIN-TREATED SUBJECTS WITH TYPE 2 DIABETES MELLITUS

by

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ABSTRACT

The Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study provide motivation for the intensive insulin therapy (IIT) in type 1 and also type 2 diabetes mellitus. Decision support systems (DSS) for the adjustment of insulin dosage in insulin-treated subjects with type 2 diabetes have the potential to attain significant importance in clinical practice by offering the means to improve glycaemic control.

The aims of the research were to extend the existing Diabetes Insulin Advisory System (DIAS) model of carbohydrate metabolism with a component representing the insulin secretion present in subjects with type 2 diabetes and to develop a decision support system, DIAS-NIDDM, to assist in clinical practice with the adjustment of insulin dosage in insulin-treated subjects with type 2 diabetes. In relation to assessing the long-term complications of diabetes, the aim was to incorporate a model that predicts steady state HbA_{1c} concentrations in response to changes in diet and insulin therapy. Furthermore, the research evaluated DIAS-NIDDM with regard to performance, clinical utility, and safety of its advice on retrospective data to justify prospective clinical testing of DIAS-NIDDM.

The new model, implemented using causal probabilistic networks (CPN), represents the insulin secretion present in subjects with type 2 diabetes and assumes a linear relationship between plasma glucose concentration and endogenous insulin secretion.

DIAS-NIDDM was used to predict patient-specific plasma glucose profiles and advise on insulin doses during a pilot study in eight subjects with type 2 diabetes, with five subjects treated by insulin. Case studies showed that the advice is plausible and safe. However, a systematic error has been identified when the system predicted *BG* values in the hyperglycaemic *BG* range.

Another evaluation step was performed as a pilot peer assessment of the insulin dose advice generated by DIAS-NIDDM. The peer blind assessment provided valuable

information about the competence of DIAS-NIDDM compared to diabetes specialists, confirming the clinical utility and the safety of the advice. However, in the peer review study, DIAS-NIDDM recommendations performed less well than advice from a clinical diabetologist, as the system does not use the subject demoghraphic data to assess the feasibility of the recommended therapy in aged and insulin resistant subjects.

A new model using stochastic differential equations has been built to describe the relationship between DIAS-NIDDM predicted plasma glucose levels and glycated haemoglobin (HbA_{1c}) at steady state conditions. The model uses two physiological compartments to represent the glycated and unglycated haemoglobin where the glycation process is controlled by the plasma glucose concentration. The HbA_{1c} assay has been modelled, in a novel approach, as a separate process in order to deal with the glycation-induced heterogeneity and the mix of cell life spans in the sample. A retrospective pilot study has been performed in order to carry out a preliminary validation of the glycation model. The accuracy of the model was excellent when predicting thirty-two HbA_{1c} retrospective measurements.

In conclusion, the results confirm that DIAS-NIDDM can generate advice that is similar in performance to the advice recommended by diabetes specialists and that the advice is safe, plausible, and of clinical utility. The system can predict steady state HbA_{1c} in response to changes in diet and insulin therapy. Despite possible further optimisations of the system, prospective clinical testing of DIAS-NIDDM is justified. The thesis, nevertheless, identifies DIAS-NIDDM as a decision support system with valuable potential.

Keywords: Bayesian networks, CPN, learning, forecasting, model-based decision support system, insulin secretion, carbohydrate metabolism, non-insulin dependent diabetes mellitus, type 2 diabetes, C-peptide, HbA_{1c}, glycated fraction, clinical trial, software life-cycle, heuristics

TABLE OF CONTENTS

TABLE OF FIGURES

TABLE OF TABLES

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ABBREVIATIONS USED

The list of the most commonly used abbreviations follows:

ACTIV-INS	(mU/L) active insulin concentration representing insulin action
BASAL-SEC	(mU/kg/h) fasting insulin secretion representing insulin secretion at fasting plasma glucose level
BG	Blood Glucose concentration
BG_b	(mmol/L) fasting blood glucose concentration
BG_j	blood glucose concentration, constant over (t_j,t_{j+1}), t_{j+1}-t_j=Δt
CHO	CarbOHydrates amount in meals
CPN	Causal Probabilistic Networks
CV	Coefficient of Variation
DCCT	Diabetes Control and Complications Trial
DIAS	The DIabetes Advisory System
DIAS-IDDM	DIAS-NIDDM running in type 1 diabetes mode
DIAS-NIDDM	The DIabetes Advisory System for NIDDM; has the ability to process both type 1 and type 2 diabetes datasets
DSS	Decision Support System(s)
ENDO-BAL	(mmol/kg/h) endogenous glucose balance representing the sum between the hepatic glucose production, insulin dependent and insulin independent glucose utilisation
F_z	conditional distribution function
Δt	sampling interval, interval over which *BG* is considered constant
ΔT	discrete time interval for cohort division, T_{i+1}-T_i
$e_{BG_{profile}}$	$\{BG_j,\ j=1...n\}$, predicted *BG* profile generalised for a period of 120 days
$e_{HbA_{1c}}$	$\{HbA^m_{1c,k},\ k=1...l\}$, absorbed HbA_{1c} values, patient data
GUT_{ABS}	GUT ABSortion
HbA_{1c}	Glycated haemoglobin concentration
HbA_{1c}^m	Glycated haemoglobin concentration measurement
I_{ABS}	Insulin ABSorption

IDDM	Insulin Dependent Diabetes Mellitus
IIT	Intensive Insulin Therapy
IR	Insulin Resistance
Is	*i*nsulin *s*ensitivity parameter
I_{SEC}	Insulin concentration due to endogenous SECretion
IT	Information Technology
k	glycation rate (h^{-1} per mmol L^{-1}), time constant
NIDDM	Non-Insulin Dependent Diabetes Mellitus
Nph	time-to-peak of *NPH* insulin
NPH	intermediate acting insulin
N_T	number of samples over period T
OD	Overt Diabetes
Peak1	unglycated haemoglobin (Vs)
Peak2	glycated haemoglobin (Vs)
Ps	*p*ancreatic *s*ensitivity parameter
q_{10}	total unglycated haemoglobin (g) at the cell origination
q_1	unglycated haemoglobin (g) in a red cell at time t after cell origination
Q1	total unglycated haemoglobin (g) over all cohorts
q_2	glycated haemoglobin (g) in a red cell at time t after cell origination
Q2	total glycated haemoglobin (g) over all cohorts
r	glycated fraction (out of the total unglycated haemoglobin) for a given cohort exposed for ΔT at BG levels $\sum_{0}^{T_i} BG_j$
RMS	Root Mean Square
SEC-ENDO	(mU/kg/h) endogenous insulin secretion representing the total insulin secretion calculated as the sum of BG stimulated insulin secretion and the basal secretion
SD	Standard Deviation
T	erythrocyte life span, $T=N_T\Delta t$
T_i	time at which cohort i originates, $i=1,..,N$, and $T_{i+1}-T_i=\Delta T$

1. Introduction

Type 2 diabetes mellitus is a heterogeneous disorder characterised by insulin deficiency due to β-cell failure often associated with insulin resistance [19;46] and accounts for about 85% of all cases of diabetes in the developed countries. Though in the early stages of their disease the subjects with type 2 diabetes achieve adequate glycaemic control with diet alone or hypoglycaemic agents, as the disease progresses, up to 50% patients may require insulin treatment [92]. A personal series of 4926 patients with diabetes type 2 documented that as the treatment stabilised, 24% of the patients were treated by insulin injections, 44% by tablets, and 32% by diet only [108]. Intensive insulin therapy (IIT) can help in achieving excellent glycaemic control in subjects with type 2 diabetes for whom the standard pharmacological therapy has failed [41].

The research and development of computer applications that assist with the control of blood glucose (*BG*) in subjects with type 1 and 2 diabetes is highly motivated by the Diabetes Control and Complications Trial (DCCT) [2;57] and the United Kingdom Prospective Diabetes Study [135]. Results clearly prove that IIT delays the onset and slows the progression of the long-term complications associated with type 1 diabetes. The results are likely to apply to type 2 diabetes [40;110;118]. Information technology (IT) can assist in the transfer of expertise from specialist diabetes centres to primary care physicians and directly to the diabetic patient according to the requirements of St. Vincent Declaration [146] bringing along the benefits of IIT documented in DCCT.

The potential impact of computer-assisted insulin dosage adjustment or computer-assisted monitoring is of clinical importance and justifies further research despite sceptical views by some health care professionals and, at the present, the limited availability of these systems to patients.

Current IT applications are able to simulate *BG* profiles in response to given carbohydrate input and insulin doses in subjects with type 1 diabetes [96].

The Diabetes Insulin Advisory System (DIAS) is such a system for subjects with type 1 diabetes which employs a model of carbohydrate metabolism implemented as a causal probabilistic network [8;76]. Clinical trials performed with DIAS show that the prediction accuracy is limited by the naturally occurring variability in the underlying physiological processes, explaining mean predictive accuracy of 2.8 mmol/L [69]. The advice on insulin doses can be generated [8] and tests of the safety of administering the advised doses were performed [10;72].

For obvious reasons, the research has focused on delivering decision support for subjects with type 1 diabetes. The perceived need for decision support with insulin treatment in type 2 diabetes is low due to the treatment alternatives and may be associated with the reluctance of clinicians to prescribe insulin. However, recent results have shown increased interest in the use of insulin for subjects with type 2 diabetes alone or in combination with tablets [92;116]. IIT improved glycaemic control in young subjects with type 2 diabetes, especially in subjects who changed more often the daily insulin dose [104]. Given the higher prevalence of type 2 diabetes and the benefits associated with improved *BG* control documented by DCCT, decision support systems may attain an important role in the treatment of subjects with type 2 diabetes, also envisaged by the European Association for the Study of Diabetes (EASD), DO IT/MFIT, [23]:

"*From a technical point of view and from the perceived substantial clinical need for decision support for NIDDM, it is probable that such systems may be the first to be widely used*"

2. Hypothesis, Aims, Objectives and Plan of Thesis

2.1 Hypothesis

This thesis examines the following hypotheses:

- DIAS-NIDDM can generate advice that is similar in performance to the advice recommended by diabetes specialists;
- The advice is plausible, safe, and of clinical utility;
- DIAS-NIDDM has the potential to predict steady state HbA_{1c} in response to changes in diet and insulin therapy;
- Proceeding with the prospective clinical testing of DIAS-NIDDM is justified.

2.2 Aims

The aims of the research were to extend the existing DIAS model of carbohydrate metabolism with a component representing the insulin secretion present in subjects with type 2 diabetes and to develop a decision support system, DIAS-NIDDM, to assist in clinical practice with the adjustment of insulin doses in insulin-treated subjects with type 2 diabetes.

In relation to the problem of assessing the long-term complications of diabetes, the aim was to incorporate a model that predicts the steady state glycated haemoglobin (HbA_{1c}) concentrations in response to changes in diet and insulin therapy.

Furthermore, the research aimed to evaluate DIAS-NIDDM with regard to its performance, clinical utility, and safety of its advice in order to justify further prospective clinical testing of DIAS-NIDDM.

2.3 Objectives

The specific objectives in relation to the decision support in insulin-treated subjects with type 2 diabetes are:

- To build a model of *BG*-stimulated insulin secretion;
- To implement the model using causal probabilistic networks (CPN);
- To use the model to develop a decision support system, DIAS-NIDDM, based on a previous DIAS model of carbohydrate metabolism for the management of insulin-treated subjects with type 2 diabetes, providing quantitative advice on the insulin therapy;
- To investigate the feasibility of insulin treatment in subjects with type 2 diabetes in the context of current treatment and evidence from diabetes trials.

The specific objectives in relation to the prediction of steady-state HbA_{1c} concentration are:

- To model the process of glycation of haemoglobin A_{1c};
- To build a CPN model based on stochastic difference equations to calculate the glycated haemoglobin HbA_{1c} from DIAS-NIDDM predicted blood glucose values;
- To include a distinct model of HbA_{1c} assay to deal with the glycation induced heterogeneity of haemoglobin.

The specific objectives in relation to the evaluation of DIAS-NIDDM and the model of HbA_{1c} concentration are:

- To test and evaluate the system both in prediction and advisory mode;
- To compare the advice given by the system with the advice suggested by clinicians;
- To perform a pilot comparative study based on statistical criteria between DIAS and DIAS-IDDM in subjects with type 1 diabetes;
- To design a questionnaire that focuses on the main parameters of diabetes control (hyperglycaemia, risk of hypoglycaemic episodes, overall control);
- To use the questionnaire in a peer review retrospective assessment of the advice generated by DIAS-NIDDM against the advice recommended by two diabetes specialists in the considering of the actual diet and the therapy administered to the insulin treated subjects with type 2 diabetes;
- To test the hypothesis that DIAS-NIDDM gives insulin advice with similar perceived clinical utility as specialised clinicians;
- To test and evaluate the capability of the system to predict steady state HbA_{1c} concentrations in response to changes in diet and insulin therapy based on a pilot retrospective study.

2.4 Plan of Thesis

Chapter Three introduces background information on the carbohydrate metabolism and highlights relevant aspects like blood glucose concentration, Kreb's cycle, insulin resistance, haemoglobin glycation and its assay, and the main diagnostic categories in diabetes.

Chapter Four introduces elements of CPN modelling, fundamental equations for probability propagation/updating, parameter learning (e.g. the instantiation/conditioning technique), problems and solutions of conditional dependency in multiple-connected networks and concepts of dynamic CPN.

Chapter Five provides details of a new model of insulin secretion implemented in CPN. The model is intended to assist with the insulin dose adjustment for insulin-treated subjects with type 2 diabetes. The assumptions and limitations of the model are presented together with simulation results.

Chapter Six proposes a new model to predict steady state concentration of HbA_{1c} according to changes in therapy using DIAS-NIDDM generated *BG* profiles. Observing the heterogeneity of the haemoglobin glycation, a new closed form relationship was developed to model the assay of HbA_{1c} concentration. Finally, the implementation of the model in CPN is detailed and specific equations for model parameter estimation are derived.

Chapter Seven is dedicated to the principles of decision support systems (DSS). The underlying decision science is categorised into knowledge-based, data-based, and model-based. A review of existing systems for both type 1 and type 2 diabetes discusses approaches adopted by other systems in the field. The characteristics of DSS are identified and a new approach is proposed to delimit the place of DSS among other software categories. The reasons for DSS high rate of failure are revised, and an enhanced life cycle process for the development of DSS is proposed.

Chapter Eight details the development of DIAS-NIDDM, such as system requirements, underlying concepts, the extended CPN model of carbohydrate metabolism, a method to generate conditional probabilities from functional relationships between variables, concepts of applied Bayesian theory, and the algorithm of insulin dosage adjustment. Software development is illustrated by means of UML design diagrams.

Chapter Nine is dedicated entirely to the evaluation of DIAS-NIDDM and the evaluation of the model of HbA_{1c} concentration. Evaluation starts with the verification of the model using an RMS optimisation criterion in a pilot study and a comparability study between the original (DIAS) and the revised (DIAS-NIDDM, running in IDDM mode) implementations of the DIAS system. The evaluation of the new models is carried out by means of retrospective pilot studies. A case study illustrates the use of DIAS-NIDDM in subjects with type 2 diabetes. Moreover, a peer review evaluation on datasets of subjects with type 2 diabetes, and an evaluation of the ability to predict steady state HbA_{1c} concentrations following changes in therapy in subjects with type 1 diabetes are performed.

Chapter Ten presents the conclusions and possibilities for future work.

Appendices present domain knowledge on haemoglobin glycation, boronate-affinity assay of HbA_{1c}, the states of CPN variables in the network, and the peer review questionnaire.

3. Diabetes

3.1 Physiology

3.1.1 Carbohydrate Metabolism

3.1.1.1 General Description

The oxidative breakdown of food after digestion converts complex molecules into simpler products through a number of reactions necessary to process the carbohydrates, fats, and proteins. These transformations are far beyond the functional capacity of the individual cell, and are done by a multi-phase intermediary metabolism. In a first phase, intestinal digestion and absorption decompose the variety of foods to only glucose and some close isomers, glycerol, fatty acids and amino acids. In phase two, the products from the phase one are oxidised and acids are produced. Finally, in the third stage, the complete oxidation of the acids remaining from the phase two takes place.

The intermediary metabolism of carbohydrate forms the physiological mechanism through which the blood glucose concentration is controlled. The 'citric acid cycle' (Kreb's cycle) is the basis for a metabolic cyclical pathway that is common to all carbon structures of all foods, where all major metabolic materials transform one into the another.

The chemical reactions and processes involved are: *glycogenesis* (the synthesis of glycogen from glucose), *glycogenolysis* (glycogen to glucose), *glycolysis* (oxidation of glucose or glycogen to pyruvate and lactate), *Kreb's cycle*, and *gluconeogenesis* (formation of glucose or glycogen from glucogenic amino acids, lactate, and glycerol) [39].

The liver is the key organ in the control of the regulation of the plasma glucose, responding sensitively to changes in the blood glucose concentration, because the hepatic cells are freely permeable to glucose (unlike other cells, hepatic cells do not need insulin for intra-cell glucose transport). When the blood glucose is high, the liver

forms glycogen. When the blood glucose is low, glycogen breaks down and glucose is released into the blood stream. At plasma glucose concentrations of 4.5-5.5 mmol/L the liver produces glucose, and the production of glucose is suppressed at above normoglycaemic concentrations [34;77;81].

3.1.1.2 Blood Glucose Regulation

The rise in the concentration of blood glucose following, for instance, meal digestion, stimulates insulin secretion by the pancreas. The insulin has many actions that tend to lower the blood glucose concentration mainly by promoting transport of glucose in the cells. The plasma glucose concentration represents the equilibrium between the rate at which glucose is entering and leaving the blood stream. In a normal subject, the concentration of the plasma glucose is normally in the range of 3.5 - 8.5 mmol/L.

The carbohydrates in the diet tend to raise the blood glucose. Following glucose ingestion, the balance maintained during fasting is disrupted and the glucose homeostasis is achieved by three processes: insulin secretion, stimulation of glucose uptake in response to hyperinsulinaemia and hyperglycaemia and, suppression of hepatic glucose production. The secreted insulin stimulates the glucose uptake by the peripheral and hepatic tissues and suppresses the hepatic glucose production. While the blood glucose concentration is high, glycogenesis is activated. The blood glucose concentration is brought back to the basal level, insulin secretion is reduced to the fasting rate, and the hepatic glucose production (glycogenolysis within minutes and glyconeogenesis hours or even days later) is resumed [81].

During fasting, there is a balance between glucose uptake and hepatic glucose production. Substrates other than glucose are converted through the citric acid cycle to glucose so that the basal blood glucose concentration is maintained (3.5-5.5 mmol/L). The blood glucose in normal subjects does not fall below 3.5 mmol/L, regardless of how low the carbohydrate intake even for very long fasting periods.

When the blood glucose is not properly regulated, as in diabetes, hypoglycaemia and hyperglycaemia are frequent. The former has negative effects on the brain supply with

energy and can lead to coma, while the latter has no immediate effect except for glycosuria, but it is harmful with regard to the long-term complications of diabetes: retinopathy, nephropathy, neuropathy, and cardiovascular diseases [64;90;110].

3.1.2 Insulin Secretion

Insulin is secreted by the β-cells in the pancreas. Glucose is the most potent physiological stimulus to the liberation of insulin from the β-cell. Connecting peptide (C-peptide) is co-secreted in equimolar fashion with insulin. Following a meal tolerance test (MTT), 75 g CHO 500 kcal, the plasma insulin concentration increases from a fasting level of 5-10 mU/L to a level of 70 mU/L on the average in normal subjects [78].

When the pancreas is excited with prolonged steps of glucose, the insulin secretion shows a two-phase pattern, an early phase secretion followed by a slowly rising second phase [120]. The infusion of glucose as ramp functions of slowly increasing concentration caused the phasic response to disappear. Studies have also shown the existence of ultradian oscillations of insulin secretion of 10-15 min period [136].

3.1.3 Insulin Resistance

In subjects with type 2 diabetes, the transport of glucose is decreased in muscles cells, adipose cells and in β–cells of the pancreas.

The skeletal muscle is the primary site responsible for insulin – stimulated glucose utilisation and the glucose transport is the rate limiting step for glucose utilisation in muscle [91;103]. The transport of glucose across muscle and adipose cell membrane is controlled by the glucose transporter proteins GLUT1 (basal transport) and GLUT4 (insulin-stimulated transport).

The GLUT2 transporter protein present on the membrane of the β cells regulates the insulin secretion, and its deficiency in type 2 diabetes can partly be responsible for the decreased insulin secretion [62].

The expression of glucose transporters and their intra-cellular translocation was decreased in diabetes type 2 subjects, though the exact mechanisms are still hypotheses [105].

Insulin treatment may be inappropriate in subjects with type 2 diabetes with low insulin sensitivity. However, biguanides are prescribed to improve insulin sensitivity [75;85;103] and can alleviate the defect of glucose cell transport when stimulated by insulin.

3.1.4 Haemoglobin Glycation

Haemoglobin is characterised by structural intrinsic heterogeneity. Moreover, in the circulating plasma, the heterogeneity of the normal adult plasma haemoglobin (Hb) is further progressed by the glycation taking place naturally where fractions are formed by the non-enzymatic attachment of glucose and its derivates to haemoglobin [30;45], see APPENDIX I.

The glycation of haemoglobin occurs slowly, continuously and nearly irreversibly over the life span of the erythrocyte [29]. The stable form of the modified glycated haemoglobin is detected by glycation specific techniques such as the boronate affinity chromatography [98].

Other glycated serum proteins (such as albumin and fructosamine), that glycate in a similar manner to the haemoglobin, also reflect the effects of a new therapy on the level of control of diabetes. Despite difficulties with their measurement processes (prone to interferences and need methodological corrections), their faster response to a change in therapy make them suitable to be used to assess the diabetic control in subjects with altered cell life span or other conditions which make HbA_{1c} measurements unusable, such as recent blood transfusion recipients.

3.1.5 The HbA_{1c} Assay

There are various methods and technologies used to measure the HbA_{1c}, resulting in inter-lab variability in practices and equipment and therefore in the subsequent lab results. However, the discrepancy has been addressed and guidelines have been promoted by the regulatory organisations [26], and the results are representative of the measured variable and standard thresholds that are lab-independent have been generally accepted [114].

Broadly, there are charge-dependent and glycation specific methods [114]. The charge-dependent methods are sensible only to the glycation at a site of haemoglobin that implies a significant change in charge due to the reaction itself (β-chain modified haemoglobin), but it suffers from interference by haemoglobin variants, other non-glycation modifications, or components formed during storage. The glycation specific methods include the boronate affinity chromatography (see APPENDIX II). The boronate affinity method is sensitive to all stable glycated haemoglobins and does not suffer from any interference induced by any of the unstable fractions of haemoglobin.

However, the assay is subject to patient specific variability of the erythrocyte's life span especially in subjects with forms of temporary or chronic blood loss. The HbA_{1c} assay may also be influenced by weekly alcohol intake when in excess of 30 units of ethanol.

3.2 Diagnostic Categories

3.2.1 Diabetes Type 1

Type 1 diabetes is a chronic disease characterised by the autoimmune destruction of insulin secreting β-cells sited in the pancreas [91]. The immediate symptom is hyperglycaemia and its observable manifestations. The treatment requires lifelong dependence on exogenous insulin for survival. The insulin is usually administered as multiple injection regimens along with diet. The aim of the treatment is to maintain the control of blood glucose as much as possible within the normal physiological limits (4 - 8.5 mmol/L). There is a constant risk that the insulin is in excess (missed meal or other processes like taking exercise) and can produce hypoglycaemia in subjects targeting optimum control. In addition to the lifelong dependence on insulin and imposed lifestyle, the diabetic has to fight and delay as much as possible the onset and progression of complications of diabetes by having a constant good glycaemic control. The glycosilated haemoglobin (HbA_{1c}) is a reliable indicator of the long-term glycaemic control. Optimum control is indicated by values of 6-7 %, while 7-8% still indicates reasonably good control. It is expected that subjects achieving very low HbA_{1c} experience higher frequency of hypoglycaemic episodes. A very negative aspect is the development of hypoglycaemia unawareness in subjects with type 1 diabetes [36].

Physical exercise can improve the overall glycaemic control directly or indirectly by improving the insulin sensitivity, but this requires adjusting the doses of insulin in order to avoid the induction of hypoglycaemia episodes due to the synergistic lowering effects on blood glucose concentration by both insulin and exercise [124;145].

Glucose counter-regulation seems to be more than a hypothesis; clinical studies have shown its presence in selected subjects with type 1 diabetes [67]. Glucose counter-regulation is a mechanism that induces hyperglycaemia. It is triggered by a hypoglycaemic episode. A typical counter-regulation begins 6-8 h after the hypoglycaemic attack and lasts up to 16-18 h. This phenomenon is especially

dangerous because the hyperglycaemia can convince the patient or clinician to increase the doses of insulin that will further increase the chances for hypoglycaemia and a vicious circle is started.

3.2.2 Diabetes Type 2

Type 2 diabetes is a heterogeneous disorder characterised by insulin deficiency due to a partial β-cell failure often associated with insulin resistance [46] and accounts for about 85% of all cases of diabetes in the developed countries.

The onset of the disease is usually at a late age. Diabetes type 2 is characterized by impaired glucose tolerance (IGT), high fasting *BG* and high random *BG*. Because of hyperglycaemia, HbA_{1c} is expected to be high. The aim of the treatment is to improve the glycaemic control. Though in the early stages of their disease subjects with diabetes type 2 achieve adequate glycaemic control with diet alone or hypoglycaemic agents, as the disease progresses up to 50% subjects may require insulin treatment [92]. Insulin treatment in subjects with diabetes type 2 is becoming common practice and the percentage of subjects on insulin treatment has been increasing. Recent studies showed that intensive insulin therapy in subjects with diabetes type 2 improves the glycaemic control [104] and can delay the onset and slow the progression of long term complications [110].

4. Causal Probabilistic Networks

4.1 Introduction

Causal probabilistic networks (CPN) emerged as applied probabilistic methods to deal with tasks requiring automated reasoning in domains where data and decision-making processes involve uncertainty. CPN are used for building models of stochastic processes in domains with inherent uncertainty and causal relations represent domain concepts [76]. Knowledge is represented as conditional probabilities and inferences are performed by inherent inference mechanisms using the Bayes' theorem.

Other approaches to deal with uncertainty are known [113]. The extensional approach (production systems) treats uncertainty as a generalized truth-value attached to a relationship and provides ways to compute the uncertainty of a relationship as a function of the uncertainties of the sub-relationships involved in an inference path. Computationally they are efficient but they have problems in grasping the semantics of the domain. With the intensional approach (model based) including CPN, the uncertainty is attached to states of the concepts or variables in a domain. The semantics of the relationships in the domain can be modelled, but the computation involved can be resource consuming.

Despite the computational merits, the extensional approaches have a series of shortcomings. The semantic deficiencies and incoherent updating result in improper handling of bidirectional inferences, difficulties in retracting conclusions, incapability to handle interaction between multiple causes or improper handling of correlated pieces of evidence (too local to recognise the common origin of information) which increases the credibility of a hypothesis. Sizeable research resources are spent for developing techniques to remedy some of the semantic deficiencies [113]. On the other hand, the intensional approaches at the price of being computationally clumsy they are semantically safe. They can handle bidirectional and correlated evidence due to a globally coherent reasoning based on local computations with ability to process context-sensitive beliefs. CPN are sound and complete inference mechanisms.

However, the computational complexity associated with the intensional approach is continuously decreasing with the current developments in hardware and software.

4.2 Propagation (Certainty Updating)

Propagation updates the *a posteriori* probabilities of variables in the model after evidence has been entered into the network nodes. Implementation schemes are based on message passing between the nodes of the network using local computations [7;87;113]. Bidirectional updating is usually necessary to update the *a posteriori* probabilities of all the variables in the network and can be implemented locally as calls to Collect-evidence and Distribute-evidence algorithms [112]. Following the propagation, the joint probability tables associated with the lumped variables are consistent.

At the lowest level, the Collect-evidence and Distribute-evidence algorithms use forward propagation (Fundamental Rule) to update $p(B)$ when updated *posterior* (or evidence) $p(A)$ is available, also used to propagate *a priori* initial probabilities in the network:

$$p(A,B) = p(B|A)p(A), \qquad 4\text{-}1$$

where $p(B)$ results after marginalisation,

and the Bayes' rule for backward propagation when $p^*(B)$ is available:

$$p^*(A,B) = p(A|B)p^*(B) = \frac{p(A,B)}{p(B)}p^*(B), \qquad 4\text{-}2$$

where $p^*(A)$ results after marginalisation.

4.3 Multiple - Connected Networks

When loops exist in the underlying network, the network is no longer singly connected and as a result the local propagation schemes are not correct any longer as the messages may be passed indefinitely around the loops [38;113]. There are three methods to cope with the problems caused by the existence of the loops: clustering, conditioning, and stochastic simulation [113]. Clustering method lumps several variables in such a way that the resulting network of clusters is singly connected (junction tree). Conditioning breaks the communication links along the loops by instantiating a select group of variables. Stochastic simulation computes updated probabilities by counting how frequently events occur after a number of simulations with variables being assigned a definite value that is used to update the other variables.

4.4 The Instantiation/Conditioning Process

Given that a CPN model has a parameter P and the evidence, $e = \{e_1,..,e_j\}$, is present for nodes $j=1,..,n-1$, the parameter's a posteriori probability distribution can be estimated by conditioning.

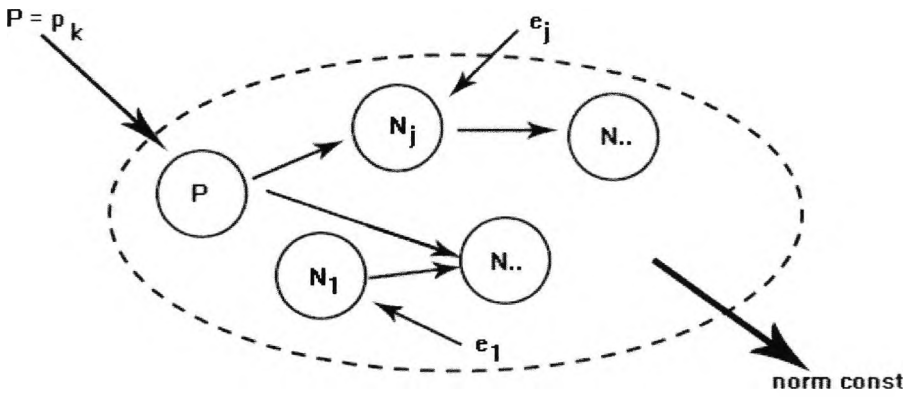


Figure 4.1 *CPN model after a global propagation generates the normalisation constant*

Node P is instantiated in each of its individual states, $P = p_k$. The probabilities in the network are updated, and a normalisation constant is calculated for each state of P. The normalisation constant is equal to the probability of the evidence inserted in the network, $p(p_k, e_1,..,e_j) = p(p_k, e)$, $k=1$ *to* S = *size(P)*, where *size(P)* is the number of states of parameter node P.

$$p(p_1|e) = p(p_1,e) / p(e)$$
$$p(p_2|e) = p(p_2,e) / p(e)$$
$$\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots$$
$$p(p_S|e) = p(p_S,e) / p(e) \qquad 4\text{-}3$$

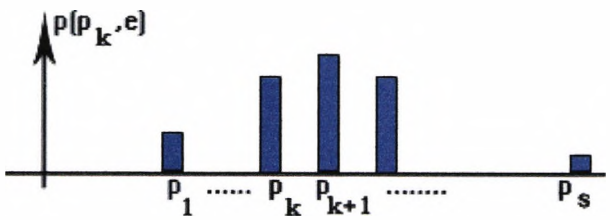


Figure 4.2 *Probability distribution for parameter node P*

After normalisation of $p(x_n, e)$, $i=1$ to n, the vector represents the probability distribution of parameter X conditioned on the evidence entered, $e=\{e_1,..,e_j\}$.

4.5 Designing and Implementing Models Using CPN

CPN have proved to be a useful knowledge-representation tool for modelling domains in which relations between concepts are expressed as causal relations with inherent uncertainty.

The scheme for CPN knowledge-representation is based on a set of nodes and a set of directed arcs quantified by conditional probability tables. Each node has a set of mutually exclusive states representing a domain concept or variable and its possible states. The state of a variable has an associated probability value that may change as new evidence becomes available. The directed arcs explicitly represent the

dependencies in the graph. The conditional probabilities quantify the strengths of the dependencies of a state of a child on the states of the parent nodes.

The process of modelling starts by selecting the domain variables. Data modelling follows, targeting the dependence between variables building the conditional probability tables for each dependency. These dependences can be simple operations (addition, substraction, etc), empirical data in tabulated form or analytical relationships [134].

4.6 Dynamic CPN

Modelling dynamic stochastic systems using temporal relationships distinctly represented in the model by means of CPN involves updating the model at discrete times. Dynamic CPN allow modelling of stochastic processes where multiple instances of static networks are interconnected by temporal relationships. Each static network represents the state of the dynamic system at a given moment or interval in time.

The model is made up of a window of slices [89], and for all the inference purposes it is assumed to represent the triangulated composite graph of the time slices.

Though in principle dynamic CPN have an infinite number of slices, propagation is carried out only in a window. Inferences within the window are performed as in conventional static networks. Moving the window forward is performed by a process of model expansion (adding a new sub-tree to the junction tree) followed by a process of model reduction (cutting off a part of the tree).

Reduction of the model results in some potential in one of the cliques (including the time interface of the slice) of the reduced junction tree that represents all the information for the future predictions to take full account about the history of the system. Model expansion requires the addition of new time slices and the triangulation of the expanded model. Propagation is carried out to update the *a posteriori* probabilities of the variables in the new time slices of the window. Backward smoothing is performed when there is interest in the effect of new evidence

on variables in past time slices that are not covered by the current model any longer. Complete information about the probabilities in the current window has to be propagated back to past time slices through interface cliques. Forecasting can be performed by expanding the window. In the case of forecasts for long periods ahead, moving the window in a number of steps is more adequate because of the limited computer resources.

DIAS-NIDDM uses an adapted scheme of dynamic CPN [84], disseminate only CPN, and the window contains only one time slice. During learning, only forward move of the window is necessary for obtaining the normalisation constants associated with the new evidence, used to update the joint probabilities of the parameters. The backward smoothing is not performed as the learnt *BG* profile is not required, leading to reductions in the computation time. The forecasting also uses only forward move of the window.

4.7 Supportive Tools

4.7.1 Hugin

Hugin®, by Hugin Expert A/S, is a powerful tool for building CPN models, with its own specification language, **Net**, which allows direct specification of the conditional probability tables.
Net is a low-level specification language and as a result large models with repetitive elements are very difficult to specify using **Net**.

4.7.2 hmm

hmm [111] is a tool for the specification of large causal probabilistic networks. This tool acts as a pre-processor to the **Hugin** ® expert system shell, generating a **Net** specification.

The specification language of **hmm** is called **CPNSPEC**. By using this language, the conditional probability tables can be described as "deep knowledge", in the form of model relations, which reflect the nature of interaction between nodes. The specification of repetitive elements in large causal probabilistic networks is done with specific language keywords.

5. Model of Insulin Secretion

5.1 Modelling Endogenous Insulin Secretion

The rise in the concentration of blood glucose following, for instance, meal digestion stimulates insulin secretion by the pancreas [144]. During its first-pass through the liver, approximately 50% of insulin is extracted by the liver and never reaches central circulation. Another peptide, C-peptide, is co-secreted with insulin in an equimolar ratio, but unlike insulin, C-peptide is not cleared by the liver to any significant extent [82;119].

In insulin treated subjects with diabetes type 2, plasma insulin includes a component due to endogenous insulin secretion and a component due to insulin injections (exogenous insulin). However, plasma C-peptide concentration is only due to endogenous secretion and can, therefore, be employed to obtain information about pre-hepatic (i.e. prior to the first-pass through the liver) insulin secretion.

During a meal tolerance test (MTT), C-peptide secretion rate has been shown to be linearly related to the concentration of blood glucose [3;78;79]. We therefore assume that this linear relationship holds between BG concentration and insulin secretion rate in the model. It is also assumed that plasma insulin concentration due to endogenous insulin secretion is linearly related to BG concentration. This is based on the observations that insulin kinetics in the plasma are linear at least in the lower physiological range of insulin concentration [80] and that plasma insulin equilibrates quickly compared to the time steps employed in DIAS systems [76]. The model of endogenous insulin concentration due to the BG stimulated insulin secretion is fully specified by (i) one measurement, fasting blood glucose concentration (BG_F), (ii) one derived value, fasting plasma insulin concentration (I_F), and (iii) one parameter, pancreatic sensitivity ($\underline{ps}$), see Figure 5.1.

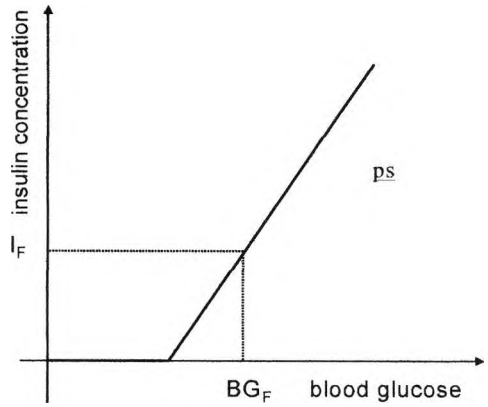


Figure 5.1 *The linear model of insulin secretion is fully specified by fasting blood glucose (BG_F), fasting insulin concentration (I_F), and pancreatic sensitivity (ps)*

The fasting C-peptide secretion rate is calculated from the fasting C-peptide concentration using a population model of C-peptide kinetics [143]. The fasting insulin secretion rate is assigned half of the value of the fasting C-peptide secretion rate assuming 50% first-pass hepatic extraction of insulin [141]. The fasting insulin concentration due to endogenous insulin secretion is computed from the fasting insulin secretion rate using a conversion factor (1 mU/L = 1 mU/kg/h). Pancreatic sensitivity *ps* represents the β-cell responsiveness to the *BG* levels elevated above the fasting *BG* level, BG_F.

Formally, the insulin concentration due to endogenous insulin secretion is calculated as

$$I_{SEC} = I_F + (BG\text{-}BG_F)\, ps \qquad 5\text{-}1$$

constrained to non-negative values.

The time to achieve equilibrium between plasma insulin concentration and its action on the glucose uptake is considered short in comparison with the time-step of 30 minutes used in DIAS-NIDDM.

5.2 Limitations of the Model

A number of simplifications were made to limit the complexity of the CPN model of *BG*-stimulated insulin secretion. The diurnal changes in pancreatic sensitivity were neglected. First-pass hepatic extraction of insulin was assumed constant and equal to 50% of the pre-hepatic insulin secretion. The mechanisms involved in the secretion of insulin other than the stimulation of insulin secretion by the postprandial levels of *BG* were not modelled.

5.2.1 CPN Model of Carbohydrate Metabolism and Endogenous Insulin Concentration Implemented Using HUGIN

The model of insulin concentration was implemented in CPN using the HUGIN shell. The model was integrated into the DIAS slice as shown in Figure 5.2.

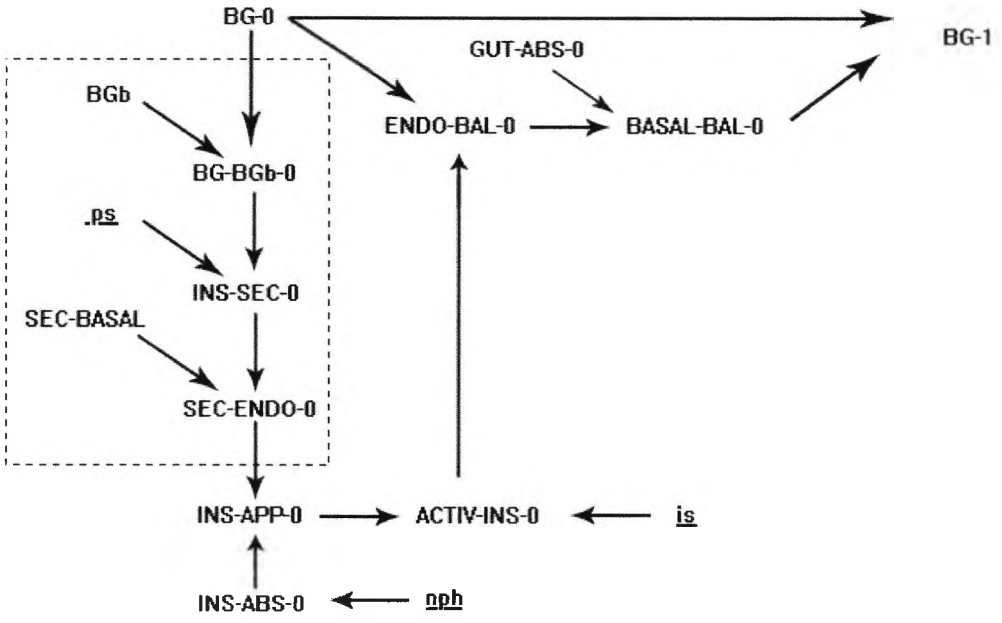


Figure 5.2 *Extended CPN model of carbohydrate metabolism includes an endogenous insulin secretion/concentration model. The endogenous model of insulin concentration consists of the nodes in the dashed box. Remaining nodes belong to the model of insulin action as implemented in DIAS*

The DIAS-NIDDM slice consists of the following nodes:

- blood glucose concentration calculated by adding the endogenous glucose balance to the blood glucose from the previous slice (*BG*, mmol/L)
- endogenous glucose balance representing the sum between the hepatic glucose production, insulin dependent and insulin independent glucose utilisation (*ENDO-BAL*, mmol/kg/h)
- active insulin concentration representing insulin action (*ACTIV-INS*, mU/L)
- insulin sensitivity representing the whole body sensitivity of glucose uptake to insulin (*is*, dimensionless)

- absorption of glucose due to meal digestion (*GUT-ABS*, mmol/kg/h)
- intermediate glucose balance representing the difference between the absorbed glucose from the gut and the endogenous balance (*BASAL-BAL*, mmol/kg/h)
- exogenous insulin absorption represents insulin appearance due to exogenous insulin (*INS-ABS*, mmol/kg/h)
- fasting blood glucose concentration (BG_b, mmol/L)
- *BG* excursion due to food intake (*BG* - BG_b, mmol/L)
- pancreatic sensitivity to *BG* level (*ps*, mU/L per mmol/L)
- insulin secretion due to the *BG* level above the fasting *BG* (*INS-SEC*, mU/kg/h)
- fasting insulin secretion representing insulin secretion at fasting *BG* level (*BASAL-SEC*, mU/kg/h)
- endogenous insulin secretion representing the total insulin secretion calculated as the sum of *BG* stimulated insulin secretion and the basal secretion (*SEC-ENDO*, mU/kg/h)
- total insulin appearance representing the sum of the endogenous insulin secretion and the exogenous insulin absorption (*INS-APP*, mU/kg/h)

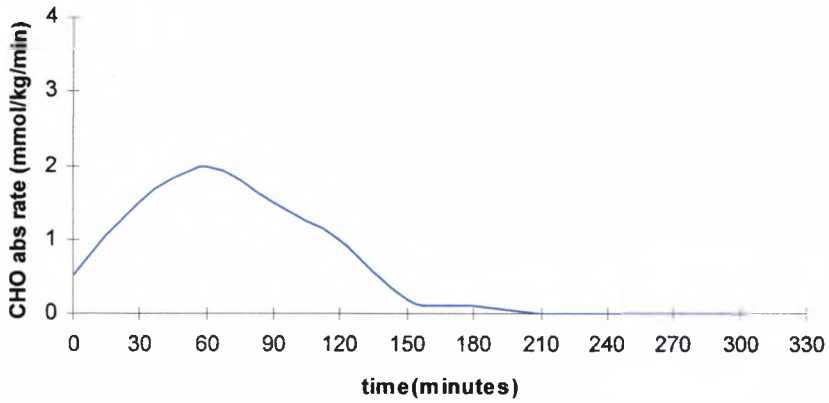
Time is suggested for each variable, subscript "*+0*" indicating time *T* and "*+1*" indicating time T_{+30} minutes.

5.3 Simulation Results

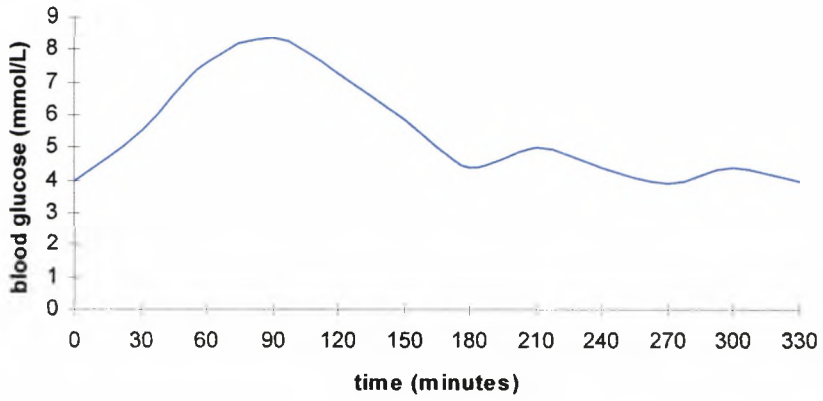
The model implemented using **Hugin** ® Runtime (Figure 5.2) has been used to simulate the effect of parameters and insulin injections on the blood glucose profile following meal digestion.

5.3.1 Simulation of the BG Profile in a Normal Subject

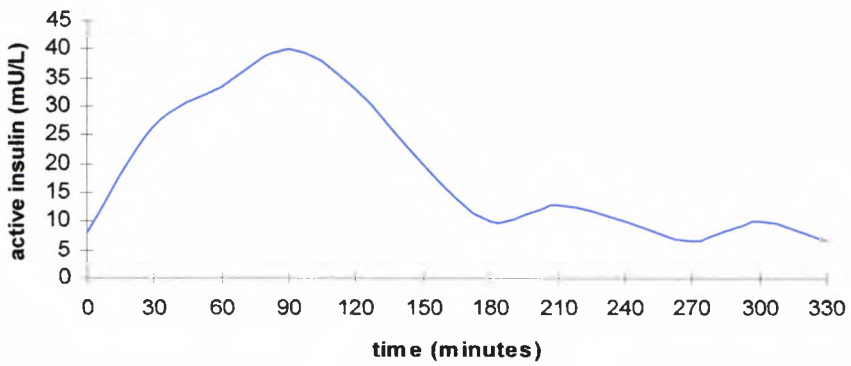
For a given driving function modelling the gut absorption after meal digestion at time 0 (Panel A), the CPN model predicted the blood glucose profile (Panel B, mean concentration is plotted) and the active insulin concentration (Panel C, mean concentration is plotted) (Figure 5.3). The model parameters were instantiated with typical values for a normal subject (insulin sensitivity = 1, pancreatic sensitivity = 10 mU/L per mmol/L, fasting insulin secretion = 6.4 mU/kg/h, fasting blood glucose = 4 mmol/L).



A



B



C

Figure 5.3 *Simulation results for a normal subject. Panel A: A driving function representing absorbed glucose from gut following meal digestion is fed into the system. Panel B: Blood glucose excursion as a result of the interaction with the endogenous insulin secretion (Panel C). Curves represent mean values*

5.3.2 Effect of Model Parameters on BG Profile

The CPN model of carbohydrate metabolism implemented in the Hugin shell was used to predict the effect of type 2 diabetes abnormalities on *BG* profile.

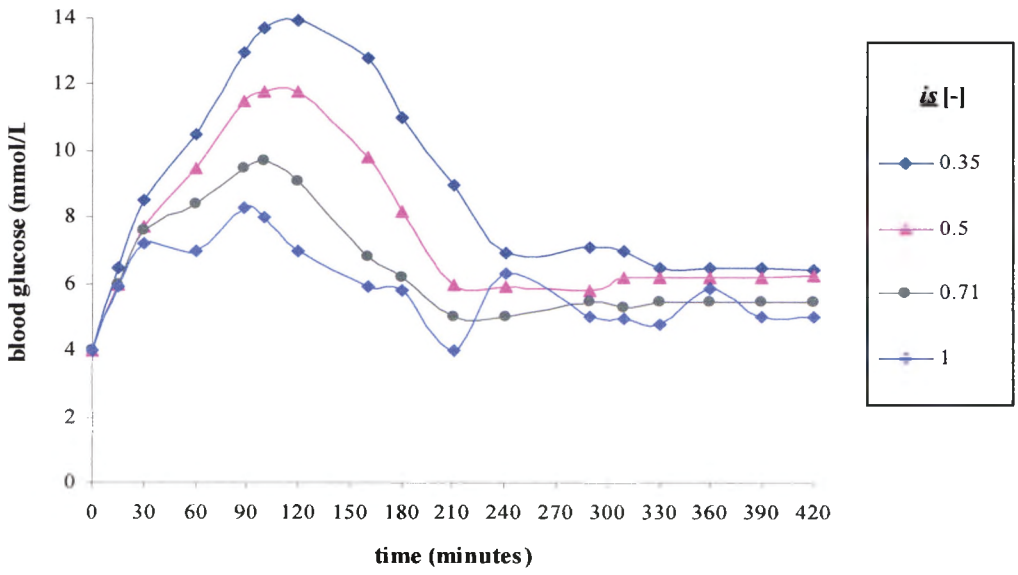


Figure 5.4 *The effect of different insulin sensitivities on BG profile. The mean insulin sensitivities used were: 0.35, 0.5, 0.71, 1. Lower insulin sensitivity results in higher BG profile*

The results shown in Figure 5.4 indicate that insulin resistance results in postprandial hyperglycaemia.

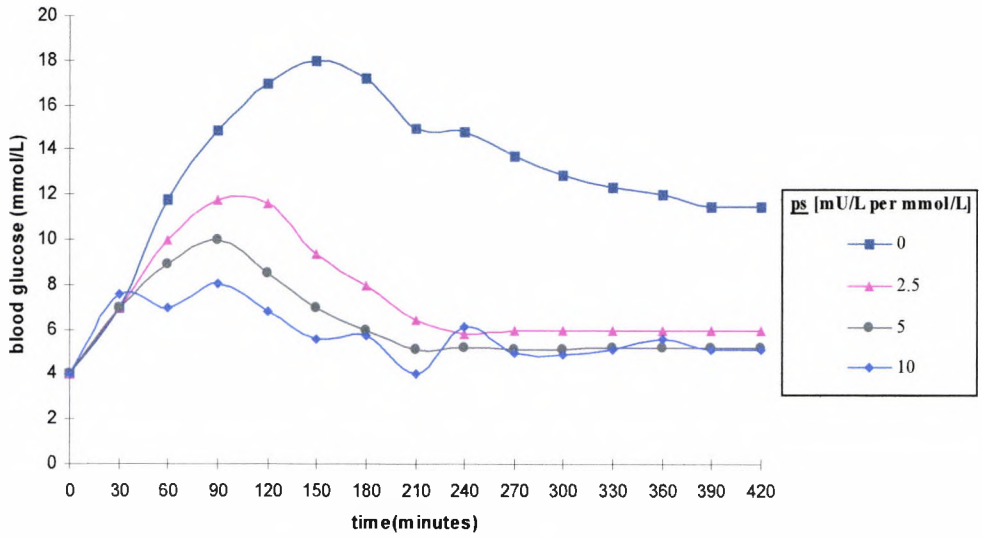


Figure 5.5 *Effect of pancreatic sensitivity on the BG profile. Pancreatic sensitivity parameter values were: 0, 2.5, 5, 10 mU/L per mmol/L. Lower pancreatic sensitivity results in higher post-prandial BG profile*

The results in the Figure 5.5 show the effects of impaired insulin secretion (simulated as low pancreatic sensitivity). Impaired insulin secretion also results in postprandial hyperglycaemia. However, when *is* and *ps* are varied so that *is*ps= constant*, the profiles are identical, except in the presence of exogenous insulin.

5.3.3 Simulating the Effect of Insulin Injections

The effect of exogenous insulin on the blood glucose profile in subjects with diabetes type 2 has been simulated. The insulin absorption at intervals of 30 minutes has been estimated using a model of insulin absorption, and the values inserted as evidence into the *INS-ABS* nodes of the model. The gut absorption due to meal digestion was also simulated. Blood glucose profiles were obtained for different doses and timings of the injection with respect to the meal ingestion, see Figure 5.6. Though the usual treatment for subjects with diabetes type 2 treated with insulin is two NPH injections, the effect of short acting insulin was also investigated.

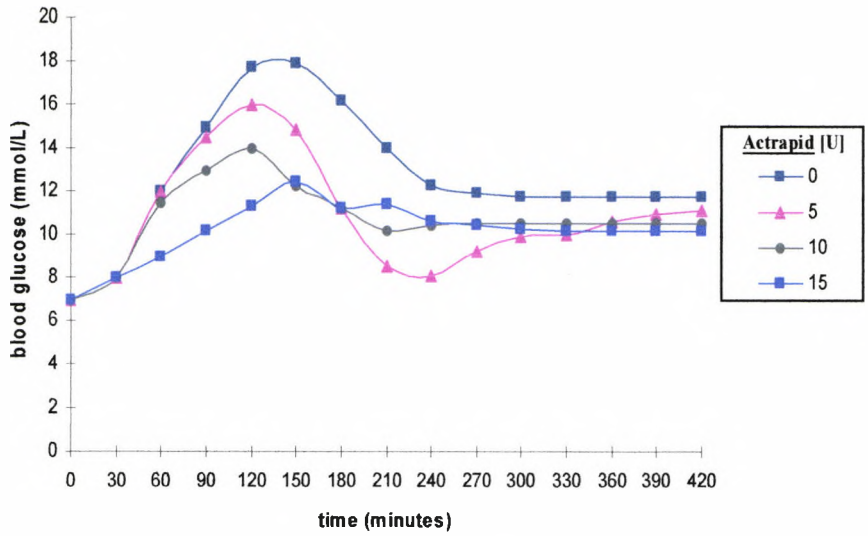


Figure 5.6 *Effect of increasing doses of short acting insulin on the BG profile. Timing of injection coincides with meal ingestion. Larger doses of Actrapid (0, 5U, 10U, 15U) insulin restore the BG levels to basal level in shorter time*

The following values for the parameters were used: $\underline{is}$ = 0.35 and $\underline{ps}$ = 2.5 mU/L per mmol/L.

5.4 Discussion on the Duration of the Slice

The addition of the model of insulin secretion to the DIAS slice rendered the system unstable if the time-step of one hour was used. A driving function simulating the gut absorption after meal ingestion was applied to the model. The predicted *BG* profile presented an 'erratic' behaviour shown in Figure 5.7.

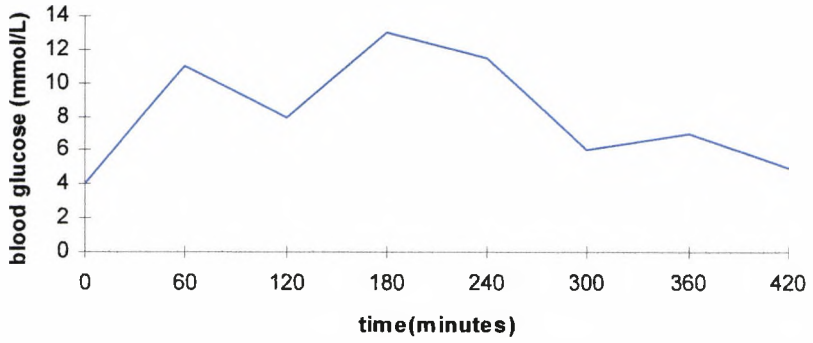


Figure 5.7 *System predicts blood glucose profile in a normal subject after meal ingestion. For the time step of one hour, the predicted BG profile has a chopped aspect due to unstable behaviour of the system*

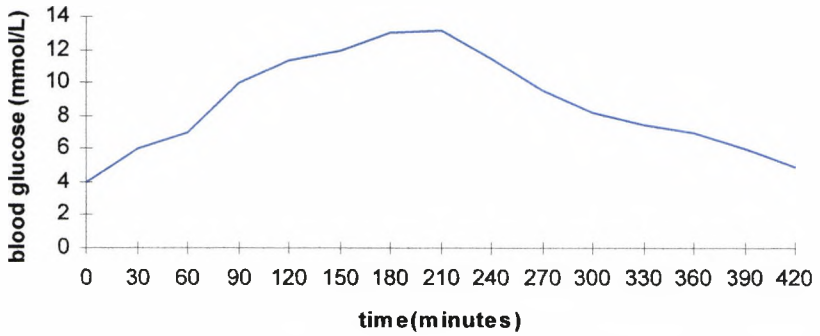


Figure 5.8 *System predicts blood glucose profile in a normal subject after meal ingestion, using a 1/2 hour time slice*

The reduction of the time step to half an hour solved the problem (Figure 5.8). Investigations for smaller time steps showed no further improvement.

5.5 Implementation as State Propagation

To cope with the computational demands due to the duration of the time slice and the intrinsic increased complexity of the DIAS-NIDDM slice, the insulin secretion/concentration model has been implemented by direct elementary probability calculus.

Figure 5.9 depicts the linear relationship between endogenous insulin secretion and the blood glucose concentration. *BG* is represented as a discrete probability distribution (dashed rectangles on the horizontal axis) and following the propagation, the insulin secretion is obtained as a discrete probability distribution (dashed rectangles on the vertical axis).

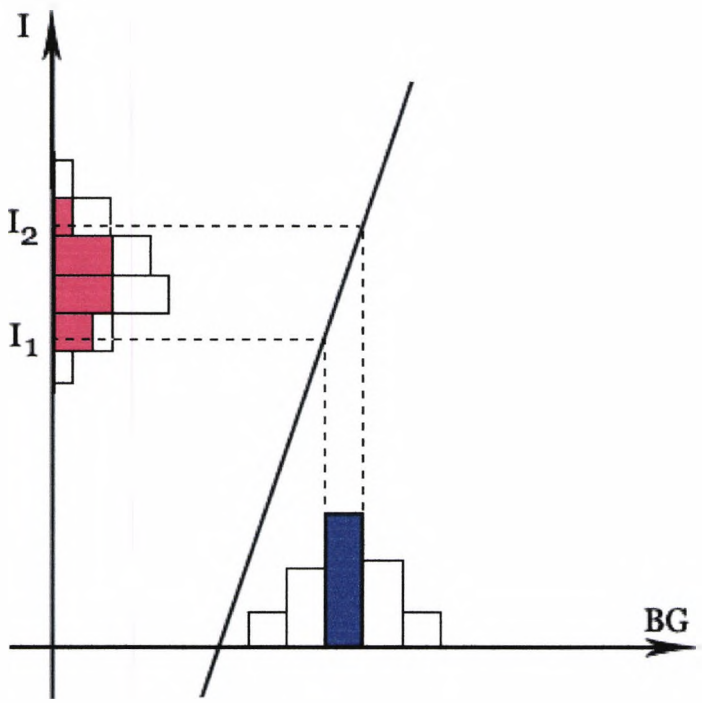


Figure 5.9 *CPN propagation using elementary probability calculus. The probability mass of a BG state interval is propagated (filled blue rectangle) and results in probability mass in several states of insulin secretion state intervals (filled red rectangles)*

Each state of the stochastic variable *BG* is propagated individually through the model and the final probability distribution of the insulin secretion is obtained by superimposing the individual results.

In essence, a given state of the stochastic *BG* variable defined by the interval $(BG_{i-1}, BG_i]$ is mapped into the interval $(I_{j-1}, I_j]$, according to the linear relationship $I=f(BG)$ with f defined by the relationship (5-1).

The probability of the *BG* state is distributed over states of the insulin secretion within interval (I_1, I_2). The exact probability each state of insulin secretion is assigned is proportional to its length, as the dependence relationship linear.

5.6 Conclusions

A new model representing the insulin secretion present in subjects with type 2 diabetes and in normal subjects was built. The relationship between *BG* and endogenous insulin secretion was assumed linear.

The first-pass hepatic extraction was accounted to 50% of the total secreted insulin. The plasma C-peptide concentration is only due to endogenous secretion and was, therefore, employed to obtain information about pre-hepatic (i.e. prior to the first-pass through the liver) insulin secretion. Other phenomena present in the insulin secretion patterns (differential effect, two-phase pattern, effect of mixed meals, and ultradian oscillations) were not modelled.

The model has been implemented in CPN

6. A New Model of Steady State HbA_{1c} Concentration

6.1 Introduction

The glycation of haemoglobin is a time-concentration dependent process and occurs continually throughout the circulatory life of the erythrocyte [29;131;137;139]. The measured glycated haemoglobin provides a means, complementary to, and more reliable than both the self-monitoring of *BG* and the recording of the symptoms (polyuria, nocturia, etc), for assessing the overall efficacy of a therapy. The HbA_{1c} assay has become an established standard in the management of diabetic subjects [60].

In normal adults, typical HbA_{1c} values are in the range 4.2-6.2%. In poorly controlled diabetics, the glycated haemoglobin may be well in excess of that in normals [30]. Diabetics brought under control, following an IIT regime, exhibit a gradual drop in HbA_{1c} and reach a new equilibrium in approximately 60 days [131;138;139]. Well-controlled diabetics may keep their HbA_{1c} near or in the normal range, with a positive impact on the delay of the development of the long-term complications of the diabetes [90].

Much interest has been shown to develop analytical closed-form relationships between plasma glucose levels and the quality of diabetic control, respectively the steady state HbA_{1c} concentration, and vice versa, calculating the mean *BG* levels associated with a measured steady state HbA_{1c} value.

Schlichtkrull [129], as early as 1965, reported the inherent difficulty in assessing the state of the diabetic control from patient data alone (hyperglycaemia, hypoglycaemia, glucosuria, etc). Schlichtkrull stated the need for a precise method to assess the efficacy of various therapies and proposed an M-Value, an index representing a cost function. The index reflects a practitioner's clinical assessment of the impact of the elevated *BG* levels *per se* and of their fluctuations on the quality of the glycaemic control.

This method can quantify the efficacy of the therapy, based on collected diabetic data alone, before a naturally occurring long-term marker like the steady state HbA_{1c} is obtained.

Nathan et al [109] developed and used a linear-regression equation relating steady state HbA_{1c} to their associated mean *BG* values. In a pilot study, the reference predictions given by the equation were analysed against those given by the participating diabetes practitioners. The practitioners were asked to predict the mean *BG* concentrations from the historical and demographic data of their patients, including fasting, post-prandial, and random *BG* measurements. The developed equation was used to predict the reference mean *BG* values according to the recorded patient HbA_{1c} measurements. The results showed that 24% of the estimates given by the practitioners were ±4.2 mmol/L in error of the reference mean *BG* value predicted by the regression equation. The study shows that practitioners have a difficulty in estimating the mean *BG* for 24-hour periods based only on patient demographic data and *BG* samples. The study also shows that the relationship between mean plasma glucose level and the symptoms of diabetes is not significant nor meaningful, therefore historical information like polyuria, fasting or random *BG* concentration measurements are weak predictors of the actual mean concentration of plasma glucose concentrations.

Research that is more recent is directed towards a physiological interpretation of the glycaemic control and of the glycation process. A new class of models of haemoglobin glycation were proposed. It has been shown that the glycation of haemoglobin contained in an erythrocyte can be described by a first order linear kinetic model [15;61;129;131;138], and that the heterogeneity of the haemoglobin due to the glycation itself commends dividing the erythrocytes in a blood sample into cohorts with the same age since their origination [129;138].

Trying to explain why the measured HbA_{1c} reflects a perceived weighted mean of preceding *BG* levels rather than simply the mean, Tahara et al [139] questionably used weight functions produced by a linear kinetic model based on the assumption that the plasma glucose level changed in a stepwise fashion. Therefore, the ability of the weight functions to represent the analysed process was compromised. Despite this

weakness, the presented model, using some scaling factors, can predict with satisfactory accuracy published HbA_{1c} kinetics data.

To conclude, several approaches have been reported that obtain early assessments of the efficacy of therapies by taking a clinical approach or by modelling the process of glycation of haemoglobin analysed from a physiological perspective. Though they are empirical and intuitive, most of them constitute clear endeavours that have improved the clinical practice in the management of diabetes.

The approach in this chapter captures a comprehensive view of the process of haemoglobin glycation complemented by a distinct model of the assay of HbA_{1c}. The new model bridges the gap between the theoretical research and the routine measurement of the parameters of diabetes. The prediction of the steady state HbA_{1c} from a profile of plasma glucose concentrations has been investigated.

It is widely recognised that it is impractical to validate a model of HbA_{1c} concentration. The complete validation would require continuous *BG* monitoring to produce sufficient *BG* measurements able to represent the *BG* excursions over a period of time that is comparable with the rate of survival of the erythrocyte. Despite the recent availability of non-invasive continuous glucose monitoring, the exhaustive validation of such a model remains impractical. The assay of the HbA_{1c} concentration in a blood sample is an averaged amount of glycated haemoglobin from a heterogeneous mix of erythrocytes with different degrees of exposure to the *BG* levels over the investigated period, and proves indispensable to any validation.

Physicians, in a more or less conscious manner, use the HbA_{1c} marker in a *feed forward* loop [31]. The extension of DIAS-NIDDM by an HbA_{1c} model can render this *feed forward* loop into a standard and more efficient *feedback* loop, directly helping the physician with the routine management of diabetes.

In this chapter, a kinetic model of haemoglobin glycation is constructed. The discrete-time equations of the model are derived. A model of the HbA_{1c} assay *per se* is derived based on the inherent heterogeneous nature of the glycation process. The basis of an

implementation using CPN is formalised and the closed form relationships are obtained.

6.2 Construction of a Compartmental Model of Haemoglobin Glycation

6.2.1 Kinetic Model of Haemoglobin Glycation

The percentage of haemoglobin that glycates is directly proportional with the time that a given erythrocyte has been exposed to plasma glucose and the glucose concentration itself. Intra-erythrocyte glucose is considered proportional to the plasma glucose concentration with a proportionality factor equal with the unity.

Therefore, the amount of glycated haemoglobin as a fraction of the total haemoglobin represents an integrated picture of the *BG* levels during the erythrocyte's life span. The life span of the red cell is approximately 120 days. However, there is important inter-subject variability of the life span, especially in subjects with forms of chronic blood loss such as anaemia, in which case the life span is appreciably shortened.

The model of the glycation of haemoglobin in one red cell/cohort of cells with the same age can be described by a two-compartment model [137]:

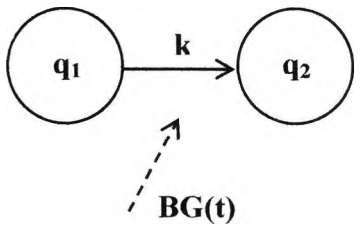


Figure 6.1 *Compartmental model of haemoglobin glycation for a cohort of red cells*

$$\frac{dq_1(t)}{dt} = - k\,BG(t)\,q_1(t) \qquad 6\text{-}1$$

$$q2(t) = q_{10} - q_1(t) \qquad 6\text{-}2$$

q_1 unglycated haemoglobin (g) in a red cell at time t after cell origination

q_2 glycated haemoglobin (g) in a red cell at time t after cell origination

q_{10} total unglycated haemoglobin (g) at the cell origination

k glycation rate (h^{-1} per mmol L^{-1}), time constant

$BG(t)$ blood glucose concentration (mmol /L)

6.2.2 Discrete Time Model of Glycated Haemoglobin

With the exception of specific experiments, plasma glucose data that are sourced by clinical trials and routine monitoring come measured at discrete moments in time, rather than as a continuous signal.

The model described by equations (6-1) and (6-2) is discretised according to an equidistant data monitoring period Δt, interval over which plasma glucose is considered constant.

Variables:

BG_j blood glucose concentration, considered constant over (t_j, t_{j+1}), t_{j+1}-t_j=Δt

Δt sampling interval

The equations of the continuous model are given by (6-1) and (6-2). Solving on $BG(t) = BG = constant$ for a cohort originating at $t=t_0=0$, gives

$$q_1(t) = q_{10}e^{-kBGt} \quad , \quad q_1(0) = q_{10} \qquad 6\text{-}3$$

$$q_2(t) = q_{10}\left(1 - e^{-kBGt}\right) \quad , \quad q_2(0) = 0 \qquad 6\text{-}4$$

for a time *step* $\Delta t = t_1 - t_0$, $BG = BG_0$,

$$q_1(\Delta t) = q_{10}e^{-kBG_0\Delta t}$$

$$q_1(2\Delta t) = \left(q_{10}e^{-kBG_0\Delta t}\right)e^{-kBG_1\Delta t} = q_{10}e^{-kBG_0\Delta t}e^{-kBG_1\Delta t} = q_{10}e^{-k(BG_0+BG_1)\Delta t}$$

.....

$$q_1(n\Delta t) = q_{10}e^{-k\left(\sum_{j=0..n-1} BG_j\right)\Delta t} \qquad 6\text{-}5$$

Relationship (6-5) represents a discrete time model of unglycated haemoglobin in a cohort originating at time $t=0$, when exposed to a BG profile $\{BG_j,\ j=0,..,n-1\}$ sampled at interval Δt.

$q_1(n\Delta t)$ can be expressed in terms of the mean BG as follows:

$$q_1(n\Delta t) = q_{10}e^{-k\left(\sum_j BG_j\right)\Delta t} = q_{10}e^{-kN\frac{\left(\sum_j BG_j\right)}{N}\Delta t} = q_{10}e^{-kN\overline{BG}\Delta t}, \qquad 6\text{-}6$$

where

$\overline{BG}$ is the mean BG associated with a sampled BG profile, $\overline{BG} = \frac{\left(\sum_j BG_j\right)}{N}$

N number of samples

The unglycated haemoglobin at red cell /cohort's clearance

$$q_1(T) = q_{10}e^{-kN_T\overline{BG}\Delta t} = q_{10}e^{-k\overline{BG}(N_T\Delta t)} = q_{10}e^{-k\overline{BG}T} \qquad 6\text{-}7$$

where

T erythrocyte life span, $T=N_T\Delta t$

N_T number of samples over period T

Relationships (6-6) and (6-7) prove that the unglycated and the glycated haemoglobin are associated with the mean plasma glucose concentrations and the dependency is exponential.

6.2.3 Generalisation of the BG profile by repetition

The precise prediction of the steady state HbA_{1c} requires the monitoring of *BG* profiles for periods comparable to the erythrocyte life span. However, it is reasonable to assume that the data collected for shorter time intervals characterise the subject's general level of control on the assumption of constant life style.

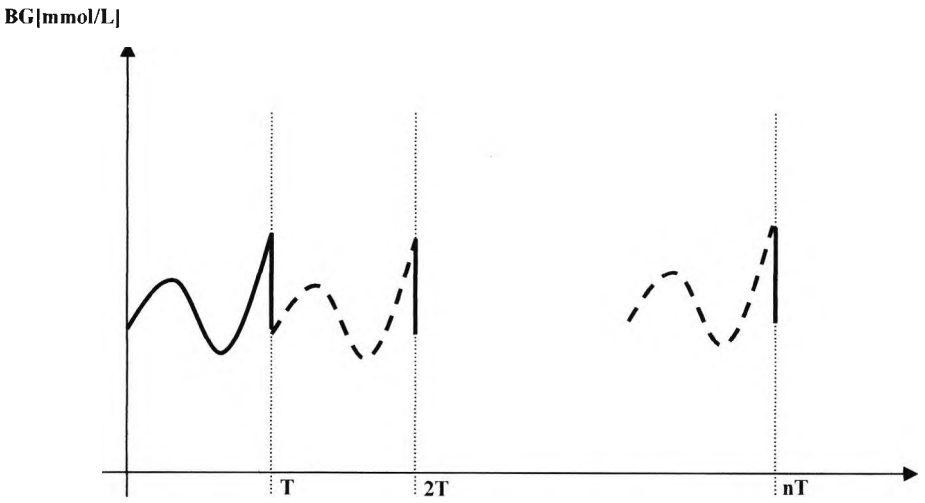


Figure 6.2 *Generalisation of a BG profile obtained by assuming the repetition of a shorter observed profile (e.g. 0-T); dashed lines represent the same profile as 0-T*

The glycated haemoglobin for one cohort is (6-5):

$$q_1 = q_{10} e^{-k(\sum_0^{nT} BG_j)\Delta t}$$

$$= q_{10} e^{-k(\sum_0^{T} BG_j + \sum_T^{2T} BG_j + \ldots + \sum_{(n-1)T}^{nT} BG_j)\Delta t}$$

that for a repeated profile with the property:

$$\sum_{(i-1)T}^{iT} BG_j = \sum_{(k-1)T}^{kT} BG_j \qquad \forall i, k \in [0,n]$$

results $q_1 = q_{10} e^{-k(n\sum_0^{T} BG_j)\Delta t}$.

6.3 Modelling the Assay of HbA_{1c}

The measurement of HbA_{1c} is a simple process. However, the heterogeneity of the haemoglobin that is induced by the glycation process itself always results in a mean value being reported. Physicians assume empirical rules like "The result depends approximately on the arithmetic means of the varying *BG* levels over 60 days" or "levels of HbA_{1c} reflect the weighted mean of preceding plasma glucose level".

These approximations are intuitive. The correct interpretation can be obtained if the process and the nature of the heterogeneity are analysed. A closed form relationship can be derived.

The assay based on glycation specific methods has the following characteristics:

- Not affected by variant haemoglobins
- No interference from labile Schiff base component since boronate retains only the stabile HbA_{1c}
- Measures mean HbA_{1c} *due to the mix of cell ages in the sample*

6.3.1 Heterogeneity of Glycated Haemoglobin

The heterogeneity of the plasma erythrocytes is caused by the existence of a mix of cell ages and due to the different degrees of exposure to plasma glucose concentrations.

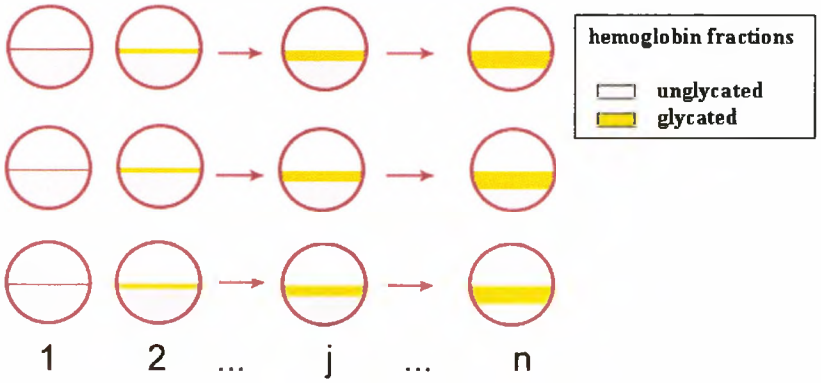
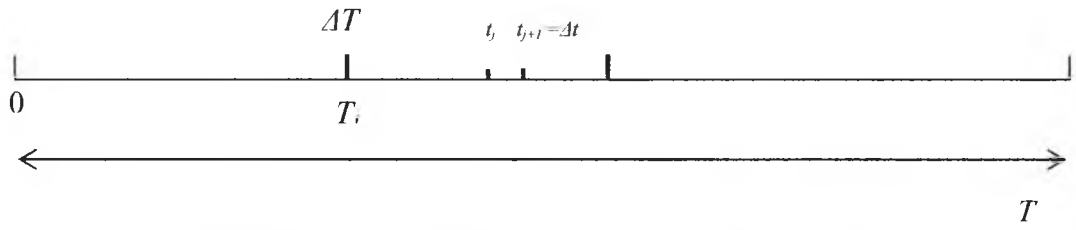


Figure 6.3 *Erythrocytes divided into cohorts in a plasma sample. Glycated haemoglobin is also represented. Cohort j at time τ from origination contains glycated haemoglobin that is proportional to the degree of exposure to the plasma glucose since its origination*

6.3.2 Steady State HbA_{1c} Model

The glycation process is taking place for the duration of time T corresponding to the erythrocyte's life span, duration divided into periods corresponding to the cohort discrete interval, ΔT, and sampling interval Δt.



T_i	time at which cohort i originates, $i=1,..,N$, $T_{i+1}-T_i=\Delta T$
ΔT	discrete time interval for cohort division, $T_{i+1}-T_i$, also considered to be the repetition interval for all practical purposes, see 6.2.3
T	life span of the erythrocyte, approximately 120 days, $T=NT_i$
N	number of cohorts in the blood sample/blood stream
BG_j	blood glucose concentration, constant over (t_j,t_{j+1}), $t_{j+1}-t_j=\Delta t$
Δt	sampling interval, interval over which BG is considered constant
$Q1$	total unglycated haemoglobin (g) over all cohorts
$Q2$	total glycated haemoglobin (g) over all cohorts
$\{BG_j, j=1..n\}$	BG profile sampled at Δt intervals
Q_{1m}	total glycated haemoglobin (g) for cohort j, $\tau = mT_1 = m\Delta T$ since cohort origination

Glycated haemoglobin for cohort m is:

$$Q_{1m} = q_{10}e^{-k\left(\sum_{0}^{T_m} BG_j\right)\Delta t} = q_{10}e^{-k\left(\sum_{0}^{m\Delta T} BG_j\right)\Delta t}$$

The total glycated haemoglobin for all cohorts in the sample is:

$$Q_1 = \sum_{m=1}^{N} Q_{1m}$$

Therefore,

$$Q_1 = q_{10}e^{-k\left(\sum_0^{T_1} BG_j\right)} + \ldots \quad q_{10}e^{-k(\sum_0^{T_2} BG_j)\Delta t} + \quad q_{10}e^{-k(\sum_0^{T_N} BG_j)\Delta t}$$

$$= q_{10}e^{-k(\sum_0^{T_1} BG_j)\Delta t}\,(1 + \; q_{10}e^{-k(\sum_{T_1}^{T_2} BG_j)\Delta t} \; + \; \ldots \quad + q_{10}e^{-k(\sum_{T_1}^{T_N} BG_j)\Delta t})$$

$$= q_{10}\, r\,(1 + r + r^{2} + \ldots + r^{N-1}) \qquad 6\text{-}8$$

The total glycated haemoglobin over all cohorts:

$$Q_2 = Nq_{10} - q_{10}\, r\,(1 + r + r^{2} + \ldots + r^{N-1})$$

$$= q_{10}(N - r\,(1 + r + r^{2} + \ldots + r^{N-1})) \qquad 6\text{-}9$$

where

$$r = e^{-k(\sum_0^{T_1} BG_j)\Delta t}, \quad r \subset (0,1) \qquad 6\text{-}10$$

r glycated fraction (out of the total unglycated haemoglobin) for a given cohort exposed for ΔT at BG levels $\sum_0^{T_1} BG_j$,

and, the BG profile on interval 0-T is considered made up of replicas of the profile 0-T_1.

The amounts of glycated /unglycated haemoglobin are numerically proportional to the voltage peaks of the spectrophotometer

$$\boldsymbol{HbA_{1c}[\%]} = \frac{Area\ Peak\,2}{Area\ Peak\,1 + Area\ Peak\,2}\, x100 \qquad 6\text{-}11$$

Peak1 - unglycated haemoglobin *(Vs)*

Peak2 - glycated haemoglobin *(Vs)*

Therefore,

$$HbA_{1c}(\%) = \frac{Q2}{Q1+Q2} x100$$

$$= \frac{q_{10}(N\text{-}r(1+r+r^{2}+\ldots+r^{N-1}))}{Nq_{10}} x100$$

$$= [1-\frac{r(1\text{-}r^{N})}{N(1-r)}]x100 \qquad 6\text{-}12$$

The relationship (6-12) is a general model suitable for calculating steady state HbA_{1c} for a blood sample exposed to a discrete-time *BG* profile of arbitrary length in time.

The model parameters are:

$\underline{k}$ - glycation rate (h^{-1} per mmol L^{-1})

$\underline{T}$ - life span of the red cell (days), derived from N in (6-12)

6.4 Integration into Existing DIAS-NIDDM Discrete-Time CPN

Models of HbA_{1c} are difficult to use and validate, as they require at a minimum the mean *BG* value or the full *BG* profiles for periods comparable to the erythrocyte life span. These are impractical to produce by standard *BG* monitoring, including continuous monitoring.

Similarly, the clinicians find it difficult to estimate the mean *BG* values when presented with patient demographic data, therapy details such as carbohydrate intake, insulin dosage, random *BG* measurements, or symptoms like polyuria, nocturia.

DIAS has been shown to deal with the unawareness of hypoglycaemic episodes and, more generally, it is able to predict *BG* values that fill in between sparsely self-monitored *BG* values [35;36], and therefore able to produce any long *BG* profiles.

DIAS-NIDDM can simulate subject specific *BG* profiles with values predicted at 30-minute intervals and with accuracies limited only by the day-to-day natural variability of glucose.

Using the developed HbA_{1c} model, DIAS-NIDDM can simulate subject specific *BG* excursions and therefore calculate their associated steady state HbA_{1c}.

The model of steady state HbA_{1c} concentration has been implemented in causal probabilistic networks (CPN).

However, with the appearance of CGMs (Continuous Glucose Monitors) [86], the use of the proposed new model of steady state HbA_{1c} concentration will be more apparent and more independent of DSS.

6.4.1 Glycated Fraction

The glycated fraction – relationship (6-10) – is a factor proportional to the degree of exposure of a newly originated cohort to the levels of plasma glucose concentration.

DIAS-NIDDM updates the value for the glycation fraction with each predicted *BG* value using a recurrent relationship. At the end of the simulation period, *r* reflects the contribution from all discrete-time glucose values.

6.4.1.1 CPN Model of Glycation Fraction

The glycation factor *r* is given by the recurrent relationship:

$$r_{j+1} = r_j e^{-kBG_j\Delta t} = re^{-k\sum_j BG_j\Delta t} = r_0 e^{-k\sum_j BG_j\Delta t} \qquad 6\text{-}13$$

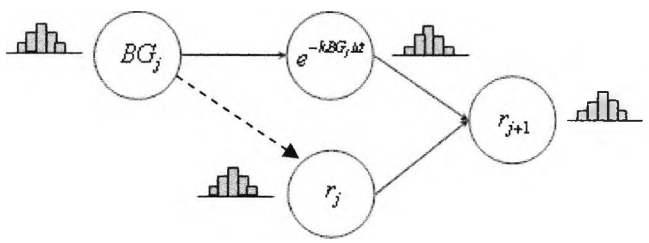


Figure 6.4 *Multiply connected network representing the glycated fraction. BG_j is produced by DIAS-NIDDM at 30-minute intervals*

The model of HbA_{1c} is isolated from the semantics of the *BG* profile. The *BG* profile could be sampled from diabetic or normal subjects, or represent *BG* measurements during a clamp or glucose bolus. The *BG* profile alone controls the glycation of the haemoglobin.

However, in DIAS, predicted *BG* values, $\{BG_j, j=1,..,n\}$, are conditionally dependent, and this dependence was considered in the model of CHO metabolism of DIAS-NIDDM.

6.4.1.2 Dealing with the Conditional Dependence

The dependency between *BG* and *r* nodes renders the CPN multiply connected. The network must be transformed into a singly connected equivalent. There are several approaches to deal with this problem: conditioning, simulating and clustering, presented in chapter 4.3. Clustering combines the conditionally dependent nodes so that the resulting graph is singly connected, and therefore the accumulation of probability mass in the midrange of *BG* variable in the case of bimodal *BG* distributions is thus avoided.

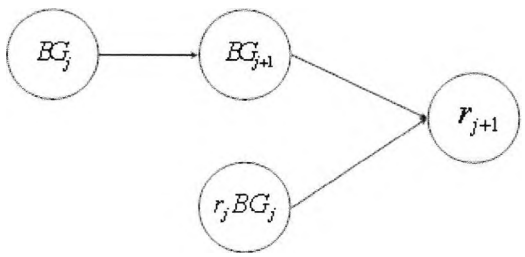


Figure 6.5 *Clustered singly connected network representing the glycated fraction*

The joint probabilities are calculated as follows:

$$\begin{aligned} p(r_{j+1}, r_j, BG_{j+1}, BG_j) &= p(r_{j+1} \mid r_j, BG_{j+1}, BG_j)\, p(r_j, BG_{j+1}, BG_j) \\ &= p(r_{j+1} \mid r_j, BG_{j+1})\, p(r_j, BG_{j+1}, BG_j) \\ &= p(r_{j+1} \mid r_j, BG_{j+1})\, p(BG_{j+1} \mid r_j, BG_j)\, p(r_j, BG_j) \\ &= p(r_{j+1} \mid r_j, BG_{j+1})\, p(BG_{j+1} \mid BG_j)\, p(r_j, BG_j) \\ &= p(r_{j+1} \mid r_j, BG_{j+1})\, p(r_j, BG_j)\, p(BG_{j+1} \mid BG_j) \end{aligned} \qquad 6\text{-}14$$

$$\begin{aligned} p(r_{j+1}, BG_{j+1}) &= \sum_{BG_j r_j} p(r_{j+1}, r_j, BG_{j+1}, BG_j) \\ &= \sum_{BG_j r_j} p(r_{j+1} \mid r_j, BG_{j+1})\, p(r_j, BG_j)\, p(BG_{j+1} \mid BG_j) \end{aligned} \qquad 6\text{-}15$$

For the first iteration:

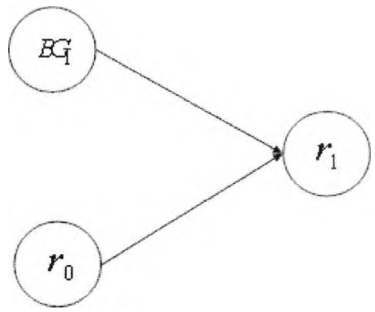


Figure 6.6 *Initialisation of the r CPN slice*

r_0 is assumed equal to the unity probability distribution to represent a newly originated cohort of erythrocytes that contains no glycated haemoglobin. Relationship $p\left(r_{j+1} \mid r_j, BG_{j+1}\right)$ implements the conditional probability for relationship $r_j e^{-kBG_{j+1}\Delta t}$. BG_1 is a converged probability distribution resulting from the lead-in flat BG probability distribution used by the initialisation of the forecast/learning operations in DIAS-NIDDM.

6.4.1.3 CPN Model of Steady State HbA_{1c}

Generalising the simulated levels of plasma glucose concentration over a period approximating erythrocyte's life span, the steady state HbA_{1c} can be expressed in terms of the glycation fractions of all the red cell cohorts in the blood sample, see equations (6-12), and it is implemented as shown in Figure 6.7.

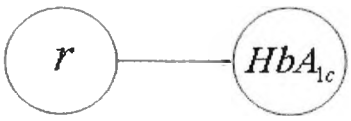


Figure 6.7 *Steady state model of HbA_{1c} concentration in terms of the glycated fraction*

The conditional probabilities were generated numerically according to the functional dependencies between nodes using the method of functional transformation.

6.5 Learning

Learning is performed using the CPN slice of the HbA_{1c} model with all the measurable variables located in the set of interface nodes and requires only the disseminate phase of the Bayesian updating and not the collect phase [84;89].

When presented with evidence for a certain position of the window, the following occurs: probability dissemination, evidence absorption, and probability normalisation.

6.5.1 Probability Dissemination

Probability dissemination calculates $p\left(HbA_{1c} \mid V_p^*, e\right)$ where $e = \{BG_j, j=0,..,n\}$.

$$p\left(HbA_{1c} \mid V_p^*, e\right) = \sum_r \frac{p\left(HbA_{1c}, r, V_p^*, e\right)}{p\left(V_p^*, e\right)}$$

$$= \sum_r \frac{p\left(HbA_{1c} \mid r, V_p^*\right) p\left(r, V_p^*, e\right)}{p\left(V_p^*, e\right)}$$

$$= \sum_r p\left(HbA_{1c} \mid r, V_p^*\right) p\left(r \mid V_p^*, e\right)$$

where $$p\left(r \mid V_p^*, e\right) = \sum_{BG_{j+1}} p\left(r, BG_{j+1} \mid V_p^*\right) \qquad 6\text{-}16$$

that is calculated using the conditional probabilities in the CPN model the glycation factor, *r* slice.

$p\left(HbA_{1c} \mid r, V_p^*\right)$ is the conditional probability table implementing formula

$HbA_{1c} = f(r, N)$

V_p^* - denotes a particular configuration of the parameters set $V_p = \{k, T\}$

Initialisation of the window movement assumed $r_0 = 1$ to account for a cohort with newly originated erythrocytes and the converged *BG* distribution from a flat lead-in period a priori distribution when the forecasting of *BG* profile commenced in DIAS. The probability dissemination is carried out for all the possible configurations of the set of parameters (V_p^*).

6.5.2 Evidence Absorption

The evidence absorption represents the inclusion of HbA_{1c}^m, the available haemoglobin A_{1c} measurement that is associated with the *BG* profile used by the dissemination phase.

$e^+ = e + \{HbA_{1c}^m\}$

Evidence absorption calculates $p\left(V_p^* \mid e^+\right)$ from $p\left(V_p^*, e\right)$.

$$p\left(V_p^* \mid e^+\right) = \frac{p\left(HbA_{1c(p)}, V_p^*, e\right)}{p\left(e^+\right)}$$

$$= \frac{p\left(HbA_{1c(p)} \mid V_p^*\right) p\left(V_p^* \mid e\right) p(e)}{p\left(e^+\right)}$$

$$\sim p\left(HbA_{1c(p)} \mid V_p^*\right) p\left(V_p^* \mid e\right) \qquad 6\text{-}17$$

The Bayesian updating equation is therefore used to estimate the *a posteriori* joint probability distribution for the set of HbA_{1c} model parameters $V_p = \{\underline{k}, \underline{T}\}$. When evidence is available at HbA_{1c} node and it used to condition the model parameters, the normalisation of the joint probability distribution of the parameters is carried out to reinforce $\sum_{V_p^*} p(V_p^* \mid e^+) = 1$.

6.6 Forecasting

Forecasting employs the joint *a posteriori* probability distribution $p(V_p \mid e^+)$ determined by conditioning the model using retrospective HbA_{1c} measurements to predict steady state HbA_{1c}.

$$p(HbA_{1c}) = \sum_{V_p^*} p(HbA_{1c} \mid V_p^*, e) p(V_p^*) \qquad 6\text{-}18$$

The evidence $e = e_{BG_{profile}} U e_{HbA_{1c}}$, where

$e_{BG_{profile}}$ = $\{BG_j, j=1 \ldots n\}$, predicted *BG* profile generalised for a period of 120 days

$e_{HbA_{1c}}$ = $\{HbA_{1c,k}^m, k=1 \ldots l\}$, absorbed HbA_{1c} values, subject data

6.7 Discussion

The glucose transport in erythrocytes is solely based on GLUT-1 (responsible for the basal transport, not insulin stimulated transport). It has been shown that in the situation of prolonged diabetic hyperglycaemia the transport capacity of glucose into the red cells decreases [152]. This aspect has not been investigated in the current work. The glucose transport in erythrocytes has been reported decreased in type 2 diabetes [152], and it is possible that HbA_{1c} measurements underestimate the plasma glucose levels. However, evidence is necessary to show that for equivalent *BG* control levels, in type 2 diabetes the HbA_{1c} values are underestimated compared with diabetes type 1 subjects. Any such significant phenomenon should reflect in the estimated $\underline{k}$ in subjects with reduced GLUT1 in erythrocytes.

Natural day-to-day variability of the *BG* levels is reflected in the prediction accuracy of DIAS-NIDDM when used for subjects with type 2 (2.2 mmol/L) and type 1 (2.8 mmol/L) diabetes [69;71;84;142]. However, the high accuracy of the HbA_{1c} prediction (0.64%, obtained in a retrospective data pilot study) based on DIAS-NIDDM predicted *BG* profiles shows that the glycation has a filtering effect on the naturally occurring intra-subject day-to-day *BG* variability.

The intuitive observation that HbA_{1c} measurement depends more on the most recent *BG* values is simply a consequence that is explained by the formation of a heterogeneous pool of cohorts of erythrocytes of the same age. A cohort contains erythrocytes of identical exposure to glucose concentrations. These are also subsequently involved in an averaging process during the laboratory assay.

The insulin dosage adjustment could potentially be based on a target HbA_{1c} value solely, or in addition to the criteria DIAS-NIDDM currently uses (penalty function – see Annex III, aimed at minimising the periods of hyperglycaemia while avoiding hypoglycaemia) potentially resulting in insulin therapies that are optimum in slowing the progress of the complications of diabetes. That could link directly the day-to-day management of insulin doses (IIT) to the DCCT results.

6.8 Conclusions

A stochastic model of haemoglobin glycation has been built to calculate HbA_{1c} from DIAS-NIDDM predicted *BG* values - the actual (predicted) glycaemic excursions are used. The HbA_{1c} assay has been modelled as a separate process to deal with the glycation-induced heterogeneity and mix of cell ages in the sample and to explain the aggregated nature of the reported HbA_{1c} laboratory measurements.

The use of the system was tested by performing a retrospective pilot study and the accuracy of the prediction was 0.64%. DIAS-NIDDM has the potential to predict the steady state HbA_{1c} in response to a change in therapy. It has been showed that *BG* levels alone control steady state HbA_{1c} levels.

7. Decision Support Systems

7.1 Introduction

The literature review revealed the current state of DSS and issues spanning their use, social-professional environment and the development methodologies.

The characteristics that uniquely identify DSS among the multitude of software applications are set out. The development and the assessment principles for a generic DSS were introduced and much of the methodology already established in software engineering from which a DSS draws on is illustrated. The principles of DSS are useful to develop a critical attitude towards DSS use, development, and formulation of its need.

7.2 Background

Following the ever increasing pressure to handle more information and knowledge in activities dominated more and more by computers and information technology realities, field specialists wanting to implement their expertise in a transferable form, stakeholders in projects or users of knowledge tools, many will come across decision support systems in their professional pursuit. Therefore, the principles of DSS and developing a critical attitude towards their impact must be part of one's curriculum as much as computer skills are nowadays so that the most is made of the available technologies, knowledge and resources and to be ultimately able to improve the outcome of activities in all domains of activity.

A decision support system (DSS) is a computer based system developed to approach a complex problem in a domain characterized as unstructured and affected by uncertainty. The solution given by the system will be approximate, and in most cases as alternative courses of action with some cost/benefit attached to them. The focus of the DSS development is on enhancing rather than replacing/imitating the user's judgment.

DSS have their origins back in '70s in the area of production planning [107]. They are currently used to improve decision-making and the outcome of processes in various domains. They have the potential to reduce costs and there is a real need for such systems [128]. There are several reported successful experiences with such systems. When designed well, DSS represent tools that add value to the decision making process.

7.3 Underlying Decision Science

Medical decision support systems employ various methodologies resulting in different approaches to decision support, such as knowledge-based systems/clinical algorithms, data-based systems and model-based systems.

The knowledge-based systems (e.g. rule-based) represent clinical knowledge as a set of rules reflecting the reasoning strategy of the medical expert. The rules are combined and provide explanations, carry out diagnosis, recommend therapies, etc. These systems do not require data for their construction. Clinical data and experience are used to build the rules.

The data-based systems such as neural networks have an adjustable internal structure that is adjusted during the training process when experience is extracted from subject data. The learnt structure is used to generalise the experience and to perform the task of classification when presented with new data.

The model-based systems are characterised by an internal structure that reflects the structure of the biological system that is being modelled. The physiological knowledge and the clinical experience are represented explicitly and used to predict the quantitative behaviour of the system in given circumstances. The model-based systems use *prior* knowledge in the internal structure of the model that is based on physiology relations. The facts are expressed through the structure of the model and the exceptions, variability in data or lack of knowledge are modelled as parameters to be adjusted according to particular subject data. The system can be used as a testbed to simulate the outcome of different therapies and by making use of utilities associated with possible outcomes, the best alternative can be recommended.

The data-based approach has theoretical limitations and requires quality data that are expensive to collect in the field of diabetes.

In conclusion, with the model-based approach it is possible to use *prior* knowledge for the construction of the systems, whereas the data-driven approach disregards the knowledge about the physiology of the system. With the model-based approach, it is possible to learn from data, which is impossible or very difficult in the case of knowledge-based approach. In contrast to the learning strategies used in data-based systems where experience is learnt from the scratch, the model-based systems use the knowledge available *prior* to their construction.

7.4 Decision Support Systems in Type 1 Diabetes

The systems perspective to DSS in diabetes mellitus is an example of dealing with complexity [31].

Intensive research on decision support systems and diabetes simulators produced a large number of systems. A variety of methodologies and approaches are used: rule-based, algorithms, compartmental modelling, time series and regression analysis, causal probabilistic networks, adaptive control, fuzzy logic, neural networks, aiming for visit-by-visit, day-to-day or dose-by-dose treatment, implemented for PC systems or hand-held devices, intended for use by the patient himself/herself or by the health-care specialist.

Hovorka et al developed a consultation system for insulin therapy [83] with the aim to assist with the insulin treatment of diabetic in-patients. The system is capable of predictions with accuracy of 2.5 mmol/L. Based on a mathematical model to describe the effect of insulin on blood glucose levels the system uses an adaptive approach to estimate patient's parameters according to the administered insulin dosage and the measured plasma glucose measurements. Both conventional insulin injection regimens and the use of insulin pumps are supported. The model of insulin absorption addresses all types of insulin (short-acting, intermediate, and long acting). The proposed therapy is produced by a generate-reject strategy according to a modified M-value model [129]. The administration of the advice generated by the system during pilot evaluation studies proved that the system accuracy improves after 3 days of pump therapy and 6 days of conventional therapy.

In UTOPIA [47;48], a statistical pattern of *BG* profiles is constructed (modal day, an aggregation of daily *BG* data used to represent the mean response to the current therapy). The relationship between regimens and statistical patterns from past visits are learnt and used to update the patient specific model that is then used to select between candidate adjustments. The modal day requires consistent lifestyle and reliable data collection, which may render the system impractical.

KADIS [96;127] uses a structured control system of glucose-insulin interaction as the underlying model. The parameter estimation is based on tests with known inputs like bolus injections of glucose and insulin. Other input profiles are assessed, like gut absorption after meals, exogenous insulin absorption profiles and physical exercise. The profiles are modified in a linear dose dependent manner to estimate glycaemic and insulinaemic responses under any lifestyle and insulin therapy. However, the identification of parameters by pre-tests is impractical for any purposes other than research. The validation of the model was illustrated on anecdotal data sets of subjects on IIT in order to demonstrate the potential use of the system.

Apple Juice [147] is a dose-by-dose insulin advisory system. A relative insulin sensitivity parameter, specific to each subject, is estimated on a regular basis at various times of day and injection sites. The system requires that the subject is highly motivated. In a similar manner, correction factors are computed to account for the effect of food, stress, and dawn phenomenon.

7.5 Decision Support Systems in Type 2 Diabetes

Decision support systems for subjects with type 2 diabetes have also been developed. The therapeutic options include oral hypoglycaemic agents and, in qualitative terms, insulin.

Artificial neural networks (ANN) have been applied to the management of both type 1 and type 2 diabetes [5]. A system based on back propagation ANN, it offers an alternative to clinical algorithms in representing clinical experience. The system is intended to support decision making when prescribing insulin regimens in type 1 and type 2 diabetes given the age, type of diabetes, desired glucose control, and could be used as a complementary add-on to an insulin dose adjustment DSS. Though the current limited number of input parameters can be approached by simpler techniques (e.g. 108 regime combinations stored in a database/table with 'reasoning' performed by simple 'if-then' rules), however, when a more complete/realistic set of clinical decision factors are addressed, the resulting combinatorial explosion when using simpler techniques makes the ANN a feasible approach. ANN present the advantage of a short response time, but the fact that the system is not transparent to the decision maker is a drawback.

DIABETES [6] is a rule-based system able to adjust insulin doses of pre-set regimens in both type 1 and type 2 diabetes. Based on production rules fired according to specific patient data, it can give explanations by using extra information associated with each rule. The system underwent the evaluation stages of verification and evaluation. The prospective clinical assessment aims to find the percentage of misdiagnoses and classify them into inference or knowledge base errors. The assessment of the system revealed that disagreement between the clinician and the system are mostly due to different patient management strategies rather than due to the final result (normoglycaemia), or due to representing the 24-hour time interval as four quarters corresponding to events like meals and *BG* measurements timing. The system fails to match diabetes specialist's ability to adjust insulin doses. For example,

the suggestion of an increased evening insulin dose in order to reduce the slight hyperglycaemia during the day is beyond system's capability.

However, the adjustment of insulin doses must be patient specific. Therefore, to avoid hypoglycaemia, DIABETES and other systems based on clinical-algorithms must advise initially small increments of insulin to fit all subjects, and as a result, finding an optimum therapy requires multiple patient sessions (compared with model-based DSS). Because of the methodology used, DIABETES rather imitates clinician's approach to insulin dose adjustment, namely advises safe changes in insulin dosage, and follows up the results, rather than advising an optimised therapy from the outset.

DIACATOR [21] is a simulator of metabolic abnormalities of type 2 diabetes based on pre-defined parameter values characterising the disease. The model, primarily intended for educational purposes, is comprehensive. Glucose toxicity, pancreatic responsiveness, hepatic insulin resistance, and tissue sensitivity to insulin are explicitly represented. The system is driven by choosing one of six pre-defined states of diabetes type 2 characterised by various degrees of insulin resistance, pancreatic sensitivity, and non-suppressed component of hepatic glucose production and can simulate the expected abnormalities in the variables of the system (insulin secretion and concentration, plasma glucose levels, etc). The *BG*-stimulated model of insulin secretion includes a main component that is proportional to the plasma glucose levels. Other capabilities like differential actions able to simulate the first phase insulin secretion and an integral component are also present. The author addresses the effect of the hypoglycaemic agents in type 2 diabetes. The sulphonylurea therapy was modelled by an additional constant factor that increases the actual pancreatic response but leaves the first phase secretion unchanged. The effect of biguanides augments insulin sensitivity and the non-suppressible hepatic glucose output by pre-set constant factors. Acarbose is simulated by a further delay in the gut absorption function that shifts the time-to-peak by a factor of two. In all cases, the effect of the drugs on the metabolism is constant during 24-hour periods. Parameter estimation and quantitative advice generation are not supported in the system.

However, the differential action of glucose on insulin secretion in subjects with type 2 diabetics is insignificant or not present [21;28]. In addition, glucose toxicity is a

reversible phenomenon [21;125], and therefore its representation in insulin advisory systems that aim to normalise the glycaemia is neither required nor important.

7.6 Other systems

Educational systems in diabetes aim at educating diabetic patients about their disease using IT. Several such systems are used for providing training in understanding the management of diabetes for patients with type 1 [69;96] or type 2 diabetes [21]. Educating patients with diabetes for the self-management of their disease is a key factor for improving individual health care.

Home blood glucose monitoring brings improvement to the control of *BG* levels only if it is used to make decisions on the therapy. Patients are helped to take control of their own treatment, but knowledge of insulin dose adjustment is limited even in the case of those motivated [56]. Moreover, it has been shown that months after a training course, the glycaemic control returns to baseline. Educational systems may help with repeated learning [102] and using interactive education can lead to an improvement in the glycaemic control by re-enforcing the acquired skills [148].

AIDA [47;94;96] is a day-to-day educational diabetes simulator based on a compartmental model which attempts to grasp the physiology of insulin action and carbohydrate absorption by two separate insulin compartments, one for plasma insulin and one for active insulin. The system is assisted by a knowledge-based module to interpret *BG* data. The system can be used as an educational tool to generate qualitative advice. A confidence interval is estimated from historical data and quantitative advice generation requires the predicted *BG* as well as the *BG* values within the confidence interval be kept in normoglycaemic limits. Using individually estimated parameters, the system can predict *BG* with accuracy of approximately 0.8 to 4.6 mmol/L [94;97]. The glycaemic effect of food is represented as a simplification of very complex physiological processes. However, this simplification is present in most systems.

DIABLOG [22] is intended for the education of diabetics on insulin therapy adjustment. The system is based on a compartmental model with some of the

parameters being time-variant to improve the accuracy of the predictions. The system uses regression equations to calculate HbA_{1c} [109] from the previous week's mean value of *BG* to allow assessment of the current therapy. Patients could change the input to the system to experiment with other therapies or a changing life style. The evaluation of the system consisted in patients filling a questionnaire.

Educational games target young patients aiming at achieving self-management skills in an interactive and challenging way [27].

Home blood glucose monitoring is required for the management of diabetes to assist in the control of the *BG* levels. In addition to the test strips, several devices are available to assist with data collection, downloading to PC, visualisation and processing. One such example is CAMIT software [117]. The patient has the possibility to keep track of his/her long-term glycaemic control and the physician can update his/her patient records during patient's regular visits. Data visualisation and interpretation features can help to detect trends and patterns in the data and indicate problems with the current therapy.

7.7 Reasons for DSS Failure

The state of DSS development and their impact on the everyday life of organisations or at an individual level had not reached significant levels as documented in early 90s [151]. Few systems were in routine clinical use or in operation outside their site of origin [42]. The situation has not improved recently. This situation is explained by certain factors that have been identified by researchers in all fields where DSS are present.

Exposure to a complex system, difficult to use and that fails to address real needs repels the user and can be the main obstacle in the widespread of such systems [65].

The predictive accuracy, which is too rarely proven by systematic validation of the decision science components of a DSS, failed to gain the trust from experts and practitioners in their targeted fields. It is unfortunate that many DSS reproduce

decision maker's natural abilities, rather than being complementary to human choice process [65;128].

The identification of those aspects where support is genuinely required fails. In medicine, whilst diagnosis was the most common purpose of decision support systems, clinicians consulted MEDLINE mainly for information on therapy and not on diagnostic support [65]. However, there is evidence that DSS improve clinical practice or patient outcome, and the proportion of DSS that lead to such improvements range from 20% for diagnostic DSS to 75% for DSS that advised on drug dosing [88]. These results are not surprising, as a diagnostic tool actually competes with physicians, imitating their natural reasoning.

Some corporations develop DSS because they are viewed as 'organizational winners', which affects their clients' view of their product. Only 6% of the DSS are used because they reduce costs [128].

The resistance to decision support from medical profession (fear of loss of rapport in clinician-patient interaction, fear of loss of control and losing the autonomy in decision making, inertia in adopting new innovations, suspicion of artificial intelligence, fear of legal liability due to lack of legal framework for decision aids) is an important deterrent [65].

A lack of development methodologies to specify explicit steps in the development process and of a coherent development philosophy that embodies values and beliefs have been reported [65].

Aims of the development are not stated clearly. If a project is used to test a novel approach/technique, then it should be made distinct from projects aiming at addressing clinical problems, to eliminate the misinterpretation and the resulting mistrust from the medical profession [65].

Excessive preoccupation with computer artifacts (tools, data structures, algorithms) dominates the problem solving. Communication between the clinicians and designers, between users and developers does not happen to the full. Academics and researches

as developers of DSS may be seeking to explore theoretical issues and generally neglect user acceptability, system performance, validation and evaluation, documentation or maintenance issues. The goals are degrees or published material rather than a fully engineered system [4;149].

Electronic Medical Records (EMR) are database systems for the centralised data collection of patient data. Considerable opportunities are offered to improve medical screening, disease prevention, research, and keeping track of patient's disease management. Interaction with decision support systems is readily possible. Despite all these advantages over the paper-based medical records, there are still serious problems. The lack of standardization regarding data formats and data communication protocols hamper data exchange between various diabetes centres.

7.8 Principles of Decision Support Systems

"It is impossible to understand the design concepts of DSS until you actually try to implement them" V. Sauter [128]

7.8.1 Background

Software engineering is a domain in which the quality of the products is almost entirely based on abstract and less tangible realities like development principles, concepts, methodologies, and development philosophies. Attributes of software products like reliability, acceptability, efficacy, scalability, robustness are not possible if the only approach is simply to write the application. Software engineering puts together numerous such principles (e.g. waterfall development life cycle, etc) and CASE tools that can guarantee quality software. It is estimated that between 60-80% of the commenced software projects are never finalised [121] and the non-compliance with the software engineering principles could explain most of the failures.

Decision support systems draw on all these aspects from software engineering. The complex problems in unstructured domains affected by uncertainty that the DSS propose to approach and solve, stresses even more and adds to the necessity of using methodologies, concepts, and philosophies for a systematic development.

7.8.2 Characteristics of DSS

Some authors [132] use broad definitions to categorise systems as DSS.

However, what makes a system able to support decision-making was carefully analysed, and only a more specific breed of software systems are considered suitable to qualify as decision support systems. These are characterised by or seen to

- Target unstructured domains
- Intrinsic problem solving of a heuristic nature
- Model uncertainty in data, knowledge, reasoning, therefore in advice
- Generate information via models or other knowledge representation paradigms by using reasoning engines; capability to infer new facts from basic data
- Usually do not give an exact solution but advise on different courses of action, each with associated costs
- Need validation against real world situations to prove their use, safety and efficacy
- Add value to decision making processes
- Being complementary to the human choice process

7.8.2.1 Domains

All domains are targeted by computer systems built to automate specific/routine tasks. The same is true for decision support systems despite the fact that limitations are possible due to limited available resources, need of decision aids is not identified, etc. Such systems have been reported in fields like:

- Economic
- Medical
- Engineering
- Legal
- Social
- Procedural
- Political
- etc

Examples of DSS can be found in medical domain, applications for the management of bed occupancy and patient flow in hospitals and vehicle routing (e.g. ambulance service), economic applications like risk analysis (risks associated with certain courses of action) or complex weather forecast applications, etc.

7.8.2.2 Uncertainty

Uncertainty is encountered at one or several of the following levels:

- data - measurement errors
- laws used for reasoning (e.g. fuzzy rules)
- inherent in the modelling methodology
- caused by approximations

The sources of uncertainty can be based in the measurement processes, stochastic laws relating domain variables, limitations of the modeling techniques or simplifications of models.

Examples:

- input data 5 +/- 0.9 units (measurement error)
- law "if input is 5 then output is 8 but it also could be 7 or 9, though less likely"

(uncertain reasoning)

7.8.2.3 Heuristics

Problem solving in complex, real world domains often has a heuristic nature; therefore, heuristics solutions are often introduced at certain levels during system design and implementation [4].

Heuristics represent "speculative, task-dependent information to aid finding a solution to a certain problem but otherwise unjustified or incapable of justification" or "a

process that may solve a given problem but offers no guarantees of doing so; the solution is plausible only";

An example of use of heuristics is the AI search where by using heuristics algorithms the search space can be drastically reduced. More examples of heuristics used in medicine are available [4].

7.8.2.4 Perceived difficulty

In structured domains, the perceived difficulty is directly correlated with the complexity of the model (how many terms, how many integrals, etc)

$$Q_1 = q_{10}e^{-k(\sum_0^{T_1} BG_j)\Delta t} + q_{10}e^{-k(\sum_0^{T_2} BG_j)\Delta t} + \ldots + q_{10}e^{-k(\sum_0^{T_N} BG_j)\Delta t}$$

In unstructured domains, the difficulty is perceived as the ability to obtain a minimal model that is able to predict the real world and not the complexity of model *per se*

$$Sale\ Volume = 1500 - 600\ Price$$
$$Cost = 1.3 - 0.00009 * Investment$$

Maximizing the rate of return could be a very difficult task when the price and investment variables are predicted from economic data, despite the simplicity of the relations of the model.

7.8.2.5 Decision Support Systems in the Domain of Software Applications

There are many ways to categorise software applications, using various criteria, most of them conflicting and at the same time confusing. However, the most fundamental criteria should be the software engineering effort and the type of the application in terms of complexity and problems solved. Software engineering is concerned primarily with the formalisation of development methodologies, with well-defined stages, ranging from problem analysis to the deployment and the maintenance of the application and the goal is to achieve software of most comprehensive quality. Figure 7.1 shows along the horizontal axis various degrees of quality according to how advanced and successful the principles of good software design were applied. A first program that one builds is usually good enough to get the desired results ('program works'). No special attention is spent towards a phased development, reliability, testing under real load, quality of the graphical user interface, etc.

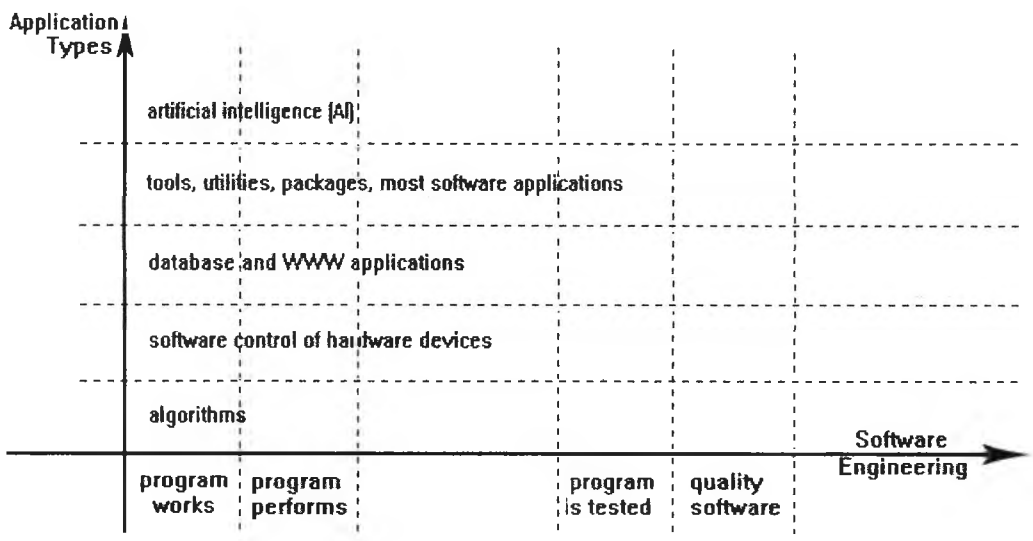


Figure 7.1 *Principles of software engineering that lead to quality software. All computer programs are/should be developed using these principles*

Quality development is based on principles of good design, is tested in the intended environment, and is developed by a professional/commercial agency, with dedicated support and maintenance resources and pleased users/customers. Quality aspect will be represented as quality software along the software engineering axis. On the other

hand, various types of applications rank from simple algorithms and programs to increasingly more specialised applications dealing with complex problems using specific techniques.

Most such applications can be classified as tools and utility programs. The set of output variables will always be the same for a given set of input data/operations, being able to perform well complex deterministic tasks, with various degrees of performance. However, the complexity of problem solving *per se* is not enough to differentiate between a tool and a DSS.

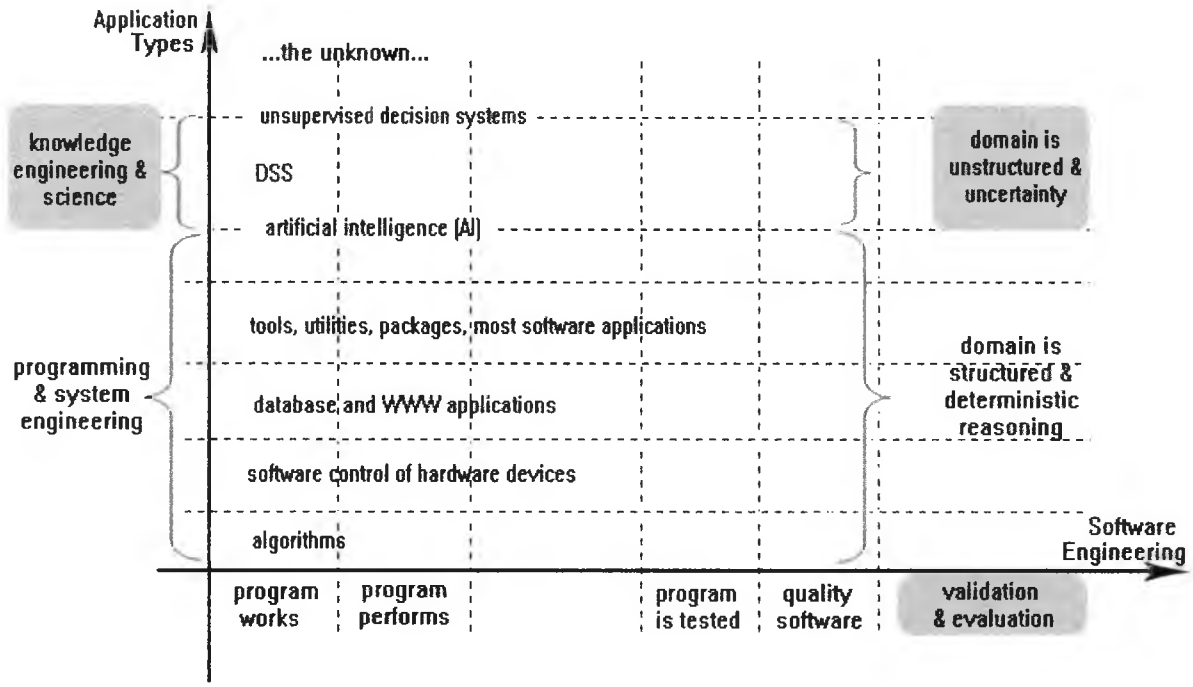


Figure 7.2 *The development of DSS and unsupervised decision systems requires that the principles of software engineering must be extended to deal with model validation and evaluation*

Decision support systems add new entries to both axes (Figure 7.2). Validation and evaluation are new necessary stages of the development that prove that the system is safe to use, accurate and achieves the outcome it is designed for in its intended environment.

DSS have particular characteristics (7.8.2) that put them on top of the applications in terms of the required expertise (knowledge engineering & science), techniques used (model based – CPN, fuzzy logic, etc, clinical algorithms, data driven neural

networks, etc), structure of the domain (unstructured) and capability to infer new facts from the input data. However, DSS are different from both certain AI applications (AI search, etc) and, depending on the system objective and predictive performance, unsupervised DSS. Nevertheless, due to their exploratory nature and approach of unstructured domains characterised by partial knowledge, they are shown to work at the boundary with the unknown world.

7.8.3 Waterfall Life-Cycle for DSS Development

After all, or first of all, DSS are software applications and therefore it is natural that their development draws much from the principles of software engineering.

The standard waterfall life-cycle (problem analysis, design, implementation, testing, validation, and maintenance, see 7.8.4) has been augmented with two more stages to cope with model development, its validation, and system evaluation (Figure 7.3, see 7.8.3.3).

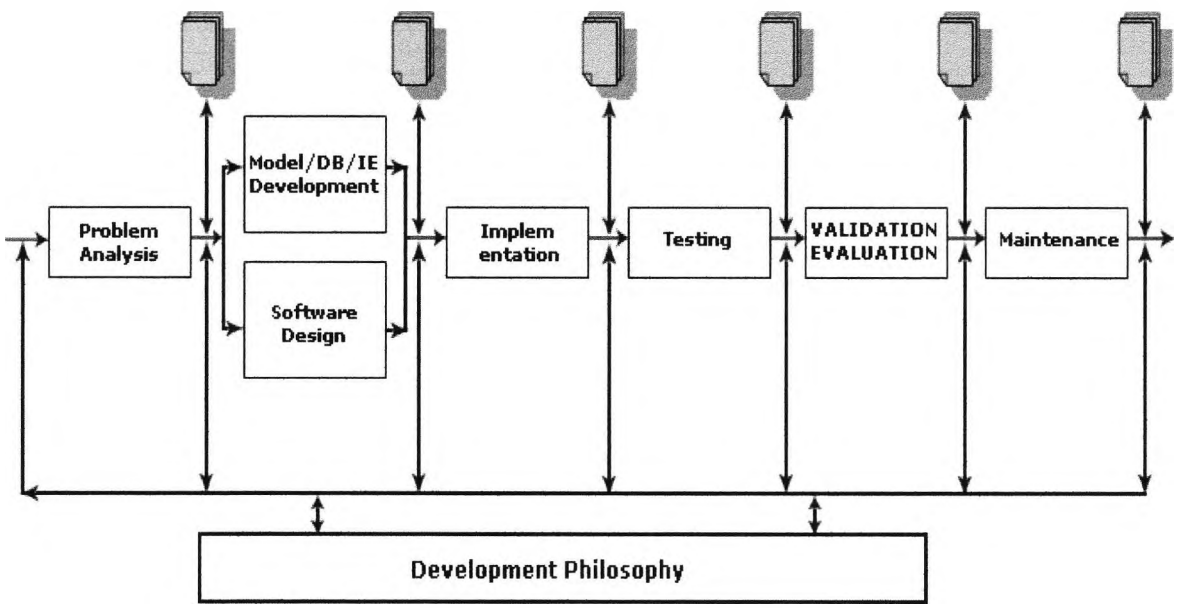


Figure 7.3 *Waterfall development life cycle including model/database(DB)/ inference engine (IE) and validation/evaluation stages. Development philosophy sets the values and beliefs that are driving the waterfall life-cycle, and in particular controls problem analysis, model/DB/IE and validation/evaluation stages*

However, DSS raise important development issues and the standard approach of the augmented waterfall life cycle is inadequate for all the purposes. Therefore, there is a need for a driving development philosophy that encompasses values and beliefs, usually set as development guidelines [65], see 7.8.3.1.

Another enhancement to the standard waterfall model is the detailed and complete flow of documentation (see 7.8.4.3).

The DSS development makes full use of the principles of software engineering - general and OO specific – and these are applied throughout.

7.8.3.1 Development Philosophy

A problem solving approach/perspective to the development of DSS has been proposed [65]. Starting with the problem and analysing its characteristics, the choice of reasoning techniques and software tools, insures no *conflict* between the *problem* and the *technique* used (Figure 7.4).

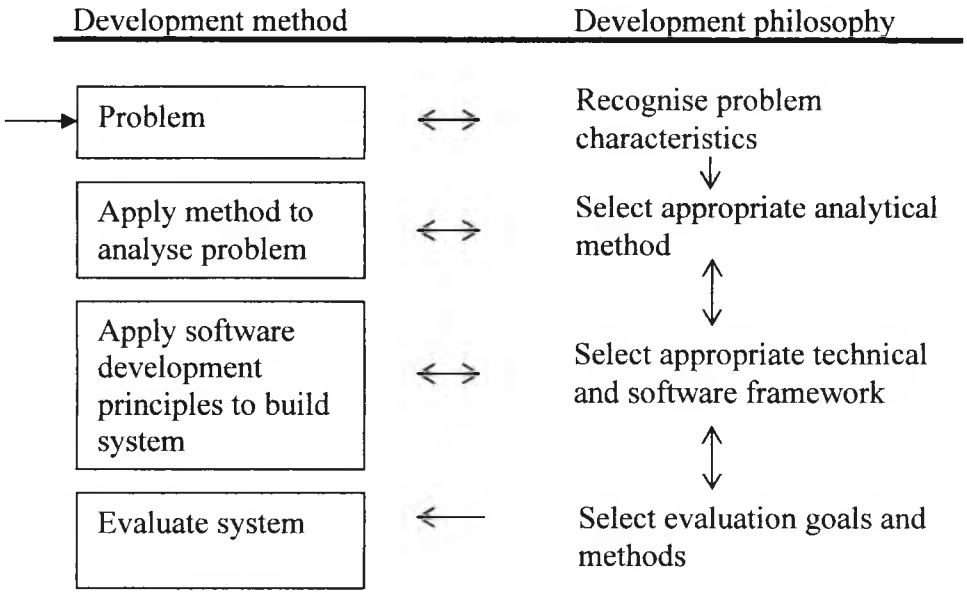


Figure 7.4 *Proposed development philosophy driving the scientific and engineering efforts (Heathfield & Wyatt [65])*

Aware of the known issues with DSS failure to be in routine use, the philosophy proposes competent guidelines to avoid similar problems.

The development philosophy is constantly critiquing the process of development, addressing the lists of limitations and issues as they arise. That is the most appropriate level for the communication and informational bridge between knowledge engineers, users, and developers.

All the stages will be driven by the practical problem, endorsed by the principles of software engineering, and directed by the development philosophy. This will establish a genuine need for the system.

7.8.3.1.1 Objectives of the System

Carson et al [31] recommend that the objectives of the system always must be set out from the outset, the purpose of the intended DSS, the full range of the potential users, the real, rather than the perceived needs. For a generic diabetes DSS, for example, the final intended use must be stated as clinical/therapeutic or educational. The end user must be specified as the diabetes specialist, diabetes nurse, general practitioner, the patient, or the system can be used as an unsupervised independent tool. The frequency of use of the system should be stated as meal-by-meal, one-off adjustment (e.g. a social event), fine-tuning of the regimen that the patient may make on a day-to-day basis, or strategic at hospital visits [31]. The modelling can be targeted at the physiological level, or as a clinical tool to generate advice on the therapy [31].

7.8.3.1.2 Conceptual Guidelines

Heathfield and Wyatt [65] suggest a development philosophy around major conceptual guidelines.

1. Analyse the problem domain and definition, the user requirements and establish the real need for the system, clearly determining the nature of decisions, therapies, and their impact on patients. Aims should be clearly stated.

2. End user requirements must be matched; therefore, some form of rapid prototyping should be used to determine exactly what functionality is required. Operational prototyping [20], using directly the languages of development, is possible, for example, with Borland RAD products. Functionality is increased incrementally while user feedback is continually obtained.

3. A model of the problem should be built, preferably using a visual modelling language like UML complemented by other means. The problem domain is understood.

4. Appropriate choice of methods, mechanisms, and tools that allow the development to be problem driven rather than software driven.

5. Evaluation is necessary in order for the system to be accepted in routine clinical use, by convincing the clinicians of the safety, accuracy, efficacy, and usability of the system.

6. Implementation, maintenance and support should be performed by a professional agency.

7.8.3.2 System Modelling

Any model represents an approximation to the real system by a set of mathematical relations and its validity has to be assessed in the context of the purpose for which the model was intended [33;53].

In predictive mode, the model serves to determine how a system would respond to a stimulus or to a change in the system.

The modelling process involves the problem/system to be analysed, the technique (laws & theories), the data relevant to the model, and the model formulation and validation.

The tools of modelling are the abstraction – the degree to which only certain aspects of a system are considered in a model - and the idealisation - structures and behaviors are approximated with more simple idealised ones. The modelling techniques can be deterministic (compartmental models), stochastic (based on Bayesian theory that take into account the random processes that affect the system, non compartmental (convolution/deconvolution), AI techniques like ANN, Fuzzy Logic, etc.

7.8.3.3 Evaluation

The validation and evaluation are critical. Depending on their success or failure, they can decide the fate of a DSS. Will it be safe to use? Does it improve the outcome of the process it is designed for? There is significant research for developing methodologies for the evaluation of DSS. Evaluation is a rather complex and expensive task involving a minimum of three stages: verification, retrospective trial and prospective studies.

Dangers of the validation are:

- study is too small;
- trial is terminated prematurely if it appears to show the desired result

These can be the consequence of practical aspects like poor recruitment rate and poor protocol compliance, raising the issue of quality of data.

7.8.3.3.1 Stages of Validation

Verification - checks for internal consistency, logical errors; computer code and model are presented in readable form to experts (e.g. publications); checks of assumptions and implications.

Retrospective trials - checks the ability of the system to produce acceptable results when presented with test cases, based on reduced scale data collection and trials.

Design of prospective studies – use of the system in intended environment, check its ability to improve the process.

7.8.4 Software Engineering

7.8.4.1 Stages of Waterfall Life-Cycle

The problem analysis deals with identifying of a set of interacting entities. However, the process is more complex for the domains approached by DSS, due to the characteristics like unstructuredness, uncertainty and the need for heuristics.

Rapid prototyping plays a crucial role in requirements analysis due to its tangible nature. The designers can interview the decision maker in an unambiguous manner and for an early user assessment by using rapid application development (RAD) tools.

The design stage represents the blue print that formally describes all the functional flows, the system architecture and the procedural design. The design documents can be turned into implementation/code using programming skills.

The exploratory nature of most DSS means that they cannot be formally specified at their outset, so drifting away is possible, especially if the development is driven by the modelling technique. For the same reason, there will be fuzzy problem definitions that possibly change over time. Therefore, the design must allow for changes at all levels and the effect of the changes must be encapsulated in modules to avoid the impact on the whole architecture.

The implementation represents coding, usually in a native high-level language. Probably this stage is almost identical in both DSS and standard application development.

Testing can be a task that is time consuming and relatively not suitable for human natural capabilities as it requires tireless attention to details. CASE tools can be used, for example Rational Rose. However, exhaustive testing is not possible, and usually a pragmatic view is adopted: "you're done testing when you run out of time or you run out of money" [121]. Testing is totally different from and only a precondition for the validation/evaluation to commence.

7.8.4.2 Object Oriented Technology

The advantage given to developers, because of key features like encapsulation, reusability of code through inheritance, etc, by the object oriented approach can be major.

Object Oriented Analysis (OOA)

Using a problem solving approach, the objects that are relevant to the problem at hand are identified. A class hierarchy is specified, object interaction and object behavior are modelled.

Object Oriented Design (OOD)

Specific data organization within classes, procedural detail of individual operations and how behavior is to be implemented are formally specified.

Object Oriented Programming (OOP)

OOP turns the design (blue print) into code usually with greater productivity than in procedural approaches.

7.8.4.3 Documentation – UML

Documents are necessary to monitor the *completion* and *correctness* (quality) of the development stages in the waterfall development process. The documents must maintain lists of limitations and issues.

There are several ways to produce documents, from standard text editors, to procedural formal languages like z and UML for the object-oriented design of systems.

The Unified Modelling Language (UML) is a visual formal specification language that provides a way to analyse and design object oriented systems. They help visualise, construct, and document artefacts of software systems or to model business processes in the targeted domain. One available implementation as a CASE package is Rational Rose product.

UML uses diagrams to produce a design in order to

- Abstract features of the design
- Show relationships between elements of design

The diagrams used are as follows

- Static class diagrams – abstract representation of the classes in the system, aggregations, compositions and generalisations
- Collaboration diagrams – show the working together between classes by message passing
- Sequence diagrams – show the order of messages and the time element and the focus of control indicates when an object is active
- Activity diagrams – describe workflows, they are very flexible in their use; they are usually understood by users when used to describe business logic flows
- Use case diagrams – used to represent user interaction with the system by means of identifying of actors; represent an effective way of communicating with the users and other stakeholders in the project;

Examples are used often in this thesis.

7.9 Summary

Both scientific and engineering endeavours behind DSS development were emphasised. An overview of the problem domains targeted by DSS showed that they are unstructured, and affected by uncertainty. The material is intended to develop a critical attitude towards the DSS use, the development and the formulation of their need. The development of *Quality* DSS does not happen by chance, but by putting good development principles into practice. Validation against real world decides if the DSS helps the decision making process and if the outcome of the process is improved.

8. DIAS-NIDDM, a Diabetes Advisory System for Insulin-Treated Subjects with Type 2 Diabetes Mellitus

8.1 Introduction

DIabetes Advisory System (DIAS) is a decision support system for the adjustment of insulin doses in subjects with type 1 diabetes [8]. The system uses CPN to implement a stochastic model of the carbohydrate metabolism. The model is employed for making predictions of blood glucose excursions for 24-hour periods. The DIAS model has been extended to represent endogenous insulin secretion aiming at building a system able to adjust the doses of insulin in insulin-treated subjects with type 2 diabetes, DIAS-NIDDM.

This chapter presents the system requirements for DIAS-NIDDM and the concepts underlying the design (generation of conditional probabilities, CPN learning and forecasting, and insulin dose adjustment) and the functionality of the system. The development section presents the solutions adopted in DIAS-NIDDM in tackling the increased computational demands introduced by the insulin secretion model (see chapter 5) and the extra parameter, pancreatic sensitivity. The integration of HbA_{1c} facilities (see chapter 6) is described. The development section illustrates the software engineering contribution.

8.2 System Requirements

The system has been developed to meet the following requirements:

- To extend the existing DIAS model of carbohydrate metabolism to represent the endogenous insulin secretion in subjects with type 2 diabetes

- To include a steady state model of the haemoglobin glycation (HbA_{1c})

- To re-engineer DIAS-NIDDM to cope with the increased computational demands

- To re-engineer DIAS-NIDDM using an object oriented paradigm

8.3 DIAS-NIDDM: Overview

DIAS-NIDDM is a PC-based system running under the Windows 95/98/2000/XP operating systems. DIAS-NIDDM models the dynamics of blood glucose given (i) carbohydrate content of meals and, optionally, (ii) insulin doses.

DIAS-NIDDM estimates patient-specific parameters and suggests insulin doses that result in a favourable blood glucose profile. DIAS-NIDDM inherits many of the DIAS features [8]. DIAS-NIDDM is based on an extended, discrete-time, discrete-state CPN model of the carbohydrate metabolism including a component representing the endogenous insulin secretion. Steady state HbA_{1c} predictions are possible due to another extension to the model.

In DIAS, the discrete time CPN model is implemented with a time-step of one hour. Due to the feedback loop introduced by representing the endogenous insulin secretion [84], a 30-minute time-step was adopted in DIAS-NIDDM to improve the stability of the predictions, see Figure 5.7. The shorter time-step and the addition of the secretion model rendered the CPN model too complex to be manipulated by standard methods of Bayesian updating implemented in the CPN shell HUGIN [7]. The repetitive design of the DIAS network was found particularly suitable to be implemented as a dynamic CPN [89]. The benefit in computational time and memory space offered by this approach determined its adoption for the implementation of DIAS-NIDDM [84]. The probability updating is performed by purpose built code that implements the Bayesian updating on dynamic CPN. The dynamic CPN approach allows parameter estimation and prediction over an arbitrarily long period. DIAS-NIDDM does not require HUGIN libraries to run.

The CPN model of insulin action has been simplified in DIAS-NIDDM by expressing the endogenous glucose balance as a linear function of the active insulin and *BG* avoiding the need to represent the insulin-dependent and the insulin-independent utilisation of the blood glucose in the network [71;133]. The conditional probability table describing the endogenous glucose balance was generated numerically using a

specialised tool [134], and subsequently, the probability generation functionality itself was implemented into DIAS-NIDDM, see 8.5.2. The conditional probability table linking the insulin secretion to the blood glucose concentration is computed at run time.

8.4 DIAS-NIDDM: Model Parameters

DIAS-NIDDM includes three parameters to represent the inter-individual differences in the carbohydrate metabolism and the insulin absorption. These parameters are: (i) pancreatic sensitivity (*ps*), (ii) insulin sensitivity (*is*), and (iii) time-to-peak of the absorption of intermediate-acting NPH insulin (*nph*).

The pancreatic sensitivity parameter (*ps*) represents the post-prandial (post-meal) ability of *BG* to stimulate insulin secretion. This parameter controls the insulin secretion and reflects the degree of impaired insulin secretion. The insulin sensitivity parameter (*is*) represents the ability of the plasma insulin to control the glucose metabolism. The ability is expressed relative to that of the normal subject. The time at which the absorption of the insulin from an NPH insulin injection attains its peak value is represented by the time-to-peak of NPH parameter (*nph*).

The first parameter, *ps*, is a new parameter, the other two parameters, *is* and *nph*, have already been present in the DIAS system. The parameters are estimated from the patient's specific data (food intake, insulin doses, *BG* measurements) recorded over a period of four days by Bayesian probability updating.

With the steady state HbA_{1c} predictive facilities added to DIAS-NIDDM, two more system parameters have been incorporated.

The glycation rate (*k*), (h^{-1} per mmol L^{-1}) represents the glycation rate. The life span of the red cell (*T*), measured in days, represents the lifespan of a red cell from its origination in the blood stream until it is eliminated, on the average after 120 days. These parameters are estimated from HbA_{1c} measurements.

8.5 Underlying Concepts

This chapter focuses on the conceptual framework and the methods underlying the development of DIAS-NIDDM system.

8.5.1 Discrete-Time Stochastic Model of CHO Metabolism

DIAS-NIDDM employs a discrete-time model of the carbohydrate metabolism. The probability distribution associated with the blood glucose concentration is calculated every 30 minutes using, repetitively, a CPN slice (Figure 8.1) in a dynamic fashion. The process is initiated using an uninformative *a priori* distribution for *BG*. The calculations start six hours prior to the beginning of the period of interest to allow *BG* to converge from the uninformative probability distribution [84].

The CPN slice has three nodes: the blood glucose concentration at time *T* (BG_{+0}), the active insulin at time *T* (I_{+0}), and the blood glucose concentration at time T_{+30} (BG_{+1}). The deterministic models of insulin absorption [8;24;83] and gut absorption [8;16] compute the insulin absorption (I_{ABS}) and the gut absorption (GUT_{ABS}) during the period *T* to T_{+30} according to the insulin injections and the carbohydrate intake, respectively. The endogenous insulin secretion (I_{SEC}) represents the insulin secreted by the pancreas.

Informally, the Bayesian updating proceeds in the following way. The probability distribution of *BG* at time *T* is inserted into the node BG_{+0}. The endogenous insulin secretion (I_{SEC}) is calculated as a probability distribution. The insulin appearance due to the exogenous insulin injections I_{ABS} (discrete value) is added to I_{SEC} to obtain the total plasma insulin. The total insulin is scaled by the insulin sensitivity parameter (*is*) and is inserted into the active insulin node (I_{+0}) (in fact, a joint probability distribution $p(BG_{+0}, I_{+0})$ is calculated, as BG_{+0} and I_{+0} are dependent).

The model of insulin action calculates the change in the probability distribution of *BG* by calculating the endogenous glucose balance (Figure 8.2) which depends on *BG* itself and the active insulin concentration.

The contribution from gut absorption GUT_{ABS} (discrete value) is added to obtain the probability distribution at time T_{+30} (BG_{+1}). The mean and standard deviation of BG_{+1} are computed and displayed on the screen. The time is incremented, the probability distribution of BG_{+1} is inserted into BG_{+0} node, and the whole process is repeated.

For each position of the CPN slice, the probability distribution of BG_{+1} can optionally be passed to the HbA_{1c} predictor that will update and accumulate the glycation fraction. At the end of the forecast period, a steady state HbA_{1c} value is predicted assuming that the simulated period can be generalised for the next 120 days, see 6.2.3.

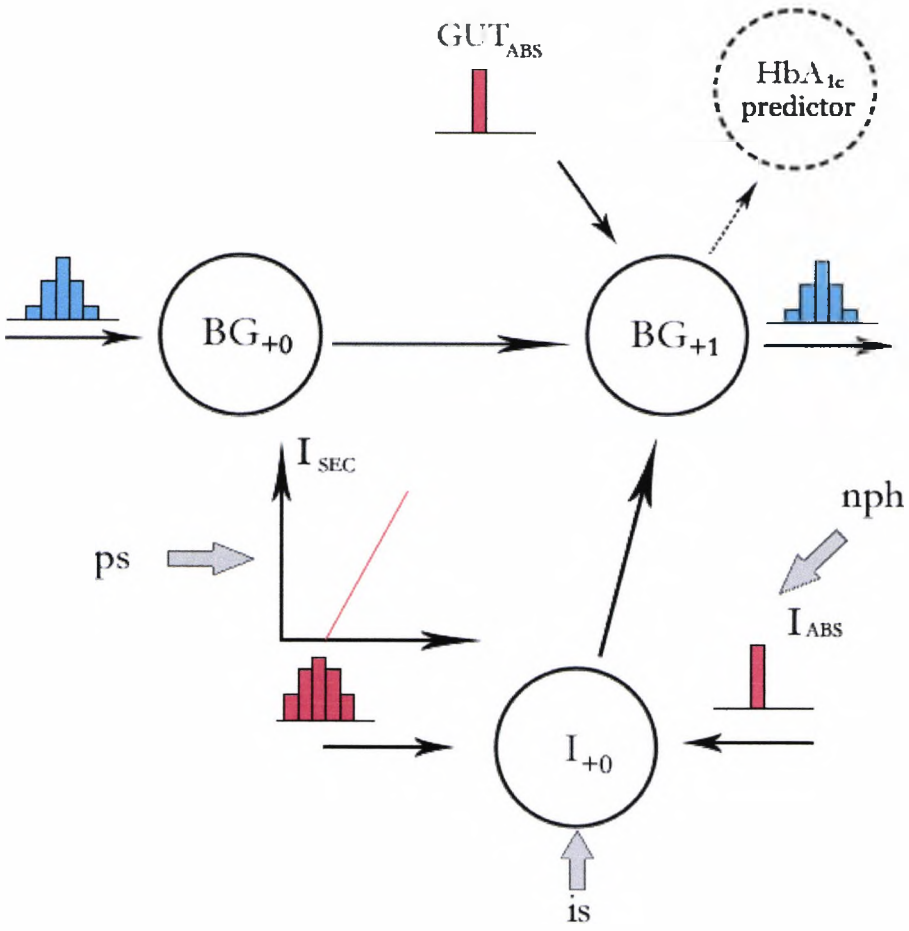


Figure 8.1 *Discrete-time stochastic model of CHO metabolism (30-minute time-step) implemented in DIAS-NIDDM. The variables in the system are represented as probability distributions. The model has three parameters: pancreatic sensitivity (ps), insulin sensitivity (is) and time-to-peak of NPH insulin (nph) and predicts BG at* T_{+30} *minutes* (BG_{+1}) *from BG at time T* (BG_{+0}). *Predicted* BG_{+1} *profiles are optionally fed into the* HbA_{1c} *predictor. For description of other variables, see text.*

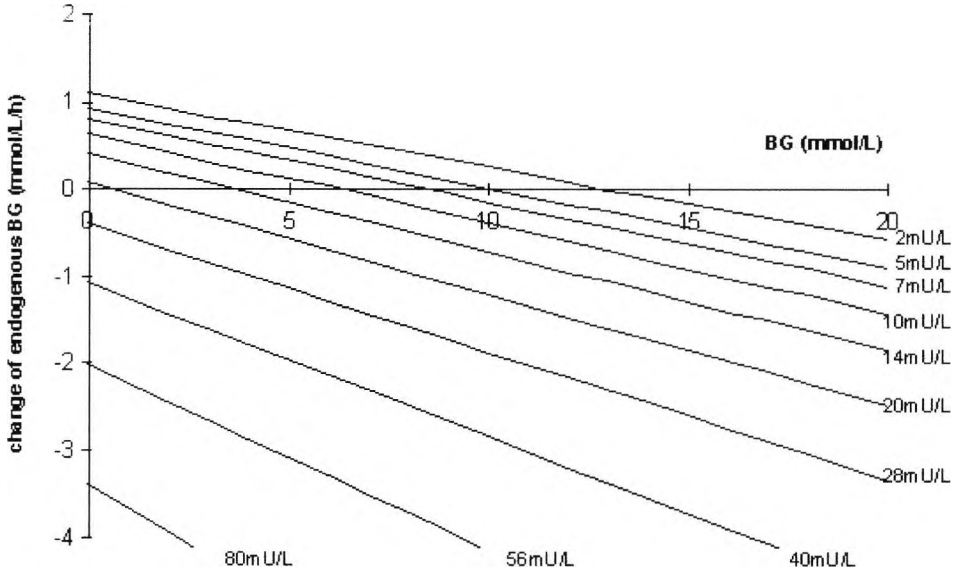


Figure 8.2 *Linear model of insulin action. The lines represent change in the endogenous glucose for various concentrations of BG and active insulin [71]*

8.5.2 Conditional Probabilities

8.5.2.1 Generation of Conditional Probabilities

The inference in the system can use both run-time and pre-calculated conditional probabilities. The model of insulin secretion was implemented as a conditional probability table, $p(I_{+0} \mid BG_{+0})$. The model of insulin action is calculated at run time and is represented as a conditional probability, $p(BG_{+1} \mid BG_{+0}, I_{+0})$. Regardless of the exact situation, the conditional probabilities are calculated from the functional relationships between a node and its ancestors [84;133;134]. The method uses the fact that the states of the nodes are adjacent, disjoint intervals, representing scalar values resulting in the continuous state space of the nodes. Functional relationships are mapped on a mathematically sound basis into conditional probabilities using the random variable transformation technique [55].

For example, the active insulin conditional probability $p(I_{+0} \mid BG_{+0})$ relates the active insulin to the BG levels. The probabilities were generated given the states of the insulin absorption, the states of *ps* and *is*, based on the functional relationship:

$$I_{+0} = f(BG_{+0}) \qquad 8\text{-}1$$

where f is a deterministic function.

An element of the conditional probability table

$$p(I_{+0,j} \mid BG_{+0,i}) \qquad 8\text{-}2$$

where $I_{+0,j}$ is the state of I_{+0} representing interval $(I_j, I_{j+1}]$ and $BG_{+0,i}$ is the i^{th} state of BG_{+0} representing interval $(BG_i, BG_{i+1}]$ is calculated as :

$$p(I_{+0,j} \mid BG_{+0,i}) \;\alpha\; \frac{\int_{\Omega} f(BG)\, d\,BG}{\int_{\Psi} f(BG)\, d\,BG} \qquad 8\text{-}3$$

where $BG \in \Omega \;\Leftrightarrow\; f(BG) \in (I_j, I_{j+1}]$ and $\Psi = (BG_i, BG_{i+1}]$.

The insulin absorption was included in this relationship to avoid a further step in the calculations. The functional relationship $f(BG)$ became:

$$f(BG) = I_F\, is + (BG - BG_b)\, ps\, is + I_{ABS}(nph)\, is \qquad 8\text{-}4$$

BG_b is the basal blood glucose concentration. $I_{ABS}(nph)$ is the insulin concentration due to the NPH insulin absorption and depends on the *nph* parameter. I_F represents the endogenous fasting insulin concentration.

Equation (8-4) indicates the mode of action of two of the system parameters: insulin sensitivity (*is*) and pancreatic sensitivity (*ps*). Insulin sensitivity scales every

component of the insulin. Pancreatic sensitivity has control on the glucose-stimulated insulin component. Time-to-peak of nph insulin (*nph*) acts on the computed I_{ABS}.

Therefore, DIAS-NIDDM can estimate *is* and *ps* parameters with higher accuracy in the presence of exogenous insulin.

8.5.2.2 Method to Generate Conditional Probabilities from Functional Relationships

The conditional probability, $p(r \mid r, BG)$, relations (6-10;6-16), updates the glycation fraction according to the contribution from a sampled *BG* concentration. The relationship is iterative, and uses the glycation fraction from the previous iteration. The calculation of an element of this conditional probability illustrates the use of the method in 8.5.2.1.

The glycation fraction $r = re^{-k\,BG\,dt}$, relationship (6-10), represents the product between r at the previous iteration and the contribution to glycation from a *BG* sample. With the following substitutions, $x = r$, and $y = e^{-k\,BG\,dt}$, $z = f(x,y) = xy$, the procedure can be generalised to generate the conditional probability for the *product* relationship between two stochastic variables *x* and *y*.

For $z \in [z_k, z_{k+1}), y \in [y_j, y_{j+1}), x \in [x_i, x_{i+1})$, the element of the conditional probability table $p(Z \mid X, Y) = p\left(Z_{z\in[z_k,z_{k+1})} \mid X_{x\in[x_i,x_{i+1})}, Y_{y\in[y_j,y_{j+1})}\right), \forall i, j, k$ can be calculated analytically by functional transformation [55].

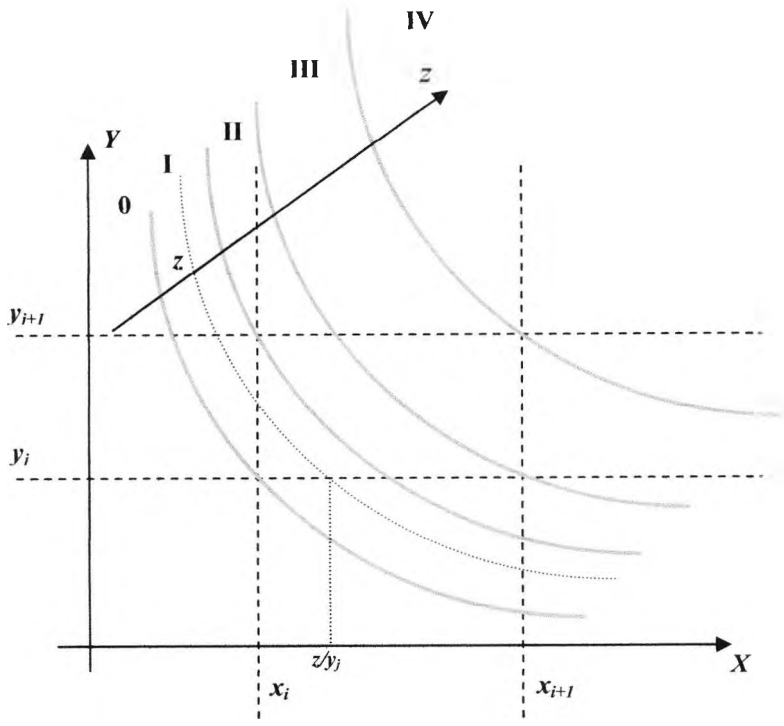


Figure 8.3 *Illustration of the functional transformation method [55]*

The calculation requires the definition of suitable cut off points,

$z_1 = x_i y_j$, $z_2 = x_i y_{j+1}$, $z_3 = x_{i+1} y_j$, $z_4 = x_{i+1} y_{j+1}$, that depend on the geometry of the actual area defined by $\left[(x_i, x_{i+1}),(y_j, y_{j+1})\right]$.

The conditional probability distribution is proportional with the area under the curve for a given z.

The area under the curve $z = xy$ and included in the rectangle $\left[(x_i, x_{i+1}), (y_j, y_{j+1})\right]$ is given by:

Case I ($z1<z<z2$)

$$F_z = \int_{x_i}^{\frac{z}{y_j}} \frac{z}{x} dx - y_j \left(\frac{z}{y_j} - x_i \right) = z \ln \frac{z}{x_i y_j} - y_j \left(\frac{z}{y_j} - x_i \right)$$

Case II ($z2<z<z3$)

$$F_z = \int_{x_i}^{\frac{z}{y_j}} \frac{z}{x} dx - y_j \left(\frac{z}{y_j} - x_i \right) - \left(\int_{x_i}^{\frac{z}{y_{j+1}}} \frac{z}{x} dx - y_{j+1} \left(\frac{z}{y_{j+1}} - x_i \right) \right) = z \ln \frac{y_{j+1}}{y_j} - x_i \left(y_{j+1} - y_j \right)$$

Case III ($z3<z<z4$)

$$F_z = \left(y_{j+1} - y_j \right) \left(\frac{z}{y_{j+1}} - x_i \right) + \int_{\frac{z}{y_{j+1}}}^{x_{i+1}} \frac{z}{x} dx - y_j \left(x_{i+1} - \frac{z}{y_{j+1}} \right) = z \left(\ln \frac{z}{y_{j+1} x_{i+1}} + 1 \right) + x_i \left(y_j - y_{j+1} \right) - x_{i+1} y_j$$

$$F_z = \begin{cases} 0, & area\,0 \\ z \ln \dfrac{z}{x_i y_i} - y_i \left(\dfrac{z}{y_i} - x_i \right), & area\,I \\ z \ln \dfrac{y_{j+1}}{y_j} - x_i \left(y_{j+1} - y_j \right), & area\,II \\ z \left(\ln \dfrac{z}{y_{j+1} x_{i+1}} + 1 \right) + x_i \left(y_j - y_{j+1} \right) - x_{i+1} y_j, & area\,III \\ 1, & area\,IV \end{cases}$$

$$p\left(Z_{[-\infty,z)} \mid X_{[x_i,x_{i+1})}, Y_{[y_j,y_{j+1})}\right) = \frac{F_z}{(x_{i+1}-x_i)(y_{j+1}-y_j)}$$

$$p\left(Z_{[z_k,z_{k+1})} \mid X_{[x_i,x_{i+1})}, Y_{[y_j,y_{j+1})}\right) = \frac{F_{z_{k+1}} - F_{z_k}}{(x_{i+1}-x_i)(y_{j+1}-y_j)} \qquad 8\text{-}5$$

Relationship 8-5 gives an element of the conditional probability for any combination of the intervals of the variables x and y.

8.5.3 Bayesian Learning

The CPN approach enables population-specific physiological knowledge and patient specific information to be mixed within a formally coherent model. Clinical studies provide population specific data related to the physiological processes of the carbohydrate metabolism. These data are used to build a model, which is only capable of qualitative predictions. Using the model for individual subject simulations requires the existence of some parameters to accommodate for the inter-patient variability.

In DIAS-NIDDM, the data collected for several consecutive days (*BG* measurements) are used to estimate the model parameters. The model is fitted to the subject by combining the estimated parameters with the population specific data making possible quantitative predictions of future states.

The parameters are assumed time-invariant during the observed period and have independent *a priori* distributions. The *a priori* distributions are uniform and are used by the system together with the plasma glucose measurements, carbohydrate intake and insulin doses. The parameter estimation procedure using the conditioning method of Bayesian updating produces the *a posteriori* joint probability distributions of the parameters.

Learning is performed using the CPN slice of the CHO model with all the measurable variables located in the set of interface nodes (in this case *BG* node) and requires only the disseminate phase of the Bayesian updating and not the collect phase [84;89] – disseminate only dynamic CPN. The learnt profile is discarded to speed up the calculations and therefore not calculated.

When presented with evidence for a certain position of the window, the following occurs: probability dissemination, evidence absorption, and probability normalisation.

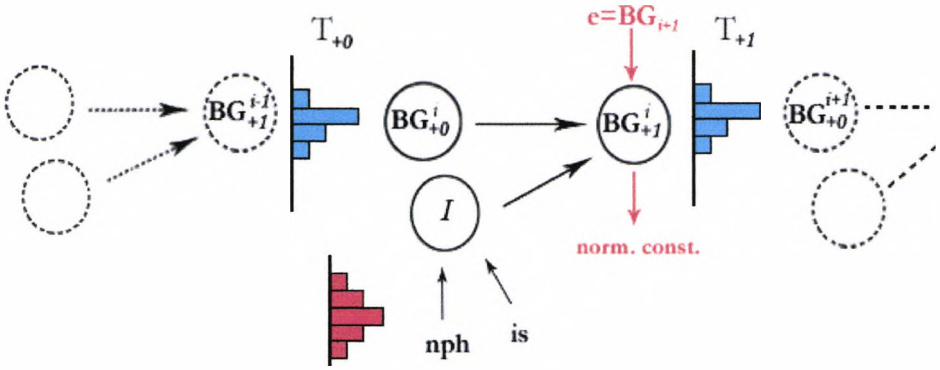


Figure 8.4 *DIAS-NIDDM CPN slice on position i. The processing stages in learning are shown: dissemination, insertion of evidence, conditioning, computing the normalisation constant.*

8.5.3.1 Probability Dissemination

The probability dissemination calculates $p\left(BG^{i}_{+1} \mid V^{*}_{p}, e^{i}_{+0}\right)$ from $p\left(BG^{i}_{+0} \mid V^{*}_{p}, e^{i}_{+0}\right)$ where $e^{i}_{+0} = \{BG^{j}_{m},\ j=0,..i\}$ is the evidence up to but not including the evidence at node BG_{+1} for the current position of the CPN slice.

$$
\begin{aligned}
p\left(BG^{i}_{+1} \mid V^{*}_{p}, e^{i}_{+0}\right) &= \sum_{BG^{*}} \frac{p\left(BG^{i}_{+0}, BG^{*}, V^{*}_{p}, e^{i}_{+0}\right)}{p\left(V^{*}_{p}, e^{i}_{+0}\right)} \\
&= \sum_{BG^{*}} \frac{p\left(BG^{i}_{+0} \mid V^{*}_{p}, BG^{*}\right) p\left(V^{*}_{p}, BG^{*}, e^{i}_{+0}\right)}{p\left(V^{*}_{p}, e^{i}_{+0}\right)} \\
&= \sum_{BG^{*}} p\left(BG^{i}_{+0} \mid V^{*}_{p}, BG^{*}\right) p\left(BG^{*} \mid V^{*}_{p}, e^{i}_{+0}\right) \qquad \text{8-6}
\end{aligned}
$$

where

$p\left(BG^{i}_{+0} \mid V^{*}_{p}, BG^{*}\right)$ - calculated from the conditional probabilities of nodes in the slice

BG^{*} - denotes states of BG variables represented as scalar intervals

V^{*}_{p} - denotes a particular configuration of the parameters set V_{p} {*is*, *ps*, *nph*}

The initialisation of the window movement assumed the converged *BG* probability distribution resulting from a flat lead-in period *a priori* distribution when the forecast of *BG* profile commenced in DIAS. The probability dissemination is carried out for all the possible configurations of the set of parameters (V_p^*).

8.5.3.2 Evidence Absorption

The evidence absorption implies the inclusion of $\{BG^{i+1}{}_m\}$, if available, the *BG* measurement covered by the time slice in position *i*.

$$e^i{}_{+1} = e^i{}_{+0} + \{BG^{i+1}{}_m\}$$

The evidence absorption calculates:

A. *a priori* probability for the observed node

$$p\left(BG^i_{+1} \mid V_p^*, e^i_{+1}\right) = \begin{cases} p\left(BG^*_{+1,k} \mid V_p^*, e^i_{+0}\right), \; if \; BG^i_m \in BG^*_{+1,k} \\ 0, \quad otherwise \end{cases} \qquad 8\text{-}7$$

$BG^*_{+1,k}$ - state representing k-th interval of *BG* variable

B. *a priori* probability of the system parameters

$$\begin{aligned} p\left(V_p^* \mid e^i_{+1}\right) &= \frac{p\left(BG^i_{+1}, V_p^*, e^i_{+0}\right)}{p\left(e^i_{+1}\right)} \\ &= \frac{p\left(BG^i_{+1} \mid V_p^*, e^i_{+0}\right) p\left(V_p^* \mid e^i_{+0}\right) p\left(e^i_{+0}\right)}{p\left(e^i_{+1}\right)} \\ &\sim p\left(BG^{*i}_{+1,k} \mid V_p^*, e^i_{+0}\right) p\left(V_p^* \mid e^i_{+0}\right) \end{aligned} \qquad 8\text{-}8$$

8.5.3.3 Probability Normalisation

When evidence is available at BG^{i}_{+1} node and it is used to condition the model parameters, the normalisation of the joint probability distribution of the parameters and of the observed node is carried out to reinforce:

$$\sum_{BG^{*}_{+1}} p\left(BG^{i}_{+1} \mid V^{*}_{p}, e^{i}_{+1}\right) = 1$$

$$\sum_{V^{*}_{p}} p\left(V^{*}_{p} \mid e^{i}_{+1}\right) = 1$$

8.5.3.4 Learning from Multiple Day Data

In DIAS-NIDDM, as opposed to DIAS [8], learning has no temporal constraints in terms of the length of the time interval employed for parameter estimation. As a result, multi-day learning in DIAS-NIDDM was implemented as continuous learning on a period spanning any selected days of collected data.

8.5.4 Forecasting

In the forecasting mode, DIAS-NIDDM predicts the dynamics of the *BG* profile for an arbitrarily long period for a given input (timing and amounts of meal intakes and insulin injections). The system parameters are assumed estimated and are employed during forecasting. The gut absorption, and the insulin absorption (this time computed using the *a posteriori* marginal of *nph*) are inserted into the nodes of the appropriate variables for the current time slice. The network is propagated and the *BG* nodes contain the predicted probability distributions. The mean and standard deviations of the nodes are displayed on the screen.

Forecasting employs the joint *a posteriori* probability distribution $p(V_p \mid e)$ determined during the learning phase. The calculation of $p(BG_{+1} \mid V_p, e)$ from $p(BG_{+0} \mid V_p, e)$ is identical to the probability dissemination 8.5.3.1. The predicted probability distribution $p(BG_{+1})$ is obtained by marginalisation

$$p(BG_{+1}) = \sum_{V_p^*} p(BG_{+1} \mid V_p^*, e) p(V_p^*) \qquad 8\text{-}9$$

with $e = e_{U_{BG_m}} = \{BG_m^j, j = 1..n\}$ representing the plasma glucose measurements.

All the above calculations are done for all configurations of the parameters; $p(BG_{+1}^i \mid V_p^*, e)$ is calculated as *(size(is) x size(ps) x size(nph))* elements of conditional probability and stored in memory,

$$p(BG_{+1}^i \mid V_p, e) = \sum_j p(BG_{+1}^i \mid V_{p_j}^*, e_{+0}^i) p(V_{p_j} \mid e_{+0}^i) \qquad 8\text{-}10$$

However, Figure 8.1 shows the causal probabilistic network at a conceptual level. In reality, nodes I_{+0} and BG_{+0} are dependent and form a cycle with node BG_{+1}. To avoid incorrect calculations in the case of probability updating in the presence of loops, a junction graph with two nodes was built, (BG_{+0}, I_{+0}) and (BG_{+1}). The propagation

scheme was implemented simply by calling "distribute evidence" in node (BG_{+0}, I_{+0}), which propagates $p(BG_{+0}, I_{+0})$ to the node BG_{+1}.

The insulin secretion model calculates each element of the conditional probability table $p(I_{+0} \mid BG_{+0}, V_p)$ at run-time. The model of insulin action was represented as $p(BG_{+1} \mid BG_{+0}, I_{+0})$ [84;133]. For each of the iterations, the system predicts $p(BG_{+1}, V_{p_j})$ based on $p(BG_{+0}, V_{p_j})$ given the evidence on meal intake, the insulin absorption, and the parameter configuration V_{p_j}.

At time T_{+0}, BG_{+0} is available (as conditional probabilities $p(BG_{+0}, V_{p_j})$ for each parameter configuration V_{p_j}). The probability distribution of BG_{+0} at this moment in time is obtained by marginalisation:

$$p(BG_{+0}) = \sum_j p(BG_{+0} \mid V_{p_j}) p(V_{p_j}) \qquad 8\text{-}11$$

and its mean and SD are displayed by the system, but not used for probability updating. Instead, a joint probability of *BG* and active insulin is obtained and used in computations:

$$p(I_{+0}, BG_{+0} \mid V_{p_j}) = p(I_{+0} \mid BG_{+0}, V_{p_j}, I_{ABS}) p(BG_{+0} \mid V_{p_j}) \qquad 8\text{-}12$$

The active insulin is obtained by marginalisation:

$$p(I_{+0} \mid V_{p_j}) = \sum_k p(I_{+0}, BG_{+0,k} \mid V_{p_j}) \qquad 8\text{-}13$$

and displayed as (mean ±SD) of

$$p(I_{+0}) = \sum_j p(I_{+0} \mid V_{p_j}) p(V_{p_j}) \qquad 8\text{-}14$$

The joint probability $p\left(BG_{+1}, BG_{+0}, I_{+0} \mid V_{p_j}\right)$ is obtained using the model of insulin action:

$$p\left(BG_{+1}, BG_{+0}, I_{+0} \mid V_{p_j}\right) = p\left(BG_{+1} \mid BG_{+0}, I_{+0}\right) p\left(I_{+0}, BG_{+0} \mid V_{p_j}\right) \quad 8\text{-}15$$

After marginalization,

$$p\left(BG_{+1} \mid V_{p_j}\right) = \sum_{r,l} p\left(BG_{+1}, BG_{+0,r}, I_{+0,l} \mid V_{p_j}\right) \quad 8\text{-}16$$

Finally, the predicted $p\left(BG_{+1} \mid V_{p_j}\right)$ at T_{+30} is obtained by a probabilistic shift of the computed $p\left(BG_{+1} \mid V_{p_j}\right)$ by an amount equal to the glucose absorbed from the gut and used in the next position of the window as $p\left(BG_{+0} \mid V_{p_j}\right)$, with the whole process being repeated.

8.5.5 Insulin Dose Adjustment

DIAS-NIDDM employs the same method to optimise insulin doses that is present in DIAS [8;76]. The penalty function was modified, see Annex III, in order to account for the interval-oriented approach used to represent the stochastic variables in the CPN model. The module was re-engineered using the object-oriented paradigm in order to speed the development and to facilitate code reusability, enforce a structure, and for increased maintainability.

The insulin dose adjustment is implemented as a search (Gauss-Newton algorithm) in the space $i = (i_1,..,i_p,..,i_{n-1})$ of insulin doses.

The algorithm minimises a risk function $\xi(i)$ and starts with some initial guess $I_0 = (I_1,..,I_p,..,I_{n-1})$. At step *k*, the risk $\xi(I_k)$ is evaluated, and the best therapy from the iterations $\{I_0,..,I_k\}$ is recorded. The evaluation of the risk function for the given insulin set requires the underlying DIAS-NIDDM CPN functionality to simulate the *BG* profiles and their associated risk/cost.

The risk function $\xi(i)$ is next evaluated for I_{k+1}, determined by the gradient along the directions of the individual insulin doses:

$$\frac{\partial \xi(i)}{\partial i_p} = \frac{\xi(I_k + \Delta I_p) - \xi(I_k)}{\Delta I_p}$$

where

$\Delta I_p = (0,..,\Delta I,..,0), p = 0..n-1$, increment of dose in position p^{-th}

$\Delta I = 0.25$ U

and is given by:

$$\underline{I}_{k+1} = \underline{I}_k + \left(c_0 \frac{\partial \xi(i)}{\partial i_0}, ..., c_p \frac{\partial \xi(i)}{\partial i_p}, ..., c_{n-1} \frac{\partial \xi(i)}{\partial i_{n-1}} \right)$$

with coefficients c_p , $p=\overline{0..n-1}$, being heuristically chosen to speed up the convergence of the search; these are calculated by approximating ξ (i) by a parabola.

The algorithm stops when the search converged ($\frac{\partial \xi(i)}{\partial i_p} \sim 0$) or the maximum number of iterations is reached (currently, the maximum number of iteration is 5).

Conceptually, the risk evaluation procedure calculates a cost for each individual interval of the stochastic variable *BG* using a *U*-shaped penalty function [76] (see Annex III). The cost is then weighted with the probability mass of the interval to calculate the actual risk associated with the predicted *BG* value. The penalty function is steeper in the hypoglycaemic range resulting in increased risk for low *BG* values/low states with non-zero probability mass. Consequently, a hypoglycaemic episode within the standard deviation of the predicted mean *BG* will result in lowered advised doses for those insulin injections that control that particular plasma glucose prediction even in the situation when the mean of the *BG* fails to predict the hypoglycaemic event.

8.6 System Development

8.6.1 Use Cases

Use case diagrams consist of use cases, actors and their associations (Figure 8.5). A use case is an observable result/behaviour of value to an actor and represents a sequence of events. An actor represents a role that people perform in using the system and interacts with the use case. Use case diagrams are effective means of communication with users and stakeholders in the project. Use cases are realised in the design phase using collaboration and sequence diagrams showing interactions between co-operating objects (behaviour specification) and they will ultimately be implemented as program components [17].

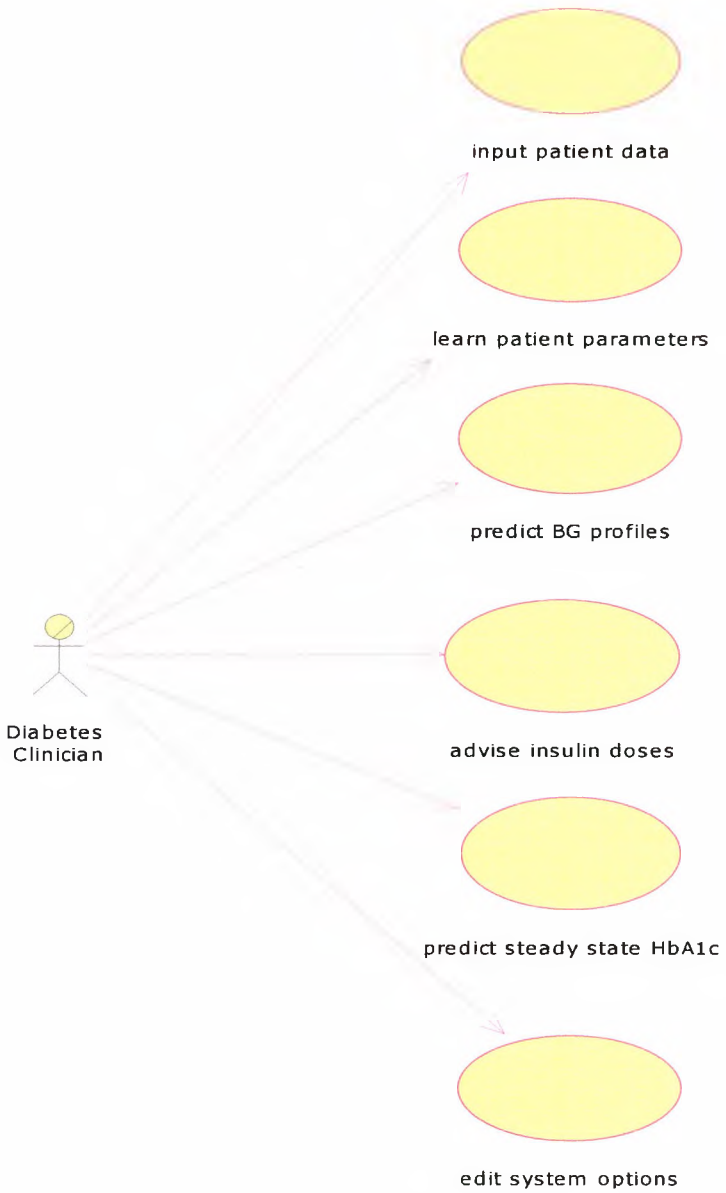


Figure 8.5 *Use case diagram showing possible ways the user can interact with the system*

8.6.2 Design Diagrams

The design is the first step in the development phase, the process in which the system is defined in sufficient detail to permit its physical realisation. However, the diagrams shown in this chapter are conceptual, and therefore some implementation details were left out in order to increase the readability.

DIAS-NIDDM has been designed in an object-oriented fashion. Data formats, interval/states of nodes and parameters were encapsulated within specialised classes, which act as information providers. Therefore, changes to data formats, number of states or actual state values/state intervals were isolated. Object Oriented Design (OOD) allowed speeding up the application development.

The design consists of class diagrams (Figure 8.6-Figure 8.8, and Figure 8.11 for the HbA_{1c} model) and collaboration/sequence diagrams (Figure 8.9, Figure 8.10 and for HbA_{1c} model integration, Figure 8.12).

Class diagrams show the software entities that will make up the system and their potential to collaborate by message passing. These diagrams picture the static view of the system described by class operations and attributes, behavioural and data management responsibilities of each class, and the relationships between the classes themselves (associations, aggregations, and generalisations).

Associations are indicated by the existence of message passing between classes.

Aggregation specifies that in addition to class attributes and operations, an instance of a class can consist of instances of other classes.

Generalisation describes relationships in which a class is a kind of another class, often referred to as inheritance or derivation in popular programming languages, and allows the inheritance of attributes and operations of a super class by a subclass.

However, the complete message passing and the implementation of a use case can only be described by interaction diagrams like collaboration and sequence diagrams that can grasp the dynamic aspects of the system.

By collaboration, objects can implement complex functionality. The realisation of a use case requires that a subset of classes get involved in collaboration and that they interact by message passing. The objects' roles are shown as a series of stimuli.

Sequence diagrams can specify to a higher degree the object interactions by including the time element. A stimulus is followed by a timed sequence of object interactions.

8.6.2.1 Static View of the System, the Class Diagrams

The system design consists of classes with specific functionality and responsibilities.

Subject class reads the patient data from the persistent storage (food intake, insulin doses and *BG* measurements). Its processing capabilities consist of the calculation of the profiles of insulin and gut absorption, providing access to time stamped blood glucose measurements and patient's demographic data, see Figure 8.6, Figure 8.8.

DiasNode class stores the definition intervals of a CPN variable, the node probability distribution, and has members for assigning and returning the probability distribution of a variable, computing the mean, median and standard deviation of the distribution. The states of the variable are encapsulated, see Figure 8.7.

Slice class has as data members instances of *DiasNode* for storing the probability distributions of BG_{+0} node, I_{+0} node, and the intermediary glucose balance node. The most important member of the class is the CPN propagation function. This function takes the probability distributions of BG_{+0} and I_{+0}, together with the gut absorption and propagates the DIAS-NIDDM CPN slice thus calculating the probability distribution of node BG_{+1}, see Figure 8.6, Figure 8.7.

ParametersNIDDM class (generalises *Parameters* class) encapsulates the information on the states of the system parameters. The CPN model of insulin secretion is

implemented by a member of this class. This method computes the probability distribution of the active insulin (I_{+0}) given the probability distribution of the blood glucose inserted in node BG_{+0} (as opposed to *ParametersIDDM* class that lacks that functionality; *ParametersIDDM* class implements the functionality specific to type 1 diabetes allowing DIAS-NIDDM to operate in DIAS-IDDM mode). The Bayesian method of conditioning for parameter estimation is coded in this class and computes the *a posteriori* parameters (learn). Finally, the forecast method uses the estimated parameters, the data supplied by the *Subject* object and the CPN propagation facilities from *Slice* and can predict the blood glucose profile for a 24-hour period or longer, see Figure 8.6, Figure 8.8.

The *JPDF* class is a utility class for saving and loading the joint probability of the parameters to and from the persistent storage and performs the runtime manipulations associated with the probability updating and the probability normalisation. The *a posteriori* joint probabilities are used during forecasting and dose adjustment, see Figure 8.6, Figure 8.11.

CPeptide class calculates the equivalent fasting endogenous insulin concentration from the measured fasting C-peptide concentration specifically for normal, type 2 diabetes and obese subjects according to sex, age and BMI data, see Figure 8.6, Figure 8.7.

TherapyInsulin generalises *Therapy* class and contains the code for insulin dose adjustment by aggregating another class instance, Buffers. The Gauss-Newton algorithm (supported by some additional heuristics to improve the convergence of the search) is used for finding the optimum insulin dosage. The risk associated with the recommended dosage is computed. *TherapyPills* class, not implemented, shows how the system can be extended to deal with the quantitative management of drugs treatment, see Figure 8.8.

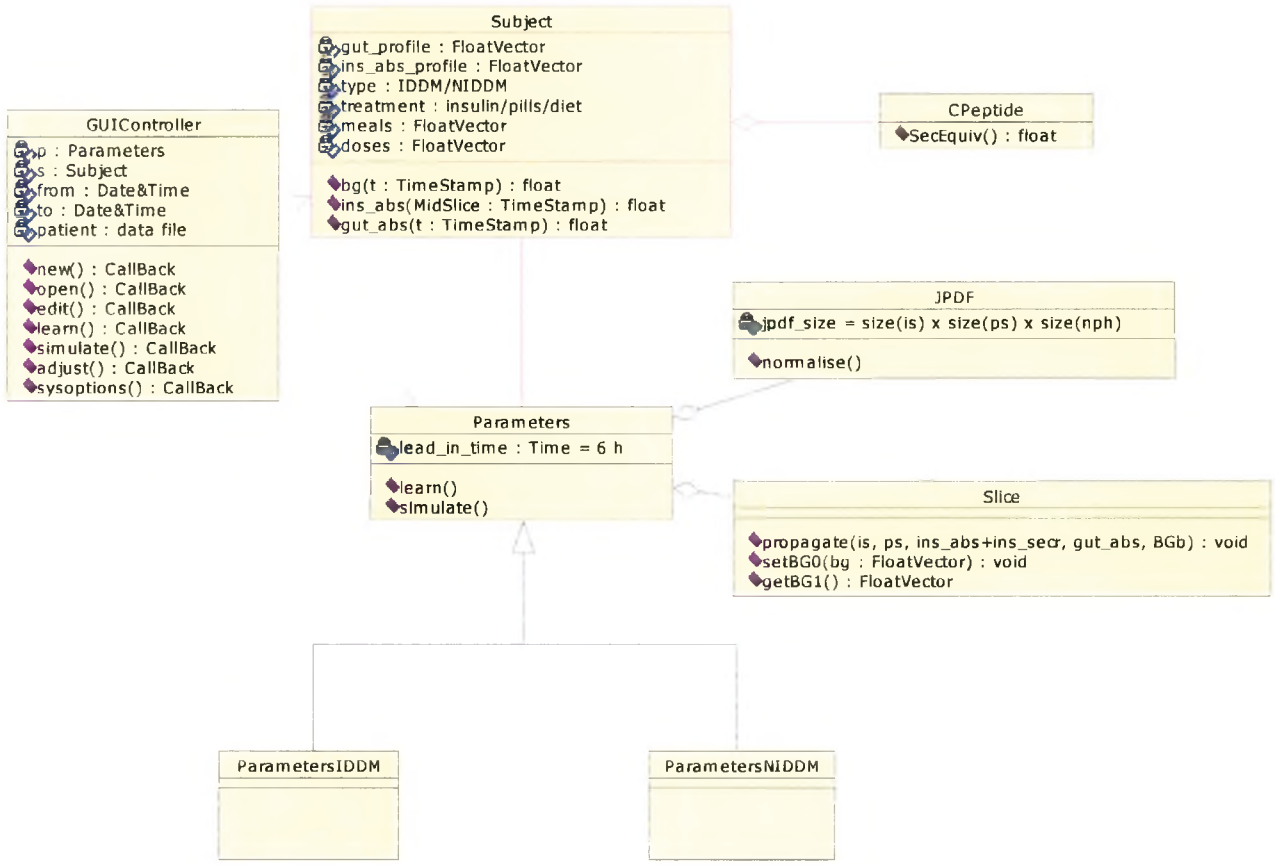


Figure 8.6 *Class diagram shows the major classes in DIAS-NIDDM with their associations and allocation of attributes and operations*

Parameters class hierarchy (Figure 8.6) is central to the system architecture. It is associated with the Subject class that has responsibilities like data management and storage (*BG*, CHO, insulin doses) but also harbours internally the models of gut and insulin absorption and aggregates a CPeptide instance. Parameters class also maintains an aggregation relationship with the JPDF class. The JPDF class manipulates the system parameters represented as a joint probability distribution $p(\underline{is}, \underline{ps}, \underline{nph} | e)$, including storage, retrieval and position encoding to facilitate single index access to elements. The Parameters class descendants (namely ParametersIDDM and ParametersNIDDM specialising the Parameters class through a generalisation relationship) will use an instance of the Slice class to which all causal probabilistic calculations are delegated. Slice class implements all the necessary CPN manipulations and manages the model of CHO metabolism (Figure 8.1). The user can

initiate flows of processing through the GUI controller. The GUIController has association relationships with the main classes of the system and can drive the interactions by its operations (e.g. learn(), etc).

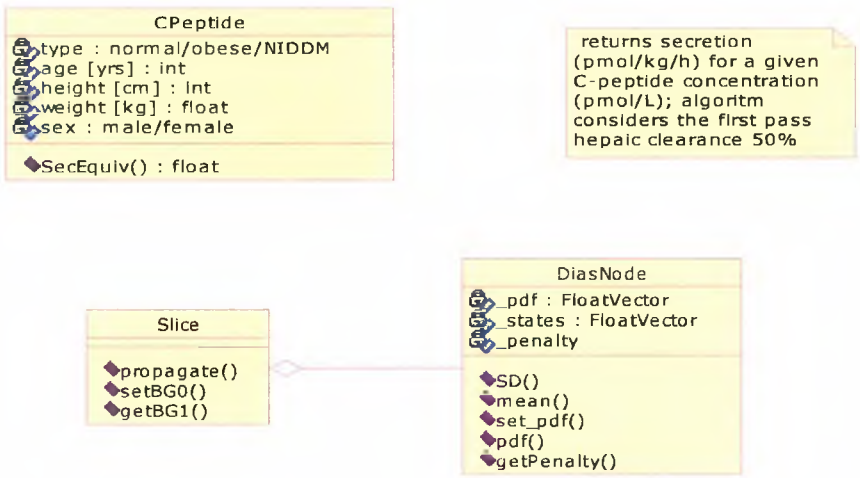


Figure 8.7 *Class diagrams showing attributes and operations of some of the utility classes. Slice has an aggregation relationship with DiasNode instances storing model stochastic variables BG_0, intermediary glucose balance and active insulin.*

The Slice class aggregates multiple instances of DiasNode class that will hold the CPN nodes (Figure 8.7). For nodes representing *BG*, a penalty can be calculated according to the cost function used to assess the outcome of any insulin regimen.

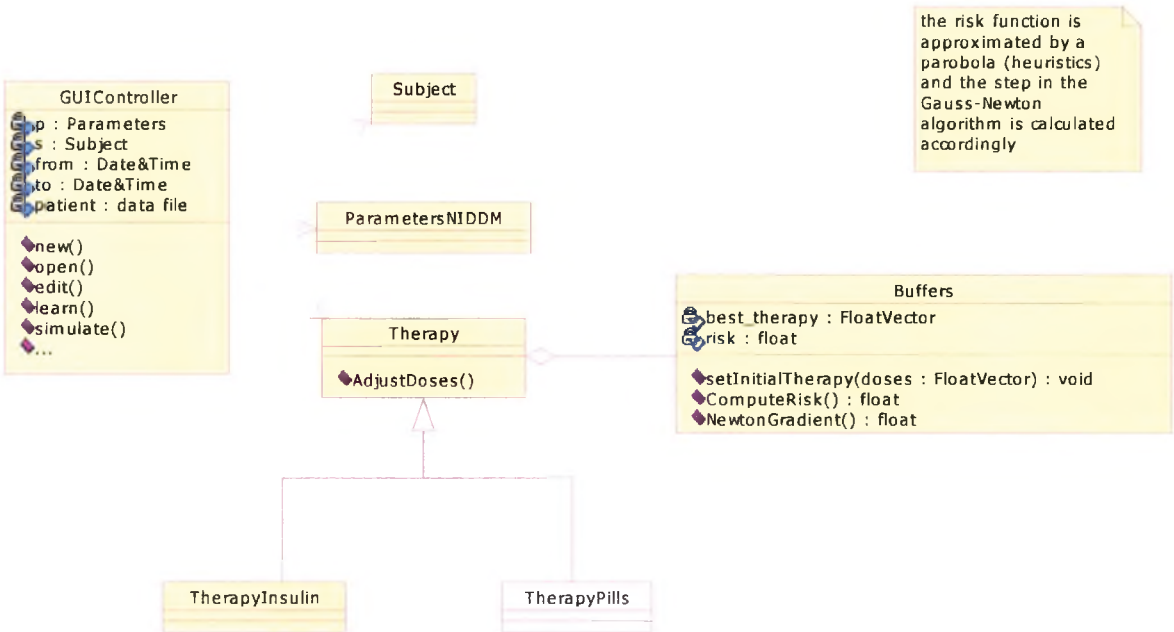


Figure 8.8 *Class diagram showing the classes necessary to realise 'Advice' use case*

The realisation of the 'Advice' use case requires a set of classes to cooperate as shown in Figure 8.8. The potential for collaboration is materialised in the attributes of the Subject class and the operations of both Parameters and Therapy derivations (TherapyInsulin and ParametersNIDDM/ParametersIDDM). However, the Gauss-Newton algorithm that is at the core of the advice generation has been implemented in the aggregated class Buffers. This class is suitably endowed with attributes for the temporary storage of initial, intermediary, and best therapies, together with operations that support the core algorithm's implementation.

8.6.2.2 Dynamic View of the System, the Realisation of the 'Advice' Use Case

The UML paradigm uses collaboration diagrams to show the interaction that takes place between a group of classes that are meaningful to, and result in the behaviour specified by, a given use case.

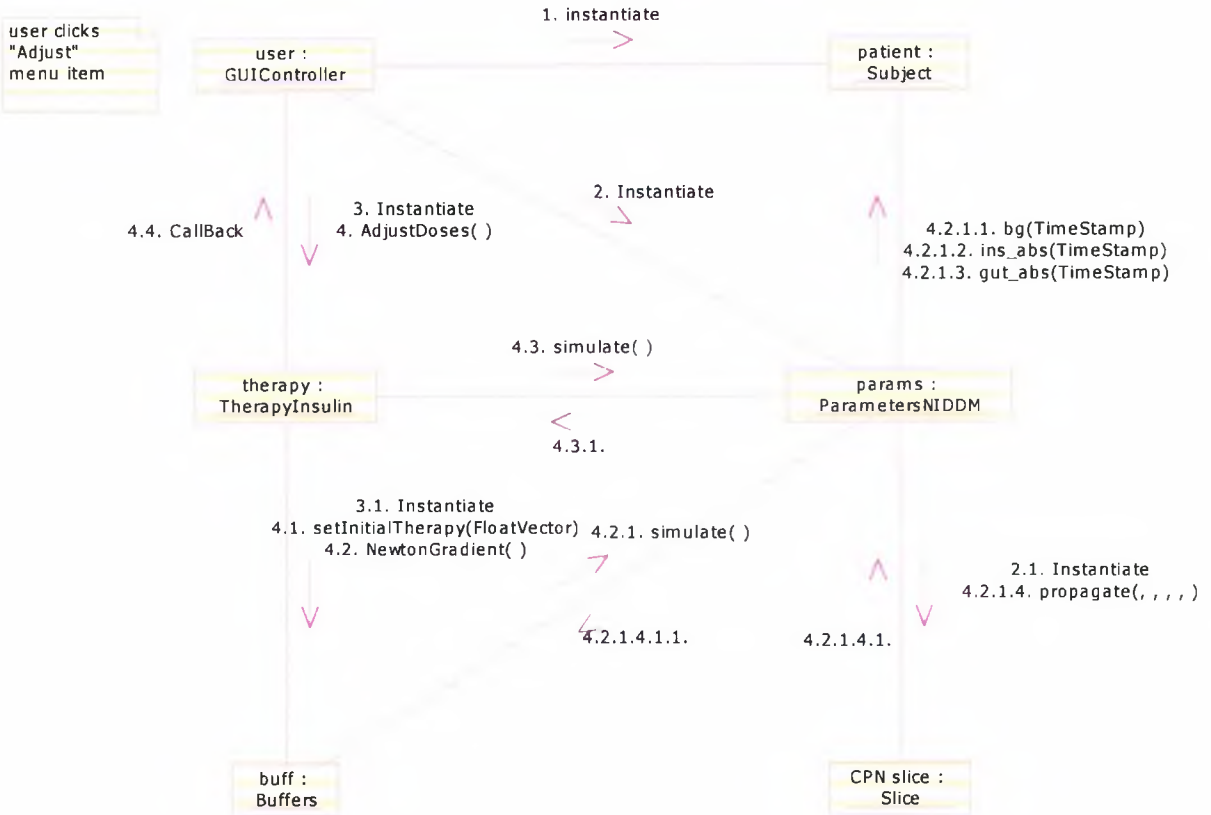


Figure 8.9 *Classes involved in the collaboration with interaction represented for the realisation of the 'Advice' use case*

Figure 8.9 shows the classes and relevant objects and stimuli that are involved to produce the functionality of the 'Advice' use case for the insulin therapy for insulin treated subjects with diabetes type 2, indexed with sequence numbers to indicate the order of firing. As result of the user action, instances of classes Subject, ParametersNIDDM, and TherapyInsulin are created. TherapyInsulin and ParametersNIDDM classes create their own aggregated utility objects (Buffers and Slice objects). AdjustDoses() stimulus triggers the actual processing. The diagram

also shows the relevant massage passing taking place to realise the specified behaviour whose details are captured in an alternative temporal sequence by the diagram in Figure 8.10.

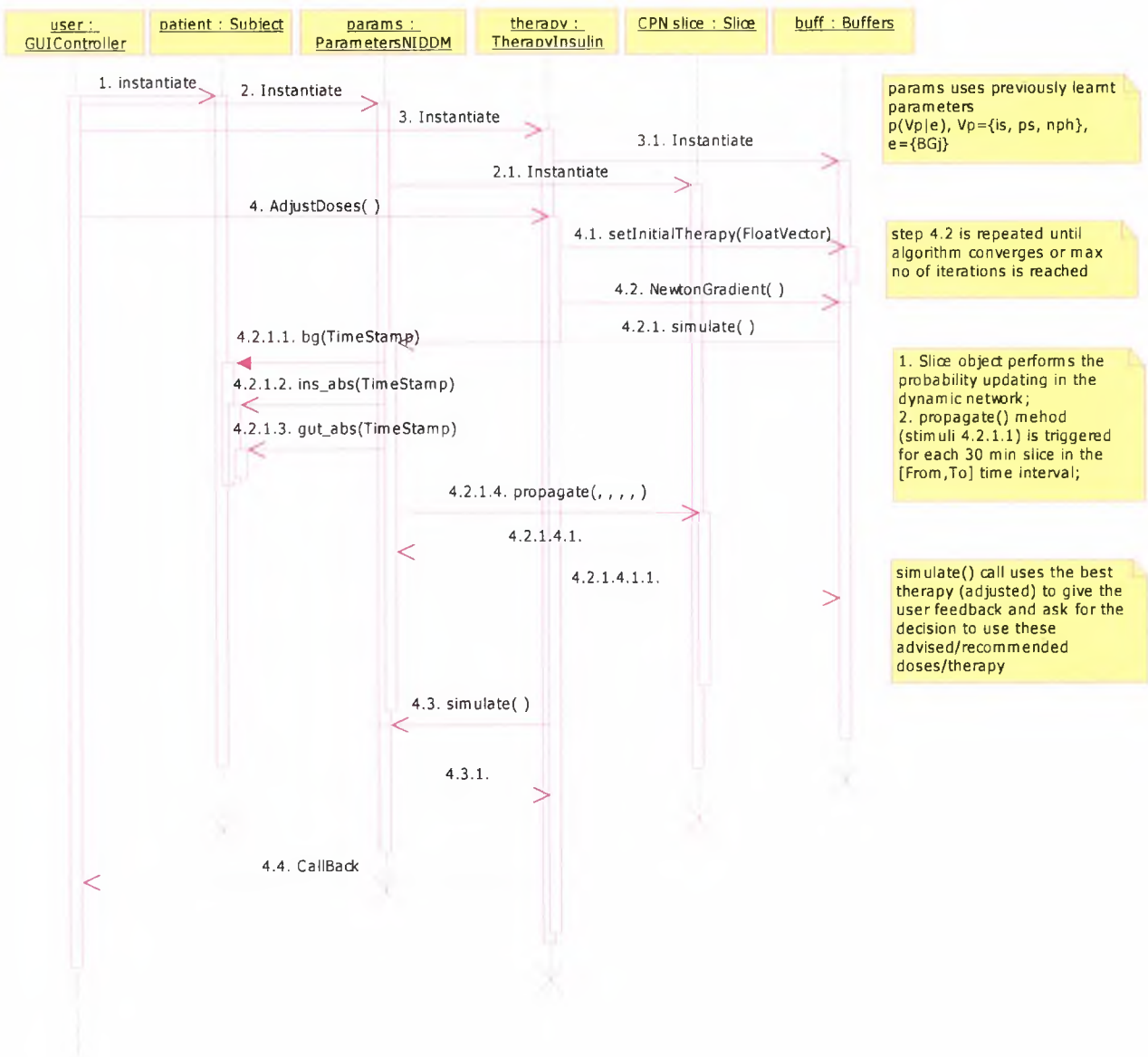


Figure 8.10 *Sequence diagram associated with Figure 8.9. It shows the sequence of messages/stimuli passed between objects to realise 'Advice' use case*

GUIController sends a message to TherapyInsulin object - AdjustDoses() - to start the processing that will generate the advice on the insulin dosage. The administered insulin doses are loaded in the Buffer object to perform the first step of the Gauss-

Newton gradient algorithm and are used as the initial vector in the search space (stimuli 4.1). The resulting *BG* profile associated with a given set of insulin doses is produced by the stimulus (4.2.1) sent to the ParametersNIDDM object that in turn delegates tasks to calculate the profiles of gut and insulin absorption to the Subject object (stimuli 4.2.1.1 to 4.2.1.3).

Inside simulate function, for each position of the CPN window, after feeding the probability distributions into the input variables of the model available at T_{+0} (BG_{+0}, I_{+0}, GUT_{ABS} and INS_{ABS}, see Figure 8.1), the propagation of the model will calculate the a posteriori probability distribution of BG_{+1} at T_{+1}.

Once the *a posteriori* discrete-time profile consisting of the probability distributions of the plasma glucose is produced, its associated risk is computed and returned for the Gauss - Newton algorithm to proceed with the next step, see paragraph 8.5.5.

The recommended insulin doses will be produced and optionally saved, optimum profile is displayed on the screen, and the control returns to the GUI by a call back.

8.6.2.3 HbA_{1c} Model Integration, the Design Diagrams

The DIAS-NIDDM model was further extended to predict the steady state HbA_{1c} associated with plasma glucose profiles (see Figure 8.1, and chapter 6). The OO architecture allowed the necessary extra functionality to be grown out of the Parameters and Slice class hierarchies, specialising them into ParametersHbA1c, rSlice and HbA1cSlice.

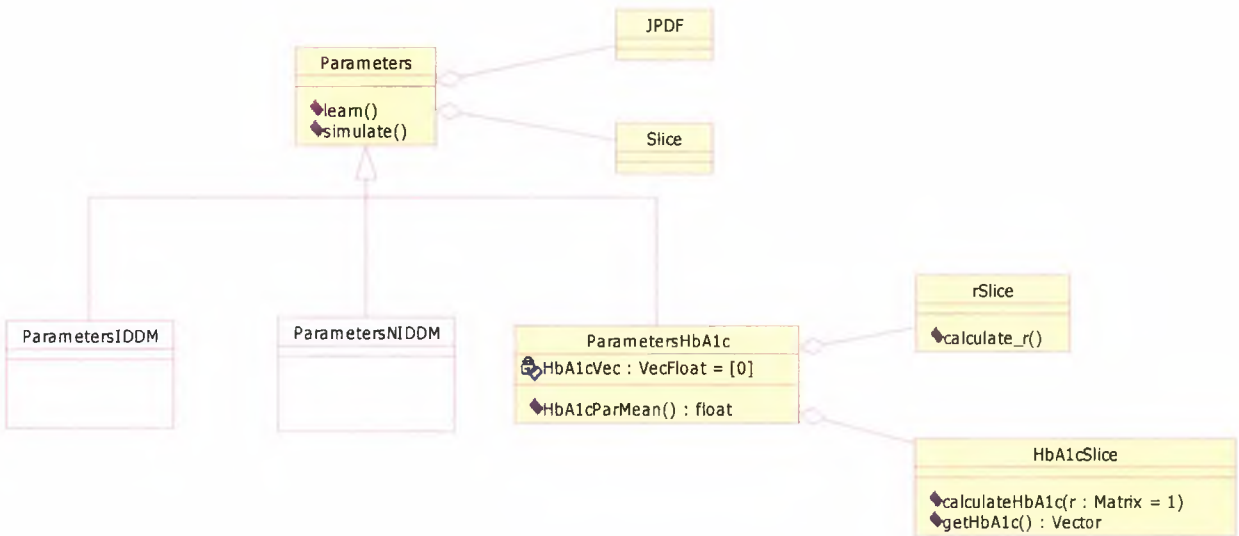


Figure 8.11 *Class diagram showing the additional classes to implement the HbA_{1c} prediction use case*

ParametersHbA1c generalises Parameters class and therefore inherits aggregated JPDF class and operations capable of parameter estimation Figure 8.11. However, ParamatersHbA1c works with the extended CPN model that implements the model of HbA_{1c} concentration, and its processing has been delegated to the rSlice and HbA1cSlice classes.

rSlice handles complex calculation of the model of glycated fraction that also generates the conditional probability tables at run time, see Figure 6.5. HbA1cSlice class implements the model of steady state HbA_{1c} see Figure 6.7.

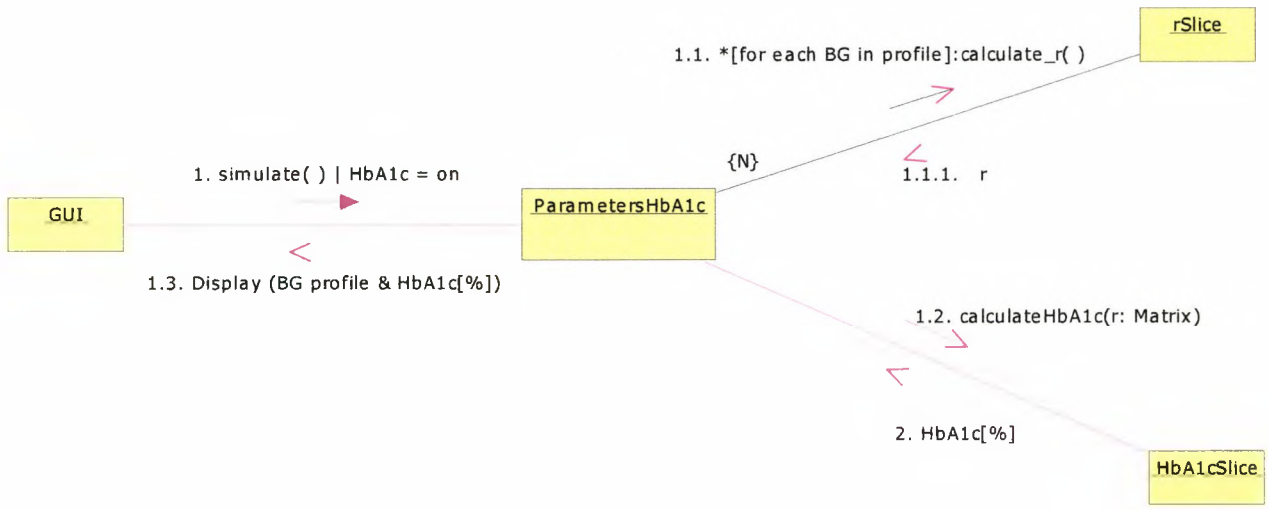


Figure 8.12 *Collaboration diagram to realise the predict steady state HbA_{1c} use case*

From a dynamic point of view, for each position of the window in the simulate operation of the ParametersHbA_{1c} class, the predicted joint probability distribution $p(BG_{+1},..|V_p)$ is passed to the rSlice object to calculate and accumulate the contribution of each BG_{+1} to the glycation factor (Figure 8.12).

At the end of the simulation period, the glycation factor represented as $p(r, V^{HbA1c}_{p})$ is used by HbA1cSlice to predict steady state HbA_{1c} and the result is displayed as percentage.

8.7 Discussion

The initial development of the model used Hugin Runtime libraries. The challenge was to implement the system in an efficient manner given that the requirements in terms of computer resources and computation time were drastically increased. The resolution of the discretisation needed a 30-minute or less time slice due to the feedback loop created when the model of insulin secretion extended the DIAS network. Covering a 24-hour period required 48 slices, twice that in DIAS.

The glucose-insulin negative feedback loop caused instabilities when the one hour-long time interval of DIAS network was used. A shorter time interval of 30 minutes has been implemented after experimenting with different time intervals (*15, 20, 30, 45* minutes).

Additionally, the model of insulin secretion increased the intrinsic complexity of the slice itself. Finally, one more parameter had to be added to represent the inter-individual variability in pancreatic sensitivity. The extended network was shown to be too complex to be handled by the HUGIN shell and the calculations became unfeasible.

Advances in design and implementation of DIAS-NIDDM were required to address these problems [84]. The principles of dynamic CPN were used for building the model. Purpose built code was implemented to handle customised CPN probability updating. Learning and forecasting were re-implemented in a time and resource efficient manner and can be performed on arbitrarily long periods.

The dependence between the active insulin and the *BG* concentration lead to the formation of a cyclic network comprising the nodes BG_{+0}, I_{+0}. The calculation of the endogenous balance required that the joint probability $p(BG_{+0},I_{+0})$ was used to make predictions. The addition of insulin absorption was initially implemented by shifting the joint probability $p(BG_{+0},I_{+0})$. However, finally, pre-computed conditional probability tables $p(I_{+0}|BG_{+0},I_{ABS})$ for the discrete range of insulin absorption were adopted to avoid the shifting of the joint table. Moreover, the joint and conditional

probability tables have a high density of elements equal to zero allowing the computation speed to be further increased by performing the probability updating avoiding meaningless operations. The strategy became effective when a threshold for the elements of the conditional probability of parameters was defined. The calculated values resulting below these thresholds were approximated by zero, and therefore not used in the algorithm. As evidence is collected and the joint probability of the parameters is updated, probabilities corresponding to the unlikely configurations of the parameter states are approximated to zero. The speed is increased by discarding these configurations from the probability updating. Therefore, learning over multiple days takes less time than the simple summation of the time taken for learning individual days.

During learning, if the observed *BG* data cannot be explained (probability of evidence entered is very small) the user is prompted and the measurement is discarded.

The lifestyle of a subject with diabetes cannot be assumed rigid and systems should allow for the flexibility of real life. In response to this reality, a day-to-day approach to management of diabetes has been implemented by several systems [8;22;96] or even a more flexible dose-to-dose approach has been adopted or is possible in some systems [8;147]. Alternatively, variations of model parameters are induced by natural fluctuations of different physiological processes. Most systems make assumptions that the parameters are constant (time invariant) over some period. In DIAS, parameters are assumed constant within a day but day-to-day variability is modelled. The errors caused by such variability are minimised using a statistical method (multi-day learning) that combines the parameters estimated on individual days [66]. It is not clear whether allowing model parameters to vary within a day can improve the prediction accuracy but it can be an elegant solution to modelling the dawn phenomenon [22].

Advice should not be based on the predicted deterministic (or mean) *BG* alone. It should also take into account the prediction accuracy in some way so that unfavourable possibilities are unlikely to occur and do not cause hypoglycaemia. The Interactive Diabetes Advisor (AIDA) developers tackled this problem by estimating a confidence interval from historical data. The quantitative advice generation ensures

that both the predicted *BG* and the confidence interval are within the normoglycaemia limits. In DIAS [8] the same problem is solved using the intrinsic properties of the CPN-based implementation. The blood glucose is predicted by the CPN model as a probability distribution that is used to compute a weighted mean of penalties [76]. Thus, both the predicted *BG* value and its confidence interval contribute effectively to the overall penalty. The predicted profile, therefore, is automatically as much as possible within the normoglycaemic limits.

A very useful feature is the ability to predict HbA_{1c} from simulated *BG* as implemented in DIABLOG [22;109], giving a "long-term" assessment of the control that is going to be achieved by the therapy at steady state.

Clinical trials showed that the prediction accuracy of DSS in diabetes is limited by the naturally occurring variability in the underlying physiological processes, explaining mean predictive accuracies of 2-3.5 mmol/L [12;69;97]. Current research is directed towards interpretation of self-monitored blood glucose and insulin data, extracting patterns or trends [47] that could make possible prediction errors below 2 mmol/L threshold.

Rather than building a model of the carbohydrate metabolism for therapy planning, the developers of DIABNET [73] modelled how clinicians interpret *BG* data and the actions taken for the management of gestational diabetes. The qualitative advice from the CPN model is mapped into quantitative advice by a linear transform action. The system is not parameterised to cope with patient specific advice.

In DIAS-NIDDM, once fitted to the patient (parameter estimation), the CPN model is used as a "testbed" that allows patient-specific simulation of various input patterns. There are no inherent management strategies built in the model. The user of the system has the freedom to choose the preferred insulin regimen and support is given with assessing its quantitative effect. In this view, insulin regimens can be designed to suit any patient and any management strategy.

8.8 Summary

The CPN model of carbohydrate metabolism used by DIAS has been extended to accommodate for the endogenous insulin secretion. DIAS-NIDDM was built using the extended CPN model with the aim to provide advice on insulin treatment in insulin-treated subjects with type 2 diabetes.

The new physiological model that predicts steady state HbA_{1c} concentrations in response to changes in therapy (diet and insulin doses) has been integrated into DIAS-NIDDM.

The chapter gives comprehensive overview and particular insights into DIAS-NIDDM development.

9. Evaluation

9.1 Introduction

The evaluation of decision support systems is critical. Depending on success or failure at this stage, the result can decide the fate of the DSS. The evaluation formally answers questions concerning safety, accuracy, and efficacy. Informally, evaluation answers practical questions like will the DSS be safe to use? Is the accuracy in the acceptable range for the target domain and problem? Does it improve the outcome of the process it is designed for? Is the system being used under the pressure of the activity in the intended environment?

The evaluation is different in scope, purpose and semantics from testing. The testing of the DSS represents only a precondition for the evaluation to commence, and it is primarily concerned with the software issues like reliability, stability, correctness of output, scalability, cross platform operation if wished or performance testing under increased load.

There is significant research to develop methodologies for the systematic validation of models and the evaluation of DSS [23;31-33;95;115;149;150].

Wyatt views the evaluation as involving two major scenarios, formative evaluation, and summative evaluation [149]. In the formative evaluation results are fed back to developers to assist them in producing a suitable system, and in the summative evaluation, a finished, complete system is evaluated.

Other authors consider that the randomised clinical trials are the only reliable approach to evaluation [23;115]. However, clinical trials are subject to biases like the check list effect (DSS will require better logging of data and actions, implicitly improving doctor's performance), contamination (doctor giving advice on control group may have learnt how DSS generates advice, therefore masking the benefits of DSS), Hawthorne effect (DSS group receiving an workstation, and the control group not, will improve their performance, also the performance of a decision maker

improves because it is being studied), placebo effect (potential effect on patients when receiving extra attention) [149].

Carson et al have documented the development of a coherent framework for the evaluation of a system [31-33], consisting of several stages: verification, validation, usability, acceptability, prospective evaluation and addressing the legal and the ethical issues.

Hejlesen et al [68] built on Wyatt's research [150]. The method was modified to cope with the observation that "individual patients have poor control despite specialist care" and that "the subjective view where different clinicians may hold different views on the importance of hypoglycaemic counter-regulation". Therefore, the authors decided in the favour of a double blind design of the evaluation that parallels that of the routine testing of new drugs to evaluate the insulin advisory capabilities of DIAS.

There are *objective* and *subjective obstacles* that affect the evaluation process. The quality of *data collection* and the *unrecorded life style* are major limiting factors [95]. Simplifications of very complex physiological processes like the glycaemic effect of the food, the effects of exercise, stress, the glucose counter-regulatory effect, and the dawn phenomenon effect on the on *BG* profile can be inaccurate. They cannot be realistically approached by simple compartmental models, and reveal lack of relevant medical knowledge [95].

DIAS has been evaluated in numerous trials. The system's behaviour was assessed at different levels: validation of the metabolic model, clinical evaluation of the system, and its use in identifying phenomena such as the dawn phenomenon and the hypoglycaemic counter-regulation. The validation of the metabolic model showed that DIAS was able to predict blood glucose profiles with a standard deviation of 2.8 mmol/L [71]. The clinical evaluation of the system proved its ability to recommend safe insulin dose adjustments and to predict hypoglycaemia [35]. A group of six patients managed by DIAS improved HbA_{1c} by 1.9% compared to 0.9% achieved in the control group [11]. While significantly reducing the recommended insulin doses, DIAS achieved a marked improvement in the frequency of measured hypoglycaemia

from 0.41 to 0.07 episodes per day [72]. In addition, DIAS led to the identification of relevant new phenomena like the dawn phenomenon [123] and the hypoglycaemic counter-regulation [67]. The identification was possible due to the large discrepancies between the predicted and the observed dynamics of the actual *BG* profile.

Despite the high RMS of both fit and prediction, of 2.8 mmol/L, comparable with the day-to-day intra-patient *BG* variability, DIAS has been shown to provide clinically safe and effective advice on insulin dosage adjustment [35;36;69].

The evaluation of DIAS-NIDDM has been organised on several stages, as follows:

A. The provision of clinical data; Data were provided by two centres, St Thomas' Hospital, London and Queen Alexandra Hospital, Portsmouth, UK.

B. Verification - checks for internal consistency, completeness, logical errors; the computer code and the model was presented in readable form to experts [84;142]; Checks of assumptions and implications were made to ensure they were according to the current state of medical knowledge.

C. Retrospective trials - low scale retrospective trials were employed to check the ability of the system to produce acceptable results when presented with test cases based on a reduced scale data collection; assessment if model/system works dynamically and is safe in operation.

i) RMS study – checks the system is optimised with respect to the root mean square of the prediction error (see paragraph 9.2)

ii) Comparability study – checks that the new interval oriented re-implementation is similar in performance to the original implementation using data from subjects with type 1 diabetes (see paragraph 9.3)

iii) Insulin adjustment pilot study – checks the insulin advising capability of the system based on data sets from subjects with type 2 diabetes; assesses the clinical usefulness and safety of the advice (see paragraph 9.4)

iv) HbA_{1c} pilot study – ability to predict HbA_{1c} steady state due to changes in treatment (see paragraph 9.6)

D. Questionnaire based peer review retrospective trial; assesses the clinical relevance of the advice on insulin dosage as recommended by the system compared to that given by diabetes specialists (see paragraph 9.5)

9.2 Model Optimisation

A series of internal consistency checks were performed, according to the verification stage of the evaluation plan. In addition to the present day-to-day intra-patient variability of *BG*, systematic errors could possibly explain some of the fit and prediction errors. An optimisation check based on the minimisation of the root mean square error of the fit and of the predictive performance was run. The presence of trend lines in the fit versus prediction was detected in DIAS and DIAS-NIDDM. However, similar trend lines were reported in AIDA (y=4.9 + 0.55x) [95].

9.2.1 Problem Identification and Formulation

A multiple data set analysis was performed. The residual of fitted *BG* represented against the measured *BG* revealed a statistically significant trend line for all diabetes type 1 data sets. A trend line with very similar parameters was subsequently identified in a study involving subjects with type 2 diabetes. The problem seems to have a common root, as it was present in both DIAS and DIAS-NIDDM.

The hypothesis that the models of endogenous *BG* balance and/or gut absorption caused the trend lines was tested. The parameters of the regression lines were identified as shown in Figure 9.1.

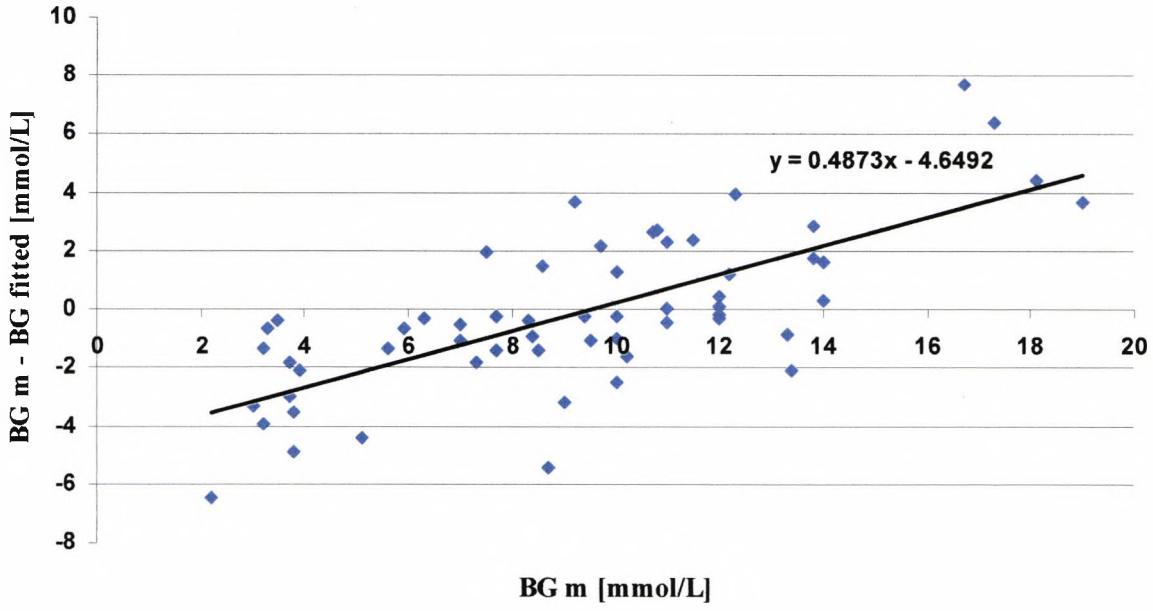


Figure 9.1 *Residual of fitted values. DIAS-NIDDM (IDDM mode), subjects with type 1 diabetes. A regression line with similar parameters and statistical significance was identified in DIAS*

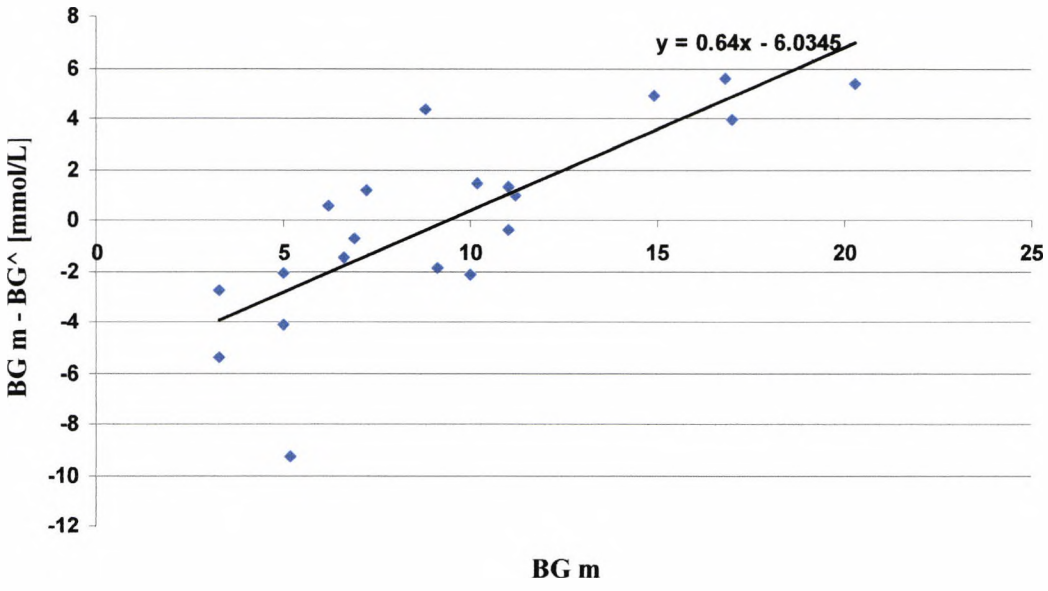


Figure 9.2 *Residual of predicted values. DIAS-NIDDM (IDDM mode), subjects with type 1 diabetes. A regression line with similar parameters and statistical significance was identified in DIAS*

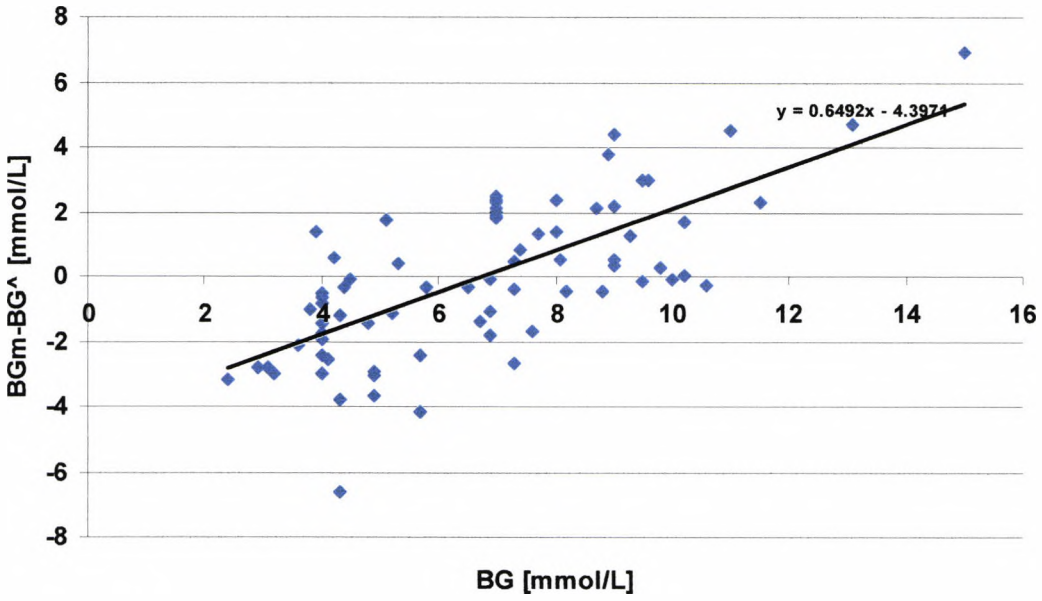


Figure 9.3 *Residual of the predicted values. DIAS-NIDDM, subjects with type 2 diabetes*

The slope for data fit was estimated with 95% probability with the confidence interval [0.36, 0.61]. The correlation was [0.57, 0.83], 95% probability, Figure 9.1. For the prediction residuals the effect is more pronounced, see Figure 9.2. Similar results were obtained in subjects with type 2 diabetes see Figure 9.3.

9.2.2 Identifying the Erroneous Module in the DIAS Carbohydrate Module

A preliminary identification procedure was performed on individual modules to check if they exhibit trend lines in their output when presented with the same data that initially revealed the abnormality.

The identification tested if the problem is due to gut absorption, insulin absorption, and/or endogenous glucose balance (insulin action) models. The correlation between gut absorption and insulin absorption versus the same range of *BG* has been investigated; see (Figure 9.4 to Figure 9.7).

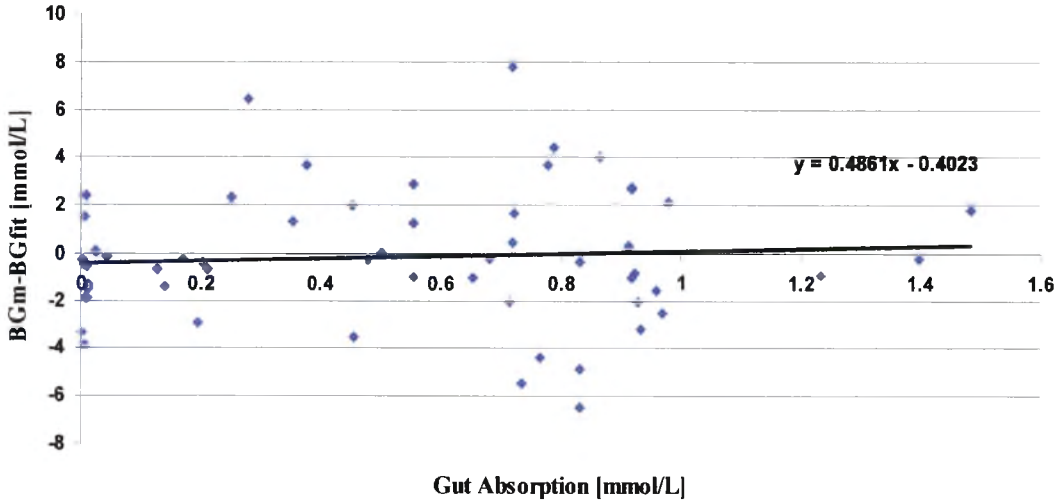


Figure 9.4 *Residuals of the BG fit error versus the gut absorption in subjects with type 1 diabetes (r = 0.0, p= NS)*

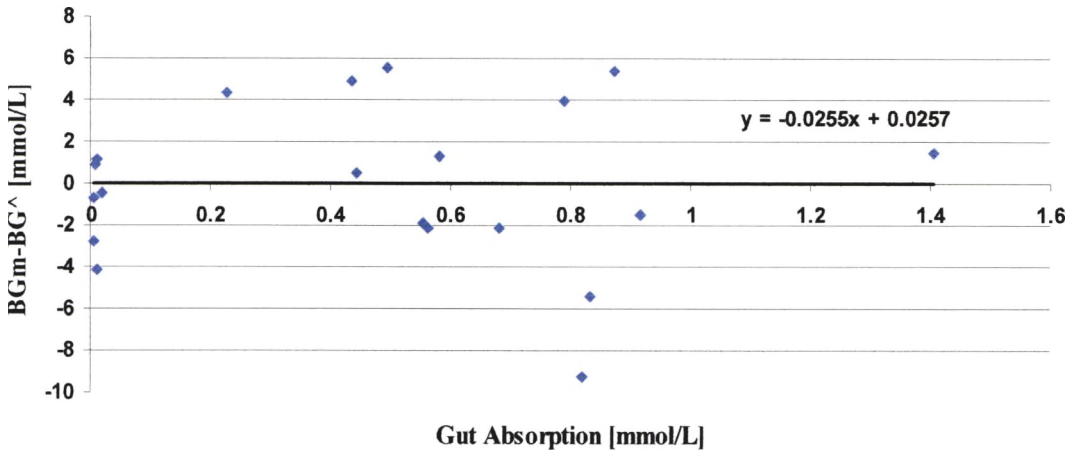


Figure 9.5 *Residuals of the BG prediction error versus the gut absorption in subjects with type 1 diabetes, (r = 0.0, p= NS)*

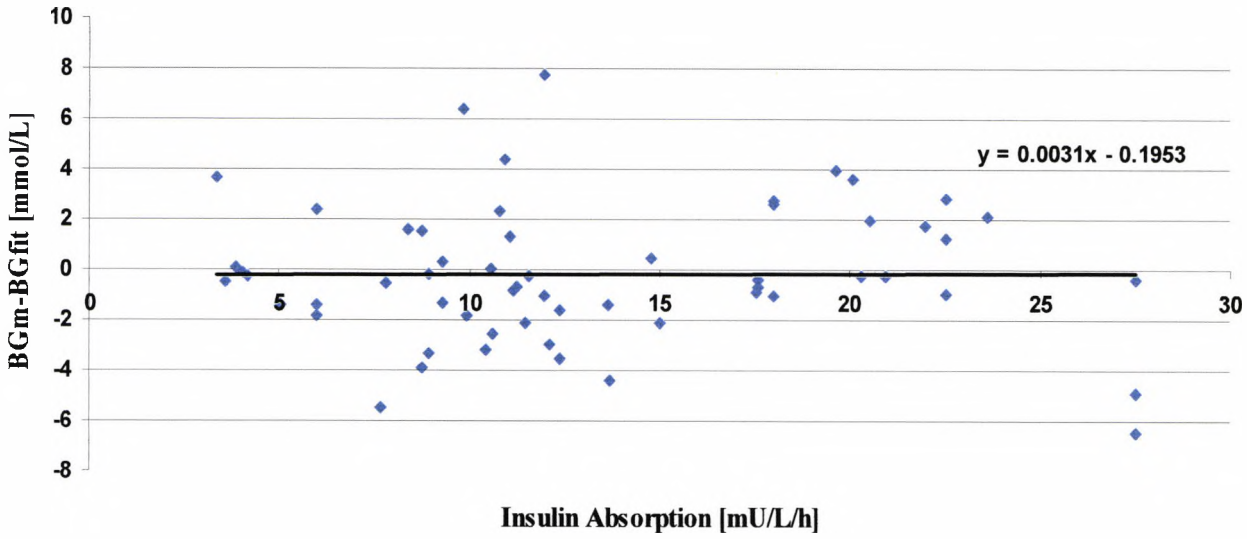


Figure 9.6 *Residuals of the BG fit error versus the insulin absorption in subjects with type 1 diabetes (r = 0.0, p= NS)*

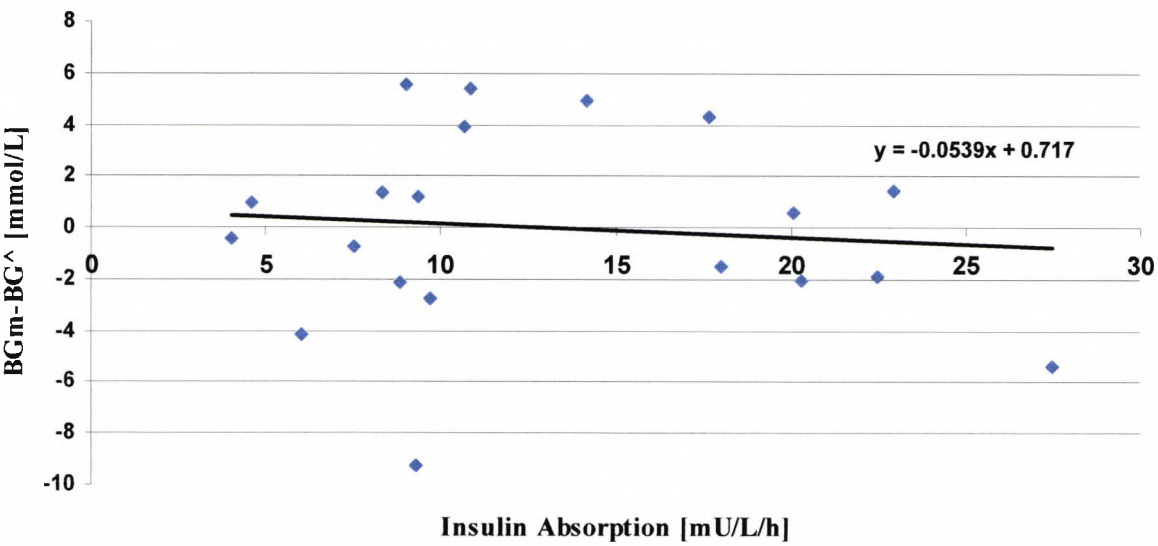


Figure 9.7 *Residuals of the BG prediction error versus the insulin absorption in subjects with type 1 diabetes (r = 0.0, p= NS)*

The results showed that correlation was not present in the relationships between gut absorption or insulin absorption and *BG* (not statistically significant).

We conclude that the correlation, which is present between the prediction/fitting errors and *BG*, is not due to systematic errors in any of the insulin or gut absorption

models. The results imply that the systematic error is due to the model of insulin action/endogenous glucose balance.

It has been assumed that the model of endogenous balance does not adequately represent the self-promotion of the glucose uptake.

The problem is specific to both the hypo and hyper ranges of the glycaemia. In order to investigate the problem, we acted on the slopes of the family of curves in the problematic regions of *BG* range. An exhaustive space search optimisation has been adopted. The performance at low range of *BG* was altered by an amplified self-promotion implemented by inserting a turning point at *BG* = 5 mmol/L. Break points in the model of endogenous glucose balance were adopted at 5 and 11 mmol/L.

9.2.3 Alterations to the Model of Endogenous Glucose Balance/Insulin Action

Using the equations of endogenous glucose balance [71], see Figure 8.2, plasma glucose can be described by a linear equation relating the insulin absorption and the plasma glucose at Δt earlier:

$$Y = DX + E \tag{9-1}$$

where

$$D = 0.5 * 5(-k1)\underline{is} * insabs - k2 + 1 \tag{9-2}$$

$$E = 0.5 * 5(-k3)\underline{is} * insabs + k4 + gutabs \tag{9-3}$$

$$k1 = 0.0024 \tag{9-4}$$

$$k2 = 0.0797 \tag{9-5}$$

$$k3 = 0.0576 \tag{9-6}$$

$$k4 = \left(4.0623 + 5 * 0.3989\right) / 5 \qquad 9\text{-}7$$

$Y - BG$ at time $t+30$

$X - BG$ at time $t+0$;

is – insulin sensitivity, DIAS/DIAS-NIDDM parameter

insabs – exogenous insulin absorption

gutabs – gut absorption due to food intake

Corrections and alterations to the regression lines were applied in three distinct modes: combined, slope and offset correction, and by insertion of break points.

9.2.3.1 Combined Correction

The equations are considered with equal correction coefficients applied in both the slope and offset terms.

$$k2 = 0.0797 * corr \qquad 9\text{-}8$$

$$k4 = \left(4.0623 + 5 * 0.3989 * corr\right) / 5 \qquad 9\text{-}9$$

9.2.3.2 Slope and Offset Correction

This mode applies specific corrections to both the overall slope and the offset of the regression lines.

$$k1 = 0.0024 * corr_1 \qquad 9\text{-}10$$

$$k2 = 0.0797 * corr_1 \qquad 9\text{-}11$$

$$k3 = 0.0576 * corr_2 \qquad 9\text{-}12$$

$$k4 = \left(4.0623 + 5 * 0.3989 corr_2\right) / 5 \qquad 9\text{-}13$$

9.2.3.3 Break Point Correction

The effect of augmented self-promotion of the glucose uptake was studied by introducing points of discontinuity $\{(BG^b_i, slope^b_i)\}$ in the linear relationships. The

regression relationships were represented as continuous linear segments with parameterised corrected slopes.

$\{BG^b_i\}$ – points of discontinuity on x axis of the regression lines

$\{slope^b_i\}$ – segment slope correction relative to the original slope

9.2.3.4 Search Space

The exhaustive search was performed on the space defined by the correction coefficients and the breaks in the linear regression equations:

$(corr_1, corr_2, \{(BG^b_i, slope^b_i)\})$.

The correction ranges were:

$corr_i$, $i=\{1,2\}$	*[0.5...1.5], step size 0.1*
$\{BG^b_i\}$	*{5, 7, 9, 11} mmol/L*
$\{slope^b_i\}$	*{1.2, 1.4}*

The size of the search space is given by individual space sizes:

$$n_{corr_1} \times n_{corr_2} \times n_{\{BG_i^b\}} \times n_{\{slope_i^b\}}.$$

9.2.3.5 Effects of Correction Factor on the Models

The individual corrections have specific effects on the regression lines. They allow exhaustive search for all modes of variation: translation, rotation around a fixed point, and breaks in the linear relationships. These corrections do not necessarily have a physiological interpretation.

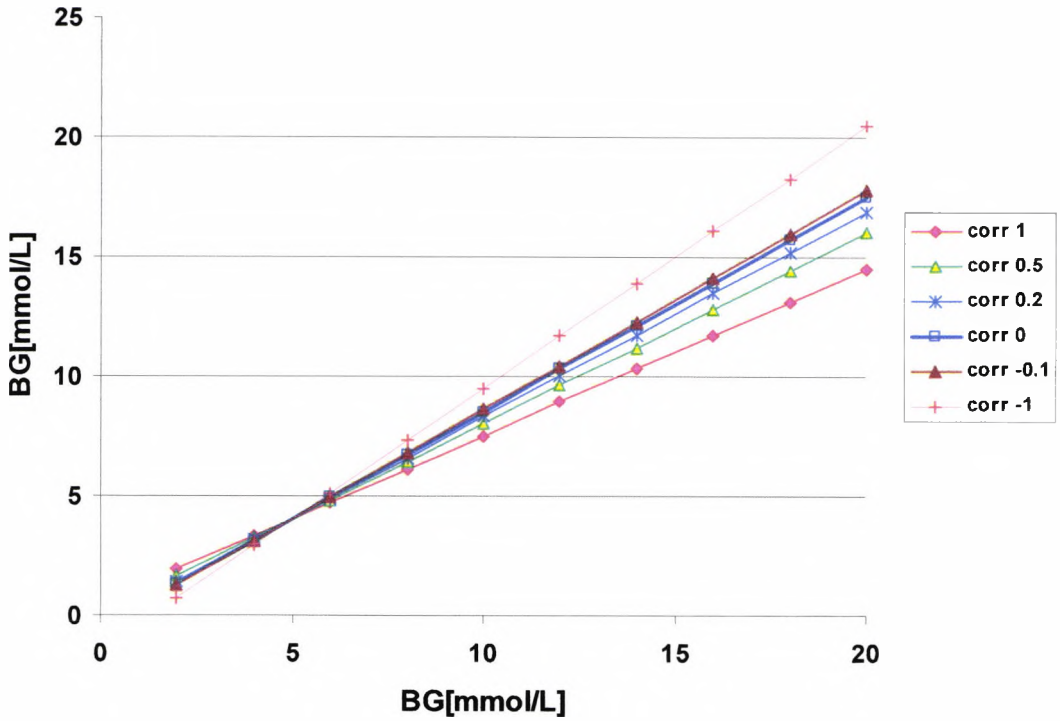


Figure 9.8 *Effect of correction on predicted BG. Cumulative effect through K2 and K4*

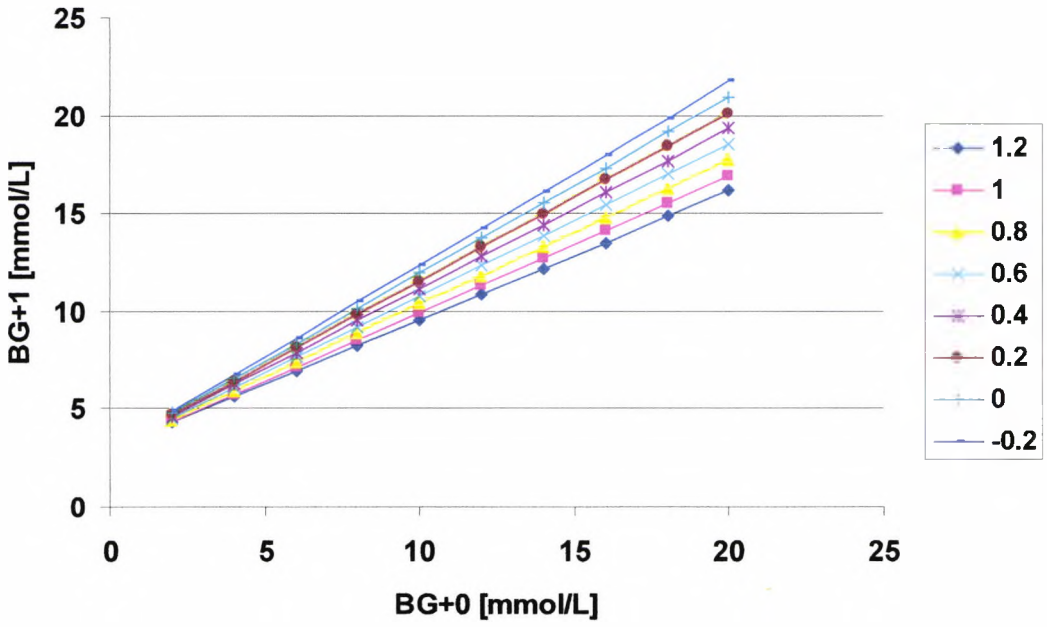


Figure 9.9 *Qualitative effect of K2 on predicted BG for a given active insulin concentration*

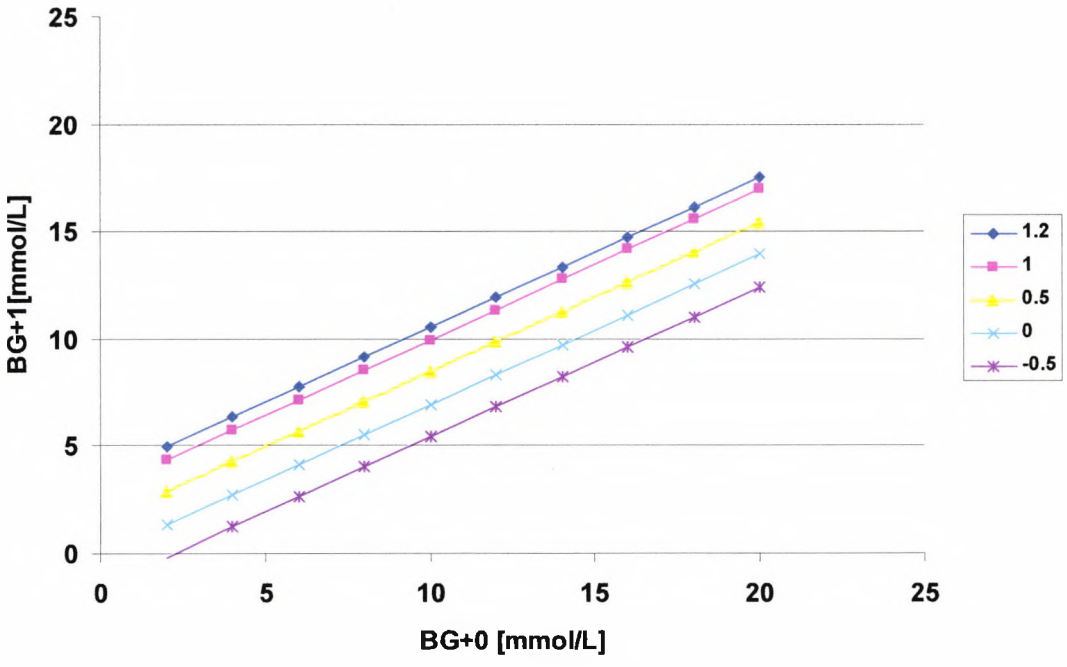


Figure 9.10 *Qualitative effect of K4 on predicted BG for a given active insulin concentration*

9.2.4 Pilot Study

The retrospective pilot study checks that DIAS-NIDDM is optimised according to the minimum root mean square of the fit/prediction error criterion. In addition, the study tries the elimination of the observed trend line by altering the regression equations describing the endogenous glucose balance.

9.2.4.1 Introduction

This study complements the comparability tests between DIAS and DIAS-NIDDM in relation to the model parameters and the predictive accuracy, see chapter 9.3 [84].

9.2.4.2 Data Protocol

Two data sets were collected according to the DIAS requirements. Subjects with RMS > 3.3 mmol/ L were discarded. Finally, two data sets of eleven respectively sixteen subjects with both type 1 and 2 diabetes were selected.

9.2.4.3 Methods

The method design is shown in the diagram in Figure 9.11. The document is produced with Rational Rose package, using UML standardisation. The document is organised in separate parallel swim lanes, one for each abstract level. The "Parameters" swim lane shows the iterative correction of the regression parameters $(corr_1, corr_2, BG_i, slope_i)$ at the utmost level of abstraction. Further down in this swim lane, concluding each configuration, the diagram shows the associated statistical results on a *per iteration* basis. The "Subjects" swim lane shows the processing of subjects data sets in a serial fashion. For each subject in the study, swim lane "Processing" describes the stream of DIAS/DIAS-NIDDM operating modes necessary to produce the estimated parameters, the *BG* simulated profiles and the residuals of the predictions.

The parameter estimation stage is performed by DIAS-NIDDM running in learning mode. The measured *BG* values are input, together with the current iteration's

correction coefficients *(corr$_1$, corr$_2$)*, and applied to the parameters of the regression equations. The internal CPN carbohydrate model self-adjusts its equations and generates the corresponding conditional probabilities describing the corresponding altered endogenous balance of glucose. The joint probability distribution of the parameters, $p(V_p|e)$, is estimated using the corrected model.

The profile simulation stage, in turn, applies the same iteration specific corrections to the regression equations ($corr_1^*$, $corr_2^*$, BG_i^*, $slope_i^*$) and employs the associated estimated parameters *(is, ps, nph)* to predict 24-hour *BG* profiles. The predicted and the measured *BG* profiles are paired and appended to a list. The list will contain data from all days of study for all subjects for the current set of corrections.

Statistics were computed on *a per* dataset *per* correction configuration basis. A set of predicted versus measured *BG* values, $\{(BG^m, \hat{BG}) | \text{ all subjects}\}$, were processed and statistically analysed. Tests for the level of significance of correlations and slopes were performed (two-tailed t test). The root mean square of the error was calculated. The statistical procedures were implemented directly into the system, and were validated against Leeds University add-on statistics package. The time necessary to process the data was in excess of one week. Several available computers were used on disjoint segments of the search space. The partial results were merged.

The "Results/Notes" swim lane shows the input and output of the operational stages in the diagram, the details of the model of endogenous balance used and the tested hypotheses. The statistics module calculates the correlation between the measured *BG* versus the predicted residuals and tests the hypothesis H_0. The parameters of the trend line – slope and offset - (the significance level was estimated by the two-tailed t test), the root mean square of the prediction and the performance of the naïve predictor were estimated.

The naïve predictor was implemented as the mean of measured *BG*. Its performance has been recorded.

Both type 1 and type 2 data sets were also analysed with DIAS and DIAS-NIDDM respectively.

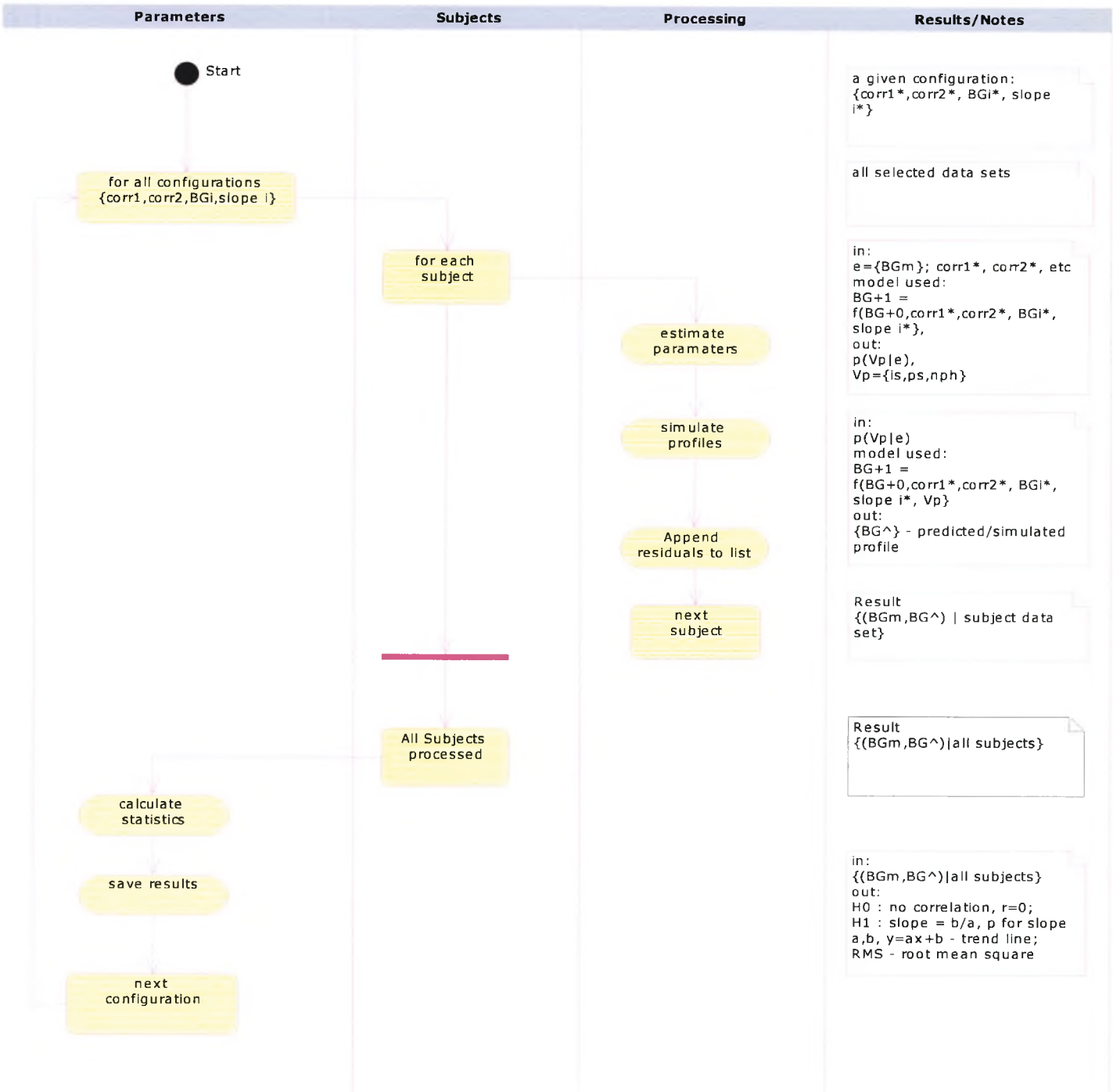


Figure 9.11 *Method design for the analysis of bias / trend line in the predictions of DIAS/DIAS-NIDDM*

9.2.4.4 Results

9.2.4.4.1 Combined Correction

The results from the combined correction are shown in Table 9-1. The same information is shown graphically in Figure 9.12. The minimum of the root mean square error (*RMS*) was obtained for the unity correction coefficient, proving that DIAS-NIDDM is optimised according to a minimum *RMS* criterion. The slope and the offsets of the trend lines present in the DIAS/DIAS-NIDDM predictions were minimised, but not eliminated, for negative correction coefficients.

corr	Slope FIT	Offset FIT	Slope SIM	Offset SIM	RMS
2.00	7.8	-5.20	8.3	-5.75	4.02
1.00	4.9	-4.65	6.4	-6.04	**2.69**
0.10	3.1	-3.16	5.4	-5.23	3.61
0.01	2.2	-2.07	3.3	-3.03	3.80
0.00	**2.1**	-1.87	3.0	-2.64	3.93
-0.01	**2.1**	-1.76	**2.9**	-2.49	3.99
-0.02	**2.1**	**-1.68**	3.0	**-2.47**	4.02
-0.03	2.2	-1.69	3.3	-2.64	4.10
-0.10	4.5	-2.60	6.0	-3.82	4.34
-1.00	6.3	-6.97	3.7	-3.93	8.00

Table 9-1 *Results from the combined correction run*

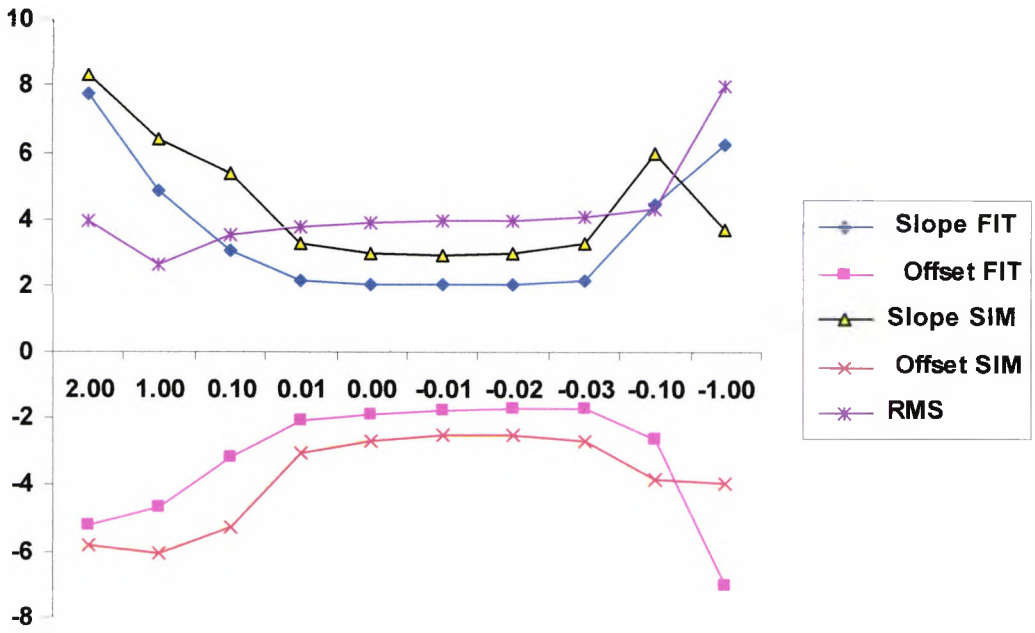


Figure 9.12 *Plot of root mean square error, slope, and offset of the trend line for a range of the correction coefficients, combined mode*

9.2.4.4.2 Slope and Offset Correction

The root mean square error for the slope and the offset correction is shown in Figure 9.13. The shape of the surface is arbitrary/not meaningful, therefore finding the minimum can be guaranteed only by exhaustive search. Figure 9.14 shows the slope of the trend line for the slope and the offset corrections applied to the regression lines. The surface is not particularly meaningful. The summary results are shown in Table 9-2 and Table 9-3 for the two data sets employed by the study.

9.2.4.4.3 Break Point Correction

The presence of break points in the regression lines (results not shown) did not improve RMS or the slope and the offset of the trend line.

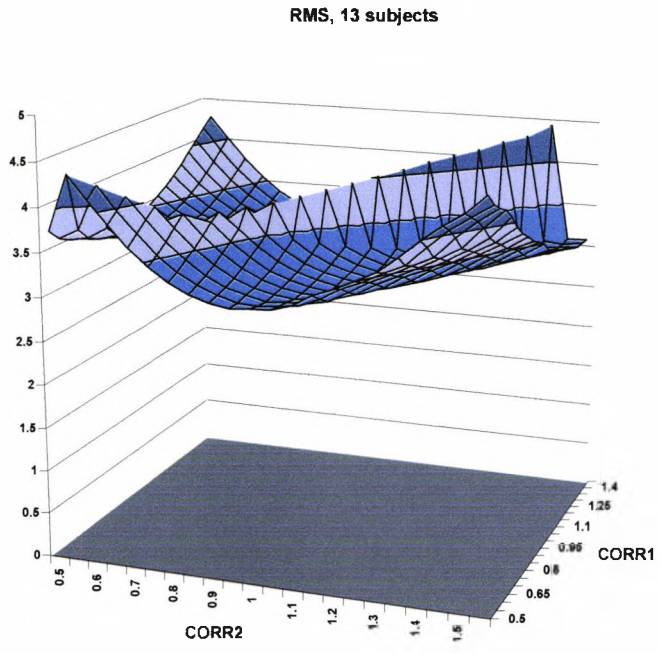


Figure 9.13 *RMS of the fit. The slope and the offset of endogenous BG model were adjusted independently in the range [0.5...1.5] of their original values*

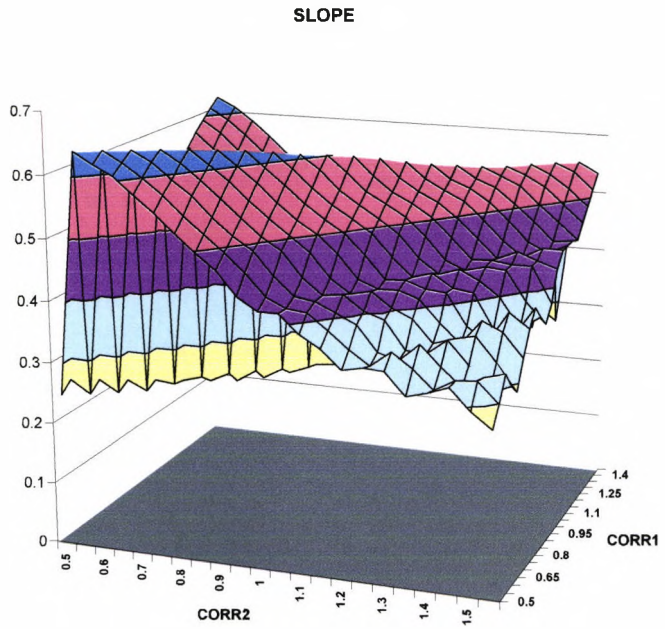


Figure 9.14 *Slope of the trend line. The slope and offset of regression endogenous BG model were adjusted independently in the range [0.5 ... 1.5] of their original values*

Dataset 1	RMS	SLOPE	$corr_1$	$corr_2$
BEST RMS	**2.91**	0.53	1.05	1.05
BEST SLOPE	3.66	**0.32**	0.75	1.40
COMPROMISE	3.49	0.35	0.70	1.20
ORIGINAL	**2.91**	**0.51**	1.00	1.00
NAÏVE	2.68	0.67	-	-

Table 9-2 *Summary of results for Dataset 1*

Dataset 2	RMS	SLOPE	$corr_1$	$corr_2$
BEST RMS	**2.60**	-	1.25	1.20
BEST SLOPE	-	**0.32**	0.60	1.20
COMPROMISE	2.89	0.37	0.80	1.15
ORIGINAL	**2.63**	**0.49**	1.00	1.00
NAÏVE	3.06	0.83	-	-

Table 9-3 *Summary of results for Dataset 2*

9.2.5 Discussion

The complete removal of the trend line could not be achieved by alterations to the regression lines of the model of endogenous glucose balance employing an exhaustive optimisation search. The modelling of some sort of saturation of the family of curves in the high *BG* range could possibly improve the prediction accuracy and eliminate the trend. However, despite a potential improvement by the use of numerical/artificial adjustments of the model, the correct solution to the systematic errors requires that the model of carbohydrate metabolism is revisited in the hyper- and especially in the hypo-glycaemic range of the plasma glucose dynamics, and physiology based facts are found in the support of any alterations.

In the glycaemia range of 6-12 mmol/L, no statistically significant trend lines were observed. The hypoglycaemia prediction capability of DIAS (and other systems based on currently available literature data) is questioned by this study. Further investigation is necessary.

The model of endogenous glucose balance [71] does not represent the hepatic glucose production separately. Recent studies [81] have revealed that this component can

account for up to 50% of the glucose lowering effect of insulin. Any inter-patient variability of the suppression of endogenous glucose production could therefore be significant in subjects with type 2 diabetes. Therefore, insulin sensitivity will represent a cumulated effect of glucose transport, insulin dependent disposal, and suppression of the endogenous glucose production as an overall glucose lowering effect.

The naïve predictor performed well in one dataset. However, results are not meaningful. Given that the naïve predictor is based on mean measured *BG*, it will always predict very well in subjects with limited *BG* excursions and in well-controlled subjects. However, the naïve predictor was outperformed on the dataset shown in Table 9-3.

Despite these findings, DIAS proved in a series of clinical studies that it can predict hypoglycaemia correctly and it can recommend insulin therapy that improves glycaemic control in subjects with type 1 diabetes and can reduce HbA_{1c}. Well-controlled subjects usually have *BG* dynamics limited at 12 mmol/L, therefore, the systematic error does not affect the prediction accuracy for practical/clinical purposes.

The presence of the trend lines may be possibly due to systematic errors in the clinical data published in the medical literature. These data sourced the building of DIAS-NIDDM models and other systems [95].

9.2.6 Conclusions

The study confirms that the current model is optimised for minimum RMS. Breaks in the regression lines (boosting predicted *BG* in high *BG* range) did not bring any improvements. At least according to the performed analysis, we cannot both minimise the RMS error and reduce the slope of the trend line at the same time. A compromise by trading RMS for slope should be avoided. The effect of the trend line on the clinical performance is not understood. However, data suggests strongly that there is a systematic error in the current medical knowledge.

9.3 Comparability Study – Dynamic CPN vs. HUGIN based DIAS Implementations

DIAS-NIDDM extends the model of carbohydrate metabolism used by DIAS and implements a model of insulin secretion to represent the endogenous insulin present in subjects with type 2 diabetes [142]. As a result, the model is computationally demanding in terms of computer resources and processing time, and the calculations became unfeasible.

The issues were addressed by simplifying the network removing distinct nodes by a process of aggregation (nodes representing renal clearance, insulin dependent utilisation, insulin independent utilisation, glucose production [69]) and by devising a more efficient dynamic CPN model [84]. In the new approach, the estimation of the model parameters eliminated the constraint of using a minimal set of four *BG* measurements and that of a fixed length of the learning period. Informally, the estimation of parameters employing multiple days of data collection has now been replaced by continuous evidence absorption.

A sensible evaluation of the re-implementation of DIAS suggests a preliminary comparability study against its original implementation [84] as a necessary step in order to draw on the results of the clinical trials in which DIAS already proved its clinical utility [35;36;68;69;72].

DIAS-IDDM is based on dynamic CPN and uses new states for the model parameters, see Annexe III. The new parameter estimation method eliminated the restrictions on the duration of learning and forecasting.

This study focuses on the comparability between the model parameters and the predicted plasma glucose concentrations as obtained with the two different implementations.

9.3.1 Subjects and Protocol

Five subjects with type 1 diabetes (male/female: 2/3, age: 45 ± 16 yr, BMI: 25.8 ± 3.5 kg/m^2, HbA_{1c}: 10.4 ± 1.1%, daily CHO: 187 ± 40g, daily insulin: 35 ± 13U) were selected from patients at Queen Alexandra Hospital, Portsmouth, UK.

Id	Sex	Age (yr)	BMI (kg/m^2)	HbA_{1c} (%)
I1	M	72	23.8	9.8
I2	F	34	25.9	10.0
I3	F	40	21.7	9.9
I4	F	49	31.2	12.3
I5	M	31	26.4	10.2

Table 9-4 *Patient demographic data*

The subjects collected data according to DIAS protocol with four measurements daily for a duration of four days. Subsequently, a specialist dietician calculated the carbohydrate content of the meals.

9.3.2 Methods

The processing of data has been performed identically for both systems. The original HUGIN based DIAS and the revisited dynamic CPN based DIAS-NIDDM were operated in IDDM (type 1 diabetes) mode. The model parameters were estimated from the data collected in the first three days of the study period. The ability to fit the *BG* measurements was assessed by running the systems in forecasting mode using the estimated parameters. The fit to the data was quantified by calculating the root-mean-square error (RMS) between the forecast and the measured *BG* values for the duration of the first three days of data collection. Similarly, the accuracy of the prediction was

assessed against the data of the fourth day in the study. Results are shown in Table 9-5.

9.3.3 Data Analysis

The *BG* fit calculated by the two systems during the first three days was compared for the two implementations. Similarly, the *BG* prediction capabilities for the fourth day were compared. Statistical methods for assessing the agreement between the two sets of data were applied [25]. Statistical tests for small samples were used in this study for assessing the statistical significance of the hypotheses (two-tailed t-test). The statistical significance of relationships was analysed with non-parametric tests (Spearman's rank correlation with a significance threshold of $p<0.05$).

9.3.4 Results

The model's *a posteriori* parameters (mean ± SD) and root-mean-square of the fit and the prediction are shown for all subjects as calculated by the two implementations of DIAS in Table 9-5.

	DIAS-IDDM				HUGIN DIAS			
ID	is [-]	nph [h]	RMS (fit) [mmol/L]	RMS (BG^) [mmol/L]	is [-]	nph [h]	RMS (fit) [mmol/L]	RMS (BG^) [mmol/L]
I1	0.87±0.09	6.3±2.7	3.5	3.2	0.83±0.18	6.9±2.6	3.4	3.7
I2	0.82±0.04	12.3±2.2	2.0	2.7	0.76±0.15	11.3±2.6	1.6	2.5
I3	0.65±0.05	10.0±2.0	4.0	4.9	1.07±0.22	8.2±2.5	4.9	5.5
I4	0.35±0.01	8.7±3.3	1.8	2.3	0.38±0.06	9.0±3.2	2.0	2.8
I5	0.53±0.01	6.0±1.8	2.3	4.8	0.64±0.14	6.9±2.4	2.3	3.8

Table 9-5 *Mean ± SD of a posteriori probability distribution of parameters, RMS of fit and prediction for the revised (DIAS-IDDM) and the original DIAS implementations based on data from five subjects with diabetes type 1*

Figure 9.15 shows the relationship between the estimated insulin sensitivity parameters given by the two implementations. No statistically significant differences

were noticed. Informally, *is* parameter values are inside one standard deviation distance from the unity line. However, DIAS-IDDM estimated insulin sensitivity with higher precision as shown by the standard deviation represented graphically. The new learning procedure employed by DIAS-IDDM allows each distinct piece of evidence (*BG* measurement) to discriminate between the states of parameters by using *flat a priori probability distributions*. However, the insulin sensitivity estimated by DIAS for subject I3 is significantly higher than that estimated by DIAS-IDDM. The difference can be explained by the fact that DIAS assumes a 70 kg body weight whereas DIAS-IDDM employs the actual subject's body weight (49 kg, body mass index 21.7 kg/m^2 for I3) in calculating the amount of active insulin.

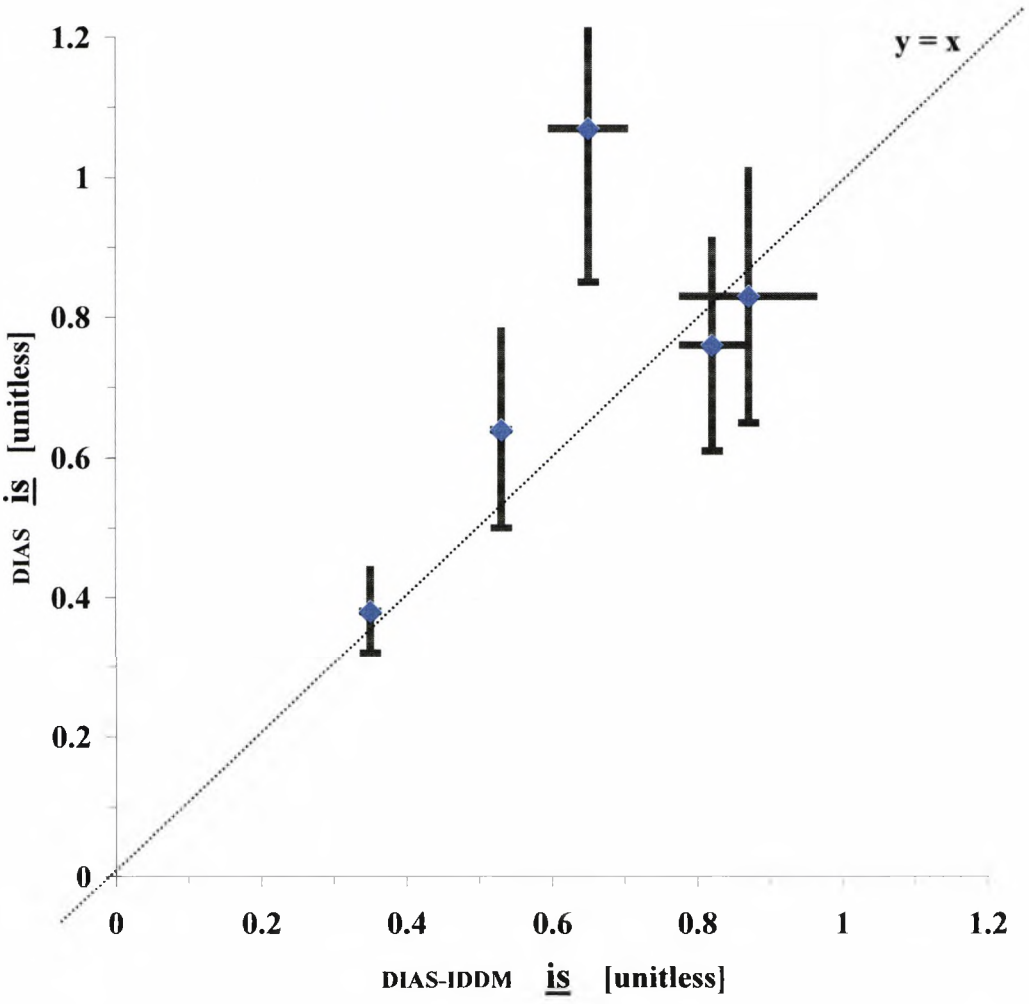


Figure 9.15 *Relationships between insulin sensitivity (is) parameter values of original (DIAS) versus revised (DIAS-IDDM) implementations. Error markers represent calculated SD*

Figure 9.16 shows the relationship between estimated time-to-peak of long acting NPH insulin (*nph* parameter) given by the two implementations. No statistically significant differences were noticed. Both implementations estimate the parameters with low precision, due to the slowly varying insulin absorption rates that cannot be distinguished accurately by evidence, and therefore the systems cannot distinguish with high confidence between the states of the *nph* parameter (for the definition of the parameter states, see Annex III).

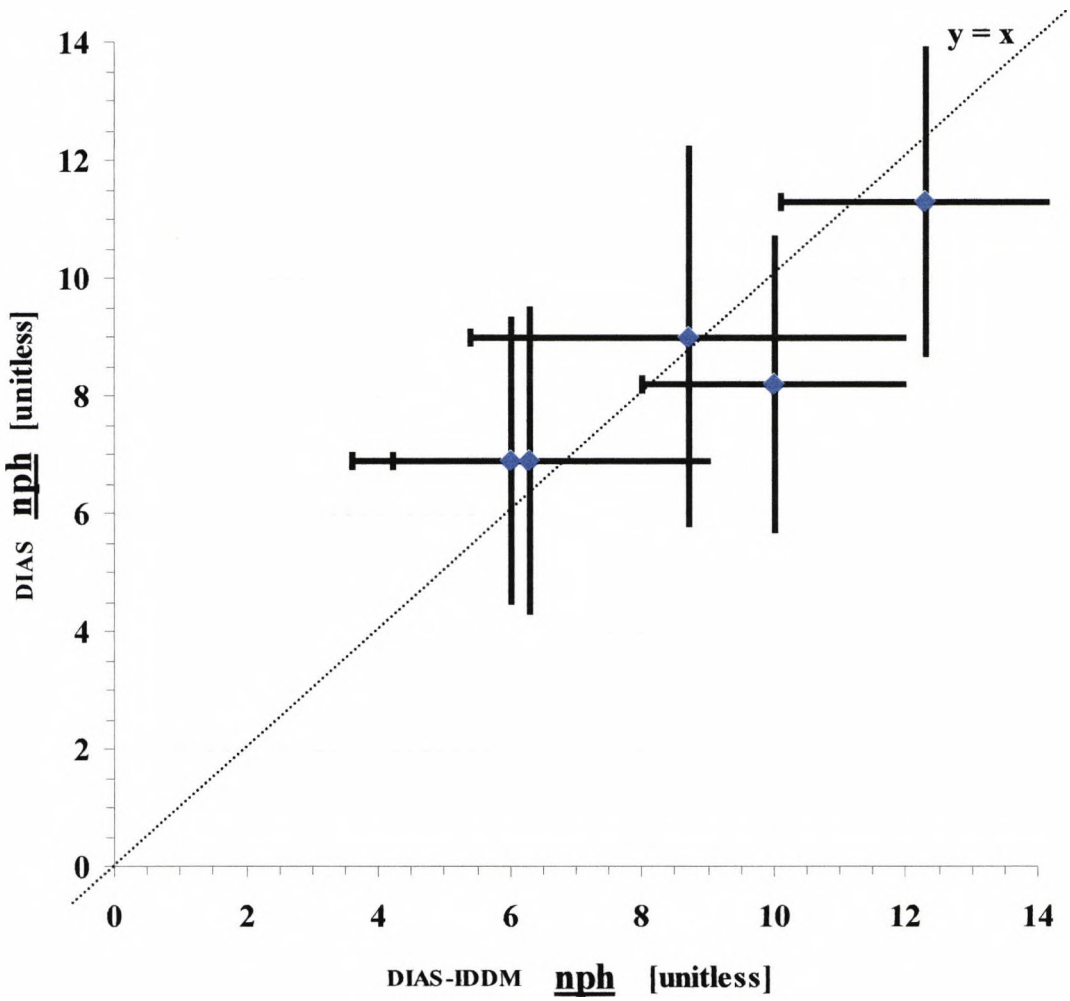


Figure 9.16 *Relationships between nph parameter values of original (DIAS) vs. revised (DIAS-IDDM) implementations. Error markers represent calculated SD*

Figure 9.17 and Figure 9.18 show root-mean-square error of the *BG* fit and of the *BG* predictions for the two implementations. No statistical difference was observed. However, the root-mean-square of the error was significantly lower in the case of

fitting compared with the prediction [84], explained partly by the day-to-day intra-patient variability in *BG*.

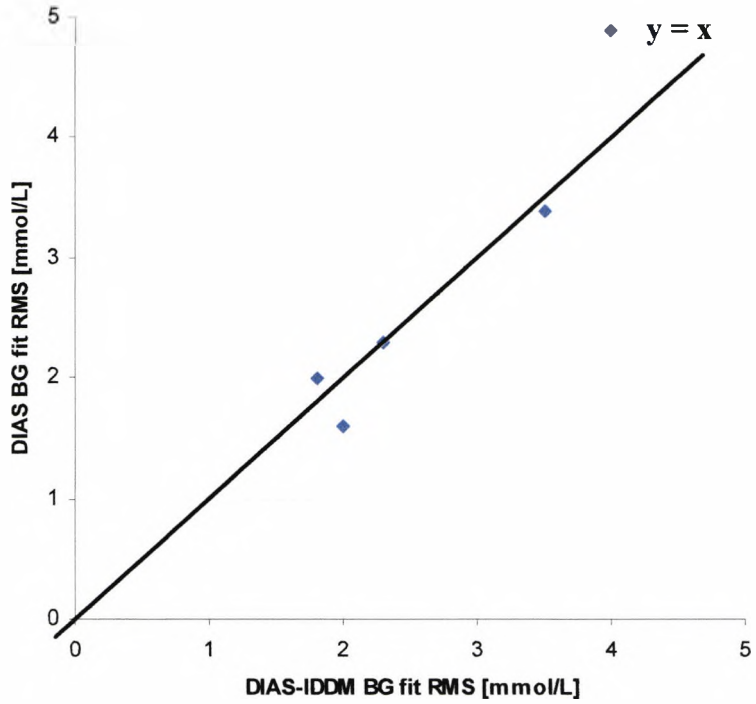


Figure 9.17 *Comparison of the fitting accuracies of revised (DIAS-IDDM) vs. original (DIAS) implementations*

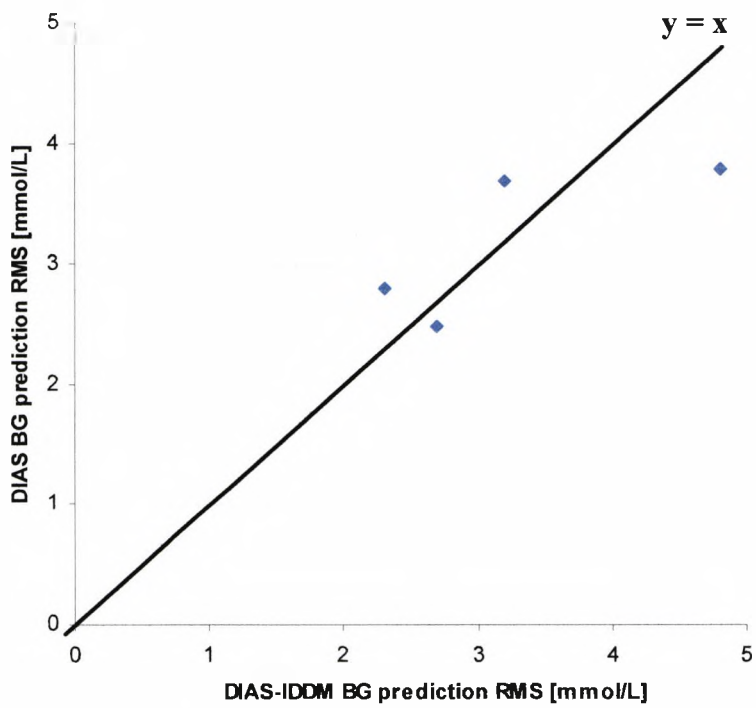


Figure 9.18 *Comparison of the prediction accuracies of revised (DIAS-IDDM) vs. original (DIAS) implementations*

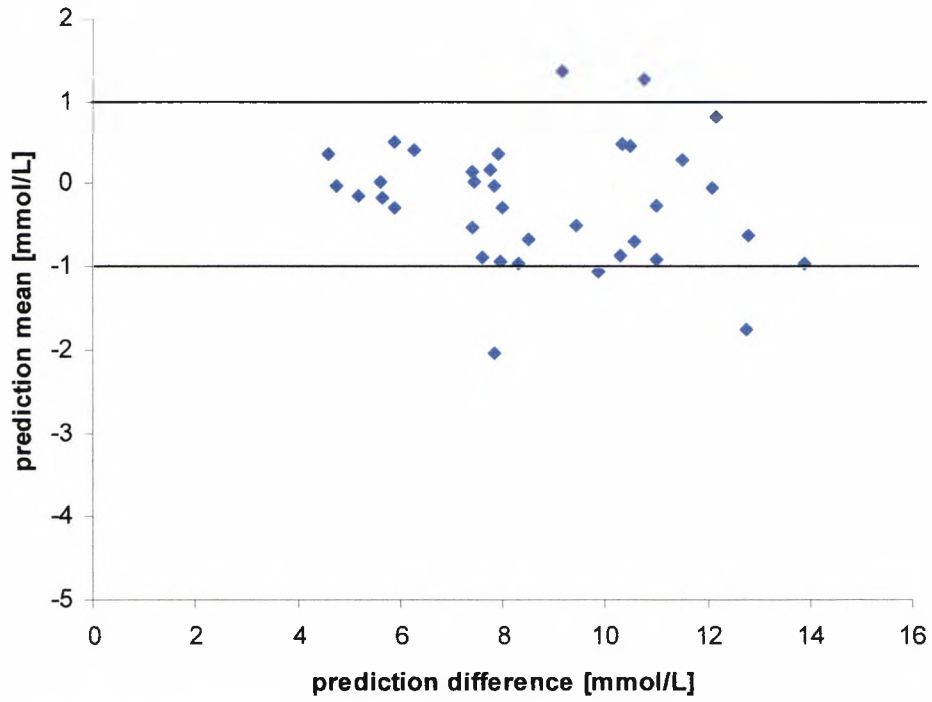


Figure 9.19 *Post-absorptive BG predictions*

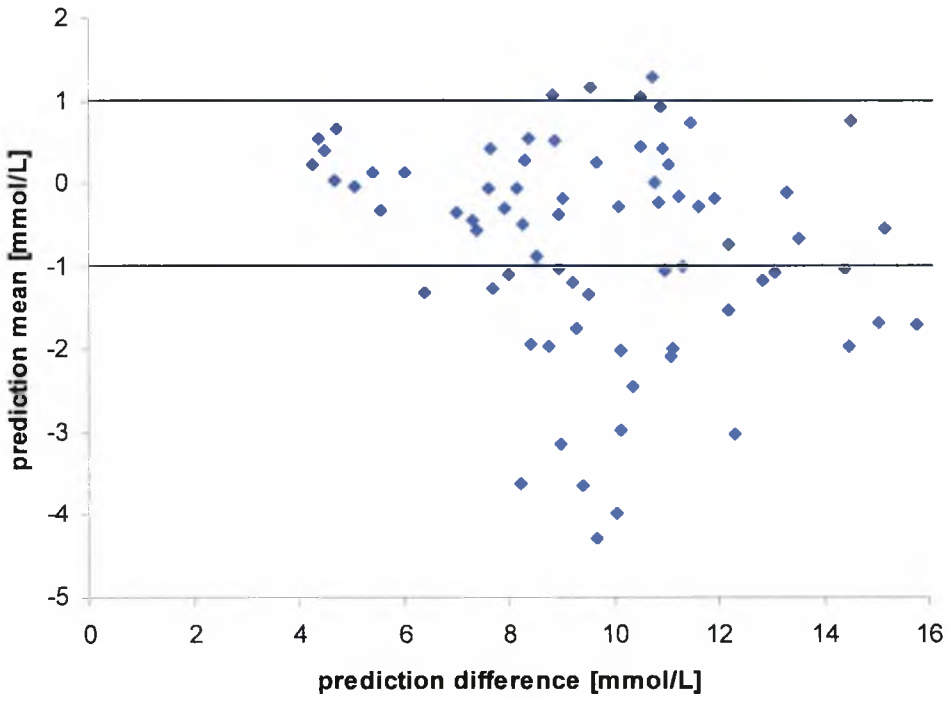


Figure 9.20 *Absorptive BG predictions*

DIAS presented a significant relationship ($r_s=0.97$, $p<0.01$, Spearman rank correlation) between plasma glucose excursions and the root-mean-square error of the *BG* fit, and that was not significant in DIAS-IDDM [84]. Bland-Altman plots were used to represent graphically the scatter gram of the difference between each pair of *BG* predictions and their calculated mean. The two systems give similar predictions of the post-absorptive *BG* values (plasma glucose at times four hours after meal ingestion) - see Figure 9.19.

The mean difference of -0.1 ± 0.8 mmol/L was considered clinically negligible. For the absorptive intervals, DIAS-IDDM provided higher predictions of *BG* values by 0.7 ± 1.3 mmol/L and a significant negative trend between differences and the average *BG* values ($r_s=-0.29$, $p<0.01$), see Figure 9.20.

9.3.5 Discussion

DIAS-IDDM uses a shorter discrete time interval that results in more accurate gut absorption dynamics that contribute to absorptive predictions resulting in higher values, and can partially explain the differences.

DIAS calculations use an average weight of 70 kg for all subjects, and can lead to inaccurate estimations of insulin sensitivity. The problem is even more noticeable in the absorptive state that is characterised by higher insulin absorption due to the exogenous pre-meal short acting insulin injections in subjects with type 1 diabetes and/or endogenous insulin in type 2 diabetes.

However, DIAS-IDDM makes use of assumptions that were not present in DIAS, such as the linear approximation of the model of endogenous glucose balance [71]. DIAS-IDDM uses a novel approach to generate conditional probabilities for mathematical relationships and that could contribute to the differences [84].

The standard protocol used by DIAS researchers currently requires the collection of pre-meal, bedtime, and fasting *BG* measurements that are used to estimate the model parameters. Postprandial/absorptive measurements are not collected. The protocol must be adjusted to collect postprandial measurements in order to improve the

accuracy of estimated parameters. The current protocol shows that the main target is hypoglycaemia avoidance and not the control of glucose excursions. *BG* excursions are equally important to control as they correlate directly to HbA_{1c}, and therefore, on the onset and the progression of the complications of diabetes.

9.3.6 Conclusions

Both systems give similar parameter estimates and the mean predictive/fit accuracy difference of -0.1 ± 0.8 mmol/L was considered clinically negligible. However, for the absorptive *BG* range, DIAS-IDDM provided higher predictions of *BG* values by 0.7 ± 1.3 mmol/L and a significant negative trend between differences and the average *BG* values (r_s=-0.29, $p<0.01$). Based on the collected data, it is not possible to demonstrate which of the two implementations provide predictions with higher accuracy for absorptive states.

9.4 Pilot Study on Subjects with Diabetes Type 2

DIAS-NIDDM was used to predict patient specific *BG* profiles and advise on insulin doses in a pilot study employing a dataset of subjects with type 2 diabetes. The study aimed at assessing the system's ability to recommend advice that is clinically useful and safe.

9.4.1 Subjects

Eight patients with non-insulin dependent diabetes mellitus and good glycaemic control ($HbA_{1c}<9\%$) were selected from the diabetic clinic at St Thomas' Hospital, London. Demographic patient data are shown in Table 9-6. One insulin-treated subject participated on three separate occasions in the study. Two subjects were treated by diet alone, one subject by an oral anti-diabetic agent (*Glibenclamide, 2.5 mg daily*), and five subjects by insulin.

ID	Sex [M/F]	Age [yr]	Years Diabetes [yr]	Treat-ment [-]	Daily CHO [g]	BMI [kg/m^2]	Fasting BG [mmol/L]	Fasting C-peptide [pmol/L]	HbA_{1c} [%]
10	M	66	10	Diet	270-290	23.5	6.3	110	7.9
11a	M	61	8	Insulin	210-260	24.0	11.0	0	7.0
11b	M	61	8	Insulin	250-350	24.4	4.2	510	7.0
11c	M	62	9	Insulin	340-380	25.0	11.0	0	7.3
12	F	66	11	Insulin	80-160	28.5	4.2	0	7.7
13	M	64	14	Insulin	140-165	27.1	9.6	710	7.1
16	F	60	5	Insulin	140-185	34.4	6.7	280	8.7
18	M	54	1	Diet	255-330	21.7	6.4	240	6.8
19	F	69	28	Insulin	170-200	27.4	4.5	1330	7.2
31	M	74	5	Tablets	250-280	25.8	6.7	240	7.5

Table 9-6 *Demographic data*

The subjects collected data over four consecutive days performing home blood glucose monitoring using a glucose meter and recording four *BG* measurements per day, three before meals and one at bedtime, see Annexe IV. The subjects also recorded composition and timing of meals. A dietician subsequently calculated the carbohydrate content of the meals.

9.4.2 Data Analysis and Results

Periods with high values of blood glucose following hypoglycaemic episodes were identified and discarded to remove the effect of hypoglycaemic counter-regulation on parameter estimation. The hypoglycaemic counter-regulation [67] is a mechanism that induces hyperglycaemia and it is triggered by a hypoglycaemic episode.

DIAS-NIDDM was run in parameter estimation mode and estimated the joint *a posteriori* probability distribution of parameters $p(ps, is, nph \mid \mathbf{e})$ for each subject, where the evidence **e** included *BG* measurements recorded by the subject. The mean and SD of each parameter were calculated from marginal distributions, $p(\underline{ps} \mid \mathbf{e})$, $p(\underline{is} \mid \mathbf{e})$ and $p(\underline{nph} \mid \mathbf{e})$, see Table 9-7.

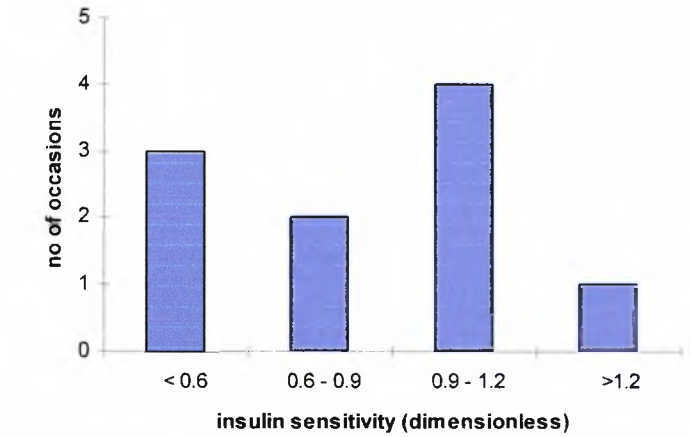
Id	Data collection (day)	Pancreatic sensitivity (mU/L per mmol/L	Insulin sensitivity (-)	Time-to-peak of NPH (h)	Inter-day variability of ps (%) *	Inter-day variability of is (%) *	DIAS-NIDDM
10	4	6.1 ± 2.7	1.1 ± 0.3	NA	17	14	IS
11a	4	1.5 ± 2.2	1.0 ± 0.0	7.3 ± 2.4	18	12	IS
11b	4	1.6 ± 0.7	0.7 ± 0.0	8.2 ± 2.1	59	29	IS
11c	4	10.1 ± 0.0	1.0 ± 0.0	5.6 ± 1.8	48	14	?
12	4	4.9 ± 2.5	0.6 ± 0.1	5.0 ± 3.0	20	29	OD
13	4	6.2 ± 3.4	0.4 ± 0.0	9.8 ± 2.8	18	11	OD
16	3	3.4 ± 1.6	0.4 ± 0.0	8.0 ± 3.2	7	0	OD
18	4	7.8 ± 2.3	1.2 ± 0.3	NA	4	14	IS
19	4	0.0 ± 0.0	0.4 ± 0.0	9.1 ± 2.6	58	10	OD
31	4	8.3 ± 2.1	1.2 ± 0.2	NA	14	10	IS
mean±SD	-	5.0 ± 3.3	0.8 ± 0.4	8.0 ± 1.6	26 ± 21	14 ± 9	-

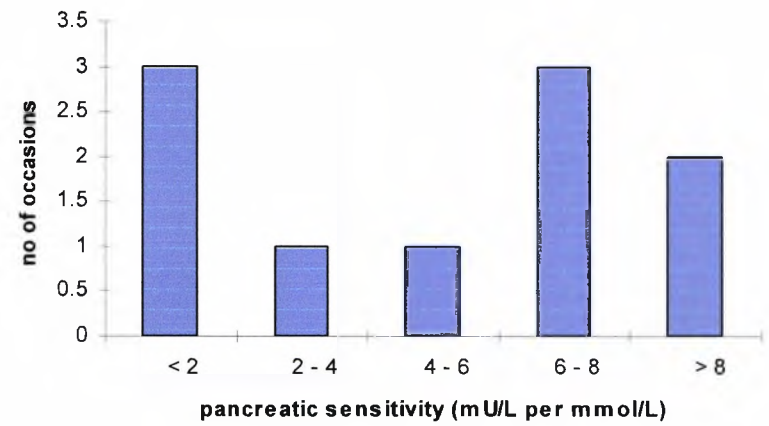
** Expressed as coefficient of variation*

Table 9-7 *Parameters (mean±SD) estimated from data (BG, food intake, insulin injections) collected over a period of up to four days. IS stands for impaired secretion, IR for insulin resistance and OD for overt diabetes (OD means both IS and IR are present). Typical DIAS-NIDDM values for a normal individual are* $\underline{ps}$ *= 8 mU/L per mmol/L and* $\underline{is}$ *= 1*

The inter-day variability of parameters $\underline{is}$ and $\underline{ps}$ were assessed. DIAS-NIDDM was run to estimate $p(\underline{ps}, \underline{is}, \underline{nph} \mid \mathbf{e})$ where **e** included evidence collected during a single day. The mean of marginal distributions $p(\underline{ps} \mid \mathbf{e})$ and $p(\underline{is} \mid \mathbf{e})$ was calculated and variability expressed as a coefficient of variation (*CV*) of the mean values, Table 9-7.

The inter-patient variability of parameter estimates (mean of marginal distributions) was assessed by plotting frequency histograms (ranges were divided into suitable intervals) see Figure 9.21.





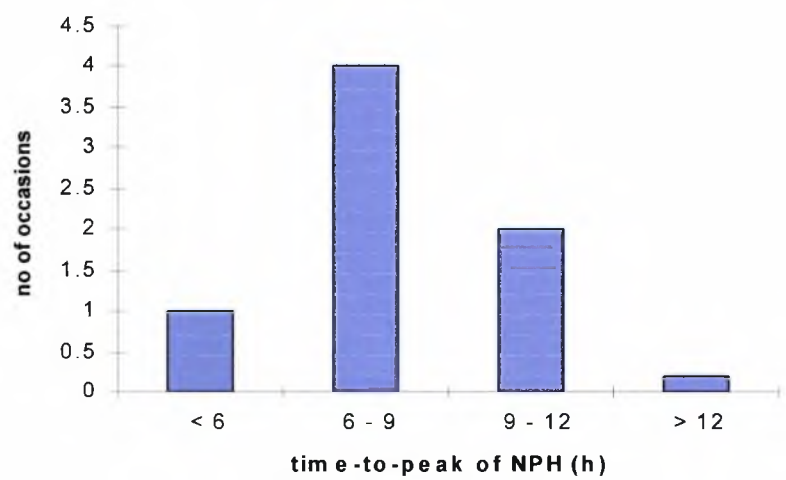


Figure 9.21 *Histograms of the parameters*

The correlation between parameter estimates was calculated from the joint *a posteriori* probability distribution of the parameters. DIAS-NIDDM was run in the prediction mode using the joint *a posteriori* probability distribution and the root mean square (*RMS*) error between predicted and measured blood glucose was computed (Table 9-8) and is shown as frequency histogram in Figure 9.22.

Id	RMS [mmol/L]	ps vs is	ps vs nph	is vs nph
10	0.8	-0.8	0.0	0.0
11a	2.7	-0.4	0.2	0.2
11b	3.3	-0.5	0.3	0.1
11c	3.6	0.0	0.0	0.0
12	1.5	-0.9	0.0	0.0
13	2.4	0.0	0.0	0.0
16	1.2	0.0	0.0	0.0
18	2.1	-0.7	0.0	0.0
19	3.8	0.0	0.0	0.0
31	1.6	-0.5	0.0	0.0
mean	2.3 ± 1.0	-0.4±0.3	0.0 ± 0.0	0.0 ± 0.0

Table 9-8 *Root mean square (RMS) error of the prediction error and the correlation between the estimated parameters*

In some subjects, the estimated parameters are highly correlated. Therefore, the probability mass is distributed across several states in the joint distribution. However, the correct mean value and the confidence intervals can be calculated for the model parameters.

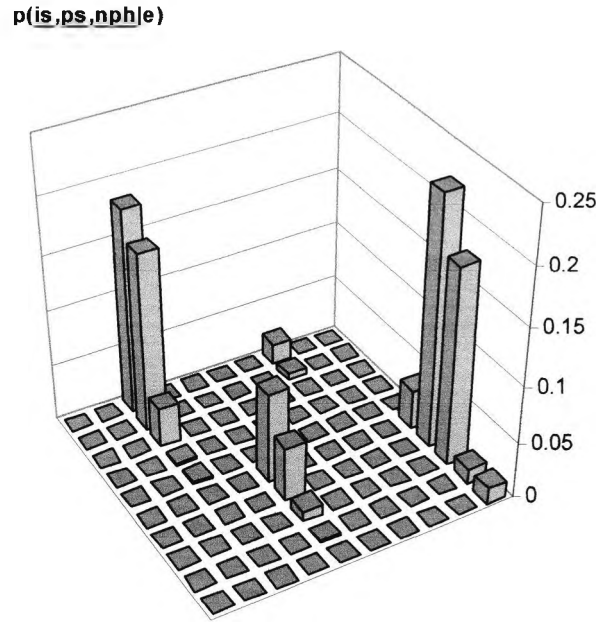


Figure 9.22 *Sample joint probability distribution p(is,ps,nph|e). States of individual parameters occupy an encoded position to allow the 2D representation on the floor of the3D graph*

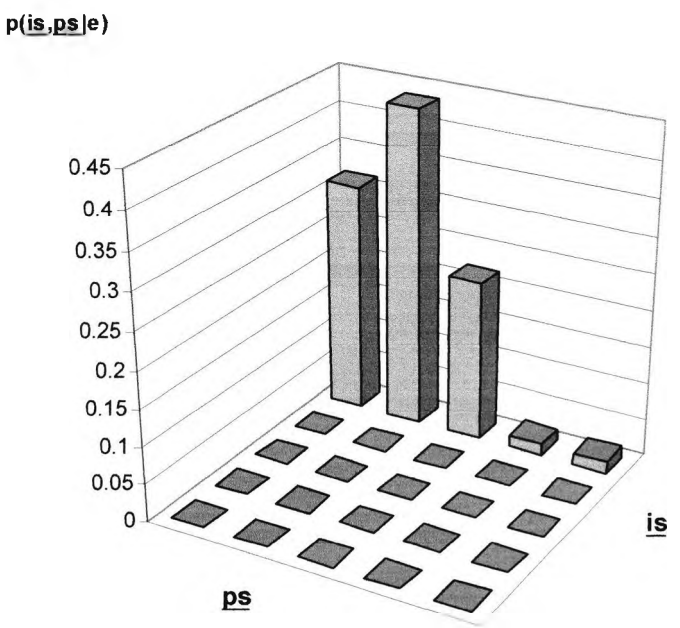


Figure 9.23 *Sample joint probability distribution p(is,ps|e) obtained by marginalisation from p(is,ps,nph|e). The position in the parameter states is and ps has been decoded, and it represents a configuration of the parameter set* $V_p^* = \{ps,is\}$

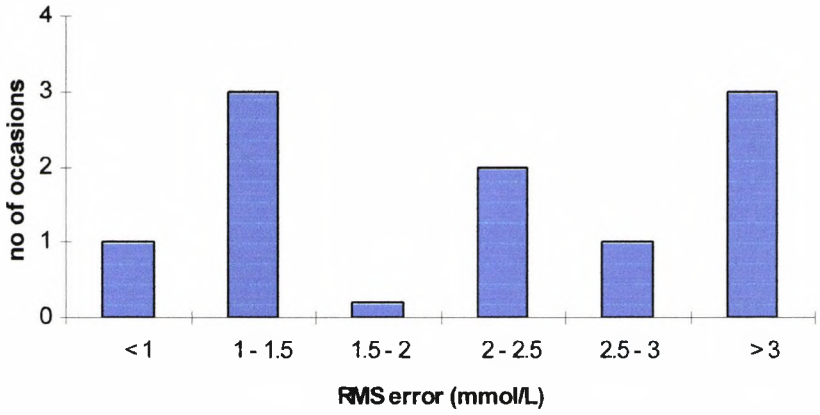


Figure 9.24 *Frequency histogram of the RMS error*

The visual assessment of the predictive accuracy can be obtained from Figure 9.25. The mean predicted *BG* is plotted against the measured *BG* with the unity line included. The plot includes *BG* data from the last day of data collection. The predicted *BG* values were obtained using parameters learnt from all but the last day data for each subject.

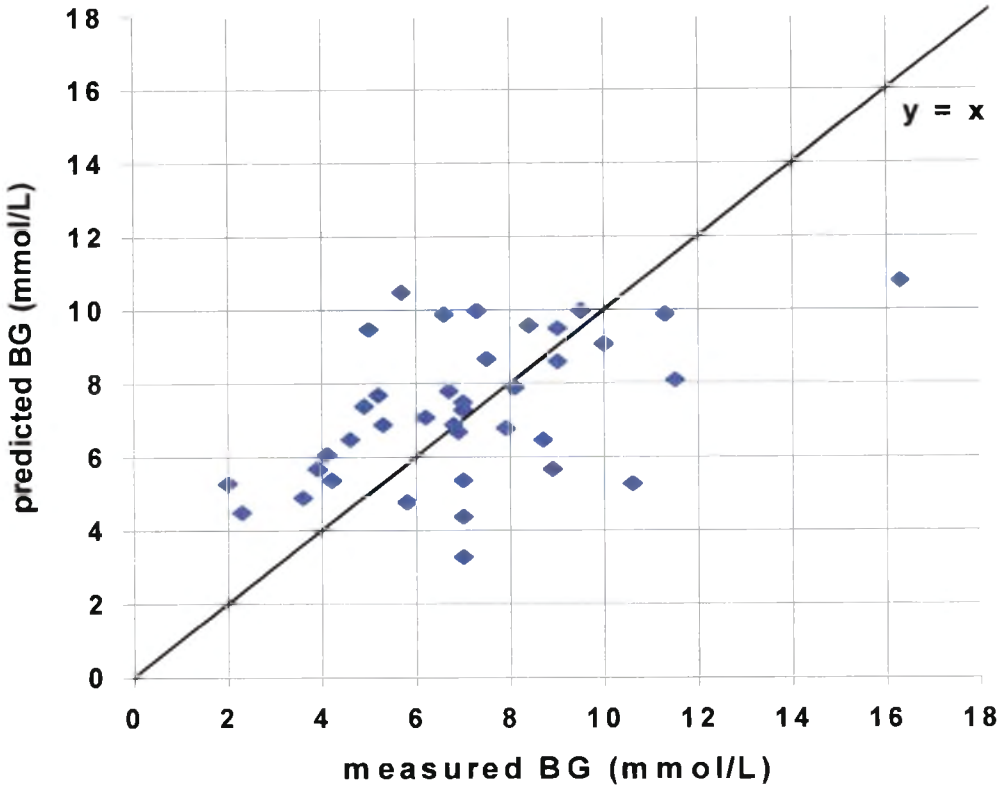


Figure 9.25 *DIAS-NIDDM predicted versus measured BG in subjects with type 2 diabetes*

DIAS-NIDDM was run in the advising mode and advice on insulin doses was generated for each day. Total daily insulin doses were calculated and the inter-day variability of the advice assessed by calculating the CV. The mean of the daily insulin amounts for each subject is shown in Table 9-9 together with the administered treatment.

Id	Administered therapy [U]	DIAS-NIDDM advice [U]	Inter-day variability of DIAS-NIDDM advice [%]*
11a	29	27	5
11b	32	21	13
11c	27	31	17
12	22	11	27
13	78	50	20
16	50	69	36
19	30	30	17

* Expressed as coefficient of variation

Table 9-9 *Total insulin doses during the study period (administered therapy) and the daily insulin as suggested by DIAS-NIDDM (DIAS-NIDDM advice). The latter was obtained as an average of advice given on each day. The inter-day variability of the advice has been assessed by calculating the coefficient of variation (CV)*

9.4.3 Case Study

The cases in this study illustrate the use of DIAS-NIDDM from a clinical point of view and demonstrate the physiological defects present in subjects with type 2 diabetes mellitus (insulin resistance, impaired secretion).

A sample screen dump of DIAS-NIDDM showing data over a period of three days is given in Figure 9.26. The CHO content of meals (grey bar) and the gut absorption (red line) are shown on the top panel. NPH injections (black bar), *BG* measurements (squares joined by red line), the predicted *BG* profile (blue line), the adjusted *BG* profile associated with the advised insulin doses (red line), active and absorbed insulin concentration (green line), and the values of the model parameters are shown on the bottom panel. *Mean ± SD* values are displayed for predicted and estimated quantities. Axes are presented on the left hand side; dashed vertical lines separate the days.

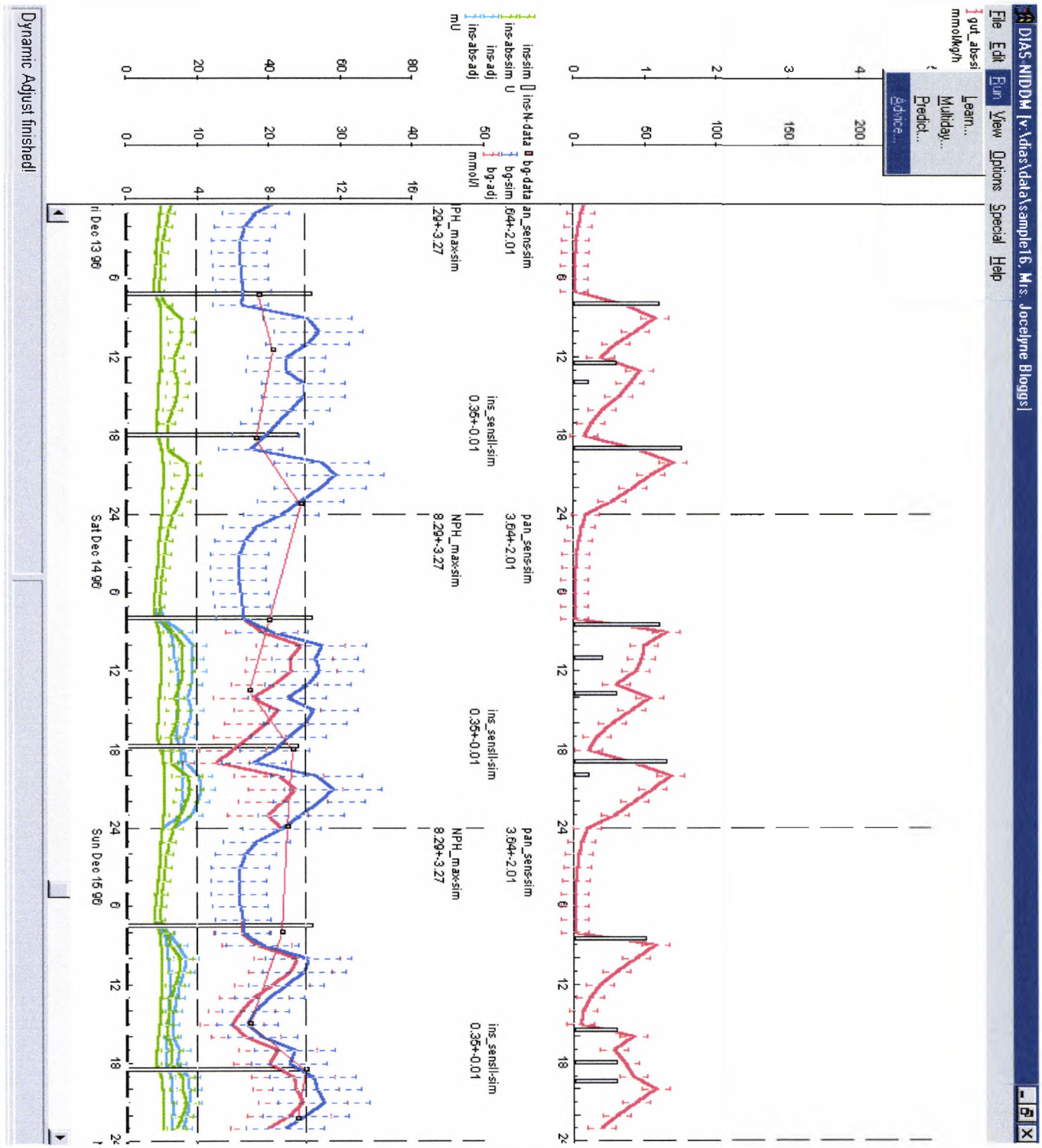


Figure 9.26 *Front end of DIAS-NIDDM. Top panel: CHO content of meals (grey bar) and gut absorption (red line). Bottom panel: NPH insulin injections (black bar), BG measurements collected from December 13 to 15 (squares joined by red line), predicted BG profile (blue line), active and absorbed insulin curves (green lines for simulation, turquoise for advice) and parameter values. The profiles were displayed as mean ± SD*

9.4.3.1 Subject on Diet Alone (Id10)

DIAS-NIDDM was run to estimate model parameters from data collected on July 7 and 8 and predicted *BG* on the same days (data fitting) and July 9 (forecasting), see Figure 9.27. Pancreatic sensitivity was slightly reduced suggesting impaired secretion. Insulin sensitivity was normal suggesting that the subject is not insulin resistant.

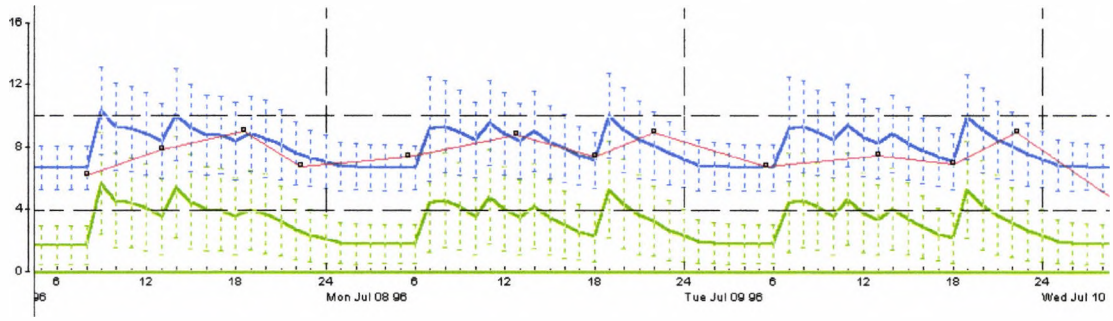


Figure 9.27 *Predicted BG profile (top line) and active insulin concentration (bottom line) for a subject on diet alone (Id10)*

The parameters were estimated with a large SD and, in consequence, *BG* profile was predicted with a large SD. Negative correlation between *is* and *ps* (-0.85) was present. Diet contained 260-280 g of carbohydrate daily and the postprandial rise in *BG* (below 9 mmol/L at all times) is still well controlled by the endogenous secretion. *BG* is predicted with high accuracy (*RMS error* 0.8 mmol/L).

9.4.3.2 Insulin-Treated Subject (Id11a) Insulin-treated subject (Id 11a) on intermediate-acting insulin in the morning, short-acting insulin before lunch and pre-mixed insulin before dinner

The estimated insulin sensitivity parameter is in the normal range whereas pancreatic sensitivity is very low suggesting that impaired insulin secretion is the main defect of carbohydrate metabolism in this subject. In comparison with the previous case subject, CHO content of the diet is high, 220-250 g daily. Good control is achieved, but in this case by the administration of 28 U of daily exogenous insulin. The distribution of injections with short acting injection before lunch and before dinner seems to compensate well for the low pancreatic responsiveness.

Observed *BG* data are within one SD of predicted *BG* (Figure 9.28) except on

September 22, 1900, when hypoglycaemia was not predicted. No immediate explanation of the hypoglycaemia is available. Un-modelled processes like exercise, stress or influence of alcohol, a missed meal, natural variability of blood glucose or an error in the *BG* measurement could explain the discrepancy between predicted and observed *BG*.

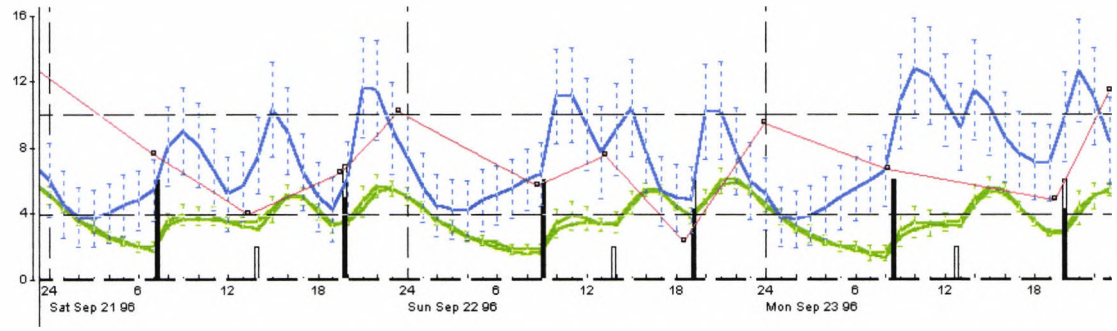


Figure 9.28 *Prediction of three-day BG profile (active and absorbed) profiles for subject (Id11a) treated by intermediate-acting insulin in the morning (black bar), soluble insulin before lunch (white bar) and pre-mixed soluble and intermediate-acting insulin before dinner (black bar)*

DIAS-NIDDM suggested slight reduction in insulin doses (Figure 9.29, the *BG* profile associated with the advised doses is higher).

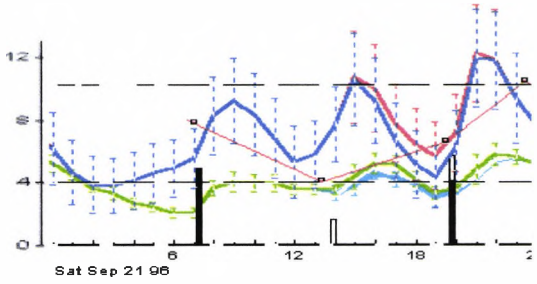


Figure 9.29 *Advised insulin doses (12 U, 3 U and 14 U) in patient Id 11a result in a slightly raised BG profile. Administered therapy was (12 U, 4 U and 14 U)*

9.4.3.3 Insulin-Treated Subject (Id16) on Twice-Daily Intermediate-Acting Insulin

The insulin sensitivity parameter suggests pronounced insulin resistance. The pancreatic sensitivity parameter suggests that insulin secretion is also impaired (overt diabetes). The prediction of 24-hour *BG* profile is given in Figure 9.30.

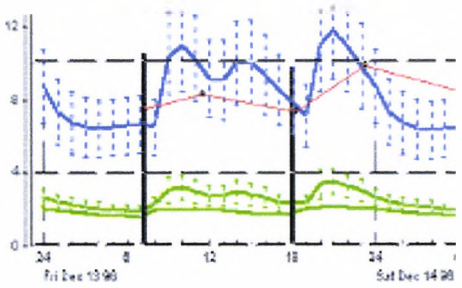


Figure 9.30 *Forecasting of the BG profile for a 24-hour period in an insulin resistant subject, Id16. Postprandial raise in active insulin due to endogenous insulin secretion controls the BG levels following meal intake at 0800 (60 g), 1230 (30 g), 1400 (10 g) and 1900 (75 g)*

The *BG* and insulin profiles associated with the advised insulin doses are shown in Figure 9.26 on December 14 and 15. DIAS-NIDDM recommended 45 U and 24 U of NPH insulin on December 15, and 56 U and 24 U on December 14. The actual therapy was 26 U and 24 U. A high BMI (34.4 kg/m^2) supports the suggestion that the subject is insulin resistant [51;52;58]. Due to the age of the subject, a tight glucose control might not be desirable and the administered therapy can be preferred to the advised therapy. The patient has the poorest blood glucose control (HbA_{1c} = 8.7%) among the investigated population. To overcome the insulin resistance and improve *BG* control, DIAS-NIDDM suggested large amounts of insulin inherently resulting in high plasma insulin concentration that, in turn, may have negative consequences such as weight gain and adversely affecting cardiovascular condition.

9.4.3.4 Insulin-Treated Subject (Id12) on Twice-Daily NPH Insulin

Low values of insulin sensitivity and pancreatic sensitivity suggest overt diabetes (Figure 9.31). A high BMI (28.5 kg/m^2) support this finding.

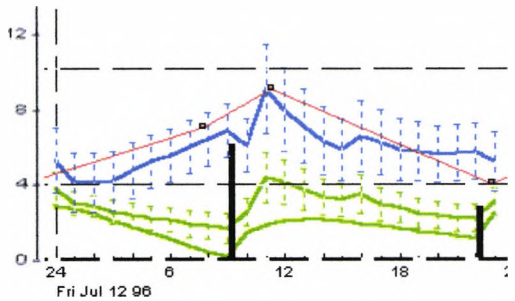


Figure 9.31 *Forecasting of the BG profile for a 24-hour period for a subject with overt type 2 diabetes (Id12). Subject is on twice-daily intermediate-acting insulin (15 U and 7 U)*

DIAS-NIDDM recommends a reduction of the daily insulin by 40% to avoid the potential hypoglycaemia at 2300 on July 12 (Figure 9.32). The advised therapy results in a predicted *BG* profile that is safe from hypoglycaemia.

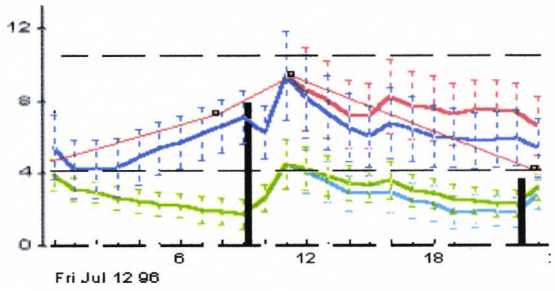


Figure 9.32 *In subject Id12, DIAS-NIDDM reduced the daily dose by 40% (6 U and 7 U) aiming to avoid low BG value at 2300. Advised doses result in higher BG and lower active insulin profiles*

9.4.4 Discussion

The parameter estimates have the potential to assist in the assessment of the patient-specific defect(s) of the carbohydrate metabolism. DIAS-NIDDM suggests that some subjects may have impaired secretion while having near normal insulin sensitivity whereas other subjects present impaired secretion and insulin resistance (overt diabetes), see Table 9-7.

The negative correlation between *is* and *ps* in subjects treated by diet or oral agents (Table 9-8) is due to the fact that DIAS-NIDDM can explain observed *BG* data by both higher pancreatic sensitivity and lower insulin sensitivity or vice versa, see (8-4). If exogenous insulin is present, this correlation is not present (except for subject 12) indicating that in the presence of exogenous insulin, DIAS-NIDDM can identify the defects of carbohydrate metabolism with higher precision.

The day-to-day variability of parameter estimates reflects among other reasons the natural variability of blood glucose concentration. The mean predictive accuracy (as root mean square error) achieved by DIAS-NIDDM in this pilot study was 2.3 ± 1.0 mmol/L.

One subject (Id 11) participated in the study on three separate occasions. The time interval between the first two occasions (11a and 11b) was approximately one month. The parameter estimates of pancreatic sensitivity on the two occasions are consistent, and they both indicate impaired secretion. The small weight gain does not explain the reduction in insulin sensitivity on the second occasion, the reduction is more likely caused by natural physiological variability, and errors present in the parameter estimation process. On the third occasion, approximately three months later, the data could not be fitted by the model accurately (large RMS error, see Table 9-8) and the parameter estimates should be interpreted with caution.

In three subjects, DIAS-NIDDM recommended lower amounts of total daily insulin or a redistribution of doses during the day. The coefficient of variation of the advised total daily insulin dose suggests that, at least according to DIAS-NIDDM criteria,

day-to-day adjustment of insulin doses is *necessary* to maintain optimum control, a fact confirmed by other studies [104].

The pilot study suggests that 30% of the studied subjects have serious secretion deficiency ($ps < 2$ *mU/l per mmol/L*) and equal percentage is presented with impaired or slightly impaired insulin secretion ($2 \leq ps \leq 6$ *mU/L per mmol/L*). Insulin resistance affects 40% of the subjects ($is < 0.6$). The high inter-patient variability of the time-to-peak of absorption of NPH insulin (*nph* parameter) indicates that this parameter needs to be estimated to make accurate predictions of the *BG* profile.

Patient Id 31 is treated with hypoglycaemic agents. DIAS-NIDDM could simulate the *BG* profile with good accuracy (RMS error 1.6 mmol/L). Future work will investigate if the effect of hypo agents could be modelled by altering insulin sensitivity and pancreatic responsiveness parameters depending on the mode of action of the agent (insulin action enhancers versus insulin secretion synthesiser).

The hypoglycaemic counter-regulation phenomenon is difficult to model due to its variable triggering and empirical relationships describing its magnitude and duration. For well-controlled subjects a therapy can be advised so that hypoglycaemia is avoided, and therefore the counter-regulation will not trigger. DIAS advice has been shown to avoid hypoglycaemia and the subsequent counter-regulatory reactions. Therefore, in contrast with other opinions [95], the integration of such a model that is capable to predict hyperglycaemic levels due to glucose counter-regulation may not be of clinical relevance, except for academic and research purposes.

In DIAS-NIDDM, once fitted to the patient (parameter estimation), the CPN model is used as a 'testbed' allowing the patient-specific simulation of various input patterns. There are no inherent management strategies built in the model. The user of the system has the freedom to choose the preferred insulin regimen and support is given with assessing its quantitative effect. With this view, insulin regimens can be designed to suit any patient and any management strategy.

Forecasting in DIAS-NIDDM uses the full joint probability distribution of parameter estimations. The system will predict *BG* with the correct confidence intervals irrespective of the correlation between model parameters.

The predictive accuracy in subjects with type 2 diabetes of 2.3 ± 1.0 mmol/L is higher than that in subjects with type 1 diabetes reported to be approximately 2.8 mmol/L [69].

"*This suggests that it is possible to predict BG in subjects with NIDDM with higher accuracy than in subjects with IDDM, possibly due to the presence of feedback control mechanism in subjects with NIDDM. Residual endogenous insulin secretion is present in these subjects and is likely to limit erratic BG values*" [84]

DIAS-NIDDM, operating in IDDM mode, fails to predict hypoglycaemia in a subject with type 1 diabetes, APV5, on May 07 11:00 pm, see Figure 9.33. However, measured *BG* is within SD of the prediction. The dose-adjustment algorithm is very sensitive to any probability mass of the predicted *BG* profile; therefore, the cost function will record an increased risk even when less probable states of *BG* variable are in the hypoglycaemic range. Therefore, the adjusted evening dose is decreased by DIAS-NIDDM and the new recommended therapy lifts the adjusted *BG* profile by about 1.8 mmol/L. The administered therapy was 22 U M1 (30% A), 8 U M2 (30% A). The recommended therapy on May 07 is 24.9 U M1 (30% A), 5.4 U M2 (30% A). In conclusion, DIAS-NIDDM increases the morning dose and safely decreases the evening dose, lowering the risk of hypoglycaemia.

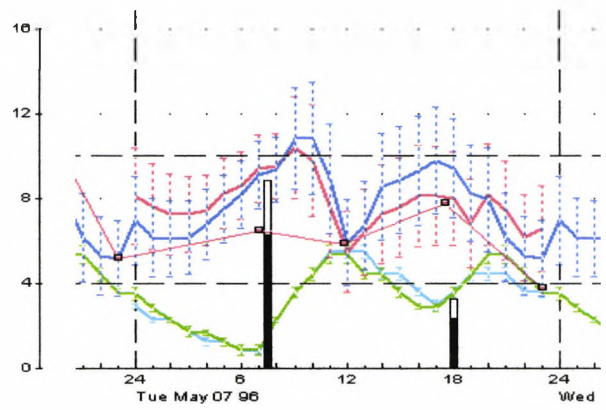


Figure 9.33 *BG measurement within one SD from the prediction are still considered by the insulin dose-adjustment algorithm*

Assessing the severity of the disease or the location of the defect can be a difficult problem. The procedures to detect abnormalities in the carbohydrate metabolism usually involve special experimental conditions, e.g. intravenous glucose and insulin [49]. An evaluation of insulin sensitivity and pancreatic responsiveness based on minimal modelling from intravenous glucose tolerance data is a popular method but requires frequent sampling to determine plasma insulin and plasma glucose concentrations [18]. In contrast, DIAS-NIDDM offers a method of evaluation of the insulin sensitivity and the pancreatic responsiveness from conventionally observed *BG* data. No special conditions such as frequent sampling are necessary. The data analysis suggests that the system can distinguish between the parameters with higher degree of accuracy if exogenous insulin is administered. However, future studies are needed to validate parameter estimates provided by DIAS-NIDDM.

9.4.5 Conclusions

DIAS-NIDDM was evaluated for clinical utility and safety of its advice on retrospective data in order to justify further prospective clinical trials.

DIAS-NIDDM was used to predict patient-specific *BG* profiles and advise on insulin doses during a pilot study in eight patients with type 2 diabetes of whom five were treated with insulin. The mean accuracy of the fit (RMS error) was 2.3±1.0 mmol/L. Compared to the administered doses the advice generated by DIAS-NIDDM was similar (±4U) in two subjects, higher by 20% (17U) in one subject and lower by 50% (11U) and 40% (12U) in two subjects. The inter-day coefficient of variation of the daily insulin advice suggests that, at least according to DIAS-NIDDM criteria, day-to-day adjustment of insulin doses is necessary to maintain optimum control.

The results confirm that DIAS-NIDDM can generate advice that is advice is safe, plausible and of clinical utility.

9.5 Pilot Peer Evaluation of the Diabetes Advisory System for Patients with Type 2 Diabetes

9.5.1 Introduction

The established method to evaluate an expert system is to conduct a blind comparison between the predictions given by the system and one expert when presented with the same cases. However, there is no such thing as the correct answer when advising the insulin doses against patient demographic and therapy data, and therefore there is no de facto gold standard.

To overcome this, a panel of judges is appointed to review the data and assign degrees of agreement to each piece of advice.

A useful variant is the peer review that is a process of review by multiple experts all given the same data [122;151;153]. It is important that the blindness aspect is preserved and the advice recommended by the system cannot be distinguished from that administered by the physicians in order to eliminate any bias.

9.5.2 Tested Hypothesis

DR1, DR2 and DIAS-NIDDM give insulin advice with similarly perceived clinical utility.

9.5.3 Protocol

Five insulin-treated subjects with type 2 diabetes and acceptable glycaemic control (HbA_{1c}<9%) were selected from the diabetic clinic at St. Thomas' Hospital. One subject participated on three separate occasions. The subjects collected data over four consecutive days performing home blood glucose (*BG*) monitoring (four *BG* measurements per day). The subjects recorded composition and timing of meals, doses and timing of insulin injections.

9.5.4 Questionnaire Based Peer Review Methodology

A pilot peer assessment of insulin dose advice generated by a Diabetes Insulin Advisory System for patients with type 2 diabetes (DIAS-NIDDM) has been carried out.

In phase one of the study [126], two diabetes specialists (DR1- doctor, DR2 - nurse) were asked to recommend alterations of insulin doses based on subject's demographic data and the therapy data recorded by the patient (Figure 9.34). DIAS-NIDDM used the same data to generate another advice on insulin doses for these subjects.

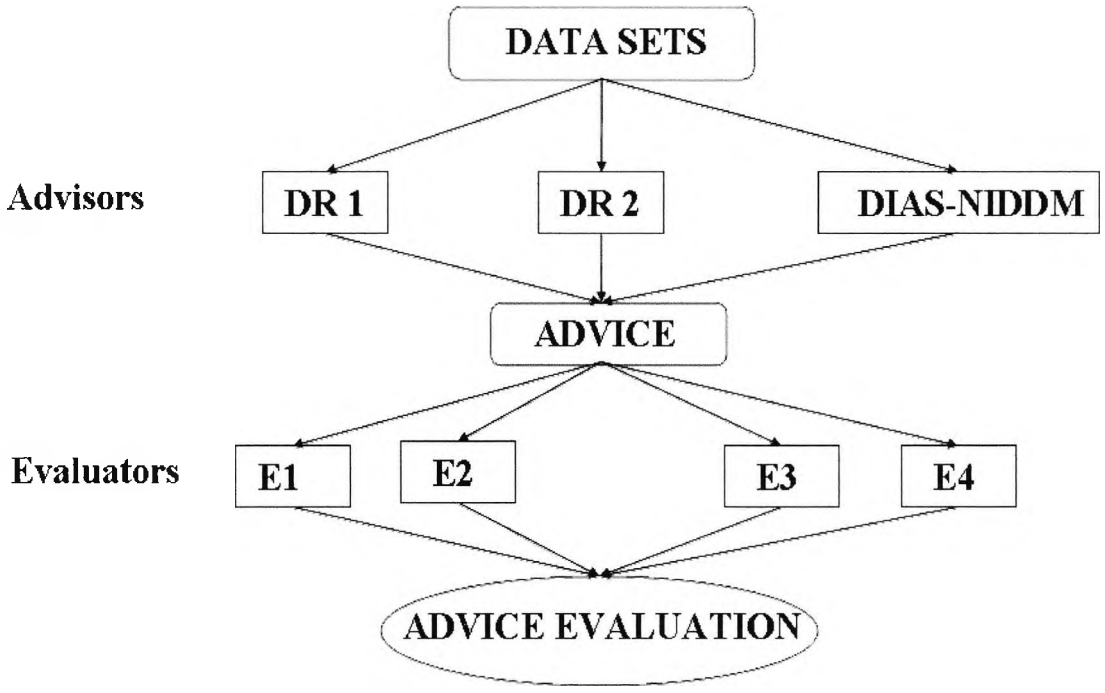


Figure 9.34 *Double blinded questionnaire based peer review methodology*

In phase two, a blind, questionnaire-based review of the advice provided by DR1, DR2 and DIAS-NIDDM was carried out. The questionnaire included identical data to those used in phase one and, in a blind fashion, the advice by DR1, DR2, and DIAS-NIDDM.

The perceived potential of each piece of advice to improve the glycaemic control of the subjects was evaluated. The questionnaire, see ANNEX IV, asked:

Compared with the administered dose,

Q1: is the advice more likely to improve overall control?
Q2: is the advice more likely to reduce the frequency of hypoglycaemia?
Q3: is the advice more likely to reduce the frequency and duration of hyperglycaemia?
Q4: would you be more likely to advise the new dose?

A Likert scale corresponding to degrees of agreement from low to high (scores 0 to 5) was used. Four respondents, diabetologists from UK hospitals, completed the questionnaire.

9.5.5 Results

The response from peers was processed on a per question basis and the scores obtained for all subjects were analysed employing nonparametric tests. We tested the hypothesis that DR1, DR2, and DIAS-NIDDM give advice with similarly perceived clinical utility. This failed to be confirmed for Q1 (total scores were, listed for DR1, DR2, DIAS-NIDDM, 77, 41, 44; p=0.03, Friedman test), Q4 (87, 44, 44; p= 0.02), Q3 (62, 39, 52; p= 0.04) but was confirmed for Q2 (78, 45, 70; p= NS). Assessed separately, the advice from DR2 and DIAS-NIDDM were similar for Q1-Q4 (p=NS, Mann-Whitney U test). In addition, the advice from DR1 and DIAS-NIDDM was similar for Q2 and Q3 (p=NS).

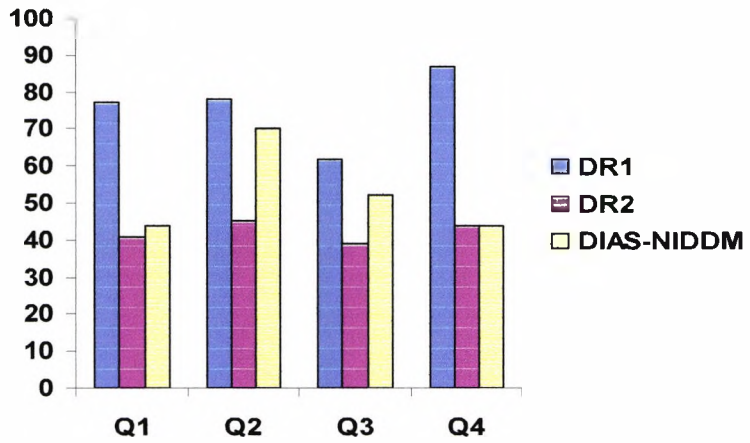


Figure 9.35 *Total scores achieved by DR1, DR2 and DIAS-NIDDM; Q1 p=0.03, Q2 p=0.01, Q3 p= 0.04, Q4 p= 0.02. Maximum score = 140*

9.5.6 Discussion

Despite the statistical significance, the clinical significance of the results is difficult to assess with confidence due to the reduced dataset of the pilot study and a low number of respondents. The evaluation methodologies involving diabetes specialists as judges may be subjective and biased (e.g. clinicians may express different views regarding glucose counter-regulation [68]). However, a peer review pilot study, though it does not substitute double blind controlled clinical trials or the full prospective clinical evaluation, it is a necessary step, providing supplementary views of the safety and acceptance of the system.

9.5.7 Conclusions

The hypothesis that DR1, DR2, and DIAS-NIDDM give advice with similarly perceived clinical utility was tested. This was only confirmed for the ability to reduce the frequency of hypoglycaemia (p=NS). However, the results showed that DR1 performed significantly better than both DR2 and DIAS-NIDDM for overall control (Q1) and personal preference (Q4). Regarding hypoglycaemia avoidance (Q2), the advice was similar. DIAS-NIDDM and DR2 performed similarly for all questions. With respect to hypoglycaemia and hyperglycaemia risk (Q2; Q3), the advice from DIAS-NIDDM was similar to the advice from DR1.

The peer blind assessment provided valuable information about the competence of DIAS-NIDDM compared to diabetes specialists, confirming the potential efficacy and the safety of the advice. The advice is similar in performance to the advice recommended by diabetes specialists.

9.6 Validation of the HbA_{1c} Model

By means of a retrospective pilot study, the ability of the new model of HbA_{1c} concentration to predict steady state HbA_{1c} and the accuracy of the predictions were assessed. The capability of the model to predict the change in the steady state HbA_{1c} according to a change in therapy was also investigated.

9.6.1 Data Collection Protocol

Data was collected from a number of ten subjects with type 1 diabetes. For each patient five to nine HbA_{1c} measurements were recorded during a period of twelve weeks, see Table 9-11. Data were collected according to the DIAS standard data protocol from the Queen Alexandra Hospital, Portsmouth, UK.

ID	Age [yr]	Height [m]	Weight [kg]	BMI [kg/m^2]
AP	72	1.75	72	23.5
BR	51	1.75	83	27.1
VOG	59	1.58	60	24.0
CMC	40	1.50	49	21.8
GH	25	1.81	91	27.8
CC	39	1.50	67	29.8
MARYL	49	1.53	73	31.2
SB	31	1.58	66	26.4
SW	45	1.68	74	26.2
BF	34	1.81	91	27.8

Table 9-10 *Demographic Data*

The subjects collected data over four consecutive days recording four *BG* measurements per day (before meals and at bedtime), meal composition, and insulin doses. The carbohydrate content of the meals was assessed by a dietician. HbA_{1c} assays were performed at most visits and were recorded.

Days with high values of blood glucose following days with hypoglycaemic episodes were discarded (effect of counter-regulation removed, as this process is not modelled

in the system). Subjects changed their treatment (insulin doses, CHO intake) as recommended by the clinician at each visit but the regimen was considered unchanged for the periods between visits. A relatively high degree of patient compliance with the recommended regimen was assumed.

9.6.2 Methods

DIAS-NIDDM was run in parameter estimation mode and estimated the joint a posteriori probability distributions of the parameters $p(\underline{is}, \underline{nph}|e)$ and $p(\underline{k},\underline{T}|e)$ at the first visit for each subject, then in prediction mode, as follows:

1. $p(\underline{is}, \underline{nph}|e)$ – DIAS-NIDDM patient specific parameters - are estimated learning from all available days with collected *BG* at the first visit - V_1

2. $p(\underline{k},\underline{T}|e)$ - HbA_{1c} model parameters - are estimated from a day considered representative at the first visit (days with missed meals or weekend were not used)

3. $p(\underline{is}, \underline{nph}|e)$ *and* $p(\underline{k},\underline{T}|e)$ estimated at visit V_1 are used to predict HbA_{1c} at ($V_2 \ldots V_9$), as applicable

4. to predict HbA_{1c} at visit V_k we use the combined therapy (CHO intake, insulin doses) and DIAS predicted *BG* profiles of all visits up to V_{k-1}

9.6.2.1 Modified Model

The objective is to predict HbA_{1c} at visit *i* using data from the previous visits, $\{\{CHO, INS \mid V_{i-1}\}, \{(\underline{is}, \underline{nph}, \underline{k}, \underline{T})|V_1\}\}$. The subjects changed to a new therapy following each hospital visit. Therefore, the model was changed to calculate correctly the steady state HbA_{1c} due to the heterogeneity of the therapy of the 120-day *BG* profile before each HbA_{1c} measurement. This was necessary when the interval between visits was smaller than the erythrocyte life span, and HbA_{1c} concentration did not reach steady state.

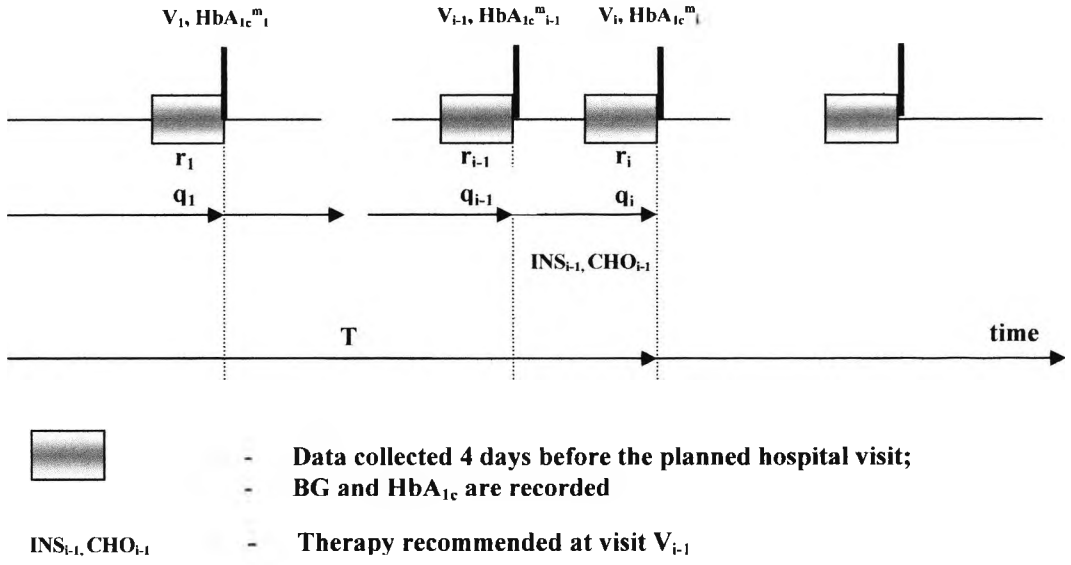


Figure 9.36 *Collected data recorded for 4 days preceding each hospital visit are assumed to characterise the regimen before each visit. Prediction of HbA_{1c} measurement at visit i reflects the therapy changes decided at previous visits*

Superimposing the effect of periods with constant therapy between the visits, the following equations were derived:

$$HbA_{1c} = \left[1 - contrib(r,q)\right] \qquad 9\text{-}14$$

$$contrib(r,q) = contrib(r_1,q_1) + contrib(r_2,q_2) + \ldots \qquad 9\text{-}15$$

Visit *2*

$$HbA_{1c}\,[\%] = \left[1 - \frac{r_1\left(1-r_1^{q_1}\right)}{N\left(1-r_1\right)} - \frac{r_0 r_1^{q_1}\left(1-r_0^{q_0}\right)}{N\left(1-r_0\right)}\right] x100$$

Visit *i*

$$HbA_{1c}\,[\%] = \left[1 - \frac{r_i\left(1-r_i^{q_i}\right)}{N\left(1-r_i\right)} - \frac{r_{i-1} r_i^{q_i}\left(1-r_{i-1}^{q_{i-1}}\right)}{N\left(1-r_{i-1}\right)} - \ldots - \frac{r_0 r_1^{q_1} r_2^{q_2} \ldots r_i^{q_i}\left(1-r_0^{q_0}\right)}{N\left(1-r_0\right)}\right] x100 \qquad 9\text{-}16$$

q_i – number of days with constant therapy preceding visit *i*

r_i – contribution to the overall glycation fraction due to *BG* preceding visit *i*

where

$$\sum_i q_i = \underline{T} \qquad 9\text{-}17$$

The equations were implemented by estimating the individual terms $\frac{r_0 r_1^{q_1} r_2^{q_2} .. r_i^{q_i} \left(1 - r_0^{q_0}\right)}{N\left(1 - r_0\right)}$ that were then substracted from the unity using the transformation method in 8.5.2.2

Equations were validated numerically. Moreover, the substitution $r_i = r \mid \forall i$ in (9-16) leads to relationship (6-12).

9.6.2.2 Data

	v1	v2	v3	v4	v5	v6	v7	v8	v9
AP	9.90	-	9.20	9.40	9.50	9.40	-	8.20	-
BR	9.90	-	9.20	-	9.40	9.60	9.70	9.00	-
VOG	9.90	-	10.00	9.60	10.00	10.30	10.10	8.50	-
CMC	9.60	-	9.50	-	9.30	9.10	8.50	8.00	7.60
GH	8.20	-	8.30	-	-	-	8.60	9.10	-
CC	9.80	-	9.50	-	9.40	-	9.40	9.10	-
MARYL	12.30	-	12.20	-	11.50	-	-	10.40	-
SB	10.20	-	8.40	-	7.60	7.20	7.10	-	-
SW	9.50	-	8.50	-	8.10	7.90	-	-	-
BF	11.30	-	9.40	-	9.20	9.90	10.90	10.70	-

*** Time between visits is variable, can be 4 days up to several weeks**

Table 9-11 *Client visits and their associated HbA_{1c} measurements*

9.6.3 Data Analysis

The accuracy of the prediction was assessed by calculating the RMS and plotting the residuals of measured versus predicted HbA_{1c}. The mean values and standard deviations of the parameters were calculated from the joint probabilities, (m_j, σ_j) for parameters $p(\underline{k}, \underline{T})$ and compared with current medical knowledge and other studies. Inter-patient variability of the parameters was estimated and shown as mean, standard deviation and visually as histograms.

9.6.4 Results

9.6.4.1 Model Characteristics

Calculations based on 36 HbA_{1c} predictions showed a root mean square error (*RMS*) of 0.64 %. Mean SD of the HbA_{1c} predictions was 4.9%. Postprandial glucose excursions result in probability mass in higher states of *BG* nodes, therefore probability mass in both higher and lower states of HbA_{1c} and, in the states of the parameters nodes, explaining high standard deviations of the predictions/estimates. The method learnt the parameters using only one HbA_{1c} measurement. Learning from more HbA_{1c} measurements is likely to reduce the uncertainty shown by the high standard deviations. Nevertheless, mean values of both HbA_{1c} and model parameters are within the physiological range.

	$\underline{k}$ [10^6 mmol/L h]	SD	$\underline{T}$ [days]	SD
AP	6.59	2.89	118	22
BR	6.93	2.83	119	22
VOG	5.56	2.92	116	22
CMC	5.38	2.90	116	22
GH	6.68	2.90	118	21
CC	6.32	2.94	117	22
MARYL	7.27	2.59	120	21
SB	7.47	2.63	122	21
SW	6.33	2.92	117	22
BF	7.82	2.40	124	20

Table 9-12 *Model Parameters $\underline{k}$ – glycation rate and $\underline{T}$ – erythrocyte life span, shown as mean and standard deviation (SD)*

The glycation rate (parameter $\underline{k}$) estimates for all the subject data were inside the interval [5.38,7.82] x 10^6 mmol/L h, with a mean of 6.64 x 10^6 mmol/L h. The length of the interval is 2.44 x 10^6 mmol/L h and it represents 31% of the upper limit of the range. The glycation is a linear irreversible reaction and its rate does not show significant inter-patient variability. A mean erythrocyte life span (parameter $\underline{T}$) of 118.7 days is in agreement with clinical knowledge, and shows insignificant inter-patient variability.

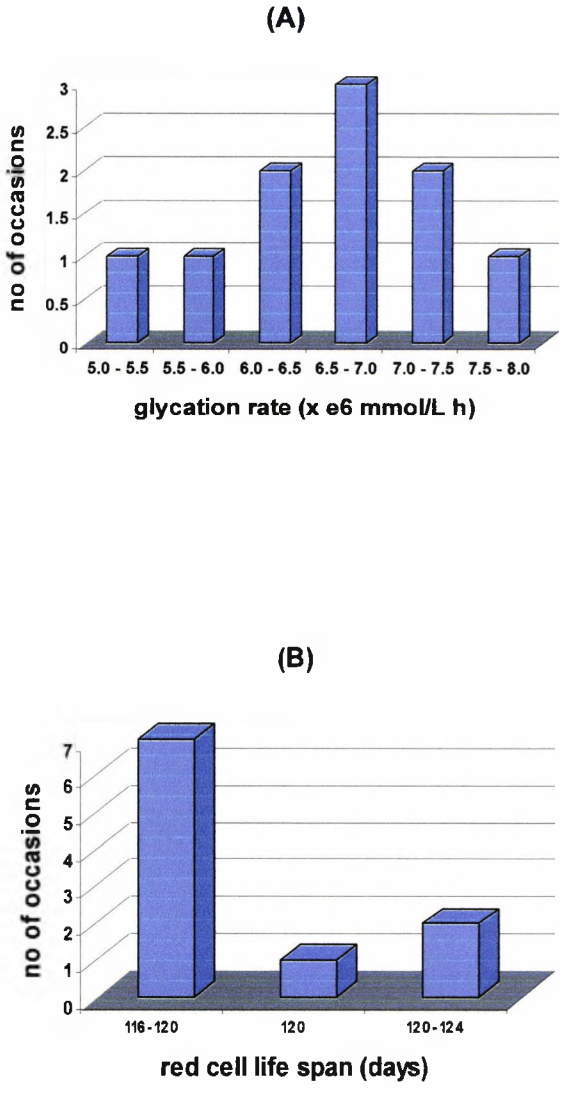


Figure 9.37 *Frequency histograms of mean values of parameter estimates: (A) $\underline{k}$, (B) $\underline{T}$*

The visual assessment of the predictive accuracy can be obtained from the residuals of the predictions. The prediction error was plotted against the measured HbA_{1c}. The plot includes HbA_{1c} data from all subjects and all visits.

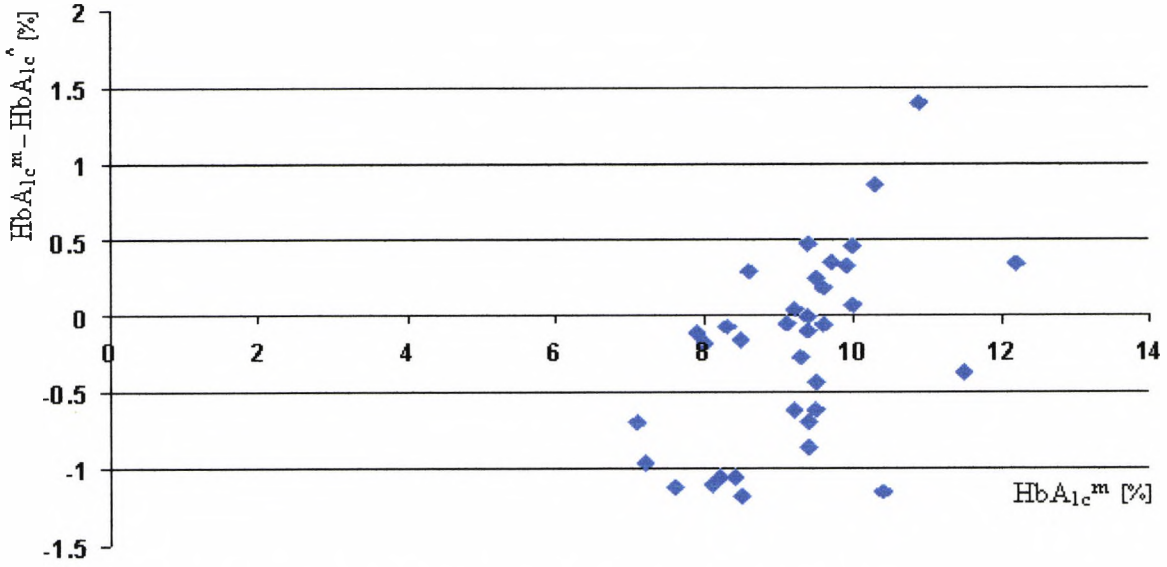


Figure 9.38 *Residual of the predicted HbA_{1c} vs. measured HbA_{1c}*

A statistically significant trend line has been observed ($y=0.28x-2.85$, $r^2=0.23$, $p<0.01$). Despite the statistical significance, the data is difficult to interpret due to both the dependence on the subjects' lifestyle and the intrinsic trend line present in the predictions of DIAS/DIAS-NIDDM systems (see paragraph 9.2).

9.6.4.2 The Response of Predicted HbA_{1c} Steady State Levels to a Change in Treatment

The model has been tested using retrospective HbA_{1c} data recorded on several occasions during out patient visits at the diabetic clinic. The regimen represented by the CHO contents of the meals and the insulin doses was changed as part of routine management of the patient.

Employing, iteratively, the therapies set up at previous visits, a steady state HbA_{1c} value was predicted for each of the visits to investigate if the model responds to the changes in treatment. The values predicted by the model were compared against the measurements.

For patient AP, and similarly for BR, VOG, GH, and BF, there was no change in therapy and the system displayed no change in the predicted HbA_{1c}.

	v3 (1)	**v4**	**v5**	**v6**	**v8**
HbA_{1c}^{m}	learn	9.40	9.50	9.40	8.20
HbA_{1c}^	-	9.49	9.24	9.40	9.25
daily CHO (g)	214	216	206	216	226
daily INS (U)	32	34	30	33	30

Table 9-13 *No change in therapy, no change in the predicted HbA_{1c}*

For patient CMC, and similarly for CC, SB and SW to a change in therapy followed a predicted change in the HbA_{1c}.

	v1	**v3**	**v5**	**v7**	**v8**
HbA_{1c}^{m}	learn	9.50	9.30	8.50	8.00
$HbA_{1c}^{\wedge}$	-	9.93	9.57	8.65	8.17
daily CHO (g)	201	125	187	181	181
daily INS (U)	18	23	25	25	25

Table 9-14 *Change in therapy followed by a change in the predicted HbA_{1c}*

For subject Maryl the change in therapy was not followed by a change in the predicted HbA_{1c}. Predicted HbA_{1c} remained constant.

	v1	v3	v5	v8	
HbA_{1c}^{m}	learn	12.20	11.50	10.40	
$HbA_{1c}^{\wedge}$	-	11.85	11.86	11.54	
daily CHO (g)	197	150	184	-	
daily INS (U)	48	56	56	-	

Table 9-15 *Slight change in therapy, no change in the predicted HbA_{1c}*

There is no immediate explanation for the model's failure (by ~ 1%) to predict a change in the steady state HbA_{1c} to match the change in therapy (slight decrease in CHO amount and increase in insulin dosage). In this particular dataset, it is possible that the mean *BG* levels were in fact produced by a lifestyle that included unrecorded exercise.

9.6.5 Conclusions

The new model of HbA_{1c} concentration was validated on a retrospective data pilot study. The accuracy of the prediction was of 0.64%. According to this model, it has been shown that *BG* levels alone control the steady state HbA_{1c} levels.

The capability of the new model of steady state HbA_{1c} concentration to reflect changes in therapy has been evaluated. A change in therapy (daily CHO contents and/or insulin doses) was followed by an expected change in HbA_{1c}, according to its improving/worsening effect on the control of *BG* levels, in nine subjects. In one subject, however, the model failed to respond to the change in therapy. Unrecorded lifestyle details, possibly exercise could justify the discrepancies.

10. Conclusions

10.1 Discussion

DIAS-NIDDM can be enhanced on several accounts.

BG meters return values with device-specific accuracy [37]. The representation of the measured *BG* in DIAS-NIDDM should reflect accurately the SD of the measuring device. Currently, the range of a discrete state of *BG* used in DIAS-NIDDM, though highly adjustable, does not consider the specific SD of the *BG* meter, therefore the error in the self-monitoring process. The states of the *BG* stochastic variable should be adjusted according to the SD of the measurements. That will have a direct effect on the estimated parameters. DIAS-NIDDM, operating in IDDM mode, by using more refined discrete states already improved the SD of estimated *is* parameter, see comparability study, section 9.3. Additionally, there is a computational difficulty in CPN modelling when the measured *BG* (the evidence) is represented by probability mass distributed across several states of the variable. However, such a method can be formalised and used in DIAS-NIDDM.

The discrepancy between the whole blood *BG* and plasma *BG* should be taken into account by a correction factor of 1.12 [43], when the *BG* meter does not include this auto correction. It is noteworthy that most meters tend to underestimate plasma *BG* by 10% compared to reference lab values.

Currently, the *BG* measurements are taken before meals, but not necessarily at particular moments in time. The time slice in DIAS-NIDDM spans from *hh:00* to past 30 min of the hour, and therefore, the timing of the *BG* measurement leads to an error of up to +/- 30 minutes. The dynamics of plasma *BG* can be fast and depends on the amount of insulin or carbohydrate intake. This error can drastically affect the estimated parameters. Either DIAS-NIDDM is adapted to take into account the exact time of the measurements, or data must be collected only at *hh:00* and *30* minutes past the hour.

DIAS/DIAS-NIDDM should have some model/logic to deal with the semantics of the recommended treatment and be aware of recommendation of high insulin dosage in subjects with advanced insulin resistance - aging/obese subjects. Hyper-insulinaemia must be a criterion in the dose adjustment procedure.

The resulting HbA_{1c} values for each advised dose should be taken into account by the generation of the advice in order to relate a therapy directly to the complications of diabetes. Nevertheless, insulin dosage adjustment could potentially be based on a target HbA_{1c} value solely, or in addition to the criteria DIAS/DIAS-NIDDM currently use (a penalty function, aimed at minimising the periods of hyperglycaemia while avoiding hypoglycaemia) potentially resulting in insulin therapies that are optimum in slowing the progress of the complications of diabetes. That could link the day-to-day management of insulin doses (in particular IIT) directly to DCCT results regarding the diabetes complications.

The mean 24-hour plasma glucose concentration, calculated from the predicted *BG* profiles, should be displayed. Moreover, the HbA_{1c} model should have the ability to calculate an *equivalent mean BG* value associated with the estimated steady state HbA_{1c}.

The glucose transport in erythrocytes has been reported decreased in type 2 diabetes [152], and therefore it is possible that HbA_{1c} measurements underestimate the plasma glucose levels. However, evidence is necessary to show that for equivalent *BG* levels in type 2 diabetes the HbA_{1c} measurements are underestimated when compared with those in subjects with type 1 diabetes. In the current model, any such significant phenomenon would be reflected in the estimated $\underline{k}$ parameter in subjects with altered erythrocyte GLUT1 glucose transport. A study is necessary to evaluate any significant differences in the estimated $\underline{k}$ parameter between subjects with type 1 and 2 diabetes.

Qualitative and quantitative advice on the drug treatment in type 2 diabetes may attain important significance. Currently, the drug treatment in type 2 diabetes is the first treatment option after diet and exercise failed to control hyperglycaemia. The effect of drugs in diabetes type 2 has been vastly analysed [14;93], modelled [21] and their effects compared [93].

Metformin [13] [14] is used worldwide and it is recommended as the drug of choice in type 2 subjects with severe obesity. It improves the sensitivity of various tissues to insulin and reduces the hepatic glucose production. There seems to be no evidence for secondary failure with metformin treatment. The treatment with metformin decreases the plasma insulin concentration, leading to less peripheral hyperinsulinaemia (also less proinsulin, a by-product leading to the development of arteriosclerosis). Metformin targets insulin resistance at its main site, the muscles. Metformin has a dose dependent effect on plasma *BG* (e.g. daily metformin 1700 mg vs. 1000 mg results in mean *BG* values of 7.3 versus 9.1 mmol/L). The peak metformin plasma concentration is also highly dependent on the dose. The insulin binding is correlated with plasma metformin levels. All the changes in the binding values are completed at the end of the first week of treatment. Metformin acts only in the presence of insulin. Treatment-induced hypoglycaemia is rare with metformin alone.

From a modelling point of view, metformin increases insulin sensitivity. Metformin has a dose dependent effect on insulin sensitivity parameter. The time profile of plasma concentration of metformin is non-trivial and the duration of its effect is less than 24 hours, inducing time variance in the 24-hour insulin sensitivity profile. Regarding the effect on the hepatic glucose production, data is contradictory.

Repaglinide [101;130] is a new beta-cell stimulating class of drug, a non-sulphonylurea insulin secretagogue inducing a plasma insulin profile similar to that following a dose of Actrapid. Repaglinide lowers post-prandial *BG* significantly when administered at meal times.

The insulin peak is at 60-90 minutes (after administration), and amounts to appreciatively a 3-fold increase compared with control type 2 diabetics. The plasma insulin concentration returns to the pre-administration levels after four to six hours (Figure 10.1) regardless of the dose of repaglinide. The effect on post-prandial rise in plasma *BG* is dose-dependent, from no effect at all to a total suppression of the rise. No further effects on the plasma glucose levels are noticed beyond a threshold dose.

A typical dose is about 0.25-1mg/kg, while a daily dose is in the range 0.50- 2 mg/kg;

The only adverse events with repaglinide are some mild hypoglycaemic episodes; therefore, the doses need to be administered in the right amounts, and decision support can be employed. The mode of action of the repaglinide on the plasma glucose profile is similar to Actrapid insulin [83], but being an oral agent, life style is not compromised (no injections, no lumps at injection site, etc).

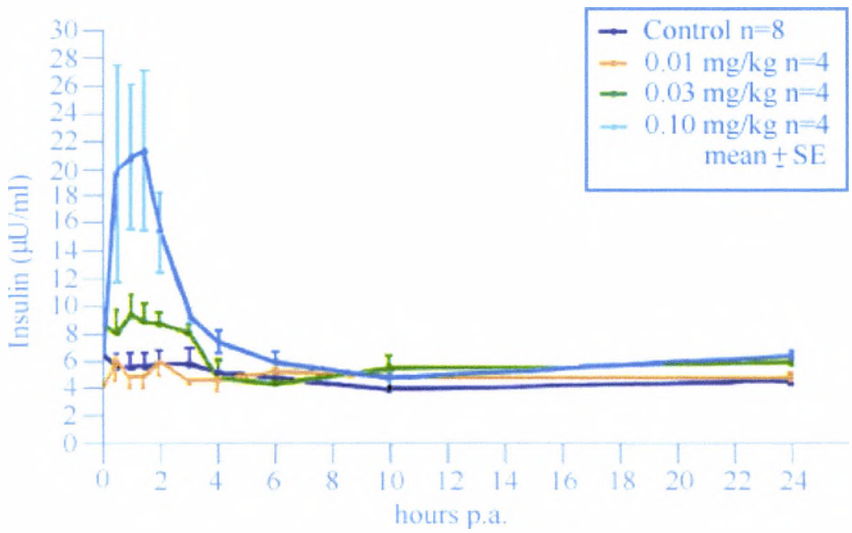


Figure 10.1 *Dose- dependent repaglinide- induced plasma insulin concentration [101]*

Currently, sulphonylureas are the first choice when a dietary and exercise approach has failed [44;63]. Unfortunately, most patients treated with sulphonylureas develop 'secondary failure' to the drug. There is a tendency of HbA_{1c} and mean BG_F to increase after the initial effect of the therapy. More importantly, it is hypothesised that the secondary failure is not due to the loss in the drug effect itself, but rather, a sulphonylureas-caused progression of the disease. Continuous exposure to high concentrations of sulphonylureas to secrete more insulin may decrease the β-cell sensitivity. In addition, high risk of prolonged hypoglycaemia is associated with the use of long-acting sulphonylureas. Sulphonylureas present a dose dependent effect significant at doses larger than 0.3 mg/kg.

From a modelling point of view, a dose-dependent constant component of insulin

secretion seems appropriate to model the effect of this drug (a component modulated by the plasma drug concentration, with the half time four to twelve hours, depending on the particular class of the sulphonylurea). However, sulphonylureas offer only a cosmetic and temporary improvement in the control of plasma glucose levels, and, despite continuous treatment, leads to second failure of the drug. The merit of implementing this drug in DIAS-NIDDM is only due to its wide clinical use and current clinical acceptance.

Acarbose [74] acts on gut absorption introducing a delay, thus delaying and attenuating the rise in plasma glucose following meal digestion. Acarbose treatment causes gastrointestinal discomfort at higher doses. It is useful only in mild forms of diabetes.

From a modelling point of view, acarbose delays the absorption of glucose from the gut, resulting in lower rises in postprandial *BG* excursions and implicitly less *BG* stimulated insulin secretion.

From a theoretical stand (due to their mode of action), a combination pills treatment between metformin and repaglinide seems to be the most desirable. Metformin is necessary especially in insulin resistant subjects (aging or obese). Metformin improves the insulin sensitivity, and repaglinide can control the postprandial rises of the plasma glucose. If the insulin is deficient, long-acting NPH insulin may be envisaged.

Is decision support needed in the management of drug-treated subjects with type 2 diabetes? That depends on a number of factors for example a proved dose dependency and non-trivial drug pharmacokinetics. However, all the drugs are dose dependent and decision support on both qualitative and quantitative advice on drug administration have the potential to be used in clinical environment. The modes of action of these drugs are relatively straightforward to integrate into the current DIAS-NIDDM model-based architecture.

DIAS was used to identify new metabolic processes. The analysis of the discrepancy between predicted and measured 24-hour plasma glucose profiles in children revealed significantly elevated (by 3.8 mmol/L) pre-breakfast *BG* values, leading to the identification of the dawn phenomenon [123].

Hypoglycaemic counter-regulation [67] in subjects with type 1 diabetes gained general acceptance by diabetes specialists [95]. The discrepancy between DIAS-predicted and measured blood glucose in subjects with hypoglycaemic episodes lead to the development of models describing the amplitude and time course of the hypoglycaemic counter-regulation.

There are still un-modelled processes in DIAS/DIAS-NIDDM: effect of stress, alcohol, life style, and others. The discrepancies between DIAS-NIDDM predicted and observed values must be analysed, and not immediately dismissed as random 'day-to-day variability of *BG*'.

During a pilot study (see 9.4), unusual *BG* dynamics were noticed on several occasions/datasets (Figure 10.2, subject 18). Despite significant amounts of CHO (100 g at 10:00 a.m.), the measured *BG* at 02:00 p.m. was only 3.5 mmol/L. DIAS-NIDDM predicted plasma glucose concentration was in excess of 8 mmol/L compared to the observed value.

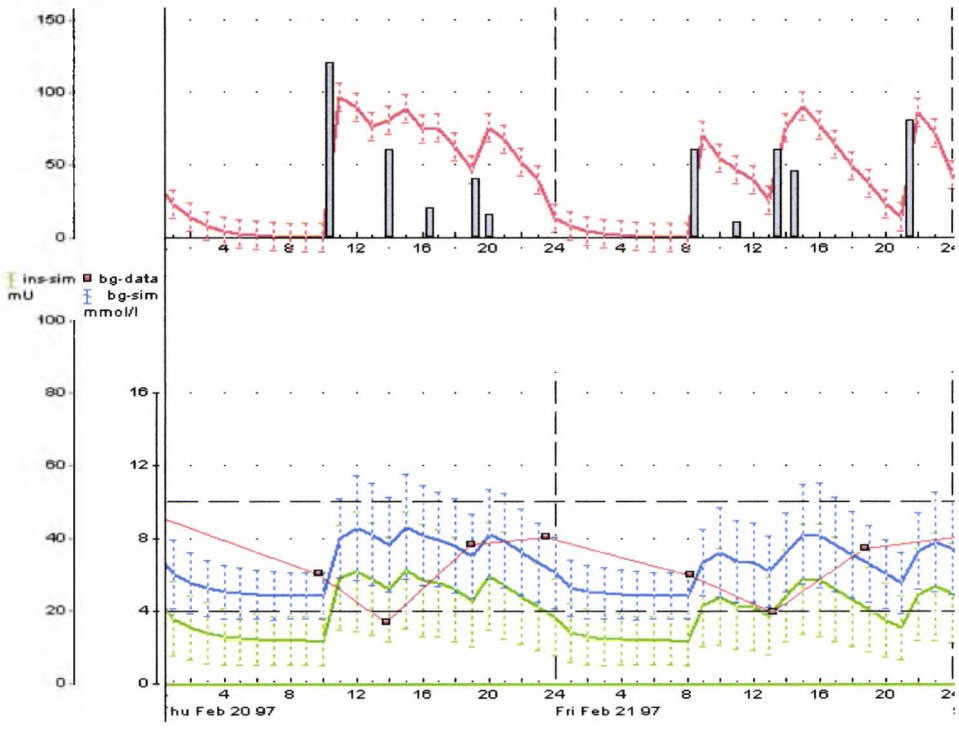


Figure 10.2 *DIAS-NIDDM cannot predict the sharp fall in observed BG levels; the fall is apparent despite considerable CHO intake (in excess of 100 g) and the fact that the subject is on diet alone (no exogenous insulin). Measured fasting C-Peptide of 240 pmol/L shows that the pancreas is still active. Therefore, could secretion be stimulated by non-glucose insulin secretagogues?*

"*If the model adequately describes the system under certain conditions, but predictions made by the model are not reflected by some sets of experimental data, further investigation may reveal a hidden interaction or the discovery of a new substance within the metabolic pathways*" [53]

The rate of insulin secretion is known to respond to non-glucose secretagogues [49;54]. In particular, Elahi showed that there is a strong association between the endogenous glucose-dependent insulinotropic polypeptide (GIP) and the enhanced insulin levels during hyperglycaemia. In addition, normal subjects in hyperglycaemic conditions (7.9 mm/L above base glucose concentration) present a two-fold increase in insulin concentration when oral fat is administered [49].

$$i(t) = f_{BG}(BG(t)) + f_{GIP}(GIP(BG(t))), \qquad 10\text{-}1$$

where $f_{GIP}(GIP(BG(t)))$ is significant during hyperglycaemia, i.e. $f_{GIP}(GIP(BG(t))) \sim f_{BG}(BG(t))$.

Moreover, it has been reported that during OGTT studies, in conditions of raised GIP levels, subjects with type 2 diabetes were misdiagnosed as normal [50]. This demonstrates a significant insulinotropic effect of GIP.

DIAS data collection protocol records CHO contents but not fat contents. Possible contents of fat in the meals/snacks can raise the endogenous GIP levels that could in turn lead to significant non-glucose stimulation of insulin secretion. The hyperglycaemia threshold necessary for the potentiation of insulin secretion [49] may be patient specific (therefore lower than 7.9 mmol/L in certain subjects).

Mari et al report a similar phenomenon of unexplained higher than expected insulin secretion, namely a daytime "circadian modulation" in a mixed meal study [99]. In a subsequent publication [100], Mari et al suggested rather a potentiation of the insulin secretion and renounced the explanation based on the previously reported circadian phenomenon. The data protocol reveals high fat content in the meals (30-35%)[100]. The observed phenomenon could be solely caused by the presence of mixed-meals-induced non-glucose secretagogues.

However, the missing link may be the content of oral fat in the mixed meals [100], and the role of oral fat as indirect non-glucose insulin secretagogue as demonstrated by Elahi's study [49]. The potentiation of non-glucose secretagogues can be strong and it coincides with the timing of the meal [99] and possibly could explain the curvature in the insulin-glucose dose response [99] and the collapsed hysteresis curves reported by Hovorka et al [78].

If this hypothesis is proved, the pancreatic sensitivity parameter in DIAS-NIDDM implicitly accounts partly for non-glucose stimulated insulin secretion in addition to the glucose-stimulated insulin secretion (DIAS collected data implicitly includes the effects of secretion due to non-glucose secretagogues and does lead to overestimates

of the *ps* parameter). However, the two secretion stimulation modes, glucose and non-glucose, should be identified, quantified, and modelled separately.

In conclusion, non-glucose secretagogues could explain the sharply falling postprandial *BG* concentration against clinical expectation. The frequency of this pattern in several datasets justifies further investigation.

The analysis of particular datasets raised the question if the hypoglycaemic counter-regulation is possible in subjects with type 2 diabetes. Subject 11b recorded a hypoglycaemic episode on Fri 13 December (measurement 06:00 pm) that is predicted by DIAS-NIDDM (Figure 10.3). The observed *BG* profile, on December 14, is considerably higher than that predicted by DIAS-NIDDM. The pattern presents certain characteristics of the hypoglycaemic counter-regulation reported in type 1 diabetes [67;70].

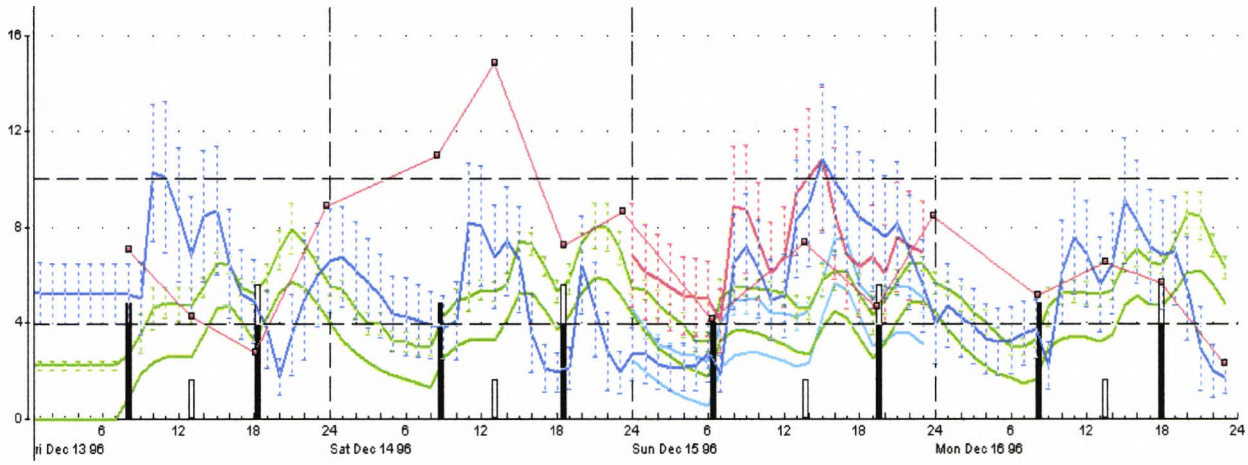


Figure 10.3 *Is glucose counter regulation a relevant phenomenon in diabetes type 2?*

The subject is on NPH insulin; the *BG* levels go high approximately six hours after the hypoglycaemic episode and remain high for about ten hours. Due to the residual insulin secretion in subjects with type 2 diabetes, it seems that *BG* does not reach a plateau that is specific to type 1 diabetes, but rather reaches a climax then falls to pre-hyperglycaemic levels.

DIAS-NIDDM suggests that the administered therapy (12 U NPH, 4 U Actrapid, 14 U Mixtard 30%) is too high. The recommended advice by DIAS-NIDDM lowers NPH dosage but slightly increases midday Actrapid dose (9.8/5.4/5.9 U). The adjusted profile is shown for December 15. This is a case in which DIAS-NIDDM handles insulin dosage in a fashion that is similar to DIAS [35] [68] [69], where insulin is decreased, and still the glycaemic control is improved, resulting probably in lowered steady state HbA_{1c} levels. The improvement in the control levels can be achieved by avoiding the hyperglycaemia caused by the counter-regulatory mechanism.

However, more evidence is needed to prove that the hypoglycaemic counter-regulation can be triggered in subjects with type 2 diabetes and to identify its characteristics/parameters.

10.2 Meeting the objectives

The specific objectives in relation to DIAS-NIDDM, to the prediction of steady-state HbA_{1c} concentration, and to the evaluation of DIAS-NIDDM and the model of HbA_{1c} concentration were met in their entirety.

In conclusion, the results confirm that DIAS-NIDDM can generate advice that is similar in performance to the advice recommended by diabetes specialists and that the advice is safe, plausible and of clinical utility. The system has the potential to predict steady state HbA_{1c} in response to changes in diet and insulin therapy. Despite possible further optimisations of the system, the proceeding with the prospective clinical evaluation of DIAS-NIDDM is justified.

10.3 Contribution to Knowledge

The thesis makes the following contributions to knowledge:

- Model of *BG*-stimulated insulin secretion implemented in CPN, see Chapter 5.
- Use of the insulin secretion model in a DSS to advise on the insulin dosage for insulin-treated subjects with type 2 diabetes, see paragraphs9.4 and 9.5.
- New steady state model of HbA_{1c} concentration including a model of HbA_{1c} assay with ability to predict steady state HbA_{1c} concentrations and the change in HbA_{1c} due to changes in therapy (daily CHO contents and/or insulin dosage), see Chapter 6

10.4 Future Work

10.4.1 System enhancements

Despite the fact that DIAS/DIAS-NIDDM operates with high performance in the normoglycaemic range, as proved in clinical trials, optimisations and enhancements are still possible (see section 10.1).

10.4.2 Validation of DIAS-NIDDM CHO metabolism parameters against estimations by other methods

DIAS-NIDDM can estimate the parameters of the carbohydrate metabolism from only a few plasma *BG* measurements, with the potential to identify the disorders of the heterogeneous type 2 diabetes. However, the estimated DIAS-NIDDM parameters must be validated against established methods of insulin and pancreatic sensitivity calculation [19;49;77;106;140]. Moreover, it has been noticed that in the absence of exogenous insulin, DIAS-NIDDM estimates diabetes type 2 parameters with uncertainty. It is advisable to administer small doses of exogenous insulin to the subjects during the data collection period.

10.4.3 Is Decision Support Needed in the Management of Drug-Treated Subjects with Type 2 Diabetes?

The review on the drugs treatment in type 2 diabetes, see section 10.1, suggests that these drugs have rich pharmacokinetic and pharmacodynamic features and their action is dosage dependent. The simulation of the modes of action of these drugs can be clinically useful to assist with the design of different strategies and to recommend quantitative advice in pharmacological treatment of diabetes type 2.

The modes of action of these drugs are relatively straightforward to integrate into the current DIAS-NIDDM architecture. The DIAS-NIDDM model should be extended to generate advice on the optimum dosage for hypoglycaemia avoidance and hyperglycaemia limitation.

10.4.4 Physiological/clinical insights

DIAS-NIDDM can help identify hidden interactions or lead to the discovery of a new substance within the metabolic pathways.

Studies are necessary to investigate the relevance of glucose-counter regulation in type 2 diabetes and the possibility of non-glucose secretagogues as found in mixed meals to lower glucose levels, see 10.1.

10.4.5 Comprehensive System Evaluation

In addition to the evaluation steps already undertaken, a comprehensive evaluation of the system must be performed, consisting of the following:

a. Validation of model parameters against other methods of metabolic parameters estimation
b. Design of prospective studies - use in intended environment, checks of the ability to improve health care outcome
c. Comprehensive evaluation - a stakeholder matrix can be represented with its dimensions corresponding to stakeholders in the system and a set of evaluation criteria [9;33]; capital and running costs need to be taken into account

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APPENDICES

I. Glycation of Haemoglobin

Haemoglobin is characterised by structural intrinsic heterogeneity, being made up of four polypeptide chains. Over 90% of adult haemoglobin, HbA, is made up of two α- and two β-chains ($\alpha_2\beta_2$). Minor fractions of HbF ($\alpha_2\gamma_2$), HbA_2 ($\alpha_2\sigma_2$) are also present [30;45].

In the circulating plasma, the heterogeneity of normal adult plasma haemoglobin (Hb) is further naturally caused as the result of glycation, where fractions are formed by the non-enzymatic attachment to haemoglobin of glucose, glucose-6-phosphate, and fructose-1,6-diphosphate. The formation of HbA_{1c} fraction is shown in Figure I.1.

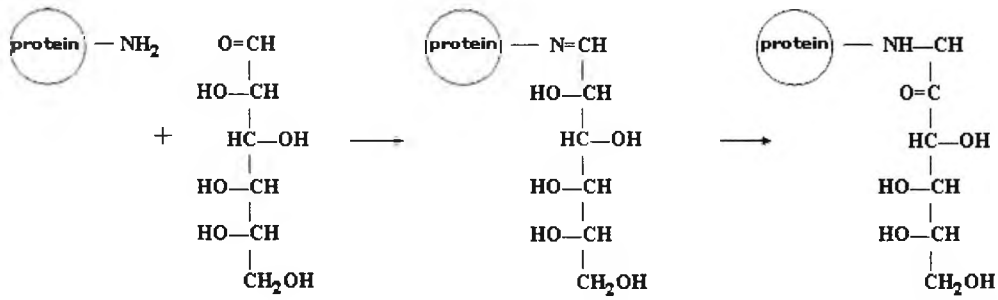

Figure I.1 *Two phase formation of HbA_{1c}. Rapid non-enzymatic attachment of glucose at the amino terminus of the β–chain of the $HbA(\alpha_2\beta_2)$ protein with formation of the Schiff Base (labile) and the slow Amadori rearrangement to yield a ketoamine (HbA_{1c}, stable), see [29;30]*

The synthesis of HbA_{1c} in humans is a process in which haemoglobin glycation occurs slowly, continuously and nearly irreversibly over the life span of the erythrocyte [29]. The stable form of modified glycated haemoglobin is detected by glycation specific techniques such as boronate affinity chromatography. The labile Schiff base form of glycated haemoglobin fluctuates with acute changes in plasma glucose concentration and its interference with the measurement of HbA_{1c} has been successfully addressed.

The glycation of serum proteins, such as albumin and fructosamine, is in many respects similar to the haemoglobin glycation, except that the attachment of glucose occurs at ε–amino groups of lysine and that the formation of a stable ketoamine occurs 4-5 times faster. Though the measurement of these glycated proteins pose some difficulties (fructosamine assay must separately measure and adjust for protein levels) and have not gained acceptance in current diabetes clinical practice, they nevertheless are valuable and of clinical interest representing a useful means of assessing the short-term glycaemic control. They respond faster to a change in therapy and correlate significantly with mean glucose levels over the preceding period. Glycated proteins monitor the changes in therapy before HbA_{1c} values begin to reflect the effects of the new therapy, and are particularly useful in the management of pregnancies complicated by diabetes. Monitoring albumin/fructosamine values may also be used for patients with altered cell life span or other conditions, which make HbA_{1c} measurements unusable, such as recent blood transfusion recipients.

II. Principles of Boronate Affinity Chromatography

The 1,2-cis-diol groups of the glycated proteins, that are not present in the non-glycated proteins, provide the basis for the separation of glycated and non-glycated components by boronate affinity chromatography [98].

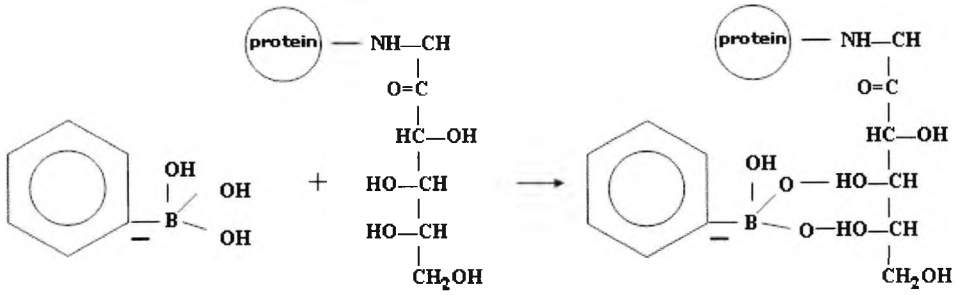

Figure II.1 *Affinity binding of glycated haemoglobin fraction (HbA_{1c}) to the Boronate affinity matrix [98]*

A boronate acid is placed on the analytical column of the high-performance liquid chromatography (HPLC) system [1]. A solution of proteins is passed through the column and the glycated component is retained by binding with the boronate as shown in Figure II.1.

The un-retained non-glycated components elute first. They are passed on to spectrophotometer detector producing a voltage peak at an approximate wavelength of 413+/-2nm for haemoglobin. In the next phase, the glycated component is also eluted from the boronate gel using a reagent and this is detected at the approximate wavelength of 280+/- 2nm. HPLC system calculates the concentration of glycated haemoglobin or plasma protein as a percentage of the total detected concentrations, using a formula based on areas of voltage peaks,

$$HbA_{1c}[\%] = \frac{Area\ Peak\ 2}{Area\ Peak\ 1 + Area\ Peak\ 2}\ x100$$

III. CPN states for the Penalty Function, the BG variable and the DIAS-NIDDM parameters

BG variable and penalty function:

BG intervals [mmol/L]	Penalties [-]
21	
19	16.00
17	12.10
15	8.80
13	5.675
11	3.075
9	1.1375
7	0.2
5	0.0375
3	4.00
2	10.00
1	16.00

e.g. *BG interval 3-5 carries a penalty of 4*
note: *penalties were derived from DIAS penalty function except for the last 3 values which were determined based on subjective assessment*

States of insulin variables in the system:

INSULIN [pmol/L]
90
75
60
50
40
35
30
25
20
16
13
10
7
5
3
0

States of insulin sensitivity:

is [-]
1.41
1
0.71
0.5
0.35

States of pancreatic sensitivity:

ps [mU/L per mmo/L]
10
5
2.5
0.5
0

States of NPH insulin variable:

nph [h]
14
10
7
5

IV. Questionnaire

The questionnaire was used for evaluation stage described in 9.5. Also, it documents the self-monitored data used in the pilot study in 9.4.

Subject Id 11a

Demographic Data:

No	Sex	Age (yr)	Duration of diabetes (yr)	Daily CHO intake (g)	BMI (kg/m^2)	Fasting BG (mmol/L)	Fasting C-peptide (pmol/L)	HbA_{1c} (%)
11a	M	61	8	210-260	24.0	11.0	0	7.0

Meal timing and amounts; BG measurements:

	Day1 Time	Data	Day2 Time	Data	Day3 Time	Data	Day4 Time	Data
Meals CHO (g)	0945	45	0715	50	0850	60	0815	80
	1330		1155	10	1320	55	1300	85
	65 1800		1325	60	1650	10	1925	85
	10 1900		1935	110	1845	95		
	105							
BG (mmol/L) Measurements	0930	10.2	0700	7.7	0845	5.7	0810	6.7
	1330	5.7	1320	4	1315	7.6	1920	4.9
	1850	4	1930	6.5	1830	2.4	2301	11.5
	2245	13.1	2323	10.2	2355	9.5		

Administered dose:

Intermediate 08:00	**Actrapid 13:00**	**Mixtard 30% 20:00**
12U	**4U**	**13U**

Advice 1:

12 U	4 U	12 U

Q1: Compared with the administered dose, is the advice more likely to improve overall control?

No					Yes
0	1	2	3	4	5

Q2: Compared with the administered dose, is the advice more likely to reduce the frequency of hypoglycaemia?

No					Yes
0	1	2	3	4	5

Q3: Compared with the administered dose, is the advice more likely to reduce the frequency and duration of hyperglycaemia?

No					Yes
0	1	2	3	4	5

Q4: Compared with the administered dose, would you be more likely to advise the new dose?

No					Yes
0	1	2	3	4	5

Advice 2:

10 U	4 U	12 U

Q1: Compared with the administered dose, is the advice more likely to improve overall control?

No					Yes
0	1	2	3	4	5

Q2: Compared with the administered dose, is the advice more likely to reduce the frequency of hypoglycaemia?

No					Yes
0	1	2	3	4	5

Q3: Compared with the administered dose, is the advice more likely to reduce the frequency and duration of hyperglycaemia?

No					Yes
0	1	2	3	4	5

Q4: Compared with the administered dose, would you be more likely to advise the new dose?

No					Yes
0	1	2	3	4	5

Advice 3:

12 U	0 U	14 U

Q1: Compared with the administered dose, is the advice more likely to improve overall control?

No					Yes
0	1	2	3	4	5

Q2: Compared with the administered dose, is the advice more likely to reduce the frequency of hypoglycaemia?

No					Yes
0	1	2	3	4	5

Q3: Compared with the administered dose, is the advice more likely to reduce the frequency and duration of hyperglycaemia?

No					Yes
0	1	2	3	4	5

Q4: Compared with the administered dose, would you be more likely to advise the new dose?

No					Yes
0	1	2	3	4	5

Subject Id 11b

Demographic Data:

No	Sex	Age (yr)	Duration of diabetes (yr)	Daily CHO intake (g)	BMI (kg/m^2)	Fasting BG (mmol/L)	Fasting C-peptide (pmol/L)	HbA_{1c} (%)
11b	M	61	8	250-350	24.4	4.2	510	7.0

Meal timing and amounts; BG measurements:

	Day1		Day2		Day3		Day4	
	Time	Data	Time	Data	Time	Data	Time	Data
Meals	0840	90	0930	90	0650	80	0905	80
CHO (g)	1315	85	1315	50	1130	70	1325	130
	2015	130	1840	90	1340	110	1805	60
	2345	15	2310	25	1955	50	2255	60
					2200	15		
					2350	25		
BG (mmol/L)	0800	7.1	0830	11	0615	4.2	0805	5.2
Measurements	1300	4.3	1300	14.9	1337	7.4	1325	6.6
	1805	2.8	1830	7.3	1920	4.7	1755	5.7
	2340	8.9	2310	8.7	2350	8.5	2255	2.3

Administered dose:

Intermediate 08:00	**Actrapid 13:00**	**Mixtard 30% 18:30**
12 U	**4 U**	**14 U**

Advice 1:

12 U	**4 U**	**12 U**

Q1: Compared with the administered dose, is the advice more likely to improve overall control?

No					Yes
0	1	2	3	4	5

Q2: Compared with the administered dose, is the advice more likely to reduce the frequency of hypoglycaemia?

No					Yes
0	1	2	3	4	5

Q3: Compared with the administered dose, is the advice more likely to reduce the frequency and duration of hyperglycaemia?

No					Yes
0	1	2	3	4	5

Q4: Compared with the administered dose, would you be more likely to advise the new dose?

No					Yes
0	1	2	3	4	5

Advice 2:

10 U	**4 U**	**12 U**

Q1: Compared with the administered dose, is the advice more likely to improve overall control?

No					Yes
0	1	2	3	4	5

Q2: Compared with the administered dose, is the advice more likely to reduce the frequency of hypoglycaemia?

No					Yes
0	1	2	3	4	5

Q3: Compared with the administered dose, is the advice more likely to reduce the frequency and duration of hyperglycaemia?

No					Yes
0	1	2	3	4	5

Q4: Compared with the administered dose, would you be more likely to advise the new dose?

No					Yes
0	1	2	3	4	5

Advice 3:

11 U	5 U	14 U

Q1: Compared with the administered dose, is the advice more likely to improve overall control?

No					Yes
0	1	2	3	4	5

Q2: Compared with the administered dose, is the advice more likely to reduce the frequency of hypoglycaemia?

No					Yes
0	1	2	3	4	5

Q3: Compared with the administered dose, is the advice more likely to reduce the frequency and duration of hyperglycaemia?

No					Yes
0	1	2	3	4	5

Q4: Compared with the administered dose, would you be more likely to advise the new dose?

No					Yes
0	1	2	3	4	5

Subject Id 11c

Demographic Data:

No	Sex	Age (yr)	Duration of diabetes (yr)	Daily CHO intake (g)	BMI (kg/m^2)	Fasting BG (mmol/L)	Fasting C-peptide (pmol/L)	HbA_{1c} (%)
11c	M	62	9	340-380	25.0	11.0	0	7.3

Meal timing and amounts; BG measurements:

	Day1 Time	Data	Day2 Time	Data	Day3 Time	Data	Day4 Time	Data
Meals CHO (g)	0635	70	0630	70	0620	70	0710	60
	1000	60	1005	50	1035	50	1000	60
	1100	25	1335	100	1335	110	1310	110
	1330	110	1605	15	1650	15	1840	40
	1835	45	1840	80	1725	15	2300	70
	2210	50	2216	30	1835	50		
					2255	30		
BG (mmol/L) Measurements	0600	9	0550	9.2	0545	6.4	0635	6.2
	1325	6.8	1330	3.1	1330	2.5	1305	16.3
	1823	9.5	1830	7.3	1816	3	1745	11.3
	2209	7.5	2216	8.7	2250	8.3	2305	2

Administered dose:

Intermediate 06:00	**Actrapid 13:30**	**Mixtard 30% 18:30**
12N	**4A**	**$14M_3$**

Advice 1:

10 U	**4 U**	**12 U**

Q1: Compared with the administered dose, is the advice more likely to improve overall control?

No					**Yes**
0	1	2	3	4	5

Q2: Compared with the administered dose, is the advice more likely to reduce the frequency of hypoglycaemia?

No					Yes
0	1	2	3	4	5

Q3: Compared with the administered dose, is the advice more likely to reduce the frequency and duration of hyperglycaemia?

No					Yes
0	1	2	3	4	5

Q4: Compared with the administered dose, would you be more likely to advise the new dose?

No					Yes
0	1	2	3	4	5

Advice 2:

12 U	4 U	14 U

Q1: Compared with the administered dose, is the advice more likely to improve overall control?

No					Yes
0	1	2	3	4	5

Q2: Compared with the administered dose, is the advice more likely to reduce the frequency of hypoglycaemia?

No					Yes
0	1	2	3	4	5

Q3: Compared with the administered dose, is the advice more likely to reduce the frequency and duration of hyperglycaemia?

No					Yes
0	1	2	3	4	5

Q4: Compared with the administered dose, would you be more likely to advise the new dose?

No					Yes
0	1	2	3	4	5

Advice 3:

14 U	6 U	14 U

Q1: Compared with the administered dose, is the advice more likely to improve overall control?

No					Yes
0	1	2	3	4	5

Q2: Compared with the administered dose, is the advice more likely to reduce the frequency of hypoglycaemia?

No					Yes
0	1	2	3	4	5

Q3: Compared with the administered dose, is the advice more likely to reduce the frequency and duration of hyperglycaemia?

No					Yes
0	1	2	3	4	5

Q4: Compared with the administered dose, would you be more likely to advise the new dose?

No					Yes
0	1	2	3	4	5

Subject Id 12

Demographic Data:

No	Sex	Age (yr)	Duration of diabetes (yr)	Daily CHO intake (g)	BMI (kg/m^2)	Fasting BG (mmol/L)	Fasting C-peptide (pmol/L)	HbA_{1c} (%)
12	F	66	11	80-160	28.5	4.2	0	7.7

Meal timing and amounts; BG measurements:

	Day1 Time		Day2 Time		Day3 Time		Day4 Time	
Meals CHO (g)	1010 1345 1845 2300	45 10 35 10	0945 1440 2235	55 15 8	1030 1230 2240	40 10 35	1020 1345 1700 2245	30 10 45 55
BG (mmol/L) Measurements	0900 1330 1845 2215	7 4 4 4	0745 1120 2250 2355	7 9 4 4.5	0850 1230 1840 2215	7 4 4 4	0945 1330 1630 2120	7 7 7 7

Administered dose:

Intermediate 10:00	**Intermediate 22:00**
15 U	**7 U**

Advice 1:

15 U	**7 U**

Q1: Compared with the administered dose, is the advice more likely to improve overall control?

No					**Yes**
0	1	2	3	4	5

Q2: Compared with the administered dose, is the advice more likely to reduce the frequency of hypoglycaemia?

No					Yes
0	1	2	3	4	5

Q3: Compared with the administered dose, is the advice more likely to reduce the frequency and duration of hyperglycaemia?

No					Yes
0	1	2	3	4	5

Q4: Compared with the administered dose, would you be more likely to advise the new dose?

No					Yes
0	1	2	3	4	5

Advice 2:

7 U	6 U

Q1: Compared with the administered dose, is the advice more likely to improve overall control?

No					Yes
0	1	2	3	4	5

Q2: Compared with the administered dose, is the advice more likely to reduce the frequency of hypoglycaemia?

No					Yes
0	1	2	3	4	5

Q3: Compared with the administered dose, is the advice more likely to reduce the frequency and duration of hyperglycaemia?

No					Yes
0	1	2	3	4	5

Q4: Compared with the administered dose, would you be more likely to advise the new dose?

No					Yes
0	1	2	3	4	5

Advice 3:

16 U	7 U

Q1: Compared with the administered dose, is the advice more likely to improve overall control?

No					Yes
0	1	2	3	4	5

Q2: Compared with the administered dose, is the advice more likely to reduce the frequency of hypoglycaemia?

No					Yes
0	1	2	3	4	5

Q3: Compared with the administered dose, is the advice more likely to reduce the frequency and duration of hyperglycaemia?

No					Yes
0	1	2	3	4	5

Q4: Compared with the administered dose, would you be more likely to advise the new dose?

No					Yes
0	1	2	3	4	5

Subject Id 13

Demographic Data:

No	Sex	Age (yr)	Duration of diabetes (yr)	Daily CHO intake (g)	BMI (kg/m^2)	Fasting BG (mmol/L)	Fasting C-peptide (pmol/L)	HbA_{1c} (%)
13	M	64	14	140-165	27.1	9.6	710	7.1

Meal timing and amounts; BG measurements:

	Day1		Day2		Day3		Day4	
	Time	Data	Time	Data	Time	Data	Time	Data
Meals CHO (g)	0830	25	0830	25	0830	60	0830	60
	1100	15	1100	15	1100	10	1045	20
	1230	30	1230	25	1230	30	1200	30
	1730	75	1730	55	1730	50	1500	15
	2000	10	2030	25	2200	15	1800	12
BG (mmol/L) Measurements	0830	5.3	0830	3.8	0830	2.9	0830	3.6
	1230	7.3	1230	9.6	1230	9	1200	7.3
	1730	3.2	1715	9	1715	8	1715	8.1
	2200	4.9	2215	4.9	2000	4.3	2000	8.9

Administered dose:

Mixtard 20% 08:30	**Mixtard 20% 17:15**
42 U	**36 U**

Advice 1:

25 U	**25 U**

Q1: Compared with the administered dose, is the advice more likely to improve overall control?

No					**Yes**
0	1	2	3	4	5

Q2: Compared with the administered dose, is the advice more likely to reduce the frequency of hypoglycaemia?

No					Yes
0	1	2	3	4	5

Q3: Compared with the administered dose, is the advice more likely to reduce the frequency and duration of hyperglycaemia?

No					Yes
0	1	2	3	4	5

Q4: Compared with the administered dose, would you be more likely to advise the new dose?

No					Yes
0	1	2	3	4	5

Advice 2:

38 U	**34 U**

Q1: Compared with the administered dose, is the advice more likely to improve overall control?

No					Yes
0	1	2	3	4	5

Q2: Compared with the administered dose, is the advice more likely to reduce the frequency of hypoglycaemia?

No					Yes
0	1	2	3	4	5

Q3: Compared with the administered dose, is the advice more likely to reduce the frequency and duration of hyperglycaemia?

No					Yes
0	1	2	3	4	5

Q4: Compared with the administered dose, would you be more likely to advise the new dose?

No					Yes
0	1	2	3	4	5

Advice 3:

44 U	34 U

Q1: Compared with the administered dose, is the advice more likely to improve overall control?

No					Yes
0	1	2	3	4	5

Q2: Compared with the administered dose, is the advice more likely to reduce the frequency of hypoglycaemia?

No					Yes
0	1	2	3	4	5

Q3: Compared with the administered dose, is the advice more likely to reduce the frequency and duration of hyperglycaemia?

No					Yes
0	1	2	3	4	5

Q4: Compared with the administered dose, would you be more likely to advise the new dose?

No					Yes
0	1	2	3	4	5

Subject Id 16

Demographic Data:

No	Sex	Age (yr)	Duration of diabetes (yr)	Daily CHO intake (g)	BMI (kg/m^2)	Fasting BG (mmol/L)	Fasting C-peptide (pmol/L)	HbA_{1c} (%)
16	F	60	5	140-185	34.4	6.7	280	8.7

Meal timing and amounts; BG measurements:

	Day1 Time	Data	Day2 Time	Data	Day3 Time	Data
Meals CHO (g)	0800	60	0830	60	0830	50
	1230	30	1100	20	1530	30
	1400	10	1345	30	1800	30
	1900	75	1900	65	1930	30
			2000	10		
BG (mmol/L) Measurements	0720	7.4	0810	8	0800	8.7
	1130	8.2	1330	6.9	1500	6.9
	1815	7.3	1800	9.3	1830	10
	2315	9.8	2355	9	2215	9.5

Administered dose:

Intermediate 07:30	**Intermediate 18:00**
26 U	**24 U**

Advice 1:

30 U	**26 U**

Q1: Compared with the administered dose, is the advice more likely to improve overall control?

No					**Yes**
0	1	2	3	4	5

Q2: Compared with the administered dose, is the advice more likely to reduce the frequency of hypoglycaemia?

No					**Yes**
0	1	2	3	4	5

Q3: Compared with the administered dose, is the advice more likely to reduce the frequency and duration of hyperglycaemia?

No					Yes
0	1	2	3	4	5

Q4: Compared with the administered dose, would you be more likely to advise the new dose?

No					Yes
0	1	2	3	4	5

Advice 2:

42 U	25 U

Q1: Compared with the administered dose, is the advice more likely to improve overall control?

No					Yes
0	1	2	3	4	5

Q2: Compared with the administered dose, is the advice more likely to reduce the frequency of hypoglycaemia?

No					Yes
0	1	2	3	4	5

Q3: Compared with the administered dose, is the advice more likely to reduce the frequency and duration of hyperglycaemia?

No					Yes
0	1	2	3	4	5

Q4: Compared with the administered dose, would you be more likely to advise the new dose?

No					Yes
0	1	2	3	4	5

Advice 3:

28 U	26 U

Q1: Compared with the administered dose, is the advice more likely to improve overall control?

No					Yes
0	1	2	3	4	5

Q2: Compared with the administered dose, is the advice more likely to reduce the frequency of hypoglycaemia?

No					Yes
0	1	2	3	4	5

Q3: Compared with the administered dose, is the advice more likely to reduce the frequency and duration of hyperglycaemia?

No					Yes
0	1	2	3	4	5

Q4: Compared with the administered dose, would you be more likely to advise the new dose?

No					Yes
0	1	2	3	4	5

Subject Id 19

Demographic Data:

No	Sex	Age (yr)	Duration of diabetes (yr)	Daily CHO intake (g)	BMI (kg/m^2)	Fasting BG (mmol/L)	Fasting C-peptide (pmol/L)	HbA_{1c} (%)
19	F	69	28	170-200	27.4	4.5	1330	7.2

Meal timing and amounts; BG measurements

	Day1		Day2		Day3		Day4	
	Time	Data	Time	Data	Time	Data	Time	Data
Meals CHO (g)	0845	40	0815	40	0820	45	0015	20
	1030	10	1000	15	1215	40	0845	40
	1130	45	1300	55	1300	15	1215	55
	1910	40	1910	50	1915	72	1900	80
	2345	35	2000	10			2330	10
BG (mmol/L) Measurements	0815	5.1	0750	4.3	0800	3.9	0800	4.2
	1320	4.3	1230	4.8	1145	3.1	1200	5.8
	1830	11	1845	6.9	1830	5.2	1835	4.1
	2330	4.4	2345	15	2350	8.8	2310	10.6

Administered dose:

Intermediate	**08:30**	**Intermediate**	**19:00**
15 U		**15 U**	

Advice 1:

14 U	**14 U**

Q1: Compared with the administered dose, is the advice more likely to improve overall control?

No					**Yes**
0	1	2	3	4	5

Q2: Compared with the administered dose, is the advice more likely to reduce the frequency of hypoglycaemia?

No					Yes
0	1	2	3	4	5

Q3: Compared with the administered dose, is the advice more likely to reduce the frequency and duration of hyperglycaemia?

No					Yes
0	1	2	3	4	5

Q4: Compared with the administered dose, would you be more likely to advise the new dose?

No					Yes
0	1	2	3	4	5

Advice 2:

15 U	15 U

Q1: Compared with the administered dose, is the advice more likely to improve overall control?

No					Yes
0	1	2	3	4	5

Q2: Compared with the administered dose, is the advice more likely to reduce the frequency of hypoglycaemia?

No					Yes
0	1	2	3	4	5

Q3: Compared with the administered dose, is the advice more likely to reduce the frequency and duration of hyperglycaemia?

No					Yes
0	1	2	3	4	5

Q4: Compared with the administered dose, would you be more likely to advise the new dose?

No					Yes
0	1	2	3	4	5

Advice 3:

11 U	5 U

Q1: Compared with the administered dose, is the advice more likely to improve overall control?

No					Yes
0	1	2	3	4	5

Q2: Compared with the administered dose, is the advice more likely to reduce the frequency of hypoglycaemia?

No					Yes
0	1	2	3	4	5

Q3: Compared with the administered dose, is the advice more likely to reduce the frequency and duration of hyperglycaemia?

No					Yes
0	1	2	3	4	5

Q4: Compared with the administered dose, would you be more likely to advise the new dose?

No					Yes
0	1	2	3	4	5

V. Publications

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Computer Methods and Programs in Biomedicine

DIAS–NIDDM—a model-based decision support system for insulin dose adjustment in insulin-treated subjects with NIDDM

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Abstract

A decision support system has been developed, Diabetes Insulin Advisory System for patients with non-insulin dependent diabetes mellitus (DIAS–NIDDM), assisting in the adjustment of insulin doses in insulin-treated subjects. DIAS–NIDDM uses a causal probabilistic network (CPN) model of carbohydrate metabolism to make stochastic predictions of blood glucose (BG) excursions. The CPN model is an extension of an existing model with an added component representing endogenous insulin secretion. A linear relationship between BG and insulin concentration due to BG stimulated insulin secretion is assumed. Model parameters (pancreatic sensitivity, insulin sensitivity, and time-to-peak of NPH insulin) are estimated by Bayesian probability updating from patient's specific data (food intake, insulin doses, BG measurements) recorded over a period of 4 days. The estimated parameters allow the system to be potentially used as a diagnostic tool to identify abnormalities of carbohydrate metabolism: impaired insulin secretion, insulin resistance and the severity of the impairments. DIAS–NIDDM was used to predict patient-specific BG profiles and advise on insulin doses during a pilot study in eight patients with NIDDM of whom five were treated with insulin. Compared to the administered insulin amount, daily insulin amount advised by DIAS–NIDDM was similar (within 4 U) in three patients, higher by 20% (19 U) in one patient and lower by 40% (18 U) and 50% (11 U) in two patients, respectively. The inter-day coefficient of variation of the daily insulin advice suggests that, at least according to DIAS–NIDDM criteria, day-to-day adjustment of insulin doses is necessary to maintain optimum control.

Abbreviations: BG, blood glucose concentration; CHO, carbohydrate amount in meals; CPN, causal probabilistic network; DCCT, Diabetes Control and Complication Trial; DIAS, the Diabetes Advisory System; DIAS–NIDDM, the Diabetes Advisory System for NIDDM; GUT_{ABS}, gut absortion; I_{ABS}, insulin absorption; IDDM, insulin dependent diabetes mellitus; IIT, intensive insulin therapy; IR, insulin resistance; is, insulin sensitivity parameter; I_{SEC}, insulin concentration due to endogenous secretion; IT, information technology; NIDDM, non-insulin dependent diabetes mellitus; nph, time-to-peak of NPH insulin; NPH, intermediate acting insulin; OD, overt diabetes; ps, pancreatic sensitivity parameter.

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Keywords: Bayesian networks; Causal probabilistic networks; Model-based decision support systems; Decision making; Carbohydrate metabolism; Non-insulin dependent diabetes mellitus

1. Introduction

Non-insulin dependent diabetes mellitus (NIDDM) is a heterogeneous disorder characterised by insulin deficiency due to β-cell failure often associated with insulin resistance [1] and accounts for $\sim 85\%$ of all cases of diabetes in the developed countries. Though in the early stages of their disease the patients with NIDDM achieve adequate glycaemic control with diet alone or hypoglycaemic agents, as the disease progresses up to 50% patients may require insulin treatment [2]. A personal series of 4926 patients with NIDDM documented that as the treatment stabilized, 24% of the patients were treated by insulin injections, 44% by tablets, and 32% by diet only [3]. Intensive insulin therapy (IIT) can help in achieving excellent glycaemic control in patients with NIDDM for whom standard pharmacological therapy has failed [4].

The research and development of computer applications that assist with the control of blood glucose in subjects with insulin dependent diabetes mellitus (IDDM) and NIDDM is highly motivated by the Diabetes Control and Complication Trial (DCCT) [5]. Results clearly prove that IIT delays the onset and slows the progression of the long-term complications associated with IDDM. The results are likely to apply to NIDDM [6]. Information technology (IT) can assist in the transfer of expertise from specialist diabetes centres to primary care physicians and directly to the diabetic patient according to the requirements of St. Vincent Declaration [7] bringing along the benefits of IIT documented in DCCT. The potential impact of computer-assisted insulin dosage adjustment or just computer-assisted monitoring is of clinical importance and justifies further research despite sceptical views by some health care professionals and, currently, the limited availability of these systems for patients.

For obvious reasons, the research has focused mainly on delivering decision support for patients with IDDM [8]. The perceived need for decision support with insulin treatment in NIDDM is low due to the treatment alternatives and may be associated with the reluctance of clinicians to prescribe insulin. However, recent results have shown increased interest in the use of insulin for patients with NIDDM alone or in combination with tablets [9]. IIT improved glycaemic control in young patients with NIDDM, especially in patients who changed more often the daily insulin dose. Given the higher prevalence of NIDDM and the benefits associated with improved blood glucose (BG) control documented by DCCT, decision support systems may attain an important role in the treatment of patients with NIDDM.

This paper describes a model of insulin concentration due to BG stimulated insulin secretion and its inclusion in the Diabetes Advisory System (DIAS). The extended DIAS system, DIAS–NIDDM, is able to assist in insulin dose adjustment in insulin-treated subjects with NIDDM. A pilot study was performed to compare the advice given by DIAS–NIDDM with the administered therapy. A number of case studies exemplify the clinical use of DIAS–NIDDM on selected data sets and illustrate the potential ability of DIAS–NIDDM to quantify the physiological abnormalities present in NIDDM.

2. Diabetes Advisory System used in insulin-dose adjustment of patients with non-insulin dependent diabetes mellitus (DIAS–NIDDM)

2.1. DIAS

The DIAS contains a model of carbohydrate metabolism implemented as a causal probabilistic network (CPN) [10,11], and is able to simu-

late BG profiles in response to given carbohydrate input and insulin doses in patients with IDDM [12]. Clinical trials performed with DIAS have shown that the mean predictive accuracy is 2.8 mmol/l [13]. The advice on insulin doses can be generated [10] and tests of the safety of administering the advised doses have been performed [13].

2.2. DIAS–NIDDM: overview

DIAS–NIDDM is a PC-based system which models the dynamics of the blood glucose for subjects with NIDDM given (i) carbohydrate content of meals and, optionally, (ii) insulin doses.

DIAS–NIDDM inherits much of DIAS features [10] and is based on an extended, discrete-time, discrete-state CPN model of carbohydrate metabolism including a component representing endogenous insulin secretion.

In DIAS, the discrete time CPN model is implemented with a time step of one hour. Due to the feedback loop introduced by representing endogenous insulin secretion [14], a 30-min time step was adopted in DIAS–NIDDM to improve stability of the predictions. The shorter time step and the addition of the secretion model rendered the CPN model too complex to be manipulated by standard methods of Bayesian updating implemented in the CPN shell HUGIN [15]. The repetitive design of the DIAS network was found particularly suitable to be implemented as a dynamic CPN [16] and the benefit in computational time and memory space offered by this approach determined its adoption for the implementation of DIAS–NIDDM [14].

The CPN model of insulin action has been simplified in DIAS–NIDDM by expressing the endogenous glucose balance (hepatic glucose production minus insulin dependent uptake by the liver and peripheral tissues and insulin independent uptake by the brain tissues) as a linear function of active insulin and BG avoiding the need to represent explicitly insulin-dependent and insulin-independent utilisation of BG in the network [17]. The conditional probability table describing the endogenous glucose balance was generated numerically using a specialised tool [18].

2.3. DIAS–NIDDM: model parameters

DIAS–NIDDM includes three parameters to represent inter-individual differences in carbohydrate metabolism and insulin absorption. These parameters are: (i) pancreatic sensitivity (*ps*), (ii) insulin sensitivity (*is*), and (iii) time-to-peak of the absorption of intermediate-acting NPH insulin (*nph*).

The *ps* parameter represents the post-prandial (post-meal) ability of BG to stimulate insulin secretion. This parameter controls insulin secretion and reflects the degree of impaired insulin secretion. The *is* parameter represents the ability of plasma insulin to control glucose metabolism. The ability is expressed relative to that of the normal subject. The time at which absorption of insulin from an NPH injection attains its peak value is represented by the time-to-peak of the *nph* parameter.

The first parameter, *ps*, is a new parameter, the other two parameters, *is* and *nph*, have already been present in the DIAS system. The parameters are estimated from patient's specific data (food intake, insulin doses, BG measurements) recorded over a period of 4 days by Bayesian probability updating.

2.4. DIAS–NIDDM: dynamic probability updating

DIAS–NIDDM uses a discrete-time model of carbohydrate metabolism. The probability distribution associated with blood glucose concentration is calculated every 30 min using, repetitively, a CPN slice (Fig. 1) in a dynamic fashion. The process is initiated using an uninformative a priori distribution for BG. The calculations start 6 h prior to the beginning of the period of interest to allow BG to converge from the uninformative distribution [14].

The CPN slice has three nodes: blood glucose concentration at time T (BG_{+0}), active insulin at time T (I_{+0}), and blood glucose concentration at time T_{+30} min (BG_{+1}). The deterministic models

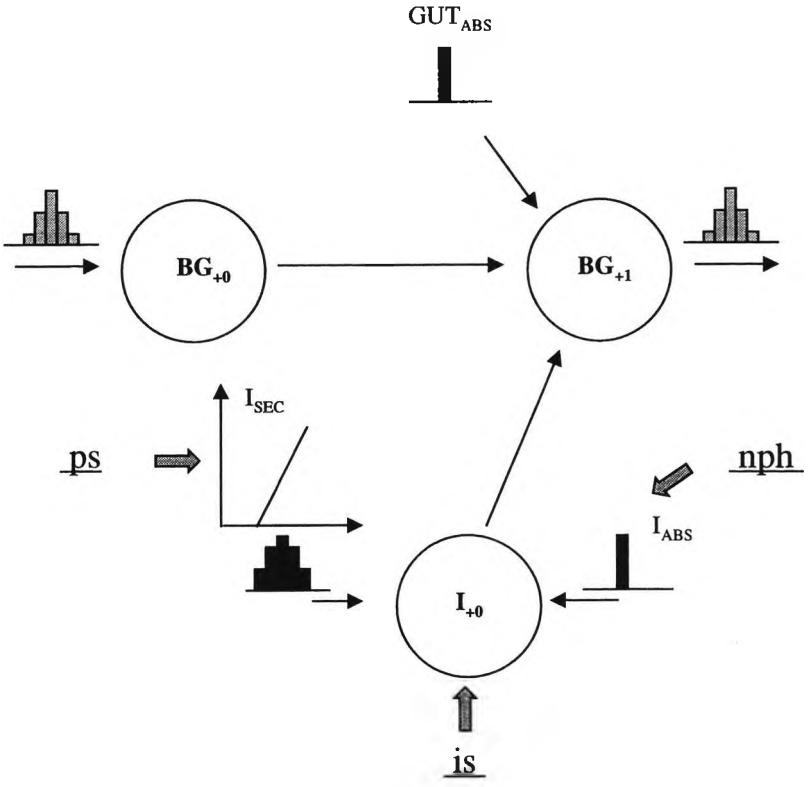

Fig. 1. Discrete-time stochastic model of CHO metabolism (30 min time step) implemented in DIAS–NIDDM. The variables in the system are represented as probability distributions. The model has three parameters: pancreatic sensitivity (*ps*), insulin sensitivity (*is*) and time-to-peak of NPH insulin (*nph*) and predicts BG at T_{+30} min (BG_{+1}) from BG at time T (BG_{+0}). For description of other variables, see text.

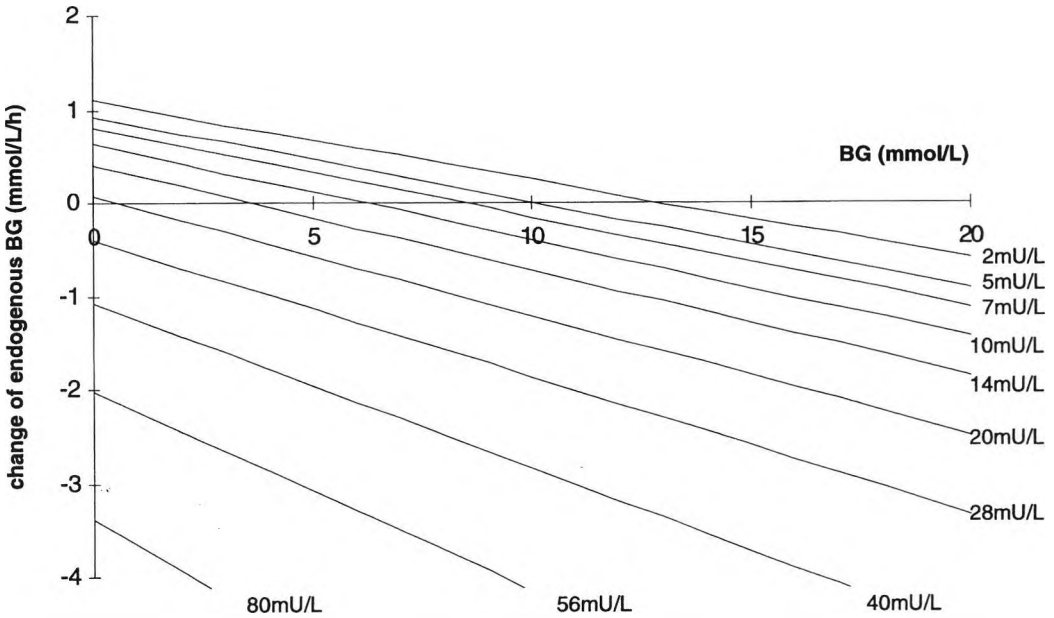

Fig. 2. The linear model of insulin action. The lines represent the change in endogenous glucose concentration per unit time for various concentrations of active insulin.

of insulin absorption [10,19,20] and gut absorption [10,21] compute insulin absorption (I_{ABS}) and gut absorption (GUT_{ABS}) during the period $T-T_{+30}$ min according to the insulin injections and T_{+30} min according to the insulin injections and carbohydrate intake, respectively. The insulin concentration (I_{SEC}) is the contribution to plasma insulin due to BG stimulated endogenous insulin secretion and fasting insulin concentration.

Informally, the Bayesian updating proceeds in the following way. The probability distribution of BG at time T is inserted into the node BG_{+0}. Endogenous insulin concentration (I_{SEC}) is calculated as a probability distribution. Insulin appearance due to exogenous insulin injections I_{ABS} (discrete value) is added to I_{SEC} to obtain the total plasma insulin. The total insulin is scaled by the *is* parameter and is inserted into the active insulin node (I_{+0}) (in fact, a joint probability distribution $p(BG_{+0}, I_{+0})$ is calculated as BG_{+0} and I_{+0} are dependent). The model of insulin action calculates the change in the probability distribution of endogenous BG per unit time. The change in endogenous BG represents the endogenous appearance (hepatic glucose production) minus the endogenous disappearance (insulin and non-insulin dependent glucose uptake) and depends on BG itself and the active insulin concentration (Fig. 2).

The contribution from gut absorption GUT_{ABS} (discrete value) is added to obtain the probability distribution of the BG at time T_{+30} (BG_{+1}). The mean and standard deviation of BG_{+1} are computed and displayed on the screen. The time is incremented and the probability distribution of BG_{+1} is inserted into BG_{+0} node and the whole process is repeated.

Detailed description of the process and the calculation of a posteriori probability distributions of parameters can be found elsewhere [14].

2.5. DIAS–NIDDM: system functions and performance

DIAS–NIDDM can be run in three modes: (i) learning (parameter estimation), (ii) predicting and (iii) advising. In the learning mode, the parameter estimation is performed using data collected during the selected period. The estimated parameters are used in the prediction mode to predict a 24-h BG profile for given food intake and insulin doses. Finally, in the advisory mode the system proposes insulin doses that result in the most favourable BG profile (in terms of a risk function [11]) for a given food intake.

When run on a PC under Windows 95 with a 133MHz Intel 80486 processor, learning over 24 h takes ~5–9 s, learning over 4 days ~9–20 s, simulation of a 24-h BG profile ~4 s, and advice generation 15–25 s for a regimen that consists of three injections. DIAS–NIDDM is implemented in the C++ language.

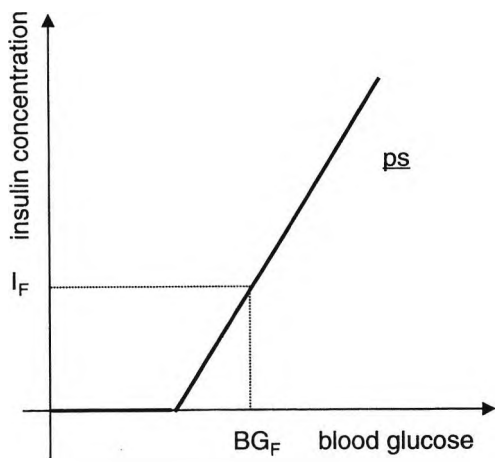

Fig. 3. The linear model of insulin secretion is fully specified by fasting blood glucose (BG_F), fasting insulin concentration (I_F) and pancreatic sensitivity (*ps*).

3. Model of endogenous insulin secretion

The rise in the concentration of blood glucose following, for instance, meal digestion stimulates insulin secretion by the pancreas. During its first-pass through the liver, ~50% of insulin is extracted. Another peptide, C-peptide, is co-secreted with insulin in an equimolar ratio, but unlike insulin, C-peptide is not cleared by the liver to any significant extent [22,23].

In insulin-treated patients with NIDDM, plasma insulin includes a component due to endogenous insulin secretion and a component due to insulin injections (exogenous insulin). However, plasma C-peptide concentration is only due to endogenous

Table 1
Demographic data

Id	Sex	Age (years)	Duration of diabetes (years)	Treatment	Daily CHO intake (g)	BMI (kg/m^2)	Fasting BG (mmol/l)	Fasting C-peptide (pmol/l)	HbA_{1c} (%)
10	M	66	10	Diet	270–290	23.5	6.3	110	7.9
11a	M	61	8	Insulin	210–260	24.0	11.0	0	7.0
11b	M	61	8	Insulin	250–350	24.4	4.2	510	7.0
11c	M	62	9	Insulin	340–280	25.0	11.0	0	7.3
12	F	66	11	Insulin	80–160	28.5	4.2	0	7.7
13	M	64	14	Insulin	140–165	27.4	9.6	710	7.1
16	F	60	5	Insulin	140–185	34.4	6.7	280	8.7
18	M	54	1	Diet	255–330	21.7	6.4	240	6.8
19	F	69	28	Insulin	170–200	27.4	4.5	1330	7.2
31	M	74	5	Hypo-agent	260–280	25.8	6.7	240	7.5

Table 2
Parameters (mean ± SD) estimated from data (BG, food intake, insulin injections) collected over a period of up to 4 days

Id	Data collection (day)	Pancreatic sensitivity (mU/l per mmol/l)	Insulin sensitivity (—)	Time-to-peak of NPH (h)	Inter-day variability of *ps* (%)[a]	Inter-day variability of *is* (%)[a]	DIAS–NIDDM suggested diagnosis
10	4	6.1 ± 2.7	1.1 ± 0.3	NA	17	14	IS
11a	4	1.5 ± 2.2	1.0 ± 0.0	7.3 ± 2.4	18	12	IS
11b	4	1.6 ± 0.7	0.7 ± 0.0	8.2 ± 2.1	59	29	IS
11c	4	10.1 ± 0.0	1.0 ± 0.0	5.6 ± 1.8	48	14	?
12	4	4.9 ± 2.5	0.6 ± 0.1	5.0 ± 3.0	20	29	OD
13	4	6.2 ± 3.4	0.4 ± 0.0	9.8 ± 2.8	18	11	OD
16	3	3.4 ± 1.6	0.4 ± 0.0	8.0 ± 3.2	7	0	OD
18	4	7.8 ± 2.3	1.2 ± 0.3	NA	4	14	?
19	4	0.0 ± 0.0	0.4 ± 0.0	9.1 ± 2.6	58	10	OD
31	4	8.3 ± 2.1	1.2 ± 0.2	NA	14	10	?
Mean ± SD	—	5.0 ± 3.3	0.8 ± 0.4	8.0 ± 1.6	26 ± 21	14 ± 9	—

IS, impaired secretion; IR, insulin resistance; OD, overt diabetes (OD means both IS and IR).
Typical DIAS–NIDDM values for a normal individual are $ps = 8$ mU/l per mmol/l and $is = 1$.
[a] Expressed as a coefficient of variation.

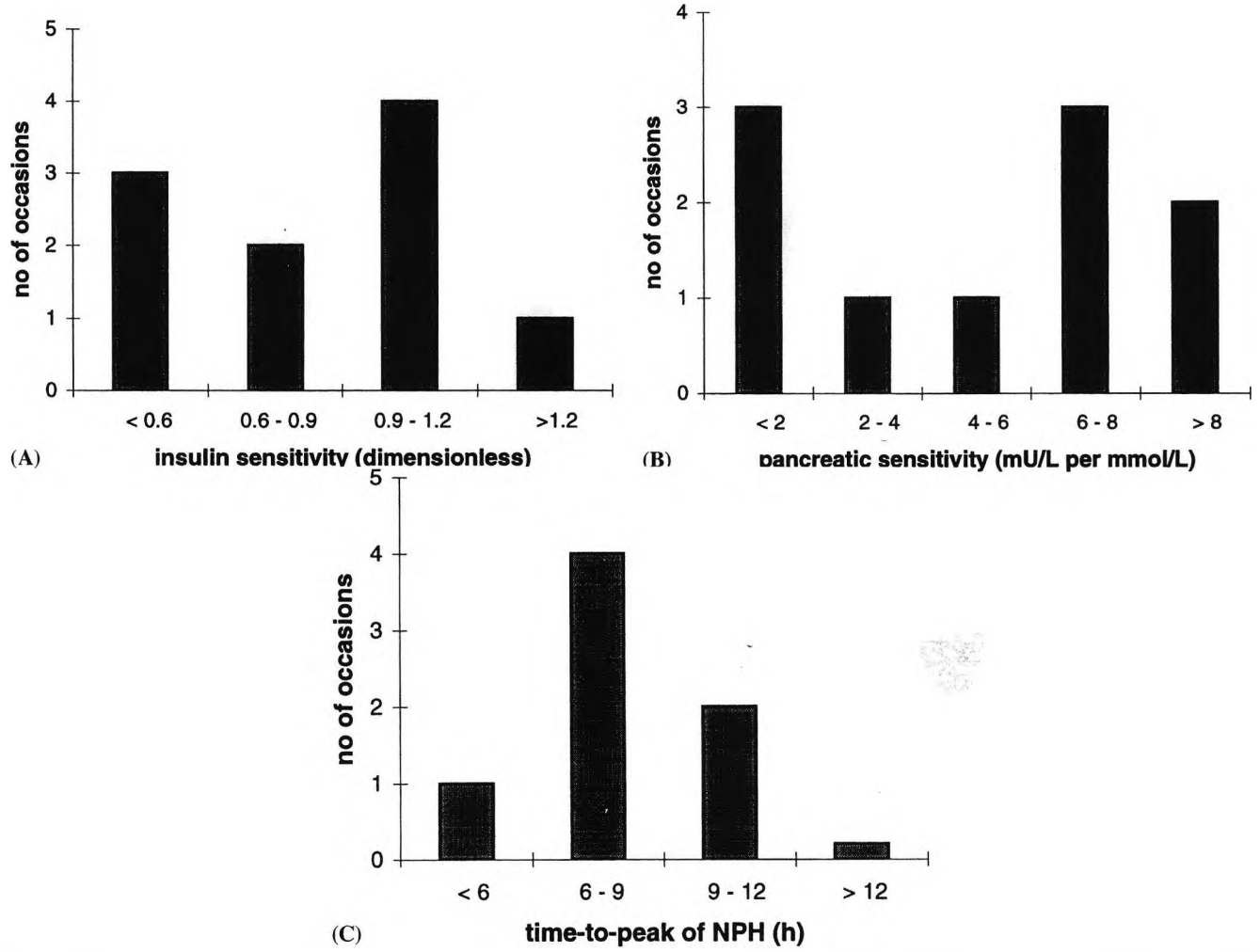

Fig. 4. Frequency histograms of mean values of parameter estimates: (A) insulin sensitivity, (B) pancreatic sensitivity, and (C) time-to-peak of NPH insulin.

Table 3
Root mean square (RMS) error of the prediction error and the correlation between the estimated parameters

Id	RMS (mmol/l)	Correlation		
		ps vs. *is*	*ps* vs. *nph*	*is* vs. *nph*
10	0.8	−0.8	0.0	0.0
11a	2.7	−0.4	0.2	0.2
11b	3.3	−0.5	0.3	0.1
11c	3.6	0.0	0.0	0.0
12	1.5	−0.9	0.0	0.0
13	2.4	0.0	0.0	0.0
16	1.2	0.0	0.0	0.0
18	2.1	−0.7	0.0	0.0
19	3.8	0.0	0.0	0.0
31	1.6	−0.5	0.0	0.0
Mean ± SD	2.3 ± 1.0	−0.4 ± 0.3	0.0 ± 0.0	0.0 ± 0.0

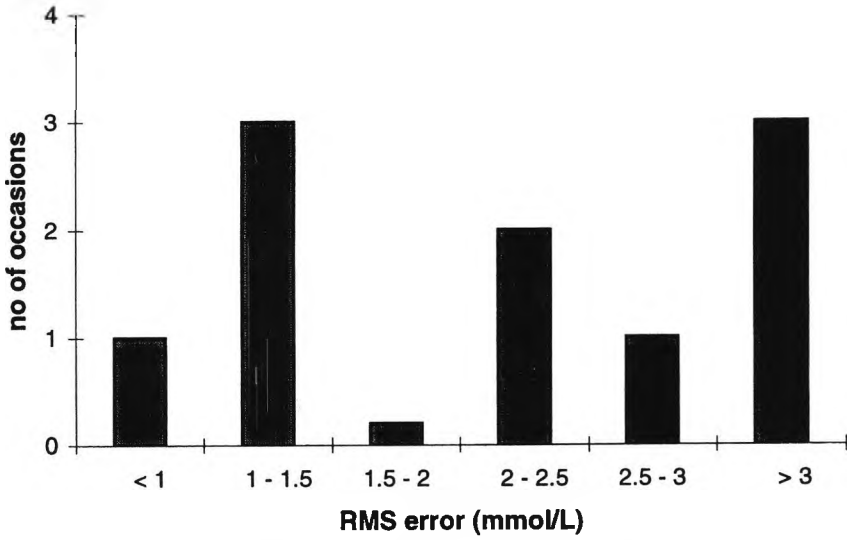

Fig. 5. Frequency histogram of the RMS error.

secretion and can be, therefore, used to obtain information about pre-hepatic (i.e. prior to the first-pass through the liver) insulin secretion.

During a meal tolerance test (MTT), C-peptide secretion rate has been shown to be linearly related to the concentration of blood glucose [24]. We, therefore, assume that this linear relationship holds between BG concentration and insulin secretion in our model. It is also assumed that plasma insulin concentration due to endogenous insulin secretion is linearly related to BG concentration. This is based on the observations that insulin kinetics in the plasma are linear at least in the lower physiological range of insulin concentration [25] and that plasma insulin equilibrates quickly compared to the time steps used in DIAS systems [11]. The model of endogenous insulin concentration due to the BG stimulated insulin secretion is fully specified by (i) one measurement, fasting blood glucose concentration (BG_F), (ii) one derived value, fasting plasma insulin concentration (I_F), and (iii) one parameter, *ps*, see Fig. 3.

The fasting C-peptide secretion rate is calculated from the fasting C-peptide concentration using a population model of C-peptide kinetics [26]. The fasting insulin secretion rate is assigned half of the value of the fasting C-peptide secretion rate assuming 50% first-pass hepatic extraction of insulin [27]. The fasting insulin concentration due to endogenous insulin secretion is computed from the fasting insulin concentration using a standard conversion factor (1 mU/l = 1 mU/kg per h). The *ps* parameter represents the β-cell responsiveness to BG levels elevated above the fasting BG level, BG_F.

Formally, insulin concentration due to endogenous insulin secretion is calculated as

$$I_{SEC} = I_F + (BG - BG_F)\, ps$$

and is constrained to non-negative values.

4. Pilot study

4.1. Subjects

Eight patients with non-insulin dependent diabetes mellitus and good glycaemic control ($HbA_{1c} < 9\%$) were selected from the diabetic clinic at St Thomas' Hospital, London. Demographic patient data are shown in Table 1. One insulin-treated subject participated on three separate occasions in the study. Two subjects were treated by diet alone, one subject by an oral anti-diabetic agent (Glibenclamide, 2.5 mg daily), and five subjects by insulin.

The subjects collected data over four consecutive days performing home blood glucose monitoring using a blood glucose meter and recording four BG measurements per day three before meals and one at bedtime. The subjects also recorded composition

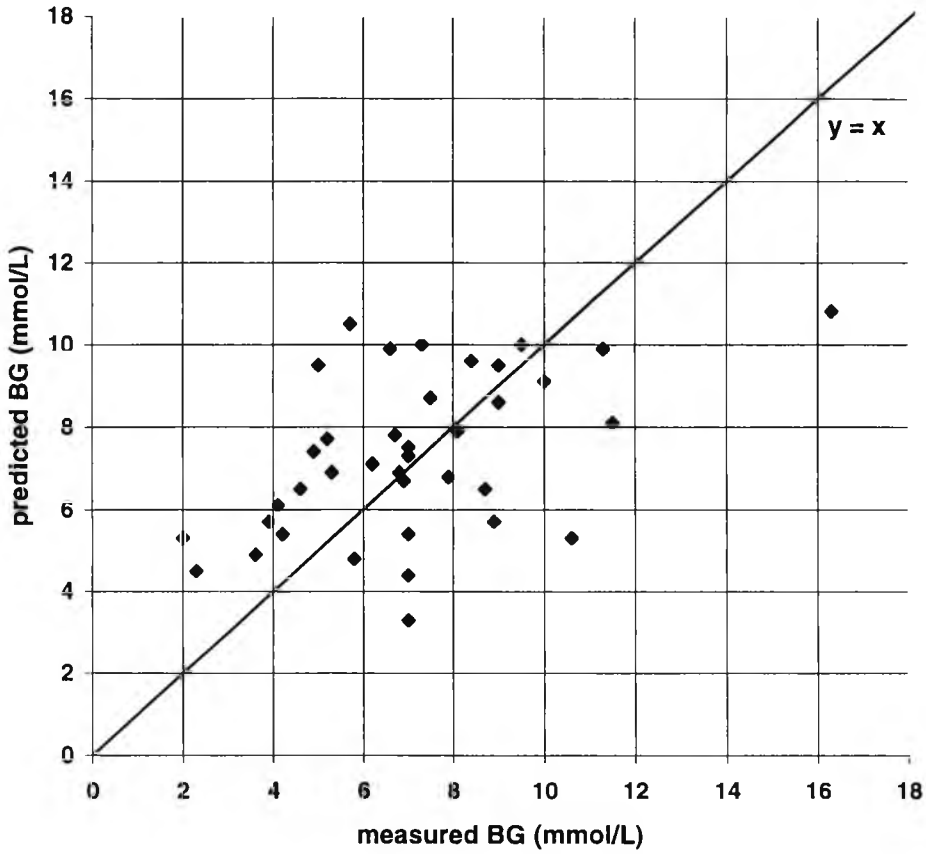

Fig. 6. Relationship between mean predicted BG and measured BG during the last day of data collection. DIAS–NIDDM predicted BG using parameters learnt from all but the last-day data. Results from all subjects are shown.

Table 4
Total insulin doses during the study period (administered therapy) and the daily insulin doses as suggested by DIAS–NIDDM (DIAS–NIDDM advice)[a]

Id	Administered therapy (U)	DIAS–NIDDM advice (U)	Inter-day variability of DIAS–NIDDM advice (%)[b]
11a	29	27	5
11b	29	30	13
11c	27	31	17
12	22	11	27
13	78	50	20
16	50	69	36
19	30	30	17

[a] The latter was obtained as an average of advice given on each day. The inter-day variability of the advice has been assessed by calculating the coefficient of variation (CV).
[b] Expressed as a coefficient of variation.

and timing of meals. Dietician subsequently calculated carbohydrate content of the meals.

4.2. Data analysis and results

Periods with high values of BG following hypoglycaemic episodes were identified and discarded to remove the effect of glucose counter-regulation on parameter estimation. Glucose counter-regulation [28] is a mechanism that induces hyperglycaemia and is triggered by a hypoglycaemic episode. In total, one 24-h period was discarded.

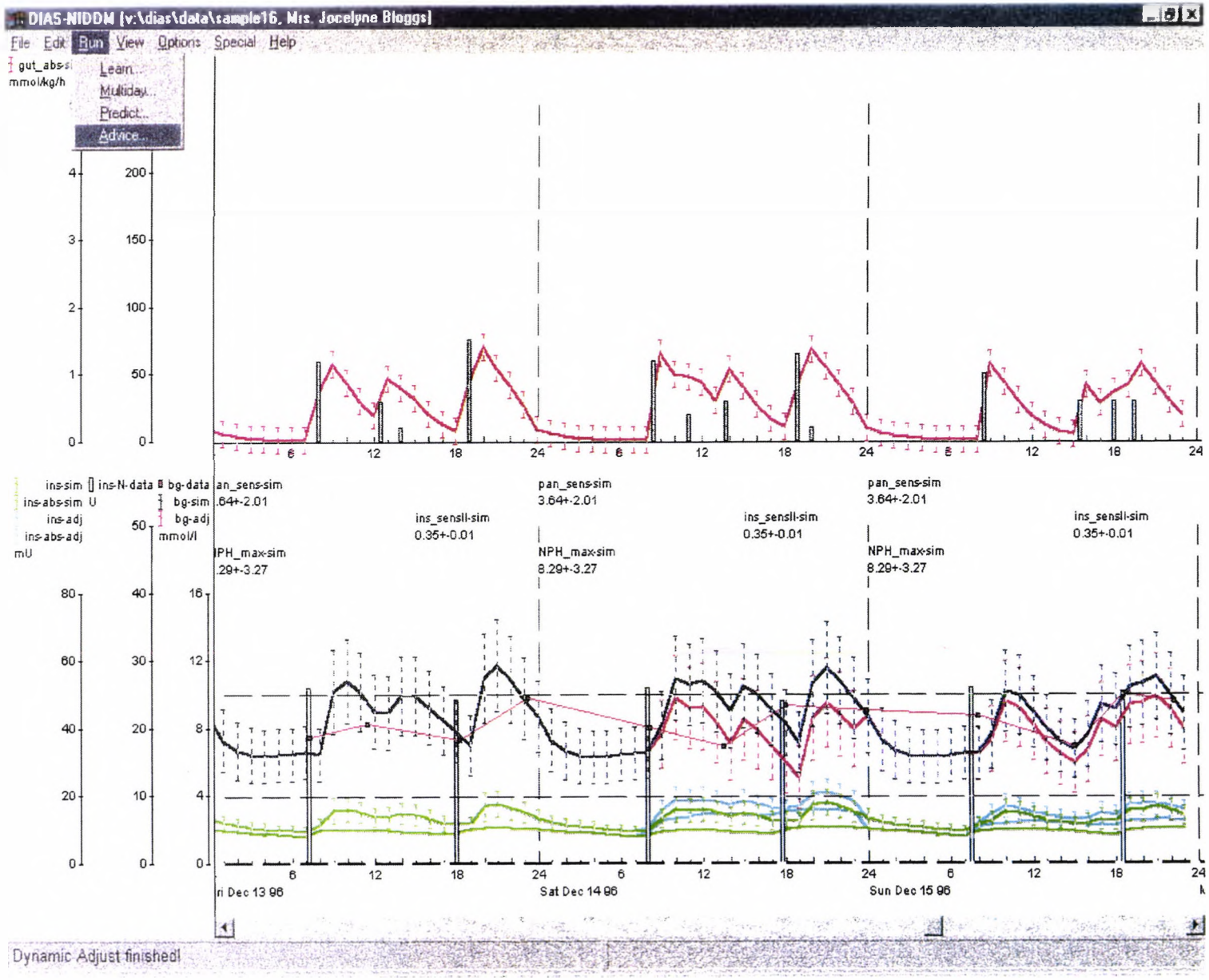

Fig. 7. Front end of DIAS–NIDDM. Top panel: CHO content of meals (grey bar) and gut absorption (red line). Bottom panel: NPH insulin injections (black bar), BG measurements collected from December 13–15 (squares joined by red line), predicted BG profile (blue line), BG profile associated with the advised doses (red line), active and absorbed insulin (green lines for simulation, turquoise for advice) and parameter values. Profiles are represented as mean ± SD.

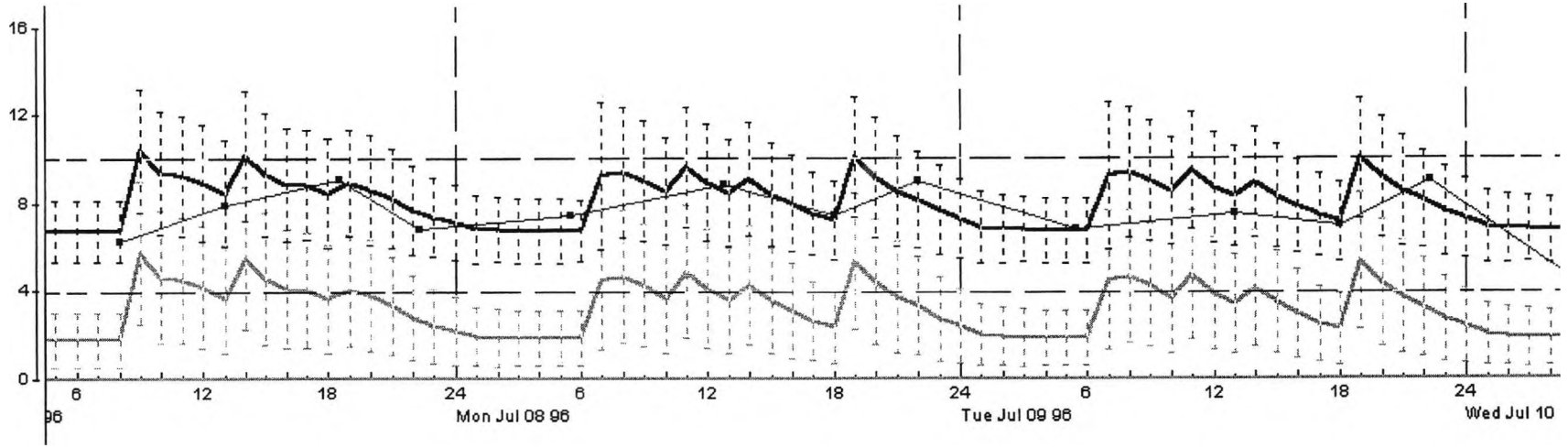

Fig. 8. Predicted BG profile (top line) and active insulin concentration (bottom line) for a subject on diet alone (Id 10).

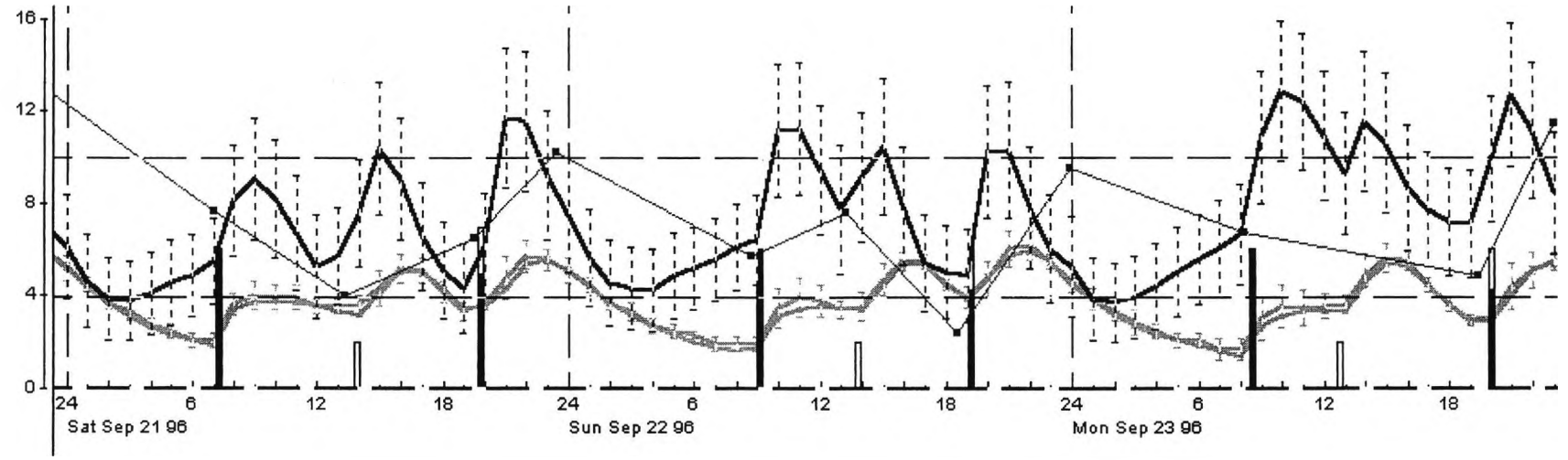

Fig. 9. Predicted 3-day BG and insulin (active and absorbed) profiles for subject (Id 11a) treated by intermediate-acting insulin in the morning (black bar), soluble insulin before lunch (white bar) and pre-mixed soluble and intermediate-acting insulin before dinner (black bar).

DIAS–NIDDM was run in the parameter estimation mode and estimated the joint a posteriori probability distribution of parameters $p(ps, is, nph \mid \mathbf{e})$ for each subject, where the evidence **e** included BG measurements recorded by the subject. The mean and SD of each parameter were calculated from marginal distributions, $p(ps \mid \mathbf{e})$, $p(is \mid \mathbf{e})$ and $p(nph \mid \mathbf{e})$, see Table 2.

The inter-day variability of parameters *is* and *ps* was assessed. DIAS–NIDDM was run to estimate $p(ps, is, nph \mid \mathbf{e})$ where **e** included evidence collected during a single day. The mean of marginal distributions $p(ps \mid \mathbf{e})$ and $p(is \mid \mathbf{e})$ was calculated and variability expressed as a coefficient of variation (CV) of the mean values, see Table 2.

The inter-patient variability of parameter estimates (mean of marginal distributions) were assessed by plotting frequency histograms (ranges were divided into suitable intervals), see Fig. 4.

The correlation between parameter estimates was calculated from the joint a posteriori probability distribution of parameters. DIAS–NIDDM was run in the prediction mode using the joint a posteriori probability distribution and the root mean square (RMS) error between predicted and measured blood glucose was computed (Table 3) and is shown as frequency histogram in Fig. 5.

The visual assessment of predictive accuracy can be obtained from Fig. 6. The mean predicted BG is plotted against the measured BG with the unity line included. The plot includes BG data from the last day of data collection. The predicted BG values were obtained using parameters learnt from all but the last-day data for each subject.

DIAS–NIDDM was run in the advising mode and advice on insulin doses was generated for each day. Total daily insulin doses were calculated and the inter-day variability of the advice assessed by calculating the CV. The mean of the daily insulin amounts for each subject is shown in Table 4 together with the administered treatment.

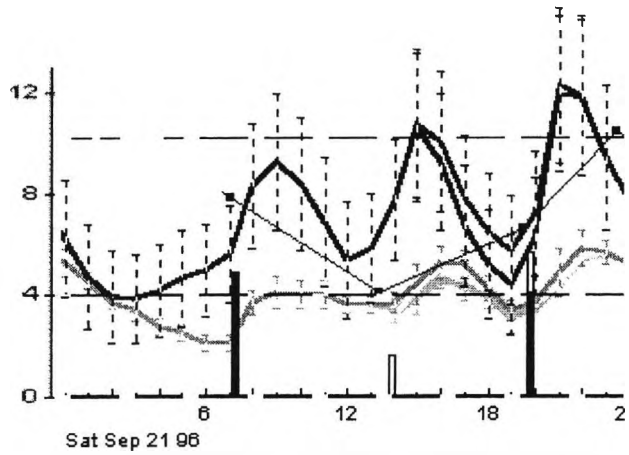

Fig. 10. Advised insulin doses (12, 3 and 14 U) in patient Id 11a result in a slightly raised BG profile. Administered therapy was (12, 4 and 14 U).

5. Case studies

The case studies exemplify the use of DIAS–NIDDM on selected data sets and demonstrate the physiological defects present in subjects with NIDDM (insulin resistance, impaired secretion).

A sample screen dump of DIAS–NIDDM showing data over a period of three days is given in Fig. 7. The CHO content of meals (grey bar) and the gut absorption (red line) are shown on the top panel. NPH injections (black bar), BG measurements (squares joined by red line), the predicted BG profile (blue line), the adjusted BG profile associated with the advised insulin doses (red line), active and absorbed insulin concentration (green line) and the values of the model parameters are shown on the bottom panel. Mean $\pm$ SD values are displayed for predicted and estimated quantities. Axes are presented on the left hand side, dashed vertical lines separate the 3 days.

5.1. Subject on diet alone (Id 10)

DIAS–NIDDM was run to estimate model parameters from data collected on July 7 and 8 and predicted BG on the same days (data fitting) and July 9 (forecasting), see Fig. 8. Pancreatic sensitivity was slightly reduced suggesting impaired secretion. Insulin sensitivity was normal suggesting that the subject is not insulin resistant.

The parameters were estimated with a large SD and, in consequence, BG profile was predicted with a large SD. Negative correlation between *is* and *ps* (-0.85) was present. Diet contained 260–280 g of carbohydrate daily and the post-prandial

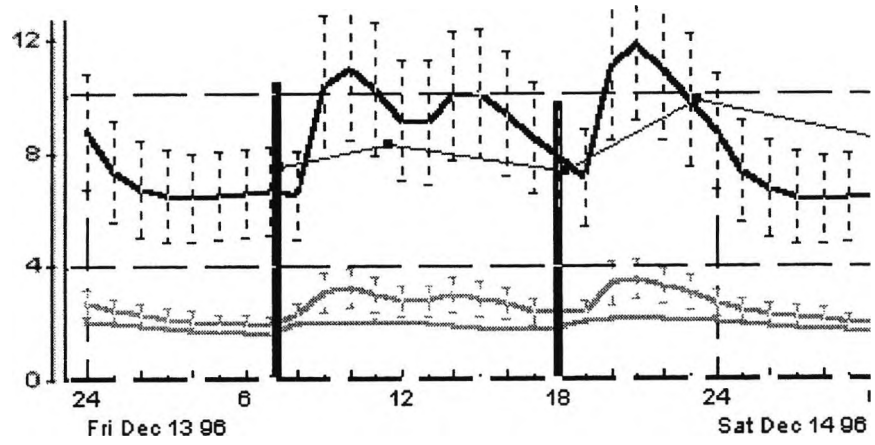

Fig. 11. Forecasting of the BG profile for a 24-h period in an insulin resistant subject, Id 16. Post-prandial raise in active insulin due to endogenous insulin secretion controls the BG levels following meal intake at 08:00 (60 g), 12:30 (30 g), 14:00 (10 g) and 19:00 (75 g).

rise in BG (below 9 mmol/l at all times) is still well controlled by the endogenous secretion. BG is predicted with high accuracy (RMS error 0.8 mmol/l).

5.2. Insulin-treated subject (Id 11a) on intermediate-acting insulin in the morning, short-acting insulin before lunch and pre-mixed insulin before dinner

The estimated insulin sensitivity parameter is in the normal range whereas pancreatic sensitivity is very low suggesting that impaired insulin secretion is the main defect of carbohydrate metabolism in this subject. In comparison with the previous case subject, CHO content of the diet is high, 220–250 g daily. Good control is achieved, but in this case by the administration of 28 U of daily exogenous insulin. The distribution of injections with short acting injection before lunch and before dinner seems to compensate well for the low pancreatic responsiveness. Observed BG data are within one SD of predicted BG (Fig. 9) except on September 22, 1900, when hypoglycaemia was not predicted. No immediate explanation of the hypoglycaemia is available. Unmodelled processes like exercise, stress or influence of alcohol, a missed meal, natural variability of blood glucose or an error in the BG measurement could explain the discrepancy between predicted and observed BG.

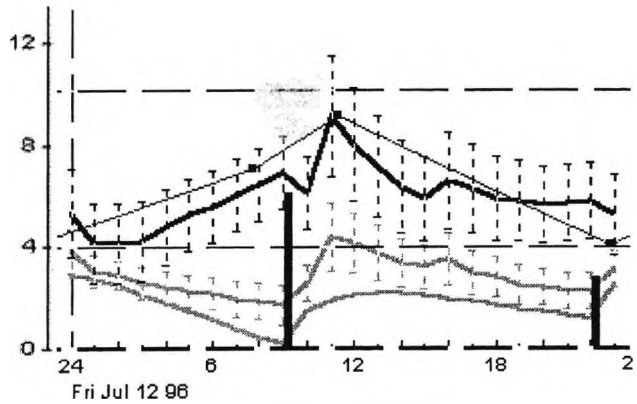

Fig. 12. Forecasting of the BG profile for a 24-h period for a subject with overt NIDDM (Id 12). Subject is on twice-daily intermediate-acting insulin (15 and 7 U).

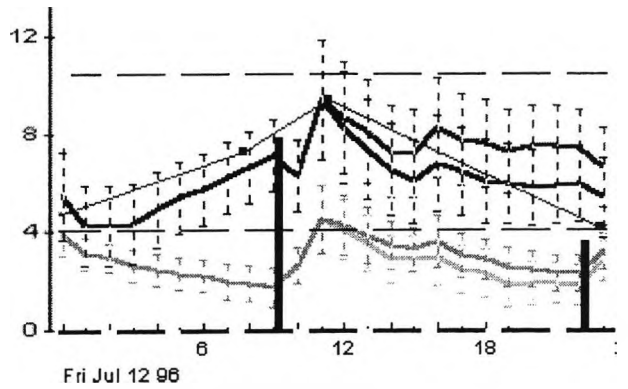

Fig. 13. In subject Id 12, DIAS–NIDDM reduced the daily dose by 40% (6 and 7 U) aiming at avoiding a low BG value at 23:00. Advised doses result in higher BG and lower active insulin profiles.

DIAS–NIDDM suggested a slight reduction in insulin doses (Fig. 10, the BG profile associated with the advised doses is higher).

5.3. Insulin-treated subject (Id 16) on twice-daily intermediate-acting insulin

The insulin sensitivity parameter suggests pronounced insulin resistance. The pancreatic sensitivity parameter suggests that insulin secretion is also impaired (overt diabetes). The prediction of 24-h BG profile is given in Fig. 11.

The BG and insulin profiles associated with the advised insulin doses are shown in Fig. 7 on December 14 and 15. DIAS–NIDDM recommended 45 and 24 U of NPH on December 15, and 56 and 24 U on December 14. The actual therapy was 26 and 24 U. A high BMI (34.4 kg/m^2) supports the suggestion that the subject is insulin resistant [29,30]. Due to the age of the patient, a tight glucose control might not be desirable and the administered therapy can be preferred to the advised therapy. The patient has the poorest blood glucose control ($HbA_{1c} = 8.7\%$) among the investigated population. To overcome the insulin resistance and improve BG control, DIAS–NIDDM suggests large amounts of insulin that inherently results in high plasma insulin concentration that may, in turn, have negative consequences such as weight gain.

5.4. Insulin-treated subject (Id 12) on twice-daily NPH insulin

Low values of insulin sensitivity and pancreatic sensitivity suggest overt diabetes (Fig. 12). A high BMI (28.5 kg/m^2) supports this finding.

DIAS–NIDDM recommends a reduction of the daily insulin by 40% to avoid the potential hypoglycaemia at 2300 on July 12 (Fig. 13). The advised therapy results in a predicted BG profile that can improve the glycaemic control.

6. Discussion

The parameter estimates have the potential to assist in the assessment of the patient-specific defect(s) of the carbohydrate metabolism. DIAS–NIDDM suggests that some subjects may have impaired secretion while having near normal insulin sensitivity whereas other subjects present both impaired secretion and insulin resistance (overt diabetes), see Table 2.

In most subjects, pancreatic sensitivity parameter was estimated with low precision (large SD), Table 2. This is due to the fact that most of the BG measurements represent pre-meal values. In the learning procedure (described elsewhere [14]) the predicted BG profiles associated with various states of the *ps* parameter return to the pre-meal BG value, making it difficult for the system to estimate precisely this parameter. Collecting post-meal BG measurements has the potential to improve precision of this parameter.

The negative correlation between *is* and *ps* in subjects treated by diet or oral agents (Table 3) is due to the fact that DIAS–NIDDM can explain observed BG data by both higher pancreatic sensitivity and lower insulin sensitivity or vice versa and also concurs with the observed hyperbolic relationship between insulin sensitivity and pancreatic responsiveness [31]. If exogenous insulin is present, this correlation is not present (except for subject 12) indicating that in the presence of exogenous insulin DIAS–NIDDM can identify the defects of carbohydrate metabolism with higher precision.

The day-to-day variability of parameter estimates reflects among other reasons the natural variability of blood glucose concentration. Learning from multiple days minimises statistically the random error caused by this variability. The mean predictive accuracy (as RMS error) achieved by DIAS–NIDDM in this pilot study was 2.3 ± 1.0 mmol/l.

One subject (Id 11) participated in the study on three separate occasions. The time interval between the first two occasions (11a and 11b) was ~ 1 month. The parameter estimates of pancreatic sensitivity on the two occasions are consistent, they both indicate impaired secretion. The small weight gain does not explain the reduction in insulin sensitivity on second occasion and the reduction is more likely caused by natural physiological variability and errors present in the

parameter estimation process. On the third occasion, ~3 months later, the data could not be fitted by the model accurately (large RMS error, see Table 3) and the parameter estimates should be interpreted with caution.

In three subjects, DIAS–NIDDM recommended lower amounts of total daily insulin or a redistribution of doses during the day. The coefficient of variation of the advised total daily insulin dose suggests that, at least according to DIAS–NIDDM criteria, day-to-day adjustment of insulin doses is necessary to maintain optimum control, fact confirmed by a recent study [32].

The pilot study suggests that 30% of the studied subjects have serious secretion deficiency ($ps < 2$ mU/l per mmol/l) and equal percentage is presented with impaired or slightly impaired insulin secretion ($2 \leq ps \leq 6$ mU/l per mmol/l). Insulin resistance affects 40% of the subjects ($is < 0.6$). The high inter-patient variability of the time-to-peak of absorption of NPH insulin indicates that this parameter needs to be estimated to make accurate predictions of the BG profile.

Patient Id 31 is treated with hypoglycaemic agents. DIAS–NIDDM could simulate the BG profile with good accuracy (RMS error 1.6 mmol/l). Future work will investigate if the effect of hypo agents could be modelled by altering insulin sensitivity and pancreatic responsiveness parameters depending on the mode of action of the agent (insulin action enhancers versus insulin secretion synthesizer).

Other approaches to computer assisted decision support in patients with NIDDM have been reported in the literature. A system based on neural networks [33] offers an alternative to clinical algorithms in representing clinical experience. The system is intended to support decision making when prescribing insulin regimens in IDDM and NIDDM given the age, type of diabetes, desired glucose control, etc. DIABETES [34] is a rule-based expert system able to adjust insulin doses of pre-set regimens in both IDDM and NIDDM. The assessment of the system revealed that disagreement between the clinician and the system are mostly due to different patient management strategy rather than in the final result (normoglycaemia). DIACATOR [35] is a simulator of metabolic abnormalities of NIDDM based on pre-defined parameter values characterising the disease. Glucose toxicity, pancreatic responsiveness, hepatic insulin resistance and the tissue sensitivity to insulin are explicitly represented. The effect of hypoglycaemic agents and insulin can be simulated. Parameter estimation and quantitative advice generation are not provided. In DIAS–NIDDM, once fitted to the patient (parameter estimation), the CPN model is used as a 'testbed' allowing the patient-specific simulation of various input patterns. There are no inherent management strategies built in the model. The user of the system has the freedom to choose the preferred insulin regimen and support is given with assessing its quantitative effect. With this view, insulin regimens can be designed to suit any patient and any management strategy.

One aim of this paper was to illustrate, on a pilot study, the clinical use of DIAS–NIDDM. We assessed the plausibility of the results by comparing them with current knowledge in diabetes. This is a necessary stage of the clinical evaluation and validation of decision support systems in the medical field [36,37]. In our opinion, further, more detailed clinical evaluation can proceed despite the small number of the subjects and the heterogeneity of the results of this pilot study.

In conclusion, the CPN model of carbohydrate metabolism used by DIAS has been extended to accommodate for endogenous insulin secretion. DIAS–NIDDM was built using the extended CPN model with the aim to provide advice on insulin treatment in insulin-treated subjects with NIDDM. The system suggested high inter-patient variability of insulin sensitivity and pancreatic responsiveness parameters. The mean accuracy of the fit (RMS error) was 2.3 ± 1.0 mmol/l. Compared to the administered doses, the advice generated by DIAS–NIDDM was similar (± 4U) in two subjects, higher by 20% (17 U) in one subject and lower by 50% (11 U) and 40% (12 U) in two subjects. The large inter-day coefficient of variation of daily insulin dose indicates that, at least according to DIAS–NIDDM criteria, day-to-day adjustment of insulin doses is necessary to achieve optimum control.

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