Development and evaluation of an intelligent handheld insulin dose advisor for patients with Type-1 diabetes

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DEVELOPMENT AND EVALUATION OF AN INTELLIGENT HANDHELD INSULIN DOSE ADVISOR FOR PATIENTS WITH TYPE-1 DIABETES

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Abstract

Diabetes mellitus is an increasingly common, chronic, incurable disease requiring careful monitoring and treatment so as to minimise the risk of serious long-term complications. It has been suggested that computers used by healthcare professionals and/or patients themselves may play a useful role in the diabetes care process.

Seven key systems (AIDA, ADICOL, DIABETES, DIAS, HumaLink, T-IDDM, POIRO) in the area of diabetes decision support, and their underlying techniques and approaches are summarised and compared. The development of the Patient-Oriented Insulin Regimen Optimiser (POIRO) for insulin-dependent (Type-1) diabetes, and its hybrid statistical and rule-based expert system is then taken forward.

The re-implementation and updating of the system for the Palm OS family of modern Personal Digital Assistants (PDAs) is described. The evaluation of this new version in a seven week, randomised, open, cross-over clinical pilot study involving eight patients on short-acting plus long-acting insulin basal-bolus regimens showed it to be easy-to-operate, reliable, not time consuming and well liked by patients.

Following this, the characteristics and use of all currently available insulin formulations, and the corresponding insulin regimens are summarised. Algorithms to provide dose advice and decision support for patients taking the new rapid-acting, intermediate-acting and premixed insulin formulations are then developed. The user interface is improved and extended, amongst others through the development and use of a model describing individual user's meal time habits. Implementation-related issues encountered are discussed, and further work and future directions are identified and outlined.

Motivated by the complex and safety-critical nature of systems such as POIRO, we also report on the use of the B abstract machine notation for the formal specification of the original POIRO system, and focusing on projects and published case studies review the use of formal methods in the development of medical computer systems.

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Introduction

Diabetes mellitus is a disorder of the carbohydrate metabolism characterised by a partial or complete inability to control blood glucose levels due to a lack of the hormone insulin and/or insulin resistance. The majority of people with diabetes have Type-2 (late onset) diabetes in which decreased production of and increased resistance to insulin leads to elevated blood glucose levels. Type-2 Diabetes Mellitus (T2DM) or Non-Insulin-Dependent Diabetes Mellitus (NIDDM) is treated with changes in diet and exercise, oral anti-hyperglycaemic (glucose lowering) drugs i.e. tablets, and in some patients also with insulin injections. In Type-1 (early onset) Diabetes Mellitus (T1DM) the pancreas' beta cells are unable to produce insulin so that the body completely lacks an endogenous insulin supply. Patients with Type-1 or Insulin-Dependent Diabetes Mellitus (IDDM) therefore, several times a day, need to give themselves insulin injections so as to control blood glucose levels.

Diabetes currently affects some two percent of the population with the number of people with diabetes forecast to double worldwide by 2010 to 221 million [9]. In the long-term, people with diabetes are two to four times more likely to suffer from cardiovascular diseases and complications such as blindness, renal failure and nerve damage. Diabetes therefore not only accounts for a substantial and increasing proportion of countries' healthcare budgets but also reduces the life expectancy and quality of life of those affected. However, recent large scale studies such as the American Diabetes Control and Complications Trial (DCCT) (e.g. [63]) and the United Kingdom Prospective Diabetes Study (UKPDS) (e.g. [26]) have shown for Type-1 and Type-2 diabetes respectively, that good glycaemic (blood glucose) control can significantly reduce the risk and delay the onset of long-term complications. These findings have changed both medical and public attitudes towards diabetes management with good glycaemic control no longer being seen merely as a desirable but as an essential outcome.

Along with these shifts in attitude it has been suggested, that computers and information technology used by healthcare professionals and/or patients could play a useful role in the diabetes care process. This thesis concerns the development and evaluation of an intelligent handheld insulin dose advisor for patients with Type-1 that is insulin-dependent diabetes.

Chapter 1 of the thesis reviews existing decision support systems (Section 1.2) in the field of diabetes management and the techniques and approaches (Section 1.3) they use to generate advice. One of the systems summarised is the Patient-Oriented Insulin Regimen Optimiser (POIRO) system (Section 1.2.7), which was jointly developed at Oxford Brookes University and the Diabetes Research Laboratories (DRL) at Oxford University. Work on POIRO formed a main part of Andrew David Jackson-Smale's PhD thesis entitled "Intelligent decision support systems for optimised diabetes therapy" [43] with clinical expertise and input to the project provided by the DRL, in particular Richard Turner and Rury Holman.

Since the publication of Jackson-Smale's thesis in 1993 there have been significant advances in both the diabetes treatment and the computing field. In view of these developments this research project and thesis builds on the work undertaken for POIRO and takes it forward. The project is again a collaboration between the Department of Computing at Oxford Brookes University and the Diabetes Trials Unit[1] at Oxford University.

Compared to the original POIRO's Epson EHT-10 device, more practical, lightweight and inexpensive handheld computers are now available and are becoming ubiquitous. Chapter 2 of this thesis discusses how the POIRO system was re-implemented and updated for such modern Personal Digital Assistants (PDAs) (Section 2.2). The chapter also describes how this updated version (POIRO MK2) was evaluated in a clinical pilot study (Sections 2.3 and 2.4).

Following this, Chapter 3 concerns the extension of the system so as to cater for the new insulin formulations and regimens now available. All insulin formulations and their characteristics and use are summarised, and corresponding decision support algorithms are developed (Section 3.2). The extended version of the system (POIRO MK3) also features an improved and extended user interface (Section 3.3) of which facilities to intelligently model a user's meal time habits form a substantial part (Section 3.3.3). The chapter also discusses implementation-related issues (Section 3.4) encountered during the development of the Palm OS versions of the POIRO system.

Motivated by the complex and safety-critical nature of the POIRO system and the benefits that use of formal methods could provide in this context, Chapter 4 of this thesis summarises the formal specification and software development work undertaken as part of this research project. The B notation and method used is introduced (Section 4.2) and the work carried out (Sections 4.3 and 4.4) as well as potential future work (Section 4.5) is outlined in the chapter itself, whilst full details in the form of two stand-alone papers are provided in Appendices D and E respectively.

Chapter 5 of this thesis follows on from Chapter 3 and describes future enhancements to be incorporated into the next version of the system (POIRO MK4). They include further additions and extensions to the handheld system used by patients (Section 5.2) as well as the development of a desktop-based clinic system for use by healthcare professionals (Section 5.3). The chapter also briefly discusses the future evaluation of the POIRO system in routine clinical practice (Section 5.4), and the wider context of computer-aided diabetes treatment in general and patient-oriented decision support in particular (Section 5.5).

[1] Both the Diabetes Trials Unit (DTU) and the Diabetes Research Laboratories (DRL) are now part of the Oxford Centre for Diabetes, Endocrinology and Metabolism (OCDEM), http://www.ocdem.ox.ac.uk/.

Chapter 1

Decision support systems in diabetes management

1.1 Diabetes decision support as a spectrum

Decision support systems are often categorised according to their intended users, e.g. physician-oriented and patient-oriented systems, or the techniques and approaches used to provide decision support, e.g. time series analysis and metabolic model-based systems. Whilst physician and patient user requirements differ, systems designed for either user group often share characteristics such as ease-of-use, functionality such as data visualisation and underlying decision support mechanisms such as time series analysis. Similarly, the increasingly common combination of two or more decision support mechanisms and/or the provision of physician- and patient-interfaces to one and the same system make categorisation difficult. Hence in the following, diabetes decision support is considered to be a spectrum (Figure 1.1) ranging from the simple to the complex, quite independent of any particular user group or decision support mechanism.

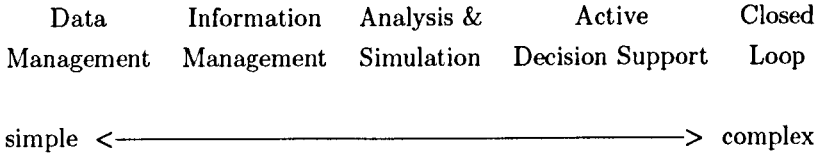


Figure 1.1: Diabetes decision support spectrum

- Data management: basic record-keeping and data collection, storage and retrieval are very simple forms of decision support.
- Information management: simple procedures can transform data into information. The inspection of a patient's record might produce a reminder that a periodic follow-up is shortly due or highlight that a certain target is or is not being met. The visualisation of home blood glucose monitoring data can provide useful information and hence support decisions.
- Analysis and simulation tools can be used to assess a situation and identify actual or potential

problems. This may then support decisions, although no suggestions or solutions have been generated by the decision support system itself.

- Active decision support includes some or all of the above plus the generation of concrete suggestions and/or solutions. However, the actual decisions are made by a person.
- Closed loop systems: operating within set parameters, the system collects and analyses data and (unless it is manually overridden) makes and implements decisions.

As will be shown in Section 1.2 quite different decision support systems can be analysed and compared using this spectrum (Figure 1.1). However, the addition of the following two dimensions might increase the usefulness of the framework.

- Single versus multi user: the existence of more than one user significantly increases the potential of a decision support system and there is considerable interest in telemedicine and collaborative shared care approaches to diabetes care.
- Individual patient versus population based decision support: initiatives and systems such as the European DIABCARE Q-Net project (e.g. [31] or [73]) that support quality monitoring and improvement on a population wide basis are very different from but no less important than systems that support decisions made with respect to or by individual patients.

For completeness, but not part of the above framework, Table 1.1 lists potential users of diabetes decision support systems, whilst Table 1.2 contains related media and devices.

people with diabetes	diabetologists	dieticians
family and friends	diabetes specialist nurses (DSNs)	medical students
general practitioners (GPs)	other specialists	

Table 1.1: Potential users of diabetes decision support systems

paper log books	plastic cards	booklets
glucose meters	mobile phones	landline phones
programmable calculators	personal computers with(out) an Internet connection	handheld computers

Table 1.2: Diabetes decision support media and devices

1.2 Existing systems

In the following seven existing diabetes decision support systems AIDA, ADICOL, DIABETES, DIAS, HumaLink, T-IDDM and POIRO are described and compared. This section is the result of an extensive literature search and review, and the seven systems outlined represent the key diabetes decision support systems to-date. Figure 1.2 shows the seven systems on the spectrum described in Section 1.1. Towards the 'data and information management' end of the spectrum, systems for both (a) diabetes

clinics and physicians, and (b) diabetes patients exist. However, these systems are not further considered here since their relative emphasis on decision support is small. In the middle of the spectrum, six key systems' purpose and functionality in terms of information management, analysis and simulation, and active decision support is depicted. Towards the 'closed loop' end of the spectrum, the ADICOL project combines automatic glucose measurements, intelligent decision making and corresponding insulin infusion.

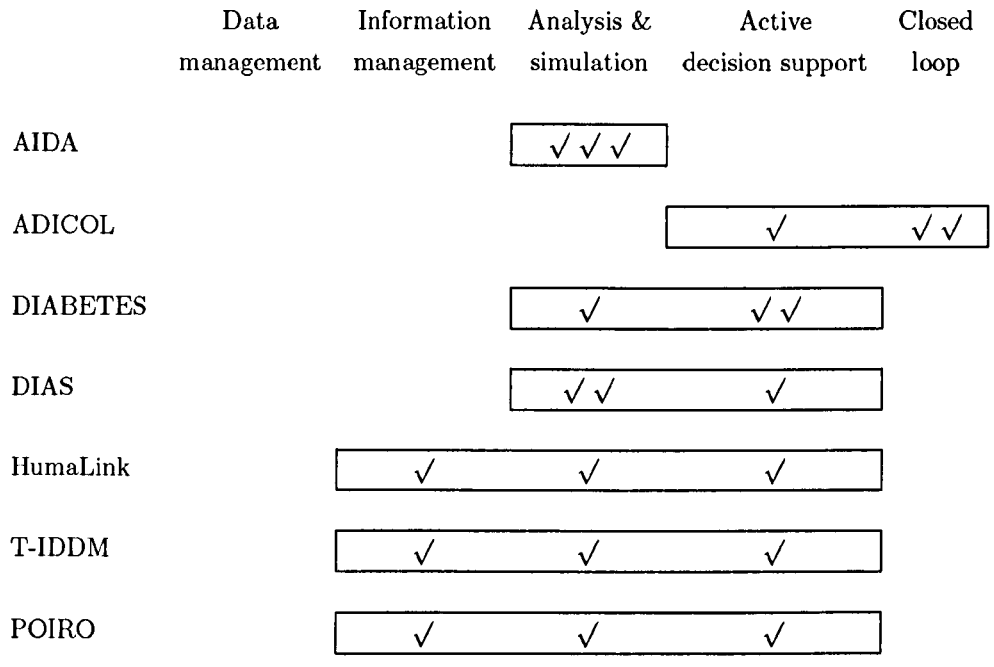


Figure 1.2: Seven existing systems on the decision support spectrum

1.2.1 AIDA

AIDA, an interactive educational diabetes simulator and originally an Automated Insulin Dosage Advisor, was developed jointly by Lehmann et al in London, UK and Semmelweis University of Medicine, Budapest, Hungary. The system may be used by clinical personnel in a clinical setting and/or in an educational setting by patients and their relatives, medical students and healthcare professionals. AIDA (v4.3) [52] can be downloaded without charge from the AIDA website http://www.2aida.org. It runs on IBM PC or compatible machines and requires 3 MB hard disk space. Alternatively, "AIDA on-line" can be used at http://www.2aida.org/online.

AIDA's underlying model contains three compartments: extracellular glucose, plasma insulin and active insulin. Flows into and out of these compartments are described by differential equations: 4 differential equations, 12 auxiliary relations and published experimental data "constitute the model which is solved by numerical integration." [53]. Altogether, the model contains 17 physiological variables, five of which are patient specific. These are the patient's body weight, renal threshold of glucose and creatinine clearance rate plus two parameters S_h and S_p. The first three can be assessed in a routine clinical setting [47]. The last two parameters model hepatic and peripheral insulin sensitivity,

and "are estimated by means of matching the BG concentrations that have been estimated from the model equations with measured BG levels" [50].

However, AIDA is expressly so intended only for educational use in that it models an 'average' or 'virtual' IDDM patient. The program already contains several example patients with particular insulin regimens and problems, and new patients can also be created or existing ones adapted. Given all patient specific details and carbohydrate intake (amount, timing) and insulin (type, amount, timing) data, blood glucose profiles can be simulated. AIDA provides no explicit explanation facilities, but the comparison of successive glucose profiles can, to a certain extent, provide insights if not explanations. Besides, AIDA highlights hypos and glucoses that fall outside a user-definable normoglycaemic range [51].

During retrospective validation of AIDA's physiological model, the model parameters S_h and S_p could be successfully estimated for 24 of 30 (80%) patients. For these observed and predicted blood glucoses for the 5-6 days following parameter estimation were compared and revealed a mean ($\pm$ SD) root mean square deviation of 1.93 $\pm$ 0.86 mmol/L. [49] discusses these results and their implications, and very importantly poses the fundamental question of "what sort of predictive accuracy will be required by such systems before they become clinically useful".

Since the launch of the AIDA website in March/April 1996 and up to May 2003 over 65,000 copies [55] of the software have been downloaded and a proliferation of papers, mainly by the developers of AIDA, have reported comments, reviews and feedback from a wide variety of AIDA users. Experiences reported cover use of the software by people on their own (e.g. at home or at work) as well as use in the more controlled and supervised environment of a workshop or education session (e.g. [89] and [90]). For a full, up-to-date listing of publications about AIDA the interested reader is referred to the http://www.2aida.org/aida/articles.htm page of the AIDA website.

Also, in 2001 Tatti and Lehmann published details [52] [88] of a randomised controlled trial methodology for evaluating the teaching utility of the AIDA simulator. Very recently, in one of their 2003 papers, based on this methodology, [91] reports on a first successful proof-of-concept pilot study involving 24 patients.

Two other recent papers [54] [55] as well as the http://www.2aida.org/aida/research2.htm section of the AIDA website extensively report on research use of the AIDA simulation software for, amongst others, the testing of decision support prototypes, the training of neural networks and blood glucose data generation for prototype validation work.

1.2.2 ADICOL

ADICOL (http://www.adicol.org) is a three-year research project involving a consortium of seven partners throughout Europe. It started on 01/01/2000 with a budget of € 5.3 million, including € 2.5 million funding from European Commission and SFr 950,000 (€ 643,000) funding from the Swiss government. The goal of the ADICOL project is to achieve ADvanced Insulin infusion using a COntrol Loop.

The ADICOL concept comprises and links (i) a subcutaneous continuous glucose sensor/monitor, (ii) an insulin infusion pump, and (iii) an expert control system. The control system makes use of a Model Predicitive Control (MPC) adaptive algorithm and runs on a PDA platform (Compaq iPAQ device, Pocket PC operating system) [95]. The MPC algorithm and the overall system have been successfully evaluated in simulation as well as in clinical studies. For further details on these studies and/or on the project itself the interested reader is referred to the project's website at http://www.adicol.org.

1.2.3 DIABETES

The DIABETES system was developed by Ambrosiadou et al at the Aristotelian University of Thessaloniki, Greece, in collaboration with Manchester Royal Infirmary, UK. It can be used for clinical decision making [5] as well as for the education of medical students and non-specialist healthcare professionals [4]. Also, the computer aided tutoring system DIABETOR is based on the DIABETES expert system [7].

DIABETES is a rule-based expert system implemented in Turbo Prolog. The early version described in [4] covers the diagnosis of diabetes, the different treatment options and the investigation of diabetic complications. The later version [5] focuses on insulin treatment and multiple regimen insulin dose adjustment. It [5] requires the following inputs: regimen type, insulin doses, blood glucose values at different times during the day, symptoms of glycaemia if blood glucose values are unknown. Using these, DIABETES provides advice on and explanations of insulin dose adjustments, the patient's glycaemic control and any follow-up actions.

A performance evaluation study of DIABETES has been carried out in two diabetological centres and three diabetic offices in Greece. It involved 600 Type-1 and Type-2 insulin-treated patients and "... a large range of different diabetic situations ..." [5]. For each patient case DIABETES' advice was compared with that given by the attendant medical experts. Answers were graded and evaluated on a scale from 0 (full agreement) to 5 (full disagreement). For 65% of patient cases, DIABETES provided advice similar (grade 0 or 1) to that of the medical experts. The evaluation also found that DIABETES is "... robust and accurate and not particularly sensitive to wrong responses by the user" [5].

In [8] Ambrosiadou et al report the use of a two round DELPHI approach to performance evaluation of and further knowledge acquisition for the DIABETES system. Altogether 100 patient cases were included and 3500 comments from the experts were collected and used to acquire new knowledge. Agreement amongst the five expert diabetologists increased significantly from 67.4% in round 1 to 84.2% in round 2. Agreement between the experts' and DIABETES recommendations changed non-significantly from 52.2% to 54.4%.

1.2.4 DIAS

The DIAS (DIabetes Advisory System) (e.g. [19] [37] [38]) system was developed jointly by the Department of Medical Informatics of Aalborg University, Denmark and the Bournemouth Diabetes & Endocrine Centre, UK. DIAS is intended as a interactive clinical tool and provides decision support for the management of IDDM.

DIAS is based on a model of the human carbohydrate metabolism implemented as a causal probabilistic network (CPN) and runs on a desktop computer. The model contains two glucose compartments, CHO (Gut compartment) and BG (blood compartment). Flows into and out of these compartments are described by differences equations using, where appropriate, the process variables GUT-ABS (gut absorption), RENAL-CL (renal clearance), INS-INDEP-UTIL (insulin independent utilisation), INS-DEP-UTIL (insulin dependent utilisation) and GLU-PROD (glucose production). The difference equations themselves are derived from differential equations found in the literature and each day is divided into 24 1 h time slices. The model's input variables MEAL and INS-INJ represent ingested carbohydrates and injected insulin respectively. INS-SENS (insulin sensitivity) and NPH-MAX (time-to-peak absorption of NPH i.e. intermediate-acting insulin) are the model's patient specific parameters and influence the quantity of active insulin (ACT-INS) and its action profile.

DIAS is operated in three modes. In *learning mode* blood glucose, insulin (type, amount, timing) and carbohydrate (amount, timing) data from one or more days is needed to estimate the INS-SENS and NPH-MAX parameters. In *prediction mode* these two parameters and insulin and carbohydrate data are then used to predict a patient's blood glucose profile. In *advisory mode* DIAS automatically and systematically changes the size of the insulin doses and using a utility measure [35] similar to Schlichtkrull's M-value [80] finds the insulin therapy with the least overall predicted risk of too low or too high blood glucoses [37].

Given DIAS' implementation of a metabolic model, explicit i.e. spelt-out explanations for proposed insulin dose changes are difficult. However, through the visualisation of meal, insulin and (predicted) blood glucose data the current and the predicted blood glucose profile can be compared. In addition, the comparison of penalty or risk scores for each insulin regimen may rationalise proposed changes.

DIAS has been clinically tested and evaluated in a number of clinical studies. These were double blind or unblinded studies involving, between them, well-controlled and poorly controlled, adult and adolescent, in-patients and out-patients in both Denmark and the UK. Hejlesen et al in [37] outline these studies as well as the DIAS system itself, and conclude that ".. DIAS can generate advice that is safe and of a quality comparable to what is available from experienced clinicians and .. may lead to either reduced HbA1c, reduced insulin doses or reduced frequency of hypoglycaemia." DIAS has also been used in the study and investigation of, amongst others, unrecognised hypoglycaemia [18], the hypoglycaemic counter-regulation phenomenon [36], impaired absorption or omission of insulin [94], and the effect of alcohol on blood glucose [75].

DIAS-NIDDM

DIAS-NIDDM (e.g. [93]) was developed at City University, London by Tudor, Hovorka and colleagues, and inherits much from DIAS. As the name suggests, DIAS-NIDDM models blood glucose profiles of patients with Non-Insulin Dependent Diabetes Mellitus (NIDDM) and thus differs from DIAS in, amongst others, the following respects:

- Insulin doses as inputs are optional.
- Endogenous insulin secretion is included in the model, whilst the modelling of insulin action has been simplified.
- An additional patient-specific parameter for pancreatic sensitivity to glucose is used.

- DIAS-NIDDM uses 30 min time steps, whilst DIAS divided each day into 24 1 h time slices.

DIASnet

Based on DIAS, DIASnet (e.g. [39] and [40]) is a new prototype system that runs as a PC application or within a web browser. It is intended for use by patients as a tool for education and communication. DIASnet's user interface is simpler and more user friendly and allows patients to retrospectively experiment with their own data. [20] reports on a six-month pilot trial with six patients which found that "while the system was helpful, difficulties with data entry hindered its use."

1.2.5 HumaLink

HumaLink [2] also called TeleDoc [57] was developed by Albisser et al in the United States. It is a voice-interactive, physician-directed, commercially available system that, via a touch-tone telephone, provides remote patients with 24 h access to insulin dose advice.

HumaLink is based on a personal computer platform and provides two user interfaces. The health professional interface is Windows based and used by the physician or case manager to access and review patient entered data. The software also automatically generates and prints reports at user-defined intervals, daily, weekly or monthly. The patient user interface can be accessed via any touch-tone telephone. Having identified themselves via their personal identification number (PIN), the patients supported by prompts and verbal instructions, via their telephone's keypad enter glucose measurements, lifestyle factors, medication details and where appropriate crisis events. Following data entry, the system advises the patients about their next medication dosages and also relays any voice-messages previously recorded by the doctor.

HumaLink can be operated in two modes: (i) physician directed automatic control and (ii) patient-directed control. In the latter automatic control i.e. advice is disabled and the system only receives data from the patient. If automatic control i.e. advice is to be enabled, the physician must, for each individual patient, interactively and in detail programme his/her own control algorithms. Using these, HumaLink then acts on behalf of the physician. It is also interesting to note, that the Food and Drug Administration (FDA), Center for Devices and Radiological Health, determined that the HumaLink technology is a medical device.

[2] reports 1 year preliminary beta-testing experience in an open study design. This involved 204 patients, from two healthcare environments, making between them over 60000 telephone calls to the HumaLink system. For active users of the system, HbA1c decreased significantly by 1.0-1.3% from 8.9-10.1% at baseline to 7.9-8.8% after 6 months, whilst the prevalence of hypo- or hyperglycaemic crisis events fell approximately threefold. Nurse and physician time effort was estimated to be 32-34 minutes, other costs \$5.56-\$5.88 per active user per month. Related reimbursement matters were resolved with the patients' medical insurance.

[57] present similar HbA1c and diabetes crisis prevalence findings. Related to fiscal issues, they report that not all insurance companies provide full or partial reimbursement. The monthly costs of running the Teledoc system are approximately \$1000 and 20 patients, for which partial reimbursement is available, would need to enrol to break even. However, the authors also report that as it stands

Teledoc should be able to accommodate 150-200 patients.

1.2.6 T-IDDM

The T-IDDM (Telematic management of Insulin Dependent Diabetic Mellitus) project was a 40 months long project funded by 710 KEURO from the European Commission and 707.46 KEURO from other sources. It involved five contractors and three associates from three European countries namely Italy, Spain, Finland [83].

The main objective of the project was the development, validation and evaluation of a telemonitoring and teleconsultation tool for diabetic patients' care [83]. The project employed a distributed architecture that consisted of a Medical Unit (MU) and several Patient Units (PU) providing decision support to physicians and patients respectively. The two units communicated with each other via public telephone lines at periodic, not a-priori known intervals, thus worked cooperatively but asynchronously [13].

The patient unit is software that runs on the patient's personal computer (PC) and where appropriate interfaces with his/her blood glucose meter. Using the PU, the patient collects home monitoring data, such as glucose readings (blood and/or urinary), insulin taken (amount, timing) and qualitative information on meals, and receives suggestions about insulin dose adjustments. The suggestions i.e. decision support provided by the PU is produced by a fuzzy controller [11] operating within parameters set by the MU [78]. At certain intervals, initiated by either the patient or the PU, all collected data is transmitted from the PU to the MU and, where appropriate, an updated therapeutic protocol is transmitted from the MU to the PU.

The MU provides various tools to support the physician during analysis and interpretation of patients' home monitoring data as well as during therapeutic protocol revision. It has a standard browser based user interface and utilises a specialised web server [77]. The data interpretation and reasoning tools available employ a variety of techniques and approaches including temporal abstraction [12], intelligent time series analysis [15], case-based decision making [60] and multi-modal reasoning [14] [59].

In the verification phase [84] of the project 12 patients at 4 sites were followed up and [86] reports a 9% reduction in HbA1c from 7.77 to 7.1% as well as reductions in mean and median blood glucose levels. The demonstration phase [85] [87] involved 6 patients, who achieved a significant HbA1c reduction of 11.4% [86]. Various other details and indexes of success have also been published in the project's deliverables which the interested reader can consult online via http://aim.unipv.it/projects/tiddm/.

M2DM

Particularly from a conceptual and technological point of view, the Multi-Access Services for Telematic Management of Diabetes Mellitus (M2DM) project follows on from the T-IDDM project. M2DM, funded by the European Commission, involved a consortium of nine partners from five European countries namely Italy, Spain, Germany, the United Kingdom and Hungary.

As summarised in [62] "[t]he M^2DM project was aimed at providing a sustainable service care to residential and mobile diabetic patients, with the final goal to increase the quality of care through

improving communication between patients and caregivers" and the project's results showed that "telemedicine management of Diabetes patients is feasible, well accepted by patients and clinical effective". For further details on the M2DM project the interested reader is referred to the project's homepage at http://aim.unipv.it/projects/m2dm/.

1.2.7 POIRO

The Patient-Oriented Insulin Regimen Optimiser (POIRO) was developed jointly at Oxford Brookes University and the Diabetes Research Laboratories, University of Oxford [41] [43]. It runs on the Epson EHT-10, a 26 x 11 x 4 cm, 616 g then commercially available handheld computer with a touch-sensitive screen.

Via a simple menu, the patient can, in any order, enter individual data items or review previously entered data. Data items are: pre meal blood glucose values, anticipated relative meal sizes (Nothing, Light, Normal, Large), expected post meal exercise levels (None, Minimal, Normal, Heavy), state of health (Well, Unwell, Very sick), insulin injections (name, amount), details of any hypoglycaemic episodes (time, severity) and free-text notebook entries. The review options include an average modal day display and a trend graph for the last thirty days.

POIRO's decision support is based on an integral, hybrid statistical and rule-based expert system, able to cope with missing data. The algorithms are based on published clinical guidelines and use all available data to suggest on a dose-by-dose basis an optimum insulin dose within physician-determined pre-set limits. Upon request, POIRO can also provide a short explanation as to why the suggested dose does or does not differ from the usual insulin dose.

POIRO has been formally evaluated in two clinical trials [43] each involving six patients with insulin-dependent diabetes. [41] reports a significant decrease in mean (SE) pre-prandial blood glucose levels: 7.5 (0.4) vs. 8.9 (0.4) mmol/L with no increase in the frequency or severity of hypoglycaemia. HbA1 levels and mean insulin doses did not change significantly. POIRO was well received by the patients, although reservations over the size and weight of the EHT-10 device were expressed [43].

This research project builds on the work undertaken for POIRO and takes it forward; further details can be found in the introduction to this thesis.

1.3 Techniques and approaches

This section examines different techniques and approaches employed in diabetes decision support systems. It briefly summarises each technique or approach and considers inputs required, processing undertaken, outputs obtained and contextual issues such as theoretical underpinnings and general applicability.

1.3.1 Case-based reasoning

As summarised in [58] case-based reasoning (CBR) "is a problem solving paradigm that exploits the specific knowledge of previously experienced situations, called cases". Each case is characterised by features, an action or solution adopted and the resulting outcome. Given a new situation, past similar

cases are identified and retrieved. These cases and their solutions can then be reused and if appropriate adapted so as to find a solution to the current situation i.e. a new case.

As is clear from the above, a decision support system using CBR requires certain features of i.e. information about a new situation as inputs. Depending on the specific system and operational setting, some of this information could be obtained from the patient's electronic medical record whilst other information would have to be entered manually or derived by and extracted from other components of the decision support system. As an example, the case-based retrieval system described in [58] and part of the T-IDDM project uses 11 patient characteristics, 13 mid-term and 3 short-term metabolic control indicators as features, 6 and 21 of which are of linear and nominal type respectively.

Given a new case's features, case-based retrieval is used to find past cases similar to the current one. This may employ various computational techniques and is computationally very expensive, especially as the system's case base and/or complexity increases. Once similar cases have been retrieved, their solutions may then be reused or adapted for the new case.

There are hence two different outputs from the CBR process: (i) a set of possibly ranked past cases similar to the current one, and (ii) a proposed solution based on these past cases. Given a suitable graphical user interface, the user, who is most likely to be a physician, can then browse through the past cases and using their professional judgement and experience accept, adapt or reject the proposed solution. As an indirect output of and dependent on the specific system, the new case's features, together with the solution adopted by the physician and the outcome achieved, may also be added to the case base.

Reality that is actual patients, past situations and decisions made by expert diabetologists form the theoretical basis of CBR. Decision support systems using CBR can thus support the dissemination of best practice through sharing of information and expertise. Fairly independent of the IT aspects, this has working practice and culture implications. From a practical point of view the acquisition and structuring of the case base, and the constraints imposed by the processing speeds of even the latest computer technology also present challenges.

1.3.2 Neural networks

Neural networks (NNs) used in a diabetes decision support system (DSS) require inputs similar to those required by systems that employ case-based reasoning. However, since NNs must be trained and possibly retrained at certain intervals, NN based systems also require a suitable set of training data, namely inputs plus corresponding correct outputs. Having been appropriately encoded or transformed, the DSS's inputs form the inputs of the NN's input neurons and will produce a certain output at the output neurons. Depending on the size and topology of the network involved, this will necessitate a certain amount of computing resources and time. Following appropriate decoding and transformation of the NN's outputs, NN based systems can provide advice on insulin regimens (e.g. [6] and [32]) and insulin dose adjustments (e.g. [61]) but cannot explain or justify that advice.

The training data set and the training process form the theoretical basis of a NN's output. During training, the NN learns from the patterns inherent in the training data. However, the knowledge thus

acquired is hidden, not explicit, and can hence not be used to explain the NN's outputs i.e. the decision support system's advice. This limits the educational value and possibly the acceptability of such systems. On the other hand, the non-explicitness of NNs potentially enables them to accommodate and exploit differences between individuals and certain amounts of uncertainty or inaccuracy in the inputs. In [61] for example, Mougiakakou et al report that compared to training with data from a variety of patients, training for a specific patient dramatically improves the system's performance, since the NNs can make use of patient characteristics hidden in the data. Liszka-Hackzell [56] using a hybrid AI technique combining the principal component method and neural networks makes similar conclusions and observing a prediction accuracy deterioration after 15 days recommends the construction of a new model, including NN retraining, about once a week.

1.3.3 Metabolic models

In the context of diabetes computing and decision support, metabolic models model the main physiological processes associated with glucose and insulin. The inputs required by such a model are hence the 'inputs' to the physiological system and certain parameters characterising that system. In practical terms, the former will be the amount of carbohydrate ingested, the type and amount of insulin taken, the insulin delivery method and site, and possibly the amount of exercise undertaken. The number and nature of patient-specific parameters will differ for each model and may include the patient's weight and insulin sensitivity.

Giving all these inputs, metabolic models can be used to simulate and predict glucose profiles for different scenarios. If required, the inputs and resulting glucose profiles can be processed further to identify and solve specific problems or to produce general suggestions as to how the patient's overall control might be improved. Furthermore, when a metabolic model's 'what if?' capabilities are combined with a suitable graphical user interface, it can become a powerful demonstration and educational tool for patients and their families as well as healthcare professionals and medical students. The ability to simulate different scenarios, also increases the explainability of any decision support provided.

Medical knowledge in the form of quantitative information about physiological processes such as glucose handling and insulin absorption and action is the theoretical basis of a decision support system based on a metabolic model. By definition such a model is a simplification and it cannot model every physiological process and every patient. Besides, for the aspects modelled, inter- and intra-patient variability poses challenges. With respect to widespread and longer-term use as an active decision support system, the accurate and complete collection of the required input data in general and the amounts and timing of carbohydrates eaten in particular, is also a significant obstacle.

1.3.4 Causal probabilistic networks

The use of Causal Probabilistic Networks (CPNs) or Bayesian networks for metabolic modelling can in some ways be considered as a compromise or hybrid between (a) metabolic models which represent medical knowledge about physiological processes using differential equations, and (b) neural network based models which implicitly model physiological processes. As described in [35] all variables in a CPN are stochastic variables linked by conditional probabilities and inferences are made through Bayesian updating of the probability distributions.

Inputs required by a CPN based decision support system such as DIAS are glucose measurements, carbohydrate intake, and type and amount of insulin taken as well as some actual or estimated patient-specific parameters. The inputs available to the decision support system are then used as evidence based on which the CPN's probability distributions are updated. Given the structure of a CPN this is conceptually relatively straightforward but computationally i.e. from an implementation point of view non-trivial, especially as the size of the CPN increases. However, Hejlesen et al have shown with the DIAS and DIAS-NIDDM systems that these and other challenges of realistic, real-life problems can be tackled.

The outputs and theoretical basis of CPN based decision support systems are very similar to those of metabolic models (Section 1.3.3). However, it might be argued that, in comparison, the data collection burden associated with a CPN based system is somewhat lessened due to a CPN's ability to cope with uncertainty. Furthermore and theoretically, CPNs might handle inter- and intra-patient variability better, since not absolute parameters but distributions of values are used.

1.3.5 Rules and algorithms

Decision support systems based on rules and algorithms process inputs i.e. produce outputs through the application of a number of *IF C THEN S* type instructions where C is some condition on or predicate over the system input and state, and S is a statement that produces outputs and/or changes the system state.

Like other systems, rule and algorithm based systems, hereafter referred to only as rule based systems, typically require blood glucose, insulin regimen and meal related information as inputs. In this context, meals can be described quantitatively or qualitatively, that is as the amount of carbohydrates ingested or the relative meal size. In addition, some systems also consider exercise, health and other factors. As patient-specific parameters rule based systems typically require details such as body weight, insulin sensitivity, glucose targets and dose limits.

Given inputs, the decision support system applies relevant rules. In situations where several rules are relevant, a strategy is needed to decide which rules to apply and in what order. Missing data can also pose challenges for rule based systems, as could situations where the user did not follow the system's advice. Various diabetes related systems (e.g. DIABETES, HumaLink and POIRO) make use of rules or a combination of rules and other techniques (e.g. [14] and [48]) to provide advice on insulin regimens and/or insulin dose adjustments. Some of these systems can also explain their advice.

Conceptually, rule and algorithm based decision support systems attempt to model experts' knowledge and reasoning. However, much of this knowledge is based on experience and cannot be made explicit, plus different experts often use different, equally valid approaches. Computationally, the number and structure of the rules used determines the amount of computing resources required. In particular, although it is widening the scope and applicability of a system, a large rule base also increases the challenges associated with knowledge representation, verification and processing.

1.3.6 Intelligent time series analysis

In the context of diabetes decision support systems, intelligent time series analysis is here considered to encompass a range of techniques that can be used to process and possibly visualise home blood glucose monitoring and other data collected over a period of time from one individual patient so as to gain insight into their past, present and likely future degree of glycaemic control.

Time-stamped blood glucose values measured and insulin doses taken are central inputs to a decision support system that employs intelligent time series analysis techniques. Depending on the specific system and its mechanisms, other data such as day time, meals' carbohydrate contents and glycosuria measurements may also be required or useful.

Given these inputs that is time series, different analyses can be performed. For example, [23] by Deutsch et al describes two approaches to time series of blood glucose data: (i) a so-called intuitive approach, and (ii) an approach based on structured time series modelling. Bellazzi et al on the other hand present work using temporal abstraction [12] and a combination of temporal abstraction and structural filtering [15].

The output of an intelligent time series analysis is an abstract, high-level description of a patient over the time period analysed. This description may be shown to and further interpreted by the healthcare professional user and/or could form an input to another component of the decision support system.

From a theoretical point of view, time series analysis is a highly data-driven approach to decision support. Hence, the quantity and quality of the input data is important. However, although there is no need for patient-specific physiological parameters such as insulin sensitivity, information about the patient's current treatment regime and targets may be required. Consequently, decision support systems that employ time series analysis can be considered to incorporate medical and experts' knowledge in two ways: (i) via the types of data analysis used, and (ii) via the analysis parameters and thresholds chosen.

1.4 Discussion

The previous two sections described different diabetes-related decision support systems and their different approaches and techniques. This last section of this chapter considers these systems in the context of the Patient-Oriented Insulin Regimen Optimiser (POIRO) system to be updated and extended as part of this thesis.

POIRO is designed to

- give patient-oriented, patient-specific dose-by-dose advice. Its primary function is thus the provision of decision support. Systems such as AIDA and DIASnet on the other hand are educational tools that do not provide patient-specific advice; DIABETES and DIAS on the other hand are not intended for patient but for healthcare professional use.
- be easy-to-use and runs on an inexpensive, small, portable handheld device. Patients thus need no prior experience with or a particular interest in computers and can carry POIRO around with them so as to obtain instant individual dose advice at the time and place it is needed. With

exception of Humalink and perhaps ADICOL, the other patient-used systems introduced above appear to require varying degrees of familarity with and access to a desktop computer.

- operate independently between patients' clinic visits. From a patient user's point of view, all that changes is that their paper logbook is replaced with an electronic logbook that also provides dose advice. From the diabetes clinic's point of view, clinic visits are extended by the tasks of setting up and updating the patients' handheld devices. However, between clinic visits no additional reviewing or monitoring of patients' logbook data is required. In this respect, POIRO differs from the Humalink, T-IDDM and DIASnet systems.

- provide dose advice explanations and interactive feedback to the user. The system's ability in particular to explain lifestyle-related insulin dose adjustments increases its user acceptability, whilst the easily accessible visual display of patients' own logbook data may have motivational effects. The insulin dose advice systems Humalink and T-IDDM introduced above do not provide comparable, equally easily accessible facilities. AIDA and DIASnet on the other hand offer sophisticated data visualisation on a desktop computer, but given the educational nature of these two systems, the data displays provided are not directly linked to the patient's own regimen, their logbook data and the advice they received from the system.

Chapter 2 following this chapter describes the updated version of POIRO, POIRO MK2, and its evaluation in a formal clinical pilot trial.

Chapter 2

POIRO for Palm OS

2.1 Introduction

The POIRO system introduced in Section 1.2.7 above was well-received by patients, but the size and cost of the Epson EHT-10 device it was based on, prevented its widespread use [43]. Since then, computer technology has changed significantly, and today more powerful handheld computers, so-called Personal Digital Assistants (PDAs), have become ubiquitous and commercially available at a fraction of the size, weight and cost of the EHT-10 device. This chapter describes how the algorithms of the original POIRO system were re-implemented on such modern PDAs, and how this new version, POIRO MK2, was evaluated in a formal clinical pilot trial.

2.2 Practicalities - Information Technological

2.2.1 Device and Programming Language Selection

In autumn 2000, when the device and programming language selection was made, a number of different manufacturers were offering a range of PDA devices. These varied in their data entry method (stylus and/or keyboard), display (monochrome or colour), cost, size, weight, memory and operating system. Palm OS, EPOC (Psion, Symbian) and Windows CE (Pocket PC) were the three most common operating systems, and through licensing agreements, PDAs from these as well as other manufacturers could run under these three operating systems.

With more than 75% market share worldwide Palm OS was by far the leading operating system. EPOC was also quite established, but Psion PDAs typically had miniature keyboard and stylus based data entry, whilst data entry based stylus only was considered preferable for the future POIRO MK2. The Windows CE operating system was at the time still relatively new and unproven.

Palm OS, EPOC and Windows CE being the three operating system options, correspondingly available programming languages, software development tools, reference material and developer support were researched. This showed Palm OS not only to be the most established and but also the best supported operating system.

Considering the factors outlined above, Palm OS was chosen as the operating system or platform on which to base the new version of POIRO. C/C++ at the time was the defacto standard program-

ming language for this platform. Consequently, the Metrowerk's CodeWarrior for Palm OS Release 6 IDE (Integrated Development Environment) and the accompanying Palm OS SDK (Software Development Kit), running on a PC (Personal Computer) under Windows 98, formed the tools used for the re-implementation of the POIRO algorithms. The actual PDA devices used during the clinical evaluation of POIRO MK2 were graphite/black Handspring Visor Deluxe models (Figure 2.1).

The fact that C/C++ are amongst the most widely used programming languages also allowed for the possibility of, in the future and relatively easily, porting the POIRO MK2 program code to a platform other than Palm OS. However, not least due to its weak typing, C/C++ is not necessarily the most suitable language for the development of safety-critical applications and hence particular emphasis was placed on programming style and software testing.

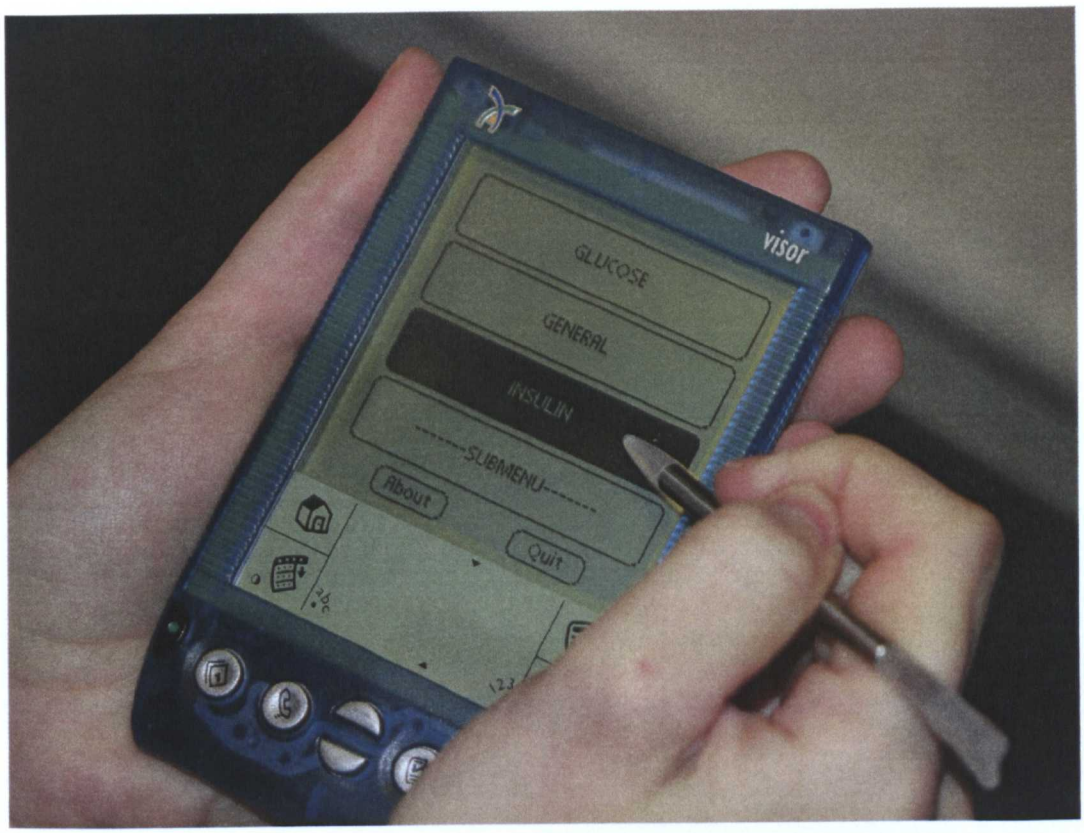
2.2.2 Re-implementation

This section will describe the re-implementation of the original POIRO algorithms, focusing on the peculiarities of the Palm OS platform and the software design and programming style adopted.

Due to significant advances in the development and manufacture of computer memory and processors, memory requirements and processing speed are today generally not amongst the key concerns of most application developers. However, since today's handheld devices typically come with only a couple of megabytes of overall memory, as opposed to the hundreds of megabytes or dozens of gigabytes of Random Access Memory (RAM) and hard disk space found in typical desktop computers, for developers of handheld applications, memory requirements are a major concern. Similarly, a handheld's processor, operating system and the context and nature of its use, make processing speed a key issue.

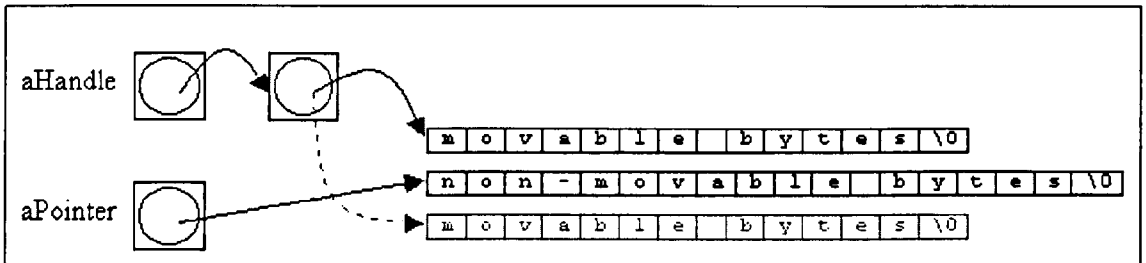
Constraints such as those described above were obviously considered by the architects of the Palm OS operating system. They resulted, from an applications developer's point of view, in a special kind of development environment, which is somewhat unusual and technical. The management of dynamically allocated memory is an example of this. Given memory constraints and the absence of automatic garbage collection, it is very important to not only consider how much memory is needed but also when and where it will be allocated and de-allocated. The existence of movable and non-movable memory chunks, a chunk is a continuous area of memory, further complicates things. As shown in Figure 2.2 non-movable and movable memory chunks are accessed via pointers and handles (pointers to pointers) respectively. The use of movable chunks requires two additional operations when accessing the memory, but on the other hand allows the moving around, by the operating system, of unlocked movable chunks and hence supports the efficient utilisation of the limited available memory.

From a software design point of view, the re-implemented POIRO system, POIRO MK2, can be divided into three components: the user interface, the database and the processing core containing the actual decision algorithms. The implementation of these components is distributed over several source code files (modules), mutually separated by the implementation layer module as shown in Figure 2.3. Such a loosely-coupled, highly modular structure was considered to improve the maintainability and understandability of the code. It was also hoped, that this software design, in connection with the use of the C/C++ programming language, will ease potential future re-implementations on platforms other than Palm OS.



Dimensions:	12.0 x 7.5 x 1.6 cm
Weight:	160 g
Display:	160 x 160 pixels (6 x 6 cm) monochrome
Operating system:	Palm OS 3.1H2
Power supply:	2 AAA batteries
PC connection:	Via USB serial cable, cradle or infrared.
Other features:	8 MB memory, Springboard^{TM} expansion slot Available in five different colours: orange, ice, green, blue (shown) and graphite (used in the pilot trial).

Figure 2.1 (original in colour): Handspring Visor Deluxe




```
Void Pointers_and_Handles_Example()
{
// Variable declarations
CharPtr  aPointer, tempPointer;
VoidHand aHandle;

// Dynamic memory allocation
aHandle  = MemHandleNew(14); // Allocate movable memory chunk.
aPointer = MemPtrNew(18);    // Allocate non-movable memory chunk.
// MemPtrNew might cause a movement of the movable chunk!


// Dynamic memory access

// Fill the movable memory chunk.
tempPointer = MemHandleLock(aHandle); // Memory chunk is temporarily non-movable.
StrCopy(tempPointer, "movable bytes\0");
MemHandleUnlock(aHandle); // Memory chunk is movable again.

// Fill the non-movable memory chunk.
StrCopy(aPointer, "non-movable bytes\0");


// Dynamic memory de-allocation/freeing
MemHandleFree(aHandle); // Free movable memory chunk.
MemPtrFree(aPointer);   // Free non-movable memory chunk.

} // Pointers_and_Handles_Example
```

Figure 2.2: Movable and non-movable memory chunks - Note: The above code is illustrative only. Hence the possibility of failed operations, NULL pointers, etc. is not considered.

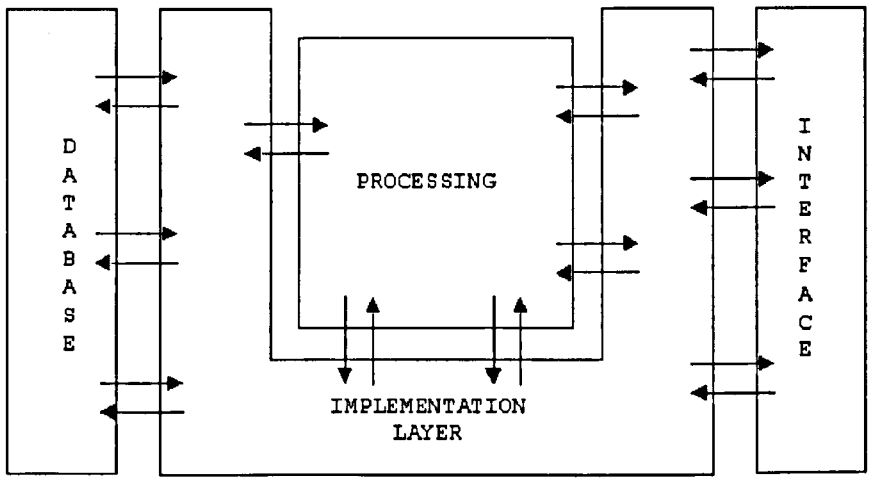


Figure 2.3: Program architecture

On the more subjective issue of programming style, it was thought that the avoidance of C/C++ specific code constructs such as `n++` or `if ((myPointer = MemPtrNew(256)) != NULL)` would minimise slips and errors by maximising the readability of the program code. Similarly full variables declarations like `long signed int n;` were given preference over shorter declarations like `int n;` and when unavoidable, particular attention was paid to the correctness of typecastings.

As part of the quality assurance process the author also undertook a thorough proofreading-style checking of the code towards the end of the coding phase. For certain critical components, like for example the routine used when searching for a recorded hypoglycaemic episode within (say) the last 8 hours, semi-formal annotations of the program code, such as those shown in Figure 2.4, were also considered valuable and appropriate, and based on the code and these annotations a second opinion on the code's correctness was sought. The software testing undertaken as part of the re-implementation process is described in the following section.

2.2.3 Software Testing and User Interface Evaluation

Given the safety-critical nature of the application, extensive systematic software testing was undertaken. Whilst some of this required simple observations of for example the display or non-display of a "High glucose - do some exercise" message, the bulk of the testing revolved around more advanced, complex criteria. These included the correctness of (i) glucose-related statistical calculations, (ii) meal-related offset calculations and processing, (iii) advised insulin doses and (iv) dealing with hypoglycaemic episodes. Based on those and other criteria, test cases were constructed and suitable test data was generated. Following the entry of the test data, relevant information recorded in the system's database was analysed. Lacking suitable alternatives all data entry was performed manually; the passing of time was simulating through the advancing of the system clock. MS Excel spreadsheets and MS Access database queries were used as tools for test data generation and post-data-entry information analysis. The testing process uncovered a number of subsequently corrected oversights and programming errors, some of which stemmed from inaccuracies or inconsistencies in the original POIRO program code.

```
s = 0;
e = N;

// NORMALLY: m = (s + e) / 2;
// HERE:
// Assumption: 20 records per day, 150 records per week === 1 record
// for every 4320 (p.d.) or 4032 (p.w.) seconds of time passed.
// Hence, "pi mal Daumen" 1 record for every 4000 seconds of time passed.
records_between_now_and_then = (now - starttime)/4000;
// mintime <= now and maxtime <= now ensure that (now - starttime) is non-negative.

if (records_between_now_and_then >= N)
     m = 0;
else
     m = (N-1) - records_between_now_and_then;

// ASSERT: 0 <= m < N  && s <= m <= e

while (s != e) /* GUARD: (s != e) */
     {
     /* INV
        (s <= m <= e) &&
        (ForAll t | 0 <= t < N & t < s . a[t] < starttime) &&
        (ForAll t | 0 <= t < N & e <= t . starttime <= a[t])
     END INV */

     GetEventRecord(m, NULL, &a_m, NULL, NULL, NULL, NULL, NULL, NULL);

     if (a_m < starttime)
          s = m + 1; // s <= m implies a reduction of the loop variant.
     else
          e = m; // Can be shown to reduce the loop variant.

     m = (s + e) / 2; // mathematically: m = (s + e) DIV 2
     // s <= m <= e can be shown.
     } // while

/* POST: (s==e) &&
         (ForAll t | 0 <= t < N & t < s . a[t] < starttime) &&
         (ForAll t | 0 <= t < N & e <= t . starttime <= a[t])
   END POST */
```

Figure 2.4: Example of semi-formally annotated code

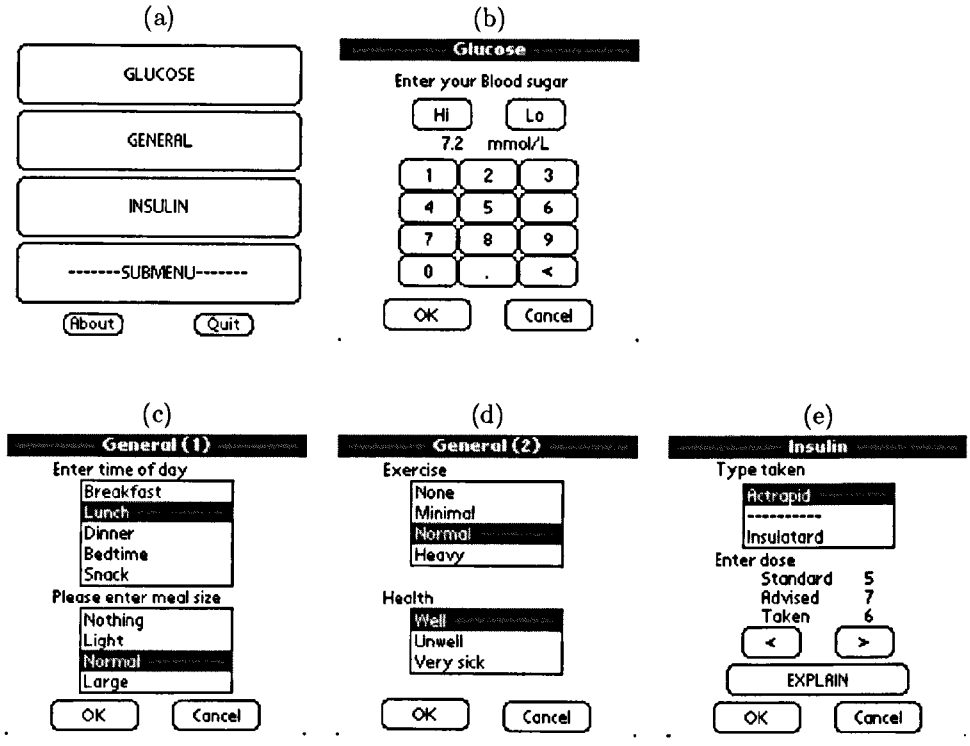


Figure 2.5: Screens accessible via the main menu - (a) Main menu, (b) Glucose entry screen, (c) Meal entry screen, (d) Exercise & Health entry screen, (e) Insulin entry screen

Due to the size of today's modern PDAs' displays, the original POIRO's user interface had to be adapted i.e. made smaller. In particular, the overall menu screen had to be divided into two separate screens: the main menu with the regularly used options and the submenu with the less frequently used ones. However, the content of most other screens remained largely unchanged. Figures 2.5 and 2.6 show the main screens of POIRO MK2.

To informally evaluate this adapted user interface two patients with diabetes, approached by the DTU, used a prototype version of POIRO MK2 for one to two weeks as an electronic logbook, that is with the advice function switched off. This provided a useful 'reality-check', several would-be-nice-to-have-this-feature ideas, and practical suggestions such as the addition of a 'PLEASE WAIT' message while the review diagrams are being drawn and the re-scaling of the diagrams' glucose axis.

2.2.4 Training and Support Material

A simple User Guide was developed for (i) use during the training session and (ii) reference use at home. On 18 A4 pages the guide showed magnified images of each screen and briefly explained how to enter the information required.

In addition, home-monitoring data for a fictional but realistic 'training patient' was devised. An adapted training version of POIRO MK2 allowed patients to practice using the device by entering data for that fictional patient. Three days of blood glucose, meal, exercise, health, insulin and other details were provided on three separate A4 sheets. This training data was designed so as to demonstrate,

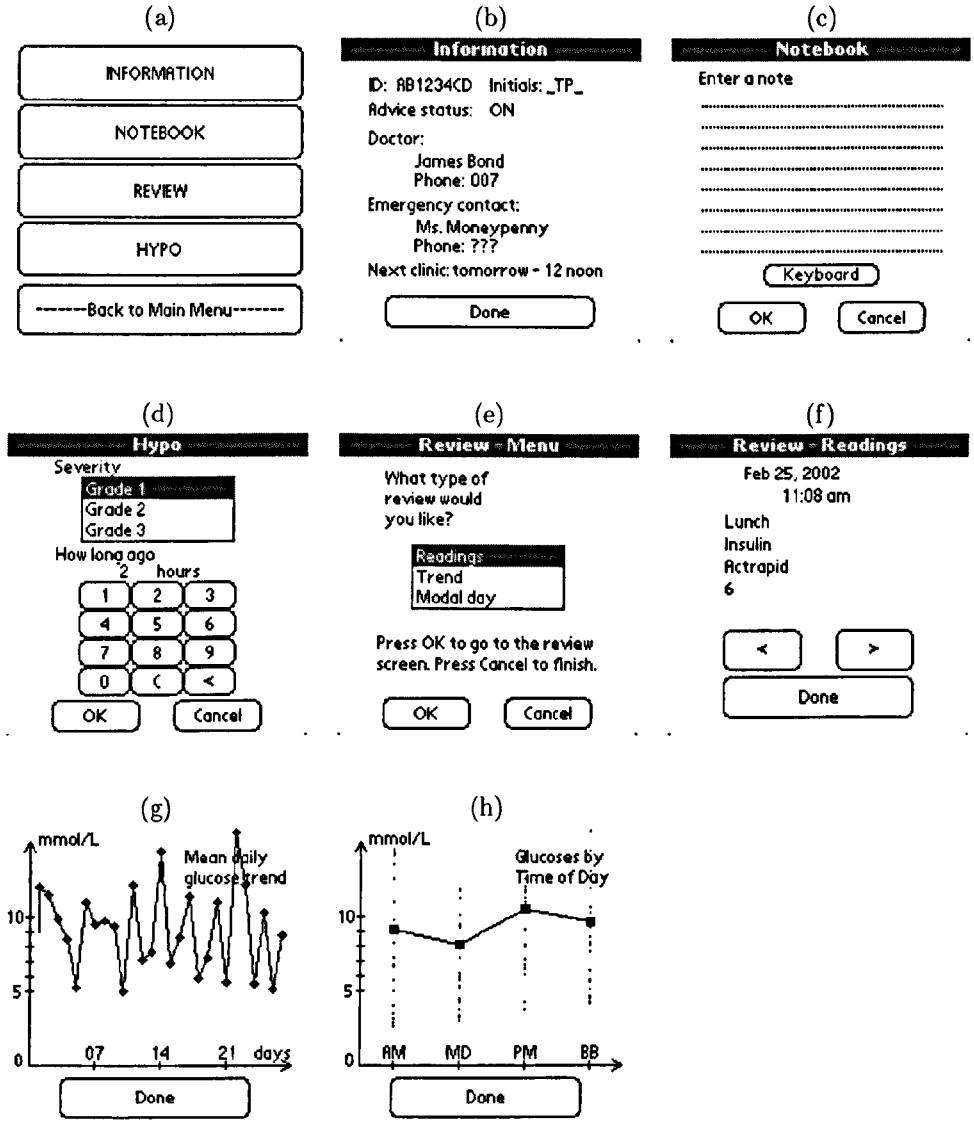


Figure 2.6: Screens accessible via the submenu - (a) Submenu, (b) Information screen, (c) Notebook entry screen, (d) Hypo entry screen, (e) Review selection menu, (f) Readings review screen, (g) Glucose trend diagram, (h) Modal day diagram

practise and reinforce

- entering of low, normal and high glucose readings,
- entering of light, normal and large meals,
- entering of minimal, normal and heavy exercise,
- requesting of an insulin dose explanation,
- changing of the taken (from the advised) insulin dose,
- making of a notebook entry,
- entering of a hypoglycaemic episode,
- use of the review screens.

In anticipation of potentially multi-user classroom-type training sessions, the user guide and training patient material were also provided in the form of a PowerPoint presentation. However, not least due to prolonged patient recruitment and for patients' convenience, five of the eight patients were trained on a one-to-one basis and four of those five in their own home.

To support the research physician, the author also collated a healthcare team reference manual which in one place contained the following:

- a copy of the patients' user guide,
- instructions, illustrated with screenshots, regarding the device setup and data transfers between the PC and the handhelds
- instructions as to how to prepare the training devices,
- a copy of the training data sheets,
- explanations and screenshots of the situations in which the device asks the patient to contact the doctor, and
- details as to how the device handles hypoglycaemic episodes.

2.2.5 Device Setup and Data Transfer Utility

The interaction of the physician's PC and the patients' handheld devices relies on two related but separate components: a device setup and a data transfer utility.

It is the device setup utility that the physician uses to customise individual patient's decision support. Hence this component is very important indeed, both in practical and physician user acceptability terms. Potentially useful features include intelligently guided data entry, information visualisation and sophisticated forms of decision support such as intelligent time series analysis and data mining. However, the development of such a physician-oriented decision support system was outside the scope of this project. Hence a fairly utilitarian approach was taken towards the development of the device setup utility - its main purpose was the setting, saving and printing of the patient specific settings.

The Palm OS standard method of transferring data between a desktop computer and a handheld is via Hotsync synchronisation using a serial or USB cable, cradle or infrared communication. During such a synchronisation operation, the conduit (if any) corresponding to each application on the handheld is invoked and the application's databases are synchronised and updated by that conduit. Conduits reside on the desktop machine and are effectively data transfer utilities, specific to each application and hence, supplied by the handheld application's developer. From a technical point of view, a conduit takes the form of a Dynamically Linked Library (DLL) with prescribed, standardised entry points. Conduits themselves use other DLLs, shipped with the Palm OS device's desktop software, to handle the low-level communication and data transfer between the desktop and the handheld.

The conduit developed for the POIRO MK2 application simply transfers all the relevant data from the handheld to the desktop, or vice versa, as determined by the physician user. A confirmation dialog and redundant data files on the desktop side were used to avoid and limit the potential damage caused by accidental, wrong-transfer-direction selections. This worked well in practice but clearly, future versions of the conduit could improve on this, namely the conduit could automatically i.e. without human intervention transfer and synchronise the data in one or both directions as appropriate.

Both the device setup and the data transfer utility were developed with Microsoft Visual C++ Version 6.0 using Microsoft Foundations Classes (MFCs) and the Palm OS Conduit Development Kit (CDK) Version 4.0.

As mentioned above Hotsync synchronisation can be carried out using a physical or an infrared connection between the handheld and the desktop computer. Experiments comparing the data transfer speed of a USB (Universal Serial Bus) cable connection with that of an infrared wireless connection proved highly interesting. As shown in Table A.6, handheld to desktop data transfers via USB were (i) virtually instant requiring less than extra 2 seconds per additional week of logbook data transferred, and were (ii) approximately 8 times faster than transfers via infrared. Consequently, a USB cable connection rather than an infrared wireless one was used during the clinical evaluation of POIRO MK2.

2.3 Practicalities - Medical

The clinical evaluation of POIRO MK2 was undertaken in 2001 and took the form of a randomised, open, cross-over pilot trial. The study involved 8 subjects and was carried out at and in close collaboration with the Diabetes Trials Unit (DTU), Oxford Centre for Diabetes, Endocrinology and Metabolism (OCDEM). Ethics approval for the study was sought from and given by the Central Oxford Research Ethics Committee (COREC), Reference C01.095 - Handheld Insulin Dose Advisor Evaluation. This section describes the practical aspects of the study (Section 2.3.1). Following this, Section 2.4 will discuss the study results.

2.3.1 Trial Protocol

The research physician Dr Silvina Gallo and the research nurse Senior Nurse Beryl Barrow recruited study participants from OCDEM outpatient clinics and local GP practices. Inclusion and exclusion criteria for participation in the study are given in Figure 2.7. Following a recruitment visit and ob-

taining of written informed consent, the subjects used POIRO MK2 for seven consecutive weeks and during this time were seen on four occasions as detailed in Figures 2.8 and 2.9.

Self-BG monitoring was carried out using the subjects' own glucose meters, which were checked and calibrated during Visit 2. HbA1c and fructosamine assays were carried out by the DTU laboratory and the Department of Clinical Biochemistry at the Royal Berkshire Hospital Reading respectively. As this was a pilot study evaluating the updated version of POIRO, no formal power calculations were undertaken. Mean and standard deviation (SD), median and interquartile range, and numbers or percentages were used to summarise normally distributed, non-normally distributed, and categorical data respectively. Paired t-tests were used to compare glycaemic control during the advice ON versus the advice OFF period. Responses to the "Attitude to Insulin Therapy" and the "Insulin Advisor Evaluation" questionnaires were tabulated and compared.

2.4 Results

2.4.1 Subject recruitment and demographic characteristics

All 8 subjects (4 male, 4 female) recruited successfully completed the study. They were mean (SD) age 48 years (13) old, with a median (interquartile range) duration of diabetes of 22 years (11.75-25.75) and a mean (SD) HbA1c of 8.1% (0.8). Full baseline data are given in Table A.1 on page 144.

2.4.2 Glycaemic control

To determine the effect of POIRO's patient-specific dose-by-dose advice on glycaemic control HbA1c, fructosamine, prandial and basal insulin doses, mean BG levels, and the number of biochemical and clinical hypoglycaemic episodes during the advice ON versus the advice OFF period were compared. We allowed 2 weeks of optimisation process during the 3 weeks long advice ON and advice OFF periods to give the algorithms time to self-adjust and impact on glycaemic control. Tables A.2 to A.4 show the results for the RUN-IN period, and the third and last week of the ON and OFF periods.

No statistically significant differences were seen in HbA1c, fructosamine or mean BG levels. With respect to insulin doses taken, basal insulin doses during the advice ON period were significantly lower (P=0.0378) than during the advice OFF period: median (interquartile range) 10.75 U (7-16.75) versus 14 U (7.75-18.75). Furthermore with advice switched ON there were significantly fewer (P=0.0417) biochemical hypoglycaemic episodes: 11 versus 24 in total.

To assess the effect of the POIRO system on the frequency of insulin dose adjustments according to lifestyle and current glucose readings, we calculated a measure called *dose change activity* which is the percentage of insulin doses that were changed, that is that are different from the previous (day's) dose of the same insulin type and taken at the same meal time. These values are also shown in Tables A.2 to A.4. As one might expect, with the dose advice switched ON insulin dose change activity was significantly higher (P=0.0115) than with the dose advice switched OFF: median (interquartile range) 62% (50-68.5) versus 29.5% (20.75-39.75). Tabulation (not shown) of meal sizes, exercise levels and states of health showed that the patients' lifestyles throughout the RUN-IN, ON and OFF periods were similar.

Inclusion Criteria

- Aged >= 21 years.
- Diagnosed with Type-1 diabetes for at least one year.
- Insulin dependent.
- Undertakes regular self-BG monitoring.
- Has hypoglycaemia awareness.
- Has given written informed consent.
- Is able to comply with and understand the study protocol requirements.

Exclusion Criteria

- Has an HbA1c > 10%.
- Has any serious underlying medical condition.
- Is participating in other studies.
- Is thought by the investigator, for any reason, to be unsuitable for participation in a clinical study.

Figure 2.7: Inclusion and Exclusion criteria

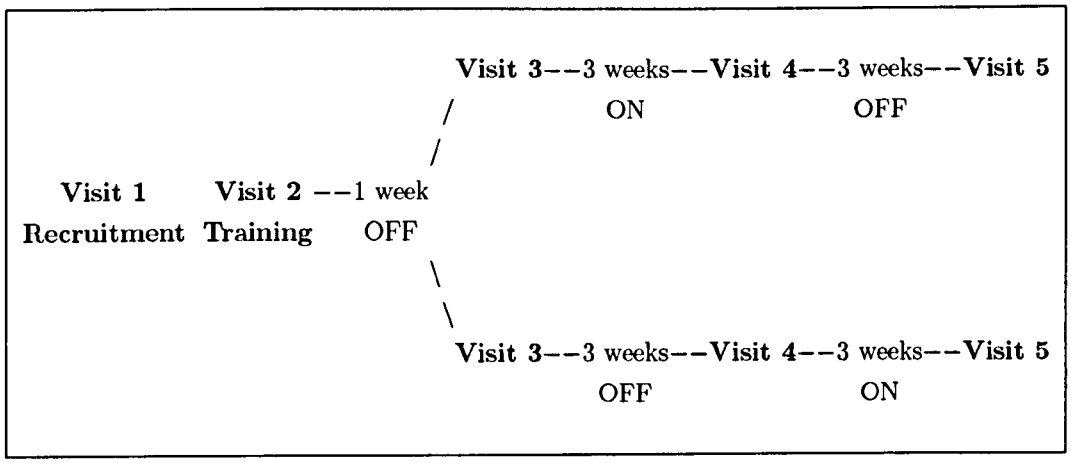


Figure 2.8: Study phases and cross-over design

Visit	1	2	3	4	5
Written informed consent taken	√				
Subject baseline data taken	√				
Interactive 2 hour training session		√			
Randomisation to ON/OFF or OFF/ON advice pattern			√		
Completion of the "Attitude to Insulin Therapy" questionnaire		√			√
Completion of the "Insulin Advisor Evaluation" questionnaire				√	√
Downloading of data from the handheld to a PC laptop			√	√	√
Blood sample taken for fructosamine and HbA1c assessment	√		√	√	√

Figure 2.9: Visits' contents

2.4.3 Patient feedback

Also shown in Table A.3 for the advice ON period are values describing the extent to which patients followed the dose advice given by the POIRO system. As can be seen five patients took the suggested insulin dose 85% or more of the time, whilst three patients (02, 04, 07) followed it 9%, 42% and 54% of the time respectively. Of the latter three patients, numbers 02 and 07 generally took more insulin than advised without an increase in the number of clinical hypos during advice ON compared to the advice OFF period. However, patient 07 recorded nine biochemical hypos during the entire three-week advice ON period and only three during the OFF period of the same length. Patient 04 took generally less insulin than advised and did not record any biochemical hypos.

Patient feedback obtained via the "Attitude to Insulin Therapy" (Section A.2.1) and "Insulin Advisor Evaluation" (Section A.2.2) questionnaires was tabulated (Sections A.3.1 and A.3.2) and compared.

Regarding attitudes to insulin therapy, all patients considered it important to avoid hypoglycaemic episodes (inappropriately low BG readings) as well as high glucose readings (Questions 6 and 8). They were regularly checking their blood glucose levels and were adjusting their insulin doses in response to try to avoid too low and too high readings (Questions 9, 10 and 11). However, they also felt that more help was needed to better control their diabetes (Question 2). Using the POIRO system did not make patient more concerned about their blood glucose levels, hypoglycaemia or high glucose readings (Questions 1, 5 and 7). Neither did using the system change patients' perception as to how much the application of insulin and the adjustment of insulin doses interfered with their daily activities (Questions 3 and 4).

No patient already used a palm top device or handheld computer and they all had little or no prior computer experience at home or at work (Questions 14 and 15). However, as reported via the POIRO evaluation questionnaires, after the short interactive training session at Visit 2 (Figure 2.9) they all felt able to understand and confident to correctly use the handheld device and program (Questions 4 and 9). The initial familarisation with POIRO took little time, reported daily usage was between 4 and 20 minutes and in general did not interfere with patients' daily activities (Questions 12 and 13).

POIRO was generally well accepted (Questions 1, 2, 10, 11, 17). Only one patient (02) was not satisfied with POIRO. He was a 72-year old man with longstanding diabetes, who found the advice too cautious as he was used to adjust insulin doses in a more aggressive way. This patient also experienced problems due to the restricted dose increments administerable with his short-acting insulin Penfill device (see also Section 5.2.4). Two other patients (04 and 07) found POIRO "not always reliable" stating for example that "sometimes my own instinct proved right" and that "on occasions it gave wrong advice due to previous days blood sugars".

The features patients liked most about POIRO were "using the device as a logbook" and "the graphics" displaying their glucose trend and modal day diagrams. The least favoured features were "having to enter data 4 times per day" and "didn't usually agree with the insulin dose advice". All patients except one (02) "would like to continue using the device".

2.4.4 Technical aspects

From a technical point of view no major problems were encountered. There were no negative comments on the processing speed or operation of the device, although subject 02 experienced problems with odd (as opposed to even) advised short-acting insulin doses, since his Penfill device could only be used to administer even doses (see also Section 5.2.4).

Patient feedback also showed that the hypo-related facilities could be usefully extended so as to if appropriate routinely record glucose readings measured whilst hypo and to then display hypoglycaemic episodes on the glucose trend graph. These user interface extension were implemented in the next version (POIRO MK3) of the system (Section 3.3).

The study also showed the POIRO MK2 implementation to be extremely robust: during 8 x 7 = 56 weeks of combined user experience no handheld program crashes were reported. In relation to the device setup utility, only one known feature caused one small problem, that was then easily rectified and prevented from happening again. With respect to the application conduit's performance, all data transfers were successful, and in line with earlier experimental results (Section 2.2.5), took between 3 and 28 seconds per transfer with each additional week of logbook data adding less than 3 seconds to the overall transfer duration (Table A.8). The only exception to this occurred during Visit 4 for Subject 04 when the handheld-to-desktop and desktop-to-handheld data transfers were both successful but took 4 min 11 s and 2 min 3 s respectively. The reason for this is unclear, but an incorrectly connected cable at the handheld and/or desktop side might be the explanation.

2.5 Conclusion

This chapter described how the original POIRO system was re-implemented for modern handheld devices, and how this new version, POIRO MK2, was evaluated in a formal clinical pilot trial.

The platform chosen for the re-implementation and further development of POIRO is the Palm OS family of Personal Digital Assistants (PDAs). Section 2.2 described the practicalities of developing the Palm OS version of the POIRO software as well as related material and desktop-computer software. Following this, Section 2.3 outlined the practical aspects of the clinical study undertaken to evaluate POIRO MK2. The results of this seven week long pilot trial were discussed in Section 2.4. No significant differences in glucose levels were seen in this small study, but basal insulin doses and the number of biochemical hypos were significantly lower with the advice switched ON. Feedback from the semi-structured questionnaires was positive: patients enjoyed using the device, found it easy to operate, reliable and not time-consuming. At the end of the study, all but one wanted to continue using the device.

The Handspring Visor device used during the evaluation study is one of a range of increasingly ubiquitous PDAs. Compared to the original system's EHT-10 device or a laptop computer, these modern PDAs are inexpensive, small and lightweight i.e. truly practical and portable devices. Based on such a device, the updated version of POIRO can thus provide instant, patient-specific dose-by-dose advice where and when it is needed.

Following the successful evaluation of POIRO MK2, two main areas for further work have been identified:

- New insulins: The rapid-acting and intermediate-acting insulins that have recently become available and established are not catered for by POIRO MK2. Chapter 3 following this chapter hence describes the next version, POIRO MK3, which extends the system accordingly.
- Use in routine clinical practice: A larger study, beyond the scope of this thesis, to evaluate POIRO in routine clinical practice is needed. The rationale for this and some related technical and organisational details are outlined in Sections 5.3 and 5.4 of Chapter 5.

Chapter 3

New insulin regimens and user interface extensions

3.1 Introduction

This chapter is concerned with the changes and extensions made to the POIRO MK2 system whose development and evaluation was described in the previous chapter (Chapter 2). Section 3.2 introduces the insulins and associated regimens to be newly incorporated into the system and then goes on to develop and describe the algorithms required for them. Section 3.3 looks at improvements and additions made to the user interface, whilst Section 3.4 is concerned with implementation-related issues highlighted by the extension of the existing system. Section 3.5 concludes the chapter.

3.2 Incorporating new insulin formulations and regimens

The original POIRO system running on the Epson EHT-10 device was developed for use by patients on a basal-bolus insulin regimen consisting of three (Breakfast, Lunch and Dinner) doses of short-acting insulin and one (Bedtime) or two (Breakfast and Bedtime) doses of longacting insulin. Its re-implementation POIRO MK2 for devices running Palm OS uses the same clinical algorithms and hence also only caters for this group of patients. However, following the advent and establishment of new types of insulin, namely intermediate- and rapid-acting insulin, as well as premixed insulin formulations, a decreasing proportion of patients are on shortacting-plus-longacting insulin regimens. Hence given the popularity as well as the advantages of the new insulins, their incorporation into the next version of the POIRO system is clearly called for.

3.2.1 Insulin formulations

General

Currently four different types of insulin are available: rapid-acting, short-acting, intermediate-acting and long-acting. When referring to these types in this thesis, the terms *rapid*, *short*, *intermediate* and *long* are used for simplicity and to facilitate readability.

Insulin is a small protein that, as shown in Figure 3.1, consists of two amino acid chains linked together by two disulfide bridges [21] [34]. It is produced by the pancreas' beta cells and is one of the hormones

involved in the regulation of blood glucose levels. Insulin works by binding to insulin receptors in the cell membrane and thereby increases the membrane's permeability for glucose as well as many amino acids and certain ions [34]. In both Type-1 and Type-2 diabetes insulin secretion is decreased. Insulin therapy therefore aims to replace (Type-1) or supplement (Type-2) the insulin secreted by the pancreas.

Highly purified animal insulin formulations such as Hypurin® Bovine Lente and Hypurin® Porcine Neutral are produced from cows' and pigs' pancreas which are a by-product of the meat industry. Bovine or beef insulin differs from human insulin at three amino acid positions (ALAnine at A8, VALine at A10, ALAnine at B30) whilst porcine or pork insulin differs only at one position (ALAnine at B30) [21]. However, with the increased availability of synthetically produced human insulins and insulin analogues use of animal insulin is becoming less common.
Human insulin can be commercially produced via semisynthesis from pork insulin or through the use of recombinant DNA technology i.e. bacteria or yeast that are genetically modified to produce insulin. Synthetically produced human insulin is identical to naturally produced human insulin.
Insulin analogues are similar but not identical to human insulin. They are 'designer insulins' developed to have particular pharmacological properties such as a rapid (or slow) onset and a short (or prolonged) duration of action. Insulin analogues are produced using recombinant DNA technology.

Insulin types

This section provides key information on each type of insulin. Details of insulin formulations currently available in the UK can be found in Tables B.1 to B.3 in Appendix B. Table B.4 contains the classification of those formulations into the rapid, short, intermediate, long and mixed types used by the POIRO system.

Short-acting insulin

Information source:	BNF [44] Section '6.1.1.1 Short-acting insulins'
Action profile	
Onset of action:	30 to 60 minutes
Peak action:	2 to 4 hours
Duration of action:	up to 8 hours
Pharmaceutical form:	Sterile solution of insulin.
Administration:	15 to 30 minutes before meals

Rapid-acting insulin

At present there are two rapid acting insulin analogues available in the UK: insulin lispro (Humalog®, Lilly) and insulin aspart (NovoRapid®, Novo Nordisk). The amino acid sequence of insulin lispro differs from that of human insulin (Figure 3.1) at two positions: LYSine at B28 and PROline at B29 instead of PROline at B28 and LYSine at B29. Insulin aspart differs from human insulin (Figure 3.1) at position B28 where ASPartate replaces PROline.

Insulin Lispro

Information source:	Humalog® Summary of Product Characteristics [28]
Action profile	
Onset of action:	approximately 15 minutes
Maximum effect:	-
Duration of activity:	2 to 5 hours
Pharmaceutical form:	Sterile, clear, colourless, aqueous solution.
Administration:	shortly before meals

Insulin Aspart

Information source:	NovoRapid® Summary of Product Characteristics [65]
Action profile	
Onset of action:	within 10-20 minutes
Maximum effect:	between 1 and 3 hours
Duration of action:	3 to 5 hours
Pharmaceutical form:	Clear, colourless, aqueous, solution.
Administration:	generally immediately before a meal

Intermediate-acting insulin

Information sources:	Summaries of Product Characteristics for intermediate insulins BNF [44] Section '6.1.1.2 Intermediate- and long-acting insulins'
Action profile	
Onset of action:	1 to 2.5 hours
Maximal effect:	3 to 15 hours
Duration of action:	11 to 30 hours
Pharmaceutical form:	insulin zinc suspension or isophane insulin
Administration:	Once or twice daily in the evening and/or morning.

Long-acting insulin

Information sources:	Summaries of Product Characteristics for long insulins BNF [44] Section '6.1.1.2 Intermediate- and long-acting insulins'
Action profile	
Onset of action:	4 to 6 hours
Maximal effect:	8 to 24 hours
Duration of action:	24 to 36 hours
Pharmaceutical form:	insulin zinc suspension (crystalline) or protamine zinc insulin
Administration:	Once or twice daily in the evening and/or morning.

Ultralong-acting insulin

Currently insulin glargine (Lantus®, Aventis Pharma) is the only ultralong-acting insulin analogue available in the UK. The amino acid sequence of insulin glargine differs from that of human insulin (Figure 3.1) in two respects: GLYcine replaces ASparagiNe at A21 at the end of the A-chain and the B-chain is extended by two ARGinine at B31 and B32. For purposes of the POIRO algorithms glargine has been classified as a longacting insulin.

Information source: Lantus® Summary of Product Characteristics [10]
Action profile:
Smooth, peakless, predictable concentration/time profile with a prolonged duration of action.
Pharmaceutical form: Clear colourless solution.
Administration: Once daily at any time, but at the same time each day.

Premixed insulins
Premixed insulins, in varying fixed ratios, contain rapid or short and intermediate or long insulin. The action profile, pharmaceutical form, and mode and timing of administration of premixed insulin are difficult to generalise since they depend on the individual formulation's components and their ratio. If the details of a specific insulin formulation are of interest, the manufacturer's Summary of Product Characteristics (SPC) accessible for example through the *electronic Medicines Compendium* at http://emc.medicines.org.uk/ can provide a useful overview of key information.

Using images from the Novo Nordisk Product Portal [66] Figure 3.2 illustrates the different insulins' action profiles and thus concludes this section.

3.2.2 Insulin regimens

Table B.5 in Appendix B lists the most commonly used insulin regimens.

- Patients with insulin-dependent diabetes typically use two types of insulin: an intermediate or longacting formulation taken once or twice daily to maintain a basal level of insulin and a rapid or short formulation before or with the main meals to cover additional insulin requirements corresponding to the carbohydrate content of the meal (Regimens 3-4 & 6-7).
- Mixed insulin formulations, in varying fixed ratios, contain rapid or short and intermediate or long insulin and thus one or two formulations taken twice daily can comprise an insulin regimen (Regimens 1 & 10).
- A mixed insulin formulation and a rapid or short insulin can also be combined (Regimens 8 & 9).
- Insulin regimens consisting of only intermediate or long insulin are typically used in the treatment of patients with Type-2 diabetes (Regimens 2 & 5).

Insulin regimens are of course specific to the individual patient and his/her habits and lifestyle, but with respect to the timing of insulin injections typically

- rapid or short insulin is taken before or with the main meals Breakfast, Lunch and Dinner.
- intermediate insulin is taken twice daily before or with Breakfast and Dinner.
- long insulin is taken once daily with the Bedtime snack or twice daily at Breakfast and Bedtime.
- mixed insulin is taken twice daily at Breakfast and Dinner, with the rapid or short component of the injections covering the insulin requirements due to Breakfast and Dinner and the intermediate or long component of the doses maintaining a basal level of insulin. Insulin requirements due to Lunch can be met either with the intermediate acting component of the Breakfast insulin dose or with a separate injection of rapid or short insulin before or with Lunch.

Figure 3.2 (original in colour): Insulin action profile illustrations: (a) short insulin, (b) intermediate insulin, (c) long insulin and (d) mixed insulin. Image source: Novo Nordisk Product Portal [66]

The decision support algorithms used by the POIRO system are described in the next section (Section 3.2.3).

3.2.3 Algorithms

General

Glycaemic control

A patient's glycaemic control is modelled based on the pre-prandial blood glucose values entered for the different times of the day. Apart from their role in the assessment of an individual insulin dose's effectiveness, these readings are used for two other important purposes:

1. The weighted average variance of the fasting blood glucose (fBG) values is used to adjust a patient's current fBG target so as to minimise the risk of hypoglycaemic episodes.

2. The weighted average glucose value for a particular time of day can be used instead of a measured value at that time of day, thereby allowing the system to cope with missing data.

The use of actual and derived glucose values in the Palm OS versions of the POIRO system does not differ from that in the original system but the way weighted averages and variances are calculated has been amended slightly.

The equations shown in (3.1) describe how the moving glucose average and variance for a particular time of day are updated when a new glucose value for that time of day is recorded. They are a rearranged but otherwise identical form of equations E4.2 and E4.3 in [43]. The difference between the weighted average and variance calculations based on (3.1) and those based on equations E4.2 and E4.3 in [43] lies in the interpretation of the variables n and dd in those equations.

$$
\begin{aligned}
new\ weight &= \frac{1}{n} + \frac{dd}{30} \\
old\ weight &= 1 - new\ weight \\
new\ average &= new\ weight * new\ value + old\ weight * old\ average \\
new\ variance &= new\ weight * (new\ value - new\ average)^2 + old\ weight * old\ variance
\end{aligned}
\tag{3.1}
$$

In equations E4.2 and E4.3 the variable n was "the total number of pre-prandial blood glucose determinations" for the time of day concerned whilst the variable dd was the "time difference in days" between the current i.e. the newly entered blood glucose value and the "previous most recently entered blood glucose" for the current time of day.

The amended calculations however define variable n as "the number of glucose determinations that contributed to the moving glucose statistics" and variable dd as "time difference in days between the newly entered glucose value and the last update of the moving glucose statistics". These revised definitions are required since a newly introduced rule governing the updating of the moving glucose

statistics means that potentially not every glucose value entered will contribute towards the moving average and variance. Hence the "when a new glucose value for that time of day is recorded" above should strictly read "when an *eligible* new glucose value for that time of day is recorded". In particular glucose values will not be eligible to contribute towards the moving statistics if the patient experienced a hypoglycaemic episode in the 12 hours prior to the glucose measurement. This is so because hypoglycaemia activates a protective counter-regulation mechanism in the body which increases the production of certain hormones so as to prevent glucose levels from decreasing even further. In the hours after a hypo the levels of these hormones and that of glucose are thus artificially elevated. Also, the consumption of a snack or larger than usual meal to counteract hypoglyaemia might result in post-hypo glucose measurements that are not representative of the usual glucose readings for that particular time of the day. With respect to patient safety it should be noted that whilst certain post-hypo glucose measurements do not contribute towards moving glucose statistics, they do contribute in other parts of the system's algorithms.

Lifestyle-related adjustments

As in the previous version of the system, a bolus (rapid or short) dose suggested by the system may differ from the usual dose for that time of the day if the pre-prandial glucose value entered is outside the target range and/or if any of the lifestyle aspects (meal size, exercise level, health status) are non-standard. Those lifestyle-related adjustments or supplementary insulin doses are essentially calculated according to the "simple relative multiplication factor system" described in [43]. Table B.6 in Appendix B shows the current system's default multipliers or multiplication factors. The multiplication factors are not constants but form part of the system's physician-determined patient-specific settings. If required the default multiplication factors can hence be adapted and customised for individual patients. For the purpose of reviewing default or individual multiplication factors and factor combinations a spreadsheet such as the one shown in Table B.7 has been devised and was found to be useful. Also, as indicated by the α and β symbols in Table B.7 the meal-size-nothing-exception rule described in [43] has been slightly revised and an additional very-low-glucose-exception rule has been introduced.

Hypoglycaemic episodes

As did the original POIRO system, the current version of the system processes hypoglycaemic episodes (hypos) by attempting to identify and if appropriate reduce the insulin dose that caused it. However, different to the original system, the current version carries out additional checks to avoid the further reduction of an already reduced insulin dose. This was one of the potential improvements identified in [43]. We have also enhanced the hypo-related data entry facilities through the addition of

- screens for the recording of blood glucose values measured whilst hypo,
- a screen to record the most likely reason, if known, for the hypo, and
- warning messages that are displayed if the patient experiences hypos too frequently.

These user interface improvements and additions are described in detail in Section 3.3.1.

Offsets

The concept of a glucose offset is central to the dose change calculations for all types of insulin. As introduced in [43] the term glucose offset in the context of the POIRO system refers to the difference

between an actually measured glucose value and the corresponding ideally expected glucose value. Equation (3.2) shows the original offset equations E4.7 and E4.8.

$$\begin{aligned} &\text{E4.7} \quad expected\ value\ =\ previous\ value\ +\ expected\ offset \\ &\text{E4.8} \quad actual\ offset\ =\ actual\ value\ -\ expected\ value \end{aligned} \tag{3.2}$$

Based on this simple $offset = actual - expected$ idea this sections describes the glucose offset concept of the POIRO MK3 system. This extended offset concept is used for the dose change calculations for short and long as well as for rapid, intermediate and premixed insulins. It is thus more generic, though admittedly also more complex.

So as to group related monitoring data together let us introduce tuples E_i of times, glucoses and meal types as described in Equation (3.3).

$$E_i = (t_i,\ g_i,\ m_i) \tag{3.3}$$

$t_i = time(E_i)$ = date and time of the monitoring data tuple

$g_i = glucose(E_i)$ = glucose level measured prior to the meal of type m_i or moving average for meal time m_i if no actual glucose reading was recorded

$m_i = meal(E_i)$ = type of meal recorded with $m_i \in \{Breakfast,\ Lunch,\ Dinner,\ Bedtime,\ Snack\}$ or $m_i = Uncertain$ if no meal was recorded yet

The date and time $t_i = time(E_i)$ of the monitoring data tuple E_i will be that of the insulin injection taken with the meal of type m_i. If that injection was not recorded, t_i will be the date and time of the glucose reading g_i. If that glucose reading is also missing that is if g_i is only a moving average then t_i will be the date and time of the meal size record for the meal of type m_i. Should this information also be missing, the tuple would take the form $E_i = (-,\ g_i,\ m_i)$.

We can now define the tuple $E_{current}$ as the monitoring data currently being entered. Note that the value $glucose(E_{current})$ corresponds to the *actual value* in Equation (3.2).

$$\begin{aligned} &glucose\_offset(offset\_type) = glucose(E_{current}) - expected\_glucose(offset\_type,\ E_{current}) \\ &offset\_type \in \{bolus\_offset,\ basal\_offset\} \end{aligned} \tag{3.4}$$

Comparison of the old and new offset definitions, Equations (3.2) and (3.4) respectively, shows that in the POIRO MK3 system we now have two distinctly different types[i] of offset. *Bolus offsets* are offsets caused by a meal and its associated bolus insulin dose. *Basal offsets* are independent of meals

and determined solely by the basal insulin dose or doses. Detailed information about how the bolus and basal offsets are calculated can be found in the two sections that follow this section.

$$expected\_glucose(offset\_type,\ E_{current}) = f(FBG\_target,\ E_1,\ E_2,\ E_3,\ E_4) \tag{3.5}$$

FBG_target = the patient's current fasting blood glucose target

$E_1,\ E_2,\ E_3,\ E_4$ = tuples of most recent monitoring data such that

$$UNION_{i=1}^{4}(meal(E_i)) = \{Breakfast,\ Lunch,\ Dinner,\ Bedtime\}$$

$$meal(E_i) = meal(E_{i+1}) + 1 \text{ for all i} = 1..3$$

$$E_c \in \{Breakfast,\ Lunch,\ Dinner,\ Bedtime\} \Rightarrow E_c = E_1 + 1$$

Generally, as shown in (3.5), every expected glucose value $expected\_glucose(offset\_type,\ E_{current})$ that corresponds to an actual glucose measurement $glucose(E_{current})$ is a function of a number of variables. With respect to $E_{current}$ please note that $glucose(E_{current})$ can not only be a glucose measurement pre-prandial to a main or snack meal but may also be a glucose with an as yet uncertain associated meal type. However, if $meal(E_{current})$ is a main meal then $meal(E_1)$ must logically precede it so that $< E_{current},\ E_1,\ E_2,\ E_3,\ E_4 >$ is a reverse of the standard meal sequence $< ...,\ Breakfast,\ Lunch,\ Dinner,\ Bedtime,\ Breakfast,\ ... >$.

Also note that if some monitoring data tuple E_j in Equation (3.5) above were to lack its $t_j = time(E_j)$ value i.e. is of the form $E_j = (-,\ g_j,\ m_j)$ then the calculation of the *expected_glucose* value will nevertheless be possible so long as $f(FBG\_target,\ E_1,\ E_2,\ E_3,\ E_4)$ does not require the $t_j = time(E_j)$ information.

This section so far described how single glucose offsets in general are calculated. So as to assess the effectiveness of insulin doses over time, the system also maintains weighted moving average glucose offsets. Equation (3.6) shows how the moving averages are calculated.

$$new\ weight = \frac{1}{n} + \frac{dd}{120}$$

$$old\ weight = 1 - new\ weight$$

$$new\ average = new\ weight * new\ value + old\ weight * old\ average \tag{3.6}$$

n = the number of single offsets that contribute to the new average offset

dd = the time difference in days between the newly calculated single offset and the last update of the moving average offset

This calculation is identical to the one used in the previous POIRO systems. Also note that depending on (i) lifestyle factors, (ii) short-term glucose trends, (iii) hypos, (iv) whether or not recent dose advice was followed and (v) the completeness and recency of the monitoring data, meaningful glucose offsets can not always be calculated. The rules that govern the appropriateness of glucose offset calculations are again those of the previous POIRO systems. However, whilst the basic principles underlying the calculation of single and average offsets have not changed, in the POIRO MK3 system a number of improvements have been made as follows:

1. With respect to the updating of moving average statistics, the rules for discarding glucose offsets following a hypoglycaemic episode have been simplified and harmonised with the equivalent rules for discarding glucose values (Section 3.2.3): glucose values measured and glucose offsets calculated in the 12 hours following a hypo are not used for the updating of the moving average offsets.

2. Following a dose change all relevant glucose offsets are reset to zero. This means that the first offset calculated thereafter is given 100% weight and the average offset is then equal to the first and last and only single offset. In the original system, even an average glucose offset based on just one single offset value could trigger an insulin dose change. Single offsets assess the effectiveness of a single insulin injection. A physician however would generally not base a permanent dose change decision on just one such piece of information. Therefore we have, in the POIRO MK3 system, amended the dose change calculation algorithms so that an average offset based on just one single offset value can no longer trigger an insulin dose change. This small extra rule should also have a stabilising influence on a patient's glycaemic control by helping to prevent too hasty and/or too frequent dose changes.

3. Implementation changes related to the extension of the system identified two omissions in the recording of offset-related timestamps i.e. the date and time at which an offset was calculated. These timestamps are required so that out-of-date i.e. too old offsets can be discarded for dose change calculation purposes. Previous implementations record timestamps for average glucose offsets but not for single glucose offsets. However, since some single offsets are used in dose change calculations their timestamps should be recorded. The POIRO MK3 system now does record and make use of those additional two offset timestamps. However, to put this correction into perspective it must be said that the timestamp omission is theoretically and conceptually important, but in practice inconsequential given

   (a) the underlying relationship between the values and timestamps of average and single offsets,

   (b) the regular and frequent, if not daily, use of the system, and

   (c) a 'discard out-of-date offset' threshold of 30 days.

4. The additions described above have increased the already existing complexity of using offsets in dose change calculations. We have therefore introduced a new offset variable. The so-called $indicative\_offset$ is an offset derived from single and average offsets and it is this indicative offset that directly determines the magnitude of any insulin dose changes. Equation (3.7) formally describes how indicative offsets are calculated.

IF

$mean\_offset$ is based on only one single offset
OR
$now - timestamp(mean\_offset) > 30\ days$
OR
$now - timestamp(last\_single\_offset) > 30\ days$
OR
$now - timestamp(lastbutone\_single\_offset) > 30\ days$
THEN
$indicative\_offset := 0.0$
ELSE (3.7)
IF
$mean\_offset > allowed\_mean\_offset$
THEN
$indicative\_offset := mean\_offset$
ELSE
IF
$(last\_single\_offset > allowed\_single\_offset$
AND
$lastbutone\_single\_offset > allowed\_single\_offset)$
OR
$(last\_single\_offset < -allowed\_single\_offset$
AND
$lastbutone\_single\_offset < -allowed\_single\_offset)$
THEN
$indicative\_offset := \frac{(last\_single\_offset + lastbutone\_single\_offset)}{2}$
ELSE
$indicative\_offset := 0.0$

This section described the general aspects of the POIRO MK3 glucose offset concept. More specific and detailed information is provided in the following three sections about dose change calculations for different types of insulin.

Short- and rapid-acting insulins

Short- and rapid-acting insulin doses, taken shortly before or with a meal, aim to meet the body's increased, meal-related insulin requirements. Shortly after the beginning of a meal, carbohydrates and other components of the meal start to be digested and blood glucose levels rise. In healthy persons, in response to the increased blood glucose concentration, the pancreas produces more insulin and thus promotes glucose utilisation and storage i.e. decreases glucose levels. This rapid glucose-insulin feedback loop tightly maintains blood glucose levels within a relatively narrow normal range. In patients with diabetes insulin production and/or the glucose-insulin feedback loop are partially or completely impaired. The purpose of the bolus insulin injections is thus the achievement of blood glucose and insulin concentration profiles that closely mimic the normal physiological response. Taking into account an insulin's action profile (see Section 3.2.1 and Figure 3.2) and typical meal sizes and compositions, ideally expected post-prandial blood glucose excursion profiles can be devised. In [43]

these are called "standard meal excursion reference curves" or "meal reference curves". Equation (3.8) follows on from Equation (3.5) and formally describes how the curves are used to calculate expected post-prandial glucose values $expected\_glucose(bolus\_offset,\ E_{current})$.

$$
\begin{aligned}
&expected\_glucose(bolus\_offset,\ E_{current}) = f(FBG\_target,\ E_1,\ E_2,\ E_3,\ E_4) \\
&= glucose(E_1) + expected\_bolus\_offset(insulin\_type,\ meal(E_1))(time\_elapsed) \\
&\\
&insulin\_type \in \{short\_insulin,\ rapid\_insulin\} \\
&meal(E_1) \in \{Breakfast,\ Lunch,\ Dinner\} \\
&time\_elapsed = time(E_{current}) - time(E_1)
\end{aligned}
\tag{3.8}
$$

Note that expected post-prandial offsets and thus bolus offsets are only calculated for *Breakfast*, *Lunch* and *Dinner* meals. Also, expected post-prandial offsets can only be calculated if an actual post-prandial glucose measurement is taken and recorded within 5 (rapid insulin) or 8 (short insulin) hours after the meal and injection concerned i.e. $time\_elapsed <= 5$ for rapid and $time\_elapsed <= 8$ for short insulin.

$$
\begin{aligned}
&expected\_bolus\_offset(short\_insulin,\ Breakfast) \\
&= ((0,\ 0.0),\ (1,\ 5.8),\ (2,\ 6.5),\ (3,\ 3.8),\ (4,\ 1.5),\ (5,\ 0.0),\ (6,\ 0.0),\ (7,\ 0.0),\ (8,\ 0.0)) \\
&\\
&expected\_bolus\_offset(short\_insulin,\ Lunch) \\
&= ((0,\ 0.0),\ (1,\ 3.5),\ (2,\ 2.8),\ (3,\ 2.3),\ (4,\ 1.1),\ (5,\ 0.0),\ (6,\ 0.0),\ (7,\ 0.0),\ (8,\ 0.0)) \\
&\\
&expected\_bolus\_offset(short\_insulin,\ Dinner) \\
&= ((0,\ 0.0),\ (1,\ 3.5),\ (2,\ 2.8),\ (3,\ 2.3),\ (4,\ 1.1),\ (5,\ 0.0),\ (6,\ 0.0),\ (7,\ 0.0),\ (8,\ 0.0))
\end{aligned}
\tag{3.9}
$$

For all coordinates $(t,\ e)$

- t is the time (in hours) that has elapsed since the insulin injection,
- e is the ideally expected post-prandial blood glucose excursion (in mmol/L),
- linear interpolation between the nearest values is used for non-integer values of t,
- extrapolation beyond (8, 0.0) is not permited and values for $t > 8$ are not defined.

Equations (3.9) and (3.10), for short and rapid-acting insulin respectively, define the expected post-prandial glucose excursion profiles used in the POIRO MK3 system. The profiles for short-acting insulin are those used in previous versions of the system. The profiles for rapid-acting insulin are new and were derived from

- the blood glucose profiles for the rapid-acting insulins Lispro and Aspart published in [74],
- the post-prandial glucose excursion data for Lispro (rapid-acting) and Humulin S (short-acting) given in [29], and
- the expected post-prandial blood glucose excursion profiles (Equation (3.9)) for short-acting insulin used by the POIRO system.

$expected\_bolus\_offset(rapid\_insulin,\ Breakfast)$ =
((0, 0.0), (20, 1.4), (40, 3.0), (60, 3.5), (80, 3.1), (100, 2.8), (120, 2.5), (140, 2.0), (160, 1.7), (180, 1.2), (200, 0.8), (220, 0.4), (240, 0.0), (260, 0.0), (280, 0.0), (300, 0.0))

$expected\_bolus\_offset(rapid\_insulin,\ Lunch)$ =
((0, 0.0), (20, 1.4), (40, 3.0), (60, 3.5), (80, 3.1), (100, 2.8), (120, 2.5), (140, 2.0), (160, 1.7), (180, 1.2), (200, 0.8), (220, 0.4), (240, 0.0), (260, 0.0), (280, 0.0), (300, 0.0))

$expected\_bolus\_offset(rapid\_insulin,\ Dinner)$ = (3.10)
((0, 0.0), (20, 1.4), (40, 3.0), (60, 3.5), (80, 3.1), (100, 2.8), (120, 2.5), (140, 2.0), (160, 1.7), (180, 1.2), (200, 0.8), (220, 0.4), (240, 0.0), (260, 0.0), (280, 0.0), (300, 0.0))

For all coordinates (t, e)
- t is the time (in minutes) that has elapsed since the insulin injection,
- e is the ideally expected post-prandial blood glucose excursion (in mmol/L),
- linear interpolation between the nearest values is used for non-integer values of t,
- extrapolation beyond (300, 0.0) is not permitted and values for $t > 300$ are not defined.

Figures 3.3 and 3.4, corresponding to Equations (3.9) and (3.10), illustrate the expected post-prandial glucose excursion profiles for short and rapid-acting insulin respectively.

As described above, the current version of the POIRO system contains six different glucose excursion profiles overall. Previously these profiles were unlikely to change and thus implemented as hard-coded constants. Recognising that expected pre-prandial blood glucose profiles may vary not only between insulin types (short versus rapid) but also between insulin formulations of the same type and of course between patients, we have, in the POIRO MK3 system, taken the opportunity not to hard-code these profiles but to incorporate them as part of the patient-specific settings. The six profiles given here are the default profiles. However, future versions of the clinic system could provide a collection of different glucose excursion profiles for different insulin formulations and/or facilities to customise profiles to individual patients' requirements.

To conclude this section, a brief discussion of the practical differences between short and rapid-acting insulin.

- From a medical point of view, injections of rapid insulin with fast onset and short duration of action provide glucose and insulin profiles that, compared to short insulin, more closely match normal physiological responses. In particular, three clinical advantages of Lispro over regular human i.e. short-acting insulin given by [16] are (i) decreased intraindividual and interindividual variability in insulin absorption, (ii) significantly reduced 1 and 2-hour postprandial glucose-level excursions, and (iii) less late postprandial hypoglycaemia.

- From a patient's point of view, rapid-acting insulin is taken just before a meal, not 15 to 30 minutes before the meal as with short-acting insulin. Clearly this is more convenient and less likely to interfere with normal work and daily routine. Nevertheless, it should be noted that rapid insulins are not suitable for all patients. For example, the insulin's rapid onset of action

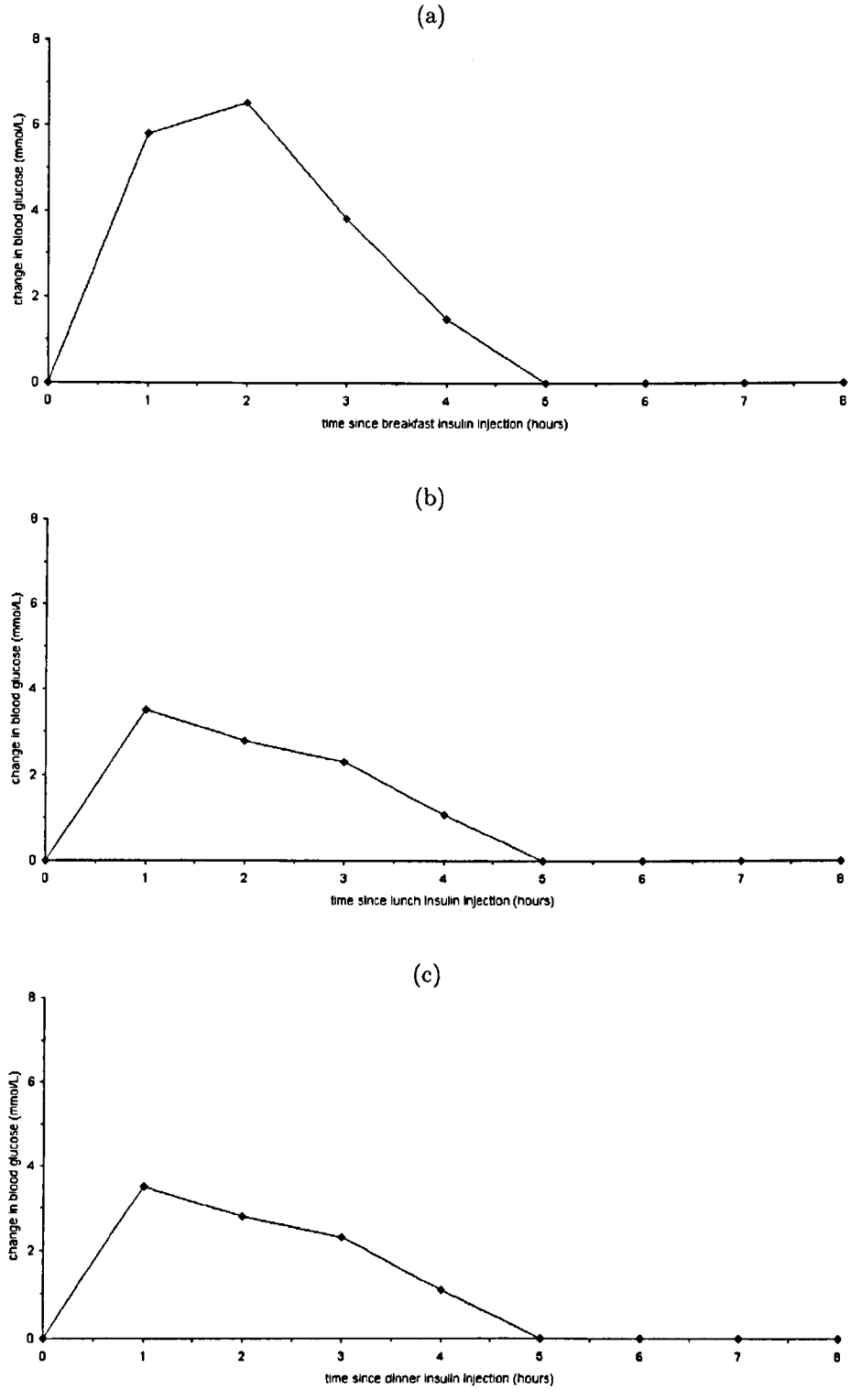


Figure 3.3: Ideally expected post-prandial blood glucose excursion profiles (short-acting insulin) - (a) Breakfast, (b) Lunch, (c) Dinner

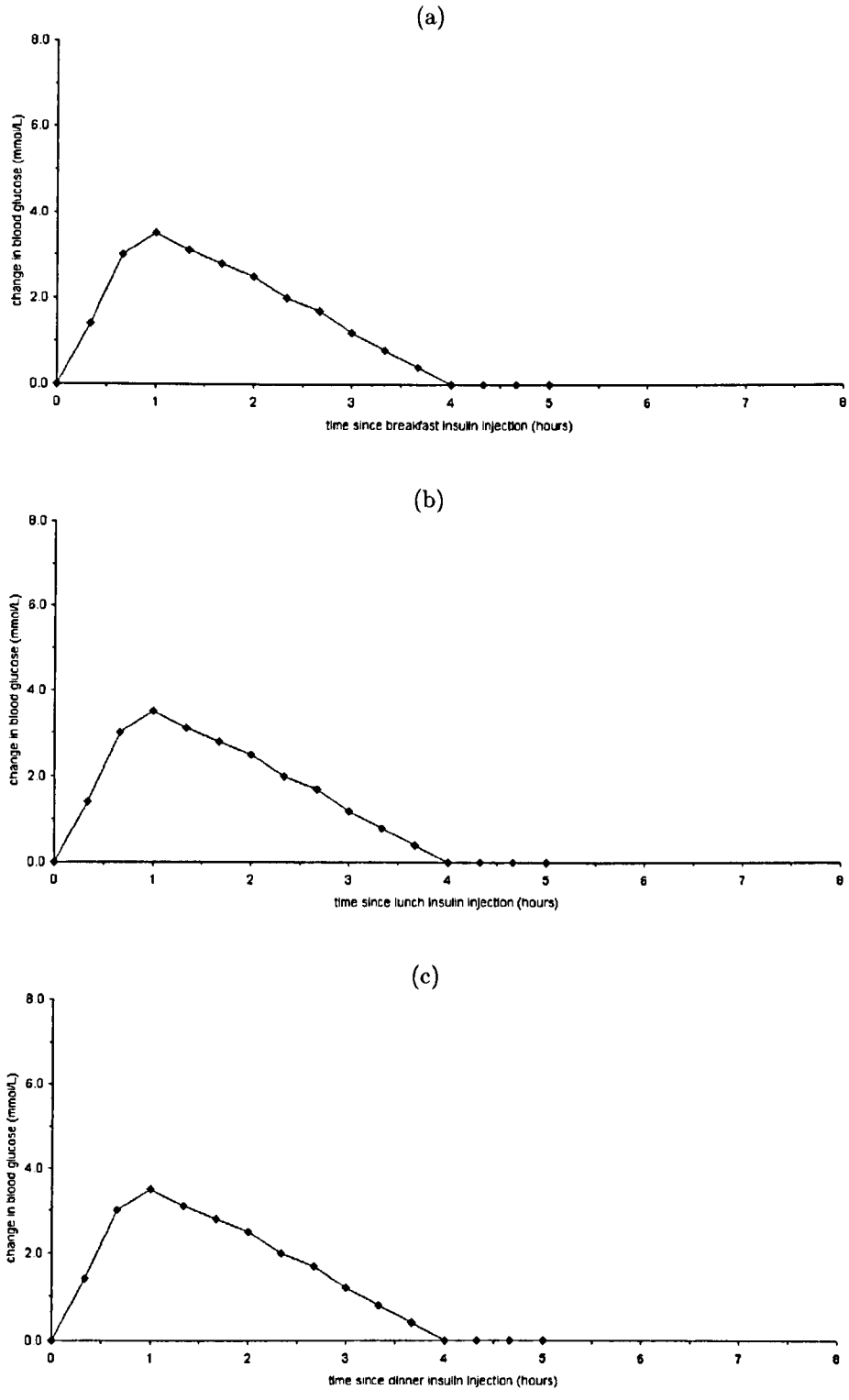


Figure 3.4: Ideally expected post-prandial blood glucose excursion profiles (rapid-acting insulin) - (a) Breakfast, (b) Lunch, (c) Dinner

means that timing is crucial since, after having taken the insulin, an unexpected delay of the corresponding meal can lead to hypoglycaemia. For this reason some patients on rapid insulin actually take their meal-related insulin doses just after the meal.

- From the information-processing point of view of the POIRO system, the shorter action profile of rapid insulin means that the post-prandial time interval during which a rapid dose's effectiveness can be meaningfully assessed is reduced from 8 to 5 hours. At the same time the steeper action profile could also cause the algorithm to be more sensitive to variation in insulin response and glucose levels. To compensate for this, the values of the *allowed_mean_offset* and *allowed_single_offset* thresholds (Equation (3.7)) for rapid dose change calculations might hence have to be higher than for short-acting insulin.

Intermediate- and long-acting insulins

Intermediate- and long-acting insulin doses aim to meet the body's basal insulin requirements. With 11 to 36 hours (Section 3.2.1 and Figure 3.2) their duration of action is much longer than that of rapid or short insulin. Hence intermediate and long insulins are taken only once or twice daily.

As in previous versions of the system, the effectiveness of the evening long-acting insulin dose, normally taken at *Bedtime*, is assessed via the following day's fasting glucose. Similarly, but new to the POIRO MK3 system, the effectiveness of the evening intermediate insulin dose, normally taken at *Dinner*, is assessed via fasting glucose values. Also new to POIRO MK3 is that the effectiveness of any morning intermediate- or long-acting insulin dose, normally taken at *Breakfast* time, is assessed via the same day's pre-*Dinner* glucose.

Besides, with respect to twice daily long-acting doses, previous system versions assumed that the total daily basal dose is always split equally between the *Bedtime* and *Breakfast* doses. In the POIRO MK3 system we relax this assumption: total daily long as well as intermediate insulin doses may be split in any proportion[ii]. Also, basal dose injection times have been extended from *Bedtime* or *Bedtime*+*Breakfast* to evening injections at *Dinner* or *Bedtime* + morning injections at *Breakfast* or *Lunch*, although we acknowledge that some of the now permissible basal dose combinations such as long insulin at *Lunch* and *Dinner* are rare in practice.

$$
\begin{aligned}
&expected\_glucose(basal\_offset,\ E_{current}) \ = \ f(FBG\_target,\ E_1,\ E_2,\ E_3,\ E_4) \\
&= \begin{cases}
FBG\_target & \text{for} \quad meal(E_{current}) \ = \ Breakfast \\
glucose(E_2) & \text{for} \quad meal(E_{current}) \ = \ Dinner \\
\text{undefined} & \text{for} \quad meal(E_{current}) \in \{Lunch,\ Bedtime,\ Uncertain\}
\end{cases}
\end{aligned}
\tag{3.11}
$$

In summary, intermediate- and long-acting dose change calculations are based on fasting i.e. *Breakfast* and/or *Dinner* basal glucose offsets. Equation (3.11) follows on from Equation (3.5) and formally describes how those basal offsets are calculated.

Premixed, biphasic insulin formulations

Premixed or biphasic insulin formulations are insulins that, in varying ratios, contain both rapid or short and intermediate or long insulin (Section 3.2.1 and Figure 3.2). From a patient's point of view,

an insulin regimen based on premixed insulins is very convenient since it requires fewer injections than the other regimens (Section 3.2.2). From a medical and information-processing point of view, premixed insulins pose a challenge since dose changes and adjustments are constrained by the formulations' mix-ratios. This section describes the insulin regimen optimisation algorithms developed for premixed insulins. However, due to time constraints, these algorithms have not been implemented in the MK3 version of the POIRO system (Table B.5).

The biggest challenge of dose change calculations for premixed insulins is deciding on the appropriateness, direction and magnitude of a dose change. This is due to the fact that any dose increase or decrease would apply to both components of the biphasic dose, something that will not always be required or desired.

The key idea behind the solution outlined in this section is to *in principle* treat premixed insulin doses *as if* they were two separate doses. This means that a 24 U dose of Mixtard® 20 for example will be processed as if it was a 4.8 U short-acting insulin dose plus a 19.2 U intermediate-acting dose. The main advantage of this approach is the reuse of the extensive, already established rules and algorithms. Built on top of the existing information processing and reasoning, the premixed insulin algorithms will then reconcile the two notionally separate doses into one actual dose. The three areas in which this will be required are (i) dose change calculations, (ii) lifestyle-related dose adjustments and (iii) hypo-related dose reductions.

Dose change calculations

For non-premixed insulins Equations (3.7), (3.8) and (3.11) are used to determine the actual glucoses' distance from the ideally expected values. Next, sensitivity factors (Equation (3.12)) are used to translate the 'distance from target' into theoretical dose changes. Finally, the absolute and relative safety parameters set by the patient's physician are used to convert the theoretical, unconstrained dose change into an actual, safe dose change.

$$\begin{aligned} insulin\_sensitivity(insulin\_type) &= \text{number of units of } insulin\_type \text{ insulin required to change the corresponding blood glucose values by 1 mmol/L} \\ insulin\_type &\in \{rapid\_insulin,\ short\_insulin,\ intermediate\_insulin,\ long\_insulin\} \end{aligned} \tag{3.12}$$

Hence, for biphasic premixed formulations of $fast\_insulin\_type$ and $slow\_insulin\_type$ insulin

$$\begin{aligned} &indicative\_bolus\_offset * insulin\_sensitivity(fast\_insulin\_type) \\ &\text{and} \\ &indicative\_basal\_offset * insulin\_sensitivity(slow\_insulin\_type) \\ &\text{with} \\ &fast\_insulin\_type \in \{rapid\_insulin,\ short\_insulin\} \\ &\text{and} \end{aligned} \tag{3.13}$$

$$slow\_insulin\_type \in \{intermediate\_insulin,\ long\_insulin\}$$

would be the theoretical, unconstrained dose changes required. Focusing not on the magnitude but the direction of the two dose changes, nine different dose change scenarios (Table 3.1) are possible.

For the three scenarios along the top-left to bottom-right diagonal it is clear that a dose decrease, no dose change and a dose increase respectively are what is required. For the remaining scenarios, and in particular the contradictory dose change directions of the bottom-left and the top-right cells, the most appropriate dose change decision is less apparent. To address this problem, we must go back to Equation (3.7) and look at how the need for a dose change is determined. Equation (3.14) extends Equation (3.7) with an $offset\_trend$ variable and shows that when the indicative offset $indicative\_offset$ is zero, there may nevertheless be an underlying trend towards a dose change if the $mean\_offset$ is inside the $allowed\_mean\_offset$ range but not zero.

IF
  $mean\_offset$ is based on only one single offset
  OR
  $now - timestamp(mean\_offset) > 30\ days$
  OR
  $now - timestamp(last\_single\_offset) > 30\ days$
  OR
  $now - timestamp(lastbutone\_single\_offset) > 30\ days$
THEN
  $indicative\_offset := 0.0$
  offset_trend := 0.0
ELSE
  IF
    $mean\_offset > allowed\_mean\_offset$
  THEN
    $indicative\_offset := mean\_offset$
  ELSE
    IF
      ($last\_single\_offset > allowed\_single\_offset$
      AND
      $lastbutone\_single\_offset > allowed\_single\_offset$)
    OR
      ($last\_single\_offset < -allowed\_single\_offset$
      AND
      $lastbutone\_single\_offset < -allowed\_single\_offset$)
    THEN
      $indicative\_offset := \frac{(last\_single\_offset + lastbutone\_single\_offset)}{2}$
    ELSE
      $indicative\_offset := 0.0$
      offset_trend := mean_offset

(3.14)

Table 3.2, an extension of Table 3.1, shows that we now have 25 different dose change combination scenarios to consider. The dose change decisions proposed in the scenario grid basically correspond to the following three rules:

1. Dose decreases required for one insulin type must, for safety reasons, always be carried out (Column 1 & Row 1).
2. Dose increases are carried out if they are required for both insulin types (Column 5 Row 5).
3. Dose increases are also carried out if an increase is required for one insulin type and a trend towards an increase is present for the other insulin type (Column 4 Row 5 & Column 5 Row 4).

With respect to the magnitude of any premixed insulin dose changes it is proposed that these are restricted to 1 U, subject to the absolute minimum and maximum dose limits set by the physician. More ellaborate calculations based for example on the insulin sensitivity factors and/or the formulation's mix-ratio could of course be devised. However, such calculations would not only increase the dose change algorithm's complexity but would also be frequently overridden by the relative dose change limit rules which state that a dose change must not exceed a certain percentage (e.g. 10%) of the current dose.

Lifestyle-related dose adjustments

As described in [43] and summarised earlier in this section, the way individual rapid and short doses are calculated takes into account lifestyle factors by multiplying the usual insulin dose D with a lifestyle-related multiplication factor f and then rounding to the nearest whole number. Correspondingly, for a mixed insulin formulation that contains $(100 * p_{fast})\%$ fast- (rapid or short) and $(100 * p_{slow})\%$ slow-acting (intermediate or long) insulin and a usual dose of D_m units, the lifestyle-adjusted suggested insulin dose should be calculated as shown in Equation (3.15).

$$\begin{aligned} D_m * p_{fast} &= \text{units of fast-acting insulin usually taken} \\ f * D_m * p_{fast} &= \text{fast-acting dose to be taken based on the lifestyle data entered} \\ round(f * D_m) &= \text{suggested mixed dose equivalent to } f * D_m * p_{fast} \end{aligned} \tag{3.15}$$

This straightforward lifestyle-adjustment calculation has however the drawback of changing the fast- as well as the slow-acting insulin components of the mixed insulin dose. Three different but not mutually exclusive approaches to mitigating this problem are proposed as follows:

1. *Single dose adjustment limits* The size of the multiplication factor f and/or the magnitude of the dose supplement $round(f * D_m) - D_m$ could be limited. Example limits might be $0.75 <= f <= 1.25$ and $-8 <= round(f * D_m) - D_m <= +4$.
2. *Multiple dose adjustment limits* The amount by which all slow-acting insulin doses taken within the last 24 hours may cummulatively differ from the usual daily slow-acting dose could be limited. If previous doses were higher than usual then this rule would limit subsequent upwards dose adjustments. At the same time, if previous doses were lower than usual then the rule would

		slow_insulin_type insulin component		
		dose decrease	no dose change	dose increase
fast_insulin_type insulin component	dose decrease	—	?	?
	no dose change	?	0	?
	dose increase	?	?	+

Table 3.1: Biphasic insulin dose change scenarios I: − = dose decrease, 0 = no dose change, + = dose increase, ? = several dose change decisions plausible

			slow_insulin_type insulin component				
			dose decrease	no dose change			dose increase
				trend towards dose decrease	no trend towards a dose change	trend towards dose increase	
fast_insulin_type insulin component	dose decrease		—	—	—	—	—
	no dose change	trend towards dose decrease	—	0	0	0	0
		no trend towards a dose change	—	0	0	0	0
		trend towards dose increase	—	0	0	0	+
	dose increase		—	0	0	+	+

Table 3.2: Biphasic insulin dose change scenarios II: − = dose decrease, 0 = no dose change, + = dose increase

allow more generous subsequent upwards dose adjustment so as to make up the daily slow-acting insulin shortfall.

3. *Dose adjustment optimisation* Based on the ideally taken doses of $f * D_m * p_{fast}$ units fast-acting and $D_m * p_{slow}$ units slow-acting insulin and other available information the dose adjustment could be optimised as described in the remainder of this section.

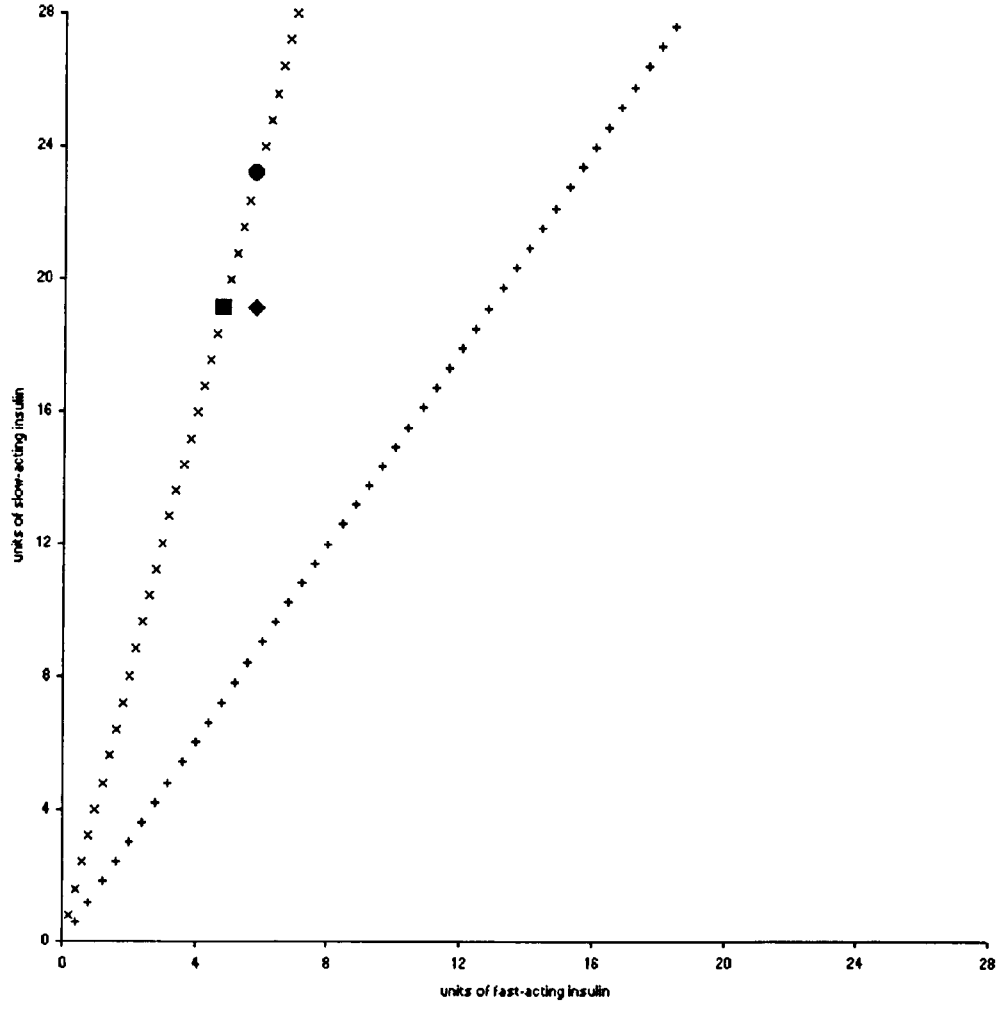


Figure 3.5: Dose adjustment optimisation I: × symbols = Mixtard® 20 insulin doses, + symbols = Mixtard® 40 insulin doses, ■ symbol = usual insulin dose (24 U Mixtard® 20), • symbol = unoptimised lifestyle-adjusted dose ($1.2 * 24\ U \approx 29\ U$), ♦ symbol = optimal lifestyle-adjusted dose ($1.2 * 24\ U * 20\% = 5.76\ U$ fast-acting plus $24\ U * 80\% = 19.2\ U$ slow-acting insulin)

A graph such as the one shown in Figure 3.5 visualises all theoretically possible solutions to the dose adjustment optimisation problem. Each data point represents one insulin dose with the x- and y-values being the number of units of fast- and slow-acting insulin in that dose. It is assumed that each patient uses two different insulin mixes e.g. Mixtard® 20 (× symbols) and Mixtard® 40 (+ symbols). The ■ symbol represents the insulin dose usually taken with the current meal, here 24 U of Mixtard® 20 insulin. Based on a lifestyle-related multiplication factor of $f = 1.2$ the • symbol indicates the unoptimised adjusted dose of 29 U Mixtard® 20 calculated according to Equation (3.15). Not coinciding with a × or + data point, the ♦ symbol shows the optimal dose of

$D_f^* = 1.2 * 24\ U * 20\% = 5.76\ U$ fast- plus $D_s^* = 24\ U * 80\% = 19.2\ U$ slow-acting insulin. The aim of the optimisation is to 'move' the optimal but not practical dose ♦ to one of the actually possible doses indicated by the × and + symbols. At first sight the most obvious way of doing this is to find the × or + dose that is closest to the optimal dose ♦ (Equation (3.16)).

$$\text{distance from optimal dose} = \sqrt{(D_f - D_f^*)^2 + (D_s - D_s^*)^2} \tag{3.16}$$

D_f, D_s = fast- and slow-acting components of a mixed dose D

D_f^*, D_s^* = fast- and slow-acting components of the optimal dose D^*

However, this does not consider the fact that responses to insulin vary between insulin types as well as patients. By using the insulin sensitivity factors (Equation (3.12)) as shown in Equation (3.17) we effectively minimise distance from the optimal dose not in terms of absolute insulin doses but in terms of relative glucose response. Visually the actual dose ◇ with the smallest distance in terms of glucose response can be determined through re-scaling of the x- and y-axis from a ratio of 1 : 1 (Figure 3.5) to ratio of $insulin\_sensitivity(fast\_insulin\_type) : insulin\_sensitivity(slow\_insulin\_type) = 1:4$ (Figure 3.6).

$$\text{distance from optimal dose} = \sqrt{\left(\frac{D_f - D_f^*}{I_f}\right)^2 + \left(\frac{D_s - D_s^*}{I_s}\right)^2} \tag{3.17}$$

$I_f = insulin\_sensitivity_{default}(fast\_insulin\_type) = 1.0\ U\ /\ mmol/L$

$I_s = insulin\_sensitivity_{default}(slow\_insulin\_type) = 4.0\ U\ /\ mmol/L$

Also note that the actual dose ◇ can be one of the × or one of the + doses i.e. the suggested dose's mix ratio may be different from that of the usual dose ■. The frequency of such mix switch scenarios will depend on the mixes used by the patient, the dose to be adjusted and the direction and magnitude of the adjustment factor f. Furthermore, occasional switches from one insulin mix to another clearly present a number of challenges in user interface terms, but especially for larger dose adjustments these could be justifiable.

Independent of changes in dose mixes, the adjustment optimisation could be improved based on the multiple dose adjustment limits idea outlined above. As shown in Equation (3.18) the deficit or surplus in slow-acting insulin taken within the last 24 hours could be used to bias the optimisation so as to keep the actual daily dose of slow-acting insulin close to the usual daily dose.

$$\text{distance from optimal dose} = \sqrt{\left(\frac{D_f - D_f^*}{I_f}\right)^2 + \left(\frac{D_s - D_s^* + \Delta D_s}{I_s}\right)^2} \tag{3.18}$$

ΔD_s = difference between actual and usual slow-acting insulin doses taken within the last 24 hours

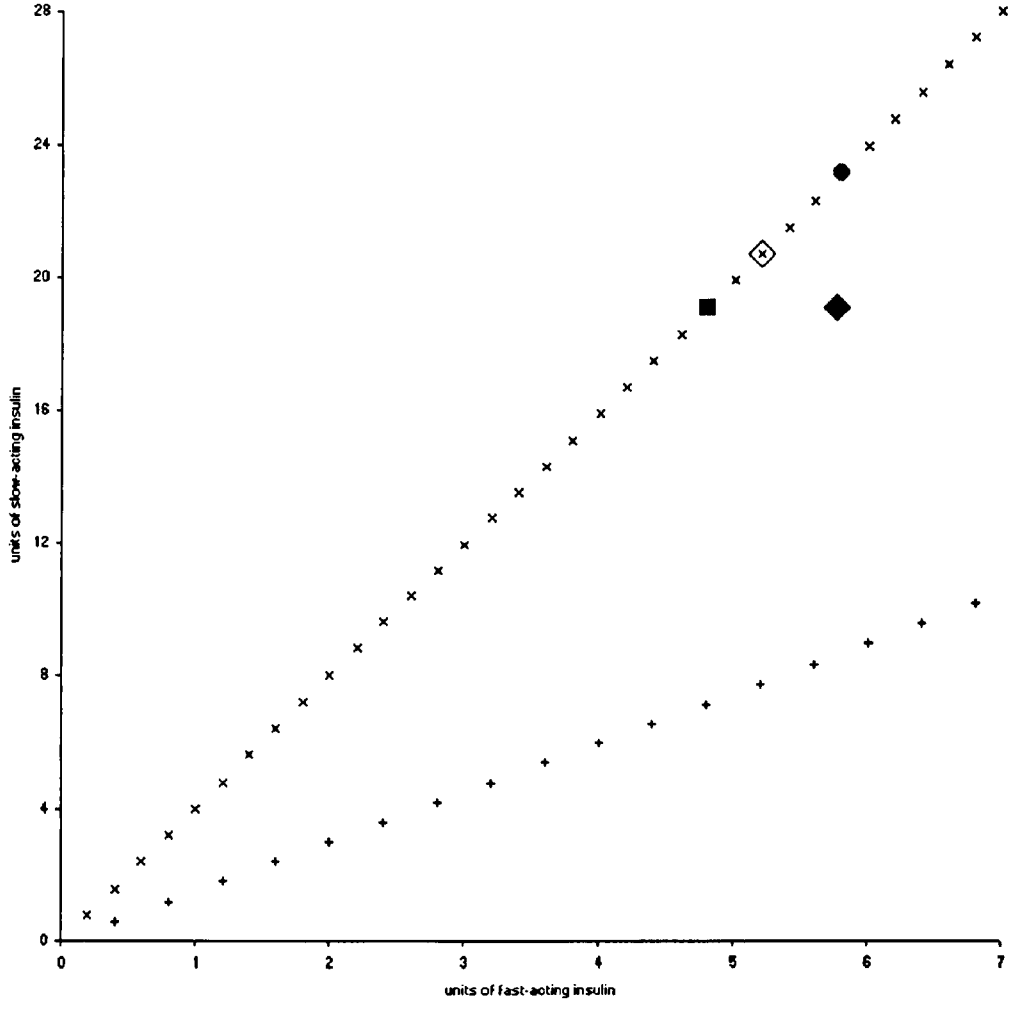


Figure 3.6: Dose adjustment optimisation II: × symbols = Mixtard® 20 insulin doses, + symbols = Mixtard® 40 insulin doses, ■ symbol = usual insulin dose (24 U Mixtard® 20), • symbol = unoptimised lifestyle-adjusted dose ($1.2 * 24\ U \approx 29\ U$), ♦ symbol = optimal lifestyle-adjusted dose ($1.2 * 24\ U * 20\% = 5.76\ U$ fast-acting plus $24\ U * 80\% = 19.2\ U$ slow-acting insulin), ◇ symbol = optimised lifestyle-adjusted dose ($26\ U * 20\% = 5.2\ U$ fast-acting plus $26\ U * 80\% = 20.8\ U$ slow-acting insulin)

Hypo-related dose reductions

Hypo-related dose reductions for mixed insulins are carried out in the same way as for non-mixed insulins. That is for the purpose of attempting to identify the insulin dose that caused the hypoglycaemic episode, mixed insulin injections are treated *as if* they were two separate injections. However, when a dose reduction for one notionally separate dose is required, the entire mixed insulin dose concerned will be reduced by the maximum amount permissible. Note that this means that both dose components are reduced, not just the component that caused the hypo. As an alternative to such an entire dose reduction, the algorithm could consider an equivalent dose change to the patient's other insulin mix. This could, in certain circumstances, produce a numerically better insulin mix for that dose. However, such a permanent dose change (as opposed to the temporary lifestyle-related dose adjustments described above) to another insulin mix would effectively constitute an alteration of the patient's insulin dose prescription and for legal, ethical and safety reasons the system can clearly not be allowed to make that kind of change. Hypo-related insulin dose reductions must therefore always be applied to the entire mixed dose concerned so as to maintain that dose's mix ratio.

3.3 Improvements and additions to the user interface

This section describes user interface related changes made to the POIRO MK2 system. Section 3.3.1 concerns new key features of the MK3 version, whilst Section 3.3.2 describes other, non-essential but desirable enhancements. Section 3.3.3 details how the system models a patient's meal time habits and thus allows the plausibility checks and intelligent selections described in Sections 3.3.1 and 3.3.2.

3.3.1 Adding new key features

Meal time plausibility checks

Every time a patient wants to request insulin dose advice they must enter the type and the size of the meal they are about to have. The default meal size selection is 'Normal', the default meal type selection is 'no selection'. If the user presses the OK button to proceed without having selected a meal type then a short reminder sound is played. As patients (a) are initially shown and taught how to use the system and then (b) become regular system users such a simple error capture mechanism was considered sufficient. However, another kind of error that can be made even by very experienced users is less easy to catch. Figure 3.7 (a) indicates that 'Dinner' is the type of meal that was selected. Given the palm-top size of modern PDAs the black bar highlighting a particular meal type selection is only about 28 by 4 mm or 82 by 11 pixels in size. It is therefore well possible for a user, instead of the intended 'Lunch', to accidentally select the adjacent 'Dinner' or 'Breakfast'. Familiarity with the system, tiredness and distraction are all factors that may contribute to such a mistake. A number of what-happens-next scenarios are possible, for example:

1. The user realises the mistake and corrects the meal time selection before pressing the OK button.
2. The user realises the mistake only after pressing the OK button. They might now be unsure as to how to best proceed to correct the error and/or to obtain 'Lunch' insulin dose advice.
3. The user initially does not realise the mistake. The insulin dose advised by the system will be wrong i.e. not a 'Lunch' dose. At this point, the user recognises the advised dose as a 'Dinner' dose and thus realises the earlier mistake. They might think that "the system should have prevented this" and might also be unsure as to how to proceed.

4. The user does not realise the mistake. The insulin dose advised by the system will be wrong i.e. not a 'Lunch' but a 'Dinner' dose. The user realises that the advised dose is wrong and takes the usual 'Lunch' dose instead. Their confidence in the system might be undermined.

5. The user does not realise the mistake and also does not realise that the advised dose is wrong. They take the advised dose which may be lower, equal to or higher than the correct dose.

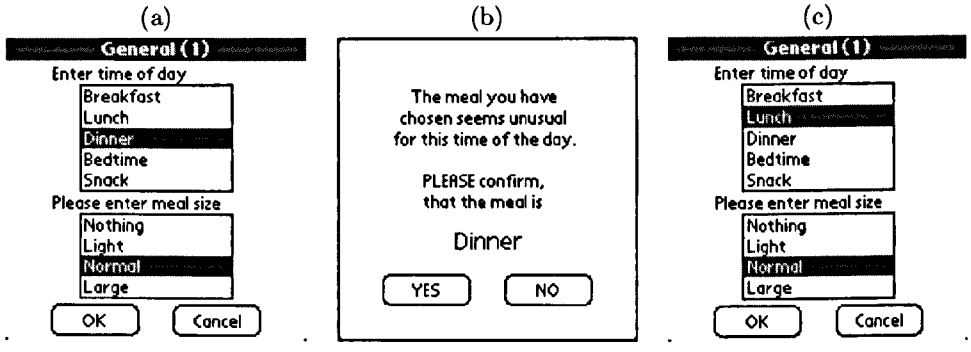


Figure 3.7: Meal time plausibility check - (a) Meal time 'Dinner' mistakenly selected instead of 'Lunch'. (b) Meal time confirmation request screen. (c) Corrected meal time selection.

POIRO MK3 introduces a new approach to this problem. When the OK button is pressed, the plausibility (see Section 3.3.3) of the meal time selected is checked and if appropriate a message requesting confirmation of the selection (Figure 3.7 (b)) is displayed. The user can thus confirm or correct (Figure 3.7 (c)) their initial selection.

Hypo context information collection

When they experience symptoms of hypoglycaemia many patients are told to and routinely do measure their blood glucose level. The screens shown in Figures 3.8 (a) and 3.8 (b) are useful for the recording of these special non-pre-prandial blood glucose values. The "When you had this hypo, did you measure your blood glucose?" screen and if appropriate the glucose entry screen are displayed after the hypo entry screen and at present simply generate a notebook entry such as "Glucose measured when hypo: 3.0 mmol/L". However, in the future other forms of information recording and processing are conceivable.

A patient experiencing a hypo also often has a good idea as to the likely reason for that hypo. Therefore the POIRO MK2 hypo entry screen was followed by a simple screen (Figure 3.8 (c)) reading "Can you enter a reason why you think you had this hypo? [YES] [NO]" and prompting users to make a notebook entry.

POIRO MK3 simplifies and improves on this by introducing a list with the most common reasons for a hypo: a small or missed meal, unexpected exercise, and alcohol intake as shown in Figure 3.8 (d). If there is no obvious reason for the hypo, the user selects the 'Unknown' option on the list. If the patient thinks that the hypo was caused by a factor other than the ones listed, they select the 'Other → Enter Note' option and after the 'Continue' button was pressed the notebook entry screen is automatically opened up. All hypo reasons are recorded as notebook entries such as "Main reason for this hypo: Small or missed meal" and they do at present not influence the way in which a hypoglycaemic episode

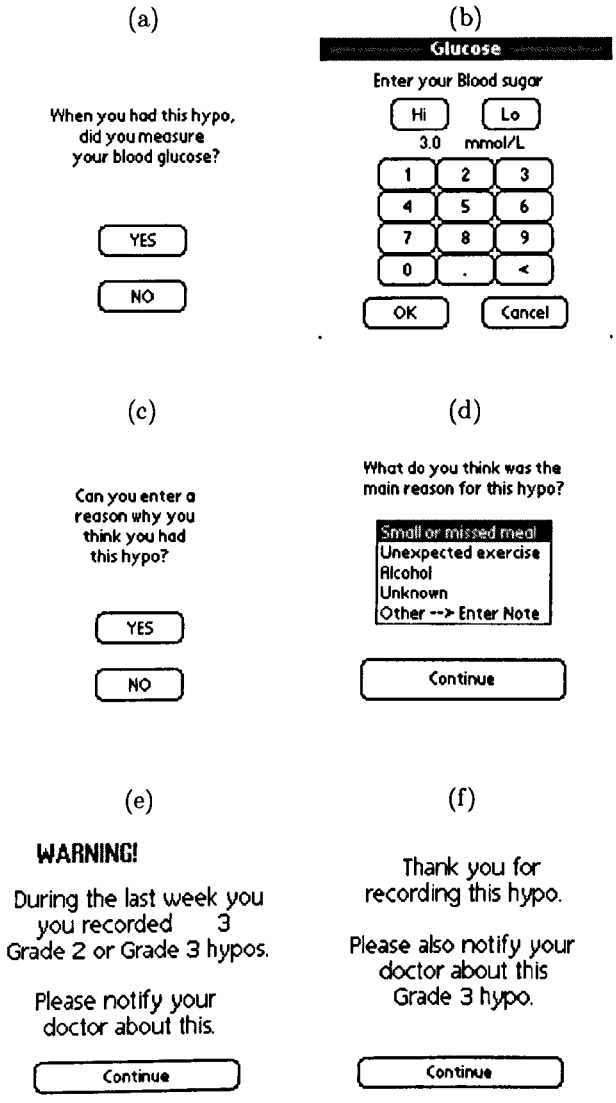


Figure 3.8: Hypo-related display screens - (a) Hypo BG measurement prompt, (b) Hypo BG entry screen, (c) POIRO MK2 hypo reason notebook entry prompt, (d) POIRO MK3 hypo reason entry screen, (e) 'Too many hypos' warning screen, (f) Grade 3 hypo warning screen.

is processed i.e. dealt with by the system.

Hypo-related data entry and processing facilities have further been extended by two warning screens. A message such as "WARNING! During the last week you recorded 3 Grade 2 or Grade 3 hypos. Please notify your doctor about this." (Figure 3.8 (e)) is displayed if the number of Grade 2 ('interfered with normal life') or Grade 3 ('required third party assistance') hypos experienced by a patient in the last week exceeds the patient-specific hypo warning threshold set by their physician. The "Thank you for recording this hypo. Please also notify your doctor about this Grade 3 hypo." message (Figure 3.8 (f)) is shown whenever a Grade 3 hypo is recorded. In the event of both warnings applying, only the Grade 3 warning message is displayed.

Handheld-desktop data transfer automation

To recall, generally that is for all Palm OS handhelds and many applications on them a Hotsync operation is used to synchronise data on the user's handheld and desktop computer. As described in Section 2.2.5 for the Insulin Advisor or POIRO MK2 program, such a synchronisation operation invokes a so-called conduit that synchronises data used and produced by the program. However, although the POIRO MK2 conduit could automatically detect which patient's handheld data it is synchronising, it required the physician user's intervention to determine the correct direction of the data transfers to be carried out. The POIRO MK3 conduit improves on this. By comparing certain timestamps on the handheld and the desktop it automatically identifies transfer requirements and then initiates the corresponding data transfers from and/or to the handheld. This was one of the potential improvements identified in Section 2.2.5. Nevertheless, we acknowledge that the mechanism used assumes that the handheld's and desktop's clocks are set correctly and are reasonably-well synchronised. Section 3.3.2 describes how such a clock synchronisation could be achieved in practice.

3.3.2 Enhancing other features

Intelligent automatic meal time selection

As described in the section on meal time plausibility checks (Section 3.3.1) the default meal selection is 'no selection' and the user, every time i.e. usually four times a day, has to manually select the type of meal they are about to have. If the device could automatically and intelligently make a default selection then this would be more convenient for the user, but more importantly it would also actively help prevent the accidentally-wrong-meal-time-selection scenarios outlined previously. POIRO MK3 offers such an intelligent automatic meal time selection facility. The patient-specific meal time habits model (see Section 3.3.3) already used to assess meal time plausibility forms its theoretical basis. In this context it should be noted that the selection algorithm developed gives the correctness of automatic selections priority over the availability of such selections. In other words, automatic selections will not always be available but when available they will almost certainly be correct. We realise that this type of intelligent user interface will not be suitable for all users and an 'enable/disable automatic meal time selections' switch is hence provided as part of the physician-determined, patient-specific set of settings.

Usual insulin doses summary screen

As shown in Figure 3.9 POIRO MK3 adds an extra page to the previous versions' one page information screen (Figure 2.6 (b) on page 34). Although the information screens are comparatively seldomly used,

the additional screen provides a convenient overview of the patient's current usual insulin doses. In particular, it is anticipated that this screen might be used during clinic visits so as to show the device's possibly updated dose settings to the patient and to thus confirm that these are the doses they are expecting.

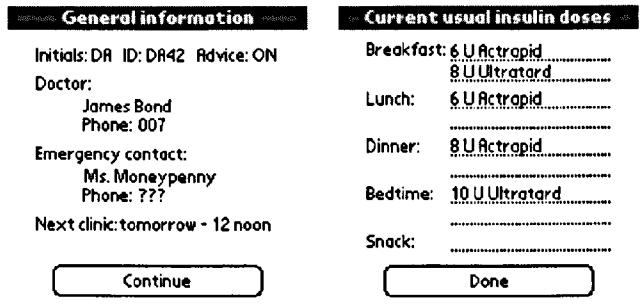


Figure 3.9: POIRO MK3 information screens

Faster and clearer review diagrams

Compared to the POIRO MK2 version, the POIRO MK3 review diagrams have been improved with respect to layout and drawing speed. As can be seen from Figures 3.10 (a) and 3.10 (b) the x-axis labels are now reversed and an arrow labelled *today* points to the current day's mean blood glucose value. The improved blood glucose trend diagram also uses *H* symbols to indicate the days on which hypoglycaemic episodes were recorded.

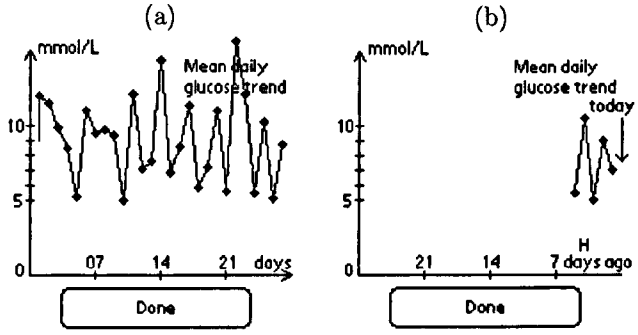


Figure 3.10: Blood glucose trend review diagrams - (a) POIRO MK2, (b) POIRO MK3.

An increase in the diagram drawing speed was one of the potential improvements identified previously. As shown in Table A.5 for POIRO MK2 the time required to calculate and draw the BG trend and modal day diagrams is eventually 23 and 41 seconds respectively. For POIRO MK3 changes (see Section 3.4) were made to reduce these times. Due to the underlying algorithms used, the diagram drawing speed is now a function of the user's frequency of review diagram use: the more frequently the diagrams are displayed, the faster they will be drawn. Assuming use once a week of both the BG trend and modal day diagrams, the POIRO MK3 average drawing time will now be about 8 seconds. More detailed information on the improved drawing times can be found in Table A.9.

Handheld-desktop clock synchronisation

The synchronisation of the handheld and desktop computers' clocks can be conceptualised as a three stage process:

1. Detection of the time difference between the handheld and desktop clock
2. Assessment of the practical relevance of that time difference
3. Adjustment of the handheld's and/or the desktop's clock

Since the conduit, which resides on the desktop computer, can read both the handheld's and the desktop's clock, the detection of the difference between the two is straightforward[iii]. Once such a time difference, if any, has been calculated, the conduit can compare it against the synchronisation assessment criteria to determine how big an adjustment, if any, should be made to either or both clocks. A simple type of criteria could take the form "Up to δ seconds of time difference between the two clocks are acceptable." where δ is a hard-coded or a user-configurable threshold value. A more complicated criteria could be "The handheld's clock may be up to δ_s seconds slower or up to δ_f seconds faster than the desktop's clock." with δ_s and δ_f hard-coded or configurable but not equal. However, the practical value of the latter or other similarly complex criteria is hard to see. For the POIRO MK3 conduit the former rule has thus been implemented.
The adjustment of the clocks can be implemented in a number of ways:

- The handheld's clock can be adjusted to that of the desktop.
- The desktop's clock can be adjusted to that of the handheld.
- Both clocks can be adjusted to a mid-way or to an externally determined value[iv].

Furthermore, the actual clock change or changes can be carried out

- manually i.e. by the user possibly following step-by-step on-screen instructions,
- automatically i.e. by the conduit and without user intervention, or
- semi-automatically i.e. with user input into extent and execution of any clock adjustments.

POIRO MK2 did not consider any time differences between the handheld and the desktop computer's clocks. POIRO MK3 conduit detects and reports but does not correct the time difference, if any, between the handheld and desktop computers' clocks. Automatic or semi-automatic clock synchronisation was intended for the conduit and theoretically the *SyncWriteSysDateTime* function lets the conduit set the system date and time on the handheld device. However, in practice and as stated in the Conduit Programmer's Reference manual "[a]lthough this function is available in all versions of the Sync Manager API, it does not work properly in any version earlier than version 2.2." [67]. Whilst one could devise a provisional work-around[v] to this problem, this was not considered appropriate and worthwhile. The implementation of the actual clock synchronisation is hence left as a future improvement.

3.3.3 Modelling meal time habits

This section describes the meal time habits model that underpins the meal time plausibility checks and the intelligent automatic meal time selection. The development of the model and the accompanying algorithms aimed to achieve the following properties:

1. Correctness: The model must accurately reflect the user's meal time habits. Furthermore, with respect to the algorithms used with the model, inability to calculate a result is always preferred over an incorrect result.

2. Adaptability: The model must adapt to the individual user's habits as well as to any habit changes over time.

3. Simplicity: Ideally the model should be easy to understand and intuitively correct. Such simplicity should also result in straightforward and fast computations.

The model

To make use of the rules given in (3.19) we must delineate Breakfast time from Lunch time, Lunch time from Dinner time and so on. However, since meal times vary between as well as within individuals, between weekdays and weekends, and generally over time this is not a trivial task. The collection, at the clinic, of additional meal time related information is theoretically possible but in practice undesirable and probably not worthwhile the effort. Instead information that is already available must be exploited as fully as possible.

> The main meal order within a day is Breakfast, Lunch, Dinner, Bedtime. (3.19)
>
> Snacks may be eaten at any time.

Corresponding to the table in the same figure, the graph shown in Figure 3.11 (b) plots the type of meal against the 24 hour clock time in the day. By somehow aggregating the times of each meal type one could divide the day into say five (Breakfast, Lunch, Dinner, Bedtime, overnight) or eight (Breakfast, between-Breakfast-and-Lunch, Lunch, between-Lunch-and-Dinner, Dinner, between-Dinner-and-Bedtime, Bedtime, overnight) possibly overlapping intervals. However, although this approach seems fairly intuitive it is likely to lack in adaptability and computational simplicity.

The final model adopted combines the use of intervals and probabilities. The 24 hour day is divided into 24 one hour intervals from 0:30 to 1:29, 1:30 to 2:29 and so on. The times of each meal type are mapped into these intervals (Figures 3.12 and 3.13). Computationally this is an inexpensive process since the addition of a new meal such as Lunch at 13:15 only requires the updating of two figures namely the Lunch 13 counter and the Lunch $\sum$ counter. The model is also adaptive and very intuitive. For example, aggregating all the Lunch data into one intervals tells us that

(a) Lunch is normally eaten between 11:30 and 15:29 and that

(b) Lunch is most often eaten between 12:30 and 13:29.

In addition, any change in meal time habits e.g. to a later lunch will be reflected in an increase in the relative frequency of 14 and 15 o'clock lunches and a decrease in the relative frequency of 12 and 13 o'clock lunches. Equation (3.20) formally summarises the meal time habits model so far.

$$MealTimeHistogram[tt][hh] = \text{the number of times a meal of type } tt \text{ was eaten between } (hh-1)\text{:30:00 and } hh\text{:29:59} \tag{3.20}$$

$$tt = Breakfast, Lunch, Dinner, Bedtime$$

$$hh = 0..23$$

(a)

Day	Breakfast	Lunch	Dinner	Bedtime
01	-	14:58	17:15	22:38
02	07:40	12:41	17:43	22:29
03	07:18	12:16	16:59	22:17
04	08:12	12:36	16:37	22:39
05	08:25	12:10	18:45	22:28
06	07:14	11:53	17:38	22:07
07	07:43	13:46	17:28	21:33
..	...	...	...	...

(b)

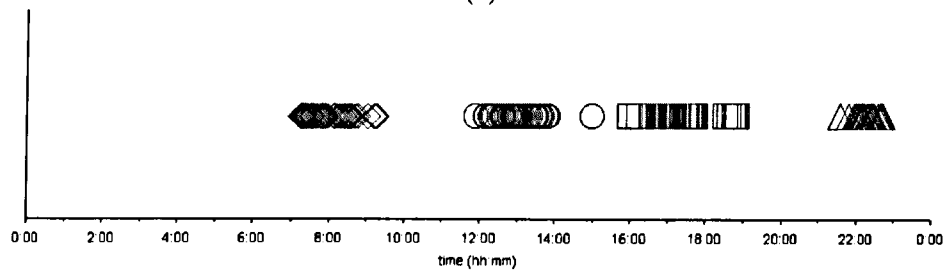


Figure 3.11: Meal time related information - (a) in tabulated form, (b) in graphical form: each symbol represents a ◇ Breakfast, ○ Lunch, □ Dinner or △ Bedtime meal

Based on Equation (3.20) and the assumption that past habits predict future behaviour Equation (3.21) describes the likelihood or probability of a meal of type tt occurring within the one hour time interval over hh.

$$
\begin{aligned}
p(tt, hh) &= \frac{MealTimeHistogram[tt][hh]}{\sum_{i=0}^{23} MealTimeHistogram[tt][i]} \\
tt &= Breakfast, Lunch, Dinner, Bedtime \\
hh &= 0..23
\end{aligned}
\tag{3.21}
$$

From Equations (3.20) and (3.21) it can be shown that the model's ability to adapt to changes in user habits decreases over time. This property and related extensions to the model are best illustrated and explained with the help of an example.

(a)

	00	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16	17	18	19	20	21	22	23	$\sum$
Breakfast	-	-	-	-	-	-	-	10	31	8	-	-	-	-	-	-	-	-	-	-	-	-	-	-	49
Lunch	-	-	-	-	-	-	-	-	-	-	-	-	9	30	7	1	-	-	-	-	-	-	-	-	47
Dinner	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2	35	6	5	-	-	-	-	48
Bedtime	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	41	6	47

(b)

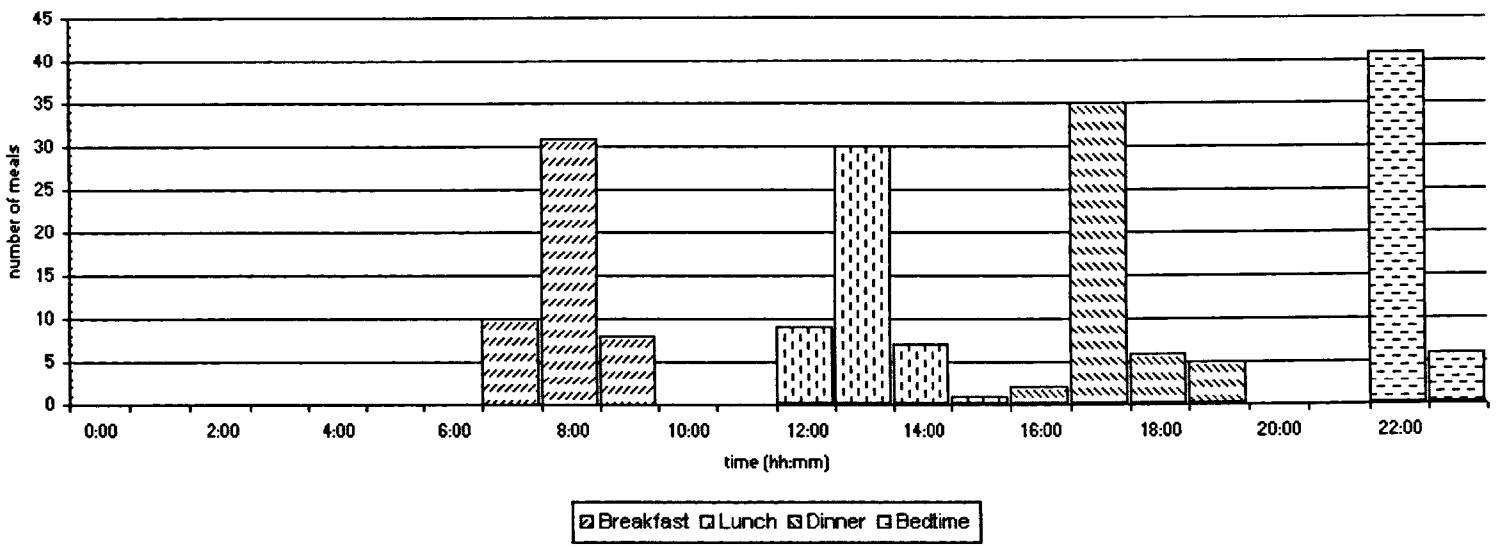


Figure 3.12: Distribution of meals throughout the day (absolute values) - (a) in tabulated form, (b) in graphical form

(a)

	00	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16	17	18	19	20	21	22	23	Σ
Breakfast	-	-	-	-	-	-	-	20	63	16	-	-	-	-	-	-	-	-	-	-	-	-	-	-	100
Lunch	-	-	-	-	-	-	-	-	-	-	-	-	19	64	15	2	-	-	-	-	-	-	-	-	100
Dinner	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	4	73	13	10	-	-	-	-	100
Bedtime	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	87	13	100

(b)

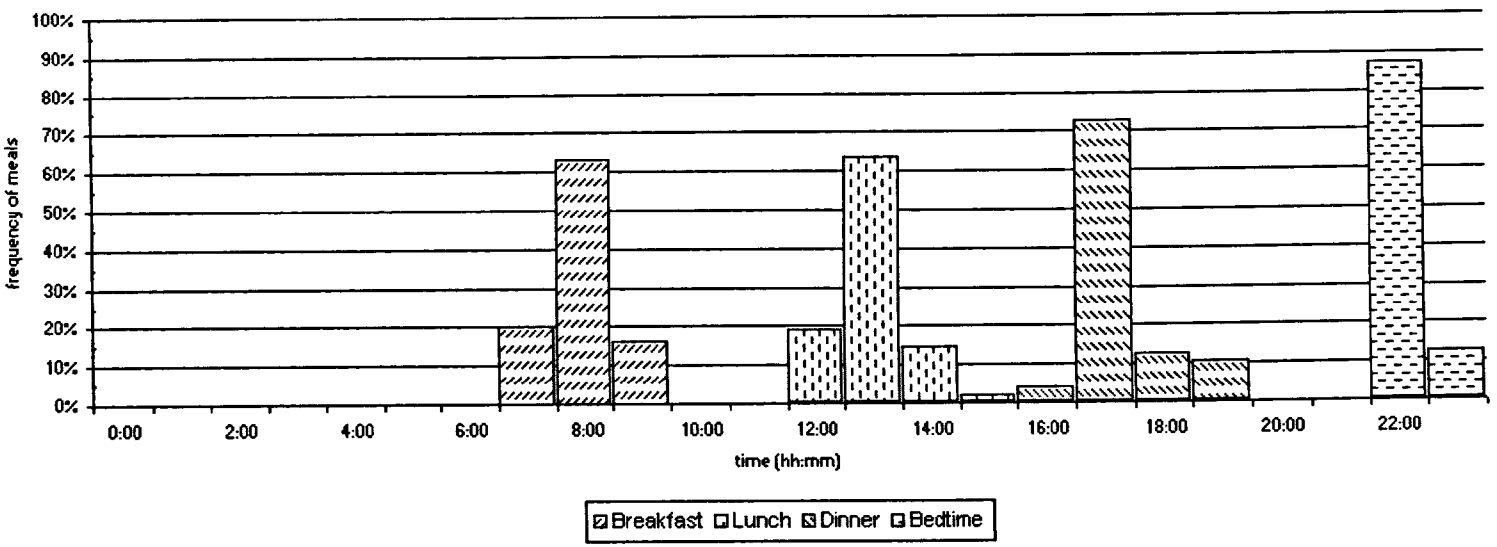


Figure 3.13: Distribution of meals throughout the day (relative frequencies) - (a) in tabulated form, (b) in graphical form

Assume that during the first week of use seven Breakfast meals have been entered so that

$$MealHistogram[Breakfast, 7] = 1$$
$$MealHistogram[Breakfast, 8] = 5$$
$$MealHistogram[Breakfast, 9] = 1$$

and hence

$$\sum_{i=0}^{23} MealTimeHistogram[Breakfast][i] = 7$$

giving

$$p(Breakfast, 7) = \tfrac{1}{7} \approx 0.1429$$
$$p(Breakfast, 8) = \tfrac{5}{7} \approx 0.7143$$
$$p(Breakfast, 9) = \tfrac{1}{7} \approx 0.1429.$$

The next Breakfast is recorded around 7 o'clock and the model is updated so that

$$MealHistogram[Breakfast, 7] = 2$$
$$MealHistogram[Breakfast, 8] = 5$$
$$MealHistogram[Breakfast, 9] = 1$$

and hence

$$\sum_{i=0}^{23} MealTimeHistogram[Breakfast][i] = 8$$

giving

$$p(Breakfast, 7) = \tfrac{2}{8} = 0.2500$$
$$p(Breakfast, 8) = \tfrac{5}{8} = 0.6250$$
$$p(Breakfast, 9) = \tfrac{1}{8} = 0.1250.$$

The addition of the 7 o'clock Breakfast increased $p(Breakfast, 7)$ by 75% from 0.1429 to 0.2500 and correspondingly decreased $p(Breakfast, 8)$ and $p(Breakfast, 9)$.

Now consider the case where the system has been used for about ten weeks and assume that at present

$$MealHistogram[Breakfast, 7] = 10$$
$$MealHistogram[Breakfast, 8] = 50$$
$$MealHistogram[Breakfast, 9] = 10$$

and hence

$$\sum_{i=0}^{23} MealTimeHistogram[Breakfast][i] = 70$$

giving

$$p(Breakfast, 7) = \tfrac{10}{70} \approx 0.1429$$
$$p(Breakfast, 8) = \tfrac{50}{70} \approx 0.7143$$
$$p(Breakfast, 9) = \tfrac{10}{70} \approx 0.1429.$$

Notice that the probabilities p are exactly the same as in the original case and that again the next Breakfast is recorded around 7 o'clock.

The updated model is now

$$MealHistogram[Breakfast, 7] = 11$$
$$MealHistogram[Breakfast, 8] = 50$$
$$MealHistogram[Breakfast, 9] = 10$$

and hence

$$\sum_{i=0}^{23} MealTimeHistogram[Breakfast][i] = 71$$

giving

$$p(Breakfast, 7) = \frac{11}{71} \approx 0.1549$$
$$p(Breakfast, 8) = \frac{50}{71} \approx 0.7042$$
$$p(Breakfast, 9) = \frac{10}{71} \approx 0.1408.$$

The addition of the 7 o'clock Breakfast increased $p(Breakfast, 7)$ by 8% from 0.1429 to 0.1549 but compared to the 75% 0.1429 to 0.2500 probability increase seen after the first week of use this increase is very small.

In the model so far, every meal contributes equally and this explains the smaller $p(Breakfast, 7)$ increase after ten weeks of system use. In practice and intuitively however, recent data should carry more weight than data that is several weeks or even months old. We therefore require some way of gradually discounting the contribution of i.e. the weight attached to historic meal time data. Equation (3.22) describes the proposed model extension.

$$\forall tt, hh : MealTimeHistogram_{discounted}[tt][hh] = \frac{MealTimeHistogram[tt][hh]}{f_{discount}} \tag{3.22}$$
$$f_{discount} = 2$$

Periodically, after a certain number $M_{discount\_threshold}$ of meals have been entered, the model's $MealTimeHistogram[tt, hh]$ values are all halved. This is not only computationally fast and simple but also preserves the model's probability values i.e. the meal habits learnt so far. The relative weight attached to recent and historic data is determined by $f_{discount}$ and $M_{discount\_threshold}$. The POIRO MK3 implementation of this model uses a $f_{discount}$ value of 2 and discounts values approximately every three weeks ($M_{discount\_threshold}$ = 84 = 3 weeks * 7 days/week * 4 meals/day).

Finally, to conclude this section and to complete the above example, discounting of

$$MealHistogram[Breakfast, 7] = 10$$
$$MealHistogram[Breakfast, 8] = 50$$
$$MealHistogram[Breakfast, 9] = 10$$

and

$$\sum_{i=0}^{23} MealTimeHistogram[Breakfast][i] = 70$$

gives

$$MealHistogram_{discounted}[Breakfast, 7] = 5$$
$$MealHistogram_{discounted}[Breakfast, 8] = 25$$
$$MealHistogram_{discounted}[Breakfast, 9] = 5$$

and

$$\sum_{i=0}^{23} MealTimeHistogram_{discounted}[Breakfast][i] = 35$$

whilst preserving

$$p(Breakfast, 7) = \frac{10}{70} = p_{discounted}(Breakfast, 7) = \frac{5}{35} \approx 0.1429$$
$$p(Breakfast, 8) = \frac{50}{70} = p_{discounted}(Breakfast, 8) = \frac{25}{35} \approx 0.7143$$
$$p(Breakfast, 9) = \frac{10}{70} = p_{discounted}(Breakfast, 9) = \frac{5}{35} \approx 0.1429.$$

The addition of a 7 o'clock Breakfast after this discounting operation would increase $p(Breakfast, 7)$ by 17% from $\frac{5}{35} \approx 0.1429$ to $\frac{6}{36} \approx 0.1667$ compared to an increase of 8% from $\frac{10}{70} \approx 0.1429$ to $\frac{11}{71} \approx 0.1549$ without discounting.

Applying the model

Equation (3.23) formally describes how the meal time habits model is used to assess the plausibility of a meal of type tt_p being recorded in the one hour time interval over hh. Informally, a main meal of a particular type tt_p is plausible as long as there is no alternative meal type tt_a more likely to be recorded at the current time. A between-main-meals snack is always plausible.

$$\begin{aligned} plausible(tt_p, hh) &= \nexists\, tt_a \;:\; p(tt_a, hh) > p(tt_p, hh) \\ plausible(Snack, hh) &= TRUE \end{aligned} \tag{3.23}$$

$$\begin{aligned} tt_p, tt_a &= Breakfast, Lunch, Dinner, Bedtime \\ hh &= 0..23 \end{aligned}$$

Equation (3.24) formally describes how the model is used to intelligently determine a default meal time selection. Informally, the automatically selected meal time $tt_{current}$ will be the meal time that logically follows the last recorded meal time tt_{prev}. However, if the meal time $tt_{current}$ is not plausible or not very likely at the current time, then no automatic selection will be made.

LET *now* BE the current system time
LET *hh* BE the current time interval so that (*hh*-1):30:00 <= *now* <= *hh*:29:59

IF a main meal was recorded within the last 24 hours THEN
    LET tt_{prev} BE the most recent such meal
    LET $tt_{current}$ BE the main meal that should sequentially follow tt_{prev}
    IF $plausible(tt_{current}, hh)$ THEN
        IF $p(tt_{current}, hh) > p_{min}$ THEN
            $auto\_selection := tt_{current}$ (3.24)
        ELSE
            $auto\_selection := none$
    ELSE
        $auto\_selection := none$
ELSE
    $auto\_selection := none$

Main meals are *Breakfast*, *Lunch*, *Dinner* and *Bedtime*.
Minimum auto-selection probability threshold $p_{min} = \frac{1}{14} \approx 0.0714$

Performance assessment and future improvements

Whilst the previous section detailed how the meal time habits model can be used to intelligently enhance the POIRO MK3 user interface, this section assesses the model's performance in that context. The section also identifies potential future improvements.

The performance of the meal time plausibility checks can be assessed through the frequency of false-positive and false-negative results, r_{fp} and r_{fn} respectively. False-positive results occur when the meal time entered by the user is really implausible and when the model falsely considers it plausible. In user interface terms, this means that a "... Please confirm that the meal is ..." message is appropriate but is not displayed. False-negative results occur when the model falsely considers a plausible meal time implausible. This means that a "... Please confirm that the meal is ..." message is displayed inappropriately.

		Meal time *tt* around *hh* o'clock is plausible?	
		YES	NO
is_plausible (*tt*, *hh*)	TRUE	true-positive R_{tp}	false-positive R_{fp}
	FALSE	false-negative R_{fn}	true-negative R_{tn}

$$\begin{aligned} \sum R &= \text{total number of results} = R_{tp} + R_{fp} + R_{tn} + R_{fn} \\ r_{fp} &= \frac{\text{number of false-positive results}}{\text{total number of results}} = \frac{R_{fp}}{\sum R} \\ r_{fn} &= \frac{\text{number of false-negative results}}{\text{total number of results}} = \frac{R_{fn}}{\sum R} \end{aligned} \tag{3.25}$$

False-positive results are of course undesirable but in practice not too problematic, since

- they can only occur if the user enters an implausible meal time, and
- they are precisely what would have occurred without the plausibility checking facility.

False-negative results on the other hand are visible to the user and thus much more serious. Inappropriate "... Please confirm that the meal is ..." messages

- can over time irritate the user and thus undermine their confidence in the system, and
- can bring about incorrect dose advice by making the user change their mind about the current correct meal time.

However, in the POIRO MK3 implementation of the meal time habits model the plausibility checking and the automatic meal time selection mechanisms work together. With respect to ensuring the plausibility of the meal data entered we should therefore try to assess the model's performance via the frequency of the following three scenarios[vi]:

O_1 An automatic meal time selection prevents the user from selecting a wrong meal time.

O_2 No automatic meal time selection is made and the $is\_plausible(tt, hh) = FALSE$ plausibility check makes the user change i.e. correct their meal time selection.

O_3 No automatic meal time selection is made and the user does not change their meal time selection in response to the $is\_plausible(tt, hh) = FALSE$ plausibility check.

By replaying the data collected during the clinical evaluation of POIRO MK2 we can estimate the frequency of the three scenarios outlined above. Table 3.3 (a) contains the results of this performance assessment, N in column 5 is the total number of meals recorded. Note that the values in columns 6 to 8 are derived from those in columns 2 to 5. Based on 4 recorded meals daily, they illustrate how many times *a year* scenarios O_1, O_2 and O_3 would be expected to occur.

With respect to the performance of the automatic meal time selection algorithm, we must consider the relative occurrences S_0, S_{1-}, S_{1+} of three possible outcomes.

S_0	no selection	The algorithm returns $auto\_selection = none$.
S_{1-}	incorrect selection	The user rejects the algorithm's $tt_{current}$ selection.
S_{1+}	correct selection	The user accepts the algorithm's $tt_{current}$ selection.

(3.26)

(a)

Subject	n(O_1)	n(O_2)	n(O_3)	N	$4 * 365 * n(O_1)/N$	$4 * 365 * n(O_2)/N$	$4 * 365 * n(O_3)/N$
01	0	0	0	191	0	0	0
02	1	1	2	203	7	7	14
03	0	0	0	197	0	0	0
04	0	0	0	194	0	0	0
05	4	1	2	204	29	7	14
06	2	0	0	206	14	0	0
07	1	0	2	196	7	0	15
08	0	0	1	191	0	0	8
				mean (SD):	7 (10)	2 (3)	6 (7)

(b)

Subject	S_0	S_{1-}	S_{1+}	g	c	$4 * 365 * g * (1 - c)$
01	23	0	168	0.88	1.00	0
02	43	0	160	0.79	1.00	0
03	16	0	181	0.92	1.00	0
04	31	0	163	0.84	1.00	0
05	47	1#	156	0.77	0.99	7
06	33	0	173	0.84	1.00	0
07	17	0	179	0.91	1.00	0
08	24	0	167	0.87	1.00	0
			mean (SD):	0.85 (0.05)	1.00 (0.00)	0.89 (2.53)

The user's meal times that day were 09:21 Breakfast, 12:02 Snack, 14:33 Lunch, 19:10 Dinner and 22:01 Bedtime. The incorrect selection would have occurred when with $p(Lunch, 12) = \frac{7}{19} \approx 0.3684$ Lunch would have been automatically selected at 12:02. Also note, that the user's altered meal time selection of *Snack* would not have been queried by the device since a *Snack* is always considered plausible.

Table 3.3: Meal time habits model performance assessment - (a) meal time plausibility checking, (b) automatic meal time selection

Hence g and c as given in Equation (3.27) describe respectively the availability and accuracy of the automatic meal time selection facility.

$$\begin{aligned} g &= \frac{\text{actual number of selections}}{\text{possible number of selections}} = \frac{(S_{1-} + S_{1+})}{(S_0 + S_{1-} + S_{1+})} \\ c &= \frac{\text{number of correct selections}}{\text{number of overall selections}} = \frac{S_{1+}}{(S_{1-} + S_{1+})} \end{aligned} \tag{3.27}$$

By replaying the data collected during the clinical evaluation of POIRO MK2 we can obtain realistic values for g and c. Table 3.3 (b) contains the results of this performance assessment. Again, note that column 7 contains derived values. Based on the daily recording of four meals, the values in this column estimate how many times *a year* the algorithm would suggest an incorrect meal time.

Although, the performance measurements as given in Table 3.3 vary slightly between users they are very encouraging overall.

- The auto-selection availability measurement g and the accuracy measurement c translate into on average less than one incorrect automatic meal time selection a year.
- The availability measurement g of 85% translates into 24 out of 28 auto-selections per week. This clearly illustrates the practical value of the selection facility, but with on average 4 non-automatic meal time selections every week it also confirms the need for a 'enable/disable automatic meal time selections' switch as described in Section 3.3.2.
- Use of the model not only enhances the system's user friendliness but also improves the correctness of the meal times entered. The frequency of O_1 and O_2 translates into an average of 9 prevented wrong meal time selections a year. This compares favourably with the frequency of O_3, some 6 wrongly questioned user meal time selections.

Since the meal time habits model only gradually adapts to the individual user's eating patterns, its initial performance will be suboptimal. However, whilst individuals' detailed eating patterns can vary considerably there are some common eating patterns shared between many individuals within a given culture or group. Thus by replacing the model's default initialisation I_0 (Equation (3.28)) with a carefully determined, culture- or group-specific stereotypical initialisation I_c we should be able to increase the model's initial learning speed as well as its overall performance.

$$I_0 = \forall tt, hh : MealTimeHistogram_0[tt][hh] = 0 \tag{3.28}$$

However, when devising a stereotypical initialisation I_c one must bear in mind that such an initialisation should facilitate but not impede the model's adaptation to the individual user's eating patterns. The initialised model must thus not contain too much stereotypical data and it is proposed that its content be limited to one week's worth of data (Equation (3.29)).

$$\forall I_c \; : \; \forall tt : \sum_{i=0}^{23} MealTimeHistogram_0[tt][i] <= 7 \tag{3.29}$$

Based on the analysis and aggregation of the meal-related data collected during the clinical evaluation of POIRO MK2, we propose one stereotypical initialisation I_1 as detailed in Equation (3.30).

$$
\begin{aligned}
I_1 \;=\; & MealTimeHistogram_0[Breakfast][07] = 1 \;\wedge \\
& MealTimeHistogram_0[Breakfast][08] = 3 \;\wedge \\
& MealTimeHistogram_0[Breakfast][09] = 2 \;\wedge \\
& MealTimeHistogram_0[Breakfast][10] = 1 \;\wedge \\
& MealTimeHistogram_0[Lunch][12] = 1 \;\wedge \\
& MealTimeHistogram_0[Lunch][13] = 4 \;\wedge \\
& MealTimeHistogram_0[Lunch][14] = 2 \;\wedge \\
& MealTimeHistogram_0[Dinner][17] = 1 \;\wedge \\
& MealTimeHistogram_0[Dinner][18] = 2 \;\wedge \\
& MealTimeHistogram_0[Dinner][19] = 2 \;\wedge \\
& MealTimeHistogram_0[Dinner][20] = 2 \;\wedge \\
& MealTimeHistogram_0[Bedtime][22] = 2 \;\wedge \\
& MealTimeHistogram_0[Bedtime][23] = 3 \;\wedge \\
& MealTimeHistogram_0[Bedtime][00] = 2 \\
& \wedge \\
& MealTimeHistogram_0[tt][hh] = 0 \text{ for all other } tt \text{ and } hh.
\end{aligned}
\tag{3.30}
$$

The results given in Table 3.4 describe to the performance of the meal time habits model initialised with the stereotypical initialisation I_1. Like the results in Table 3.3 they were obtained through the replaying of the POIRO MK2 meal data. The methodological weakness of using the POIRO MK2 data for the derivation of the initialisation I_1 as well as for the performance assessment of the I_1 based model is acknowledged. However, since the initialisation I_1 is quite generic and could thus well have been obtained in another way, the results in Table 3.4 are still valid.

Comparison of the performance of the I_0 and I_1 based models shows that the use of a stereotypical model initialisation I_c can improve the availability g of automatic meal time selections without decreasing their accuracy c. However, such an initialisation's impact on meal time correctness (scenarios O_1, O_2, O_3) is more difficult to assess due to the relatively limited amount of meal data available. Nevertheless, it can be seen from Table 3.4 that the frequency and preventability of wrong meal time selections varies noticably between individuals. Detailed inspection of the O_3 scenarios for subjects 5 and 7 as annotated with the footnotes highlights two important points:

- Even an adaptive user-specific meal time habits model cannot realistically reflect that user's habits at all times and in all possible situations. Ideally, the system should be able to recognise any temporarily unusual meal patterns, for example via the number of automatic selections and plausibility checks rejected by the user. If that number were to exceed a certain threshold within (say) the last week then the visible part of the automatic selection and plausibility checking system could temporarily switch itself off. For established users comfortable with the system,

(a)

Subject	n(O_1)	n(O_2)	n(O_3)	N	$4 * 365 * n(O_1)/N$	$4 * 365 * n(O_2)/N$	$4 * 365 * n(O_3)/N$
01	0	0	0	191	0	0	0
02	2	2	0	201*1	15	15	0
03	0	0	0	197	0	0	0
04	0	0	0	194	0	0	0
05	4	1	3*2	204	29	7	21
06	2	0	0	206	14	0	0
07	1	0	5*3	196	7	0	37
08	0	0	1	191	0	0	8
				mean (SD):	8 (10)	3 (5)	8 (14)

(b)

Subject	S_0	S_{1-}	S_{1+}	g	c	$4 * 365 * g * (1 - c)$
01	10	0	181	0.95	1.00	0
02	25	0	176	0.88	1.00	0
03	5	0	192	0.97	1.00	0
04	22	0	172	0.89	1.00	0
05	32	1*4	171	0.84	0.99	7
06	21	0	185	0.90	1.00	0
07	12	0	184	0.94	1.00	0
08	13	0	178	0.93	1.00	0
			mean (SD):	0.91 (0.04)	1.00 (0.00)	0.89 (2.53)

*1 Note that this figure is 2 less than the equivalent in Table 3.3 on page 82. This is due to the model's prevention of wrong meal time selections which would have meant that in this case less duplicate corrective meal entries would have been necessary.

*2 One lunch recorded at 17:24. Two dinners recorded at 21:27 and 21:39.

*3 Two lunches recorded at 19:42 and 20:36. Three dinners recorded at 21:53, 21:57 and 22:41.

*4 This incorrect selection is the same as the one annotated in Table 3.3.

Table 3.4: Performance assessment of meal time habits model initialised with I_1 - (a) meal time plausibility checking, (b) automatic meal time selection

one might also consider providing an option that allows them to manually turn this aspect of the user interface on or off.

- Even given the compact size of today's modern PDAs users will realistically not always carry the device with them so as to record data (and request advice) in real time. If it is to be recorded at all, a certain amount of data will thus be recorded retrospectively. However, such data not only misinforms the meal time habits model but also interferes with the decision support algorithms. In the future, one could attempt to use the meal time habits model to identify when data is being recorded retrospectively. Such detection would then allow either

  (a) the collection of extra information about the actual time of the insulin injection taken and the associated glucose reading, meal size and so on, or

  (b) the full or partial discarding of the retrospectively recorded and thus effectively timestampless data with respect to its use by the decision support algorithms.

Finally, based on the model description and assessment given in this section (Section 3.3.3), we identify the following three aspects of the model as areas where future improvements and extensions can be made.

1. *Optimisation of model parameters.* The parameters $f_{discount}$ and $M_{discount\_threshold}$ govern the relative weight the model attaches to recent and historic meal data. However, whilst the present parameter values of 2 and 84 respectively seem to work well, those values have not been determined empirically. It is therefore likely that the model parameters' values could be optimised, if a sufficiently large amount of meal-related data from a large number of individuals were available.

2. *Identification of typical meal time patterns.* Through the analysis of meal-related data from a large number individuals from different backgrounds a selection of stereotypical model initialisations I_c could be developed and assessed. However, the overall number of such stereotypical eating patterns used at any one time should be kept low so as to simplify the process of matching an individual user to an appropriate model initialisation.

3. *Snacks and post-prandial glucose readings.* Currently, snack-related data does not form part of the meal time habits model. However, for users who

   (a) regularly take between-meals snacks and insulin doses, and/or

   (b) frequently measure 2-hour post-prandial glucose levels

   snack-related model extensions could be valuable. Furthermore, depending on circumstances, such extensions might even be necessary, since highly variable eating patterns combined with regular snacks can increase the number of incorrect automatic meal time selections $S_{1\_}$ with the algorithm automatically selecting a main meal when the user intends to only have a between-meals snack.

3.4 Implementation issues

This section outlines and discusses the implementation-related issues encountered during the development and implementation of the POIRO MK3 system. Section 3.4.1 is about the code size and code structure limitations of the Palm OS platform and the solutions adopted to overcome them.

Section 3.4.2 looks at program execution speeds and their assessment with particular emphasis on differences due to (a) the amount of data entered and (b) the handheld device used. Section 3.4.3 concerns data transfers between handheld and desktop computers. Section 3.4.4 considers the bigger range of programming languages now on offer for the development of Palm OS applications. The section also briefly discusses the variety and features of widely commercially available handheld devices and the opportunities that these offer for future patient-oriented medical decision support systems.

3.4.1 Code size and code structure limitations

The addition of extra insulin types means not only that the POIRO system now caters for a greater number of insulin regimens (Table B.5) but also that the decision support algorithms' complexity and the size of their implementation has increased. This section outlines the code size and code structure limitations thus encountered and the strategies and solutions adopted to overcome them.

The main indication of the Palm OS platform specific code structure limitations encountered is the appearance of "*CallingProcedureName* 16-bit code reference to *CalledProcedureName* is out of range." messages during linking. These link errors occur when one procedure calls another procedure that, in the compiled machine code, is more than a $2^{16-1} = 32768$ byte jump away. A number of not mutually exclusive approaches can be used to eliminate or reduce the number of such link errors.

- Choosing the highest possible "Smaller Code Size" optimisation level offered by the compiler reduces the overall size of the code generated and thus results in or facilitates the elimination of some of the link errors.

- By changing the link order of the source code files, the jump distance of procedure calls can be reduced. This is the first work around the Palm documentation suggests for the "16-bit reference out of range" link error [69]. However, since files' code sizes are not uniform and file dependencies complex such rejigging of the linking order can remove as well as introduce link errors. As a Palm OS application grows in size and complexity, link errors become increasingly difficult to remove through systematic manual changes of the link order. In the CodeWarrior for Palm OS Release 6 Integrated Development Environment (IDE) used for the development of the POIRO MK2 and MK3 implementations, no facilities for automated link order determination or optimisation exist. In cases where a feasible link order could eventually be found manually, automatic link order optimisation support would have been very welcome. However, we also acknowledge that (i) a feasible link order will not always exist, and that (ii) determining the existence or absence of a feasible link order is a non-trivial problem due to the high number of possible link orders, $n!$ possibilities for n files, and the potentially complex inter-dependencies between source code files.

- Changing from the compiler's default "Small" code model to the "Smart" code model is the second link error work around suggested by the Palm documentation [69]. As another part of the documentation [70] explains, use of the smart code model resolves out of range references by generating extra code that simulates 32-bit references. However, for the POIRO MK3 system the smart code model was not adopted, because the extra instructions generated would have taken the overall size of the code over the 64K maximum resource size limit. This would then have required that the application be divided into several smaller segments, but segmenting an

existing application requires considerable effort and adds extra complexity to the code. For the POIRO MK3 system alternative link error work arounds were thus explored first.

- The use of so-called jump islands is the third link error work around suggested by the Palm documentation [69]. For the elimination of a "*ProcedureA* 16-bit code reference to *ProcedureB* is out of range." link error this involves the creation of small jump island procedure *ProcedureAtoB* located, via the manually chosen link order, within the permissible 32768 byte jump distance of both *ProcedureA* and *ProcedureB*. With the jump island in place *ProcedureA*, instead of calling *ProcedureB* directly, calls *ProcedureAtoB* and *ProcedureAtoB* then calls *ProcedureB*. The auxiliary procedure *ProcedureAtoB* thus bridges the too-large jump distance between the two main procedures *ProcedureA* and *ProcedureB*.
  Through the introduction of six jump islands totalling 120 bytes in code, the otherwise unsurmountable link error problems encountered during the implementation of the POIRO MK3 system could be overcome. Furthermore, so as to minimise their impact on the application's execution speed, the six jump islands used were added not in the core areas but in the less frequently executed areas of the program code.

- The fourth and final link error work around suggested by the Palm documentation [69] involves the creation of a so-called dynamic jump table that allows the programmer to handle long i.e. > 32K jumps themselves. However, since the introduction of a small number jump islands had already removed the existing link errors, the feasibility and merits of this approach with respect to the POIRO MK3 implementation were not investigated.

In addition to the above, two other approaches perhaps specific to the POIRO MK3 system have been useful for code size reduction and link error elimination.

- Changing the source code structure can reduce the size of the machine code the compiler generates. For example, within a procedure *BigProcedure*, replacing a call to a procedure *SmallProcedure* (not called by a procedure other than *BigProcedure*) with the actual code of *SmallProcedure* removes the need for procedure call and parameter passing machine code instructions. This technique is called in-lining. However, although the compiler used offered in-lining options as one of its language settings, manual textual replacements could often obtain further improvements.

- Changing the distribution of source code across different files can remove link errors by increasing the number of feasible link orders. Specifically, in the POIRO MK2 implementation (Section 2.2.2 and Figure 2.3) the full decision support algorithm implementation was contained in the *process.c* file which compiled into 22452 bytes of code. In contrast, in the POIRO MK3 implementation, the approximate equivalent functionality is divided across 6 source code files totalling 29224 = 23698 + 1370 + 1208 + 1074 + 952 + 922 bytes of code.

Palm OS platform specific code size limitations were also encountered during the implementation of the POIRO MK3 system. However, in constrast to the code structure limitations i.e. the link errors, the code size limitations were not apparent during the compiling and linking of the extended program. It was only when a transfer of the application from the desktop to the handheld was attempted, that the problem manifested itself via a rather non-specific "- Invalid handheld file deleted: InsAdv.prc" error message in the Hotsync Log.

As the Palm documentation explains, there is as such no maximum limit on the size of an application [68]. However, each Palm OS application is a collection of resources and if any of the resources is larger than approximately 64K the application will, as experienced with POIRO MK3, fail to transfer to the handheld device [71]. To overcome this problem, the application's code resource must be either reduced in size or converted into multiple code segments. For the POIRO MK3 system, code size reduction was both preferred, feasible and sufficient to avoid the complex introduction of multiple code segments.

The main code size reductions achieved during the development of the POIRO MK3 implementation involved manual reviewing of the source code with the aim of transforming it in a way that reduces the size of the compiler-generated machine code whilst, for safety and practical reasons, maintaining the source code's readability. Significant code size reductions were made through the removal of the implementation layer module that formed part of the POIRO MK2 implementation's program architecture (Figure 2.3). In particular, with respect to patient-specific settings this means that the processing and the interface modules are no longer fully isolated from the implementation details of the settings database module. However, this disadvantage is outweighed by the code size reductions achieved. Furthermore, note that the code size reductions here also inadvertently entail increases in processing speed.

3.4.2 Program speed and speed assessment

The increased complexity of the POIRO MK3 algorithms means that the time that is required for some calculations will be longer than their POIRO MK2 equivalent. This is not only intuitively the case, but also became apparent during testing. In particular, it was observed that short but noticable amounts of time were required not only for program start-up and diagram drawing but also for the core functionalities of entering data and requesting dose advice. Two important questions needed to be answered in this context:

1. How do calculation speeds change as more data is recorded over time?
2. How do calculation speeds differ between devices?

From a theoretical point of view, analysis of the system's algorithms can reveal the relative changes in calculation speed to be expected. For example, when searching an array of N equally common elements, a binary search's complexity is of order $O(log_2 N)$ and a linear search's complexity is of order $O(N)$. However, real algorithms are often more complex. The algorithms associated with drawing glucose trend and modal day diagrams for example combines binary and linear searches. Therefore we must, in our approach to the above two questions, take a more practical point of view.

Using the handheld device's internal clock and a simple purpose-built form, the time taken for any calculation or process of interest can be stopped and displayed. For seven of the most time-intensive and time-critical processes this was done; 70 days of fictitious but representive, semi-randomly generated monitoring data were entered into the POIRO MK3 system running on a Palm V device and response times were measured and recorded. The timing results are summarised in Table 3.5 and the following interesting points should be noted:

- A normal distribution of calculation times cannot be assumed. Results are therefore given as

median and interquartile range. For measurements other than the program start-up time the sample size was generally 70.

- With the exception of the diagram drawing[vii], the amount of time required for the different calculations or processes did not change as the amount of monitoring data entered increased. Searches in the events database are the only component of the decision support algorithms' implementation that is dependent on the amount of monitoring data recorded. The absence of a change in calculation times is thus due to the efficient search algorithms[viii] used to access the events database.

- Considerable changes to and restructuring of the program start-up code mean that, as a side effect, program start-up is now (a) much faster than in the POIRO MK2 system and (b) no longer dependent on the amount of data recorded. Also note that with a duration of 1.66 seconds the time required to start the program is now less than the 3 second duration of the "About" screen flash shown when the POIRO system is launched.

- The times required to record glucoses differs between times of the day with *Breakfast* values being recorded much faster than *Lunch*, *Dinner* and *Bedtime* glucoses. This is due to the fact that *Breakfast* glucoses are not used to calculate the offset caused by the previous meal's bolus insulin dose.

- The time required to record meals differs between times of the day. *Breakfast* and *Dinner* recording times are higher than those for *Lunch* and *Bedtime*. This is due to the fact that *Breakfast* and *Dinner* meal recordings entail the calculation of the offset caused the the previous basal insulin doses. The difference between *Breakfast* and *Dinner* recording times is likely to be due to the structure, content and size differences of the portion of the events database that must be searched during the basal offset calculation process.

- The glucose and meal recording times given in Table 3.5 assume that data is entered in a glucose-then-meal order as taught during training and suggested by the main menu order (Figure 2.5 (a) on page 33) and the missing data prompt. However, data entry in a meal-then-glucose order is also permitted and it is both theoretically and experimentally clear that the combined glucose and meal recording times for this data entry order is marginally faster than that for the glucose-then-meal order. Despite this, glucose-then-meal data entry is the encouraged option because for it the difference between and the ratio of glucose and meal entry times is lower and thus preferable in usability terms. From a practical point of view, this could mean that a user experiences two equally long delays of (say) 1 second when recording the glucose and then the meal data as opposed to (say) a 0.2 second meal entry delay followed by a 1.5 second glucose entry delay.

- The dose advice calculation times for bolus insulin taken at different times the day are essentially equal; the variability in response times to advice requests is due to differences in the monitoring data and not of any practical significance.

- The difference between dose advice calculation times for morning and evening basal insulin is likely to be due to differences in the portion of the events database used to generate dose advice.

- The considerable difference between basal and bolus dose advice calculation times is explained by the complexity of the basal dose calculation algorithm[ix]. However, if a delay of between 1.5

and 2 seconds were considered unacceptable, changes to the algorithms' implementation could be made. The dose advice calculation could be broken down into small fragments of code which are then executed not in response to an insulin type selection on the insulin form but during system idle time e.g. in between the user looking at and selecting an item from (say) the main menu.

- With respect to diagram drawing, three times are given. The second and third times ("Trend diagram drawing" and "Modal day diagram drawing") of 1.63 and 1.21 seconds respectively are the time typically required to retrieve and draw the glucose trend and modal day diagram. The first time ("Trend diagram update & drawing") of 3.50 seconds, based on once daily review diagram use, is the time typically required to update the pre-calculated diagram data and then to retrieve and draw the trend diagram. The difference of approximately 1.9 seconds between the first and second times can be directly attributed to the updating of the pre-calculated diagram data, but it should be noted that this extra delay is (a) incurred only once every day and is (b) in its magnitude dependent on the frequency with which review diagrams are viewed. More detailed information on this topic is given in Section 3.3.2.

- All calculation and processing times are stable i.e. essentially constant over time and do not represent delays that would be considered practically significant or unacceptable. Use of handhelds newer than the Palm V device used for this speed assessment is likely to decrease times further. Independent of the device used it would, from a usability point of view, be useful to know how long a delay i.e. processing time would be acceptable for core functionality such as recording data and requesting advice. For the future implementation of the mixed insulin algorithms this would then help identify where speed improvements and/or "PLEASE WAIT" messages would be appropriate. One might also want to conjecture that a few seconds of calculation time may well be quite acceptable to most users as long as it is clear that progress towards the generation of expert advice is being made.

In summary, calculation and processing times remain stable over time and are, in particular on inexpensive basic handheld devices, not impractical or unacceptably long. The remainder of this section looks at the way in which processing speed differs between handheld devices.

When comparing the execution speeds of one program run on different devices, three different speed components must be considered:

1. The relative speed with which general calculations and operations are carried out.

2. The relative speed with which data can be written to permanent storage i.e. into a palm record database.

3. The relative speed with which data can be retrieved from permanent storage i.e. from a record database.

So as to allow an objective, comparative measurement of these speed components, a straightforward mini demonstration and measurement program was written. This palm application, called *FibDemo*, repetitively calculates, stores, retrieves and averages the first 45 numbers of the Fibonacci series (1, 1, 2, 3, 5, 8, ...). Since the program does not require any user or other inputs its behaviour can easily be reproduced on different devices. Table 3.6 shows the results of running and timing the Fibonacci series calculations on nine different handheld devices. The *Calculate* operation generates

Calculation or Process	Clock ticks taken (100 ticks = 1 second) median (interquartile range)			
Program start-up:	165 (165-166)			
Trend diagram update & drawing:	350 (331.5-355)			
Trend diagram drawing:	163 (152-164)			
Modal day diagram drawing:	121 (121-122)			
	Breakfast	Lunch	Dinner	Bedtime
Glucose recording:	30 (27-37.75)	90 (73-114)	95.5 (74-120)	87.5 (75.25-113)
Meal recording:	72 (71-77)	39 (39-40)	96 (93-107)	54 (52-55)
Bolus insulin dose advice:	43 (43-43)	43 (43-44)	43 (43-44)	
Basal insulin dose advice:	169 (161-174.5)			185 (181-195)

Table 3.5: Program speed assessment results

the Fibonacci series and stores it in an array. The *Store* operation permanently stores the Fibonacci series held in the array into a simple database. The *AverageArray* and *AverageDatabase* operations average the 45 Fibonacci numbers held in the array and the database respectively. When looking at and analysing the details in Table 3.6 the following three points are worth noting:

- Access to data held in permanent storage i.e. in a database (*AverageDatabase* column) is significantly more time-consuming than access to data held in non-permanent storage i.e. in global or local variables (*AverageArray* column).
- Writing to permanent storage (*Store* column) is more time-consuming that reading from it (*AverageDatabase* minus *AverageArray* column). This is what one would expect given the way memory is managed by the Palm operating system.
- Between device comparison seems to show that more memory as opposed to more processing power is going to make the most practical timing-difference for an application that makes intensive use of permanent storage.

These results suggest that use of a higher-specification handheld device can improve the execution speed of a Palm OS application. However, the exact extent of such an improvement will depend on the individual device and application concerned. With respect to the POIRO system, future work that quantifies between-device performance differences would be both useful and interesting.

3.4.3 Data transfers between handheld and desktop

With a more sophisticated clinic-desktop system planned for the new versions of POIRO, a number of changes to the data transfer conduit were required. In the POIRO MK2 system data transferred from or to the handheld was stored in local files using a fixed format. Both the conduit and the device setup program used this data format to read from and write to the files. However, the clinic end desktop system to be used with future versions of POIRO will be more complex than the relatively simple device setup utility used during the clinical evaluation of POIRO MK2. In particular, such a system is likely to

- have several different users,
- be a distributed system with a main central as well as temporary local databases,
- provide multiple views of and access modes to the data stored, and eventually
- partially or fully integrate with standard electronic patient record and other relevant systems.

These are four reasons why the conduit and the clinic desktop system should (a) not use their own file and data format and (b) be de-coupled i.e. made independent of each other. In the MK3 version of POIRO this separation and format independence has been achieved through the use of a Dynamically Linked Library (DLL). Based on the data to be transferred to and from the handheld, the POIRO conduit specifies the required functionality and interface of the DLL. A DLL corresponding to these requirements is then supplied as part of the software that handles data storage on the clinic end. The phrase 'handles data storage on the clinic end' should in this context be given a wide sense of meaning in that it can include data transmission across networks as well as data conversion (import/export) functionality. Also note that

Manufacturer & Device	Palm OS version	Memory		Processor Type & Speed	Ticks taken per operation[a]			
		Total	Free		Calculate	Store	AverageArray	AverageDatabase
Palm V	3.1	2 MB	98%	Motorola DragonBall 16 MHz EZ	0.0705	25	0.0388	6.0
Handspring Visor Deluxe	3.1H2	8 MB	85%	Motorola DragonBall 16 MHz EZ	0.0486	32	0.0268	5.4
Handspring Visor Deluxe	3.1H2	8 MB	99%	Motorola DragonBall 16 MHz EZ	0.0486	20	0.0268	4.7
Palm m105	3.5.1	8 MB	99%	Motorola DragonBall 16 MHz EZ	0.0706	18	0.0388	6.1
Palm m500	4.0	8 MB	99%	Motorola DragonBall 33 MHz VZ	0.0354	10	0.0194	3.2
Palm m515	4.1	16 MB	66%	Motorola DragonBall 33 MHz VZ	0.0348	10	0.0190	3.9
Sony Clie	4.1	16 MB	52%	Motorola DragonBall 33 MHz VZ	0.0315	12	0.0175	3.2
Palm Tungsten W	4.1	16 MB	68%	Motorola DragonBall 33 MHz VZ	0.0353	14	0.0193	6.3
Palm Tungsten T	5.0	16 MB	92%	Texas Instruments OMAP 1510 144 MHz ARM	0.0236	2	0.0145	0.6

Sources of Processor Type & Speed Information

- Palm: Personal Communication (Email) from Palm Europe Customer Service, 07 November 2003.
  http://www-5.palmone.com/uk/en/products/tungsten-w/specs.html, 06 November 2003.
  http://www-5.palmone.com/uk/en/products/tungsten-t/specs.html, 06 November 2003.
- Handspring: http://support.handspring.com/esupport/forms/hsResolutionView.jsp?ResolutionId=6703&ResType=RESEARCH, 06 November 2003.
- Sony: http://reviews.zdnet.co.uk/hardware/handhelds/0,39023879,10000236,00.htm, 07 November 2003.
  http://www.dealtime.co.uk/xPF-Sony_Clie_PEG_T625C, 07 November 2003.

Table 3.6: FibDemo processing speed measurements for different handheld devices

[a]Measurements given for the *Calculate*, *Store*, *AverageArray* and *AverageDatabase* operations are based on 10000, 1, 10000 and 10 operations respectively.

(i) the conduit is now completely isolated from implementation issues such as data storage formats and locations, and that

(ii) the *event* + *timeofday* + *choice* code and *setting* + *timeofday* + *choice* code classification adopted for event and setting records respectively allows for considerable changes to the content and quantity of data transferred *without* changes to the conduit or the DLL.

The remainder of this section briefly summarises the clinic end data transmission and storage architecture developed by Nicholas Goodwin as part of his MSc project [33]. Invoked by the handheld conduit, the DLL residing on the desktop machine generates Extensible Markup Language (XML) messages which are stored locally for subsequent transmission to a central server. When an internet connection becomes available client software, again residing on the desktop machine, transmits the queued XML messages with the data to the central server where the data is then stored in a central database. In reverse, the desktop client software can also request and receive data in the form of XML messages, store it locally and then via the DLL supply it to the conduit if and when required. Figure 3.14 taken from [33] illustrates the overall architecture[x]. For full details the interested reader is referred to Goodwin's dissertation entitled "The Design and Implementation of a Protocol using XML to Collate Medical Results from Portable Devices" [33].

Figure 3.14 (original in colour): Data transmission and storage architecture proposed by Goodwin [33]

3.4.4 Programming languages, devices and connectivity

Since the original device and programming selection was made in autumn 2000 (Section 2.2.1) a number of technological and commercial developments have happened in the handheld market.

- The number of manufacturers and the variety of commercially available handheld devices has increased. However, whilst handheld computers are generally becoming more ubiquitous, quarter-by-quarter sales figures vary geographically and some regions are seeing a decline in sales growth.
- Compared to 2000 the Palm OS operating system has lost market share, whilst Microsoft's Pocket PCs have gained market share. Second quarter figures for 2003 by Gartner [82] put the worldwide market share of Palm OS-based PDAs at 51.4% by number of shipments and 41.0% by revenue in terms of end-user spending. This compares to 35.9% and 47.7% respectively for Microsoft Pocket PC PDAs with the difference between shipment and revenue shares being due to the higher average selling price of Pocket PCs.
- Compared to 2000, a much wider range of programming languages and tools is now available for Palm OS application development.
- So-called smartphones combining mobile phone, personal digital assistant and internet access functionality are becoming increasingly available. Also, many higher-end personal digital assistants now have in-built wireless capability.

The remainder of this section discusses the above developments in the context of the POIRO system.

- The increase in ownership of handheld computers supports the idea of basing the POIRO system on such portable devices and thus to make decision support available where and when needed.
- Although the Palm OS operating system lost market share compared to 2000 it is still the market leader. Furthermore, based on the premise that POIRO is to run on an easy-to-use, inexpensive but reliable and well-supported device, Palm OS was the right platform to choose. The interface of the main alternative devices, Pocket PCs, is very different from that of Palm OS PDAs. Similar to a Personal Computer's graphical user interface, it is more complex and thus less suitable for use by people with little or not computer experience. From a technical point of view, a complex operating system with a sophisticated interface and feature-rich applications
  (a) requires more processing power and memory, both of which translate into higher device costs and/or a trade-off in program speed, and
  (b) could detrimentally affect the system's stability i.e. increase the frequency of system crashes. For inexperienced computer users in particular such crashes and any accompanying incomprehensible or alarming-sounding error messages could seriously undermine confidence in the POIRO system and its advice.
- The wider range of programming languages now available for Palm OS application development includes not only C/C++ but also BASIC, Java and PASCAL. In addition, a number of tools and suites exist to support rapid application development (RAD), relational databases on the palm and the development of conduits synchronising with standard relational databases. Tool support for user interface and database related development aspects of any application can save time and effort, but this comes at a price.

- For database-related code as found in the POIRO system in particular it is likely that any automatically generated code would, compared to manually written code, carry a significant overhead in terms of memory requirements and record access speed. This is due to the fact that an automatic code generator, as opposed to a human developer, cannot know if, when and how often data items are stored and subsequently accessed. Note here that although considerable amounts of monitoring data are collected, processed and stored by the POIRO system, the majority of that data is essentially historic data and only a small fraction namely the most recent part of the events database is used to provide decision support.
- Through the use of code-generating tools, the developer not only partially relinquishes control over some of the application's code but also places trust in and relies on the correctness of the tool used, its documentation and its output. For applications such as POIRO were safety is critical, this issue of reliance and correctness is particularly important. Of interest in this context is also recent research by analyst company Meta Group which found that "Code generators do not produce clean code." and that for critical systems one "cannot rely on automatic code generation tools" [79].
- Competent use of any new tool or development environment requires an initial investment of time and effort in learning and tutorial-type practice development work. In a research setting and for one-off use of the tool concerned, this may not always be the most appropriate use of time and resources.

However, once an application such as POIRO moves away from being a research prototype towards wider use and integration with existing Electronic Patient Record (EPR) systems and databases, use of a development suite that supports integrated front-end (handheld device) to back-end (clinic end systems) application development would seem most appropriate.

- Smartphones, handhelds and glucose meters with in-built wireless capabilities offer exciting possibilities for future mobile diabetes decision support. Section 5.5.2 in Chapter 5 outlines some potential uses of this relatively new technology and also considers likely obstacles and barriers to its wider adoption.

3.5 Conclusion

This chapter described the MK3 version of the POIRO system and the additions and improvements it incorporates compared to previous versions.

All currently available types of insulin (Section 3.2.1) and associated insulin regimens (Section 3.2.2) were summarised. Decision support algorithms for three previously unsupported types of insulin (rapid, intermediate, premixed) were developed and described in Section 3.2.3. With the exception of those for premixed insulin, these new algorithms were also implemented. This brings the POIRO MK3 system up-to-date so that it now caters for a wide range of patients with Type-1 diabetes. In addition, the handheld application's user interface was improved and extended (Section 3.3) thus now allowing even easier and faster access to expert decision support. A number of implementation-related issues raised by the system extensions and recent technological developments in the area of handheld computing were discussed in Section 3.4.

This concludes this chapter as well as the current phase of the POIRO project. The next stage of the project, beyond the scope of this thesis, will be to combine both the results of the pilot clinical evaluation of the POIRO MK2 system (Chapter 2) and the extensions and updates incorporated in the MK3 version described in this chapter (Chapter 3) into a larger-scale, clinic-setting evaluation study (see Chapter 5).

Notes

[i] Jackson-Smale refers to the difference between a fasting (pre-Breakfast) glucose and the patient's fasting glucose target as offset [43] but does not clearly point out that this offset is quite different from the meal-related offsets as defined in Equations E4.7 and E4.8.

[ii] If the daily basal dose is split 50:50 between the morning and evening injections, then the POIRO MK3 system also provides a facility to, if required, couple the doses so as to maintain the 50:50 split when dose changes are made. The effectiveness of coupled basal doses is assessed via the fasting glucoses.

[iii] We assume that both computers' clocks are set to the same time zone.

[iv] If the clocks were previously set to 15:25 and 15:35 hours then 15:30 would be one possible mid-way value. An externally determined value could be obtained from the user or from a networked time server.

[v] Fact 1: Any application on the handheld can use the Time Manager's *TimSetSeconds* function to set the date and time on the handheld. Fact 2: The conduit resides on the desktop but can create and modify databases on the handheld. Fact 3: After a HotSync operation has occurred, an application is sent the *sysAppLaunchCmdSyncNotify* launch code. Based on these three facts a conduit could effectively adjust the clock on the handheld device by storing the magnitude and direction of the required change in a small database on the handheld. Upon receipt of the *sysAppLaunchCmdSyncNotify* launch code the application on the handheld would look for this database and could then use the *TimGetSeconds* and *TimSetSeconds* functions to make the clock adjustment. In this context it should be noted that a considerable amount of time can elapse between the conduit's creation of the small database and the handheld application's use of it. However, since the information communicated is relative (e.g. "Set clock 5 minutes forward.") and not absolute (e.g. "Set clock to 15:30.") this does not pose a problem.

[vi] Note that O_2 and O_3 are similar but not identical to a true-negative and false-negative result respectively because

(1) the three scenarios combine plausibility checks and automatic meal time selection, and

(2) O_2 and O_3 only apply in the $auto\_selection := none$ meal time selection case.

[vii] The system pre-calculates, stores and displays the glucose data for the last four weeks. The processing times measured when less than 28 days of data had been entered were therefore slightly lower but also more variable but subsequently stabilised.

[viii] For all but the simplest searches, a mixture of interpolation, binary and linear search algorithms is used. Given a database that is essentially a chronologically sorted array containing several weeks or months of day, interpolation is used estimate the position at which searching must start. This is followed by a binary search that determines the exact position from which forward or backward linear searches are then carried out.

[ix] A basal insulin dose change is only permitted if the last day's basal dose advice was always followed. One or more basal insulin doses taken at different times during the day thus need to be retrieved and checked if present. This takes time.

[x] The yellow box labelled "GlucoWatch Conduit" shows that the proposed architecture may also be used to transmit data from sources other than the POIRO handheld system. The GlucoWatch® (http://www.glucowatch.com) by Cygnus Inc. is a relatively new continuous glucose monitoring device. The yellow box labelled "Events and Settings Review" is the desktop-based software the physician or Diabetes Specialist Nurse (DSN) uses to (a) set up the handheld device and (b) review monitoring data recorded by the patient.

Chapter 4

Formal specification and software development

4.1 Introduction

The following chapter summarises formal specification and software development work carried out as part of this PhD research project. The work was motivated by the complex and safety-critical nature of the POIRO system and by the benefits that use of formal methods in this context could provide. Section 4.2 provides a brief overview of and introduction to the B notation and method. Section 4.3 briefly outlines how the original version of POIRO system was formally specified in B. A full account of this specification work has been published as a 16-page conference paper [76] reproduced in Appendix D. Following on from this specification, Section 4.4 summarises the use of formal methods in medical computing to-date as identified by a case study and application-oriented literature survey. The full literature survey, in the form of a stand-alone review paper in Appendix E, summarises some nineteen case studies and projects in six categories (diagnostic programs, patient monitoring, radiation therapy, robotically assisted surgery, information systems, miscellaneous) and then goes on to discuss and compare different projects' experiences, including our own. Section 4.5 identifies and outlines potential future work beyond the scope of this thesis. Section 4.6 concludes the chapter.

4.2 The B notation and method

Formal methods can be defined as the use of mathematics in the specification and development of correct software. *Correct software* in this context is software whose implementation meets its specification. Safety-critical systems, such as aircraft, railway signalling or nuclear power plant control systems, in particular are one but not the only area in which formal methods have been and are being used.

B is a notation and method for computer-aided formal software development from specification through to program code. This section provides a necessarily brief introduction to B. For more detailed information Wordsworth's "Software engineering with B" [96] or Schneider's "The B-method: an introduction" [81] are recommended. "The B-book: assigning programs to meanings" [1] by Jean-Raymond Abrial, the inventor of B, is the B reference text or 'B bible'. Other textbooks and material are also available.

4.2.1 The MACHINE construct

The starting point of any development in B is a formal specification of the system concerned. Using the B Abstract Machine Notation (AMN) one or a combination of several abstract MACHINEs are developed. These, on an abstract level, formally and concisely specify the system's state and its operations. VARIABLES and CONSTANTS of in-built or user-defined type comprise a MACHINE's state, whilst PRE-conditioned OPERATIONS describe how that state can change. An INITIALIZATION clause deterministically or non-deterministically specifies each machine's initial state. A machine's INVARIANT, a conjunction of boolean expressions over its state, describes properties that must be invariant and true at all times.

4.2.2 The REFINEMENT construct

REFINEMENTs are constructs that refine an abstract MACHINE. *Refining* in this context means that the refinement R rewrites the state and operations of the abstract machine M in more concrete i.e. less abstract terms. Refinement involves data refinement, operations refinement or a combination of the two.

In data refinement, an abstract variable is replaced by one or more concrete variables. For example, an abstract variable *data_values* that is a set of natural numbers $\mathbb{N}$

$data\_values \subseteq \mathbb{N}$ e.g. $data\_values = \{231, 186, 987, 42\}$

can be refined into an injective[i] sequence $data\_valuesSEQ$ of elements of the same type

$data\_valuesSEQ : iseq(\mathbb{N})$ e.g. $data\_valuesSEQ = [186, 42, 987, 231]$

with

$data\_values = ran(data\_valuesSEQ)$

as the glueing invariant that describes the relationship between *data_values* and $data\_valuesSEQ$. Using a sequence rather than a set imposes an order on the elements stored. $data\_valuesSEQ$ is thus less abstract i.e. more concrete than *data_values*. A sequence of elements is also less abstract because it is, compared to the set, more similar to an actual programming construct such as an array or a linked list.

In operation refinement, an abstract operation is rewritten in more concrete terms. For example, consider the following abstract version of an $AverageOfSet$ operation that returns the average of the set of numbers *data_values*.

$numerator,\ denominator \longleftarrow AverageOfSet\ =$
PRE[ii]
$data\_values \neq \{\}$
THEN
ANY
$nn,\ dd$
WHERE
$nn \in \mathbb{N}\ \wedge\ dd \in \mathbb{N}_1\ \wedge\ nn * card(data\_values) = sum(data\_values) * dd$
THEN
$numerator := nn\ ||\ denominator := dd$
END
END

This operation abstractly defines the average value of a set of numbers. Also note that the operation's return value is described non-deterministically. For $data\_values = \{231, 186, 987, 42\}$ return values $1446, 4$ or $723, 2$ or $2169, 6$ and so on would all be correct.

Now consider the following refined i.e. more concrete version of the AverageOfSet operation.

$numerator,\ denominator \longleftarrow AverageOfSet\ =$
BEGIN
$numerator := sum(data\_values)\ ||\ denominator := card(data\_values)$
END

This refinement removes the abstract operation's non-determinism by specifying exactly how the numerator and denominator should be calculated. It thus made the operation more concrete and for $data\_values = \{231, 186, 987, 42\}$ the return values will be 1446 and 4.

Data and operation refinement are often combined. Consider the following abstract version of an $MinMaxOfSet$ operation that returns the minimum and maximum of the set of numbers $data\_values$.

$minimum,\ maximum \longleftarrow MinMaxOfSet\ =$
PRE
$data\_values \neq \{\}$
THEN
$minimum := min(data\_values)\ ||\ maximum := max(data\_values)$
END

Using just the data refinement $data\_valuesSEQ : iseq(\mathbb{N})\ \wedge\ data\_values = ran(data\_valuesSEQ)$ described above, the operation would be rewritten as follows.

$minimum,\ maximum \longleftarrow MinMaxOfSet\ =$
BEGIN
$\quad minimum := min(ran(data\_valuesSEQ))\ ||\ maximum := max(ran(data\_valuesSEQ))$
END

However, if the elements in the sequence $data\_valuesSEQ$ were kept in ascending order i.e. if

$$\forall(i,j).(1 \leq i \leq j \leq size(data\_valuesSEQ) \Rightarrow data\_valuesSEQ[i] \leq data\_valuesSEQ[j])$$

where added to the refinement's invariant, then $MinMaxOfSet$ could also be refined into

$minimum,\ maximum \longleftarrow MinMaxOfSet\ =$
BEGIN
$\quad minimum := first(data\_valuesSEQ)\ ||\ maximum := last(data\_valuesSEQ)$
END

since by definition the minimum and maximum value of the ascending order sequence would always be the first and the last value in the sequence.

However, note that whilst the ascending order sequence makes the refinement of the $MinMaxOfSet$ operation easier, it may also make the refinement of other operations (e.g. adding or removing elements) more difficult so that other alternative refinements may well be more appropriate.

4.2.3 The IMPLEMENTATION construct

Following one or more steps of refinement (Figure 4.1), the last refinement step refines a REFINEMENT construct into an IMPLEMENTATION construct, from which ANSI C program code can then automatically be generated.

Section 4.2.1 to 4.2.3 provided a brief overview of the B method's specification and development process. However, for brevity, (i) details of machine, refinement and implementation construct development and (ii) the use of multiple constructs to structure developments have not been discussed.

4.2.4 Proof obligations and proofs

Using the B method we can develop or derive a program, through a number of steps as outlined above and in Figure 4.1, directly from its specification. At each step of the development process a number of so-called proof obligations (POs) arise. If all these POs can be discharged i.e. proved correct, then we have proven that the final implementation i.e. program code is correct with respect to its specification. The remainder of this section provides an overview of selected categories of proof obligations.

For a MACHINE (as well as a REFINEMENT and IMPLEMENTATION) construct one proof obligation is that the construct's INITIALIZATION clause must always establish the INVARIANT. For example, the

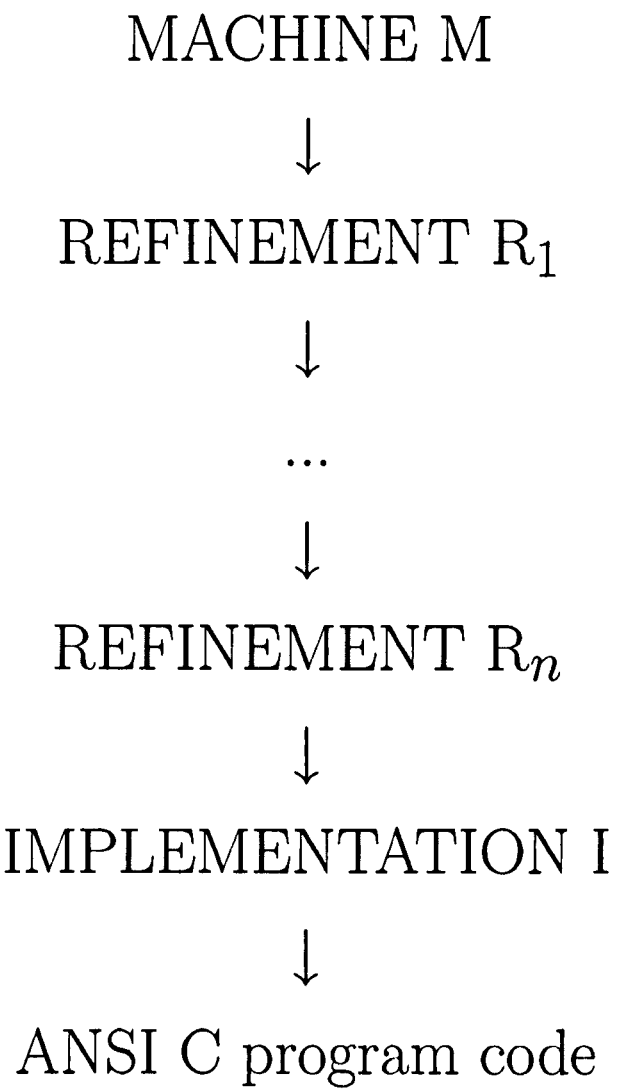


Figure 4.1: B method overview

INITIALIZATION $T1DMpatients := \{Alfred, Benjamin, Charles, David\} \;||$
$T2DMpatients := \{Charles, David, Edward, Frederick\}$

would establish the

INVARIANT $card(T1DMpatients) \leq 10 \;\wedge\; card(T2DMpatients) \leq 10$

but not the

INVARIANT $card(T1DMpatients) \leq 10 \;\wedge\; card(T2DMpatients) \leq 10 \;\wedge$
$T1DMpatients \cap T2DMpatients = \{\}$

Another proof obligation is that each operation, if called within its PRE-condition, must always maintain the construct's invariant. For example, given the last INVARIANT above for

$RegisterNewT1DMPatient(newPatient) \;=$
PRE
$newPatient \in PERSON$
THEN
$T1DMpatients := T1DMpatients \;\cup\; \{newPatient\}$
END

that proof obligation would not be satisfied but for

$RegisterNewT1DMPatient(newPatient) \;=$
PRE
$newPatient \in PERSON \;\wedge$
$card(T1DMpatients) < 10 \;\wedge$
$newPatient \notin (T1DMpatients \cup T2DMpatients)$
THEN
$T1DMpatients := T1DMpatients \;\cup\; \{newPatient\}$
END

it would be satisfied.

Finally, specific to REFINEMENT and IMPLEMENTATION constructs, proof obligations concerned with the equivalence of the abstract and the concrete i.e. refined state and operations arise.

4.2.5 Tool support

The B method is supported by two commercial software toolkits:

- The *B Toolkit* (http://www.b-core.com/) by B-Core (UK) Limited, Harwell, Oxford, UK.
- The *Atelier B* (http://www.atelierb.societe.com/) by ClearSy in France.

These toolkits provide

- editing,
- syntax and type checking,
- animation,
- automatic and interactive proof,
- document markup and printing

and other facilities. In addition, a number of other tools (as opposed to full commercial toolkits) are being developed by and within the B community. These include the U2B (UML to B) translator[iii] and the ProB animator and model checker[iv] being developed at the University of Southampton as well as Click'n'Prove[v] by Abrial and Cansell in France.

4.3 The formal specification of the POIRO system

This section summarises how the B notation was used to formally specify the original version of POIRO system. Full details of this work have been presented at the 3rd International Conference of B and Z Users in June 2003 in Turku, Finland. A reproduction of the corresponding paper [76] published in the conference's proceedings is provided in Appendix D from page 186 onwards.

The motivations for developing a formal specification of the POIRO system were threefold.

- Firstly, POIRO is a *safety-critical* system with multiple, related and possibly missing inputs which are processed according to complex clinical guidelines. These system characteristics make a formal specification of what the system does valuable.
- Secondly, the *knowledge* embedded in the POIRO system, i.e. the rules and concepts it uses to generate advice, is *complex*. We thus wanted to explore the possibility of using a formal specification in B as a form of knowledge representation and documentation.
- Thirdly, the project hoped to explore the *feasibility and viability* of producing a formal specification of a future or an existing medical computer system.

Prior to the start of this formal specification project the author had experience of using both the Z formal specification notation[vi] and the B notation & method. However, B was chosen over Z because of the existence in general of comprehensive, established, industrial-strength toolkits to support the method (Section 4.2.5) and the local availability in our department of the B-Toolkit in particular. Specification notations, methods or toolkits other than Z, B and the B-Toolkit were not considered or investigated.

The overall specification developed comprised fifteen MACHINE constructs. Descriptions of the structure, content and size of those machines as well as illustrative extracts can be found in Section 3 of the paper i.e. in Section D.3 of Appendix D from page 189 onwards. We thus here only briefly remark on the scope of the B specification work undertaken.

- The POIRO system and algorithms specified were those of the original system. This system provided dose advice for patients on a SHORT_ACTING plus LONG_ACTING insulin regimen only, but not for those on other regimens.

- The POIRO system's information display and intelligent message screens were not included in the formal specification.
- Only the handheld part of the POIRO system was specified, the desktop part and the conduit connecting the handheld and desktop parts were not considered.
- The project's aim was to develop a B specification only of the POIRO system. Specification-through-to-program-code use of the B method (Figure 4.1) that is refinement, implementation or proof work was neither intended nor attempted. See also Section 4.5 below.

Details of the specification process (as opposed to the specification end product) are discussed in Section 4 of the paper i.e. in Section D.4 of Appendix D from page 196 onwards.

Finally, the paper concludes (Section D.5) that the use of an abstract machine notation such as B for the formal specification and documentation of an existing knowledge-based medical decision support system such as POIRO is both feasible and viable.

The next section (Section 4.4) of this chapter summarises Appendix E's stand-alone literature survey paper on the use of formal methods in medical computing to-date. This is followed by Section 4.5 which identifies and outlines how the B specification work undertaken so far could, beyond the scope of this thesis, be taken further.

4.4 Formal methods in medical computing

With many medical computer systems being safety-critical, one would expect that medical computing is an area in which formal methods are frequently used. The stand-alone literature survey paper provided in Appendix E and summarised here thus set out to investigate the use of formal methods in the development of medical computer systems.

A systematic and comprehensive literature search was undertaken to identify published accounts of relevant case studies, applications and projects. The bibliographic resources and databases used covered medical as well as computing publications and included amongst others and listed here in no particular order:

- the ACM Digital Library (http://portal.acm.org),
- the IEEE Computer Society Digital Library (http://www.computer.org/publications/dlib/),
- PubMed (http://www.pubmed.com),
- Web of Science (http://wos.mimas.ac.uk),
- the Google (http://www.google.com) search engine, and
- electronic and printed tables of contents of relevant conference proceedings.

Reference lists and authors' names of already identified, relevant papers and forward i.e. citation search facilities were also used to find further publications.

Section 1 of the literature survey paper summarises the published work identified, some nineteen case studies and projects in total. The accounts are grouped into the following categories:

- diagnostic programs (Section E.1.1),
- patient monitoring (Section E.1.2),
- radiation therapy (Section E.1.3),
- robotically assisted surgery (Section E.1.4),
- information systems (Section E.1.5), and
- miscellaneous (Section E.1.6).

Section 2 of the paper summarises our own experience of formally specifying the POIRO system. Section 3.1 compares the experiences of the different case studies and projects under these headings:

- Academic versus commercial use of formal methods.
- New versus existing systems and the use of formal methods.
- To prove or not to prove.
- Formal methods training and support material.
- Tool support for formal methods.
- Critical and non-critical system components and formal methods.
- Combining different methods and notations.

Section 3.2 looks at the wider issues surrounding the use of formal methods in medical computing. The survey paper concludes (Section E.4) that formal methods can be successfully used in the development of a diverse range of medical computer systems.

4.5 Future work

This last section of Chapter 4 discusses how the B specification work undertaken so far could, beyond the scope of this thesis, be taken further. Two characteristics in particular make the POIRO or Insulin Advisor B specification interesting as a case study:

1. The problem domain and size. The specification describes an actual and existing safety-critical medical decision support system.
2. The computing platform on which the specified system is used. The Insulin Advisor is designed to run on small, portable handheld devices such as Personal Digital Assistants (PDAs) or smartphones. The memory and processor capacity of these computers is small compared to that of personal or other desktop computers.

4.5.1 Comparison of the toolkits supporting the B method

As stated in Section 4.2.5 above, currently two commercial toolkits supporting the B method are available. They are (in alphabetical order): *Atelier B* by ClearSy and the *B Toolkit* by B-Core (UK) Limited. For the B specification work undertaken so far the B Toolkit was used because of its local availability in our department and the author's familiarity with its interface and documentation. However, it is known that the B Toolkit and Atelier B differ in some respects and have their respective

strengths and weaknesses. The Insulin Advisor B specification could thus be used as one of possibly several realistic size case studies to compare the two toolkits.

1. The 'original' Insulin Advisor B specification having been developed using the B Toolkit, the first step of such comparative work would be the transfer of the construct i.e. MACHINE files to Atelier B. In theory, this should be easily done, but in practice we understand that there are small differences in the B notation accepted by the different toolkits[vii]. Note also in this context, that at present no ISO or other standard for the B notation and method exists.

2. Following the B Toolkit to Atelier B transfer and if required the systematic and carefully documented adaptation of the Insulin Advisor B specification, the toolkits' processing of the development could be compared. For each construct i.e. machine, the time required for the following tasks could be determined, tabulated and compared:

   - Analysis (Syntax and Type-Checking),
   - Proof Obligation Generation,
   - Proof Obligation Discharging,
   - ASCII to LaTeX document mark-up.

   Focusing not on speed but capability, the automatic provers' ability to discharge proof obligations could also be compared.

3. Whilst the results of 2. would be of interest as such, they would only represent one set of measurements i.e. they would not be generalisable. However, with two toolkit installations set up on the same or on two comparable machines, one could then go on to develop a simple protocol to carry out the same type of measurements for other B developments, including developments that contain refinement and implementation constructs. If a range of such developments[viii] from published or unpublished sources could thus be measured, this would allow a more meaningful and objective comparison of the two toolkits' respective processing capabilities and speed.

4. Independent of the Insulin Advisor B specification but related to 2. and 3. above, the functionality of and practical differences between the B Toolkit and Atelier B could be compared. Such comparative work would focus on analysis of the user interfaces and the ways in which different groups of users carry out particular tasks. For example:

   - learner users use only a relatively small subset of the available user interface elements, but would very much value helpful error messages in response to commonly made mistakes such as missing & symbols and undeclared variables.
   - proficient users who regularly use a toolkit will 'know their way around the interface' and are familiar with the most commonly encountered error messages. Other issues would thus be more important to them.

This section outlined how the Insulin Advisor B specification could be used in a mini-research project to compare the two available toolkits that support the B method. The findings of the project should then be used to decide on the toolkit to use for further i.e refinement and implementation work on this case study (Section 4.5.3). However, also note that whilst such comparative research and its publication would also be of wider, practical and academic interest, it would effectively constitute an assessment and comparison of competing commercial products. The challenges and difficulties this could present are acknowledged.

4.5.2 Animation, model checking and proofs

As mentioned in Section 4.2.5, in addition to the two commercial toolkits, a number of other tools for B are also available and/or being developed. Where applicable, use of these tools with the Insulin Advisor B specification case study would be likely to provide new insights into and findings about our case study and possibly also the tool used. For example,

- a tool such as ProB could be used to animate and model check the case study, whilst
- a tool such as Click'n'Prove could help tackle the previously unattempted, labour-intensive task of interactive i.e. non-automatic proofs.

Referring back to the specification-to-refinement-to-implementation-to-code steps of the B method as illustrated in Figure 4.1 and the proof obligations associated with each step (Section 4.2.4), it is clear that such proof and model checking work would constitute an essential prerequisite step for meaningful refinement and implementation work on all or part of the case study as proposed in the following section.

4.5.3 Refinement and implementation

Following the selection of the toolkit to be used, refinement and implementation work on the Insulin Advisor B case study could be approached as outlined below. Note that the proposed work does not aim to develop a full specification-refinement-implementation route re-implementation of the Insulin Advisor application, but rather focuses on specific issues related to the use of the B method for Palm OS application development.

1. The subset of C/C++ used for Palm OS application development is well defined and documented e.g. in the reference manual supplied with the Software Development Kit (SDK). However, the way the graphical user interface and files (permanent storage) in particular are used in Palm OS developments, is substantially different from their desktop equivalents. A first step in 'B for Palm OS' refinement and implementation work would thus be

   (i) a preliminary investigation of how B and the Palm OS SDK could be used together, and

   (ii) an identification of language and/or Insulin Advisor specification aspects that

      (a) are of particular relevance and interest, and/or that

      (b) might present difficulties or challenges later on.

2. Following on from the above, the original Insulin Advisor B specification should then, based on the aspects and features of interest, be reduced to a partial specification then to be refined and implemented. For example,

   - if the user interface were to be the focal aspect of interest, the partial specification might contain only the *InsulinAdvisor* machine's *EnterGlucoseEvent*, *EnterMealEvent*, *EnterExerciseEvent*, *EnterHealthEvent*, *CalculateAdvisedDose*, *EnterInsulinEvent* and *EnterHypoEvent* operations together with those user-defined types and variables of other machines that are used in those seven operations' pre-conditions.
   - if permanent storage (files, databases) were to be the focal aspect of interest, the partial specification might contain only the variables and operations of the *DATABASE* machine. Interface and advice generation should be removed from the development thus effectively turning the project into an electronic logbook albeit one without a user interface.

Also note that incidentally the number of proof obligations to arise in a partial specification should be significantly smaller than that of the full specification.

3. Following the specification-through-to-program-code development of at least one partial specification, the next step would be to integrate the generated program code with other conventionally or formally developed code. Comparative assessments of the code size, memory requirements and execution speeds of automatically generated and conventional code would form an important part of this last step of work.

Finally, with respect to the skills and expertise required for the work proposed above, (a) practical experience of all aspects of specification-through-to-program-code use of the B method on realistic and multiple machine but not necessarily large projects, and (b) knowledge of using B in the development of software for non-desktop computer platforms such as Palm OS would seem to be essential. However, whilst having experience of conventional software development for Palm OS and a thorough understanding of the Insulin Advisor system and its B specification, we to-date do not have experience in the above areas. If potential future work as outlined in this section were to be carried out it would thus have to take the form of a collaborative project with at least one other academic or non-academic institution.

4.6 Conclusion

This chapter summarised the formal specification and software development work carried out as part of this PhD research project. Section 4.2 provided an overview of the B notation and method used in this work. Section 4.3 outlined how the original version of POIRO system was formally specified in B. Section 4.4 summarised a case study and application-oriented literature survey of the use of formal methods in medical computing to-date. Section 4.5 identified and outlined potential future work beyond the scope of this thesis.

Notes

[i]An injective sequence does not contain duplicate elements. For example, $data\_valuesSEQ = [186, 42, 987, 231]$ would be injective whilst $data\_valuesSEQ = [186, 42, 987, 231, 42]$ would not be. However, with respect to refinement please note that sets may be refined into injective as well as into non-injective sequences.

[ii]When comparing the abstract and more concrete version of an operation, please note that the more concrete version need not repeat the operation's PRE-condition since it already implicitly forms part of it.

[iii]http://www.ecs.soton.ac.uk/ cfs/U2Bdownloads/U2Bdownloads.htm

[iv]http://www.ecs.soton.ac.uk/ mal/systems/prob.html

[v]http://www.loria.fr/ cansell/cnp.html

[vi]For an introduction to and further information on Z the interested reader is referred to:

- Lightfoot DE (2001) Formal specification using Z. Second Edition. Basingstoke: Palgrave.
- Spivey JM (1988, 1992) The Z notation: a reference manual. Out of print but available to download in electronic form from `http://spivey.oriel.ox.ac.uk/~mike/zrm/`
- Z User Group: `http://www.zuser.org/`

[vii]Examples:

- Reviewers of our paper presented at ZB 2003 remarked that some constructs we used with the B Toolkit such as the "SETS EVENT PROPERTIES EVENT $\triangleq$ N" in the DATABASE machine (Figure D.3) would not be accepted by Atelier B, and that the B-Book [1] on that very point states that "Given sets [..] denote *independent types*. As a consequence, no predicate in the properties clause can impose any equality or inclusion relationships between them."
- When upgrading our installation of the B Toolkit from Version 'Beta 4.38a' to Version 'Release 5.1.12' we noticed one small change in the B notation accepted by the new toolkit version. The earlier 'Beta 4.38a' version accepted definitions clauses such as the "DEFINITIONS MARRIED $\triangleq$ dom(husband $\cup$ wife); SINGLE $\triangleq$ person $-$ MARRIED" in the B-Book's MACHINE Data_Base construct on pages 258 to 260. The newer 'Release 5.1.12' however rejected such and similar definitions on the grounds that MARRIED is locally defined i.e. defined in the same machine and definitions clause. The way to overcome this problem is of course to rewrite SINGLE as "SINGLE $\triangleq$ person $-$ dom(husband $\cup$ wife)" but use of such a workaround not only reduces readability but is also inconvenient if adopted on a larger scale in a previously accepted B development.

[viii]Also of relevance and interest in this context is the problem of usefully and ideally automatically quantifying the size and complexity of B developments e.g. [24].

Chapter 5

Future enhancements

5.1 Introduction

This section follows on from Chapter 3 and describes planned or suggested future work on the POIRO system. Section 5.2 outlines potential additions and extensions to the handheld application. However, further work on the handheld application, and in particular the implementation of the premixed insulin formulation algorithms, is desirable prior to but not essential for a future clinical evaluation of the POIRO system. The development, on the other hand, of a non-research-prototype clinic end desktop system as described in Section 5.3 is required. Section 5.4 concerns the next stage of the clinicial evaluation of the POIRO system, a larger-scale study to determine the decision support system's potential to improve glycaemic control as well as its impact on and performance in routine clinical practice. Section 5.5 takes a wider view of the area of patient-oriented diabetes decision support specifically looking at current and likely future advances in diabetes therapy and technology and the practical and organisational changes they would entail.

5.2 Additions and extensions to handheld system

5.2.1 Implementation of premixed insulin formulation algorithms

Section 3.2.3 in Chapter 3 described the algorithms developed to provide insulin dose advice and decision support for patients using premixed insulin formulations. In the POIRO MK3 version of the system these algorithms have not been implemented (Table B.5). The implementation of the premixed algorithms is thus one of the next steps in the further development of the POIRO handheld application. Challenges likely to be encountered during the implementation process include the code size, structure and execution speed issues as previously outlined in Section 3.4. In addition, the following brief implementation-related guidance and information might be useful:

- The current patient-specific settings already record the type and if appropriate mix ratio of the insulin formulations used. For example, "$s------$" and "$i------$" respectively are the codes for short-acting and intermediate-acting insulins such as Actrapid® and Insulatard® whilst a "$m20s80i$" code stands for a premixed formulation such as Mixtard® 20 that contains 20% short- and 80% intermediate-acting insulin (Table B.4).

- Similarly, the post-prandial blood glucose excursion profiles used by the system are recorded not as hard-coded constants but as patient-specific variable settings. This allows the easy addition

of profiles that correspond to the various mixed insulins' short- or rapid-acting components; Figures 3.3 and 3.4 on pages 56 and 57 show the default profiles for short and rapid insulin.

- Glucose average and glucose offset calculations will be largely unaffected by the addition of premixed insulin formulations. The only amendments required derive from the need to treat one mixed insulin dose as two notionally separate doses.

- To simplify the process of treating one mixed insulin dose as two separate ones, it would seem useful to introduce an additional logbook event type *kInsulinComponent*. At present, events of type *kInsulin* are used to record insulin dose details including the insulin type and the number of units taken and advised. For a 10 U Mixtard® 20 dose such an event record could for example contain the information *"insulin type: mixed taken dose: 10 U suggested dose: 9 U usual dose: 11 U"*. Given the logbook event type *kInsulinComponent* this *kInsulin* event record would still be kept but for mixed insulins two *kInsulinComponent* event records *"insulin type: short taken dose: 2 U suggested dose: 1.8 U usual dose: 2.2 U"* and *"insulin type: intermediate taken dose: 8 U suggested dose: 7.2 U usual dose: 8.8 U"* would also be recorded. To the user these additional and redundant records would of course be invisible. For the system however, they would offer the advantage of being able to easily search for and retrieve (say) a short-acting *kInsulinComponent* or *kInsulin* event record if only short-acting insulin information is required. This 1+2 events recording system also allows the convenient implicit storage of dose mix information[i] thus removing the need for "20% of 11 U is 2.2 U" type calculations.

5.2.2 User interface changes

This section outlines four potential changes to the handheld application's user interface. With the exception of the redesigned hypo entry screen, these changes would be extensions to the existing interface and functionality.

Hypo entry screen

At present, on the hypo entry screen (Figure 5.1 (a)) users record how many hours ago they experienced the hypo. Although this calculator-style entry facility is easy to use, not least because it resembles the glucose entry screen, it has two disadvantages:

1. Information is lost due to rounding. A hypo that occurred around 45 minutes ago is recorded as having happened 1 hour ago.

2. Absolute to relative time conversions are needed. If a hypo is experienced at 2.15 pm but recorded only at around 4 pm then this requires that "2.15 pm" be converted into "about 2 hours ago".

An alternative hypo entry screen such as the one shown in Figure 5.1 (b) would allow hypo time recording that is more precise but no more difficult than that of the current entry screen. Also note that the alternative screen prototype uses the descriptive definitions of the three hypo severity grades.

Logbook review facility

Currently the logbook review facility displays data record-by-record in reverse-chronological order. This is useful if one wants to go through very recent data, but with around 20 records entered each day reviewing anything beyond the last day's data is impractical. Future versions of the handheld

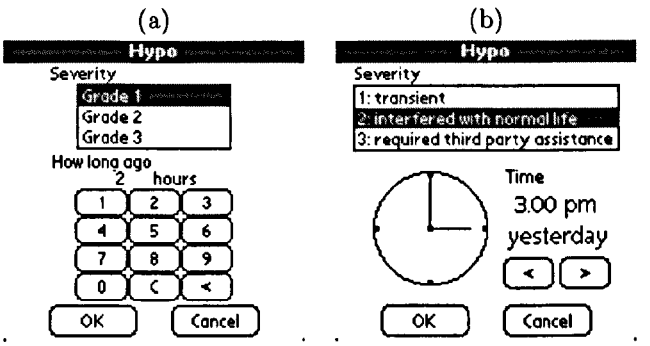


Figure 5.1: Hypo entry screens - (a) POIRO MK2 and MK3, (b) Future versions (prototype)

application should therefore (i) provide data displays on a dose-by-dose or day-by-day rather than a record-by-record basis, and (ii) support easier i.e. day-by-day or week-by-week navigation through the logbook.

Further work in this area should involve actual patient users familiar with the POIRO system so as to ascertain expectations about and likely use of a logbook review facility. As a minimum such an electronic facility would provide at-a-glance-information equivalent to that of a paper logbook, ideally it would also add extra value for example through visualisation (see below). The usability and technical challenges such an extension of the logbook review facility would present are acknowledged.

Review diagrams

The present glucose trend and modal day review diagrams could be augmented and extended in a number of ways.

- When the stylus is put down anywhere within a diagram, the current coordinates could be displayed.
- Glucoses other than those of the last 28 days could be made visually accessible through for example a four-week-wide 'window' that can be 'moved across' the glucose data.
- The review diagrams and the logbook facility could be linked.
  - One tap on a data point in a diagram could briefly display more details about it whilst two successive taps would open up the relevant section of the patient's logbook.
  - A "Draw this data" kind of button in the logbook would allow navigation in the opposite direction i.e. from the patient's logbook to its visualisation.

However, as has become clear during the implementation of the current review diagrams (Section 3.3.2) the realisation of even fairly basic data display facilities presents significant programming challenges. More advanced display facilities such as those outlined above would present additional user interface and usability challenges. Before commencing implementation work, one should therefore ascertain the likely use for and desirability of more sophisticated review diagrams (see Section 5.2.3 below).

User-defined reminder alarms

A simple facility that allows users to set themselves reminder alarms could be incorporated in future versions of the POIRO system. Although such user-defined reminder alarms would be expected to be used only infrequently, they could be particularly helpful for certain groups of users, such as:

- patients who do not perform daily home blood glucose monitoring, but take measurements on perhaps one or two fixed days each week.
- patients who regularly or occasionally take 2-hour post-prandial blood glucose measurements.

5.2.3 Technical and performance-related issues

Usage of non-core functionality

The non-core functionalities of the POIRO system include

- dose explanations accessible via the EXPLAIN button on the insulin menu (Figure 2.5 (e)),
- information screens (Figure 3.9) with contact and usual insulin dose details,
- the notebook entry facility (Figure 2.6 (c)),
- readings review screens (Figure 2.6 (f)),
- the glucose trend diagram (Figure 3.10 (b)), and
- the glucose modal day diagram (Figure 2.6 (h)).

Up to now the use and usefulness of these features has been assumed but has not been further investigated. Future work should therefore attempt to answer the following three important questions:

1. Do patients continue to use non-essential features once initial curiosity and novelty wears off?
2. How, why, when and for how long are the different features used?
3. Do the diagrams have motivational effects?

Some answers to these questions can be obtained fairly easily. A straightforward extension of user interface would allow the recording of the date and time when a particular screen was opened and closed. Combined with the logbook entries this data could give some insight into the frequency, context and duration of use of non-core functionality. Independent of or in conjunction with this, qualitative rather than quantitative insights should be obtained through user interviews.

Whether or not the review diagrams have motivational effects is one of the most interesting but also one of the most difficult-to-answer questions in this context. However, if the diagrams had a perceived or actual motivational effect for some users could this information be put to good use? In particular, would the occasional diagram display, intelligently initiated by the system, be a welcome and interesting interlude in the otherwise routine activity of glucose-monitoring and insulin-taking? The answers to these latter questions are practically relevant, since they have the potential to change the review diagrams from a non-essential to a key motivational feature of the POIRO system.

Handheld device clock changes

Section 3.3.2 in Chapter 3 looked at the way the handheld and desktop computer's clocks could be synchronised. This section is concerned with the problem of clock changes made on the handheld. If we assume that the handheld's clock is always synchronised against a reasonably accurate desktop clock, there are only a limited number of circumstances under which users would want to make changes to the handheld clock:

- Travel between different time zones[ii].
- Twice annual changes to and back from summer time.
- Adjustments by a few minutes if (a) the last clock synchronisation was, in the user's opinion, slightly inaccurate or if (b) the user prefers to use a clock that *on purpose* runs a few minutes fast (or slow).

The correct handling of handheld clock changes is particularly important in the following two contexts:

1. The event database's records are stored sequentially in chronological order. This ordering property must always be maintained as all database search routines make use of it. Achieving this in practice is easy: as part of the settings integrity checks carried out at program start-up the current date and time *now* is compared against the timestamp of the most recently recorded event *last_event_record*. If $now < timestamp(last\_event\_record)$ then the handheld's clock must have been changed backwards since the recording of the most recent event. The recording of additional event records in such circumstances might not maintain the chronological ordering property. Program start-up would thus be aborted with an appropriate message to the user.
2. In a distributed architecture such as the one proposed by Goodwin [33] for this project (see Section 3.4.3 and Figure 3.14) it is very unlikely that the different computers' clocks are perfectly synchronised. Whenever a connection is made between a handheld and a desktop computer it would therefore be useful to detect and keep a record of any clock differences between the two. Similarly, it makes sense to capture and maintain information about any clock changes made on the handheld. Since each user-initiated clock change results in the sending of a *sysAppLaunchCmdTimeChange* launch code, the POIRO handheld application can easily detect clock changes. However, apparently the extent or direction of a clock change is not one of the launch code's parameters and can thus not be recorded.

From a practical point of view, records about clock changes can also be used, at the next program start-up, to (a) inform the patient user about the last clock change, and to (b) ask them to check and confirm the new date and time settings. The handheld application can thus ensure (i) that the clock change was actually made and intended by the patient user and (ii) that any data subsequently collected is correctly timestamped.

Permanent storage limitations

Although today's modern handheld computers come with increasingly larger amounts of memory (e.g. Table 3.6), the possibility of running out of permanent storage space is at least theoretically still an issue. Thus to avoid loss of data and ensure continuity of operation, future versions of the POIRO system could adopt one or a combination of the following strategies:

- Respond. When the amount of memory available falls below a certain threshold an appropriate warning message is displayed and the user is asked to remove some data and/or applications (e.g. games) from the handheld.
- Prevent. When the POIRO application is installed it creates a 'memory reserve' i.e. a database of records of random data. If the amount of actually available memory were to approach or reach zero, the POIRO system could tap into its reserve so as to continue operating. If and when subsequently more actual memory becomes available again, the memory reserve can be replenished again.
- Cope. In the event of both actual and reserve memory running out the POIRO system can, as a last resort, start overwriting old logbook data.

Of the above strategies alerting and involving the user is clearly the most practical and easy-to-implement choice, though it will not support continued operation once memory runs out. Use of a memory reserve on the other hand can, depending on the reserve's size, ensure continued operation for a considerable time. If the reserve's size is chosen appropriately, the user can thus continue using the POIRO application until at least the next clinic visit. Overwriting of old logbook data and the loss of as yet untransferred data can thus be avoided.

5.2.4 Miscellaneous

Restricted dose increments

So far, the POIRO system provides dose advice for patients with insulin delivery devices that allow dose adjustments in 1.0 U increments. However, some devices have other, restricted dose increments of 2.0 U or 0.5 U. For example, one of the participants in the pilot evaluation study of POIRO MK2 used a Penfill device that allowed him to take only even doses of short-acting insulin. When the computer repeatedly advised odd doses this understandably caused irritation. Devices with dose increments of 0.5 U are mainly used in children[iii] or by thin adults. Future versions of the POIRO system should therefore (i) consider and possibly record what types of insulin injection devices a patient uses, and (ii) ideally be able to provide dose advice in the appropriate dose increments.

From an implementation point of view, accommodating dose increments other than 1.0 U is relatively straightforward, essentially requiring only changes to dose rounding rules and some interface-related adaptations. From a practical point of view, such a system extension would require that each patient's dose increment details are systematically elicited and recorded so as to then be available to the handheld application. Whether or not such extra across-the-board effort would be justified needs to be carefully assessed and will partly depend on the proportion of patients, within the POIRO target population, who use insulin delivery devices with dose increments other than 1.0 U.

mmol/L versus mg/dL glucose measurements

So far, the POIRO system requires blood glucose concentrations to be recorded in $mmol/L$, the unit of measurement most commonly used in the UK. However, in a number of other countries blood glucose concentrations are measured in mg/dL. It would therefore be useful extend the POIRO system so that it can also accept mg/dL glucose measurements. The conversion factor between $mmol/L$ and mg/dL blood glucose concentrations is 18 (Equation (5.1)).

$$\text{blood glucose concentration conversion: } 1\ mmol/L\ =\ 18\ mg/dL \tag{5.1}$$

5.3 Development of a desktop clinic end system

5.3.1 Overview

This section concerns the development of a non-research-prototype clinic end system to be used in further clinical evaluation studies of the POIRO system. On a very abstract level such a clinic end system would consist of three components:

- A database to store the clinic's patients' home-monitoring and other data.
- A software application to allow the physician to access the database in order to set and review patients' settings and data.
- Communications software that, invisible to the user, manages the transmission and storage of data.

Work carried out by Nicholas Goodwin as part of his MSc project covers the database and communications software components of the clinic end system. The data transmission and storage architecture proposed in his MSc dissertation [33] has already been summarised elsewhere in this thesis (Figure 3.14). The structure and design of the central clinic database is summarised[iv] in Figure 5.2 taken from [33].
With a database and required communications software already developed, Sections 5.3.2 to 5.3.4 below thus focus on the functionality and user interface of the software application to be used by the patients' physicians and/or Diabetes Specialist Nurses (DSNs). Section 5.3.2 looks at the use of the POIRO system in the multi-user environment of a real-world diabetes clinic. Section 5.3.3 is concerned with the clinic system's core functionality of setting and updating patients' individual settings. Section 5.3.4 looks at how patients' logbook data can be reviewed and visualised.

5.3.2 POIRO in a multi-user, real-world environment

A real-world, routine diabetes out-patient clinic is a diverse environment with multiple physicians, nurses, patients, computers and glucose meters.

Multiple clinic system users

Different groups of diabetes clinic staff will use the software application in different ways. As will be explained in Section 5.3.3 two different views of i.e. user roles in the system have been identified. Having started the software application, users will via a standard log-in screen identify themselves to the system and thus be presented with the user interface that corresponds to their assigned user role. Such an authentication mechanism is also required for other purposes such as (i) ensuring that only authorised personnel can access and/or change data in the system and (ii) maintaining records and documentation about decisions made and actions taken. The possibility of multiple and concurrent users also gives rise to 'distributed system issues' such as the problem of two users wanting to simultaneously access and/or update the same patient's record. Although such issues are clearly not unique to the POIRO clinic end system, they must be anticipated and addressed through technical and/or organisational means.

Figure 5.2 (original in colour): Structure and design of the central clinic database developed by Goodwin [33]

Multiple patients

All patient users, past and present, must be uniquely identified. In a research setting with only a small number of patients, staff can determine IDs and user names. In a non-research setting, the clinic system must take on this task: administrative and identifying information (surname, first name, date of birth, NHS or clinic number, etc.) must be collected and stored, and unique patient IDs and handheld user names must be generated and issued. Depending on the size and working practices of the diabetes clinic itself, some form of *is_registered_with* patient-physician allocation might also have to be recorded and managed. Similarly, a *is_used_by* device-patient allocation will be needed (see below).

Multiple devices

Records about who uses which devices are needed to support fully automatic transfers of settings and data between the devices and the clinic system. Note that a device in this context could be a handheld computer with the POIRO application as well as a suitable glucose meter. Further note that, in reality, the system must support a many-to-many relationship between devices and patient users because (i) devices are lost/stolen, broken or otherwise replaced, and (ii) devices may not be owned by but, in the context of an evaluation study, be lent to patients so that one device can, over time, be used by several patients.

5.3.3 Setting and updating patient-specific settings

The setting and updating of patient-specific settings is the core functionality of the POIRO clinic system. The first part of this section briefly describes and categorises the settings themselves. The second part looks at how the process of setting and updating patients' settings can be intelligently supported.

Descriptions and categorisation

All settings are categorised as either 'basic' or 'advanced'. Basic settings include administrative and standard insulin prescription details, advanced settings are related to the POIRO system. The two different views of i.e. user roles in the system correspond to the two setting categories. In the basic view all the basic settings are visible and can be changed; in the advanced view the basic as well as the advanced settings are accessible. The basic plus advanced categorisation of settings and system views is based on the fact that basic settings are frequently changed and easy to understand, whilst the advanced settings are less frequently changed and more complex to understand and/or change.

In addition to the basic and advanced system views, an administration view or mode allows the changing of system defaults and clinic staff user administration. The former may include tasks such as the adding or removing of insulin formulations or the changing of defaults for patient-specific settings such as dose safety limits. Note here, that the manner in which such changes to default settings are propagated through the system is a critical as yet unaddressed question requiring further work.

Table B.8 on page 181, in no particular order, lists the basic administrative settings. These are the settings transferred to and required by the handheld application. If appropriate, the clinic system may well hold additional information of this type.

Table B.9 on page 182 lists the basic insulin-related settings. Since patients typically take different types and different doses of insulin, actual insulin-related settings are identified via the setting and additional information given in the column labelled 'Key' in Table B.9. For example, patients typically use two different insulins, hence values of 1 and 2 for *insulin_slot*. Similarly, insulins of a particular type are taken at different times of the day, hence the *time_of_day* + *insulin_slot* compound key for the minimum, usual and maximum insulin dose settings.

Table B.10 on page 183 follows on from Table B.9 and contains the advanced insulin-related settings. Again, note that additional information in the column labelled 'Key' is used to distinguish between information related to, for example, different types of insulin.

Table B.11 on page 184 contains the advanced glucose-related settings. A further $5 + 4 + 4 + 3 = 16$ settings describe how bolus insulin doses should be adjustment according to the current BG level, meal size, exercise level and health status. Those settings are the multiplication factors listed in Table B.6 on page 178 and are thus not repeated here. Similarly, 3 settings describing stereotypical or actual meal time habits in the form of meal time histograms (Section 3.3.3 and Equation (3.30)) are not repeated here for brevity.

Having thus here briefly introduced all settings, the next part of this section shows corresponding sample screen layouts and considers how the process of setting and updating patient-specific settings can be intelligently supported.

Intelligent process support

The determining and inputting of patient-specific settings is an important and relatively complex task. To ensure the correct and safe operation of the POIRO handheld application, each patient's settings must be (i) medically sound, (ii) appropriate for that patient and (iii) consistent with each other. In practice, this means that the settings must satisfy a number of constraints. By intelligently supporting the process of inputting settings, the clinic system can not only enforce the satisfaction of those constraints but can also make setting up or updating devices easier and faster for the user.

We begin this section with three figures showing the basic, advanced and administrative insulin-related settings screens. Using those screens as illustrative examples, we will then discuss the types of intelligent process support the clinic system should provide. Figure 5.3 shows the screen used to input the patient's insulin prescription. This screen is available in both the basic and the advanced view of the system. The screen shown in Figure 5.4 is only available in the advanced view of the system. It is used to, if required, adapt POIRO-specific insulin-related settings to suit the individual patient's circumstances. Note that this screen (Figure 5.4), for reference only and thus greyed out, also displays the insulin prescription details input on the basic screen (Figure 5.3). The screen shown in Figure 5.5 is only available in the administrative view of the system. It is used to input and update the list of available insulin formulations and their associated POIRO-specific default settings.

Drop-down lists and combo boxes

Predefined drop-down lists, such as those for insulin formulations in Figure 5.3, (i) make the selection of an item fast and easy, and (ii) help ensure that only valid data is entered. In Figure 5.3 the first

Figure 5.3 (original in colour): Basic insulin-related settings screen

(upper) formulation list contains only bolus (rapid and short) and mixed insulins catered for by the system whilst the second (lower) list contains basal (intermediate and long) and mixed insulins. As a result, (i) entry of unsupported and/or unusual insulin regimens, for example consisting of two bolus or two basal insulins, is impossible and (ii) between-user and between-patient consistency in setting entry and display is automatically enforced[v]. For patients who take two mixed insulin formulations, the interface will also check and ensure that the formulations chosen on the two lists are not identical.

The 'Insulin name to display' combo boxes in Figure 5.3 are linked to their adjacent 'Insulin formulation' drop-down list. When the user selects an insulin formulation, the corresponding[vi] display name is automatically filled in by the system. This not only simplifies the selection of a display name, but more importantly also ensures that an insulin formulation change is always accompanied by a display name change[vii]. Also note that a combo box supports item selection from a list as well as free text entry. Individual patients' insulin display names can thus differ from the defaults suggested by the system. Plausible default vs. customised display name pairs include Actrapid vs. Regular, Ultratard vs. Basal and Humalog vs. Lispro.

The use of drop-down lists and combo boxes in the manner described and illustrated above can be generalised. For example, in other parts of the clinic system, predefined drop-down lists can be used to input a patient's doctor and nurse name or to choose an insulin formulation's type (Figure 5.5). Actions triggered by such a list selection can automatically fill in the doctor or nurse's contact phone number or the formulation's default settings.

Figure 5.4 (original in colour): Advanced insulin-related settings screen

Patient-specific insulin dose settings and default dose limits

When inputting insulin doses a number of constraints must be satisfied.

1. Dose inputs must be numeric i.e. 10 not 10 U or accidently $1O$ (capital o instead of zero).
2. Doses must fall into a medically sound range of for example 0 to 99 units.
3. Using their injection device, it must be possible for the patient to take the insulin doses prescribed. For example, a patient with a device to inject even numbers of insulin units between 2 and 42 cannot take doses of 7 or 43 units. See also Sections 5.2.4 and B.1.
4. The patient's total daily dose of insulin and its split into individual doses must be medically sound and plausible.

Checking and enforcing the first three constraints is easily achieved. With respect to the fourth constraint, the soundness and plausibility of the doses input will depend on a number of factors (insulin requirements, body weight, insulin formulations taken, lifestyle, etc). Further work on algorithms to intelligently distinguish correct and mistyped dose inputs is needed.

In addition to the standard insulin presciption details such as *Breakfast: 6 U Actrapid + 8 U Ultratard Lunch: 6 U Actrapid Dinner: 8 U Actrapid Bedtime: 10 U Ultratard* the patient's physician must set minimum and maximum dose limits within which the POIRO system is allowed to optimise i.e.

Figure 5.5 (original in colour): Administrative insulin-related settings screen

change the patient's prescribed usual dose of insulin. Hence, the settings screen (Figure 5.3) contains three insulin doses for each meal time and insulin formulation, a minimum, a usual and a maximum dose. Also note that for these data triples the property

$$minimum\_dose <= usual\_dose <= maximum\_dose \tag{5.2}$$

must be maintained and that constraints 1 to 3 above also apply.

To support the determination and setting of the minimum and maximum doses, the system should be able to automatically calculate default minimum and maximum dose limits. [43] states that the "dose limits may be set to plus or minus 50% of the starting dose or 6 units, whichever is the greater"[viii]. We can formalise this as

$$\begin{aligned} minimum\_dose_{default} &= \min(usual\_dose - 6,\ 0.5 * usual\_dose) \\ maximum\_dose_{default} &= \max(usual\_dose + 6,\ 1.5 * usual\_dose) \end{aligned} \tag{5.3}$$

and it can easily be shown that Equation (5.3) satisfies the property given in Equation (5.2). By checking or ticking the relevant "Use default minimum and maximum dose limits" box, the user can

automatically fill or update the minimum and maximum dose limits with the defaults.

In addition to the above default dose limits calculation facility, we must consider how best to check and enforce constraint 3 and the dose ordering property defined in Equation (5.2) if the user manually inputs or adapts the minimum and maximum limits. Assume a hypothetical insulin prescription change from 5 to 8 U made by a physician wanting to maintain the existing ± 2 U safety limits. The old dose setting would be (minimum: 3, usual: 5, maximum: 7) whilst the new settings would be (minimum: 6, usual: 8, maximum: 10). Simple analysis shows that of the 3! = 6 possible dose change sequences only one sequence ((minimum: 3, usual: 5, maximum: 7) ⟶ (minimum: 3, usual: 5, maximum: 10) ⟶ (minimum: 3, usual: 8, maximum: 10) ⟶ (minimum: 6, usual: 8, maximum: 10)) actually maintains the dose ordering property for all intermediate states. Checking and enforcing the dose ordering property whenever a single insulin dose or dose limit changes is thus not optimal as it would inappropriately and unnecessarily restrict the order in which users can input or update data. The following alternative approach is hence proposed.

$$
\begin{array}{rl}
cursor & \text{the currently selected dose input field, if any; } none \text{ otherwise} \\
slot(cursor) \in \{1,2\} & \text{the number of the current insulin formulation} \\
time(cursor) & \text{the meal time of currently selected dose input field} \\
dose(ww, ss, tt) & ww \text{ dose of insulin formulation number } ss \text{ at meal time } tt \\
 & ww \in \{minimum, usual, maximum\}
\end{array}
\tag{5.4}
$$

Using variables $cursor$, $slot(cursor)$, $time(cursor)$, $dose(ww, ss, tt)$ as defined in Equation (5.4) we can describe movements of the cursor as $cursor' \neq cursor$ and dose or dose limit changes at the current cursor position as $dose'(ww, slot(cursor), time(cursor)) \neq dose(ww, slot(cursor), time(cursor))$. Following the Z specification language's notation $cursor'$ (spoken "$cursor$ prime") denotes the value of the $cursor$ variable after the cursor movement or dose update operation.

We can now precisely express how the dose ordering property can be maintained by, but not necessarily throughout, an insulin prescription change process such as the one mentioned above.

$$
\begin{array}{l}
((cursor = none \ \wedge \ cursor' \neq none) \ \vee \ (cursor \neq none \ \wedge \ cursor' = none)) \\
\Rightarrow \\
dose(minimum, ss, tt) \ <= \ dose(usual, ss, tt) \ <= \ dose(maximum, ss, tt)
\end{array}
\tag{5.5}
$$

Equation (5.5) states that the dose ordering property must be satisfied at the beginning and at the end of any insulin dose review process.

$$
\begin{array}{l}
slot(cursor) \neq slot(cursor') \\
\Rightarrow \\
dose(minimum, ss, tt) \ <= \ dose(usual, ss, tt) \ <= \ dose(maximum, ss, tt)
\end{array}
\tag{5.6}
$$

Equation (5.6) states that the dose ordering property must be satisfied when moving from one insulin formulation to the other.

$$\begin{aligned}&(slot(cursor) = slot(cursor') \ \wedge \ time(cursor) \neq time(cursor')) \\ &\Rightarrow \\ &dose(minimum, ss, tt) \ <= \ dose(usual, ss, tt) \ <= \ dose(maximum, ss, tt)\end{aligned} \tag{5.7}$$

Equation (5.7) states that the dose ordering property must be satisfied when moving, within one insulin formulation, from one meal time to another.

Informally, Equations (5.6) and (5.7) state that the dose ordering property will only be checked and enforced if the user moves from one (minimum, usual, maximum) data triple to another. With respect to the (minimum: 3, usual: 5, maximum: 7) $\longrightarrow$ (minimum: 6, usual: 8, maximum: 10) settings change example given above, this means that now not only one but all of the $3! = 6$ possible dose change sequences will be permitted by the system.

$$\begin{aligned}&(slot(cursor) = slot(cursor\_target) \ \wedge \\ &(time(cursor) \neq time(cursor\_target) \\ &\wedge \\ &dose(minimum, slot(cursor), time(cursor)) \ <= \ dose(usual, slot(cursor), time(cursor)) \ \wedge \\ &dose(usual, slot(cursor), time(cursor)) \ > \ dose(maximum, slot(cursor), time(cursor))) \\ &\Rightarrow \\ &(cursor' = cursor \ \wedge \\ &dose'(ww, ss, tt) = dose(ww, ss, tt) \\ &\wedge \\ &\text{MESSAGE\_TO\_USER("WARNING: The current } time(cursor) \text{ usual dose of} \\ &dose(usual, slot(cursor), time(cursor)) \text{ U } name(slot(cursor)) \text{ insulin exceeds the} \\ &\text{corresponding maximum dose of } dose(maximum, slot(cursor), time(cursor)) \text{ U."))}\end{aligned} \tag{5.8}$$

As shown in Equation (5.8) we can also formalise the system's intended behaviour when an insulin formulation or meal time move from *cursor* to *cursor_target* is attempted whilst the dose ordering property is not satisfied. Note here that any pop-up warning messages displayed to the user should (a) be as specific as possible, and (b) not obscure the dose input fields to be corrected. In addition, visual aids such black-to-red font colour changes in or an arrow pointing to the relevant input fields could be used to help users easily identify and correct the dose settings concerned.

The above process of (i) considering when and how to most appropriately check and enforce constraints on patient-specific settings, and (ii) designing helpful and specific messages to the user, need also be applied to other settings and constraints in the clinic system. These include but are not limited to

glucose target, multiplication factors and allowable offset settings.

Formulation-specific settings and defaults

This section concerns settings specific to (a) each insulin formulation and (b) the POIRO system. By their very nature, these settings are (i) not as easy to understand as dose settings and (ii) the same initally for all and generally for most patients. The setting screen (Figure 5.4) that allows patient-specific adaptation of these advanced settings is therefore only available in the advanced view of the system. To facilitate the input and updating of the formulation-specific settings, the screen displays the standard basic settings in greyed-out form alongside the advanced setting and also, in the form of a tick box, supports the use of formulation-specific defaults. The constraints on the values of the settings are easily understood and enforced: values must lie in a medically sound and safe range. However, further work on actual lower and upper range limits, for example for insulin sensitivity and allowable offsets, is still needed.

The values of the formulation-specific defaults are input via the administrative settings screen (Figure 5.5). As these default settings will affect the settings and thus treatment of virtually all patients using that insulin formulation particular care must be taken with their input and updating. Hence,

- only insulin formulations listed on the administrative settings screen (Figure 5.5) can be used with the POIRO system i.e. appear on the drop-down insulin formulation list of the basic settings screen (Figure 5.3).
- insulin formulations must be classified as being *rapid*, *short*, *intermediate*, *long* or *premixed* insulins. For each of the five types of insulin, the clinic system supplies hard-coded insulin type-specific default settings. However, note that actual insulin formulation-specific settings may differ from the relevant type-specific default settings.
- range and possibly other constraints on the formulation-specific default settings must be identified and enforced.
- the way in which changes to default settings are propagated through the system i.e. applied to existing patients must be carefully considered and unambiguiously defined. Further work on this complex and important issue is needed.

5.3.4 Reviewing and visualising patients' logbook data

Reviewing and visualising patients' logbook data is not a core functionality of the clinic system and is thus only briefly considered here. A minimal, basic clinic system to be used in a further clinical evaluation study of the POIRO system should replicate the data review and visualisation facilities available on the patients' handhelds. In addition, a facility to print any displayed glucose trend or modal day review graphs, e.g. for patients to take home with them, would be desirable.

In a comprehensive clinic system, the functionality and development of advanced logbook review and visualisation facilities would constitute an interesting research project in its own right. For example, for information on and a discussion of "Web-enabled analysis and visualisation of diabetic clinic data" the interested reader is referred to Joanne Callow's MSc dissertation [17] with that title which aimed

"to program a web server to display the diabetic clinical data in a variety of forms, as appropriate to the clinical and user requirements, in order to both warn of problems and inform clinical decisions".

5.4 Evaluation in clinical practice

Following on from Chapter 3, one of the key activities in future work on this project, beyond the scope of this thesis, will be the evaluation of the POIRO system in routine clinical practice. This section briefly considers some of the medical, information technological and practical aspects of such an evaluation study.

5.4.1 Study proposal

The study proposal currently being discussed and developed intends a further evaluation of the POIRO system to take place in a routine diabetes outpatient clinic. Participants would be recruited from amongst the patients attending the clinic and the study would comprise three parallel study arms or groups as follows:

- standard care provided by Diabetes Specialist Nurses (DSNs)
- DSN care plus use of POIRO as an electronic logbook with the advice function switched OFF
- DSN care plus use of POIRO as an electronic logbook with the advice function switched ON

Study outcomes of interest would be

- the utility of the POIRO device that is (a) its ability to improve glycaemic control and (b) the speed and durability of such improvements. This can be assessed via standard measurements such as HbA1c, mean and fasting BG values and the frequency of hypoglycaemic episodes.
- patient satisfaction with their treatment as well as with the POIRO device. Treatment satisfaction can be assessed with established validated questionnaires. Feedback on the POIRO device would be obtained using a structured questionnaire similar to the one used in the pilot study.
- the time and effort involved for the DSNs. This information is likely to be more difficult to collect and measure. However, analysis of (a) clinic visit frequency and duration, and (b) patient phone contacts' frequency, duration and content as well as structured interviews with the DSNs could be used to provide insight. In principle, it is considered that use of POIRO will
  - initially increase workload in the form of training and longer consultation times, but will
  - after that decrease workload once patients start to make dose adjustment decisions on their own with the help of POIRO and without the need to phone their diabetes clinic.

With glycaemic control as the key outcome, calculations can be carried out for the sample size i.e. the number of study participants required to "have a high chance of detecting, as statistically significant, a worthwhile effect *if it exists*, and thus to be reasonably sure that no such benefit exists if it is not found in the trial" [3]. Using the data from the pilot study, such calculations indicate that a sample size of $3 * 16 = 48$ would be required for the three-arm parallel study outlined above.

5.4.2 Information Technology

The clinic-end desktop-based system to be used by the DSNs must not only be fully developed and thoroughly tested but must also be robust and able to support all relevant aspects of the evaluation study. In particular, the clinic system differs from the device setup utility used in the pilot study in that it

(i) will be used not by one member of the research team but by multiple diabetes clinic staff, and

(ii) is more complex and used in a different context[ix].

Appropriate training sessions must hence be designed and delivered, and supporting material and documentation will also be required.

With respect to the handheld device to be used by participating patients, a suitable make and model must be chosen and a sufficient number of these devices acquired. In this context, it must be pointed out that (i) since the start of this PhD project a larger number and wider range of devices have become available and that (ii) older models such as the Handspring Visor device used in the pilot study are no longer manufactured.

5.4.3 Current status

An evaluation study of POIRO in routine clinical practice is, by its very nature, a considerably larger undertaking than the inital pilot study, particularly in terms of time, staff and resources. Funding to support such further work is currently being sought.

5.5 The wider context

This section explores the wider context of computer-aided diabetes treatment in general and patient-oriented decision support in particular. Section 5.5.1 considers advanced data analysis possibilities enabled by electronic, as opposed to paper logbook, home-monitoring data collection. Section 5.5.2 looks at recent advances in diabetes-related medical and computing technology. Finally, Section 5.5.3 discusses computer-aided chronic disease management in the context of healthcare organisation and infrastructure.

5.5.1 Advanced data analysis

The following sections explore advanced data analysis possibilities for data from (i) individual patients, and (ii) groups of patients. The focus of this exploration is mainly on the content of the data and its analysis. Practical, technical questions surrounding for example data collection, aggregation, storage and retrieval are not discussed. Also note that in context of patient group level analysis relatively straightforward and/or standard types of analysis are not considered. Such analyses include calculations of group averages, trends over time and proportions of patients with glycaemic control within/outside a certain range or above/below certain treatment targets. This selective exclusion is justified with the fact that such analysis and audit facilities are more appropriately provided within an overall Electronic Patient Record (EPR) system.

Individual patients

Investigating the causes of hypoglycaemic episodes

When a patient's home-monitoring data is downloaded from their handheld device and/or reviewed by their physician, the clinic system can attempt to analyse any recorded clinical or biochemical hypos. Factors that may help identify patterns include

- lifestyle data (meal sizes, exercise levels, health status),
- insulin doses advised and taken,
- hypo causes identified and recorded by the patient (Figure 3.8 (d) on page 69),

as well as time considerations such as

- absolute and relative times of the data, e.g. *"between 6 and 8 pm"* or *"between dinner and bedtime"*,
- days of the week, in particular weekdays versus weekends,
- times of the month or year.

Where likely associations between one or a combination of factors and hypoglycaemic episodes are identified, this information could then potentially help prevent future similar episodes.

Insulin requirements and insulin sensitivity

A patient's total daily dose of insulin is proportionate to their body weight with typical requirements between 10 and 80 U for Type-1 and between 12 and 120 U for insulin-treated Type-2 diabetes. With the clinic system having glucose and insulin home-monitoring data as well as patients' basic demographic details available the actual absolute (U) and relative (U/kg) doses taken and resulting blood glucose values can be analysed. Given a sufficiently large amount of data, this may allow the calculation of an estimate for patients' sensitivity to insulin. Insulin sensitivity describes how a patient responds to insulin i.e. by how much blood glucose levels decrease or increase if the corresponding insulin dose is increased or decreased respectively. Insulin sensitivity is expressed as a percentage[x] (HOMA % S) with 100% being average sensitivity, values above 100% representing heightened sensitivity and values below 100% indicating decreased insulin sensitivity or insulin resistance. Insulin sensitivity depends on individuals' weight and genetic make-up, and it changes during illness and with the taking of certain medications. At present, insulin sensitivity is a characteristic that is difficult to measure. However, given measurements that fall within or outside certain ranges, insulin sensitivity can, to the physician, provide valuable feedback on a patient's state of health.

Insulin dose adjustments

Given a sufficiently large amount of data to filter out day-to-day variation and noise 'short-term change in insulin ΔU versus change in blood glucose ΔBG' analyses could be beneficial in two ways, through

(i) the optimisation of the dose change response or insulin sensitivity factors as defined in Equation (3.12). At present, for example for long-acting insulin the POIRO system uses an average

sensitiviy factor of 4.0 U/mmol/L for all patients and all doses. Further work could allow this value to be customised to individual patients and possibly even individual doses, in recognition of the fact that average responses to insulin vary both between patients and within patients throughout the day.

(ii) Tailoring of lifestyle-related multiplication factors to individual patients. For example, analysis of comparable large meals, insulin doses taken and glycaemic results measured might show that for some patients and/or some meals larger supplementary insulin doses i.e. multiplication factors are needed, whilst others require less supplementary insulin.

Related to the multiplication factor tailoring above, the clinic system could and should also perform a simple analysis of the relative frequency of non-standard meal sizes, exercise levels and health. This will help identify any data entry misunderstandings, that is situations where over a period of time, for example the majority of a patient's lunches are recorded as light i.e. less than normal whereas such light lunches are in fact the normal size of lunch for that patient.

Groups of patients

This section gives two brief examples as to how home-monitoring data from multiple patients could be used assess and improve the effectiveness of the POIRO system's algorithms.

- The analysis of actual and corresponding ideally expected post-prandial blood glucose excursions could identify opportunities
  - (a) to modify and improve the expected BG excursions profiles currently used, and/or
  - (b) to extend the algorithms that process and seek to reduce the difference between actual and expected glucose excursions.
- Given analysis techniques to tailor individual patients' insulin sensitivity and lifestyle-related dose adjustment factors, customised factors from a representative group of patients could be aggregated with a view to, if appropriate, adjusting the system's current default factors.

5.5.2 Technological advances

Glucose sensors

The development of accurate, non-invasive, continuous glucose sensing and monitoring devices is a very active research and development area at present. The GlucoWatch^{TM} (http://www.glucowatch.com) by Cygnus Inc. (http://www.cygn.com) was the first such commercially available device. It is worn like a wristwatch and uses a low electric current to pull glucose through the skin. In the latest version of the device, the *GlucoWatch® G2^{TM}*, "glucose readings are provided as frequently as every 10 minutes for up to 13 hours of continuous monitoring time" [42]. However, due to a number of factors devices such as the GlucoWatch do not yet replace conventional glucose meters and it is likely to be a few years still until non-invasive, continuous glucose sensing devices become as widely available and routinely used as glucose meters are today.

However, once non-invasive, continuous glucose sensing technology becomes widely used, patients and their healthcare providers will potentially have huge amounts of near-real-time monitoring data available to them. The management, analysis, and appropriate and constructive use of such data will

present considerable challenges and is likely to require some form of intelligent, mobile, computerised decision support.

Insulin delivery

At present, most diabetic patients on insulin therapy use syringes or pen type injection devices to take their insulin, whilst some use continuous subcutaneous insulin infusion (CSII) pumps. Not specific to diabetes, the field of alternative drug delivery methods is an active research area.

- Needleless injections systems,
- small inhaler devices able to control and measure the dose dispensed, and
- implants containing a depot of a drug whose gradual release can be externally controlled,

are three examples of alternative drug delivery methods to recently receive public as well as medical interest and press coverage. Specific to diabetes and insulin therapy

- oral insulin pills,
- skin patches,
- an oral spray, and
- inhaled insulin

are amongst the alternative insulin delivery technologies currently being developed and/or trialled [64].

Device connectivity

So far glucose meters, handheld or desktop computers and mobile phones have, in practice, been relatively unconnected with each other, despite the fact that various accessories (cables, cradles, software) are available to connect them. However, things are rapidly changing.

- Technologies such as Bluetooth enable secure, fast, wireless connections between devices of different types regardless of manufacturer or model.
- Many mobile phones and Personal Digital Assistants are now web-enabled and/or have in-built wireless capabilities. A range of so-called smartphones, a hybrid of a mobile phone and a PDA, have recently become commercially available and may present a one-device alternative for people currently using both a mobile phone and a PDA.
- Glucose meters are becoming smaller and often more technologically sophisticated.
  - Many meters allow the downloading of stored measurement data onto a desktop computer using a particular cable/cradle and special software.
  - TheraSense (http://www.therasense.com) in June 2002 launched their *FreeStyle Tracker System* [92] which is a glucose meter in the form of a Handspring Springboard module to be plugged into any Handspring Visor handheld device. This solution thus combines a glucose meter and diabetes management software in one place and on one device.
  - Glucose meters with wireless data transmission capabilities, such as the *Paradigm Link*^{TM} *Blood Glucose Monitor* [72] and *GlucoMON*^{TM} [25], are starting to become commercially available.

The technology is thus now available to easily, wirelessly link a patient's glucose meter and PDA up not only with each other but via a mobile phone potentially also with their clinic or some other central data processing centre (see below). However, it must also be noted that whilst such technology offers exciting new diabetes management opportunities, it also raises security issues (e.g. [46]) and is likely to, in the long-term and as discussed in the next section (Section 5.5.3), have a significant impact on existing healthcare organisation and infrastructure.

5.5.3 Diabetes care and patient-oriented decision support

This section considers patient-oriented decision support and the impact its wider adoption would have on the organisation and provision of diabetes care and the surrounding healthcare infrastructure.

Diabetes is a chronic disease that requires continuous management and monitoring. This task is at present shared between the patient and their diabetologist or GP (General Practitioner). Patients carry out home blood glucose monitoring and keep a paper logbook of glucose readings, insulin doses taken and possibly other data as well. At diabetes clinic visits every three to four months, the logbook data and longer-term indicators such as HbA1c or Fructosamine levels are used to assess glycaemic control and to, if required, change and adjust the treatment regimen.

However, their diabetes clinic and doctor are no longer the only source of information and advice for patients with diabetes. The Internet with a range of websites by diabetes groups[xi], pharmaceutical companies[xii], patients themselves and others is becoming a commonly used resource for information, education and support.

Handheld or desktop computer diabetes management software, for use with patients' own monitoring data, is also widely available on or via the Internet. Some of this software is sold or freely distributed by glucose meter manufacturers for use with their meters. Other software is produced by other companies or individuals and is distributed commercially or as shareware. The target user group or target market for these kinds of products are clearly well-motivated and computer-literate individuals. The key functionalities provided by such software are (a) data collection and (b) data presentation and visualisation, but for legal and safety reasons, it cannot provide actual, concrete dose advice to patients.

Any safe use of trustworthy, patient-oriented decision support software that does provide dose advice, requires supervision from and the involvement of the patient's healthcare team:

- When patients start using the software, they receive appropriate training and the software is set up and customised to suit them and their treatment.
- At regular or irregular intervals, patients, possibly remotely, transmit their collected home-monitoring data to their diabetes clinic.
- At the diabetes clinic, a member of the healthcare team reviews and monitors incoming data transmissions and provides feedback to patients, for example via e-mail, text messages or over the phone.

Whilst a relatively simple idea in principle, actual widespread and routine use of patient-oriented decision support software as described above would have a significant impact on the way diabetes care is provided. Amongst other things, it would mean

- empowerment, that is more involvement and responsibility, for patients,
- potentially fewer visits to the diabetes clinic and at the same time
- more frequent reviews of patient's monitoring data and treatment.

Furthermore, considerable investments in IT equipment, software and staff training would be required, and depending on the healthcare system concerned, questions of financial reimbursement and insurance cover would need addressing.

Related and also of interest is the relatively recent emergence of on-line services[xiii], as opposed to software, that help patients collect and manage diabetes home-monitoring data. Patients collect their usual data and periodically transmit it to the service provider either on-line, by phone or fax, or even by post. At the service's central data processing centre the data is then reviewed and analysed, and feedback is provided to the patient. Some services, with the patient's permission, also make monitoring data and/or feedback summaries available to the patient's physician.

Finally, a brief summary of the routine practice use currently envisaged for the POIRO system.

- The POIRO decision support program runs on a small handheld computer. This device and the program are initally set up by the patient's physician but then operate independently between clinic visits.
- The decision support program provides patient-specific dose-by-dose advice (a) according to published clinical guidelines and (b) within patient-specific physician-determined safety limits.
- At routine clinic visits data is downloaded from the handheld device to the clinic's central database and the physician reviews the patient's treatment, program settings and safety limits.
- Between routine visits patients may, as usual and if required, be in telephone contact with their diabetes clinic. Also, if the patient's glycaemic control is poor and/or if their preset dose limits are reached, then the program advises that they contact their physician and/or diabetes clinic.

The concept of POIRO is thus that of an easy-to-use, portable electronic logbook that provides dose advice where and when the patient needs it so as to optimise insulin treatment and improve glycaemic control and quality of life. Furthermore, POIRO was designed to operate independently between clinic visits and its routine use would thus not have to rely on the currently still relatively high technological requirements and complexity of frequent remote patient-to-clinic or clinic-to-patient data transmissions and the increased diabetes clinic workload they would create.

5.6 Conclusion

This chapter considered future work, outside the scope of this thesis, on the POIRO project. Section 5.2 looked at additions and extensions to the handheld system and Section 5.3 concerned the future development of a desktop clinic system. Section 5.4 briefly outlined some medical, information technological and practical aspects of a clinical study to evaluate use of the POIRO system in routine clinical practice. Finally, Section 5.5 considered the wider context of computer-aided diabetes treatment and patient-oriented decision support.

Notes

[i]The *kInsulin* events record the insulin type as 'mixed' but do not specify the mix ratio.

[ii]The issue of international travel across time zones and the consequences for insulin dose timings and so on are not addressed by the POIRO system. However, this does not prevent a user from travelling and/or changing the handheld's clock.

[iii]Total daily insulin doses are proportionate to body weight. For young children, as opposed to adults, a 1 U dose increase or decrease would thus constitute a relatively large proportion of their total daily insulin dose.

[iv]For more details and the full table definitions the interested reader is referred to Appendix 3 of Goodwin's dissertation [33].

[v]Without this mechanism two insulin ordering possibilities, here Actrapid + Ultratard and Ultratard + Actrapid, would always exist. This would unnecessarily increase the interface's complexity.

[vi]The default display name for each insulin formulation is set up via the administrative insulin-related settings screen (Figure 5.5). Table B.4 in Appendix B contains suggested display names for all formulations currently available in the UK.

[vii]Without this mechanism it is possible that, for example, an Human Actrapid® (short) to Humalog® (rapid) insulin formulation change remains invisible to the patient-user if the clinic-user forgets to update the 'Insulin name to display' setting from Actrapid to Humalog.

[viii]Other, more flexible, insulin type, diabetes clinic and/or physician-specific default calculation rules are of course possible.

[ix]The pilot study utility was, after the inital device setup, only used to switch patients' advice status from ON to OFF or vice versa. This was done whilst the patient attended the study visit i.e. without the patient present. In contrast, in a routine practice setting, the clinic system will be used to review and if appropriate update all settings, not just the advice status. This task is likely to be carried out as part of the patient's consultation with the DSN, one consultation amongst many in the busy, daily schedule of the outpatient clinic.

[x]Note that the use of the term 'insulin sensitivity' here in measurement but not in conceptual terms differs from that of Equation (3.12).

[xi]e.g. Diabetes UK http://www.diabetes.org.uk

[xii]e.g. Novo Nordisk http://www.novonordisk.co.uk

[xiii]e.g. iControlDiabetes http://www.icontroldiabetes.com

Discussion and Conclusion

This section discusses the POIRO system and the work carried out for this research project in relation to other diabetes decision support systems and the delivery of diabetes care, and thus concludes this thesis.

Large studies such as the American Diabetes Control and Complications Trial (DCCT) [63] and the United Kingdom Prospective Diabetes Study (UKPDS) [26] have shown that good blood glucose (BG) control significantly reduces the risk and delays the onset of serious long-term complications in Type-1 and Type-2 diabetes respectively. In patients with Type-1 i.e. insulin-dependent diabetes such tight control is achieved through intensive insulin therapy i.e. multiple daily injections of insulin and careful adjustment of each individual dose so that it matches current BG levels and lifestyle parameters such as food intake and exercise.

Glycaemic control can be assessed via short-term indicators such as the average BG values routinely measured by patients themselves using home blood glucose monitoring devices (glucose meters), and also via longer-term indicators such as the percentage of glycosylated haemoglobin A1c (HbA1c) in the blood, typically determined from samples taken at patients' regular diabetes clinic visits. An additional important indicator of glycaemic control is the relative frequency of hypoglycaemic episodes i.e. inappropriately low blood glucose levels. Since the symptoms of hypoglycaemic episodes (hypos) include sweating and increasing mental confusion leading to coma, the frequency of hypos is not only an important control indicator in itself, but also a major barrier to achieving and maintaining tight blood glucose control.

The design, implementation and evaluation of patient-oriented interventions that improve blood glucose control and thereby reduce the risk of long-term complications, is an active and important research area. Non information technology (IT) based interventions include educational programs such as DAFNE (Dose Adjustment For Normal Eating, e.g. [22]) which teach patients "how to adjust their insulin injections to fit their life and food rather than the other way around" [27], and decision and dose adjustment rules based on paper or a plastic card (e.g. [45]). Appropriate use of IT can augment and complement such 'traditional' interventions.

- Class-based educational programs can benefit from demonstration and simulation software such as AIDA (Section 1.2.1) or DIASnet (Section 1.2.4).
- Internet or multimedia-based packages can provide opportunities for self-education through the use of interactive material at the individual user's convenience and own pace of learning. See also Section 1.2.3 on the DIABETES and DIABETOR systems.

In addition, software has the potential to simplify patients' daily self-management/data collection tasks, and to improve communication with their doctor.

- Electronic logbooks can allow easy recording of blood glucose measurements, insulin doses taken and other details.
- Dietary software may assist in the counting and recording of the amounts of carbohydrate consumed.

Electronic logbook type software can typically also generate simple data summaries that, for example, include data averages and percentages of values within certain limits or above/below target values as well as graphical displays of the home-monitoring data recorded. These provide feedback to the patient, and may also motivate and sustain motivation for regular blood glucose monitoring and self-management. To patients' doctors printed (as opposed to handwritten) logbook data, and summary reports and graphs also provide an easily accessible overview of glucose control since the last diabetes clinic visit.

The Humalink, T-IDDM and POIRO systems summarised in Sections 1.2.5, 1.2.6 and 1.2.7 respectively all include electronic logbook type functionality. HumaLink and T-IDDM also provide facilities for asynchronuous communication, in between scheduled clinic visits, between patients and their healthcare providers.

The next logical step, after electronic recording and summary analyses of home-monitoring data, is the use and more complex analysis of that data so as to help make and improve future treatment decisions. With respect to physician users, DIABETES (Section 1.2.3), DIAS (Section 1.2.4) and the T-IDDM Medical Unit (Section 1.2.6) provide this type of functionality. Patient-oriented decision support is provided by Humalink (Section 1.2.5), the T-IDDM Patient Unit (Section 1.2.6) and POIRO (Section 1.2.7).

Different decision support systems as well as other interventions can be compared around the three criteria of suitability, impact and effectiveness.

- Suitability: Attendance at a class-based educational program with multiple sessions held at certain times and at a certain place may not be suitable or convenient for many patients due to travel distances, and work, family or other commitments. Similarly, computer-based interventions requiring a PC and/or an Internet connection may exclude patients without a computer and/or limited computer experience and interest. Furthermore, software is typically also suitable only for certain groups of patients e.g. Type-1 diabetes patients treated with short-acting and long-acting insulin in the case of the original POIRO system.

  Following the work described in Chapters 2 and 3 of this thesis, the latest version of POIRO is based on an inexpensive handheld device, is easy to operate, and does not require prior computer experience. In addition, the system now caters for patients using short- and long-acting as well as rapid- and intermediate-acting insulins. POIRO is thus now suitable for a wide range of Type-1 diabetes patients. Algorithms supporting premixed insulin formulations have also been developed but not yet implemented. Furthermore note that although work has to-date been limited to Type-1 diabetes, the system and its algorithms could, as they are and following

appropriate evaluation, be used for insulin-treated Type-2 diabetes.

- Impact: Most types of computer-based and other diabetes treatment interventions will have some kind of impact on patients' daily life, and on healthcare professionals' working patterns and workload. For example, approaches using carbohydrate counting require that patients carefully analyse and record what they will eat so as to balance carbohydrate intake and insulin injections. Telephone or Personal Computer based systems such as Humalink and T-IDDM (Sections 1.2.5 and 1.2.6) require frequent access to and use of these facilities. Healthcare professionals reviewing monitoring data from and communicating with patients, between scheduled clinic visits (e.g. Humalink and T-IDDM), must adapt their everyday working patterns and workload to accommodate these activities.

  The impact of the updated POIRO system on patients' lifestyle is minimal. Carbohydrate counting is not required since meals sizes are recorded in relative and descriptive terms i.e. no meal, a light meal or a large meal compared to the patient's usual i.e. normal meal size. The system is also able to cope with missing data and imposes no restrictions on the timing of blood glucose measurements and meals, or on the size of insulin doses taken i.e. patient can choose not to follow the system's advice. Furthermore, the small size and weight of the handheld computer used makes it practical for patients to carry POIRO around with them as part of their diabetes kit so as to be able to obtain dose-by-dose advice where and when it is needed. However, one drawback of this mobile, instant decision support approach is that currently real-time recording of data is required. Future versions should improve on this, so that data collected without the device at hand can still be recorded and correctly processed later on i.e. retrospectively (see also Section 3.3.3).

  From a healthcare provision point of view, POIRO operates independently between regular diabetes clinic visits, but of course within physician-determined and patient-specific parameters and limits. 'Traditional' treatment is thus complemented and improved, but no extra data needs to be remotely transmitted and reviewed. Furthermore, since POIRO will help patients with insulin dose adjustments on occasions such as a larger than usual celebratory meal or increased levels of exercise whilst on holiday, it is considered that the number of phone calls to the diabetes clinic seeking advice in such situations will decrease. However, prompted by the device, patients will still phone the clinic if preset dose limits are reached or if glycaemic control deteriorates. In practice, a certain number of calls related to the operation of and the advice given by the device are also likely. In a more general sense, the use of POIRO in routine clinical practice, and for example the system's impact in terms of staff and patient training, consultation times and so on remains to be evaluated in a larger clinical study as outlined in Section 5.4.1.

- Effectiveness: An intervention's effectiveness can be assessed in terms of (a) glycaemic control, (b) patient's quality of life and treatment satisfaction, and (c) its cost-benefit ratios.

  (a) In this context, changes in glycaemic control are usually described as changes in HbA1c and frequency of hypoglycaemia. Of interest are the speed and magnitude of any improvements as well as their durability over time. In particular, it is important to design evaluation studies so as to distinguish any changes caused by the computer system, educational pro-

gram, etc itself from changes attributable to simply taking part in a research or evaluation study. Also interesting to note in this context is that changes in patients' knowledge about and understanding of diabetes do not necessarily translate into improvements in glycaemic control.

(b) Changes in patients' quality of life and satisfaction with their treatment can be assessed using standard, validated questionnaires.

(c) Cost-benefit ratios or balances calculated by health economists consider the time and cost associated with an intervention against its benefits i.e. improved treatment outcomes. With respect to diabetes, improved glycaemic control reduces the risk of serious long-term complications such as cardiovascular disease, blindness, kidney failure and nerve damage, and thus the human and monetary costs to the healthcare system and society associated with these complications. In the short-term and for patients themselves interventions that include remote data transmissions could in principle increase the time interval between diabetes clinic visits, thereby directly reducing the direct and indirect cost and time of travelling to and attending the diabetes clinic.

With respect to evaluating the effectiveness of the POIRO system, we have successfully completed a proof-of-concept pilot study as described in Chapter 2. The next stage now is the system's evaluation in routine clinical practice as outlined in Section 5.4.1.

This concludes the brief discussion, in terms of their suitability, impact and effectiveness, of patient-oriented interventions to improve glycaemic control.

Focusing specifically on this research project and how it has taken the original POIRO system forward in view of recent developments in the diabetes treatment and computing fields, the work described in this thesis can be summarised as follows:

- The original POIRO system was re-implemented and updated for the Palm OS family of modern Personal Digital Assistants (Section 2.2). The new version, POIRO MK2, was then successfully evaluated in a clinical pilot study (Sections 2.3 and 2.4).
- At the same time, the current literature in the field was reviewed, and existing systems were identified (Section 1.2) and their underlying techniques and approaches compared (Section 1.3).
- Furthermore, all types of insulin and insulin regimens now available were researched and summarised, and corresponding decision support algorithms were developed and implemented for POIRO MK3 (Sections 3.2 and 3.4).
- We have also improved and added facilities to the POIRO's user interface (Section 3.3), and as part of these enhancements developed and applied an adaptive model which describes a user's meal time habits (Section 3.3.3).
- Motivated by the complex and safety-critical nature of the dose advisor system, we have used the B notation and method (Section 4.2) to develop a formal specification of the POIRO decision support system (Section 4.3 and Appendix D).
- Additionally, and related to this, we have investigated and reviewed the use of formal methods in the development of medical computer systems (Section 4.4 and Appendix E).

- Last but not least and building on the evaluation and extension work carried out, we have in considerable detail identified and described future enhancements and work on the POIRO research project (Sections 5.2 to 5.4). The wider context of computer-aided diabetes treatment, patient-oriented decision support, and the POIRO system was also discussed.

We have hence demonstrated how increasingly ubiquitous handheld computers and expert system software can be combined into an easy-to-use, patient-oriented tool to support the day-to-day monitoring and management of Type-1 diabetes today, and potentially that of other chronic diseases in the future.

Appendices

Appendix A

Pilot Study Data

A.1 Clinical data

- World Health Organization (WHO) Body Mass Index (BMI) classification: <18.5 kg/m^2 underweight, 18.5-25 kg/m^2 healthy weight, >25 kg/m^2 overweight, >30 kg/m^2 obese.

$$\text{Body Mass Index} = \frac{\text{Weight in kilograms}}{(\text{Height in metres})^2}$$

- World Health Organization-International Society of Hypertension (WHO-ISH) definitions and classification of blood pressure levels (mmHg) (Reproduction of Table 1 in [97])

Category	Systolic	Diastolic
Optimal	< 120	< 80
Normal	< 130	< 85
High-normal	$130 - 139$	$85 - 89$
Grade 1 hypertension (mild)	$140 - 159$	$90 - 99$
Subgroup: borderline	$140 - 149$	$90 - 94$
Grade 2 hypertension (moderate)	$160 - 179$	$100 - 109$
Grade 3 hypertension (severe)	≥ 180	≥ 110
Isolated systolic hypertension	≥ 140	< 90
Subgroup: borderline	$140 - 149$	< 90

When a patient's systolic and diastolic blood pressures fall into different categories, the higher category should apply.

- HbA1c normal range: 4.7-6.4%
- Fructosamine normal range: 205-285 umol/L
- Biochemical hypo: blood glucose reading <= 3.5 mmol/L
- Dose change activity: Percentage of insulin doses that were changed, that is that are different from the previous (day's) dose of the same insulin type and taken at the same meal time.

		01	02	03	04	05	06	07	08	All
Advice group		ON/OFF	ON/OFF	OFF/ON	ON/OFF	OFF/ON	OFF/ON	ON/OFF	OFF/ON	
Base line data										
Age	years	50	72	44	39	38	62	47	34	48 (13)
Gender	M/F	F	M	M	F	F	M	F	M	4/4
Height	cm	154	175	167	160	159	183	162	173	167 (10)
Weight	kg	99.0	72.5	62.9	52.0	85.8	89.4	42.6	70.2	72 (19)
Body Mass Index (BMI)	kg/m^2	42	24	23	20	34	27	16	23	26 (8)
Ethnicity		All Caucasian.								
Diabetic complications		NO	neuropathy	retinopathy	NO	NO	NO	retinopathy	NO	
Time since diagnosis	years	23	43	11	11	25	21	28	12	22 (11.75-25.75)
Hypertension		NO	YES	YES	NO	NO	NO	NO	NO	
Smoker		Never	Ex	Never	Never	Ex	Ex	Ex	Ex	
Dislipemia		NO	NO	NO	NO	NO	NO	NO	NO	
Past medical history		YES	NO	YES	NO	NO	NO	YES	NO	
Systolic blood pressure	mm Hg	136	146	117	130	125	147	113	121	
Diastolic blood pressure	mm Hg	83	80	68	85	87	85	73	73	
Waist circumference	cm	114	93	80	66	87	102	66	89	87 (17)
HbA1c	%	7.7	8.4	7.9	8.4	6.8	8.8	7.4	9.1	8.1 (0.8)
Fructosamine	umol/L	324	366	410	431	323	418	381	514	396 (63)
Prandial insulin dose	U/day	24	22	20	12	18	50	16	12	19 (15-22.5)
Basal insulin dose	U/day	37	24	18	6	14	14	4	8	14 (7.5-19.5)

Table A.1: Base line data

		01	02	03	04	05	06	07	08	All
Advice group		ON/OFF	ON/OFF	OFF/ON	ON/OFF	OFF/ON	OFF/ON	ON/OFF	OFF/ON	
RUN-IN										
HbA1c	%	7.3	7.9	8.0	8.5	6.8	8.5	7.5	9.2	8.0 (0.8)
Fructosamine	umol/L	323	318	421	401	320	381	417	468	381 (56)
Prandial insulin dose	U/day	24 (24-26.5)	25 (24-27.5)	21 (20.5-23)	16 (16-16)	19 (18-21)	50 (50-50)	21 (17-22.5)	28 (26.5-28.75)	22.5 (20.5-25.75)
Basal insulin dose	U/day	37 (37-37)	24 (24-24)	18 (18-18)	6 (6-6)	14 (14-14)	14 (14-14)	4 (4-4)	8 (8-8)	14 (7.5-19.5)
Mean daily BG	mmol/L	9.3	8.0	9.3	9.9	6.7	8.6	8.5	9.6	8.7 (1.0)
pre-Breakfast		6.1	8.1	6.8	11.2	6.5	4.8	12.0	5.7	7.7 (2.6)
pre-Lunch		11.0	8.5	11.8	9.9	6.1	10.6	7.1	15.5	10.1 (2.9)
pre-Dinner		9.3	8.2	9.5	11.1	5.7	8.1	7.5	5.3	8.1 (1.9)
pre-Bedtime		11.0	7.4	9.1	7.6	8.6	10.8	7.3	12.5	9.3 (1.9)
Biochemical hypos	number	2	3	4	0	5	7	3	5	29
Clinical hypos	number	0	1	1	2	0	0	4	0	8
Dose change activity	%	33	61	25	0	46	8	71	30	31.5 (20.75-49.75)

Table A.2: RUN-IN period data

		01	02	03	04	05	06	07	08	All	
Advice group		ON/OFF	ON/OFF	OFF/ON	ON/OFF	OFF/ON	OFF/ON	ON/OFF	OFF/ON		
ON											
HbA1c	%	7.2	8.3	7.6	8.3	6.7	7.9	8.0	9.4	7.9 (0.8)	n.s.
Fructosamine	umol/L	373	360	379	439	350	388	419	414	390 (31)	n.s.
Prandial insulin dose	U/day	33 (31.5-34)	28 (27-29)	20 (17.5-21)	16 (16-16)	18 (16.25-19)	52 (48-56.5)	19 (17-21)	32 (30.5-33.5)	24 (18.75-32.25)	n.s.
Basal insulin dose	U/day	33 (32-34)	22 (21.5-24)	15 (14-15)	7 (7-7)	11 (11-12)	10.5 (10-11)	2 (2-2)	7 (5.5-8.5)	10.75 (7-16.75)	0.0378
Mean daily BG	mmol/L	10.0	12.5	7.3	9.4	7.8	11.4	8.7	10.1	9.7 (1.7)	n.s.
pre-Breakfast		12.5	14.6	8.5	10.0	8.8	9.0	9.1	7.4	10.0 (2.4)	n.s.
pre-Lunch		7.1	14.2	8.5	10.2	7.9	12.8	7.1	14.7	10.3 (3.2)	n.s.
pre-Dinner		10.3	9.0	5.8	8.9	5.2	10.8	10.4	7.6	8.5 (2.1)	n.s.
pre-Bedtime		10.3	12.8	6.6	8.5	9.3	13.0	8.3	10.9	10.0 (2.2)	n.s.
Biochemical hypos	number	2	0	2	0	3	1	1	2	11	0.0417
Clinical hypos	number	0	0	0	2	1	0	1	0	4	n.s.
Dose change activity	%	70	68	50	14	57	78	67	50	62 (50-68.5)	0.0115
Advice followed	%	100	9	93	42	85	100	54	100	89 (51-100)	-

Rightmost column: ON vs. OFF comparison using paired t-tests. n.s. = not significant at P = 0.05 level.

Table A.3: Advice ON period data

		01	02	03	04	05	06	07	08	All
Advice group		ON/OFF	ON/OFF	OFF/ON	ON/OFF	OFF/ON	OFF/ON	ON/OFF	OFF/ON	
OFF										
HbA1c	%	7.0	7.9	7.7	8.6	7.0	8.1	7.7	9.4	7.9 (0.8)
Fructosamine	umol/L	316	327	442	421	315	342	410	386	370 (51)
Prandial insulin dose	U/day	32 (32-32)	26 (22-26)	20 (20-21)	16 (16-16.5)	21 (19-22)	50 (50-50.5)	18 (14.5-20)	28 (28-28)	23.5 (19.5-29)
Basal insulin dose	U/day	34 (34-34)	21 (21-22)	18 (18-18)	7 (7-7)	14 (14-14.5)	14 (14-14)	3 (3-3)	8 (8-8)	14 (7.75-18.75)
Mean daily BG	mmol/L	9.1	8.1	5.9	9.8	8.8	8.8	7.3	11.0	8.6 (1.5)
pre-Breakfast		6.6	10.1	6.1	11.2	5.7	6.8	8.8	9.4	8.1 (2.1)
pre-Lunch		10.3	8.5	5.3	8.9	8.5	10.5	6.3	18.1	9.6 (3.9)
pre-Dinner		10.5	5.5	5.8	8.7	10.1	7.3	7.4	5.1	7.6 (2.1)
pre-Bedtime		9.2	8.3	6.5	10.5	10.8	10.7	6.6	11.3	9.2 (1.9)
Biochemical hypos	number	3	5	5	0	4	4	1	2	24
Clinical hypos	number	0	0	4	4	0	4	1	0	13
Dose change activity	%	22	45	33	17	38	17	58	26	29.5 (20.75-39.75)

Table A.4: Advice OFF period data

A.2 Questionnaires

A.2.1 Attitude to Insulin Therapy

General

1. Are you concerned about your blood glucose levels?

1. Not at all 2. Moderately 3. Very much

2. Do you think you need more help with controlling your diabetes?

1. Yes 2. No

If yes, what would be helpful to you?

3. How much does the application of insulin interfere with your daily activities?

1. Not at all 2. Moderately 3. Very much

4. How much does the adjustment of insulin doses interfere with your daily activities?

1. Not at all 2. Moderately 3. Very much

5. How concerned are you about hypoglycaemic episodes?

1. Not at all 2. Moderately 3. Very much

6. How important is it for you to avoid hypoglycaemic episodes?

1. Not at all 2. Moderately 3. Very much

7. How concerned are you about high glucose readings?

1. Not at all 2. Moderately 3. Very much

8. How important is it for you to avoid high glucose readings?

1. Not at all 2. Moderately 3. Very much

9. Do you try to avoid consistently high glucose readings?

1. Yes 2. No

If yes, how do you avoid them?

Insulin dose adjustment

10. How often do you check your blood glucose levels?

1. Weekly 2. Daily 3. Only at clinic visits

11. Do you adjust your insulin doses according to your blood glucose levels?

1. Never 2. Sometimes 3. Daily

If no, why not?

12. How difficult do you find adjusting your insulin dose?

1. Not at all 2. Moderately 3. Very much

13. How satisfied are you with your understanding/knowledge of your diabetes?

1. Not at all 2. Moderately 3. Very much

Computer experience

14. How much experience do you have in using computer technology (Personal Computers (PCs), game consoles, retail/supermarket check-out technology etc)

14.a. at home?

1. None 2. Moderate 3. Considerable

14.b. at work?

1. None 2. Moderate 3. Considerable

15.a. Do you already use a palm top device or handheld computer?

1. Yes 2. No

15.b. If yes, which model:

16. Any further comments:

A.2.2 Insulin Advisor Evaluation

Insulin Advisor

1. Did you enjoy using the Insulin Dose Advisor?

1. Yes 2. No

If no, why not?

2. Was the device easy to use?

1. Yes 2. No

If no, why not?

3. How long did it take to familiarize yourself with:

3.a. the device?

3.b. the program?

4. Did you feel that the education you received before using the Insulin Advisor was adequate to understand and use the device?

1. Yes 2. No

How could we change or improve it?

5. How often did you use the printed material you received together with the Insulin Advisor?

1. Never 2. Sometimes 3. Regularly

Do you have any suggestions for improvements to the printed material?

6. What did you like most about the Insulin Dose Advisor?

1. Using the device as a log-book.
2. Following the advice.
3. The graphics.
4. Using the notebook facility.
5. Using the computer.
6. Other (please specify)

7. What did you like least about the Insulin Dose Advisor?

1. Having to enter data 4 times per day.
2. Didn't usually agree with the insulin dose advised.
3. Found it too time consuming.
4. Found it too difficult to carry around.
5. Found it too complicated to use.
6. Other (please specify)

8. What did you find most difficult about using the device?

9. How confident are you with your ability to use the device appropriately?

1. Not at all 2. Moderately 3. Very much

10. Did you find the Insulin Advisor useful?

1. Yes 2. No

11. Do you think the Insulin Advisor is reliable?

1. Yes 2. No

If no, why not?

12. Did using the device interfere with your daily activities?

1. Yes 2. No

If yes, how?

13. Approximately, how long did you use the device each day?

Any comments:

Insulin dose adjustments

14. While using the Insulin Advisor, did you worry about your diabetes

1. Less than before 2. More than before 3. About the same

Please give explanation or a reason:

15. Have you changed the number of times you altered your insulin dose?

15a 1. Yes 2. No

15b If yes, how often do you alter your dose now?

16. Since using the device, do you feel more confident about changing your insulin dose in response to an abnormal reading?

1. Yes 2. No

If no, why not?

17. Would you continue using the device?

1. Yes 2. No

If no, why not?

18. Any further comments:

A.3 Questionnaire responses

A.3.1 Attitude to Insulin Therapy

General

1. Are you concerned about your blood glucose levels?

	1. Not at all	2. Moderately	3. Very much
Visit 2:	1	5	2
Visit 5:	0	7	1

2. Do you think you need more help with controlling your diabetes?

	1. Yes	2. No
Visit 2:	8	0
Visit 5:	6	2

If yes, what would be helpful to you?

Visit 2:

- need help to recognize hypos
- ways of gaining tighter control
- to confirm my own ideas/actions
- when BG levels are too high or too low, deciding best course of action
- advise on diet plus insulin dosage
- to stablish why the BG levels vary for no apparent reason

Visit 5:

- easy access to the palm at any time
- from time to time, I do. But I feel happy with help given by clinic nurses etc
- sometimes, when ill and not sure what step to take
- advise on insulin doses
- to establish why the blood glucose levels vary for no apparent reason

3. How much does the application of insulin interfere with your daily activities?

	1. Not at all	2. Moderately	3. Very much
Visit 2:	3	5	0
Visit 5:	5	3	0

4. How much does the adjustment of insulin doses interfere with your daily activities?

	1. Not at all	2. Moderately	3. Very much
Visit 2:	4	4	0
Visit 5:	5	3	0

5. How concerned are you about hypoglycaemic episodes?

	1. Not at all	2. Moderately	3. Very much
Visit 2:	1	5	2
Visit 5:	0	7	1

6. How important is it for you to avoid hypoglycaemic episodes?

	1. Not at all	2. Moderately	3. Very much
Visit 2:	0	1	7
Visit 5:	0	0	8

7. How concerned are you about high glucose readings?

	1. Not at all	2. Moderately	3. Very much
Visit 2:	0	5	3
Visit 5:	0	4	4

8. How important is it for you to avoid high glucose readings?

	1. Not at all	2. Moderately	3. Very much
Visit 2:	0	2	6
Visit 5:	0	0	8

9. Do you try to avoid consistently high glucose readings?

	1. Yes	2. No
Visit 2:	7	1
Visit 5:	7	1

If yes, how do you avoid them?

Visit 2:

- check BG levels
- test BG at least twice a week and adjust insulin according to the results
- adjusts insulin levels

- if BG has been consistenly high, I would adjust my insulin intake
- eating less/correct types of food
- by increasing insulin

Visit 5:

- lots of water
- increasing actrapid and ultratard if this seems necessary. Amending my diet.
- adjusting insulin doses
- monitor sugar levels regulary and take exercise to reduce levels when necessary
- try adjusting nsulin doses or meal size
- by increasing insulin

Insulin dose adjustment

10. How often do you check your blood glucose levels?

	1. Weekly	2. Daily	3. Only at clinic visits
Visit 2:	1	7	0
Visit 5:	1	7	0

11. Do you adjust your insulin doses according to your blood glucose levels?

	1. Never	2. Sometimes	3. Daily
Visit 2:	0	4	4
Visit 5:	0	5	3

If no, why not?

Visit 5:

- I usually like to wait a day or two to see if readings are constant

12. How difficult do you find adjusting your insulin dose?

	1. Not at all	2. Moderately	3. Very much
Visit 2:	4	4	0
Visit 5:	5	3	0

13. How satisfied are you with your understanding/knowledge of your diabetes?

	1. Not at all	2. Moderately	3. Very much
Visit 2:	0	6	2
Visit 5:	0	4	4

Computer experience

14. How much experience do you have in using computer technology (Personal Computers (PCs), game consoles, retail/supermarket check-out technology etc)

14.a. at home?

	1. None	2. Moderate	3. Considerable
Visit 2:	4	4	0
Visit 5:	4	3	1

14.b. at work?

	1. None	2. Moderate	3. Considerable
Visit 2:	6	1	1
Visit 5:	4	3	1

15.a. Do you already use a palm top device or handheld computer?

	1. Yes	2. No
Visit 2:	0	8
Visit 5:	0	8

15.b. If yes, which model:

NOT APPLICABLE

16. Any further comments:

Visit 2:

- use E-mail and a word processor

A.3.2 Insulin Advisor Evaluation

Insulin Advisor

1. Did you enjoy using the Insulin Dose Advisor?

	1. Yes	2. No
Visit 4:	7	1
Visit 5:	7	1

If no, why not?

Visit 4:

- The advice given was often unsuitable a) my penfill can only cope with units in 2 and b) I found that I was advised to lower ultratard too much.

Visit 5:

- It suggested actrapid doses which could not be taken with a Penfill syringe. I felt that the ultratard doses suggested were too low, experience seemed to endorse this.

2. Was the device easy to use?

	1. Yes	2. No
Visit 4:	8	0
Visit 5:	8	0

If no, why not?

NOT APPLICABLE

3. How long did it take to familiarize yourself with:

3.a. the device?

Visit 4:

- NO TIME AT ALL
- a day
- 1-2 HRS
- VERY QUICKLY
- MINUTES
- VERY QUICKLY AFTER USING 1
- NOT LONG
- COUPLE OF DAYS

Visit 5:

- not long
- LESS THAN A DAY
- 1-2 HRS
- TRAINING PERIOD
- MINUTES
- VERY QUICKLY APPROX 1 DAY
- 10 MINS
- COUPLE OF DAYS

3.b. the program?

Visit 4:

- NO TIME AT ALL
- a day
- 1-2 DAYS
- VERY QUICKLY
- MINUTES
- LONGER 2 DAYS AT MOST
- NOT LONG
- COUPLE OF DAYS

Visit 5:

- LESS THAN A DAY
- 1-2 HRS
- TRAINING PERIOD
- MINUTES
- PERHAPS 2-3 DAYS
- 10 MINS
- COUPLE OF DAYS

4. Did you feel that the education you received before using the Insulin Advisor was adequate to understand and use the device?

	1. Yes	2. No
Visit 4:	8	0
Visit 5:	8	0

How could we change or improve it?

Visit 4:

- it was very good
- everything seemed OK
- there are a couple of things that might have been explained eg the difference between standard and usual doses. However too long-winded an explanation could be counterproductive

Visit 5:

- it was first class training
- all seems ok

5. How often did you use the printed material you received together with the Insulin Advisor?

	1. Never	2. Sometimes	3. Regularly
Visit 4:	3	4	0
Visit 5:	2	5	0

Do you have any suggestions for improvements to the printed material?

Visit 4:

- just needed it for the first day or so
- it was clear and easy to follow

- no
- No. For people who struggle with technology I think it's perfect
- I found the pre-use instruction sufficient. I therefore didn't need the printed material. Consequentely I can't make my comment

Visit 5:

- no
- all very clear and easy to understand
- no. It was good for people not familiar with technology
- no

6. What did you like most about the Insulin Dose Advisor?

	Visit 4:	Visit 5:
1. Using the device as a log-book.	5	5
2. Following the advice.	2	2
3. The graphics.	1	3
4. Using the notebook facility.	2	1
5. Using the computer.	1	0
6. Other (please specify)	1	2

Visit 4:

- comparing advice with my own interpretation

Visit 5:

- seeing levels as an average in graph format over several weeks was really helpful in changing doses
- observing the advice, but I didn't always follow it

7. What did you like least about the Insulin Dose Advisor?

	Visit 4:	Visit 5:
1. Having to enter data 4 times per day.	2	2
2. Didn't usually agree with the insulin dose advised.	3	2
3. Found it too time consuming.	0	1
4. Found it too difficult to carry around.	0	0
5. Found it too complicated to use.	0	0
6. Other (please specify)	4	5

Visit 4:

- Found it a little frustrating for a couple of days as I thought I was doing just fine on my own!!! Got used to agreeing with it though.

- Didn't ALWAYS agree with the advice.
- Sometimes I found it a little difficult to understand how the Advisor reached its conclusions.
- No problems.

Visit 5:

- my fingers were sore towards the end (finger-prick)
- would like to be able to enter hypos into the graph
- having to fit more than one thing in my bag
- sometimes uncertain about how the dose was reached
- no problems

8. What did you find most difficult about using the device?

Visit 4:

- quick and easy to use, just disagree with advise given
- the quit buttom does not always function easily
- nothing
- nothing
- taking the lid off
- cancelling incorrect data entered

Visit 5:

- nothing
- nothing
- quit button slightly irritating, as it did not always respond easily
- nothing
- nothing
- having confidense to follow the advice
- nothing

9. How confident are you with your ability to use the device appropriately?

	1. Not at all	2. Moderately	3. Very much
Visit 4:	0	1	7
Visit 5:	0	1	7

10. Did you find the Insulin Advisor useful?

	1. Yes	2. No
Visit 4:	7	1
Visit 5:	7	1

11. Do you think the Insulin Advisor is reliable?

	1. Yes	2. No	
Visit 4:	6	2	1x Yes mostly
Visit 5:	6	1	1x Yes mostly, 1x no answer

If no, why not?

Visit 4:

- not completely, sometimes my own instinct proved right
- on occasions it gave wrong advice due to previous days blood sugars

Visit 5:

- Its reliability depends on what is fed into it. See above.
- I sometimes felt more confident using personal experience, but generally I found it to be reliable.
- Advice not always reliable to control blood sugars.

12. Did using the device interfere with your daily activities?

	1. Yes	2. No
Visit 4:	2	6
Visit 5:	2	6

If yes, how?

Visit 4:

- I had no confidence in its advise. My finger-tips were getting sore!!!
- Only sometimes, when giving a day out, was not always able to take with me due to activity.

Visit 5:

- It was sometimes a nuisance on social occasions, eg. before a dinner party. I didn't take it with me if I was having a meal in a restaurant, but I did in friends' houses.
- sometimes (rare)

13. Approximately, how long did you use the device each day?

Visit 4:

- 6 MINS
- 4 minutes for the machine, plus 8 minutes for testing
- A FEW MINUTES
- APPROX 4 MINS
- 15 MINS
- 12 minutes including blood test
- 5 TO 10 MINUTES
- 15 MINS

Visit 5:

- 10 mins
- 20 min, five for each text
- 10 MINS DAY MAX
- LESS THAN 5 MINUTES
- 20 MINS
- 10-12 MINUTES
- 10 MINS MAX
- COUPLE MINS

Any comments:

Visit 4:

- found it much easier and quickier than writing in a log book
- approx 4 mins. Hardly any time at all

Insulin dose adjustments

14. While using the Insulin Advisor, did you worry about your diabetes

	1. Less than before	2. More than before	3. About the same
Visit 4:	1	4	3
Visit 5:	1	2	5

Please give explanation or a reason:

- Less/Less
  Visit 4: although I have not had any real problems in the past using the device is like having somebody to consult with you.
  Visit 5: it is like having a diabetes specialist on hand to consult whenever you want
- More/More
  Visit 4: I had to think about what action to take when I disagreed with the advice given
  Visit 5: I began to loose confidence in my ability to manage my diabetes
- More/More
  Visit 4: I was unsure for quite a long period of the testing time and sometimes found the davice a little disturbing
- More/Same
  Visit 4: At first I was concerned that I was doing everything wrong. But it didn't last long.
- More/Same
  Visit 4: Since my diagnosis (11 years ago) I've been advised to a) work out my own doses b) never change my doses without consulting my doctor c)only to change my doses after several days of observation. I don't know worry more about my DBT but I'm perhaps more aware of

what I can do to keep it under control.
Visit 5: I felt the same amount of concern but now I feel more in control

- Same/Same
  Visit 5: because I wasn't depending on the advice

15. Have you changed the number of times you altered your insulin dose?

	15a 1. Yes	2. No
Visit 4:	5	3
Visit 5:	5	2

15b If yes, how often do you alter your dose now?

Visit 4:

- more frequent check leads to more frequent alterations
- varies but seing a graph in front of me makes it easy to balance and to adjust levels
- SLIGHTLY MORE FREQUENTLY
- DAILY
- ALMOST DAILY

Visit 5:

- NO IDEA
- DAILY
- DAILY
- DAILY ON COMPUTER ADVICE
- HAVE ALTERED ULTRATARD DOSE

16. Since using the device, do you feel more confident about changing your insulin dose in response to an abnormal reading?

	1. Yes	2. No
Visit 4:	7	1
Visit 5:	7	1

If no, why not?

Visit 4:

- I think that my experience and knowledge of my condition is superior to that of the machine. This is a purely personal comment

Visit 5:

- Because I need to think I knew what I was doing, and I'm getting a bit too old, at 72 to learn "new tricks".

17. Would you continue using the device?

	1. Yes	2. No
Visit 4:	7	1
Visit 5:	7	1

If no, why not?

Visit 4:

- Because I have no confidence in the advice it gives to ME.
- I wish I had had one of those when I first started with my DBT; Im sure I would have got my DBT under control in no time at all.
- I was not confident to always follow advice for high blood sugars and was frequently proved wrong. I would like to use the device for longer to obtain a better routine of taking advice. Although I found 4th data entry at night a tie.

18. Any further comments:

Visit 4:

- It could be of v great help to new diabetic or those who have not had the benefit of excellent advice and support from the diabetic clinic here
- although it would not work for all people the option to put a snack between meals in might be an advantage as in reality this does alter the graph also hypos if the glucose readings could be entered into the graph it might be significant
- I think you should be able to go back and alter an entry after completing, as sometimes you do the entry and realize that you have clicked the wrong thing ie the insulin you're about to take.

Visit 5:

- I think this is a very useful piece of equipment for (a) younger and (b) new diabetics
- it would be very useful to be able to enter hypo readings in the graph
- having used the device I feel more confident and I am therefore more flexible about changing my insulin dose
- device should have option between normal times to enter readings ie mid afternoon and get advice on for example whether you need more insulin or food

A.4 Technical data

A.4.1 Pre-study experimental program speed assessments (POIRO MK2)

The experimental program speed assessments reported below made use of a Handspring Visor handheld device and corresponding USB connection cable as well as a PC laptop computer with an in-built infrared port.

Program start-up and review diagram drawing

Table A.5 shows the results of experimental assessments of the program start-up and review diagram drawing speeds for different durations of system use i.e. different logbook sizes. Each day's logbook data typically comprised four main meals (Breakfast, Lunch, Dinner, Bedtime) with 5 associated event records (Glucose reading, Meal size, Exercise level, Health status, Insulin dose).

All delays are of noticable length. Also note that the drawing times for the glucose trend and modal day diagrams (Figure 2.6 on page 34) increase linearly during the first four weeks of system use but then remain constant at approximately 23 and 41 seconds respectively. This upper boundary on the diagram drawing speed is explained by the fact that the diagrams display only the four most recent weeks of glucose data.

Logbook size (in days)	Program Start-up	Glucose Trend	Modal Day
5	6	4	7 (2)
10	5	8	14 (4)
15	6	11.5	22 (6)
20	5	15.5	29 (7.5)
25	6	19.5	36 (9.5)
30	5	23	42 (11)
35	5	22	40 (10)
40	5	22	40 (10)
45	5	22	40 (10)
50	5	22	40 (10)
55	5	22	40 (10)
60	5	23	41 (10.5)
65	6	23	41 (10.5)
70	5	23	41 (11)

Values shown are the process durations in seconds measured using a stopwatch.

Modal Day values shown in (brackets) are the time elapsed until the visible start of the glucose modal day diagram drawing.

Table A.5: Program start-up and review diagram drawing speeds

Hotsync data transfers via USB and infrared connection

Table A.6 shows the results of experimental assessments of the Hotsync data transfer speeds for different durations of system use (different logbook sizes) and different types of handheld-to-desktop connection (Universal Serial Bus (USB) cable and infrared wireless connection). Each day's logbook data typically comprised four main meals (Breakfast, Lunch, Dinner, Bedtime) with 5 associated event records (Glucose reading, Meal size, Exercise level, Health status, Insulin dose). Infrared (IR), wireless Hotsync operations were carried out using the evaluation version of the IRLink v1.5 software (http://www.iscomplete.com) supported by 3Com's IR Enhance Update. The infrared connection speed was, on the desktop (laptop), set to 57.6 kbps (see below for further details). To minimise interference and maintain consistent transmission circumstances, the handheld and laptop computers' infrared interfaces were during Hotsync operations placed in close proximity to each other.

Logbook size (in days)	Infrared connection	USB cable connection	Infrared : USB ratio
5	38	8	5
10	54	8.5	6
15	62	10	6
20	73	10	7
25	85	12	7
30	98	13	8
35	109	14.5	8
40	121	15.5	8
45	134	16	8
50	145	18	8
55	157	19.5	8
60	165	21	8
65	178	21	8
70	189	23.5	8

Values shown are the Hotsync durations in seconds measured using a stopwatch.

Table A.6: Hotsync data transfer speed: USB cable versus infrared connection

Table A.7 shows the results of experimental assessments of the Hotsync data transfer speeds for different handheld-to-desktop infrared connection speeds. As can be seen increasing the connection speed from 38.4 to 57.6 kbps lowers the Hotsync duration times i.e. increases the Hotsync data transfer speed. However, also note that the 50% connection speed increase only increases the Hotsync data transfer speed by approximately 27% from 22 to 16 seconds additional transfer time per additional week of data.

However, further increasing of the infrared connection speed from 57.6 to 155.2 kbps is counterproductive in that it increases transfer times more than tenfold. Observation via the laptop's Infrared Monitor Status screen showed that at this connection speed communication efficiency dropped due

frequent retransmissions of data. It would appear that the handheld device's slower data reception and data processing speed is the cause of this and thus the overall limiting factor for wireless, infrared-based Hotsync operations.

Logbook size	**Infrared connection speed**		
(in days)	**38.4 kbps**	**57.6 kbps**	**115.2 kbps**
35	128	109	1143
55	187	157	1614
70	237	189	1964

Values shown are the Hotsync durations in seconds measured using a stopwatch. Infrared connection speeds were set via the laptop's Infrared Monitor Options.

Table A.7: Hotsync data transfer speed: Different infrared connection speeds

A.4.2 Actual Hotsync data transfer durations

Transfer direction	Record Type	01	02	03	04	05	06	07	08
Before Visit 2 (Device Setup)									
Desktop → Handheld	Settings	3 / 144	3 / 144	3 / 144	3 / 144	3 / 144	3 / 144	3 / 144	3 / 144
During Visit 3									
Handheld → Desktop	Events	3 / 146	3 / 149	3 / 149	126 / 148	3 / 149	2 / 156	3 / 148	3 / 135
	Settings	3 / 149	3 / 151	2 / 149	125 / 145	2 / 151	3 / 150	3 / 146	2 / 150
Desktop → Handheld	Settings	3 / 144	3 / 144	3 / 144	123 / 144	3 / 144	4 / 144	3 / 144	3 / 144
During Visit 4									
Handheld → Desktop	Events	10 / 557	11 / 628	11 / 599	10 / 572	11 / 625	10 / 611	11 / 581	22 / 528
	Settings	3 / 186	3 / 182	3 / 161	4 / 184	3 / 161	3 / 149	3 / 170	6 / 152
Desktop → Handheld	Settings	4 / 144	4 / 144	3 / 144	4 / 144	3 / 144	3 / 144	3 / 144	6 / 144
During Visit 5									
Handheld → Desktop	Events	16 / 970	17 / 1025	18 / 1033	17 / 1014	18 / 1064	18 / 1048	18 / 1011	16 / 956
	Settings	3 / 144	3 / 144	3 / 193	3 / 163	4 / 193	4 / 191	3 / 144	4 / 198

Values shown are *transfer duration in seconds / number of records transferred* and were derived from timestamp and other information automatically recorded as part of the data transfer process.

Table A.8: Hotsync data transfer durations

A.4.3 Post-study experimental program speed assessments (POIRO MK3)

The experimental program speed assessments reported in this section made use of a Handspring Visor handheld device.

Improved review diagram drawing

Table A.9 shows the results of experimental assessments of the review diagram drawing speeds of the POIRO MK3 system. Different to the MK2 version of the system

- drawing speeds are now independent of the logbook size[1], and instead
- drawing speeds are now dependent on the frequency with which diagrams are viewed by the user: the more often diagrams are used, the quicker they will be drawn and vice versa.
- Furthermore, glucose trend and modal day diagrams are now drawn equally fast, and
- should the user wish to review more than one diagram on any one day, then the second and subsequent diagrams that day will be drawn virtually instantly.

Frequency of diagram use	Glucose Trend	Modal Day
Daily	2	2
Weekly	8	8
Monthly	29	29

Values shown are the diagram drawing durations in seconds measured using a stopwatch.

The times shown refer to the *first* diagram drawn on any one day. Subsequently drawn diagrams (of either type) are drawn in less than 1 second. 'Daily' means 'every day', 'Weekly' means 'every 7 days', and 'Monthly' means 'every 28 days or less frequently'.

Table A.9: Improved review diagram drawing speeds

[1] with the exception of less than monthly diagram use

Appendix B

Insulin and system details

B.1 Insulin formulations

Extracted/Compiled from the British National Formulary database *BNF No. 45 (March 2003)* [44] Tables B.1 to B.3 gives details of the insulin formulations available in the UK at the time.

Following on from Tables B.1 to B.3, Table B.4 for each insulin formulation available in the UK shows the default display name, insulin type and insulin code used by the POIRO MK3 system.

Most of the insulin formulations listed are available in several forms of packaging varying in

- type (vial, cartridge, prefilled disposable injection device),
- size (e.g. 1.5 mL, 3 mL, 10 mL),
- injection device required (e.g. syringe, Autopen®)
- possible dose adjustments (e.g. 0.5 units, 1 unit, 2 units),
- dose range (e.g. 1-16 units, 2-78 units).

Clearly, a comprehensive, up-to-date database containing all this information could form a very useful part of the clinic/desktop end of the POIRO system. In particular, the links between (a) the insulin formulation and packaging prescribed and (b) the injection device used by the patient and its possible dose adjustments and range could faciliate the entering and validation of a patient's insulin settings. *Example: A patient with a 2-32 units injection device cannot take odd doses or doses outside the 2-32 units range. Hence, the minimum, usual and maximum dose prescribed by the doctor and any doses suggested by the POIRO system must be even doses and within the 2-32 units range.*

No.	Formulation and Trade Name	Default Display Name	Insulin	
			Type	Code
1	Hypurin® Bovine Neutral	Hypurin Regular	short	*s*------
2	Hypurin® Porcine Neutral	Hypurin Regular	short	*s*------
3	Pork Actrapid®	Actrapid	short	*s*------
4	Human Actrapid®	Actrapid	short	*s*------
5	Human Velosulin®	Velosulin	short	*s*------
6	Humulin S®	Humulin S	short	*s*------
7	Insuman® Rapid	Insuman Rapid	short	*s*------
8	NovoRapid®	NovoRapid	rapid	*u*------
9	Humalog®	Humalog	rapid	*u*------
10	Lantus®	Lantus	long	*l*------
11	Hypurin® Bovine Lente	Hypurin Lente	long	*l*------
12	Human Monotard®	Monotard	mixed	*m*30*s*70*l*
13	Humulin Lente®	Humulin Lente	long	*l*------
14	Human Ultratard®	Ultratard	long	*l*------
15	Humulin Zn®	Humulin Zn	long	*l*------
16	Hypurin® Bovine Isophane	Hypurin NPH	intermediate	*i*------
17	Hypurin® Porcine Isophane	Hypurin NPH	intermediate	*i*------
18	Pork Insulatard®	Insulatard	intermediate	*i*------
19	Human Insulatard® ge	Insulatard	intermediate	*i*------
20	Humulin I®	Humulin I	intermediate	*i*------
21	Insuman® Basal	Insuman Basal	intermediate	*i*------
22	Hypurin® Bovine Protamine Zinc	Hypurin Lente	long	*l*------
23	NovoMix® 30	NovoMix 30	mixed	*m*30*u*70*i*
24	Humalog® Mix25	Humalog Mix25	mixed	*m*25*u*75*i*
25	Humalog® Mix50	Humalog Mix50	mixed	*m*50*u*50*i*
26	Hypurin® Porcine 30/70 Mix	Hypurin 30/70 Mix	mixed	*m*30*s*70*i*
27	Pork Mixtard 30®	Mixtard 30	mixed	*m*30*s*70*i*
28	Human Mixtard® 10	Mixtard 10	mixed	*m*10*s*90*i*
29	Human Mixtard® 20	Mixtard 20	mixed	*m*20*s*80*i*
30	Human Mixtard® 30	Mixtard 30	mixed	*m*30*s*70*i*
31	Human Mixtard® 30 ge	Mixtard 30	mixed	*m*30*s*70*i*
32	Human Mixtard® 40	Mixtard 40	mixed	*m*40*s*60*i*
33	Human Mixtard® 50	Mixtard 50	mixed	*m*50*s*50*i*
34	Humulin M2®	Humulin M2	mixed	*m*20*s*80*i*
35	Humulin M3®	Humulin M3	mixed	*m*30*s*70*i*
36	Humulin M5®	Humulin M5	mixed	*m*50*s*50*i*
37	Insuman® Comb 15	Insuman Comb 15	mixed	*m*15*s*85*i*
38	Insuman® Comb 25	Insuman Comb 25	mixed	*m*25*s*75*i*
39	Insuman® Comb 50	Insuman Comb 50	mixed	*m*50*s*50*i*

Table B.4: POIRO MK3 Insulin Details

B.2 Insulin regimens

Table B.5 gives details of the different insulin regimens catered for by the Insulin Advisor system.

No.	First Insulin#1	Second Insulin#2	POIRO MK2	POIRO MK3	POIRO MK4
	none	none	Not an insulin regimen.		
	rapid	none	Uncommon insulin regimen.		
	short	none	Uncommon insulin regimen.		
1	mixed	none	NO	NO	YES
2	none	intermediate	NO	YES	YES
3	rapid	intermediate	NO	YES	YES
4	short	intermediate	NO	YES	YES
	mixed	intermediate	Uncommon insulin regimen.		
5	none	long	NO	YES	YES
6	rapid	long	NO	YES	YES
7	short	long	YES	YES	YES
	mixed	long	Uncommon insulin regimen.		
	none	mixed	See 'mixed' and 'none' above.		
8	rapid	mixed	NO	NO	YES
9	short	mixed	NO	NO	YES
10	mixed	mixed	NO	NO	YES

#1 One of 'none', 'rapid', 'short', 'mixed'.

#2 One of 'none', 'intermediate', 'long', 'mixed'.

Table B.5: Insulin regimens

B.3 Lifestyle adjustments

Glucose level	Very low	0.75
	A bit low	0.90
	In range	1.00
	A bit high	1.10
	Very high	1.15
Meal size	Nothing	0.00
	Light	0.60
	Normal	1.00
	Large	1.40
Exercise level	None	1.20
	Minimal	1.10
	Normal	1.00
	Heavy	0.75
Health status	Well	1.00
	Unwell	1.10
	Very sick	1.15

Table B.6: Default multiplication factors

Multiplication factor grid reading and interpretation examples:

1. Moving horizontally across columns 6 to 9 and looking at row 5 shows how adjustments will be made for different meal sizes when the glucose reading entered is very high.

2. Moving diagonally from column 10 in row 2 to column 13 row 5 shows how an increase in exercise will compensate for an increase in glucose levels.

3. Moving diagonally from column 13 row 2 to column 10 row 5 shows how a decrease in exercise and an increase in glucose levels will compound to increase insulin requirements.

				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
				Glucose level					Meal size				Exercise level				Health status		
				0.75	0.90	1.00	1.10	1.15	0.00	0.60	1.00	1.40	1.20	1.10	1.00	0.75	1.00	1.10	1.15
				Very low	A bit low	In range	A bit high	Very high	Nothing	Light	Normal	Large	None	Minimal	Normal	Heavy	Well	Unwell	Very sick
1	Glucose	0.75	Very low						0.00$^{\alpha}$	0.45$^{\alpha}$	0.75$^{\alpha}$	0.75$^{\alpha}$	0.75$^{\alpha}$	0.75$^{\alpha}$	0.75$^{\alpha}$	0.56$^{\alpha}$	0.75	0.83	0.86
2		0.90	A bit low						0.00	0.54	0.90	1.26	1.08	0.99	0.90	0.68	0.90	0.99	1.04
3		1.00	In range						0.00	0.60	1.00	1.40	1.20	1.10	1.00	0.75	1.00	1.10	1.15
4		1.10	A bit high						0.25$^{\beta}$	0.66	1.10	1.54	1.32	1.21	1.10	0.83	1.10	1.21	1.27
5		1.15	Very high						0.33$^{\beta}$	0.69	1.15	1.61	1.38	1.27	1.15	0.86	1.15	1.27	1.32
6	Meal size	0.00	Nothing	0.00$^{\alpha}$	0.00	0.00	0.25$^{\beta}$	0.33$^{\beta}$					0.00	0.00	0.00	0.00	0.00	0.00	0.00
7		0.60	Light	0.45$^{\alpha}$	0.54	0.60	0.66	0.69					0.72	0.66	0.60	0.45	0.60	0.66	0.69
8		1.00	Normal	0.75$^{\alpha}$	0.90	1.00	1.10	1.15					1.20	1.10	1.00	0.75	1.00	1.10	1.15
9		1.40	Large	0.75$^{\alpha}$	1.26	1.40	1.54	1.61					1.68	1.54	1.40	1.05	1.40	1.54	1.61
10	Exercise level	1.20	None	0.75$^{\alpha}$	1.08	1.20	1.32	1.38	0.00	0.72	1.20	1.68					1.20	1.32	1.38
11		1.10	Minimal	0.75$^{\alpha}$	0.99	1.10	1.21	1.27	0.00	0.66	1.10	1.54					1.10	1.21	1.27
12		1.00	Normal	0.75$^{\alpha}$	0.90	1.00	1.10	1.15	0.00	0.60	1.00	1.40					1.00	1.10	1.15
13		0.75	Heavy	0.56$^{\alpha}$	0.68	0.75	0.83	0.86	0.00	0.45	0.75	1.05					0.75	0.83	0.86
14	Health	1.00	Well	0.75	0.90	1.00	1.10	1.15	0.00	0.60	1.00	1.40	1.20	1.10	1.00	0.75			
15		1.10	Unwell	0.83	0.99	1.10	1.21	1.27	0.00	0.66	1.10	1.54	1.32	1.21	1.10	0.83			
16		1.15	Very sick	0.86	1.04	1.15	1.27	1.32	0.00	0.69	1.15	1.61	1.38	1.27	1.15	0.86			

Exceptions

α If the glucose level is "Very low" the meal and exercise components of the overall multiplication factor must not exceed 1.0.

β Meal size "Nothing" combined with glucose level "A bit high" or "Very high" requires a total factor of 0.25 and 0.33 respectively, regardless of exercise and health.

Table B.7: Default multiplication factor grid

B.4 Patient-specific system settings

Setting	Description
Device number	Identifies the handheld device currently used by the patient.
Centre number*	Identifies the patient's diabetes clinic.
Patient number	Patient's diabetes clinic, hospital or study reference number.
PDA user name	PDA Hotsync user name e.g. patient's initials or name.
User password**	Optional password required to start the POIRO handheld application.
Doctor's name	Doctor's i.e. diabetologist's
Doctor's phone number	name and contact details.
Nurse's name	Diabetes specialist nurse's
Nurse's phone number	name and contact details.
Next clinic appointment	Date and time of next clinic appointment.
Advice status	ON: POIRO provides dose advice. OFF: POIRO acts as electronic logbook only.
Intelligent meal prompting switch	Enables or disables the intelligent meal time prompting facility (Section 3.3.2).
Insulin regimen*	Code identifying the patient's insulin regimen.
Hypo warning threshold	Upon exceeding of this threshold a warning message advising the patient to contact their doctor will be displayed (Section 3.3.1 and Figure 3.8 (e)).
Glucose measurement unit**	$mmol/L$ or mg/dL depending on the glucose meter used.

* = Setting is automatically generated and thus invisible to the clinic system user.

** = Setting is not yet used in MK3 version of the POIRO system.

Table B.8: Basic administrative settings

Setting	Key	Description
Insulin formulation	insulin_slot	Formulation name e.g. 'Human Mixtard® 20'.
Insulin code*	insulin_slot	Code for the insulin formulation, see Table B.4.
Displayed insulin name	insulin_slot	Insulin name used on the handheld e.g. 'Mixtard 20'.
Insulin dose increments**	insulin_slot	Possible dose increments, see Section 5.2.4.
Minimum dose	time_of_day + insulin_slot	Minimum permissible usual dose.
Usual dose	time_of_day + insulin_slot	Prescribed usual insulin dose.
Maximum dose	time_of_day + insulin_slot	Maximum permissible usual dose.

insulin_slot $\in$ {1, 2}

time_of_day $\in$ {Breakfast, Lunch, Dinner, Bedtime, Snack}

* = Setting is automatically generated and thus invisible to the clinic system user.

** = Setting is not yet used in MK3 version of the POIRO system.

Table B.9: Basic insulin-related settings

Setting	Key	Description
Permissible percentage dose decrease Permissible percentage dose increase	insulin_slot insulin_slot	Maximum percentage by which the usual dose may be decreased or increased in any one dose change.
Allowed mean offset Allowed single offsets	insulin_slot insulin_slot	If the actual offsets are outside the permissible range, dose changes are required (Section 3.2.3).
Insulin sensitivity factor	insulin_slot	Used to convert glucose offsets into dose changes, see Equation (3.12).
Linked basal doses switch	NONE	ON: Basal doses for different times of the day must be and stay the same. OFF: Basal doses can be optimised independent of each other (Section 3.2.3).
Post-prandial BG excursion profile	time_of_day	Used to calculated ideally expected glucose values (Section 3.2.3).

time_of_day $\in$ {Breakfast, Lunch, Dinner}

Table B.10: Advanced insulin-related settings

Setting	Description and/or default value
Minimum recommended blood glucose (at any time)	3.0 mmol/L
Maximum recommended blood glucose (at any time)	15.0 mmol/L
Fasting blood glucose (FBG) target	5.0 mmol/L
Minimum permissible FBG target	5.0 mmol/L
Maximum permissible FBG target	10.0 mmol/L
Maximum coefficient of BG variation (CV)	Parameters used to adjust the FBG target so as to reflect and minimise the
Numbers of CV above minimum	risk of nocturnal hypos. Default values are 3.5 and 2.0 respectively.
Glucose range limits	Glucose values used to classify out-of-range BG readings as 'Very Low', 'A bit
	low', 'A bit high' or 'Very high'. Default values are 3.0, 4.5, 10.0 and 15.0.

Table B.11: Advanced glucose-related settings

Appendix C

Handheld Insulin Dose Advisor

Published [30] in the Abstract Book of the American Diabetes Association's 62nd Scientific Sessions held in June 2002 in San Francisco, California.

Abstract Number: 1933-PO
Abstract Category: Clinical Therapeutics/New Technology
Authors: SILVINA GALLO
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BERYL A. BARROW
LISA BLACKWELL
JOHN L. NEALON
RURY R. HOLMAN.

Optimizing insulin therapy in diabetes is essential to help avoid complications and hypoglycemia. However, it is a complex problem requiring patients to adjust for many different factors when deciding how much insulin to give. To assist with this process, we have developed a palm top decision support program to advise patients concerning individual insulin doses. The program uses simple menus to enter pre-prandial capillary blood glucose values, meal type and size, intended exercise levels and state of health. Eight type 1 diabetic patients (four male) on basal bolus insulin regimens have completed a prospective, randomized, crossover, open, pilot study comparing two consecutive three week periods with and without the dose advice function switched on. They were mean (SD) age 48 y (12), BMI 26 kg/m2 (7.5), A1C 8.1 % (0.7), fructosamine 396 umol/L (59), median (interquartile range) duration of diabetes 22 y (12 to 26), insulin dose 0.5 U/kg (0.4 to 0.6). No significant differences were seen in fasting blood glucose, fructosamine, insulin doses over this short period but there was a trend to fewer hypoglycemic episodes with advice switched on. A semi-structured questionnaire, assessing attitudes towards diabetes and insulin therapy, provided positive feedback. All subjects enjoyed using the dose advisor, found it easy to operate, reliable and not time consuming. At the end of the study all but one wanted to continue using the device, felt more confident in their ability to adjust insulin doses according to high or low glucose readings and reported that they would be willing to alter their insulin doses more often in the future. This pilot study showed the hand held dose advisor program to operate satisfactorily in clinical practice, to be well accepted, reliable, easy to operate and not time consuming. Larger trials are required to assess its potential to improve glycemic control and minimize hypoglycaemia in the longer term.

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