Computer assisted diabetes care: a 6-year retrospective

E.D. Lehmann*, T. Deutschb

aAcademic Department of Radiology, St. Bartholomew’s Hospital, London, UK
bCentre of Information Technology, Semmelweis University of Medicine, Budapest, Hungary

Abstract

Over the past 6 years we have designed a number of computer-based prototypes for the provision of therapeutic advice and the generation of glycaemic predictions in insulin-dependent (type 1) diabetic patients. In this paper we provide an overview of some of this work, and describe our experiences in trying to develop such methods for clinical use. We review, as an example, a model of the glucoregulatory system which has been developed for patient and medical staff education about type 1 diabetes mellitus, as well as possibly for therapeutic use. Using individualised parameter values the predictions of the model can be applied to generate 24-h simulations of patient blood glucose profiles. Previous preliminary retrospective validation work performed with this model has revealed a mean predictive accuracy for blood glucose simulations of approximately 2 mmol/l. Conceptual limitations of such modelling approaches are considered. We comment that such ‘mechanistic’ models may lack the necessary sophistication and flexibility to represent the complexity of the human glucoregulatory system and the challenges it has to face. Although such methodologies may therefore not be suitable for safe and effective application in routine clinical practice, we conclude that the evolution of such a system for demonstration/educational purposes could have widespread clinical utility as an interactive teaching tool.

Keywords: Diabetes mellitus; Dynamic simulation; Modelling; Education; Insulin dosage adjustment

1. Introduction

The management of patients with insulin-dependent (type 1) diabetes mellitus requires regular insulin injections and the monitoring of the patients’ metabolic status. The Diabetes Control and Complications Trial (DCCT) — a long-term, randomized, prospective North American trial — has demonstrated conclusively that intensive insulin therapy can delay the onset and slow the progression of retinopathy, nephropathy, and neuropathy in highly motivated patients with type 1 diabetes mellitus[1] — findings that confirm previous reports of a link between glycaemic control and diabetic complications [2]. One way of achieving the goals demonstrated by the DCCT as well as implementing the requirements of the St. Vincent Declaration [3] in routine clinical practice is likely to be through the use of information technology (IT) [4].

Current IT applications permit the collection, storage, display and analysis of patient home
monitoring blood glucose (BG) data. Computerised clinical records and databases also offer great opportunities for more selected medical follow-up, with much improved screening and health promotion/disease prevention. The DCCT results, showing the significant benefits of tight glycaemic control in type 1 diabetic patients, have also renewed interest in the utilisation of decision-support tools to assist in the transfer of diabetes-related knowledge from specialist secondary and tertiary referral centres to primary care, as well as possibly directly to patients [5]. We have recently reviewed elsewhere the application of computers in diabetes care [6,7].

In this paper we provide an overview of the application of computer support tools for diabetes management and summarise the development of a prototype computer system with which we have been closely involved. The importance of systems validation is highlighted, both in terms of testing model predictive capabilities and evaluating therapeutic advice. Limitations of our prototype identified by such validation studies are considered and the potential role of the system as an educational tool is reviewed. The paper concludes with a discussion of the strengths and limitations of current computational techniques described in the literature to assist in the provision of diabetes care.

2. Diabetes management — computer support

The management of patients with type 1 diabetes mellitus requires them to regularly monitor the status of their carbohydrate metabolism using home BG monitoring equipment. During consultations, physicians examine data collected by their patients in order to identify clinically important patterns that might indicate problems with the current therapeutic regimen; e.g., excessive BG values after meals or systematically low BG readings before lunch. Having done this it may be necessary for physicians to suggest modifications to the therapeutic regimen in order to improve patients' glycaemic control.

Insulin therapy may be adjusted as part of various control schemes that operate on different time scales [8]. Although diabetes care is potentially a data-rich field of medicine (which has therefore attracted considerable interest from both computer scientists and informaticians), routine diabetes management in most hospital clinics and general practices generally operates in data-limited conditions most often relying on only a few BG observations or a larger set of data collected at different times over a longer period. Table 1 illustrates this, showing BG data collected over 12 days by three type 1 diabetic patients attending six-monthly hospital outpatient clinic appointments at a tertiary referral centre in London. Two other patients seen that morning by one of the authors (E.D.L.) reported monitoring their BG levels but did not write the values down, while another three patients did not bring their log books with them to the clinic!

Long-term diabetes management involves temporary readjustment of patient therapy whenever the home monitoring BG data show evidence of deviation from preselected therapeutic targets. Adjustments, if required, are made at patient-physician encounters, the intention being that such adjustments should be applicable until the next visit, provided that due to unacceptable deterioration of symptoms/glycaemic control the patient does not need to seek medical help sooner.

Decision making at these visits involves (i) setting nutritional and BG targets, (ii) selecting times to observe the response to current therapy, (iii) summarizing and interpreting home monitoring BG data, (iv) assessing the quality of control achieved with the current regimen, and (v) suggesting how to modify the current treatment regimen when necessary. Depending on the time scale of the advice required prototype computer systems for generating therapeutic advice can recommend changes in timing or dosage of single injections, daily treatment plans, or longer-term management protocols. In addition to providing recommendations for the basic insulin dosage, such programs can also provide guidance about what to do in response to both extreme out-of-range BG levels, or in anticipation of substantial deviations from the normal course of events which are known to affect glucose metabolism. These functions involve intensive data processing.
and decision-making based on features extracted from the data collected.

Non-diabetes-specialists may need assistance in both analyzing and interpreting patients' home monitoring BG data, and selecting patient tailored therapeutic control actions on the basis of these data. To assist data collection several BG measuring devices are available [9]. These contain non-volatile memory and CPUs which are capable of receiving, storing and processing patient entered data with respect to self-monitored BG concentrations. Some of these devices can also cope with estimated dietary intake, anticipated physical exercise and insulin doses. Furthermore, some hand-held devices can provide therapeutic advice based on entered BG, insulin and activity data [10–13].

Any analysis of large quantities of data however requires that the data should first be interpreted. Data interpretation aims to detect clinically important patterns within the data. Various methods such as statistically-supported knowledge based data interpretation and time series analysis have been suggested to support data mining and feature extraction from noisy, incomplete and often poor-quality BG data [14,15]. One of the data condensing techniques is the so called 'modal day' aggregation of daily BG data that is frequently used to represent the 'mean response' of the patient to the current therapy. Fig. 1a shows a 'modal day' BG profile based on (Fig. 1b) data collected over a 6-day period by a 22-year-old female type 1 diabetic patient treated with twice daily intermediate acting NPH (isophane) injections.

A wide spectrum of qualitative and quantitative approaches has been reported in the literature to assist in the delivery of effective treatment. Techniques of optimal and adaptive control have been extensively used in designing optimal operating conditions for glucose-controlled insulin infusion devices [16–18]. Different algorithmic, knowledge-based and model-based approaches have also been used to advise on patient management in outpatient clinics both for insulin dosage adjustment [7,19–22] and for diet planning [23,24]. Methods at the data-limited end of the spectrum have mostly been based on fuzzy logic and qualitative reasoning to draw appropriate therapeutic conclusions [7,19–22].

| Table 1 |
| Samples of home monitoring blood glucose data (nmol/l) collected by three patients with insulin dependent (type 1) diabetes mellitus over a 12-day period, demonstrating the data-limited environment in which much diabetes management operates |

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Data from (a) a 35-year-old man; (b) a 54-year-old overweight woman; and (c) a fit 26-year-old man.
Algorithmic and rule-based approaches generally use ‘features’ in patient BG profiles as guides for making adjustments to the basic insulin dosage. A typical example is given here, following Skyler and co-workers [25]: ‘if pre-lunch BG is greater than 7.2 mmol/l for two to four days in a
row, increase the pre-breakfast regular insulin by 1 or 2 units. Such rulesets cannot be complete; in particular, they do not contain any information about possible control actions for situations which are not explicitly stated or for which more that one feature requiring insulin dosage adjustment occurs (e.g., hypoglycaemia and hyperglycaemia in different periods of the day).

In more data-rich situations quantitative models also offer an efficient means of characterizing patients’ carbohydrate metabolism and guiding therapy in a more rational way. Hence mathematical models have been used by a number of groups as a means of simulating or predicting BG levels in type 1 diabetic patients. More recent approaches such as the Causal Probabilistic Network (CPN) technique have allowed explicit representation and processing of uncertainty in patients’ metabolic status based on estimated probability distributions of various model parameters, and their impact on the confidence intervals of model-based glycaemic predictions to be assessed [26,27].

For any decision support system to be used in diabetes management it is essential to clearly define the objectives of the proposed computer system, in particular would the final intended use be (i) clinical/therapeutic, or (ii) educational? If the purpose is for clinical use, who is the intended user — a patient, a nurse, a primary care physician (general practitioner) or a hospital specialist? If the purpose is to generate therapeutic advice, what is the proposed frequency of use — meal-by-meal, day-by-day, or at clinic visits every week, month or every 6 months? The complexity of generating advice on a day-by-day or meal-by-meal basis is unlikely to be required to generate necessarily far more general advice for a patient attending a diabetes out-patient clinic every half year.

3. Development history

The conceptual approach that we adopted for making the required expertise for the management of type 1 diabetic patients more widely available, rather than using stand-alone mathematical models or a set of rules, was based on an integrated methodology linking a logical physician-like reasoning methodology with quantitative modelling in order to provide therapeutic advice to the referring clinician.

The latest prototype that we have developed is called AIDA (an Automated Insulin Dosage Advisor). The prototype has targeted the most common diabetes management situation in which the patient’s basic insulin dosage is adjusted, if necessary, at each physician visit and the new dosage is applied until the time of the next patient-physician encounter. Patients are assumed to follow a consistent lifestyle including a fixed insulin dosage regimen. Within this framework any alteration to the current dosage is based on an overall assessment of the patient’s glycaemic response to this regimen as derived from the raw home monitoring BG data. This typical response, often called the ‘modal day’ glycaemic profile, summarizes individual daily data into a ‘mean’ representative profile. The AIDA program addresses the problem of insulin dosage adjustment with the proviso that this characteristic BG response is known. In other words, issues related to optimising home BG monitoring and feature extraction have intentionally not yet been addressed.

We have reported elsewhere an overview of the key stages in the earlier development of AIDA [28]. Briefly, the latest Mk. II implementation (version 2.3) of the system has evolved through a number of different generations of earlier prototypes. The first, a simulator developed by Boroujerdi et al. [29], used non-linear differential equations to provide a one-compartment glucose model linked to a complex physiological model with free and bound insulin compartments [30]. A general purpose simulation engine using a fourth-order Runge-Kutta method was applied to solve the equations [31] allowing the system to provide 24-h simulations of an individual’s BG profile on the basis of the patient’s carbohydrate intake and insulin regimen. Therapeutic advice could not, however, be generated. This facility was provided by a prototype developed by Deutsch et al. [32] which adopted a knowledge-based system (KBS) approach derived from artificial intelligence (AI) techniques to generate clinically useful advice.
The rule-base of the prototype used ‘period orientated’ knowledge-based reasoning to analyse BG profiles and hypoglycaemic episodes in insulin-treated diabetic patients. Qualitative insulin algebra was also introduced to predict changes in the BG profile brought about by alterations in the patient’s insulin regimen [33].

These two computational approaches were brought together in a ‘Metabolic Prototype’, the concept of which involved establishing a patient database which combined BG, nutritional and insulin injection data with information on special events (e.g., times of hypoglycaemic episodes). This database was then used by the knowledge-based insulin-dosage advisory module and by the simulator for examining the proposed effects of insulin or dietary advice on predicted glycaemic control.

The KBS which was incorporated in the Mk. I version of the system used the BG measurements and times of any hypoglycaemic episodes in meal-related periods of the day. It suggested alternative control actions related to the insulin or dietary regimen. The advice generated was given in qualitative terms indicating the direction of the adjustment(s) required in order to improve the patient’s glycaemic control. The reasoning method was based on a ruleset encapsulating knowledge about insulin pharmacodynamics and the effect of food absorption on glucose metabolism. This advisory module was implemented on an IBM PC in MicroPROLOG using an APES expert system shell [34]. Once the advice had been generated the simulation module could then be used to examine the effects of these suggestions on the patient’s BG profile.

As a first step towards a full scale clinical evaluation of the system, work was performed to separately validate the individual components of the prototype. Preliminary testing using standard patient test cases [35] demonstrated the potential clinical applicability of the knowledge-based component of the advisory module [36–38]. However, the range of test cases used only covered a portion of the spectrum of diabetic management. Due to the lack of any facilities for automated parameter estimation in the complex physiological model [29], a pre-requisite for the routine use of the system in a clinical setting, a simplified clinical model of glucose-insulin interaction in type 1 diabetes mellitus was developed [39]. This utilised Berger and Rodbard’s [40] model of insulin kinetics alongside a new model of glucose pharmacodynamics based, in part, on experimental data from the literature [41].

The model contained separate compartments for plasma and ‘active’ insulin, the latter being responsible for glycaemic control while insulin was removed from the former by hepatic degradation. The model incorporated a single glucose pool representing extracellular glucose into which glucose entered via both intestinal absorption and hepatic glucose production. Glucose was removed from this space by insulin-independent glucose utilisation in red blood cells (RBC) and the central nervous system (CNS) as well as by insulin-independent glucose utilisation in the liver and periphery. Hepatic and peripheral handling of glucose in the model were dealt with separately; the net hepatic glucose balance (NHGB) being positive (production) or negative (utilisation) depending on the BG and insulin levels. The relationships were derived from nomograms given in Guyton et al. [41]. Insulin affected NHGB characterised by a liver sensitivity parameter, $S_h$, as well as enhancing peripheral glucose utilisation described by a peripheral sensitivity parameter, $S_p$. Glucose excretion from the extracellular space took place above the renal threshold of glucose (RTG) as a function of the creatinine clearance rate (CCR). Fig. 2a summarises the anatomical basis and physiological functions of the model, a more detailed description of which can be found elsewhere in this journal [42]. The rate of gastric emptying in the model was defined as a function of the carbohydrate content of the meal ingested.

The purpose of the model was to simulate steady state responses to a given insulin therapy and dietary regimen. Simulations were carried out over a 2-day period using a first order Euler integration method with a 15-min step size. The second day’s BG and plasma insulin profiles were considered as approximate steady state profiles and as such were displayed on the computer screen as the results of the simulation (Fig. 2b). A parameter estimation routine was implemented
Fig. 2. (a) Schematic summarising the anatomical basis and physiological functions of the model. A.G., arterial plasma glucose (mmol/l); B.G., blood glucose (mmol/l); G.A.R., glucose absorption rate (mmol/h); I.I.G.U., insulin independent glucose uptake (mmol/h/kg); N.H.G.B., net hepatic glucose balance (mmol/h/kg); P.G.U., peripheral glucose uptake (mmol/h/kg); U.G.E.R., urinary glucose excretion rate (mmol/h); insulin (mU/l); time (h). Modified from Lehmann and Deutsch [28]. From the Journal of Biomedical Engineering (Biological Engineering Society, London) with the permission of the publishers Butterworth-Heinemann Ltd ©.
Fig. 2. (b) Front end of the model showing the results of a simulation after parameter estimation/fitting is complete. Upper panel: observed (○) and predicted blood glucose levels. Lower panel: Insulin and carbohydrate intake with predicted plasma insulin curve. An observed hypoglycaemic episode occurred at 10:45 am. Data from Lehmann and Deutsch [28]. From the Journal of Biomedical Engineering (Biological Engineering Society, London) with the permission of the publishers Butterworth-Heinemann Ltd ©.

whereby values for $S_h$ and $S_p$ which gave the best ‘fit’ between observed and predicted data were automatically determined. Parameter values for which there was a conflict of trends between the two data sets in any time period were assigned a very poor fit by using a ‘penalty’ score for such cases. Following parameter estimation, if the best fit obtainable was greater than 3 mmol/l, then the clinician was informed that it was not possible to fit the model to the data sufficiently accurately to permit individual patient parameterisation and simulation to be performed.

The model was first externally linked to the old PROLOG KBS [43] and then more closely integrated with it in order to provide the Mk. I version of AIDA [44]. A multitasking version of this system was made available for 80386 based machines running Windows 3.0. This allowed the display of multiple windows showing different parts of the system in operation. For example the data entry screen could be displayed in one window with the results of a simulation in a second and advice from the knowledge-based system (KBS) in a third. Fig. 3 demonstrates an example of this where the ‘baseline’ curve in the ‘display’ window shows a simulation performed following parameter estimation. The lower (‘ADVICE’) window shows the two suggestions from the KBS as to how the patient’s BG profile might be improved. The glycaemic effect of each of these two pieces of advice have been simulated in the upper (‘DISPLAY’) window where it can be seen that advice number (1) to ‘increase the before breakfast NPH dose by 2 units’ results in a near normalisation of the BG profile [44].
This KBS, however, had specific data requirements needing BG measurements before the three main meals and at bedtime. If these measurements were not available therapeutically advice could not be generated. Furthermore, the timing of the insulin injections needed to correspond quite closely with the meal times as all processing within the KBS was carried out with reference to meal related periods of the day. As such the data requirements of the old KBS were much less flexible than those of the model; the latter, via its quantitative approach, having virtually no data entry limitations. The importance of this lay in the fact that while quite a lot of patients could provide data which could be used with the model, this same data would not necessarily work with the old KBS.

Therefore, a revised KBS was developed. This was linked to the model and provided alternative suggestions whereby the quality of the patient’s glycaemic control could be improved [45]. The reasoning approach used by the new KBS has been previously reviewed elsewhere in this journal [42], and is summarised in Table 2.

For the purposes of generating therapeutic advice, each day was divided into 13 consecutive time periods of variable duration. Before reasoning started, all hypoglycaemic episodes and the BG readings made by the patient were allocated to one of these periods. Therapeutic targets were then defined in terms of lower and upper limits for the BG level in these different time periods. Usually higher values were permitted for periods overnight in order to reduce the risk of nocturnal hypoglycaemia. In order to correct BG values which were either too high or too low, appropriate therapeutic adjustments in the current insulin regimen were selected. Changes which could be made included adjusting the dose and/or timing of the insulin injection(s) and shifting the intermediate acting insulin injection (if present) between the
evening meal and bedtime. Alterations to the insulin regimen were generated on the basis of the precomputed glycaemic effect of insulin dosage or timing adjustments in different periods of the day [28].

As the KBS could provide a number of different pieces of advice for any one set of patient data the link with the model provided an opportunity to identify the ‘optimal’ suggestion for an individual patient (Fig. 4). This was done by the use of an insulin dosage optimisation algorithm which adjusted the insulin regimen in the direction advised by the KBS and assessed the quality of glycaemic control that resulted upon simulation of this advice; the appropriateness of each suggestion being determined in terms of a deviation from normoglycaemia (DFN) parameter which provided a value for the difference between the predicted BG profile and a predefined acceptable normoglycaemic range (4–10 mmol/l). The DFN value was determined in terms of the area of the predicted BG curve which lay outside the normoglycaemic range; BG values below the lower normoglycaemic threshold carrying a penalty weighting of a factor of 2 (compared with hyperglycaemic values)

Table 2
Summary of the reasoning process used by the therapeutic advisor

- Locate ‘hypos’ and BG values in the different daily periods
- Select patient-specific BG targets in the different daily periods (target list)
- Classify the BG response in the different daily periods and select out-of-range type BG problems to be solved (problem list)
- Generate all candidate adjustments in the current insulin therapy which are expected to solve at least one problem on the problem list
- Filter these suggestions for contradictions and possible side effects
- Rank-order alternative control actions
- Present final suggestions in a problem-oriented and control-oriented way

From Lehmann and Deutsch [28]. BG, blood glucose. Modified from the Journal of Biomedical Engineering (Biological Engineering Society, London) with the permission of the publishers Butterworth-Heinemann Ltd ©.

as hypoglycaemic episodes were viewed as far more serious (potentially life threatening) events which the system needed to be able to avoid.

The optimisation algorithm iterated through the model and the DFN calculator, assessing the deviation from normoglycaemia, and adjusting the insulin regimen in one unit increments in the direction suggested by the KBS. The iterations for that particular piece of advice ceased when the DFN parameter started to increase (i.e., worsen). Having completed its iterations the system then presented its advice in an easy to interpret format, selecting the insulin dosage adjustment which resulted in the smallest predicted deviation from normoglycaemia. Fig. 5a shows an example of optimisation ‘in progress’ for the data shown in Fig. 2b while Fig. 5b shows advice from the system once optimisation is complete.
Fig. 5. (a) Insulin dosage optimisation 'in progress'. As a 'hypo' occurred within 6 hours of the morning Actrapid injection, the 7:30 a.m. Actrapid dose is being decreased in 1 unit increments. (b) Insulin dosage optimisation completed — demonstrating how the risk of 'hypo' at 10:45 a.m. could be reduced by decreasing the 7:30 a.m. Actrapid dose from 5 units to 2 units.
4. System testing

It is our experience that too little effort in this field is directed towards the very real and important issue of prototype validation. It may be useful to distinguish here between the terms verification, validation and clinical evaluation — all of which are different. We have previously defined these terms in relation to knowledge-based systems [46]. Similar definitions can apply to mathematical models. Briefly, verification refers to internal static checks of the model which involves establishing that the representation encoded within the model is compatible with current medical knowledge, or in practice a simplification of current medical knowledge which has widespread agreement. An important component of such verification work is the presentation of the model to external experts, in a readable form, for judgements concerning its validity and underlying assumptions.

Validation refers to testing performed in order to check the accuracy of the results given by the system. This must normally be performed both at the level of the individual module — does this component produce the results intended when used in isolation? — and at the level of the integrated system — do all the components working together produce the intended results? [47]. The results of such validation studies are normally judged against clinical criteria — for example observed BG measurements for the predictive accuracy of a model.

Clinical evaluation refers to testing via prospective randomised controlled trials as to whether the use of the system in its intended environment is effective in improving the process and outcome of clinical care; e.g., does this system improve glycaemic control. Normally this latter assessment is a test of a system plus a user compared with either an unaided user or a user aided by an alternative system [48]. While these three distinct components of the evaluation process can be identified, it is necessary for them to form an integral part of the development of any system. Furthermore, during such system development, assessments of human factors will be required, addressing such questions as to whether the system is useful and usable and whether it meets end user requirements.

Preferably such work should form part of the development cycle of the prototype. After all, the renewed interest in quality assurance for the delivery of diabetes care, highlighted by the St. Vincent Declaration [3], needs to also translate into quality assurance in the development of such computer systems. Such quality control — which is well recognised in industry — requires the development process to include rigorous validation studies, as often systems can become too complex for such work to be undertaken later. If such endeavours progress to a stage where the system is planned to be used for generating therapeutic advice for patients, such concerns become paramount. People put a lot of trust in computers and can completely accept what they say as fact. Given this, special care needs to be taken to ensure that the advice from the computer is appropriate as well as safe. As Bergman and Buchanan [49] have highlighted, without formal, well conducted validation studies, what confidence can physicians, nurses, dieticians or diabetes educators have in the safety of a computer program?

Why have so few systems undergone such formal validation studies? One reason must be the time and effort involved, which should not be underestimated. Another may be the need for access to patients and a considerable amount of clinical data — something which informaticians working without close clinical collaboration do not necessarily have. A third factor — not to be dismissed — is the realisation that many of today’s systems would not ‘pass’ such stringent tests, and that non-clinicians who may be responsible for leading system development projects may not appreciate the very real clinical need for such formal validation studies.

4.1. Testing predictive capabilities

A model of the glucoregulatory system such as the one included in AIDA can be validated at several different levels. For example, it should be possible to separately validate the insulin and glucose parts of the model. For the insulin component, the model’s predictions of plasma insulin
levels could be compared with patients’ measured free plasma insulin concentrations. Such a validation study would not need a large number of patients, just simply patients with a wide range of different injected insulin doses. Observed and predicted values could then be compared, not only based on correlation coefficients — but rather using formal Bland-Altman statistics [50]. In AIDA’s case, only by undertaking such studies would it be possible to establish, for example, whether the non-complex insulin model that we have adopted is suitable and sufficiently refined for individual patient use. Specific questions which could be addressed would include asking is the lack of patient specificity in the insulin part of a model of the glucoregulatory system important? Also, as Bergman and Buchanan [49] have pointed out, is not taking into account insulin antibodies of importance when modelling the glucoregulatory system in patients with type 1 diabetes mellitus?

The need for formal validation studies of the glucose part of a model may be more apparent. It is necessary to compare observed and predicted BG values, as guides for generating therapeutic advice. Furthermore, users have a right to know how accurate the model’s predictions really are. Such studies obviously need to be done in sufficient numbers of patients to make the results meaningful. Such work becomes especially important if one plans for the model to be adopted into routine clinical practice. An important caveat with such work, however, is that if a system is tested with a certain dataset and as a result changes are made to the system, it is invalid to use the same dataset to report further validation results. New data are clearly needed.

In this regard we believe that it might be useful for collaborative groups to build up a large standardised database of patient data against which different models, intended for clinical use, could be tested and their results objectively compared. If such a database is not available some form of prospective data collection is required. We have previously outlined a clinical protocol which could be used to assess the predictive accuracy of such models of the glucoregulatory system [46].

The AIDA prototype has not yet had its insulin model tested as outlined above, mainly due to the practical and purely logistical difficulties of taking venous blood samples and measuring free plasma insulin levels a known time post-injection in diabetic patients. It is noted, however, that there is general acceptance [49] that the insulin model of Berger and Rodbard is almost certainly not complex enough for individual patient use (it was after all originally developed solely for educational purposes [40]).

Any validation of the glucose component of a glucoregulatory model must also test out the insulin component. This has been done in a preliminary manner for the AIDA prototype [51]. In the most recent study using clinical and nutritional data from 30 patients over a 5–6-day period, in conjunction with the parameter estimation technique described, the model’s predictions have been compared with the patients’ observed BG measurements [52]. The model was found to only be able to make reasonably accurate glycaemic predictions for some patients, having a predictive accuracy ranging from 0.8 to 4.6 mmol/l with a mean (± S.D.) of 1.93 ± 0.86 mmol/l. One fundamental question that was not addressed, however, was what sort of predictive accuracy will be required by such systems before they become clinically useful. From a physician’s viewpoint it is not at all apparent that a predictive capability with a mean error of 2 mmol/l will be that useful in clinical practice. However, this all clearly depends on how such predictive capabilities are related to variabilities inherent in the observed data.

As every diabetologist knows even patients who are on stable insulin regimens with relatively fixed meal times (and quantities of carbohydrate ingested) as well as stable exercise patterns — often can exhibit quite variable BG profiles (e.g., Fig. 1b — for a type 1 diabetic patient over a 6-day period). This might quite possibly explain the wide range of observed versus predicted BG values generated by such models (e.g., mean differences — AIDA: 1.9 mmol/l [52]; CPN: 3.2 mmol/l [53]). Natural variability sets a limit for any system’s predictive performance; i.e., the predictive accuracy of the
system cannot be better than the natural variability or 'noise' in the input BG data. As a result of this natural variability in the BG data, increasing interest is focusing on trying to identify patterns or trends in these data which might be extracted [15] and potentially be more amenable than the individual BG measurements to modelling or advice generation [14].

Evaluating a diabetes management system in patients assumed to be in a 'steady state' poses a number of additional conceptual and practical problems. Due to the very large temporal intra-subject variability in daily data (see Fig. 1b), we would need a sophisticated technique to extract typical steady state patterns from these noisy observations which could serve as a profile of reference for making comparisons with simulated data. Unfortunately, such methods are not yet available. As a consequence, we could only test AIDA's predictive performance using retrospective data over a period of a few days, as outlined above [52]. As a result such evaluation results can provide only limited information and do not allow formal prospective clinical trials to be initiated.

However, in clinical practice, it is likely to be the ability to identify and predict when patients are at risk of hypoglycaemia which will be of paramount medical significance. If a system is able to reliably predict hypox in the day — and this can be demonstrated consistently in a large number of patients — other factors including the overall glycaemic predictive accuracy may become less important. However, confidence in the modelling approach adopted would be much increased by knowledge of the accuracy of both its glycaemic and hypoglycaemic predictions — as the two are clearly related. Moreover, it should be recognised that if a model is to be used in conjunction with some form of advisor which generates suggestions for the doctor, nurse or patient to follow, it may well be that a physiological model is not actually required and a far simpler heuristic (or other) rule-based approach may suffice.

4.2. Testing advice generated

Validating the advice generated by such clinical/therapeutic systems is an unclear field at present. Such validation work can never be a one-off process because a good validation study (at least initially) will raise more questions than it answers. Furthermore, there are many different ways of treating a diabetic patient. For example, a reduction in insulin injected, an increase in carbohydrate eaten or a decrease in the amount of exercise taken may all be appropriate longer-term ways of avoiding hypoglycaemia. Also accepted medical practice varies among different groups of doctors in different countries, and can also change with time as medical science develops — so there is rarely one 'right' answer that could be used as a 'gold standard'.

However, one of the fundamental ethical principles on which medicine is based is 'primum non nocere' (above all do no harm), and this surely must be a basic objective of any computer system intended for clinical/therapeutic use. This may seem obvious and at the same time unnecessarily negative — but one definitive validation criterion against which all such prototypes could be tested is 'would this advice harm the patient?'. If the answer was ever 'yes' clearly further refinements/modifications to the system would be required, thus emphasising the need for the validation process to be an essential and integral part of the development cycle of any prototype.

Another criterion which needs to be assessed is 'would a patient be happy to follow this advice?'. A therapeutic system which could technically optimise a patient's BG profile with one regimen change may be clinically useless if, for example, it suggested massive changes in the treatment regimen which patients were not happy with. Regardless of one's political views, conservatism is still strongly indicated in this field!

A third and very obvious criterion is what clinicians think of the advice — although given that they often do not agree amongst themselves [37], quite what the gold standard should be re-
mains unclear. Various peer review [54–56] and statistical protocols [57] have been described which may have a role in the analysis of data from such validation studies — however, the simple answer is that the clinicians testing out the prototype need to be satisfied that they have a deep enough understanding of how the system works and are content with the advice that it gives, in a sufficiently large number of patients, before proceeding on from retrospective validation analyses to prospective clinical studies.

Things obviously become a lot more straightforward once one starts undertaking prospective studies, simply because there are only a handful of hard endpoints that one needs to consider; BG, fructosamine and HbA1c (glycosylated haemoglobin) levels. Demonstrating that a particular computer system generates reliable and safe advice consistently, which improves glycaemic control, is the panacea that so many researchers in this field have been seeking.

However, in our opinion to demonstrate the reliability and safety of a computer system requires extensive retrospective studies, ensuring rigid safety controls are built into the code. Ideally the results of such work should be widely disseminated to reassure fellow workers and potential users of the safety of the prototype. Obviously, data obtained from prospective studies could be analysed retrospectively to assess, for example, the predictive accuracy of the system. However, clearly such approaches are less amenable to refinements and modifications being made to the system, as part of the development-validation cycle. Furthermore, once changes are made to a system it needs to be thoroughly re-validated. The potential risks of later litigation [58] which may result if such stringent repeat validation studies are not performed always needs to be considered.

Demonstrating safety, reliability and efficacy (improved glycaemic control) on its own however may not be enough. Mike Albisser did this with his Insulin Dosage Computer (IDC) in the 1980s — the number and size of successful clinical evaluation studies reported with the IDC being most impressive [10–12,59]. The relative lack of widespread use of this system probably largely relates to it being based on empirical/algorithmic methods. Given this, it could never explain its reasoning — either to patients or physicians. We believe that as we approach the 21st century, prototype computer systems intended for clinical use will need to be able to justify their reasoning [4]. Therefore, to the triad of requirements of safety, reliability and efficacy we perhaps should add another pre-requisite, namely that the decision-making process should always be challengeable [60].

So where do we go from here? The development of systems for clinical/therapeutic use would almost certainly be accelerated by the compilation of a standard large dataset of patient cases (n > 100) in electronic format which could be used for the testing not only of current systems — but also of future prototypes; the availability of suitable patient data at present being a major obstacle to the systematic testing and formal validation which will be a pre-requisite for the application of such systems in routine clinical practice. Undoubtedly, the development and comparison of many current prototypes in this field would have been accelerated by the availability of such a dataset. Furthermore, the presence of such a database would remove many of the obstacles to performing thorough retrospective validation studies as part of the development cycle.

We believe that it will only be by establishing the safety, reliability and clinical utility of such systems that the diabetes community will come to accept such decision support systems alongside other similar high technology devices as the BG meter and insulin pump. However, without well conducted large-scale retrospective validation and prospective clinical evaluation studies we remain unconvinced that it will be possible to demonstrate such safety, reliability and efficacy to the diabetes community.

5. AIDA: a clinical or educational tool?

Limitations of the current AIDA approach can be related both to conceptual problems and problems arising from the current implementation. The model itself is clearly not refined enough, not
coping with important processes such as exercise or stress — which greatly affect the lives of many diabetic patients. Also it does not allow the simulation of transient conditions. Furthermore, current modelling of the glycaemic effect of food in terms of the overall carbohydrate content of the meal is a well recognised simplification of a very complex physiological process. In this latter case, however, data are simply not available in the literature about the glycaemic indices and absorption times to peak of a wide variety of foods. For example, the glucose absorption profile following the ingestion of, say, 50 grams of carbohydrate in a hamburger, on its own, may differ quite substantially from that when an identical quantity of carbohydrate is ingested as a meal of chips. Also the glucose absorption profile will be completely different, once again, if the hamburger and chips are eaten together. Quite what happens to glucose absorption when tomato sauce and vinegar are added to this meal no one quite knows!

Clearly, current modellable knowledge of the processes involved in the absorption of food from the gut is severely limited, and this needs to be recognised when attempting to utilise such models for individual patient glycaemic prediction. Furthermore, the lack of a flexible interface to external data collection devices [9] and other pre-processing systems, as well as the lack of a proper database causes difficulties. Also, it is clear to us both that the current parameter estimation technique employed within AIDA is not, at present, refined enough since it provides no error estimates for parameter values.

Separate from any potential use as a therapeutic/decision support tool the AIDA system may have application as an educational/demonstration tool. Many of the issues highlighted above, however, still apply. While the graphical display is quite appealing the system lacks a polished front end and data entry facility. Furthermore, it is not at all clear at present for whom AIDA could be used as an educational tool. With regard to patients, many have argued that the display(s) are too complex, while for medical or nursing students further facilities would be required. For example the system at present is unable to teach — rather it can only be used as a demonstration tool (with someone who knows what they want to do 'taking the controls' to show someone else). Given this, a great deal of programming work would be required to turn the current AIDA prototype into a refined teaching tool. Also to be truly educational these days would require multimedia computer-aided learning facilities which can only really be provided in a dedicated Windows environment.

Probably the only clear educational application of the current AIDA v2.3 system is for doctors or nurses to teach medical students or nursing students, via demonstrations, the principles of insulin-dosage and dietary adjustment in type 1 diabetes mellitus. However, such a task is not without its own difficulties. Unfortunately, skills such as these are not generally taught, certainly not in many UK medical schools [61]. Given this, many medical students qualify with little or no practical knowledge of what to do with an asymptomatic diabetic patient with a random BG of 25 mmol/l. This may, in part, explain the difficulty of getting AIDA used as a demonstration/teaching tool in such circumstances. If such practical training was normally provided [61,62], then probably such demonstration/simulation tools would find a niche in many medical school curricula. A related supplementary educational application might be as a demonstration tool for use by diabetic specialist nurses, one of their jobs in the UK being to transfer expertise and experience from the secondary or tertiary hospital setting to general practice nurses who may have relatively little specialist knowledge about insulin-dosage or dietary adjustment in diabetes [63].

While these are areas in which the current AIDA system could almost certainly be applied, evaluating the benefit of such an approach would be much harder to do. While the clinical/therapeutic application of such systems have very definite endpoints (improved glycaemic control) which can be assessed, in education things are not quite so clear. Designing a study to show that a specialist nurse plus a computer was a better diabetes educator than a nurse alone would be fraught with difficulties and its conclusions would undoubtedly be open to many different interpretations.
6. Discussion

AIDA was originally designed as part of a comprehensive diabetes management system that supported visit-by-visit type insulin dosage adjustment. The system was planned to work together with a data processing and interpretation system as an assistant for generating recommendations to improve glycaemic control in type 1 diabetic patients. Although the development of AIDA made an important contribution to this end and has provided a lot of useful experience, some drawbacks associated with this approach have forced us to rethink the structure and functionality of such a comprehensive advisory program [64] intended for routine outpatient clinic/general practice use. These experiences are closely related to the limitations of the assumptions and methodology underlying the AIDA concept which have become apparent during the preliminary testing of the program.

Qualitative reasoning has been introduced to mimic the way in which diabetologists try to interpret BG data and select control actions to correct the problems identified. Introducing qualitative BG categories to replace continuous measurement data, time intervals to replace the time points at which BG data were sampled, and problems in the glucose supply all help to formulate a technical description about what is observed, using a terminology which should be clear to fellow clinicians. Adding a parametric model description to this is intended to enhance our capability to understand how particular BG patterns are generated as a result of glucose-insulin interactions by fitting a physiologically-based model to the patient's data. Both techniques, however, have limitations.

Problem-oriented reasoning is a useful means of guiding actions but the single problem oriented view adopted in the current implementation of AIDA (v2.3) is unable to cope with situations in which more than one problem is present. This inability is more pronounced when the problems are of a different nature; for example, if data show hyperglycaemia in one period of the day and severe hypoglycaemia occurs in another period — especially if these periods overlap or the events are causally interrelated (for example, with rebound hypoglycaemia). The inability of the AIDA system to cater for such complex or conflicting situations is a severe limitation of the current approach, especially as it would be in such difficult cases that the computer's assistance would be most useful.

There are problems with the quantitative model too. In spite of the robustness of the parameter estimation algorithm (total enumeration rather than a gradient, steepest descent or other sophisticated search method) the program can fail to fit the patient's data adequately. The disagreement is not quantitative in nature but clearly qualitative; i.e., in some periods of the day the program simply is unable to reproduce the observed trend in the data. For example, the simulated BG curve may increase between breakfast and lunch at all values of the insulin sensitivity parameters ($S_B$ and $S_p$) but nevertheless the observed data may exhibit a clear falling trend. In such cases the model (i.e., what we know about glucose handling in diabetes) and/or its inputs (the patient’s insulin regimen, diet, stress, activity, etc. that have been recorded) are unable to explain the BG profile that has been observed.

These problems arise from the lack of medical knowledge about the wide range of exogenous and endogenous factors that may affect patients' glucose metabolism. The impact of some inputs are oversimplified while the presence of other underlying disturbances simply are not known. This imbalance between the detailed description of organ level glucose handling and our inability to specify and describe model inputs is the primary factor behind the relatively poor predictive performance of our model. However, it should be apparent that these problems are not AIDA-specific, but rather are general to all currently applied modelling approaches.

In this context a more sophisticated parameter estimation technique, including the recently introduced CPN approach [26], can offer only little help since 'blaming' some model parameters for any discrepancy between observed and computed data is unjustified. Converting uncertainty in model inputs such as an extra meal or unrecorded stress which are clearly non-random into an esti-
mated probability distribution for some selected model parameters such as insulin sensitivity does not seem to us to be the method of choice.

The lack of a sophisticated, automatic method for computing optimal adjustments is an additional deficiency of the current version of AIDA (v2.3). However, as we have pointed out before, defining the ‘best’ treatment itself is a difficult task — the solution to which depends on several patient characteristics as well as the risks of hypoglycaemia which may result from an attempt to improve glycaemic control. For example, a preprandial BG of 12 mmol/l may be perfectly acceptable in an 84-year-old type 1 diabetic man living on his own, whereas for an 18-year-old recently diagnosed diabetic patient attempts would be made to tighten glycaemic control.

However, the major problem with an AIDA-like approach lies elsewhere, and possibly accounts for the relative lack of impact of all such models in clinical diabetes care. As mentioned previously, adjusting the basic insulin dosage involves two interrelated problems. The first is to extract patterns from noisy home monitoring BG data, while the second is to recommend control actions whenever an improvement in glycaemic control is required. AIDA intentionally addressed the second problem leaving the first task unresolved. This separation and reversing of tasks, however, raises a number of difficult issues.

There are different temporal patterns that can be extracted from raw BG data. Daily patterns, trends and some longer cycles need to be considered. The ‘modal day’ aggregation of data is just a single pattern that one can try to extract from individual observations. Building an advisory system relying solely on that ‘modal day’ BG profile may be an oversimplification that cannot be justified. Therapeutic recommendations should respond to a variety of patterns in longer-term BG data, and the temporal evolution of other markers such as HbA1c or fructosamine equally need to be considered. This means that data mining and interpretation should precede insulin dosage adjustment. The latter could properly be designed on the basis of the various patterns that can be extracted from various monitored signals which contain all relevant information hidden within the large quantity and poor quality BG data collected by so many type 1 diabetic patients.

7. Conclusions

Over six years’ experience first with the Metabolic Prototype and more recently with AIDA has led us to several conclusions. Although evident, but still often neglected, is the need for specifying the system’s users, the services to be provided and the clinical context in which the program is intended to be used. Parallel to the design and development, the method of evaluation should also be described along with a set of criteria according to which the system’s performance and function will be judged.

We have concluded that the most important issue in supporting long-term diabetes management is data summarization and interpretation; i.e., coping with a large amount of self-monitored BG data. Understanding what these data mean, extracting patterns of clinical importance, and establishing measures of confidence associated with such data and patterns (daily patterns, weekday versus weekend differences, trends, etc.) that have been extracted from these data, are prerequisites for building a treatment advisory system for practical clinical use.

We believe that the horizons of AIDA’s single-problem oriented world need to be extended with the view of a sequential controller. Data collected in the current time period should be combined with the expertise accumulated during the previous patient-physician encounters. We must be able to analyse whether current data are or are not in harmony with predictions and if not, explain the causes of such discrepancies. Such analyses may result in a revised complex picture about the patient that may be regarded as a patient specific model.

This construct could serve as a repository of metabolic knowledge about the patient — which would evolve over time. This accumulated knowledge would need to encompass the rich complexity which we are able to learn about a particular patient during the course of their therapy which is much more than just a regularly updated set of
numerical parameter values in a glucose homeostatic model.

These considerations put model-based techniques in diabetes management into another perspective. Given the complexity of, and the great number of factors affecting, glucose metabolism we think data-driven pattern extraction methodologies are more appropriate to extract diverse features from home monitoring BG data than model-based parametric patient-specific knowledge acquisition which forces an a priori structure to data which may not fit. Discrepancies between observed and simulated data most often may serve as a further source for extracting patterns of possible clinical significance.

Merging qualitative and quantitative reasoning although didactically appealing may not offer substantial advantages for clinical use in diabetes care. Most often, especially if the physician adopts a conservative strategy for adjusting insulin dosage, a control decision involves an adjustment of a single insulin dose or injection time of limited extent (say, maximum 20%). Predicting the effect of such a small change on the daily BG profile is straightforward and does not need computer assistance. On the other hand, if one is confronted with difficult clinical situations involving several problems, directly selecting a multiple adjustment decision (that involves more than one insulin component) is not supported by the qualitative advisor. Furthermore, the effect on glucose metabolism is also unpredictable in qualitative terms. Thus in some cases the rule-based reasoning is too simple and trivial, but becomes insufficient in other more challenging cases.

In addition to this in a restricted range the glucoregulatory system obeys linear dynamics and this behaviour could be learned using methods of linear systems analysis. For example, linear transfer function models [33,38] or other ‘black box’ type techniques might be used to explore the effect of small changes in insulin dosage on BG. Such models could equally provide all the information that is needed for making patient-tailored optimal management decisions.

It must be noted that although AIDA does not seem to be suited for therapeutic use, its conceptual structure, reasoning technology and computer implementation offers an efficient means for both patients and health-care workers to understand glucoregulation in type I diabetes mellitus and for gaining insight into the mechanism of decision making involved in diabetes management. It is of high illustrative power in analyzing and treating simulated patients [65], a feature which we believe with refinement could prove very useful for patient and health-care worker/student education.

8. System availability

A copy of the latest version of AIDA reviewed here and a user guide are available for health-care professionals without charge by writing to Dr. E.D. Lehmann by email at: aida@globalnet.co.uk or at the MR Unit, Department of Imaging, National Heart and Lung Institute, Royal Brompton Hospital, Sydney Street, London SW3 6NP, UK. The AIDA software runs on IBM PC or compatible 80386/486/Pentium based machines and requires approximately 2.2 Mb of hard disk storage space. Dr. Lehmann would be particularly interested in hearing from fellow clinicians who wish to use the system as an educational demonstration tool.

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Addendum

Since the preparation of this article a revised, updated Mk. III version of AIDA (v4.0) has been developed with the assistance of a type I diabetic
patient. This new version [66] which is intended solely for educational/teaching/demonstration purposes is much easier to interact with than previous versions. It has been completely re-engineered and incorporates a new, dedicated data entry screen and case scenario database. Forty educational case scenarios are provided as standard, and further case scenarios can be added by the user, as required. The new software, intended for international use, can now handle blood glucose measurements in both mmol/l and mg/dl. Unlike previous versions, AIDA v4.0 caters for a wide variety of commonly used insulin preparations, including premixed (biphasic) preparations. It also utilises a modified version of its knowledge-based system (KBS) to identify possible problems in the case scenario data. A list of suggestions which might correct some of these problems can also be generated as a prompt to the sort of insulin dosage adjustments that users might like to try simulating with AIDA. The interactive application of this KBS offers educational opportunities which might otherwise not be available to patients/students/healthcare workers using the software on their own. The new system is available without charge on the Internet from the following World Wide Web site: http://www.pcug.co.uk/~diabetes/aida.htm [67].

References


