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Compartmental models for glycaemic prediction and decision-support in clinical diabetes care: promise and reality

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Abstract

This paper reviews and critically appraises the application of compartmental models for generating glycaemic predictions and offering clinical decision support in diabetes care. Comparisons are made with alternative algorithmic-based approaches. Unresolved issues raised for model-based techniques include the relative lack of input data necessary for generating reasonable blood glucose predictions, and the high level of uncertainty associated with such predictions which limits their use as guides for therapeutic insulin-dosage adjustments. It is concluded that compartmental model-based approaches, while not offering much benefit for clinical/therapeutic application, will have a role to play as research tools and for educational use. By contrast it is proposed that algorithmic-based approaches, especially in conjunction with telemedicine and Internet applications, are likely to see growing use for day-to-day therapeutic decision support. Randomised controlled clinical trials however will be required, together with other evaluation efforts, before algorithmic-based approaches—like any other clinical technique—can be widely adopted into routine medical practice.

Keywords: Diabetes mellitus; Compartmental models; Algorithms; Insulin-dosage adjustment; Glycaemic predictions; Computer systems

1. Introduction

For many years there has been academic interest in the application of computers in diabetes [1–3]. Since 1993, with the publication of the main results from the Diabetes Control and Complications Trial (DCCT) [4], it has become increasingly apparent that improved glycaemic

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control is a pre-requisite for reducing the incidence of later life diabetic complications. The increasing realisation that more needs to be done to tighten blood glucose (BG) control has brought with it renewed interest in the application of information technology (IT) in diabetes care [5–12]. As a result views have shifted from a belief that computers might be a useful adjunct to routine therapy for some diabetic patients, to a recognition that without IT it will simply not be possible to deliver the DCCT benefits of intensive insulin therapy to a wide range of patients in routine clinical practice.

Given this, there is now a great deal of clinical interest in the development of computer systems to assist in the transfer of diabetes-related knowledge from specialist centres to primary care settings, as well as directly to patients [10–12]. Recently more advanced systems have been proposed, aimed at supporting both doctors and patients in making appropriate decisions, and facilitating information exchange between them via telecommunication [13]. It is against this background that this review has been compiled.

Optimal diabetes treatment can only be delivered as an adaptive regime that requires patients to be monitored frequently in their everyday environment. Monitoring serves to check conditions that may require management actions, and equally to match outcomes with expected results. Patient data are processed to yield clinically relevant information. This information is gradually updated and refined resulting in a patient specific model (PSM). This model serves as a guide for control actions that may refer to the basic insulin regimen as well as to a single dose in response to acute hyperglycaemia, or in anticipation of an unusually large meal or sport activity before unwanted elevation or depression of the BG level is produced.

There are a great variety of methods that can be used to build and refresh PSMs and to adjust insulin therapy accordingly [14]. In the following, two different techniques (compartmental models and algorithms) are critically appraised. It is suggested that compartmental model-based computational techniques may have relatively little utility for generating glycaemic predictions and offering decision support in routine clinical practice. Conversely algorithms may in fact offer a robustness and reliability which will permit much wider application in real life conditions.

2. Compartmental models

Compartmental models offer powerful tools for understanding, predicting and controlling processes. Adaptive model-based control of diabetic patients involves the sequential fitting of a dynamic model to patient data—using the 'refined' model subsequently to compute prospective insulin dosage regimens.

Compartmental models of the glucoregulatory system are composed of sub-models that describe the main processes affecting glucose metabolism in diabetic patients. A typical compartmental model can be found within the AIDA system—a prototype computer program that started its life attempting to be an automated insulin dosage advisor [15–20]. It contains a single extracellular glucose compartment and separate compartments for plasma and 'active' insulin, the latter being responsible for coordinating fuel storage and mobilisation into and out of various depots. Fig. 1 summarises the compartmental structure of the model, the functions of which have been previously described in detail in this journal [19].

The AIDA model contains two patient-specific parameters that reflect hepatic and peripheral insulin sensitivities. When building a PSM these parameters are estimated by means of matching the BG concentrations that have been estimated from the model equations with measured BG levels.

A model, once properly fitted to patient data, can be simulated to examine the effects of alternative control actions on the patient's BG profile. The appropriateness of each adjustment can be quantified in terms of a performance measure which indicates the benefit (or negative effect) associated with a particular therapy. Alternative therapies can then be evaluated by comparing their respective performance measures, and the therapy with the maximal (or minimal) value of this criterion can thus be recommended.

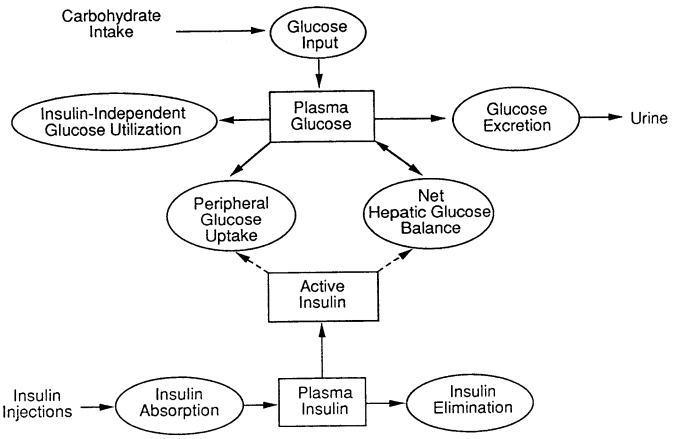

Fig. 1. Compartmental structure of the AIDA model. Reproduced from Lehmann et al. [18] with the kind permission of Medical Informatics, (c) Taylor & Francis, London.

The parameter estimates that characterise the carbohydrate metabolism of the patient are inevitably associated with some uncertainty. This uncertainty arises from the large number of factors that may affect glucose metabolism in addition to the temporal variations which can occur in each individual, and the errors associated with the sampling and the measurement procedures that have been used.

Uncertainty surrounding a PSM is often expressed as the standard error of the estimate computed by the fitting algorithm. Causal probabilistic networks (CPN) offer a general scheme for representing this uncertainty [21,22]. Rather than defining insulin sensitivity as a single value, it is given as a probability distribution function which shows the extent to which the different ranges of individual parameter values can explain the observed data.

If one uses the causal probabilistic model of carbohydrate metabolism, the BG levels can be predicted as a probability distribution over time while the optimal insulin treatment is selected as that having the maximal value for the expected value of the performance criteria.

Conceptually this scheme of model-based adaptive control seems to be appealing, perhaps explaining why compartmental models of glucose–insulin interaction, like AIDA, have been proposed in the past to be of potential use for clinical therapy planning in diabetes care. Using the AIDA model as an example we have sought to critically appraise whether the data are available to support such contentions.

2.1. Accuracy of model-based glycaemic predictions

Identifying a model and parameterising it to fit BG data has taxed researchers for many years—so far without much success. Why?

Every clinician is aware that a diabetic patient on the same insulin regimen, resting in bed, eating at the same time each day a dietician-prescribed standard diet can have quite different BG readings from day to day. For example Table 1 shows BG data from an 18-year-old type 1 diabetic patient resting in bed on the same insulin regimen for 6 consecutive days [23]. Clearly the patient's glucose metabolism is not very regular or consistent. From the modelling perspective endocrine processes must be taking place which are not, at present, fully understood and/or which cannot be explicitly modelled. Given this, BG predictions generated by quantitative models cannot be better than the natural variability which exists in the BG data.

However, BG data provide absolute criteria against which the predictive accuracies of such models can be assessed. Unfortunately very few

Table 1
Blood glucose data from an 18-year-old insulin-dependent (type 1) diabetic patient resting in bed on the same insulin regimen for 6 consecutive days.

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

Data from Lehmann et al. [23]. Blood glucose values are given in mmol/l.

models have their predictive accuracies demonstrated in this way. For example, even though the diabetes-computing field is blessed with an abundance of data it is rare to see comparisons of observed versus model-predicted BG data. In this respect a systematic review of the literature on the application of computers in diabetes care did not reveal a single such graphical plot [8,9].

Fig. 2 shows a simple regression graph of observed (measured) BG versus predicted BG derived from a study of 24 patients, followed over a 4–5 day period [24]. Predicted BG data were obtained from the AIDA model [15]. This simple plot communicates a great deal of information to other researchers, as well as to practising clinicians, about the model being tested in the sample cohort. As can be seen there is considerable scatter in the data. For individual measurements (or patients) the BG predictions may be a considerable way off the line of identity. However, it needs to be recognised that such plots are relative simplifications of complex associations. For example the predictive capability of such models will also vary with time.

Nevertheless data such as these—simply expressed as a mean root mean square deviation between observed and predicted BG data of 1.9 mmol/l—led us to realise some years ago that such quantitative compartmental models were not reliable enough for making glycaemic predictions or thereby deriving clinical therapeutic decisions for individual patients [24,25]. It is noted, even though the original data were for the most part derived from a highly selected cohort of patients [26], that the best fit curve exhibited qualitatively different patterns with respect to observed data in six out of 30 patients (20% of the group) [24]. It is of interest, however, that other researchers have suggested models with even poorer predictive accuracies, e.g. 2.8–3.5 mmol/l, to be of potential use for clinical decision making [5,27,28].

Clearly a poor overall predictive capability, on its own, does not preclude all forms of clinical use. Graphs like Fig. 2 show overall scatter but it should be apparent that how well a model can predict an individual patient's BG profile will vary from patient to patient. Parameter estimates could improve over time, thereby narrowing confidence limits of glycaemic predictions. Furthermore, predictive accuracy clearly depends on the time horizon of the prediction. Short term simulations may be quite good, while longer term predictions may be associated with larger errors. By contrast steady state model-based simulations may be sufficient for predicting trends and the mean typical response to an alteration in the regimen that has been recommended.

One suggestion has been to accept that there is inherent variability in the BG data and look at probabilities or 95% confidence intervals for the model predictions [29,30]. For example, a broad confidence interval to simulations might indicate a high risk of hypoglycaemia. Conceptually, this notion is appealing. In practice, however, the error bars (or 95% confidence limits) will generally be very wide and to a doctor it might seem

difficult to accept that such predictions can really be of clinical use.

Clearly it could be argued that if the confidence interval for the prediction is not that large, such models may provide a means for testing various control actions, however, such an approach remains to be evaluated clinically.

2.2. Compartmental models—unresolved issues

Apart from uncertainties over predictive accuracies—there are several concerns regarding modelling approaches. Problems may arise from (i) the lack of relevant medical knowledge that would be needed to describe all important factors and processes affecting glucose metabolism, (ii) methodological difficulties that appear when dealing with complex metabolic systems, and (iii) the quality of data patients report as raw material for state assessment and control.

Clearly there is an imbalance between the depth of description of endogenous glucose handling and ignorance regarding perturbations that affect glucose dynamics substantially. As we have previously highlighted in this journal [31], current modelling knowledge of the glycaemic effect of food is very limited. Basing the entire assessment of the effect of food on the overall carbohydrate content of the meal is a well recognised simplification of a very complex physiological process. However, data are simply not available in the literature about the glycaemic indices and absorp-

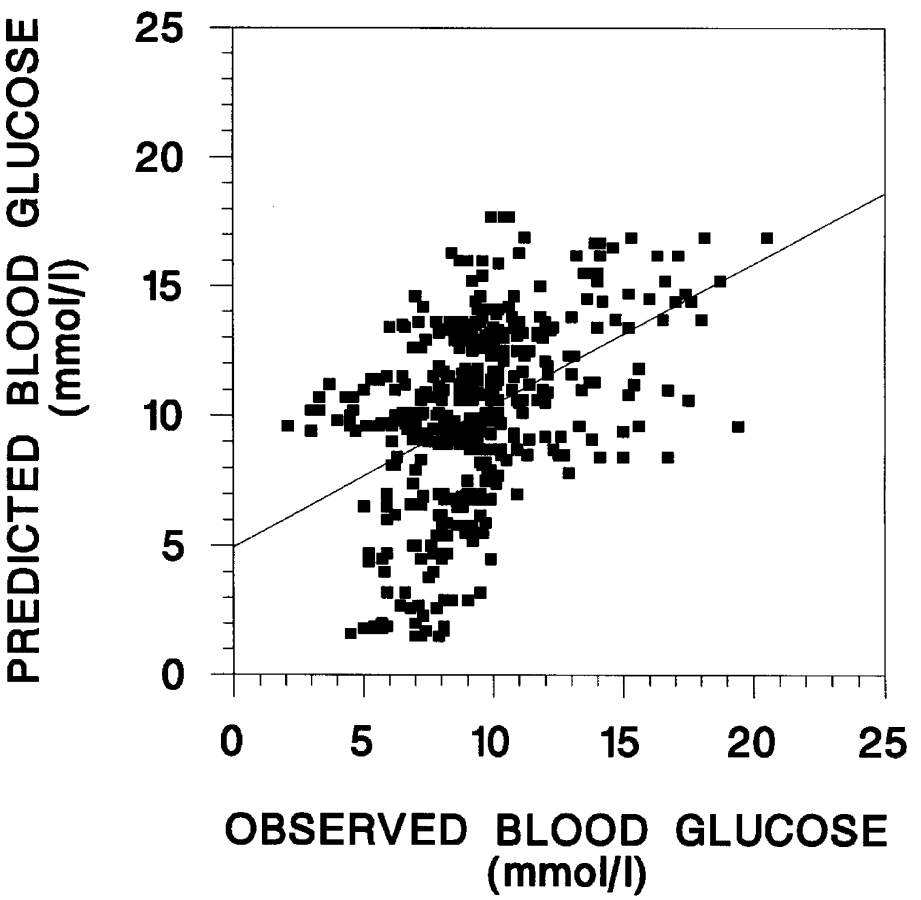

Fig. 2. Observed versus predicted blood glucose values for a compartmental model of glucose–insulin interaction in diabetes. Data from Lehmann et al. [24], from 24 insulin-dependent (type 1) diabetic patients followed up for 4–5 days. Regression line equation: $y = 4.9 + 0.55x$ ($R = 0.45$).

tion times to peak of a wide variety of foods. Furthermore, these indices on their own may not be enough. Recently Worthington [32] introduced three parameters—glycaemic value, fractional turnover rate and transport delay—for modelling the glycaemic effect of food. However, it is not clear whether the effects of multiple foods are simply additive, or more complex interactions occur.

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

Even if we described each unit process with sufficient precision a methodological problem would still persist. Hedbrant et al. [33] have suggested that in a fairly complicated system one has to accept a weak description of the whole system despite sharp descriptions of the individual components. The components (e.g. liver, pancreas, muscle or β-cells) are handled separately and described within certain confidence intervals. When these descriptions of the components are put together, the description of the overall performance turns out to be very weak, due to the merging of the confidence intervals.

We believe, however, that the major limitations of such model-based approaches come from the data collection process. Both artificially stable and hectic but unrecorded lifestyle conditions make model-based control rather illusory. To generate data for such models, in an attempt to control the clinical test environment, the volunteers or patients are often subjected to somewhat artificial conditions, such as fixed meal times and contents and limited exercise. As Chao [34] has highlighted, models developed to accurately describe such patients may suffer from circular reasoning and be incorrect for the average diabetic patient. Also, most patients are reluctant (or unable) to record all relevant lifestyle events (stress, exercise, food intake, etc.) with a consistency and precision that would be needed to build an adequate PSM.

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

The aforementioned difficulties are reasons for our opinion that such models may not be ideal vehicles for individual patient glycaemic prediction, and that the use of compartmental models is impractical for therapy planning [31].

These problems affect both short-term and longer-term control situations. When planning compensatory actions (i.e. reacting to acute hyperglycaemia) our ignorance about the initial and past conditions makes models even less helpful. Such short-term control actions (i.e. increasing the dose of a short-acting insulin) basically depend on the sequence of events that has led up to the current untoward situation. If, for example, the hyperglycaemia has resulted from a rebound effect any increase in the insulin dosage would be strongly contraindicated. Furthermore the model does not help too much in selecting what to do since the rebound phenomenon is usually not included in the model. Models are also of limited use in predicting longer-term events (i.e. planning anticipatory control actions) when the reliable description of a variety of influencing factors is missing.

The aforementioned difficulties perhaps explain why no such compartmental models have been successfully applied in routine clinical practice in diabetes care to date.

3. Algorithms

As indicated in the preceding section, compartmental models may not be ideal—being unnecessarily complicated without offering tangible rewards. If this is the case they could potentially be replaced by simpler techniques.

Table 2
Algorithms for adjusting insulin dosages using a 'split-and-mixed' insulin dosage regimen with patient home monitoring of blood glucose (BG) levels

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

Derived from Skyler et al. [36]. Scenario: hypoglycaemia (low BG) not explained by unusual diet/exercise/insulin.

Actually, optimal decisions can be selected according to some guidelines (algorithms) that contain direct instructions of what to do in different therapeutic situations. Clinical algorithms encapsulated as production rules or mathematical formulae, reflect the heuristics of the routine therapeutic strategy which attempts to lead the patient to progressively better control by suggesting stepwise changes to the dose or distribution of insulin in response to the observed patterns/problems of glycaemic control. The inference engine operates in a backward and/or forward chaining mode controlling the invocation of rules that lead to the selection of the control action(s) required.

Clinical algorithms may recommend changes to the basic insulin dosage regimen as well as to the anticipatory/supplementary insulin adjustments which may be required. For instance, increases in the basal insulin dose may be made to counteract high BG levels which exceed the target range. Adjustments may be made if either there is excess postprandial glycaemia or if the BG has not returned to an acceptable level before the next meal. To help obviate adjustments being made for random variations in BG, hyperglycaemia should be evident for at least 2 days before an incremental adjustment is made, and the patient should be sure that alterations in food intake or activity cannot explain such out-of-range BG findings [35–37].

Simple algorithms by their very nature cannot cope with situations not explicitly stated. It follows that such guidelines would contain built-in safeguards such as referral to a specialist if the situation became too complex or if unanticipated events arose. Moreover, since their reasoning is close to the way that physician experts make decisions, users can easily follow the suggestions they provide although they may disagree with the heuristics that have been adopted.

The first set of such production rules was published by Skyler et al. in 1981 [36] (Table 2). Similar algorithms have been developed and implemented by other groups and computer devices that work with either blood or urine glucose measurements for the split-mixed regimen, for continuous subcutaneous insulin infusions (pump therapy), and for various other insulin regimens have been made available commercially [38,39].

Perhaps the most widely distributed such device was the Insulin Dosage Computer (IDC) [38]. In addition to suggesting adjustments in the patient's basic insulin dosage, this program also allowed immediate control actions to be made whenever a pre-meal BG value was much higher or lower than the reference level set for that time period. The IDC was customised by setting its parameters for each patient, including the BG target and some safety parameters such as the maximum allowable insulin dose [37].

A number of clinical studies performed in the late 1980s demonstrated significant improvements in glycosylated haemoglobin (HbA_1) levels

with a reduction in the incidence of hypoglycaemia following use of the IDC [40–42]. This device, however, could not explain or justify its reasoning—either to patients or health-care professionals. This may account for its relative lack of widespread use. However, a similar conceptual approach, integrated via a telemedicine system, forms the basis of the newer HumaLink prototype [39]. While encouraging preliminary safety and efficacy results have been reported by the system developers [43], major evaluation issues do still remain to be addressed [44], and there is a very real need for independent evaluation studies of the system to be performed.

Finally, of relevance to any consideration of algorithms, will be the fact that they can be embedded in knowledge based systems in which production rules—combined with information about the dynamics of insulin action—allow reasoning also in situations not anticipated [20,44]. Such programs can also offer explanations in terms of a complete trace of steps that show how the management problem has been solved. It is also noted that like the PSM these algorithms can also be assessed and refreshed over time by analysing their performance in achieving and maintaining good glycaemic control. Such algorithms could potentially be derived automatically based on case scenarios recorded in log books using inductive rule-based learning.

4. Discussion

So where does this leave us? There remain a whole host of problems with the application of compartmental models for clinical/therapeutic use. Just some of these have been outlined above. These explain why the use of such techniques have not been supported by clinical efficacy studies.

Things obviously however do rather depend on the purpose of seeking computer-based assistance. If users require to analyse why a patient may be going hypoglycaemic overnight—or what the contribution of the glucose counter-regulatory process might be—clearly some kind of a mechanistic model is required. However, most doctors do not look to IT to help them in this way. It is rare for a competent diabetologist or endocrinologist not to know how to improve a given patient's glycaemic control. This obviously may not be the case for general primary care physicians—but to manage patients with diabetes non-specialists are unlikely to require such complex (physiological) analyses either [25]. Moreover, in practice, even detailed models lack the capability to explain what is going wrong specifically in a particular individual diabetic patient.

Model-based approaches may work reasonably in well-motivated patients with engineering/computing backgrounds. In this respect, Worthington [29] has suggested that model-based glycaemic predictions should not be compared with an 'abstract notion of perfection', but rather with the alternative which would typically preclude the patient from increased flexibility. This is a valid point since, in principle, models do enable physicians to derive statements about the patient state at time points or over intervals different from those at which measurements were made. There could, however, still be dangers inherent in relying on a model if one does not know its predictive accuracy. This is especially the case given the high level of uncertainty regarding inputs, and quite often the lack of knowledge of initial values of all variables included in the model equations. The latter becomes increasingly important when short term advice is sought. Moreover the frequency of data collection that would ideally be required for efficient use of compartmental models does not seem to be realistic for widespread routine clinical application. Furthermore it seems to be illogical estimating parameters of a mathematical model whose input variables are left unrecorded in patient log books.

We believe that if researchers wish to claim deep knowledge in their systems by applying 'physiological' models they need to demonstrate this, and evaluate their prototypes accordingly. We urge the presentation of BG data as shown in Fig. 2 so that other researchers can see for themselves the robustness of the approach being adopted. Such pooling of data and analysing

them in a combined fashion, as shown in Fig. 2, clearly does not provide the most sophisticated of analyses—however, it does offer a means of establishing the broad predictive accuracy of a model in a range of patients and situations—as would be found in routine clinical practice. In fact simple correlations are not the only way of viewing such data. Bland–Altman plots [45] provide another graphical representation, allowing systematic biases in the data to be ascertained much more easily.

Clearly if possible such analyses should only form one of a variety of tests used for assessing the performance of a model; such evaluation work not being undertaken in isolation, but rather involving objective comparisons of a range of models. Such endeavours would be greatly assisted if different models could be objectively compared, against the same datasets [31,46].

While we do not regard compartmental models as having much to offer for clinical use, (especially if similar or better overall control performance can be achieved by simpler means), it should be apparent that they do offer considerable utility as diagnostic and research tools [47,48], as well as for educational use [49,50]. In this respect, elsewhere in this journal, experience with the Internet release of an interactive educational version of the AIDA simulator is presented [51,52]. In addition to such use, compartmental models can also be applied for compiling the rule set of management guidelines and for testing the ultimate algorithms to be adopted clinically [34].

5. Conclusion

Our conclusion is not reached lightly, but rather is a considered opinion based on over 7 years of research into the application of IT in diabetes care [15,16,23,43,49–55]. Although we clearly need models of the process of the delivery of clinical care we support a data-driven approach in which specific problems trigger specific actions according to individually tailored guidelines [35].

Over a considerable period of time it has become apparent to us that algorithmic-based approaches do seem to warrant closer attention since they do offer a computational robustness and practicality which appears difficult to provide, at present, by other means. They can be published and easily reviewed by both clinicians and patients [36]. Such peer review allows their appropriateness and generalisability to be established. Custom tailored rules are also suitable for adaptive control. Furthermore by their very nature safety features can be incorporated into algorithms (provided of course the algorithms are followed), therefore offering reassurance to clinicians and patients alike.

Using management guidelines assumes that patient's problems are identified properly. Problems can be detected by direct observations, data mining and/or using autoregressive time series models that also allow potential risky situations to be identified [56]. Detecting typical daily patterns, drifts or long term cycles such as those resulting, for example, from the menstrual cycle would allow the insulin dosage to be fine-tuned according to the long-term fluctuations in the insulin demand of the patient.

We believe that avoiding false warnings and not reacting to artifacts in the data, while being able to react to hidden but clinically relevant patterns in patient BG data, constitutes one of the major challenges for IT in diabetes management. In the coming years we expect that complex compartmental models will be used increasingly solely for research and educational ventures, with algorithmic-based approaches being applied more-and-more for clinical use. In this respect we should emphasise that these comments apply specifically to compartmental models, as opposed to more general model-based approaches.

Any approach for achieving glycaemic control needs to rely on some kind of model to provide a framework. However, the depth of this model should correspond to the level of our understanding of what is going on and the quantity and quality of data that are available as guides for control actions. In this respect, while we recognise the broader need for mod-

els, we suggest that the complexity of any models used should closely match the control situations being faced in everyday clinical practice. Fortunately for educational use, the application of models is much more straight-forward, as they can provide deeper insight into the processes underlying the observed behaviour.

With regard to algorithms, once medico-legal issues have been fully addressed, we would expect to see increasingly comprehensive algorithms applied within home monitoring BG meters. Even in their current form algorithmic-based supervisory 'watchdog' functions could be envisaged.

Clearly randomised controlled clinical trials will be required, together with other evaluation efforts, before algorithmic-based approaches—like any other clinical technique—can be widely adopted into routine medical practice. However, we expect that the prospect of intermittent human review of home monitoring BG data by means of ground-based and mobile telemedicine systems, as well as possibly via the Internet, will at least address some of the current concerns about algorithms—making them able to explain their reasoning, report what they are doing and how they work, and justify why they are doing so.

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