A physiological model of glucose–insulin interaction in type 1 diabetes mellitus

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ABSTRACT

A clinical model of glucose–insulin interaction in insulin-dependent diabetes mellitus has been developed for patient and medical staff education. The model attempts to reflect the underlying (patho)physiology of insulin action and carbohydrate absorption in quantitative terms such as insulin sensitivity, volume of glucose and insulin distribution and maximal rate of gastric emptying. The model's predictions also allow a 24 h simulation of patient blood glucose profiles to be generated. A description of the model is provided and its operation illustrated by clinical case studies of insulin-treated diabetic patients. The possible use of the model as a tool for automated insulin dosage adjustment is explored.

Keywords: Computer simulation, physiological model, type 1 diabetes mellitus, insulin dosage adjustment

INTRODUCTION

Diabetes mellitus is a major chronic disease in industrialized countries. It affects 3% of the population of Europe and approximately 100 million people worldwide. While the incidence of the disease is currently on the increase in western society, the incidence and severity of the later life complications which accompany it can be considerably reduced if the diabetic patient receives effective treatment leading to good glycaemic control. In general such treatment attempts to achieve normoglycaemia by maintaining a careful balance between diet, physical activity and insulin therapy. However, education of the diabetic patient to achieve this balance requires a level of clinical expertise which, although present in specialized diabetes units and some general practices with an interest in diabetes, is not always to be found in other sectors of the health service. One way of making this clinical expertise more widely available is to use information technology.

A number of computer-based approaches to aid in the treatment or long-term management of diabetic patients have been previously reported in the literature. These include knowledge-based systems to advise on patient management in out-patient clinics, computer algorithms for insulin dosage adjustment and mathematical models for predicting or simulating patient blood glucose levels.

Berger and Rodbard have developed a computer program for the simulation of insulin and glucose dynamics following the subcutaneous injection of insulin. Their program incorporates a pharmacokinetic model of insulin action to calculate the time course of plasma and ‘active’ insulin for various combinations of popular insulin preparations. With the use of a pharmacodynamic glucose model to describe the dependence of glucose dynamics on plasma insulin and glucose levels, their program can also predict the expected time course of plasma glucose in response to a change in insulin dose, timing or regimen. However, their system has not been designed for individual patient parameterization and simulation.

Numerous other stand-alone mathematical models of the glucoregulatory system in insulin-dependent (type 1) diabetes mellitus exist. We have, however, developed a physiological model of glucose–insulin interaction for patient and medical staff education about insulin-dependent diabetes as part of a more complex diabetes data management system. The integration of the model into this complex system is described elsewhere in this journal in a separate paper by Lehmann and Deutsch.

The model developed, in part, draws on Berger and Rodbard’s pharmacokinetic model of insulin action which has been implemented in conjunction with a new model of glucose pharmacodynamics based on experimental data from the literature. The model can provide a suitable framework to characterize individual diabetic patients quantitatively and predict the blood glucose profile which is expected to be produced by an adjustment in the diet and/or insulin dosage regimen. This new model attempts to provide an anatomically explicit basis for patient education about insulin-dependent diabetes as part of a more complex diabetes data management system. The integration of the model into this complex system is described elsewhere in this journal in a separate paper by Lehmann and Deutsch.

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simulations, with different functions for different organs within the body. The model potentially has application as a tool for automated insulin dosage adjustment based on home blood glucose monitoring data. Clinical case studies will be presented and the possible use of the model as a vehicle for automated insulin dosage adjustment will be explored.

MODEL DESCRIPTION

The glycaemic response of an insulin-treated diabetic patient goes through transitory steady-state glucose bases leading to a new steady-state glycaemic profile following a change in the insulin regimen or diet. The purpose of our model is to simulate these steady-state glycaemic and plasma insulin responses independently of the initial values from which the simulation is started.

Figure 1 shows the anatomical basis of the model which assumes a patient completely lacking endogenous insulin secretion. It contains a single glucose pool representing extracellular glucose (including blood glucose) into which glucose enters via both intestinal absorption and hepatic glucose production.

Glucose is removed from this space by insulin-independent glucose utilization in red blood cells (RBCs) and the central nervous system (CNS) as well as by insulin-dependent glucose utilization in the liver and periphery; the latter taking place mostly in muscle and adipose tissue. Hepatic and peripheral handling of glucose in the model are dealt with separately. Glucose excretion takes place above the renal threshold of glucose as a function of the creatinine clearance (glomerular filtration) rate.

By separating the hepatic and peripheral handling of glucose in the model it is possible to assign different patient-specific insulin sensitivity parameters to glucose–insulin interactions in the liver and periphery. As shown schematically in Figure 1, peripheral glucose uptake takes place as a function of both insulin and plasma glucose levels; the former enhancing glucose uptake according to the peripheral insulin sensitivity parameter, $S_p$, which has a normalized value between 0 and 1. $S_p$ multiplied by the insulin level gives the effective insulin level responsible for the control action.

As the liver both produces and utilizes glucose
depending on the blood glucose and insulin levels, we have modelled hepatic glucose handling in terms of the 'net hepatic glucose balance' which is computed as the sum of gluconeogenesis, glycogen breakdown and glycogen synthesis data derived for different blood glucose and insulin levels from nomograms given in Guyton et al. 21. This representation of hepatic glucose handling was chosen in order to avoid the use of non-physiologically based mathematical functions to describe hepatic function. 7,11,12,15. Table 1 shows how the net hepatic glucose balance varies as a function of glucose and normalized insulin levels. Sp, the hepatic insulin sensitivity parameter, which also has a normalized value between 0 and 1, allows computation of the effective insulin level which controls hepatic glucose handling.

The net hepatic glucose balance for any arterial blood glucose level between 1.1 mmol l⁻¹ and 4.4 mmol l⁻¹ is computed by interpolation between the values shown on the curves in Figure 1. Capillary blood glucose values measured using home monitoring blood glucose meters are approximately 25% lower than the arterial blood glucose levels which are given in Guyton et al. 21. Hence, in our model we use the capillary blood glucose levels which correspond to the arterial blood glucose data given in Table 1.

The data shown in Table 1 are based on the steady-state plasma insulin level which is normalized with respect to a basal level, \( I_{\text{basal}} \). Note that for low blood glucose values there is an automatic compensatory increase in hepatic glucose production (positive balance) and at high blood glucose levels the net action of the liver is to take up glucose from the blood (negative balance).

Glucose enters the portal circulation via first-order absorption from the gut. The rate of gastric emptying which provides the glucose flux into the small intestine in the model is assumed to be controlled by a complex process maintaining a relatively constant glucose supply to the gut during carbohydrate absorption apart from the ascending and descending phases of the gastric emptying process.

The duration of the period in which glucose entry from the stomach into the duodenum is constant and maximal has been defined as a function of the carbohydrate content of the meal ingested. Thus the time course of the systemic appearance of glucose is described by either a trapezoidal or a triangular function depending on the quantity of carbohydrate in the meal.

The function of the kidneys to excrete glucose has been modelled in terms of two patient-specific model parameters: the renal threshold of glucose and the creatinine clearance (glomerular filtration) rate.

The model contains separate compartments for plasma and 'active' insulin. Insulin is removed from the former by hepatic degradation while the latter is responsible for glycaemic control. The activation and deactivation of insulin are assumed to obey first-order kinetics. The only insulin input into the model comes from the absorption site following subcutaneous injection.

### MODEL EQUATIONS

Four differential equations along with twelve auxiliary relations and the experimental data from Guyton et al. 21 constitute the model which is solved by numerical integration. The change in the plasma insulin concentration, \( I \), is given by the following equation:

\[
\frac{dI}{dt} = I_{\text{abs}} - k_e \cdot I
\]

where \( k_e \) is the first-order rate constant of insulin elimination, \( I_{\text{abs}} \) is the rate of insulin absorption and \( V_i \) is the volume of insulin distribution. The build-up and the deactivation of the 'active' insulin pool, \( I_a \), is assumed to obey first-order kinetics:

\[
\frac{dI_a}{dt} = k_1 \cdot I - k_2 \cdot I_a
\]

where \( k_1 \) and \( k_2 \) are first-order rate constants which serve to describe the delay in insulin action. The rate of insulin absorption is modelled according to Berger and Rodbard:

\[
I_{\text{abs}}(t) = s \cdot \frac{t \cdot T_{50} \cdot D}{t(T_{50} + t)^2}
\]

where \( t \) is the time elapsed from the injection, \( T_{50} \) is the time at which 50% of the dose, \( D \), has been absorbed and \( s \) is a preparation-specific parameter defining the insulin absorption pattern of the different types of insulin catered for in the model (regular, intermediate, lente and ultralente).

A linear dependency of \( T_{50} \) on dose is defined as:

\[
T_{50} = a \cdot D + b
\]

where \( a \) and \( b \) are preparation-specific parameters, the values of which are given in Berger and Rodbard along with values for \( s \). If the insulin regimen consists of more than one injection and/or components, \( I_{\text{abs}} \) becomes the sum of the individual \( I_{\text{abs}} \) contributions resulting from the different multicomponent injections.

The steady-state insulin profile, \( I_{ss} \), corresponding to a given regimen, is computed by using the superposition principle assuming three days to be enough to reach steady-state conditions:

\[
I_{ss}(t) = I(t) + I(t + 24) + I(t + 48)
\]

\[
I_{ss}(t) = I(t) + I(t + 24) + I(t + 48)
\]

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### Table 1 Net hepatic glucose balance (mmol h⁻¹) as a function of the arterial blood glucose level, \( AG \), and plasma insulin level, \( I \), calculated from Guyton et al. 21. \( S_p \) is a patient-specific hepatic insulin sensitivity parameter which has a normalized value between 0 and 1.

<table>
<thead>
<tr>
<th>Effective plasma insulin (( S_p ), ( I_{\text{basal}} ))</th>
<th>( AG = 1.1 ) mmol l⁻¹</th>
<th>( AG = 3.3 ) mmol l⁻¹</th>
<th>( AG = 4.4 ) mmol l⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>291.6</td>
<td>160.0</td>
<td>78.3</td>
</tr>
<tr>
<td>1</td>
<td>194.6</td>
<td>114.6</td>
<td>53.3</td>
</tr>
<tr>
<td>2</td>
<td>129.3</td>
<td>66.0</td>
<td>-1.7</td>
</tr>
<tr>
<td>3</td>
<td>95.7</td>
<td>46.5</td>
<td>-54.3</td>
</tr>
<tr>
<td>4</td>
<td>85.9</td>
<td>-22.0</td>
<td>-76.0</td>
</tr>
<tr>
<td>5</td>
<td>76.3</td>
<td>4.3</td>
<td>-85.0</td>
</tr>
<tr>
<td>6</td>
<td>60.0</td>
<td>-10.0</td>
<td>-92.0</td>
</tr>
<tr>
<td>7</td>
<td>62.0</td>
<td>-25.3</td>
<td>-97.3</td>
</tr>
<tr>
<td>8</td>
<td>52.0</td>
<td>-43.3</td>
<td>-101.0</td>
</tr>
<tr>
<td>9</td>
<td>48.0</td>
<td>-47.3</td>
<td>-104.0</td>
</tr>
<tr>
<td>10</td>
<td>41.7</td>
<td>-49.3</td>
<td>-106.7</td>
</tr>
</tbody>
</table>
i.e. the steady-state response results from the composite effect of injections given for three subsequent days. It is evident that this summation is not needed for regular insulin preparations (e.g. actrapid) but it should be used for other, longer acting, insulin preparations whose half time of absorption is higher, especially when larger doses are given.

Since the experimental data provided by Guyton et al.\textsuperscript{21} refer to equilibrium conditions, the insulin level equilibrated with the steady-state active insulin is considered when computing the net hepatic glucose balance and peripheral glucose uptake. In other words, at any time during the simulation, we have steady-state $I_{s}(t)$ and $I_{eq}(t)$ values, but use:

$$I_{eq}(t) = k_{2} \cdot I_{eq}(t)/k_{1}$$

(6)
as the insulin level responsible for the hepatic and peripheral control action, where $I_{eq}(t)$ is the insulin level in equilibrium with $I_{eq}(t)$.

Assuming a single compartment for extracellular glucose, the change in glucose concentration with time is given by the differential equation:

$$\frac{dG}{dt} = G_{in}(t) + N \cdot G_{out}(t) - G_{out}(t) - G_{in}(t) - G_{ren}(t)$$

(7)

where $G$ is the plasma glucose level, $G_{in}$ is the systemic appearance of glucose via glucose absorption from the gut, $G_{out}$ is the overall rate of peripheral and insulin-independent glucose utilization, $N \cdot G_{out}$ is the net hepatic glucose balance, $G_{ren}$ is the rate of renal glucose excretion and $V_{G}$ is the volume of distribution for glucose.

Assuming a classical Michaelis-Menten relationship between glucose utilization and the plasma glucose concentration, with a constant $K_{m}$ such that insulin concentration is reflected in different values of the maximal rate of the transport process, we can write:\cite{20}

$$G_{out}(G, I_{eq}) = \frac{G \cdot c \cdot S_{p} \cdot I_{eq} + G_{1}(K_{m} + G)}{G_{X} \cdot (K_{m} + G)}$$

(8)

where $c$ is the slope of the peripheral glucose utilization versus insulin level relationship, $G_{1}$ is the insulin-independent glucose utilization and $G_{X}$ is a reference glucose level. The amount of glucose in the gut, $G_{gut}$, following the ingestion of a meal containing $Ch$ millimoles of glucose equivalent carbohydrate is defined as:

$$G_{gut}(t) = \int_{0}^{t} k_{gabs} \cdot G_{gut}$$

(9)

where $k_{gabs}$ is the rate constant of glucose absorption from the gut into the systemic circulation and $G_{gut}$ is the rate of gastric emptying which is shown as a function of time in Figure 2a. The duration of the period $T_{maxge}$ for which gastric emptying is constant and maximal ($V_{maxge}$) is a function of the carbohydrate content of the meal ingested:

$$T_{maxge} = (Ch - \frac{1}{2} V_{maxge} \cdot 2(T_{ascge} + T_{desge})/V_{maxge}$$

(10)

where $V_{maxge}$ is the maximal rate of gastric emptying and $T_{ascge}$ and $T_{desge}$ are the respective lengths of the ascending and descending branches of the gastric emptying curve which have default values in the model of 30 min (0.5 h) (Figure 2a).

However, for small quantities of carbohydrate (below approximately 10 g) such values cannot be used because there will never be time for the gastric emptying curve to plateau out. In such cases $T_{ascge}$ and $T_{desge}$ are defined as:

$$T_{ascge} = T_{desge} = 2 Ch / V_{maxge}$$

(11)
giving a triangular function as shown in Figure 2b. Equation (11) is only used when the quantity of carbohydrate ingested falls below a critical level ($Ch_{crit}$) which is defined as:

$$Ch_{crit} = [(T_{ascge} + T_{desge}) V_{maxge}]/2$$

(12)

Using linear interpolation the rate of gastric emptying for meals containing $Ch$ millimoles of carbohydrate greater than $Ch_{crit}$ can therefore be defined, according to the time elapsed from the start of the meal, $t$, as follows:

$$G_{empt} = \begin{cases} V_{maxge} / T_{ascge} & t \leq T_{ascge} \\ V_{maxge} & T_{ascge} < t \leq T_{ascge} + T_{maxge} \\ V_{maxge} - (V_{maxge} / T_{desge}) & (t < T_{ascge} - T_{maxge}) \\ 0 & \text{elsewhere} \end{cases}$$

(13a)

$$G_{empt} = V_{maxge}, T_{ascge} < t \leq T_{ascge} + T_{maxge}$$

(13b)

$$G_{empt} = V_{maxge} - (V_{maxge} / T_{desge}) (t < T_{ascge} - T_{maxge})$$

(13c)

$$G_{empt} = 0; \text{elsewhere}$$

(13d)
When implementing the system for computer simulation separately. This characteristic of the model is utilized to compute absorption profiles for any meal can be computed as a function of $G$ and $P_{in}$. This means that the plasma glucose level, a library of plasma insulin profiles and 'active' insulin levels can be computed a priori for any dose (currently less than 40 units) and preparation of insulin (regular, intermediate, lente and ultralente). This computation assumes that insulin absorption and elimination are not patient specific, apart from the reference insulin level following any meal with carbohydrate intake during meals, the systemic appearance curves of glucose following any meal with a carbohydrate content between 0–60 g can be computed a priori and stored for use as appropriate during the simulation. The storage is made for 6 h at 15 min intervals.

Since patients completely lacking endogenous insulin secretion the plasma insulin level following subcutaneous injection does not depend on the blood glucose level, a library of plasma insulin profiles and 'active' insulin levels are stored for 1 day (24 h) at 15 min intervals.

Simulations are carried out over a 2 day (48 h) period using first-order Euler integration with a 15 min step size. The second day's blood glucose and plasma insulin profiles are assumed to represent steady-state profiles as responses to the current insulin therapy and diet plan. These profiles are displayed on the computer screen as the results of the simulation.

A parameter estimation routine has been implemented whereby values for $S_p$ and $S_n$ which give the best 'fit' between the observed and predicted data are automatically determined. The fit is assessed for any combination of $S_p$ and $S_n$ in the range of 0 to 1 using a step size of 0.1 for both parameters. In the present form of the model these two parameters are used to make the model patient-specific. This is in addition to the patient's body weight, renal threshold of glucose and creatinine clearance rate which can be assessed independently in the clinic.

In determining the fit hypoglycaemic episodes are assigned a blood glucose value of 1.0 mmol l$^{-1}$. Fit is assessed using modified least-squares criteria to calculate the difference between the two data sets at the observed time points. Parameter values for which there is a conflict of trends between the observed and predicted data in any time period are assigned a blood glucose value of 1.0 mmol l$^{-1}$. For example if the observed data shows a marked decrease in a given period while there is an increase in the simulated glycaemic profile in the same period, a penalty score is assigned apriori. Simulations are carried out over a 2 day (48 h) period using first-order Euler integration with a 15 min step size. The second day's blood glucose and plasma insulin profiles are assumed to represent steady-state profiles as responses to the current insulin therapy and diet plan. These profiles are displayed on the computer screen as the results of the simulation.

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An insulin dosage optimization routine has also been implemented whereby different qualitative therapeutic strategies can be automatically selected by the system depending on the deficiencies in the blood glucose control observed. Minimization of the total amount of daily insulin injected is the overall objective of the optimization algorithm which tries to find the simplest change in the insulin regimen required to achieve normoglycaemia. As such the default strategy is to 'decrease insulin' but an alternative strategy to 'increase insulin' has also been provided for

### COMPUTER IMPLEMENTATION

As the only exogenous source of glucose in the model is carbohydrate intake during meals, the systemic appearance curves of glucose following any meal with a carbohydrate content between 0–60 g can be computed a priori and stored for use as appropriate during the simulation. The storage is made for 6 h at 15 min intervals.

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### Table 2: Patient-independent model parameter values calculated from Berger and Rodbard and Guyton et al.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k_e$</td>
<td>5.4 h$^{-1}$</td>
<td>Insulin elimination rate constant</td>
</tr>
<tr>
<td>$k_i$</td>
<td>0.025 h$^{-1}$</td>
<td>Parameter for insulin pharmacodynamics</td>
</tr>
<tr>
<td>$k_a$</td>
<td>1.25 h$^{-1}$</td>
<td>Parameter for insulin pharmacodynamics</td>
</tr>
<tr>
<td>$k_{basal}$</td>
<td>10 mU l$^{-1}$</td>
<td>Reference basal level of insulin</td>
</tr>
<tr>
<td>$K_m$</td>
<td>10 mmol l$^{-1}$</td>
<td>Michaelis constant for enzyme-mediated glucose uptake</td>
</tr>
<tr>
<td>$G_{in}$</td>
<td>0.54 mmol h$^{-1}$ kg$^{-1}$</td>
<td>Insulin-independent glucose utilization per kg body weight</td>
</tr>
<tr>
<td>$G_N$</td>
<td>5.3 nmol l$^{-1}$</td>
<td>Reference value for glucose utilization</td>
</tr>
<tr>
<td>$c$</td>
<td>0.015 mmol h$^{-1}$ kg$^{-1}$ m$^{-1}$ U$^{-1}$</td>
<td>Slope of peripheral glucose utilization versus insulin line</td>
</tr>
<tr>
<td>$k_{gabs}$</td>
<td>1 h$^{-1}$</td>
<td>Rate constant for glucose absorption from the gut</td>
</tr>
<tr>
<td>$V_{max, a}$</td>
<td>190 mmol h$^{-1}$</td>
<td>Maximal rate of gastric emptying</td>
</tr>
<tr>
<td>$V_{f}$</td>
<td>0.142 kg$^{-1}$</td>
<td>Volume of distribution for insulin per kg body weight</td>
</tr>
<tr>
<td>$V_{C}$</td>
<td>0.221 kg$^{-1}$</td>
<td>Volume of distribution for glucose per kg body weight</td>
</tr>
</tbody>
</table>

Glucose input via the gut wall, $G_{in}$, can be modelled by:

$$G_{in} = k_{gabs} \cdot G_{gut}$$

(14)

Values for these model parameters, which have been derived from Berger and Rodbard and Guyton et al. are given in Table 2. All parameters except $S_p$ and $S_n$ are assumed to be patient independent.

The rate of renal glucose excretion, $G_{ren}$ in the model is defined as:

$$G_{ren} = GFR(G - RTG); \text{ if } G > RTG$$

(15a)

$$G_{ren} = 0; \text{ elsewhere}$$

(15b)

for blood glucose values ($G$) above the renal threshold of glucose ($RTG$) where $GFR$ is the glomerular filtration (creatinine clearance) rate. Default parameter values in the model have been set for $RTG$ and $GFR$ at 9.0 mmol l$^{-1}$ and 100 ml min$^{-1}$ respectively. These default values are used for all patient cases except where renal dysfunction is suspected and the clinical parameters are actually measured. As shown in Figure 1, the renal excretion of glucose ($G_{ren}$) is zero for blood glucose values below the renal threshold of glucose (Equation [15b]).

It is noted that the insulin and glucose parts of the model are only linked by equation (8) and when computing the net hepatic glucose balance as a function of $G$ and $P_{in}$. This means that the plasma and 'active' insulin profiles as well as the glucose absorption profiles for any meal can be computed separately. This characteristic of the model is utilized when implementing the system for computer simulations.
cases of persistent hyperglycaemia. Strategies to 'decrease regular insulin' and 'decrease longer acting insulin' have also been implemented to cater for cases when hypoglycaemic episodes occur — the exact strategy chosen being dependent on the timing of the 'hypo' in relation to the preceding insulin injection.

The current system runs under DOS on an IBM PC or compatible. A multitasking version is also available for 80386 based machines running Windows 3.0. This allows the display of multiple windows showing different parts of the system in operation. For example, the data entry screens can be displayed in one window with the results of a simulation in a second and patient-specific model parameters in a third. The number of windows displayed at any one time is wholly dependent on the memory capabilities of the machine being used.

All code for the model and connected data processing has been implemented in Turbo Pascal (Borland International, v.5.5). The current implementation, running on an IBM PS/2 Model 70 386 at 25 MHz with an Intel 80387 numerical co-processor, takes less than 1 s to perform a simulation, less than 25 s to perform parameter estimation and less than 20 s to perform insulin dosage optimization. On a 25 MHz IBM PS/2 Model 95 486 insulin dosage optimization and parameter estimation both take less than 10 s to perform. This speed is, to a great extent, achieved by precomputing and storing the plasma insulin levels following subcutaneous insulin injection and the systemic appearance curves for glucose following a meal.

**CLINICAL EXAMPLES**

**Figure 3** shows the front end used for accessing the model. The upper panel displays the observed (measured) blood glucose readings recorded by a 70 kg male, insulin-dependent diabetic patient on a three times daily insulin injection regimen using home blood glucose monitoring equipment. The blood glucose data displayed can either be readings from a single day or the averaged glycaemic profile computed from a number of days' data. The averaging process used to generate such 'modal' day blood glucose profiles has been previously described elsewhere[6]. The lower panel of the screen represents a composite display of information regarding insulin and carbohydrate intake as well as hypoglycaemic reactions. The distribution of bread equivalent units (10 g carbohydrate) can be seen as can the three times daily actrapid and NPH injections that the patient was prescribed.

**Figure 3a** shows the screen display while parameter estimation is in progress. Given the insulin and carbohydrate intake shown in the lower panel, the system performs simulations at 10% increments of the values of both $S_h$ and $S_p$. As such the light grey area on the graph, made up in this case from 95 separate simulations, constitutes the 'search space' for the parameter estimation routine.

In the example shown in **Figure 3a** a penalty score (x.x) has been assigned to the fit for parameter values of $S_h$ and $S_p$ of 0.5 and 1.0 respectively, because in the period between supper and bedtime there was a clear increase in the observed blood glucose level (from 5.3 mmol l$^{-1}$ to 9.3 mmol l$^{-1}$); however, in the corresponding period the simulator predicted a clear decrease in the blood glucose level (from 6.5 mmol l$^{-1}$ to 5.0 mmol l$^{-1}$ for the same parameter values). Such conflict in the trends means that the predicted curve does not match the observed data closely enough.

**Figure 3b** shows the best traditional least-squares fit, obtained by the parameter estimation routine, which also closely matches the trends in the observed data. The curve shows the predicted blood glucose profile for the patient's carbohydrate and insulin intake shown in the lower panel in **Figure 3a**. The mean deviation between observed and computed values was 1.0 mmol l$^{-1}$ for hepatic and peripheral insulin sensitivities of 0.6 and 0.3 respectively.
A clock function has been implemented to permit closer inspection of the simulated data. This allows two cursors to be moved along the blood glucose and plasma insulin profiles, and for the predicted values of each variable to be read off the curves at relevant time points. This function is particularly useful for assessing the maximum and minimum blood glucose levels at different times during the day.

*Figure 3c* demonstrates the use of the model as an educational tool where the glycaemic effect of missing a morning injection is simulated for this patient. The hyperglycaemia which would result is predicted to reach a maximum of 16.8 mmol l\(^{-1}\) at 13:30 h.

Another clinical example of the use of the model is given in *Figure 4a* which shows graphically data collected by a 22-year-old, female, insulin-treated diabetic patient who was receiving twice daily NPH injections. As the patient was overweight (75 kg) she had been placed by a dietitian on a restricted diet (60 g carbohydrate per day) to lose weight. *Figure 4a* shows the predicted blood glucose and plasma insulin levels for this patient's current treatment regimen after parameter estimation was performed. The mean deviation between observed and predicted blood glucose values was 0.8 mmol l\(^{-1}\) for hepatic and peripheral insulin sensitivity parameters of 0.2.

Using these parameter values insulin dosage optimization has been performed as shown in progress in *Figure 4b*. For this a target therapeutic range has been defined (from 4 to 10 mmol l\(^{-1}\)) and the system has determined that the guiding strategy to reach this target range should be to 'increase insulin'. This strategy was chosen because no 'hypos' occurred during the day and the overall blood glucose profile was raised, with an observed maximum blood glucose value of 10.6 mmol l\(^{-1}\) at 21:30 h and a predicted maximum of 11.9 mmol l\(^{-1}\) at 9:45 h (*Figure 4a*).

The guiding strategy is implemented within the overall strategy of the optimization algorithm which is the minimization of the total amount of daily insulin. This is achieved, as shown in *Figure 4c*, by increasing the 18:00 h and 8:00 h insulin by 10 and 15 units of NPH respectively. Having implemented this change the simulated blood glucose profile now gives a predicted maximum of 9.9 mmol l\(^{-1}\) at 10:00 h with a predicted minimum of 4.2 mmol l\(^{-1}\) overnight; blood glucose values which would be totally acceptable to a clinician.

**DISCUSSION**

The model presented here focuses on the adjustment of insulin and/or diet in the insulin-treated diabetic patient. In contrast to previously developed heuristic rule-based expert systems and linear models for insulin dosage or dietary adjustment\(^{16, 20}\) this model can be interpreted in physiological terms and is therefore more readily understandable to a clinician; the anatomical basis of the model further aiding its interpretation by providing explicit functions for different organs within the body.

In developing the model we have followed the principles usually associated with the minimal-model approach, to find a concise mathematical formulation to represent the major physiological systems with the fewest possible parameters. As such the model has intentionally been kept simple. For example we have not, at present, attempted to model the role of ketones in the fasting type 1 diabetic patient, nor have we tried to model the change in the renal threshold of glucose which takes place with age. Other complicating factors, such as glucose transporters, which help mediate insulin-independent glucose utilization in certain muscle beds within the body, have not been modelled. With increasing complexity the number of
parameters for the model increases and so do the difficulties of determining their values for individual patients.

We do not believe that a set of differential equations with individually tailored parameters can be used to model all patients in any conditions. However, as we have shown, such an approach does appear to work in a strictly defined domain for some patients. The proportion of patients for which this approach can be applied has not, as yet, been evaluated. However, we feel that it is important for the computer to be able to recognize those patients for whom model fitting cannot be performed with sufficient precision and by implication those patients for whom the model cannot be used. If this is not possible we believe that the model will lose credibility with clinicians and only be useful as an educational tool.

Determination of clinical parameters is a key requirement for the use of the system with individual patient data. We have developed a parameter estimation approach which not only minimizes the least-squares difference between observed and predicted data sets but also assesses the direction of change in the data. In this way it is possible for the computer to reject parameter values for which there is a good ‘traditional fit’ as assessed by least-squares criteria, but clearly contradictory trends in the observed and simulated data. If no parameter values satisfy both criteria then the computer informs the clinician that the model cannot be fitted to the patient’s data. Such a situation might occur, for example, if an attempt is made to fit the model to data where rebound hyperglycaemia follows a hypoglycaemic episode.

Further testing of the model is required to determine whether it is suitable for individual patient parameterization which is a key requirement for clinical use. Depending on the proportion of patients for which the model can be used further refinements might be appropriate. However, the system in its current form clearly has a role as an educational tool separate from its potential role as a patient simulator.

In this respect it provides both a pharmacodynamic and physiological basis with which to plan therapeutic strategies for insulin-dependent diabetic patients. The model is currently undergoing testing at St Thomas’ Hospital, London.

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