

A CLINICAL MODEL OF GLUCOSE-INSULIN INTERACTION

E.D. Lehmann¹ and T. Deutsch^{2,3}

¹Department of Endocrinology and Chemical Pathology, UMDS St. Thomas' Hospital, London, U.K. ²Computer Centre, Semmelweis University, Budapest, Hungary. ³MIM Centre, Department of Systems Science, City University, London.

ABSTRACT

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

INTRODUCTION

Diabetes mellitus is a major chronic disease in industrialised countries. It affects 3% of the population of Europe and approximately one hundred million people worldwide. It is a disorder which results from under production or reduced action of the hormone insulin and is characterised by high blood glucose levels. It is a lifelong condition which has a variety of debilitating and life-threatening complications. These include retinopathy, nephropathy and peripheral neuropathy as well as the more acute problems of hypoglycaemic and hyperglycaemic coma.

While the incidence of diabetes mellitus 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 control¹. In general such treatment attempts to achieve normoglycaemia by maintaining a careful balance between diet, physical activity and

¹ Correspondence to: E.D. Lehmann, EURODIABETA Office, Rm 124 (5NW), Department of Endocrinology and Chemical Pathology, United Medical and Dental Schools, St. Thomas's Hospital, Lambeth Palace Road, London SE1 7EH, U.K.

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insulin therapy. However, education of the diabetic patient to achieve this balance requires a level of clinical expertise which although present in specialised diabetes centres, 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^{2,3}.

OVERVIEW OF THE MODEL

The purpose of the model is to simulate steady state glycaemic and plasma insulin responses to a given insulin therapy and dietary regimen. In this way the problems of selecting appropriate initial values from which to start the simulation are overcome and the second day's response is taken as being representative of the current insulin therapy and diet plan. The structure of the model is summarised below in Figure 1.

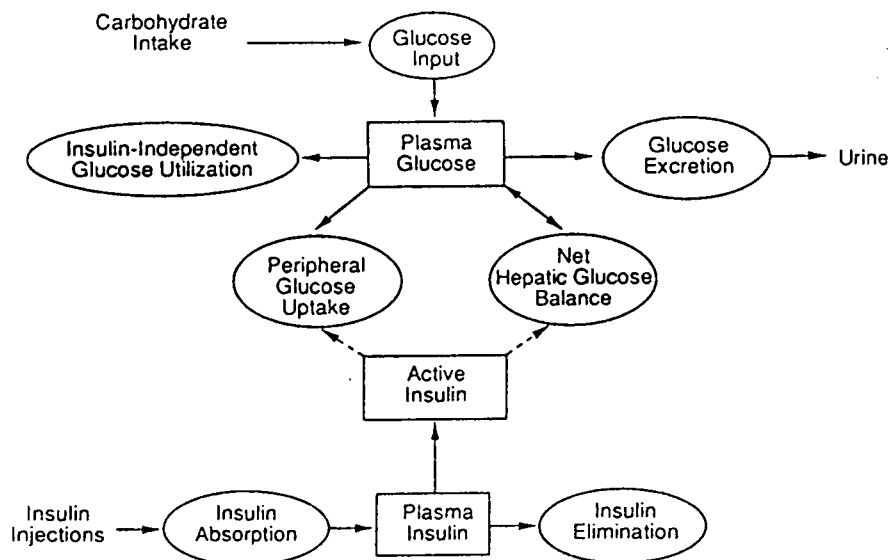


Figure 1. Structure of the model

GLUCOSE MODEL

The model 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 utilisation in red blood cells, the central nervous system and

viscera as well as by insulin-dependent glucose utilisation in the liver and periphery. Glucose excretion from the model takes place above the renal threshold of glucose as a function of creatinine clearance.

Hepatic and peripheral handling of glucose in the model are dealt with separately. The net hepatic glucose balance being positive (glucose production) or negative (glucose utilisation) depending on the blood glucose and insulin levels. The relationships are given in the form of nomograms by Guyton *et al*⁴ as shown schematically in Figure 2a. Note for low blood glucose values the automatic compensatory increase in hepatic glucose production.

As shown schematically in Figure 2b, peripheral glucose uptake occurs as a function of both insulin and blood glucose levels. Insulin affects the net hepatic glucose balance characterized by a liver sensitivity parameter, S_h , as well as enhancing peripheral glucose utilisation described by a peripheral sensitivity parameter, S_p .

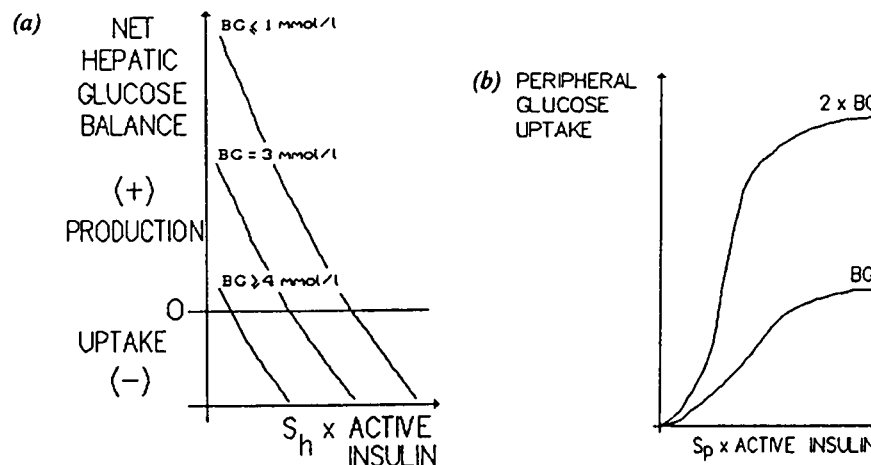


Figure 2. Schematics showing how (a) the net hepatic glucose balance and (b) the peripheral glucose uptake both vary as a function of blood glucose (BG) and active insulin. S_h and S_p are a patient specific sensitivity parameters for liver and periphery which have normalised values between 0 and 1.

The rate of gastric emptying 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 length of these periods depends on the composition of the food ingested. 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 triangular function depending on the quantity of carbohydrate in the meal. For meals of less than 10g of carbohydrate a triangular function is used, while above 10g a trapezoidal function is applied, as shown in Figure 3a. Figure 3b shows how the function of the kidney is modelled in terms of the renal threshold of glucose and creatinine clearance.

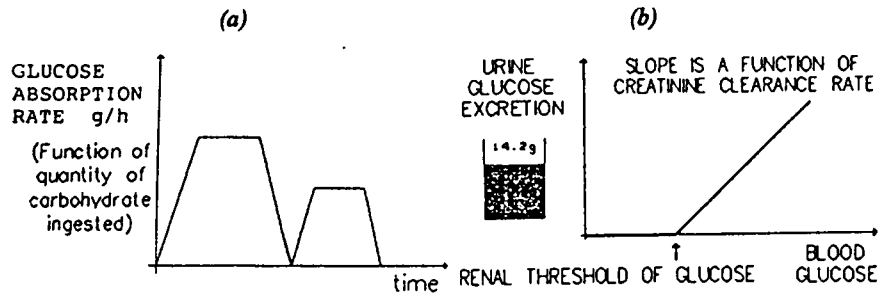


Figure 3. Schematics showing (a) the systemic appearance of glucose with time and (b) the excretion of glucose by the kidneys above the renal threshold; the degree of glycosuria being a function of the creatinine clearance rate.

INSULIN MODEL

The model assumes a patient completely lacking endogenous insulin secretion. Thus, the only insulin input into the model comes from the absorption site following subcutaneous injection. The pharmacokinetics of insulin absorption in this model have been derived from a recent description of that process by Berger & Rodbard⁵, the individual's weight being used as a patient specific model parameter for calculating the volume of insulin distribution as well as the regression coefficients of the insulin-level vs peripheral glucose utilisation relationship (Figure 2b). The model contains separate compartments for plasma and 'active' insulin, the latter being responsible for glycaemic control while insulin is removed from the former by hepatic degradation as shown schematically in Figure 4a.

We found the Berger-Rodbard model⁵ of insulin kinetics to be suitable for modelling the delay in insulin action:

$$dI_a/dt = k_1 I - k_2 I_a \quad [1]$$

where I and I_a represent plasma and active insulin levels respectively, and k_1 and k_2 are rate constants which serve to describe the delay in action of insulin (Figure 4b). If we integrate equations describing insulin kinetics for 3 days, we get the response following any dose of insulin, $I(t)$ and $I_a(t)$. We are interested, however,

in modelling the steady state insulin response. We computed this by using the superposition principle of linear systems:

$$I_{ss}(t) = I(t) + I(t+24) + I(t+48) \quad [2]$$

$$I_{ass}(t) = I_a(t) + I_a(t+24) + I_a(t+48) \quad [3]$$

i.e. the steady state response resulting from the composite effect of injections given for three subsequent days. It is evident that this summation is not needed for regular (actrapid) preparations 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*⁴ refers to steady state 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 $I_{ss}(t)$ and $I_{ass}(t)$ values, but use:

$$I^*(t) = k_2 I_a / k_1 \quad [4]$$

as the insulin level responsible for the control action, where $I^*(t)$ is the insulin level in equilibrium with $I_a(t)$. Peripheral glucose utilisation is then computed according to Berger & Rodbard⁵ taking the I^* plasma insulin levels into consideration. The actions of different insulin preparations are illustrated overleaf in Figure 5.

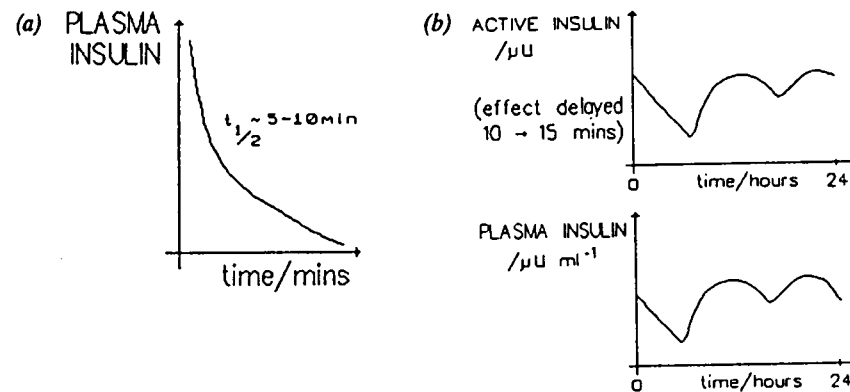


Figure 4. Schematics showing (a) the insulin degradation function used and (b) the delay in insulin action obtained by using 'active' insulin (calculated from Berger & Rodbard⁵).

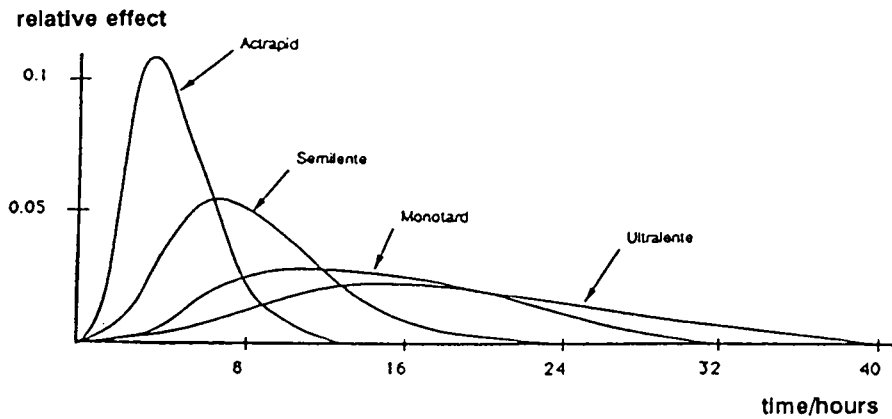


Figure 5. Insulin profiles (modified from Hovorka et al⁶).

THE SYSTEM IN PRACTICE

In order to speed up the integration of the system, the insulin and glucose parts of the model have been separated, as shown in Figure 1. As the only exogenous source of glucose in the model is carbohydrate intake during meals, the systemic appearance curves for glucose following any meal with a carbohydrate content between 0-60g can be computed *a priori* and stored for use as appropriate during the simulation. The storage is made for 6 hours at 15 minute intervals. Assuming a complete lack of endogenous insulin secretion, the plasma insulin level following subcutaneous injection does not depend on the blood glucose level, and as such can also be computed and prestored prior to integrating the glucose part of the system. By doing so, a library of plasma insulin profiles and 'active insulin' levels can be computed for any dose (currently less than 40 units) and preparation of insulin (regular, NPH, lente and ultralente). This computation assumes that insulin absorption and elimination are not patient specific, apart from the volume of insulin distribution which is a function of the patient's body weight. The steady state plasma and active insulin levels are stored for 1 day (24 hours) at 15 minute intervals. Simulations are carried out over a 2 day (48 hour) period using first order Euler integration with a 15 minute step size. The second day's blood glucose and plasma insulin profiles are theoretical steady state profiles and as such are displayed on the computer screen as the results of the simulation.

A parameter estimation routine has been implemented whereby values for S_b and S_p which give the best 'fit' between the observed and predicted data are automatically determined. Fit is assessed using a modified least squares criteria to calculate the difference between the two data sets at the observed time points. In determining the fit hypoglycaemic episodes are assigned a blood glucose value of

1.5 mmol/l. Parameter values for which there is a conflict of trends between the observed and predicted data are assigned a very poor fit by using a 'penalty' score for such cases.

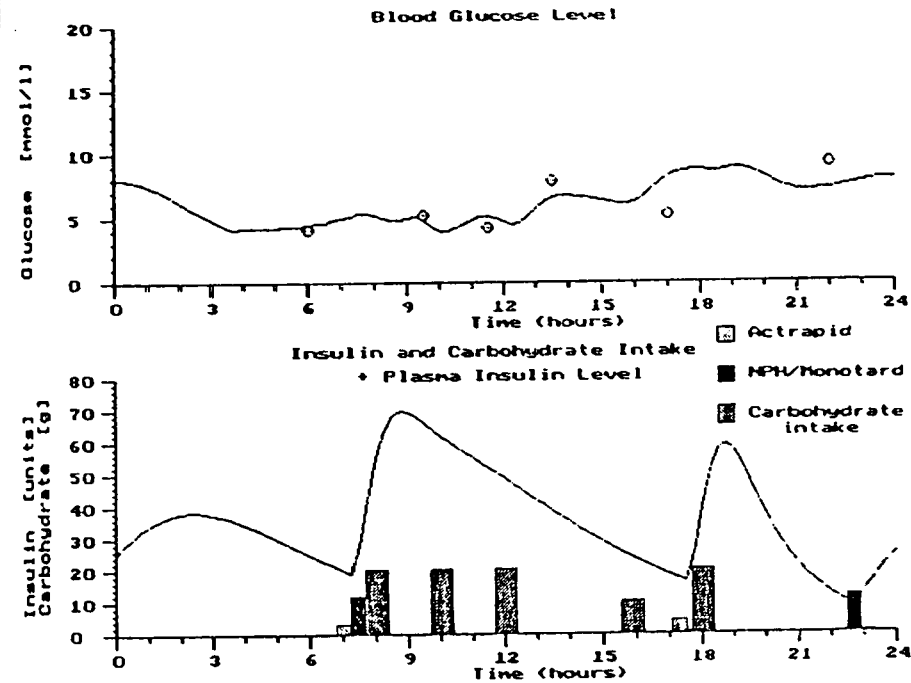


Figure 6. Front end display showing the results of a simulation. Upper panel: observed (e) and predicted blood glucose levels. Lower panel: Insulin and carbohydrate intake with predicted plasma insulin curve.

An insulin dosage optimisation routine has also been implemented whereby different qualitative therapeutic strategies can be automatically selected by the system depending on the quality of blood glucose control observed. Minimisation of the total amount of daily insulin injected is the overall objective of the optimisation 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 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.

Figure 6 shows the front end used for accessing the model. The upper panel displays the observed (measured) blood glucose readings recorded by a patient 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 elsewhere⁷. 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 (10g carbohydrate) can be seen as can the three times daily actrapid and NPH injections that the patient was prescribed. Superimposed on these graphs is a 24 hour simulation after fitting was performed. The lower curve shows the predicted plasma insulin level for the insulin injection regimen while the upper curve shows the predicted blood glucose profile for the patient's carbohydrate and insulin intake. The mean deviation between observed and computed values was 1.0 mmol/l for hepatic and peripheral insulin sensitivities of 0.6 and 0.3 respectively.

A more comprehensive clinical example of the use of the model is given overleaf in Figure 7 which shows graphically data from a 60kg, female, insulin-treated diabetic patient. The corresponding numerical data is given for comparison in Table 1. Once again the distribution of bread equivalents can be seen in the lower panel which also shows the four times daily actrapid and NPH injections that the patient was prescribed. As before we have superimposed a 24 hour simulation after fitting was performed. The overall fit obtained was 1.6 mmol/l for hepatic and peripheral insulin sensitivities of 0.6 and 1.0 respectively.

The following day the patient's insulin was adjusted by her doctor; being decreased by one unit of actrapid in the morning and increased by 2 units of NPH at lunchtime. This data is also shown numerically in Table 1 with the changes highlighted. Using the previously determined insulin sensitivity parameters ($S_h = 0.6$ and $S_p = 1.0$) a 24 hour simulation has been performed. Figure 8 shows blood glucose data for the day *after* the insulin regimen changes were made (i.e. day 3) with the predicted curve superimposed. The mean deviation between observed and predicted values was 2.0 mmol/l.

As can be seen from Figure 8 using previously estimated parameter values for this patient it has been possible to use the model to produce a reasonable simulation. Taking this a stage further it might be possible to plan therapeutic adjustments in this patients' insulin dosage regimen on the basis of predictions from the model. However, this would obviously require the validity of the model to be formerly assessed as part of a rigorous medical validation.

The system currently 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 machine⁸. All code for the model and connected data processing has been implemented in PASCAL.

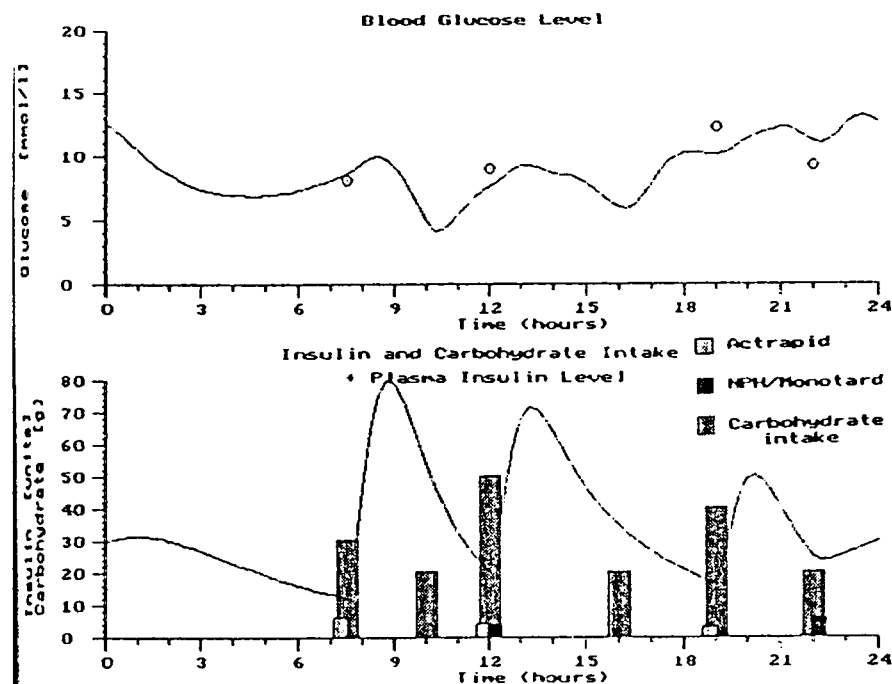


Figure 7. Results of a simulation for a 60kg, female, insulin-treated diabetic patient after parameter estimation has been performed.

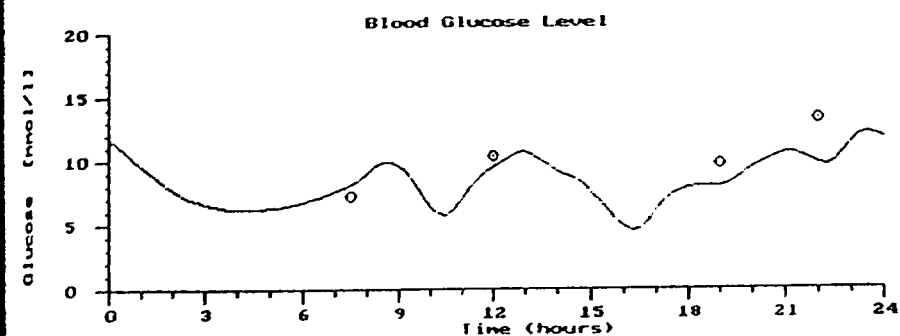


Figure 8. Predicted glycaemic levels compared with observed blood glucose measurements the day after changes were made to the patient's insulin regimen.

Clinical data	Time	Value (day 1)	Value (day 3)	Change
breakfast	07:30	30g	30g	no change
mid-morning snack	10:00	20g	20g	
lunch	12:00	50g	50g	
afternoon snack	16:00	20g	20g	
supper	19:00	40g	40g	
bedtime snack	22:00	20g	20g	
actrapid injection	07:30	6 units	5 units	
actrapid injection	12:00	4 units	4 units	+2 units
NPH injection	12:00	4 units	6 units	
actrapid injection	19:00	3 units	3 units	
NPH injection	22:00	6 units	6 units	
blood glucose	07:30	8.1 mM	7.3 mM	new values
blood glucose	12:00	9.0 mM	10.4 mM	
blood glucose	19:00	12.2 mM	9.8 mM	
blood glucose	22:00	9.2 mM	13.3 mM	

Table 1. Clinical data for a 60kg, female, diabetic patient before (Figure 7) and one day after (Figure 8) changes were made to her insulin regimen.

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 for insulin dosage or dietary adjustment⁷⁻¹⁰ this model can be interpreted in physiological terms and is therefore more readily understandable to a clinician. In developing this 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.

We do not believe that a human being can simply be modelled by a series of differential equations. 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 recognise those patients for whom parameter estimation cannot be performed 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 education 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 minimises 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. There are certain other clinical situations in which the model will not work. However, such 'limitations' are present in the use of *all* compartmental physiological models and are not specific to this system.

Further testing of the model is required to determine whether it is suitable for individual patient parameterisation which is a key requirement for clinical use. However the system clearly has a use 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-treated diabetic patients. The model is currently undergoing testing at St. Thomas's Hospital, London.

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