

A PHYSIOLOGICAL MODEL OF GLUCOSE-INSULIN INTERACTION

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ABSTRACT

A physiological 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. An overview of the model is presented and its operation illustrated by a case study from a 24 year old insulin-treated diabetic patient.

INTRODUCTION

Diabetes mellitus is a major chronic disease in industrialised countries. 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 control [1]. 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 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 IT.

OVERVIEW OF THE MODEL

The purpose of the model is to simulate steady state responses to a given insulin therapy and dietary regime. In this way the problems of selecting appropriate initial values from which to start the simulation are overcome.

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 as a function of the creatinine clearance rate.

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 & Rodbard [2], 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 v's peripheral glucose utilisation relationship. The model contains separate compartments for plasma and 'active' insulin, the latter being responsible for control while insulin is removed from the former by hepatic degradation. 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* [3] as shown schematically in Figure 1. 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 .

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.

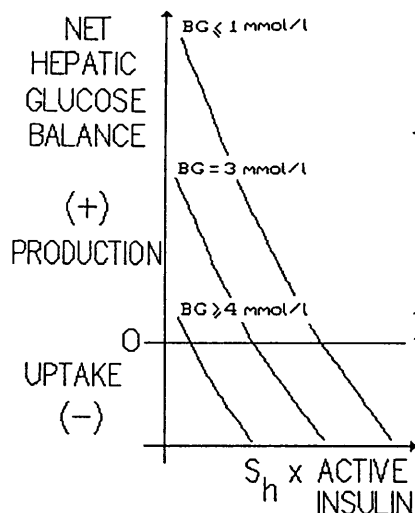


Figure 1. Schematic showing how the net hepatic glucose balance in the model varies as a function of both blood glucose (BG) and active insulin. Note for low blood glucose values the automatic compensatory increase in hepatic glucose production. S_h is a patient specific liver sensitivity parameter which has a normalised value between 0 and 1.

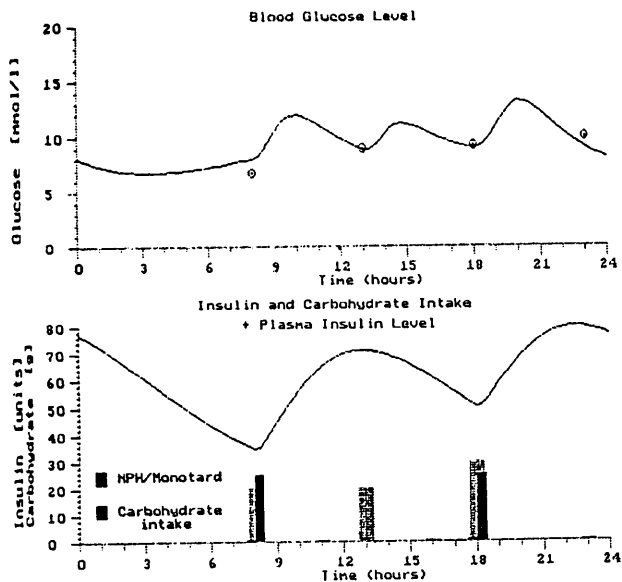


Figure 2. Front end display showing the results of a simulation. Upper panel: observed (o) and predicted blood glucose levels. Lower panel: Insulin (25 units NPH morning and evening) and carbohydrate intake with predicted plasma insulin curve.

THE SYSTEM IN PRACTICE

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 least squares criteria to calculate the difference between the two datasets 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.

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 2 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 elsewhere [4]. The lower panel of the screen represents a composite display of information regarding insulin and carbohydrate intake as well as hypoglycaemic reactions.

The 24 year old, female, diabetic patient who collected the data shown in Figure 2 was overweight (75kg) and had been placed by a dietician on a restricted diet to lose weight (70g carbohydrate per day). The distribution of bread equivalent units (10g carbohydrate) can be seen in the lower panel which also shows the twice daily NPH injection regimen 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 twice daily NPH injection regimen while the upper curve shows the predicted blood glucose profile for the patient's carbohydrate and insulin intake. The fit obtained was 0.8 mmol/l for hepatic and peripheral insulin sensitivities of 0.2.

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

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 adjustment [4] 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 pharmacological systems with the fewest possible parameters. As such the model has intentionally been kept simple.

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 model 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.

ACKNOWLEDGEMENTS

This work was supported by a grant from the EEC AIM (Advanced Informatics in Medicine) Exploratory Action [EURODIABETA Project No. A1019]. Computer equipment was provided by IBM.

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