GLUCOSIM: A SIMULATOR FOR EDUCATION ON THE DYNAMICS OF *DIABETES MELLITUS*

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Abstract- **Glucose-insulin interactions in healthy and insulin-dependent diabetic humans are simulated using an overall and a detailed model based on pharmacokinetic diagrams of insulin and glucose. Both models are capable of predicting blood glucose and insulin levels, total glucose uptake and renal glucose excretion. The simulator is integrated with a graphical user interface to provide a user-friendly environment for performing virtual experiments with various characteristics, diet and exercise conditions.**

***Keywords*: Diabetes, glucose-insulin dynamics, simulation**

I. INTRODUCTION

Virtual experiments, simulation experiments with the mathematical model of a system, are valuable tools for student education. The possibility of self paced learning by experimenting with virtual simulated systems opens new horizons [1]. This is especially important in understanding biological systems that display complex dynamic behavior. This work focuses on developing a simulator to study dynamic variations in glucose and insulin in human body.

Several organs, hormones and enzyme systems are involved in the regulation of the blood glucose levels in humans. Insulin, a hormone secreted by pancreatic beta cells, is the most important hormone in the regulation of blood glucose levels. It influences the rates of glucose utilization by the tissues and regulates its storage as fuel, helping to keep blood glucose concentrations within a narrow range of about 80-120 mg/dl.

Diabetes is often described as a disease of carbohydrate metabolism, characterized by elevated blood sugar [2]. Because of destroyed beta cells or insulin insensitivity, the body cannot use the blood glucose for energy. Statisticians list diabetes among the top 10 causes of death in the USA. It affects 5% of the population and the number of diabetic patients is increasing at a rate of about 6% a year [3]. There are two main types of diabetes mellitus: insulin-dependent (IDDM) and noninsulin-dependent (NIDDM). In IDDM, the pancreatic beta cells are destroyed therefore there is none or little insulin available. Subcutaneous insulin injections, diet and exercise are essential in the treatment, therefore reduce the frequency of diabetic complications. In NIDDM, the insulin is not effective. It may be controlled by diet, exercise and sometimes oral medications.

Modeling the glucose-insulin interaction requires an understanding of the physiological and metabolic processes that determine the observable behavior. Chemical reactions and transport processes form an integrated network when modeling the glucose-insulin interaction in human body. Mathematical models of insulin-dependent (type-I) diabetes mellitus have been reported in the literature [4] [5] [6] [7]. We have extended and utilized two mathematical models [4] based on pharmacokinetic diagrams of glucose and insulin (Figures 1,2) which represent the transport of glucose and insulin through the major vessels to the capillaries.

The glucose diagram (Fig. 1) contains tissues including heart, brain, liver, kidney and muscle where glucose is used for energy. Glucose excretion by kidney and gastrointestinal tract where exogenous glucose enters the blood, are also included. The diagram for insulin (Fig. 2) includes subcutaneous tissue as a source for insulin. It is assumed that the pancreas of a diabetic patient does not produce any insulin. Removal and degradation of insulin occurs mostly in liver, kidney and peripheral tissue. They degrade one-half, one-third and one-sixth, respectively, of the insulin presented to them, regardless of the plasma concentration of insulin. Changes in blood flow would change these fractions, but the model flows are constant [8]. Mass balances for the coupled glucose and insulin models yield a set of simultaneous ordinary differential equations.

II. MODEL

The detailed model is a flow-limited model for diabetes mellitus based on the work of Puckett [4]. A mass balance equation is written for each compartment in the model. The compartments represent actual body regions (Table I). The advantage of this type of modeling is that the model design is based on an understanding of the physiology and simulations that can yield insight into the physiological processes [8]. The main disadvantage of these models is that the personal variations in physiological parameters are not taken into account. Therefore, the outputs are average values thus, the simulator should be used for only educational purposes rather than providing medical advice. For a typical organ

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Abstract

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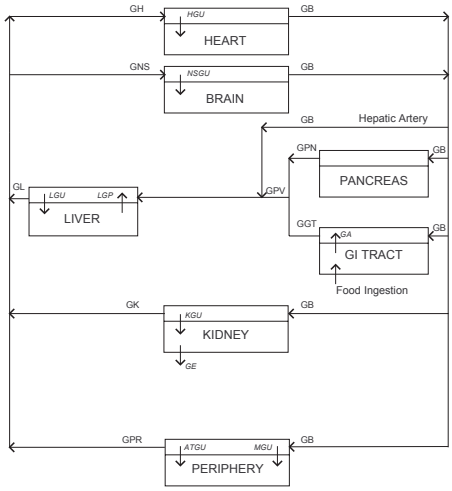

Figure 1. Pharmacokinetic Diagram of Glucose

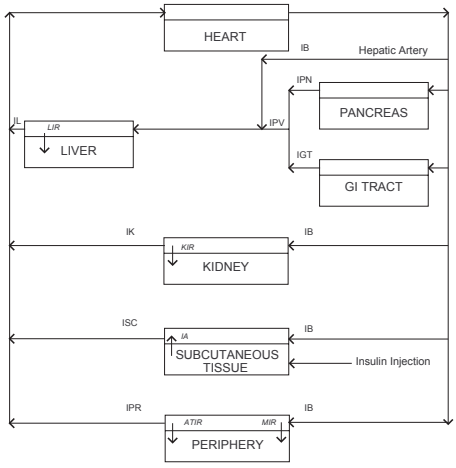

Figure 2. Pharmacokinetic Diagram of Insulin

such as liver, mass balances for glucose (G_L) and insulin (I_L) concentrations are

$$\frac{dG_L}{dt} = \frac{1}{V_L}(Q_{HA}G_B + Q_{PV}G_{PV} - Q_L G_L - LGU + LGP) \quad (1)$$

$$\frac{dI_L}{dt} = \frac{1}{V_L}(Q_{HA}I_B + Q_{PV}I_{PV} - Q_L I_L - LIR) \quad (2)$$

where, LGP is liver glucose production rate, LGU is liver glucose utilization rate, LIR is liver insulin removal rate, Q_L is liver volumetric flow rate, and V_L is the effective volume in liver. Other organs are modeled similarly using rate expressions available in the literature (Table I).

TABLE I. Effective Volumes and Rates

Insulin Model Parameters		
Organ or Tissue	Vascular Flow Rate (l/min)	Vascular Volume (l)
Brain	0.42	0.25
Heart and Lungs	3.12	0.98
Liver	0.9	0.54
Gut	0.72	0.43
Kidney	0.72	0.41
Periphery	1.08	0.75
Hepatic Artery	0.18	-
Glucose Model Parameters		
Organ or Tissue	Vascular Flow Rate (l/min)	Vascular Volume (l)
Brain	0.59	0.35
Heart and Lungs	4.37	1.38
Liver	1.26	0.76
Gut	1.01	0.6
Kidney	1.01	0.57
Periphery	1.51	1.04
Hepatic Artery	0.25	-
Organ	Rate	Reference
Liver	Glucose Uptake and Production	[9]
	Insulin Removal	[8]
Gut	Glucose Absorption	[10]
Brain	Glucose Uptake	[9]
Kidney	Glucose Excretion	[8]
	Glucose Uptake	[9]
	Insulin Removal	[4]
Heart	Glucose Uptake	[3]
Muscle	Glucose Uptake	[9]
	Insulin Removal	[4]
Subcutaneous Tissue	Insulin Transport	[4]

In the overall model, it is assumed that changes in blood glucose and insulin concentrations for each tissue are fast and the balances are in quasi-steady state shortly after a disturbance (i.e. the carbohydrate intake). The resulting algebraic equations are incorporated in the glucose and insulin balances in the blood, yielding an overall model with two differential equations. In the detailed model all differential equations are preserved and it is possible to see the changes in glucose and insulin concentrations in individual tissues before reaching quasi-steady state. Both models are capable of simulating the observed behavior of blood glucose and insulin levels for a diabetic patient. Fig. 3 represents the simulation results of these models for glucose absorption, total glucose uptake and liver glucose production rates.

III. CASE STUDIES

To test the simulation capabilities of the detailed model, blood glucose and insulin concentrations of a 70 kg diabetic patient is simulated over a 24-hour period of time for repetitive food intake. Regular insulin is injected 30 min prior to each meal. Table II displays the medication schedule and a case where the patient misses the third insulin injection.

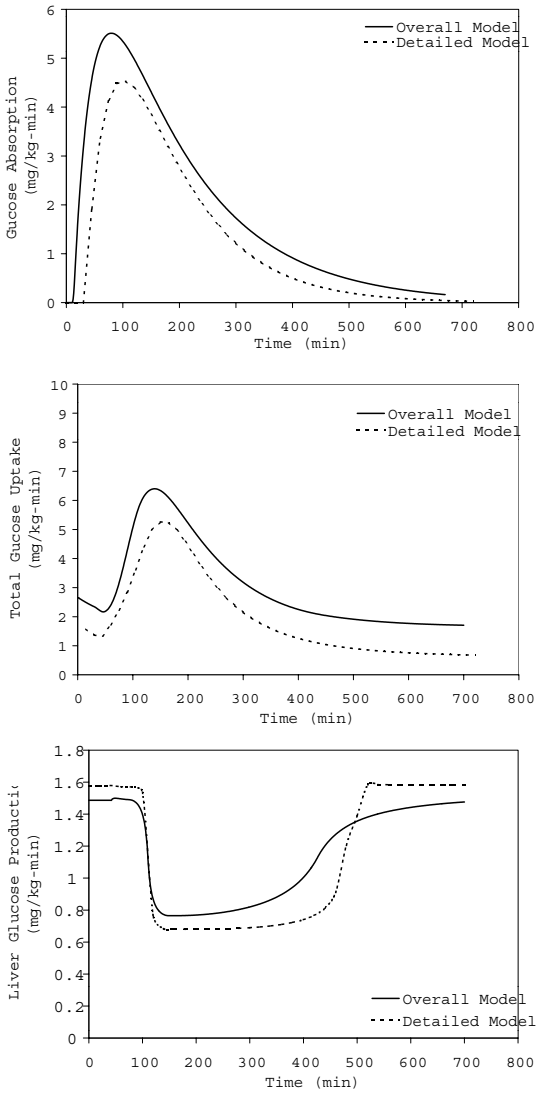

Figure 3. Time Course of (a) Glucose Absorption Rate, (b) Total Glucose Uptake Rate, (c) Liver Glucose Production Rate

TABLE II. Case Studies

Medication Schedule				
Time (hr)	08:30	11:30	16:30	21:50
CHOM (mg/kg)	1000	950	1100	750
Insulin Units	11	12	13	7.5
Case I				
Time (hr)	08:30	11:30	16:30	21:50
CHOM (mg/kg)	1000	950	1100	750
Insulin Units	11	12		7.5

Figures 4a and 4b show the response of a patient under regular medication schedule. Blood glucose level is within the acceptable limits. The vertical solid lines indicate the carbohydrate content of the meal and the amount of injected insulin, respectively. When one injection is missed, the blood glucose level overshoots until the fourth injection which brings it back to its acceptable range (Fig. 5b).

IV. GRAPHICAL USER INTERFACE

A MATLAB based user-friendly graphical user interface (GUI) was designed and integrated with the MATLAB code written for the mathematical model. The £rst window offers three options, a “Help” button, an “Information” button and a “Start Simulation” button. They introduce the capabilities of the simulator, provide some background information on diabetes, and start the simulation respectively. After choosing the “start simulation” button, three options are given to the user: oral glucose tolerance test, a healthy person and a diabetic patient.

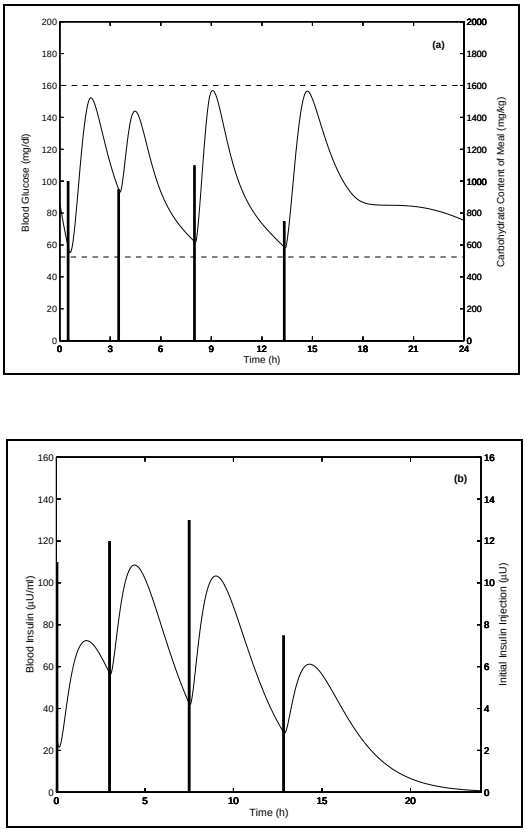

Figure 4. (a) Blood Glucose and Carbohydrate Content of the Meal (b) Blood Insulin and Insulin Injection for a Patient Under Medication Schedule

The second window is designed to provide the user flexibility in assigning different values to input variables

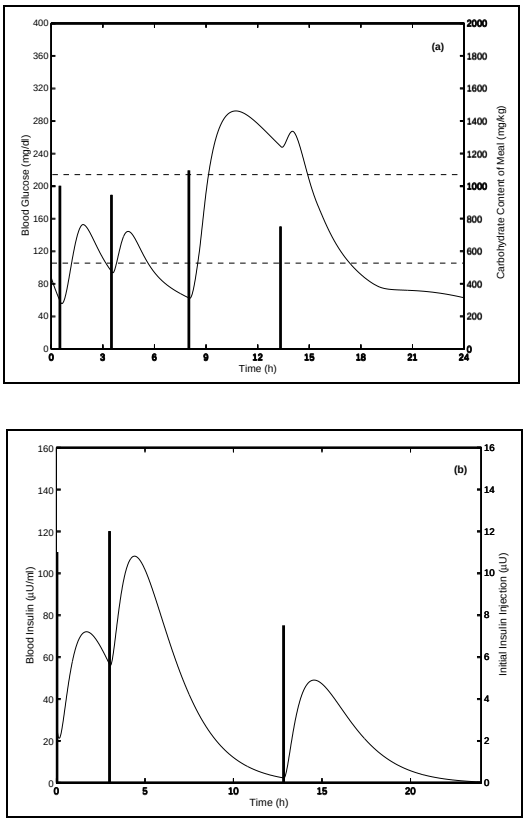

Figure 5. (a) Blood Glucose and Carbohydrate Content of the Meal (b) Blood Insulin and Insulin Injection for Case I

such as insulin dosage for a diabetic patient, and to observe the effects of the daily exercise and carbohydrate intake on glucose and insulin pro£les. Default values are given in Fig. 6 for a diabetic patient. From the nutritional database window for the carbohydrate content of various nutrients, the user can choose different combinations of food to examine their effects. Simulation results are found to be in good agreement with literature [4].

V. CONCLUSIONS

A simulator is developed to make virtual experiments that show the effects of changes in food intake and therapy on glucose levels in insulin-dependent diabetes mellitus.

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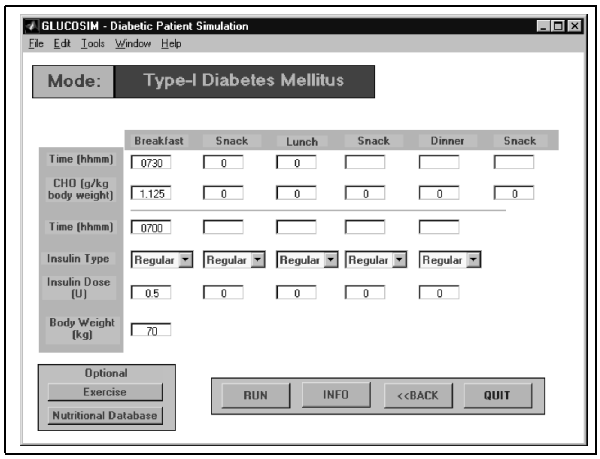

Figure 6. Simulation Window

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