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MATHEMATICAL MODELING OF BLOOD GLUCOSE METABOLISM AND THE ARTIFICIAL PANCREAS DEVELOPMENT

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Abstract. *Mathematical modelling constitutes an important step in the implementation of a cloded-loop blood (plasma) glucose control system (artificial pancreas). The endocrine-metabolic system related to the level of blood glucose is highly complex, involving several intermediate processes of production, storage and use of substrata (as the glucose, the glycogen or the glucose-6-phosphate) and hormones (as the insulin, the glucagon and the adrenaline). In this context, mathematical models can be used for non accessible parameters estimation , as well as for simulation and analysis of control algorithms performance. In this work, the role of mathematical modelling as a fundamental part on the development of an artificial pancreas is discussed. Based on the current literature, a physiologic model (with 9 compartments) relative to the whole body is presented and simulated. The resulting model intends to describe the interactions between substrata and hormones in the portal circulation as well as in the sistemic circulation and includes some important extensions from the clinical point of view, as the explicit dependance on the patient's diet, a submodel for the glucose absorption for the gastrointestinal tract and the consideration of physical activity and exhibition to stress. Finally, its potential applications are presented.*
Key words: *Glicemic Control, Artificial Pancreas, Mathematical Modelling.*

1. INTRODUCTION

Everyday, when people feed, they supply the body with a series of nutrients, which are responsible for the maintenance of internal balance. This balance is only possible when starting from a group of organic chemical processes that makes possible the cellular life, through the production of energy for the several physiologic systems, a process called metabolism. Due to the fact that all cells need fuel for permanent energy production, the ability to store and to release nutrients in a regulated way is essential for health and life. Basically, four main nutrient fuels exist: glucose, glycogen, proteins and fats. Each type of fuel nutrient has a different role in the energy balance of the human body. The endocrine factors that control the metabolism of each nutrient are physiologically optimized by complex control systems.

In this context, the carbohidrates metabolism is of relevant importance. In the daily feeding, three carboidrate sources exist: the starch (available in almost all the victuals), the

lactose (available in milk) and the sucrose (available in sugar-cane). In the intestine, these three types of sugars suffer the action of enzymes, and they are transformed mainly in glucose (in very smaller proportion, galactose and frutose are also produced). Then, glucose is oxided easily by all cells to produce energy (ATP) and this is the only fuel nutrient for most of the neural cells. The glycogen, other important fuel nutrient (a highly polimerized glucose) is stored as crystalline deposits in the liver and in the skeletal musculature. This way, glucose can be considered the main fuel nutrient.

The balance in the level of blood glucose is essential for good health. Such level is physiologically maintained inside a narrow strip (± 10 to 20% of the normal value, around 100 mg/dl of blood) even in case of great variations in the ingestion of victuals and metabolic use. If this level falls below about 30 mg/dl of plasma, the cerebral function is harmed severely, and death can happen. On the other hand, the increase of rate of blood glucose above the limit of physiologic control is associated in general to a serious pathology of the endocrine-metabolic system refered to the glucose metabolism: the diabetes mellitus.

The diabetes mellitus is a pathology associated to the change of carboidrate metabolism characterized by the total inadequacy (diabetes type 1) or partial inadequacy (diabetes type 2) of insulin secretion. It is also associated to the outlying resistance to the action of the hormone. The insulin is the main hormone responsible for regulation of the glucose concentration in the blood and is secreted by B cells of the Islets of Langerhans, located in the endocrine portion of the pancreas.

The diabetes is considered a problem of public health nowadays, being the third death cause according to the World Organization of Health, behind cardiovascular problems and cancer (ADJ, 1997). In this context, added the fact of complicated diseases diabetes can cause, the importance of the study of this problem becomes evident, under the medical or the bioengineering points of view. The objective of the researches carried nowadays is to provide an artificial solution for the individual insulin deficiency, which remains incurable. As a multidisciplinar problem of difficult solution, the accomplishment of an artificial pancreas depends on several technologies that constitute real challenges (as the availability of a reliable, non-invasive glucose sensor, for measurements in real time). In this context, control engineering plays an important role, as important as the other areas, and the achievement of optimized algorithms that can be appropriately applied to this problem constitutes a field of intense research.

Historically, the studies on control of blood glucose levels (from a bioengineering point of view) start at the end of the 60's and beginning of the 70's, when some important works have been published in the area of mathematical modelling of biomedical systems (Ackerman and Gatewood, 1969) as well as in preliminary definition of an artificial pancreas (Pagurek et al., 1972 ; Spencer, 1978), leading to the first tentatives on the reproduction of natural control of insulin secretion for the pancreas. Since that time, researches have been developed trying to contemplate the different scientific and technological aspects involved in the closed-loop control, as biosensores according to invasive or non-invasive techniques (Horgan, 1985 ; Duncan et al., 1985), insulin pumps getting smaller all the time and even body implantable (Dario et al., 1996), medical quality materials, and finally control algorithms that have intrinsec characteristics according to the complexity of the physiological control (Trajanowski & Wach, 1996 ; Worthington, 1997) .

In this paper, the importance of the mathematical modelling is emphasized under two points of view: as a basic tool for analysis and scientific research and also as a fundamental step for design of an optimized control system, since one has to consider the several particularities involved in the blood glucose dynamics.

In the sequence, the differences between a physiological simulator model and a simpler control model that includes individual patient informations are presented. Then, basic

concepts involved in modelling the glicemic control physiological system are breafly described. Finally, an extension of the dynamic model of Finkelstein & Carson (1986) is presented, where important details from the clinical and conceptual points of view are considered. In this sense, the proposed model includes the patient's diet, a submodel for the glucose absorption in the gastrointestinal tract and the influences of physical activity and exhibition to stress in hormones and plasma glucose. Simulation results for two typical conditions are presented. In conclusion, the model potential for future applications is evaluated.

2. MATHEMATICAL MODELS AND THE ARTIFICIAL PANCREAS.

Generally speaking, mathematical models are necessary for several reasons in physiologic systems (Ackerman & Gatewood, 1969): isomorfic representation, experimental data reduction, classification of diagnoses, tests of hypotheses and project of experiments. The first objective constitutes an important step from the theoretical point of view since any attempt for system simulation must incorporate the whole available knowledge. Main dynamic aspects must be clearly identified, so that the generated insights allow the optimization of experimental procedures, as well as additional hypotheses that make model reduction possible. Given this, other objectives should allow the experimental validation of reduced models.

A good model may also be used for pathology diagnosis through the analysis of parameters changes (for instance, sensibility to the insulin or intolerance to the glucose). Hypotheses that are physiologically reasonable can be tested either; reducing the number of necessary experiments to characterize the dynamics of certain substratum or drug in a given organ or area.

Therefore the availability of a proven physiologic model that describes the main dynamic characteristics of the enzymatic processes to transform the substrata, at least in the liver, is of fundamental importance to understand the complex system dynamics. A model like this can be built from enzymological data available in the literature and validated for control system evaluation. On has always to have in mind that for ethical reasons the number of *in vivo* experiments should be quite small and the real experiments should not have faults under any circumstance.

3. THE PHYSIOLOGIC RELEASE OF HORMONES FOR THE PANCREAS AND THE METABOLISM OF CARBOIDRATES IN THE LIVER.

After a meal, the gastrointestinal tract absorbs glucose to a rate of around 50g/h (Thurman et al., 1986). In the sequence, glucose enters portal circulation (the portal vein gives access to the liver) and stimulates the insulin release from B cells located at the pancreas Islets of Langherhans, besides reducing the secretion of the hormone glucagon of A cells. Then, glucose enters the liver, which will provide regulation of its circulating levels through storage in the Glycogen form. The portal insulin, reaching the liver, is degraded in levels that can reach up to 70% (50% is the mean value) (Montague, 1983). When body requests energy and there is no food intake, the stored glycogen should be appropriately metabolized; in this case, the liver allows glycogen decomposition (glicogenolisis). The resulting glucose is added to the glucose synthesized by other precursors as the lactato (gliconeogenesis) and sent to the systemic circulation. Finally, glucose accomplishes its fundamental role as fuel nutrient when is absorbed by the peripheral tissues, as the skeletal muscle and the adipose tissue, and provides the basic energy for the central nervous system (CNS) and for the red blood cells.

Note that insulin is the principal hormone for decrease of blood glucose levels, while the counterregulatory hormone glucagon is responsible for signaling the need of circulating glucose increase. Physiologically, the blood glucose level is restricted to values between 80 and 100 mg / dl of plasma volume (4.5 to 5.5 glucose mM). After a meal, it can reach picks of about 140 mg / dl (or 8 mM). Moreover, the practice of physical activities and the exhibition to sharp stress may induce significant modifications in the glicemic profile. Physical activity leads to an increasing demand of available glucose due to the increasing required energy. In this case the liver releases additional glucose through the glicogenolisis: the rate of glycogen transformation increases up to 6 times, while in parallel there occurs an excitation of the glucose-6-phosphate transformation to plasma glucose, with increases up to 4 times the normal glucose levels (Thurman et. al, 1986). On the other side, stress causes the activation of the sympathetic nervous system that, through auxiliary hormones, inhibits accutely the insulin and stimulates the glucagon secretion (Taborski, 1989), a sequence that may cause hiperglicemia.

4. THE MATHEMATICAL MODEL

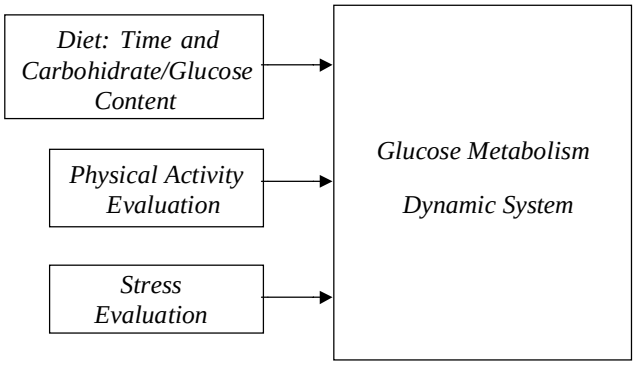
The general mathematical model adopted is represented in Fig. 1: main inputs are meal schedule and diet type (glucose content), the physical activity and an eventual stress situation. The pancreas, portal circulation, liver and sistemic circulation subsystems are shown in Figs. 2, 3, 4 and 5, respectively.

4.1 Submodels for feeding, absorption of gastrointestinal glucose, stress and physical activity.

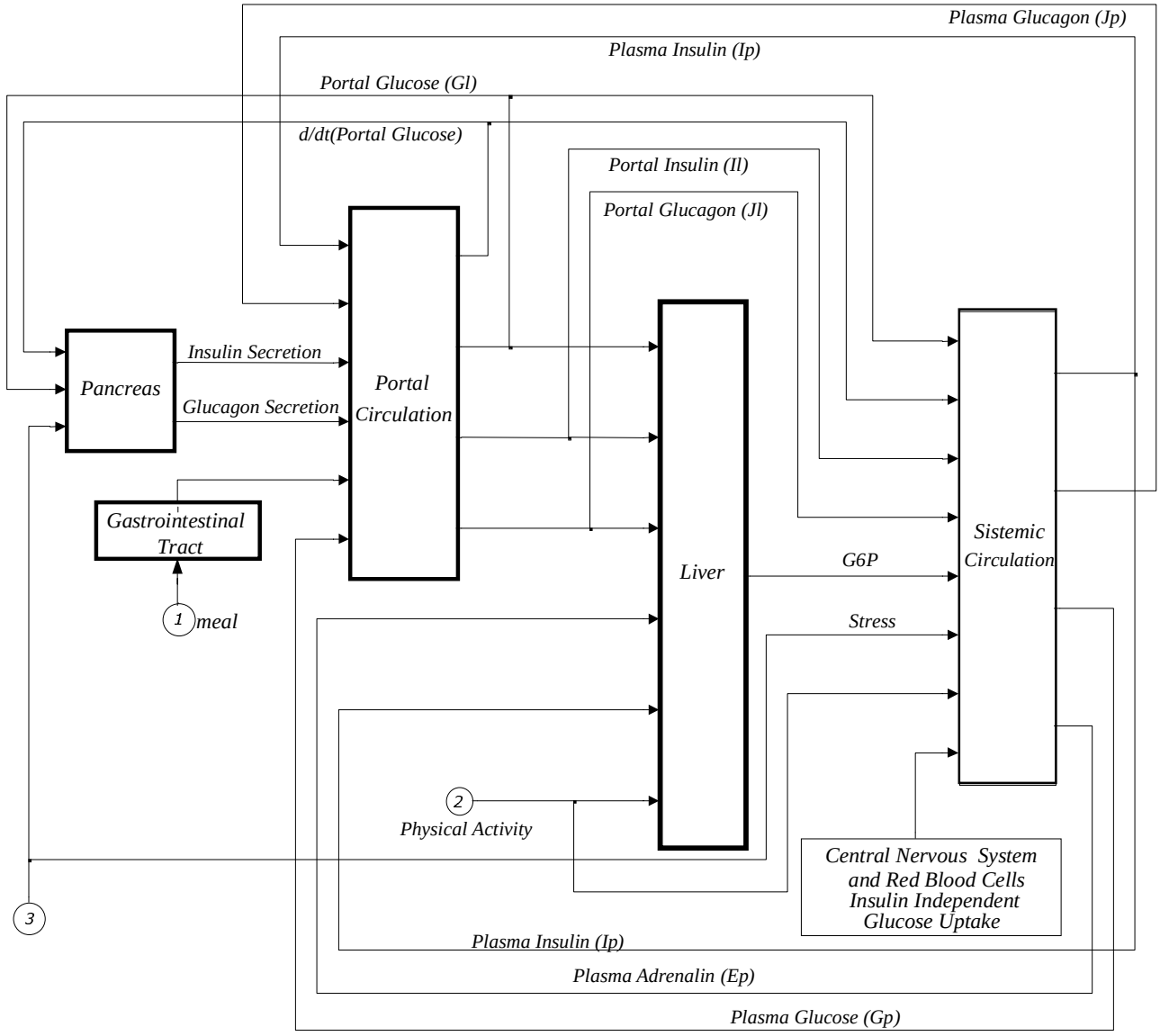
Starting from a specific food profile in each one of the daily meals, a database associates to each meal content the mean values of their glucose contents, considering the available data about feeding in Brazil (ENDEF, 1977). These values are supplied to the gastrointestinal tract subsystem, together with the informations about the meal schedule, considering a constant rate for glucose absorption (50 g of glucose per hour).

The effects of sharp stress can induce an increase up to 3 times the plasma glicemic levels (Taborski, 1989). The physiological effect of insulin inhibition and glucagon secretion activation is modeled as a pulse, starting at the moment stress occurs and lasting about ten minutes, and a first order system with time constant τ=3 min. The resulting value is subtracted from the insulin rate and added to the glucagon rate secreted by the pancreas.

The effects of physical activities are considered since the instant the increase on glicogenolisis occurs (according to item 3.). A pulse of width 6 is simulated at the beginning of the physical activity in series with other first order system with time constant τ=4 min. The resulting value is then applied as an excitation for glycogen release. In the same way applying a pulse of width 4 in the same first order system, the excitation for transformation of glucose-6-phosphate is simulated in plasma glucose.



(a)



(b)

Figure 1 - Mathematical model for glucose metabolism:
general scheme (a) and main subsystems (gastrointestinal tract, pancreas, portal circulation, liver and sistemic circulation) (b).

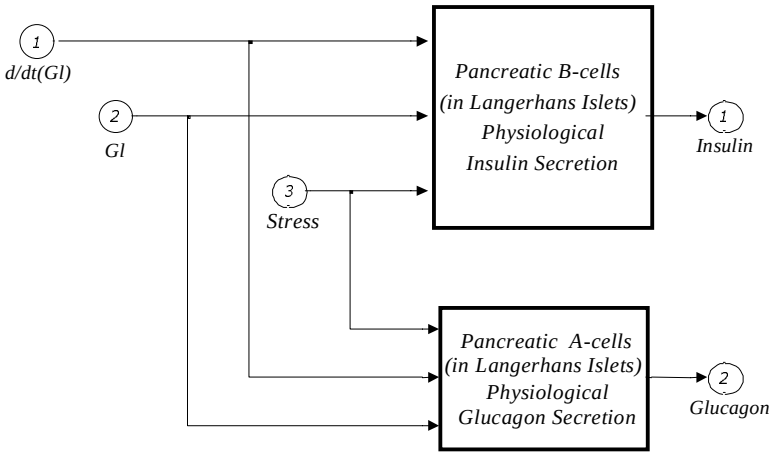


Figure 2 - Pancreas submodel.

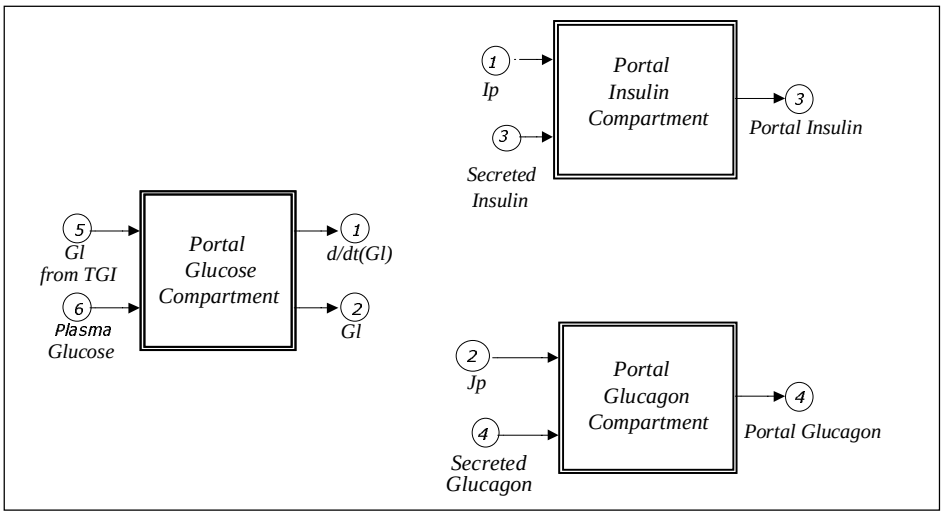


Figure 3 - Portal circulation submodel.

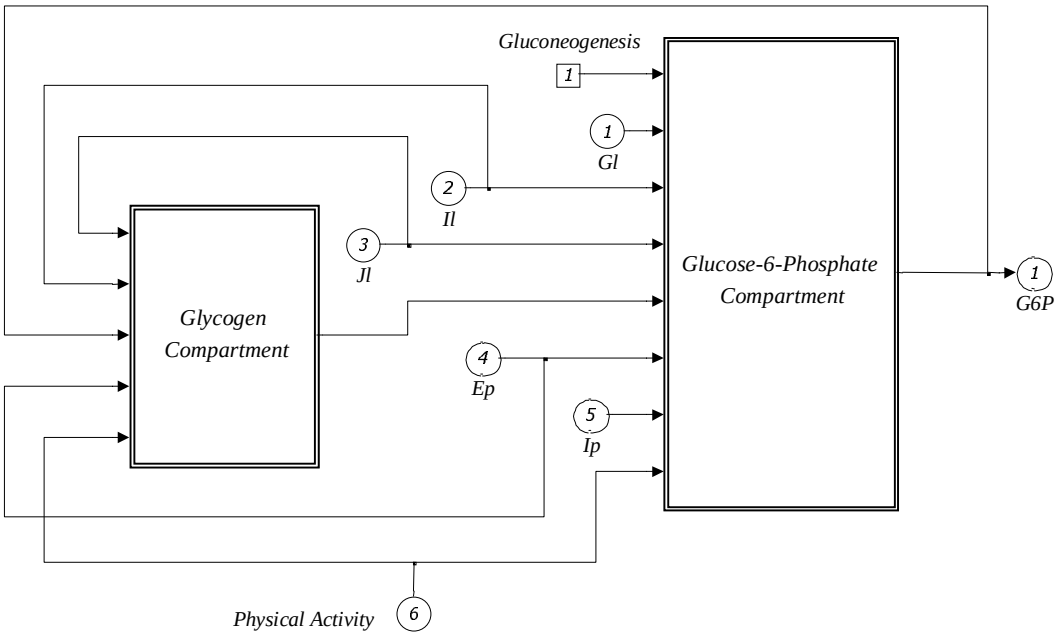


Figure 4 - Liver metabolism submodel.

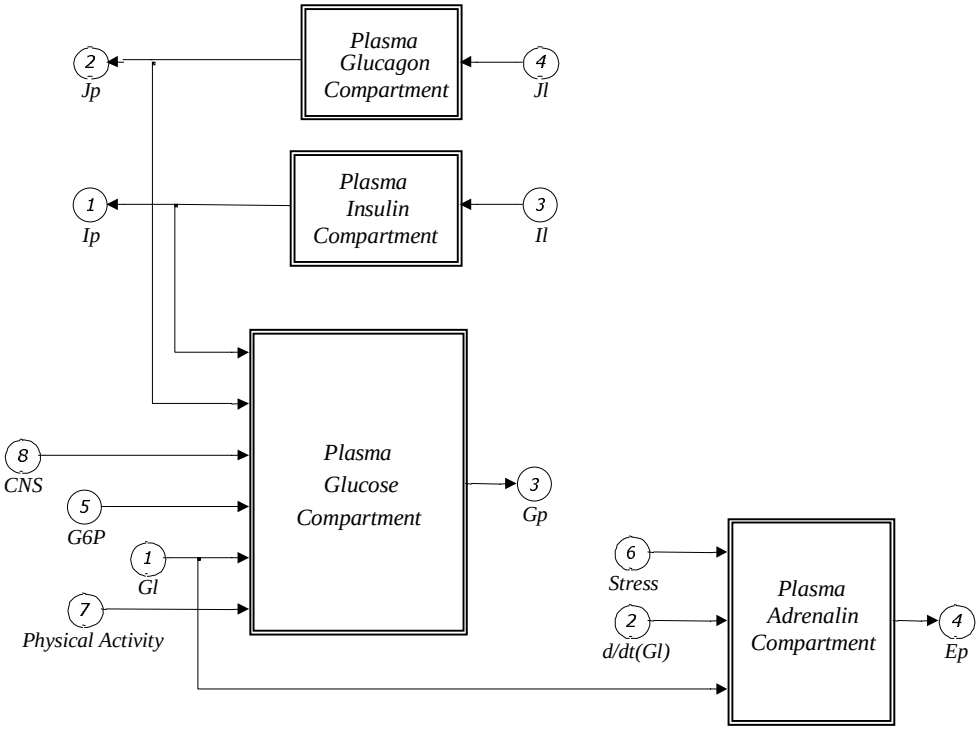


Figure 5 - Sistemic circulation.

4.2 Compartmental submodels.

The physiological model of Finkelstein & Carson (1986) has been used as the basis for general model construction. This compartmental model describes the dominant enzyme dynamics due to the glucose metabolism in the liver, based on enzymologic data from the literature and on the non-linear model for enzyme dynamics of Briggs-Haldane. The Briggs-Haldane equation is a general approach for steady-state, that does not require the balance restriction between enzyme and substrate that appears in the classical formulation of Henri-Michaelis-Menten (Segel, 1993):

$$\frac{v}{V_{máx}} = \frac{[S]}{K_m + [S]} \quad , \tag{1}$$

where: $[S]$ indicates the substrate concentration, K_m is the Michaelis constant for that enzyme, and $v/V_{máx}$ indicates the relative velocity of the reaction.

Finkelstein & Carson (1986) use a compartmental model (based on mass balance for each dynamic subsystem) considering nine compartments: plasma glucose, portal glucose, plasma insulin, portal insulin, plasma glucagon, portal glucagon, hepatic glycogen, glucose-6-phosphate and plasma adrenaline. For the complete description of the 9 first order differential equations see the original work of Finkelstein & Carson (1986).

5. SIMULATION RESULTS

The simulations were accomplished in an integrated software environment (MATLAB 5.0 / Simulink 2.0)™ for a complete day, starting midnight (0 min) and considering 24 hours (1440 min). The initial conditions were: glucose (both portal and plasmatic): 0.005 M; Insulin (both): 30 mU; Glucagon (both): 0.32 μg; Glucose-6-Phosphate: 0.0003 M; Glycogen: 0.25

M; Plasma Adrenalin: 0.16 mg. Simulations were performed for two cases. In the first (Fig.6), 4 meals were considered: at 7 h (420 min) a breakfast with 40 g of glucose; at 12 (720 min) a meal with 120 g of glucose; at 16 (960 min) a coffee-break with 30 g of glucose and at 21 (1260 min) a dinner with 120 g of glucose. In the second case (Fig. 7), only two meals were considered: at 12 hours (720 min) a meal with 120 g of glucose content, and at 20 (1200 min) a dinner with 100 g of glucose. In this last case, one has also considered that the individual has developed physical activities at 7 (420 min) for half an hour, and also at 18 (1080 min), for 1 hour. Besides that, at 14 (840 min), the individual has been exposed to intensive stress.

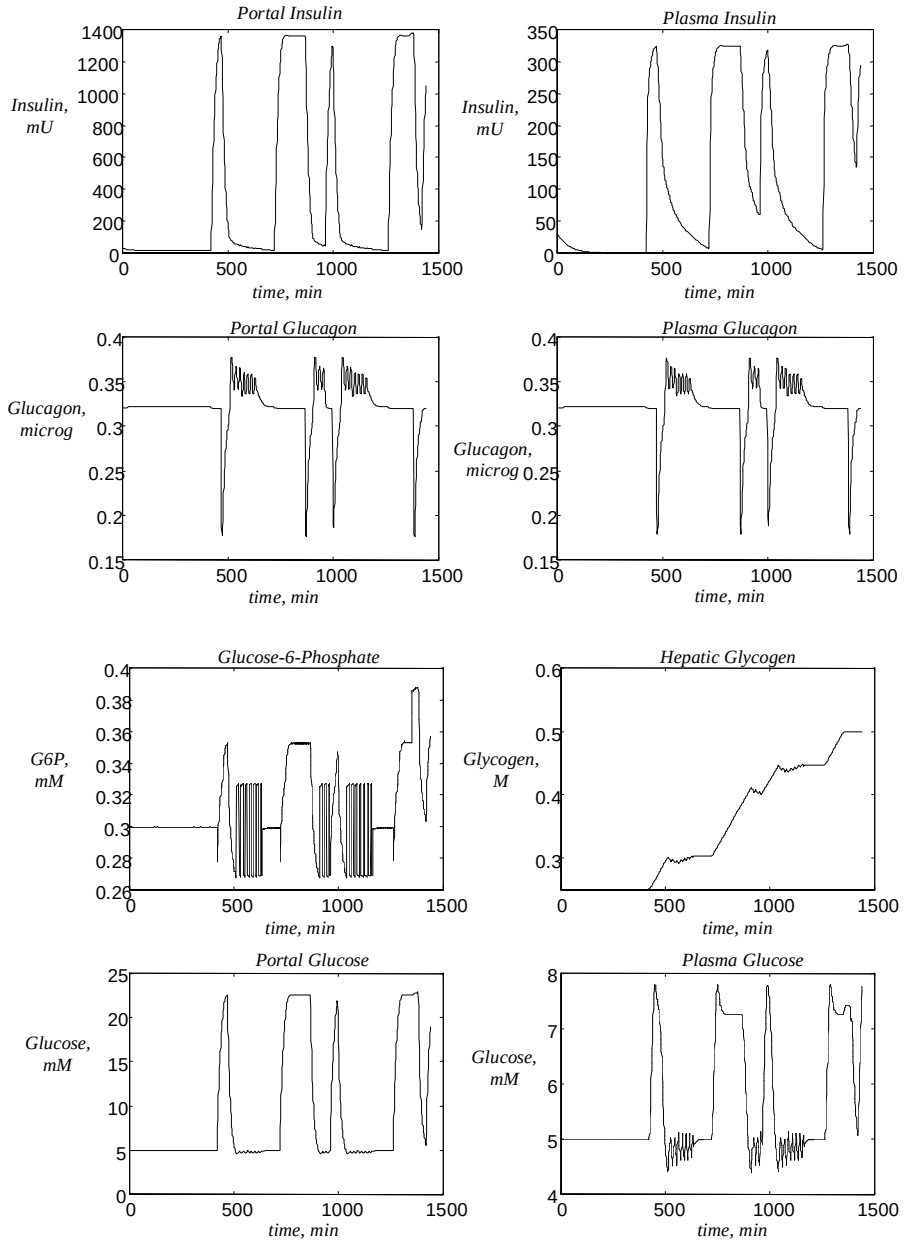


Figure 6.
Simulation results for case #1.

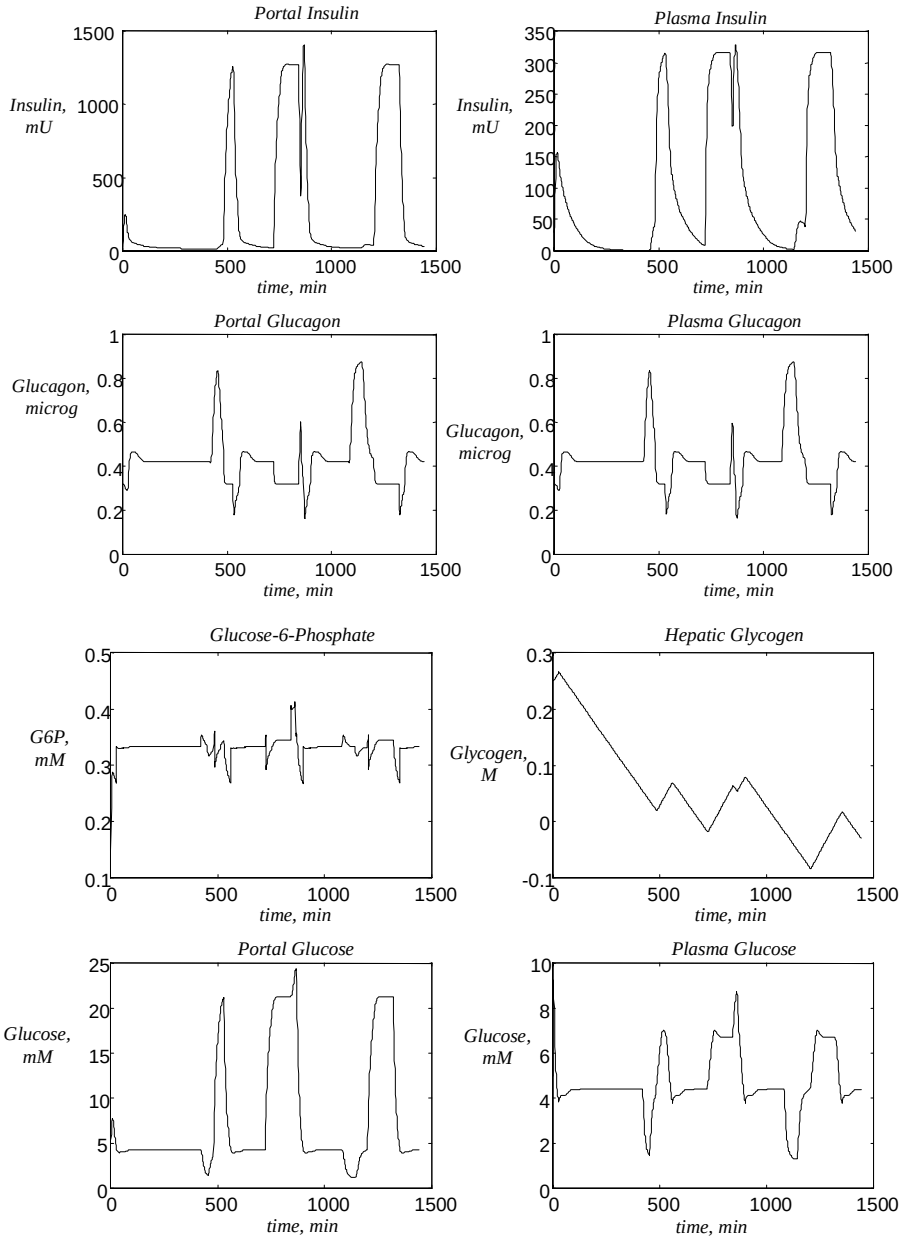


Figure 7.
Simulation results for case #2.

6. ANALYSIS AND CONCLUSIONS

From simulated results quite generic aspects of physiological glicemic control can be observed: first, depending on the glucose ingestion from a carbohidrate-rich meal, the pancreas secretes a high content of insulin almost instantaneously, associated with a considerable glucagon inhibition. The peaks of glucose in the portal circulation reach around 20 mM, due to the high glucose absorption rate from gut.

In case #1, where there is a considerable energy intake from four meals, the liver stores increasing quantities of glucose in glycogen form. Some oscilations on glucose-6-phosphate dynamics can be observed, due to the switching form of the model equations. The plasma glucose reaches around 8 mM, and the time to return to the normal level of 5 mM depends on the glucose intake.

In case #2, the glucose intakes from meals are very limited and the blood glucose peaks are somewhat smaller than the case # 1. A significant decrease of blood glucose at physical

activities and considerable and sustained peaks at the stress time can be observed. The hepatic glycogen storages decrease dangerously, affecting the plasma glucose peak values and limiting the hiperglicemic glucagon action.

Based on this physiological model, some important insights on the dynamic nature of the endocrine-metabolic system can be achieved. The glucose informations on the meal data allow more realystic simulations, while the stress and physical activity submodels represent daily facts with substantial effects on blood glucose level.

Besides that, the importance of this mathematical simulator lies on the extension for pathological state (diabetes) simulation, where different control algorithms can be tested and their performance analysed. As a next step, the model must be reduced to a more simplistic one to be used for control design and artificial pancreas development.

On the other side, this model should be expanded to consider some diferent levels of stress and physical activity peaks, or other physiological phenomena, for instance the 'Down Phenomenon' or the 'Somogyi Effect' (matinal hiperglicemic factors).

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