Modeling Glucose-Insulin Behavior in Ill Patients (DM Type2)

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Abstract. In this paper we analyze a mathematical model (called MINMOD) that describes the interactions between glucose and insulin in human subjects, in order to realize an adequate model for ill patients, suffering from *Diabetes Mellitus* (DM) Type 2. Our model has been tested on the basis of clinical data and it has correctly reproduced glucose and insulin reply and temporal evolution, according to experimental data test. This model could, in the future, contribute to predict glucose and insulin behavior in ill patients and suggest the adequate treatment.

1. Introduction

Insulin is a protein, made up of 51 amino acids. It is secreted by the pancreas, by means of the so-called "β-cells", in small quantities, which can be highly increased, in order to answer to several inputs (sugars, first of them glucose), amino acids, vagus activity.

It helps glucose and lipids storage in target cells, which are important energy sources. It affects cells growth and the metabolism of many tissues. Besides, it promotes the protein synthesis, increasing the amino acids transport and stimulating ribosome activity. Finally, it helps glycogen synthesis, restoring it after every muscular activity.

It is brought by the bloodstream to specific receptors that have been discovered in quite all the tissues membranes. However, biological effects due to the interaction insulin-receptors have been found in few tissues: liver, muscle, adipose tissue.

Glucose is the most important physiological stimulation for insulin secretion. Insulin reply to a protracted glucose stimulation of the β-cells is split into two phases: a first, high, secretion, rapidly decreasing, and a second, delayed, secretion peak, during all the stimulation period.

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When glucose is no more able to stimulate the β-cells, in the human subject several dysfunctions appear, among which one of the most serious is the so-called "diabetes mellitus" (DM). It is characterized by hyperglycemia, due to a complete absence of insulin or to a partial deficit, related to its reduced biological efficiency. DM can be classified in three forms (see [7]):

a) DM type 1, insulin-dependent (IDMM); it is characterized by a quite complete absence of insulin secretion; it represents the 10-15 % of all the DM pathologies;
b) DM type 2, insulin-independent (NIDMM); it is characterized by a low insulin secretion, associated to tissue refractoriness to insulin activity; it represents the 85-90 % of all the DM pathologies;
c) secondary DM; it includes forms of insulin-refractoriness, connected to other serious diseases, such as muscular dystrophy, myotonic dystrophy etc.

In order to model the mechanism of glucose regulation in the blood, we need to evaluate quantitatively how insulin controls the glucose absorption by the tissues and the stimulation action, done by glucose, on insulin production by the pancreas β-cells.

This information is clinically highly relevant, because it permits to diagnose and classify different pathologies, and consequently to distinguish the forms of glucose intolerance due to DM of type 1 and 2 from secondary DM.

Clinical experience is in general based on experimental tests (IVGTT, IVITT etc.). Unfortunately, these techniques are sometimes not efficient. Consequently the need of satisfactorily mathematical models, able to reproduce insulin-glucose concentrations and temporal behaviors, has recently highly increased.

Several models are presented in classical literature. Already in 1965, Ackerman et al. [1] supplied the first model which studied the interactions between glucose and insulin simultaneously. In early Seventies Grodsky [10] studied models able to explain insulin secretion behavior due to glucose stimulus. The most important result of this study was the description of the multiphase insulin response. Modifying Grodsky's model, Guyton et al. [11] developed a model, on computer, considering some glucose metabolism features, in healthy subjects. The model takes into account heart rate, blood flow, breathing rate etc, and it assumes constant production of fractional insulin, from liver and kidneys.

All this works treat insulin and glucose interaction with highly complexity degrees. Yet, in clinical application, only simple models can find direct utilization. The model which found more interesting applications, in medical practice, is the so called MINMOD by Bergman and Cobelli in the early Eighties. More recently, new interest has been devoted to this topics (see, for example, [2], [5], [6], [9]), trying to improve the original model, for example introducing delays, or suggesting new ones.

We study a MINMOD model, which describes the temporal evolution of insulin and glucose, according to the following compartmental scheme:

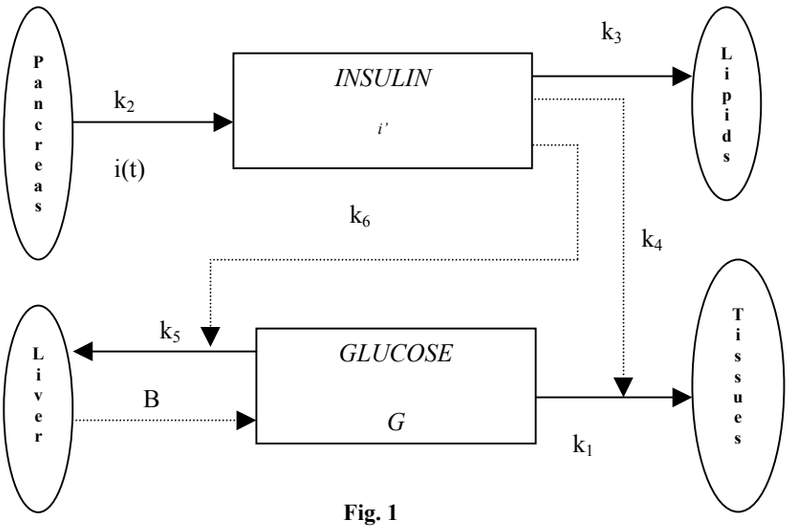

Fig. 1

This model is considered as an optimal model if we require the following assumptions must be fundamental for the simulation of glucose distribution kinetics, following glucose injections:

1) it is sufficient to assume that injected glucose distributes into a single compartment;

2) glucose disappearance occurs in proportion to the plasma glucose concentration;

3) insulin in a compartment remote from plasma (peripheral) accelerates the disappearance of glucose.

The compartments glucose-insulin are represented by functionals, which act on the input functions and whose values are the output functions of the model.

The parameters and variables of the model are the following:

- insulin and glucose concentration in plasma: i' and G; their units are, respectively, μU/ml and mg/dl;
- concentration of insulin input: i(t); its unit is μU/ml;
- glucose concentration in plasma at time 0: B_0; its unit is mg/dl $[minute]^{-1}$;
- concentration of net hepatic glucose: $B = B_0 - (k_5 + k_6\ i')G$; its unit is mg/dl$[minute]^{-1}$;
- kinetics of insulin in the remote compartment: k_2 , k_3; their unit is $[minute]^{-1}$;
- effect of glucose to enhance its disappearance: k_1 , k_5; their unit is $[minute]^{-1}$;
- effect of remote insulin to enhance glucose disappearance: k_4 , k_6 ; their unit is ml / μU $[minute]^{-1}$.

2. The Mathematical Model

In order to analyze the temporal evolution of glucose and insulin, we need to know the temporal variation of the input i(t), described by its kinetic equation; the explicit expression of i(t) is given by $i(t) = I(t) - I_b$, where I(t) and I_b respectively represent the temporal evolution and the basal value of insulin concentration.

The model considered for the mathematical analysis of the system takes into account the following rearrangements:

$X(t) = (k_4 + k_6)\, i'(t)$
$p1 = k_1 + k_5$
$p2 = k_3$
$p3 = k_2 (k_4 + k_6)$

The parameters k_i, according to medical experience, can be considered constant.

Thus, the model can be represented by the following system of nonlinear differential equations:

$$\begin{cases} \dfrac{dG}{dt} = -[p_1 + X(t)]G(t) + p_1 G_b & G(0) = G_0 \\ \dfrac{dX}{dt} = -p_2 X(t) + p_3[I(t) - I_b] & X(0) = 0 \\ \dfrac{dI}{dt} = -nI(t) + \gamma[G(t) - h]t & I(0) = I_0 \end{cases}$$

where the first and second equations describe the glucose disappearance, while the third equation rules insulin kinetics.

The estimate of the parameters for a young healthy patient was obtained in [13], by means of a computer routine, based on a modified Marquardt's nonlinear least squares method (see [8], [12]), which uses clinical experimental data, showing the behavior of glucose and insulin during a so-called "frequently-sampled intravenous glucose tolerance" (FSIGT) clinical test, performed in a time interval of 3 hours, which is the optimal one, since in it no significant metabolic variations are observed. The values obtained are the following:

$p_1 = 0.03082 \quad p_2 = 0.02093 \quad p_3 = 0.00001062 \quad G_0 = 287.0$

$n = 0.3 \qquad \gamma = 0.003349 \qquad h = 89.5 \qquad I_0 = 403.4$

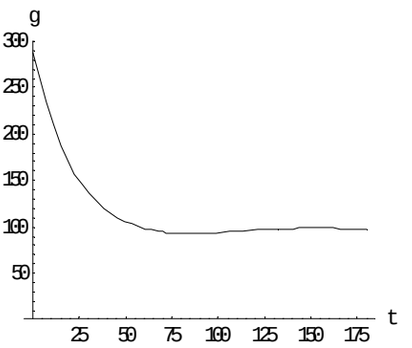

Fig. 2. Temporal evolution of glucose for a young healthy patient.

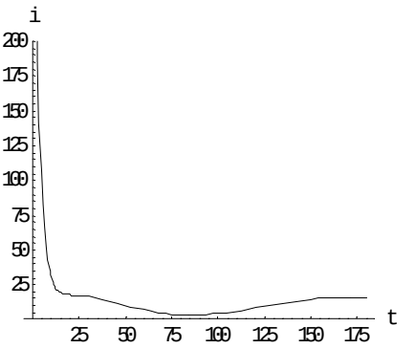

Fig. 3. Temporal evolution of insulin for a young healthy patient.

The parameters estimation for an elderly healthy patient are:

$p_1 = 0.01572 \quad p_2 = 0.01301 \quad p_3 = 0.000004031 \quad G_0 = 293.8$

$n = 0.3606 \qquad \gamma = 0.00178 \qquad h = 105.5 \qquad I_0 = 241.0$

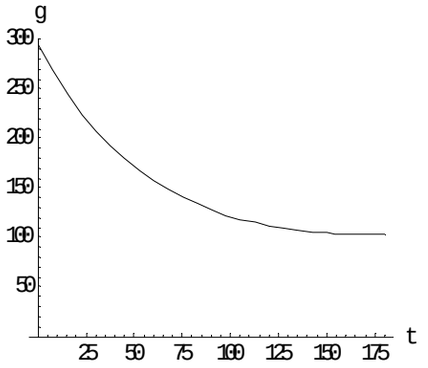

Fig. 4. Temporal evolution of glucose for an elderly healthy patient.

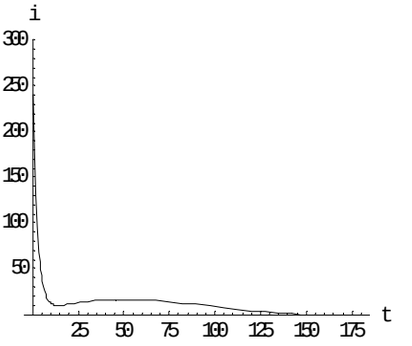

Fig. 5. Temporal evolution of insulin for an elderly healthy patient.

In both cases, the ingestion of meal at time $t_0 = 0$ implies an initial glucose enhancement, followed by a decreasing phase. Then glucose tends to become stable and later on little oscillations appear around the equilibrium point. Hyperglycemia immediately induces insulin release, followed by a decrease, faster than the corresponding phase in glucose (see, for example, [14]). The slope of the graphs and the duration of the stabilization period depend on the patients' age, as shown in Figs. (2, 3, 4, 5).

3.The Ill Patient

For an ill patient (DM type 2), the differential system must be modified, taking into account partial absence of insulin response and the need of periodic injections of pharmacological agents (e.g. tolbutamide), in order to stimulate insulin receptors, represented by an additive input term, which causes rapid peaks in the graph of insulin temporal evolution, as shown in Figs. (6 and 7). In order to reproduce the experimental data shown in [6], we have translated the injection in mathematical terms by means of a step function with small support, where the height A represents the peak of insulin secretion following the tolbutamide injection (300 mg, see [13]), due to the experimental fact that the tolbutamide injection is approximately constant and short lasting. In [13] the patient receives only one injection, whose duration is taken equal to 1 sec.

$$\begin{cases} \dfrac{dG}{dt} = -[p_1 + X(t)]G(t) + p_1 G_b & G(0) = G_0 \\ \dfrac{dX}{dt} = -p_2 X(t) + p_3[I(t) - I_b] & X(0) = 0 \\ \dfrac{dI}{dt} = -nI(t) + \gamma[G(t) - h]t + A\chi_E(\mathrm{t}) & I(0) = I_0 \end{cases}$$

where E is the set corresponding to the temporal periods during which the injections are performed and χ_E represents the characteristic function of the set E.

Applying the usual least square technique and integrating the differential system gives the following result (the dots are the experimental data, obtained from [13]):

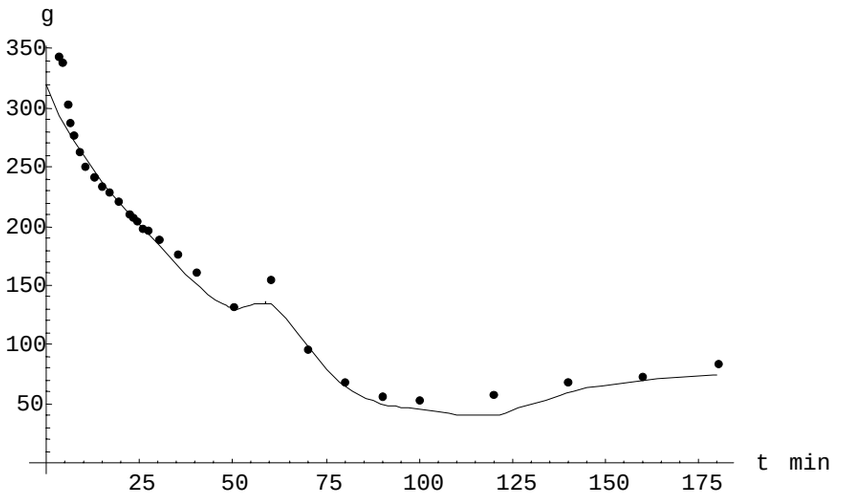

Fig. 6. Temporal evolution of glucose for an ill patient

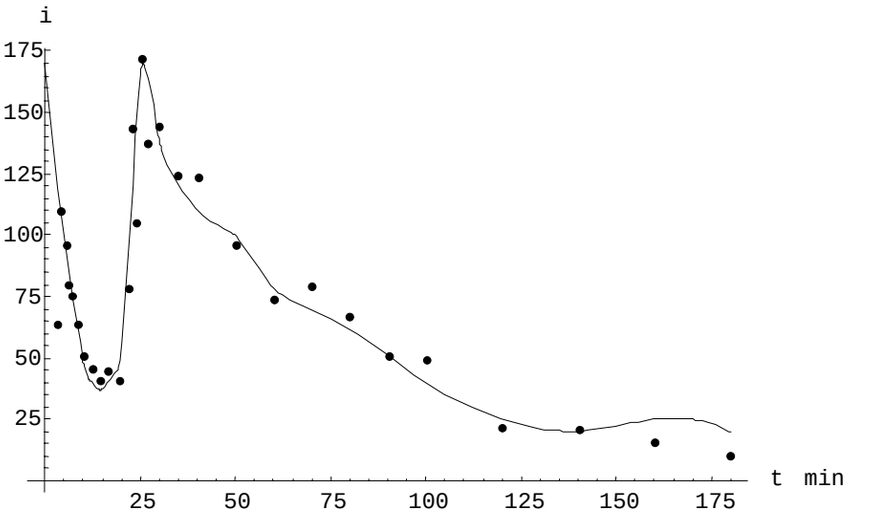

Fig. 7. Temporal evolution of insulin for an ill patient

4. Comments and Further Developments

The model we have analyzed has shown correct insulin responses to glucose variations (in particular peaks) in a young and in an elderly healthy patient, as in an ill one, even if, in the last case, the insulin responses are artificially generated by means of pharmacological agents (e.g. tolbutamide) which stimulate the peripheral tissues insulin receptors, due to their inefficiency caused by DM type 2.

Moreover, since the modified model can reproduce in a sufficiently appropriate way glucose and insulin temporal evolution for an ill patient, suffering from diabetes mellitus type 2, this model could, in the future, if tested with further experimental data, contribute to predict glucose and insulin behavior in ill patients and suggest the adequate treatment.

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