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Generalized sensitivity analysis of the minimal model of the intravenous glucose tolerance test

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ABSTRACT

Generalized sensitivity functions characterize the sensitivity of the parameter estimates with respect to the nominal parameters. We observe from the generalized sensitivity analysis of the minimal model of the intravenous glucose tolerance test that the measurements of insulin, 62 min after the administration of the glucose bolus into the experimental subject's body, possess no information about the parameter estimates. The glucose measurements possess the information about the parameter estimates up to three hours. These observations have been verified by the parameter estimation of the minimal model. The standard errors of the estimates and crude Monte Carlo process also confirm this observation.

1. Introduction

Diabetes or Diabetes Mellitus (DM) is one of the oldest diseases of man having its description in the Egyptian manuscript about 3000 years ago [1]. It is a disorder of endocrine system and metabolism characterized by hyperglycemia either due to inadequate production of insulin by the Pancreas or its defective action on mobilizing the glucose molecule into the respiring cells and tissues [2]. The exact point where its onset occurs is unknown [3]. However, it is a group of metabolic disorders resulting due to the malfunction of the glucose-insulin system in the body. Diabetes is described as a chronic hyperglycemic condition either due to the inadequate insulin secretion by the pancreas or due to its defective action resulting from the decreased sensitivity of the target cells. The former is called the *Type 1* (Insulin dependent) and the later is called the *Type 2* diabetes (Non-insulin dependent). The two types are mostly similar in the sense that the insulin is not used up by the body resulting in altered metabolism of the glucose leading to a hyperglycemic condition in the affected individuals [4]. Raised blood glucose level is associated with polyuria, polydipsia and polyphagia. Long-standing hyperglycemic condition affects almost every organ of the body leading to several complications. Commonly associated complications include atherosclerotic changes in heart and peripheral blood vessels resulting in cardiovascular and cerebrovascular diseases, diabetic foot, diabetic retinopathy, diabetic neuropathy, chronic renal failure and ketoacidosis. Chronic uncontrolled diabetes mellitus also results in Charcot joints, amputations and sexual dysfunction [2].

The glucose and insulin concentrations in blood are quantified by the glucose tolerance tests. Glucose tolerance tests measure how well the body's cells absorb glucose after its administration into the body. There are several tests in use in the medical and clinical research. The Oral Glucose Tolerance Test (OGTT) is usually used to study the gestational diabetes. The hyperinsulinemic clamp tests are mostly used to determine the sensitivity of the body's tissues to insulin [5]. The hyperglycemia clamp tests are used to determine the sensitivity of the β-cells to glucose. These two clamp techniques have complex procedures to be applied, and inflict severe side effects like hyperhidrosis, palpitations, fainting, convulsions and even coma on the experimental subject. The Intravenous Glucose Tolerance Test (IVGTT) has a simple procedure, fewer side effects and rich information. That is why, it has been in extensive use in the diabetes research. The IVGTT eliminates variations due to gastro-intestinal factors unlike the OGTT [6]. Its procedure unlike the clamp techniques is simpler.

Bergman et al. [7] gave the minimal model of glucose-insulin dynamics in early eighties on the basis of the IVGTT. Since then, more than 500 studies related to the minimal model have been found in the literature. The IVGTT provides important information, in particular, about the first-phase and the second-phase insulin responses to glucose, insulin sensitivity and glucose effectiveness. The test has enabled the researchers better characterize individuals at increased risk for developing *Type 2* diabetes. The Minimal Model, along with the IVGTT, has been the reference method to estimate the parameters necessary for all indexes of the metabolic portrait of a person. The IVGTT has simple procedure and its analysis produces rich information along with the minimal model which best describes it [8].

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Table 1
Description of the parameters θ used in the minimal model along with their nominal values θ_0 taken from the Ref. [10].

θ	Units	Description	θ_0
p_0	mg/dl	Theoretical glucose concentration in plasma at time $t = 0$	291.2
p_1	1/min	Rate constant of insulin-independent glucose uptake in muscles, and adipose tissue	0.0317
p_2	1/min	Rate constant for decrease in tissue glucose uptake ability	0.0123
p_3	$\text{min}^{-2}(\mu\text{U/ml})^{-1}$)	Rate constant for the insulin-dependent increase in glucose uptake ability in tissue per unit of insulin concentration above I_b	4.92×10^{-6}
p_4	$(\mu\text{U/ml})\text{min}^{-2}(\text{mg/dl})^{-1}$	Rate constant for insulin secretion by the pancreatic β-cells after the glucose injection and with glucose concentration above p_5	0.0039
p_5	mg/dl	Threshold value of glucose in plasma above which the pancreatic β-cells secrete insulin	79.0353
p_6	1/min	First order decay rate for insulin in plasma	0.2659
p_7	μU/ml	$p_7 + I_b$ is the theoretical insulin concentration in plasma at time $t = 0$	357.8
G_b	mg/dl	Basal pre-injection level of glucose	60
I_b	μU/ml	Basal pre-injection level of insulin	7

The study of the minimal model requires the estimation of the parameters to find the indexes necessary for the diagnosis of diabetes. For this purpose, proper measurements of the glucose and insulin after the IVGTT are important. The importance of measurements for the estimation of parameters can be adjudged by two tools; one is the sensitivity of the model outputs with respect to the parameters, others are the Generalized Sensitivity Functions (GSFs) which quantify the changes in the parameter estimates due to the changes in the measurements. There are two limitations as far as the sensitivity analysis is concerned; the sensitivity analysis does not indicate the dependencies between parameters and it does not consider any parameter estimation procedure. This difficulty is overcome by the GSFs which represent the sensitivity of parameter estimates with respect to measurements of model outputs and are the result of a parameter estimation procedure. Since, in general, it is assumed that the measurements for a model output are given as model output for a nominal parameter plus noise, so the GSFs can also be considered as characterizing the sensitivity of parameter estimates with respect to the nominal parameters.

We apply the theory of the generalized sensitivity functions to the minimal model of the glucose-insulin dynamics. In Section 2, we simply describe the procedure of the IVGTT and the minimal model. In Section 3, the sensitivity and generalized sensitivity functions are briefly described. We give the detail of the numerical scheme of our later work in Section 4. The sensitivity analysis and the generalized sensitivity analysis of the model are presented in Section 5. Then the information collected from the generalized sensitivity analysis of the minimal model are summarized and verified by the parameter estimation in Section 6. The further verification of the parameter estimates is made by the Monte-Carlo verification in Section 7. The conclusion of the whole analysis is given in Section 8.

2. Materials

2.1. Intravenous glucose tolerance tests

The intravenous glucose tolerance test is a physiological experimental procedure in which a bolus containing 0.3 gram glucose per kilogram of the experimental subject's body weight is injected intravenously. The blood samples are taken to measure the subject's plasma glucose and insulin concentrations usually for the next three hours. There are other time sampling schemes; some spreading over long time interval up to five hours and some over short time interval up to one hour. However, the three hour time sampling schemes are the most referenced and standard ones with the minimal model in the literature. So, we take the measurements for glucose and insulin concentrations in plasma during the IVGTT at the sampling times $t_1, \cdots, t_{24}$ (in minutes) up to three hours [9] as depicted in Table 2.

2.2. The minimal model

In the minimal model, the concentrations of glucose, insulin and interstitial insulin in the plasma are defined as the states of the system. Since the IVGTT consists of injecting glucose into bloodstream of the experimental subject [8], it increases the plasma concentration of the glucose, and in return, a corresponding increase in the plasma insulin concentration is observed by the secretion of the insulin by the pancreas. The minimal model of glucose-insulin kinetics describes the time courses of these concentrations. The model as developed in [7] is given by the set of the following three differential equations:

$$\begin{aligned} \dot{G}(t) &= -p_1(G(t) - G_b) - X(t)G(t), \quad G(0) = p_0, \\ \dot{X}(t) &= -p_2X(t) + p_3(I(t) - I_b), \quad X(0) = 0, \\ \dot{I}(t) &= p_4 t \max(0, G(t) - p_5) - p_6(I(t) - I_b), \quad I(0) = p_7 + I_b, \end{aligned} \tag{1}$$

where $G(t)$ is the glucose concentration in plasma at time t, measured in mg/dl. $I(t)$ is the insulin concentration in plasma at time t measured in μU/ml, and $X(t)$ describes the effect of insulin on the net glucose disappearance (remote insulin action) with unit 1/min.

The interpretation of all the other parameters is given in the Table 1. The minimal model together with the IVGTT gives the following metabolic portrait of an experimental subject:

1. Glucose effectiveness S_G, the rate constant of the insulin-independent glucose uptake in muscles and adipose tissues, $S_G = p_1$.

Table 2
Numerical data for the measurements of glucose and insulin.

i	1	2	3	4	5	6	7	8
$t_i[min]$	0	2	4	6	8	10	12	14
$y_G(t)[mg/dl]$	290.77	274.52	261.19	246.67	231.28	220.48	208.19	195.5
$y_I(t)[\mu UI/ml]$	364.11	219.4	136.04	85.843	59.659	47.375	38.938	36.311
i	9	10	11	12	13	14	15	16
$t_i[min]$	16	19	22	27	32	42	52	62
$y_G(t)[mg/dl]$	185.2	170.42	156.96	139	122.01	101.1	82.814	72.552
$y_I(t)[\mu UI/ml]$	34.719	33.703	33.933	32.298	30.675	21.191	13.441	7.4106
i	17	18	19	20	21	22	23	24
$t_i[min]$	72	82	92	102	122	142	162	182
$y_G(t)[mg/dl]$	66.732	61.42	58.581	56.229	55.997	54.266	56.719	58.192
$y_I(t)[\mu UI/ml]$	5.4352	7.2606	5.944	8.4158	6.1955	7.5298	7.214	6.0815

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