



A POLYNOMIAL LINEAR REGRESSION APPROACH TO ESTIMATE SENSITIVE PARAMETERS IN THE NOVEL DOUBLE DIABETES MODEL

RASHIDA HUSSAIN¹, ASMA ARBAB¹, SALAHUDDIN², MOHAMMAD MUNIR³,
NASREEN KAUSAR^{4,*} AND ASGHAR ALI¹

¹*Department of Mathematics, Mirpur University of Science and Technology, Mirpur-AJK, Pakistan*

²*Department of Mathematics, Jazan University, Jazan, Kingdom of Saudi Arabia*

³*Department of Mathematics, Government Postgraduate College, Abbottabad, Pakistan*

⁴*Department of Mathematics, University of Agriculture, Faisalabad, Pakistan*

* *Corresponding author:* kausar.nasreen57@gmail.com

ABSTRACT. Sensitivity analysis characterizes the changes in the model outputs due to the changes in the model parameters. In this article, we estimate the most sensitive parameters in the Novel Double Diabetes Model (NDDM) through the polynomial linear regression approach; this way we develop a direct relation between the sensitivity analysis and the parameter estimation. The NDDM has more than seventeen parameters, and estimating them simultaneously is difficult. We select the most commonly used five parameters in the glucose-insulin dynamics for the sensitivity analysis. The model outputs-glucose concentrations in the plasma and the subcutaneous compartments are sensitive to the selected parameters whereas the insulin concentrations in the plasma and the subcutaneous compartment are sensitive only to the insulin transfer rate from the subcutaneous to the plasma compartment. System sensitivity of the model for the selected parameters is also in agreement with the individual sensitivities of the parameters. Consequently, we estimate the parameters which are more sensitive by the polynomial linear regression approach.

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1. INTRODUCTION

Mathematical Modeling possesses a pivotal position in understanding the different physiological processes [12]. One of the most important biological processes is the glucose-insulin regulatory system [5], [1]. In order to understand the physiological behavior of this system, various mathematical models have been proposed by different scientists, and are available in the literature. Some of these models are very helpful for the development of a closed-loop algorithm in order to control the blood- glucose concentration in the body [18].

Bergman et al. proposed the four compartmental mathematical model of glucose-insulin kinetic on the basis of the Intravenous Glucose Tolerance Test (IVGTT) [3] in the late seventies. This model is commonly used in the mathematical theory and in the clinical research to understand the glucose-insulin system. A detailed study and analysis of this model is found in [13]. In literature, more than 500 studies based on minimal model have been found [13]. Hovarka et al. [6], Sorenson [16] and Puckett [15] modified minimal model and focused on Type-1 diabetic patients [18]. Topp et al., Roy et al., introduced mathematical models [4], which deal with Type-2 diabetes, however, these models ignore the effect of delays. Inclusion of the delay factors are useful for the better understanding of the oscillatory behavior of the insulin and glucose regulatory system.

Researchers suggested two delays, Hepatic Glucose Production(HGP) delay and Insulin Secretion(IS) delay to be relevant to the oscillations of glucose and insulin. HGP delay was considered as the time taken for “remote insulin” to stimulate HGP to secrete glucose. IS delay is defined as the time for the elevated plasma glucose to change the insulin secretion. Sturis et al., [17] proposed compartmental model similar to Bergman minimal model and introduced HGP delay to study oscillating behavior of glucose and insulin. Li et al., in [9], and [10] proposed one-compartment models, considering IS and HGP delays explicitly. The combined effect of the two delays was considered by using the sum of the two delays and proposed that the combined effect of the two delays influenced the dynamics of the glucose-insulin feedback mechanism, but not each individual delay.

The novel double diabetes model studied in [5] considered the effect of two delays with subcutaneously injected insulin and glucose measurements. Insulin administered via subcutaneous has the advantage to make the management of diabetes more effectively than intravenous. Through sensitivity analysis of the novel double diabetes model, it is possible to investigate the behavior of the system which provides rich information for the diabetes control.

In the present study, we present a novel diabetes model in Section 2. The sensitivity analysis is briefly described in Section 3 and the sensitivity studies of the NDDM model is made in Subsection 3.1. The detail of numerical implementation for the model is given in Section 4 and the results are discussed in Section 5. The general solution of the model is presented in Section 6 and the selected parameters are estimated in Section 7. The conclusion of the whole analysis is given in Section 8.

2. NOVEL DOUBLE DIABETES MODEL

Novel double diabetes model consists of a set of six ordinary differential equations and seven sub-functions [18]. This model has seventeen parameters. The description of all state variables, sub-functions and parameters of the model are described in Table(1), Table(2), and Table(3) respectively [18].

$$\begin{aligned}
 \dot{G}_p &= G_{in} + HGP - U_{ii} - E - k_1G_p + k_2G_i \\
 \dot{G}_i &= k_1G_p - k_2G_i - U_{id} \\
 \dot{Q}_{1a} &= Pu - k_{a1}Q_{1a} - LD_a \\
 \dot{Q}_{1b} &= u(1 - p) - k_{a2}Q_{1b} - LD_b \\
 \dot{Q}_2 &= k_{a1}Q_{1a} - k_{a1}Q_2 \\
 \dot{I}_p &= \alpha S + k_{a1}Q_2 + k_{a2}Q_{1b} - k_e I_p
 \end{aligned}
 \tag{2.1}$$

The seven sub-functions used in the model are described below:

(1)

$$U_{id} = \beta \times f_3(G_i) \times f_4(Q_{1a}, Q_{1b}, Q_2),$$

where

$$f_3(G_i) = 0.01G_i/V_g,$$

and

$$\begin{aligned}
 f_4(Q_{1a}, Q_{1b}, Q_2) &= 4 + \frac{90}{[1 + \exp(Z)]}, \\
 Z &= -1.772\log[(Q_{1a} + Q_{1b} + Q_2) \times (1/v_{ii} + 0.03/e)] + 7.76.
 \end{aligned}$$

(2)

$$HGP(I_p) = \frac{160}{1 + \exp\left(0.29\left(\frac{I_p}{v_{ip}} - 7.5\right)\right)},$$

(3)

$$S(G_p) = \frac{210}{1 + \exp\left(5.21 - \frac{0.03G_p}{V_{gp}}\right)},$$

(4)

$$U_{ii} = -72\left(1 - \exp\left(-8.267 \times 10^{-4}G_p\right)\right),$$

(5)

$$E(G_p) = \begin{cases} 0.0005[G_p - 339BW] & \text{if } G_p > 339BW, \\ 0 & \text{if } G_p < 339BW, \end{cases}$$

Variable	Definition	Unit
G_p	Amount of glucose in plasma compartment	mg
G_i	Amount of glucose in subcutaneous compartment	mg
Q_2	Amount of insulin in subcutaneous compartment (slow channel)	mU
Q_{1a}	Amount of insulin in subcutaneous compartment (slow channel)	mU
Q_{1b}	Amount of insulin in subcutaneous compartment (fast channel)	mU
I_p	Amount of insulin in plasma compartment	mU

Table 1. State Variable of the Novel Model

Variable	Definition	Unit
G_{in}	Glucose intake rate	Pmg min ⁻¹
U_{ii}	Insulin independent glucose utilization	mg min ⁻¹
U_{id}	Insulin dependent glucose utilization	mg min ⁻¹
E	Renal excretion	mg min ⁻¹
S	Insulin secreted by pancreas	mu min ⁻¹
LD_a	Local insulin degradation	mu min ⁻¹
LD_b	Local insulin degradation	mu min ⁻¹

Table 2. Sub-Functions of the Novel Model

(6)

$$LD_a(Q_{1a}) = V_{\max-LD} \times Q_{1a} / (K_m-LD + Q_{1a}),$$

(7)

$$LD_b(Q_{1b}) = V_{\max-LD} \times Q_{1b} / (K_m-LD + Q_{1b}).$$

The mechanism of delays plays a vital role in physiological system [18]. In the model, two delay parameters τ_1 and τ_2 are used which enhance the accuracy of the glucose-insulin system under examination.

Glucose moves in arteries and peripherals. Brain and Central Nervous System(CNS) use glucose without insulin dependency, this mechanism is known as insulin independent glucose utilization U_{ii} . Liver, muscles and adipose tissue use glucose depending upon insulin; this mechanism is known as insulin dependent glucose utilization U_{id} .

Parameter	Definition	Values
k_e	Insulin clearance rate of plasma by kidney & liver	0.37 min^{-1}
k_1	Transfer rate from plasma to subcutaneous glucose compartment	0.032 min^{-1}
k_2	Transfer rate from subcutaneous to plasma glucose compartment	0.02 min^{-1}
k_{a1}	Transfer rate from insulin subcutaneous (slow channel) to plasma insulin compartment	0.14 min^{-1}
k_{a2}	Transfer rate from insulin subcutaneous (fast channel) to plasma insulin compartment	0.13 min^{-1}
p	Proportion of insulin flux passing through slow channel	0.55
$V_{\text{max-LD}}$	Saturation rate for continuous infusion and bolus	235 mUmin^{-1}
$k_{\text{m-LD}}$	Insulin mass at which insulin degradation is equal to half maximal value	65 mU
e	Insulin exchange rate between plasma and subcutaneous	0.2 min^{-1}
τ_1	HGP delay	37 mgmin^{-1}
τ_2	Insulin Secretion delay(IS)	45 mgmin^{-1}
v_{ii}	Insulin distribution volume in subcutaneous compartment	7 L/kg
v_{ip}	Insulin distribution volume in plasma	3.15 L/kg
v_{gp}	Glucose distribution volume in plasma	8.4 L/kg
v_{gi}	Glucose distribution volume in subcutaneous compartment	7 L/kg

Table 3. Parameters of the Novel Model

3. SENSITIVITY ANALYSIS

Since novel model is a compartmental model with six outputs G_p, G_i, Q_{1a}, Q_{1b} and Q_2 , we consider a multiple-output system with the measurable outputs [8], [14] modeled by

$$(3.1) \quad f(t, \theta) = \text{col}(f_1(t, \theta), \dots, f_\ell(t, \theta)), \quad 0 \leq t \leq T,$$

where $T > 0$ is fixed. The open set, $\theta \in U \subset R^p$, is the set of admissible parameters. We assume that the output model given by Equation (3.1) is a valid description of the real system for all $t \in [0, T]$ and $\theta \in U$ and the component outputs $f_k, k = 1, \dots, \ell$, are sufficiently smooth. θ is the vector of parameters which is to be

estimated. The sensitivity of the model output f_k with respect to the parameter component θ_n , represented by $s_{\frac{f_k}{\theta_n}}$, is defined by.

$$s_{\frac{f_k}{\theta_n}}(t) = \lim_{\Delta\theta_n \rightarrow \infty} \frac{\Delta f_k(t, \theta) / f_k(t, \theta)}{\Delta\theta_n / \theta_n}, \quad n = 1, \dots, r, \quad k = 1, \dots, \ell.$$

The above result simplifies to

$$(3.2) \quad s_{\frac{f_k}{\theta_n}}(t) = \frac{\partial f_k(t, \theta)}{\partial \theta_n} \cdot \frac{\theta_n}{f_k(t, \theta)}, \quad n = 1, \dots, r, \quad k = 1, \dots, \ell.$$

Here assume that f_k and θ_n are non-zero $k = 1, \dots, \ell$, and $n = 1, \dots, r$. The sensitivity function describes the behavior of model function output by changing the parameters' values [11]. It quantifies to which parameter is the model output is the most or less sensitive. The sensitivity functions are used in the parameter identification problems [7].

The system sensitivity with respect to a model parameter θ_n over time interval $[0, T]$ describes the sensitivity of all model outputs $f_k, k = 1, \dots, \ell$ with respect to θ_n , and is defined by the following relation [13].

$$(3.3) \quad s_{\theta_n} = \left(\sum_{k=1}^{\ell} \left(s_{\frac{f_k}{\theta_n}}(t) \right)^2 \right)^{1/2}, \quad n = 1, \dots, r.$$

3.1 Sensitivity Analysis of the NDDM. In order to check the sensitivity of the parameters $(k_1, k_2, k_{a1}, k_{a2}, k_e)$, we use all parametric values except $(k_1, k_2, k_{a1}, k_{a2}, k_e)$ in the model. Then, the model equations become

$$(3.4) \quad \begin{aligned} \dot{G}_p &= -k_1 G_p + k_2 G_i + \frac{160}{1 + \exp(0.0921 I_p - 2.175)} - 72 (1 - \exp(-8.267 \times 10^{-4} G_p)) \\ \dot{G}_i &= k_1 G_p - k_2 G_i - 2.97024 \times 10^{-3} G_i - \frac{0.0668304 G_i}{1 + 20658.4 (Q_{1a} + Q_{1b} + Q_2)^{-1.772}} \\ \dot{Q}_{1a} &= 5.5 - k_{a1} Q_{1a} - \frac{235 Q_{1a}}{65 + Q_{1a}} \\ \dot{Q}_{1b} &= 4.5 - k_{a2} Q_{1b} - \frac{235 Q_{1b}}{65 + Q_{1b}} \\ \dot{Q}_2 &= k_{a1} Q_{1a} - k_{a1} Q_2 \\ \dot{I}_p &= \frac{88.2}{1 + \exp(5.21 - 3.5714 \times 10^{-3} G_p)} + k_{a1} Q_2 + k_{a2} Q_{1b} - k_e I_p. \end{aligned}$$

4. NUMERICAL IMPLEMENTATION

We take $\theta = (k_1, k_2, k_{a1}, k_{a2}, k_e)$, then a system of sensitivity equations is obtained using Equation (3.2) with respect to θ . Taking the initial condition as $G_p(0) = 15, G_i(0) = 14, Q_{1a}(0) = 2, Q_{1b}(0) = 1.5, Q_2(0) = 1.5, I_p(0) = 1$, we solve the system of sensitivity equations by using the Matlab ode solver *ode45* over the time interval $[0, 10]$.

5. RESULTS

In first subsection, we find the sensitivities of the model outputs with respect to the model parameters, and in the second subsection we find the system sensitivity of the whole model output.

5.1 Sensitivites. Sensitivity analysis identifies the parameters to which the model output is the most or the least sensitive [2]. The sensitivities of the model outputs with respect to the selected parameters are given in the following parts.

- (1) **Sensitivity of G_p with respect to Parameters $k_1, k_2, k_{a1}, k_{a2}, k_e$:** Sensitivity of the plasma glucose, G_p , with respect to the parameters k_1, k_2, k_{a1}, k_{a2} and k_e is presented in Figure (1). It shows that the plasma glucose, G_p , is sensitive to all five parameter upto 10 minutes. This means the changes in the true value of these parameters change G_p output.

The Parameter k_1, k_2 are the glucose transfer rates modeling the material exchange between the plasma and the subcutaneous region. Since the output, G_p , is sensitive to k_1 and k_2 , these parameters affect the evaluation of the glucose concentration in the plasma glucose region. If k_1 is greater in amount, then the glucose transfers from the plasma to the subcutaneous compartment and extra glucose moves back from subcutaneous to the plasma compartment through k_2 , then the glucose level tends to normal range. If k_1 is smaller in amount, then less amount of glucose transfers from the plasma to the subcutaneous compartment through k_2 and less glucose moves from the subcutaneous to the plasma compartment, then the glucose level increases from normal range that leads to diabetes.

The model output, G_p , is sensitive to the paramters k_{a1}, k_{a2} . The glucose-insulin regulatory system shows large variation due to small changes in these parameters. If the transfer rates, k_{a1}, k_{a2} , are greater, than more insulin moves from the subcutaneous tissues to the plasma, and maintain the blood glucose level.

Plasma glucose, G_p , is also sensitive to the insulin clearance rate, namely k_e . When k_e decreases, its results is shown in higher plasma insulin that maintains the blood glucose level. When it increases, the results is shown in terms of low plasma insulin that leads to diabetes.

The combined sensitivity of the output, G_p , for the selected parameter is presented in Figure (3) (upper panel) which shows that G_p is the most sensitive to the parameters k_1, k_e, k_{a1} and less sensitive to the parameters k_2 , and k_{a2} .

- (2) **Sensitivity of G_i with respect to Parameters $k_1, k_2, k_{a1}, k_{a2}, k_e$:** Sensitivity of the subcutaneous glucose, G_i , with respect to the selected parameters is presented in Figure (2). The combined sensitivity of the output, G_i , for the selected parameters is presented in Figure (3) (lower panel) which shows that G_i is the most sensitive to the parameter k_1 than the other four parameters.

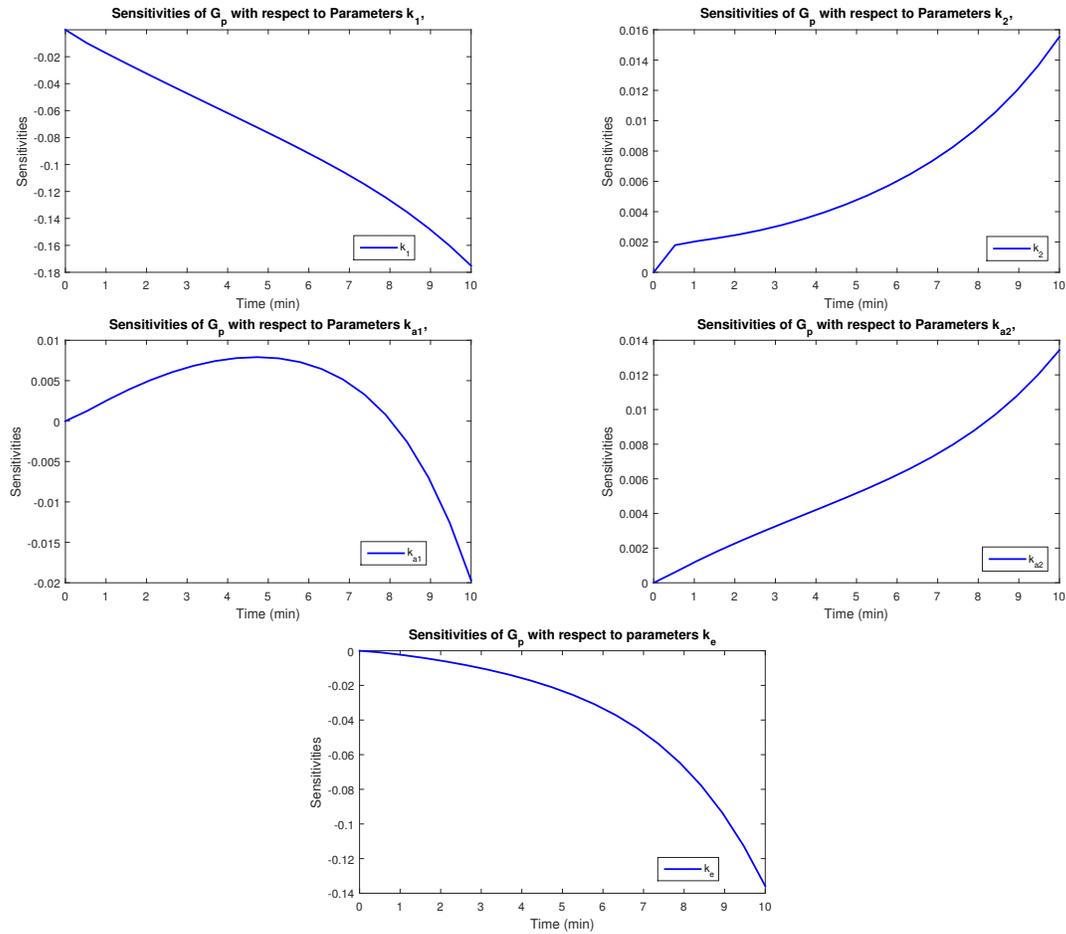


Fig. 1. Sensitivity of G_p w.r.t the Selected Parameters.

(3) **Sensitivity of Q_{1a} , Q_{1b} , Q_2 and I_p with respect to the Parameters $k_1, k_2, k_{a1}, k_{a2}, k_e$:** The combined sensitivities of the outputs Q_{1a} , Q_{1b} , Q_2 and I_p w.r.t the parameters $k_1, k_2, k_{a1}, k_{a2}, k_e$ are presented in Figure (4).

It is observed that Q_{1a} , Q_2 and I_p outputs are not sensitive to the four parameters k_1, k_2, k_{a2} and k_e upto 10 minutes. This means the changes in the true value of the parameters k_1, k_2, k_{a2} and k_e do not bring changes in Q_{1a} , Q_2 and I_p output. These output are only sensitive to k_{a1} for the 1 minutes. This implies that changes in parameter, k_{a1} , will change in the outputs Q_{1a} , Q_2 and I_p in the beginning and not afterwards. Moreover, Q_{1b} is not sensitive to all the five parameters k_1, k_2, k_{a1}, k_{a2} and k_e upto 10 minutes. This implies the changes in the true value of the parameters k_1, k_2, k_{a1}, k_{a2} and k_e do not bring change in the output, Q_{1b} .

5.2 System Sensitivities. System sensitivities of the parameters combine the individual affects of the sensitivities of both glucose and insulin with respect to all parameters. Using Equation (3.3), the system sensitivities of the model is evaluated, and is presented in Figure (5). The information given by the time

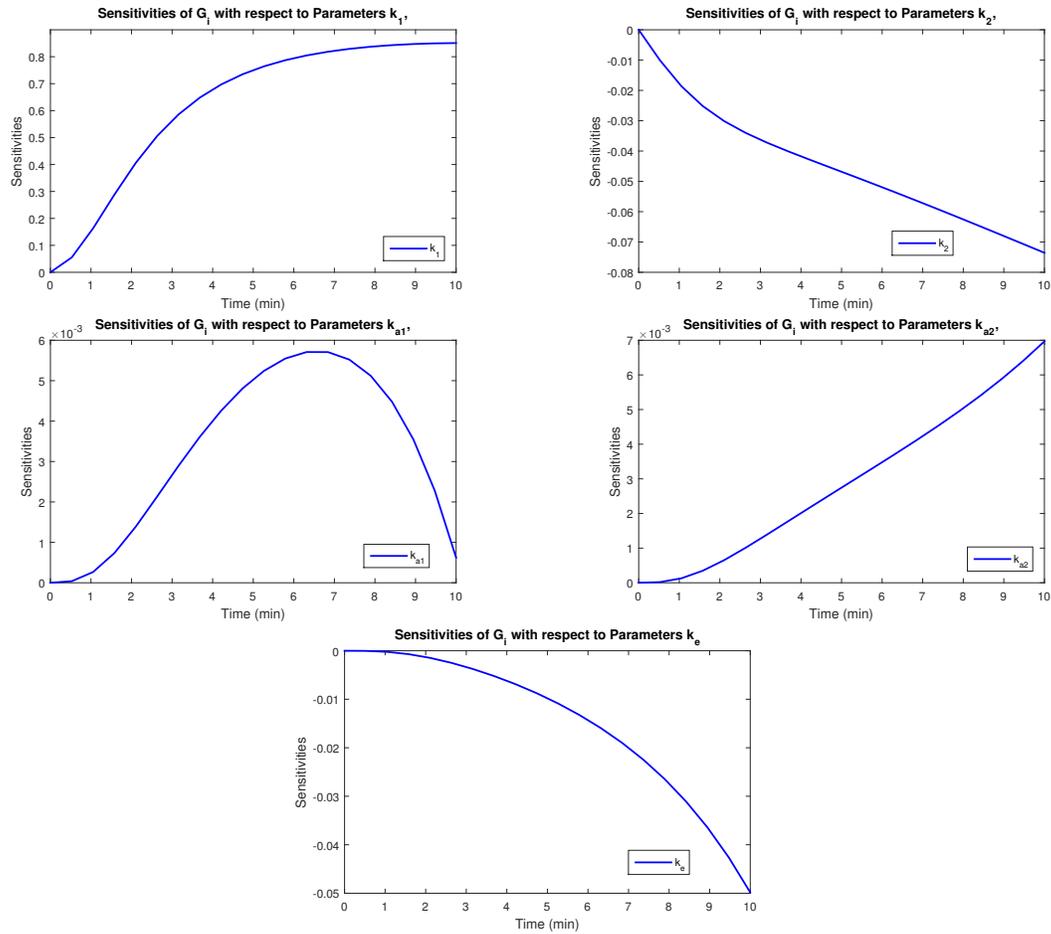


Fig. 2. Sensitivity of G_i w.r.t the Selected Parameters.

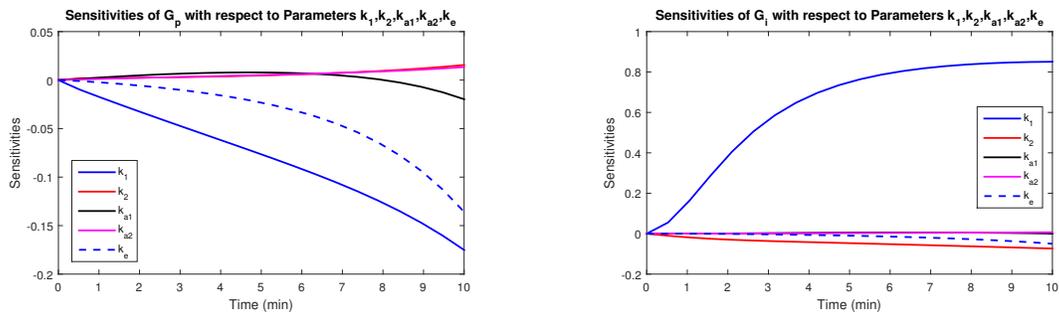


Fig. 3. Sensitivity of G_p and G_i w.r.t the all selected Parameters.

courses of the system sensitivities are more or less similar to the information given by their individual sensitivities. The system sensitivities indicate that the model output of the whole glucose-insulin regularity system is the most sensitive with respect to the parameter k_{a1} than all the other parameters. From the system sensitivity, we quantify that the parameters in the descending order of their sensitivities are $k_{a1}, k_1, k_e, k_{a2}, k_2$. From these results, we observe that the novel double diabetes model is majorly affected by the

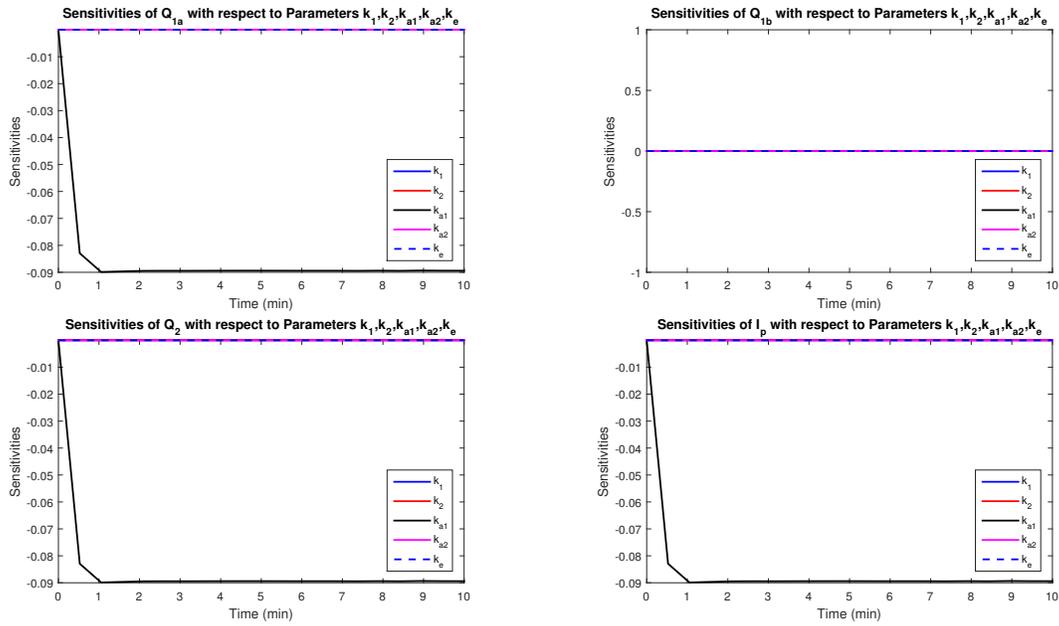


Fig. 4. Sensitivity of the Insulin Variables w.r.t the Selected Parameters.

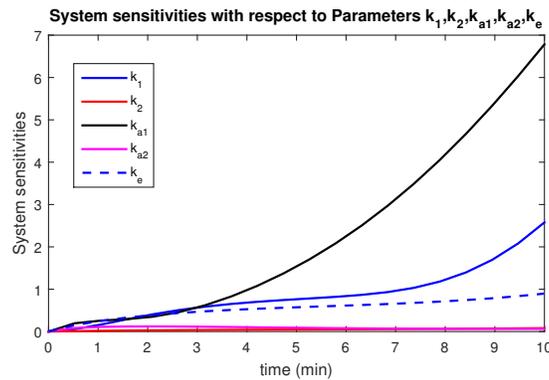


Fig. 5. System Sensitivity of Model

rate at which insulin is injected through subcutaneous tissues. Model is also affected by the rate at which glucose move from plasma to subcutaneous tissues and insulin clearance rate through the kidney and liver at which insulin deactivates. k_{a2} and k_2 are the least sensitive, this means the changes in the true value of the parameters k_{a2} and k_2 do not bring any major change in the model output.

The sensitivity analysis signifies that the parameters are identified by the availability of data for any compartment $G_p, G_i, Q_{1a}, Q_{1b}, Q_2, I_p$. In order to estimate model parameter, we need to find the general solution.

6. LINEARIZATION AND GENERAL SOLUTION

NDDM is nonlinear system. We linearize it about the equilibrium point. The equilibrium point is obtained by putting the rate of change of each state to zero, and then assigning values to parameters [18], as given in Table 3. We get the feasible equilibrium point as

$$(6.1) \quad (G_p, G_i, Q_{1a}, Q_{1b}, Q_2, I_p) = (0.7235, 1.0066, 1.5, 1.2, 1.5, 2.2982).$$

To estimate the parameters, $(k_1, k_2, k_{a1}, k_{a2}, k_e)$, we use the model Equation (3.4) and linearize it using the Jacobin matrix given by Equation (6.2) about the equilibrium point given in (6.1).

$$(6.2) \quad A = \begin{bmatrix} \frac{\partial G_p}{\partial G_p} & \frac{\partial G_p}{\partial G_i} & \frac{\partial G_p}{\partial Q_{1a}} & \frac{\partial G_p}{\partial Q_{1b}} & \frac{\partial G_p}{\partial Q_2} & \frac{\partial G_p}{\partial I_p} \\ \frac{\partial G_i}{\partial G_p} & \frac{\partial G_i}{\partial G_i} & \frac{\partial G_i}{\partial Q_{1a}} & \frac{\partial G_i}{\partial Q_{1b}} & \frac{\partial G_i}{\partial Q_2} & \frac{\partial G_i}{\partial I_p} \\ \frac{\partial Q_{1a}}{\partial G_p} & \frac{\partial Q_{1a}}{\partial G_i} & \frac{\partial Q_{1a}}{\partial Q_{1a}} & \frac{\partial Q_{1a}}{\partial Q_{1b}} & \frac{\partial Q_{1a}}{\partial Q_2} & \frac{\partial Q_{1a}}{\partial I_p} \\ \frac{\partial Q_{1b}}{\partial G_p} & \frac{\partial Q_{1b}}{\partial G_i} & \frac{\partial Q_{1b}}{\partial Q_{1a}} & \frac{\partial Q_{1b}}{\partial Q_{1b}} & \frac{\partial Q_{1b}}{\partial Q_2} & \frac{\partial Q_{1b}}{\partial I_p} \\ \frac{\partial Q_2}{\partial G_p} & \frac{\partial Q_2}{\partial G_i} & \frac{\partial Q_2}{\partial Q_{1a}} & \frac{\partial Q_2}{\partial Q_{1b}} & \frac{\partial Q_2}{\partial Q_2} & \frac{\partial Q_2}{\partial I_p} \\ \frac{\partial I_p}{\partial G_p} & \frac{\partial I_p}{\partial G_i} & \frac{\partial I_p}{\partial Q_{1a}} & \frac{\partial I_p}{\partial Q_{1b}} & \frac{\partial I_p}{\partial Q_2} & \frac{\partial I_p}{\partial I_p} \end{bmatrix}$$

Putting the value of the corresponding entries in the Jacobian matrix A , we get the matrices A, A^2, A^3, \dots , as follow.

$$A = \begin{bmatrix} -k_1 - 0.05946 & k_2 & 0 & 0 & 0 & 1.59065 \\ k_1 & -k_2 - 0.00301 & -0.00002 & -0.00002 & -0.00002 & 0 \\ 0 & 0 & -k_{a1} - 3.451 & 0 & 0 & 0 \\ 0 & 0 & 0 & -k_{a2} - 3.4855 & 0 & 0 \\ 0 & 0 & k_{a1} & 0 & -k_{a1} & 0 \\ 3.5506 * 10^{-3} & 0 & 0 & k_{a2} & k_{a1} & -k_e \end{bmatrix},$$

$$A^2 = \begin{bmatrix} k_1^2 + 0.11892K_1 & k_2(-k_1 & -0.00002k_2 & -0.00002k_2 & -0.00002k_2 & 1.59065(-k_1 \\ +k_1k_2 + 0.00919 & -k_2 - 0.06247) & + 1.59065k_{a2} & + 1.59065k_{a1} & -k_e - 0.05946) \\ k_1(-k_1 & k_1k_2 + k_2^2 & -0.00002(-k_2 & -0.00002(-k_2 & -0.00002(-k_2 & 1.59065k_1 \\ -k_2 - 0.06247) & +0.00602k_2 & -3.454) & -k_{a1} - 3.48851) & -k_{a2} - 3.4885) \\ 0 & +0.00001 & (-k_{a1} - 3.451)^2 & 0 & 0 & 0 \\ 0 & 0 & 0 & (-k_{a2} - 3.4855)^2 & 0 & 0 \\ 0 & 0 & -2k_{a1}^2 - 3.451k_{a1} & 0 & (k_{a1})^2 & 0 \\ 3.5506 * 10^{-3}(-k_1 & 3.5506 * 10^{-3}k_2 & k_{a1}^2 & k_{a2}(-k_{a2} - k_e - 3.4855) & -k_{a1}^2 - k_e k_{a1} & 0.00565 + k_e^2 \\ -k_e - 0.05946) & & & & & \end{bmatrix} \dots$$

General solution is

$$(6.3) \quad x(t) = \exp(At)x(0) + \int_0^t \exp(A(t-\tau))Bu(\tau) d\tau,$$

where

$$\exp(At) = I + At + A^2t^2/2! + A^3t^3/3! + \dots + A^k t^k/k! + \dots,$$

$$B = \begin{bmatrix} 1 & 1 & 0 & 0 & 0 & 0 \\ 1 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 \end{bmatrix},$$

$$u = [0 \quad 0 \quad 1 \quad 1 \quad 1 \quad 0]^T.$$

When we neglect A^3 , and the higher power of A , we get,

$$\exp(At) = I + At + A^2t^2/2!.$$

The general solution then becomes

$$(6.4) \quad x(t) = [G_p(t) \quad G_i(t) \quad Q_{1a}(t) \quad Q_{1b}(t) \quad Q_2(t) \quad I_p(t)]^T,$$

$$(6.5) \quad \begin{aligned} G_p(t) = & 150 + t[-150k_1 + 132k_2 + 13.69095] + t^2[75(k_1)^2 + 6.533(k_1) \\ & + 9(k_1)(k_2) - 66(k_2)^2 - 4.12(k_2) + 3.5789(k_{a2}) \\ & + 3.49(k_{a1}) - 2.386k_e - 0.133] + t^3[-9.9 \times 10^{-6}k_2 \\ & + 0.265k_{a2} + 0.265k_{a1}] + t^4[(-k_1 - 0.05946) \\ & \times (-3.3 \times 10^{-6}(k_2) + 0.265(k_{a1}) + 0.265(k_{a2}) - 1.67 \\ & \times 10^{-5}) + 9.9 \times 10^{-6}(k_2)^2 + 1.735(k_2) - 1.7 \\ & \times 10^{-6}(k_{a1})(k_2) - 1.7 \times 10^{-6}(k_{a2})(k_2) \\ & + 0.1319(k_{a2})^2 + 1.4096(k_{a2}) + 0.13266(0.37)(k_{a2}) \end{aligned}$$

$$\begin{aligned}
& + 0.132(0.37)(k_{a1}) + 0.39766(k_1)(k_{a2}) + 0.397(k_1)(k_{a1}) \\
& + 0.0236(k_{a1}) + 0.0017] + t^5[-2.5 \times 10^{-3}k_1^3 - 2.5 \\
& \times 10^{-3}k_1^2 + 0.021k_1 + 0.534k_{a2}k_1^2 + 0.515k_1k_{a2} \\
& + 28.38k_{a2} + 0.13k_1k_{a2}^2 + 1 \times 10^{-3}k_1k_e^2 \\
& + 2.65 \times 10^{-3}k_e^2 + 0.1325k_1k_{a2}^2 + 0.265k_e k_1k_{a2} \\
& + 0.1325k_e k_{a2}^2 + 0.469k_e k_{a2} + 7.88 \times 10^{-3}k_{a2}^2 \\
& + 0.027k_{a2} + 5.9 \times 10^{-5}k_1k_e + 1.57 \times 10^{-4}k_e - 2.34 \times 10^{-4}],
\end{aligned}$$

$$\begin{aligned}
G_i(t) = & 132 + t(150k_1 - 132k_2 - 0.397608) + t^2(-149.6k_2 - 146.58k_1 + 66k_1k_2 \\
& + 66k_2^2 + 4.4 \times 10^{-5}k_{a2} - 9.36903) + t^3(6.96992 \times 10^{-5} + 3.3 \times 10^{-6}(k_{a1} + k_2 \\
& + k_{a2}) + t^4(0.26511k_{a2}k_1 - 0.1326k_{a1}k_1 - 0.39771k_2k_1 + (1.5 \times 10^{-5}) \\
& \times (k_1k_2 + k_2^2 + 0.00602k_2 + 0.00001) + ((-k_2 - 0.00301) \times (3.3 \times 10^{-6}(k_2 \\
& + k_{a1} + k_{a2}))1.16259 \times 10^{-5}) + ((-3.3 \times 10^{-6}) \times (k_{a2} + 3.4855))^2 \\
& + ((-5 \times 10^{-6}) \times (-k_2 - k_{a1} - 3.4885) \times (k_{a2} + 3.4855) + (-3.333 \times 10^{-6}) \\
& \times (k_{a1} + 3.451))^2 + ((-5 \times 10^{-6}) \times (-k_2 - 3.454) \times (k_{a1} + 3.451) \\
& - 0.3977k_1k_2 - 0.3977k_1k_{a1} + 3.3 \times 10^{-6}k_{a1}^2 + 1.138 \times 10^{-5}) \\
& + t^5((0.5)k_1 \times (-k_1 - k_2 - 0.06247) \times (-9.9 \times 10^{-6}k_2) + 0.265k_{a1} \\
& + 0.265k_{a2} + 0.5 \times (k_1k_2 + k_2^2 + 0.00602k_2 + 0.00001) \times (1.32 \times 10^{-5}k_2 \\
& + 3.3 \times 10^{-6}(k_{a1} + k_{a2}) + 2.30241 \times 10^{-5}) + (-1.66 \times 10^{-6}) \times (-k_2 - k_{a1} - 3.4885) \\
& \times (k_{a2} + 3.4855))^2 + (1.666 \times 10^{-6}) \times (k_2 + 3.454) \times (k_{a1} + 3.451))^2 \\
& + 0.13255k_1k_{a1}^2 + (0.13255) \times (-k_1k_2k_{a2}^2 - k_e k_1k_2 - 3.4855k_1k_{a2}) \\
& - 1.3255(k_1k_{a1}^2) - 1.3255k_1k_e k_{a1} - 1.6 \times 10^{-6}(k_2 + k_{a2} \\
& + 3.4885) - 5.52 \times 10^{-6}k_{a1}(k_2 + k_{a2} + 3.4885)),
\end{aligned}$$

$$\begin{aligned}
Q_{1a}(t) = & t + t^2(-0.5(k_{a1} + 3.451)) + t^3(0.167(k_{a1} + 3.451)^2) \\
& + t^4(0.25(k_{a1} + 3.451)^3) + t^5(0.083(k_{a1} + 3.451)^4) - (k_{a1} + 3.451)^3),
\end{aligned}$$

$$\begin{aligned}
Q_{1b}(t) = & t + t^2(-0.5k_{a2} - 1.7443) + t^3(0.167(k_{a2} + 3.4885)^2) \\
& + t^4(0.083(k_{a2} + 3.4885)^3) + t^5(0.083(k_{a2} + 3.4885)^4),
\end{aligned}$$

$$\begin{aligned}
Q_2(t) = & t + t^3(-0.667k_{a1}^2 - 2.251k_{a1}) + t^4(0.167(2k_{a1}^2 \\
& + 3.451k_{a1})k_{a1} - 0.167(k_{a1})^3 + 0.167(k_{a1}(k_{a1} + 3.451)^2) \\
& + 0.25(-2k_{a1}^2 - 3.451k_{a1})(k_{a1} + 3.451)) + t^5(0.083(k_{a1})^2)(-2k_{a1}^2 \\
& - 3.451k_{a1}) + 0.083(k_{a1}^4) + 0.083(k_{a1} + 3.451)^2(-2k_{a1}^2 - 3.451k_{a1})
\end{aligned}$$

and

$$\begin{aligned}
I_p(t) = & 4.3 + t(0.5325 + 4.5k_{a2} + 4.4k_{a1} - 1.3k_e) + t^2(-0.26625k_1 - 0.26625k_e \\
& - 1.5831 \times 10^{-3} + 0.2343k_2 + 0.551k_{a1}^2 - 2.25k_{a2}(-k_{a1} - k_e - 3.4885) \\
& - 2.2k_e k_{a1} + 2.15k_e^2 - 2.2k_e k_{a1} + 0.5k_{a2} + 0.5k_{a1}) + t^3(0.5k_{a1}^2 \\
& - 0.167k_{a2}^2 - 0.5k_e k_{a1} - 0.167k_e k_{a2}) + t^4(8.87 \times 10^{-8}k_2 - 4.69 \\
& \times 10^{-4}k_{a2} - 4.69 \times 10^{-4}k_{a1} - 0.083k_e^2 k_{a1} - 0.25k_e^2 k_{a2} \\
& + 0.167k_{a2}(k_{a2} + 3.4885)^2) + 0.25k_{a2}(-k_{a2} - k_e - 3.4885)(k_{a2} + 3.4885) \\
& + 0.167(-k_{a1}^3 - 3.451k_{a1}^2) + 0.167k_e k_{a2}(k_{a2} + k_e + 3.4885)) \\
& + t^5((1.7755 \times 10^{-8}k_2) \times (-k_1 - k_e - 0.005946) + (4.7 \times 10^{-4}k_{a2}) \\
& \times (-k_1 - k_e - 0.05946) + (4.71 \times 10^{-4}k_{a1}) \times (-k_1 - k_e - 0.05946) \\
& + (5.85 \times 10^{-9}k_2)(-3k_2 - k_{a1} - k_{a2} - 10.431) + (0.08k_{a1}^2) \\
& \times (k_{a1} + 3.451)^2 + 0.08k_{a2}(-k_{a2} - k_e - 3.4885)(k_{a2} + 3.4885)^2 \\
& + 0.08k_{a2}(0.00565 + k_e^2)(-k_{a2} - k_e - 3.4885) - 0.08k_e k_{a1}(0.00565 + k_e^2)).
\end{aligned}$$

General solution of the novel double diabetes does not exist in the closed form. Different methods of parameter estimation exist in literature. For example, the maximum likelihood method, methods of moments, Cramer-von Mises method, and the least square method etc. Since general solution of model is in the complex form, we are unable to convert solution into probability density function. So, Estimation method like maximum likelihood method, methods of moments, Cramer-von Mises method are not used for estimation purposes in this case. However, model differential equation yields solution in the form of a polynomial regression. So, polynomial regression least square method is the appropriate method for the parameter estimation of the model in this case.

7. POLYNOMIAL REGRESSION LEAST SQUARE APPROACH

Polynomial regression least square method is used to estimate the rate parameters k_1, k_2, k_{a1}, k_{a2} by the collection of data of the model output, G_p . Through sensitive analysis of G_p with respect to parameters, it

t	0	120	90	150	120	300
$G_p(t)$	150	210	240	225	250	215

Table 4. Numerical measurements of G_p

has been observed that G_p is more sensitive with respect to k_1, k_{a1}, k_e rather than k_2, k_{a2} . So, we assign parametric values from Table 3 to k_2 and k_{a2} , we only estimate the sensitive parameters k_1, k_{a1} , and k_e are estimated. From Equation (6.5), taking:

$$\begin{aligned}
 \beta_0 &= 150, \\
 \beta_1 &= -150k_1 + 132k_2 + 13.69095, \\
 \beta_2 &= 75k_1^2 + 6.533k_1 + 9k_1k_2 - 66k_2^2 - 4.12k_2 + 3.5789k_{a2} \\
 &\quad + 3.49k_{a1} - 2.386k_e - 0.133, \\
 \beta_3 &= -9.9 \times 10^{-6}k_2 + 0.265k_{a2} + 0.265k_{a1}.
 \end{aligned}
 \tag{7.1}$$

and similarly adjusting β_4 and β_5 , then $G_p(t)$ becomes:

$$G_p(t) = \beta_0 + \beta_1t + \beta_2t^2 + \beta_3t^3 + \beta_4t^4 + \beta_5t^5.
 \tag{7.2}$$

The Equation (7.2) yields polynomial regression model

$$G_p(t) = Q\beta.
 \tag{7.3}$$

We consider the measurement scheme of $G_p(t)$ against the values of time T as given in Table(4) [18].

Then the least square estimates $\hat{\beta}$ are determined by

$$\hat{\beta} = (Q'Q)^{-1}Q'G_p(t).
 \tag{7.4}$$

By using data, Equation (7.4) becomes

$$G_p(t) = \begin{bmatrix} 1 & 0 & 0 & 0 & 0 & 0 \\ 1 & 120 & 14400 & 1728000 & 207360000 & 2.48832 \times 10^{10} \\ 1 & 90 & 8100 & 729000 & 65610000 & 5904900000 \\ 1 & 150 & 22500 & 3375000 & 506250000 & 7.59375 \times 10^{10} \\ 1 & 120 & 14400 & 1728000 & 207360000 & 2.48832 \times 10^{10} \\ 1 & 300 & 90000 & 27000000 & 810000000 & 2.43 \times 10^{12} \end{bmatrix} \times \begin{bmatrix} \beta_0 \\ \beta_1 \\ \beta_2 \\ \beta_3 \\ \beta_4 \\ \beta_5 \end{bmatrix}$$

Here

$$Q = \begin{bmatrix} 1 & 0 & 0 & 0 & 0 & 0 \\ 1 & 120 & 14400 & 1728000 & 207360000 & 2.48832 \times 10^{10} \\ 1 & 90 & 8100 & 729000 & 65610000 & 5904900000 \\ 1 & 150 & 22500 & 3375000 & 506250000 & 7.59375 \times 10^{10} \\ 1 & 120 & 14400 & 1728000 & 207360000 & 2.48832 \times 10^{10} \\ 1 & 300 & 90000 & 27000000 & 8100000000 & 2.43 \times 10^{12} \end{bmatrix},$$

$$\beta = \begin{bmatrix} \beta_0 \\ \beta_1 \\ \beta_2 \\ \beta_3 \\ \beta_4 \\ \beta_5 \end{bmatrix}$$

and,

$$(Q'Q)^{-1}Q' = \begin{bmatrix} 1 & 0 & 0 & 0 & 0 & 0 \\ -0.0293 & -0.0753 & 0.1330 & 0.0493 & -0.0753 & 0.0005 \\ 0.0002 & -0.0011 & -0.0034 & -0.0035 & -0.0011 & -0.0055 \\ 0 & 0 & 0 & -0.0001 & 0 & 0.0001 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

Now Equation (7.4) becomes

$$\hat{\beta} = (Q'Q)^{-1}Q'G_p(t) = \begin{bmatrix} 150 \\ 4.0964 \\ -3.2647 \\ -0.0219 \\ -0.0017 \\ 0 \end{bmatrix},$$

which gives $\beta_0 = 150$, $\beta_1 = 4.0964$, $\beta_2 = -3.2647$, $\beta_3 = -0.0219$, $\beta_4 = -0.0017$ and $\beta_5 = 0$.

To solve the system of linear Equations (7.1) after substituting the values of regression coefficients β_0, \dots, β_5 , we use *Mathematica* software. We have gotten back the values of the sensitive parameters called the estimated values of them. These estimates are given in Table(5).

Parameters	Estimated values
k_1	0.0816
k_{a1}	-0.2126
k_e	1.5895

Table 5. Estimated Values of Sensitive Parameter

8. CONCLUSIONS

- (1) Plasma glucose G_p and subcutaneous glucose G_i are sensitive with respect to all selected parameters $k_1, k_2, k_{a1}, k_{a2}, k_e$.
- (2) Two insulin subcutaneous compartments Q_{1a}, Q_2 and one plasma insulin compartment I_p are sensitive with respect to k_{a1} .
- (3) Insulin subcutaneous compartments Q_{1b} is not sensitive with respect to all parameters.
- (4) The system sensitivity of the model output is also in agreement with the individual sensitivity of the parameters.
- (5) The sensitivity analysis signifies that parameters are identified by availability of data for any compartment $G_p, G_i, Q_{1a}, Q_{1b}, Q_2, I_p$.
- (6) Finally, we concluded that model output G_p is more sensitive with respect to k_1, k_{a1}, k_e rather than k_2, k_{a2} . Therefore, sensitive parameters k_1, k_{a1}, k_e are estimated using polynomial regression least square method and found closed to the literature value.
- (7) In a future work, we want to implement this method to a more precise and studied model so that the results are more close to the real values.

Conflicts of Interest: The author(s) declare that there are no conflicts of interest regarding the publication of this paper.

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