European Journal of Molecular & Clinical Medicine
ISSN 2515-8260 Volume 07, Issue 02, 2020

Mathematical modeling of Glucose, Insulin, β-Cell Mass: Homotopy Perturbation Method Approach

K. Saranya[1],T. Iswarya[2*] , V. Mohan[1] , K. E.Sathappan[2] L. Rajendran[3]
[1]Department of Mathematics, Thiagarajar College of Engineering, Madurai-625 015, Tamilnadu, India.
[2]PG and Research Department of Mathematics, Alagappa Govt Arts college, Karaikudi-630003, Tamilnadu, India.
[3]Department of Mathematics, AMET (Deemed to be University), Chennai 603112, Tamilnadu, India
*Corresponding author T. Iswarya(iswarya3005@gmail.com)

Abstract

The theoretical model of nonlinear differential equations having three variables(glucose, Insulin, β-cell mass) with thirteen parameters has been discussed in this manuscript for the first time. The model consists of a reaction-diffusion equation system that includes a nonlinear term related to enzymatic reaction kinetics. This paper provides the theoretical and numerical solutions of the nonlinear differential equation system.The homotopy perturbation method (HPM) is used to find analytical expressions of the glucose, Insulin, and β-cell mass respectively. A comparison is also provided between analytical approximation and numerical simulation. A reasonable agreement between theoretical and simulation results is founded.

Keywords: Mathematical model, glucose, Insulin, β cell mass kinetics,Homotopy perturbation method, Non-linear equations.

1. Introduction

The human body uses many mechanisms to regulate the concentration of glucose in the blood.The rates of glucose utilization and release from specific organs within the body are measured quantitatively by the concentrations of enzymes/ hormones and indirectly by the central nervous system.Regular physical activities, which may involve a number of types of controlled exercise, enhances insulin sensitivity, increases cardiorespiratory health, enhances glycaemic regulation, decrease the risk of cardiovascular mortality, and improves psychosocial well-being.

Now days, diabetes is a provocative disease that results in the death of beta cells containing insulin. According to the international diabetes federation reports, 463 million people living with diabetes.Diabetes-associated microvascular and macrovascular complications are becoming a health care problem worldwide. This paper discusses the modelling of Glucose,

Insulin system, which are the essential materials used to treat diabetes. The regular injection of insulin from recombinant human or animal sources also required current therapies. The materials and techniques used to produce closed-loop systems for type 1 diabetes therapy are the subject of several reviews. The following two types of treatments and the materials are used for diabetes: (i)Artificial pancreases made up of cells containing insulin trapped in a polymeric biomaterial: and (ii) synthetic pancreases produced by continuous glucose control incorporation.

Many scientists have studied the nature and diagnosis of this disease; these studies are either experimental or theoretical. The language of mathematics is widely used to describe a myriad of naturally occurring phenomena. This is partly because mathematical modelling, along with theoretical analysis allows for a qualitative description or understanding of systems as they are. It can also help estimate parameters based on which dynamical behavior is expected from a given system, or it can aid in the understanding of which parameters are most significant for the behavior. No rigorous analytical solutions have been reported, to our knowledge, for non-steady-state glucose, insulin and β-cell mass concentration. In this paper, we derived the analytical expression of non-steady-state concentration of glucose, insulin and β-cell mass using HPM.

2.Mathematical formulation of the problem:

Consider a mathematical model composed of glucoselevel *(G),* insulin level *(I)* and β cell mass. Many parameters have been takenwhich include the parameter of physical activities. The model for glucose, insulin and β cell mass dynamics are (Topp *et al.,* 2000)defined as follows:

Glucose Dynamics:

$$\begin{aligned}\frac{dG}{dt} &= Pr\,oduction - Uptake \\ &= \left[P_0 - \left(E_{G0P} + S_{IP} I\right)G\right] - \left[U_0 - \left(E_{G0U} + S_{IU} I\right)G\right] \quad (1) \\ &= R_0 - \left(E_{G0} + S_I I\right)G\end{aligned}$$

where G is the concentration of glucose in the blood and t the time. P_0 and U_0 are therates of glucose production and uptake at zero glucose. E_{G0P} and E_{G0U} are glucose effectiveness at zero insulin for production and uptake. S_{IP} , S_{IU} are insulin sensitivity for production and uptake, and I represent blood insulin concentration $R_0 = P_0 - U_0$ is the net rate of production at zero glucose, $E_{G0} = E_{G0P} + E_{G0U}$ is the total glucose effectiveness at zero insulin, and $S_I = S_{IP} + S_{IU}$ is the total insulin sensitivity.

Insulin Dynamics:

$$\frac{dI}{dt} = Secretion - Clearance = \left(\frac{\beta \sigma G^2}{\alpha + G^2}\right) - (k\,I) \quad (2)$$

where secretion and clearance are rates normalized by insulin's volume of distribution. k is a clearance constant which represents the combined insulin uptake at the liver, kidneys and insulin receptors. β is the mass of pancreatic β cells. All β-cell mass are assumed to secreteinsulin at the same maximal rate σ, and $G^2/(\alpha + G^2)$ is a Hill function that describes a sigmoid rangingfrom 0 to 1 which reaches half its maximum at $G = \alpha^{1/2}$.

β-Cell Mass Dynamics:

$$\frac{d\beta}{dt} = Formation - Loss = \left(r_{1r}G - r_{2r}G^2\right)\beta - \left(d_0 - r_{1a}G + r_{2a}G^2\right)\beta \quad (3)$$

$$= \left(d_0 - r_1 G + r_2 G^2\right)\beta \quad (4)$$

where formation and loss represent the rates at which β-cell mass is added to or removed from the population r_{1r} and r_{2r} are rate constants d_0 is the death rate at zero glucose and r_{1a} and r_{2a} are constants by substitutingreplication and death cell into Eqn.(3), we obtain the equation for β-cell mass dynamics.Also $r_1 = r_{1r} + r_{1a}$ and $r_2 = r_{2r} + r_{2a}$ are constants. A model of glucose kinetics, insulin and β-Cell mass pathways to diabetes can be written as follows (Topp *et al.*, 2000):

$$\frac{dG}{dt} = R_0 - \left(E_{G0} + S_I I\right)G \quad (5)$$

$$\frac{dI}{dt} = \frac{\beta \sigma G^2}{\alpha + G^2} - kI \quad (6)$$

$$\frac{d\beta}{dt} = \left(d_0 - r_1 G + r_2 G^2\right)\beta \quad (7)$$

Steady state solution of the Eqns.(5)-(7) becomes

Steady- state solution	$r_1 = 0.84 \times 10^{-3}\, mg^{-1} dl\, d^{-1}$, $r_2 = 0.24 \times 10^{-5}\, mg^{-2} dl^2 d^{-1}$ $d_0 = 0.06 d^{-1}, R_0 = 864\, mg\, dl^{-1} d^{-1}$, $E_{G0} = 1.44 d^{-1}, k = 432 d^{-1}$ and $\sigma = 43.2\, \mu U\, ml^{-1} d^{-1}$	Trivial equilibrium point (Topp *et al.*, 2000)
$G = \frac{r_1 + \sqrt{r_1^2 - 4 r_2 d_0}}{2 r_2}$	G=67.7	G=600

$I=\frac{1}{S_I}\left(\frac{R_0}{G}-E_{G0}\right)$	$I=15.7$	$I=0$
$\beta=\frac{Ik\left(\alpha+G^2\right)}{\sigma G^2}$	$\beta=1.8218$	$\beta=0$

For the case of non steady state,initial conditions are represented as follows:

$$G(t=0)=G_{ini} \quad (8)$$

$$I(t=0)=I_{ini} \quad (9)$$

$$\beta(t=0)=\beta_{ini} \quad (10)$$

3.Approximate analytical expression for the concentrationof glucose, insulin and β -Cellmass using HPM

Recently, many researchers have extensively used HPM in material and chemical engineering to solve several non-linear problems (Haario et al., 1994, He *et al*.,1999,2000 & 2003).J. H. He used the HPM to solve the light hill equation (He *et al*., 2006), the Duffing equation (He *et al.*, 2006)and the Blasius equation (Kalachev *et al*.,2003). The homotopy perturbation method is a simple and approximate method. In this approach p is a small embedding parameter and, few iterations are required to achieve the approximate analytical solutions.Using modified homotopy perturbation method, the concentration of glucose is obtained as follows:

$$G(t)=n_0+n_1e^{-Pt}+S_II_{ini}n_1\left(e^{-pt}-1\right)+S_Im_0n_1\left(1-e^{-pt}\right)-\frac{S_Im_1n_0}{(k-p)}\left(e^{-kt}-1\right)-\frac{S_Im_1n_1}{k}\left(e^{-(k+p)t}-1\right) \quad (11)$$

Solving equation (6) using initial condition (9), the concentration of Insulin is obtained as follows:

$$I(t)=I_{ini}+\frac{n_0^2\beta_{ini}\sigma}{\alpha+G_{ini}^2(k-l)}\left[e^{-lt}-e^{-kt}\right]+\frac{n_1^2\beta_{ini}\sigma}{\alpha+G_{ini}^2(k-l-2p)}\left[e^{-t(l+2p)}-e^{-kt}\right]+\frac{2n_0n_1\beta_{ini}\sigma}{\alpha+G_{ini}^2(k-p)}\left[e^{-pt}-e^{-kt}\right] \quad (12)$$

Solving equation (7) using initial condition (10), the concentration of β -Cell mass is obtained as follows:

$$\beta(t)=\beta_{ini}e^{d_0t}+\frac{\left(r_1n_0-r_2n_0^2\right)}{d_0}\left[e^{d_0t}-1\right]-\frac{\left(r_1n_1-2r_2n_0n_1\right)}{d_0+p}\left[e^{-pt}-e^{d_0t}\right]+\frac{r_2n_1^2}{d_0+2p}\left[e^{-2pt}-e^{d_0t}\right] \quad (13)$$

where the constant are

$p=\left(E_{G0}+S_I I_{ini}\right),\ n_0=\frac{R_0}{p},\ n_1=G_{ini}-\frac{R_0}{p}, m_0=\frac{m}{k}, m=\frac{\beta_{ini}\sigma G_{ini}^2}{\alpha+G_{ini}^2}, m_1=I_{ini}-\frac{m}{k},$

$l=d_0-r_1 G_{ini}+r_2 G_{ini}^2$

4. Limiting cases

Case 1: Assume that $dI/dt=0$.

Solving the equations(5) and (7) for the corresponding initial conditions $G(t=0)=G_{ini}$ and $\beta(t=0)=\beta_{ini}$,we obtain

$$G(t)=\frac{R_0}{E_{G0}+S_I I_{ini}}+\left(G_{ini}-\frac{R_0}{E_{G0}+S_I I_{ini}}\right)e^{-\left(E_{G0}+S_I I_{ini}\right)t}, \quad (14)$$

$$\beta(t)=\beta_{ini}\,exp\left(\frac{m_2\left(2p_0 r_2+r_1\right)}{p}-\frac{m_2^2 r_2}{2p}\right)exp\left(\frac{-m_2 e^{-pt}\left(2p_0 r_2+r_1\right)}{p}-\frac{m_2^2 r_2 e^{-2pt}}{2p}+p_0 t\left(p_0 r_2+r_1\right)-d_0 t\right) \quad (15)$$

$$I(t)=\frac{\beta\sigma\left(G(t)\right)^2}{k[\,\alpha+\left(G(t)\right)^2\,]}$$

where $p_0=\frac{R_0}{E_{G0}+S_I I_{ini}}, m_2=G_{ini}-\frac{R_0}{E_{G0}+S_I I_{ini}}, p=\left(E_{G0}+S_I I_{ini}\right)$

Case 2: Assume that $dG/dt=0$

Solving equations(6) and (7) for the corresponding initial conditions $I(t=0)=I_{ini}$ and $\beta(t=0)=\beta_{ini}$ we obtain,

$$\beta(t)=\beta_{ini}\,exp\left(l_1 t\right), \quad (16)$$

$$I(t)=\left(I_{ini}+\frac{\beta_{ini}\sigma G_{ini}^2}{\left(\alpha+G_{ini}^2\right)\left(l_1+k\right)}\right)e^{-kt}-\frac{\beta_{ini}\sigma G_{ini}^2 e^{l_1 t}}{\left(\alpha+G_{ini}^2\right)\left(l_1+k\right)}, \quad (17)$$

$$G(t)=\frac{R_0}{E_{G0}+S_I I},$$

where $l_1=\left(-d_0+r_1 G_{ini}-r_2 G_{ini}^2\right)$,

Case 3: Assume that $d\beta/dt=0$

Solving equations(5) and (6) for the corresponding initial conditions $G(t=0)=G_{ini}$ and, $I(t=0)=I_{ini}$, yields

$$G(t) = n_0 + n_1 e^{-pt} + S_I I_{ini}\, n_1\left(e^{-pt} - 1\right) + S_I m_0 n_1\left(1 - e^{-pt}\right) - \frac{S_I m_1 n_0}{(k-p)}\left(e^{-kt} - 1\right) - \frac{S_I m_1\, n_1}{k}\left(e^{-(k+p)t} - 1\right) \quad (18)$$

$$I(t) = I_{ini} + \frac{n_0^2 \beta_{ini}\sigma}{\alpha + G_{ini}^2 (k-l)}\left[e^{-lt} - e^{-kt}\right] + \frac{n_1^2 \beta_{ini}\sigma}{\alpha + G_{ini}^2 (k-l-2p)}\left[e^{-t(l+2p)} - e^{-kt}\right] + \frac{2n_0 n_1 B_{ini}\sigma}{\alpha + G_{ini}^2 (k-p)}\left[e^{-pt} - e^{-kt}\right] \quad (19)$$

$$\beta(t) = 0$$

5.Numerical simulation

The nonlinear reaction equations (5)-(7) are also solved numerically by using Scilab program (Appendix D.To validate our analytical results, numerical solutions are compared to our results obtained in Tables 1 to 3 and in Fig.1.The close agreement between the analytical and simulation resultsis noted. Highest possible error between the analytical results and the results of the simulation for glucose concentration of glucose, insulin, β-cell mass are0.44%, 2.83% and 2.71%, respectively.

6.Resultsand Discussion

Diabetes mellitus is a category of genetic diseases with the primary symptom being increased blood glucose concentration. In this paper mathematical model of β-cell mass, insulin, and glucose kinetics are discussed. The proposed model has successfully revealed results for different possible scenarios. For example, the glucose concentration of a diabetic patient dose not decline in time, which form evidencethat the person suffers from diabetes.

Figures 2 (a) and 2(c-e) show that an increase of total insulin sensitivity (S_I),net rate of production at zero glucose (R_0),initial concentration of insulin (I_{ini}) and initial concentration of glucose (G_{ini})lead to an increase in the concentration of glucose. Figure 2(b) it is found that the concentration increases when the parameter glucose effectiveness at zero insulin(E_{G0}) decreases.From Figures 3(a-b) and 3(e-i), it is observedthat the concentration of insulin increases when all of the following parameters decrease:Total insulin sensitivity (S_I), total glucose effectiveness at zero insulin(E_{G0}), equilibrium constant for dissociation (α),clearance constant (k), death rate at zero glucose (d_0), initial concentration of glucose (G_{ini}) and initial concentration of insulin (I_{ini}). However, the concentration of insulin increases when any of the parameters:Net rate of production at zero glucose (R_0), the maximal rate of secrete insulin(σ)

and the initial β-cell mass (β_{ini})increases.From Figures 4 (a),(b),(d-h), it is evidentthat the concentration of β-cell massalso increases when the parameter,total insulin sensitivity (S_I),total glucose effectiveness at zero insulin(E_{G0}), death rate at zero glucose (d_0), rate constant (r_1), initial concentration of insulin (I_{ini}) also increases. Figures4(c),(f),(i) it is noted that the concentration of β-cell mass increases when the parameter net rate of production at zero glucose (R_0), rate constant (r_1) and initial concentration of glucose (G_{ini}) decreases.

Eqs. (14) & (15) characterizes the analytical expressions of the concentration of glucose and β-cell masswhen $dI/dt = 0$ $\left(i.e\ I = \frac{1}{S_I}\left(\frac{R_0}{G} - E_{G0} \right) \right)$Figures 5(a)&(b) represents insulin is increases when the concentration glucose & β-cell mass decreases.Eqs. (16) & (17) characterizes theanalytical expressions of the concentration of β-cell mass and insulin when $dG/dt = 0$ $\left(i.e\ G = \frac{r_1 + \sqrt{r_1^2 - 4r_2 d_0}}{2r_2} \right)$ From Figures 6(a-b) it is reported that glucose is increases when the concentration β-cell mass& Insulin increases.Eqs. (18) & (19) represents the analytical expressions of the concentration of glucose and insulin when $d\beta/dt = 0$ $\left(i.e\ \beta = \frac{Ik\left(\alpha + G^2\right)}{\sigma G^2} \right)$ From Fig 7(a) & (b) it is inferred that an increase in β-cell massleads to increases of glucose & insulin .

7.Differential sensitivity analysis of parameters

Sensitivity analysis of the parameters is given in Figures. 8(a-c). From the analysis it is inferred that,total glucose effectiveness at zero insulin (E_{G0}) have more impact in the concentration of glucose. In contrast the parameter maximal rate of secrete insulin(σ),equilibrium constant for dissociation(α),clearance constant $(k)$and initial β-cell mass(β_{ini}) accounts for only small changes in the concentration of glucose. It is also informed that the parameterstotal insulin sensitivity (S_I), death rate at zero glucose (d_0), rate constant (r_1)*and* (r_2) have more impact in the concentration of insulin. In contrast the parameter equilibrium constant for dissociation(α) accounts for only small changes in the concentration of insulin. It is observed that the reaction

and diffusion parameters rate constant (r_2) have more impact in the concentration of β-cell mass.In contrast the parametertotal insulin sensitivity (S_I), net rate of production at zero glucose (R_0), initial concentration of glucose (G_{ini})accounts for only small changes in the concentration of β-cell mass.

8.Conclusion.

In this paper, the theory of glucose, insulin, and cells kinetics is described as a mathematical model.The approximate analytical solutions of system of non-linear reaction equations are provided using the new approach HPM method.The obtained analytical results will be useful to know the behavior of the reaction systems. The accuracy of the analytical solutions were shown to be very satisfactory when compared with numerical simulation data.This model was extended to various nonlinear problems in biomedical and infectious diseases.

Table 1. Concentration of glucose is compared with simulation results for various values of time, *t*, and other parameters(Topp *et al*., 2000).
$S_I = 0.72\, ml\,\mu U^{-1} d^{-1}, E_{G0} = 1.44\, d^{-1}, R_0 = 864\, mg\, dl^{-1} d^{-1}, \sigma = 43.2\, \mu U\, ml^{-1} d^{-1}, \alpha = 20{,}000\, mg^2 dl^{-2}$,
$k = 432 d^{-1}, I_{ini} = 0$ *and* $\beta_{ini} = 0$

Time t(days)	Concentration of*glucose* $G\ (mg\, dl^{-1})$								
	when $G_{ini} = 0$			when $G_{ini} = 250\ (mg\, dl^{-1})$			when $G_{ini} = 500\ (mg\, dl^{-1})$		
	Simulation	Eq.(11)	deviation of error %	Simulation	Eq.(11)	deviation of error %	Simulation	Eq.(11)	deviation of error %
0	000.19	000.19	0.00	250.00	250.00	0.00	500.00	500.00	0.00
0.25	188.30	188.90	0.00	355.10	360.20	1.41	531.50	531.48	0.00
0.5	310.50	310.50	0.00	427.30	430.90	0.83	551.70	551.68	0.00
0.75	396.80	396.20	0.15	479.80	480.70	0.18	565.90	565.90	0.00
1	462.30	460.60	0.36	519.20	518.30	0.17	576.60	576.60	0.00
1.25	505.50	501.90	0.71	544.00	542.40	0.29	583.50	583.50	0.00

1.5	540.00	538.50	0.27	563.00	560.50	0.44	588.70	588.70	0.00
1.75	563.80	554.10	1.72	577.70	572.10	0.97	592.00	592.00	0.00
2	580.20	566.70	2.32	594.00	580.40	2.34	594.40	594.38	0.00
	Average error %		0.614	Average error %		0.731	Average error %		0.00

Table 2. Concentration of insulin is compared with simulation results for various values of time, *t*, and other parameters(Topp *et al*., 2000).

$S_I = 0.72\,ml\,\mu U^{-1}d^{-1}, E_{G0} = 1.44\,d^{-1}, R_0 = 864\,mg\,dl^{-1}d^{-1}, \sigma = 43.2\,\mu U\,ml^{-1}d^{-1}, \alpha = 20{,}000\,mg^2dl^{-2}$, $k = 432d^{-1}, I_{ini} = 0$ *and* $\beta_{ini} = 0$

Time t(days)	Concentration of *insulin I* $\left(\mu U\,ml^{-1}\,d^{-1}\right)$								
	when $I_{ini} = 0$			when $I_{ini} = 0.5\left(\mu U\,ml^{-1}\,d^{-1}\right)$			when $I_{ini} = 1\left(\mu U\,ml^{-1}\,d^{-1}\right)$		
	Simulation	Eq.(12)	deviation of error %	Simulation	Eq.(12)	deviation of error %	Simulation	Eq.(12)	deviation of error %
0	0.0039	0.0041	4.87	0.5000	0.4800	4.16	0.0120	0.0120	1.66
0.1	0.0568	0.0586	3.07	0.0554	0.0530	4.52	0.0216	0.0220	1.81
0.2	0.2539	0.2547	0.31	0.0789	0.0801	1.49	0.0846	0.0834	1.43
0.3	0.5211	0.5174	0.71	0.1766	0.1769	0.16	0.1644	0.1577	4.24
0.4	0.8141	0.8027	1.42	0.2910	0.2892	0.62	0.2468	0.2389	3.30
0.5	1.1060	1.084	2.02	0.4116	0.4069	1.15	0.3245	0.3100	4.67
0.6	1.3810	1.3470	2.52	0.5319	0.5234	1.62	0.3941	0.3788	4.03
0.7	1.6310	1.5850	2.90	0.6473	0.6344	2.03	0.4540	0.4365	4.00
0.8	1.8530	1.7940	3.28	0.7553	0.7376	2.39	0.5050	0.4830	4.55
0.9	2.0470	1.975	3.64	0.8544	0.8318	2.71	0.5400	0.5110	5.37
1.0	2.1980	2.114	3.97	0.9354	0.9083	2.98	0.5770	0.5430	5.8
	Average error %		2.610	Average error %		2.166	Average error %		3.714

Table 3. Concentration of β-cell massis compared with simulation results for various values of time, *t,* and other parameters(Topp *et al*., 2000).
$S_I = 0.72\, ml\,\mu U^{-1} d^{-1}, E_{G0} = 1.44\, d^{-1}, R_0 = 864\, mg\, dl^{-1} d^{-1}, \sigma = 43.2\, \mu U\, ml^{-1} d^{-1}, \alpha = 20{,}000\, mg^2 dl^{-2}$,
$k = 432 d^{-1}, I_{ini} = 0$ *and* $\beta_{ini} = 0$

time t(days)	Concentration of β-cell mass (mg)								
	when $\beta_{ini} = 1(mg)$			when $\beta_{ini} = 1.2(mg)$			when $\beta_{ini} = 1.4(mg)$		
	Simulation	Eq.(13)	deviation of error %	Simulation	Eq.(13)	deviation of error %	Simulation	Eq.(13)	deviation of error %
0	1.0000	0.9800	2.00	1.2200	1.2000	1.63	1.4200	1.4000	1.40
0.5	1.0610	1.0400	1.97	1.2870	1.2670	1.55	1.4940	1.4730	1.40
1.0	1.0780	1.0570	1.94	1.3120	1.2910	1.60	1.5250	1.5030	1.44
1.5	1.0330	1.0110	2.12	1.2730	1.2520	1.64	1.4930	1.4710	1.47
2.0	0.9446	0.9221	2.38	1.1930	1.1700	1.92	1.4190	1.3960	1.62
2.5	0.8321	0.8089	2.78	1.0880	1.0650	2.11	1.3210	1.2980	1.74
3.0	0.7051	0.6811	3.40	0.9690	0.9450	2.47	1.2090	1.1850	1.98
3.5	0.5687	0.5440	4.34	0.8407	0.8160	2.93	1.0880	1.0630	2.29
4.0	0.4255	0.4060	4.58	0.7058	0.6804	3.59	0.9607	0.9352	2.65
4.5	0.2766	0.2620	5.27	0.5655	0.5389	4.70	0.8283	0.8020	3.17
5.0	0.1381	0.1299	5.93	0.4350	0.4100	5.74	0.7050	0.6780	3.82
	Average error %		3.337	Average error %		2.716	Average error %		2.089

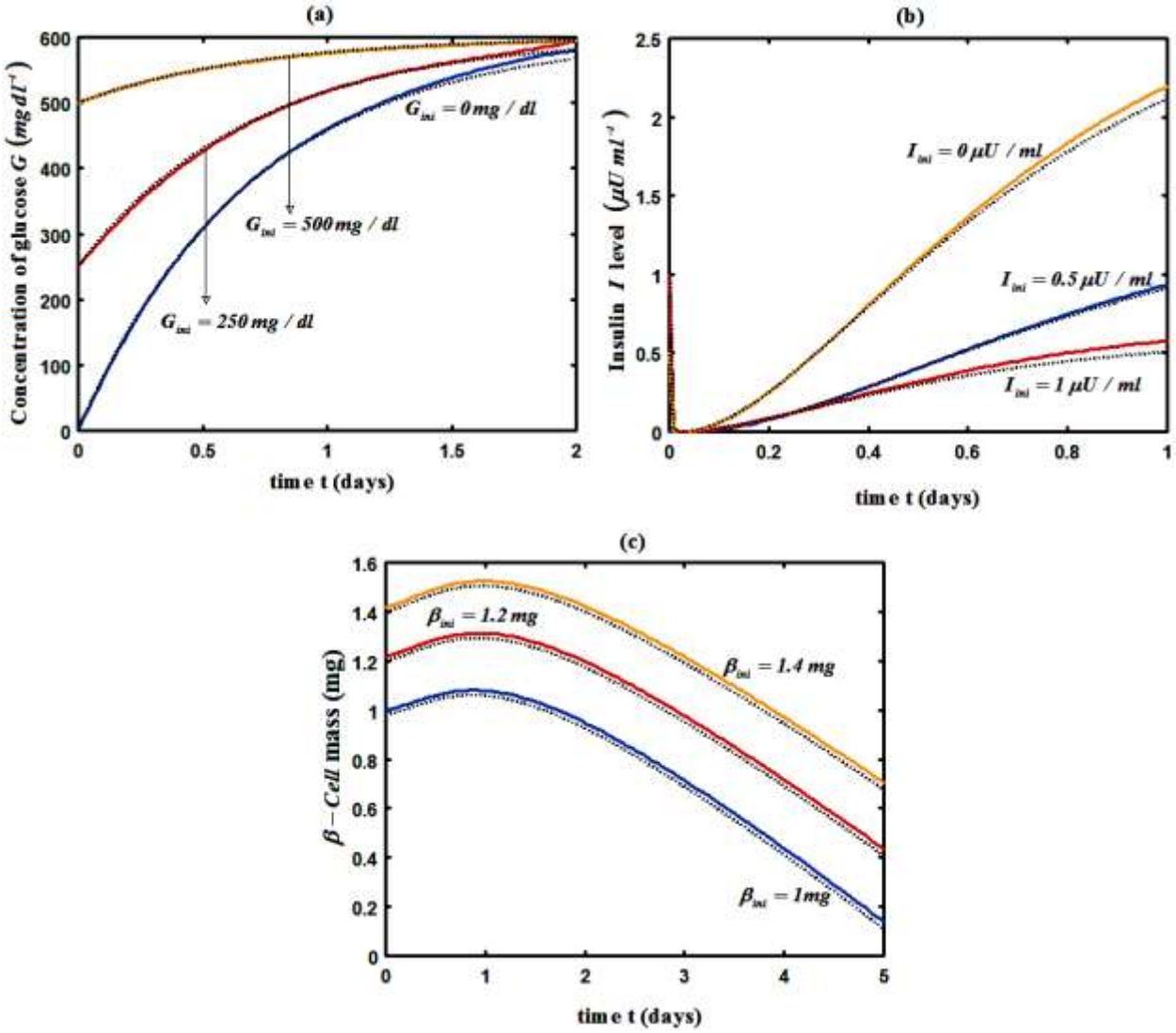

Fig 1. Comparison between the analytical expression of concentration of glucose Eq.(11), Insulin Eq.(12) β-cell mass Eq.(13)and simulation results for some experimental parameters:

$S_I = 0.72\, ml\, \mu U^{-1} d^{-1}, E_{G0} = 1.44\, d^{-1}, R_0 = 864\, mg\, dl^{-1} d^{-1}, \sigma = 43.2\, \mu U\, ml^{-1} d^{-1}, \alpha = 20{,}000\, mg^2 dl^{-2}$,
$k = 432 d^{-1}, d_0 = 0.06 d^{-1}, r_1 = 0.84 \times 10^{-3}\, mg^{-1}\, dl\, d^{-1}$ and $r_2 = 0.24 \times 10^{-5}\, mg^{-2}\, dl^2\, d^{-1}$

(a) $I_{ini} = 0,\ \beta_{ini} = 0\ G_{ini} = 0.01 mg\, dl^{-1}, I_{ini} = 0.01\, \mu U\, ml^{-1} d^{-1}$.

(b) $G_{ini} = 0, \beta_{ini} = 1mg$

(c) $G_{ini} = 0.01 mg\, dl^{-1}, I_{ini} = 0.01\, \mu U\, ml^{-1} d^{-1}$

A dotted and solid line represents the analytical and numerical solutions respectively.

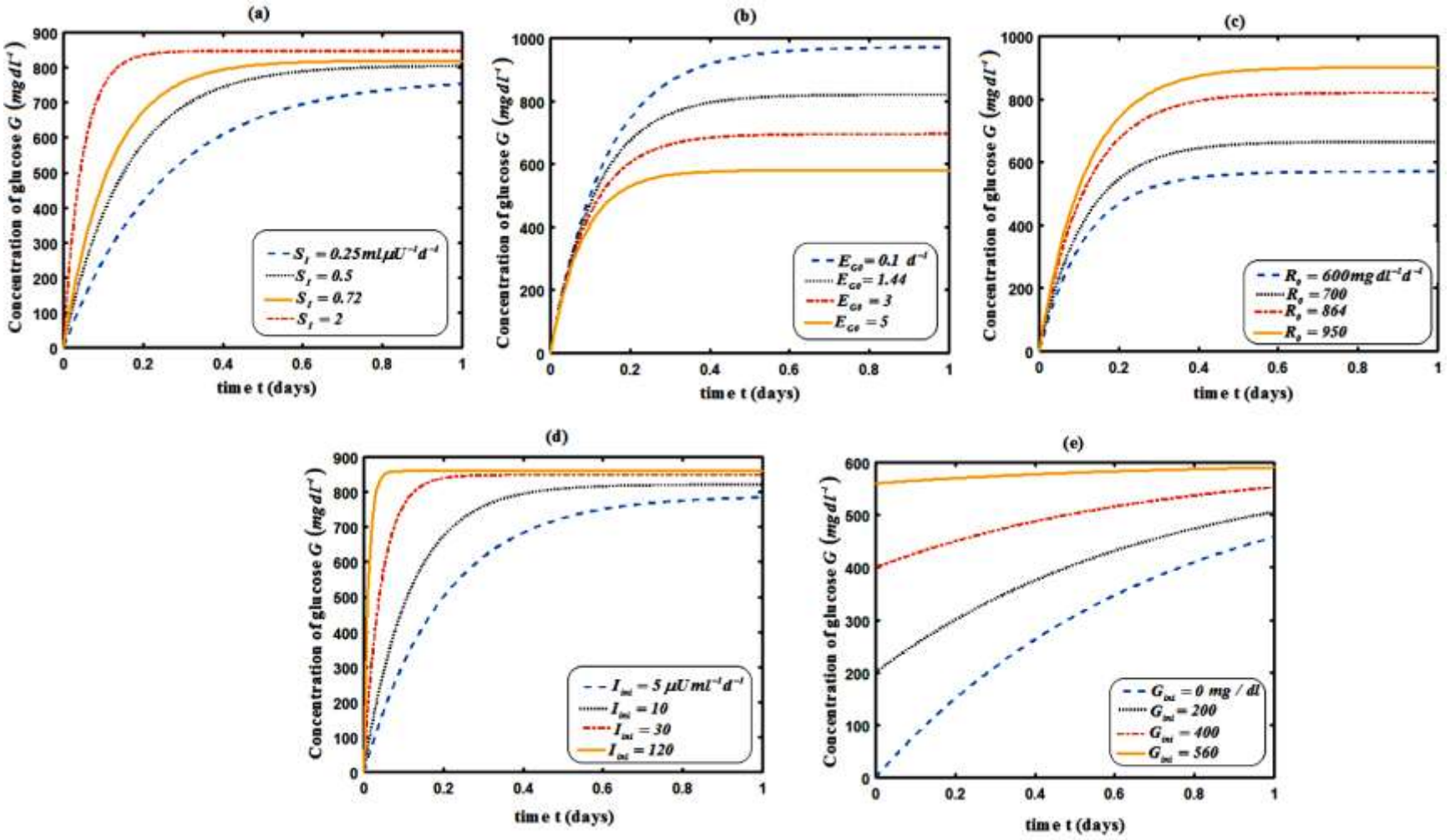

Fig 2. Plot of concentration profile of glucose *G*, versus time*t* calculated using Eq.(11)for various experimental values of parameters.
$S_I = 0.72\,ml\,\mu U^{-1}d^{-1}, E_{G0} = 1.44\,d^{-1}, R_0 = 864\,mg\,dl^{-1}d^{-1}, \sigma = 43.2\,\mu U\,ml^{-1}d^{-1}, \alpha = 20{,}000\,mg^2dl^{-2}, k = 432d^{-1},$
$G_{ini} = 0, I_{ini} = 10\,\mu U\,ml^{-1}d^{-1}, \beta_{ini} = 0$

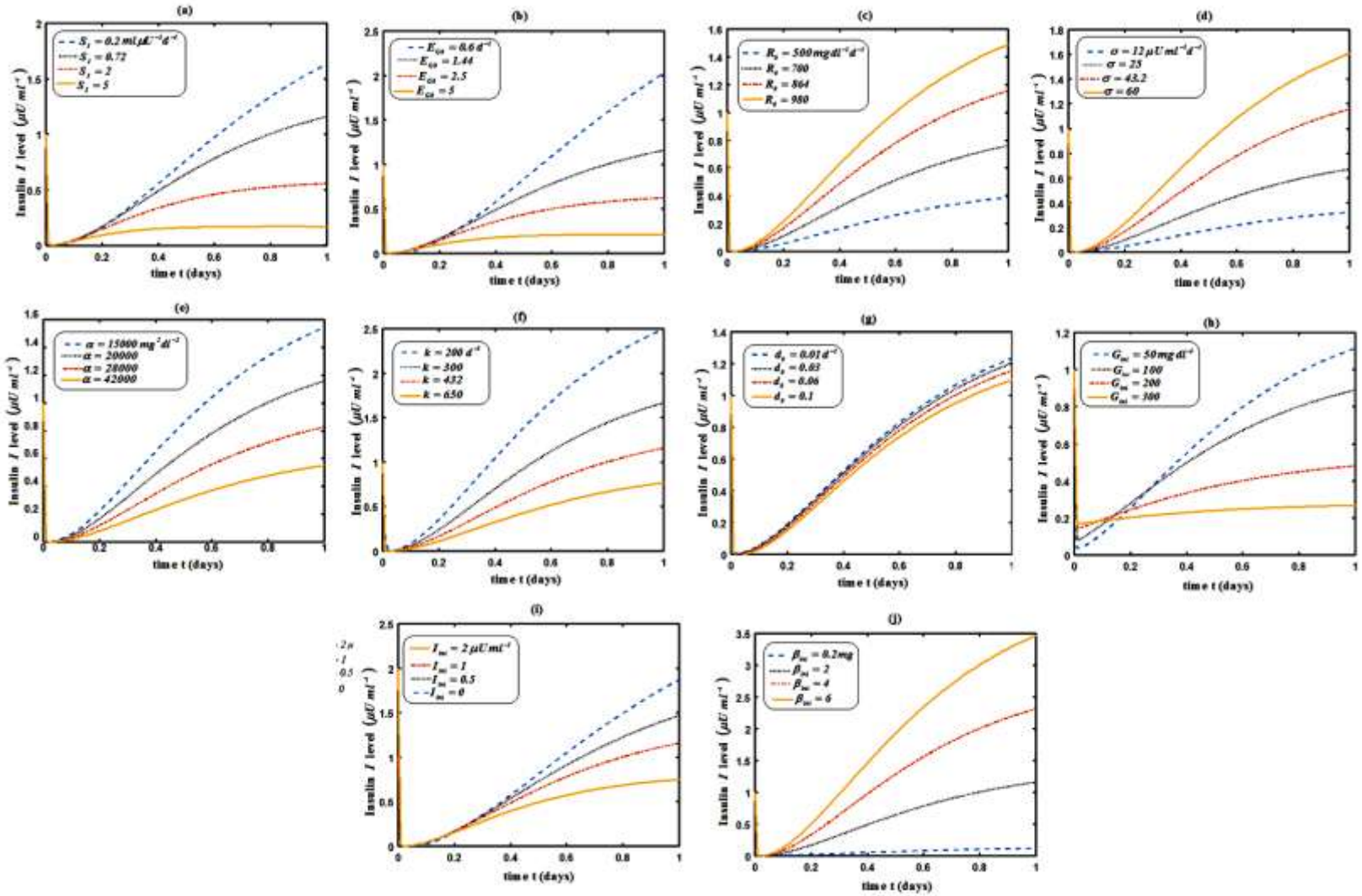

Fig. 3. Plot of Insulin level I, versus time$t$ calculated using Eq.(12) for various values of experimental parameters

$S_I = 0.72\,ml\,\mu U^{-1}d^{-1}, E_{G0} = 1.44\,d^{-1}, R_0 = 864\,mg\,dl^{-1}d^{-1}, \sigma = 43.2\,\mu U\,ml^{-1}d^{-1}, \alpha = 20{,}000\,mg^2dl^{-2}, k = 432d^{-1}, d_0 = 0.06\,d^{-1}$

$r_1 = 0.84\times10^{-3}\,mg^{-1}\,dl\,d^{-1}, r_2 = 0.24\times10^{-5}\,mg^{-2}\,dl^2\,d^{-1}, G_{ini} = 0, I_{ini} = 1\,\mu U\,ml^{-1}d^{-1}$ and $\beta_{ini} = 2\,mg$

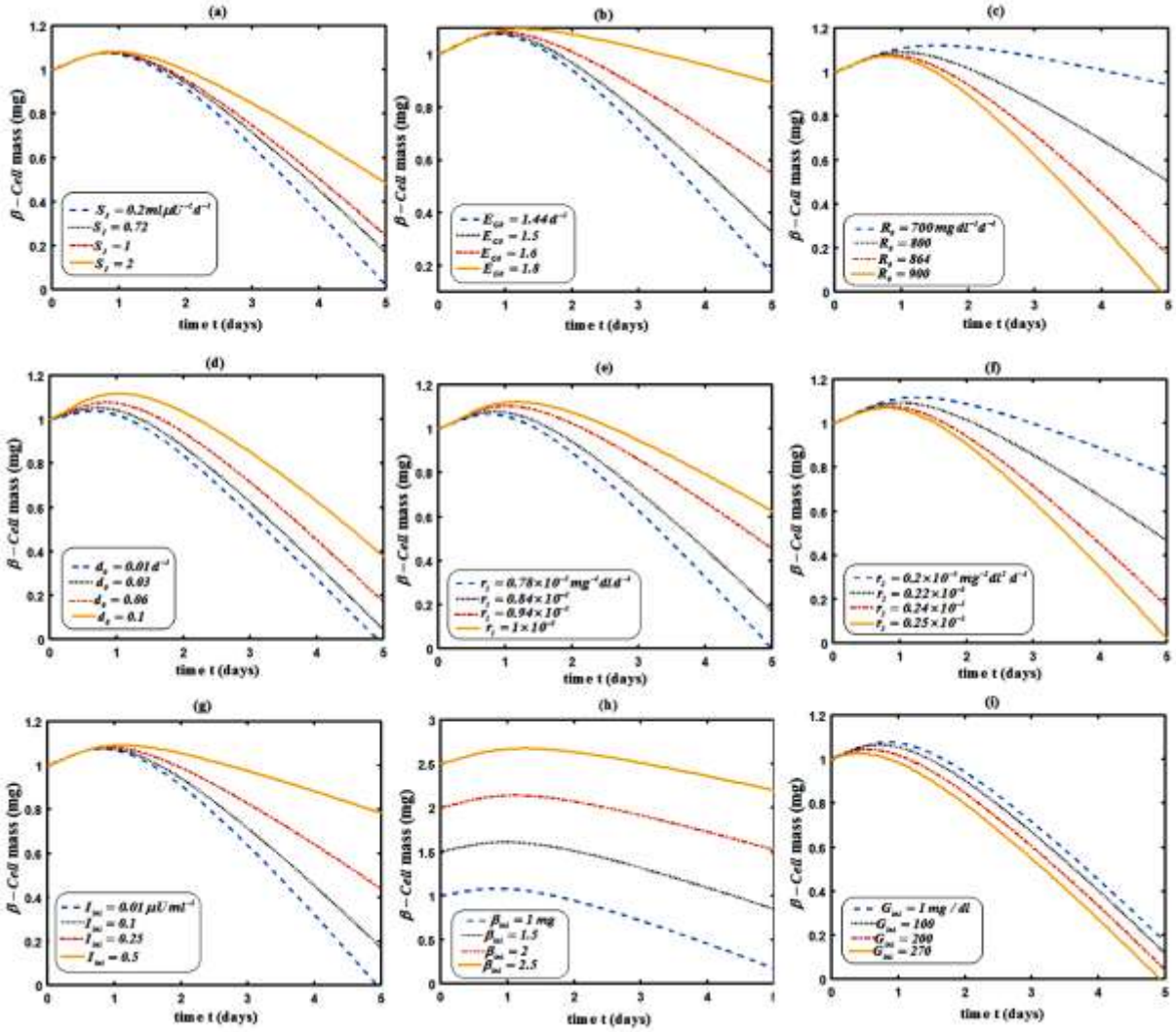

Fig. 4. Plot of concentration profile of $\beta - cell$, versus time*t* calculated using Eq.(13) for various experimental values of parameters $S_I = 0.72\,ml\,\mu U^{-1}d^{-1}, E_{G0} = 1.44\,d^{-1}, R_0 = 864\,mg\,dl^{-1}d^{-1}, \sigma = 43.2\,\mu U\,ml^{-1}d^{-1}$, $\alpha = 20{,}000\,mg^2dl^{-2}, k = 432d^{-1}, d_0 = 0.06d^{-1}$ $r_1 = 0.84\times10^{-3}\,mg^{-1}\,dl\,d^{-1}, r_2 = 0.24\times10^{-5}\,mg^{-2}\,dl^2\,d^{-1}, G_{ini} = 1\,mg\,dl^{-1}, I_{ini} = 0.1\,\mu U\,ml^{-1}d^{-1}$ *and* $\beta_{ini} = 1\,mg$

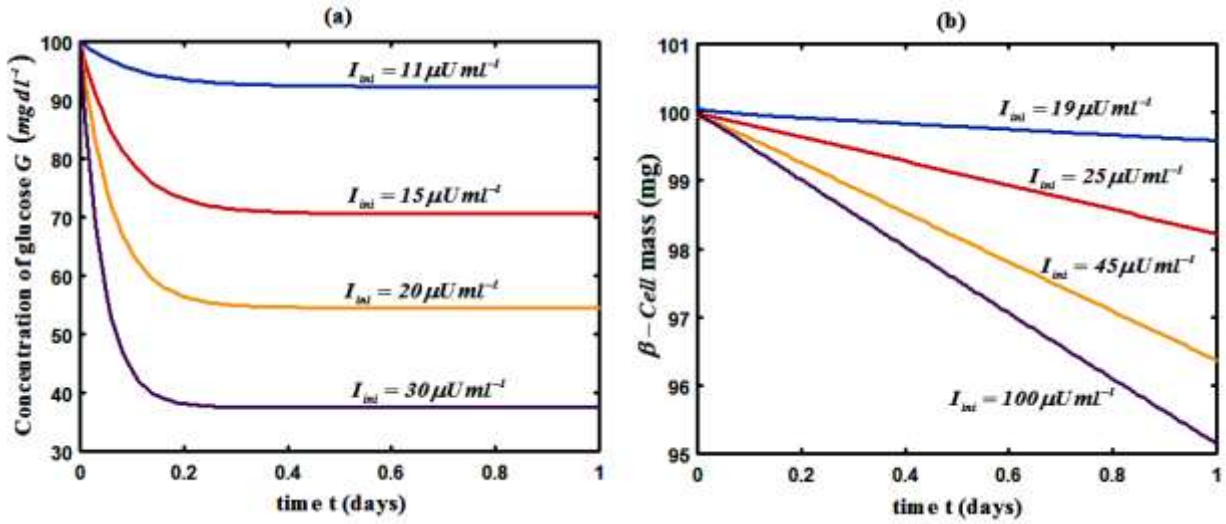

Fig. 5. Plot of concentration profiles of glucose G, β-cell massversus time$t$ calculated using Eq.(14) and Eq.(15) for various experimental values of parameters.

(a) $S_I = 0.72ml\mu U^{-1}d^{-1}, E_{G0} = 1.44\,d^{-1}, R_0 = 864mgdl^{-1}d^{-1}, G_{ini} = 100mgdl^{-1}$ and various values I_{ini}

(b) $S_I = 0.72ml\mu U^{-1}d^{-1}, E_{G0} = 1.44\,d^{-1}, R_0 = 864mgdl^{-1}d^{-1}, G_{ini} = 50mgdl^{-1}\beta_{ini} = 100mg$ and various values of I_{ini}

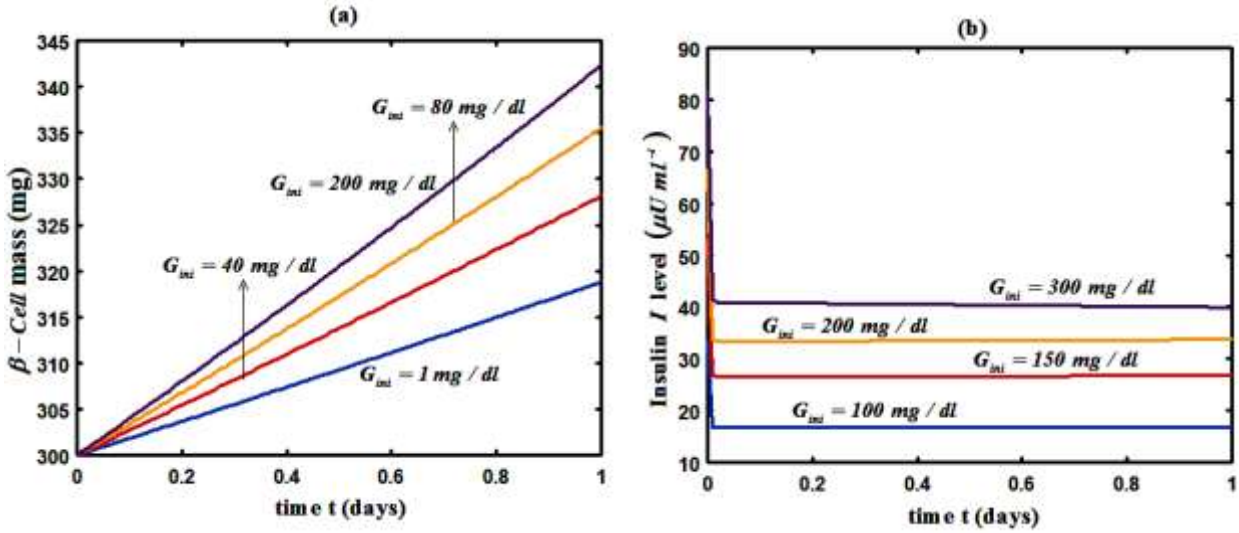

Fig. 6. Plot of concentration profiles of β-cell mass, insulin I versus time$t$ calculated using Eq.(16) and Eq.(17) for various experimental values

(a) $d_0 = 0.06d^{-1}, r_1 = 0.84\times10^{-3}mg^{-1}\,dl\,d^{-1}, r_2 = 0.24\times10^{-5}mg^{-2}\,dl^2\,d^{-1}, \beta_{ini} = 100mg$ and various values of G_{ini}

(b) $\sigma = 43.2\,\mu U\,ml^{-1}d^{-1}, \alpha = 20{,}000mg^2dl^{-2}, k = 432d^{-1}, d_0 = 0.06d^{-1}\ r_1 = 0.84\times10^{-3}mg^{-1}\,dl\,d^{-1}$, $r_2 = 0.24\times10^{-5}mg^{-2}\,dl^2\,d^{-1}, I_{ini} = 0, \beta_{ini} = 500mg$ *and various values of* G_{ini}

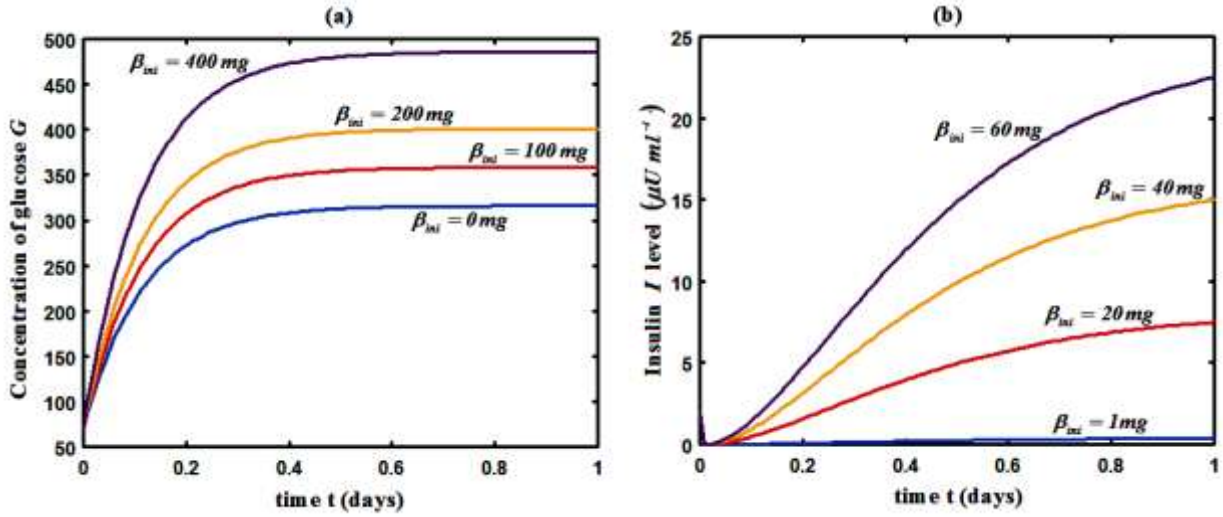

Fig. 7. Plot of concentration profiles of G, insulin I versus time t calculated using Eq.(18) and Eq.(19) for various experimental values

(a) $R_0 = 864,\ E_{G0} = 1.44,\ S_I = 0.72, G_{ini} = 10, I_{ini} = 0, \sigma = 43.2, \alpha = 20000, k = 432$ and various values of β_{ini}

(b) $d_0 = 0.06,\ r_1 = 0.84 \times 10^{-3}, r_2 = 0.24 \times 10^{-5}, G_{ini} = 0,\ I_{ini} = 100, \alpha = 20000,\ k = 432,\ \sigma = 43.2$
$R_0 = 864,\ E_{G0} = 1.44,\ S_I = 0.72$ and various values of β_{ini}

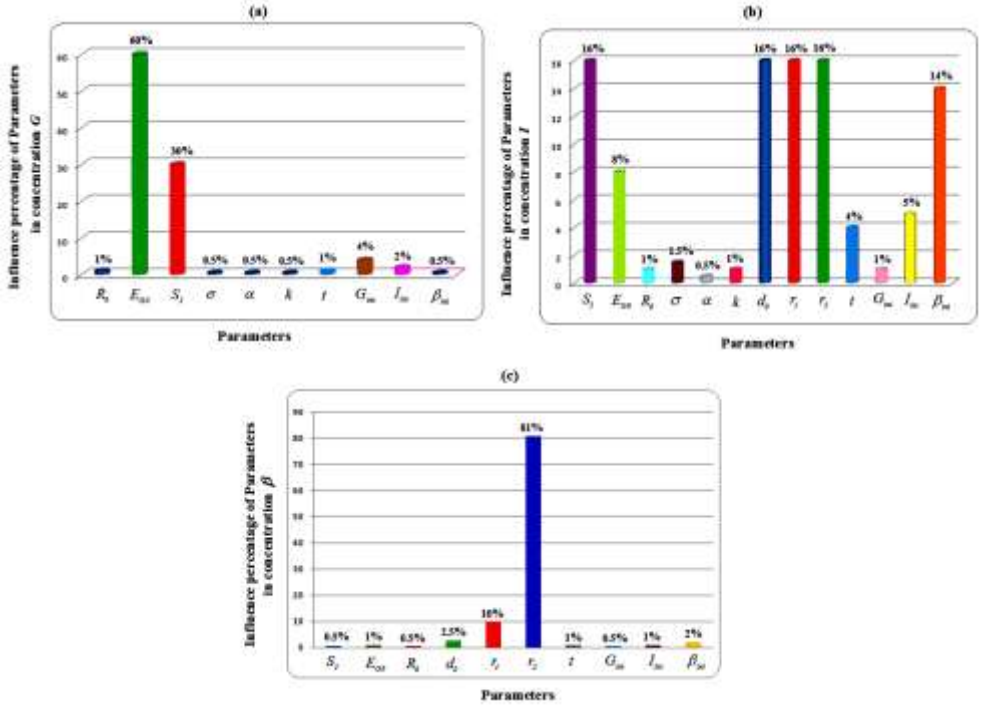

Fig. 8. Influence percentage of parameters in different concentrations: (a) Glucose G; (b) Insulin I; (c) $\beta - Cell$

Nomenclature

Symbols	Description	Units
G	Concentration of glucose	$mg\,dl^{-1}$
I	Insulin level	$\mu U/ml$
β	β-cell mass	mg
$S_I = S_{IP} + S_{IU}$	Total insulin sensitivity	$ml\,\mu U^{-1}\,d^{-1}$
$E_{G0} = E_{G0P} + E_{G0U}$	Total glucose effectiveness at zero insulin	d^{-1}
R_0	Net rate of production at zero glucose	$mg\,dl^{-1}d^{-1}$
σ	Maximal rate of secrete insulin	$\mu U\,ml^{-1}\,d^{-1}$
α	Equilibrium constant for dissociation	$mg^2\,dl^{-2}$
k	Clearance constant	d^{-1}
d_0	Death rate at zero glucose	d^{-1}
$r_1 = r_{1r} + r_{1a}$	Rate constant	$mg^{-1}\,dl\,d^{-1}\ (or)\ mol^{-1}dl\,d^{-1}$
$r_2 = r_{2r} + r_{2a}$	Rate constant	$mg^{-2}\,dl^2\,d^{-1}\,(or)\,mol^{-1}dl\,d^{-1}$
G_{ini}	Initial concentration of glucose	$mg\,dl^{-1}$
I_{ini}	Initial concentration of Insulin	$\mu U/ml$
β_{ini}	Initial β-cell mass	mg
t	Time	Days

REFERENCES

1. HAARIO, H.,& SEIDMAN, T.I., (1994).Reaction and diffusion at a gas/liquid interface, II.
2. *SIAM J Math Anal*,**25**, 1069-1084.
3. HE, J.H. (2006) Homotopy perturbation method for solving boundary value problems. *Phys*
4. *Lett A*. **350**, 87- 88.
5. HE, J.H. (2006) Some asymptotic methods for strongly nonlinear equations. *Int J Mod Phys B*.
6. **20**, 1141-1199.
7. HE, J.H. (2003) Homotopy perturbation method: A new nonlinear analytical technique. *Appl*

8. *Math Comput***135**, 73-79.
9. HE, J.H. (2000) A coupling method of homotopy technique and a perturbation technique for
10. non-linear problems. *Comput Methods Appl Mech Eng***35**, 37-43.
11. HE, J.H. (1999) Homotopy perturbation technique. *Comput Methods Appl Mech Eng* **178**,
12. 257-262.
13. KALACHEV, L.V. & SEIDMAN, T.I. (2003) Singular perturbation analysis of a stationary
14. diffusion/reaction system exhibiting a corner-type behavior in the interval interior. *J Math*
15. *Anal Appl*,**288**, 722-743.
16. TOPP, B., PROMISLOW, K.,DEVRIES,G.,MIURAA, R. M., & FINEGOOD, D.T.,(2000).A
17. Model of β-Cell Mass, Insulin, and Glucose Kinetics: Pathways to Diabetes. *J. theor. Biol.*
18. **206**, 605-619.
19. YASINI, S.H, NAGHIBI-SISTANI, M.B & KARIMPOUR A. (2009) Agent-based simulation
20. for blood glucose control in diabetic patients. *International Journal of Biomedical and*
21. *Biological Engineering*,**3**,9