Journal of the Nigerian Association of Mathematical Physics,
Volume 8 (*November 2004*).

A periodic-type dose effect of insulin in the blood glucose level of a diabetes milletus subject

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Abstract

We investigated in this paper the effect of a periodic-type insulin dose on a diabetic patient. An appropriate matching condition is introduced in our problem by expressing the insulin dose using a Fourier series expansion. Our result gives insight to the state of the patient over a period of administration. Clearly, there is the possibility of hypoglycemia. Hence a great care is needed while trying to inject the patient periodically.

Keywords: Periodic-type insulin dose, Diabetic patient, Matching condition, Laplace transform.

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1.0 Introduction

Mathematical models to account for the state of a patient infected with diabetes mellitus abound in the literature. These research works try to give answer to the pathologic situation of the patient. Some of the researches modeled in the literature put into account the division of the beta cells. Gita et al. [5] gave a generalized non-linear mathematical model, which incorporates beta-cell kinetics, a glucose-insulin feedback system and gastrointestinal absorption term for glucose. A numerical simulation is used to analyse the plasma glucose and insulin level. Davis [4] in his work developed a mathematical model for the study of insulin-dependent diabetic mellitus. Mbah [7] working after him generalized Davies model. He solved his problem by linearising the non-linear term. Koriko [6] in his recent work investigated the criteria for stability of a diabetic mellitus mathematical model. Adewale and Ayeni [3] studied the existence and uniqueness of solution of a mathematical model used for the study of insulin dependent diabetes mellitus. Adebile [1] in a recent work solved the non-linear generalized mathematical model in Mbah [7] and Koriko [6] without linearising the non-linear term. His attempt for solution was the use of asymptotic analysis. In another paper, Adebile and Koriko [2] investigated the effect of variable glucose disappearance rate on blood glucose level.

In the literature there are different type of insulin, some are short term, intermediate and long-term acting, all these, in an attempt to meet the diverse need of the diabetic. The possibility of given insulin periodically to patient either by self-administration, medical expert or electronically controlled means has been mentioned in the literature. Our desire in this paper is to give insight mathematically to the state of the diabetic when insulin is administered periodically. We shall consider the effect of other basic parameters such as the glucose disappearance rate, the half-life of the insulin and so on which may determine the effect of short, intermediate or long term acting.

In the first section we considered the introduction, Section 2 gives the mathematical formulation. We look at the method of solution in section 3 and the result and discussion is given in the final section.

2.0 Mathematical formulation

The governing equations we consider as in Mbah [7]. These are

$$\frac{dX}{dt} = a_1 z(t) - a_2 XY - a_3 X + a_4 (X_0 - X) \tag{2.1}$$

$$\frac{dY}{dt} = b_1X - b_2Y + b_3w(t) \tag{2.2}$$

$$x(t_0) = x_0\ ,\ \ y(t_0) = y_0 \tag{2.3}$$

where a_1, a_2, a_3, a_4, b_1, b_2, b_3 are as defined in Mbah [7]

$z(t)$: measure of glucose intake

$w(t)$: measure of the insulin dose

t_o: the initial time of interest for the study.

We assume that the patient feeds normally as it is the case in Mbah [7] (therefore the fourth term of (2.1) can be neglected) and also we take $Z(t) = Qe^{-k(t-t_o)}$ (2.4) as in [7]. As we have mentioned in section 1 we model our insulin dose(s) is different form from that of [7]. Our model for insulin injection is:

$$w(t) = \begin{cases} \sin w(t); 2n\pi < w(t-t_o) < (2n+1)\pi \\ \\ 0, (2n+1)\pi < w(t-t_0) < 2(n+2)\pi \end{cases} \tag{2.5}$$

where $\eta \in$ N,(N is the set of natural numbers). We non-dimensionlize the equations (2.1) - (2.5) using the following dimensionless variables:

$$\frac{x}{L} = \bar{x},\ \ \frac{y}{L} = \bar{y},\ \ \frac{t-t_o}{(t_h - t_o)} = \bar{t}\ ,\ \ \frac{w}{w_0} = \bar{w}\ ,\ \ \ w_o = \frac{1}{t_h - t_o} \tag{2.6}$$

where L = 200/unit, t_o = 8 reference to Mbah [7], t_h = half-life of insulin. Our dimensionless equations (dropping the bars (-)) are

$$\frac{dX}{dt} = \alpha_1 z^{-\lambda t} - \alpha_2 XY - \alpha_3 X \tag{2.7}$$

$$\frac{dY}{dt} = \beta_1 X - \beta_2 X - \beta_2 w(t) \tag{2.8}$$

$$x(0) = x_0\ ,\ \ y(0) = y_0 \tag{2.9}$$

where $\alpha_1 = \frac{d_1 a_1 Q}{L}\ ,\ \ \alpha_2 = d_1 a_1 QL\ ,\ \ \alpha_3 = d_1 a_3$

$$\beta_1 = d_1 a_1,\quad \beta_2 = d_1 b_2 \quad\ \beta_3 = \frac{d_1 a_3}{L}\ \ ,\ \ k = kd_1 \tag{2.10}$$

$$w(t) = \begin{cases} \sin \Omega t; \dfrac{2n\pi}{\Omega} < t < \dfrac{(2n+1)\pi}{\Omega} \\ \\ 0; \dfrac{(2n+1)\pi}{\Omega d_1} < t < \dfrac{(2n+2)\pi}{\Omega d_1} \end{cases}$$

where $\Omega = wd_1$

For the purpose of our study we introduce an approximate equation for w(t) – (see Marion [8]), as a matching procedure from one dose to another dose. Hence

$$w(t) \approx \frac{1}{\pi} + \frac{1}{2}\sin \Omega t - \frac{2}{3\pi}\cos 2\Omega t - \frac{2}{15\pi}\cos 4\Omega t \tag{2.11}$$

3.0 Method of solution

We first linearize the second term of (2.1) by using $X \cong \overline{X} = x_o$ as in [7] we now use the Laplace transform procedure to find solution to the system of differential equations. Taking the Laplace transform of the equation (2.7) – (2.9) we have:

$$(s+\alpha_3)x+\alpha_2 X\ y = x_0 + \frac{\alpha_1}{s+\lambda} \tag{3.1}$$

$$-\beta_1 x + (s+\beta_2)y = y_0 - \beta_3\left\{\frac{1}{\pi s}+\frac{\Omega}{2(s^2+\Omega^2)}-\frac{2s}{3(s^2+4\Omega^2)}-\frac{2s}{5\pi(s^2+16\Omega^2)}\right\} \tag{3.2}$$

The solution to (3.1) and (3.2) are

$$x = \frac{x_o(s+(\lambda-\tau))(s+(\beta_2-\tau))}{(s+(\lambda-\tau))(s^2+\mu^2)} + \frac{\alpha_1(s+(\beta_2-\tau))}{(s+(\lambda-\tau))(s^2-\mu^2)} - \frac{\alpha_2 X y_o}{s^2-\mu^2}$$
$$+\frac{\alpha_2 X\ \beta_3}{\pi(s-\tau)(s^2-\mu^2)} + \frac{\alpha_2 \Omega\ X\ \beta_3}{2\left((s-\tau)^2+\Omega^2\right)(s^2-\mu^2)}$$

$$-\frac{2(s+\tau)\alpha_2 X\beta_2}{3\pi\left\{(s-\tau)^2+4\Omega^2\right\}(s^2-\mu^2)} - \frac{2\alpha_2 X\beta_3(s-\tau)}{15\pi\left\{(s-\tau)^2+16\Omega^2\right\}(s^2-\mu^2)} \tag{3.3}$$

$$y = \frac{y_0(s+(\alpha_3-\tau))}{s^2-\mu^2} - \frac{\beta_3(s+(\alpha_3-\tau))}{\pi(s-\tau)(s^2-\mu^2)} - \frac{\Omega\,\beta_3(s+(\alpha_3-\tau))}{2\left\{(s-\tau)^2+\Omega^2\right\}+(s^2-\mu^2)}$$
$$+\frac{2\beta_3(s-\tau)(s+(\alpha_3-\tau))}{3\pi\left\{(s-\tau)^2+4\Omega^2\right\}(s^2-\mu^2)} + \frac{2\beta_3(s-\tau)(s+\tau(\alpha_3-\tau))}{15\pi\left\{(s-\tau)^2+16\Omega^2\right\}(s^2+\mu^2)}$$
$$+\frac{x_o\beta_1(s+(\lambda-\tau))}{(s+(\lambda-\tau))(s^2+\mu^2)} + \frac{\alpha_1\beta_1}{(s+(\lambda-\tau))(s^2-\mu^2)} \tag{3.4}$$

Taking the inverse Laplace transforms of the equation (3.3) and (3.4) we have

$$x = A_1 e^{-at} + A_2\ cosh\,\mu t + A_3\ \frac{sin\,h\mu\, t}{u} + A_4 e^{Tt} + A_5 e^{\tau t}\ cos\,h\Omega\, t + A_6 e^{\tau t}\ \frac{sin\,h\Omega\, t}{\Omega}$$
$$+A_7 e^{\tau t}\ cos\,h2\Omega\, t + A_8 e^{\tau t}\ \frac{sin\,h2\,\Omega\, t}{2\Omega} + A_9 e^{\tau t}\ cos\,h4\Omega\, t + A_{10} e^{\tau t}\ \frac{sin\,4\Omega\, t}{4\Omega} \tag{3.5}$$

$$y = B_1 e^{\tau t} + B_2\ cos\,h\mu\, t + B_3\ \frac{s\,in\,h\,\mu\, t}{\mu} + B_4 e^{\tau t}\ cosh\,\Omega\, t + B_5 e^{\tau t}\ \frac{s\,in\,h\,\Omega\, t}{\Omega} +$$
$$+B_6 e^{\tau t}\ cos\,h2\Omega\, t + B_7 e^{\tau t}\ \frac{s\,inh\,2\,\Omega\, t}{2\Omega} + B_8 e^{\tau t}\ cosh\,4\Omega\, t + B_9 e^{\tau t}\ \frac{\sinh 4\Omega\, t}{4\,\Omega} + B_{10} e^{-at} \tag{3.6}$$

Using the inverse Laplace transform translation property we have

$$X(t) = xe^{\left(\frac{\alpha_3+\beta_2}{2}\right)t} \tag{3.7}$$

and

$$Y(t) = y\,e^{\left(\frac{\alpha_3+\beta_2}{2}\right)t} \tag{3.8}$$

where $A_i, B_i, i = 1,\Lambda\ 10$ are constants given by

$$A_1 = \left[x_o - \left\{\frac{(a+b)x_o}{a} - \frac{1}{a}\left[\frac{((a+b)-a)x_o\mu^2 + a^2 b\,x_o}{a^2-\mu^2}\right]\right] + \frac{1}{a}\left[\frac{\alpha_1(a\,b)-\mu^2}{a^2-\mu^2} - \alpha_1\right]$$

$$A_2 = \frac{(a+b)x_o}{a} - \frac{1}{a}\left[\frac{((a+b)-a)x_o\mu^2 + a^2 b x_o}{a^2-\mu^2}\right] + \frac{1}{a}\left[\alpha_1 - \alpha_1\frac{(ab-\mu^2)}{a^2-\mu^2}\right] + \frac{\alpha_2 X\beta_3}{\pi(-\tau^2+\mu^2)}$$
$$+\frac{\tau\,\alpha_2\Omega\ X\beta_3}{\left\{(\mu^2+\tau^2+\Omega^2)^2 - 4\mu^2\tau^2\right\}} - \frac{2}{3\pi}\cdot\frac{\alpha_2 X\beta_3\left\{(\mu^2+\tau^2+4\Omega^2)-2\tau^2\right\}}{\left\{(\mu^2+\tau^2+4\Omega^2)^2-4\mu^2\tau^2\right\}} - -\frac{2}{15\pi}$$
$$\cdot\frac{\alpha_2 X\beta_3\left\{(\mu^2+\tau^2+16\,\Omega^2)-2\,\tau^2\right\}}{\left\{(\mu^2+\tau^2+16\,\Omega^2)^2-4\mu^2\tau^2\right\}} = \frac{1}{2}C_{21} - \frac{2}{3\pi}C_{22} - \frac{2}{15\pi}C_{24}$$

$$A_3 = \frac{-\{(a+b)-a\}x_o\mu^2 + a^2bx_o}{a^2-\mu^2} + \frac{\alpha_1\left(ba-\mu^2\right)}{a^2-\mu^2} - \alpha_2 X\ y_o + \frac{\alpha_2 X\beta_3\tau}{\pi\left(-\tau^2+\mu^2\right)}$$

$$+\frac{1}{2\tau}\left\{\frac{C_{21}}{2}\left(\mu^2+\tau^2+\Omega^2\right) - \frac{2}{3\pi}\left[C_{22}\left(\mu^2+\tau^2+4\Omega^2\right)-\alpha_2X\beta_3\right] - \frac{2}{15\pi}\left[C_{24}\left(\mu^2+\tau^2+16\Omega^2\right)-\alpha_2X\beta_3\ \right]\right\}$$

$$A_4 = -\frac{1}{\pi\tau}\left\{\frac{\alpha_2 X\ \beta_3\tau}{\left(-\tau^2+\mu^2\right)}\right\},\ A_5 = -\frac{\tau\alpha_2\Omega X\beta_3}{\left\{\left(\mu^2+\tau^2+\Omega^2\right)^2-4\mu^2\tau^2\right\}},\ A_6 = -A_5\left\{\tau - \frac{\left(\mu^2+\tau^2+\Omega^2\right)}{2\tau}\right\},$$

$$A_7 = \frac{2}{3\pi}\cdot\frac{\alpha_2X\beta_3\left\{\left(\mu^2+\tau^2+4\Omega^2\right)-2\tau^2\right\}}{\left\{\left(\mu^2+\tau^2+4\Omega^2\right)^2-4\mu^2\tau^2\right\}} = \frac{2}{3\pi}A_{7m},\ A_8 = \frac{2}{3\pi}\left(A_{7m}\tau - \frac{1}{2\tau}\left\{A_{7m}\left(\mu^2+\tau^2+4\Omega^2\right)+\alpha_2X\beta_3\right\}\right)$$

$$A_9 = \frac{2}{15\pi}\cdot\frac{\alpha_2X\beta_3\left\{\left(\mu^2+\tau^2+16\Omega^2\right)-2\tau^2\right\}}{\left\{\left(\mu^2+\tau^2+16\,\Omega^2\right)^2-4\,\mu^2\tau^2\right\}} = -\frac{2}{15\pi}A_{9m}\qquad ,$$

$$A_{10} = +\frac{2}{15\pi}\left(A_{9m}\tau - \frac{1}{2\tau}\left\{A_{9m}\left(\mu^2+\tau^2+4\Omega^2\ \right)+\alpha_3X\beta_3\ \right\}\right)$$

$$B_1 = \frac{-\beta_3(\tau+d)}{\pi\left(-\mu^2+\tau^2\right)},\ B_2 = y_0 - \frac{\beta_3}{\pi\tau}\left\{\frac{-\left(\mu^2+d\tau\right)}{-\mu^2+\tau^2}-1\right\} - \frac{\alpha_1\ \beta_1}{\left(a^2-\mu^2\right)} - \frac{1}{2}\frac{\Omega\,\beta_3\left\{\left(\mu^2+\tau^2+\Omega^2\right)+2\,\tau d\ \right\}}{\left\{\left(\mu^2+\tau^2+\Omega^2\right)-4\mu^2\tau^2\right\}} +$$

$$\frac{2}{3\pi}\frac{\beta_3\left\{\left(d-\tau\right)\left(\mu^2+\tau^2+4\Omega^2\right)+2\tau\left(d\tau-\mu^2\right)\right\}}{\left\{\left(\mu^2+\tau^2+4\Omega^2\right)-4\mu^2\tau^2\right\}} + \frac{2}{15\pi}\frac{\beta_3\left\{\left(d-\tau\right)\left(\mu^2+\tau^2+16\Omega^2\right)+2\tau\left(d\tau-\mu^2\right)\right\}}{\left\{\left(\mu^2+\tau^2+16\Omega^2\right)^2-4\mu^2\tau^2\right\}}$$

$$= -\frac{1}{2}B_{21} + \frac{2}{3\pi}B_{22} + \frac{2}{15\,\pi}B_{24}$$

$$B_3 = y_0d - \frac{\beta_3}{\pi}\left(1 - \frac{\left(d+\tau\right)\tau}{-\mu^2+\tau^2}\right) + x_0\beta_1 + \frac{\alpha_1\beta_1a}{a^2-\mu^2} - \frac{1}{2}\cdot\frac{1}{2\tau}\left\{B_{21}\left(\mu^2+\tau^2+\Omega^2\right)-\Omega\beta_3\right\}+$$

$$\frac{2}{3\pi}\cdot\frac{1}{2\tau}\left\{B_{22}\left(\mu^2+\tau^2+4\Omega^2\right)-\beta_3\left(d-\tau\right)\right\} + \frac{2}{15\pi}\cdot\frac{1}{2\tau}\left\{B_{24}\left(\mu^2+\tau^2+16\Omega^2\right)-\beta_3\left(d-\tau\right)\right\}$$

$$B_4 = \frac{1}{2}\cdot\frac{\Omega\,\beta_3\left\{\left(\mu^2+\tau^2+\Omega^2\right)-2\tau\mathrm{d}\right\}}{\left\{\left(\mu^2+\tau^2+\Omega^2\right)^2-4\mu^2\tau^2\right\}} = -\frac{1}{2}\left(-B_{41}\right),\quad B_5 = -\frac{1}{2}\left[B_{41}\left\{-\tau + \frac{\left(\mu^2+\tau^2+\Omega^2\right)}{2\,\tau}\right\} + \frac{\Omega\,\beta_3}{2\tau}\right]$$

$$B_6 = -\frac{2}{3\pi}\frac{\beta_3\left\{\left(d-\tau\right)\left(\mu^2+\tau^2+4\Omega^2\right)-2\tau\left(d\tau-\mu^2\right)\right\}}{\left\{\left(\mu^2+\tau^2+4\Omega^2\right)^2-4\mu^2\tau^2\right\}} = \frac{2}{3\pi}\left(-B_{62}\right),$$

$$B_7 = \frac{2}{3\pi}\left[\beta_3 + B_{62}\tau - \frac{1}{2}\left\{B_{62}\left(\mu^2+\tau^2+4\Omega^2\right)-\beta\left(d-\tau\right)\right\}\right]$$

$$B_8 = -\frac{2}{15\pi}\frac{\beta_3\left\{\left(d-\tau\right)\left(\mu^2+\tau^2+16\Omega^2\right)-2\tau\left(d\tau-\mu^2\right)\right\}}{\left\{\left(\mu^2+\tau^2+16\Omega^2\right)^2-4\mu^2\tau^2\right\}} = \frac{2}{15\pi}\left(-B_{84}\right),$$

$$B_9 = \frac{2}{15\pi}\left[\beta_3 + B_{84}\tau - \frac{1}{2\tau}\left\{B_{84}\left(\mu^2+\tau^2+16\Omega^2\right)-\beta_3\left(d-\tau\right)\right\}\right],\ B_{10} = \frac{\alpha_1\beta_1}{a^2-\mu^2}$$

4.0 Result and discussion

For the purpose of our figures, we have used the following equivalents for easy graphical work: $\beta_2 \equiv bet2$ $\beta_3 \equiv bet3$ $\alpha_1 \equiv alph1$ $\alpha_2 \equiv alph2$ $\lambda \equiv lmda$ $d_1 \equiv d1$ $alph3 \equiv \alpha_3$. All other symbols in the text have the usual meaning on the figures. The profile of the blood glucose level is clearly dependent on a number of parameters.

From Figure 1-5, the parameters affecting the blood glucose levels significantly are *w, d1, bet2, lmda and alph2*. In figure 1 (a) and (b), we noted the blood glucose levels, X; is dependent on *w*. Within the first period of the insulin injected, there is still a slight rise in the blood glucose level for *w = .25 and w = .5*. When *w = .75* and *w* = 1, the initial rise does not last as in the cases of *w < 0.75* before the consequent fall in the blood glucose level. From Figure1b, we can see that further dose of insulin will bring the glucose level to the desired normal as in the case for *w = 0.5* which does not give the desired therapy to a normal state in earlier doses. Our result revealed the variation in time of the onset of hypoglycemia for different dose selection. In Figure 2(a) and (b) the effect of the half-life time d_i, is evident. When this is smaller there is a rise in the blood glucose level than when it is greater. Smaller values of d_1 is likely to promote hyperglycemia and the greater the values, hypoglycemia can set in if this is not monitored or regulated.

In Figure 3(a) and (b), the effect of *bet2* is similarly observed. Increase in *bet2* provokes an increase in blood glucose levels slightly above the smaller *bet2*. It is however, noted that at a higher *bet2*, there is the possibility of earlier lowering of the blood glucose levels. Higher *bet2* from this figure too even in the first period of injection of insulin can provoke hypoglycemia.

From Figure 4(a) and (b) the effect of *lmda* is instructive. Increase in *lmda* enables the reduction in blood glucose level. Blood glucose level is higher when *lmda* is higher. In the consequent period of insulin injection the rise earlier in blood glucose level exhibit a fall.

In Figure 5(a) and (b), the effect of *alph2* in the earlier period of insulin injection is not significant but in the consequent period as in fig. 5(b), the difference is noticeable. For some *alph2* the rise in blood glucose level is higher for smaller values of *alph2*. However, for a high value of like *alph2,* the increase in blood glucose level exhibits a fall in consequent period.

These results clearly support the reports in medical literature of short and long time acting insulin. The parameters *w, bet2, alph2 and* d_1 can be regulated to promote this feature for a desired treatment. The desire for a periodic administration of insulin for a diabetic is good because of the inability of some diabetics to administer rightly and/or also at the right time. The need for further research work to corroborate the experimental findings is important. This work has given insight to the state of the diabetic and the parameters to be monitored and regulated are revealed. Certainly, criteria to avoid hyperglycemia or hypoglycemia or their respective state comas must be investigated. Furthermore, the model for insulin injection for short time and long time acting must be investigated.

Fig. 1a

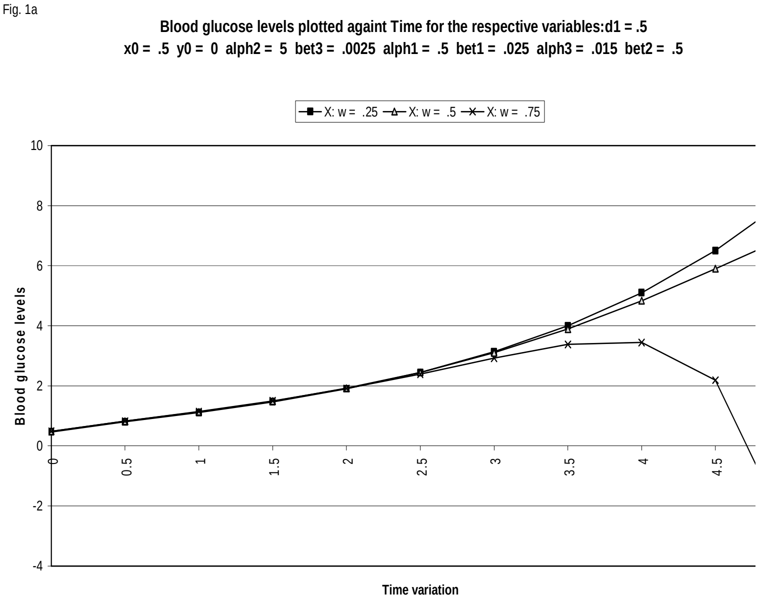


Fig. 1b

Blood glucose levels plotted againt Time for the respective variables:d1 = 0.5
x0 = .5 y0 = 0 alph2 = 5 bet3 = .0025 alph1 = .5 bet1 = .025 alph3 = .015 bet2 = .5

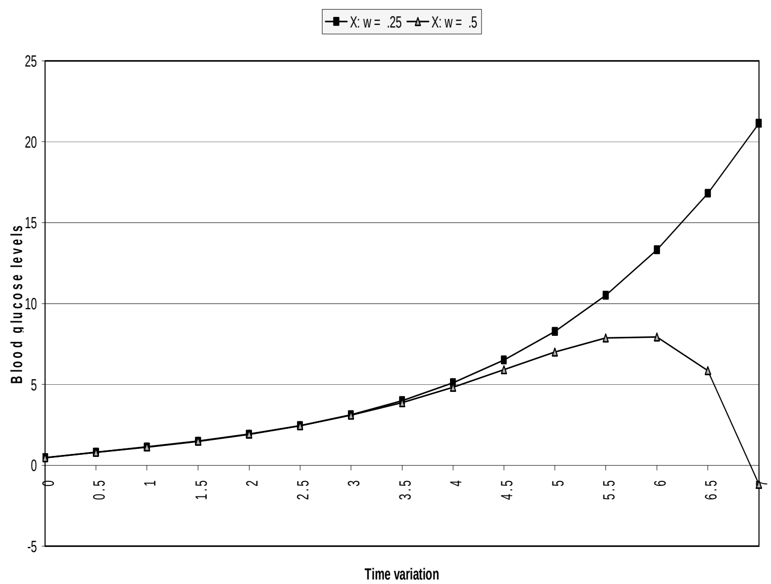


Fig. 2a

Blood glucose levels plotted againt Time for the respective variables:w = 0.5
x0 = .5 y0 = 0 alph2 = 5 bet3 = .0025 alph1 = .5 bet1 = .025 alph3 = .015 bet2 = .5

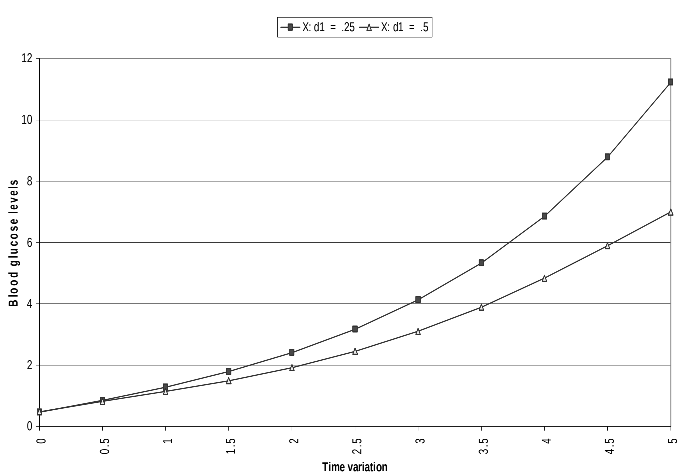


Fig. 2b

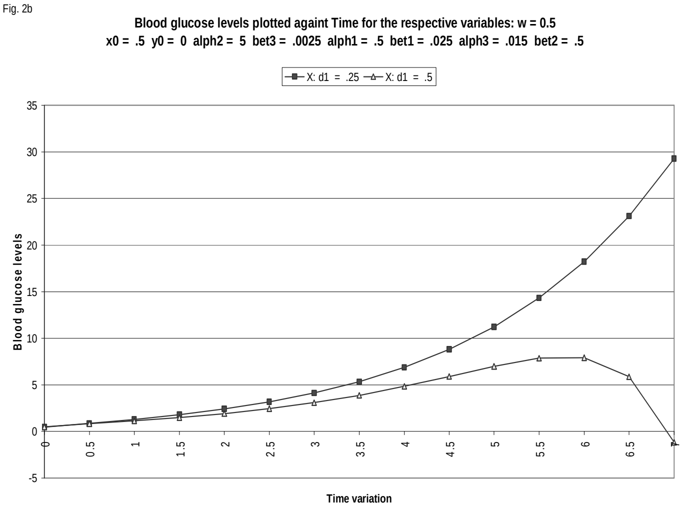

Blood glucose levels plotted againt Time for the respective variables: w = 0.5
x0 = .5 y0 = 0 alph2 = 5 bet3 = .0025 alph1 = .5 bet1 = .025 alph3 = .015 bet2 = .5
X: d1 = .25
X: d1 = .5
35
30
25
20
15
10
5
0
-5
Blood glucose levels
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
5
5.5
6
6.5
Time variation

Fig. 3a

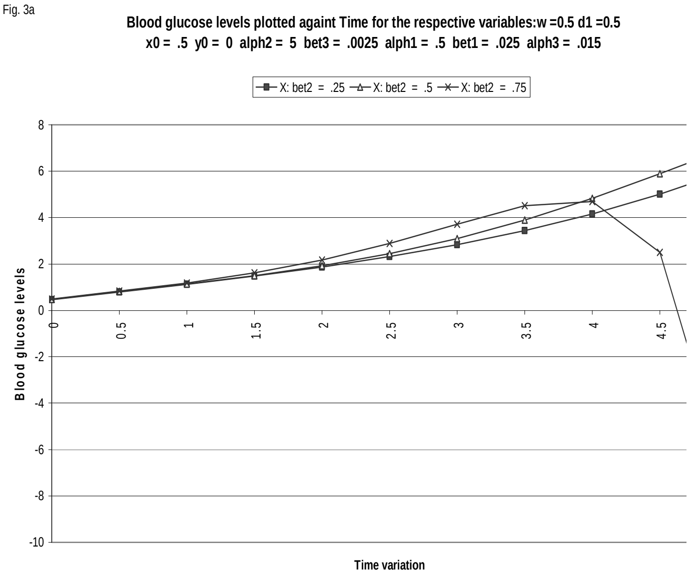

Blood glucose levels plotted againt Time for the respective variables:w =0.5 d1 =0.5
x0 = .5 y0 = 0 alph2 = 5 bet3 = .0025 alph1 = .5 bet1 = .025 alph3 = .015
X: bet2 = .25
X: bet2 = .5
X: bet2 = .75
8
6
4
2
0
-2
-4
-6
-8
-10
Blood glucose levels
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
Time variation

Fig. 3b

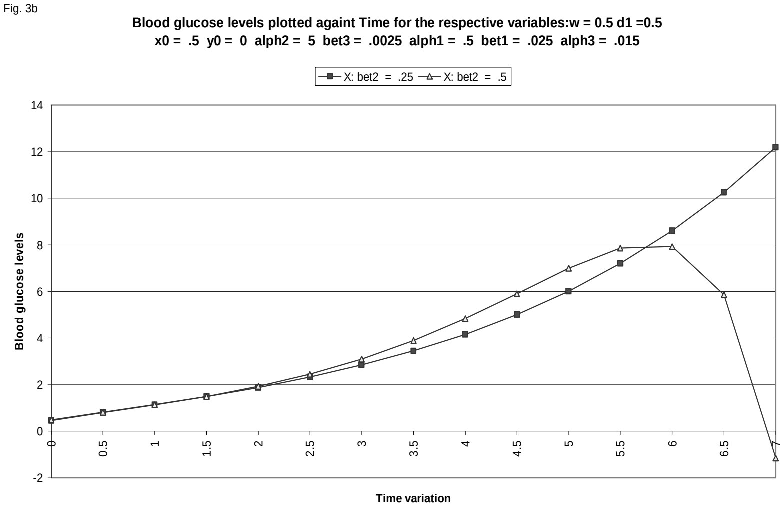


Fig. 4a

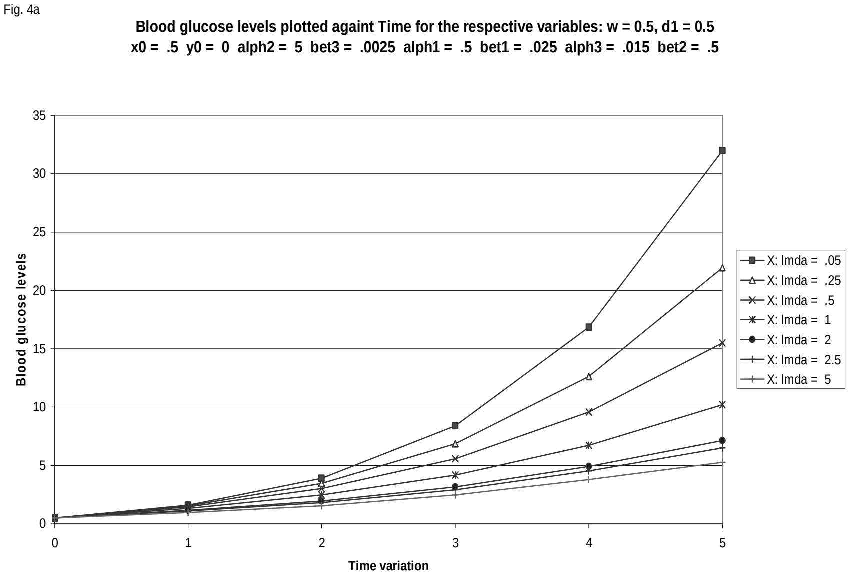


Fig. 5a

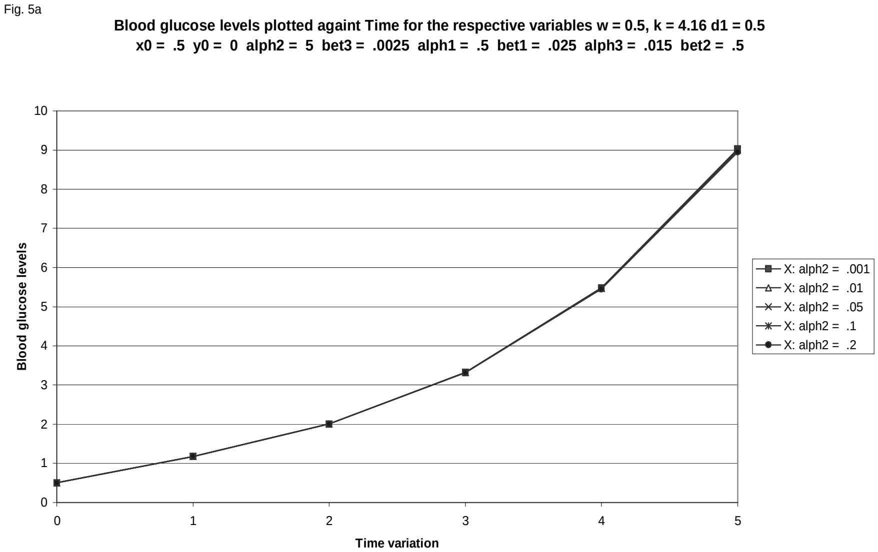
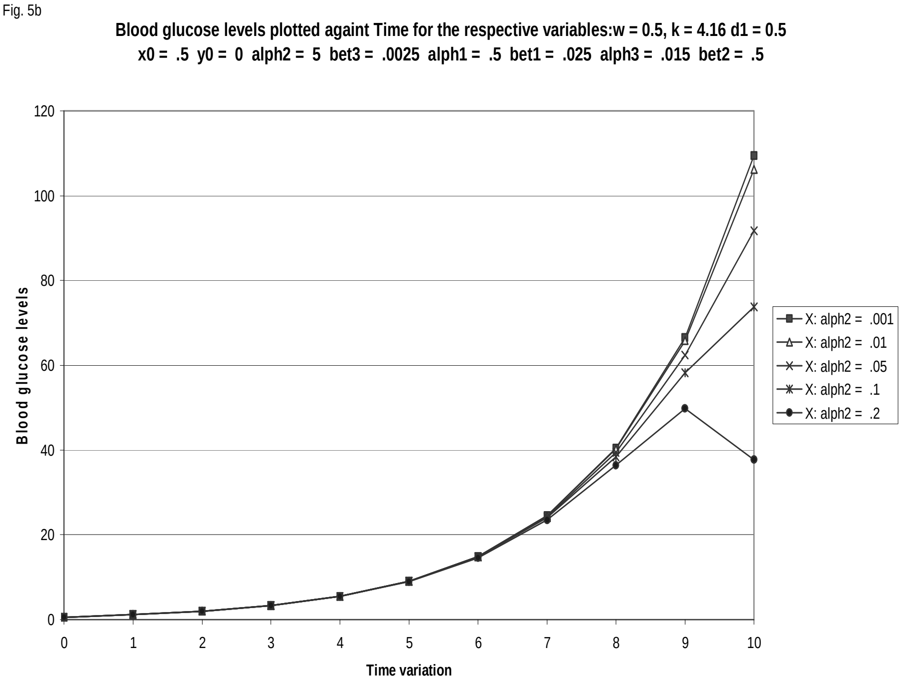


Fig. 5b



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