The Impact of Obesity on Predisposed People to Type 2 Diabetes: Mathematical Model

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Abstract. Several mathematical models have been developed to simulate, analyse and understand the dynamics of β-cells, insulin and glucose. In this paper we study the effect of obesity on type 2 diabetes in people with genetic predisposition to diabetes. Equilibrium analysis and stability analysis are studied and the model shows three equilibrium points: a stable trivial pathological equilibrium point P_0, a stable physiological equilibrium point P_1 and a saddle point P_2. A simulation is carried out to understand the models behaviour.

Keywords: Type 2 diabetes, obesity, mathematical modeling, equilibrium analysis, stability analysis.

1 Introduction

According to the International Diabetes Federation (IDF) 2013, 8.3% of adults (382 million people) are living with diabetes all over the world with a particular growing trend of type 2 diabetes. [1]

Obesity is thought to be the primary cause of type 2 diabetes, especially for people having a genetic predisposition to the disease [2, 3]. Actually, an elevated level of Free Fatty Acids (FFA) leads to a chronic insulin resistance and thus β-cell apoptosis that consequently raises the blood glucose level [4].

Several studies have been carried out in order to understand the dynamics of insulin and glucose leading to diabetes. Bolie (1961) introduced a simple linear model, using ordinary differential equations in glucose and insulin [5]. Bergman et al. published the minimal model [6]. Diverse models based on the minimal model were published by different authors, including Derouich and Boutayeb (adding physical effort) [7], Roy and Parker dealt with the interaction between insulin, glucose and FFA [8]. Other authors introduced the dynamics of β-cells in the mechanisms leading to diabetes. Topp et al incorporate the β-cell mass,

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insulin, and glucose kinetics [9]. Hernandez et al. proposed an extension of the Topp model by adding the surface insulin receptor dynamics [10]. Boutayeb et al. extended Topps model by stressing the effect of genetic predisposition to diabetes [11].

Our model is based on mathematical models published by Boutayeb et al[11], Roy et al[8] and Hernandez et al[10].

2 The Mathematical Model

In this model we assume, for glucose dynamics that the concentration of glucose in the blood is determined by a differential equation of the form:

$a - bG(t) - cI(t)R(t)G(t) + m_1(F(t) - F_b)$[9, 10].

Where $G(t)(g/l)$ is the concentration of glucose that increases by a rate a (in $mg/(dl.d)$) (glucose production by liver and kidneys) and decreases by a rate $bG(t)$ where b in (d^{-1})(independent of insulin) and a rate $cI(t)R(t)G(t)$ representing the glucose uptake due to insulin sensitivity c[10].We assume that the concentration of glucose increases by a rate $m_1(F(t)-F_b)$ where m_1 (in $l/d\mu mol$) which is the effect of FFA on glucose uptake.

Insulin dynamics is governed by the differential equation of the form: $\frac{d\beta(t)}{1+R(t)}\frac{G(t)^2}{e+G(t)^2} - fI(t) - fR(t)I(t)$, which has the same expression used by Henandez et al. Where $I(t)(\ (\ \mu U)/ml)$ is the plasma insulin concentration [10]. The dynamics of β-cell mass for predisposed people to type 2 to diabetes[2] as used in the model of Topp et al. takes the form: $(-g + hG(t) - iG(t)^2)$. Where $\beta(t)$ (mg) is the β-cell mass [10].

For the insulin receptors dynamics we keep the expression used by Hernandez et al.: $j(1 - R(t)) - kI(t)R(t) - lR(t)$. Where $R(t)$ is the insulin receptor [10]. The concentration of FFA increases by a rate $m_3(G(t) - G_b)$which represents the excess glucose used in lipogenesis and decreases by $m_2(F(t) - F(t)_b)$ which is the effect of the rate of insulin on FFA. Where $F(t)$ $(\ (\ \mu mol)/l)$

So, the model is written as follows:

$$\frac{dG(t)}{dt} = a - bG(t) - cI(t)R(t)G(t) + m_1(F(t) - F_b)$$

$$\frac{dI(t)}{dt} = \frac{d\beta(t)}{1 + R(t)}\frac{G(t)^2}{e + G(t)^2} - fI(t) - fR(t)I(t)$$

$$\frac{d\beta(t)}{dt} = (-g + hG(t) - iG(t)^2)$$

$$\frac{dR(t)}{dt} = j(1 - R(t)) - kI(t)R(t) - lR(t)$$

$$\frac{dF(t)}{dt} = -m_2(F(t) - F(t)_b) + m_3(G(t) - G_b)$$

3 Equilibrium Analysis

The steady state solutions are the solutions of the equations:

$$\begin{aligned} a - bG(t) - cI(t)R(t)G(t) + m_1(F(t) - F_b) &= 0 \\ \frac{d\beta(t)}{1+R(t)}\frac{G(t)^2}{e+G(t)^2} - fI(t) - fR(t)I(t) &= 0 \\ -g + hG(t) - iG(t)^2 &= 0 \\ j(1-R(t)) - kI(t)R(t) - lR(t) &= 0 \\ -m_2(F(t) - F(t)_b) + m_3(G(t) - G_b) &= 0 \end{aligned}$$

This model has three equilibrium points:
$P_0(G_0, I_0, \beta_0, R_0, F_0), P_1(G_1, I_1, \beta_1, R_1, F_1)$ ans $P_2(G_2, I_2, \beta_2, R_2, F_2)$
• The first equilibrium point $P_0 = (G_0, I_0, \beta_0, R_0, F_0)$ is a trivial pathological point.
With:

$$\begin{aligned} G_0 &= \frac{m_1 m_3 G_b - a m_2}{m_1 m_3 - m_2 b}, \\ I_0 &= 0, \\ \beta_0 &= 0, \\ R_0 &= \frac{j}{j+1}, \\ F_0 &= \frac{a m_3 - b m_3 G_b - m_1 m_3 F_b + m_2 b F_b}{-m_1 m_3 + m_2 b} \end{aligned}$$

• The second equilibrium point $P_1 = (G_1, I_1, \beta_1, R_1, F_1)$ is a physiological point.

With:

$$\begin{aligned} G_1 &= \frac{h - \sqrt{h^2 - 4ig}}{2i}, \\ I_1 &= \frac{-jG_b + aj + jm_1F_1^* - jm_1F_b + la + lm_1F_1^* - lm_1F_b}{ak - cjG_1^* + m_1kF_1^* - m_1kF_b}, \\ \beta_1 &= \frac{fI_1^*(R_1^*+1)(e+G_1^{*2})}{dG_1^*}, \\ R_1 &= \frac{ak - cjG_1^* + km_1F_1^* - km_1F_b)}{(G_1^*(bk - cj - cl}, \\ F_1 &= \frac{2m_2iF_b + hm_3 - m_3\sqrt{h^2 - 4ig} - 2im_3G_b}{2im_2} \end{aligned}$$

The third equilibrium point $P_2 = (G_2, I_2, \beta_2, R_2, F_2)$
with:

$$
\begin{aligned}
G_2 &= \frac{h + \sqrt{h^2 - 4ig}}{2i}, \\
I_2 &= \frac{-jG_b + aj + jm_1F_2^* - jm_1F_b + la + lm_1F_2^* - lm_1F_b}{ak - cjG_2^* + m_1kF_2^* - m_1kF_b}, \\
\beta_2 &= \frac{fI_2^*(R_2^* + 1)(e + G_2^{*2})}{dG_2^*}, \\
R_2 &= \frac{ak - cjG_2^* + km_1F_2^* - km_1F_b}{G_2^*(bk - cj - cl)}, \\
F_2 &= \frac{2m_2iF_b + hm_3 + m_3\sqrt{h^2 - 4ig} - 2im_3G_b}{2im_2}
\end{aligned}
$$

The conditions of existence of the equilibrium points are presented in the following Table:

Table 1. Conditions of existence

	Coordinates	Conditions of existence
P_0	$(G_0, I_0, \beta_0, R_0, F_0)$	$\frac{m_1m_3}{m_2} < b,\ \frac{a}{b} > G_b$
P_1	$(G_1, I_1, \beta_1, R_1, F_1)$	$\frac{h-\sqrt{h^2-4ig}}{2i} < G_b\ ,\ bk > c(j+l)$
P_2	$(G_2, I_2, \beta_2, R_2, F_2)$	$\frac{h+\sqrt{h^2-4ig}}{2i} > G_b,\ bk > c(j+l)$

4 Stability Analysis

The stability analysis based on variational principle is used. The variational matrix of the system at any point $P_i (i = 0, 1, 2)$ is written as:

$$
\begin{pmatrix}
-b - cIR & -cRG & 0 & -cIG & m_1 \\
\frac{2d\beta Ge}{(R+1)(e+G^2)^2} & -f - fR & \frac{dG^2}{(R+1)(e+G^2)} & \frac{-d\beta G^2}{(R+1)^2(e+G^2)} - fI & 0 \\
(h - 2iG)\beta & 0 & -g + hG - iG^2 & 0 & 0 \\
0 & -kR & 0 & -j - kI - l & 0 \\
m_3 & 0 & 0 & 0 & -m_2
\end{pmatrix}
$$

4.1 The Stability Analysis of the P_0

The eigenvalues of the variational matrix at P_0:

$$\lambda_1 = -j - l$$

$$\lambda_2 = -g + hG - iG^2$$
$$\lambda_3 = -\frac{1}{2}b - \frac{1}{2}m_2 + 1/2\sqrt{4m_1m_3 + b^2 - 2bm_2 + m_2^2}$$
$$\lambda_4 = -\frac{1}{2}b - \frac{1}{2}m_2 - 1/2\sqrt{4m_1m_3 + b^2 - 2bm_2 + m_2^2}$$
$$\lambda_5 = -f - fR$$

Since: $\lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5 < 0$ (following the conditions of existence in Table1) we conclude that the point P_0 is stable.

4.2 The Stability Analysis of the P_1:

The calculus of P_1s eigenvalues is computed using numerical approximation by Maple, showing that P_1 is a stable node.

4.3 The Stability Analysis of the P_2:

We put:

$$A = b + cIR$$
$$B = cRG$$
$$C = cIG$$
$$D = \frac{2d\beta Ge}{(R+1)(e+G^2)^2}$$
$$E = \frac{dG^2}{(R+1)(e+G^2)}$$
$$F = f + fR$$
$$J = \frac{d\beta G^2}{(R+1)^2(e+G^2)} + fI$$
$$K = kR$$
$$L = j + kl + l$$
$$M = (h - 2iG)\beta$$

Given the characteristic polynomial,

$\lambda^5 +$
$(n + L + F + A)\lambda^4 +$
$(m_1m_3 + m_2L + m_2F + nA - KJ + LF + LA + DB + FA)\lambda^3 +$
$(m_1m_3L - m_1m_3F - m_2KJ + m_2LF + m_2LA + m_2DB + m_2FA - KDC - KJA +$
$LJA + LDB + LBD + LFA + MBE)\lambda^2 +$
$(m_1m_3KJ - m_1m_3LF - m_2KDC - m_2KJA + m_2LDB + m_2LFA + m_2MBE -$
$KEMC + LMBE)\lambda +$
$m_2KEMC - m_2LMBE$

Following the conditions of existence of P_2 given in Table1: $m_2KEMC - m_2LMBE < 0$, whereas the coefficient of the highest order is positive. We conclude that P_2 is unstable since the necessary condition of routh Hurwitz is not satisfied.

5 Simulation

Our simulation is based on the parameters given in Table 2. [8–11].

Table 2. Parameters for an average healthy person

Param	Value	Units	Biological Interpretation
a	864	$\frac{mg}{dl\ d}$	glucose production rate by liver when G =0
b	1.44	d^{-1}	glucose clearance rate independent of insulin
c	0.85	$\frac{ml}{\mu U\ d}$	insulin induced glucose uptake rate
d	43.2	$\frac{\mu U}{ml\ d\ mg}$	β-cell maximum insulin secretory rate
e	20000	$\frac{mg^2}{dl^2}$	gives inflection point of sigmoidal function
f	216	d^{-1}	whole body insulin clearance rate
g	0.06	d^{-1}	β-cell natural death rate
h	0.572-3	$\frac{dl}{mg\ d}$	determines β-cell glucose tolerance range
i	0.252e-5	$\frac{dl^2}{mg^2 d}$	determines β-cell glucose tolerance range
j	2.64	$\frac{1}{d}$	insulin receptor recycling rate
k	0.02	$\frac{ml}{\mu U d}$	insulin dependent receptor endocytosis rate
l	0.24	d^{-1}	insulin independent receptor endocytosis rate
m_1	0.0864	$\frac{l}{d\mu mol}$	the effect of plasma FFA on glucose uptake
m_2	43.2	d^{-1}	the influence of insulin
m_3	97.92	ml^{-1}	the rate constant representing plasma FFA concentration
G_b	98	$\frac{md}{dl}$	the basal glucose concentration
F_b	380	$\frac{\mu mol}{l}$	the basal FFA concentration

Using the parameters giving in Table 2 yields the results presented in Table 3.

Table 3. Stability analysis using the values of parameters given in Table 2

equilibrium points(G, I, β, R, F)	Stability
(679, 0, 0, 0.9, 1698.2)	stable
(82, 12.65, 853.32, 0.85, 343.7)	stable
(145, 6.13, 211.25, 0.88, 486.6)	instable

In this model we considered the effect of obesity on type 2 diabetes. It was shown in the first point P_0 that an elevated rate of FFA has an impact on insulin secretion and insulin-resistance and hence on the development of type 2 diabetes.

The results of the simulation using parameters given in Table2 with (I(0)=6.5, β(0)=220, R(0)=0.87 and F(0)=580) are illustrated by Fig1, Fig2, Fig3, Fig4 and Fig5.

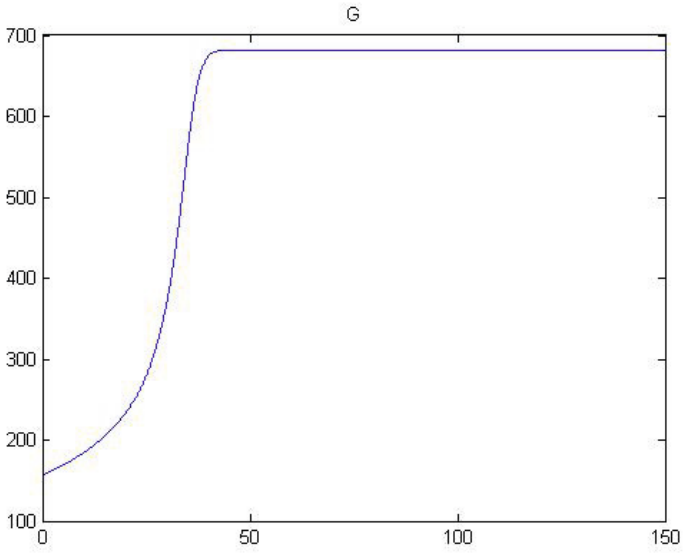

Fig. 1. Plot of the trajectory of G over 150 days

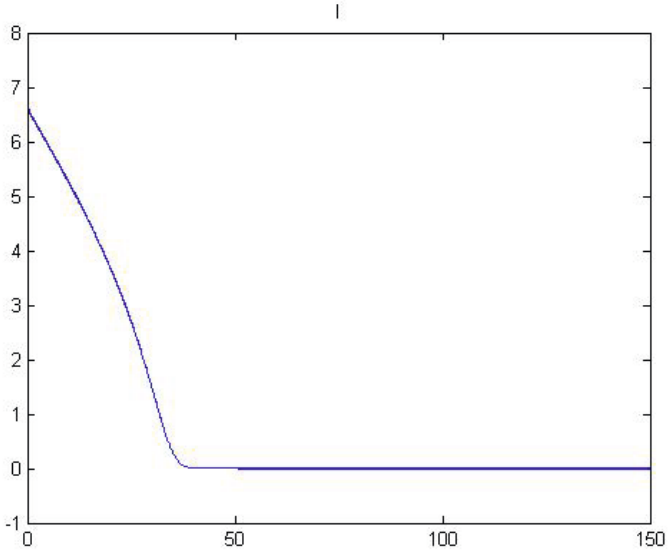

Fig. 2. Plot of the trajectory of I over 150 days

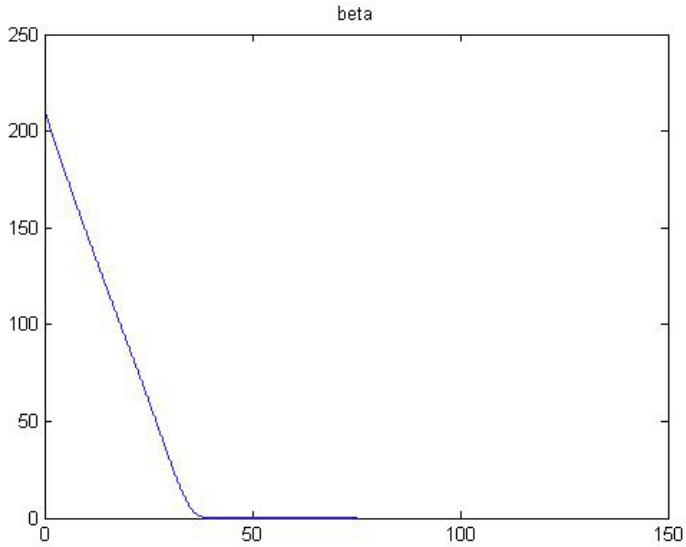

Fig. 3. Plot of the trajectory of β over 150 days

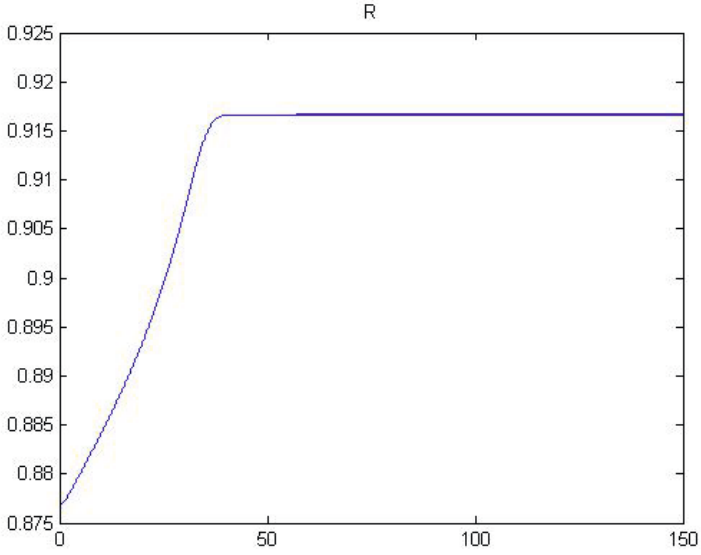

Fig. 4. Plot of the trajectory of R over 150 days

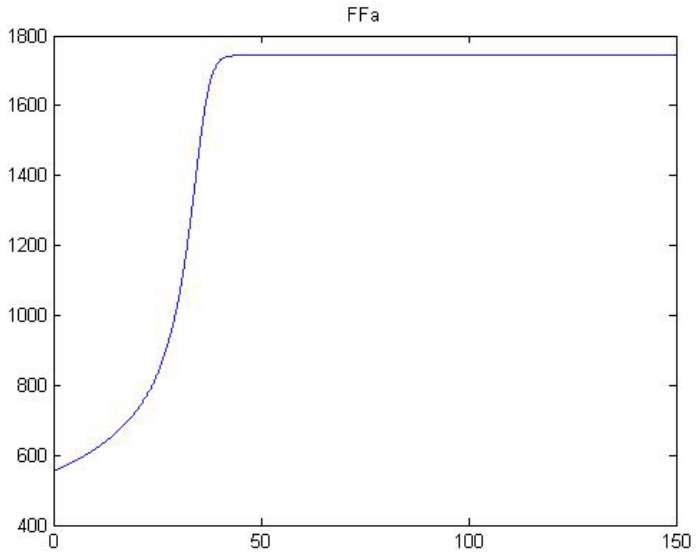

Fig. 5. Plot of the trajectory of FFA over 150 days

The mathematical model has three equilibrium points: a stable pathological point corresponding to an hyperglycemic state with zero level of β-cell mass and insulin $P_0(679, 0, 0, 0.9, 1698)$, and a high level of FFA, a stable physiological point with basal values of FFA, glycemia, insulin, insulin receptor and β-cell mass $P_1(82, 12.645, 853.32, 0.85, 343.7)$, and an unstable saddle point with intermediate values of FFA, glycemia, insulin, insulin receptor and β-cell mass $P_2(145, 6.13, 211.25, 0.88, 486.6)$.

6 Conclusion

In this model we considered the effect of obesity on type 2 diabetes in presence of pre-disposition to diabetes on the dynamics of β-cells, insulin, glucose, insulin receptors and Free Fatty Acids (FFA). It was shown that the pathological and physiological equilibrium points are stable and the saddle equilibrium point with intermediate values of Glucose, Insulin, β-cell mass, insulin receptors and FFA is unstable. An elevated rate of FFA, leads to an evolution towards the pathological point (G=679,I=0,β=0,R=0.9,FFA=1698.2). This model confirms that FFA has an impact on insulin secretion and insulin-resistance and hence on the development of type 2 diabetes for people with predisposition to diabetes.

References

1. International Diabetes Federation: IDF Diabetes Atlas fifth edition 2013 update. Brussels, Belgium (2013)
2. Poitout, V., Robertson, R.P.: Fuel Excess and -Cell Dysfunction. Endocrine Reviews 29, 351-366 (2008), http://dx.doi.org/10.1210/er.2007-0023
3. Beale, S.: Deteriorating Beta-Cell Function in Type 2 Diabetes a Long-Term Model. Quarterly Journal of Medicine, 96, 281-288 (2003), http://dx.doi.org/10.1093/qjmed/hcg040
4. Turpeinen, A., Takala, T., Nuutila, P.: Impaired Free Fatty Acid Uptake in Skeletal Muscle But Not in Myo-cardium in Patients With Impaired Glucose Tolerance. DIABETES 48 (June 1999)
5. Bolie, V.: Coefficients of normal blood glucose regulation. Journal of Applied Physiology 16, 783–788 (1961)
6. Bergman, R.N., Finegood, D.T., Ader, M.: Assessment of Insulin Sensitivity in Vivo. Endicrine Reviews 6(1), 45–86 (1985)
7. Derouich, M., Boutayeb, A.: The effect of physical exercise on the dynamics of glucose and insulin. Journal of Biomechanics 35, 911–917 (2002)
8. Roy, A., Parker, R.S.: Dynamic Modeling of Free Fatty Acids, Glucose, and Insulin: An Extended Minimal Model. Neurosiences 8(9), 617–626 (2006)
9. Topp, B., Promislow, K., De Vries, G., Miura, R.M., Finegood, D.T.A.: Model of -Cell Mass, Insulin, and Glucose Kinetics: Pathways to Diabetes. Journal of Theoretical Biology 99A, 605-619 (2000), http://dx.doi.org/10.1006/jtbi.2000.2150
10. Hernandez, R.D., Lyles, D.J., Rubin, D.B., Voden, T.B., Wirkus, S.A.: A Model of -Cell Mass, Insulin, Glucose and Receptor Dynamics with Applications to Diabetes. Tech-nical Report, Biometric Department, MTBI Cornell University (2001), http://mtbi.asu.edu/research/archive/paper/model-%CE%B2-cell-mass-insulin-glucose-and-receptor-dynamics-applications-diabetes
11. Boutayeb, W., Lamlili, M., Boutayeb, A., Derouich, M.: Mathematical Modelling and Simulation of β-Cell Mass, Insulin and Glucose Dynamics: Effect of Genetic Predisposition to Diabetes. J. Biomedical Science and Engineering 7, 330–342 (2014)