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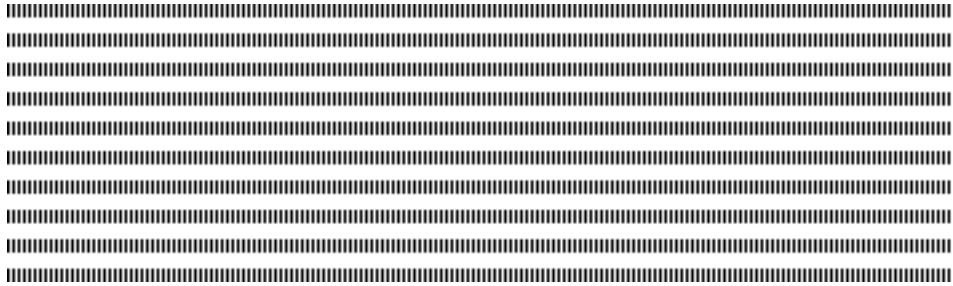
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A mathematical model

On the effect of growth hormone on glucose homeostasis

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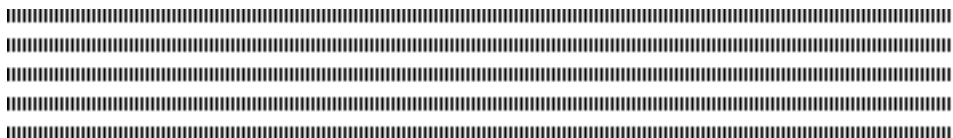


RÉSUMÉ. Prolongeant un précédent modèle publié dédié à l'interaction entre les cellules β , l'insuline, le glucose, les récepteurs d'insuline et les acides gras libres, cet article propose un modèle mathématique introduisant l'effet de l'hormone de croissance sur l'homéostasie du glucose. L'analyse de stabilité a été suivie d'explication pratique des points d'équilibre. Enfin, la simulation a illustré comment les cellules β , l'insuline, le glucose, les récepteurs d'insuline, les acides gras libres et l'hormone de croissance peuvent varier en fonction des différentes valeurs de certains paramètres.

ABSTRACT. Extending an existing model devoted to the interaction between β -cell mass, insulin, glucose, receptor dynamics and free fatty acids, in glucose regulatory system simulation, this paper proposes a mathematical model introducing the effect of growth hormone on the glucose homeostasis alongside the other variables. Stability analysis is carried out and pragmatic explanation of the equilibrium points is emphasized. Finally, simulation illustrated how β -cell mass, insulin, glucose, receptor dynamics, free fatty acids and growth hormone may vary with different values of some parameters in the model.

MOTS-CLÉS : Modèle, Equilibre, Stabilité, Simulation, Cellules β , Insuline, Glucose, Récepteurs d'insuline, Acides gras libres, Hormone de croissance.

KEYWORDS : Model, Equilibrium, Stability, Simulation, β -Cell Mass, Insulin, Glucose, Receptor, Free Fatty Acids, Growth Hormone



1. Introduction

During the last decades, an important number of publications were devoted to mathematical modeling applied to diabetes. We cite in particular, the papers presenting a model of β -Cell Mass, Insulin, and Glucose Kinetics [17], mathematical modeling and simulation of β -Cell Mass, Insulin, and Glucose dynamics: effect of genetic predisposition to diabetes [4], dynamic modeling of Free Fatty Acids, Glucose, and Insulin: an extended minimal model [14], a model of β -Cell Mass, Insulin, Glucose and Receptor Dynamics [8] and the impact of obesity on predisposed people to type 2 diabetes: a mathematical model of β -Cell Mass, Insulin, Glucose, Receptor Dynamics and Free Fatty Acids [5]. For more publications on modeling for diabetes, we refer to the following reviews [1]-[3], [6], [11]-[13] and [15]. In this paper, we consider the effect of Growth Hormone (GH) on glucose homeostasis, extending the previous model published by Boutayeb W et al. [5]. While growth hormone is well known to promote growth in children by acting on a number of tissues and organs, its importance for adults is less known. It doesn't cause growth in adults but it plays a major role in metabolism, muscle mass function, lipid control and glucose homeostasis. The idea of investigating growth hormone was mainly motivated by a review article published by Kim S-H and Park M-J in 2017 on the effects of growth hormone (GH) on glucose metabolism and insulin resistance in human [9]. The review article summarized the main findings of several studies on this subject as follows:

- 1) Investigating the effects of growth hormone (GH) on glucose metabolism have demonstrated that GH increases glucose production through gluconeogenesis and glycogenolysis from the liver and kidney.

- 2) Growth hormone stimulates lipolysis which results in free fatty acid (FFA) flux from adipose tissue to circulation.

- 3) Increased FFA in circulation can induce insulin resistance. Meanwhile, increase in FFA uptake by hepatocytes results in promotion of hepatic lipid oxidation and accumulation of Acetyl-CoA, yielding an increase of blood glucose levels.

- 4) Interaction between insulin and GH downstream of receptor activation in the skeletal muscle and adipose tissue provides another alternative mechanism mediating GH-induced resistance.

Consequently, growth hormone can be introduced in a mathematical model besides other hormones and factors like glucose, insulin, beta-cells, insulin receptors and free fatty acids (FFA).

2. The mathematical model

Our model is an extension of the model of Boutayeb et al. [5] which involves five variables (glucose, insulin, β -cell mass, insulin receptors and free fatty acids) governed by the five following nonlinear differential equations :

$$\frac{d\beta}{dt} = (-g + hG(t) - iG(t)^2) \beta(t) \quad (1)$$

$$\frac{dI}{dt} = \frac{\beta dG^2}{(1+R)(e+G^2)} - fI - fRI \quad (2)$$

$$\frac{dG}{dt} = a - (b + cRI)G + m_1(F - F_b) \quad (3)$$

$$\frac{dR}{dt} = j(1 - R) - kIR - lR \quad (4)$$

$$\frac{dF}{dt} = -m_2(F - F_b) + m_3(G - G_b) \quad (5)$$

where β -cell mass $\beta(t)$, insulin $I(t)$, glucose $G(t)$, insulin receptors $R(t)$ and growth hormone $GH(t)$ are all functions of time, from which t was omitted for simplicity. All the coefficient parameters, their interpretation and values are recalled in Table 1.

Parameter	Value	Units	Biological Interpretation
a	864	$\frac{mg}{dl \cdot d}$	glucose production rate by liver when $G = 0$
b	1.44	d^{-1}	glucose clearance rate independent of insulin
c	0.85	$\frac{ml}{\mu U \cdot d}$	insulin induced glucose uptake rate
d	43.2	$\frac{\mu u}{ml \cdot d \cdot mg}$	β -cell maximum insulin secretory rate
e	20,000	$\frac{mg^2}{dl^2}$	gives inflection point of sigmoidal function
f	216	d^{-1}	whole body insulin clearance rate
j	2.64	d^{-1}	insulin receptor recycling rate
k	0.02	$\frac{ml}{\mu U \cdot d}$	insulin dependent receptor endocytosis rate
l	0.24	d^{-1}	insulin independent receptor endocytosis rate
g	0.03	d^{-1}	β -cell natural death rate
h	0.5727e-3	$\frac{dl}{mg \cdot d}$	determines β -cell glucose tolerance range
i	0.2523e-5	$\frac{dl^2}{mg^2 \cdot d}$	determines β -cell glucose tolerance range
m_1	0.0864	$\frac{1}{d \cdot \mu \cdot mol}$	constant rate
m_2	43.2	d^{-1}	constant rate for FFA production
m_3	97.92	ml^{-1}	constant rate for Glucose production
F_b	11	$\frac{mg}{dl}$	basal value of Free Fatty Acids
G_b	98	$\frac{mg}{dl}$	basal value of glucose

Table 1. Parameters in Insulin, Glucose, FFA, β cells & Receptors equations used by [5]

In our model, we add growth hormone dynamics, by including a sixth differential equation for $GH(t)$ and by exhibiting the interaction of GH with glucose and FFA as follows:

$$\frac{d\beta}{dt} = (-g + hG(t) - iG(t)^2) \beta(t) \quad (6)$$

$$\frac{dI}{dt} = \frac{\beta dG^2}{(1 + R)(e + G^2)} - fI - fRI \quad (7)$$

$$\frac{dG}{dt} = a - (b + cRI)G + m_1(F - F_b) + cGH \quad (8)$$

$$\frac{dR}{dt} = j(1 - R) - kIR - lR \quad (9)$$

$$\frac{dF}{dt} = -m_2(F - F_b) + m_3(G - G_b) + x(GH - GH_b) \quad (10)$$

$$\frac{dGH}{dt} = p - wGH - s(F - F_b) - zR \quad (11)$$

From equation (11), the rate of the growth hormone GH is increased by the rate of production of GH by the somatotropic cells (p), occurring in the pituitary gland. It is decreased by the rate of GH clearance/absorption by the liver (w), the rate of uptake of GH by Fat cells (s) and by the rate of uptake of GH by receptor cells (z). Growth hormone also increases the rate of glucose (c) as well as the rate of FFA (x). Parameters (and their values) used in the GH equation are given in Table 2 below. Other nonlinear and more complicated interactions of GH with β -cells, insulin and receptors will be addressed in further future research work.

<i>GH</i> Coefficients in equations	Value	Units	Biological Interpretation
p	363	$\frac{m\mu g}{min}$	GH production rate by somatotropic cells
w	136	$\frac{ml}{min}$	GH clearance rate by the liver
s	0.1	$\frac{ng\ l}{d\ ml\ \mu\ mol}$	rate of uptake of GH by Fat cells
z	2	$\frac{ng\ l}{d\ ml\ \mu\ mol}$	rate of uptake of GH by receptor cells
x	200	$\frac{ml\ \mu\ mol}{l\ d\ ng}$	constant rate for GH production
GH_b	5	$\frac{ng}{ml}$	basal value of growth hormone

Table 2. Parameters and their values used in the growth hormone equation [16]

3. Stability analysis

3.1. Equilibrium points

The equilibrium points satisfy:

$$\frac{d\beta}{dt} = \frac{dI}{dt} = \frac{dG}{dt} = \frac{dR}{dt} = \frac{dF}{dt} = \frac{dGH}{dt} = 0 \quad (12)$$

From equations (6) & (12):

$$\text{either (a) } \beta = \beta_0^* = 0, \quad \text{or (b) } -g + hG - iG^2 = 0 \quad (13)$$

Case (a): By direct substitution of $\beta = 0$ into equations of insulin and receptors (7) & (9), we get three values:

$$\beta = \beta_0^* = 0, \quad I = I_0^* = 0, \quad R = R_0^* = \frac{j}{j+l} \quad (14)$$

Substituting these values, into the original system gives the algebraic expressions for G_0^*, F_0^*, GH_0^* as solutions to the following linear system

$$\begin{pmatrix} b & -m_1 & -c \\ 0 & s & w \\ m_3 & -m_2 & x \end{pmatrix} \begin{pmatrix} G \\ F \\ GH \end{pmatrix} = \begin{pmatrix} a - m_1 F_b \\ p + sF_b - z\frac{j}{j+l} \\ m_3 G_b - m_2 F_b + xGH_b \end{pmatrix}$$

with

$$GH_0^* = \frac{\gamma}{\theta} \quad (15)$$

$$F_0^* = -\frac{w}{s}GH_0^* + \frac{1}{s} \left(p + sF_b - z\frac{j}{j+l} \right) \quad (16)$$

$$G_0^* = \frac{a - m_1 F_b + m_1 F_0^* + cGH_0^*}{b} \quad (17)$$

such that θ and γ are given by

$$\theta = s(xb + cm_3) - w(m_1 m_3 - m_2 b).$$

$$\gamma = sb(m_3 G_b + xGH_b - m_2 F_b) - sm_3(a - m_1 F_b) - (m_1 m_3 - m_2 b) \left(p + sF_b - z\frac{j}{j+l} \right).$$

Hence, a first equilibrium point is

$$P_0 = (\beta_0^*, I_0^*, G_0^*, R_0^*, F_0^*, GH_0^*) = \left(0, 0, G_0^*, \frac{j}{j+l}, F_0^*, GH_0^* \right) \quad (18)$$

in which G_0^*, F_0^* and GH_0^* are respectively given by (15), (16) and (17).

Case (b) : $(-g + hG - iG^2) = 0$ has two roots

$$G_1^* = \frac{h + \sqrt{h^2 - 4ig}}{2i}$$

and $G_2^* = \frac{h - \sqrt{h^2 - 4ig}}{2i}$ Taking $G = G_n^*$ ($n = 1, 2$) and considering

$$\frac{dR}{dt} = \frac{dG}{dt} = \frac{dGH}{dt} = \frac{dF}{dt} = 0$$

yields the following nonlinear system:

$$\begin{aligned} j(1 - R) - kRI - lR &= 0 \\ bG_n^* - m_1F - cGH + cRIG_n^* &= a - m_1F_b \\ sF + wGH + zR &= p + sF_b \\ -m_2F + xGH &= -m_3(G_n^* - G_b) - m_2F_b + xGH_b \end{aligned}$$

The nonlinearity term RI in $\frac{dG}{dt}$, is then replaced by $RI = \frac{j}{k} - \frac{j+l}{k}R$, derived from $\frac{dR}{dt} = 0$ and the system is re-arranged as a linear system of three unknowns F , GH and R , as follows :

$$\begin{pmatrix} m_1 & c & \delta \\ m_2 & -x & 0 \\ s & w & z \end{pmatrix} \begin{pmatrix} F \\ GH \\ R \end{pmatrix} = \begin{pmatrix} \alpha \\ \lambda \\ \mu \end{pmatrix}$$

Where:

$$\begin{aligned} \delta &= \frac{c(j+l)}{k} G_n^*, & \alpha &= \frac{cj}{k} G_n^* + bG_n^* - a + m_1F_b, \\ \lambda &= m_3(G_n^* - G_b) + m_2F_b - xGH_b, & \mu &= p + sF_b. \end{aligned}$$

The solution of this system is given by:

$$R_n^* = \frac{(\mu m_1 - \alpha s)(x m_1 + c m_2) + (w m_1 - c s)(\lambda m_1 - \alpha m_2)}{(x m_1 + c m_2)(z m_1 - \delta s) - \delta m_2(w m_1 - c s)} \quad (19)$$

$$GH_n^* = \frac{(\alpha m_2 - \lambda m_1)}{(x m_1 + c m_2)} - \frac{\delta m_2}{(x m_1 + c m_2)} R_n^* \quad (20)$$

$$F_n^* = \frac{\alpha}{m_1} - \frac{\delta}{m_1} R_n^* - \frac{c}{m_1} GH_n^* \quad (21)$$

then, expressions for I_n^* and β_n^* follow from substitutions and are given by :

$$I_n^* = \frac{j}{k} \frac{1}{R_n^*} - \frac{j+l}{k} \quad (22)$$

$$\beta_n^* = \frac{fI_n^* + fI_n^*R_n^*}{d} \frac{(1+R_n^*)(e+G_n^{*2})}{G_n^{*2}} \quad (23)$$

Consequently, the second and third equilibrium points P_n , $n = 1, 2$ are given by :

$$P_n = (\beta_n^*, I_n^*, G_n^*, R_n^*, F_n^*, GH_n^*), \quad n = 1, 2; \quad (24)$$

using equations (19) to (23).

3.2. Stability Analysis

The Jacobian of the system is given by:

$$\begin{bmatrix} -g + hG - iG^2 & 0 & \frac{(h-2iG)\beta}{(1+R)} \frac{G}{(e+G^2)} \left(1 - \frac{G^2}{(e+G^2)}\right) & -fI - \frac{\beta d}{(1+R)^2} \frac{G^2}{(e+G^2)} & 0 & 0 & 0 \\ \frac{d}{(1+R)} \frac{G^2}{(e+G^2)} & -f - fR & -cRI - b & -cIG & m_1 & c & 0 \\ 0 & -cRG & 0 & -kI - l - j & 0 & 0 & 0 \\ 0 & -kR & 0 & 0 & -m_2 & x & 0 \\ 0 & 0 & m_3 & 0 & -m_2 & x & 0 \\ 0 & 0 & 0 & -z & -s & -w & 0 \end{bmatrix}$$

Using parameters' values listed in Tables 1 and 2, we evaluate the Jacobian at each equilibrium point P_0 , P_1 and P_2 given by equations (18) and (24). Then eigenvalues of resulting matrices $J(P_n)$, for $n = 0, 1, 2$ are computed to classify the equilibrium points, as follows: The eigenvalues of the Jacobian $J(P_0)$ at P_0 are :

$$-1.24, -44.16, -69.23, -2.88, -412.56, -0.81$$

All the eigenvalues of the Jacobian $J(P_0)$ are negative, hence P_0 is a stable pathological point which indicates that a diabetic person with a complete apoptosis of β -cells is in a state of no return. In this case treatment of diabetes must be by exogenous injection of insulin. The eigenvalues of the Jacobian $J(P_1)$ at P_1 are :

$$-383, -44.42, -24.64, -2.88, -69.23, -0.005$$

Similarly, all the eigenvalues of the Jacobian $J(P_1)$ are negative, hence P_1 is a stable physiological point. In opposition to the previous case, here stability means that a person having values of the six variables in the required physiological range will remain in a healthy state as far as the values vary within the vicinity of the healthy ranges. The eigenvalues of the Jacobian $J(P_2)$ at P_2 are :

$$-401, -69, -44, -10.26, 0.1, -2.88$$

In the case of P_2 , one of the eigenvalues is not negative and hence, this equilibrium point is a saddle point, which means, that a person living with these values of the six variables may evolve towards a physiological or a pathological state.

3.3. Classification and interpretation of equilibrium points

Using the parameter values given in Tables 1 and 2 yields equilibrium points with numerical values as follows:

$$(a) \quad P_0 \{ \beta = 0, I = 0, G = 680, R = .92, F = 1681, GH = 1.7 \},$$

This equilibrium point is considered as a pathological equilibrium point in which insulin and β -cell mass are equal to zero and consequently a very high value of glucose (680 mg/dl) occurs, indicating a dangerous hyperglycemia as it happens in people with type1 diabetes at a late diagnosis. This pathological point is also associated with a high level of FFA (1681 $\mu\text{mol/l}$) and a relatively low value of GH (1.7 ng/ml) which is in agreement with known biological statements since, under physiological conditions, high levels of glucose and FFA inhibits secretion of growth hormone [7].

$$(b) \quad P_1 \{ \beta = 855, I = 12.67, G = 82, R = .84, F = 333, GH = 2.7 \}$$

This second equilibrium point is considered as a physiological equilibrium point in which all the variables have usual average physiological values. Indeed, it shows that glucose (82 mg/dl) is in the range of a no diabetic person, the β -cells are functioning normally and consequently, insulin is also in the physiological range (12.74 $\frac{\mu\text{U}}{\text{ml}}$). Similarly, free fatty acids and growth hormone correspond to a normal physiological state.

$$(c) \quad P_2 \{ \beta = 211.6, I = 6.14, G = 145, R = .88, F = 475, GH = 2.6 \}$$

The third equilibrium point is between the physiological and the pathological states. It indicates low values of β -cell mass (211 mg) and insulin (6.14 $\frac{\mu\text{U}}{\text{ml}}$) and consequently a value of glucose (145 mg/dl) exceeding the threshold needed for a no diabetic person. Free fatty acids appear also to be higher while the level of GH is in the acceptable range. This intermediate equilibrium point is practically interesting since it implies three possibilities of evolution:

- Evolution towards the pathological point if apoptosis of β -cells is continued until the death of all cells, yielding zero insulin production.

- Evolution towards the physiological point if apoptosis of β -cells is stopped and eventually reversed in such a way to increase production of insulin. This could be the case of obese people doing no physical activity and eating unhealthy diet who change their behavior completely to do physical activity, loose weight and eat healthy diet.

- No evolution or small perturbations around high levels of glucose and FFA, and low levels of insulin and β -cells.

Variation in concentrations of β cells, insulin, glucose, receptors, FFA and growth hormone is illustrated by the Figure below.

NOTE. — In the physiological state (in case of no diabetes), reference values for β -cells mass, insulin, glucose, FFA and growth hormone fall within the following ranges :
 β -cell mass = 850 mg, $I = 10 \mu U/ml$, $G = 100 mg/dl$ (FFA) $F = 380 \mu mol/ml$,
 Growth hormone: $GH < 5ng/ml$ for men and $GH < 10ng/ml$ for women.

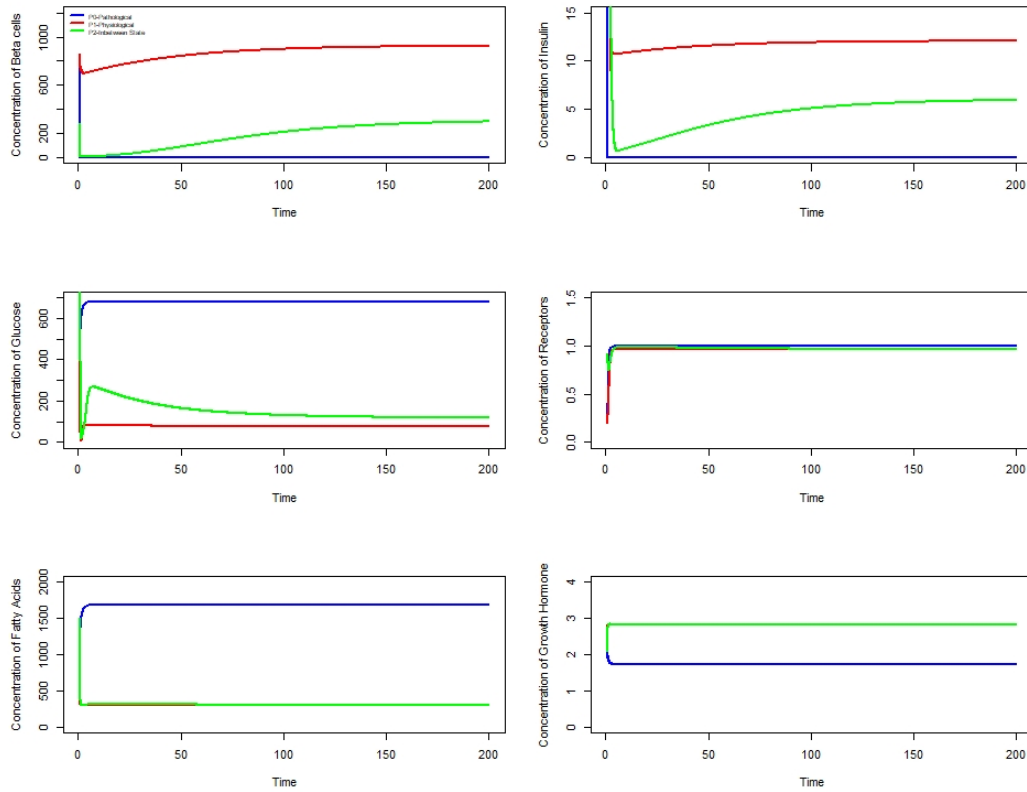


Figure 1. Concentrations of β cells, insulin, glucose, receptors, FFA and growth hormone

4. Simulation

4.1. Insulin sensitivity (c)

Studies have shown that on the one hand, physical exercise can increase insulin sensitivity by 36% and on the other hand, insulin resistance due to obesity and/or other factors can decrease insulin induced glucose uptake by 50% to 100% [4], [8], and [17]. Following this, a simulation was carried out with different values of the parameter c to check how the intermediate equilibrium point P_2 may vary. It was found that variation of c does not affect glucose, insulin receptors, FFA nor GH but it affects β -cells mass and insulin as indicated in Table 3.

c -value	β -cell mass	Insulin
1	180	5.19
0.85	212	6.14
0.42	429	12.98

Table 3. Variation of β -cell mass and insulin with respect to c -values

4.2. Production of GH by the somatotropic cells (p)

Simulation with different values of the parameter p have shown that, in the intermediate equilibrium point P_2 , values of β -cell mass, Insulin, Glucose, Insulin Receptors are not affected while FFA and GH increase with increased values of p as indicated in Table 4

p -value	FFA	Growth hormone
363	475.4	2.59
400	476.6	2.86
600	483.4	4.32
900	493.6	6.52

Table 4. Variation of FFA and growth hormone with respect to p -values

4.3. Growth Hormone clearance / absorption by the liver (w)

Simulation with different values of the parameter w have shown that, in the intermediate equilibrium point, values of β -cell mass, Insulin, Glucose, Insulin Receptors are not affected while FFA and GH decrease with increased w as indicated in Table 5.

<i>w</i> -value	FAA	Growth hormone
20	543.2	17.25
80	483.7	4.39
300	468.8	1.17
136	475.4	2.59

Table 5. Variation of FFA and growth hormone with respect to *w*-values

5. Conclusion

While there is an abundant literature on mathematical models dealing with glucose dynamics in interaction with insulin, very few models are devoted to the effect of growth hormone on glucose homeostasis. To our knowledge, this paper is the first to introduce the combined interaction between the variables glucose, insulin, free fatty acids (FFA) and growth hormone. Local stability analysis showed that, beside the stable pathological and stable physiological equilibrium points, there is a saddle point with levels of β -cells mass and insulin lower than the corresponding values required in the physiological case. The unstable point indicates also a value of glucose higher than the value needed in a nondiabetic person. Pragmatically, this intermediate equilibrium point refers to a prediabetic stage and our mathematical model indicates that evolution towards diabetes may be avoided or at least delayed provided efficient action on risk factors like obesity/overweight, unhealthy diet, physical inactivity and smoking. Simulations using different values of parameters illustrated the importance of insulin sensitivity and how to avoid insulin resistance caused mainly by weight excess and lack of physical activity. The rates of production and clearance (and eventually deficiency) of growth hormone were also used to simulate variation of free fatty acids and growth hormone.

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