A MODEL OF β-CELL MASS, INSULIN, GLUCOSE, AND RECEPTOR DYNAMICS WITH APPLICATIONS TO DIABETES

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Abstract

Approximately 15.7 million people in the United States suffer from diabetes mellitus, of which about 90% are classified as type II [13]. Most cases of type II diabetes mellitus are characterized by high blood glucose levels resulting from chronic insulin resistance, [30], which then leads to significant β-cell mass reduction from "β-cell exhaustion" and/or "glucose toxicity" [1].

Existing mathematical models of β-cell mass, insulin, and glucose kinetics contribute to the study of the disease by qualitatively and quantitatively describing different pathways to diabetes. Successful models of a complex system are often malleable, in that they can be extended to include further components, and consequently be a more complete representation of the system. Insulin receptor dynamics have not been previously considered in modeling the glucoregulatory system, yet are important in the pathogenesis of the disease as chronic insulin resistance is associated with the down-regulation of these receptors at the surface of muscle cells. We incorporate the dynamics of insulin receptors into an existing mathematical model, resulting in a four dimensional system of nonlinear ordinary differential equations. Through analytical calculations and numerical simulations we conclude that coupling receptor dynamics is valuable in that our system extends previous models to include a fourth

significant factor in diabetes, gives improved quantitative results in describing β-cell mass, and provides a theoretical justification for experimentally observed receptor behavior.

1 Introduction

Diabetes mellitus is a syndrome characterized by chronic hyperglycemia and disturbances of carbohydrate, fat, and protein metabolism associated with absolute or relative deficiencies in insulin secretion and/or insulin action [1]. Although a number of specific causes of diabetes mellitus have been elucidated, the etiology and pathogenesis of the more common types of diabetes are poorly understood, and the extent of the heterogeneity among these more common types remains uncertain [1]. Type I diabetes (also known as juvenile onset or insulin-dependent diabetes) is due to an autoimmune attack on the insulin secreting β-cells. Type II diabetes (also known as adult onset or non-insulin-dependent diabetes) is associated with a deficit (approximately 50 percent decrease) in the mass of β-cells (resulting in reduced insulin secretion) due to the development of a "resistance" to the action of insulin and the resulting hyperinsulinemia and/or hyperglycemia. Although defects in either insulin secretion or insulin action may be the initial pathologic process that eventually leads to type II diabetes, most individuals with the fully developed syndrome show impairments both of insulin secretion and insulin mediated glucose disposal, or "insulin resistance" [1].

Diabetes is a chronic disease that has no cure. In the United States alone, the financial costs of type II diabetes exceeds 98 billion dollars annually (44 billion dollars in direct medical costs and 54 billion dollars in indirect costs such as disability and premature mortality), and the suffering incurred is enormous [13]. In addition, diabetes is a leading cause of death by disease in Canada [12]. Diabetes, if left untreated, can slowly damage both small and large blood vessels in the body, resulting in a variety of complications such as: heart disease, stroke, high blood pressure, blindness, kidney disease, nervous system disease, limb amputations, and erectile dysfunction [13]. With careful management, these complications can be delayed and even prevented [12].

2 Biological Background

Blood glucose in non-diabetic humans is maintained within a precise concentration range. Many factors affect the circulating levels of glucose such as food intake, rate of digestion, excretion, exercise, psychological state, and reproductive state [19]. These influences, individually or in combination, constantly affect the physiological processes that regulate plasma glucose levels. The glucose level may drop momentarily due to muscular activity,

especially if food intake is limited. This diminished level of blood glucose is recognized by certain cells in the pancreatic *Islets of Langerhans* called the alpha (α) cells. These cells then release glucagon, a hormone that acts on the cells of the liver to induce the release of glucose. Thereby bringing the blood glucose level back to normal. If, on the other hand, blood glucose is elevated, as occurs after a meal, other pancreatic islet cells, beta (β) cells, release the hormone insulin. Insulin induces the uptake of glucose from the blood into the liver and other cells (such as muscle cells). Thus the glucose level of the blood is lowered to the normal circulating concentration, see figure 1. Lack of insulin, therefore, results in a serious inability to lower blood glucose, (low glucose tolerance) which results in diabetes mellitus.

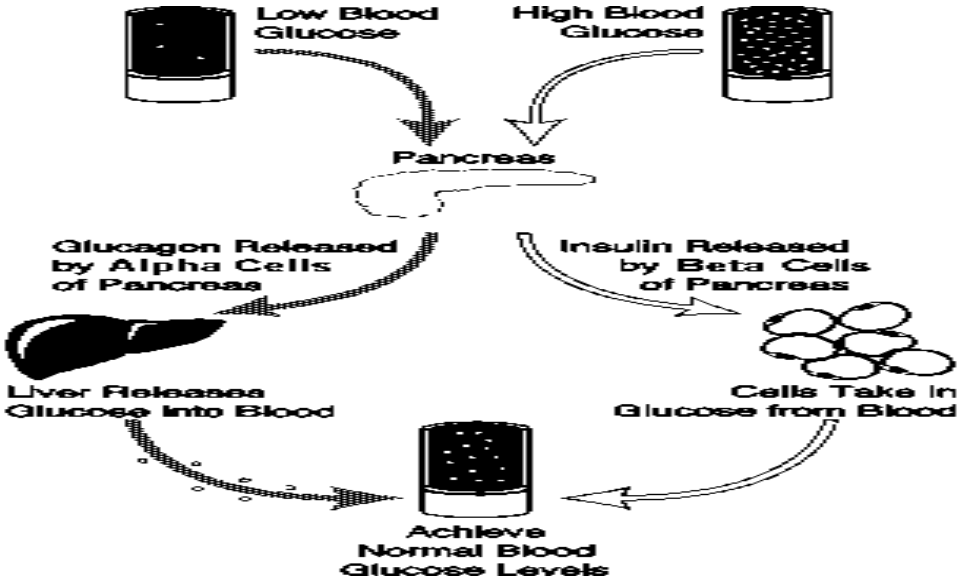

Figure 1: Schematic diagram [25] of the glucoregulatory system.

The ability to lower blood glucose depends on the responsiveness of the pancreatic β-cells to glucose and the sensitivity of the glucose utilizing tissues to the secreted insulin. Thus, both pancreatic β-cell responsiveness and insulin sensitivity contribute to glucose tolerance [2]. Low glucose tolerance in lean individuals is associated with diminished β-cell response to glucose (approximately 77% less than lean individuals with good glucose tolerance), whereas low glucose tolerance in obese individuals is associated with decreased insulin sensitivity (approximately 60% less than lean individuals with good glucose tolerance) [2]. Insulin resistance is frequently considered the primary lesion underlying the potential development of type II diabetes, and this insulin resistance both precedes and contributes to its development

[30]. Figure 2 illustrates the process by which glucose is taken into muscle cells by the GLUT4 glucose transporter protein and figure 3 delineates the relationship between insulin binding to the insulin receptors on muscle cells and the subsequent migration of the GLUT4 glucose transporter protein to the cell surface for intake of glucose.

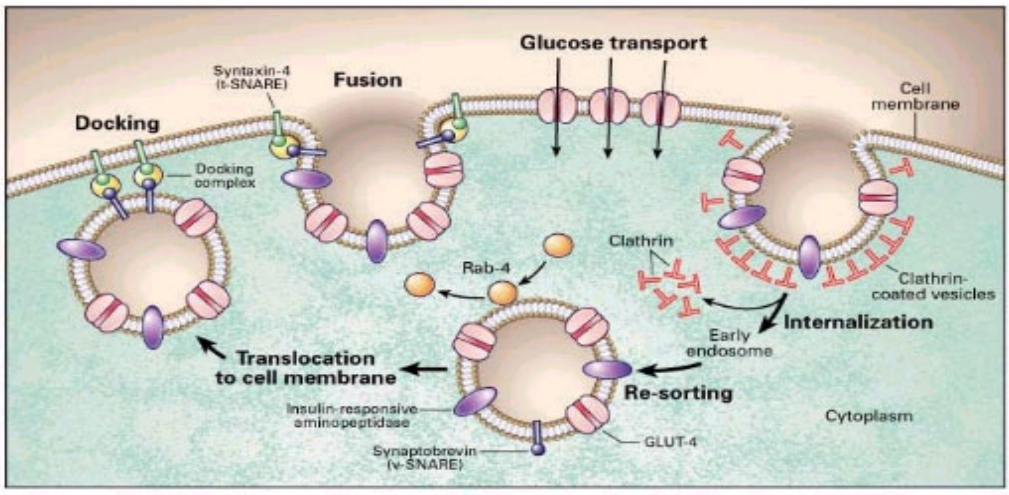

Figure 2: This diagram ([33] as cited in [14]) illustrates how the GLUT4 glucose transporter protein migrates to the cell surface in response to insulin and undergoes conformational changes, facilitating the entrance of glucose into the muscle cell.

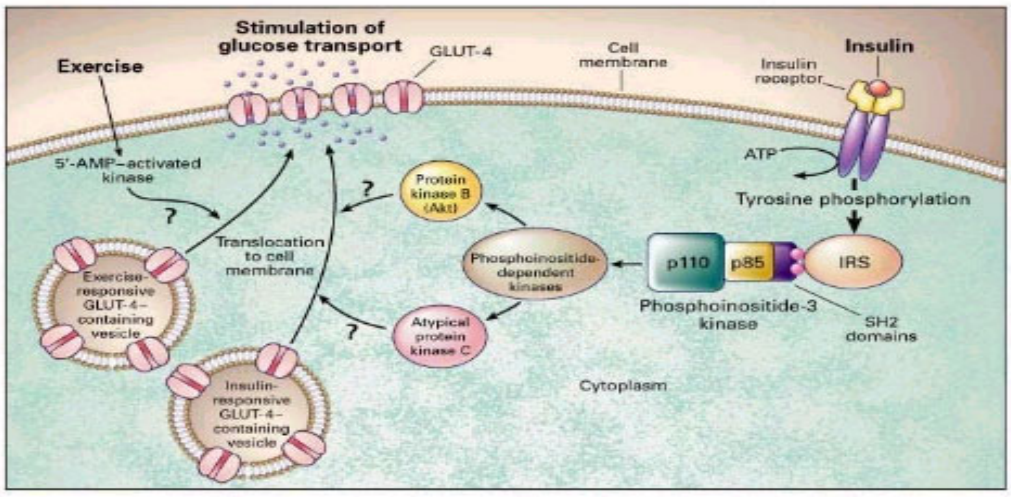

Figure 3: This diagram ([33] as cited in [14]) illustrates how insulin binds to its receptor on the surfaces of muscle cells and causes the GLUT4 glucose transporter protein to migrate to the cell surface and undergo conformational changes, facilitating the entrance of glucose into the muscle cell. Note that consistent exercise increases muscle cell GLUT4 concentrations by about 26 ± 11 % [9],[10]. It is of interest to note that this increase in GLUT4 concentrations correlates directly with the increases in insulin sensitivity caused by this consistent exercise [9].

Although type II diabetes is associated with insulin resistance, insulin secretory defects, and insufficient β-cell mass, each of these defects can also be found in people without diabetes [36]. Insulin-stimulated glucose disposal is reduced by 50-100 percent in individuals with type II diabetes as compared to non-diabetic controls [Finegood, 1997, as quoted in [36]]. However, insulin resistance of a similar magnitude has been documented in many non-diabetic individuals, including obese subjects, or during pregnancy, puberty, and aging [Finegood, 1997, as quoted in [36]]. Therefore, normal glucose levels can be maintained in individuals with insulin resistance via increases in blood insulin levels. In addition, it has been suggested that glucose homeostasis can be maintained despite significant loss of β-cell mass and/or function when an individual has normal insulin sensitivity [36]. β-cell mass is reduced by 40-50% in individuals with type II diabetes when compared with weight matched non-diabetic subjects, [Kloppel, *et al.*, 1985, as cited in [36]]. Interestingly, 80-90% of β-cell mass is lost *before* the onset of hyperglycemia in individuals who develop type I diabetes [Kloppel, *et al.*, 1985, as cited in [36]]. These statements suggest that a greater β-cell mass is required in the presence of insulin resistance. This is also consistent with the observation of a 43% higher β-cell mass in normoglycemic individuals with obesity due to insulin resistance [Kloppel, *et al.*, 1985, as cited in [36]]. The impact of β-cell mass in the pathogenesis of all forms of diabetes should not be underestimated. In the non-diabetic state, the amount of β-cell tissue is obviously tightly regulated and may be the main factor responsible for the maintenence of euglycemia [37]. It has been suggested that all of the characterized secretory abnormalities, such as the loss of glucose induced insulin secretion, are secondary to inadequate β-cell mass (inadequate for whatever degree of insulin resistance is present) [37]. In addition, it is now accepted that diabetes does not occur unless insulin secretion can no longer compensate for a given amount of insulin resistance [37].

It is well-known that the rate of insulin clearance plateaus as plasma insulin concentration rises. When insulin, under physiologic conditions, binds to cell surface receptors on cultured or freshly isolated cells, the hormone receptor complex is internalized (no longer on the surface of the cell) and therefore is unable to cause a cellular response to insulin until it is recycled and moves back to the cell membrane. See figure 4 for a diagram of an insulin receptor embedded in the surface of a cell. While internalized, a series of intracellular events ensues that dissociates the hormone from its receptor. A number of experimental observations suggest that insulin receptor internalization is the major mechanism by which cell surface insulin receptors are "down-regulated" [18]. The internalization and subsequent recycling of the insulin receptor requires insulin binding. This insulin-induced regulation, mediated by internalization, decreases the concentration of insulin receptors on the cell surface and is therefore a potential factor in clinical insulin resistance [18]. Thus, we see that the insulin receptor has a pivotal role in the study of insulin resistance.

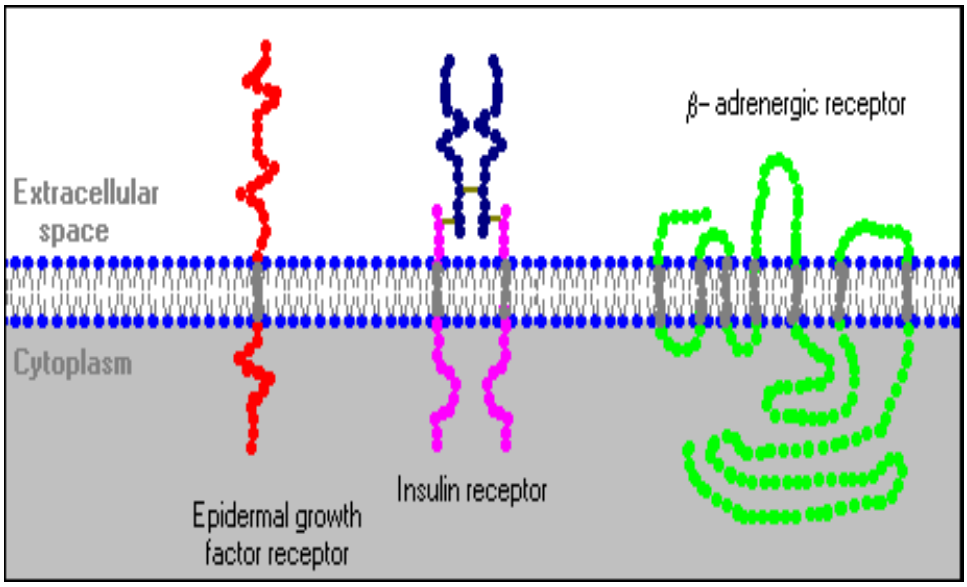

Figure 4: Diagram [5] of an insulin receptor in the cellular cytoplasmic membrane.

Insulin resistance has been demonstrated in both skeletal muscle and adipose tissue from insulin resistant people, and defects at these sites are responsible for the majority of their altered metabolic profile [31]. Skeletal muscle accounts for approximately 75% of whole body glucose disposal, thus, in insulin resistant subjects, the decreased muscle glucose uptake accounts for most of the decrement on whole body glucose disposal [7, 31]. Therefore, in our model, we focus our study on insulin receptor dynamics to those of muscle cells.

3 Model Development

3.1 The Model of Topp, *et al.*

Our model is an extension of the model of Topp, *et al.* [36], which consists of three variables (β-cell mass, insulin, and glucose) in three nonlinear ordinary differential equations as follows:

$$\frac{dG}{dt} = a - (b + cI)G, \tag{1}$$

$$\frac{dI}{dt} = \frac{d\beta G^2}{(e + G^2)} - fI, \tag{2}$$

$$\frac{d\beta}{dt} = (-g + hG - iG^2)\beta, \tag{3}$$

where G is the blood glucose concentration (measured in $\frac{mg}{dL}$), I is the blood insulin concentration (measured in $\frac{\mu U}{mL}$), and β is the β-cell mass (in mg). A table of parameter values and their biological interpretations used by Topp, *et al.* for this model follows:

Parameter	Value	Units	Biological Interpretation
a	864	$\frac{mg}{dl\ d}$	glucose production rate by liver when $G = 0$
b	1.44	$\frac{1}{d}$	glucose clearance rate independent of insulin
c	0.72	$\frac{ml}{\mu U\ d}$	glucose clearance rate dependent of insulin
d	43.2	$\frac{\mu U}{ml\ d\ mg}$	β-cell maximum insulin secretory rate
e	20,000	$\frac{mg^2}{dl^2}$	determines inflection point of sigmoidal function
f	432	$\frac{1}{d}$	insulin clearance rate for muscles,liver and kidneys
g	0.06	$\frac{1}{d}$	β-cell natural death rate
h	0.00084	$\frac{dl}{mg\ d}$	determines β-cell glucose tolerance range
i	0.0000024	$\frac{dl^2}{mg^2\ d}$	determines β-cell glucose tolerance range

For normal parameter values, this model has two stable equilibria representing physiological ($\beta = 300, I = 10, G = 100$) and pathological ($\beta = 0, I = 0, G = 600$) steady states, and a saddle point at ($\beta = 37, I = 2.8, G = 250$). The model predicts that there are three pathways in prolonged hyperglycemia: (1) the physiological equilibrium can be shifted to a hyperglycemic level, (2) the physiological and saddle points can be eliminated through bifurcation and then the only steady state is the pathological steady state, and (3) progressive defects in glucose and/or insulin dynamics can drive glucose levels up at a rate faster than the adaptation of the β cell mass can drive the glucose levels down.

Since the average mass of β-cells in a normal individual has been found to be 850 mg [17], the physiological steady state at ($\beta = 300, I = 10, G = 100$) seems quantitatively unreasonable. In our model (in addition to adding insulin receptor dynamics), we adjust some of the parameters used in this model based on data in the literature and obtain a more realistic physiological steady state of ($\beta = 856.95$, $I = 12.70$, $G = 82$, $R = 0.84$). It is of interest to note that even if the appropriate changes in parameter values are substituted into this model, the β-cell mass at the physiological steady state is closer to 850 mg, yet still quantitatively unreasonable (502 mg), suggesting that the addition of the receptor dynamics is an important factor in this quantitative improvement.

3.2 Modified Model

In our model of the glucose regulatory system, we study fasting plasma glucose and insulin concentrations, β-cell mass, and surface insulin receptor dynamics. The system is of the form:

$$\frac{dG}{dt} = a - (b + cRI)G, \tag{4}$$

$$\frac{dI}{dt} = \frac{d\beta G^2}{(1+R)(e+G^2)} - fI - fRI, \tag{5}$$

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

$$\frac{dR}{dt} = j(1-R) - kIR - lR, \tag{7}$$

where G is the blood glucose concentration (measured in $\frac{mg}{dl}$), I is the blood insulin concentration (measured in $\frac{\mu U}{ml}$), β is the β-cell mass (in mg), and R is the fraction of insulin receptors on the surface of the muscle cells. A table of normal parameter values for an average healthy person and their biological interpretations for this model follows:

Param	Value	Ref	Units	Biological Interpretation
a	864	[36]	$\frac{mg}{dl\,d}$	glucose production rate by liver when $G = 0$
b	1.44	[36]	$\frac{1}{d}$	glucose clearance rate independent of insulin
c	0.85	†[36]	$\frac{ml}{\mu U\,d}$	insulin induced glucose uptake rate
d	43.2	[36]	$\frac{\mu U}{ml\,d\,mg}$	β-cell maximum insulin secretory rate
e	20,000	[36]	$\frac{mg^2}{dl^2}$	gives inflection point of sigmoidal function
f	216	†[36, 30, 28]	$\frac{1}{d}$	whole body insulin clearance rate
g	0.03	[4, 3]	$\frac{1}{d}$	β-cell natural death rate
h	0.5727502102e-3	[37]	$\frac{dl}{mg\,d}$	determines β-cell glucose tolerance range
i	0.2523128680e-5	[37]	$\frac{dl^2}{mg^2\,d}$	determines β-cell glucose tolerance range
j	2.64	[34]	$\frac{1}{d}$	insulin receptor recycling rate
k	0.02	†[34]	$\frac{ml}{\mu U\,d}$	insulin dependent receptor endocytosis rate
l	0.24	[34]	$\frac{1}{d}$	insulin independent receptor endocytosis rate

†Number has been revised and the revision is explained in the following paragraphs.

In equation 4, we assume a person eats regularly, thus glucose can be secreted at a constant rate by the liver and kidneys while fasting. The following nonlinear ordinary differential

equation represents glucose dynamics in our model:

$$\frac{dG}{dt} = a - (b + cRI)G,$$

where G is the blood glucose concentration (in $\frac{mg}{dl}$), a is the constant secretion (into the bloodstream) of glucose by the liver and kidneys measured in $\frac{mg}{dl\,d}$ and $b + cRI$ represents the total body glucose uptake rate and is proportional to G. (When cells of the body uptake glucose, it is removed from the bloodstream.) Here, b represents glucose effectiveness (the ability of the body to remove glucose from the bloodstream independent of insulin concentration) and is measured in $\frac{1}{d}$, and cRI represents the glucose uptake rate due to insulin sensitivity (c), insulin concentration (I), and the fraction of insulin receptors available on the surface of the muscle cells (R), and is measured in $\frac{1}{d}$. Notice that higher values of b, c, R, and I lead to an increased glucose uptake rate and, subsequently, a lower blood and/or plasma glucose concentration. Notice that the value of c that we use is slightly higher than that used by Topp *et al.* This adjustment accounts for the fact that our insulin sensitivity (c) is multiplied by R in equation 4. It has been shown that a reasonable value for R at equilibrium is approximately .85 (with slight variation) [34, 29], and our value of c was derived by solving the equation $.85 * c = .72$, so that $cR \approx .72$ under normal basal conditions because this is consistent with the model of Topp, *et al.*.

Insulin is secreted by the β-cells in the endocrine pancreas and cleared by the liver, kidneys, and insulin receptors. The relationship between the extracellular glucose concentration and the rate of insulin secretion has been shown to follow a sigmoidal function in plasma glucose concentration [20]. It also depends on the β-cell mass and fraction of receptors on the cell surfaces, as they relate to insulin resistance [15, 36]. For simplicity, and without significant loss of accuracy, we assume the normal rate of insulin clearance at the muscle cell receptors to be equal to the rate of clearance at liver and kidneys [30] (other sources of insulin clearance are small enough to be considered negligible). Therefore, as previously shown, the following nonlinear ordinary differential equation represents insulin dynamics in our model:

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

where I represents the plasma insulin concentration (in $\frac{\mu U}{ml}$), $\frac{d}{1+R}$ is the rate at which a single β-cell will secrete insulin (in units of $\frac{\mu U}{ml\,mg\,d}$) and d is the maximal β-cell insulin secretory rate. It has been shown that β-cells adapt to insulin sensitivity [15, 22]. Therefore, it is reasonable to assume that β-cells reach their maximal secretory capacity when $R = 0$ because they are compensating for the insulin resistance caused by the loss of insulin receptors from the muscle

cells. $\frac{G^2}{e+G^2}$ represents the sigmoidal relationship between plasma glucose concentration and insulin secretion (e in units of $\frac{mg^2}{dl^2}$). Here, f is the insulin clearance rate (in units of $\frac{1}{d}$). The fI term is the insulin clearance by liver and kidneys, while fRI is the insulin clearance at the muscle cell receptors. The value of f used by Topp, *et al.* [36] is $432/d$, which represents combined insulin clearance at liver, kidneys, and muscle. Using this, and our assumption that insulin clearance by muscle is roughly equal to the clearance by liver and kidneys, we obtain $f = 216/d$.

The dynamics of β-cell mass does not depend directly on the fraction of available insulin receptors. Therefore, we use the equation derived by Topp, *et al.* (equation 3) in our model. The equation (rewritten in logistic form) is as follows:

$$\frac{d\beta}{dt} = -g\beta + hG\left(1 - \frac{G}{h/i}\right)\beta,$$

where β represents β-cell mass (in mg), g is the death rate of the β-cells at zero glucose measured in $\frac{1}{d}$, and h ($\frac{dl}{mg\,d}$) and i ($\frac{dl^2}{mg^2\,d}$) are constants that determine the β-cell glucose tolerance range. It has been suggested that the natural death rate, g, of β-cells is 0.03 per day [4, 3]. Studies have shown that a glucose concentration between 82 and 145 $\frac{mg}{dl}$ cause β-cell mass to increase, while β-cell mass decreases for concentrations outside this range [37]. Since the β-cell mass equation is logistic in glucose, $\frac{d\beta}{dt}$ is positive between the roots (*i.e.*, β-cell mass is increasing). To find values for h and i consistent with this glucose tolerance range, we set equation 6 equal to zero (assuming that $\beta \neq 0$), with $g = 0.03$, and obtain the quadratic equation $-0.03+hG-iG^2 = 0$. Solving this quadratic for h and i, with $G = 82$ and $G = 145$ (system of two equations), yields $h = 0.5727502102e-3$ and $i = 0.2523128680e-5$.

On the surface of muscle cells the fraction of insulin receptors decreases by both natural endocytosis and insulin-induced down regulation, and increases due to a natural recycling of the internalized receptors. We have developed the following nonlinear ordinary differential equation to represent insulin receptor dynamics:

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

where j is the recycling rate of internalized receptors measured in $\frac{1}{d}$, k is the insulin induced down-regulation rate of the surface receptors measured in $\frac{dl}{\mu U\,d}$, and l is the natural endocytosis rate of the surface receptors measured in $\frac{1}{d}$. Studies have shown that insulin bound receptors will internalize at a rate of $0.11\frac{1}{h}$ [34]. In our model, k must have units of $\frac{ml}{\mu U\,d}$. To determine the value of k, we substituted values of all other parameters into our system, and solved for equilibrium points as functions of the parameter k. Graphs of the saddle and physiological equilibria as functions of k are given in figures 5, 6, and 7. We found G to be

independent of changes in k. Through inspection of realistic basal levels of I, β, and R, we were able to determine that a reasonable value of k is 0.02 $\frac{ml}{\mu U\, d}$, and then validate this value through computer simulations.

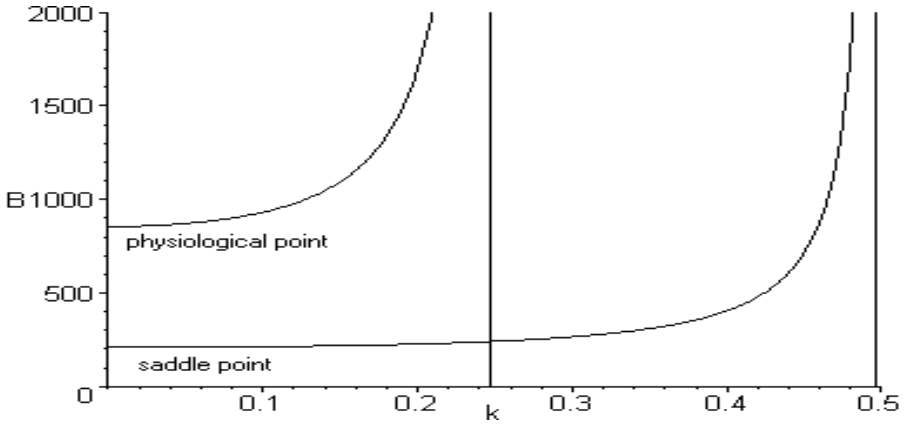

Figure 5: Diagram of the k parameter, or insulin dependent receptor endocytosis rate, *vs.* β-cell mass at physiological and pathological equilibria.

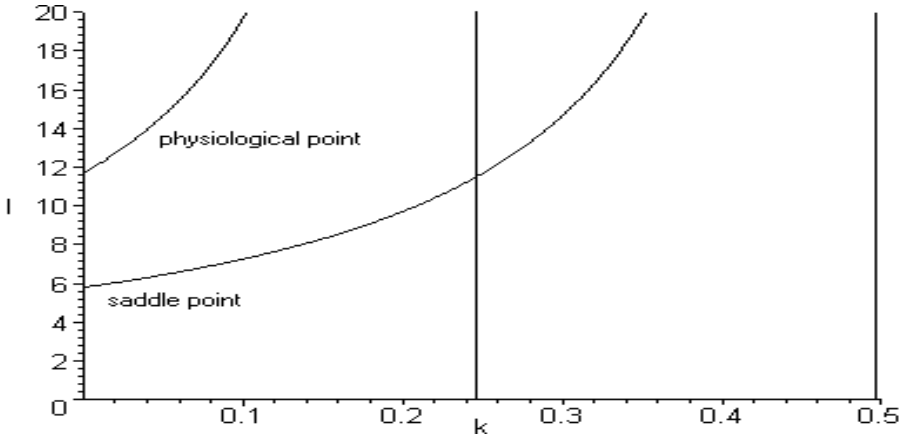

Figure 6: Diagram of the k parameter *vs.* I (Insulin) at physiological and pathological equilibria.

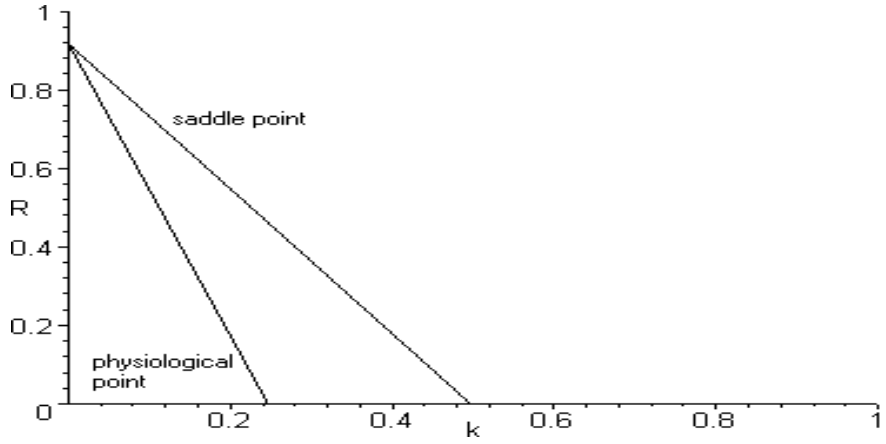

Figure 7: Diagram of the k parameter *vs.* R (fraction of total insulin receptors on the cell surfaces) at physiological and pathological equilibria.

4 Model Behavior

This system has three equilibria at $(0, 0, 600, 0.917)$, $(208.31, 6.04, 145, 0.88)$, and $(856.95, 12.70, 82, 0.84)$, in (B, I, G, R), for parameter values of an average healthy individual. They are a stable node, saddle point, and stable node, respectively. Using the notation of Topp, *et al.* [36], we call the first equilibrium a "pathological" point, and the third a "physiological" point. When the initial conditions are ($\beta = 850$, $I = 15$, $G = 85$, $R = .9$), which are levels of a typical non-diabetic person, the system goes to the physiological equilibrium. For all reasonable initial conditions, the system goes to one of the two stable steady states, rather than entering any type of limit cycle or chaotic path.

It is interesting to observe that the values at the physiological equilibrium point match well with what various studies have shown. In particular, the β-cell mass predicted by our model for an average healthy individual is 856.95 mg, which is very close to the observed value of 850 mg [17]. Another point to notice is that the value of R at the physiological equilibrium ($R = 0.84$) is consistent with studies that have found the fraction of insulin receptors at the cell surface to range between 0.85 and 0.95 [34].

The plot of the trajectories in figure 8 for the four variables over 3 days shows that each variable's trajectory travels directly toward its equilibrium value. Notice that the plots correspond to what should be expected biologically, that is, insulin and glucose are directly proportional to each other, but inversely related to surface receptors, and β-cell mass is nearly constant.

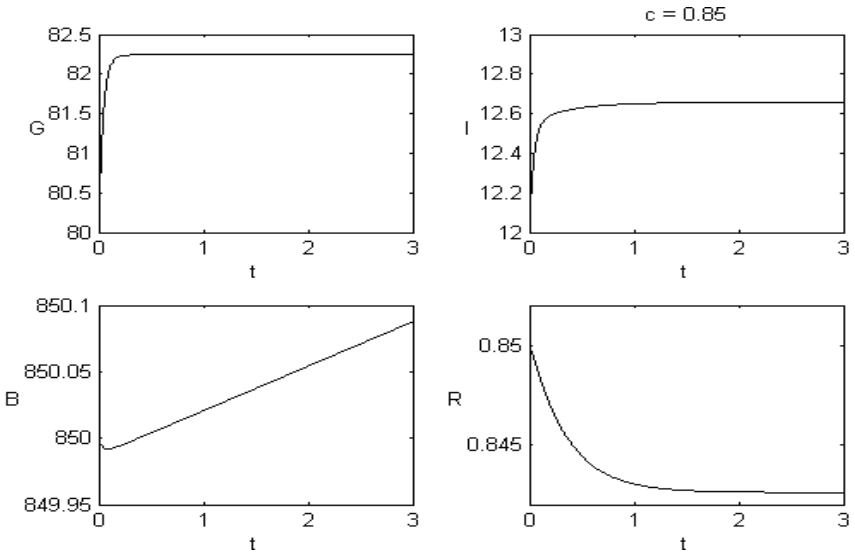

Figure 8: Plot of the trajectories of G, I, β, and R over 3 days with normal parameter values and average normal initial conditions.

It is of interest to study the effects of changes in certain parameter values on the steady states (only positive parameter values are considered). It can be calculated (from equation (6)) that the values of glucose at the physiological and saddle equilibria are given by the expressions $\frac{h \pm \sqrt{h^2 - 4ig}}{2i}$. The values of g, h, or i can be altered in such a way that all three equilibria still lie in the solution space, there are no changes in stability, trajectories still converge to the physiological equilibrium, but glucose levels become elevated. In fact, defects in the β-cell mass equation having this effect represent one pathway to diabetes (regulated hyperglycemia, see figure 9). This pathway is qualitatively consistent with the findings of Topp, *et al.*

The physiological and saddle equilibrium points have real values if and only if $h^2 - 4ig \geq 0$. Severe diabetes is predicted to occur when these equilibria are imaginary because the pathological steady state (which lies in the solution space for all parameter values) becomes a global attractor. This is what was referred to as the bifurcation pathway to diabetes by Topp, *et al.* We see that defects in the dynamics of β-cells can cause significant changes for the entire system. Bifurcation diagrams of the equilibrium values for G with respect to any one of g, h, or i can be determined, as demonstrated in figures 10, 11, and 12. Biologically, changes in g represent changes in the β-cell death rate. If the death rate is too high (i.e., the value of g is high enough to make the saddle and physiological equilibria complex),

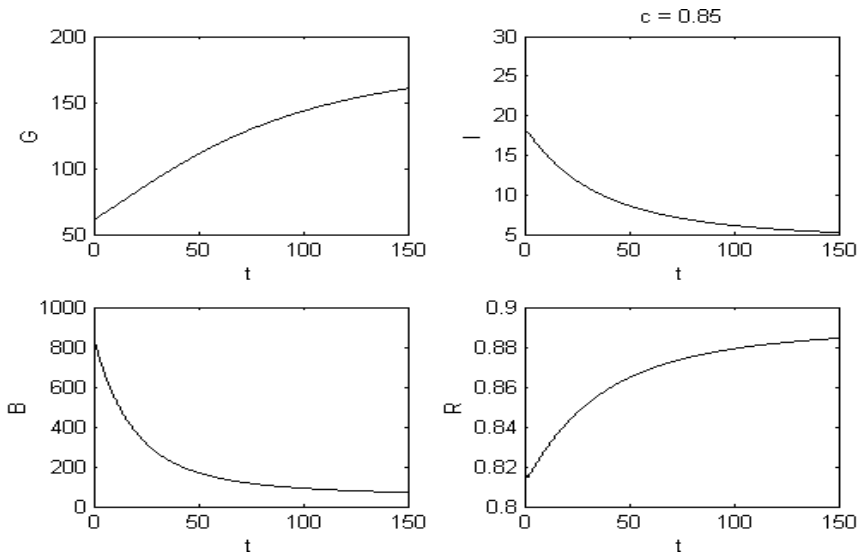

Figure 9: Plot of the trajectories of G, I, β, and R with normal parameter values and average normal initial conditions, except that both g and h are changed to represent defects in β-cell mass dynamics. This is the "regulated hyperglycemia" pathway to diabetes.

then trajectories will approach the pathological equilibrium, since it is the only real stable point (figure 13). Changes in h and i, which can also cause equilibrium values to become imaginary, represent changes in the range of glucose concentrations at which β-cell mass will increase. For example, with our normal parameter values, β-cell mass will increase for glucose concentrations between 82 and 145 mg/dl and decrease for concentrations outside that range.

Changes of c in the glucose equation (4) are also of interest since this parameter affects insulin sensitivity. Studies suggest that with exercise, insulin sensitivity can be increased by 36%, a change that would cause the physiological equilibrium to be $\beta = 628.95$, $I = 9.13$, $G = 82$, and $R = .86$. This result is consistent with the current literature [7, 8, 9, 10, 22] in that the basal insulin level is decreased while glucose remains normal. Studies indicate that the insulin resistance associated with aging may be a direct result of lack of exercise [26]. Therefore, exercise is a key factor in the prevention of insulin resistance.

Insulin induced glucose uptake has also been shown to be decreased by 50-100% in both diabetic and non-diabetic individuals [2, 36]. Simulation of an individual with insulin resistance where c is decreased by 60% [2] gives results consistent with the current literature in that insulin and β-cell mass are elevated while glucose levels remain relatively constant [2, 18, 28, 29, 34, 36]. It is of interest to note that though glucose levels are initially elevated,

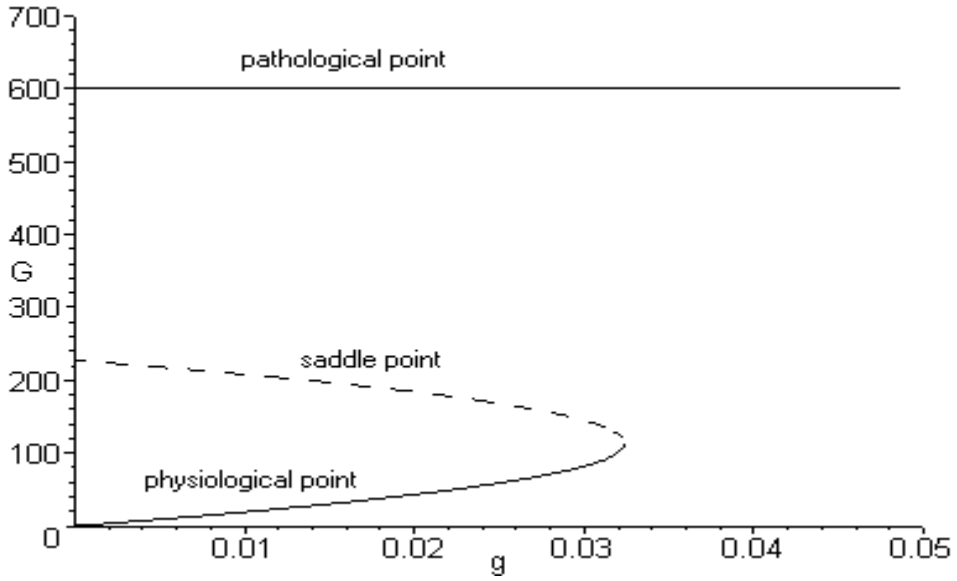

Figure 10: A bifurcation diagram of G *vs.*g, where a saddle-node bifurcation occurs at $g = 0.0325$, and a transcritical bifurcation occurs at $g < 0$.

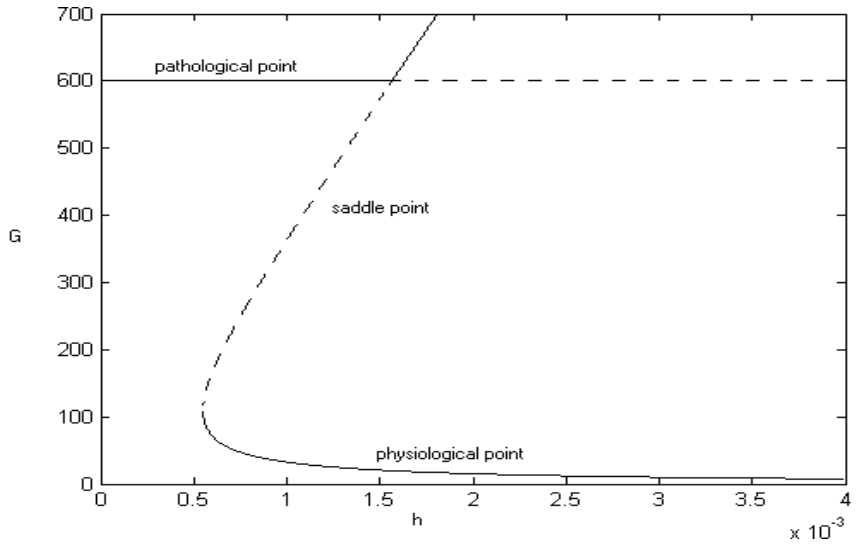

Figure 11: A bifurcation diagram of G *vs.*h, where a saddle-node bifurcation occurs at $h = 0.00055$, and a transcritical bifurcation occurs at $h = 0.00156$.

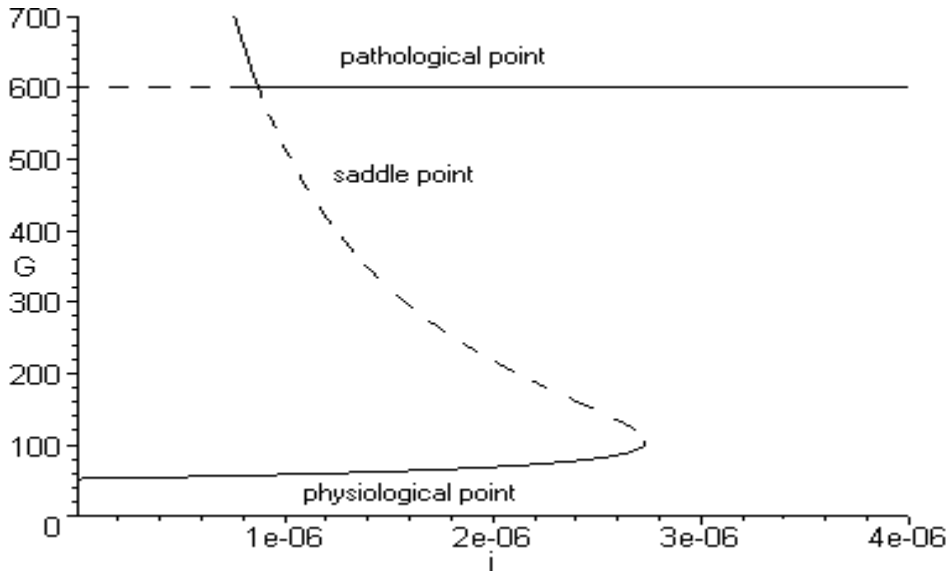

Figure 12: A bifurcation diagram of G *vs.*i, where a saddle-node bifurcation occurs at $i = 2.73e-6$, and a transcritical bifurcation occurs at $i = 8.71e-7$.

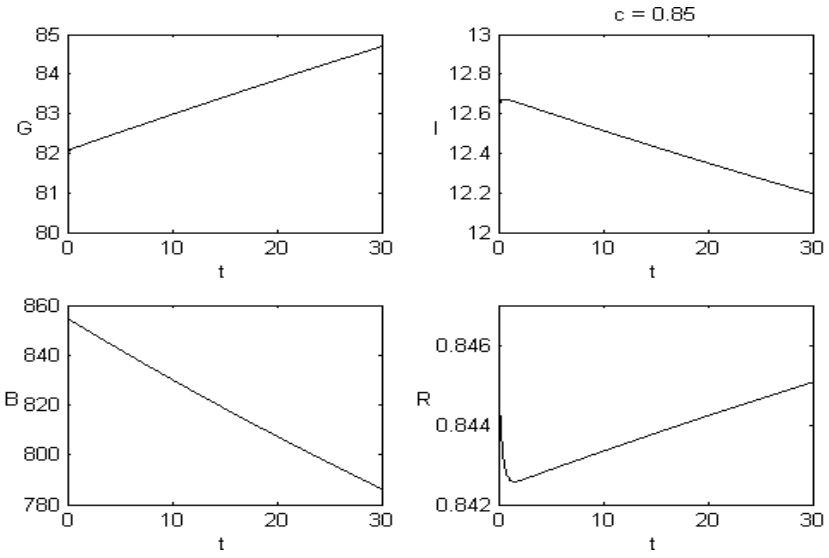

Figure 13: Bifurcation pathway to diabetes, where $g = .033$, and all other parameters are kept at their normal values.

they will reach an equilibrium value of 82 $\frac{mg}{dl}$ once insulin levels (and β-cell mass) are high enough. In fact, this simulation will go to the following equilibrium point: $\beta = 2179.38$, $I = 36.61$, $G = 82$, and $R = .73$. Notice that a β-cell mass of 2,179 mg may be physiologically impossible. If this is the case, then this individual will not be able to produce enough insulin to counter the insulin resistance, glucose levels will rise, β-cell mass will diminish, and diabetes will ensue. We have noted that an important future improvement to the model would be to place an upper bound on β-cell mass. Currently, an infinite capacity for β-cell mass has been assumed, and this is certainly not the case!

When c is decreased by 60% as previously and d is increased from 43.2 to 80 (higher β-cell secretory capacity) in order to further simulate the physiology of insulin resistance [28], a more realistic equilibrium value is attained: $\beta = 1176.86$, $I = 36.61$, $G = 82$, and $R = .73$. Notice that all equilibrium values are equal to the previous one, except that β-cell mass is decreased to a physiologically possible level. This is consistent with the literature [2, 4, 28]. In addition, it is also interesting to simulate what happens when insulin resistant individuals exercise consistently. So, when c is decreased by 60% as before and is then increased by 36% [22] in order to simulate consistent exercise, we reach the following equilibrium: $\beta = 1596.45$, $I = 25.37$, $G = 82$, and $R = .78$. Notice that insulin concentrations are decreased, yet glucose levels remain the same, when compared to an insulin resistant individual who does not consistently exercise. We also see that the fraction of insulin receptors on the cell surfaces is increased (because of reduced insulin concentrations) and β-cell mass is relatively constant. This is also consistent with the current literature [4, 7, 8, 9, 10].

For any initial conditions for which the system is driven to the physiological equilibrium with normal parameter values, decreasing c (insulin sensitivity) to a low enough level causes the trajectory to instead converge to the pathological point, see figure 14 where $c = 0.1$. This exemplifies the pathway to diabetes referred to by Topp, *et al.* as "dynamical hyperglycemia," where a trajectory is driven across the separatrix, or defects in the glucose and insulin equations cause the system to go to the pathological point even though the number of equilibria and stability of each equilibrium point is unchanged.

It is currently accepted that diabetes occurs when β-cell mass can no longer compensate for the level of insulin resistance that is present [4, 37]. Since it is reasonable to assume that different individuals will have varying values of maximal insulin secretion rates, it is interesting to study the behavior of various levels of insulin resistance at differing values of d (maximum β-cell insulin secretory rate). It is possible that an individual can have a decreased response to insulin (below normal c value), with β-cells which have an increased capacity to compensate for this (increased maximum insulin secretion represented by an elevated d value). The decrease in the value of c alone is enough to drive trajectories to the pathological equilibrium, but the increase in d offsets this effect and keep trajectories approaching the physiological point. This phenomenon has a biological interpretation of

being insulin resistant, but not diabetic. Possible values that create this effect are $c = 0.2$ and $d = 60$.

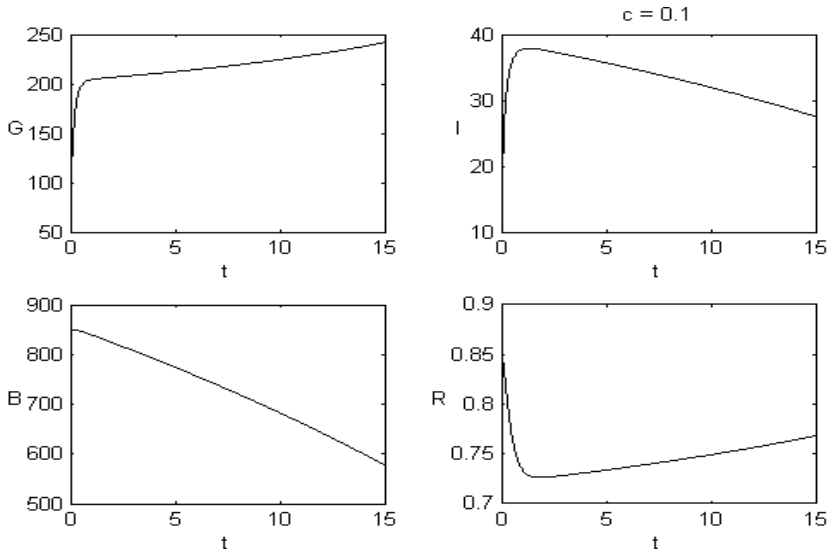

Figure 14: Trajectories of G, I, β, and R under average normal initial conditions (basal levels) with a low c value (high insulin resistance). Notice that this individual becomes diabetic. Initially, the β-cells compensate for the insulin resistance by secreting more insulin, but the change in the insulin is so strong that the β-cells cannot compensate enough. Their mass diminishes because of the hyperglycemia that results from the rapid change in insulin resistance. Then, insulin levels fall and severe hyperglycemia ensues. This represents the "dynamical hyperglycemia" pathway to diabetes.

Since nearly half of all insulin uptake is dependent on insulin receptors on the surface of muscle cells, it is interesting to observe the effects of changes in the receptor equation (7). The parameter (j) represents the recycling rate of internalized receptors. It is natural to speculate that a low recycling rate would lead to increased basal insulin levels. To explore such a speculation, we decrease j to 1.85 (a 30% change), and observe that the physiological equilibrium becomes $\beta = 863.5$, $I = 13.7$, $G = 82$, $R = .78$. The natural insulin receptor endocytosis rate independent of insulin is represented by l. To examine how changes in l affect the system, we increase its value to 0.312 (a 30% change). The result is a shift in the physiological equilibrium to $\beta = 858.9$, $I = 13.02$, $G = 82$, $R = .82$. Changing j and l simultaneously to $j = 1.85$ and $l = 0.312$ made the physiological equilibrium $\beta = 867.3$, $I = 14.14$, $G = 82$, and $R = .76$. It is important to note that the effect of changing these parameters simultaneously was greater than the combined effect of changing each individually (*i.e.*, the effect was greater than additive).

5 Discussion and Conclusions

In this paper, we adapt a model of β-cell mass, insulin, and glucose kinetics and consider the effects of insulin receptor dynamics in the glucose regulatory system. Our model predicts that under normal conditions, basal levels of β-cell mass, insulin, glucose, and insulin receptors will approach the physiological equilibrium state of $\beta = 856.95$, $I = 12.70$, $G = 82$, and $R = 0.84$. Defects in the parameters regulating β-cell mass (g,h, and i) are important in leading to diabetes in that they can either create hyperglycemic glucose levels at the physiological equilibrium point, or cause a saddle-node bifurcation that leaves the pathological equilibrium as a global attractor. Studies have shown that exercise can increase insulin sensitivity by 36%. This increased insulin sensitivity will decrease the required insulin levels for a constant glucose concentration. By reducing the equilibrium insulin levels, a lower β-cell mass is required, and the fraction of insulin receptors on the cell surface can increase. Our model predicts that the new equilibrium will be shifted to $\beta = 628.95$, $I = 9.13$, $G = 82$, and $R = 0.86$. On the other hand, a sedentary lifestyle, along with obesity, can lower insulin sensitivity by 50-100%. Our model predicts that a person whose insulin sensitivity drops by 60% will be hyperinsulinemic, or insulin resistant.

Our model of the glucoregulatory system with receptor dynamics is significant for several reasons. By adding receptor behavior to equations describing β-cell mass, insulin, and glucose, the model includes factors that are known to be important in the pathogenesis of diabetes, but which have not previously been considered together. A useful mathematical study should ideally describe as much relevant phenomena as possible without sacrificing accuracy or clarity, and considering receptor dynamics is an improvement along these lines. In addition, our system of equations is valuable in that it improves the quantitative predictions of β-cell mass values given by the model of Topp, *et al.* Average normal β-cell mass in a healthy individual is about 850 mg [17]. The former model predicts the β-cell mass to be much lower than this, as the mass at the physiological equilibrium point is 300 mg. We predict a physiological β-cell mass of 856.95 mg, which is a significant improvement. Furthermore, our model provides a theoretical justification for the fact that, on average, approximately 85% of insulin receptors are on the surface of muscle cells, because $R = 0.84$ at the physiological equilibrium point. As previous studies have not considered receptor dynamics with β-cell mass, insulin, and glucose kinetics, our model gives a natural explanation for this quantitative behavior of receptors.

The dynamics of diabetes are very complex. Though we have added a fourth dimension to the theoretical study of the glucose regulatory system, many more could be considered. Possible extensions to our model include the other hormone secreting cells in the *islets of Langerhans*, such as α and δ cells. These cells secrete the hormones glucagon and somatostatin (respectively) which also help to regulate glucose and insulin. Also, adjustments should

be made to the β-cell equation (6) in order to place a bound on β-cell mass. In addition, it would be worthwhile to conduct further research in an effort to quantify the dynamics of insulin sensitivity and incorporate insulin sensitivity dynamics into the model.

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