My βIG Fat Math Model: β-Cell Compensation and Type 2 Diabetes

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Abstract

In this work we mathematically explore the biological consequences of the effect of over-nutrition, fat accumulation, and β-cell function in a model of the progression of Type 2 diabetes (T2D). More specifically, we focus on the effects of fat mass in the liver and the mechanism underlying the initiation and progression of β-cell failure. This mathematical model is based on a previous model that considers glucose-insulin and β-cell mass dynamics. We incorporated fat (assumed to grow linearly), the direct effect of insulin sensitivity, and the effect of β-cell sensitivity in our model. We assumed that β-cell sensitivity embodies a logistic response by initially increasing as fat accumulates due to the compensatory response triggered by increased glucose levels. As fat continues to accumulate, β-cell sensitivity decreases due to β-cell failure and eventually β-cells begin to die. The threshold at which β-cell compensation fails marks the clinical onset of T2D, which with time can progress to the stage where it is no longer reversible due to severe loss of β-cell mass. Using the theory of dynamical systems we analyze the various stages of T2D, investigate whether weight loss in the pre-diabetic and diabetic stages would reverse T2D, and study when this treatment strategy is no longer effective.

B Introduction

The possibility of recovering from Type 2 diabetes (T2D) in the pre-diabetic and diabetic stages through diet interventions is of current interest to many researchers today [27]. T2D has long been described as an incurable progressive disease. Traditionally individuals over the age of 40 were thought to have the most risk of diabetes however, recent evidence show obesity has become one of the major contributing factors to T2D [13, 22]. Approximately 4 to 8% of children and 10 to 20% of adults worldwide are obese and nearly 35.7% of new T2D cases are obese adolescents [22]. Nearly 150 to 220 million individuals were predicted to become diabetic by 2010 and 300 million by 2025 worldwide [30]. In 2010, the International Diabetes Foundation reported more than 300 million individuals had diabetes exceeding the predicted number for 2025 [30, 32].

This epidemic of T2D is rapidly spreading globally and has become one of the major health treats due to the changes in lifestyle including behavioral and environmental factors [2, 5, 11, 30]. In the long-term, diabetes left untreated causes or exacerbates conditions such as heart, kidney, and nervous system disease, stroke, high blood pressure, erectile dysfunction, blindness, and limb amputations; many of these diseases being the leading causes of death in the U.S. [25]. Furthermore, a study by Dr. Yale predicts obese children diagnosed with diabetes before age 20 are susceptible to additional complications in the

long-term from T2D and now a body mass index (BMI) > 30) serves as a clinical indicator for risk of T2D [31].
Overnutrition, inactivity, and other environmental factors contribute to weight gain. Overweight individuals consuming excessive glucose-content meals can progress to pre-diabetic stages where β-cell compensation is initiated and later progress to the diabetic stage where β-cell dysfunction occurs leading eventually to β-cell loss [28]. Below, we present background on the glucose-insulin regulatory system, β-cell function and compensation, β-cell sensitivity, insulin resistance, and the effects of fat accumulation in the liver.
Several mathematical models have been developed to describe the mechanisms underlying glucose-insulin regulation [25, 27, 38], however few consider fat as either a direct or indirect effect on liver insulin sensitivity [35]. The model proposed investigates the effects of fat in both the blood by free fatty acids (FFA) and in the liver as triglycerides (TG). The impact of fat on insulin sensitivity are not well understood. Recent findings suggest a link between TG, FFA, and insulin sensitivity although these mechanisms are not consistent in the literature [34–37].
When does T2D become irreversible and when does β-cell overcompensation fail? The research presented aims to describe the dynamics of insulin, glucose, β-cell mass, and fat change. The findings of our model will offer information on the threshold values of insulin resistance, β-cell overcompensation, and fat mass by considering the stability analysis of relevant parameters. The model will also be compared to the data of the study by Lim et al. [16]. The long-term goal of this line of research is to arrive at clinical recommendations for intervention strategies dependent on the stage of progression of T2D.

C Overview of Progression of Type 2 Diabetes

Type 2 diabetes (T2D) is characterized by the progressive decline of β-cell function and terminal insulin resistance [29]. T2D is understood to be incurable although a change in diet and regular physical activity can lead to reduced symptoms and prevent the onset of diabetes [16, 22], both treatment and intervention strategies targeted to obese individuals [3]. In 2011, a study concluded T2D was reversible by modifying caloric intake and glucose content [16]. Differences in glucose levels, insulin concentration, and fat mass in both the pancreas and liver were collected to test whether or not negative energy balance alone could restore insulin sensitivity, release β-cells from excessive exposure to fatty acids, and reverse β-cell overcompensation. The 12-week follow-up of the 8-week study concluded that 9 of the 11 obese individuals with T2D (less than 4 years) were recovered. These findings are indeed remarkable and offer plausible preventative and intervention strategies that require further investigation. Overnutrition and lack of physical activity can lead to both insulin resistance and β-cell dysfunction [18]. The initiation of insulin resistance and β-cell compensation define the pre-diabetic stage of T2D. Progression of β-cell dysfunction and failure mark the clinical onset of T2D and is the point of interest in this research.
It has been understood that insulin-glucose mechanisms behave in a negative feedback loop [23] where a rise in glucose level triggers the release of insulin from β-cells which in turn, lowers glucose levels, causing insulin levels to decline. However, this feedback mechanism occurs only if liver cells can detect insulin. Often patients with excess FFA's or adipose tissue may develop insulin resistance where the liver does not respond to insulin effectively. Blood glucose levels increase and β-cells must then compensate for the elevated blood glucose by eventually overworking, known as " "overcompensation". This cascading effect is supported in literature suggesting insulin resistance is a prerequisite in this progression of T2D. The proposed mathematical model is a simplification of the dynamics connecting fat accumulation, glucose-insulin regulation, and β-cell mass. Findings can contribute to health education, prevention and intervention strategies, and future research.

C.1 Glucose-Insulin behave in a Negative Feedback Loop

The body metabolizes food into glucose, one of the body's primary source of energy. Glucose is transported throughout the body through the blood. When blood glucose level rises, β-cells within the

pancreas respond by secreting a hormone called insulin. Insulin molecules attach to receptors on liver cells in order to signal these cells to absorb glucose. Hence, insulin is a hormone which aids in lowering the blood glucose to normal glucose levels, known as normoglycaemia. Glucose-insulin regulation for a normal individual behaves in a negative feedback loop [23]. A rise in amount of blood glucose triggers β-cells to release insulin, moreover insulin secretion increases. The uptake of glucose by liver cells reduces blood glucose levels and hence insulin levels also decline.

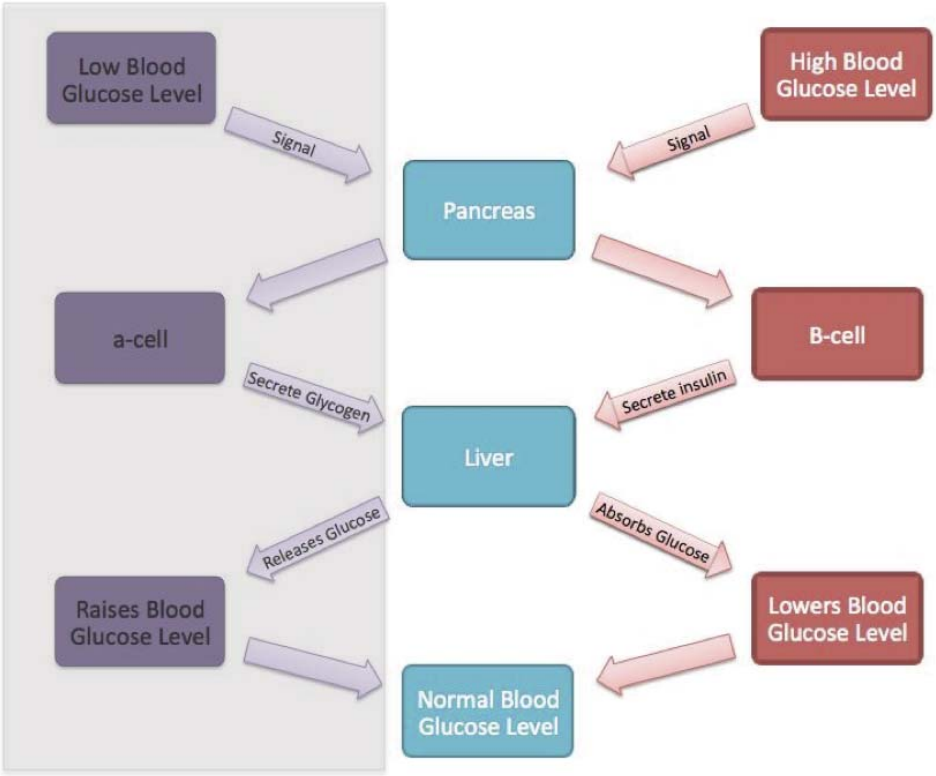

Figure 2: Flow chart for glucose-insulin regulatory system: negative feedback loop

C.2 Role of β-cell sensitivity, β-cell compensation, and development of β-cell failure

Consider Figure 4(a), for a normal individual, the secretion of insulin is triggered by the rise in blood glucose levels β-cells synthesize and secrete insulin into the blood stream. The insulin binds with insulin receptors on liver cells and glucose is absorbed from the blood stream. Insulin sensitivity refers to liver cells' response mechanism to the insulin. As insulin sensitivity decreases more insulin is needed to effectively reduce blood glucose levels and β-cells begin to expand in order to secrete more insulin into the blood stream Figure 4(b). In this cycle some of the β-cells start dying because they have been overworked. This is called β-cell depletion. When this happens, the β-cells mass decreases causing less insulin to be secreted which normally reduces the glucose levels in the blood. But this time, the glucose

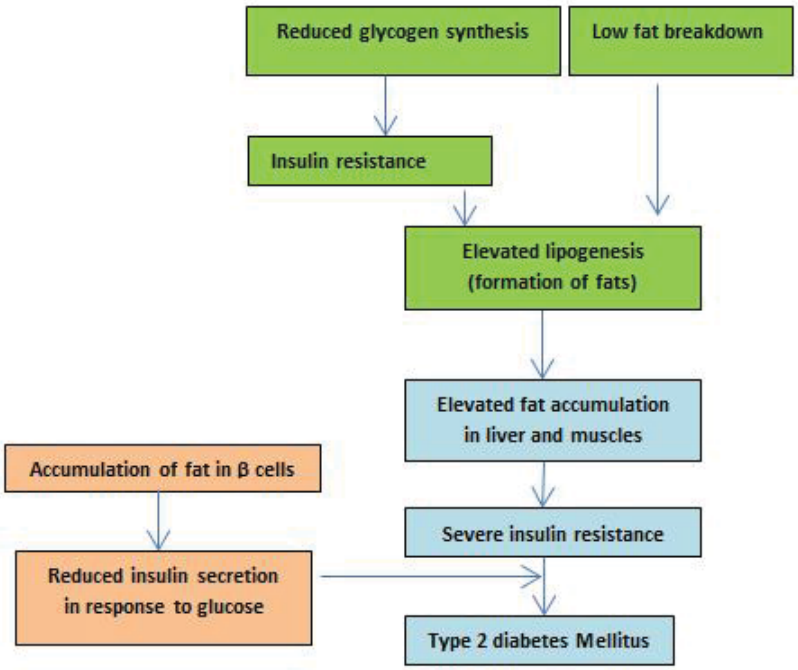

Figure 3: The development of Type 2 diabetes: considering Insulin Resistance and β-cells

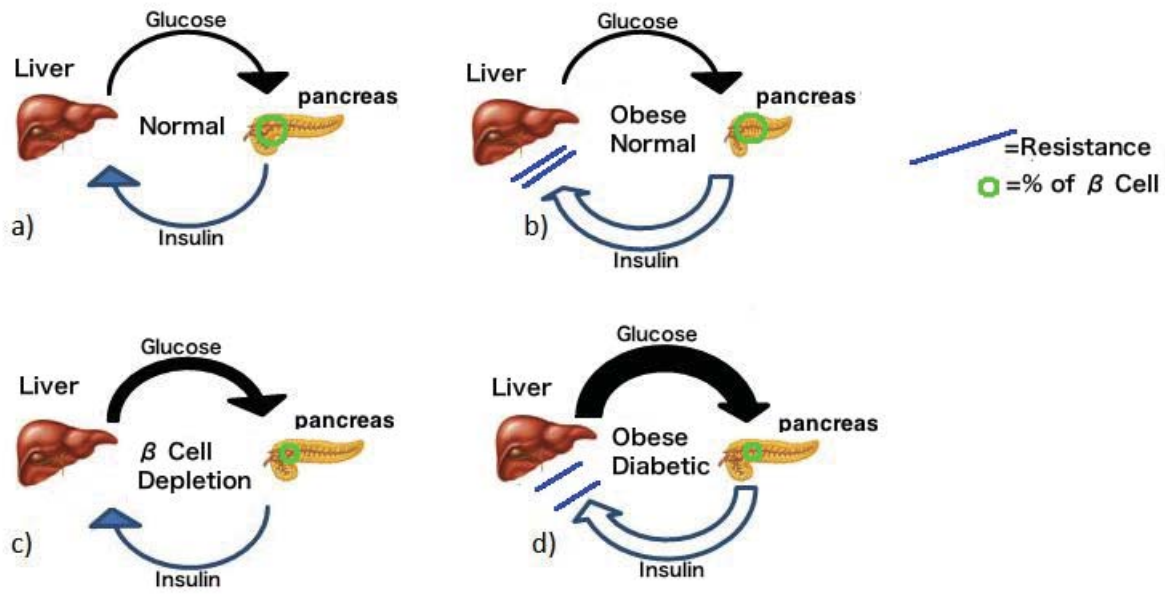

Figure 4: β-cells and the insulin pathway

levels rise because the liver does not receive enough insulin from the β-cells Figure 4(c). In Figure 4(d), the liver is insulin resistant and thus unresponsive to insulin. Since we have β-cell depletion, the glucose levels in the blood stays high. In order return to normalglycemia a person has to resort to insulin shots.

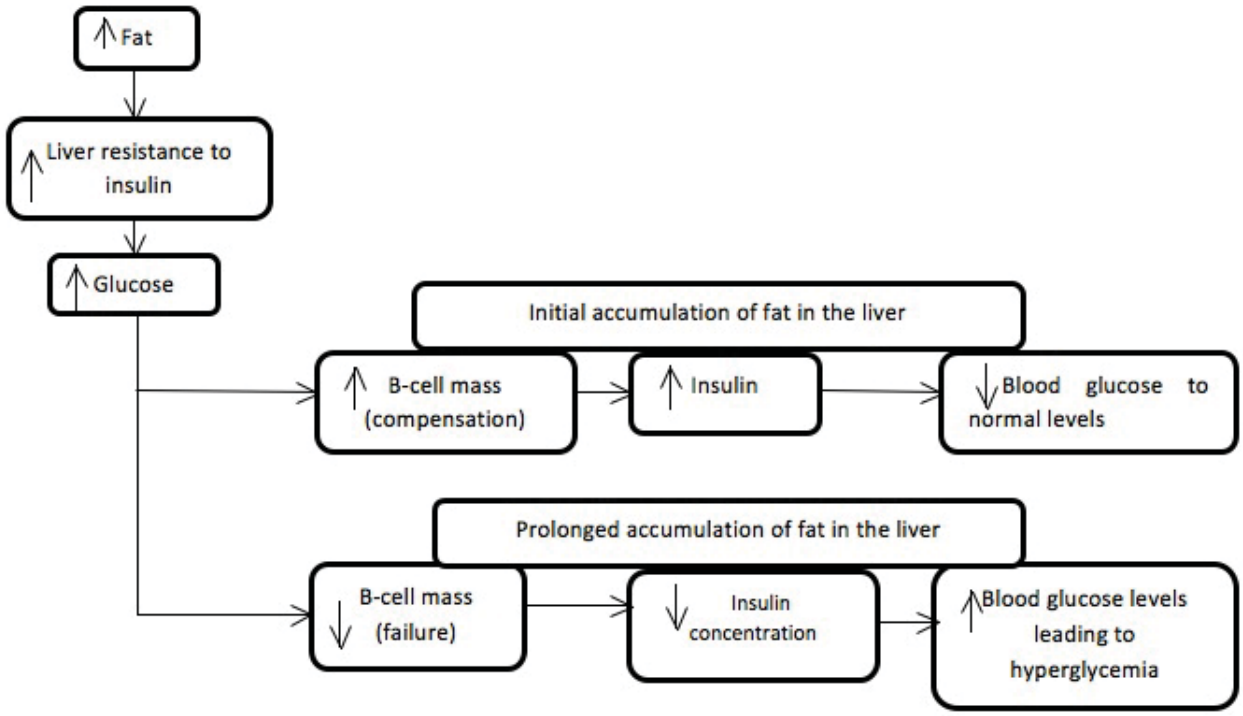

Figure 5: Short-term fat accumulation can lead to the progression of β-cell compensation during the initial stages. Long-term fat accumulation influences β-cell failure.

C.3 Adipose Tissue and Free Fatty Acids (FFAs) in the Liver and Insulin Sensitivity

The liver plays a key role in glucose level regulation by removing up to 50% of glucose in the blood. Weight-gain leads to fat accumulation in the body. Excessive free fatty acids (FFAs) in the blood prevents liver cells to respond appropriately to insulin. Under normal conditions the presence of insulin activates liver cells to take up glucose. When glucose is absorbed by liver cells it is stored as either glycogen or fatty acids which are broken down when blood glucose levels are low. Excess fatty acids accumulate in the liver where they are converted into triglycerides which make up fatty tissue around the liver. Furthermore, adipose tissue in the liver triggers the production of more fat. Overweight individuals are at a higher risk of T2D marked by increased susceptibility to insulin resistance and β-cell overcompensation.

Insulin sensitivity refers to how well liver cells respond to insulin. Adipose tissue in the liver prevents insulin molecules to bind to liver cell receptor sites and also causes liver cells to be unable to recognize the presence of insulin. High blood glucose levels are maintained in the blood and continuously rise as glucose buildup increases. In consequence, β-cells expand and overwork in order to compensate for the excess glucose present. Consequently, the β-cell mass begins to decrease because the cells are unable to sustain the high demand for insulin secretion for longer periods of time. β-cells then become dysfunctional and potentially die off over time. When β-cell mass decreases, the amount of insulin secreted also decreases leading to elevated blood glucose concentration. At this point, the liver is unable

to bring down the glucose level in the blood, and the person is diagnosed as diabetic.

Free fatty acids (FFA) are acids that can be transported in the bloodstream and may potentially have a central role in the liver-insulin sensitivity [35]. High FFA concentration has been shown to stimulate hepatic glucose production and inhibit insulin-stimulated glucose uptake, leading to high blood glucose concentrations [35]. TG can be accumulated in the liver as triglycerides (TG). The source of TG could be either excess glucose in the blood, free fatty acids, and/or the diet [37]. Therefore, measuring the amount of FFA in the blood could give us an estimate of the overall sensitivity of the liver. Also, liver sensitivity has been linked directly to FFA even before they are stored as TG in the liver ([35], [36]). The intent of this research is to investigate the role of adipose tissue and FFA's on β-cell compensation and reversal of T2D.

D βIG Fat Math Model

D.1 Basic Model: Topp et. al.

Mathematical models of insulin and glucose dynamics are widely available in the literature but few consider the dynamics of β-cell mass coupled with glucose-insulin dynamics [27]. Topp *et al.* (2000) was one of the first to describe the negative feedback loop using a system of three nonlinear ordinary differential equations observed in insulin-glucose regulation and incorporate long-term dynamics of β-cell mass. The model presented is an expansion of previous work which includes the physiological response of plasma glucose concentration (G), insulin concentration (I), and β-cell mass (B) [27] . Where the change in plasma glucose concentration with respect to time ($\frac{dG}{dt}$) depends on the amount of glucose secreted naturally by the liver, a, and how much is lost naturally b, or removed by the uptake induced by insulin that is dependent on insulin sensitivity, S_I. Insulin changes with respect to time ($\frac{dI}{dt}$) based on the amount secreted by the β-cells given their sensitivity to high glucose concentration, S_I, and the clearance rate, k, representing uptake of insulin by the liver, kidneys, and insulin receptors. Lastly, change in β-cell mass ($\frac{dB}{dt}$) depends on growth induced by increasing levels of glucose, h, death by overcompensation, m, and natural cellular death, g. Following are the equations used in the Topp paper:

$$\frac{dG}{dt} = a - (b + S_I I)G, \tag{2}$$

$$\frac{dI}{dt} = \frac{dBG^2}{e + G^2} - fI, \tag{3}$$

$$\frac{dB}{dt} = (-g + hG - mG^2)B \tag{4}$$

where G represents plasma glucose concentration, I represents insulin concentration, and B represents β-cell mass. Definitions of parameters are listed in Table 1. In the following sections 1 to 3 we propose three modifications to the model which incorporates thre

E Model 1: Adipose Tissue effects on Insulin Sensitivity

Our first model considers the fat accumulation in the liver in the form of adipose tissue. Here we focus on AT and its effect on the system. The equation governing the change in, AT, the rate of change of triglycerides in the liver.

$$\frac{dG}{dt} = a - \left(b + \frac{S_I I}{1+\tau AT}\right) G \tag{5}$$

$$\frac{dI}{dt} = \frac{dAT(1-\frac{AT}{k})BG^2}{e+G^2} - fI \tag{6}$$

$$\frac{dB}{dt} = (-g + hG - mG^2)B \tag{7}$$

$$\frac{dAt}{dt} = AT(G, I) \tag{8}$$

The new equation introduced is $\frac{dAT}{dt}$ which accounts for the amount of adipose tissue assumed to be in the liver. For this model AT's accumulate in the liver at a rate jG. The term $\frac{pAT}{1+\Lambda I}$ denotes the degradation of TG that is dependent on the amount of insulin present as well as the amount of AT present.

$$\frac{dTG}{dt} = jG - \frac{pAT}{1+\Lambda I} \tag{9}$$

where j is AT accumulation, p is AT degradation in the liver, and Λ is the rate at which insulin prevents AT tissue to be degraded from the liver.
In this case insulin liver sensitivity depends on the amount of fat in the liver $S_I(AT) = \frac{S_{I0}I}{1+\tau AT}$ illustrating how the increase of fatty acids around the liver induces liver-insulin sensitivity to decrease. In our model, we assume that insulin cell sensitivity is affected by fat in a logistic manner. When the amount of fat is small, β cells increase in size in order to compensate for the liver insulin resistance. After some point of prolong compensation,k/2,β-cells begin to die due to overwork. We model this initial increase followed by a decrease in β-cell mass that is promoted by fat induced insulin resistant with. A logistic effect $dAT(1-\frac{AT}{k})$ on the sensitivity of β-cells.

E.1 Time series

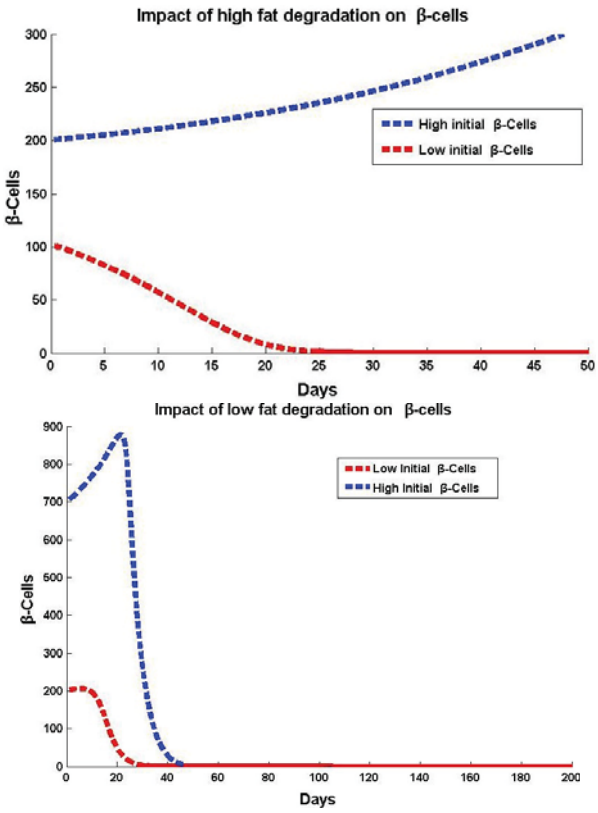

Figure 6: **(a) β-cell mass versus time with a high AT degradation p (top) and (b) β-cell mass versus time with a high AT degradation p (bottom).** For high degradations of AT depending on the initial conditions of β-cells the individual will tend to physiological state or pathological if β-cells are low, but if there is a low fat degradation β-cells will always tend to pathological

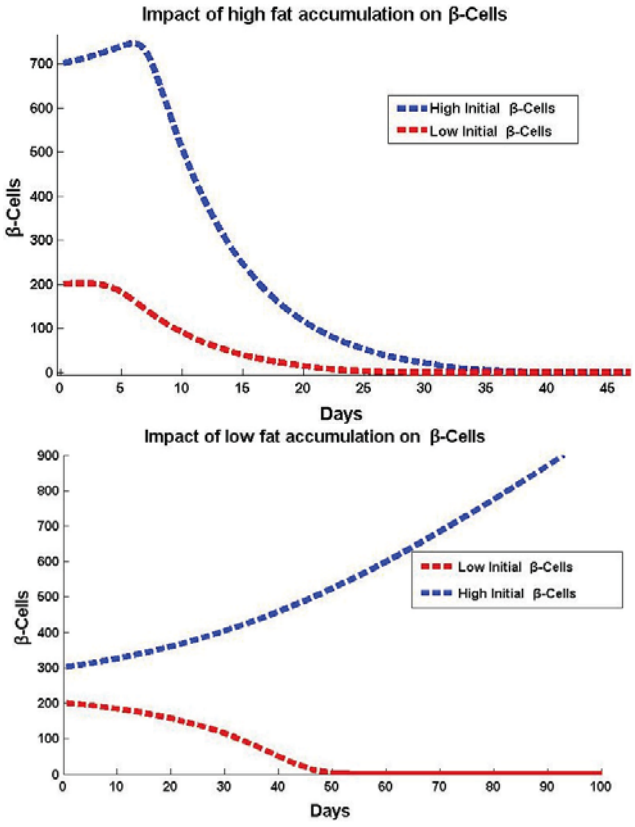

Figure 7: **(a) β-cell mass versus time with a high AT accumulation j top) and (b) β-cell mass versus time with a high AT accumulation j (below).** For high accumulation of AT an individual will always tend to go to pathological state, but for low fat accumulations the individual will either tend to physiological with high β-cells or pathological if β-cells are low

E.2 Bifurcation Analysis

The four bifurcation diagrams corresponding all the variables in our system with respect to the degradation of fat, p, are utilized to gain insight into the various stages of $T2D$. Here as before we fixed all parameters and vary only p. We note a vertical asymptote where at that point the model is not biologically relevant. When p low when is to the left of the asymptote for the unstable equilibrium corresponding to $G = 250$ the only fixed point for insulin is zero. When p is larger than this value, there is bi-stability, with low initial conditions for β cell mass, β-cell mass decreases. You can reach the point of no return in two ways. One by not decreasing your fat enough or by decreasing your β-cell mass to a point where you cannot recover. Fat accumulated, j, can also be used as a bifurcation parameter. When fat accumulation in the liver is high, than the only fixed point that exists is for zero insulin that corresponds to the pathological equilibrium point. The point of no return in this case is denoted by the rate at which you accumulate fat in the liver. If you accumulate a high amount of AT in the liver your beta cells will tend to pathological. If you decrease your fat accumulation in the liver, then your β-cell mass can stabilize to the physiological equilibrium point. The point of no return however is reached also depending on how much β-cells you have. If your β-cells mass is already below the unstable manifold, then your β-cell mass will decrease even if you do not accumulate much AT in your liver.

E.3 Analysis of parameters a, j and p on both β-cell sensitivity and insulin sensitivity

Presented here are the effects of three parameters on β-cell sensitivity and insulin sensitivity. We consider endogenous glucose production by the liver illustrated by the parameter a, rate of adipose tissue production, j, and rate of adipose tissue degradation p. The relationships with glucose production and adipose tissue degradation rate are curvilinear and linear. Here, we plotted the relationships corresponding to the different equilibrium points. An increase in glucose production, a, leads to the increase in β-cell sensitivity and a decrease in insulin sensitivity whereas, an increase in the rate of adipose tissue breakdown, p, leads to the decrease in β-cell sensitivity.

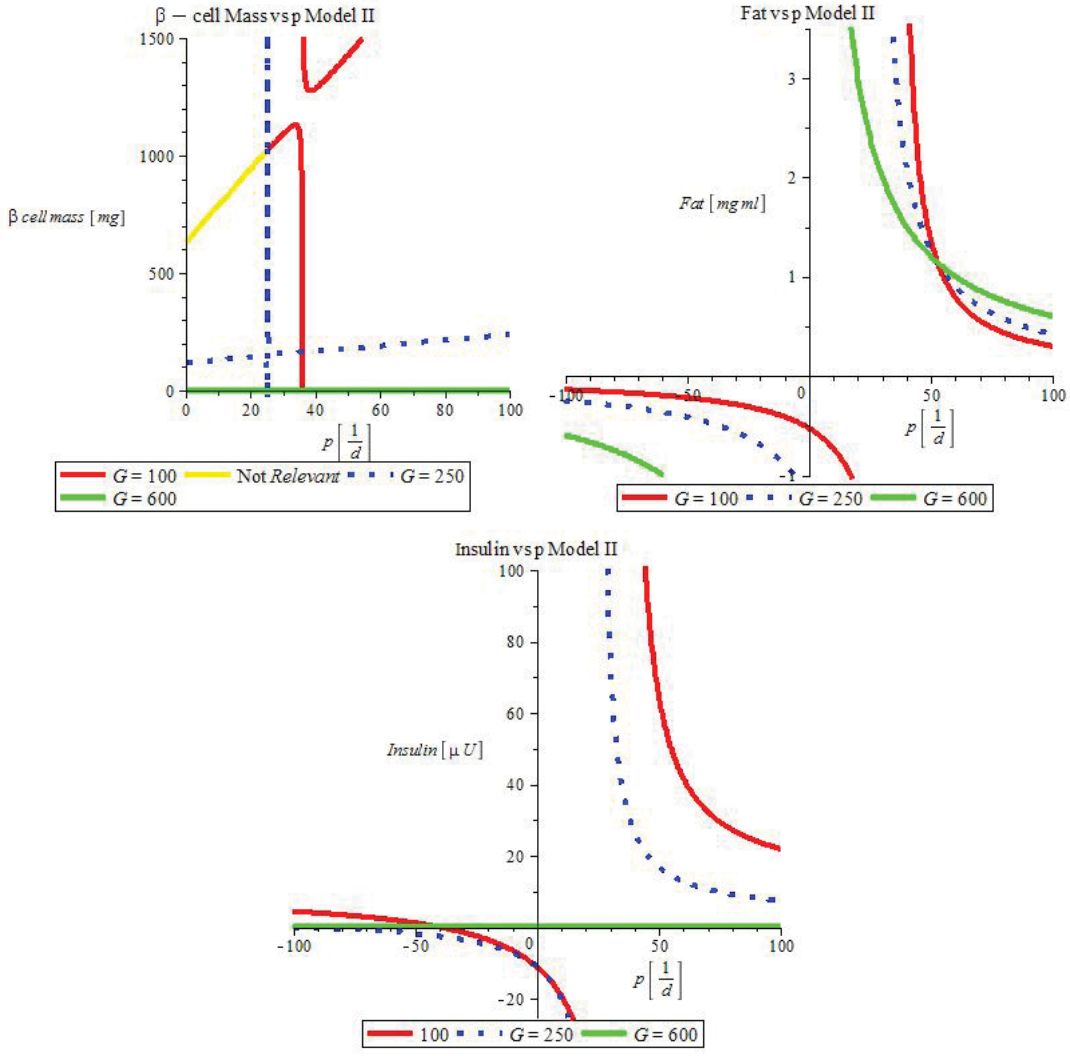

Figure 8: **(1) Adipose tissue vs p and (2) Insulin vs p, and (3) β-cell versus** pCurves represent the equilibrium points corresponding to the steady state values of glucose G= 600,250 and 100 (see legend) for various p values. The bifurcation diagrams for the AT degradation in the liver. To the left of the blue asymptote no matter how much β-cell mass the individual has is going to tend to go to the pathological state. For higher AT degradations to the right of the blue asymptote if β-cell mass is above the unstable manifold β-cell mass will tend to physiological state but if they are below the unstable manifold they will tend to go to the pathological state.

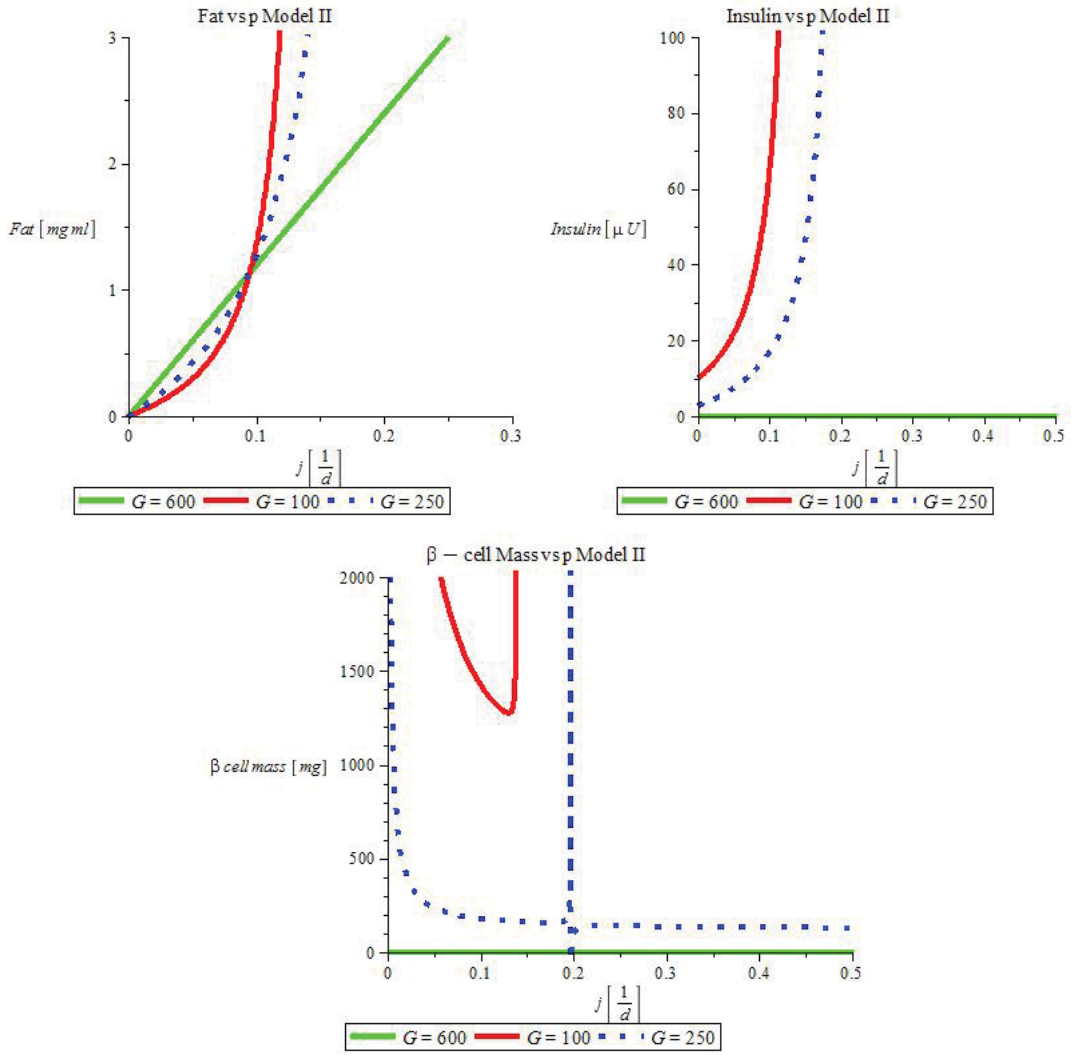

Figure 9: **(1) Adipose tissue vs j and (2) Insulin vs j, and (3) β-cell versus j** Curves represent the equilibrium points corresponding to the steady state values of glucose G= 600,250 and 100 (see legend) for various j values. The bifurcation diagrams for the AT accumulation in the liver. To the left of the blue asymptote that is with low AT tissue accumulation reaching a physiological state is possible given that /*beta*-cell mass is above the unstable manifold. For high AT accumulation to the right of the blue asymptote if β-cell mass will always tend to go to pathological state. .

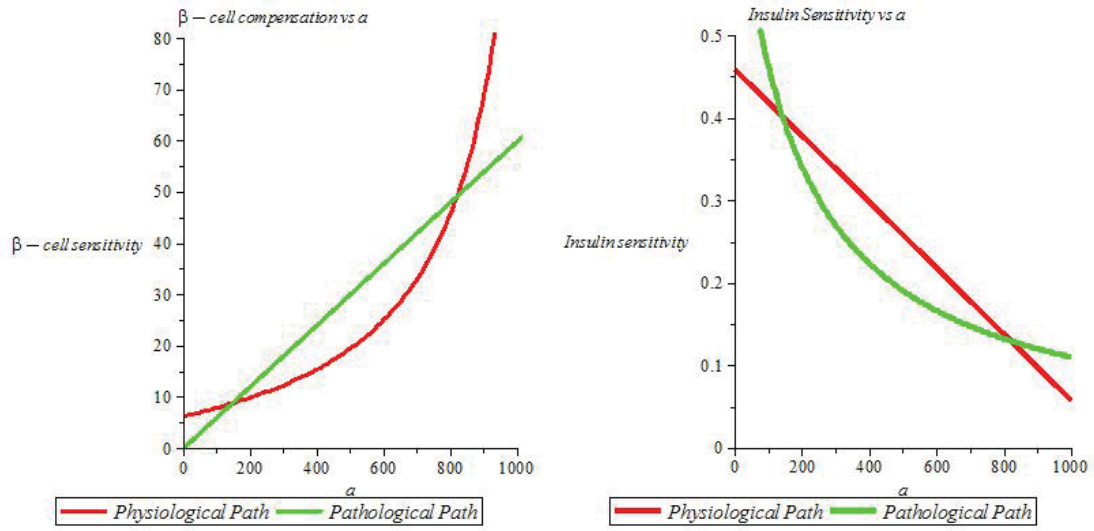

Figure 10: An increase in a leads to an increase in β-cell sensitivity and decrease for insulin sensitivity for both the pathological and physiological states.

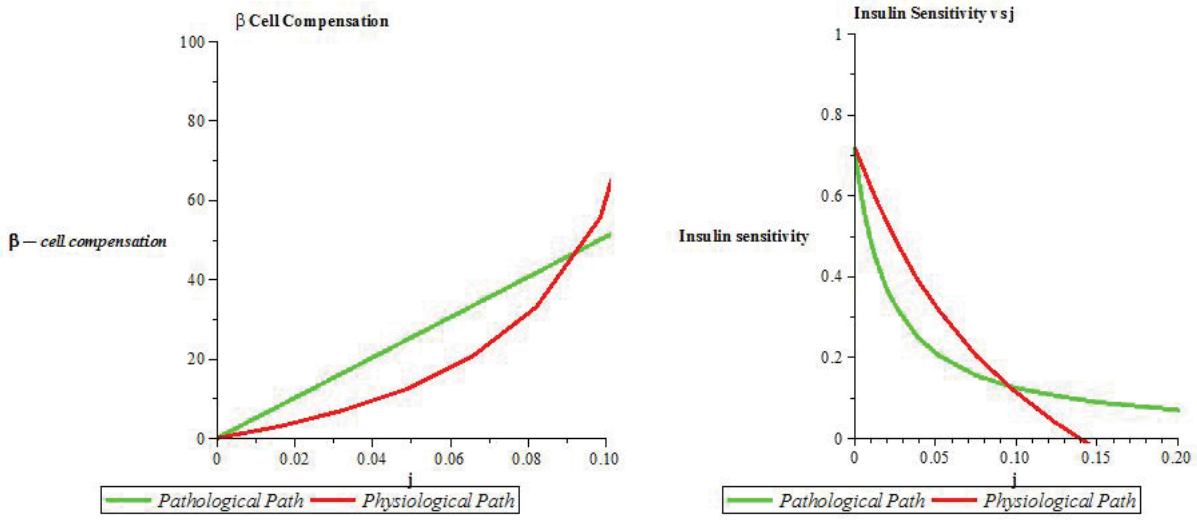

Figure 11: An increase in **j** leads to an increase in β-cell sensitivity and decrease for insulin sensitivity for both the pathological and physiological states.

F Model 2: Fat Accumulation as a Linear Function

We proposed a simple model of fat to see if the more complicated equation for fat, which models more realistic aspects of this mechanism were necessary to show the effect of fat on the system (4)-(6). The simple fat differential equation includes Λ, the rate of fat production and p, the rate of fat degradation. This simpler model includes the effects of fat accumulation in the liver, on liver sensitivity, as well as β-cell sensitivity to glucose. The model is given by equations (4)-(6) where $S_I(F)$ represents the insulin resistance as a function of fat and $S_\beta(F)$ describes the β-cell resistance as a function of fat.

$$\frac{dG}{dt} = a - (b + \frac{S_{I0}I}{1+\tau F})G \tag{10}$$

$$\frac{dI}{dt} = \frac{dF(1-\frac{F}{k})BG^2}{e+G^2} - fI \tag{11}$$

$$\frac{dB}{dt} = BG(h - mG) - gB \tag{12}$$

$$\frac{dF}{dt} = \Lambda - pF \tag{13}$$

where $S_I(F)$ represents the insulin resistance as a function of fat and $S_\beta(F)$ describes the β-cell resistance as a function of fat.

F.1 Bifurcation Analysis for parameters g, m, and h

Bifurcation parameters were found in g, m, and h where the stability and number of steady-state solutions of glucose changed as the parameters were varied. The long term behavior (or steady state) of an individual depends on the initial conditions of glucose, insulin, β-cell mass, and fat. This analysis considers three separate bifurcation diagrams for β-cell mass growth due to compensation (h), β-cell mass death due to overcompensation, and natural death rate of β-cell mass (g). (See Figure 12 to Figure 14). Note that dashed lines (- - -) represents unstable steady-states and solid lines (—-) represent the stable steady-states. For this analysis we found that bifurcation was found to be similar of those for Topp *et al.*'s model [27]. The long term behavior that the system achieves for a particular an individual depends on the initial conditions of glucose, insulin, β-cell mass, and fat.

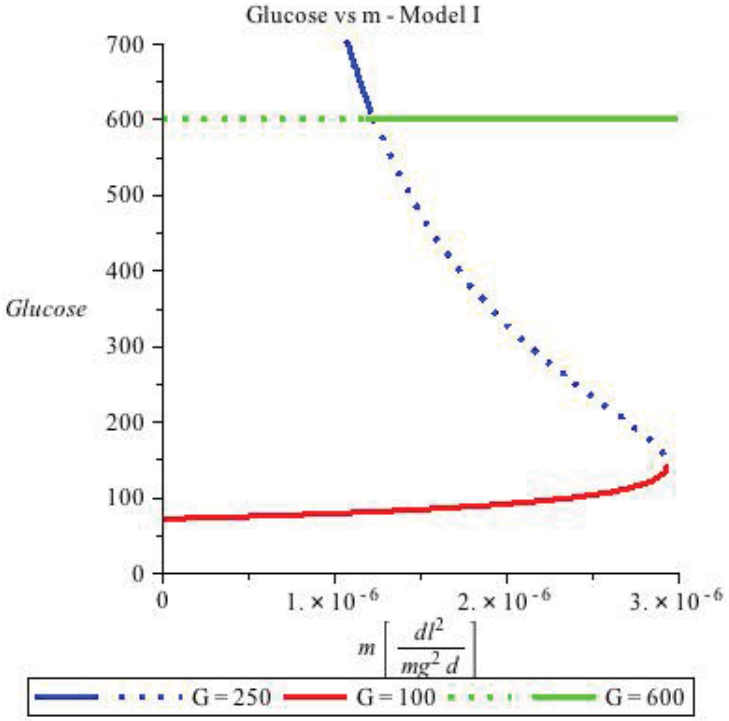

Figure 12: Bifurcation Diagram where the fixed points of glucose are plotted as a function of the rate at which β-cells mass decreases due to overcompensation and m, which is glucose tolerance. For Region 1, there only exists two stable equilibria points. This means that in this region for levels of G below 600 the long term G level will be approximately 75. In Region I, when G $>$ 600 there solutions go to the stable equilibrium point with high levels of glucose. Again, in Region II, there exists 2 stable equilibria points. If glucose levels are above G_2^*, then they would continue to rise and a pathological equilibrium is reached. However, if glucose levels are below G_2^* for a given value of m, glucose tolerance, then the β-cells can compensate without dying since in this region glucose remains low. Region III has only one equilibrium point, G_3^* which is stable. In this region, the rate at which the β-cell mass loss is very high and pathological.

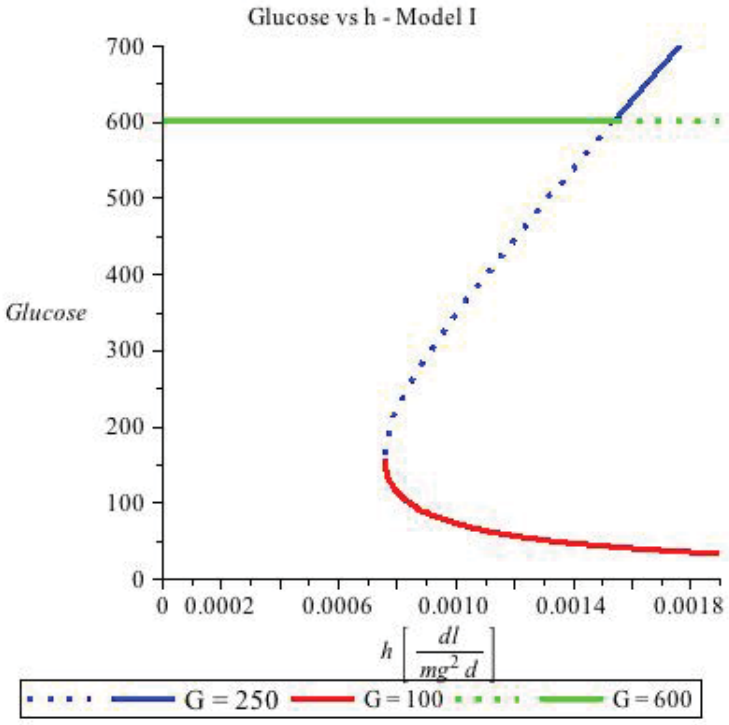

Figure 13: Bifurcation diagram of fixed points of glucose as a function of the rate at which β-cell mass increases due to compensation, h. The solid line represents the stable equilibria of the glucose level and unstable saddle point is represented by the dashed line. In Region I the development of the disease is inevitable since all initial conditions of glucose lead to a pathological fixed point corresponding to $G^* = 600$. For Region II there are two stable equilibria. In Region III, the model is outside of its feasibility range because h cannot be larger than 0.0015 since β-cell mass will grow to an unrealistic level. As h increases, the greater the β-cell mass will expand due to compensation in the presence of excess glucose.

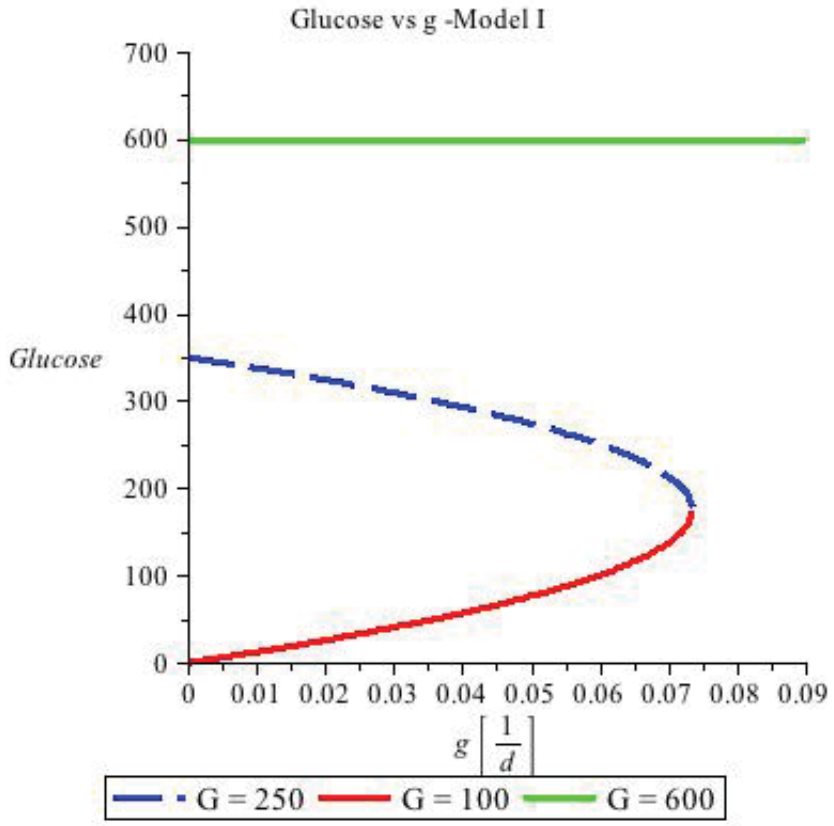

Figure 14: Analysis of glucose and parameter g, which represents β-cell natural death rate at zero glucose. For all positive rates of cellular death glucose will converge to either a physiological stable ($G = 100$) steady-state or a pathological stable ($G = 600$) steady-state. Hence, the outcome will depend on the initial conditions of glucose, insulin, fat, and β-cell sensitivity.

In Figure 12, blood glucose levels may rise or decrease in order to reach normoglycemia depending on the initial amount of glucose and a given value of m, where m represents the β-cell glucose tolerance range. Glucose is reduced in response to the amount of insulin secreted by the β-cells. At low values of glucose tolerance, m, the amount of β-cell mass decreased because the compensation in this case would be small. At high values of glucose tolerance, m, the amount of β-cell mass loss due to compensation is higher. Consider the regions: I, II, and III.

Region I When the rate of β-cell mass loss due to compensation is relatively small, the individual's blood glucose level will reach either a physiologically stable blood glucose level at G_1^* or a pathologically stable blood glucose G_2^* depending on the amount of initial glucose present. If an individual has a glucose level below G_3^* their glucose level will converge to G_1^*. If their glucose level is above G_3^* then the individual will converge to the pathologically stable insulin level G_2^*. Individuals with a blood glucose $< 100\ \frac{mg}{dl}$ are considered healthy. Individuals with a physiologically stable glucose level at G_1^* would be non-diabetic and are likely to have normal glucose-insulin regulation with little to no need of β-cell compensation. Individuals with a pathologically stable glucose level at G_2^* would have an extremely large amount of glucose present which could lead them to hyperglycemic shock. Sustaining this glucose level would be nearly impossible because this would most likely lead to death if hyperglycemia is maintained in the long-term.

Region II When the rate of β-cell mass loss due to compensation is slightly higher, the blood glucose levels will reach a physiologically stable blood glucose level at G_1^* or a pathologically stable blood glucose G_3^* depending on the amount of initial glucose. If an individual has glucose level below G_2^*, their glucose level will converge to G_1^*. If their glucose level is above G_2^* then the individual will likely converge to the pathologically stable glucose level G_3^*.

Individuals with a physiologically stable glucose level at G_1^* would be borderline diabetic. These individuals may be experiencing some β-cell dysfunction since their glucose tolerance value, m, is higher. This may contribute to a slight rise in their blood glucose level. The increase in glucose could also be due to a decrease in β-cell sensitivity or due to a rise in fat accumulation in the liver, which would decrease the livers ability to absorb excess glucose. Individuals with a pathologically stable glucose level at G_3^* would have an extremely large amount of glucose present which could lead them to hyperglycemic shock. An individual who converges to this stable glucose level would be unable to sustain this glucose level for very long. Sustaining this glucose level would be nearly impossible because this would most likely lead to death. This would be a pathologically stable glucose level due to a larger amount of β-cell loss.

Region III When the rate of β-cell mass loss due to compensation is relatively high, the individual's blood glucose level, can converge to the pathologically stable blood glucose $G_3^* = 600$.

Now, we consider parameter, h, in Figure 13.

Region I When the rate at which β-cell mass increases due to compensation is small there is only one pathologically stable glucose level, G_3^*. The β-cells in all individuals in this region would be unable to compensate for the increase in glucose. In this case, individuals reach a pathological stable point, $G_3^* = 600$, independent of initial conditions. Individuals in this region would already be considered diabetic for their inability to compensate for the excess glucose. When h is low this could be the result of long term β-cell exhaustion.

Region II When the rate of β-cell mass increases due to compensation is in this region the individuals blood glucose level will converge to either a physiologically stable blood glucose level at G_1^* or a pathologically stable blood glucose G_3^* depending on the amount of initial glucose present.

Individuals with a physiologically stable glucose level at G_1^* would be healthy individuals with β-cells able to compensate in response to excess glucose. Pre-diabetic individuals who converge to G_1^* would be able to maintain a normal blood glucose level over time.

Individuals with a pathologically stable glucose level at G_3^* would have an extremely large amount of glucose present even though β-cells are increasing in mass to compensate. This would mean that even though the β-cells are expanding and secreting more insulin, the amount of glucose present is too high to obtain a homeostatic state. Having a G_3^* blood glucose level could lead an individual into hyperglycemic shock. Sustaining this glucose level would be nearly impossible because this would most likely lead to

death. As before, this would be a pathologically stable glucose level due to the extreme amount of β-cell loss.

Region III: When the rate of β-cell mass increases due to compensation is in a high range the individuals blood glucose levels will converge to either a physiologically stable blood glucose level at G_1^* or a pathologically stable blood glucose G_3^* depending on the amount of initial glucose present. However given the value of the glucose levels for G_1^* and G_3^* in this region these are not realistic and therefore this region is not representative of reality or sustainable. If an individual has a glucose level below G_2^* the glucose level will converge to G_1^*. If the glucose level is above G_2^* then the individual will converge to the pathologically stable glucose level G_3^*.

Individuals with a physiologically stable glucose level at G_1^* would be considered to have a normal or low blood glucose level as long as the glucose level did not reach 0. Individuals whose β-cells are able to expand and compensate at a higher rate may end up having a lower blood glucose level which would result in hypoglycemia in the long-term. The over compensation would lead to too much insulin being secreted and a lower glucose level. If h, β-cell mass growth due to compensation, increases too much this may be biologically impossible because β-cell mass would need to increase as a response to the presence of high amounts of glucose.

Lastly, the fixed points of glucose are plotted as a function of the rate at which β-cells die naturally, g Figure 14. The saddle point is represented by the dashed line and the stable fixed points are represented by the solid lines. There is a saddle-node bifurcation when $g = 0.0735$. In Region I there are two stable equilibria. In Region II there is only the pathological fixed point.

Region I When the rate of β-cell natural death is low, blood glucose level will converge to either a physiologically stable blood glucose level at G_1^* or a pathologically stable blood glucose G_3^* depending on the amount of initial glucose present. If an individual has a glucose level below G_2^* then glucose level will converge to G_1^*. If glucose level is above G_2^* then the individual will likely converge to the pathologically stable insulin level G_3^*.

Individuals with a blood glucose level at G_1^* have more β-cells available to respond to the amount of glucose and therefore blood glucose levels are low or normal. As the value of g increases, so does the amount of glucose present since there is less β-cell mass are available to secrete insulin. As g increases the individual will go from healthy or pre-diabetic to diabetic, and severe diabetic for $g > 0.0735$.

The stable glucose level G_3^* would mean there is a large amount of glucose present. An individual who converges to this stable glucose level would be unable to sustain this glucose level for very long even if they had little to no natural β-cell death. Sustaining this glucose level would be nearly impossible because the amount of glucose present would be too high to regulate.

Region II: When the rate of β-cell natural death is larger than 0.0735 the blood glucose level will always converge to the pathologically stable blood glucose G_3^*. In this case an individual would be losing a large amount of β-cells and it would be impossible to reach a normal blood glucose level.

In conclusion, the bifurcation diagram with g, m, and h led to similar results for that of the Topp model. However, this analysis did not lead to any conclusions about fat change. Hence, in the next analysis we consider varying parameters introduced in the differential equation of fat.

F.2 Analysis with parameters p and j

The parameters j and p represent the constant rate of fat accumulation and fat degradation, respectively. Since bifurcations were not found with parameters j and p. A steady-state analysis was conducted for β-cell mass. Simulations were implemented for varied initial conditions of β-cells mass and also, modified cases of high and low j and p. In Figure F.2 and Figure F.2 we consider the long-term qualitative behavior of high and low β-cell mass (2 cases) with low fat degradation and high fat degradation, respectively.

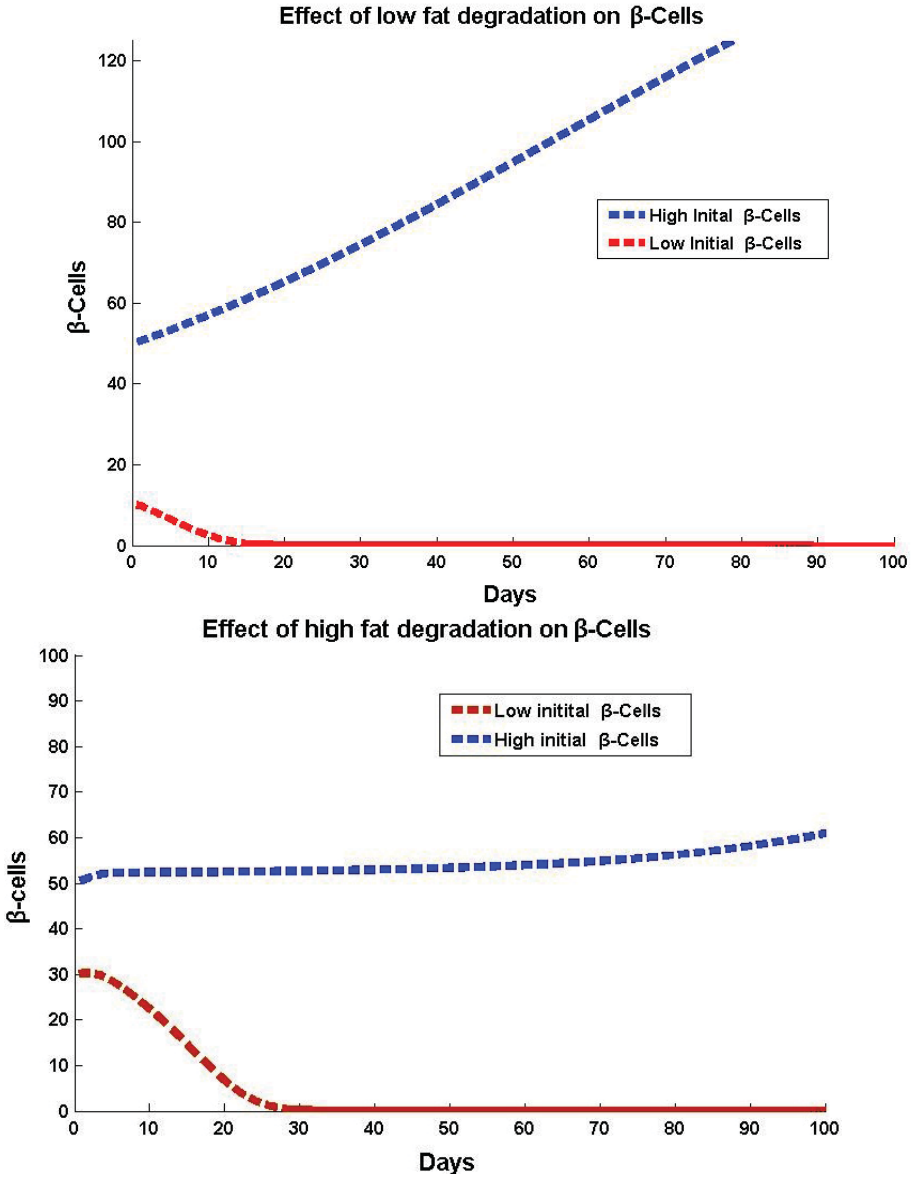

Figure 15: The rate of fat degradation, $\mathbf{p}$, is varied for two sets of initial conditions of β-cell mass. For either a low (left) or high $\mathbf{p}$ (right) may lead to a physiological (i.e. healthy) steady-state depending on your initial β-cell mass.

G Future Work: Model 3 on Free Fatty Acids effect on Insulin Sensitivity

This second model attempts to show the effect of free fatty acids (FFA) in the development of diabetes.

$$\frac{dG}{dt} = a - (b + \frac{S_{I0}I}{1 + \tau FFA})G \tag{14}$$

$$\frac{dI}{dt} = \frac{dFFA(1 - \frac{FFA}{k})BG^2}{e + G^2} - fI \tag{15}$$

$$\frac{dB}{dt} = BG(h - mG) - gB \tag{16}$$

$$\frac{dFFA}{dt} = \frac{Gj}{1 + \Lambda I} - pFFA \tag{17}$$

The accumulation of FFA in the blood stream is dependent of glucose and insulin [35] [37]. Insulin has the effect of preventing the accumulation of FFA [35]. Although insulin has opposite effects on FFA and TG, these two have similar effects on liver sensitivity [35]. FFA are being degraded at a rate p that depends on the amount of FFAs that are already in the bloodstream.

H Conclusion

In this paper we present an extension of the model by Topp. *et al.* Our model incorporates the dynamics of liver fat, F, into their model of glucose, insulin, and β-cell mass to explore the role of liver sensitivity to insulin and the mechanism of β-cell overcompensation. As liver fat increases, the liver's sensitivity to insulin decreases. For small increases in liver fat our model assumes insulin will increase initially, via β-cell function mimicking the compensation phase. However, after a threshold value k/2 of increased liver fat, β-cells begin to dysfunction and will eventually die. We explored three different formulations for fat accumulation: a linear case where liver fat increases and degrades independent of insulin and glucose; and two nonlinear cases where it increases and degrades dependent on insulin and glucose.
There were two stable equilibria for the linear model for the parameter values in Table 1 $(B = 0, I = 0, G = 100, andF = .4)$ for the pathological point, which implies that over time an individual's diabetes progresses into a severely unhealthy state and for the physiological case $(B = 871.29, I = 11.6, G = 100, F = .4)$, which implies that a person is at a biologically healthy state. For a healthy individual, the normal amount of β-cell mass in the pancreas is estimated to be around 850 mg. The aim of the nonlinear model was to describe how β-cells adapt to the decrease in liver sensitivity towards glucose over time in response to liver fat. Our model takes into account the effect of β-cell adaptation (compensation), 'exhaustion" (dysfunction), and death. By explicitly incorporating the dynamics of fat into this model, we are able to have a more physiologically relevant interpretation for both liver fat and β-cell sensitivity, corresponding to more physiologically accurate glucose and insulin dynamics in diabetic and non-diabetic individuals. We also consider the dynamics of liver fat accumulation in response to a decrease in insulin sensitivity. It is important to observe this process in particular on diabetic and pre-diabetic individuals to observe its role in the progression of T2D.
The nonlinear model displayed a stable equilibrium of $B^* = 0, I^* = 0, G^* = 600, F^* = 1.2$ for the pathological fixed point and $B = 853.29, I = 11.637, G = 100, F = 0.4$ for the physiological fixed point which is more accurate in measuring β-cell mass for a healthy individual at 853.29 mg. This model gives more accurate fixed points while incorporating physiologically relevant fat dynamics at the pathological equilibrium point. Liver fat for an obese individual is considered to be between 1.7 to 90 mg/ml [27]. The steady state value for the physiological equilibrium point corresponding to fat is .4 mg/ml which is below the typical range for an obese person. Our pathological equilibrium point is within the ranges for obese diabetic individuals. Figure 7, indicates that β-cell mass will decrease to zero for a wide range of p, the rate for fat degradation. The figure β *cells versus* p shows that when the initial β-cell mass is beneath the unstable manifold, β-cell mass will decrease.
Now by investigating liver fat accumulation, j, instead of the degradation, Figure 8, indicates that β-cell mass will decrease to zero for a wide range of j. The figure β *cells versus* j shows that when the initial β-cell mass is beneath the unstable manifold, β-cell mass will decrease regardless if j is small. If β-cell mass gets this low enough then they cannot recuperate and go back to normal, β-cells will eventually die and we call this the point of no return. This shows that the most important aspect in recovery in our model depends on β-cell adaptation driven by both insulin resistance and β-cell sensitivity, which in turn are driven by fat accumulation in the liver. However, it is not clear whether Type 2 Diabetes is still reversible if severe β-cell dysfunction was developed (e.g. passing the threshold point) in response to significant weight loss. Further research is needed on fat accumulation and fat degradation in both the liver and pancreas and how it impacts β-cell adaptation.
A better understanding of the role of fat mass in β-cell dynamics could offer insight into alternative treatment or intervention strategies. More specifically, diet interventions for the pre-diabetic and diabetic, and also the borderline overweight and obese. Connections between muscle mass and diabetes, potentially also correlated with obesity, have also been made in recent research [39] Our findings will possibly give insight into targeted prevention strategies to more susceptible populations.

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I Appendix

I.1 Analytical Work on Fixed Points when $B = 0$ and $B \neq 0$

$$\frac{dG}{dt} = a - (b + \frac{S_{I0}I}{1+\tau F})G \tag{18}$$
$$\frac{dI}{dt} = \frac{dFBG^2}{e+G^2} - fI \tag{19}$$
$$\frac{dB}{dt} = BG(h - mG) - gB \tag{20}$$
$$\frac{dF}{dt} = \Lambda - pF \tag{21}$$

To find the equilibrium of the system above, we set the left hand side equal to zero. Equation 14 becomes

$$\beta^*(G^*(h - mG^*) - g) = 0$$
$$\text{If } B^* = 0 \text{ then } G^* = \frac{a}{b}$$
$$G^*(h - mG^*) - g = 0$$
$$G^*(h - mG^{*2}) - g = 0$$
$$-mG^{*2} + G^*h - g$$

Next we apply the quadratic formula

$$G^*_{1,2} = \frac{-hpm\sqrt{h^2 - 4(-g)(-m)}}{-2m}$$
$$= \frac{h \pm \sqrt{h^2 - 4(g)(m)}}{2m}$$

Thus, there are two positive real solutions for glucose,G, if $h^2 - 4gm \geq$, 1 real positive solution if $h^2 = 4gm$, and no real solutions otherwise. For the latter case, $\beta \equiv 0$ in order to satisfy equation (14) = 0. If $B = 0$, then $G = \frac{a}{b}$. Thus, there are three potential equilbrium points for glucose, G^*, where

$$G^*_1 = \frac{a}{b}$$

(when $B^* = 0$), a constant depending on a $\neq b$ and

$$G^*_{2,3} = \frac{h}{2m} \pm \frac{\sqrt{h^2 - 4gm}}{2m}$$

when ($B^* \neq 0$)

We have two equilibria if $h^2 - 4gm \geq 0$

$$\begin{aligned}
\Rightarrow \frac{a}{b} &= \frac{h}{2m} + \frac{\sqrt{h^2 - 4gm}}{2m} \\
2m\frac{a}{b} &= h + \sqrt{h^2 - 4gm} \\
(2m\frac{a}{b})^2 &= (\sqrt{h^2 - 4gm})^2 \\
4m^2\frac{a^2}{b^2} - 4\frac{hma}{b} + h^2 &= h^2 - 4gm \\
\frac{ma^2}{b^2} - \frac{ha}{b} &= -g \\
G^* &= \frac{a}{b}(\frac{ma}{b} - h) + g
\end{aligned}$$

2. Now using the characteristic polynomial and setting $\lambda = 0$, we vary h. Next let the original $h = h_1$. This is obtained when setting $\lambda = 0$ where $h =$ constant for equilibria at

$$G^* = \frac{h}{2m} \pm \frac{\sqrt{h^2 - 4gm}}{2m}$$

This is obtained when setting $\lambda = 0$ where h=constant for equilibria at $G^* = \frac{h}{2m} \pm \frac{\sqrt{h^2-4gm}}{2m}$
1. For

$$G_2^* = \frac{h}{2m} + \frac{\sqrt{h^2 - 4gm}}{2m}$$

we get $h = h_1, h = h_2$ where $h_1 = 0.00154$, and $h_2 = 0.0007589$
2. For

$$G_3^* = \frac{h}{2m} - \frac{\sqrt{h^2 - 4gm}}{2m}$$

we get $h = h_2$.

J Table of Parameters

Table 7: Table of parameters

Parameter	Value	Units	Biological Interpretation	Reference
a	864	$\frac{mg}{dl \cdot d}$	Glucose production rate by the liver when G=0	[27]
b	1.44	$\frac{1}{d}$	Glucose clearance rate independent of insulin	[27]
S_{I0}	0.72	$\frac{ml}{\mu U dmg}$	Initial Insulin Sensitivity $\frac{ml}{\mu U d}$ (S_{I0})	[27]
c	0.72	$\frac{1}{mg}$	Conversion factor	Estimated
τ	*vary*	$\frac{1}{mg}$	Conversion factor	Estimated
$\hat{d}$	43.2	$\frac{\mu U}{d \cdot ml \cdot mg^2}$	Conversion factor	[27]
d	43.2	$\frac{\mu U}{mgd}$	Conversion factor	Estimated
e	20,000	$\frac{ml^2}{dl^2}$	Determines the inflection point of the sigmoidal function	[27]
f	432	$\frac{1}{d}$	Insulin clearing rate for muscle, liver, and kidney	[27]
g	0.06	$\frac{1}{d}$	β cell natural death rate at zero glucose	[27]
h	$0.84X10^{-}3$	$\frac{dl}{mg \cdot d}$	Determines β cell glucose tolerance range	[27]
m	$0.24X10^{-}5$	$\frac{dl^2}{mg^2 \cdot d}$	Determines β cell glucose tolerance range	[27]
j	0.1	$\frac{1}{d}$	Constant rate of fat accumulation	Estimated
k	270	$\frac{mg}{ml}$	Conversion factor	Estimated
p	50	$\frac{1}{d}$	Constant rate of fat degradation	Estimated
Λ	0.09	$\frac{ml}{mu}$	Conversion factor	Estimated
t	1	$\frac{dl}{mg}$	Conversion factor	Estimated