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DEVELOPMENT OF A COMPUTATIONAL MODEL OF GLUCOSE TOXICITY IN THE PROGRESSION OF DIABETES MELLITUS

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Abstract. Diabetes mellitus is a disease characterized by a range of metabolic complications involving an individual's blood glucose levels, and its main regulator, insulin. These complications can vary largely from person to person depending on their current biophysical state. Biomedical research day-by-day makes strides to impact the lives of patients of a variety of diseases, including diabetes. One large stride that is being made is the generation of techniques to assist physicians to "personalize medicine". From available physiological data, biological understanding of the system, and dimensional analysis, a differential equation-based mathematical model was built in a sequential matter, to be able to elucidate clearly how each parameter correlates to the patient's current physiological state. We developed a simple mathematical model that accurately simulates the dynamics between glucose, insulin, and pancreatic β-cells throughout disease progression with constraints to maintain biological relevance. The current framework is clearly capable of tracking the patient's current progress through the disease, dependent on factors such as latent insulin resistance or an attrite β-cell population. Further interests would be to develop tools that allow the direct and feasible testing of how effective a given plan of treatment would be at returning the patient to a desirable biophysical state.

1. **Introduction.** Hyperglycaemia is a physiological state characterized by excessive levels of the simple sugar glucose in the blood. Chronic levels of glucose in the blood have been described in the literature as a frequent symptom of a variety of metabolic diseases [39]. No other disease is more frequently associated with this condition than diabetes mellitus (DM), as hyperglycaemia is not only a symptom, but the principal aggravating factor of this disease that impacts the lives of over 25 million Americans and their families as of 2012, per the American Diabetes Association (ADA) [1]. Another key element beside glucose, that is always considered in DM is insulin. Insulin is a multi-domain peptide hormone produced by β-cells in

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the pancreas. Normally, its principal function is to regulate the metabolism of carbohydrates and fat by binding to the cell membrane of skeletal muscle and fat tissue to signal for the absorption of free-flowing blood glucose. However, the effectiveness of this signal can vary depending on multiple factors, including the nature of the insulin molecule, its receptor on the cell membrane's surface, the stability and nature of the cell membrane, the reactivity of the cellular environment, and a wide variety of considerations that are still amply being researched [6]. Nonetheless, the overall extent and impact these facets have upon the effectiveness of the insulin molecule to signal the absorption of glucose is collectively referred to as insulin resistance [26]. It has also been shown that fat-consumption exacerbates the rate at which this resistance progress [18, 27, 32]. As insulin resistance develops, the process of glucose absorption is hindered, and despite the body attempting to over-produce insulin to attempt and stabilize glucose levels, glucose begins to accumulate in the blood, commencing the manifestation of hyperglycaemia [29]. As insulin resistance develops, its comorbid impact on hyperglycaemia generates an unstable environment that impacts all of the biomolecule's in its vicinity, including lipids, proteins, and perhaps most importantly, DNA [24]. These genetic mutations cause changes in the kinetics of a variety of biomolecules, including the insulin hormone and its receptor. As one would expect, research has confirmed that this, in turn, over time, causes yet an even more severe manifestation of insulin resistance [44]. A graphical representation of this feedback loop [30] is observable in Figure 1.

These glucose-insulin dynamics are what define the form of diabetes mellitus known as Type 2 DM. Normally, Type 2 DM is distinguished from other forms of diabetes due to the body's unusual elevation in levels of insulin attempting to cope with its insulin resistance. This condition of elevated insulin concentration is denominated hyperinsulinemia [10]. However, if a diabetic does not take care of himself, his condition could be aggravated and pass on to more complicated stages of diabetes mellitus, including dependence on exogenous insulin. This may in fact sound contradictory, as previously mentioned, this condition is characterized by hyperinsulinemia, an excess of insulin, but eventually, the body is unable to sustain the level of production required to cope with this insulin resistance. The body then resorts to more extreme mechanisms of glucose elimination that do in fact lower blood sugar levels, but produce reactive oxidative species, generating a very unstable environment [31, 32]. This environment is eventually too unstable for even the source of insulin, the β-cells of the islet of Langerhans, to be able to survive.

In the end, this results in an overall inability to produce insulin all together, lowering the levels of insulin, but continuing to exacerbate the hyperglycaemia that has developed with pre-existing stages of diabetes [27, 33]. This final stage, characterized by the inexistence of β-cells, is denominated Type 1 DM, and was previously thought only to occur in juveniles. A graphical representation of the adverse effects of chronic hyperglycemia on β-cell function is shown in Figure 2. It has been demonstrated that what causes its appearance in the youth is a much more cataclysmic and abrupt death of β-cells we are yet to fully understand, but that adults can also develop this type of condition if not cautious with their nutrition [16]. With this level of understanding of what phenomena affect their rate of change, the dynamics of glucose, insulin, fat, and β-cell mass, one could develop an elementary model capable of simulating these dynamics.

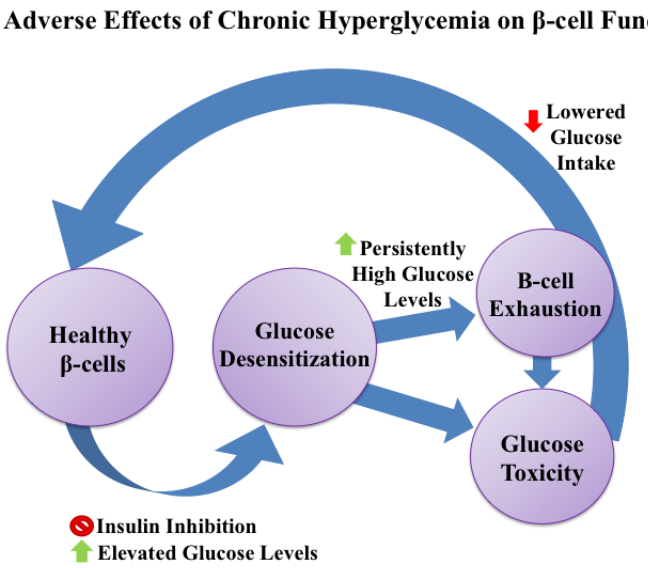

FIGURE 1. Initially, the β-cells in the pancreas function aptly at maintaining glucose homeostasis and they are said to be in a healthy state. However, when an ineffective communication is established between insulin and its receptor in the liver, the glycemic levels start to rise, leading to the development of a phenomenon termed glucose desensitization, the adaptive mechanisms the β-cell undergoes in response to this short exposure to high intakes of glucose. While the β-cell could return to a physiological status with moderation of food consumption, constant glucose ingestion could steer to a potentially pathological state in which concomitant β-cell exhaustion (depletion of the intracellular insulin reserve) and glucose toxicity (irreversible effects on β-cell function after prolonged exposure to hyperglycemic levels) are observed.

2. **Methodology.** Many authors have proposed models of the dynamics we are interested in, but their attempts have frequently recurred to over fit the data available and result in models that make biologically unreasonable assumptions [19, 42, 43]. Therefore, the approach we shall be taking is parting from the biological knowledge of the system, and constructing a model that eventually produces the behavior diabetes mellitus exhibits as it progresses. As what is understood are the factors that impact the rates of change of these populations, hence, the mathematical structure we implemented are differential equations. We utilize the simple Forward Euler Method programmed in Python 2.7 to simulate the evolution of the differential equations that will be derived from biological intuition.

2.1. **Modelling glucose-insulin dynamics.** It is clear that any given entity has parameters that increase and decrease their rates of change. Amongst these, the fundamental influences that will commence our construction of the mathematical model shall be the mutual effects of glucose and insulin on one another. The rate of change of glucose (G) decreases proportionally to the amount of insulin (I) in the

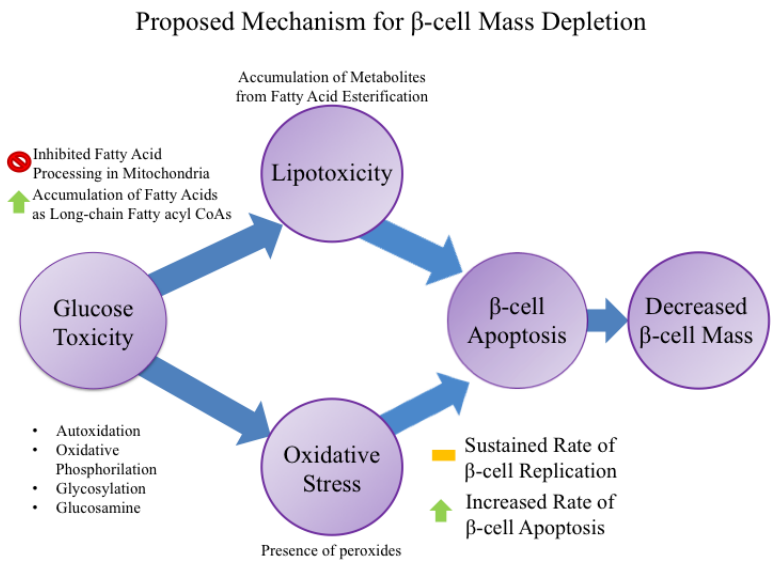

FIGURE 2. One of the proposed ways through which glucose toxicity leads to β-cell dysfunction and apoptosis is through the generation of chronic oxidative stress in the β-cell due to alternative methods of glucose processing that generate reactive oxidative species as products. These species have been observed to form peroxides that are highly toxic to some essential cellular organelles. Moreover, when hyperglycemia is complemented by hyperlipidemia, a subsequent accumulation of fatty acids as long-fatty acyl CoAs is observed in the cell. The chronic levels of fatty acids leads to the buildup of metabolites derived from fatty acid esterification which play a role in the aforementioned damages in β-cell function via mitochondrial stress. When damages to the organelles is detected by the cell, it undergoes a process of programmed cell death otherwise-known as β-cell apoptosis. While this critical level of oxidative stress increases the rate of apoptosis considerably, the rate of replication remains constant. Thus, this leads to a considerable depreciation of β-cell mass and, ultimately, a loss of glucose homeostasis.

system (variables and parameters in our models are detailed on Table 1). That is to say:

$$\frac{dG}{dt} = -bI \tag{1}$$

Now, insulin increases in response to the amount of excess glucose available in the system. Selecting $100\frac{mg}{dL}$ as the threshold value of glucose [35] would result in an equation like the following:

$$\frac{dI}{dt} = c(G - 100) \tag{2}$$

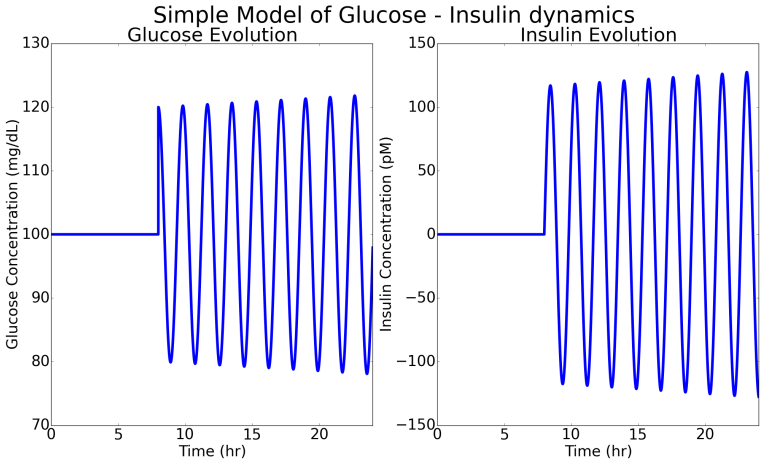

FIGURE 3. Simulation representing the fundamental assumption that glucose levels are reduced by insulin, whilst insulin increases in response to excess glucose. These phenomena are captured in equations 1 and 2. For this simulation we are using parameter values $b = 0.58$ that corresponds to amount of glucose absorbed per insulin molecule, and $c = 2 \times 10^{-5}$ that corresponds to the insulin release signal. Shortcomings of these graphs include the un-ending oscillations and the existence of negative concentrations of insulin. This was corrected by fixing $\frac{dI}{dt}$ to 0 when glucose concentrations are lower than $100\frac{mg}{dl}$. This characteristics was maintained in all further simulations.

Initiating a glucose spike of 20 $\frac{mg}{dL}$ corresponding to a breakfast at 8 am, [22, 34, 37] and simulating equations 1 and 2 utilizing a basic forward Euler method generates the graph observed in Figure 3. This figure generates the quite interesting and fundamental characteristic that these two populations oscillate with one another. However, it also has a series of characteristics that are biologically unfeasible. First off, insulin takes on negative values for its concentration, which is inaccurate for an individual. Moreover, these negative values are the reason glucose values increase, despite not having consumed any more food. This characteristic is necessary, and suggests the existence of a mechanism the body utilizes to increase glucose levels, even while fasting. Such a mechanism does exist and this would be glycogenolysis, the breaking of polymeric glycogen into its monomer, glucose, to restore the amount of glucose to a stable level. Selecting 120 $\frac{mg}{dL}$ as the threshold below which glycogenolysis is conducted, and selecting the amount of glycogen to be broken down to be proportional to the distance of its current level of glucose concentration from the threshold [39, 41]. One obtains the following equation:

$$\frac{dG}{dt} = a(120 - G) - bI \tag{3}$$

Simulating once again using equations 2 and 3, Figure 4 is produced. From this simulation, the satisfactory result of the values tending towards an equilibrium in between meals consumed at 8 AM, 12 PM, and 5 PM (breakfast, lunch, and

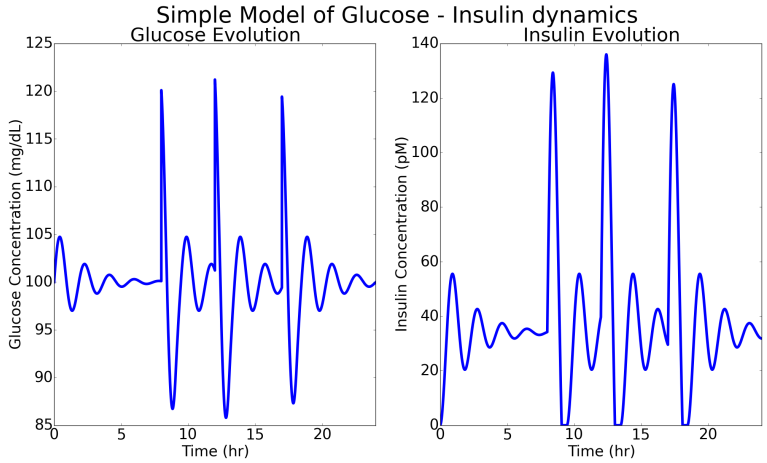

FIGURE 4. Glucose - Insulin dynamics model with glycogen breakdown. This model incorporates the breakdown of glycogen to restore glucose levels, and the previously mentioned elimination of negative insulin values. This is achieved by replacing the usage of equation 1 by equation 3. For this simulation we are using parameter values $a = 1$ that correspond to the glucagon production rate, $b = 0.58$ and $c = 2 \times 10^{-5}$ that corresponds to the insulin release signal. Incorporated corrections in this model include reducing oscillations over time, however, the model does not begin at an equilibrium. Moreover, the reason insulin reduces seems to be due to high levels of glucose, which is biologically unreasonable.

dinner, respectively) is obtained. However, just as glucose increased in an unrealistic manner in Figure 4, insulin decreases unrealistically as well and this needs to be taken into consideration. The reason $\frac{dI}{dt}$ would become negative and in turn cause a decrease in insulin levels was due to glucose going beneath the threshold level of 100 $\frac{mg}{dL}$. Insulin would then decrease proportional to the degree of glucose deficiency the system was under at the moment. This is not what happens physiologically, if not, insulin naturally diminishes due to its physiological half-life resultant of its clearance. Therefore, a correction factor that involves this half-life in our equation for insulin would then result in the following equation:

$$\frac{dI}{dt} = c(G - 100) - dI \tag{4}$$

This is not the only information Figure 4 offers. One can note that the system is noticeably perturbed even before its initial glucose intake at 8 AM. This is due to the initial values of 100 $\frac{mg}{dL}$ for G and 0 pM for I not being legitimate equilibrium values for G and I. Instead, one should set the differential equations to 0 and attempt to determine the values of G and I from here. This results in a system with 2 equations and 2 unknowns, which can be solved to result in the following two equations, where SSG and SSI are the values for Steady-State Glucose and

Steady-State Insulin, respectively:

$$SSG = \frac{120ad + 100bc}{ad + bc} \tag{5}$$

$$SSI = c\frac{SSG - 100}{d} \tag{6}$$

Simulating the new equations 3 and 4 with these new initial values (equations 5 and 6) results in the very well-behaved graphs of Figure 5 . Now, despite much work having been put in, these equations only offer information towards glucose-insulin dynamics, and truly contain no component that would drive an eventual development of diabetes mellitus. Nonetheless, as one varies the parameters a, b, c, and d, the form and behavior of the resultant simulations change. Therefore, what this suggests is that as diabetes mellitus progresses, what is truly occurring is that these "constants" are actually evolving, and they contain the manifestation of important features of disease dynamics.

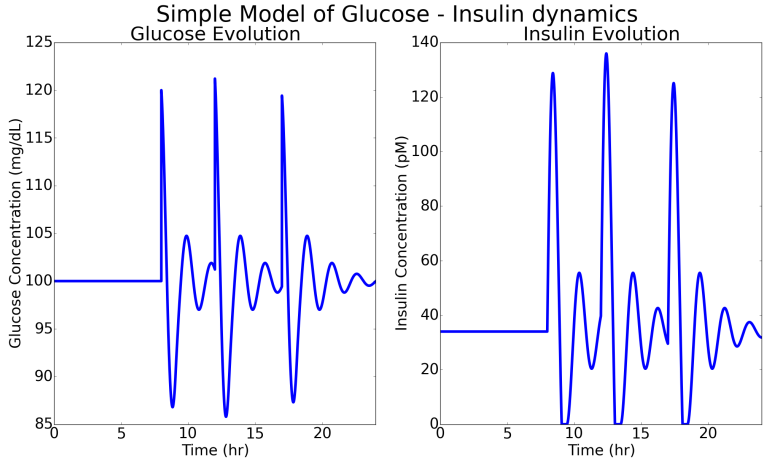

FIGURE 5. Glucose - Insulin dynamics model with baseline values. Simulation incorporating the existence of stable baseline values, and the incorporation of insulin half-life as the cause of its decay over time. These produced qualitatively satisfactory simulations of glucose-insulin dynamics. This is achieved by utilizing equations 3 - 6. For this simulation we are using parameter values $a = 1$, $b = 0.58$, $c = 2 \times 10^{-5}$, and $d = 4 * \ln(2) \approx 2.77$ that correspond to the insulin decay rate with an insulin half life of approximately 15 minutes.

2.2. **Dimensional analysis of dynamics.** We propose the usage of dimensional analysis to reveal the features each constant governs and how these may be determined. Table 1 contains a listing of each parameter, its determined value and corresponding units. The first we shall analyze is the last constant added (d), whose units should be $\frac{1}{hour}$ to satisfy the dimensions of equation 4. As previously stated, this component was incorporated to that equation to satisfy the notion of insulin's decay in the body. Therefore, the constant d is nothing other than a rate constant

that can be determined from the half-life of insulin. With this being reported in the literature to be approximately 15 minutes ($\frac{1}{4}$ hours), d can then be determined to be: $d = \frac{\ln 2}{\frac{1}{4}hr}$. Continuing on with the constant a of equation 3, one can observe it also has units of $\frac{1}{hour}$. However, it is not truly a decay constant, but instead it describes the amount of glycogen released per unit of deficiency of glucose, and also, it incorporates the average length of glycogen that is cleaved into simple glucose monomers. For its determination, we propose the observation of how glucose levels gradually rise after the injection and degradation of an insulin bolus.

Moving away from the simpler units of constants a and d, the constant b has a seemingly more complex dimensional measurement of $\frac{mg(Glucose)}{pmol(Insulin)} \times \frac{L}{dL \times hr}$. Focusing on the portion that relates Glucose and Insulin, one notes that these units are related to the amount of glucose that is absorbed per a given amount of insulin in the blood. This is effectively a measurement of how sensitive, or resistant, the muscle tissue is currently to insulin, so that it can begin to absorb glucose molecules. Therefore, the modulation of this constant would allow one to model the effects of insulin resistance. Figure 6 shows how reducing the constant b by a factor of 0.5 every 24 hours results in both hyperglycaemia, and hyperinsulinemia.

In addition, the constant c also has similar complex units of $\frac{pmol(Insulin)}{mg(Glucose)} \times \frac{dL}{L \times hr}$, and although it does seem to allude to a sensitivity of glucose, it is not of the muscle tissue, but the β-cells who produce the insulin in response to the glucose. If we assume that the β-cells in themselves remain equally responsive to changes of glucose, but that it is the amount of β-cells that gradually reduce, then a decay in the value of c could be related to the gradual death of the β-cell population. Figure 7 shows how reducing this constant by a factor of 0.5 every 24 hours results, similarly to the reduction of b in hyperglycaemia, but, quite distinctly, it does not result in hyperinsulinemia. Instead, as would our biological intuition suggest, the levels of insulin also diminish due to the body's inability to produce it anymore without β-cells.

Compounding these two effects at a rate of 0.7 for both constants, we obtain Figure 8. The results of this model are rather intriguing as we can see that the qualitative behavior of hyperinsulinemia and afterwards insulin deficiency that one would expect from the development of diabetes mellitus, is achieved as insulin resistance and β-cell decay occur at roughly the same rate. These experiments still are just qualitative in nature and suffer from the previously criticized practice of making unrealistic assumptions, such as the spontaneous generation of insulin resistance and death of β-cells every 24 hours. Therefore, it is our responsibility to incorporate elements that stem from nutritional habits and their influence on the glucose-insulin dynamics, and these elements will eventually generate these effects of β-cell decay and insulin resistance.

2.3. **Fat-enriched diets.** Each day, the simulation incorporates an injection of 20 $\frac{mg(Glucose)}{dL}$ corresponding to the person consuming a carbohydrate-rich meal. However, unhealthy feeding habits do not only have to do with our sugar intake, if not many other constituents such as vitamins, minerals, and, arguably most relevant, fat content. Many reports have established that consuming a diet rich in lipids and other hydrocarbons leads to the deposition of adipose tissue, which interrupts the effectivity of the signal processing that occurs between insulin molecules and the muscle tissue [11, 12, 15, 20, 25, 36, 46]. As the fat supply is adjunct with the subject's continuous consumption, the addition of fat should occur simultaneously to

TABLE 1. Parameters utilized for model development.

Parameter	Description	Value/Range	Units	References
G	Glucose	Initial calculated through SSG Variable	$\frac{mg}{dL}$	[3, 22, 23, 34, 35, 37, 39, 41]
I	Insulin	Initial calculated through SSI Variable	pM	[3, 23, 35]
F	Fat	Estimated SSG Variable $F(0) = 0$	TBD	[11, 12, 15, 20, 25, 36, 46]
a	Glucose from glycogen breakdown	$[0.5 - 2]$	$\frac{1}{hr}$	[3, 4, 7, 17, 23]
b	Glucose metabolized due to insulin release	$[0.5 - 0.8]$	$mg \times \frac{dL}{mg} \times \frac{1}{hr}$	[5, 13]
c	Insulin released in response to excess glucose	$[1.5 - 2.5] \times 10^{-5}$	$pM \times \frac{dL}{mg} \times \frac{1}{hr}$	[14, 35, 38, 40]
d	Insulin decay	$[2.5 - 3]$	$\frac{1}{hr}$	[28, 35]
g	Glucose elimination through oxidation	$[1 - 10] \times 10^{-5}$	$\frac{1}{hr}$	[2, 45]
$\phi(F)$	Insulin resistance function	$(h, i$ and j selected for this to span from approximately 1 to 0) Variable	Unitless	[11, 12, 15, 20, 25, 36, 46]
f	Fat consumption over time	$[4.5 - 7]$	TBD	[11, 12, 15, 20, 25, 36, 46]
k	Rate of β-cell death per oxidized glucose	$[0.01 - 0.001]$	$\frac{dL}{(hr \times mg(Glucose))}$	[11, 18, 27, 31, 32, 36]
β	β-cell population	$1,000,000$ initial Variable	β-cells	[8, 18, 31]

the subject consuming his glucose. This would result in a "step-like" function that gradually increases over time, as can be observed in Figure 9. Mathematically, this

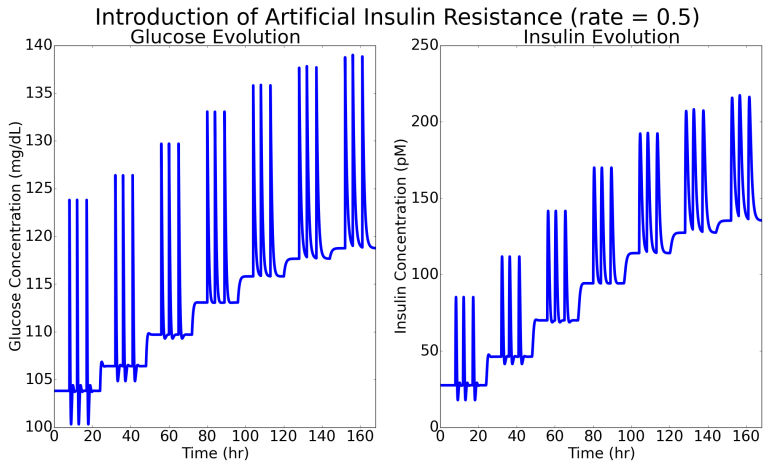

FIGURE 6. Insulin Resistance Model. Simulation utilizing the previously established glucose-insulin dynamics, with insulin resistance being artificially aggravated over time. Equations are the same as in Figure 5 with reducing values of b at each period of 24 hours by half (0.5) with an initial value of $b = 0.58$ and parameter values of $a = 1$, $c = 2 \times 10^{-5}$ and $d = 4 * \ln(2) \approx 2.77$.

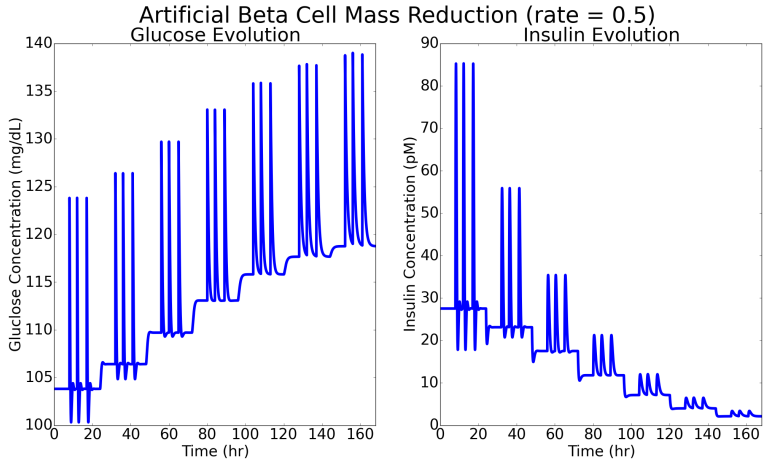

FIGURE 7. Simulation utilizing the previously established glucose-insulin dynamics, with $\beta-$cells being artificially decimated over time. Equations are the same as in Figure 5 with reducing values of c at each period of 24 hours by half (0.5) with an initial value of $c = 2 \times 10^{-5}$ and parameter values of $a = 1$, $b = 0.58$ and $d \approx 2.77$.

can be difficult to incorporate in an equation, but Figure 9 also shows that a linear function dependent on time can easily capture, especially over long periods of time such as weeks or days, this step-like increase in fat content. It is clear that although fat consumption is linear, it is not all deposited as adipose tissue, and the effect

of this deposition, has no reason to be linear itself as well. The dynamic observed suggests more of a latency period as the person accumulates weight, then a decadence period where the person's health begins to severely decline, until it reaches a point where it cannot realistically continue to get much worse than it is. This sort of description fits that of a logistic function that could be processing this fat intake and converting it into an impact of insulin resistance. These revelations about fat intake allow us to update equation 3 with the creation of two more equations that describe fat (F) and insulin resistance ($\phi(F)$):

$$\frac{dF}{dt} = f \tag{7}$$

$$\phi(F) = \frac{1}{h + e^{-iF+j}} \tag{8}$$

$$\frac{dG}{dt} = a(120 - G) - b\phi(F)I \tag{9}$$

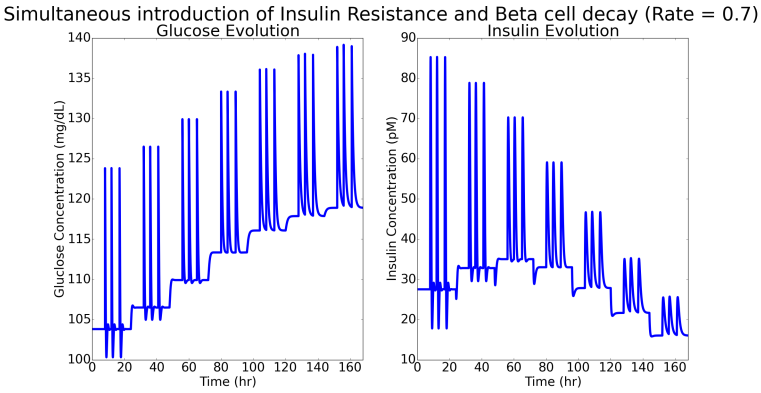

FIGURE 8. The incorporation of $\beta-$cell decay and Insulin Resistance was simulated simultaneously, to correlate their physiological importance with modelled disease progression. Development and decline of hyperinsulinemia is clearly observable. The observed simulation is the result of simultaneous reduction of constants b and c by a factor of 0.7 in the previously established equations 3 and 4 for insulin dynamics. For this simulation we are using parameter values $a = 1$, $b = 0.58$, $c = 2 \times 10^{-5}$ and $d = 4 * \ln(2) \approx 2.77$.

2.4. **Impact of hyperglycaemia on β-cell decay.** Hyperglycaemia that results from the gradual deposition of adipose tissue leads to a phenomenon known as Glucose Toxicity, where the body resorts to extreme mechanisms in an attempt to reduce the glucose concentration to feasible levels. As previously mentioned, the mechanism commonly utilized generates reactive oxidative species and, depending on how many are generated, more and more β-cells with susceptibility would die. Nonetheless, an underlying amount of β-cells with considerable resistance should remain, as the population is typically not completely obliterated, but instead continues slowly decaying. This suggests that there is an interaction between the

remaining β-cell population and any glucose that exceeds a given threshold. Selecting this threshold as 200 [21, 22] that is considered unusually high for a normal person, results in the following equations:

$$\frac{d\beta}{dt} = -k\beta(G-200) \tag{10}$$

$$\frac{dI}{dt} = c\beta(G-100) - dI \tag{11}$$

$$\frac{dG}{dt} = a(120-G) - b\phi(F)I - g(G-200) \tag{12}$$

It is important that one incorporate gating factors that do not permit factors, such as the ones just stated act before the threshold values are surpassed, and do not act if the parameter is below that given threshold. For example, if left incorrect, these equations would result in the β-cell population growing out of control whilst glucose is beneath 200, as its derivative will be positive. This is not true, as research reveals that the natural replication rate of β-cells is typically canceled out by its rate of apoptosis, resulting in a rate of change of 0 under non-extreme physiological conditions (See [8, 9, 18, 27, 31]).

With this final addition, it is now possible to model a disease dynamic that is only driven by the nutritional and metabolic patterns of the subject. Results of this model are present in Figure 10.

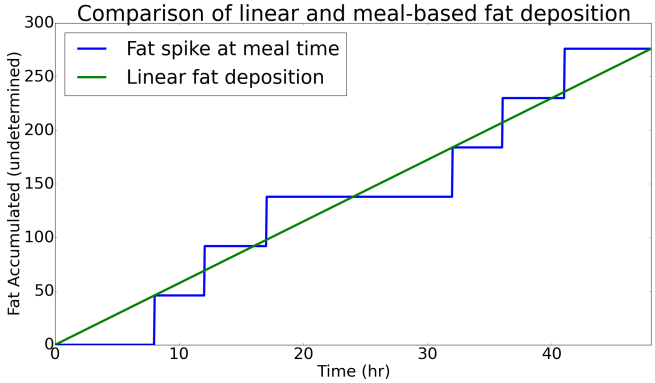

FIGURE 9. Inclusion of Fat deposition. Comparison of the usage of a step-like function of fat deposition, with that of a linear function. It is evident that this is a convenient way of achieving an equal effect.

3. **Conclusion.** Diabetes mellitus is definitely a complex disease that requires a lot of attention due to the vast population it impacts worldwide. Furthermore, the attention it requires should be provided in the most effective manner possible, for which tools that offer comprehensive understanding of the disease's dynamics must be crafted. The model we proposed has been constructed to align with the biological description of the system, and utilized very few unorthodox assumptions. We believe this model offers a prime example of how biomathematical models should be developed. Continuously, there was a cycle where a biological phenomenon suggested a certain set of equations, but after simulating them, one uncovered that

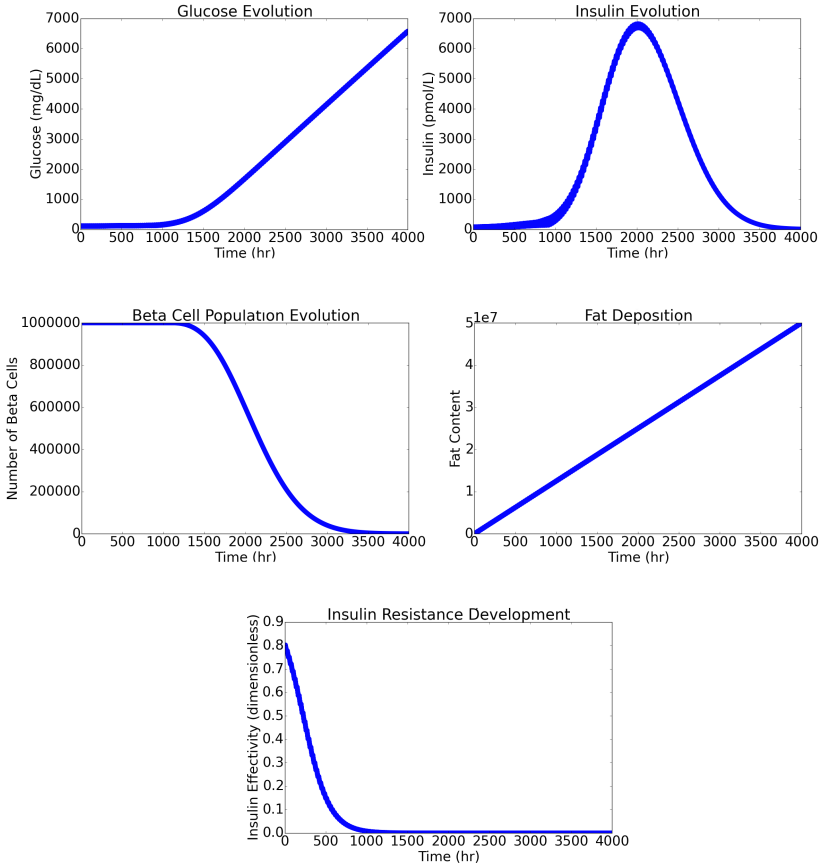

FIGURE 10. Complex Model of Glucose, Insulin, $\beta-$cell mass and Fat Dynamics. Simulation of insulin resistance progressing as a function of fat consumption, and $\beta-$cell decay being proportional to glucose in extreme excess. These factors are captured by the modified equations 7, 8 and 10 - 12. For this simulation we are using parameter values $a = 1$ that correspond to the glucagon production rate, $b = 0.58$ that corresponds to amount of glucose absorbed per insulin molecule, $c = 2 \times 10^{-5}$ that corresponds to the insulin release signal, and $d = 4 * \ln(2) \approx 2.77$ that correspond to the insulin decay rate with an insulin half life of approximately 15 minutes.

certain biological phenomena had been neglected. The gradual development of a model that included the feedback loop described in Figure 1 was not only powerful, but simple enough to continue shedding light on previously unconsidered aspects of the disease dynamics. Even with our careful approach on the modeling, Figure 10 in itself does not answer all questions with respect to how the disease progresses. For example, insulin concentrations seem to elevate to levels much too extreme for the β-cells to realistically sustain such a high concentration. Incorporating the notion of an insulin reserve could potentially shed light on the period in which a Type 2 diabetic becomes insulin dependent. Another possibility is to incorporate a change

in metabolic activity on behalf of the subject, and verify the possibility of reversing the progression of this vicious disease. Much work remains to be done, and perhaps the mathematical methods implemented are not the most rigorous. However, we cannot sacrifice insight for mathematical beauty, for our goal must be to reveal the truth behind these mechanisms, and that truth, might just as well be extremely complex.

4. **Future work.** As the model stands, it satisfactorily identifies fat deposition as the underlying mechanism to the disruption of glucose-insulin dynamics. However, characterization of fat consumption trends in healthy and unhealthy individuals, and the incorporation of an elucidated fat-deposition mechanism will be fundamental in understanding the effect the diet of the patient will have on disease progression. In addition, incorporation of contributions to fat deposition such as physiological activity to characterize fat removal in the system, will assist heavily in diagnosing a regimen for treatment in terms of recommended exercise and diet modifications. As it has been elucidated to be the driving force of disease progression, it is clear this work should be of utmost precedence. Thankfully, the methodical construction of this model would allow seamless integration of this data once adequate sources of experimental data are identified. Furthermore, with a complete and biologically feasible model, statistical characterization would be the stepping stone towards clinical implementation. Developing an adequate correlate between model predictions and patient prognosis would require extensive sensitivity analysis between parameters, as well as the identification of reliable clinical assays which could be developed to locate the patient's current state in terms of disease progression. This would require an extended collaboration of clinicians, laboratory specialists, and our own computational team to unravel this interdisciplinary problem of clinical implementation, and achieve the final goal of meaningfully impacting the patient.

Author's contributions. The authors declare that they have no competing interests. The conception and design of the project was originally proposed by MCA and modified collectively by all authors. The first draft of the manuscript and all coding for simulations and graphs was performed by DTPR. The flow charts on Figure 1 and Figure 2 as well as the narrative explaining the mechanisms that was crucial for our mathematical model was performed by VLTT. All the authors participated in revising the manuscript critically for important intellectual content. All authors have given final approval of the version to be published and agree to be accountable for all aspects of the work.

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