Insulin and GLP-1R Agonist Drugs in Type II Diabetes Management

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0 Abstract

The goal of the project was to evaluate the efficacy of exogenous insulin, glucagon-like peptide-1 receptor (GLP-1R) agonist drugs, and a combination of both in the treatment of type II diabetes. Type II diabetes causes the body to become insulin-resistant, resulting in dangerously high blood glucose levels. Untreated type II diabetes can lead to kidney failure, blindness, and an increased risk of cardiovascular disease. With over 35 million cases in the US, patients commonly take an exogenous insulin or GLP-1R drug to regulate their blood glucose levels. As such, understanding the dosing and effect of these drugs on the human body has become a critical field of research. For our study, we compared Humalog, a rapid-acting insulin, and Ozempic, a GLP-1R agonist drug. Through using known relationships between blood glucose, glucagon, and insulin, we expanded the Bergman Minimal Model to develop reasonable mathematical relationships between compartments using Hill models. Using our model, we developed an optimal dosing plan for a diabetic individual reaching a peak blood glucose of 225 mg/dL. Our model found that taking 4 units of Humalog per meal or 0.75 mg/wk of Ozempic can effectively control blood glucose to levels comparable to a healthy individual.

1 Introduction & Background

In the U.S., more than 35 million people have diabetes, and over 90% have Type 2 diabetes, specifically [2]. In healthy patients, we expect high blood glucose to result in the production of insulin, which drives metabolic processes like glycogenesis, fatty acid synthesis, etc. in order to store energy and regulate blood glucose [6]. On the contrary, decreased blood glucose causes the synthesis of glucagon, which drives reverse processes like glycogenolysis, fatty acid metabolism, and even gluconeogenesis in order to increase blood glucose. The result is an intricate negative feedback loop that keeps blood glucose relatively stable.

However, In type 2 diabetes, a person's body fails to respond to insulin in a normal manner, causing blood glucose to spike to dangerously high levels. As this process continues, diabetic individuals can develop damage to organ systems like the pancreas, which can further the severity of diabetes as insulin production is ceased altogether. If left unmanaged, constant levels of high blood glucose can lead to cardiovascular issues, nerve damage, kidney disease, and uncontrolled weight gain or loss. While there are many methods of coping and managing Type 2 diabetes, the main treatment for Type 2 diabetes is managing a person's insulin levels through insulin injection treatments (usually in the form of pens) such as Humalog and Novolog, or Glucagon-Like Peptide-1 agonist (GLP-1 Agonists) treatments like Ozempic and Trulicity.

Insulin injection treatments function by injecting an insulin analog directly into the patient. These insulin analogs will thus supplement the body's endogenously produced insulin with the intent of decreasing blood glucose to healthy levels. The second form of treatment, GLP-1 agonists, function by binding to GLP-1 receptors, which then stimulate glucose-independent insulin to be released into the bloodstream. Unlike direct insulin injections, GLP-1 agonists function by increasing endogenous insulin production instead of utilizing an external source of insulin. Common effects of GLP-1 agonist binding include insulin release, appetite suppression, and reduction of glucose output. Our mathematical model incorporates two drugs to treat insulin, Humalog and Ozempic. Humalog (generically known as Lispro) is a short-term acting insulin-injecting pen taken 10-15 minutes before each meal used to represent our direct insulin injection treatment option. Ozempic (generically known as Semaglutide) serves to represent our GLP-1 agonist drug, and is taken once a week to treat type 2 diabetes. The goal of the model is to analyze and draw conclusions on how Ozempic and Humalog work within the body to treat diabetes, while also providing a framework with which we can predict the effects of various treatment options on different individuals.

To accomplish this, we utilize mathematical pharmacokinetic pharmacodynamic (PK/PD) models to track the concentration and effect of Humalog and Ozempic as they move through various organ systems and

accomplish their goal of eliminating diabetic symptoms. PK modeling is essential in predicting the rate of drug transport and excretion, and serves as a foundation for estimating drug concentrations in various tissues. With the results of the PK model, we can then use PD modeling to predict how different drug concentrations in certain tissues can impact the body's physiological response. Combining these two models together allows us to determine how different drug dosing patterns and parameters can influence the effectiveness of the drug and its impact on various patient populations. These results would thus allow researchers to properly inform patients on treatments that would best alleviate and manage their symptoms and health.

2 Model Development

2.1.1 Conceptual Model

The following conceptual model was developed based on Bergman's Minimal Model of Glucose regulation [1]. Similar to the Bergman model, our model utilizes the concept of a "remote" insulin compartment to represent the time delay between insulin entering the bloodstream and the effect of insulin taking place. Our model extends the Bergman model by including a similar set of compartments to represent glucagon, which we expect to behave similarly to insulin from a pharmacokinetic standpoint. Additionally, a simple compartment model was developed to analyze glucose levels in the bloodstream as well. The interactions between the different compartments are represented by colored arrows, with green arrows representing upregulation and red arrows representing downregulation, allowing us to ultimately analyze the pharmacodynamic effects of our drug of interest as well. Lastly, a separate compartment to store bloodstream Ozempic levels was developed.

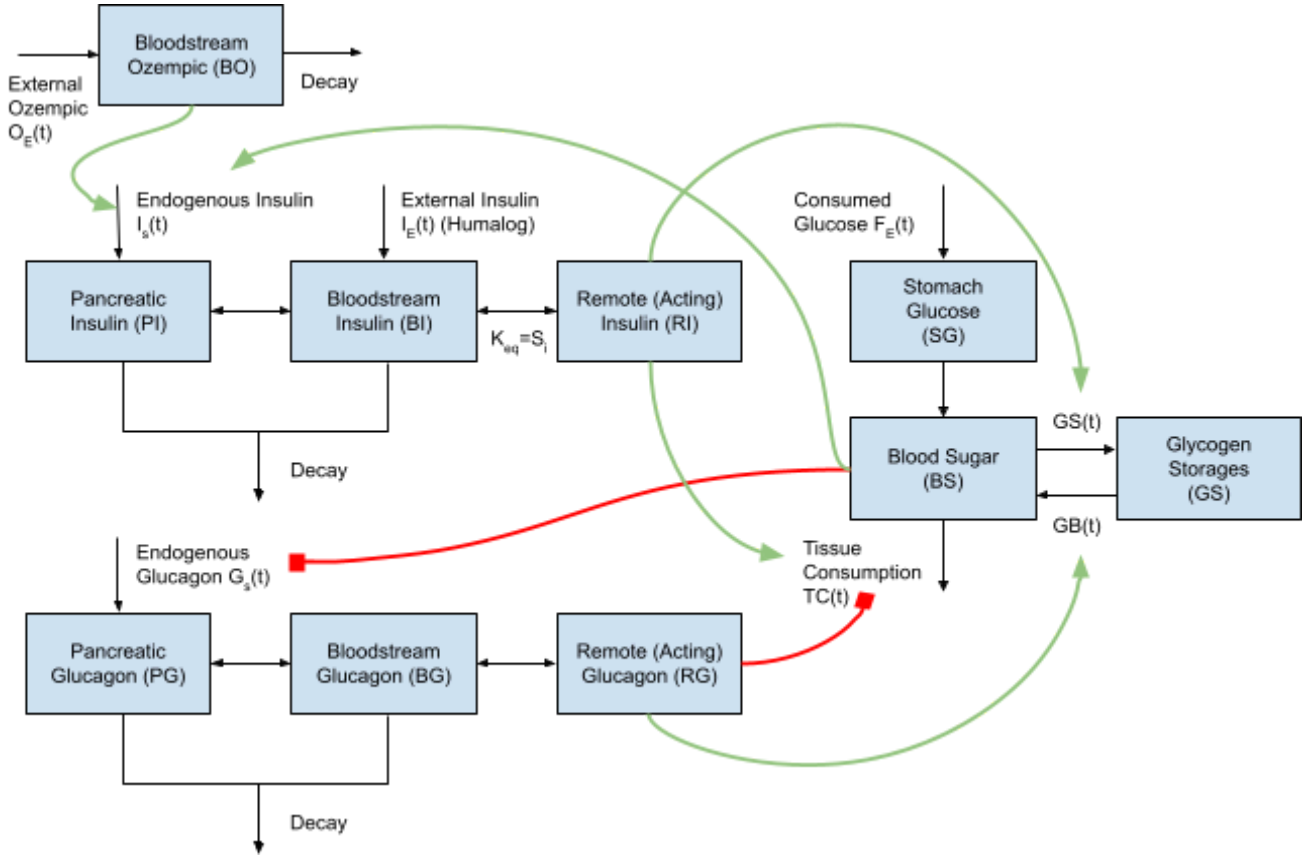


Figure 1: Conceptual Diagram for our Compartment Model

To understand the model relationships, we must first understand the relationship between glucose, insulin, and glucagon. As previously stated, we expect high levels of blood glucose to upregulate endogenous insulin production, as well as decrease levels of glucagon [6]. This is captured by our regulatory arrows where blood glucose inhibits endogenous glucagon production and boosts endogenous insulin production. The exact relationship between blood glucose is further explored in section 2.1.4. We also seek to capture the impact insulin and glucagon have on blood glucose. More specifically, we expect insulin to decrease blood glucose, while glucagon should increase blood glucose [6]. This can be captured in our conceptual model by having remote insulin upregulate glycogen synthesis and tissue consumption of glucose, both of which would remove glucose from the bloodstream. Similarly, glucagon will have the opposite effect of upregulating glycogen breakdown and decreasing tissue consumption of glucose. These relationships are further explored in section 2.1.4 as well.

Lastly, our model factors into account two different drug types. Humalog, which is an external insulin, is represented as a direct input into the bloodstream, $I_p(t)$ since Humalog is typically injected and would have a rapid effect on blood concentration [7]. Ozempic, a GLP-1 agonist, is also injected, and thus is also represented as a direct input into the bloodstream, $O_E(t)$, and follows a first-order decay rate as per assumption 6 below. Our model is also capable of modeling different diets by varying the consumed

glucose function, $F_E(t)$, which represents the rate of food entering the stomach. Glucose, once in the stomach, will diffuse into the bloodstream, from which it is either stored temporarily as glycogen or consumed by tissue undergoing respiration.

2.1.2 Key Model Assumptions and Facts

1) The movement of molecules from one compartment to another occurs mostly on a first-order basis. *Since no complex reaction occurs when a molecule like insulin travels from the pancreas to the bloodstream, first-order rate laws are the simplest way to capture this behavior.*
2) The behavior of upregulation and downregulation can be modeled as similar to Hill equations or genetic regulation. *Hill kinetics and genetic regulation equations are commonly used to analyze pharmacodynamic effects since they typically capture the idea of ligand-receptor binding effectively [8]. For example, we can treat glucose as a ligand, that upon binding, causes an increased rate of insulin synthesis. Alternatively, we pretend insulin/glucagon acts as an activator/repressor respectively, which can increase/decrease the rate of glucose consumption from its basal rate.*
3) Glycogen can store an infinite amount of glucose. *In reality, excess glucose is typically stored in adipose tissue as triglycerides, however, the modeling of this is complicated and can be simplified by assuming no upper bound in glycogen storage. A discussion in the conclusion is included to address approaches for eliminating this assumption.*
4) All glucose is either metabolized or stored, and none is excreted by the kidney. *Glucose is typically fully utilized in the body, and glucose present in urine is typically an indicator of kidney failure [9].*
5) To quantify type II diabetes, we use a normalized insulin sensitivity value. This value controls the equilibrium between bloodstream insulin and remote insulin. *Smaller sensitivities result in decreased remote insulin for the same bloodstream insulin, which can be interpreted as a diabetic individual being less receptive to insulin. This value is defined similarly by the Bergman model [1]*
6) A combined decay term is used to represent the half-life of hormones, which accounts for the effects of both the liver and the kidney. *Half-life is a commonly researched pharmacokinetic parameter and is thus the easiest way to quantify elimination [10].*

2.1.3 Key Parameters

Parameter	Description and Justification
$I_E(t)$	**External insulin** - Injected directly into the bloodstream from our drug of choice, Humalog. The dosing schedule is described in more detail below. Once in the bloodstream, external insulin functions similarly to endogenous insulin, just with

	a different half-life.
$O_E(t)$	**External Ozempic** - Injected directly into the bloodstream. Ozempic acts as an activator for insulin secretion. Once in the bloodstream, Ozempic decays at a first-order rate. The dosing schedule is also described in more detail below.
$F_e(t)$	**Input glucose** - This function depends on the type of food eaten, its glycemic index, and when it's eaten. Higher glycemic foods result in larger $F_E(t)$, and thus higher blood glucose. More complex carbs result in $F_E(t)$ being spread over a longer period of time. For example, eating simple sugars like candy bars can be modeled as delta functions, while complex carbs like whole wheat can be modeled as rect functions.
S_i	**Insulin sensitivity -** Represented mathematically as the ratio between the rate of bloodstream insulin towards remote insulin and the reverse rate. Lower S_i results in increased bloodstream insulin needed to have the same metabolic effect. This value differs from person to person and is the key indicator of the severity of diabetes.
$I_s(t)$	**Endogenous insulin secretion rate** - Regulated by bloodstream glucose levels. Insulin is directly secreted into the pancreas, and can subsequently move to the bloodstream.
$G_s(t)$	**Endogenous glucagon secretion rate** - Regulated by bloodstream glucose levels. Glucagon is directly secreted into the pancreas, and can subsequently move to the bloodstream.
GS(t)	**Glycogen synthesis rate** - Higher GS(t) indicates more glucose is being siphoned into glycogen, and is upregulated by high levels of remote insulin
GB(t)	**Glycogen breakdown** - Similar to GS(t), GB(t) is regulated by high levels of glucagon. High levels of GB(t) result in increased blood glucose and breakdown of glycogen stores
TC(t)	Amount of **glucose consumed** by the body - There is a baseline rate of glucose being consumed, which can be further increased or decreased by the amount of remote insulin or glucagon

Table 1: Table of Key Model Parameters

The table above summarizes key parameters and functions that underlie the model. A list of all parameters and their values, such as each chemical's decay rate and movement rate constants, is provided in the appendix table 1A and 2A.

For our choice of $F_E(t)$, we chose to have our individual eat 3 meals at 7 AM, 12:30 PM, and 6 PM. The meals sum to roughly 2400 calories, which is the typical calorie requirement of an average human male [11]. Converting to an equivalent amount of glucose yields around 200g of glucose per meal if the source of calories is exclusively glucose. We created two sample diets, one where the individual eats candy as their source of calories (foods with high glycemic index), and a more realistic diet of oats and beans

(foods with low glycemic index). For the candy diet, $F_E(t)$ is modeled as delta functions with an area of 200g since glucose is readily available for the body [12]. On the other hand, for the oat and bean diet, $F_E(t)$ is modeled as a rectangle function over 2 hours, also with an area of 200g, since complex carbohydrates take more time for the body to process.

Both $I_E(t)$ and $O_E(t)$ are represented as delta functions as well since both drugs are injected into the body. The amount of drug varies depending on the individual, and part of our modeling goal is to sweep through different dosages to determine the optimal dosing to keep blood glucose levels normal. For Humalog, individuals take their doses 15 minutes before every meal, while Ozempic is a once-weekly injection [13][14].

Lastly, S_I will also vary depending on how diabetic an individual is. For our model, we utilize a normalized S_I value, where a healthy individual has an S_I value of 1. Depending on the severity of diabetes, S_I will decrease significantly. A parametric sweep of varying S_I as well as G_I (the same concept except for glucagon) is analyzed in our model results, and can be used to estimate parameters for different patients by measuring their blood glucose following a sugar (high glycemic index) meal. To analyze the efficacy of our model, we created two virtual patients with identical parameters, only differing in S_I: A healthy patient with $S_I = 1$ and a severely diabetic patient with $S_I = 0.55$.

2.1.4 Pharmacodynamic Relationships

A key goal of our pharmacodynamic model is to accurately capture our external drugs' effect on bloodstream glucose. In this section, we present the key equations involved in our pharmacodynamic model, focusing on the equations developed for $I_s(t)$, $G_s(t)$ and TC(t). The equations representing GS(t), and GB(t) follow nearly identical forms and thus are listed in the appendix along with the remaining first-order differential equations with numerical values for all constants listed.

As per assumption 2, we treat glucose as a repressor for glucagon production, $G_s(t)$, and an activator for insulin production, $I_s(t)$. Further, we know Ozempic, which is a GLP-1 agonist, also increases endogenous insulin secretion, so we consider Ozempic as a second activator of insulin production. In general, because we are treating activation and repression in a gene regulation context, we can model activators using the equation $r = \frac{k_m[A]^n}{K^n+[A]^n}$, or $r = (1 + \frac{k_m[A]^n}{K^n+[A]^n})$ for activators in which we still expect some basal production rate, such as is the case with Ozempic. On the other hand, repressors can be modeled as $r = \frac{k_m K^n}{K^n+[A]^n}$. To capture the activating effects of both Ozempic and glucose on insulin production, we multiply the two equations together, pulling out any coefficients to yield:

$$I_s(t) = \left(\frac{k_{BS}[BS]^{n_I}}{K_I^{n_I}+[BS]^{n_I}}\right) \cdot \left(1 + \frac{k_O[BO]^{n_O}}{K_O^{n_O}+[BO]^{n_O}}\right)$$

$$G_s(t) = \left(\frac{k_g K_g^{n_g}}{K_g^{n_g}+[BS]^{n_g}}\right)$$

Tuning the parameters to fit experimental data yields the graphs below. (Note that the insulin curve is plotted for when [BO] = 0. Values and explanations for all coefficients can be found in appendix table 1A and 2A.)

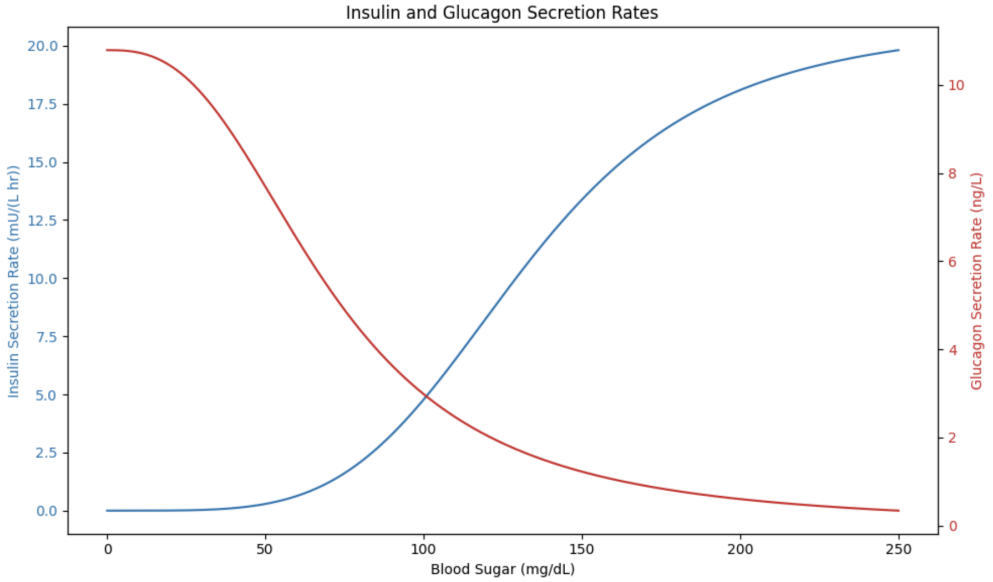


Figure 2: Hill Models for Insulin and Glucagon Secretion

The formula for tissue consumption follows a similar logic, whereby remote insulin (RI) serves as an activator, while remote glucagon (RG) serves as a repressor. Additionally, we wanted to capture that the rate of tissue consumption is proportional to the blood glucose levels themselves since glucose transporters mainly functioned via passive diffusion [15]. This, combined with the baseline metabolic demands yielded the equation below:

$$TC(t) = k \cdot \frac{[RI]^{n_{RI}}}{K_{RI}^{n_{RI}}+[RI]^{n_{RI}}} \cdot \frac{K_{RG}^{n_{RG}}}{K_{RG}^{n_{RG}}+[RG]^{n_{RG}}} \cdot [BS] + k_0$$

Although it appears complex, the above equation is simply the product of two hill equations, one for remote insulin as an activator, and one for remote glucagon as a repressor, all scaled by the individual's blood glucose level. Additionally, there is a factor k_0 representative of the baseline consumption of glucose. The result is an equation that results in faster tissue consumption of glucose when insulin is high

and glucagon is low, while still always maintaining a baseline consumption rate that can be interpreted as the metabolic demands of vital organs like the brain or the heart.

3 Model Results

3.1 Validating Model Response

To evaluate whether our model's results are reasonable, we simulate the blood glucose (mg/dL), blood insulin (mU/L), and blood glucagon (pg/mL) levels throughout the day given three meals of 200g of simple carbohydrates, or foods with a high glycemic index, (modeled as "candy meals") for two virtual patients as stated in the model development. Illustrated in Figure 1 below, we see the expected spike in bloodstream glucose as soon as the meal is consumed, resultant spike in bloodstream insulin levels, and a dip in bloodstream glucagon level as bloodstream glucose increases. These values peak at 216.7 mg/dL and 92.9 mU/L for bloodstream glucose and insulin respectively and we see a minimum blood glucagon value of 15.7 pg/mL for our healthy patient. Two hours after the meal, the healthy patient's bloodstream glucose level is approximately 132.2 mg/dL, below the accepted threshold for healthy individuals of 140 mg/dL[5]. For a diabetic patient (Figure A1), we see that the bloodstream glucose level has a higher peak than that of a healthy individual with a maximum value after a 200g meal of 248.1 mg/dL. Additionally, we find that our diabetic patient has a higher maximum value of bloodstream insulin at 102.9 mU/L and a lower minimum bloodstream glucagon value at 10.0 pg/mL. Two hours after the meal, our diabetic patient's bloodstream glucose level is approximately 227.7 mg/dL, above the ideal threshold for diabetic patients being treated of 180 mg/dL[5]. Thus, we can confirm that our model is capable of capturing reasonable blood glucose results for diabetic individuals.

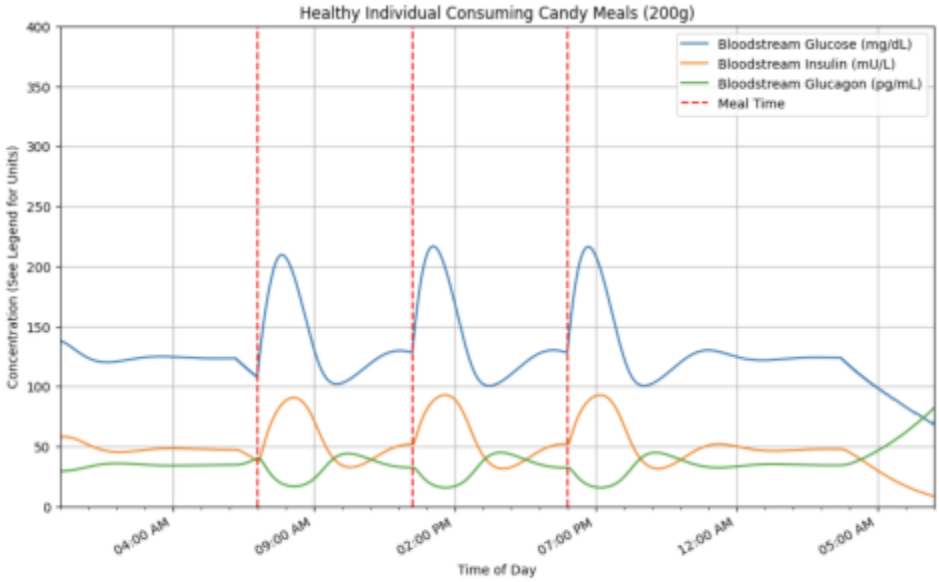
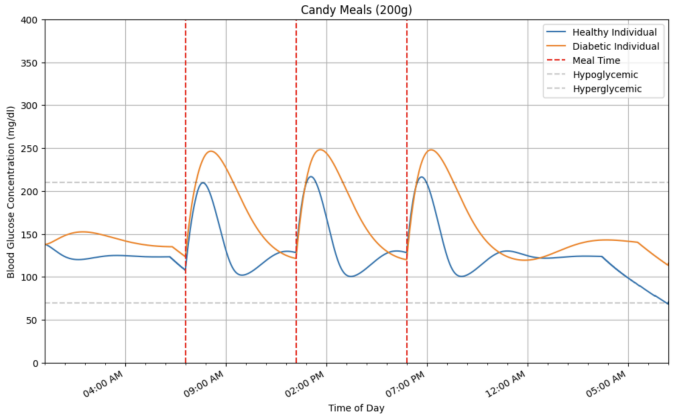


Figure 3: Healthy Patient on Simple Carbohydrate Meals

3.2 Effect of Meal Types in Diabetic Patient Bloodstream Levels

Given the wide variety of food consumed by individuals, we sought to model bloodstream responses to meals of predominantly simple carbohydrates ("candy meals") and complex carbohydrates for both healthy and diabetic patients. We see from our results that healthy and diabetic patients respond similarly to simple carbohydrate meals (Figure 4A) and similarly to complex carbohydrate (foods with a low glycemic index) meals (Figure 4B), following a rapid increase in bloodstream glucose levels after the "candy meal" and a slower increase in bloodstream glucose levels after the complex carbohydrates meal. However, as expected, we see that the diabetic patient has a higher peak bloodstream glucose level, 248.1 mg/dL vs 216.7 mg/dL for the candy meal and 226.0 mg/dL and 184.5 mg/dL for the complex carbohydrate meal for diabetic vs. healthy patients respectively. Additionally, we find that the diabetic patient has a longer recovery time, or takes more time to return to baseline bloodstream glucose levels than the healthy patient after meals, averaging 3.0 hours and 1.6 hours for the simple carbohydrate and 3.2 hours and 1.7 hours for the complex carbohydrate meal for diabetic vs. healthy patients respectively.

A.



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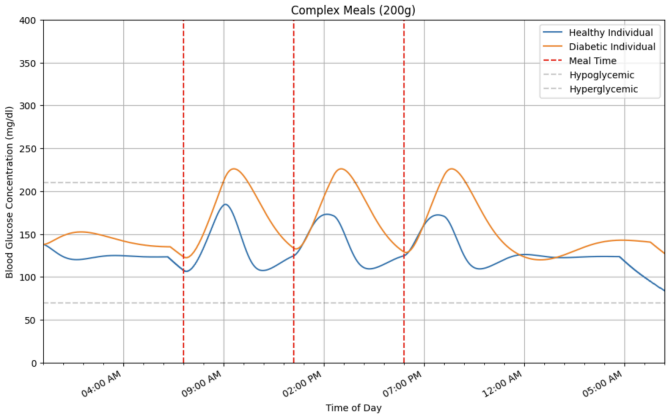


Figure 4: Simple vs. Complex Carbohydrate Meals

3.3 Classifying Virtual Patient Population

To effectively utilize our model, we recognize that each individual will have different degrees of insulin sensitivity, glucagon sensitivity, among other parameters. To visualize how different values in our parameter space correspond to different measurable biomarkers, a parameter sweep was conducted on insulin sensitivity and glucagon sensitivity, shown in Figure 5 below. The projection on the xy plane visualizes the value of the maximum bloodstream glucose concentration. The red diabetic region indicates individuals with peak blood glucose values >200 mg/dL. The green healthy region indicates a blood glucose between 175 mg/dL and 200 mg/dL, and the yellow region represents individuals with low blood glucose <175 mg/dL. Notably, the two virtual patients with normal glucagon sensitivity and SI of 0.55 and 1 selected thus correspondingly fall in the severely diabetic range and healthy range respectively. As expected, decreased insulin sensitivity causes increased blood glucose, while decreased glucagon

sensitivity causes decreased blood glucose. This parameter sweep can be used to assist in personalized medicine, as any individual's max blood glucose level could be matched with a unique set of parameters, and subsequent treatment plans can be tested on this virtual patient. However, more parameter sweeps across multiple different biomarkers must be conducted to effectively fit parameters to individual patients.

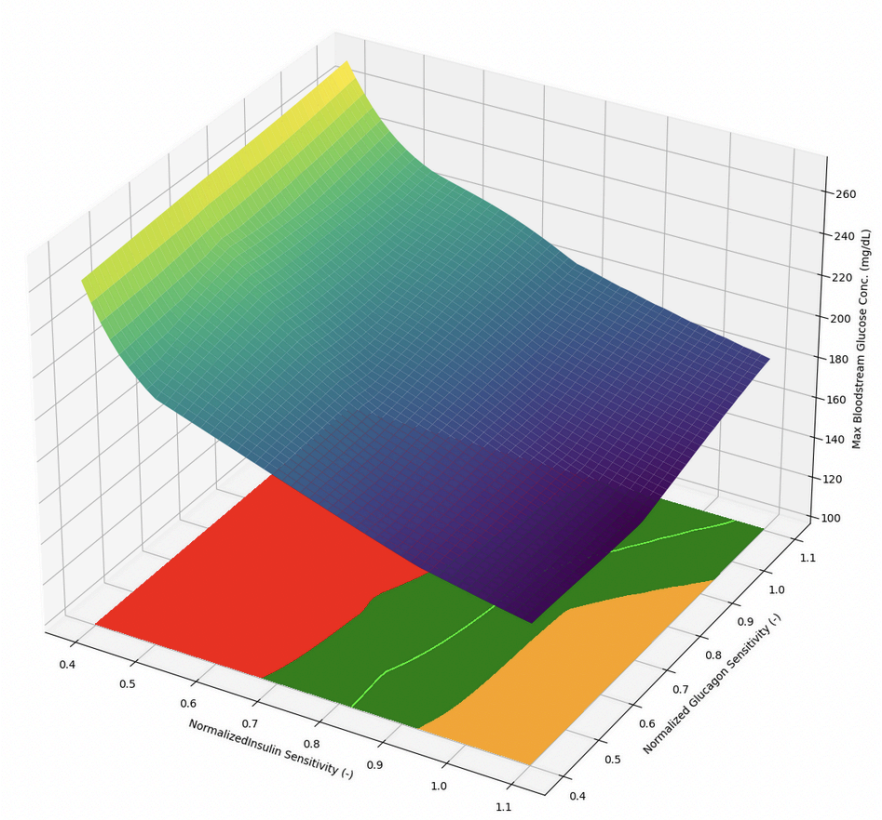


Figure 5: Parametric Sweep of Different Sensitivity Values

3.4.1 Analysis of Ozempic vs. Humalog Treatments

Using our model, we identify optimal dosing strategies for our chosen diabetic virtual patient, either through a combination of both drugs, Humalog alone, or Ozempic alone. To do so, we created a 3D plot (Figure 6) to show maximum bloodstream glucose concentrations after consuming a complex carbohydrate meal with varying doses of Humalog and Ozempic (y- and x- axes respectively). The projection on the xy plane visualizes the effectiveness of these therapies, with the effective treatment regimens colored in dark green and the most optimal relationship between Ozempic and Humalog as a combination treatment is indicated by the light green line (maintains a peak of 185 mg/dL for the bloodstream glucose concentration). The same projection as Figure 5 is used for this figure as well. When we vary the dosing for Ozempic (GLP-1 agonist) and Humalog (our exogenous insulin injection), we see that the optimal dosing for a combination treatment of the two drugs is around 0.5 mg/week Ozempic and

2 units Humalog, resulting in a peak blood glucose of around 185 mg/dL. Additionally, we see that treatments of only Ozempic or only Humalog yield effective results within ranges of 0.75 mg/wk and 4 units/meal respectively. Any doses greater than these ranges (either combination or lone drug) result in low blood glucose levels after meals, and any doses less than these result in higher blood glucose levels than advised. Note that this optimal treatment applies only for our specific virtual patient. Different individuals will have different SI values and thus will have a different treatment curve.

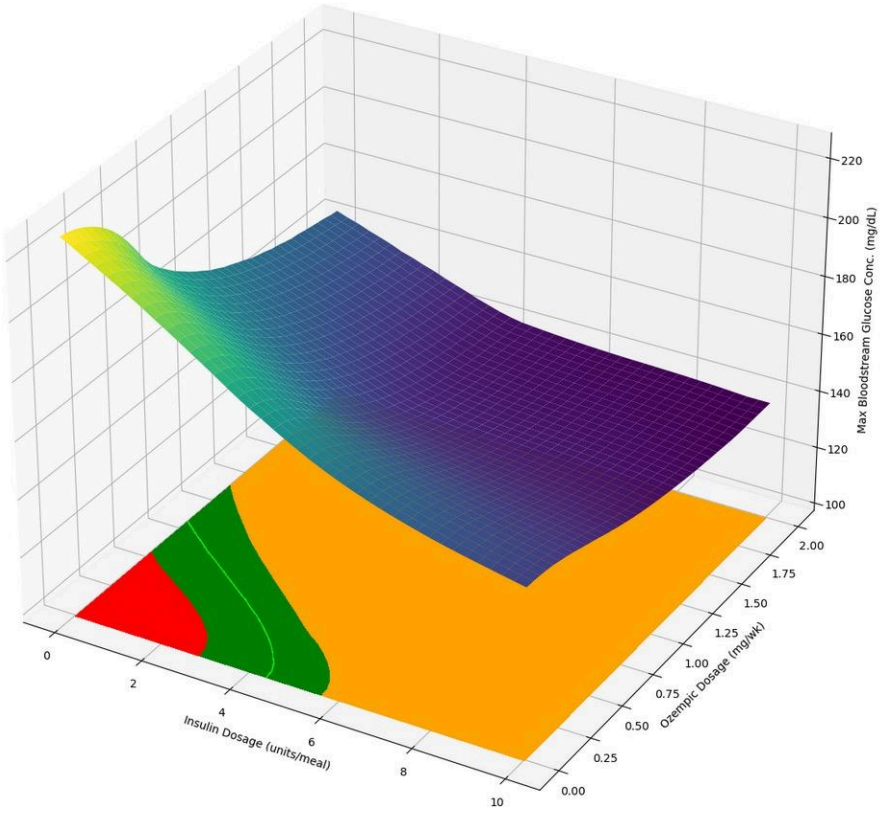


Figure 6: Parametric Analysis of Bloodstream Glucose Response vs. Humalog and Ozempic Dosages

3.4.2 Treatment Variations

Using our successful treatments from the aforementioned parametric analysis, we can evaluate the results of these dosing strategies by comparing the bloodstream glucose levels to the baseline healthy individual and diabetic individual without treatment. To quantitatively evaluate our proposed treatments, we compare peak bloodstream glucose concentrations and bloodstream glucose recovery times from Figure 7 below. For the glucose concentrations, we see that our healthy individual has a maximum of 183.9 mg/dL, diabetic without treatment has a maximum of 225.9 mg/dL, treatment with 4 units of Humalog/meal maxes at 188.2 mg/dL, treatment with .75 mg Ozempic per week maxes at 187.7 mg/dL, and a combination treatment of 2 units of Humalog per meal and .5 mg Ozempic per week maxes at 185.7 mg/dL. In terms of recovery time, it takes 1.71, 1.68, 1.94, and 1.76 hours for the healthy individual,

diabetic individual treated with Humalog only, diabetic individual treated with Ozempic, and diabetic individual on combination treatment only to return to baseline bloodstream glucose concentrations; in contrast, it takes the diabetic individual 3.20 hours to return to baseline levels. These results indicate that any of the three treatment options we model successfully regulate bloodstream glucose concentrations within a reasonable window of time, and the diabetic individual on treatment of only Ozempic has a marginally more "normal" response to glucose, although these results depend heavily on our parameters tuned above.

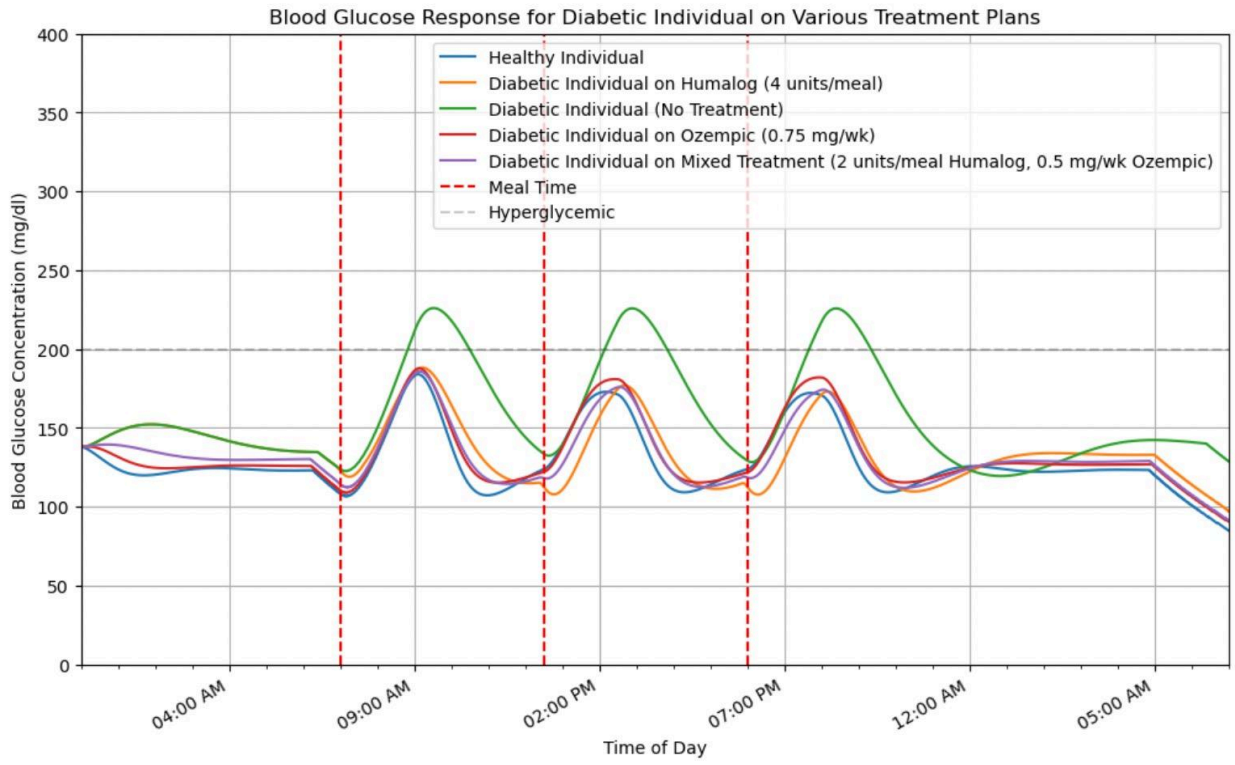


Figure 7: Blood Glucose Responses to Varied Treatment Strategies

4 Discussion

Our model has been shown to capture key physiological trends in response to individuals consuming food, and can model different behavior for individuals with different severity of diabetes and diet preferences. We validated our mathematical model by predicting the physiological response to consuming meals for a healthy and diabetic virtual patient. Additionally, we used our model to predict optimal dosing strategies for a severely diabetic virtual patient and found that they fall in line with clinical recommendations [13][14]. The suggested drug dosages were shown to combat the effects of low endogenous insulin production and prevent plasma glucose concentration from rising to dangerous levels when the patient eats a meal. Additionally, our model provides an avenue for rudimentary prediction of

the interactive effect of taking multiple drugs at once, and thus can serve as a starting point to provide confidence intervals for clinical trials. In fact, this is arguably the greatest purpose for our model, as we are now able to test a large variety of experimental setups relating insulin treatment and diabetes instantaneously on a virtual population. By using a parameter sweep to match real, experimentally measured biomarkers such as peak blood glucose, etc., we can construct a profile of any unique patient and test a variety of treatments to determine effectiveness.

4.1 Sensitivity Analysis

Parameter	% Change in Parameter	% Change in Max Bloodstream Glucose	% Change in Recovery Time
$k_{d,I}$	+10%/-10%	+4.73%/-4.47%	+13.10%/-11.02%
$k_{d,G}$	+10%/-10%	-0.76%/-3.12%	+1.12%/+4.37%
k_0	+10%/-10%	+2.56%/-2.79%	+0.42%/-1.04%
K_g	+10%/-10%	+2.17%/-1.21%	+8.65%/-5.06%
K_I	+10%/-10%	5.57%/-4.96%	10.34%/-7.81%

Table 2: Sensitivity Analysis Results

A sensitivity analysis was performed on our model to determine the robustness and flexibility of our model. Five key parameters were selected to adjust, $k_{d,I}$, the insulin decay rate, $k_{d,G}$, the glucagon decay rate, k_0, the rate of transfer of glucose in the stomach to the bloodstream, K_g, the concentration of glucose at which glucagon secretion is repressed by 50%, and K_I, the concentration of glucose at which insulin secretion is activated by 50%. As shown, changing any of these parameters by 10% does not result in a disproportionately increased change in our two key output metrics, maximum bloodstream glucose and recovery time. These results indicate that our model is relatively stable, and isn't overfit to select key parameters. Additionally, this indicates that our model can represent different patients by subtly tweaking different parameters to match the measured values for each specific individual, without fear of the model becoming overly chaotic.

4.2 Strengths and Weaknesses

To start, our model produces reasonable physiological responses to consuming a variety of meals. Additionally, a key strength of the model lies in its ability to test novel and potentially unsafe treatment combinations in a virtual space. Although our results do not truly reflect the real world, they can serve as very real guides and estimates to improve the efficacy and timing of clinical trials. In addition, our model captures many different parameters to explain the complex physiology that underlies glucose metabolism, ranging from insulin sensitivity, glucagon sensitivity, and food uptake rate to name a few. In doing so, our model thus has a large parameter space to work with that can enable our model to more accurately capture a diverse population pool.

However, as with all mathematical models, our model is not without significant limitations. For example, our model only takes into account glycogenesis and glycogenolysis as the major metabolic processes regarding storing and releasing glucose. As a result, we are unable to model the long term storage of glucose into fats, and by extension, our model performs poorly when examining patients in a prolonged fasting state. Because of this, we see our virtual patients "starve" if they do not regularly consume meals on a daily basis, with blood glucose levels eventually approaching zero. Additionally, our model does not completely capture all the mechanisms regulating blood glucose. For example, our model does not account for the inhibitory effect of Ozempic on glucagon secretion.

Lastly, and perhaps less of a limitation of our specific model but more of mathematical models in general, it is impossible to fully capture the underlying physiological details for each individual. As such, our model will only at best provide a prediction interval for the effect of different treatment options. We must keep this idea in mind as we make decisions and analyze the results of our model. What we have provided is simply a model of the real world, and not reality itself.

4.3 Incorporating Weight Loss in Future Work

The "miracle" weight loss effect of drugs like Ozempic is a major factor for its belting into prominence. Therefore, an extension of our model could be used to simulate these weight loss effects. To do so, we must understand the most important factors of weight and, more specifically, body composition which are most basically represented as a thermodynamic relationship between energy consumed and energy exerted, most typically in units of kilocalories.

Energy consumed is directly related to the food that we eat. The three primary macronutrients that make up our food are proteins, fats, and carbohydrates, each of which has a specific caloric value which are 9 kcal/gram, 4 kcal/gram, and 4 kcal/gram respectively. However, the exact attribution of each macronutrient and its energy value, as well as its particular use in the body is beyond the scope of the original model and this exercise. Therefore, using the value of 4 kcal/gram of carbohydrate as our

conversion factor for glucose will be sufficient in outlining the theory of the model. The glucose input function of the model can easily be converted to an energy input model.

Additionally, we consider glycogen stores in the development of a weight loss function. Glycogen stores, typically in muscle tissue, are a fast acting alternative to breaking down tissue for supplementing glucose levels. This means that upon entering a calorie deficit the body does not immediately shift to a catabolic phase and start to burn fat. Glycogen stores must first be depleted to a level where their conversion to glucose still does not meet the needs of the system. Therefore, we propose a factor, most likely implemented as a Hill function, that relies on remote glycogen levels to indicate a shift of the body from fat anabolism to catabolism.

This brings us to Ozempic's particular effect on this weight loss extension of the model. Ozempic's primary effect is to support insulin in converting plasma glucose into glycogen. A secondary action of this is that glycogen plays a dominant role in signaling hunger. Hunger is felt when the body's glycogen stores have been depleted. Therefore the sustained effects of converting glucose to glycogen means that satiety is felt sooner and lasts longer. With less hunger, there will be diminished food uptake and thus less energy input to the system.

To address the energy consumed portion, a standard method to determine the amount of energy exerted by a person is using a Typical Daily Energy Expenditure (TDEE) calculator. The calculator uses information such as sex, height, weight, body fat percentage, and general details of your lifestyle to give an estimate of the number of kilocalories you can expect to use in a day. These calculators are ubiquitous and have more than enough accuracy to outline energy exertion for the average population.

With those two parts of the model accounted for we can now join them together to give a general weight function. For this weight function we will primarily only focus on weight gained or lost in grams of fat. This is a reasonable assumption given that fat loss and gain is a much more expedient process than say muscle tissue loss and gain, which particularly relies on an anabolic regimen to facilitate growth. A general conversion is that it takes approximately 7700 kilocalories to gain 1 kilogram of fat and with that we have the last main component of the model.

Compiling all the components gives us a basic weight loss function that looks like :

$$\frac{dW(t)}{d(t)} = \frac{E(t)}{7.7\ g}$$

$$E(t) = (G(t) \cdot 4\frac{kcal}{g} - EE)$$

4.4 Ethics and Costs

The recent boom in development and research of GLP-1R agonist drugs presents great potential in treatment and management for millions of patients in the US alone. While these drugs are mainly used to manage type II diabetes, they may have also begun to be prescribed for weight loss in patients with

obesity. With this, these drugs have recently risen in popularity due to celebrities and social media touting the drug as a weight loss drug rather than the originally intended diabetes treatment. As a result, people have been seeking the drug through off-label prescriptions as well as online. This creates an issue as patients with type II diabetes may not be able to receive their treatment since shortages may occur. Additionally, due to the popularization through social media, patients taking GLP-1R drugs may not be educated on the side effects and risks of the medication. Education is critical as the side effects are unknown for those who do not fall under the criteria and thus create health issues. Similarly, diversity in clinical trials should be emphasized. While, misuse and off-label prescriptions cannot be fully eliminated, the risks may be reduced through development and testing of drugs and can also be managed through proper prescriptions. When prescribing diabetes drugs, the physicians must take into account patient background, insurance coverage or lack thereof, and other social determinants that will help narrow down the best treatment approach.

For diabetic patients primarily taking insulin injections, insulin cost becomes a massive factor in consistently following through with treatment or potentially avoiding treatment due to the steep prices. Big pharmaceutical companies, including Eli Lilly, Novo Nordisk, and Sanofi, dominate 90% of the American insulin market, determining the price of insulin and thus the price of a healthy and reasonable quality of life. In the context of the distribution of diabetes in America, we see that this disparity becomes even more concerning as lower income communities see higher rates of diabetes than more socioeconomically well off communities. Additionally, due to the history of racial segregation in the US, these lower income communities tend to have higher concentrations of minorities as well, and we see this reflected in the racial distribution of diabetes. This prevalence can be attributed to several determinants such as quality of food available in these lower income communities, the quality of food that individuals can afford to purchase, the availability of quality healthcare, and the ability of individuals in these areas to take the time to seek appropriate care and treatment[16]. As such, these sky high costs pose a tremendous barrier to treatment, and patients may continue to live with diabetes without treatment, leading to conditions like heart disease, nerve damage, blindness, kidney failure and amputations.

Even more concerning than the availability of Ozempic or the distribution of diabetes is the cost of obtaining diabetes treatment. While the two physicians who originally isolated insulin and presented it as a form of diabetes regulation sold the patent to Eli Lilly for a whopping $1 in 1921 after winning the Nobel Prize, the cost of insulin has since surged. For patients who require daily doses with each meal, insulin now costs over $275 per vial, and is the 6th most expensive liquid in the world. For Humalog, specifically, depending on your insurance coverage, you may pay anywhere from nothing to $189 or $345 (with federal and private insurance, respectively) or over $500 without insurance. After coming under fire for massively inflated insulin prices, Eli Lilly recently unveiled a significant cost reduction by over 70%,

to a much more affordable $35 for qualifying patients. For Ozempic, the cost without insurance soars above $900 for .5 mg. Depending on your insurance plan and the preferred drug list in your state, the cost with insurance coverage varies greatly.

5 Conclusion

The comprehensive assessment and simulation of blood glucose, insulin, and glucagon levels through various meal types and treatment scenarios in healthy and diabetic individuals have yielded insightful results. The validation of our model against expected physiological responses indicates its ability to generate reasonable outcomes, accurately mirroring the expected blood glucose spikes post-meal consumption for both healthy and diabetic patients. Notably, diabetic patients exhibit higher peak bloodstream glucose levels and longer recovery times compared to their healthy counterparts, emphasizing the impact of meal composition on their glucose response. The analysis of treatment strategies involving Ozempic, Humalog, and their combination demonstrates the effectiveness of these therapies in managing bloodstream glucose concentrations, aligning closely with established standard dosages in real-world practice. Moreover, the parametric analysis unveils optimal dosing combinations that maintain blood glucose within acceptable ranges, showcasing the potential clinical utility of our model in guiding treatment decisions. The sensitivity analysis highlights the model's stability and adaptability, indicating its potential to represent individual variations by fine-tuning specific parameters without compromising its performance.

Despite the robustness of our model, there remains much room for improvement. Some qualitative flaws of our model include that the gender of patients was not accounted for in both the pharmacokinetic and pharmacodynamic modeling to analyze the effects of Ozempic, Humalog, and the Mixed treatments. Prior research has shown that blood glucose levels are lower in women than men, something our model doesn’t factor and therefore cannot be used to predict for [17]. Additionally, other important demographic factors like race and socioeconomic status were not imputed into our model. Between different races, literature has shown that Black and Asian communities are more likely to see a higher prevalence of diabetes than others [18]. However, both of these demographic factors play a role within social determinants of health, which have a major impact on onset of diabetes in various populations.

Additionally, endorsing drugs such as Ozempic solely based on mathematical models can be risky and shortsighted. While Ozempic was successful in lowering blood glucose concentrations in diabetic patients per our developed mathematical model, there are additional implications to consider. Ozempic has been commonly utilized as a weight-loss drug, as customers do not have to have diabetes in order to access the drug. The growing hype of Ozempic-esque drugs has led to GLP-1 agonist drugs to be perceived as “miracle” weight loss drugs rather than as medical treatments for conditions like diabetes. As a result,

there are often supply shortages with weight loss drugs like Ozempic, which can cause diabetic individuals to seek other expensive or less effective treatment options. For the model itself, while the simplicity and ease of use in modeling Ozempic's effects on insulin serve as strengths, its limitation in accounting for Ozempic's negative influence on glucagon secretion underscores a potential area for enhancement in future iterations to make our model even more comprehensive and representative of the physiological processes after meals.

Taking all of our results into consideration in the context of diabetes treatment, it is difficult to make treatment recommendations based on the mathematical results of our models. In reality, factors like patient demographics and various social determinants of health must be considered before making these decisions. Overall, our model stands as a valuable tool in evaluating treatment efficacy and cost-effectiveness, contributing to the understanding and optimization of therapeutic interventions for diabetes management in clinical settings.

6 Appendix

Appendix Table 1A: Table of Mathematical Equations used in our Expanded Bergman Model

Compartment/ Equation	MathematicalEquation
$F_E(t)$	$F_E(t) = 200(\delta(t-7) + \delta(t-12.5) + \delta(t-18))$ (Candy Diet) $F_E(t) = 100(rect((t-8)/2) + rect((t-12.5/2) + rect((t-18)/2))$ (Complex Diet) (Both functions repeat daily)
$I_E(t)$	$I_E(t) = HumalogDosage \cdot \delta(t - mealtime + 15)$, (per meal)
$O_E(t)$	$O_E(t) = OzempicDosage \cdot \delta(t)$, (repeats weekly)
$I_s(t)$	$I_s(t) = 2100(\frac{[BS]^{4.4}}{132^{4.4}+[BS]^{4.4}}) \cdot (1 + \frac{1.125[BO]^2}{100^2+[BO]^2})$
$G_s(t)$	$G_s(t) = (\frac{1000 \cdot 72^{2.7}}{72^{2.7}+[BS]^{2.7}})$
GS(t)	$GS(t) = \frac{[RI]^4}{300^4+[RI]^4}$
GB(t)	$GS(t) = \frac{[RG]^3}{150^3+[RG]^3}$
TC(t)	$GS(t) = \frac{1}{2}\frac{[RI]^3}{300^3+[RI]^3} \cdot \frac{150^3}{150^3+[RG]^3} \cdot [BS] + 15$
[BI]	$\frac{d[BI]}{dt} = I_E(t) - k_{d,I}[BI] - k_{0,I}([BI] - [PI]) - k_{1,I}[BI] + k_{2,I}[RI]$
[PI]	$\frac{d[PI]}{dt} = I_S(t) - k_{d,I}[PI] + k_{0,I}([BI] - [PI])$
[RI]	$\frac{d[RI]}{dt} = k_{1.I}[BI] - k_{2.I}[RI]$
[BG]	$\frac{d[BG]}{dt} = - k_{d,G}[BG] - k_{0,G}([BG] - [PG]) - k_{1,G}[BI] + k_{2,G}[RI]$
[PG]	$\frac{d[PG]}{dt} = G_s(t) - k_{d,G}[PG] + k_{0,G}([BG] - [PG])$
[RG]	$\frac{d[RG]}{dt} = k_{1.G}[BG] - k_{2.G}[RG]$
[SG]	$\frac{d[SG]}{dt} = F_E(t) - k_0[SG]$

[BS]	$\frac{d[BS]}{dt} = [SG] - TC(t) - GS(t) + GB(t)$
[GS]	$\frac{d[GS]}{dt} = GS(t) - GB(t)$
[BO]	$\frac{d[BO]}{dt} = O_E(t) - k_{d,O}[BO]$
S_I	$S_I = \frac{k_{1,I}}{3.705 \cdot k_{2,I}}$

Appendix Table 2A: Table of Parameters and Respective Values

Parameter	**Description**	**Value**
$k_{d,I}$	Insulin decay rate, has a half life of 5 minutes [x].	$8.31 \frac{1}{hr}$
$k_{0,I}$	Rate of diffusion from pancreatic insulin to bloodstream insulin	$10 \frac{1}{hr}$
$k_{1,I}$	Rate of diffusion from bloodstream insulin to pancreatic insulin	$17.78 \cdot S_I$
$k_{2,I}$	Rate of diffusion from remote insulin to bloodstream insulin	$4.8 \frac{1}{hr}$
$k_{d,G}$	Glucagon decay rate, has a half life of 15 minutes [x].	$2.77 \frac{1}{hr}$
$k_{0,G}$	Rate of diffusion from pancreatic glucagon to bloodstream glucagon	$20 \frac{1}{hr}$
$k_{1,G}$	Rate of diffusion from bloodstream glucagon to pancreatic glucagon	$2.223 \frac{1}{hr}$
$k_{2,G}$	Rate of diffusion from remote glucagon to bloodstream glucagon	$0.6 \frac{1}{hr}$
k_0	Rate of absorption of gastrointestinal glucose	$1.25 \frac{1}{hr}$
$k_{d,O}$	Ozempic decay rate, has a half life of 1 week [x].	$4.12 \cdot 10^{-3} \frac{1}{hr}$

Figure A1: Diabetic Patient on Simple Carbohydrate Meals

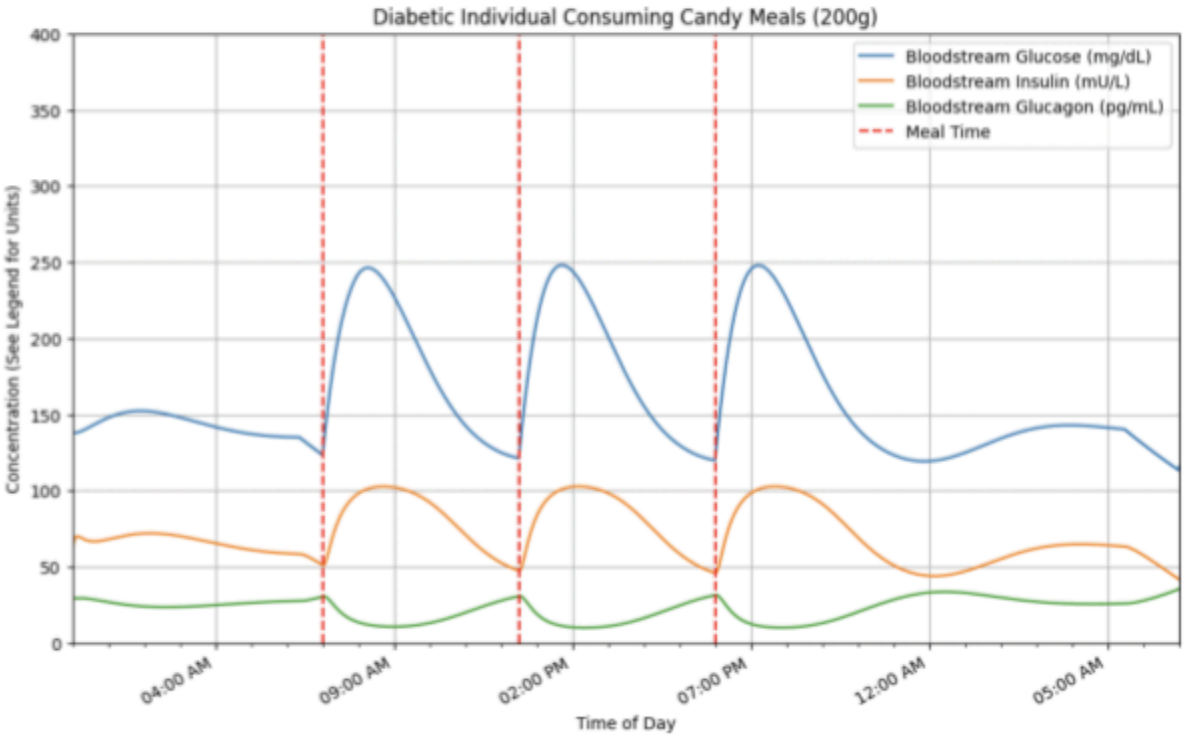


Figure A2: Parametric Analysis of Bloodstream Glucose Levels vs. Insulin Sensitivity and Time

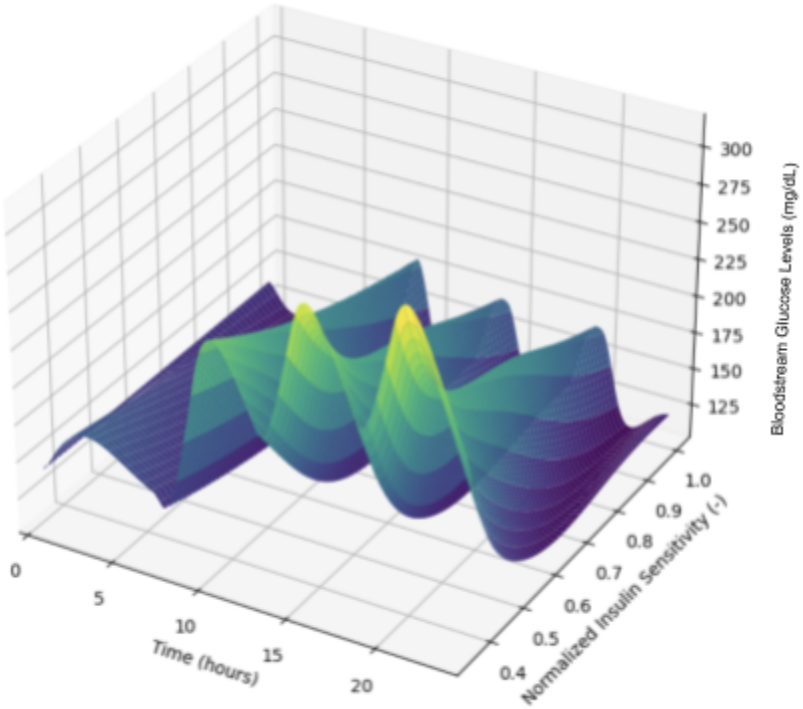
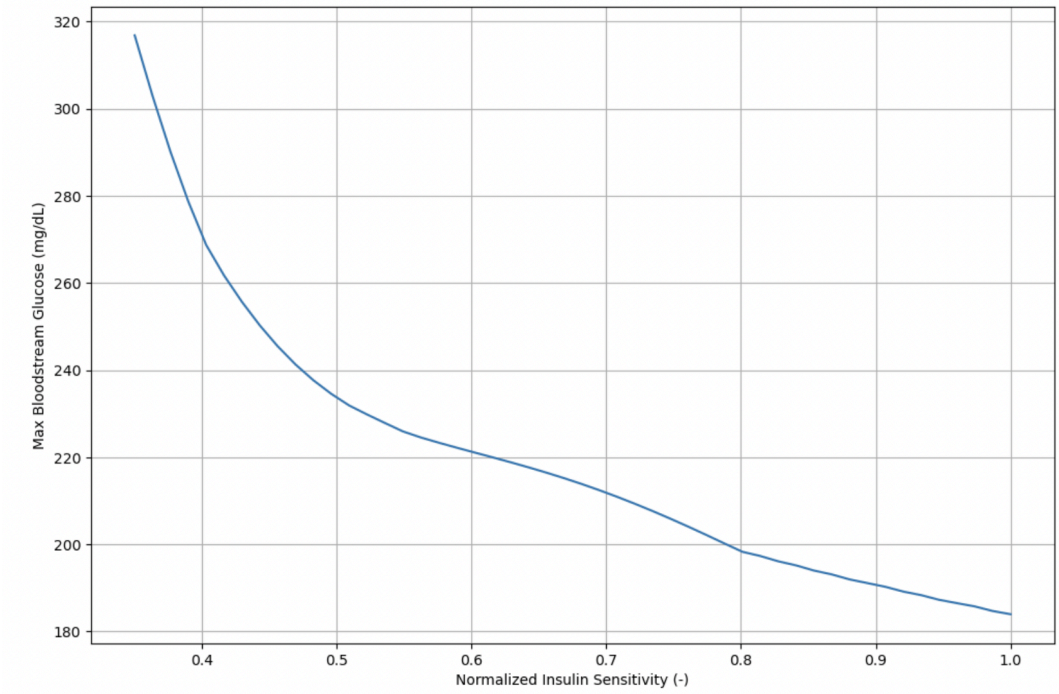


Figure A3: Maximum Bloodstream Glucose Levels vs. Normalized Insulin Sensitivity



Model Code C1:

Code here: https://colab.research.google.com/drive/1dgI0DvRT2_oVy15uwNcSyaANvzLXGlGK

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