Spring 1-1-2014

Personalized Control of Diabetes Using a Two-Delay Model

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Personalized control of diabetes using a two-delay model

by

Stephen M. Kissler

B.S., University of Colorado Boulder, 2014
M.S., University of Colorado Boulder, 2014

A thesis submitted to the
Faculty of the Graduate School of the
University of Colorado in partial fulfillment
of the requirements for the degree of
Master of Science
Department of Applied Mathematics
2014
This thesis entitled:
Personalized control of diabetes using a two-delay model
written by Stephen M. Kissler
has been approved for the Department of Applied Mathematics

David Bortz

Vanja Dukic

Sriram Sankaranarayanan

Date ________________

The final copy of this thesis has been examined by the signatories, and we find that both the content and the form meet acceptable presentation standards of scholarly work in the above mentioned discipline.
Diabetes cases worldwide have risen steadily over the past decades, lending urgency to the search for more efficient, effective, and personalized ways to treat the disease. Current treatment strategies, however, may fail to maintain ultradian oscillations in blood glucose concentration, an important element of a healthy alimentary system. Building upon recent successes in mathematical modeling of the human glucose-insulin system, we show that both food intake and insulin therapy likely demand increasingly precise control over insulin sensitivity if oscillations at a healthy average glucose concentration are to be maintained. We then suggest guidelines and personalized treatment options for diabetic patients that maintain these oscillations. To do so, we develop a closed-form criterion to indicate the presence of blood glucose oscillations in our model. We show that for a type II diabetic, both blood glucose levels can be controlled and healthy oscillations maintained when the patient gets an hour of daily exercise and is placed on a combination of Metformin and sulfonylurea drugs. We note that insulin therapy and an additional hour of exercise will reduce the patient’s need for sulfonylureas. Results of a modeling analysis suggest that a typical type I diabetic’s blood glucose levels can be properly controlled with a constant insulin infusion between 0.45 and 0.7 µU/ml-min. Lastly, we note that all suggested strategies rely on existing clinical techniques and established treatment measures, and so could potentially be of immediate use in the design of an artificial pancreas.
Dedication

To my mother and father.
I am deeply indebted to a number people for their consistent guidance and support through this endeavor. I would like to extend particular thanks to Dr. David Bortz for overseeing this work and serving as a consistent academic mentor. I would also like to thank Dr. Vanja Dukic for being an equally influential research adviser. Thanks also to Cody Cichowitz for his work on the initial stages of this project, for his medical expertise and especially for his unfailing friendship and encouragement. This work would not have been possible without Anne Dougherty’s tireless support and encouragement that inspired me to undertake mathematical research. Special thanks is also due to Scot Douglass, who has consistently challenged me to maintain focus on the most important questions. Finally, I would like to thank the Boettcher Foundation whose financial and personal support have given me the freedom to thrive as a scholar.
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Diabetes mellitus refers to a range of conditions characterized by chronic high levels of glucose in the blood. The disease can be debilitating, with long-term risk factors including peripheral neuropathy, cardiovascular disease, blindness, and even death [4, 14, 28]. Diabetes cases are increasing in the United States and in the world as a whole; in the United States, the number of diagnosed cases has doubled since 2000 and more than tripled since 1990, with current figures estimating about 25.8 million cases [16, 17]. The disease poses a serious risk for developing countries, with large masses of people moving away from agrarian diets to cheap urban diets of fatty and sugary foods [26]. With no known cure, lifelong treatment is generally the only option. Treatments are often very involved; a patient normally must take daily medications, make routine physician visits, and, in some cases, check blood sugar and inject insulin multiple times per day.

The American Diabetes Association (ADA) recommends a combination of diet, exercise, medication, and insulin therapy to treat diabetes. These treatments primarily aim to lower blood glucose concentration (BGC) to a healthy level [6]. However, another important factor is often overlooked: blood glucose levels in non-diabetic individuals also fluctuate by about 10% every two hours or so. These so-called ultradian oscillations (i.e., taking place multiple times each day) were first noted by Hansen in 1923, and various studies since have underlined their prominence and functional importance in regulating glucose concentration [22, 24, 34, 35]. The root cause of these oscillations is not fully understood, though evidence suggests that delayed feedback between insulin-producing pancreatic β-cells and the liver may be a significant contributing factor [30]. As
these oscillations are natural and indicative of healthy insulin dynamics, any effective treatment strategy should aim to maintain these oscillations.

Assigning treatments to diabetic individuals becomes even more complicated by the fact that ‘diabetes’ refers to such a broad range of conditions. No two patients have the same ability to utilize glucose, the same insulin production rate, or the same lifestyle, and thus no two treatments can be identical. Recently, there has been a push to develop algorithms that provide straightforward rules for developing treatment plans based on an individual’s particular physiology and lifestyle [20, 32]. In our experience, these algorithms are primarily heuristic and so, despite providing valuable guidelines for doctors, they cannot be easily programmed into medical devices. A major goal of this work is to better quantify a patient’s physiological and lifestyle traits, as well as the necessary medical adjustments that should be made, so that such algorithms can be more easily implemented in silico.

With these points in mind, our goal is to develop a systematic strategy to determine a personalized treatment plan for lowering a diabetic’s BGC to within the ADA-specified range (between 70 and 130 mg/dl before meals [5]). This treatment plan should retain the ultradian glucose oscillations observed in healthy individuals and should rely on existing standard treatment measures, i.e. diet, exercise, insulin therapy, and/or medication. It should be straightforward enough to be programmed into a medical device such as an artificial pancreas. Finally, the information necessary to personalize the treatment plan should be readily available from existing clinical procedures. To accomplish these goals we will study a mathematical model of the human glucose-insulin system that explicitly accounts for the treatment methods proposed by the ADA. Ultimately, we hope to lay the mathematical framework for an algorithm to be implemented in an artificial pancreas that responds to meals, exercise, and other important environmental factors with minimal user input. This would reduce the overall burden borne by people with diabetes, allowing them to live freer, healthier, and simpler lives.

In the remainder of this introduction, we set forth some essential facts about diabetes and discuss the mathematical background necessary to understand our model. Then, in Chapter 2 we set
forth our model and discuss some of its characteristics. In Chapter 3, we develop the mathematical theory that provides an explicit criterion for instability (oscillations) in delay differential equation systems of a particular form, into which our model falls. In Chapter 4, we analyze the model to identify medical and behavioral interventions that may be effective in controlling a person’s BGC while maintaining blood glucose oscillations. Chapter 5 sets forth two case studies in which we demonstrate how our results could guide treatment strategies for a hypothetical type II and type I diabetic. We conclude with a summary and with directions for further research.

1.1 Physiological background

Diabetes diagnoses usually fall into one of a few categories, including type I, type II, and gestational diabetes. Prediabetes is a condition in which a patient has elevated blood glucose levels, but whose BGC is not yet high enough for a diagnosis of true diabetes to be made. We will focus primarily on type I and type II diabetes, since, unlike gestational and pre-diabetes, patients with these conditions normally remain with them for the rest of their lives, and because they characterize the vast majority of all people with diabetes (type II diabetics make up 90-95% of all people with diabetes, and type I diabetics make up another 5-10% [3]). Before discussing the causes and consequences of these particular types of diabetes, it is important first to describe how the human body regulates glucose and insulin.

1.1.1 The human glucose-insulin system

The human body requires energy from sugars to function. The most important of these sugars is glucose, into which much of the food we ingest is converted. Once ingested, glucose is transported into cells, where glycolysis produces energy for the cells to function. Not all cells take up glucose equally; the cells of the central nervous system tend to take up all of the glucose that is available to them up to a certain threshold, no matter the conditions. Glucose uptake by muscle and fat cells, on the other hand, is regulated by the hormone insulin. The presence of insulin encourages cellular glucose uptake, thus reducing the concentration of the sugar in the blood. Conversely, when
insulin is largely absent, cells slow their uptake of glucose, keeping blood glucose concentrations high. In a healthy human being, elevated levels of glucose in the blood stimulate the pancreas (in particular, the pancreatic β-cells) to produce insulin. It takes approximately five minutes for this newly-produced insulin to cross into interstitial space and become available to cells [30]. This release of insulin encourages the body’s muscle and fat cells to take up the glucose that is newly available to them, which decreases blood glucose concentration.

After a while, insulin builds up, and in order to keep blood glucose levels from dropping too low, the body must produce more glucose. The primary glucose-producing organ in the body is the liver, though the kidneys can also contribute up to 25% of the body’s internal glucose production. It takes about 15 minutes before the liver can respond to elevated glucose levels [30]. When it does, it secretes more glucose into the blood stream (this is referred to as hepatic glucose production), and blood glucose levels rise again. This feedback loop is likely responsible for the observed ultradian oscillations in human blood glucose concentrations. In most people, this process keeps fasting blood glucose levels controlled below 100 mg/dl.

It is important to note that our model does not explicitly account for glucagon, a hormone also produced by the pancreas that stimulates hepatic glucose production. We have chosen to omit glucagon because, unlike insulin, glucagon is not stable outside of a laboratory setting and therefore cannot be reliably injected to control blood glucose levels. So, including glucagon in the model would not aid in our final goal of determining viable treatments for diabetes. We note that, despite this omission, our model still gives credible blood glucose profiles.

With this background, we can now more closely examine how diabetes develops in humans. We will begin with a discussion of type II diabetes, due to its much higher prevalence than type I.

1.1.2 Type II diabetes

In the previous section, we noted that muscle and fat cells take up glucose best in the presence of insulin. In a type II diabetic, this process is impaired - these cells’ insulin sensitivity is reduced, meaning that insulin is less effective in stimulating glucose uptake from the blood. This leads
to elevated blood glucose levels. Eventually, this deterioration of insulin sensitivity can impair pancreatic insulin secretion; in fact, significant impairment often happens before a diagnosis of diabetes is ever made [12, 37]. The accompanying elevated blood glucose levels are a risk factor for further chronic conditions such as blindness and peripheral neuropathy.

Type II diabetics often develop the disorder late in life. Risk factors include genetics, low physical activity, and obesity. Often, a person will first go through a prediabetic stage, in which fasting blood glucose levels fall between 100 and 126 mg/dl [3]. When fasting blood glucose levels meet or exceed 126 mg/dl, a diagnosis of diabetes is made. Once undergoing treatment, the target blood glucose concentration for a type II diabetic is between 70 and 130 mg/dl before meals [5].

A diabetic patient’s insulin sensitivity can be measured using a few different methods. The oral glucose tolerance test (OGTT) is done by administering a bolus of glucose intravenously and charting the patient’s blood glucose concentration over the following two or more hours [19]. Fitting this data to an empirical model then gives a quantity for insulin sensitivity [11]. However, since no two people digest and transport glucose in the same way, this strategy is prone to errors. The most reliable alternative method is the glucose clamp technique, in which a patient is given a continuous stream of intravenous glucose solution until his or her blood glucose concentration levels out at some hyperglycemic set-point. The rate of insulin infusion can reliably determine the patient’s insulin sensitivity. Due to its invasiveness, this procedure is generally used for data collection in small studies and not for diagnostics. Insulin sensitivity can be strongly affected by exercise; aerobic exercise can improve insulin sensitivity almost immediately, and the effect can last for days [33]. To our knowledge, the model of the human glucose-insulin system that we present here is the first to explicitly account for the effect of exercise.

1.1.3 Type I diabetes

While also characterized by chronic high blood glucose levels, type I diabetes arises from a disorder in insulin production rather than insulin uptake. Type I diabetes is normally the result of an auto-immune attack on pancreatic $\beta$-cells, which normally produce insulin. This fully impairs
these cells’ function, making a type I diabetic incapable of producing his or her own insulin. As a result, this disorder is generally more severe than type I diabetes and requires closer attention and more comprehensive control. In addition to the chronic long-term conditions that type II diabetics might suffer, type I diabetics also run the risk of more acute conditions, such as seizures from low blood glucose levels that result from injecting too much insulin or not ingesting enough food.

Type I diabetes is normally present from childhood, with genetics being the primary risk factor for the disease. Due to its severe effect on blood glucose concentration, it is usually recognized quickly. Type I diabetics must pay close attention to their levels of physical activity and amount of food intake in order to keep control of their blood glucose levels. They must check their blood glucose levels through finger pricks and inject insulin multiple times daily. Like type II diabetics, type I diabetics should aim to keep their blood glucose concentration between 70 and 130 mg/dl before meals [5].

1.2 Mathematical background

In the preceding discussion of the physiological characteristics of diabetes, we noted two processes that involve an inherent delay: the release of insulin from pancreatic β-cells into interstitial space, and the release of glucose from the liver after it has been triggered by elevated insulin levels. As a result, delay differential equations provide a natural framework with which to model this system. Delay differential equations are much like ordinary differential equations with the addition of one or more terms that depend not on the system’s current state, but on the system’s state some amount of time earlier. Here is a very simple delay differential equation:

\[ \frac{dx}{dt} = \alpha x(t) + \beta x(t - \tau) \]

\[ x(0) = x_0 \]

\[ x(t) = g(t), t \in [-\tau, 0) \]
Here, $\alpha$, $\beta$, $\tau$, and $x_0$ are all constants, and $g(t)$ is some pre-defined function of $t$ that does not necessarily satisfy the differential equation. The function $g(t)$ is often called the “preshape” or “initial history” of the set of equations [13, 41]. Delay differential equations of the above form can be solved numerically; many popular computing programs include packages to solves such systems, such as MATLAB’s dde23 and Mathematica’s NDSolve. They can also be solved analytically using the well-studied Lambert W function, as developed by Asl and Ulsoy [7]. Briefly, we can take the Laplace transform of Equation (1.1) to arrive at the characteristic equation

$$se^{st} = \alpha e^{st} + \beta e^{s(t-\tau)}$$

To solve for $s$, we must solve the equation

$$s = \alpha + \beta e^{-st}$$

With some manipulation of terms, we can arrive at the form

$$\tau(s - \alpha)e^{\tau(s-\alpha)} = \beta\tau e^{-\alpha\tau}$$

Recognizing this as having the form

$$W(z)e^{W(z)} = z$$

where $W(\cdot)$ is the Lambert W function, we can write

$$W(\beta\tau e^{-\alpha\tau}) = \tau(s - \alpha)$$

Solving for $s$ gives

$$s = \frac{1}{\tau}W(\beta\tau e^{-\alpha\tau}) + \alpha$$

The Lambert W function has an infinite number of branches, and thus $s$ has an infinite number of possible values. Thus, the solution to Equation (1.1) takes the form

$$x(t) = \sum_{j=-\infty}^{\infty} C_j e^{s_j t}$$

where $C_j$ are constants that can be determined from the initial condition $x_0$ and initial history $g(t)$. 

Since the glucose-insulin system involves two substrates, we need a system of differential equations, rather than a single equation, to fully describe the physiology of diabetes. We can easily extend Equation (1.1) to a system:

\[
\frac{dx}{dt} = Ax(t) + Bx(t - \tau) \tag{1.2}
\]

where \(A\) and \(B\) are coefficient matrices and \(x\) is a vector. We are particularly interested in the conditions under which such a DDE system transitions from stable to unstable. In our case, this information will determine the onset of blood glucose oscillations. To find this transition point, we examine the linear(ized) system’s stability eigenvalues. These eigenvalues are the solution to the equation

\[
|A + Be^{-s\tau} - sI| = 0
\]

where the vertical bars denote the determinant and \(I\) is the identity matrix. Because of the transcendental nature of this equation, there are an infinite number of values of \(s\) that satisfy this equation, and thus an infinite number of eigenvalues. The rightmost eigenvalues tend to drive the system’s stability, and fortunately it can be shown that only a finite number of such eigenvalues exist [27]. Generally, when the dominant eigenvalues lie in the left half of the complex plane, solutions to Equation (1.2) will be stable, and when they lie in the right half of the complex plane, solutions to (1.2) will be unstable (i.e. oscillatory or unbounded).

Solving and analyzing delay differential equations becomes somewhat more complicated in the case of systems with multiple delays. Yi and Ulsoy [41] have given the analytical solution for general systems with a single delay, and Bortz has given the analytical solution for a single equation with two delays [13]. The solution of a system of delay differential equations with two delays remains an open question. In Chapter 3 we will examine such a system and use some of the above strategies to derive a criterion for instability of the solution, which holds when the model equations have particular form.
1.3 Original Contributions

The original contributions of the research presented here can be summarized as follows:

- We present a model of the human glucose-insulin system that can be adjusted to reflect the physiological abnormalities present in diabetes. In particular, to the authors' knowledge, this model is the first to explicitly account for the significant effect of exercise.

- We present a closed-form sufficiency condition for the existence of unstable solutions of delay differential equation systems with particular structure.

- We provide a systematic theory that, with proper verification, can suggest what adjustments to insulin sensitivity and pancreatic efficiency must be made to bring a diabetic person’s blood glucose concentration to an acceptable level, and to maintain ultradian oscillations.

- We demonstrate that insulin therapy can reduce the need to improve pancreatic efficiency, but also makes tighter control on insulin sensitivity necessary to maintain ultradian blood glucose oscillations.

Chapter 2

Mathematical Formulation

We represent the human glucose-insulin system as a set of differential equations. For clarity, consider Figure 2.1, which provides a schematic diagram of the system. As noted in the introduction, ingested food is converted to glucose, which fuels bodily functions and encourages the production of insulin. This insulin, in turn, slows down further glucose production to prevent a buildup of glucose in the bloodstream. The mathematical model that describes this process is given by Equations (2.1) - (2.2):

\[
G' = G_{in} + f_1(I(t - \tau_2)) - f_2(G(t)) - \gamma[1 + s(m - m_b)]f_3(G(t))f_4(I(t)) \\
I' = I_{in} + \beta f_5(G(t - \tau_1)) - \frac{V_{max}I(t)}{K_M + I(t)}
\]

(2.1) (2.2)

For clarity, let us explain the links between the terms in Equations (2.1) and (2.2) and the processes depicted in Figure 2.1. We first note that glucose concentration \((G)\) can increase via two pathways: (1) ingestion and (2) production by the liver. We first consider ingestion, for which we represent glucose intake rate by \(G_{in}\). We make this term constant because, if it were instead periodic (as in the case of multiple daily meals), this periodicity would automatically induce ultradian glucose oscillations. Simon et al. [34] demonstrated that ultradian glucose oscillations exist in healthy individuals even when ingesting glucose at a constant rate, and we want to ensure that our model accounts for this behavior.

We next consider hepatic glucose production, denoted by \(f_1(I(t - \tau_2))\). The equation for \(f_1\) is given in Table 2.2 and its shape in Figure 2.2. Insulin inhibits hepatic production, so it makes
Glucose ($G$) 

Insulin ($I$) 

Ingestion

Insulin Infusion

Pancreas

Clearance

Liver

Muscle/Fat

CNS

Figure 2.1: Schematic diagram of the human glucose-insulin system. Solid lines denote production/consumption of a substrate (glucose or insulin), dotted lines denote inhibition by a substrate, and dashed lines denote encouragement by a substrate. Ingested food is converted to glucose, which the body uses to fuel biological processes. Glucose also stimulates pancreatic $\beta$-cells to produce insulin, which in turn inhibits the liver’s production of glucose. The central nervous system (CNS) processes glucose without insulin, whereas insulin enhances glucose uptake by muscle and fat cells. Thus, when blood glucose levels are high, insulin is produced to stimulate glucose uptake and to slow the production of further glucose from the liver. When blood glucose levels are low, insulin is produced more slowly and the liver’s production of glucose speeds up. This feedback loop helps to keep a person’s blood glucose levels in a state of oscillatory homeostasis.
sense that \( f_1 \) would be a decreasing function of insulin concentration. We represent the hepatic production delay (noted in Section 1.1.1) with \( \tau_2 \), the amount of time (in minutes) required for a change in insulin concentration to affect hepatic glucose production.

Glucose concentration can also decrease via two pathways, namely (1) utilization by the central nervous system and (2) utilization by muscle and fat cells. Glucose utilization by the central nervous system (CNS) does not depend on insulin concentration; these cells will use all of the glucose available to them up to a threshold. We represent this behavior with \( f_2 \), whose equation is given in Table 2.2 and shape in Figure 2.2. Muscle and fat cells, on the other hand, do rely on the presence of insulin to take up glucose; thus, we represent their consumption with the product \( f_3(G(t)) \cdot f_4(I(t)) \). Here we arrive at the first complication that diabetic illness introduces; the muscle and fat cells of type II diabetics are less sensitive to insulin, and thus cannot take up glucose from the blood stream as easily a non-diabetic person’s cells. The scaling factor \( \gamma \) accounts for this; \( \gamma \) can take values from 0 to 1, with 0 corresponding to no ability for muscle and fat cells to take up glucose, and 1 corresponding to a non-diabetic person’s glucose uptake ability. Thus, lower values of \( \gamma \) correspond to more severe cases of diabetes. The additional factor, \( [1 + s(m - m_b)] \), accounts for the positive effect of exercise on insulin sensitivity [21]. Here, \( m \) corresponds to minutes of moderate to vigorous physical activity (MVPA) per day. 60 minutes per day of MVPA (\( m_b = 60 \)) is considered average; any less than this decreases glucose tolerance and any more increases glucose tolerance, with the effect of exercise more significant for individuals with better baseline glucose tolerance (\( \gamma \) close to 1). Nelson et al. observed a decrease in insulin resistance corresponding to an increase in physical exercise; this data is well-modeled by the line \( y = 1.9127 - 0.0072x \) [33]. The slope of this line, interpreted as the percent increase in glucose tolerance for each additional minute of exercise, provides the rationale behind multiplying by \( s = 0.0072 \) in Equation (2.1).

Now let us justify the equation for insulin concentration, Equation (2.2). Like glucose, there are two pathways by which insulin concentration can increase: (1) insulin infusion and (2) pancreatic \( \beta \)-cell production. We let the insulin infusion \( I_{\text{in}} \) be a constant since periodic insulin infusion would only make sense if glucose intake were also periodic. We represent pancreatic \( \beta \)-cell production with
the function $f_5(G(t - \tau_1))$, defined in Table 2.2 and with form given in Figure 2.2. As illustrated in the schematic diagram, elevated blood glucose encourages pancreatic insulin production. As noted in Section 1.1.1, there is a delay before the pancreas can respond to changes in blood glucose, for which $\tau_1$ accounts.

Finally, there is one significant way for insulin concentration to decrease, which is through metabolism by human insulin-degrading enzyme (IDE) [8]. As an enzymatic reaction, we quantify insulin degradation with Michaelis-Menten kinetics using the term $\frac{V_{\text{max}} I(t)}{K_M + I(t)}$. Here, $V_{\text{max}}$ is the maximum insulin clearance rate and $K_M$ is the enzyme’s half-saturation value [40].

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Units</th>
<th>Range</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\beta$</td>
<td>–</td>
<td>0 – 1</td>
<td>Relative pancreatic $\beta$-cell function</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>–</td>
<td>0 – 1</td>
<td>Relative insulin sensitivity</td>
</tr>
<tr>
<td>$G_{\text{in}}$</td>
<td>mg/dl-min</td>
<td>0 – 1.08</td>
<td>Glucose intake rate</td>
</tr>
<tr>
<td>$I_{\text{in}}$</td>
<td>$\mu$U/ml-min</td>
<td>0 – 2</td>
<td>Insulin infusion rate</td>
</tr>
<tr>
<td>$K_M$</td>
<td>$\mu$U/ml</td>
<td>2300</td>
<td>Insulin degrading enzyme’s half-saturation concentration</td>
</tr>
<tr>
<td>$m$</td>
<td>min</td>
<td>0-120</td>
<td>Daily minutes of physical activity</td>
</tr>
<tr>
<td>$m_b$</td>
<td>min</td>
<td>60</td>
<td>Baseline minutes of physical activity</td>
</tr>
<tr>
<td>$s$</td>
<td>1/min</td>
<td>0.0072</td>
<td>Rate of insulin sensitivity increase per minute of exercise</td>
</tr>
<tr>
<td>$V_{\text{max}}$</td>
<td>$\mu$U/ml-min</td>
<td>150</td>
<td>Maximum insulin clearance rate</td>
</tr>
</tbody>
</table>
Figure 2.2: Functional forms of $f_1$, $f_2$, $f_4$, and $f_5$, from [30]
Table 2.2: Definitions of functions $f_1$ - $f_5$ from model equations (2.1) and (2.2). Parameter values are given in Table 2.3.

<table>
<thead>
<tr>
<th>Modeling Term</th>
<th>Physiological Process</th>
</tr>
</thead>
<tbody>
<tr>
<td>$f_1(I) = R_g/(1 + \exp(\alpha(I/V_p - C_5)))$</td>
<td>Hepatic glucose production</td>
</tr>
<tr>
<td>$f_2(G) = U_b(1 - \exp(-G/(C_2V_g)))$</td>
<td>CNS glucose utilization</td>
</tr>
<tr>
<td>$f_3(G) = G/(C_3V_g)$</td>
<td>Muscle/fat glucose utilization</td>
</tr>
<tr>
<td>$f_4(I) = U_0 + (U_m - U_0)/(1 + \exp(-\beta \ln(I/C_4(1/V_i + 1/(E t_i))))))$</td>
<td>Muscle/fat insulin uptake</td>
</tr>
<tr>
<td>$f_5(G) = R_m/(1 + \exp((C_1 - G/V_g)/a_1))$</td>
<td>Pancreatic insulin production</td>
</tr>
</tbody>
</table>

Table 2.3: Parameter values for functions $f_1$ – $f_5$ (from [31], [38], and [39])

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Units</th>
<th>Values</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha$</td>
<td>liter/mU</td>
<td>0.29</td>
<td>Scaling factor; sets hepatic sensitivity to changes in insulin</td>
</tr>
<tr>
<td>$\beta$</td>
<td>–</td>
<td>1.77</td>
<td>Scaling factor</td>
</tr>
<tr>
<td>$a_1$</td>
<td>mg/liter</td>
<td>300</td>
<td>Scaling factor; sets pancreatic sensitivity to changes in glucose</td>
</tr>
<tr>
<td>$C_1$</td>
<td>mg/liter</td>
<td>2000</td>
<td>Glucose concentration at which pancreas is most efficient</td>
</tr>
<tr>
<td>$C_2$</td>
<td>mg/liter</td>
<td>144</td>
<td>Scaling factor; sets CNS cell sensitivity to changes in glucose</td>
</tr>
<tr>
<td>$C_3$</td>
<td>mg/liter</td>
<td>1000</td>
<td>Scaling factor; sets muscle cell sensitivity to changes in glucose</td>
</tr>
<tr>
<td>$C_4$</td>
<td>mU/liter</td>
<td>80</td>
<td>Scaling factor; sets muscle cell sensitivity to changes in insulin</td>
</tr>
<tr>
<td>$C_5$</td>
<td>mU/liter</td>
<td>26</td>
<td>Insulin concentration at which liver is most efficient</td>
</tr>
<tr>
<td>$E$</td>
<td>liter/min</td>
<td>0.2</td>
<td>Insulin transport rate from plasma into cells</td>
</tr>
<tr>
<td>$R_g$</td>
<td>mg/min</td>
<td>180</td>
<td>Maximum hepatic glucose production rate</td>
</tr>
<tr>
<td>$R_m$</td>
<td>mU/min</td>
<td>210</td>
<td>Maximum pancreatic insulin production rate</td>
</tr>
<tr>
<td>$t_i$</td>
<td>min</td>
<td>100</td>
<td>Exponential time constant for intercellular insulin degradation</td>
</tr>
<tr>
<td>$U_0$</td>
<td>mg/min</td>
<td>40</td>
<td>Low-insulin limiting rate of muscular glucose consumption</td>
</tr>
<tr>
<td>$U_b$</td>
<td>mg/min</td>
<td>72</td>
<td>Maximum glucose utilization rate by brain and nerve cells</td>
</tr>
<tr>
<td>$U_m$</td>
<td>mg/min</td>
<td>940</td>
<td>High-insulin limiting rate of muscular glucose consumption</td>
</tr>
<tr>
<td>$V_g$</td>
<td>liter</td>
<td>10</td>
<td>Volume of the body into which glucose can diffuse</td>
</tr>
<tr>
<td>$V_i$</td>
<td>liter</td>
<td>11</td>
<td>Intercellular volume</td>
</tr>
<tr>
<td>$V_p$</td>
<td>liter</td>
<td>3</td>
<td>Volume of plasma in the body</td>
</tr>
</tbody>
</table>
Chapter 3

Stability eigenvalues of a two-delay system

As noted in the introduction, we are interested in knowing when the solution of the model given in (2.1)-(2.2) is oscillatory. Before proceeding with an analysis of the model, we will here introduce some theory that will identify when such oscillations exist. In particular, we develop a closed-form expression that guarantees that the model’s steady state is unstable. In this section, we show instability of a linear system of DDEs with particular form can be inferred from the derivative of its characteristic equation, whose roots we can express in closed form. This framework will allow us to make conclusions about the stability of the glucose-insulin model in upcoming chapters.

Consider the delay differential equation system

\[ x'(t) = A x + B x(t - \tau_1) + C x(t - \tau_2) \] (3.1)

where \( A, B, \) and \( C \) are coefficient matrices of the form

\[
A = \begin{bmatrix} a_1 & a_2 \\ 0 & a_4 \end{bmatrix}, \quad B = \begin{bmatrix} 0 & 0 \\ b_3 & 0 \end{bmatrix}, \quad C = \begin{bmatrix} 0 & c_2 \\ 0 & 0 \end{bmatrix} \] (3.2)

Assuming solutions of the form \( e^{\lambda t} \), we arrive at the following eigenvalue equation:

\[ |A + e^{-\lambda \tau_1} B + e^{-\lambda \tau_2} C - \lambda I| = 0 \] (3.3)

The eigenvalues \( \lambda \) that satisfy this equation, and particularly the dominant eigenvalue(s) (i.e. the root(s) with largest real part), determine the system’s stability; henceforth, we will refer to them as the model’s stability eigenvalues. If we evaluate the determinant, the eigenvalue equation becomes

\[ a_1 a_4 - (a_1 + a_4)\lambda + \lambda^2 - a_2 b_3 e^{-\tau_1 \lambda} - b_3 c_2 e^{-(\tau_1 + \tau_2)\lambda} = 0 \] (3.4)
This is very nearly the form of the exponential polynomial studied in [13]; the only difference is the additional $\lambda^2$ term. We would like to be able to say something about the roots of this equation; namely, we would like to have a criterion that guarantees that the dominant eigenvalue(s) lie in the right half plane. We can arrive at such a criterion by relying on an extension of the Gauss-Lucas theorem (a generalization of Rolle’s theorem), which states that the convex hull of the set of roots of a polynomial $P$ contains all roots of its derivative. If we take the derivative of the left hand side of (3.4) and re-define $\tilde{\tau}_2 = \tau_1 + \tau_2$, $\alpha = \frac{1}{\tau}(a_1 + a_4)$, $\beta = -\frac{1}{2} \tau_1 a_2 b_3$, and $\gamma = -\frac{1}{2} \tilde{\tau}_2 b_3 c_2$, the equation takes the form

$$\lambda = \alpha + \beta e^{-\tau_1 \lambda} + \gamma e^{-\tilde{\tau}_2 \lambda} \quad (3.5)$$

Due to the two exponential terms in this equation, the Lambert W solution presented in the introduction does not apply. Even so, the one-delay problem still has many similarities to the one introduced here. Specifically, both problems involve exponential polynomials and therefore belong to the same general class. As such, both have an infinite cascade of roots, a finite number of which lie to the right of any vertical line in the complex plane. Using the framework Bortz presents in [13], we can solve analytically for the roots $\tilde{\lambda}_i$ that satisfy this equation. For convenience, we summarize the solution here. The roots are

$$\tilde{\lambda}_j = \frac{1}{\tau} (\ln_j \gamma_2 + \ln(\frac{1}{\ln_j \gamma_2}) + \ln \tau + v_j) + \alpha_1 \quad (3.6)$$

where $\tau = \tau_1 / \tilde{\tau}_2$, $\alpha_1 = \alpha \tau_1$, $\gamma_2 = (\gamma \tau_1) e^{-\alpha_1 \tau}$, and $v_j$ is given by

$$v_j = \sum_{k=0}^{\infty} \sum_{n=1}^{\infty} m^k h_{m,k} \frac{\mu^m \sigma^k}{m!} \quad (3.7)$$

where $\beta_2 = (\beta \tau_1) e^{-\alpha_1}$, $\sigma = \frac{1}{\ln \gamma_2}$, $c = \left(\frac{\beta_2}{\gamma_2}\right) \left(\frac{\gamma_2 \tau_1}{\ln \gamma_2}\right)^{(\frac{\mu-1}{\sigma})}$, $\mu = \frac{\ln \tau + \ln(1/Ln \gamma_2)}{Ln \gamma_2} - c$, $m^k$ denotes a rising factorial$^1$, and

$$h_{m,k} = \frac{\sum_{l=0}^{m-1} \sum_{p=0}^{l} \sum_{q=0}^{2m-2-l} a_{k l m p q} B_{2m-2-l-q,m-1-p}(F_{m-l-q+p}) \Gamma(q) (F_{q-1})}{(-1 + c \tau^{-1})^{2m+k-1}}.$$  

$^1$ Here, $m^k$ is defined as $m(m + 1) \ldots (m + k - 1)$. This is also sometimes denoted by the Pochhammer symbol $m^{(k)}$, but we avoid this notation here to prevent confusion with the parentheses notation for differentiation.
Here, $F_n = \{(-1)^n(1 + e\tau^{-n})\}_{i=1}^n$, $\mathbb{B}_{l,p}$ are the partial Bell polynomials [2, 9, 10], and

$$\hat{a}_{kilmq} = \frac{(-1)^p(k + m)\Gamma(m)\Gamma(m - p)\Gamma(k + m + p)}{q!!\Gamma(2 + k + l)\Gamma(-l + m)\Gamma(-1 - l + 2m - q)}.$$

Note that these $\tilde{\lambda}_j$, in general, do not solve the original equation (3.4). However, we can now invoke the following extension to the Gauss-Lucas theorem:

**Conjecture 1.** If $P$ is an exponential polynomial with complex coefficients, then all zeros of $P'$ belong to the convex hull of the set of zeros of $P$.

We were unable to find any formal proof for this statement, and we leave it without proof here. The extension seems reasonable, however, since the exponential terms in (3.4) can be interpreted as polynomials of infinite degree, and since it holds for the examples we examined. Under our notation, this conjecture states that the roots $\tilde{\lambda}_i$ of (3.5) belong to the convex hull of the roots $\lambda_i$ of (3.4). We note that, if we draw a vertical line through the dominant eigenvalue(s) $\lambda_i$ of (3.4), the region to the left of this line will cover the convex hull of the roots of that equation (if it did not, then some root would have to lie to the right of the dominant eigenvalue, which is a contradiction). The extended Gauss-Lucas theorem guarantees that the roots of (3.5) lie within this region. So, it is impossible for a root of the derivative (3.5) to lie to the right of the dominant eigenvalue(s) of (3.4), and thus the real part of the derivative’s dominant eigenvalue provides a lower bound for the real part of the dominant eigenvalue of (3.4). Therefore, if the dominant eigenvalue of (3.5) has positive real part, one can conclude that the solution of the DDE system (3.1) is unstable.

### 3.1 Example

We can make the previous argument clearer by examining a specific case. Consider the equation

$$\lambda^2 - a\lambda + be^{-\tau_1\lambda} + ce^{-\tau_2\lambda} = 0$$

(3.8)
where $a = -2$, $b = 0.0008$, $c = 0.08$, $\tau_1 = 1$, and $\tau_2 = 5$. We choose these parameters to ensure that the convergence criterion

$$\left| \frac{\beta \tau_1 e^{-\alpha \tau_1}}{(\gamma \tau_1 e^{-\alpha \tau_1^2 / \tau_2} \ln \gamma \tau_1 e^{-\alpha \tau_1^2 / \tau_2})} \right| < 1$$

from [13] holds, where $\alpha = \frac{a}{2}$, $\beta = \frac{b}{2}$, and $\gamma = \frac{c}{2}$. Taking the derivative of (3.8) and substituting in these values, we obtain

$$\lambda - \alpha - \beta e^{-\tau_1 \lambda} - \gamma e^{-\tau_2 \lambda} = 0 \quad (3.9)$$

This is now of the same form as Equation (3.5). Figure 3.1 depicts the roots of this equation. According to the Gauss-Lucas theorem, of these roots should lie within the convex hull of the roots of Equation (3.8). The dominant eigenvalue lies at approximately -0.2611, so the dominant eigenvalue of Equation (3.8) should have real part greater than this.

![Figure 3.1: Plot of rightmost roots of Equation (3.9), computed using the expansion (3.6). The horizontal axis is the real part of $\lambda$ and the vertical axis is the imaginary part of $\lambda$.](image)

To check this, we can observe where the roots of Equation (3.8) lie by plotting a contour surface of its inverse so that the roots become poles. Figure 3.2 depicts this contour with the roots of the derivative overlaid. Note that, as expected, the dominant eigenvalue of Equation (3.8) lies to the right of the rightmost root of its derivative. Furthermore, we note that the rightmost derivative root lies \textit{between} the two rightmost stability eigenvalues; this has been the case for every example
we tried. This is particularly useful in the case where the dominant stability eigenvalues are a complex conjugate pair, since the rightmost derivative root’s real part equals the real part of the conjugate pair. In other words, the rightmost derivative root specifies the vertical line on which the dominant stability eigenvalues lie. Figure 4.3 in Section 4 depicts an instance of this important case.

Note that it might appear from Figure 3.2 that some of the roots of the derivative lie outside of the convex hull of the roots of 3.8. This is simply due to having a limited plot window. As noted in the introduction, both 3.8 and its derivative have an infinite cascade of roots. Figure 3.2 implies that the complex hull of these roots is a wedge with vertex at the dominant eigenvalue. Due to the infinite root cascade, the angle of this wedge tends to approach 180°. Because of this, we refrain from saying anything about the convex hulls of either set of roots except that they are fully contained in the half-plane whose barrier is the vertical line through the rightmost root of that set. Fortunately, this is all we need to make our conclusion about the stability of system (3.1).
Figure 3.2: Contour plot of \( (\lambda^2 - a\lambda + be^{-\tau_1\lambda} + ce^{-\tau_2\lambda})^{-1} \), the inverse of Equation (3.8), with the analytic roots of its derivative overlaid. The horizontal axis is the real part of \( \lambda \) and the vertical axis is the imaginary part of \( \lambda \). The darker regions of the contour plot correspond to the eigenvalues of Equation (3.8). Note that the dominant eigenvalue of (3.8) lies to the right of the dominant eigenvalue of its derivative. This is a generally true statement for problems of this type - that the real part of the dominant eigenvalue of the derivative will provide a lower bound for the real part of the dominant eigenvalue of the original equation.
Chapter 4

Model Analysis

We now return to our study of the model of the human glucose-insulin system set forth in Chapter 2. Here, we will demonstrate how the model allows us to propose treatment strategies for diabetes. We will also substantiate our hypothesis that insulin therapy intensifies the need for diabetic patients to more tightly control their insulin sensitivity. Since type I and type II diabetes differ so significantly in origin and in the type of therapy required, we will address them separately here, starting with the more prevalent type II.

4.1 Type II diabetes

To lay the groundwork to find conditions under which BGC will be controlled at an acceptable level and will oscillate, we consider the fasting case with no insulin therapy, i.e. \( G_{in} = I_{in} = 0 \). This corresponds to the conditions one would expect for an individual undergoing diagnostic tests for diabetes, which are normally done after a fast of at least eight hours [6]. We will first demonstrate how to determine an individual’s steady state (or average) BGC, and will then show how to determine whether that person’s glucose concentration oscillates.

To simplify our analysis, we note that we can combine the information given by \( \gamma \) and \( m \) into a single parameter \( \kappa \equiv \gamma [1 + s(m - m_b)] \) that describes a person’s overall glucose uptake efficiency. The lowest physiologically possible value for \( \kappa \) occurs when \( \gamma = m = 0 \), for which \( \kappa = 0 \). A feasible upper value for \( \kappa \) occurs when \( \gamma = 1 \) and \( m = 120 \) (that is, two hours of moderate to vigorous physical activity daily, which seems reasonable for the most active individuals), giving \( \kappa = 1.432 \).
We will assume that $\kappa$ can range between 0 and 1.5.

In order to estimate the patient’s average BGC we calculate the system’s steady state, setting $G' = I' = 0$, $G(t) = G(t - \tau_1) = G^*$, and $I(t) = I(t - \tau_2) = I^*$. The constants $G^*$ and $I^*$ are the glucose and insulin steady states, respectively; all that remains is to solve for them. Since $G$ and $I$ arise in functions $f_1 - f_5$ as exponents, bases of exponents, and linear terms, it is very difficult to solve for the steady states $G^*$ and $I^*$ analytically. We instead do so numerically using the default Trust Region algorithm implemented in MATLAB’s `fsolve` function. Figure 4.1 depicts solutions of the glucose steady state for varying $\beta$ and $\kappa$, with all other parameters $(\tau_1, \tau_2, V_{\text{max}}, K_M)$ held constant. It is immediately apparent from Figure 4.1 that pancreatic efficiency $\beta$ is much more important than insulin sensitivity $\kappa$ for determining a patient’s average BGC. As expected, increasing either $\beta$ or $\kappa$ will lead to a lower BGC.

Now we would like to determine when a person’s glucose concentration will oscillate. To do so, we linearize the model with respect to the substrates ($G$ and $I$) about the steady state, and then find which parameter values yield eigenvalues with real part in the positive half-plane. The linearization gives three Jacobian matrices:

$$J_0 = \begin{bmatrix} -f_2'(G^*) - \kappa f_3'(G^*)f_4(I^*) & -\kappa f_3(G^*)f_4'(I^*) \\ 0 & V_{\text{max}}K_M/((K_M+I^*)^2) \end{bmatrix}$$

$$J_1 = \begin{bmatrix} 0 & 0 \\ \beta f_5'(G^*) & 0 \end{bmatrix}$$

$$J_2 = \begin{bmatrix} 0 & f_1'(I^*) \\ 0 & 0 \end{bmatrix}.$$

The linear system is then

$$\begin{pmatrix} G(t) \\ I(t) \end{pmatrix}' = J_0 \begin{pmatrix} G(t) \\ I(t) \end{pmatrix} + J_1 \begin{pmatrix} G(t - \tau_1) \\ I(t - \tau_1) \end{pmatrix} + J_2 \begin{pmatrix} G(t - \tau_2) \\ I(t - \tau_2) \end{pmatrix}.$$

Assuming solutions of the form $e^{\lambda t}$, we arrive at the following eigenvalue equation:

$$|J_0 + e^{-\lambda \tau_1}J_1 + e^{-\lambda \tau_2}J_2 - \lambda I| = 0 \tag{4.1}$$
Figure 4.1: This figure depicts a person’s steady state (average) blood glucose concentration as a function of pancreatic efficiency $\beta$ and insulin sensitivity $\kappa$. It is apparent, according to the model, $\beta$ affects blood glucose concentration much more strongly than $\kappa$. Also, small increases in $\beta$ for a very poorly-functioning pancreas result in much more dramatic changes in blood glucose concentration than similar changes for an already well-functioning pancreas. Other model parameters are held fixed at: $\tau_1 = 5$, $\tau_2 = 15$, $V_{max} = 150$, and $K_M = 2300$. 
Note that this linearized model and eigenvalue equation (4.1) match the form given in Chapter 3. Following the framework set forth there, we can differentiate the determinant in Equation (4.1) and calculate the derivative's roots analytically. Figure 4.2 provides these roots for a non-diabetic individual. Note that the rightmost root has positive real part, so we expect the solution to oscillate. Plotting the inverse of the determinant (4.1) and looking for poles allows us to identify the stability eigenvalues for this non-diabetic person; this is depicted in Figure 4.3. Note that, as expected, the dominant (rightmost) eigenvalues lie in the positive half plane, indicating stable blood glucose oscillations.

![Figure 4.2: Roots of the derivative of the stability eigenvalue equation (4.1) for a non-diabetic individual, with $\tau_1 = 5$, $\tau_2 = 15$, $\beta = 1$, $\gamma = 1$, $m = 60$, $V_{max} = 150$, and $K_M = 2300$. The rightmost root lies in the right half-plane, which, according to the formulation in Chapter 3, indicates that the glucose steady state is unstable (i.e. oscillatory).](image)

The eigenvalues move as the model parameters change, with increasing values of $\beta$ and decreasing values of $\kappa$ tending to induce a leftward shift in the eigenvalues. The dominant eigenvalues eventually cross the imaginary axis into the negative real half-plane, indicating the disappearance of ultradian glucose oscillations. Figure 4.4 depicts just how the real part of the dominant eigenvalue changes for various pancreatic efficiencies ($\beta$) as a function of insulin sensitivity ($\kappa$).

We are now in a position to determine which parameter values give an overall healthy blood
Figure 4.3: Contour plot of the logged-inverse of the determinant given by the left-hand side of Equation 4.1, with roots of its derivative (same as in Figure 4.2) overlaid. The poles (lighter regions) indicate the stability eigenvalues of the linearized model. These eigenvalues correspond to a non-diabetic individual, with $\tau_1 = 5$, $\tau_2 = 15$, $\beta = 1$, $\gamma = 1$, $m = 60$, $V_{\text{max}} = 150$, and $K_M = 2300$. Note that the dominant (rightmost) stability eigenvalues lie in the positive half-plane, indicating stable oscillations in blood glucose concentration. Note also that the rightmost derivative root gives a good approximation for the real part of the model’s dominant stability eigenvalue.
Figure 4.4: This plot indicates how the real part of the linearized system’s dominant eigenvalue changes with insulin sensitivity $\kappa$ for a few fixed values of $\beta$. The region below the $Re(\lambda) = 0$ line corresponds to a stable solution, while the region above corresponds to oscillatory solutions. It appears that higher values of both $\beta$ and $\kappa$ will tend to give rise to oscillatory solutions.
glucose profile, marked by oscillatory glucose oscillations in a moderate (80-120 mg/dl) range. First, we would like to determine which values of $\beta$ and $\kappa$ give steady state solutions between 80 and 120 mg/dl. To do so, we note that, given the steady state values $G^*$ and $I^*$, we can solve for the parameters $\kappa$ and $\beta$:

$$
\kappa = \frac{-f_2(G^*) + f_5(I^*)}{f_3(G^*)f_4(I^*)} \quad (4.2)
$$

$$
\beta = \frac{V_{\text{max}}I^*}{f_1(G^*)(K_m + I^*)} \quad (4.3)
$$

To find the $\kappa - \beta$ isocline for the upper glucose threshold, we set $G^* = 120$ (equal to the highest acceptable BGC) and vary $I^*$ from 0 $\mu$U/ml to some high value (100 $\mu$U/ml is sufficient); thus, $\kappa$ and $\beta$ become parametric functions with respect to $I^*$. This isocline is depicted in Figure 4.5 by the line that separates Regions I and IV from regions II and III (the “glucose concentration threshold”). All values of $\beta$ and $\kappa$ in the fasting case yield average glucose concentrations above 80 mg/dl, so we do not show a similar curve for this lower glucose threshold.

Next, we want to determine which $\beta$ and $\kappa$ values yield oscillatory solutions. We solve numerically for which $\beta$ and $\kappa$ make the real part of the dominant eigenvalue calculated in Equation (4.1) equal to zero, indicating a change in sign in that eigenvalue’s real part. The result is depicted in Figure 4.5, with the line that separates Regions I and II from Regions III and IV (the “oscillation threshold”).

Let us now take a closer look at Figure 4.5. In Regions III and IV we can expect blood glucose oscillations, and in Regions II and III we will observe blood glucose concentrations in an acceptable range (i.e. $G^* < 120$mg/dl). So, for a patient to have a healthy (non-diabetic) glucose and insulin profile, he or she should have physiological parameters $\kappa$ and $\beta$ that graphically would appear in Region III.\(^1\)

When we introduce nutrition (external glucose input), we anticipate needing tighter requirements on the parameters to maintain a healthy average blood glucose concentration and stable

---

\(^1\) We here omit $\beta$ values less than 0.05. For such low $\beta$, pancreatic disability is so acute that the clinical diagnosis would likely be type I diabetes, which we consider separately at the end of this section. Mathematically, a singularity lies in this parameter range that makes numerical solutions difficult to identify.
Figure 4.5: Separation of the parameter space under fasting conditions ($G_{in} = 0$) yielding (I) stable, hyperglycemic solutions; (II) stable, euglycemic solutions; (III) oscillatory, euglycemic conditions; and (IV) oscillatory, hyperglycemic conditions. The oscillation threshold line corresponds to the $\beta$ and $\gamma$ values that make the real part of the dominant eigenvalue equal to zero. The glucose concentration threshold line corresponds to the $\beta$ and $\gamma$ values that hold blood glucose concentration fixed at the upper threshold of 120 mg/dl.
glucose oscillations. We account for nutrition in the model by setting $G_{in} = 1.08 \, \text{mg/dl}$ (following [31]) and repeating the above analysis. The result is a similar partition of the parameter space, depicted in Figure 4.6. Here, Regions II* and III* give solutions in which the steady state glucose concentration is less than $120 \, \text{mg/dl}$, and Regions I* and II* give stable glucose oscillations.

Ideally, we would like to know which physiological parameter values will give a person a healthy blood glucose profile in both the fasting and exogenous glucose input cases. To illustrate where these parameters should lie, we can overlay the plots in Figures 4.5 and 4.6 and mark the region for which both the fasting and the nutrition circumstances predict stable oscillatory glucose concentrations below $120 \, \text{mg/dl}$. This information is depicted by the shaded region in Figure 4.7. We observe that if a patient’s pancreatic efficiency $\beta$, insulin sensitivity $\gamma$, and physical activity $m$ can be adjusted through medication and exercise so that they lie in this region, the patient’s diabetes will be sufficiently controlled. We also note that this region fills only a portion of the larger region that would give rise to healthy average blood glucose concentrations while ignoring ultradian oscillations; that is, simply reducing a diabetic person’s blood glucose levels to a normal range, as is the goal of current treatment strategies, may not be enough to induce the oscillations that are characteristic of a healthy blood-glucose profile.

For one more illustration, let us show how insulin therapy might assist a patient’s treatment strategy. We might expect that insulin therapy will reduce the need for a well-functioning pancreas (i.e. $\beta$ can be lower), but the effect on insulin sensitivity ($\kappa$) is more difficult to predict. To address this point, we introduce constant insulin infusion into the model at a rate of $I_{in} = 0.2 \, \mu \text{U/ml-min}$ and again determine which $\beta$ and $\kappa$ values yield oscillatory glucose concentrations in a healthy range under fasting and constant nutrition. We depict these results in Figure 4.8. As predicted, we see that incorporating insulin therapy makes possible a healthy glucose profile at lower $\beta$ values. However, the region shrinks in the $\kappa$-direction, suggesting that with insulin therapy a patient will need to maintain even tighter control over their insulin sensitivity through some combination of exercise and medication.
Figure 4.6: Separation of the parameter space under constant nutrition conditions \( (G_{\text{in}} = 1.08) \) yielding (I) oscillatory, hyperglycemic solutions; (II) oscillatory, euglycemic solutions; (III) stable, euglycemic conditions; and (IV) stable, hyperglycemic conditions. The oscillation threshold line corresponds to the \( \beta \) and \( \gamma \) values that make the real part of the dominant eigenvalue equal to zero. The glucose concentration threshold line corresponds to the \( \beta \) and \( \gamma \) values that hold blood glucose concentration fixed at the upper threshold of 120 mg/dl.
Figure 4.7: Overlay of fasting and constant-nutrition region plots (Figures 4.5 and 4.6). The shaded area indicates parameter values that yield oscillatory glucose concentrations in a healthy range for both fasting and constant nutrition.

Figure 4.8: Overlay of fasting and constant-nutrition region plots with insulin therapy ($I_{in} = 0.2 \mu U/ml\cdot min$). The shaded area indicates parameter values that yield oscillatory glucose concentrations in a healthy range for both fasting and constant nutrition.
4.2 Type I diabetes

In the case of type I diabetes, the pancreas is incapable of producing insulin (i.e. \( \beta = 0 \)), and so healthy glucose levels can only be maintained through the injection of external insulin. It is not possible to induce stable glucose oscillations under these conditions, but we can still determine how much insulin is required to keep glucose within a range of 80-120 mg/dl. Starting with the steady state relation

\[
0 = G_{in} - f_2(G^*) - \kappa f_3(G^*) f_4(I^*) + f_5(I^*)
\]

\[
0 = I_{in} - \frac{V_{max} I^*}{K_M + I^*}
\]

we can solve for \( \kappa \) and \( I_{in} \) as follows:

\[
\kappa = \frac{G_{in} - f_2(G^*) + f_5(I^*)}{f_3(G^*) f_4(I^*)}
\] (4.4)

\[
I_{in} = \frac{V_{max} I^*}{(K_M + I^*)}
\] (4.5)

As before, we first consider the fasting case, where \( G_{in} = 0 \). Holding \( G^* \) fixed at 80 mg/dl and 120 mg/dl and treating \( I^* \) as a parametric variable we can outline a region in which, for a given \( \kappa \), we can find how much insulin \( (I_{in}) \) is required to maintain a healthy blood glucose concentration. We can repeat this process with the “full nutrition case” where \( G_{in} = 1.08 \text{mg/dl-min} \), producing a second such region that gives the required insulin when a person receives nutrition. These regions are depicted in Figure 4.9. The lighter area between the regions depicts the insulin infusion rates that would be effective when glucose intake is somewhere between fasting and full nutrition. As one might expect, the amount of insulin required increases sharply when the body’s insulin sensitivity \( (\kappa) \) becomes low.
Figure 4.9: This plot indicates how much insulin is required for a type I diabetic to maintain a healthy BGC given insulin sensitivity $\kappa$. The dark upper band indicates the insulin infusion rates that will keep a type 1 diabetic’s BGC at an acceptable level with “full nutrition” ($G_{in} = 1.08$ $mg/dl \cdot min$). The dark lower band indicates the insulin infusion rates necessary to keep a fasting type 1 diabetic’s BGC at an acceptable level ($G_{in} = 0$). The lighter region in between the two bands corresponds to the insulin required to maintain an acceptable BCG for nutrition levels between fasting and full.
Chapter 5

Hypothetical Case Studies

5.1 Type II diabetic treatment

To illustrate the value of the analysis in Section 4, let us consider a hypothetical type II diabetic. The patient’s fasting glucose is measured at 130 mg/dl, higher than the ADA’s 125 mg/dl threshold for diabetes diagnosis [6]. The patient’s doctor measures the patient’s pancreatic efficiency and insulin sensitivity using a euglycemic glucose clamp or an oral glucose tolerance test and the minimal model, two techniques that have been used in the past to characterize a patient’s disease [11, 15, 23, 36]. Results show that the patient’s pancreas functions at 40% of normal efficiency and that the patient’s insulin sensitivity is 40% that of an average non-diabetic person. The patient lives a largely sedentary life, so the amount of moderate to physical activity per day the patient receives ($m$) is virtually zero. From this information, the doctor can readily deduce the parameter values $\beta = 0.4$ and $\kappa = 0.4 \cdot [1 + 0.0072 \cdot (0 - 60)] = 0.23$. Figure 5.1 shows the model’s prediction of the patient’s glucose and insulin profile; note that the patient is certainly hyperglycemic, since the patient’s blood glucose concentration regularly exceeds 130 mg/dl. By placing the patient’s particular $\beta$ and $\kappa$ values on the plot in Figure 4.7 it becomes apparent that the patient requires an increase in both pancreatic efficiency and insulin sensitivity. There are now several options that could help re-establish glycemic control. To increase the patient’s insulin sensitivity, the doctor could place the patient on a medication such as Metformin that would increase $\gamma$ to 0.7, along with introducing 60 minutes of physical activity per day [29]. Then, to decrease the patient’s BGC, the doctor could increase the patient’s pancreatic efficiency $\beta$ to 0.6 using sulfonylurea drugs [1]. Note
that Hardy et al. [25] found that medication and lifestyle changes (i.e. exercise) can yield up to at 50% increase in pancreatic efficiency, so this increase from 40% to 60% of normal is reasonable. The model’s prediction for this scenario is depicted in Figure 5.2. Alternatively, the doctor could prescribe insulin therapy in the form of $0.2 \, \mu U/ml\cdot min$ administered continuously by an artificial pancreas; then, the patient’s pancreatic efficiency would only have to increase to about 0.4 through the use of sulfonylureas. An additional 60 minutes of daily exercise would increase the patient’s insulin sensitivity enough to give the patient a healthy blood glucose profile, depicted in Figure 5.3. This example illustrates how, with proper verification and validation, our analysis and proposed model could help characterize a specific individual’s disease and inform medical care. Our results make it easy to consider multiple treatment options involving medication, changes in lifestyle, and/or medical technology, allowing the patient to choose the lifestyle changes and therapies that work best him or her.

5.2 Type I diabetic treatment

Let us now consider a different patient, a type I diabetic ($\beta = 0$) whose insulin sensitivity is about 75% that of an average non-diabetic person ($\gamma = .75$), and who receives about an hour of exercise per day ($m = 60$). Figure 5.4 shows this patient’s glucose and insulin profiles in the absence of treatment; with a fasting steady state BGC greater than three times the ADA-suggested upper value (and matching levels that Nathan et al. describe as “severely uncontrolled diabetes” [32]), an intervention is clearly necessary. Figure 5.4 also includes a phase portrait of the glucose and insulin concentrations, demonstrating clear stable oscillations. Similar phase portraits arise from the remaining glucose-insulin profiles that will be presented, and are omitted here. To make use of the information depicted in Figure 4.9, the patient’s doctor could first calculate the patient’s particular $\kappa$-value; in this case, $\kappa = 0.75[1 + 0.0072(60 - 60)] = 0.75$. From Figure 4.9, we see that an insulin infusion rate between 0.45 and 0.7 $\mu U/ml\cdot min$ from an artificial pancreas could adequately control the patient’s BGC, depending on the patient’s glucose intake rate. Figure 5.5 depicts the patient’s glucose and insulin profiles with full nutrition ($G_{in} = 1.08$) and an insulin infusion rate of
$I_{in} = 0.65 \mu U/ml\cdot min$; with a BGC of 100 mg/dl, the patient’s glucose levels are adequately controlled.
Figure 5.1: Glucose and insulin profiles and phase plane for a type II diabetic with no treatment ($G_{in} = 0$, $I_{in} = 0$, $\tau_1 = 5$, $\tau_2 = 15$, $\beta = .4$, $\gamma = .4$, $m = 0$, $V_{max} = 150$, $K_M = 2300$)
Figure 5.2: Glucose and insulin profiles for a type II diabetic under the first treatment strategy \((G_{in} = 1.08, I_{in} = 0, \tau_1 = 5, \tau_2 = 15, \beta = .6, \gamma = .7, m = 60, V_{max} = 150, K_M = 2300)\)

Figure 5.3: Glucose and insulin profiles for a type II diabetic under the second treatment strategy \((G_{in} = 1.08, I_{in} = 0.2, \tau_1 = 5, \tau_2 = 15, \beta = .4, \gamma = .7, m = 120, V_{max} = 150, K_M = 2300)\)
Figure 5.4: Glucose and insulin profiles for a type I diabetic with no treatment \((G_{in} = 0, I_{in} = 0, \tau_1 = 5, \tau_2 = 15, \beta = 0, \gamma = .75, m = 60, V_{max} = 150, K_M = 2300)\)

Figure 5.5: Glucose and insulin profiles for a type I diabetic with insulin therapy \((G_{in} = 1.08, I_{in} = 0.65, \tau_1 = 5, \tau_2 = 15, \beta = 0, \gamma = .75, m = 60, V_{max} = 150, K_M = 2300)\)
Chapter 6

Conclusions

With this work, we have provided the necessary tools to identify personalized treatment strategies for diabetic patients based on current clinical recommendations, with the important addition of explicitly accounting for the effect of exercise on insulin sensitivity. We have furthermore shown that common treatment strategies may omit the ultradian glucose oscillations normally observed in healthy individuals, and so we lay a framework to ensure that these oscillations are also maintained. In doing so, we have developed mathematical theory that provides a closed-form condition to indicate the presence of blood glucose oscillations. In particular, we have shown that a type II diabetic’s blood glucose levels should be adequately controlled and oscillations will be maintained when the patient gets an hour of daily exercise and is placed on a combination of Metformin and sulfonylurea drugs to increase his or her insulin sensitivity and pancreatic efficiency, respectively, to 70% and 60% of normal. Insulin therapy and an additional hour of exercise reduce the patient’s need for sulfonylureas, requiring those drugs to increase the patient’s pancreatic efficiency to only 40% of normal. Similarly, we have proposed that a particular type I diabetic’s blood glucose levels can be properly controlled with a constant insulin infusion between 0.45 and 0.7 $\mu$U/ml-min, if the patient takes in glucose at a constant rate. With proper verification, the model presented here could serve as a valuable clinical tool, helping to provide diabetic patients with a range of treatment options.

A logical next step is to account for non-constant glucose infusion from meals and for periodic insulin infusion due to injection, in order to more closely represent the day-to-day variability in a
diabetic person’s glucose and insulin intake. We note that, following previous work in this field, our model does not explicitly account for the effect of glucagon. While this does not seem to negatively impact the model’s ability to replicate the human glucose regulatory system, future models might achieve even better physiological correspondence by accounting for this additional hormone. We also note that other organs, such as the kidneys, supplement the liver’s glucose production. Accounting for these organs’ effects in future models might yield further insights into the onset of blood glucose oscillations and could broaden treatment options.

Mathematically, the clearest next step is to prove the conjecture presented in Chapter 3, which extends the Gauss-Lucas theorem to exponential polynomials. Another important step would be to fully extend the analytic solution for delay differential equations with two delays presented in [13] to systems of DDEs with two delays. This would allow for an even more complete analysis of the model, providing explicit stability conditions and providing greater insight into the model parameters’ effects on the overall solution.

Ultimately, we hope that this work will aid in development of an algorithm to determine precisely when and how much insulin should be injected to maintain a diabetic person’s BGC in a healthy range, given their activity levels, pancreatic efficiency, and insulin sensitivity. We envision applying this algorithm to an artificial pancreas which, with a small amount of initial programming and information from an embedded accelerometer, would require minimal user input. A recent review of existing devices calls for “smart control algorithms” for that better control glucose and insulin oscillations; we anticipate that this work will respond directly to that call [18]. The development of such a device would undoubtedly allow people with diabetes to live freer, simpler, and healthier lives.


