A Pattern Matching Algorithm for Self-Adjusting Basal Rates in Insulin Pump Systems

A Dissertation Presented for the
Doctor of Philosophy
Degree
The University of Tennessee, Knoxville

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May 2024

DEDICATION

This dissertation is dedicated to my brother, Jackson. From the very beginning, you have always been the thing I loved to protect the most. Wherever you went, I was not far behind, and vice versa. When I think back to our childhood, we really had the best; full of so many fun memories on vacations, hanging out with family and playing out in the neighborhood together. We really had it good because we really do have the greatest parents ever. Being your big sister has truly been one of my greatest joys in life so far. On January 17, 2005, our lives truly changed forever, when we found out that you were diagnosed with type 1 diabetes. My heart truly broke for you to have to take on such a huge burden at such a young age. As you grew up and graduated from injections via syringe to insulin pens to an insulin pump, I saw the evolution of the technology that kept you alive and how it really did make your life a little bit easier each time. Seeing this, I knew very early on that I wanted to have a hand in making a difference in type 1 diabetes Research, specifically with technology, as I truly believe innovation in this area is the greatest thing we can do until we find a cure. You have always been and will always be not only my little brother, but my hero. The strength and courage you had to have at such a young age will always be one of the most unbelievable things to me. There would be no dissertation without you. Thank you for helping me discover my passion and purpose on this Earth. I love you.

This dissertation is also dedicated to my parents, Lori and Dwayne. I truly would not have made it where I am today if it wasn't for the love, support and guidance that each of you have given me from the very beginning of it all. You both have always pushed me to be not only the best student, but the best person I can be. Being away from home for the past 10 years was the hardest thing of my life, but with the countless trips and memories we have all made in Knoxville together, I will always look back on this time with so much happiness and gratitude. Thank you

both for always making sure I know that I'm loved and supported, no matter what obstacles I've had to go through in life. Thank you both for helping me fall in love with the greatest school in the world. Orange will always be my favorite color. I love you both more than words could ever describe.

ACKNOWLEDGEMENTS

I would like to thank Dr. Richard Komistek for your guidance throughout my time at the Center for Musculoskeletal Research. Your knowledge and passion for research has truly affirmed my passion to pursue a career in research as well. Thank you for always pushing me. Without you, this PhD would not have been possible.

Thank you to Dr. Michael LaCour for your guidance and knowledge throughout my time at CMR. You have been an invaluable resource throughout my education and have taught me to be persistent and persevere through it all.

Thank you to Dr. Donald Ryder and Dr. Michael Stewart for giving me THE opportunity of a lifetime: being in The Pride of The Southland Band. Growing up the biggest Tennessee fan, being in the Pride and looking up to 102,455 screaming fans while "Opening the T" was always a dream. Anytime someone asks me about my time in the Pride, I always smile and tell them it truly was the best decision I have ever made. The memories, friendships and lessons learned are parallel to none. Being apart of the most prestigious collegiate marching band in the country will always be one of my greatest accomplishments in life and out of all the things that I have learned, learning that I will never get tired of hearing Rocky Top is one of the greatest. Go Vols and Go Pride.

Thank you to Mrs. Julie Knoefel for your unwavering support and guidance while at Tennessee. Whether it was helping me get my classes figured out, sorting through endless paperwork for graduation or even our countless little talks and check ins, you always greeted me with a smiling face and made me feel like I had someone in my corner cheering me on. My appreciation for you is more than I could ever describe.

Finally, I would like to thank my CMR co-workers Garett Dessinger, Seth Coomer, Jarrod Nachtrab, Thang Ngyuen and Viet Ngyuen for your support and assistance along the way. I wish each of you the best of luck in your future.

ABSTRACT

In a Type 1 Diabetic, Insulin can be administered in a pump system. There are two types of insulin that must be given: basal and bolus. Basal insulin is a long-acting form of insulin that works in the background while fasting, while Bolus insulin is rapid/short acting given in response to food to immediately begin working to lower blood sugar.

Modeling in Diabetes can be represented by algorithmic approaches ranging from simple autoregressive models of the continuous glucose monitor time series to multivariate nonlinear regression techniques of machine learning. Other examples of modeling in Diabetes include prediction models of hypoglycemia and even non-linear models of glucose. Regardless of technique, modeling can be used to accurately predict vital trends regarding something as prominent as glucose levels. Data from predicting trends in glucose levels can then be used to potentially influence other parameters within technology like an insulin pump system.

With this being said, if a pattern-matching algorithm could be developed to allow for a "personalized" basal rate, then blood sugar could be more controlled and reflect overall normal levels. This project aims to satisfy this proposal by 1) Developing a pattern-matching method that utilizes multiple stored glucose readings and basal rates in order to predict a new, suggested basal rate. 2) The new Basal Rate and predicted Glucose Levels will be displayed on the user interface of a developed GUI and allow for the user to accept or decline any change; thus, allowing for more controlled glucose readings throughout the day.

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CHAPTER 1: INTRODUCTION

1.1 DIABETES MELLITUS

Diabetes Mellitus is a metabolic disease that is centered around uncontrolled, elevated glucose levels in response to a lack of production, or response, to insulin. Insulin is considered one of the body's most important hormones, as it works to bind to glycoprotein receptors on the surface of cells, ultimately beginning the process of glucose utilization and the lowering of the amount of sugar in the blood [1–3]. This disease can be categorized in several ways, two of those being type 1 diabetes (T1D) and type 2 diabetes (T2D). T1D is a result of the lack of insulin secretion, due to the destruction of insulin producing, pancreatic beta cells by the body's own immune system, making this an auto-immune disease that elevates glucose levels in the blood. T2D is a result of a defective insulin response, where the body's pancreas is still able to produce insulin, however, does not properly respond to this hormone, again, leading to uncontrolled glucose levels [3]. While the pathologies, diagnoses and treatments for both T1D and T2D are different, both leave patients with uncontrolled, elevated glucose levels that if left untreated can lead to serious complications and even be fatal.

1.1.1 TYPE 1 DIABETES

Type 1 diabetes is an autoimmune disease that is characterized by the destruction of the pancreatic beta cells. This occurs when the insulin-producing pancreatic beta cells are destroyed by the body's own immune system, making it an autoimmune disease, as illustrated in Figure 1. Destruction of these beta cells leads to a decrease in insulin production, unchecked glucose production by the liver and ultimately fasting hyperglycemia. Therefore, glucose that is taken from food cannot be stored in the liver anymore, however it remains in the blood stream, which

then becomes detrimental to the body. As a result of this, the blood sugar of those affected by type 1 diabetes is no longer properly regulated by their own body. While glucose is essential in the human body to act in conjunction with Insulin, helping to raise sugar in our blood, too much glucose in the bloodstream can lead to a host of problems, all of which can be ultimately fatal if left untreated. For an average type 1 diabetic, a glucose reading of 0-60 milligram/deciliter would be considered a low blood sugar, a glucose reading of 60-170 mg/dl would be considered healthy or a target range depending on weather you are fasting or eating, etc., and a glucose reading of 170 mg/dL would be considered a high reading. If the patient is in the low range, they would want to obtain some form of sugar in order to raise their glucose levels, and if the patient is considered in the high range, they would want to take insulin in order to help lower and regulate their blood sugar to get them back down in the target range that was just described. To suffice for the lack of insulin production, injections or pump systems are used to manually deliver this hormone, thus regulating the level of sugar in the blood.

Common symptoms of this disease include increased fluid intake, frequent urination, extreme weight loss and fatigue, diminished vision, as well as irritability or mood changes [4]. Once the symptoms are present, diagnosis occurs after a blood sugar test, as well as a glycated hemoglobin test, otherwise known as an A1C test. A blood sugar test can be performed by pricking the finger and allowing the blood to be read through a glucose meter; a reading of more than 200 mg/dl can suggest diabetes. An A1C test reveals the average blood sugar level for the past 2 to 3 months. This test measures the percentage of blood sugar attached to hemoglobin, the oxygen carrying protein in red blood cells [5]. A normal A1C reading is anywhere between 5 and 5.5%, while anything higher than 5.7% can also suggest diabetes [5].

This dissertation will focus on those affected by type 1 diabetes. The cause and development of type 1 diabetes is unclear; however, it is thought to possibly stem from a combination of genetic and environmental factors, which many researchers believe those affected inherit a T1D causing gene that can then be triggered by an environmental factor, such as a virus [6]. Type 1 diabetics' immune system attacks the insulin producing beta cells of the pancreas, making it an auto-immune disease. Due to the lack of Insulin in a type 1 diabetic, Insulin must be administered via injection, a pump system, or an artificial pancreas. A healthy pancreas produces insulin in two different ways: basal insulin and bolus insulin. Basal insulin, often referred to as "background insulin" helps to regulate glucose levels while the body is fasting, between mealtimes, and is released continuously 24 hours a day. On the contrary, bolus insulin is secreted by the pancreas to help manage rise in glucose level in the blood in response to the intake and digestion of food [7]. As a Type 1 Diabetic now has to intake supplemental insulin via one of the methods described above, this insulin is likewise delivered in the forms of both basal and bolus insulin, as both are necessary for maintaining glucose level. Regardless of the method of treatment, all Type 1 diabetics must constantly be checking and assessing their glucose levels to make sure their disease is being managed properly. Ideally, they need to also manage their carbohydrate intake and stay active with daily exercise.

1.1.2 Current Methods of Treatment

Current methods of insulin administration consist of injections via syringe, insulin pumps paired with continuous glucose monitoring (CGM) and an artificial pancreas. The method of treatment that will be focused on in this dissertation is the insulin pump paired with a CGM. The Insulin pump itself consists of a detachable pump device that is attached usually at the hip using a belt clip and the temporary infusion site that is usually inserted in the abdomen area.

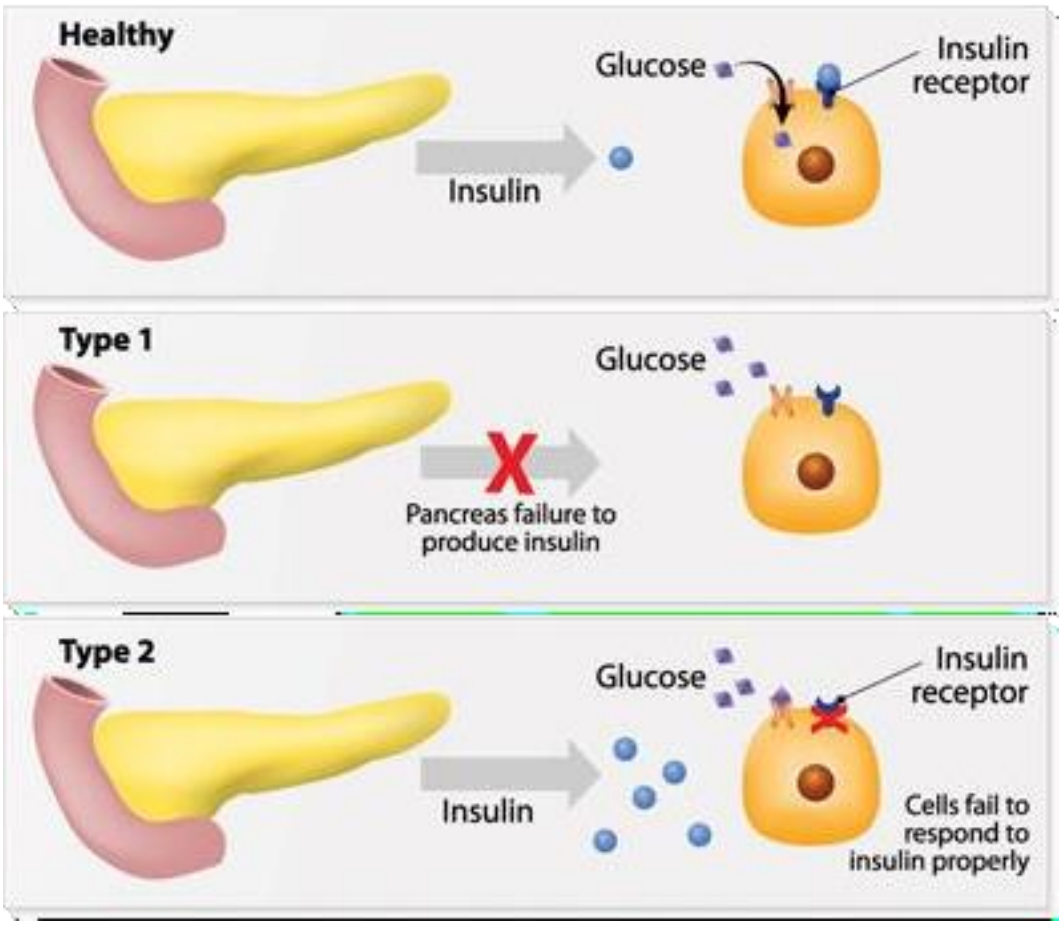


Figure 1: Schematic diagram showcasing the differences between a (top) healthy pancreas, (middle) pancreas of a Type 1 diabetic and a (bottom) Type 2 diabetic. Image from (primemedic.com).

The temporary needle or tube, known as a canula, that is inserted in the body is used to deliver insulin. For example, the Dexcom G6 or G7 continuous glucose monitor is a widely used system that is compatible with various Insulin Pump Systems, one being the t:slim X2 Insulin Pump, that can be seen in Figure 2. The pump system itself has a reservoir that contains short-acting insulin, allowing the patient to bolus after a meal or if their blood sugar is higher as well as program what is known as a basal rate. The basal rate is a specified number of units of insulin a user will receive every hour, on the hour. The pump system allows a user to administer both types of insulin. A very crucial aspect to the insulin pump system is what are known as the "pump settings". Your basal rate can influence all pump settings and vice versa. Each of these pump settings play a very crucial role in the overall diabetes management through this mechanical system. Some of the most prominent settings that can be found embedded within most insulin pumps are target blood glucose, insulin-to-carbohydrate ratio, insulin sensitivity factor and duration of insulin action.

Target Blood Glucose is the desired blood glucose level of the user that is programmed into the pump system. This can be programmed as a single overall target for the entire day or can be programmed as a target "range". Most pumps will allow the user to set multiple targets for different times of the day. The bolus calculator of the pump system uses the specified target in order to determine how much of "correction insulin" to recommend to the user in cases of high blood sugar.

Insulin-to-carbohydrate ratio (I:C) is the ratio that represents the number of grams of carbohydrates that will be covered by 1 unit of insulin (i.e., an insulin-to-carbohydrate ratio of 1:15 means that 1 unit of insulin will cover every 15 grams of carbohydrates that the user would eat.

Figure 2: T:Slim X2 Insulin Pump with compatible Dexcom G6 continuous glucose monitor. Image from (Dexcom.com).

For example, if a user ate a meal that contained 60 carbs and had an I:C of 1:15, then the pump system would recommend 4 units of insulin to be administered. Also, it should be noted that the I:C varies based on activity of the person with diabetes and if it occurred during fasting or eating.

Insulin Sensitivity Factor (ISF), otherwise known as a Correction Factor (CF) is a ratio that represents how much one unit of insulin is predicted to lower blood sugar (i.e., If 1 unit of insulin will drop your blood sugar by 25 mg/dl, then the ISF would be 1:25). For example, if your target blood sugar is 100 mg/dl and your current glucose level is 175 mg/dl, your pump would recommend delivering 3 units of insulin with an ISF of 1:25. An insulin pump system is also capable of pre-programming different ISF's during different times of the day; this can be helpful when considering that many people seem to be more insulin resistant in the morning time, thus would need to yield a higher ISF/correction factor.

Duration of Insulin Action (DIA) is a value that represents how long a bolus of insulin will take to finish lowering blood glucose. This time starts when bolus insulin is administered and ends when the bolus is no longer actively lowering blood glucose levels. When boluses are given too close together, hypoglycemia or insulin stacking can occur. Because DIA can and will vary from user to user, calculating this value is vital to prevent frequent lows if you underestimate and frequent highs if you overestimate. Diabetes Educator Gary Scheiner states that the DIA of an adult can have a DIA of 4-4.5 hours, while children have a DIA of 3-3.5 hours [8].

Unlike a single reading from a blood glucose meter, a CGM provides real-time, dynamic information about the speed and direction (trending higher or lower) of your glucose levels. Most CGM's will obtain a glucose reading from the user once every 5 minutes, equating to 288 blood glucose readings for a single day.

The CGM also makes this process very easy for the user, as it does not require much user interaction at all. Having continuous feedback on diet, exercise, and insulin requirements from a CGM can help you make more informed treatment decisions [9].

While all of these current methods described above are suitable ways to manage this disease, each have their shortcomings as well. Injections must happen multiple times a day, leaving room for infection to occur if proper injection techniques aren't practiced. Pump systems can also malfunction causing a mis-dosing issue with the insulin amount which can be very dangerous and lead to a diabetic coma or even ketoacidosis, which will be discussed in more detail below.

1.1.3 Complications in Type 1 Diabetes

In addition to hyperglycemia, or high blood sugar, there are other major chronic complications that can arise as a result of the body's ability to no longer regulate blood glucose autonomously, such as diabetic ketoacidosis, nephropathy (both peripheral and autonomic), retinopathy/macular edema and even diabetic foot diseases [10]. If a Type 1 Diabetic is not constantly monitoring their glucose levels and monitoring their Insulin administration properly, the likelihood of the patient developing one of the complications is much higher. Illustrated in Figure 3, Diabetic ketoacidosis (DKA) is a very serious complication that can be fatal and is the most common complication of those listed above. When a patient does not have enough insulin to allow blood sugar into their cells for energy, the liver begins to break down fat as a fuel source. The process of breaking down this fat to use for energy produces acids known as "ketones". When the level of ketones in the body is produced at a high rate, in high amounts, the level of ketones can be dangerous and even fatal [11]. Often, DKA can even be an initial sign of T1D diagnosis, as many are unaware of the increased blood glucose level prior to diagnosis.

1.1.4 TYPE 2 DIABETES

Type 2 diabetes has major issues of Insulin resistance and impaired Insulin secretion. As you can see in Figure 5, Insulin cannot bind with the special receptors, so Insulin becomes less effective at stimulating glucose uptake and at regulating the glucose release. There must be increased amounts of Insulin to maintain glucose level at a normal or slightly elevated level. However, there is enough Insulin being produced to prevent the breakdown of fats and production of ketones. Unlike Type 1, pancreatic beta cells are not recognized as a foreign body and attacked, so levels of Insulin production still occur. Type 2 diabetes can be treated with oral medication, Insulin injections, glucose monitoring, increased exercise and even a more regulated diet. Common symptoms of this disease are similar to those of type 1 diabetes. However, Type 2 diabetes is also often associated with obesity and is a much more common diagnosis than T1D, although Type 2 diabetes can be managed with changes in diet and exercise. If caught in the beginning stages, planned weight loss can sometimes reverse the disease [12].

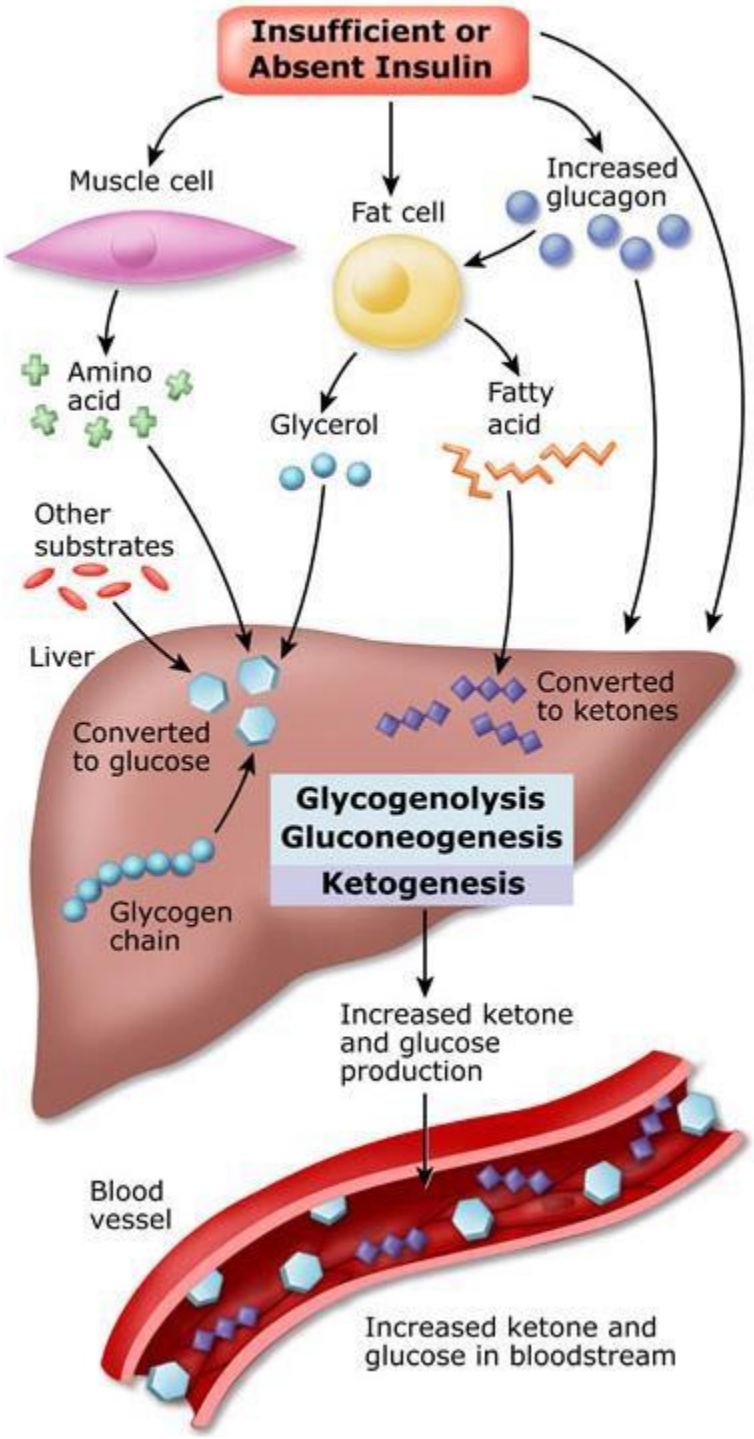


Figure 3: Schematic Diagram showing the processes leading to DKA. Image from (dtc.uscf.edu).

1.2 Anatomy and Function of the Human Pancreas

1.2.1 Anatomy

The pancreas is located in the superior portion of the abdomen, posterior of the stomach and anterior of the lumbar (L1-2) spine and is an elongated organ that consists of the head, body and the tail. The right side of the organ, known as the head, is the widest portion of the pancreas and constitutes about 50% of the entirety of the pancreas and lies along the curve of the duodenum, which is the beginning of the small intestine [13]. The left side of the organ contains the body of the pancreas, which then stretches superiorly, attaching to the tail of the pancreas, ultimately ending around the spleen as seen in Figure 4 [14]. As illustrated in Figure 5, the arterial blood supply of this organ comes from both the celiac and upper mesenteric arteries; likewise, the venous drainage of this organ is carried through the splenic and super mesenteric veins, ultimately draining into the portal vein [15]. Innervation of the pancreas is comprised of both parasympathetic and sympathetic innervation, innervating both endocrine and exocrine structures and blood vessles, respectively. The pancreas functions in both the endocrine and exocrine system. The main components of the exocrine pancreas are known as the acinar and duct tissue, while the main component of the endocrine pancreas is known as the islets of Langerhans, which can be seen in Figure 6.

1.2.2 The Role of the Pancreas in the Exocrine System

In general, the exocrine system is represented by a series of glands throughout the body that work together to secrete, or release, substances through a multitude of ducts directly into the bloodstream or your body's surface [15].

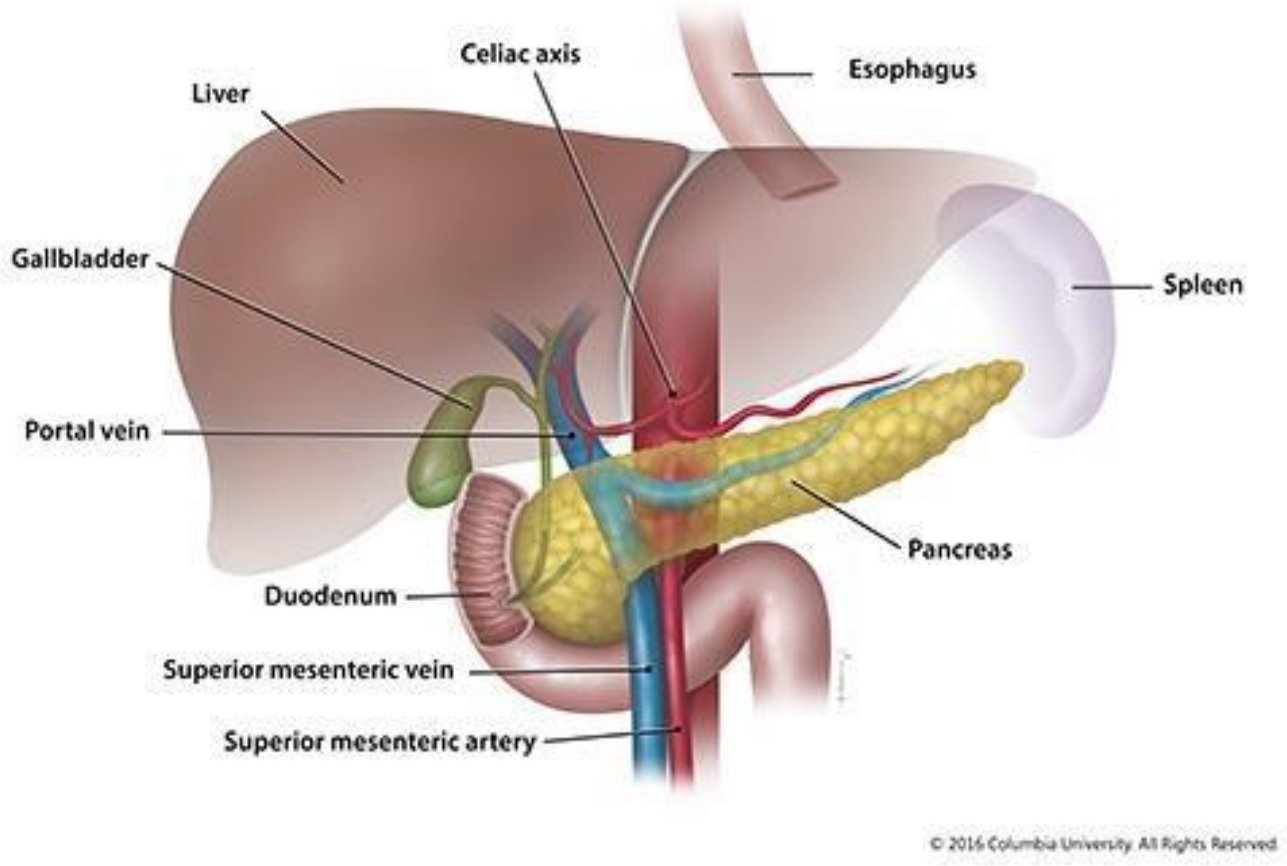


Figure 4: The anatomical position of the Pancreas with the organs and vessels that surround it. Image from (columbiasurgery.org).

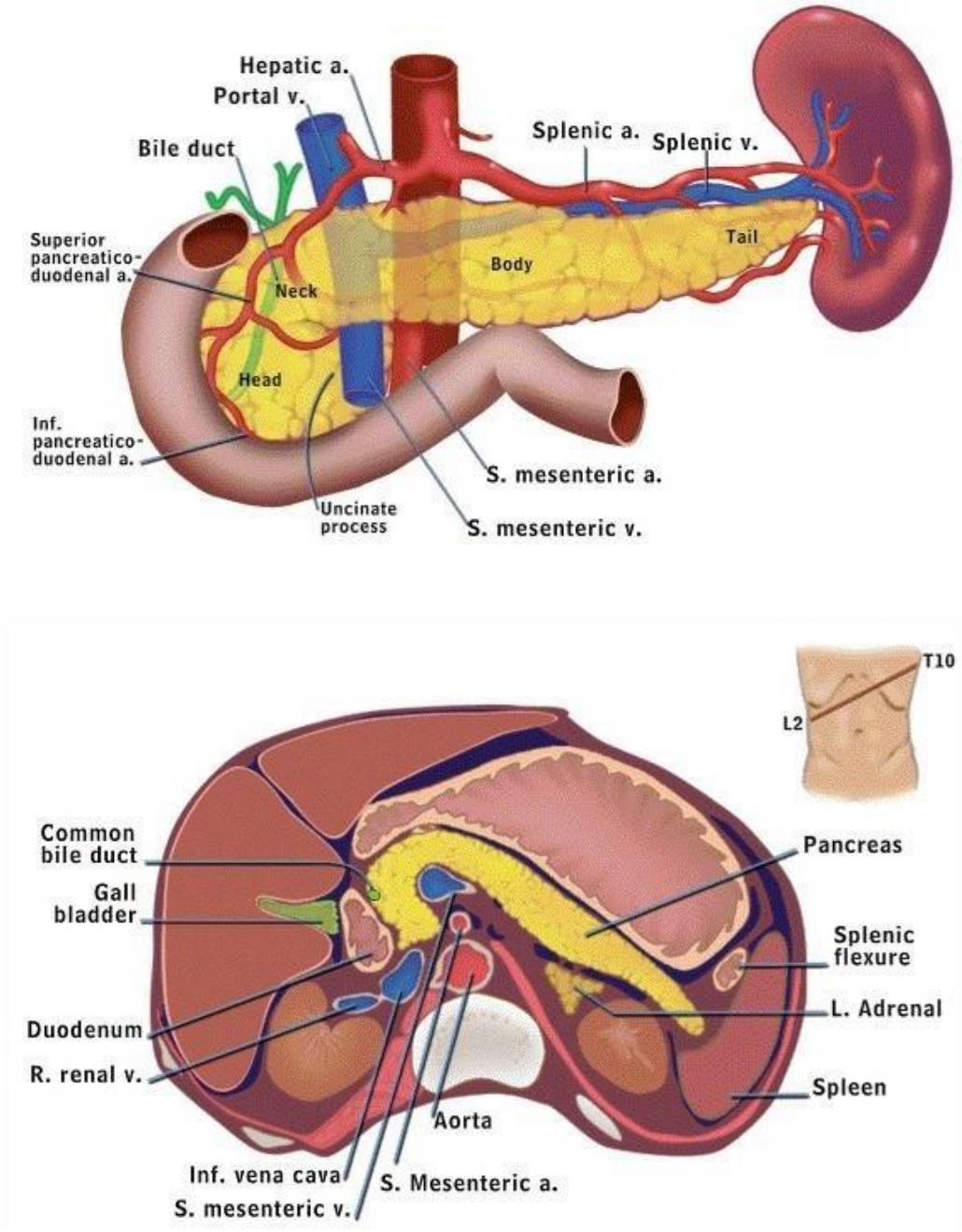


Figure 5: (top) anterior and (b) cross-sectional view of the arterial blood flow and venous drainage systems that make up the pancreas in reference to their surrounding structures. Image from (*The Exocrine Pancreas* by Stephen J. Pandol).

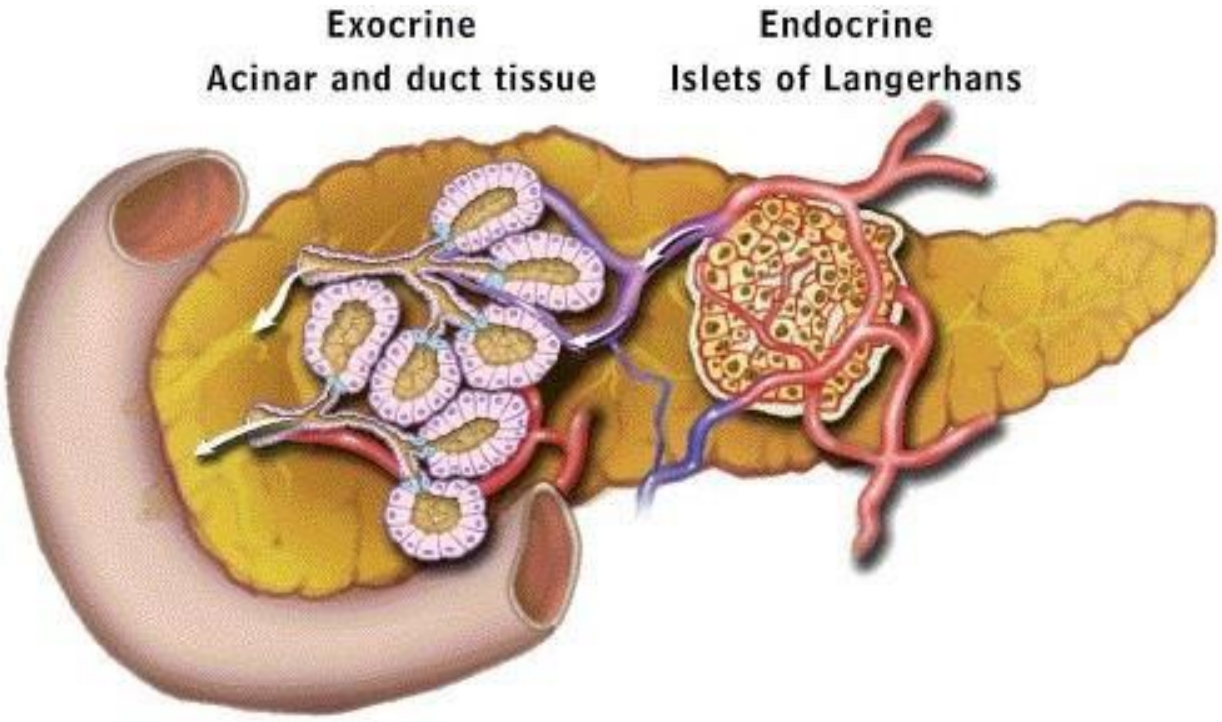


Figure 6: Overview of the exocrine and endocrine pancreas, and the functional units that make them up. Image from (*The Exocrine Pancreas* by Stephen J. Pandol).

Common examples of the exocrine system at work in the body are glands that help to secrete things such as sweat, tears, saliva and even digestives fluids [16]. The exocrine pancreas is specifically responsible for secreting digestive enzymes, water and ions into the duodenum of the gastrointestinal (GI) tract. For the flow of pancreatic digestive enzymes to be successful, the production of water and ions are highly necessary, which makes them a very important part of the exocrine system in this case. The digestive enzymes secreted by the pancreas are paramount for breaking down food to various molecular structures, much of which are essential for living, that can then be absorbed by the entire GI tract, to prevent instances of malnutrition. The functional unit of the exocrine pancreas is made up of a tiny cluster of cells resembling a berry shape, known as an acinus and its draining duct, which connects the acinus to the duodenum. The purpose of the pancreatic acinus is primarily the production and secretion of digestive enzymes, such as amylase, lipase and trypsin, via the 15-100 acinar cells the acinus is comprised of [17]. This cluster of cells is organized around a lumen, which is the connection point of the draining duct that aids in the secretion of these enzymes, while they wait to be activated once reaching the duodenum.

1.2.3 The Role of the Pancreas in the Endocrine System

Aside from aiding in digestion by synthesizing, storing and secreting enzymes, the pancreas is also responsible for making certain hormones that travel through the bloodstream to aid in various processes. Two of these hormones are insulin and glucagon. While insulin acts to lower the amount of sugar in the blood, glucagon acts to raise the amount of sugar in the blood. In order for many prominent organs in the body to function properly, the level of sugar in your bloodstream must be managed properly. When we consume food, Insulin moves glucose from the blood to muscle, liver and fat cells as Insulin level increases. The primary functions of

Insulin includes the transport and metabolism of glucose for energy, stimulation of storage of glucose in the liver and muscle, serves as the signal of the liver to stop releasing glucose, among others. Both Insulin and Glucagon maintain a constant level of glucose in the blood by stimulating the release of glucose from the liver.

The functional unit of the endocrine pancreas is comprised of multiple islands of aggregates of cells, known as the islets of Langerhans. As seen in Figure 7, the islets of Langerhans are composed of several types of hormone-producing cells, such as α or A cells (responsible for glucagon secretion), β or B cells (responsible for Insulin production and secretion), δ or D cells (responsible for somatostatin secretion) and PP cells (responsible for pancreatic polypeptide secretion) [18].

Two key hormones that aid in the regulation of carbohydrate, fat and protein metabolism are both the A cells and B cells. As previously mentioned, the pancreatic A cells are responsible for secreting glucagon, which then releases glucose from glycogen stores in the liver, as a response to low blood glucose [19]. On the contrary, pancreatic B cells secrete Insulin, which works to lower glucose level while traveling through the bloodstream, as a response to elevated blood glucose. Both hormones are paramount for glucose homeostasis throughout the body [20].

It is important to note here, that those who suffer from type 1 diabetes have a problem with their pancreas recognizing their insulin-producing beta cells as foreign bodies, thus attacking and destroying them leaving the patient to solely rely on the various external insulin deliveries that must be made throughout the day via one of the many methods as previously discussed before. Further explanation of both type 1 and type 2 diabetes will be discussed in the coming chapters.

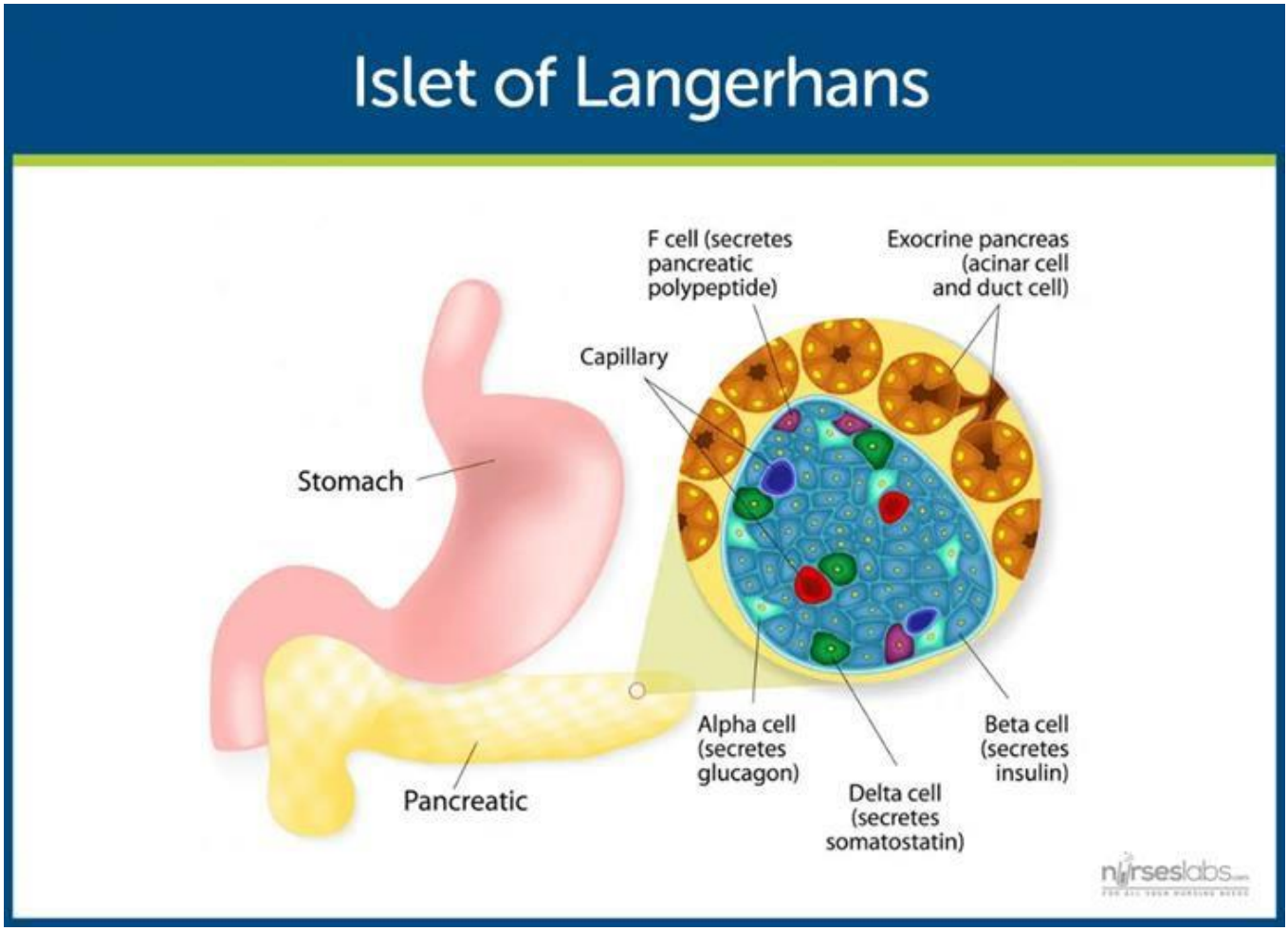


Figure 7: Diagram of the various cell types that make up the Islet of Langerhans within the Pancreas. Image from (nurselabs.com).

1.3 TYPE 1 DIABETES ANALYSIS

The main goal of those working in type 1 diabetes research is to develop drugs and technologies to make the lives of those affected easier. Unfortunately, minimal progress has been made with regard to finding a cure, despite reports of islet cell injections that have reported variable results [21,22]. T1D research consists of many different disciplines, however disease prevention and maintenance seem to be at the forefront. Disease prevention requires a deeper understanding of the disease itself including histology as well as cellular, organ and systemic physiology of all anatomy affected by this disease. Disease maintenance largely focuses on the technology and drugs used to keep patients alive. This kind of research can be used to optimize every aspect of drug delivery with a common consensus of stabilizing glucose levels, keeping the patient healthier.

Current methods of analyzing various aspects of T1D , whether it be prevention or maintenance, commonly involve in-vivo testing and clinical trials. Both methodologies of analysis are key instruments to further investigate disease related processes and can provide valuable information and insight into the current state of the art of T1D research. On the contrary, these methods of testing can be expensive with the cost of subject recruitment, data collections, researchers and other materials required to carry out the associated study. These methods can also be very time consuming with the time associated with proper testing and analysis needed to extract valuable and accurate information regarding either approach of T1D research. Therefore, it can be challenging to improve the current state of the art of technology that is used to maintain and sustain the drug delivery needed for a Type 1 Diabetic.

Mathematical modeling can be utilized in many ways surrounding type 1 diabetes that aid researchers, doctors, and patients in disease management and even prevention by illustrating real

life problems in mathematical solutions. It is a fast and cheaper way to analyze the technology and drugs used by these patients, making it easier for the disease to be studied, technology to advance and even making it easier to bring new drugs to clinical trials [23]. In addition, to help

combat the time and cost-consuming nature of in-vivo testing and clinical trials, simulation models have helped to provide opportunity to continue studying this disease from additional viewpoints and objectives by being able to generate the behavior of a model given many different parameters to predict endless outcomes [24]. Recently, both the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have both included modeling and simulation techniques as top priorities in supporting efficient drug development and aiding in the facilitation of regulatory decision making [25]. There are currently many different methods of mathematical models that exist surrounding type 1 diabetes, and the benefits of such models can greatly help many aspects of diabetic research. However, it is also important to note that each different model also comes with its own limitations and assumptions that should be carefully considered when selecting the most appropriate model for a given analysis.

In summary, mathematical modeling is an innovative tool that provides users with methods to aid in prevention and treatment of those affected by type 1 diabetes by utilizing numerous time and cost-efficient methods that will be further discussed in the next chapter. The benefits from the various models are endless and are continuously being further evaluated and developed in order to improve the lives of those affected by this disease. The work in this dissertation focuses on the disease maintenance aspect of T1D research with a concentration in predictive mathematical modeling approaches. Predictive modeling in diabetes is a very popular area of diabetic research and can help pave the way for better control over blood sugar and overall management of the disease itself. In the case of this dissertation, it can potentially be used to yield more normalized glucose levels by predicting better basal rates, that is working in the background to try and maintain normal blood sugar levels.

CHAPTER 2: BACKGROUND

2.1 LIFESTYLE THERAPY TO LOWER BLOOD SUGAR

Whether a person's body fails to produce enough or any insulin (i.e. T1D) or uses insulin inefficiently (i.e. T2D), there are avenues for lowering blood sugar without the use of a drug, such as injection of insulin. For Type 2 Diabetics, there are options to lower blood glucose, such as exercise, diet, sleep and stress management, may very well help control blood sugar and often allow patients suffering from this disease to produce glucose levels in a non-diabetic range, ultimately allowing the patient to enter complete or partial remission of this disease [26]. However, for Type 1 Diabetics who rely solely on insulin delivery to control glucose levels, using naturally remedies in combination with insulin only helps to control and lower blood sugar, allowing for the patient to use insulin more efficiently, either through the use of an insulin pump or a manual syringe. Both Type 1 and Type 2 Diabetics can benefit from natural ways to lower their blood sugars, ultimately allowing them to have more controlled glucose levels and in turn use their medications, whether it be insulin or some form of oral diabetic drug, more efficiently.

2.1.1 EXERCISE AND DIET MANAGEMENT

Dr. Salwa J. Zahalka, MD states that the combination of exercise with medication therapy, "forms the cornerstone of diabetes therapy" [27]. Regular exercise has been proven to have a direct correlation with improving insulin sensitivity in Diabetics, meaning that the cells in their bodies can more efficiently utilize the sugar in their blood and naturally help to lower blood sugar. During exercise, muscles in the body use up their glucose supply as they contract. Once this supply is diminished, the same muscles can utilize the excess sugar in the blood to continue to obtain more energy, without the need to use any insulin. This ultimately allows the exertion of more energy during this time of physical activity, thus lowering blood sugar. The American

Diabetes Association (ADA) states that physical activity can "lower your blood glucose up to 24 hours or more after your workout" due to the increased insulin sensitivity it yields and recommends a diabetic to participate in both aerobic activities, as well as resistance training, at least three days a week [28]. Not only is exercise known to greatly and effectively lower blood sugar, but it is also believed to reduce the incidence of T2D itself. A study by Warburton et al, yielded that even minute changes in physical activity led to "great reductions" in T2D occurrence [29]. While exercise can't solve the problems of T1D alone, it is believed to provide great benefit to the patient regarding insulin use. In a study by Ramalho et al, T1Ds who regularly participated in exercise showed to have anywhere from a 6-18% reduction in the total daily dose of insulin they used in a given day [30].

Along with exercise, a more controlled diet has also been shown to provide great efforts with regard to lowering overall blood glucose levels in both Type 1 and 2 Diabetics. One way to help lower blood sugar with your diet is to strictly manage your carb intake. Although insulin helps the body to manage carbs, decreasing the amount of carbs you intake can reduce the frequency of "sugar spikes" or spikes in your blood sugars, which can then require an increased amount of external insulin and a less medialized glucose curve. Alongside decreasing carb intake, it can also be beneficial to lower your fat intake, as the fat, in combination with high carb intake, leads to the release of glucose levels at unexpected times during the day, often at high magnitudes. The information in Figure 8 details an example of how increased carbohydrate intake can lead to "sugar spikes" versus foods that are lower in carbohydrates and higher in proteins or fats, which not only take longer to digest, but also result in less glucose conversion. Aside from a lower carb diet, increasing minerals such as magnesium and chromium in diets can have a direct, positive relationship with lowering blood sugar. According to Grady Health,

minerals such as these help to regulate blood sugar and in turn high blood sugar levels have been linked to deficiencies in both of these minerals [31]. An increase in fiber has also been linked to a reduction in blood sugar, as one of fiber's main targets is to slow the body's digestion of carbohydrates, as well as sugar absorption. By helping the body to slow down the digestion of carbohydrates, this can yield more gradual increases in blood sugar, versus the "sugar spikes" previously mentioned. Gradual increases, instead of "sugar spikes", ultimately help the Diabetic to control their glucose levels in a safer, more healthy way.

2.1.3 Sleep and Stress Management

Aside from increased physical activity and a more controlled diet, adequate amounts of sleep and healthy stress management techniques have also been shown to aid in lowering glucose level. The body's natural "fight or flight" response, cortisol, is the primary stress hormone that is responsible for releasing stored glucose in the body, ultimately raising blood sugar levels and increasing heart rate as well as blood pressure [32]. Released from the adrenal glands, cortisol releases glucose and inhibits insulin production, so that the glucose will be able to be used immediately, which can cause problems for Diabetics who are dependent on insulin. Figure 9 demonstrates the effects that increased cortisol can have on insulin secretion, as well as glucose level. Previous studies have shown that sleep deprivation or, in extreme cases insomnia, can be responsible for increased cortisol levels throughout the day, which can then promote glucose intolerance [33]. Similar to sleep deprivation, stress, both acute or chronic, yields a flow of cortisol throughout the body. Cortisol can then cause insulin levels to fall and glucagon levels to rise, ultimately increasing the among of glucose in the bloodstream. In a study by Sharma et al, it is said that high levels of stress over time can "cause insulin resistance and lead to diabetes" [34].

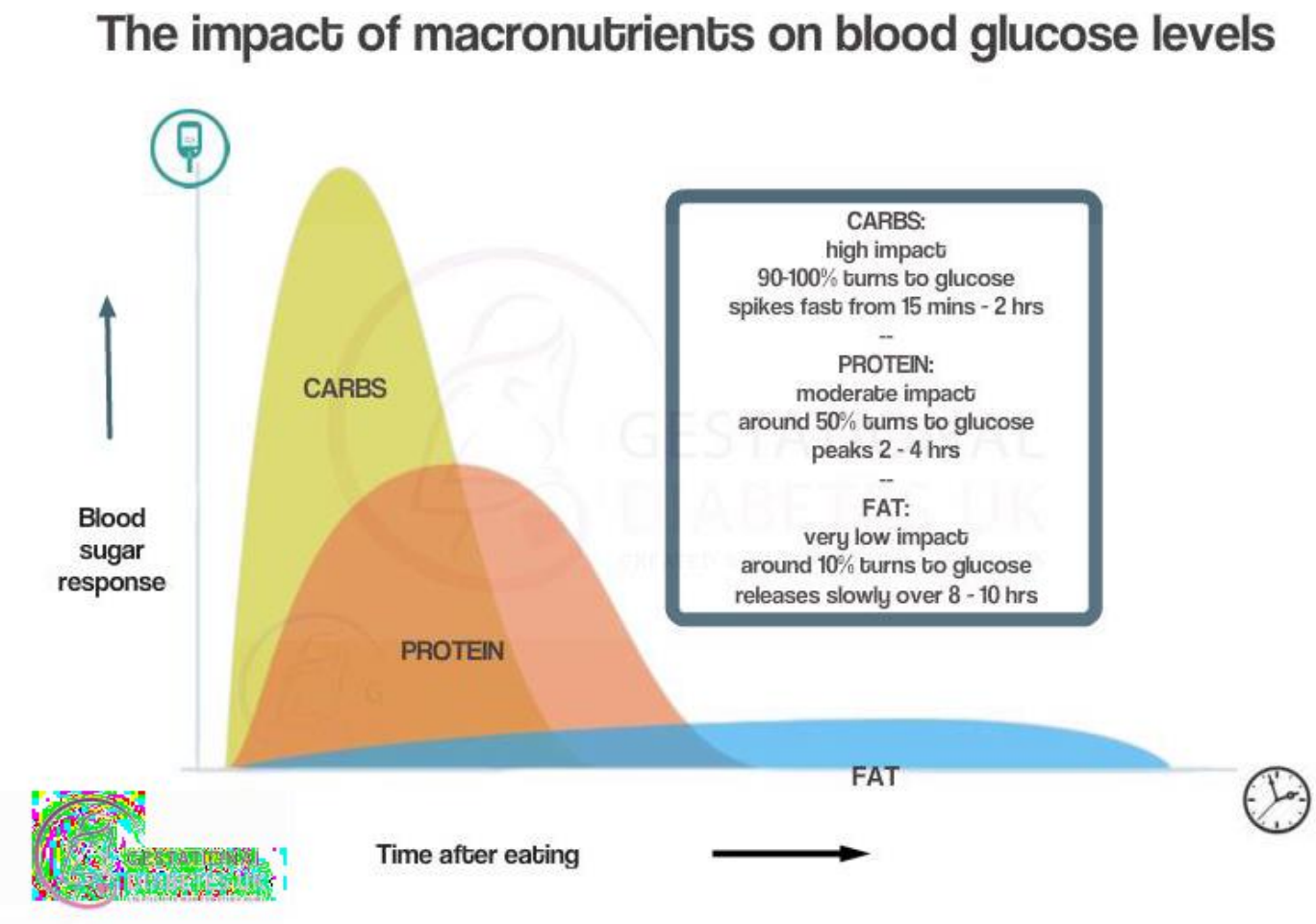


Figure 8: Schematic showcasing the effects of certain macronutrients on blood glucose levels.

Image from (gestationaldiabetes.co.uk).

Both proper sleep and stress management can help an individual more efficiently manage their blood sugar levels and see lower levels throughout the day. Techniques to practice better management of these lifestyle therapies are encouraged by doctors and researchers to help lower not only blood sugar, but A1C levels alike [35].

2.2 Oral Hypoglycemic Medications

Oral Hypoglycemic Agents (OHA) are a class of drugs that help to reduce the overall amount of sugar in the blood. However, they are different from and should not be referred to as "insulin." Primarily utilized by type 2 diabetics, OHAs help the body to lower glucose level by stimulating the functioning pancreas to produce insulin. This class of drugs is usually prescribed to type 2 diabetics in conjunction with strong recommendations for lifestyle changes, such as diet and exercise, to not only help lower blood sugars as they occur, but to ultimately help achieve optimal glycemic control [36]. OHAs are administered in the form of a tablet with various doses dependent on what is recommended by a healthcare professional. Glipizide, an OHA used for lowering and controlling glucose level of a diabetic, comes in 2 different doses and is usually taken once a day in the morning to help maintain healthy glucose levels throughout the day in response to food, by helping to promote insulin production [37]. Previous studies regarding this classification of drugs even suggest that they can reduce A1C levels - a measurement that represents your average blood glucose level over the past 2-3 months - by 0.5-1.5% [38].

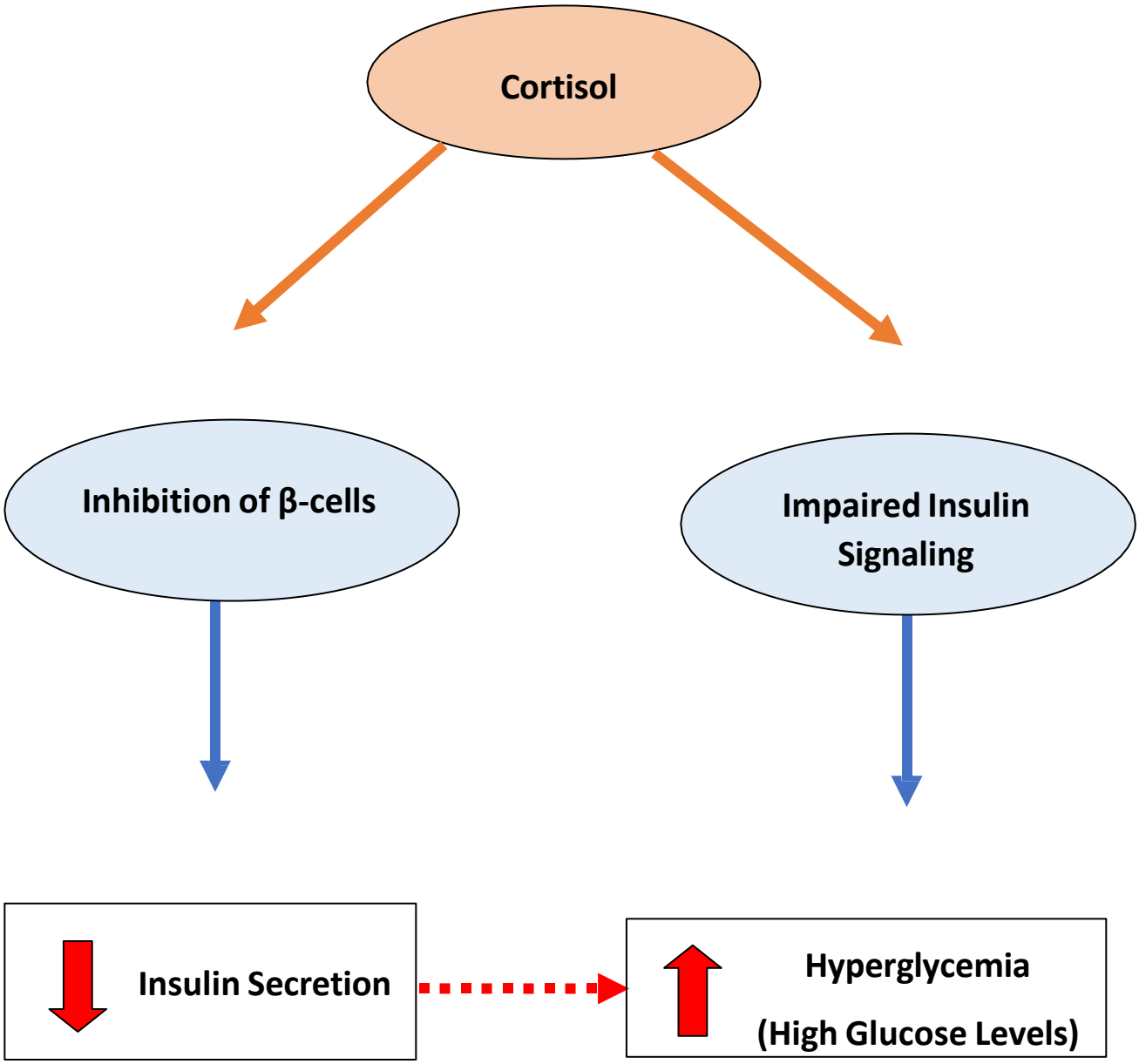


Figure 9: Flowchart showing the effect of the hormone, cortisol, on both glucose levels and insulin secretion.

2.3 Alternate Methods of Insulin Delivery

Aside from manual injections and insulin pump systems, alternate methods of insulin delivery, both oral and non-oral, have been at the forefront of insulin research, even being referred to as the "current direction of insulin research" [39]. While subcutaneous insulin delivery and oral hypoglycemic agents (OHA) are two of the most utilized forms of insulin delivery, both have their drawbacks and can be onerous for patients. Alternatively, more non-invasive insulin delivery methods may allow for a decrease of patient's anxiety and stress. A newer area of insulin research lies within inhalational insulin. In recent years, Afrezza, an inhaled insulin, was approved by the Food and Drug Administration (FDA) and offers patients an alternate insulin delivery consisting of an even quicker acting, safer insulin in comparison to previous attempts of inhaled insulin [39]. Not only does pulmonary administration provide a bigger surface area and good vascularization but offers excellent drug absorption via the large capillary network available. A study conducted by Black et al found that inhaled insulin was "just as effective" as other methods of insulin delivery, thus effective for lowering glucose level [40].

Another alternative method of lowering and managing glucose levels through insulin delivery comes in the form of microneedle-based insulin transdermal delivery systems. Micro-needle (MN) delivery systems come in a variety of different forms. However, regardless of this, all MN systems have been proven to "effectively deliver insulin through skin stratum corneum (outermost layer of the skin) in a minimally invasive and painless way" [41]. In Figure 10, the advantages and disadvantages of many methods of MN for insulin delivery are highlighted. One form of MN delivery that works to effectively lower glucose level is the glucose-responsive MN patch. This MN is a patch that's applied to the skin, containing an array of MN that harbors a

glucose-sensing unit, to allow for the detection and release of insulin into the body, working to actively lower blood glucose levels. It is also paired with a glucose sensing device, serving to reduce the occurrence of hypoglycemic tendencies, allowing for strict glucose control. A study conducted by Ullah et al, showed very promising results in a group of diabetic rats who were treated with MN versus a control group, where the MN treated diabetic rats exhibited a significant decrease in blood glucose level over a span of 5 hours, where roughly "53% of the incapsulated insulin was released within the first hour of delivery" [42].

2.4 Continuous Glucose Monitoring Systems

Continuous glucose monitors (CGMs) are devices that measure a patient's glucose levels without the need for a manual finger prick. Having evolved over the years, this technology exists to make the life of the patient not only easier, but also provides real-time, dynamic data in order for the patient to make more confident decisions regarding their glucose levels, keeping them healthy and maintained. While there are various types of CGMs on the market, two of the main types are real-time CGMs and intermittently scanned CGMs [43]. Consisting of a sensor, a transmitter, and a handheld receiver such as a smartphone, real-time CGMs provide the patient continuous, real-time data, usually providing a glucose reading to the patient every 3-5 minutes, depending on the technology used [44]. The real-time CGMs are most commonly used due to the user-friendly interface that allows you to easily share data with family members or healthcare professionals and provides alerts to the patient, usually warning the wearer of blood sugar changes that may require user intervention, allowing for the safe and preventative management of glucose levels.

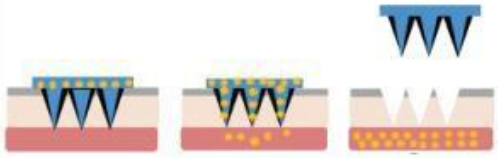
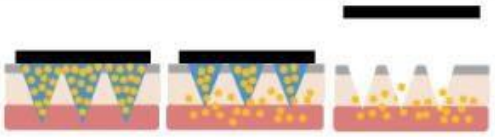
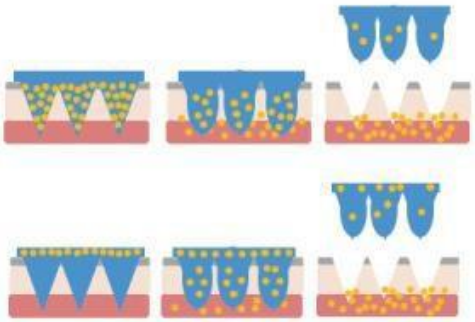
MNs Types	Figures	Advantages	Disadvantages
Solid MNs		High mechanical strength Reasonable drug load	Poor dose accuracy Two application process Poor biocompatibility
Coated MNs		High mechanical strength Used for drugs with low doses	Low drug load Poor biocompatibility Formulation migration during production and storage
Hollow MNs		Precise dosage High drug load Faster delivery rate	Requirement of auxiliary devices Poor mechanical strength Poor biocompatibility
Dissolving MNs		Easy manufacturing Control of drug release	Poor mechanical strength Dose limitation Poor biocompatibility
Hydrogel MNs		No residual in skin Easy manufacturing Control of drug release	Poor mechanical strength

Figure 10: Chart showcasing various forms of utilizing Micro-needles in insulin delivery. Image from (Zhao et al).

An example of a real-time CGM (Dexcom G6), with its corresponding sensor, transmitter and receiver is shown in Figure 11. On the other hand, intermittently scanned CGMs function similarly to real-time CGMs, consisting of the same components. However, the user must manually scan their reader or smart-phone device over the transmitter to obtain any glucose readings. Intermittently scanned CGMs also only store glucose readings every 15 minutes opposed to the influx of stored glucose values of a real-time CGM [44].

Regardless of the type of CGM a patient uses, the sensor that is placed on a patient's stomach or arm is responsible for measuring fluid levels underneath the skin, providing the patient with blood glucose levels allowing them to have more personalized care, with hopes of helping users easily manage their blood sugar levels. A study from Beck et al, pertained to a randomized group of type 1 diabetics using a CGM compared with a control group and found that patient's using a CGM and noticed a 1% reduction in their overall A1C levels after 24 weeks of use, with an additional 50% of subjects experiencing more than a 1% reduction [45]. Multiple studies also demonstrated a significant decrease in time spent in a hypoglycemic state of patients using a CGM, making the ability to maintain a lower blood sugar more accessible [45–47]. It is evident that the integration of CGMs into diabetic care not only gives the patient a more confident control over their glucose levels, but also a safer, personalized experience overall.

2.5 Programmed Basal Rates in Insulin Pump Systems

Basal Rates are arguably one of the most important settings to define in an insulin pump system. On average, basal insulin tends to account for anywhere from 25-50% of the total daily insulin delivered by a type 1 diabetic, accounting for roughly one-third to one-half of the day [48].

Figure 11: T:Slim X2 Insulin Pump with compatible Dexcom G6 continuous glucose monitor.

Image from (Dexcom.com).

Pediatric Endocrinologist Dr. Saleh Adi has stated that basal rates are highly variable and can differ from “day-to-day, patient-to-patient, age-to-age and even hour-to-hour” and emphasizes the constant change in basal rates, especially throughout childhood, highlighting that these rates should constantly be evaluated on a week-to-week basis [49]. Dr. Adi also documented that basal rates are “highly individualized and vary from day-to-day”, meaning that no two patients are the same, and what is learned from one patient can rarely be applied to another [49]. Since all individuals are uniquely different, it is evident that the need to optimize the use of basal insulin with patient-specific, real-time data, is great and would ultimately yield more controlled glucose levels amongst many type 1 diabetics. The software that is utilized in Insulin pump systems can be classified by the type of control utilized, either considered open-loop or closed-loop methods.

2.5.1 Open Loop Systems

Insulin delivery through open loop systems demands that a patient is self-administering insulin at various points throughout the day. This method can be represented by subcutaneous insulin injections via a syringe, as well as through an insulin pump system. If delivered through an injection, a slow acting insulin will be injected in the early morning time to provide basal insulin, helping to regulate glucose levels throughout the day, while the body is fasting. In addition to this slow acting insulin, a more fast or rapid acting insulin will be administered prior to meals to combat the breakdown of carbohydrates and release of sugars into the blood stream, helping the patient to manage potential sugar-spikes induced by the breakdown of food. Aside from injections, insulin pumps can be utilized without the use of a CGM, requiring the user to manually enter their glucose level in preparation of insulin delivery, still making it an open loop

system. Regardless, all forms of open-loop delivery require some form of patient involvement, requiring the patient to live somewhat of a predictable lifestyle [50].

2.5.2 Closed Loop Systems

Insulin delivery through closed-loop systems requires very little intervention from the patient due to the insulin pump acting as the delivering mechanism for glucose per the information received from the CGM. This process detects blood-glucose levels with a continuous glucose sensor and receiver by continuously monitoring and giving feedback, which is then utilized in an algorithm to automatically provide the right amount of insulin at the right time—much like a normal pancreas would do naturally. In 2016, the FDA approved what is known as the artificial pancreas (AP) system. Artificial pancreas systems take over the majority of blood-sugar management, ultimately making it a closed-loop system [51,52].

Aside from a fully closed-loop delivery system, many users operate using a hybrid closed-loop system, still requiring some degree of patient intervention. This delivery system allows the patient to feel still in control of insulin deliveries, with the benefits of a fully closed-loop system, calculating insulin deliveries more precise and often, ultimately keeping the patient within their target glucose range longer yielding more stable levels [53]. In Figure 12, a schematic diagram of a hybrid-closed loop system with all working components is described. Regardless, the closed-loop delivery method is a vital advancement in insulin delivery technology, as it not only increases patient compliance, but also allows for more personalized care and control over glucose levels. A study by conducted by Sophie Templer of St Vincents Hospital in Sydney, Australia, states that when comparing with traditional, open-loop insulin

pump therapy, closed-loop systems “have been shown to reduce hypoglycemia, improve mean glucose levels, and increase time spent in the target glycemic range” [54].

2.6 Adjusting Basal Rates Manually

Often referred to as the foundation of Insulin pump therapy, making certain that a patient’s basal rates are as precise as possible throughout the 24-hour period can be is very crucial and can have a big impact on various other pump settings as well. Any change that is made to a basal rate can affect parameters such as insulin-to-carb ratio and insulin sensitivity factors. According to current Diabetes Educator Gary Scheiner, “Basal rates need to be fine-tuned before finalizing any other settings on the pump” [55]. Whether the basal rate is set correctly or incorrectly plays a major role in a patient’s own glucose level and ultimately A1C levels. If set correctly, it will allow patients to have a more controlled, normalized glucose reading on a day-to-day basis. However, if set incorrectly, a patient can experience a constant up and down pattern of both extreme high and low readings simultaneously. Since basal rates within an insulin pump system will vary depending on the user, there are many factors to consider when determining what the requirements should be for specific basal rate; some of these factors can include sex, age, weight and even if there is any insulin secretion still occurring in the body. Before age 21, a patient is still said to be in their “growth” years and will need to adjust accordingly compared to someone who is above the age of 21 and is said to be predominantly done growing. While an individual is still growing, hormones such as cortisol and certain growth hormones are still being produced during the night, which in turn allow the liver to release extra glucose into the blood, thus requiring higher nighttime basal rates to be considered.

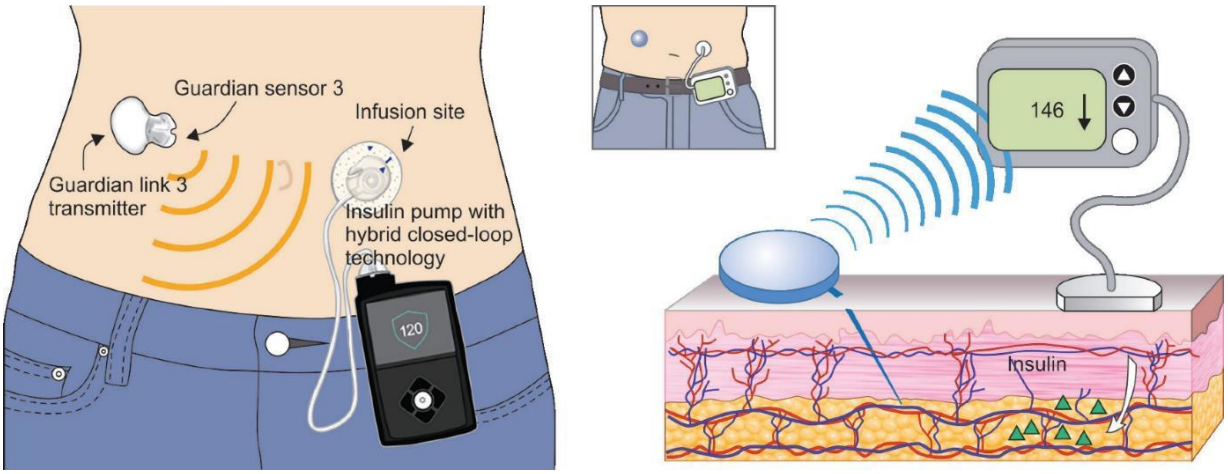


Figure 12: Schematic diagram of the mechanism of a hybrid closed-loop insulin delivery system.

Image source from (pjn.sbvjournals.com).

Once above the age of 21, patients will be encapsulated by what is known as the "dawn phenomenon." This effect means that the production of hormones that allow stimulation of glucose release from the liver are heightened in the early morning hours. Patients who are in the dawn phenomenon will tend to have higher basal rates in the early morning; peaks in basal rates most often will occur during these hours as well.

Regardless, when trying to find what the right basal rate is, each patient will need to pay close attention to their overall glucose levels associated with each of the specified basal rates. According to Gary Scheiner MS, CDE, "the right basal rate is the one that holds your blood sugar at a fairly constant level when you have not eaten or bloused for several hours and are not exercising" [55].

2.6.1 Basal Rates Determined by Healthcare Professionals

Endocrinology is a specialty within biology and medicine that refers to the study of the endocrine system in the human body, making endocrinologists the specialty doctors that regularly see and care for type 1 diabetics, in conjunction with nurses and diabetes educators. Depending on the age of the patient, it is standard practice to see an endocrinologist every six months to one year to check in on the overall health of the patient, check A1C levels, as well as re-adjust basal rates if necessary. While there is not one right or wrong method of adjusting basal rates, each healthcare professional has their own way of calculating and suggesting new basal rates to their patients. A common method to suggest new, starting basal rates to patients transitioning to insulin pump therapy is what's known as the "total daily insulin dose" (TDD) method. This method is based off the total amount of insulin that an individual patient would use in a given day, including both basal and bolus deliveries. An individual's TDD is determined by their weight in pounds, divided by 4. Once the TDD is calculated, endocrinologists can then

follow the formula for calculating the amount of basal insulin by first reducing the TDD by 25%, and then dividing the amount in half for both basal and bolus insulin [56]. While many researchers suggest that of the TDD, 50% should be delivered as basal and 50% delivered as bolus insulin, other studies suggest that basal insulin should only comprise roughly 30% of TDD [57]. Regardless, endocrinologists rely on various methods to suggest initial rates, and monitor the patient's glucose response in order to make adjustments if needed.

2.6.2 Fine-Tuning Tests

Every Insulin Pump system will allow users to program different basal rates over the course of a day, corresponding to specified times. To find what your ideal basal rates are, the practice of utilizing a fine-tuning test is very common. This test will allow for a patient to isolate both their glucose levels and basal rates and truly understand the effect that they each have on each other, allowing a user to make changes accordingly. For a fine-tuning test, certain rules must be followed to get the most accurate results. These following rules are as follows [55]:

1. No food should be digested.
2. No bolus insulin should be working during the basal test.
3. Your liver should be producing its "normal" amount of glucose.
4. Allow basal insulin to be delivered uninterrupted
5. Maintain your normal level of physical activity.
6. Monitor blood glucose levels correctly.

As previously mentioned, a Basal Test will allow for a user to isolate their glucose response to changes in their basal rate and ultimately study the effect that changes in the basal rate can have on their glucose levels throughout the day. Four different fine-tuning tests can be performed for four different times of the day: Overnight, Morning, Afternoon, and Night. Each test has the user check their blood sugar at various times. However, if a user has a continuous glucose monitor then the blood sugar will be automatically checked once every five minutes. Although wearing a continuous glucose monitor can provide more real-time, dynamic data, it is still recommended that users check their blood sugar manually as well, in order to prevent any reading errors or inaccuracies. Fasting will also occur within certain time intervals throughout the fine-tuning process. Figure 13 shows a complete breakdown of the fasting and blood sugar reading schedule.

Once the user has completed the fine-tuning test for the desired time of day, it is time to look at the glucose readings over that time interval and make changes accordingly. The changes that will be applied to the patient's current basal rates are based upon the current basal rates themselves, the magnitude of the change in glucose levels as well as the sensitivity of the pump system itself. The change of the blood sugar during the test can be classified as either a "modest" (30-60 mg/dl) or "large" (>60 mg/dl) change. If the change is less than 30 mg/dl, then no change in basal rate is recommended. The current basal rate is classified into either a range of 0.00-0.35 units/hour, 0.40-1.00 units/hour or greater than 1.00 units/hour. Based upon these two factors, a change is recommended: either 0.1, 0.2 or 0.3 units/hour. It is important to remember that each change can either be classified as a negative or positive change. Depending on whether the blood sugar change is in the positive or negative direction, the user would either add or subtract the suggested change to/from their current basal rate.

Test	Eat & bolus no later than:	Check blood sugar at:	OK to eat & bolus again after:
Overnight	7 pm (eat dinner, then skip evening snacks)	11 pm, 1 am, 3 am, 5 am, 7 am	7 am
Morning	3 am (have a bedtime snack, then skip breakfast and morning snack)	7 am, 9 am, 11 am, 12 noon	12 noon
Afternoon	8 am (eat breakfast, then skip morning snack, lunch and afternoon snacks)	12 noon, 2 pm, 4 pm, 6 pm	6 pm
Evening	2 pm (eat late lunch, then skip afternoon snack and have a late dinner)	6 pm, 8 pm, 10 pm, 11 pm	11 pm

Figure 13: Chart displaying the Basal Test Schedule for Overnight, Morning, Afternoon and Evening. Image from (diatribe.org).

Blood Sugar Change During Test	Current basal level (units/hr)		
	0.0-0.35	0.4-1.0	>1.0
Modest 30-60 mg/dl (1.7-3.3 mmol/L)	Adjust by 0.05 (if pump allows) or 0.1	Adjust by 0.1	Adjust by 0.2
Large >60 mg/dl (>3.3 mmol/L)	Adjust by 0.1	Adjust by 0.2	Adjust by 0.3

Figure 14: Chart displaying the changes that will be applied to the current basal rates. Image from (diatribe.org).

Figure 14 shows a complete breakdown of the suggested changes. Because the insulin doesn't tend to peak until 1-2 hours after being administered, any changes made to the basal rates should be made roughly one hour prior to the blood sugar changes.

2.7 MATHEMATICAL MODELING TECHNIQUES

Various applications of mathematical modeling currently exist and are utilized for many different areas of type 1 diabetes research. Regardless of what research is being conducted, it is important to select the most appropriate modeling technique by making sure the previous literature, research and fundamentals associated with each technique are comprehended. While there are a multitude of models that have been derived, a limited number of them address the utilization of basal insulin, let alone offer predictions of optimized basal rates based upon patient specific data, yielding lower, more-controlled glucose levels.

During a literature search, a patent entitled "Insulin Pump Having a Weekly Schedule" by Michael Blomquist was discovered [58]. Blomquist worked to develop a method for setting an insulin delivery rate for an insulin pump. Blomquist's innovation, in working with Tandem Diabetes Care, Inc., is a method for setting an insulin delivery rate for an insulin pump. This method allows for one or more daily basal rate patterns to be stored in the pump, associated with certain days, and to be executed on the specified days. The current research differs by using previously stored data to go through this pattern matching algorithm and make these adjusted basal rates while also suggesting them to the user to assign to these specified days/times. Another search led to a study entitled, "Predicting the Optimal Basal Insulin Infusion Pattern in Children and Adolescents on Insulin Pumps" by a team of medical doctors in Germany. This group, led by Paul-Martin Holterhus, aimed to develop and cross-validate a mathematical prediction model for an optimal basal rate infusion pattern for pediatric patients with type 1 diabetes [59]. This dissertation

aims to take this a step further and say “Yes, it is pinnacle to find the most optimal basal rate pattern for type 1 Diabetics, but it is also just as crucial to personalize this to every individual user also. The methodologies presented within this dissertation suggest that the most logical way to do this than to use a patient’s own glucose data to achieve this optimization.” Bryan Mazlish, working with Bigfoot Biomedical Inc, also had similar claims, as his aim was to develop a “method of facilitating delivery of a discretionary dose of insulin to a user includes: enabling the user or a caregiver to specify, via a computer-based user interface, parameters associated with a discretionary delivery of insulin that may be delivered to the user; subsequently receiving data that represents the user's glucose level during a period of time associated with the discretionary delivery; automatically determining, with a computer-based processor, based on the received data, if, when and how much discretionary insulin should be delivered to the user during the period of time associated with the discretionary delivery; delivering insulin to the user during the period of time associated with the discretionary delivery according to the automatic determination; and delivering insulin to the user with the insulin delivery device according to a non-discretionary insulin delivery schedule unless a discretionary insulin delivery mode has been triggered” [60]. While the claims made by Mazlish are similar, he discusses applying all claims in regard to bolus insulin primarily. Again, this dissertation deals exclusively with basal insulin and the effect it has solely with glucose level response.

CHAPTER 3: OBJECTIVES AND CONTRIBUTIONS

3.1 DISSERTATION OBJECTIVES

In the previous chapter, limitations and disadvantages of the current methods of treatment of type 1 diabetes were outlined and the need for a more controlled and guided method of determining optimized basal rates in Insulin Pump systems was discussed. As previously mentioned, if a pattern-matching algorithm could be developed to allow for a "personalized" basal rate, then glucose level could be more controlled and ideally reflect overall more healthy levels. The first objective of this dissertation is to develop a fully functional software package that can be utilized within an Insulin Pump system, paired with any continuous glucose monitor (CGM) system for either Type 1 or Type 2 Diabetics that can be used to analyze patient specific data to predict more ideal basal rates and the glucose levels associated with each new basal rate. The second objective of this dissertation is to then utilize these pattern-matching algorithms to successfully read in hand-selected CGM images of glucose level trends, along with other patient specific data, predict optimized basal rates and visually display to the user the predicted glucose response of the updated rates for approval. These objectives are not only for validating our own methodologies, but also to gain a better understanding of the role of basal insulin in a Type 1 Diabetic and how we can better utilize this type of Insulin to have a better control on overall glucose levels, as one would expect to see in a healthy pancreas. This software ultimately needs to be able to safely suggest new basal rates that will lower a diabetic patients glucose values based on the new basal rates, all based on an individual patient's data, consisting of current glucose levels and current basal rates.

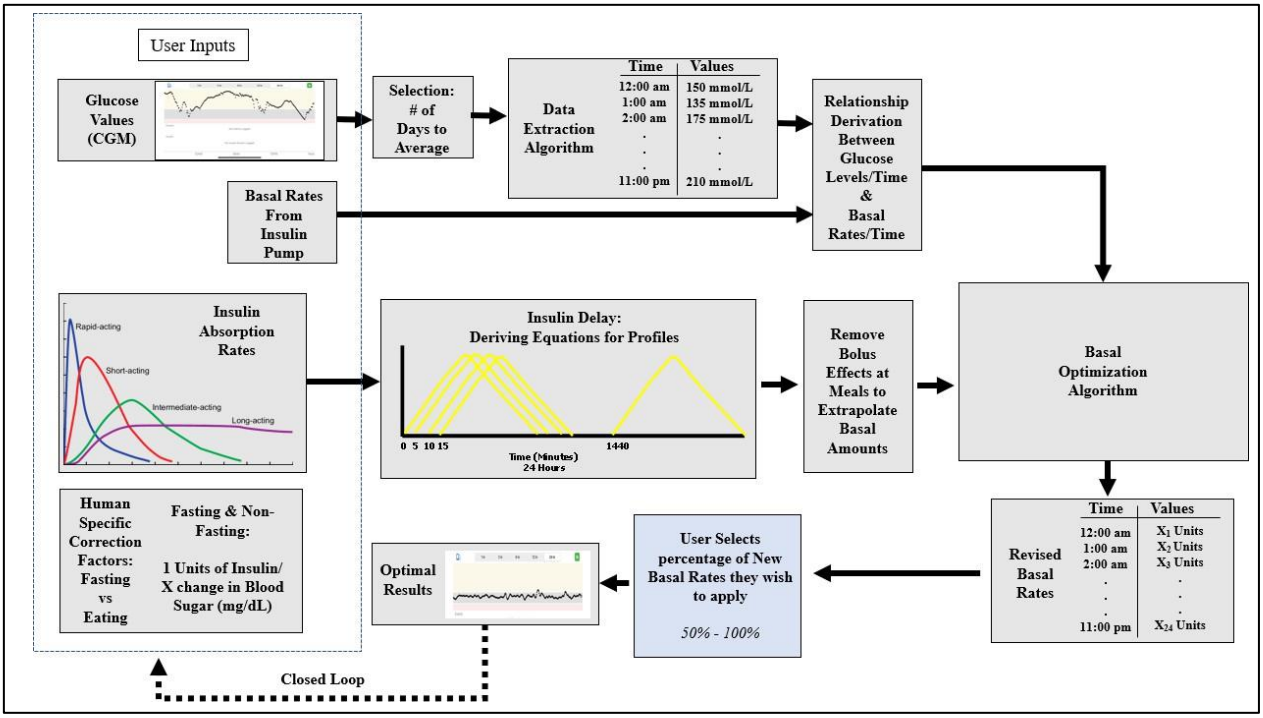


Figure 15: Dissertation main objectives and subtasks breakdown.

Being able to accurately establish the relationship between basal insulin and glucose level is crucial for improving the use of establishing effective, safe and healthy basal rates for Type 1 Diabetics. In order to satisfy the main objectives of this dissertation, there are two tasks that are required to be done upon the completion of this dissertation:

1. Developing a basal optimization algorithm that then utilizes the previous stored glucose readings, as well as other various patient specific inputs to suggest optimized basal rates accurately and safely for each unique patient.
2. Optimizes glucose levels using an algorithm that can further derive the relationship between glucose levels, basal rates and time to visually show the user the glucose levels that are predicted with each change in basal rate for a better understanding of the effects of the optimized Insulin delivery they would be manually agreeing to.

Each of the two tasks listed above includes separate subtasks. In order to first read in data to be utilized throughout this program, various methods of data extraction must be considered and developed. The different forms of data entry and formatting used in this program can range from either directly extracting glucose data via images of glucose trends from Dexcom Clarity software for the Dexcom sensors, for the Abbott Libre sensors and from the Medtronic sensors. Alternatively, the software package can extract glucose data in the form of excel or vector data in the occasion that images are not available for use. With that being said, this first sub-task requires utilizing image processing techniques to be able to develop an algorithm that efficiently and accurately reads glucose levels by developing an image processing algorithm that utilizes multiple stored glucose readings to accurately and efficiently extract and store glucose data with corresponding times to be used for further analysis. Regardless of the data source, extracting glucose readings requires user input where the user can decide how many

and what specific days to select. This is important for a user to be able to be in complete control of what days are used as a basis of the trends used in further analysis of the data to suggest new basal rates. Developing an algorithm that suggests more optimized basal rates requires additional user input, such as original basal rates as well as the ratio expected for one unit of Insulin to lower glucose level, known as a correction factor, as well as being able to accurately model the drug profile of Insulin in the body. This task also requires creating the ability for a user to be able to select varying percentages of the suggested changes, so that user control and comfort is at the forefront of implementing updated basal rates.

Next, it is important to develop another algorithm to derive and assess updated glucose levels which requires a further understanding of the relationship between Insulin delivery and glucose response in the human body to be able to visually relay the outcomes of varying basal rates on their glucose levels. It is also paramount to be able to have a deep understanding of the drug profile utilized within the Insulin Pump system, which is a fast-acting Insulin. Predicted glucose levels are calculated as a combination of the drug profile, the amount of Insulin being delivered, as well as the effectiveness of the drug at a certain point in time, which can be further understood by harnessing the drug profile and utilizing curve-fitting techniques to establish a polynomial representing how efficient Insulin is post-delivery.

With the completion of this dissertation, different studies were conducted utilizing the entirety of this program to not only validate the methodologies utilized herein, but to also test multiple clinically relevant hypotheses to generate applicable, meaningful results in hopes to harness basal insulin to better control glucose levels amongst a diverse population of Type 1 Diabetics. The first study conducted utilized data from a Type 1 Diabetic who upon initial inspection, maintained fairly consistent glucose levels, not far off from their ideal glucose level

range, however, wants to see if their rates could be more optimized to yield glucose levels even more consistent and on average, closer to their target glucose level, established in their Insulin pump system. The second study utilized data from a Type 1 Diabetic who, on average, displayed glucose levels that were much more inconsistent and higher than the previous subject. This subject could greatly benefit from a program as such, as the ultimate goal of this project and a Type 1 Diabetic is to maintain consistent glucose levels that are within a healthy range by harnessing the influence of their established basal rates have on their glucose levels, as one would expect to see in a healthy pancreas. The details pertaining to each task required to achieve the objectives of this dissertation will be discussed in the following chapters.

3.2 CONTRIBUTIONS

This dissertation focuses on the development and implementation of multiple pattern-matching algorithms in an Insulin Pump system, with specific emphasis on optimizing the Basal Insulin utilized by a Type 1 Diabetic on a day-to-day basis. The entirety of this project allows for a Type 1 Diabetic to possess more control and comfort in changing their basal rates to allow for more controlled glucose levels, along with various algorithms for image processing of selected and customizable images via their personal Continuous glucose monitoring sensor, basal predictions as well as predicted glucose predictions as a result of the predicted basal. These are all useful tools to help a patient more efficiently utilize present data in order to optimize the use and function of Basal Insulin on a daily basis. The contributions of this research include:

1. The development of a basal optimization algorithm that utilizes pre-existing, patient specific data (i.e., present basal rates and glucose levels, correction factors) to predict and suggest new, optimized basal rates to the user, in hopes to better control glucose levels and the use of bolus insulin.

2. The development of an algorithm that derives and assesses a patient's glucose values that are associated with the change in basal rates, allowing the user to not only visually see the relationship between updated basal rates and their associated glucose levels for more comfortable decision-making, but also aid researchers and patients in better understanding the individualized relationship between their own body and the basal Insulin response to various rates.
3. A database of patient specific data for two unique individuals consisting of various glucose profiles, showcasing the diversity and complexity of glucose response not only between person to person, but also as an individual.
4. A customizable data extraction algorithm that allows users to easily pair with their continuous glucose monitoring system to select numerous combinations of days of glucose level trends, with the ease of a screenshot, for use of basal prediction algorithm.
5. The inclusion and representation of unique Insulin profiles to accurately model the delivery and effects of various amounts of Insulin in the human body. An Insulin profile consists of things such as duration of the drug (how long the drug is actively working in the body), onset time (how long until the drug begins working in the body) and peak time (how long the drug is working in the body until it reaches its maximum efficiency).
6. A user-friendly GUI containing various tools, mentioned above, to help visualize to the user all suggestions/changes to basal insulin and the associated glucose response, in hopes to allowing decision-making more efficient and comforting. The GUI was designed to offer the user an easy and positive experience during usage of the program.

CHAPTER 4: METHODS

This dissertation must satisfy two main goals. As previously mentioned, the first goal of this dissertation is to develop a fully functional software package that can also be utilized within an Insulin Pump system, paired with any continuous glucose monitor (CGM) system for either Type 1 or Type 2 Diabetics. This software package can then be used to analyze patient specific data to predict more ideal basal rates and the glucose levels associated with each new basal rate. The second objective of this dissertation is to then utilize these pattern-matching algorithms to successfully read in hand-selected CGM images of glucose level trends, along with other patient specific data, predict optimized basal rates and visually display to the user the predicted glucose response of the updated rates for approval. Each of these main objectives requires several sub-tasks that are deemed necessary to ultimately satisfy both objectives.

First, a sufficient patient database, consisting of 10 patients with associated user inputs must be created with a selection of multiple days defined by the patient chosen for analysis. It is important to note here that the individual drug profile of the Insulin delivered to each patient is understood and modeled accurately as this has a direct effect on the Insulin delay and absorption rates for the patient.

Once all patient inputs have been defined, a data extraction algorithm must be developed that satisfies multiple modalities of reading in patient data, whether that be images of individual glucose plots, or explicit numeric data of all glucose values extracted straight from Dexcom Clarity software. Once the relationship between glucose levels, basal rates and time has been established, the basal optimization algorithm can successfully be implemented offering the individual user revised basal rates, ultimately allowing them to be in complete control of the percentage of the revised rates that they wish to apply yielding more controlled glucose levels.

4.1 CREATION OF PATIENT DATABASE

In order to satisfy the main objectives of this dissertation, the first task is to develop a patient-specific database of 10 patients that accurately and effectively model various trends and patterns universally demonstrated and studied by type 1 diabetics across the world. Examples of these various trends include, but are not limited to, common glucose spikes in the late-evening or nighttime as well as glucose crashes in the early mornings or earlier in the day. The patient database in this dissertation, as previously mentioned, includes one validation patient who is a long-time type 1 diabetic and manages their diabetes very well. This validation patient has agreed to take part in testing the suggested basal rate patterns yielded from the algorithm herein and provide real-time feedback and results to validate and test the results discussed in the next chapter. The remaining nine patients in this dissertation include Dexcom data from two other type 1 diabetics who willingly provided their data to be analyzed, as well as seven other patients that were created to help further understand and analyze how the basal prediction algorithm operates and can potentially serve as a unique, effective tool for type 1 diabetics to use in order to optimize their current basal rates in hopes of having a greater control on their overall glucose levels.

In order for a patient to be able to be analyzed by the algorithm developed in this dissertation, certain patient inputs must be known, such as original glucose levels of various patient-selected days, original basal rates associated with those days and times, the type of Insulin being utilized, as well as the patient-specific correction factors; all are settings that can be extracted or determined from the user's pump and/or Dexcom system. While the validation subject and other two sets of real-patient data all provided the associated basal rates and patient inputs needed for analysis, the remaining seven synthetic patients will be analyzed with varying

basal rates, as well as varying correction factors, under the assumption of the utilization of short or rapid-acting Insulin.

4.1.1 DEXCOM G6 SOFTWARE

All glucose data analyzed in this study is provided by Dexcom software, used in conjunction with various Insulin pump systems. Glucose data from Dexcom software is able to be extracted using either individual images of daily glucose trends (Figure 16) or via a CSV file, which can be easily customized and extracted from a patient's Dexcom Clarity portal. Dexcom Clarity is an online application that allows a patient to view various glucose trends, as selected by the user, and easily study various trends, patterns and statistics associated with each individual day (Figure 17). This tool allows a patient to intentionally select data to be analyzed with the algorithm presented in this dissertation so that a patient is in complete control of what days or glucose trends that they would like to use to optimize their current basal rates. Each CSV file contains helpful information for the purposes of this analysis, such as glucose values associated with each individual timestamp over a 24-hour period, as well as urgent highs and lows, which is defined by each individual user (Figure 18). It is important to note that the Dexcom G6 software will not read glucose levels above 400 or lower than 40 mg/dL. If a user has a glucose reading at any point that registers as 400 mg/dL or higher, the data extracted from the Dexcom software will read as "high", likewise, if a user has a glucose reading that registers as 40 mg/dL or lower, the data extracted from the Dexcom software will simply read as "low". For the purposes of analysis in this algorithm, all "high" readings will be assumed to be exactly 400 mg/dL and all "low" readings will be assumed to be exactly 40 mg/dL. The Dexcom software utilized in this dissertation extracts glucose values every 5 minutes each hour, resulting

in a total of 12 glucose readings each hour and a total of 288 individual glucose values over a 24-hour period.

4.1.2 Creation of Each Individual Patient

Patients 1 and 2 provided individual images of glucose trends for a number of days via their Dexcom Clarity software, as well as any basal rates used associated with each individual time step over a 24-hour period, correction factors, target glucose levels and the Insulin that was utilized within their individual pump system (Figures 19-20). Patient 3 provided a CSV file of their glucose readings for multiple days, along with all basal rates used for the glucose trends provided, as well as the same inputs provided by patients 1 and 2 (Figure 21). As previously mentioned, each of these inputs are crucial for a full analysis within this proposed program. Human specific correction factors are determined by a healthcare provider to help define the effect that a single unit of Insulin has on blood sugar and are unique to each individual. Insulin type is important to help understand and accurately model the drug profile of the Insulin that is being delivered to the patient to effectively model the rate at which the Insulin is being administered, playing a big part in the resulting glucose response. Aside from the first three patients in this study that were able to provide real data, the remaining seven patients data were individually created and developed using a format very similar to that which is produced by extracting a CSV file from the Dexcom Clarity software. Each of these patient's data sets, comprised of 7 days' worth of individual glucose curves, were created with the desire and intent to showcase specific, realistic trends modeled by type 1 diabetics on a daily basis, spanning a week.

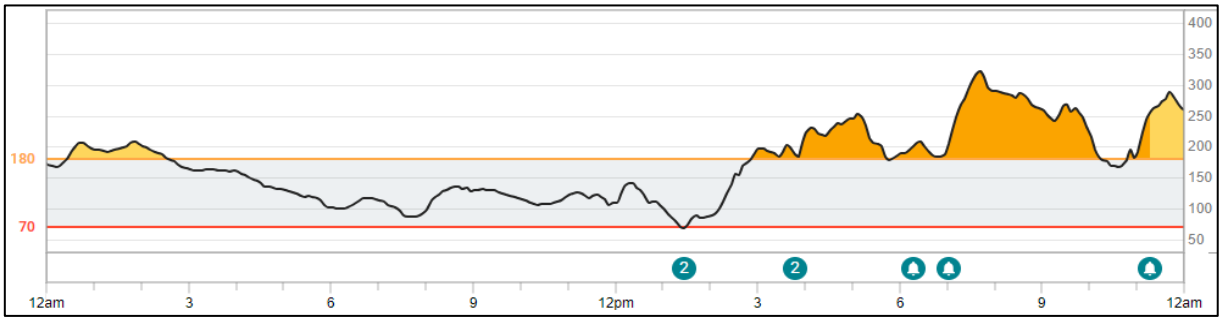


Figure 16: An example of a daily glucose plot exported from the Dexcom G6 Clarity Software.

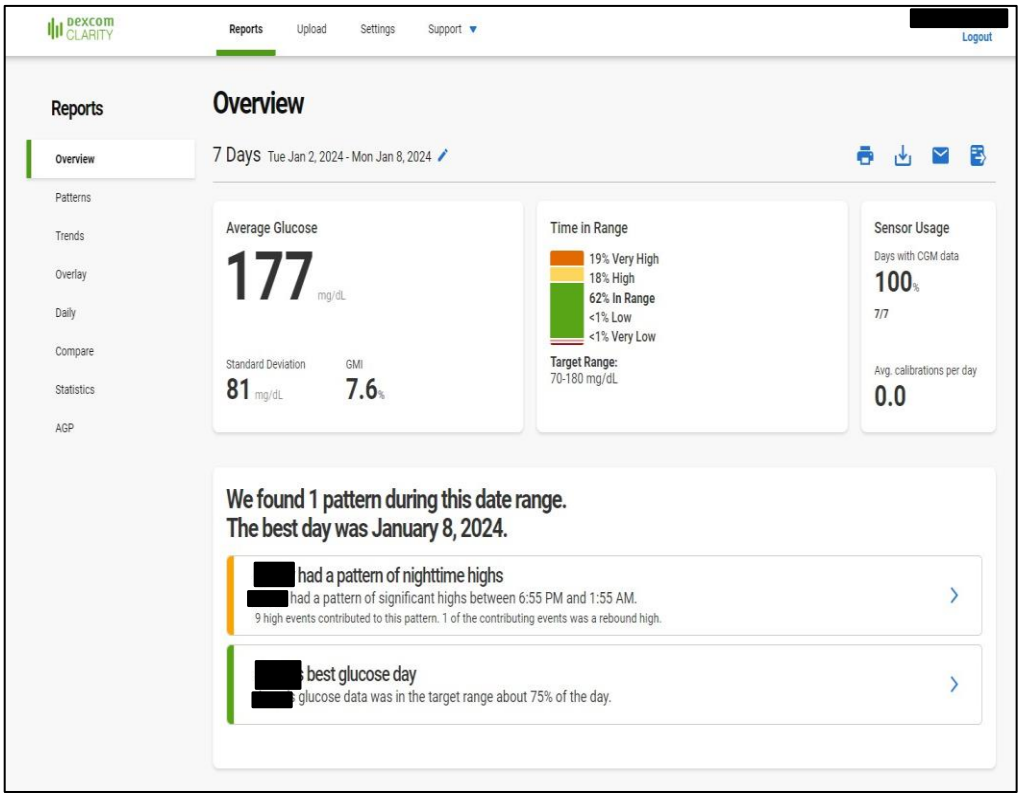


Figure 17: User Interface of date selection overview from Dexcom Clarity Software.

Index	Timestamp (YYYY-MM-DDThh:mm:ss)	Event Type	Event Subtype	Patient Info	Device Info	Source Device ID	Glucose Value (mg/dL)	Insulin Value (u)	Carb Value (grams)	Duration	Transmitter Time	Transmitter ID
1		FirstName		Jenny								
2		LastName		Knuckles								
3		Device			Dexcom G6 Mobile App	iOS G6						
4		Alert	Fall			iOS G6						
5		Alert	High			iOS G6	200					
6		Alert	Low			iOS G6	80					
7		Alert	Signal Loss			iOS G6				0:20:00		
8		Alert	Rise			iOS G6						
9		Alert	Urgent Low			iOS G6	55					
10		Alert	Urgent Low Soon			iOS G6	55					
11	2024-01-02T00:01:49	EGV				iOS G6	291				8353274	8YNUBY
12	2024-01-02T00:06:48	EGV				iOS G6	293				8353574	8YNUBY
13	2024-01-02T00:11:49	EGV				iOS G6	303				8353874	8YNUBY
14	2024-01-02T00:16:49	EGV				iOS G6	309				8354174	8YNUBY
15	2024-01-02T00:21:49	EGV				iOS G6	316				8354474	8YNUBY
16	2024-01-02T00:26:48	EGV				iOS G6	328				8354774	8YNUBY
17	2024-01-02T00:31:48	EGV				iOS G6	334				8355074	8YNUBY
18	2024-01-02T00:36:48	EGV				iOS G6	346				8355374	8YNUBY
19	2024-01-02T00:41:49	EGV				iOS G6	337				8355674	8YNUBY
20	2024-01-02T00:46:48	EGV				iOS G6	319				8355974	8YNUBY
21	2024-01-02T00:51:48	EGV				iOS G6	299				8356274	8YNUBY
22	2024-01-02T00:56:49	EGV				iOS G6	286				8356574	8YNUBY
23	2024-01-02T01:01:49	EGV				iOS G6	289				8356874	8YNUBY
24	2024-01-02T01:06:49	EGV				iOS G6	293				8357174	8YNUBY
25	2024-01-02T01:11:49	EGV				iOS G6	304				8357474	8YNUBY
26	2024-01-02T01:16:48	EGV				iOS G6	308				8357774	8YNUBY
27	2024-01-02T01:21:49	EGV				iOS G6	307				8358074	8YNUBY
28	2024-01-02T01:26:49	EGV				iOS G6	306				8358374	8YNUBY
29	2024-01-02T01:31:49	EGV				iOS G6	303				8358674	8YNUBY
30	2024-01-02T01:36:49	EGV				iOS G6	296				8358974	8YNUBY
31	2024-01-02T01:41:49	EGV				iOS G6	285				8359274	8YNUBY
32	2024-01-02T01:46:49	EGV				iOS G6	276				8359574	8YNUBY
33	2024-01-02T01:51:49	EGV				iOS G6	267				8359874	8YNUBY
34	2024-01-02T01:56:49	EGV				iOS G6	255				8360174	8YNUBY

Figure 18: Example of an exported CSV file from the Dexcom Clarity Software, including necessary information for basal rate analysis.

Some patients displayed more patterns of severe hyperglycemic episodes later in the afternoons through the nights, while other patients displayed the same hyperglycemic episodes in the hours of the early morning through the late morning, until either Insulin is delivered as a result of something such as carb intake, when mealtimes for the day usually begin. Other trends that were modeled were those of more sporadic spikes in glucose levels throughout the day versus more controlled, rises and falls in glucose values, whether considered high or low for each individual patient. Regardless of the trend displayed, glucose patterns were carefully developed to effectively model the desired trend. Because these remaining patients are synthetic, necessary user-inputs, such as initial basal rates, Insulin type, correction factors and target glucose values were made to be assumptions, also with the intention to model them to be realistic scenarios one would likely find in a real data set. Once each patient's data set was finalized with all 288 glucose readings for a number of days, the associated CSV file was saved and ready to be later read into the program. All individual patient data can be seen below (Figures 19-28).

Table 1: Table showcasing user inputs necessary for analysis for patient 1.

Patient	Data Extraction Method	Insulin Type	Target Glucose Value	Time	Original Basal Rates	Insulin Sensitivity (Correction Factors)
				12:00 AM	0.9	30
				1:00 AM	0.9	30
				2:00 AM	1.1	30
				3:00 AM	1.1	30
				4:00 AM	1.1	30
				5:00 AM	1.2	30
				6:00 AM	1.2	30
				7:00 AM	1.6	30
				8:00 AM	1.6	30
				9:00 AM	1.6	30
				10:00 AM	1.4	30
		Rapid		11:00 AM	1.4	30
		Insulin	mg/dL	12:00 PM	1.5	30
				1:00 PM	1.5	30
				2:00 PM	1.5	30
				3:00 PM	1.4	30
				4:00 PM	1.4	30
				5:00 PM	1.4	30
				6:00 PM	1.2	30
				7:00 PM	1.2	30
				8:00 PM	1.1	30
				9:00 PM	1.1	30
				10:00 PM	1.1	30
				11:00 PM	1.1	30

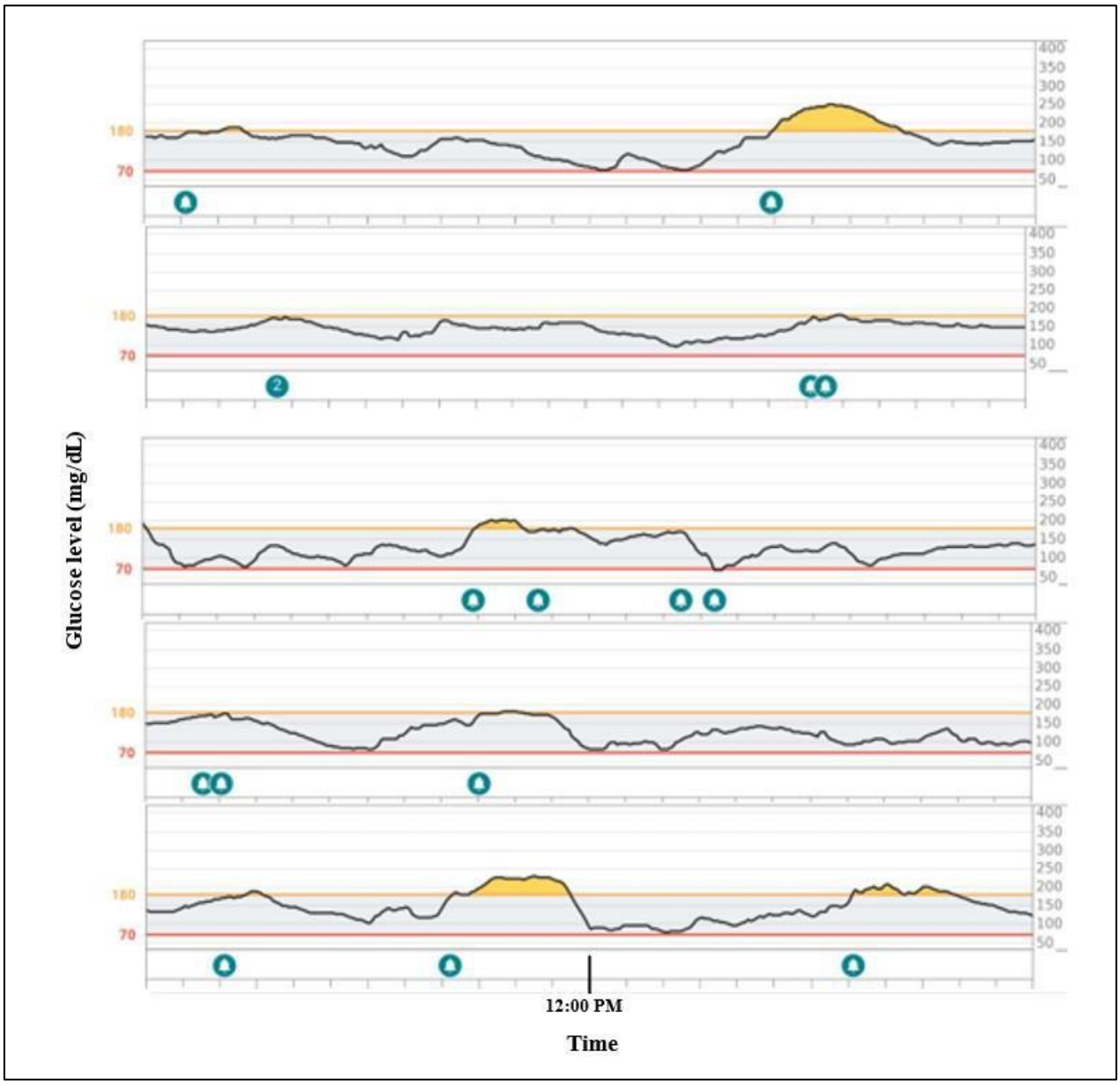


Figure 19: Original Dataset for Patient 1 exported using a Dexcom image. This image only contains a few plots provided by this subject as an example.

Table 2: Table showcasing user inputs necessary for analysis for patient 2.

Patient	Data Extraction Method	Insulin Type	Target Glucose Value	Time	Original Basal Rates	Insulin Sensitivity (Correction Factors)
2	Dexcom Image	Rapid Acting Insulin	110 mg/dL	12:00 AM	1.0	30
				1:00 AM	1.0	30
				2:00 AM	1.0	30
				3:00 AM	1.0	30
				4:00 AM	1.0	30
				5:00 AM	1.0	30
				6:00 AM	1.0	30
				7:00 AM	1.0	30
				8:00 AM	1.0	30
				9:00 AM	1.0	30
				10:00 AM	1.0	30
				11:00 AM	1.0	30
				12:00 PM	1.0	30
				1:00 PM	1.0	30
				2:00 PM	1.0	30
				3:00 PM	1.0	30
				4:00 PM	1.0	30
				5:00 PM	1.0	30
				6:00 PM	1.0	30
				7:00 PM	1.0	30
				8:00 PM	1.0	30
				9:00 PM	1.0	30
				10:00 PM	1.0	30
				11:00 PM	1.0	30

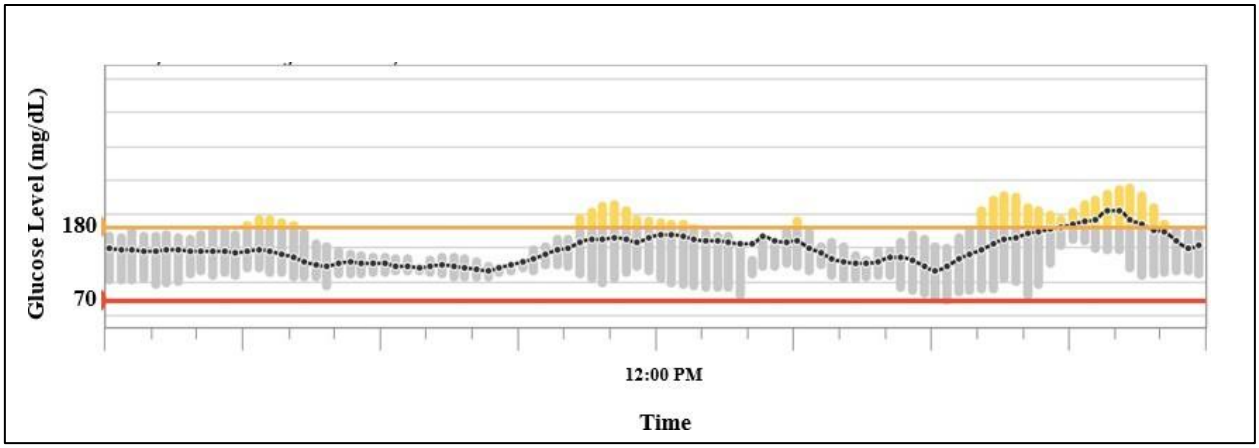


Figure 20: Original Dataset for Patient 2 exported using a Dexcom image. Average Image provided for a span of 7 days.

Table 3: Table showcasing user inputs necessary for analysis for patient 3.

Patient	Data Extraction Method	Insulin Type	Target Glucose Value	Time	Original Basal Rates (Units)	Insulin Sensitivity (Correction Factors) (mg/dL)
3	CSV File	Rapid Acting Insulin	110 mg/dL	12:00 AM	0.95	50
				1:00 AM	0.95	50
				2:00 AM	0.95	50
				3:00 AM	1.0	50
				4:00 AM	1.0	50
				5:00 AM	1.0	50
				6:00 AM	1.15	50
				7:00 AM	1.15	50
				8:00 AM	1.15	50
				9:00 AM	1.15	50
				10:00 AM	1.15	55
				11:00 AM	1.15	55
				12:00 PM	1.15	55
				1:00 PM	1.15	55
				2:00 PM	1.15	55
				3:00 PM	1.15	55
				4:00 PM	1.15	55
				5:00 PM	1.15	35
				6:00 PM	1.15	35
				7:00 PM	1.15	35
				8:00 PM	1.15	35
				9:00 PM	1.15	35
				10:00 PM	1.15	35
				11:00 PM	0.85	45

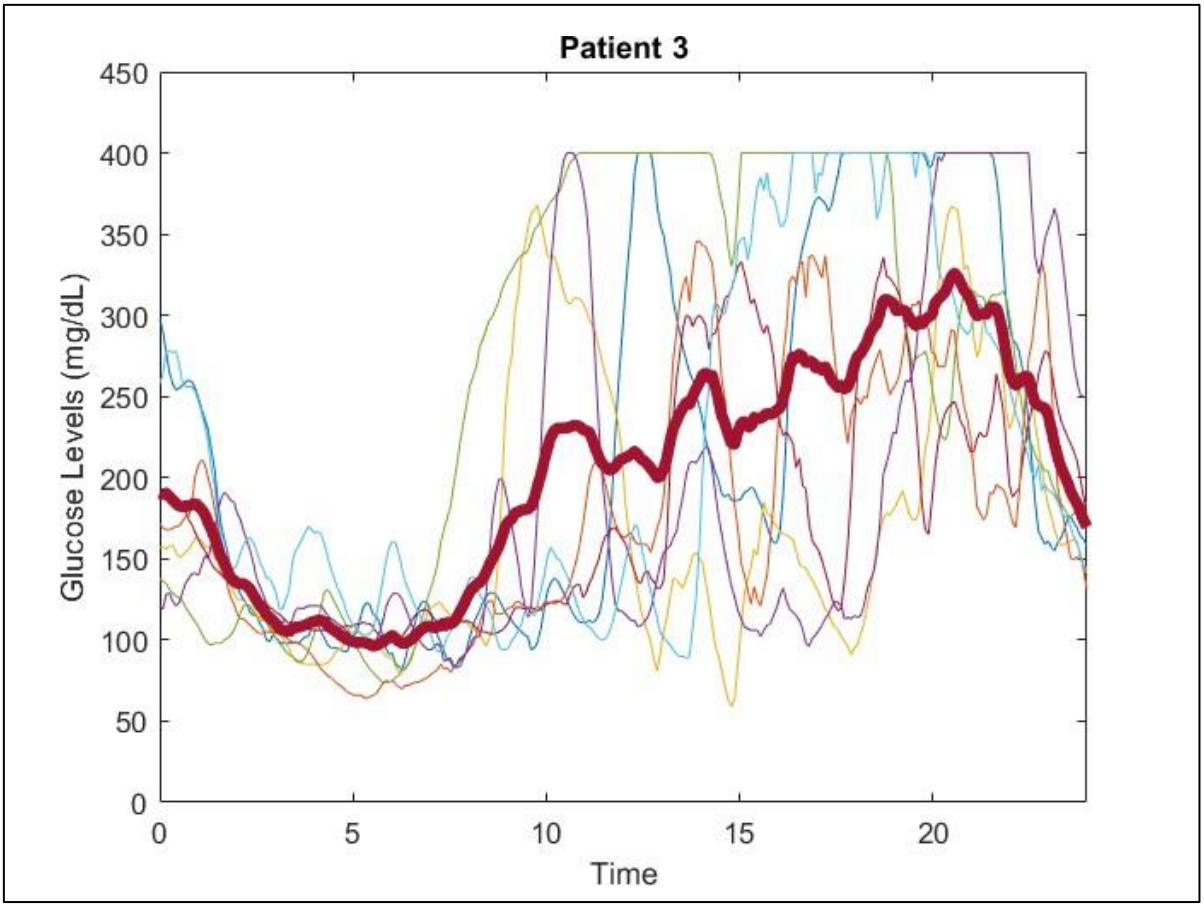


Figure 21: Original Datasets for Patient 3 exported using a CSV file. Each colored line represents an individual day, while the thick, red line represents the average glucose curve of all days combined.

Table 4: Table showcasing user inputs necessary for analysis for patient 4.

Patient	Data Extraction Method	Insulin Type	Target Glucose Value	Time	Original Basal Rates	Insulin Sensitivity (Correction Factors)
4	CSV File	Rapid Acting Insulin	110 mg/dL	12:00 AM	1.0	45
				1:00 AM	1.0	45
				2:00 AM	1.0	45
				3:00 AM	1.0	45
				4:00 AM	1.0	45
				5:00 AM	1.0	45
				6:00 AM	1.0	45
				7:00 AM	1.0	45
				8:00 AM	1.0	45
				9:00 AM	1.0	45
				10:00 AM	1.0	45
				11:00 AM	1.0	45
				12:00 PM	1.0	45
				1:00 PM	1.0	45
				2:00 PM	1.0	45
				3:00 PM	1.0	45
				4:00 PM	1.0	45
				5:00 PM	1.0	45
				6:00 PM	1.0	45
				7:00 PM	1.0	45
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				10:00 PM	1.0	45
				11:00 PM	1.0	45

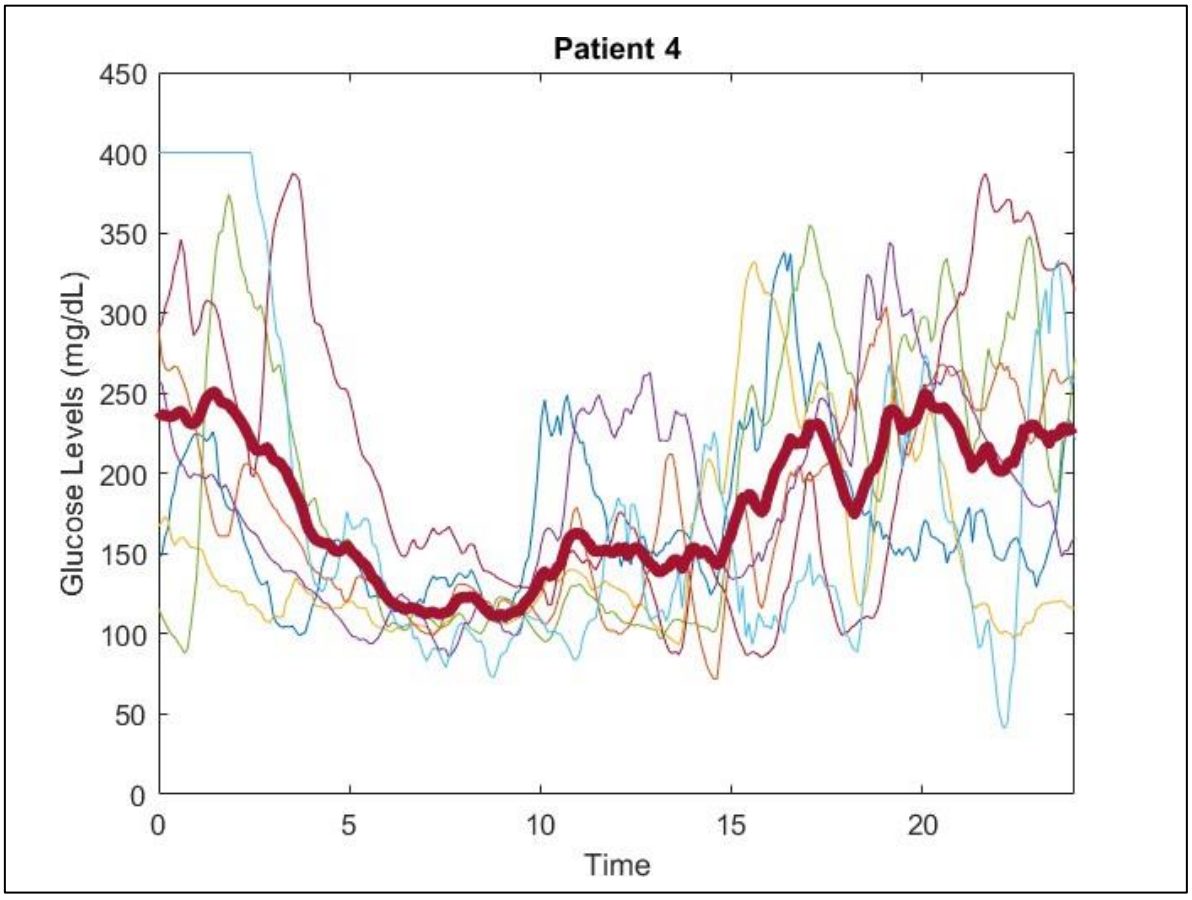

Figure 22: Original Dataset for Patient 4 exported using a CSV file. Each colored line represents an individual day, while the thick, red line represents the average glucose curve of all days combined.

Table 5: Table showcasing user inputs necessary for analysis for patient 5.

Patient	Data Extraction Method	Insulin Type	Target Glucose Value	Time	Original Basal Rates	Insulin Sensitivity (Correction Factors)
5	CSV File	Rapid Acting Insulin	110 mg/dL	12:00 AM	0.95	50
				1:00 AM	0.95	50
				2:00 AM	0.95	50
				3:00 AM	0.95	50
				4:00 AM	0.95	50
				5:00 AM	1.2	50
				6:00 AM	1.2	50
				7:00 AM	1.2	50
				8:00 AM	1.2	50
				9:00 AM	1.2	50
				10:00 AM	1.4	50
				11:00 AM	1.4	50
				12:00 PM	1.4	50
				1:00 PM	1.4	50
				2:00 PM	1.4	50
				3:00 PM	1.4	50
				4:00 PM	1.4	50
				5:00 PM	1.45	50
				6:00 PM	1.45	50
				7:00 PM	1.45	50
				8:00 PM	1.45	50
				9:00 PM	1.2	50
				10:00 PM	1.2	50
				11:00 PM	1.2	50

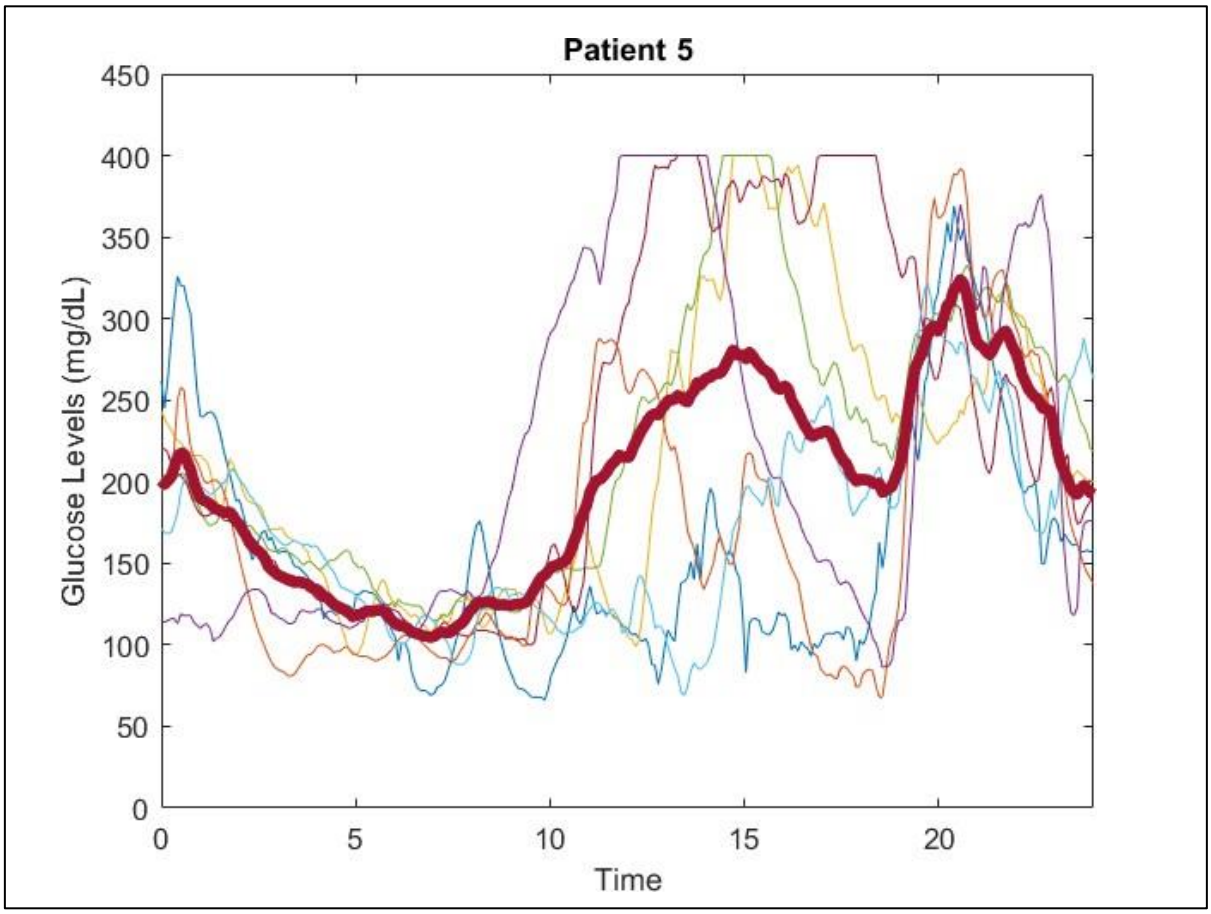

Figure 23: Original Dataset for Patient 5 exported using a CSV file. Each colored line represents an individual day, while the thick, red line represents the average glucose curve of all days combined.

Table 6: Table showcasing user inputs necessary for analysis for patient 6.

Patient	Data Extraction Method	Insulin Type	Target Glucose Value	Time	Original Basal Rates	Insulin Sensitivity (Correction Factors)
6	CSV File	Rapid Acting Insulin	110 mg/dL	12:00 AM	1.0	50
				1:00 AM	1.0	50
				2:00 AM	1.0	50
				3:00 AM	1.0	50
				4:00 AM	1.0	50
				5:00 AM	1.0	50
				6:00 AM	1.0	50
				7:00 AM	1.0	50
				8:00 AM	1.0	50
				9:00 AM	1.0	50
				10:00 AM	1.0	50
				11:00 AM	1.0	50
				12:00 PM	1.0	50
				1:00 PM	1.0	50
				2:00 PM	1.0	50
				3:00 PM	1.0	50
				4:00 PM	1.0	50
				5:00 PM	1.0	50
				6:00 PM	1.0	50
				7:00 PM	1.0	50
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				9:00 PM	1.0	50
				10:00 PM	1.0	50
				11:00 PM	1.0	50

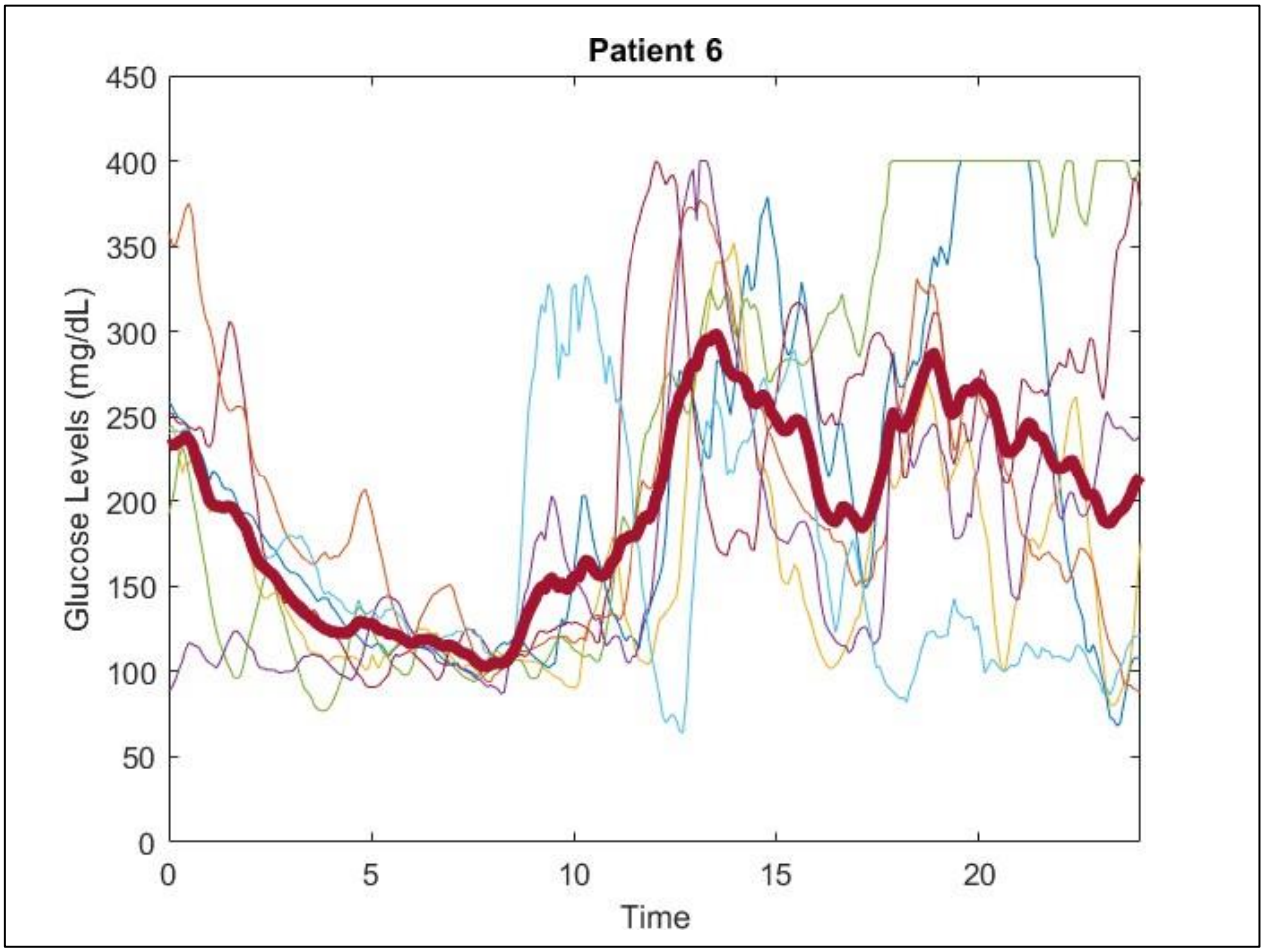

Figure 24: Original Dataset for Patient 6 exported using a CSV file. Each colored line represents an individual day, while the thick, red line represents the average glucose curve of all days combined.

Table 7: Table showcasing user inputs necessary for analysis for patient 7.

Patient	Data Extraction Method	Insulin Type	Target Glucose Value	Time	Original Basal Rates	Insulin Sensitivity (Correction Factors)
7	CSV File	Rapid Acting Insulin	110 mg/dL	12:00 AM	0.95	40
				1:00 AM	0.95	40
				2:00 AM	0.95	40
				3:00 AM	1.0	40
				4:00 AM	1.0	40
				5:00 AM	1.0	40
				6:00 AM	1.15	40
				7:00 AM	1.15	40
				8:00 AM	1.15	40
				9:00 AM	1.15	40
				10:00 AM	1.15	40
				11:00 AM	1.15	40
				12:00 PM	1.15	40
				1:00 PM	1.15	40
				2:00 PM	1.15	40
				3:00 PM	1.15	40
				4:00 PM	1.15	40
				5:00 PM	1.15	40
				6:00 PM	1.15	40
				7:00 PM	1.15	40
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				10:00 PM	1.15	40
				11:00 PM	0.85	40

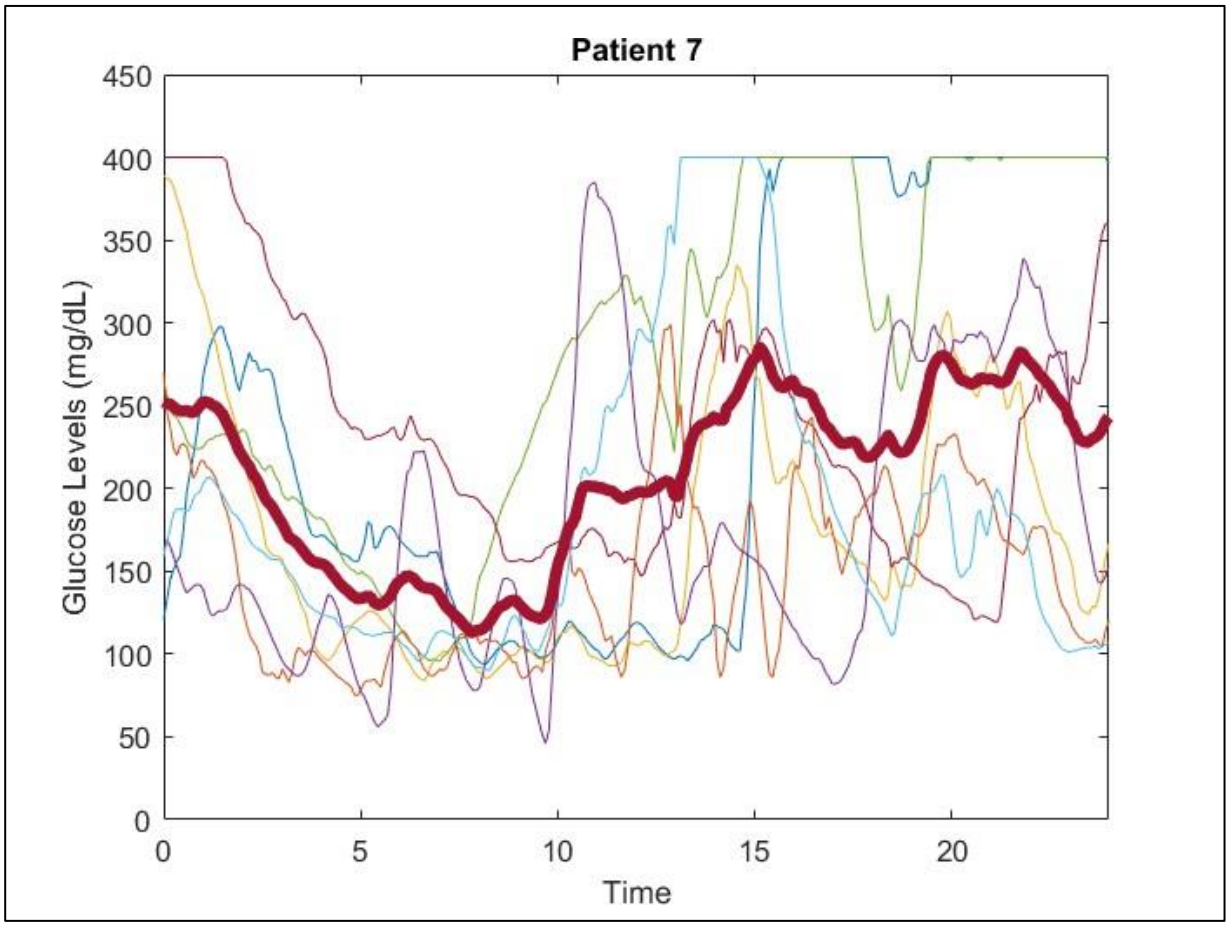

Figure 25: Original Dataset for Patient 7 exported using a CSV file. Each colored line represents an individual day, while the thick, red line represents the average glucose curve of all days combined.

Table 8: Table showcasing user inputs necessary for analysis for patient 8.

Patient	Data Extraction Method	Insulin Type	Target Glucose Value	Time	Original Basal Rates	Insulin Sensitivity (Correction Factors)
8	CSV File	Rapid Acting Insulin	110 mg/dL	12:00 AM	1.0	35
				1:00 AM	1.0	35
				2:00 AM	1.0	35
				3:00 AM	1.0	35
				4:00 AM	1.0	35
				5:00 AM	1.0	35
				6:00 AM	1.0	35
				7:00 AM	1.0	35
				8:00 AM	1.0	35
				9:00 AM	1.0	35
				10:00 AM	1.0	35
				11:00 AM	1.0	35
				12:00 PM	1.0	35
				1:00 PM	1.0	35
				2:00 PM	1.0	35
				3:00 PM	1.0	35
				4:00 PM	1.0	35
				5:00 PM	1.0	35
				6:00 PM	1.0	35
				7:00 PM	1.0	35
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				10:00 PM	1.0	35
				11:00 PM	1.0	35

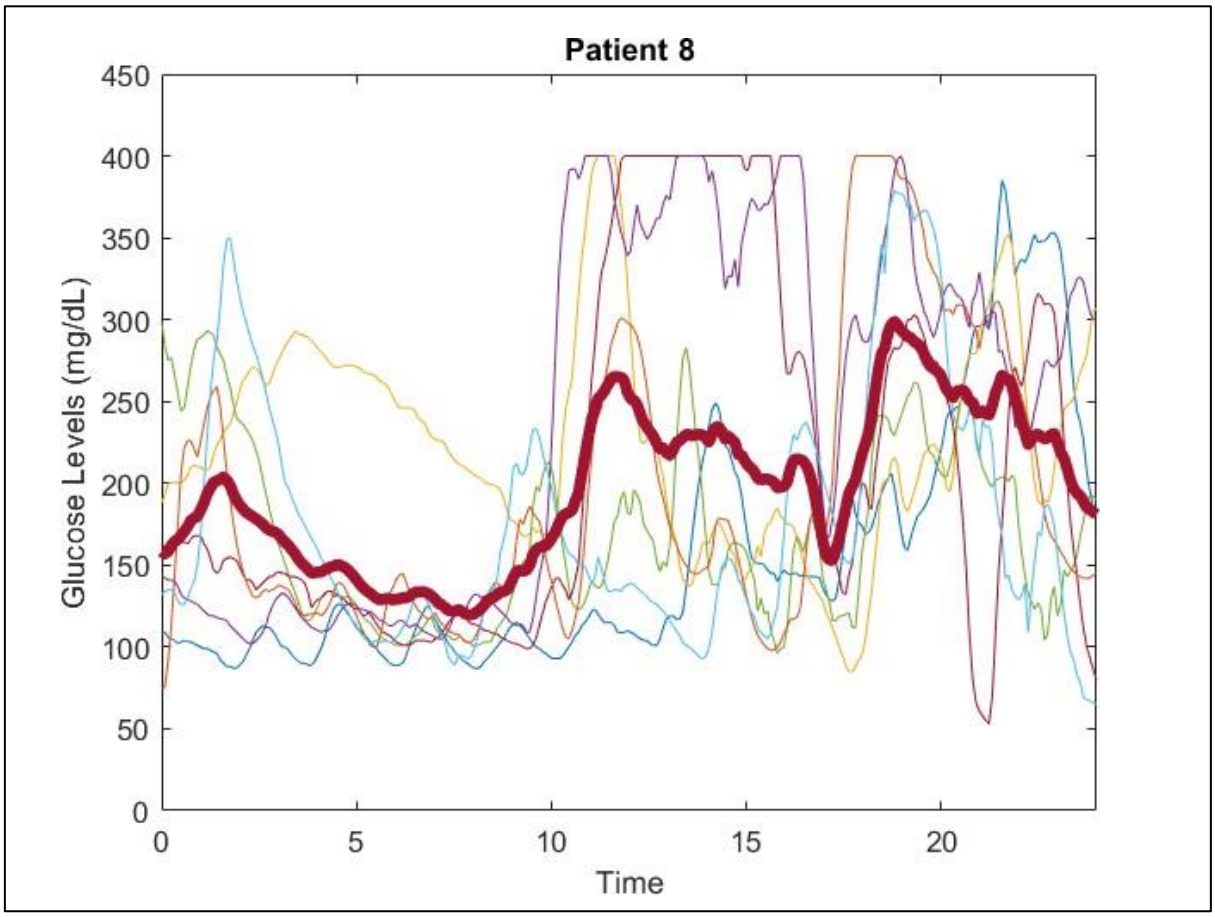


Figure 26: Original Dataset for Patient 8 exported using a CSV file. Each colored line represents an individual day, while the thick, red line represents the average glucose curve of all days combined.

Table 9: Table showcasing user inputs necessary for analysis for patient 9.

Patient	Data Extraction Method	Insulin Type	Target Glucose Value	Time	Original Basal Rates	Insulin Sensitivity (Correction Factors)
9	CSV File	Rapid Acting Insulin	110 mg/dL	12:00 AM	0.95	45
				1:00 AM	0.95	45
				2:00 AM	0.95	45
				3:00 AM	1.0	45
				4:00 AM	1.0	45
				5:00 AM	1.0	45
				6:00 AM	1.15	45
				7:00 AM	1.15	45
				8:00 AM	1.15	45
				9:00 AM	1.15	45
				10:00 AM	1.15	45
				11:00 AM	1.15	45
				12:00 PM	1.15	45
				1:00 PM	1.15	45
				2:00 PM	1.15	45
				3:00 PM	1.15	45
				4:00 PM	1.15	45
				5:00 PM	1.15	45
				6:00 PM	1.15	45
				7:00 PM	1.15	45
				8:00 PM	1.15	45
				9:00 PM	1.15	45
				10:00 PM	1.15	45
				11:00 PM	0.85	45

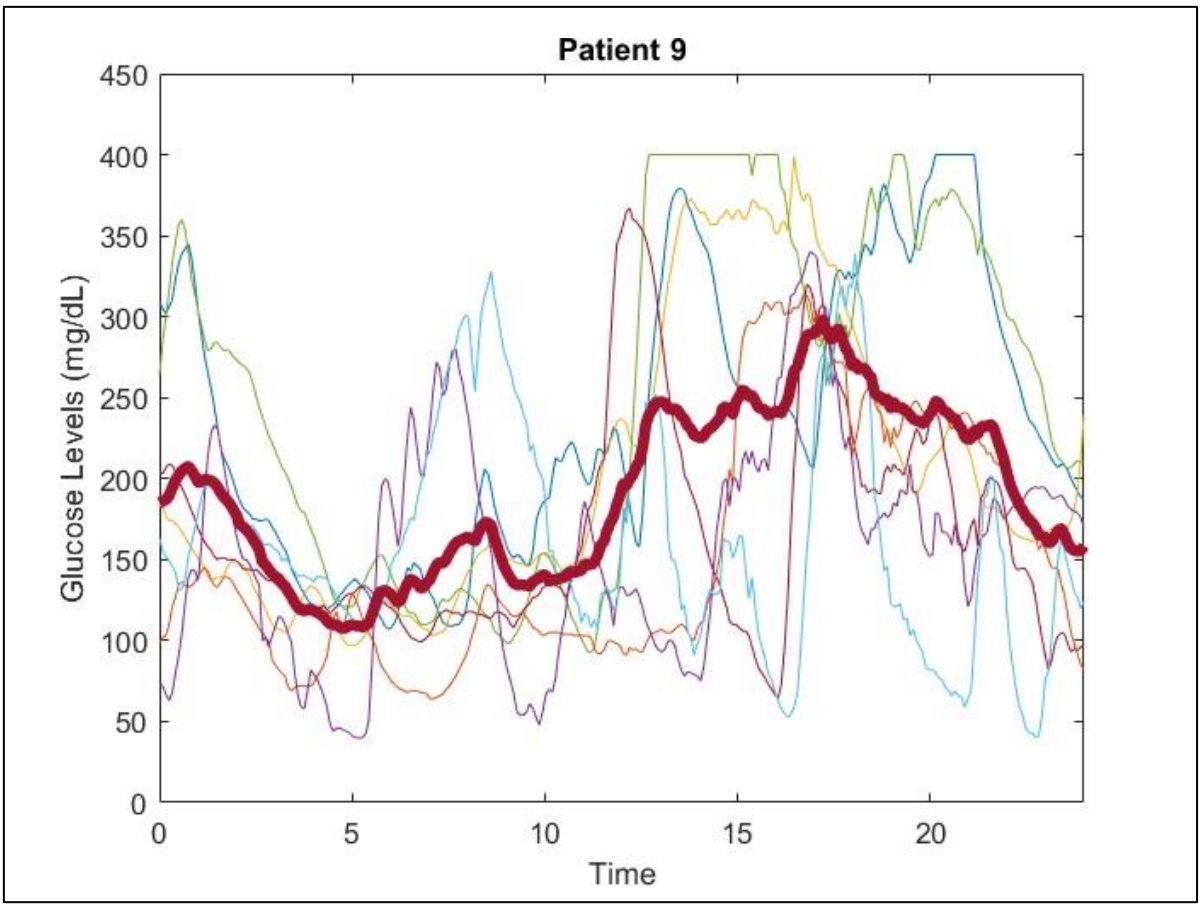


Figure 27: Original Dataset for Patient 9 exported using a CSV file. Each colored line represents an individual day, while the thick, red line represents the average glucose curve of all days combined.

Table 10: Table showcasing user inputs necessary for analysis for patient 10.

Patient	Data Extraction Method	Insulin Type	Target Glucose Value	Time	Original Basal Rates	Insulin Sensitivity (Correction Factors)
10	CSV File	Rapid Acting Insulin	110 mg/dL	12:00 AM	0.9	50
				1:00 AM	0.9	50
				2:00 AM	1.1	50
				3:00 AM	1.1	50
				4:00 AM	1.1	50
				5:00 AM	1.2	50
				6:00 AM	1.2	50
				7:00 AM	1.6	50
				8:00 AM	1.6	50
				9:00 AM	1.6	50
				10:00 AM	1.4	50
				11:00 AM	1.4	50
				12:00 PM	1.5	50
				1:00 PM	1.5	50
				2:00 PM	1.5	50
				3:00 PM	1.4	50
				4:00 PM	1.4	50
				5:00 PM	1.4	50
				6:00 PM	1.2	50
				7:00 PM	1.2	50
				8:00 PM	1.1	50
				9:00 PM	1.1	50
				10:00 PM	1.1	50
				11:00 PM	1.1	50

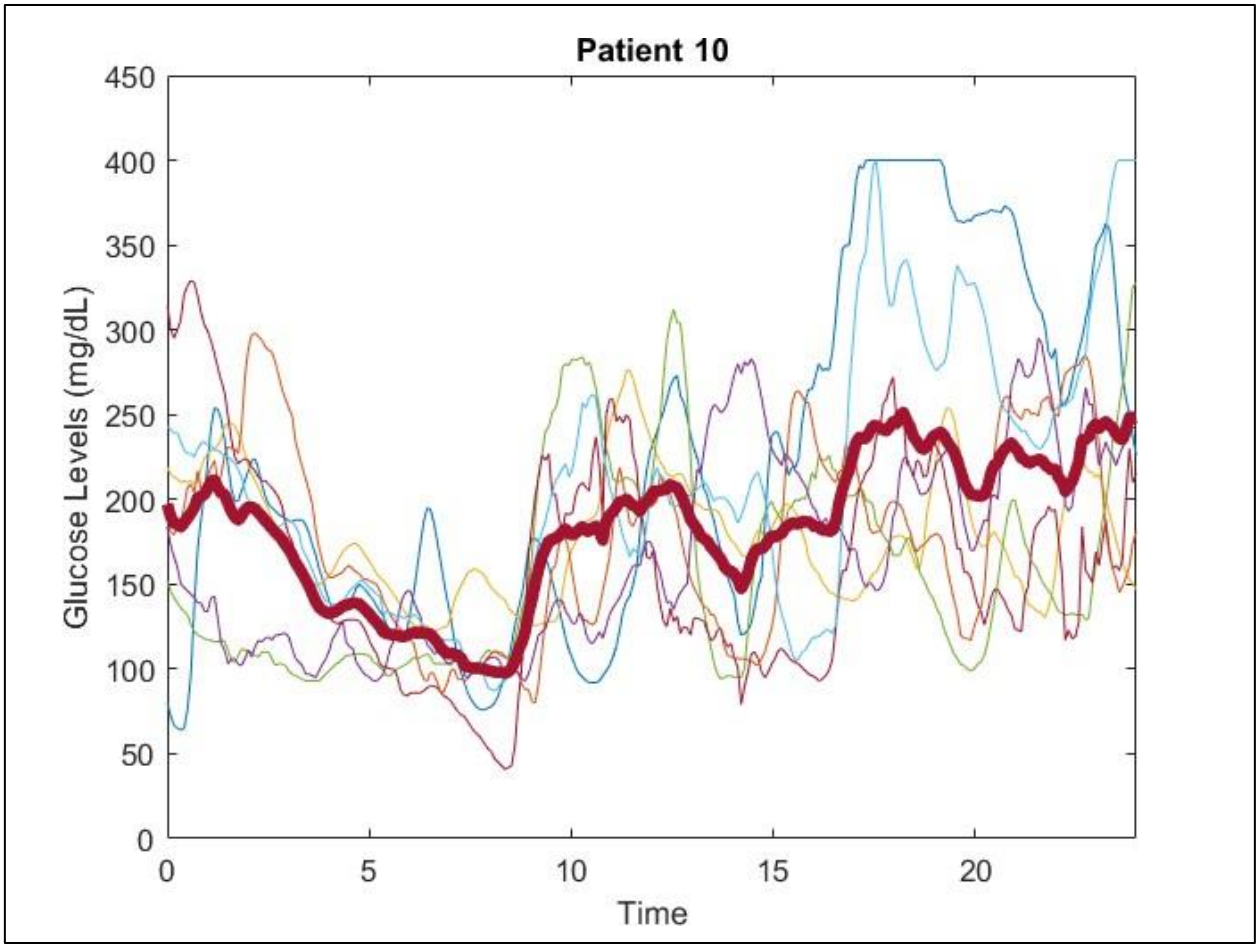


Figure 28: Original Dataset for Patient 10 exported using a CSV file. Each colored line represents an individual day, while the thick, red line represents the average glucose curve of all days combined.

Table 11: Table showcasing user inputs necessary for analysis for patient 11.

Patient	Data Extraction Method	Insulin Type	Target Glucose Value	Time	Original Basal Rates	Insulin Sensitivity (Correction Factors)
11	CSV File	Rapid Acting Insulin	110 mg/dL	12:00 AM	0.9	50
				1:00 AM	0.9	50
				2:00 AM	1.1	50
				3:00 AM	1.1	50
				4:00 AM	1.1	50
				5:00 AM	1.2	50
				6:00 AM	1.2	50
				7:00 AM	1.6	50
				8:00 AM	1.6	50
				9:00 AM	1.6	50
				10:00 AM	1.4	50
				11:00 AM	1.4	50
				12:00 PM	1.5	50
				1:00 PM	1.5	50
				2:00 PM	1.5	50
				3:00 PM	1.4	50
				4:00 PM	1.4	50
				5:00 PM	1.4	50
				6:00 PM	1.2	50
				7:00 PM	1.2	50
				8:00 PM	1.1	50
				9:00 PM	1.1	50
				10:00 PM	1.1	50
				11:00 PM	1.1	50

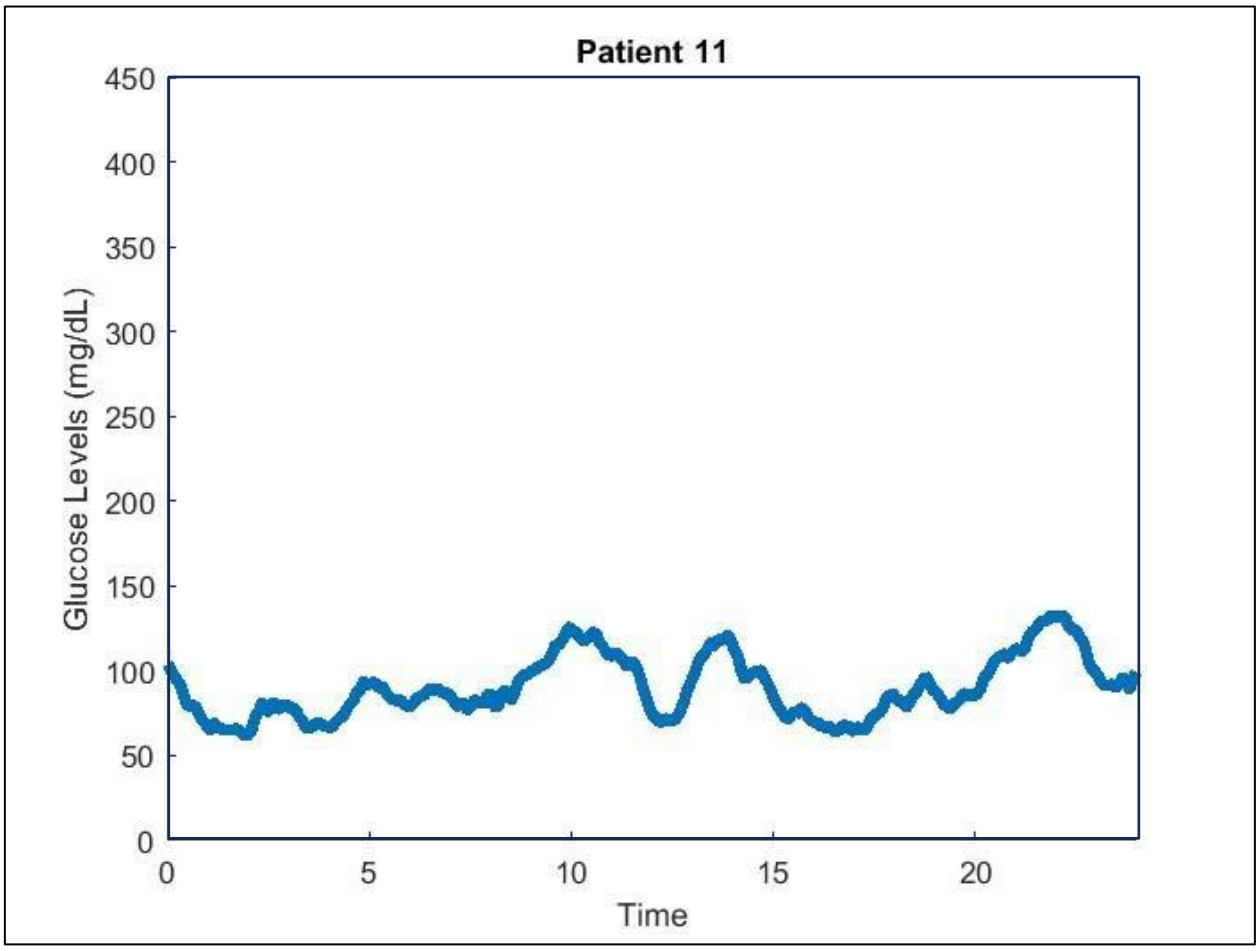


Figure 29: Original Dataset for Patient 11 exported using a CSV file. Average Image provided for a span of 7 days.

4.2 BASAL OPTIMIZATION ALGORITHM

The model developed as a part of this dissertation is a dynamic mathematical model. This model operates using time-dependent changes in relation to known inputs, such as basal rate and glucose level. Each extracted glucose level is associated with a specific time step, which is also then associated with a specific basal rate that is delivered at the specified time. It is very important that each input variable is bound by the exact time the event is taking place, so that each output can be suggested to the user and then applied at the appropriate time to give optimal results and effect on overall glucose levels. Additionally, the model developed as a part of this dissertation is an explicit mathematical model, as all inputs to the system are known. Both concepts have been developed to be able to suggest basal rates more efficiently and accurately to a type 1 diabetics by reducing the time spent calculating optimized rates as well as more confidently predicting rates, by using patient-specific data, that will offer more controlled glucose levels for each individualized patient.

4.2.1 ALGORITHM FRAMEWORK

The goal of the basal optimization algorithm is to analyze patient specific data to predict more ideal basal rates and the glucose levels associated with each new basal rate and to then utilize these pattern-matching algorithms to successfully read in hand-selected CGM images of glucose level trends, along with other patient specific data, predict optimized basal rates and visually display to the user the predicted glucose response of the updated rates for approval. The driving force of this algorithm is the dynamic mathematical model that operates using time-dependent changes in relation to glucose level and associated basal rate. The first step of this algorithm is the preparation and implementation of the known patient-specific inputs, with an

emphasis on extracting the glucose data from one of the two different modalities, either being an image of the glucose trends or the discrete numerical data exported from the Dexcom Clarity software. After ensuring the user inputs are successfully loaded into the model, the next step is to simultaneously derive the relationship between glucose levels, basal rates and time, while also deriving the appropriate drug delivery profile. Finally, before basal rates can be optimized, it is important to remove effects of bolus insulin around mealtimes to extrapolate basal amounts. After this step, the basal optimization algorithm is ready to run to predict new glucose levels and produce the revised basal rates, ultimately allowing the user full control in selecting the percentage of the suggested, revised basal rates that they wish to apply, yielding the optimal results in hopes of providing more controlled, stabilized glucose levels throughout the day. An overall flowchart of the framework for this program can be seen below (Figure 30).

Because the algorithm is set up to take in any number of days of glucose levels over a 24-hour period, if the user wishes, they would be able to then take the results produced and run them back through the algorithm for a number of future iterations. However, it is important to note, while the algorithm is equipped to execute this, it may not be suggested, as the results produced still need to be actually tested by the user first, as there are a number of external factors that also affect glucose response in an individual and could indeed influence the results.

4.2.2 Data Extraction Algorithm

Glucose data can be chosen by the user to be extracted one of two ways: an image from or an exported CSV file, both easily obtained from their Dexcom Clarity application. If the image method is chosen, the user will read in a specified number of images displaying glucose trends, where it will then undergo image processing techniques to ultimately convert the glucose curve into numeric data used for analysis.

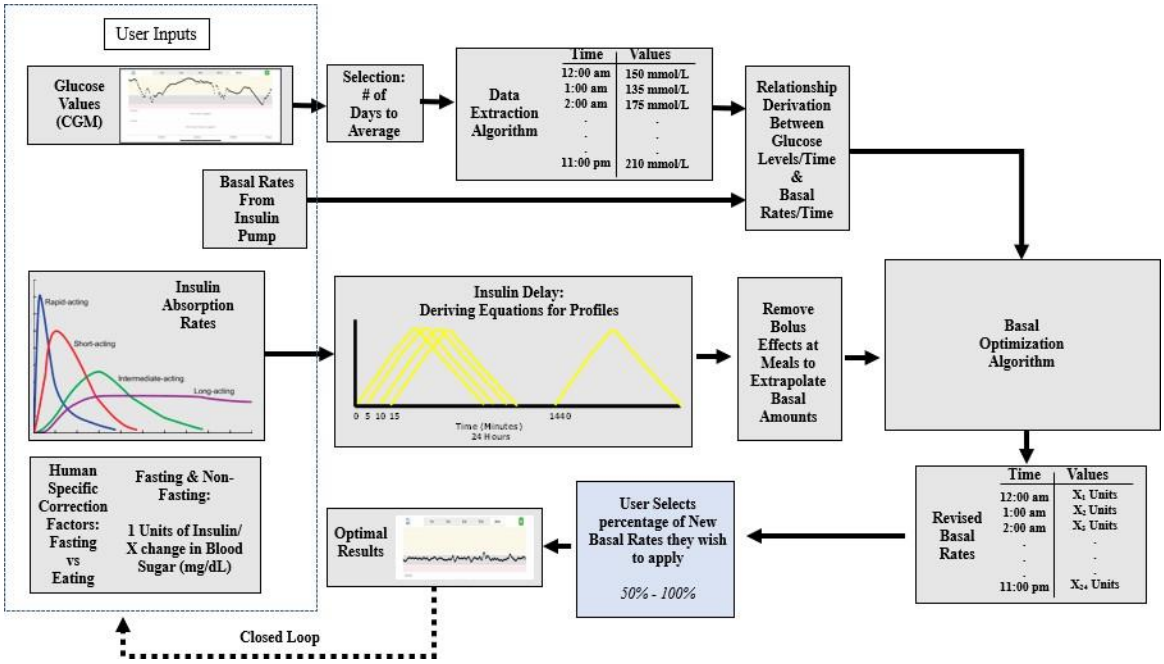


Figure 30: Flowchart showing the overall framework of the algorithms housed within this program.

First, the program will ensure that all images are properly scaled and resized to confirm that all images read into the program are comparable to one another. After the number of pixels in both the vertical and horizontal directions have been defined, a portion of the top of the image, where any title may exist, is removed to ensure that the program is detecting only black pixels corresponding to the glucose curve. Using pre-defined RGB Triplet methodologies, pixels identified as having a true black hue, using the RGB Triplet [0 0 0], are identified in both the horizontal (x) and vertical (y) directions. Once the black pixels have been identified, both the precise x and y location of each pixel is identified and saved. Finally, the x and y axes are scaled based on the height of the resized image in order to define the upper and lower limits of each axis in correspondence with the original glucose image (Figure 30). This ensures that the glucose levels are accurately extracted and displayed to the user, as well as correspondence with the associated time-step, before proceeding further with the algorithm.

It is important to note here, that the glucose trend displayed on the Dexcom image can either be a singular image of the average trend over a period of days or multiple images of the average glucose trend for a number of individual days selected by the user, with the program being equipped to handle both scenarios. Because the basal optimization algorithm makes predictions based upon the average glucose value at each timestep, if the uploaded Dexcom image fed into the program consists of multiple images of singular days, then the overall average glucose curve will be derived by calculating the mean y value, or value corresponding to glucose level, at each time step, resulting in the final average glucose curve that will be used for further analysis.

On the contrary, if the patient opts to upload their data with the exported CSV file, the program will first read in the associated file, containing information such as time-step, date and

glucose levels and store them with their respective dates. Next, time-steps for each of the individual patient's data will be displayed alongside the average glucose curve, as explained above. Regardless of method, the basal optimization algorithm will be making recommended suggestions based upon the average glucose level at each individual hour, as any change in basal rate is always recommended to change on the hour, regardless of time of day. With this being said, once the average glucose curve is displayed, the program will then take the readings that comprise each hour and average them together, ultimately providing the program with 12 average glucose readings for each hour to then be used for further analysis. While Dexcom images may provide for more efficient user interaction, either method guarantees a specified, customizable range of dates selected, allowing the user to be in complete control of what days and glucose data are used to predict more optimized basal rates.

4.2.3 Modeling the Drug Profile and Deriving Relationships

Modeling the individual drug profile of the Insulin being administered by the pump system is crucial to the analysis and optimization of basal rates. As previously mentioned, many types of Insulin exist and all have different profiles that include characteristics of the drug, such as onset-time, peak-time and duration, that all must be modeled to accurately exhibit the rate at which the Insulin is being administered once the delivery process begins. For example, all of the insulin pump systems utilized in this study delivered a rapid-acting insulin. Regardless of the type of insulin being administered, it is important to both recognize and then implement characteristics of the drug in order to make sure that it is being modeled as accurately as possible, ultimately developing a drug profile that allows for the increase in individual patient customization, as well as a more accurate way to develop algorithms with the intent to house it in insulin pump software.

```
% defines new image with same size as original image
    ave_pixel = [];
    newImageAve = zeros(size(newImage,1),size(newImage,2),size(newImage,3))+255;

% Going through all rows (x)
    for j=1:size(newImage,2)
        averagePoint = [];
      % Going through all columns (y)
        for i=1:size(newLauren,1)
          if newImage(i,j,1)<=100 && newImage(i,j,2)<=100 && newImage(i,j,3)<=100

% Getting the x & y location for each individual pixel in one column
              averagePoint = [i,j];
           end
        end

% If column contains black pixels, then save the x,y location, otherwise continue
        if (~isempty(averagePoint))

% [pixel locations of all pixels, pixel location of new detected pixel]
            ave_pixel = [ave_pixel;averagePoint];

% Making the detected points black
            newImageAve(averagePoint(1),averagePoint(2),1) = 0;
            newImageAve(averagePoint(1),averagePoint(2),2) = 0;
            newImageAve(averagePoint(1),averagePoint(2),3) = 0;
        else
            continue
        end
    end
```

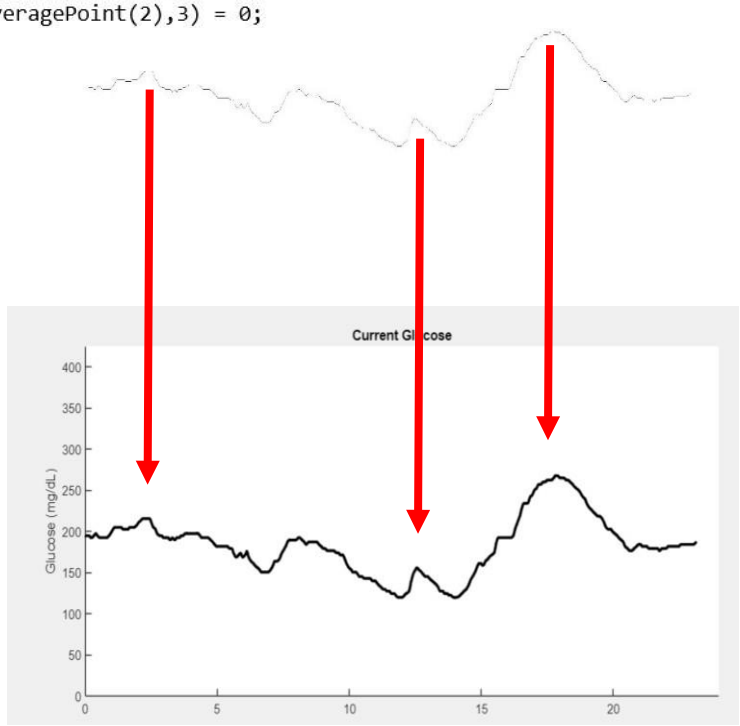


Figure 31: Schematic demonstrating the image processing algorithm. These calculations allow for data extraction through Dexcom image input.

This Insulin is known to have an onset-time of anywhere from 0-15 minutes, a peak time of anywhere between 1-2 hours and an overall duration of 4 hours. It is important to note that because every individual's body can respond differently to Insulin, while there being a number of external factors that can influence glucose response to Insulin delivery, that these numbers may slightly fluctuate from person to person. For the purposes of analysis in this dissertation, the onset time is assumed to be a point that exists between 0-15 minutes, the peak time to be 2 hours and the duration of the drug to be effective for a total of 4 hours post-delivery.

These characteristics combined help us to determine how effective the drug is at a certain point in time and help to break down the total amount of Insulin on board at any point in time over a 24-hour period. To model this profile as accurately as possible, polynomial curve fitting within MATLAB was utilized, fitting the effectiveness (%) with the known duration and peak time of the type of Insulin used. This helps to define an equation that can be applied at every time-step during the delivery process to try and replicate the amount of Insulin being administered. To accomplish this, it was important to first understand what is occurring at the initial time of delivery, especially in terms of Basal Insulin. When a basal rate is set for each hour, that means that that total rate was being delivered within that hour period. As an example, a basal rate of 1.2 means that 1.2 units of insulin will be divided into equal increments (0.108 units) and delivered every 5 minutes over a period of 1 hour, until all 1.2 units are utilized within the given hour timeframe (Figure 31).

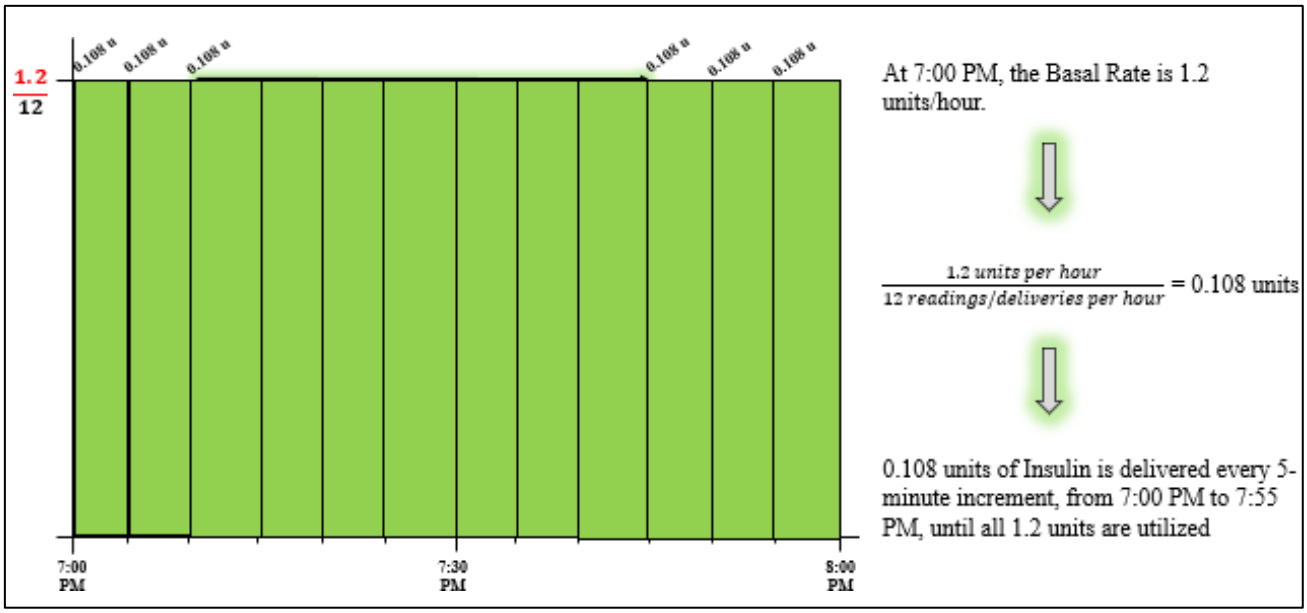


Figure 32: Breakdown of the micro-deliveries of Insulin over a span of hour.

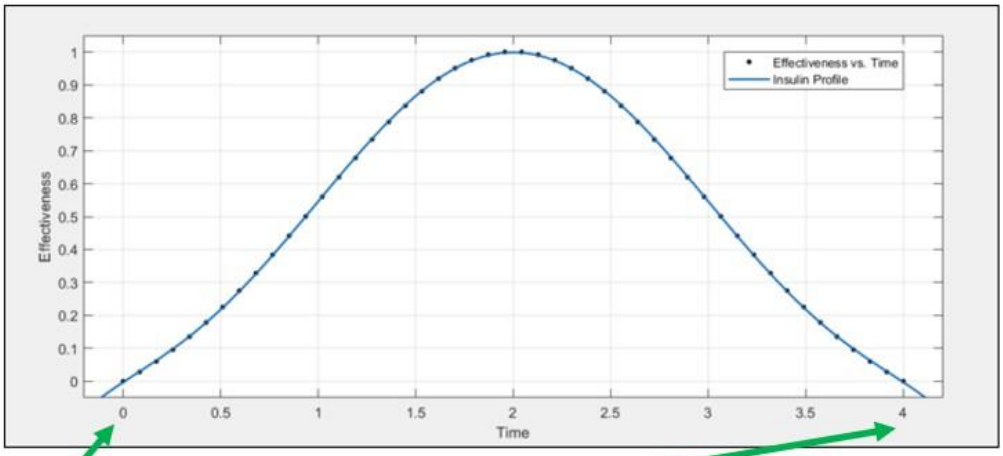
Knowing this, the next step was then to apply the 6^{th} order polynomial at each time increment to model the effectiveness of each incremented delivery (Figure 32). Ensuring the area underneath the curve was equivalent to 1, this meant that the entirety of the basal rate upon each hour was being completely utilized. Because Insulin is being delivered constantly and always on board, this ultimately led to this polynomial being applied at all 288 timesteps within a 24-hour period. With each delivery having its own unique profile at each time step, this ensures the confidence to utilize more accurately how effective the drug is every 5-minute increment.

To ensure that the drug profile of the Insulin utilized was accounted for, each delivery will apply the polynomial, as described above, at every hour mark, where a basal rate is initially administered. This curve will begin on each initial Insulin delivery, will peak 2 hours after delivery, and will then begin its decent down until all Insulin has been delivered, 4 hours after being administered (Figure 33). For example, if 1.2 units of Insulin is delivered at 12:00 PM, then by 2:00 PM, the Insulin will "peak" or be the most effective at this point in time, and will continue working to lower blood glucose until 4:00 PM. It is worth noting here that although the effects of the Insulin at lowering blood glucose have a duration of 4 hours, the total Insulin delivery of 1.2 units that is delivered at 12:00 PM will be completely delivered by 1:00 PM, microdosing a total 12 deliveries of 0.1 units every 5 minutes. Allowing the program to execute delivery this way ensures that the most important characteristics, such as onset time, peak time and duration, of the Insulin are modeled and represented, which is important for predicting glucose response of the newly, suggested basal rates.

Polynomial (6 Order) → $f(z) = p1*z^6 + p2*z^5 + p3*z^4 + p4*z^3 + p5*z^2 + p6*z + p7$

Coefficients

p1 = -0.009767
p2 = 0.1172
p3 = -0.4697
p4 = 0.6323
p5 = -0.1121
p6 = 0.3912
p7 = -0.003013




```
for i=1:48 % duration of Insulin; x=(i)
      p1 = -0.009767;
      p2 = 0.1172.
      p3 = -0.4697;
      p4 = 0.6323;
      p5 = -0.1121;
      p6 = 0.3912;
      p7 = -0.003013;
      InsulinPoly(i) = p1*x^6 + p2*x^5 + p3*x^4 + p4*x^3 + p5*x^2 +
                       p6*x + p7;
end
```

Figure 33: 6th order polynomial used to model the effectiveness of Insulin at each delivery over its entire duration.

Insulin Type	Onset Time	Peak Time	Duration
Rapid Acting Insulin (i.e., Humalog®)	0-15 minutes	2 hour	4 hours

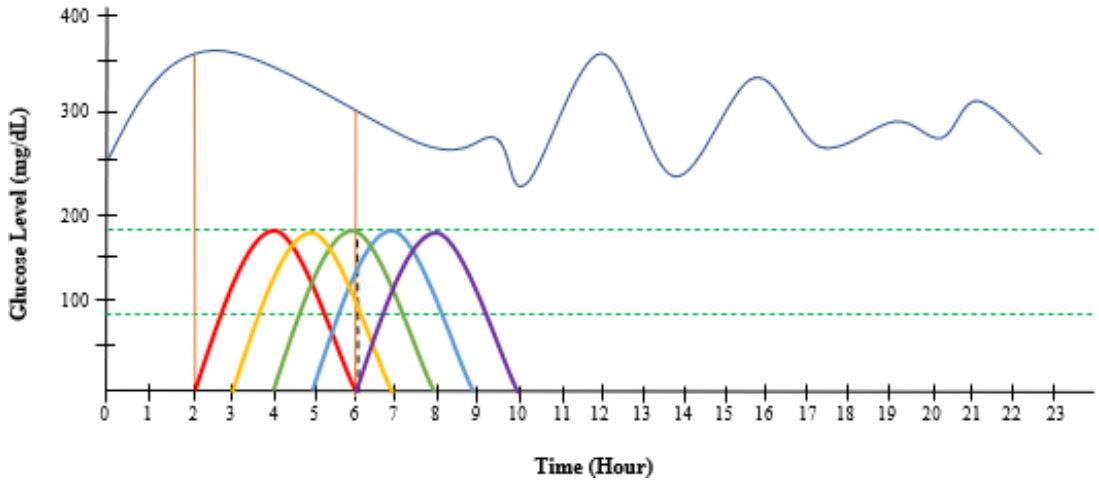


Figure 34: Summarized drug profile for the type of Insulin used in this analysis.

4.2.4 Removing the Effect of Bolus Insulin at Mealtimes

Often times, severe spikes in glucose level, or “sugar spikes”, can occur around mealtimes, when a patient is experiencing an influx of carbohydrates being converted to glucose molecules. Depending on the amount of Insulin currently being delivered to the patient, whether it be from basal Insulin or corrections made with bolus Insulin, patients can see these spikes and they can potentially contribute to an untrue depiction of the true effect that the current basal rates are having on the glucose levels. Often times, postprandial, the time during or just after mealtime, elevations “contribute to the hyperglycemic exposure of diabetes” [61]. While basal insulin therapies are effective at combatting this, studies have shown that “postprandial hyperglycemia limits success in maintaining overall glycemic control beyond the first 5 to 10 years after diagnosis” [61]. To help isolate the effect the current basal rates are having on the glucose response of the individual, removing bolus effects at meals to extrapolate basal amounts can serve as a helpful tool for users of this algorithm to not only truly understand the effectiveness of their current basal rates, but can also even offer them an opportunity to compare the effects that their current carbohydrate intake is having on their glucose levels.

To help combat this potential scenario, the option to remove certain hyperglycemic episodes has been built into the program. After having the patient’s glucose trends, with their average glucose trend displayed, the patient will have the option to tell the program the start time, as well as the end time a certain mealtime is occurring. Next, the time that is defined by the patient as the specified start of mealtime will be stored, and the glucose value at that timestep will remain constant until the specified end of mealtime.

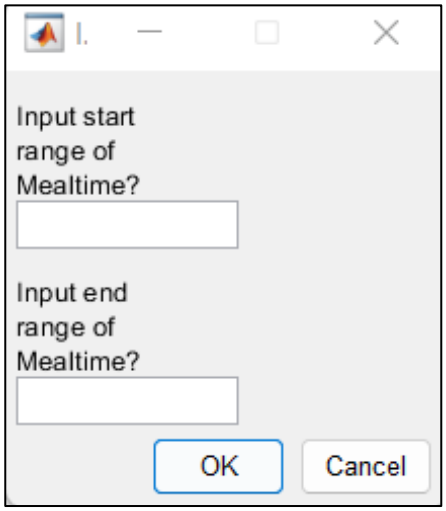


Figure 35: Program prompting the user to enter both the start and end of mealtime or a hyperglycemic episode.

```
switch patselect_num

case 3
    for i=1:7
    numDays = 7;

    AverageGL =
(Day{1}+Day{2}+Day{3}+Day{4}+Day{5}+Day{6}+Day{7})./numDays

    for j=mealtime_num(1):mealtime_num(2)
    AverageGL(j)=AverageGL(mealtime_num(1));
end
```

mealtime_num(1) versus mealtime_num(2)

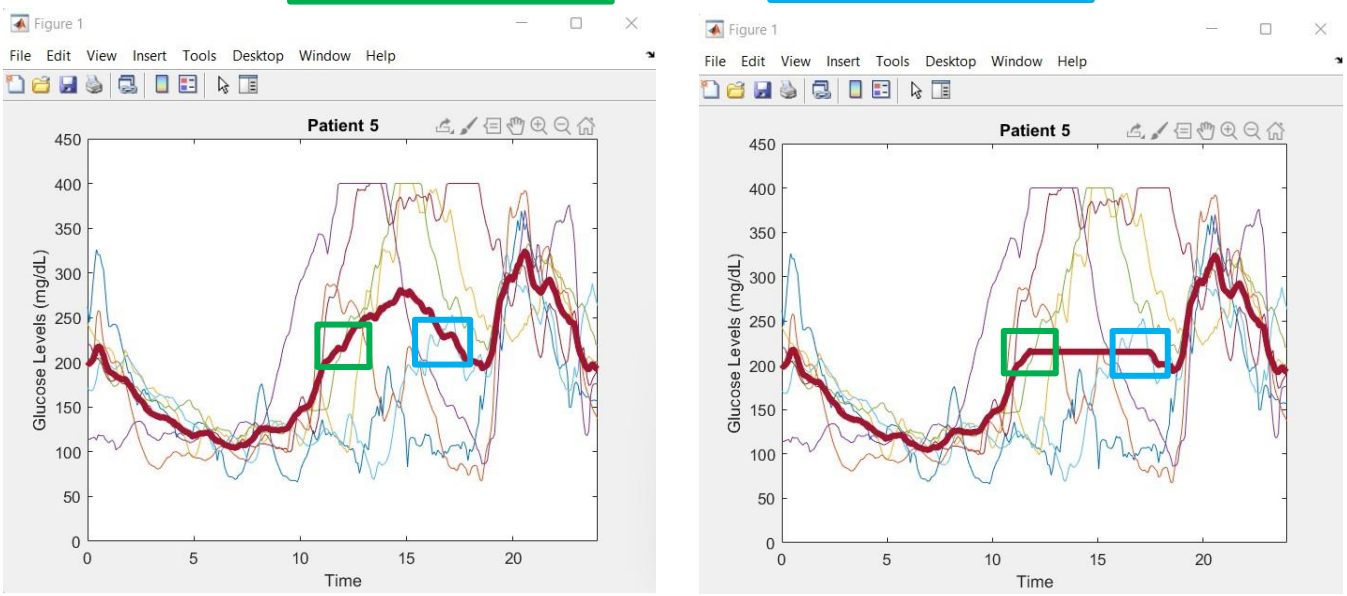


Figure 36: Before (left) and after (right) patient average glucose data once bolus effects of mealtimes have been extrapolated or hyperglycemic episodes have been eliminated.

The glucose trends will then be updated and displayed to the user, showcasing the removal of the "sugar spike" induced by the ingestion of carbohydrates, and allow the user to proceed with the rest of the analysis with this updated trend (Figure 34-35).

It is important to note here that because glucose response for every individual can look very different and depend on a number of external factors, that this feature is not necessary and is built into program as a tool for users to help better understand the relationship between their usual carb intake and the effect that it has on their glucose response.

4.2.5 Optimizing Basal Insulin

4.2.5.1 Considerations when Optimizing Basal Rates for More Controlled Glucose

Before proceeding with the development of the basal optimization algorithm, there were several important considerations to make regarding a patient's current glucose pattern and insulin delivery information. Specifically, 6 key points that must be considered:

1) How far away is the observed blood glucose level from their target glucose level?

2) What is the magnitude of the rise and fall of the observed blood glucose level from one hour to the next?

3) What is the current basal rate at each increment of time?

4) How much Insulin is being actively delivered at each time step?

5) How effective is each Insulin delivery at its corresponding time step?

6) How much will a single unit of Insulin be predicted to lower or raise blood glucose level?

Each of these points all also pose alternative things to consider when connecting the dots between each, such as: making sure to make any adjustment to basal rate before the blood glucose level starts to rise or fall, making certain to adjust in appropriate increments and

importantly adjusting the basal rate on the hour, where deemed necessary. While all the above points have been discussed in this and previous chapters, it is important to reiterate that each key point above plays an important role in attempting to optimize and suggest new basal rates to any patient utilizing this algorithm. This next section will focus on each of the considerations above, as well as how they all work together in unison to confidently suggest new rates to a patient, with hopes of yielding more stabilized, controlled glucose levels overall.

4.2.5.2 The Suggestion of New Basal Rates

In order for new basal rates to be suggested, first, the change between each hour needs to be calculated, in combination with calculating the distance away from the patient defined target glucose value to the current glucose value, otherwise known as the "error". Calculating both of these numbers helps to consider the magnitude of both the rise and fall of blood glucose level, which is an important key point to consider when trying to assign new basal rates for any user. With other important user-inputs pre-defined, such as correction factor and original basal rates, new basal rates are now ready to be calculated. Starting at 12:00 AM and continuing through the remaining 23 time-steps, each average glucose level at that hour will be assigned an error value that is based upon varying ranges of magnitudes anywhere from 0 to 70 mg/dL or greater, in both the positive and negative directions to cover both instances of a rise or fall in blood glucose (Figure 36). Next, the change in glucose level from hour to hour will be assessed with pre-assigned levels of both positive and negative changes, representative of the magnitudes of both rise and fall (Table 1, Figure 37). Within each case, the current basal rate will then be considered, as making sure changes occur in appropriate increments to not "shock" the system with a severe spike in basal Insulin delivered.

Error(i) = (AverageGL – TargetGL);

.

.

.

Error(16) = (250 mg/dL – 110 mg/dL)

Error(16) = 140 mg/dL

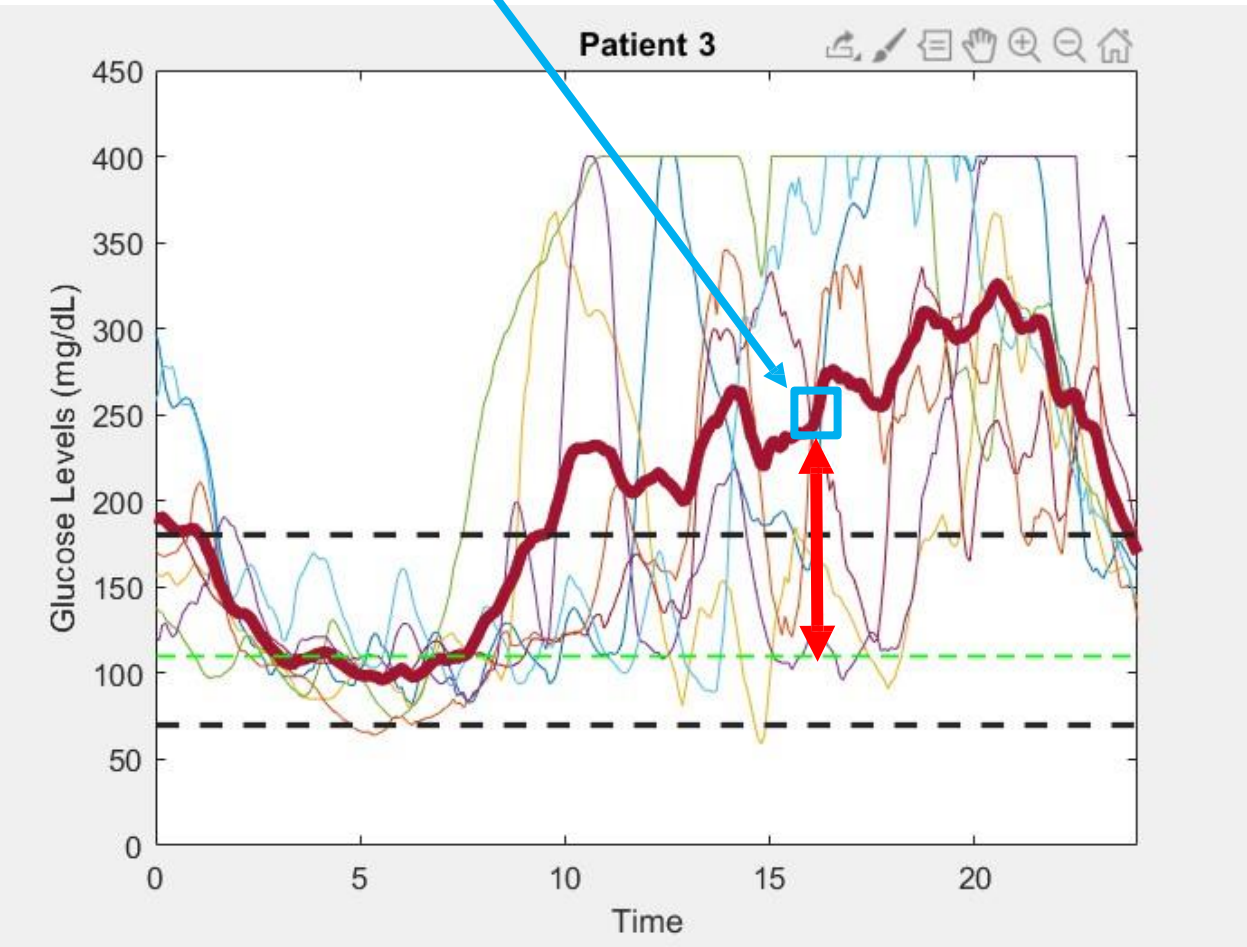


Figure 37: Schematic showing how the error value is determined based upon target glucose level.

It is worth noting here that any changes in basal rate are strongly recommended to occur in smaller increments versus larger to prevent severe and sometimes fatal crashes in glucose level due to potential cases of “Insulin stacking” or having too much Insulin already on board at the time another delivery is made, as reiterated by diabetes educator Gary Scheiner, MS, CDE [62].

As seen below in Table 11, at each hour time-step, the new basal rate will be predominantly determined by first assessing the current basal rates, as well as the change in glucose level per hour. Because the effects of the Insulin do not peak until an hour or two after initial delivery, this is important to consider, as the either increase or decrease in blood glucose levels can tell us the direction of the anticipated change in basal rate, whether it needs to increase or decrease, and by what magnitude this needs to occur. While the current concept of adjusting basal rates based upon the magnitudes of change in glucose and current basal rate was inspired by work of diabetes educator, Gary Scheiner, it felt important to expand upon the current suggestions to make sure that as many cases and possible scenarios were represented when assessing each patient’s data and offering new suggestions. With this being said, the current basal suggestion table that was utilized in this program contains both positive and negative level changes for both either increases or decreases in new basal rate, all based upon the magnitude of the changes in glucose level as well as the magnitude of the current basal rate, keeping in mind the desire to avoid any drastic changes in current basal rate, as deliveries are occurring each hour, with the effects of each delivery spanning multiple hours at a time. Current basal rates are assigned varying levels of magnitudes and ultimately this is where the suggested change in basal rate is saved to the program to then be displayed graphically to the user, as well as calculating a

predicted glucose response, which is also displayed graphically to the user and will be discussed more in the following section.

4.2.5.3 Predicting Blood Glucose Response for Optimized Basal Rates

Although it is not a major goal or contribution of this dissertation to develop a supplemental algorithm to also predict and suggest the expected glucose response from the suggested change in basal rate, it is still important to give the patient some idea or insight about the potential effects each change in basal rate might have on their blood glucose after running the basal optimization algorithm. It is worthwhile to note that due to the human body being very complex and the individuality that is necessary when creating an algorithm for something such as glucose response in an individual, that the predicted glucose response in this dissertation would need more research and further development, potentially with a cross-disciplinary team of collaborators in the field as well as increased resources; this will be further discussed in the future works section later.

To give the user an idea of this phenomenon, an equation was created taking into account the things mentioned previously that we know have a direct correlation with glucose response in an individual: correction factors, otherwise known as Insulin sensitivity, determined by a healthcare professional, the amount of Insulin being administered at each time step, as well as the effectiveness of the Insulin at every point in time [63–65]. The first part of this equation involves the difference in both the current as well as the new, suggested basal rate, where the equation can be seen below (Figure 39). Taking the difference between both the original basal rate and the predicted, suggested basal rate allows us to truly focus on and isolate the effect that the actual suggestion is having on glucose response; ultimately, the difference of the old and

Table 12: Table showcasing the increments of changes applied to the various cases of current basal level and glucose change per hour. Table expanded upon from that suggested by Gary Scheiner [62].

	Current Basal Level (units/hour)		
	0.0 – 0.35	0.4 - 1.0	> 1.0
Level 1 Change 0-10 mg/dL	± 0.05	± 0.15	± 0.25
Level 2 Change 11-25 mg/dL	± 0.1	± 0.2	± 0.3
Level 3 Change 26-40 mg/dL	± 0.15	± 0.25	± 0.35
Level 4 Change >41 mg/dL	± 0.25	± 0.35	± 0.45

	Current Basal Level (units/hour)		
	0.0 – 0.35	0.4 - 1.0	> 1.0
Level 1 Change 0-10 mg/dL	± 0.05	± 0.15	± 0.25
Level 2 Change 11-25 mg/dL	± 0.1	± 0.2	± 0.3
Level 3 Change 26-40 mg/dL	± 0.15	± 0.25	± 0.35
Level 4 Change >41 mg/dL	± 0.25	± 0.35	± 0.45

```
PreviousIndex = i - 1;
        if (PreviousIndex) < 1
            PreviousIndex = 24;
        end

% Level 1 Positive Change

if ChangeGL(i) >= 0 & ChangeGL(i) <= 10
   if Basal1(PreviousIndex) <= 0.35 % LowBR
                NewBasal1(PreviousIndex) =
Basal1(PreviousIndex) + 0.05;

   elseif Basal1(PreviousIndex) <= 1.00 &
Basal1(PreviousIndex) > 0.35 % IntermediateBR
                NewBasal1(PreviousIndex) =
Basal1(PreviousIndex) + 0.15;

   elseif Basal1(PreviousIndex) > 1.00 % HighBR
                NewBasal1(PreviousIndex) =
Basal1(PreviousIndex) + 0.25;
        end
```

Figure 38: Schematic showcasing a Level 1 Change during the Basal Algorithm.

```
for i=1:288 % Insulin Deliveries
    j = 1:48 % Duration of Insulin

    Change(i) = (((NewBasal1(i)-Basal1(i)))* CF(i) *InsulinPoly(j);

    PredictedGlucose(i) = GlucoseAVG_hour(i)-Change(i);
end
```

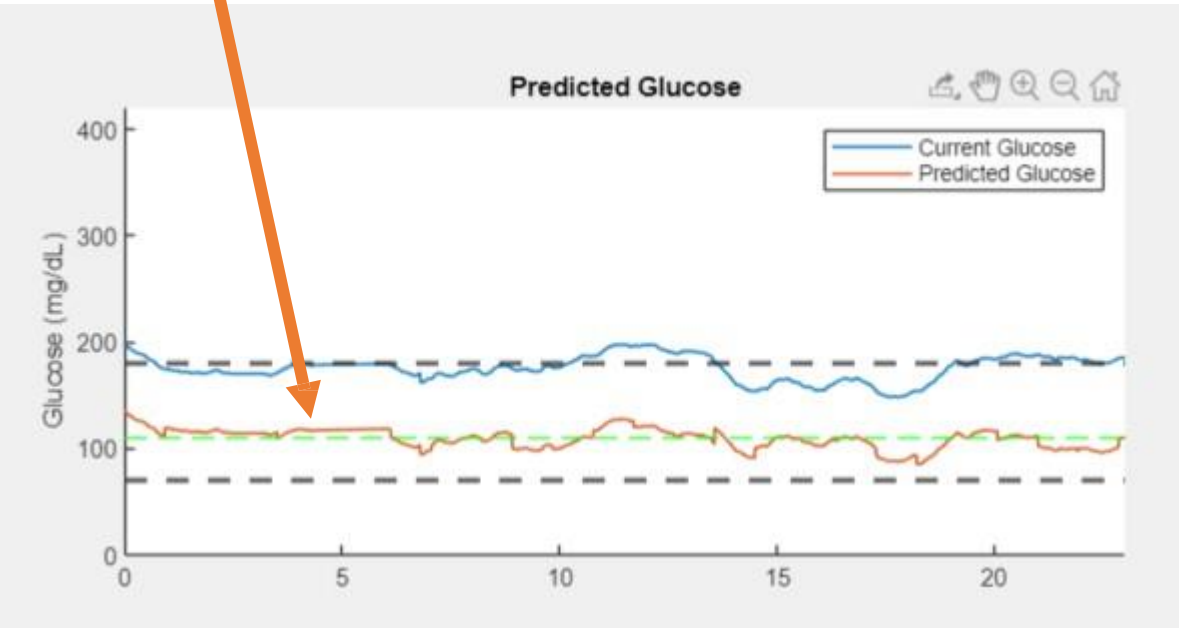


Figure 39: Schematic demonstrating the change in glucose level at each time step and the calculation for the predicted glucose level. These calculations will be different for each patient due to the differing basal rates, as well as the patient's unique correction factors.

optimized basal rates give insight to the effect the optimized rate has on the current glucose levels. Next, this calculated difference is then multiplied by the correction factor, which is usually provided by a healthcare professional. Finally, both of these numbers are multiplied by the pre-calculated polynomial mentioned in the previous section, representing the effectiveness of the Insulin at any point in time (Figure 38).

Overall, this equation is believed to be a good measure of predicting blood glucose response for the suggested, optimized basal rates suggested by the program, with the intent to give the user an idea of not only the effect that changes of basal rate can have on glucose response, but also a generalized idea of what glucose response to expect with the new basal rates.

4.3 Graphical User Interface Development and Implementations

The model presented in this dissertation, housing the basal optimization algorithm, is a novel concept and serves as a pioneer for diabetic research at the University of Tennessee, Knoxville campus within the Tickle College of Engineering. Because of this, all features in this GUI are novel and serve as a promising foundation for future work and research for further development of this work, or diabetic research at this institution in general. A Graphical User Interface (GUI) has been developed that contains all the algorithms involved in the complete analysis from the implementation of user inputs all the way through producing optimized basal rates for each individual user. The features within this GUI have been created to help give the user not only an easy, efficient experience in optimizing current basal rates within an Insulin pump system, but also a tool to help better understand and provoke thought into the relationship between carbohydrate intake, basal rate settings and the individual's glucose response. It is important for me to take a moment here to thank Dr. Richard Komistek for entrusting in me and

allowing me to take on a project like this, as it holds a very special place in my heart, knowing the magnitude that this disease can have on not only those affected, but their families as well. The overview of the basal optimization algorithm and other capabilities of this model are shown in the figures that follow in the section below.

4.3.1 Data Extraction Tools – Loading Dexcom Images

The GUI is shown in Figure 39. The program has been designed to extract data from one of two methods: one being that of directly loading in "screenshots" of glucose trend images directly from the patient's Dexcom Clarity software. This option offers the patient complete and total customization and an unlimited quantity of days analyzed with the ease of simply taking a screenshot of their individual trends either on their mobile device, iPad or computer. Before selecting the "Load Dexcom Images" button, the user will enter their target glucose value into the empty field labeled "Target GL", and the program will then store this value that is needed later in the analysis when predicting optimized basal rates. When the patient selects the "Load Dexcom Images" button, this program will read in all selected images and first resize and scale each image to be identical to one another, for ease of data extraction. Next, using the RGB Triplet method, each pixel, in both rows and columns will be looped through to detect anything defined to be a black hue (RGB Triplet [0 0 0]). After all black pixels are identified and the glucose curve is extracted from the rest of the image, the axes will be scaled using a ratio of max pixel height of the image to the maximum y-axis of the original Dexcom image, as well as the same for the x-axis in reference to time. Once this has been completed, the culmination of all loaded Dexcom images will be displayed graphically to the user on the top left graph, with the associated patient name. Along with the individual curves, the average glucose curve will be

calculated and displayed in a more prominent line width, signaling to the user and program that this is the blood glucose curve that will be used for any further analysis (Figures 39-40).

4.3.2 Data Extraction Tools – Loading CSV Files

The alternative method of uploading data for a user is that of uploading an extracted CSV file straight from the Dexcom Clarity software, that can also be done with the same ease and convenience as the alternative method as described above – right from the user's phone, tablet or computer. Before selecting the "Load Patient Profile" button, the user will enter their target glucose value into the empty field labeled "Target GL", and the program will then store this value that is needed later in the analysis when predicting optimized basal rates. When the user selects the "Load Patient Profile" button, the program will prompt the upload of the CSV file, as well as prompting the patient to specify which glucose data to use for analysis.
Once this has been specified, it will ask the user if there are any mealtime ranges to account for, if the user wants to eliminate any instances of sudden hyperglycemia that they wish to not be taken into account when further analyzing their data and ultimately suggesting new basal rates. This tool is completely voluntary and not required, however, is recommended to use if there are clear, evident instances of sugar spikes at any point in their data as this may influence the suggested basal rates that's output by the program.

Once the appropriate data has been established by the user, likewise as above, the individual glucose daily trends will be displayed along with the average glucose curve in a more prominent line width, once again signifying to the user and program that this is the glucose data that will be used for the remainder of the analysis.

Figure 40: GUI overview when the patient opens the program.

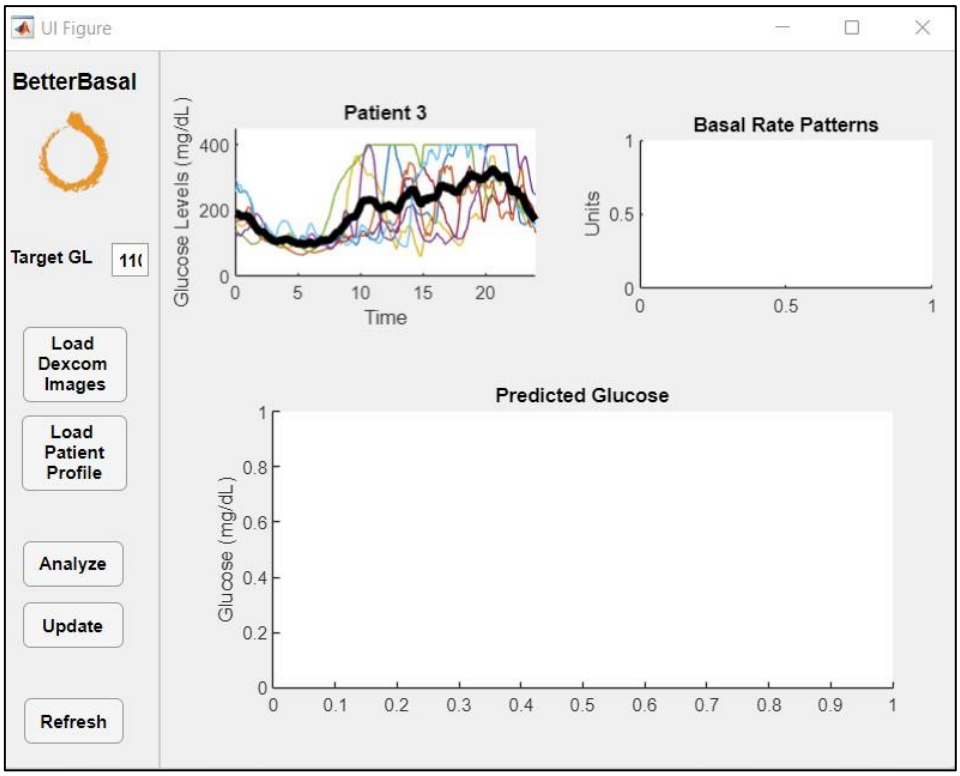


Figure 41: GUI after patient loads in their specified data.

4.3.3 Data Analysis Features

The “Analyze” button will allow the user to proceed with analysis once the data selected for analysis has been viewed and accepted by the user. Regardless of data upload/extraction method selected, the analysis of the data and suggestion of optimized basal rates will remain the same. Once users select this button, the program will immediately begin to calculate the inputs necessary to determine new basal rates, such as the average glucose level for each time-step, the distance between the target value and the current glucose reading, as well as the change in glucose level between each hour mark. After this, the program will calculate new, suggested basal rates as described in the previous section and present the suggested basal rates, along with the current basal rates graphically to the user on top right “Basal Rate Patterns” graph located on the GUI (Figure 41).

Simultaneously, the program will calculate a prediction of the expected blood glucose response pertaining to the new, suggested basal rates, paired with the current basal rates associated with the user’s current basal rates. The program will also display this graphically to the user in the bottom right corner of the GUI on the “Predicted Glucose” space located on the bottom center of the GUI (Figure 42).

At this point in the program, the analysis is complete and the user will be prompted to specify what percentage of the suggested changes that they would like to implement, ranging anywhere from 0-100%, allowing the user the flexibility and comfortability of feeling safe when selecting new basal rates, also allowing them to make even more minute changes to their rates if so desired (Figure 43). At this point, the program can be re-run at any point with any combination of days that the user wishes, to view a multitude of different simulations.

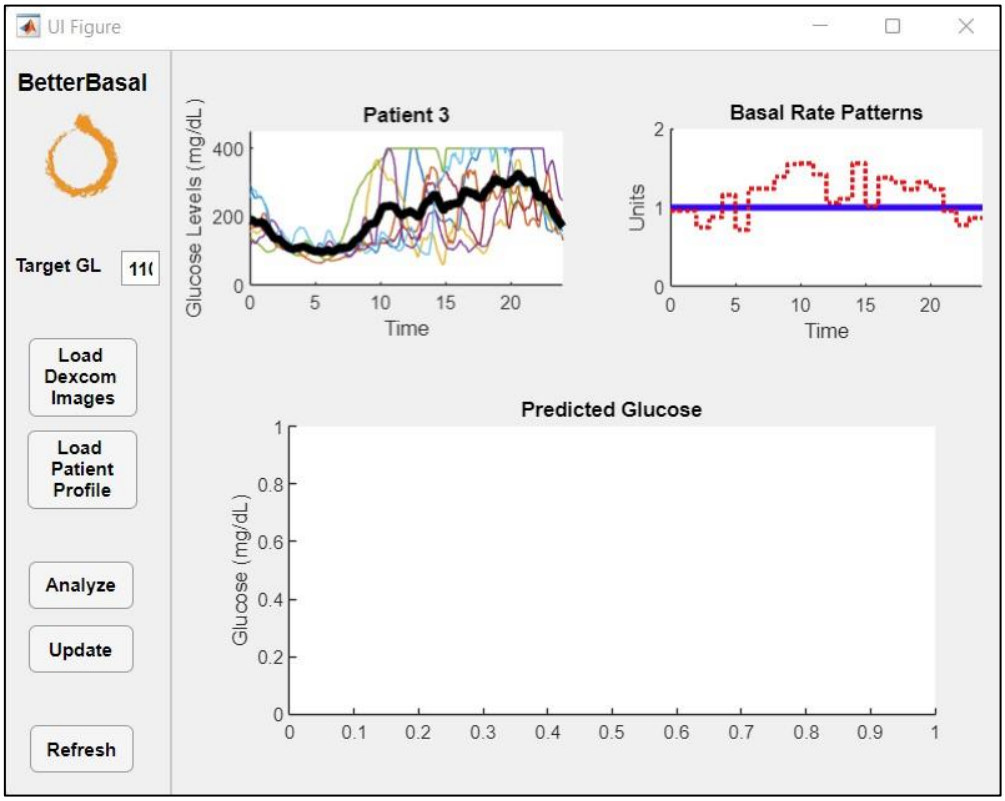


Figure 42: GUI showing the program after basal rate suggestions have been presented to the user (red) compared to current rate(s) (blue).

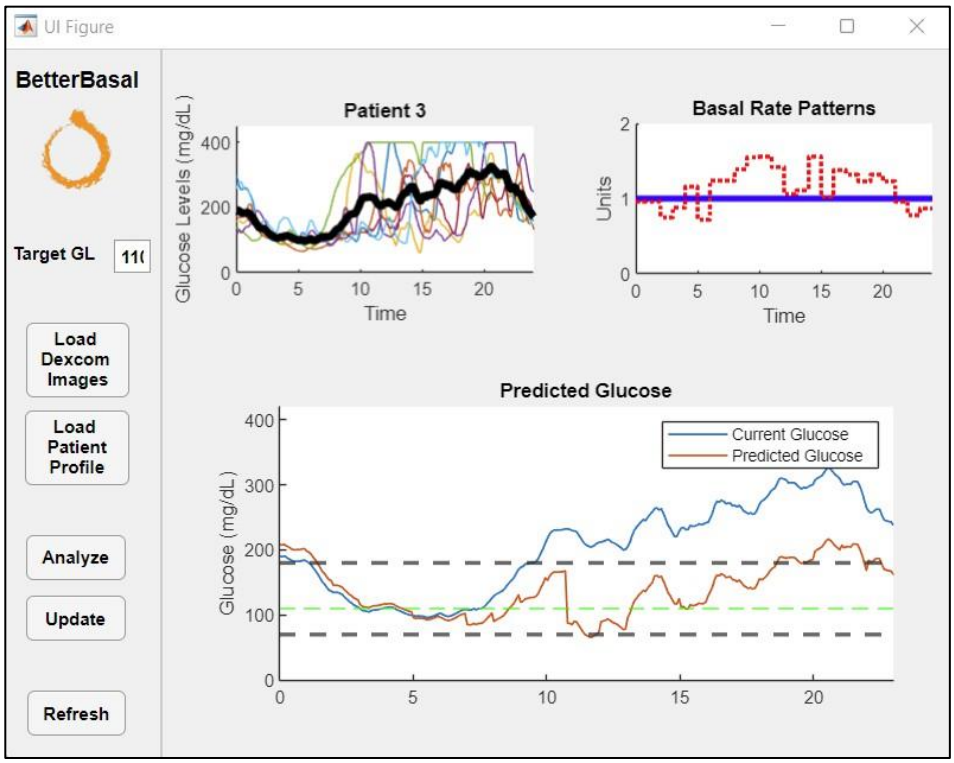


Figure 43: GUI once glucose prediction has been shown to the user and all analysis has been completed.

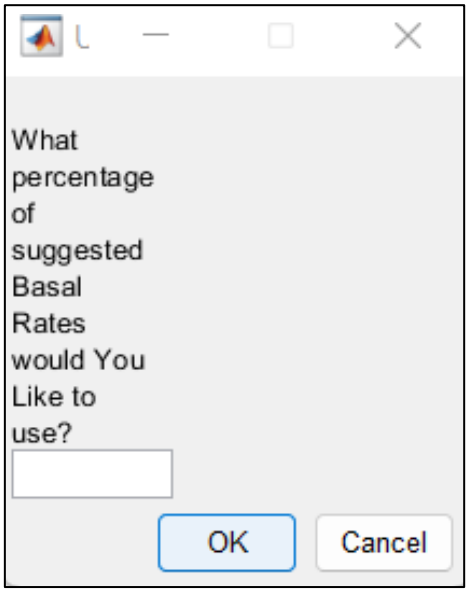


Figure 44: Program prompting the user for input on the percentage of the new, suggested basal rates that they would like to use.

CHAPTER 5: ASSUMPTIONS AND LIMITATIONS

5.1 ASSUMPTIONS

While implementing and testing this model, various assumptions were made. To be able to accurately understand and analyze the model and results presented herein, it is crucial to address and discuss all assumptions made within this dissertation. The assumptions are outlined as follows:

1. As every patient is unique in what type of insulin is utilized, the unique profiles for each drug also consist of their own defined insulin profile, involving pump settings such as duration, onset and peak time of the specific insulin being delivered. For the purposes of validating this research, the insulin profile and associated pump settings matched those of the patient used for the validation.
2. For modeling the type of Insulin delivered, rapid or short-acting insulin was chosen. Since each type of insulin and patient have their own unique response to insulin, absorption rate was modeled with suggestions from the validation patient, as well as literature surrounding both rapid and short-acting insulins.
3. When extracting glucose values for a given patient, if a patient is missing glucose values at any certain time-step, that value was calculated as an interpolation between the nearest two readings on both sides of the absent glucose value.
4. Any real-time, patient-specific data read into this model is a representation of data extracted from any of the Dexcom continuous glucose monitoring systems, also paired with Dexcom Clarity software, which is used to extract necessary data for analysis.

5. The patient does not possess or practice any lifestyle modifications that greatly affect glucose level, such as (but not limited to) weight loss, illness, insomnia, high-carb diets, etc.
6. For the purpose of this research, it is assumed that all initial pump settings are accurate and have been proven successful for the individual patient, whether confirmed by a healthcare professional or not, in order to yield the most accurate analysis and proposed basal rates possible.
7. This current research assumes that the individual patient is consuming approximately three meals a day around time-step intervals most commonly associated with breakfast (7:00 AM– 9:00 AM), lunch (11:00 AM -1:00 PM) and dinner (5:00 PM - 8:00 PM). Keeping this in mind is important, as the patient is consuming an undisclosed number of carbohydrates each mealtime, requiring an amount of bolus insulin being actively delivered during each mealtime.

5.2 LIMITATIONS

While implementing and testing this model, various limitations were also defined. These limitations are as follows:

1. The current research proposed in this dissertation only contains one validation patient. Diabetes and a person's reaction to insulin can be very dangerous. Therefore, only a single patient was used for validation because he is an experienced researcher and manages excellent control of his diabetes. While a singular validation patient serves the purpose of validating the methodologies described herein, to further develop and confirm that this proposed model is serving a large, diverse group of patients to the best of its abilities, multiple validation subjects should be utilized and their results studied.

2. This dissertation contains glucose levels, associated basal rates, and other patient-specific data from only three real patients. The rest of the data used in this research study, to demonstrate how the model works, is comprised of synthetic data, drafted based upon previous knowledge and current literature.
3. The model was not utilized with other continuous glucose monitoring systems, outside of Dexcom, to integrate and extract patient specific data. However, for patients utilizing this CGM system, data was successfully and accurately extracted.
4. This current research does not currently possess the ability to detect and properly adjust for lifestyle modifications possessed by the individual patients, therefore this is important for a user to reader to keep in mind when a patient is utilizing this program to adjust their basal rates for more controlled, desirable glucose values.
5. The only insulin modeled in this research was rapid or short-acting insulin, which has its own unique drug profile, containing important pieces of information/properties that are crucial for proper analysis yielding safe and effective basal rates for each individual user. Further development of this model suggests that the ability to add more individual drug profiles would be potentially helpful for patients.
6. This model prepares for any missing glucose information by the method of interpolation between other nearby glucose readings, taking into account the overall trend of the glucose pattern. Modifying this information to define accurate glucose levels for any missing time-step would require user intervention that was not available or possible during this research.
7. The result of the basal prediction algorithm is only a recommendation based upon patient-specific data as inputs such as glucose levels, associated basal rates/time-steps,

and correction factors. Other inputs that could be helpful to an even more individualized experience, that have been shown to affect glucose level such as age, sex and if any insulin secretion remains, would serve beneficial to the user and should be pursued in the continuation of this model.

8. Using a program such as MATLAB to develop this model can yield drawbacks associated with slower run-time as it is an interpreted language. The development of the algorithms herein using MATLAB also can provide potential difficulties in developing real-time applications. It is important to continue to build on this research to provide an even more dynamic patient experience, especially with the hope of integration with a continuous glucose monitoring company's present software.

CHAPTER 6: RESULTS AND DISCUSSION

The primary objective of this work is to offer a software package to suggest optimized basal rates to a type 1 diabetic to allow for each individual user to have more controlled, stabilized glucose levels. This program allows users to input patient-specific data, such as multiple days of glucose data and basal rates, as well as other important insulin pump settings for an overall personalized experience. Initial development of this software has been complete, with the potential opportunity for further development and integration within a continuous glucose monitoring system.

The software was used to analyze 11 patient-specific profiles and generate comparisons of basal optimization to both current and predicted glucose trends for each patient. As previously mentioned, because this involves a very sensitive application dealing with live patients and overdosing of Insulin can be fatal, there is only one patient who is serving as a live validation patient (Patient 1), testing and implementing the suggested basal rates in real-time. The remaining 10 patients (Patient 2-11) will have their results theoretically modeled using the software.

6.1 BASAL OPTIMIZATION AND PREDICTED GLUCOSE: INDIVIDUAL PATIENT ANALYSIS

Across the world, a large number of type 1 diabetics struggle finding an optimal basal rate pattern that helps to not only control and stabilize their glucose levels, but to also help them reduce the amount of bolus corrections needed on a daily basis to correct common high glucose levels or even severe hyperglycemic episodes [66]. While one theory is that a variety in basal rate patterns could lead to better control on glucose levels throughout the day, others believe that the high variability could possibly be correlated with potential complications in some type 1 diabetics. In a study by Markus Laimer, et al. assessing the variability of basal rate profiles in

Insulin pump therapy, it was concluded that “higher variation in daily basal rates may identify patients who are more difficult to treat regarding glycemic goals” [66]. Another study by Yukari Mitsui et al., states that it is “necessary to establish an adequate Insulin algorithm that takes individual characteristics into account” [67]. Regardless, it is a safe assumption to make that there is a need for research and studies dedicated to taking a deeper learning approach regarding basal rate patterns and their relations with a diverse population of type 1 diabetics.

This analysis herein strives to identify optimal basal rate patterns for patients who contain variations in their daily basal rate patterns, as well as for patients who maintain very few or even one basal rate pattern a day. To ensure that the patient population within this dissertation is diverse and represents many different variations of basal rate patterns, it was important to carefully create synthetic patients who demonstrating specific, targeted glucose trends seen amongst many type 1 diabetics. Each section below contains further information on the types of glucose trends demonstrated, as well as more patient-specific information in culmination with the full analysis of the basal optimization algorithm.

6.1.1 Patient 1 Analysis

The first patient in this dissertation serves as the validation patient for the basal optimization algorithm. As previously mentioned, due to the nature of the severity in suggesting any change in insulin delivery, especially with basal rates, can be very dangerous and should be done so at the patient’s own risk or under the supervision of a healthcare professional. Because this patient is a long-time type 1 diabetic and has very good management of their diabetes and overall control on their glucose levels, they voluntarily offered to serve as a source of validation and test out basal rates suggested by the program herein this dissertation and provide real-time

feedback of the overall process from start to finish. In general, Patient 1 presented a pattern of glucose levels that remained fairly stabilized throughout the day, with negligible highs occurring around what appear to be mealtimes. This patient often stayed within their target glucose range of 70-180 mg/dL, on average, throughout the day. It is worthwhile to note here that, while an algorithm like this would serve a great deal to patients who have less control of their glucose levels and experience many periods of fluctuating highs and glucose spikes throughout the day, patients who are already existing within their target glucose range may still want to optimize their basal rates and achieve even more stabilized glucose curves, aiming to stay as close to their target value as possible, appearing to be the case with this first patient.

Regarding other pertinent patient-specific information, this patient had 9 basal rate patterns over the course of 24 hours, a consistent correction factor of 30 and had a target glucose value of 110 mg/dL for all 7 days. This patient used a Dexcom image to upload their glucose data and utilized a rapid acting Insulin.

The first important area of interest to assess is the overall glucose level and the change after basal optimization algorithm. After the initial analysis and before implementation of the suggested rates, Patient 1 showed overall success in lowering their glucose levels. Before analysis, this patient had an average glucose level of 175 ± 7.04 mg/dL (range, 162 to 199). Using this software to, Patient 1 presented an average predicted glucose level of 108 ± 9.32 mg/dL (range, 85 to 136), ultimately predicting a glucose reduction on average of 38.29%. Another vital area to assess is the amount of time spent both inside and outside of the target glucose range of 70-180 mg/dL. Before analysis, Patient 1 exhibited 216 out of 288 (75%) glucose readings inside their target range and the remaining 72 out of 288 (25%) readings

outside of their target range. After analysis, Patient 1 exhibited all readings (100%) inside their target range with no readings outside of their target range.

Regarding basal rates, this patient was suggested to increase their overall basal Insulin delivery from 30.60 units a day to 36.40 units, remaining similar in overall basal Insulin delivery. It is important to note here that a drastic increase in total basal delivery per day would not be ideal or recommended to a patient, as all basal adjustments should be adjusted in conservative, small increments to make sure it is overall safe with the patient and ultimately gives them time to implement any changes and assess their individual glucose response. Patient 1 saw an increase in the number of individual rates over a 24-hour period. This patient was suggested both increases and increases in basal rates around critical times that greatly contributed to the stabilization of glucose levels presented with their predicted glucose response.

Table 13: Table displaying both original and new basal rate patterns suggested by the basal optimization algorithm for Patient 1.

Basal Rate	New Basal Rate
0.9	1.1
0.9	1.1
1.1	1.2
1.1	1.2
1.1	1.2
1.2	1.2
1.2	1.5
1.6	1.5
1.6	1.9
1.6	1.9
1.4	1.6
1.4	1.6
1.5	1.7
1.5	1.9
1.5	1.7
1.4	1.8
1.4	1.6
1.4	1.7
1.2	1.6
1.2	1.6
1.1	1.6
1.1	1.4
1.1	1.4
1.1	1.4

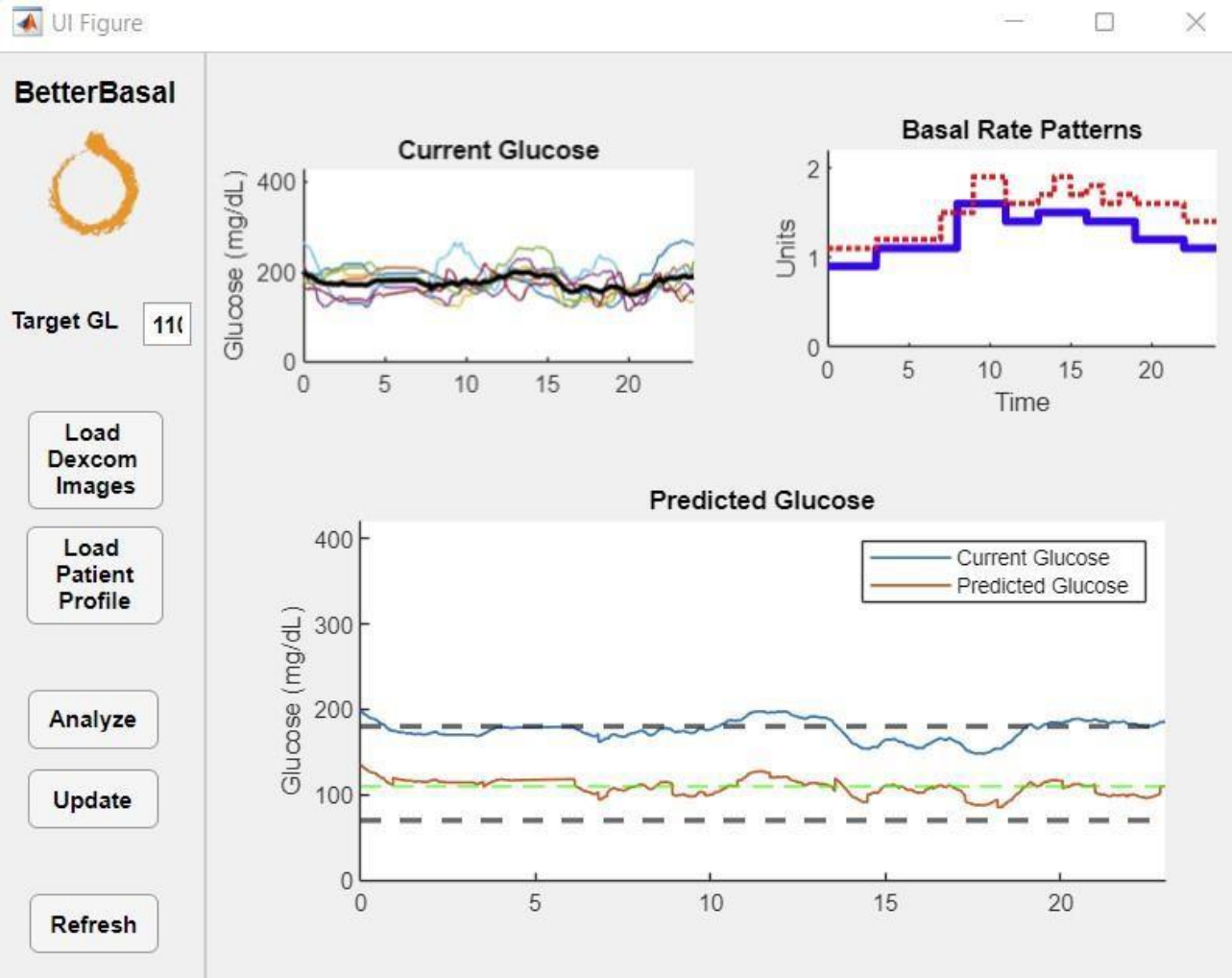


Figure 45: Results for Patient 1 presented to the user in the GUI window.

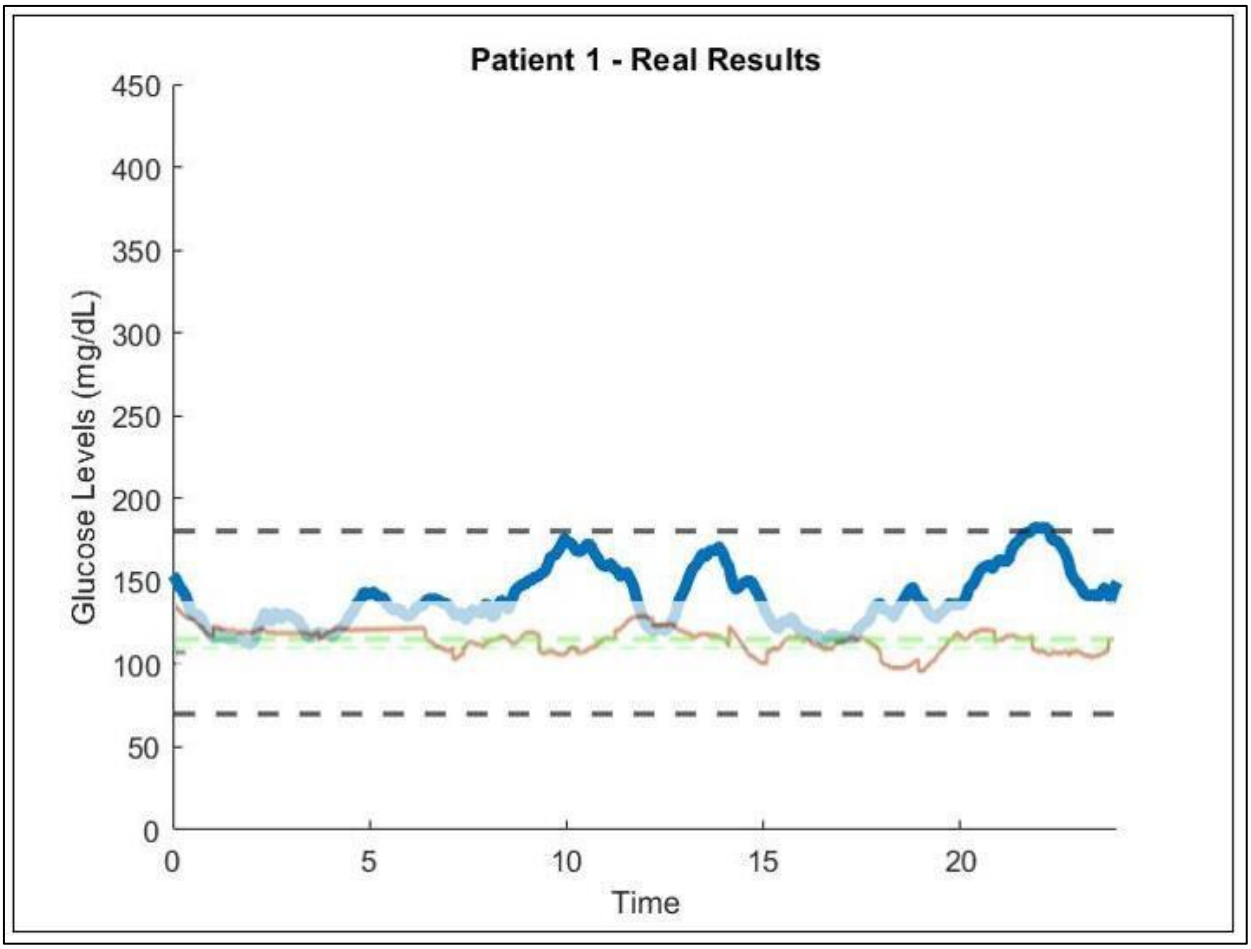


Figure 46: Patient 1's real-time glucose values (blue) after using and implementing suggested basal rates from this program, compared to the predicted glucose response (orange).

Because Patient 1 also served as the validation patient, the real-time results are displayed above (Figure 45). After the analysis and implementation of basal suggestions, Patient 1 still showed overall success in harnessing the basal optimization in order to overall lower their glucose levels. After the utilization of the suggestions from the basal optimization algorithm, this patient had an average glucose level of 140 ± 18.03 mg/dL (range, 112 to 183), still presenting a glucose reduction, on average of 20.00%. Another vital area to assess is the amount of time spent both inside and outside of the target glucose range of 70-180 mg/dL. As mentioned previously, before analysis, Patient 1 exhibited 216 out of 288 (75%) glucose readings inside their target range and the remaining 72 out of 288 (25%) readings outside of their target range. After analysis, Patient 1 exhibited negligible readings outside of their target range as can be seen in the figure above (Figure 45).

6.1.2 Patient 2 Analysis

Patient 2 presented an overall pattern of consistently stabilized glucose levels that exist in between their target glucose range of 70-180 mg/dL, on average, on a daily basis. Negligible high readings exist what appears to be later in the evening, however, outside of this, Patient 2 exists very close to their target glucose value of 110 mg/dL throughout the day. The patient who voluntarily provided this data did not receive the revised, suggested basal rates, again, due to the sensitivity of making adjustments in basal insulin and their associated glucose response to any of the changes. The future direction of this dissertation and the work done throughout, when paired with a team of healthcare professionals and even diabetic supply companies, would allow for the proper study to allow more individuals to test the suggested rates to only add to the validation provided by patient 1; this will be further discussed in the following chapter regarding future

work. Patient 2 had one single basal rate pattern over the course of 24 hours, a consistent correction factor of 30 and had a target glucose value of 110 mg/dL for all 7 days. This patient used a Dexcom image to upload their glucose data and utilized a rapid acting Insulin.

The first important area of interest to assess is the overall glucose level and the change after basal optimization algorithm. Before analysis, this patient had an average glucose level of 138 ± 9.59 mg/dL (range, 120 to 151). After analysis, this patient presented an average glucose level of 108 ± 20.44 mg/dL (range, 87 to 139), ultimately seeing a glucose reduction, on average of 21.73%. Another vital area to assess is the amount of time spent both inside and outside of the target glucose range of 70-180 mg/dL. Before analysis, Patient 2 exhibited 252 out of 288 (88%) glucose readings inside their target range and the remaining 36 out of 288 (22%) readings outside of their target range. After analysis, Patient 2 exhibited all readings (100%) inside their target range with no readings outside of their target range. In regard to basal rates, this patient was suggested to increase their overall basal Insulin delivery from 24.00 units a day to 25.39 units, remaining similar in overall basal Insulin delivery. It is important to note here that a drastic increase in total basal delivery per day would not be ideal or recommended to a patient, as all basal adjustments should be adjusted in conservative, small increments to make sure it is overall safe with the patient and ultimately gives them time to implement any changes and assess their individual glucose response. Patient 2 saw an increase in the number of individual basal rates over a 24-hour period. This patient was suggested to have both increases and decreases in basal rates around critical times that greatly contributed to the stabilization of glucose levels presented with their predicted glucose response. It is worthwhile to note here, that this patient, before analysis, already exhibited good control over their glucose levels, therefore changes and suggestions made were very minimal.

Table 14: Table displaying both original and new basal rate patterns suggested by the basal optimization algorithm for Patient 2.

Basal Rate	New Basal Rate
1.0	0.9
1.0	0.9
1.0	0.9
1.0	0.9
1.0	1.2
1.0	0.9
1.0	0.9
1.0	1.2
1.0	1.2
1.0	1.3
1.0	1.2
1.0	1.2
1.0	0.9
1.0	1.2
1.0	0.9
1.0	0.9
1.0	1.2
1.0	0.9
1.0	1.3
1.0	1.3
1.0	1.3
1.0	1.0
1.0	0.9
1.0	0.9

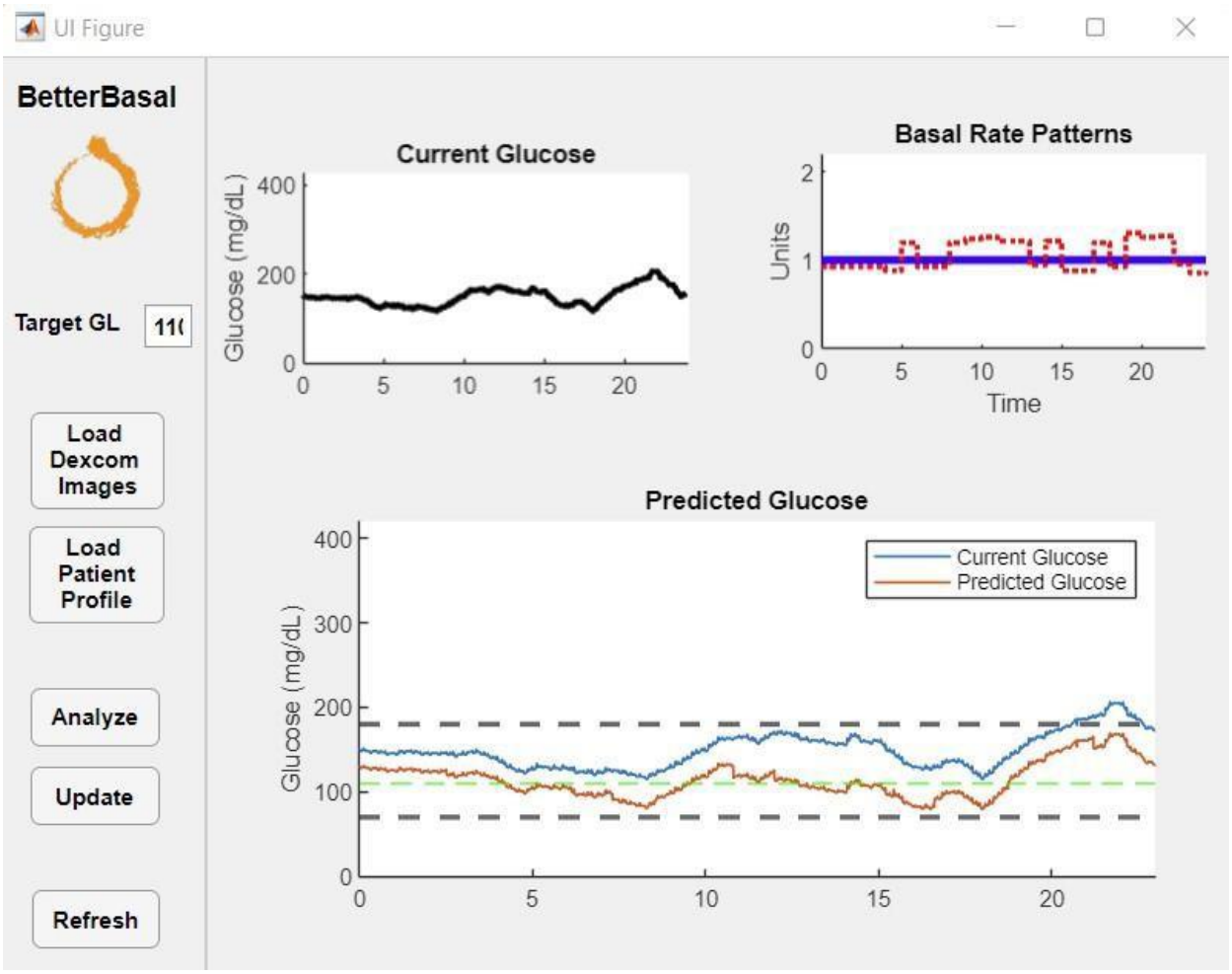


Figure 47: Results for Patient 2 presented to the user in the GUI window.

6.1.3 PATIENT 3 ANALYSIS

Patient 3 presented a pattern of daytime highs with significant highs occurring, on average, between 9:00 AM and 11:30 PM. A steady rise in glucose level begins around 7:00 AM and continues to rise throughout the remainder of the day. It isn't until the late evening that it appears the glucose levels begin to drop, continuing to decline throughout the early morning times. Multiple reasons may exist regarding why this patient sees over 50% of their day existing in a constant state of hyperglycemia. One reason to speculate this glucose trend is extremely high could be a combination of lifestyle changes and lack of bolus deliveries throughout the day, regarding either deliveries due to mealtimes or even corrections needed depending upon activity level, stress level or even lack of sleep. All these things mentioned in previous chapters and in the patient profiles hereafter all have a strong, positive correlation with an increase in glucose level [33,68]. Regarding other pertinent patient-specific information, this patient had 4 basal rate patterns over the course of 24 hours, a consistent correction factor of 50 and had a target glucose value of 110 mg/dL for all 7 days. This patient used a CSV file to upload their glucose data and utilized a rapid acting Insulin.

The first important area of interest to assess is the overall glucose level and the change after basal optimization algorithm. After the analysis, Patient 3 showed overall success in harnessing the basal optimization in order to overall lower their glucose levels. Before analysis, this patient had an average glucose level of 203 ± 69.41 mg/dL (range, 96 to 326). After analysis, this patient presented an average glucose level of 138 ± 60.00 mg/dL (range, 81 to 237), ultimately seeing a glucose reduction, on average of 32.02%. Another vital area to assess is the amount of time spent both inside and outside of the target glucose range of 70-180 mg/dL. Before analysis, Patient 3 exhibited 102 out of 288 (35%) glucose readings inside their target

range and the remaining 186 out of 288 (65%) readings outside of their target range. After analysis, Patient 3 exhibited 135 out of 288 readings (47%) inside their target range and the remaining 153 out of 288 readings (53%) outside of their target range. In regards to basal rates, this patient was suggested to increase their overall basal Insulin delivery from 23.45 units a day to 28.59 units, remaining similar in overall basal Insulin delivery. It is important to note here that a drastic increase in total basal delivery per day would not be ideal or recommended to a patient, as all basal adjustments should be adjusted in conservative, small increments to make sure it is overall safe with the patient and ultimately gives them time to implement any changes and assess their individual glucose response. Like the previous patients above and below, Patient 3 saw an increase in the number of individual rates over a 24-hour period. This patient was suggested to have both increases and increases in basal rates around critical times that greatly contributed to the stabilization of glucose levels presented with their predicted glucose response.

Table 15: Table displaying both original and new basal rate patterns suggested by the basal optimization algorithm for Patient 3.

Basal Rate	New Basal Rate
0.95	0.9
0.95	0.7
1.0	0.83
1.0	1.16
1.0	0.72
1.15	1.09
1.15	1.33
1.15	1.48
1.15	1.64
1.15	1.65
1.15	1.51
1.15	0.97
1.15	1.02
1.15	1.65
1.15	0.92
1.15	1.47
1.15	1.56
1.15	1.47
1.15	1.56
1.15	1.47
1.15	1.02
1.15	0.83
1.15	0.92
0.85	0.72

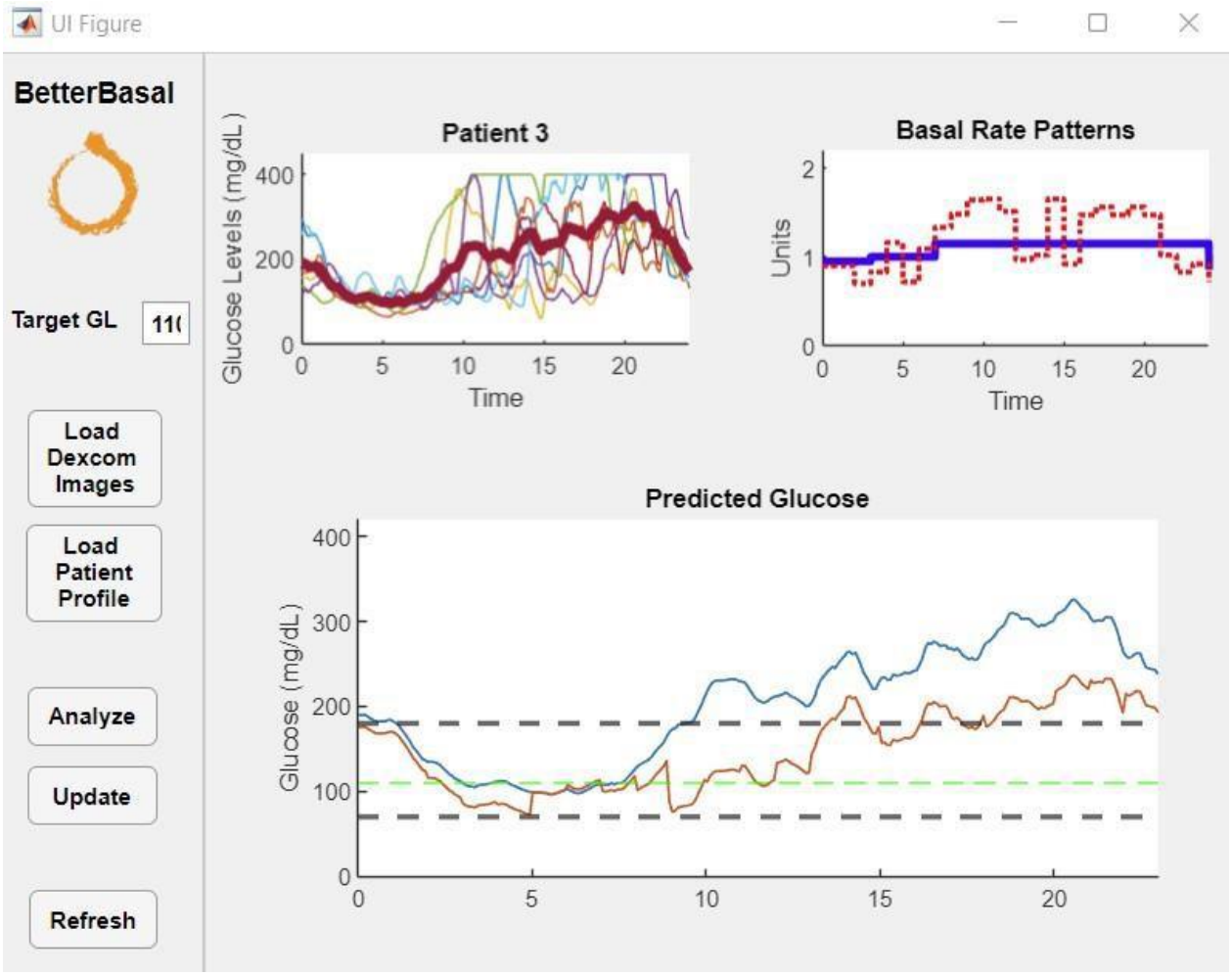


Figure 48: Results for Patient 3 presented to the user in the GUI window.

6.1.4 PATIENT 4 ANALYSIS

Patient 4 presented a pattern of daytime highs with significant highs occurring, on average, between 11:00 AM and 11:00 PM. A steady but consistent rise in glucose level begins around 11:00 AM and continues to rise, while it appears for a bolus correction to be made around late afternoon, potentially due to a late lunch or even a late afternoon workout. Shortly after, a significant glucose spike occurs with this patient, around 7:00 PM, feeding into significant highs until the glucose levels begin to come back down 9:00 PM, where another bolus correction was likely to be administered. This patient also saw higher glucose levels while they were sleeping, during a period of fasting. This is also another common trend for type 1 diabetics known as the "dawn phenomenon". The dawn phenomenon is recognized as a rise in blood sugar in the early morning hours, usually while an individual is still sleeping, when hormones that your body naturally produce cause an increase in glucose level [69]. This pattern observed in a large population of type 1 diabetics, and when paired with high cortisol levels as the body is waking up, can lead to severe, sometimes dangerous, hyperglycemic episodes. Regarding other pertinent patient-specific information, this patient had 1 single basal rate pattern over the course of 24 hours, a consistent correction factor of 45 and had a target glucose value of 110 mg/dL for all 7 days. This patient used a CSV file to upload their glucose data and utilized a rapid acting Insulin.

The first important area of interest to assess is the overall glucose level and the change after basal optimization algorithm. After the analysis, Patient 4 showed overall success in harnessing the basal optimization in order to overall lower their glucose levels. Before analysis, this patient had an average glucose level of 180 ± 44.25 mg/dL (range, 111 to 251). After analysis, this patient presented an average glucose level of 123 ± 34.21 mg/dL (range, 73 to 185), ultimately seeing a glucose reduction, on average of 31.67%. Another vital area to assess is the

amount of time spent both inside and outside of the target glucose range of 70-180 mg/dL. Before analysis, Patient 4 exhibited 144 out of 288 (50%) glucose readings inside their target range and the remaining 144 out of 288 (50%) readings outside of their target range. After analysis, Patient 4 exhibited 281 out of 288 readings (98%) inside their target range and the remaining 7 out of 288 readings (2%) outside of their target range. In regard to basal rates, this patient was suggested to increase their overall basal Insulin delivery from 24.00 units a day to 25.82 units, remaining similar in overall basal Insulin delivery. It is important to note here that a drastic increase in total basal delivery per day would not be ideal or recommended to a patient, as all basal adjustments should be adjusted in conservative, small increments to make sure it is overall safe with the patient and ultimately gives them time to implement any changes and assess their individual glucose response. Like the previous patients above and below, Patient 4 saw an increase in the number of individual rates over a 24-hour period. This patient was suggested to have both increases and increases in basal rates around critical times that greatly contributed to the stabilization of glucose levels presented with their predicted glucose response.

Table 16: Table displaying both original and new basal rate patterns suggested by the basal optimization algorithm for Patient 4.

Basal Rate	New Basal Rate
1.0	1.0
1.0	1.23
1.0	0.9
1.0	0.8
1.0	1.0
1.0	0.8
1.0	0.9
1.0	1.2
1.0	0.8
1.0	1.24
1.0	1.26
1.0	1.0
1.0	0.9
1.0	1.26
1.0	1.26
1.0	1.32
1.0	1.32
1.0	0.8
1.0	1.41
1.0	1.27
1.0	0.9
1.0	0.9
1.0	1.27
1.0	1.27

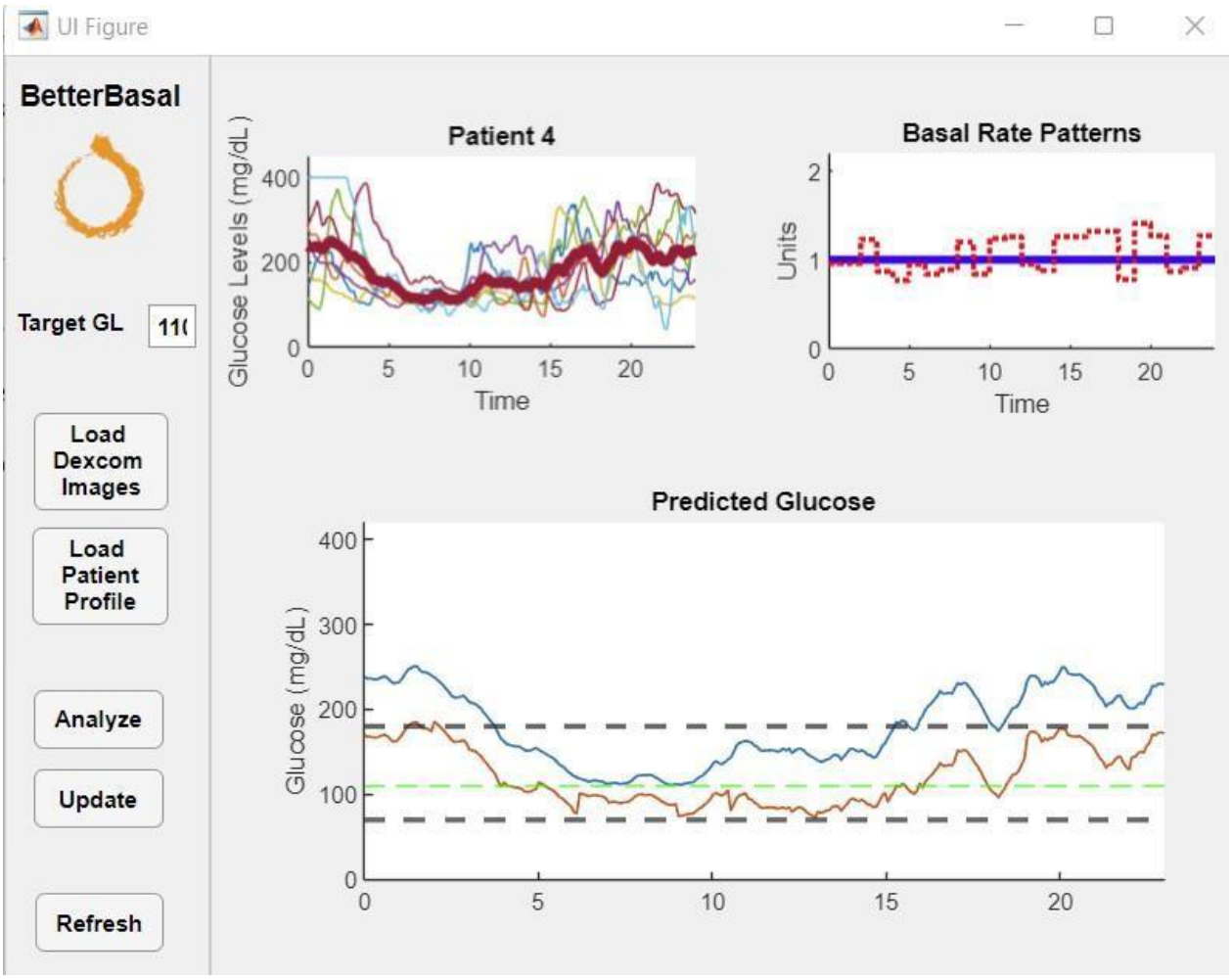


Figure 49: Results for Patient 4 presented to the user in the GUI window.

6.1.5 PATIENT 5 ANALYSIS

Patient 5 presented a pattern of daytime highs with significant highs occurring, on average, between 11:00 AM and 11:00 PM. A steady but consistent rise in glucose level begins around 11:00 AM and continues to rise, while it appears for a bolus correction to be made around late afternoon, potentially due to a late lunch or even a late afternoon workout. Shortly after, a significant glucose spike occurs with this patient, around 7:00 PM, feeding into significant highs until the glucose levels begin to come back down 9:00 PM, where another bolus correction was likely to be administered. Regarding other pertinent patient-specific information, this patient had 5 basal rate patterns over the course of 24 hours, a consistent correction factor of 50 and had a target glucose value of 110 mg/dL for all 7 days. This patient used a CSV file to upload their glucose data and utilized a rapid acting Insulin.

The first important area of interest to assess is the overall glucose level and the change after basal optimization algorithm. After the analysis, Patient 5 showed overall success in harnessing the basal optimization in order to overall lower their glucose levels. Before analysis, this patient had an average glucose level of 199 ± 61.28 mg/dL (range, 105 to 324). After analysis, this patient presented an average glucose level of 126 ± 25.12 mg/dL (range, 87 to 192), ultimately seeing a glucose reduction, on average of 36.68%. Another vital area to assess is the amount of time spent both inside and outside of the target glucose range of 70-180 mg/dL. Before analysis, Patient 5 exhibited 108 out of 288 (38%) glucose readings inside their target range and the remaining 180 out of 288 (62%) readings outside of their target range. After analysis, Patient 5 exhibited 278 out of 288 readings (97%) inside their target range and the remaining 10 out of 288 readings (3%) outside of their target range. In regards to basal rates, this patient was suggested to increase their overall basal Insulin delivery from 29.95 units a day to

31.22 units, remaining similar in overall basal Insulin delivery. It is important to note here that a drastic increase in total basal delivery per day would not be ideal or recommended to a patient, as all basal adjustments should be adjusted in conservative, small increments to make sure it is overall safe with the patient and ultimately gives them time to implement any changes and assess their individual glucose response. Like the previous patients above and below, Patient 5 saw an increase in the number of individual rates over a 24-hour period. This patient was suggested to have both increases and increases in basal rates around critical times that greatly contributed to the stabilization of glucose levels presented with their predicted glucose response.

Table 17: Table displaying both original and new basal rate patterns suggested by the basal optimization algorithm for Patient 5.

Basal Rate	New Basal Rate
0.95	0.9
0.95	0.85
0.95	0.8
0.95	0.9
0.95	0.8
1.2	1.0
1.2	0.9
1.2	1.53
1.2	1.5
1.2	1.53
1.4	1.9
1.4	1.8
1.4	1.8
1.4	1.76
1.4	1.76
1.4	1.22
1.4	1.18
1.45	1.2
1.45	1.81
1.45	1.95
1.45	1.3
1.2	1.0
1.2	0.88
1.2	1.02

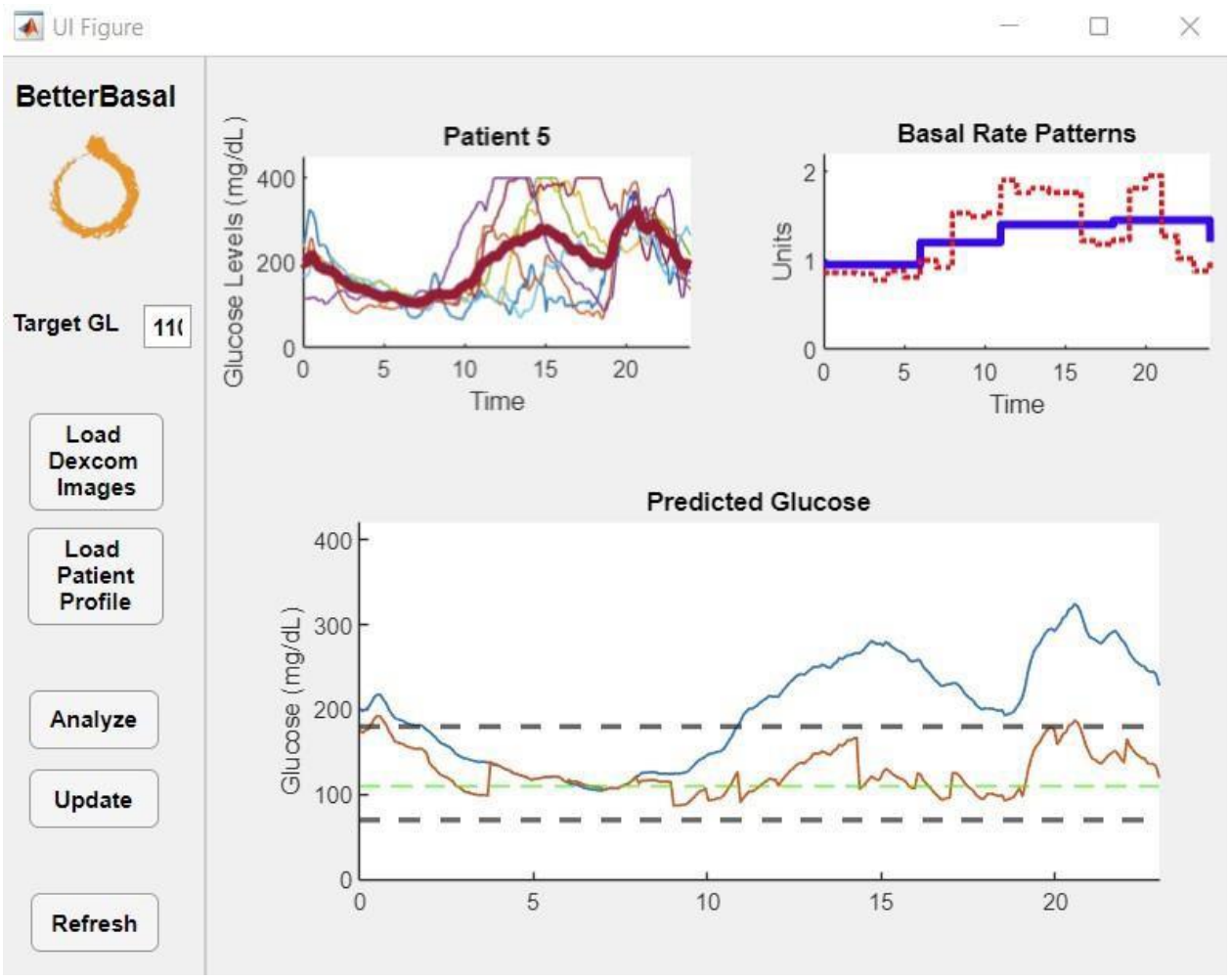


Figure 50: Results for Patient 5 presented to the user in the GUI window.

6.1.6 PATIENT 6 ANALYSIS

Patient 6 presented a pattern of daytime highs with significant highs occurring, on average, between 3:00 PM and 2:00 AM. A significant glucose spike occurs with this patient, beginning around lunchtime, feeding into significant highs for the remainder of the day. This could be a common glucose trend for someone forgetting to bolus for a meal around lunchtime, or even blousing after the fact, as their current basal rates are not high enough during this range to account for near the magnitude of rise in glucose level present. It can be very common in younger adolescent patients or even young adults to commonly either forget to bolus for a meal or not bolus enough to account for the intake of carbohydrates that they are consuming, making this a situation that was important to model when creating patients. Regarding other pertinent patient-specific information, this patient had 1 single basal rate pattern over the course of 24 hours, a consistent correction factor of 50 and had a target glucose value of 110 mg/dL for all 7 days. This patient used a CSV file to upload their glucose data and utilized a rapid acting Insulin.

The first important area of interest to assess is the overall glucose level and the change after basal optimization algorithm. After the analysis, Patient 6 showed overall success in harnessing the basal optimization in order to overall lower their glucose levels. Before analysis, this patient had an average glucose level of 194 ± 55.87 mg/dL (range, 103 to 298). After analysis, this patient presented an average glucose level of 147 ± 55.87 mg/dL (range, 78 to 216), ultimately seeing a glucose reduction, on average of 24.23%. Another vital area to assess is the amount of time spent both inside and outside of the target glucose range of 70-180 mg/dL. Before analysis, Patient 6 exhibited 115 out of 288 (40%) glucose readings inside their target range and the remaining 173 out of 288 (60%) readings outside of their target range. After analysis, Patient 6 exhibited 245 out of 288 readings (85%) inside their target range and the

remaining 43 out of 288 readings (15%) outside of their target range. In regards to basal rates, this patient was suggested to increase their overall basal Insulin delivery from 24.00 units a day to 25.09 units, remaining similar in overall basal Insulin delivery. It is important to note here that a drastic increase in total basal delivery per day would not be ideal or recommended to a patient, as all basal adjustments should be adjusted in conservative, small increments to make sure it is overall safe with the patient and ultimately gives them time to implement any changes and assess their individual glucose response. Like the previous patients above and below, Patient 6 saw an increase in the number of individual rates over a 24-hour period. This patient was suggested both increases and increases in basal rates around critical times that greatly contributed to the stabilization of glucose levels presented with their predicted glucose response.

Table 18: Table displaying both original and new basal rate patterns suggested by the basal optimization algorithm for Patient 6.

Basal Rate	New Basal Rate
1.0	0.9
1.0	0.9
1.0	0.8
1.0	0.88
1.0	1.2
1.0	0.86
1.0	0.91
1.0	0.8
1.0	1.29
1.0	1.26
1.0	1.26
1.0	1.32
1.0	1.41
1.0	1.0
1.0	0.9
1.0	0.8
1.0	0.9
1.0	1.41
1.0	1.32
1.0	1.0
1.0	0.9
1.0	0.9
1.0	0.9
1.0	1.41

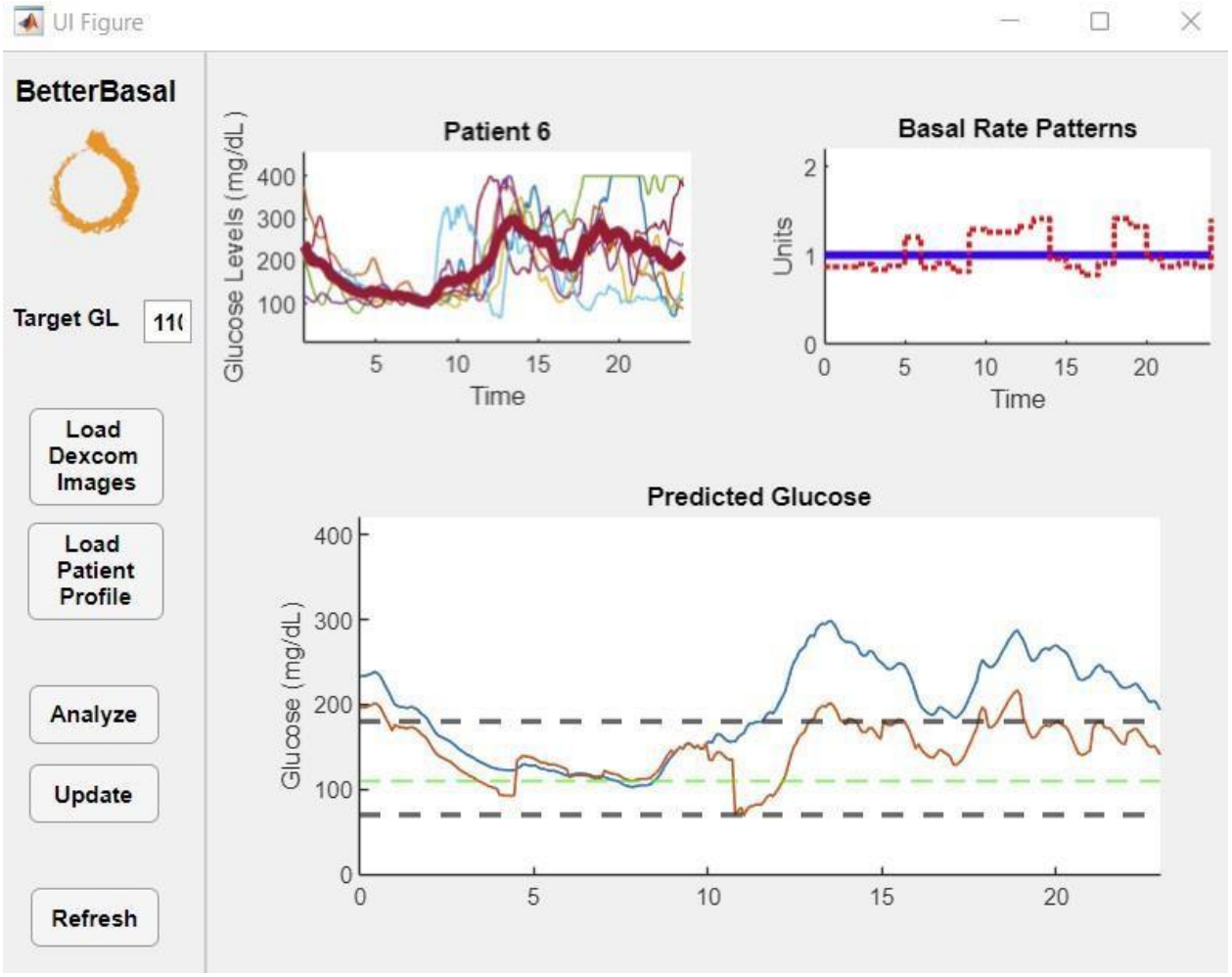


Figure 51: Results for Patient 6 presented to the user in the GUI window.

Table 19: Table displaying both original and new basal rate patterns suggested by the basal optimization algorithm for Patient 6 including the mealtime removal feature utilized.

Basal Rate	New Basal Rate
1.0	0.9
1.0	0.9
1.0	0.8
1.0	0.9
1.0	1.2
1.0	0.9
1.0	0.9
1.0	0.8
1.0	1.3
1.0	1.3
1.0	1.3
1.0	1.3
1.0	1.2
1.0	1.2
1.0	1.2
1.0	1.2
1.0	0.9
1.0	1.4
1.0	1.3
1.0	1.0
1.0	0.9
1.0	0.9
1.0	0.9
1.0	1.4

Patient 6 was also analyzed using the mealtime removal feature to help further isolate the basal Insulin effects, by removing hyperglycemic spikes. Like the original analysis of this patient, after the mealtime removal, Patient 6 showed shared success in harnessing the basal optimization in order to overall lower their glucose levels. Before analysis, this patient had an average glucose level of 183 ± 46.91 mg/dL (range, 103 to 287). After analysis, this patient presented an average glucose level of 109 ± 31.00 mg/dL (range, 71 to 187), ultimately seeing a glucose reduction, on average of 40.44%. Regarding the amount of time spent both inside and outside of the target glucose range of 70-180 mg/dL, before analysis, this patient exhibited 115 out of 288 (40%) glucose readings inside their target range and the remaining 173 out of 288 (60%) readings outside of their target range. After analysis, this patient exhibited 247 out of 288 readings (86%) inside their target range and the remaining 41 out of 288 readings (14%) outside of their target range. In regard to basal rates, this patient was suggested to increase their overall basal Insulin delivery from 24.00 units a day to 25.99 units, remaining similar in overall basal Insulin delivery, which is an increase of 0.90 units, compared to the patient without utilizing the mealtime removal feature. Like the previous analysis of this patient, Patient 6 saw an increase in the number of individual rates over a 24-hour period. This patient was suggested to have both increases and increases in basal rates around critical times that greatly contributed to the stabilization of glucose levels presented with their predicted glucose response.

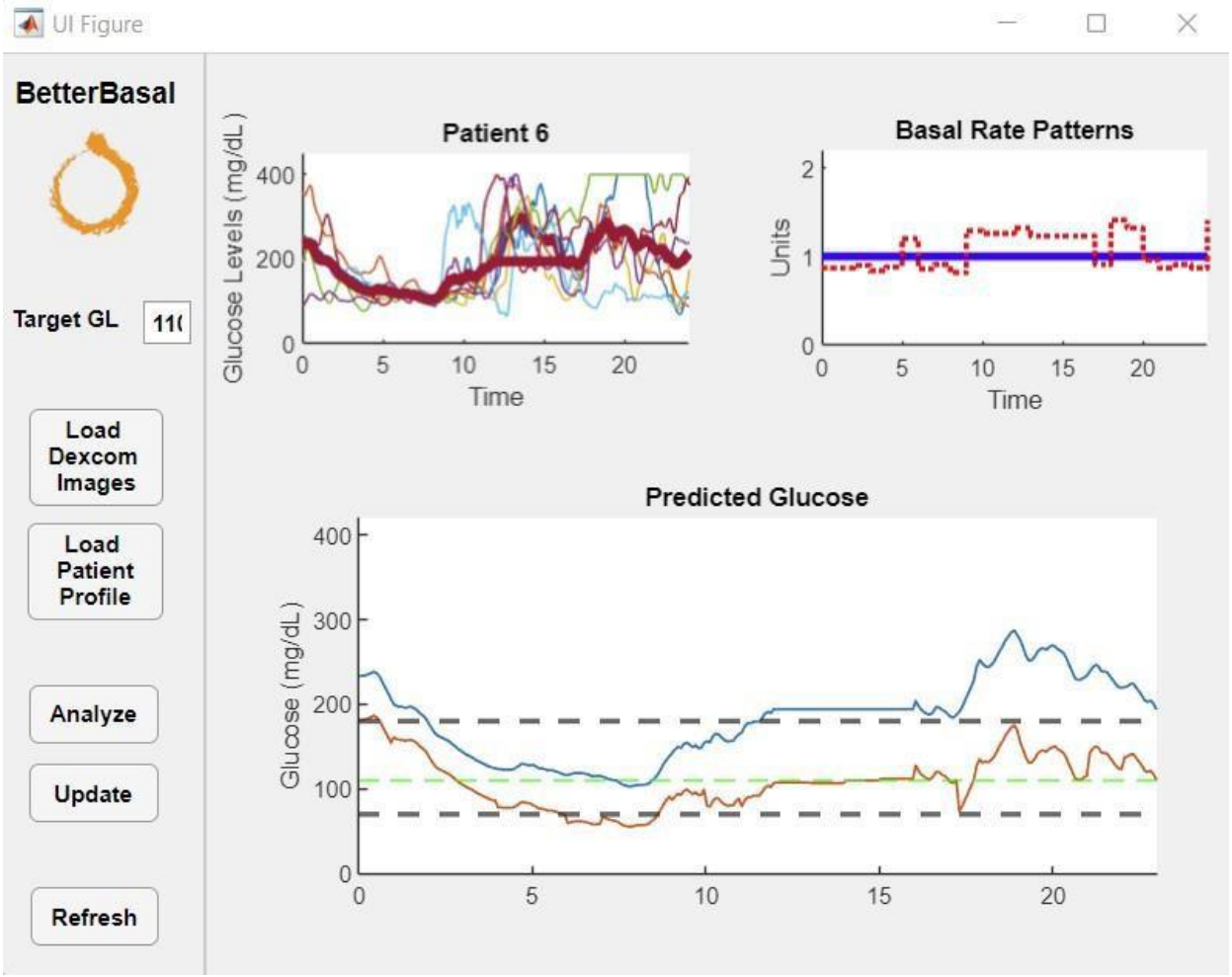


Figure 52: Results for Patient 6 utilizing the meal removal feature presented to the user in the GUI window.

6.1.7 PATIENT 7 ANALYSIS

Patient 7 presented a pattern of nighttime highs with a pattern of significant highs, on average, between roughly 7:00 PM and 2:00 AM. This patient also displayed a pattern of daytime highs with significant highs occurring, on average, between 2:00 PM and 7:00 PM. With this being said, on average, this patient remained in a constant hyperglycemic state for 50% of their glucose trend. This patient was created to try and model an individual who is experiencing a sickness and even potentially taking medications that can have a strong effect on glucose response. Being a part of the body's defense mechanism for fighting any illness, an increased amount of glucose is in turn released into the bloodstream, ultimately making it more challenging to control glucose levels from day to day [70,71]. As sickness is unavoidable, many diabetics struggle controlling their glucose levels during this time, making this another scenario vital to represent during this analysis. Temporarily adjusting basal rate patterns while sick can potentially help the patient get better control of their glucose levels while their body is working to fight off the illness, with some healthcare professionals suggesting an initial increase or decrease by roughly 20-30% of current basal rates [71]. Regarding other pertinent patient-specific information, this patient had 4 different basal rate patterns over the course of 24 hours, a consistent correction factor of 40 and had a target glucose value of 110 mg/dL for all 7 days. This patient used a CSV file to upload their glucose data and utilized a rapid acting Insulin. The first important area of interest to assess is the overall glucose level and the change after basal optimization algorithm. After the analysis, Patient 7 showed overall success in harnessing the basal optimization in order to overall lower their glucose levels. Before analysis, this patient had an average glucose level of 208 ± 52.04 mg/dL (range, 113 to 285). After analysis, this patient presented an average glucose level of 146 ± 47.16 mg/dL (range, 72 to 222), ultimately

seeing a glucose reduction, on average of 29.81%. Another vital area to assess is the amount of time spent both inside and outside of the target glucose range of 70-180 mg/dL. Before analysis, Patient 7 exhibited 89 out of 288 (31%) glucose readings inside their target range and the remaining 199 out of 288 (69%) readings outside of their target range. After analysis, Patient 7 exhibited 173 out of 288 readings (60%) inside their target range and the remaining 115 out of 288 readings (40%) outside of their target range. In regards to basal rates, this patient was suggested to increase their overall basal Insulin delivery from 23.45 units a day to 28.15 units, remaining similar in overall basal Insulin delivery. It is important to note here that a drastic increase in total basal delivery per day would not be ideal or recommended to a patient, as all basal adjustments should be adjusted in conservative, small increments to make sure it is overall safe with the patient and ultimately gives them time to implement any changes and assess their individual glucose response. Like the previous patients above and below, Patient 7 saw an increase in the number of individual rates over a 24-hour period. This patient was suggested both increases and increases in basal rates around critical times that greatly contributed to the stabilization of glucose levels presented with their predicted glucose response.

Table 20: Table displaying both original and new basal rate patterns suggested by the basal optimization algorithm for Patient 7.

Basal Rate	New Basal Rate
0.95	1.18
0.95	0.82
1.0	0.8
1.0	0.9
1.0	0.88
1.15	1.24
1.15	0.94
1.15	0.9
1.15	1.48
1.15	1.55
1.15	1.65
1.15	1.02
1.15	1.02
1.15	1.65
1.15	1.56
1.15	0.97
1.15	0.92
1.15	1.02
1.15	1.47
1.15	1.65
1.15	1.02
1.15	1.47
1.15	0.92
0.85	1.12

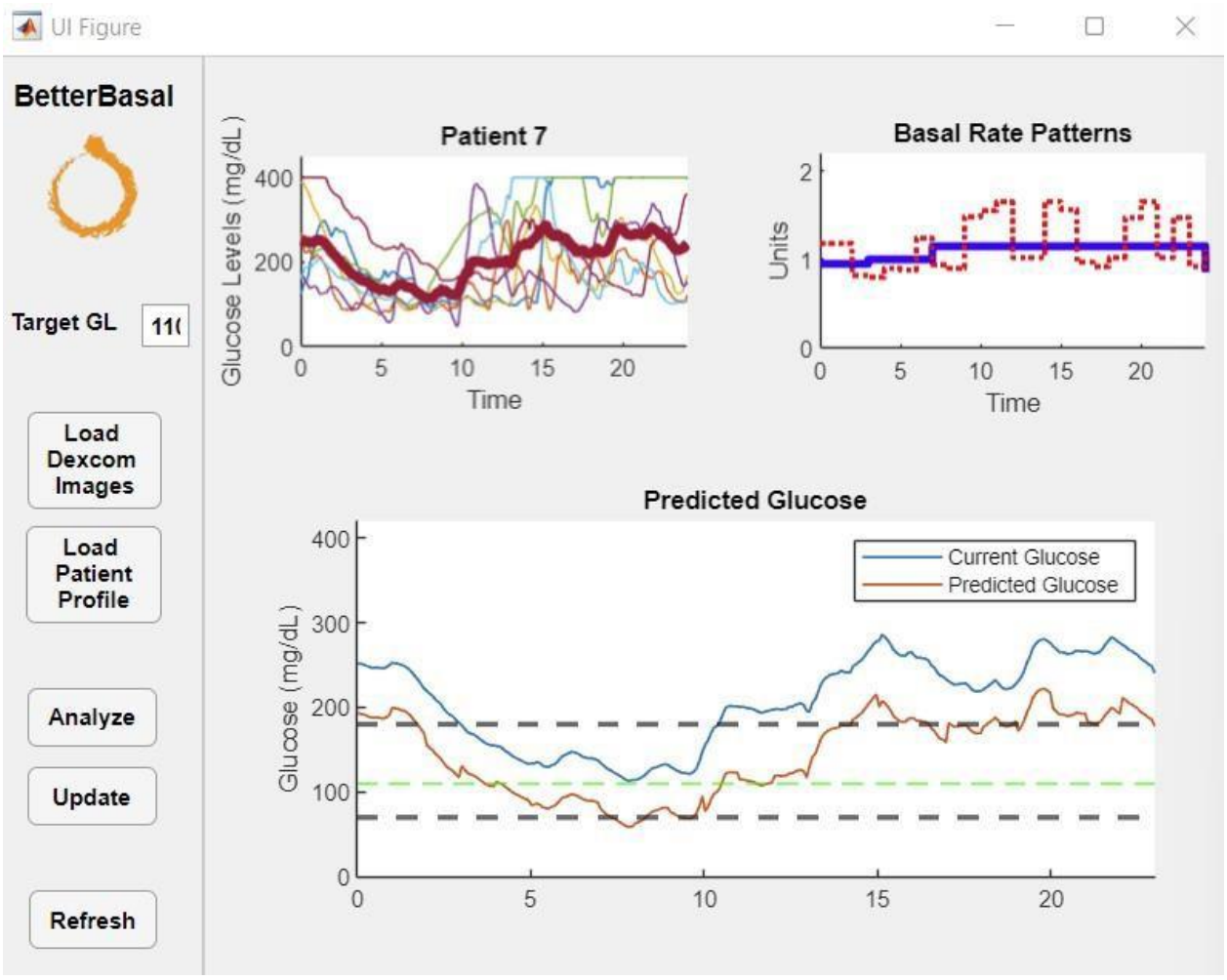


Figure 53: Results for Patient 7 presented to the user in the GUI window.

6.1.8 PATIENT 8 ANALYSIS

Patient 8 presented a pattern of daytime highs with significant highs occurring, on average, between 6:00 PM and 11:00 PM. Another noticeable glucose spike occurs around 12:00 PM, which likely can be attributed to mealtime, thus an influx of carbohydrates digesting and quickly converting to glucose causing the glucose level to spike until a self-administered bolus of Insulin begins to work by lowering the glucose levels. Unlike most other patients, a pattern of nighttime highs wasn't prevalent enough to note. It is important to note here that this does not mean that the patient did not experience high glucose readings overnight, however, on average severe highs during this time frame were not present. Regarding other pertinent patient-specific information, this patient had 1 single basal rate pattern over the course of 24 hours, a consistent correction factor of 35 and had a target glucose value of 110 mg/dL for all 7 days. This patient used a CSV file to upload their glucose data and utilized a rapid acting Insulin.

The first important area of interest to assess is the overall glucose level and the change after basal optimization algorithm. After the analysis, Patient 8 showed overall success in harnessing the basal optimization in order to overall lower their glucose levels. Before analysis, this patient had an average glucose level of 196 ± 48.07 mg/dL (range, 120 to 299). After analysis, this patient presented an average glucose level of 137 ± 25.70 mg/dL (range, 76 to 201), ultimately seeing a glucose reduction, on average of 30.10%. Another vital area to assess is the amount of time spent both inside and outside of the target glucose range of 70-180 mg/dL. Before analysis, Patient 8 exhibited 116 out of 288 (40%) glucose readings inside their target range and the remaining 172 out of 288 (60%) readings outside of their target range. After analysis, Patient 8 exhibited 274 out of 288 readings (95%) inside their target range and the remaining 14 out of 288 readings (5%) outside of their target range. In regards to basal rates, this

patient was suggested to increase their overall basal Insulin delivery from 24.00 units a day to 25.43 units, remaining similar in overall basal Insulin delivery. It is important to note here that a drastic increase in total basal delivery per day would not be ideal or recommended to a patient, as all basal adjustments should be adjusted in conservative, small increments to make sure it is overall safe with the patient and ultimately gives them time to implement any changes and assess their individual glucose response. Like the previous patients above and below, Patient 8 saw an increase in the number of individual rates over a 24-hour period. Like many of the other patients presented in this analysis, an important area of concern pre-analysis was the elevation in glucose values beginning just after noon, rising consistently throughout the remainder of the day, and into the early morning hours. Post-analysis, this patient saw suggested increases in basal rates during the important time-periods of 10:00 AM-12:00 PM, as well as 6:00 PM-8:00 PM, greatly contributing to the stabilization of glucose levels presented with their predicted glucose response.

Table 21: Table displaying both original and new basal rate patterns suggested by the basal optimization algorithm for Patient 8.

Basal Rate	New Basal Rate
1.0	1.32
1.0	1.23
1.0	0.9
1.0	0.9
1.0	0.9
1.0	0.9
1.0	1.2
1.0	0.9
1.0	1.24
1.0	1.26
1.0	1.41
1.0	1.27
1.0	0.9
1.0	1.23
1.0	0.9
1.0	1.0
1.0	0.8
1.0	1.41
1.0	1.41
1.0	0.9
1.0	0.9
1.0	1.0
1.0	0.9
1.0	0.8

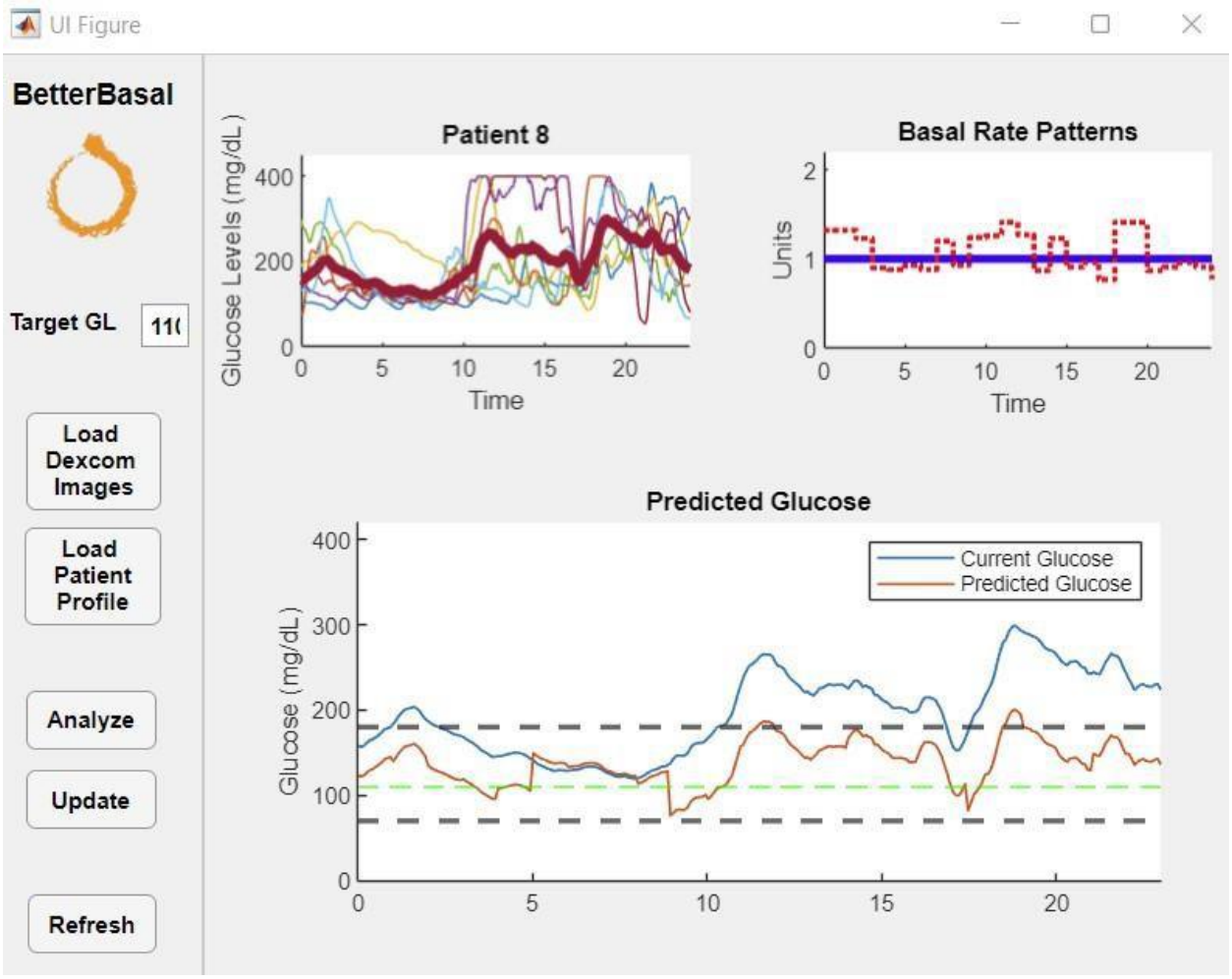


Figure 54: Results for Patient 8 presented to the user in the GUI window.

6.1.9 PATIENT 9 ANALYSIS

Patient 9 presented a pattern of nighttime highs with a pattern of significant highs, on average, between roughly 12:00 AM and 1:00 AM. This patient also displayed a pattern of daytime highs with significant highs occurring, on average, between 12:00 PM and 10:00 PM. It is not uncommon for certain diabetics, for a multitude of reasons, to exhibit a constant state of hyperglycemia throughout the latter half of the day. There could be many reasons for this such as not accounting for carbohydrate intake properly, increased activity or even suffering from a common cold. Regardless, for the purpose of trying to represent a diverse patient population as possible, including a patient like this for analysis purposes is important. Regarding other pertinent patient-specific information, this patient had 4 different basal rate patterns over the course of 24 hours, a consistent correction factor of 45 and had a target glucose value of 110 mg/dL for all 7 days. This patient used a CSV file to upload their glucose data and utilized a rapid acting Insulin.

The first important area of interest to assess is the overall glucose level and the change after basal optimization algorithm. After the analysis, Patient 9 showed overall success in harnessing the basal optimization in order to overall lower their glucose levels. Before analysis, this patient had an average glucose level of 191 ± 52.27 mg/dL (range, 107 to 298). After analysis, this patient presented an average glucose level of 132 ± 49.54 mg/dL (range, 61 to 231), ultimately seeing a glucose reduction, on average of 30.89%. Another vital area to assess is the amount of time spent both inside and outside of the target glucose range of 70-180 mg/dL. Before analysis, Patient 9 exhibited 137 out of 288 (48%) glucose readings inside their target range and the remaining 151 out of 288 (52%) readings outside of their target range. After analysis, Patient 9 exhibited 184 out of 288 readings (64%) inside their target range and the

remaining 104 out of 288 readings (36%) outside of their target range. In regards to basal rates, this patient was suggested to increase their overall basal Insulin delivery from 23.45 units a day to 27.6 units, remaining similar in overall basal Insulin delivery. It is important to note here that a drastic increase in total basal delivery per day would not be ideal or recommended to a patient, as all basal adjustments should be adjusted in conservative, small increments to make sure it is overall safe with the patient and ultimately gives them time to implement any changes and assess their individual glucose response.

Patient 9 saw an increase in the number of individual rates over a 24-hour period. An important area of concern pre-analysis was the elevation in glucose values beginning just after noon, rising consistently throughout the remainder of the day, and into the early morning hours. Post-analysis, this patient saw suggested increases in basal rates during the important time-periods of 11:00 AM-1:00 PM, as well as 12:00 PM-1:00 AM, greatly contributing to the stabilization of glucose levels presented with their predicted glucose response. It is important to note here, that with any raise in basal rate, it is important to assess the surrounding basal rates, to help ensure that the potential of Insulin stacking is avoided. With this being said, while average glucose levels were nearing the low 100's around 6:00 AM-7:00 AM, technically within the target range for this patient, a reduction in basal rate between 3:00 AM-5:00 AM, will help potentially balance the average 0.25 unit increase in basal rate during this time period. The lowest basal rate suggested after analysis was 0.80 units compared to the original 0.85 units, while the maximum basal rate suggested post-analysis was 1.65 units, compared to the original 1.15 units.

Table 22: Table displaying both original and new basal rate patterns suggested by the basal optimization algorithm for Patient 9.

Basal Rate	New Basal Rate
0.95	1.22
0.95	0.85
1.0	0.78
1.0	0.86
1.0	0.91
1.15	1.24
1.15	1.44
1.15	1.55
1.15	0.94
1.15	0.98
1.15	1.44
1.15	1.65
1.15	1.65
1.15	0.97
1.15	1.56
1.15	1.02
1.15	1.65
1.15	0.97
1.15	0.97
1.15	1.02
1.15	0.97
1.15	0.92
1.15	0.92
0.85	1.12

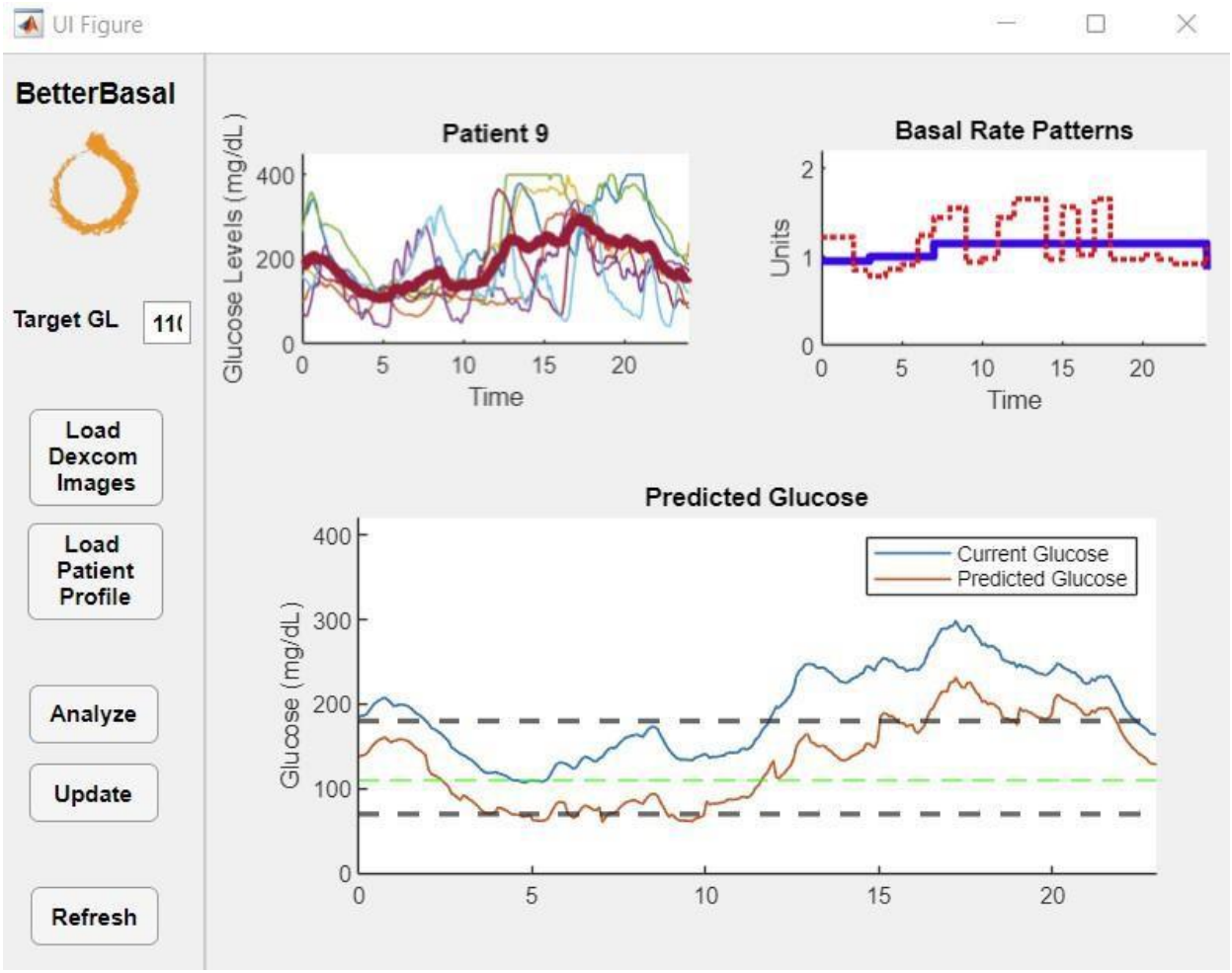


Figure 55: Results for Patient 9 presented to the user in the GUI window.

6.1.10 PATIENT 10 ANALYSIS

Patient 10 presented a pattern of nighttime highs with a pattern of significant highs, on average, between roughly 1:00 AM and 3:00 AM. This patient also displayed a pattern of daytime highs with significant highs occurring, on average, between 3:00 PM and 5:00 PM. High glucose readings are extremely common around postprandial, during or after mealtime, where this patient is experiencing their daytime highs. Unlike the previous patient, this patient seemed to have better control on their glucose levels, specifically regarding extreme daytime highs. Regarding other pertinent patient-specific information, this patient had 9 different basal rate patterns over the course of 24 hours, a consistent correction factor of 50 and had a target glucose value of 110 mg/dL for all 7 days. This patient used a CSV file to upload their glucose data and utilized a rapid acting Insulin.

The first important area of interest to assess is the overall glucose level and the change after basal optimization algorithm. After the analysis, Patient 10 showed overall success in harnessing the basal optimization in order to overall lower their glucose levels. Before analysis, this patient had an average glucose level of 183 ± 42.36 mg/dL (range, 98 to 251). After analysis, this patient presented an average glucose level of 119 ± 29.93 mg/dL (range, 64 to 187), ultimately seeing a glucose reduction, on average of 34.97%. Another vital area to assess is the amount of time spent both inside and outside of the target glucose range of 70-180 mg/dL. Before analysis, Patient 10 exhibited 112 out of 288 (39%) glucose readings inside their target range and the remaining 176 out of 288 (61%) readings outside of their target range. After analysis, Patient 10 exhibited 271 out of 288 readings (94%) inside their target range and the remaining 17 out of 288 readings (6%) outside of their target range. In regard to basal rates, this patient was suggested to increase their overall basal Insulin delivery from 30.6 units a day to

31.94 units, remaining similar in overall basal Insulin delivery. It is important to note here that a drastic increase in total basal delivery per day would not be ideal or recommended to a patient, as all basal adjustments should be adjusted in conservative, small increments to make sure it is overall safe with the patient and ultimately gives them time to implement any changes and assess their individual glucose response.

Patient 10 saw an increase in the number of individual rates over a 24-hour period. An important area of concern pre-analysis was the elevation in glucose values beginning just before noon lasting the remainder of the day. Post-analysis, this patient saw suggested increases in basal rates during the important time-periods of 9:00 AM-12:00 PM, as well as 3:00 PM-6:00 PM, greatly contributing to the stabilization of glucose levels presented with their predicted glucose response. The lowest basal rate suggested after analysis was 0.8 units compared to the original 0.9 units, while the maximum basal rate suggested post-analysis was 2.0 units, compared to the original 1.6 units.

Table 23: Table displaying both original and new basal rate patterns suggested by the basal optimization algorithm for Patient 10.

Basal Rate	New Basal Rate
0.9	1.13
0.9	0.81
1.1	0.87
1.1	0.85
1.1	0.94
1.2	0.99
1.2	0.88
1.6	1.28
1.6	2.07
1.6	2
1.4	1.76
1.4	1.76
1.5	1.32
1.5	1.27
1.5	1.85
1.4	1.72
1.4	1.9
1.4	1.76
1.2	1.07
1.2	0.98
1.1	1.51
1.1	0.92
1.1	1.51
1.1	0.79

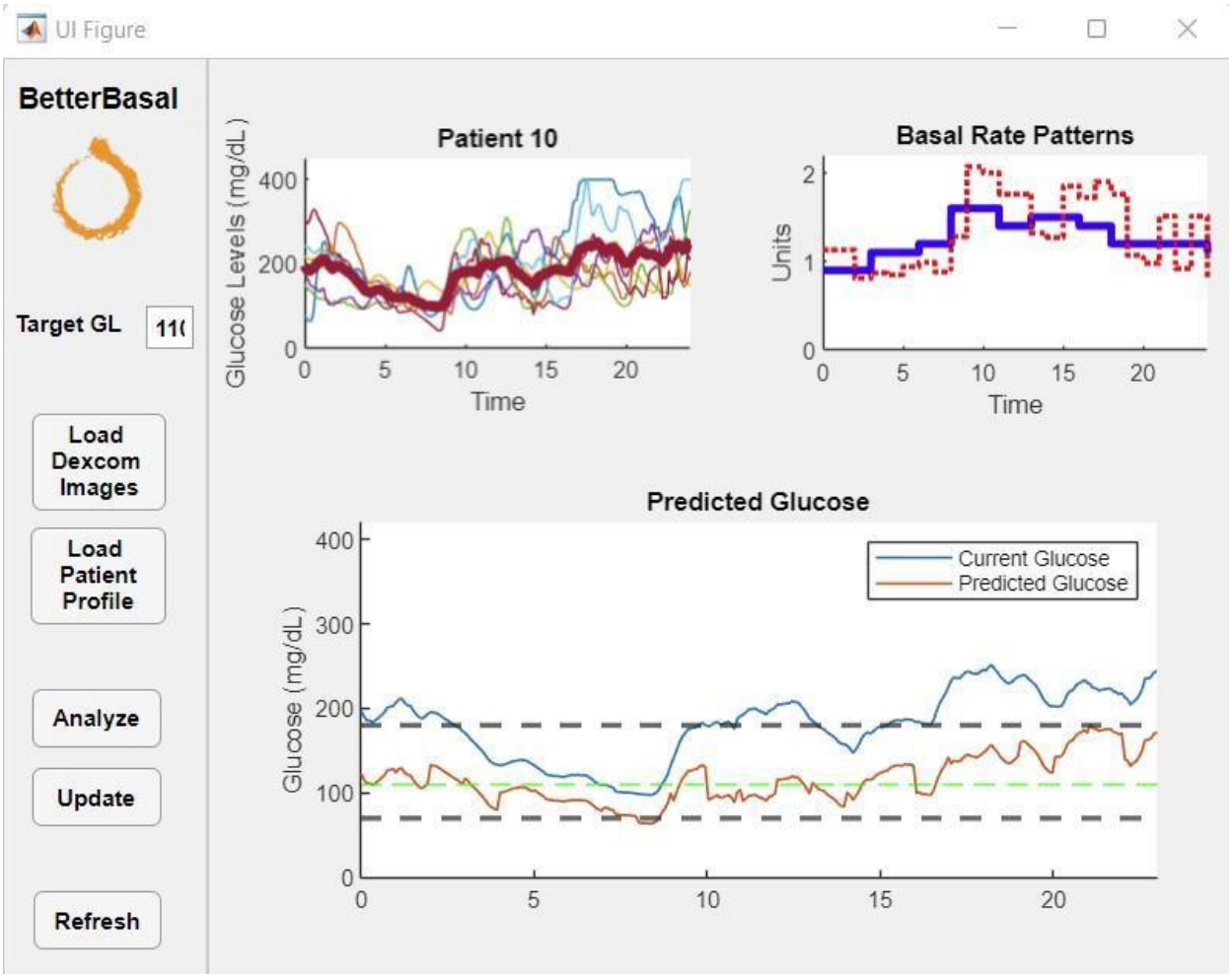


Figure 56: Results for Patient 10 presented to the user in the GUI window.

6.1.11 PATIENT 11 ANALYSIS

Unlike previous patients, Patient 11 presented an overall pattern of lower glucose levels throughout the day, on average. Areas of interest pre-analysis were in the early morning hours from roughly 1:00 AM to 8:00 AM, a significant low around 12:00 PM, as well as low glucose values in the late afternoon early evening around 4:00 PM to 6:00 PM. Unlike the previous patient, this patient seemed to have better control on their glucose levels, specifically regarding extreme daytime highs. Regarding other pertinent patient-specific information, this patient had 9 different basal rate patterns over the course of 24 hours, a consistent correction factor of 50 and had a target glucose value of 110 mg/dL for all 7 days. This patient used a CSV file to upload their glucose data and utilized a rapid acting Insulin.

The first important area of interest to assess is the overall glucose level and the change after basal optimization algorithm. After the analysis, Patient 11 showed overall success in harnessing the basal optimization in order to overall raise their glucose levels. Before analysis, this patient had an average glucose level of 99 ± 13.94 mg/dL (range, 79 to 135). After analysis, this patient presented an average glucose level of 117 ± 15.18 mg/dL (range, 88 to 155), ultimately seeing a rise in glucose level, on average of 18.06%, closer to the patient's target glucose value of 110 mg/dL. Another vital area to assess is the amount of time spent both inside and outside of the target glucose range of 70-180 mg/dL. Both before and after analysis, this patient displayed all glucose readings over a 24-hour period inside their target range. In regard to basal rates, this patient was suggested to decrease their overall basal Insulin delivery from 30.6 units a day to 25.8 units. This patient, unlike the others, displayed overall lower glucose patterns, with the majority of initial readings being below their target value of 110 mg/dL. Knowing this,

we would expect to see the predicted basal rates for this patient decrease across the board, yielding an overall decrease in total basal insulin utilized for the day.

Like the previous patients above, Patient 11 saw an increase in the number of individual rates over a 24-hour period. An important area of concern pre-analysis was the elevation in glucose values beginning just before noon lasting the remainder of the day. Post-analysis, this patient saw suggested decreases in basal rates during the important time-periods of 12:00 PM into the late afternoon, greatly contributing to the stabilization of glucose levels presented with their predicted glucose response. The lowest basal rate suggested after analysis was 0.8 units compared to the original 0.9 units, while the maximum basal rate suggested post-analysis was 1.2 units, compared to the original 1.6 units.

Table 24: Table displaying both original and new basal rate patterns suggested by the basal optimization algorithm for Patient 11.

Basal Rate	New Basal Rate
0.9	0.8
0.9	0.8
1.1	1
1.1	1
1.1	1
1.2	1
1.2	1
1.6	1.2
1.6	1.2
1.6	1.2
1.4	1.2
1.4	1.2
1.5	1.2
1.5	1.2
1.5	1.2
1.4	1.2
1.4	1.2
1.4	1.2
1.2	1
1.2	1
1.1	1
1.1	1.1
1.1	1.1
1.1	0.8

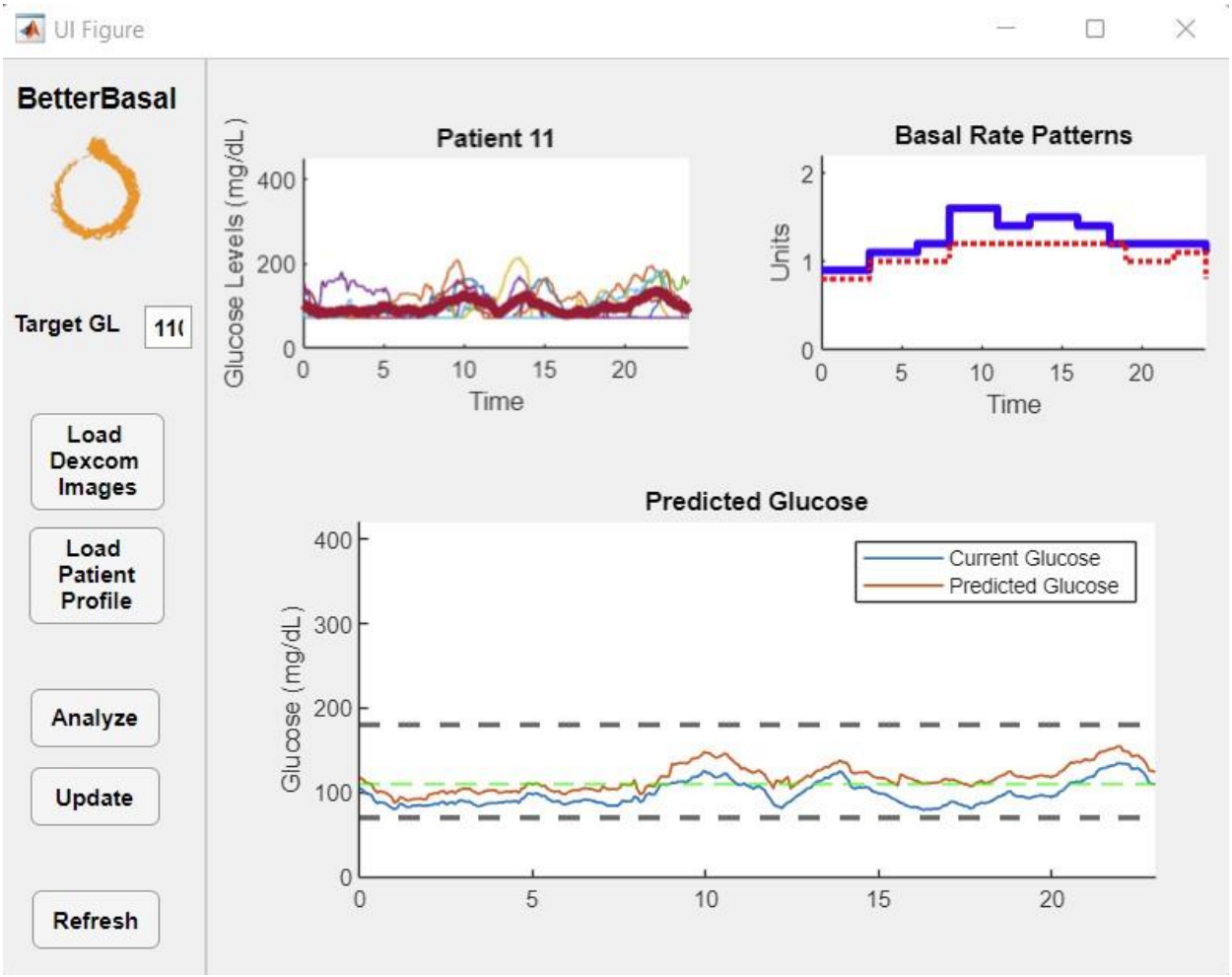


Figure 57: Results for Patient 11 presented to the user in the GUI window.

6.2 DISCUSSION

In this dissertation, an algorithm has been developed to help a type 1 diabetic utilizing an Insulin pump system, paired with a continuous glucose monitor, optimize their basal rates in order to stabilize and maintain good control over their blood glucose levels on a daily basis. It has been shared thought amongst the diabetic community that being able to harness and take full advantage of utilizing basal Insulin, will not only help stabilize glucose values, but reduce the amount of bolus or correction Insulin deliveries needed while doing so. While there has been research that attempts to utilize mathematical modeling to calculate better basal rate patterns, none have yet worked to utilize stored glucose data over an infinite amount of days, paired with a continuous glucose monitoring system, while also predicting the glucose response of sed basal adjustments. Although predicting an individual patient's optimal basal rate pattern usually requires an increased number of individualized rates on a daily basis, as well as the redistribution of the total basal Insulin amount, the results from the ten patients' analysis clearly shows the benefits of this principal while drastically reducing average glucose levels, as well as increasing the amount of time the individual spends in their desired target glucose range. Additionally, the results above showed that the average glucose level of an individual user can undergo a glucose reduction of up to 40.44%, with the amount of time spent in the patient's desired target range, in some cases, reaching 100%, with the latter experiencing 47% in their target range. The results from this dissertation indicate that utilizing patient-specific inputs such as glucose trend data, current basal rate patterns, correction factors and modeling of the individual drug profile are all crucial components of predicting both more optimal basal rate patterns as well as the associated glucose response. While the results above show very promising results in allowing for better overall glycemic control, the human body alone is very complex, and as every individual patient is unique,

this means that every user of this software will have different glucose response from person to person. It is also important to note that there is more information needed about each individual patient, such as lifestyle changes discussed throughout this dissertation, in order to help optimize basal rate patterns with even tighter constraints. Thus, additional information should be considered when further developing this dissertation or any basal optimization algorithm.

While other groups have worked to optimize basal rate patterns in type 1 diabetics, this dissertation differs in the ability to harness individual patient data in conjunction with open, hybrid, or closed loop delivery systems in order to use as one of the main sources of information to optimize basal rate patterns, along with additional patient specific information. The results from this study also displayed minimal changes in total amounts of basal Insulin utilized over a 24-hour period, as it is strongly recommended to adjust basal rates in small increments, to allow the user to assess glucose response before deciding to make more changes with a higher magnitude, overall. Assuming the users utilizing this basal optimization algorithm are currently administering their basal Insulin as less than half of their total daily Insulin delivery, patients who are either drastically increasing their basal rate patterns or even practicing disproportionately high basal rates, more than 50% of their total daily dose, are "likely to result in a slow downward trend in glucose over time", as shown in a study by Rayhan A. Lal, et al; ultimately aligning with a core belief of this dissertation as shown in the results above [72]. Another theory tested within the results of this dissertation was the removal of potential bolus effects around mealtime helping to further isolate basal Insulin, thus offering a potentially better optimization of suggested basal rate patterns for each individual user. Aligning with this belief, a study by Palerm, et al. agreed by saying, meal related Insulin doses can pose as a challenge even suggesting that skipping meals during initial testing may even help combat this challenge when attempting to adjust basal Insulin infusion rates

in type 1 diabetics [73]. While this analysis was not performed on every subject in the results section, it still is the belief that more research is needed in assessing the effects in determining if the removal of severe glucose spikes or mealtime related bolus effects is completely necessary or not. It is a belief in this dissertation that a user of this algorithm should be able to personally decide if this should be necessary depending on a case-by-case basis even with the ability to run various simulations to help come to that decision.

In the results sections above, we examined the vital factors that influence and help contribute to the overall success of both optimizing individual basal rates, as well as help to predict the anticipated glucose response. The focus of this dissertation was to attempt to utilize as many patient-specific inputs and factors as possible, to personalize the experience for each individual user. The findings discussed in the results section above indicate that no two patients are alike and that because glucose data is very unique and diverse from person to person, as well as the unlimited combinations of basal rate patterns that exist, predicting basal rates and glucose response for a user must include previously stored, patient-specific data for the best chance at offering a user basal rate patterns that will deem success in maintaining good glucose patterns on a daily basis.

The software developed herein this dissertation yields numerous applications for not only users of Insulin pump systems and continuous glucose monitors, but also diabetic supply companies developing and maintaining the current software that exist within diabetic technology for Insulin pump systems. It is believed that the work initiated by this dissertation, when paired with diabetic supply companies working on developing and innovating the software of both Insulin pump systems and continuous glucose monitoring systems, as well as a stronger clinical perspective and increased resources, will offer an even better starting point when trying to integrate basal optimization software within their own devices. Although it may be challenging to predict

optimal basal rate patterns and the glucose response those suggestions yield, the findings in this study suggest that putting importance on not only patient-specific input, but the modeling of the individual drug profile of the Insulin utilized offers superior benefit and better results.

CHAPTER 7: SUMMARY AND FUTURE WORK

7.1 SUMMARY

The first objective of this dissertation was to develop a basal optimization algorithm that utilizes previous stored glucose readings, as well as other various patient specific inputs, to suggest optimized basal rates accurately and safely for each unique patient. The second objective of this dissertation was to optimizes glucose levels using an algorithm that can further derive the relationship between glucose levels, basal rates and time to visually show the user the glucose levels that are predicted with each change in basal rate for a better understanding of the effects of the optimized Insulin delivery they would be manually agreeing to.

To achieve this objective, the research involved the development of multiple versions of the software, with each iteration adding value to the prior. The development tasks involved with the development of this software involved the input of patient specific information, data extraction algorithms for two unique data input methods, the modeling of the Insulin drug profile, the suggestion of basal rates based upon the patient specific inputs, as well as the implementation of all things combined in order to suggest a logical glucose response profile. Figure 29 within the Methods section provides a detailed breakdown of the overall framework of this algorithm, necessary for the overall success in the optimization of basal rate patterns and its associated glucose response for numerous individual patients. For the past four years, many versions were developed and reiterated to test for not only accuracy and the ability to help improve a patients overall glucose value, but also the inclusion of the accuracy in modeling the specific type of Insulin administered by each patient. Due to the nature of this research and the severity of any change in automated Insulin delivery, there was only one validation patient, who has been a long-time diabetic and is very involved in their diabetic management with a desire to

achieve a more optimized and stable glucose curve. Active feedback from this validation patient was used and integrated within the program with each update and iteration.

The first objective was successfully achieved as demonstrated by the GUI shown in Figure 39 within the Methods section. This software is fully capable of analyzing multiple patients with an unlimited amount of glucose data and has been proven successful in overall lowering average glucose levels with the suggestion of different basal rate patterns. The tools developed within this dissertation can be utilized by diabetic supply companies with the further development of current and prospective software that are utilized within current and future Insulin pump systems paired with continuous glucose monitoring systems. The results shown within this dissertation have been validated by the validation patient through the testing and implementation of suggested basal rates in a real-life scenario, providing real-time, beneficial feedback along the way. The second objective involved predicting the glucose response of the suggested changes and presenting them to a patient in a user-friendly way, ultimately allowing them to make more informed decisions with basal rate adjustments and feel comfortable doing so. The current software conducted analysis looking at the before and after comparison of important factors such as average glucose levels as well as the time spent both inside and outside of the patient's pre-defined target range.

7.2 FUTURE WORK

In the future, the initial framework presented in this dissertation could be continuously developed and more analyses conducted in order to help promote further discussion and research in basal optimization, with the hope of collaboration of a multi-disciplinary team of researchers,

clinicians and diabetic supply companies. Future ideas and goals for program improvement are as follows:

1. Add and model multiple types of Insulin and their associated drug profiles for a wider range of patient eligibility.

2. Implement the ability for a patient to define various lifestyle changes with both certain days as well as certain time periods for a more accurate and beneficial basal rate suggestion.

3. Implement the ability for a patient to enter bolus Insulin deliveries as well as carbohydrate consumption.

4. Implement an algorithm to automatically detect and removal mealtime bolus effects, as well as extreme glycemic spikes due to various lifestyle events.

5. Implement a feature to extract all numeric data, such as predicted basal rates with associated glucose levels, so the patient can easily see what changes are being suggested with each time-step.

6. Collaborate with clinicians as well as diabetic supply companies in order to enhance various features already present with the algorithm, with a stronger clinical perspective.

7. Collaborate with diabetic supply companies to conduct a real, live study with actual patients with the intent for them to actually implement the suggestions in basal rates.

8. Increase the total number of real-live patients within the simulation database.

The suggestions and enhancements above will help improve the software and algorithms within, as well as the overall efficiency and accuracy of the program itself, ultimately making it a

valuable tool for type 1 diabetics. Being able to conduct further studies with an increased amount of live patient data, especially with a clinician's perspective, will only help further the discussion and innovation in optimizing basal rate patterns in an Insulin pump system.

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VITA

Lauren Ansley Smith was born on October 26, 1995, in Conyers, GA to Dwayne and Lori Smith. Growing up right next door in Covington, GA, Lauren was raised the biggest Tennessee fan and had a dream of being in the Pride of the Southland marching band one day. In 2014, Lauren started her journey at UTK as a member of the Pride of the Southland and began her undergraduate career. Lauren graduated with her Bachelor of Science degree in Biomedical Engineering at the University of Tennessee, Knoxville in 2019, where she transitioned straight into graduate school, earning her master's degree in biomedical engineering along the way. Lauren will graduate with a Doctor of Philosophy in Biomedical Engineering with a concentration in Biomechanics this May 2024.

After graduation, Lauren will apply both the hard and soft skills learned throughout her time in graduate school, or even the many life-learned lessons in band, and decide to use her skills to help others in some way. She is beyond grateful for the endless support and pride expressed by my family and closest friends.