Recurrent Neural Networks and Prediction of Teenage Type 1 diabetes Blood Glucose Values in Wisconsin

I. Literature Review:

Type 1 diabetes is a growing problem among young Americans. With 1.5 million Americans facing this issue and an increasing per capita incidence, type 1 diabetes care is key to retaining a healthy populace (*National diabetes statistics report 2020*, 2020). Type 1 diabetes is not only becoming a more pervasive issue, but the cost to uphold current care techniques results in excessive health care spending. As of 2019, over 10% of International healthcare spending was spent solely on diabetes, with American diabetes care making up 43% of total spending (*IDF Diabetes Atlas 9th edition 2019 ,* 2019)

Type 1 diabetes is an autoimmune disorder where the immune system attacks beta cells in the pancreas. The beta cells in the pancreas synthesize and secrete insulin through the process of glucose-stimulated insulin secretion. However, since the immune system destroys type 1 diabetics' beta cells, their insulin synthesization and secretion are lacking, resulting in hyperglycemia. Hyperglycemia is when someone's blood sugar is abnormally high, with symptoms developing when blood glucose exceeds 200 mg/dL (*Hyperglycemia in diabetes*., 2020) . Eventually, once the type 1 diabetic has had type 1 diabetes over an extended period, typically a number of years which varies for each individual, they become entirely dependent on artificial insulin to maintain their blood sugar and avoid moments of high and low blood sugar. Diabetics measure their management of blood glucose through the use of a1c. A1c is a benchmark used to measure average blood glucose levels over the last 3 months. A1c is measured by finding the percentage of hemoglobin, a protein in blood, that is surrounded by sugar, typically higher in diabetics (*All About Your A1C*, 2018). When type 1 diabetics incur more hypoglycemic and hyperglycemia excursions, this percentage increases, causing their average blood sugar (a1c) to increase.

According to the Centers for Disease Control and Prevention, teenagers have the highest a1c levels from any age group (Miller et al., 2015, p.971). Greater a1c levels are primarily due to the critical process in every teenager's life: puberty. During puberty, teenagers secrete testosterone and estrogen from the pituitary gland. Both testosterone and estrogen decrease the body's insulin efficiency (Moller et al., 1991). When people with type 1 diabetes undergo puberty, their body goes through the process of hyperinsulinemia in order to counteract the worsened insulin efficiency their body faces during puberty. Hyperinsulinemia means that the body releases an abnormally high amount of insulin. However, since type 1 diabetics cannot undergo hyperinsulinemia, their blood sugars tend to increase as their body becomes more resistant to insulin. Since type 1 diabetics tend to be younger than the average type 2 diabetics, type 1 diabetics need to maintain good diabetes management to minimize chances for future complications due to type 1 diabetes.

Type 1 diabetes can create more complications the longer one has type 1 diabetes. Since current techniques are not as effective as the pancreas in managing a1c, a type 1 diabetic's increased a1c can cause several issues later in life. According to the United Kingdom National Health Service, type 1 diabetics are at significant risk for diabetic retinopathy. They can prevent retinopathy by better managing blood glucose levels, cholesterol, and blood pressure. Retinopathy is diagnosed in several different forms: background, pre-proliferative, and proliferative. In background retinopathy, tiny bulges in the back of the retina form, causing slight bleeding in the soft tissues. In pre-proliferative retinopathy, the bleeding becomes worse through poor blood pressure. Prolife (Prevention-Diabetic Retinopathy., 2018) rative retinopathy is when the damaged tissue scars and new blood vessels become weaker. The retina is tissue in the back of the eye that receives light and converts it into neural signals, which our brain converts to sight. Since scar tissue is formed in the retina due to retinopathy, it causes a spot in the retina, which cannot convert light to a neural signal and leads to a black dot in a person's eyesight. Also, in certain cases, type 1 diabetes can cause neuropathy, which is damage to the kidney. Unregular blood sugars can damage the kidneys' blood vessels and hinder its ability to clean blood. There are several more complications; however, the ones previously mentioned are the most common and dangerous. While diabetes can cause complications, it can also cause immediate danger. Type 1 diabetes makes hypoglycemia and hyperglycemia much more common, sometimes resulting in death. In 2016, over 1.5 million diabetes-related deaths resulted from hyperglycemia (Diabetes [fact sheet], 2020). Type 1 diabetes is a dangerous disease that comes with the chance of many complications if one survives it. Due to its severity, type 1 diabetics must maintain adequate blood glucose levels to avoid retinopathy, neuropathy, and death due to hyperglycemia.

Due to the numerical nature of type 1 diabetes management, the use of statistical models and innovative computer analysis is the most beneficial way to prevent hyperglycemic and hypoglycemic excursions. Most type 1 diabetics today use simple methods to measure and monitor their blood glucose levels. These methods generally include the use of a blood glucose monitor and a poker to feed to the blood glucose monitor. However, in recent years, diabetes management has revolutionized. In 1999, Medtronic invented the continuous blood glucose monitor (CGM) and forever changed how diabetics care for their diabetes. Today, there are more options for people to use CGMs, the most popular being Abbott with the Freestyle libre and Freestyle libre 2, Dexcom with the G6, Medtronic with the Guardian connect and Guardian sensor 3, and Senseonics with the Eversense. All have different statistics but still output a continuous number with five-minute intervals (Continuous Glucose Monitors). With the advent of CGMs, diabetics have better understood the patterns behind their blood glucose levels and can more easily manage their diabetes. In recent years, the medicine industry has moved towards collecting larger amounts of data, which technology has made possible. In the case of type 1 diabetes, the CGM's advent has allowed doctors to collect more data easier and made it possible to improve diabetes care. Big data is exceptionally friendly to neural networks and machine

learning. They take large amounts of data and try to create a model to analyze such data. A simple mathematical model is not able to predict it and would need a very complex solution if one exists. Machine learning and neural networks are perfect for predicting blood glucose numbers due to the availability of data and the subject's complex nature. However, the use of neural networks and machine learning is not new to the prediction of blood glucose numbers in diabetics, yet, there is no specialization in this crucial aspect, resulting in a lack of efficiency in diabetes care. In order to maximize our ability to prevent deaths and complications, a more specialized approach is required. Current research in the use of machine learning to predict blood glucose values in type 1 diabetics is fairly limited. Mostly because large amounts of data are difficult to access and research. One such study, by Dr. Martinsson, used a LSTM recurrent neural network to predict blood glucose values in a variety of subjects. In Dr. Martinsson's study data was collected through the Ohio T1DM database (Martinsson, 2020). This database does not focus on a particular age group, when specialization may be required. Hence the difference between this research paper and Dr. Martinsson's. Other current research varies in methods of prediction and datasets. Other popular methods will be discussed in the methodology section.

II. Methodology:

In order to predict the blood glucose levels in teenage type 1 diabetics in Wisconsin a quantitative design-based research was conducted. The goal of the research is to create an operational and accurate recurrent neural network. To predict blood glucose levels in Type 1 diabetics, a significant amount of data is required to maximize accuracy. Since recurrent neural networks are not new to type 1 diabetes prediction, this study focuses specifically on teenagers ages 13-19, in Wisconsin. The measure of accuracy is based on the comparison between the recurrent neural network's predicted blood glucose numbers and the actual blood glucose numbers from the study participants. Once graphed, a line of best fit will be taken and measure the slope. If perfectly accurate, the line of best fit will have a slope of one, indicating a perfect linear relationship between predicted results and given results. The study participant used Novolog for all insulin injections, consisting of basal and bolus injections, throughout the day. The difference between basal and bolus injections are fairly simple. Basal injections are small regular injections used to counteract the natural rise of blood glucose levels in type 1 diabetics. Bolus injections are irregular injections used to correct blood sugar after eating. Once any person eats food the body digests the carbohydrates and transfers them into sugar for the body. In normal people, sugar is regulated through the use of insulin, hence the use of bolus injections. Novolog is a short acting insulin with a peak effectiveness around 40-50 minutes in, and a continued tail 3-5 hours after initial injection. The participant used an omnipod for daily insulin injections of both basal and bolus. Data collection and processing will be further analyzed in the next paragraph.

Data collection and processing:

Data was collected using a program called Tidepool, Tidepool is an app available to the public for download. It allows users to upload data from their Continuous Glucose

Monitor (CGM). As discussed before, the CGM records blood glucose numbers continuously in periods of 5 minutes. However, the CGM sensor must be replaced every 7-10 days leading to gaps in the data. In order to work around this issue, the missing data was omitted from the final database. Tidepool allows data to be downloaded and collected so that it can be imported into the TensorFlow recurrent neural network. Additional data was collected on daily basal and bolus injections using the Omnipod Personal Diabetes Manager (PDM). TensorFlow is a deep learning program developed by Google, that allows the researcher to edit and run the predictive algorithm. Data was then split into three training groups, which is described later in the Recurrent Neural Network section.

Deep Learning Method:

When deciding how to analyze the data the researcher has many different options, with the advent of big data, a deep web of options have emerged from deep learning. When considering prediction, the researcher needs an option that learns on it's own. The researcher initially planned to use a supported vector machine (SVM). A support vector machine takes two classes or groups of data and finds a separating line or hyperplane to follow the general trend of that data. This is done by drawing support vectors from the two nearest differing data points from each class of data. Typically used as classification or regression telling whether this input is most likely to be this or that. Therefore, use of a support vector machine would not work, as classification is not descriptive enough and does not predict a blood glucose number, but rather a range. In addition, the researcher is searching for a single output, and not an estimation range that classification techniques provide. Other similar options include random forest and decision tree classification techniques but were quickly discarded due to their similar use as support vector machines. Therefore, a multilayer recurrent neural network was used, because it can predict an integer value and does not rely on classification techniques.

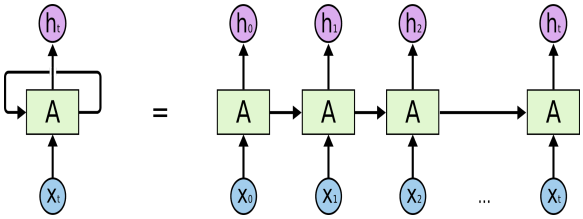
Recurrent Neural Network:

A recurrent neural network aims to emulate a neuron to create artificial learning. It takes an input value and outputs a prediction. In this case, it takes a blood glucose value and outputs a blood glucose value at the end. A recurrent neural network creates a network of many neurons to make a prediction. It does this by assigning each neuron a weight and a bias. The weight and the bias of each neuron determines whether the neuron will fire or not based on an activation function set by the researcher. However, when humans make decisions they use memory to make a better decision, which neural networks aim to repeat by making it recurrent. When a neural network is recurrent, the initial prediction goes back into the A cell (Figure 1) in order to add short term memory to the next prediction, and therefore learn. This process is called back propagation, which is when the initial prediction is looped back into an earlier layer of the recurrent neural network to adjust the weights and biases to then create a stronger prediction. To adjust the weights and biases a loss function is defined. The loss function selected used a negative log likelihood function based on the Gaussian probability function (seen below).

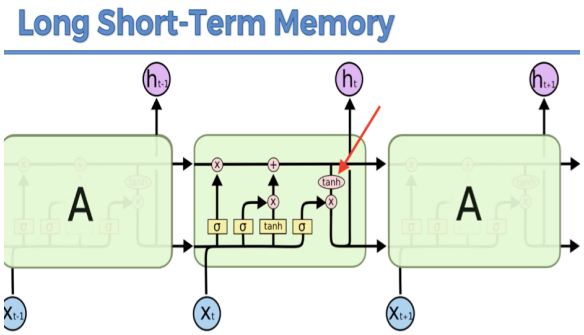
$$\mathcal{L} = \frac{1}{k}\sum_{i=0}^{k} -\log\left(\mathcal{N}(y_i|\mu_i, \sigma_i^2)\right)$$

In this case, k is the iterations, y_i is the actual value, μ_i is the mean, and σ_i is the standard deviation of x_i input values.

To get the recurrent neural network to analyze and process the data it must learn in a supervised manner, meaning it must be checked by the actual values or target data, similarly to the SVM. Therefore, data must be classified into 3 groups: a training set, a validation set, and an optimization set to create enhanced hyperparameters. In this study, data is split so that 60% makes the training set, 20% the optimization set, and the last 20% for improving hyperparameters. Recurrent neural networks take the initial 60% of data and create an initial prediction and return that prediction to create an even better one. Below is a diagram of a recurrent neural network, each cell labeled with an A is a long-short term memory cell (LSTM cell)$_2$, and the x_t and h_t values are weights adjusted by the recurrent neural network, with t representing the number of iterations and h_t being the adjusted weight. A series of these neurons are connected to work through a decision making process.



(figure 1)

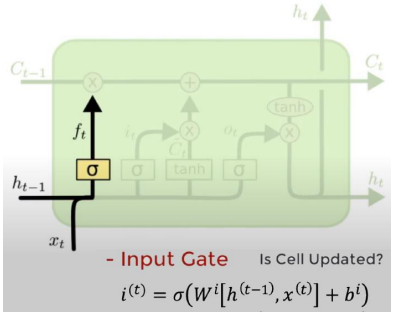


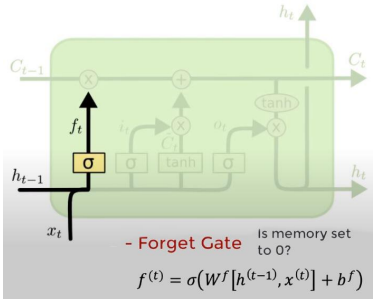
(figure 2)

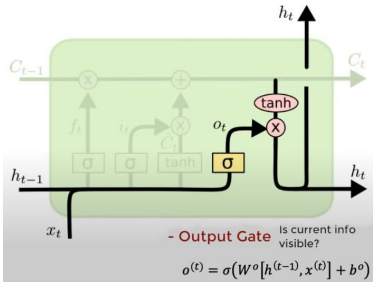
Long-Short Term Memory:

Furthermore, the recurrent neural network relies on long short term memory (LSTM)$_2$, in order to combat the vanishing gradient problem and emulate long term memory. The vanishing gradient problem occurs when changes to the weights of the variable, or in other words their importance, become so small they do not change it at all. This is an issue as since the weights no longer change, the recurrent neural network stops learning. The work around for this is LSTM, which basically allows the program to read, write, or replace the weights using a gated mechanism. Recall weights are the importance of certain aspects of information, such as carbohydrate intake, or insulin intake. The gated mechanism is defined by three gates, the input gate$_3$, the forget gate$_4$, and the output gate$_5$. Each gate uses sigmoid functions defined by their weights and biases to determine which gate should trigger. If the input gate is triggered the weight is adjusted accordingly, if the forget gate is triggered the altered weight is set back to it's default value, and if the output gate is triggered the adjusted weight is outputted. All of this allows the recurrent neural network to continue to learn, and prevents any glitches or errors due to the math involved. This is useful for blood glucose predictions because it allows the

machine learning algorithm to better catch the underlying trends and create a better guess once one of these trends begin. Such trends typically occur after eating food or exercise when blood glucose becomes erratic.







(from left to right, figure 3, figure 4, figure 5)

Recurrent Neural Network Final Structure:

In order to accurately predict blood glucose values, the researcher used a similar recurrent neural network to Dr. Martinsson's paper (Martinsson, 2020). The recurrent neural network has multiple layers to create predictions that get more accurate the more the recurrent neural network's weights change. The recurrent neural network, as mentioned, uses an activation function to decide what neurons are fired, in this case the chosen activation function is pictured below. Below, h_t is the prediction value, tanh is hyperbolic tangent, *W* and *U* are weight matrices, x_t is the input value, h_{t-1} is the previous prediction, and **b** is the bias associated with the specific neuron.

$$\mathbf{h}_t = \tanh(W\mathbf{x}_t + U\mathbf{h}_{t-1} + \mathbf{b})$$

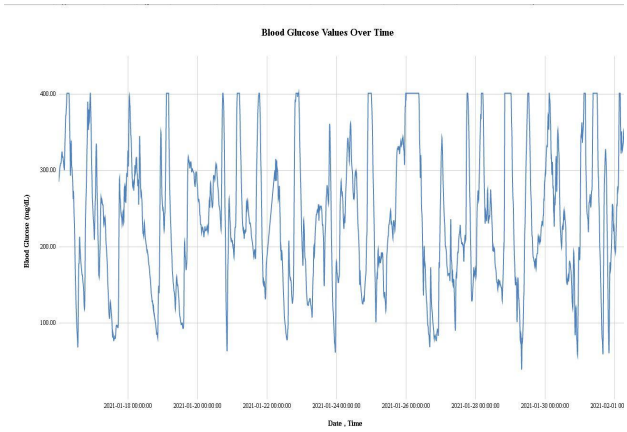
The network architecture consists of several layers, 2 hidden base layers, 512 LSTM units, and 1 output node. The two hidden base layers consist of 216 and 512 neurons respectively. The following is standard, and the exact numbers are not particularly important, except for replication. The recurrent neural network uses an adam optimizer with a batch size of 1024 units, a learning rate of 10^{-3}, and early stopping criterion to 20 epochs. The structure of this neural network was based off of another researcher's work in the field, due to it's success. This previous success helped speed up the design of the recurrent neural network, and allowed the researcher to focus on optimization towards teenage data.

III. ***Results:***

Initial Data Collection:

Initially 27,642 data points were collected from October 25th, 2020 to February 1 st, 2021. All data points were collected from one participant. The selected participant was 17 years old during the time of research, and has had type 1 diabetes for over 14 years. Therefore, the participant is past the initial insulin honeymoon phase where the body still produces insulin. For the purpose of this research data was restricted to a two week period from,

January 18 th, 2021 to February 1 st, 2021[6]. In addition, the participant's a1c was calculated as recurrent neural networks in other studies tended to have more difficulties with higher a1c values. In this case, the participant's a1c was 8.77, which is elevated. This two week period was chosen to match other research in this field and compare the results. As mentioned in the methodology section, gaps in the data due to CGM changes were omitted from the final dataset leading to a final dataset of 4634 data points, as shown in figure 6. This dataset was exported through Tidepool into a spreadsheet, and then compiled for analysis in TensorFlow. As shown in figure 6, any values over 400 are truncated and lead to these plateaus in the data. The implications of this will be discussed in the limitations section of the discussion.



(figure 6)

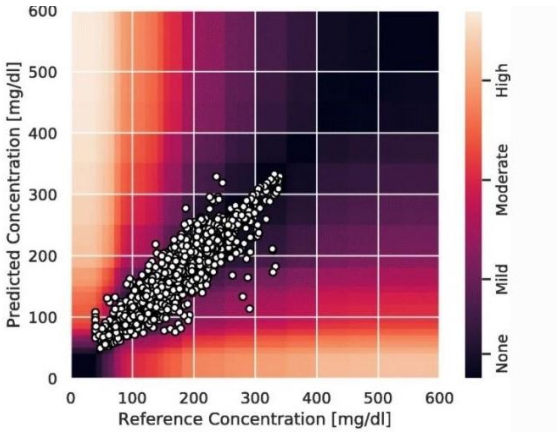
Recurrent Neural Network Performance:

The recurrent neural network's performance was measured using Root Mean Squared Error (RMSE).

$$RMSE = \sqrt{\sum_{i=1}^{n} \frac{(\hat{y}_i - y_i)^2}{n}}$$

Where n is the amount of predicted values, $\hat{y}_i$ is the predicted value set, and y_i is the actual value set.

The use of RMSE is typically used in machine learning to describe the accuracy of the trained recurrent neural network. The issue with RMSE is deciding what is an accurate value. Since that is relative based on other prediction methods on accuracy, this research will compare the RMSE of Dr. Martinsson's paper due to their relatively similar recurrent neural networks. Essentially the RMSE, details the distance between the actual value and the predicted value, similar to the distance formula. The neural network outputted an RMSE of 21.68. In Dr. Martinsson's paper he denotes the RMSE as he changes the number of LSTM modules. For the purpose of comparison, the RMSE chosen was correlated with 512 LSTM modules as this recurrent neural network had that amount. Compared to Dr. Martinsson's RMSE of 20.2 , means that this researcher's recurrent neural network was 7.33% less effective at predicting blood glucose values. In addition, the recurrent neural network created a surveillance error grid for preparation for eventual clinical use. The surveillance error grid allows doctors to assess the risk of trusting the recurrent neural network's prediction. The surveillance error grid is shown in figure 7.



(figure 7)

The surveillance error grid directly compares the predicted values and the actual values. If every value was predicted perfectly, the slope of the graph would be 1. However, the recurrent neural network is not perfectly accurate. As seen in figure 7, it particularly struggles with values above 250 mg/dl. Indicating that this recurrent neural network would do better with patients with a lower a1c.

IV. Discussion:

Conclusion:

The objective of this study was to create an accurate predictive model to help prevent hypoglycemic, and hyperglycemic excursions. Differing from other papers by providing single integer outputs, and 2 sources of error. Since accuracy is relative to the field of study, to gain an understanding of what the RMSE means it was compared to a similar paper by Dr. Martinsson (Martinsson, 2020). Comparing the two RMSE and using standard error calculation to find the percentage error, it is clear that this researcher's recurrent neural network was statistically less accurate. Since both recurrent neural networks have very similar architecture and very different data processes it suggests that the cause for this error is not due to the machine learning method. However, the reasons for that will be discussed later in the limitations section. Furthermore, since the RMSE indicates a significantly poor result, it is safe to conclude that any practical use of this prediction method will require more improvement. In addition, because of the variance of blood glucose after eating it is preferable for patient's to have a lower a1c to benefit from this predictive method.

Limitations:

Several limitations hindered the recurrent neural network leading to inconsistent results, as seen in figure 7, and a worse than expected RMSE value. To begin, the dataset created was not optimally suited to create accurate predictions. This is in large part due to the overall lack of diversified participants, and low dimensional data. The lack of diversified participants creates a problem where the recurrent neural network learns to predict the given dataset, and not the general problem. This creates huge problems for this research, because the end goal is to use it in a practical field. Additionally, the lack of dimensional data leads to extra inaccuracy. This is most in part due to the great variable movements to blood glucose after a person eats or doses, as well as, the dawn phenomenon, which is also more common in teenagers. The dawn phenomenon is where a type 1 diabetic's blood glucose rises during 3 a.m. to 8 a.m.. This is because during the dawn hours of the day, the body uses extra glucose and secretes hormones that makes the body more resistant to insulin to prepare for the upcoming day. This dawn phenomenon creates a difficult situation and is why the recurrent neural network does not just struggle in the higher or lower blood glucose ranges, as seen in figure 7, but also during

the 100 mg/dL to 300 mg/dL range. This variability from external sources leads to late responses to increases or decreases in blood glucose. To combat this more dimensional data collection is recommended, this will be discussed in more detail during the future research section.

Additionally, CGM's are not perfectly accurate, especially in the lower and upper regions of blood glucose. This is compounded in the 400+ mg/dL range of blood glucose because Dexcom does not read values above 400 and instead limits them to 401 mg/dL. This results in heightened inaccuracy during higher predictions, and makes the prediction method better for certain individuals based on their a1c. Furthermore, Dexcom's G6 CGM has reported inaccuracies because of its own 15 minute lag commonly found in devices that use interstitial fluid readings. All of these factors compound in accuracy, and create additional problems for the recurrent neural network to predict.

Finally, while data collection is the most clear complication in this study, it is fair to say that perhaps this style of recurrent neural network is not the appropriate method of prediction. This is primarily because while the RMSE in this study and Dr. Martinssons are statistically different for 512 LSTM units. Dr. Martinsson's RMSE with 21.05 with not LSTM units, and this study's RMSE of 21.68 with 512 LSTM units. These comparative RMSE values are statistically equivalent because of their 2.99% error. Since these RMSE values are statistically similar, they suggest that perhaps an architectural change to the recurrent neural network, or move away from a recurrent neural network could lead to better results.

Future Research:

The goal of this research, as previously stated, is to create a predictive blood glucose model to prevent hypoglycemic and hyperglycemic excursions. The eventual objective of this research was for wider implementation in clinical or personal settings. Any future research in this topic should go towards improving the overall prediction methods, and mitigating external factors. To mitigate external factors, future research must focus on multidimensional data, greater sample size, and more accurate initial blood glucose readings. Future research should begin with looking for better methods of prediction, as suggested in the limitations section. Future research on using recurrent neural networks should aim to reduce external factors by requiring participants to collect daily bolus, basals, carbohydrate intakes, and times of each input. Future research will have to decide whether to continue with CGMs for a greater quantity of data, or traditional finger prick glucometer tests for more accurate data.

Final Conclusion:

To end, this study finds that recurrent neural networks need not to specialize towards different age groups to better predict blood glucose numbers. Additionally, it is recommended that anyone looking for the practical use of this predictive method should already have a good a1c value.

Word Count: 4210

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