Modeling Type One Diabetes with a Linear Response Function Based Model

Physics Honors Thesis

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Abstract

Type one diabetes occurs when the pancreas stops producing glucose reducing insulin. Regular injections of exogenous insulin are required for survival but the amount is difficult to determine to maintain optimal blood glucose levels. The goal of this research is to create a new blood glucose model that can predict future blood glucose levels in response to carbohydrate and insulin stimuli. We use a linear combination of kernel functions and use least squares to find the response functions. This simple model is able to fit the existing data as well as existing models but needs refinement so it has some predictive value. Future research could add biological knowledge and nonlinearity to this model.

1 Introduction

1.1 The Blood Sugar Control System

The body possesses many systems that regulate chemical concentrations in the blood. One of the most important systems controls blood sugar levels. Most of the cells in the body use glucose as fuel to operate[3]. When food is

eaten and digested, blood glucose rises. Then the pancreas receives signals to release insulin into the bloodstream, letting cells use the glucose for growth and energy. The liver also plays a role in glucose regulation by storing glucose in glycogen when insulin is detected and releasing it between meals (e.g. at night). In a type-one diabetes patient, we simulate this by delivering a burst of insulin in the first bite of food. Then a steady stream of insulin is released to control blood glucose.

1.2 Diabetes Description

Diabetes is a disorder that drastically impacts the body's ability to handle glucose with insulin. The causes of diabetes are various or unknown but the primary result of the disease is persistent elevated blood glucose levels. For people with diabetes, the pancreas does not automatically release the correct amount of insulin to keep control of blood sugar, instead, the pancreas either produces little or no insulin, or the cells do not have an appropriate response to released insulin. Thus, blood glucose will increase and is excreted through urine. Although the blood glucose level is high, cells cannot use blood glucose for growth and energy, and the body loses its main source of fuel. The classic symptoms of untreated diabetes are weight loss, polyuria (frequent urination), polydipsia (increased thirst), and polyphagia (increased hunger). Its long-term complications include to damage to blood vessels, eyes, nerves. There is no known cure for diabetes and management is usually essential for survival. It is divided into three major categories: type 1, type 2, and gestational. Gestational diabetes is a temporary resistance to insulin during pregnancy that affects approximately 18 percent of pregnancies [1]. Type 2 diabetes is the most common kind of diabetes and occurs the cells in the body become resistant to insulin. Type 1 diabetes occurs when the body's immune system destroys the insulin producing cells of the pancreas [4]. Injections of exogenous insulin are required to survive in the case of type 1 diabetes as toxic levels of sugar will otherwise accumulate.

2 Model

Our model takes in tuning parameters, insulin administered, and carbohydrates and outputs a predicted blood sugar value at a certain time. It uses response functions to predict the impact of a certain quantity of insulin of

carbohydrates on the blood sugar level. For example, the response function, $F^C(t)$, gives the change in blood sugar for one gram of carbs eaten. Each response function is in turn divided into multiple kernel functions. The tuning parameters are the weights for each kernel function. Each individual kernel function should look like a step function that is perhaps smoothed. The total response function should look like a smoothed step function that is zero for times less than zero (no influence before stimulus). The transient behavior of the blood sugar level is determined by the intermediate values of the response function. This is the primary behavior that we would like to predict because low or high blood sugar spikes are uncomfortable and often dangerous.

2.1 Detailed Description

Each response function (for carbs, insulin, and liver) is in the following format.

$$F(t) = \sum_{i=1}^{m} a_i \phi^\sigma(t - t_i) \tag{1}$$

Where ϕ^σ is a kernel function and m is the number of kernel functions used to make a response function (typically 20). We use the probability density function of the Gaussian as the Kernel estimation for the derivative of the response function $F'(t)$. Thus, the kernel function for response function $F(t)$ is the cumulative distribution function of the Gaussian.

$$\phi^\sigma(t) = \frac{1}{2}(1 + \text{erf}(\frac{t}{\sqrt{2}\sigma})) \tag{2}$$

σ determines the time scale of the kernel function. Our function accepts data in $m \times 2$ matrices. Each data point is a row with a time and a value. There are six data matrices: the insulin matrix, the carb matrix, the liver matrix, and their corresponding coefficient matrices. Consider the carb response function. A^C is the coefficient matrix for carbs shown below.

$$\begin{pmatrix} \tilde{t}_1^C & a_1^C \\ \tilde{t}_2^C & a_2^C \\ \vdots & \vdots \\ \tilde{t}_m^C & a_m^C \end{pmatrix}$$

This makes a response function in the following way.

$$F^C(t, A^C) = \sum_{i=1}^{m} a_i \phi^\sigma(t - \tilde{t}_i) \tag{3}$$

It is possible to reformulate it as a convolution of distributions. Convert the data into a distribution with the following identification.

$$A^C \to \mathbb{A}^C = \sum_{i=1}^{m} a_i^c \delta_{\tilde{t}_i^C} \tag{4}$$

Substituting 4 into 3 we get

$$F^C(t, A^C) = \phi^\sigma * \mathbb{A} = \sum_{i=1}^{m} \phi^\sigma * (a_i^C \delta_{\tilde{t}_i^C}) = \sum_{i=1}^{m} a_i \phi^\sigma (t - t_i) \tag{5}$$

The total response function is a combination of the individual response functions. c_i is the amount of carbs given at time t_i^C

$$G(t, I, A^I, C, A^C, L, A^L) = \sum_{i=1}^{n} c_i F^C(t - t_i^C, A^C) \tag{6}$$

Formatting the carb dosage and timing data matrix, C, as a distribution $\mathbb{C}$ as in 4 gives

$$G(t, C, A^C) = \sum_{i=1}^{n} \sum_{j=1}^{m} c_i a_j \phi^\sigma (t - t_i^C - \tilde{t}_j^C) \tag{7}$$

The total response function is

$$G(t, I, A^I, C, A^C, L, A^L) = \mathbb{C} * \mathbb{A}^C * \phi_C^\sigma - \mathbb{I} * \mathbb{A}^I * \phi_I^\sigma + \mathbb{L} * \mathbb{A}^L * \phi_L^\sigma \tag{8}$$

We would like to evaluate the model function at the blood sugar measurement times and minimize the difference between the model and the measurements. Given the measured blood sugar as a function of time, $B(t)$, define a function

$$M(A) = \|G(t, I, A^I, C, A^C, L, A^L) - B(t)\|_2^2 = \sum_k (G(t_k, I, A^I, C, A^C, L, A^L) - B(t_k))^2 \tag{9}$$

Our goal is to use the blood sugar measurement, insulin dosage, and carb consumption data to train the model. The error between the model and actual blood sugar is given by $M(A)$ this corresponds to minimizing M.

2.2 Implementation Details

MATLAB was used to implement the model. For loops in MATLAB are notoriously inefficient so we would like to find a way to complete computations using matrix operations instead of iterations. There are m $\tilde{t}_i$'s and n t_i's that are used in each convolution where m determines the granularity of the response function and n is determined by the number of data values (i.e. insulin doses and times or meal quantities and times). If we create a matrix with entries $W_{ij} = c_i a_j$ and a matrix of all the times in 7 with entries $T_{ij} = t - t_i^C - \tilde{t}_j^C$. The contribution of the carb response to the blood sugar function is then given by $W^{ij}\phi^\sigma(T_{ij}) = \sum_i \sum_j W_{ij}\phi^\sigma(T_{ij})$.

3 Goals for Modeling

The goals of this research is to create a modular model that can be easily expanded and altered to better model data. The objectives are: First, create a model that fits existing data well. Second, see that the response functions are in fact reasonable. Third, predict when blood sugar will spike below or above healthy values.

4 Model fitting

We attempted many tests of the model to predict blood glucose behavior but most were unsuccessful. The base problem was a conflict between the model being able to fit the data and the model having realistic intermediate values. The metric we used to test the model's ability to fit data was the following.

$$E(M) = \frac{\|M(A)\|_2}{\mathcal{F}(\mathcal{B})} \tag{10}$$

where $\mathcal{F}(\mathcal{B})$ is some function to normalize the range of the error metric. Error values should range from zero to one. A value of zero indicates a perfect fit while a value of one indicates a model with little ability to explain blood sugar fluctuations. When evaluating a certain model, it is important to generate control models to judge performance. Two kinds of controls were used in evaluating the data from the model: average and random. An average control model uses a coefficient matrix with columns of contiguous ones.

For example, a daily average (or offset) model matrix is $A_{ij} = \delta_{f(t_i),j}$ where $f(t_i) = \text{floor}(t_i) - \min_k \text{floor}(t_k)$ counts what day t_i is on. Average model matrices were often a part of the model so an additional type of control is also needed. The model matrix was sometimes substituted with random numbers for comparison purposes. We would like to use physical knowledge of the system to add predictive value. Using non-negative least squares (NNLS) to find the response functions makes them monotonic. However, this reduces the freedom of fit and the fit quality according to our metric 10. The full dataset was too large to handle with Matlab's general constrained least squares algorithm. However, the algorithm for non-negative least squares is more efficient and supports larger problem sizes. While the kernel function parameters are constrained to be non-negative, some tuning parameters may not be constrained. For a problem such as

$$\min_{x \geq 0} \|Ax + By - b\|_2 \tag{11}$$

we must convert the unconstrained variables to non-negative variables. Set $y = y_+ - y_-$ The problem 11 is equivalent to

$$\min_{x, y_+, y_- \geq 0} \|Ax + By_+ - By_- - b\|_2 \tag{12}$$

5 Data

We tried several different ways to fit the data. Several types of preprocessing were used to

Table 1: Residual norms and ratios

		All Data		All Data	Lunch Data
	Data Norm	8521.3	With Offsets	2946.2	1049.6
Model Matrix	LS	0.3868	LS	0.9455	0.7495
	NNLS	0.4125	NNLS	0.9699	0.7896
Control Matrices	Random	0.99	Random	0.98872	0.9489
	Average	0.3947			

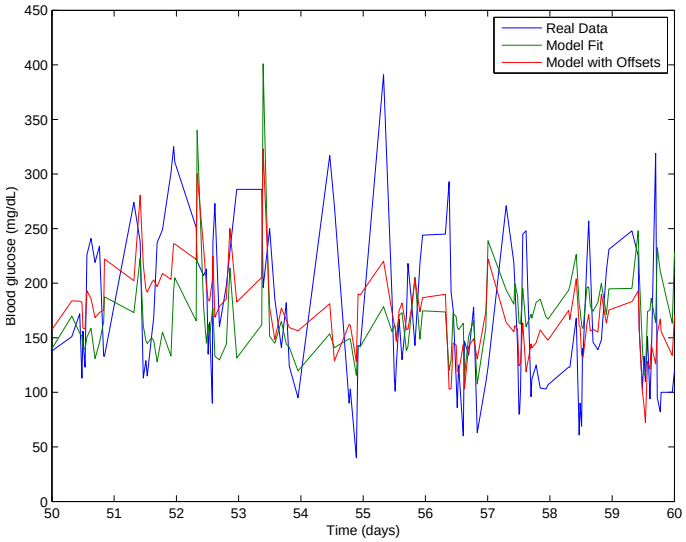

Figure 1: Actual blood sugar values compared with fit data.

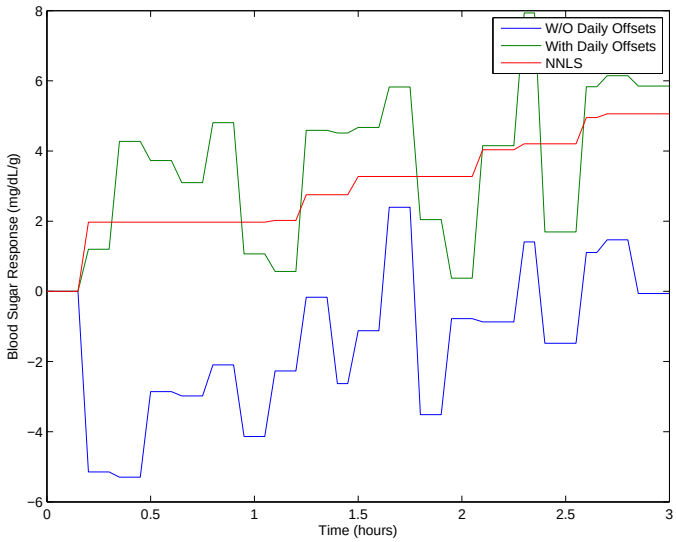

Figure 2: Lunchtime blood sugar response to glucose.

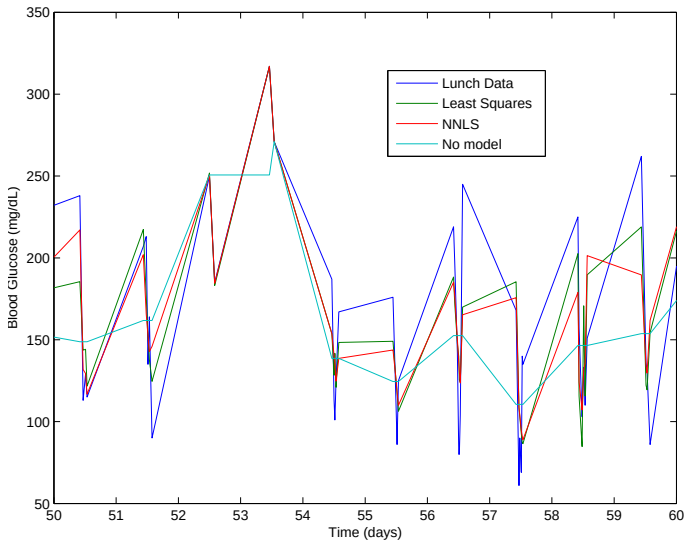

Figure 3: Lunchtime blood sugar data compared to model.

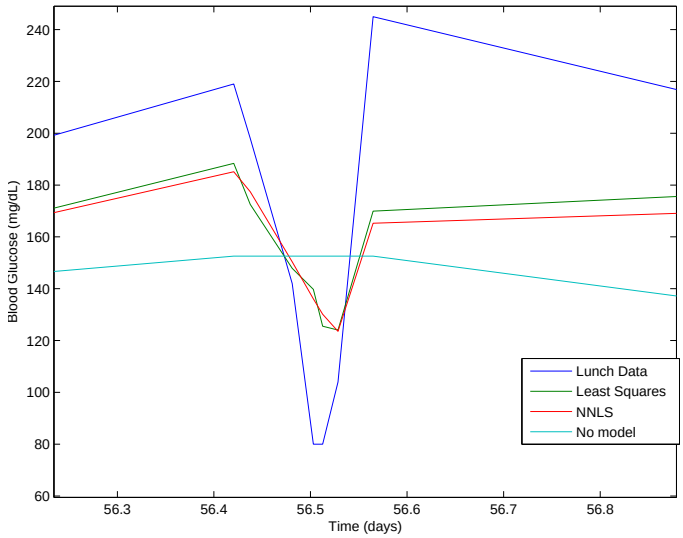

Figure 4: Lunchtime blood sugar data compared to model. (Detail)

6 Discussion

The first use of the model was thought to be successful because the model explained 59 or 61% of the blood sugar data depending on whether or not non-negative least squares was used. This appeared to be very good compared to the 1% explained by random chance. However, an average explains 61% of the data as well. Examining the fit showed that the model was quite flat and not fluctuating with the data. Another attempt tried to use daily offsets to improve the model. However, the models only explained 3 or 5% of the data compared to 1% for random. The most promising results were found when fitting to a lunchtime subset of the blood sugar data. In this case, the daily offsets were essential to the model and the baseline model was the daily average model. The model fit with least squares explained 25% of the data and 21% when fit with non-negative least squares. This compares favorably to the 5% explained by the random matrix. An example of the plausibility of the model is explored in figure 2. The response function is nonsensical when daily offsets are not utilized. The function goes negative which suggests that glucose administration decreases blood glucose levels, an obviously unphysical result. When daily offsets are used, the function does not go negative but it does oscillate which is again unphysical. With non-negative least squares, a reasonable, monotonic response function is obtained. From figure 4 it is clear that the model is able to follow some of the data and the fitting method does not appear to change much. However, the NNLS fit is less oscillatory which is a good indicator that NNLS reduces overfitting. The success of this model is in the midrange of the models considered in [2]. Many of these models are more sophisticated. Some use multiple compartments which account for different reservoirs of glucose in the body while our model only has one compartment, the bloodstream. More compartments could be added but more data would be needed to train the model. The model did not have enough predictive value to forecast dangerous blood sugar events.

7 Conclusion

This research was largely successful in creating an algorithm capable of explaining blood sugar fluctuations of a type 1 diabetic. Several factors tended to improve the plausibility of the model. Due to uncertainties and complexities in biological systems, models tend to drift away from reality without

corrections. This was incorporated into the model by adding daily offsets. Another problem is that the calculated dose response of both glucose and insulin were unrealistic (i.e. negative or non-monotonic). This was the result of 'overfitting' and the problem was reduced by using non-negative least squares to fit the model matrix. With these adjustments, we were able to fit the data as well as some existing models. The model was able to fit approximately 21 percent of the data which is in the midrange in the models created in [2]. However, our model is much simpler and does not use as much biological information and has greater potential for improvement.

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