Glucose Concentration Simulation for Closed-Loop Treatment in Type 1 Diabetes

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Abstract—People with Type 1 diabetes do not produce sufficient insulin that would regulate the increases in blood glucose following food intake. Currently many diabetic patients use blood glucose monitors and knowledge of what food they have eaten to administer appropriate doses of insulin. The insulin injections may be done manually or with an automated pump device. A closed-loop control system based on automatic monitoring of blood glucose levels and automatic administration of insulin would ease the burden of self-observation and treatment for many people. However, difficulties and reliability have limited widespread clinical application. The purpose of this project was to develop a simulation of blood glucose concentration in the body based on food intake, rates of digestion, rates of glucose concentration, and insulin-controlled storage of excess blood glucose into body stores. The simulation was developed in LabView. The program simulates the net flow of glucose into and out of the blood. Food intake is selected and converted into glycemic load as it enters the digestive system. Then glucose is gradually digested and enters the blood system, which increases the blood glucose concentration. Consumption of glucose by body tissue decreases the blood glucose concentration. Based on insulin concentration in the blood, excessive blood glucose can be moved to body stores, such as liver, fats and muscle. This simulation should be useful toward development of closed-loop control systems for diabetes management.

Index Terms—glucose monitoring, glycemic load, insulin, LabView, physiology, simulation.

I. Introduction

Currently many diabetic patients use blood glucose monitors and knowledge of what food they have eaten to administer appropriate doses of insulin. The insulin injections may be done manually or with an automated pump device [1]-[3]. A closed-loop control system based on automatic monitoring of blood glucose levels and automatic administration of insulin would ease the burden of self-observation and treatment for many people. However, difficulties and reliability have limited widespread clinical application. Following food intake digestion converts the food into fuel molecules, such as glucose and fatty acids. The type of food affects the rate of digestion, with sugars and low-fiber carbohydrates being digested faster than foods with high fiber content or high fat content [4]-[5]. The digestion generated fuel molecules of glucose and fatty acids are absorbed from the small intestine into the blood stream at a rate primarily determined by the supply of fuel molecules, not on the need to meet body consumption or negative feedback system to maintain homeostasis of blood glucose concentration. Thus following food intake and digestion, the rapid rise in glucose absorbed into the bloodstream disrupts homeostasis, leading to a large rise in blood glucose concentration.

The physiological system of negative feedback to restore blood glucose (BG) levels back to homeostasis levels involves glucose sensors and the releases of insulin from pancreatic cells during periods of high BG levels. The insulin acts to have energy storage cells (muscle, liver and kidney) absorb more glucose, thus reducing BG levels back toward homeostasis levels.

Diabetes is a disease that affects the endocrine system. In a healthy human, the endocrine system maintains a blood glucose level by emitting the hormone insulin when needed. Insulin catalyzes the storage of glucose in the form of fat. A person with Type 1 diabetes does not produce insulin causing the accumulation of glucose in the blood, which can cause heart and blood vessel disease, nerve and kidney damage, coma and death [6]-[7]. Currently in the United States there are 29.1 million people that are diagnosed with diabetes and 1.4 million of these people that are diagnosed with Type 1 diabetes [8].

State of the art clinical practice for Type 1 diabetes involves skilled use by the patient of 1) glucose monitor system and 2) insulin pump system [1]-[3], [9]. These systems are separate systems. The insulin pump system is an open loop control system for therapy. The insulin pump system does not monitor blood glucose level, and so cannot automatically determine the dose of insulin to administer. Instead, the patient needs to manually input into the insulin pump system information that determines the dose and timing of insulin injections. To do this, patients need to continually monitor their blood glucose levels; and if the levels are high, inform the insulin pump of this high condition, which will result supplement dose of insulin.

Whenever the patients drink or eat something containing sugar or carbohydrates, they need to calculate the carbohydrate content and inform the insulin pump system, which will result in what the bolus dose of insulin should be according to the carbohydrate contents of the food and beverage. Many patients are unskillful at accurately monitoring the amount and timing of the food or drink they consume. Thus, the insulin pump administers doses of insulin that map poorly
with the rise of blood glucose from food intake. As a result, blood glucose levels are not always managed well, sometimes too high and sometimes too low. For example, patients may accidentally have the pump administer too much insulin that is not balanced by food intake. Thus, a case of hypoglycemia results. After the diabetic patients inform the system of how much [10] they are going to eat, they need help to monitor the actual blood glucose level and automatically adjust the dose when the level goes too high or too low, indicating an error in the prediction of how much they were going to eat or drink.

The purpose of this project was to develop a simulation of blood glucose concentration in the body based on food intake, rates of digestion, rates of glucose concentration, and insulin-controlled storage of excess blood glucose into body stores. The simulation was developed in LabView (National Instruments, Austin, TX). LabView is a high-level programming language with mathematical functions, graphical user interface, and graphing tools, and an intuitive programming style, making it suitable as a platform for biomedical simulations and analysis [9]-[11]. The program simulates the net flow of glucose into and out of the blood. Such simulations would help the development and testing of closed loop systems that may be able to both continuously monitor blood glucose concentrations and administer appropriate doses of insulin. This may lead to improved quality of life for individuals with Type 1 diabetes.

II. Materials and Methods

A. Blood Glucose Target Levels

The goal of the simulation was to mimic the overall physiology. Food intake was an input. The type and quantity of food was used to calculate the glycemic load for that meal. The glycemic load was absorbed over time into the bloodstream from the gastrointestinal (GI) tract. Normal blood glucose concentration is around 100 mg/dL, with a low being below 85 mg/dL. Physicians of the diabetic patient usually have a treatment goal to maintain blood glucose level below 180 mg/dL even after large meals [1].

B. Assumptions Used in Simulation

The following assumptions were used for the implementation of the simulation described in this paper.

1. Glycemic Load = 1 g carbohydrate from glucose
2. Patient maintained constant level of low physical activity during the simulation
3. Patient weight = 62 kg.
4. Patient’s total blood volume = 5 L.
5. Starting/target blood glucose = 100 mg/dL
6. Normal range of blood glucose after a meal = 70 – 140 mg/dL
7. A meal will be mostly digested after about 2 hours
8. 1 unit of insulin = 0.0347 mg
9. The time interval for the simulation was 5 minutes

C. Equations Used in Simulation

First, the intake of food was converted to Glycemic Load (GL) [6]:

\[ GL = F_{gls} \cdot \left( \frac{M_f}{M_i} \right) \]

where \( F_{gls} \) is glycemic load per serving for a type of food, \( M_i \) is the mass of the food eaten, and \( M_h \) is the mass of that food type per serving. The consumed GL was added to the total grams of glucose being stored in the gastrointestinal tract (GI). The unit of GL equals one gram of glucose.

\[ GI_{new} = GI_{old} + GL \]

where \( GI_{new} \) is the new value of grams of glucose in the gastrointestinal tract after eating, and \( GI_{old} \) was the old value before eating.

After eating the amount of insulin to administer was determined based on the GL of the food eaten. The dose was calculated in the simulation as follows.

\[ \Delta I = \frac{GL}{15} - 1.1 \]

where GL is the glycemic load of the food that was eaten. This determined the amount of new insulin to administer, adding to the existing amount of insulin already in the body.

\[ I_{new} = I_{old} + \Delta I \]

where \( I_{new} \) is the amount after administration of the new dose of insulin, and \( I_{old} \) was the amount in the body before administration. The rate of insulin disposal by the body that was used in the simulation was \( \frac{1}{12} \) of \( I \) (the amount of insulin remaining in the body) each 5-minute period. This rate has a time constant of \( \tau \) hour, and most of food would be digested by about two hours. The remaining amount of insulin would be decreased by this amount of insulin disposal.

\[ I_{new} = I_{old} - \frac{I_{old}}{12} \]

Every 5-minute period, the amount of glucose absorbed into the bloodstream was estimated to be \( \frac{1}{12} \) of the glycemic load remaining in the GI.

\[ G_{ab} = \frac{1}{12} \cdot GI \]

where \( G_{ab} \) is the amount in grams of glucose absorbed into blood from GI. How glucose is measured in the blood is not as grams of glucose, but as a concentration, typically mg/dL. Based on the assumption of 5L of blood, the grams \( G_{ab} \) was converted to concentration as follows.

\[ \Delta BG_S = G_{ab} \cdot \frac{1}{5L} \cdot \frac{1L}{1000mg} = \frac{1000mg}{g} \]
where ΔBG is the change in BG concentration from supply. This change in BG was then added to the whole blood glucose concentration levels.

\[ BG_{\text{new}} = BG_{\text{old}} + \Delta BG \]

where \( BG_{\text{new}} \) is the blood glucose concentration after the change, and \( BG_{\text{old}} \) was the value before the change.

The glucose consumed in the brain, muscle and other tissues each day on average was called BMT [7]. For the patient being simulated, the amount of glucose consumed each day by each tissue type, and for the body as a whole was as follows.

\[ BMT = \frac{150 \text{ g}}{\text{day}} + \frac{100 \text{ g}}{\text{day}} + \frac{100 \text{ g}}{\text{day}} = \frac{350 \text{ g}}{\text{day}} \]

Thus, on average, the 62 kg human modeled by the simulation consumed 350 grams of glucose each day. Based on the assumption of sedentary lifestyle and ignoring differences in consumption with the day and night cycle, the average glucose consumed each 5-minutes period was calculated as follows.

\[ BMT5 = \frac{350 \text{ g}}{\text{day}} \cdot \frac{1 \text{ day}}{24 \text{ hr}} \cdot \frac{1 \text{ hr}}{60 \text{ min}} \cdot 5 \text{ min} = 1.215 \text{ g} \]

where BMT5 is the amount of glucose consumed on average during each 5-minute period. As glucose was consumed by the body, the concentration of glucose in the blood would decrease by a proportionate amount. The BMT5 amount was converted to how much concentration of glucose in the blood would decreases each 5 minutes. The total volume of blood was 5 L.

\[ \Delta BG_C = (1.215 \text{ g}) \cdot \frac{1 \text{ L}}{5 \text{ L}} \cdot \frac{10 \text{ mL}}{1 \text{ L}} \cdot \frac{1000 \text{ mg}}{\text{g}} = 24.3 \text{ mg/dL} \]

\[ BG_{\text{new}} = BG_{\text{old}} - \Delta BG_C \]

where ΔBGc was the change in blood glucose concentration due to body consumption.

Between meals, with the lack of new BG from the GI, and the continual consumption, ΔBGc, by the body, the BG levels would drop below healthy levels. During low BG conditions, glucose is restored to the system by release from energy stores in the liver and kidney. The constant LK 11.14 mg/dL represents the amount of glucose added to the blood from the liver and kidney over a period of 5 minutes. This glucose is added to the blood only if the GI glucose availability is below a certain set threshold. The calculation was formulated from a chart labeled “Mechanisms and sources of glucose release into the circulation in the postabsorptive state” [8]. Hepatic contribution was listed as 8.0 µmol/(kg min) and Renal contribution at 2.0 µmol/(kg min). The rates were converted from µmol/(kg min) to mg/dL densities using the molecular weight of glucose (180.1559g/mol) [9] and the human weight of 62 kg. Both kidney and liver additions were summed into a single value.

\[ LK = \frac{8.0 \text{ µmol}}{\text{kg mins}} + \frac{2.0 \text{ µmol}}{\text{kg mins}} = \frac{10 \text{ µmol}}{\text{kg mins}} \]

where LK is the rate of restoration of glucose from the liver and kidney during periods of low BG. The rate was converted to mass per each 5-minute period using the mass of the patient in the simulation.

\[ LK_5 = LK_\text{s} \cdot \frac{1}{5 \text{ L}} \cdot \frac{1}{10 \text{ mL}} = 11.14 \text{ mg/dL} \]

where \( LK_\text{s} \) is the mass of glucose restored each 5-minute period during periods of low BG. This amount was converted to the resulting change in BG for the blood volume of patient used in the simulation.

\[ \Delta BG_{LK} = LK_5 \cdot \frac{1}{5 \text{ L}} \cdot \frac{1}{10 \text{ mL}} = 11.14 \text{ mg/dL} \]

where \( \Delta BG_{LK} \) is the change in blood glucose for a 5-minute period of low BG due to restoration from the liver and kidney. This value was added the the BG concentration.

\[ BG_{\text{new}} = BG_{\text{old}} + \Delta BG_{LK} \]

The amount of insulin, I, in the body would work to decrease the level of BG due by increasing storage of glucose within the muscle, liver and kidney. The estimated decrease in BG for each 5-minute period was related to the amount of I in the body at that time,

\[ \Delta BG_I = I (50 \text{ mg/dL}) \cdot \frac{1}{6} \]

where \( \Delta BG_I \) is the amount of decrease in BG levels due to the work of insulin, I. This amount of change, \( \Delta BG_I \), would reduce the blood glucose concentrations, BG, as follows.

\[ BG_{\text{new}} = BG_{\text{old}} - \Delta BG_I \]

These equations were used in the implementation of the simulation for the prototype discussed in this paper.
conversion was based on the 5 L of blood and a body mass of 62 kg used in this study.

The next step of the simulation reduced BG due to the consumption of glucose by the body, such as by tissues of the brain, muscles, and rest of body. For the prototype the human was considered to have a constant, moderate level of activity and consumption that would reduce BG by 24.3 mg/dL per each 5-minute period [12].

The next step of simulation managed the movement of insulin from the blood to body stores due to the effect of insulin. Body stores would include the liver, muscle, and fats. For the prototype, these storage tissues were considered as a unit. In general, one unit of insulin was considering to reduce BG by 50 mg/dL. For a 5-minute period an estimated amount of 0.17 of 50 mg/dL for each remaining IU in the blood was reduced from BG. This amount was added to the stores.

Insulin has a half-life. This decrease of I in blood was simulated by reducing I by a factor of 0.115 for each 5-minute period [13].

III Results

To test the physiological simulation, the simulation data was compared to the data of a published study entitled “The effects of meal glycemic load on blood glucose levels of adults with different body mass indexes” [14]. The study data used measured blood glucose levels at 15-minute intervals after a high glycemic load meal. The data taken from the simulation is the result of blood glucose levels taken every 5 minutes after eating 350 g of porridge (a food with a high glycemic load). Both data sets were tracked for 2 hours. In Fig. 2 a graph that depicts this comparison. Both data sets output similar polynomials and both remained within the normal range of blood glucose after a meal (70 – 140 mg/dL).

D. Prototype Model of Simulation

The algorithm for the prototype made a simulation pass once each 5 minutes. The interval was based on the relatively slow time frame for the processes of digestion, blood circulation and net glucose movement into and out of the blood.

The first step of the simulation as shown in Fig. 3 was to handle any food intake. Based on the user input of the mass and type of food, a table of food data [6] was used to calculate the number of servings and GL for the meal. Based on the GL the number of insulin units (I) was calculated with GL divided by 15 [1]. To handle small snacks which may barely keep up with the constant glucose demand by the body, the I for a meal was reduced by 1.1 units. This new I value was added to any remaining I still in the blood from the last meal.

The next step of simulation as shown in Fig. 1 was to calculate how much glucose would move from the GI to the blood due to digestion during the 5-minute period. Considering that much of the meal may be digested within about one or two hours, the amount still in the GI was divided by 12 and this amount of glucose was subtracted from the GI and added to the blood. A conversion of grams of glucose to change in blood concentration was calculated [12]. The
Three specific cases were simulated and have their results shown in Fig. 4-6.

The simulation was run for a case of a meal that was eaten at time = 0. The meal consisted of 350 grams of porridge. The simulation calculated and administered the appropriate dose of insulin for this meal. Fig. 4 shows the result of these simulations. During the 2-hour period of the simulation, some glucose entered the blood from the gastrointestinal (GI) tract each 5-minutes as shown by the red trace. Likewise, some glucose moves from the blood to storage based on the action of the insulin as shown by the green trace. The white trace shows the resulting blood glucose (BG) levels. BG was maintained within a safe range with a maximum of about 130 mg/dL, well below the target maximum of 180 mg/dL.

A second simulation was run for the same meal, with no insulin administered. This was to model Type 1 diabetic patient who ate but took non-insulin. The BG levels rose higher to over 800 mg/dL. This high level was much higher than safe target maximum of 180 mg/dL (Fig. 5).

A third simulation was run for a case of a larger meal. The meal consisted of 450 grams of porridge. The simulation calculated and administered the appropriate dose of insulin for this meal. Fig. 6 shows the results of this simulations. The white trace shows the resulting blood glucose (BG) levels. BG was not maintained as well as the smaller meal of 350 grams. BG rose up to about 200 mg/dL. This was much lower than the untreated case of non-insulin (Fig. 5), but a little above the safe target 180 mg/dL. The simulation algorithms need more development to safely maintain BG levels for varying size of meals.

**IV. Discussion and Future Direction**

The simulation results appear to indicate that the algorithm has promise for the closed-loop control of the insulin administration based on the glycemic load of food intake and the blood glucose level. More development of the algorithm and testing is required.
Future work includes extending the time of the simulation to over 24 hours so that a full day’s blood glucose fluctuations can be simulated and observed.

Predictive measurements will later be included in the simulation so that the equation can predict blood glucose due to food intake and can dose insulin before food is ingested, therefore preventing a high glycemic meal from causing blood glucose levels from ever getting too high.

Individual parameters will be part of the user interface in the final phase of the simulation. Users will input values such as weight, height, age and gender and the logic will take these values into account.

The end goal is to use the simulation in a clinical trial where diabetic patients (and nondiabetic patient controls) are dosed insulin based on the simulation calculations and under the careful supervision of a physician.

V. References