Glucose Sensor and Insulin Injector

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Abstract – As diabetes is the seventh leading cause of death in the United States [1] and its increase in prognosis has coincided with an increase in obesity rates, the development of medical devices to assist diagnosed individuals has become increasingly important. For those who are insulin dependent, it has long been a practice that they must inject themselves with one or several doses of insulin throughout the day. It is especially important that these individuals must monitor their glucose levels as constant levels of hyperglycemia or hypoglycemia can lead to deadly health problems as time goes on. In this design project, a constant glucose monitoring system was created using the concentration of glucose in the interstitial fluid. This monitoring system is specifically based on the enzymatic reaction between glucose and glucose oxidase. This feeds a voltage to an insulin pump system that pumps out a certain amount of insulin based on the current blood glucose level and the insulin sensitivity of an individual. Key elements of the circuit design for the insulin pump system include the use of an astable 555 timers to control the timing of insulin doses and determine pump rate, operational amplifiers (op-amps) to adjust for insulin sensitivity and different colored LED lights to alert the patient of their current glucose concentration.

I. INTRODUCTION:
A. Pathophysiology of Diabetes Mellitus

One in ten individuals in the United States have been formally diagnosed with diabetes [1]. With such a large portion of the population affected, there is a necessity for the development of medical devices that can help diagnosed individuals effectively and conveniently manage their condition. There are two separate types of diabetes mellitus, which are known as Type 1 and Type 2.

Type 1 diabetes is a hereditary condition that is usually diagnosed in early childhood but can also be diagnosed in adolescents. The pancreas of individuals with Type 1 diabetes produces very little quantities, or absolutely no insulin. Insulin is a hormone which enables blood sugar to enter cells where it is utilized as an energy source in cellular processes such as cellular respiration (whose inputs are glucose and oxygen). In individuals with Type 1 diabetes, an auto-immune response triggers the destruction of the beta cells in the pancreas which are responsible for producing insulin [2]. Without insulin, glucose concentrations can increase in the bloodstream which can lead to potentially dangerous adverse physiological effects in the nervous, digestive, and circulatory systems.

In comparison to Type 1 diabetes which is commonly diagnosed in early childhood, Type 2 diabetes is known as a lifestyle disease and is statistically more commonly developed in older adults. There is a strong positive correlation between the development of Type 2 diabetes and obesity. Although Type 2 was formerly known as “late-onset diabetes”, a higher percentage of the younger population is developing it due to upwards trends in obesity in the United States.

Physiologically, Type 2 diabetes is characterized by the fact that the pancreas does not produce sufficient insulin and/or the cells are not receptive to insulin, leading to poor glucose uptake [2].

B. Continuous Glucose Monitoring System (CGM)

There are generally two kinds of glucose monitoring systems available to diabetes patients: lancing devices with test strips and what are known as continuous glucose monitoring systems (CGMs). While the lancing devices are more commonly used, CGMs are a better and more efficient alternative. Lancing devices require the patient to prick their fingers and measure glucose levels directly from the droplets of blood that are placed onto the test strips. This is not a continuous measurement, but rather, it requires that the patient makes sure to regularly check glucose levels in order to avoid a hyperglycemic or hypoglycemic episode.

CGMs, on the other hand, allow the patient to measure glucose levels continuously. Unlike the lancing devices, CGMs monitor glucose concentrations from the interstitial fluid under the epidermis, through transcutaneous probes that are placed directly under the skin. These electrodes generate an electrical current that varies depending on the glucose concentration in the interstitial fluid [3]. This data is communicated to another device, which displays the glucose levels for the patient to see at any time during the day. These systems measure and report glucose levels every few minutes throughout the day and can even be used to generate trends about these levels over time. In this way, CGMs are far more efficient, and can help to reduce hyperglycemic or hypoglycemic episodes, by alerting the patient as soon as glucose levels are out of normal range. For our design, we chose to develop a CGM that outputs data to an insulin pump, for controlled insulin release that depends on glucose levels during the day. This device is meant for both Type 1 and Type 2 patients.

C. Insulin Pumps

The American Diabetes Association recommends the use of either these pumps for continuous infusion of insulin, or three or more daily injections, which are known as multiple daily injections (MD1), in order to maintain healthy blood sugar levels [3]. Insulin pumps are becoming an increasingly popular alternative for individuals with diabetes and are often favored over traditional insulin injections utilizing syringes and needles. The purpose of these pumps is to mimic circadian rhythm the body naturally had for insulin release [4]. Statistically individuals that utilize insulin pumps have less hypoglycemia episodes than those who utilize the traditional injection method [5]. Hypoglycemia can be caused by waiting too long between meals, not eating sufficient calories, or excessive insulin injections. Insulin pumps enable users to have greater flexibility in when they can eat, sleep and exercise making them optimal for individuals with varied schedules, or with special circumstances, such as competitive athletes or adolescents with eating disorders [3]. They are specifically recommended for individuals that have hemoglobin A1c levels >7.0% [3]. These devices are highly customizable and can be programmed to deliver continuous small amounts of rapid acting insulin (basal dose) and give
additional bonus doses (bolus dose) at mealtimes [5]. This basal dose, or background insulin accounts for 40-50% of total insulin [6].

Some insulin pumps are attached to thin tubes and are inserted into the body via a thin needle, while others attach directly without tubing. Pumps with the latter configuration are referred to as pump patches. Typically, they consist of a needle catheter which is either made of Teflon or steel and is inserted into subcutaneous tissue [3]. These pumps can be worn on various locations of the body, but typically are worn on the abdomen, or on the upper leg [3]. A majority of insulin pumps only utilize rapid-acting insulin, such as aspart, lispro, glulisine or U-500 insulin [3].

II. DESIGN
A. Continuous Glucose Monitor Design:

The glucose monitor is based on the enzymatic reaction between glucose and glucose oxidase. The reaction will occur on the reference electrode in the electrochemical cell, glucose oxidase will catalyze the reaction between glucose and oxygen, which produce gluconic acid and hydrogen peroxide, as shown below [7]:

$$\beta - D - \text{glucose} + H_2O + O_2 \xrightarrow{\text{GOx}} \text{GNS} + H_2O_2$$

The hydrogen peroxide produced in the enzymatic reaction is further decomposed in the electrochemical reaction as shown below [7]:

$$H_2O_2 \rightarrow O_2 + 2H^+ + 2e$$

The free electrons generated in this reaction will produce a small amount of current that is proportional to the glucose concentration of the fluid. By injecting a microneedle with the electrodes under the skin, the glucose monitor is able to determine the glucose concentration of the interstitial fluid continuously by measuring the current generated.

B. Analog to Digital Converter

The first component of the insulin pump following the analog voltage source from the sensor design is the analog to digital converter. The input is logic-controlled utilizing a 2-input AND gate with inputs d0 and d1. The ADC works by inputting a DC voltage (10 volts) into the negative terminal of an op-amp and the analog voltage signal from the sensor into the positive terminal. This will create a basic comparator that cycles between the op-amp’s negative power supply (0 volts) and the positive power supply (3.3 volts) depending on which positive terminal. The working electrode provides a potential for the electrochemical reaction to occur. The reference electrode is the site where enzymatic reaction takes place. Based on the Michaelis-Menten [7] model, the glucose concentration can be determined based on the reaction rate of the enzymatic reaction using:

$$v = \frac{V_m[S]}{K_m + [S]} \Rightarrow [S] = \frac{V_m}{v-V_m}$$

The ratio is being used.

C. 555 Timer and Op-Amps

Each 555 timer is used to time how long each pump of insulin is released for. This is then followed by an inverter and another op amp. The inverter reverses the time which the timer is high for while the op amp is used to amplify the voltage to adjust for an individual’s insulin sensitivity.

III. ANALYSIS
A. Continuous Glucose Monitor Analysis

The glucose monitor is composed of three parts, the power circuit, the electrochemical cells and the measuring circuit. The power circuit provides a potential for the electrochemical reaction to occur in the electrochemical cells. The power circuit functions by first reducing a 3V DC voltage source to 1.5V with a voltage divider circuit. The output voltage of the voltage divider is inputted into the positive terminal of the operational amplifier that monitors that output of the voltage divider. Another voltage divider is used to reduce the voltage further to 0.6V which is inputted into the electrochemical cell through the working electrode to allow the electrochemical reaction to occur.

The electrochemical cell is a two-electrode system [8], the working electrode provides a 0.6V potential for the electrochemical reaction while the reference electrode is the site where enzymatic reaction takes place. Based on the Michaelis-Menten [7] model, the glucose concentration can be determined based on the reaction rate of the enzymatic reaction using:

$$v = \frac{V_m[S]}{K_m + [S]} \Rightarrow [S] = \frac{V_m}{v-V_m}$$

The hydrogen peroxide produced in the enzymatic reaction will be decomposed into water and free electrons. Using the Cottrell Equation [7], the electrochemical reaction rate can be calculated using the current as shown below:

$$\frac{I(t)}{nFD_S} = c_0 = v$$

where I(t) is the current at a given time, n is the number of electrons transferred, F is the Faraday’s constant, Do is the diffusion coefficient, Co is the concentration, and t is time.
Since one glucose will produce one hydrogen peroxide, the assumption that the reaction rate for both reactions are equal can be made. Therefore, the glucose concentration can be determined based on the current measured using the following equation:

\[ I(t) = \frac{v_n F D_0 t^{\frac{1}{2}}}{\pi^2} \]  

Using the glucose concentration level within the physiological interest, 0.5 mM/L to 10 mM/L which is 10 mg/dL to 180 mg/dL, \( D_0 = 6 \times 10^{-6} \) [9], \( t = 60s \) and \( F = 96485 \) C/mol, the range of the current output is calculated to be 6.3A to 63A.

With the range of the current output from the electrochemical cell calculated, the current signal will be processed in the measuring circuit. The first part of the measuring circuit is the transimpedance amplifier, where the current will be converted to voltage. The voltage output can be calculated using:

\[ V = -IR \]  

where \( R \) is 28 kΩ.

Then the output voltage of the transimpedance amplifier will pass through an inverting operational amplifier where the signal will be amplified before going into the insulin pump. The final voltage output of the measuring circuit can be calculated using:

\[ V_{out} = \frac{-R_2}{R_1} V = \frac{-R_2}{R_1} IR \Rightarrow V_{out} = I \times 168k\Omega \]  

where \( R_1 = 100k\Omega \) and \( R_2 = 600k\Omega \). Plugging in the current range, the glucose monitor will output a voltage between 1V to 10V and have a sensitivity of \( \frac{9V}{170mg/dL} \).

### B. Insulin Pump Analysis

1. Analog to Digital Converter Analysis

The ADC works via the principles of comparators and voltage division to determine the section that the analog signal of the will induce at its output. Voltage division and the resistance values of the Analog to Digital Converter determine the negative voltage input of the op-ap through the formula:

\[ V_n = \frac{R}{R + R_{eff}} V_{DC} \]  

where \( V_n \) is the voltage going into the negative terminal of the op-amp, \( R \) is the total resistance of the resistors below the op-amp and \( R_{eff} \) is the total resistance above the op-amp. \( V_{DC} \) in our circuit is 10 volts but can be greater to give a larger range of voltage values per section. Resistances can also be changed to change the numerical values of the boundaries of the sections. The comparators work through the relationship:

\[ V_{sensor} \leq V_n \Rightarrow V_{out} = 0V \]  
\[ V_{sensor} > V_n \Rightarrow V_{out} = 3.3V \]

2. Astable 555 Timer Analysis

Following the comparators are the astable 555 timers, used to control how long each burst of insulin is released for and how long the pump remains off for. The timing is based on the daily basal rate of an average weight person, 140 lb, with a 45% basal to 55% bolus rate. Additionally, we calculated the basal rate to occur for 19 hours throughout the day and the bolus for 5 hours; the bolus rate accounts for the
time before eating a meal and the 2 hours after eating that you have to check your glucose levels for.

The total daily insulin dose can be estimated by using the following equation [10]: 

\[ \text{Daily Insulin Dose} = \frac{\text{weight (lb)}}{4} \]  

(11) 

Therefore, the estimated daily insulin needed is about 35 units, where 15.75 units are basal and 19.25 units are for the bolus rate; the hourly basal and bolus rates are 0.83 U/hr and 3.85 U/hr, respectively. These values are used to determine how much insulin is pumped for a normal glucose level. Additionally, it was set to have 30 pumps of insulin per minute, where each pump delivers 460 µU for the basal rate and 2mU for the bolus rate. Therefore, the period for each pump is 2 seconds, and \( T_{\text{low}} \) and \( T_{\text{high}} \) on the timer was set to be 45% and 55% of the period, respectively. \( T_{\text{low}} \) on an astable 555 timer is calculated using: 

\[ T_{\text{low}} = R_2 C \ln(2) \]  

(12) 

where \( R_2 \) is the resistor connected to the discharge and trigger pin on the timer, \( C \) is the capacitance used. The capacitor was arbitrarily set to 10 µF and \( T_{\text{low}} \) is 0.9 seconds; therefore, \( R_2 \) is 0.1298 MΩ. \( R_1 \) on the timer was found using: 

\[ \text{Period} = (R_1 + 2R_2)C \ln(2) \]  

(13) 

Therefore, \( R_1 \) was found to be 28.9 kΩ. 

The 555 timers for the hypoglycemic and hyperglycemic levels were calculated to be 45% and 55% of the period, respectively. \( T_{\text{low}} \) on an astable 555 timer is calculated using: 

\[ T_{\text{low}} = R_2 C \ln(2) \]  

(12) 

where \( R_2 \) is the resistor connected to the discharge and trigger pin on the timer, \( C \) is the capacitance used. The capacitor was arbitrarily set to 10 µF and \( T_{\text{low}} \) is 0.9 seconds; therefore, \( R_2 \) is 0.1298 MΩ. \( R_1 \) on the timer was found using: 

\[ \text{Period} = (R_1 + 2R_2)C \ln(2) \]  

(13) 

Therefore, \( R_1 \) was found to be 28.9 kΩ. 

The overall gain from the op-amps is 

\[ \text{gain} = \frac{50}{s} \]  

(17) 

where \( s \) is how many mg/dl 1 unit of insulin decreases an individual’s blood glucose level. \( S \) is set by the potentiometer, with a maximum resistance of 75 kΩ; this was set to 75 kΩ as it seemed to be a reasonable estimate for a person with a high insulin sensitivity. The potentiometer resistance in Ω corresponds to a person’s sensitivity such that a value of 30kΩ represents 30 mg/dl. 

Additionally, the upper and lower power rails on the op amps were set to ±15V to allow for a larger range of insulin sensitivities to be set. At lower values, the op-amps will max out at a higher insulin sensitivity; however, at 15V, the lowest insulin sensitivity that can be set is 11 mg/dl, where the op-amp will max out at 15V. 

IV. DISCUSSION 

As mentioned previously, we are looking to develop a device that would simultaneously monitor and control glucose levels, via a CGM that connects to an insulin pump. This device is targeted for use by both Type 1 and Type 2 diabetes patients. This was accomplished by adding potentiometers which enable the user to change the amount of insulin pumped based on their insulin sensitivity. While our design works in simulation (see Appendix A, Figure 5), there are still both areas for improvement and more considerations that we would need to make. To begin with, we do recognize that our design is a bit more complex than it perhaps needs to be. In practice, it would be far more efficient to determine a way to achieve the same result with just one 555 timer, rather than 3, for example. A possible way to achieve this is as follows: we could have one 555 timer corresponding to the hypoglycemic level as we do now, then have the normal level op-amp and the hyperglycemic level op-amp activating switches of separate 555 timers. These switches will lead to a second and third part of the circuit that activate the LED and change the value of the capacitance (by introducing more capacitors) in the astable 555 timer, thus changing \( T_{\text{high}} \) and \( T_{\text{low}} \) for the pump to fit the values of the normal level and hyperglycemic pump rates. In this way, it could be possible to achieve the same result with fewer components. This is one consideration that we can make and analyze more in depth in the future.
Moreover, we would also need to look into a design for the physical insulin pump, so it is more than just hardware. Ideally, we would want to develop a model that is compact and comfortable to wear. This would be important, as the patient will be wearing the device for extended periods of time. Additionally, it would be ideal for the CGM to transmit data to another device, such as a smartphone, for the patient to view their glucose levels in real time. This would require slight modifications to our circuit design for the CGM, and it is another direction that we can take with this project going forward.

All in all, this project has brought us one step closer to developing a design that provides an efficient and convenient solution to treating diabetes. As diabetes diagnoses are rapidly on the rise, it would be beneficial to have a device like this in the market. We believe that our proposed design, if implemented, would be effective in reducing the frequency of hyperglycemic or hypoglycemic episodes in patients, which can potentially be life-threatening if not handled with care.

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REFERENCES

[1]: Centers for Disease Control and Prevention, Centers for Disease Control and Prevention, www.cdc.gov/.
V. APPENDIX

A. Continuous Glucose Monitor Circuit

Figure 1. The CGM circuit is shown here, where the top circuit shows the input voltage circuit and the bottom circuit shows the measuring circuit.

Figure 5. The circuit simulation of the measuring component of the CGM is shown here.
B. Insulin Pump Circuit

1. Insulin Pump

Figure 2. The insulin pump circuit is shown here with the DAC, 555 timers, inverters, op-amps, and LED matrix.

2. Logic Control Input

Figure 3. The logic-controlled input of the insulin pump is shown here. A logic of 00 corresponds to a basal rate insulin output while a logic of 11 corresponds to a bolus rate insulin output.