Amperometric Continuous Glucose Monitor

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***Abstract*—Global epidemiology studies highlight the increasing prevalence of diabetes mellitus. In response, glucose monitors must adapt to the increasing need for accurate and minimally-invasive glucose monitoring for diabetes patients. The goal of this project is to design a continuous glucose monitoring sensor that inputs blood glucose concentration from a sensor inserted into the subcutaneous fat layer under the skin and outputs information to the insulin pump about how much insulin is needed. In our bioinstrument, a current is produced by a reduction-oxidation reaction occurring at the electrode due to the interaction of glucose from the blood sample and glucose oxidase, an enzyme that is placed at the electrode. The monitoring system then uses an integrator that measures the voltage across a capacitor when a current is applied. If this voltage exceeds the threshold of 250 mV (which correlates to a current of 6 μA), a timer will be triggered to indicate that blood glucose levels are hyperglycemic (meaning too high), or above 9 mmol/L. In our report, an LED will subsequently be turned on whenever the timer is triggered to indicate a wireless signal being sent to an insulin pump to inject 1 unit of insulin into the patient.**

Keywords—glucose monitor, biosignal processing, insulin pump, biosensor

I. Introduction

The prevalence of diabetes has quadrupled in the past three decades and current global studies determined that 1 in 11 adults have diabetes [2]. In the United States, the CDC found that 11.3% of Americans are diagnosed with diabetes mellitus and 23.0% of Americans do not know they have it [5]. If global diabetes trends increase and 592 million people are diagnosed with diabetes mellitus in 2035, accurate and consistent glucose monitoring will be imperative to prevent further health complications in diabetes patients [1,3].

This report demonstrates the use of amperometric biosensing as used in continuous glucose monitoring (CGM) to measure blood glucose concentration (BGC). Amperometric biosensors work by measuring the output current produced by the reduction-oxidation reaction produced at the electrode [7]. The relationship between glucose concentration and output current is shown in *Figure 1*. Since blood glucose levels range in between roughly 5 mmol/L and 10 mmol/L, we are only concerned with the linear segment of this relationship [*Figure 1*].

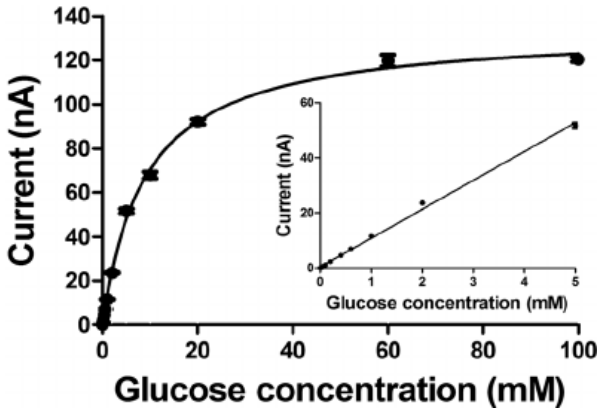

Figure 1: Current (nA) as a function of glucose concentration (mmol/L). The graph on the right shows the linearity in this relationship for smaller glucose concentrations. [9]

Various enzymes can be used in the detection of glucose in glucose monitoring (Glucose oxidase, Glucose dehydrogenase with PQQ, NAD or FAD) [11]. Glucose is oxidized by an enzyme placed at the electrode in the presence O_2 to produce gluconic acid and hydrogen peroxide [7, *Equation 1.1*]. Hydrogen peroxide goes through another redox reaction that results in a flow of electrons to generate a current proportional to the BGC in the sample [7, *Equation 1.2*].

$$\text{Glucose} + O_2 \xrightarrow{glucose\ oxidase} \text{Gluconic acid} + H_2O_2 \quad (1.1)$$

$$H_2O_2 \rightarrow 2H^+ + O_2 + 2e^- \quad (1.2)$$

In order to measure the current generated by this reaction, we must relate the BGC to the rate of the reaction [12]. The rate of this enzymatic reaction is governed by the Michaelis-Menten equation [*Equation 2*][12].

$$v = \frac{k_{cat} \cdot k_A \cdot e_0 \cdot [C_6H_{12}O_6]}{k_{cat} + k_A \cdot [C_6H_{12}O_6]} \quad (2)$$

In the Michaelis-Menten equation, v is the rate of product formation (mol/s), $[C_6H_{12}O_6]$ is the concentration of glucose (mM), k_{cat} is the catalytic constant (s^{-1}), k_A is the specificity constant ($mM^{-1}s^{-1}$), and e_0 is the enzyme quantity (mol) [*Equation 2*].

The rate of the reaction can then be related to the generated current by *Equation 3* [8]. The current (C/s) is the product of the electrons produced per mol of glucose (C/mol) and the rate of product formation per unit time in the reaction (mol/s) [*Equations 2,3*].

$$I = 2 \cdot F \cdot v \quad (3)$$

When a current is produced in the circuit, the capacitor will begin to charge. Since we cannot directly measure the current at the electrodes, we can measure the voltage across the capacitor which will be proportional to the generated current. The relationship between current and voltage across a capacitor is given by Ohm's Law for a capacitor [*Equation 4*], where dt is the period of an astable timer [*Equation 5*].

$$\frac{dV}{dt} = \frac{I}{C} \quad (4)$$

$$T = (R_1 + R_2) \cdot C \cdot ln(2) \quad (5)$$

In this report, we will demonstrate how these mathematical relationships are used to measure BGC by measuring the voltage across a capacitor in continuous glucose monitoring.

II. Methods

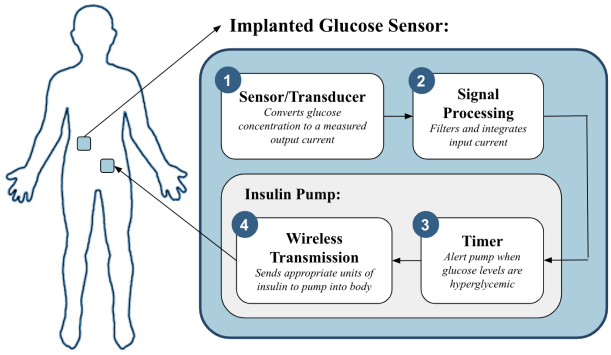

Figure 2: Schematic of continuous glucose monitor design with four main parts labeled: the sensor/transducer, signal processing, timer, and wireless transmission.

The design of our bio instrument is broken down into the four main parts, which includes 2 devices attached to the body. The first device is the glucose biosensor, which contains an electrode that is implanted subcutaneously under the skin, and it can be placed anywhere on the body. The second device is the insulin pump, which is inserted subcutaneously on the abdomen area.

The sensor transduces the glucose concentration into a measured current. Second, the current signal is processed, which outputs the filtered signal integrated over time. Third, the output signal is sent to a timer, which will be triggered whenever the glucose level is hyperglycemic for 3 seconds, meaning above 9 mmol/L. And finally, the information is wirelessly transmitted to the insulin pump to let it know how much insulin should be injected into the body

A. Current, Voltage, and Concentration

For our monitor, we are assuming that the quantity of enzyme (e_0) on our electrode is 0.1 nmol. Using this quantity along with known enzyme kinetic values for glucose oxidase[14], we calculated the following currents and voltages for a range of blood glucose concentrations [*Equations 2,3,4,5*].

Glucose Concentration (mmol/L)	*Electrode Current (μA)*	*Voltage Across Capacitor (mV) After 3.6 s*
5.0	3.9	140
7.0	5.4	190
9.0	6.9	250
11.0	8.5	300

Table 1: Electrode current (μA) and voltage across capacitor (mV) for three glucose concentrations, where k_{cat} = 741 s^{-1}, k_A = 40 $mM^{-1}s^{-1}$, and e_0 = 0.1 nmol [14].

For this study, we will be using the third concentration of 9 mmol/L as our threshold to indicate hyperglycemic BGC. Once the BGC reaches 9 mmol/L, a current of 6.9 mmol/L will be generated via the oxidation of glucose and hydrogen peroxide, meaning we will measure a voltage of 250 mV across the capacitor.

B. Integrating Glucose Monitor Circuit

The glucose monitoring circuit is composed of 5 components: a voltage source buffer, enzymatic electrode, integrator controlled by an astable 555 timer, comparator, and an insulin pump.

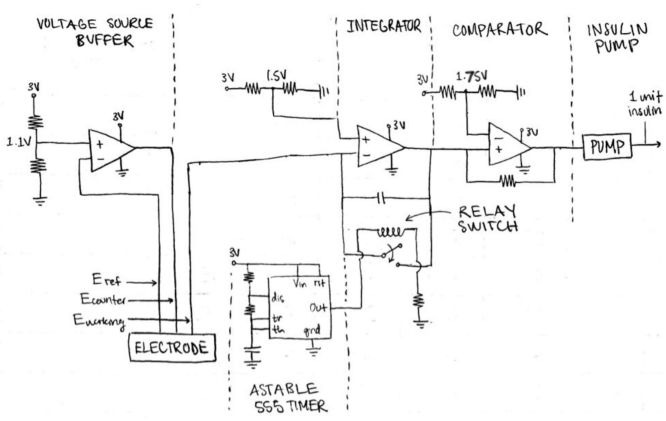

Figure 3: CGM circuit diagram using an integrator to determine the BGC in a sample. The five main components are labeled (voltage source buffer, integrator, comparator, astable 555 timer, insulin pump).

The electrode works with a -400 mV potential across the working and reference/counter electrodes.. This potential is achieved by using a voltage source buffer which provides a 1.1V potential at the reference/counter electrodes relative to ground, and using an integrator that provides a 1.5V potential at the working electrode relative to ground. The electrode then generates a current that is proportional to BGC in the sample.

The integrator uses the current generated by the electrode to charge the capacitor at the integrator. The charge time is controlled by a 555 timer and a relay switch. At first, the voltage at the threshold of the 555 timer is at zero, and takes 5.7 seconds to get to the 2V trigger in the case of hyperglycemia to turn off the relay. Afterwards, the relay is subsequently turned off for 0.3s and the 555 capacitor is discharged back down to 1V. Upon further cycles, the 555 timer switches on the relay switch for 3.6 second periods and switches off for 0.3 second periods [*Equation 5*]. When the relay switch is in the "on" position, the capacitor at the integrator begins to charge, and when it is turned off, the capacitor at the integrator is shorted and the voltage across it turns to zero, thus resetting the integration. By this method, the voltage at the output of the integrator is equal to the voltage across the capacitor relative to 1.5 V (from the input).

The comparator serves as an indicator for hyperglycemia. When the output voltage of the integrator (1.5V + voltage across the capacitor) exceeds 1.75V, this indicates that the voltage across the capacitor is 250mv and thus the BGC is 9 mmol/L or above. This value sets the threshold of the comparator, and thus the output of the comparator signals hyperglycemia to the insulin pump. Once this signal is wirelessly transmitted to the insulin pump, it will secrete 1 unit of insulin into the bloodstream of the patient.

III. Results

The circuit was simulated with the The Falstad Java applet with the component values shown in *Figure 4*. An LED light at the output of the comparator represents the insulin pump, which secretes 1 unit of insulin to the body when it is lit.

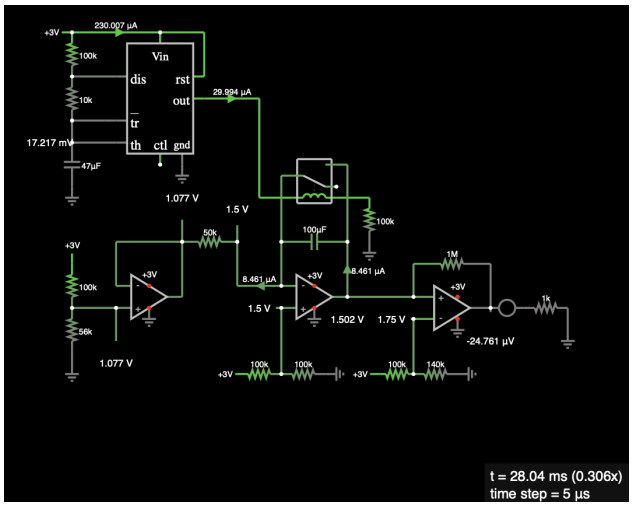

Figure 4: Circuit diagram created on Falsad at the start of the integration, with a current of 8.46µA (11.0mM glucose).

Figure 4 indicates an output voltage of 1.5V at the integrator at the beginning of the integration when a constant current of 8.46µA is applied to the capacitor. After 3.6 seconds, the output voltage of the integrator goes above the 1.75 threshold of the comparator, thus triggering the LED to turn on [*Figure 5*].

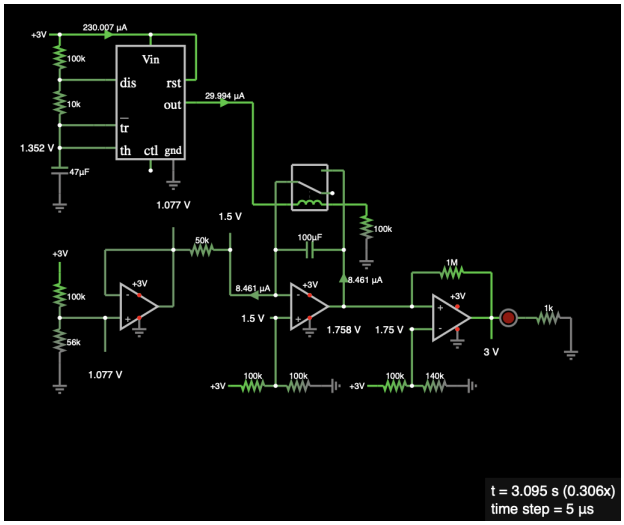

Figure 5: Circuit diagram created on Falsad at 3 seconds after the start of the integration with a current of 8.46 µA. The output of the comparator is high, which sends a signal to the "pump" (LED) to secrete insulin.

Thereafter, the 555 timer turns off and triggers the relay switch to short the capacitor and reset the output voltage of the integrator back to 1.5V. After 0.3 seconds, the integration can start again.

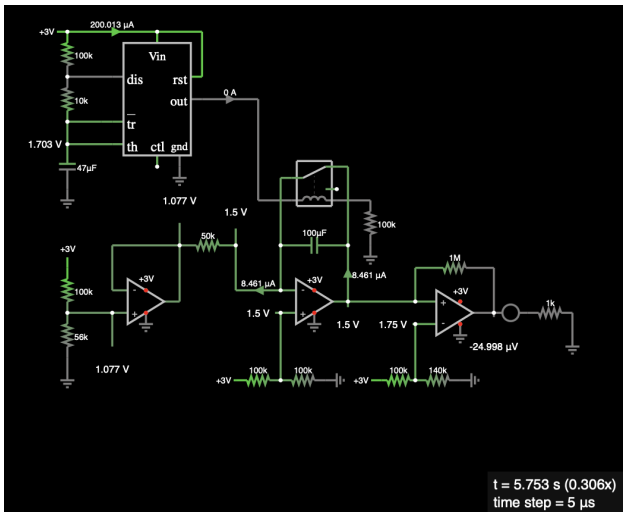

Figure 6: Circuit diagram at the reset of the integrator, the capacitor is shorted by a relay switch controlled by a 555 timer.

The following graph indicates the voltage across the capacitor for the 3.6 second interval of integration for the four glucose concentrations in *Table 1* [Figure 7].

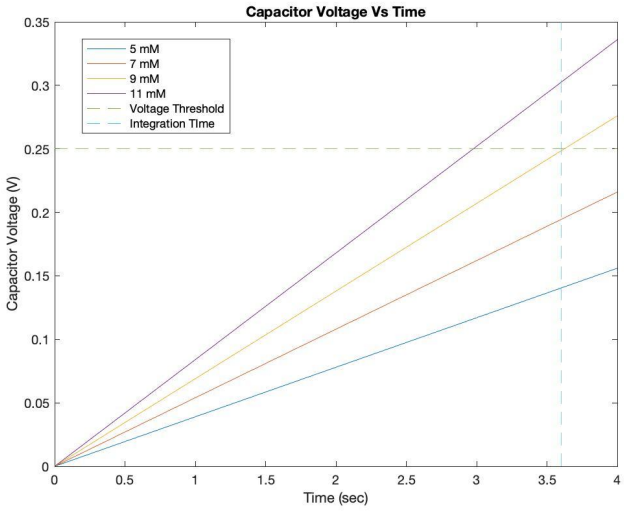

Figure 7: MATLAB plot of voltage across capacitor (mV) vs. time (sec) for the four glucose concentrations (5 mmol/L, 7 mmol/L, 9 mmol/L, 11 mmol/L).

IV. Discussion

Epidemiologists are currently investigating whether diabetes diagnoses are correlated with COVID-19 case outcomes. Obesity, a risk factor for type 2 diabetes, is linked to abnormal ventilation and can contribute to reduced residual lung capacity and chest wall elasticity [4]. Case studies have shown diabetes diagnoses rapidly increasing in adolescent populations [5]. These increasing numbers demonstrate that there is a crucial need for minimally invasive glucose monitors that provide abundant BGC information to prevent further health complications. The continuous glucose monitor design proposed in this study allows for patients to determine when they are hyperglycemic, and a corresponding insulin dosage is delivered directly through an insulin pump.

A. Limitations

Considerations for the proposed continuous glucose monitor design must be made in order to assess applicability. Although our design is able to accurately and continuously measure the blood glucose levels, there exist some sources of error due to the nature of current biosensors. For example, sensors presume the principle of linearity exists during calibration of the device, thus a misrepresentative concentration of glucose during calibration may negatively affect the device's ability to trigger as glucose levels spike. In addition, since the electrodes are coated with the Glucose Oxidase, the sensor may experience drift as the enzyme begins to leak over time. As a result, the sensor drift increases the output reading independent of the patient's actual BGC. Finally, the use of enzymatic reactions as the precursor of the final BGC introduces an element of inaccuracy as substrate inhibition limits the sensor's sensitivity at extremely high glucose levels [10].

B. Advantages

The amperometric glucose monitor presents a minimally invasive method, since the electrodes only protrude into the subcutaneous layer of fat underneath the epidermis, as compared to self monitoring devices, which require several invasive finger pricks throughout the day [6]. Furthermore, the continuous glucose monitor provides constant reassurances to the patient as it can administer readings every few minutes, thus quickly informing a patient as they begin to approach hyperglycemia. Continuous measurements allow for improved predictability as well as better treatment decisions [6]. Finally, to minimize the source of errors related to sensors, our design utilizes multiple sensors in a closed-loop. The use of multiple sensors increases the accuracy of the amperometric glucose monitor as the system decides to retrieve information from the sensor that is experiencing the least drift, or is calibrated correctly. This feature increases the life expectancy of the monitor, as the sensitivity is maintained for a longer period of time.

C. Future Steps

As we recognize the advantage of using a minimally invasive method to measure BGC, we would like to develop a completely non-invasive continuous glucose monitor for the future of this product. A method that is currently researched is a band strapped to the patient's wrist. The band utilizes light biosensors to

measure the BGC using visible Near-Infrared Spectroscopy [13]. Another feature our continuous glucose monitor could implement is real-time feedback, in order to specialize in areas such as athletic performance. For example, a marathoner could base his refuel timings on their BGC. Moreover, we intend to incorporate a second 555 timer made to trigger at a minimum level of BGC, thus alarming the patient as they approach hypoglycemia as well as hyperglycemia.

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