Glucose Monitoring for Diabetes

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***Abstract*—In this report, we designed a blood glucose point of care test that informed patients when the blood glucose level was abnormal. The test strip was developed based on a three electrode system, with enzymes immobilized on top of the working electrode to convert glucose concentration into current signals. Current to voltage converter, Instrument amplifier and comparators were designed to give red light signals when glucose concentration is outside of normal levels. Result shows accurate outputs under different simulated scenarios. Our design provides an accurate model for glucose level monitoring and serves as the basic design for other chemical concentration tests.**

I. Introduction

Diabetes affects millions of patients worldwide, breaking patients' regulation of blood glucose levels and weakening overall health **[citation 1]**. Most diabetes patients have either weakened or damaged insulin, the signaling molecule that, upon binding to the insulin receptors, signals cells to store blood glucose inside. Malfunctioned insulin diminished the regulatory effects on glucose concentration, causing hyperglycemia (high glucose level) and hypoglycemia (low glucose level). Misregulated glucose level is often associated with fatigue, due to insufficient energy conversion from glucose**[citation 2]**. Constant hyperglycemia is also associated with heart disease, as higher glucose level often leads to higher blood pressure, introducing higher force and, hence, damage to heart valves **[citation 3]**.

Typical treatments usually involve adjusting glucose levels manually by chemical intervention, such as injecting insulin. Since manual intervention requires knowing the concentration of blood glucose, an accurate reading of glucose levels becomes utterly important for patients' treatment.

II. Motivation and Goal

Most available glucose test strips relied on color indicators to measure the concentration of blood glucose. Specifically, Horseradish peroxidase is a common indicator that changes color depending on the amount of reaction originating from glucose **[citation 4]**. However, because of the enzyme instability, the color indicator-based test strip could only provide a rough estimation of blood glucose.

In comparison, enzyme based test strips relied on either current or voltage that is proportional to the chemical reactions. As electrodes are generally more sensitive and reliable, enzyme-electrode based test strips are the best approach for good glucose readings.

The goal of our project is to design and simulate three-electrode glucose test strips. The test strip will accurately read the glucose concentration and return light signals that tell patients whether their glucose level is normal or abnormal.

III. Circuit Design and Simulation Results

A. Sensor

Before we dive into the circuit design, we first need to understand how the biosensor we are using, an enzyme-electrode based glucose test strip, works. The strip consists of three different electrodes, a working electrode, a reference electrode, and a counter electrode. As shown in Fig. 1, the electrodes are connected to the reaction area, onto which a drop of sample is dropped. A potential is applied between the working electrode and the reference electrode, the test strip will undergo an electrochemical reaction producing a current based on the concentration of glucose.

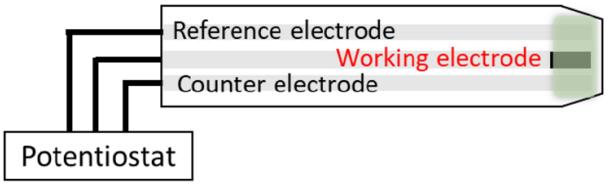


Fig. 1. Schematic diagram of test strip, green area showing reaction zone.

The equivalent of the electrode sensor is shown in Fig. 2. The capacitors C_{WE} and C_{CE} represent the double layer capacitor of the working electrode and the counter electrode, where R_{WE}, R_{CE}, and R_{RE} represent the charge-transfer resistance. R_{S1} and R_{S2} express the solution resistance **[citation 5]**. The double layer capacitances and resistances are very small relative to charge-transfer resistance, therefore they can be ignored. We will be using this model for the circuit simulation.

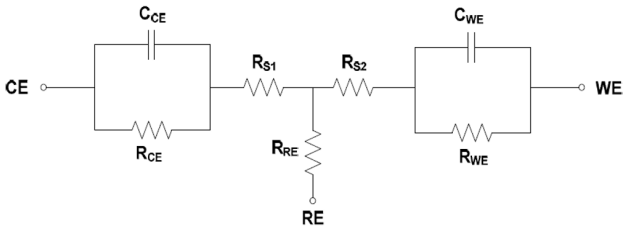


Fig. 2. Equivalent circuit of glucose test strip.

The design of the working electrode is shown in Fig. 3. When the blood samples were delivered into the system, blood first went through the outer layer that filtered components of blood, such as catalase and red blood cells. Filtering is essential to prevent components interfering with our reaction. The filtered samples were then entered the enzyme layer, where glucose oxidase is immobilized. Through glucose oxidase, glucose will react with water and generate hydrogen peroxide. As a result, the concentration of glucose will be proportional to the concentration of hydrogen peroxide. The samples were then filtered once again to ensure only hydrogen peroxide can contact platinum electrodes. With a production of a current, hydrogen peroxide is oxidized by platinum electrodes. The resulting current will be proportional to the concentration of hydrogen peroxide **[citation 6]**.

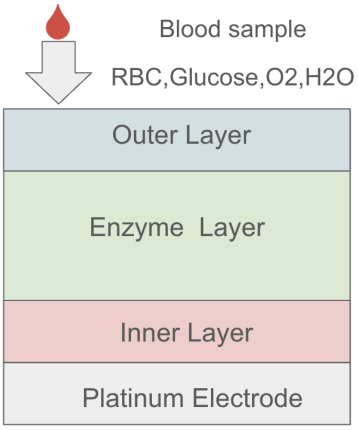


Fig. 3. Illustration for working electrodes.

B. *Reference Data*

Due to limited resources and time, we resorted to using data measurements conducted by other researchers shown in Fig. 4. The test strip used in the experiment underwent cyclic voltammetry electrochemical reaction with potential going from 0V to ±0.4 V. Different currents were generated for standard solutions with different concentrations, namely, 38 mg/dL, 119 mg/dL, 220 mg/dL, 310 mg/dL, and 478 mg/dL **[citation 7]**.

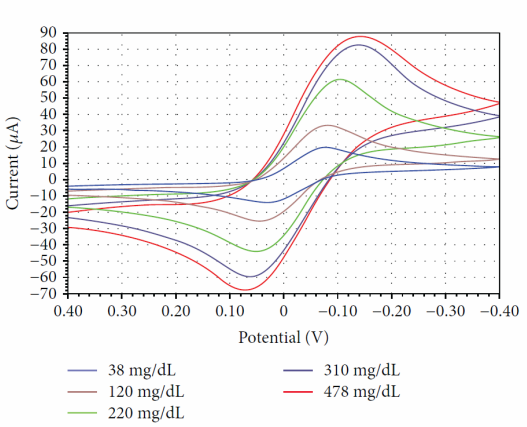


Fig. 4. Electrochemical reaction current vs applied potential in the range of ±0.4V using standard solutions of different concentrations.

Utilizing this graph, we get a frame of reference of the range of currents we will obtain based on concentration of glucose. To keep the design less complicated, as this is the first design, we finalized the lookup table shown in Fig. 5, which shows the glucose levels and their corresponding current as well as the corresponding output.

Glucose Level	Glucose Concentration	Current@0.4V	Led Color
Low	120 mg/dL	Below 12 μA	Red
Normal	120-220 mg/dL	12 μA - 25 μA	Green
High	220 mg/dL	Above 25 μA	Red

Fig. 5. Lookup table for glucose level at applied potential of 0.4V.

C. *Potentiostat and Readout Circuit*

The circuit structure that allows us to read the current value of the test strip is called a potentiostat. Its purpose is to provide a stable bias potential to the electrodes. The circuit has three terminals which we can connect to the sensor model mentioned above. The working terminal is then connected to a readout circuit that serves to detect and amplify the sensor signal and convert it to a form which can be modulated or transmitted **[citation 8]**. Since we can't test the circuit with an actual test strip, we instead use an ideal current source to represent the electrochemical current from the reaction shown in Fig. 6.

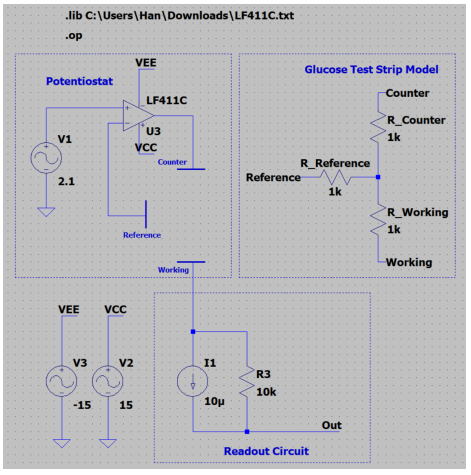


Fig. 6. Schematic of potentiostat circuit

D. Current to Voltage Converter

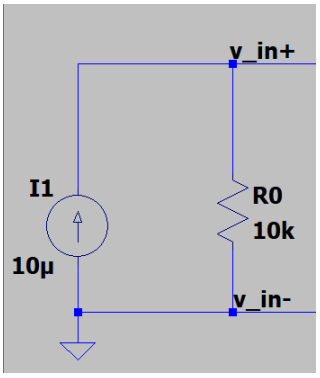


Fig. 7. Schematic of I-V converter

The first stage is the current to voltage converter. As mentioned above in the sensor design part, we need to convert the current measured by the sensor to voltage, so that we could pass it to the Instrumentation amplifier. Since we haven't actually measured the current with the device, for convenience purposes, we assume the input is an ideal current of 10uA in this case. We choose the R0 to be 10k ohms, which leads to the output voltage (v_in+ - v_in-) of this converter to be $10uA \ * \ 10k\Omega \ = \ 0.1V$.

We do not need to worry about the resistances connected in parallel with R0 because the I-V converter is connected to an instrumentation amplifier. The input impedance of an instrumentation amplifier is infinity. R0 in parallel with infinity is just R0. As a result, the voltage across R0 in this case is always 0.1V.

E. Instrumentation Amplifier

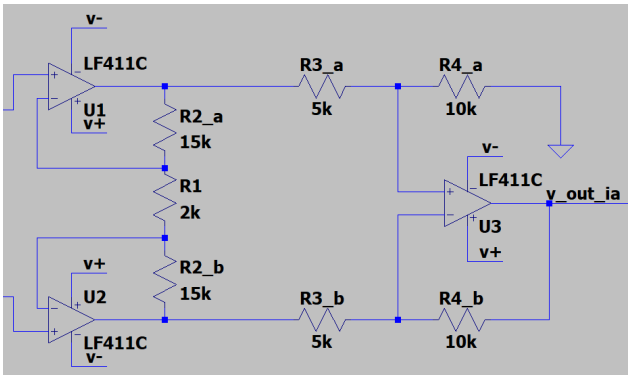


Fig. 8. Schematic of Instrumentation Amplifier

The second stage of the design is an instrumentation amplifier, which is used to amplify the small voltage input signal we generated from the I-V converter. The reason we choose the instrumentation amplifier is easy, because it has large gain, low noise, and high CMRR.

We use LF411C op-amp models in our design, and they are powered with +15V and -15V power supply. Since we do not want the LF411C op-amp to saturate, we selected our gain of the instrumentation amplifier to be 32V/V.

The gain equation is given below:

$$Av(gain) \ = \ -(1 + 2 * \frac{R2}{R1}) * \frac{R4}{R3}$$

From the equation above, we choose R1 = 2kΩ, R2 = 15kΩ, R3 = 5kΩ, and R4 = 10kΩ. With these values, we have the gain of the first stage(including U1 and U2) =

$$1 + 2 * \frac{R2}{R1} \ = \ 1 \ + \ 2 * \frac{15k}{2k} = 16V/V$$

and gain of the second stage(including U3) =

$$\frac{R4}{R3} \ = \ \frac{10k}{5k} \ = \ 2V/V$$

This arrangement makes the gain of the first stage > gain of the second stage, which increases the stability of our design. The total gain is achieved by combining the 2 stages gain, which is 32V/V.

F. Comparators

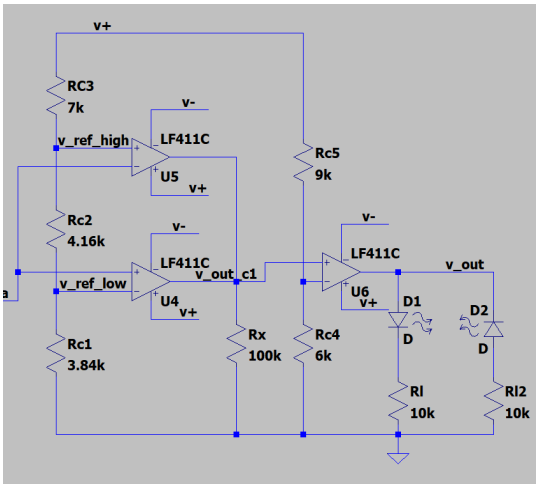


Fig. 9. Schematic of comparators

The goal of designing the comparator circuit here is to differentiate normal glucose level and too high or too low glucose level. If the glucose level is normal, the green LED light will be turned on. If the glucose level is too high or too low, the red LED will be turned on.

The design of the comparator can be divided into two parts, the first part is consist of two stacked op-amps (U4 and U5) and 4 resistors (Rc1, Rc2, Rc3, and Rx), and the second part is consist of 4 resistors (Rl, Rl2, Rc4 and Rc5), 2 LED (D1 and D2), and 1 op-amp.

In the first part of the comparator, we connect the output of the instrumentation amplifier (name it vin_c) to vin+ of U4 and vin- of U5. Op-amp U4 will amplify the difference between vin_c and v_ref_low, and Op-amp U5 will amplify the difference between v_ref_high and vin_c. Since the outputs of the 2 Op-amps are connected together, the output of first stage comparator (v_out_c1) only has 3 situation:

- If vin_c < v_ref_low, output of U4 will be -15V (the negative supply voltage), and output of U5 will be +15V(positive supply voltage). This will give us v_out_c1 = 0V since the 2 outputs are connected together.

- If v_ref_low < vin_c < v_ref_high, output of U4 will be +15V(the positive supply voltage), and output of U5 will be +15V(positive supply voltage). This should give us v_out_c1 =30V, but since the upper limit is set by the positive supply voltage, the v_out_c1 is clipped at 15V.

- If vin_c > v_ref_high, output of U4 will be +15V(the positive supply voltage), and output of U5 will be -15V(negative supply voltage). This will give us v_out_c1 = 0V.

The choice of Rc1, Rc2, and Rc3 values is based on the upper limit and lower limit of the glucose value. As mentioned before, the lower bound of normal glucose level is 120 mg/dL, which induces a current of 12uA. The upper bound is 220 mg/dL, which induces a current of 25uA. If we pass 12uA and 25 uA through our circuit, we will have the output of the instrumentation amplifier equal to 3.84V and 8V, respectively. By setting up a simple voltage divider circuit, we find Rc1 = 3.84kΩ, Rc2 = 4.16kΩ, and Rc3 = 7k Ω.

However, the problem with the first stage is that it cannot generate v_out_c1 = -15V(negative supply voltage) to turn on the reversely connected LED(D2). v_out_c1 only generates voltage as low as 0V, which is not sufficient to turn on a LED that has a threshold voltage of 0.7V. As a result, we connect a second stage comparator circuit, which can pull the output voltage as low as -15V to make the LED in working range..

The choice of Rc4 and Rc5 is based on the DC sweep result of v_out_c1 versus i_in. We want to make sure that v_out = -15V when i_in >25uA or i_in < 12uA. Based on this, we set up a voltage divider circuit and select Rc4 and Rc5 to set the reference voltage at v- of U6. The use of Rx is to draw the current from previous stage output to ground. Rl and Rl2 are used to prevent LEDs from breakdown, because v_out has magnitude of 15V >> 0.7V, which might burn the diodes.

G. *Full circuit diagram and simulation results*

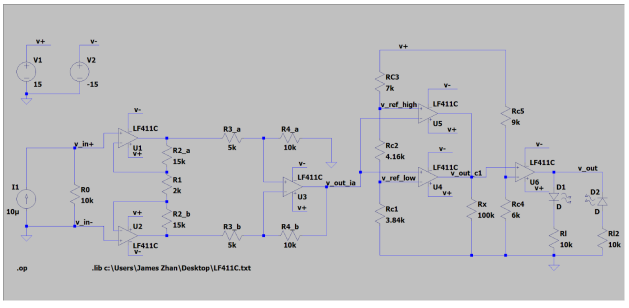
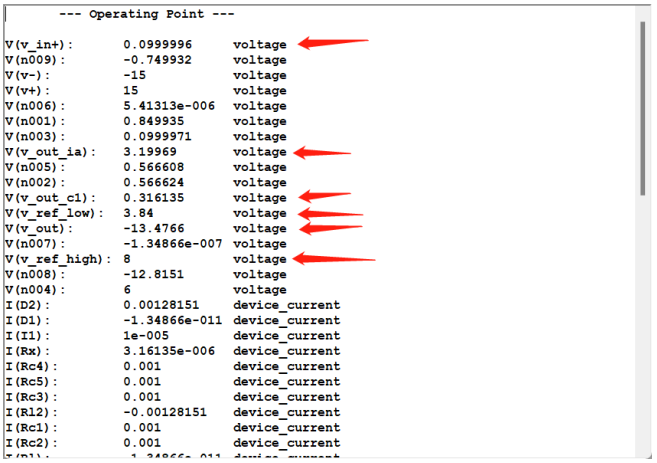


Fig. 10. Schematic of full circuit

Using LTspice, we did DC operating point and DC sweep simulations, and the results met our expectations.



--- Operating Point ---

V(v_in+):	0.0999996	voltage
V(n009):	-0.749932	voltage
V(v-):	-15	voltage
V(v+):	15	voltage
V(n006):	5.41313e-006	voltage
V(n001):	0.849935	voltage
V(n003):	0.0999971	voltage
V(v_out_ia):	3.19969	voltage
V(n005):	0.566608	voltage
V(n002):	0.566624	voltage
V(v_out_c1):	0.316135	voltage
V(v_ref_low):	3.84	voltage
V(v_out):	-13.4766	voltage
V(n007):	-1.34866e-007	voltage
V(v_ref_high):	8	voltage
V(n008):	-12.8151	voltage
V(n004):	6	voltage
I(D2):	0.00128151	device_current
I(D1):	-1.34866e-011	device_current
I(I1):	1e-005	device_current
I(Rx):	3.16135e-006	device_current
I(Rc4):	0.001	device_current
I(Rc5):	0.001	device_current
I(Rc3):	0.001	device_current
I(Rl2):	-0.00128151	device_current
I(Rc1):	0.001	device_current
I(Rc2):	0.001	device_current

Fig. 11. DC operating point result

The above graph shows the DC operating point voltages. We can see all the values are very close to our calculations. The output of the I-V converter is approximately 0.1V, same as out hand calculation. The output of the instrumentation amplifier is approximately 3.2V, also same as out hand calculation. The only thing that is a bit off is v_out, which should be -15V given I_in =10uA but it is actually -13.5V. This is probability because the device models we are using have a minimum limit of -13.5V for supply voltage.

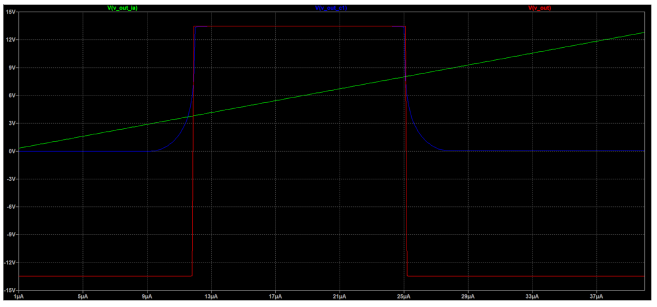


Fig. 12. DC sweep result

We also did a DC sweep for v_out, ranging I_in from 1uA to 40uA. The waveform of v_out is exactly the same as our expectations. When I_in < 12uA, v_out =-13.5V, turning on red LED D2; when 12uA < I_in < 25uA, v_out =+13.5V, turning on green LED D1; when I_in > 25uA, v_out =-13.5V, turning on red LED D2.

H. *Limitations and future improvements*

Indeed, there are some limitations to our design and we proposed possible future improvements.

- A platinum electrode is not ideal for point of care tests due to its high costs. Future improvement may include finding an alternative electrode (such as a platinum coated carbon-based electrode).
- Variations in sample conditions, such as pH, could influence both the reaction and the readings. Future improvements need to account for the variation, such as adding buffers to the solution.

- We do not have actual measured data of current value with respect to the glucose concentration.
- LF411C op-amps are usually powered by a 15v and -15v supplies, which might lead to high power consumption. Future improvements may include finding more energy efficient op-amp models.
- There are no differentiations for high glucose level or low glucose level. We may assign more LED colors to indicate different levels..

IV. Conclusion

In this study, we analyzed an enzyme-electrode based glucose test strip, and based on its electrochemical reaction, designed a glucose level LED indicator. One advantage of our design is that the result is easy to interpret, with green light indicating normal glucose level and red light indicating abnormal glucose level. Another advantage of our design is that the component values of the circuit design are straightforward based on mathematical expression, which can be easily adjusted according to data measurement. We hope that this design can serve as the foundation for future glucose and other chemical testing designs.

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