Tracking Progression of Parkinson's Disease with an EOG

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***Abstract*—Patients with Parkinson's Disease (PD) often exhibit impaired motor functions, which can include unwanted small, rapid motions of the eye. Such movements, called saccades, can inhibit a patient's ability to read and scan their visual environment. Saccades are relatively easy to measure and can act as a biomarker for the progression of PD which can help with patient treatment and care. Our circuit design utilizes an electrooculogram (EOG) to measure the small movements of the eye in patients exhibiting these symptoms. In the simulated design, electrode pairs around a person's eye measure the horizontal and vertical movements and generate a voltage signal. This voltage signal is amplified and filtered so that only the rapid eye movements (saccades) remain. The frequency of these saccades, also known as inter-saccadic intervals (ISI), can be a key biomarker for Parkinson's Disease.**

Keywords—*Parkinson's Disease, saccades, electrooculogram, inter-saccadic intervals*

I. INTRODUCTION

A. Parkinson's Disease and Saccades

Parkinson's disease is a progressive, neurodegenerative condition caused by the death and destruction of dopaminergic cells in an area of the basal ganglia, called the substantia nigra. This loss of cells causes damage to the central nervous system (CNS) and can cause symptoms such as tremors, slowness in movement, limb stiffness, and postural instability [9]. Saccades are also very common in patients with PD and begin in the first of five stages of disease progression. These quick eye movements occur normally in healthy eyes, especially during non-rapid eye movement (REM) sleep [5]. However, PD patients often unwillingly experience these small movements with their eyes open. According to Pretigiani and Optican (2017), saccades can be used to track the progression of PD: "Anomalies are more evident in voluntary than reflexive saccades in the initial stages, but visually guided saccades may also be involved at later stages" [4].

B. Electrooculogram

Clinical applications of the EOG were first discovered in 1962 and are often used in clinical practice today. An EOG measures the electrical potential of the eye between the cornea and Bruch's membrane [3]. Measurements can be observed by placing electrodes on the skin outside of the eye, which will detect changes in the vectors of the electric field due to eye movement. Eye movements can be described in three different axes. The horizontal (movement of the eye towards and away from the nose), vertical (movement of the eye up and down with slight rotation towards the nose), and torsional (rotates the top of the eye towards the nose with a slight depression and away from the nose with a slight elevation) [10].

C. Goal of Design

Motor neurons in the brain control the muscles surrounding the eyes. These muscles have electrical activity for controlling the position of the eye and a phasic component for controlling eye movement velocity which is integrated to control eye movement, including saccades [10]. Our goal is to create a circuit designed to safely measure the changes in electrical activity of an eye of a patient with PD, enabling the disease progression to be tracked for proper clinical treatment.

II. SIMULATING THE CIRCUIT

A. Scope of Design

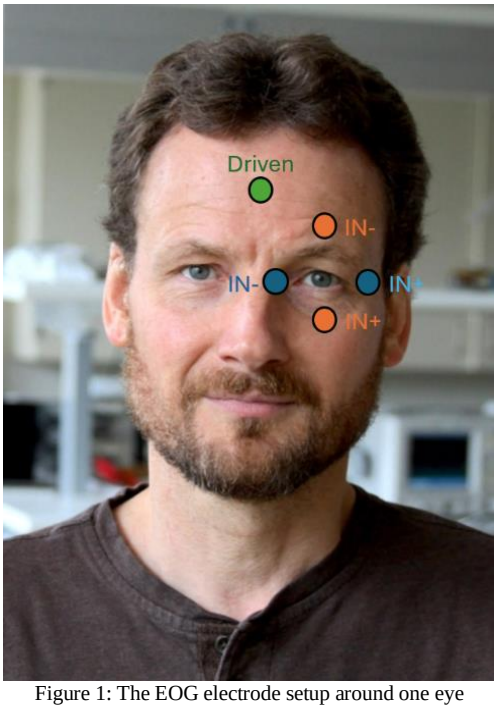


Figure 1: The EOG electrode setup around one eye

For our EOG design, we will have four electrodes surrounding one eye, shown in Figure 1. Two electrodes will

be placed to the right and left of the eye while the other two electrodes will be situated above and below the eye. This allows for EOG measurements in the horizontal and vertical directions, which are necessary for analyzing the saccades of the user. Our EOG design also incorporates a driven electrode shown in green of Figure 1, which serves as the active ground. This reduces the likelihood of mismatched impedance through the usage of operational amplifiers to drive the ground potential. This driven electrode helps to minimize any voltage drops and any distorted output signals that are caused by mismatched impedance. Impedance matching is important for our EOG circuit design because we want a high-efficiency transfer of signals with low probability of signal distortions to accurately analyze healthy signal readings from a healthy person versus an individual with PD. Without this driven electrode, there exist signal reflections that negatively reduce the circuit's performance and will display a distorted output signal [11].

B. Circuit Overview

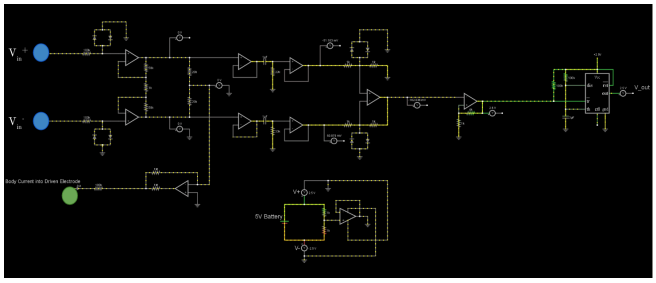


Figure 2: The full circuit design for a pair of horizontal electrodes around one eye

Figure 2 shown above is our full EOG circuit design, where the blue dots represent a pair of horizontal electrodes and the green dot is the driven electrode (See also, page 7 for enlarged figure). This circuit design would be used for horizontal (shown as blue electrodes) and for vertical (shown as orange electrodes) movement, but for clarity, we will only be reviewing the circuit design for horizontal movement. For this full circuit diagram, the ground is defined as the ground from the battery. The ground of the driven right leg (DRL) component is equivalent to the ground from the driven electrode. To briefly overview the diagram, our circuit design sends the input signals from the electrodes to a differentiable input stage. This ensures a smooth output signal based on the fluctuations of the received input signal from the electrodes. Then, the signal passes through an active grounding which aims to maintain a steady voltage level and helps reduce any noise. Next, the signals pass through a passive high-pass filter to eliminate unwanted frequencies (such as from blinking) and through a differential amplifier to amplify the remaining saccadic frequencies. Next, there is an inverting hysteric comparator to assist in further stabilizing the signal, and a monostable 555 timer to relate a time interval to the received input electrode signals. Lastly, the output voltage signal will be displayed via a monitor. All power used by the circuit comes from a 5-volt battery.

C. Electrodes

The electrodes are responsible for obtaining voltage signals from the eyes. Each electrode has an impedance which is represented by a resistor. Typically, these resistors are about 100kΩ each. In our circuit, the electrodes around the eyes are all silver-silver chloride. Having the same type of electrode for each circuit is important because an electrode impedance mismatch can decrease the common-mode rejection ratio (CMRR) by affecting the differential gain. When considering the effect of common-mode signals, the voltage at the output of the amplifier would be

$$V_o = A_d V_d + A_{cm} V_{cm}$$

where V_o is the output voltage of the amplifier, A_d is the differential gain, V_d is the differential voltage at the amplifier's input, A_{cm} is the common-mode gain, V_{cm} is the common-mode voltage at the amplifier's input. Ideally, A_{cm} would be zero and CMRR would be infinite.

It is expected that the electrodes will measure a voltage in the millivolt range based on experimental values for PD as stated in [7]. In the simulation, a value of 6 mV was used. Since this value is small, shielding around the electrode wires can be used to reduce common-mode signals such as noise. For example, a twisted cable pair or coaxial cable configuration can be used to decrease the noise at the electrodes and thus decrease the common-noise signals so that there's little to no common mode signal the differential amplifier can amplify.

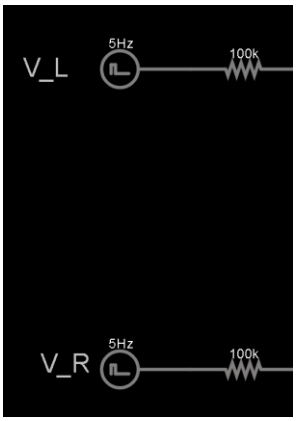


Figure 3: Representation of horizontal electrodes in Falstad simulation circuit

Figure 3 shows the horizontal electrodes in the simulation circuit. V_L is the voltage signal from the left electrode while V_R is the voltage signal from the right electrode. An A/C voltage source with a pulse waveform was used to represent the input signal that the electrodes would obtain. The pulse waveform was selected because it matched what was expected from saccadic eye movements. While the eye is moving, voltage created by changes in the electric field increases and stays constant until the eye stops moving. At this point, the voltage signal drops down to 0 mV. The resistors (previously described as electrode impedances) in series with V_L and V_R are both standard values of 100kΩ.

D. Fully Differentiable Input Stage

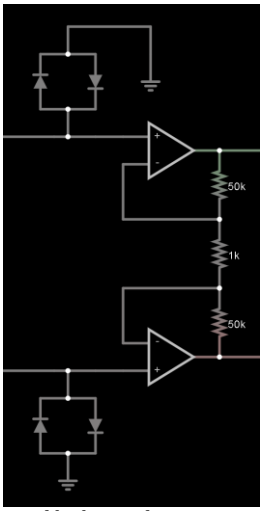


Figure 4: Fully differential high impedance gain stage with double diode bidirectional clipping

This stage (depicted in Figure 4) amplifies the signals from the electrode and decreases the effects of common-mode signals. The gain for this stage is

$$A_d = 1 + \left(2\frac{R_2}{R_1}\right)$$

where R_2 = 50 kΩ ± 1% and R_1 = 1 kΩ ± 1%. The worst-case gain would occur when the gain is at its lowest possible value. This would happen when R_2 is 1% lower and R_1 is 1% higher than they should be. Thus,

$$A_{d,worst-case} = 1 + \left(2 \cdot \frac{49.5k\Omega}{1.01\,k\Omega}\right) \approx 99$$

Assuming resistance values are accurate, we would expect an $A_d = 101$. Furthermore, the common-mode gain for this design is $A_{cm} \approx 1$ and as a result,

$$CMRR = \frac{A_d}{A_{cm}} = \frac{101}{1} = 101$$

or about 40 dB.

E. Active Grounding and Power Source

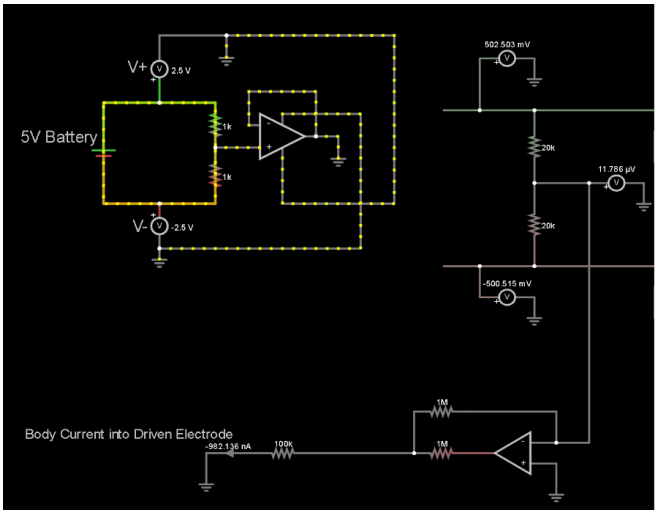


Figure 5: Active grounding and 5V battery circuit components.

All stages of the circuit are powered with a 5 V battery (shown in Figure 5), so all the op-amps in those stages have voltage rails from +2.5 V to –2.5 V.

The purpose of the active grounding is to achieve effective common-mode rejection and prevent a mismatch between electrode impedances from lowering the CMRR. The DRL active grounding lowers the right leg impedance by using a feedback gain of

$$1 + \frac{R_f}{R_d}$$

In the simulation, the feedback gain from the active grounding is

$$1 + \frac{1M\Omega}{100\,k\Omega} = 11$$

Our circuit was designed to only draw 2.5 µA from the patient, so R_o must equal 1 MΩ.

F. Passive High-Pass Filtering

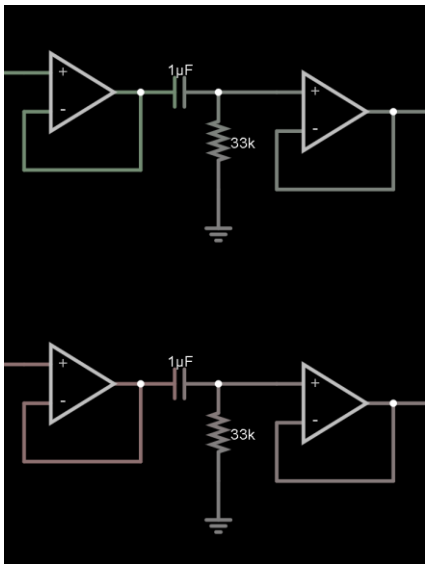


Figure 6: Passive high-pass filter.

The passive high-pass filtering is present to filter out the lower frequencies that correspond to smooth pursuit eye movements. Typical ISI measurements are between 180-200 milliseconds, or roughly 5-5.56 Hz [7]. Since PD patients experience a higher frequency of saccades, the ISI measurements will be shorter. Thus, we want to let any frequencies higher than 5 Hz pass through the filter unattenuated.

The cut-off frequency for the high-pass filter was calculated using the formula:

$$F_c = \frac{1}{2\pi RC}$$

We let C = 1 µF and then tried to find the smallest resistance value R that would still give us F_c < 5 Hz. We found the worst-case scenario by using the tolerances of each component. Since we used 1% tolerances, the worst case occurs when the actual resistance is 1% smaller than the nominal resistance because a smaller value in the denominator leads to a bigger cut-off frequency. We found

that the resistor had to be at least 33 kΩ to make the inequality above true.

G. Differential Amplifier

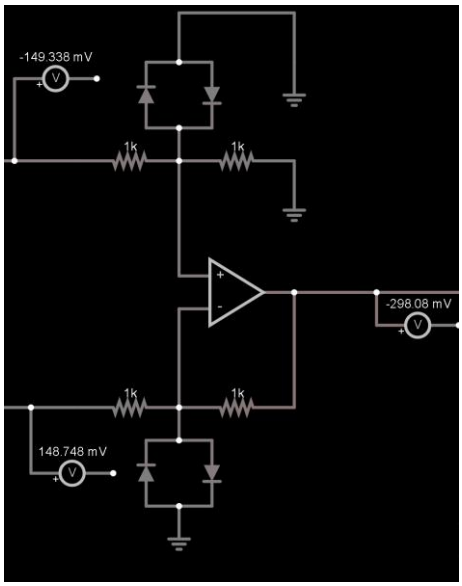


Figure 7: Differential amplifier design.

The differential amplifier takes the outputs from the high-pass filters and takes the difference between the two voltages. This component outputs a waveform that has peaks or valleys when the eyes quickly rotate horizontally in either direction which occurs during a saccade. We chose a gain of 1 for this component so that our overall differential gain remains ~101 from the fully differentiable gain stage.

We expect an output signal of ~600 mV. To ensure our amplifier is not overdriven by high voltage inputs, we use two sets of double diode bidirectional clipping. These diodes prevent voltages higher than the forward voltage (~0.7 V or 700 mV) from flowing into our amplifier. Any voltage greater than |700 mV| will flow through the diodes instead of the amplifier. Any voltage between –700 mV and +700 mV will completely flow through the amplifier with the current through the diodes equal to zero.

H. Inverting Hysteretic Comparator

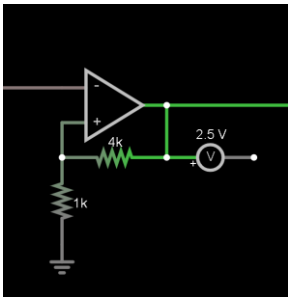


Figure 8: Inverting hysteretic comparator design.

The Inverting Hysteretic Comparator Takes the output from the differential amplifier and converts the signal into a square wave. The output of the comparator is high (equal to V^+) when the input drops lower than 1/5th the negative voltage rail and switches low (equal to V^-) when the input voltage raises higher than 1/5th the positive voltage rail. These values are calculating by the following:

$$V_{reff}^{+} = \frac{1\ k\Omega}{1\ k\Omega + 4\ k\Omega} \cdot V^{-}$$

$$V_{reff}^{-} = \frac{1\ k\Omega}{1\ k\Omega + 4\ k\Omega} \cdot V^{+}$$

where $V^+ = +2.5V$ and $V^- = -2.5V$

I. Monostable 555 Timer

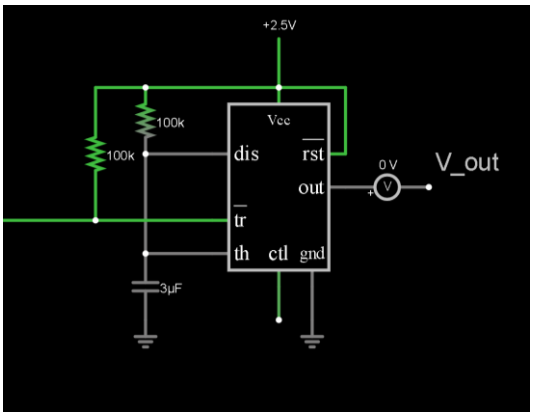


Figure 9: Monostable 555 timer design.

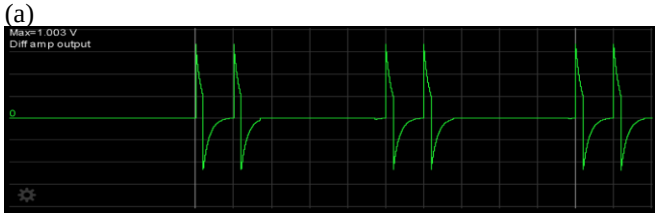
The monostable 55 timer uses the square wave output from the inverting hysteretic comparator as its input and outputs a pulse on every falling edge of that input. Each falling edge of the input represents the start of one saccade. The pulse width of the output wave is matched with the duration of one saccade (~300 ms) so that one full saccade can be translated to one pulse. The pulse width is determined by the following:

$$T = \ln(3)\, RC$$

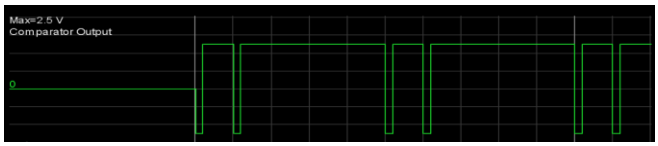
$$330\ ms = (1.1)(100 \times 10^{3}\Omega)(3 \times 10^{-6}F)$$

J. Output Signals

(a)



(b)



(c)

Figure 10: Output signals from different parts of our circuit design. (a) Output signal from differential amplifier. (b) Output signal from the inverting hysteretic comparator. (c) Output signal from the monostable 555 timer.

Figure 10 (a) shows the output signal from differential amplifiers. The differential amplifier outputs a pulse wave where each grouping of peaks represents one saccade. One

thing to note is since this is the output of only one pair of electrodes that tracks horizontal direction, there is another identical circuit with a similar output for the vertical direction for the second pair of electrodes monitoring vertical movement.

Figure 10 (b) shows the output signal from inverting hysteretic comparator. The comparator takes output from differential amplifier as an input signal. We can synchronize figure 10 (a) and (b) and confirm that it is inverting and has hysteresis. When output signal of differential amplifier is positive and above V_ref(+) = 0.5V, comparator output is –2.5V. However, when output signal of differential amplifier is negative and below V_ref(-) = -0.5V, comparator output is +2.5V until differential amplifier output passes V_ref(+).

Figure 10 (c) shows the output signal from the monostable 555 timer, which takes output of comparator as an input. Synchronizing with figure 10 (b) and (c) shows that monostable 555 timer generates a single pulse of constant width upon a falling edge at the output of comparator. Width of pulse is determined by the R and C value of the timer, width = R*C*ln(3). R and C values were chosen to capture the full saccade without being triggered twice for the pulse within the same saccade, which the width is 330 milliseconds. Eventually, square wave outputted from the timer represents each saccade and time difference between square wave is called inter saccadic interval (ISI). Using ISI, we can calculate frequency of saccades.

III. CONCLUSION

A. Summary

From our design, we successfully got an output signal of EOG, given as a voltage peak of differential comparator output. By inputting the EOG signal into an inverting hysteretic comparator and monostable 555 timer, we were eventually able to get square waves that represent each saccade and have a width of 333 milliseconds. By analyzing the time between square waves, we can get the frequency of saccades, which can be used to diagnose severity of PD and track progression of the disease. Moreover, it could be used to test the effectiveness of PD medication or treatment.

B. Weaknesses

We have objectively reviewed our design and we have identified several factors that can be seen as weaknesses. First, the output signals of our design are from a simulation and not from an actual human subject. This is critical because there are many factors that could affect the output signal when it is applied to human subjects. For example, there is biological variability among human subjects or patients. Variability in physiological parameters or movement artifact can impact the output of the device. Moreover, there could be noise from components of our design itself. Second, for our design to achieve its goal (diagnosing PD severity and progression) it needs well-trained physicians to analyze the signal and give diagnosis. It requires extra time and costs to have a physician. According to the University of Medicine and Health Sciences, it takes at least 12 years of education and training to become a doctor who has neurology as a medical specialty [12]. Lastly, our design can only give fractional information about PD based on eye movements. PD is a disease that has many biomarkers besides eye movements such as tremor in different parts of body. However, our device is limited to observing and measuring based on eye movements.

C. Plans for Improvement

Based on weaknesses we have identified; we have come up with several plans to make improvements in our design. First, to deal with potential differences in outcome between simulation and human subjects, we will go through clinical trials as many as possible in human subjects. This way, we will be able to face practical problems in our design and biological variability and make changes or adjustments in our design. Second, to be able to replace physicians and reduce costs and time, we will develop machine learning (ML) algorithms and implement them with a microcontroller (MC). ML algorithms will sensitively distinguish saccades patterns and be able to classify into different PD severity and progression. MC can collect output signals as input and run ML algorithms to give a diagnosis. ML algorithms and MC are essentially doing what physicians are supposed to do, reading signals and giving a diagnosis. Lastly, we will develop an integrated sensor that can give a better picture of PD. An integrated sensor is a sensor where different biosensors are integrated into one and can collect different biomarkers of the disease. For example, we can integrate our design with Inertial Measurement Unit (IMU) or accelerometer so that we can capture two different biomarkers of PD: saccades in eye movements and tremor of body parts. One of the capabilities of IMU and accelerometer is that it can measure a change of acceleration, which fits with the characteristic of tremor of PD. According to Parkinson's Foundation and Parkinson's UK, tremor tends to start asymmetrical usually at one part of body during early stage of the disease and it may get worse and spreads out to other body parts as PD progresses [13] [14]. Therefore, integrating IMU or accelerometer with our design can give better picture about severity and progression of PD.

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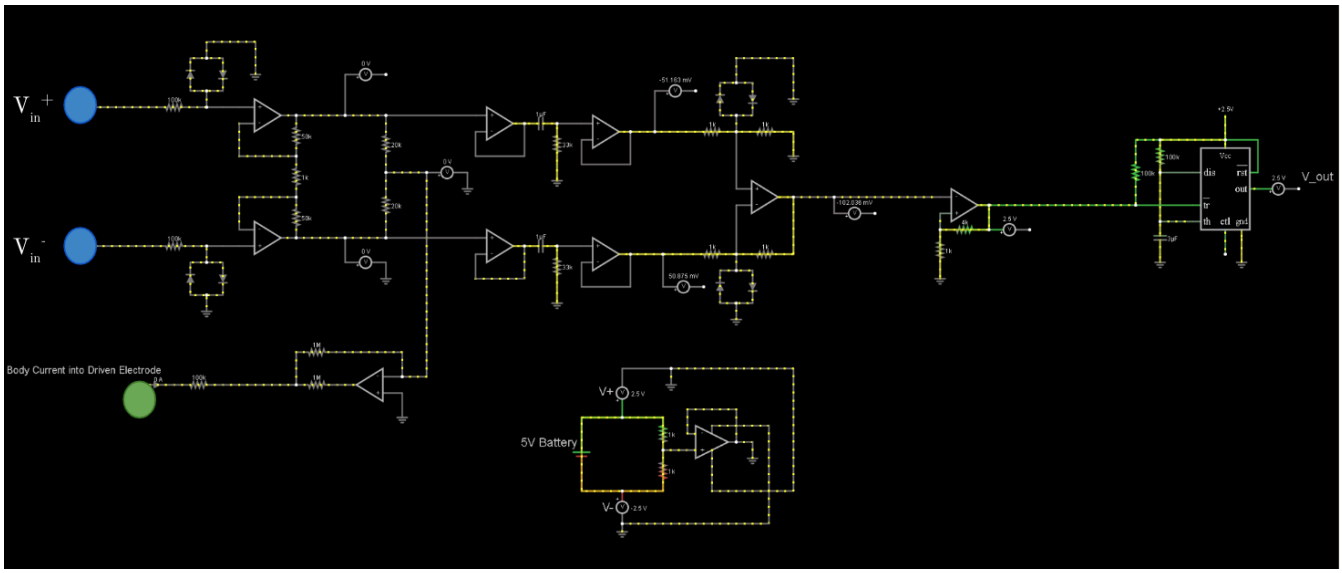

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