Utilizing Interphase Gap in Sinusoidal Waveform Stimulation Currents to Minimize Threshold Currents for Retinal Implants

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Over 170 million people are affected by retinal degeneration globally; therefore, this is the leading cause of irreversible blindness. Retinal degeneration is caused by age-related macular degeneration (AMD) or retinitis pigmentosa (RP) and there is no cure for these diseases. However, new technology surrounding restoring vision for those with retinal degeneration is in development. One of the most promising technologies being developed is retinal implants. Retinal implants are the only FDA-approved treatment for retinal degeneration and they are being surgically implanted across the globe. Retinal implants work by using a stimulation current to elicit neural responses from the brain. However, if too high stimulation currents are used to elicit neural responses, retinal-tissue damage can occur and the visual processing unit (VPU) will require charging more often. This paper looks at a method to solve these problems by sending a sinusoidal stimulation pulse with varying interphase gap durations to identify lower minimum threshold currents in a single ganglion cell model. Results seen in the single-cell model are validated at the epiretinal layer in a network-level model.

Keywords: Retinal Degeneration, Retinal Implants, Retinal Tissue Damage, Stimulation Current, Threshold Current

I. INTRODUCTION

Retinal degeneration is a progressive retinal disease most often caused by retinitis pigmentosa (RP) or age-related macular degeneration (AMD), for which there is no cure approved by the Food And Drug Association. Over 170 million people in the world suffer from AMD and over 92,000 people with RP [1, 2]. Retinal degeneration often starts with a person losing fragments of vision but over time as the disease progresses, people often develop irreversible blindness [3].

However, new technologies surrounding restoring vision are in development known as retinal prostheses or retinal implants. Retinal implants are currently the only FDA-approved treatment for retinal degeneration and therefore research into making the device safer and more feasible is growing largely.

Retinal implants seek to use electric stimulation to elicit a neural response in the brain seen as phosphenes in the vision [4]. Electrical stimulation causes neurons to reach the threshold potential and further depolarize the neurons; therefore, causing an action potential. The action potential is responsible for the introduction of the phosphenes in the patient with retinal implant's vision. Using electric stimulation to elicit a neural response is not new and was discovered long ago; however, being able to accurately represent the surrounding environment using phosphenes and electrical stimulation has been a tough task [4]. But most importantly, the safety of the retinal implant has been a larger concern for both users and medical professionals [4]. If higher intensity currents are sent through the electrodes to retinal layers, the potential for nerve and retinal tissue damage is elevated. Though retinal implant systems like Argus II can process images into neural signals, the current intensities injected by the electrodes into the retinal surface are still a large problem waiting to be solved.

Therefore, we wish to make retinal implants safer by using a smaller minimum threshold current. The minimum threshold current is defined as the amount of current required for the neuron to fire an action potential. This would allow for a smaller amount of current to be sent each time for the neural response to be elicited, therefore making the device safer with less potential for neural and retinal damage. Attempts to optimize various parameters have been done before such as using an interphase gap in biphasic pulses, developing and using asymmetric waveforms, or changing the frequency of the pulse.

Based on successes seen in varying interphae gap values in biphasic pulses with [8] and using only a sinusoidal waveform pulse in [9], we sought to combine the two to identify whether our work on sinusoidal waveforms integrated with interphase gap durations can be used as a means to lower the minimum threshold current required for stimulation of ganglion cells. [9] notes that the use of sinusoidal pulses in retinal implants is beneficial as it provides larger control over neuronal activation and has important implications.

This paper seeks to analyze the effects of changing the format of sending currents to a sinusoidal form and varying interphase gap durations on the sinusoidal wave. Threshold currents for each of the interphase gap values and the trend between minimum threshold current and interphase gap duration was analyzed. These results were validated in a network-level model capable of testing at the subretinal and epiretinal layers with multiple cells to ensure the accuracy of the results. For the purpose of this research, we tested with the retinal implant being simulated at the epiretinal layer.

Based on our current research, we have found that the minimum threshold current required in sinusoidal-shaped pulses can be decreased using an interphase gap duration. This addition of the interphase gap can lead to future retinal implant devices including this novel sinusoidal waveform with options of configuration such as interphase gap.

II. METHODS

To approach the problem of finding whether interphase gaps in sinusoidal pulses are capable of lowering minimum threshold currents for stimulation of retinal neurons, five main steps were taken. A neuron model was developed to identify the number of neurons that spike based on the input stimuli pulse. Next, a sinusoidal pulse was developed based on parameters identified in [8]. After this, the sinusoidal pulse was modified to add interphase gap durations between the anodic and cathodic phases of the pulse. Based on the new pulse, minimum threshold currents were found for varying interphase gap duration values in a single cell model. Once the relationship between interphase gap durations in sinusoidal pulses and minimum threshold current was found, a network-level model was constructed. This model included a subretinal and epiretinal layer but we tested our stimulation current at the epiretinal layer. Similar to the single-cell model methods, minimum threshold currents for the network level model were found as well.

A. Development of the Single Cell Neuron Model

To develop and model an accurate representation of the single ganglion cells in the retina, we generated a computational model based on the tiger salamander retinal single ganglion cell model outlined in [6]. As compared to the Hodgkin-Huxley model which has 3 ion channels, the Fohlmeister model was selected for its accurate modeling of single retinal ganglion cells and wide use in the research of retinal prostheses. Moreover, this single-compartmental model was selected for its active spike generation, incorporation of 5 different ion channels (sodium, calcium, and three different potassium channels), and leakage along with its simplicity. The equation for the neuron model can be found in Equation 1. Values of the ion and capacitative currents can be found in [6] and [7]. Values of $g_{K,\,Ca}$ and V_{Ca} were modeled after equations listed in[6] to maximize the accuracy of the neuron model. Variables of (m, h, c, n, a, h_A) were modeled after equations found in [6].

$$C_m\frac{dV}{dt} + \bar{g}_{Na}m^3h(V - V_{Na}) + \bar{g}_{Ca}c^3(V - V_{Ca}) + (\bar{g}_K n^4 + \bar{g}_A a^3 h_A + \bar{g}_{K,Ca})(V - V_K) + \bar{g}_L(V - V_L) = I_{stim} \quad (1)$$

The respective alpha and beta equations used for each sub-variable of (m, h, c, n, a, h_A) can be found in [6].

B. Generating Sinusoidal Pulses with Interphase Gap

To generate a sinusoidal wave, the python library of Pulse2Percept was used. A standard sine wave was generated and then downsampled. Based on the downsampled array, the array was altered using computation tools to insert an interphase gap duration (IPG) while maintaining desired frequency values. Parameter values from the tiger salamander retinal test such as frequency, pulse width, and the number of pulses were used from [8].

Values such as stimulation duration and pulse gap were further calculated to implement interphase gap within the sinusoidal wave while maintaining the desired frequency of 167 Hertz, pulse width of 0.46 milliseconds. Based on stimulation duration and frequency, the length of each pulse was calculated, and thereafter, values of the interphase gap, pulse width, and pulse gap were taken into consideration when generating the final pulse. For the purpose of generalizing a relationship between IPG and minimum threshold current, we tested values of interphase gap (in milliseconds): [0, 0.12, 0.24, 0.34,0.46, 0.92, 1.38, 1.84].

After the neuron model and pulse were constructed allowing for varying interphase gaps, a spike monitor function was written to identify the number of spikes that take place with a given current value.

C. Finding Minimum Threshold Current on the Single Cell Model

However, since the stimulation current within the pulse was varying with time since different millisecond values had different amplitudes of current, a timed array was generated and implemented to ensure the current values follow the sine wave pulse. Therefore when implemented in the neuron model, values from the timed array were sampled at an interval of every 0.01 millisecond.

Now that the input stimuli pulses, spike monitor, and neuron model were generated, the target number of spikes was set at 50% of the number of the electrical pulses and was based on the work of [8]. 30 pulses were sent in our simulations and therefore the target spikes value was set at 15 spikes. Based on the end goal of finding the minimum threshold current required for stimulation at each distinct interphase gap value, a bisect function modeled after the

bisection method, which worked by providing a range of current and continually testing values halfway through a newly created range. Depending on whether the spikes at the tested amplitude were greater than or less than the target spikes, it would bisect the new range either to the right or the left. The bisect function was derived from the Pulse2Percept library in Python. Results from the bisect function, which outputted minimum threshold currents for the interphase gap value tested on was stored and plotted to generalize a relationship between interphase gap duration in a sinusoidal waveform and the minimum threshold current required.

D. Validating results on the Network-level Model

A network-level model was created and based on the work of [10]. The network level model allowed for testing at the epiretinal and subretinal layers; however, for this project, the epiretinal layer was chosen. Interphase gap duration values obtained from [8] were still used on this model to ensure that results are consistent with what was seen in the single ganglion cell model developed. Sinusoidal pulses with the same waveform were used as well for the network-level model. Like the single ganglion cell model, 30 pulses had been sent for the same stimulation duration and the target spike value was set at 15 spikes. After all parameter values to test on the network level were identified, simulations using Brian2Genn were conducted to identify minimum threshold currents for each interphase gap value. The use of GPU systems was necessary to speed up simulation time and conduct such computationally intensive operations.

III. RESULTS

We designed a new sinusoidal waveform input stimuli pulse with different IPG values ranging from 0 milliseconds to 1.84 milliseconds. We seek to use the generated sinusoidal pulse to find lower minimum threshold current values that make retinal implants safer devices as well as make the visual processing unit use less power.

A. Sinusoidal Pulse Generation

The sinusoidal stimuli pulse was generated for the neuron model to take in as input. Figure 1 shows a sinusoidal input stimuli pulse with an interphase gap of 1.84 milliseconds inserted between the anodic and cathodic phases. The frequency was maintained at 167 Hz, the pulse width at 0.46 milliseconds, the stimulation duration at 179.64 milliseconds, and each pulse was calculated to be 5.988 milliseconds. In the case of Figure 1, the pulse gap was 3.223 milliseconds because the interphase gap had been 1.84 milliseconds. Based on the formula derived to calculate the pulse gap for each interphase gap duration, the input stimuli pulses were individually generated.

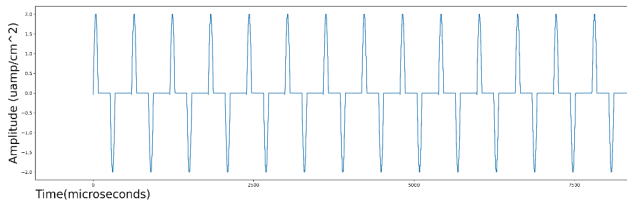

FIG. 1: Displays a generated sinusoidal pulse of 2 microamps/cm^2 amplitude with a pulse width of 0.46 milliseconds, frequency of 167 hertz, and an interphase gap of 1.84 milliseconds.

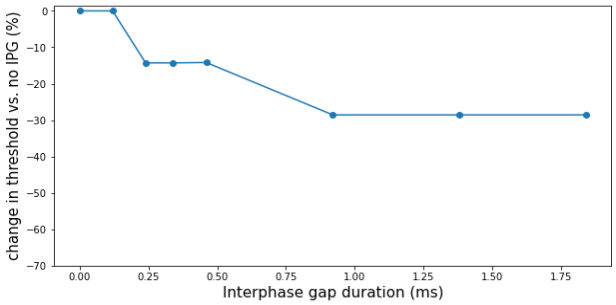

FIG. 2: Shows the percent change between minimum threshold current for each interphase gap value tested at a single ganglion cell model. Displays trend of how minimum threshold values change as interphase gap duration increases from 0 ms to 1.84 ms

Interphase Gap(ms)	Minimum Threshold Current($microamps/cm^2$)
0	87.5
0.12	87.5
0.24	75.0
0.34	75.0
0.46	75.0
0.92	62.5
1.38	62.5
1.84	62.5

TABLE I: Minimum threshold current for single-cell model

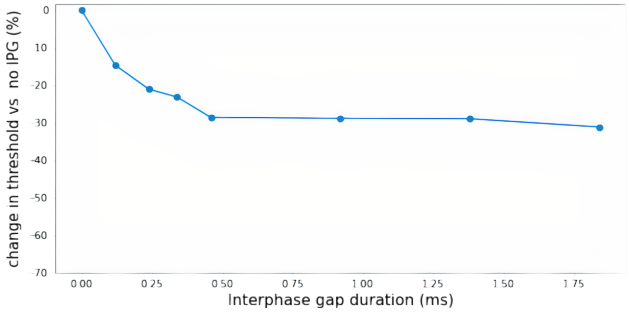

FIG. 3: Shows the percent change between minimum threshold current for each interphase gap value tested at the network-level model within the epiretinal layer. Displays trend of how minimum threshold values change as interphase gap duration increases from 0 ms to 1.84 ms

Interphase Gap(ms)	Minimum Threshold Current($microamps/cm^2$)
0	3.5449
0.12	3.0225
0.24	2.7939
0.34	2.7204
0.46	2.5276
0.92	2.5195
1.38	2.5156
1.84	2.4375

TABLE II: Minimum threshold current for network-level model

B. Single-cell Model

After the input stimuli pulses were generated, they were tested in the single-cell model. After it was inputted into the neuron model and had minimum threshold currents found for, results were gathered. Results derived from Figure 2 show the percent change in minimum threshold current from the initial starting value of 0 milliseconds of interphase gap present for the single-cell model. However, it is noted that as the interphase gap increases from 0 milliseconds to 1.84 milliseconds, the minimum threshold current calculated required for 15 spikes decreases by ~28.57% in the single ganglion cell model setting. Table I displays the calculated minimum threshold current for the single-cell model at each individual interphase gap duration value. Like identified in the overall change in the minimum threshold current values, the table also supports the decrease in the minimum threshold current.

C. Network-level Model

Based on the input stimuli pulse generated, it was tested on the network-level model to derive minimum threshold currents for each of the interphase gap values. Figure 3 displays the percent change in the minimum threshold current from the range of interphase gap duration values between 0 milliseconds to 1.84 milliseconds in a network-level model setting at the epiretinal layer. Based on data from Figure 3, the minimum threshold current required for 15 spikes had dropped ~31.3% from the value of the minimum threshold current with 0 milliseconds of interphase gap present. Table II goes on further to display the individual calculated required minimum threshold current for each interphase gap duration value and displays the similar dropping trend in required minimum threshold current for stimulation.

IV. DISCUSSION AND CONCLUSION

Based on results from the single-cell and network-level model, a trend of the interphase gap durations in sinusoidal pulses affecting minimum threshold current can be identified. For the single-cell model, it is noted that as interphase gap values increase from 0 milliseconds to 1.84 milliseconds the minimum threshold current required for stimulation drops. Previous work in [8] with a single cell model in a biphasic pulse also shows decreases in minimum threshold current with ~25% decrease as IPG increases from 0 milliseconds to 1.84 milliseconds. Based on our sinusoidal pulses with the varying interphase gaps, a ~28.57% decrease in minimum threshold current was noted from 0 milliseconds to 1.84 milliseconds. The results are consistent with those of biphasic pulses; however, with the added benefits of sinusoidal pulses providing larger control over neuronal activation and access to specific neuron classes, the use of sinusoidal pulses with interphase gaps is viable and therefore advantageous to use.

In order to verify the results of the single-cell model, a network-level model was developed and used with simulations containing multiple ganglion cells, photoreceptors and layers allowed for more realistic testing. The network-level model displays the trend between interphase gap duration in sinusoidal pulses and the minimum threshold current but at a network level model in the epiretinal layer. Similar to the single-cell model, a ~31.3% drop in minimum threshold current required for 15 neuron spikes were identified. Therefore, results of the epiretinal layer in the network-level model are consistent with the trend and results identified in the single ganglion cell model. Therefore, adding interphase gaps to sinusoidal pulses has large implications since if current can be stimulated at safe levels, the added benefits of a sinusoidal pulse make it very beneficial for retinal implants.

For future studies in retinal implants and optimizing electrical stimulation parameters, we seek to look at whether similar trends are noted at different layers such as the subretinal layer but most importantly testing at the suprachoroidal layer. Current knowledge on modeling the suprachoroidal layer is quite limited but it is known the surgical procedures in the suprachoroidal layer are much safer. Therefore testing at the suprachoroidal layer would have large implications for future research in retinal implants because making the device safer is a large priority. Along with this, we seek to look at the effects of different parameters on the minimum threshold current required for stimulation such as discretization of sinusoidal pulses which represents the level of downsampling, pulse width of the anodic and cathodic, the use of asymmetric pulses where the cathodic and anodic phase have varying lengths and widths, and triplet pulses.

Because the push for the safety of retinal implants is largely increasing since retinal implant devices are just beginning to get FDA approved and undergoing clinical trials with patients. Therefore the need to find different methods to efficiently lower the minimum threshold current required for stimulation of neurons is growing at a rapid pace.

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