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

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UC SANTA BARBARA
Research Mentorship Program

Overview

- **Retinal Degeneration** –Age Related Macular Degeneration (AMD) and Retinitis Pigmentosa (RP) – is the most common cause of **irreversible blindness**
- **Retinal Implants** are currently **most effective** and only FDA-approved assistive product for Retinal Degeneration on the market
- Retinal Implants work by **sending a stimulation current** through **electrodes** on the **retina**, and in the process **stimulating neurons** in the brain which provide a form of vision which allows for interpretation of large letters
- However, the **current** used to **stimulate** the brain's neurons can occasionally be **too strong** leading to **permanent damage** to retinal and brain tissue.
- We seek to solve this problem by developing a **neuron model** for a single retinal ganglion cell
- After developing the model, we will develop a sinusoidal pulse with varying interphase gap values ranging from 0 milliseconds to 1.84 milliseconds.
- Lastly, newly generated sinusoidal pulse with varying IPG values will be **tested** in a larger **network model** setting to validate results and trends visible in the single-cell model

Retinal Implants

How do Retinal Implants work?

- Work by taking **surrounding visual information** through a camera and converting it into **electrical signals** sent through **electrodes placed on or within the retina** [1]
  - The **electrode placement** plays an important role in the **amount of current** needed to **stimulate** the **neuron cells**
  - Looked at epiretinal layer for the purpose of this research
- The retinal cells convert these **electrical signals** to phosphenes that are **viewed as flashes of lights** in an array-structure with varying brightness levels

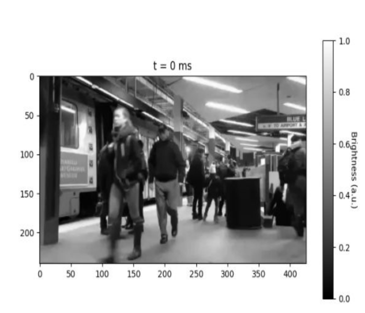

Figure 1: Pre-processed original camera feed

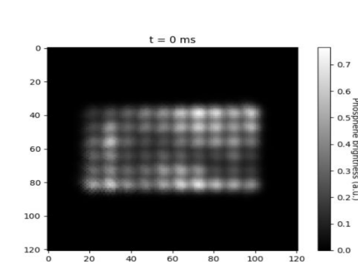

Figure 2: Patient's vision with Argus II implant

Problems with Retinal Implants

- When delivering the stimulation current through electrodes, the **current** can be **too high** [1]
- This can lead to **permanent neural and permanent tissue damage** in the eye
- High stimulation currents can cause the visual processing unit (VPU) to require frequent charging

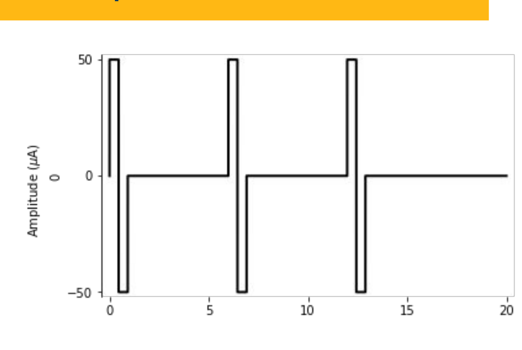

Figure 3: Current method of delivering stimulation current for neurons

Solving this problem

- To solve this problem, we look to **mathematically model** the **response of neurons** to current
- Based on the model, we seek to **vary the form of current** from what is currently used to a **sinusoidal form** with **interphase gap durations** added in between of the anodic and the the cathodic phase

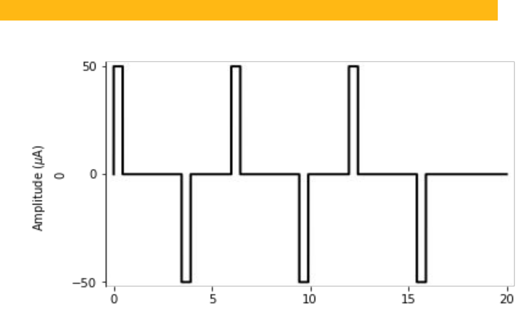

Figure 4: Biphasic pulse with interphase gap added

- Sinusoidal pulses provide increased access to specific neuron classes and assist in neuronal activation
- We seek to combine success seen in interphase gap durations and sinusoidal pulses to identify whether the success of both will be mirrored into sinusoidal pulses with interphase gap
- Test at the epiretinal layer to see whether applicable to retinal implants
- By doing this, we seek to **lower minimum threshold current** and contribute to Retinal Implants becoming **safer** and **more accessible** to the public

Finding Lower Minimum Threshold Currents

Developing a Neuron Model

- In order to approach the large problem of finding a **lower minimum threshold current**, a neuron model capable of identifying the number of spikes needed to be developed
- A **neuron model** can be used to model retinal cells and their response reaction to **input stimulus current**
- Therefore, we decided to use model developed by Fohlmeister et. al 1997 [6].
- The Neuron model can be modeled by Equation 1

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

- Model was **computationally generated** using Python Library: **Brian2**
- **Values** of Calcium Voltage and Capacitive current of Potassium/Calcium were **modeled** using equations listed in Fohlmeister et. al 1990[5] and Fohlmeister et. al 1997 [6]

Calculating Minimum Threshold Current

- **Number of Pulses** to be sent as stimulus current was set at **30 pulses** and was identified using values listed in Weitz et. al 2014
- Weitz et. al 2014[8] identifies that target number of spikes are equal to the number of pulses sent as stimulus current divided by 2. Therefore, target number of **spikes** was **set at 15** .
- After preparing the pulse and neuron model, I**nterphase Gap Duration values** were **identified** from Weitz et. al 2014 as **[0, 0.12, 0.24, 0.34,0.46, 0.92, 1.38, 1.84]**.
- **Values of Interphase Gap** were **tested upon** to identify minimum stimulus current **required to produce target spike**s
- **Trend was identified** by looking at **average percent change** over change in interphase gap duration

Generating the Sinusoidal Pulse

- The computational Stimulus current pulse was generated using the python library: **Pulse2Percept**
- A **sinusoidal curve** with **derived frequency, pulse width, pulse count, and pulse gap** was **generated** based on the work of Weitz et. al 2014[8]
- **Interphase gap** was added by **splitting sinusoidal curve** at the anodic and cathodic phase and appending values of 0 stimuli current **in between** for the time of interphase gap being looked at
- Functions were written to ensure **interphase gap doesn't affect** overall **frequency**
- **Frequency** set at 167 Hertz, **stimulation duration** which was calculated to be 180 ms, and **pulse width** set at 0.46 milliseconds
- Pulse was **discretized** at level of 50 to ensure optimal sine curve shape and number of pulses being set at 30
- Sinusoidal Pulse was **downsampled** into a Timed Array using Brian2 to get data points which can be inputted into the neuron model generated previously generated
- **Timed array** was altered to correct units to ensure compatibility with the neuron model

Network-level model

- Network level model with multiple cells and layers was created for more realistic testing
- Goal is to validate whether trend and relationship identified in the single cell model is consistent in more realistic environments
- Sinusoidal Pulse previously generated with same interphase values was inputted as stimulus current into Network-level model to ensure and verify trend noted in Single Ganglion Retina Cell Model generated previously

Effects of Interphase Gap Duration on Minimum Threshold Current

Sinusoidal Pulse Generation

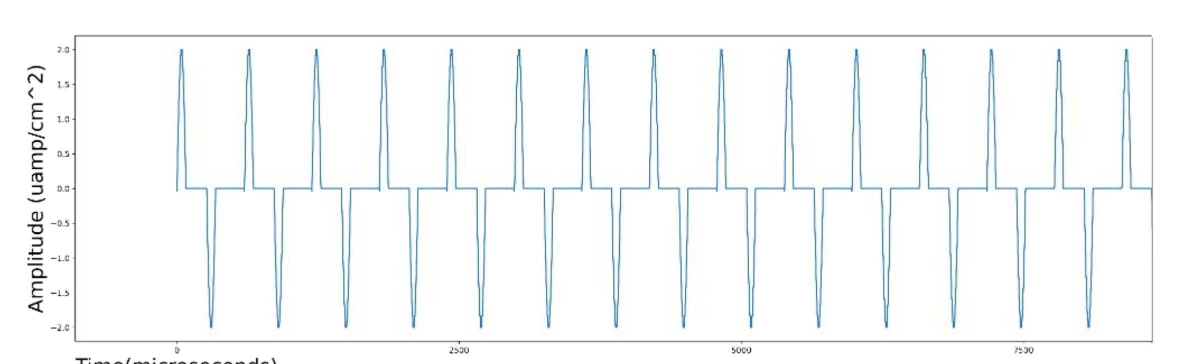

Figure 5: Displaying sinusoidal pulse generated with amplitude of 2 milliamperes of current and an interphase gap of 1.84 milliseconds. Interphase gap can be found in between anodic and cathodic phase.

IPG vs. Minimum Threshold Current

- Single cell model shows a trend of minimum threshold current required for 15 spikes out of 30 pulses decreasing as interphase gap duration value increases
- Network-level model also shows trend of minimum threshold current decreasing as interphase gap value duration increases
- Both show a decrease of almost 30 percent in the minimum threshold current as interphase gap duration increases from 0 milliseconds of 1.84 milliseconds
- Single cell model trend of decreasing is consistent with what is seen in the network level model at the epiretinal layer

Minimum Threshold Current

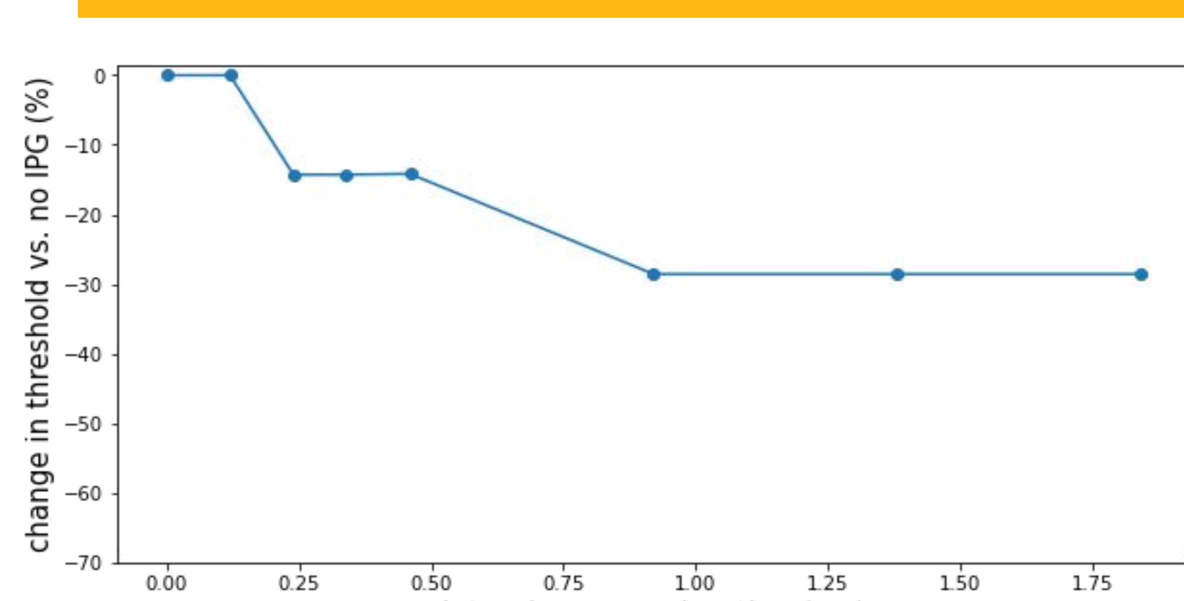

Figure 6: Displaying overall percent change in minimum threshold current as interphase gap duration increases from 0 milliseconds to 1.84 milliseconds for a single cell model

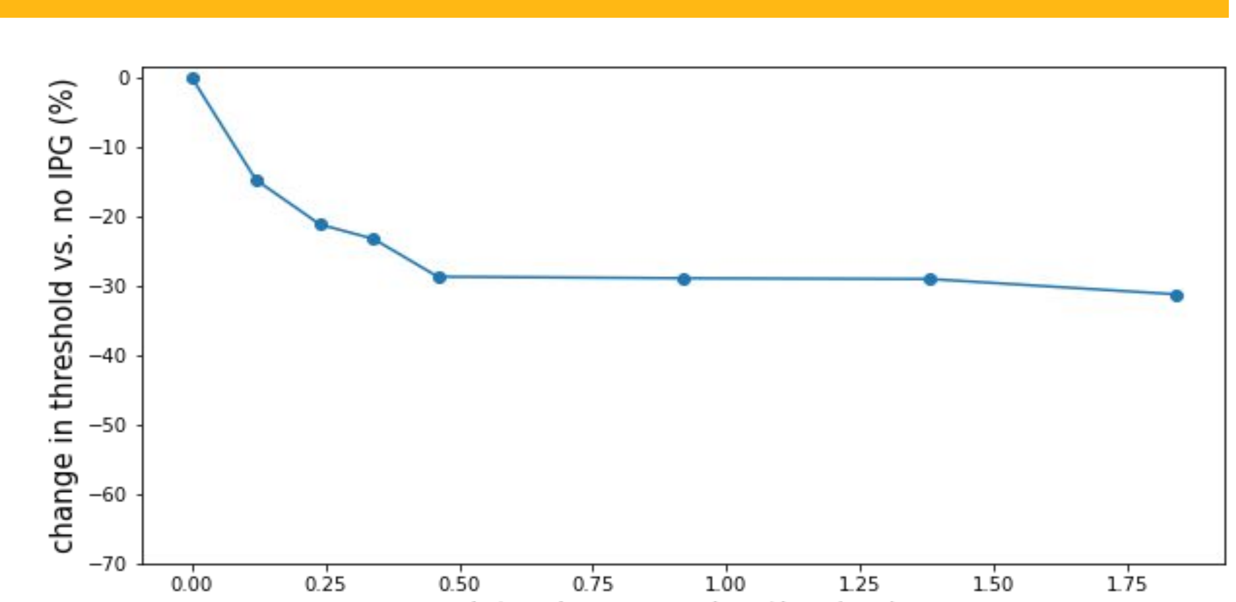

Figure 7: Displaying overall percent change in minimum threshold current as interphase gap duration increases from 0 milliseconds to 1.84 milliseconds for a network level model

Overall Trend

- Identified trend in single cell-model that as interphase gap value increased from 0 milliseconds to 1.84 milliseconds, the minimum threshold current value had decreased
- Based on our sinusoidal pulse with interphase gap, a ~28.57% decrease in minimum threshold current was noted
- Network-level model testing had shown similar results of a decreasing minimum threshold current as values of interphase gap duration increased
- Based on testing on the network level model, ~31.3 % decrease in minimum threshold current.
- Results from network-level model support the results of the single cell model as both displaying a decreasing trend in minimum threshold current

Future work

Develop a new neuron model with more ion channels to get more accurate number of spikes

Develop and test on a new suprachoroidal layer because of its success in the past

Find new parameters to research and alter to further lower minimum threshold current

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