In silico analysis of CA3 replay prolongation and naturalistic sequence activity under pulsatile optogenetic stimulation

Pavan Nathani[1, 5], Ved Shenoy[2, 5], Jasper Turnidge[3, 5], Derek Wang[4, 5]

Centennial High School, Frisco, TX 75035[1]; West Windsor-Plainsboro High School South, Princeton Junction, NJ 08550[2]; Kehillah Jewish High School, Palo Alto, CA 94303[3]; High Technology High School, Lincroft, NJ 07738[4]; Boston University, Boston, MA 02215[5]

Introduction

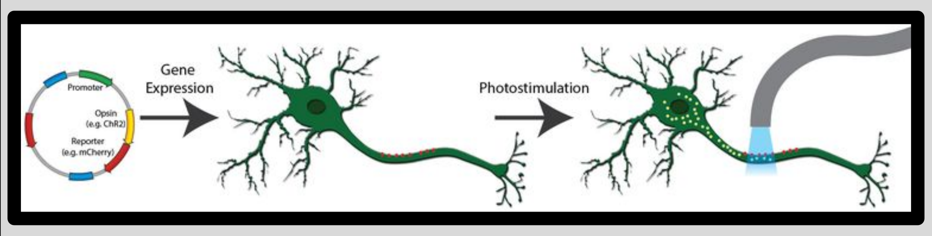

Figure 1. Optogenetics Workflow[5]

Optogenetics

- **Introducing** light-sensitive proteins into neurons to manipulate their activity using a light stimulus

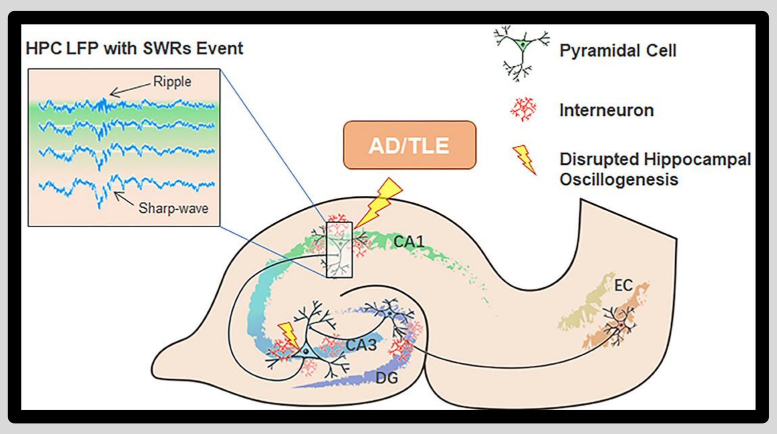

Figure 2. SPW-Rs in Hippocampus[6]

Sharp Wave Ripples (SPW-Rs)

- **CA3 region** of the hippocampus exhibits **sharp wave ripples** (SPW-Rs) responsible for "**replay**" (sequential neural reactivation)
- **Prolongation** of SPW-Rs through optogenetics has been shown to improve memory during maze learning[3]

Stimulus Information

- **Light** parameters (**frequency, waveform, duration**, etc.) used to stimulate neurons affect resulting neural activity, including replay extension quality
- **Effect** of light parameters in single light pulses on replay has been explored[4], but not in repeated pulses (**pulsatile stimulation**)

Objective

- **Optimize** light parameters for **pulsatile** input patterns

Methods

Optimization Metrics

- **Temporal distortion (Cohen's d)** is proportional to mean difference in interthreshold interval (IThI) between given waveform and control sequence
  - Higher value associated with less naturalistic neural activity, hypothesized to decrease learning efficiency ("less" optimal)
- **Sequence Length** is number of neurons spiked over stimulation course
  - Higher value associated with more prolongation, hypothesized to be indicative of improved memory ("more" optimal)

Light Parameters

- **Duty cycle** of **repeated square waveform** is proportion of its period when the pulse is active
  - For duty cycle 0.5, waveform spends equal time active and inactive
- **Frequency (Hz) is** pulses delivered per second
- **Input Duration (ms)** is length of optogenetic stimulation
- **Within IMA (iso-maximum-amplitude) waveforms**, the maximum amplitude of the current was kept constant
- **Within IP (iso-power) waveforms**, the total area of the waveform over the duration was kept constant, scaling the waveform as necessary

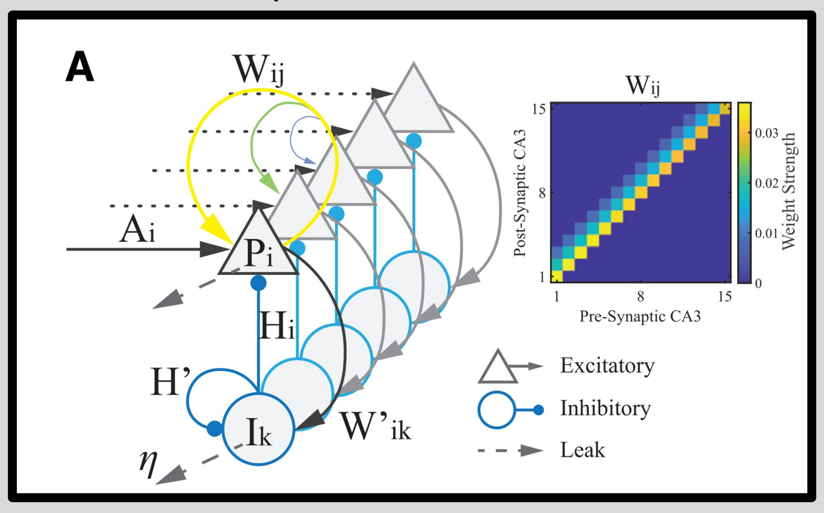

Figure 3. Sparse recurrent excitatory feedback architecture[4]

Model

- **Simulations** were run on a **rate-based model** of 15 CA3 pyramidal neurons
  - Region chosen for its extensive recurrent architecture and hypothesized involvement in memory
- **Control**
  - 20 ms wide cue pulse was delivered to first node in sequence to mimic "sharp wave" portion of SPW-Rs
  - Without further stimulation, cue pulse induced sequences of length 7 on average
- **Parameters** (above) were varied and effectiveness was determined by balancing selected optimization metrics (above)

Results

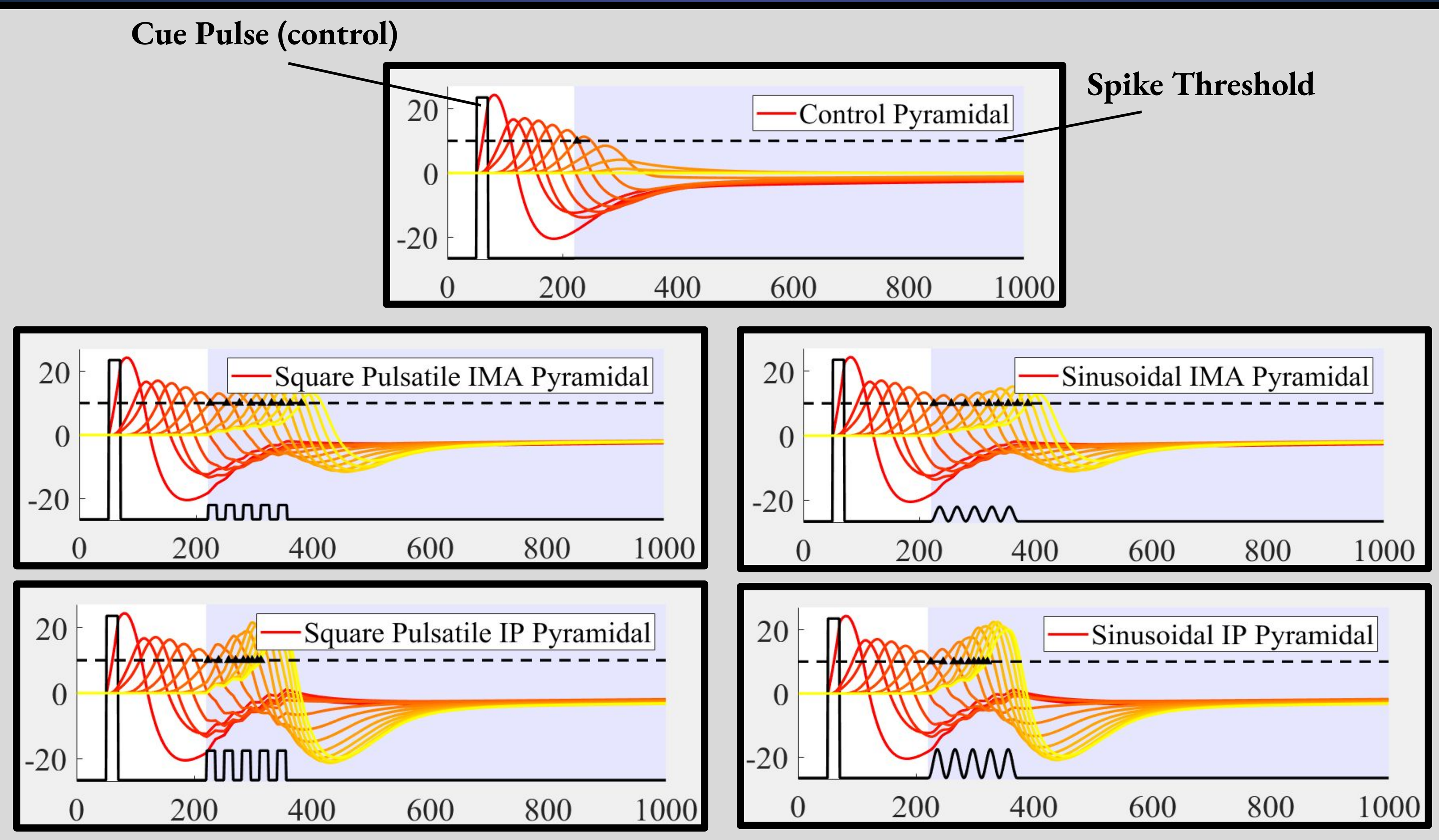

Figure 4. Example simulations measuring voltage of 15 neurons over time (ms) for individual trials under 20ms control input, with addition of varying waveform optogenetic stimulation (in black). All spikes recorded following optogenetic stimulation marked with triangles.

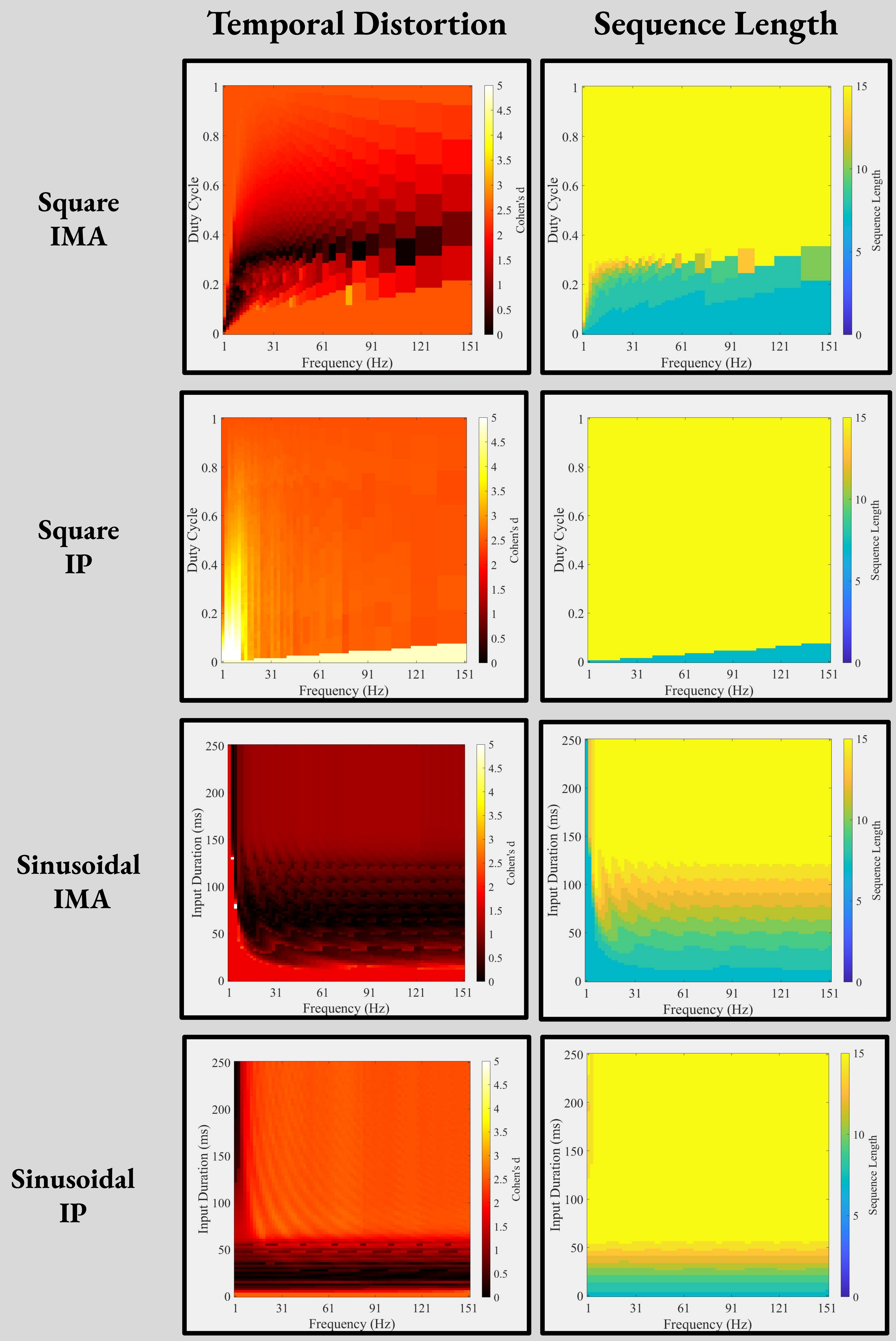

Figure 5. Parameter space characterization of repeated square waveforms across frequency (Hz) and duty cycle, sinusoidal waveforms across frequency and input duration (ms). Heatmaps represent effect size of temporal distortion of interthreshold intervals away from control sequence (left) and sequence length (right).

Discussion

Conclusions

- **Square Waveform**
  - Pulses with max amplitude of 0.09 had optimal duty cycle 0.3-0.5
  - Higher amplitude square waves exhibit lower temporal distortion at higher frequencies for duty cycles greater than 0.1
- **Sinusoidal Waveform**
  - Pulses with max amplitude of 0.09 and input durations between 110-130 ms best balanced temporal distortion and sequence length
  - Higher amplitude sinusoidals performed better with input durations between 50-55 ms across frequencies

Limitations

- Natural heterogeneity seemed to disperse optimal ranges
- Activity is limited to neural circuits in the CA3 exhibiting SPW-Rs, and optimal optogenetic parameters vary depending on the circuit in contention
- A number of criteria could be used to evaluate the effectiveness of waveforms
  - Analysis was limited to naturalistic neural activity and ability to extend sequences
- Due to the small number of neurons simulated (15), certain waveforms may be capable of extending sequences even further, but were not observable within our model

Future Direction

- Though it requires modification of control group, analyzing pulsatile stimulation on larger time scale may yield more relevant results
- Broader range of irregular stimulation (double sinusoidal waveforms, poisson spike train, etc.) may perform differently, but pose challenges in parameter space

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