Simulated Propagation of V1 Neuron Activity as a Function of the Frequency and Amplitude of Electrical Microstimulation

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Abstract
This study is a proof of concept demonstration for BrainPoke, a neural simulation tool for studying intracortical microstimulation (ICMS). The simulations adapted a previously published comprehensive model of V1 [2,3]. The model includes a simplified reconstruction of V1 layers 2, 3, 4 and 6 using simple models [11] for electrophysiological behaviors of excitatory and inhibitory neurons. The model was used to characterize the spread of cell response to pulsed currents from simulated electrodes with varying locations, frequencies and currents. Current spread was modelled using a previously reported ICMS model [1]. This is a first attempt to simulate signal propagation through V1 at the neuronal level. Our results provide key insights into the breath of signal penetration from cortical stimulation. The presented model can be customized with different stimulation parameters in order to examine the effects of various cortical stimulation intensities.

Author Keywords
cortical activation; electrical stimulation; visual cortex; Izhikevich model.

CSS Concepts
•**Applied computing**~Life and medical sciences~Computational biology~Biological networks•**Human-centered computing**~Human computer interaction (HCI)~Empirical studies in HCI•**Computing methodologies**~Modeling and simulation~Simulation types and techniques~Discrete-event simulation

INTRODUCTION
A growing field of research is concerned with the development and refinement of cortical visual prostheses for the blind. Microelectrode arrays, which can be implanted in the visual cortex to stimulate visual percepts, are one method of increasing interest. Despite some initial success using this method, there exists uncertainty as to the degree of propagation caused by electrode stimulation; in other words, how far a given signal will travel and which neural populations will be activated is severely understudied. This issue is especially significant given that certain solutions for enhancing the effects of electrode stimulation involve increasing the electrical current. For instance, it has long been known that increasing the frequency, amplitude, or duration of a pulse can

increase the brightness of the associated percept [9,15]. But it is, as of yet, unknown how such parameters affect the spread of neural modulation. Although in vivo experiments in humans are difficult, simulating models of the visual cortex can allow us to make inferences around this question.

In order to successfully accomplish this the relevant properties of area V1 should be modeled. The primary visual cortex is made up of an intricate and complicated structural arrangement of cells. It is divided into 6 horizontal layers with specific connectivities. Layer 2/3 neurons receive inputs from layer 4 excitatory neurons, as well as cortical feedback from higher order areas such as perigeniculate nucleus (PGN) and lateral geniculate nucleus (LGN). The layers are themselves organized into functional columns. Cells within each column share response properties [18]. Indeed, each layer has distinct functions and proportions of cell populations; however the neural types can broadly be classified as inhibitory and excitatory, and of the excitatory neurons in V1, most are regular spiking neurons[12]. Therefore the cell types are often simplified when modeling this area of cortex.

BACKGROUND

Several studies have attempted to measure the propagation of an electrical signal through the cortex. Using neuroimaging and microstimulation methods, the interconnectivity between V1 and it's inputs has been investigated[14] as well as the connectivity between the layers of the visual cortex [13]. It has been repeatedly observed that a long-lasting inhibition occurs following short excitatory responses caused by electrical pulses[10]. Furthermore, the spread of activation varies depending on the feedforward and feedback connections intrinsic to the visual system. Stimulation to area V1 causes a feedforward propagation of the signal to V4, resulting in either excitation or inhibition. Microstimulation to V4, conversely, causes hardly any activation back to V1, but rather causes reductions in firing rates through inhibitory feedback. Electrical stimulation has also been observed to cause a considerable spread of activation- sometimes millimeters away- even at low currents [10]. Given that the primary visual cortex has a thickness of about 2mm, this is sizeable spread.

Although neuroimaging studies provide key insights, it can be challenging to determine what is occuring at a cellular level and which cell properties are responsible for variation in neural responses. Therefore, complementary methods involve using computer-based models to simulate the neural response to cortical stimulation. Using such models, greater insight has been gained into neural processes at the cellular level[1]. Antolik et al. developed a comprehensive cortical model to investigate a host of parameters at once; however in this study light penetration from an LED array was modeled as opposed to current spread from an electrode array[3].

Indeed, while computational modeling has become a central method in vision science, there have been few attempts to specifically characterize neural responses to exogenous electrical microstimulation. Therefore, much is still unknown about the distal effects of electrical current as a function of amplitude and frequency or how to mitigate spread of activation to non-target areas.

MATERIALS AND METHODS

This project relies on the development and implementation of 3 models- a model of primary visual cortex, a model of a scalable electrode array that has the ability to stimulate cortex via an electrical pulse train, and a model of current propagation through cortical tissue.

Model of primary visual cortex:

The visual cortex model is loosely based on a previously validated model, Mozaik[2]. Using experimentally derived parameters that are defined in this framework we have designed a model for a 5mm x 5mm patch of cortex that includes the infra-granular layer 6 in addition to layers 2/3 and 4. Each layer in our model is populated by 10,000 simulated neurons in an 85:15 excitatory to inhibitory ratio previously identified in mammalian visual cortex[6]. This equal distribution of neurons between layers is consistent with anatomical findings for layer 2/3 and 4 but is an assumption made

for layer 6. The number of neurons modelled is an extremely significant down-sampling ranging from .4%[6] to .98% [2,6] of the actual density for V1 neurons.

Neuron model

We include two basic neuron classes in our model of primary visual cortex, excitatory and inhibitory. The excitatory population in layer 2/3 and 6 consists of pyramidal neurons and layer 4 consists of spiny stellate neurons [2]. Both excitatory cell types can be treated as regular spiking (RS) neurons which fire tonic spikes with adapting frequency in response to injected pulses. In V1 other classes of pyramidal and stellate neurons with different firing properties are present i.e. chattering neurons that fire at high frequency [16]. We have opted to exclude these other cell types as regular spiking neurons comprise the majority of excitatory neurons in the neocortex which includes V1[12]. Inhibitory neurons in all modeled layers were modeled as inhibitory interneurons.

All neurons were modeled as adaptive, single compartment integrate and fire units. This model is ideal for computational simulations neural system spiking in response to current injection. The model describes the membrane potential of a neuron in terms of synaptic inputs and injected current received and does not directly model membrane voltage and conductances as the Hodgkin and Huxley model does [7].

Izhekivich Model

$$V' = h^{-1}(.04V^2 + 5V + 140 - u)$$
$$u' = abv - au$$

$$if(V > V_t)\begin{cases} V = c \\ u = u + d \end{cases}$$

$h = simulation\ frequency(hz)$
$V = voltage(mV))$
$V_t = threshold\ voltage$
$a = recovery\ time\ constant$
$b = sensitivity\ of\ recovery\ variable$
$c = post\ spike\ reset\ value$
$d = outward\ minus\ inward\ current(pA)$
$u = recovery\ variable$

Figure 1 - The Izhekivich Model

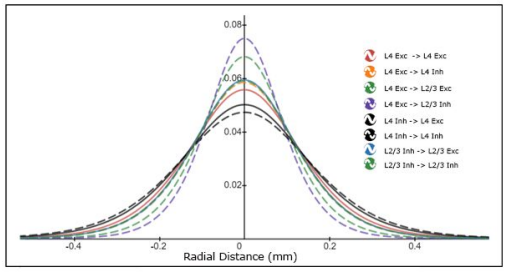

Figure 2 - Probability of synapse formation

The change in membrane potential, given by V(t), over time is described by the standard equations of Izhikevich neurons[11] shown in Figure 1.

Our model records a spike any time the membrane potential crosses a predefined threshold voltage (Vt). The simulation frequency (h) was kept at 100 hz and the other parameters match a previous Izhikevich model of V1[5] for excitatory (regular spiking) and inhibitory (fast spiking) neurons.

Synaptic Connectivity

In order to reduce complexity, synaptic connectivity in layer 2/3 was simplified by excluding thalamocortical synapses as we are only interested in current spread within the region of neurons surrounding the electrode. Additionally, we have excluded cortical feedback to perigeniculate nucleus (PGN) and lateral geniculate nucleus (LGN) (see future directions for discussion of why these simplifications should be updated in subsequent iterations).

In V1, each neuron makes on average 5800 synapses. Based on rate of synaptic failure and the number of synapses that originate from outside of the cortex into the modeled layers, we have modeled 1000 synapses per excitatory cells and 20% fewer for inhibitory cells to account for their smaller size [4]. The extent of neural connectivity is dependent on geometric distance between neurons. The probability that neurons synapse decreases with distance. For simplicity, we have disregarded the role of functionally based connectivity but this could be addressed in future iterations of this model.

Antolik et al. [2] normalized the probability of potential connectivity between presynaptic and postsynaptic neurons based on neuron class and location to obtain a probability density function(pdf). These pdfs were used to generate local connectivity distance dependent profiles (Figure 2). Each neuron was cycled through random neuron pairings and formed a synapse if a randomly generated value was less than the calculated probability between those two neurons. There was a possibility for the same two neurons to synapse multiple times. Each neuron repeated this until it reached 1000 synapses (excitatory cells) or 800 synapses (inhibitory cells). For simplicity, the pdfs found between layers 4 and 2/3 were used for the analogous connections between layer 2/3 and 6.

Synapses

Synapses were represented as a postsynaptic voltage change for every presynaptic spike. Several studies examining the strength of individual synapses in cortex have found that synaptic strengths are generally weak and that synaptic strength is dependent on presynaptic and postsynaptic neuron types. The weights in this simulation were set to be .5mV which is within the range of EPSPs in V1[17].

Electrode and stimulation

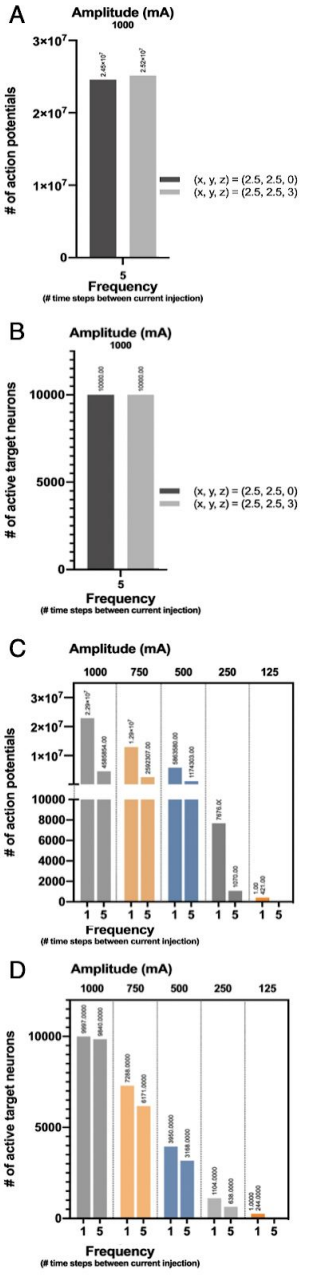

Figure 3. Single Electrode Simulation.
(Legend on last page)

Simulated electrodes are assigned a 3D location within the modeled portion of V1. The electrode is circular and is assigned a radius of 0.1mm. The electrode can be set to a specific current(mA), frequency, and timing offset.

Current propagation
Current propagation following stimulation via a point source electrode was modeled as in Aberra et al., 2018[1] using the following equation:

$$V_e(x,y,z) = \frac{I}{4\pi\sigma\sqrt{(x-x_0)^2 + (y-y_0)^2 + (z-z_0)^2}}.$$

The formula models the extracellular potential *Ve* at the location of each compartment of each individual neuron (x,y,z) for a microelectrode delivering current I centered at (x0,y0,z0). We assumed a homogenous, isotropic medium with conductivity σ = 0.276 S/m.

Experiment
Two proof of concept experiments were conducted to evaluate the efficacy of the simulation. For each experiment, a randomized neural network was generated and used for every trial of the experiment.

The first experiment featured a single electrode located either within the layers or 2mm from the nearest layer. This demonstrated the difference between an intracortical prosthesis (CORTIVIS[20]) and an extracortical device (Orion[21]). At both locations, varying stimulation frequencies and amplitudes were tested. Layers 2/3 were simulated at z=2, layer 4 at z=3, and layer 6 at z=4. The electrode was located in the center of the patch (x=2.5, y=2.5) and varied between z=0 and z=3. At each location, the electrode current was simulated at 1000, 750, 500, 250, and 125 mA. The simulation timestep was 1/100 of a second and the electrode pulsed every 1 timestep (100Hz) or every 5 timesteps (20Hz). Results were recorded from every layer 6 neuron.

The second experiment was largely a repeat of the first experiment with the addition of a second electrode and an additional stimulation frequency of every 20 timesteps (5Hz). The electrodes were simulated at opposite corners (x,y=0,0 and x,y=5,5) and varied between z=0 and z=3. This experiment represented the area between two electrodes and attempted to demonstrate the interaction between them.

RESULTS

Single electrode results. (Figure 3)
In the case of a single simulated electrode, the only current strong enough to penetrate from a simulated extracortical (z=0) electrode was 1000 mA. With this high of a current, every single target electrode elicited a response (Figure 3-A/B).

Reducing amplitude while keeping location and frequency constant leads to a general trend of a reduction in both number of action potentials fired (Figure 3-C) and number of active target neurons (Figure 3-D). Reducing frequency 5x caused a reduction in number of neurons activated and number of action potentials fired leading to the same general trend over all amplitudes tested.

Notably, we see the highest number of targets cells fire the most at the highest frequency combined with the highest amplitude and the lowest numbers at the lowest frequency with the lowest amplitude.

Multiple electrode results. (Figure 4)
The second experiment results largely mirrored the first experiment. Again, the only current strong enough to penetrate to layer 2/3 was 1000 mA. With the electrodes spaced at this distance (~7mm radial distance) only half of the target layer cells fired (Figure 4-A). This implies that extracortical stimulation is plausible for stimulating discrete neural populations. An interesting result is that changing the simulated depth of the multiple electrodes did induce a large change in the number of action potentials (Figure 4-B) which was not present for the single electrode experiment. When both electrodes were simulated at a depth of z=3, the

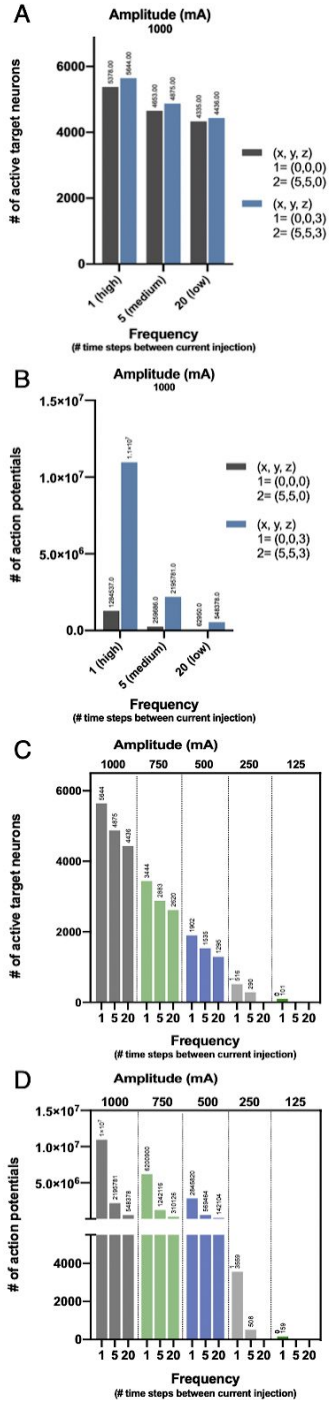

Figure 4. 2 Electrode Simulation.
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results followed an identical pattern to the single electrode results for number of target cells that fired (Figure 4-C) and the number of total action potentials (Figure 4-D).

DISCUSSION

This study sets the groundwork for a realistic simulation of intracortical microstimulation, but there are many obvious limitations and simplifications. These results are by no means biologically relevant. Gross oversimplifications have been made and a lot of work is still needed. This proof of concept is promising, as a medically useful simulation would be extremely impactful. Current cortical prosthesis testing is poorly understood and stimulation parameters available to patients are very limited. Testing new electrode locations, amplitudes, and frequencies on real patients is extremely risky as it can lead to seizures, brain damage, or even death.

Future Directions

Many other factors beyond frequency play a role in the degree of neural activation; these factors should be examined in future research. For instance, the structural morphology and orientation of axons influences the degree of activation and signal propagation between neurons. Most previous attempts to model and simulate cortical activation have used simplified depictions of neurons; however recent attempts to model morphology have indicated that this is indeed a relevant factor when considering the effects of cortical stimulation [1]. Additional factors also contribute to neural excitation and signal propagation, for instance, cellular properties, such as membrane voltage, leak conductance, ion channel density and myelination [8,19]. These parameters, along with a more realistic temporal model, should be included in future versions in order to elucidate how both neuronal properties and network connectivity influence V1 function. Determining these unknowns remains critical for the development and refinement of cortical prostheses.

Separate studies have examined some of these parameters, such as morphology [1] and membrane voltage [7], leaving the state of this field of research somewhat disjointed. Further research should attempt to reconcile the differences between these models to determine whether findings are consistent dependent upon the parameters chosen for inclusion in the model.

Future research in this area should focus on expanding the model to include other cell types and filling in the blank or oversimplified parameters. Including some form of functional connectivity to represent the columnar structure of V1 could provide meaningful insights as to what the patients of cortical prostheses are perceiving.

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Figure 3. Single Electrode Simulation.
A. The number of target neurons activated by a single simulated electrode. B. The number of action potentials in response to a single simulated electrode. A,B. Dark grey bar corresponds to electrode position (x,y,z)= (2.5,2.5,0). Light grey bar corresponds to electrode position = (2.5,2.5,3). Both electrodes stimulate the cortex at 1000mA at a frequency of 5 time steps between pulses. C. Number of action potentials in response to pulses from a single electrode. D. Number of activated neurons in response to pulses from a single electrode. C,D In both figures the electrode positions were held constant. Electrode 1 (x,y,z)=(2.5,2.5,3). Each electrode stimulated with a pulse of 1000, 750, 500, 250, 125 mA at 2 different frequencies per amplitude 1, and 5 time steps in between pulses. There were 3000 total time steps per experiment.

Figure 4. 2 Electrode Simulation.
A. The number of target neurons activated by 2 simulated electrodes. B. The number of action potentials in response to 2 simulated electrodes. A,B. Grey bar corresponds to electrode 1 position =(0,0,0) electrode 2=(5,5,0). Blue bar corresponds to electrode 1 position= (0,0,3) electrode 2= (5,5,3). Both electrodes stimulate the cortex at 1000mA, once at a high frequency of 1 time step between pulses and a lower frequency of 5 time steps between pulses. C. Number of active target neurons in response to pulses from 2 electrodes. D. Number of action potentials in response to pulses from 2 electrodes. C,D In both figures the electrode positions were held constant. Electrode 1 (x,y,z)=(0,0,3) electrode 2=(5,5,3). Each electrode stimulated with a pulse of 1000, 750, 500, 250, 125 mA at 3 different frequencies per amplitude 1, 5, and 20 time steps in between pulses. There were 3000 total time steps per experiment.

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