# A Multi-Channel Electrode for Chronic Recording and Safe Current-Steered Stimulation

Ben Pearre[1,a,¤], Jun S. Song[1,c], Timothy J. Gardner[1,d]

[1] Department of Biology, Boston University, Boston, Massachusetts, United States of America

Author [a] contributed the original Matlab and LabView implementations and most of the manuscript. Author [b] performed the surgeries and histologies.

¤ Corresponding author: bwpearre@gmail.com (BP)

## Abstract

Long-term recording enables.... stimulation enables...

Big electrodes — effective for low-voltage stimulation, but damage going in, gliosis on timescales like a month.

Current steering — dbs: no learning control. "Adaptive" dbs, model-based coarse-grained current steering.

Small electrodes (under 10 mm) cause less acute and chronic damage, but are delicate. We have developed an electrode design in which groups of electrodes support each other during insertion.

We show that the bundled electrodes splay in the brain.

We present preliminary results showing that these electrodes can remain capable of recording individual spikes for a year after implantation, even when also used to stimulate.

We present preliminary evidence that the spatial scale of the splaying is sufficient to allow the steering of current between the electrodes, and that this allows some degree of high-dimensional control over the brain's response to stimulation.

# 1 Introduction

# 2 Materials and Methods

## 2.1 Electrode construction

Electrode arrays were constructed as described in [1]. The charge transfer capacity of one of the stimulation electrodes was enhanced by electrodeposited iridium oxide. [2] describes the electrochemistry of charge transfer.

## 2.2 Splay histology

Electrode bundles were implanted into birds, all to a depth of roughly 3 mm. Most of these were "dummy" uncoated and blunt-cut rather than fire-sharpened as in [1], with 10–16 channels (fibres). The birds were killed, and their brains sectioned roughly perpendicularly to the electrodes, with a slice thickness of 50 $\mu$m.

Sanne: what slice thickness?

Sanne: check exclusion criteria.

The following criteria were used to exclude observations:

- Individual fibres were excluded if they were lying flat on the surface of the tissue (visible as side-on cylinders).

- Bundles were excluded if they were implanted in fibres of passage.

I'm about a day from finishing software to do all-to-all comparison. For the draft (and possibly first submission, if time is tight) this suffices.

Clustering was done by hand. The set of distances between electrodes was computed by measuring the distance between each electrode and its nearest neighbour. Bundles were clustered as follows:

Why 10 $\mu$m?

**Splayed:** All electrodes were more than 10 $\mu$m from each other, or at most one pair was closer.

How many?

**Partial:** Some electrodes were more than 10 $\mu$m from each other.

All-to-all, or nearest-neighbour?

**Clumped:** All electrodes were within 10 $\mu$m of each other.

Would it make sense to automatically cluster the splay data? Or to change the criteria? I can think of some changes. . .

Examples of these three categories are shown in Fig. 1.

## 2.3 Recording

Recordings of spontaneous activity were done using an Intan RHD2000 amplifier at 20 kHz, with a hardware high-pass filter at 200 Hz.
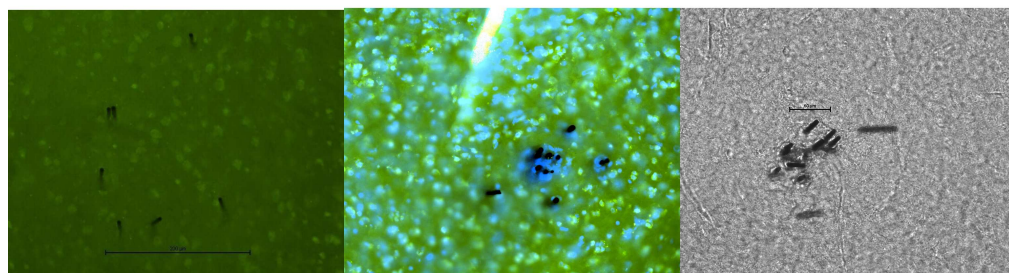
**Figure 1.** Splay types, left to right: examples of full splay, partial splay, and clumped. In all images, black circles are electrode shafts; in many cases the slicing plane is not quite orthogonal to the electrodes, yielding oblong images. In the bright-field image on the right, three of the electrode slices were pulled out of the tissue during slicing, and appear to lie flat on the slide. Since their original locations cannot be determined, we have ignored them.

## 2.4 Stimulation: Zebra finch antidromic HVC ← X

A common technique for locating HVC in the zebra finch involves implanting a stimulating electrode in Area X and looking for a an antidromic response, which is visible in HVC but not in the surrounding tissue.

We will use the following definitions:

**Channel:** Our electrodes have 16 separate carbon fibres, each one of which we consider a separate channel, since each is connected to a separate amplifier. Some work better than others, and usually about 75% of them have low enough impedance to use. We refer to these as active channels, or just channels.

**Pulse:** A biphasic charge-balanced square wave of current. Each phase is 200 $\mu s$ long, and there is no interpulse interval.

**Current-steering configuration (CSC):** The configuration defining which channels receive the positive half of their biphasic pulse first, or vice versa.

**Pulse train:** A sequence of 10 identical pulses delivered simultaneously to all active chennels at 25 Hz. This is slow enough that pulses do not interfere with each other, and is used to detect the reliability of the response.

- Programming the Plexon stimulator for one pulse train requires about 2 seconds.

Move timing notes to Discussion of compromises required for this experiment?

**Threshold scan:** A series of pulse trains, each of which has the same CSC but a   45
different current, designed to find the minimum current for this CSC that will   46
antidromically induce a response in HVC. The algorithm is described below.   47

- A threshold scan generally requires roughly 15 pulse trains, and thus takes   48
  on the order of 30 seconds.   49

**Voltage scan:** The Plexon hardware can deliver a current-controlled pulse to each of   50
16 channels independently, but only allows monitoring of the voltage delivered   51
on one channel at a time. A voltage scan involves sending the same pulse train   52
once per active electrode, monitoring a different one each time.   53

- A voltage scan requires delivering one pulse train per active electrode,   54
  taking a total of about 30 seconds.   55

This does not require full reprogramming of the Plexon! Just setting the monitor channel is faster, but my code does not take advantage of this, and fully reprogrammes the Plexon each time.

We used a Plexon stimulator to control stimulation in AreaX, and recorded from   56
HVC using a Tucker-Davis Technologies RZ5 amplifier. The Plexon self-monitoring   57
channels were recorded on a National Instruments PCI-6251 data acquisition card   58
using the session-based interface of Matlab (various versions from 2014a through   59
2015b) on Windows 8.1.   60

We used MATLAB to control the stimulation and acquisition as follows: the   61
National Instruments card is set to record an adequate number of samples of the   62
Plexon self-monitoring channels at 100 kHz, initiated through software, and sending   63
out a TTL pulse at the beginning of acquisition. The Plexon stimulator begins   64
stimulating upon receipt of that TTL pulse, and the TDT begins recording at 24.414   65
kHz (the device's native frequency) on the same signal. Whenever the Plexon is   66
actively delivering current (i.e. during each pulse within the train) it sends out its own   67
TTL pulse: this signal is recorded by the TDT along with the HVC electrode voltages   68
in order to align stimulation pulses with the recording. The alignment precision is   69
limited only by the sampling rate of the TDT.   70

**Response detection**   The antidromic response in HVC occurs roughly 3–8 ms after   71
the stimulation pulse, and is highly stereotyped.. Fig. 2 shows an example of a   72

[citation needed]

pronounced HVC response. In order to detect this reliable response to stimulation, we   73
measure the cross-correlation between the recorded response for each pulse in a train   74
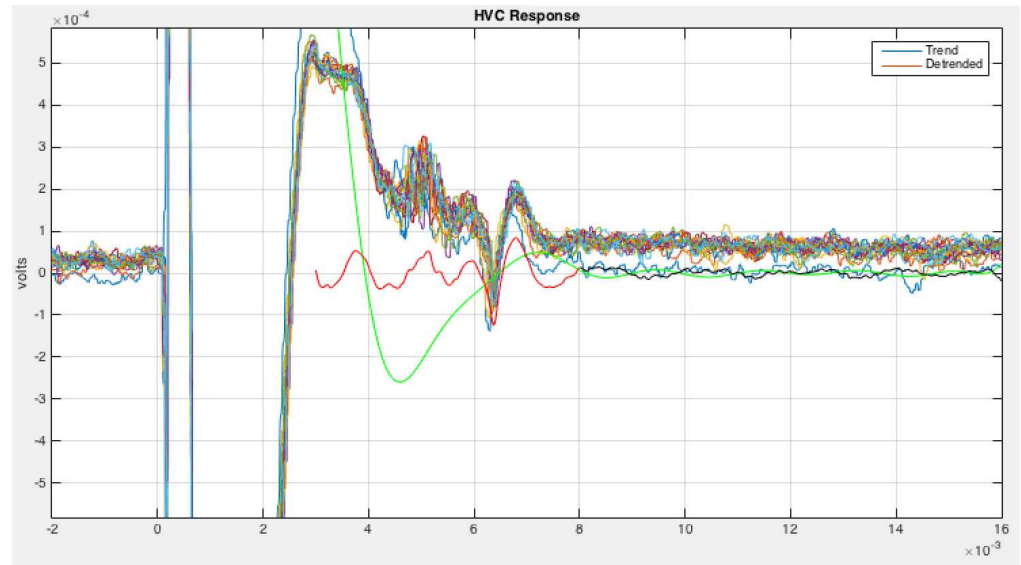
**Figure 2.** An example of a clear response in HVC. The horizontal axis is time, in milliseconds relative to the onset of a stimulation pulse. Here, the stimulation is a 400-$\mu$s biphasic pulse of 3 $\mu$A, in which voltage peaked at 1.6 V. Stimulation was repeated 20 times, with each response aligned to its respective pulse and shown as a separate colour. Various response activity can be seen, but the most pronounced is at 6.2 ms post-onset. *This figure is but a placeholder. I have better detrending now, and all responses will be in the same colour, etc...*

and each other, which provides a robust way of separating neural response from noise. Because the HVC amplifier's response to the transient stimulation pulse in Area X can persist into the time of interest (3–8 ms), each response is first de-trended using a maximum-likelihood fit over the region 2–25 ms using an eigth order Fourier Series, which removes post-stimulation decay while leaving intact spike-sized signals. The cross-correlation threshold above which a response is identified is chosen by visual inspection.

As the bird ages, the skull grows down from the implantation site. For shallow installations such as HVC (depth $\simeq 200\mu m$, the quality of the HVC recordings diminishes as electrodes are forced out of contact with the brain. This makes it more and more difficult over time to measure the antidromic response. The above cross-correlation technique is more sensitive than the technique typical of acute or short-term response measurements, in which a pronounced spike is often clearly visible. We believe that we are measuring an antidromic response because it is on the correct timescale and appears near the expected stimulation threshold.

Need to prevent antidromic response transmission and see if "measured response" disappears as it should! But this requires more birds, and a more complex experiment.

Cite papers giving timing and stimulation threshold.

**Threshold scan**  What parameters are required in order to reliably elicit an antidromic response to stimulation in Area X? How can this threshold be found quickly, while minimising the risk of exceeding safe stimulation voltages? How can this process be made robust to noise?

> How can we establish how much robustness to noise is required?
>
> Perhaps write a pseudocode block instead of this mess?

After choosing a CSC, we begin stimulating at a current that is known to be below threshold. While no response is seen, the current is increased gradually (by a factor of $\alpha \approx 1.1$) until either a response is detected or the voltage or current limit is exceeded. In the latter case, a lack of response is reported, and we move on to the next CSC. If a response is found, then the step size is decreased ($\alpha \leftarrow \alpha^{2/3}$) and we reduce the current until the response disappears. This process is repeated until the step size drops below a limt ($\alpha < 1.02$).

While a larger step size would result in a faster search, and a binary search would be easier to described, this ad-hoc approach makes it unlikely that we will stimulate with a current that significantly exceeds the minimum required for a response.

**Voltage scan**  Once the minimum current required in order to achieve a response is identified, we perform a voltage scan at that current, in order to measure the peak voltage delivered to each electrode.

## 3 Results

### 3.1 Splay histology

After exclusion, 22 arrays, implanted into 13 different birds, each yielded at least 3 measurable electrodes. See Table 1 for the raw data and Fig. 3 for visualisations thereof.

> Perhaps take out the table and just use the graphs?

> An image of "typical" damage done by "micro"electrodes would be nice, but it's hard to show what's typical of the ~~competition~~ prior work with any credibility. Letting people compare vs. their own experiences is the best, but not everyone (e.g. me) will know what's typical.
>
> I have data on how long post-implant the birds lived, which needs to come along with this figure, if not the rest of the paper.

Fig. 4 shows some examples of the damage done to the brain in the vicinity of tle electrodes. Visual inspection shows little damage in the vicinity of single electrodes, and slightly more in clumped electrode groups. Visual inspection can give some indication of the damage done to the brain and the likelihood of achieving good electrical contact with neurons, but we are more interested in the ability to record signals (see Section 3.2).

| # Good electrodes | Inter-electrode distance ($\mu$m) | | |
|:---:|:---:|:---:|:---:|
| | Mean | StdDev | Max |
| 3 | 5.0 | 0 | 20.0 |
| 10 | 6.0 | 2.1 | 52.9 |
| 16 | 6.3 | 6.3 | 48.3 |
| 4 | 7.5 | 5.0 | 35.8 |
| 6 | 16.7 | 18.9 | 44.8 |
| 9 | 7.7 | 5.5 | 107 |
| 14 | 12.8 | 12.1 | 15.2 |
| 8 | 14.7 | 17.8 | 108 |
| 15 | 15.1 | 10.2 | 163 |
| 15 | 19.3 | 19.1 | 128 |
| 5 | 22.0 | 27.7 | 103 |
| 9 | 28.2 | 35.8 | 148 |
| 11 | 31.8 | 28.1 | 103 |
| 8 | 35.9 | 30.6 | 228 |
| 13 | 76.5 | 152 | 167 |
| 5 | 51.4 | 28.1 | 51.5 |
| 3 | 20.0 | 0 | 123 |
| 6 | 73.5 | 35.5 | 128 |
| 8 | 38.5 | 35.2 | 142 |
| 9 | 47.4 | 31.5 | 208 |
| 5 | 126 | 63.5 | 214 |
| 16 | 62.0 | 58.9 | 829 |

**Table 1.** Raw data. Each row shows the statistics from one electrode array. "Good" electrodes is the the number of carbon fibre electrodes in each bundle that appeared to still be firmly fixed in the neural tissue after slicing.
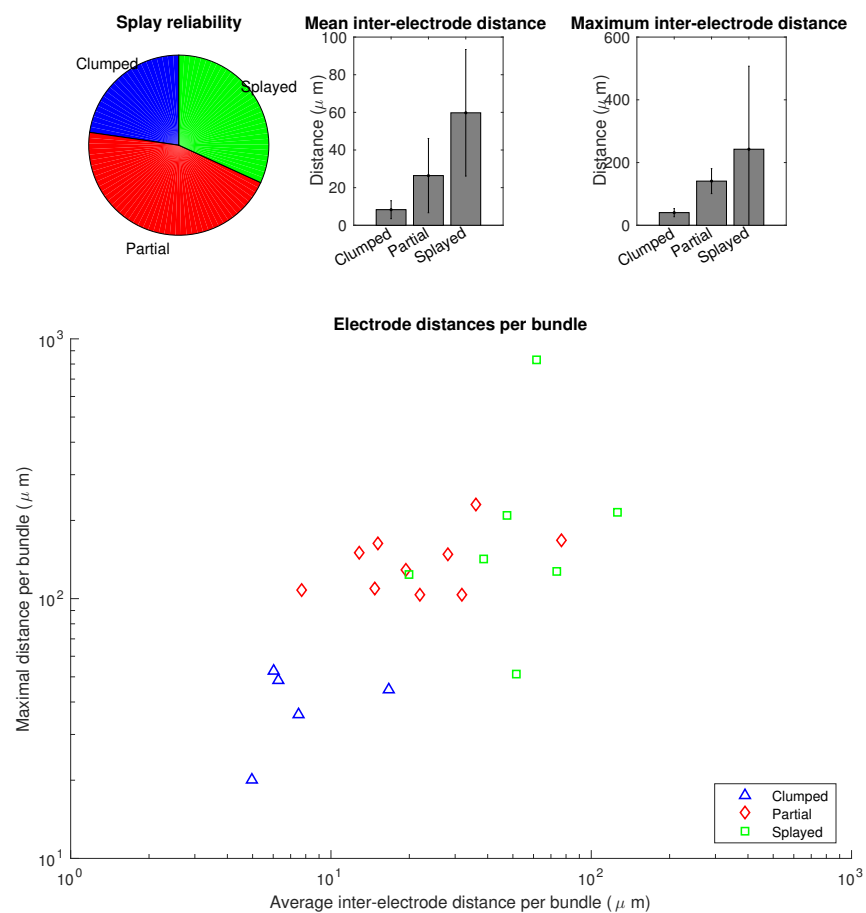
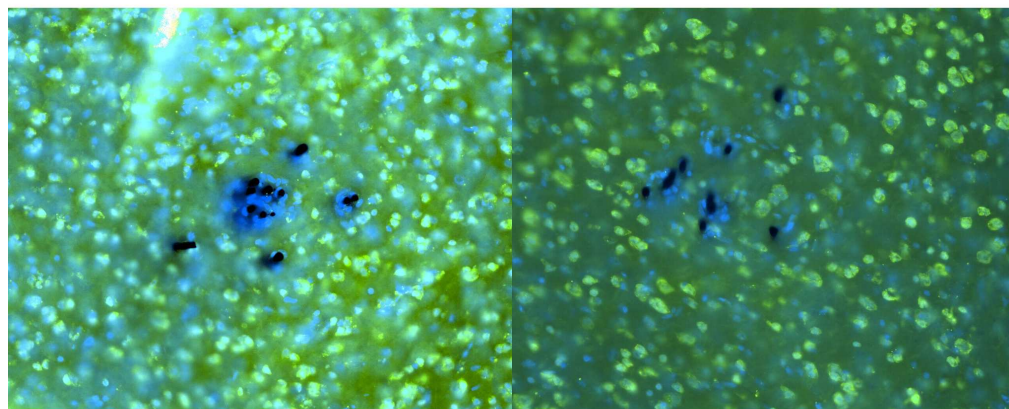**Figure 3.** Splay histology data from Table 1.

**Figure 4.** Damage. Neural nuclei are shown in green (stained with NeuN) and all cells in blue (DAPI). The presence of non-neural cells indicates damage, and is notable in the vicinity of the largest non-splayed electrode bundle, and nearly absent around individual electrodes.

## 3.2 Chronic recording 118

**HVC** Long-term recording in HVC is difficult due to skull regrowth interfering with 119

electrodes implanted only a few hundred microns from the surface: after 10 months, 120

we had difficulty picking up antidromic response in our two remaining birds. 121

**Area X** More telling of the potential of these electrodes is the recording of 122

spontaneous activity in Area X, which was still easily seen in several channels after a 123

I don't think I have data showing good- year. 124
activity yield early on.

## 3.3 Stimulation 125

**Minimising stimulation voltage** 126

**Controlling the antidromic response** 127

## 4 Discussion 128

[3] showed that injecting current into tissue causes neurons whose axons are very close 129

to the stimulation site to fire, rather than neurons whose bodies are at greater 130

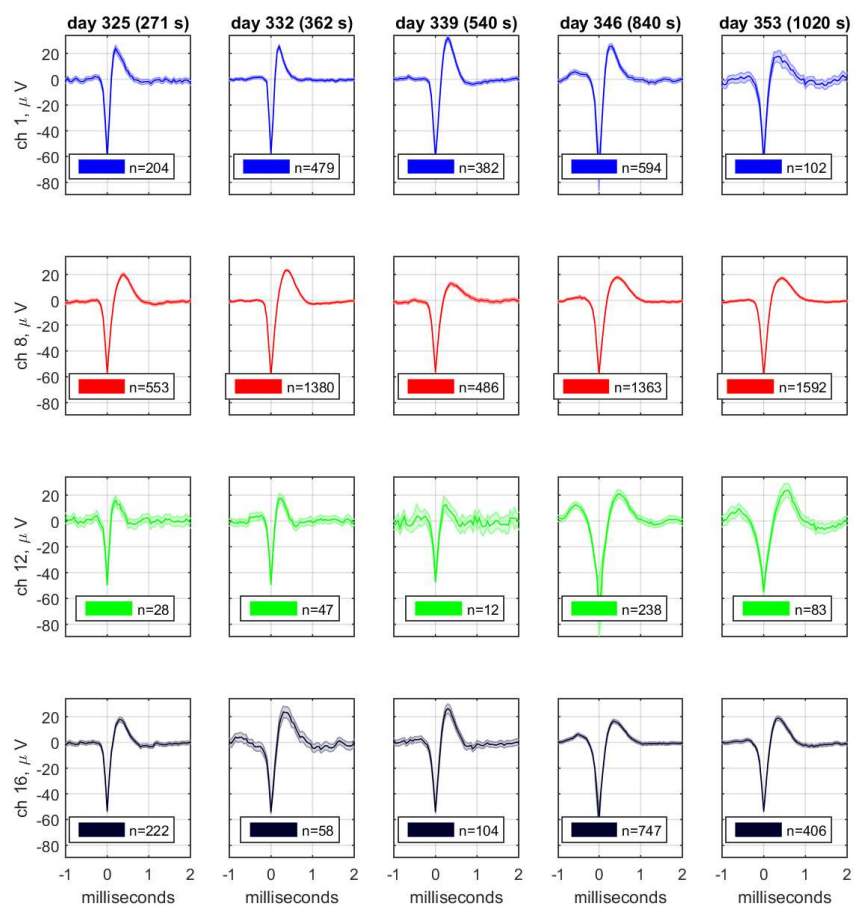distances. As a result, the set of neurons that respond to a stimulation pulse is highly 131

**Figure 5.** Some of the electrodes in Area X record spikes after nearly a year. The column titles show the day post-surgery and the number of seconds of recorded data (for bird lw94rhp). Each row is one electrode (shown here: only the four best channels of 16). Legends show the number of spikes; shaded region is mean $\pm$ 95% confidence.
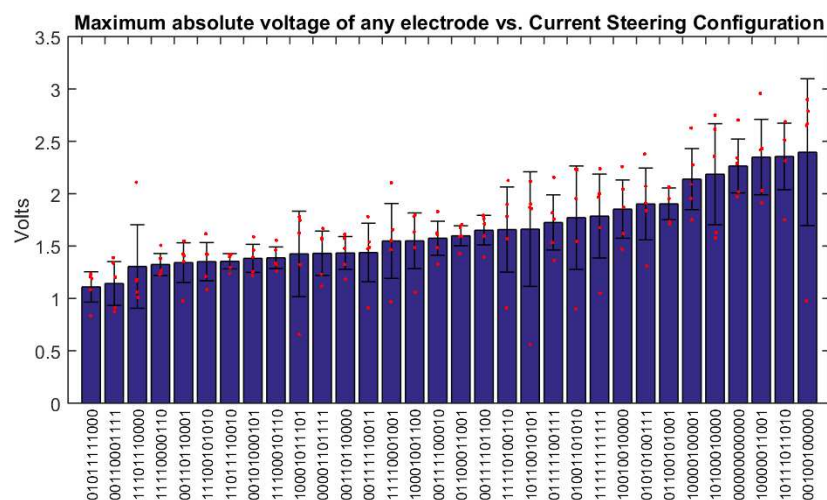
**Figure 6.** The peak X stimulation voltage required in order to achieve biologically effective levels of stimulation in HVC varies with different current-steering configurations. Here are 32 different configurations, over 5 trials each. The X axis lists the configuration (each of the 11 active electrodes delivers a positive-first "0" or negative-first current-controlled pulse "1" pulse). The Y axis shows the maximum voltage across any electrode. Error bars are 95% confidence intervals (n=5), and red dots are the individual trials. For some CSCs, not all trials evoked a response before our 3V threshold was exceeded, and so the true number is higher.
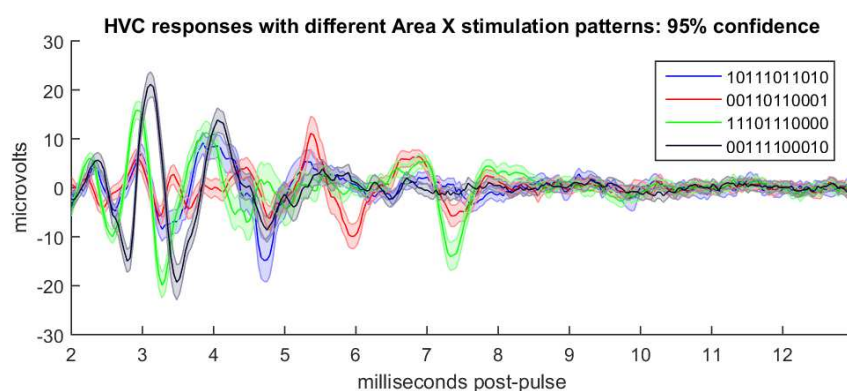


**Figure 7.** Different CSCs delivered to Area X can induce different responses antidromically in HVC. Here are four of the most distinct responses to four of the 32 CSCs shown in Fig. 6. Shading is 95% confidence, n=198.

sensitive to electrode location, but has spatial extent similar to that of the neuron's                    132
dendritic tree. Furthermore, they showed that neurons stimulated in this manner                            133
seldom stimulate downstream neurons synaptically.                                                          134

Splaying electrode arrays with learning stimulation software may be able to exploit                        135
these properties. First consider each of the $n$ electrodes in our array separately. $n$ sites             136
stimulated at a given current gives $n$ different random sets of $k_n$ neurons that will fire,             137
and increasing the current changes the size of $k$. There may exist multiple downstream                    138
neurons $y$ such that directly-stimulatable neurons from several of our $n$ sets synapse                   139
onto $y$. This creates a search problem: how to stimulate the $n$ sets in a way that                       140
reliably stimulates $y$ enough to cause it to spike? This requires search over current                    141
delivered to each group in $n$ in order to control which neurons are recruited, and                       142
timing of stimulation delivery to each group in $n$, so that the downstream neuron is                     143
reliably triggered. Different values of current and timing delivered into the $n$ groups                   144
may trigger different downstream neurons, so the search problem is: find as many                          145
different downstream neurons as possible.                                                                  146

Furthermore, it seems likely that directly-stimulatable neurons may synapse onto                          147
others that are directly-stimulatable, once or $r$ times removed. This suggests a further                 148
dynamic for the timing search, in which different timings for stimulating the $n$ sets                    149
may trigger different firing sequences. This enlarges the space of inducible dynamics                     150
considerably, and suggests the possibility of inducing Hebbian learning.                                  151

Whereas Histed used single electrodes, we use miltichannel arrays. Rather than a                          152
16-channel array providing $n = 16$ groups of neurons, different current-steering                         153
configurations may lead to a much higher value of $n$. For such an electrode there are                    154
$2^{16}$ current-steering configurations even without manipulating current pulse                          155
magnitude or timing.                                                                                      156

# References                                                                                              157

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