Subspace Matching Thalamic Microstimulation to Tactile Evoked Potentials in Rat Somatosensory Cortex

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Abstract—We show experimental results that the evoked local field potentials of the rat somatosensory cortex from natural tactile touch of forepaw digits and matched thalamic microstimulation can be qualitatively and quantitively similar. In ongoing efforts to optimize the microstimulation settings (e.g., location, amplitude, etc.) to match the natural response, we investigate whether subspace projection methods, specifically the eigenface approach proposed in the computer vision community (Turk and Pentland 1991 [1]), can be used to choose the parameters of microstimulation such that the response matches a single tactile touch realization. Since the evoked potentials from multiple electrodes are high dimensional spatio-temporal data, the subspace projections improve computational efficiency and can reduce the effect of noisy realizations. In computing the PCA projections we use the peristimulus averages instead of the realizations. The dataset is pruned of unreliable stimulation types. A new subspace is computed for the pruned stimulation type, and is used to estimate a sequence of microstimulations to best match the natural responses. This microstimulation sequence is applied in vivo and quantitative analysis shows that per realization matching does statistically better than choosing randomly from the pruned subset.

I. INTRODUCTION

Providing sensory feedback directly to the central nervous system is one of the ambitious goals of next generation neuroprosthetics and brain-machine interfaces. Specifically, feedback via artificial stimulation [2], [3], [4], [5], [6], [7], [8] may provide input to somatosensory cortex just as cursor or robot movement may be derived as the output of the motor cortex.

To recreate more naturalistic feedback for tactile neuroprosthetics tasks, our group has been investigating strategies to optimize stimulation such that the evoked neural responses are as similar as possible to those from natural tactile stimulations [9], [10], [11], [12]. A divergence method can be used to judge if the evoked potentials or spike trains match the type from natural sources. Ideally, psychometric experiments would be the final gold standard. However, a quantitative distance metric per realization is necessary in the operation of an optimal microstimulation feedback system. For local field potentials, cross-correlation or Euclidean distance are

reasonable metrics. In this work we investigate data-driven subspace projection methods (i.e., principal component analysis) [1] and their effect on the similarity measures: we estimate the maximum variance preserving subspaces for the microstimulation evoked responses, and match each natural stimuli realization to a peristimulus average using Euclidean distance.

A. Stimulation optimization in the central nervous system

Artificial stimulation (either electrical microstimulation or optogenetic) of the central nervous system can be used as a clinical tool for identifying, stabilizing, or imprinting neural activity. Optimizing deep brain stimulation for treatment has predominantly focused on patient outcome [13] or the anatomical extent of the microstimulation [14]. Work in feedback on neuroprosthetics has been concerned with the discriminability and/or repeatability of neural response, wherein quantitative similarity measures on the evoked neural responses (either local field potentials or spikes) are used to assess the outcome of closed-loop microstimulation control [15]. Reliability is important if the goal is to imprint the same (and possibly arbitrary) neural response for a specific external sensory event. Alternatively, in this work we investigate the goal of optimizing the artificial stimulation such that the evoked response is as close as possible to a natural response. In this work, the closest is chosen from a discrete set of microstimulation configurations (electrode(s) and amplitude of single biphasic pulses). A key limitation of this work is the parameter space must be kept small for a manageable discrete search. If every parameter is allowed to vary the number of microstimulation configurations grows combinatorially, especially when multiple pulses at different times are allowed. Alternatively, an inverse control approach can search the continuous space [16].

B. Thalamic electrical microstimulation

Local field potentials were recorded from a multielectrode array in the somatosensory cortex (S1) during both natural tactile stimulation (light "thwacks" of forepaw digits and palm) and microstimulation in the somatosensory region (VPL) of the thalamus. Stimulating in the thalamus is chosen because it avoids the artifacts produced by intra-cortical stimulation. By choosing a location earlier in the somatosensory pathway the existing neural structures carry the evoked response to the cortex. Though requiring a more difficult implantation, the thalamic microstimulation appears to deliver more naturalistic evoked responses; however, only

psychometric experiments can tell if these translate to actual perceptions.

II. METHOD

The method consists of a subspace identification/pruning with training data followed by matching the natural responses to a newly chosen stimulation sequence. The chosen stimulation sequence can then be applied in vivo and evaluated quantitatively. Specifically, training consists of an initial subspace identification from a training sequence of stimulations, stimulation type pruning with an entropy criterion, re-estimation of the subspace, and matching a specific stimulation type to each natural stimulus.

A. Notation

We introduce the following notation: capital letters A will denote sets or matrices, $|A|$ denotes the cardinality of set A, and boldface letters indicate vectors $\mathbf{a}$.

B. Sets of evoked responses

The initial microstimulation modeling dataset consists of a set $S = \{(Y_i, a_i, t_i)\}_{i=1}^{|S|}$ of neural responses recorded at sampling rate F_s and corresponding microstimulation parameters settings where an L-length M-channel evoked response for stimulation i at time t_i is denoted $Y_i \in \mathbb{R}^{L \times M}$ and the microstimulation parameter settings are indexed by $a_i \in A = \{1, \ldots, |A|\}$. A is defined as an index set for a discrete set of possible microstimulation settings—i.e., each index a is representative of the complete spatio-temporal aspects of short ($< 10\mathrm{ms}$) biphasic current pulses. The dataset notation is misleading because the modeling dataset consists of one long modeling sequence with stimulations occurring with pseudo-random truncated Gaussian intervals instead of independent trials—for instance, pairs of the windows Y_i, Y_j such that $i \neq j \wedge |t_i - t_j| < L/F_\mathrm{s}$ will be overlapping. The occasional overlap does introduces a bias into the peristimulus averages, and it can be ameliorated by only using the non-overlapping time lags when computing the averages, but this approach is not addressed here.

Similarly, the recording (at same sampling frequency F_S) during natural tactile stimulation via thwacking different forepaw digits or pads consists of a long sequence of tactile touches or "thwacks". Since each thwack will be matched with a corresponding stimulation we denote the set of natural stimulations as $T = \{(X_i, d_i, t_i)\}_{i=1}^{|T|}$ where $X_i \in \mathbb{R}^{L \times M}$ is a L-length M-channel evoked response for thwack i at time t_i at location indexed by d_i.

C. Subspace identification

An eigenspace decomposition [1] is used to find the principal subspace of the peristimulus evoked responses. This is used twice in the overall method: first, with the full set of stimulation types A, and then again after with a pruned subset $A^\star \subseteq A$. The first N coefficients in the subspace $c_1, \ldots, c_N \quad N \leq |A^\star|$ are used for pruning and matching.

The overview of the method follows (where A, S may be replaced with $A^\star \subseteq A$ and $S^\star \subseteq S$ without loss of generality):

1) Estimate the peristimulus average for all responses

$$\bar{Y} = \frac{1}{|S|} \sum_{i=1}^{|S|} Y_i \quad Y_i \in \mathbf{R}^{L \times M} \tag{1}$$

2) Estimate a peristimulus average for each response type

$$\bar{Y}_a = \frac{1}{|\mathcal{I}_a|} \sum_{i \in \mathcal{I}_a} Y_i \tag{2}$$

$$\mathcal{I}_a = \{i \in \{1, \ldots, |S|\} : a_i = a\} \quad a \in A$$

3) Form a matrix of the centered and vectorized peristimulus averages

$$\hat{Y} = \left[\mathrm{vec}(\bar{Y}_1 - \bar{Y}) \cdots \mathrm{vec}(\bar{Y}_{|A|} - \bar{Y}) \right] \in \mathbf{R}^{(L \cdot M) \times |A|} \tag{3}$$

4) Compute the cross-covariance matrix between the centered peristimulus averages

$$C = \hat{Y}^{\mathrm{T}} \hat{Y} \in \mathbf{R}^{|A| \times |A|} \tag{4}$$

5) Find the eigenvalues and left eigenvectors such that

$$USW^{\mathrm{T}} = C, \quad U = \left[\mathbf{u}_1 \cdots \mathbf{u}_{|A|} \right] \in \mathbf{R}^{|A| \times |A|} \tag{5}$$

where U and W are unitary matrix with orthogonal columns and S is diagonal with eigenvalues as its elements

6) Define the vectors of the eigenspaces of the peristimulus averages $\mathbb{R}^{L \cdot M}$

$$\mathbf{v}_j = \hat{Y} \mathbf{u}_j \in \mathbf{R}^{L \cdot M}, \quad j \in \{1, \ldots, |A|\} \tag{6}$$

7) For any response $Z \in \mathbf{R}^{L \times M}$ find the projection into the subspace spanned by each vector

$$\tilde{z}_j = \mathbf{v}_j^{\mathrm{T}} \mathrm{vec}(Z - \bar{Y}) \quad j \in \{1, \ldots, N\} \tag{7}$$

8) Define the function f_S that projects any response $Z \in \mathbf{R}^{L \times M}$ to the N-dimensional eigenspace

$$f_S(Z) = [\tilde{z}_1 \cdots \tilde{z}_N]^{\mathrm{T}} = [\mathbf{v}_1 \cdots \mathbf{v}_N]^{\mathrm{T}} \mathrm{vec}(Z - \bar{Y}) \tag{8}$$

D. Parameter pruning via classification entropy

The peristimulus average for each response type is projected via $f_S : \mathbb{R}^{L \times M} \mapsto \mathbb{R}^N$

$$\tilde{\mathbf{y}}_a = f_S(\bar{Y}_a) \tag{9}$$

Each realization in S is then assigned to the nearest mean in the subspace using Euclidean distance.

$$\hat{a}_i = \mathrm{argmin}_{k \in A} \|\tilde{\mathbf{y}}_k - f_S(Y_i)\| \quad i \in \{1, \ldots, |S|\} \tag{10}$$

As a surrogate for the entropy of the evoked responses for each stimulation type, we find the entropy over the set of discrete assignments for a given class. Let $p_a(k) \quad k, a \in \{1, \ldots, |A|\}$ be the proportion of the realization of stimulation type a which had nearest mean $\tilde{\mathbf{y}}_k$ in the subspace

$$p_a(k) = \frac{|\{i \in \{1, \ldots, |S|\} : \hat{a}_i = k \wedge a_i = a\}|}{|\{i \in \{1, \ldots, |S|\} : a_i = a\}|}. \tag{11}$$

Then the entropy of the assignments for stimulation type a is

$$H_a = \sum_{k \in A} -p_a(k) \log_2 p_a(k)\}. \tag{12}$$

Define the pruned subset $A^\star$ using an upper threshold on the entropy as half the maximum entropy $A^\star = \{a \in A : H_a < 0.5 \log_2(|A|)\}$. The pruned dataset is then $S^\star = \{(Y_i, a_i) \quad \forall i \in \{1, \ldots, |S|\} : a_i \in A^\star\}$.

E. Matching to natural stimulation

A new projection function $f_{S^\star} : \mathbb{R}^{L \times M} \mapsto \mathbb{R}^N$ is computed for $S^\star$ reusing (1)–(8). Then each natural stimuli realization $(X_i, d_i, t_i) \in T$ of type d_i and at time t_i is matched to the nearest peristimulus average in the subspace (an explicit search for the minimum distance per peristimulus average is also made over small shifts in alignment around t_i since the natural response may not be perfectly aligned).

$$\check{a}_i = \arg\min_{k \in A^\star} \|\tilde{\mathbf{y}}_k - f_{S^\star}(X_i)\| \quad i \in \{1, \ldots, |T|\} \tag{13}$$

The microstimulation sequence $\big((\check{a}_1, t_1), \ldots, (\check{a}_{|T|}, t_{|T|})\big)$ can then be applied in vivo in order to evoke responses that match the natural stimuli evoked responses. The set of novel evoked responses and corresponding microstimulation type and times will be denoted $U = \{(U_i, \check{a}_i, t_i)\}_{i=1}^{|T|}$.

We use Euclidean distance (not in the identified subspace) as the similarity measure between evoked responses.

III. DATA COLLECTION

A female Long-Evans rat (Hilltop, Scottsdale, PA) was anesthetized with isofluorane, and 32 channel Michigan Probes (NeuroNexus Inc.) electrode arrays were inserted into the hand region of primary somatosensory cortex (S1). The arrays had four (15μm thick) iridium shanks, each with 8 contacts (100μm spacing), and the shanks were positioned to span 1.2mm in the anterior–posterior direction. The bottommost contact was inserted to a depth of 1.2mm from the pial surface. The circular electrode surfaces had a diameter of 40μm. Another array with two rows (500μm spacing) and 8 columns (250μm spacing) was inserted into VPL thalamus, approximately 6.5mm beneath the pial surface. The array was made of platinum iridium (MicroProbes Inc) with 1250μm^2 of exposed tip metal.

All animal procedures were approved by the SUNY Downstate Medical Center IACUC and conformed to National Institutes of Health guidelines. Neural recordings were made using a multichannel acquisition system (Tucker Davis). Local field potential data was pre-amplified 1000x (filter cutoffs at 0.7Hz and 8.8kHz) and digitized at 25kHz. LFPs were further filtered from 1Hz to 300Hz using a 3rd order Butterworth filter.

The experimental procedure involved delivering 210 tactile touches to the rat's forepaw (repeated for digit pads 1–4 and two sites on the palm) using a motorized probe. The motor was controlled by a PD controller that poised 4mm above the surface of the skin and momentarily pressed down for two different hold times (150 and 200ms) and three amplitudes

(3, 5, and 10 degrees in the direction of the skin), alternating pseudorandomly to deliver 35 presentations of each setting.

After this procedure, we switched the VPL array to stimulation mode using a mechanical switch, and delivered a pseudorandom sequence of biphasic, bipolar, 200μs wide pulses through the 8 non-overlapping adjacent pairs in the array. 3 amplitude settings (10, 20 and 30μA) were tested, and all configurations were delivered 40 times, $|A| = 24$.

After numerically matching each tactile touch to a suitable stimulation, we delivered them to the thalamus and recorded the S1 responses.

IV. RESULTS

To assess the in vivo performance of the subspace matching, the generated microstimulation sequence $\big((\check{a}_1, t_1), \ldots, (\check{a}_{|T|}, t_{|T|})\big)$ was applied immediately following computation. The microstimulation response set U was recorded and then compared with the actual natural response set T. A qualitative comparison of an excerpt can be seen in Fig. 1.

For quantitative analysis, 0.25s intervals were extracted from the microstimulation response beginning at the time of stimulation; equal length segments were also extracted for the corresponding time in the natural response, and the set $\{\|U_i - X_i\|\}_{i=1}^{|T|}$ of Euclidean distances between each corresponding natural and the *matched* stimulation response was calculated (a different set was formed for each thwack location). Furthermore, the set of Euclidean distances between each natural response X_i and an *unmatched* microstimulation response U_{j_i} was calculated $\{\|U_{j_i} - X_i\|\}_{i=1}^{|T|} \quad \forall j_i \in \{1, \ldots, |U|\} \wedge \check{a}_{j_i} \neq \check{a}_i$ (the unmatched response is in the same dataset U but with a different stimulation type); since different types had unequal occurrences this set was calculated with replacement. Finally, the set of Euclidean distances between each natural response X_i and a *shuffled* microstimulation response U_{j_i} was calculated $\{\|U_{j_i} - X_i\|\}_{i=1}^{|T|} \quad \forall j_i \in \{1, \ldots, |U|\} \wedge U_{j_i} \neq U_i$ (same stimulation type but permuted indexes).

The average of the distances is an indication of how well the evoked responses from the entire stimulation sequence emulated the thwack recording T. Three separate hypothesis tests were performed per thwack location on the similarity between: matched and unmatched, matched and shuffled, and shuffled and unmatched responses. The surrogate distributions for the null hypotheses were created by 500 Monte Carlo calculations of the distance between the thwack responses and randomly ordered stimulation responses (either matched or unmatched). The hypothesis test for unmatched stimulation types was rejected with $p < 0.1$ for digit 1 and digit 2 thwack locations. For these digits the chosen stimulation sequence evoked a response much closer to thwack response than a random stimulation sequence with different stimulation types drawn from $A^\star$. The hypothesis test for matched stimulation types but shuffled order was not rejected with $p > 0.1$ on all thwack location—that is, the actual order of when the stimulations occurred in the sequence (as long as they were the same type) was not significantly
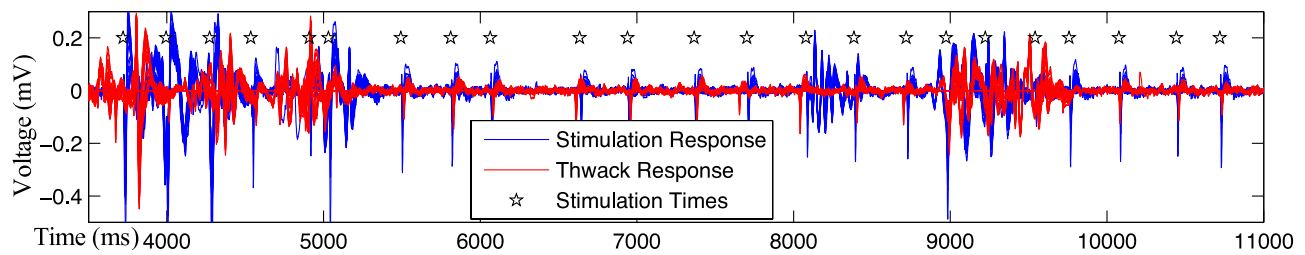
Fig. 1. Local field potentials across the 16 S1 channels for natural (digit 1) and microstimulation evoked responses. Microstimulation times are marked by stars.

different. A comparison of the distribution of distances for unmatched and shuffled matched was made with a one-sided Kolmogorov-Smirnov hypothesis test between the matched and shuffled CDFs for each digit. The divergence on all digits was significant at a level of 0.05. Fig. 2 shows empirical CDFs with only 50 Monte Carlo runs.
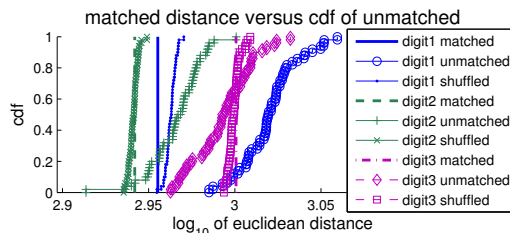

Fig. 2. Comparison of total error between thwack responses and stimulation responses. Matched distance is shown versus empirical cumulative distribution functions of the null hypotheses. Digits 2 and 3 matched responses were significantly smaller than unmatched responses.

V. Discussion

We have proposed a complete algorithm to match specific microstimulation parameters to natural stimuli realizations in an attempt to recreate somatosensory perceptions. Subspace identification and parameter pruning are used to identify a set of stimulation settings that evoke reliable responses; then each natural stimulus realization is matched to the closest peristimulus average in the subspace. The sequence of matched stimulations represents a novel microstimulation sequence that was then applied in vivo. Both quantitative and qualitative results demonstrate the success of the method in further experiments. The subspace method is computationally efficient, but the method is limited to the original set of configurations by the lack of modeling. To our knowledge this is the first in vivo study of microstimulation optimization to match natural responses, and one of the first to use thalamic microstimulation to produce cortical responses. However, this is only a preliminary investigation into thalamic microstimulation as a surrogate for natural tactile feedback, as full psychometric evaluation is needed to verify whether artificially matched evoked responses are indicative of true perception.

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