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Stimulus representation in rat primary visual cortex: multi-electrode recordings with micro-machined silicon probes and estimation theory

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Abstract

The study of neural population codes relies on massively parallel recordings in combination with theoretically motivated analysis tools. We applied two multi-site recording techniques to

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record from cells throughout cortical depth in a minimally invasive way. The feasibility of such experiments in area 17 of the anesthetized rat is demonstrated. Bayesian reconstruction and the interpretative framework of Fisher information are introduced. We demonstrate applicability and usefulness of Bayesian stimulus reconstruction and show that even small numbers of neurons can yield a high degree of representational accuracy under favorable conditions. Results are discussed and future lines of research outlined.

Keywords: Population coding; Bayesian reconstruction; Fisher information; Multi-site recording technology; Visual cortex

1. Introduction

Stimulus representation in the mammalian visual system is achieved by large groups of neurons. To study the means by which neural populations achieve high coding performance, theoretical approaches are needed to identify potentially critical parameters of population codes as well as recording techniques for the simultaneous acquisition of signals from large neural numbers. Massively parallel recordings are required because neural interactions or only very briefly generated spatio-temporal activity patterns may play a critical role for stimulus representation. A further requirement for recording techniques is the capacity for reliable isolation of single units from all cortical layers, since cells in different layers may serve different functions in information processing as indicated by their different connectivity patterns. For these reasons, we chose multi-site, silicon-based electrodes [2,8,1,12,7,10] which promise the acquisition of large neural numbers throughout cortical depth.

In this contribution we present results of an integrated approach combining electrophysiological recordings with silicon-based multi-site probes in the rat primary visual cortex, an analysis of the neural population code based on Bayesian reconstruction and the interpretative framework of Fisher information.

Neural encoding strategies can be assessed using the framework of *Fisher information* [9,6,14,3,11,15]. Fisher information employs the joint probability distribution $P(n_1,\ldots,n_N;\vec{x})$ of the spike count vector $(n_1,\ldots,n_N)$ obtained from a population of N neurons during some time interval upon the presentation of a stimulus $\vec{x}$. The stimulus $\vec{x}=(x_1,\ldots,x_D)$ is characterized by D features in a D-dimensional stimulus space. The Cramér–Rao inequality [6] gives a lower bound on the expected estimation error $\varepsilon^2_{i,\min}$ the ith feature for an arbitrary but unbiased estimator. In the case of a diagonal Fisher information matrix, it is given by $\varepsilon^2_{i,\min}=1/J_{ii}(\vec{x})$, where the denominator is the Fisher information associated to the ith feature.

The joint probability distribution $P(n_1,\ldots,n_N;\vec{x})$ can, in principle, be determined empirically. However, additional assumptions, e.g. statistically independent firing of neurons, considerably reduce the amount of data required. Using assumptions of this type, Fisher information can be used to derive encoding strategies that yield especially small estimation errors, and thus allow for accurate stimulus representation. Recently,

considerable progress has been achieved in this direction. For the influence of different tuning widths in multiple stimulus features and how they can be used to assess optimality in codes, see [3,11]. These results give hints as to what effects can be expected in empirically obtained distributions $P(n_1,\ldots,n_N;\vec{x})$.

While Fisher information and the Cramér–Rao inequality yield (in the unbiased case) estimates on the highest achievable neural encoding performance, in this paper, we use a Bayesian reconstruction method to assess the actual encoding accuracy of neurons in rat primary visual cortex for motion directions of drifting gratings. A comparison of the results obtained from the use of Fisher information and the Cramér–Rao inequality on the one hand with results from Bayesian reconstruction on the other hand is not straightforward; if stimulus features are visual angles, the approach for features measured in real numbers [13] has to be modified. This is because the error estimate of the mean rate given by the Cramér–Rao inequality needs to be backtransformed to an error estimate of the angle in a more complicated manner than in the case of features measured in real numbers (Etzold et al., in preparation).

2. Materials and methods

2.1. Recording technology

Recordings were performed with two types of micro-machined multi-site recording probes in addition to standard varnish-coated tungsten electrodes. One micro-machined probe was provided by a joint project of two groups at the California Institute of Technology and at Stanford University, the other was provided by the Center for Neural Communication Technology of the University of Michigan sponsored by NIH NCRR Grant P41-RR09754. The Caltech/Stanford probes (see Fig. 1) were micro-machined at Stanford's Center for Integrated Systems.

The CalTech/Stanford probes feature 32 co-planar electrodes on a silicon substrate with silicon-nitride passivation. Electrodes are 100 μm^2 gold, with typical impedances of 1–4 MΩ at 1 kHz. The probe shafts' outlines are defined by a plasma etch and are designed to minimize insertion resistance, resulting in dimpling comparable to tungsten electrodes upon insertion [5]. Recordings were made using electrodes in tetrode arrangements.

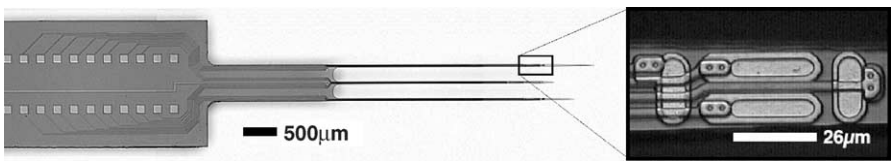


Fig. 1. Micrograph of Caltech/Stanford T1 probe. Inset on the right shows an enlarged view of four electrodes in tetrode configuration on one T1-shank. Each electrode's surface area equals 100 μm^2.

2.2. Animals, preparation and maintenance

The results presented here are based on recordings in the primary visual cortex (area 17) of five rats (Brown Norway, 300–380 g). They were anesthetized with an i.m. injection of ketamin/xylacin/chlorpromacin (10 mg/0.4 mg/1 mg/100 g b.w.) during surgical preparation and maintained with a nitrous oxide/oxygen (30/70%)–isoflurane (0.5%) gas mixture during the recording session. During surgery animals were placed in a stereotaxic apparatus, body temperature was kept constant, and the heart rate was monitored continuously. The cornea was protected with a non-refractive contact lens throughout the experiment. The scalp was removed, and a small (2×2 mm) bone window above the left visual cortex was drilled (centered at AP $= +1$ and $L = 3.25$ mm from lambda), the dura reflected and, after electrode positioning, the cortical surface covered with 3% Agar in Ringers solution to prevent drying of the brain and decrease pulsation. All procedures used in this study were performed in accordance with the guidelines for the welfare of experimental animals issued by the Federal Government of Germany, approved by local authorities and conformed to the guidelines of the National Institutes of Health for the care and use of laboratory animals.

2.3. Recording and visual stimulation

Signals were amplified with conventional electrophysiological instrumentation (filter: 350–3000 Hz) and displayed on an oscilloscope. In addition, spike activity were digitized (sampled at 25 kHz) and stored on computer disk for offline analysis, which started with spike sorting.

Response properties and appropriate receptive field (RF) boundaries of cortical cells were determined qualitatively with visual stimuli generated by a hand-held pentoscope and projected on a tangent white screen. Then RFs were centered on a monitor (EIZO FlexScan F87) positioned 57 cm from the animal. Stimuli consisted of whole screen black and white gratings, moving with constant velocity (5–20°/s) and spatial frequency (0.08–0.6 cycl deg) (cf. [4]). Background illumination was kept below 1 cd/m^2, and stimulus intensities ranged from 7 to 10 cd/m^2. Each experiment consisted of several blocks of trials in which 18 stimuli with particular moving direction were presented in a pseudo-random order.

2.4. Bayesian reconstruction

Once the direction dependence of the firing rates of a group of direction-sensitive cells is known, the Bayes approach directly addresses the inverse problem: given the firing rates of one or more of these cells, what is the stimulus that triggered them? A method to derive the stimulus from the neural firing is called a *reconstruction algorithm* (e.g. [13]).

Bayesian reconstruction needs various distribution functions derived from the data. The first one is the prior probability $P(x)$ for a single direction x to occur. This function is determined by the experimenter and was flat in our case: all stimuli appeared equally often. The second distribution needed for reconstruction is the conditional probability

$P(\mathbf{n}|x)$, which is the probability for numbers of spikes $\mathbf{n}=(n_1,\ldots,n_N)$ to occur, given the direction of the presented stimulus. If we assume that the spikes have Poisson distribution and that different cells are statistically independent of one another, we obtain the expression

$$P(\mathbf{n}|x)=\prod_{i=1}^{N}P(n_i|x)=\prod_{i=1}^{N}\frac{(\tau f_i(x))^{n_i}}{n_i!}\exp(-\tau f_i(x)), \tag{1}$$

where $f_i(x)$ is the average firing rate of cell i during presentation of the stimulus x, and τ is the length of the time window for counting the spikes. The average firing rate $f_i(x)$ is also called the *tuning function* of cell i.

Given the number of spikes fired by a population of cells within a fixed time interval, the goal is to compute the probability distribution of the direction of the stimulus. Under the assumptions mentioned above, this is achieved by applying the Bayes formula in its final form

$$P(x|\mathbf{n})=C(\tau,\mathbf{n})P(x)\left(\prod_{i=1}^{N}f_i(x)^{n_i}\right)\exp\left(-\tau\sum_{i=1}^{N}f_i(x)\right), \tag{2}$$

where $C(\tau,n)$ is a normalization factor which can be determined by the normalization condition $\sum P(x|\mathbf{n})=1$. The Bayesian reconstruction method thus computes the probability for each stimulus direction, given the number of spikes of all the cells within the analysis time window. From this probability distribution the direction of the presented stimulus can be estimated by various estimators. We applied the maximum a posteriori (MAP) estimator

$$\hat{x}_{\text{Bayes}}=\arg\max_{x}P(x|\mathbf{n}), \tag{3}$$

where the direction of the stimulus is reconstructed by taking the most probable direction of the stimulus.

3. Results

Successful multi-site recordings were obtained from rat area 17 throughout cortical depth. Example traces from seven recording sites are shown in Fig. 2. A high signal-to-noise ratio was obtained in both multi-site probe types used in our experiments. The example traces shown were obtained during high activity levels, i.e. most of the signals result from neural activity and are much larger in size than hash during low-activity, background phases. No systematic differences between probe types in recording quality or neural yield have been noticed so far.

Of all 101 neurons recorded so far, 90% were visually responsive, many of which were orientation or direction tuned. Typically, tuning properties changed substantially over time (Fig. 3). Thus, for our current purposes we can conclude that the new recording technique leaves the cortical tissue functional and allows for the investigation of population coding mechanisms.

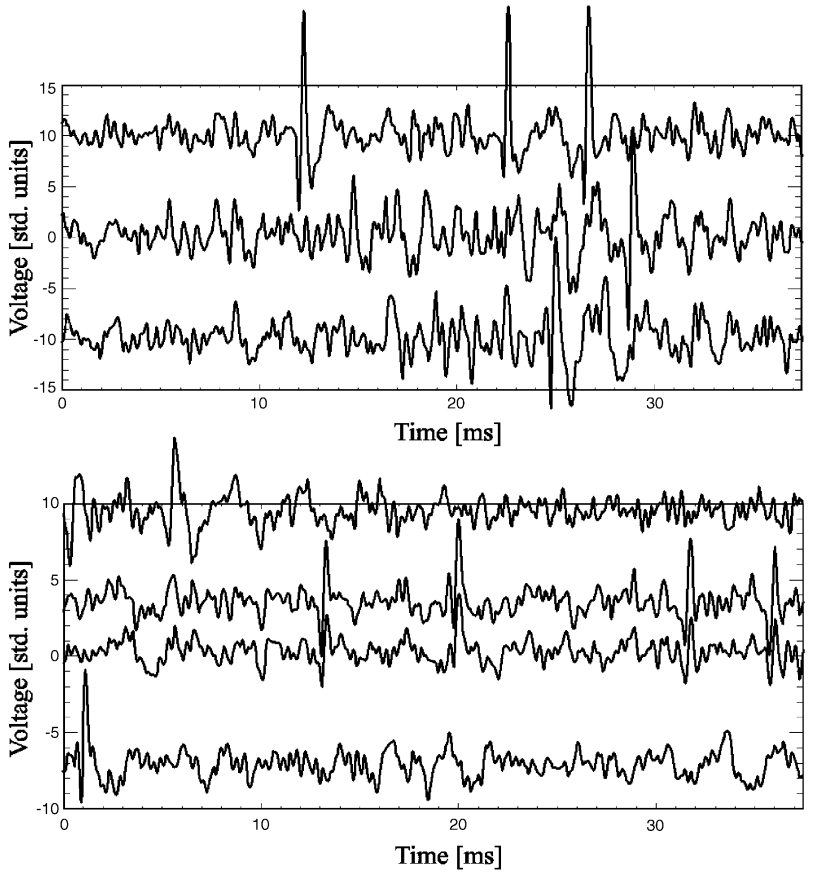
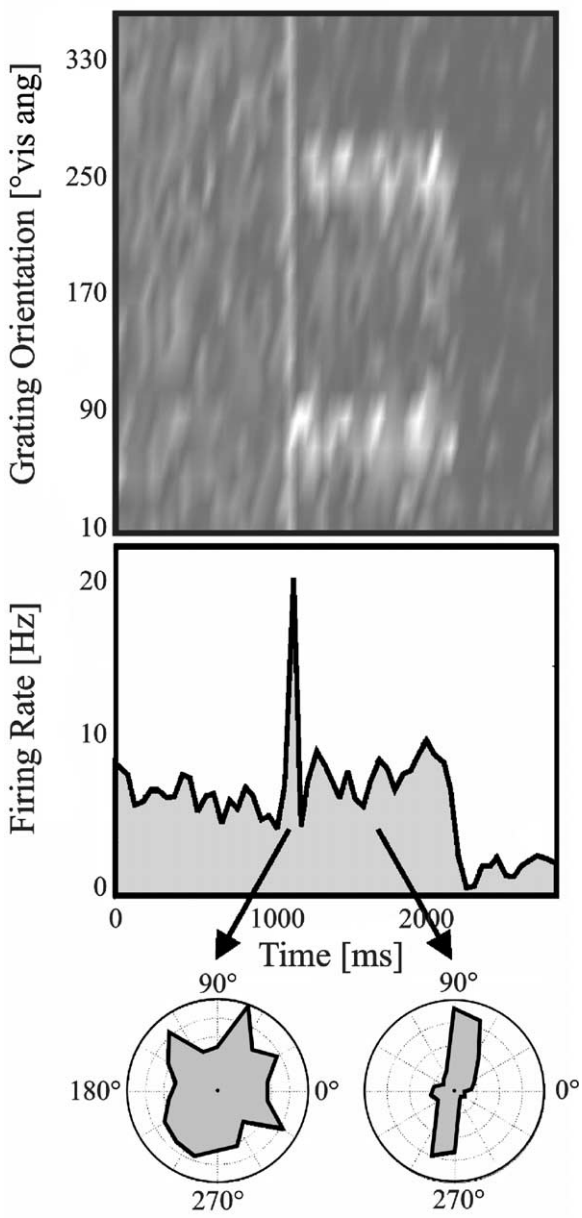


Fig. 2. Three channel simultaneous recordings with a Michigan probe (top) and four channels from a T1 probe (bottom) over 37.5 ms during cortical activation. Signals were *z*-transformed for comparison and shifted upwards/downwards within the two sub-plots ffTun or display purposes. Data was obtained from sites with a 200 μm or larger spatial separation. However, the two central stretches in the bottom plot were recorded from two sites of the same tetrode arrangement. Therefore, these two signals are highly correlated. Nevertheless, not all spike activity of one channel appeared on the other one as well. Therefore, the stereo-capability of the tetrode-like geometrical arrangement of recording sites is useful for spike sorting purposes.

Fig. 3. Tuning Properties of a single neuron recorded in rat primary visual cortex. The upper graph shows firing rate as a function of time (*x*-axis) and stimulus orientation (y-axis) coded by color. Lighter colors indicate firing rates higher than average, darker colors, firing rates lower than average. Below, the PSTH is depicted which was computed as the average firing rate over *all* stimulus conditions (marginal distribution) of the above plot. Shown is a time interval of 2800 ms. The stimulus was turned on at 1000 ms and switched off at 2000 ms. Stimulus presentation leads to a steep increase of firing rate (to about 20 Hz on average) for about 100 ms. The tuning curve of the first 150 ms (shown as a polar plot on the lower left) shows only a weak modulation. A clear directional (orientational) tuning is only apparent after the initial burst of activity. The tuning curve of all spikes fired in the time period between 1150 and 2000 ms after stimulus onset shows two peaks around 70–90° and 250–270° of visual angle. In this phase, both response enhancement and suppression as compared to the pre-stimulus interval lead to the cell's tuning properties. Therefore, in the PSTH averaged over all stimulus conditions (middle) firing rates during stimulation are only slightly higher than that before stimulus onset. Stimulus offset leads to a strong suppression of activity in all stimulus conditions tested, lasting for about 1 s.

With Bayesian reconstruction the current stimulus configuration can be estimated based on the neurons' firing rates. As an illustration, Fig. 4 shows the probability distribution of neural responses to different stimuli, $P(\mathbf{n}|x)$. The cell fires most vigorously to horizontal grating stimuli (i.e. vertical motion directions). Due to the cell's high selectivity, only at high firing rates (above 20 Hz) the actual stimulus orientation



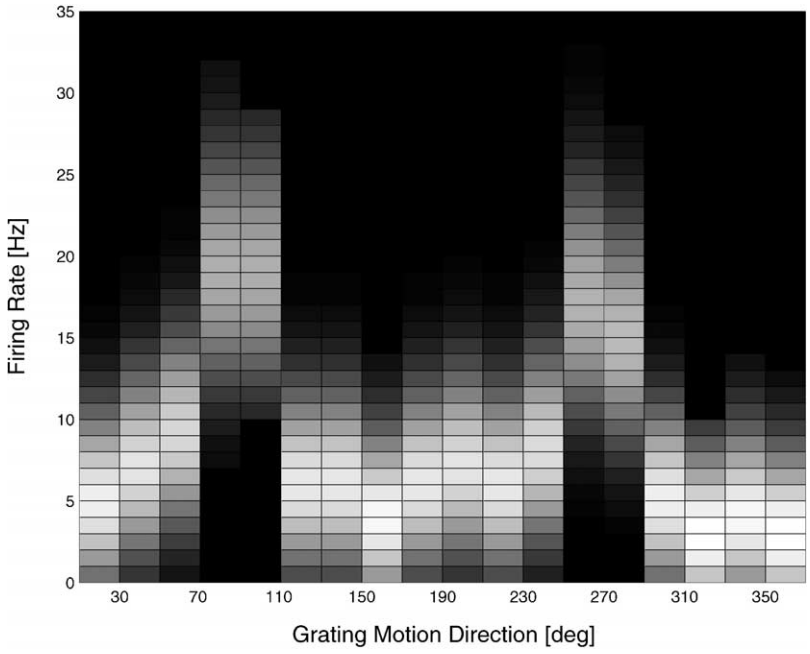


Fig. 4. Bayesian analysis of responses of neurons in rat cortical area V1 to drifting gratings. The conditional probability estimate (gray-scale coded with lighter colors indicating higher probability values) of response (depicted along the y-axis as mean firing rate in Hz) of a single neuron to a given stimulus direction (x-axis). For each of 18 directions, a Poisson distribution with the same mean as the recorded response of the cell, normalized to have an area equal to 1, was used as an estimate of the conditional probability distribution, $P(\mathbf{n}|x)$. Note that the actual stimulus orientation can be estimated with an acceptable error margin only at high firing rates (approx. 20 Hz and higher). This analysis is based on the same data as that of Fig. 3 for illustrative purposes.

can be estimated with an acceptable error margin. Intuitively, the quality of stimulus estimation should improve as increasing numbers of neurons are combined for this analysis. Fig. 5 illustrates this point, showing that the minimal square error of stimulus orientation decreases with population size.

Fig. 5 also shows that good estimation accuracy is already achieved with a small number of neurons. However, this result is based on an analysis of the whole response period. As Eq. (1) shows, resolution depends in a linear fashion on the amount of time the cells have at their disposal. With less time available, reliable coding can only be achieved with larger number of neurons.

4. Summary and conclusions

Our experiments demonstrate the feasibility of multi-site recordings in the rat visual cortex with two kinds of micro-machined multi-site recording probes. Importantly, spike activity was successfully recorded throughout cortical depth, and visually triggered,

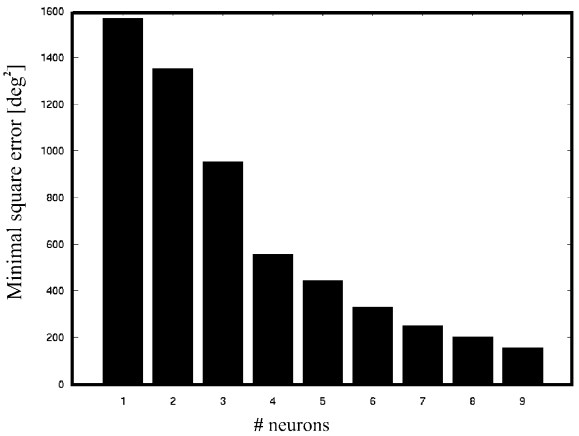


Fig. 5. Application of the Bayesian reconstruction algorithm to assess the minimum square error a population of cells makes in the reconstruction of the presented stimulus. Reconstruction error drops with an increasing number of cells in an exponential fashion. A MAP estimator was used for this analysis, because this estimator is quite robust against noisy fluctuations in the cells' activity, for it will still reconstruct the stimulus under noisy circumstances, unless noise becomes overall dominant. Thus, the reconstruction exhibits both robustness against noisy inputs and high degrees of accuracy.

orientation- or direction-tuned responses provide evidence for the integrity of the tissue after probe insertion. Thus, the activity of many cells can be simultaneously monitored with a minimal number of cortical penetrations.

We have shown that Bayesian reconstruction and the MAP estimator based on responses of small groups of neurons can yield good reconstruction results. However, data was sampled over long time intervals for this analysis. Eq. (1) implies that the resolution achieved by a population of cells depends, in a linear fashion, on the amount of time the cells have at their disposal. Thus, shorter analysis periods have to be traded for larger neural numbers, if coding accuracy is to be maintained. Furthermore, each additional stimulus feature adds a new dimension to the stimulus space, requiring a multiplication of the number of coding neurons.

How neural population size can compensate for shorter analysis intervals is one of the objectives of our future research. This will have to take deviations from Poisson assumptions into account, consider the role of neural correlations and exploit the fine temporal structuring of responses to address the question how multiple stimulus dimensions can be rapidly represented by one set of active neurons in rat visual cortex.

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