

# Neurostatistics: Applications, challenges and expectations<sup>‡</sup>

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### SUMMARY

Brain function and its relations to cognition and behavior can be elucidated only by the use of various complementary methods. Over the past 20 years, we have been studying the brain mechanisms underlying spatial processes using different methods, including the recording of single cell activity in behaving monkeys, functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG) in human subjects, all performing the same tasks. These methods provide partially overlapping perspectives, resulting in a gain in knowledge beyond the province of the individual method. A common aspect in this endeavor is the statistical analysis of the data acquired by different methods, especially regarding the encoding of information in unitary elements (single cell activity in neurophysiology, blood oxygenation level-dependent (BOLD) activation of voxels in fMRI, magnetic field strength in MEG) and the decoding of information from ensembles. In this paper we illustrate the various approaches, their data analysis and possible applications to medicine in the context of operations in space. Published in 2007 by John Wiley & Sons, Ltd.

KEY WORDS: reaching movement; maze solving; mental tracing; spatial cognition

### 1. INTRODUCTION

Behavioral neuroscience is unthinkable without statistics. Both behavior and neuroscience are based on variation of measurements; hence they depend and thrive on statistics. In our work over the past 25 years, we have come across different methodologies to assess brain function and relate it to specific behavioral variables. We believe that no single method can provide all answers,

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hence the need to employ complementary technologies to acquire knowledge about brain function and its relations to behavior from different perspectives. First come standard and venerable methods from experimental psychology by which behavioral responses are quantified and their relations to stimuli or other controlled variables and factors are assessed. Typical examples from sensory psychophysics include the sigmoid-shaped psychometric function for stimulus detection, which plots the probability of perceiving a stimulus against stimulus intensity, and the subjective magnitude estimation function, which plots the perceived intensity of a stimulus against its intensity. A different set includes a host of chronometric functions, in which the response time (RT) to a stimulus is plotted against some property of the stimulus set; classical examples in this category include the monotonic increase of the RT with stimulus uncertainty, angle of mental rotation, number of elements being scanned in memory, etc. The great value of these experimental psychological functions lies in the fact that they constrain the interpretation of the data to specific hypotheses and hence provide the foundation for meaningful experimental designs of neural studies to test these hypotheses. From the viewpoint of statistics, all of these psychological functions belong essentially to the broad class of regression functions, including linear regression in the original scale of measurements (e.g. RT in mental rotation and memory scanning), linear in a transformed scale (e.g. semi-log transformation in the RT versus stimulus uncertainty case and log-log transformation in subjective magnitude estimation, stemming from a power function in the original scale), logistic regression in the case of the psychometric function, more general association analyses for multinomial responses, etc. Now, when neural studies come into the picture, we still remain interested in statistical association, but we need to take into account the peculiarities of the new measurements. Currently, there are several major classes of neural signals that are being acquired over time during performance of specific tasks: neural spikes from individual cells, blood oxygenation level-dependent (BOLD) signal from functional magnetic resonance imaging (fMRI), electrical signal from electroencephalography (EEG), magnetic signal from magnetoencephalography (MEG), optical imaging signal, infrared signal through the skull, etc. All of these signals, except for the spike trains, are essentially analog signals sampled at certain frequencies. Commonly, spike trains are converted to analog signals for analysis but, of course, they are point processes requiring specialized treatment [1].

In general, there are two major objectives in behavioral neuroscience. One deals with the problem of encoding of information in neural activity. The early studies by Mountcastle and his colleagues in the somatosensory system provide excellent examples of this application and are summarized nicely in his recent book [2]. The other objective deals with the decoding of information from neural activity. For continuous variables, methods such as the population vector [3-5] can be used; for categorical variables, discriminant classification methods are appropriate [6]. In what follows, we exemplify the neural encoding and decoding with respect to behaviors studied using various neural recording methods in monkeys and human subjects.

## 2. DIRECTION OF ARM MOVEMENT IN SPACE: SINGLE CELL ACTIVITY AND MEG

### 2.1. Encoding the direction of arm movement: directional tuning

When monkeys move their arm in different directions, the activity of single cells in various motor areas of the brain varies in a systematic fashion with the direction of movement, such that cell activity is highest when the movement is in a certain direction (the cell's preferred direction) and decreases gradually for movements farther away from the preferred direction. A plot of cell



Figure 1. Directional tuning of a motor cortical cell. Top panel: spike trains recorded during movements of the monkey in eight different directions indicated in the center diagram. Trials are aligned to the onset of movement (M). T, onset of stimulus. Bottom panel: cosine-fitted directional tuning curve. See text for details (adapted from [7]).

activity against the direction of movement yields a directional tuning curve (Figure 1). Figure 1 also illustrates the fact that a particular discharge rate (off the peak) provides ambiguous information about the direction of the movement, since it corresponds to symmetric directions on either side of the peak. This broad directional tuning is a common feature in all motor areas where it has been investigated [8].

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Figure 2. Neuronal population vectors for eight movement directions. Each cluster of solid lines consists of the same preferred directions of 243 cells recorded in the motor cortex. The length of the preferred direction vector varies accordingly from movement to movement. The dashed arrows indicated the direction of the calculated neuronal population vector (adapted from [3]).

# 2.2. Decoding the neuronal population activity to retrieve the direction of movement: the neuronal population vector and the neural movement trajectory

A unique decoding of movement direction from the discharge of single cells is not plausible. Although, in principle, such a decoding could be based on just the cell discharge at the peak of the curve, one would have to reject, in that case, the rest of the curve as irrelevant, which is not reasonable. Instead, it is obvious that the directional information is distributed among cells in a population, such that a unique decoding of movement direction could be obtained using a population decoding method. For this to be feasible, a crucial property is needed, namely that different cells have different preferred directions, and this is what has been found [9]. How, then, from such an ensemble of directionally tuned cells can the direction of specific movement be decoded? A decoding method, called the neuronal population vector, was proposed in 1983 for 2-D arm movements [3] and further generalized for free 3-D reaching movements [4, 5]. It is based on the following principles: (a) The preferred direction of a cell is a stable property, remaining relatively constant for all movements. It could reflect, e.g. weighted synaptic connections of the cell to various motoneuronal pools in the spinal cord, *via* interposed interneuronal pathways [10, 11]. (b) The actual discharge of the cell during a movement in a particular direction serves as a weighting factor of the preferred direction vector. Finally, (c) the sum of these weighted preferred direction vectors is the neuronal population vector that yields an accurate prediction of movement direction (Figure 2) [3–5]. When calculated at short time intervals, the population vector yields instantaneous velocity signals (Figure 3) [12], the integration of which, in turn, yields a predicted movement trajectory [5]. This neural representation of the movement trajectory in space typically precedes the execution of the movement but the actual lead depends on the curvature of the movement trajectory, such that the higher the curvature, the longer the neural lead [13]. Although the original decoding application was in the motor field, which still remains a major focus [14–19], the method is quite general and has been applied successfully to a host of other problems [20-26].



Figure 3. Time-varying neuronal population vector (NPV) for two movement directions (adapted from [12]).



Figure 4. Prediction of movement trajectory by MEG. Actual (dark lines) and MEG-predicted (grey lines; cubic-spline smoothed) X- and Y-trajectories using 20 time-points per sensor (adapted from [31]).

Finally, two aspects of the population vector approach should be distinguished. The first concerns the idea of extracting unique information from a neuronal ensemble—this is the essence of the approach. The second point concerns the specific statistical method (or algorithm) by which this is achieved. The original application [3, 5, 17] employed a weighted linear summation of components but subsequent work has extended the population vector approach by introducing additional statistical methodologies best suited for different applications [27–30].

# 2.3. Decoding the neuronal population activity from the MEG signal: predicting movement trajectory

Recently, the population decoding method has been used successfully to extract useful information about the trajectory of an upcoming movement from an ensemble of MEG signals recorded in human subjects (Figure 4) [31]. This underscores the power of the population decoding scheme and opens the way for potentially non-invasive control of prosthetic devices.

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### 3. DIRECTION OF MENTAL TRACING: SINGLE CELL ACTIVITY AND fMRI

Similar considerations to the above also apply to mental operations. A case in point is mental tracing. In behavioral experiments, human subjects and monkeys fixated their eyes in the center of a display and indicated whether a path emanating from the fixation point outward exited or not [32, 33]. The path was embedded in an orthogonal maze. It was found that the RT of both monkeys and humans increased as a linear function of the length of the path and the number of turns in it. These findings suggested that the path is mentally traversed, from the center (i.e. the fixation point) outward. Next, the activity of single cells in the posterior parietal cortex was recorded in monkeys during performance of the task. The task design was modified such that (a) all paths (exit and no-exit) were straight, without turns, (b) they varied in radial direction (eight directions, every  $45^{\circ}$ , starting from  $0^{\circ}$  at 3 O'clock), and (c) were presented randomly mixed with respect to the exit status from trial to trial. This arrangement allowed for an assessment of the variation of cell activity as a function of the direction of the maze path. This design was equivalent to the arm movements in eight directions discussed in the preceding paragraph, with the difference in the present case that instead of arm movements we had directions of mental tracing. Remarkably,



Figure 5. Spike trains of a parietal cell directionally tuned to the direction of mental tracing of a maze path (adapted from [33]).

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Figure 6. Time-varying neuronal population vector during mental tracing of a maze path (adapted from [21]).

the results of this study were formally very similar to those obtained for the arm movement: cell activity was directionally tuned (Figure 5). The common factor in both cases was direction in space, be it direction of movement or direction of mental tracing. As in the movement case, the preferred directions of the directionally tuned cells were distributed throughout the directional range  $(0-360^\circ)$ . This wide dispersion of the preferred directions set the stage for testing the possibility of decoding the direction of mental tracing using the population vector approach above. Indeed, the population vector, calculated at short time intervals, pointed in the direction of the maze path being mentally traced (Figure 6) [33].

The recording of the activity of single cells possesses, without a doubt, the finest grain for associating brain function with behavior. This advantage is somewhat offset by the fact that only very small neural volumes can be studied with this method. In a way, there is gain in precision and depth but there is loss in extent. In contrast, modern functional neuroimaging methods provide the extent at the cost of precision. The most commonly used such method is the fMRI. The exact relations between underlying neural activity and the strength of the BOLD signal are not known but it is widely believed that, overall, what 'lights up' in an fMRI experiment roughly corresponds to what is found to be activated in intracortical electrophysiological cell recordings [34]. Given that rough correspondence, we investigated the detailed activation patterns in the superior parietal lobule of human subjects performing the maze path tracing task [35]. We performed these experiments at a high magnetic field strength (4T) to reduce the area of spatial uncertainty regarding the origin of the activated BOLD signal [36]. The experimental design was the same as that used in the neurophysiological experiments above. There were eight task periods, one for each one of eight radial maze path directions. Each task period was preceded by a control period in which a regular grid of the same spatial frequency as the mazes was presented. The voxel size was  $1.56 \times 1.56 \times$ 5 mm. We found that, of those voxels that showed a significant directional effect in an ANOVA, 51 per cent of the voxels were directionally tuned (Figure 7). This percentage is remarkably close to the 53 per cent observed for cells in the neurophysiological studies above. The directional tuning of

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Figure 7. Directional tuning curve of a single voxel (fMRI) in the superior parietal lobule during mental tracing of a maze path (adapted from [35]).



Figure 8. Prediction of the direction of mental tracing of a maze path by the neuronal population vector using fMRI in the superior parietal lobule (adapted from [35]).

single voxels suggests a coherent tuning of local neuronal populations contributing to the change of the single-voxel BOLD signal. Standardized tuning curves were also very similar for single cells and single voxels.

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Preferred directions ranged throughout the directional continuum of  $360^{\circ}$ . Voxels with similar preferred directions tended to cluster together: on the average, there were seven same-direction clusters per slice, with an average cluster membership of five voxels/cluster and an average nearest-neighbor same-direction inter-cluster distance of 13.1 mm. On the other hand, the average nearest-neighbor inter-cluster distance between a given direction and all other directions was 3.1 mm. This suggests a patchy arrangement such that patches of directionally tuned voxels, containing voxels with different preferred directions, alternate with patches of non-tuned voxels. Finally, the population vector predicted accurately the direction of the maze path (with an error of  $12.7^{\circ}$ , Figure 8) and provided good estimates (with an error of  $29^{\circ}$ ) when calculated within parts of the superior parietal lobule. Altogether, these findings document a new, orderly functional organization of this area with respect to mental tracing.

### 4. CONCLUSIONS

The discussion above underscores the intimate relation among neurophysiology, fMRI and MEG in actual and mental spatial-motor functions, a relation that was documented using practically identical methods of statistical analyses. The encoding of behavioral or cognitive variables on the activity of single elements and the decoding of these variables from neuronal ensembles form two inextricably related complementary approaches that underlie practically all research in behavioral neuroscience.

# 5. STATISTICAL CHALLENGES AND EXPECTATIONS

As can be appreciated from this review, the statistical methods involved in behavioral neuroscience research are rich and diverse. Many problems can be, and have been, investigated using classical statistical methods. However, it is not surprising that the correct application of such methods is still an issue in the field, for several reasons. First of all, neuroscientists commonly have minimal or non-existent training in statistics, and, therefore, are much less sensitive to some basic principles and assumptions underlying statistical analysis. Secondly, part of the problem of abuse of statistics lies in the proliferation of statistical packages, both general purpose (e.g. SPSS, MATLAB, etc.) and specialized (e.g. SPM for fMRI), which are frequently used without a clear understanding by the user of the statistical principles involved in a particular application. In general, such packages offer all kinds of diagnostics but these are rarely being taken advantage of. Finally, another disturbing trend is that more and more neuroscience journals are now systematically downplaying the Methods section of the paper by, e.g. (a) placing it at the end of the paper, (b) making its font small and, in some cases, hardly readable, or (c) making it less accessible by allocating it to a 'supplementary material' section which can be retrieved only through the Internet. Unfortunately, these are signs of our times on the decline of appreciation of rigorous statistics. It cannot be overemphasized that an educational mission of statisticians to enlighten neuroscientists and journal editors in all of these matters is badly needed and would be very much appreciated by the neuroscience community.

On the positive side, a strong interest in neuroscience and associated statistics has been expressed and pursued rigorously by professional statisticians in various fields, including non-parametric regression [37], Bayesian methods for decoding neural activity [30, 38], interactions between neuronal spike trains [39], analyzing neuronal ensemble activity [40, 41], statistical neuronal signal processing [42], etc. (see [29] for review). This rejuvenation of *neurostatistics* can only bring a breath of fresh air to systems neuroscience and associated applications, such as neuroprosthetics [14, 15, 43].

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