Statistical significance of phase-encode maps in the presence of response latency variance

A. A. Rao[1], T. M. Talavage[1]
[1]Purdue University, West Lafayette, IN, United States

Introduction

Phase-encode mapping [1] is used to detect spatial variation of response properties by continuous measurement and has been used to reveal retinotopy [2, 3] and tonotopy [4]. Multiple sweeps of a stimulus are presented while slowly varying (in either direction) a property of interest. The latency of the average response, relative to the duration of one sweep is used to evaluate the variation of sensitivity to the varied stimulus property across cortex. The technique inherently assumes spatial invariance of response latency. However response latency has (in the occipital cortex) a variance, over space, estimated about 23 s^2 for 32 s stimulation [5]. This variance affects confidence in the identification of phase-encode maps, which rely on the hypothesis test (H_0: absence of map; H_1: presence of map). This work approximates the statistical significance (p-values) of observed maps in the presence of spatial non-stationarity of response latency for retinotopy and tonotopy studies.

Methods

Simulations were performed given that the ground truth was unknown in human data. Two-dimensional complex-valued data, representing the DFT of the data measured on the cortical surface, were generated and stored in a matrix. The phase component contained the response latency at each voxel. The matrix comprised three rows of $K \in \{3, 4, 5, 6, 7\}$ "true" voxels assumed to be of in-plane resolution 3mm x 3mm. The magnitude values were generated as i.i.d. Gaussian random variables with $\mu=10$ and $\sigma^2 \in \{0, 1, 4\}$. To evaluate the probability of missed detection (P_{MD}), the phase (latency) data end-points were generated as random variables with densities shown in Figs.1 (a) and 2(a) in the tonotopic and retinotopic cases, respectively. The end-points were found to fall in the first and last thirds of the response cycle [4] with greater compression toward the middle in the tonotopic case (due to asymmetry of tuning curves of auditory neurons) than the retinotopic case (due to symmetry in the receptive fields of photoreceptors). Intervening points in each row were uniformly spaced between end-points. To evaluate the probability of false alarm (P_{FA}), latencies in the entire matrix were generated as i.i.d. random variables with densities drawn from the full possible range, as shown in Figs.1 (b) and 2(b). The 3xK data matrix was bilinearly interpolated to a size 7 x (3(K-1) +1) to model a 1mm tessellated surface. Latency noise was then added to the phase as a uniformly distributed random variable in the range [0, L] cycles where $L \in \{0.10, 0.15, 0.20, 0.25\}$ with L=0.25 corresponding to a variance of 22 s^2 (consistent with [5]) for a 64 s stimulus cycle. Subsequently, data were spatially filtered using a nearest neighbor averaging kernel. Finally the rows of the phase matrix were checked for monotonic progressions. Monotonicity of rows required end-point difference of 0.33 to 1.00 cycles and successive voxel difference greater than -0.05 cycles. Observation of a map required at least four (of seven) consecutive rows showing monotonicity.

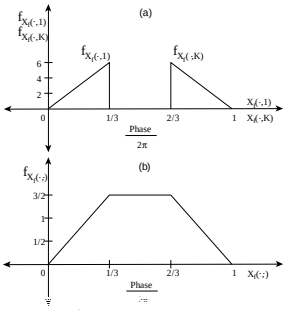

Fig.1: Phase densities for (a) P_{MD} (b) P_{FA} in tonotopy.

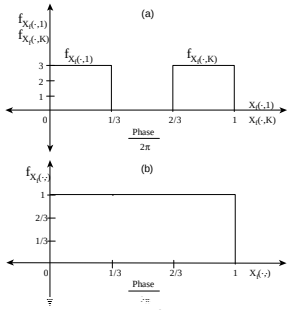

Fig.2: Phase densities for (a) P_{MD} (b) P_{FA} in retinotopy.

	Retinotopy		Tonotopy	
K	P_{FA}	P_{MD}	P_{FA}	P_{MD}
3	3.07×10^{-2}	4.50×10^{-4}	9.28×10^{-3}	2.51×10^{-3}
4	1.46×10^{-2}	1.80×10^{-4}	6.09×10^{-3}	2.53×10^{-3}
5	4.98×10^{-3}	1.96×10^{-4}	3.01×10^{-3}	3.89×10^{-3}
6	1.35×10^{-3}	2.96×10^{-4}	1.41×10^{-3}	5.00×10^{-3}
7	3.61×10^{-4}	3.40×10^{-4}	5.83×10^{-4}	4.95×10^{-3}

Table 1: Empirical (worst case) error rates for L=0.25, $\sigma/\mu=0.2$.

Results

Table 1 shows error rates for tonotopy and retinotopy under a subset of parameters, with one million simulations performed for each set. P_{FA} was essentially independent of L and σ, but exponentially inversely proportional to the physical length of the map (K). P_{FA} decreased from 0.03 (K=3) to 0.0004 (K=7) in retinotopy simulations and from 0.01 (K=3) to 0.0006 (K=7) in tonotopy simulations. P_{MD} increased with L and σ; the former being dominant. The worst-case P_{MD}, occurring at L=0.25, was approximately 0.0005 in retinotopy and 0.005 in tonotopy simulations. Introduction of spatial correlation into latency noise lowered P_{MD} by up to an order of magnitude, but left P_{FA} unaltered. Change in μ (strength of response) had minimal impact on error rates as long as the ratio σ/μ was held constant. Greater extent of spatial smoothing led to an increase in P_{FA} and decrease in P_{MD}.

Discussion

These simulations provide a basis to assign p-values (equivalent to P_{FA}) to maps as opposed to individual voxels. As an example, these results can be applied to compute the statistical significance of tonotopic maps observed in [4]. Four observations 11.5-21mm in length, corresponding to K=4 voxels (worst-case $P_{FA}<0.0061$ from Table 1) required monotonic progression detection in 4 of 6 subjects. Under a Bernoulli trial model of independent observations across subjects, P_{FA} or $p<2.1\times10^{-8}$.

P_{MD} was lower in retinotopic than tonotopic mapping, as expected. However P_{FA} for the tonotopic case was lower for K<6, comparable for K=6, and higher for K>6. Spatial filtering was found to be the dominant operation in this experimental dependence of P_{FA}.

The results indicate that careful selection of time-varying stimuli and size of cortical areas to be examined are critical to success of phase-encode experiments. The study highlights a tradeoff in stimulus design with longer duration of localized stimulation desired for better signal-to-noise ratio, but shorter duration for finer mapping.

Conclusions

Spatial non-stationarity of response latency reported in [5] does not limit accuracy of observed maps. Rather, the size of the cortical area is the dominant factor in the confidence level. Non-stationarity of latency was found to be more likely to contribute to failure to observe a map than to produce a false positive assessment of cortical organization. The observations of estimated error rates have, for the first time, facilitated an empirical assessment of the statistical significance of phase-encode maps observed on both an individual subject and group basis. These procedures may be extended to other phase-encode mapping studies to establish confidence levels for multiple-voxel regions as the fundamental unit of fMRI signal detection.

References

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