Information Theoretic fMRI Time-Series Analysis

Eric Cosman, Jr., John Fisher III & William Wells III

Artificial Intelligence Laboratory
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139

http://www.ai.mit.edu

The Problem: Functional Magnetic Resonance Imaging (*f*MRI) assesses brain activity by taking a volumetric sampling of blood flow (BOLD) in the head, over time. Due to the fine temporal and spatial resolution with which *f*MRI can non-invasively evaluate blood flow, it is often used in experiments designed to determine what regions of the brain are engaged during different activities. These include protocols whereby subjects perform repetitive motor or cognitive tasks, or attend to sensory stimuli, while being scanned by *f*MRI . We are developing Information Theoretic (IT) techniques to analyze the relationship between such protocols and *f*MRI time series.

Motivation: By measuring blood flow, *f*MRI provides only an indirect indication of cognitive function. In fact, cerebral blood flow and the *f*MRI signal may be affected by factors extrinsic to the experimental protocol, including unrelated cognitive processes, lapses in the subject's attention to the protocol, cardiac and respiratory fluctuations, scanner noise, and other non-Gaussian, colored noise [3, 7]. Furthermore, while the BOLD response has been modeled for certain types of tasks and in certain brain regions, observed non-linearities have not been accounted for [1].

We propose using Information Theoretic techniques to model the dependency between an *f*MRI time-series and its corresponding experimental protocol. The IT framework is appealing in that it is a principled methodology requiring few assumptions about the structure of the *f*MRI signal, and the nature of uncertainty (i.e. Gaussianity). It is capable of detecting unknown nonlinear and higher-order statistical dependencies, and is straightforward to implement.

Previous Work: Our work has centered on the block-paradigm protocol for brain activity experiments. In block protocols, a brain region's involvement in a task or perception is inferred by contrasting the functional response of that region between known periods of subject activity and inactivity. In [8], we presented an approach for calculating *f*MRI activation maps by estimating the mutual information between an encoding of the experimental protocol and *f*MRI voxel time-series. Subsequently in [6], we demonstrated the equivalence of the method to a statistical hypothesis test when the underlying densities are unknown. As a consequence, the computation of the activation map can be formulated as a binary MAP detection problem using the Ising model as a spatial prior and solved *exactly* in polynomial time [2]. Such a prior has been used to encode a relationship between adjacent voxels in *f*MRI .

Approach: We combine Information Theoretic principles with adaptive estimation of temporal dependency, both in estimating statistics relating a voxelwise *f*MRI time series to its past and to the protocol, *and* in quantifying the degree of that dependency [5].

Following [4], we model the *f*MRI time series as a random process, whose current sample may be dependent on its finite past and on side information in the form of the experimental protocol and, possibly, confounding signals. As the amount of *f*MRI data is limited (e.g. 60 time samples per voxel over an 180 sec. experiment), we assume that this dependency may be summarized in lower dimensional functions. These functions are trained to be maximally informative with respect to the current *f*MRI sample.

The dependence can then be quantified by the Information Theoretic concept of *entropy rate* (ER), which evaluates the average uncertainty about future values conditioned on the past and possibly side information. With this concept, a generalization of our method using mutual information [8], we form an activation statistic T as the difference between the *f*MRI entropy conditioned only on its past, and the *f*MRI entropy conditioned both on its

past and on the experimental protocol.

$$T = h\left(y_k|\{y\}_0^{k-1}\right) - h\left(y_k|\{y\}_0^{k-1},\{u\}_0^k\right) \quad (10)$$

$$\approx h\left(y_k|f_a\left(\{y\}_{k-M_y}^{k-1}\right)\right) - h\left(y_k|f_a\left(\{y\}_{k-M_y}^{k-1}\right),f_b\left(\{u\}_{k-M_u}^{k}\right)\right) \quad (11)$$

Where y_k is a voxel's *f*MRI signal at time k, and where f_a, f_b represent a signal model based on the finite past of y_k, $\{y\}_{k-M_y}^{k-1}$, and an interval of the protocol encoding, $\{u\}_{k-M_u}^{k}$. Differential entropy is denoted $h()$, which in practice we evaluate using Parzen density estimates. In [5], we show that using this ER statistic is equivalent to a statistical hypothesis test deciding whether the *f*MRI signal is dependent on the protocol encoding, when the underlying joint density is unknown.

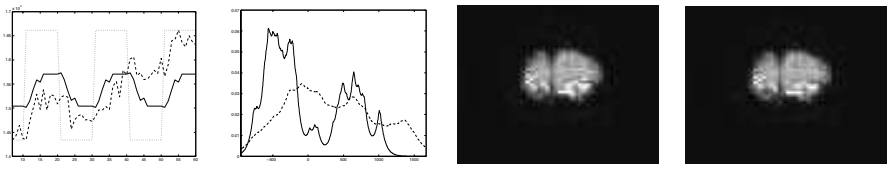

Figure 1: Visual task experiment. *(a) f*MRI signal (dash), protocol encoding (dot), and linear estimate of the *f*MRI based on the protocol (solid). *(b)* The model estimation error due only to the *f*MRI past (dash) has similar variance, but much greater entropy than the error when the protocol is included in the model (solid). A classical F-test fails to detect this "partial responder", whereas our ER statistic does. *(c)* An ER activation map and *(d)* F-test activation map of the visual cortex during the protocol.

Future Work: So far, we have restricted ourselves to linear functions of the past, a special case of the more general approach described in [4], and have shown the advantage of an entropy-rate hypothesis test for detecting particular types of activations that can be hidden from classical tests. Now we are exploring whether IT training of *f*MRI signal models could highlight more complex forms of protocol dependency. We are also interested in extending this approach from block-paradigm to event-related experimental protocols that are now common in the field. Event-related protocols are more powerful and are characterized by rapid, randomized presentation of stimuli. In the manner of [6], we may also incorporate spatial priors into our entropy-rate hypothesis testing framework, extending the approach to account for the shape of the cerebral cortex where most higher brain function is localized.

Research Support: J. Fisher was supported in part by an NSF ERC grant, Johns Hopkins Agreement #8810274. E. Cosman was supported under NSF award #IIS-9610249. W. Wells was supported by the same ERC grant, and by NIH 1P41RR13218.

References:

[1] A. M. Dale and R. L. Buckner. Selective averaging of rapidly presented individual trail using fmri. *Human Brain Mapping*, 5:329–340, 1997.

[2] D. M. Greig, B. T. Porteous, and A. H. Seheult. Exact maximum a posteriori estimation for binary images. *Journal of the Royal Statistical Society. Series B (Methodological)*, 51(2):271–279, 1989.

[3] S. J. Hanson and B. M. Bly. The distribution of bold susceptibility effects in the brain is non-gaussian. *NeuroReport*, 12(9):1971–1976, July 2001.

[4] J. W. Fisher III, A. T. Ihler, and P. A. Viola. Learning informative statistics: A nonparametric approach. *Proceedings of 1999 Conference on Advances in Neural Information Processing Systems 12*, 1999.

[5] J. W. Fisher III, E. Cosman Jr., C. Wible, and W. M. Wells III. Adaptive entropy rate for fmri time-series analysis. *MICCAI*, 2001.

[6] J. Kim, J. W. Fisher III, A. Tsai, C. Wible, A. Willsky, and W. M. Wells III. Incorporating spatial priors into an information theoretic approach for *f*mri data analysis. *Third International Conference on Medical Image Computing and Computer-Assisted Intervention*, 1935:62–71, October 2000.

[7] P. L. Purdon and R. M. Weisskoff. Effect of temporal autocorrelation due to physiological noise and stimulus paradigm on voxel-level false-positive rates in fmri. *Human Brain Mapping*, pages 239–249, 1998.

[8] A. Tsai, J. Fisher III, C. Wible, W. M. Wells III, J. Kim, and A. Willsky. Analysis of functional mri data using mutual information. *Second International Conference on Medical Image Computing and Computer-Assisted Intervention*, 1679, September 1999.