CS 229 Final Project Report

Learning to Decode Cognitive States of Rat using Functional Magnetic Resonance Imaging Time Series

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I Background

Recent fMRI studies have observed that the functional connectivity between different brain regions may exhibit significant dynamic changes when people are at rest [1]. Despite the little-known nature of the temporal dynamics at rest, it's still possible for us to localize those 'dynamic sources' by comparing the fMRI time series at 'rest-state' to 'anesthetized-state', a mental state characterized by a profound loss of conscious and a more 'stable' baseline condition of the brain. However, as both states are 'task-free', we are unable to reference an external task waveform and utilize linear regression method to pre-select the voxels/regions of interest [2,3]. It naturally becomes a problem dealt with machine learning project. Patterns that are informative with respect to the differentiation of 'rest-state' and 'anesthetized-state' may likely have strong neurobiological relevance, and are hypothesized to be a potential candidate for the 'dynamic source' in the rat brain.

For the specific project, advantages of using rat as the object are twofold: (i) the cognitive mental states of rats are anticipated to be less complicated compared to human beings, along with the smaller voxel amount, the dimensionality of classification features can be greatly reduced without losing useful information; (ii) anesthesia can be easily accomplished in rats.

II Problem Illustration

i. Object

The fMRI datasets from 3 rats were analyzed in the present project. Each rat underwent an 8-min 'rest-state' scan and an 8-min 'anesthetized-state' scan.

Preprocessing of the fMRI time series consisted of: slice-time correction, motion correction, low-frequency drift detrending. Signal amplitudes were further scaled to percentage change.

ii. Classifiers

Classifiers were trained using short intervals of rat fMRI data known to correspond to either 'rest-state' or 'anesthetized-state'. After training, the classifier was supposed to determine whether an unseen segment of fMRI dataset corresponded to a 'rest-state' or 'anesthetized-state'.

The analysis consisted of five steps:

(a) Choose p elements (voxels/ networks) that will enter the classification analysis;

(b) Define measures of brain activity (voxel intensity/ functional connectivity/ time-frequency coherence) and corresponding samples;

(c) Use a subset of trials to train the classifier via Support Vector Machines (SVMs);

(d) Use 10-fold cross validation to test the generalization error of the classifier;

(e) Map the weighting of each element.

The primary focus of the present project was step (a) and (b) → Section III IV V. From now on, let $\{x^i\}$ denote the fMRI time series of voxel i after preprocessing, $\{x^i_{+1}\}$ denote the 'rest-state' time series, $\{x^i_{-1}\}$ denote the 'anesthetized-state' time series.

In Section III, p voxels/clusters were pre-selected based on various dimensionality reduction methods. Considering that the fMRI time series were temporally correlated with each other, the modified voxel intensity: $\{y^i = \overline{|x^i|}\}$, i.e. average of the absolute voxel intensities across five consecutive time points, was chosen as the measure of brain activity;

In Section IV, p networks were generated via independent component analysis (ICA). Network connectivity measure: sliding-window Pearson correlation and wavelet transform coherence, were introduced to characterize the brain activity.

III Feature Selection – Voxel Intensity

Since the number of voxels inside the rat brain is large (>20,000 with the protocol in the present data acquisition), including all voxels for classification analysis is sub-optimal: (i) it would increase the computation complexity and be quite time-consuming, given the large feature dimension; (ii) machine learning algorithms, like SVM, might degrade their performances if the number of voxels conveying the discriminative information is much smaller compared to the total number of voxels [3,4], which is always true under the small-world assumption of brain models, this is also confirmed by the results of the present project. Thus, it's reasonable and helpful to perform a dimensionality reduction prior to SVM classification. Three dimensionality reduction approaches were implemented in the project.

i. Significance-based feature selection Under the hypothesis that informative patterns only consist of voxels that show a significant difference between 'rest-state' and 'anesthetized-state', it would therefore be reasonable to restrict our analysis to those 'significant' voxels, which can also simply the interpretation of the final results.

Previous studies have demonstrated that the raw voxel intensity of fMRI time series $\{x^i\}$ can be well fitted by Gaussian models, noting that our modified observations $\{y^i = \overline{|x^i|}\}$ actually follow folded normal distributions, a simple two-sample t test used by previous literatures [2,3] might introduce bias into the present testing model. To address this problem, non-parametric Wilcoxon's rank-sum tests were introduced in addition to t-test to select those 'significant voxels':

{'significant' voxels}↔{ t test: p<0.01} & {rank-sum test, p<0.01}

ii. Principal Component Analysis Consider the fact that in fMRI studies, $N_{voxels} \gg N_{observations}$ always hold, the computation of SVM can be greatly reduced via the PCA kernel trick, while preserving all the feature information: specifically, $\{y^i_{+1}\}^z$ and $\{y^i_{-1}\}^z$ were temporally concatenated, $\{\}^z$ denotes z transformation (zero-centered and divided by its standard derivation, to avoid the improper mapping due to significant differences in signal intensity under two states). However, $\{y^i_{+1}\}$ and $\{y^i_{-1}\}$ were taken as the training samples of SVM, so here existed an inconsistency between PCA mapping and SVM training. Later, we can notice a difference between various data reduction methods, the inconsistency here was thought as a candidate source to the observed differences.

iii. Clustering Analysis I also utilized cluster-analysis methods to accomplish dimensionality reduction, i.e. separated the rat brain into various small regions, and simplified each small region as a single feature. Due to the slow computation of K-means clustering method, I chose Normalized-cut method (http://www.cis.upenn.edu/~jshi/software/) to perform the clustering analysis, which takes each voxel as a node, and recast the image segmentation as a graphic partition problem (in the current analysis, I chose the Pearson correlation with threshold 0.1 as the weight measure). The observation corresponding to each cluster is derived as follows: for each voxel within the cluster, sum up its correlation with all the other voxels within the same cluster, choose 20 voxels with the highest summation of correlation values, and take the average of their observations.

To be more confident with the clustering result, I also compared the clustering results from N-cut method with those from K-means method for a couple of datasets. A measure of similarity SIM_{K-N} between the generated clusters is defined as follows:

Let C^i_K, C^i_N denote the cluster index of voxel i resulted from K-means methods and Normalized-cut methods:

$$SIM_{K-N} = \frac{\sum_{i=1,..N_{vox}} \sum_{j=1,..N_{vox}} \mathcal{I}\{\mathcal{I}\{C^i_K = C^j_K\} = \mathcal{I}\{C^i_N = C^j_N\}\}}{\sum_{i=1,..N_{vox}} \sum_{j=1,..N_{vox}} 1}$$

i.e. the ratio of cases that two methods give consistent clustering results with respect to a voxel-pair (two voxels are within the same network or not), I assume that the larger extent that the two clusters overlap with each other, the more reliable the clustering result is. $SIM_{K-N} > 95\%$ in the tested datasets indicated a convincing clustering result, shown in Figure 2.

The classifiers trained after dimensionality reduction worked surprisingly well, the generation error in the 10-fold cross validation were 0 for all the three approaches. However, the discriminative patterns were inconsistent across rats (Figure 1 c,d) and dimensionality reduction methods (Figure 1, a, b, c), $|w_i|$ larger than 30% of the max($|w_i|$) was to approximate $p < 0.05$ [6].

IV Feature Selection – Network Connectivity

As mentioned above, previous machine learning approaches to fMRI analysis were mainly confined to voxel/ROI intensities, I was especially interested to see whether choosing features that can characterize connectivity behaviors, which attracts the primary attention of fMRI researchers, can also give informative discriminations between various mental states. Again, the dimensionality issue becomes more problematic when it comes to the connectivity behavior, as

$$N_{feature} = \binom{N_{voxel}}{2} = \sigma(N_{voxel}^2)$$

Therefore, I attempted to explore the connectivity at the network level instead of the voxel level. Independent Component Analysis (ICA) method (via a matlab based toolbox: http://mialab.mrn.org/software/gift/) was utilized to generate the networks(ICs), to be consistent with prior literatures, IC number was set to be 30 [7,8]. Networks of interest(NOI) were further chosen through visual inspection, resulting 10~20 networks per rat.

i. sliding-window Pearson correlation analysis To get the time-varying observations of the connectivity between different network pairs, the sliding-window correlation coefficient [1] was introduced, Figure 3:

The sliding-window correlation between two network time series (x and y) is defined as $\rho(t) = corr(x_t^{t+w-1}$ *and* $y_t^{t+w-1})$*, where w is the window size,* x_t^{t+w-1} *and* y_t^{t+w-1} *denote the portion of the time series from t to t+w-1, corr( ) denotes the computation of Pearson correlation coefficient.*

Not surprisingly, like using voxel intensity as the feature, SVM gives 0% training error in 10-fold cross validation. However, features (network-pairs) with the maximum$|w_i|$are still not consistent across rats. Taking together the result from Section III, 0% training error indicates that 'rest-state' and 'anesthetized-state' are highly separable, inconsistency across methods/rats may likely imply a wide-spread discriminative patterns, or perhaps due to rats' individual differences, as the mental states of rats are less controllable compared to human beings.

ii. wavelet transform coherence(WTC) analysis Classifiers trained by voxel intensity and Pearson correlation have achieved perfect generative performance, but the discriminative patterns (voxels/network-pairs) are not consistent across rats. I further extended the features into the frequency domain, hoping to explore whether the discriminative patterns of different rats reside in similar frequency bands (Figure 4 a).

WTC(http://www.pol.ac.uk/home/research/waveletcoherence/) offers a measure of the time-varying coherences within different frequency bands for each network pair [1]:

$$R^2(n,s) = \frac{|<s^{-1}W^{XY}(n,s)>|^2}{|<s^{-1}W^X(n,s)>|^2|<s^{-1}W^Y(n,s)>|^2} \quad 0 \le R^2(n,s) \le 1 \ ,$$

$W^{XY}(n,s) = W^X(n,s)W^{Y*}(n,s)$*, where* $W^X(n,s)$ *is the wavelet transform of signal x, denoting the amount of power in X as a function of time (n) and frequency (s).*

To simplify the computation, I further separated the frequency into four frequency bands: 0~0.02Hz, 0.02~0.05Hz, 0.05~0.16Hz, 0.16~0.2Hz (TR, the sampling rate is 1s) by averaging the WTC falls into the corresponding frequency range (Figure 4 b).

For *N* network pairs, we therefore got $4\binom{N}{2}$ features, by taking the coherence value at different time spots as a sample and applying SVMs to the WTC results, we got the weightings $\{w_i^j, j = 1, \dots, 4, i = 1, \dots 4\binom{N}{2}\}$ of the coherence of different network pairs across different frequency bands.

For each rat, the discrimination level of a specific frequency band W^j is defined as:

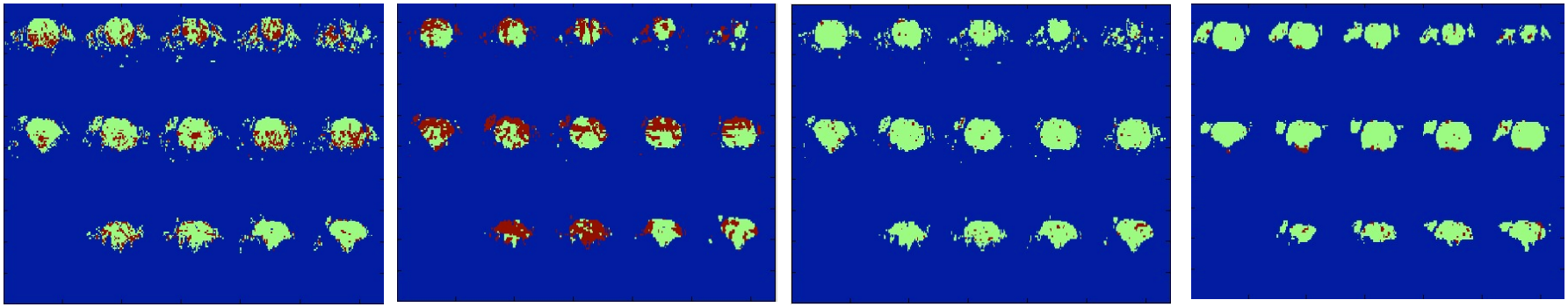
$$W^j = \frac{\Sigma_i |w_i^j|}{\Sigma_k \Sigma_i |w_i^k|}, \qquad i = 1, \dots, 4\binom{N}{2}, j = 1, \dots, 4$$

W^j reflects how discriminative the between-network coherences within the *j* th frequency band is compared to other frequency bands.

As shown in Figure 5, the 3 rats showed a similar pattern: the most discriminative information mainly resided in the low-frequency bands. This result is in accordance with general acknowledgement that 'rest-state' is characterized by low-frequency fluctuations.

Figure 1 Feature Mapping after dimensionality Reduction, green: brain mask (15 slices), red: voxels surpassing the thresholds

Rat 02 **Rat 02** **Rat 02** **Rat 03**



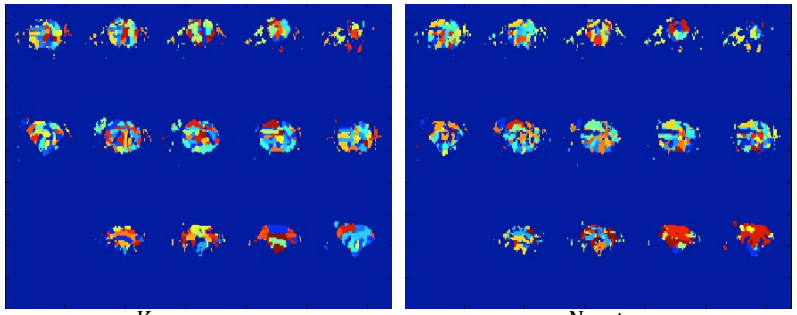
(d) T-test & Wilcoson-test ($p<0.05$), No dimensionality reduction

(c) N-cut methods, ($|w_i| > 0.3\max(|w_i|)$) With dimensionality reduction

(b) PCA methods, ($|w_i| > 0.3\max(|w_i|)$) With dimensionality reduction

(a) PCA methods, ($|w_i| > 0.3\max(|w_i|)$) With dimensionality reduction

Figure 2 Clustering results of K-means and N-cut (similarity = 0.966)



K-means N-cut

Figure 3 Illustration of Sliding-window Pearson correlation

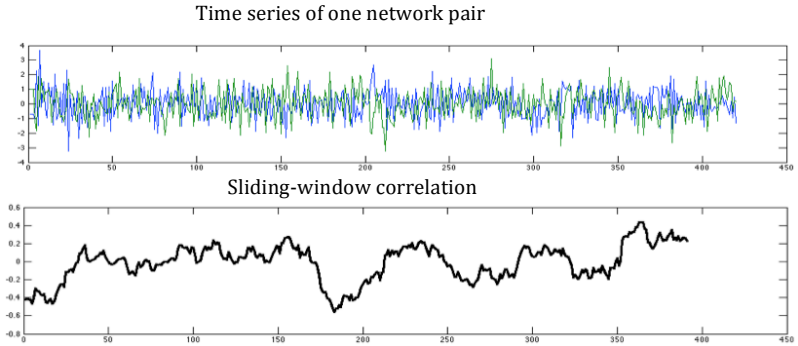
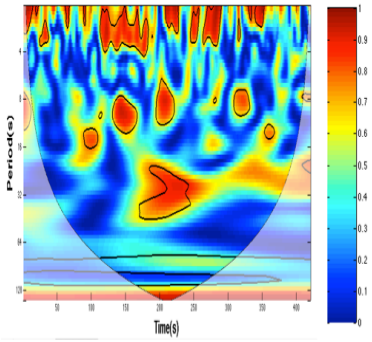
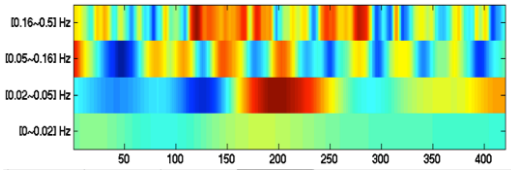


Figure 4 Illustration of WTC

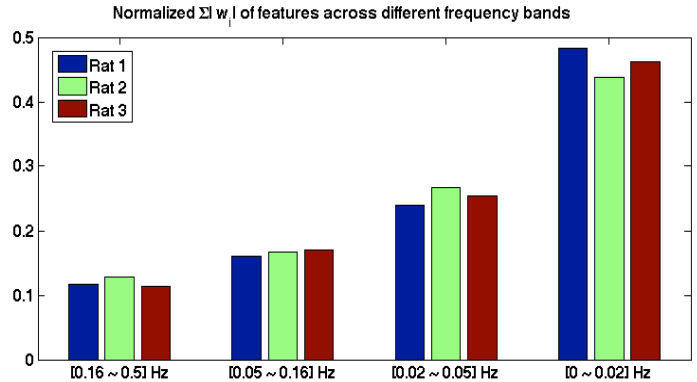


(b) WTC of a network pair



(a) Time-varying WTC across 4 different frequency bands for each network pair

Figure 5



V Feature Selection-Revisit

Feature selection methods introduced in Lecture Note 5 and Recursive Feature Elimination (RFE) proposed in [4] were also tested in the present study to see whether they could improve the generalization performance of the classifiers. As mentioned in section II and III, using the mean absolute value $\{y^i = \overline{|x^i|}\}$ as the voxel intensity resulted in 0% generalization error for all dimensionality reduction cases (which could not be further improved). Instead, I used the raw voxel intensity $\{x^i\}$ to train the classifiers, 100 clusters generated by the Normalized-cut method were chosen as the features.

i. mutual information + forward feature selection

(a) KL divergence was utilized as a criterion to sort the 100 features;

(b) Forward feature selection & 10-fold cross validation were combined to find the optimum features;

ii. RFE

while (~stop)

(a) Train SVMs using 10-fold cross valiation;

(b) Compute the scoring function of each feature:

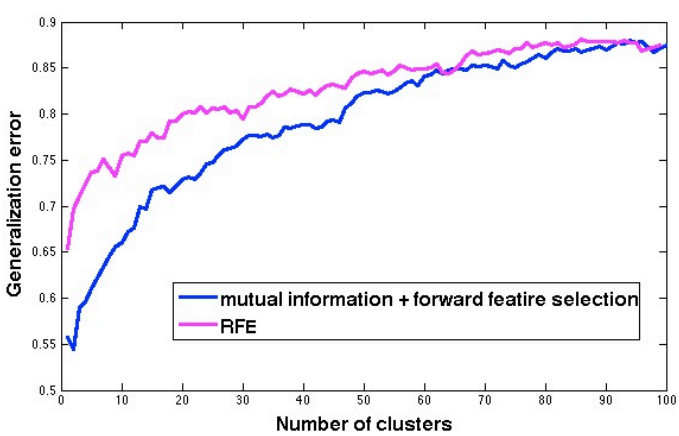
$$S_{RFE}(v) = \frac{\sum_{i=1}^{10} |w_i(v)|}{10}, v = 1,..100,$$

(c) Sort the features based on $S_{RFE}(v)$

(d) Eliminate features with smallest scores

end

The results are shown below:



It turned out that the raw voxel intensity was not an informative feature for classification. Inclusion of more features (clusters) could only introduce more noisy/irrelevant information and degrade the performance of the classifier.

VI Summary

In the present project, I've tried to apply machine learning knowledge to detect patterns (voxel intensity/ network connectivity) that are informative respect to the differentiation of 'rest-state' and 'anesthetized-state' in rats. Results indicated that: (a) Both voxel-intensity-based and network-connectivity-based feature selection methods can result in minimum classification error; (b) The trained classifiers are sensitive to the dimensionality reduction methods & rats' individual differences in the present study; (c) WTC analysis showed that the network coherence differences between 'rest-state' and 'anesthetized-state' mainly reside in the relative low frequency band.

VII Acknowledgement

I gratefully acknowledge Dr. Gary Glover in Radiology Department and Emily Ferenczi in Neuroscience Department for rat fMRI data acquisition.

VIII References

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