TIME VARYING BRAIN CONNECTIVITY MODELING USING FMRI SIGNALS

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ABSTRACT

Inferring brain connectivity networks has been increasingly important for understanding brain functioning. It is suggested that brain is inherently non-stationary and the dynamic patterns of brain networks may provide deeper insights into brain function. However, the majority of current models assume that brain connectivity networks have time invariant structures, neglecting the variability in brain interactions over time. To investigate time varying brain connectivity networks, a stick time varying model is presented in this paper. Simulation results demonstrate that the proposed method could improve the accuracy in estimating time-dependent connectivity patterns. It is also applied to real fMRI data set for studying time-varying resting-state brain connectivity networks.

Index Terms— fMRI, time varying, brain connectivity network, resting state

1. INTRODUCTION

Functional magnetic resonance imaging (fMRI) is a popular non-invasive neuroimaging technology for studying brain activities. Inferring brain connectivity networks using fMRI signals provides a promising way to study interactions between distinct brain regions. A broad range of mathematical models have been proposed to study the interactions between different brain regions. However, most current methods assume the time invariant connectivity structure that is not able to represent temporal variations of the underlying neuro-activities. With the stationary assumption, the inferred brain connectivity possibly represents an averaged version of connectivity patterns across time [1]. Recently emerging evidence suggests that the dynamic brain connectivity patterns could provide great insights into brain activities [2].

To infer time-varying brain connectivity, several sliding window based approaches have been reported, where brain connectivity networks are assumed to change smoothly over time. Within each selected sliding window, different network modeling methods such as correlation [3, 4], covariance [5] and Independent Component Analysis (ICA) [6] can be applied to learn the time-dependent connectivity patterns. Another category of methods can be referred as time-frequency based models. For instance, coherence analysis and Granger causality analysis based on wavelet transforms have been employed to study both resting state and task related fMRI signals [7, 8].

Several studies have demonstrated that functional networks inferred from stationary methods may indeed be driven by a few critical BOLD time points [1, 9]. These critical time points could be used as change points to segment the fMRI samples into small segments. With the piece-wise stationary assumption, methods previously used to learn static brain connectivity networks could be applied to data samples within each segment [1, 10, 11].

The above three categories of methods, the sliding window based, time-frequency based and change point detection based multivariate approaches, all assume that multiple brain regions have same temporal variations at the same time scale. While different pairs of brain regions may exhibit different time variability [2]. To discover dynamic structures/coefficients over time, several time-varying dynamic Bayesian Network (DBN) approaches have been proposed, although not in the area of brain connectivity modeling [12, 13, 14].

Since it is not clear whether the observed dynamic changes in brain interactions are due to the measuring noise, randomized fluctuations or the underlying cognitive modulations, to reduce the influence of noise, it is reasonable to assume that brain connectivity patterns would change smoothly except at several abrupt changing points. In other words, the temporally adjacent networks are likely to share common edges than temporally distant networks as described in the weighted regression model [12].

In this paper, we propose a stick time varying regression model to estimate non-stationary brain interactions in a temporally penalized weighted regression fashion. A difference penalty is added into the weighted regression model to be able to estimate smooth changing as well as abrupt changing con-

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nectivity patterns. More importantly, the proposed method allows the multi-stability among multiple brain regions.

2. METHOD

Multivariate linear regression models have been widely used to infer neural interactions. For instance, Structural Equation Modeling (SEM) estimates the brain interactions at zero lag [15]. The autoregressive multivariate (MAR) model focuses on the lagged interactions between distinct brain ROIs [16]. With the sparsity assumption, LASSO (Least Absolute Shrinkage and Selection Operator) and group LASSO methods were also explored [17]. In the regression model used in our paper, the fMRI time course of a Region of Interest (ROI) is regarded as the response variable, and is predicted from the time courses of other ROIs at zero-lag as,

$$Y = X\beta + e \tag{1}$$

where vector Y with length T means the time course of one brain ROI, X means the predictor matrix based on the time courses of other ROIs, β is the coefficient vector and e means the Gaussian noise vector. Due to the non-stationary nature of brain activities, the time dependent regression model becomes,

$$Y_t = X_t\beta^t + e \tag{2}$$

where t represents the time index and we need to estimate the regression coefficients at each time point respectively. Based on previous studies, connections between brain regions can be considered as a sparse network [17]. One computationally efficient approach to promote sparsity in the coefficient vector is to use an l_1 penalty on the regression coefficients. In order to estimate the time varying structures/coefficients, one reasonable assumption about resting state brain connectivity is that the underlying networks are changing smoothly over time. Following [12], we can estimate the coefficients at each time point separately in a time varying model (TV) as,

$$\hat{\beta}^{t^*} = \underset{\beta^{t^*}}{\operatorname{argmin}} \sum_{t=1}^{t=T} W^{t^*}(t)\left(Y_t - X_t\beta^{t^*}\right)^2 + \lambda\left\|\beta^{t^*}\right\|_{l_1} \tag{3}$$

where $W^{t^*}(t)$ is the weight of observations from time t when we estimate the coefficients at time t^*. In general, $W^{t^*}(t)$ can be defined as any kernel function. In this paper, we use $W^{t^*}(t) = \frac{exp(-(t-t^*)^2/h)}{\sum_{t=1}^{T} exp(-(t-t^*)^2/h)}$, which is a Gaussian Radial Basis Function (RBF) kernel and h means the kernel band width. λ is the parameter of sparse penalty which controls the sparsity in the learned coefficient vector.

With the smooth changing assumption, temporally adjacent coefficients are more likely to be similar than temporally distant coefficients. However, in the weighted regression model as well as sliding window based models, the estimated brain connectivity structures/coefficients would still suffer from random noise. In addition, the smooth changing assumption may not work well for piece-wise stationary networks with abrupt changes. Therefore, we propose incorporating the difference penalty into our model and name it the stick time varying (sTV) model. The difference penalty used in the fused regression model serves for detecting change points to segment piece-wise stationary data [13]. By introducing the difference penalty into the weighted regression model, sTV model could estimate smooth changing as well as abrupt changing connectivity patterns and thus is more flexible compared with previous approaches for time-varying brain connectivity modeling.

With the difference penalty, we have the model as,

$$\begin{aligned}\underset{\beta^{t^*}, t^* \in R^T}{\text{minimize}} & \sum_{t^*=1}^{T}\sum_{t=1}^{T} W^{t^*}(t)\left(Y_t - X_t\beta^{t^*}\right)^2 + \lambda\sum_{t^*=1}^{T}\left\|\beta^{t^*}\right\|_{l_1} \\ & + \gamma\sum_{t^*=2}^{T}\left\|\beta^{t^*} - \beta^{t^*-1}\right\|_{l_1}\end{aligned} \tag{4}$$

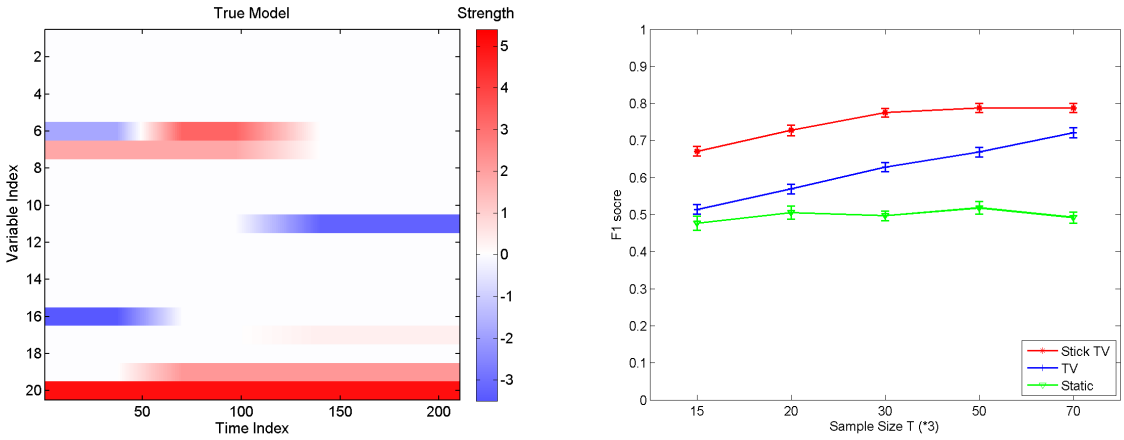
where γ is parameter of difference penalty which is designed to control the difference between adjacent coefficients. This optimization problem can be solved by the coordinate descent algorithm. We use the CVX optimization toolbox in this paper [18].

The parameters of the stationary regression model are usually determined by cross validation (CV) which separates the data into training set and testing set. However, in the time varying model, since each sample corresponds to a certain time point, the structures and coefficients may be different across time. The ordinary CV approach can not be used directly in our time-varying case. To perform the cross validation, we first perform up-sampling by a factor of two: the odd samples represent the original data points and even samples are the interpolated data points. For the purpose of model selection, we assume that the corresponding even samples have the same temporal properties as those of odd samples. Treating the odd samples as the training set and even samples as the testing set in simulation studies, we could use CV to select the optimal parameters of the model in Eq. 4.

To make inference of brain connectivity networks, for each ROI one by one, we treat the specific ROI as the response vector and other ROIs as predictor matrix. In this way, we could learn the sparse time-varying interactions between distinct brain regions.

3. SIMULATION RESULTS

In order to compare the performances of the proposed method (sTV) with the time varying model (TV) in [12] and the (stationary) sparse regression model, we performed simulations in this section. The simulated data were generated from a



(a) (b)

Fig. 1: (a) An example of simulated time varying model. The color represents the coefficient strength. (b) F1 scores of the proposed method, the time varying model in [12] and the LASSO model.

Gaussian model with certain changing structures and coefficients. More specifically, the data were generated as follows:

(1) We first generated 3 different anchor coefficient vectors A^1, A^2, A^3 with each corresponding to 20 variables (P=20). The length of data samples corresponding to each anchor coefficient vector was setted as T and the total length was 3*T. To generate the time changing coefficient vectors β^t $(t = 1, \cdots, 3T)$, we first setted $\beta^1 = A^1$, $\beta^{T+1} = A^2$ and $\beta^{2T+1} = A^3$, and then interpolated a number of coefficient vectors between them. An example of the time varying $\{\beta^t\}$ is shown in Fig. 1 (a).

(2) The design matrix X was randomly generated, containing $3T$ observations and P predictors. The error vector e followed iid Gaussian noise $\sim N(0, 1)$. The response vector Y was generated by $Y^t = X^t\beta^t$ with $t = 1, \cdots, 3T$.

We compared the proposed stick time varying model with the time varying model in [12] and the static sparse regression model (LASSO). The cross validation was used for parameter selection in sTV and TV models as discussed before, and the traditional 10 fold CV was used for the LASSO model.

In the simulation, we tested the performances of the algorithms as a function of the number of time points T. For reliable assessment, each procedure was repeated one hundred times and we compared the averaged performances of different algorithms. F1 score was employed to quantitatively evaluate the general performance by considering both the Type I and Type II error rates, as shown in Fig. 1 (b). We compared F1 scores at sample size $T = 15, 20, 30, 50$ and 70 respectively. Compared with other two methods, our simulation results demonstrated that the proposed stick time varying model could yield higher accuracy in recovering time dependent coefficients. It could estimate smooth changing coefficients as well as sudden change patterns and thus it allows to accurately estimate the underlying time-varying brain connectivity patterns.

4. REAL APPLICATION AND DISCUSSION

In this section, we apply the proposed method to a real fMRI study. Twelve Parkinson's Disease (PD) subjects and ten healthy control subjects were recruited from Pacific Parkinson's Research Center (PPRC) at the University of British Columbia (UBC). All the experiments were approved by the Ethics Board at UBC. A 3 Tesla scanner (Philips Gyroscan Intera 3.0T; Philips Medical Systems, Netherlands) equipped with a head-coil was used to collect data in the resting state. fMRI was sampled at 0.5 Hz. 4 mins signals were used in the time varying analysis and 48 Freesurfer-derived ROIs (listed in Table 1) were chosen in this study.

For each subject, the penalty λ and γ were fixed as 0.4. Though studies have been conducted on the time variations in the connectivity networks, it's still not clear the time scale of the brain activities. In this resting state study, we want to compare the relative difference modulated by the disease state. The bandwidth was chose as 32s (16 points), which is sufficiently long to remove noise and also can capture enough variability in temporal patterns.

For the temporal connectivity patterns, we found 21 common connections (defined as appearing at least at one time point) that appear in all subjects in the normal group (Fig. 2 (a)) and 12 common connections in the PD group (Fig. 2 (b)). The results demonstrated that more stable connections were identified in the normal subjects. Similar observations were noted when selecting other parameters in our study. More specifically, some bilateral ROIs were involved in the stable connections. For instance, Left and Right ACC (L6/R6),

Table 1: The index and names of 48 brain ROIs. 'L' represents the brain left side and 'R' represents the brain right side.

Index	Name	Index	Name	Index	Name
L1/R1	L/R Cerebellum	L9/R9	L/R PFC	L17/R17	L/R ctx-inferiortemporal
L2/R2	L/R PMd	L10/R10	L/R Pallidum	L18/R18	L/R ctx-lateraloccipital
L3/R3	L/R PMv	L11/R11	L/R Putamen	L19/R19	L/R ctx-middletemporal
L4/R4	L/R Pre-SMA	L12/R12	L/R Somatosensory	L20/R20	L/R ctx-precentral
L5/R5	L/R SMA-proper	L13/R13	L/R Thalamus-Proper	L21/R21	L/R ctx-precuneus
L6/R6	L/R ACC	L14/R14	L/R ctx-caudalmiddlefrontal	L22/R22	L/R ctx-superiorparietal
L7/R7	L/R Caudate	L15/R15	L/R ctx-cuneus	L23/R23	L/R ctx-superiortemporal
L8/R8	L/R Cerebellum-Cortex	L16/R16	L/R ctx-inferiorparietal	L24/R24	L/R ctx-supramarginal

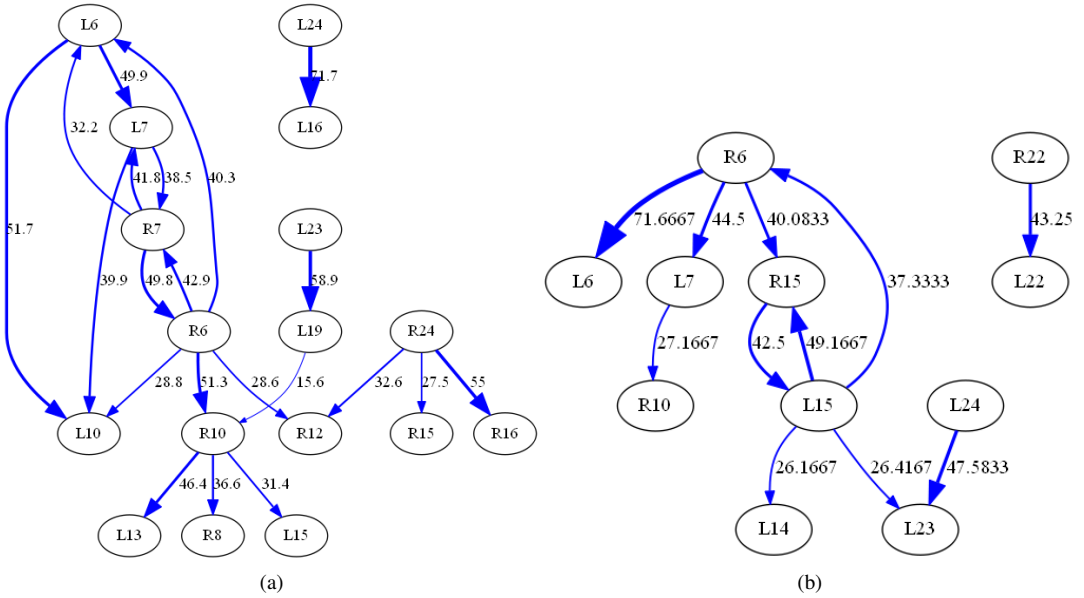


Fig. 2: (a) Common connections detected in the normal control group. (b) Common connections detected in the PD group. The common connections are defined as those connections appearing at least at one time point in all the subjects in the group. The label of the connection represents the averaged duration (time points) of the connection.

Left and Right Caudate (L7/R7) and Left and Right Pallidum (L10/R10) were found in the normal group. Left and Right ACC (L6/R6), Left and Right ctx-cuneus (L15/R15) and Left and Right ctx-superiorparietal (L22/R22) were found in the PD group. The bilateral ROIs were found to be more stable in the time varying connectivity networks which is consistent with previous studies [2].

Due to the space limit of this paper, we could not fully elaborate the choice of the parameters and the interpretation of the time varying connectivity results. We would discuss them in detail in our future extended paper.

Studying dynamic properties of brain connectivity patterns is important for understanding brain function. In this paper, a penalized weighted regression time varying model is proposed. It could estimate smooth changes as well as abrupt changing patterns in connectivity networks. Compared with previous multivariate time varying approaches introduced for fMRI brain connectivity modeling, the sTV can model the ROIs multi-stability and thus is more flexible in real applications. It is worth noting that the parameters such as bandwidth themselves are of great interest. It could provide great insights into the time scale of brain activities. Another concern in time varying resting state brain connectivity analysis is how to interpret the learned time dependent connectivity patterns. The large inter-subject variability among different subjects makes the interpretation more difficult when compared with the task-related fMRI brain connectivity patterns. The disease related changes of the underlying time-varying patterns in brain connectivity might be potential biomarkers and deserve further investigation in the future studies.

5. REFERENCES

[1] Xiao Liu and Jeff H Duyn, "Time-varying functional network information extracted from brief instances of spontaneous brain activity," *Proceedings of the National*

Academy of Sciences, vol. 110, no. 11, pp. 4392–4397, 2013.

[2] R. Matthew Hutchison, Thilo Womelsdorf, Elena A. Allen, Peter A. Bandettini, Vince D. Calhoun, Maurizio Corbetta, Stefania Della Penna, Jeff H. Duyn, Gary H. Glover, Javier Gonzalez-Castillo, Daniel A. Handwerker, Shella Keilholz, Vesa Kiviniemi, David A. Leopold, Francesco de Pasquale, Olaf Sporns, Martin Walter, and Catie Chang, "Dynamic functional connectivity: Promise, issues, and interpretations," *NeuroImage*, vol. 80, no. 0, pp. 360 – 378, 2013.

[3] R Matthew Hutchison, Thilo Womelsdorf, Joseph S Gati, Stefan Everling, and Ravi S Menon, "Resting-state networks show dynamic functional connectivity in awake humans and anesthetized macaques," *Human brain mapping*, 2012.

[4] Nora Leonardi, Jonas Richiardi, Markus Gschwind, Samanta Simioni, Jean-Marie Annoni, Myriam Schluep, Patrik Vuilleumier, and Dimitri Van De Ville, "Principal components of functional connectivity: A new approach to study dynamic brain connectivity during rest," *NeuroImage*, vol. 83, no. 0, pp. 937 – 950, 2013.

[5] Elena A Allen, Eswar Damaraju, Sergey M Plis, Erik B Erhardt, Tom Eichele, and Vince D Calhoun, "Tracking whole-brain connectivity dynamics in the resting state," *Cerebral Cortex*, 2012.

[6] Unal Sakoglu, Godfrey D Pearlson, Kent A Kiehl, Y Michelle Wang, Andrew M Michael, and Vince D Calhoun, "A method for evaluating dynamic functional network connectivity and task-modulation: application to schizophrenia," *Magnetic Resonance Materials in Physics, Biology and Medicine*, vol. 23, no. 5-6, pp. 351–366, 2010.

[7] Catie Chang and Gary H Glover, "Time–frequency dynamics of resting-state brain connectivity measured with fmri," *Neuroimage*, vol. 50, no. 1, pp. 81–98, 2010.

[8] Joao Ricardo Sato, Edson Amaro Junior, Daniel Yasumasa Takahashi, Marcelo de Maria Felix, Michael John Brammer, and Pedro Alberto Morettin, "A method to produce evolving functional connectivity maps during the course of an fmri experiment using wavelet-based time-varying granger causality," *Neuroimage*, vol. 31, no. 1, pp. 187–196, 2006.

[9] Enzo Tagliazucchi, Pablo Balenzuela, Daniel Fraiman, and Dante R Chialvo, "Criticality in large-scale brain fmri dynamics unveiled by a novel point process analysis.," *Frontiers in Physiology*, vol. 3, no. 15, 2012.

[10] Mingzhou Ding and Jianfeng Feng, "Spatio-temporal granger causality: A new framework," *NeuroImage*, vol. 79, pp. 241–263, 2013.

[11] Ivor Cribben, Ragnheidur Haraldsdottir, Lauren Y. Atlas, Tor D. Wager, and Martin A. Lindquist, "Dynamic connectivity regression: Determining state-related changes in brain connectivity," *NeuroImage*, vol. 61, no. 4, pp. 907 – 920, 2012.

[12] Le Song, Mladen Kolar, and Eric P Xing, "Time-varying dynamic bayesian networks," *Advances in Neural Information Processing Systems*, vol. 22, pp. 1732–1740, 2009.

[13] Mladen Kolar, Le Song, and Eric P Xing, "Sparsistent learning of varying-coefficient models with structural changes," in *Advances in Neural Information Processing Systems*, 2009, pp. 1006–1014.

[14] Zhaowen Wang, E.E. Kuruoglu, Xiaokang Yang, Yi Xu, and T.S. Huang, "Time varying dynamic bayesian network for nonstationary events modeling and online inference," *Signal Processing, IEEE Transactions on*, vol. 59, no. 4, pp. 1553–1568, 2011.

[15] AR McIntosh, CL Grady, LG Ungerleider, JV Haxby, SI Rapoport, and B Horwitz, "Network analysis of cortical visual pathways mapped with pet," *The Journal of Neuroscience*, vol. 14, no. 2, pp. 655–666, 1994.

[16] Pedro A Valdes-Sosa, Jose M Sanchez-Bornot, Agustin Lage-Castellanos, Mayrim Vega-Hernandez, Jorge Bosch-Bayard, Lester Melie-Garcia, and Erick Canales-Rodriguez, "Estimating brain functional connectivity with sparse multivariate autoregression," *Philosophical Transactions of the Royal Society B: Biological Sciences*, vol. 360, no. 1457, pp. 969–981, 2005.

[17] Xiaohui Chen, Z.Jane Wang, and Martin J. McKeown, "Fmri group studies of brain connectivity via a group robust lasso," in *Proceedings of 2010 IEEE 17th International Conference on Image Processing*, 2010.

[18] Michael Grant, Stephen Boyd, and Yinyu Ye, "Cvx: Matlab software for disciplined convex programming," 2008.