FREQUENCY-SPECIFIC NON-LINEAR GRANGER CAUSALITY IN A NETWORK OF BRAIN SIGNALS

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ABSTRACT

We propose a novel algorithm to extract frequency-band specific and non-linear Granger causality (Spectral NLGC) connections between components of a multivariate time series. The advantage of our model over traditionally used VAR based models, as demonstrated in simulations, is the ability to capture complex dependence structures in a network. In addition to the simulations, the proposed method uncovered non-linear dynamics in an epileptic seizure EEG data. Spectral NLGC gives new meaningful insights into frequency specific connectivity changes at the onset of epileptic seizure. Results of both simulated and brain signals confirm the viability of the proposed algorithm as a good tool for exploration of directed connectivity in a network.

Index Terms— Electroencephalograms, Directed connectivity, Multi-layer perceptrons, Networks, Spectral dependence.

1. INTRODUCTION

There is a keen interest to investigate the intricate interdependence of neuronal activity between brain regions in a network. Methods are being developed to characterize and estimate connectivity because network activity is key to understanding perception, cognition, behaviour. Moreover, brain connectivity appears to be promising as a feature for discrimination and classification (e.g., healthy vs ADHD patients) [1]. There are broadly two categories of brain connectivity measures: functional and effective connectivity. Effective connectivity aims to quantify the influence one channel has on other channels. Model-based measures used in current studies assume linear directed connections between the channels. One limitation of these methods is that they may misrepresent non-linear relationships and hence produce inconsistent and misleading estimates of the underlying connectivity network.

Granger causality (GC) is a powerful measure that is being used to analyze effective connectivity in multichannel brain signals. It quantifies the extent to which the past activity from one channel helps to improve prediction of the present activity at another channel [2]. In neuroscience, GC has been widely investigated under the context of a vector autoregressive (VAR) model [3, 4, 5] which assume that the underlying connectivity is linear. In some studies, GC analysis is implemented using kernel functions that can model non-linear relationships [6]. However, for kernel-based methods, the kernel function has to be manually selected and the set of kernel functions might not necessarily be suitable to represent the specific non-linear relationships in the data.

Here, we propose a novel frequency-specific non-linear Granger Causal(Spec NLGC) connectivity estimation algorithm. We utilize auto-regressive Multi-Layer Perceptron(MLP) for modelling complex non-linear relations as they have shown impressive forecasting performance in the past [7]. Due to black box nature of neural networks, there is a lack of interpretability of the causal relationship between different channels. To take advantage of the non-linear modelling capability of MLP and ensure the interpretability of the network output to infer Granger causal networks, we utilize component-wise MLPs(cMLPs) as described by Tank et al[8]. Traditional MLPs uses a single network with as many outputs as number of channels to model the whole time-series data. In contrast, component-wise MLPs described in [8], utilizes one independent MLP per channel, each with single output. It is shown that use of cMLP with group-lasso penalty gives superior Granger causal connectivity estimates. However, one limitation of MLPs is that they do not identify the specific underlying oscillatory activity that drives the non-linear Granger causality between channels which is important for many biological signal analysis. To overcome this major limitation, we propose Spec NLGC algorithm. We shall demonstrate in the simulations and EEG analysis that this algorithm has the ability to capture non-linear relationship between channels and – more importantly – also identify driving the oscillatory activity. We use non-linear mixtures of AR(2) processes to simulate the possible non-linear connections in EEG data and use it to evaluate the performance of our algorithm.

The remainder of this paper is organized as follows: Section 2 discusses the architectures of cMLP used for NLGC and Spec NLGC. In Section 3, performance of the method is evaluated on synthetically generated non-linear data benchmarking it against traditional VAR-LASSLE method [9] and VAR based PDC methods [5]. Moreover, GC connectivity analysis was on conducted on an epileptic seizure EEG data which was previously analyzed in [10, 11]. In Section 4, we conclude with some discussions on future research scopes.

2. METHODS

2.1. Component-wise MLP model and Regularization

Most biological signals (e.g., brain signals) are non-linear and non-stationary. A generalization of the classical VAR(K) [9] model would be to model the current values $X(t)$ using past values $X_1(t'), X_2(t'), ..., X_N(t')$ using some non-linear function $g(.)$ such that:

$$X(t) = g(X_1(t'), X_2(t'), ..., X_N(t')) + \epsilon(t)$$

where $t' < t$. To capture potential non-linearity in the dependence structure of the time series, $g(.)$ will be modeled using neural networks. To ensure interpretability of the inferred directed GC connections, we will use individual neural networks for each of the channels. The model for the i-th time-series uses a different and independent neural network as follows:

$$X_i(t) = g_i(X_1(t'), X_2(t'), ..., X_N(t')) + \epsilon_i(t)$$

A sufficient condition of X_j to not Granger-cause X_i will be $g_i(.)$ to be independent of $X_j(t')$ (we write, $X_j \not\to X_i$). The above can be easily inferred once the trained weights for each network g_i is known.

The architecture of the component-wise Multi-Layer Perceptrons (cMLPs)[12] used to model non-linear function $g_i(.)$ is shown in figure 1. We implement cMLPs of single hidden layer $h^1(t) \in \mathbb{R}^H$ with H neurons. Denote the weights and bias terms to be W^1, W^2 and b^1, b^2 respectively. Then, decomposing the weights of the first layer we write, $W^1 = \{W^{11}, W^{12}, ..., W^{1K}\}$, where K is the model lag. Equations for the cMLPs are as follows:

$$Hidden\ layer:\ h^1(t) = \sigma\left[\sum_{n=1}^{K} W^{1n} X(t-n) + b^1\right]$$

$$Output\ layer:\ X_i(t) = W^2 h^1(t) + b^2$$

The non-linear activation function $\sigma(.)$ used here is a sigmoid function. From the equation for the hidden layer, we observe that the j-th series and its past values will not affect the i-th series if j-th row of W^{1n} matrix is zero $\forall n \in \{1, 2, ..., K\}$. This would imply **no GC connection** from X_j to X_i. Here, the hierarchical penalty was utilized to induce sparsity [13] so to "preserve" the lower lag terms. The use of hierarchical penalty gives connectivity estimates that are insensitive to the choice of large model lag K [8]. The final optimization equation becomes:

$$\min_{W^1, W^2, b^1, b^2} \sum_{t=n}^{T} \left[X_i(t) - g_i(X(t-1), \ldots, X(t-K))\right]^2 + \lambda \sum_{j=1}^{p} \sum_{n=1}^{K} \|(W^{1n}_{:j}, \ldots, W^{1K}_{:j})\|_2$$

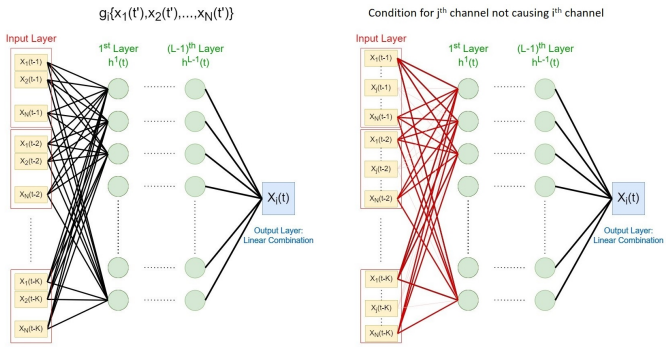


Fig. 1. Left figure shows the cMLP Network Architectures as proposed in [8]. Right figure depicts the cMLP with trained weights such that j^{th} channel is not causing i^{th} channel

2.2. Non-Stationarity and Frequency Band Specific GC

Previous studies have found out existence of frequency band specific connections in time series data acquired from EEG, LFP, fMRI [14, 15]. To investigate frequency band specific connections, the observed signals are filtered into traditionally used frequency bands in EEG data analysis which are delta(0.5-4.0 Hz), theta(4.0-8.0 Hz), alpha(8.0-12.0 Hz), beta(12.0-30.0 Hz), gamma(30.0-50.0 Hz). The Butterworth filter of order 3 for filtering as described in [16]. As a result, there will be a total of 5 set of time-series, with N channels. We will find the GC connections for each of these 5 filtered data after normalizing data of each band, which will give us the estimates regarding frequency specific connectivity in the signals. This gives us our overall spectral non-linear GC(Spec NLGC) method. Our simulation results demonstrate that the proposed method is able to accurately estimate frequency specific connection without increasing the computation load any further.

Non-stationary behaviour in EEGs occurs during the onset of an epileptic seizure [17]. We have taken a overlapping time-windowed approach as used in [18] while dealing with actual EEG data. The number of time-points in the window was chosen carefully, as less number of time points would lead to poor training of the neural networks, on the other hand high number of time points in each interval would make our assumption of interval-wise stationarity invalid. As we normalized our data before feeding into cMLPs, the optimal choice of network hyper-parameters is insensitive to change in amplitude or power of time series which generally arises in case of non-stationarity.

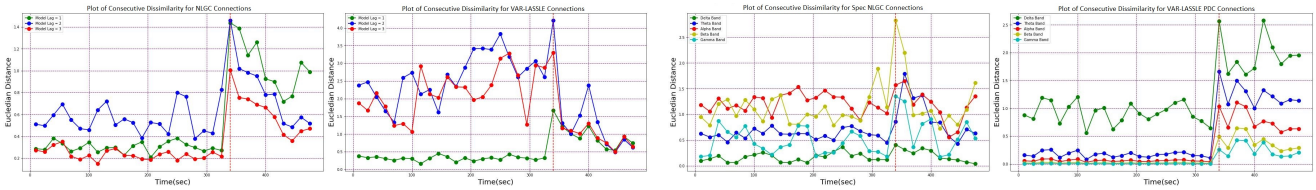
3. EXPERIMENTS

3.1. Performance Evaluation using Simulations

The performance of Spec NLGC method is evaluated on synthetic data generated using non-linear mixtures of AR(2) pro-

Method	2 dB	5 dB	10 dB	15 dB	20 dB
VAR-LASSLE(1)	0.42 ±0.01	0.42±0.02	0.41±0.01	0.41±0.01	0.41±0.01
NLGC(1)	0.62 ±0.03	0.72±0.05	0.84±0.02	0.82±0.02	0.8 ±0.03
PDC(1)	0.26 ±0.03	0.23±0.00	0.25±0.03	0.23 ±0	0.24 ±0
Spec NLGC(1)	0.79 ±0.02	0.82±0.01	0.9 ±0.01	0.91±0.02	0.81±0.02
VAR-LASSLE(2)	0.41 ±0.03	0.41±0.02	0.41±0.01	0.42±0.03	0.44±0.02
NLGC(2)	0.45 ±0.03	0.45±0.06	0.71±0.05	0.87±0.02	0.9 ±0.05
PDC(2)	0.32 ±0.03	0.26±0.05	0.24±0.06	0.14±0.03	0.11 ±0
Spec NLGC(2)	0.63±0.035	0.68±0.07	0.8 ±0.02	0.9 ±0.03	0.92±0.03
VAR-LASSLE(3)	0.4 ±0.02	0.4 ±0.03	0.44±0.02	0.43±0.02	0.43±0.02
NLGC(3)	0.36 ±0.06	0.42±0.03	0.75±0.04	0.88±0.03	0.93±0.00
PDC(3)	0.26 ±0.05	0.27±0.05	0.29±0.03	0.17±0.04	0.28±0.10
Spec NLGC(3)	0.65 ±0.07	0.74±0.06	0.91±0.03	0.98±0.01	0.99±0.00

Table 1. AUPR Values for Evaluation of Spec NLGC Using Synthetic Data



(a) Comparison between NLGC and VAR-LASSLE

(b) Comparison between Spec NLGC and PDC

Fig. 2. Plots of Consecutive Dissimilarity of GC Connections

cesses. AR(2) processes are particularly used as they resemble brain time series data and are often used for the modelling of EEG data [16]. We have carried out our analysis for different SNR values: {2 dB,5 dB,10 dB,15 dB,20 dB} using AWGN. The noise analysis of NLGC methods have not been performed in previous studies and is very crucial while evaluating algorithms for EEGs. For all the simulation experiments that follows, the number of hidden neurons is chosen to be 100. The performance is measured for detection capability of Granger causal connectivity on the synthetic data using AUPR scores[19]. Model lags of 1,2,3 were chosen in our experiments. Proximal gradient descent with a line search is used for training the cMLP networks. Contrary to the method used for evaluation in [8], the AUPR values are calculated without taking into consideration the diagonal entries. Simulations for 5 random realizations of synthetic data is done and mean and median absolute deviation(MAD) for AUPR in each case is tabulated in table 1, with method name, model lag used and SNR values.

3.1.1. Overall Non-Linear GC Connectivity

NLGC is applied on synthetically generated data without any filtering to check the performance of the method under additive noise of different power. We used an $N = 10$ channel non-linear data, with two set of AR(2) latent sources. To induce non-linearity, we will use $\tau(x) = -2 + 0.556x^2$ as transfer function. We pass a lagged version of latent signal through the $\tau(x)$ and then add it to channel it is supposed to cause. The total number of true connectivity values is chosen to be 18, out of possible 90 non-diagonal connections.

3.1.2. Frequency Specific NLGC Connectivity

Spec NLGC is applied on synthetically generated data with frequency specific connections. Non-linear connections is induced such that the spectrum of the individual time series does not deviate much from the original linear one. This ensures that the ground truth frequency specific connectivity is preserved. Specifically, we have used the transfer function:

$$\tau(x) = \begin{cases} a(\frac{x}{a})^d, & \text{if } |x| \leq a \\ x, & \text{if } |x| > a \end{cases}$$

We have chosen a = 1.5 and d = 3. The function $\tau(x)$ here can be though as inducing a non-linearity in which results in a channel causing the other if it's amplitude is more than a particular threshold a at a particular time. Similar to previous case, we generated a 5 channel time series data such that the X_2 causes X_1 in theta band, and causes channel X_3,X_4 in beta band. And, the channel X_5 causes X_1,X_4 in gamma band, and causes X_3 in alpha band. We have 6 actual connections out of total 100 possible connections(25 for each band). From the simulation results, we can observe that the GC connections are estimated very close to the ground truth values.

From the results in table 1, we observe the non-linear methods perform much better than traditional VAR-LASSLE and PDC methods. AUPR scores increase on taking higher model lags for non-linear methods. The classification is almost random for traditional methods as the ground truth connections are non-linear. We have reported AUPR scores as

the ground truth has low number of true connections, but AUROC scores also shows similar performance improvement in case of non-linear methods.

3.2. Analysis of seizure EEG data

We apply our non-linear Granger causality methods to an 18-channel EEG data recorded during an epileptic seizure. Each channel has total of 50000 time points, recorded at a sample rate of 100 Hz. According to the attending neurologist, the ictal activity begins around the 340 seconds mark(i.e., at 34,000 time point). Previous studies have confirmed that the strength and pattern of directed connectivity in the brain fluctuates during epilepsy [20]. To the best of our knowledge, past studies involving frequency specific non-linear directed connections has not been performed on this EEG data. In the next two subsections, we apply proposed methods to detect changes in time-evolving connectivity in the 18 channels of the data and compare it with results of traditional methods. We used a time-windowed approach considering the quasi-static nature of EEG signals using a 50% overlap and 2000 time samples in each window. There will be overlap of 500 time-points on each side, leading to a total of 33 GC connectivity matrices. cMLPs hyper-parameters are not changed throughout different time windows. The change in connectivity pattern is measured in terms of Euclidean distance(ED) between consecutive NLGC matrices as a dissimilarity measure. It captures the changes in the NLGC connectivity patterns or strengths.

$$ED(t) = \sqrt{\sum_{all\ i,j} \mid [GC(t)]_{i,j} - [GC(t-1)]_{i,j} \mid^2}$$

3.2.1. *Overall connections on EEG data*

We estimated time evolving directed connectivity with NLGC for model lags K = 1,2,3. Consecutive dissimilarities between time evolving GC matrices using the estimated time evolving GC connections is shown in figure 2(a). We can see that during the onset of epilepsy(marked by the red dotted line), there is a sudden jump in consecutive dissimilarity and the dissimilarity remains high during the epilepsy region. This observation suggests that our NLGC algorithm is able to infer the sudden changes in brain connectivity that occurs during onset of epileptic seizure. For VAR based GC method, the result obtained is not much useful in detecting the onset point of the epilepsy. There is no appreciable sudden rise in the dissimilarity measures when the epilepsy begins for model lag of 2 and 3. This is in contrast to what we saw in the case of NLGC based connections where all model lags results gave insightful information. The estimated NLGC connections is visualized using the eConnectome[21] toolbox in figure 3.

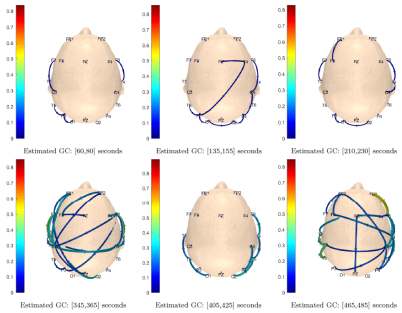


Fig. 3. Propagation of NLGC connections from left to right hemisphere during seizure

3.2.2. *Frequency specific connections on EEG data*

We estimated the frequency band specific connectivity in the EEG data using Spec NLGC. A total of 5 time evolving GC connectivity matrix is estimated using the cMLP networks for model lag = 1. The time evolving dissimilarity for each of the band as shown in figure 2(b). We can observe a sudden increase in the dissimilarity during the onset of epilepsy occurs mostly in the theta, beta and gamma bands. Thus, we observe that for different frequency bands the change in directed connectivity networks is different. Past studies [22] have reported the phenomena of increase in high frequency oscillations during epilepsy. Thus, it might be possible that Spec NLGC is able to infer the rapid fluctuations of non-linear GC connections that are present at high frequencies for the given data. In the plot of consecutive PDC dissimilarity for each of the frequency bands, sudden change in frequency specific connectivity is more appreciable for lower frequency bands. This is an inconsistent result with regards to past neuroscience studies. Thus, our new Spec NLGC method is giving more meaningful results as the connectivity changes were more prominent in the on the high frequency bands.

4. CONCLUSIONS

We have introduced and evaluated performance of a frequency band specific non-linear Granger causality framework combining Butterworth filters and component-wise MLP networks with hierarchical penalty. Simulation results on non-linear data shows the huge improvement on use of proposed methods over traditional methods. Implementation on epileptic EEG data provides novel findings about time evolving connectivity pattern between different EEG channels. Frequency band specific connectivity gave insight into which bands have more connectivity changes during the onset of an epileptic seizure. Our proposed Spec NLGC is a promising new tool in directed connectivity analysis of multi-channel time series. Integration of Spec NLGC with sophisticated approaches to deal with non-stationarity can be explored in future studies.

5. REFERENCES

[1] Chun-Ren Phang, Chee-Ming Ting, S. Balqis Samdin, and Hernando Ombao, "Classification of EEG-based effective brain connectivity in schizophrenia using deep neural networks," in *2019 9th International IEEE/EMBS Conference on Neural Engineering (NER)*. Mar. 2019, IEEE.

[2] C. W. J. Granger, "Investigating causal relations by econometric models and cross-spectral methods," *Econometrica*, vol. 37, no. 3, pp. 424, Aug. 1969.

[3] Maciej Kamiński, Mingzhou Ding, Wilson A. Truccolo, and Steven L. Bressler, "Evaluating causal relations in neural systems: Granger causality, directed transfer function and statistical assessment of significance," *Biological Cybernetics*, vol. 85, no. 2, pp. 145–157, Aug. 2001.

[4] L Harrison, W.D Penny, and K Friston, "Multivariate autoregressive modeling of fMRI time series," *NeuroImage*, vol. 19, no. 4, pp. 1477–1491, Aug. 2003.

[5] Luiz A. Baccalá and Koichi Sameshima, "Partial directed coherence: a new concept in neural structure determination," *Biological Cybernetics*, vol. 84, no. 6, pp. 463–474, May 2001.

[6] Xiaohai Sun, "Assessing nonlinear granger causality from multivariate time series," in *Machine Learning and Knowledge Discovery in Databases*, pp. 440–455. Springer Berlin Heidelberg, 2008.

[7] Maziar Raissi, Paris Perdikaris, and George Em Karniadakis, "Multistep neural networks for data-driven discovery of nonlinear dynamical systems," 2018.

[8] Alex Tank, Ian Covert, Nicholas Foti, Ali Shojaie, and Emily B Fox, "Neural granger causality," *IEEE Transactions on Pattern Analysis and Machine Intelligence*, pp. 1–1, 2021.

[9] Lechuan Hu, Norbert J. Fortin, and Hernando Ombao, "Modeling high-dimensional multichannel brain signals," *Statistics in Biosciences*, vol. 11, no. 1, pp. 91–126, Dec. 2017.

[10] Hernando Ombao, Jonathan Raz, Rainer von Sachs, and Wensheng Guo, ," *Annals of the Institute of Statistical Mathematics*, vol. 54, no. 1, pp. 171–200, 2002.

[11] Hernando Ombao, Rainer von Sachs, and Wensheng Guo, "SLEX analysis of multivariate nonstationary time series," *Journal of the American Statistical Association*, vol. 100, no. 470, pp. 519–531, June 2005.

[12] Hassan Ismail Fawaz, Germain Forestier, Jonathan Weber, Lhassane Idoumghar, and Pierre-Alain Muller, "Deep learning for time series classification: a review," *Data Mining and Knowledge Discovery*, vol. 33, no. 4, pp. 917–963, Mar. 2019.

[13] Cristina Gorrostieta, Mark Fiecas, Hernando Ombao, Erin Burke, and Steven Cramer, "Hierarchical vector auto-regressive models and their applications to multi-subject effective connectivity," *Frontiers in Computational Neuroscience*, vol. 7, 2013.

[14] Felix Siebenhühner, Shennan A. Weiss, Richard Coppola, Daniel R. Weinberger, and Danielle S. Bassett, "Intra- and inter-frequency brain network structure in health and schizophrenia," *PLoS ONE*, vol. 8, no. 8, pp. e72351, Aug. 2013.

[15] Changwei W. Wu, Hong Gu, Hanbing Lu, Elliot A. Stein, Jyh-Horng Chen, and Yihong Yang, "Frequency specificity of functional connectivity in brain networks," *NeuroImage*, vol. 42, no. 3, pp. 1047–1055, Sept. 2008.

[16] Hernando Ombao and Marco Pinto, "Spectral dependence," 2021.

[17] P. Indic, R. Pratap, V. P. N. Nampoori, and N. Pradhan, "Significance of time scales in nonlinear dynamical analysis of electroencephalogram signals," *International Journal of Neuroscience*, vol. 99, no. 1-4, pp. 181–194, Jan. 1999.

[18] Gaelle Bettus, Fabrice Wendling, Maxime Guye, Luc Valton, Jean Régis, Patrick Chauvel, and Fabrice Bartolomei, "Enhanced EEG functional connectivity in mesial temporal lobe epilepsy," *Epilepsy Research*, vol. 81, no. 1, pp. 58–68, Sept. 2008.

[19] Dan Hendrycks and Kevin Gimpel, "A baseline for detecting misclassified and out-of-distribution examples in neural networks," 2018.

[20] S. Balqis Samdin, Chee-Ming Ting, Hernando Ombao, and Sh-Hussain Salleh, "A unified estimation framework for state-related changes in effective brain connectivity," *IEEE Transactions on Biomedical Engineering*, vol. 64, no. 4, pp. 844–858, Apr. 2017.

[21] Bin He, Yakang Dai, Laura Astolfi, Fabio Babiloni, Han Yuan, and Lin Yang, "eConnectome: A MATLAB toolbox for mapping and imaging of brain functional connectivity," *Journal of Neuroscience Methods*, vol. 195, no. 2, pp. 261–269, Feb. 2011.

[22] G. A. Worrell, L. Parish, S. D. Cranstoun, R. Jonas, G. Baltuch, and B. Litt, "High-frequency oscillations and seizure generation in neocortical epilepsy," *Brain*, vol. 127, no. 7, pp. 1496–1506, May 2004.