PREDICTION OF MULTIFOCAL EPILEPTOGENIC ZONES USING NORMALIZED TRANSFER ENTROPY

P. Kale[1], T. Gilmour[2], V. J. Acharya[3], J. Acharya[3], T. Subramanian[3,4], M. Almekkawy[1]
[1]School of Electrical Engineering and Computer Science, Penn State University, University Park, PA
[2] Department of Electrical Engineering, John Brown University, Siloam Springs, AR
[3]Department of Neurology and [4]Neural and Behavioral Sciences, Penn State, College of Medicine, Hershey, PA
pxk51@psu.edu, tgilmour@jbu.edu, [vacharya, jacharya]@pennstatehealth.psu.edu, [tus16, mka9]@psu.edu

Abstract— Stereo-EEG with multiple intra-cerebral depth electrodes is a pre-surgical tool for monitoring and analyzing the electrophysiological signals from the brain. The standard method of evaluating these signals by visually identifying the changes in the EEG signal is being slowly replaced by the transfer entropy that accurately accounts for non-linearity and incorporates dynamic interactions between the systems. Partial epilepsy can arise from a single focus or have multifocal onset. Knowing the number of epileptic foci and their location is essential to guide the choice of treatments recommended to the patient. Epilepsy that initially appears to be unifocal, based on simple visual analysis, may turn out to be multifocal on more detailed evaluation. In this paper, we computed the directional information transfer for all possible pairs of the 80 signals that were collected from the brain of an epileptic patient. We have localized the epileptogenic zones (EZs) and identified multiple seizure focal points in the patient from the plots obtained. Understanding such multifocal onset patients and avoiding focused surgical resections in such patients may be important to avoid surgical failures and morbidity.

1. INTRODUCTION

Epilepsy is characterized by an onset of unpredictable seizures. It is the fourth most common neurological disorder that affects people of all ages. For up to 70% of the cases, Anti-epileptic drugs (AEDs) aid in controlling the seizures [1] and surgery is often recommended for the drug-resistant cases. Drug-resistant epilepsies are mostly partial in nature. This implies that most of the seizing activity is concentrated in focal regions identified as the epileptogenic zones (EZs) [2]. Difficulty arises in locating these zones and pinpointing the areas of the brain that is to be cut out to regain regular functionality in a patient. The pre-surgical analysis of the intra-cerebral Electroencephalographic (iEEG) signals helps isolate regions of interest [3] [4]. Depth electrodes capture these electrical activities of the brain. The interactive relationships between these signals help determine the EZs prior to surgery. In which case, the signal processing techniques facilitate in quantifying the information which cannot be otherwise obtained from an image.

Over the past decade, there has been an increase in research in the field of neural assemblies and finding novel techniques to compute information transfer between neurons. Transfer entropy is one of the most frequently used measures [4] [6]. Thus far, the linear measures such as correlation, coherence and directed transfer function accounted for functional connectivity between disparate brain regions. These functions generally provide a degree of similarity between the signals but they fail to accommodate the higher order moments. Other measures such as mutual information account for higher order moments but fail to provide any directionality information [8]. The transfer entropy technique introduces the concept of directional information transfer between two signals in a probabilistic approach. It does not impose any constraints on the model or characteristics of the signals. Thus it is an effective tool for nonlinear computations of complex circuits [5], [9]. It incorporates the dynamics of all individual subsystems involved and quantifies their interactions [9]. Methods to improve the transfer entropy to increase accuracy and robustness have been proposed in [3] and [4] which automatically localized the EZs. Previous work in this area involved collecting EEG signals from the surface of the brain [3], we believe that to obtain accurate results for the location of focal points we should be looking closely at how the signals propagate within the brain rather than observing the surface activity. Some work also involved using depth electrodes to capture the activities of the brain [5], [6], but these signals were collected from brains of guinea pigs and anesthetized cats, respectively with small observation time. These experiments however gave an insight into the relationships between points on the auditory cortex of a cat, showing promising results of applying transfer entropy on neural network analysis [6]. In addition, TE established nonlinear information transfer between cortex and basal ganglia for Parkinson's disease [7]. The present application shows NTE analysis for the data collected from a patient with epilepsy using depth electrodes placed strategically in the brain to observe seizures.

In general, for patients with drug-resistant epilepsy and a single epileptic focus, we can offer traditional surgery (resection/laser ablation) after detailed pre-surgical evaluation that may or may not include invasive monitoring with intra-cerebral depth or subdural electrodes. For patients with multifocal epilepsy, surgical resection is generally not performed, but we can offer neuro-stimulation devices-responsive neuro-stimulation (RNS) if there are two distinct foci or Vagus nerve stimulation if there are more than two foci or the foci are not well identified. Knowing the number of foci and their location is therefore essential to guide the choice of treatment. For this experiment, we select a patient who is

resistant to the AEDs and who is monitored under invasive video-EEG. The electrodes inserted into his brain during monitoring capture the signals of the brain in real time. The pre-surgical analysis of these signals provides the surgeons with an idea of the origin of these seizures. Our experiment led us to believe that the seizing activities occur deep within the brain from where the information disperses in multiple directions. This also paved way to assume that epilepsy is multifocal in onset.

2. Materials and Methods

2.1 Transfer Entropy

Let x and y be two simultaneously measured stationary spike trains. Transfer entropy computes the deviation of the system from the assumption of the generalized Markov's property, i.e.

$$p\left(x_{t+1}\middle|x_t^k\right) = p(x_{t+1}|x_t^k, y_t^l)$$

where $x_t^k = (x_t, x_{t-1}, x_{t-2}, \dots, x_{t-k+1})^T$ and $y_t^l = (y_t, y_{t-1}, y_{t-2}, \dots, y_{t-l+1})^T$ are the state vectors at time t of dimension k and l, respectively.

Transfer entropy measures the amount of mutual information transfer from x to y. It is derived using the Kullback-Leibler divergence:

$$TE_{y\to x} = \sum p(x_{t+1}, x_t^k, y_t^l) log \frac{p(x_{t+1}|x_t^k, y_t^l)}{p(x_{t+1}|x_t^k)}$$

$$= \sum p(x_{t+1}, x_t^k, y_t^l) log \frac{p(x_{t+1}, x_t^k, y_t^l)p(x_t^k)}{p(x_{t+1}, x_t^k)p(x_{t+1}, x_t^k)}$$

This quantity represents the amount of predictability of the future values of x by having prior knowledge of the past values of x given past values of y.

For computational simplicity of transfer entropy we assume $k = l = 1$. To estimate the probability density functions (PDFs), normalized histograms with 10 bins spanning the dynamic range of the signal were used. We chose 10 bins heuristically given the typical length of our data recordings to allow a good trade-off between PDF resolution and sufficiently large bin count. Sometimes the spike trains collected do not represent their true distribution. To remove this kind of bias, we subtract the mean of estimates of the transfer entropy in randomly time-shuffled versions of the same data.

2.2 Normalization

We define the normalized transfer function (NTE) by

$$NTE_{y\to x} = \frac{TE_{y\to x} - TE_{y\to x}^{shuffled}}{H(x_{t+1}|x_t^k)} \in [0,1]$$

The NTE represents the fraction of information in x not explained by its own past which is explained by the past of y. We also compute the NTE at different time shifts between the two signals, comparable to 250ms before and after the zero-delay point, with 5ms increments. This estimated the unidirectional transfer entropy at different time lags. Since it is based on conditional probability, transfer entropy between two perfectly correlated signals will be zero. Thus it is necessary to time shift signals slightly before and after the zero-delay.

2.3 Experiment

The patient had non-lesion temporal lobe epilepsy with bi-temporal independent interictal spikes. Despite surgery, the patient had symptoms of epilepsy. The stereo-EEG with 8 depth electrodes showed EEG onset in the right amygdala and hippocampus. However, on computing the NTE there was no peak observed between the amygdala or hippocampus and the neocortical electrode contacts on the right side. In contrast, there was clear NTE in two depth electrodes between the left amygdala and deep contacts in the posterior orbitofrontal cortex and the corresponding superficial contacts in the temporal and frontal cortices suggesting multifocal information transfer.

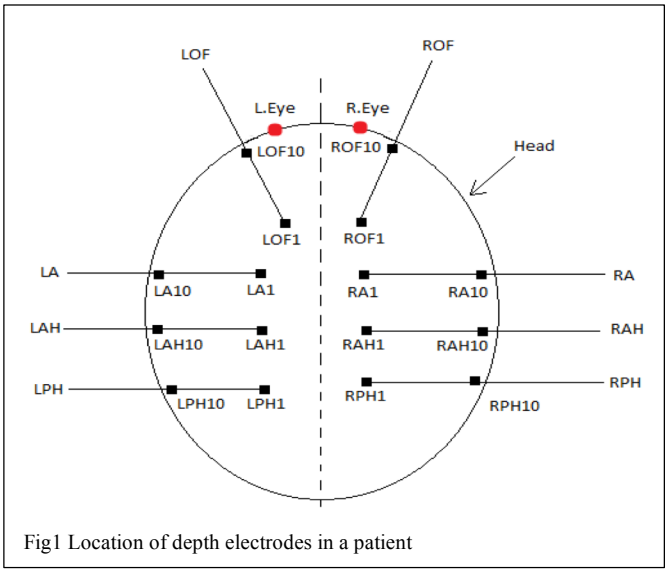


Fig1 Location of depth electrodes in a patient

Fig. 1 gives the position of electrodes in the brain of the patient. LA stands for left amygdala, LAH for left anterior hippocampus, LPH for left posterior hippocampus and LOF for left orbitofrontal positions. The same is true for the placement of electrodes on the right side of the brain. The number 1 represents the deepest point of the electrode that is in the deeper parts of the brain and number 10 represents the superficial electrode that is near the surface of the brain (cortex). The depth electrodes simultaneously capture the electrophysiological activities in the brain. The eight electrodes used to capture these activities in-turn have 10 points of contact. The spike trains captured at these points are converted into a form that can be easily processed by a computer. Each converted signal is then mapped to the location of its origin. Thus we obtain 40 signals on each hemisphere of the brain.

3. Results and Discussion

We calculate the NTE values for each pair of signals. These values are then carefully plotted on a grid to observe any patterns that would augment our understanding of the

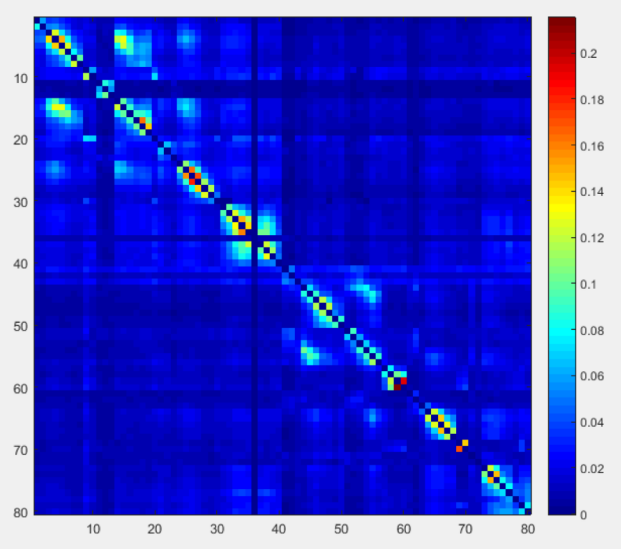
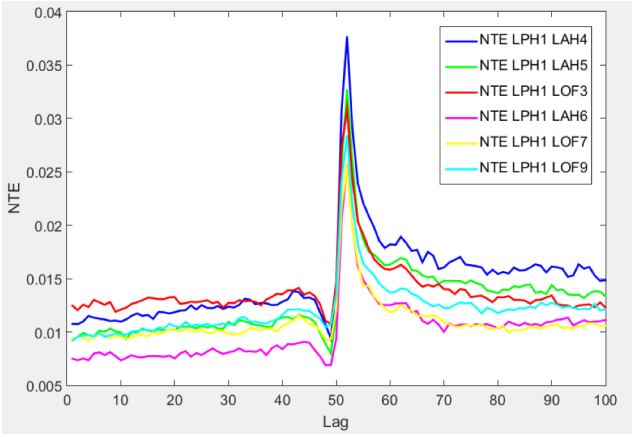


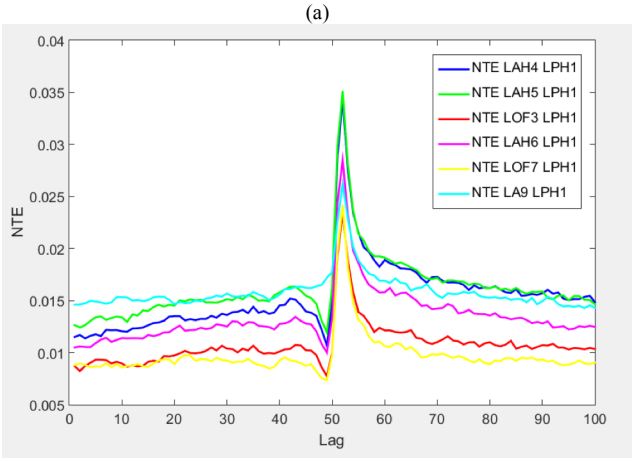
Fig2 Maximum NTE for each pair of signal. The signals on the left side are plotted on the first half of the x-axis followed by the signals on the right. For the y-axis, the top half represents the left side signals followed by the right side signal in the bottom.

neurological disorder. The matrix of data is constructed using the maximum value of NTE from each pair of signals. It is ordered such that the axes have the signals collected from the left hemisphere of the brain first followed by the signals collected from the right hemisphere of the brain. Points 1-10 are contacts of electrode LA, 11-20 of LAH, 21-30 of LPH, 31-40 of LOF, 41-50 of RA, 51-60 of RAH, 61-70 of RPH and 71-80 of ROF. All the interactions of the left hemisphere signals with other left hemisphere signals are observed in the top left corner, top right represents the interactions of the left hemisphere signals with the right hemisphere signals, bottom left represents interactions of the right hemisphere signals with the left hemisphere signals while the bottom right suggests interactions between a pair of right hemisphere signals. The values obtained are color coded. The points in the matrix that have the highest value of NTE are colored deep red as seen in Fig.2. These points indicate major activity in that particular point of contact in the electrode, identifying itself as an EZ. The value of NTE for the signal with itself is obviously expected to be high. Hence those points are all considered to be zero; this increases the readability of the plot.

We clearly observe higher levels of activity in the top left and bottom right quarters of the grid suggesting that there are interactions only within a particular hemisphere and that there are little or no interactions between the two hemispheres of the brain. We observe, in the top left quarter of the grid (Fig. 2), multiple dark spots suggesting simultaneous activity at different locations of the brain supporting our assumption of multifocal onset of epilepsy. Even in a particular hemisphere of the brain there are certain signals that interact strongly with neighboring points than others (Fig. 3, 4 and 5). To analyze this, the above grid is further broken down; from these smaller grids we isolate points that show maximum NTE in that grid region.



(a)

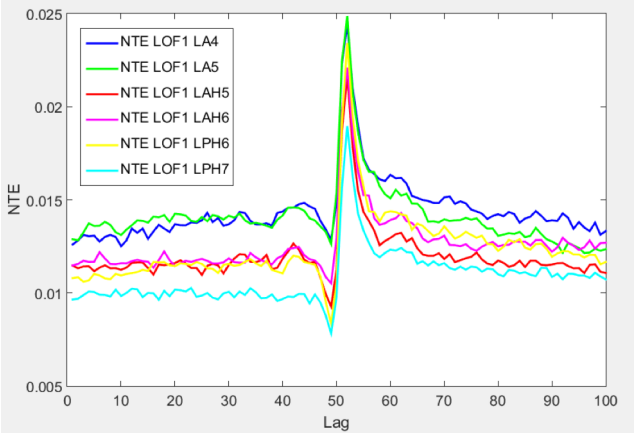


(b)

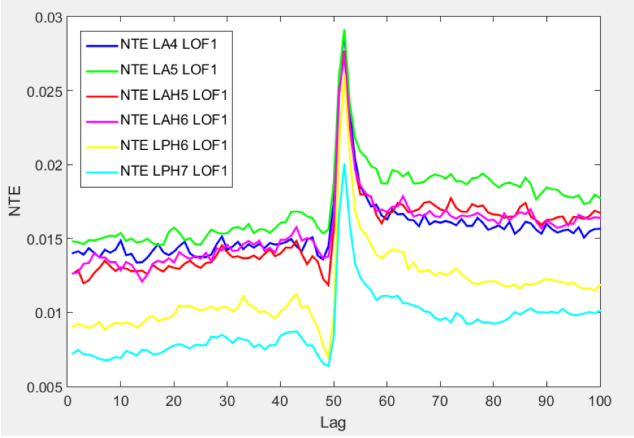
Fig3 Plots the maximum values of NTE computed from (a) the deepest point of the LPH electrode to the 79 remaining signals, (b) the 79 remaining signals to the deepest point of the LPH electrode.

In Fig. 3(a), we compute the NTE from LPH1 (the deepest point on the LPH electrode) with all the remaining signals collected from both sides of the brain. We picked the signals which interacts the most with LPH1, we also found that the inverse interacts for the pair of signals to be high as shown in Fig. 3(b). Similarly, Fig. 4(a) shows the plot for signals which interacts the most with LOF1 (the deepest point of the LOF electrode) and the inverse interactions are plotted in Fig. 4(b). Fig. 5(a) shows the signals which interacts the most with RA1 (the deepest point of the RA electrode) and the inverse interactions are shown in Fig. 5(b).

We observe that there is comparatively higher activity on the left hemisphere than on the right one. Comparing Fig. 3 and 4 with 5, we observe that despite the right hand signals having maximum NTE they do not peak at points that promise activity. This translates to continuous peaking in the spike train collected at that point, probably noise from artifact that may be present at the time of collecting the data.

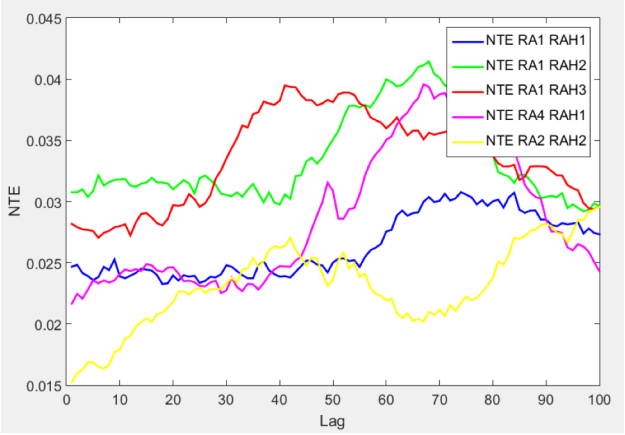


(a)

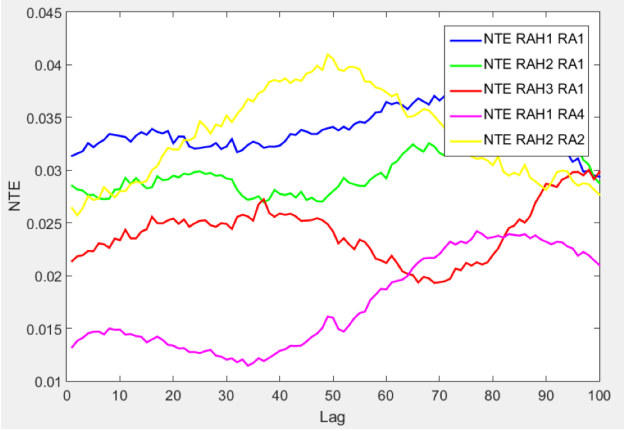


(b)

Fig4 Plots the maximum values of NTE computed from (a) the deepest point of the LOF electrode to the 79 remaining signals, (b) the 79 remaining signals to the deepest point of the LOF electrode.



(a)



(b)

Fig5 Plots the maximum values of NTE computed from (a) the deepest point of the RA electrode to the 79 remaining signals, (b) the 79 remaining signals to the deepest point of the RA electrode.

4. Conclusion

NTE can be used as a powerful tool in the measure of non-linearity between two points in the brain. In the present experiment, our algorithm computes NTE to identify the origin of the epileptogenic signals. The simultaneous appearance of red spots at multiple locations at a given time instant validates our assumption that epilepsy could have multifocal onset. The ease with which these pre-surgical computations can be performed effectively reduces the cost of expensive medical treatments or a surgery that could have been avoided. Additional studies from AED patients with focused epilepsy will be needed to confirm our findings in this patient.

5. References

[1] Engel Jr, J. V. N. P. (1993). Outcome with respect to epileptic seizures. *Surgical treatment of the epilepsies*, 609-621.

[2] Rosenow, F., & Lüders, H. (2001). Presurgical evaluation of epilepsy. *Brain*, *124*(9), 1683-1700.

[3] Lin, K., Wang, Y., Xu, K., Zhu, J., Zhang, J., & Zheng, X. (2016, August). Localizing seizure onset zone by convolutional transfer entropy from iEEG. In *Engineering in Medicine and Biology Society (EMBC), 2016 IEEE 38th Annual International Conference of the* (pp. 6335-6338). IEEE.

[4] Sabesan, S., Good, L. B., Tsakalis, K. S., Spanias, A., Treiman, D. M., & Iasemidis, L. D. (2009). Information flow and application to epileptogenic focus localization from intracranial EEG. *IEEE Transactions on neural systems and rehabilitation engineering*, *17*(3), 244-253.

[5] Yang, C., Jeannès, R. L. B., Bellanger, J. J., & Shu, H. (2013). A new strategy for model order identification and its application to transfer entropy for EEG signals analysis. *IEEE Transactions on Biomedical Engineering*, *60*(5), 1318-1327.

[6] Gourévitch, B., & Eggermont, J. J. (2007). Evaluating information transfer between auditory cortical neurons. *Journal of Neurophysiology*, *97*(3), 2533-2543.

[7] Gilmour, T. P., Lagoa, C., Jenkins, W. K., Rao, A. N., Berk, M. A., Venkiteswaran, K., & Subramanian, T. (2012, December). Transfer entropy between cortical and basal ganglia electrophysiology. In *Signal Processing in Medicine and Biology Symposium (SPMB), 2012 IEEE* (pp. 1-5). IEEE.

[8] Schreiber, T. (2000). Measuring information transfer. *Physical review letters*, *85*(2), 461.

[9] Sabesan, S., Narayanan, K., Prasad, A., Iasemidis, L. D., Spanias, A., & Tsakalis, K. (2007). Information flow in coupled nonlinear systems: Application to the epileptic human brain. *Data Mining in Biomedicine*, 483-50