Non Linear Analysis of the Effect of Stimulation on Epileptic Signals Generated at Right Hippocampus

Siri Dhathri Kataru and Sunitha R.(✉)

Department of Electronics and Communication Engineering, Amrita School of Engineering, Amrita Vishwa Vidyapeetham, Bengaluru, India
r_sunitha@blr.amrita.edu

Abstract. Epilepsy is a neurological disorder which is a result of excessive electric discharge between the neurons of brain. Epileptic seizures can be treated with Anti Epileptic Drugs (AEDs), surgery and stimulation. In this study, Epileptor a dynamical system model is used to generate epileptic seizure signals in The Virtual Brain-a simulation framework and electrical Deep Brain Stimulation (DBS) has been used to reduce the effect of epilepsy. The non- linear dynamics of the simulated signals with and without Deep Brain Stimulation has been analyzed using various entropy methods and Hurst Exponent. It is observed that the entropy values of the signals stimulated with DBS are greater than those of the non-stimulated epileptic seizure signals emphasizing an increase in randomness. Also, it is observed that the effect of DBS reduces the predictability of the signal as the Hurst exponent reduces.

Keywords: Epilepsy · Seizure · Epileptor · Deep brain stimulation · Entropy · Hurst exponent

1 Introduction

Epilepsy is a disorder in which the central nervous system is affected due to abrupt electric discharges between the neurons of brain and which is characterized by spontaneous recurrences. An Epileptic seizure is defined as a "transient occurrence of symptoms due to abnormal and excessive neuronal activity in the brain" [1]. Most of the times, Epilepsy occurs due to genetic defects or due to injuries in brain [2] and may sometimes cause death of the individual. Symptoms of seizures depend upon from where the abnormal signals originate in the brain and it has been observed that thirty percent of the Epileptic patients suffer from medically refractory epilepsy [2, 5, 6]. Epileptic seizures can be identified through brain scans such as EEG, CT, MRI, fMRI etc.

Treatments for Epilepsy include Anti Epileptic Drugs (AEDs), abscission, Neurostimulation etc. Neurostimulation be of different forms including Vagus Nerve Stimulation (VNS), Spinal cord stimulation, Transcutaneous brain stimulation and Deep Brain Stimulation (DBS) [5]. It was found that stimulation frequencies less than 12 Hz or

S. M. Thampi et al. (Eds.): SIRS 2019, CCIS 1209, pp. 376–384, 2020.
https://doi.org/10.1007/978-981-15-4828-4_31

greater than 70 Hz are more efficient in diminishing the seizures [6] and also higher amplitude stimulus were found to be better in abating the seizures [7]. DBS has been found to be effective in cerebellum, hippocampus, subthalamus, anterior thalamus, hypothalamus and brain stem [3, 5, 6]. A few complications as part of DBS include site pain, infection at the implant site, dizziness, migration etc. [3].

Different types of models that are already available in the literature help us to mimic the already present data or analyse the demeanor of a system under new conditions. A neural model has been portrayed as a group of equations which depict the activity of a neuron or a network of neurons [8]. Such models could be used to find out which therapies most suitably can treat epilepsy [8]. Neuronal models have been categorized into different sub divisions as spatial scale models (micro and macro scale) and deterministic or stochastic models [2]. Macro-scale models are used to provide interactions between networks of neurons whereas micro scale models are concerned with modeling the activity of individual neurons such as ion channel, neuronal architecture and communication between neurons. Micro-scale models give highest accuracy of communication between neurons [2].

The FitzHugh–Nagumo model which has two state variables as membrane potential and recovery variable has been implemented as a micro scale neuron model [2, 9]. Hodgkin- Huxley is also found to be a low dimensional dynamic system model which describes the generation and propagation of the action potential in neuron. Deterministic models gave precise predictions unlike stochastic models which give probabilities. Stochastic modeling could be used when the system is levied to sudden quirks and could predict the seizures [9]. Stochastic models were also used to predict the seizure onset and to observe the dynamics during ictal and inter-ictal states of seizure [10]. Wilson-Cowan model is found to be a low dimensional lumped deterministic model with two state variables describing excitable population firing and inhabitable population firing [2, 10]. Markov model is found to be stochastic in nature which has three states: Normal, Pre-seizure and seizure states. This could predict the probability of transitions between the states [10]. Another attempt was also made to model the EEG rhythm based on fractional Brownian motion and fractional Gaussian noise once the multirate filterbank could separate the various frequency bands in the EEG [22].

In this study, the Epileptor model from "The Virtual Brain" simulation platform has been used to model the epileptic signals with and without stimulation. Non linear methods like entropy and Hurst Exponent have been used to analyze the dynamics of epileptic signal with and without stimulation. Entropy gives the measure of randomness of a system. It also measures the amount of chaos a signal possesses. A signal is said to be more informative if the entropy of the signal is greater [11].

2 Methodology

2.1 The Virtual Brain

The Virtual Brain (TVB) is a large scale neuroinformatics online simulation platform which allows multiple users to handle the data [12, 13] and can be installed for various operating systems such as Linux and Windows. It has been installed in the Windows 10 operating system for this study. TVB uses a blend of both tractoraphic data and existing

cortical connectivity information to create connectivity matrix to construct the brain networks. TVB supports two types of stimulations [7, 12], surface based stimulation and region based stimulation. In surface based stimulation, each region of the cortex is taken as a node and each node is modeled by neural mass models. This includes short range and long range connectivity [7]. In region based stimulation, each region is considered as a node which results in inclusion of only short range connectivity [7].

TVB also has the Brain Visualizer where one can see how the epileptic signal is being transferred from one region to the other. Figure 1 shows the Brain Visualizer, in which the dark red coloured regions represents the epileptic zones, light red represents the regions with less epileptic intensity and the pale red represents the regions with no epileptic activity.

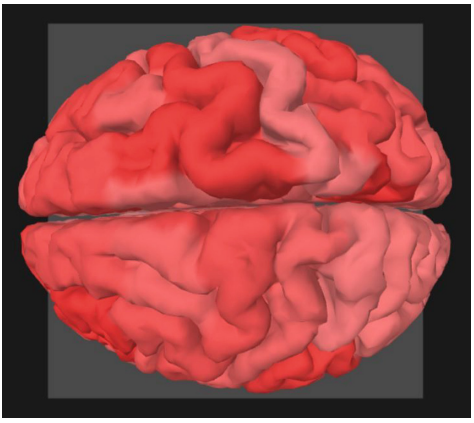

Fig. 1. Brain Visualizer generated in TVB (Color figure online)

The simulation results of TVB are stored in HDF5 file format and have been analysed in the Python using various packages.

2.2 Epileptor

The Epileptor model is a dynamic model in TVB which has been used to generate an epileptic signal in this study. Using five state variables in three different time scales, Epileptor generates epileptic seizure signals. The state variables x_1 and y_1 describes the fast discharges on the fastest time scale and the state variables x_2 and y_2 describe the spike and wave events on the intermediate time scale. The permittivity variable z describes the slow processes like ion concentration, tissue oxygenation and energy consumption. Switching between the ictal and inter-ictal states is governed by the permittivity variable [14–16]. The following equations describe the coupling between the state variables of the Epileptor model.

$$\dot{x}_2 = -y_2 + x_2 - x_2^3 + I_{rest2} + 0.002g(x_1) - 0.3(z - 3.5) \tag{1}$$

where $g(x_1) = \int_{t_0}^{t} e^{-\gamma(t-\tau)} x_1(\tau) d\tau$

2.3 Analysis of Epileptic Signals

Non-linear methods of analysis such as Approximate Entropy, Sample Entropy and Hurst Exponent have been used to analyze and validate the effect of Deep Brain Stimulation on right Hippocampus.

Approximate Entropy. Approximate Entropy (ApEn) is described by Pincus as the complexity of a time series signal [4, 14, 17] and it gives the measure of the similarity level of the signal [18]. The following equations represent the Approximate entropy [4, 14].

$$ApEn(M, m, r) = \Phi^m(r) - \Phi^{m+1}(r) \tag{2}$$

where $\Phi_m(r) = \frac{\sum_i^{M-m+1} lnC_i^m}{M-m+1}$

Here r is the tolerance specified as 20% of the standard deviation, M is the number of data points of the signal, m is the number of samples each data point is divided into and lnC_i^m is the conditional probability for m segments corresponding to i^{th} data point.

Moorman and Richman detailed ApEn as a self matching algorithm in which each data point is compared with itself [18]. It was observed that this aspect of self match led to bias in results because of which the approximate entropy showed more resemblance than which is actually present. Also, ApEn is highly dependent on length of records [18].

Sample Entropy. Sample Entropy (SampEn) has been coined to abolish the short comings observed in the Approximate Entropy [18]. It is found that sample entropy works better for short data sets and is less effective to noise [18, 19]. The following equation governs the Sample Entropy.

$$SamEn = \ln \frac{B^m(r)}{A^m(r)} \tag{3}$$

Where $B^m(r)$ represents the probability that two data points of the signal would match for m samples and $A^m(r)$ represents the probability that two data points of the signal are identical for m + 1 samples with a tolerance of r which is found to be twenty percent of the standard deviation of the signal.

Hurst Exponent. Hurst Exponent indicates the long term memory of the system which is generating the signal. The value of Hurst Exponent is expected to be in the range amidst 0 and 1for bio signals. The value of Hurst exponent in each moment will determine the demeanor of the signal in the successive moment. Value of Hurst exponent between 0 and 0.5 indicates an anti- persistent system i.e. the system behaves disparately in two consecutive moments. A value between 0.5 and 1 indicates a persistent system i.e. any two consecutive moments depict a similar behaviour. A Hurst exponent of 0.5 emphasizes that the system is highly random [20, 21].

3 Results and Discussion

The "Epileptor" model in "The Virtual Brain" has been used to model the epileptic signals of the right Hippocampus (rHc) with and without stimulation. The stimulation feature in TVB has been used to generate pulse and Gaussian stimuli and is applied to the right Hippocampus. The approximate entropy, sample entropy and the Hurst exponent of different signals simulated in TVB with and without stimulation (DBS) have been calculated using the Python platform. The value of tolerance (r) and m (number of samples each of the M segments the signal is divided) for sample entropy and approximate entropy is chosen to be 20% of the standard deviation of the signal and 2 respectively. Sigmoidal and an improvised version of the Sigmoidal coupling by name Jansen-Rit coupling have been used to generate the epileptic signals in which the difference coupling function between pre and post synaptic activity is used. The following are few of the simulations and observations inTVB.

Figure 2 shows the epileptic signal generated at rHc with difference coupling. An integration step size of 0.01220703125 ms and a sampling period of 0.98 ms have been used for simulating the signal. Figure 3 shows the pulse stimulated rHc signal with an onset of 200 ms, pulse width of 2000 ms, time period of 2000 ms, amplitude of 2 and a scaling factor of 20. Figure 4 shows the Gaussian stimulated rHc signal with a sigma of 3000, midpoint of 3500 ms, amplitude of 2 and an offset of 1.

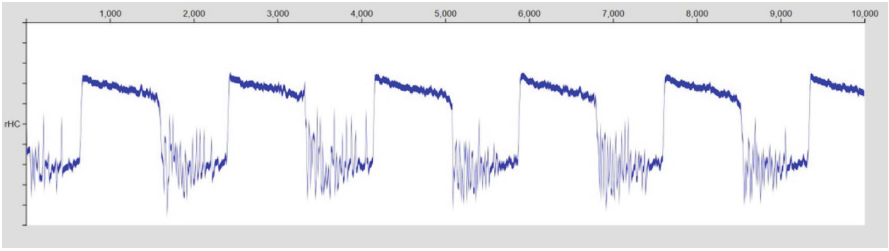

Fig. 2. Epileptic signal generated at right Hippocampus with Difference coupling

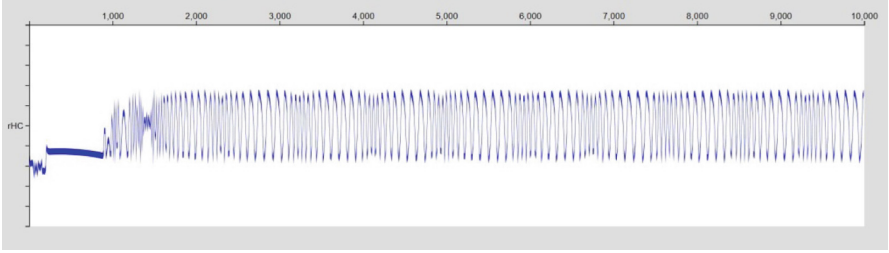

Fig. 3. Pulse stimulated rHc signal with onset = 200 ms, pulse width = 2000 ms, time period = 2000 ms, amplitude of 2, scale = 20

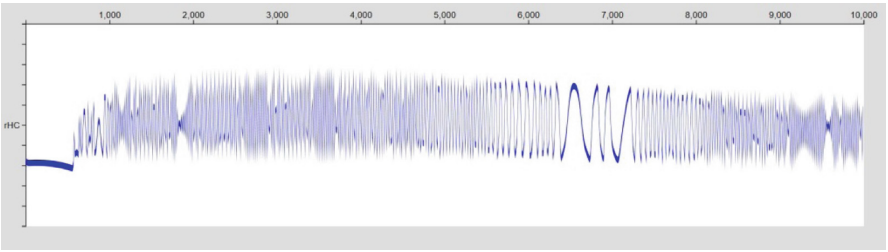

Fig. 4. Gaussian stimulated rHc signal with sigma = 3000 ms, midpoint = 3500 ms, amplitude = 2, offset = 1, scale = 50

From the above three figures, we can see that the stimulated signal is observed to be more irregular and unpredictable than the normal signal and the Gaussian pulse has been observed to have more effect in subsiding the seizures than pulse stimulus. The sample entropy, approximate entropy for m = 2 and Hurst exponent of the signals shown in Figs. 2, 3 and 4 are tabulated in Table 1, which emphasizes the fact that application of DBS made the signal more random.

Table 1. ApEn, SampEn and Hurst Exponent of signals with Difference coupling shown in Figs. 2, 3 and 4

Epileptic signal	ApEn	0.046
	SampEn	0.011
	Hurst Exponent	0.874
Pulse Stimulated signal	ApEn	0.207
	SampEn	0.089
	Hurst Exponent	0.361
Gaussian stimulated signal	ApEn	0.224
	SampEn	0.094
	Hurst Exponent	0.341

Figure 5 shows the epileptic signal generated at right Hippocampus with Sigmoidal JansenRit coupling. An integration step size of 0.01220703125 ms and a sampling period of 0.98 ms have been used for simulating the signal. Figure 6 shows the pulse stimulated rHc signal with an onset of 0 ms, pulse width of 1600 ms, time period of 1865 ms and amplitude of 2 with a scaling factor of 20. Figure 7 shows the Gaussian stimulated rHc signal with a sigma of 1000 ms, midpoint of 3700 ms, amplitude of 2 and an offset of 0.

Again, It can be observed that the stimulated signal is more random than the normal signal can also be noticed that Gaussian stimulated signal is more random than Pulse stimulated signal.

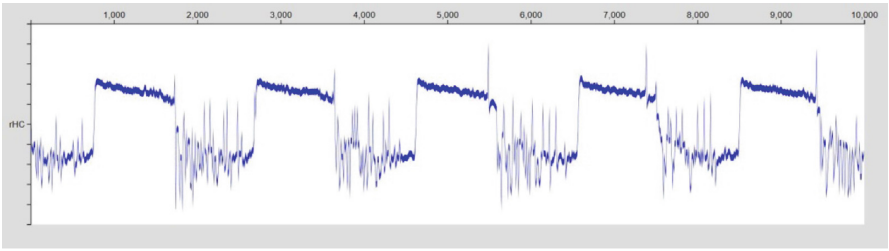

Fig. 5. Epileptic signal generated at right Hippocampus with Sigmoidal Jansen Rit coupling

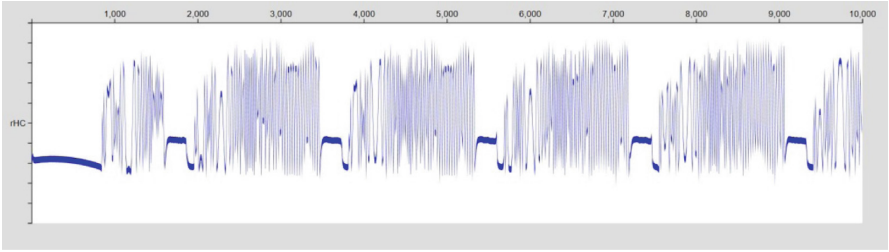

Fig. 6. Pulse stimulated signal at rHc with onset = 0 ms, pulse width = 1600 ms, time period = 1865 ms, amplitude = 2, scale = 20

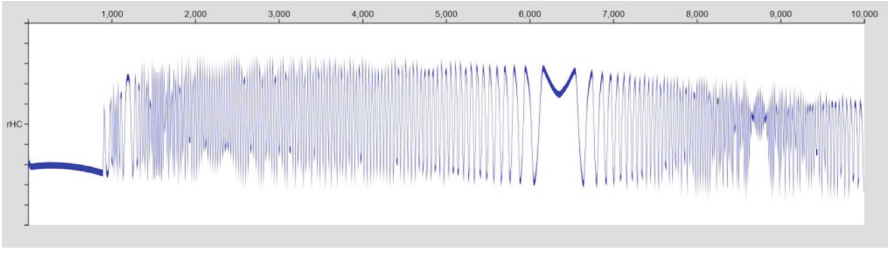

Fig. 7. Gaussian stimulated signal with sigma = 1000 ms, midpoint = 3700 ms, amplitude = 2, offset = 0, scale = 20

These results have been quantified in Table 2 using the Approximate entropy and the Sample entropy for m = 2. The Hurst Exponent of these signals has also been calculated and shown in Table 2.

From the tabulated results, it can be understood that entropy can be used as one of the measures to explore the effect of DBS. Stimulation with appropriate parameters is found to increase the entropy and thereby reduces predictability of the signal. Decrease in Hurst Exponent indicates that the signal is more irregular.

Table 2. ApEn, SampEn and Hurst Exponent of signals with SigmoidalJansenRit coupling shown in Figs. 5, 6 and 7

Epileptic signal	ApEn	0.065
	SampEn	0.014
	Hurst Exponent	0.832
Pulse stimulated signal	ApEn	0.184
	SampEn	0.061
	Hurst Exponent	0.725
Gaussian stimulated signal	ApEn	0.230
	SampEn	0.084
	Hurst Exponent	0.321

4 Conclusion

The Epileptor model in TVB has been used to generate epileptic signals with and without DBS. The entropy values and the Hurst exponents of the signals found reveal that the right Hippocampus could generate more random and unpredictable signals when stimulated with DBS than the epileptic signals generated without stimulation. The study also could reveal the dependency of DBS on the width of the stimulating pulse, as increase in the width of the triggering pulse could increase the randomness. The effect of stimulus can further be analyzed in detail to explore better ways of applying DBS to reduce the effect of Epilepsy and can be validated using clinical data.

References

1. Baier, G., Goodfellow, M., Taylor, P.N., Wang, Y., Garry, D.J.: The importance of modeling epileptic seizure dynamics as spatio-temporal patterns. Front. Physiol. **3**, 1–7 (2012)
2. Stefanescu, R.A., Shivakeshavan, R.G., Talathi, S.S.: Computational models of epilepsy. Seizure **21**(10), 748–759 (2012). Foster, I., Kesselman, C.: The Grid: Blueprint for a New Computing Infrastructure. Mor-gan Kaufmann, San Francisco (1999)
3. Klinger, N., Mittal, S.: Deep brain stimulation for seizure control in drug-resistant epilepsy. Neurosurg. Focus **45**(2), E4 (2018)
4. Acharya, U.R., Molinari, F., Sree, S.V., Chattopadhyay, S., Ng, K.H., Suri, J.S.: Automated diagnosis of epileptic EEG using entropies. Biomed. Signal Process. Control **7**(4), 401–408 (2012)
5. Fisher, R.S., Velasco, A.L.: Electrical brain stimulation for epilepsy. Nat. Rev. Neurol. **10**(5), 261–270 (2014)
6. Laxpati, N.G., Kasoff, W.S., Gross, R.E.: Deep brain stimulation for the treatment of epilepsy: circuits, targets, and trials. Neurotherapeutics **11**(3), 508–526 (2014)
7. Costers, L.: Second semester examination period dynamical diseases : modelling the effect of stimulation-based interventions on intrinsic brain dynamics. An application to epilepsy Master Thesis II submitted to obtain the degree of Master of Science in Psychology (2016)

8. Holt, A.B., Netoff, T.I.: Computational modeling of epilepsy for an experimental neurologist. Exp. Neurol. **244**, 75–86 (2013)
9. Jarray, R., Jmail, N., Hadriche, A., Frikha, T.: Innovations in Bio-Inspired Computing and Applications, vol. 735. Springer, Cham (2018). https://doi.org/10.1007/978-3-319-01781-5
10. Soltesz, I.: Computer modeling of epilepsy. Epilepsy **9**, 1–18 (2012)
11. Dhanya, E., Sunitha, R., Pradhan, N.: Power spectral scaling and wavelet entropy as measures in understanding neural complexity. In: 12th IEEE International Conference Electronics, Energy, Environment Communication Computation Control (E3–C3), INDICON 2015, vol. 2015-Janua, pp. 1–6 (2016)
12. Jirsa, V., et al.: The virtual brain: a simulator of primate brain network dynamics. Front. Neuroinform. **7**, 10 (2013)
13. Woodman, M.M., et al.: Integrating neuroinformatics tools in TheVirtualBrain. Front. Neuroinform. **8**(April), 1–9 (2014)
14. Jirsa, V.K., Stacey, W.C., Quilichini, P.P., Ivanov, A.I., Bernard, C.: On the nature of seizure dynamics. Brain **137**(8), 2210–2230 (2014)
15. Proix, T., Bartolomei, F., Chauvel, P., Bernard, C., Jirsa, V.K.: Permittivity coupling across brain regions determines seizure recruitment in partial epilepsy. J. Neurosci. **34**(45), 15009–15021 (2014)
16. Jirsa, V.K., et al.: The virtual epileptic patient: individualized whole-brain models of epilepsy spread. Neuroimage **145**, 377–388 (2017)
17. Kumar, Y., Dewal, M.L., Anand, R.S.: Features extraction of EEG signals using approximate and sample entropy. In: 2012 IEEE Students' Conference Electrical Electronics and Computer Science Innovation for Humanity SCEECS 2012, pp. 1–5 (2012)
18. Richman, J.S., Moorman, J.R.: Physiological time-series analysis using approximate entropy and sample entropy. Am. J. Physiol. Heart Circ. Physiol. **278**(6), H2039–H2049 (2000)
19. Song, Y., Liò, P.: A new approach for epileptic seizure detection: sample entropy based feature extraction and extreme learning machine. J. Biomed. Sci. Eng. **03**(06), 556–567 (2010)
20. Namazi, H., et al.: A signal processing based analysis and prediction of seizure onset in patients with epilepsy. Oncotarget 7(1), 342–350 (2015)
21. Stan, C., Cristescu, C.M., Cristescu, C.P.: Computation of hurst exponent of time series using delayed (log-) returns. Application to estimating the financial volatility. UPB Sci. Bull. Ser. A Appl. Math. Phys. **76**(3), 235–244 (2014)
22. Gupta, Anubha, et al.: A novel signal modeling approach for classification of seizure and seizure-free EEG signals. IEEE Trans. Neural Syst. Rehabil. Eng. **26**(5), 925–935 (2018)