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Role of Neuro Transmitters in Epilepsy

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Abstract: *A biologically plausible neural structure which exhibits spontaneous, stochastic transitions between low activity state and high activity state has to be constructed (by combining in vivo Electro physiology data analysis) using artificial neural networks modeling. Such a model with simple neuro dynamics has to reproduce many observed behavior of the epileptic seizure. To model the epileptic EEG signals and the dynamical properties of the actual and modeled signals are compared. Chaotic invariants like correlation dimension (D), largest Lyapunov exponent (λ1), Hurst exponent (H) and Kolmogorov entropy (K) are used to characterize the dynamical properties of the actual and modeled signals. Biological neural systems consist of billions of neurons interconnected via sets of individual synaptic weights. From literature study it reveals that the focal epilepsy (Enhanced excitability) is due to impaired Gamma Amino Acids (GABA ergic) inhibitory feedback. Enhanced excitatory receptor sensitivity has been identified in Kindled rodents as well in focal epilepsy. Hence this research focuses to construct a model network comprising of populations of inter neurons with GABA ergic connections, and such a model has to reproduce certain observed behavior of epileptic oscillations in the pyramidal membrane potential.*

Keywords: *Correlation Dimension, Epileptic EEG signals, Gamma Amino Acids, Neuro Dynamics*

1. INTRODUCTION

The recent research studies in the field of neuro transmitters have provided significant informations about the excitatory and inhibitory receptor sensitivity and its role in the cause of epilepsy. The enhanced excitability due to impaired ?-amino butyric acid inhibitory feedback (GABAergic) has revealed its importance in many types of focal epilepsy. Hence one can consider that epileptic seizure is due to impaired excitatory input to GABAergic inter neurons. Enhanced excitatory receptor sensitivity (most characteristically involving N-methyl-D-aspartate (NMDA) receptors) has been identified in kindled rodents and in focal epilepsy in humans.

Drugs that enhance GABA-mediated inhibition are anticonvulsant in many syndromes of generalized and focal epilepsy.

Synchronous activity of groups of neurons leads to epileptical disorder. Such a functional disorder of neural network is due to the excitability of individual elements of neural network and these results in altered properties of voltage sensitive ionic channels. Such an epileptic disorders irresponsible for change in ion transporter properties (such as changes in the synthesis, release, re-uptake, or postsynaptic action of inhibitory or excitatory neurotransmitters) and even changes in the anatomic or functional connection properties of cells. Study of neurotransmission in epilepsy has three areas of research interest. Thus one may ask, first, whether alterations in neurotransmitter systems provide the basis for epilepsy ?. Second, what role different transmitter systems play in the evolution of seizure activity? Third, how changes in synaptic function, induced by antiepileptic drugs (AEDs) or other therapeutic interventions, contribute to the suppression of seizures. This review focuses predominantly on inhibitory (γ-aminobutyric acid; GABAergic) and excitatory (glutamatergic) neurotransmission. In this research we have made an effort to provide a bridge between primarily ionic events and issues related to the operation of neural networks.

In this research we have made an effort to develop a model network comprising two populations of interneurons. One population corresponds to the slow $GABA_A$ synapse and other to the fast $GABA_A$ synapse. Simulation results showed that the two populations of inter neurons could include epileptic oscillations in the pyramidal membrane potential and this epileptic oscillation was most occurrent with interaction between the two populations. We hypothesized that inhibition through the $GABA_A$ synapse plays important role in neuronal membrane oscillations.

Epileptic seizure signal modeling is used as a tool to identify pathophysiological EEG changes potentially useful in clinical diagnosis. The recent research in the field of nonlinear time series analysis and constructing experimental deterministic (stochastic) dynamical model for a nonlinear system have given a better approach to analyze the behavior of nonlinear system. This new approach has provided a better insight about the way in which the brain works. The EEG can be characterized by using indices initially derived for

the study of deterministic dynamical systems [4, 7]. Nonlinear methods of modeling the signals are more advantageous over the traditional spectral techniques. Most of the studies undertaken until now have been carried out on a single channel EEG. The nonlinear characteristics of EEG were studied to test the differences among groups of normal and diseased epileptic EEG [3, 14] or different sleep stages. Researchers have applied certain nonlinear techniques for prediction of epileptic seizures [12, 10], characterization of sleep phenomena and monitoring of anaesthesia deepness [9]. Nonlinear systems can exhibit a wide spectrum of dynamical behaviors, which include fascinating chaotic dynamics. A chaotic system is deterministic, but the system output is not predictable in the long run. Conventional signal modeling techniques assume that these signals are generated by some linear system driven by random noise, but they are not appropriate to model the nonlinear dynamics.

2. GABAERGIC INHIBITION IN EPILEPSY

GABAergic inhibition is prominent through out the brain. A high proportion of synaptic connections are GABAergic in nature. Feedback inhibitory systems are common feature in the networks of neocortex, hippocampus, and deep brain nuclei. GABA ergic neurons show great diversity in anatomic detail. GABAergic systems undoubtedly serve to play an important role in limit or the spread of seizure activity. Activation during seizure activity is evidenced by increase of extra cellular concentration of GABA in the surrounding or contralateral cortex during focal seizure activity. GABA is synthesized in GABAergic nerve terminals by the enzyme glutamic acid decarboxylase [1].

The impaired GABA mediated inhibition give rise to various pattern of epileptic seizure [8]. Thus it has also been proposed that cerebral hypoxidischemia in the neonatal period leads to selective damage to GABAergic interneurons in the cortex. Early experiments examined in monkey cortex [13], have suggested that an episode of hypoxidischaemia early in life could produce a selective loss of GABAergic terminals. Recent studies in rats exposed in the neonatal period to hypoxidischaemia, shows an increase rather than a decrease in immunostaining for glutamic acid decarboxylase (GAD) [15]. Focal epilepsy induced in monkeys have selectively reduced the number of GABAergic somata and synaptic boutons [16]. Hilar lesions following limbic seizures induced by pilocarpine in rats are associated with loss of mRNA for GAD in the dentate gyrus [15]. In kindled rats, GABA-mediated responses may be potentiated. In humans, immunocyto-chemistry for GAD has not shown any preferential loss of GABAergic interneurons in the hippocampus in anterior temporal lobectomy specimens. Overall, the evidence for a defect in GABAergic systems can be considered as a major cause of epilepsy [8]. Indeed, a widely favored etiological hypothesis for temporal lobe epilepsy is that of the dormant basket cell, which suggests that recurrent inhibition in the hilus of the dentate gyrus is impaired because of failure of the excitatory input to GABAergic interneurons [18]. Changes have been reported in GABA NBZD receptors or in GAD staining in some genetic models of epilepsy in rodents. There is increase of GAD 67 immunostaining in the inferior colliculus of genetically epilepsy in rats [17] and increases in the number of GAD staining neurons in the hippocampus of epileptic gerbils. There is decrease in GABA/BZD binding in genetic syndromes. GABA uptake is impaired in a genetic model of temporal lobe epilepsy [16]. In kindled rats, there is evidence that the stimulated release of GABA is enhanced in CA1 [6].

3. EXCITATORY TRANSMISSION AND GLUTAMATE RECEPTORS

The capacity of glutamate or its structural analogues to induce seizures when focally injected in the neocortex or in subcortical nuclei was reported by Joel J [11]. The possibility that abnormal glutamate metabolism or transport might contribute to epilepsy. Plasma glutamate levels are higher in patients with generalized epilepsy and in a genetic rodent model of epilepsy [5]. In kindled rats, the basal concentration of glutamate in the extracellular fluid in hippocampus or cortex is increased [6]. Substantial evidence shows that abnormal expression or enhanced function in glutamate receptor subtypes plays an important role in various acquired forms of epilepsy [1,2]. Electronically kindled limbic seizures in rats show clear evidence for altered functional properties of NMDA receptors [6]. A similar enhanced responsiveness to NMDA is evident in cortical slices derived from human epileptic foci. Genetic forms of epilepsy may also be associated with abnormal glutamate responses.

4. DATA DESCRIPTION

The EEG data for analysis were obtained from the EEG database. Two sets each containing 30 single channel EEG segments of 23.6-sec duration, were composed for this study. The EEG dataset consists of segments taken from surface EEG recordings that were carried out on five patients using a standardized electrode placement scheme. Patients were relaxed in an awake state with eyes open and data are collected. Epileptic EEG dataset contains data recorded during seizure activity. All EEG signals were recorded by 128-channel amplifier system, digitized with a sampling rate of 173.61 Hz and 12-bit A/D resolution. All the datasets were preprocessed and tested for stationarity and nonlinearity before estimating the chaotic invariants.

5. BIOLOGICALLY PLAUSIBLE NEURAL NETWORK BASED EPILEPTICAL SEIZURE MODEL.

We have constructed a model network comprising the pyramidal cell, SP inter neurons (str. Pyramidale) and SLM inter neurons. In our model network, the SLM interneurons (s = 40) and SP interneurons (p = 40) are connected in all to all fashion within and between the populations. Althogh there

is no evidence for the connections between the SLM interneurons, we have assumed these connections by the slow $GABA_A$ synapses. We also assumed the connections between the SP and SLM interneurons. Each interneuron makes synapses on the target pyramidal cell.

In our model each interneuron is described by a single compartment and obeys the current balance equation.

$$C_M\, dV_m/dt = I_{leak} + I_{act} + I_{syn} + I_{inject} \quad (1)$$

Where V_m is memrane potential and $C_M = C_m * S$ where S is the surface area and the membrane capacitance constant C_m = 1.0 microfarad /cm².

The leak current is $I_{leak} = (V_m - E_L)/R_m$ has a membrane resistance $R_M = R_m/S$ with membrane resistance constant R_m = 10,000 Ω cm² and E_L = –65 mV. The compartment is a cylinder of length l =1.0 ìm and diameter d = 0.4 µm. The activating current I_{act} consists of I_{Na} and I_K, both of which are of the Hodgkin-Huxley type and are the modified form of Traub and Miles. The model pyramidal cell obeys Eq. (1). Activating current I act is used to investigate the passively induced changes in the membrane potential. The synaptic current I syn consists of fast and slow $GABA_A$ current. We have assumed the activation scheme for the slow $GABA_A$ R/C as follows

$$G + R \leftrightarrow GR \leftrightarrow O,$$

Where G is the transmitter GABA, R is the receptor, GR is the GABA bounded receptor and O is the activated receptor channel.

The slow $GABA_A$ current $I_{GABA,slow} = g_{GABAA,slow} o (V_m - E_{cl})$, Where $GABA_{A\ slow}$ has the maximal synaptic conductance and E_{cl} is the reversal potential and o is the normalised concentration of activated channel O. The activated channel O obeys the following equation.

$$Do/dt = \delta c \quad (2)$$

Where c is the normalized concentrations of GABA bounded receptor GR. We assumed that c obeys the first order kinetics proposed by Destexhe *et al.*

$$dc/dt = \alpha F(V_{pre})(1-c) + \beta c \quad (3)$$

Where $F(V_{pre})$ is the normalized concentration of GABA in the synaptic cleft and is assumed to be function of the presynaptic membrane potential V_{pre}

$$F(V_{pre}) = 1/(1+\exp(-V_{pre}/2)) \quad (4)$$

The channel activation rate constants α, β, γ and δ are set so that the $I_{GABAA\ slow}$ can reproduce the best fit curve of the slow $GABA_A$current [87]. With rate constants α = 12 ms^{-1}, β = 0.15ms^{-1}, γ = 0.058ms^{-1}, δ = 0.0225ms^{-1}, and $g_{GABAAslow}$ = 1.6 nS/ interneuron, We have a good approximation of fitting current of τ_{rise} = 5ms and τ_{decay} = 50ms.

For the fast $GABA_A$ current, we have employed the model current proposed by Wang and Bzsaki. Model currents of fast and slow $GABA_A$synapse are shown in Fig. 1. $g_{GABAA,slow}$ = 0.3 mS/cm² and $g_{GABAA,fast}$ = 0.2 mS/cm² for interneurons.

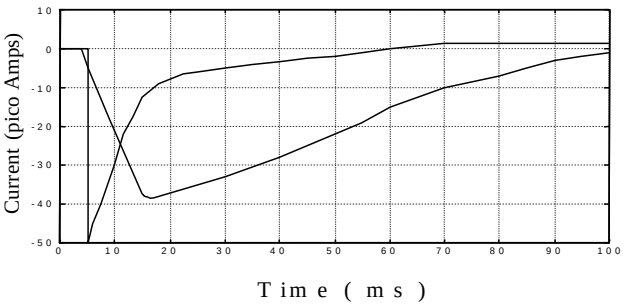

Figure 1: Modeled Slow GABA and Fast GABA Currents

We have modeled hippocampal network consisting of many pyramidal and inhibitory neurons. Each pyramidal neuron contains different ionic conductance and the neurons are randomly interconnected with excitatory & inhibitory synopsis.

The cortical microcircuit network was constructed from SLM and SP interneuron cells, and the phenomenon of synaptic depression was taken into consideration. The network contains 2 excitatory and 1 inhibitory populations of cells. Each population contains 40 cells. S population refers to SLM cells, P population refers to SP neuron cells. The s, p, g upper indices refer to the three population, the ss, sp, pg, gs upper indices to the connections between the populations. The state of a cell is described by it's membrane potential V with the corresponding indices. The output activity of a cell is denoted by the letters s, p, g, respectively. The connection matrices between two populations are denoted by w, while the strength parameters & the decaying parameters is represented by c and d stands for the depression factor, i for the input. r is a random variable with uniform distribution between 0 and 1. Two types of connections were used: Local and Random. The connection matrix of self excitation in the s population was random, each element of the matrix chosen with uniform distribution over [0,1], and all the other connections were of local type.

The network activities are described with the following equations.

The input excitation and connection to the s^{th} populations are given by

$$i_n(t) = \sum_m w_m^{is} \Sigma(r^i(t) - th^i) \quad (5)$$

The j^{th} neuron's activation value of s population of neuron is described by following equation

$$V_j^s(t) = c^s V_j^s(t-1) + i_j(t-1) + c^{ss} \Sigma(w_{jk}^{ss} d_k^{ss}(t-1) s_k(t-1) + c^{gs} \Sigma(w_{jl}^{gs} g_1(t-1) k^l s_j(t) = \Sigma (V_j^s(t) - th^s) \quad (7)$$

The depression connection between s to s population are given by

$$D_k^{ss}(t) = d_k^{ss}(t-1) + c^{d+} (1 - d^{ss}_k(t-1)) - c^{d-} s_k(t) \quad (8)$$

The e^{th} neuron output in p population of neuron is describer by

$$V^{p}_{e}(t) = c^{sp} \Sigma\, w_{eq}^{\ sp}\, s_{q}(\text{t}-1) \quad (9)$$

$$p_e(t) = \Sigma(V_e^{qp}(t) - th^{p}) \quad (10)$$

The l^{th} neuron's activation value of 'g' population of neurons is describer by

$$V_l^{g}(t) = i_{\text{l}}(t-1) + c^{pg} \Sigma\, w_{lf}^{\ pg} p_f(t-1) \quad (11)$$

The l^{th} neuron's out put of 'g' population of neurons is describer by

$$g_l(t) = \Sigma\,(V_l^{g}(t) - th^{g}) \quad (12)$$

The following values have been taken to simulate the neural circuit

$th^{i} = 0.8$, $th^{s} = 0.8$, $th^{p} = 6.4$, $th^{g} = 1.6$, $c^{s} = 0.7$, $c^{ss} = 2.2$, $c^{sp} = 1$, $c^{pg} = 3$, $c^{gs} = 3$, $c^{d+} = 0.01$, $c^{d-} = 0.005$.

6. RESULTS AND DISCUSSIONS

To activate the network, we have injected steady current to the pyramidal cell and SP interneurons. For the low values of self-excitation, the system in the basin is at stable fixed point and thus only relatively small random changes are observable in the activity level of cells due to the random input patterns. The network gives short 'answers' to the input. In case of sufficiently high self-excitation ($c^{ss} > 0.7$), the lower fixed point looses its stability and an irregulated oscillation emerges by the random input. In case of higher self excitation a high activity fix point appears. On short time scales both the oscillations & the high fix point are stable, but the synaptic depression makes these high activity states unstable, slowly driving the system from the high fix point down to the oscillatory regime and further, into the stability regime of low fix point. In this low activity state the depressing factor slowly recovers (Fig. 3) and the state becomes unstable and the random input is able to launch the system suddenly into high activity state. The result is a complex behavior with suddenly starting & terminating seizures (Fig. 2). The internal dynamics of a model seizure is very similar to the observed behavior. The similarity is more pronounced if we compare the reconstructed pseudo attractors in different stages of the seizures. A similar trajectory structure appears in the seizure's second stage on ? = 10 msec delay plot. Similar trajectory structure appears in the seizure's third stage on ? = 30 msec delay plot (refer Fig. 4 & 5).

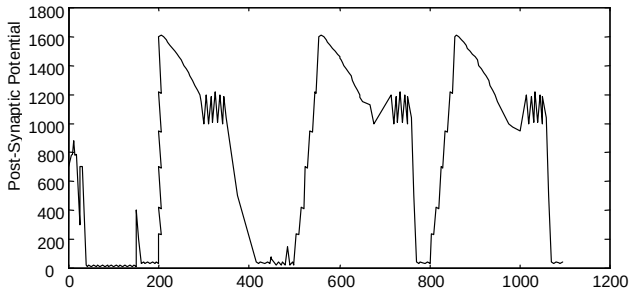

Figure 2: Slow Dynamics of Epileptical Seizures

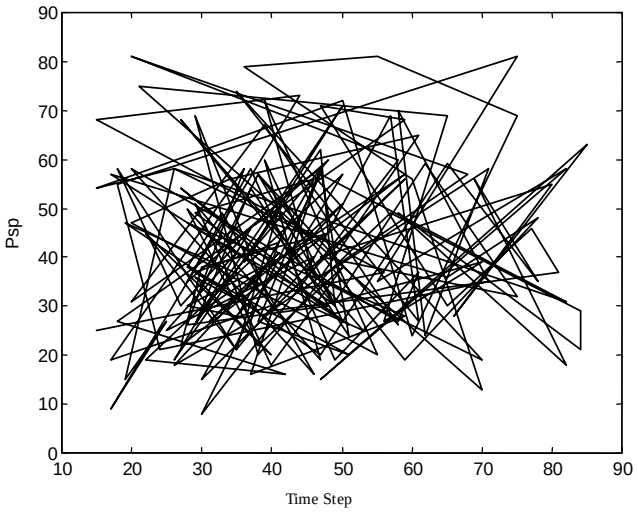

Figure 3: Synaptic Depression Makes these High Activity States Unstable, Slowly Driving the System from the High Fix Point Down to the Oscillatory

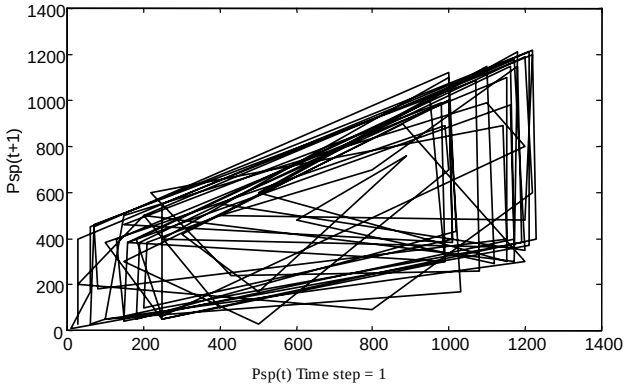

Figure 4: Ttrajectory Structure Appears in the Seizure's Second Stage on ? = 10 m sec Delay Plot of the Results from the Model with ? = 1m sec Time Step

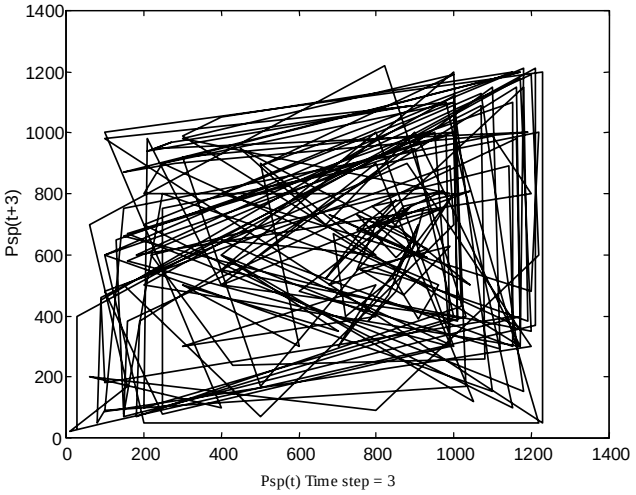

Figure 5: Trajectory Structure Appears in the Seizure's third Stage on the = 30msec Delay plot to = 3m sec Time Steps Delay Plot of the Model-seizure

Table 1
Chaotic Invariants Analysis

Chaotic Invariants	*Original*	*NN*
D	4.8768	4.7731
λ_{max}	0.2036	0.1903
H	0.3248	0.3124
KSEN	0.6033	0.5876
APEN	0.7096	0.6932
SEN	–0.2215	–0.2333
REN	–0.1927	–0.2121
$D^{Higuchi}$	1.5132	1.4972
D^{Katz}	1.8649	1.8123

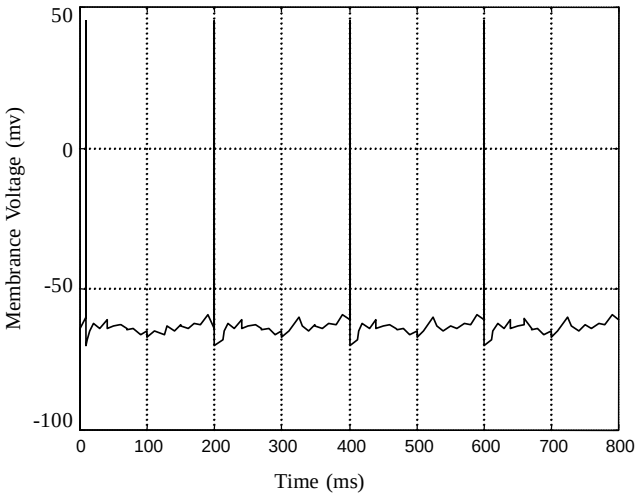

Figure 6: Normal Activities SP and SLM Interneurons (The Output Activity of a Cell)

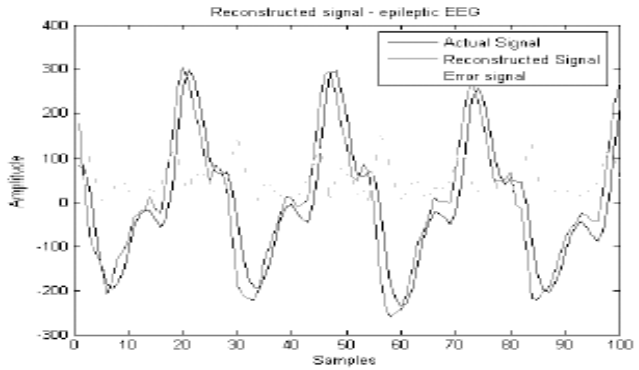

Figure 7: Background EEG Signal Reconstructed using NN Model

Table 1 to Table 2 shows results of analysis of actual and the reconstructed background, epileptic EEG signals using AR and NN modeling techniques. The chaotic invariants such as correlation dimension D, Lyapunov exponent λ_{max}, Hurst exponent H , and entropy measures such

Table 2
Chaotic Measures of Epileptic EEG

Chaotic Invariants	*Original*	*NN*
D	3.9407	3.8513
λ_{max}	0.1845	0.1734
H	0.3563	0.3397
KSEN	0.4926	0.47910
APEN	0.6484	0.6278
SEN	-0.735	-0.7432
REN	0.195	-0.1993
$D^{Higuchi}$	1.3546	1.2983
D^{Katz}	1.5139	1.4511

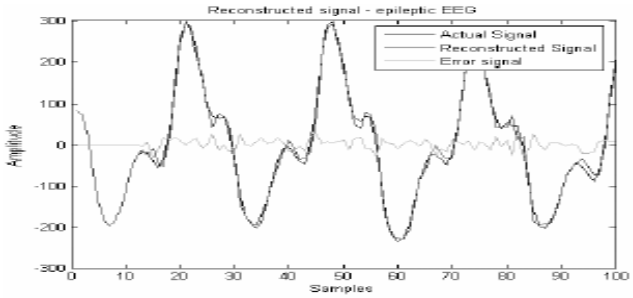

Figure 8: Epileptic EEG Signal Reconstructed using NN Model

as Kolmogorov Sinai entropy KSEN , approximate entropy APEN , spectral entropy SEN , Renyi's entropy REN and fractal dimension measures computed using Katz and Higuchi's algorithms ($D^{Higuchi}$ and D^{Katz}).

The estimates of the largest Lyapunov exponents for reconstructed normal EEG signal of the NN model is 0.1903, while that for the AR model is 0.1876. The results are given in Table 1. Again, it can be clearly seen that the results for the output of the NN model is very close to that of the original signal. The correlation dimension estimate for the normal EEG signal of both the models is given in Table 1. From the correlation dimension estimate of the output of the NN model it can be seen that the NN model can preserve the characteristics of the original signal very well. Results of the chaotic analysis of the modeled signals of the background and epileptic EEG signals also indicate the NN model output is quite similar to that of the original signal. Similarly the correlation dimension estimate for chaotic epileptic EEG signal of both the models is given in Table 2. From the correlation dimension estimate of the output of the NN model it can be seen that the NN model can preserve the characteristics of the original signal very well.

7. CONCLUSIONS

With irregular variation of injected GABA current, certain oscillation with different frequency waves (ranging from 1Hz to 40 Hz) were induced in the pyramidal membrane potential (as shown in Fig. 6). The abrupt change in fast and slow

GABA Currents causes these Epileptic oscillations. The autocorrelation of the observed behavior of Epileptic Seizure and the component of the pyramidal membrane potential is carried out. These results indicate that the slow GABA Synapse underlies the Epileptic oscillations in the pyramidal potential.

Further we have changed the architecture of the model network to investigate the role of interactions between SP and SLM, The following three cases were considered:

1. SLM & SP were separated
2. Only projections from SLM to SP existed
3. Only projections from SP to SLM existed.

In all these three cases almost similar oscillations were induced in the pyramidal membrane potential and autocorrelation analysis of the pyramidal oscillation was performed. Separation of the two SLM & SP or one-way projections from SLM to SP gave weaker autocorrelation than the reciprocal projections between the two SP interneurons. The results indicate that interaction between the interneurons, especially from SLM to SP through GABA synapse plays an important role to generate epileptic seizure oscillations in the pyramidal membrane potential and which is consistent with experimental observations.

The behavior of the model system is similar to the real epilepsy, and strengthening of the inhibition could eliminate the seizures. The seizure activities are generated by combinations of excitatory synaptic currents and intrinsic voltage dependent membrane currents.

We have concluded that the slow GABAA synapse (irregular alteration, impaired inhibition of GABA Current) plays an important role in generation of Epileptic oscillations in the pyramidal membrane potential, which is one among the contribution in this research. Although it is not well known about the interaction between the SP interneurons and SLM interneurons, our results indicated the existence of synaptic connections from the SLM interneurons to the SP interneurons via the slow GABA A synapses.

The chaotic invariants estimate of the actual and the NN modeled normal, background and epileptic EEG signals are compared. From the results it can be seen that the values of the NN modeled signal are closer to the slow dynamics of original signal. From all of these comparisons, it can be concluded that the NN model captures the underlying dynamics of the EEG signal very well compared to the Biologically plausible Neural Network (NN) model.

REFERENCES

[1] Babb T. L., Pretorius J. K., Kupfer W. R., Crandall P. H. Gluta-mate Decarboxylase-immunoreactive Neurons are Preserved in Human Epileptic Hippocampus. *J. Neurosci* 1989; 9: 2562-74.

[2] Bekenstein J. W., Lothman E. W. Dormancy of Inhibitory Inter Neurons in a Model of Temporal lobe Epilepsy, **2**, 101-110.

[3] Besthorn C., H. Sattel, C. Geiger Kabisch, R. Zerfass, H. Förstl, "Parameters of EEG Dimensional Complexity in Alzheimer's Disease," *Electroenceph. Clin. Neurophysiol.* **95**, 1995.

[4] D. J. Amit, H. Gutfreund and H. Sompolinsky (1987) Information Storage in Neural Networks with Low Levels of Activity. *Physical Review* **A 35**, 2239-2303.

[5] During M. J., Spencer D. D. Extracellular Hippocampal Glutamate and Spontaneous Seizure in the Conscious Human Brain. Lancet 1993; 341: 1607-1610.

[6] Evidence for a Chronic Loss of Inhibition in the Hippocampus After Kindling: Electrophysiological Studies. *Epilepsy Res.* 1989; 4: 90-9.

[7] Harris F. S., Rhoton A. L. Anatomy of the Cavernous Sinus: A Microsurgical Study. *J. Neurosurg* 1976; 45: 169-80.

[8] Hufnagel A., Burr W., Elger C. E., Nadstawek J., Hefner G. Localization of the Epileptic focus During Methohexital-induced Anaesthesia. Epilepsia 1992; 33: 271-284.

[9] Im H. K., Im W. B., Hamilton B. J., Carter D. B., VonVoigtlanderPF. Potentiation of Gamma-aminobutyric Acid-induced Chlo-ride Currents by Various Benzodiazepine Site Agonists with the (Subtypes of Cloned Gamma-aminobutyric Acid Type A Receptors).

[10] J. Wackermann, "Beyond Mapping: Estimating Complexity of Multichannel EEG Recordings," *Acta Neurobiol. Exp.*, **56**, 197-208, 1996.

[11] K. G. Kramlinger, R. M. Post, Ultrarapid and Ultradian Cycling in Bipolar Affective Illness, Br. J. Psychiatry **168** (1996), 314-323.

[12] King G. L., Knox J. J., Dingledine R. Reduction of Inhibition by Benzodiazepine Antagonists, Ro 15- 1788, in the Rat Hippocampal Slices. *Neuroscience* 1985; 15: 371-378.

[13] Sloper J. J., Johnson P., Powell TPS. Selective Degeneration Ofinterneurons in the Motor Cortex of Infant Monkeys following Controlled Hypoxia: A Possible Cause of Epilepsy. BrainRes 1980; 198-204.

[14] Nadia A. Chuzhanova, Antonia J. Jones, and S. Margetts (1998), Feature Selection for Genetic Sequence classi_cation." *Bioinformatics* **14**(2), 139-143.

[15] Obenaus A., Esclapez M., Houser C. R. Loss of Glutamatedecarboxylase mRNA-containing Neurons in the Rat Dentategyrus following Pilocarpine-induced Seizures. *J. Neurosci* 1993; 13: 4470-85.

[16] Ribak C. E., Hunt C. A., Bakay RAE, Oertel WH. A Decrease in the Number of GABAergic Somata is Associated with the Preferential loss of GABA-ergic Terminals at Epileptic foci. Brain Res 1986; 363-390.

[17] Romijn H. J., Janszen AWJW, Van Marle J. Quantitative im-munoflourescence Data Suggest a Permanently Enhanced GAD67/GAD65 Ratio in Nerve Endings in Rat Cerebral Cortex Damaged by Early Postnatal Hypoxiaischemia Brain Res 19946; 657: 245-257.

[18] Sloviter R. S. Permanently Altered Hippocampal Structure, ex-citability, and Inhibition after Experimental Status Epilepticus in the Rat: the “Dormant Basket Cell” Hypothesis and its Possible Relevance to Temporal Lobe Epilepsy. Hippocampus 1991; 1: 41-66.