Modeling signal transmission and robustness in biological neural networks

Christos Kotsavasiloglou, Alkiviadis Kalampokis, Panos Argyrakis and Stavros Baloyannis

***Abstract*—** In this paper we present computational model based on first principles with the purpose to study the behavior of biological neural networks. A network is constructed using as elementary building blocks DLA clusters, a structure well known in solid state physics, giving thus the network spatial structure, and in this way differentiating the model from most previous studies in this field. The blocks are paced randomly on 2D-space and synapses are formed where neighboring blocks overlap. The behavior of the network is studied, focusing not only on signal transmission and analysis, but also on the results of synapse loss, common in biological systems under certain diseases, such as Alzheimer's and Parkinson's. The network's response follows the same basic characteristics as real biological systems under similar circumstances, and the importance of the spatial structure of the network in this behavior is examined..

***Keywords*—** Neural Network, Synapse Degradation, DLA, computational model, Alzheimer's, Parkinson's.

I. Introduction

THE elementary unit of the central nervous system is the neuron. Every neuron communicates with thousands of other neurons through synapses. In the presynaptic part of the synapse, the electrical signal activates a chain of complex chemical processing which ends with the release (exocytosis) of the neurotransmitter in the synaptic cleft. The molecules of the neurotransmitter are bound to the receptors of the postsynaptic part of the synapse causing an exchange of ions through the membrane of the second neuron changing the electric potential of it. So, the new voltage, called postsynaptic potential propagates through the second neuron. Neurons are not connected to each other in a random pattern. They are aggregated in formations, called nuclei, or they are located in layers, as in the cerebral cortex. Collections of neurons wherever they are located always have a specific function.

Neurons and synapses are age depended. It is well known that after the age of 20 there is a gradual decrease of the number of synapses and neurons in many areas of the brain [1,2]. This loss does not affect the person's performance mentally or otherwise at levels that can be considered as manifestations of a disease. Persons over 60 or 70 can accomplish complex mental tasks although they have a gradual loss of synapses that started years before. This is the normal aging of the brain. The difference among the normal aging and the disease is the rate of the synapse or neuron loss. There are experimental data [3,4] which show that in the case of the disease the rate of synapse loss is statistically significant compared with normal aging. It seems that there is a critical point, beyond which there are clinical manifestations of the disease.

This evidence motivates us to investigate if this is a property that can be simulated in similar complex systems. Such a study is important both from the theoretical point regarding the function of neural networks, but additionally it will help to answer the question of what part (percentage) of the brain neural networks can be incapacitated before total loss of functions will occur? How does this loss come about? Apparently, if we know this answer we will be able to predict the details of how and when does the human brain degrade, differentiate the degradation in normal age from that in a disease, and will possibly help in the search for a treatment.

There are many citations in the literature about such relationships, for different parts of the brain, with a variety of different answers. However, they are all either qualitative or the data have a very large dispersion, and furthermore, there is no theoretical basis to explain, or establish, such a relationship. The present paper attempts to shed some light in this direction by utilizing a complex computational model [5,6]. Brain function is quantitatively described by network activity, a (see below), and we investigate this activity as a function of the neural loss and other net parameters.

Since the connectivity pattern between the neurons is very complicated it is reasonable to assume that the relationship between synapse loss and network activity is not simply linear. Two neurons can be connected at several different points via different synapses. Thus, removing a single synapse does not necessarily preclude any connectivity between these two neurons. This behavior cannot be simulated when neurons are described as points. It is, thus, very important to treat the individual neurons not as simple binary entities, but as units with internal structure, and this is the approach taken in the present study. Each neuron (cell) is made of a very large number of parts, as a real one is. We believe that not considering the neuron as one single unit, as practically all theoretical models up to now have done, is the only possible way to address our basic question.

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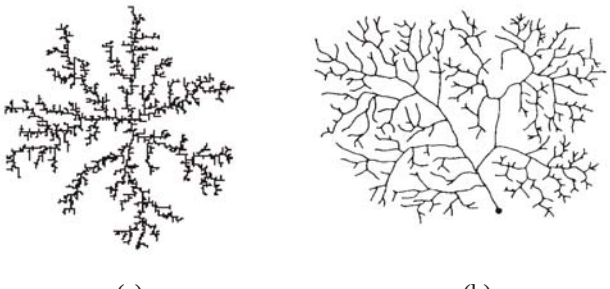
II. The Model

We introduce a computer simulation model of a neural network that is based on a collection of dendritic structures that are called diffusion limited aggregates (DLA). These entities originated in solid state physics [7], but nevertheless, resemble very much the picture of the backbone of an actual brain neuron, and this is why we adopt them. Fig. 1 contains one DLA simulated structure, and a camera lucida [8] drawing of a Purkinje neuron. We can see that both units posses a dendritic nature. Thus, each neuron is made of several thousands of building blocks placed according to the DLA model on a lattice. At this stage no differentiation is made for the soma, axon, etc. but all building blocks are treated equally. With the exception of the work of Caserta et al [9] there have been no other references in the literature of a similar work, as far as the authors are aware. The network is constructed by placing a number of these units randomly in space at high densities. Such a network made of only 8 units is shown in Fig. 2. Because the neurons are closely packed there is a large overlap between them, especially on the branched dendrites. These overlaps will be treated as the synapses in our model. In this model a synapse can be declared active or inactive at will, and this is one of the external parameters that we can control. In each synapse connecting neurons A and B the signal can propagate only in one direction mean only from A to B or from B to A, and this direction is chosen at random when the network is formed. Also, the value of the signal must be greater than the synapse threshold, θ. Thus, each synapse is assigned a θ value. The signal transfer from one unit to the next is not instantaneous, but the transmission is delayed for a certain time, called the synaptic delay, *SD*, since signal transfer in the synapse is about 1000 times slower than the transfer inside a neuron. After firing the synapse goes into a refractory period, *RP*, during which the synapse cannot be active any more, but must necessarily remain passive. All synapses are characterized as either excitatory or inhibitory. The fraction of each (out of the total number of synapses) is f_e and f_i, respectively. The identity of each synapse is determined at random with a probability according to that fraction. Generally, the excitatory (inhibitory) characterization describes the property that brings closer (further away) the synapse signal value to the synapse threshold.

We will first study signal transport throughout the network. This process is dynamic in nature, and thus we define the smallest increment of time to be the actual time that it takes for the signal to transfer from one lattice point to its nearest neighbor inside the same neuron. Originally, at time $t=0$ some initial signal is randomly given to a small subset of the neural network. This signal is allowed to travel throughout the system, i.e. both inside the neurons and also, when reaching a synapse, to transfer to adjacent neurons. This is done by "transferring" the signal to all of its nearest neighbor sites, and incrementing time by one time unit. Next, this step is repeated and time advances.



(a) (b)

Fig. 1 Resemblance between a DLA cluster (a) and a camera lucida drawing of a Purkinje neuron (b).

III. Results

The behavior of the neural network described here is monitored via the network activity that it exhibits, as a function of time. The activity a is defined as the fraction (out of the total) of the active units at a given time. Thus a=(neurons that are active/total number of neurons in the system). In Fig. 3 we show the response of the neural network to a change in the values of the parameters discussed. Specifically, we have a network with refractory period RP=300, synaptic delay SD=800, and a fraction f_e=0.8 of excitatory synapses. We vary f_s, the fraction of synapses used, from f_s=0.2 to f_s=1.0. We observe that the activity exhibits an oscillatory behavior. It starts from a zero value, increases during the first 10000 steps, and then reaches an "equilibrium" value. This value is higher for the larger fraction of active synapses, as expected, since there are more pathways by which the signal can spread throughout the network. Thus, it ranges from about a=0.2 (for f_s=0.2) to a=0.4 (for f_s =1.0). We notice that the relation is far from linear, but actually sublinear, implying that in a system such as the present one, due to the large number of units and interconnections, one needs only a small fraction of active synapses for the signal propagation. Conversely, if a large number of synapses is destroyed over time, this does not lead to catastrophic consequences for the operation of the neural net.

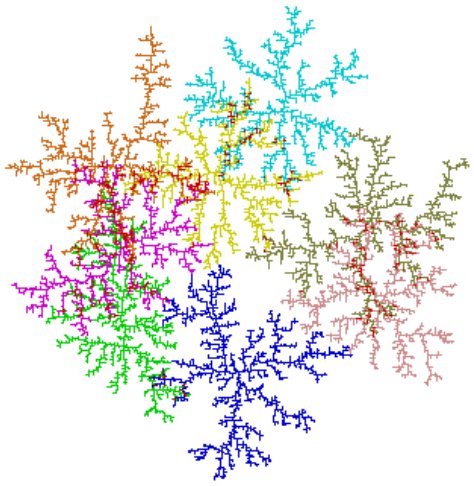


Fig. 2 A collection of eight DLA clusters built on a 350x350 lattice. The mean cluster size is 2200 sites.

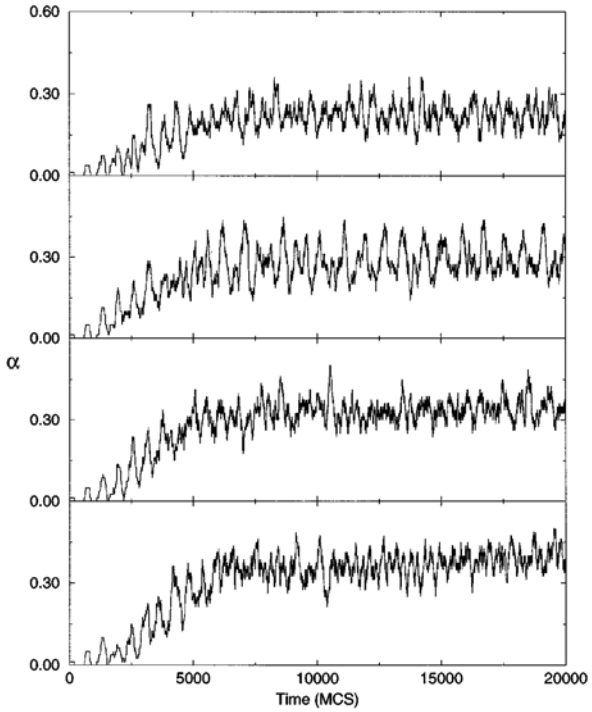


Fig. 3 Normalized (neuron) activity vs. time (in Monte Carlo steps – MCS). *RP*=300, *SD*=800, f_e=0.80. The four diagrams depict the percentage of the synapses that is used, *f s* , which is (bottom to top): f_s=1.0, 0.75, 0.50, 0.20.

We see that the activity time series is not fully periodic. However, there is obviously some "approximate" periodicity as the distance between the peaks is almost constant. This means that some new information may be revealed in it, and this is presented in the following paragraph.

A. Signal Analysis

In order to quantitatively interpret the periodicity of the activity signals presented above we performed an analysis of several of these signals, according to the method of Grassberger and Procaccia [10]. In this method the signal is treated as a time series for which a possible characteristic fractal dimension can be derived.

In Fig. 4 we plot the correlation function *C(l)* vs. *l* in log-log form for several different numbers of characteristic parameters of our system (*m)*. We see that for small *m* the slopes of the ensuing curves increase, but after *m*=5 (approximately) the slopes become constant. We performed the same analysis for some more such signals, resulting is similar curves, and similar fractal dimensions. The implication of this analysis is that for our system the minimum embedding dimension is approximately in the range of m=5-6, signifying that this is the number of parameters that is necessary to describe the system. This number most probably maps the total number of parameters used in the simulation, and thus it includes the refractory period, the synaptic delay, the percentage of synapses used, and the percentage of excitatory synapses (total of four parameters).

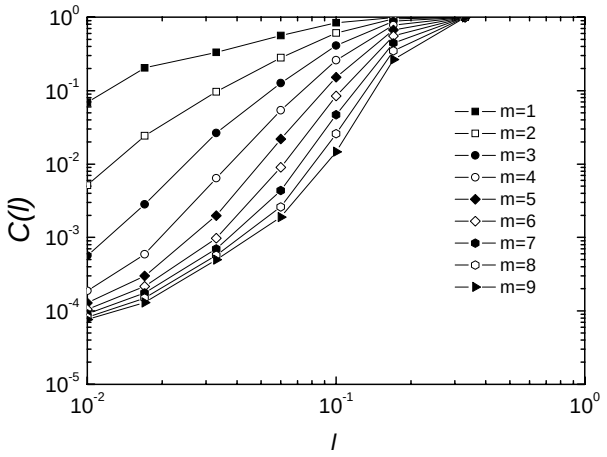


Fig. 4 The correlation coefficients *C*(*l*) vs *l* for the signal of Fig. 3, for different number of system parameters (m).

B. Network behavior with the loss of synapses

In this paragraph we are going to discuss in detail what happens when the synapses in the network stop functioning. We will do this by changing the value of the parameter f_s, the fraction of synapses used. The results are given in Figures 5-7. In all three figures we plot the network activity vs. f_s, but varying different parameters in each case. In Fig. 5 we vary the refractory period, in Fig. 6 we vary the synaptic delay, while in Fig. 7 we vary the fraction of excitatory synapses.

In all figures the behavior is the same. We see that there is a sharp drop in the activity around the value f_s=0.2-0.3, which must be a critical value or critical threshold for neural networks. Above and below this critical value the increase is almost linear, while there is a crossover between the two regions at the 0.2 or 0.3 value. This result implies that a neural network can sustain destruction of its synapses up to 70% or 80% maximum, and still operate normally. After this point there is a catastrophic degradation, leading to zero activity.

In Figure 8 we employ neurons of size 50 and 190 units,

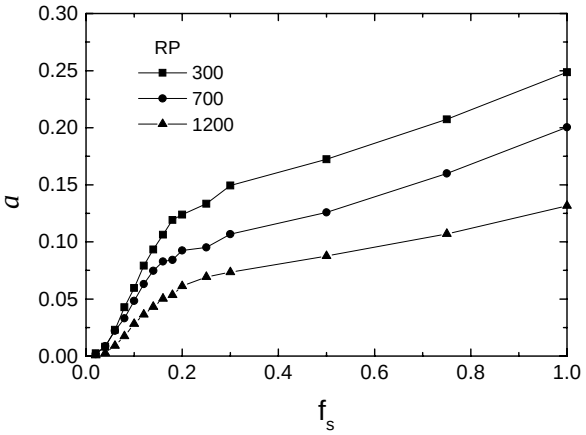


Fig. 5 System activity *a* vs. the fraction of the synapses used, f_s, for various values for the refractory period *RP*=300, 700, 1200. *SD*=800, f_e=0.8. Mean neuron size 2200, lattice 800x800.

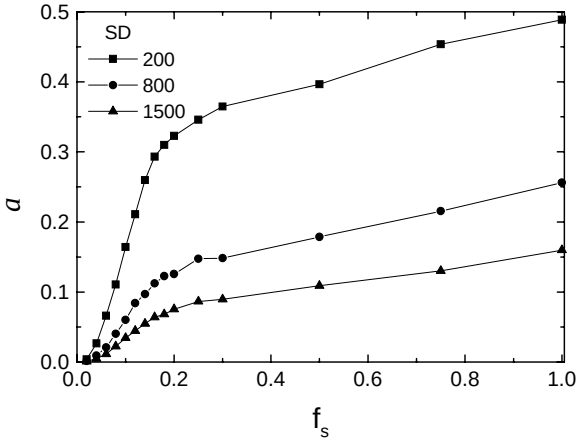


Fig. 6 System activity *a* vs. the fraction of the synapses used, f_s, for various values for the synaptic delay. *SD*=200, 800, 1500. *RP*=200, f_e=0.8.

which are 10 and 40 times smaller than the size (2200 units) used in the previous figures. We immediately observe that we do not have the catastrophic breakdown at the critical value, as we did earlier, but instead we have a rather smooth behavior. Thus, this is clear evidence that the internal neuron structure plays a dominant role in the appearance of a breakdown of the entire network, as it has been hypothesized before. Systems that use neurons as single point elements cannot exhibit this behavior.

The concept of disease in the CNS is unique because during the process of cell destruction the CNS reacts with a continuous remodeling of the dendritic structure of the remaining neurons in order to maintain its functionality (neuronal plasticity). Obviously, there is a critical point, which differentiates the healthy state from that of disease. This critical point is a function of many factors, where the most important is the number of the remaining functional cells and the number of synapses and, of course, the overall metabolic capacity of the neurons for the synthesis of the neurotransmitters. Other factors, such as the functionality of the blood supply system (arteriols and capillaries), etc. can be mentioned, but these almost always manifest themselves as decrease of cell number.

A disease that has been extensively studied in the last decades is Alzheimer's disease, which is well known that results in a tremendous loss of neurons. Microscopically this neuronal depletion is observed in the cerebral cortex, in the nucleus basalis of Meynert and Locus Coeruleus [11]**.** It is found that the same loss occurs in the substantia nigra of patients with Alzheimer disease, where the number of neurons was reduced in the range 97-78% of the control values from the medial to the lateral substantia nigra [12].

A typical example of neuronal depletion and the manifestation of a disease is the substantia nigra and the Parkinson disease [13]. It has been found that there is a loss of 91% in the lateral ventral tier of the substantia nigra and 71% and 56% in the medial ventral tier and dorsal tier, respectively [14]. The same authors suggest that the onset of symptoms starts at around 68% of cells in the lateral ventral tier and 48% in the caudal nigra as a whole [14].

Other authors have reported a 76% decrease of pigmented neurons in the entire substantia nigra in respect to control values [15]. The same is true using different methods of investigation. A correlation between single section and dissector counts for estimating the pigmented neurons in the pars compacta of the substantia nigra showed 75% and 55% decrease, respectively [16].

These are only a few of several dozen studies of similar nature that we are aware of. They all point to the same conclusion: patients with diseases have well above 50% of the constituent neurons destroyed, a conclusion in good agreement with our theoretical model. They are all experimental, over a wide time period, referring to several different brain sections, a wide variety of patients, all pointing to the same conclusion, as in the present study.

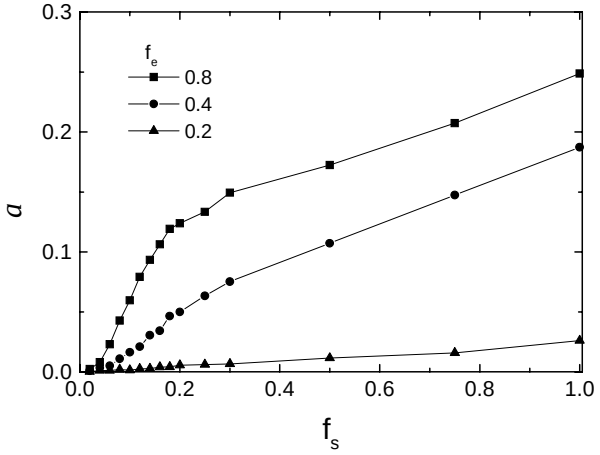


Fig. 7 System activity *a* vs. the fraction of the synapses used, f_s, for various values of the excitatory synapses ratio, f_e=0.8, 0.4, 0.2. *SD*=800, *RP*=300.

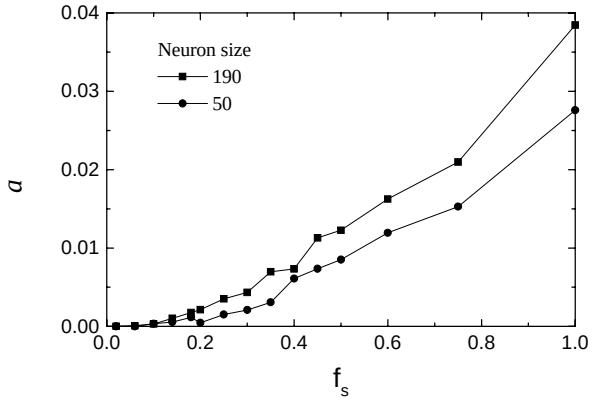


Fig. 8 Plot of network activity (*a*) vs. the percentage of synapses used (f_s). (a) with squares: Mean neuron size 190, Lattice 300x300, Distance between neurons 13 lattice sites, f_e=0.8, *RP*=100, *SD*=100. (b) with triangles: Mean neuron size 50, Lattice 100x100, Distance between neurons 5 lattice sites, f_e=0.8, *RP*=5, *SD*=5.

IV. Conclusions

Building a model to simulate the behavior of biological neural networks is a task extremely difficult if at all possible at the present time. So, one has to choose carefully the subset of parameters and functions that will go in the model, and of course should be very careful in the interpretation of the results of the model. Following this concept we have attempted to build a very basic model incorporating a set of functions and parameters for which it is known from physiology that they are very important in the dynamics of neural networks in living organisms. These characteristics include the presence of excitatory and inhibitory synapses, the propagation time in the synapse, the refractory period, etc. The main novelty of our model, is that the neuron is not treated as the smallest unit of the network, a mathematical point with no physical substance, but is built of thousand smaller blocks, giving it a ramified dendritic structure, which, as we have showed in the previous paragraph plays an important role in the signal transfer. Thus, we describe the geometrical structure of the neuron and subsequently the geometrical distribution of the synapses. The main missing feature of the model at this stage is that it maintains its structure unchanged during the simulation time, whereas we know well that there is a continuous remodeling of the dendritic neural structure. This feature, among others is a topic of a future study.

In the previous paragraphs we have shown that the activity of a net made of DLA structures produces a very complex, "chaotic"-looking signal, which, upon elaborate analysis is found to contain information about the magnitude of the system parameters. This signal is the response of the system to the random impulse presented. A detailed approach shows that it is far from random or white noise, but it quantitatively gives a measure of the ability of the neural net to sustain its activity. Every set of initial conditions that is used, leads to a characteristic fractal dimension, which is always monotonic, and within a given range. The numerical value of the fractal dimension gives information about the signal magnitude and other characteristics, making it a useful quantity to monitor.

The other important result is the behavior that the network exhibits with the loss of synapse. The loss of functionality is not linear as synapses are removed, but there is instead a catastrophic decrease of the functions, after a critical point of around 20-30% of active synapses (80-70% loss). The model agrees quantitatively with several experimental observations in the literature, and is also in agreement with studies done on various types of networks, including the Internet, the WWW etc., examining their vulnerability to attacks [17, 18]. It gives a first handle at distinguishing the degradation of synapses due to age vs. due to one of the well known diseases, such as Parkinson's or Alzheimer's. In the aging process one expects a linear loss of neurons/synapses. This loss occurs gradually, it affects very little the CNS, which continues to function satisfactorily until late in one's life. Therefore, if no disease has appeared the critical damage will occur, but it will occur quite late. On the other hand, if a disease has appeared, then, relatively early in one's life the symptoms of the catastrophic damage will become evident.

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