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Robustness in biological neural networks

Alkiviadis Kalampokis[a], Christos Kotsavasiloglou[b], Panos Argyrakis[a,*], Stavros Baloyannis[b]

[a] *Department of Physics, University of Thessaloniki, GR-54124 Thessaloniki, Greece*
[b] *Department of Neurology I, School of Medicine, University of Thessaloniki, GR-54124 Thessaloniki, Greece*

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Abstract

We present a computational model to study the robustness and degradation of dynamics on a network that includes a large number of units and connections between them. Each unit has an internal structure and it is connected to other units through contact points. These contact points correspond to the synapses of the biological neural networks. We monitor the network activity as a function of time, after we initiate an input signal at random in the network. We vary the number of connections (as a function of several properties of each connection), and observe that there exists a critical crossover value regarding the loss of connections below which all network activity decreases at a much faster rate than the expected normal loss. This crossover value is in the range of 70–80% loss. A similar critical value observed in biological neural networks may define the limit between the healthy state and the disease. Correlations between the computational and the biological model are discussed.

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Keywords: Neural network; Synapse degradation

1. Introduction

There has been considerable interest [1–4] recently in the properties of networks, mainly due to the emergence of scaling laws that have been discovered in a very large number of different types of networks examined, such as the World Wide Web, the Internet, the citation patterns in publications, the chemical network of a cell, and

* Corresponding author.
E-mail address: panos@kelifos.physics.auth.gr (P. Argyrakis).

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numerous other cases which range from the natural sciences, to social sciences, to medicine, or other complex systems that are encountered in daily life. The novelty brought by these studies is that many network characteristics, which seemed to be random, are now found to obey deterministic equations by which one can predict such important properties as the growth of the network, its robustness to external attacks, and other properties of interest. Nevertheless, all previous work has been limited to the geometrical (static) properties only, several of which are now well understood. However, one would like to extend this knowledge to dynamic properties, such as, e.g., signal propagation on a network. This task is considerably more complicated, because it involves the superposition of two stochastic but independent processes, namely, the random connectivity of the network nodes (static property) and the random signal diffusion (dynamic property). A model that addresses both of these characteristics, namely, the internal structure and signal transfer between the elementary units could possibly pertain to the biological neural networks.

Neural networks are made of elementary units (cells), the neurons, which are interconnected together in a complex pattern with a definite structure, resulting in a picture that involves very rich dynamics, as it depends on a multitude of parameters. They form the basis of the central nervous system (CNS). The points of physical contact between the neurons are the so-called synapses. These are the equivalent of a connection between two nodes in a generalized network. It is through the synapses that the electrical signals propagate through the networks. It is now well understood that it is the collective character of the neural units together with their connectivities that make all functions of the living organism possible. Isolated neurons or collections of neurons without interconnecting synapses can perform no function at all. There are several physical and chemical processes occurring at the synapses which determine indirectly the functions of the network as a whole. Naturally, any degradation of the synapses, or total destruction of them, will immediately reflect on the signal processing through the neural network, and its robustness. But it is well known that such degradation and loss routinely occur with advancing age in the CNS and the human brain. This loss occurs without any manifestation of a disease. It is strongly believed that the rate of loss of cells in this case is linear. However, in the presence of a disease there is a neuronal loss with a much faster rate of cell destruction, e.g. exponential. In this regard there exists experimental evidence [5], that normal aging is accompanied by a gradual loss of neurons, whereas a very severe decrease appears in patients with a neural disease, regardless of age.

Until now there is no clear relationship between the loss of neurons and the occurrence of the first disease symptoms. In the case of the substantia nigra there are no clinical signs until at least 50% of the nigral neurons are lost [6]. Similar findings exist for other cerebral regions. In order to improve our understanding of the early stages of nervous system diseases, we believe that it is imperative to investigate the details of such relationship, between the neuronal loss and the impairment of the nervous system functions. In particular, a crucial question is, whether this relationship is linear in the entire range or if there is some critical threshold, beyond which there is a characteristic difference and a very fast degradation. This 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? 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 ultimately help in the search for a cure.

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. There is a total lack of a theoretical basis for such relationship. The present paper attempts to shed some light in this direction by utilizing a complex computational model recently developed [7]. We map the brain function to a quantity called network activity, a (see below), and investigate this activity as a function of the neural loss and other net parameters.

Since we know that the connectivity pattern between the neurons is very complicated, it is reasonable to assume that this relationship is not simply linear. Two neurons can be connected at several different points via different synapses. Thus, when a single synapse is removed this does not necessarily preclude any connectivity between these two neurons. Assuming that this is true we see that it is very important to treat the individual neurons not as simple binary entities, but one is forced to take into account their internal structure. This is exactly what we do in the present study. Each neuron (cell) is made of a very large number of parts, as a real one is. We believe that if we consider the neuron as one single unit, as practically all theoretical models until now have done, that it is difficult to address our basic question.

2. The model

We recently [7] introduced a computer simulation model of a neural network that is based on a collection of dendritic structures, the so-called diffusion-limited aggregates (DLA). These entities originated and are derived from solid-state physics [8], 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 [9] drawing of a Purkinje neuron. We can see that each unit possesses a dendritic nature. The only related study until now utilizing similar structure is that of Caserta et al. [10]. A collection of these units placed randomly in space at high densities make up an entire neural network. Such a network is shown in Fig. 2. 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. Because they are closely packed there is a large overlap between them, especially on the branched dendrites. These overlaps can be thought of being the synapses. In the model a synapse can be declared active or inactive at will, and this is one of the external parameters that we control. Each synapse is a one-way channel, meaning that the signal can be propagated only along one of the two directions. In order for this to happen the value of the signal must be greater than the synapse threshold, θ. Thus, each synapse is assigned a θ value. The procedure of the signal transfer from one unit to the next is not instantaneous, but the

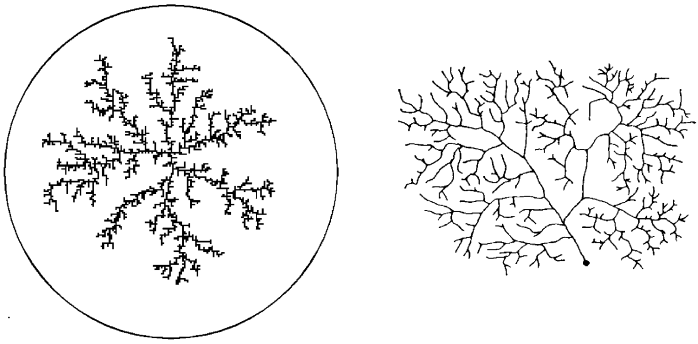

Fig. 1. (a) A simple isolated DLA cluster, and (b) a camera lucida drawing of a typical Purkinje neuron.

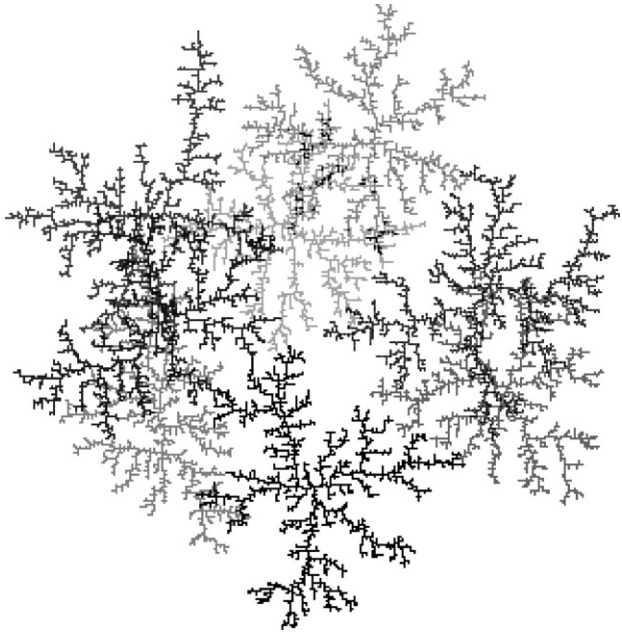

Fig. 2. A collection of eight DLA clusters built on a 350×350 lattice. The cluster mean size is 2200 sites.

transmission is delayed for a certain time, called the synaptic delay, *SD*, as it is well known that the signal transfer in the synapse is of the order of 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.

Our interest is focused on the details of 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. This time unit is arbitrary, typically in computer simulations it is called one (1) Monte-Carlo Step (MCS). While it could be related to actual time (e.g. ms) in a real system, at this stage we will not attempt to do so. At any rate, this timing is the smallest time increment required for these processes, and as such it is probably much smaller than the time it takes for a neuron to remodel its structure. 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 again and thus again and time advances up to a certain limit.

3. Results

Initially, we investigate the connectivity properties of the generated structures. We do this by using the parameter f_s, which is the fraction of active synapses out of the total number of sysnapses. Thus, here $0 < f_s < 1.0$, and it is treated as a parameter. An $f_s = 1$ value means that all synapses are active (allowed), while at the other limit an $f_s = 0$ value means that neurons are not connected at all, as no synapses exist. Following Ref. [3], we define as S the fraction of neurons that are contained in the largest cluster formed. Thus, $S = 1$ when $f_s = 1$. Additionally, when a large number of the connections is cut-off, then we see that we have the formation of small isolated clusters (islands). We also define here as $\langle s \rangle$ the average size of these isolated clusters. We calculate these quantities for the entire f_s range, and the results are shown in Fig. 3. We see that S initially starts at 0, and pretty fast reaches a constant value of 1, meaning that practically all units quite fast are part of the largest cluster. No small clusters exist, but only in the very beginning. Complementary to this is the behavior of $\langle s \rangle$ in the same figure. The peak observed in the mean size of the isolated clusters indicates a critical point at about $f_s = 0.01$ implying the existence of a point below which the network loses its connectivity, while it is quite stable at f_s values greater than that of the critical point. We note here that this analysis is based only on the spatial properties of the model and thus, this critical point reflects only static characteristics of the network. No comparison can be made at this point between the behavior of the model system and actual biological neural networks. These results are in excellent (qualitative) agreement with the model of (Ref. [3], Fig. 3), even though the networks are quite different. Nevertheless, their connectivity properties are quite the same. This point implies that the connectivity patterns are quite general for all networks, regardless of their detailed structure.

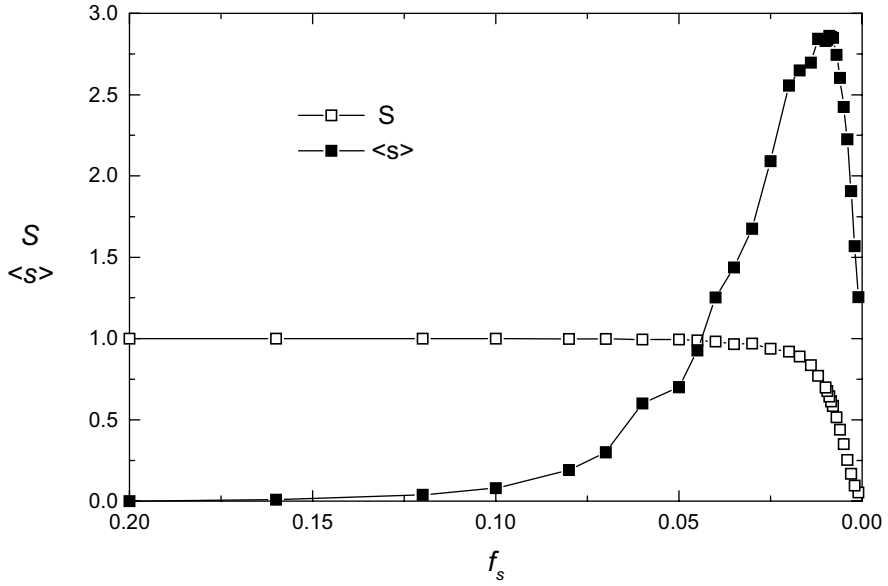

Fig. 3. Network fragmentation under random failures of neuron synapses. The relative size of the largest cluster (S) and the mean size of the isolated clusters ($\langle s \rangle$) are plotted as a function of the percentage of the network synapses used (f_s). Note that the 0 of the x-axis is on the right of the plot.

We next monitor the activity, a, of the entire network, which is defined as the ratio of (active neurons/total number of neurons). An active neuron is one that carries signal in any part of it. Thus, $0 < a < 1$ at all times. We examine in detail the network activity as a function of the fraction of active synapses, f_s. We saw above the two limiting cases of $f_s = 0$ and 1. Our interest now is in the intermediate range. We cover the entire f_s range in detail. The results are given in Figs. 4–6. In all three figures we plot the network activity vs. f_s, but varying different parameters in each case. In Fig. 4 we vary the refractory period, in Fig. 5 we vary the synaptic delay, while in Fig. 6 we vary the fraction of excitatory synapses. In all these figures the behavior is quite similar. Starting at the right of each diagram we see that initially there is a linear decrease of a, up to a certain value which is around the value $f_s = 0.2$–0.3. Then, at this point starts a much sharper decrease of a, eventually leading down to zero. This intersection point of the two linear segments constitutes a crossover, whose value must be a critical value or critical threshold for such networks. Above and below this crossover value the decrease is linear, but with very different slopes in the two regions. The crossover between the two regions is around the value $f_s = 0.2$ or 0.3. This result implies that a neural network could sustain destruction of its synapses up to 70% or 80% maximum, and still operate normally. After this point there is a crossover leading to a degradation, and subsequently to zero activity. Note that this crossover behavior characterizes the dynamics of the signal transfer and it is qualitatively and quantitatively different than the crossover behavior of S and $\langle s \rangle$ of Fig. 3, which was characteristic of the geometry (static) of the clusters formed.

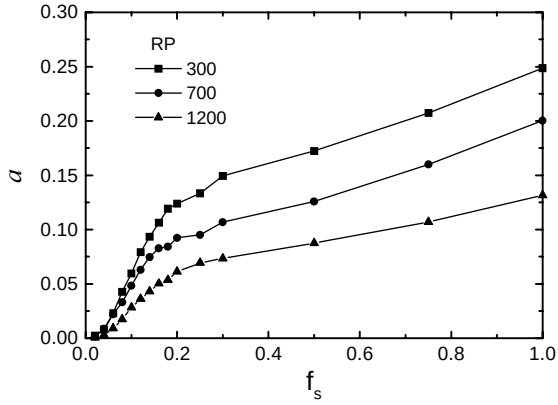

Fig. 4. System activity a vs. the fraction of the synapses used, f_s, for various values for the refractory period $RP = 300, 700, 1200$. $SD = 800$, $f_e = 0.8$. Mean neuron size 2200, lattice 800×800.

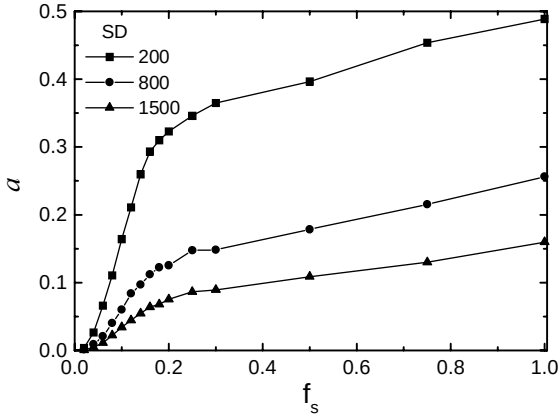

Fig. 5. System activity a vs. the fraction of the synapses used, f_s, for various values for the synaptic delay. $SD = 200, 800, 1500$. $RP = 200$, $f_e = 0.8$.

In Fig. 7, we employ neurons of size 50 and 190 units, 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 crossover 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.

A direct comparison between this (or other) computational model and a biological one it is not possible at this stage. This is because of the differences in the complexity of each system and our limited knowledge about the functions of the synapse. However,

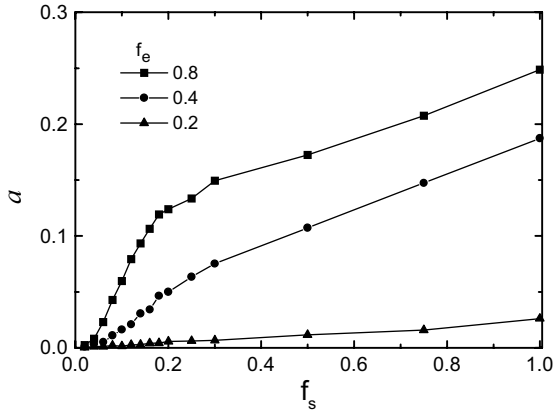

Fig. 6. System activity a vs. the fraction of the synapses used, f_s, for various values of the excitatory synapses ratio, $f_e = 0.8, 0.4, 0.2$. $SD = 800$, $RP = 300$.

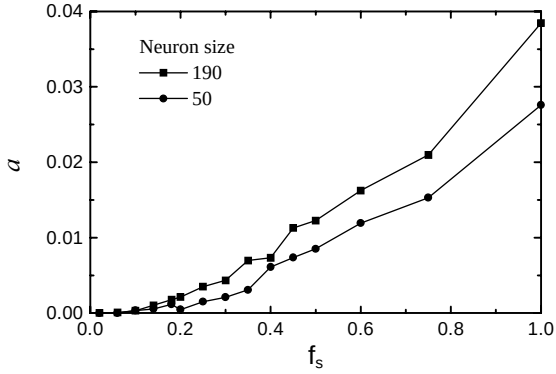

Fig. 7. Plot of network activity: a vs. the percentage of synapses used (f_s). With squares: Mean neuron size 190, Lattice 300×300; distance between neurons 13 lattice sites, $f_e = 0.8$, $RP = 100$, $SD = 100$. With circles: mean neuron size 50, Lattice 100×100; distance between neurons 5 lattice sites, $f_e = 0.8$, $RP = 5$, $SD = 5$.

there are interesting similarities that must be underlined. The critical point for the appearance of the crossover behavior observed in the simulation may correspond to the borderline between health and disease in the CNS. 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 crossover point is a function of many factors, where the most important is the number of the remaining functional cells and the number of synapses together with the overall metabolic capacity of neurons for the synthesis of neurotransmitters. Other factors, such as the functionality

of the blood supply system (arteriols and capillaries), etc., are very important, but these almost always manifest themselves initially as a decrease of the metabolic functionality, and then as neuronal loss.

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's disease. 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 [13]. 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 [13]. Other authors have reported a 76% decrease of pigmented neurons in the entire substantia nigra in respect to control values [14]. All these studies point to the same conclusion: patients with neural diseases have well above $\frac{1}{2}$ of the constituent neurons destroyed. They are all experimental, over a wide time period, referring to several different brain sections, a wide variety of patients, pointing to the same conclusion, as in the present study.

The model presented here has attempted to include most of the principal characteristics of the CNS. This includes the geometrical structure of the elementary unit and subsequently the geometrical distribution of the synapses, the presence of excitatory and inhibitory synapses, the propagation time in the synapse, etc. One drawback of the model at this stage is that it maintains its structure intact during the simulation time, whereas we know well that there is a continuous remodeling of the dendritic neural structure. But as mentioned earlier, our time domain is too short for such remodeling to take place. Additionally, the synapses in this model were randomly created and not as a consequence of dynamic interactions between neurons in response to particular stimuli, which is what happens in reality. Our main hypothesis is that the brain exhibits a similar crossover behavior in its functions as the model, all depending upon the structure of the neurons and their synapses. In other words, the brain has an inherent resistance to the manifestation of diseases due to its geometrical structure.

4. Conclusions

Summarizing, we have presented a theoretical neural net model, and studied its robustness as a function of the synapses present. The model itself is made of DLA clusters that resemble neural cells, and as such it is only a zeroth-order approximation. We find that such systems undergo through two different regimes when the number of their synapses is decreased. First, there is a linear decrease of their functions. This decrease goes up to a certain point, at which time starts a second regime, in which there is sharp change in the rate of this decrease, the rate (slope) becoming much

faster. The crossover point where this occurs is around 20–30% of active neurons (80–70% loss). In order for this model to become of functional importance, it is necessary to accept that neurons have a complicated internal structure approaching in nature the real one. The model agrees with several experimental observations in the literature. It gives a first handle at distinguishing the degradation of synapses due to age vs. 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 throughout the entire range. This loss occurs gradually, it affects the CNS very little, 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 damage will become evident, as the organism goes through the crossover change in the rate of loss.

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