

Multiple Sclerosis plaques on nervous pathways: A computational model using Neural Networks

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Abstract. This work presents a computational model of Multiple Sclerosis (MS) plaques affecting the normal axon transmission in nervous pathways. Some biological features observed in the axon membrane are considered, namely the local dynamics of the internode interaction, and the nature in which the axon sheathing is organised within and among internodes. The idea behind the model is to utilize an artificial feed-forward neural network composed of threshold units, representing two areas of the nervous system connected by long-range myelinated axons, i.e. a nervous pathway. This pathway is then subjected to the effects of artificially generated MS-plaques. The resulting delays in the signal propagation are made possible by changes in the conduction regime of the internodes, whose insulation was affected by the MS-plaques. The reductions in velocity conduction were then utilised to discard some axons, which were considered to be failing in the delivery of their signals within a varying time window, this measured in the target area. Finally, the consequences of plaques growth were investigated. The model at hand did not consider temperature or ectopic stimulation and assumed only single spikes in the network for each stimulus. The computer simulations revealed that (a) transversal damages to the pathway are generally more devastating to neurocommunications than longitudinal destruction to the myelin, and (b) increases on the plaques size (i.e. plaques growth) cause the pathway to be just less efficient.

Keywords: Multiple Sclerosis, MS-Plaques, Neural Networks, Computer Simulations

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1 Background

1.1 Nervous System, axons and nervous pathways

The nervous system (NS) is an impressive result of evolution and is largely responsible for the survival and adaptation of individuals to their natural environment. Per Brodal describes the nervous systems in his seminal book [1] as a complicated highly organised network for communication and information processing.

In order to have all its several structures interconnected and consequently to have all its functions performed, the nervous system utilises a massive number of different connection routes, i.e. pathways. Nervous pathways are also utilised to send or receive signals to/from the muscles and visceral organs.

Regarding neurocommunications, the existing mechanisms are of electrical and chemical nature [12]. Nevertheless the latter is predominant in almost all body's biological systems, both communication mechanisms are omnipresent in the nervous system. These mechanisms interact in a very efficient and effective manner.

From a histological perspective, the NS is composed of two types of tissue, the neuronal and the glial tissues. The first performs all signal processing and computation and the latter is responsible for all support and protection.

Axons, which are projections of the neuronal soma, are the main constituent of the nervous pathways. Regarding sheathing, axons can present or not a protection layer composed of a lipoprotein called myelin. Functionally, this myelin sheathing (a) speeds up the transmission of the neuron's action potentials, while it saves in the axon diameter for equivalent results, and (b) avoids ectopic discharges within the propagation matter. Figure 2 shows the continuous propagation of the signal along an unmyelinated axon, as opposed to the saltatory manner observed in myelinated axons, refer to figure 1.

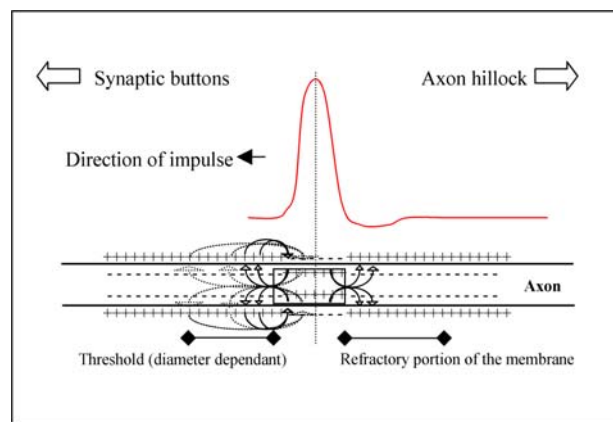


Figure 1: Signal transmission in an unmyelinated axon

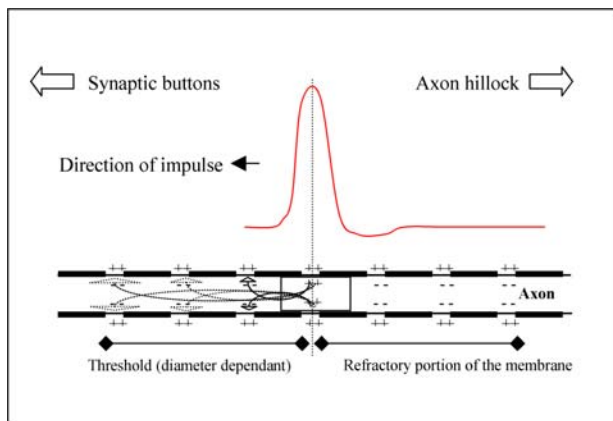


Figure 2: Signal transmission in a myelinated axon

These two forms of signal propagation are explained by three properties presented by the axonal membrane, namely (a) to offer resistance to electrical current flow, (b) to accumulate electric charges, and (c) to present active electrochemical permeability.

Equations 1 and 2, describe how the axonal membrane responds symmetrically either in time (π) or space (λ), in order to present changes of 63 % after stimulation, i.e. $1 - \frac{1}{e}$. The first equation, time constant, represents the delays of the membrane to hyper/hypo-polarisation. The second equation, space constant, represents the amplitude loss in the signal from the peak value when the distance from the signal source increases. Both constants are important for understanding the signal conduction because they determine ‘how quick’ will be the membrane response, and ‘how far’ will be the excitability threshold of the membrane. Note that the time constant is only dependent on the membrane resistance (R_m) and capacitance (C_m), while the space constant depends on the quotient membrane resistance (R_m) over the internal resistance (R_a).

$$\pi \approx R_m.C_m \quad (1)$$

$$\lambda \approx \sqrt{\frac{R_m}{R_a}} \quad (2)$$

Finally, the Goldman-Hodgkin-Katz (GHK) constant field equation (see equation 3) explains how electrical signals (V_m) can be evoked and conducted along the axonal membrane. These potentials are generated based on various ionic concentrations change (e.g. Sodium, Potassium, and Chlorine). These ions move *in* and *out* through the membrane via special ionic channels, referred as voltage-gate channels.

$$V_m = \frac{R.T}{F} \ln \frac{P_K[K^+]_{out} + P_{Na}[Na^+]_{out} + P_{Cl}[Cl^-]_{in}}{P_K[K^+]_{in} + P_{Na}[Na^+]_{in} + P_{Cl}[Cl^-]_{out}} \quad (3)$$

1.2 Multiple Sclerosis Plaques

Multiple Sclerosis (MS) is one of the many degenerative diseases that affect the nervous system. In MS a gradual process removes the sheathing of the myelinated axons. This condition is characterised by disseminated inflammatory lesions to the myelin sheathing of nerve fibres, i.e. the MS-Plaques [9].

MS-plaques are ‘hallmarks’ of the Multiple Sclerosis disease and are ubiquitous on various nervous pathways of MS patients [4]. This means that any part of the electrical insulation of the axons within the NS can be put into disruption.

Although the MS pathogenesis is not fully understood, some clinical evidences point out that MS aetiology maybe due to disturbances of the immune system [5]. Some other possible acknowledged causes that may give rise to the disease are prior viral infection, genetic inheritance and environmental factors [9]. This work will not address the unsolved medical aspects of MS, especially those concerning therapy.

The direct result of MS-plaques action is loss or reduction in the signal amplitude and velocity between any two communicating areas within the nervous system. Further consequences can be bad synchronisation, de-coupling of cortical areas and other communication related problems.

From an engineering perspective, one can assume that these inflammatory processes are solely communication problems between different areas that need to ‘converse’ through a given path.

The demyelinating processes cause a reduction in the quality of the membrane insulation of the axon. Consequently, the transmission speed of the longitudinal current on the axon is markedly slowed down. If the demyelination process continues the membrane physical properties change drastically and irreversibly. This noxious phenomenon brings out all the inconveniences of unmyelinated axons, i.e. slowness of signal propagation leading to a possible decoupling of the two areas. In extreme cases, inflammation and demyelination can even totally block the communication between the two previously communicating cortical regions.

1.3 Artificial Neural Networks

Artificial Neural Network - ANN, also called connectionist models, is a prominent sub-field of Artificial Intelligence. It normally uses distributed representation of the data. The models are able to acquire, keep and use the non-linear relations between input and outputs, i.e. the available knowledge about tasks to be performed.

Neural Network methods are greatly inspired by the nervous systems of animals, and represent nowadays one of the most important sets of techniques for modelling and solving real world problems [6].

In addition to the distributed manner in which knowledge is stored, the intelligent learning algorithms existing in ANN models confer features such

as robustness, generalisation ability (i.e. learnability), and adaptability (i.e. plasticity).

2 Model

The model presented here incorporates into an artificial neural network some of the biological features observed in the axon membrane and described in previous sections. The objective was to better understand the anomalous and complex communication behaviour presented by a nervous pathway connecting two distinct cortical regions, when it is affected by MS-plaques - see also [3] [2]. Previous work such as Koles72 [8] just addressed single nervous fibres, this, an oversimplification of the problem.

The initial aspect devised in the proposed model was to include into a multi-layer neural model the physiological transmission delays observed when an action potential propagates in a healthy axon. It is important to highlight that most of the widely used artificial neural networks, including MLP, assume an ideal axonal propagation, i.e. signal propagation without delays. In most cases this can be assumed with no further problems. However, in the application at hand such assumption is no longer possible because delays are precisely the aspect disrupted when MS-plaques impinge and damage long-range pathways.

Among all considered biological features, two are of great importance for tackling the current problem, namely (a) the local dynamics of the internodes interaction, and (b) the nature in which the axon sheathing is organised. Interestingly, the inclusion of these two features into the model caused a reduction in the complexity and the volume of computation required. The first of the two mentioned features refers to the kind of activity in a myelinated axon membrane. These activities are constituted imminently of local interactions that occur in the vicinity of the Ranvier nodes with signal transmission orientated towards the synaptic terminations. This means that the activation of one node is the main cause of triggering activation along the internodal region of the consecutive Ranvier node. Computationally, this also means that the propagation of the action potentials along a single axon can be processed in a discrete and sequential manner. The second feature mentioned before also allowed discrete and sequential simulations by varying the membrane insulation effectiveness. In other words, the model allows transversal axonal resistances to be simulated in either binary or in a more complex manner.

When sclerotic plaques affect axons, the myelin layers are likely to be removed all at once within the affected internode. Here partial and total damage to the layers are simulated, i.e. homogeneous and inhomogeneous damage to the myelin among different part of the axonal insulation.

The latter part of this work deals with plaques growth, i.e. the proposed model was also used to foresee the noxious effect to the neighbouring internodes of the expansion in the plaque sizes. It was assumed that the plaque size increases occurs chiefly along the same axon rather than to distant ones.

Figure 3 presents an schematic view of long-range connections between two

cortical areas that are subject to MS-plaques. The areas affected by MS lesions, indicated by grey ellipses, have distinct degrees of impact on slowing down the signal propagation, i.e. different inflammation epicentres r each of which is proportional to the density of the damage to the pathway sheathing.

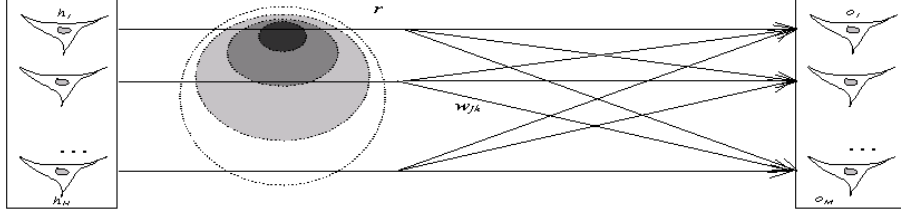


Figure 3: Schematic view of a long-range nervous pathway and MS-Plaques

The explanation and consequences of the delays are expressed by equations 4, 5, 6 and 7. The first equation represents the output of the network (i.e. target area) computed as the forward path of the widely known Multi-layer Perceptron architecture, this proposed in 1986 by Rumelhart, Hinton and William in the famous book PDP [10]. The idea behind this network was first proposed by Paul Werbos in 1974 [11]. The second equation specifies a criterion to exclude the axons that ‘fail’ to deliver their signals within an expected time-window. In such criterion, the failing axons have their contributing signals discarded of the overall sum when the corresponding transmission time (t_j) fits without the time window measured in the target area. This time window is variable, and was considered in the simulations linearly proportional ($\tau \geq 1$) to the ‘normal’ transmission time of the considered axon \bar{t}_j , see equation 6.

Finally, equation 7 shows how a particular axon transmission time is calculated. Where t_{node} is the transmission time for one internode, and d_{node} is the additional delay imposed or not, to it by MS-Plaque lesions.

All together, the assumptions above are believed to accommodate the important physiological fact of the MS disease, i.e. the variable slowness of evoked behavioral function. Also, the way the model was conceived contributes to maintain low its computational complexity, whereas keeps high its plausibility.

$$O = \left(\sum_{k=1}^M \sigma \left(\sum_{j=1}^H (h_j \cdot w_{jk} \cdot \mu_j) \right) \right) + \epsilon \quad (4)$$

$$\mu_j = 1, \text{ iff } (t_j \leq T_{window}) \vee \mu_j = 0, \text{ otherwise.} \quad (5)$$

$$T_{windows} = \pm(\bar{t}_j \cdot \tau), (\tau \in \mathbf{R}_+^*) \quad (6)$$

$$t_j = \sum_{node=1}^n t_{node} \cdot d_{node} \quad (7)$$

3 Simulations

3.1 Overview

Prior to the model simulations two steps were performed, namely (a) generation of a lesion-like data set and (b) generation of synaptic-like information of the simulated pathway. The first data set was generated to produce the delays on the signal propagation when simulating an affected nervous pathway. The second data set generated was used to depict an arbitrary non-linear relationship of distinct cerebral regions, when those communicate one with each other via long-range myelinated pathways. This data set (network synapses) was obtained by training the modified Multi-Layer Perceptron (MLP) network utilised, with the backpropagation algorithm.

The simulations were organised in three distinct groups. In the first group, comparisons between the discrepancies of control and abnormal predicted values were proceeded. The second group, involved the same kind of comparison, as well as a varying a time-window on the target cortical area for including or excluding delayed signals. The latter simulations carried out here, different from the previously described two, analyses delays on signal transmission when the MS-lesions considered present increases in their severity, i.e. size.

The speed of transmission of the normal myelinated axons was calculated using a linear approximation, which was proportional to the axon diameter. The considered value was 6 *m/sec* for each μm of the axon diameter [7].

3.2 MS-Plaque: lesion-like data generation

In order to observe the delays on the signal propagation in an affected nervous pathway it was necessary some numerical values that could represent the MS-Plaque lesions. This was achieved by generating various matrices each one containing an specific MS-plaque layout.

The elements of these lesion-like matrices symbolize the internodes of all axons constituting the pathway. In other words the lines and columns of these artificially created ‘plaques’ represent the axons and the internodes of a given pathway, some of which, defective in function.

The plaque load configuration was generated by a fully parameterized interface constructed to produce MS-lesions like of various kind. The most important parameters of this routine are (i) the percentile of axons affected; (ii) the percentile of internodes affected within a single axon; (iii) the severity of the demyelination; (iv) the spatial distribution pattern of the plaques; and (v) the uniformity of the plaques within the pathway, assuming two possible values: uniform or non-uniform. Note that all these parameters can be deduced from currently available medical imaging methods.

Three spatial configurations were devised for the generation of the plaques namely, (a) spatially grouped, (b) moderately grouped, or (c) randomly scattered. Figure 4 contains examples of these distinct kinds of generation regimes. In the figure, darker shades of the gray scale represent more severe lesions.

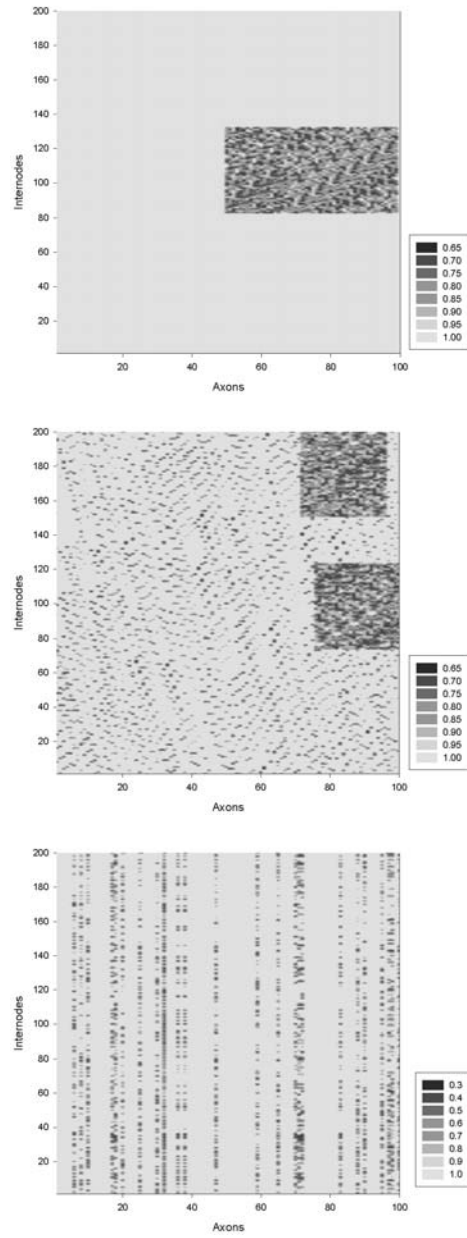


Figure 4: Generated MS-plaque loads: (a)Spatially-grouped (b)Moderately-grouped (c)Scattered

A total of 24 distinct plaques-like, eight in each generation regime, were utilised in all three simulations to follow. The investigated features in the generated plaque loads, were varied in a two-step factorial design as seen in table 1. The columns severity, axons and internodes affected refer to the percentage of the absolute values calculated on an axon that is 300 *mm* long, have 25 myelin layers, and has internodes of 1.5 *mm* long. All of the plaque loads generated, in a way, affect differently the ‘physiology’ of the long-range pathway and consequently the transmission time. Thus, the abnormal values observed in the target cortical area are result of distinct configurations of these MS-plaques. In figure 4, the top views (a),(b), and (c) correspond to the generated plaque loads 7, 16 and 18 of table 1.

<i>Plaque load</i>	<i>Generation regime</i>	<i>Severity</i>	<i>Axons affected</i>	<i>Internodes affected</i>	<i>Lesions produced</i>
1	S-grouped	70%	25%	25%	1250
2	S-grouped	70%	25%	50%	2500
3	S-grouped	70%	50%	25%	2500
4	S-grouped	70%	50%	50%	5000
5	S-grouped	35%	25%	25%	1250
6	S-grouped	35%	25%	50%	2500
7	S-grouped	35%	50%	25%	2500
8	S-grouped	35%	50%	50%	5000
9	M-grouped	70%	25%	25%	1244
10	M-grouped	70%	25%	50%	2485
11	M-grouped	70%	50%	25%	2490
12	M-grouped	70%	50%	50%	4973
13	M-grouped	35%	25%	25%	1132
14	M-grouped	35%	25%	50%	2487
15	M-grouped	35%	50%	25%	2169
16	M-grouped	35%	50%	50%	4978
17	Scattered	70%	25%	25%	1245
18	Scattered	70%	25%	50%	2496
19	Scattered	70%	50%	25%	2487
20	Scattered	70%	50%	50%	4974
21	Scattered	35%	25%	25%	1145
22	Scattered	35%	25%	50%	2488
23	Scattered	35%	50%	25%	2485
24	Scattered	35%	50%	50%	4982

Table 1: Parameters utilized for lesions generation

3.3 Pathway: synaptic-like data generation

This second preparatory step aims to create a realistic environment for the simulations to be carried out here. By that, the authors mean that the simulated pathway necessitates of artificial axons and their associated synapses. To produce such an environment, a MLP network is used and trained to learn the non-linear relationship of communicating cerebral regions.

This routine is executed only once, as the non-linear relation learnt by the network and the synaptic-like data are assumed to be constant throughout all simulations. As a consequence of that, the network output should be the same unless external factors cause disruption to the network functioning. And this is exactly what happens when the MS-Plaque data is applied to part of the axons. Later on, these observable disruption are measured and compared.

The selected network topology for all the simulations was kept as simple as two input cortical areas, connected via 100 ‘myelinated’ axons to a third area ‘distant’ from the others. Each axon has the same physical characteristics specified in the previous sub-section.

Eight arbitrary input-output pairs were used as stimuli (i.e. training/testing patterns) to the network. The generated plaques effects are then tested when this set of eight patterns is presented to the network (i.e. simulated pathway).

3.4 Comparing control and abnormal predicted values

The common procedure among all simulations is to compare the network output when control data are used (i.e. no plaques), to predictive values produced by the MS-plaque model when plaque-like data are utilised.

In the particular case of the first group of simulations the aim is to observe the discrepancies between control and abnormal predicted values. Note that inputs to all topologies tested here were the same, and the output results for the normal case were used as the baseline.

Figure 5 shows the square errors between control and abnormal outputs for all testing patterns. The thick solid line represents control results and the other lines represent output errors for the various tested MS-Plaques, i.e. the averages among various groups of features investigated. Note that the number of affected axons and internodes, and the severity of the plaques are the grouping criteria used for plotting the graph rather than the overall regime of generation. The chart also shows that there are no other natural candidates for generating output differences than (a) the absolute number of damaged internodes, (b) percentages of internodes affected and (c) average severity of the plaques. Among all these factors no one seems to be as influential as the percentage of affected axons. To observe this, refer to the sub-title of the same figure, specifically when the percentage of affected axons assumes the tested value of 50%. Conversely, the graph also shows that when this feature assumes the other possible value tested, i.e. 25%, the output errors fall to the lowest level possible.

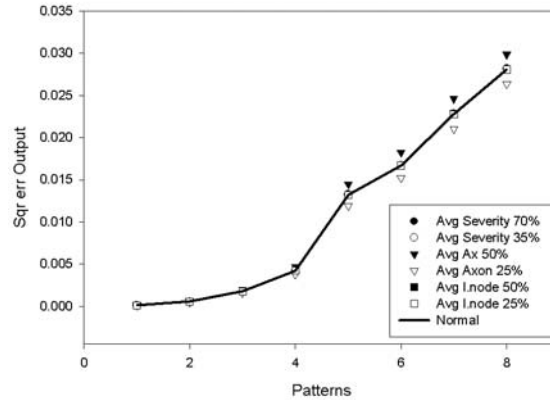


Figure 5: Output error under various MS-Plaque configurations

3.5 Comparing control and abnormal predicted values considering varying time-window

This group of simulations involves the same kind of comparison presented before, i.e. comparison between control and abnormal output of the network. However, on this occasion a time-window was used on the target cortical area for including or excluding axons that have their signals delayed more than expected.

The objective of the present set-up is to investigate how the output values produced by the MS-plaque model change when the generated plaques are simulated using a variable time window to monitor the number of axons that fail to deliver their signal to the target area. Thus, given extra time it may be possible that some failing axons can achieve their goal that is of delivering signals to the output. Consequently, the output error is likely to be reduced.

The two graphs presented in figure 6 show how additional processing time can reduce (top) the number of failing axons and (bottom) the output square error to all the plaques simulated. In other words, the graphs show how the ‘pathway’ behaves when ‘plaques’ damage it, requiring now more time to transmit the necessary signal.

3.6 Simulation of MS-Plaque growth

The latter simulations presented here, different from the previous two, analyses the impact in the signal transmission (i.e. delays) when some of the MS-plaques utilised present size increases. The embedded idea here is of predicting impacts on neurocommunications of progressive growth of MS-plaques. Ultimately, this progression is responsible for most of the observable clinical effects characteristic of the disease. The present simulation also incorporates the previous notions

of varying time-window and the comparison of normal and abnormal outputs.

Before discussing the results a new concept needs to be looked at, that is plaque growth regimes. The need for defining growth regimes for the plaque arose when the algorithm that calculates the ‘new’ plaque load was to be implemented. The problem was then how to implement changes to the plaques so they were characterised as having increased their damaging features on the myelin.

At the time of writing this work, three distinct methods had been devised for the plaques to evolve. The first devised mode of plaque ‘growth’ was produced (i) by modifying the severity of individual damages to the internodes leading to decreases in the axonal overall transmission speed; a second growth regime was produced when (ii) new internodes of the same already affected axons were induced to be also affected (longitudinal growth). This means that if internodes of affected axons without any damage to its myelin are located within the vicinity of an pre-existing plaque, those are likely to become affected. The last devised growth regime uses the same principle as explained before, but this time it was applied to (iii) neighbor axons (i.e. transversal growth). Although not necessarily the most plausible of the three devised growth regimes for the MS-plaques, the first case was the one selected to illustrate the idea of having plaque load evolving through time.

Figure 7 presents three top views of plaque load 16, under different stages of evolution, growth-wise. Darker colors indicate 10%, 20%, and 30% of increase in the damage impinged to myelin. Compare them to the initial configuration presented in figure 4 (b) for this same plaque load.

The simulation results for all plaque loads and three stages of growth investigated (10%, 20%, and 30% of size increase) show that the number of failing axons and the output square error exhibit a clear progressive tendency to be zeroed when more time is allowed for the pathway to process. Note that advanced stages of plaque growth only require more time for convergence. Figure 8 shows this phenomenon observed as the decreasing number of failing axons. And figure 9 accounts for the output square error. Both figures refer to plaque load 16, and analyze decreases as a function of time.

Physiologically this effect could be interpreted as what happens with MS patients, when they are performing some motor tasks. These patients have their movements slowed down, but are able to perform them until the late stages of their diseases. Of course this is subject to the lesions load and the natural idiosyncratic evolution of the disease. A more specific example of that and ubiquitous in MS patients, is a symptom called double vision. This common symptom of MS is a result of inflammatory processes of the optic nerve causing asymmetric conduction delays in the two visual pathways.

4 Conclusion

The various results produced here show that computational models can exhibit some of the features observed in biological systems affected by MS.

It was found that the number of affected axons was consistently the most influential factor causing transmission delays. This feature surpassed all the other ones investigated, namely the number of internodes affected and the severity of individual attacks on internodes. Thus, transversal damage to the pathway is more devastating to neurocommunications than longitudinal destruction to myelin, i.e. plaques layout can be a more relevant feature than their own size.

Finally, the authors suggest that other features not simulated here such as synaptic changes, multiple spikes in the network for each stimulus, axonal ectopic activation and temperature effects should be considered for future extensions of this model.

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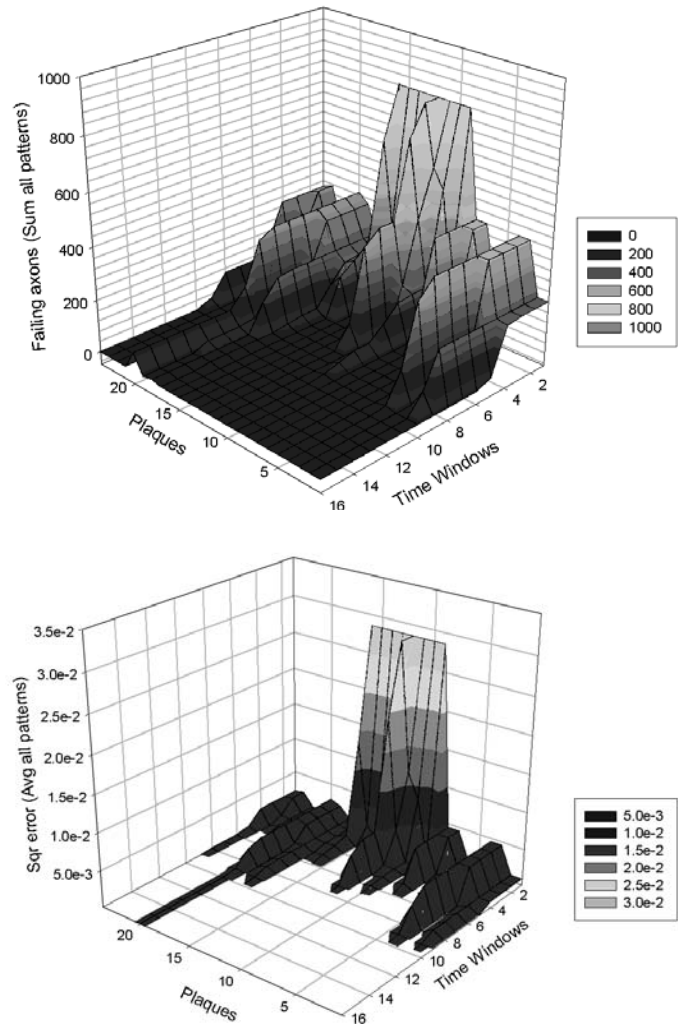


Figure 6: (top)Number of failing axons and (bottom)Output square error, both per time-windows

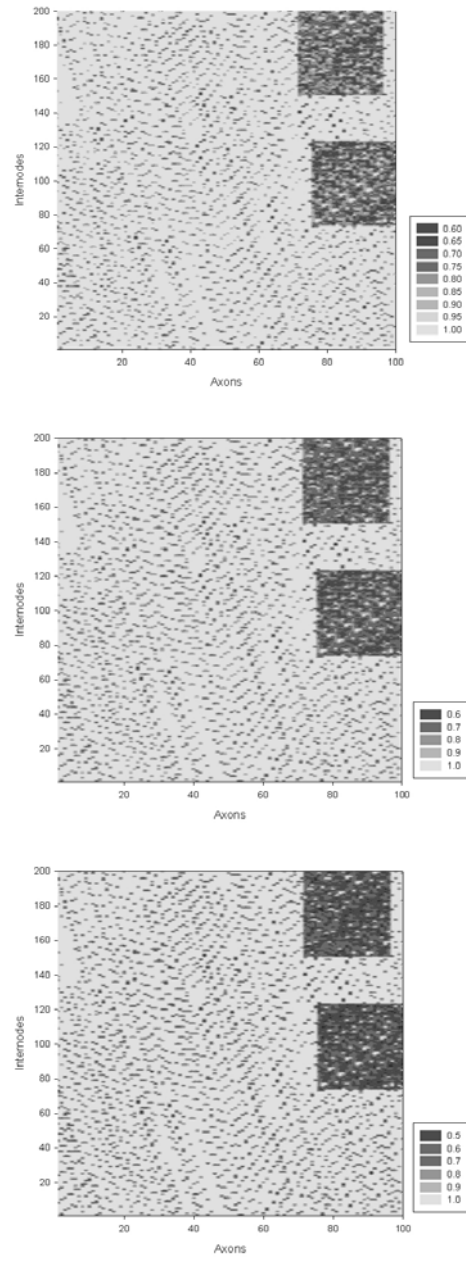


Figure 7: Plaque load 16 at 10% (top) 20% (center) and 30% (bottom) of increased 'damage' to neurocommunications

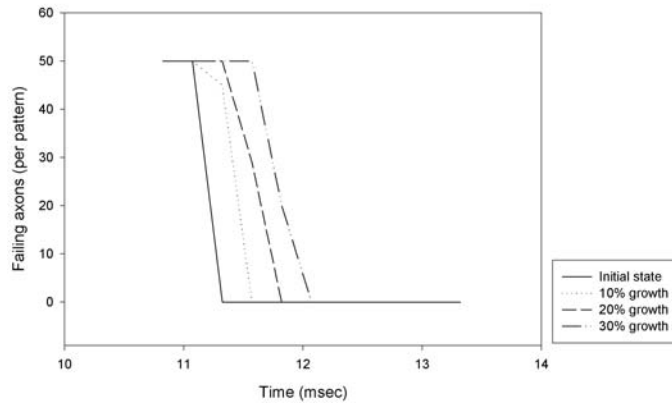


Figure 8: Number of failing axons (average of all patterns, three growth stages, plaque load 16)

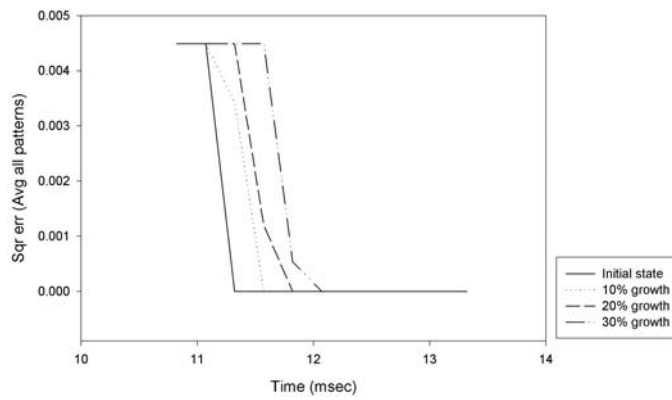


Figure 9: Output square error (average of all patterns, three growth stages, plaque load 16)