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# Artificial Neural Networks Used to Study the Evolution of the Multiple Sclerosis

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## 1. Introduction

The multiple sclerosis (ME) is an illness degenerative chronicle of the central nervous system. At the moment is considered that it doesn't have cure although exists effective medication and the investigation on their causes is an active field of investigation.

The objective of this article is to develop a model more precise, based on the use of the Artificial Neural network (ANN), to study the evolution of the illness in the patients with EM.

## 2. Important

This article presents a model to study the evolution of the illness ME using ANN. The implementation and validation of the pattern was carried out in the programs of Biomedical Engineering and of Systems of the ITM.

The article is organized in the following way: the first chapter presents an introduction to the ME, studying the possible forms of the evolution of the illness. In second chapter exposes the model of the evolution of the illness using ANN and the validation tests. The article concludes showing the main conclusions of this investigation.

## 3. Information

### 3.1 The multiple sclerosis

A special study on the ME is beyond the environment of this unit. In ((NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKEN, 2010) offers an excellent treatment with specific references. In this section a brief revision is presented with the purpose of providing a basic knowledge on the matter.

The ME is an illness degenerative and chronicle of the central nervous system. At the moment is considered that it doesn't have cure although exists effective medication and the search on their exact causes are ignored and is a field of active investigation.

The ME can present a series of symptoms that appear in buds or that they progress slowly along the time. They are distinguished several subtypes of multiple sclerosis and many affected present forms different from the illness with the step of the time...

Because of their effects on the central nervous system, it can have as consequence a reduced mobility and disability in the most severe cases. Fifteen years after the appearance of the

first symptoms, if it is not treated, at least the patients' 50% conserves a high degree of mobility. Less than 10% of the sick persons they die because of the consequences of the multiple sclerosis or of their complications.

It is, after the epilepsy, the most frequent neurological illness among the young adults and the most frequent cause in paralysis in the western countries. It affects approximately at 1 of each 1000 people, in particular to the women. It is presented when the patients have between 20 and 40 years. (Noseworthy et to the., 2000; Rivera 2000).

**Description.** The ME is characterized by two phenomena:

Appearance of focuses spread in the brain and partially also in the spinal marrow caused by the attack of the system immune against the sheath of myelin of the nerves, like is illustrated in the figure 1.

The neurons, and especially their axons is damaged by diverse mechanisms.

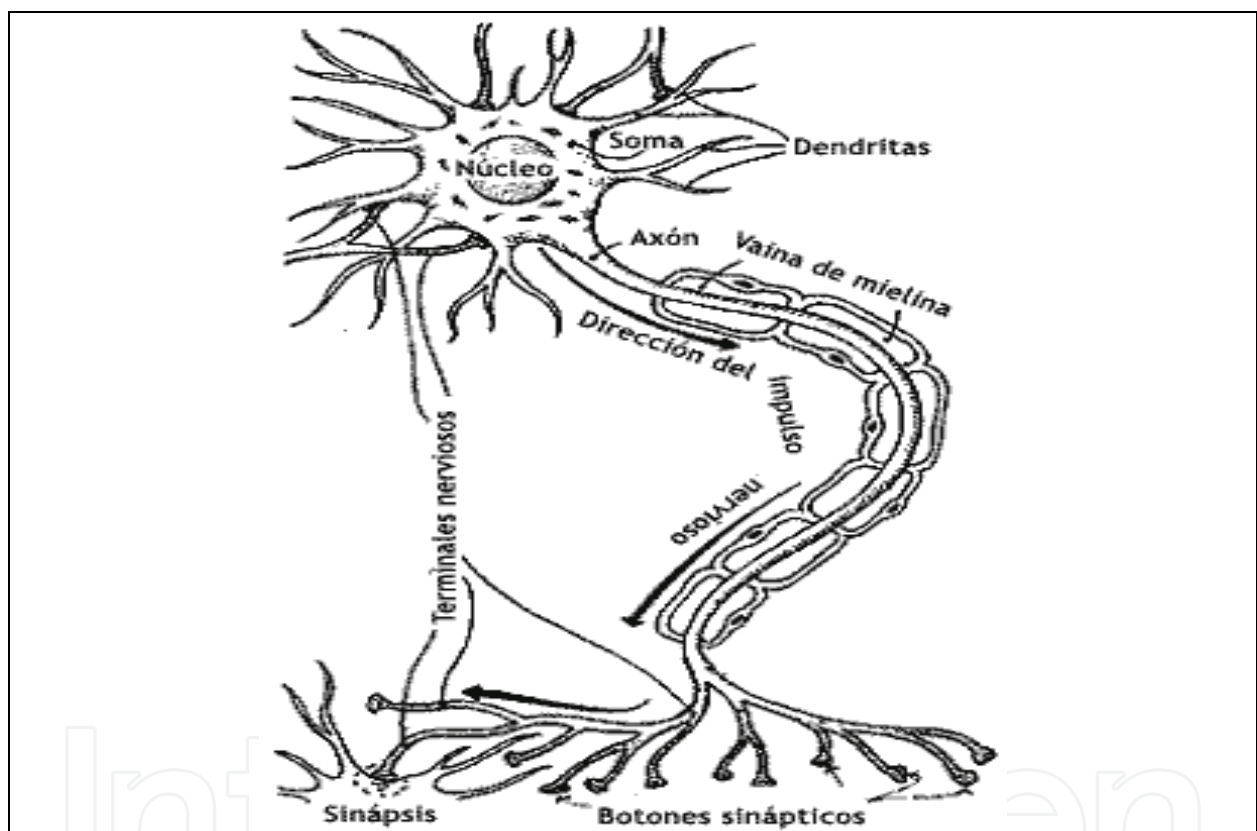


Fig. 1. Myelin

As a result, the neurons of the brain lose partial or totally their transmission capacity, causing the typical symptoms of drowsiness, tickling, spasms, paralysis, tires and alterations in the view.

In the variant Remittent-Recurrent has also been detected in the nervous tissue, or cut of the axons of the neurons, that makes permanent sequels.

**Treatment.** Cure doesn't exist for the ME. However we have been several medications that are effective in their treatment (Gutiérrez-Alvares et to the., 2001), braking the development of the illness and combatting the symptoms.

The remittent-recurrent variant only has treatments approved by the FDA (Administration of Foods, for its initials in English - Food and Drug Administration) and the EMEA

(European Agency of medications - European Medicines Agency). At the moment, they are three interferons (Blackish et al., 2003) (Avonex, -well-known Betaseron in Europe like Betaferon (The IFNB, 1993; Paty et al., 1993, Jacobs et al., 1996, (Yong et al., 1998) and Rebif (PRISMS, 1998; PRISMS, 2001), a group of called polipéptidos Copaxone, a called immunosuppressive Mitoxantrone and finally an antibody called monoclonal Natalizumab and marketed as Tysabri. The clinical rehearsals (Freedman, 1998; Durelli et al., 2002; Panitch et al., 2002; Clanet et al., 2002) on the different medications they demonstrate that they are not comparable because they correspond to different study designs.

The primary progressive ME is very difficult of trying. The corticosteroids to high dose every three months can have some effect. In principle a treatment preventive cash doesn't exist for the primary progressive ME. The treatment of the symptoms, and the rehabilitation by means of physiotherapy, occupational therapy, have an important paper. It is very important, equally, the evaluation on the part of a neuropsychologist to be able to approach any deficit cognitive that could be established.

**Epidemiology.** It is believed that MS occurs when a combination of environmental factors in genetically predisposed to buy it.

**Environmental factors.** In northern Europe, North America and Australasia continental one in 1,000 people suffers from MS. In Central Europe is the inflammatory disease most common central nervous system. In contrast, in the Arabian Peninsula, Asia, Central and South America continental frequency is much lower. Sub-Saharan Africa is extremely rare. With notable exceptions, there is a north-south gradient in the northern hemisphere and south-north in the southern hemisphere, with lower frequencies in the equatorial areas. The climate, diet, geomagnetism, toxins, sunlight, genetic factors and infectious diseases have been proposed as possible causes of these regional differences. It has been postulated that some environmental factor in childhood may play an important role in the development of MS in adult life.

**Genetic factors.** MS occurs mainly in Caucasians. It is 20 times less common among Canadian Inuit than among other Canadians living in the same region. It is also rare among American Indian tribes of North America, Australian Aborigines and the Maori of New Zealand. These examples indicate that genetics plays an important role in the development of the disease. (Noseworthy et al., 2000) MS is not hereditary. However, the disease is influenced by the genetic constitution of the individual and has been shown that there are genes that are associated with an increased risk of contracting the disease. These genes, which are being studied, are not sufficient to diagnose the disease.

**Diagnosis.** The diagnosis of MS is complex (Thompson et al., 2000; Poser et al., 1983, Fazekas et al., 1988; Offenbacher et al., 1993; Paty et al., 1988). It requires evidence of a dissemination of lesions over time and space in the CNS. That means that not only must have at least two separate injuries verifiable by clinical symptoms or MRI, in addition there must be evidence of new symptoms or injuries in a range of 30 days. (McDonald et al., 2001)

The conductivity studies of the optic nerve, sensory and motor also provide evidence of the existence of the disease, since the process of demyelination involves a reduction of conduction velocity of nerve signals. The study was done by comparing the reaction times with preset measurements.

**Symptoms.** The central nervous system lesions that cause MS does not always manifest as clinical symptoms directly detectable and clearly attributable to the disease, which sometimes tends to minimize the first signs. However, the origin of MS is present and begins to progress.

Although in some instances at the beginning of MS accumulates little disability and quality of life is not too concerned, the reality is that the substrate of the disease is developing. There is abundant clinical and scientific evidence indicate that what happens in the early stages of MS, largely depends on its further development. In other words, injuries today in the central nervous system are the cause of disability in the morning, so that if not prevented now, tomorrow will be too late for recovery. MS detection is key as soon as possible to act in time.

It has been shown that early treatment significantly reduced the number of shoots and their intensity. Affected individuals may exhibit a wide range of symptoms, but differ widely from each other, both in the type of symptoms and in their degree. In principle, can be classified according to the area affected the nervous system: derived from optic nerve damage, resulting from damage to the spinal cord (in particular those related to mobility are of this type) and derived from brain damage.

The following are the most common: asthenia (fatigue), muscle loss, muscle weakness, uncoordinated movements, dysphagia (trouble swallowing), dysarthria (speech problems), respiratory failure, dyspnea (breathing problems) spasticity (muscle stiffness), muscle spasms, cramps, muscle twitching (small but widespread muscle vibration), sexual dysfunction, vision problems (loss, double vision, nystagmus), cognitive problems (difficulty performing simultaneous tasks, to follow instructions, loss of short-term memory, depression), emotional lability (inappropriate laughing and crying without psychological effects), constipation secondary to immobility.

**Types of MS:** In most cases sclerosis begins with acute onset of symptoms in a space that varies from hours to days, usually called a flare, attack or episode. Later speaking of relapse. The first symptom is often the optic neuritis, an inflammation of the optic nerve that causes impaired vision and pain when moving the eye. However, not all patients with optic neuritis develop MS. Sensory disturbances such as numbness or tingling are also common early symptoms. In principle, MS can start with any of the symptoms associated with the disease.

**Benign MS.** In benign MS cases after one or two attacks, the recovery is complete. The disease worsens over time and usually less severe symptoms. These cases are identified only when it is a small permanent disability after 10 or 15 years after the first attack, which was identified at the time as relapsing MS. In this case, loss of vision or sensory symptoms (numbness or tingling) as initial symptoms are signs of a benign prognosis. Disturbances in gait and fatigue are signs of a negative prognosis.

**Relapsing-remitting MS.** Especially in the early stages of the disease, the symptoms diminish or disappear spontaneously over a period that can last from days to months. This type of course is called relapsing-remitting. New relapses may occur within weeks or several years and are unpredictable. These relapses may include the above symptoms and / or new ones. However, MRI studies show that nerve damage in these patients can continue even when symptoms have subsided. It has been known long ago that MS never sleeps, so the importance of preventive treatment is great. Many patients remain at this stage the rest of their life.

**Secondary progressive MS.** In many cases, the disease changes after several years and symptoms begin to slowly progress with or without relapses tax. It is not known yet but its etiology.

**Primary progressive MS.** 10% of all affected individuals have a chronic progress from the beginning without remission. It is called primary progressive and often appears with leg weakness and alterations in gait and urinary bladder. They appear to be degenerative and



inflammatory processes that play a dominant role in this type. In cases where the primary progressive form of relapse is usually imposed on talk of progressive relapsing.

Other forms of multiple sclerosis, to be for many different diseases, which are grouped under the collective name of "border forms" of multiple sclerosis. (Noseworthy et al., 2000; Rivera, 2003)

An overview of different types of MS, is shown in Figure 2.

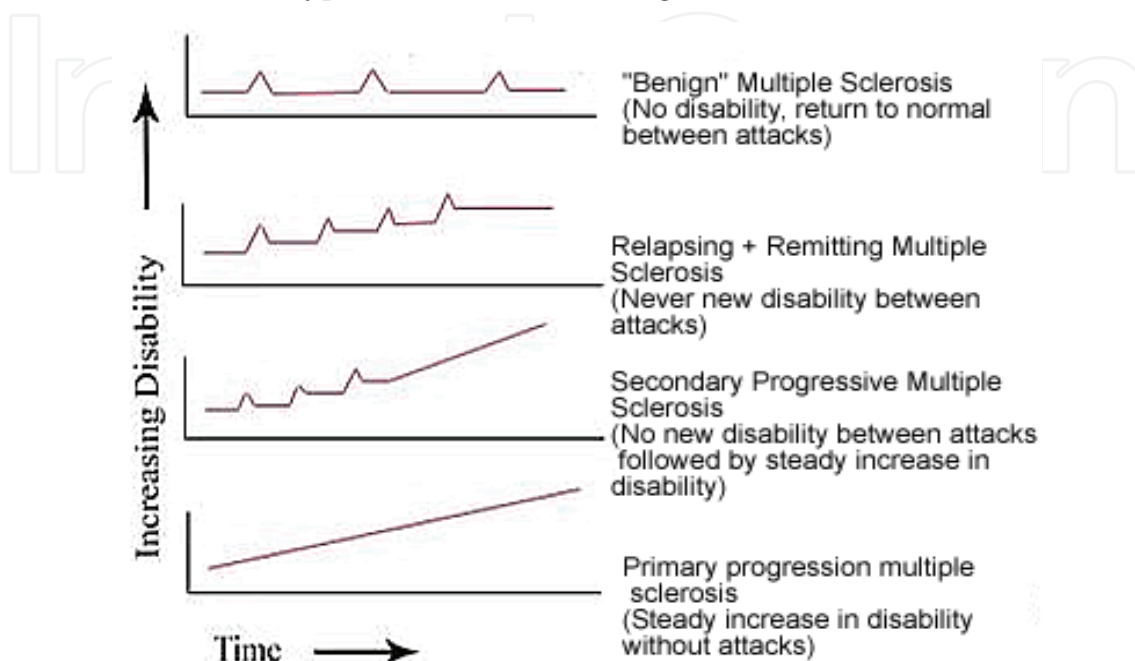


Fig. 2. Different types of evolution of MS

**Demyelination.** In health, there is a barrier between the central nervous system and the blood called blood-brain barrier, which consists of endothelial cells lining the blood vessel walls.

For unknown reasons, in patients with amyotrophic this barrier does not function well, and autoreactive T cells cross it.

Since that time, an inflammatory process appears. The inflammation is provided by other immune cells and soluble factors, such as cytokine and antibody. Because of this abnormal behavior of the immune system, MS is considered an autoimmune disease.

Widely accepted is that a particular subtype of lymphocytes, called CD4 cells, Th1-T, have a key role in the development of the disease. Under normal circumstances, these lymphocytes can distinguish between own and other cells. In a person with MS, however, the cells recognize healthy parts of the central system as foreign and attack them as they would a virus. In MS, the party attacked is myelin, a fatty substance that covers the axons of nerve cells and is important for proper nerve transmission. (Hafler et al, 1989)

The inflammation eventually leads to the opening of the blood-brain barrier, which can lead to problems such as edema. It also causes the activation of macrophages, metalloproteinases and other proteases and cytokines. Eventually lead to the destruction of myelin, a process called demyelination.

**Remyelination.** Original Oligodendrocytes form the myelin sheath are not able to recreate the cover once it is destroyed. However, the brain is able to recruit stem cells that migrate from other unknown regions of the brain, differentiate into mature oligodendrocytes and

recreate the myelin sheath. This new cover is often not as thick or effective as the original and repeated attacks remielinizaciones reaction will become less effective (Hauser et al., 1986, Trapp et al, 1998), until a plaque around the axons damaged (Tintoré et al, 2001; Tintoré et al, 2003), as illustrated in Figure 3.

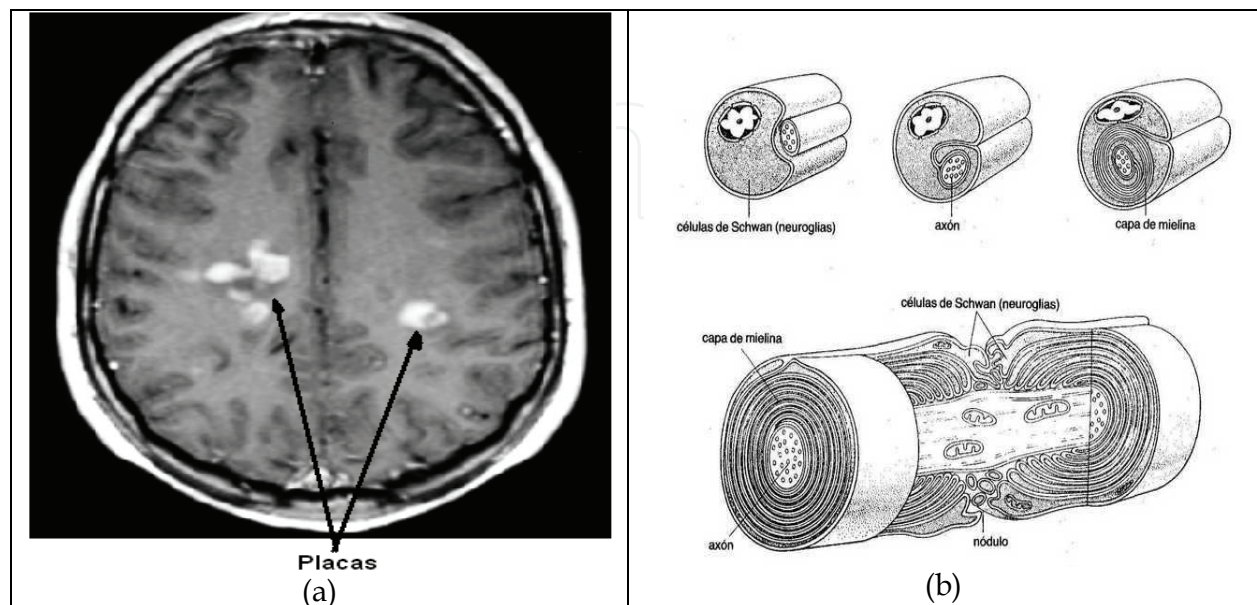


Fig. 3. Plaques (a) by the degeneration of myelin (b).

Remyelination is one of the reasons why, especially in the early stages of the disease, symptoms tend to diminish or disappear after days to months.

### 3.2 Study case

Respecting the confidentiality of a patient's medical information and confidentiality within ethical and legal framework in force, and himself as to the custody of the records of Magnetic Resonance, and not be subject to experimental research without their fully informed and free consent, is presented below for anonymous study of a patient diagnosed with MS since 2003, in control, receiving Betaferon Ampoules applied every 1.5 days. Her medical history (from the onset, January 2003 to March 2010), the number of relapses and MRI examinations performed, are illustrated in Figure 4.

The results of the MRI examinations are as illustrated below.

#### MR1 (June 2003). CERVICAL SPINE.

Symptoms: Patient 28, female, with three-month history of pain in the cervical region radiating to the upper limbs, back and neck.

Conclusion: One is transverse myelitis at the level of C2-C3 and C3-C4, involving mainly the left hemicord. Twelve months after the onset of the disease, the patient fully recovered with no sequelae.

#### MR2 (January 2006). BRAIN AND CERVICAL SPINE.

Symptoms: lower limb anesthesia.

Conclusion: EM Process signed demyelinating type of activity. Probable secondary left hippocampal sclerosis. Twelve months after the start of the second relapse, the patient is left with permanent recovery (lower extremities are slightly grassy).

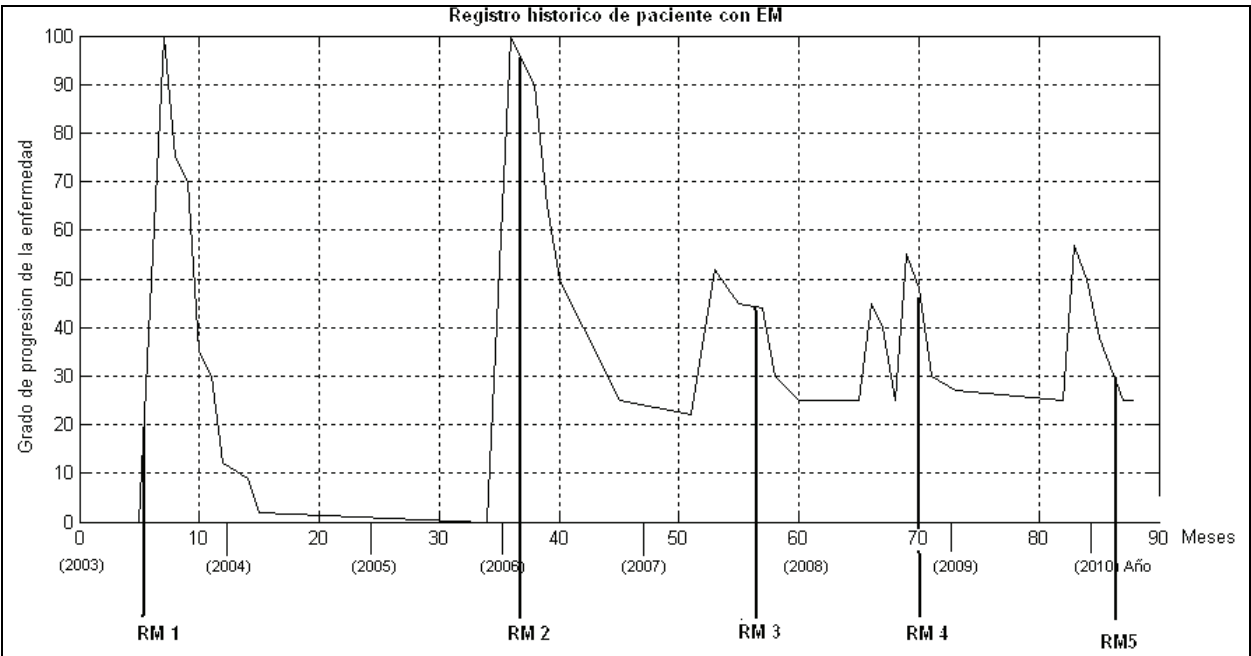


Fig. 4. Historical record of a patient with MS

**MR3 (September 2007). BRAIN AND CERVICAL SPINE.**

Symptoms: lower limb paresthesias.  
Conclusion: Board demyelinating left side up to C3. Described small central disc protrusion at C3-C4 and C5-C6. MS stable with respect to previous control in January 2006.

**MR4 (October 2008). CEREBRAL**

Symptoms: lower limb paresthesias, twitching.  
Conclusion: Injuries globular and plate engaging the white matter, periventricular, predominantly periatrinal, there are also other injury involving the left cerebral pendulum. These alterations are stable with respect to the cranial MRI September 2007, without showing enhancement postcontrast no increase in their sizes.

**MR5 (March 2010). CEREBRAL**

Symptoms: lower limb paresthesias, twitching.  
Conclusion: Patients with MS DX unchanged compared to the 2008 study. There is emerging injury and alterations in the stable known time interval. Satisfactory.  
Below in Table 1 summarizes the patient's history with MS.

Episode	Extent of disease progression.	Improvement achieved by the end of the episode.	Time between episodes
1 (Jun. 2003)	100%	100%	
2 (Ene. 2006)	100%	85%	30 meses
3 (Sep. 2007)	50%	85%	20 meses
4 (Oct. 2008)	50%	80%	13 meses
5 (Mar. 2010)	50%	80%	12 meses

Tabla 1. Registro histórico de recaídas.



### 3.3 Modeling the historical record of the disease ms with ANN.

Theory and modeling of the ANN is inspired by the structure and functioning of nervous systems, where the neuron is the fundamental element. There are neurons of different shapes, sizes and lengths, and attributes that determine their function and utility.

A detailed study of the ANN is beyond the scope of this unit. In [Row, 2000; Martin del Brio, 2002] offers an excellent study with specific references.

To solve the approximation problem posed in Figure 4, the use of a heuristic approach, based on intuition and experimentation to select the topology of the ANN. This will have an input neuron (time measured in months), one output neuron (Measurement of relapse) and two hidden layers, each with 15 neurons, as illustrated below.

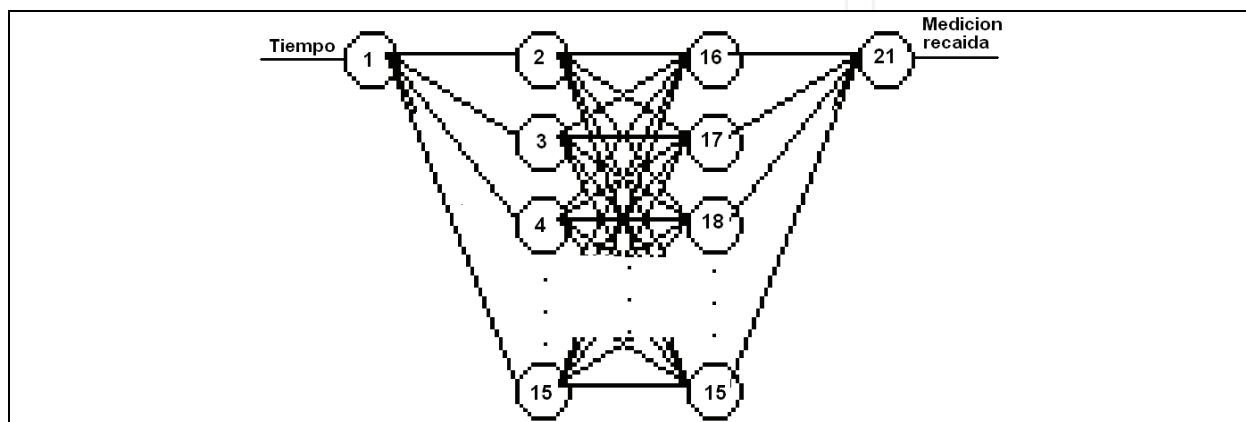


Fig. 5. Architecture of RNA used

The model validation tests were performed using the Neural Network Toolbox for MATLAB ®. The weights of the network is randomly initialized once. We use the training algorithm for second order Trainlm be considered the fastest, with a maximum 3000 iterations and a final error in the approximation of 0.01

Figure 6 shows the curve Approximation to the historical series of relapses That Had the patient with MS in the Period from January 2003 to March 2010. As Shown, the ANN Properly mapping the time series. Note That the final error in the Approximation Was 0.01, Which Is Considered a good measure.

## 4. Conclusions

MS is a chronic inflammatory demyelinating disease of the central nervous system that causes progressive disability of the individual. After an initial clinical syndrome develops the form of the disease relapsing-remitting (RRMS) that leads to a secondary phase of progressive disability. The goal of treatment is to reduce the frequency and severity of relapse and delay the onset of the secondary phase.

There are currently no established clinical evidence to allow a prognosis or to decide a therapeutic response to MS, although there is promising research that need to be confirmed, as the detection of anti-MOG antibodies (serum antibody against myelin glycoprotein of oligodendrocytes, Myelin oligodendrocyte glycoprotein) and anti-MBP (antibody against myelin basic protein, Myelin basic protein) as predictors of progression to disease introduced (Tintoré et al 2003). The uncertainty is one of the psychological aspects are more difficult to carry in MS.

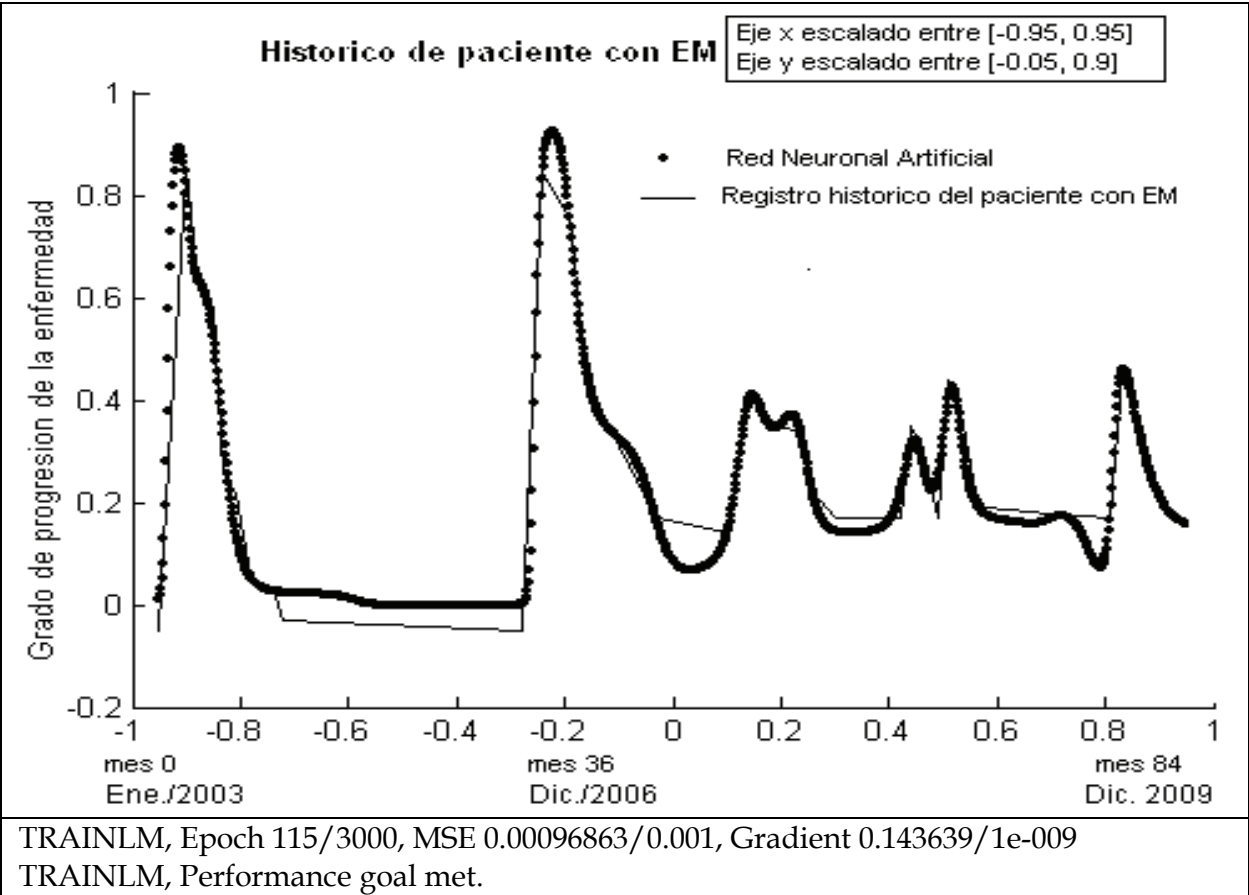


Fig. 6. Diagnosis of MS disease progression by using RNA.

The aim of this paper is to develop a more accurate model based on the use of Artificial Neural Networks, to study the evolution of the disease in patients with MS. The final error obtained in approximating the time series of relapses was 0.01, which is considered a good measure.

The method proposed to date to predict the efficiency of the treatment of relapsing-remitting MS is by clinical criteria and monitoring of active lesions by MRI examinations. As a way of contributing to the reliability of diagnosis and treatment efficiency is proposed in this paper to map the time series records of relapse using a ANN. Its use helps the doctor evaluate, more agile, the variation of the disease and its impact in the medium and long term.

Furthermore, long known that MS never sleeps, so the importance of preventive treatment is great. Many patients remain at this stage the rest of their life. In this case, using the model proposed in this paper helps the physician to improve their diagnoses in terms of disease trends. Likewise, the ANN used to evaluate the response has been the patient to the treatment of this disease, coupled with the clinical and MRI outcomes. With the ANN could be predicted more accurately in the first months of therapy if the patient responds or not to therapy.

Moreover, the drugs used in the treatment of MS are only "partially effective" (Anderson, 1997). Therefore, physicians need to evaluate their response by MRI, and clinical criteria that include measuring the frequency of relapses and measuring the degree of disability progression. In this case, the use of an ANN, helps the doctor to study the variation of the

disease and raise more swiftly changes when treatment is not effective before they produce a greater neurological damage.

The diagnosis of MS using ANN during treatment to detect changes in the state of neurological inflammation of the sick and to assess the effect of different drugs on injuries. The effectiveness of the diagnosis in ANN depend on the correct measurement of the frequency of relapses and the degree of progression of the disease.

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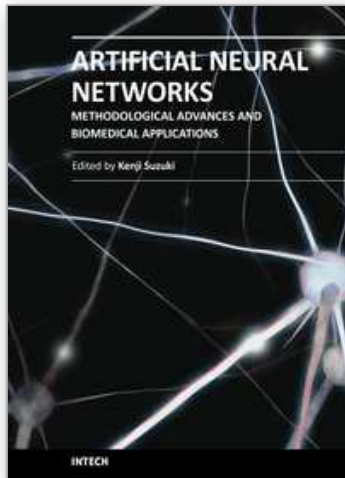
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Artificial neural networks may probably be the single most successful technology in the last two decades which has been widely used in a large variety of applications in various areas. The purpose of this book is to provide recent advances of artificial neural networks in biomedical applications. The book begins with fundamentals of artificial neural networks, which cover an introduction, design, and optimization. Advanced architectures for biomedical applications, which offer improved performance and desirable properties, follow. Parts continue with biological applications such as gene, plant biology, and stem cell, medical applications such as skin diseases, sclerosis, anesthesia, and physiotherapy, and clinical and other applications such as clinical outcome, telecare, and pre-med student failure prediction. Thus, this book will be a fundamental source of recent advances and applications of artificial neural networks in biomedical areas. The target audience includes professors and students in engineering and medical schools, researchers and engineers in biomedical industries, medical doctors, and healthcare professionals.

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