International Journal of Enhanced Research in Science, Technology & Engineering
ISSN: 2319-7463, Vol. 8 Issue 1, January -2019, Impact Factor: 4.059

Artificial neural networks in the methodological approach of artificial intelligence for diagnosis of breast cancer by means of multilayer perceptrons systems evidenced by the advent of genome editing

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ABSTRACT

The ancient historical surgical manuscripts show us some cases of breast cancer and the procedures presented note that there was no treatment for the disease. In contrast to this perspective the recent cases would evolve in terms of the health of those affected and is no longer the case of most cancers. Nowadays in some countries more than 60% of people diagnosed will live more than five years after diagnosis. And for some cancers, the five-year survival rates are close to 90%. In this article the classification of malignant and benign breast cancer tumor is based on the cellular descriptions are gathered by microscopy and applied in an artificial intelligence methodology that uses artificial neural networks to solve the diagnostic system. The generalization ability to produce reasonable outputs for neural networks not found during training enables neural networks to find high-level solutions to compelling (large-scale) problems that are inconceivable. In the search for medical solutions, genomic editing with homologous recombination (HR) (human genetic targeting) methodology in human hematopoietic stem cells (HSCs) has the ability and effectiveness to reveal relationships of gene function and potentially to transform the curative hematological gene and cell therapies.

Keywords: artificial intelligence, artificial neural networks, diagnostic system, diagnosis of breast cancer, genome editing.

HOW TO CITE THIS ARTICLE

Vicente Tiburcio dos Santos Junior, "Artificial neural networks in the methodological approach of artificial intelligence for diagnosis of breast cancer by means of multilayer perceptrons systems evidenced by the advent of genome editing", International Journal of Enhanced Research in Science, Technology & Engineering, ISSN: 2319-7463, Vol. 8 Issue 1, January -2019.

1. INTRODUCTION

The disordered growth of breast cells is the main feature of breast cancer. The genes responsible for regulating the growth of cells and keeping them healthy may undergo mutations and abnormal changes, when this occurs they develop the cancer. Genes make up the nucleus of each cell, which acts as the "control system" of each cell. When the old cells die, new healthy cells take over representing when a normal process happens in our bodies where cells are replaced in an orderly way resulting in cell growth. Genetic mutations, over time, can change cells by "binding" certain genes and "turning off" others in a cell. A tumor originates when the irregularly-modified cell gains the ability to continue dividing uncontrollably and producing more identical cells. The tumor may be benign (not harmful to health) or malignant (dangerous to health). Benign tumors are not cancerous: their cells are close to normal appearance, grow slowly and do not invade nearby tissues or spread to other parts of the body. Malignant tumors are cancerous. Less commonly, breast cancer can begin in the stroma tissues, which include fatty and fibrous connective tissues of the breast [14].

The female breast has always been a symbol of beauty, fertility and femininity. In illness, however, it has challenged doctors since antiquity. Surgery, which dominated cancer therapy, inevitably caused disfigurement when the scalpel incision was applied to the breast. The history of breast cancer is a complex maze of attempts to understand the wily nature of this hormone-responsive cancer and the will of physicians to conquer it by physical removal (surgery), cell destruction (chemo-radiotherapy) or targeted therapy to cell receptors (biomodulation). It is also a saga of intense exploration to find the tools to enable early diagnosis [15].

Artificial neural networks are a relatively effective method of multivariate analysis. The aim of this study was to investigate the ability of neural networks to differentiate between benign and malignant conditions of breast cancer based on the pattern of nine input variables.

2. REDUCTION OF BREAST CANCER WITH CRISPR / CAS9 GENOME EDITING

Breast cancer has become the most common cancer among women in the world. The molecular profile of breast cancer reveals the heterogeneous nature of the development and progression of the disease, governed by genes that control cell growth, proliferation and differentiation. The evolution of breast cancer appears to be driven by aberrant gene expression leading to gain of function or activation of downstream signal pathways [29]. Insights into these gene expression profiles and cancer genomic abnormalities began to revolutionize the classic paradigm of breast cancer treatment, which was based on pathological and clinical manifestations [30]. New therapeutic principles of personalized medicine have emerged to combine anti-cancer drugs with molecular alterations unique to the proliferation of cancerous cells [31].

Currently, even with the evolution of systems that are conducive to the development of molecularly targeted drugs for clinical practice, the main challenge is the identification of antineoplastic biomarkers as targets for accurate treatment; thus, adverse reactions associated with off-target and total cost can be minimized [32]. Timely, the advent of a genome-editing technology with short sequence repeats grouped at regular intervals (CRISPR) which are the nuclease system of associated proteins (Cas9) or CRISPR / Cas9 facilitated identification. CRISPR / Cas9 exists naturally in archaea and bacteria as part of an adaptive immunity mechanism for bacteriophage defense [25]. The system is composed of the Cas9 nuclease and a guiding species RNA (gRNA) which has sequence specific city relative to an adjacent protospacer motif (PAM) that may differ between different Cas9 orthologs [26, 27]. The system has been adapted for mammals to use on various platforms and is highly friendly.

CRISPR / Cas9 has two main components: a chimeric single guidewire RNA (gRNA) and the Cas9 DNA endonuclease. Notably, the gRNA carries Cas9 to a target genomic sequence [33, 34]. The idiosyncrasy for the target is defined by the complementarity of the 20 nucleotides at the 5 'end of the siRNA at the desired genomic sites. Cas9-mediated DNA cleavage at the target site is initiated by an adjacent protospacer motif (PAM) located immediately downstream of the target sequence. Cas9-induced double-strand breaks (DSBs) undergo non-homologous junction error prone repair [35], which introduces mutations to disrupt the integrity and functions of target genomic sites. This development specifies the impact of CRSPR / Cas9 mediated genome editing on the search for and identification of molecular targets against breast cancer. It focuses on a somatic genome editing theme mediated by CRISPR / Cas9, transcription and dependence on protein degradation in breast cancer.

Genomic editing with homologous recombination (HR) (human gene targeting) methodology in human hematopoietic stem cells (HSCs) has the ability and effectiveness of revealing gene-function relationships and potentially transforming the curative hematological gene and cellular therapies. However, there are no comprehensive and reproducible protocols to direct HSCs to HR. This development produces a detailed protocol for the production, enrichment and in vitro and in vivo analyzes of HR-directed HSCs, combining CRISPR / Cas9 technology with the use of rAAV6 and flow cytometry. Using this protocol, researchers can introduce unique nucleotide changes into the genome or longer genetic cassettes with the accuracy of genome editing. Along with our troubleshooting and optimization guidelines, researchers can use this protocol to simplify the editing of the HSC genome at any locus of interest. The in-vitro HSC allocation protocol and analyzes can be completed within 3 weeks, and long-term HSC graft analyzes in vivo on immunodeficient experimental cells can be obtained at 16 weeks. This protocol allows the manipulation of genes for investigation of gene functions during hematopoiesis, as well as for the correction of genetic mutations in HSC transplantation-based therapies for diseases such as sickle cell disease, beta-thalassemia and primary immunodeficiencies.

Genome engineering as well as being a powerful research tool, is also being developed to cure human diseases, including those of the blood and the immune system, most of which can be categorized as still having a great need for unmet medical solution. Ex-vivo gene engineering mediated by nucleotides by RH in stem and progenitor hematopoietic cells (HSPCs) may launch optimize on the function of the stem cell gene through precise genetic manipulations and may potentially define a curative strategy for incurable hematological diseases. The CRISPR / Cas9 Type II genome-editing system guided by RNA uses a single protein, Cas9, which is guided by a single chimeric guiding RNA (sgRNA) to target DNA by Watson-Crick base pairing. Its simplicity and robustness, is proving to be the

most widely designed nuclease used for editing mammalian genomes. The high editing performance of a plasmid-based CRISPR / Cas9 system in cell lines did not translate into high editing activity in primary cell types, such as human primary T cells and HSPCs [36]. Protection of both sgRNA terminals with chemically modified nucleotides enhances the stability of sgRNA and renders the "RNA-based CRISPR / Cas9 system highly efficient in primary HSPCs and T cells. In addition, delivery of pre-complexed Cas9 ribonucleoprotein (RNP) with chemically modified sgRNAs consistently increased activity on T [36,37] and CD34 + HSPCs (R.O.B., D.P.D. and M.H.P., data not shown). Multiple publications also showed efficient genome editing in T9 cells and HSPCs [38,39] without modified sgRNAs in the context of Cas9 RNP delivery. In the analysis, however, a direct comparison with synthetic sgRNAs with modifications was not performed, and it is still possible that the generally more active form of an sgRNA, even in the context of RNP delivery, is one that is synthetically manufactured with final modifications that protect against degradation of endogenous exonuclease and innate immune stimulation. HR genome editing in HSCs allows investigation of the function of the HSC gene as well as the ex vivo correction of disease-causing mutations for the development of the next generation of gene and cell therapies. Combining the CRISPR / Cas9 system delivered as RNPs with delivery of homologous donors via rAAV6, we routinely achieved> 20% (and up to 77%) HR frequencies in CD34 + HSPCs in vitro at various human loci, and evaluated the high reporter expression via FACS after successful HR at the intended locus 1-3 days after electroporation. It is important to note that the classification of this highly reporter HSPC population enriches cells with targeted integration and also prevents the inefficient potential of HSC targeting by removing non-targeted HSCs that may compete for bone marrow reconstitution. CFU assays usually result in 30-50% colony formation with> 60% of colonies being CFU-GM and <5% being CFU-GEMM, but results may vary depending on the source of HSPC. After transplantation into NSG experimental cells, the human graft is generally observed in all transplanted experimental organisms, and with the transplantation of enriched HSPCs, it is generally observed that> 80% of the human cells are reporters. It is imagined that this methodology will be widely used to study the biology of HSPC and to advance in the field of gene and cellular therapy for blood and immune system disorders [24].

3. ARTIFICIAL NEURAL NETWORKS

Artificial intelligence systems in artificial neural networks, commonly called “neural networks” have been motivated since the beginning by the recognition that the human brain computes in a totally different way from the conventional digital computer.

The brain presents itself as a highly complete, non-linear, parallel computer (information processing system). This has the ability to organize its structural constituents, known as neurons, to perform certain calculations (e.g., pattern recognition, motor perception and control) in a rather considerable volume over relatively small fractions of time.

In comparative analysis with human vision, which has in its characteristics the task of information processing.

The visual system has as function to provide a representation of the environment that surrounds us and, more importantly, provide the information needed to interact with the environment.

To be specific, the brain routinely performs perceptual recognition tasks (for example, recognizing a familiar face embedded in an unfamiliar scene) by approximately 100-200 [ms], whereas tasks of much less complexity can take much longer on a powerful computer.

At birth, a brain already has a considerable structure and the ability to construct its own rules of behaviour, which we usually refer to as “experience.” In fact, experience builds up over time, in the first two years since birth there is much development (i.e., hardwiring) of the human brain, but development goes well beyond this stage.

A brain with flexibility comes down to a “developing” nervous system: flexibility allows the developing nervous system to adapt to its surrounding environment.

Just as plasticity seems to be essential for the functioning of neurons as processing units of information in the human brain, so does neural networks made of artificial neurons [1].

4. BENEFITS OF NEURAL NETWORKS

A neural network derives its computing power through [2], first, a massively distributed structure and, secondly, its ability to learn and thus generalize. Generalization refers to the production of reasonable outputs from neural networks for inputs not found during training (learning). These two information capabilities enable neural networks to find good solutions to complex (large-scale) problems that are intractable. In order to maintain effectiveness, neural networks cannot provide the solution by working individually. For optimization, they need to be integrated into a set of systems engineering. Specifically, a complex problem of interest becomes a relatively simple, and neural number of tasks. Networks receive a subset of the tasks that correspond to their inherent capabilities. This becomes important to

recognize, however, that we have a long way to go (if we can) before we can build a computer architecture that mimics the human brain.

Neural networks offer the following useful properties and features:

1. Non-linearity. An artificial neuron can be linear or non-linear. Composed of an interconnection of non-linear neurons, it is itself non-linear. In addition, non-linearity is of a special type in the sense that it is distributed throughout the network.

Non-linearity is a highly important property, particularly if the mechanism responsible for generating the input signal (e.g., speech signal) is inherently non-linear.

2. Input and output mapping. A popular learning paradigm, called teacher learning, or supervised learning, involves modifying the synaptic weights of a network by applying a set of labeled training examples or task examples. Each example consists of a unique input signal and a corresponding desired response (target). It is presented with an example chosen at random from the set, and the synaptic weights (free parameters) of the network are modified to minimize the difference between the desired response and the actual network response produced by the input signal in accordance with an appropriate statistical criterion. The network formation is repeated for many examples as a whole, until the network reaches a steady state where there are no more significant changes in the synaptic weights.Examples may be reapplied during the training session, but in a different order.

The network learns from the examples by constructing an input-output mapping for theproblem at hand. Such an approach brings to mind the study of nonparametric statistical inference, which is a branch of statistics that deals with model-free estimates, or, from a point of view, *tabula rasa* learning [17]; the term "non-parametric" is used here to mean the fact that no previous assumption is made in a statistical model for the input data. Consider, for example, a task of pattern classification, where the requirement is to assign an input signal representing a physical object or event to one of several pre-specified categories (classes). In a non-parametric approach to this problem, the requirement is to "estimate" arbitrary decision limits in the input signal space for the pattern classification task using a set of examples and to do this without invoking a probabilistic distribution model. A similar view is implicit in the learning paradigm supervision, which suggests a close analogy between the input and output mapping by a neural network and non-parametric statistical inference.

3. Adaptability. Neural networks have an integrated ability to adapt their synaptic weights to changes in the environment addressed. In particular, a neural networktrained to operate in a specific environment can be easily trained to deal with changes in operating environmental conditions. In addition, when operating in a non-stationary environment (i.e., where statistics change over time), a neural network can be designed to change its synaptic weights in real time. The natural architecture of a neural network for pattern classification, signal processing and control applications, along with the adaptability of the network, makes it a useful tool in the classification of adaptive patterns, adaptive signal processing and adaptive control.

As a general rule, it can be said that the more adaptable we make a system, all the while ensuring that the system remains stable, the more robust its performance is when the system is needed to operate in a non-stationary environment. It should be emphasized, however, that adaptability does not always lead to robustness; in fact, one can do just the opposite. For example, an adaptive system with short duration constants changesrapidly and therefore tend to respond to spurious disturbances, causing a drastic degradation in system performance. To obtain all the benefits of adaptability, the main system time constants must be long enough for the system to ignore spurious perturbations, and still short enough to respond to significant changes in the environment; the problem described here is referred to as the stability-plasticity dilemma [18].

4. Evidential response. In the context of pattern classification, a neural network can be designed to provide information not only on which particular pattern to select but also on trust in the decision made. This latter information can be used to reject ambiguous patterns if they arise and thus improve the rating performance of the network.

5. Contextual Information. Knowledge is represented by the very structure and state of activation of a neural network. Every neuron in the network is potentially affected by the overall activity of all other neurons in the network. Consequently, contextual information is naturally treated by a neural network.

6.Fault Tolerance. A neural network, implemented in the form of hardware, has the potential to be inherently fault tolerant, or capable of robust computing, in the sense that its performance degrades gracefully under adverse operating conditions. For example, if a neuron or its connection links are damaged, remember that a stored pattern is impaired in quality. However, due to the distributed nature of the information stored on the network, the damage must be extensive before the overall network response is seriously degraded. Thus, in principle, a neural network exhibits a graceful degradation in performance rather than catastrophic failure. There is some empirical evidence for robust computing, but

it is often uncontrolled. To be sure that the neural network is indeed fault-tolerant, it may be necessary to perform corrective measures in the design of the algorithm used to train the network [19].

7.VLSI Implementability. The massively parallel nature of a neural network makes it potentially quick to calculate certain tasks. It shows a suitable network for implementation using VLSI (very large integrated scale) technology. One particular virtue of VLSI is that it provides a means of capturing behavior truly complex in a highly hierarchical way [20].

8. Uniformity of Analysis and Design. Basically, neural networks enjoy universality as information processors. We say this in the sense that the same notation has been used in all domains that involve the application of neural networks. This feature manifests itself in different ways:

• Neurons, in one form or another, represent an ingredient common to all neural networks.
• This commonality allows sharing theories and learning algorithms in different applications of neural networks.
• Modular networks can be built through seamless integration of modules.

5. MULTI-LAYER PERCEPTRONS

The multi-layer perceptron is a perceptron type network with at least one middle layer. With the publication of the book Perceptrons[21] in the late 1960s, the multilayer perceptron network was proposed as an attempt to overcome the limitations found in simple perceptron. It was then necessary to develop a more sophisticated training algorithm capable of automatically defining the weights for this type of network. The training algorithm of this network is a generalization of the delta rule proposed by Widrow & Hoff for the training of Adaline. MLP training was originally done using an algorithm called backpropagation of the error, known as backpropagation. This algorithm consists basically of two steps: Positive propagation of the functional signal: during this process all weights of the network are kept fixed; and Backpropagation of the error: during this process the network weights are adjusted based on an error measure per base. The error signal is propagated in the opposite direction to the propagation of the functional signal, hence the name of the error propagation.

A typical MLP network has three main characteristics: the neurons of the intermediate layers (and eventually those of the output layer) have a non-linear activation function of the sigmoidal type (e.g., logistic function or hyperbolic tangent). The network has one or more intermediate layers. The network has a high degree of connectivity.

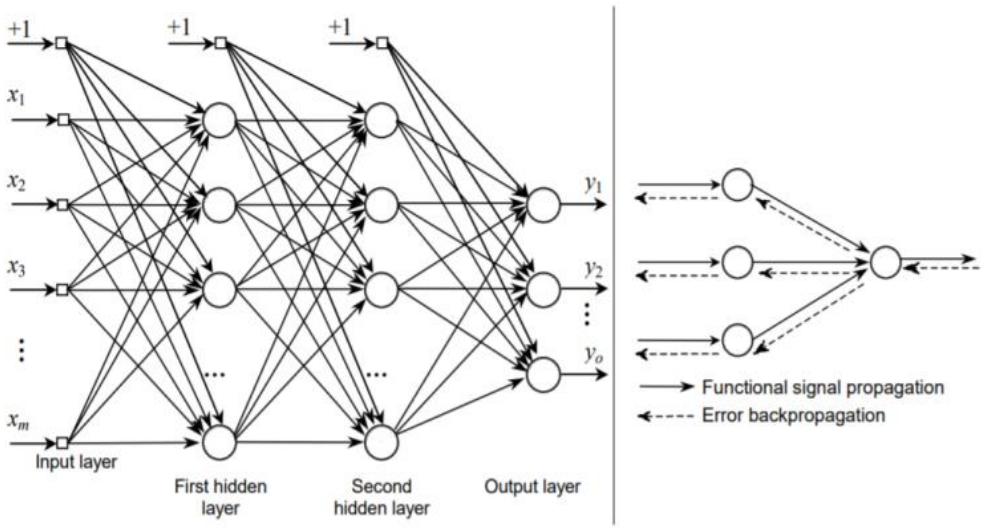


Figure 1: Multi-layer perceptron.

6. CLASSIFICATION PROBLEMS EXAMPLE

Diagnosis of breast cancer. The simulation aims to classify a tumour as benign or malignant based on the cellular descriptions collected by microscopic examination. The input attributes are, for example, the agglomerate thickness, the uniformity of the cell size and shape, the amount of marginal adhesion, and the frequency of cores discovered. The total set consists of nine entries, two exits, constituting 699 examples. All entries are continuous; 65.5% of the examples are benign. This creates entropy of 0.93 bits for example. A division of the data is presented with a sequence: 50% of the standards of each class are randomized for training (adjustment of the network's synaptic weights); 25% for validation; 25% for tests (evaluate the classification capacity of the network). The proportions between classes are not complete. They are in training groups (350 examples), validation (175 examples) and test (174 examples). To avoid that the

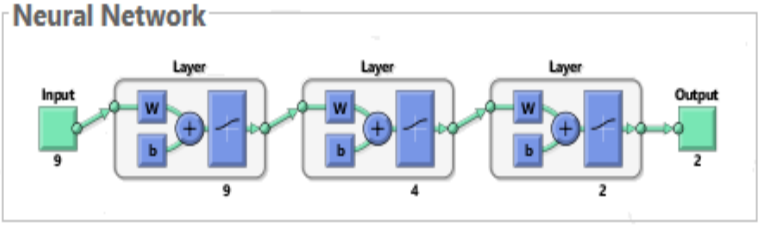
network converges to a single type, we use a partitioning and random organization of the presented data, adjusting the parameters of the network, the system will recognize the differentiation between benign and malignant cancer with less amount of epochs, of the validation set for the training set occurring the knowledge generalization which represents the best expected procedure for the neural network. As already shown, a neural network derives its computational power through, first, a massively distributed structure and, secondly, its capacity to learn and, therefore, to generalize. Generalization refers to the production of reasonable outputs of neural networks for inputs not found during training (learning). The Validation aims to accompany the learning of the generalization and specialization network, periodically to each set number of iterations (times) the network uses the validation data to perform the procedure of generalization improvement and with this producing more reasonable outputs. It is recommended that training be interrupted when the error in the validation set reaches a minimum value. From this point, it is assumed that the network would only learn irrelevant details of the training set. The error for training data would be getting smaller, but the error for new data (validation) would be getting higher and higher. In this example the following stopping criterion is used: Interrupt training when the validation error goes up for 5 consecutive iterations.The neural network presents the following results through the simulation with the MATLAB computational software, where the inputs of the network were defined with values in the fax between 0 and 1, the neurons of the hidden and output layers have a sigmoid activation function, (backpropagation), and SSE (sum of quadratic errors) defines the error used. Maximum number of iterations: 15,000; Learning rate: 0.01; Minimum training error criterion: 0.01; Criterion of the maximum number of validation failures: 5; Minimum gradient criterion: 0; Iterations between on-screen displays: 10; Maximum time (in seconds) for training: infinity.A first set of results is shown in the table1 (classification problems). This table contain the results of 10 runs training a linear neural network for the dataset [22]. The network had no hidden nodes, just direct connections from each input to each output. The output units used the identify activation function, i.e., their output is just the summed input.

Table 1 - Results of 10 runs training a linear neural network.

Problem	Training Set meanstddev	Validation Set mean stddev	Test Set mean stddev	Test Set classification mean tddev
cancer	3.95 0.52	3.77 0.47	4.77 0.49	5.00 0.61
Problem	Overfit mean stddev	Total Epochs mean stddev	Relevant Epochs mean stddev	
cancer	5.36 10.21	87 51	79 51	

bool_in=0
real_in=9
bool_out=2
real_out=0
training_examples=350
validation_examples=175
test_examples=174
0.4 0.1 0.1 0.1 0.2 0.3 0.2 0.1 0.1 1 0
0.7 0.2 0.4 0.1 0.3 0.4 0.3 0.3 0.1 0 1
0.3 0.1 0.1 0.1 0.2 0.1 0.2 0.1 0.1 1 0
0.1 0.1 0.1 0.1 0.2 0.1 0.2 0.1 0.1 1 0
0.3 0.1 0.1 0.1 0.2 0.1 0.2 0.1 0.1 1 0
[further data lines deleted]

The results of these trainings give a first impression of how difficult the problems are. There are some interesting observations to be made when compared to the results obtained with simulated neural network in the MATLAB program.



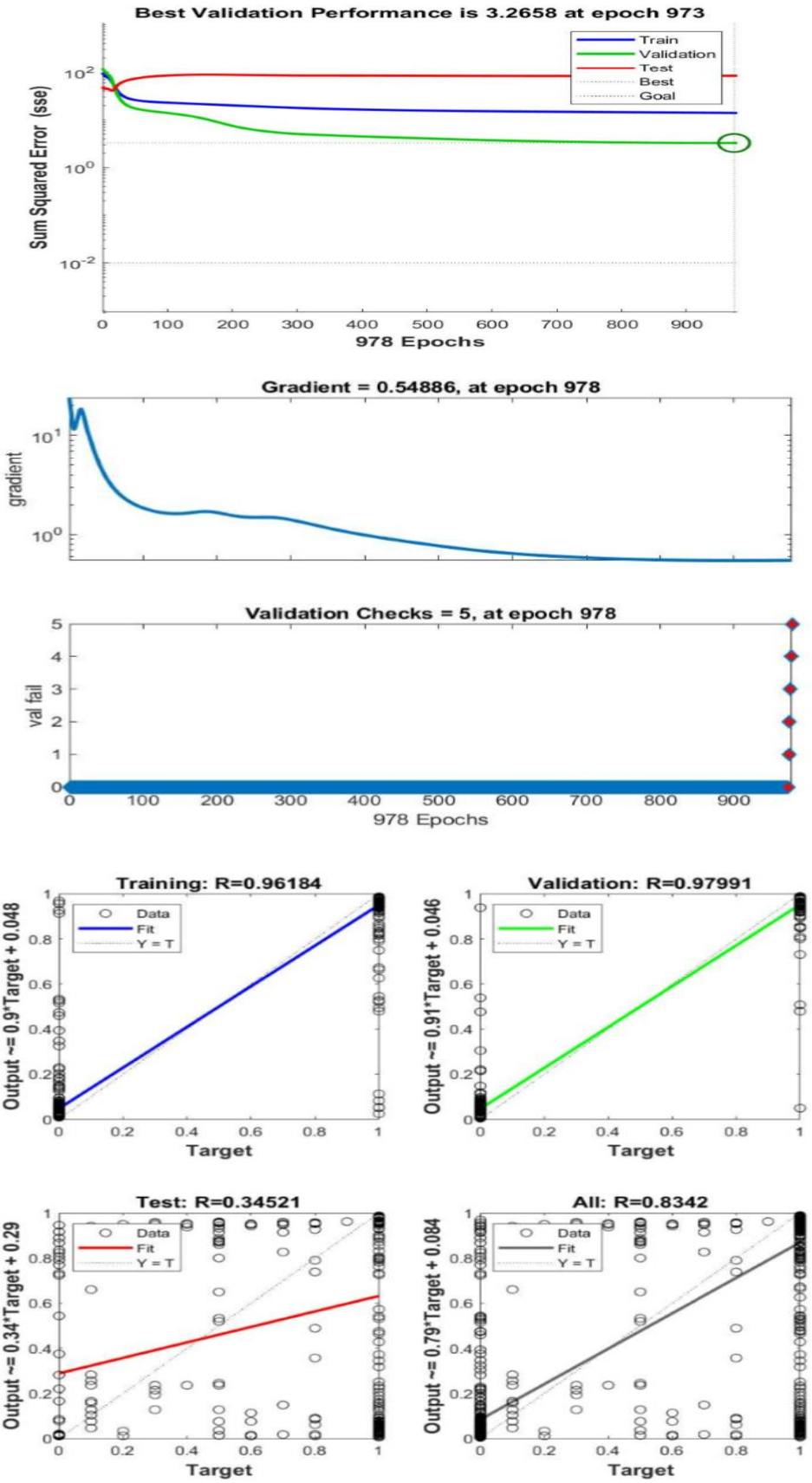


Figure 2: Neural network architecture and the results provided by MATLAB.

Usually what matters when training a neural network is its generalization performance. The value also used to characterize generalization performance is the error in a set of tests. A test set is a set of examples that were not used during the training process. This test set error is therefore the primary result for any learning problem used. As noted in the graph the number of the best value for training and the validation resemble values computed for comparating.

CONCLUSION

The treatment of dates of entry with a relatively high number of variable and amplitude served to prove the main differentials of the artificial neural network with respect to the generalization, where a directional potential is defined for the system when it refers to the production of results Neural networks for inputs not found during training (learning). The two information resources allowed the neural network to find excellent solutions to the problem of the global system that stands out by its association of data, which became imperceptible when comparing the results with the well-defined network architecture that gives more support the system in question, in this case featured in the diagnostic of breast cancer. To maintain a solution, since neural networks cannot provide an individual workaround. For optimization, they should be included in a set of systems engineering [22]. Specifically, a problem of interest becomes a relatively simple and neural number of tasks. How to redesign a subset of tasks that are inherent to your skills. This becomes important to recognize, however, that we have a long way to go (if we can) before we can build a computer architecture that mimics the human brain and is applicable to problem solving. It was verified with the analysis of the data compared with the standard system that the neural networks have an integrated capacity to adapt their synaptic weights to the changes in the environment addressed. In this particular, the neural network trained to operate in a specific environment can be easily trained to deal with changes in operating environmental conditions. In addition, when operating in a non-stationary environment (i.e., where statistics change over time), a neural network can be designed to change its synaptic weights in real time. The natural architecture of a neural network for standardization, signal processing, and control applications, together with the adaptability of the network, makes it a useful tool in the classification of adaptive patterns, adaptive signal processing and adaptive control. Its proven efficacy in a high degree of reliability for the diagnosis of breast cancer.

Research into the function of the HSCA gene can be accomplished by genomic editing by RH in HSCs[24], as well as the ex vivo correction of disease-causing mutations for the development of the next generation of gene and cell therapies.

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