Explicit Formulation of Magnetic Fields Effects on Skin Collagen Synthesis Via Neural Networks

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Abstract

It is well known that the electricity and electrical equipment which emits electromagnetic fields (EMFs) are used increasingly. Thus many people are subjected to environmental extremely-low-frequency -especially 50-60 Hz- electromagnetic fields. This study focused on two purposes: First one was planned to observe experimentally whether the skin of guinea pigs was affected by magnetic fields by determining the collagen synthesis in the skin exposed to 50 Hz magnetic fields of 1 mT, 2 mT and 3 mT with the periods of 4 hours/day and 8 hours/day for 5 days which were determined by Woessner's method. Secondly, it was aimed to get analytical expression to model the ELF effect on hydroxyproline concentrations in the skin using Neural Networks (NNs). One of the important tasks regarding these types of studies, there will be no need to extent the experiments for different range of EMFs exposing animals although the experimental results serve as a database for researchers. The experimental results as learning data and the training of the feed forward NN are applied to neural networks by using a novel approach for the selection of optimal NN architecture. The accuracy of the chosen optimal NN model is defined by standard deviation STD=0.03 and correlation coefficient R=0.98 which is found to be quite high.Thus parametric studies as a formulation are performed to see the influence of each parameter by using the proposed NN model. At the end, this NN training causes to determine the EMFs effect on tissues without exposing tissues to EMFs and without using too many guinea pigs.

Key words: Optimal NN, modeling, hydroxyproline, ELF EMF

INTRODUCTION

Many people are subjected to environmental extremely-low-frequency (ELF) electromagnetic fields (EMFs), especially to those of 50-60 Hz, with the increasing use of electricity and equipment which emits EMFs. There are many epidemiological and laboratory reports of possible association between exposure to EMFs and serious health problems, such as tumor development or cancer promotion [1-7]. It has been reported in the studies performed with tissue and tissue systems that exposure to low intensity EMF has an effect on synthesis of biomolecules (DNA, RNA, protein), tissue division, tissue surface properties, binding, and efflux and influx of calcium through membranes [6-15].

Previously, low intensity direct currents (LIDCs) were used in our research laboratory for healing skin wounds. Patient with Fournier's gangrene was healed by applying 100 μA-150 μA constant current for 18 days following two months of treatment and surgical operation [16]. Collagen synthesis was investigated by determining the hydroxyproline content of the granulation tissue formed on the base of the wound [17, 18]. The results of another investigation about constant current effect on collagen synthesis of skin wounds showed that hydroxyproline content of current-applied wounds was higher than in control wounds at the 7th and 12th day of wounding. Collagen synthesis in skin wounds of rabbits was also found to be promoted by the effects of LIDC applied at intensities of 200 μA and 400 μA, 8 hours/day for 48 and 72 hours [19, 20].

ELF magnetic fields effects on collagen synthesis were investigated in our Bioelectromagnetics Laboratory by means of ongoing studies. Guinea pigs were exposed to the magnetic fields of 1 milliTesla (mT), 2 mT and 3 mT, with the periods of 4 hours/day and 8 hours/day for 5 days in 6 different groups. Skin hydroxyproline concentrations of guinea pigs exposed to the 1 mT field were found decreased. The magnetic fields of 2 mT and 3 mT increased the hydroxyproline concentrations of exposed guinea pigs [21, 22].

Neural Networks are computer models that mimic the biological nervous system [23]. They have been used to serve as a robust tool for the formulation and modeling of complex relationships that exists between dependent and independent variables where this relationship can not be effectively modeled by conventional regression methods. There are various studies in literature on the NN modeling Electric field effect on tissues and enzymes [24-26] and recently, ELF Magnetic Fields' Effects on Lipid Peroxidation and Myeloperoxidase Activity in Kidney is formulated by using Genetic Programming in [27]. However, NNs have not been used as a tool for the formulation and the modeling of ELF magnetic fields effect on hydroxyproline concentrations in the skin so far which is the main scope of this study. Therefore, this study is planned to use Neural Network as a tool to formulate and model ELF effects on the skin of guinea pigs was affected by magnetic fields by determining the collagen synthesis in the skin exposed to 50 Hz magnetic fields of 1 mT, 2 mT and 3 mT with the period of 4 hours/day and 8 hours/day for 5 days. One of the important tasks regarding these

types of studies is the formulation and the modeling of these kind effects for further use without waste of animal which will form as a database for researchers. Furthermore, although it is not in the scope of this study, but parametric studies should be performed to see the influence of each parameter by using the proposed (optimal) NN model.

The rest of the paper is organized as follows: In the following section, it is explained Materials and Methods used in the experiments. In Section 3, A brief description of Neural Networks is summarized and subsequently, optimal neural network selection is emphasized. In Section 4, application of optimal Neural network to experimental data and its results are given. In Section 5, explicit formulation of ELF effects on the skin collagen synthesis of guinea pigs is defined. In Section 6, we discuss the results. Conclusions are presented in Section 7.

MATERIALS AND METHODS

The experimental works were conducted on sixty–three weighing 250-300 grams male guinea pigs. The experimental protocol was reviewed and approved by the Laboratory Animal Care Committee of Gazi University (Report no: 36-7838).

A specially designed pair of Helmholtz coils [28] was used to generate magnetic fields. The animals were kept in the laboratory at a room temperature of 23°C, a day and night cycle of 12 hours and an ambient geomagnetic field of 30 μT. Seven groups of Guinea pigs were formed to have one control group and six experimental groups which were exposed to 50 Hz magnetic fields of 1 mT, 2 mT and 3 mT, respectively, for a period of 4 hours/day and 8 hours/day for 5 days. The control group was also kept under the same conditions as the other animals without being exposed to any magnetic fields. When the exposure times ends, it was determined the skin hydroxyproline concentrations of exposed and unexposed guinea pigs. The term "skin" refers to epidermis and to the papillary and reticular layers of dermis, excluding the panniculus adiposus and panniculus carnosus. In order to take the specimens, hairs were carefully removed with electric clippers.

Procedure to Remove the Standard Specimens: Skin samples of each guinea pig were taken under sterilized conditions. Skin samples were cut at a specific site (left gluteal region) of each animal using surgical blade no.15 without bleeding under anesthesia with ether. They excised in sections measuring 1.5 cm x 1.5 cm were packed in aluminum foil and stored in the freezer (-20 °C) for two hours.

Determination of Skin Hydroxyproline Content: Hydroxyproline content of skin samples excised from exposed and unexposed animals was determined with Woessner's method [29]. At the end of the application of magnetic fields, skin samples were taken and hydrolyzed, without any preliminary purification, by adding 6 N HCl for 3 hours at 130°C. Several drops of 0.02% methyl red indicator were added to the hydrolysate. The pH value of sample solutions was adjusted to 6-7 with dilute HCl and 2.5 N NaOH. Two milliliters of each sample solution were transferred to tubes and their optical densities were determined spectrophotometrically at 557 nm by adding chloramine-T, perchloric acid and p-dimethyl-aminobenzaldehyde solutions according to Woessner's method [19-21]. The hydroxyproline concentrations were determined directly from the standard curves which were obtained daily with freshly prepared standard solutions.

Statistical Approach: Mann-Whitney U test was used to statistical analysis in order to compare experimental results of exposed and control groups with respect to the magnetic field intensity.

Experimental Results

Skin hydroxyproline content of a total of 63 guinea pigs was determined. Hydroxyproline levels of exposed groups were compared with controls by Mann–Whitney U test. Skin hydroxyproline concentrations and statistics of field exposed and control groups were given in Table 1.

Table 1. Skin hydroxyproline content of field-exposed and control groups

Daily Exposure Periods for 5 days	Magnetic Fields	Hydroxyproline* (mg/g wet weight)
4 hours	1 mT	23.38±2.60
	2 mT	34.25±3.50
	3 mT	28.13±2.88
8 hours	1 mT	25.00±3.76
	2 mT	28.15 ±2.46
	3 mT	31.90 ± 4.10
Controls	-	25.69 ± 2.46

(*) x ± sd: mean ± standard deviation

The results of statistical analysis were as follows:

(i) A magnetic field of 1 mT decreased the skin hydroxyproline concentration of exposed animals, but the decreases were not statistically significant for both of the exposure periods ($p>0.05$).

(ii) A magnetic field of 2 mT increased the skin hydroxyproline concentration of exposed animals, the increase was statistically significant for the exposure period of 4 hours/day ($p<0.05$).

(iii) A magnetic field of 3 mT increased the skin hydroxyproline concentration of exposed animals, and the increase was found to be statistically significant for the exposure period of 8 hours/day ($p<0.005$).

Hydroxyproline levels of exposed groups and controls is illustrated in Figure 1.

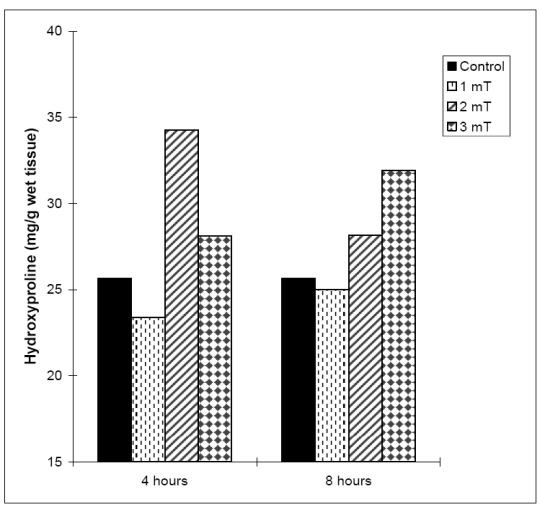


Figure 1. Changes in skin hydroxyproline levels of field exposed and control groups.

A BRIEF DESCRIPTION OF NEURAL NETWORKS

A Neural Network is accepted as a 'machine' that has remarkable ability to derive meaning from complicated data by the way biological nervous systems [23, 30]. It is designed to model the way in which the brain performs a particular task or function of interest which is usually implemented using electronic components or simulated in software on a digital computer. Neural networks are an information processing technique built on processing elements, called *neurons* that are connected to each other. A biological neuron is made up of dendrites, synapses, axon and the cell body where the dendrites receive signals from other neurons and the axon serves to form synaptic connections with other neurons. The cell body of a neuron sums the incoming signals from dendrites. If input signals are sufficient to stimulate the neuron to its threshold level, the neuron sends an impulse to its axon. The basic element of an artificial neural network composed of weights, bias ,and an activation function is shown in Figure 2.

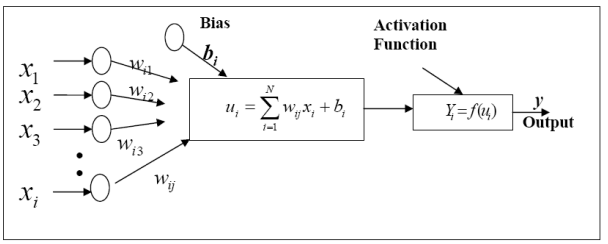


Figure 2. An Artificial Neuron Model

The internal signal u_i is defines as

$$u_i = \sum_{j=1}^{H} w_{ij} x_j + b_i \quad (1)$$

where x_j , w_{ij} and b_i represent input, weighting and bias values, respectively. The signal u_i is transformed as the output using a scalar-to-scalar function called an "activation or transfer function". The output signal *y* is expressed as

$$y = f(u_i) \quad (2)$$

The activation functions work to introduce nonlinearity into the neural networks which makes NNs so powerful.

Neural networks are commonly classified by their network topology, i.e. feedback, feedforward. All learning methods used for adaptive neural networks can be classified into two major categories as Supervised and Unsupervised learning. The most widely used supervised training method for training multilayer neural Networks is back propagation algorithm which is simple and easily applicable. It is based on the generalized delta rule and was popularized by Rumelhart et.all [31]. In the supervised learning algorithm, there is a pair of input and corresponding output.The algorithm is simply based on a weight correction procedure. It consists of two passes: a forward pass and a backward pass. In the forward pass, first, the weights of the network are randomly initialized and an output set is obtained for a given input set where weights are kept as fixed. The error between the output of the network and the target value is propagated backward during the backward pass and used to update the weights of the previous layers.

Selection of Optimal NN Model

Neural network model performances mainly depends on the network architecture and parameter settings. One of the most difficult tasks is to find an optimal Neural Network architecture which is based on determination of numbers of optimal layers and neurons in the hidden layers by trial and errormethod. The performance of the NN may be influenced by the initially assigned weights and other related parameters. However there is no well defined way in order to find optimal network architecture and parameter settings. But still, trial and error procedure remains valid although it is generally time consuming.

Considering NN applications, various Backpropagation Training Algorithms are used with the randomly assigned initial weights for each run time which considerably changes the performance of the trained NN even all parameters and NN architecture are kept constant. This situation causes to have extra difficulties for the selection of optimal NN architecture and parameter settings. To overcome this difficulty a program has been developed to handle the trial and error process automatically in Matlab. It experiences various number of layers and neurons in the hidden layers both for first and second hidden layers for a constant epoch for several times. Thus it selects the best NN architecture with the minimum MAPE (Mean Absolute % Error) of the testing set, as the training of the testing set is more critical. As an example, a NN architecture with 1 hidden layer with 7 nodes is tested 10 times and the best NN is stored where in the second cycle the number of hidden nodes is increased up to 8 and the process is repeated. The best NN for cycle 8 is compared with cycle 7 and the best one is stored as best NN. This process is repeated N times where N denotes the number of hidden nodes for the first hidden layer. This whole process is repeated for changing number of nodes in the second hidden layer. More over this selection procedure is experienced for different backpropagation training algorithms such as trainlm, trainscg and trainbfg. It begins with simplest NN architecture with 1 hidden node for the first and second hidden layers and ends up with optimal NN architecture. The optimal NN model selection process and its application in detail can be found in [32, 33].

NEURAL NETWORK APPLICATION AND RESULTS

This section covers the application of optimal neural network based on experimental results shown in Table 1 in order to formulate and model the effect of 50 Hz magnetic fields of 1 mT, 2 mT and 3 mT on the amount of skin collagen.

The experimental results are formed as train and test sets. The patterns in test set are randomly selected among the experimental database which are shown in bold characters in Table 2. The optimal NN architecture was found to be 3-5-1 NN architecture with logistic sigmoid transfer function (logsig). Quasi-Newton backpropagation (BFGS) is used as the training algorithm. The experimental values and results obtained by proposed NN model and their predictions are given in Table 2. Statistical parameters

Table 2. Results of NN model vs Experimantal results

Magnetic Field (mT) (50 Hz)	Time (hr)	Control Group	TEST	NN	TEST/NN
1	**4**	**20.74**	**17.75**	**20.50**	**0.87**
1	4	23.74	21.90	22.15	0.99
1	4	24.08	22.32	22.35	1.00
1	4	25.75	23.00	23.43	0.98
1	4	26.45	24.15	23.97	1.01
1	**4**	**26.50**	**24.23**	**24.01**	**1.01**
1	4	26.83	25.35	24.30	1.04
1	4	28.20	25.50	25.78	0.99
1	4	28.62	26.15	26.38	0.99
1	8	20.74	19.65	19.51	1.01
1	**8**	**23.74**	**21.73**	**22.55**	**0.96**
1	8	24.08	22.61	22.84	0.99
1	8	25.75	24.76	24.33	1.02
1	8	26.45	24.99	25.16	0.99
1	8	26.50	25.02	25.23	0.99
1	**8**	**26.83**	**25.13**	**25.75**	**0.98**
1	8	28.20	28.71	29.56	0.97
1	8	28.62	32.37	31.79	1.02
2	4	20.74	30.00	29.13	1.03
2	4	23.74	30.37	31.05	0.98
2	**4**	**24.08**	**31.56**	**31.39**	**1.01**
2	4	25.75	32.74	33.63	0.97
2	4	26.45	34.91	34.93	1.00
2	4	26.50	35.28	35.04	1.01
2	4	26.83	36.03	35.75	1.01
2	**4**	**28.20**	**36.25**	**39.49**	**0.92**
2	4	28.62	41.14	40.90	1.01
2	8	20.74	24.89	24.93	1.00
2	8	23.74	25.34	25.83	0.98
2	8	24.08	25.88	26.01	1.00
2	**8**	**25.75**	**27.98**	**27.32**	**1.02**
2	8	26.45	28.16	28.14	1.00
2	8	26.50	28.96	28.21	1.03
2	8	26.83	29.46	28.67	1.03
2	8	28.20	30.52	31.18	0.98
2	**8**	**28.62**	**32.25**	**32.15**	**1.00**
3	4	20.74	24.49	24.63	0.99
3	4	23.74	26.11	25.72	1.02
3	4	24.08	26.16	25.93	1.01
3	4	25.75	26.79	27.46	0.98
3	**4**	**26.45**	**27.28**	**28.42**	**0.96**
3	4	26.50	28.04	28.49	0.98
3	4	26.83	29.97	29.03	1.03
3	4	28.20	30.26	31.77	0.95
3	4	28.62	34.03	32.76	1.04
3	**8**	**20.74**	**25.21**	**26.44**	**0.95**
3	8	23.74	27.21	28.26	0.96
3	8	24.08	30.25	28.62	1.06
3	8	25.75	30.77	31.05	0.99
3	8	26.45	31.38	32.44	0.97
3	**8**	**26.50**	**33.87**	**32.54**	**1.04**
3	8	26.83	34.27	33.27	1.03
3	8	28.20	36.50	36.62	1.00
3	8	28.62	37.65	37.68	1.00
				MEAN	**1.00**
				***STD**	**0.03**
				***R**	**0.98**

***STD:** Standard Deviation, **R:** Correlation Coefficient

* Bold sets are test sets

of normalized values of learning and training sets are presented in Table 3. The performance of the proposed NN model vs. experimental result is shown in Figure 3.

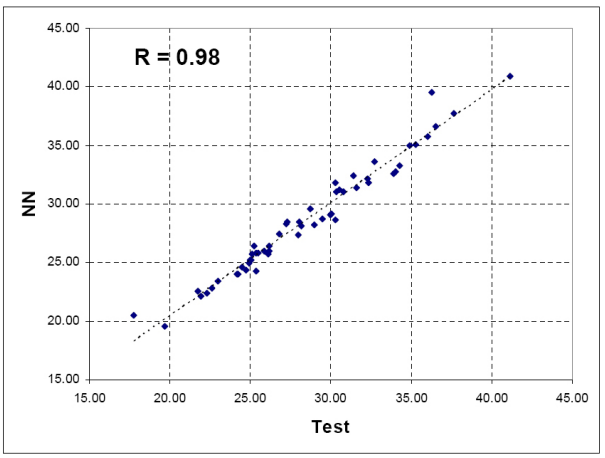


Figure 3. Performance of NN vs Test Results

EXPLICIT FORMULATION

The trained NN in this study does not serve as a black box anymore as it is considered in most of the NN studies. The main aim is to present the hydroxyproline output (HO) as a function of Magnetic Field (MF), time (t) and Control Value (CV). The explicit formula of the trained NN is obtained using the weights of the trained network given as follows:

$$Net_j = \sum_{i=1}^{n} w_j x_i \tag{3}$$

where Net_j is the weighted sum of the jth neuron for the input received from the preceding layer with n neurons, w_{ij} is the weight between the jth neuron and the ith neuron in the preceding layer, x_i is the output of the ith neuron in the preceding layer. The output of the jth neuron out_j is calculated with a sigmoid function as follows:

$$out_j = f\left(Net_j\right) = \frac{1}{1+\exp\left(-kNet_j\right)} \tag{4}$$

where k is a constant used to control the slope of the semi-linear region.

Recalling Eqs (1) and (2) the explicit formula is obtained by using the weights of the trained network given step by step as follows:

$$u_i = \sum_{i=1}^{N} w_{ij} x_i + b_i \quad \text{and} \quad Y_i = f(u_i) \tag{5}$$

where u_i is the summation of the ith node and Y_i is the output of transfer function of this summation. The inputs *MF, t, CV* should be first normalized by 3, 8 and 28.62 respectively and then enter to the equations shown below. The output in the NN model is normalized by 41.14. Thus the hydroxyproline output HO will be

$$HO = 41.14(A+B+C+D+E-3.347) \tag{6}$$

where *A, B, C, D* and *E* functions are defined as follows

$$A = \left[\frac{4.041}{1+e^{-(-12.45MF+11.22t-6.62CV+11.79)}}\right]$$

$$B = \left[\frac{0.69}{1+e^{-(2.96MF+0.78t+12.51CV-16.31)}}\right]$$

$$C = \left[\frac{-3.86}{1+e^{-(-7.71MF+25.43t-1.86CV-11.71)}}\right]$$

$$D = \left[\frac{3.76}{1+e^{-(11.13MF+21.81t+7.06CV-27.28)}}\right]$$

$$E = \left[\frac{3.6}{1+e^{-(-15.93MF+6.56t+30.74CV-35.43)}}\right]$$

DISCUSSION

Considering Figure 1 and Table 1, hydroxyproline concentrations of guinea pigs exposed to the 1 mT field were found decreased with respect to controls. Electromagnetic fields of 2 mT and 3 mT increased the hydroxyproline concentrations of exposed guinea pigs, 2 mT was found to be more effective than 3 mT for the exposure times of 4 hours/day, whereas 3 mT was found more effective than 2 mT for the exposure times of 8 hours/day [21, 22].

It is obvious from statistical results given in Table 3 as the standard deviation STD=0.03 and the correlation coefficient R=0.98 which is found to be quite high that the proposed NN model accurately learned to map the relationship between varying parameters. On the other hand, as duration increases up to 8 hours, the difference between 2 mT and 3 mT decreases. A detailed parametric study should perhaps be the scope of another article to see the effects of ELF magnetic field different exposing time.

The experimental results of skin hydroxyproline concentration are formulated by neural network as shown in Eq (6), thus there will be no need to extend the experiments for different range of electrical currents exposing animals for different duration of time. This formula can be used as

Table 3. Statistical Parameters for optimum NN Model

	MAPE (%)	**Mean** (Test / NN)	**STD** (Standard Deviation)	**R** (Correlation Coefficient)
Test set	4.34	0.98	0.05	0.97
Train Set	1.76	1.00	0.02	0.99

(**MAPE:** Mean Absolute Percentage Error)

an interpolation function to produce new data values without doing related experiments.

CONCLUSION

In this study, skin hydroxyproline levels of guinea pigs exposed to 50 Hz magnetic fields of 1 mT, 2 mT and 3 mT were formulated and modeled using the optimal NN with parametric studies i.e. exposure duration. The accuracies of the proposed NN models are defined by the standard deviations (3%) and correlation coefficients found to be quite high (98%) for the ordered data sets. As a result of this study, it can be concluded that NNs can be effectively used to formulate and model complex relationships especially where no valid models exist as in the case of hydroxyproline levels in the skin considered in this study. Furthermore the proposed NN enables to determine the possible triggering level(s) through studying a greater number of application periods and field intensities without additional experimental studies in the ongoing parts of our study. NNs are in general treated as black box in most of the studies in literature. However this study has presented that NNs can be modeled as an analytical expression in the form of an explicit formulation which will enable the the proposed NN model for further use by other researchers. As a future work, some of other soft computing methods with a detailed parametric study of these kind of experiments should perhaps be the scope of another article.

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