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A method of gene diagnosis based on Hopfield neural network

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ABSTRACT

The stability of discrete Hopfield neural networks not only has an important theoretical significance, but also is the foundation of the applications of the networks. Security of the algorithm is discussed .ANN originated has been applied in all aspects of life and production, especially in intelligent control, nonlinear function approximation and environmental parameters forecast assessment. Be similar to the human's brain mechanism, a neural network complete the tasks by the process of learning (training) and use (associative memories). Normally, the neural network can be assured used only after thorough study. According to the dynamic characteristics of the interconnections between nerve cells in Hopfield network, this paper discusses the application of Hopfield network model in gene diagnosis, points out the network problems and puts forward the solutions.

Keywords: Artificial neural network, Gene diagnosis, Weight

INTRODUCTION

In recent years, the application of neural network has made great achievements, pattern recognition is one of the earliest and most extensive field in this research area. Artificial neural network is a nonlinear, adaptive information processing system consisting of a large number of interconnected processing elements. It is based on the research results of modern neuroscience, it attempts to process information by simulating the information processing, memorization of information of the brain neural network.

Artificial neural network has four basic characteristics:

(1) Nonlinear characteristics
The nonlinear characteristics is the common properties in nature[1]. Brain wisdom is a nonlinear phenomenon. Artificial neurons are in two different states, one is the activation state ,and the other is the inhibition state, this behavior is a nonlinear relationship in mathematics. The artificial neural network composed of threshold neurons has better performance, it can improve the fault tolerance and storage capacity.

(2)Non-limitation characteristics
A neural network is usually composed of a lot of neurons[2], the overall behavior of a system does not only depend on the characteristics of a single neuron, but also depends on the connection and interaction of the neurons. It simulates the non-limitation of brain through a large number of connections among the neurons. Associative memory is a typical example of non limitation.

(3)Non-qualitaty characteristics
Artificial neural network has the ability of adaptive, self-organizing, self-learning[3]. The information processed in artificial neural network can be a variety of changes, and the nonlinear dynamic system is also changing at the same time. We describe the evolution of artificial neural network system using iterative process.

(4)Non-convexity
The evolution of a system depends on a particular state function under certain conditions. For example, an energy function, its extreme value corresponds to a stable state of the system. The non-convexity means that there are some extreme values in this function, so there are some stable equilibrium states in this system, this leads the diversity of evolution of the system.

In a neural network, the processing unit can represent different objects, such as characters, letters of an alphabet, figures, or some abstract model. The types processing of unit are divided into three categories: the input unit, the output unit, the hidden unit. The input unit receives the signal and data from the outside, the output unit export the results of the system; the hidden unit is between the input unit and the output unit, it can't be seen from outside.

A neural network is a king of computing model, it is composed of a large number of nodes (neurons), each node is a specific output function, it is called activation function[4]. Each connection between two nodes represents a value, it is called weight, the weight means the strength between nodes. The output is related to the weight, activation function and the connection mode of the neural network.

Figure 1 shows that, a1-an are the components of the input vectors;
Matrix A is the input vector, matrix A' is the transposed vector of matrix A;
w1-wn are the weight of each synapse;
Matrix W is the weight vector;
b is the polarization;
F is a transfer function, usually it is a nonlinear function;
t is the output of a neuron;

The transfer function is shown in Formula (1):

$$t = f(WA' + b) \tag{1}$$

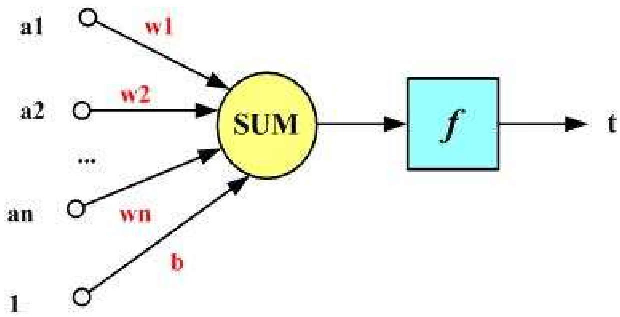

Figure 1. The function of a single neuron

The function of a single neuron is to calculate the inner product of the input vector and the weight vector[5],and the inner product is processed through a nonlinear transfer function, then it produces a scalar result.

Another function of a single neuron is to divide an n-dimensional vector space into two parts using a hyper plane, the hyper plane is called decision boundary. Given an input vector, a neuron can judge the vector on which side of the hyper plane.

The function of the hyper plane is:

$$Wp+b=0 \tag{2}$$

Where W is the weight vector;
b is the polarization;
p is the vector on the hyper plane.

1.1. *Hopfield neural network*
In 1982, a physical scientist of California Institute of Technology USA, J. J. Hopfield presented a model of Hopfield neural network, introduced the concept of computing power, and given the network stability criterion.

In 1984, J. J. Hopfield presented Continues Hopfield Neural Network, created a new way of neural network for associative memory and optimization calculation, and gave a strong impetus to the development of neural network.

Structure of the Hopfield neural network: Hopfield neural network model is composed of a single layer of interconnected neurons, there is no self-connected neurons[5], that is: $W_{ii} = 0$, the connections among neurons are symmetrical, that is: $W_{ij} = W_{ji}$, each neuron is connected with other neurons, the output signal of a neuron may be feedback to itself from other neurons, the weight between i-th neuron and j-th neuron is W_{ij}:

$$W_{ij} = \begin{cases} \sum_{s=1}^{m} x_i^s x_j^s & , i \neq j \\ 0 & , i = j \end{cases} \tag{3}$$

In Hopfield neural network there n neurons, where the input of any neuron is $X_i(t)$,the output is $X_i(t+1)$, they are functions of time, they are the states of neurons at time t. Figure 2 and Figure 3 are the structure diagrams of Hopfield neural network.

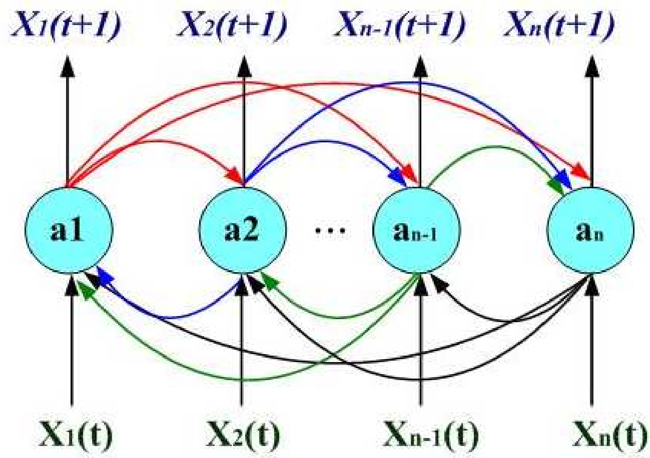

Figure 2. Structure diagram of Hopfield neural network (1)

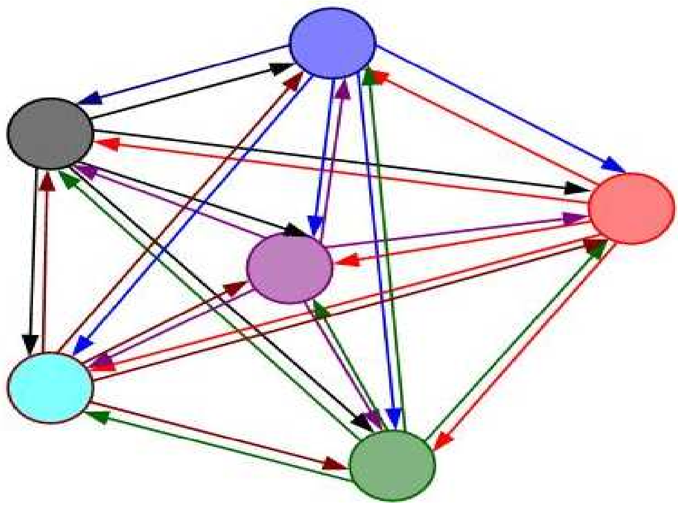

Figure 3. Structure diagram of Hopfield neural network (2)

Matrix calculation of Hopfield neural network:In Hopfield neural network, neurons actually are a kind of linear threshold units. In Figure 2 ,x_1,x_2,…,x_n are the input of adaptive linear elements at time t, it is described as a vector in formula (4):

$$X = (x_1, x_2, ..., x_{n-1}, x_n)^T \quad (4)$$

The output of Hopfield neural network is:

$$Y = X^T W = (y_1, y_2, ..., y_n)^T \quad (5)$$

here W is a matrix, and

$$W = \begin{bmatrix} 0 & w_{12} & w_{13} & \cdots & w_{1n} \\ w_{12} & 0 & w_{23} & \cdots & w_{2n} \\ w_{13} & w_{23} & 0 & \cdots & w_{3n} \\ \cdots & \cdots & \cdots & 0 & w_{4n} \\ w_{1n} & w_{2n} & w_{3n} & \cdots & 0 \end{bmatrix} \quad (6)$$

and $$y_k = \sum_{\substack{i=1 \\ i \neq k}}^{n} w_{ik} a_i \quad (7)$$

The two-value output of Hopfield neural network is:

$$a_k(t+1) = \mathrm{sgn}\,(y_k - \theta_k) = \begin{cases} 1 & y_k \geq \theta \\ -1 & y_k < \theta \end{cases} \quad (8)$$

And $$y_j(t+1) = f(u_j(t)) = \begin{cases} 1 & u_j > 0 \\ -1 & u_j < 0 \end{cases} \quad (9)$$

Hopfield Neural Network is composed of two forms: continuous Hopfield neural network and discrete Hopfield neural network.

1.2. *Discrete Hopfield neural network*

Discrete Hopfield neural network is a kind of two-valued function, the output of neurons are "1" and "-1" , "1" and "-1" are used to describe the neurons in the activation and inhibition[6].

We studied the discrete Hopfield neural network composed of three neurons, its structure diagram is shown in Figure 4.

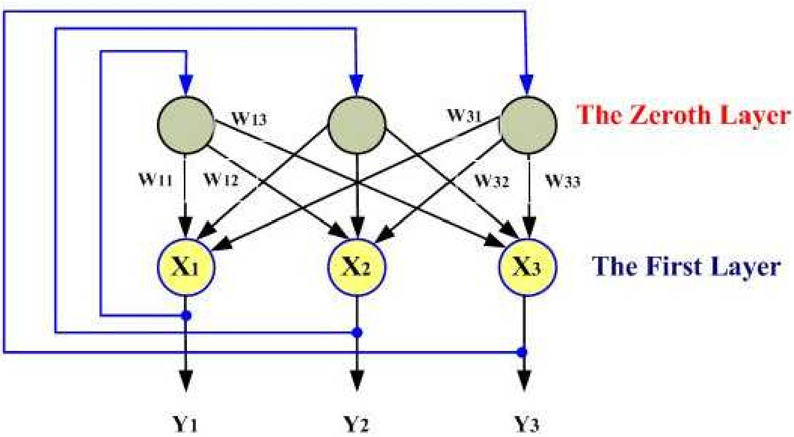

Figure 4. Structure diagram of Hopfield neural network composed of three neurons

In Figure 4,the zeroth layer is only the input of the network, they are not real neurons, so the zeroth layer has no calculating function. There are real neurons in the first layer, the first layer calculates the accumulation of the product of the input and the weight. If the output information is greater than the threshold value, the output value is 1, or it is -1.We studied the status of the nodes in discrete Hopfield neural network, yj(t) is the j-th neuron, it is the status of node j at time t, the next status of the node at time t is shown in formula (10) and formula (11).

$$y_j(t+1) = f(u_j(t)) = \begin{cases} 1 & u_j > 0 \\ -1 & u_j < 0 \end{cases} \quad (10)$$

and $u_j(t) = \sum_{i=1}^{n} W_{ij} y_i(t) + x_j - \theta_i$ (11)

In discrete Hopfield neural network, the state of the network is a collection of information of neurons. For an N-neuron network, the state at time t is an n-dimensional vector, so the network has 2n states. Because Yj(t)(j=1,2,…,n)=0 or 1,so the n-dimensional vector Y(t) has 2^n states. For a Hopfield neural network composed of three neurons, its output layer are 3-bit binary number, each binary number is a network status, so there are 8 network status, they are shown in Figure 5.

According to the dynamic mode, the discrete Hopfield neural network evolves from an initial state to the direction of the energy reducing. At last the it reaches a steady state.

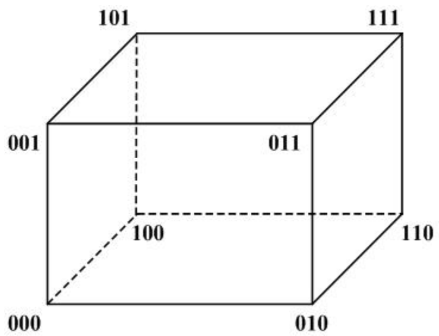

Figure 5. Network state of Hopfield neural network composed of three neurons

In Figure 5, each vertex of the cube represents a network state. so for an N-neuron network, there are 2n network state, they correspond to the vertices of an n-dimensional hypercube. If the discrete Hopfield neural network is a a stable network, then add an input vector in the network, then the network state will change, it transfer from a vertex of the hypercube to another vertex, and it eventually stabilizes at a specific vertex.

1.3. *Continues Hopfield Neural Network*

Continues Hopfield Neural Network is similar to discrete Hopfield neural network, the difference is that the transfer function is no longer a jump function, but a continuous function[7].Usually the continuous function is:

$$g(u) = 1/(1+e^{-u}) \quad (12)$$

Because of its continuity in time, the manner of its implementation is parallel mode, processing data can be carried out simultaneously. Two conclusions can be drawn from the energy function and dynamic formula of continues Hopfield neural network, one is when the transfer function of neurons in network is monotonically increasing and the weight matrix of the network is symmetric, the energy of the network will decrease or remain the same with the changing of the time, and the other is that when and only when the output of the neurons do not change over time, the network energy will not change.

When Hopfield neural network is used as associative memory, It can be divided into two stages: The learning phase and the associative stage[6].

1.4. *Learning rules of Hopfield neural network*

Learning rules are algorithms changing the connection strength of weight among neurons, and make the knowledge structure suitable for the surrounding environment.

If two neurons are excited at the same time, the increase of the connection strength is proportional to the product of their excitation.

Parameter y_i is the activation value (output) of neuron I, parameter y_j is the activation values of neuron I, wij is the weight between neuron I and neuron j, Hebb learning rules can be expressed as formula(8):

$$\Delta w_{ij}(k) = \eta \cdot y_i(k) y_j(k) \tag{8}$$

Where η is the learning rate.

The task of the learning phase is: when the Hopfield neural network is used as associative storage, the assignment rule of the weight is called apposition storage rule[8]. Suppose that there are m sample vectors X_1, X_2,... X_m to be stored in Hopfield neural network, adjusting the weight W_{ij} according to the Hebb learning rules, the storage of samples become the attractors of the Hopfield neural network system.

1.5. ***Memory process of Hopfield neural network***

The task of the memory phase is: after the W_{ij} has been adjusted, input incomplete or disturbance information to the Hopfield neural network system, make it be an associative keyword, change the state of neuron according to dynamic rules[9], the final steady state is the attractor .

In discrete Hopfield neural network the function of neurons is a sign function, The states of network nodes have only two values: +1 and -1,from the perspective of dynamics, if the initial state of the network node is X(t),the weight is W_{ij} , after running t steps, the system is in state X(t+1),it is shown in formula (9).

$$X_i(t+1) = \mathrm{sgn}[\sum_{j=1}^{N} W_{ij} X_j(t) + \theta_i] \tag{9}$$

The energy function is bounded, the system must reach a stable state eventually, or reaches a few cycle state, these states are the attractors of nonlinear dynamic system, the local minimum points of a energy function.

EXPERIMENTAL SECTION

2.1. ***Problem description***

In clinical medicine, one of the best diagnostic method on infectious diseases is the method of pathogen diagnosis, and among the method of pathogen diagnosis the most reliable method is the gene diagnosis. However, at present the clinical medicine for many diseases, especially for the virus infectious diseases, there is no good etiological diagnosis method. The commonly used method of enzyme linked immunosorbent assay, radioimmunoassay, cannot achieve the purpose of gene diagnosis.PCR polymerase chain reaction is the most advanced DNA detection method, while because of some unpredictable reagent and chemical reaction, the credibility of detection greatly reduces, it will result in both false positives and false negatives. And there are requirements for test specimens, the storage time of specimens cannot be too long, this causes the test is not accurate In some cases, such as the method of medical examination, the victim was found after a long time, and his identity could not be determined, it is usually used gene detection method, but after the body corrupted, nucleic acid have dissolved, it only left debris.

In this paper, we proposed a novel method of gene diagnosis based on Hopfield neural network, and this improves the feasibility and accuracy of gene diagnosis. Using the self associating function of Hopfield neural network, we built a gene bank, the fragments of specimens can be recovered.

The problems of DNA untwisting, sequencing of samples are not the main issue of this paper. At present, these technologies has matured in the medical field.

2.2. ***DNA samples***

The base pair sequence has four combination, we used two neurons to detect a base pair, if some parts of DNA bases were lost, they can be regarded as any kind of base pairs randomly. According to the algorithm of Hopfield neural network, the system can converge to the standard state.

In this system we used 60 neurons to detect 30 base-pair sequences, We used the following method to mark the four base pairs: A-T corresponds to the input value(1,1),T-A corresponds to the input value (1,-1),C-G corresponds to the input value(-1,-1),G-C corresponds to the input value(-1,1),here A represents the adenine, T represents the thymine, C represents cytosine, G represents guanine. A only matches T,C only matches G, the missing parts of DNA bases can be any base pairs, and they are can be 0.

We provided 4 groups of samples, they were shown in below:

The first group of sample: the input is "A-T C-G A-T A-T A-T A-T T-A A-T A-T C-G A-T C-G A-T A-T A-T T-A A-T G-C A-T A-T A-T C-G A-T A-T A-T A-T G-C A-T A-T A-T", the corresponding digital vector is (1, 1, -1, -1, 1, 1, 1, 1, 1, 1, 1, 1, 1, -1, 1, 1, 1, 1, -1, -1, 1, 1, -1, -1, 1, 1, 1, 1, 1, 1, 1, -1, 1, 1, -1, -1, 1, 1, 1, 1, 1, 1, -1, -1, 1, 1, 1, 1, 1, 1, 1, 1, -1, 1, 1, 1, 1, 1, 1, 1).

The standard is "G-C C-G A-T T-A A-T A-T T-A A-T A-T C-G A-T A-T A-T A-T A-T A-T A-T G-C A-T A-T A-T A-T A-T A-T A-T A-T A-T A-T A-T C-G", the corresponding digital vector is (-1, 1, -1, -1, 1, 1, 1, -1, 1, 1, 1, 1, 1, -1, 1, 1, 1, 1, -1, -1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, -1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, -1, -1).

The second group of sample: the input is "A-T C-G A-T G-C T-A A-T C-G C-G A-T T-A T-A T-A C-G G-C A-T T-A A-T G-C G-C C-G T-A T-A G-C A-T G-C A-T A-T G-C A-T A-T", the corresponding digital vector is (1, 1, -1, -1, 1, 1, -1, 1, 1, -1, 1, 1, -1, -1, -1, -1, 1, 1, 1, -1, 1, -1, 1, -1, -1, -1, -1, 1, 1, 1, 1, -1, 1, 1, -1, 1, -1, 1, -1, -1, 1, -1, 1, -1, -1, 1, 1, 1, -1, 1, 1, 1, 1, 1, -1, 1, 1, 1, 1, 1).

The standard is "A-T C-G G-C G-C T-A A-T C-G C-G A-T A-T T-A T-A C-G G-C C-G T-A T-A G-C G-C C-G T-A T-A G-C A-T G-C A-T A-T T-A A-T A-T", the corresponding digital vector is (1, 1, -1, -1, -1, 1, -1, 1, 1, -1, 1, 1, -1, -1, -1, -1, 1, 1, 1, 1, 1, -1, 1, -1, -1, -1, -1, 1, -1, -1, 1, -1, 1, -1, -1, 1, -1, 1, -1, -1, 1, -1, 1, -1, -1, 1, 1, 1, -1, 1, 1, 1, 1, 1, 1, -1, 1, 1, 1, 1).

The third group of sample: the input is "A-T O-O O-O O-O A-T O-O C-G O-O O-O C-G T-A O-O O-O T-A T-A T-A T-A O-O O-O T-A A-T O-O O-O A-T A-T O-O O-O O-O O-O O-O"(O means the deletion of base pairs), the corresponding digital vector is (1, 1, O, O, 0, 0, 0, 0, 1, 1, O, O, -1, -1, 0, 0, 0, 0, -1, -1, 1, -1, 0, 0, 0, 0, 1, -1, 1, -1, 1, -1, 1, -1, 0, 0, 0, 0, 1, -1, 1, 1, 0, 0, 0, 0, 1, 1, 1, 1, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0).

The standard is "A-T A-T A-T A-T A-T C-G C-G C-G C-G C-G T-A T-A T-A T-A T-A T-A T-A T-A T-A T-A A-T A-T A-T A-T A-T G-C G-C G-C G-C G-C ", the corresponding digital vector is (1, 1, 1, 1, 1, 1, 1, 1, 1, 1, -1, -1, -1, -1, -1, -1, -1, -1, -1, -1, 1, -1, 1, -1, 1, -1, 1, -1, 1, -1, 1, -1, 1, -1, 1, -1, 1, -1, 1, -1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, -1, 1, -1, 1, -1, 1, -1, 1, -1, 1).

The fourth group of sample: the input is "A-T C-G G-C C-G C-G C-G O-O O-O O-O A-T T-A C-G T-A C-G C-G A-T A-T O-O A-T A-T A-T A-T A-T A-T A-T C-G A-T A-T A-T A-T", the corresponding digital vector is (1, 1, -1, -1, -1, 1, -1, -1, -1, -1, -1, -1, 0, 0, 0, 0, 0, 0, 1, 1, 1, -1, -1, -1, 1, -1, -1, -1, -1, -1, 1, 1, 1, 1, O, O, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, -1, -1, 1, 1, 1, 1, 1, 1, 1, 1).

The standard is "C-G C-G C-G C-G C-G C-G C-G C-G C-G C-G C-G C-G C-G C-G C-G A-T A-T A-T A-T A-T A-T A-T A-T A-T A-T A-T A-T A-T A-T A-T", the corresponding digital vector is (-1, -1, -1, -1, -1, -1, -1, -1, -1, -1, -1, -1, -1, -1, -1, -1, -1, -1, -1, -1, -1, -1, -1, -1, -1, -1, -1, -1, -1, -1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1).

The first and the second group samples can be considered as a variation in the gene, or wrong detection in chemical process. The third and the fourth groups of specimens can be considered as the gene is not complete.

2.3. *Algorithm*

This is a standard algorithm of Hopfield neural network, it is based on two valued neural networks.

First assign the 4 element x1,x2,…,xn of pattern vector X to the corresponding neurons, the vector is the initial state of the corresponding neurons, that is $a_i(0) = xi$.

Then operated according to the dynamic characteristics of SGN function, repeated iterative calculation, until the system convergenced.

When the neural network reached a steady state, The output of neurons is the standard sample matching the input pattern mode of X, and it completed the information memory.

After the network was established, input a stochastic vector to the network, through the simulation network, we can obtain the output of the network, the input delaying at the end of training, the lay delaying at the end of training. By adjusting the number of batch data and the time step of network simulation, we can get different output.

RESULTS AND DISCUSSION

After running the program, it can be found that the expected results of all four groups samples were obtained by calculating. Through the analysis of the calculating process, it can be found that the system has reached a steady state only after two iterative computation on the first and the second groups of samples. This shows that the system has strong function of self association, in theory it is feasible for gene diagnosis.

We use the noise average of 0, mean square error in the range of [0,0.5], interval of 0.05 white noise model to detect this neural network, it produced 100 groups of samples from each different variance of white noise, then we used these samples to simulate the network, and calculated the error rate of 100 groups of samples according to the simulation results. In order to test the system, we tested the first group of specimens, and added the noise average of 0,then we analyzed the output, we found that, after learning, Hopfield neural network can correctly identify all samples.

Compare the method proposed in this paper with the methods using BP neural network to identify genetic samples in the references [3,10], under the same conditions of white noise mentioned above, it can be found that before the noise level is greater than 0.3, the fault tolerance of the system is greater than that of BP neural network, but when the noise level is greater than 0.3, the fault tolerance of Hopfield neural network is weaker than that of BP neural network.

The simulation results show that, before the variance of noise is greater than 0.15, the Hopfield neural network system can identify genetic samples correctly, by adjusting the simulation time and steps constantly, we can improve the ability of fault tolerance of the system.

CONCLUSION

The simulation results show that the method is feasible in theory. Genes can be identified quickly. But there are still many difficulties. The number of biological gene sequence is very large, so it need the same number of neurons, at present it is very difficult to achieve the goal: On a microcomputer, we often complete the iterative calculation through multi cycle, it makes the advantages of neural computation almost reduce to 0,and it requires a vector computer. The communication and the synchronization among neurons is also a problem. Only considering a new type of computer architecture can give full play to all the advantages of a neural network. In addition, it need to build a large gene bank, that can provide enough standard samples. The performance of Hopfield neural network limits the number of samples is less than the number of neurons, it also requires a huge number of neurons.

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