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Analysis of Disease Association and Susceptibility for SNP Data Using Emotional Neural Networks

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Abstract—**The risk of some complex diseases are likely related to single nucleotide polymorphisms (SNPs), which are the most common form of DNA variations. Rapidly developing bioinformatics have made it possible to recognize a group of SNPs as the risk/protective factors of a specific disease, which are related to the possibility of the sample be infected. However, a particular algorithm to consider this kind of tendency information together is still in need. In this paper, inspired form the process that human beings to make a decision, we regard the risk/protect factor in the gene variations as the emotional of our nervous system. In this way, we regard these SNP combination factor as prior knowledge and use the emotional neural networks (ENN) to analysis the disease susceptibility. By sending this kind of information to ENN and using particle swarm optimization with hierarchical structure (PSO_HS) to train the parameters, we get a better result of susceptibility classification. The experimental results about real dataset shows that consider the risk/protect factor by emotional neural networks improve the performance of disease susceptibility analysis.**

I. Introduction

THE risks of developing some complex diseases are influenced by single nucleotide polymorphisms (SNPs), which are the most common form of DNA variations. Searching for genetic factors that influence phenotype, such as a disease, is the major goal of modern geneticists. Increasing empirical evidence suggests that interactions among loci contribute widely to complex human disease[1, 2]. Some studies is about to look for the most disease associated (risk) and the most disease resistant (protective) k SNP sets[3, 4]. Some other researchers have also discovered many SNP interactions pairs or groups which are related the possibility for us to suffer the disease[5, 6]. Furthermore, this kind of information is used to classify of normal and disease people. However, it is clear that the DNA variation is not the only decisive factor for us to get sick or not. It's just a kind of tendency information that may be helping us to know the tendency for a particular person to be sick or not. So a method which can use these tendency features in the classification is in need.

Emotion is biological and psychological process in humans. When we are difficult to choose and help us to make a decision, the emotion can give us a tendency [7]. Our behavior is not only depending on this kind of tendency information, what's more, emotions are sometimes regarded as the antithesis of reason. However, on the other hand, many researchers have already notice the fact that emotion can develop and work hand in hand and play an important role in human decision-making process[8-10]. Researchers studying in the field of neuroscience, psychology and cognitive sciences also indicating the surprising role of emotions in human intelligent behavior, and emphasizing that emotions are inseparable from every action of perception and cognition[11]. By using the emotion, which is a kind of tendency information, our brains make better decision. Can we use the tendency information: risk/protect factor to improve our artificial intelligence systems? It seems a good idea, but before we try to use 'feeling' information in our research, there are still some works expressed serious doubt about the idea that machines might actually "have" feelings[12, 13]. It is difficult to define if the artificial intelligence algorithm can have feeling. However, we can argue that intelligent machines "need" emotions, albeit simulated, in order to perform better when learning more complex tasks, and when modeling the learning and decision making functions of a human[7]. Furthermore, Emotional Neural Networks which is one of this kind of method, has already been successful used in blood cell type identification, facial recognition and other fields[14-16]. In these researches, the tendency emotional factor makes the process faster and gets better result.

It's a pity that most of them are just about image, and so does to the way they get the emotional features in the raw data. In different areas, we have different tendency information, so we need the particular method to define and use this kind of prior knowledge. In this paper, we want to explore the emotional neural networks to a larger range. According to the risk/protect factors in the genes, we get a value about the tendency about the sample to be sick. And then, in order to consider this priori knowledge in the process of classification, we use an Emotional Neural Networks with special structure. By training the unusual neural network architecture, some researchers use Gradient-descent Based method, which is based on the difference (error) between the

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actual output of the neural network and the desired (target) output. However, for the classification problems, we often use the classification accuracy or Q_9 as measurement indexes. In order to change the evaluation index and adapt the novel architecture, we use the particle swarm optimization with hierarchical structure (PSO_HS). The experimental results about the real data base show that the proposed algorithm is faster and also has the higher accuracies compared with the other methods.

The paper is organized as follows: Section 2 briefly introduces the problem and gives the related formulation. The detail of emotional system learning algorithm and the PSO with hierarchical structure (PSO_HS) are provided in Section 3. The section 4 is about dataset, we also provide the process of experimental design and the results. Finally, we give our conclusions in Section 5.

II. Problem formulation

In this paper, we try to use the SNP data to analysis the disease association and susceptibility, and regard the SNP risk/protect factors as emotional information. This section is about the problem formulation.

A. SNP data

At first, we assume that there are m samples and each of them organized by n SNPs. Then, we use $\sum=\{0,1,2\}$ to denote the value of SNPs, where 0 and 1 represent for homozygous sites with major and minor alleles, respectively, 2 is stands for heterozygous sites.

B. Risk/protective factors

According to researches about Genome wide association study(GWAS), we know that SNPs can increase or decrease the risk developing a disease[17]. The multiple SNPs can be modeled as causation/prevention of a disease often is regard as the risk/protective factor. Here, we use the odds ratio to measure the risk/protective factor, which is defined as follows:

$$\text{OR\_risk}=\frac{d/(D-d)}{h/(H-h)} \tag{1}$$

$$\text{OR\_protective}=\frac{h/(H-h)}{d/(D-d)} \tag{2}$$

Where h and d are the number of controls (health) and cases (disease) with specified alleles, respectively. D and H are the number of controls and case, respectively. So, when the OR_protective (OR_risk) is larger, there will be a stronger relationship between the combination of SNPs and the positive (risk) tendency about disease.

III. Methods

A. The architecture of Emotional Neural Networks

The architecture of this novel EMM is explained in details in the following subsections. Generally, the ENN only has one hidden layer. So, we can assume the ENN in this paper is consists of three layers: output layer with j neurons, hidden layer with h neurons and input layer with i neurons.

The architecture and the configuration of the neural network during feed forward calculations are shown at Figure 1. The input of each neuron i in the input layer is XI_i and output value of the is YI_i.

$$YI_i=XI_i \tag{3}$$

The hidden layer neurons are processing neurons, and in this paper, we use the sigmoid activation function. By this

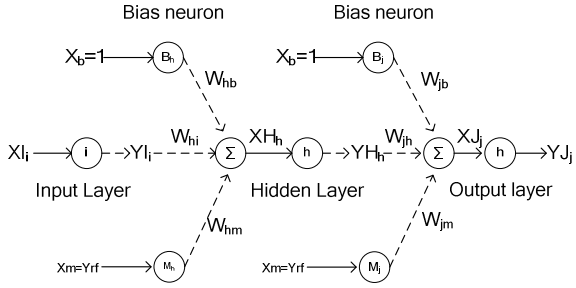

Fig. 1. Architecture and configuration about emotional neural network

way, the output value of each neuron in hidden layer is defined as:

$$YH_h=\left(\frac{1}{1+\exp(-XH_h)}\right) \tag{4}$$

Where the input and output values of hidden layer neuron h are XH_h and YH_h, respectively. The input to a hidden layer neuron XH_h is calculated using the conventional total potential TP_{hc}, the hidden layer bias potential TP_{hb} and the hidden layer emotional potential TP_{hm}.

$$XH_h=TP_{hc}+TP_{hb}+TP_{hm} \tag{5}$$

Where TP_{hc} is defined as:

$$TP_{hc}=\sum_{i=1}^{r}W_{hi}\bullet YI_i \tag{6}$$

W_{hi} is the weight from hidden neuron h to input neuron i, and YI_i is the output of first layer neuron i. r is the total number of neurons in the input layer.

Where TP_{hb} is defined as:

$$TP_{hb}=W_{hb}\bullet X_b \tag{7}$$

W_{hb} is the weight from hidden neuron h to the hidden layer bias neuron b, and X_b is the input value to the bias neuron, in this part, it is always set to 1.

Where TP_{hm} is defined as:

$$TP_{hm}=W_{hm}\bullet X_m \tag{8}$$

W_{hm} is the weight from hidden neuron h to the hidden layer emotional neuron m, and X_m is the input value (risk factor/protect factor) to the emotional neuron.

$$X_m=Y_{rf} \tag{9}$$

where Y_{rf} are accumulated by the risk/protect factors Y_{nrf}, with a power index W_{nrf}, the n_{max} is the number of the risk factor in total dataset.

$$Y_{rf}=\sum_{n=1}^{n_{\max}} W_{nrf}\bullet Y_{nrf} \tag{10}$$

Similarly to the hidden layer, we use the sigmoid function to activate each processing neurons in the output layer. The output of each output layer neuron is:

$$YJ_j=\frac{1}{1+\exp(-XJ_j)} \tag{11}$$

where XJ_j and YJ_j are the input and output values of the neuron j in output layer, respectively. The XJ_j is calculated by the total potential (TP_j)of all input values from the previous hidden layer, and the bias and emotional neurons. Therefore, the input to an output layer neuron is:

$$XJ_j=TP_{jc}+TP_{jb}+TP_{jm} \tag{12}$$

TP_{jc} is defined as:

$$TP_{jc}=\sum_{h=1}^{l} W_{jh}\bullet YH_h \tag{13}$$

where W_{jh} is the weight from output neuron j to hidden neuron h, and YH_h is the output of hidden neuron h, l is the maximum number of hidden layer neurons.

TP_{jb} is defined as:

$$TP_{jp}=W_{jb}\bullet X_b \tag{14}$$

Where W_{jb} is the weight from output neuron j to the output layer bias neuron b, and X_b is the input value to the bias neuron, in this paper it is set to 1.

TP_{jm} is defined as:

$$TP_{jm}=W_{jm}\bullet X_m \tag{15}$$

Where W_{jm} is the weight from output neuron j to the output layer emotional neuron m, and X_m is the accumulated input patterns values as presented to the emotional neuron. Similarly, X_m is calculated as in Equation (9).

B. Train ENN by PSO_HS

The architecture of emotional neural network is different from the traditional neural networks. In order to train the network parameters, we use a kind of modified PSO algorithm. In standard BPSO, each particle is treated equally, so, every particle uses identical functions to update. However, this is far from the real situation in a social group (organization). According to sociology, individuals have different status in a social/hierarchical group, and individuals should be differentiated according to the status[18]. Therefore, we use the novel PSO algorithm based on this process, called PSO with hierarchical structure (PSO_HS) in this paper.

In Basic PSO, A particle *i* is both described by its position x_i and velocity v_i. During the 'fly', each particle adjusts its position according to its own experience and the experience of its all other particles, making use of the best position encountered by itself (p_i) and all the others (p_g) by (16)and(17):

$$\begin{aligned} v_{ij}(t+1)&=v_{ij}(t)+c_1r_1(p_{ij}(t)-x_{ij}(t))\\ &\quad+c_2r_2(p_{gj}(t)-x_{ij}(t)) \end{aligned} \tag{16}$$

$$x_{ij}(t+1)=x_{ij}(t)+v_{ij}(t+1) \tag{17}$$

Where v_{ij} is the velocity of the j*th* dimension of i*th* particle, x_{ij} is the position of the j*th* dimension of i*th* particle, r_1 and r_2 are random numbers between 0 and 1, and c_1 and c_2 are about the degree of influences of p_i and p_g on the particle's velocity, respectively. The velocity v_{ij} is within a range of [$-V_{max}$, V_{max}] to prevent the particle from 'flying' out of the solution space.

In PSO_HS, particles are divided into two classes, which can be regard as 'leaders' and 'followers', according to their classification performances. We use different update strategies for them. During the iteration, if a current follower gets a better performance than a current leader, it will switch to be a leader in the next iteration. This process helps the swarm escape from local minima. By this way, a number of particles, which have better fitness value, are chosen as the leaders. The leaders are used to seek the construct of creativity and innovation [17]. Leaders' decisions are more likely to be accepted by other members of the group, i.e., followers are likely to make their own decisions mainly based on leaders'. [18].

Base on this method, the behavior lead the direction of the particles and the behavior of the followers can be modeled as random walk toward the leaders. So, the leaders just use Eqs. (16) and (17) to update the parameter. For the followers, at the tth iteration, they change the (16) to (18):

$$\begin{aligned} v_{ij}(t+1)&=v_{ij}(t)+c_1r_1((\sum_{j=1}^{K} p_{ij}(t))-x_{ij}(t))\\ &\quad+c_2r_2((\sum_{j=1}^{K} p_{gj}(t))-x_{ij}(t)) \end{aligned} \tag{18}$$

This means that the follows work follow the leaders. In this paper, all the weight from one neuron to another, the weight about emotional neuron and all the bias need to be trained and optimization. The expression of each particle is shown in Fig. 2.

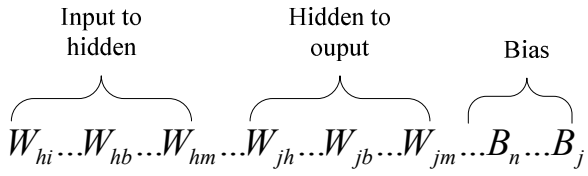

Fig. 2. The expression of particles combining the power and bias in the neural networks

By using the novel PSO_HS method, we can get the optimized parameter according to the fitness function. However, for the classification problem, the traditional mean square error is not work very well. So, in next subsection, we will discuss about the fitness function design.

C. Fitness function design

In this paper, the evaluation/fitness function is used to measure the particular neural network, which is corresponding to a particle. The evaluation criteria are sensitivity (Sn), specificity (Sp) and accuracy (Acc). They are defined as follows.

$$Sn = \frac{TP}{TP + FN} \tag{19}$$

$$Sp = \frac{TN}{TN + FP} \tag{20}$$

$$Acc = \frac{TP + TN}{TP + FP + FN + TN} \tag{21}$$

Where the TN, FN, TP and FP are defined as follows:

True negative (TN): sample does not have disease and the prediction is correct.

True positive (TP): sample has disease and the prediction is correct.

False negative (FN): sample has disease and the prediction is incorrect.

False positive (FP): sample does not have disease, but the prediction is incorrect.

IV. Experimental results and comparisons

A. Dataset

In this paper we test our algorithm on three datasets: Autoimmune_disorder (AD), Crohn's disease (CD) and Lung cancer(LC) [19]. The detail information of those dataset is shown in TableI.

TABLE I
NUMBER OF SNPS AND SAMPLES

Dataset	Number of SNPs	Number of cases	Number of controls
AD	108	378	646
CD	103	144	243
LC	141	322	273

B. SNP risk/protect factor

We use the formulation in the section 2 to find the risk_factor. Because if the SNP number group is too big, the number of case (control) with specified alleles will be too small. So, we just try 2 and 3 as the number of the SNP groups in this paper. At the Table II, we give the risk/protect factors be picked out from the case-control database. According to the table, we can notice that these kind of risk/protect factor is exist in our database. By using this part of information, we get the emotional factor about the neural network. At the next step, we will use it in classification.

TABLE II-I
AUTOIMMUNE DISORDE

SNP-pair	Specified alleles	Number of cases/case	Number of controls/control
6,108	2,2	8/378	0/646
75,108	0,1	6/378	0/646
13,66	2,0	28/378	12/646
52,108	2,2	2/378	36/646
31,108	1,2	1/378	42/646
47,101	1,1	17/378	78/646
82,93	0,2	0/378	27/646
24,38	0,1	0/378	273

TABLE II-II
CROHN'S DISEASE

SNP-pair	Specified alleles	Number of cases/case	Number of controls/control
60,93	1,2	5/144	0/243
35,82	1,2	4/144	0/243
63,87	1,2	4/144	0/243
32,103	0,2	12/144	46/243
21,86	2,2	8/144	31/243
47,101	2,2	0/144	13/243
10,82	2,1	0/144	14/243
67,94	0,1	0/144	14/243

TABLE II-III
LUNG CANCER

SNP-pair	Specified alleles	Number of cases/case	Number of controls/control
21,66	1,0	15/322	0/273
19,22	1,2	11/322	0/273
17,39	2,2	25/322	3/273
23,40	0,1	19/322	1/273
20,70	1,2	15/322	1/273
25,57	0,0	238/322	148/273
34,97	1,0	0/322	10/273
41,116	0,1	0/322	11/273

C. Experimental results about classification

In this paper, we compare with some basic traditional neural networks: BP, RBF and Pattern recognition network (PRN). What's more, we compare with some methods that have already published in some other papers IBPSO[20],PA[21],HPG[22]. The evaluation criteria are sensitivity (Sn), specificity (Sp) and accuracy(Acc). They are shown in Table III.

In the table we can see at the most case, our method get the best performance, the experiment about the real database prove that our ENN is useful.

TABLE III-I
AUTOIMMUNE DISORDE

METHOD	SN	SP	ACC
BP	0.7778	0.4421	0.6538
RBF	0.8395	0.2211	0.6109
PRN	0.7390	0.5000	0.6430
IBPSO	0.3703	0.9180	0.7158
PA	0.7039	0.7756	0.7491
HPG	0.6853	0.7911	0.7520
ENN	0.5449	0.9304	0.7881

TABLE III-II
CROHN'S DISEASE

METFOD	SN	SP	ACC
BP	0.6065	0.4444	0.5463
RBF	0.8852	0.0833	0.5876
PRN	0.7750	0.2220	0.6030
IBPSO	0.8478	0.9588	0.9174
PA	0.8682	0.9713	0.9328
HPG	0.8611	0.9548	0.9198
ENN	0.8420	0.9740	0.9310

TABLE III-III
LUNG CANCER

METHOD	SN	SP	ACC
BP	0.7500	0.6891	0.7315
RBF	0.7205	0.7407	0.7315
PRN	0.6760	0.7310	0.7080
IPSO	0.8977	0.8426	0.8724
PA	0.9068	0.8570	0.8840
HPG	0.9192	0.8607	0.8924
ENN	0.9060	0.9650	0.9440

V. CONCLUSION

In this paper, we pick out the SNP combination from the whole data base, and put this kind of tendency information together to influence the susceptibility classification. By using the ENN and PSO_HS, we consider the tendency information about the SNP. The experimental result shows that this kind of information is helpful. So, it is a good way for us to use the ENN to deal with the prior or tendency information. There is still a long way for us to use this information as good as the way our brain use emotional information. However, this is a start for us to work in the future.

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