The Sixteenth International Symposium on Artificial Life and Robotics 2011 (AROB 16th '11),
B-Con Plaza, Beppu,Oita, Japan, January 27-29, 2011

Neural network with exponential output neuron for estimation of physiological activities from protein expression levels

Kazuhiro KONDO[†] Kunihito YAMAMORI[‡] Ikuo YOSHIHARA[‡]

[†] *Graduate School of Eng., Univ. of Miyazaki*
[‡] *Faculty of Eng., Univ. of Miyazaki*
(Tel :+ 81 985 58 7589; Fax :+ 81 985 58 7589)
(kondo@taurus.cs.miyazaki-u.ac.jp,{yamamori,yoshiha@cs.miyazaki-u.ac.jp})

Abstract: Many people expect the third function of foods called as physiological activities that affect our health condition. However, measurement of a physiological activity is troublesome and measurements for all kinds of foods are not impractical. Therefore a system which can easily estimate physiological activities is required. We have proposed a method to estimate physiological activities of foods from protein expression levels using artificial neural networks (ANNs). Estimation of physiological activity using conventional ANN has a problem that physiological activities take positive real number more than 1.0, but dynamic range of ANN is limited from 0.0 to 1.0. So measured physiological activities has to be scaled by dividing the maximum one. But this normalization gives undesirable influence to acceptable error level which is a parameter to terminate training process.

To solve this problem, we employ exponential function as the activation function in output neurons. By using exponential function in output neurons, ANN can directly handle physiological activities as the training signals those are more than 1.0. Experimental results show that our method improves accuracy than conventional ANN with scaled training samples for anti-oxidant activity, anti-inflammation activity and anti-angiogenic activity.

Keywords: physiological activities, protein expression level, exponential activation function, artificial neural network.

I. INTRODUCTION

Foods have three functions; the first is nutrition, the second is taste and the third is biological regulation. The third function of foods attracts attention in recent years because many people expect that the third function of foods will be useful to keep their health and prevent diseases. The third function of foods is measured as physiological activities. However, measurement of physiological activity is troublesome because it needs many sophisticated manual operations, and measurements for all kinds of foods are impossible. Therefore a system which can easily reveal physiological activities is required. For this objective, we have proposed a method to estimate physiological activities from protein expression levels because protein expression levels closely relate to cell condition and some kinds of protein expression levels can be measured at once.

Togo et al. [1] tried to estimate physiological activities by Bayesian classifier. Kamiguchi et al. [2] proposed to estimate physiological activities by multiple regression analysis. But these methods did not achieve enough estimation accuracy. Tsukuda et al. [3] showed that artificial neural network (ANN) could achieve good estimation accuracy of physiological activities.

Estimation of physiological activities using conventional ANN has a problem. Physiological activities sometimes take positive real number more than 1.0, but dynamic range of a conventional ANN is limited from 0.0 to 1.0. So physiological activities have to be normalized for estimation by conventional ANN. But normalization leads undesirable influence for acceptable error level to terminate training process. To avoid this undesirable influence, we employ exponential function as the activation function in output neuron. By using exponential function in output neuron, ANN can directly handle physiological activities as the training signals those are more than 1.0.

II. ESTIMATION OF PHYSIOLOGICAL ACTIVITIES BY CONVENTIONAL ANN

We use artificial neural network (ANN) [4] for estimation of physiological activity. An ANN has an input layer, a hidden layer and an output layer. An output of neuron j is calculated by Equation (1),

$$o_j^i = f(\sum_k \mathbf{x}^i \mathbf{w}_{jk}), \quad (1)$$

where $\mathbf{x}^i (i = 0,1,2,\ldots,I)$ is the *i*-th input vector, $\mathbf{w}_{jk} (j = 0,1,2,\ldots,J, k = 0,1,2,\ldots K)$ is a weight vector between the neuron j and the neuron k. $f(x)$ is an activation function. Weight update algorithm of artificial neural network is usually back-propagation algorithm. Back-propagation algorithm minimizes the error between the calculated output o and the desired output y based on the steepest descent method. When the sum of the error define by Equation (2) becomes less than acceptable error level E', training process is terminated.

$$E = \sum_i^I \sqrt{(o^i - y^i)^2} \quad (2)$$

where o^i and y^i is the output of ANN and the desired output for the *i*-th training sample, respectively.

Estimation of physiological activity by conventional ANN has a problem. Physiological activities sometimes take positive real number more than 1.0, but dynamic range of ANN is limited from 0.0 to 1.0. So physiological activities have to be normalized for estimating by conventional ANN. Since dynamic range of physiological activities is usually from 0.0 to 3.0, previous works divide physiological activities by the maximum one. If the acceptable error level to terminate training process is decided based on the original physiological activity, the scaled acceptable error level will become too small to terminate training process. If the acceptable error level is decided based on the scaled physiological activities, and it is large enough to terminate training process, obtained error will become too large because it is multiplied by the maximum value of the physiological activity. Kuno et al. [5] proposed Amplitude Extended Neural Networks to solve this problem. Amplitude Extended Neural Network introduces two parameters k and l into sigmoid function as $y = k/(1+e^{-lx})$. The parameter k adjusts amplitude of sigmoid function and the parameter l adjusts slope of sigmoid function. Dynamic range of Amplitude Extended Neural Network is extended from 0.0 to k, but we have to decide two parameters for each physiological activity.

III. ANN WITH EXPONENTIAL OUTPUT NEURON

We employ exponential function $f(x) = e^{tx}$ as the activation function in output neuron. Here we introduce a parameter t into exponential function to adjust its slope. By using exponential function as the activation function in output neuron, ANN can directly handle the physiological activity as the training signals those are more than 1.0. Since normalization is unnecessary for proposed ANN, the error does not increase by rescaling. Exponential function is suitable for handling large physiological activities that is difficult to handle by sigmoid function.

Fig. 1 shows a sample of three layer ANNs. The ANN has an input layer, a hidden layer, and an output layer. All neurons of an input layer connects all neurons in hidden layer, and a neuron of hidden layer connects all neurons in output layer. Constitution of our proposed neural network is three layer model and the activation function of the output neuron is exponential function, and that in other layers is sigmoid function.

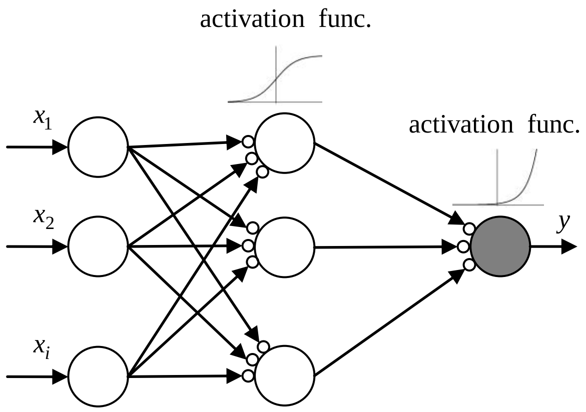

Fig. 1 Neural network with exponential output neuron

We evaluate proposed ANN by preliminary exercises. An artificial data are generated by following equations data1~data4. An input consists of three dimensional vector (a_1, a_2, a_3), and an output is a scalar y. The elements of input vector is decided at random. The range of the elements in a input vector is 0.0 to 3.0. The x in the following equations is sum of the elements of input vector $x = a_1 + a_2 + a_3$. All x satisfy the condition $0.0 \le x \le 5.0$. The output y is normalized by dividing the maximum value for conventional ANN. Table 1 shows ANN parameters for preliminary exercise. We continue the training process until it arrives at the maximum epoch.

- data1: $y = x^2$
- data2: $y = x^2 - 2x + 1$
- data3: $y = x^3$
- data4: $y = 5/(1 + e^{-x})$

Table 2 shows mean square errors between the theoretical y and the output of ANN.

Table 1 ANN parameter for preliminary exercises.

Training rate	0.4
Momentum	0.7
Maximum epoch	20,000
The number of input neurons	3
The number of hidden neurons	2
The number of output neurons	1
Slope of exponential function t	1/256
The number of training sample	400

Table 2 Mean square error of preliminary exercises.

	data1	data2	data3	data4
convetional ANN	0.184	0.204	0.220	0.132
proposed ANN	0.163	0.193	0.134	0.123

Proposed ANN could obtain more accurate approximation model than conventional ANN as shown in Table 2. Mean square error of conventional ANN becomes larger than proposed ANN because the error of conventional ANN becomes large by rescaling. Table 2 also says that proposed ANN is suitable for the model equation approximation like as quadratic or cubic function.

IV. PHYSIOLOGICAL ACTIVITIES ESTIMATION

ANN needs appropriate training samples to make a suitable model. Measured physiological activities and protein expression levels include relatively large noise come from cell condition and measurement environment. We solve this problem by exception of outlier using Smirnov-Grubbs test.

Physiological activities and protein expression levels are measured in multiple times for a constituent of the food, and these are not corresponded each other. It means that we do not construct appropriate training samples consisting of a physiological activity as a training signal and protein expression levels as input signals. We use simple linear regression analysis to correspond a physiology activity and protein expression levels. We make all the available combination between the physiological activities and the protein levels for a constituent of the food, and apply simple linear regression analysis for these combinations. The combination that has the lowest residual is selected as the adequate training sample.

We use thirty kinds of constituents for three concentrations as training samples. A part of the constituents as shown in Table 3. The constituent is given to HepG2 cells, then protein expression levels and physiological activities are measured, respectively. So a data-set involves 90(=30 × 3) measured values. We measure the expression levels of following proteins; Survivin, HSP70, XIAP, FADD, TXNRD1, HSP90, MxA, tNOX, NQO1, ERK2, p53 and Bcl2.

We compared conventional ANN with proposed ANN for six kinds of physiological activities. These experiments run ten times with the same parameter. Table 4 shows training parameters, and Table 5 shows the number of samples. We evaluate each method by estimation accuracy defined by Equation (3).

$$accuracy = \frac{\text{Number of estimated samples}}{\text{Total number of samles}} \times 100, \quad (3)$$

where the number of estimated samples means that the number of samples they satisfied the error less than 0.2.

Table 3 Samples of constituents and their concentrations

	concentrations(μM)		
LipoicAcid	100	300	1000
EGCG	7	20	50
Genistein	10	20	60
Daizein	25	50	150
Glycitein	10	30	100
Qurcetin	5	15	60

Table 4 ANN parameters for estimation experiments

Training rate	0.4
Momentum	0.7
Maximum epoch	20,000
The number of input neurons	13
The number of hidden neurons	6
The number of output neurons	1
Slope of exponential function t	1/256
Acceptable error level	0.2

Table 5 The number of sample

physiological activity	The number of training sample	The number of testing sample
anti-oxidant	627	128
anti-proliferative	642	131
anti-inflammation	637	130
anti-angiogenic	642	131

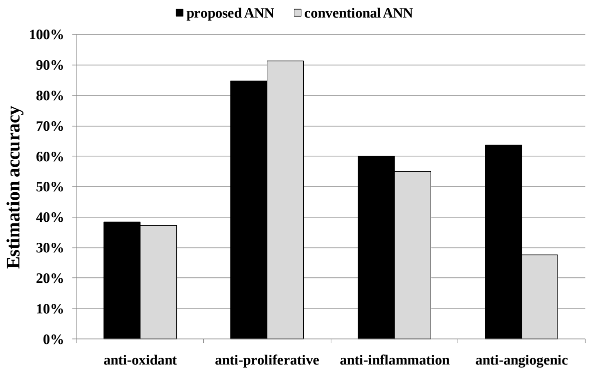

Fig. 2 Results of estimation accuracy

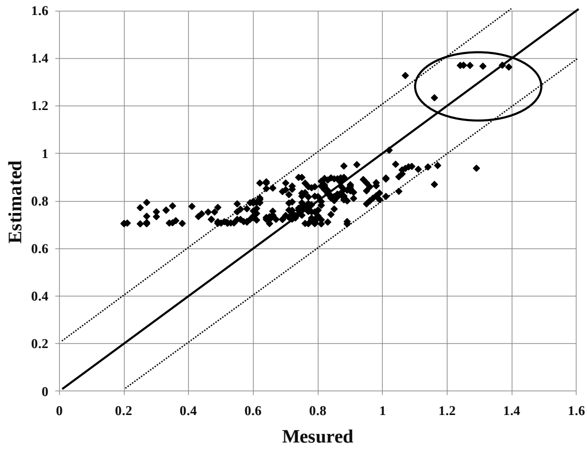

Fig. 3 Scatter diagram for anti-angiogenic activity

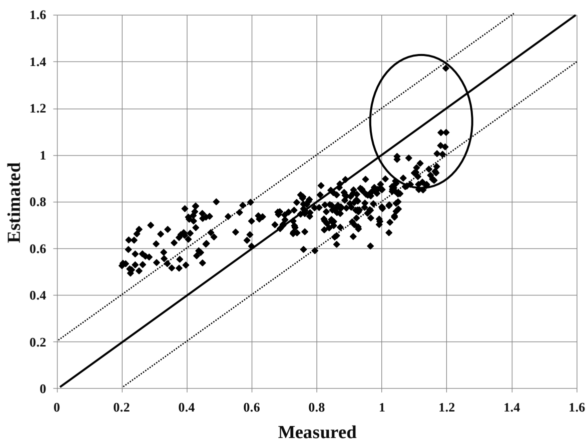

Fig. 4 Scatter diagram for anti-inflammation activity

Fig. 2 shows estimation result of four physiological activities (anti-oxidant, anti-proliferative, anti-inflammation, anti-angiogenic activity) using proposed ANN and conventional ANN. Proposed ANN is more accurate than conventional ANN with normalization for anti-oxidant activity, anti-inflammation activity and anti-angiogenic activity. Fig. 3 and Fig. 4 show estimation results for the anti-angiogenic activity and the anti-inflammation activity by scatter diagram where the x-axis is measured value and the y-axis is estimated value. In Fig.3 and Fig.4, the dotted-line shows boarder that satisfies ±0.2 of measured values. Proposed ANN can estimate relatively large physiological activity shown in circles in Fig. 3 and Fig.4.

V. CONCLUSIONS

In this paper, we proposed a neural network with exponential output neuron and applied it to estimate physiological activities from protein expression levels. Experimental results showed that our method achieved more accurate than conventional ANN with normalization for anti-oxidant activity, anti-inflammation activity and anti-angiogenic activity. Furthermore it could realize to directly use measured physiological activities as training samples. However, proposed neural network couldn't follow small physiological activity. It is future subject that estimation by multi-model ANNs to estimate both of large and small physiological activities.

REFERENCES

[1] Togo S. (2008), Estimating physiological activities of functional foods form protein expression levels using baysian classifier, The Thirteenth International Symposium on artificial Life and Robotics 2008, pp.853-856, OS12-3.

[2] Kamiguchi M. (2008), Estimation of Physiological Activity Values from Protein Expression Levels with Multiple Regression Analysis, Memoirs of the Faculty of Engineering, University of miyazaki, No.37, pp.269-273.

[3] Tsukuda S. (2007), Estimation of physiology Activity in Foods with Neural Network from Insufficient Data, Memoirs of the Faculty of Engineering, University of miyazaki, No.36, pp.345-350.

[4] Sholom WM., Nitin I. (1998), PREDICTIVE DATA MINING., Morgan Kaufmann Publishers, Inc, San Francisco, California.

[5] Kuno T. (2009), Development of Physiological Activity Estimation System of Foods Using Amplitude Extended Neural Networks, The fourteenth International Symposium on artificial Life and Robotics 2009, pp.853-856.