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Development of Physiological Activity Estimation Method of Foods Using Amplitude Extended Neural Networks

Toru KUNO[1)], Mayumi KAMIGUCHI[1)], Kunihito YAMAMORI[2)], Ikuo YOSHIHARA[2)], Kiyoko NAGAHAMA[2)]

[1)]1-1, Gakuen Kibanadai-nishi, Miyazaki, 889-2192, Japan, Graduate School of Engineering, University of Miyazaki
[2)]1-1, Gakuen Kibanadai-nishi, Miyazaki, 889-2192 , Japan, University of Miyazaki
[3)] 16500-2, Higashi Kami-Naka, Sadowara, 880-0303, Japan, Miyazaki Prefectural Industrial Foundation

(Tel : +81 985 58 7589; Fax : +81 985 58 7589)
(Email address {kuno, yamamori}@taurus.cs.miyazaki-u.ac.jp)

Abstract: We developed a system to estimate physiological activities of foods from protein expression levels using artificial neural networks (ANNs). Since protein expression levels and physiological activities are measured in multiple times for a constituent, we employ a simple regression analysis to find appropriate correspondence between physiological activities and protein expression levels. The range of physiological activities are from 0 to Z (Z >1), they cannot directly use training signals of ANNs because the output of a neuron is limited from zero to one. To tackle this problem, we introduce two parameters K and l to the activation function of our system like as ($\boldsymbol{f(x) = \frac{K}{1+e^{-lx}}}$). Our system is based on three-layer ANN and back-propagation algorithm is employed as training algorithm. Experimental results showed that our system can estimate more accurate than that of ANNs with normalized training samples for antioxidant stress activity.

Keywords: physiological activity, protein expression level, functional foods, artificial neural networks

I. INTRODUCTION

Since the third function of foods which is effect to physiological activities for human is useful to keep health and prevent diseases, many people pay attention to some foods that have relatively large effect [1]. A way to evaluate the function of foods is direct measurement of their physiological activities. However, it is difficult because there are many kinds of foods in the world, and their physiological activities are also different in seasons and places. The other way to evaluate the function of foods is estimation from their constituents, but it is also difficult because it needs to be clear the complicated interactions between these constituents and human. So a new method to estimate physiological activities of foods is required.

Some researchers proposed methods to estimate physiological activities by artificial neural networks (ANNs) [2]-[5]. For example, Tsukuda *et al*. [2] showed that artificial neural networks (ANNs) could achieve good accuracy to estimate some physiological activities. In this research, ANNs train the relations between the protein expression levels and the physiological activities when constituents of foods are poured for human cells. After training process, the protein expression levels by extraction of foods are presented to ANNs.

ANNs need many appropriate training samples to make a better model equation. Protein expression levels and physiological activities are measured in multiple times for a constituent. However, previous works took an average of measured values, then these average values were composed to a training sample. This operation decreases the total number of training samples. To solve is problem, we utilize all measured values to make enough numbers of training samples. Because the physiological activities and the protein expression levels were independently measured for a constituent, it is needed to find an appropriate correspondence between them. To find an appropriate correspondence, we employ simple regression analysis. The correspondence with the smallest p-value is selected from all the available correspondences.

The range of physiological activities as the training signals are from 0 to Z (Z > 1), physiological activities are usually normalized because the output of neurons is limited from zero to one. At that time, acceptable error will become too small to terminate training process by normalization. To solve this problem, we use amplitude extended neural networks (AENNs). AENNs have two parameters K and l in the activation function of our system like as $f(x) = \frac{K}{1+e^{-lx}}$. The K adjusts amplitude of sigmoid function and the l adjusts slope of sigmoid function. By using the sigmoid function with these parameters, it does not need to normalize training signals.

Table 1 A part of constituents and concentrations for training samples.

		concentrations(μM)		
aliphatic acid	RosmarinicAcid	5	15	50
	LipoicAcid	100	300	1000
	ArachidonicAcid	15	45	100
	CLA12C	1	3	10
	CLA9C	10	30	100
…				
anti-virus	IFN	100	300	1000
	Ribavirin	2	10	30

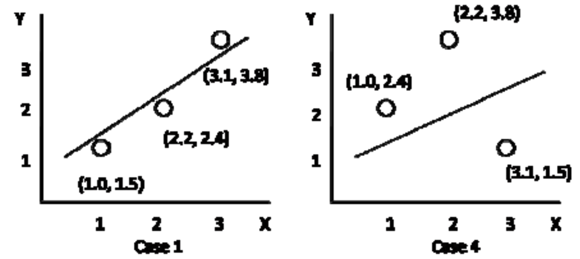

Fig.1 Correspondence between the protein expression levels and the physiological activities.

II. PREPROCESSING

1. Constituents for training sample

We use thirty kinds of constituents of foods and medicines, a part of them is shown in Table 1. The constituents and medicines are poured over HepG2 cells in three concentration levels, then protein expression levels and physiological activities are measured, respectively. The protein expression levels and physiological activities are measured in six times for each constituent. So the number of training sample is $540(=30\times3\times6)$. The kinds of proteins are as follows; Thioredoxin, Survivin, HSP70, XIAP, FADD, TXNRD1, HSP90, MxA, tNOX, NQO1, ERK2, p53 and Bcl2. We adopt the following three physiological activities; anti-proliferative activity, anti-inflammatory activity and anti-oxidant stress activity.

2. Correspondence of protein expression levels with physiological activities

Since the protein expression levels and the physiological activities are respectively measured, it is needed to find an appropriate correspondence between the protein expression levels and the physiological activities even if they are observed by the same constituent and the same concentration. For this correspondence, we use simple regression analysis, whose concept is illustrated in Fig.1. The X-axis and the Y-axis in Fig.1 denote the protein expression levels and the physiological activities, respectively.

Table 2 Correspondence and p-value.

case	(X_1, Y_1)	(X_2, Y_2)	(X_3, Y_3)	p-value
1	(1.0, 1.5)	(2.2, 2.4)	(3.1, 3.8)	0.13
2	(1.0, 1.5)	(2.2, 3.8)	(3.1, 2.4)	0.69
3	(1.0, 2.4)	(2.2, 1.5)	(3.1, 3.8)	0.64
4	(1.0, 2.4)	(2.2, 3.8)	(3.1, 1.5)	0.80
5	(1.0, 3.8)	(2.2, 1.5)	(3.1, 2.4)	0.53
6	(1.0, 3.8)	(2.2, 2.4)	(3.1, 1.5)	0.03

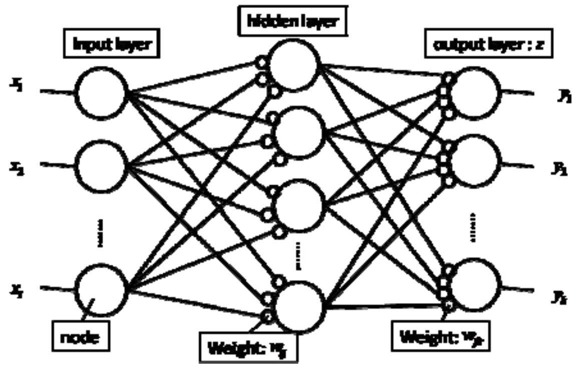

Fig.2 The structure of ANNs.

Here explains how to correspond between protein expression levels and physiological activities by simple regression analysis. Let the protein expression levels be measured as {1.0, 2.2, 3.1}, and let the physiological activities be measured as {1.5, 2.4, 3.8}. In this case, six combinations of correspondence are available as shown in Table 2. We execute single regression analysis for all combinations. In Fig.1 the left shows the case 1 and the right shows the case 4. We select the case with minimum *p*-value among all combinations, then case 6 is selected. The *p*-value expresses probability that the protein expression levels have no relation with the physiological activities.

III. AMPLITUDE EXTENDED NEURAL NETWORKS

Fig.2 shows a sample of three layers ANNs [6]. The ANNs has an input layer, a hidden layer and an output layer. A node of the input layer connects all nodes in the hidden layer, and a node of the hidden layer connects all nodes in the output layer. Equation (1) and Equation (2) express the input and output in the neuron *j* on the layer *L*, respectively.

$$x_j^L = \sum_i O_i^{L-1} w_{L-1,i}^{L,j}, \tag{1}$$

$$O_j^L = f(x_j^L), \tag{2}$$

where $w_{L-1,i}^{L,j}$ denotes the weight from the neuron *i* on the layer *L*-1 to the neuron *j* on the layer *L*. Sigmoid function described in Equation (3) is usually used as activation function,

Table 3 Training parameters.

	K	l	Physiological activity		Accept error	η	ε	Max iteration	Hidden neurons
			Min.	Max.					
anti-proliferative activity	2.0	0.8	0.30	1.14	0.06	0.4	0.7	20000	6
anti-inflammatory activity	2.0	0.8	0.06	1.59	0.14				
antioxidant stress activity	2.5	0.2	0.01	2.68	0.2				

$$f(x) = \frac{1}{1+e^{-x}}. \qquad (3)$$

Since the range of physiological activities as the training signals are from zero to Z (Z >1), the training signals are usually divided by the maximum physiological activity for normalization. At that time acceptable error is also divided, it will become too small to terminate training process. To avoid normalization of physiological activities, we employed two parameters *K* and *l* in sigmoid function,

$$f(x) = \frac{K}{1+e^{-lx}}. \qquad (4)$$

K adjusts the amplitude of sigmoid function and the *l* adjusts the slope of sigmoid function. By using sigmoid function with these parameters, it does not need to normalize training signals.

The error *E* is defined as follow,

$$E(p) = \frac{1}{2}\left(T(p) - O_i^L(p)\right)^2, \qquad (5)$$

for the training sample *p*. To minimize $E(p)$, we obtain the following rule derived from $\frac{\partial \mathrm{E}}{\partial \mathrm{w}_{\mathrm{L-1,i}}^{\mathrm{L,j}}} = 0$.

$$\Delta w_{L-1,i}^{L,j}(p) = \eta \cdot f'(\mathrm{x}_\mathrm{j}^\mathrm{L}(p)) \cdot \left(T(p) - O_i^L(p)\right) + \varepsilon \Delta w_{L-1,i}^{L,j}(p-1), \qquad (6)$$

$$f'(\mathrm{x}_\mathrm{j}^\mathrm{L}(p)) = \frac{l \cdot K \cdot e^{-lx_j^L(p)}}{(1+e^{-lx_j^L(p)})^2}, \qquad (7)$$

where η is rate parameter and ε is inertia parameter. The error of hidden neurons is defined by Equation (8),

$$\delta_\mathrm{i}^{\mathrm{L-1}} = \sum_\mathrm{j} \mathrm{w}_{\mathrm{L-1,i}}^{\mathrm{L,j}}\, \delta_\mathrm{j}^\mathrm{L}(p), \qquad (8)$$

$$\delta_\mathrm{j}^\mathrm{L}(p) = f'\left(\mathrm{x}_\mathrm{j}^\mathrm{L}(p)\right) \cdot \left(T(p) - O_i^L(p)\right), \qquad (9)$$

where *z* is the index of the output layer. The weight update rule is obtained as Equation (10).

$$w_{L-1,i}^{L,j}(p+1) = w_{L-1,i}^{L,j}(p) + \Delta w_{L-1,i}^{L,j}(p). \qquad (10)$$

IV. EXPERIMENTS AND DISCUSSIONS

We compared estimation accuracy between convention ANNs with normalized samples and our AENNs without normalization. The parameters of experiments are as follows;

- Network size : 13-6-1 (13 input neurons, 6 hidden neurons, 1 output neuron)
- runs : 10 run
- number of test sample : 72
  - 4 extracts
    - extract of blueberry leaf by boiled water
    - extract of blueberry leaf by ethanol
    - extract of onion leaf by boiled water
    - extract of tea leaf by boiled water
  - 3 concentrations
  - 6 samples

We change *K* from 1.0 to 3.0 with 0.5 step and we also change *l* from 0.1 to 1.0 with 0.2 step. These *K* and *l* were decided by preprimary experiments. The conditions of experiments are summarized in Table 3.

A. *Anti-proliferative activity*

Fig.3 shows the average estimated value of anti-proliferativity activity. ANN can estimate the anti-proliferativity activity 4 samples within acceptable error for all 12 samples (4/12). AENNs can estimate the anti-proliferativity activity 3 samples within acceptable error for all 12 samples (3/12). The result by ANNs without averaging was 39/72 and that of AENNs was 36/72.This results showed that ANNs and AENNs could estimate activity with the almost same accuracy.

B. *Anti-inflammatory activity*

Fig.4 shows the average estimated value of anti-inflammatory activity. ANN can estimate 8/12 and AENNs can estimate 7/12 for anti- inflammatory activity. The result by ANN without averaging was 43/72 and that of AENNs was 40/72. ANN and AENNs could estimate activity with the almost same accuracy.

C. *Antioxidant activity*

Fig.5 shows the average estimated value of antioxidant stress activity. ANN can estimate 8/12 and

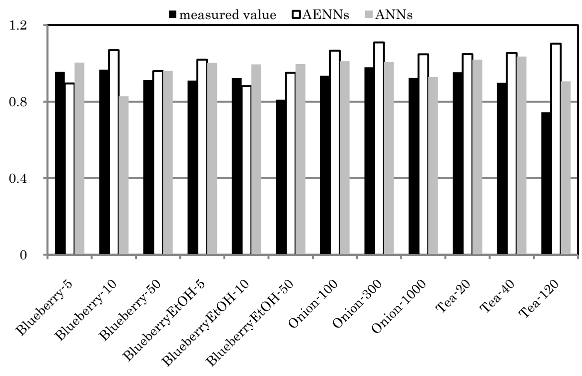

Fig.3 Estimated values of anti-proliferativity activity

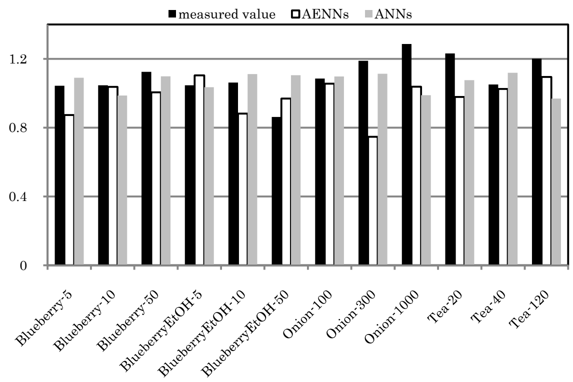

Fig.4 Estimated values of anti-inflammatory activity

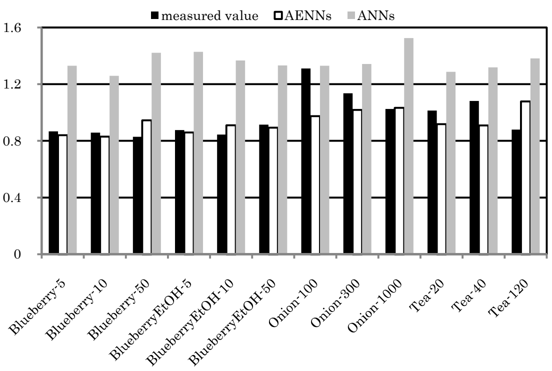

Fig.5 Estimated values of antioxidant stress activity

AENNs can estimate 7/12 for anti- inflammatory activity. The result by ANN without averaging was 15/72 and that of AENNs was 46/72. The error of conventional ANN is large, because the error is multiplied by the maximum value of the training samples as the inverted normalization process on other hand, out AENNs does not need the inverted normalization process, so it can be said that the AENNs are suitable for estimation with large physiological activities.

V. CONCLUSIONS

We develop a physiological activity estimation system from protein expression levels using amplitude extended neural networks. Since protein expression levels and physiological activities are separately measured, we employ simple regression analysis for finding an appropriate correspondence between protein expression levels and physiological activities. And AENNs adjust the amplitude of sigmoid function to avoid normalization of physiological activities, it is suitable to estimate some kinds of large physiological activities. The experimental result showed that our system could estimate antioxidant stress activity more accurate than conventional ANNs with normalization.

It remains to adjust the parameters K and l automatically through training process as a future work.

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