Quantitative structure activity relationships for medicines based on use of neural networks

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Abstract

We have researched quantitative structure activity relationships between molecular structure of medicines and physiological activity. Since they are non-linear, neural networks are useful tool to research them. There are many ranks for the non-linearity; therefore, the neuron function must be selected carefully. As the results of some trial calculations, we find the sigmoid-linear functions pair. We call the neural network constructed of the pair as ANN. The inter- or extrapolation abilities of the ANN are excellent; therefore, ANN is a superior predictor for the relationships. We evaluated the anticarcinogenic medicines, Carboquinone derivatives, by the developed ANN and leave-one-out method.

1. Introduction

Many papers have been published for quantitative structure activity relationships (QSAR), where many kinds of fitting methods were adopted [1-3]. Since the neural networks have prominent ability for non-linear fitting [4], we are sure that it is useful and practical for QSAR, by using the neural networks medicine's physiological activities can be simulated [5].

It is a reasonable expectation, but calculating on the relationships, we often find examples that the quantitative relations don't revise the results based on the linear multi regression methods. It is interpreted usually that the strangeness seems to be arisen by uncertainty for physiological activity. Under such a condition and small number of observation data, the non-linear fitting ability is not required so much, but fitting ability around whole data. It is certain that there are many ranks for the non-linearity. If the considerations were true, some suppositions in the multi layer neural network calculations should be reexamined, that are neuron-functions, estimations for the BP-learning, and scaling process for input data. Especially, since the functions of neuron-functions influence the potential among the learning data, the reexaminations are necessary.

2. Selection of neuron's function

2.1 Selection theory

Since any neuron-function is not determined in learning, we can adopt other functions instead of the sigmoid function. The functions must be differential, and be desirable to have extrapolating functions. If inappropriate functions for the target phenomena are chosen, the estimations will be unacceptable.

We adopt situations that target phenomenon is represented by continuous functions, and it is increasing plainly until one peak point, and it doesn't change rapidly. The restrictions are reasonable for QSAR. Under the restrictions, we considered selections of neuron functions on the second and third layers. The following function pairs are practical:

(1) sigmoid for 2nd layer and sigmoid for 3rd layer,
(2) sigmoid and linear functions,
(3) sine and linear functions,
(4) quadratic and linear functions.

The case (1) is a standard and reference.
The case (2) is same as "Analogue type Neural Network (ANN)". Function of the ANN is,

$$f=\sum_{j}^{M} \mathbf{C}j\mathbf{S}j\left(\sum_{i}^{N} \mathbf{A}i\mathbf{x}i+\mathbf{B}\right) \qquad (1).$$

Where the number of 1st layer is N, that of 2nd layer is M, and 3rd layer is 1. If the number of 3rd layer is plural, "f" is replaced by a vector f. The coefficient **C** is connected-value between neurons on 2nd and 3rd layer. **A** is connected-value between 1st and 2nd layer, and **B** is a bias. The **x** is input datum, and **S** means sigmoid function. Therefore, non-linear function of the ANN arises from sigmoid functions on 2nd layer only. If the sigmoid functions are replaced by others, the network-function is changed. As an example, if the replacement is ortho-normal set, the function of the ANN is equivalent to "otho-normal finite expansion". Since the equation (1) is finite expansion, the condition of the convergence is not zero but small positive number (about 10**-4). The convergence speed is faster with 30 times than that of standard neural network.

The method of ANN is near by radial function method [6,7]. Recently genetic programming method [8] is well known as a superior prediction method, which generates explicit functions in order to represent phenomena. Cross terms between descriptors are also generated. So, one part in the variation space of the genetic programming method is equivalent to the ANN.

The ANN has superior facility for extrapolations than that of all sigmoid functions. We believe the character is suitable in forecasting or QSAR. A selection reason for the case (3) and (4) is same as ANN. The (3) is conceived from Fourier-series, and the (4) is done from Maclaurin expansion term in the sine function. They would be stiffer than that of sigmoid function; and the character is required in QSAR under uncertain observations as well as