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Artificial neural networks to evaluate the boron concentration decreasing profile in Blood-BPA samples of BNCT patients

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ABSTRACT

For the prediction of decay concentration profiles of the *p*-boronophenylalanine (BPA) in blood during BNCT treatment, a method is suggested based on Kohonen neural networks. The results of a model trained with the concentration profiles from the literature are described.

The prediction of the model was validated by the *leave-one-out method*. Its robustness shows that it is mostly independent on small variations. The ability to fit retrospective experimental data shows an uncertainty lower than the two compartment model used previously.

1. Introduction

During BNCT irradiation the patient remains isolated in the irradiation room and in most cases no samples can be taken in that period. However, to determine the irradiation time is essential to know the blood boron concentration to preserve the healthy tissue and to ensure enough dose to the tumor to reach tumor control.

The aim of this study was to implement a method based on Kohonen neural networks (Zupan and Gasteiger, 1999) to predict the boron profile during the isolation period, over 60 min in our melanoma irradiations (Menéndez et al., 2009) and to compare it with the two compartment model (biexponential decay) (Kiger et al., 2001) employed to predict the boron profile.

Concentration profiles of various lengths from published data (Table 1) were used.

2. Data

The data set in the study consists originally of 68 concentration profiles recorded at different (not equidistant) time intervals. Profile 62 was included to check only the capability of the program for extreme cases but then discarded regarding statistical aspects. The concentration profiles consist of 13–33 points all starting with zero time and zero concentration, but ending at a wide variety of time recordings from 250 up to more than 400 min. However, most of the profiles have concentrations up to at least 400 min. The time elapsed between concentration recordings vary considerably among the profiles as well as within each profile. An average profile has about 5 concentrations between the zero point and the maximum one, with the remaining 8–25 points extending over quite different time spans until the final measurement.

For the *training* stage of the net, to make the data comparable among themselves, the concentration profiles were interpolated to 41 points in 10 min intervals between zero and 400 min. The profiles that finish before 400 min were extrapolated by the slope of the last available concentration interval recorded.

In the present work, the 20×20 Kohonen model has 400 neurons to adapt 67 concentration profiles (Fig. 2). This was made in 300 epochs of training, which means that all 67 profiles were cyclically sent through the network 300 times and each profile was relocated each time according to its weight corrections that were constantly adapted to minimize the distance between the inputted profile and the selected neuron, after the input of each profile.

3. Modeling

The Kohonen network is an unsupervised learning method, what means that no mathematical functions or target vectors are needed for modeling the system.

Kohonen is an artificial neural network (ANN) method that, in principle, is a non-linear 2-dimensional clustering of *m*-dimensional objects (samples) $X=(x_1,x_2, \ldots, x_i, \ldots, x_m)$ onto the plane of $N \times N$

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Table 1
Concentration profiles recovered from the literature.

Case no.	Reference
1–4	Kiger et al. (2003)
5–7	Ryynänen et al. (2002)
8–10	Kiger et al. (2001)
11	Coderre et al. (1997)
12–20	Riley (1997)
21–26; 29–40, 42–60	Kiger (2000; pp. 441, 602–608, 610–620, 622–629)
61–66	Liberman et al. (2004)
67–71	Menéndez et al. (2009)
27, 28 and 41	Empty

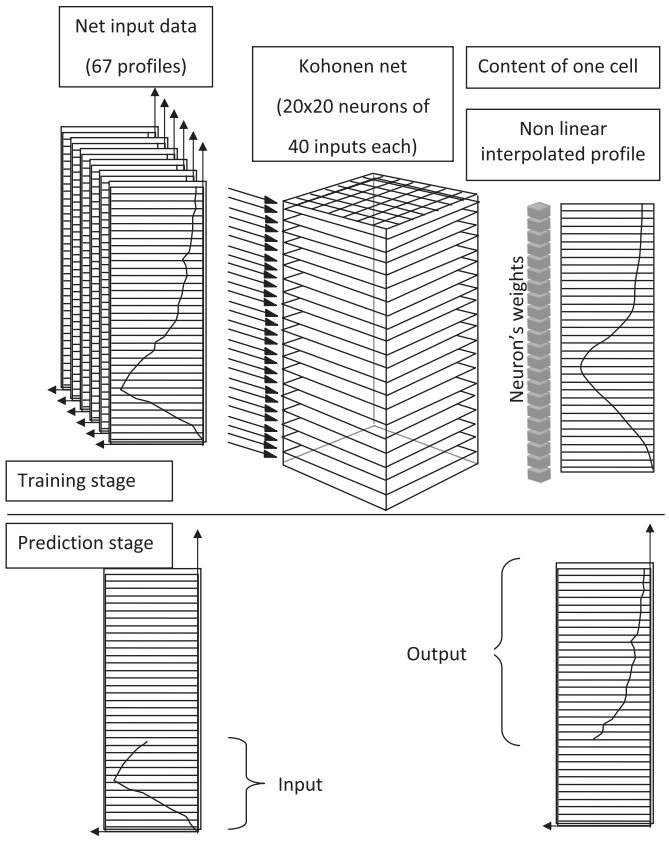

Fig. 1. 20×20 Kohonen network has 40 weight layers, i.e. each neuron is represented as 40-dimensional vector, $W_j=(w_{j1}, w_{j2}, \ldots, w_{j40})$ able to receive any 40-dimensional concentration profile in the form, $X=(x_1, x_2, \ldots, x_{40})$.

neurons. In our case the Kohonen network consists of 400 neurons distributed in the 20×20 plane. Each neuron has 40 weights, which means that the network can be adapted to 40-dimensional objects (time–concentration profiles) $X=(x_{t1},x_{t2}, \ldots, x_{ti}, \ldots, x_{t40})$ (Fig. 1). Furthermore, Kohonen artificial neural network (Zupan and Gasteiger, 1999; Kohonen, 1995) was selected as the preferred model because it can handle inputs of variable lengths like the present case requires. This problem, named as *missing data* had been theoretically proposed (Zupan et al., 1997). Then, profiles of different lengths, i.e. the profiles having less than 40 point can be managed.

In this way the Kohonen network can be trained with all data or with some missing ones. The incomplete data profiles can be used in the training data set as well as to predict results. In our case we have used the incomplete data for both events.

The data collection contains 19 profiles that are not complete (the concentrations are not recorded up to 400 min). To consider all data as inputs, the profiles were entered to the training of the Kohonen network as they were obtained up to the last point and the *missing* concentration values up to 400 min added with values of -9999 as a flag.

These values signal to the program of the Kohonen learning to do the distance calculation according to the *neurons per weight* principle. It is necessary to take into account that in the Kohonen neural network *all* weights in *all* neurons of the network are adapted and have specific values depending on the entire neighborhood regardless if the neurons were excited during the learning period or not and even if they were excited but the values of some specific variables were not defined.

4. Results

In order to test models, the outputs of which were series of boron concentrations consisting of several points x_i (each time a different number of them) quantitatively, we have to define a measure of agreement between the sought and the actually predicted result. Taking a complete concentration profile of 40 concentration values as an example of a real case test, then the first, let us say p points (points up to 60 min after over passing the maximum), are fed into the computer model as query input, while the remaining 40-p points are used for comparison with the predicted data.

The main assumption is that the profile applied in this test was not used for the generation of the model and can thus be regarded as an 'unknown' to the computer.

To test the prediction ability of the proposed method we have cut off all 67 concentration profiles at the time point extending 60 min over the time at which the maximal concentration was reached, i.e. to the maximal point plus six further points. This means that the truncated inputs have between 9 and 20 values, depending on the position of the maximal concentration. The remaining descending concentration profile of 19–30 concentration values has to be predicted if the first part is input to the model.

The prediction is based on the winning neuron in the Kohonen network, which is excited by the input of the first truncated part of the profile.

To obtain the actual prediction ability the *leave-one-out* procedure was employed. To do this, 67 models were made with 66 actual profiles, leaving out of the modeling procedure one of them each time. Each of these 67 models was tested by only one profile; the one that was left out of the generation of the particular model. As an example, Fig. 2 describes the profiles 4 and 56 in two extreme situations, very good and not so good, respectively, showing how good Kohonen model can be if enough data covering the entire concentration–time range are available.

On the other hand, the case 56 is also an example in which even for a relatively weak agreement between the input and the model, rather good predictions can still be obtained.

Different problems might arise by using Kohonen ANN for predictions when data are associated to an experimental spread and/or when there are not enough data to cover the entire concentration/time range.

The average root mean squared prediction error (RMSPE) of the 67 profiles is the average quadratic error/concentration profile from 60 min after the peak concentration up to 4 h from the beginning of the infusion. RMSPE was calculated for the ANN and compared to the RMSPE for the biexponential model (BE) algorithm (Kiger et al., 2003).

This last model (BE) had been used to fit the complete curve, up and down parts of it, but there were no predictions of the decreasing side using the points from the starting time until those which scarcely overshoot the peak. Being the prediction of the decreasing side of the curve the most important aspect of the modeling in order to work out the radiation's dose of BNCT, we

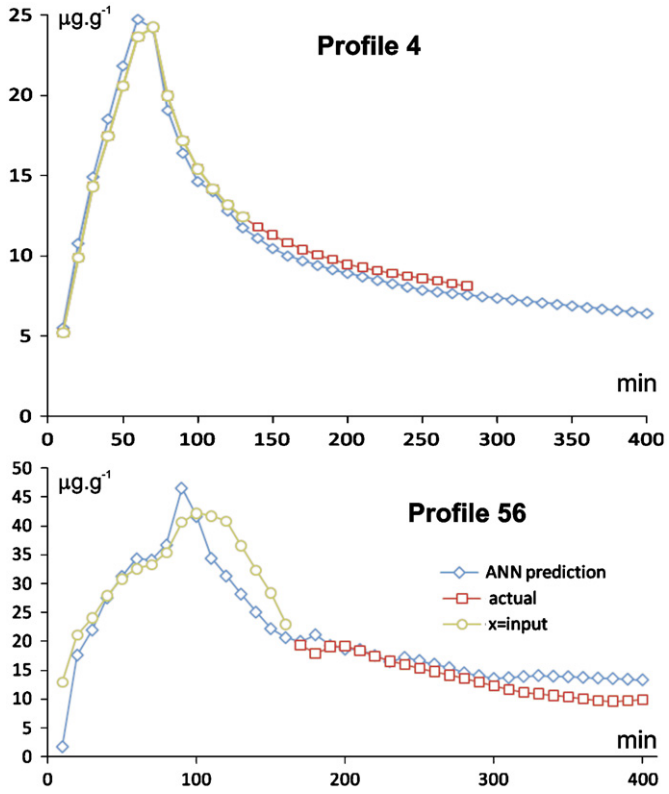

Fig. 2. Examples of the Kohonen model: case 4 very good and 56 poor agreement.

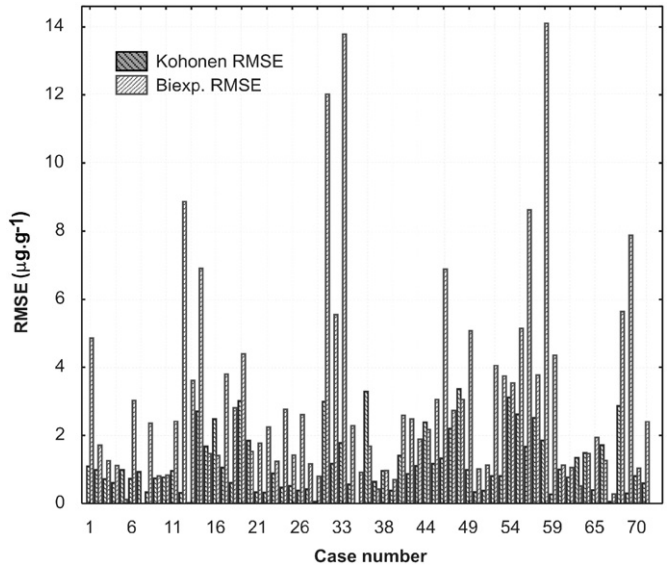

Fig. 3. RMSPE of the 67 profiles from 60 min after the maximum concentration up to 4 h after the beginning of the patient F-BPA infusion for the artificial neural network (ANN) Kohonen and the biexponential model (BE).

recalculated it using the same concept applied for ANN. The error was calculated for every one of the original experimental points of the curves located after passing 60 min of the peak's time, using the previous points to calculate the parameters of the BE model. The RMSPE comparison of both methods is shown in Fig. 3.

For most profiles the RMSP prediction for ANN Kohonen model has lower values than the BE. To be precise, the BE model should involve more than 3 concentration values during the 60 min over passing the maximum.

5. Conclusions

Usually, the standard modeling techniques require the knowledge of a mathematical analytical function in advance. The parameters of that function are determined on the basis of the best agreement between the experimental and estimated data (Ryynänen et al., 2002).

Differently, the ANN's have the property of not requiring that knowledge to adapt the relationship between the experimental and estimated data. Then, any likely deviation of the analytical function shape selected by the previous methods could be successfully traced.

Another advantage of the models of this type is that it could be constantly improved by adding new data to the training matrix. The data addition contributes to enhance the training stage as well as to reduce the prediction error.

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