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ANALYSIS OF TIME SERIES
OF BIOMEDICAL DATA BY ARTIFICIAL
NEURAL NETWORKS

ANALIZA VREMENSKIH SERIJA
BIOMEDICINSKIH PODATAKA VEŠTAČKIM
NEURONSKIM MREŽAMA

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Ključne reči

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Abstract

A novel application of artificial neural networks (NNs) to modeling biomedical systems from the time series data that the systems generate is proposed. The systems are allowed to be nonlinear and/or nonstationary. The method consists of training a NN by error backpropagation algorithm for the prediction of a biomedical time series signal, and then examining the connection-weight-space (CWS) of the NN to extract information about the signal generator mechanism. A novel feature, "normalized vector separation" (NVS) is also proposed to measure the separation of two arbitrary states in the CWS and use it to track the state changes of the system. A new method to estimate the order of the system from the time series data including noise by calculating degree of randomness is also proposed. The performance of the methods is examined with synthetic signals, and then successfully applied to sleep-wake rhythm and clinical EEG. Analysis of synthetic data indicates that the NVS can track the system down to a signal-to-noise ratio of 3.5dB. Sleep-wake hour data for three months from normal subjects were analyzed. The underlying system was modeled by NNs and dynamic changes of the model were captured. Secondly, clinical data obtained from three patients undergoing carotid endarterectomy of the brain showed that EEG could be modeled with a small root-means-squared-error by the proposed method, and the blood perfusion state of the brain could be monitored via NVS.

INTRODUCTION

Most of the time series signals observed in disciplines such as biology and medicine are nonstationary. Such signals arise as a result of complex dynamics of an underlying nonlinear system, which is often not directly accessible to an observer. It is usually possible to characterize the states of the system by analyzing the externally accessible signals. For instance, in medical diagnosis, physiological signals are routinely used to probe the state of the underlying system, i.e., the human or a particular organ system. The complexity and low signal-to-noise ratio of real-world nonlinear signals often make it a challenging task to use them in critical applications [1, 2, 3]. Furthermore, the vast majority of the classical pattern classification techniques are tailored to linear analysis, and thus relatively less effective with highly nonlinear data.

Neural networks (NNs) have recently been proposed as a robust tool in nonlinear signal classification. They have also been extensively studied in their ability to capture the

dynamics of a complex system via self-learned input-output mappings. The objective of this paper is to demonstrate that both of these capabilities provide a novel solution to the problem of characterization of nonlinear time series data. The existing literature proposes several NN-based solutions to the problem. In the most ubiquitous approach, a multi-layer perceptron-like NN is trained using the error back-propagation algorithm [4].

The training data set consists of the time series data at the input and the a priori known classes of the corresponding data at the output. The NN is expected to discover the mapping between the input and output via supervised training, such that it can accurately classify even previously unseen data.

Recent research further substantiates the merits of artificial intelligence as a tool in the clinical setting. It is suggested that NN may be a better solution for nonlinear medical decision support systems than conventional statistical techniques [5, 6, 7]. These approaches have had many successes, but depended on the direct mapping between the input sig-

nals and the a priori known (output) class to which each input data belonged.

It was often found that large NNs were needed for the task. The size of NNs depended heavily on the nature of the particular task at hand. NNs have been used to predict or characterize nonlinear time series [8, 9, 10, 11]. The issue of time-variant time series prediction has been investigated in [9].

Concepts used in NN-based time series prediction provide a solid starting point for the novel work presented in this paper. The fundamental premise of the paper is that once a low capacity of the NN is trained to accurately predict the given nonlinear time series at all points, the connection-weight-space (CWS) of the NN has captured sufficient information on the state of the underlying system generating the time-series. The theoretical foundation for this is provided by the Universal Approximation Theorem [12] and Takens's Theorem [13].

The CWS of the NN can be used as an excellent space to characterize and dynamically track state changes of the system. Note that the capacity of the NN should be much smaller than the training data presented to the network, so that pure memorization can be ruled out.

The method proposed in this paper involves two steps:

(1) NN-based time series prediction followed by (2) analysis of the CWS.

In this paper, a new method to conveniently track the state of a nonlinear system through NN-based time-series prediction followed by CWS analysis is proposed. After the plausibility and robustness of the proposed technique was assured by simulations on data generated from known linear or nonlinear dynamical systems, successful application of this method to sleep-wake rhythm was performed [14, 15, 16]. Then clinical EEG data analysis obtained from three patients undergoing carotid endarterectomy (CEA) surgery of the brain was conducted [17]. The proposed technique results in diagnosing the state change in the EEG even when the traditional technique fails.

METHOD

1. Estimation of time series by neural networks

Techniques to identify linear dynamical systems have been developed [18, 19, 20, 21]. When the time series output of a system $\dots, x_{-1}, x_0, x_1, \dots$ is expressed as

$$x_t + \sum_{i=1}^m a_i x_{t-i} = e_t, \tag{1}$$

where e_t is a time series of Gaussian white noise with the average of 0, it is called m -th order auto-regressive (AR) process. When it is expressed as

$$x_t = e_t + \sum_{i=1}^m b_i e_{t-i}, \tag{2}$$

it is called n -th order moving average (MA) process. When it is expressed as

$$x_t + \sum_{i=1}^m a_i x_{t-i} = e_t + \sum_{i=1}^n b_i e_{t-i}, \tag{3}$$

which is a process mixed above two processes, it is called m, n -th order mixed auto-regressive moving average (ARMA) process. System identification is the estimation of

parameters a_i and b_i , and orders m and n in such a way that the estimation error of x_t is minimized in the above model if the system can be regarded as linear.

In the analysis of biological and medical systems, it is impossible to ignore their nonlinearity. Artificial neural networks (NNs) are mathematical models into which multi-layered structures and plasticity of the biological neural systems are incorporated. They are one of powerful approaches to analysis of nonlinear systems. We propose a method using NNs to identify the dynamics of the biomedical systems that generate time series data.

Consider a sampled time series $\{x_n, n=1, 2, \dots, N\}$ of length N . By Takens's theorem [13, 23] it is theoretically possible to exactly model the time series by a nonlinear AR process of the form:

$$x_n = g [x_{n-1}, x_{n-1}, \dots, x_{n-D}]. \tag{4}$$

NNs can approximate the above function $g[\cdot]$ since it has been proved that NNs with an arbitrary number of neurons are capable of approximating any uniformly continuous function [11, 23].

NN estimates a value x_t from D preceding data $x_{t-D}, \dots, x_{t-2}, x_{t-1}$. NNs are composed of multiple layers, an input layer, one or more hidden layers and an output layer, which is shown in Figure 1. Each layer contains a number of units. They have feedforward couplings. There is no coupling between the units in the same layer. The number of units in the input layer corresponds to the number of input data. Input units output the input value without any calculation. Output and hidden units have multiple inputs. Generally NN can have any number of output units. For the present problem the number of output units is one. The weighted sum u of the inputs u_i to a unit is calculated as

$$u = \sum_i w_i u_i. \tag{5}$$

The output y of the unit is given by a linear function of u or some monotonically increasing and saturating function such as

$$y = \tanh(u) \tag{6}$$

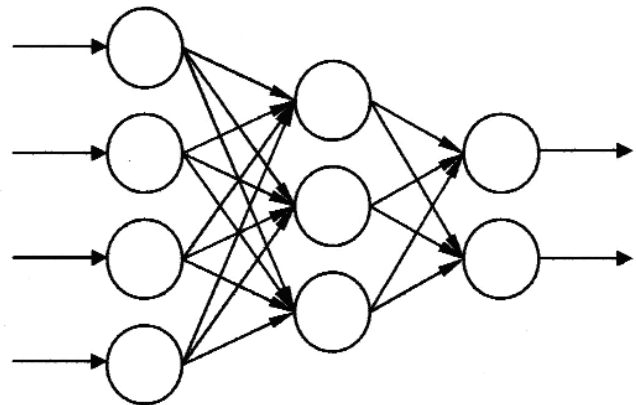


Figure 1. A multilayered neural network

The coupling weights are given random values initially. The output of NN usually has a large error to an arbitrary input pattern. NN are trained with training patterns. In train-

ing phase, the target value to each input pattern is given. The coupling weights between units are modified so that the error of the output decreases using the steepest descent method in the following way.

In the training phase, the target value is x_t and the output of a unit is denoted by o_t . Error function F and error ε_t are defined as

$$F = \frac{1}{2} \sum_{t \in S_t} \varepsilon_t^2 \quad (7)$$

$$\varepsilon_t = o_t - x_t, \quad (8)$$

where S_t is the set of training patterns. In order to minimize the error function F , the weight w_i is modified by Δw_i given as

$$\Delta w_i = -\eta \frac{\delta F}{\delta w_i}, \quad (9)$$

where η is a positive constant.

The errors of output units are clear since they are the difference between the output and target values. Those of hidden units, however, are not specified explicitly. For the modification of coupling weights associated with hidden units, we employ the backpropagation algorithm, which was proposed for learning of multilayer perceptron [4]. In this algorithm the error signal is propagated backwards, in the direction from the output layer to the input layer. The error signal of a hidden unit is the weighted sum of the error signals of the units to which the hidden unit outputs.

After the errors become sufficiently small, the input patterns that are not used in the training phase are presented and it is examined whether the NN can speculate with sufficiently small error. It is called test phase. If this is accomplished, it can be stated that the NN have acquired the dynamics of the target system.

By Monte Carlo simulations on synthetic data generated from a linear model (auto regression AR (2) model) and a nonlinear model (Mackey-Glass model [24, 25]), the robustness of the proposed technique and its plausibility in practical use was assured.

2. Pre-analysis of data

There are many techniques previously proposed in order to determine optimal neural networks [26], [27]. Most of them are based on selecting the optimal structure for a network in the context of discrete classification problems [28], [29]. As reported in [28], the goodness of time series prediction largely depends on the fact that dynamics is dominantly deterministic.

The signal-to noise ratio of data from biological or medical systems is often significantly low. When the NN are trained with the sequence of random data of average value zero, the output of the trained NN is zero to any input because no system dynamics is included in the training data. The output does not coincide with the target value of the input pattern either for training data or test data.

In order to develop a model of a biomedical system from clinical data, rigorous pre-analysis of the data is necessary. The pre-analysis characterizes the dynamical system and provides valuable information on its nature. In many cases through characterization, it is possible to find out whether the system is linear or nonlinear, deterministic or nondeterministic. For this purpose various measures of time series

such as approximate entropy, auto-correlation, average mutual information and number of false nearest neighbors [30, 31, 32] are evaluated. It is important at this stage to understand the difference between deterministic and nondeterministic systems because the former can be models and predictable but the latter cannot.

A method based on Lipschitz condition [33] that appears to work as a measure of continuity is introduced here to investigate whether the time series is deterministic or nondeterministic. The continuity assessment is a useful indicator of randomness if it is known that the deterministic component of the underlying data is smooth.

Let x denote the input vector (i_1, i_2, \dots, i_n) and y denote the output. Consider input vectors x_1, x_2, \dots, x_{N-n} and the corresponding output y_1, y_2, \dots, y_{N-n} . If x_i and x_j are very similar, then y_i and y_j are also very similar for deterministic data, while y_i and y_j can be quite different for random data. We evaluate the difference $|y_i - y_j|$ for y_j corresponding to all x_j in a neighborhood of each x_i as a measure of randomness of the data. The measure R is defined here as

$$R = \frac{1}{\sum_i |\Delta_i|} \sum_{i=1}^{N-n} \sum_{j \in \Delta_i} f(z_{ji}), \quad (10)$$

where (11)

$$\Delta = \{j \mid \frac{|x_j - x_i|}{\sqrt{n} x_{rms}} \leq \beta, i \neq j\}, \text{ if } x_j \text{ exists} \quad (12)$$

$$\Delta = \{j \mid \min_j \frac{|x_j - x_i|}{\sqrt{n} x_{rms}} \leq \beta, i \neq j\}, \text{ otherwise}$$

and $|\Delta_i|$ x_j in the neighborhood Δ_i . The x_{rms} and y_{rms} are root mean squared values for the data and output respectively, and $\sqrt{n} x_{rms}$ is the mean length of vector x_i in n -dimensional space. Then z_{ji} is given by

$$z_{ji} = \frac{|y_j - y_i|}{y_{rms}} \bigg/ \frac{|x_j - x_i|}{\sqrt{n} x_{rms}}. \quad (13)$$

A function $f(z_{ji})$ is a kind of logistic function expressed as

$$f(z_{ji}) = 0, \text{ if } \frac{|x_j - x_i|}{\sqrt{n} x_{rms}} \text{ and } \frac{|y_j - y_i|}{y_{rms}} \leq \beta \quad (14)$$

$$f(z_{ji}) = 1 - (1 + \alpha z_{ji}) \exp(-\alpha z_{ji}), \text{ otherwise} \quad (15)$$

where α and β are constantly positive.

Assume that data x_1, x_2, \dots, x_N are obtained by sampling a deterministic single-valued function of time. Then it is expected from Eqs. (14) and (15) that $f(z_{ji})=0$ because $y_i \cong y_j$ for all x_j existing within the neighborhood Δ_i (Eq. (11)) of any x_i . The value R will therefore be approximately zero where the number of data N is large. On the other hand, if the data are taken from random function, $f(z_{ji}) \cong 1$ because y_j is independent of y_i . This will lead $R \cong 1$ for a large number of data. The value R for any data will take a value between zero and one, which means the degree of randomness is expressed by R . It is a measure of regularity versus randomness. Larger R values correspond to greater randomness and unpredictability, and smaller values to more instances of recognizable patterns or feature in the data.

The advantages and applications of this method are:

- (1) It is simple and easy to implement;
- (2) It does not require a large amount of data to analyze;

(3) It can be useful in neural network modeling to analyze biomedical rhythm data, because it helps to determine the optimal network;

(4) It can be useful in clinical data analysis.

3. Coupling weight analysis

We define the coupling weight space (CWS) of the NN as the vector space spanned by all the coupling weights in the NN. A point in CWS is represented by a weight vector (WV). We carry out the coupling weight analysis in the following procedure in order to investigate the change of system dynamics (Figure 2).

(P1) Divide the total data with length N into segments of

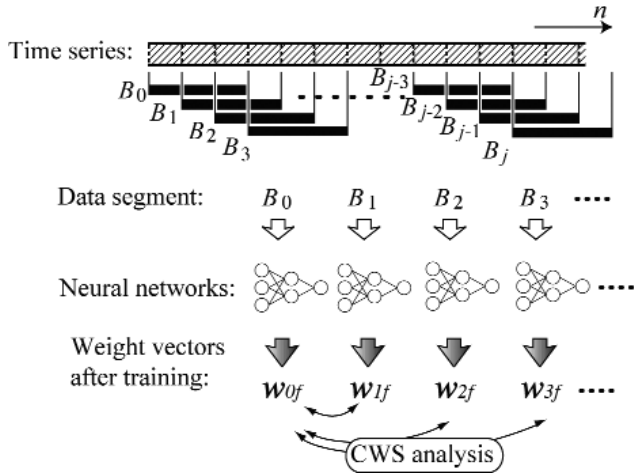


Figure 2. Coupling weight space analysis of neural networks

length M , with the segment overlap length L . Let the time series data in the j -th segment be represented by $x_j(n)$, $n=1, 2, \dots, M$ and $j=1, 2, \dots, J$, where J is the total number of segments contained in the data of length N .

(P2) Carry out steps (P3)-(P5) for all J segments.

(P3) Consider the segment $x_j(n)$. Let N_T^j denote the neural network associated with the j -th segment. Initialize the WV of N_T^j according to a uniform probability density function in $[-1, 1]$ and W_{j0} denote the initialized WV.

(P4) Train the network with the data in j -th segment using the error backpropagation algorithm. The training data for the input is given by the set $z_j=(x_j(n), x_j(n-1), \dots, x_j(n-D+1))$, and the corresponding data for the output is given by the sample $x_j(n+k)$. Note that the training is carried out in sequence for all the training input/output pairs, $\{z_j, x_j(n+k)\}$ ($n=D, D+1, \dots, M-k$). Let the learning rate be denoted by η .

(P5) The training is deemed to have completed for N_T^j when all the training input/output pairs have been presented for a predetermined number of times q of training epochs. Once the training is over, obtain the trained WV and express it by W_{jf} .

As the main outcome of steps (P1)-(P5), we get a set of trained NNs $\{N_T^j, j=1, 2, \dots, J\}$, represented by the end-of-training WV set given by $\{W_{jf}, j=1, 2, \dots, J\}$. We use the same initial WV to have the same random values, i.e., $W_{1b} = W_{2b} = \dots = W_{Jb}$.

Due to the facts that (a) W_{jf} are the results obtained by minimizing the k -step estimation error in the sense of backpropagation learning, and (b) the number of training samples far exceed the number of free parameters in N_T^j , the estimated W_{jf} should indeed identify the underlying system.

We propose two measures that describe the relative positions of W_{jf} in the CWS and thus help us characterize/track the states of the system under study. The concept of CWS proposed in this paper allows us to represent each N_T^j as a point in the CWS. Two different states “u” and “v” of a system occupy two separate positions in the CWS. This separation of the two WVs can be captured in their angular separation in CWS as defined by

$$\lambda_{uv} = \cos \theta_{uv} = \langle W_{uv}, W_{vf} \rangle / |W_{uf}| |W_{vf}|, \quad (16)$$

where “ $\langle W_{uv}, W_{vf} \rangle$ ” denotes the inner product of the two WVs W_{uf} and W_{vf} . The measure λ_{uv} has the advantage that it inherently evaluates the amount of correlation between the two states. However, it has the disadvantage that it only evaluates the angular separation of the two vectors in CWS and thus is blind to pure radial separations. Furthermore, because cosine of θ has a very low gradient near 0 degree, changes of θ tends to get discounted for small θ .

We define another measure, normalized vector separation (NVS), γ_{uv} , given by

$$\gamma_{uv} = |W_{uf} - W_{vf}| / \{|W_{uf}| |W_{vf}|\}^{1/2} \quad (17)$$

Note that the measure γ_{uv} is dimensionless, and is sensitive to both angular and radial separation of WVs.

Analysis of synthetic data generated from a linear model (auto regression AR (2) model) and a nonlinear model (Mackey-Glass model [24, 25]) indicates that the NVS can track the system down to a signal-to-noise ratio of 3.5dB.

RESULTS

1. Sleep-wake data analysis

First the application of the present approach to the system identification of the signal source for the rhythm of sleep and wake is described. Sleep-wake rhythm is one of the circadian rhythms. The source activity is regulated by homeostasis so as to keep the period constant fluctuating simultaneously by non-rhythmic perturbations in daily life [34].

In the measurement, 10 subjects recorded their own Sleep hours (S) and Wake hours (W) data were taken during three months. Due to the amount and recording period of the data, the hours were recorded by themselves. The data may include measurement errors, influence of external conditions or other environmental sources. They are still useful for preparatory basic investigation. It was observed that the data have a certain tendency allowing to classify them into two categories, regular (six subjects) and irregular (4 subjects). The main interest here is the regular components of the data. Two data from subject A and B were focused on in this paper.

The n -th day data of Sleep and Wake are denoted by S_n and W_n . The sum of S_n and W_n is denoted by SW_n , $n=1, \dots, N$, where N is the total days and $N=91$. The data are converted to the deviation from their mean hours and scaled by a factor h to normalize the values in the range of -1 and 1 by the equation

$$x_n = (SW_n - 24)/h, \quad (18)$$

where $h=6$ was used.

To determine the number of input units, the degree of randomness R was calculated for different number of input data of two subjects A and B. The average value of R for 30 calculations were obtained, respectively, with number of input data $D=2, 3, \dots, 7$. The parameters α and β in Eqs. (14) and (15) were set to 0.4 and 0.01, respectively. The R values start with a much lower values with $D=2$ than random data, increase as D increases, and then finally decrease as D increases further. The R value for random data decreases monotonically with the increase of D . When the R values for the subjects finally decrease, they are similar to that for random data. It is reasonable to deem that the higher dimensional inputs may not represent the real dynamic properties of the subjects. Therefore it was concluded that the optimal number of input units is 2 for both subjects A and B.

Networks with only one hidden layer and two hidden layers were tested with different number of hidden units. The numbers of the units in the layers are denoted by l_1 and l_2 , respectively. It was found that when the network has two hidden layers and $l_1 = l_2 = 2$, it made the root mean squared (RMS) error smaller than other networks. The RMS error for each subjects with this case were in the range between 0.04 and 0.07

The network has acquired the regularity in the data. The analysis of coupling weight space (CWS) was performed to elucidate the system change. As the index of separation of the different weight vectors (WVs), their angular separation by Eq. (16) was used in this study. The angular separation λ was more than 0.8 for Sleep+Wake data. It is speculated that the properties of the system are considered to be maintained. The λ value was kept almost constant for a while after fast gradual change. Its duration is more than 20 days. It is therefore deemed that the dynamics of sleep-wake rhythm may adjusted occasionally by some environmental change and then kept in a steady state for some period.

2. EEG data analysis

Secondly the application of the present approach to EEG analysis is described. The work described in this paper used a clinical EEG signal acquisition system (Model 7T18, DP1100, NEC Medical Systems, Japan) during clinical operation. The EEG was acquired at a sampling rate of 200 samples/s and a resolution of 16 bits/sample, using the standard electrode placement by the International Standard 10/20 system [35].

The EEG signals were measured from three different patients, PA-1 to PA-3, who underwent carotid endarterectomy (CEA) surgery at The University of Tokushima Teaching Hospital, Tokushima, Japan. As a part of the CEA procedure, internal carotid arteries (ICA) were systematically occluded several times during the operation. To investigate whether CEA can be safely performed on a given patient, an exploratory occlusion of the right or left ICA was performed as the first occlusion. If the results of the exploration were acceptable, the CEA was performed on the second occlusion. It is possible that some patients may develop severe ischemic complications due to the temporary occlusions. In order to monitor the situation, surgeons intra-operatively recorded EEG data from the patients. EEG data were used as an indication of the gross level of blood perfusion in the brain.

In this study the occlusion of the ICA is associated with three "brain states" (B1)-(B3) as

- (B1): before the surgeon induced occlusion of ICA;
- (B2): during the surgeon induced occlusion of ICA;
- (B3): after the surgeon induced occlusion of ICA.

We attempted to estimate the brain state prevailing at a given time, based on the proposed NN method. The data provided us with a great opportunity to investigate the clinical feasibility of the proposed method in tracking the state of the brain using EEG signals, while blood perfusion levels to the tissues changed due to the occlusions. Note that in all of three cases patients suffered from natural occlusions of one branch of the ICA, and the CEA surgery was performed by the surgeon to cure the disease. As a step in the surgery the surgeon induced temporary occlusions to the required branch of the carotid artery, making sure to collect EEG data from the appropriate EEG electrodes.

For the patient PA-1, who suffered from left ICA complete occlusion and underwent right ICA surgeon induced occlusion, we used the EEG signals obtained from five electrodes of the right side brain. Similarly we used the EEG signals from four electrodes of the left side brain for the patient PA-2 and PA-3, who suffered from right ICA complete or relatively mild occlusion and underwent left ICA surgeon induced occlusion. We investigated whether the present method can accurately model all the EEG signals. We used the following parameters: $k=1$; $N=210,002$; $M=1,002$; $L=0$; $\eta=0.001$; $D=2$. The number of hidden units was set to three.

In all experiments, steps (P1)-(P5) proposed in the previous section were followed. Then the WV set was evaluated. For all WVs we calculated γ_{oj} using Eq. (17). Note that we fixed $u=0$ in all cases; thus the system change from the segment 0 was tracked. The NN-estimated values of EEG $\hat{x}(n+k)$ over the domain $n=D, D+1, \dots, N-k$ were calculated. As the result of the calculation of the error between the NN-estimated values and the measured values, we confirmed that all the EEG signals were properly modeled with the proposed method. The measure γ_{oj} changed reflecting the change of the brain state during the operation.

Conclusions

A novel method using a moving average type of feedforward multilayered neural networks dealing with time series data is presented. It can conveniently capture the states and monitor the state changes of the underlying biomedical systems such as sleep-wake rhythm and brain states under an surgical operation. The method proposed in this paper is robust to observation noise. It is concluded that the initial weight selection of the neural networks does not pose any remarkable threat to the convergence of the coupling weights. A relatively small size of the network is needed, which makes the proposed method an attractive alternative to existing techniques.

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Apstrakt

Predložena je nova primena veštačkih neuronskih mreža (NM) za modeliranje biomedicinskih sistema od vremenskih serija podataka koje sistemi generišu. Modelirani sistemi su nelinearni i/ili nestacionarni. Method se sastoji od obučavanja NM algoritmom prostiranja greške unazad za predikciju vremenske serije biomedicinskog signala, i potonjeg ispitivanja prostora-težinskih-veza (PTV) NM za ekstrakciju informacije o mehanizmu generatora signala. Predložena je i nova karakteristika, "normalizovana separacija vektora" (NSV), kao mera separacije dva proizvoljna stanja u PTV i njeno korišćenje za praćenje promene stanja sistema. Takođe je predložen novi metod za procenu reda sistema iz vremenske serije podataka sa uključenim šumom, izračunavanjem stepena slučajnosti. Primena metoda je ispitana sa veštačkim signalima, a potom je uspešno primenjena na ritam budnost-spavanje i klinički EEG. Analiza veštačkih podataka indicira da NSV može pratiti sistem sve do odnosa signal-šum od 3,5 dB. Analizirani su tromesečni vremenski časovni podaci budnost-spavanje na normalnim subjektima. Primenom NM modeliran je sistem i nađene su promene modela. Osim toga, klinički podaci na tri pacijenta podvrgnuta karotidnoj endararektomiji mozga pokazali su da se EEG može modelirati sa malom srednjom kvadratnom greškom, i da se stanje krvne perfuzije mozga može pratiti putem NSV.

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