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Application of Wavelet Neural Networks for Monitoring of Extraction of Carbon Multi-Functional Medical Nano-Agents from the Body

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Abstract

In the given study the new approach to solution of the problem of monitoring the removal of luminescent nanocomposites and their components from the body with urine is proposed. The monitoring is performed by luminescence spectra with the help of classical perceptron type neural networks and of wavelet neural networks. A comparative analysis of the results obtained with application of multilayer perceptrons and wavelet neural networks is carried out.

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Keywords: wavelet neural networks; luminescent carbon nanocomposites; spectroscopy

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1. Introduction

At the present time, methods of targeted drug delivery for reduction of adverse effects and for correction of the dosage of drugs are actively developed in the modern biomedicine. Nanomaterials are very promising for this purpose [1,2]. Modern medical nanoagents are nanocomposites consisting of luminescent nanoparticle carrier with synthetic coating to which drug is attached [1,2]. Metal nanoclusters, semiconductor quantum dots, carbon nanomaterials are currently used as luminescent drug carriers [1,2]. Some of the most promising nanomaterials for biomedicine due to their high biocompatibility and non-toxicity are carbon nanoparticles – nanodiamonds, carbon quantum dots etc. [3-5]. Currently, carbon multifunctional nanocomposites are successfully used for the diagnostics and treatment of various diseases, including oncological diseases [6,7].

Obviously, when using such nanomaterials in medicine, it is necessary to pay attention to the removal of drug carriers and other components of nanocomposites from the body. Such control is carried out, for example, by means of labeling by radioactive substances – gamma-scintigraphy [8], magnetic resonance and other types of tomography [9,10]. However, these methods are expensive and characterized by the presence of ionizing radiation. Luminescent visualization of nanoparticles is an alternative method, which has sufficiently high sensitivity and is relatively cheap [11]. A serious limitation of luminescent visualization of nanoparticles in biological objects is the presence of own fluorophores in biotissues - tryptophan, tyrosine, phenylalanine, etc. [12]. The total fluorescence spectrum of natural fluorophores ranges from 250 nm to 700 nm and usually overlaps significantly with the luminescence spectra of carbon nanoparticles [13,14], which makes it difficult to observe the movement of luminescent nanoparticles in vivo and in vitro. In order to solve this problem, new nanoparticles are synthesized, whose luminescence weakly overlaps with autofluorescence [15,16], or laser scanning confocal microscopy [17], multiphoton microscopy [18], etc. are used. These methods are effective but expensive.

In recent years, adaptive methods of data analysis, primarily artificial neural networks (ANNs), have been increasingly used to solve biomedicine problems [19]. Use of neural networks when working with complex biological objects is especially attractive, because it does not require construction of any accurate model of the studied object. ANN were successfully used to solve inverse problems of optical spectroscopy and pattern recognition in biology and medicine [20-25]. The authors of the study [23] elaborated a method for the diagnosis of skin cancer, in which using deep artificial neural networks solved the problem of classifying 757 skin disease types. In the study [24], the authors predicted the level of cytotoxicity of the nanocomposite on the basis of its size. The authors of the study [25] tried to predict drug-carrier size on the basis of molecular weight of the carrier and the weight ratio of the carrier and the drug.

Despite the wide application of adaptive methods of data analysis in biomedicine, the studies on the use of ANN for optical imaging of nanoparticles in biomaterial, i.e. for the recognition of luminescence of nanoparticles against the background of autofluorescence, are unknown to the authors of this article. Previously, we demonstrated the principle possibility of optical imaging of carbon nanoparticles in biotissue using neural network algorithms [13,14]. The problems of identification and determination of concentration of nanodiamonds and carbon dots in chicken protein [13,14,26] and urine [26] were successfully solved with the use of ANN [26]. In the publication [27], we solved a more complex multi-parameter problem of optical imaging of nanoparticles in biotissue: we developed an ANN-based method of determining which nanoparticles - nanocomposites themselves and/or their components - and in what amount are present in human urine. It was shown that a multilayer perceptron can be used for simultaneously detection of the fluorescence of nanocomposite consisting of graphene oxide (nGO) covered by copolymer (Cop) with attached folic acid (FA) - nGO+Cop+FA, and its components nGO+Cop, FA against the background of autofluorescence of human urine. At the same time, it is possible not only to detect, but also to determine the concentration of these nanoparticles in urine: sufficiently low detection thresholds for concentration were obtained (see below). The ways of increasing the accuracy of determination of the concentration of nanoparticles using various methods of selection of significant input features or methods of the choice of a specific methodology for the use of multilayer perceptrons were demonstrated.

In the present study, the new approach to the solution of the problem of monitoring the removal of luminescent nanocomposites and their components with urine is proposed. The monitoring is performed by luminescence spectra with the help of classical perceptron type neural networks and wavelet neural networks. A comparative analysis of the results obtained with application of multilayer perceptrons and wavelet neural networks is carried out.

2. Experiment

The problem of monitoring the excretion of nanocomposites nGO+Cop+FA and their components from the body with urine by luminescence spectra was solved on model samples. Nanocomposite nGO+Cop+FA and its components were introduced into urine in known quantities and in various combinations, the luminescence spectra of the suspensions were recorded, and thus a database for application of neural network technologies was created. The "experiment-based" approach was used [28], i.e. the ANN training was conducted on the experimental data – on the spectra of photoluminescence of the prepared suspensions of nanocomposites and their components in urine.

Nano-graphene oxide particles were covered by PEG-PEI copolymers conjugated to folic acid by specialists from Pharmaceutical Sciences Laboratory, Faculty of Science and Engineering, Åbo Akademi University (Turku, Finland) with the help of the method described in [29]. As it is known, folic acid is necessary for organism for the development and growth of new cells, including cancer cells [30]. Therefore, tumors of some types of cancer actively "take" free folic acid (expression of receptors) from the organism and use it for their growth [30]. In this regard, folic acid ligands which block the receptors and prevent further introduction of folic acid into the cell are used for cancer therapy. Exactly these ligands of FA were attached to the surface of nGO+Cop nanocomposites.

Preliminary studies of the integrity of nanocomposites nGO+Cop+FA in suspensions when pH changed from 5 to 8 showed that the initial nanocomposites with high probability disintegrated into nGO+Cop and FA components. Therefore, a three-parameter inverse problem was solved to determine the presence and concentration of the most probable particles in urine - nGO+Cop+FA, nGO+Cop and FA. Suspensions of nanoparticles in urine were prepared with all possible 8 combinations of substanses - {nGO+Cop+FA}, {nGO+Cop}, {FA}, {nGO+Cop+FA, nGO+Cop}, {nGO+Cop+FA, FA}, {nGO+Cop, FA}, {nGO+Cop+FA, nGO+Cop, FA}, {urine without nanoparticles} - in urine from three donors in the concentration range of each component from 0 mg/l to 2.15 mg/L.

Photoluminescence spectra of all the prepared samples were recorded in the range of 410-800 nm using laser spectrometer. Excitation of Raman scattering and luminescence was performed by the radiation of the diode laser (wavelength 405 nm, power 50 mW) [27]. Each spectrum contained 1785 channels/wavelengths. In total, 1461 photoluminescence spectra were obtained (Fig.1). Bands with maximums at 470 nm are Raman valence bands of OH-groups. Broad bands with maximum in the region of 520 nm are spectra of the superposition of photoluminescence of urine and/or nanoparticles. Processing of the obtained spectra consisted of subtraction of the pedestal caused by elastic light scattering, normalization to the spectral sensitivity of the device, and normalization of the spectra to the area of the valence vibrations of OH-groups of urine.

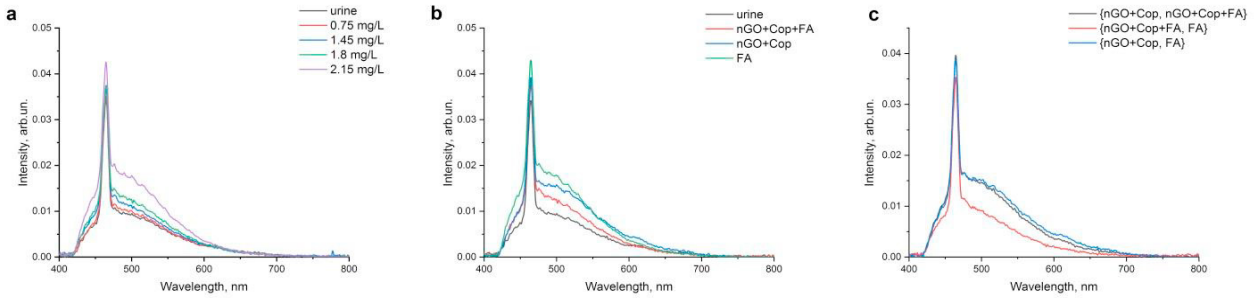

Fig.1. Photoluminescence spectra of (a) urine and nGO+Cop nanocomposites in urine at different concentrations; (b) urine, nGO+Cop+FA nanocomposites and their components at the concentration of 2.15 mg/L in urine; (c) three-component suspensions of nanoparticles in urine at concentrations: 1.8 mg/L for {nGO+Cop, nGO+FA}; 2.15 mg/L for {nGO+Cop, FA}; 1.45 mg/L for {nGO+Cop+FA, FA}.

3. Results

3.1. Application of multilayer perceptrons

The entire array of photoluminescence spectra of the prepared samples was divided into training, validation and test sets randomly in the ratio 70:20:10. Thus, the sets included 991, 300, and 168 patterns (spectra) respectively.

At the first stage, we used multilayer perceptrons (MLPs) trained with the full set of input features - 1785 spectral channels. The following architectures of MLP were trained: with one hidden layer (HL) - N01 (with 40, 80, 160, 240, 360 neurons in the HL), with two HLs - N02 (with (40+20), (80+40), (160+80), (240+120), (360+180) neurons in the HLs), and a deep architecture with seven HLs - N07 (with (360+180+180+180+180+40+20) neurons in the HLs). In all cases, 5 identical MLPs with various initial values of weight coefficients were trained. The results of their application were averaged in order to reduce the influence of the choice of initial weight coefficients. All ANN architectures had 3 outputs, corresponding to the classes nGO+Cop+FA, nGO+Cop, and FA. Fig.2 presents the results obtained with all of these MLP architectures, trained with the full set of input features.

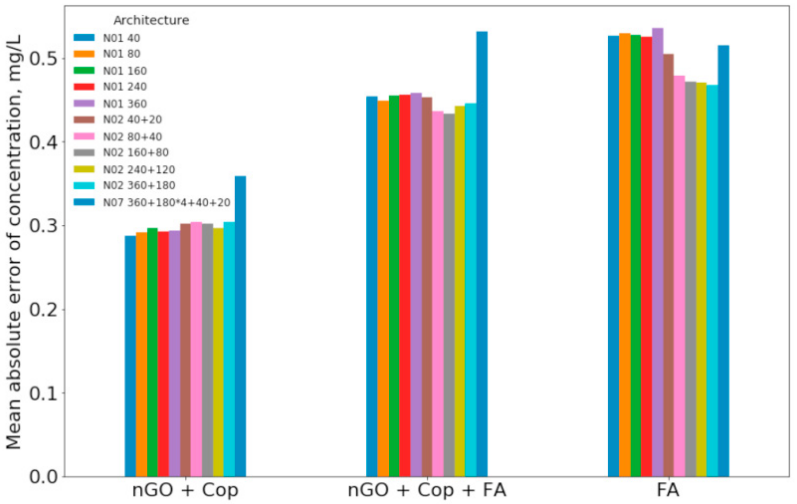

Fig.2. Results obtained by training all the multilayer perceptron architectures with the full set of input features.

The minimum mean absolute error (MAE) in determining the concentration of nanoparticles on the test set, obtained using various MLPs trained with the full set of input features, was 0.29 mg/L for nGO + Cop nanocomposite with N01 (40) architecture, 0.43 mg/L for nGO + Cop + FA with N02 (160+80), and 0.47 mg/L for FA with N02 (360+180). This is 13.4% for the nanocomposite nGO + Cop, 20.2% for nGO + Cop + FA, 21.7% for FA of the maximum content of nanoparticles in urine.

As it is known, the quality of training and work of ANN essentially depends on the input dimension of the problem. It often happens that not all of the input features are equally informative, while the best ANN architecture has a very large number of weighting coefficients. In this case, the reduction (compression) of the number of the used input features can lead to the improvement of ANN approximation of the required dependence due to the simplification of the approximating function (neural network). Therefore, at the second stage of this study, the MLPs were trained with new input features extracted from the initial feature set. The following feature extraction algorithms were used: 1) Aggregation, assuming calculation of average values in every N channels at the input of a neural network. 2) Principal Component Analysis (PCA) [31]. 3) Discrete Wavelet Transform (DWT) [32-34]. 4) Continuous Wavelet Transform (CWT) [35-37]. In Fig.3, the results obtained by MLPs trained with the sets of input features extracted by the specified algorithms, are presented.

One can see that the best results are obtained with both kinds of wavelet transform, the difference between which is insignificant. The best values of the MAE of determination of nanoparticles concentration on the test set was 0.20 mg/L for nGO+Cop nanocomposite (CWT, 222 features, N02 (360+180)), 0.40 mg/L for nGO+Cop+FA (DWT, 236 features, N01(240)), and 0.39 mg/L for FA (DWT, 457 features, N02 (360+180)). This is 9.2% for nanocomposite nGO+Cop, 18.5% for nGO+Cop+FA, 18.1% for FA relative to the maximum content of nanoparticles in urine.

Comparative analysis of the obtained values of MAE of determination of the nanoparticles concentration in urine using training with the full set of features and with the best subset of extracted features showed that the extraction procedure allowed us to reduce the error of determination of the concentration by 8.4% for nGO+Cop+FA, by 17.0% for FA, and by 31.7% for nGO+Cop relative to the maximum content of nanoparticles in urine.

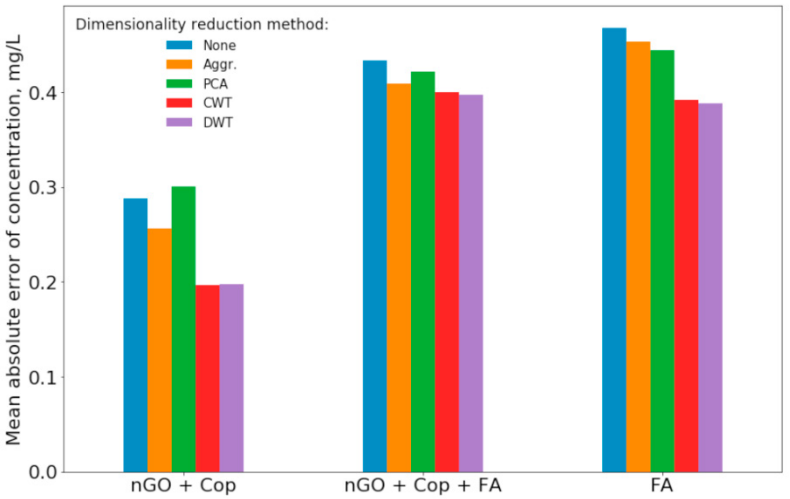

Fig.3. Results obtained by training multilayer perceptrons on input data sets with dimensionality reduction.

3.2. Application of a wavelet neural network

Wavelet neural networks (WNN) were first introduced in 1992 and the universal approximation property was also proved for them [38,39]. WNN have demonstrated a better quality of the solution with a smaller number of parameters in small-scale problems, as compared to classical ANN and to the ordinary wavelet transform. However, the complexity and instability of the learning process and the problems with large dimension of the input data lead to limited spread of this type of neural networks.

Since the number of input features directly affects the number of wavelet functions in each neuronal element, in this study we used extremely compressed input data (PCA algorithm, only 4 PCs). As cores of neuronal elements, the Mexican Hat wavelet was used normalized to its own power value, to preserve the amplitude range being less than unit. Besides the wavelet-neuronal elements, direct connections between the input and output layers were used.

Note that in the current implementation of the WNN, the issues of choosing the optimal network training parameters (learning rate (LR), momentum (LM) and the training gradient method, especially in case of using different types of neuronal elements), its structural elements (number of neuronal elements (NNE), type of wavelet function, initial initialization of weights) are still open. In this study, the grid search method was used to find optimal training parameters (LR and LM were changed in the range [0.5, 0.0000000005]), and the classical gradient descent algorithm was used. NNE was also varied (number of neurons: 4, 10, 20, 40, 80, 100). Each network had only one output, so for each suspension component, its own network was trained.

The best MAE values achieved by WNN were: 0.46 mg/L for nGO+Cop (LR = 0.05, LM = 0.5, NNE = 20), 3.4 mg/L for nGO+Cop+FA (LR = 0.05, LM = 0.34, NNE = 4), 4.1 mg/L for FA (LR = 0.05, LM = 0.026, NNE = 40). As we can see, only for nGO+Cop the achieved result was comparable with that of MLP.

This proves the possibility of using WNN for spectroscopy applications, but complex investigation of topology and parameters of the network is required. During the process of solving the studied problem, the strong dependence on weight initialization was observed: randomly generated weights in two successive trials could lead to results that differ for an order of magnitude. On the other hand, classical SGD method demonstrated frequent divergence of the solution or an extremely low rate of convergence. For this reason, modern modifications of SGD or novel gradient methods like Adagrad, Adam etc. should be used in future studies.

4. Conclusion

In this study, the problem of monitoring the removal of luminescent nanocomposites and their components from the body with urine was solved by luminescence spectra using classical multilayer perceptron neural networks and

wavelet neural networks. Comparative analysis of the results obtained with these two types of ANN showed that use of multilayer perceptrons trained with the sets of input features extracted with the help of Discrete Wavelet Transform provided the following mean absolute errors of determination of the nanoparticles concentration in urine: 9.2% for nanocomposite nGO+Cop, 18.5% for nGO+Cop+FA, 18.1% for FA relative to the maximum content of nanoparticles in urine. As for the result of use of wavelet neural networks, satisfactory error of determination of nanoparticles concentration in urine was obtained only for nGO+Cop – 21% relative to the maximum content of nanoparticles in urine. However, these are only the first results of using WNN to solve the studied problem. The ways for the successful implementation of wavelet neural networks are proposed.

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