

Machine learning in the analysis of UV-induced fluorescence spectroscopy data in the diagnosis of Parkinson's disease

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A new approach to the diagnosis of Parkinson's disease (PD) is demonstrated, based on the analysis of UV-induced skin autofluorescence using machine learning methods. The study included 123 participants (23 controls, 16 patients with nonspecific neurological disorders and 84 patients with PD). Spectral data was processed by the principal component method (reduction from 150 to 30 features) and classified by five algorithms. The best results were achieved by a fully connected neural network (ROC-AUC = 0.80, sensitivity = 0.92) and logistic regression (ROC-AUC = 0.79). The results support the potential of non-invasive skin spectroscopy as a screening tool for the early diagnosis of PD in clinical practice. Key words: Parkinson's disease, fluorescence, optical spectroscopy, skin, aberrant proteins, advanced glycation end products, machine learning, neural networks, diagnostics.

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1. Introduction

Parkinson's disease (PD) is a chronic progressive neurodegenerative disease accompanied by typical motor symptoms: resting tremor, bradykinesia, muscular rigidity and postural instability. Besides motor disorders, the disease often shows in cognitive decline, depressed states, vegetative dysfunction and sleep disorders [1]. Parkinson's disease ranks second after Alzheimer's disease among neurodegenerative diseases. Since the early 1990s, PD prevalence in the world doubled and by 2019 the number of patients exceeded 8.5 mln people. The disease is characterized by rapidly growing disability and mortality [2]. Regardless of advances in symptomatic treatment, there is currently no effective neuroprotective treatment, which makes early diagnostics one of the key issues in disease progression control. However, PD detection at symptomless stages is complicated by the lack of specificity of initial presentations and limitation of the existing diagnostic tools. Diagnosis is usually based on clinical symptom assessment. Meanwhile, updated epidemiological data reported by the American Parkinson Disease Association demonstrate sustained growth of the number of new cases, which emphasizes the need for implementing sensitive and noninvasive diagnostic approaches [3].

A key element of PD pathogenesis is abnormal aggregation of alpha-synuclein — a protein that is accumulated not only in the central nervous system structures, but also in peripheral tissues, including epidermis and skin nerve endings [4]. Such accumulations have proven to facilitate formation of chronic inflammatory skin state associated with activity of receptors for advanced glycation end products

(RAGE) [5]. Advanced glycation end products (AGEs) and their interaction with alpha-synuclein affect the autofluorescence spectra of tissues, which reflects typical biochemical changes in skin of PD patients [6]. Simultaneously, melanin metabolism disorder in PD [7] can reduce optical skin absorption in particular spectral range, offering additional opportunities for noninvasive analysis of optical parameters of tissues. Prospects of optical biopsy, a technique based on noninvasive analysis of the optical response of tissues, are increasing against this background. This technique is used to detect structural metabolic changes at the cellular level without the need for biomaterial sampling. Wu et al. have reported that skin and nail plate fluorescence parameters can serve as predictive markers of PD, demonstrating a statistically significant correlation with the presence of disease [8].

Findings obtained earlier from noninvasive UV-induced *in vivo* spectroscopy of skin demonstrated a high potential of this method as a tool for neurodegeneration assessment in PD [9]. During the experiment, distinct differences in radiation spectra were identified between the control and PD groups. It was assumed that spectral differences identified in some ranges probably reflected metabolic disorders associated with peripheral accumulation of alpha-synuclein and accompanying changes in biochemical tissue profile and could mark system metabolic disorders associated with neurodegeneration progression. Thus, optical tissue biopsy is a promising area for creating noninvasive tools for early assessment of metabolic disorders pathogenetically associated with PD. Further development of spectroscopic and machine learning approaches for analysis of biophotonic

signals can substantially improve the accuracy and repeatability of predictive diagnostic models.

The objective of this study was to develop and validate the automated classification of PD patients on the basis of spectral characteristics of UV-induced skin autofluorescence using machine and deep learning algorithms, and to evaluate the diagnostic value of this approach for potential use in clinical practice.

2. Materials and methods

Spectrofluorometer description

Spectrofluorometer block diagram includes the following components (Figure 1): information about spectra can be received using a spectrometer; radiation from the test object flows to the spectrometer through a quartz window, rotating mirror, condensing lens and interference cutoff light filter that are installed using the SMA905 coupling on the spectrometer input aperture. Fluorescence is excited by pseudo-longitudinal UV LED light focused to produce a parallel beam using a condensing quartz lens and filtered to remove spurious fluorescence using a light filter. Wood's glass can be used as the latter. UV light filter, lens and LED are interconnected by an applicable coupling. A hardware and software LED control device is used for switching on/off the LED simultaneously with the start of spectrometer. Signal from the control device is applied to the LED driver providing the required current level using a built-in battery (not shown). The battery is charged from the control power supply. Measurement signal is started by a command from PC. A USB hub is used to connect USB devices — the spectrometer and controller. Data transfer to PC and power supply are provided via a USB cable. Spectrofluorometer components, except for the outlet window, are mounted on a hard metal mounting plate that additionally serves for spectrometer cooling and is placed within the device housing.

UV-induced skin autofluorescence detection procedure

Spectral characteristics of UV-induced skin autofluorescence were measured in all participants using an original portable spectrofluorometer with a UV LED excitation source (central wavelength 375 nm) on the basis of the STS-VIS OCEAN OPTICS spectrometer. Additional spectral sensitivity calibration wasn't performed for the detector. Measurements were performed on the ventral surface of the forearm. Spectrum analysis covered an electromagnetic radiation range from 400 to 680 nm with a recording resolution 1.87 nm (a total of 150 spectral points). To eliminate the influence of daily metabolic tissue activity fluctuations and associated autofluorescence intensity oscillations, all measurements were performed in the first half of the day. Spectrum was recorded from each point 8 times. Measurement of one spectrum, including

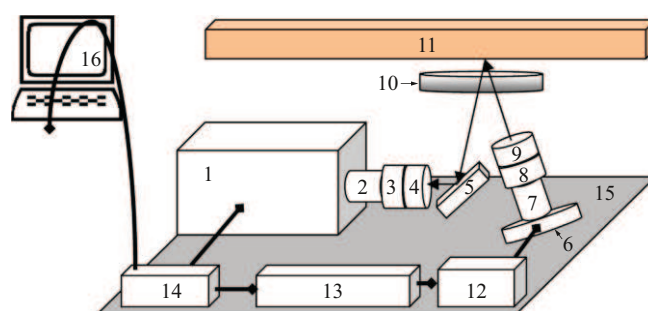


Figure 1. Spectrofluorometer block diagram: 1 — spectrometer, 2 — SMA905 coupling, 3 — interference cutoff light filter, 4 — condensing lens, 5 — rotating mirror, 6 — UV LED, 7 — coupling, 8 — condensing quartz lens, 9 — light filter (Wood's glass), 10 — quartz window, 11 — test piece, 13 — hardware and software LED control device, 14 — USB hub, 15 — mounting metal plate, 16 — PC.

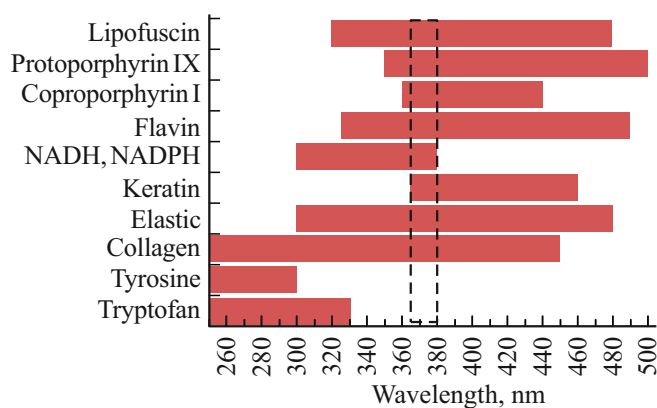


Figure 2. Intense absorption bands of main tissue fluorophores.

dark signal recording, took 8 s. Relative spread of spectral amplitude values was 1% max.

The task of metabolic status control by the skin autofluorescence spectrum involves fluorescence excitation in fluorophores included in skin. As can be seen from the data shown in Figure 2, absorption bands of most significant fluorophores intersect at 365–380 nm.

Reduced forms of nicotinamide adenine dinucleotide (NADN and NADPH) with their luminescence band peak at 440–470 nm and oxidized forms of flavin coenzymes (FAD and FMN) with their peak at 520–540 nm are of the main interest for luminescence analysis of living cells. When radiation with a wavelength of 385 nm and larger is selected, NADN and NADPH fluorescence will be „disabled“ making the redox fluorimetry complicated.

Movement into a short-wavelength region is only helpful when passing to the tryptophan band peak 280 nm, thus „enabling“ the tryptophan fluorescence. Less significant shifts to a short-wavelength region not only add tissue autofluorescence information, but also increase the radiation damage risk to a great extent

Study design and participant specifications

A multilevel sample involving three stratified groups of participants selected in accordance with clearly defined inclusion/exclusion criteria was formed for this study. Patients of the Russian Center of Neurology and Neurosciences participated in the study, the work was carried out in accordance with the decision of the Local Ethics Committee.

Control group ($n = 23$) consisted of apparently healthy male and female individuals in the 50–80 age range with no previous history of neurological disorders, who has undergone a medical examination to verify the absence of significant disturbances.

Comparison group ($n = 16$) included male and female patients (50–80 years old) with non-disabling neurological symptoms, in particular, muscle contraction headache syndrome, reportable degenerative-dystrophic changes of vertebral structures with various degrees of severity, and clinical and instrumentally confirmed signs of discirculatory encephalopathy.

PD group ($n = 84$) consisted of verified male and female patients aged 50–80 years with idiopathic Parkinson's disease. Degree of functional misadaptation of all participants in this group was evaluated using the Unified Hoehn & Yahr Staging Scale and corresponded to degrees of disabling 1–3.

Exclusion criteria included decompensated chronic diseases, in particular, uncontrolled hyperglycemia (type 2 diabetes without adequate pharmacologic correction), end-stage renal disease requiring replacement renal therapy, and progressive hepatic dysfunction with synthetic organ dysfunction.

For the purpose of solving the problem of binary classification (PD/not PD), the initial set of observation was divided into two non-intersecting subsamples: training and test. Training sample included data for 83 participants and was used to select and validate model parameters. Due to a limited dataset, the validation sample was not formed separately. Test sample contained 40 individuals, 20 patients from which had clinically verified PD, and 20 participants had no PD, which ensured balanced representation of classes during final classifier quality evaluation.

Preliminary data processing and analysis

The obtained spectral arrays were subjected to standard normalization via alignment relative to sample average and scaling in accordance with z-score normalization. This procedure provided comparability of features and removed the influence of individual differences in absolute values of fluorescence intensity.

To reduce the feature space dimensionality and find insights in the data structure, the principal component analysis (PCA) was used to identify maximum variance areas in the initial spectral data. PCA is a linear orthogonal transformation that projects data to a new coordinate space in such a way as to maximize the variance along the several first axes. This makes it possible to significantly reduce

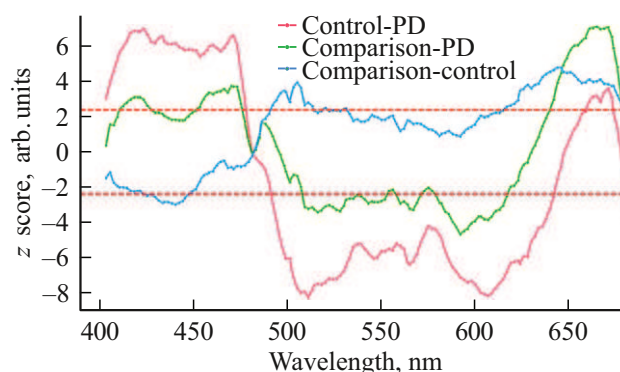


Figure 3. Z scores in the Mann–Whitney test depending on the wavelength for three pairs of comparison groups. Horizontal dashed lines denote critical scores $Z_{crit} = \pm 2.39$ at the significance level $\alpha = 0.05$ with the Bonferroni correction.

Table 1. Neural network training parameters

Parameter	Value
Hidden sizes	[64,32]
Learning Rate	0.0005
Batch size	256
Epochs	100
Learning Rate Gamma	0.95
Learning Rate Step Size	5
Positive Class Weight	0.05

the computational complexity of future model training while retaining the feature informativity.

Statistical significance of differences between groups was evaluated using the nonparametric Mann–Whitney test with the Bonferroni correction.

Machine and deep learning models

The following classification methods were used as basis algorithmic approaches: logistic regression (LR), support vector machine (SVM), random forest (RF) ensemble method and gradient boosting (GB) decision tree algorithm. The first three models were implemented using Scikit-learn (version 1.6.1) in Python 3.13, while the gradient boosting was deployed via the specialized XGBoost (version 3.0.1) library using optimization by classification metrics. Automatic class balancing was used for all models.

Feedforward neural network (FNN) architecture was additionally developed, including two hidden layers with ReLU (rectified linear unit) and an output layer with sigmoid activation function. Neural network was implemented using the PyTorch (version 2.6.0) framework and was trained by stochastic optimization on a validation sample to prevent re-training.

Neural network was trained using the Adam optimizer and binary cross-entropy as a loss function. Model training parameters are listed in Table 1.

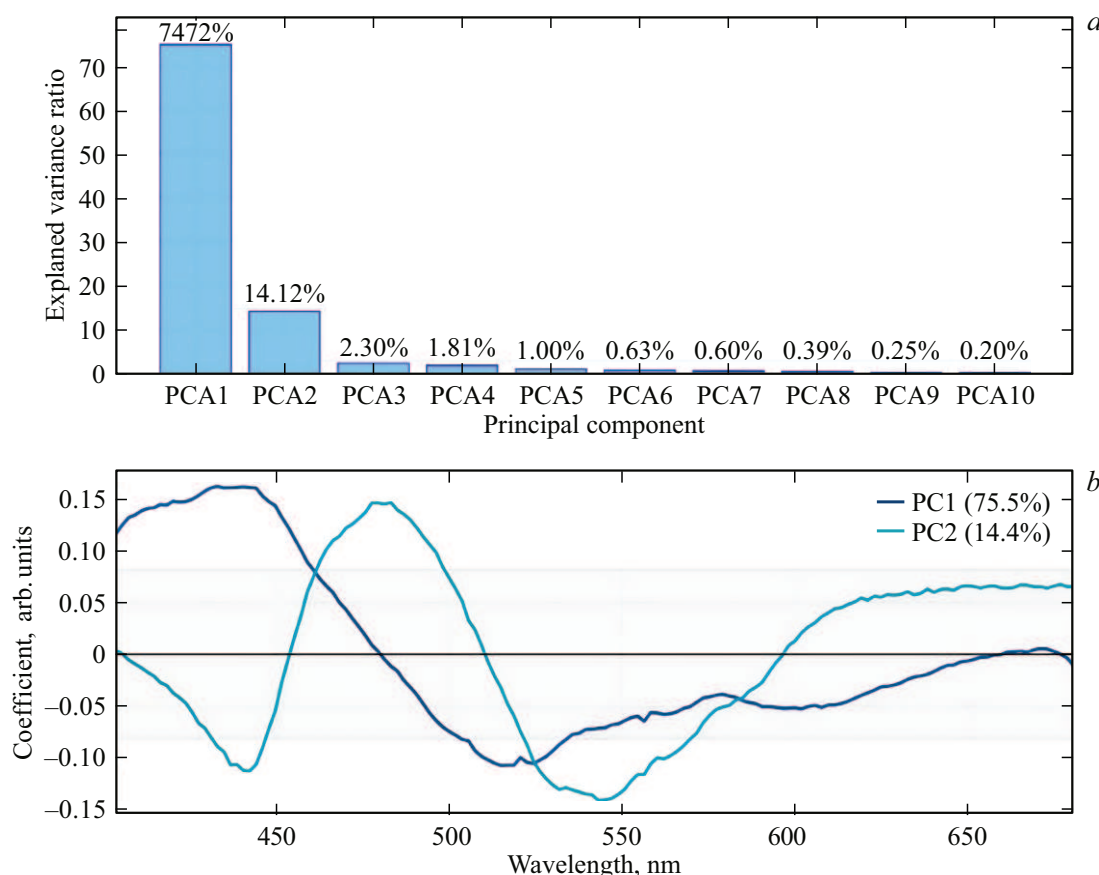


Figure 4. (a) Histogram of explained data variance by the PCA method for 10 principal components, cumulative explained variance for 10 components is 96%. (b) Weight distribution for the first two components, grey area corresponds to the IQR range.

Table 2. Classification metrics estimated on a test dataset. Accuracy (AC), precision (PR), recall (RE), specificity (SP), receiver operating characteristic — area under curve (ROC-AUC) metrics were used

Model	Accuracy	Precision	Recall	ROC-AUC
LR	0.75	0.79	0.79	0.79
SVM	0.68	0.69	0.86	0.71
RF	0.65	0.65	0.92	0.72
GB	0.75	0.75	0.90	0.76
FNN	0.73	0.71	0.92	0.8

3. Results and discussion

Statistical analysis of spectral differences

To verify the previous results, statistical analysis was performed using the Mann–Whitney criterion with the Bonferroni multiple comparison correction. At $\alpha = 0.05$ (critical value $Z_{\text{crit}} = \pm 2.39$), significant differences are observed in the Control-PD and Comparison-PD pairs, while there are almost no differences in the Comparison-Control pair in the selected range, except for the 600–680 nm region (Figure 3).

Significant differences confirm the previous findings and indicate the specificity of obtained spectral changes exactly for PD. Differences in the Control-PD pair can be associated with a change of concentration and spatial distribution of endogenous fluorophores in PD patients' skin.

Reducing data dimensionality using the principal component analysis

Data analysis using the principal component method made it possible to reduce the feature space dimensionality from 150 to 30 principal components, while selection of a larger number of components didn't yield a significant growth of classification accuracy. Cumulative explained variance for 30 principal components was approximately 97.5%, suggesting that almost all informativity of initial spectral data was maintained.

Analysis of the explained variance distribution has shown that the main contribution was made by the first 10 principal components (Figure 4, a) that account for about 96% of cumulative variance. This indicates that there is a relatively small amount of independent spectral features that define differences between the groups. The next components make the lowest contribution, however, their inclusion

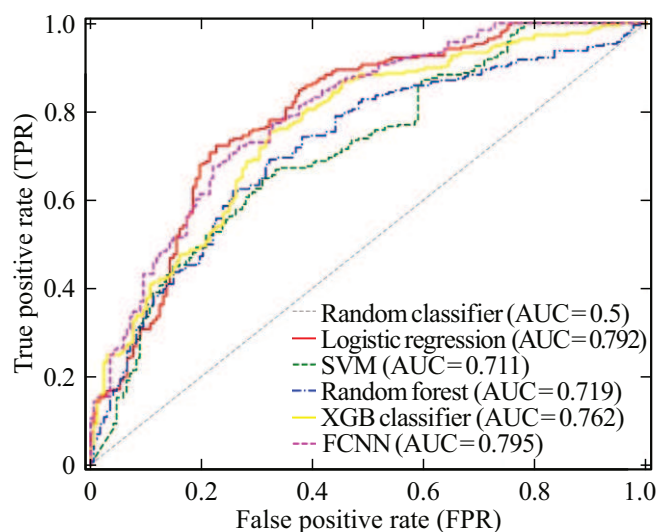


Figure 5. ROC curves (receiver operating characteristic curves) for five given machine and deep learning models. Area under curve (AUC) for each model is shown in the key. Diagonal dashed line corresponds to a random classifier (AUC= 0.5).

into the model enhances higher classification stability and consideration of thin spectral features.

The first 10 principal components (PC) explain 96% of variability, where PC1 reflects the general fluorescence level (intensity variation throughout the spectrum, maximum data variance), and PC (2–10) reflect the spectrum shape (relative intensity differences at different wavelength ranges associated with accumulation of AGEs and with other biomarkers). PC(11–30) represent thinner spectral features with a small share of useful information.

Figure 4, *b* shows the weight distribution of initial features for the first two components. It can be seen that a region corresponding to NADH fluorescence makes the main contribution. The second component also reflects NADH fluorescence (~ 475 nm) and flavin fluorescence (~ 525 – 575 nm).

Classification results

Classifier training on a training dataset after dimensionality transformation and subsequent evaluation of metrics on a test dataset gave results listed in Table 2.

Analysis of findings shows that LR and FNN models have demonstrated the best performance having achieved ROC-AUC values of 0.79 and 0.80, respectively (Figure 5). These indicators show an adequate predictive potential of the developed models for solution of the problem of binary classification of PD patients.

3D data visualization by the first three more informative PCA features (Figure 6) shows a complex class distribution, nevertheless, logistic regression can separate $\sim 75\%$ of objects, indicating potential separability in higher dimensionalities. Spatial separation is also observed (many

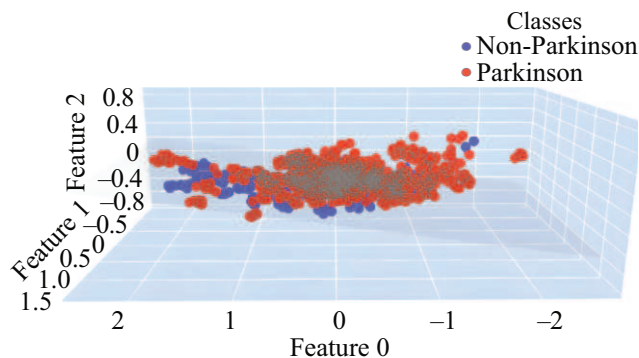


Figure 6. 3D data visualization (by the first three PCA features) with a built separating boundary for logistic regression.

negative class objects are in the left part of the diagram, unlike the positive class).

FNN model has shown the highest recall (Recall = 0.92), which is particularly important in terms of medical diagnostics, because it minimizes the risk of omission of truly ill patients (false negative results). At the same time, LR model has demonstrated better precision (Precision = 0.79), reducing the probability of false positive diagnoses.

SVM, RF and GB models have shown several lower results by ROC-AUC (0.71–0.76), however, they were also characterized by high recall (0.86–0.92). Relatively low precision of these models can be associated with lower generalization capability in a limited data volume and susceptibility to re-training on a training sample.

FNN model is optimized for recall maximization, while LR demonstrates a balanced precision-recall ratio. Their complementarity implies that ensemble methods (stacking or weighted voting) can be used to achieve a synergetic effect and to increase ROC-AUC.

Note that the results have been obtained on a total sample of 123 participants and increasing the sample size for finer tuning of model hyperparameters and more stable learning is an important task for future studies. Dataset extension will also allow for full validation with independent validation sampling to increase the reliability of generalization ability estimate and to reduce the re-training risk.

4. Conclusion

This study demonstrates that UV spectroscopy of skin with machine learning algorithms can be used for PD diagnostics. Statistical analysis has detected spectral differences between groups, which confirms biological feasibility of the method. PCA has reduced data dimensionality to 97.5% of informativity. Feedforward neural network (ROC-AUC = 0.80, recall = 0.92) and logistic regression (ROC-AUC = 0.79) models have shown the best results. Noninvasive, fast and potentially automated method can serve as a screening diagnostic tool for PD.

Compliance with ethical standards

All studies involving volunteers and patients were performed in accordance with a decision of the local ethics committee of the Russian Center of Neurology and Neurosciences with an informed consent signed by patients.

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Declaration of competing interest

The authors declared that they had not any conflict of interests.

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