Medical diagnosis using NIR and THz tissue imaging and machine learning methods

Yury V.Kistenev[a,d,e*], Valery V. Tuchin[a,b,c], Alexey V. Borisov[a,d,e], Ekaterina N. Lazareva,[a,b] Viktor V.Nikolaev[a,e], Daria K. Tuchina[a,b], Denis A. Vrazhnov[a,e], Irina Yu. Yanina[a,b]

[a]Laboratory of Biophotonics, Tomsk State University, Tomsk, Russia
[b]Department of Optics and Biophotonics, Saratov State University, Saratov, Russia
[c]Institute of Precision Mechanics and Control of the RAS, Saratov, Russia
[d]Siberian State Medical University, Tomsk, Russia
[e]Institute of Strength Physics and Materials Science of Siberian Branch of the RAS, Tomsk, Russia

ABSTRACT

The problem of extracting useful information for medical diagnosis from 2D and 3D optical imaging experimental data is of great importance. We are discussing challenges and perspectives of medical diagnosis using machine learning analysis of NIR and THz tissue imaging. The peculiarities of tissue optical clearing for tissue imaging in NIR and THz spectral ranges aiming the improvement of content data analysis, methods of extracting of informative features from experimental data and creating of prognostic models for medical diagnosis using machine learning methods are discussed.

Keywords: medical diagnosis, NIR and THz imaging, tissue optical clearing, machine learning

1. INTRODUCTION

NIR and terahertz (THz) molecular spectroscopy and imaging are of great urgency in medical diagnosis due to their ability to fast and noninvasive detection of molecular biomarkers in a tissue. The basic requirement for chemical imaging using biophotonics technologies is the optical detection of a molecular species or a chemical change. This requirement can be achieved by detecting the optical response of either an endogenous biomarker or a sensor sensitive to a specific chemical change. These processes are commonly referred to as optical biopsies, in contrast to the traditional physical biopsies. Optical biopsy using various techniques including reflectance, absorption, laser-induced fluorescence, Raman scattering can provide information about specific biochemical markers and a complete examination of an organ avoiding the sampling.[1]

In the NIR region (500-4000 cm^{-1}) there are vibrational absorption bands of molecules, characteristic frequencies of deformation of intramolecular bonds, rotations of molecular groups. The molecular spectroscopy and imaging of biological tissues in the terahertz (THz) spectral is very promising for medical applications.[2] This technique can provide information about rotation and low-frequency vibrational modes of biological macromolecules, deformations of hydrogen bonds.[3-5] THz spectroscopy allows us to study the interaction of water and hydrogen structures with other molecules present of biological tissues, such as amino acids, peptides, DNA, proteins.[6]

The development of computer-aided diagnostic (CAD) systems has become a hot topic in recent years. Progress in this field is caused by fast development and widespread usage of digital image processing, pattern recognition, and machine learning techniques. Pattern-recognition-based techniques provide probabilistic discrimination of biomarker profiles, which forms the basis for assessing diagnostic accuracy.[7] Machine learning allows one to discover functional relationships from examples based on features rather than from manual verification of entire experiments. Compared to conventional approaches, these methods are more efficient in handling multi-dimensional data analysis such as distinguishing phenotypesthat is defined by a high number of features.[8]

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The key challenge to use machine learning for medical diagnosis is existence of latent dependences between measured features set and human state variations due to pathological processes.

The major goal of this paper is to discuss methods of extracting of informative features from experimental data and creating of prognostic models for medical diagnosis using machine-learning methods accounting for peculiarities of tissue optical clearing for tissue imaging in NIR and THz spectral ranges aiming the improvement of content data analysis.

2. A MACHINE LEARNING PIPELINE

Digital presentation of an experimental data is a base for effective data preprocessing to remove artifacts, to select useful parts of an image and to improve greatly the quality of future analysis.

Typical image preprocessing includes denoising, smoothing, color and brightness normalization, image segmentation andregion of interest (ROI) selection, feature extraction, classification and diagnosis.

The most popular denoising approaches include rank filtration (removal of point noise), wavelet and Fourier filters to smooth out the sharp luminance noise bursts, Sobel and Canni filters (linear diffusion filtering method) to increase the contrast of the boundaries of areas of interest, interpolation methods. The main advantages of wavelet transformations are[9]:

- Unlike the Fourier transform, wavelets can be well localized in time and in frequency. If it is necessary to analyze different processes in the signal, wavelets allow one to consider the specified scale conversion levels (filtration).
- Wavelets have a wide range of mother wavelets with various degree of smoothness.
- Wavelets help to identify and describe some hidden signal characteristics, in particular, its symmetry.

The disadvantage of the wavelet transformation is the relative computational complexity and the need for a correct choice of the mother wavelet.

The methods of diffusion filtration (MDF) of 1-D and 2-D signals have been actively developing during the past two decades and currently offer a set of effective algorithms sufficient to extract the content-relevant information from the initial array of noisy and distorted data, i.e. allow within certain limits to manage the data processing depending on the required conditions. MDFs are of considerable interest in analysis of medical images.[10,11] The disadvantage of MDF is that it does not allow to clean the input signal from noise components preserving the content-relevant information, since Gaussian filtering simultaneously smooths out not only a noise but also informative part of the signal, which in many cases is characterized by large gradients.

Image retrieval using visual content is still an unsolved problem due to the semantic gap between image features and their meaning. Recently, the content-based image retrieval using metadata that describes image content was proposed. Image retrieval systems can exploit text descriptions to search only using keywords. Under this approach, text based image retrieval may be effective to retrieve related images when the user knows an appropriate keyword combination to express information need. The weakness of the method is connected with using of only text abstract, when the image visual content is completely ignored.[12]

Image segmentation techniques include region-based, and contour-based approaches.[13,14] Region-based approach try to find partitions of the image into sets corresponding to coherent image properties such as brightness, color and texture. To find similar groups of pixels, the different methods of clustering are used, in particular, K-means algorithm, which is widely used for its efficiency and speed. Also, standard segmentation methods or modified versions of them, like Otsu thresholding, hidden Markov model, watershed algorithm, active contours, cellular automata, grow-cut technique, as well as new approaches, like fuzzy sets, neural networks, can be used for selecting image regions and further feature extraction.[15] Sometimes ROI selection is combined with feature extraction, like in case of scale invariant feature transform (SIFT). A number of approaches for effective texture representation have been proposed during the past decades. Among them, the local binary pattern, based on analysis of gray-level differences between a pixel and its neighbors, is the most popular.[16] Contour-based approach usually starts with a first stage of edge detection, followed by a linking process that seeks to exploit curvilinear continuity.[13]

"Pattern" approach requires the selection of the informative (significant) features allowing to separate one group of objects from another and then build the corresponding classifier. The feature extraction techniques are necessary to build mathematical models of ROI and to make their classification. Various criteria are considered for selection of ROI, in particular, the total brightness of pixel groups, their geometric features (shape, location, connectivity). To find similar groups of pixels, the different methods of clustering can be used. The pixel groups can be separated by more specific characteristics, for example, by the configuration of gradients in the vicinity of each pixel in a given region. These techniques can include gradients, textural, graph, and morphological features.[11] In addition, there are special methods for allocating points of interest, for example, MSER (Maximally Stable Extreme Regions).

The comparative study of fourteen models of feature extraction, including Gabor-like filters, histograms of oriented gradients (HOG), SIFT model, texton model, that have been shown to perform well have been carried out.[17] Five tests have been done. The first two regard scene categorization using color photographs and line drawings. The third test addresses invariance properties of models on animal vs. non-animal recognition. The fourth test is about local vs. global information in the context of recognizing jumbled scenes. The final test involves object recognition over two large datasets. HOG model was shown to provide the best results of recognition practically over all tests.

The problem of weak distinguishability of feature vectors in high dimension features space is known (see, for example Ref. 18). Dimensional reduction of features space simplifies the classification, visualization and compression of multidimensional data.[19] To solve this problem, the methods provided the separation of informative features of object and reducing the contribution of non-informative features and, in some cases, the noise component should be used. Among them, there are continuous and discrete methods of separation of informative features.[20-22]

Continuous methods include the method of principal component analysis (PCA), factor analysis, isomap, diffusion maps, multilayer autoencoders, method of multidimensional scaling, etc.[23-25] Although linear methods are attractive for selection of important information by reducing dimensionality and also visualizing data, the scope of their application is limited by the fact that they cannot adequately process complex nonlinear data that contain hidden nonlinear structures.

In the last decade, a number of nonlinear methods of dimension reduction have been developed, for example, geometric methods for features selection[26], the method of nonlinear dimensional reduction[27], the method of local isomaps, Laplacian Eigen maps (LEM).[28] The method of isoimages allows one to reconstruct low-dimensional nonlinear structures in multidimensional data sets, but it is possible to lose significant information when the size of the neighborhood in the data array is larger than the distance between the elements of the structure.

The nonlinear kernel method of the principal components is close to the ordinary (linear) PCA. In this method, linear operations of a conventional PCA are performed with a nonlinear kernel of the primary (input) data. Similar is the Maximum Variance Unfolding (MVU) method,[23,30] which is based on the convex optimization of the objective function and finds applications in multidimensional data analysis.

The method of diffuse mappings[31] is based on using the family of embeddings of the data set into a Euclidean space (possibly of minimal dimension) whose coordinates can be calculated with the help of eigenvectors and eigenvalues of the diffusion operator. The Euclidean distance between points in an immersed manifold is interpreted as the "diffusion distance" between the probability distributions concentrated at these points. By combining the local similarities on different scales, the diffusion maps provide the global description of the data set. It should be noted that in comparison with other methods, the diffuse mapping algorithm is noise-proof.

Nonlinear methods are able to operate with complex varieties of the real data which are nonlinear in the sense that they do not form the linear space but can geometrically be regarded as a certain geometric manifold. In particular, this is the case for real data which form a strongly nonlinear variety. It should be noted that nonlinear methods demonstrate efficiency on artificial data sets, but on the real data the dimension reduction is less convincing since the application of this or another method depends on the nature of the analyzed data.

Discrete methods include so-called filters, i.e. algorithms based on the selection of a subset of the original set of characteristics (Pearson's criterion, mutual information based on the Shannon information criterion and the Kulbak-

Lebler divergence). Among the discrete methods, there are the filters, the methods of "wrappers" (the classifier is considered as a black box with the input of the generated feature sets and the result of classification is evaluated) and "built-in" methods that optimize the methods of "wrappers" to reduce the number of repeated classifications.

There are supervised and unsupervised learning classification methods. Supervised learning means training the classifier when the certain set of vectors is available for which belonging to one of the classes is known. Trained appearance models are replacing simple intensity and gradient models as a component in segmentation systems, and statistical shape models that describe the typical shape and shape variations in a set of training shapes have replaced free form deformable models in many cases.[32]

To train the classifier, a part of the data should be is used (training sample). When classifiers are trained, there is a danger that the classifier will be too well adjusted for training data, which will lead to the impossibility of correctly classifying new (unseen) data. This problem is called "overtraining" or "overfitting" of the classifier. Deciding on the quality of the resulting classifier on the basis of a test on the training data may lead to the fact that retraining (if it exists) may not be detected. A more adequate estimate is the evaluation of performance on a test suite-a set of data classified by class, but not used in the training process.

In the paper[33], an unsupervised learning approach called convolutional denoising sparse autoencoder is proposed based on the theory of visual attention mechanism and deep learning methods to provide image classification to a group images into corresponding semantic categories. The method starts with saliency detection to get training samples for unsupervised feature learning. Then, samples are processed by the denoising sparse autoencoder, followed by convolutional layer and local contrast normalization layer.

In the paper[34], the process of classifying the medical image was carried out using fuzzy decision tree (FDT) with evolutionary clustering. The feature descriptors of the images are extracted using local diagonal extrema pattern. The extracted features are passed to fuzzy particle swarm optimization clustering algorithm to obtain optimal fuzzy partition space for each attribute, which are then later used for inducing FDT. The proposed was tested on emphysema CT images to classify the patient’s lung tissue into normal, centribulor emphysema, and paraseptal emphysema. The proposed framework was shown to improve the classification accuracy.

In spite of examples of successful application of machine learning for medical diagnosis the are risks associated with applying of these methods as a “black box” to perform diagnosis. A flexible learning system in a high-dimensional feature space can behave unexpectedly and this can be difficult to detect.[32] Thus, an instrumental or computer-stage reduction of a feature space under controlled conditions to understand driven factors for pathological stage data variations is very important.

3. TISSUE OPTICAL CLEARING

A principal limitation of the *in vivo* optical imaging methods for the purposes of medical diagnostics is caused by the complex nature of the transfer of optical radiation in biological tissues due to scattering and strong absorption by contained in the tissues water and number of chromophores, such as hemoglobin, collagen, lipids, etc. One of the abilities to improve the quality of *in vivo* optical imaging is a reversible control of the optical properties of tissues under the influence of various physical-chemical factors.[35] One the approaches for that is to use a so called immersion tissue optical clearing (TOC) based on the interaction of various chemical agents, such as solutions, gels, oils, with tissues which ensure soft tissue dehydration and matching of the refractive indices of its structural components and the surrounding media (interstitial fluid and cytoplasm).[36,37] The use of immersion agents with hyperosmotic properties (glycerol, sugars, etc.) leads to a reversible dehydration of the tissue, which significantly changes the nature of the propagation of optical radiation through the tissues, i.e. the decrease of scattering and water absorption, and as a result less light beam attenuation and blurring.[38,39] Positive effect has been achieved for various optical and THz modalities, including Raman spectroscopy and multiphoton microscopy.[40-43]

TOC agents are divided into two categories, including solvent-based and aqueous-based ones. Most of them can preserve fluorescence of proteins, but are not compatible with lipophilic dyes. A rapid and versatile TOC method based on Triethanolamine and Formamide using was proposed.[44] The results show that this approach cannot only efficiently clear embryos, neonatal brains and adult brain blocks, but also preserve fluorescent signal of both endogenous fluorescent proteins and lipophilic dyes, and be compatible with virus labeling and immunostaining.

A combination of optimized TOC approach based on benzyl alcohol, benzyl benzoate immersion that results in minimal change in tissue volume with whole-organ large scale multiphoton microscopy mosaic imaging and image stitching was carried out.[45] This approach provided the ability to clear and image whole fixed lungs and reveal the global spatial distribution of fibrillary collagen throughout the organ at high resolution.

Recently, a combination of TOC and complex wave front shaping was proposed in optical coherent tomography (OCT).[46] TOC agents reduced optical inhomogeneity of a scattering sample, and the wave front shaping of illumination light controls multiple scattering, resulting in an enhancement of the penetration depth and signal-to-noise ratio. The penetration depth enhancement is further demonstrated for *ex vivo* mouse ears, revealing hidden structures inaccessible with conventional OCT imaging.

A combination of TOC and mechanical compression was used to measure absorption spectrum of beta-carotene.[47] The mechanical compression causes a decrease of skin absorption due to the reducing of total blood content at the area of compression, while TOC allows to change diffuse reflectance of the tissue.

Similar methods allow one to control *in vivo* optical features of the tissue, which can be useful for machine learning data analysis.

The tissue self-optical clearing is one of the ways to control tissue optical properties. This approach can be illustrated by the adipose tissue. Adipocytes with triglyceride (TG) droplets constitute the main cellular component of adipose tissue. Absorption of the human adipose tissue is due to absorption of hemoglobin, lipids, and water.[48] Its scattering is a very complex phenomenon and strongly depends on the temperature.[49-52] The optical coherence tomography studies demonstrated essential reduction of light scattering on the cellular level due to the phase transition of TG localized in cell lipid droplets from crystalline to liquid phase at the temperatures above 35°C.[52]

Recently, it was shown that photodynamic/photothermal effects induced in adipose tissue stained with brilliant green or Indocyanine Green (ICG) under irradiation at 442⁄597 nm or 808 nm, respectively, lead to lipolysis of fat cells.[53,54] Fat cell lipolysis can also be induced in the course of low-level laser therapy.[55,56] The final products of cell lipolysis contribute to TOC of the cell layers over entire body sites, where the cells are expressed for lipolysis. Local fat cell lipolysis is the breakdown of lipids and involves hydrolysis of TGs into glycerol, which works as a TOC agent, and free fatty acids, which are good enhancers of tissue permeability.[55-61] The change in permeability and stability of the cell membrane occurs in this case due to the structural defects of the membrane bilayer as a result of the membrane lipids oxidation.

It was proved that due to light-induced cell membrane porosity, the intracellular content of the cell percolates through the arising temporal pores into the interstitial space.[62] As a consequence, the refractive index (RI) of the interstitial fluid (initially equal to $n_i \approx 1.36$)[63] becomes closer to the RI of the matter inside the adipocytes, mostly lipids of a lipid droplet (RI of lipids, $n_a \approx 1.44$).[64] Due to the RI matching, the tissue sample becomes optically more homogeneous and more transparent to light.[49,51,62-64]

Modified transmittance images of selected adipocyte in subcutaneous human fat tissue layer are presented in Fig. 1. First, the images were converted to grayscale, digitized. Then, all values of pixel brightness, corresponding to condition $T \leq 0.41$, were assigned to zero values; and corresponding to condition $T \geq 0.59$, it equal to 255. The remaining brightness values were equal to 150. Initial cell (Fig1a) is well recognized by its membrane (neighbor cells are connecting selected cell are seen, other underneath cells are also seen through selected cell). Fig. 1b presents the same cell in 10 min after staining by ICG dye. After 1-min irradiation of the stained cells by a continuous wave (CW) diode laser (808 nm) with the power density of 250 mW⁄cm^2 nothing is happened immediately, but in 16 min after laser irradiation, signs of TOC are well seen due to laser induced lipolysis (Fig. 1d).

The accuracy in the difference of two images is required to be found for medical purposes. The use of TOC can lead to a reduction in processing time as useful information is less hidden behind noise, caused by strong light scattering. Thus, TOC can act as a kind of filter, but not as a mathematical (as a physical). The image contrast (components) is physically increased; hence, it can use a simple technique for processing the signal in the border area. The solution of problems of monitoring and simulation involve the processing of statistical information about the observed phenomenon. Often, the term statistical processing of data means the exclusion of anomalous values. For that, mathematical algorithms with time delay are usually used. Instead, TOC may help for exclusion of anomalous values (see Fig.1d).

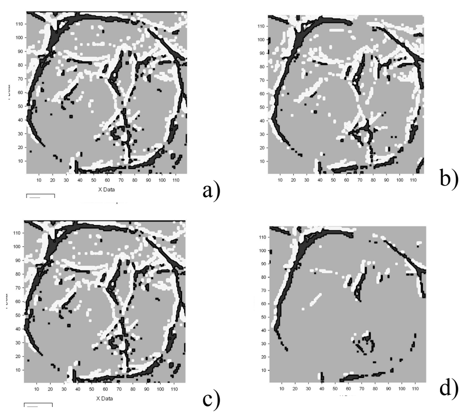
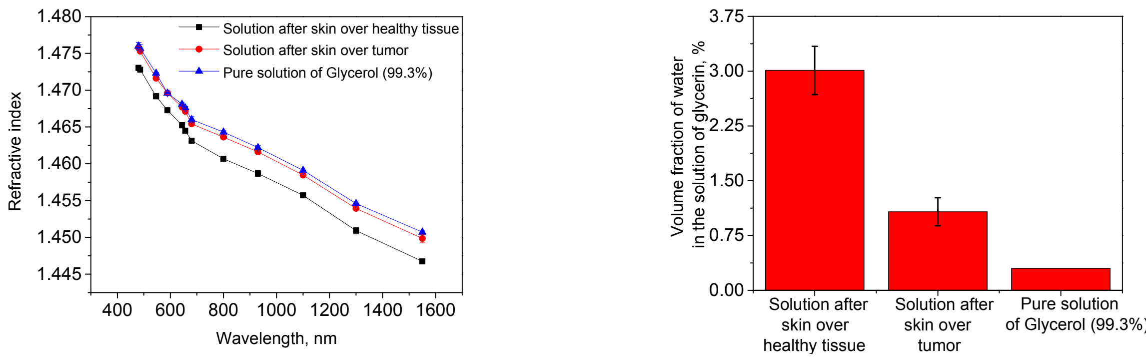


Figure 1. Modified transmittance images of selected adipocyte in subcutaneous human fat tissue layer (through selected cell other underneath cells are seen): initial cell (a), in 10 min after staining by ICG (b); after 1-min irradiation the stained cell by a continuous wave (CW) diode laser (808 nm) with the power density of 250 mW/cm^2; in 16 min after laser irradiation, signs of OC are well seen (d). The sample temperature was kept at 41°C.

An image contrast enhancing due to dehydration and TOC in the area of pathology is extremely important for diagnosis of precancerous states, early cancer stages and other diseases.[34,37,40,64-68] For example, recent *in vivo* experiments on the TOC of the skin of rats with developed tumor over the tumor area and healthy tissue have shown an improvement of imaging, which can be used to develop optical methods for demarcation of tumor boundaries. Figure 2 shows refractive index dispersion and volume fraction of water in the glycerol solution after *in vivo* dehydration measurements by using initial 99.3% glycerol solution action on skin areas over healthy and tumorous tissue.[69] The dehydration of a healthy rat skin area was found as (3.01 ± 0.33)%, and for rat skin area over a tumor it was only (1.08 ± 0.19) %, because of lack of water in skin caused by the overhydrating of the neighbor tumor tissue. This result is generally consistent with the data from the work of the Tromberg group [70], obtained on the basis of spectral measurements for areas of healthy tissue and carcinoma of the female breast, for which the volume of bulk water in healthy tissue was on average 15-16%, and in the tumor about 30%. It should be noted that water is the main absorber in the terahertz spectral range and its reversible displacement from skin provides increasing of a terahertz radiation penetration depth.[71] Evidently, that similar adjustment of tissue optical properties can improve the selection of ROI for further digital image processing and analysis.

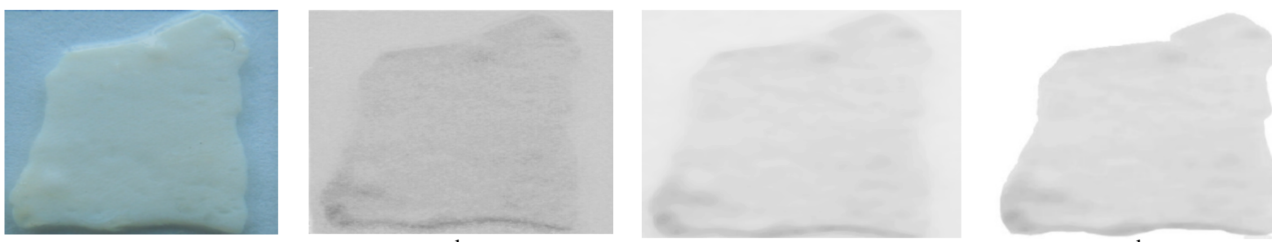
During diffusion of immersion agents into the tissue and subsequent tissue dehydration the packing of tissue components is changing.[36] Thus it is necessary to take into account the temporal dependences of the packing of tissue components, which can be accounted by measuring geometrical parameters, such as thickness and square, of investigated tissue sample. This also allows one to get the most complete information about tissue water content and its alterations. It takes the previous assessment of these parameters of the tissue during TOC by selected immersion agent.



a) b)

Figure 2. Data for initial 99.3% glycerol solution and diluted glycerol solution in the course of *in vivo* experiment on dehydration of skin areas over healthy and tumorous tissues: (a) dispersion of the refractive index; (b) the volume fraction of water in the glycerol solutions.[69]

NIR and THz tissue imaging and spectroscopy are widely used for assessment of tissue water loss.[2,36,38,72] The digital image processing can be used for square measurements.[73,74] Such processing proposes obtaining of hue component of the tissue digital image with further glare and brightness noise reduction by digital filters, calculation of number of pixels occupied by the sample and their conversion into the square units. The example of image processing is presented in Fig. 3.



a b c d

Figure 3. The digital image of a skin sample (a), the color hue-component image (b), the image processed by median filter (c), result of image processing (d).

CONCLUSION

The progress in computer-aided diagnostic systems development is connected with digital image processing, pattern recognition, and machine learning techniques. Pattern-recognition approach demands selection of informative features in dependence of specificity of a pathological process. An instrumental or computer-stage reduction of a feature space under controlled conditions to understand driven factors for pathological stage data variations is very important. One of the abilities to improve the quality of *in vivo* optical imaging is a reversible control of the optical properties of tissues due to tissue optical clearing. Similar methods allow one to control *in vivo* optical features of the tissue, which can be useful for machine learning data analysis.

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