Possibilities of laser spectroscopy for monitoring the profile dynamics of the volatile metabolite in exhaled air

Kistenev Yu.V., Shapovalov A.V., Borisov A.V., Knyazkova A.I.[1]

Tomsk State University, Russian Federation, 634050, Tomsk, Lenina av., 36

Abstract

In this work we studied applicability of the laser spectroscopy for fixing differences in composition of exhaled air depending on the position of the body in different physical states. Using principal component analysis we show that the use of the laser spectroscopy methods is sufficiently effective to solve this problem and provide additional opportunities for the comprehensive study of the human condition.

This work was partially supposed by the Federal Target Program for Research and Development, Contract No. 14.578.21.0082 (unique identifier of applied scientific research and experimental development RFMEFI57814X0082).

exhaled air, laser photoacoustic spectroscopy, principal component analysis, support vector machine

Introduction

There is a growing understanding in modern medicine that the human condition studies along with the genome and proteome are to consider biochemical phenotype or metabolome. The metabolome is a collection of metabolites of low molecular weight (such as intermediate metabolic products, hormones, signaling molecules and other secondary metabolites). Metabolites are the intermediate products and end-products of metabolic reactions. The metabolites of metabolomics are generally defined as ones with molecular size not more than 1 kDa [1].

Metabolites are intermediates of biochemical reactions that play an important role in linking the different biochemical pathways operating in a living cell. Metabolite level depends on the activity of the enzymes that catalyze their conversion. In turn, the concentration and properties of enzymes are a complex function of various regulatory processes, including the regulation of transcription and translation, regulation of protein-protein interactions and allosteric regulation of enzyme activity by their interaction with metabolites. Metabolome is a biochemical phenotype of the organism, which is the final result of the interaction of the genotype with the environment. Unlike the genome, transcriptome and proteome, the metabolome is directly related to the biological functions of the body [2].

[1] E-mail: yuk@iao.ru, shpv@phys.tsu.ru, borisov@phys.tsu.ru, a_knyazkova@bk.ru

22nd International Symposium Atmospheric and Ocean Optics: Atmospheric Physics, edited by Gennadii G. Matvienko, Oleg A. Romanovskii, Proc. of SPIE Vol. 10035, 100350B ·

A guide on volatile organic compounds (VOC) contained in the exhaled air (872 VOC), saliva (359 VOC), blood (154 VOC), milk (256 VOC), skin secretions (532 VOC), urine (279 BWT), faeces (BWT 381) of healthy people is presented in [3]. This guide of VOCs that presents in the secretions of healthy people is useful for understanding the metabolic pathways and is an important step in order to distinguish between healthy and diseased states by the use of VOC. The analysis showed that only 12 VOCs (0.7% of the total) are present in all substances: acetaldehyde, 2-propanone (acetone), benzaldehyde, 1-butanol, 2-butanone, hexanal, heptanal, octanal, pentanol, benzene styrene, toluene. Seven of them have a carbonyl group, the latter three compounds are derived from the substances contained in tobacco smoke, and also characteristic pollutants in urban areas, along with the alkyl benzene and benzene, toluene.

In the world, the intensive work is carried out on non-invasive diagnosis of various diseases, based on the control of volatile metabolites markers. Potential advantages of such methods of diagnosis are a non-invasive, easy to use, the minimum cost of the study, and the suitability for continuous monitoring. Several components of the exhaled air are closely correlated with their concentrations in the vessels, thereby eliminating the need for drawing blood analysis [4], wherein the analysis of the exhaled air does not require preconditioning of the sample, in contrast to the study of the blood or urine.

In carrying out the diagnostic tests it is necessary to consider that the relatively slowly varying metabolic processes associated with inflammatory responses, may be applied biochemical response of the organism to changes in external conditions or physical stress.

For example, it has been shown in [5] that during physical exercise (oxidative stress), the concentration of ketones (heptanone-2, heptanone-3), phenol and identified aldehydes (detsenal, octadetsenal), and acetol in exhaled air significantly decreased, due, apparently, with a predominance of the alternative metilglioxal way of carbohydrate metabolism. Thus, the dynamics of the concentration of saturated hydrocarbons in exhaled air may be an indicator of the body's response to oxidative stress, and acetol level do an indicator of human fitness, the adequacy of physical activity, and as an indicator of the development of hypoxic conditions [6].

The authors of [5] studied in real time the composition of exhaled air when changing the body position of healthy volunteers with the use of proton transfer reaction of mass spectrometry (PTR-MS). The volunteers carried out two options of change in body position. The first sequence was: sitting, standing, lying down or sitting. The second one was: lying down on his/her left or right side, lying on his/her stomach or back. Each position was maintained for two minutes.

It was established that the first exercise in relation to the "sitting" position, the concentration of isoprene, furan and acetone in the exhaled air increased by 24%, 26%, 9%, respectively. In the "standing" position the growth was 63%, 36%, 10 %, respectively. In the second exercise, in relation to the initial position "lying on back" concentrations of isoprene, furan in the exhaled air increased by 29% and 16%, respectively, in the "lying on his/her right side" and the "lying on his/her stomach."

It has been noted that the stroke volume is reduced in the last positions, while the causes of the observed changes should be linked to the ventilation / perfusion ratio, and not just one perfusion.

Comparing of metabolite analysis methods in the exhaled air [7] (Table 1) shows that the laser spectroscopy methods have fairly optimal set of parameters and present a high practical interest to study the profile of the markers in the exhaled air.

Table 1. Comparison of characteristics of research methods

Analytical methods	Operation mode	The limit of detection	Sensitivity	Specificity
SIFT-MS	Direct / Real time	ppbv	High	High
PTR-MS	Direct / Real time	pptv	High	Medium-high
IMS	Real-time	ppbv	Medium	Medium
GC-MS	Pre-concentration	pptv-ppbv	Very high	Very high
LAS	Real-time	ppbv	High	High
Sensor arrays	Reference to a database	ppbv	Medium	Medium

In the first column of Table 1 there are written mass spectrometry: SIFT-MS - ion-flow Mass Spectrometry, PTR-MS - Mass Spectrometry with the reaction of proton transfer, GC-MS - gas chromatography mass spectrometry with thermal desorption or solid-phase microextraction SPME, LAS - laser absorption spectroscopy, IMS - mass spectrometry of mobile ions.

This paper analyzes the possibilities of laser spectroscopy to monitor the dynamics of the profile of volatile metabolites in the exhaled air. Spectra study was carried out using the laser photo-acoustic spectroscopy gas analyzer "LaserBreese" (produced by "Special Technologies, LTD., Novosibirsk, Russia). This analyzer is intended for registration of the composition of gas samples using broadband optical parametric oscillator (tuning range of 2.5 micron - 10.6 micron) and optical-acoustic detector.

In this study, a group of 10 volunteers performed the following sequence of changes in body position: lying down, sitting, standing, exercise (jogging) (10 minutes in each state). Sampling was carried out at the end of each stage of the exercise.

The experimental data on each sample of exhaled air (SAE) included the data: the length of the waves λ_i^s, the relative absorption coefficient α_i^s; technical parameters of control pk_i^s that characterizes the device error for each wavelength value.

The analyzer used in this study provides rearrangement of the radiation source wavelength with irregular pitch on the wavelength, so that all the spectra obtained were brought to a uniform scale of the wavelength in accordance with the following formula:

$$\lambda_i = \lambda_{\min}^s \exp\left(\frac{\lambda_i^s - \lambda_{\min}^s}{\lambda_{\max}^s - \lambda_{\min}^s} \log\left(\frac{\lambda_{\max}^s}{\lambda_{\min}^s} \right) \right)$$

Here λ_i is a value of the wavelength on a uniform scale, λ_i^s , $\lambda_{\max}^s$, $\lambda_{\min}^s$ are arbitrary, maximum and minimum values of the wavelength range with the highest range of wavelengths. In this paper, the parameters were: $\lambda_{\min}^s$ = 2.5 micron, $\lambda_{\max}^s$ = 10.6 micron.

For each the absorption spectrum of SAE α_i^s and in the range $\Delta\lambda_i = \lambda_{i+1} - \lambda_i$ of technical control parameter pk_i^s the averaging was carried out. All values in the intervals $\Delta\lambda_i$ with technical parameters $pk_i^s < 0.01$ were excluded from further consideration. An example of the experimental spectrum is shown in Figure 1.

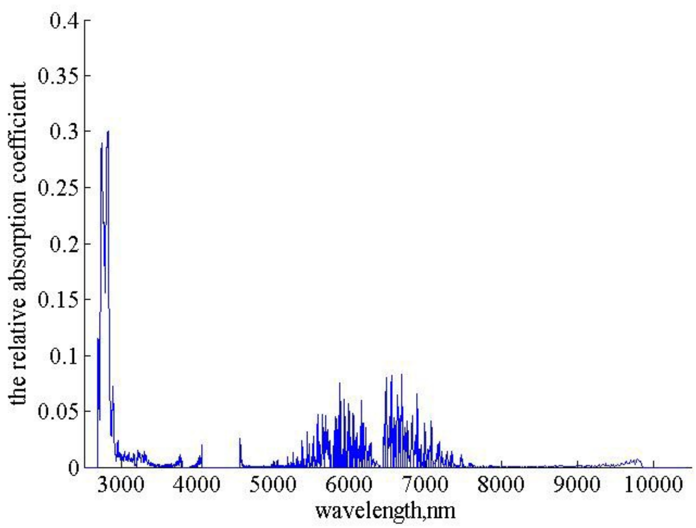


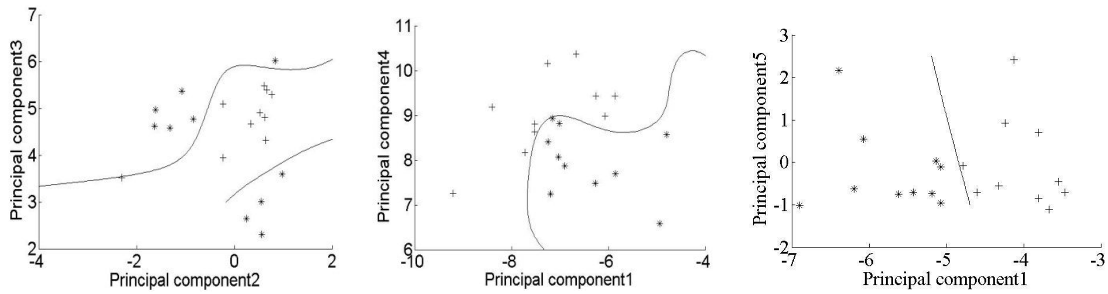
Figure 1. An example of the SAE absorption spectrum of healthy volunteers except for the value of the relative absorption coefficient due to device error.

For data analysis, the method of principal component analysis (PCA) has been used. Application of the PCA to the analysis of multicomponent gas mixture can be found, for example, in [8-10].

For the application of PCA, we introduce a data matrix $\mathbf{Z} = (\mathbf{Z}_1, ..., \mathbf{Z}_m)$ with columns $\mathbf{Z}_i$. Use of the PCA to this matrix assumes its representation in the form Z = TP^t + E. Here a loading matrix $\mathbf{P} = (\mathbf{Y}_1, ..., \mathbf{Y}_L)$ has columns $\mathbf{Y}_j$, T is a score matrix, and E is an error (residual) matrix [10-11].

Figure 2 shows projections of the objects during the performance of these exercises: lying, sitting, standing, exercise (jogging), i.e. the dependence of the third principal component (PC) in the "lying" position on the second PC in the "sitting" position, the fourth PC in the "sitting" position on the first PC in the "standing" position, the fifth PC in the "standing" position on the first PC in the "jogging" for cases a, b, c, respectively.

In each case the principal components are considered for 10 spectra of 20 for each of the positions. Obviously, the points are grouped in the space PC.



a b c

Figure 2. The dependence of the principal components of each other for the chain of actions: lying / sitting, sitting / standing, standing / exercise (jogging). Here, "+" and "*" correspond to different physical states.

The analysis of the SAE spectra in terms of the PCA results in the fact that LOAG can be used to fix differences in the exhaled air composition depending on the body position in the same way as is done in [7].

The information contained in SAE spectra allows one not only to capture differences in the composition of exhaled air depending on the position of the body, but also to talk about the composition and concentration of gases within the SAE [9-10] as well as to carry out various studies to identify pathologies [13].

Thus, the use of LOAG is relevant to the medical practice and allows one to a comprehensive study of the human physical conditions.

Acknowledgements

This work was partially supposed by the Federal Target Program for Research and Development, Contract No. 14.578.21.0082 (unique identifier of applied scientific research and experimental development RFMEFI57814X0082).

References

[1] Ellis, D.I. and Goodacre, R. (2006) Metabolic fingerprinting in disease diagnosis: biomedical applications of infrared and Raman spectroscopy. Analyst 131, 875—885. DOI:10.1039/b602376m

[2] Ellis, D.I., Dunn, W.B., Griffin, J.L., Allwood, J.W. and Goodacre, R. (2007) Metabolic Fingerprinting as a Diagnostic Tool. Pharmacogenomics, 8(9), 1243—1266.

[3] Amann A., Al-Kateb H., Flynn C., Filipiak W., Khalid T, Osborne D, Ratcliffe N. M. Costello B de L. A review of the volatiles from the healthy human body, — №8. — 2014. — P. 014001 (29 pp.).

[4] Cao W. Breath Analysis: Potential for Clinical Diagnosis and Exposure Assessment, Clinical Chemistry. — №52., 5. — 2006. — P. 800-811.

[5] Sukul P., Trefz P., Kamysek S., Schubert J.K., Miekisch W. Instant effects of changing body positions on compositions of exhaled breath, J Breath Res. 2015 Nov 19;9(4):047105. doi: 10.1088/1752-7155/9/4/047105.

[6] Mardanov P.G., Orlov O.I., Markin A.A., Tsar'kov D.S., Mukhamedieva L.N. The study of molecular markers of oxidative stress in exhaled air of healthy human, Aerospace and Environmental Medicine. 2010 T-44, number 6 Year: v. 44-48. (in Russian).

[7] Lourenço, C., Turner, C. Breath Analysis in Disease Diagnosis: Methodological Considerations and Applications. Metabolites 4, 465-498 (2014).

[8] Kistenev Yu. V., Borisov A. V., Shapovalov A. V. Determination of component concentrations in models of exhaled air samples using principal component analysis and canonical correlation analysis, Proc. SPIE 9810, XII International Conference on Atomic and Molecular Pulsed Lasers, 98101Z (December 15, 2015); doi:10.1117/12.2225575.

[9] Kistenev Yu.V., Shapovalov A.V., Borisov A.V., Vrazhnov D.A., Nikolaev V.V., Nikiforova O. Y. Applications of principal component analysis to breath air absorption spectra profiles classification, Proc. SPIE 9810, XII International Conference on Atomic and Molecular Pulsed Lasers, 98101Y (December 15, 2015); doi:10.1117/12.2225565.

[10] Jackson J.E. A user's guide to principal components — s.l.: N.Y.: John Wiley, 1991. — 592 c.

[11] Jolliffe I.T. Principal Component Analysis; 2d — s.l.: Springer NY, 2002. — 487 c.

[12] Kistenev Yu.V., Bukreeva E.B., Bulanova A.A., Kuzmin D.A., Tuzikov S.A., Yumov E.L., "Laser spectroscopy and chemometric study the specific features of air exhaled by patients with lung cancer and chronic obstructive pulmonary disease," Physics of Wave Phenomena, 22, 3, 210-215 (2014).

[13] Bukreeva E.B., Bulanova A.A., Kistenev Y. V., Kuzmin D.A., Tuzikov S.A., Yumov E.L. Analysis of the absorption spectra of gas emission of patients with lung cancer and chronic obstructive pulmonary disease by laser optoacoustic spectroscopy. Proc. SPIE 8699, Saratov Fall Meeting 2012: Optical Technologies in Biophysics and Medicine XIV; and Laser Physics and Photonics XIV, 86990K (2013)