



Gas analysis in medicine: New developments

K. G. Zenov, I. B. Miroshnichko, N. Yu. Kostykova, D. B. Kolker, Yu. V. Kistenev, M. K. Starikova, and P. N. Mishin

Citation: [AIP Conference Proceedings](#) **1688**, 030001 (2015); doi: 10.1063/1.4935996

View online: <http://dx.doi.org/10.1063/1.4935996>

View Table of Contents: <http://scitation.aip.org/content/aip/proceeding/aipcp/1688?ver=pdfcov>

Published by the [AIP Publishing](#)

Articles you may be interested in

[The beauty of simple adaptive control and new developments in nonlinear systems stability analysis](#)

[AIP Conf. Proc.](#) **1637**, 89 (2014); 10.1063/1.4904568

[Quantitative Analysis in Nuclear Medicine Imaging](#)

[Med. Phys.](#) **34**, 1522 (2007); 10.1118/1.2716416

[Twenty years' development of acoustic microscopy for medicine and biology](#)

[J. Acoust. Soc. Am.](#) **120**, 3192 (2006); 10.1121/1.4788037

[Development of a new instrument for performing microwave thermal analysis](#)

[Rev. Sci. Instrum.](#) **71**, 168 (2000); 10.1063/1.1150179

[The history and development of medical physics instrumentation: Nuclear medicine](#)

[Med. Phys.](#) **14**, 146 (1987); 10.1118/1.596105

Gas Analysis in Medicine: New Developments

K. G. Zenov^{1, a)}, I. B. Miroshnichko^{1, 2)}, N. Yu. Kostykova¹⁾, D. B. Kolker^{1, 2, 3)},
Yu. V Kistenev⁴⁾, M. K. Starikova¹⁾, P. N. Mishin⁴⁾

¹Special technologies, Ltd, Novosibirsk

²Novosibirsk State Technical University, Novosibirsk

³Novosibirsk State University, Novosibirsk

⁴Tomsk State University, Tomsk

^{a)}Corresponding author: zkg@ngs.ru

Abstract. In this article we discuss the method of early diagnosis of bronchopulmonary diseases based on the analysis of absorption spectra of biomarkers in the human exhaled air. For the analysis of absorption spectra of human exhaled air gas analyzer based on laser photo-acoustic spectroscopy (LPAS) was designed. A method for analysis of exhaled air samples from patients with lung cancer in comparison with the target and comparison group by LPAS was developed. This work is promising for screening of lung cancer.

INTRODUCTION

Currently, development of modern methods for diagnostics of various diseases is targeted primarily at non-invasive procedures, efficiency of sampling, interpretation of results and absence of harmful effects on the human body. In the past few years breath tests analyzing exhaled air for the presence of a specific set of biomarkers corresponding to a specific disease are investigated [1].

Gas analyzers based on the method of gas chromatography (GC) or laser photo-acoustic spectroscopy (LPAS), chemiluminescent sensors, devices based on technology of electrochemical sensors ("electronic nose") are currently evaluated to approach this problem. GC and PAS based systems are the most suitable for the multicomponent analysis of exhaled air.

Gas analyzers based on GC have high sensitivity and specificity, which reaches 83% and 95% respectively [2]. However, highly qualified personnel is able to interpret the results are required for operating a GC system. Also rather expensive consumables are required for GC.

Gas analyzers based on laser photo-acoustic spectroscopy have a sensitivity and specificity of 85% and 80%, respectively [2]. Compared with GC they do not require expensive consumables and specially trained personnel.

LASER PHOTOACOUSTIC SPECTROSCOPY

The method of laser photo-acoustic spectroscopy (LPAS) is based on photo-acoustic effect. LPAS is based on generating of acoustic waves in a gas excited by a modulated laser beam at the wavelength corresponding to the absorption line of gaseous samples. For measuring the parameters of these acoustic waves sensitive microphones are used. Photo-acoustic detector (PAD) is used for acquiring absorption spectra. At low concentrations, the signal from the microphone is [3]:

$$U_S = P_s \cdot S_{PAS}(f) \cdot \sigma(\lambda) \cdot n \quad (1),$$

where: P_s – laser power (W), S_{PAS} – sensitivity of PAD ($V \times cm/W$) at frequency of pump radiation f (Hz), $\sigma(\lambda)$ – the absorption coefficient of gaseous component ($atm^{-1} \times cm^{-1}$), depending on radiation wavelength λ (nm), n – concentration of gaseous component (atm).

To compensate the influence of laser source power variation it is necessary to normalize the PAD signal. To achieve this laser radiation reflected on a power meter (e.g., pyroelectric detector) (Fig. 1) by a beam splitter.

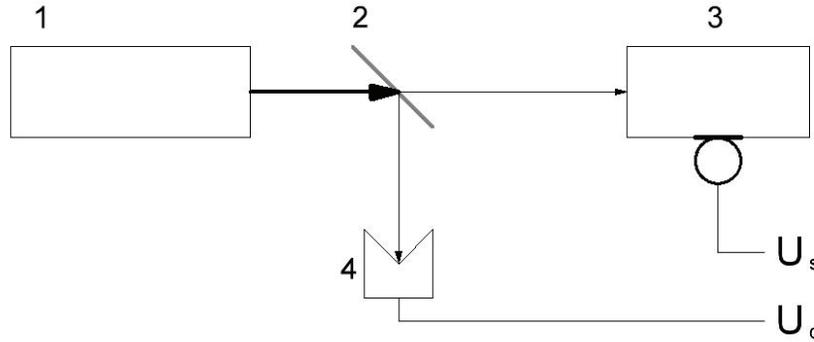


FIGURE 1. Optical setup. 1 – radiation source, 2 – beam splitter, 3 – PAD, 4 – power meter

Signal measured by power meter is:

$$U_d = S_d \cdot P_d \quad (2)$$

where: P_d is radiation power measured by power meter (W), S_d is power meter sensitivity (V/W). Then considering

$$P_s = (1-R) \cdot P_L, \quad P_d = R \cdot P_L \quad (3)$$

where: P_L – laser power (W), R is reflectivity of beam splitter, relationship of PAD signal to power meter signal is

$$\frac{U_s}{U_d} = K \cdot \sigma(\lambda) \cdot n \quad (4),$$

where

$$K = \frac{1-R}{R} \cdot \frac{S_{PAS}}{S_d} \quad (5)$$

where: U_s is PAD signal (V), U_d – power meter signal (V), K is calibration coefficient determined by experiment (cm).

The relationship U_s/U_d depends on concentration of one or few gas components and their respective absorption coefficients at fixed wavelength. Using a laser source with continuously tunable wavelength allows to obtain absorption spectra of gaseous component or gas mixtures including human exhaled air.

The absorption spectrum of a multicomponent test gas mixture was recorded to confirm the gas analyzer operating wavelength range (fig. 2).

Components of the gas mixture such as H_2O , N_2O , CH_4 , CO_2 , C_2H_2 relate to biomarkers of different diseases. Other gas components (CF_4 , $CHCl_3$, SF_6) are used as additional reference points. The absorption profile of the sulfur hexafluoride SF_6 is used for determining the upper limit of the device working range. As shown in Fig. 2 the working wavelength range is from 2.5 to 10.73 μm . The composition of the test gas mixture as well as the presence of certain components (H_2O , N_2O , CH_4) providing several absorption peaks in the operating wavelength range allow to estimate the operation error of the device at fixed points. In case the measured wavelength of absorption peaks of reference gases differ from calibration table, the user can recalibrate the device without involving highly qualified experts. Recording of the spectrum of binary gas mixtures and comparison with spectra shown in databases were made. Nitrogen was used as the buffer gas in binary gas mixtures, and the test substance as the second component.

Absorption spectrum of acetone in the range of 6.5 to 8 microns is shown on the Fig. 3 as an example of absorption spectrum of a gas mixture obtained by our device.

Spectrum from NIST database (www.nist.gov), obtained by Fourier spectrometer IFS66V (Bruker) using data processing 3-Term BH Apodization (resolution 0.4820 cm^{-1}) was used for comparison with the obtained results. The compared absorption spectra have similar contour shape, but there are differences. The absence of narrow absorption peak at wavelengths between 6875 nm and 7324 nm is due to broader lasing line of LaserBreeze gas analyzer, compared to the resolution of the Fourier spectrometer IFS66V.

The performed research confirmed the possibility of obtaining spectra with line width sufficient for the analysis of human exhaled air for early non-invasive diagnostics of a number of human diseases.

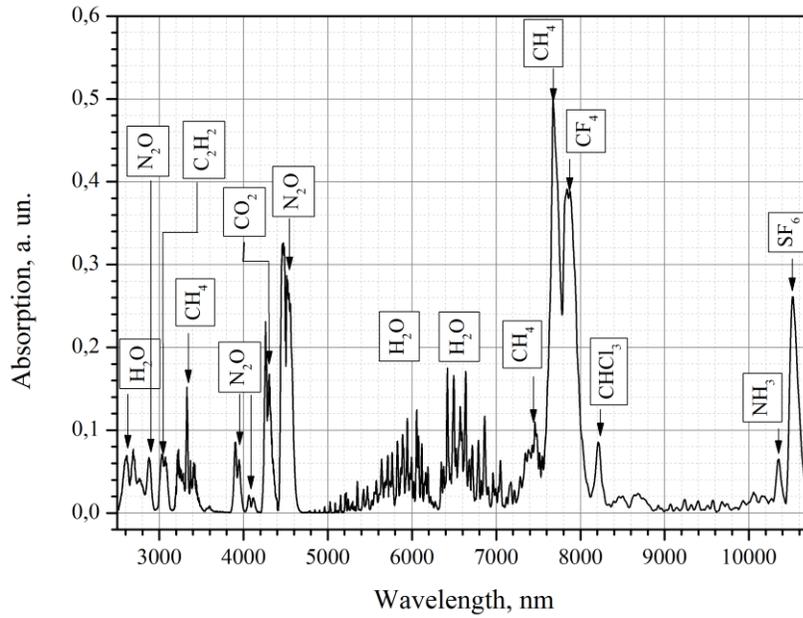


FIGURE 2. Absorption spectrum of the multicomponent gas mixture

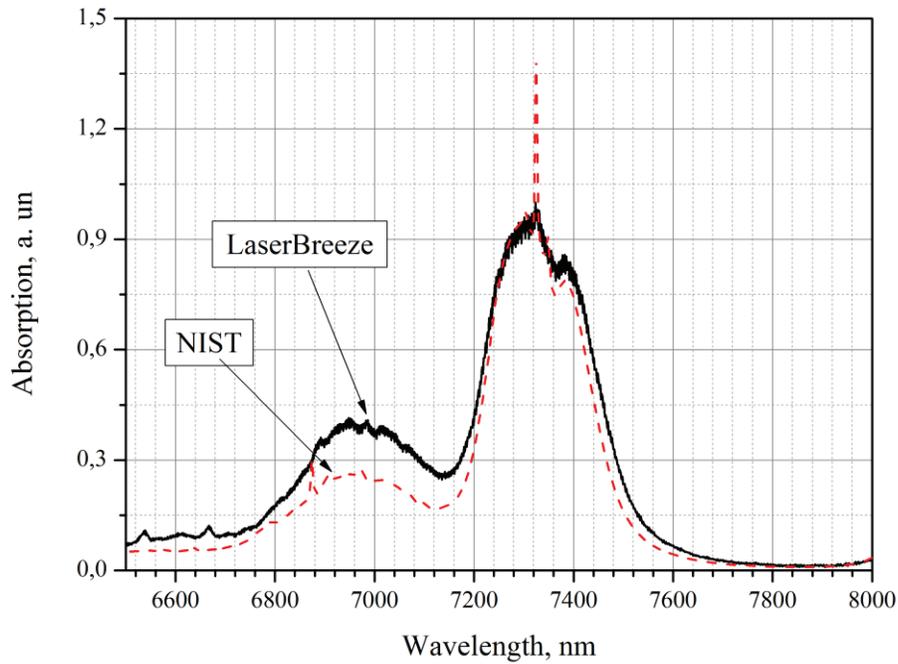


FIGURE 3. Absorption spectrum of acetone.

EXPERIMENTAL SETUP

LaserBreeze gas analyzer was developed in the Special Technologies Ltd. laboratory. The LaserBreeze appearance is shown in Fig. 4.



FIGURE 4. The LaserBreeze gas analyzer appearance

The developed gas analyzer consists of a radiation source, photo-acoustic detector (PAD) with sample preparation unit and electronic control unit. An optical parametric oscillator (OPO) is used as a laser radiation source which provides radiation wavelength tuning in the spectral range from 2.5 to 10.73 μm . OPO is pumped by a Nd:YLF laser at a wavelength of 1.053 μm . Exceedingly wide wavelength tuning range was obtained by using two types of nonlinear elements: fan-out PPLN structure and mercury thiogallate HgGa_2S_4 (HGS). The use of fan-out PPLN structures in an OPO provides continuous wavelength tuning in spectral range 2.5 to 4.5 μm at a constant temperature via precision linear transverse movement of the structure relative to the pump beam [4]. The second OPO tunes in the range from 4.5 to 10.73 μm by total rotation of HGS crystals with respect to the OPO cavity axis [5].

The double channel resonant PAD was used for recording the absorption spectra of gaseous samples [6]. PAD consists of reference cell, which contain gas mixture (acetone, nitrous oxide, methane, tetrafluoromethane, sulfur hexafluoride). The reference cell is used for the spectral absorption lines biomarker binding with respect to the absorption lines of the reference gases.

EXPERIMENT

The experimental research was carried out according to the principles of Good Clinical Practices. The protocol of the research was approved by the Ethic Committee of the Siberian State Medical University (Tomsk, Russia), Ref. Number 2882 on 24 November 2011. All participants were informed about details of the research and signed "Informed agreement" for the actions carried out. The study involved 11 healthy nonsmoking volunteers (control group) and seven patients with COPD (target group). The COPD patients were males with verified diagnoses who passed treatment at the Pulmonological Division of the Regional State Autonomous Institution of Public Health "Municipal Clinical Hospital No. 3" (Tomsk, Russia). The average age of this group was 59.6 years. We did not include COPD patients with an unverified diagnosis, the presence of pneumonia, asthma, and other respiratory pathologies. The control group consisted of conventionally healthy nonsmoking male volunteers. Inclusion criteria were the absence of acute illness within two weeks prior to sample collection, without chronic pathologies of bronchopulmonary, cardiovascular, digestive, urinary and reproductive systems, and the absence of the factor "smoking" in anamnesis vitae. The average age in this group was 21.1 years.

All samples were taken before or 30–40 minutes after meals. The smoking volunteers did not smoke for 30min or a longer time before sampling. In addition, the examinees rinsed their oral cavities by continuous-flow water before sampling. Exhaled air was collected in standard 10-ml test tubes through a plastic pipe. The procedure was as follows: an examinee made two or three quiet exhales into a plastic pipe. Under these conditions, the auxiliary breathing musculature was not used, in contrast to, for example, deep breath and exhale. Then the test tube was rapidly closed by a sterile cotton wad. After the collection, the samples were marked and analyzed by *LaserBreeze*.

RESULTS AND CONCLUSIONS

The interpretation of the absorption spectra of the exhaled air is a difficult task. The absorption lines of various substances that the gas mixture contains often locate very close to each other. For example, the majority of hydrocarbons absorption lines locate near 3.3 microns. This is due to valent vibrations of C - H bond. Therefore, for analysis of the absorption of exhaled air it is necessary to use statistical methods for data processing. The method of data processing by means of statistic instruments was described in detail in work [7].

Absorption spectra of exhaled air for target and control groups were recorded with LaserBreeze. Then the spectra were processed with use of special statistical soft-ware "ViDaExpert" for visualization of multidimensional data.

The results of the processing are presented in Fig. 5 and 6.

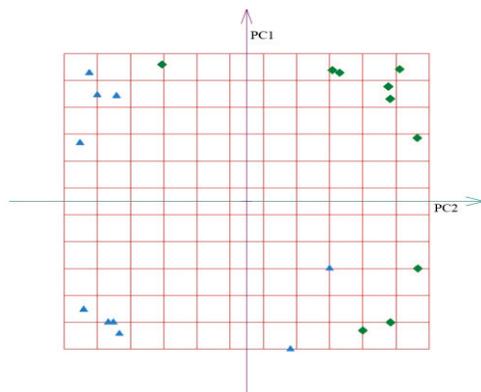


FIGURE 5. Spatial distribution of the exhaled air samples from the COPD patients (the diamond icons) and healthy volunteers (the triangle icons). The feature set includes absorption coefficients of the sample in the range of 2.59 to 2.817 μm . The axes correspond to the first (PC1) and the second (PC2) principal components.

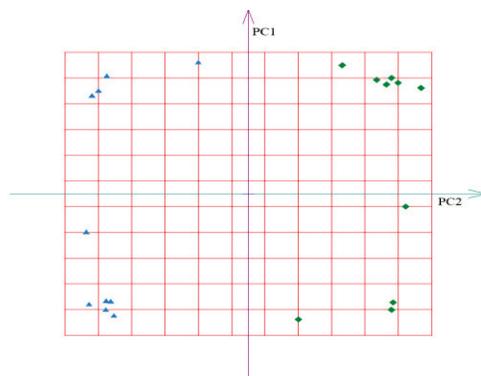


FIGURE 6. Spatial distribution of the exhaled air samples from the COPD patients (the diamond icons) and healthy volunteers (the triangle icons). The feature set includes absorption coefficients of the sample in the range of 2.96 to 3.58 μm . The axes correspond to the first (PC1) and the second (PC2) principal components.

Figures 5 and 6 show that the method of IR LPAS allows to separate patients with COPD and healthy nonsmoking volunteers reliably.

The developed gas-analyzer allows recording the spectrum of exhaled air in the range from 2.5 to 10.73 μm that allows detection of up to 20 biomarkers. Moreover the device enables to obtain the spectrum of the vapor substances in the mid-IR range. Laser sources combining fan-out PPLN structure and mercury thiogallate crystals based OPOs allow the construction of versatile instruments. Moreover, as shown by the records of absorption spectra of exhaled air, a part of the spectral range is not informative. Not informative spectral intervals provide the opportunity to simplify the optical scheme without loss of information about the composition of the sample, thereby reducing the cost of the instrument and the time of the study.

ACKNOWLEDGMENTS

The work was carried out with support of Federal Target Program R&D (Agreement № 14.578.21.0082, the unique identifier of applied researches and experimental development (project) RFMEFI57814X0082).

REFERENCES

1. V. L. Vaks and etc., *Physics-Uspekhi (Advances in Physical Sciences)* **184**, 739-758 (2014).
2. R. L. Manser and etc., *Cochrane Database of Systematic Reviews (The Cochrane Library, NY, 2010)*.
3. Y. N. Ponomarev and etc., *Laser optical-acoustic spectroscopy of intermolecular interactions in gases (RASCO, Tomsk, 2000)*.
4. D. B. Kolker and etc., *Instruments and Experimental Techniques* **1**, 50-54 (2014).
5. N. Yu. Kostyukova and etc., *Laser Phys. Lett.* **12**, 095401 (2015).
6. C.-M. Lee and etc., *Optical Engineering* **46**, 064302 (2007).
7. B. G. Ageyev and etc., *Bulletin of Siberian medicine* **4**, 116-120, (2012)