Summary of Ph.D. Thesis

The development of photoacoustic devices for breath analysis applications

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1. Introduction

Analysis of exhaled air can provide both non-invasive and continuous information on the metabolic and physiological state of an individual. Breath analysis is a rapidly developing research discipline that holds great potential for real time and cost effective bio-monitoring applications including medical diagnosis, therapeutic monitoring, assessment of previous exposure, or for investigation of physiological processes of the human body. Breath samples can be taken from practically everyone regardless of their age or health conditions (also from mechanically ventilated patients). Collecting breath samples poses minimum risk to the person that collects the samples and the sampling can be repeated with optional frequency. Breath analysis is now used in clinical practice to monitor asthma, diagnose transplant organ rejection, diagnose Helicobacter pylori infection, detect blood alcohol concentration, and monitor breath gases during anaesthesia, mechanical ventilation, and respiration. Recently, measurement of hydrogen and methane in breath has become a widespread clinical test for assessing malabsorption. Despite its great advantages the number of tests used clinically is still limited. This can be partially explained by the inadequate instrumentation and the lack of standardized breath sampling methods.

Several medical research groups of the University of Szeged are conducting research based on the analysis of the gas composition of breath. Gas chromatographs were used for their experiments, but those instruments could not provide continuous sampling, adequate accuracy, and in situ measurements. It was proposed in 2009 that photoacoustic spectroscopy based gas detectors developed by the Photoacoustic Research Group at University of Szeged could be utilized for medical research. In the last two decades our research group has constructed photoacoustic gas detectors that were successfully applied under harsh field conditions and provided reliable, real time measurements with high selectivity and accuracy.

The cooperation between the Photoacoustic Research Group and several medical research groups of the University of Szeged started in 2009. I have joined this work from the beginnings. The main motivation of my work was to develop new instruments and gas sampling methods that allow accurate, well reproducible and real time gas concentration measurements for medical studies.

2. Objectives and methods

My aim was to develop photoacoustic spectroscopy based instruments and adequate gas sampling methods for the analysis of the gas composition of breath.

Generally used (closed) photoacoustic cells of our research group require gas handling units and their response time is at least 10 seconds. However, low response time (few seconds and even sub-second) detection has an important role in breath analysis. Therefore, I constructed a new photoacoustic cell that requires no gas handling unit and thereby it enables shorter response time.

I examined the photoacoustic spectroscopy based quantification of methane and hydrogen sulfide (the most important components for the cooperating medical research groups) in breath. The spectral interferences and molecular relaxation effects caused by the high carbon dioxide and water vapour content of breath was studied for both methane and hydrogen sulfide.

I have constructed several photoacoustic instruments and developed gas sampling chambers as well as methods for breath sampling of animals and humans in cooperation with researchers of the Institute of Surgical Research, University of Szeged. I also participated in the interpretation of the data obtained during the experiments.

I initiated joint research activities with *Institute of Breath Research (University of Innsbruck)* to study the changes of exhaled methane profiles. I investigated the exhalation kinetics of methane experimentally and theoretically.

3. New scientific results

1. I have prepared a fully opened photoacoustic cell that does not require gas handling unit and provides sub-second response time. The photoacoustic cell is a cylindrical resonator opened on both ends having a relatively large diameter of 34 mm. The acoustic design and signal generation was optimized for the excitation of a specially selected combination mode that enables the minimization of the acoustic energy losses at the open ends and external noise suppression by differential detection scheme. The efficiency of the external noise suppression was proved experimentally. The minimum detectable concentration of water vapour was ~80 ppmV [1].

2. I have investigated the photoacoustic spectroscopy based quantification of hydrogen sulphide in widely varying gas mixtures containing more than 2 V/V% carbon dioxide. The instrument has a wide dynamic concentration range (6-7200 ppmV). I have optimized the measurement cycle of a photoacoustic hydrogen sulfide detector that operates in a mobile monitoring station of a natural gas processing plant. Its optimized signal generation overcomes the problems caused by the widely varying gas composition of industrial gases (changing of the speed of sound, spectral interferences). I have developed a simplified calibration method that takes advantage of the nearby absorption line of carbon dioxide and enables *in situ*, fast and economical calibrations [2].

3. I have developed a photoacoustic system for real time, sub-ppmV quantification of methane concentration in exhaled air. I have investigated the effects of the main components of breath on the photoacoustic detection of methane. I have compared the photoacoustic instrument with a gas chromatograph (considered as a standard method), and the results of the two systems were in very good agreement. I have constructed sampling chambers for

rodents, and developed measurement protocols to determine the endogenous methane concentration in cooperation with the researchers of the Institute of Surgical Research, University of Szeged. I have also adapted the photoacoustic instrument to measure methane in human exhaled air that allowed its use in several medical research projects [3].

4. I have investigated the effects of hemodynamic and respiratory parameters on the exhaled methane concentration with the instrument described in point 3. I have determined that during physical activity (75 W) alveolar methane level of the volunteers (methane-producers) decreased by a factor of 3-4 compared to the methane level at rest. I have shown that significant alterations of exhaled methane concentration occur even at rest, which can be related to ventilation changes. I have compared the experimental data with values originating from the Farhi equation (classical pulmonary inert gas elimination theory): the Farhi equation can describe quantitatively the changes of the methane concentration under non-exercise conditions, while during workload the theory consistently overestimates the methane concentration. These results are implemented in the interpretation of the experiments conducted at Institute of Surgical Research, University of Szeged [4].

4. Publications

The results are based on the following publications:

1. Z. Bozóki, A. Szabó, Á. Mohácsi, G. Szabó: A fully opened photoacoustic resonator based system for fast response gas concentration measurements
Sensors and Actuators B (2010) 147 206-212
IF (2010): 3.368

2. A. Szabó, Á. Mohácsi, G. Gulyás, Z. Bozóki, G. Szabó: In situ and wide range quantification of hydrogen sulfide in industrial gases by means of photoacoustic spectroscopy
Measurement Science and Technology (2013) 24 065501 (7 p)
IF (2013): 1.352

3. E. Tuboly, A. Szabó, G. Erős, Á. Mohácsi, G. Szabó, R. Tengölics, G. Rákhely, M. Boros: Determination of endogenous methane formation by photoacoustic spectroscopy
Journal of Breath Research (2013) 7 (4) 046004 (9 p)
IF (2013): 3.590

4. A. Szabó, V. Ruzsanyi, K. Unterkofler, Á. Mohácsi, E. Tuboly, M. Boros, G. Szabó, H. Hinterhuber, A. Amann: Exhaled methane concentration profiles during exercise on an ergometer
Journal of Breath Research (2015) 9 (1) 016009 (9 p)
IF (2014): 4.631

Other publications:

5. E. Tuboly, A. Szabó, D. Garab, G. Bartha, Á. Janovszky, G. Erős, A. Szabó, Á. Mohácsi, G. Szabó, J. Kaszaki, M. Ghyczy, M. Boros: Methane biogenesis during sodium azide-induced chemical hypoxia in rats
American Journal of Physiology – Cell Physiology (2013) 304(2):C207-214
IF (2013): 3.674

6. A. Szabó, Zs. Tarnai, Cs. Berkovits, P. Novák, Á. Mohácsi, G. Braunitzer, Z. Rakonczay, K. Turzó, K. Nagy, G. Szabó: Volatile sulphur compound measurement with OralChroma^{TM}: a methodological improvement
Journal of Breath Research 9 (2015) 016001 (8 p)
IF (2014): 4.631

Selected conference posters, presentations:

7. A. Szabó, V. Ruzsanyi, K. Unterkofler, Á. Mohácsi, E. Tuboly, M. Boros, G. Szabó: Dynamics of breath methane concentration profile determined by photoacoustic spectroscopy
International Association of Breath Research Conference 2015, Vienna, 2015.09.14-16.

8. A. Szabó, Á. Mohácsi, E. Tuboly, M. Boros, Z. Tarnai, C. Berkovits, Z. Rakonczay, K. Turzó, K. Nagy, G. Szabó: Kilélegzett gáz analízis fotoakusztikus elven alapuló mérőberendezéssel
Kvantumelektronika 2014: VII. Szimpózium a hazai kvantumelektronikai kutatások eredményeiről, Paper P55, Budapest, 2014.11.28.

9. E. Tuboly, B. Babik, G. Bartha, G. Kisvári, V. Serédi, Á. Mohácsi, A. Szabó, A. Végh, G. Szabó, M. Boros: Methane Release In Humans Under Oxido-Reductive Stress Conditions. ESSR Brendel Prize Winner

Journal of Surgical Research 186(2) 592-593 (2014)
9th Annual Academic Surgical Congress, San Diego (USA) 2014.02.04-06.

10. E. Tuboly, B. Babik, G. Bartha, V. Serédi, Á. Mohácsi, A. Szabó, G. Szabó, M. Boros: Methane release in humans under oxido-reductive stress conditions
European Surgical Research 50(Suppl.1.) BC05 (2013)
48th Congress of European Society for Surgical Research. Istambul, 2013. 05.29.–06.01.

11. E. Tuboly, B. Babik, G. Bartha, V. Serédi, Á. Mohácsi, A. Szabó, G. Szabó, M. Boros: Átmeneti hypoxiát követő metánképződés szívműtéten átesett betegekben
Magyar Sebészet 66: p. 114. (2013); Magyar Sebész Társaság Kísérletes Sebészeti Szekció XXIV kongresszusa. Debrecen (Hungary), 2013.06.13-15.

12. A. Szabó, Z. Tarnai, C. Berkovits, Á. Mohácsi, K. Turzó, Z. Rakonczay, K. Nagy, G. Szabó: Methodological study of halitosis measuring devices
Breath Analysis Summit 2013 – International Conference on Breath Research, Saarbruecken/Wallerfangen (Germany) 2013.06.09-12.

13. A. Szabó, Á. Mohácsi, E. Tuboly, G. Erős, M. Boros, G. Szabó: Portable Photoacoustic Methane Sensor for Medical Research
11th International Conference on Optical Technologies for Sensing and Measurement, AMA Conferences 2013: Proceedings OPTO 2013 P101, Nürnberg, 2013.06.14-16.

14. E. Tuboly, A. Szabó, D. Garab, G. Bartha, Á. Janovszki, Á. Mohácsi, A. Szabó, J. Kaszaki, G. Szabó, M. Boros: A mitokondrium diszfunkció által okozott metánképződés és gyulladásos reakció mérsékelése L-α-glicerilfoszforilkolin kezeléssel
A Magyar Élettani Társaság LXXVI. Vándorgyűlése, Debrecen (Hungary), 2012.06.10-13.

15. A. Szabó, Á. Mohácsi, P. Novák, D. Aladzic, K. Turzó, Z. Rakonczay, G. Erős, M. Boros, K. Nagy, G. Szabó: Diode laser based photoacoustic gas measuring instruments intended for medical research

Progress in Biomedical Optics and Imaging – Proceedings of SPIE 84272J (2012), SPIE Photonics Europe 2012, Brüsszel, 2012. április 16-19.

16. P. Novák, M. Móra, D. Aladzic, A. Szabó, Á. Mohácsi, Z. Rakonczay, K Turzó, G. Szabó, K. Nagy: Assessment of halitosis in a student population in Hungary
Journal of Dental Research 90:(Spec. Iss. B.) Paper 507 (2011)