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TDLS instrument development for medical screening diagnostics

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Introduction

Idea to use concentration of different molecules in exhaled human breath for disease diagnosis has long term history. We've started this work using TDLS more than 15 years ago [1-3].

1. A.I.Kuznetzov, K.L.Moskalenko, A.I.Nadezhdinskii and E.V.Stepanov, Sensor Based on Tunable Diode Lasers and Mid-IR-Fiber Optic and Their Diagnostic Applications in Medicine and Enviromental Protection, Journal de Physique IV, 1, C7-253 (1991)
2. K.L.Moskalenko, N.Ya.Sobolev, I.A.Adamovskay, E.V.Stepanov, A.I.Nadezhdinskii, Susan McKenna-Lawlor, Tunable diode lasers application for fully automated absolute measurements of CO and CO2 concentrations in human breath, Proc.SPIE, 2205, 440-447 (1994)
3. K.L.Moskalenko, A.I.Nadezhdinskii, E.V.Stepanov, Tunable diode laser spectroscopy application for ammonia and methane content measurements in human breath, Proc.SPIE, 2205, 448-452 (1994)

Trace gas analysis in exhaled human breath

More than 400 different molecules were detected in exhaled human breath. See for example [4], who reviewed about the molecules that have been found in human breath and whose biochemical pathways are known or whose biochemical pathways can be postulated and have been shown to be useful clinically.
Many groups are working in this direction and obtained very interesting results. However, this approach continues to be in Labs.
Reason: the approach under consideration assumes link between molecule and disease. Hence, it considers one instrument (molecule) for one disease, for one specialist. As result it is cost non-effective.

4. Risby, T.H., Trace gas analysis in exhaled human breath for disease diagnosis, Johns Hopkins Med. Inst., Baltimore, MD, USA;

Screening medical diagnostics

Here we'd like to consider alternative approach. Human body is complicated optimized system. Any disease will remove it from equilibrium and can be detected.

Example: temperature. All human has equilibrium temperature 36.6^{o}C. Temperature change by 1^{o}C (0.3 %) is disease signature. Similar is true for trace molecules concentration in blood. In equilibrium they have some value. Disease presence will shift equilibrium leading to significant change of trace molecules concentration in blood. The goal is to determine markers than can be used for screening medical diagnostics.

Human body is energetic system. Similar to explosives (see A1) ammonia can be considered as marker for very complicated processes from nitrogen in food to ammonia in blood. Any diseases in body subsystems involved in this complicated process will lead to ammonia concentration variation in blood. The same is true to other important elements in human body (C, O, S).

Breath is not best solution for screening medical diagnostics. In present paper we are proposing to use gas flow from palm for trace molecules detection.

The approach was accepted and program of Moscow government started this year. Its preliminary results are presented.

Molecules in atmosphere and in exhaled human breath

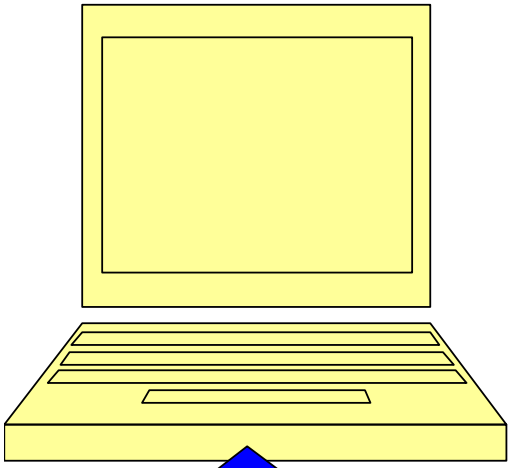
Preliminary as molecules to be detected we've selected H_2O, CO, CO_2, NH_3, and CH_4.

Molecule	CO_2	CO	NH_3	CH_4
Atmosphere	330 ppm	0.15 ppm	50 ppt	1.7 ppm
Human breath	3 %	0.5-1 ppm	100-300 ppb	4-6 ppm

Some molecules concentration in atmosphere (US Standard atmosphere) and in human breath as was measured in [2, 3].

In present paper results of TDLS based instrument to detect ammonia from palm (development, calibration, and tests) will be presented.

Block-scheme



TDLS module

USB

Digital

NI DAQ

Electronics

Reference channel

DL

Fiber splitter

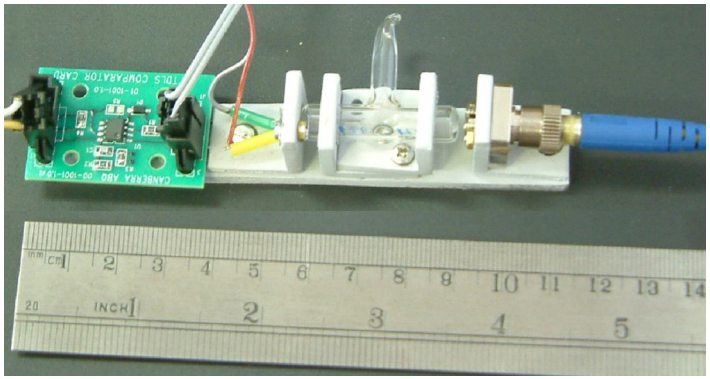
Analytical channel

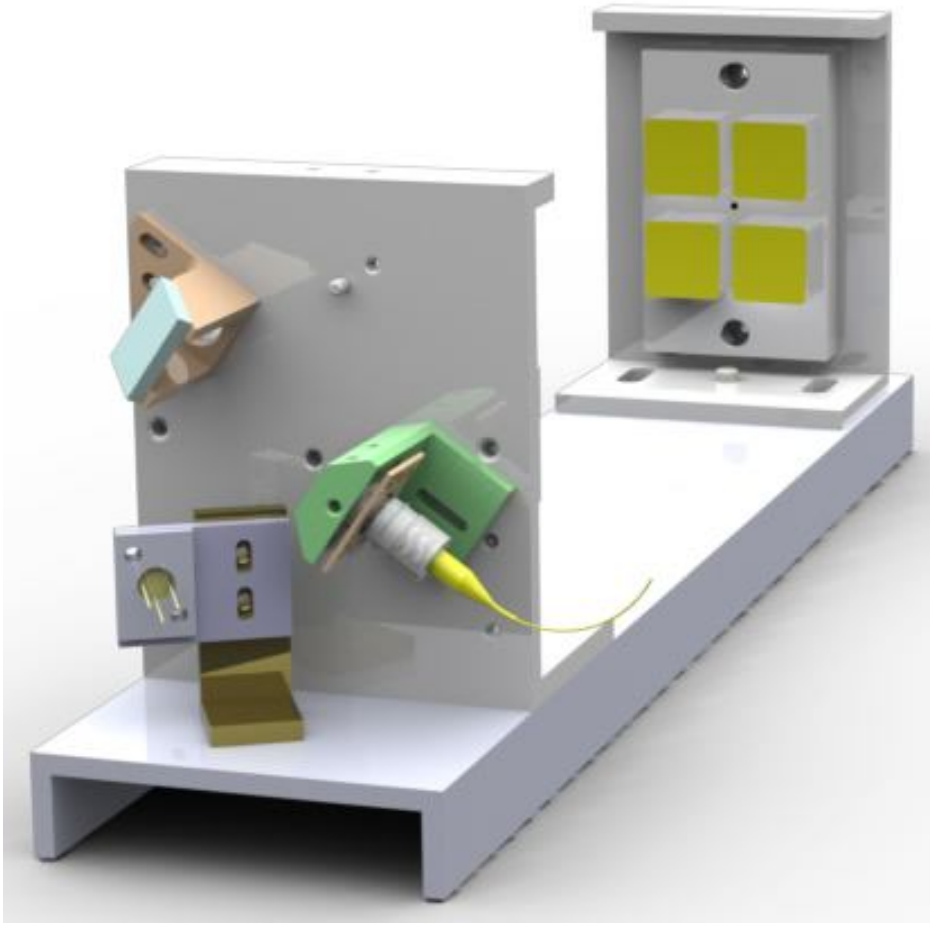
Arrows: blue – digital connection, red – analog signals, black – optical fibers.

Analytical and reference channels

Reference channel module view.

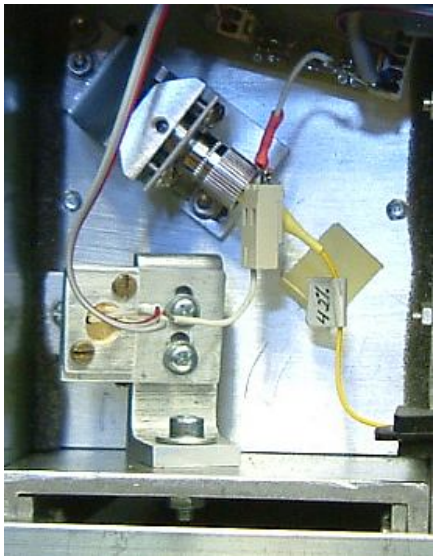
Left to right: preamplifier, PD, reference cell, and fiber cable from DL.





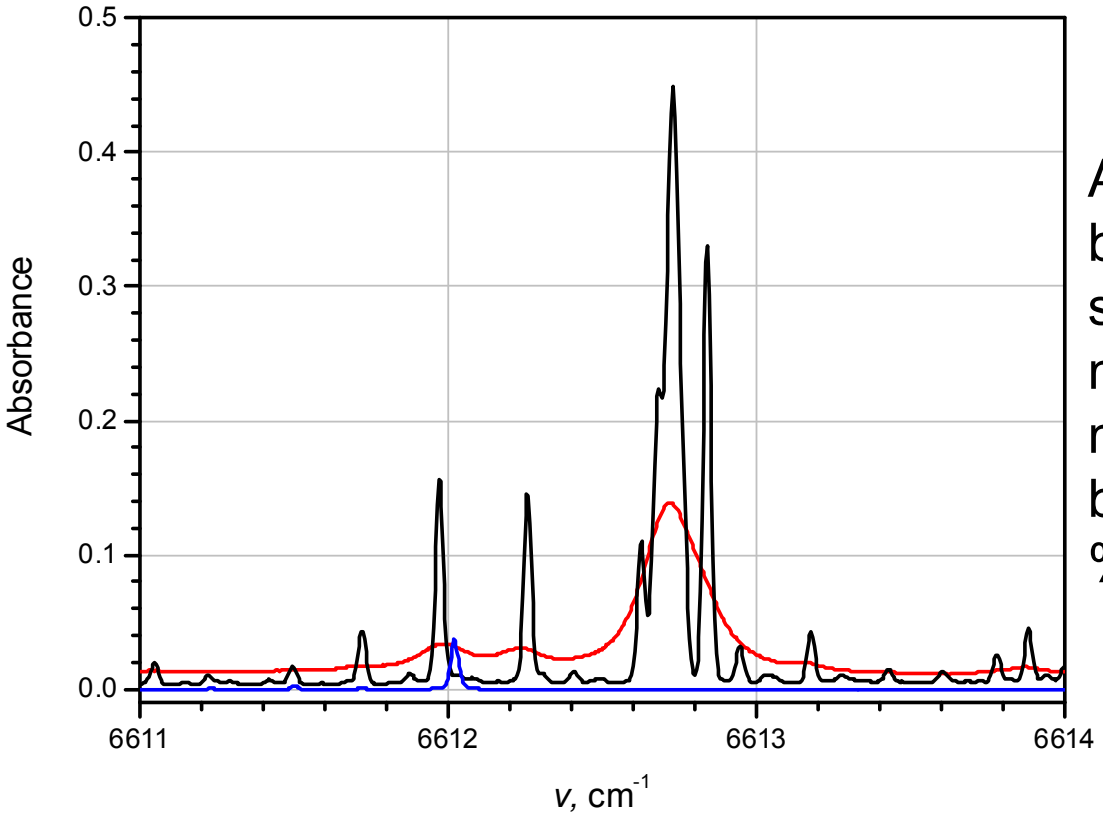
Analytical channel module layout drawing: “Chernin” matrix optical system (L = 39 m), DL fiber input into cell, mirror, and PD to detect DL light from cell.

Analytical channel module view with DL fiber input, mirror, and PD



Analytical spectral range to detect NH_3

Analytical spectral range for ammonia detection was selected using “Line-by-Line” software developed for spectra simulation (see C2). Selection requirements: intensive NH_3 line, minority influence of humidity.

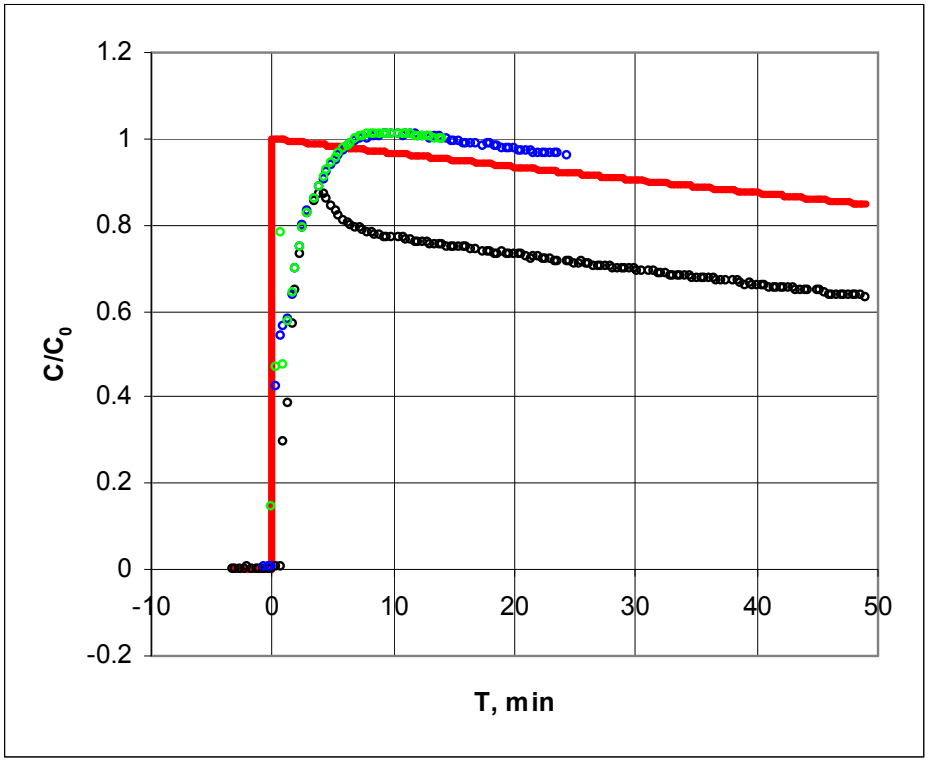


Absorbance spectra recorded by DL in use for spectral range selected: L = 2 m; black – 2.13 mBar of pure NH_3; red - 2.13 mBar of NH_3 in 1 Bar of dry air; blue – atmosphere air with 50 % humidity.

Analytical spectral line to detect ammonia for screening medical diagnostics. At the beginning data from http://vpl.astro.washington.edu/spectra were used for ammonia absorption cross-section (accuracy ~ 10 – 20 %).

NH_3 cross-section calibration

To improve accuracy, NH_3 cross-section calibration was performed. In volume V with air in glass box at time t=0 by syringe was injected calibrated volume v of pure ammonia. TDLS measured C using PNNL cross-section data (see above).



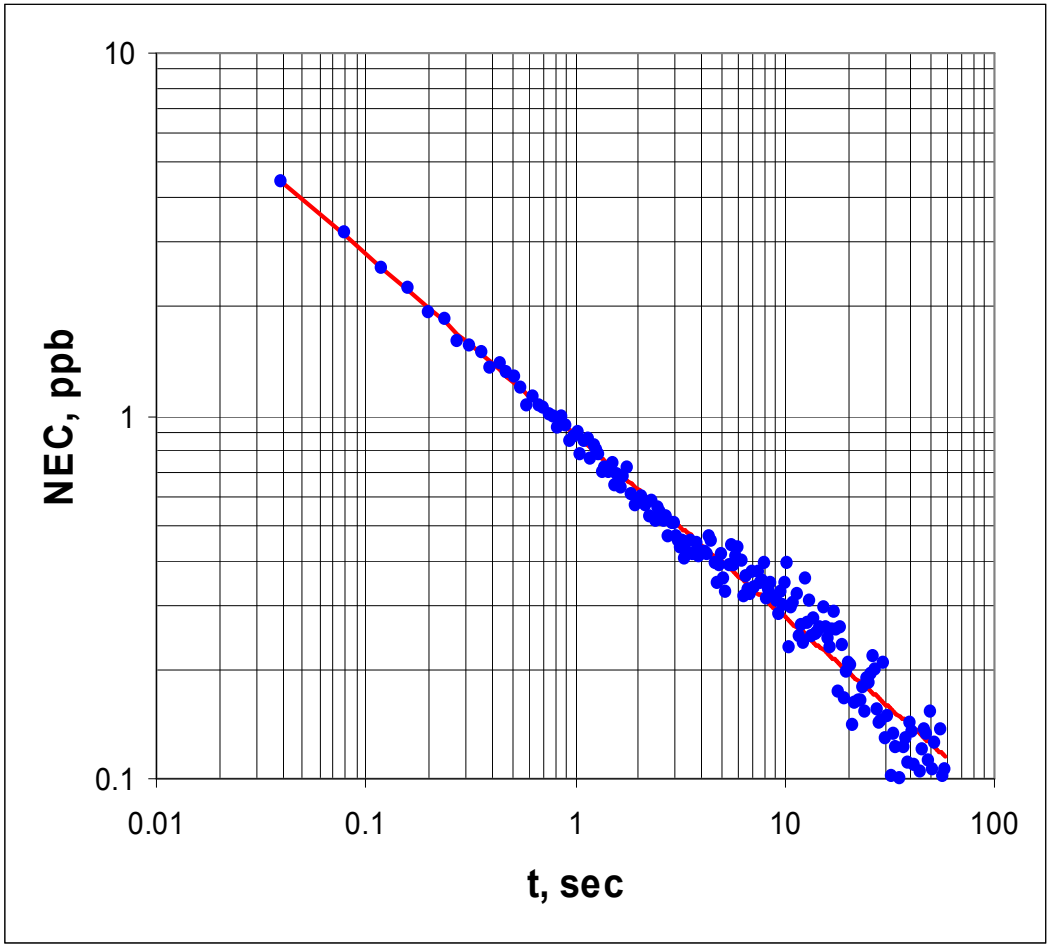
Concentration by definition is:

$$C_0 = v/V$$

Circles are result of TDLS measurements for first (black), second, and third injections. Just after injection one can see concentration increase due to molecular diffusion. After 10 min diffusion process is finished. Difference between first and other injections is due to one ammonia molecular layer absorbed on glass walls.

For second and third injections very good reproducibility can be observed with concentration decrease. So, concentration can't be considered as calibrated one. However, its interpolation to t = 0 provides NH_3 cross-section calibration with accuracy better than 1 %. Previously used value was corrected by 5 %.

Minimum detectable concentration



NH_3 NEC (Noise Equivalent Concentration) for instrument developed as function of averaging time.

NEC is determined by fundamental limit due to DL quantum noise.

For screening medical diagnostics time of single measurement below 1 min is acceptable. For these averaging times for instrument developed minimum detectable ammonia concentration is between 100 ppt – 1 ppb.

What is measuring?

Goal: measure marker molecules concentration in blood.

Water in blood is evaporating through skin. This process depends on race. People from south have smaller water evaporating through skin with respect to northern ones.

Marker molecules in blood are evaporating from skin proportionally to their concentration in blood. Resume: ratio of evaporated flows from skin of marker molecule to water has to be measured.

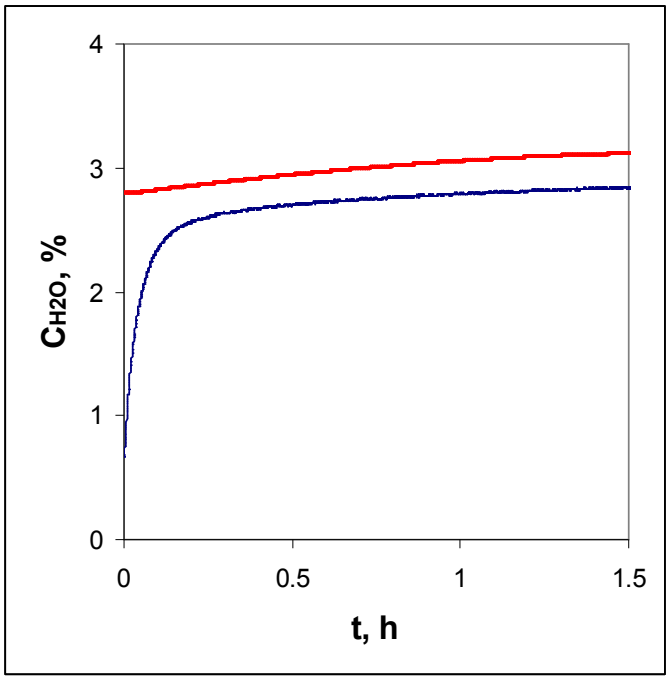
Part of evaporation molecular flow from skin is collecting by the system – subject for optimization.

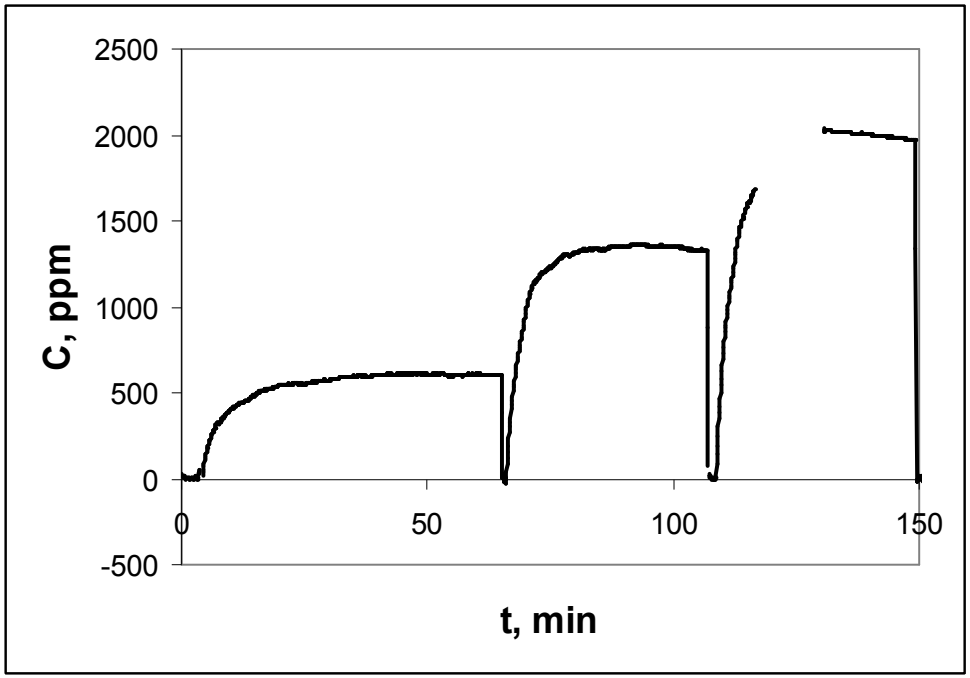
TDLS measures concentration of marker molecule inside “Chernin” cell. It is proportional to marker molecule evaporation flow rate and gas exchange time in cell – subject for optimization.

TDLS measures average concentration inside “Chernin” cell. It depends on gas flow thought cell (memory effects) – subject for optimization and filling factor calibration.

Ammonia flow calibration

TDLS to measure H_2O and NH_3 was installed in glass box with 100 ml water sample. 1, 2, 3 ml of NH_3:H_2O=1:10 solution were then added to the sample.





Blue – H_2O in box as measured; red - saturated vapor due to sample temperature changing.

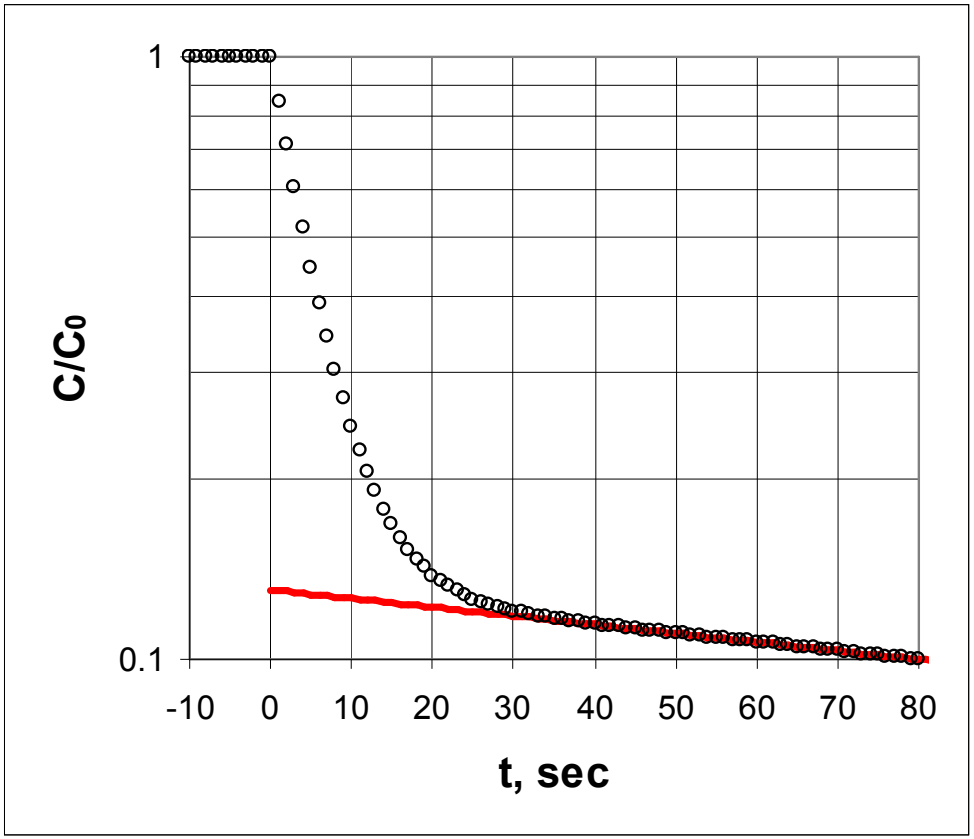
NH_3 in box for 3 calibrated samples. Ammonia concentration above sample is 20 times higher than in solution.

$$\left.\frac{\partial N_{H_2O}}{\partial S \partial t}\right|_{t=0} = 0.85 \frac{\mu mol}{\sec * cm^2}[1-\eta]$$

$$\left.\frac{\partial N_{NH_3}}{\partial S \partial t}\right|_{t=0} = 16 \frac{\mu mol}{\sec * cm^2} C$$

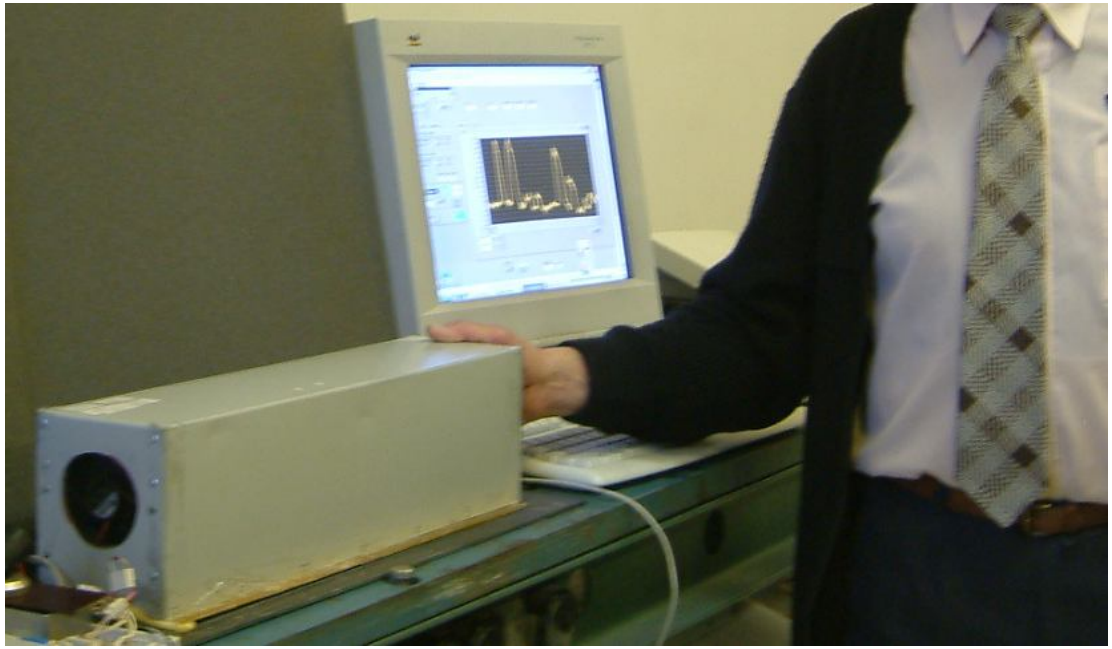
Filling factor calibration

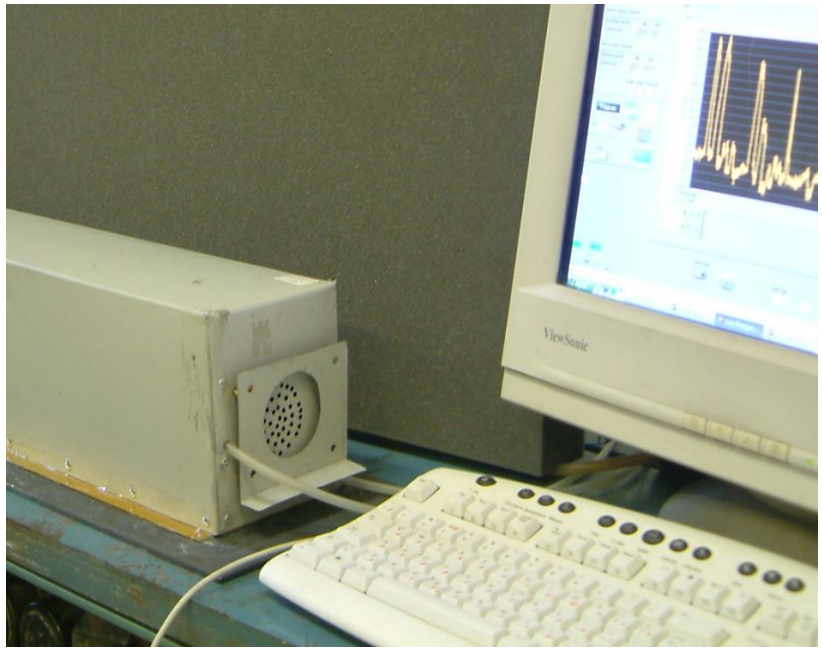
Special gas flow was organized to prevent NH_3 molecules interaction with mirrors and cell walls as well as interaction of dust and moisture with mirrors for field applications. As result not all cell volume was filled by gas flow. So, filling factor F has to be calibrated. Filling factor is determined by gas flow geometry and doesn't depend on particular molecule. For filling factor calibration we've used methane impurity (it is simpler than NH_3).



The cell was filled with methane gas mixture. Constant value of measured concentration can be observed. At t = 0 ventilator was switched on and outer air (low methane) removed mixture with high methane concentration. Methane concentration as measured by TDLS dropped quickly during some sec. Long concentration tail is due to methane diffusion. Interpolating this tail to t = 0 (red line) fill factor was determined. It was found 0.8 – 0.9.

Laboratory instrument prototype





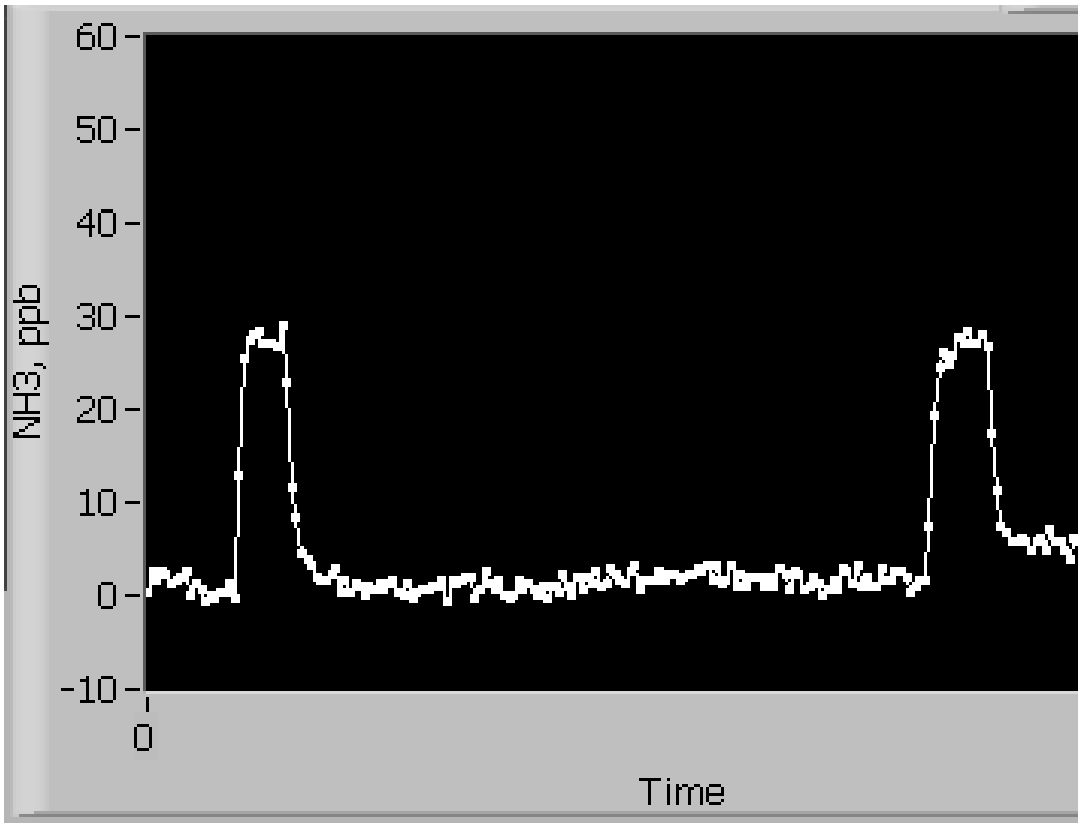
Laboratory prototype was developed to detect trace NH_3 flow from patient palm for screening medical diagnostics.

Peaks on computer screen correspond to different patients investigation. Characteristic measurement time for single patient is around 30 sec.

Ammonia detection

Similar to explosives (see A1) ammonia can be considered as marker for very complicated processes from nitrogen in food to ammonia in blood. Any diseases in body subsystems involved in this complicated process will lead to ammonia concentration variation in blood. Liver and kidney are responsible for ammonia removing from human body. Their dysfunctions will lead to NH_3 concentration increasing in blood.

Example of screening diagnostics of two healthy patients. Ammonia concentration is practically the same. Some memory effect of instrument developed can be observed (subject for gas flow optimization).
Both significantly higher and lower NH_3 concentrations for patients with different diseases were observed during preliminary medical tests.



Conclusion

By this paper we are starting development of TDLS based medical screening diagnostics.

The approach was approved and Moscow government program started this year including instrument development and its tests in clinics.

Possible molecular markers for medical screening diagnostics were considered and selected.

Laboratory prototype for trace ammonia detection from palm was developed, calibrated, and tested.