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Irene Ventrillard-Courtillot, Thierry Gonthiez, Christine Clerici, Daniele Romanini. Multispecies breath analysis faster than a single respiratory cycle by optical-feedback cavity-enhanced absorption spectroscopy. *Journal of Biomedical Optics*, 2009, 14, pp.064026. 10.1117/1.3269677 . hal-00997478

HAL Id: hal-00997478

<https://hal.science/hal-00997478v1>

Submitted on 16 May 2023

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Multispecies breath analysis faster than a single respiratory cycle by optical-feedback cavity-enhanced absorption spectroscopy

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1 Introduction

Laser spectroscopy applied to quantitative analysis of trace gases in human breath is promising as a diagnostic technique to investigate various diseases.¹ Breath analysis techniques available today may be fast and easy in application and, by their noninvasive character, bear no health hazards to patients. However, very few techniques offer real-time results, while most require sample collection and offline laboratory analysis (e.g., by gas chromatography or mass spectrometry). This demands a complex and expensive handling of collected samples and introduces delays comparable to those of traditional blood analysis. Thus, breath analysis is today rarely practiced in medical offices likely because it does not present enough advantage with respect to blood screening. Laser-based spectroscopy might change the situation because it permits real-time measurements with a very good selectivity and sensitivity using inexpensive, compact, and robust instruments that can be operated inside a medical office. Laser spectroscopy could make breath analysis a routine patient-screening technique.

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Abstract. We demonstrate a first application, of optical-feedback cavity-enhanced absorption spectroscopy (OF-CEAS) to breath analysis in a medical environment. Noninvasive monitoring of trace species in exhaled air was performed simultaneous to spirometric measurements on patients at Bichat Hospital (Paris). The high selectivity of the OF-CEAS spectrometer and a time response of 0.3 s (limited by sample flow rate) allowed following the evolution of carbon monoxide and methane concentrations during individual respiratory cycles, and resolving variations among different ventilatory patterns. The minimum detectable absorption on this time scale is about $3 \times 10^{-10} \text{ cm}^{-1}$. At the working wavelength of the instrument (2.326 μm), this translates to concentration detection limits of ~ 1 ppbv (45 picomolar, or $\sim 1.25 \mu\text{g}/\text{m}^3$) for CO and 25 ppbv for CH₄, well below concentration values found in exhaled air. This same instrument is also able to provide measurement of NH₃ concentrations with a detection limit of ~ 10 ppbv; however, at present, memory effects do not allow its measurement on fast time scales. © 2009 Society of Photo-Optical Instrumentation Engineers. [DOI: 10.1117/1.3269677]

Keywords: breath analysis; laser spectroscopy; carbon monoxide; methane; cavity enhanced absorption spectroscopy.

Paper 09220R received Jun. 4, 2009; revised manuscript received Sep. 10, 2009; accepted for publication Oct. 6, 2009; published online Dec. 11, 2009.

Breath analysis application of high-resolution laser spectroscopy in a high-finesse optical cavity^{2,3} has already been demonstrated in several occasions. For instance, cavity ring down spectroscopy (CRDS) was applied to the measurement of nitric oxide (NO)⁴ in the diagnostic of asthma or the investigation of other lung diseases, to the analysis of the carbon isotope ¹³C/¹²C ratio⁵ in the screening of peptic ulcers, to the measurement of ethane (C₂H₆),⁶ which is indicative of oxidative stress, to the monitoring of hydrogen cyanide (HCN)⁷ as a diagnostic tool for cyanide poisoning and for cyanide-producing bacterial infections. Off-axis integrated cavity output spectroscopy (ICOS) was also applied to C₂H₆,⁸ as well as to NO and CO₂ measurements.⁹ Cavity-enhanced absorption spectroscopy (CEAS) with a frequency comb laser was applied to monitoring of CO, CO₂, and NH₃.¹⁰ A major advantage of CRDS as compared to CEAS and ICOS techniques (which are basically one technique) is that it allows quantitative measurement of sample absorption coefficients without need for calibration.³ This means that in a medical office, CRDS would not require periodic calibration contrary to CEAS methods for which calibration gas samples of known concentration are usually required.

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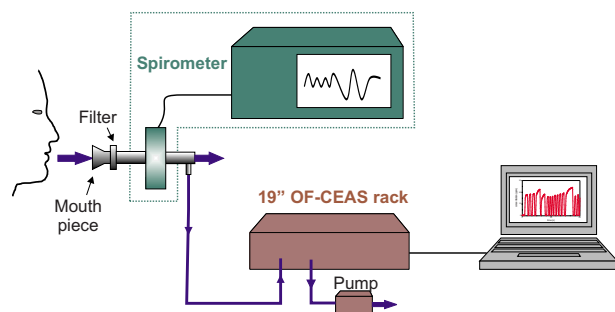


Fig. 1 Schematic of the gas handling system: OF-CEAS and spirometric breath analysis are performed simultaneously.

In this paper, we report on breath analysis performed by optical-feedback cavity-enhanced absorption spectroscopy (OF-CEAS).¹¹ This is a CEAS implementation that exploits optical feedback (OF) to achieve efficient injection of radiation from a continuous wave laser into a high-finesse ($F > 10,000$) optical cavity. Although the name does not indicate this, OF-CEAS also includes single-point CRDS measurements interleaved with fast CEAS measurements covering a full laser scan. This makes the technique calibration free¹² while benefiting of a vast improvement in the time needed for producing absorption spectra with a very low baseline noise (below 10^{-9} cm^{-1} for a single acquisition spectrum). In addition, OF-CEAS spectra possess a high precision on the frequency scale: Data points are separated by a cavity-free spectral range (FSR), $\text{FSR} \sim 150 \text{ MHz}$, with each point defined to $\sim 10 \text{ kHz}$. High spectral resolution allows high selectivity and simultaneous measurements of different compounds even over the small ($\sim 1 \text{ cm}^{-1}$) spectral region, which is accessible by rapid current tuning of a diode laser.¹³ This is a key point in breath analysis because exhaled air is a highly complex gas mixture. Linearity and reproducibility of OF-CEAS measurements are at the percent level for concentrations ranging over more than three decades.¹⁴ The small cavity volume allows sample exchange rates of several Hertz to be easily achieved. Operation at low pressure (0.2 bar, typically) contributes to fast sample exchange and also allows better separation of absorption lines thanks to the reduced pressure broadening. This improves selectivity while not penalizing the detection limit of molecular mixing ratios, because peak line intensities do not decrease significantly with pressure until the associated Lorentzian broadening approaches the Doppler broadening (typically, around 0.1–0.2 bar). The fast acquisition rate is useful in breath analysis because it allows discriminating the response of the organism with different ventilatory patterns. Finally, as previously demonstrated with field measurements in harsh environments,^{12,13,15} OF-CEAS instruments are compact and robust and can function in the field unattended or operated by nonspecialists.

In order to demonstrate the adequacy of OF-CEAS with respect to medical requirements, real-time online measurements were carried out at Bichat Hospital (Paris) on patients subject to traditional spirometric measurements of air inspired and expired for different ventilatory protocols (Fig. 1). These preliminary measurements occurred in the frame of bronchial inflammation diagnostics. Recent clinical and toxicological studies indicated a correlation between CO and bronchial

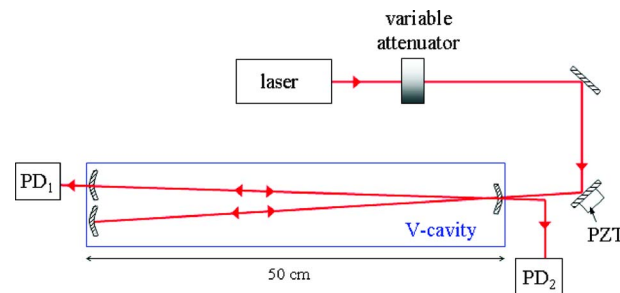


Fig. 2 Optical setup for OF-CEAS based on a V-shaped cavity. PD: photodiodes. PZT: piezoelectric actuator.

inflammation.^{16,17} Also, a recent work indicated that endogenous CO production reflected acute organ dysfunction in critically ill patients.¹⁸ Thus, the OF-CEAS spectrometer was optimized for this molecule by tuning a distributed feedback (DFB) diode laser (the same used in previous studies¹³) around 4297.7 cm^{-1} ($\approx 2.326 \mu\text{m}$ air wavelength). In this configuration, CO sensitivity is $\sim 2 \text{ ppbv}$ (parts per billion by volume) for an acquisition time of 0.1 s. Furthermore, around this same wavelength, methane (CH_4) is measured simultaneously with a sensitivity of 45 ppbv. This molecule is of interest as possible tracer for liver or renal diseases.¹ To our knowledge, there is only one previous example of fast (sub-second resolution) breath analysis by absorption spectroscopy, and it also concerned CO using a CRDS-based instrument with a sideband CO laser source in the midinfrared range (close to $5 \mu\text{m}$).¹⁹

2 Experimental Set-up

As detailed theoretical and experimental descriptions of the technique may be found in previous publications,^{11,12,15} we give here just a brief overview of the technique and technical details complementary to those mentioned above.

In a typical OF-CEAS setup (Fig. 2), a DFB diode laser is coupled to a high-finesse ($F \sim 3 \times 10^4$) three-mirror V-shaped cavity. Thanks to this particular geometry, OF from the cavity to the laser occurs only when the laser frequency matches one of the cavity resonances. When the laser frequency is swept through a resonance and resonant OF occurs, this induces a collapse of the laser spectrum width to below the cavity linewidth, plus a locking of the laser frequency, resulting in the efficient injection of the laser field into the cavity mode. Rather than the narrow and noisy transmission peak observed in the absence of OF, an intense, broad, and smooth “bump” is obtained at cavity output. It may be shown that this cavity transmission pattern is the same as it would be produced by an ideal monochromatic source slowly tuning through the cavity resonance: The frequency locking mentioned above corresponds, in fact, to a slowdown of the laser frequency tuning in correspondence to the cavity resonance. This implies that the maximum of the bump, readily measured with high S/N and normalized to the incident laser intensity, corresponds to the maximum of the cavity mode transmission function, easily related to cavity losses.

In contrast to the somewhat complex physics underlying OF-CEAS, its optical layout is simple and composed of few basic elements (Fig. 2): A collimated DFB diode laser and a

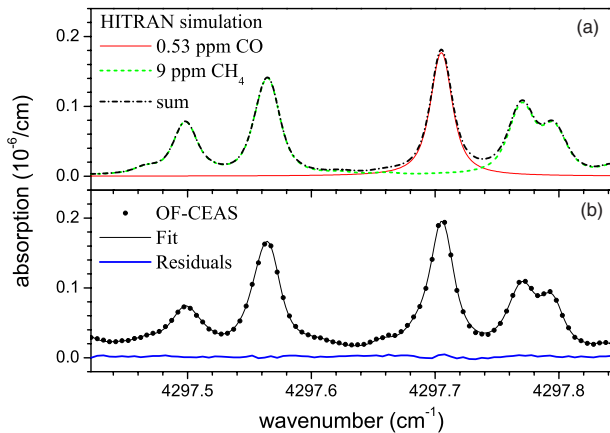


Fig. 3 (a) Plot of the HITRAN simulation of CO and CH₄ absorption lines in the spectral region scanned by OF-CEAS measurements shown in (b). A single absorption line of CO is present while there are several for CH₄. Pressure and temperature for the simulation are the same as in the measurement cell (140 mbar, 300 K). OF-CEAS measurements correspond to a spectrum of expired air, recorded in 110 ms by sweeping the DFB laser frequency. Data points are highly defined in frequency and uniformly spaced by the free spectral range of the optical cavity (148.59 MHz). The multiline fit, performed in real time, and the residuals are plotted in the same graph as the measurements.

V-shaped three-mirror high-finesse cavity, two steering mirrors (one on a low-voltage piezodisk), an adjustable attenuator (e.g., a polarizer) and two photodiodes. Contrary to other CRDS or CEAS implementations, there is no optical isolator, no fast optical switch, no high-voltage cylindrical piezoactuator for cavity-length modulation. In addition, no frequency-scale calibration devices are needed (etalon or else). Indeed data points in a OF-CEAS spectrum are obtained on the highly uniform frequency grid of the longitudinal cavity modes. It should be noted that, in the present application, the changes in analyzed gas composition, affecting its refraction index and thus the effective cavity length, give rise to a displacement of the cavity modes by almost a full cavity-free spectral range. However, the laser scan rate is sufficiently fast that the instrument is able to adapt to these changes without being perturbed. About 10 scans occur during a full change of cavity content from room air to expired air. The cavity-mode displacement during a single scan is actually negligible.

Our OF-CEAS instruments, including electronics for control and data acquisition, fit inside a 19-in. rack (45 × 59 × 13 cm) and weigh <30 kg. The optical breadboard is temperature stabilized and insulated from acoustic and mechanical vibrations. Because the gas sample is driven continuously through the optical cavity, its flow rate and pressure are servo-controlled by two proportional electrovalves placed at the inlet and outlet of the cavity, with a vacuum pump connected at the outlet. A laptop PC connected via a USB port to the control electronics, runs Labview software for real-time data processing. Such spectrometers have already run during several weeks without maintenance and outside an air-conditioned laboratory.

With respect to the OF-CEAS instrument used here, the wavenumber span of laser scans was 0.42 cm⁻¹ (an example of spectrum is given in Fig. 3), and the scanning repetition

rate was 9 Hz. However, the effective response-time limitation came from the gas exchange rate inside the measurement volume, consisting in the V-shaped high-finesse cavity. The best compromise we could find with our small membrane pump (KNF model no. N813.3ANE) was obtained by setting a flow of 8 mL/s with a cavity pressure of 140 mbar. By considering the rising and falling edges of recorded time series of breath CO and CH₄ measurements, we conclude that the effective response time for 1/e change in a concentration value is ~0.3 s. In the future, this limit could still be significantly lowered by using a larger pump to increase the flow rate or (better) to decrease the pressure in the cavity. Also, the V-shaped cavity in the OF-CEAS instrument used here was 50 cm long with a 5-mm internal-channel diameter, for a total volume of ~18 cm³, but in more recent setups, we successfully reduced the channel diameter to 4 mm, with a sample volume of ~12 cm³.

Exhaled concentrations of CO and CH₄ data were recorded while patients were subject to pulmonary functional tests using a standard medical spirometer (Jaeger Master Screen PFT by Viasys Healthcare). This apparatus records the flow rate of air that is breathed in and out as a function of time. Beside providing ventilation rates (referring to the total volume per minute of air taken into the lungs), calculation of tidal volume (volume of air displaced between normal inhalation and exhalation), and vital capacity (maximum volume of air that can be expelled after maximum inhalation) is also obtained. The gas inlet of the OF-CEAS spectrometer was connected to a pickup tube inserted transversally into the main flow through a hole into a short cylindrical section inserted after the standard disposable mouth piece and the spirometer (Fig. 1). The mouthpiece includes a filter to retain microdroplets in exhaled air to prevent patient cross-contamination and cross-contamination of the equipment.

The filter present in the mouthpiece turned out to be sufficient to avoid perturbation or degradation of the high-finesse cavity; thus, no other filtering or sample conditioning (drying...) was used. The negligibly small (and constant) flow extracted off the main breathing flow was conveyed by a 1-m 1/8-in. stainless steel tube directly to the OF-CEAS instrument.

3 Breath Analysis

Figure 3(a) gives an example of the OF-CEAS spectra recorded during exhalation by a patient. It consists of absolute linear absorption values thanks to the CRDS calibration procedure performed periodically as needed.¹² Absorption values are then computed without any calibration measurements with reference gas samples or with zero air, before or after the tests. It is to be noted that the spectrum baseline is not zero because it corresponds to the empty cavity losses (principally mirror coating scattering and absorption).

CO and CH₄ concentrations are computed in real time by a multiline fit of the absorption spectra.¹² Fitting results are converted into absolute concentration values using the HITRAN 2004 database,²⁰ or by using more precise line-intensity parameters deduced from reference spectra of calibrated gas samples preliminarily recorded by OF-CEAS.

Figure 4(a) shows a spirogram recorded while a subject with nose clips breathed spontaneously in seated position.

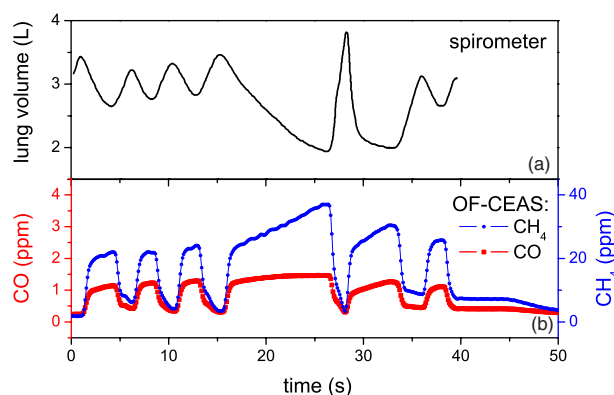


Fig. 4 (a) Lung volume recorded with a spirometer during different ventilatory phases (see text). (b) CO and CH₄ concentrations measured by OF-CEAS. Note that CO scale (left) is expanded by a factor of 10 compared to that for CH₄ (on the right). These measurements are for a nonsmoker patient.

Breathing in the tidal volume is followed by a slow deep exhalation, a deep inhalation, and a forced fast and complete exhalation. CO and CH₄ concentrations measured by OF-CEAS during the same period are plotted in Fig. 4(b). The spectrometer response time allows one to clearly identify the different ventilatory phases. Furthermore, these measurements illustrate the advantage of fast concentration monitoring during the breathing-out phase compared to a single mean-value measurement. Here, during the first deep exhalation (between 15 and 25 s), a difference in the two concentration trends can be seen: while CH₄ concentration keeps increasing, CO reaches a steady state after ~10 s. A similar behavior for CO was already reported by fast CO monitoring using a more sophisticated midinfrared laser spectrometer.¹⁹

The sensitivity of the OF-CEAS spectrometer can be estimated from the noise on the measurements of ambient air (containing ~0.24 ppmv of CO and 1.8 ppmv of CH₄). For an acquisition time of 0.3 s, the standard deviation on the fit of the spectrum is $3 \times 10^{-10} \text{ cm}^{-1}$ corresponding to 1 ppbv for CO and 25 ppbv for CH₄. This difference arises mainly from the fact that the CO absorption line is ~25 times stronger than the main one of CH₄ (Fig. 3). By averaging, the standard deviation decreases as the square root of the acquisition time, as expected for white noise. The best sensitivity is reached in ~2 s: 0.3 ppbv for CO and 7 ppbv for CH₄. As previously mentioned, the OF-CEAS spectrometer was optimized for CO monitoring but, if more accurate CH₄ measurements are required, the DFB laser can be easily tuned to a spectral region where this molecule has stronger absorption lines (but no CO line is available) allowing CH₄ monitoring with a standard deviation of 3 ppbv in 0.3 s.

The sensitivity of the spectrometer in the spectral region used in this work is well adapted to both CO and CH₄ concentrations found in exhaled air. Monitoring of nonsmoker patients (Fig. 4) have shown CO concentrations ranging from 1 to 2 ppmv (parts per million in volume), while for smokers this can rise to several tens of parts per million in volume (Fig. 5). CH₄ measurements turned to be very different from patient to patient: it could be <1 ppmv or up to 100 ppmv. Previous works were driven to study the relation between

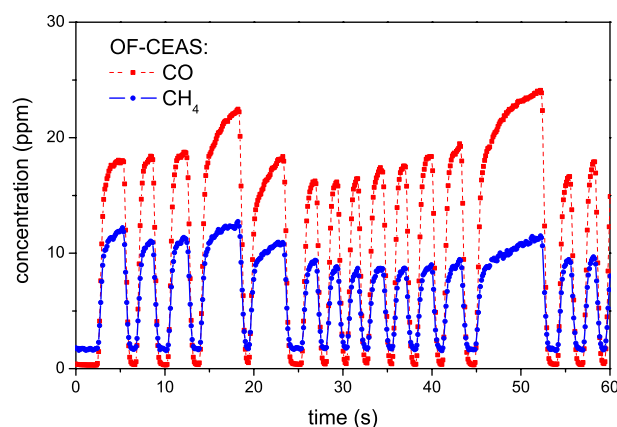


Fig. 5 OF-CEAS concentration traces in the breathing of a smoker. Note the tenfold increased CO level.

methane in exhaled breath and dietary components.²¹ In the frame of future work, it would be interesting to regularly monitor a sample of patients to study the potential correlations of concentrations values with different parameters such as the meal timetable or the diet.

4 Conclusions

These measurements demonstrate that OF-CEAS is well suited for breath analysis. The instrument we developed can be easily operated in a medical office and permits repeating measurements as often as required with low stress and no risk for the patient. The fast acquisition rate may be used for simultaneously monitoring of the variation in concentration of different species inside individual exhalation events. The accessible concentration range for CO and CH₄ is perfectly adapted for exhaled air where molar fractions of these molecules typically vary from 1 to 100 ppmv. This spectrometer can monitor, at the same time, water and ammonia, which should have medical relevance. However, measurements of these species are affected by large memory effects, which would require important changes in the gas-handling system before providing a time response comparable to those displayed for CO and CH₄. An even larger choice of molecules would be available by changing the DFB diode laser in the 2–2.7- μm range: For example, sub-parts per million in volume level detection of N₂O, H₂CO, or HCCH should be readily feasible. Extension to quantum cascade lasers is under investigation and very promising for extending OF-CEAS to sub-parts per billion in volume fast measurement of these and other species of known importance for breath analysis, such as NO, ethylene, or ethane.

This work is preliminary to more systematic clinical work. In particular, extensive diagnostic statistics will be realized with CO measurements in the frame of a study on bronchial inflammation. It should be noted that, although abnormally high CO levels are systematically produced by smoking in healthy patients, which constitutes a serious interference factor for CO breath screening, there are classes of patients where this does not constitute a serious limitation, such as children.

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