Off-Axis Integrated Cavity Output Spectroscopy with a Mid-Infrared Interband Cascade Laser for Real-Time Breath Ethane Measurements

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Cavity enhanced tunable diode laser absorption spectroscopy is an attractive method for measuring small concentrations of gaseous species. Ethane is a breath biomarker of lipid peroxidation initiated by reactive oxygen species. A non-invasive means of quickly quantifying oxidative stress status has the potential for broad clinical application. We present a simple, compact system using off-axis integrated cavity output spectroscopy with an interband cascade laser and demonstrate its use in real-time measurements of breath ethane. We demonstrate a detection sensitivity of 0.48 ppb / Hz¹/².

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1. Introduction

Measurement of breath biomarkers is a non-invasive method for diagnosing a variety of physical conditions that may require immediate medical attention. Elevated levels of ethane in breath are
indicative of possible oxidative stress, which results from lipid peroxidation, the attack of cell membranes by reactive oxygen species [1,2]. All cells have a complex antioxidant defense system since a few percent of the oxygen molecules used in normal cellular respiration are converted to reactive oxygen species by mitochondria leakage. Elevated oxidative stress has many possible causes, including exposure to ionizing radiation, biological or chemical toxins, chronic disease, physical exhaustion, and poor nutrition. A portable system capable of measuring ethane in breath at the ppb level in real time has potential use in clinical and military environments, where a quick diagnosis can enable rapid treatment.

First demonstrated in the 1970s, tunable diode laser absorption spectroscopy is a powerful technique for measuring concentrations of gaseous species [3]. Ethane has many absorption features that can be targeted for this application. Several wavelengths near 3.4 μm have relatively strong absorption lines that do not overlap strongly with spectral features of other breath gases (like water vapor, carbon dioxide, and methane). The recent development of CW tunable interband cascade lasers (ICLs) has enabled compact, milliwatt-level sources at the infrared wavelengths of interest for ethane detection. Despite the relative strength of the fundamental absorption features in the mid-infrared, detection of ppb concentrations with commercially available detectors requires long path lengths. For example, the ethane line measured in this work has a peak absorption coefficient of \( \approx 2 \times 10^{-6} / \text{ppb-m} \) at a pressure of 0.1 atm, so that detection of 1 ppb with a system having a noise equivalent detection limit of \( 10^{-3} \) (typical of simple direct ratiometric measurements) requires 500 meters of path. Many approaches to obtaining long optical path lengths from limited physical lengths have been demonstrated. The simplest approach involves a multi-pass cell, of which Herriott [4] and White [5] cells are common types. Although such a cell was used in combination with lead-salt diode
laser to demonstrate sub-ppb ethane detection in an online system [6], these cells demand relatively large apertures (and therefore cell volume) in order to achieve the required path length for the breath ethane application [7].

Several cavity enhanced absorption techniques have been proven recently, including cavity ringdown spectroscopy (CRDS [8], sometimes known as cavity leak-out spectroscopy [9]), and integrated cavity output spectroscopy (ICOS, [10,11]). CRDS involves resonant coupling of the laser beam to a high-finesse optical cavity, and requires active locking of the laser frequency to the cavity length and then rapidly turning off the injected laser power. Comparison of the intracavity optical power decay constant with and without sample present leads to a unique identification of the optical absorption and sample concentration. The active cavity stabilization and high-speed electronics required by CRDS make it less attractive for clinical applications. ICOS was developed as a means of exploiting the long path length available from a resonant cavity with highly reflective mirrors without the complexity of active locking. In order to facilitate averaging of resonant modes in the cell, off-axis ICOS (OA-ICOS) involves intentionally spoiling the spectral and spatial alignment of the laser to the cavity axial and transverse modes. In this way, the long optical path associated with the resonant absorption cavity can be realized without the need for active locking to a single axial cavity mode. The resulting system uses CW lasers where absorption (and therefore concentration) is measured using simple ratiometric detection. Sensitivity can be further enhanced through wavelength modulation and lock-in detection.

We report progress on the development of a portable instrument for real-time measurements of ethane in breath using OA-ICOS with an ICL source. To the best of our knowledge, this demonstration is the first combining the simplicity of the non-resonant off-axis
ICOS design with compact and efficient mid-infrared ICL technology. A brief overview of OA-ICOS is first presented, followed by a description of our instrument design, including descriptions of the ICL and OA-ICOS parameters. Measurement results include the ethane lineshape and real-time breath profiles from two human subjects. The final section describes future possibilities, including ways to increase sensitivity and instrument simplicity.

2. Background

2.1 Off-Axis Integrated Cavity Output Spectroscopy

Tunable diode laser absorption spectroscopy involves sweeping the laser wavelength across an absorption feature and measuring the power transmitted through a sample of interest. Absorbance is determined by normalizing the measured laser power to a reference signal, and concentration is calculated by integrating the absorbance spectrum following the Beer-Lambert law:

$$I = I_0 \exp(-\alpha CL).$$

The measured intensity $I$ scales exponentially with absorption coefficient $\alpha$ (1/ppm-m), concentration $C$ (ppm), and path length $L$ (m). The intensity $I_0$ is measured in the absence of any absorbing medium. Cavity enhancement is a good way of achieving long interaction lengths, so that small gas concentrations can be detected in a small sample volume.

Cavity ring down spectroscopy involves aligning a laser beam to a Fabry-Pérot cavity formed by highly reflective mirrors. The laser frequency is locked to the cavity axial mode, and its spatial profile ideally excites a single transverse mode in the cavity. The resulting cavity finesse can be very large, so that the effective path length in the cell given by $L_{CRDS} = L_{cell} / (1 - R)$ is limited only by the cell length $L_{cell}$ and the mirror reflectivity $R$.

However, as predicted by the well known Fabry-Pérot theory, the transmission is unity only when the laser is exactly resonant with the cavity and drops precipitously with small
deviations from resonance. Hence the full benefit of the long optical path is obtained only at the expense of active cavity stabilization.

Like CRDS, OA-ICOS employs a Fabry-Pérot cavity formed by highly reflective mirrors. The tight spectral and spatial alignment tolerance of CRDS is avoided in OA-ICOS by intentionally avoiding resonant coupling to a single cavity mode. When a laser beam is aligned to a stable optical cavity in an off-axis manner, it can be forced to follow a path that produces a series of spots tracing an elliptical pattern on each mirror before the retracing its path. A similar arrangement is used in a multi-pass Herriott cell [4], where holes in the input and output mirrors allow the beam to enter and exit the cell after the pattern becomes re-entrant. In OA-ICOS, the mirrors have no physical holes, and the spots simply retrace the original ellipse repeatedly. The collection of spots on the output mirror is imaged onto a detector, which measures the integrated cavity output from all spots together (hence the name of the technique). If the path repeats after $m$ round trips, the free spectral range of the resulting cavity is effectively $1/m$ times that of the on-axis cavity [12,13], so that the axial mode spacing decreases with the number of passes. As the axial modes get closer together, the cavity transmission becomes a weaker function of laser frequency, thereby reducing noise on the transmitted signal when the frequency is swept across the absorption line, without the need for active cavity stabilization. Noise from unwanted resonant coupling to cavity modes can be further reduced by dithering the mirror spacing, so that the modes move slightly in time. Note that the ICOS cell (like any resonant cavity) has a low-pass frequency response, with 3-dB cutoff frequency given by $f_{3dB} = 1/(2\pi\tau)$, where the cavity lifetime $\tau = L_{cell} / (c[1 - R])$. This frequency response must be taken into account when choosing a modulation frequency and detection bandwidth.
2.2 Ethane Spectroscopy

Hydrocarbons have many absorption features in the mid-infrared, mainly arising from stretching of C-H bonds. Figure 1 shows HITRAN [14] simulations showing the spectroscopy of ethane and other potential interfering compounds commonly found in breath. The ethane absorption feature near 2986.7 cm⁻¹ (3.348 μm) is relatively strong and free from overlap with methane, and is therefore attractive for use in the breath measurement application. The continuum absorption of water in this spectral region is strong only at very high concentrations that can be easily removed with a commercially available gas dryer inserted into the breath sampling line.

3. Experiment

3.1 Laser

Clinical and field applications of a breath ethane spectrometer require a compact and portable system with potential for low materials cost. Interband cascade lasers (ICLs) [15] are semiconductor sources designed to allow efficient generation of mid-infrared wavelengths through electronic transitions between energy bands formed by a quantum confinement. A series of quantum wells creates the band structure, through which electrons cascade down in energy, resulting in generation of multiple photons from a single electron. Unlike quantum cascade lasers (QCLs), which exploit intersubband transitions within the conduction band, ICLs use interband transitions (between the conduction and valence bands), whose higher energy difference translates to longer wavelengths. The laser linewidth is made suitably narrow for spectroscopic applications by integrating a distributed feedback (DFB) structure on the ICL gain medium. The laser source used in this work is a DFB ICL from Maxion Technologies. The device was
operated under liquid nitrogen cooling at a temperature of 86 K in order to reach the line of interest near a frequency of 2986.7 cm\(^{-1}\) (3.348 \(\mu\)m). The output power was \(\approx\) 4 mW at current of 25 mA. Figure 2 shows a photograph of a laser bar mounted on a submount suitable for use in a liquid nitrogen dewar. Wire bonds connect the pins to the nine lasers on the bar, one of which is connected to the drive electronics at any time. Figure 3 shows the current-dependent spectral tuning behavior and current-voltage characteristics of the laser used in this work. The displayed spectra are limited by the resolution of the FTIR spectrometer with which they were taken, and only serve to illustrate the tuning range. The laser spectral width was determined to be \(<\) 0.01 cm\(^{-1}\) by tuning the laser across a methane absorption feature of known spectral width (this data is not shown). The spectral tuning rate with current at low frequencies was measured to be \(\approx\) 0.04 cm\(^{-1}\) / mA, more than adequate for the target ethane absorption feature at the desired pressure with modest \(<\) 10 mA) peak-to-peak current modulation.

3.2 OA-ICOS System Design and Characterization

Several factors must be considered when designing a system for real-time breath measurement based on OA-ICOS. The cell volume must be minimized in order to limit its fill time, so that multiple points can be measured during a single breath. At the same time, the mirrors must be as large as possible to maximize the separation between spots and limit crosstalk from axial resonances. For clinical applications, the system should fit on a small cart that can be rolled into a medical office, so the physical length of the cell must also be limited in order to minimize the system footprint.

Based on the above considerations, the system shown in Figure 4 was implemented. The laser beam is collected by a collimating lens (\(f = 1.25\) cm) and coupled to the ICOS cell in an off-axis manner using two turning mirrors. The cell length is 57 cm and the mirror diameter is
5 cm, where the internal volume of the cell is limited to 630 cm³ by making the cell diameter slightly small than that of the mirrors, each of whose specified reflectivity \( R = 0.9998 \) and radius of curvature is 1 m. A breathing valve is used to split the breath into three paths. Commercial instruments (not shown in Figure 4) are used to measure CO and CO₂, while the third path goes through a Nafion® membrane and through the OA-ICOS cell using a small oil-free diaphragm pump (also not shown). The Nafion® removes residual moisture and any other polar molecules that are possible interfering species. A 580-μm-diameter flow-limiting orifice allowed measurements to be taken at a constant flow rate of roughly 50 standard cm³/s.

As discussed in Section 2.1, the effective path length possible with this cell length and mirror reflectivity is \( L_{\text{eff}} = L_{\text{cell}} / (1 - R) = 2850 \) m, and the cutoff frequency is \( f_{3dB} = 16.7 \) kHz. Any modulation signal used in measuring concentration must be below this value in order to appear on the detector. Therefore, we choose to ramp the laser current (and wavelength) at 500 Hz, a frequency high enough to be away from power line harmonics, but sufficiently low that any structure on the absorption trace has frequency components below \( f_{3dB} \). Three piezoelectric transducers (Thorlabs PE4) on the input mirror are modulated sinusoidally in time, dithering the mirror separation by a maximum displacement of 11.6 microns at a frequency of 178 Hz. As discussed in Section 2.1, this motion reduces the residual noise from axial alignment by moving the cavity modes. The mirrors were heated to 60°C using strip heaters wrapped around the mounting flanges, and the cell body was heated to 55°C to prevent condensation inside the cell.

Light leaving the cell is focused onto a liquid nitrogen cooled InSb detector using an off-axis parabolic reflector (f=5 cm). The detector responsivity is 2 A/W, and is followed by amplifiers and filters with transimpedance gain of \( 2 \times 10^7 \) V/A and 3-dB frequency of 10 kHz,
respectively. The measured dark current noise was 3 pA / Hz\(^{1/2}\), and typical DC voltage was 100 mV, so the detector-limited noise equivalent absorbance is 6 \times 10^{-4} / Hz^{1/2}.

The cell volume (630 cm\(^3\)) and target pressure (0.17 atm = 130 Torr) result in an effective air volume of 108 standard cm\(^3\). A typical healthy individual can produce roughly 1000 cm\(^3\) in a single exhalation, so the relatively low cell volume is flushed about 10 times in a single online measurement. Data acquisition electronics in a personal computer were used to tune the laser frequency with a current ramp and capture the detector output voltage. Software and a graphical user interface were developed to calculate and report running averages of absorption spectra and integrated absorbance in real time.

The ethane absorption feature of interest near 2986.7 cm\(^{-1}\) is a group of unresolved transitions, for which the HITRAN database contains only calculated oscillator strengths and no measured data. Single-pass measurement of a calibrated mix of ethane in nitrogen (949 ppb) showed considerably weaker (roughly half) the peak absorption than that predicted by HITRAN. Figure 5 shows a simple single-pass ethane absorption measurement near the line of interest along with a HITRAN calculation. The highly reflective mirrors were replaced with transparent windows for this measurement, which was made using a high concentration so that the single 57 cm path length would result in strong absorption signal. The measured peak absorption coefficient is 1.7 \times 10^{-3} / ppm-m at 85 Torr (slightly above 0.1 atm).

In order to estimate the actual path length in the OA-ICOS cell, a calibrated low-concentration mix of 100 ppb ethane in nitrogen was measured. Figure 6a shows the measured detector voltage when the laser current was ramped linearly from 2 mA (below threshold) to 30 mA. Note that the frequency and amplitude are inversely proportional. Cursors (not shown) defined in the graphical user interface specify the part of the waveform where the laser is below
threshold for zero offset correction. A second set of cursors is used to define sections away from
the absorption dip, where a third-order polynomial is fit to the voltage baseline (dashed curve).
Figure 6b shows the absorbance spectrum calculated by normalizing the detector voltage to the
baseline fit. The peak value of this lineshape is used to determine the path length using the
measured absorption coefficient \(1.7 \times 10^{-3} / \text{ppm-m}\). In this example, the peak absorbance is
0.23, so that the effective path length is \(L_{\text{eff}} \approx 1350 \text{ m}\), from which the inferred mirror reflectivity
is \(R_{\text{eff}} = 0.9996\). Combining this path length and absorption coefficient with the detector-limited
noise equivalent absorbance \((6 \times 10^{-4} / \text{Hz}^{1/2})\) predicts a noise equivalent detection limit of
0.13 ppb / Hz^{1/2}.

The path length calibration was performed periodically and recorded for use in scaling
the measured concentrations in the breath samples. The trace shown uses 0.5 second averaging
(250 sweeps at 500 Hz), so the effective system bandwidth including the 10 kHz low-pass filter
is 40 Hz. The minimum detectable absorbance is determined by the fluctuations in the wings of
the absorbance spectrum. In this case, the measured minimum detectable absorbance is
\( \approx 7 \times 10^{-3} \), so the noise-equivalent absorbance is \(1.1 \times 10^{-3} / \text{(Hz)}^{1/2}\). With the measured path
length (1350 m) and absorption coefficient \((1.7 \times 10^{-3} / \text{ppm-m})\), the noise-equivalent detection
limit is 0.48 ppb / (Hz)^{1/2}. This value is higher than the detector noise limit predicted above. The
extra noise comes from incomplete suppression of the on-axis resonances in the cavity. Off-axis
alignment should suppress these resonances, and has been proven effective at near-infrared
wavelengths [12]. However, the non-ideal beam profile of the mid-infrared ICL results in
overlap of spots on the mirrors, which produces the residual resonance. One solution to this issue
is better spatial filtering before coupling to the cell (at the expense of lower overall power
transmission to the detector).
3.3 Breath Measurements

The Johns Hopkins University Bloomberg School of Public Health Institutional Review Board approved the protocol used in this study. Informed verbal consent was obtained from all study participants prior to sample collection. Breath measurements were performed by the subject breathing through a disposable low-pressure-drop bacterial filter (Resp-Bac™, Princeton, MN) into the mouth port of a three-way non-rebreathing valve (NRV, Hans Rudolph, Inc., Kansas City, MO). The expiratory port of this valve has a restrictor that controls the flow of the exhaled breath to 50 ml/s at a mouth pressure of 10 cm of water. The breath is sampled from a single breath using a restricted breathing maneuver. A portion of the breath was drawn into the dryer apparatus at the cell input. Room air was found to have a finite and variable background ethane concentration (1-10 ppb), so a short amount of time with room air background was recorded before and after each breath sample. Carbon monoxide and carbon dioxide concentrations were simultaneously recorded using commercial instruments (Logan Research Model LR 250 CO monitor and Novametrix Model 615 capnograph). Correlation between the temporal variations of the three gases can provide important physiological information. The overall system rise time for the ethane spectrometer was measured to be roughly 2.5 seconds.

Cigarette smokers are known to have elevated levels of ethane in breath. A typical breath sample from a smoker is shown in Figure 7, where measurements were taken 30 minutes after the subject last smoked a cigarette. The subject was instructed to start breathing after 20 seconds, so that the room air background could be recorded. The ethane data are shown with a 2-second running average. Correlation between the CO₂ and ethane waveforms is evident. The peak CO concentration is 23 ppm. Data from a non-smoker with elevated ethane is shown in Figure 8. The ethane and CO₂ traces are again correlated, though the CO level is considerably lower for the non-smoker.
4. Discussion and Conclusions

We have designed and implemented a spectrometer for real-time measurements of ethane in breath using off-axis ICOS and an interband cascade laser. The noise-equivalent detection limit was shown to be 0.48 ppb / (Hz)$^{1/2}$. The instrument concept was proven through online measurements of breath from subjects exhibiting elevated ethane levels. The signal-to-noise ratio in these profiles is not quite adequate for measurements of a population of “normals”, who exhibit typical exhaled breath ethane levels down to or below 1-2 ppb [17,18]. Clinical applications will ideally require higher signal to noise ratio. For example, Halmer et al demonstrated online breath measurements with a detection limit of 0.27 ppb / (Hz)$^{1/2}$ in [16] using cavity leak-out spectroscopy with a mid-infrared light source based on bulk difference frequency generation. Similarly, Skeldon et al in [6] showed detection of 0.2 ppb in 0.8 seconds (equivalent to 0.18 ppb / (Hz)$^{1/2}$) in online measurements with a multi-pass cell and a lead salt diode laser. The OA-ICOS system proposed in this paper can be improved to achieve lower detection limits through several means. A large contributor to the system noise observed in this system is incomplete suppression of the residual on-axis resonances. This noise can be reduced by improving the spatial mode of the laser beam through spatial filtering or fiber coupling. Increasing the laser power will also enable improved performance. We are exploring both options for the next generation system, as they may allow reaching the performance of cavity ringdown systems with a single diode laser source and a simple OA-ICOS architecture.

Despite having the mirrors heated to well above room temperature, we observed measurable degradation in mirror reflectivity over time after mirror cleaning and mounting on the cell. This drop resulted in lower path length (and therefore sensitivity) over time. The
reflectivity could be restored by simple solvent cleaning, indicating possible contamination by condensed liquids. A cold trap (as used in [16]) may be needed to prevent this degradation.

In ongoing studies, we will incorporate compact laser drive and detection electronics in a form factor suitable for use in a clinical environment, where the instrument can be rolled into and out of a laboratory on a cart as needed. We will also investigate the use of wavelength modulation spectroscopy for increased sensitivity and compact electronics, using a platform developed at PSI for remote methane leak detection [19]. This technology has been used to develop a portable carbon dioxide sensor based on OA-ICOS for use in climate change studies [20]. We will also investigate the possibility of increasing the power coupled through the cell. More power naturally increases the system signal to noise ratio by increasing the DC power on the detector. Higher power also allows flexibility in spatial filtering of the beam for optimal off-axis alignment, where better separation between spots on the mirrors results in a reduction in optical noise from residual on-axis resonance.

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References


List of Figures

Fig. 1: HITRAN calculations showing spectroscopy of ethane and potential interfering species in the spectral region of interest

Fig. 2: Photograph of laser submount. The laser bar containing nine emitters is on the top edge and wire bonded to the submount pins

Figure 3: Laser characteristics

Fig. 4: Photograph of OA-ICOS ethane spectrometer. Beam from laser in dewar is collimated and aligned to cell. Subject breath passes through filter and valve, and then is dried by Nafion tubing before passing through a flow-limiting orifice to the cell. Signal from InSb detector is amplified and processed by PC. Pump, CO monitor, and CO₂ capnograph not shown

Fig. 5: Single-pass absorption measurement of ethane line near 2986.7 cm⁻¹ with HITRAN calculation. Measured peak absorption coefficient is $1.7 \times 10^{-3}$ / ppm-m, significantly lower than that predicted by HITRAN

Fig. 6: Measurements of 100 ppb bottled mix at 85 Torr, a) Detector signal with baseline fit, b) Absorbance spectrum calculated from detector signal – cursors indicate limits for calculating integrated absorbance
Fig. 7: Measurements of CO, CO$_2$, and ethane from subject 30 minutes after smoking cigarette; ethane data shown with 2 second running average

Fig. 8: Measurements of CO, CO$_2$, and ethane from non-smoker with elevated ethane signal; ethane data shown with 2 second running average
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Fig. 2.
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