



Development of Quantum-Cascade Laser Based Biosensor Technology

Thomas L. Harman [UHCL] / Frank K. Tittel [Rice U] / John C. Graf [NASA-JSC] / Yury Bakhirkin [UHCL]

Abstract

The principle objective of this project is the development of new types of sensitive, selective, real-time gas sensors based on continuous wave and pulsed quantum cascade lasers for various chemical sensing applications ranging from medical diagnostics to monitoring spacecraft air quality. Tunable laser absorption spectroscopy in the mid-infrared spectral region is a sensitive analytical technique for trace gas quantification. Nitric Oxide (*NO*) detection from exhaled breath is of particular interest for the diagnosis of lower airways inflammation associated with a number of lung diseases and illnesses. Investigation focuses upon the feasibility of detecting *NO* in expired human breath as a potential non-invasive medical diagnostic tool. A gas analyzer based on a CW mid-infrared quantum cascade laser operating at ~ 5.2 μm and off-axis integrated cavity output spectroscopy (ICOS) has been developed to measure *NO* concentrations in human breath. A compact sample cell, 5.3 cm in length with a volume of < 80 cm^3 , suitable for on-line and off-line measurements during a single breath cycle, has been designed and evaluated. A noise-equivalent (SNR = 1) sensitivity of 10 parts-per-billion by volume (ppbv) of *NO* was achieved. The combination of off-axis integrated cavity output spectroscopy with wavelength modulation resulted in a 2 ppbv noise-equivalent sensitivity.

Introduction

Nitric oxide detection is important for a number of applications, such as atmospheric pollution monitoring,¹ vehicle exhaust control,^{2,3} and non-invasive medical diagnostics of various lung diseases by means of *NO* concentration measurements in expired breath.^{4,5} In fact, exhaled breath contains a large number of molecular species at ultra-low concentrations (ppbv), some of which are possible biomarkers for a variety of human illnesses and diseases. Trace gas quantification in breath is inherently non-invasive and, in some cases, can obviate the need for invasive surgical procedures, such as biopsies. *NO* is involved in many biochemical processes and performs important functions in human physiology, such as immune reactions, regulation of platelet function, and neurotransmission.⁶⁻¹³ In 1998, the Nobel Prize in Physiology and Medicine recognized discoveries concerning the role of *NO* in the cardiovascular system.

DIAGNOSIS—Super-sensitive sensors, capable of analyzing human breath, are providing a new methodology for medical diagnosis of diseases. Dr. Thomas Harman, Chair of the Department of Computer Engineering at UHCL, is a principal investigator in this advanced research which involves leading scholars at Rice University in Houston.



NITRIC OXIDE DETECTION—Dr. Frank K. Tittel, Abercrombie Professor at Rice University in the Department of Electrical and Computer Engineering, develops sensors as non-invasive devices to diagnose human breath for the detection of diseases and human illnesses in the lower airways.

Concentrations of oral exhaled nitric oxide (*eNO*) originating from the lower airways in the absence of asthma and acute respiratory illnesses typically vary from 5 to 20 ppbv.^{9,10} Nasal nitric oxide (*nNO*) originating from the nasal cavity has higher concentrations in the range of 40 to 200 ppbv.^{9,10} Humming, a voice maneuver, has been reported to produce 200 to 500 ppbv of *NO* in expired breath.^{6,8}

Concentrations of *eNO* are reduced below typical levels for patients with cystic fibrosis¹² and for smokers.¹³ Elevated *eNO* concentrations in expired breath are principally associated

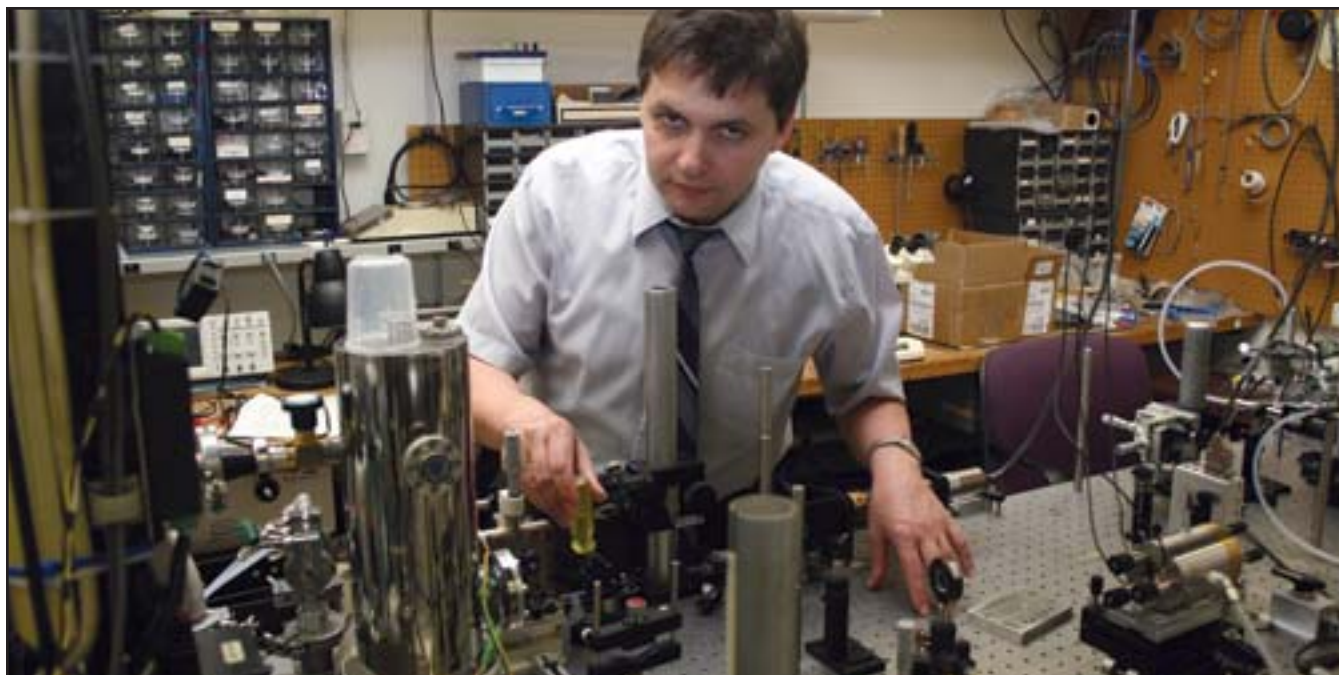
with inflammation of the lower airways. One of the most investigated inflammatory processes is asthma. Asthma is a chronic inflammatory disorder of the lower airways, which results in increased levels of *eNO* in human exhaled air.⁹ Non-invasive diagnostics of asthma are of great importance since it afflicts millions of adults and children worldwide. Early diagnosis and intervention in asthma cases can lead to a significant reduction in hospitalizations. Typical asthmatic *eNO* levels in exhaled breath range from 20 to 80 ppbv.^{9,10} Therefore, *NO* detection and quantification at ppbv levels in human exhalation is an important medical diagnostic challenge.¹⁰

A number of different analytical methods, both optical and non-optical, have been developed to measure ultra low concentrations of various gases and, in particular, *NO*. Non-optical approaches include mass-spectrometry and gas chromatography. The main drawbacks of these techniques are size and cost of the apparatus, the need for sample conditioning and consumables, and the inability to make real-time on-line measurements. The most advanced optical techniques are based upon either chemiluminescence or laser absorption spectroscopy. Chemiluminescence is widely applied in measuring *eNO* levels from both children and adults. This is a FDA approved technique with a minimum detection sensitivity of < 1 ppbv.¹¹ Two companies, Sievers and more recently Aerocrine, have developed analyzers based on a chemiluminescence approach for high precision real time *NO* monitoring. This technique requires calibration at the same humidity and temperature as breath and measures *NO* or *NO_x* gases by reducing them to *NO*.

Another optical method for precise *NO* measurements is based on the Zeeman and Faraday effects, making use of the paramagnetic properties of *NO*. Background-free Faraday Laser Magnetic Resonance Spectroscopy (Faraday-LMRS)

measures only nitric oxide in human breath.^{8,14,15} The method was evaluated in a clinical environment for on-line *NO* monitoring with a detection sensitivity of ~1 ppbv.⁸ However, the need for a magnetic field of more than 1000 Gauss and its inability to measure non-paramagnetic gases limits the applicability of Faraday-LMRS for clinical diagnostics. An ideal *eNO* sensor platform should be able to measure other gases in exhaled breath (for example, *CO* and *CO₂*) for calibration and standardization purposes.¹⁶

In this work, we investigate tunable laser absorption spectroscopy (TLAS) as an effective technique for sensitive and selective *NO* monitoring. The mid-infrared spectral range is ideally suited for TLAS since most molecular gases possess strong fundamental rotational-vibrational lines in this region. The *NO* molecule has a strong absorption band around 5.2 μm (1900 cm^{-1}) with a highest line intensity of $\sim 6.04 \times 10^{-20} \text{ cm}^{-1}/(\text{molecule} \times \text{cm}^{-2})$ for the R(7.5) lines at 1903.1 cm^{-1} . High resolution TLAS with a tunable single frequency mid-IR laser can resolve *NO* absorption features and selectively access *NO* spectral lines at low (≤ 100 Torr) pressure without interference from *CO₂* and *H₂O*. This is particularly important in the development of biomedical gas sensors for breath analysis. Several types of CW spectroscopic laser sources operate in the mid-IR spectral region. These include the optical parametric oscillator, coherent sources based on different frequency generation, lead-salt diode lasers, and quantum cascade (QC) lasers. QC lasers were selected for this work because of their potential to meet the spectroscopic source requirements for compact, sensitive and selective gas detectors.¹⁷ Two continuous wave distributed feedback (DFB) QC lasers were utilized in our sensor architecture, as described in section 2. Each of these lasers has a spectral width of ≈ 3.0 MHz, and, together, they provide a total single mode tuning



BREATH ANALYSIS—Dr. Yury Bakhirkin, Post-Doctoral Aerospace Fellow, investigates tunable laser absorption spectroscopy (TLAS) as an effective technique for sensitive and selective monitoring of carbon dioxide in the lungs.

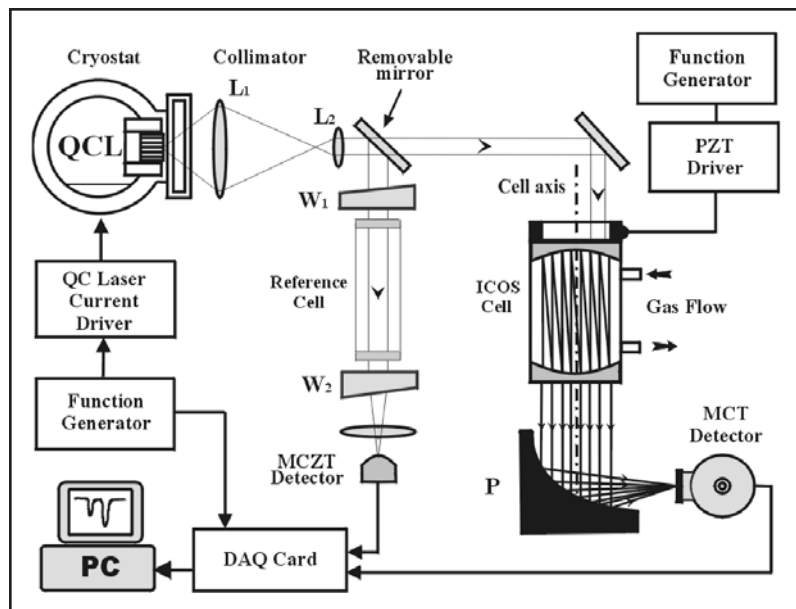


Figure 1. Off-Axis ICOS experimental arrangement; L1 and L2 are two collimating lenses, W1 and W2 are two 30° wedged uncoated ZnSe windows for frequency calibration, QCL—quantum cascade laser inside the cryostat, and P is an off-axis parabolic mirror.

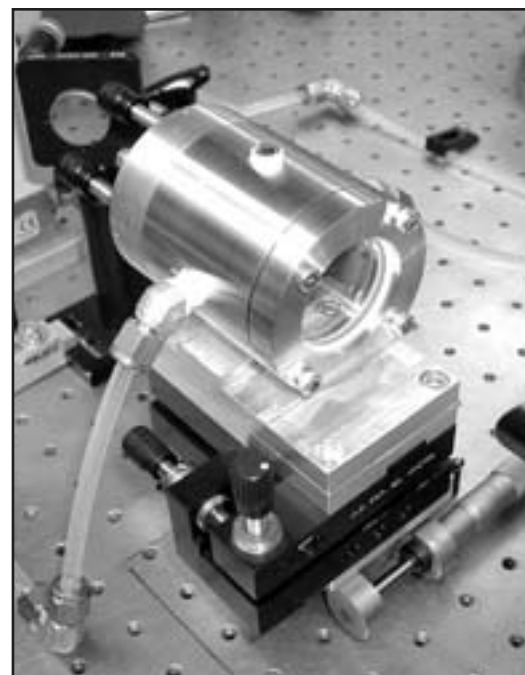


Figure 2. Compact OA- ICOS Gas Cell

range of $> 10 \text{ cm}^{-1}$. In order to obtain detection sensitivities at ppbv or sub ppbv levels, long optical pathlengths ($\geq 30 \text{ m}$), usually realized in multipass absorption cells, are used.^{16, 18-20} As can be deduced from the results presented by Nelson et al.,²⁰ a sensitivity of $0.7 \text{ ppb/Hz}^{1/2}$ can be achieved using a multipass cell with a 36 m path and a 0.3 liters volume (Aerodyne Research, Inc., Model AMAC 36).

Another approach for achieving long optical pathlength and minimizing the gas cell volume is the use of a cavity that consists of two ultra low-loss dielectric mirrors ($\sim 100 \text{ ppm}$) separated by a few cm. In this manner, effective optical pathlengths of hundreds of meters can be realized. Absorption in the cavity can be measured from the change in the cavity ringdown time or from the time-integrated cavity output. The first method, known as cavity ringdown spectroscopy (CRDS), has been successfully applied to measure *NO* concentration at ppbv levels.^{17,21}

The second approach for measuring time-integrated cavity output is based upon the excitation of a dense spectrum of transverse cavity modes and time averaging of cavity output. In this scheme, the more modes are excited, the easier it is to suppress the related cavity throughput fluctuations. This method was first reported by two groups almost simultaneously and is referred to as integrated cavity output spectroscopy (ICOS) or cavity enhanced absorption spectroscopy (CEAS).^{22,23} ICOS is less technically demanding than CRDS, as it does not require fast time-resolved measurements and either high laser pulse energies or narrow cw laser linewidths. ICOS with an on-axis laser-cavity configuration has been used to measure *NO* with a detection limit of 16 ppbv.¹⁹ Off-axis ICOS (OA-ICOS) was proposed and implemented in the near IR because it provides increased spectral density of cavity modes and, thus, minimizes the noise in the

resulting absorption spectra.²⁴⁻²⁶ In OA-ICOS the laser beam is directed off-axis with respect to the cavity axis. In this paper, we describe the use of the OA-ICOS technique with a CW mid IR QC laser to measure *NO* concentrations in a compact absorption cell (76 cm^3). A *NO* analyzer with a noise-equivalent (SNR = 1) sensitivity of 10 ppbv for OA-ICOS and 2 ppbv when using OA-ICOS with wavelength modulation was demonstrated and used to detect *NO* in nasal breath samples. The time required for data acquisition to obtain the reported sensitivity was 15 s in both cases.

Technical Plan and Equipment

The experimental arrangement is shown in Fig. 1. The laser source utilized in the experiments is a continuous wave distributed feedback quantum cascade laser (CW DFB QC laser) manufactured by Lucent Technologies Inc, operating at a single frequency at liquid nitrogen (LN_2) temperature.²⁷ A laser chip containing several QC lasers with output at $\sim 5.2 \mu\text{m}$ ($\sim 1920 \text{ cm}^{-1}$) is mounted on a cold finger inside a LN_2 cryostat with one laser selected for usage. For better beam stability, a special design of the LN_2 cryostat (Cryo Industries Model # DET-1746-SLN) was used. The cryostat has a rigid support for the LN_2 reservoir, which prevents mechanical displacement of the cold finger to which the QC laser is attached during the refilling process of the cryostat and the entire LN_2 holding period. A current driver (Wavelength Electronics, MPL-5000) is used to operate the QC lasers. A current ramp with a maximum frequency of 5 kHz was applied to tune the laser frequency. We used two QC lasers in this work with respective tuning ranges of $1911.5\text{--}1917.5 \text{ cm}^{-1}$ and $1918.0\text{--}1923.0 \text{ cm}^{-1}$. The threshold current of each laser is $\sim 300 \text{ mA}$ and the maximum output power varies from 18 to 25 mW (depending on the wavelength and laser).

The QC laser radiation was collimated with two positive lenses (see Fig. 1). The first lens L_1 is an aspheric $ZnSe$ lens with an effective focal length (EFL) of 25.4 mm, a diameter of 27.94 mm, and broadband antireflection coatings (3-12 μm). The second lens L_2 is a CaF_2 bi-convex lens with a diameter of 12.7 mm and an EFL 13 mm. The collimator length is 130 mm, the distance between the QC laser output facet and L_1 is 18 mm. Approximately 80 percent of the emitted power is collected assuming a divergence of 60° and a Gaussian beam envelope. The collimated beam diameter is about 3 mm and can be made divergent or convergent by changing the position of L_2 relative to L_1 . This degree of freedom is important for optimal laser cavity mode coupling. Another advantage of the collimator is that by its use a simple routine is possible to perform optical alignment and re-alignment for different QC lasers on the same chip. A $He-Ne$ laser is used for coarse alignment, since the 5.2 μm radiation is not visible. The final alignment of collimating lenses was performed with an IR camera (Thermovision).

The laser beam exiting the collimator is directed to the compact OA-ICOS cavity described in section 2 (see also Fig. 2). For spectroscopic measurements, laser radiation is scanned over a specific spectral range containing the gas absorption features of interest. Laser radiation is coupled into the cavity via the accidental coincidence of the laser frequency with a cavity mode.

Radiation exiting the cell is focused onto a LN_2 cooled photovoltaic $HgCdTe$ detector (1 mm^2 sensitive area) with a built-in 10^4 V/A transimpedance preamplifier (Kolmar Technologies, Model KMPV8-1-J1/DC). An off-axis parabolic mirror (3 inch in diameter and 3-inch focal length, 1 inch = 25.4 mm) is used to collect the transmitted cavity output, which was focused onto the detector area, thereby maximizing the light signal. A PC with a LabView 6.1 software based data acquisition and processing system is used for data accumulation, storage, and time averaging. Averaging of many laser frequency scans results in smoothing of the cavity resonance spikes.

The reflection coefficient or mirror losses at a specific wavelength can be estimated from the cavity decay time of the TEM_{00} mode, assuming that the reflectivity is uniform across the entire mirror surface.²⁸ The intensity of a light pulse, trapped in an optical resonator, decreases exponentially with a time constant determined by the cavity finesse. In the case of a stable evacuated cavity formed by two identical mirrors and negligible Mie and Rayleigh scattering losses, the decay time τ_{empty} for the TEM_{00} cavity mode or cavity ringdown time is defined only by the cavity length and the reflection coefficient (R) of the mirrors

$$\tau_{empty} = \frac{L}{c} \frac{1}{(1 - R)} \quad (1)$$

where L is the cavity length (5.3 cm) and c is the speed of light. For equation (1) we should consider the maximum experimental value of the decay time since the TEM_{00} mode has the lowest diffraction losses and, thus, the maximum ringdown time. We measured $\tau_{empty} = 0.7 \mu\text{s}$, hence $R \approx$

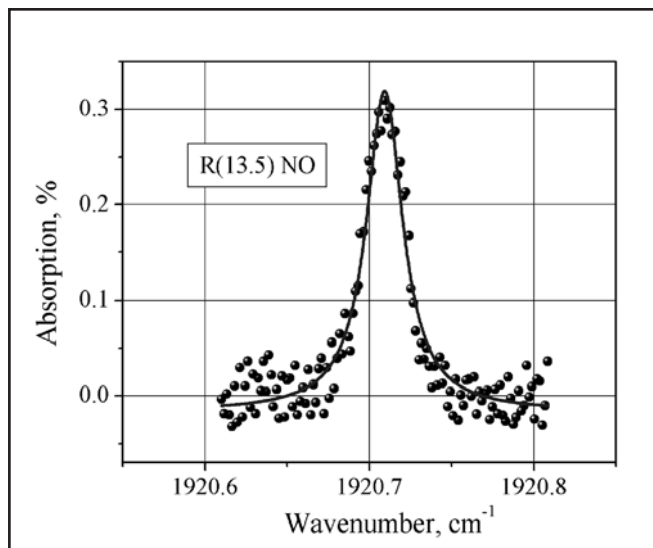


Figure 3. Voigt Fit of the R(13.5) NO Absorption Line Data (same 95 ppbv NO in N_2 mixture).

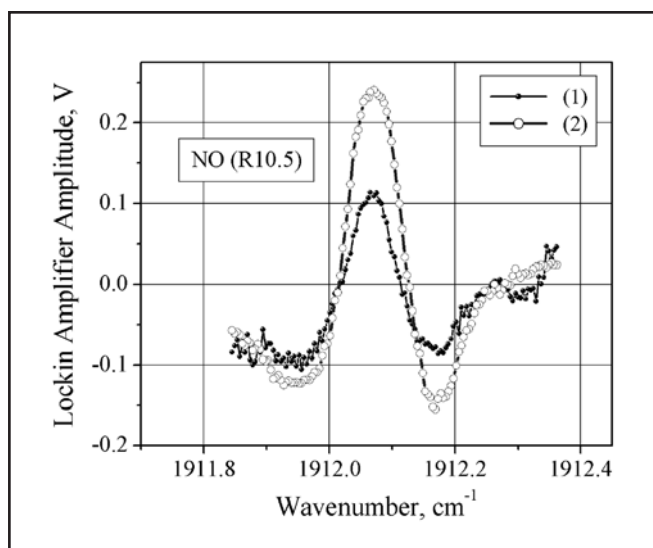


Figure 4. NO concentration measurement from nasal breath (1) using wavelength modulation applied to OA-ICOS. A NO Concentration of 53 ppbv was measured in nasal breath. (2) NO: N_2 calibration mixture, 95 ppbv NO.

99.975%, or 250 ppm in terms of mirror losses. The QC laser linewidth has been estimated as described by Kosterev et al.²¹ From the cavity transmission resonance spikes, we obtain 2.9 MHz and 3.5 MHz for the linewidths of the two cw QC lasers used in this work.

The principal limitation to the detection sensitivity of ICOS is the cavity mode noise that results from incomplete averaging of the optical cavity transmission. This problem becomes more pronounced in the case of a short optical cavity. This can be explained by the larger FSR and, hence, wider gaps between the cavity transmission peaks, as well as higher mechanical stability of the short cavity. Our observations have shown that even for off-axis beam alignment, natural cavity instabilities like acoustic noise and temperature

variations are not sufficient to average out the cavity mode structure. Therefore, in addition to laser scanning, the length of the cavity is dithered by PZT actuators at 200 Hz. The PZT mirror displacement amplitude corresponds to > 7 FSR of the modes resulting from off-axis alignment and, therefore, is sufficient to wash out the throughput spikes. The absorption signal is extracted from a measurement of the time-integrated light intensity that leaks out of the cavity.

A gas flow system enables us to control flow rate and perform NO concentration measurements at reduced pressures (in order to eliminate line broadening and minimize interference by other gases) and known flow conditions. A pressure controller can provide gas cell pressures ranging from 1 to 100 Torr. The gas flow system is also configured to permit off-line NO measurements of breath samples collected in special medical breath bags (Quintron, Model # QT00830-P).

Experimental Activity

According to the HITRAN database,²⁹ the fundamental absorption band for NO is located in the region from 1780 cm^{-1} to 1950 cm^{-1} . The optimum NO target wavelength is 1900.08 cm^{-1} for the R(6.5) component when taking into account maximum line intensity and minimum interference from nearby absorption lines from other trace gas species.³⁰ The maximum intensity for R(6.5) lines is $S = 6.0 \times 10^{-20} cm^{-1}/(molec \times cm^{-2})$. However, the two QC lasers available for our investigations cover the spectral ranges:

- 1) 1918.0–1923.0 cm^{-1} (QC laser #1), and
- 2) 1911.5–1917.5 cm^{-1} (QC Laser #2),

which do not overlap this line. Therefore a different choice of target wavelength was required.

The OA-ICOS technique was tested using two calibration mixtures of NO in N_2 (Scott Specialty Gases, Inc) with known NO concentrations of 490 ppbv and 94.9 ppbv, respectively, at a pressure of 100 Torr. The NO concentration for the first mixture was independently measured using CRDS²¹ and, for the second calibration mixture, the NO concentration was determined by means of chemiluminescence. The time integrated transmitted intensity of the OA-ICOS cell filled with two $NO-N_2$ calibration mixtures was measured for 5×10^4 averaged scans of the R(13.5) NO line at 1920.7 cm^{-1} . The laser scan frequency was 3 kHz. The measured absorption spectra are in good agreement with the HITRAN simulation for an effective absorption pathlength of 80 m. An estimate of the detection sensitivity can be obtained from the deviation of the best-fit coefficients for a Voigt fit of the NO absorption line, which yields a noise equivalent sensitivity of 10 ppbv for 1σ deviation of the best-fit coefficient. Experimental results together with the fitting curve are given in Fig. 3.

Feasibility experiments using OA-ICOS and wavelength modulation spectroscopy (WMS)³¹ were performed in order to determine biogenic NO concentrations from nasal exhaled air. The QC laser #2 current was scanned across the NO line by a triangular current ramp at a frequency of 8 Hz. A sinusoidal dither of $f \sim 5$ kHz (maximum for the laser current driver used in this work) was superimposed on the QC laser

current ramp. The second harmonic ($2f$) signal of the OA-ICOS cavity output was sampled with a lock-in amplifier and averaged using a data acquisition card (DAQ Card 6062E, National Instruments) and LabView software. The amplitude of the $2f$ spectra is directly proportional to the NO concentration, which can be retrieved from calibration measurements. Fig. 4 depicts $2f$ spectra of the R(10.5) NO line at 1912.07 cm^{-1} for the 95 ppbv $NO:N_2$ calibration mixture as well as for collected nasal NO . The nNO concentration was deduced to be 53 ppbv. It is apparent from these results (see Fig. 10 and Fig. 11) that wavelength modulation spectroscopy yields a better detection sensitivity than direct absorption spectroscopy. The increase of the SNR is > 5 and the noise equivalent detection sensitivity is ~ 2 ppbv. The SNR can be further improved by using a faster QCL current driver, which will enable us to achieve optimum values for the laser current ramp and sinusoidal dithering frequencies.

Conclusions

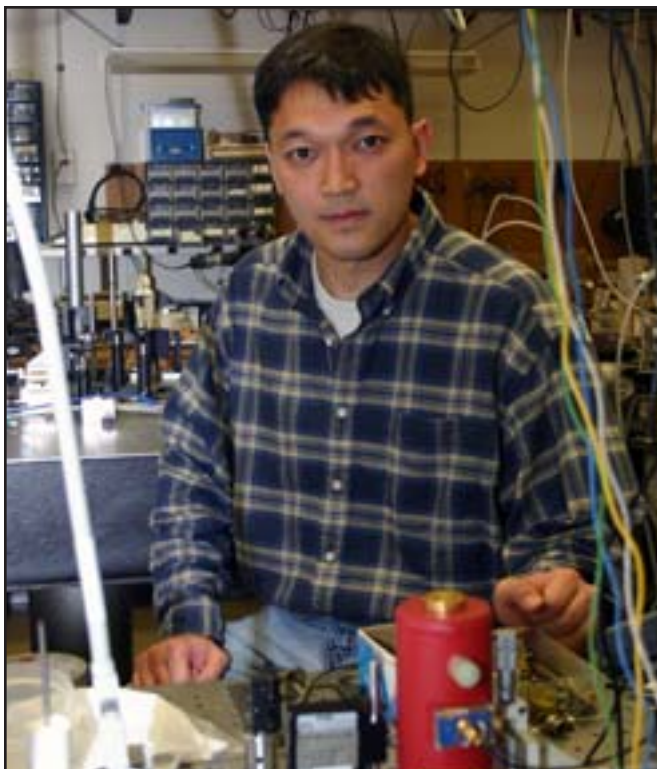
A CW QC laser-based NO sensor using a compact OA-ICOS cell has been developed, and its performance characteristics have been investigated and compared with previous gas analyzer designs based on CRDS and ICOS. The OA-ICOS-based sensor offers a similar noise equivalent sensitivity of 10 ppbv as a CRDS based sensor platform, but is easier to align and more robust in long term operation. Feasibility experiments of biogenic nNO concentration measurements from the nasal cavity have been performed by adding wavelength modulation to improve the detection sensitivity. A wavelength modulation spectroscopy noise equivalent sensitivity of 2 ppbv has been achieved. The total data acquisition and averaging time was 15 s in the both cases. Although this time exceeds a typical breath cycle duration, the time required for a single data point measurement is much shorter (< 1 s). Therefore, the described NO measurement procedure can be modified to measure NO concentration as a function of breath cycle phase. To achieve this goal, primary data should be collected during several breath cycles and subsequently sorted and averaged separately depending on the breath-cycle phase.

Acknowledgments

We acknowledge the assistance of Dr. Anatoliy Kosterev in providing numerous useful discussions and support. Financial support of the work performed by the Rice group was provided by the Institute for Space Systems Operations (ISSO), the National Aeronautics and Space Administration (NASA), the Texas Advanced Technology Program (TATP), the National Institute of Health (NIH) via a sub contract from Physical Sciences, Inc., and the Welch Foundation.

References

- ¹M. W. Sigrist. *Air Monitoring by Spectroscopic Techniques*. New York: John Wiley & Sons, 1994.
- ²D. D. Nelson, J. L. Jimenez, G. J. McRae, M. S. Zahniser, and C. E. Kolb. "Remote Sensing of NO and NO_2 Emission from Heavy-Duty Diesel Trucks Using Tunable Diode Lasers," in *Application of Tunable Diode and Other Infrared*



JET PROPULSION LABORATORY—Dr. Chung M. Wong, Post-Doctoral Fellow at the NASA Jet Propulsion Laboratory, joined researchers at Rice University laboratories to study a new type II interband cascade laser operating at 3.5 microns.

Sources for Atmospheric Studies and Industrial Processing Monitoring II. Ed. Alan Fried. *Proc.*, SPIE 3758 (1999): 180-90.

³W. H. Weber, T. J. Remillard, R. E. Chase, J. F. Richert, F. Capasso, C. Gmachl, A. L. Hutchinson, D. L. Sivco, J. N. Baillargeon, and A. Y. Cho. "Using a Wavelength-Modulation Quantum Cascade Laser to Measure *NO* Concentration in the Parts-per-Billion Range for Vehicle Emissions Certification," *Appl. Spectrosc.* 56 (2002): 706-14.

⁴S. A. Kharitonov and P. J. Barnes. "Clinical Aspects of Exhaled Nitric Oxide," *Eur. Respir. J.* 16 (2000): 781-92.

⁵S. A. Kharitonov and P. J. Barnes. "Exhaled Markers of Pulmonary Disease," *Am. J. Respir. Crit. Care Med.* 163 (2001): 1693-722.

⁶B. Gaston, J. M. Drazen, J. Loscalzo, and J. S. Stamler. "The Biology of Nitrogen Oxide in the Airways," *Am. J. Respir. Crit. Care Med.* 149 (1994): 538-51.

⁷K. Bhagat and P. Vallance. "Nitric Oxide 9 Years Out," *J. R. Soc. Med.* 89 (1996): 667-73.

⁸P. Murtz, L. Menzel, W. Bloch, A. Hess, O. Michel, and W. Urban. "LMR Spectroscopy: A New Sensitive Method for On-Line Recording of Nitric Oxide in Breath," *J. Appl. Physiol.* 86 (1999): 1075-80.

⁹D. H. Yates. "Role of Exhaled Nitric Oxide in Asthma," *Immunol. Cell Biol.* 79 (2001): 178-90.

¹⁰L. Prieto. "Measurements of Exhaled Nitric Oxide Concentration in Asthma. Technical Aspects and Clinical

Usefulness," *Alergol. Immunol. Clin.* 17 (2002): 72-87.

¹¹N. Binding, W. Muller, P. A. Czeschinski, and U. Witting. "NO Chemiluminescence in Exhaled Air: Interference of Compounds from Endogenous or Exogenous Sources," *Eur. Respir. J.* 16 (2000): 499-503.

¹²H. W. Shin, C. M. Rose-Gottron, R. S. Sufi, F. Perez, D. M. Cooper, A. F. Wilson, and S. C. George. "Flow-Independent Nitric Oxide Exchange Parameters in Cystic Fibrosis," *Am. J. Respir. Crit. Care Med.* 165.3 (2002): 349-57.

¹³M. Maniscalco, V. Di Mauro, E. Farinara, L. Carratu, and M. Sofia. "Transient Decrease of Exhaled Nitric Oxide After Acute Exposure to Passive Smoke in Healthy Subjects," *Arch. Environ. Health.* (2002) 57.5 437-40.

¹⁴G. Litfin, C. R. Pollock, R. F. Curl, Jr., and F. K. Tittel. "Sensitivity Enhancement of Laser Absorption Spectroscopy by Magnetic Rotation Effect," *J. Chem. Phys.* 12 (1980): 6602-05.

¹⁵H. Ganser, W. Urban, and J. M. Brown. "The Sensitive Detection of *NO* by Faraday Modulation Spectroscopy with a Quantum Cascade Laser," *Molecular Physics* 101 (2003): 545-50.

¹⁶C. Roller, K. Namjou, J. D. Jeffers, M. Camp, A. Mock, P. J. McCann, and J. Grego. "Nitric Oxide Breath Testing by Tunable-Diode Laser Absorption Spectroscopy: Application in Monitoring Respiratory Inflammation," *Appl. Opt.* 41 (2002): 6018-29.

¹⁷A. A. Kosterev and F. K. Tittel. "Chemical Sensors Based on Quantum Cascade Lasers," *IEEE J. Quantum. Electron.* 38 (2002): 582-91.

¹⁸E. V. Stepanov, P. V. Zyrianov, and V. A. Miliaev. "Single-Breath Detection with Tunable Diode Lasers for Pulmonary Disease Diagnosis," in *ALT'98 Selected Papers on Novel Laser Methods in Medicine and Biology*. Eds. A. M. Prokhorov, V. I. Pustovoy, and G. P. Kuz'min. *Proc.*, SPIE 3829 (1999): 103-09.

¹⁹L. Menzel, A. A. Kosterev, R. F. Curl, F. K. Tittel, C. Gmachl, F. Capasso, D. L. Sivco, N. J. Baillargeon, A. L. Hutchinson, A. Y. Cho, and W. Urban. "Spectroscopic Detection of Biological *NO* with a Quantum Cascade Laser," *Appl. Phys. B* 72 (2001): 859-63.

²⁰D. D. Nelson, J. H. Shorter, J. B. McManus, and M. S. Zahniser. "Sub-Part-Per-Billion Detection of Nitric Oxide in Air Using a Thermoelectrically Cooled Mid-Infrared Quantum Cascade Laser Spectrometer," *Appl. Phys. B.* 75 (2002): 343-50.

²¹A. A. Kosterev, A. L. Malinovsky, F. K. Tittel, C. Gmachl, F. Capasso, D. L. Sivco, J. N. Baillargeon, A. L. Hutchinson, and A. Y. Cho. "Cavity Ringdown Spectroscopic Detection of Nitric Oxide with Continuous-Wave Quantum-Cascade Laser," *Appl. Opt.* 40 (2001): 5522-29.

²²A. O'Keefe. "Integrated Cavity Output Analysis of Ultra-Weak Absorption," *Chem. Phys. Lett.* 293 (1998): 331-36.

²³R. Englen, G. Berden, R. Peters, and G. Meijer. "Cavity Enhanced Absorption and Cavity Enhanced Magnetic Rotation Spectroscopy," *Rev. Sci. Instrum.* 69 (1998): 3763-69.

²⁴J. B. Paul, L. Larson, and J. G. Anderson. "Ultrasensitive Absorption Spectroscopy with a High-Finesse Optical Cavity and Off-Axis Alignment," *Appl. Opt.* 40 (2001): 4904-10.

²⁵D. S. Baer, J. B. Paul, M. Gupta, and A. O'Keefe. "Sensitive Absorption Measurements in Near-Infrared Region using Off-Axis Integrated-Cavity-Output Spectroscopy," *Appl. Phys. B* 75 (2002): 261-65.

²⁶V. L. Kasyutich, C. E. Canosa-Mas, C. Pfrang, S. Vaughan, and R. P. Wayne. "Off-Axis Continuous-Wave Cavity-Enhanced Absorption Spectroscopy of Narrow-Band and Broadband Absorbers Using Red Diode Lasers," *Appl. Phys. B* 75 (2002): 755-61.

²⁷F. Capasso, C. Gmachl, R. Paiella, A. Tredicucci, A. L. Hutchinson, D. L. Sivco, J. N. Baillargeon, and A. Y. Cho. "New Frontiers in Quantum Cascade Lasers and Applications," *IEEE Select. Topics Quantum Electron.* 6 (2000): 931-47.

²⁸J. M. Herbelin, J. A. McKay, M. A. Kwok, R. H. Ueunten, D. S. Urevig, D. J. Spenser, and D. J. Benard. "Sensitive Measurement of Photon Lifetime and True Reflectances in an Optical Cavity by a Phase-Shift Method," *Appl. Opt.* 19 (1980): 144-47.

²⁹L. S. Rothman, A. Barbe, D. C. Benner, L. R. Brown, C. Camy-Peyret, M. R. Carleer, K. Chance, C. Clerbaux, V. Dana, V. M. Devi, A. Fayt, J. M. Flaud, R. R. Gamache, A. Goldman, D. Jacquemart, K. W. Jucks, W. J. Lafferty, J. Y. Mandin, S. T. Massie, V. Nemtchinov, D. A. Newnham, A. Perrin, C. P. Rinsland, J. Schroeder, K. M. Smith, M. A. H. Smith, K. Tang, R. A. Toth, J. V. Auwera, P. Varanasi, and K. Yoshino. "The HITRAN Molecular Spectroscopic Database: Edition of 2000 Including Updates through 2001," *J. Quant. Spectrosc. Radiat. Transfer* 82 (2003): 5-44.

³⁰S. D. Wehe, D. M. Sonnenfroh, M. G. Allen, C. Gmachl, and F. Capasso. "Quantum-Cascade Laser-Based Sensor for CO and NO Measurements in Combustor Exhaust Flows," AIAA 2001-3317, 37 Joint Propulsion Conference and Exhibit, Salt Lake City, UT, July 8-11, 2001.

³¹D. S. Bomse, A. C. Statton, and J. A. Silver. "Frequency Modulation and Wavelength Modulation Spectroscopies: Comparison of External Methods Using a Lead-Salt Diode Laser," *Appl. Opt.* 31 (1992): 718-31.

Publications

Bakhirkin, Y. A., A. A. Kosterev, C. Roller, R. F. Curl, and F. K. Tittel. "Mid-Infrared Quantum Cascade Laser-Based Off-Axis Integrated Cavity Output Spectroscopy for Biogenic Nitric Oxide Detection," *Appl. Opt.* 43.11 (2004): 2257-66.

Kosterev, A. A., Y. A. Bakhirkin, F. K. Tittel, S. Blaser, Y. Bonetti, and L. Hvozdar. "Photoacoustic Phase Shift as a Chemically Selective Spectroscopic Parameter," *Appl Phys B* (2004). (Accepted for publication.)

Presentations

Bakhirkin, Y. A., A. A. Kosterev, R. F. Curl, F. K. Tittel, and M. Allen. "Off-Axis Integrated Cavity Output Spectroscopy for Nitric Oxide Detection in Human Breath Using a Quantum Cascade Laser," 87th OSA Annual Meeting, Tucson, AZ, Oct. 5-9, 2003.

Tittel, F. K., A. A. Kosterev, Y. Bakhirkin, C. B. Roller, D. Weidmann, and R.F. Curl. "Quantum Cascade Laser

Applications Chemical and Environmental Analysis," NEST-INFN & Scuola Normale Superiore Colloquium, Pisa, Italy, Nov. 7, 2003.

Bakhirkin, Y. A., A. A. Kosterev, C. Roller, R. F. Curl, and F. K. Tittel. "Wavelength Modulation Off-Axis Integrated Cavity Output Spectroscopy for Biogenic NO Detection in Human Breath," Conference on Lasers and Electro-Optics/International Quantum Electronics Conference (CLEO/ IQEC 2004), San Francisco, CA, May 16-21, 2004.

McCurdy, M., Y. Bakhirkin, A. Kosterev, R. F. Curl, M. G. Allen, and F. K. Tittel. "Off-Axis Integrated Cavity Output Spectroscopy for Nitric Oxide Detection in Human Breath Using a Quantum Cascade Laser," AAAAI Meeting, San Francisco, CA, March 19-23, 2004.

McCurdy, M. R., Y. A. Bakhirkin, C. Roller, A. A. Kosterev, R. F. Curl, and F. K. Tittel. "Off-Axis Integrated Cavity Output Spectroscopy for Nitric Oxide Detection in Human Breath Using a Quantum Cascade Laser," 21st Annual Houston Conference on Biomedical Engineering Research (HSEMB), Houston, TX, Feb. 12-13, 2004.

Tittel, F. K., Y. Bakhirkin, R. F. Curl, A. A. Kosterev, S. So, D. Weidmann, and G. Wysocki. "Applications of Quantum Cascade Lasers in Trace Gas Analysis and Chemical Sensing," 6th International Conference on Mid-Infrared Optoelectronics Materials and Devices, St. Petersburg, Russia, June 28-July 1, 2004.

Tittel, F. K., A. A. Kosterev, Y. A. Bakhirkin, C. Roller, D. Weidmann, and R. F. Curl. "Mid-Infrared Quantum Cascade Laser Sensors for Gas Analysis and Medical Diagnostics," Photonics West 2004, San Jose, CA, Jan. 25-29, 2004.

Tittel, F. K., Y. Bakhirkin, R. F. Curl, A. A. Kosterev, M. McCurdy, C. Roller, S. So, D. Weidmann, and G. Wysocki. "Current Applications of Quantum Cascade Laser in Trace Gas Analysis and Chemical Sensing," International Workshop on Quantum Cascade Lasers, Sevilla, Spain, Jan. 4-8, 2004.

Funding and proposals

"Photonic Technologies for Early Detection of Human Disease." NASA-National Cancer Institute, Rice University PI, Apr. 1, 2002-Mar. 31, 2005, \$377,000.

"Quantum Cascade Laser Based Sensors for Chemical and Environmental Analysis." Texas Advanced Technology Program, Rice University PI., Jan. 1, 2002-Mar. 31, 2005, \$115,000.