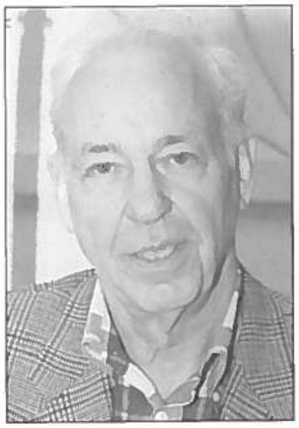
Development of Quantum-Cascade Laser Based Biosensor Technology

Thomas L. Harman, Frank K. Tittel, John C. Graf, Yury Bakhirkin

Abstract—The development of new types of sensitive, selective, real-time gas sensors is based on continuous wave and pulsed quantum cascade lasers for various chemical sensing applications, such as medical diagnostics, environmental monitoring, and industrial process control. Tunable laser absorption spectroscopy in the mid-infrared spectral region is a sensitive analytical technique for trace gas quantification. During the past year a nitric oxide (*NO*) gas sensor was developed based on a novel thermoelectrically cooled, continuous wave, distributed feedback quantum cascade laser operating at 5.45 μm (1835 cm^{-1}) and off-axis integrated cavity output spectroscopy (OA-ICOS) combined with a wavelength modulation technique. Its purpose is to determine *NO* concentrations at the sub-ppbv levels that are essential for such applications. The sensor employs a 50 cm-long high-finesse optical cavity that provides an effective pathlength of ~ 700 m. A noise equivalent (SNR = 1) minimum detection limit of 0.7 ppbv with a 1 second observation time was achieved.


Dr. Thomas L. Harman


Dr. Frank K. Tittel

THE DEVELOPMENT OF COMpact optical sensors for nitric oxide detection is of interest for a number of applications, such as environmental monitoring,[1] atmospheric chemistry,[2] industrial process control,[3] combustion studies,[4] and medical diagnostics.[5,6] *NO* is involved in many vital physiological processes in the human body. For example, an elevated level of *NO* in exhaled breath is correlated with airway inflammation in asthmatic patients. Knowledge of *NO* concentrations in the exhaled breath of these patients may allow health care providers to adjust therapeutic drug dosages.[7,8] For medical diagnostics purposes, it is essential to time-resolve the *NO* concentration as a function of a breath cycle phase, because corresponding air samples originate in the different parts of the respiratory tract. This application requires a sensor response time of ≤ 1 second and a *NO* minimum detection sensitivity of < 1 ppbv. Such high sensitivity, rapid response measurements are possible with laser absorption spectroscopy in the fundamental absorption band of *NO*.

Distributed feedback quantum cascade lasers (DFB QCLs) operating in a pulsed or continuous wave (CW) mode are promising spectroscopic sources because of their narrow linewidths, single mode operation, tunability, output power, reliability, and compactness. Until recently CW operation of QCLs was possible only at cryogenic temperatures, and room temperature (RT) operation was only realized with pulsed operation at low duty cycle. Recent developments in QCL technology now permit CW operation at room temperature.[9,10]

A number of approaches utilizing QCLs for the optical sensing of trace *NO* have been reported. Background-free Faraday modulation spectroscopy has been demonstrated to be capable of measuring biogenic nitric oxide with a sensitivity of a few ppbv.[11,12] Mid-infrared spectrometers based on a QCL and a multipass cell absorption platform achieve a minimum *NO* detection limit of ≤ 1 ppbv.[1,6,13] A technique based on Cavity Ringdown Spectroscopy (CRDS) reaches a noise equivalent sensitivity at the sub-ppbv level in several seconds using a comparatively small sample volume because of a long optical pathlength obtained with ultra-high reflectivity mirrors (R ~ 99.99%).[14-16] Another approach is integrated cavity output spectroscopy (ICOS),[17,18] which also uses low-loss mirrors.

In 2001, an ICOS-based biogenic *NO* sensor utilizing a quantum cascade laser was reported by our group.[19] More recently, we demonstrated a noise equivalent sensitivity of 10 ppbv in 15 seconds for *NO* using a compact (~ 5 cm long, ≤ 80 cm^3 volume) off-axis (OA)-ICOS cell and a liquid nitrogen (LN_2) cooled CW DFB QCL, operated at ~ 5.2 μm.[20] The OA-ICOS

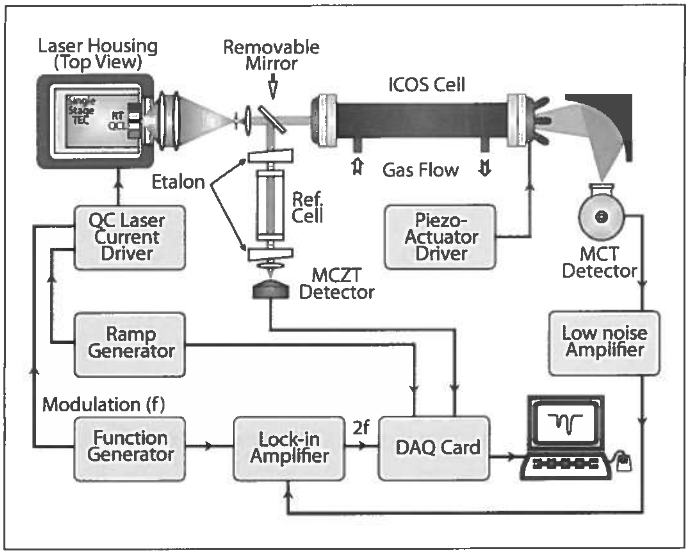


Figure 1. TEC-CW-DFB QCL based OA-ICOS sensor. MCT is a cryogenically-cooled photovoltaic *HgCdTe* detector, and MCZT is a thermoelectrically-cooled *HgCdZnTe* photodetector (Vigo System, Model PVMI-10.6).

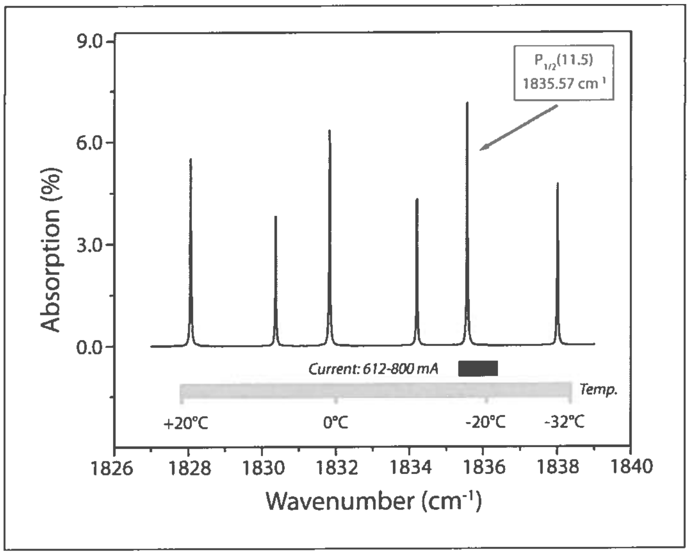


Figure 2. HITRAN-based simulation of an absorption spectrum for a *NO* (N_2 mixture in the tuning range of a TEC CW DFB QCL operating at 5.45 μm. The total pressure of the mixture is 200 Torr; pathlength is 700 m; a concentration of *NO* is 94.9 ppbv. The *NO* absorption line $P_{1/2}(11.5)$ at 1835.57 cm^{-1} (denoted by arrow) was used for the concentration measurements reported in this work.

approach combined with a wavelength modulation (WM) technique showed a 5-fold sensitivity enhancement with the same data acquisition time. M. L Silva et al.[21] obtained a minimum detection sensitivity of < 1 ppbv in 4 s for *NO* in human breath using an ICOS cell and a thermoelectrically cooled (TEC) pulsed QCL.

In this work, we use a novel and now commercially available TEC, CW, DFB quantum cascade laser fabricated by our collaborating team from the University of Neuchatel, Switzerland.[9] DFB CW QCL characteristics, such as a narrow laser spectral width (≤ 3 MHz[16]), necessary for efficient laser-to-cavity coupling and high average power, make CW TEC QC lasers more suitable than pulsed QCLs for ICOS-based sensor platforms for real world applications, avoiding the size and complications of liquid nitrogen cooling required by earlier QC lasers. The basic sensor platform is an OA-ICOS configuration with a 50 cm-long optical cavity. A wavelength modulation technique (harmonic detection) was implemented in order to reach sub-ppbv levels of *NO* detection sensitivity.

Methodology and Equipment

A schematic of the ICOS-based sensor is depicted in Fig. 1. A TEC CW DFB QCL, operating at 5.45 μm[9], was installed in a compact evacuated QCL housing. The housing was equipped with a 25 mm diameter CaF_2 window and a single-stage thermoelectric cooler (Melcor Corporation, Type UT8-12-40F1) that provides thermal control of the QC laser. A minimum QCL temperature of −32°C can be achieved when the laser housing is at reduced pressures (typically ~ 10^{-3} to 10^{-4} Torr) and the hot side of TEC is actively water-cooled. A three-lens collimator (see Fig. 1) was employed to achieve optimum coupling of the QCL radiation to the OA-ICOS cavity. The first lens after the QCL is a 25 mm diameter *ZnSe* aspherical lens with an antireflection coating, and a 12.7 mm effective focal length. This reduces spherical aberration thereby improving the quality of the beam coupled to the OA-ICOS cell. An iris diaphragm in the focal point of the second lens serves as a spatial optical filter to minimize fringes caused by the collimator lenses and the laser housing output window and reduces back-reflection to the QCL by a factor of 5. The second and third lenses also have diameters of 25 mm and effective focal lengths of 500 mm and 63 mm, respectively. The collimated QCL beam incident on the OA-ICOS cavity has a diameter of 2.3 mm. Highly reflective 50.8 mm diameter concave mirrors (1 m radius of curvature) separated by a 50 cm stainless steel spacer form the optical OA-ICOS cavity.

The same set of mirrors used in our previous study at a frequency of 1920 cm^{-1} (5.2 μm)[20] was employed in this work. The reflection coefficient for the ultra-low loss mirror set at 1920 cm^{-1} was estimated to be $R \geq 99.975$ % using a CDRS approach.[20] According to the mirror specifications, the reflection coefficient at a laser frequency of 1836 cm^{-1}, which was used in the current study, is the same (with a discrepancy of ± 0.005%) according to the manufacturer (Los Gatos Research, Inc.).

The longer cavity length of 50 cm was chosen in order to enhance the *NO* detection limit of the OA-ICOS technique. The cavity was aligned off-axis with respect to the laser beam providing improved cavity mode noise suppression. The suppression of cavity mode noise is the critical factor determining the sensitivity of the ICOS technique.[18,20] Further mode noise suppression sensitivity enhancement was obtained by averaging the cavity resonances by dithering the cavity length using an assembly of 3 piezo-electric actuators attached to one of the resonator mirrors (See Fig. 1). The mirror was moved back and forth with a frequency of ~ 200 Hz and a maximum translation travel of ~ 15 μm.

The CW QCL utilized in this work was a 3 mm long, 14 μm wide, junction-up mounted DFB laser with a high reflection coating evaporated on its back facet. Spectral output, current and temperature tuning range, and rate of the QCL were evaluated using:

1) a 10 cm reference cell filled with a calibration mixture of $NO + N_2$;
2) an air-spaced Fabry-Perot etalon, which consists of two wedged ZnSe windows; and
3) HITRAN database simulated spectra, which were compared with the experimental results.

The laser operated at temperatures of up to +20°C with a total tuning range from ~ 1827 cm^{-1} (+20°C) to ~ 1838 cm^{-1} (–32°C). The temperature tuning rate was ~ 0.2 cm^{-1}/K. A temperature controller (Wavelength Electronics, Inc., Model MPT-10000) provides a long-term temperature stability δT of about ≤ 0.01°C, limiting the spectral line shift to ≤ 0.002 cm^{-1} which is negligible compared to the *NO* linewidth at 200 Torr (0.032 cm^{-1}). At a fixed temperature of the laser thermal sink, the frequency of the output radiation can be tuned by varying the QCL current. A current driver (Wavelength Electronics, Inc., Model MPL-2500) was used to operate the QCL. Temperature and current spectral tuning ranges of the QCL are depicted in Fig. 2 together with a HITRAN based simulated absorption spectrum of an $NO - H_2O - N_2$ mixture. The combined *NO* absorption line $P_{1/2}(11.5)$, which is a superposition of two lambda doubling components centered at 1835.57 cm^{-1}, was selected for concentration measurements as it is the most intense line in the QCL tuning range. A strong interference from H_2O throughout the entire spectral output range of the QCL can be avoided by using commercially available Nafion dryer assembly (Perma Pure LLC) with an appropriate length and flow rate to meet breath analysis requirements. The $P_{1/2}(11.5)$ line was reached at a temperature of –21°C and a current of ~ 778 mA. Two function generators (Stanford Research Systems, Model DS345) were utilized for QCL current ramping and for frequency modulation in applying the wavelength modulation (WM) technique. The QCL ramp and WM frequencies were ~ 1 kHz and ~ 50 kHz respectively.

The ICOS cavity output signal was focused onto a LN_2 cooled photovoltaic *HgCdTe* detector with a built-in transimpedance preamplifier (Kolmar Technologies, Model KMPV8-1-J1/DC) by means of an off-axis aluminum parabolic mirror. After additional amplification (gain factor was 10^3) and filtering (low-pass filter was set to 1MHz) by a low noise amplifier (Stanford Research Systems, Model SR560), the detector signal was fed into a lock-in amplifier (Stanford Research Systems, Model SR 830) for second harmonic (2f) processing. The output of the lock-in was acquired by a data acquisition card installed in a PC using LabView 7.1. After further averaging, the data were stored in preparation for fitting. Initial feasibility *NO* concentration measurements with a long cell were made without the wavelength modulation technique. In this case, the amplified photodetector signal was directed straight to the data acquisition card. The QC laser linewidth estimated at ~ 35 ± 3 MHz was determined mainly by the current ripple on the QCL driver current source.

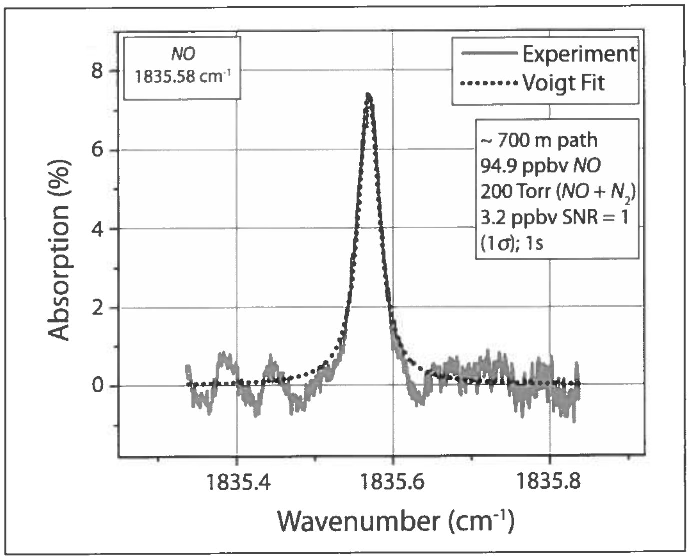


Figure 3. Measured OA-ICOS spectrum of a 94.9 ppbv *NO*: N_2 calibration mixture fitted by a Voigt function. Fit parameters: Lorentzian linewidth is ~ 2.61 × 10^{-2} cm^{-1} that is in a good agreement with a HITRAN predicted value of 2.63 × 10^2 cm^{-1}, Gaussian (Doppler) width is ~ 0.41×10^{-2} cm^{-1}. Minimum detectable *NO* concentration is 3.2 ppbv, obtained from the deviation of the area under absorption curve δA. Time constant (data acquisition time) is 1 s.

Experimental Activity, Results and Discussion

A calibration mixture (Scott Specialty Gases, Inc.) of a 94.9 ppbv *NO* in N_2 as the balance gas was used for the evaluation of the QCL based *NO* sensor system. The *NO* concentration was certified by the supplier using a chemiluminescence technique (*NO* analyzer by GE Analytical Instruments, formerly Sievers). A diluter was used to obtain up to 5 times lower *NO* concentration levels. Measurements were made at a constant flow rate of ~ 100 sccm as adhesion to the ICOS cavity walls may affect the precision and accuracy of the *NO* concentration measurements. Pressure levels were varied from 50 to 200 Torr. A gas flow system described in detail in Bakhirkin et al.[20] was utilized for measurement pressure and flow control.

Initial *NO* concentration measurements with the 50 cm-long ICOS cell were made without applying wavelength modulation. The QC laser output was scanned by current with a frequency of 1 KHz across the absorption line. The cavity output signal was sampled, averaged, and processed using a data acquisition card and PC. Results are depicted in Fig. 3. The solid curve shows a 94.9 ppbv *NO* absorption line obtained from averaged ICOS signals. An absolute value of the absorption was obtained taking into account an offset resulting from the bimodal characteristic of the QCL. The number of acquired averages of spectra was 1000 and the typical data acquisition time 1 s. The dotted line represents a Voigt fit with parameters: Lorentzian width of ~ 2.61 × 10^{-2} cm^{-1} that is in a good agreement with the HITRAN predicted value of 2.63 × 10^{-2} cm^{-1} and a Gaussian linewidth of ~ 0.41 × 10^{-2} cm^{-1} determined by the temperature of the gas. Comparison between fitted data and HITRAN simulated spectra yielded an effective optical pathlength of 700 m provided that

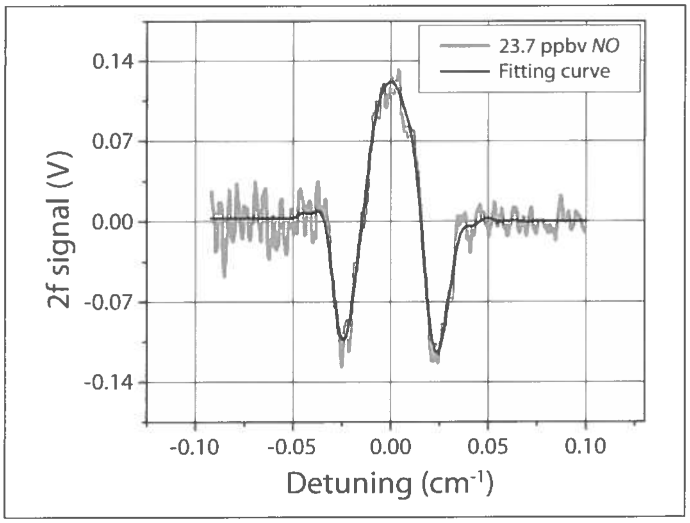
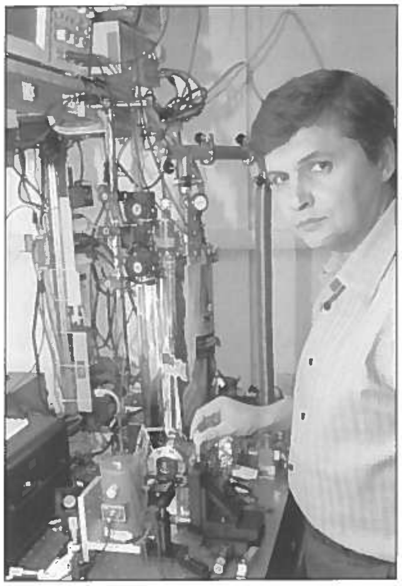


Figure 4. Averaged measured (2f) signal for a *NO* concentration of 23.7 ppbv and fitting curve, obtained using a general linear fitting procedure.[28] The standard deviation, σ, of the fit coefficients corresponds to 0.7 ppbv.

the line shape obeys a Voigt profile at 200 Torr. This is in a good agreement with our previous results for a compact 5.3 cm long cell obtained with the same set of mirrors that provided a 75 m effective optical pathlength. The effective optical pathlength scales with the physical length of the ICOS cavity. The discrepancy between the measured (~ 700m) and theoretical (~ 2000 m) effective optical pathlength of the OA-ICOS derived from the cavity ringdown time is attributed to several factors, such as: (1) non-homogeneity of the reflectivity across the 2 inch diameter mirror surfaces and, therefore, an uncertainty of the cavity decay time, (2) a large number of higher order transverse modes that are involved in OA-ICOS based gas measurements with higher diffraction losses than for the TEM$_{00}$ mode which leads to a decrease of the effective optical pathlength, and (3) tilting of the PZT driven mirror which affects the OA-ICOS cavity alignment and, therefore, results in a decrease of the cavity finesse.

In order to improve sensitivity toward the *NO* target limit of $\leq$ 1 ppbv required for breath analysis, wavelength modulation spectroscopy (WMS)[13,22-25] was added to the OA-ICOS-based sensor platform. In this case, the QCL current is modulated at a high frequency ν, and the wavelength is tuned slowly across the spectral line of interest by means of a current ramp with a frequency Ω ($\nu >> \Omega$). The detector output is processed by a lock-in amplifier referenced to the modulation frequency 1f or 2f (first and second harmonic detection respectively). This type of detection results in a significant improvement in the signal-to-noise-ratio (SNR).[22] The amplitude of a WMS-based signal scales linearly with gas concentration,[23] which facilitates calibration and a quantitative gas concentration measurement.

The OA-ICOS-based sensor can also benefit from applying WMS as reported in Refs. 20, 26, and 27. In the present work, WMS parameters (amplitude, modulation frequency and modulation function) and the gas pressure inside the ICOS cavity were optimized in order to maximize the signal. Sinusoidal modulation at ν together with a triangular ramp at Ω was found to result in the optimum SNR. The frequencies were Ω = 1 KHz and ν = 50 KHz, respectively. The lock-in amplifier output was averaged using a data acquisition card and LabView-based software. A WMS signal for calibrated *NO* concentration was fitted using a general linear fit procedure,[28] as shown in Fig. 4. A 1σ deviation if the amplitude as a fit result corresponds to 0.7 ppbv.



Dr. Yury A. Bakhirkin, Research Associate, conducts research with Dr. Frank K. Tittel and Dr. Harman.

Conclusions

An OA-ICOS-based *NO* sensor, which exploits the recent availability of a CW TEC DFB QCL operating at 5.45 μm and a 50 cm-long high finesse optical cavity, demonstrated the feasibility of detecting and quantifying *NO* concentrations at a level of $\leq$ 1 ppbv in 1 s. The OA-ICOS technique yields a minimum *NO* detection sensitivity of ~ 3 ppbv in 1 s. A combination of OA-ICOS and a 2f WMS technique leads to minimum *NO* detection levels of ~ 0.7 ppbv. Additional improvement in sensitivity can be obtained by using a more powerful (~50 mW) single frequency CW QCL[10] operating at 1900.1 cm^{-1} (optimum frequency for interference free *NO* detection[21]) and recently available 50 ppm ultra-low loss mirrors (instead of the 250 ppm mirrors used in this work).

Acknowledgments

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