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Quantum Cascade Laser-Based Nitric Oxide Detection in Exhaled Breath of Patients with Chronic Obstructive Pulmonary Disease

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Abstract: A continuous wave quantum cascade laser operating at 5.45 μm coupled with an integrated cavity output spectroscopy technique and wavelength modulation is being used for detection of nitric oxide in exhaled breath of subjects with chronic obstructive pulmonary disease.

Exhaled nitric oxide (NO) is becoming widely recognized as a marker of airway inflammation, aiding in therapeutic monitoring of asthma patients. Chronic obstructive pulmonary disease (COPD) is a disease of the airway that affects over 12 million Americans. Symptoms, functional abnormalities, and complications of COPD can all be explained on the basis on underlying airway inflammation and the resulting pathology. Exhaled NO correlates with airway inflammation in COPD, and the trend of NO concentration over time in a particular COPD patient may aid therapeutic monitoring [1]. Exhaled NO data, measured using the instrument described here, are being included with other indices of inflammation in a pilot study to evaluate the anti-inflammatory effect of curcumin in COPD patients. For the pilot study, the Rice Laser Science Group is collaborating with Amir Sharafkhaneh, MD, a pulmonologist at the Michael E Debakey Veterans Affairs Medical Center (VAMC, Houston, TX). The study is a randomized, controlled trial of 40 subjects with severe COPD – 30 drug and 10 placebo subjects. The subjects are seen monthly for three months, and receive increasing dosages of curcumin or placebo at each visit. Exhaled breath, sputum, and blood samples are obtained at baseline and at the end of each month. Lung function testing and symptoms questionnaires are completed at each monthly visit. The results of this study will aid in determining the role of NO in therapeutic monitoring of COPD patients.

In this work we investigate tunable laser absorption spectroscopy as an effective technique for sensitive and selective NO monitoring. The mid-infrared spectral range also known as the molecular “fingerprint” region is ideally suited for tunable laser absorption spectroscopy since most gases possess strong fundamental rotational-vibrational lines.

Mid-infrared spectrometers based on a quantum cascade laser and a multipass cell absorption platform achieve a minimum NO detection limit of ≤ 1 ppbv. Cavity Ringdown Spectroscopy technique reaches noise equivalent sensitivity at the sub-ppbv level in several seconds using a comparatively small sample volume because of extremely long pathlength obtained with ultra-high reflectivity mirrors (R ~ 99.99%). Another approach, which uses such “super” mirrors, is integrated cavity output spectroscopy (ICOS). Recently a minimum detection sensitivity of < 1 ppbv in 4 s for NO in human breath using an ICOS cell and a pulsed thermoelectrically cooled quantum cascade laser was reported [2]. In another study, a noise equivalent sensitivity of 10 ppbv in 15 second was demonstrated for NO using a compact (~5 cm long, ≤ 80 cm^3 volume)

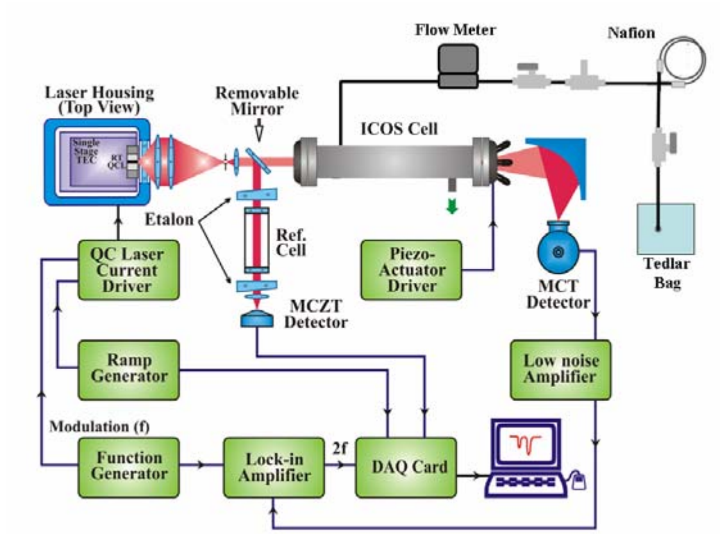

Figure 1. Thermoelectrically cooled continuous-wave distributed feedback quantum cascade laser-based off-axis ICOS sensor. MCT is cryogenically cooled photovoltaic HgCdTe detector and MCZT is a thermoelectrically cooled HgCdZnTe photodetector.

ICOS cell and a liquid nitrogen cooled, continuous wave, distributed feedback quantum cascade laser, operated at ~ 5.2 μm [3].

In this work we use a novel thermoelectrically cooled, continuous wave, distributed feedback quantum cascade laser fabricated by Prof. J. Faist and his team at the University of Neuchatel, Switzerland [4]. The integrated cavity output spectroscopy (ICOS) based sensor layout is depicted schematically in Fig. 1. The laser, operating at 1836 cm^{-1} (5.45 μm), was installed in a compact quantum cascade laser housing. Highly reflective, 50.8 mm diameter, mirrors (ROC = 1 m) separated by a 50 cm stainless steel spacer form the optical off-axis ICOS cavity. The reflection coefficient of the ICOS mirrors at the operational quantum cascade laser frequency of 1836 cm^{-1} was measured to be R ≥ 99.975 % using a cavity ring-down spectroscopy approach, which corresponds to an absorption loss of 250 ppm. The cavity was aligned in an off-axis geometry that resulted in improved cavity mode noise suppression, which is a critical factor in determining the sensitivity of the ICOS technique. Further sensitivity enhancement was obtained by averaging of 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 is translated along the optical axis with a frequency of ~ 200 Hz and a maximum distance of ~ 15 μm. The piezo-electric movement of the mirror over several free spectral ranges in a single current ramp increases the probability of quantum cascade laser radiation coupling to the ICOS cavity, thereby increasing the power inside the cavity and enhancing the leak-out power to the photodetector.

The combined NO absorption line centered at 1835.57 cm^{-1} and CO_2 lines at 1836.09 cm^{-1} and 1836.26 cm^{-1} were selected for concentration measurements as they were the most intense lines in the laser tuning range that were also free from interference of water lines (See Fig. 2). A strong interference from H_2O throughout the entire spectral output range of the QCL can be avoided by using a commercially available Nafion dryer assembly (Perma Pure LLC) with an appropriate

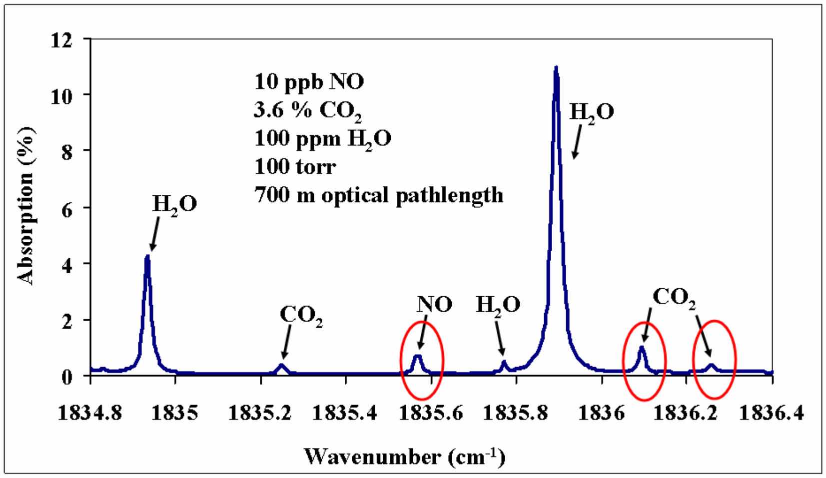

Figure 2. HITRAN-based simulation of an absorption spectrum for an exhaled breath sample in the tuning range of the laser-based sensor. The total pressure of the sample is 100 Torr; pathlength is 700 m; concentrations of NO, H_2O (after Nafion dryer), and CO_2 are 10 ppbv, 100 ppmv, and 3.6% respectively. The NO absorption line at 1835.57 cm^{-1} and CO_2 lines at 1836.09 cm^{-1} and 1836.26 cm^{-1} (red ovals) are used to make concentration measurements.

length and flow rate to reduce the H_2O concentration to ~100 ppmv. A 4 m long Nafion tube is able to reduce the absolute concentration of water vapor from ~ 6×10^4 ppmv (100% of relative humidity at 36°C, which is typical for human breath) to a ~ 100 ppmv level at 40 mL/min. Breath is collected in manner that follows the American Thoracic Society 2005 recommendations for lower airway exhaled NO collection. Breath is collected in Tedlar bags at a constant exhalation flow rate of 2 L/min and a mouth pressure of 8 cm H_2O. CO_2 is measured to examine the efficacy of normalizing the exhaled NO plateau to CO_2 concentration of each breath sample.

In summary, a quantum cascade laser-based sensor employing a 50 cm long OA-ICOS gas cell with an effective pathlength of ~ 700 m is being used to detect exhaled NO in COPD patients as part of a clinical trial. A noise equivalent (SNR = 1) detection limit of ~1 ppbv in 1 second, based on 2f harmonic detection of the ICOS cavity output is routinely achieved. Preliminary data of the pilot study to evaluate the anti-inflammatory effect of curcumin in COPD patients will be presented.

REFERENCES

1. W. J. C. Beurden, P. N. R. Bekhuijzen, F. W. J. M. Smeenk. "Exhaled biomarkders in COPD: their potential role in diagnosis, treatment, and prognosis." Monaldi Arch Chest Dis 57:5-6, 258-267, 2002.
2. M. L. Silva, D. M. Sonnenfroh, D. I. Rosen, M. G. Allen, and A. O'Keefe, "Integrated Cavity Output Spectroscopy Measurements of Nitric Oxide levels in Breath with a Pulsed Room-Temperature Quantum Cascade Laser", to appear in Applied Physics B.
3. Yu. A. Bakhirkin, 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 NO Detection, Applied Optics, 43, 2257, 2004.
4. S. Blaser, D. A. Yarekha, L. Hvozdara, Y Bonetti, A. Miller, M. Giovannini, and J. Faist, Room-temperature, continuous-wave, single mode quantum-cascade lasers at 5.4 μm", Appl. Phys. Lett., 86, 041109-1, 2005.