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14. ABSTRACT

Every woman over 50 is recommended to have mammograms to monitor for breast cancer. The goal is to detect breast cancer as early as possible. The problems with the technique are well known and range from the exposure to X-rays to the difficulty of analysis, to patient resistance. Normal human breath contains a complex mixture of volatile organic compounds (VOCs). A number of these VOCs have been identified as candidate markers of various cancers (e.g. formaldehyde in breast cancer). Although breath analysis has been shown to have great potential as a diagnostic tool, most of the compounds of interest are exhaled in picomolar concentrations. Real-time breath analysis for these compounds is not possible with existing technology. Cavity ringdown spectroscopy (CRDS) is a measurement of the rate of absorption of a sample within a closed optical cavity, rather than the standard measurement of the absorbed signal strength over a given sample path. It maintains much of the simplicity of classical absorption spectroscopy, but has been demonstrated to provide an increase in sensitivity of up to 10,000 times. The objective is to evaluate the potential of CRDS to provide real-time formaldehyde concentrations in exhaled breath for the purpose of the detection of breast cancer.

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Introduction:

Normal human breath contains a complex mixture of several hundred volatile organic compounds (VOCs). A number of these compounds have been identified as candidate markers of various cancers (e.g. formaldehyde in breast cancer). Although breath analysis has been shown to have great potential as a diagnostic tool, most of the compounds of interest are exhaled in picomolar concentrations and may also be highly reactive and volatile. Real-time breath analysis for these compounds is not possible with existing technology. Cavity ringdown spectroscopy (CRDS) is a measurement of the rate of absorption of a sample within a closed optical cavity, rather than the standard measurement of the absorbed signal strength over a given sample path. It maintains much of the simplicity and advantages of classical absorption spectroscopy, but has been demonstrated to provide an increase in sensitivity of up 10,000 times. The specific goal was to determine the sensitivity of cavity ringdown spectroscopy to detect formaldehyde under conditions simulating those present in exhaled breath and evaluate the technique's potential in establishing the validity of biomarkers in exhaled breath. The establishment of formaldehyde levels in the breath as a reliable biomarker for breast cancer would significantly improve both testing and detection rates. This could result in a significant impact on the success of treatment, as well as reduce the financial burden of treating breast cancer on the economy as a whole. The proposed research did not aim to achieve all these goals but it was hoped that this work would provide the crucial first step along the path, a real-time noninvasive diagnostic "breathanalyzer".

Body

Background: Every woman over 50 is recommended to have a yearly mammograph to monitor for breast cancer. The goal is to detect the cancer as early as possible as 5-year survival rates improve dramatically with early detection. The problems with the technique are well known and range from the difficulty of analysis to patient resistance. Breath analysis may provide a novel approach to providing an alternative diagnostic technique.[1-6] Pauling and his coworkers reported in 1977[6] that normal human breath contains a complex mixture of several hundred volatile organic compounds (VOCs). A number of these compounds have been identified as candidate markers of various cancers: formaldehyde in the case of breast cancer (other examples include various alkanes in lung cancer).[3-9] Nevertheless, while breath analysis has been shown to have great potential as a diagnostic tool, most of the compounds of interest are exhaled in picomolar concentrations. To detect such low concentration levels using standard laboratory equipment, such as a HPLC or a GC/MS, requires the collection of samples using complicated protocols to permit accurate analysis. For example, volatile markers of lipid peroxidation, ethane and pentane, are usually cryotrapped and analyzed by gas chromatography. However, the potential for isoprene to co-elute with pentane[10-11] can lead to an overestimation of pentane concentrations. Acetone concentrations in breath have been used to indicate diabetes mellitus.[2] Alcohol levels are routinely measured by breath analysis and the production of acetaldehyde in breath in alcohol studies has been measured.[13] However, as the title VOC implies, the compounds of interest are volatile and often highly reactive. This means that the sample collected does not necessarily reflected the true composition of the breath but rather results in the measurement of the reaction byproducts. This result greatly complicates any analysis. To circumvent the problems associated with sample collection, preparation and analysis, there exists a need for a small relatively inexpensive instrument capable of providing a highly selective ultratrace real-time measurement of a variety of volatile molecular compounds present in exhaled breath. Although significant progress has been made in the areas of electronic noses and other solid-state detectors,[14] significant problems remain with these technologies. The development of mid-IR tunable diode lasers has allowed the use of optical techniques such as laser absorption spectrometry as a noninvasive breath diagnostic.[15-17] Molecules such as N_2O, CO_2, and CO as well as the ratio, $^{12}CO_2/^{13}CO_2$, have been measured in the breath of cigarette smokers with a mid-IR tunable diode laser absorption spectrometer.[15] However, even with the use of a multi-pass cell, the concentration in the breath is so low that the sensitivity of a traditional laser absorption spectroscopy is insufficient to allow accurate measurement of the molecules of interest.[18] For instance, an improvement in detection limits of approximately 50 times is required to accurately measure formaldehyde in the breath. Such an improvement in detection limits is not achievable using these methods.

However, optical techniques have the selectivity required and we proposed to provide the required sensitivity by applying a new technique - cavity ringdown spectroscopy - to the problem. The sensitivity inherent to this technique will allow the development of a breath analyzer with the capabilities to monitor in real-time the actual concentrations of a variety of

VOCs in human breath. Such an instrument has the potential to be an extremely valuable medical diagnostic tool. The objective of the proposed effort is to evaluate cavity ringdown spectroscopy to measure formaldehyde in exhaled breath and facilitate the development of breath analysis as a diagnostic tool for breast cancer.

Concept: In its original form,[19] cavity ringdown spectroscopy (CRDS) is implemented by injecting and trapping a laser pulse in a stable optical cavity formed from two highly reflective mirrors (see Figure 1). The intensity of the light in the cavity decays exponentially with time at a rate determined by the round trip losses experienced by the laser pulse.

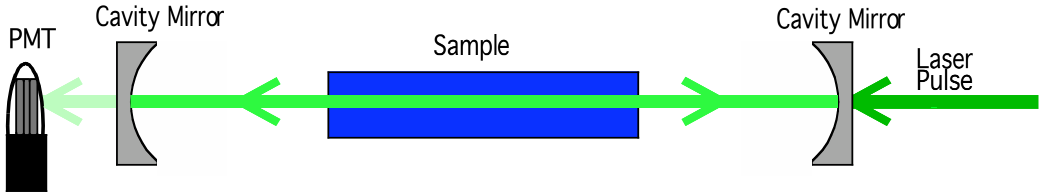


Figure 1: Basic optical configuration for cavity ringdown spectroscopy.

When the dominant losses are the mirror reflectivity and absorption from a sample species in the cavity, the time constant for the exponential decay is given by

$$\tau = \frac{d}{c[(1-R)+\alpha l_s]} \qquad (1)$$

where d is the cavity length, R is the effective reflectivity of the cavity mirrors, α is the familiar Beer's Law absorption coefficient of a sample in the cavity, l_s is the length of the optical path through the sample, and c is the speed of light. As the laser wavelength is varied, the ringdown time will decrease at the absorption wavelength of the sample (i.e. α increases). Measuring the ringdown time using an empty cavity (i.e. $\alpha = 0$) gives the reflectivity of the mirrors.

The high sensitivity of the technique stems from the large number of passes the light pulse makes through a sample. For 99.99% reflectivity mirrors in a 1-meter long cavity, the ringdown time is approximately 33.4 μs for an empty cavity. This is equivalent to a 10-kilometer pathlength traveled during the first time constant! Simply put, this means that a CRDS instrument has the potential to improve sensitivity by a factor of up to 10,000 over commercially available absorption-based instruments. During early research by the PI's group,[20-26] the sensitivity of CRDS was demonstrated by a scan of an empty cavity (open to the laboratory air) over the spectral region centered on 253 nm. This scan indicated not only the presence of absorption due to a very weak molecular oxygen band but also the presence of elemental mercury (Hg). This signal corresponded to Hg background level of 10 ppt and a detection limit below 0.1 ppt. [The source of the Hg vapor was traced to a waste container holding low-level liquid Hg waste (< 10 ppm) that a student had left the lid off. Capping the container dropped the background Hg level in the laboratory below the CRDS detection limit.]

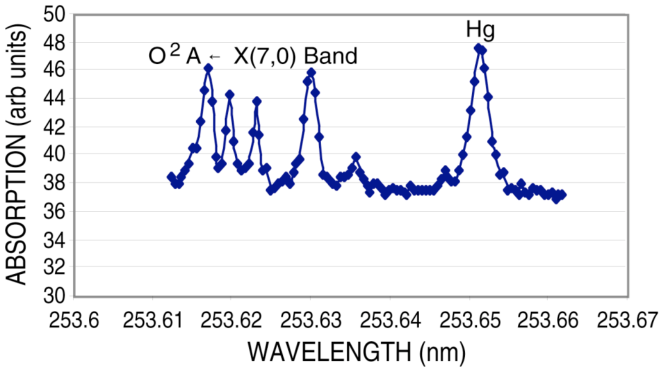


Figure 2: Cavity Ringdown Spectroscopy Hg detection limit < 0.1 part per trillion (Tao, Mazzotti, Winstead,& Miller. Analyst 125, 1021 (2000).

However, in this proposal it is molecular CRDS that is of interest. At the time of writing the original proposal, as far as the authors were aware, CRDS had never been used for breath analysis. However, whether for fundamental molecular structure studies or for applications in areas such as combustion studies, plasma processing, or environmental measurements, CRDS has proven its capability to detect and measure ultratrace molecular species or weak molecular absorptions under hostile environments (see Figure 3). Although a complete review of molecular spectroscopy using CRDS is beyond the scope of this report, reviews are available for further information concerning molecular spectroscopy using CRDS(20, 23, 27-30).

To provide small near-room temperature tunable light sources over the optimum spectral for the detection of formaldehyde, the choice of potential light sources was limited to either mid-IR Quantum Cascade diode lasers, Pb-salt or difference frequency generation (DFG) lasers (see

Table 1).[31] At the time of writing the initial proposal, the lasers with the most potential for this application appeared to be the QCLs, so we proposed to use such a laser for this effort.

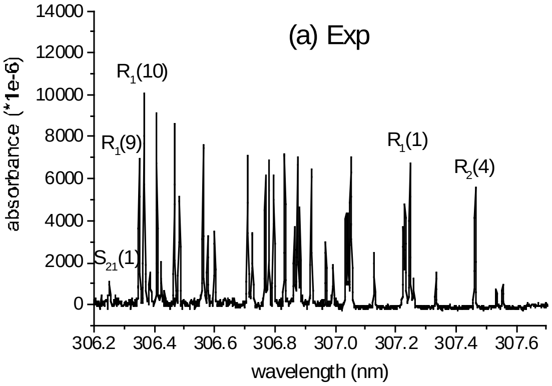


Figure 3 Part of the CRD spectrum of the OH $A^2\Sigma^+ - X\,^2\Pi$ (0-0) band recorded in an ICP

Table 1: The relative strengths of H_2CO absorption lines as a function of wavelength

Wavelength (µm)	Relative Absorption Strength
0.35	1
1.76	100
3.5	50,000

Interferences:

As mentioned above, over 300 compounds have been identified in exhaled breath. In such complex mixtures it is very likely that the spectral absorption features will overlap. In this case, when the dominant losses are the mirror reflectivity and absorption from a sample containing two overlapping species in the cavity, the time constant for the exponential decay is given by

$$\tau = \frac{d}{c\left[\left(1-R\right)+\alpha_A l_s + \alpha_B l_s\right]} \qquad 2)$$

where d is the cavity length, R is the reflectivity of the cavity mirrors, α (= $\alpha_A + \alpha_B$) is the Beer's Law absorption coefficient of a sample in the cavity, l_s is the length of the **o**ptical path through the sample, and c is the speed of light. Scanning the laser wavelength, the ringdown time decreases when tuned to an absorption wavelength of the sample (i.e. α increases). Once the mirror reflectivity has been measured (i.e. $\alpha = 0$) and a sample introduced, CRDS provides an absolute measure of the absorbance, αl_s.[20,21] However, if both α_A and α_B contribute then the resulting change in ringdown time does not give a correct measure of either component.

However, to succeed as a diagnostic requires, among other things, a determination and elimination of any background absorptions or interferences caused by other constituents of breath impacting the sensor performance. For example, it is well known that sulfur dioxide (SO_2) absorbs UV radiation in the same spectral region as mercury (253 nm) resulting in a significant problem for most mercury detection equipment. However, for CRDS, as equation 2 demonstrates, the ringdown time will incorporate absorption due to the concentration of both SO_2 and mercury. The PI and associates noted[20-26] in related research, that the presence of isotopic structure during a scan of the mercury 253 nm line raised the possibility (later, confirmed) that absorbance components of complex mixtures can be separated (Fig 4a).[27,28] For example, using a gas mixture containing 1.2 ppb mercury and 2175 ppm SO_2 respectively (Fig. 4b) the five mercury isotope peaks obtained using CRDS are easily resolved above the SO_2 background absorption, and by scanning across the peaks, it is possible to accurately extract BOTH the Hg and SO_2 concentrations.

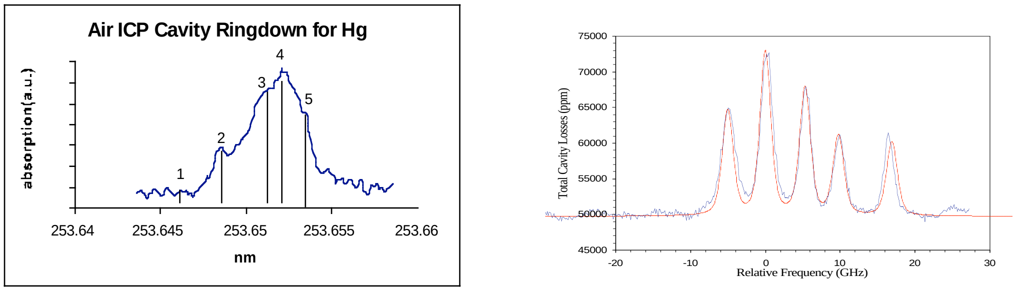


Figure 4: Isotopic Mercury pressure. a) atmospheric pressure scan mercury in high temperature ICP plasma using dye laser.[22,26] b) high resolution laser scan 1.8 ppb Hg, 2000 ppm SO_2 @ 110 torr, temperature 473 K. Experimental data (blue), theory (red).[28]

By utilizing the fine absorption structure it has been demonstrated that accurate determination of individual components, down into the ppt range, can be successfully achieved. In addition it has also been shown that none of the other components of flue gas effected the ability of the CRD instrument to accurately determine the mercury concentration. This was confirmed by during a field test (by the PI) of a prototype Hg CRDS system at NETL Pittsburgh coal-powered pilot plant.[27] After a week-long test, no problem was evident from the presence of particulates (increase in scattering) and the exhaust gases did not negatively impact the mirror reflectivity.

To briefly summarize, this research provides further confirmation that cavity ringdown spectroscopy provides both high sensitivity and selectivity, yet remains an inherently simple technique. It provides an absolute measure of the absorbance, αl_s, a self-calibrating feature that differentiates CRDS from other relative optical measurements such as emission, laser-induced fluorescence (LIF) or resonantly enhanced multiphoton ionization (REMPI). In addition, unlike fluorescence detection, CRDS is not affected by quenching from molecular species in the surrounding gas, thereby providing an accurate measurement of the concentration in complex environments.

Key Research Accomplishments

We proposed an innovative science-driven program to evaluate the full potential of cavity ringdown spectroscopy (CRS) as a powerful new analytical technique for the detection of ultra-trace levels of formaldehyde under environmental conditions simulating exhaled breath. In so doing, this program aimed to provide a significant advance beyond the presently available technology. The intended procedure was to build upon the experience already gained in using CRDS to measure VOC's of environmental interest. Once a laser emitting at the optimum IR wavelength (3550 nm) was obtained, experiments were proposed to establish the optimum performance of CRDS. The intention of these results would set the stage for the development of a prototype CRDS-based breathanalyzer and eventually, in the future, allow studies to establish the viability of using formaldehyde as a biomarker to detect the presence of breast cancer.

The results obtained in this effort confirmed again the sensitivity and selectivity of cavity ringdown spectroscopy. However, due to technical difficulties beyond our control we are unable to give a definite answer to the questions asked in our initial proposal. We are still working to circumvent these technical difficulties and expect to produce definitive results in the near future. Nevertheless the following results were obtained:

a) built and tested a formaldehyde CRDS system and obtained formaldehyde detection limits in the UV region
b) developed a labview program to control the laser and collect and analyze the results
c) tested a quantum cascade laser for CRDS
d) trained a postdoctoral fellow in CRDS techniques and introduced undergraduate students to research in laser spectroscopy and experimental techniques
e) gained ability to develop a frequency-difference laser to provide tunable light source
f) presented the results of this research at The 4th Era of Hope in Philadelphia, Pennsylvania June 8-11, 2005 and The“32nd FACSS conference, October 9-13, 2005 Quebec City, Canada.

Outcomes

The statement of work in the original proposal detailed the exploratory effort required to design, construct and evaluate a prototype IR cavity ringdown spectrometer to facilitate breath analysis as a diagnostic tool. The individual tasks to be performed and progress made in each are described below.

Overview of the Project

This research grant was awarded during the period of time the PI accepted a position at the University of Tulsa. This change in position and institution resulted in significant delays in the project. Progress was hindered by several different factors including

1) Unavailability of Mississippi State University dye laser system. A dye laser (Lambda Physik Scanmate) was purchased using the PI’s startup funds enabled us to meet this objective.

2) The late withdrawal (after acceptance) of original postdoctoral associate and the associated delays in finding a replacement.

However, the most significant problem encountered was the inability of the supplier to meet the specifications re quantum cascade laser, the delays involved, and the resulting need to develop an alternative light source. Further details are discussed below.

As the effect of these delays on the project became evident, a 12 month no-cost extension was requested in June 2004. A description of the tasks and results obtained are given below.

Task 1: Breath Analysis CRDS System Development:

As proposed, a CRDS system was designed and constructed to allow for optimum detection of formaldehyde. This involved the modification of an existing CRDS system (Figure 5).
To achieve the required sensitivity, it is necessary to use the formaldehyde fundamental absorption lines in the IR (around 3.55 μm). This required major hardware changes in particular the light source (tunable laser), associated optics, ringdown mirrors, and detectors.

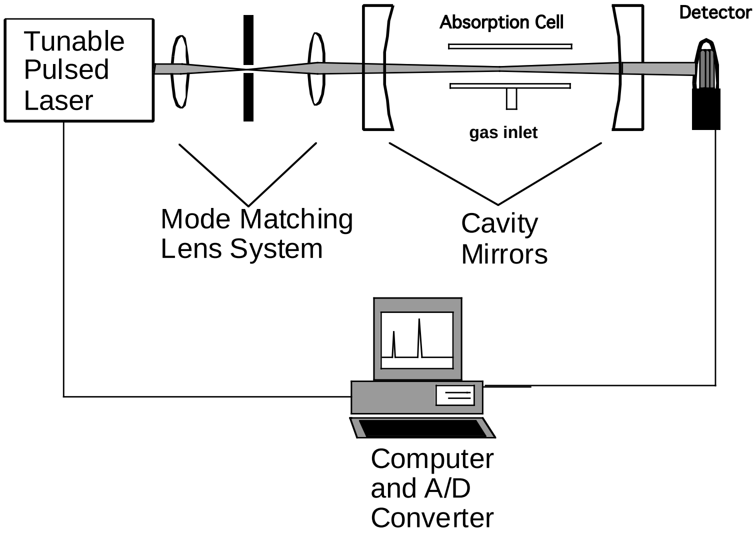


Figure 5: A schematic diagram of a cavity ringdown spectrometer.

IR Laser Developments:

A Quantum Cascade Diode laser was ordered with an initial delivery date of March 2004. This item was not an off-the-shelf item and had had to be built with an approximately 4-month lead-time. In addition to the actual laser, support infrastructure (temperature controller, pulse generator detector, etc.) for the QCL source was also purchased. The support instrumentation arrived on schedule. Unfortunately, the manufacturing process for the QCL was unsuccessful at the first attempt. After discussions with the supplier, it was decided that they would try again with the next delivery date set for September 2004. As a part of this decision, a demonstration QCL laser ($\lambda = 4.5\ \mu m$) was provided by Aples Laser to evaluate. Although not the required wavelength, it nevertheless, provided the opportunity to explore the properties and behavior of quantum cascade lasers as a light source for cavity ringdown spectroscopy.

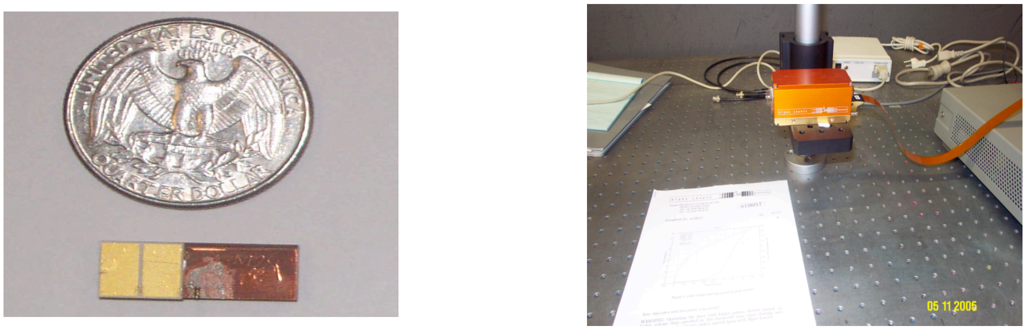


Figure 6: A Quantum Cascade Laser

From the results of these series of experiments, it became evident that at room temperature operation, the beam quality and the broad output line width of the quantum cascade laser output raised serious questions regarding their suitability for the work proposed. In addition, the demonstration QCL failed unexpectedly within a month or so of our receiving it. This raised additional doubts about the state of the technology. At this point, we began to examine possible replacement light sources, such as Pb-salt and frequency difference lasers discussed in the original proposal. The Pb-salt was too expensive (and requires LN_2-cooling). It was decided that the frequency difference laser was the most likely candidate to replace the QCL as the light source. Although several of the more expensive components required were available in-house (e.g. tunable 1550 nm diode laser), no funds were available for the additional components required.

Following another failure of the QCL to meet specifications, discussions were held with the supplier (Boston Electronics) regarding the order. One option was to accept an off-the-shelf QCL. This would, at least, allow the support instrumentation to continue to be useable.

However, this would have meant the end of the IR research, the heart of the project, and we were not ready to accept that. After further discussions, it was agreed to cancel the order. The supplier also agreed to accept the return of the support hardware. This agreement allowed us to move to the second choice light source discussed in the original proposal. It also allowed us to take advantage of progress in frequency-difference laser technology(discussed further below).

Difference-Frequency Laser: During the time we were waiting for the QCL to be constructed, developments in difference-frequency lasers indicated that they appeared to be the more promising technology for the wavelength range required. In the middle of August 2005, after a third unsuccessful attempt to build a QCL to meet specifications, and following discussions with the supplier, the QCL order was cancelled. Using an in-house tunable NIR diode laser (New Focus Model 6427) together with the purchase of a high power diode laser we began the development of a difference-frequency laser. Difference-frequency generation of 3 – 5 μm light[33] has become an increasingly attractive alternative to the other possible source - Pb-salt lasers. These advantages include, most importantly, the higher spatial beam quality needed for cavity ringdown spectroscopy, as well as not requiring cryogenic cooling and the associated issues of temperature cycling, mode-hop-free operation and, finally, cost.

Figure 7 is a schematic of the DFG-based cavity ringdown spectrometer. The DFG laser uses two pump sources and driver electronics together with the fiber optics for polarization control and beam combining. The cavity is the same as the UV system with the exception that the UV mirrors are replaced by 3.3 μm, 99.97% reflectivity mirrors (Los Gatos Research Inc.). The mid-IR DFG source is constructed using diode-laser sources at 1 and 1.5 μm. One source is a 6 mW tunable DFB telecommunication laser (New Focus Model 6427) with -70 dB of isolation was used to seed an Erbium-doped fiber amplifier. The other source, a 150 mW, 1080 nm diode laser was purchased by Lumics.

The DFG generation is performed by imaging the fiber output (f = 10 mm, AR coated lens) into a 10 mm W x 1.0 mm T x 40 mm L Periodically Poled, Lithium Niobate (PPNL) crystal (Deltronic Crystal Industries Inc,.). The PPNL crystal contains nine quasi-phase matched periods going from 29,60: 29.80: 29.90: 30.00: 30.10: 30.20: 30.30: 30.40: 30.60 μm. The PPNL crystal is mounted in a temperature controlled oven (HC Photonics). The crystal output is collimated by a CaF_2 lens and residual pump light is removed using a Ge filter. The mid-IR is then directed into the ringdown cavity.

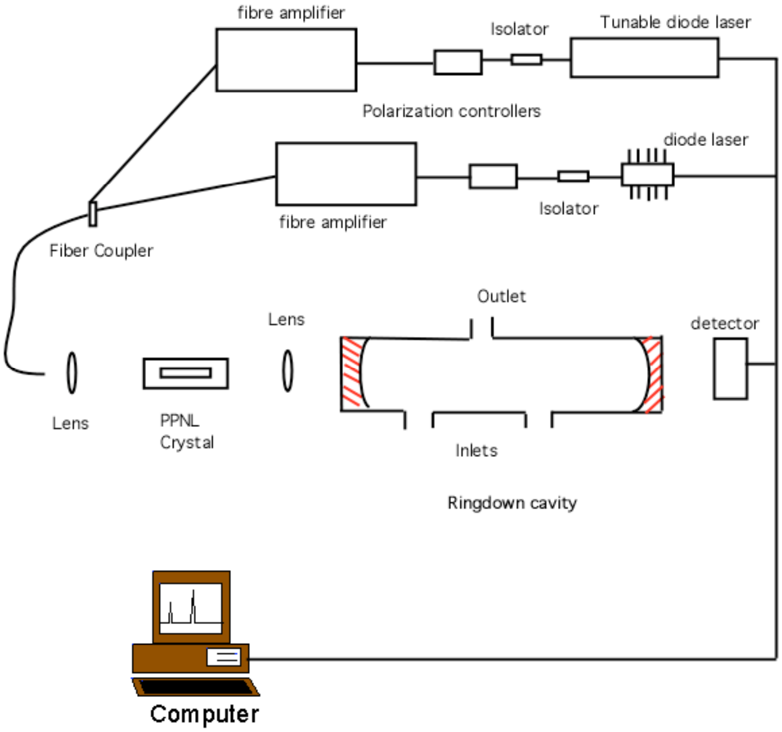


Figure 7: Schematic of DFG laser

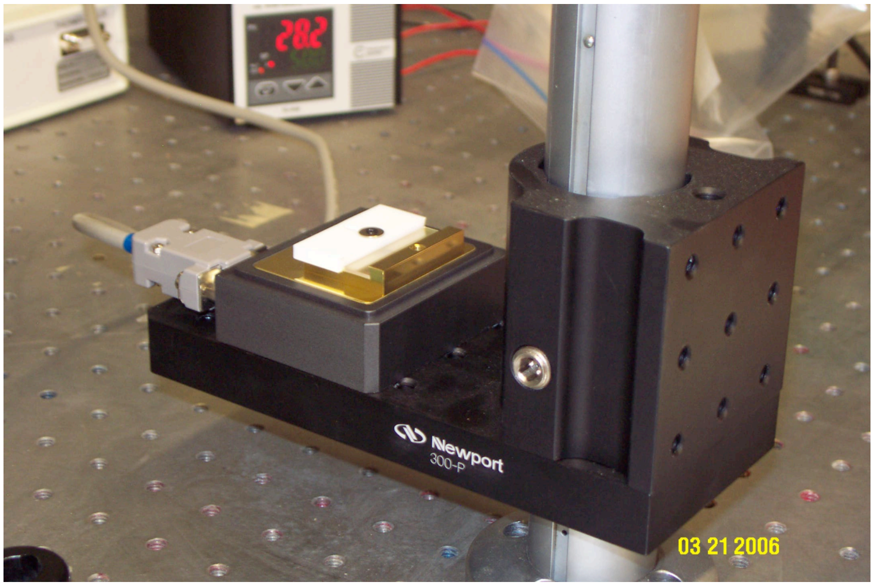


Figure 8: The Periodically Poled, Lithium Niobate (PPNL) Crystal

It had been hoped to have this system operational in time to meet all the tasks laid out in the original proposal. However, the IR laser development was slower than expected. Etalon effects proved more troublesome than expected resulting in the need to replace the connector with FC/APC connectors (8^o off-angle fiber connections) have delayed the development. Initial studies also indicate that the output from the 1080 nm diode would still be insufficient indicating that it is necessary to also amplify this component. A Yb fiber amplifier is being developed in-house using double-clad Yb fiber pumped by 2 W 980 nm diode lasers. The outputs from the amplifiers will then be combined using a fiber multiplexer.

{NOTE: This effort is continuing. At present, two students working on this project for their senior thesis and the laser is expected to be completed shortly.}

UV laser:

In the original statement of work, it was stated that while we were waiting for the QCL to be constructed, research would be focused on the UV absorption of formaldehyde using an existing narrow linewidth dye laser system. However, in moving from Mississippi State University to the University, access to the dye laser and cavity ringdown system was no longer available. To fulfill this promise, a used narrow line (0.03 cm^{-1}) 10 Hz dye laser (Lambda Physik, Scanmate 2E) was purchased (using the PI's internal startup funds) and installed (late 2004). Startup problems (faulty laser electronics) delayed full-time operation until April 2005. However, once the laser was installed, a UV CRDS cavity was designed, constructed, and evaluated as follows:

Cavity Design: For these experiments a 74 cm long cavity was constructed. The effective sample pathlength was set at 12.5 cms. The additional length allowed the mirrors to be protected from possible contamination while still providing a long enough sample path length. The mirrors were plano-concave with a 6 meter radius of curvature and were coated for maximum reflectivity at the appropriate wavelength (99.99% at 340 nm, Los Gatos Inc.). The laser beam is spatially filtered and mode matched into the cavity using a small homemade telescope. A narrowband interference filter was used to reject background radiation prior to the detection electronics.

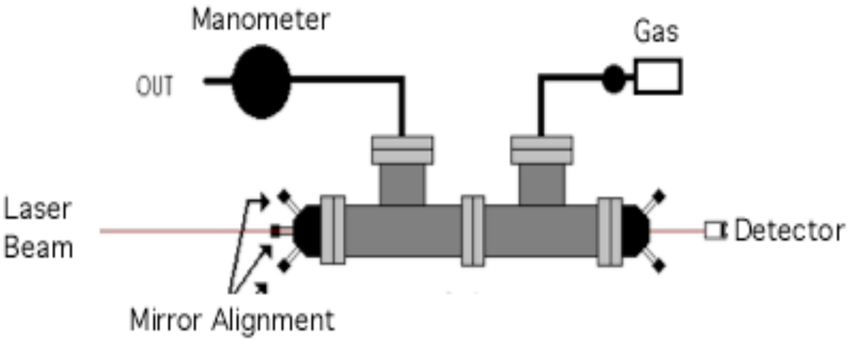


Figure 9: Cavity Schematic

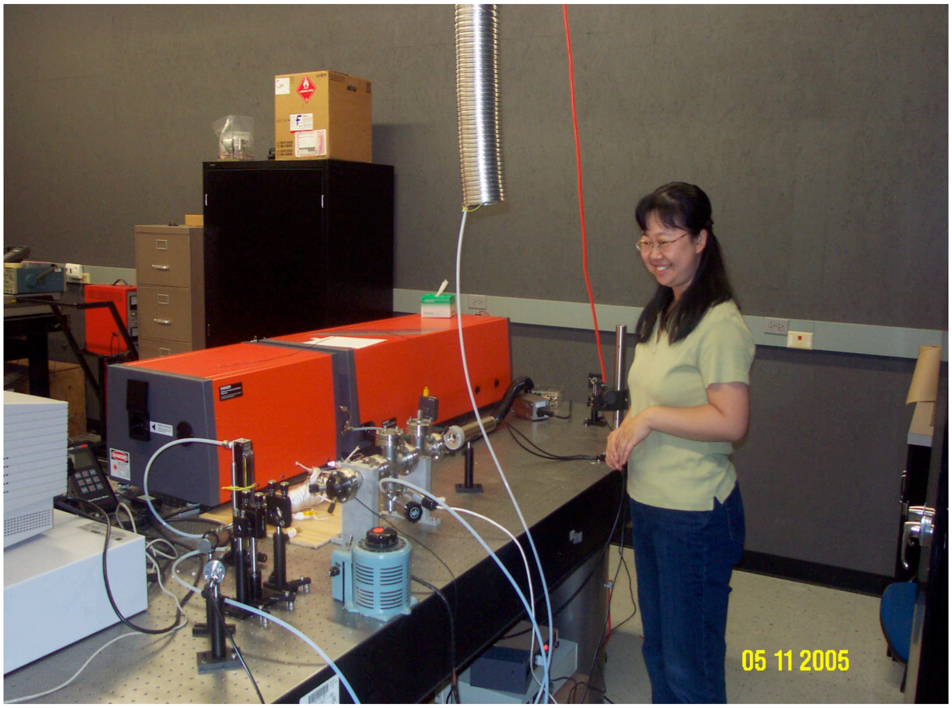
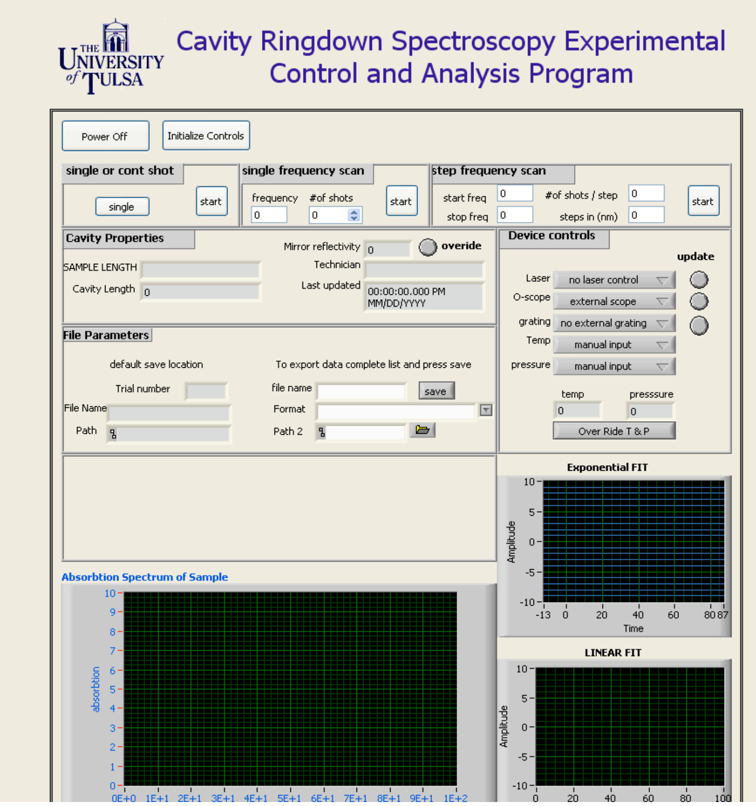


Figure 10: A photograph of the UV cavity ringdown system.

Data acquisition: The signal from the detector (photomultiplier tube in the UV), placed behind the second cavity mirror, was initially digitized by a 200 MHz digital oscilloscope and transferred by a GPIB interface to a personal computer. The decay time constant is calculated from the ringdown signal and displayed on-line. The full ringdown waveform can be saved for later analysis if desired. The time constants were processed off-line to obtain the peak height and integrated absorbance values. To enhance the data acquisition speed, a fast analog-to-digital converter (GaGa CompuScope 1250 – 1M) was purchased, and installed, to replace the digital oscilloscope.

Task 2: Software Modification: Modify an existing LabView software packet to analyze the data and control the diode laser and sampling system. An undergraduate, Thomas Holler, undertook a senior research thesis (in association with the postdoctoral research associate) to develop a LabView program to control the new dye laser system and collect and analyze the data. The software package is working satisfactorily and is designed such that additional modifications can be implemented as needed.



THE UNIVERSITY of TULSA

Cavity Ringdown Spectroscopy Experimental Control and Analysis Program

frequency 0
#of shots 0
start freq 0
stop freq 0
#of shots / step 0
steps in (nm) 0
Mirror reflectivity 0
Cavity Length 0
Last updated 00:00:00.000 PM MM/DD/YYYY
Laser no laser control
O-scope external scope
grating no external grating
Temp manual input
pressure manual input
temp 0
presssure 0

Figure 11: Front Panel of CRDS LabView Interface

Task 3: Sample delivery system: A formaldehyde delivery system was designed, built and tested. A formaldehyde permeation tube (5 ppm/min @ 100 C, uncertified. VICI Inc.) was enclosed in a temperature controlled enclosure, preheated nitrogen gas, was then flowed through the enclosure at a controllable flowrate. As the permeation tube was not certified, we used cavity ringdown spectroscopy to measure the concentration and to evaluate the losses in the delivery system.

The calculation of H_2CO concentration

$$\tau_0 = \frac{l_c}{c[(1-R)+\alpha_b l_c]}$$

where, l_c is the cavity length, c is the speed of light, R is the reflectivity of the mirrors and α_b is the absorption coefficient for various background losses.

$$\tau_1 = \frac{l_c}{c[(1-R)+\alpha_s l_s + \alpha_b l_c]}$$

α_s is the absorption coefficient of the sample species of interest, l_s is the pathlength. through the sample,

$$\alpha = \frac{l_c}{c l_s}\left[\frac{1}{\tau_1} - \frac{1}{\tau_0}\right]$$

In our experiment, *lc*=74cm, *ls*=12.5cm.

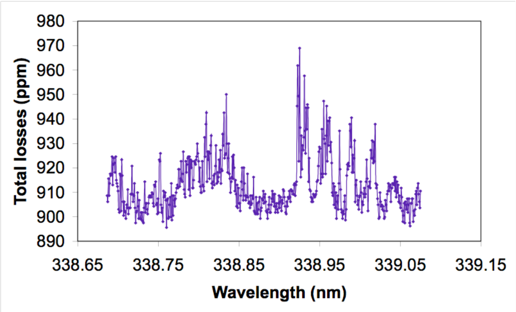


Figure 12: CRDS scan of H_2CO

For example, for an empty cavity the ringdown decay time was 1.89 µs. Therefore, in this case for a flow rate of 400cc/min passing through the system, the ringdown decay time was 1.279µs.

$$\alpha = \frac{l_c}{cl_s}\left[\frac{1}{\tau_1} - \frac{1}{\tau_0}\right] = \frac{74}{3\times10^8\times12.5}\left[\frac{1}{1.279\times10^{-6}} - \frac{1}{1.89\times10^{-6}}\right]$$

$$= 1.973\times10^{-8}\times2.53\times10^{5} = 5.0\times10^{-3}\,m^{-1}$$

$$\alpha = N\sigma$$

N is the number of molecules, σ is the absorption cross-section, 5.5×10^{-24}m^2.

and

$$N = \frac{\alpha}{\sigma} = \frac{5\times10^{-3}}{5.5\times10^{-24}} = 0.91\times10^{21}\ \mathrm{m}^{-3}$$

This yielded an H_2CO concentration of 5.3 ppm. A result in excellent agreement with the uncertified concentration (5ppm) of the permeation tube, as given by the manufacturer.

It was determined early in the project that formaldehyde has a tendency to stick to the walls of the chambers and tubing. The result above was achieved following extensive testing and experimentation to ensure that these losses where reduced to a minimum. This was achieved by both design changes to ensure the mirrors were not affected and by maintaining chambers and sample lines at elevated temperatures. Figure 13 is a plot of a scan across a formaldehyde spectral line for a blank (N_2 only) and 5 ppm H_2CO (in N_2).

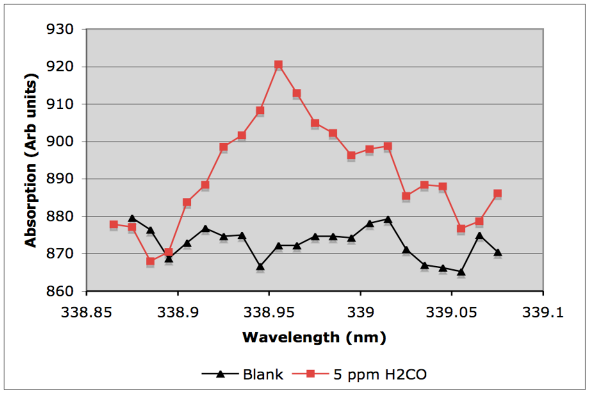


Figure 13: CRDS scan of 5 pmm H_2CO and a Blank

Task 4: CRDS system optimization: Due to the lack of a suitable IR laser source during the project, it was not possible to fully optimize the system. Detection limits in the UV were established for the dye laser system (0.2 ppm) which is, as expected from complementary studies performed by the PI,[20-28] are in good agreement with the theoretical predictions. The fact that the dye laser operated at 10 Hz places restrained the ability to rapidly average the data thereby placing a limit on data points obtained ultimately impacting accuracy of the measurements.

Although it was also not possible to directly evaluate methods to eliminate or avoid possible interference in the 3.3 μm region, results obtained by complementary studies[20-28] indicate that the potential of CRDS for the detection of formaldehyde in complex environment of the breath remains high.

Task 5: Data Dissemination:

Results from this work was presented at two conferences "The 4th Era of Hope in Philadelphia, Pennsylvania June 8-11, 2005 and the "32nd FACSS conference October 9-13, 2005 Quebec City, Canada. Once the frequency-difference laser is completed, we intend to publish the results in a peer-reviewed publication.

Reportable Outcomes

Two papers were presented that incorporated results produced by this project:

1) A poster at the 4th Era of Hope in Philadelphia, Pennsylvania June 8-11, 2005

and

2) A presentation at the"32nd FACSS conference, October 9-13, 2005 Quebec City, Canada.

Conclusions

This project was an exploratory effort pushing the edges of technical laser development. Over the time period of this effort, Cavity Ringdown spectroscopy has become a mature technique. However, its major drawback remains its need for tunable narrow linewidth light sources at the required wavelength. The formaldehyde results we obtained in the UV region for (like many other CRDS measurements the PI has made)[20-28] were very close to the theoretical limits. However, the sensitivity of the technique in that spectral region is inadequate for use as a formaldehyde breathanalyzer. It requires a suitable source in the IR. Our inability to obtain such a suitable laser source is the primary cause that has prevented this project from providing a definitive result with respect to the application of cavity ringdown spectroscopy to the early detection of breast cancer. As such, the results obtained were inconclusive.

Although the grant period has ended, it is our intention to continue the project to evaluate the performance of the system. It is expected that the DFG laser will be operational by the end of next summer and with the assistance of graduate and undergraduate students this research will be brought to a satisfactory conclusion.

Benefits to Society: Apart from providing the foundation for a novel ultra-sensitive diagnostic tool to study the real-time composition of exhaled breath and its implications to a wide range of medical conditions, this project has the potential to have a significant impact on a much broader slice of society. Although this explorative effort can not yet claim to have successfully reached its original goals, society has benefited by the training this research has, and continues, to provide for the next generation's workforce.

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Appendix:

Conference Abstracts

1) The fourth Era of Hope meeting for the Department of Defense (DOD) Breast Cancer Research Program (BCRP) was held on June 8-11, 2005 in Philadelphia, Pennsylvania.

AN EXPLORATORY STUDY OF CAVITY RINGDOWN SPECTROSCOPY AS A NONINVASIVE BREATH DIAGNOSTIC FOR BREAST CANCER

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Background: Human breath contains a complex mixture of several hundred volatile organic compounds (VOCs). A number of these compounds have been identified as candidate markers of various cancers (e.g. formaldehyde in breast cancer). Although breath analysis has been shown to have great potential as a diagnostic tool, most of the compounds of interest are exhaled in picomolar concentrations, highly reactive and volatile and real-time breath analysis for these compounds is not possible with existing technology. Cavity ringdown spectroscopy (CRDS) is a measurement of the rate of absorption of a sample within a closed optical cavity, rather than the standard measurement of the absorbed signal strength over a given sample path. It maintains much of the simplicity and advantages of classical absorption spectroscopy, but has been demonstrated to provide an increase in sensitivity of up 10,000 times. Utilizing CRDS, real-time breath analysis at the picomolar levels required for biomarker applications may be possible.

Objective: To evaluate the potential of cavity ringdown spectroscopy to provide real-time measurements of formaldehyde concentration in exhaled breath for the purpose of the detection of breast cancer.

Specific Aims: To determine the sensitivity of cavity ringdown spectroscopy to detect formaldehyde under conditions simulating those present in exhaled breath and evaluate the technique's potential in establishing the validity of biomarkers in exhaled breath.

Study Design: A study will be initiated to evaluate the formaldehyde CRDS spectrum using pulsed dye and diode laser systems. Analytical UV cavity ringdown spectroscopy techniques will be developed for the detection of gas-phase formaldehyde in a sample chamber developed to simulate the variations in gas flow, humidity, etc., present in exhaled breath.

Relevance: Every woman over 50 is recommended to have yearly mammograms to monitor for

breast cancer with the primary goal of early detection. The problems with this technique are well known and range from the exposure to X-rays, the difficulty of analysis, to patient resistance. The establishment of formaldehyde levels in the breath as a reliable biomarker for breast cancer could significantly improve both testing and detection rates resulting in a significant impact on the success of treatment, as well as reduce the financial burden of treating breast cancer on the economy as a whole. The proposed research does not aim to achieve all these goals but it could provide the crucial first step along the path, a real-time noninvasive diagnostic “breathanalyzer”. Finally, the successful application of CRDS to the detection of formaldehyde in exhaled breath may provide the foundation for other medical applications using a cavity ringdown-based “breathanalyzer.”

2) 32nd Federation of Analytical Chemistry & Spectroscopy Society Conference October 9 – 13, 2005 Quebec City, Canada.

Progress in Analytical Cavity Ringdown Spectroscopy
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Abstract.

As cavity ringdown spectroscopy has become a mature absorption technique, applications have increased. New applications include the development of environmental and medical monitors using elemental, molecular and isotopic measurements. This paper presents recent progress and results in these areas.

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