Slide 1

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Photonic Technologies for Early Detection of Human Disease

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OUTLINE

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Banff, Canada
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- Motivation and Technology Issues for Physiological Monitors based on expired Human Breath
- Mid-IR QC Laser based Gas Sensors
- Examples of QCL-based Breath Measurements
- Outlook and Summary

Slide 2

Tunable Laser Absorption Spectroscopy (TLAS) for Breath Analysis

- TLAS provides rapid, sensitive and selective concentration measurements of target gases
- TLAS is capable of measuring multiple target gases with a single laser (important for standardizing exhaled breath analysis)
- Pulsed thermoelectrically cooled QC lasers make it possible to design compact, portable and robust TLAS based sensors

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Slide 3

Target Gases – 1
(ImmediateBiomarker Candidates)

| Molecule	Formula	Trace Concentration in Breath (ppb)	Biological/Pathology Indication
Nitric Oxide	NO	6 - 100	Inflammatory and immune responses (e.g., asthma, COPD), vascular smooth muscle response
Carbon Monoxide	CO	400 - 3000	Hyperbilirubinemia, smoking response, CO poisoning, vascular smooth muscle response, platelet aggregation, jaundice, diabetes, cystic fibrosis
Hydrogen Peroxide	H_2O_2	1 - 5	Airway Inflammation, Oxidative stress
Carbonyl Sulfide	COS	100 – 1000	Liver disease and acute allograft rejection in lung transplant recipients
Formaldehyde	HCHO	400 - 1500	Cancerous tumors, breast cancer

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Target Gases -2

Molecule	Formula	Trace Concentration in Breath (ppb)	Biological/ Pathology Indication
Pentane	$CH_3(CH_2)_3CH_3$	4 - 20	Lipid peroxidation, oxidative stress associated with inflammatory diseases, immune responses, transplant rejection, breast and lung cancer
Ethane	C_2H_6	3 - 100	Lipid peroxidation and oxidative stress
Carbon Dioxide isotope ratio	$^{13}CO_2/^{12}CO_2$	$4 - 5 \times 10^5$	Marker for Helicobacter pylori infection associated with peptic ulcers and gastric cancer, drug clearances rates
Methane	CH_4	1000 - 8000	Digestive function, colonic fermentation
Ammonia	NH_3	100 - 500	Hepatic encephalopathy, liver cirrhosis, fasting response
Acetone	C_3H_6O	1000 - 5000	Fasting response, diabetes mellitus response, ketosis

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Direct Laser Absorption Spectroscopy
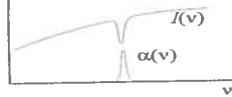
Absorber
Gas, Liquid or Solid
Laser Source
Detector
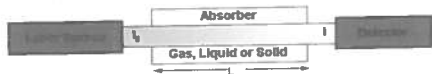
Beer-Lambert's Law of Linear Absorption

$$I(\nu) = I_0 \cdot e^{-\alpha(\nu) \cdot P_a L}$$

$\alpha(\nu)$ - absorption coefficient [$cm^{-1} atm^{-1}$]; L – path length [cm]

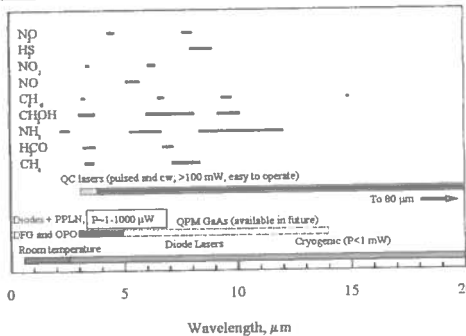ν - frequency [cm^{-1}]; P_a - partial pressure [atm]

$$\alpha(\nu) = C \cdot S(T) \cdot g(\nu - \nu_0)$$

C - total number of molecules of absorbing gas/atm/cm^3 [molecule·cm^{-3}·atm^{-1}]

S - molecular line intensity [cm ·molecule^{-1}]

$g(\nu - \nu_0)$ - normalized lineshape function [cm], (Gaussian, Lorentzian, Voigt)

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Spectral Coverage by Diode & QC Lasers

N_2O
H_2S
NO_2
NO
CH_4
CH_3OH
NH_3
H_2CO
CH_4

QC lasers (pulsed and cw, >100 mW, easy to operate)

To 80 μm

Diodes + PPLN P~1-1000 μW   QPM GaAs (available in future)
DFG and OPO
Room temperature   Diode Lasers   Cryogenic (P<1 mW)

0   5   10   15   20

Wavelength, μm

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Key Characteristics of Quantum Cascade Lasers
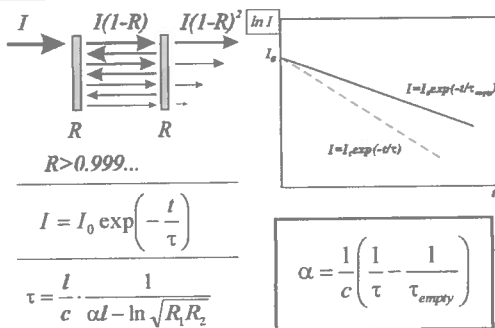
- Laser wavelengths cover entire range from 3.5 to 66 μm determined by layer thickness of same material
- Intrinsically high power lasers (determined by number of stages)
  - CW:~100 mW @ 80°K, mWs @300 °K
  - Pulsed: 1 W peak at room temperature, ~50 mW avg. @ 0 °C (up to 80 % duty cycle)
- High Spectral purity (single mode: <kHz - 330MHz)
- Wavelength tunable by current or temperature scanning
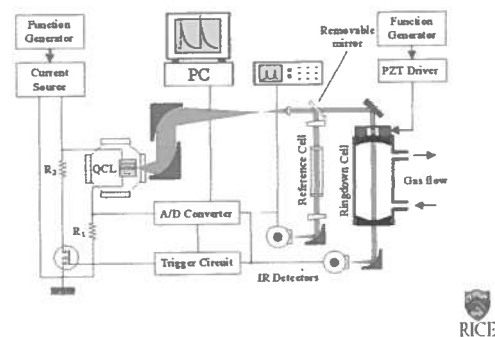- High reliability: low failure rate, long lifetime, robust operation and reproducible emission wavelengths

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Exhaled Nitric Oxide

- **"Asthma is a chronic inflammatory disorder of the lower airways..."**
  - Working definition (NHLBI, 1995)
- FDA approved for monitoring of a patient's response to anti- inflammatory treatment - Approved April 30, 2003
- **Main Applications:**
  - Monitoring chronic airway inflammation by longitudinal eNO breath measurements
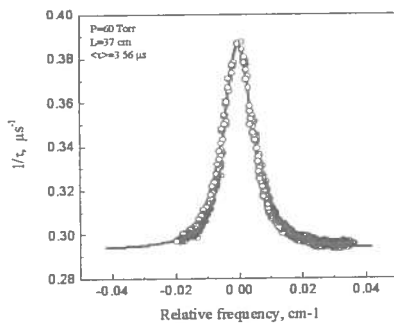 - Monitor the effectiveness and compliance of anti-inflammatory therapies
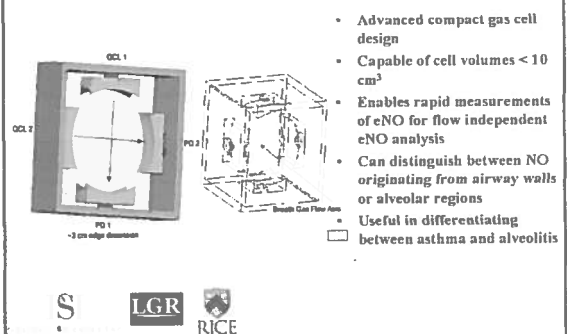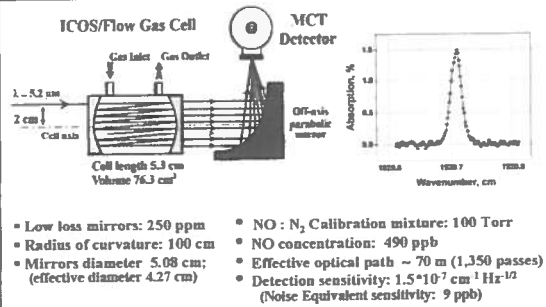
Cavity Ring-Down Spectroscopy

$$I \quad I(1-R) \quad I(1-R)^2$$

$$R > 0.999...$$

$$I = I_0 \exp\left(-\frac{t}{\tau}\right)$$

$$\tau = \frac{l}{c} \cdot \frac{1}{\alpha l - \ln\sqrt{R_1 R_2}}$$

$$\alpha = \frac{1}{c}\left(\frac{1}{\tau} - \frac{1}{\tau_{empty}}\right)$$

CRDS Based Gas Sensor

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NO Absorption Spectrum in N_2
(Unresolved Lines at 1921.599 and 1921.601 cm^{-1})

Cavity Enhanced Spectroscopy of Breath Samples

- Advanced compact gas cell design
- Capable of cell volumes < 10 cm^3
- Enables rapid measurements of eNO for flow independent eNO analysis
- Can distinguish between NO originating from airway walls or alveolar regions
- Useful in differentiating between asthma and alveolitis

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Off-Axis CW Integrated Cavity Output Spectroscopy (ICOS) of NO @ 1920.7 cm⁻¹

- Low loss mirrors: 250 ppm
- Radius of curvature: 100 cm
- Mirrors diameter 5.08 cm; (effective diameter 4.27 cm)
- NO : N₂ Calibration mixture: 100 Torr
- NO concentration: 490 ppb
- Effective optical path ~ 70 m (1,350 passes)
- Detection sensitivity: 1.5*10⁻⁷ cm⁻¹ Hz⁻¹ᐟ² (Noise Equivalent sensitivity: 9 ppb)

Novel compact gas cell design for Off-Axis ICOS

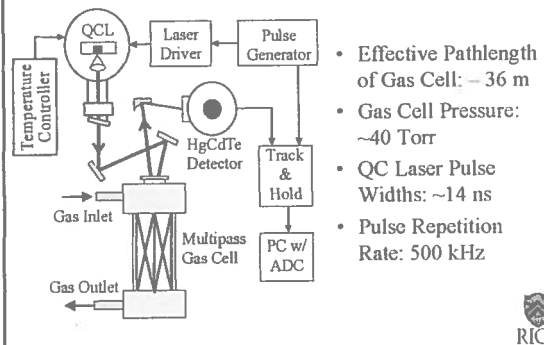Adjustment screws are utilized to make RHS mirror astigmatic

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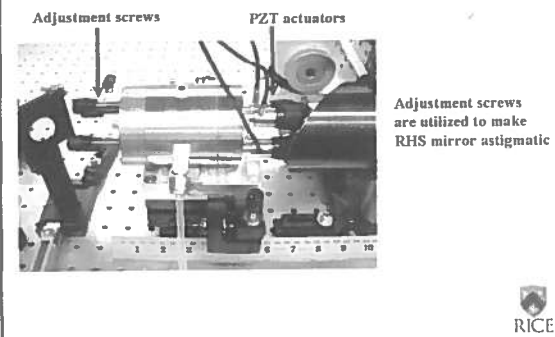
Exhaled Carbonyl Sulfide

- A recent study by the T. H. Risby group at John Hopkins University demonstrated elevated levels of COS could have a diagnostic role in the detection of acute allograft rejection in lung transplant recipients
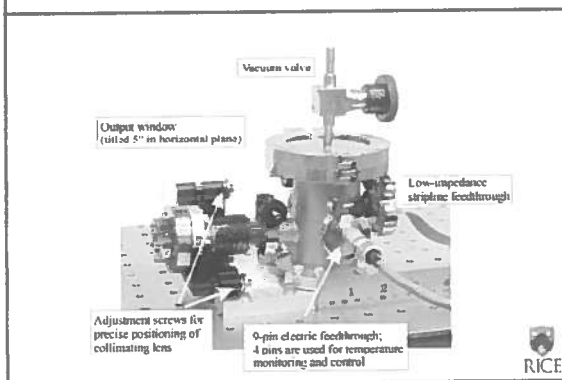 - S. M. Studer, et. al., J. of Heart and Lung Transplantation, 20(11), 1158-66 (2001).

Measured with gas chromatography and flame photometric detection

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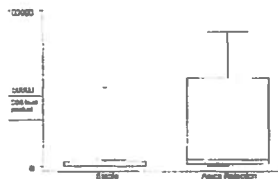
QC-LAS Gas Sensor Architecture

- Effective Pathlength of Gas Cell: ~ 36 m
- Gas Cell Pressure: ~40 Torr
- QC Laser Pulse Widths: ~14 ns
- Pulse Repetition Rate: 500 kHz

TEC cooled QC Laser Housing

Measured and Simulated Absorption Spectra for a 13.2 ppm COS Concentration at 2053 cm⁻¹

HITRAN 2000

Measured Absorption spectra for ~500 ppb of COS mixed with breath and N₂

COS is calibrated to 500-ppb +/- 2% with a gas cylinder
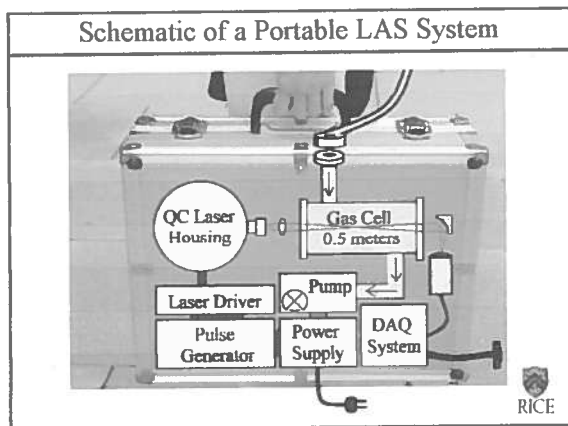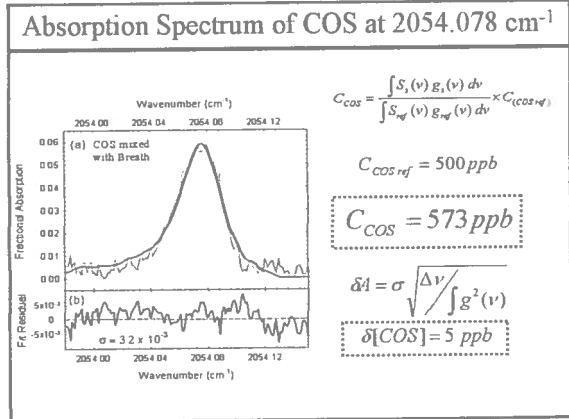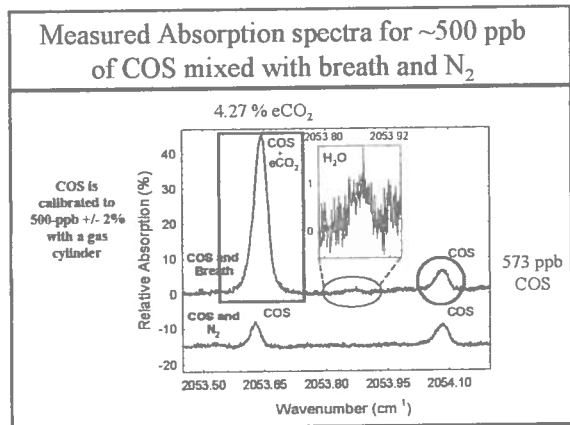
4.27 % eCO₂

573 ppb COS

Absorption Spectrum of COS at 2054.078 cm⁻¹

$$C_{COS} = \frac{\int S_s(v)\, g_s(v)\, dv}{\int S_{ref}(v)\, g_{ref}(v)\, dv} \times C_{(COS\, ref)}$$

$$C_{COS\, ref} = 500\, ppb$$

$$\boxed{C_{COS} = 573\, ppb}$$

$$\delta A = \sigma \sqrt{\frac{\Delta v}{\int g^2(v)}}$$

$$\boxed{\delta[COS] = 5\, ppb}$$

Schematic of a Portable LAS System
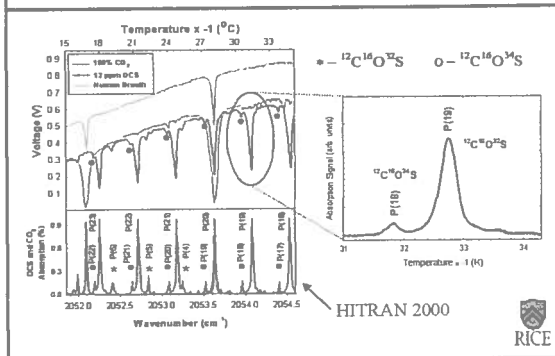
Summary and Future Directions

- **Quantum Cascade Laser based Trace Gas Sensors**
  - Compact, tunable, and robust designs can be realized
  - High sensitivity ($<10^{-4}$) and selectivity (3 to 300 MHz)
  - Fast data acquisition and analysis
  - Detected trace gases: NH_3, CH_4, N_2O, CO_2, CO, NO, H_2O, COS, C_2H_5OH and isotopic species
- **Applications in Exhaled Breath Analysis**
  - eNO: asthma, and alveolitis (e.g. interstitial pneumonia or idiopathic pulmonary fibrosis)
  - ET-CO: neonatal non-hemolytic hyperbilirubinemia
  - OCS: acute allograft rejection in lung transplant recipients
- **Future Directions**
  - Develop advanced compact gas cell for rapid eNO analysis
  - Begin clinical studies of exhaled COS analysis
  - Place a robust and portable point-of-care mid-IR laser spectrometer in a clinical setting

QC laser-based measurements of CO trace gas above cell cultures

- Measured CO production rates of viable cultures of vascular smooth muscle cells
- Achieved a detection limit of for CO of ~20 ppb

Measured CO production above cultured cells compared to control measurements without cell cultures

$y = 143.54 + 55.881x\ R = 0.90345$

Important in understanding the kinetic or time dependent production of CO in heme catabolism

CO Production Rate ~ 44 ppb/h