Advances in Optical Diagnostic Technologies in Medicine

F.K. Tittel, A.A Kosterev, Y.Bakhirkin, C.Roller, S. So, M. McCurdy and G. Wysocki

Rice Quantum Institute,
Rice University
Houston, TX 77005
http://www.ece.rice.edu/lasersci/

OUTLINE

Alumni College Weekend

Houston, TX

Feb. 26, 2005

- General Introduction to Lasers in Medicine and Life Sciences
- Motivation and Technology Issues for Non-invasive, Real-time Monitoring of Exhaled Human Breath
- Mid-Infrared Laser based Gas Sensor Platforms
- Examples of Breath Measurements: NO, CO and COS
- Summary and Outlook

Main Thrust of U.S. Laser Activities in 2005 and Beyond

1. Laser Devices

New VUV to IR (Tunable Solid State) Lasers, Short Wavelength Lasers, Femtosecond Technology, High Power Lasers

2. Optical Communications and Information Technology (Photonics)

Fiber Optics, Semiconductor Lasers, WDM Devices, Optical Data Storage (Holography)

3. Surface Engineering

Integrated Optics, Microelectronics (Photolithography)

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Main Thrust of U.S. Laser Activities in 2005 and Beyond (Continued)

4. **Industrial Applications**

5. **Medical and Biomedical Applications**

6. **Laser Spectroscopy and Remote Sensing**

7. **Photophysics**

   Quantum Optics, Nonlinear Optical Processes, Laser Fusion, Nanotechnology

8. **Laser Chemistry**

   Chemical Reactions and Kinetics, Combustion, Isotope Separation

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Unique Properties of Laser Light

- Intensity
- Monochromaticity (Coherence)
  - Spectral Resolution
  - Temporal Resolution
- Directionality
- Wavelength Tunability
- Efficiency

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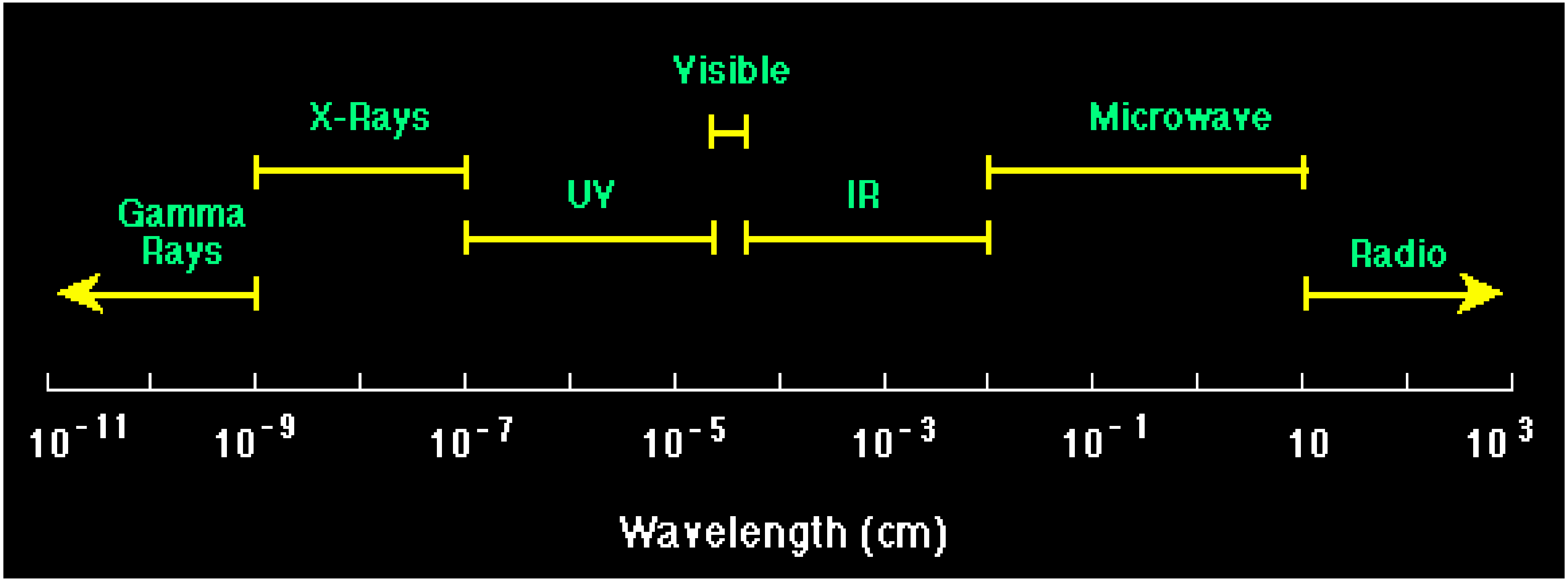
Electromagnetic Spectrum (X-ray to THz)



Laser Types

- **Lasers can have different:**
  - Lasing media (gases, solids, semiconductors, liquids)
  - Mode of pumping (optical, discharge, electrical, chemical)
  - Output mode (pulsed, cw, quasi cw)
  - Wavelengths (from XUV to far-IR)
- **Important laser types include:**
  - Semiconductor diodes
  - Nd: glass, Nd:YAG, Ti: sapphire
  - Carbon dioxide, Excimer

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Motivation & Technology Issues for Optical Diagnostic Technologies in Medicine

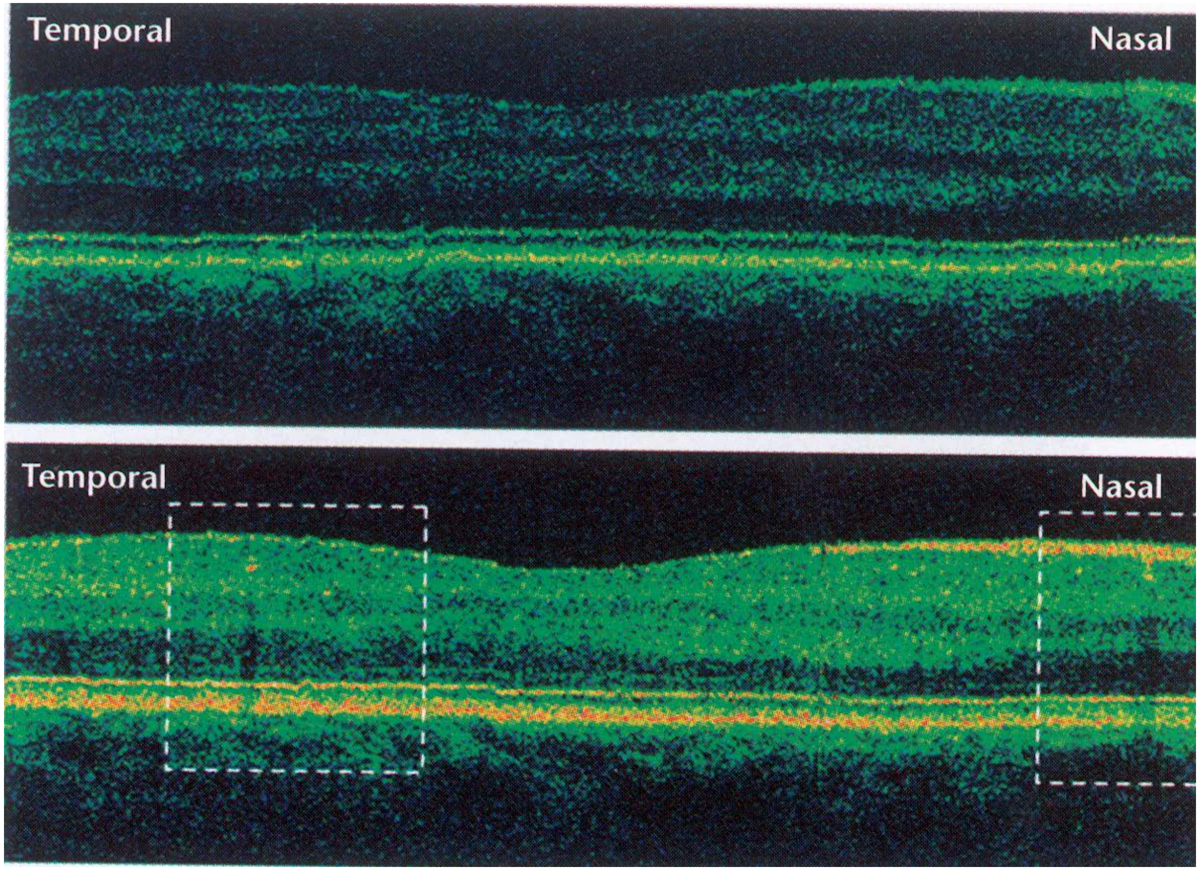
Applications of Optical Diagnostic Technologies in Medicine and the Life Sciences - Biophotonics

- **Breath Analysis**
- Lasers in Ophthalmology
- Cancer Diagnostics and Therapy
- Bio-imaging applications: Scattering Spectroscopy & Tissue Trans-illumination
- Tissue Engineering
- Applications in the Life Sciences
  - Laser manipulation – laser tweezers
  - Energy Transfer in DNA Complexes
  - Correlation Spectroscopy in Microbe Movements

Optical Coherence Tomography (OCT)

a)

b)



In vivo OCT tomograms (a) and with (b) adaptive optics. The use of adaptive optics increases the transverse resolution of the OCT image to **5-10 μm,** and improves the signal to noise ratio by up to 9 dB

Effect of Air Pollution – NO_X

- Ambient nitric oxide (aNO) is a major component of smog.
  - Automobile exhaust is a primary source.

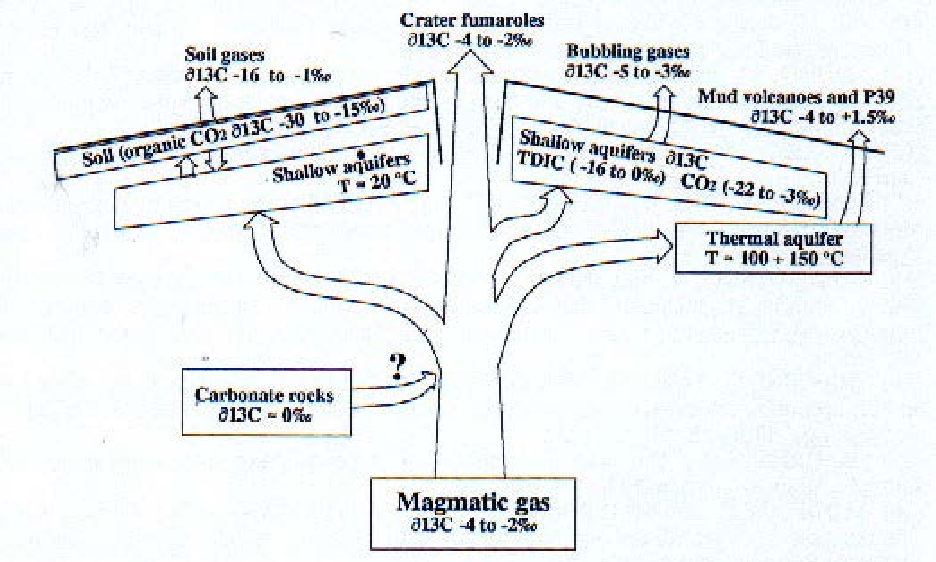
Worldwide Megadirty Megacities

	Population, m		Sulphur dioxide	Particulate matter	Lead	Carbon monoxide	Nitrogen dioxide	Ozone
	1990, ext.	2000, proj.						
Bangkok	7.16	10.26	○	●	▨	○	○	○
Beijing	9.74	11.47	●	●	○	-	○	▨
Bombay	11.13	15.43	○	●	○	○	○	-
Buenos Aires	11.58	13.05	-	▨	○	-	-	-
Cairo	9.08	11.77	-	●	●	▨	-	-
Calcutta	11.83	15.94	○	●	○	-	○	-
Delhi	8.62	12.77	○	●	○	○	○	-
Jakarta	9.42	13.23	○	●	▨	▨	○	▨
Karachi	7.67	11.57	○	●	●	-	-	-
London	10.57	10.79	○	○	○	▨	○	○
Los Angeles	10.47	10.91	○	▨	○	▨	▨	●
Manila	8.40	11.48	○	●	▨	-	-	-
Mexico City	19.37	24.44	●	●	▨	●	▨	●
Moscow	9.39	10.11	-	▨	○	▨	▨	-
New York	15.65	16.10	○	○	○	▨	○	▨
Rio de Janeiro	11.12	13.00	▨	▨	○	○	-	-
Sao Paolo	18.42	23.60	○	▨	○	▨	▨	●
Seoul	11.33	12.97	●	●	○	○	○	○
Shanghai	13.30	14.69	▨	●	-	-	-	-
Tokyo	20.52	21.32	○	○	-	○	○	●

Source: United Nations ● High pollution ▨ Moderate to heavy pollution ○ Low pollution - No data available

Volcanological applications

- CO_2 the most abundant component of volcanic gases after H_2O
- $\delta^{13}C$ is a sensitive tracer of magmatic vs. hydrothermal or groundwater contributions to volcanic gases
- Monitoring $\delta^{13}C$ can be used in eruption forecasting and volcanic hazard assessment



Hippocrates, 460 BC

Hippocrates considered the odor of exhaled breath an important tool in diagnosing diseases

Motivation of laser based breath analysis

- Exhaled breath biomarkers have diagnostic and therapeutic potential. Breath biomarkers have particular clinical appeal because they are:
  - Non-invasive
  - Repeatable or continuous
  - Real-time
  - Applicable as markers of many diseases, exposure & susceptibility

What is breath?

- Any molecule that has a measurable vapor pressure can be present in exhaled breath
- Breath is a reflection of composition of inspiratory air and endogenously produced molecules
- Sampling breath is non-invasive; can be collected from mouse to man, and from neonate to elderly
- Can sample breath temporally without exposing subject to any risk

Composition of exhaled breath

- <u>Bulk matrix</u> (99.99999%)
  - Nitrogen
  - Oxygen
  - Water
  - Carbon dioxide
  - Inert gases
- <u>Trace components</u> (<1ppm)
  - Endogenous molecules
  - Exogenous molecules

Trace components of breath

- Approximately 300 compounds have been identified in breath
- Endogenous origins
  - Ethane (0-10 ppb), pentane (0-10 ppb), isoprene (50-200 ppb), acetone (0-1 ppm), ethylene, ethanol, methanol, acetaldehyde, isopropanol, carbon monoxide (0-10 ppb), nitric oxide (1-50 ppb), sulfides, amines, ammonia (0-1 ppm),
- Exogenous origins
  - Reflection of the composition of inhaled air: indoor and outdoor pollution
  - Reflection of prior consumption of foods, or beverages
- Typically [exogenous]>[endogenous]

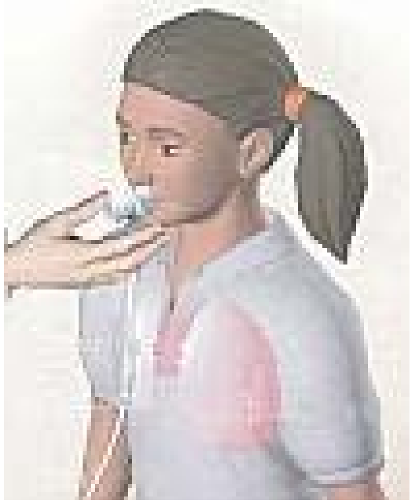
Important Biomedical Target Gases

Molecule	Formula	Biological/Pathology Indication
Pentane	$CH_3(CH_2)_3CH_3$	Lipid peroxidation, oxidative stress associated with inflammatory diseases, transplant rejection, breast and lung cancer
Ethane	C_2H_6	Lipid peroxidation and oxidative stress
CO_2 isotope ratio	$^{13}CO_2$ / $^{12}CO_2$	Marker for Heliobacter pylori infection, Gastrointestinal and hepatic function
Carbonyl Sulfide	**COS**	**Liver disease and acute rejection in lung transplant recipients (10-500 ppb?)**
Carbon disulfide	CS_2	Schizophrenia
Ammonia	**NH_3**	**Hepatic encephalopathy, liver and renal diseases, fasting response**
Formaldehyde	**HCHO**	**Cancerous tumors, breast cancer (400-1500 ppb)**
Nitric Oxide	**NO**	**Inflammatory and immune responses (e.g., asthma) and vascular smooth muscle response (6-100 ppb)**
Hydrogen Peroxide	H_2O_2	Airway Inflammation, Oxidative stress (1-5 ppb)
Carbon Monoxide	**CO**	**Smoking response, CO poisoning, vascular smooth muscle response, platelet aggregation (400-3000 ppb)**
Ethylene	**$H_2C{=}CH_2$**	**Oxidative stress, cancer**
Acetone	CH_3COCH_3	Fasting response, diabetes mellitus response, ketosis

Exhaled NO and CO in Diseases

Exhaled Nitric Oxide

- Asthma
- Chronic obstructive pulmonary disease
- Cystic fibrosis
- Bronchiectasis
- Primary ciliary dyskinesia
- Rhinitis
- Interstitial lung diseases
- Pulmonary hypertension
- Occupational diseases
- Infections Chronic cough
- Lung cancer
- Lung transplant rejection
- Adult respiratory distress syndrome
- Diffuse Panbronchiolitis



Exhaled Carbon Monoxide

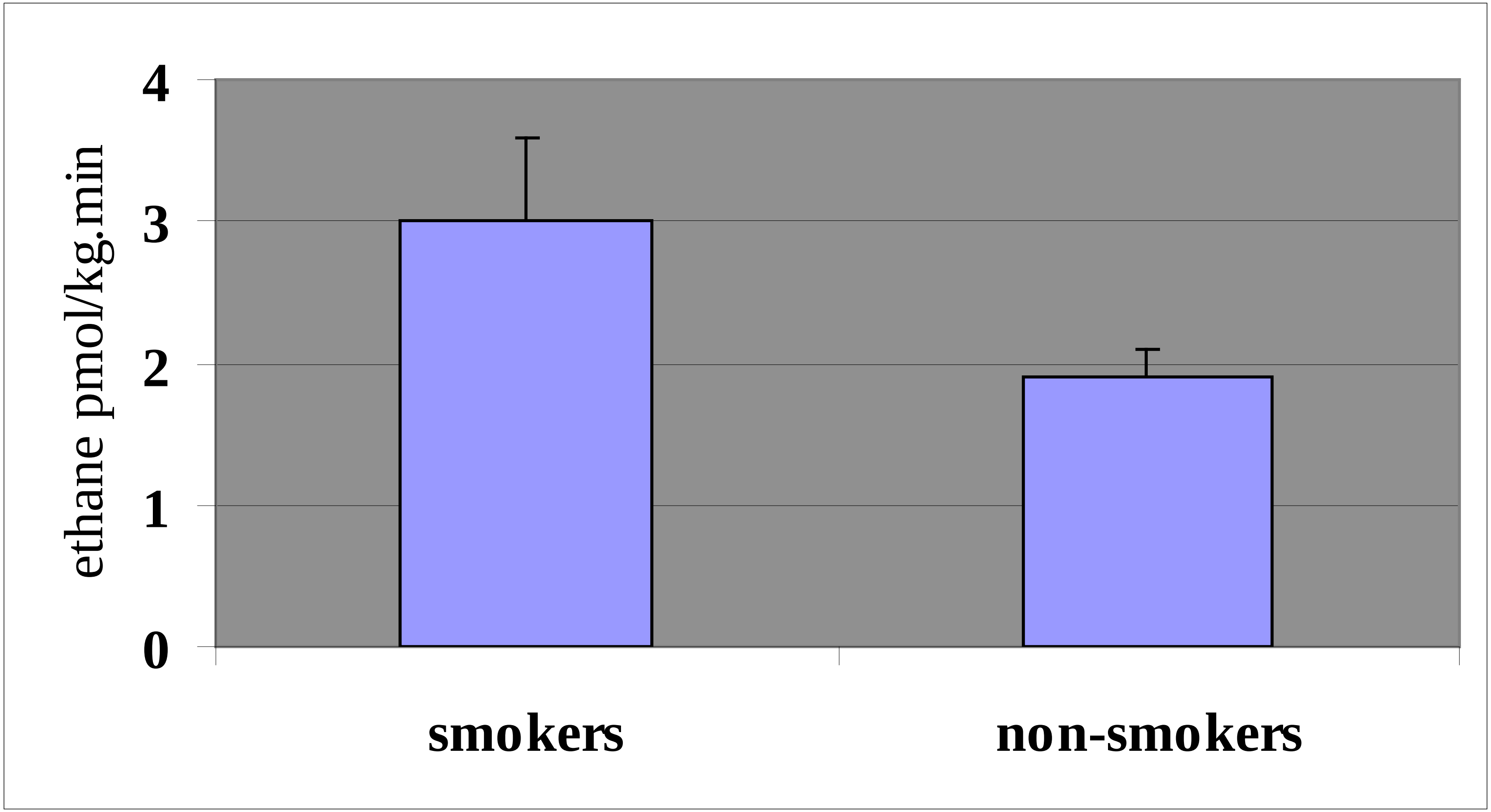
- Asthma
- Chronic obstructive pulmonary disease
- Bronchiectasis
- Cystic fibrosis
- Primary ciliary dyskinesia
- Rhinitis
- Interstitial lung diseases
- Allergic rhinitis
- Infections
- Smoking status

Non-lung conditions

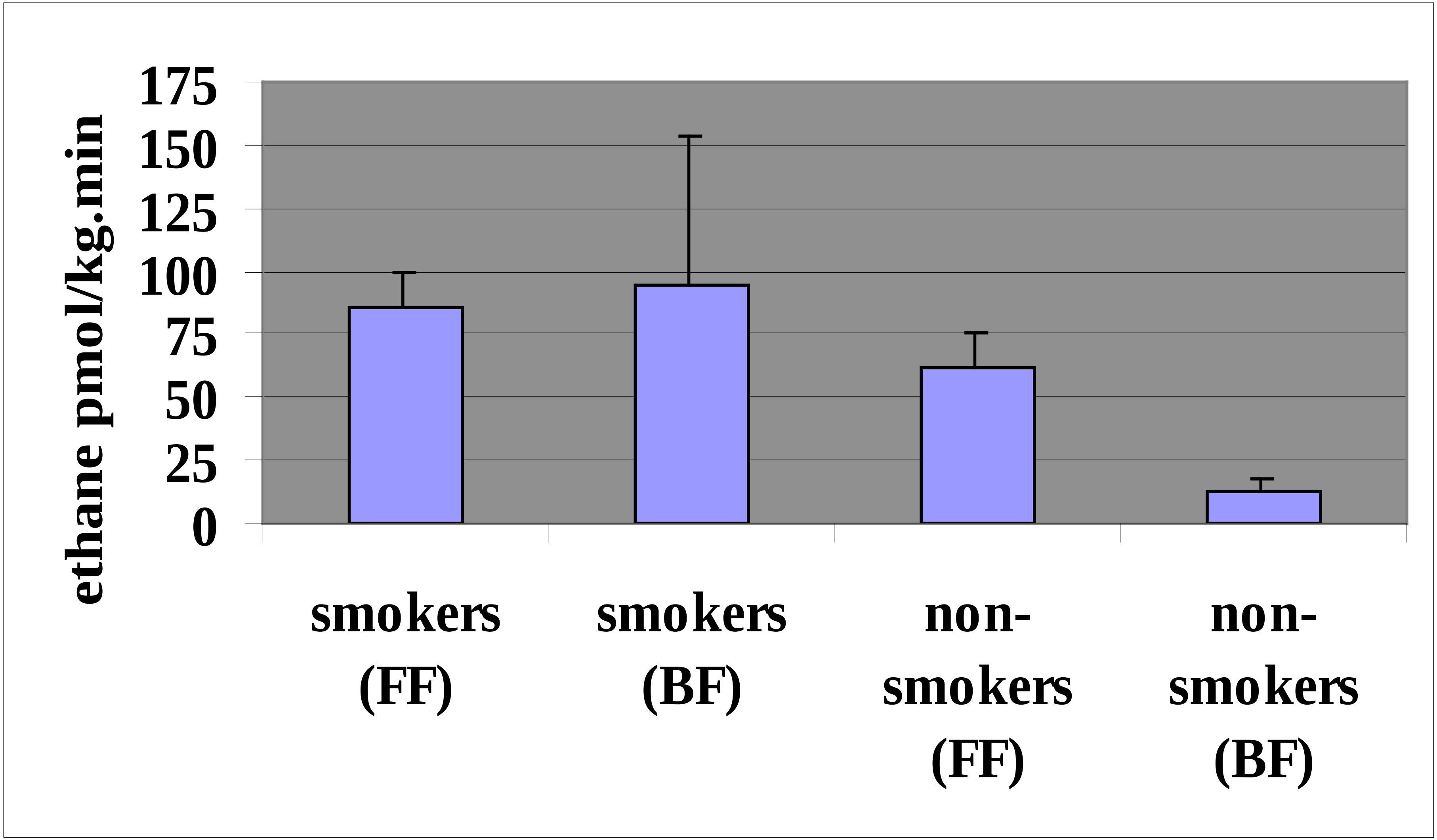
- Systemic inflammation in critical care patients
- Diabetes (hyperglycemia)

Kharitonov SA and Barnes PJ. *Exhaled markers of pulmonary disease.* Am J Respir Crit Care Med. 2001 Jun;163(7):1693-722.

Maternal cigarette smokers



Neonates of mothers that smoke



Aircrafts at Warfield ANG, MD

A-10 Warthog

C-130

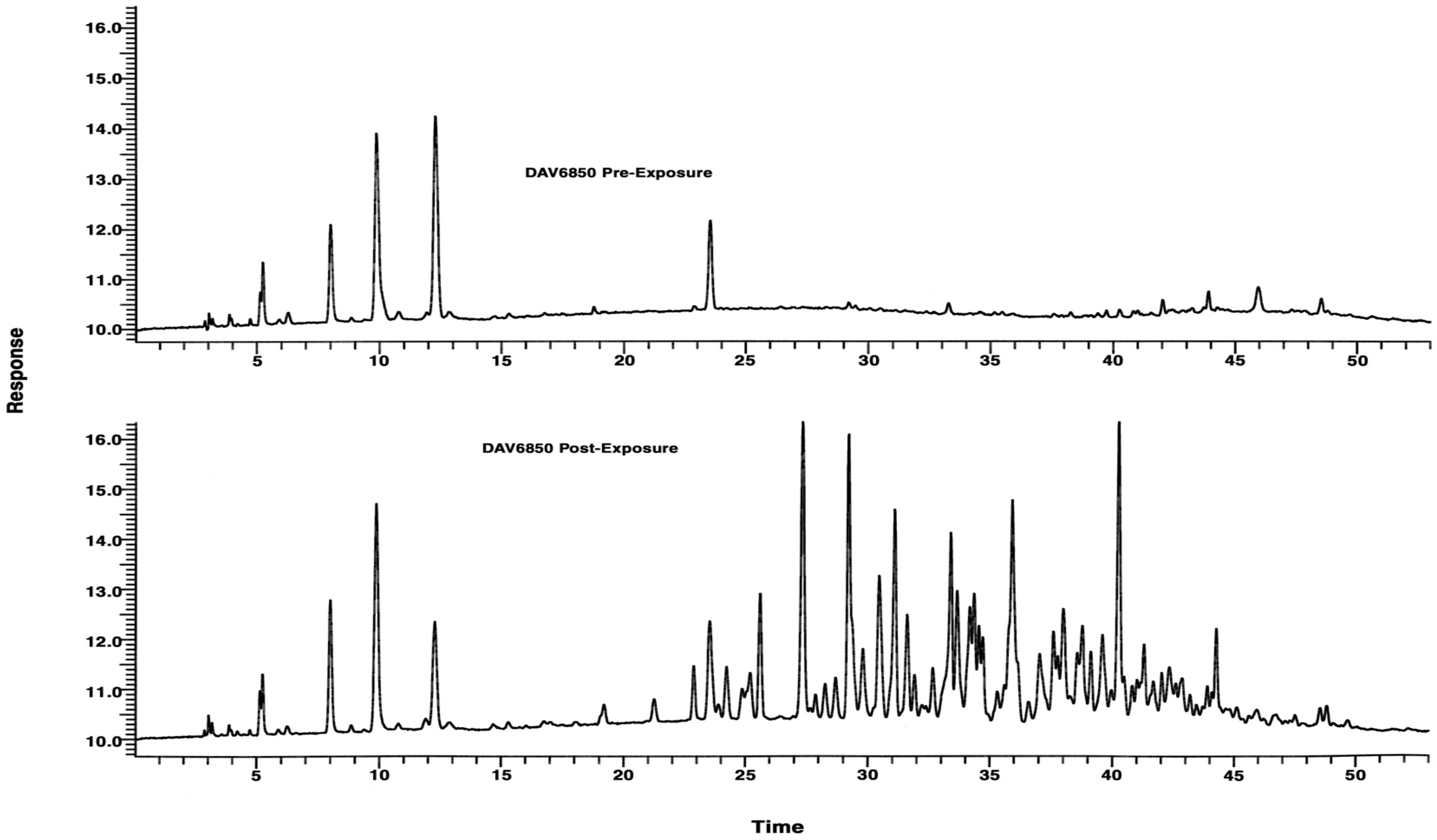
Warfield Air National Guard

- **Goal:**
  - To quantify individual exposure to JP-8 and correlate JP-8 exposure with adverse health effects

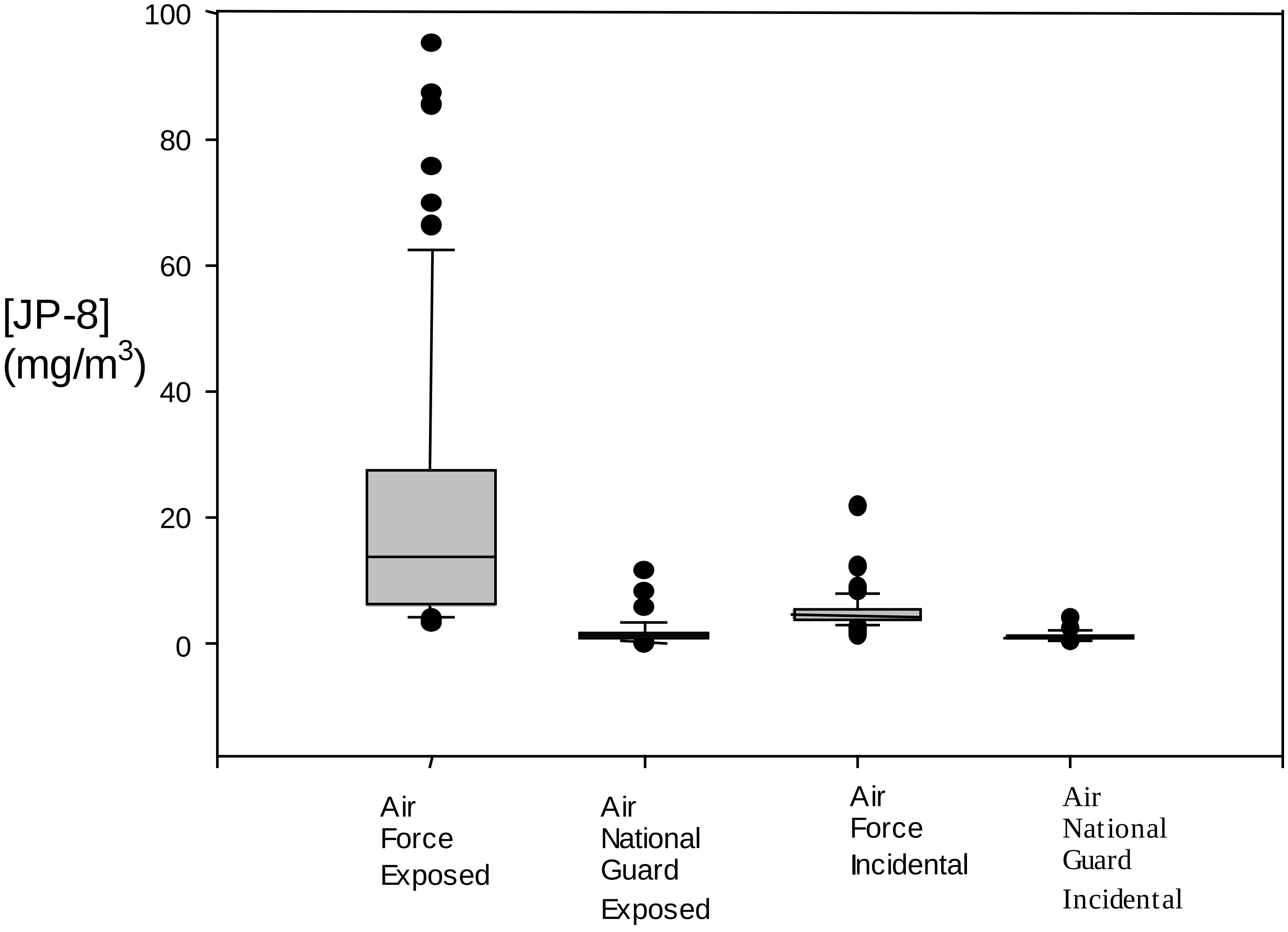
- **Requirements:**
  - Provide a breath sample before work (pre)
  - Provide a breath sample after work (post)

  - Breath was used to quantify exposure and potential effects of JP-8 exposure hydrocarbons, CO, NO, and sulfur-containing compounds

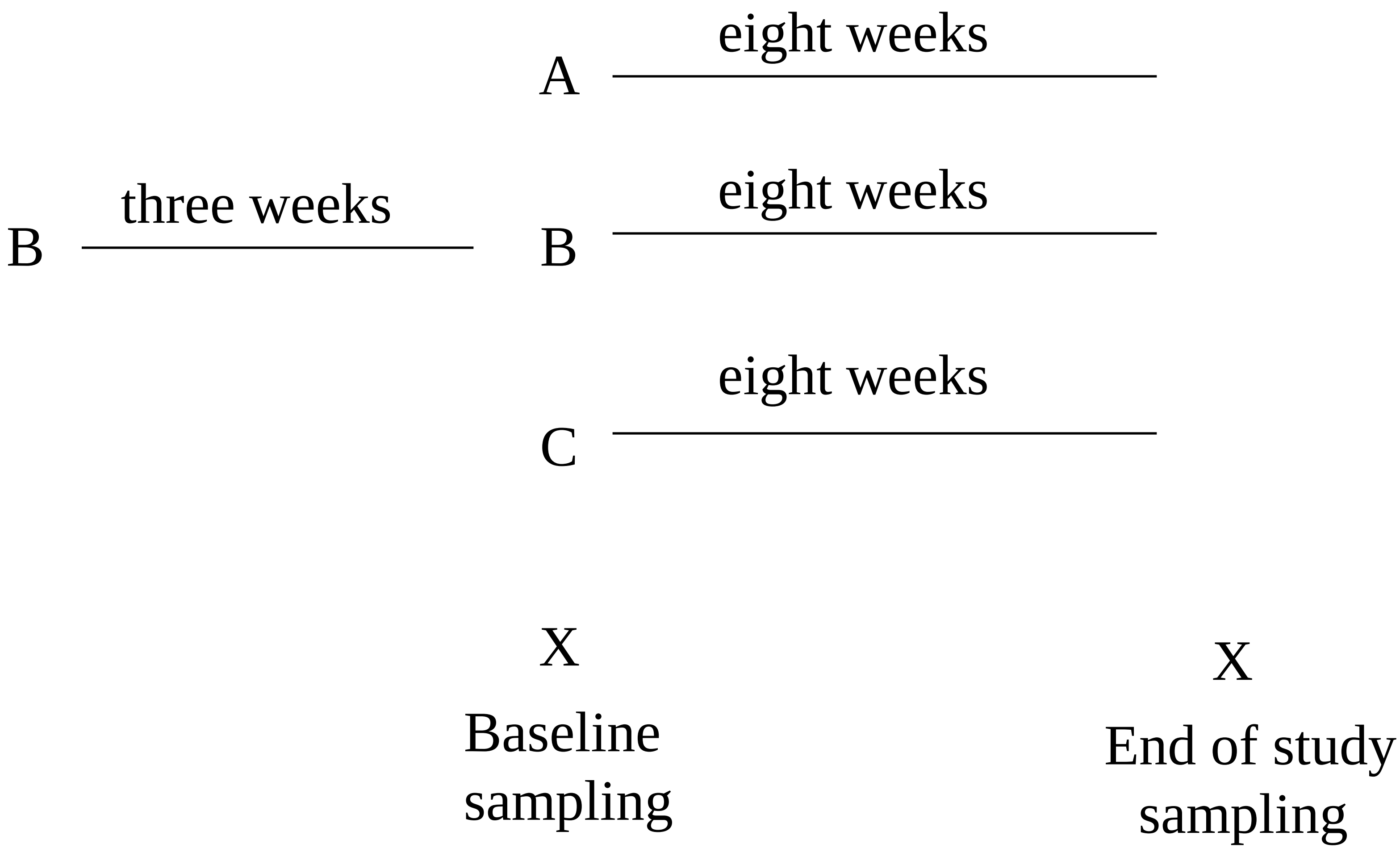
Human Subject Exposed to JP-8



Total JP-8 Base Comparison



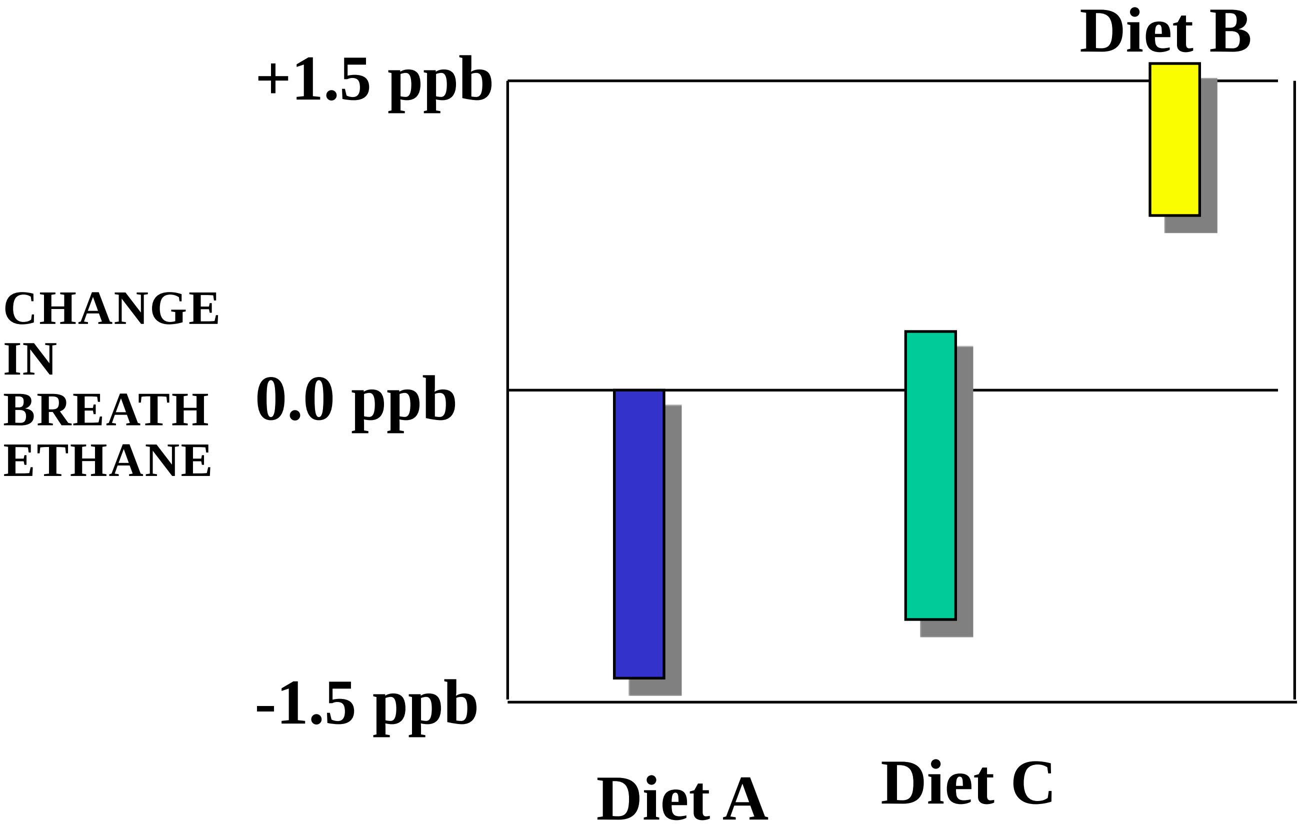
Study design of breath analysis from rats based on diet



Diet (%) for exhaled ethane from rats

	B	C	A
Fat	37	37	27
saturated	16	16	6
monounsaturated	13	13	13
polyunsaturated	8	8	8
Carbohydrate	48	48	48
Protein	15	15	15
Cholesterol	300 mg	300mg	300mg
Fruits/Vegs	100 g/day	500 g/day	500 g/day

Change in breath ethane from baseline to end of study



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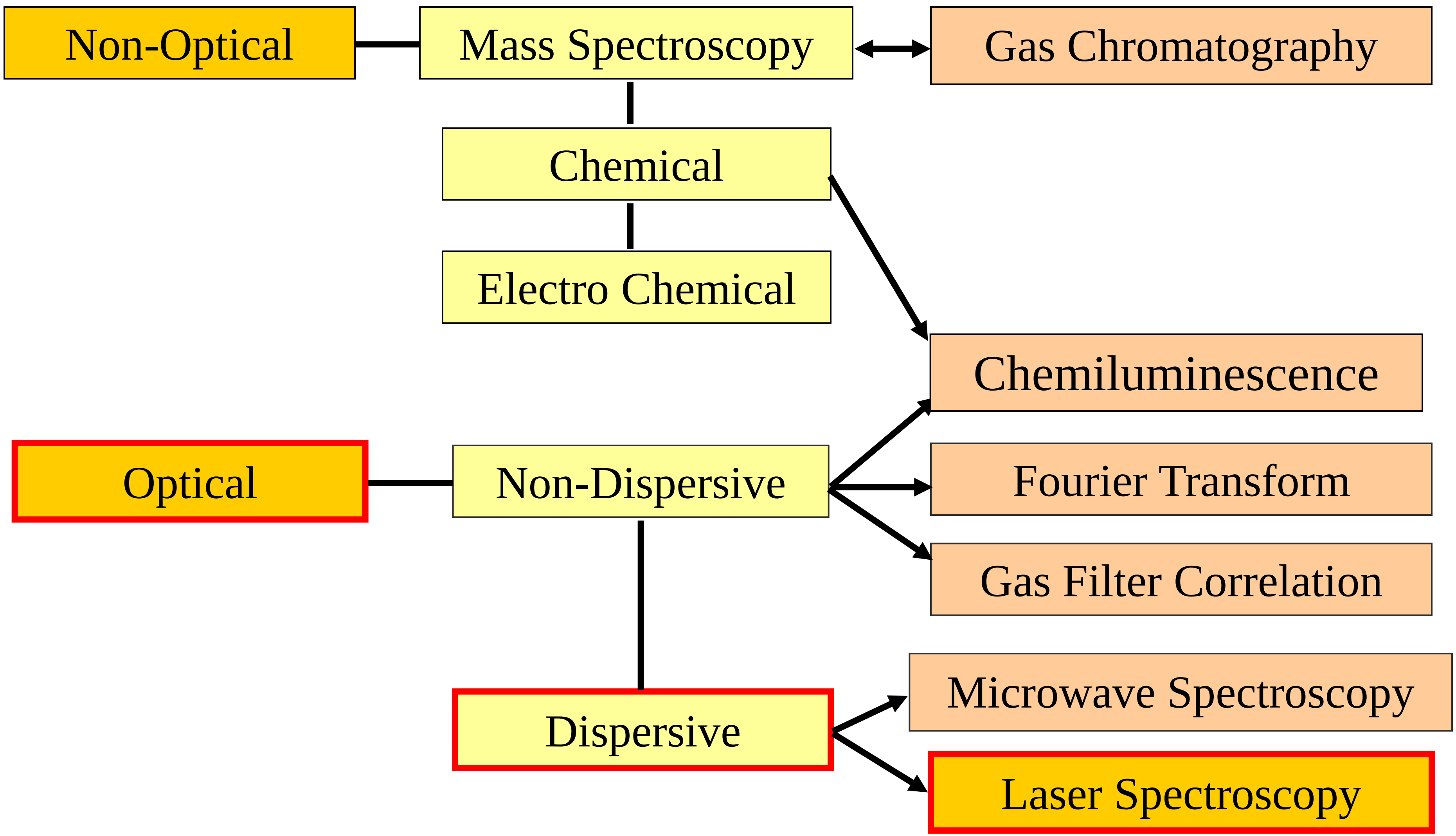
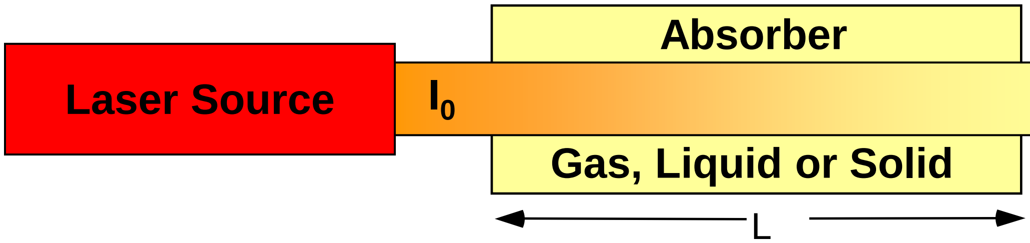
Laser Absorption Spectroscopy

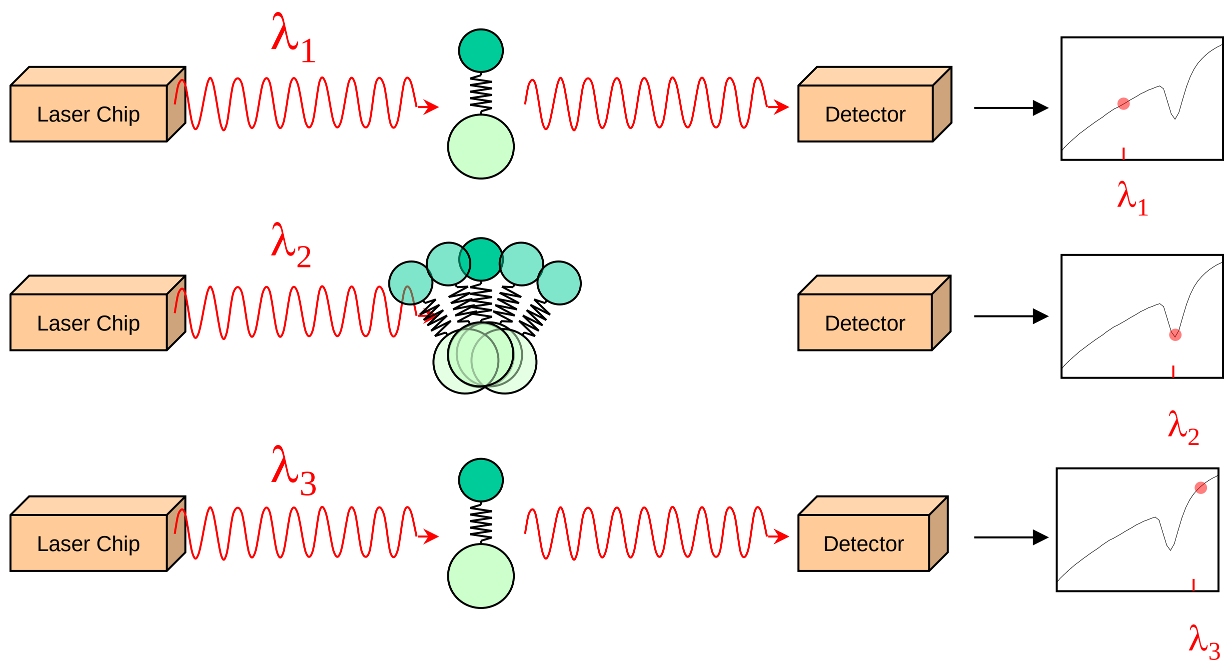
Existing Methods for Trace Gas Detection



Tunable Diode Laser Absorption Spectroscopy (TDLAS)



Molecules absorb infrared light:



CW IR Source Requirements for Laser Spectroscopy

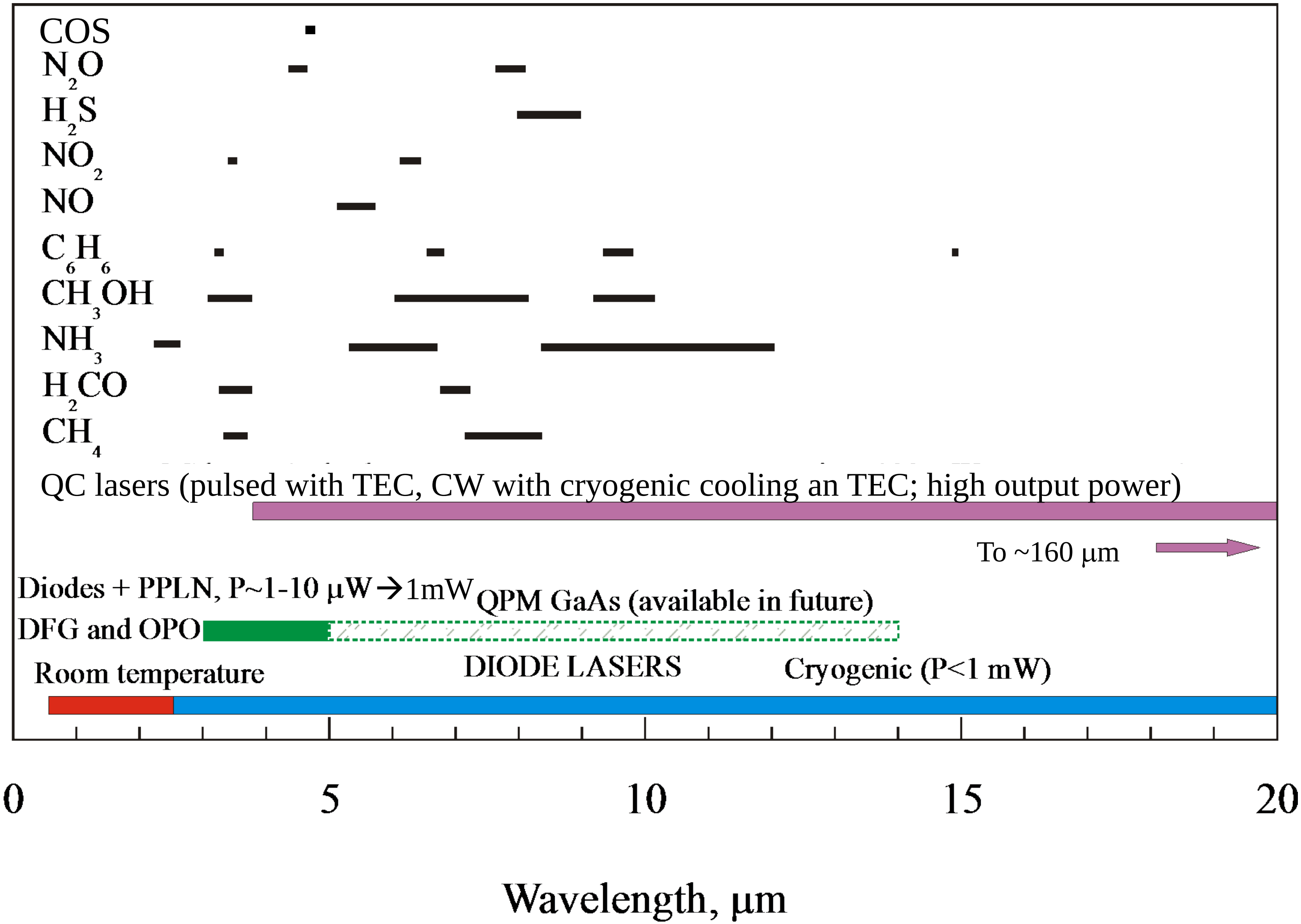
REQUIREMENTS

- **Sensitivity (% to ppt)**
- **Selectivity**
- **Multi-gas Components**
- **Directionality**
- **Rapid Data Acquisition**
- **Room Temperature**
- **Field deployable**

IR SOURCE

- **Power**
- **Narrow Linewidth**
- **Tunable Wavelengths**
- **Beam Quality**
- **Fast Time Response**
- **No Consumables**
- **Compact & Robust**

Molecular Absorptions and Laser Sources



Sensitivity Enhancement Techniques

- **Optimum Molecular Absorbing Transition**
  - Overtone or Combination Bands (NIR)
  - Fundamental Absorption Bands (MID-IR)
- **Long Optical Pathlength**
  - Multipass Absorption Cell (White, Herriot)
  - Cavity Enhanced and Cavity Ringdown Spectroscopy
  - Open Path Monitoring (with retro-reflector)
  - Fiberoptic Evanescent Wave Spectroscopy
- **Spectroscopic Detection Schemes**
  - Frequency or Wavelength Modulation
  - Balanced Detection
  - Zero-air Subtraction
  - Photoacoustic Spectroscopy
  - **N**oise **I**mmune **C**avity **E**nhanced-**O**ptical **H**eterodyne **M**olecular **S**pectroscopy (NICE-OHMS)

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Laser Absorption Spectroscopy (LAS) for Breath Analysis

- LAS based sensors can realize sensitive, selective and fast concentration measurements of specific medically relevant target gases (e.g NO, CO & COS
- LAS is capable of detecting and quantifying multiple gas species with a single laser which is important for standardizing exhaled breath analysis data
- Lasers make it possible to design compact, portable, robust and autonomous LAS based sensors

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III

Nitric Oxide (NO) Detection

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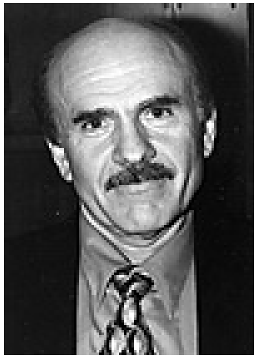
The Nobel Prize in Physiology or Medicine 1998



Robert F. Furchgott

1/3 of the prize

USA

SUNY Health Science Center
Brooklyn, NY, USA

b. 1916

Louis J. Ignarro

1/3 of the prize

USA

University of California School of Medicine
Los Angeles, CA, USA

b. 1941

Ferid Murad

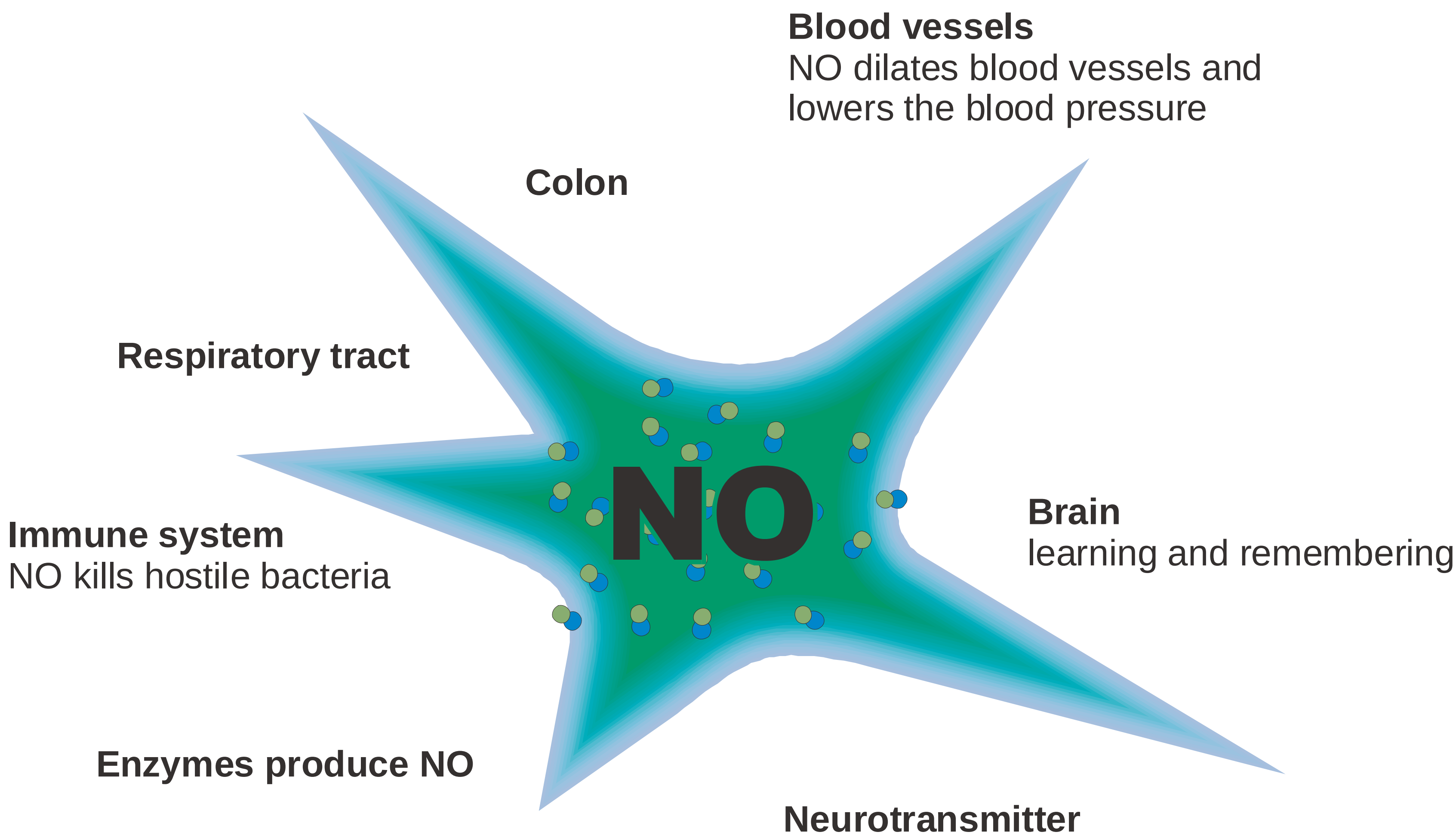
1/3 of the prize

USA

University of Texas Medical School at Houston
Houston, TX, USA

b. 1936

Nitric oxide: Various Human Functions



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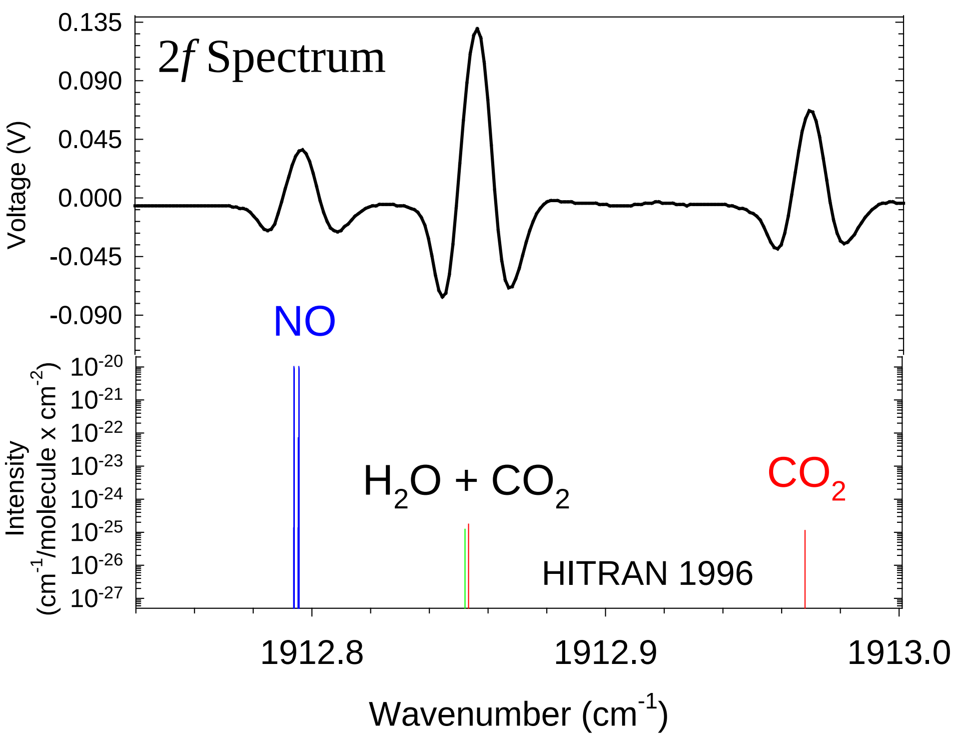
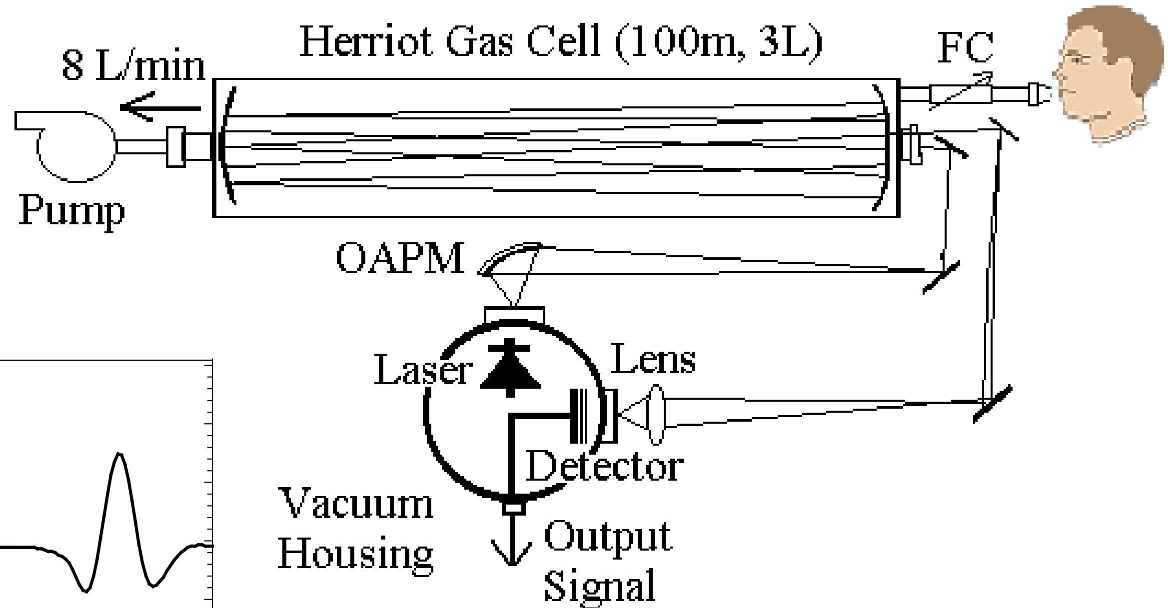
Nitric Oxide Breath Sensor





Self-calibrating sensor

Patient’s own exhaled CO_2 is the calibration gas

Why Adopt eNO Analysis

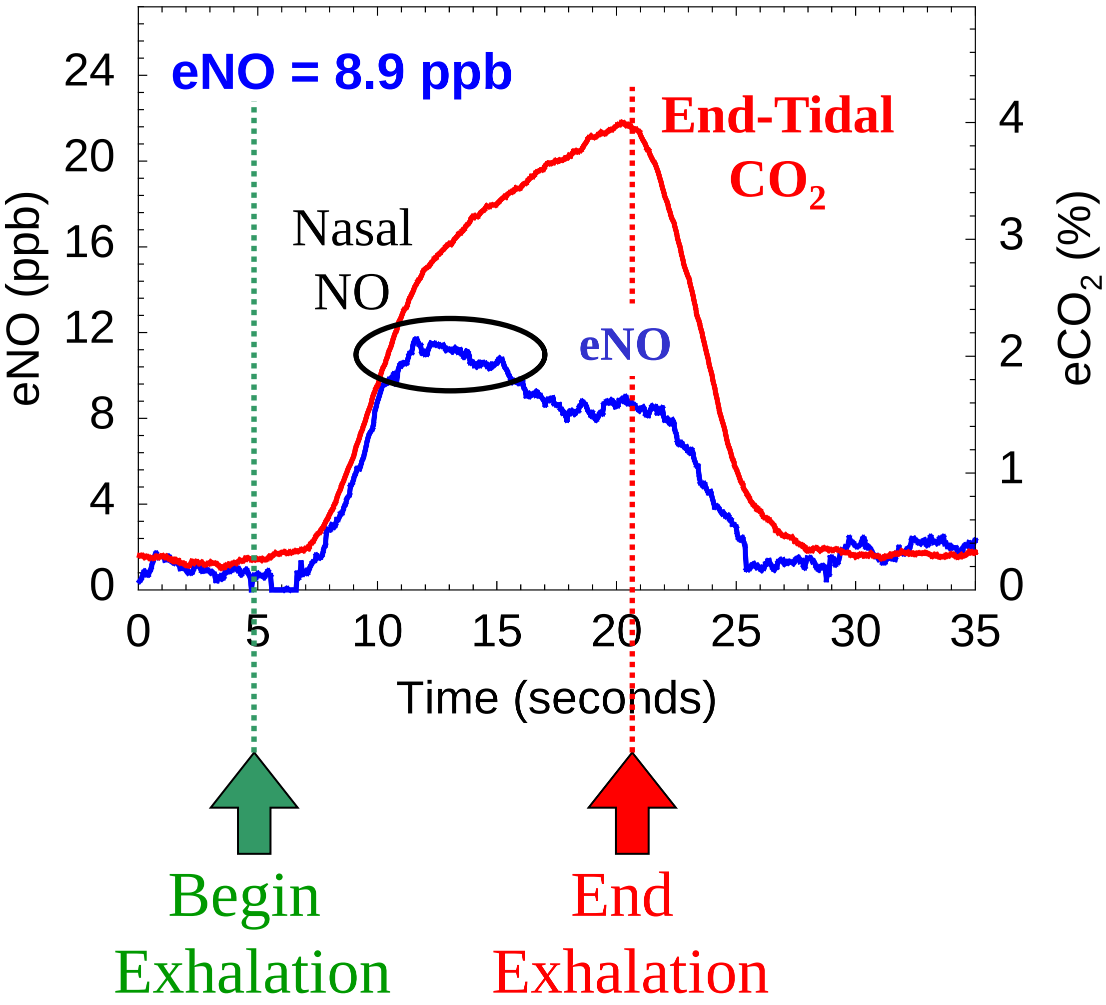
- 17 million Americans have asthma
- Asthma is the #1 chronic disease among children
- Asthma rates are increasing at near epidemic rates
- No routine point-of-care clinical procedures to assess lower airway inflammation
- NAEPP Guidelines are not widely followed
- When properly managed
    - 78% reduction in hospitalizations
    - 73% reduction in emergency room visits

"Under-treatment of inner-city asthma is the rule rather than the exception",

Dr. Kristin Riekart, Johns Hopkins

eNO and eCO_2 Trends

Single Exhalation Against Resistance (10-20 sec)



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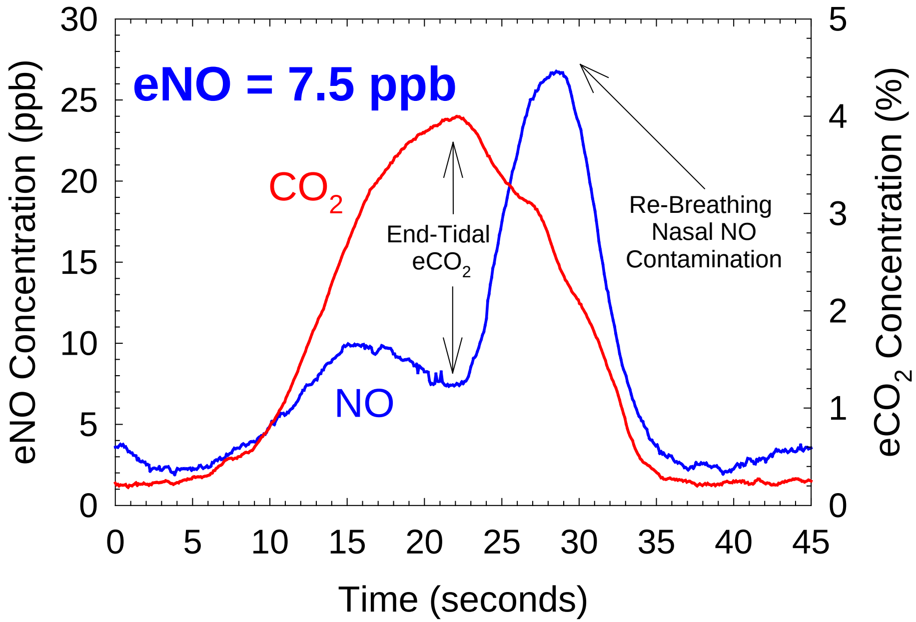
Advantages of Simultaneous exhaled NO and CO_2

- Verify Correct Breath Donations
- Determine eNO Concentrations
- Serves as Internal Indicator of Instrumental Factors

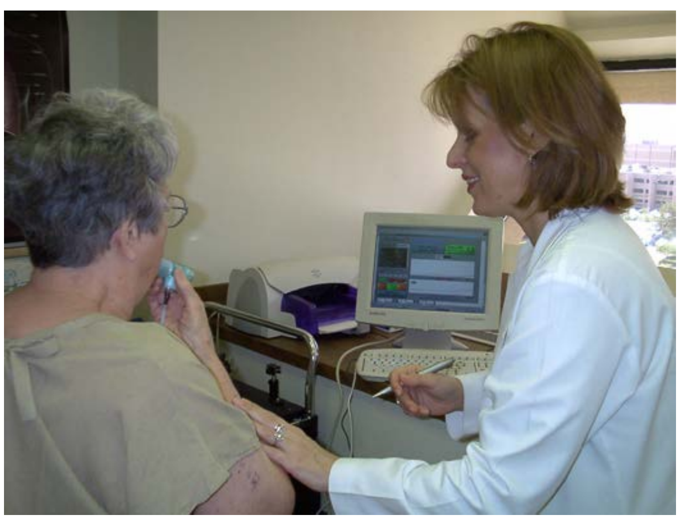
We can now deduce *instrumental* vs. *physiological*

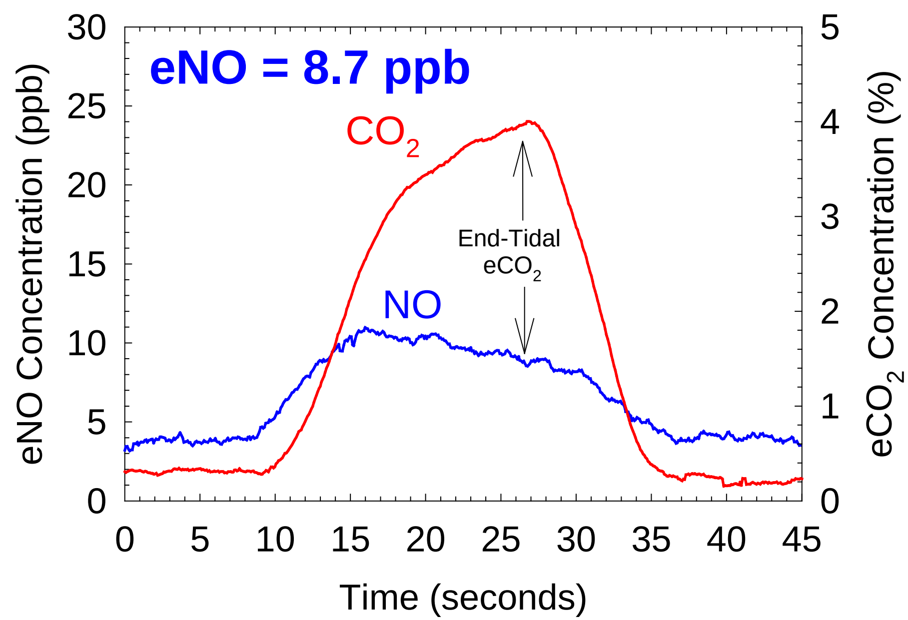
Variation in Exhalation



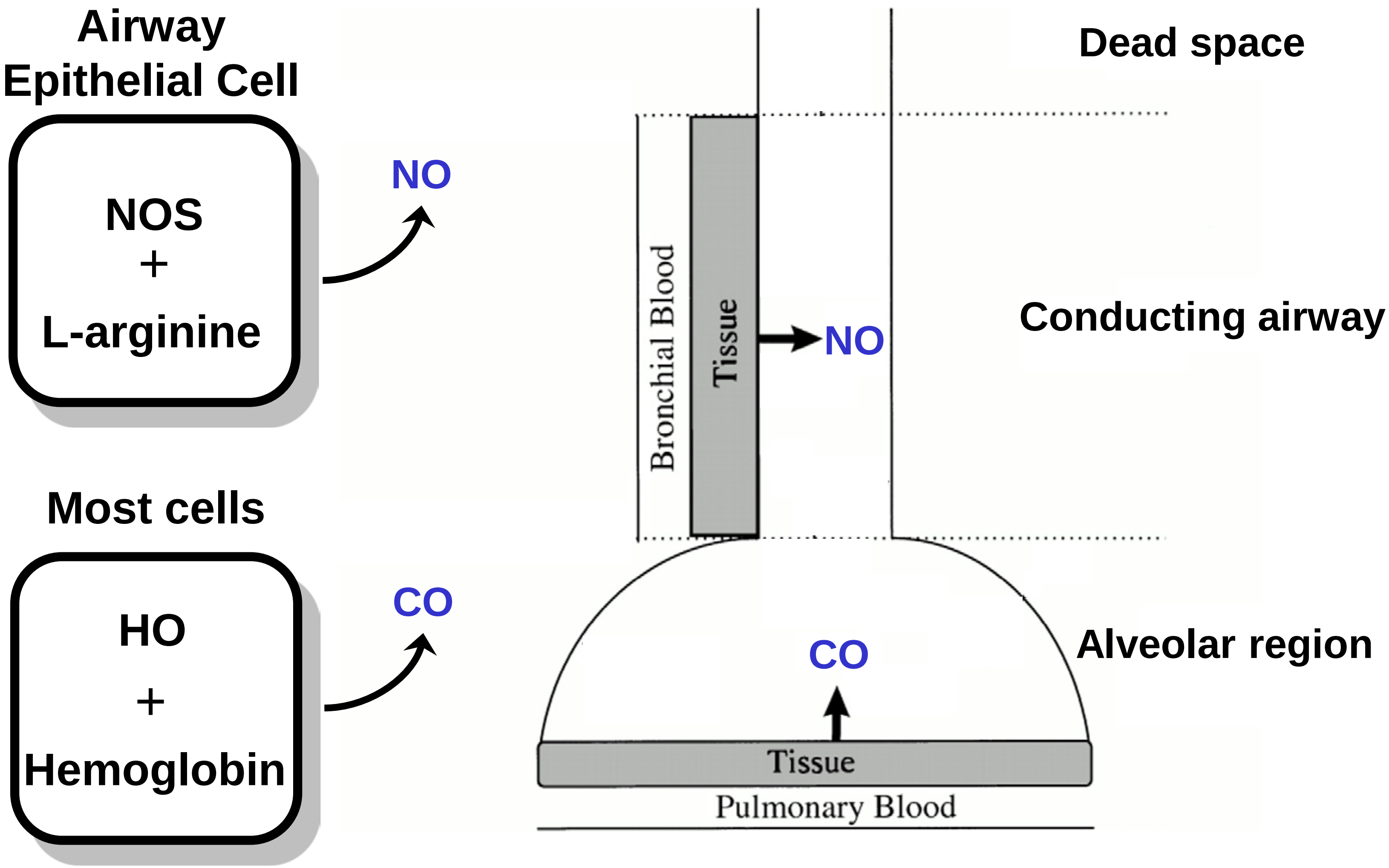
Nasal NO Contamination

End-tidal CO_2 can be used to determine eNO levels and can account for variations in exhalation maneuvers between patients





Sources of NO and CO



Point of Care
Exhaled Nitric Oxide Instrumentation

- **Chemiluminescence (Aerocrine & Sievers)**
  - Used for over ten years to measure eNO in both children and adults
  - FDA approval has been granted, March 2003 (product code MXA)
  - Inter-study reproducibility issues
  - Requires calibration at same humidity and temperature as breath
  - Issues regarding explosive reactions to anesthesia
  - Three consumables: clean air, ozone, and NO calibration gas
- **TDLAS**
  - Used to measure eNO in both children and adults
  - Demonstrated internal-calibration using exhaled CO_2 levels
  - No consumables

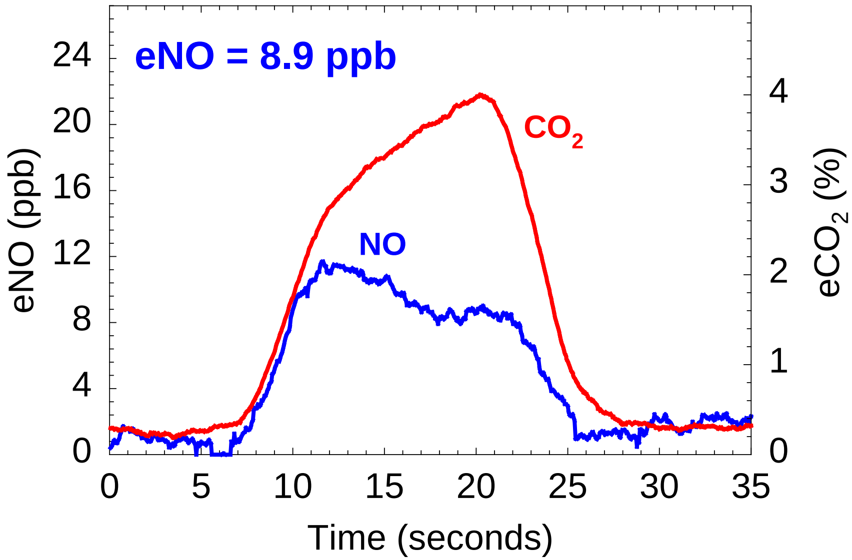
Asthmatic Examples

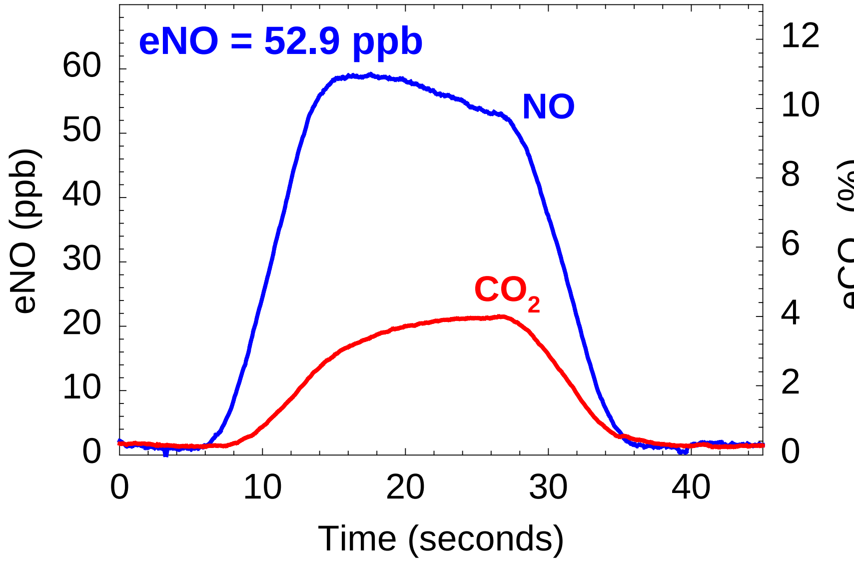
Age 5, Female, Mild-Persistent Corticosteriod <u>Treated</u>

Age 14, Male, Mild-Persistent <u>Non-Treated</u>

Normal Airway

Inflamed Airway





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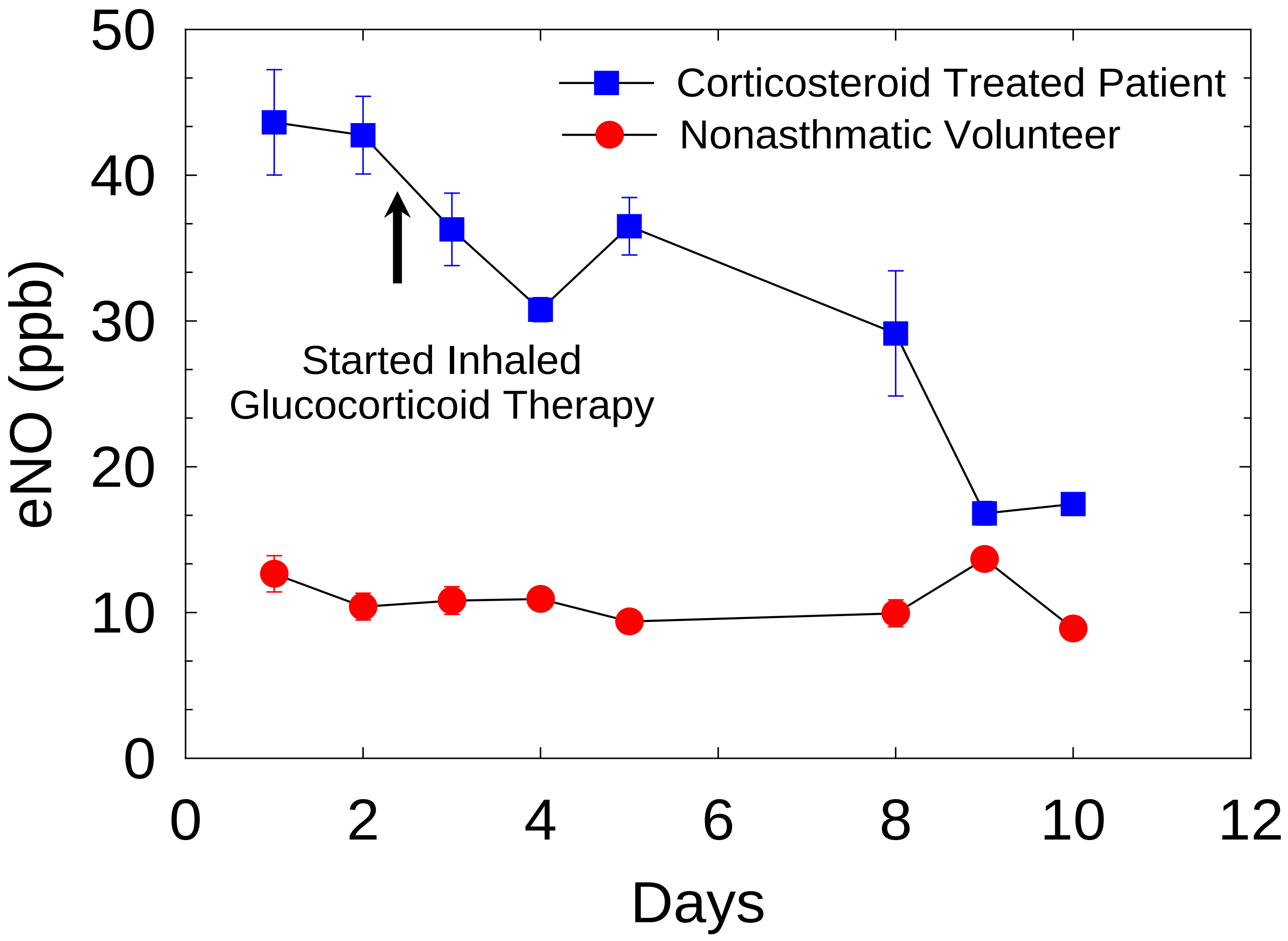
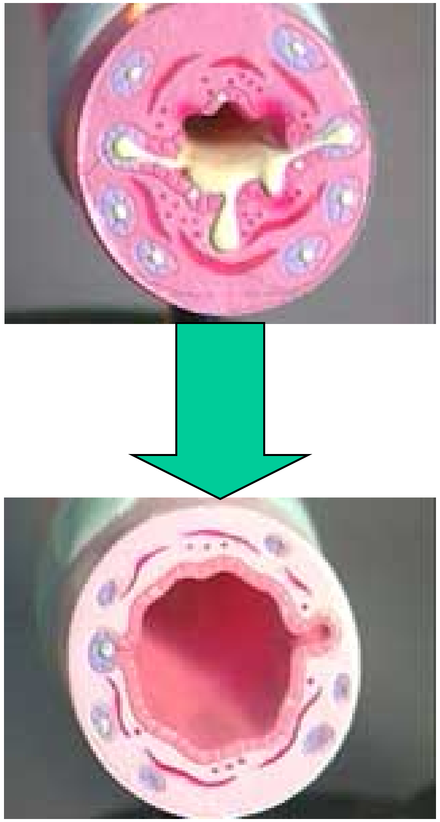
Therapy Monitoring





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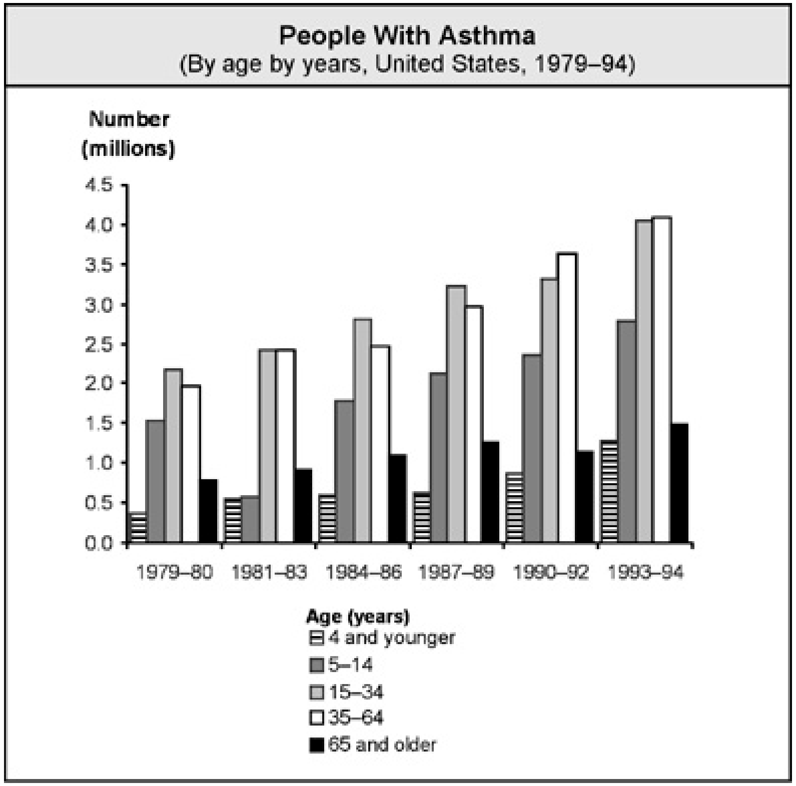
Children and Asthma

"Physicians need to diagnose asthma early and accurately… Untreated inflammation leads to more severe symptoms, airway injury, and a worse long-term prognosis."
S. F. Steinbach, M.D., ***Contemporary Pediatrics***, October 2000

"Officials in many school systems estimate… asthma among their students at 3% to 4%. But a number of studies… suggest the *correct number is closer to 15%*",
R. L. Wolf, M.D., Associate Professor of Pediatrics, University of Chicago.
M. Pinkowish, ***Patient Care***, *Feb 15, 2000*

A Growing Problem



Source: CDC, NCHS. Surveillance for Asthma—United States, 1960–1995. *Morbidity and Mortality Weekly Report* 47(SS-1);1-28, 1998.

Current Research

- TDLAS offers robust and routine measurement of lower airway eNO
- The breath donation procedure is simple, rapid, non-invasive, and suitable for children and adults
- eNO can be useful a marker for lower airway inflammation and overall respiratory health in populations
- Currently conducting clinical research in collaboration with the American Lung Association
- Want to examine large social issues associated with asthma

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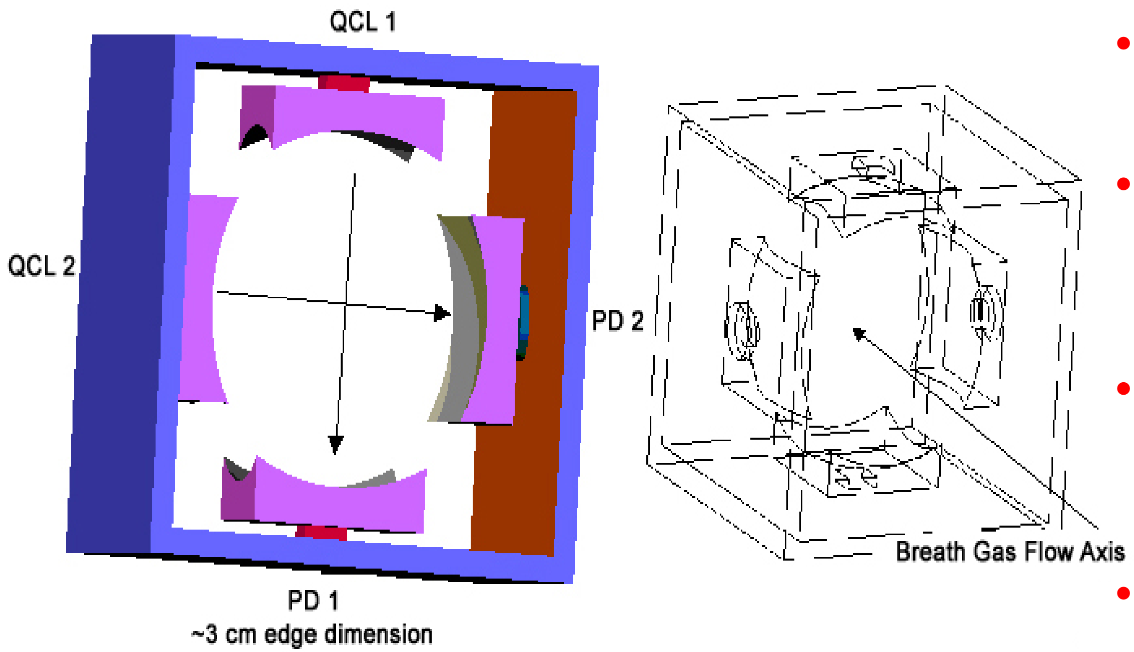
Cavity Enhanced Spectroscopy of Breath Samples



- **Advanced compact gas cell design**
- **Capable of cell volumes < 100 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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Ultra-sensitive Absorption Spectroscopy Techniques

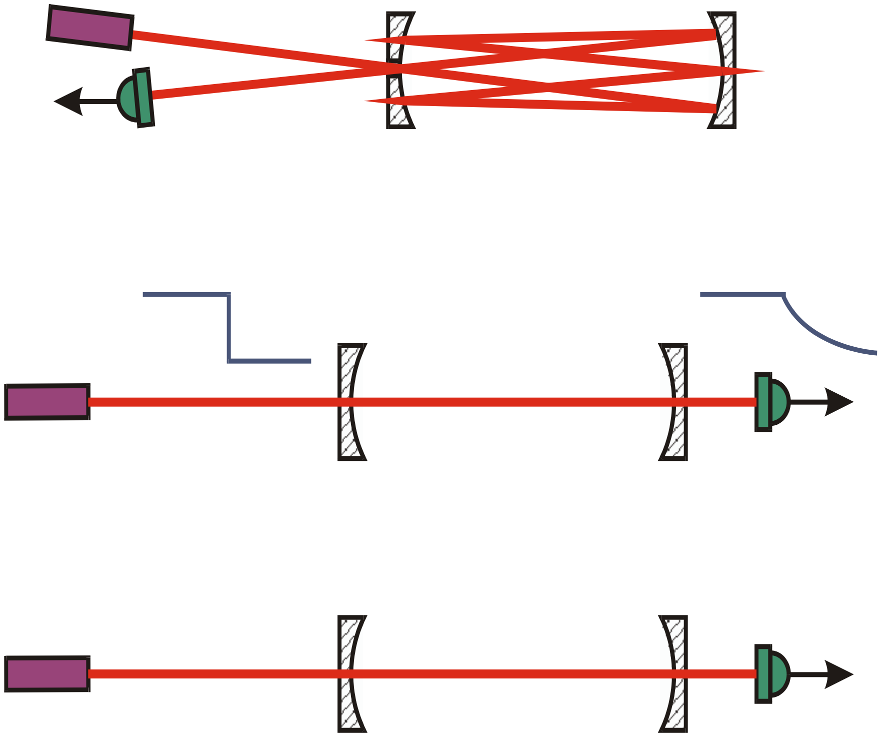
Traditional

1. Multipass cell spectroscopy

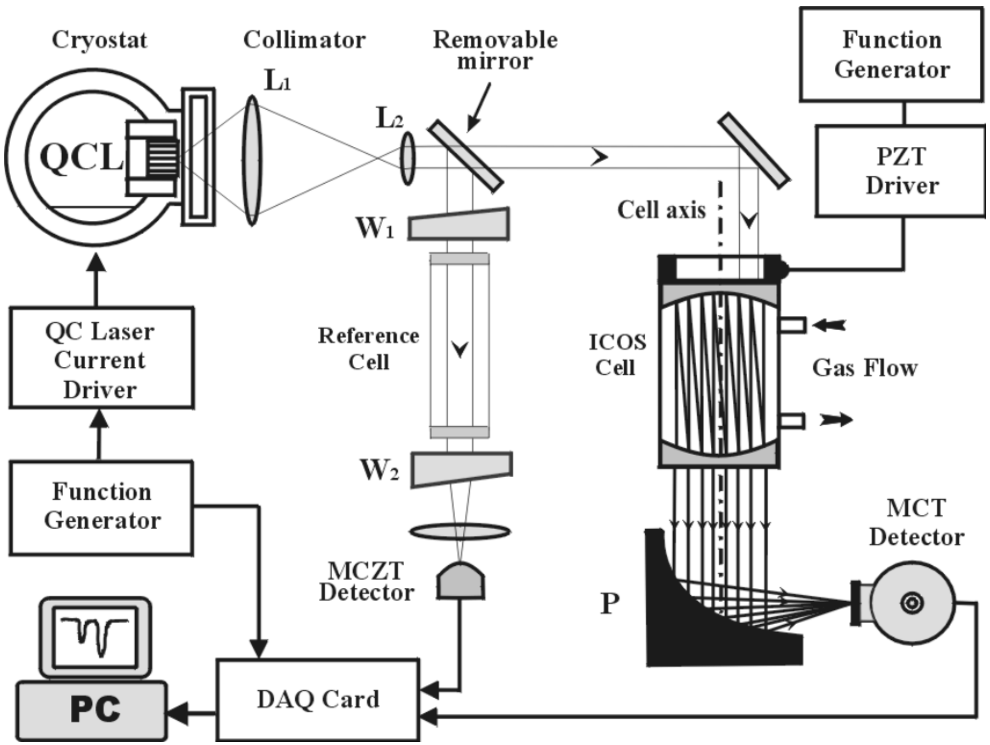
Capable of Compact Gas Cells

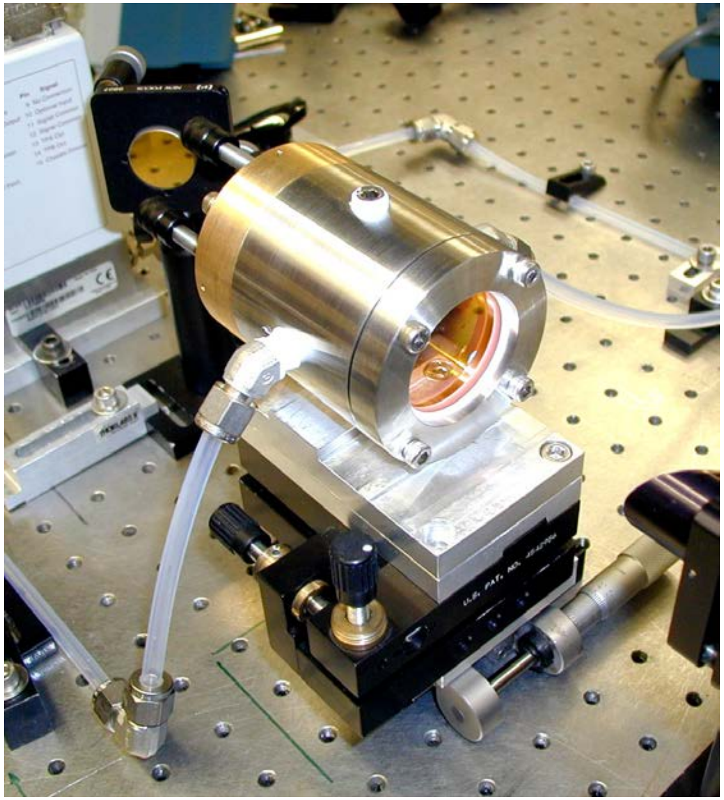
2. Cavity Ringdown Spectroscopy (CRDS)

3. Integrated Cavity Output Spectroscopy (ICOS)



Off-Axis Integrated Cavity Output Spectroscopy Based Gas Sensor





- Novel compact gas cell design of length: 3.8 – 5.3 cm and cell volumes < 80 cm^3 ;
- Low loss mirrors (ROC 1m):~60-250 ppm, R~99.975, L_{eff} =170-800 m
- Rapid eNO concentration measurements during a single breath cycle.are feasible

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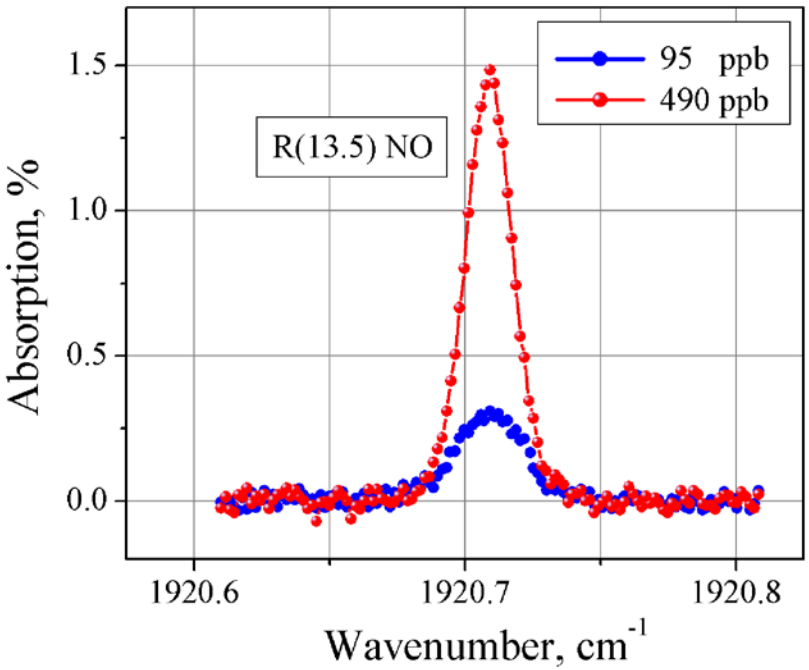
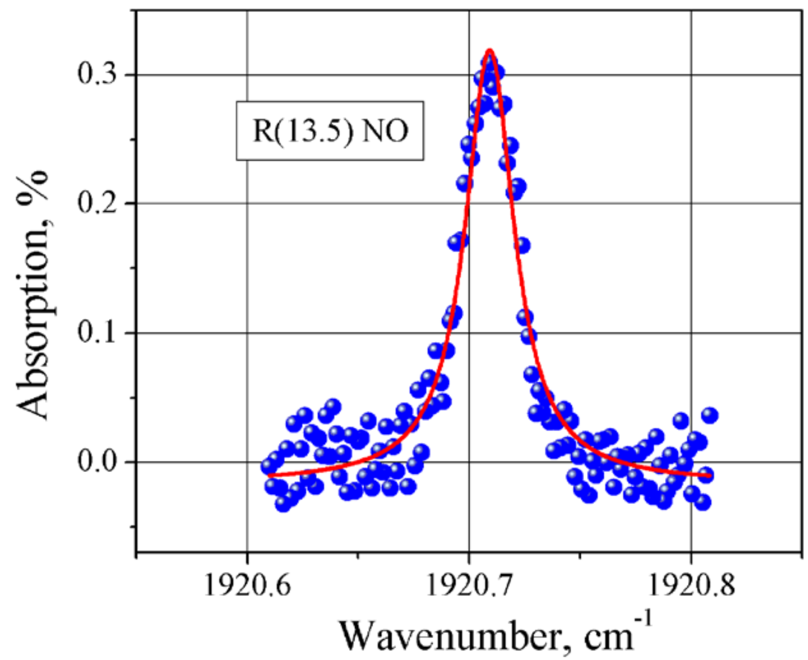
Off-axis ICOS Detection of NO at 1920.7 cm^{-1}





- 95 and 490 ppb NO/N_2 calibration mixture at 100 Torr total pressure
- Effective optical path ~ 70 m (1,350 passes)

- Voigt fit of measured NO absorption line at 1920.7 cm^{-1} for a concentration of 95 ppb

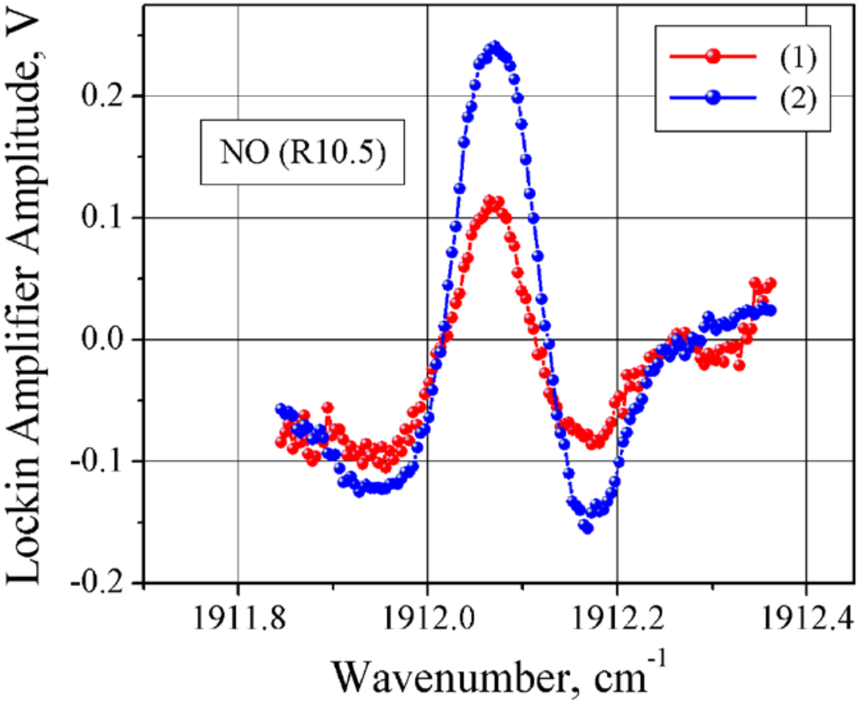
Noise-equivalent sensitivity is 10 ppb for 1σ deviation of the best fit coefficient.

Detection sensitivity: 1.0×10^{-7} cm^{-1} $Hz^{-1/2}$

RICE

NO from Nasal Exhaled Air
(OA-ICOS and wavelength modulation spectroscopy)

Medically approved collection bag
for human breath samples



Averaged 2f signal of the OA-ICOS cavity output

(1) Nasal NO concentration: 53 ppb
(2) 95 ppb NO/N_2 calibration mixture

RICE

IV

Carbon Monoxide (CO) Detection

Exhaled NO and CO in Diseases

Exhaled Nitric Oxide

- Asthma
- Chronic obstructive pulmonary disease
- Cystic fibrosis
- Bronchiectasis
- Primary ciliary dyskinesia
- Rhinitis
- Interstitial lung diseases
- Pulmonary hypertension
- Occupational diseases
- Infections Chronic cough
- Lung cancer
- Lung transplant rejection
- Adult respiratory distress syndrome
- Diffuse Panbronchiolitis

Exhaled Carbon Monoxide

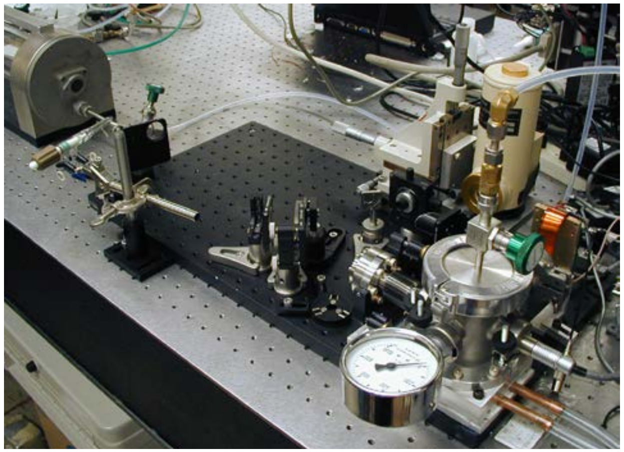
- Asthma
- Chronic obstructive pulmonary disease
- Bronchiectasis
- Cystic fibrosis
- Primary ciliary dyskinesia
- Rhinitis
- Interstitial lung diseases
- Allergic rhinitis
- Infections
- Smoking status

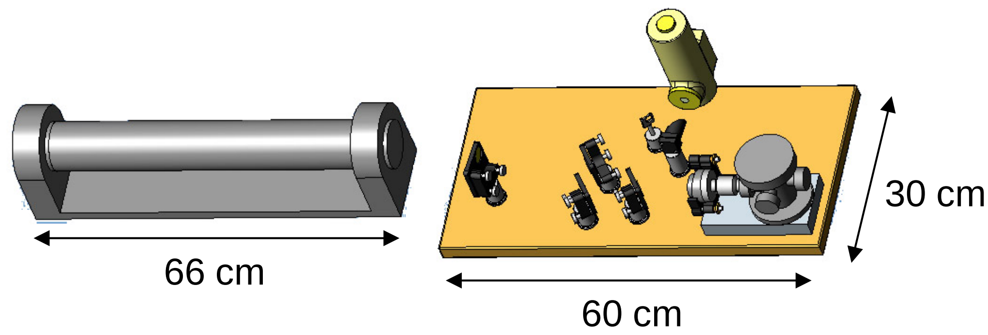
Non-lung conditions

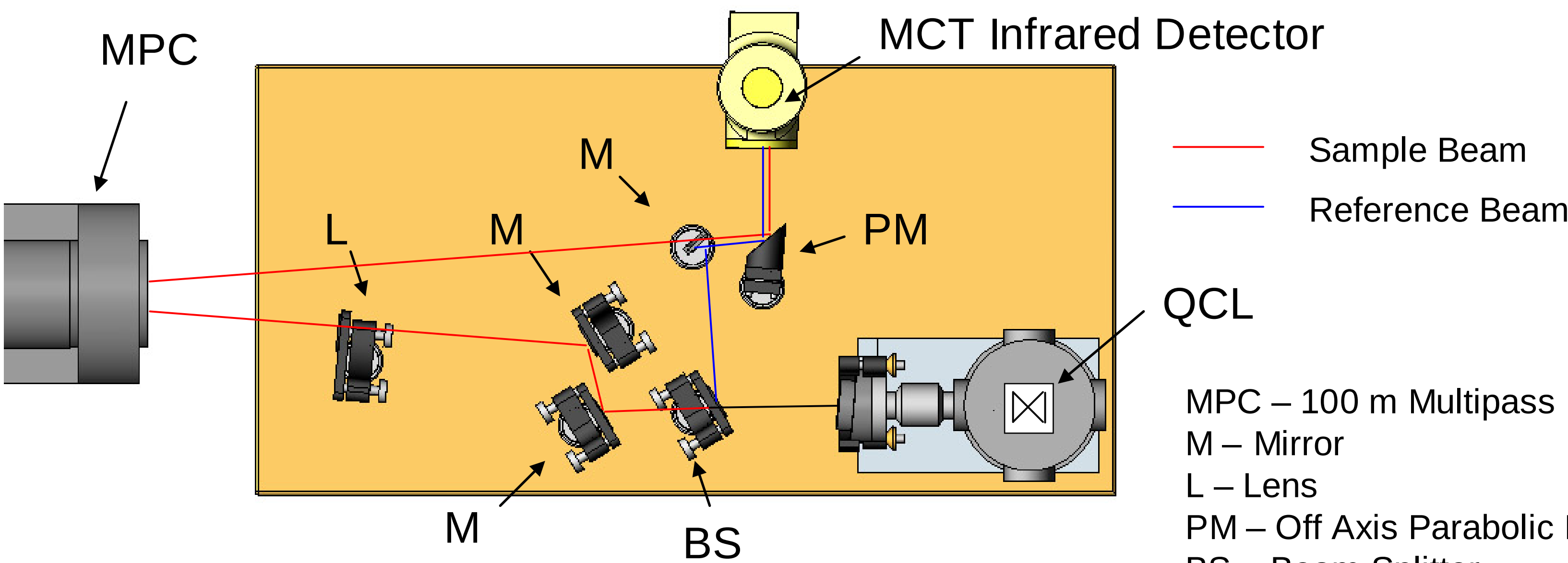
- Systemic inflammation in critical care patients
- Diabetes (hyperglycemia)

Kharitonov SA and Barnes PJ. *Exhaled markers of pulmonary disease.* Am J Respir Crit Care Med. 2001 Jun;163(7):1693-722.

Carbon Monoxide (CO) Sensor Architecture





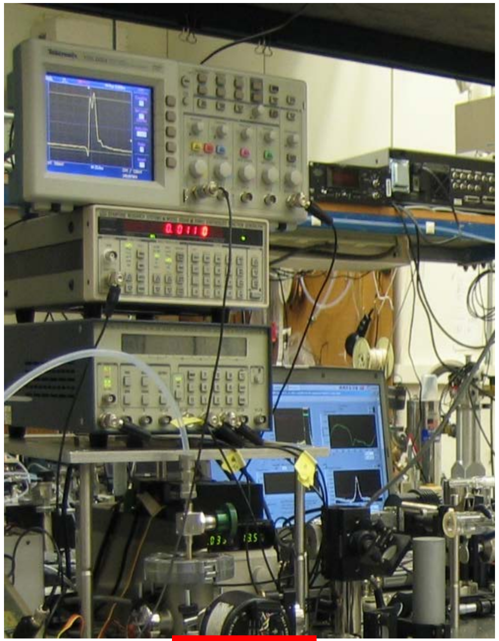


MPC – 100 m Multipass Herriott Cell
M – Mirror
L – Lens
PM – Off Axis Parabolic Mirror
BS – Beam Splitter
QCL – Quantum Cascade Laser

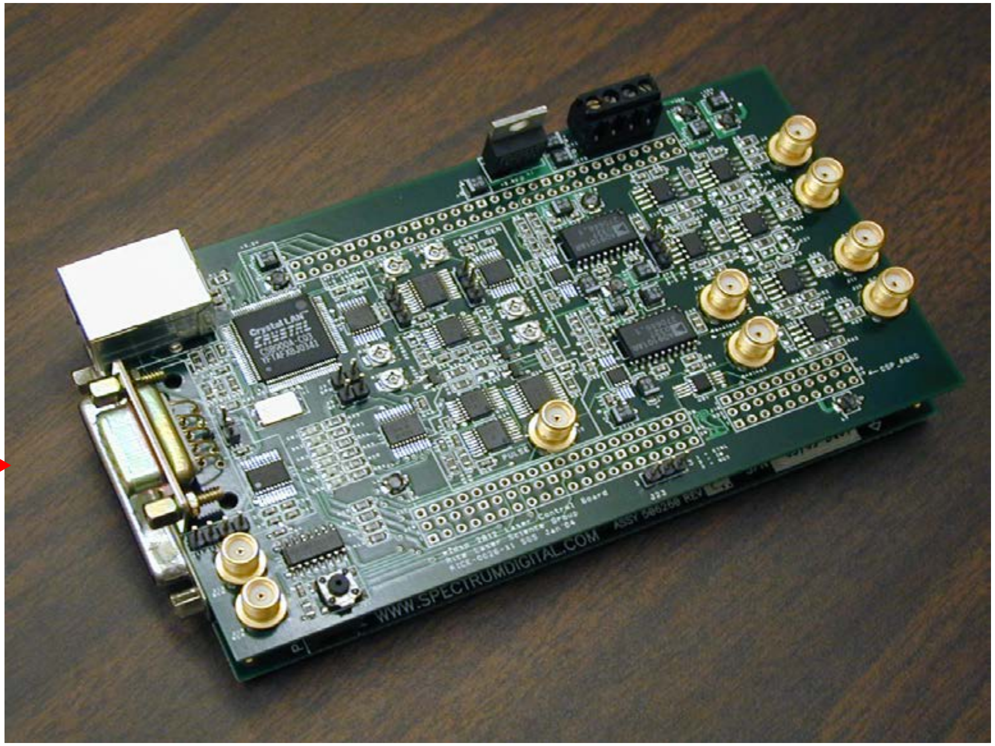
Motivation for DSP

- Portability and Integration
  - Field campaigns
  - Sensor networks
- Advanced control of system
  - Modulation and feedback
- Fast data acquisition
  - Co-averaging of spectra for lower detection limit
- Faster processing
  - Polynomial fitting routines
  - Fast multiply-accumulate for filtering
- Low power
  - Battery powered sensors

DSP System Controller Card

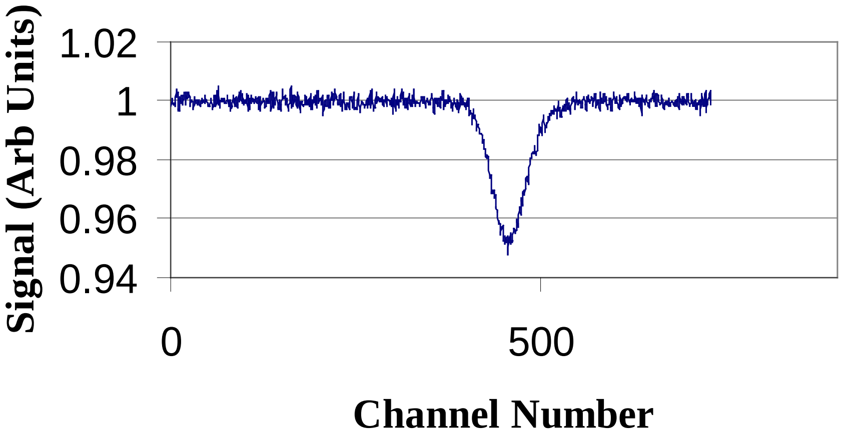


- Compact for clinical/hospital use
- Dimensions: 5.35 in x 3.00 in x 1.50 in
- Ethernet, Serial, JTAG access for control and read out
- Flash memory for long term storage
- PC independent operation
- Up to 12.5 MSPS 12-bit ADC



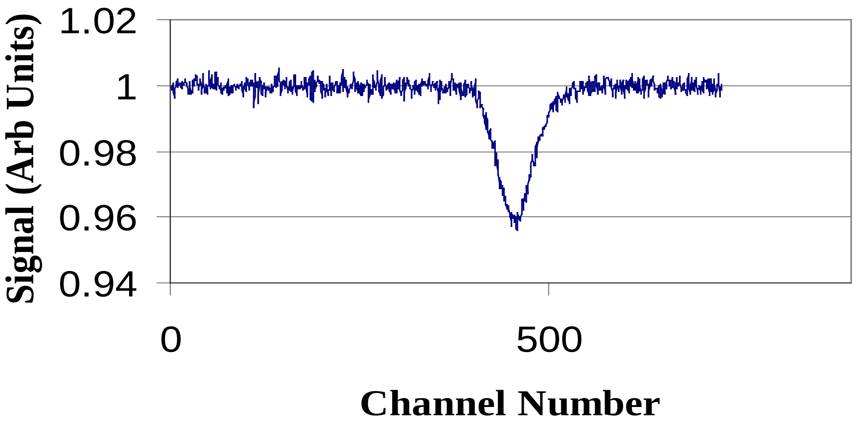
Exhaled CO from a Non-Smoker

10s Breath Hold Absorption Spectrum



$C_{CO} = 2.7$ ppm

Continuous Breath Sampling Absorption Spectrum

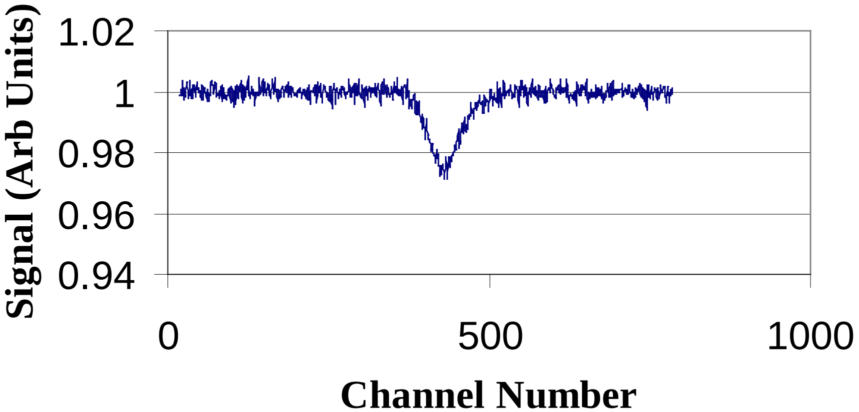


$C_{CO} = 2.3$ ppm

- 10 second breath holding increases the exhaled CO concentration.

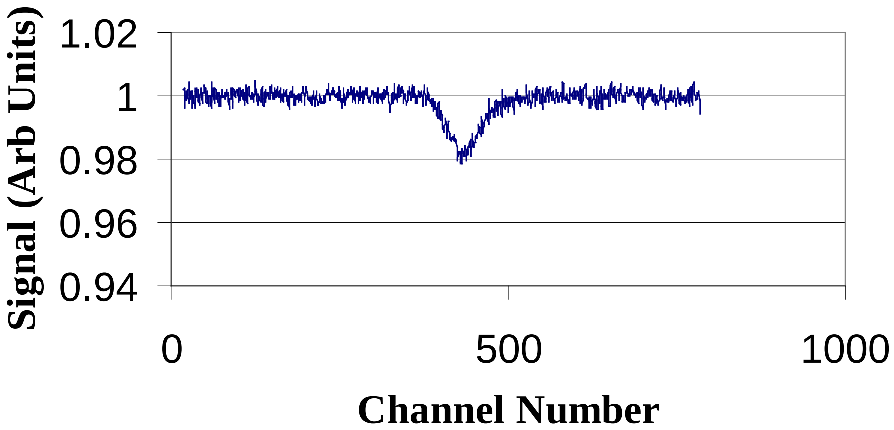
Exhaled CO from a Smoker

10s Breath Hold Absorption Spectrum



C_{CO} = 1.4 ppm

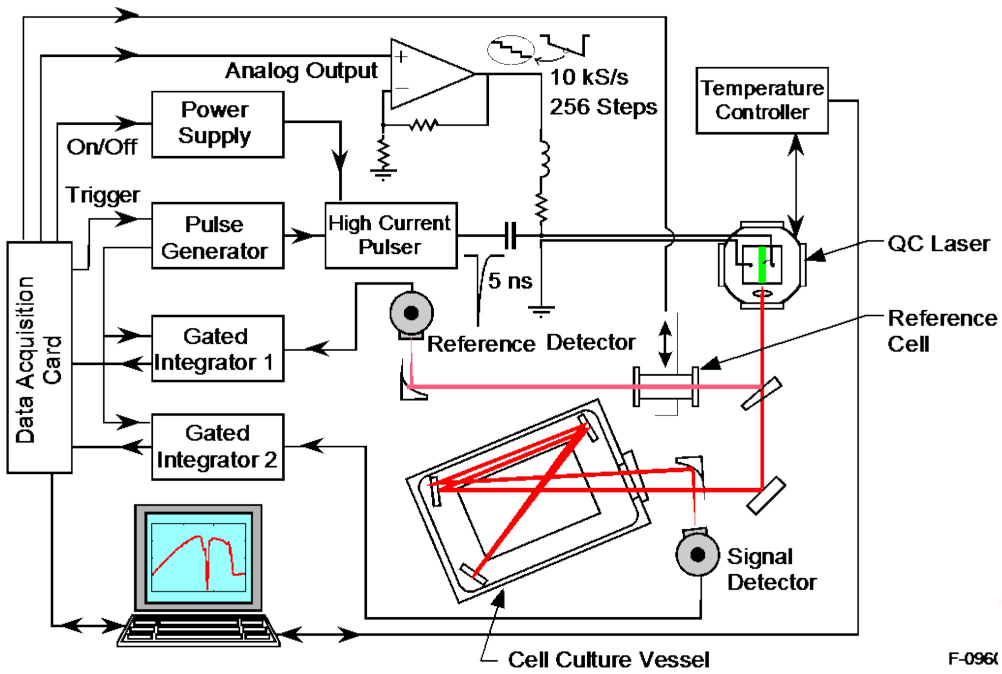
Continuous Breath Sampling Absorption Spectrum

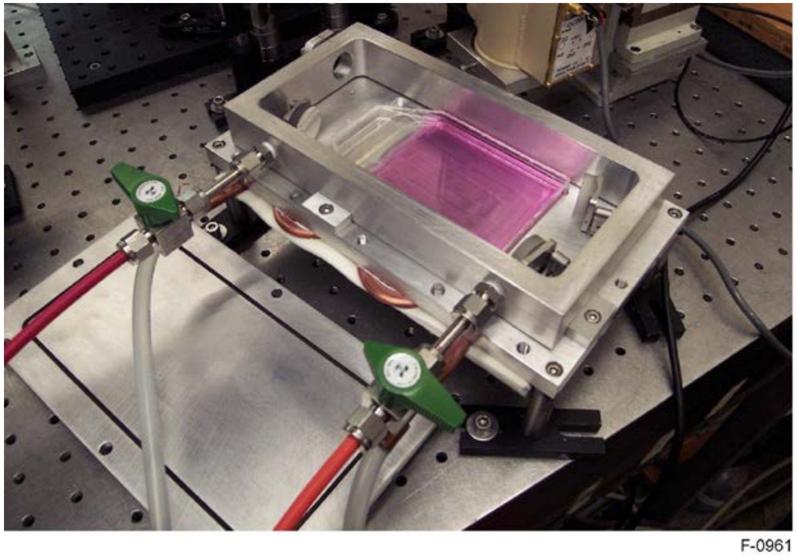


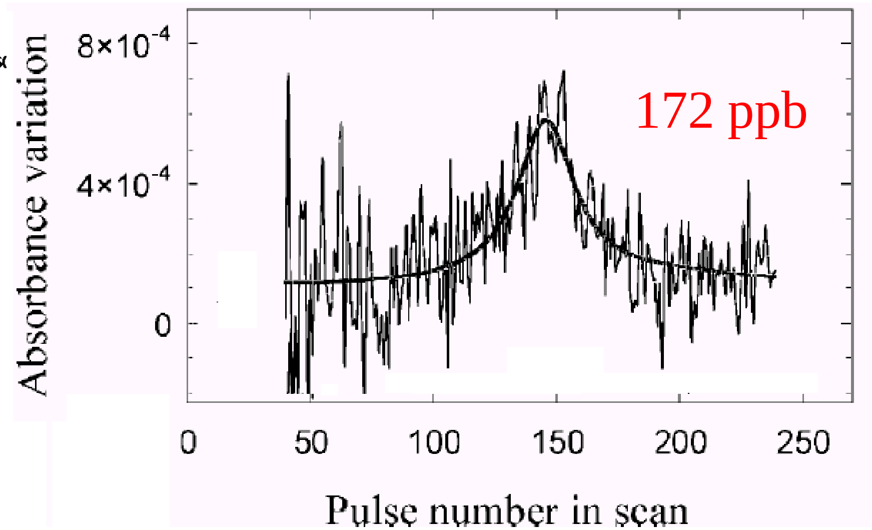
C_{CO} = 1.0 ppm

- 10 second breath holding increases the exhaled CO concentration.
- Environmental conditions and time since last cigarette appear to significantly affect exhaled CO concentration

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

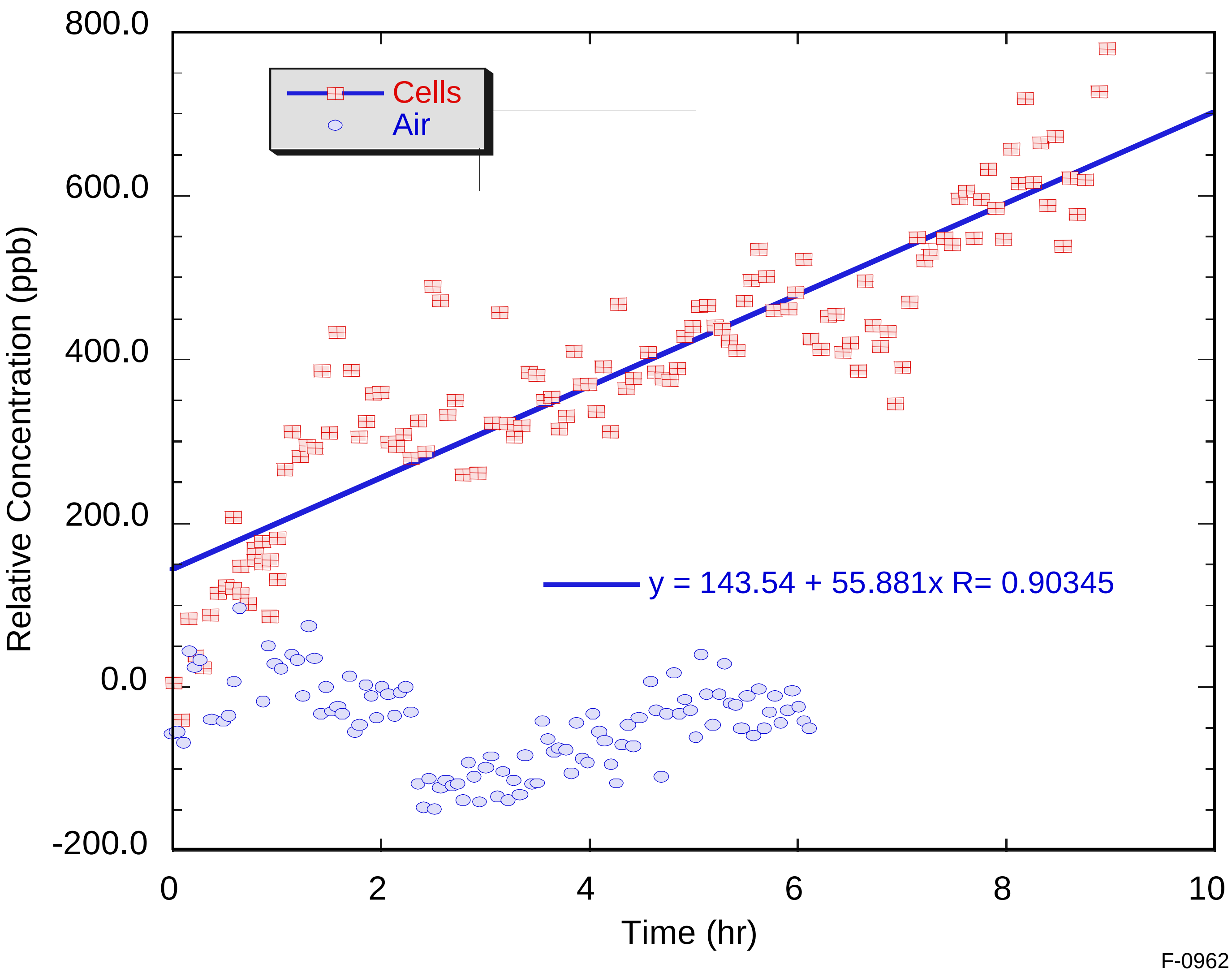






- Measured CO production rates of viable cultures of vascular smooth muscle cells
- Achieved a detection limit of for CO of ~20 ppb

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



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

CO Production Rate

~ 44 ppb/h

RICE

V

Carbonyl Sulfide (OCS) Detection

Motivation for OCS detector design

- **Breath analysis is a non invasive way of human disease detection**

- **Elevated COS concentrations in exhaled breath have been reported in lung transplants recipients suffering from acute rejection**

  S.M. Studer et.al.,"Patterns and Significance of Exhaled-Breath Biomarkers in Lung Transplant Recipients with Acute Allograf Rejection", J. of Heart and Lung Transplant, 20(11), 1158 (2001)

- **As well as in patients with liver disease**

  S.S. Sehnert et.al., "Breath biomarkers for detection of human liver diseases: preliminary study", Biomarkers, 7(2), 174 (2002)

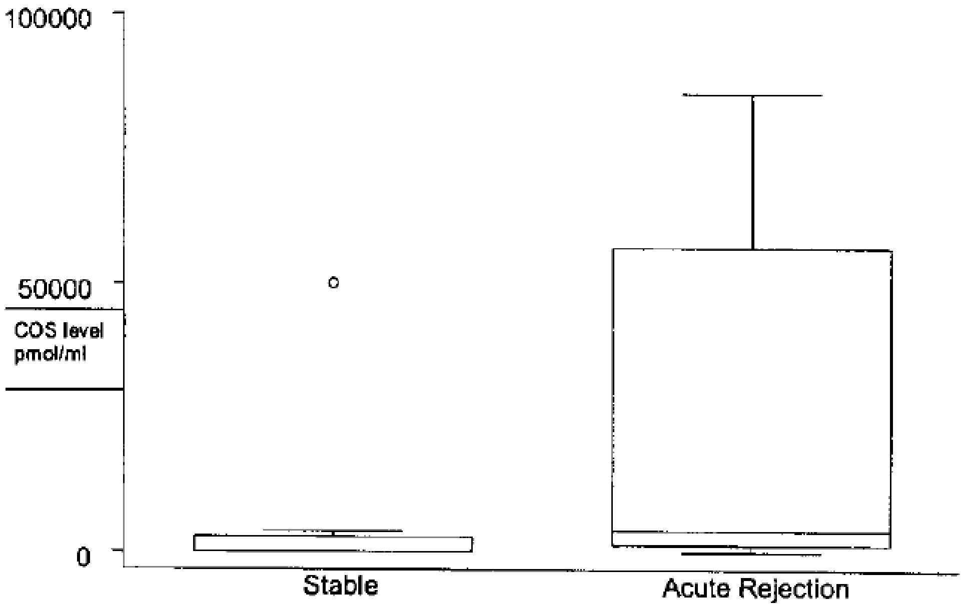
- **Application of quantum-cascade (QC) lasers allows the design of a compact sensitive, and selective trace-gas sensor**

- **Goal: non-invasive rapid, *in situ* detection of trace-gases in exhaled human breath**

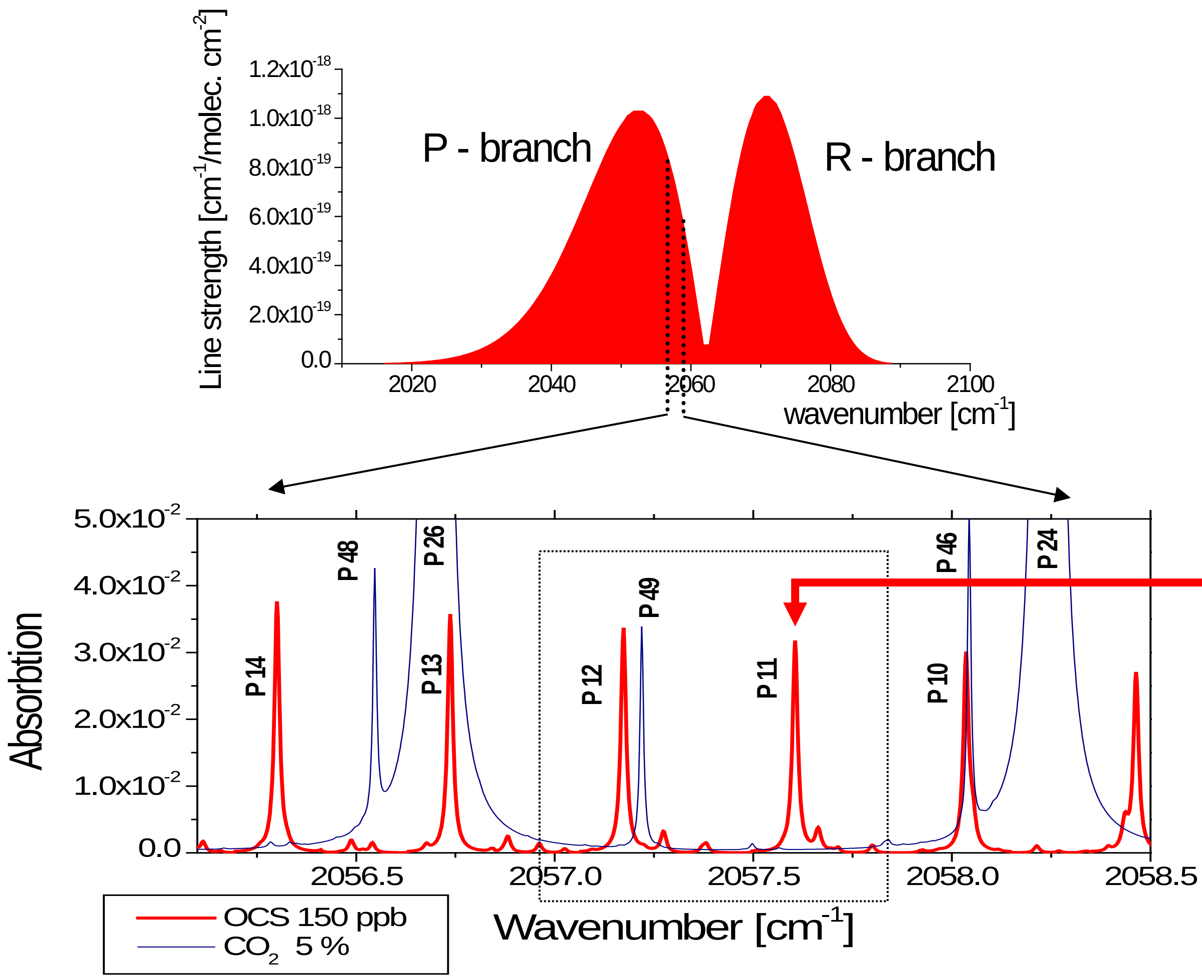
Exhaled Carbonyl Sulfide

- A 2001 study by the T. H. Risby group at John Hopkins University demonstrated that 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 ionization detection

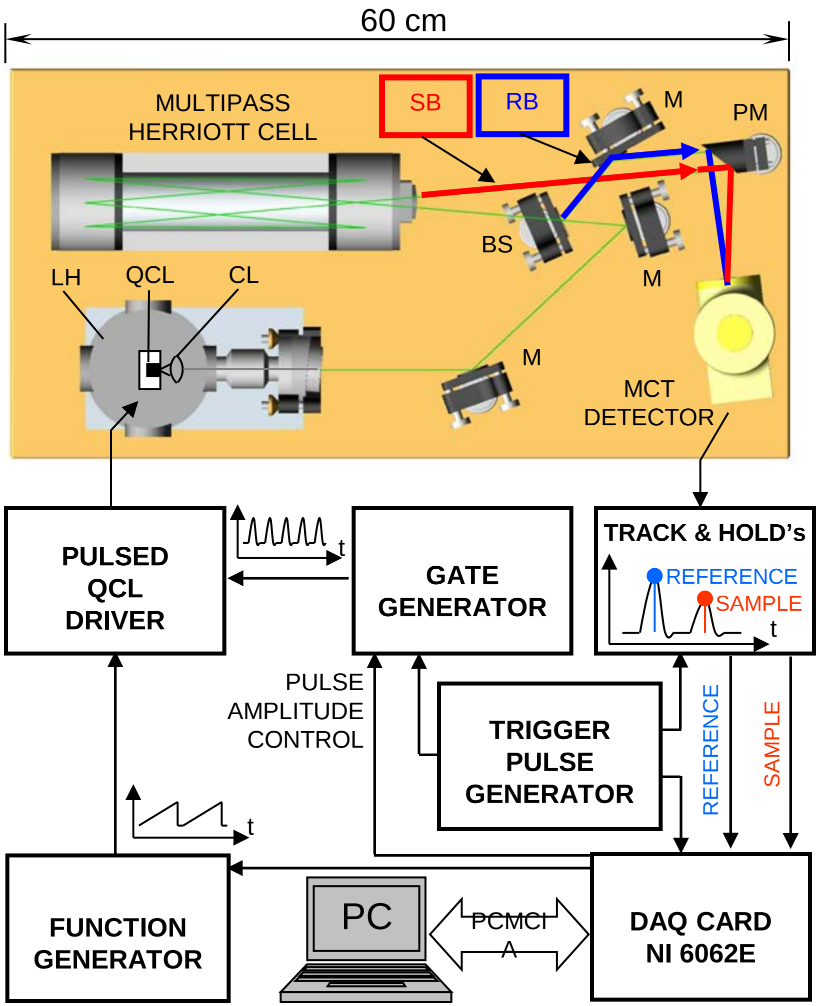


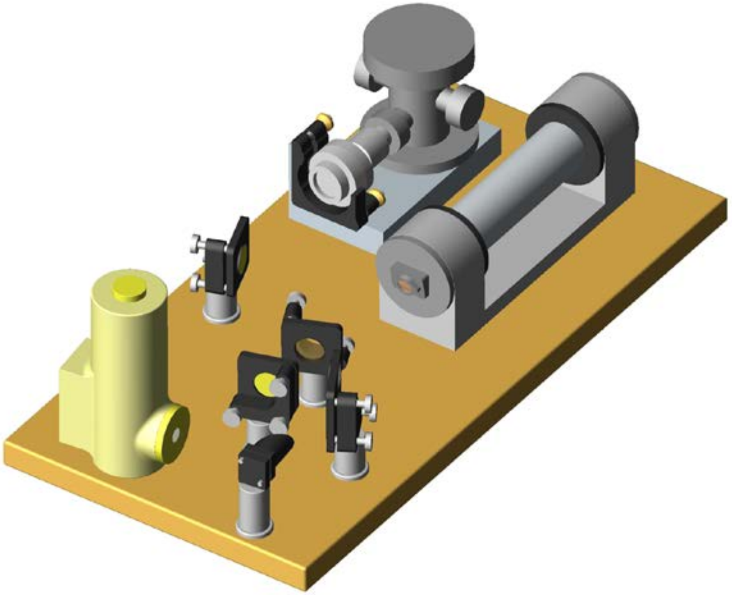
OCS ro-vibrational ν_3 spectrum at ~ 4.85μm

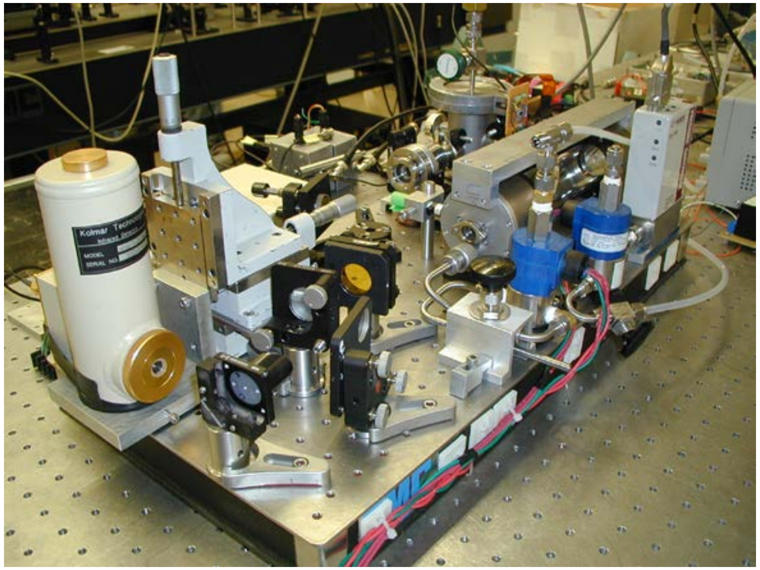


- OCS line intensity:
- 7.49·10^{-19} cm^{-1}/molecule·cm^{-2}
- Minimal spectral interference by nearby CO_2 and H_2O absorption lines
- Availability of a CO_2 line within the fast tuning range of the QCL for ventilation monitoring simultaneously with an OCS measurement

OCS Sensor Architecture





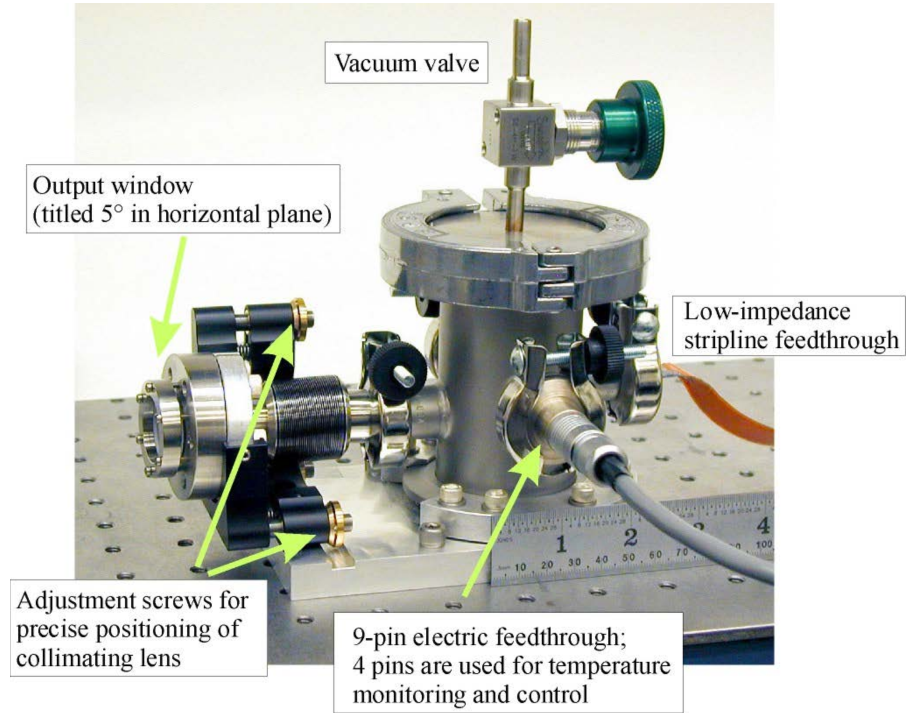


QCL – quantum cascade laser chip
LH - laser housing
CL – collimating lens
SB – sample beam

RB – reference beam
M – mirror
BS – beam splitter
PM – off-axis parabolic mirror

G. Wysocki et al. Applied Optics 43, 6040-6046, 2004

TEC cooled QC Laser Housing and Breath Collection Apparatus

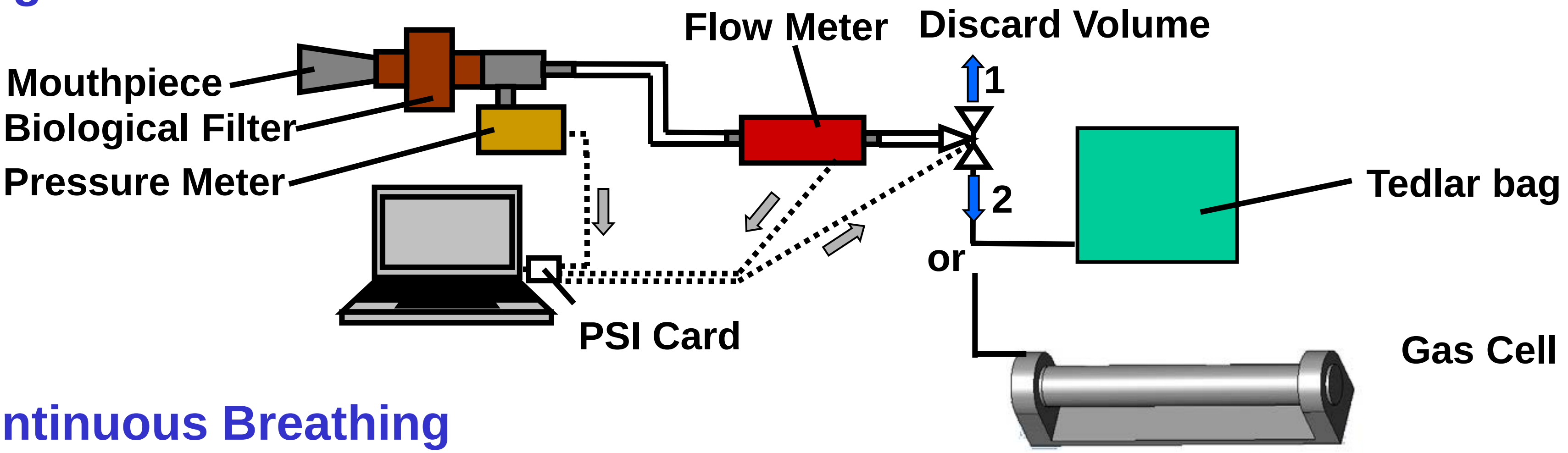


Monitoring breathing

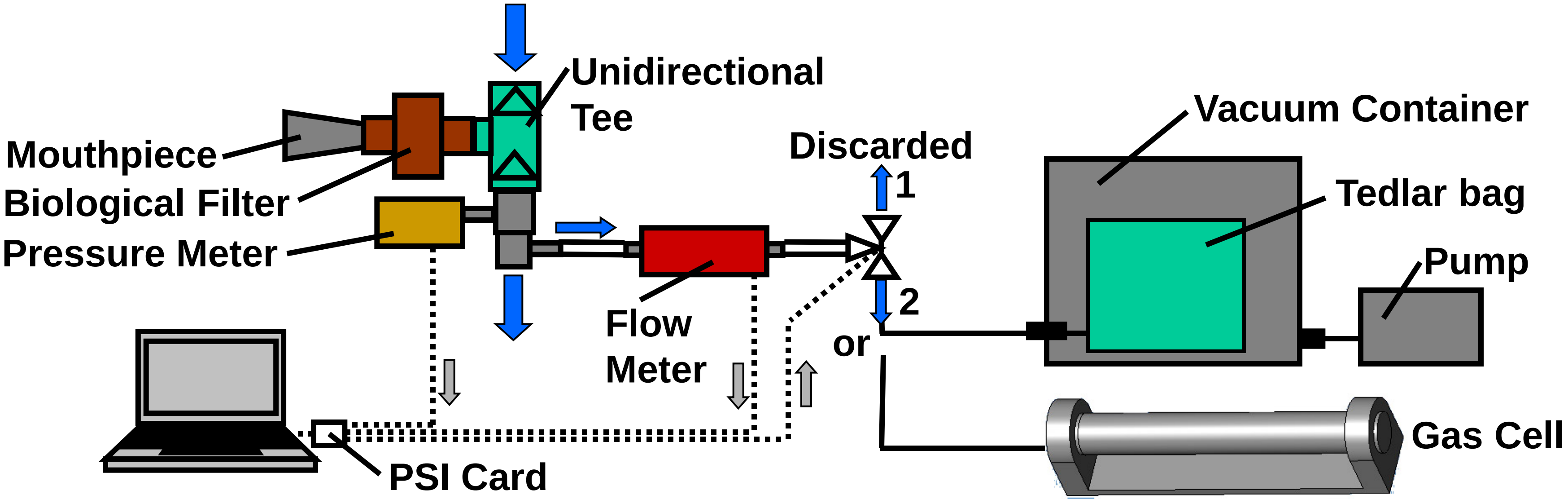
- Single breath
  - Control expiratory flow
  - Control mouth pressure
  - Monitor concentration of carbon dioxide
- Multiple breaths
  - Measure flow
  - Monitor frequency
  - Monitor mouth pressure
  - Monitor concentration of carbon dioxide

Breath Collector Configurations

Single Breath

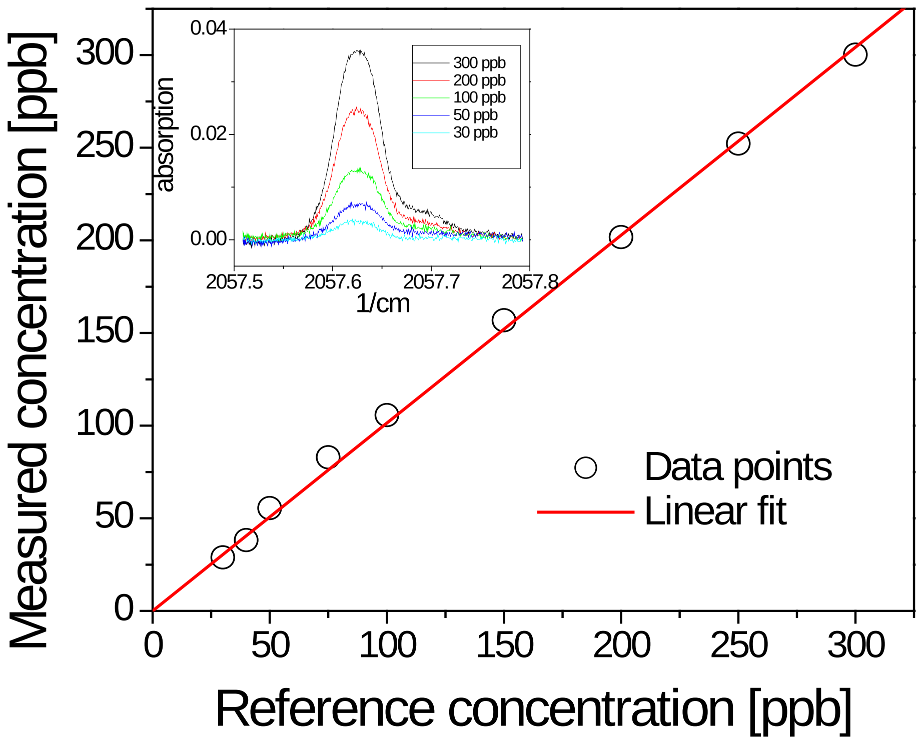


Continuous Breathing



OCS Concentration Calibration of QCL Sensor

Calibration curve

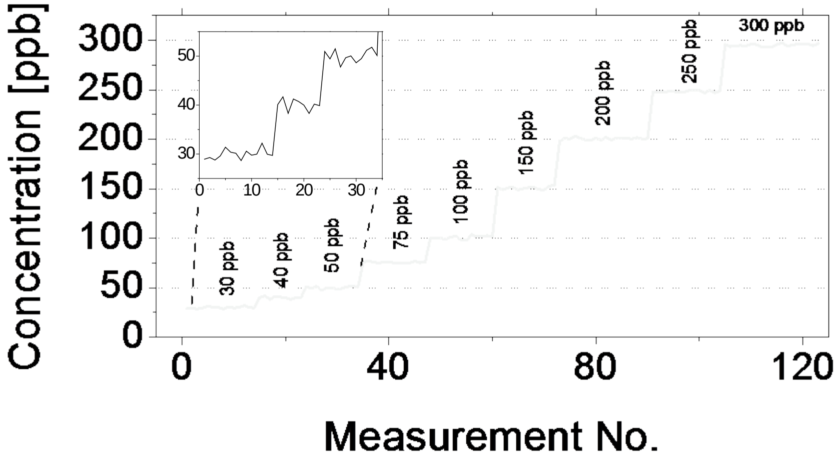


1000 spectra averaged acquired within t = 4 s
and fitted to 300 ppb OCS reference spectrum

Theoretical sensitivity:

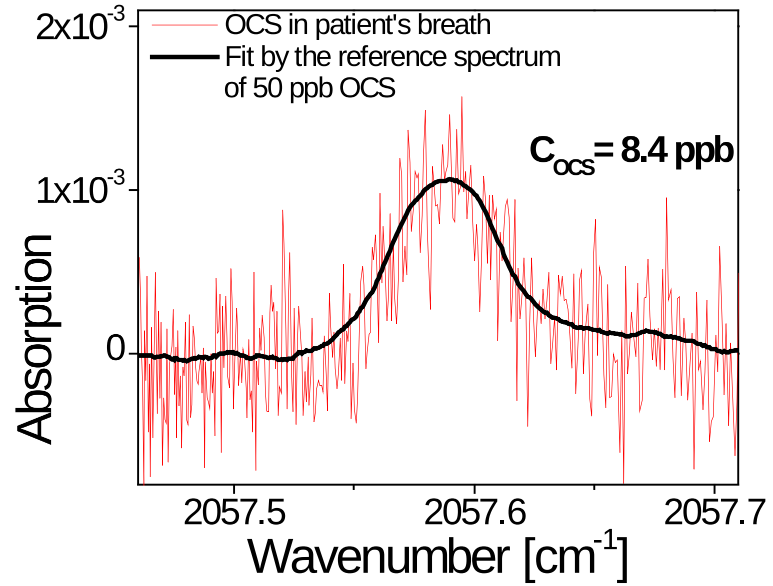
$$0.27\ ppb \cdot \sqrt{1000/100} = 0.85\ ppb$$

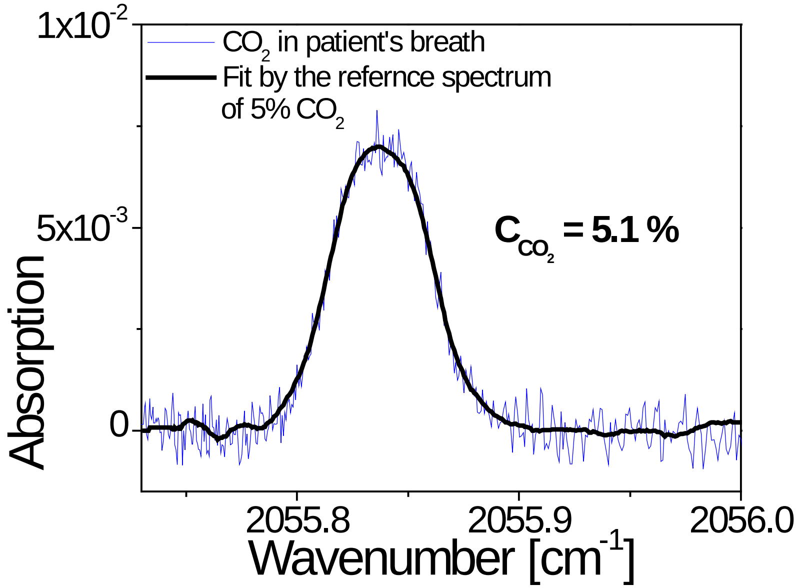
Scattering of the concentration measurement: **σ = 1.2 ppb**



100 spectra averaged acquired within t = 0.4 s
and fitted to 300 ppb OCS reference spectrum

OCS and CO_2 Concentration Measurements in Exhaled Breath

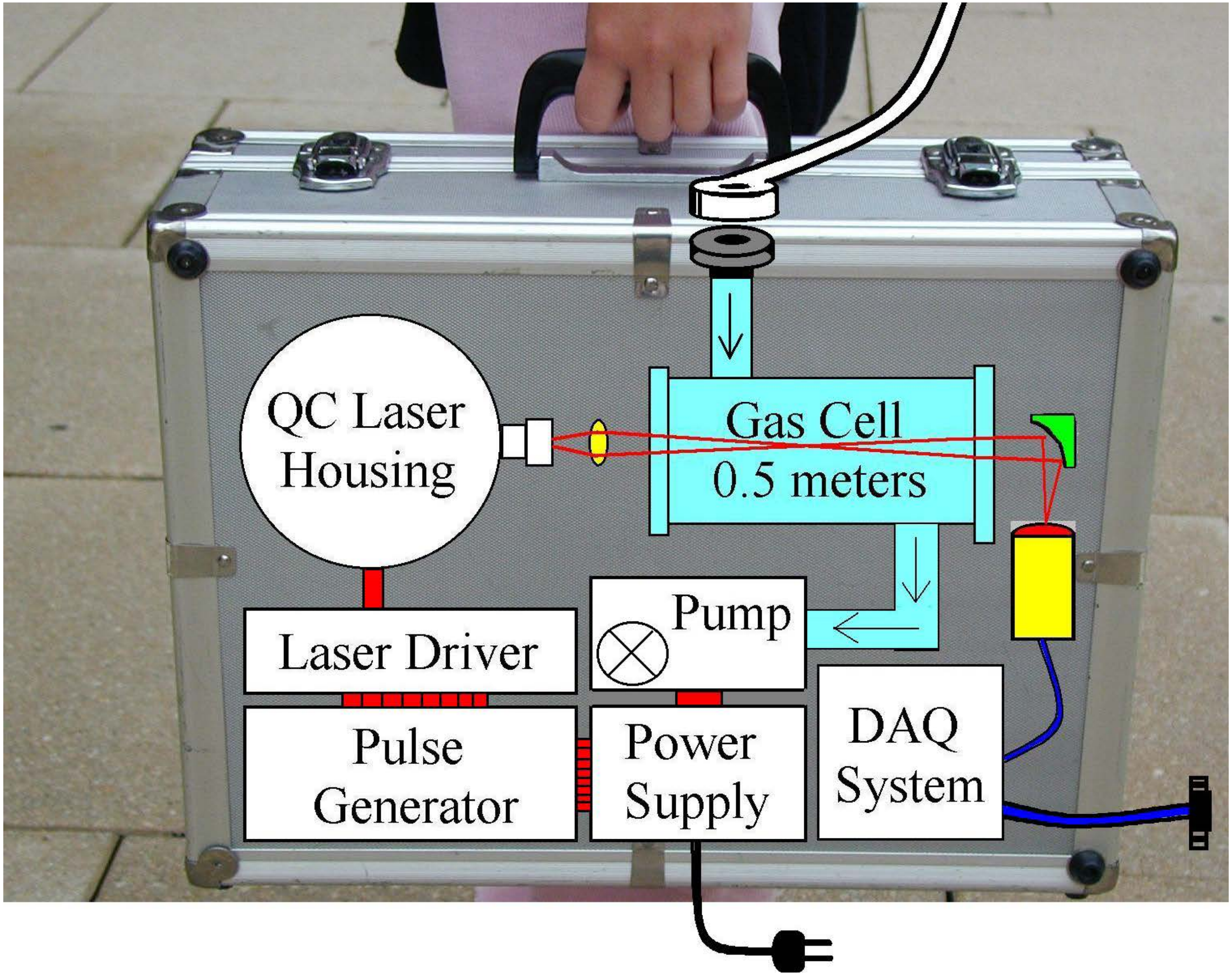




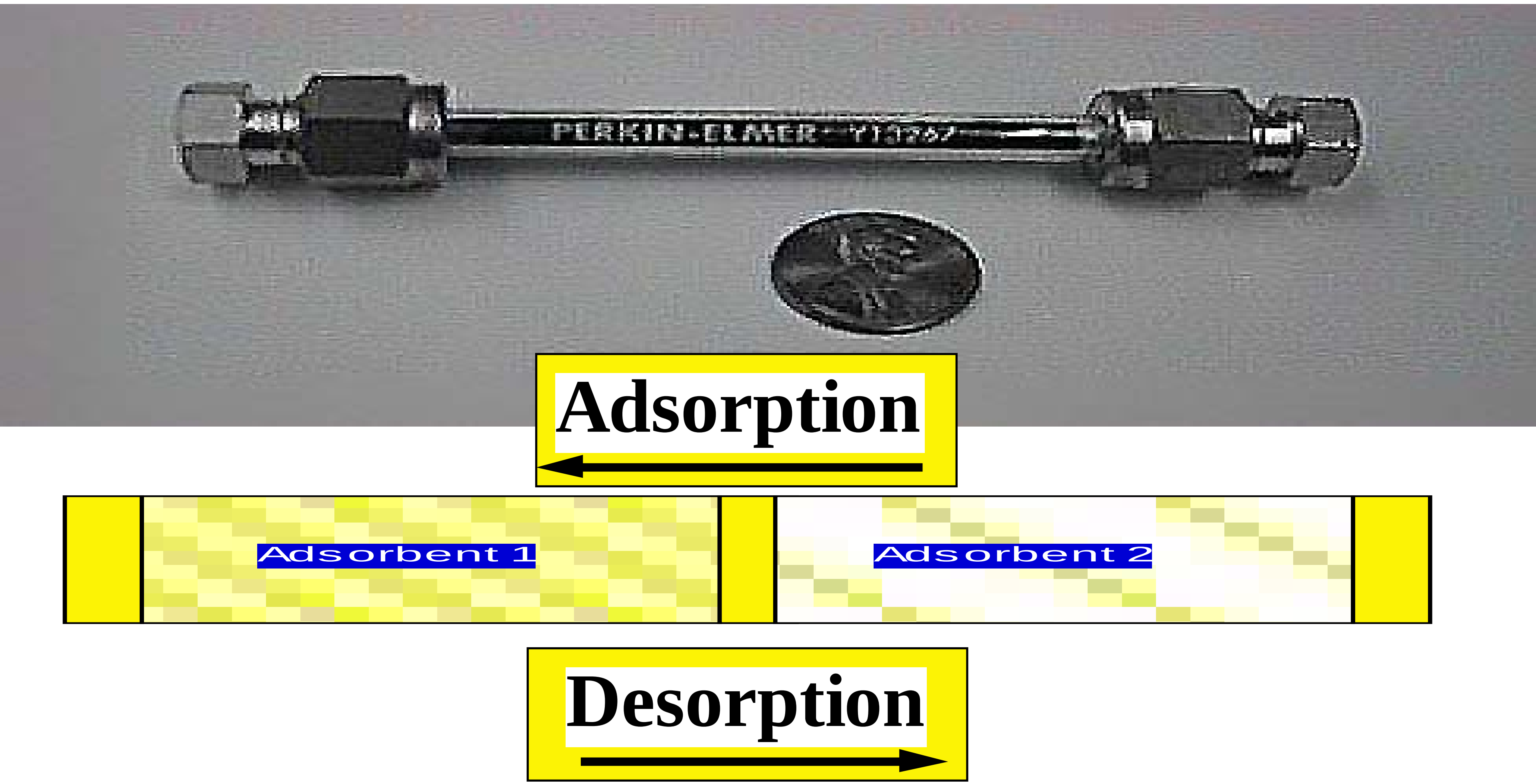
- Sample was taken from lung transplant patient suffering from bronchiolitis*
- Sampling was performed using chemically inert 1 liter tedlar sampling bags and analyzed within 2 hours after collection
- Spectrum was measured at a total pressure of 60 torr

* The authors wish to thank Dr. Remzi Bag and Carolyn M. Paraguaya from Baylor College of Medicine, Houston, TX for supplying breath samples

Schematic of a Portable LAS System



Thermal Gas Desorption Tube



VI

Emerging Optical Technologies in Medicine

RICE

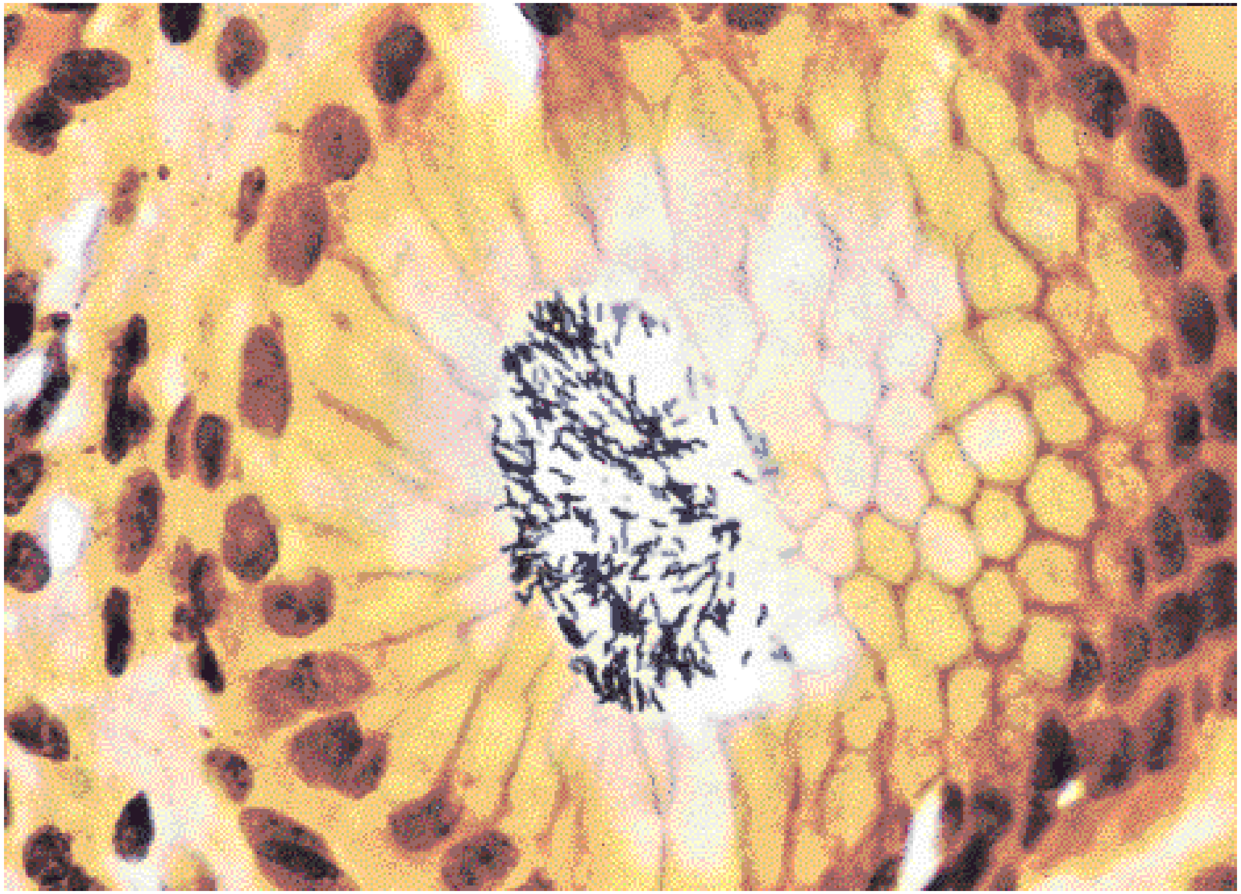
Important Biomedical Target Gases

Molecule	Formula	Biological/Pathology Indication
Pentane	$CH_3(CH_2)_3CH_3$	Lipid peroxidation, oxidative stress associated with inflammatory diseases, transplant rejection, breast and lung cancer
Ethane	C_2H_6	Lipid peroxidation and oxidative stress
CO_2 isotope ratio	$^{13}CO_2$ / $^{12}CO_2$	Marker for Heliobacter pylori infection, Gastrointestinal and hepatic function
Carbonyl Sulfide	**COS**	**Liver disease and acute rejection in lung transplant recipients (10-500 ppb?)**
Carbon disulfide	CS_2	Schizophrenia
Ammonia	**NH_3**	**Hepatic encephalopathy, liver and renal diseases, fasting response**
Formaldehyde	**HCHO**	**Cancerous tumors, breast cancer (400-1500 ppb)**
Nitric Oxide	**NO**	**Inflammatory and immune responses (e.g., asthma) and vascular smooth muscle response (6-100 ppb)**
Hydrogen Peroxide	H_2O_2	Airway Inflammation, Oxidative stress (1-5 ppb)
Carbon Monoxide	**CO**	**Smoking response, CO poisoning, vascular smooth muscle response, platelet aggregation (400-3000 ppb)**
Ethylene	**$H_2C{=}CH_2$**	**Oxidative stress, cancer**
Acetone	CH_3COCH_3	Fasting response, diabetes mellitus response, ketosis

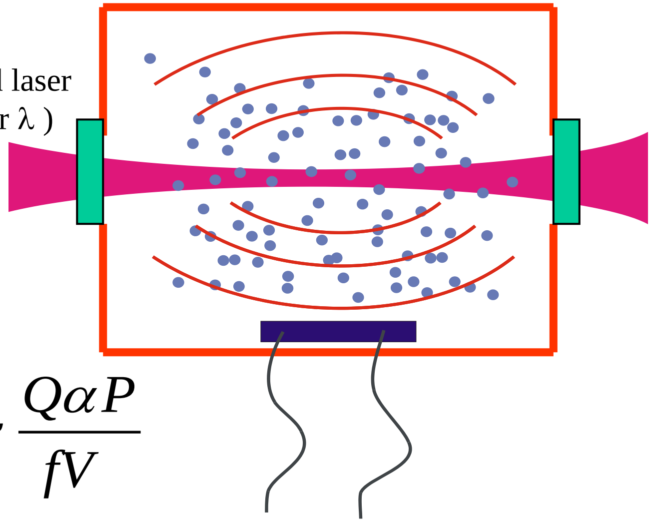
Background of Helicobacter Pylori

- *Helicobacter Pylori* is a common bacteria infecting over 50% of the world's population
  - Incidence of infection decreases in developed countries (e.g. good sanitation = less infections)
- Risk of peptic and gastric ulcers increased tenfold in patients infected with H. Pylori
  - Over 4 million people in the US, accounting for over $5 billion annually

H. Pylori

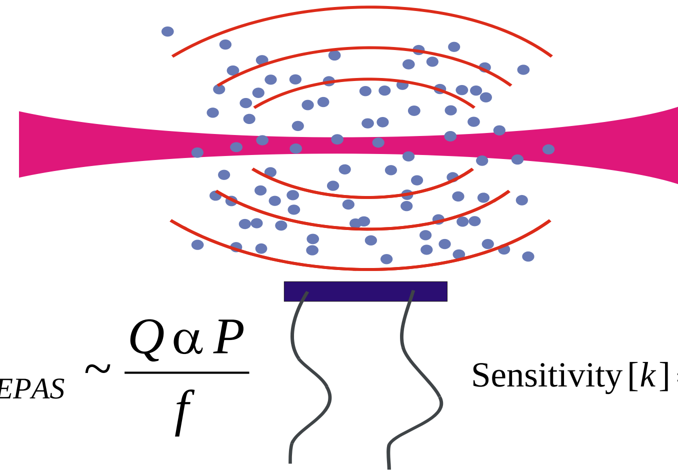


Laser based Photoacoustic Spectroscopy



$$S_{PAS} \sim \frac{Q\alpha P}{fV}$$

Traditional PAS:
Resonant cell, broadband microphone
Cell dimensions ~(sound wavelength)/2

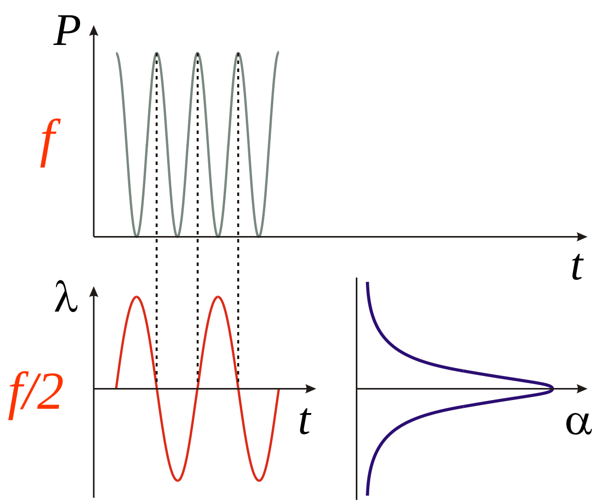


$$S_{QEPAS} \sim \frac{Q\alpha P}{f}$$

$$\text{Sensitivity}\,[k] = \frac{\text{cm}^{-1} \times \text{W}}{\sqrt{\text{Hz}}}$$

QEPAS:
Piezoelectric quartz crystal, optional cell

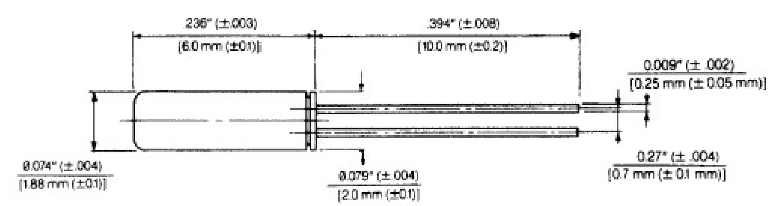
Wavelength modulation and 2*f* detection



(4508) (de02762)

RALTRON

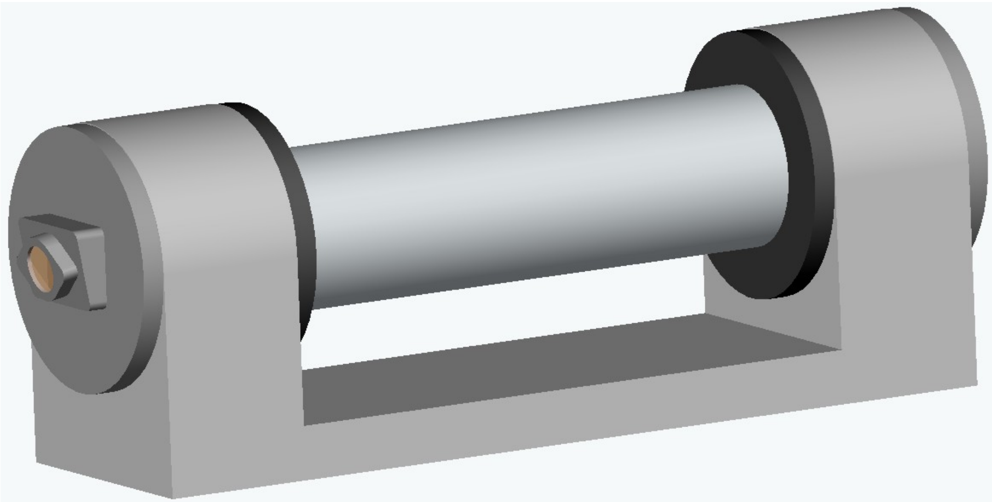
WATCH CRYSTAL TUNING FORKS

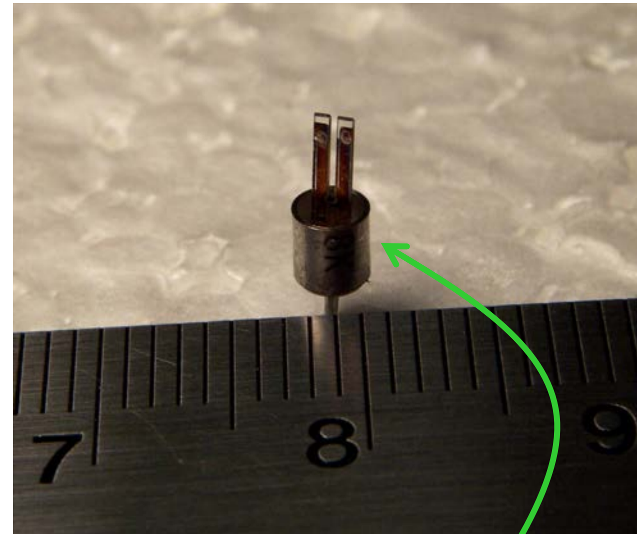


R26

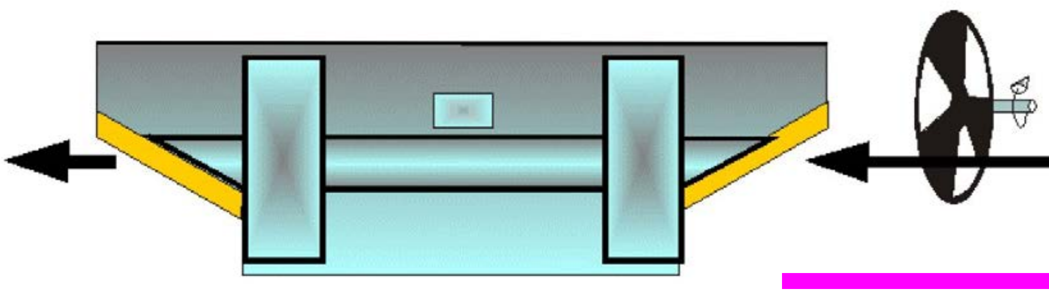
Frequency: 32.768kHz ±30ppm. **Operating temperature:** −10°C to +60°C.
ESR: 35kohms max. **(R26)**; 50kohms max. **(R38)** .

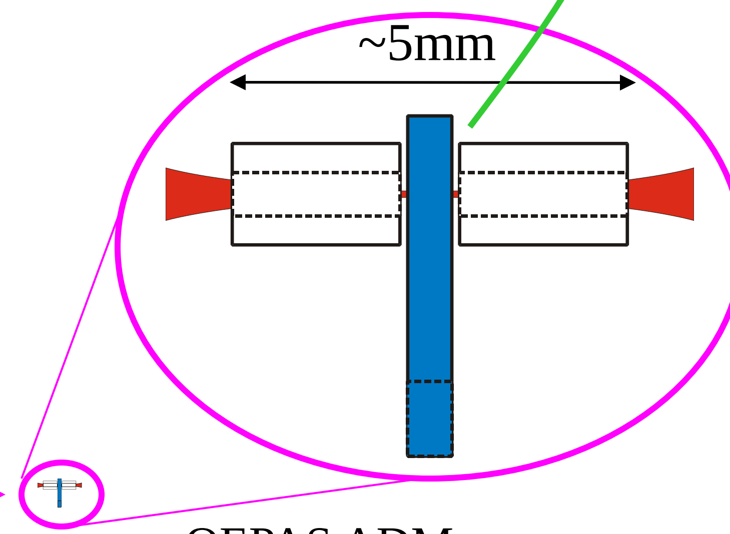
Comparative Size of Absorbance Detection Modules (ADM)





Optical multipass cell (100 m):
l~70 cm, *V*~3000 cm^3

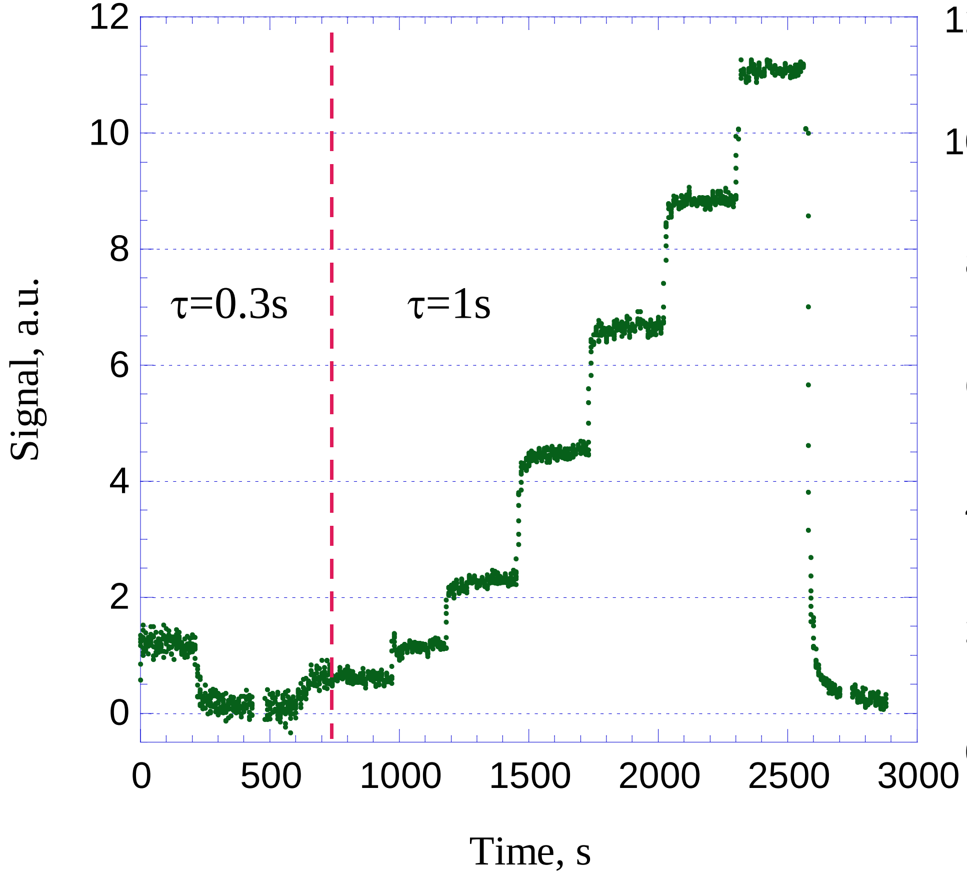


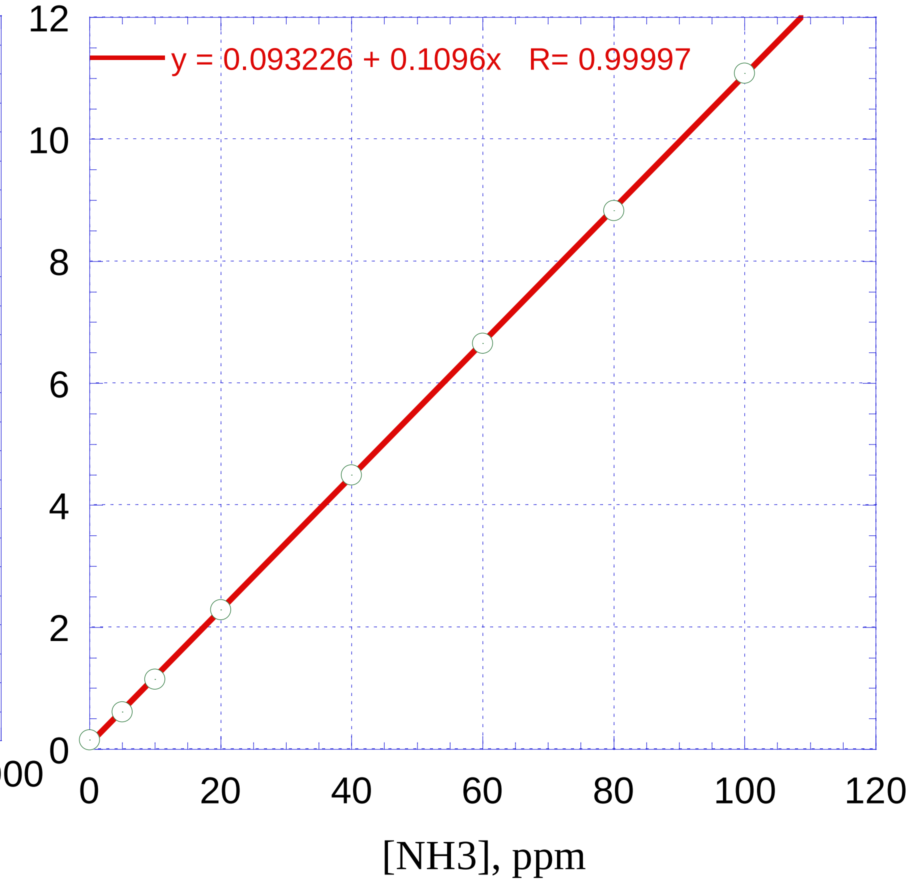


Resonant photoacoustic cell (1000 Hz):
l~60 cm, *V*~50 cm^3

QEPAS ADM:
l~0.5 cm, *V*~0.05 cm^3

Calibration and Linearity of QEPAS based NH_3 Sensor





Noise –equivalent (1s) concentration (NEC). for τ=1s time constant is 0.65 ppmv for 38 mW excitation power

90 last points of each step averaged

(Traditional PAS* – 1.5×10^{-9} $cm^{-1}W/\sqrt{Hz}$)

***Webber et al., APPLIED OPTICS April 2003 Vol. 42, No. 12, p.2119**

Noise-equivalent absorption (NEA) coefficient $k=7.2\times10^{-9}$ $cm^{-1}W/Hz^{1/2}$

Merits of QE Laser-PAS based Trace Gas Detection

- Immune to ambient and flow acoustic noise, laser noise and etalon effects
- Dramatic reduction of sample volume (< 1 mm^3)
- High sensitivity (ppm to ppb gas concentration levels) and excellent dynamic range
- Applicable over a wide range of pressures
- Temperature, pressure and humidity insensitive
- Rugged and low cost compared to LAS that requires a multipass absorption cell and infrared detector(s)
- Potential for optically multiplexed concentration measurements

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 (C,O,S)
- **Medical Applications in Exhaled Breath Analysis**
  - **eNO**: many lung diseases such as asthma and alveolitis (e.g. interstitial pneumonia or idiopathic pulmonary fibrosis)
  - **COS**: lung transplant rejection & liver diseases
  - eCO: pulmonary diseases, neonatal non-hemolytic hyperbilirubinemia, diabetes
- **Future Directions**
  - Develop advanced gas sensor for eNO and COS detection
  - Place a robust and portable point-of-care mid-IR laser based gas sensor in a clinical setting
  - Investigate other gas phase biomarkers of human diseases

RICE