Breath analysis and diagnosis by quartz enhanced photoacoustic spectroscopy (QEPAS)

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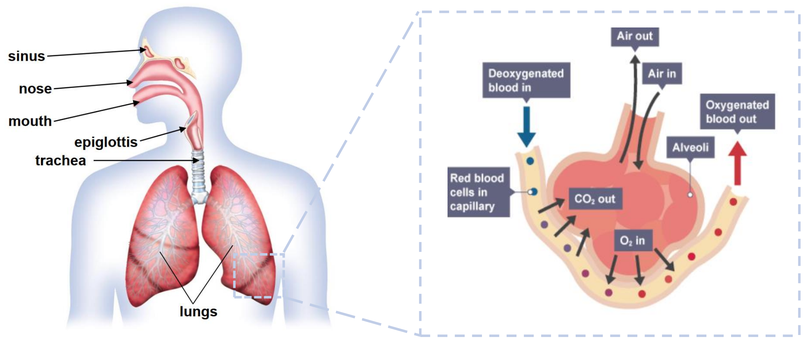
- A biomarker is a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions. [1]
- Gases found in the exhaled breath are investigated as biomarkers as a direct link exists between their presence (concentration level, variations,...) and some diseases.
- As part of a collaboration with Montpellier hospital, QEPAS is used as an investigation technique for exhaled breath gases related to cardiovascular diseases.

Exhaled breath composition



Respiratory compartments and gas exchanges

Main compounds (%)		
CO_2 (~5), oxygen (~14), nitrogen (~77), water vapor		
Others (ppmv-ppbv)	**Associated diseases**	**Required working range**
Carbon monoxide (CO)	Inflammation CVD*	1-10 ppmv
Nitric oxide (NO)	Asthma CVD	10-50 ppbv
Acetone (C_3H_6O)	Diabete CVD [2]	0-10 ppmv > 300 ppbv
Benzene (C_6H_6)	Lung cancer Breast cancer	0-10 ppbv
Methane (CH_4)	Food intolerance	2-10 ppmv
Isoprene (C_5H_8)	CVD	> 100 ppbv

*CVD: cardiovascular diseases

Cardiovascular diseases = 1st cause of death in the world →

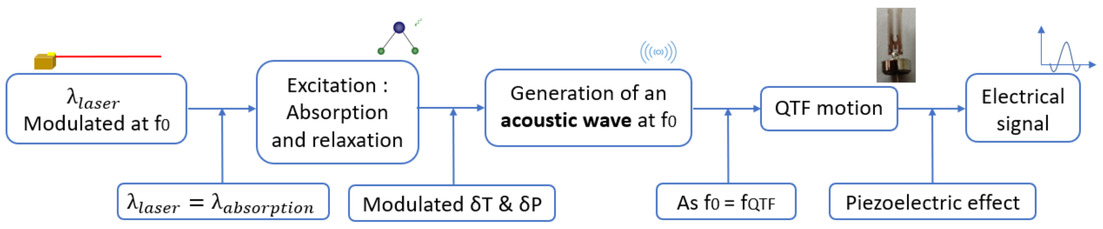
Traditional diagnosis steps (non exhaustive) :
- Family tree investigations
- Blood tests
- Cardiac catheterization

→ **Late, invasive and expensive**

Investigation of exhaled breath gas matrix constitutes an **easy and non invasive access** to body metabolisms →

Identification and quantification of gaseous compounds

Quartz Enhanced PhotoAcoustic Spectroscopy

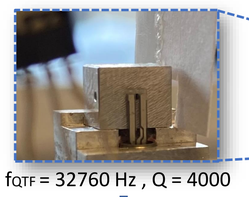


Working principle of QEPAS.

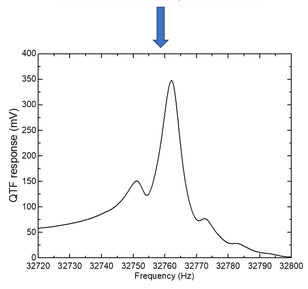
The laser used is an infrared source as absorption lines of molecules are more intense in this spectral range. A lock-in amplifier is used to modulate the laser and demodulate the signal collected from the QTF. This electrical signal is proportional to the concentration of gas.

- ✓ **Sensitive** : ppbv range detection
- ✓ **Selective** : distinguish one species among others
- ✓ **Low cost** compared to other optical technics
- ✓ High potential of **miniaturization**

Commercial quartz tuning fork widely used in watch industry



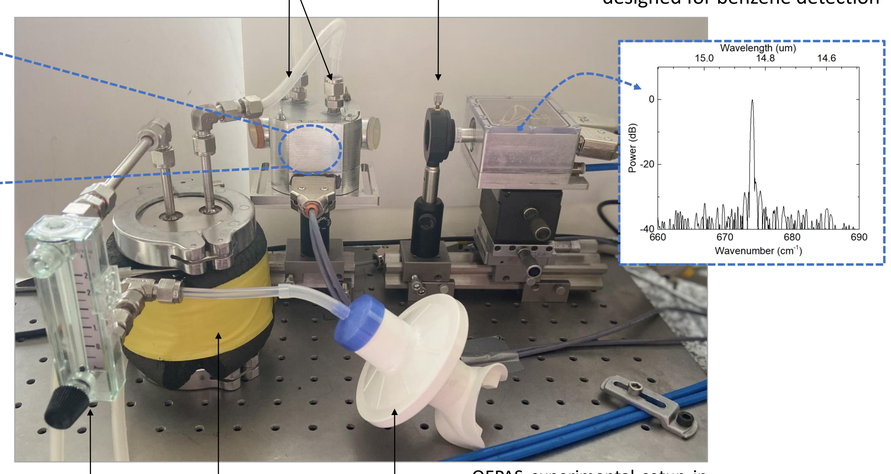
f_{QTF} = 32760 Hz , Q = 4000



QTF characterization

Gas inlet/oulet — Optical lens

Distributed feedback Quantum cascade laser (DFB-QCL). Laser spectrum at 14.9 µm designed for benzene detection

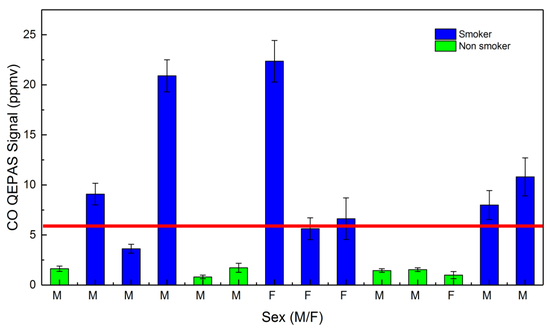


Flowmeter — Bubble bath — Mouthpiece

QEPAS experimental setup in off beam configuration [3]

QEPAS for exhaled breath investigation

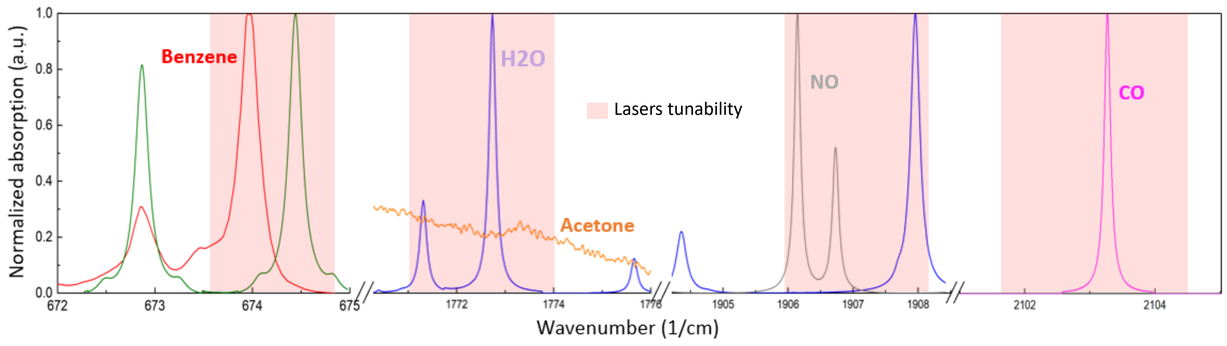
Exhaled CO measurement at 4.7 µm [4]



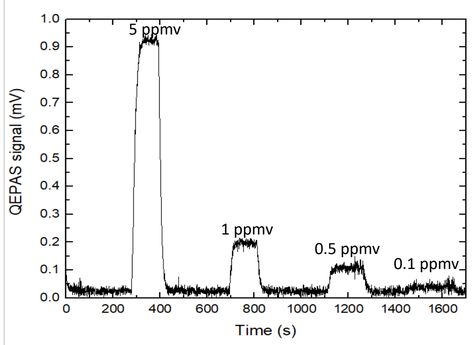
CO in healthy non smokers **< 6 ppm**
CO in healthy smokers **> 6 ppm**

QEPAS system limit of detection (LOD) : **20 ppbv in 1s**
Medical sensor (Medisoft) LOD = 1 ppm in 1s

→ System is able to differenciate between two groups
→ Results agree with sensor used in medical routine



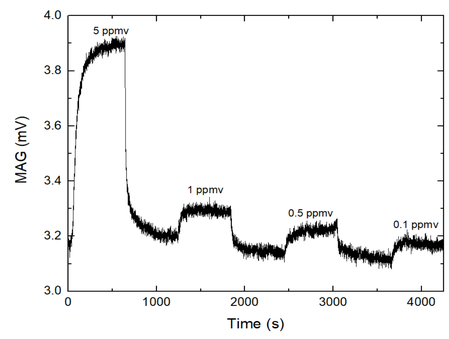
NO measurement at 5.2 µm



NO in healthy patients **< 50ppbv**
LOD of QEPAS system : **80 ppbv in 1s**

Very low concentration in the exhaled breath

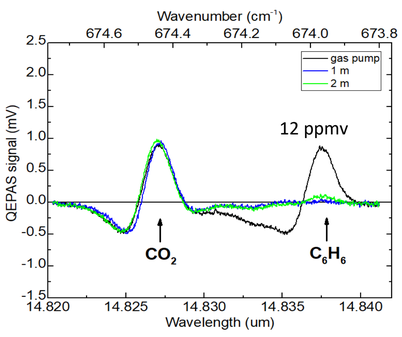
Acetone measurement at 5.6 µm



LOD of QEPAS system : **17 ppbv in 1s**

Laser not selective for acetone

Benzene measurement at 14.9 µm



First investigation of benzene in gas station to estimate users exposure

Safety recommendations in France : 1ppm for 8 hours

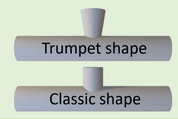
LOD of QEPAS system : **30 ppbv in 1s** [5]

Improvements ?

Laser's power +++
Higher absorption line

$$S \propto \frac{Q\,P\,\alpha}{f_{QTF}}$$

S: QEPAS signal [V]
Q: quality factor of the QTF
P: laser power [W]
α : absorption coef. of the gas [cm^{-1}]
f_{QTF}: resonance frequency [Hz]



Trumpet shaped microresonator to imitate sound enhancement in musical instruments

- Infrared based sensors achieving very high performances can be used to detect exhaled breath gases in medical applications.
- Working in the exhaled breath is far from calibrated laboratory circumstances, some physiological conditions need to be considered in sensors developpement:
  - Inter and intra subject differences that need standardized procedures.
  - Very low concentration to detect that pushes the sensor to its limits.
  - Water vapor present in very high amount that causes instability in the measurement. Many approaches are investigated to take into account water contribution: use of bubble bath to stabilize the humidity, custom QTF especially designed for QEPAS that are less affected by humidity, real time correction to overcome loss of signal [6].
- In medical routine at Montpellier hospital, Medisoft sensor is used for respiratory compartments exploration by measuring gases such as NO, CO, CO_2,… Some of theses gases are defined as biomarkers in CVD. Futur team work aims to compare QEPAS results to the commercial sensor results.

[1] Biomarkers definition : https://www.fda.gov/drugs/biomarker-qualification-program/about-biomarkers-and-qualification
[2] Gouzi, F., Ayache, D., Hedon, C., Molinari, N., & Vicet, A. (2021). Breath acetone concentration: too heterogeneous to constitute a diagnosis or prognosis biomarker in heart failure? A systematic review and meta-analysis. *Journal of Breath Research*.
[3] Kosterev, A. A., Bakhirkin, Y. A., Curl, R. F., & Tittel, F. K. (2002). Quartz-enhanced photoacoustic spectroscopy. *Optics letters*, *27*(21), 1902-1904.
[4] Maurin, N., Rousseau, R., Trzpil, W., Aoust, G., Hayot, M., Mercier, J., ... & Vicet, A. (2020). First clinical evaluation of a quartz enhanced photo-acoustic CO sensor for human breath analysis. *Sensors and Actuators B: Chemical*, *319*, 128247.
[5] Ayache, D., Trzpil, W., Rousseau, R., Kinjalk, K., Teissier, R., Baranov, A. N., Bahriz, M. & Vicet, A. (2022). Benzene sensing by Quartz Enhanced Photoacoustic Spectroscopy at 14.85 µm. *Optics Express*, *30*(4), 5531-5539.
[6] Rousseau, R., Maurin, N., Trzpil, W., Bahriz, M., & Vicet, A. (2019). Quartz tuning fork resonance tracking and application in quartz enhanced photoacoustics spectroscopy. *Sensors*, *19*(24), 5565.