Sensor Array Systems in Breath Analysis: Insights from Lung Cancer Detection Projects -Presentation of the ongoing ALCOVE project-

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(Sensing of Atmospheres and Monitoring)

Outline

1. Lung cancer and E-nose (briefly)
2. PATHACOV project
3. ALCOVE project (video)
4. Take-home messages

1. Lung cancer and e-nose

- Lung cancer (LC) is one of the most common and deadly forms of cancer.
- Screenings are carried out late (asymptomatic disease): the later the screening, the lower the chances of survival.
- Diagnosis equipment is <u>expensive, not portable, requires trained personnel</u> and

Screening campaign:
Doubts on scans on the entire at-risk population:
Undesirable effects, management of abnormalities, insufficiently defined frequency of checks!

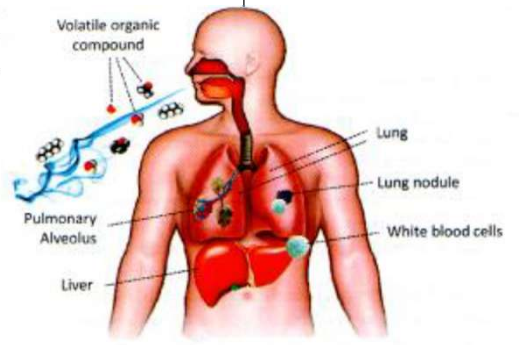
→ **<u>early diagnosis, simple and non-invasive</u> are requested by pulmonologists: e-nose (SAS) ?**

Volatilome for Lung cancer:
VOC biomarkers? no yet a consensus on a list of specific compounds/the efficiency
NO single compound like acetone for diabete?

"Breathprint"? → e-nose?

- numerous studies but samples size too low
  exceptionally above 100 for non-healthy patients
- results not convincing

The timeless story of electronic nose !!!???



II - PATHACOV

PATHACOV
HUMAN DISEASES DIAGNOSIS BY VOC ANALYSIS IN BREATH

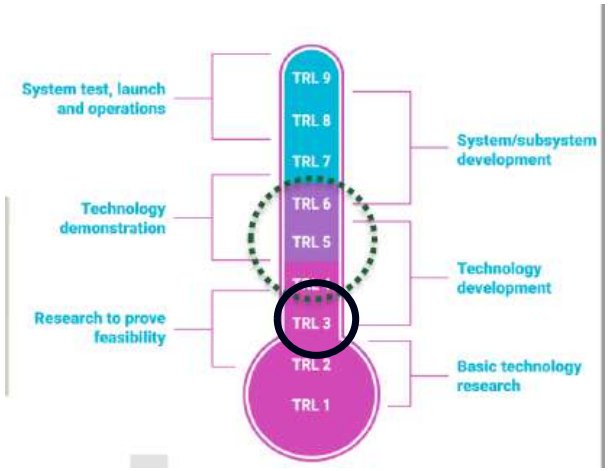
2018 - (end of) 2022
11 partners
doctors, mathematicians, chemists, physicists, electronic engineers, computer scientists…

Large-scale study in various French and Belgian hospitals

- Determining a VOC signature marker for LC (“breathprint”)
- Developing one e-nose (including sampling)

Interreg France-Wallonie-Vlaanderen
Wallonie
West-Vlaanderen

CHU Amiens Picardie
CHU Lille
CHU de Reims
MateriaNova Materials R&D Centre
Liège université
Université de Lille
eurasanté Entreprendre et Réussir
IMT Lille Douai École Mines-Télécom IMT-Université de Lille
KU Leuven
UMONS Université de Mons
Université de Reims Champagne-Ardenne



https://pathacov-project.com/

PATHACOV

HUMAN DISEASES DIAGNOSIS
BY VOC ANALYSIS IN BREATH

- **SAM lab: One e-nose system development**
  1. with commercial sensors + integration of new sensors
  2. sampling system

- **New sensors**: Synthesis and study of materials, manufacture of sensors and ability to detect markers

  metal oxide sensor (ZnO) ; polymer ; polymer and FET transistor (confidential)

- **Clinical study**: 1 400 subjects (650 patients and 750 control people (control: smoker, non-smoker)

  → VOC markers of bronchopulmonary cancer (ReCIVA® mask, GC-MS, data analysis by Machine learning – confidential-)
  VOC signature (breathprint) obtained (confidential)

  But not for e-nose development

PATHACOV
HUMAN DISEASES DIAGNOSIS BY VOC ANALYSIS IN BREATH

Why clinical study was not used for e-nose develop…ent?

Essential prerequisites for starting the study:

- Obtaining all "administrative" authorisations
- Sufficient supplies of equipment
- Setting up the data collection system (tested on the Lille CHU team for Reciva)
- Consideration of patient targeting, the patient's journey after the diagnosis (psychologically difficult!) and the proposal to take part in the study (explanations, consent, data collection, patient follow-up).

Before the other recruiting hospital centres can begin the study, the principal investigator (Lille University Hospital) must:

- Integrate all recruiting centres into the study protocol
- Initiate patient recruitment
- Draw conclusions / Improve operating procedures
- Obtain sufficient supplies of the necessary equipment for all recruiting centres (electronic nose, RECIVA masks, gloves, etc.)
- Set up each centre: training, equipment, etc.

2 years between
the Authorisation of the study protocol by the « Commission de Protection des Personnes (CPP) » and authorising inclusion of the first patient (due to time to acquire equipment and administrative concerns)

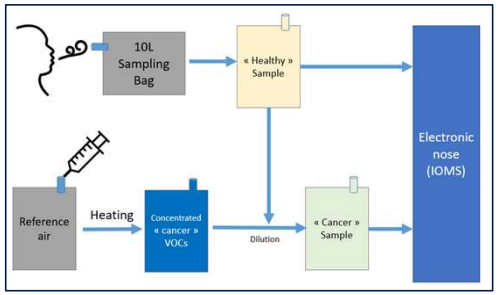
In addition, new sensors cannot be developed in few weeks without knowing the target compounds and their concentration

II - PATHACOV

- **"Artificial" Real breath**

protocol validated by the ULiège-CHU ethics committee (Pr. Schleich)

Participant Breath sampling



best methodology we found to reduce the intersubject variability

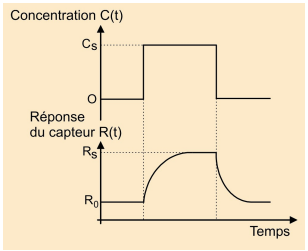
- same "environment" (local, T, RH and air exchange); same operator
- Time: no restrictions, "nothing by mouth" 12 hours before sampling
  (i.e., no smoking, teeth brushing, chewing, or eating. Drinking water was allowed).
- 5 minutes to acclimatise and rest (seated position). Fill in the questionnaire
- They were given water for mouth rinsing before blowing in a bag
- Inhale to full capacity then blow into bag.
- Successive exhalations until +/- 8L of exhalation is obtained (whole breath)
- Storage: max 03 hours before measurement

FEP sampling bag through a spirometry saliva filter in a Polytetrafluoroethylene (PTFE) holder

E-Nose measurement

- cycle: reference air (humidity-saturated air – synthetic air or filtered ambient air –); 5min/5min
- thermostated
- Feature: one/sensor = raw signal difference (stable conductance)

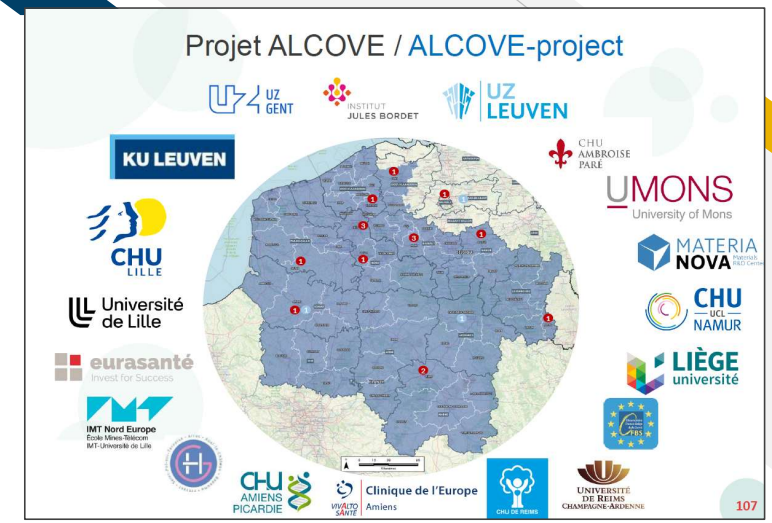
- not in-line sampling (if direct blowing = no stable signal)
- "Off-line" sampling: 2 steps in the same device
  1. Breath stored in a medium by sampler
  2. Medium is connected to AOS



III - ALCOVE

2025-2028

ALCOVE | Interreg | Cofinancé par l'Union Européenne / Medegefinancierd door de Europese Unie | France - Wallonie - Vlaanderen | CrossS3 ALCOVE



https://alcove.crosss3.eu/

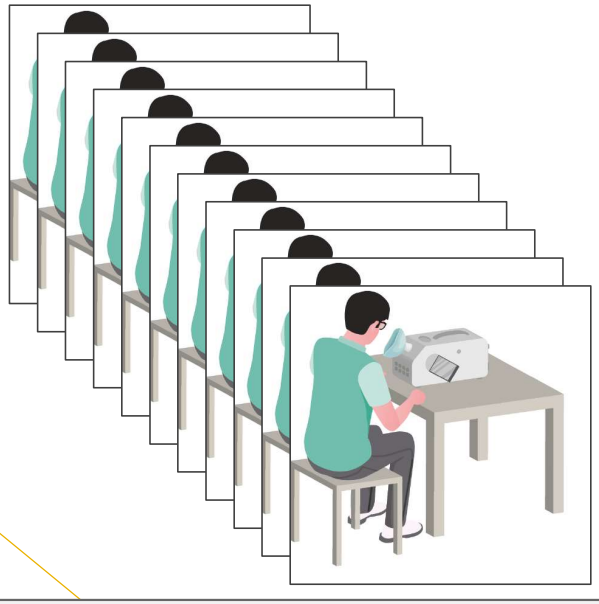
Development of 11 devices; Distributed in 5 clinic centers

- **Clinic study on 246 LC patients** (eligible or not to surgery)
  and 246 healthy « risky » subjects
- **17 partners**
- **9 hospitals**
- **one partner for technology transfer toward industrial world**

Video ALCOVE ISOCS.mp4

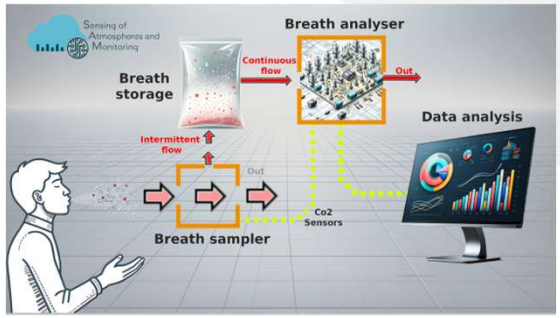
III - ALCOVE

11 e-noses



Sampling Patient breath for clinical study in several hospital centers

blowing in a « specific sampler »
- reduced bag volume: < one liter
- very low-pressure resistance to help patients suffering from respiratory diseases
- several blowing; a wait of few seconds before sending the breath through the analyser (new "capnography"approach)



Patent pending - No right to show the technology or the results

Clinical study

First step

- Analysis of breath sample simultaneously by ReCIVA® /GC-MS analysis and e-noses (white box) linked with Pathacov VOC biomarkers
- Accuracy rate of classification (percentage of correct classification) 80 % ± 5 % (min. 75 %): 246 patients statistically needed

Second step (only if accuracy criteria reached)

- Validation of the « real » performance of the e-noses
- Only e-noses(no RECIVA)
- Same population than step 1 but with more ration of early LC (70%)

IV. Take home messages

- Comparing to Environmental applications, Medical ones are more
  - ✓ humanly satisfying
  - ✓ subject to numerous research project calls
  - ✓ funded
  - ➢ **but also constraining (ethical aspects, etc):**

The prototype must comply with many aspects that require time before the clinical trial itself.
So, it's better to have **a longer development time**.

- ➢ Need to comply with medical device standards (risk analysis and risk minimization).
- ➢ Need to comply with standards for electronics and software in the medical environment (radiation, electrical safety, data security).
- ➢ Need for robustness, ease of use, and comfort for the patient.
- ➢ Need to develop monitoring tools for the personnel involved (training, user manual).
- ➢ Monitoring of hygienists to assess the risks of cross-contamination and disinfection needs, and adaptation of the prototype according to these needs.
- ➢ Maintenance/repair/calibration/supplies logistics must be determined to keep the prototypes in working order throughout the study.

IV. Take home messages

- Scientifically, easier for certain aspects (indoor, cycle,…) and interesting
  but less performing (due to breath composition and "lack of knowledge on biomarkers (volatilome))
  chemical analysis (individual biomarkers) ↔ **sensor array- (BreathPrint)**

- **AI**: YES BUT DO NOT NEVER NEVER FORGET THE QUALITY OF THE DATA (YOUR SENSOR SIGNAL) !
  (large volume of data)

Media like it!

« Medical Applications: The notion of risk is so important…

Given the performance of current chemical sensors, I must admit that I'm not comfortable with medical projects. ISOCS scientist community need to be careful about the message we send to medical partners who are expecting a lot from this technology" AC Romain.

Thanks for your attention

Sensing of Atmospheres and Monitoring

Project Leader
CHU Lille

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