An electronic nose in respiratory disease

Dragonieri, S.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: https://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
CHAPTER 1

Introduction
EXHALED BREATH ANALYSIS

Smelling breath to diagnose diseases dates back to the ancient medicine. Past physicians knew that several diseases alter the odour of a patient’s breath, for example diabetes, liver diseases and kidney diseases. Exhaled odour was attributed diagnostic value, but this practice has been abandoned today because of the introduction of modern diagnostic technologies.

During the 1970’s Pauling et al. detected more than 200 components in human breath by gas chromatography [1]. Nowadays it is well-known that human exhaled breath contains over 3000 volatile organic compounds (VOCs) in gas phase, which can be detected by gas chromatography and mass spectrometry (GC-MS) [1,2]. These include for example alkanes, aromatic compounds, benzene derivatives, acetone, dimethyl sulphide, phenol and many others. These VOCs are produced during all metabolic processes, as well as during disease processes in the airways or elsewhere in the body. It has been shown that VOCs analysis may potentially be used for a non-invasive marker of lung cancer [3-6] and lung inflammatory diseases such as asthma [7-8], cystic fibrosis [9] and COPD [10].

GC-MS is considered to be the gold-standard test for exhaled breath analysis, because it allows large spectrum specific identification of VOCs, aiding to find new pathophysiological pathways. However, GC-MS usage in medical applications has been limited by a list of technical needs making this approach not optimal for volatiles profiling in breath oriented to diagnostic activities. Therefore, the worldwide demand for intelligent, fast and inexpensive measurement systems for clinical diagnosis is increasing.
ELECTRONIC NOSE TECHNOLOGY

A major challenge for modern medicine is to achieve effective disease diagnoses through early detection of pathophysiological or disease conditions to allow quick corrective or curative treatments, but at the same time limiting the invasiveness and costs of diagnostic treatments. Human biology is highly complex and diagnostic devices have primarily the task of capturing (bio)markers that relate to the individual health-state and to translate those into analytically useful signals able to support a particular diagnosis and/or to suggest further more directed examinations. This requires a chain of instrumental elements (sensors, analytical algorithm) that are determining the instrument’s diagnostic performance. Hence performance indicators include: selectivity for single or multiple components, instrumental sensitivity (limits of detection and quantification), dose-response relationships and eventually positive and negative predictive values for disease.

With regard to the analysis of complex gases, technological developments during the past decades have provided chemical sensing and identification devices that are capturing signatures of VOC mixtures. These are called “electronic noses” (see Fig.1). Rather than identifying individual molecular constituents of VOC mixtures, electronic noses provide a so-called ‘smell print’ which in relation to exhaled air is referred to as ‘breath print’ (see Fig.2). Herewith electronic noses are mimicking mammalian olfactory system for smells [11].

The concept of electronic noses is very challenging to engineers involved in building better, cheaper and smaller sensor devices. A better understanding of the reception, signal transduction and odour recognition mechanisms for mammals (awarded by the Nobel Prize in 2004) [12] combined with achievements in material science, microelectronics and computer science has led to significant advances in this area. Most of the existing electronic noses are
based on chemical gas sensors, although recently innovative working principles have been exploited in the attempt to reproduce the functioning of the bio-olfactive receptors [13].

In the past years, electronic nose technology has been tested in every conceivable field dealing with odours and/or odourless volatiles and gases, in particular in food and beverage industry, environmental monitoring, military purposes and very recently for diagnosis diseases [13,14].

After the introduction of electronic noses in the biomedical setting, VOCs pattern analysis of the exhaled breath has become a feasible option, due to the ability to perform on-board, mostly real-time analysis and discrimination of “breathprints” as derived from the composite nano-sensors arrays of electronic noses. This can be obtained by pattern recognition without providing information of the individual molecular components [13,14]. Such high-throughput analysis essentially represents an ‘omics’ approach, similar to genomics, transcriptomics and metabolomics [15].

To date, electronic nose technology has been applied in several medical fields, including the detection of ear, nose and throat infections, cerebrospinal fluid leak, venous leg ulcer infections, urinary tract infections, renal dysfunction, bacterial vaginosis, transplant rejection and diabetes mellitus [14,16,17]. In respiratory medicine electronic noses have been used in the detection of asthma [7,18], COPD [18], pulmonary sarcoidosis [19], and in the detection of Mycobacterium Tuberculosis infections [20] and ventilator-associated pneumonia [21]. In addition, a number of studies with different electronic nose technologies suggest that exhaled breath profiling may be applicable in the diagnosis of lung cancer [22-26], as well as in pleural malignant mesothelioma [27,28].

The above proof studies (to which the chapters in this thesis have contributed) have shown promising results in the detection of several respiratory diseases, indicating that - if adequately validated - electronic nose technology can have the potential to become a convenient device in the doctor’s office because of its cheapness, non-invasiveness,
portability, virtually real-time analysis and ease to use (see Fig.3 and 4). Then electronic nose
technology may be used as diagnostic tool for selecting patients for additional diagnostic
procedures, as a screening tool for excluding disease in patients at risk, for patient
subphenotyping and for monitoring patients to optimize disease management.

Figure 1. One of the commercially available electronic noses
**Figure 2.** The combination of the signal from all sensors generates the so-called “breathprint”

**Figure 3.** An example of setup for exhaled breath collection
AIMS AND OUTLINE OF THIS THESIS

The present thesis was built on 5 studies aimed to test the capacity of electronic noses to discriminate well-characterized patients with airway or parenchymal diseases from controls. This can be considered as the very first step in assessing the diagnostic accuracy of electronic noses in respiratory medicine [29].

Figure 4. Exhaled breath collection
1. In chapter 2 we aimed to assess whether an electronic nose could discriminate exhaled breath of patients with asthma from healthy controls.

2. In chapter 3 we aimed to investigate whether an electronic nose could distinguish the VOCs pattern in exhaled breath between patients with lung cancer and individuals with COPD.

3. In chapter 4 we aimed to examine the ability of an electronic nose in classifying exhaled breath of patients with malignant pleural mesothelioma from healthy controls and from subjects without mesothelioma but with a similar professional asbestos exposure.

4. In chapter 5 we aimed to extend the findings from chapter 4 by using GC-MS analysis in order to identify individual molecular VOCs capable of discriminating among the three groups.

5. In chapter 6 we aimed to explore the diagnostic accuracy of electronic noses for pulmonary sarcoidosis.

6. In chapter 7 we summarize all findings and discuss the implications for further implementation.
REFERENCES


breath of patients with malignant pleural mesothelioma from controls. Lung Cancer 2012;75:326-331.
