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Clinical evaluation of the electronic nose in the diagnosis of ear, nose and throat infection: a preliminary study

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Abstract

The term electronic nose describes an electronic system that is able to mimic the human sense of smell. Electronic noses have been developed over the last 10 or more years to perform a variety of identification tasks in various industries. More recently electronic noses have attracted new interest in their application in the field of medical diagnosis. The aim of this study is to explore the use of an electronic nose to identify and classify pathogens associated with ear, nose and throat (ENT) infections. In this study 90 bacterial swab samples were collected from 90 patients with ENT infections. Some of these samples were analysed immediately with a commercial electronic nose (Cyranose C320). Similar numbers of swabs were also taken from the same site of infection and were sent for microbiology culture and sensitivity. The electronic nose diagnosis was compared with the microbiology diagnosis and it was found that the electronic nose diagnosis was correct in 88.2 per cent of the cases, which is an encouraging result.

Key words: Electronics; Medical; Smell; Otorhinolaryngologic Disease; Infection; Microbiology

Introduction

The electronic nose is an instrument that has been developed as a simplified model of the human olfactory system. Gardner and Bartlett defined an electronic nose as 'An instrument, which comprises an array of electronic chemical sensors with partial specificity and an appropriate pattern recognition system, capable of recognizing simple or complex odours'.[1]

The electronic nose system is designed for automated detection and classification of odours, vapours, and gases. It can also perform simple odour discrimination and provide measurement of odour intensity. The two main components of an electronic nose are the sensing system and the automated pattern recognition system. The sensing system can be an array of several different sensing elements (e.g. chemical sensors), or it can be a single sensing device (e.g. spectrometer), or it can be a combination of the two.[2]

In this paper we describe the use of a commercial handheld electronic nose, the Cyrano Sciences' Cyranose 320 (Figure 1). Briefly, this portable electronic instrument comprises an integrated chemical sensor array, followed by a pattern recognition sub-system that acts as a signal processing system. The instrument settings, defined methods and raw data can be swapped, stored and further processed on a Windows-based PC using PC nose software (current release 6.5). The system consists of 32 individual carbon black polymer composite resistive sensors configured into an array. When the sensors are exposed to vapours or aromas they swell, reducing conductance between the carbon sensors. This in turn increases the total resistance of the film, which is monitored as the sensor signal. The responses from all sensors in the array form a response pattern or 'smell-print'. The sensor technology yields a distinct response signature for each vapour regardless of its complexity and produces a 'smell-print' specific to a stimulus. This overall response can be visualized in a 2D or 3D representation using principal components analysis (PCA).[3]

Materials and methods

Patients involved in this study were recruited from the department of Otorhinolaryngology/Head and Neck surgery at the Birmingham Heartlands and Solihull NHS Trust. Clinically indicated bacteriological swabs were taken from 90 patients suffering from ear, nose and throat (ENT) infections.

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FIG. 1
Photograph of the commercial handheld electronic nose (Cyranose 320, Cyrano Sciences Inc.)

Specimen collection

For the first 34 patients, three swabs were collected from the infected area of each patient: swab A was sent in the culture medium for microbiological culture; swab B was kept in the culture medium for 60 minutes (wet swab); swab C was kept in the culture medium for 24 hours (wet swab).

Swabs B and C were then removed from the culture media and each one was kept in a closed clinical vial for five minutes before analysis by the electronic nose. This five minutes' period allowed the bacteria present to produce sufficient volatile aromatic compounds in the vial for the electronic nose to measure and hence useful data to be recorded.

The closed vial, containing the swab, was analysed five times by the electronic nose to obtain five readings from each swab. Thus 10 readings were collected from every patient (five from swab B and five from swab C). The total number of readings recorded by the electronic nose from this group of patients was 340 (170 from swab B and 170 from swab C).

It was felt that this method of swab sample collection was too complicated and time consuming for the practical medical application of electronic nose technology in the future. Thus in the next 56 patients, dry swab samples as well as wet swab samples were collected.

In this group of patients, three swabs were also collected from each patient. Swab A and Swab B

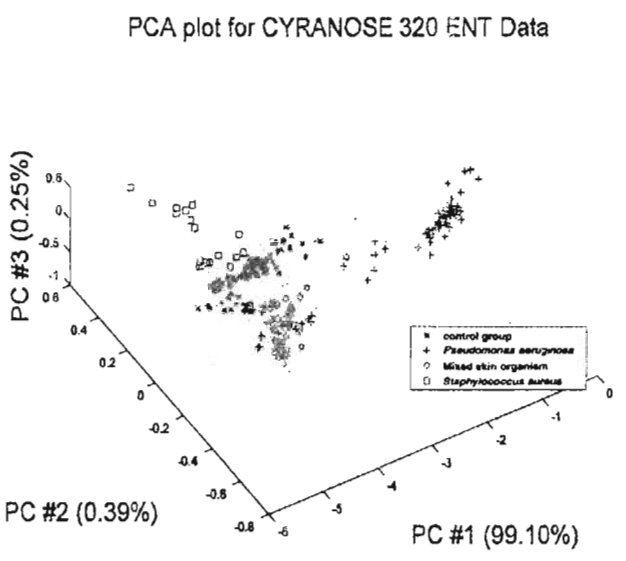

FIG. 2
Wet data 3-D plot with bacteria type assignment.

were processed as above. Swab C (dry swab) was not kept in any culture medium and was tested instantly by the electronic nose after being kept dry in the clinical vial for five minutes. The total number of readings recorded by the electronic nose from this group of patients was 560 (280 from swab B and 280 from swab C).

The total number of readings collected by the electronic nose from both groups was 900, of which 280 were collected from dry swabs.

Another group of bacterial swabs (control group) were collected from 10 medical staff who were supposed to be clinically free from bacterial infection (six nasal swabs and four ear swabs). Only two swab samples were taken from each person and they were processed as swab B and swab C in the above group of patients (i.e. the wet swab left in culture medium for 60 minutes and dry swab). The data obtained by electronic nose from those swabs were used for cross validation against data obtained from real patients (Figures 2 and 3).

Results

Forty-seven patients were clinically diagnosed with otitis externa, 31 patients with chronic suppurative otitis media and 12 patients with nasal vestibulitis. Six different types of organisms were identified by microbiological culture. They were: *Staphylococcus aureus* (43 patients), *Pseudomonas aeruginosa* (14 patients), mixed skin organisms (20 patients), *Aspergillus niger* (two patients), mixed anaerobes (one patient) and *Streptococcus pneumoniae* (one patient). There were nine cases with no bacterial growth recorded.

Data analysis

The data-set was analysed by the University of Warwick based on the principles of engineering, mathematics and statistics using data pre-

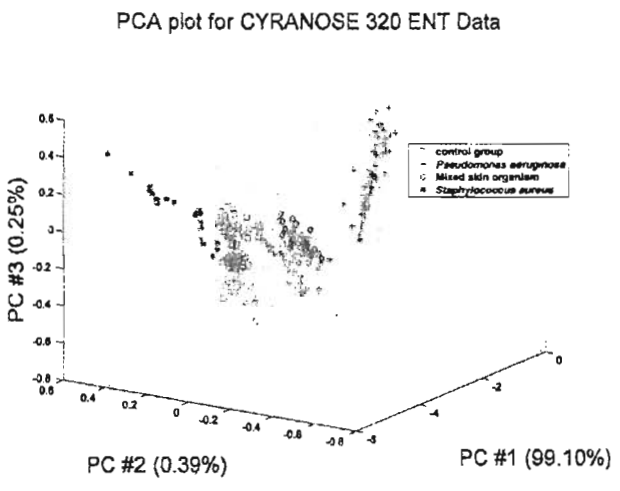

FIG. 3
Dry data 3D plot with bacteria type assignment.

processing techniques. Commercial software (*Matlab.6*) was used for data analysis. Some analysis was also performed using commercial software provided by Cyrano Sciences called *ENSoft320*®.

Data from the 32-element sensor array was subjected to PCA to explore the nature of the responses and possibility of linear vector decomposition; the high dimension data may then be presented by either a 2-D or 3-D principal component plot. The distinct location of each sample or group of samples in the plot suggests a distinguishable response signature for each sample. Figures 2 and 3 show 3-D plots of the wet and dry samples with the type of bacteria present assigned using the microbiological results. It can be seen from these figures that different types of organisms give different, but specific, patterns of response and lie in distinct locations in the plots.

The *ENSoft320* algorithm was used to analyze the wet and dry data separately and was able to correctly classify 88.2 per cent of the bacteria in the wet samples and 70.8 per cent of the bacteria in the dry samples. These results were achieved after assigning the bacteria type to the data with the aid of the microbiological results. This analysis showed the ability of the electronic nose to detect the presence of bacteria in a given sample and also the ability of this technology to discriminate between different organisms.

Discussion

The sense of smell is a subjective diagnostic tool for physicians and it has been supplanted in the modern age by more objective laboratory tests. Efforts to produce a biological olfactory system artificially in order to distinguish volatilized molecules have been relatively primitive until the last 10 years. Recent developments in polymer chemistry have led to the development of new, inexpensive conducting polymer-based resistive sensors.[4] Since then, electronic nose technology has been applied in various industries such as food quality and control, cosmetics, environmental monitoring and military applications. More recently, research has been directed towards health and medical diagnosis.[5]

An obvious application of the electronic nose technology to medicine is to identify the presence or absence of micro-organisms and also to help to classify them. The first attempt to identify micro-organisms with the electronic nose was made by Craven *et al.*[6] in 1994. The ability of the electronic nose to assist in the diagnostic questions encountered in the field of medicine has been shown in a few studies.

Parry *et al.*[7] used the electronic nose to distinguish between infected and non-infected leg ulcers. Beta-haemolytic streptococci were identified in bacteriological cultures from 14 of 24 chronic venous leg ulcers in 21 patients. Multi-element odour detection (MEOD) analysis demonstrated a significant difference in odour in those ulcers from which beta-haemolytic streptococci were isolated ($p < 0.01$). They stated that this new technology has the potential to detect pathogenic organisms instantaneously in the clinical setting.

Pavlou *et al.*[8] used an electronic nose system with 14 conducting polymer sensors to differentiate between anaerobic bacteria grown in vitro on agar media. The cultures of *Clostridium* sp. and *Bacteroides fragilis* were grown on blood agar plates and incubated in sampling bags for 30 minutes before head space analysis of the volatiles. PCA, genetic algorithms and artificial neural networks were used to analyse the data and it was possible to differentiate between agar blanks and individual bacterial species. Their results suggested the potential value of application of electronic nose technology in early diagnosis of microbial pathogens.

Few applications of the electronic noses technology have been used in the field of otolaryngology. Boilot *et al.*[9] used the Cyranose 320 to identify bacteria commonly associated with eye and ear, nose, and throat (ENT) diseases. Pure laboratory cultures were used and the electronic nose was used to sample the headspace of sterile glass vials containing a fixed volume of bacteria in suspension. They reported the correct classifications of 97.3 per cent of unknown eye bacteria and 97.6 per cent of unknown ENT bacteria.

Thaler *et al.*[10] investigated the ability of an electronic nose to distinguish cerebrospinal fluid (CSF) from serum. The electronic nose was able to distinguish CSF from serum in 18 of 19 patients. The data points for 18 of 19 CSF and 18 of 19 serum samples were within statistically distinct cluster groups, suggesting that the device is able to identify an unknown sample as CSF or serum.

In this study an electronic unit has been taken to the point-of-care (POC) and hence applied in a practical situation, as swabs were taken from patients with bacterial infection during their consultation in the clinic – this is believed to be

the first example of a POC application of an electronic nose. Specifically, a different swab collection strategy was used; initially wet swabs were collected that were tested by the electronic nose after leaving them in culture media for 60 minutes and 24 hours. In the next set of experiments, dry samples as well as wet samples were collected.

- **The term electronic nose describes an electronic system capable of mimicking the human sense of smell**
- **The aim of the study is to explore the use of the electronic nose to identify the pathogens associated with ear, nose and throat infections**
- **Bacterial swab samples were taken from 90 patients with ENT infections. They were analysed by the electronic nose and also sent for microbiology culture and sensitivity**
- **The electronic nose diagnosis was compared with the microbiology diagnosis and was found to be correct in 88.2 per cent of cases**

It should be emphasized here that this system is not being proposed as a replacement for a clinician's diagnosis but rather to supplement other diagnostic methods. It also helps the clinician deliver better service as the electronic nose system has the potential advantage of making decisions 24 hours per day, seven days per week. It should also be emphasized that the diagnostic results obtained by the electronic nose system are best regarded as complementing microbiology results rather than competing with them.

An 88.2 per cent successful classification rate was observed for the wet swabs and a 70.8 per cent classification rate for the dry swabs. Although the data-set was not large, it was possible to obtain very consistent classification for the different bacteria clusters. This study suggests that the electronic nose is able to identify specific bacterial pathogens with accuracy and speed, even with a small sample quantity, at the point-of-care. However further trials are needed to evaluate the performance of the electronic nose over a longer period of time.

The diagnostic results obtained in this study and other studies suggest that a suitably trained electronic nose system should be able to achieve in excess of around 90 per cent accuracy. Given appropriate training the electronic nose results should be very reproducible.

Conclusion

Electronic nose technology has advanced rapidly with the advent of organic semiconductor arrays. This powerful technology is only beginning to be introduced in the field of medicine, but is promising in its potential to assist in medical diagnosis. In this preliminary study the ability of the electronic nose to detect and distinguish between different types of micro-organisms causing ear, nose and throat infection has been demonstrated. Electronic nose technology is a non-invasive, rapid and relatively inexpensive new diagnostic tool and the authors believe that it has enormous potential for clinical screening in the field of otolaryngology and in medicine as a whole.

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