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Analysis of breath samples for lung cancer survival

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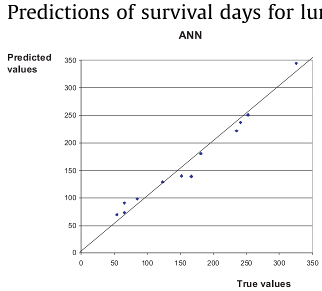
HIGHLIGHTS

- Analyses of exhaled air offer a large diagnostic potential.
- Patientswith diagnosed lung cancer were studied using an electronic nose.
- Excellent predictions and stable models of survival day were obtained.
- Consecutive measurements were very important.

GRAPHICAL ABSTRACT

Predictions of survival days for lung cancer patients.



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ABSTRACT

Analyses of exhaled air by means of electronic noses offer a large diagnostic potential. Such analyses are non-invasive; samples can also be easily obtained from severely ill patients and repeated within short intervals. Lung cancer is the most deadly malignant tumor worldwide, and monitoring of lung cancer progression is of great importance and may help to decide best therapy. In this report, twenty-two patients with diagnosed lung cancer and ten healthy volunteers were studied using breath samples collected several times at certain intervals and analysed by an electronic nose. The samples were divided into three sub-groups; group d for survivor less than one year, group s for survivor more than a year and group h for the healthy volunteers. Prediction models based on partial least square and artificial neural nets could not classify the collected groups d, s and h, but separated well group d from group h. Using artificial neural net, group d could be separated from group s. Excellent predictions and stable models of survival day for group d were obtained, both based on partial least square and artificial neural nets, with correlation coefficients 0.981 and 0.985, respectively. Finally, the importance of consecutive measurements was shown.

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1. Introduction

In the past, the scent of exhaled air has been used to diagnose diseases, such as diabetes or liver disease. Presently, a large diagnostic potential is associated for the analyses of exhaled air by means of electronic nose (EN). Such analyses are non-invasive; samples can also be easily obtained from severely ill patients and repeated within short intervals. The analyses may give information concerning various metabolic pathways and disorders.

There is a complex mixture of a number of volatile organic compounds (VOC) in exhaled air, arising from volatile constituents in the blood. This was first reported by Pauling et al. [1], who

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combined gas chromatography with mass spectroscopy (GC–MS). Since then, many studies have been performed to associate specific VOCs with certain diseases, such as mercaptanes and alkanes with liver disturbances [2] and various amines with uremic diseases [3]. GC–MS identified alkanes, alkane derivates and benzene derivates in exhaled air from lung cancer patients [4] and combinations of multiple VOCs discriminated patients with lung cancer from non-cancer patients [5]. The use of GC–MS for the detection of biomarkers is, however, of limited use in clinical practice, due to its complexity of handling and the very huge and complex data obtained. The emerging technology of the electronic noses in the 80s offered an alternative approach. They were originally described as a synthetic olfaction [6], since they operated in a similar way as the olfactory sense. Thus, an electronic nose consists of a gas sensor array with partially overlapping selectivities, a data collecting unit and signal processing routines for pattern recognition. When the gas sensor array interacts with the VOC in a breath sample, a characteristic fingerprint will be generated which can be recognized with previously recorded fingerprints using pattern recognition routines. Electronic noses have gained a considerable interest since their first appearance, and have found many applications in fields and recently in the medical area also [7–9]. Thus, bacteria were identified [10] and the number of applications has grown considerably, including many diagnostic fields [11], most of them concern lung diseases, such as lung cancer [5] and asthma [12].

Lung cancer is the most deadly malignant tumor worldwide with an overall 5-year survival below 15%. If diagnosed and treated at an early stage the 5-year survival increases considerably to approximately 50%. A number of new and more efficacious anti-cancer treatments have been introduced during the last five years. High costs and unpredictable efficacy of these drugs, necessitates access to a method for monitoring, prediction of outcome and/or drug tailoring. Monitoring of lung cancer progression by means of analyses of biomarkers or reliable scoring of well being is presently lacking, and it is therefore obvious that cheap and simple methods are needed for this purpose.

To enable monitoring progress of the disease, it appears clear that several measurements must be done at certain time intervals. Furthermore, measurements before and after treatment may be done to document effects of a certain treatment. Follow-up studies by means of GC–MS [13] and nanomaterial based sensor array after lung cancer surgery have been done [14], but mostly cross sectional studies have been made by means of the e-nose technique [4]. Although repeated measurements by means of a seven sensor e-nose was done in subjects with chronic obstructive pulmonary disease to study reproducibility [15], true longitudinal studies to establish the utility of ENs for monitoring disease progression and pharmacological response have, however, not been published. The findings of Poli et al. [13] in a three years follow up study of GC–MS results showed that surgery of lung cancer influenced concentrations of some exhaled VOCs, suggesting that measurements of exhaled VOCs could be useful in monitoring the disease.

Although some biomarkers and certain gene signatures have been claimed to serve as prognostic and predictive tools, the gain in overall survival has not been shown [16]. Prospective studies on the efficacy of EN in prediction of outcome have not been reported previously either and we therefore performed a pilot study with the aim of questioning whether signals from EN might predict outcome of disease in patients with end stage lung cancer during palliative chemotherapy.

It is described in this paper how an electronic nose was used to "predict" survival of a group of patients suffering from lung cancer, by analysis of a series of samples of exhaled breath collected at specific time intervals before and after chemotherapy. The prediction model obtained can then be able to predict expected survival for new patients, giving a measure of the severity of their diseases. It is also expected that effects of treatment may be indicated. As more new information obtained from new patients will be added to the prediction model, it will become more and more accurate by time.

2. Materials and methods

2.1. Multivariate data analysis (MVDA)

In many analytical fields, there is an increasing use of MVDA to investigate and get an overview of large amount of data, and this is a key technique when evaluating sensor fingerprints from the sensor array in the electronic nose. Two basic principles are used, one is to find structure and correlations between samples, the other is to make a prediction model from calibration sets, and use this to predict the real data. For the first principle, principal component analysis (PCA) is most often used [17], and for the second, there are many alternative methods of which partial least square, also called projection to latent structure (PLS) [18] and artificial neural nets (ANNs) [19] are often used. ANNs consist of an input layer, one or more hidden layers and an output layers. The layers are connected with each other with logarithmic transfer functions, and by training, the method of backpropagation of errors is often used. When dealing with non-linear data, ANNs often give better predictions compared with linear methods such as PLS. Since ANNs are vulnerable to larger amount of input variables, the most important variables given from regression coefficients in the PLS modelling can be chosen.

There are various ways to determine the validity of a prediction model. The correlation coefficient is often used as well as the root mean square error of prediction (RMSEP). In many practical applications, the RPV (relative predicted deviation) value is used. This is defined as the standard deviation of the whole dataset divided by the standard error of prediction. For a useful model, this value should be 2 or higher.

The software SIRIUS 6.5 (Pattern Recognition Software, PRS, Bergen, Norway) was used for PLS analysis, and the software Brainmaker (California Scientific Software, USA) for ANN analysis.

2.2. The electronic nose (EN)

The EN was obtained from Applied Sensor AB (Linköping, Sweden) model 2010, which is normally used for sequential analysis using a sample carousel and an injector needle. The EN was modified by disconnecting the carousel and attaching a sample collecting tubing to the injector needle. Alumina bags containing breath samples were placed in a specially designed sample holder and attached to the sample collecting tubing. This tubing was thermostated to 55 °C and the sample holder was thermostated to 40 °C to avoid water condensation.

The sensor array in the EN consisted of 10 metal–oxide–semiconductor field effect transistors (MOSFET) and 12 metal oxide semiconductor (MOS) sensors.

These two sensor types represent two different sensing classes. MOS sensors are more sensitive for stable alkanes compared to MOSFET sensors, while the latter ones are more sensitive for nucleophilic compounds (e.g. ammoniac, amines). Each of the 22 sensors in the array has its own individual sensing profile, and by using a multivariate approach, each component of the mixture of the VOC can be identified.

2.3. The sample bags

In contrast to commercially available bags, which may be permeable to various gases and may contain emissions from glue or plastics, our sample bags are impermeable to gas diffusion (even for hydrogen gas) and do not emit VOCs. Thick alumina foil (thickness

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