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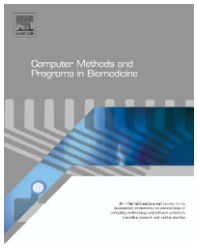

Classifying algorithms for SIFT-MS technology and medical diagnosis☆,☆☆

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ABSTRACT

Selected Ion Flow Tube-Mass Spectrometry (SIFT-MS) is an analytical technique for real-time quantification of trace gases in air or breath samples. SIFT-MS system thus offers unique potential for early, rapid detection of disease states. Identification of volatile organic compound (VOC) masses that contribute strongly towards a successful classification clearly highlights potential new biomarkers. A method utilising kernel density estimates is thus presented for classifying unknown samples. It is validated in a simple known case and a clinical setting before–after dialysis. The simple case with nitrogen in Tedlar bags returned a 100% success rate, as expected. The clinical proof-of-concept with seven tests on one patient had an ROC curve area of 0.89. These results validate the method presented and illustrate the emerging clinical potential of this technology.

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1. Introduction

Selected Ion Flow Tube-Mass Spectrometry (SIFT-MS) is a relatively new analytical technique for the real-time quantification of volatile organic compounds (VOCs) [1,2]. It relies on chemical ionisation of trace gas molecules in air or breath samples introduced into a helium carrier using H_3O^+, NO^+ and/or O_2^+ precursor ions. Hence, the identity of a contaminant can be found by comparison of the mass of the product ions with an existing database. The sensitivity of the instrument is currently around five parts per billion in real-time.

The SIFT-MS system can offer unique capability in the early and rapid detection of a wide variety of diseases, infectious bacteria and patient conditions. This outcome can be achieved by creating disease and normal mass scan datasets using SIFT-MS, and developing classification methods to identify an unknown patient as normal or diseased. By identifying

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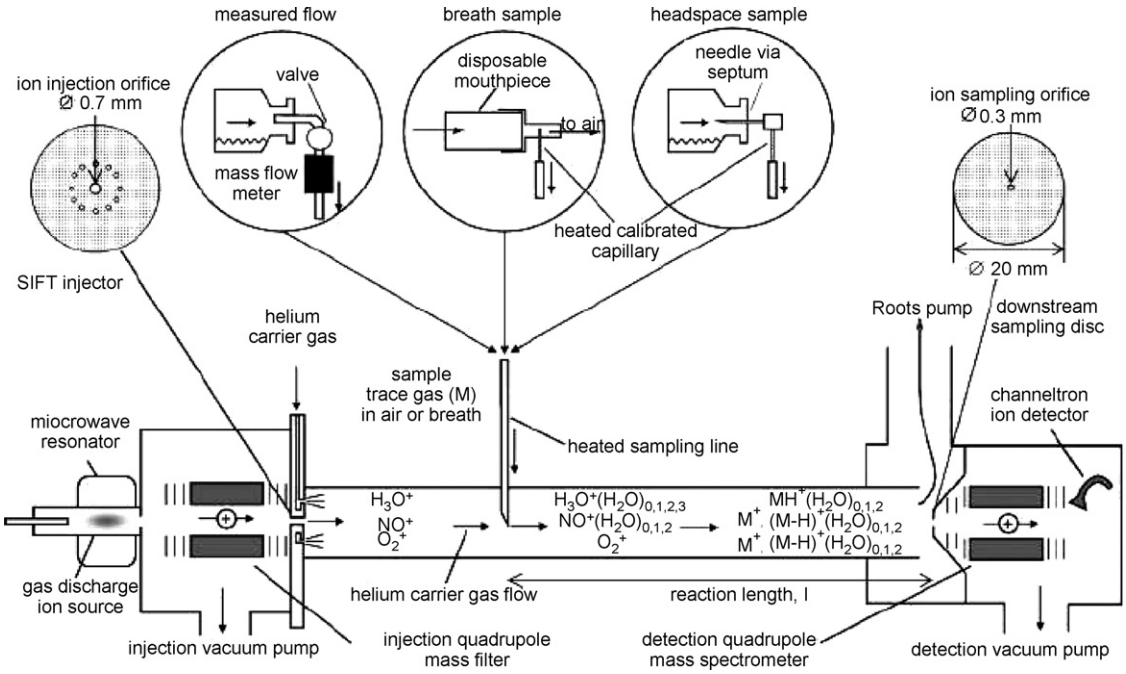

Fig. 1 – SIFT-MS [3].

which masses (and therefore, VOCs) contribute most strongly towards a successful classification, biomarkers for a particular disease state can be discovered.

SIFT-MS is a quantitative mass spectrometric method that exploits the chemical ionisation of positively charged precursor ions that react with the VOCs in an air or breath sample. H_3O^+, NO^+ and O_2^+ precursor ions are typically used, since they do not react with the main compounds found in air or breath (N_2, O_2, CO_2 and Ar). The process steps are summarised below, and illustrated in Fig. 1.

1. Precursor ions are generated by passing water through a microwave discharge.
2. A quadrupole mass filter is used to select the required precursor ion based on its mass/charge ratio.
3. The precursor ion is injected into a fast-flowing inert carrier gas (helium), which carries the precursor ion, and drawn in test sample, along the flow tube.
4. The precursor ion reacts with the VOCs from the sample to form product ions.
5. A representative proportion of the product ions then pass through a small orifice at the downstream end of the flow tube, and into a differentially pumped quadrupole mass spectrometer that filters ions according to mass.
6. The selected product ions pass to the channeltron particle multiplier/detector where they are counted.

SIFT-MS can be used in a variety of applications, ranging from environmental and agriculture sciences, such as analysing exhaust gases, polluted town air and soil emissions, to food safety and medical science, such as smoking, cancer, and infectious diseases.

This paper presents new classification methods and tests for the classification of sets of mass scan data. This process is broken into four steps:

1. Pre-processing to remove noise from the raw mass scan data.
2. Creating probability distributions for each of the two test classification groups.
3. Obtaining a classification and a reliability measure for that classification.
4. Identifying useful biomarkers.

Two cases are presented. The first case is a simple direct validation study that aims to differentiate 'dry' nitrogen samples from 'wet' nitrogen samples. The second case study uses the classification model in a clinical setting to determine the differences between dialysis patients before and after treatment, thus examining kidney function, which has direct application in critical care and drug dosing. The classification model is also able to determine which masses are most useful in this classification, and therefore, those compounds that act as biomarkers for kidney function.

2. Methodology

The study methodology is divided into three sections:

1. Experimental design for the validation study and dialysis case study.
2. Pre-processing of mass scan raw data.
3. Statistical analysis, including classification, prediction error estimation, reliability, and sensitivity/specificity analysis.

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