This article has been accepted for publication in a future issue of this journal, but has not been fully edited. Content may change prior to final publication. Citation information: DOI 10.1109/TBME.2015.2409092, IEEE Transactions on Biomedical Engineering

Sex and Smoking Status Effects on the Early Detection of Early Lung Cancer in High-Risk Smokers using an Electronic Nose

Annette McWilliams*, Parmida Beigi*, Akhila Srinidhi, Stephen Lam, and Calum E. MacAulay

***Abstract*— Objective: Volatile Organic Compounds (VOC) in exhaled breath as measured by electronic nose (e-nose) have utility as biomarkers to detect subjects at ris of having lung cancer in a screening setting. We hypothesize that breath analysis using an e-nose chemo-resistive sensor array could be used as a screening tool to discriminate patients diagnosed with lung cancer from high-risk smokers.**

Methods: Breath samples from 191 subjects – 25 lung cancer patients and 166 high-risk smoker control subjects without cancer – were analyzed. For clinical relevancy, subjects in both groups were matched for age, sex, and smoking histories. Classification and Regression Trees and Discriminant Functions classifiers were used to recognize VOC patterns in e-nose data. Cross-validated results were used to assess classification accuracy. Repeatability and reproducibility of e-nose data were assessed by measuring subject-exhaled breath in parallel across two e-nose devices.

Results: E-nose measurements could distinguish lung cancer patients from high-risk control subjects, with a better than 80% classification accuracy. Subject sex and smoking status impacted classification as area under the curve results (ex-smoker males 0.846, ex-smoker female 0.816, current smoker male 0.745 and current smoker female 0.725) demonstrated. Two e-nose systems could be calibrated to give equivalent readings across subject-exhaled breath measured in parallel.

Conclusions: E-nose technology may have significant utility as a non-invasive screening tool for detecting individuals at increased risk for lung cancer.

Significance: The results presented further the case that VOC patterns could have real clinical utility to screen for lung cancer in the important growing ex-smoker population.

***Index Terms*—Breath analysis, electronic nose, sensor array, Volatile Organic Compounds, lung cancer, pattern recognition.**

This paper was submitted for review on 9 June 2014. This work was supported by Funding for this work was provided by the Canadian Cancer Society (grant #19246) and the Canadian Cancer Society – Ontario Division (grant #19805). *These authors contributed equally to this work. P. Beigi is with the Electrical and Computer Engineering department, University of British Columbia during completion of this work; Vancouver, BC, Canada, e-mail: parmidab@ece.ubc.ca. Dr. A. McWilliams is with the Department of Respiratory Medicine, Sir Charles Gairdner Hospital, Nedlands, Perth, Western Australia, Australia, email: annette.mcwilliams@health.wa.gov.au. A. Srinidhi is with Point Grey Research, Vancouver, BC, Canada, email: akhila.srinidhi@gmail.com. Drs. S. Lam and C. MacAulay are affiliated with the Department of Integrative Oncology, BC Cancer Research Centre, Vancouver, BC, Canada, e-mail: slam2@bccancer.bc.ca; cmacaula@bccrc.ca.

I. INTRODUCTION

LUNG cancer is the leading cause of cancer death worldwide, with the number of deaths attributable to lung malignancy increasing steadily for years [1]. Lung cancer is usually diagnosed in its later stages and as a result its 5-year survival rates are very poor. Earlier clinical identification and management of disease would greatly increase survival rates [2]. Computed tomography (CT) is one of the most commonly used imaging methods to diagnose lung cancer. The recently published NLST study has shown that low dose CT (LDCT) reduces mortality from lung cancer when used for early detection. CT, however, is relatively expensive, involves radiation and is associated with false positive results that necessitate further CT follow-up or invasive diagnostic procedures [3, 4]. There is an identified need for inexpensive, reliable, and non-invasive methods capable of identifying individuals at risk of harboring lung cancer. This type of targeted approach will improve the efficacy of an early lung cancer detection program utilizing LDCT.

It has long been known that human breath provides useful information on health conditions [2, 5]. Respiratory diseases such as asthma, chronic obstructive pulmonary disease (COPD) and cystic fibrosis may be identified from the breath odor [6]. This is due to the existing equilibrium between compounds in the alveolar air and pulmonary blood once gas exchange has occurred in the lungs [7]. Recently, exhaled breath analysis has been introduced as a possible diagnostic tool to identify the presence of diseases such as lung cancer [8-12].

Exhaled breath contains mixtures of many volatile organic compounds (VOCs) as identified by gas chromatography (GC) and mass spectrometry (MS) [13-16]. It is known that several diseases and altered metabolism may cause unique VOC signatures [17-19]. Many studies have sought useful chemical mixtures in breath that characterize lung cancer: many VOCs quantified by GC-MS have been identified in exhaled breath samples, combinations of which can characterize lung malignancies [20-25]. However, GC-MS methods are complex, expensive, time-consuming, require expert analysis, and do not produce real-time results – all of which limit the utility of this approach in clinical practice [21, 26]. A non-invasive tool to monitor the olfactory signal and to recognize VOC patterns is electronic nose technology [27, 28].

This article has been accepted for publication in a future issue of this journal, but has not been fully edited. Content may change prior to final publication. Citation information: DOI 10.1109/TBME.2015.2409092, IEEE Transactions on Biomedical Engineering

An electronic nose (e-nose) is a VOC recognition device consisting of an array of sensors (chemo-resistive, acoustic, pyroelectric, optical, etc.) with partially overlapping sensitivities that can produce digital "smell-prints" of specific VOCs. The chemo-resistive sensors used in this work can be highly sensitive to specific VOCs in human breath; they detect effects of VOCs through a chemical reaction and accordingly generate an electrical impulse. These sensors may be electrodes coated with reactive compounds. Once these sensors are exposed to exhaled breath – depending on the existing chemical constituents – the sensors' electrical conductance characteristics change, causing a measurable resistance change. Data obtained from a sensor array is then analyzed using pattern recognition techniques to obtain a unique response pattern corresponding to a specific odor. The e-nose is capable of non-invasive measurement of breath samples as well as real-time analysis of breath chemicals – both of which make it attractive for wide application as a screening technology.

The Cyranose 320 (Smiths Detection Inc.), which was used for this work, is one type of portable e-nose system consisting of 32 polymer composite sensors. Once a gas mixture passes across the sensor array, its chemical components induce reversible changes in the electrical resistance of the sensors. Sensors are made cross-responsive, so that the detection of a particular VOC is based on a 32-dimensional response pattern of the array rather than a single sensor. According to the chemical diversity of the array material, resistance changes in the 32 sensors results in a unique pattern of electrical resistance differences ("smell-prints"). During the measurement process the Cyranose 320 records its operational state (measuring subject air, measuring control air, purging sample chamber, etc.) in addition to the outputs of the 32 sensors. The operational state is recorded as a flag status variable.

Here, we hypothesize that breath profiling by e-nose is capable of differentiating patients with early stage, potentially curable lung cancer from matched high-risk control subjects without lung cancer. Several recent studies have been conducted on e-nose applications for detection of lung cancer [8-11]. Tran et al. [11] employed an e-nose system consisting of an array of 6-channel coated chip sensors to discriminate lung cancer patients from control subjects consisting of smokers, non-smokers, and patients with respiratory disorders. Their results included response curves from each channel for parameters such as rate to peak height, peak height, rate to recovery, and area under the curve, with significant differences observed between test groups. Machado et al. [9] also applied the Cyranose 320. They showed 71.4% sensitivity and 91.9% specificity for the identification of lung cancer patients, though their comparison groups were not well matched as the control group consisted of patients with several types of pulmonary diseases. Dragonieri et al. [8] used the same e-nose system for the discrimination of non-small cell lung cancer, COPD patients, and non-smoker healthy controls. They reported 85% classification accuracy for distinguishing lung cancer patients from COPD patients and, analyzing two sets of measurements (to confirm reproducibility), an average of 85% for the identification of lung cancer patients from healthy controls, Mazzone et al. [10] used colorimetric sensor array technology to discriminate lung cancer patients from controls, with 73.3% sensitivity and 72.4% specificity. The authors also mentioned that if experiments focused on one histological disease subtype only – e.g. lung squamous cell carcinoma – then model accuracy would be improved. This led them to conclude that patients with various lung cancer histologies could be distinguished accurately. Cheng et. al. [29] also investigated the use of Cyranose 320 to distinguish the exhaled breath of smokers and non-smokers and reported a classification accuracy of 95%.

Although studies have assessed e-nose potential for distinguishing lung cancer patients from controls, a well-matched control group has generally not been used to facilitate comparisons and many of the included lung cancers were of more advanced stage [8-11]. To address these issues, we included stringent demographically-matched sets in both control and lung cancer groups – and only included patients with clinical Stage I/II lung cancer. Also, to account for potential confounding effects due to smoking, we recruited current or former smoking subjects only (i.e. excluding never smokers). A key novelty of this study then is the comparison of a well-matched set of high risk current/former smokers to lung cancer patients with the same demographic risk indicators: age, sex, similar number of pack-years of smoking history, and smoking status. The aims of this study were 1) to test the proposed hypothesis on well-matched patient groups and validate the classification model, 2) to assess the effects of sex and smoking on e-nose measurements, 3) to assess system reproducibility (in consideration of downstream clinical utility), 4) to evaluate if "time of day" impacted e-nose responses, and 5) to study if changing the equipment could introduce a systematic bias to the exhaled breath data for a more accurate analysis. This paper is organized as follows: Section II describes study methods; Section III describes experimental analyses; Section IV presents the experimental results and discussions; and Section V provides our conclusions based on our work.

II. Materials and Methods

A. Study Population and Design

We applied a combined cross-sectional case-control study design to delineate lung cancer patients from high-risk heavy smokers without detected cancer. Control subjects were individuals at risk for lung cancer who were involved in a lung cancer screening study and lung cancer patients were from local referrals, recruited from the BC Cancer Agency (BCCA) and Vancouver General Hospital (VGH). The Review of Ethics Board of the University of British Columbia approved this study. Informed consent was obtained in all participants.

A total of 206 subjects participated in this study. Data for our primary analysis were derived from 191 current/former smokers placed into two categories based on diagnosis at the time of enrollment: lung cancer patients and non-cancer

This article has been accepted for publication in a future issue of this journal, but has not been fully edited. Content may change prior to final publication. Citation information: DOI 10.1109/TBME.2015.2409092, IEEE Transactions on Biomedical Engineering

control cases. (Fifteen cases [206 – 191] were held in reserve as a test set.) Subjects ranged in age from 45-79 years, could be male or female, and were restricted to current and ex-smokers with smoking histories of ≥20 pack-years. Clinical features of this population are described in Table I (age and pack-years values are expressed in the form of mean ± SD). No statistically significant differences were observed between the "High-risk Smoker" and "Lung Cancer" groups in terms of sex, overall smoking status, and pack-year histories. A significant difference in the age of the patients was noted ($p = 0.01$, t-test), however we also note a high degree of overlap in the ages of these cohorts. There was also a statistical difference in the distribution of COPD between the control and lung cancer cases (note COPD status for 4 of the lung cancer cases were not available. No statistical differences in scores were observed i) based on age differences or ii) based on any combination of age/ sex/ smoking /COPD.status variables.

TABLE I
CLINICAL CHARACTERISTICS OF THE STUDY POPULATION

Characteristics	High-risk Smokers	Lung Cancer
Patients (n)	166	25
Age (y) ± SD	62.8 ± 6.7	66.5 ± 6.0
Sex (M|F)	86|80	12|13
Current Smokers (n)	87	9
Former Smokers (n)	79	16
Pack-years (n) ± SD	45.6 ± 17.8	47.5 ± 20.6
COPD Status (Y|N)	68 | 97	17 | 4
High blood pressure	50	7
High Cholesterol	45	4
Congestive Heart Failure	0	1
Transient Ischemic Attack	4	2
Asthma	21	4
Bronchitis	39	7
Pneumonia	42	6
Diabetic	9	2

The "High-risk Smokers" category contained 166 control subjects with high risk for lung cancer. These patients were recruited as part of a LDCT-based early lung cancer detection program at the BCCA. They showed no evidence of lung cancer on baseline CT or CT scan surveillance (mean follow-up time was 15.2 months). The second group contained 25 patients with a histologically-confirmed diagnosis of lung cancer. Table II shows the clinical characteristics of patients diagnosed with lung cancer with respect to their lung cancer histological subtypes. The distribution of co-morbidities for these cancer patients and controls are shown in Table 1. There were no statistically significant differences in the co-morbidities between the controls and the cancer patients. Four of the lung cancer patients had previous cancers (lung, cervical, colon and breast). All cancer diagnoses were confirmed with cytology, biopsy, or surgical resection and the reported staging is post-surgery for all but 3 patients and all but one patient had a PET scans to further inform their staging. One patient had concurrent breast cancer for which they had started chemotherapy otherwise all patients were sampled prior to treatment.

TABLE II
COMPOSITION OF LUNG CANCER PATIENTS

Cancer Type	Number	Mean tumor diameter	Sex (M|F)
Small Cell Lung Carcinoma	1	20.0 mm	1|0
Non-Small Cell Lung Carcinoma	2	6.4 mm	0|2
Adenocarcinoma	20	20.0 mm	11|9
Squamous Cell Carcinoma	2	28 mm	2|0

For all the different classification training methodologies used in this study we divided these 191 subjects into at least two independent groups: a learning set and a test set. The classifier we sought to define would distinguish lung cancer patients from high-risk smokers based on a predictive relationship. The predictive relationship was defined by non-blind analysis of a defined learning set. After the model was constructed, blind analysis was performed on the test set to validate the predicted model. A addition data set consisted of measurements from 15 healthy non-smokers subjects. Data from these cases were used to assess inter-system reproducibility and exhaled VOC sensitivity to subject fasting.

B. Exhaled Breath Collection

The breath collect for all cases were acquired in the same clinical setting at the BCCA. Subjects breathed humidified medical air. Exhaled breath was collected in Mylar gas-sampling bags (Fig. 1). Briefly, patients first inhaled and exhaled medical air for alveolar washout. Three deep (vital capacity) breaths were taken, with exhaled air vented to the room. System valves were next turned and all the exhaled air was collected in sampling bags (with entire breath samples collected, not just an alveolar fraction). Three to five exhaled breaths filled collection bags sufficiently. The breathing circuit was closed and had no exposure to ambient air. Collected exhaled breath was sampled by the e-nose five times ($l = 1..5$), with this process interspersed with bursts of humidified medical air to flush the circuit. Humidified air was tested as the baseline against which VOCs from each patient were measured. The pattern of sensor responses to the VOCs present was recorded during the five repeat measurements.

C. Data Processing and Statistical Analysis

The typical raw signal obtained from an e-nose sensor as well as the flag variables is shown in Fig. 2. Data is color coded by the flag variable status, which determines the stage of the experiment, at the time of the measurement. The raw signal required correction for baseline drift. Baseline data points (time points when the flag variable had values 1 and 7 and the system was full of humidified medical air) were fitted using a 5^{th} order polynomial, which was then used to predict the baseline during data measurements (time points when flag variable was 3), which were subtracted from the raw signal. After this, each of the five baseline corrected e-nose data measurements was fitted by a double exponential curve to extract the rise time and amplitude of each sensor response to each of the five samplings of exhaled breath.

This article has been accepted for publication in a future issue of this journal, but has not been fully edited. Content may change prior to final publication. Citation information: DOI 10.1109/TBME.2015.2409092, IEEE Transactions on Biomedical Engineering

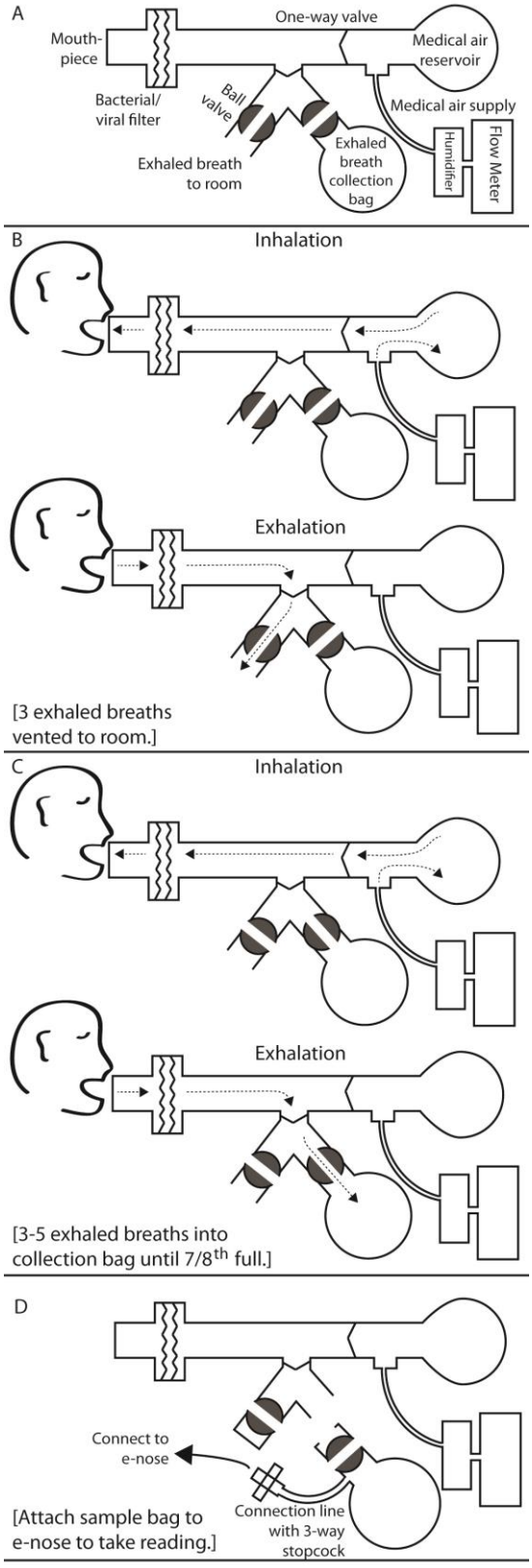


Fig. 1. Schematic of system framework and sample collection.

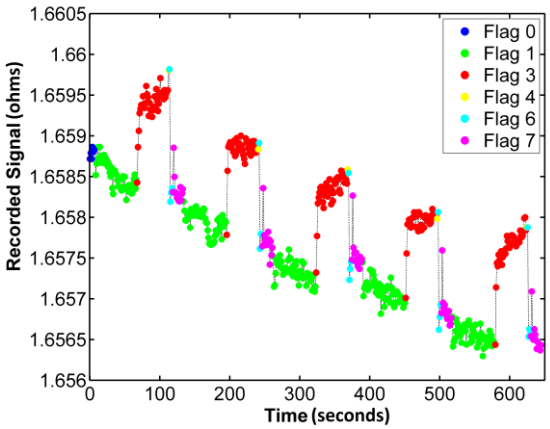


Fig. 2. Typical raw sensor response, with highlighted flags.

Finally, the value predicted by the double exponential at the midpoint of the measuring process was recorded for each of the five samplings. Fig. 3 shows an example of a sensor's fully processed and fit data. All 32 sensor e-nose array responses (S_1,…, S_{32}) were processed this way. After this correction there was no statistically significant difference between any of the five measurements and for the majority of analysis (unless specifically stated otherwise) we averaged over the five measurements to determine the most representative sensor response for the breath analysis. Our analysis differs from previous works [8-11] in that we used resistance changes in combinations of two sensors rather than as individual sensors, as no correlation with exhaled breath from cancer patients vs. high risk controls was observed in individual sensor data.

For i = 1,…, 32:

- Baseline Drift Correction:
  1. For each measurement instance (l = 1, …, 5), find all data points with flag 1 (baseline samples) and last 10 flag 7 data points (trial end).
  2. Remove the first five baseline data points.
  3. Fit baseline data with a 5th order polynomial.
     - Let $BL_{i,\,fit}$ be the fitted polynomial.
     - Let $S_{i,\,BL\_corr}$ be the baseline corrected signal: $S_{i,\,BL\_corr} = S_i - BL_{i,\,fit}$.
- Response Extraction for each sensor:
  For l = 1, …, 5: (each of the measurement instances)
  1. Fit flag 3 data points of each measurement instance, with a double exponential function. ($T_{i,\,l\,fit}$)
  2. Set the representative measure to be the midpoint of the fit function $T_l = T_{i,\,l\,fit}(t_M)$, (where t_M is the mean of flag 3 time points for the measurement instance l.

Fig. 3. Data processing: an example of fully processed sensor data and the five sensor responses measured.

For each combination of pairs of sensor data, a regression line for only the measurements from the high-risk controls was calculated. To make the regression analysis robust to outlier data, we excluded the 5% most variable cases from the linear fitting process. For each sensor pair, the data were projected onto and along the linear regression line determined for that pair using the following process: for each sensor pair S_iS_j, we let α and $\hat{S}_i$ be defined as follows:

$$\alpha \triangleq -tan^{-1}(m), \quad (1)$$

$$\hat{S}_i \triangleq S_i - b, \quad (2)$$

This article has been accepted for publication in a future issue of this journal, but has not been fully edited. Content may change prior to final publication. Citation information: DOI 10.1109/TBME.2015.2409092, IEEE Transactions on Biomedical Engineering

where m and b are the slope and the intercept of S_iS_j regression line for the control samples onto which the data were projected. The projection of the data onto this new axis was accomplished using the following equation.

$$\begin{bmatrix} x'_{S_iS_j} \\ y'_{S_iS_j} \end{bmatrix} = \begin{bmatrix} \cos(\alpha) & -\sin(\alpha) \\ \sin(\alpha) & \cos(\alpha) \end{bmatrix} \times \begin{bmatrix} S_j \\ \hat{S}_i \end{bmatrix}. \quad (3)$$

Following the projection of all patient and control subject data onto these regression lines, most transformed data $(x'_{S_iS_j}, y'_{S_iS_j})$ showed some degree of separation between exhaled breath from cancer patients vs. high risk controls (this is represented in later figures).

D. Classification and Model Validation

To classify data by cancer status, we used Classification and Regression Trees [30] as well as Discriminant Function Classifiers [31]. Prior to any classification methods being applied, we reduced the dimension of the feature space in two ways: 1) a Mann-Whitney-Wilcoxon (MWW) test was performed to extract the 25 most discriminant descriptors in the transformed feature space and 2) we visually assessed scatter plots of the transformed pairs of sensor readings and selected the 25 most discriminant pairings based on the visual perception of two study authors (CM, PB).

1) Classification and Regression Trees: Classification and regression tree (CART) analysis is a non-parametric greedy technique for building predictive models from the data using decision trees (Statistica, Version 10, Stat Soft Inc.). Where there are numerous features in the data with complex non-linear interactions, building a single global model is not an efficient choice. In such cases, greedy algorithms using trees which combine the locally optimal structures to build a global optimal model is an appropriate solution. We used CART as a binary classifier to categorize data into cancerous and non-cancerous groups. To increase the generalizability of the trees generated by CART, we limited the number of nodes in the trees to ~2-3 by altering stopping conditions.

2) Discriminant Function Analysis: Forward stepping Discriminant Function Analysis (DFA) (Statistica, Version 10, Stat Soft Inc.) is another statistical tool used to determine a set of predictors for building a classification model. DFA creates discriminant functions corresponding to linear combinations of predictors which maximize between-group differences relative to within-group differences of the datasets to be separated. To assess analysis robustness and the likely accuracy of the predicted model for subsequent data, we partitioned data into training and test sets in multiple ways.

2.1) K-fold Cross Validation: In this approach, data were randomly split into K groups. For each K-fold test, one group is removed from the set and is considered as the test set, while the remaining K−1 groups form the training set. The model is built on the training set and is validated on the test set. This procedure is repeated for each of the K folds and K results are finally averaged to produce the K-fold estimate of the classification accuracy.

2.2) Instrumentation Bias Corrections: During preliminary analysis of the data, changes in instrumentation configuration were observed to add a correctable systematic bias. More specifically, these changes were related to medical air supply sources (was found to be minimal) and gas-sampling bags (which are discussed in greater detail in Section II.H., below, but were found to be large enough to affect results). To fully evaluate the possible effects of this bias, we set the data collected in the original configuration as the training set and the bias-adjusted data collected using the alternate configuration as the test set, thus intentionally maximizing the effect this bias (and our attempted corrections) might have on the generalizability of the classification process.

2.3) Repeated Random Sampling Spanning Instrumentation Bias Groups: Here, the dataset was randomly split into a 2/3 training set and a 1/3 test set, making sure to equally distribute the bag biased data between the training and test sets. Similar to the previous approaches (above), the model was predicted on the training set and was evaluated on the test set for each split. We performed this random procedure ten times and averaged the classification outcomes to estimate the overall accuracy the system was likely to achieve on a new data set.

E. Discriminating Subject Breath samples

To reduce the dimensionality of the data and to extract the most discriminant features, we performed Mann-Whitney *U* test as well as visual feature selections on relative distances. The most discriminant features were then used as inputs to several classification algorithms. CART was used as the first approach to find the classification model where we limited the number of nodes in the trees to 2-3 to minimize overtraining. Ten-fold global cross validation was done to estimate generalized performance of the CART model on new data. For the DFA models the data was treated in three different ways:

1) Samples Containing All the Data (AD): A descriptive model was predicted on a random 2/3 of the data and tested on the remaining 1/3 of the data. This random sampling was done nine additional times and in this way 10-fold cross validation was performed on the model obtained from the training set to assess how well the model could be generalized.

2) Samples Containing Data from Bag I Training (B1T): DFA was performed on the data collected using the first bag type as the training set. After the classification model was computed from the training set, its predictive accuracy was evaluated by employing it on the independent test set (bias-adjusted data collected using the second bag type.)

3) Samples Containing Randomly Selected Data (RSD): Repeated random sampling tests were performed on the data to evaluate its robustness in differentiating cancer patients from high-risk control subjects. The original dataset was divided ten times into the training set (2/3 of each bag type) and the test set (the remaining samples.) This differed from the AD analysis insofar as RSD group would have an even distribution of bag types in each set (whereas the AD group sampled data without consideration for bag type). After the classification model was computed for the training set in each split, the model was validated on the test set. The results were finally averaged to produce a single estimation.

This article has been accepted for publication in a future issue of this journal, but has not been fully edited. Content may change prior to final publication. Citation information: DOI 10.1109/TBME.2015.2409092, IEEE Transactions on Biomedical Engineering

F. Reproducibility and Repeatability

For the e-nose to be of clinical utility for screening high risk subjects, it must be possible to calibrate multiple e-nose systems such that the measures made on one system are comparable to those on another system. This will allow a classification methodology trained on one system to be applied to data acquired on additional systems. We therefore must be able to duplicate the systems behavior in different settings. To evaluate our ability to calibrate multiple systems, we next compared the exhaled breath results obtained from two e-nose devices that measured the same exhaled breath at the same time. Fig. 4 shows the schematic diagram of the experimental setup and results and discussion of these results are provided in subsequent sections.

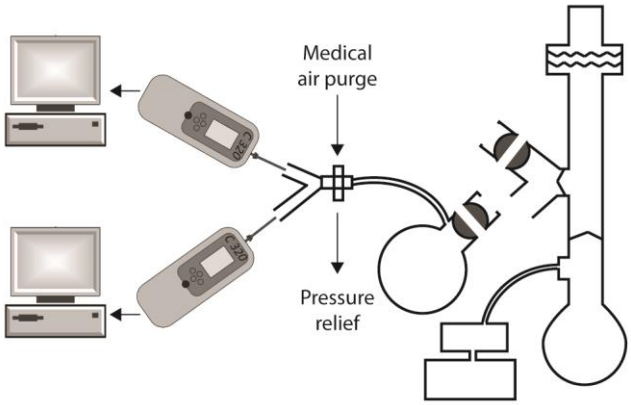


Fig. 4. Schematic for reproducibility experiment (see also Fig. 1).

G. Evaluating the pre- and post-prandial analysis

To examine the possibility that the fasting state of the subject/patient could affect the concentrations of VOC present in exhaled breath, we included a comparison of eight individuals' e-nose responses from when they were in the pre- and post-prandial states in order to study if that is a potential factor in affecting the VOC patterns. For this study pre-prandial was after a minimum of 8 hours of fasting (the usual fasting of no food from 12:00am till time of measurement). Post –prandial indicated measurements within 2 hours of food consumption (no dietary restrictions were implemented).

H. Evaluating Possible Systematic Bias

Over the duration of this study the system used to collect the exhaled air from the subjects and patients unavoidably changed. As the system was based upon the comparison of exhaled breath against humidified control air (medical grade air, Air Liquide Canada Inc., Quebec) over the duration of the study, eight different tanks of medical air were consumed. Thus a systematic bias associated with the different tanks used was possible. Further, with study recruitment ~2/3 complete, we switched from commercially produced air collection bags to in-house produced air collection bags. This equipment alteration could also have introduced a systematic bias to the exhaled breath data. Both of these possible bias sources would have manifested as distinct biases observable over time as the air tanks were replaced or as in-house airbags were used.

1) Medical Air Supply Batch Effects: As standard operating procedure, every day that subject/patient exhaled breath sample was measured, a calibration sample was measured (humidified medical air). We referred to these calibration measurements as calibration controls and they were used to evaluate systematic bias and system drift over the duration of the project. Over the life-time of this project, the medical air tank was replaced seven times (for a total of eight tanks being used). We plotted the measurements obtained from the calibration controls over time and compared them to the 5-trial data measurements obtained from 191 subjects to see if changing the medical air tank affected the measurements.

2) Gas-Sampling Bag Effects: During this study, exhaled breath collection bags were changed from commercially produced bags to bags produced in-house. To assess if this bag type switch led to systematic biases in the data, we traced data obtained from subjects over time and highlighted measurements obtained from each bag type.

III. Experimental Results

As discussed in Section II, in addition to the evaluation of e-nose potential in discriminating lung cancers from control subjects, this study contains several experiments regarding the potentially effective factors in e-nose responses. The outcomes of such experiments as well as the classification performance of the e-nose system are provided in subsections below.

A. Results Discriminating Subject Breath samples

We first assessed whether pre-processed data could distinguish lung cancer patients from high-risk smokers. As noted, while no single sensor differentiated cancer patients, by observing combinations of sensors, patients with lung cancer could be delineated. Fig. 5 shows the 2D plot of Y'_{ij} versus X'_{ij} for a sensor combination as an example.

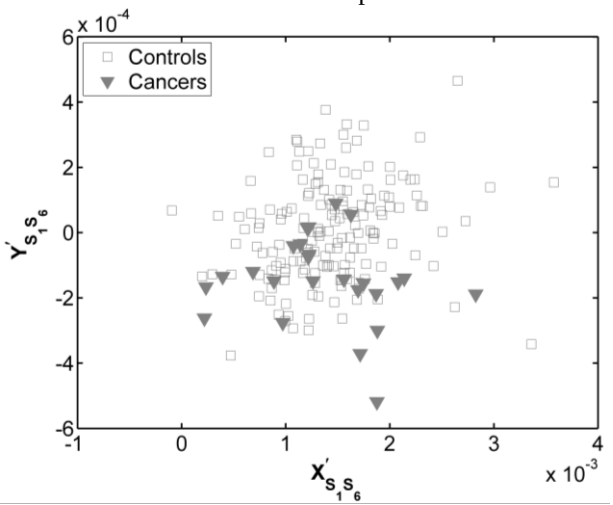


Fig. 5. Two-dimensional plot of Y'_{ij} versus X'_{ij} for $Sensor_1$-$Sensor_6$ smell-prints, showing the discrimination of lung cancer patients (triangles) from high-risk smokers (squares).

CART was used as the first approach to generate a classification model. Classification results obtained by CART – particularly specificity, sensitivity, and the 10-fold global cross-validation classification accuracy are summarized in Table III. Table IV shows the Area Under the Curve (AUC) of

This article has been accepted for publication in a future issue of this journal, but has not been fully edited. Content may change prior to final publication. Citation information: DOI 10.1109/TBME.2015.2409092, IEEE Transactions on Biomedical Engineering

the ROC for both the training and test sets for the three different training test set splits. Fig. 6 shows the ROC curves for both the training and test sets for the different set splits used to train the DFA models (AD, B1T, RSD).

TABLE III
CART APPROACH: PREDICTION ACCURACY OF E-NOSE SYSTEM IN LUNG CANCER DETECTION

Number of Features Used	2	3	4
Specificity	63.3%	81.3%	81.3%
Sensitivity	96%	84%	88%
Validation Set(s)	65%	80.6%	75.4%

TABLE IV
DFA APPROACH: PREDICTION ACCURACY OF E-NOSE SYSTEM IN LUNG CANCER DETECTION

Approach	AD	B1T	RSD
ROC AUC Training	0.838	0.836	0.836
ROC AUC Test	0.766	0.797	0.803

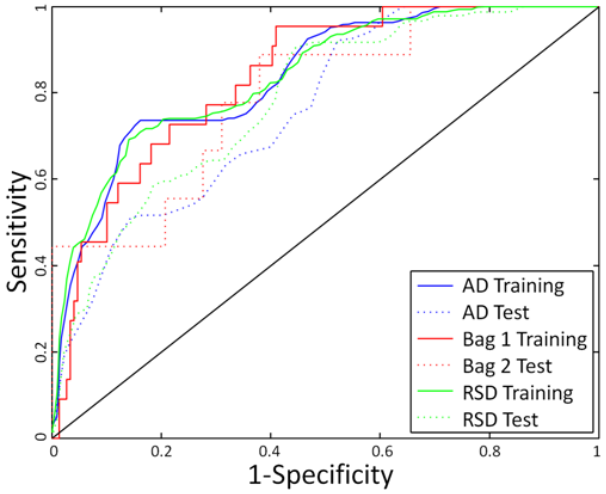


Fig. 6. DFA Receiver Operating Characteristic curves for three different training-test set models.

Not unexpectedly, the best classification prediction on the 10-fold cross-validation test sets occurred using the RSD training-test set methodology. The DFA for each of the three training-test set splits on average the forward stepping DFA selected between 3–4 features from the 25 available. There were two features ($Y'_{9,18}$, $Y'_{6,20}$) in the intersection between the features selected by the CART models and the 3–4 most frequently selected features across the 10–fold cross validation DFA models. We selected these two features for a more detailed analysis across the four demographically definable sub sets within the data (Male, Female, Current Smokers and Former Smokers). To avoid effects due to differences in cancer subject frequency, all analyses were performed only for non-cancer subjects. Also, due to the smaller number of cases in the subgroups (1/2 to 1/4 of the full set), we limited all group/ subgroup analysis to the two features selected above.

We found a statistically significant difference (p=0.016, MWW) between males and females subjects for one of the features ($Y'_{9,18}$). When we examined this difference further we found while there was no difference between the subgroups ex-smokers male vs. ex smokers females (p=0.78), there was a statistically significant difference between the subgroups of current smokers male vs. current smokers females (p=0.0075) for $Y'_{9,18}$. When we examined if this difference would affect a DFA model's ability to correctly classify cases we observed the behavior in Fig. 7. The ability of a DFA model to correctly predict sample classification in the RSD test set appeared to depend to a small degree on the sex of the subject (Male ex-smoker AUC 0.846, Male current smoker AUC 0.745 vs. Female ex-smoker AUC 0.816 and Female current smoker AUC 0.725). Also, the smoking status of the subjects appeared to impact the sample classification prediction by the DFA model to a larger degree: Ex-smoker male AUC 0.846 and Ex-smoker female AUC 0.816 vs. Current smoker male AUC 0.745 and Current smoker female AUC 0.725 (see Fig. 7).

B. Evaluating Effects of COPD

For the 186 cases (165 controls and 21 cancers) with known COPD status we did not find any statistically significant correlation between the scores used to differentiate lung cancer cases from controls across COPD status for the individual sensors or combinations. We were able to use the enose sensor data to train a discriminate function analysis (DFA) to differentiate between COPD and non COPD cases (P=0.00004). This DFA had superior performance for the recognition of COPD in current smokers compared to the ex-smoker group results. However this COPD DFA score was not statistically significantly different between the controls and the cancer cases (p=0.07). These results indicate that while the enose could differentiate between COPD and non COPD cases in agreement with the much more detailed analysis performed by Fen et al.[19,32,33] the features or feature combinations the COPD DFA used were different (and to some extent orthogonal to) the features and feature combinations used to differentiate cancer cases from controls.

C. Evaluating Reproducibility and Repeatability of E-nose Systems

For this evaluation, we employed two e-nose systems and obtained array responses for 15 samples on both systems. We then used this data to generate a translation matrix based upon sensor means for the 15 samples enable the adjustment of sensor measurements made on the second system to be equivalent to those that would have been recorded if the first system had been used.

From an analysis of the 5-series measurements from seven non-smoking subjects sampled in parallel by the two systems (35 measurements in total), we observed that the two systems could be made substantially equivalent with a sensor by sensor average linear correlation R value of 0.69 with a range of 0.11 to 0.96 across the 32 sensors. However ~10–12 sensors had

This article has been accepted for publication in a future issue of this journal, but has not been fully edited. Content may change prior to final publication. Citation information: DOI 10.1109/TBME.2015.2409092, IEEE Transactions on Biomedical Engineering

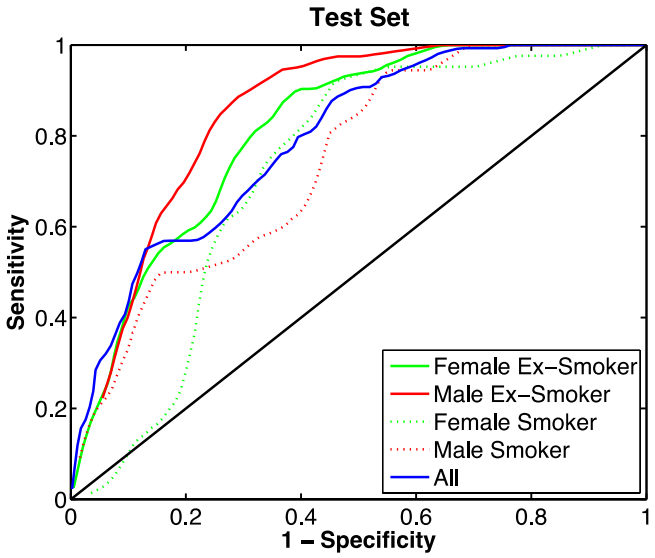


Fig. 7. DFA Receiver Operating Characteristic curves for the four demographic subgroups using the RSD 10-fold test set results.

very low readings (non-detectable reactions to the VOC mixture exhaled by non-smokers) as seen in their very low signal to noise ratios (<3) as defined as the average variance between individuals divided by the average variance within the five repeat measurement instances for each individual. For those sensors with a S/N > 3, 1) the average R value was 0.79 and 2) a plot of the R value as a function of the sensors' S/N demonstrated an extremely strong correlation of larger R values with sensors that had larger S/N ratios. This indicates that the e-nose measurements from different systems were strongly correlated but that the level of VOCs in the exhaled breath of non-smokers was at the lower limit of detectability by these systems. The relationship between sensors across both systems was the same, which is within error of repeated measures. Systems could be calibrated to record very similar values for the same sample. Comparisons of the two e-nose system responses are shown in Fig. 8.

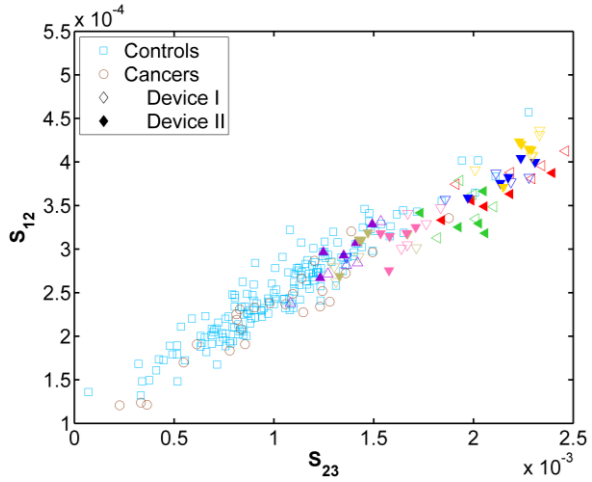


Fig. 8. 2D scatter plot of S_{23}-S_{12}: reproducibility test for two devices. Open circles and squares are the average sensor measurements for cancer subjects and the ever smokers. The solid triangles are the five repeat measures for each non-smoking subject measured by system 2 and the open triangle are the same subjects measured by system 1.

D. *Results evaluating the pre- and post-prandial analysis*

Fig. 9 shows the two-dimensional scatter plot of eight non-smoker healthy samples as well as the control subjects. In the plot, each arrow line corresponds to the directional path from pre- to post-prandial measurements for each subject. Generally post-prandial samples recorded readings that were closer to the high-risk subjects, which all were analyzed in the post-prandial state. It appears that the fasting– non-fasting state can affect some combinations of e-nose sensors (two states are significantly different for 37% of sensor combinations), however 99.94% of the combinations were not significant when corrected for multiple comparisons.

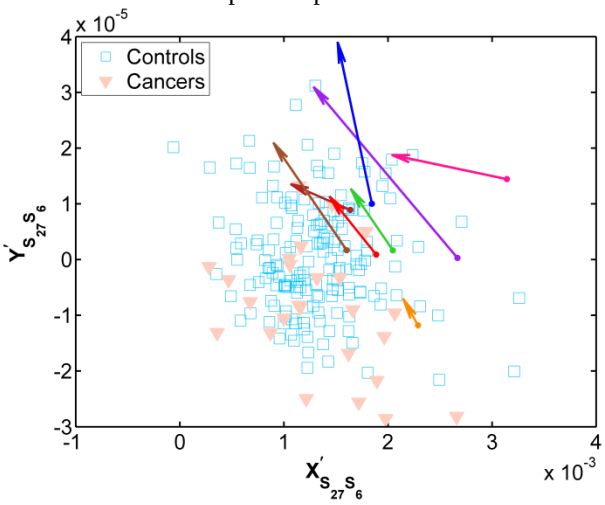


Fig. 9. Plot evaluating the pre and postprandial effects for the combination of sensor 6 and 27 data. Each Arrow depicts the data variation from pre-prandial state to postprandial state.

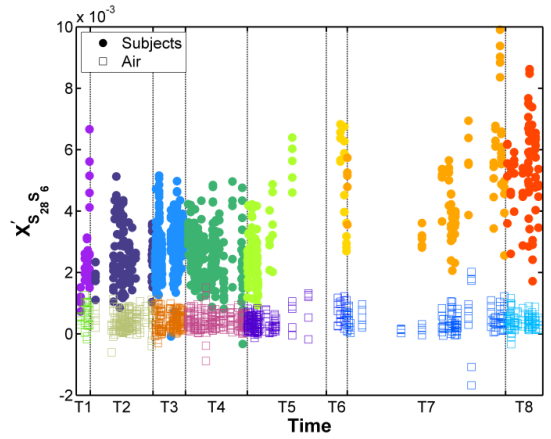
For almost all the sensor pairs that were found to have some ability to differentiate cancer subjects from high-risk smokers the change between the pre and post-prandial state subject measurements was in the opposite direction than that which separated the high-risk smokers from the cancer subjects. This suggests that some of the differences in VOCs between cancer subjects and high-risk normal subjects may be associated with metabolic activity associated with available energy. Essentially this observation is consistent with the energy model of cancer cellular metabolism. Specifically cancer cells are constantly in a metabolically challenged state (less energy and metabolites available than optimal due to their programming for uncontrolled growth). Normal or smoke damaged lung cells in a fasting individual are likely to be closer to this state than the cells in a non-fasting individual in which metabolites and energy are more readily available.

E. *Evaluation of Systematic Effects*

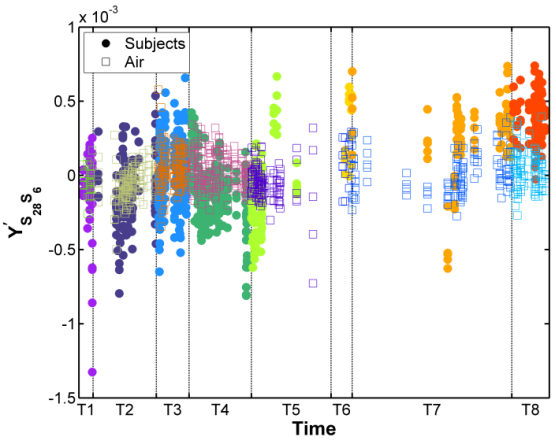
Fig. 10 shows scatter plots of all the data for the sensor combination (6 & 28) from volunteers (no patients) and humidified control air as a function of time. It shows the measurements obtained for 191 subjects (filled circles) as well as the humidified control air data (open boxes). As seen in the scatter plots, the e-nose system could detect subtle differences between medical air supply batches (differences in the open boxes for the eight air tanks); however these differences were

This article has been accepted for publication in a future issue of this journal, but has not been fully edited. Content may change prior to final publication. Citation information: DOI 10.1109/TBME.2015.2409092, IEEE Transactions on Biomedical Engineering

significantly smaller than subject-to-subject differences.



(A)



(B)

Fig. 10. Assessment of systematic bias associated with different air tanks: X'_{ij} (for $Sensor_6$-$Sensor_{28}$ smell-prints) and Y'_{ij} measurements ordered by the time that they were made.

In the scatter plots in Fig. 11 we can see the systematic bias introduced by the different sample bags on the recorded measurements. Fig. 11 shows this analysis for the $X'_{28\ 6}$ measurement combination in which there is an obvious bag bias. A noticeable shift in both of $X'_{28\ 6}$ and $Y'_{28\ 6}$ measurements was observed in Fig. 10 as well. Specifically, the data measured after the new batch of bags was installed (Bag II), deviates from the data collected using the first bag type (Bag I). We conclude that the new sampling bag type was the cause of the bias observed in the time trend. This bias was corrected by adjusting the collected data from both types of bags to have statistically the same average characteristics for the ever-smoker subject data (see Fig. 12). The corrected data, after removing the additive effects of bag type, were used for all the classification analyses.

IV. Discussion

Profiling to detect biomarker patterns in exhaled breath is an emerging field in cancer research [8-11,34,35]. Multiple studies mainly evaluating e-nose application to distinguish lung cancer patients from control subjects have been

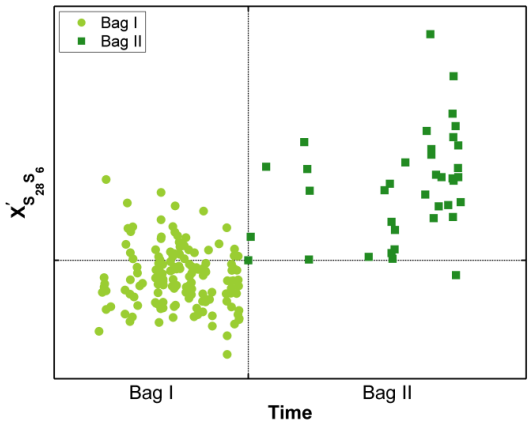
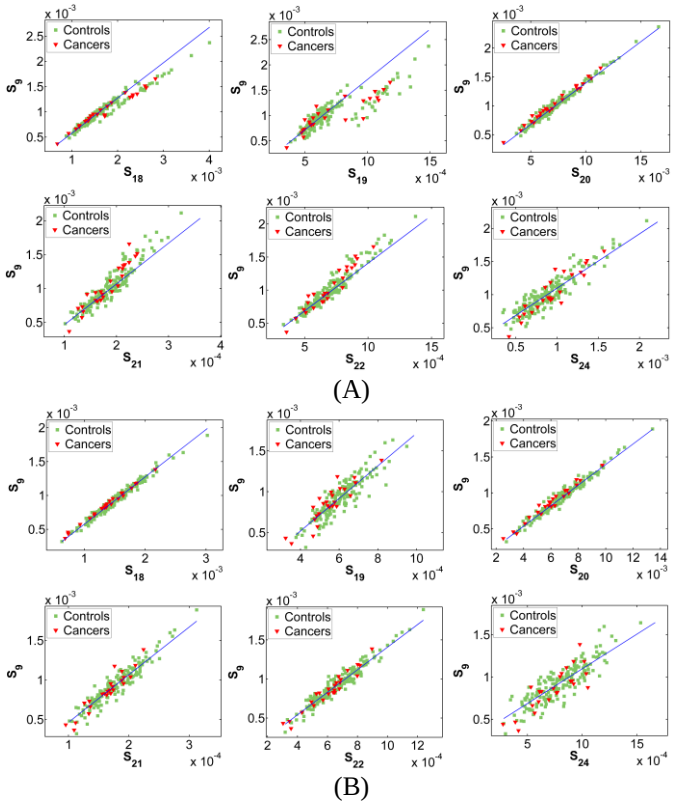


Fig. 11. Effect assessment of the use of different air bags: $X'_{28,6}$ smell-prints ordered by the time that they were measured.



(A)

(B)

Fig. 12. Correction of the Bias introduced by a change of air collection bags for eight sensor pair combinations. Figure A shows the subject data prior to the bias correction and figure B shows the same data after bias correction.

conducted, however appropriate control group selection has not always been performed. Examples of this include the lack of current/former smoking controls, inappropriate control patients, and demographically mismatched test groups. The above referenced studies – many of which included evaluation of the same e-nose system we evaluate here – typically had control groups comprised of individuals with varied smoking statuses and other respiratory disorders or pulmonary diseases (e.g. COPD). A variety of enose sensor systems have been evaluated. One such is the 6 sensor system (E-nose Mk2 and Mk3, E-nose Pty., Ltd) described by Tran et al [11], for the

This article has been accepted for publication in a future issue of this journal, but has not been fully edited. Content may change prior to final publication. Citation information: DOI 10.1109/TBME.2015.2409092, IEEE Transactions on Biomedical Engineering

detection of lung cancer. In their study on 33 non-smokers, 11 ex-smokers, 18 smokers, 11 controls with respiratory disorders and 16 lung cancers (stage not described) they found no significant differences in their breath measurements between the 4 non cancer groups. Further 3 of their measurement parameters were statistically different between the cancers and the controls and while they did not give any classification performance results visual inspection of their figures suggests at least a sensitivity of 56% with a specificity of 78%. Peng at al[34] evaluated a sensor system based upon 9 chemiresistors assembled from gold nanoparticles and organic functionalities specifically designed to be sensitive to VOCs detected to be different between controls and lung cancer patients. They studied 56 healthy controls (39 nonsmokers, 17 smokers; average age 45y) and 40 late stage (3-4, smoking and average age unknown) lung cancer patients and found complete separation between the two groups for two PCA features and no differences with respect to sex, age or smoking status.

The control-case classification performance reported here falls between these two studies. However the difference of the results between these 2 studies and with the work presented here highlights the difficulty with comparisons when different definitions between the control and cancer groups are used and when different technologies are evaluated.

Many groups have used gas chromatography - mass spectrometry (GC-MS) to identify lung cancer VOCs. In a review of this VOC literature by Hakin et al[35] the possible mechanisms which give rise to these VOCs is discussed. This review also noted that the variance in control groups in their reviewed clinical studies is an issue when comparing the results of studies. Interestingly this review suggested that induction of cytochrome p450 enzymes by smoking could lead to the acceleration of catabolism of oxidative stress products modifying associated VOCs in the breath. Interestingly our group has found that the expression of these genes can be reversibly and irreversibly modified [36] by smoking and may react differently between the sexes [37-39]. Other pathways who's behavior could modify VOC in breath are carbohydrate metabolism, and the glycolysis/gluconeogenesis pathways. The known alterations in these pathways associated with cancer and their associated effects on VOCs[35] would be consistent with the pre-post prandial cancer non cancer results we observed. For this work, we have used well-matched patient groups according to demographic risk indicators: age, similar number of pack-years of smoking, and smoking status. We have investigated the ability of the e-nose to distinguish patients diagnosed with lung cancer from high-risk smokers with benign or no lesions. While earlier studies evaluated lung cancer patients that were typically older and possessed of longer smoking histories (compared to controls), we tested our hypothesis in a study cohort comprised of only current or former smokers with similar pack-year consumption histories and negligible age differences between cancer and control groups. Our data suggest that a subject's sex can impact the delineation of that individual's cancer (or non-cancer) status – and that the smoking status of the subject can make a large difference in the classification accuracy of e-nose data. Our results suggest that an e-nose system is likely to work better on ex-smokers than current smokers at least for lung Adenocarcinomas. It would appear that the changes associated with active smoking to some degree masks the changes in VOC associated with patients with cancer. Further it appears that these VOC changes are larger in males than in females. This is not totally surprising in that other studies have shown differences in the responses of males vs. females to the carcinogens in cigarette smoke [37-39]. The majority of analyzed cases were lung adenocarcinomas (Table II), a fact that could impact the utility of our findings to wider lung cancer populations. Also a larger cohort of lung cancer patients is needed to facilitate a more robust analysis of VOC changes to disease. For the e-nose system to be clinically useful, it must be possible to calibrate multiple systems to respond in the same manner (i.e. within the error of repeating a sample measurement on the same system). We were able to generate substantially equivalent results for the same subject VOCs measured on two systems through bias removal normalization. In theory this should make possible the translation of a classification function from one system to another without having to train the second system. However in practice, this needs to be demonstrated on a prospective sample population. In addition, we have assessed the potential systematic bias on the sensor array response, introduced by the alterations in the equipment (medical air tank and collection bag type) and found these to be systematic and correctable.

In this study we demonstrated that the e-nose, when used as a screening tool, should be able to correctly differentiate high-risk smokers/ex-smokers from subjects with lung cancer. This can be done with accuracy between 75%-85% (depending on the algorithm used). The concentration of the exhaled VOCs from the subjects in this work is at the edge of the sensitivity of the current e-nose system: a study involving a larger set of cancer patients using a more sensitive e-nose system is needed to improve the accuracy of our analysis and demonstrate the true screening potential of exhaled VOC readings, particularly across differences in subject sex and smoking status.

V. Conclusion

We have demonstrated the potential of e-nose technology to distinguish lung cancer patients from matched high-risk smokers, adding to the evidence that measurements of exhaled VOCs (as measured by an e-nose) can be used as a lung cancer screening tool. Smell-prints of high-risk smokers were significantly distinct from those diagnosed with lung cancer and these differences seem to depend to some degree on subject sex and smoking status. Further measurements on multiple devices can be demonstrated to be repeatable and reproducible.

VI. Acknowledgement

The authors would like to acknowledge technical inputs by Myles McKinnon.

This article has been accepted for publication in a future issue of this journal, but has not been fully edited. Content may change prior to final publication. Citation information: DOI 10.1109/TBME.2015.2409092, IEEE Transactions on Biomedical Engineering

REFERENCES

[1] R. Lozano et al, "Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010," *Lancet*, vol. 380, no. 9859, pp. 2095-128, Dec 15, 2012.

[2] F. Di Francesco et al, "Breath analysis: trends in techniques and clinical applications," *Microchemical Journal*, vol. 79, no. 1-2, pp. 405-410, Jan, 2005.

[3] P. Batra et al, "Evaluation of intrathoracic extent of lung cancer by plain chest radiography, computed tomography, and magnetic resonance imaging," *Am Rev Respir Dis*, vol. 137, no. 6, pp. 1456-62, Jun, 1988.

[4] S. J. Swensen et al, "Lung cancer screening with CT: Mayo Clinic experience," *Radiology*, vol. 226, no. 3, pp. 756-61, Mar, 2003.

[5] R. A. Dweik, and A. Amann, "Exhaled breath analysis: the new frontier in medical testing," *J Breath Res*, vol. 2, no. 3, Sep, 2008.

[6] M. Corradi et al, "Increased nitrosothiols in exhaled breath condensate in inflammatory airway diseases," *Am J Respir Crit Care Med*, vol. 163, no. 4, pp. 854-8, Mar, 2001.

[7] H. K. Wilson, "Breath analysis. Physiological basis and sampling techniques," *Scand J Work Environ Health*, vol. 12, no. 3, pp. 174-92, Jun, 1986.

[8] S. Dragonieri et al, "An electronic nose in the discrimination of patients with non-small cell lung cancer and COPD," *Lung Cancer*, vol. 64, no. 2, pp. 166-70, May, 2009.

[9] R. F. Machado et al, "Detection of lung cancer by sensor array analyses of exhaled breath," *Am J Respir Crit Care Med*, vol. 171, no. 11, pp. 1286-91, Jun 1, 2005.

[10] P. J. Mazzone et al, "Exhaled breath analysis with a colorimetric sensor array for the identification and characterization of lung cancer," *J Thorac Oncol*, vol. 7, no. 1, pp. 137-42, Jan, 2012.

[11] V. H. Tran et al, "Breath Analysis of Lung Cancer Patients Using an Electronic Nose Detection System," *IEEE Sensors Journal*, vol. 10, no. 9, pp. 1514-1518, 2010.

[12] A. G. Dent, T. G. Sutedja, and P. V. Zimmerman, "Exhaled breath analysis for lung cancer," *J Thorac Dis*, vol. 5, no. Suppl 5, pp. S540-S550, Oct, 2013.

[13] B. Moser et al, "Mass spectrometric profile of exhaled breath--field study by PTR-MS," *Respir Physiol Neurobiol*, vol. 145, no. 2-3, pp. 295-300, Feb 15, 2005.

[14] L. Pauling et al, "Quantitative analysis of urine vapor and breath by gas-liquid partition chromatography," *Proc Natl Acad Sci U S A*, vol. 68, no. 10, pp. 2374-6, Oct, 1971.

[15] M. Phillips, "Method for the collection and assay of volatile organic compounds in breath," *Anal Biochem*, vol. 247, no. 2, pp. 272-8, May 1, 1997.

[16] J. D. Pleil, and A. B. Lindstrom, "Measurement of volatile organic compounds in exhaled breath as collected in evacuated electropolished canisters," *J Chromatogr B Biomed Appl*, vol. 665, no. 2, pp. 271-9, Mar 24, 1995.

[17] R. H. Brown, and T. H. Risby, "Monitoring distant organ reperfusion injury by volatile organic compounds.," *Disease Markers in Exhaled Breath*, N. Marczin, S. Kharitonov, M. Yacoub and P. Barnes, eds., pp. 258-280, London: Marcel Dekker, 2002.

[18] B. Buszewski et al, "Human exhaled air analytics: biomarkers of diseases," *Biomed Chromatogr*, vol. 21, no. 6, pp. 553-66, Jun, 2007.

[19] N. Fens et al, "Exhaled breath profiling enables discrimination of chronic obstructive pulmonary disease and asthma," *Am J Respir Crit Care Med*, vol. 180, no. 11, pp. 1076-82, Dec 1, 2009.

[20] C. Belda-Iniesta et al, "New screening method for lung cancer by detecting volatile organic compounds in breath," *Clin Transl Oncol*, vol. 9, no. 6, pp. 364-8, Jun, 2007.

[21] S. M. Gordon et al, "Volatile organic compounds in exhaled air from patients with lung cancer," *Clin Chem*, vol. 31, no. 8, pp. 1278-82, Aug, 1985.

[22] M. Phillips et al, "Prediction of lung cancer using volatile biomarkers in breath," *Cancer Biomark*, vol. 3, no. 2, pp. 95-109, 2007.

[23] M. Phillips et al, "Detection of lung cancer using weighted digital analysis of breath biomarkers," *Clin Chim Acta*, vol. 393, no. 2, pp. 76-84, Jul 17, 2008.

[24] M. Phillips et al, "Detection of lung cancer with volatile markers in the breath," *Chest*, vol. 123, no. 6, pp. 2115-23, Jun, 2003.

[25] M. Phillips et al, "Volatile organic compounds in breath as markers of lung cancer: a cross-sectional study," *Lancet*, vol. 353, no. 9168, pp. 1930-3, Jun 5, 1999.

[26] A. Amann et al, "Applications of breath gas analysis in medicine," *International Journal of Mass Spectrometry*, vol. 239, no. 2-3, pp. 227-233, Dec 15, 2004.

[27] J. W. Gardner, and P. N. Bartlett, *Electronic Noses: Principles and Applications*, New York: Oxford University Press, 1999.

[28] E. R. Thaler, and C. W. Hanson, "Medical applications of electronic nose technology," *Expert Rev Med Devices*, vol. 2, no. 5, pp. 559-66, Sep, 2005.

[29] Z. J. Cheng et al, "An electronic nose in the discrimination of breath from smokers and non-smokers: a model for toxin exposure," *J Breath Res*, vol. 3, no. 3, pp. 036003, Sep, 2009.

[30] L. Breiman et al, J *Classification and Regression Trees*, Belmont, CA: Wadsworth & Brooks, 1984.

[31] R. A. Fisher, "The use of multiple measurements in taxonomic problems," *Annals of Eugenics*, vol. 7, pp. 179-188, Sep, 1936.

[32] Fens N et al, " External validation of exhaled breath profiling using an electronic nose in the discrimination of asthma with fixed airways obstruction and chronic obstructive pulmonary disease." Clin Exp Allergy. 2011 Oct;41(10):1371-8. doi: 10.1111/j.1365-2222.2011.03800.x. Epub 2011 Jul 7.

[33] Fens N et al, "Subphenotypes of mild-to-moderate COPD by factor and cluster analysis of pulmonary function, CT imaging and breathomics in a population-based survey," COPD. 2013;10:277–285. doi: 10.3109/15412555.2012.744388.

[34] Peng G et al, "Diagnosing lung cancer in exhaled breath using gold nanoparticles," *Nat Nanotechnol*. 2009 Oct;4(10):669-73

[35] Hakim M et al, "Volatile organic compounds of lung cancer and possible biochemical pathways," *Chem Rev*. 2012 Nov 14;112(11):5949-66.

[36] Chari R et al, "Effect of active smoking on the bronchial epithelium transcriptome," *BMC Genomics*. 29(8):297, 2007.

37] A. F. Gazdar, and M. J. Thun, "Lung cancer, smoke exposure, and sex," *J Clin Oncol*, vol. 25, no. 5, pp. 469-71, Feb 10, 2007.

[38] M. P. Rivera, "Lung cancer in women: differences in epidemiology, biology, histology, and treatment outcomes," *Semin Respir Crit Care Med*, vol. 34, no. 6, pp. 792-801, Dec, 2013.

[39] H. A. Wakelee et al, "Lung cancer incidence in never smokers," *J Clin Oncol*, vol. 25, no. 5, pp. 472-8, Feb 10, 2007.

BIOGRAPHIES

Dr. Annette McWilliams is a Respiratory Physician who previously worked at the British Columbia Cancer Agency and Vancouver General Hospital, focusing primarily on early detection and treatment of lung cancer. Dr. McWilliams now works at Sir Charles Gairdner Hospital in Perth, Australia and is Head of Respiratory Medicine at Fiona Stanley Hospital.

Parmida Beigi received her BSc degree in Electrical Engineering from Sharif University of Technology, Iran. She completed her MASc degree in Electrical Engineering at Simon Fraser University, Canada in 2011. She is currently completing her PhD in Biomedical Engineering at the University of British Columbia, Canada.

Akhila Srinidhi completed her BEng at Visvesvaraya Technological University (Bangalore, India) in 2010. She received her MEng in Biomedical Engineering from the University of British Columbia (Vancouver, Canada) in 2012. She is currently pursuing biomedical research in Melbourne, Australia.

Dr. Stephen Lam completed his MD at the University of Toronto and his FRCPC training in Internal Medicine and Pulmonary Medicine at the University of British Columbia, where he is currently Professor of Medicine. Dr. Lam currently chairs the Provincial Lung Tumor Group and directs the MDS-Rix Early Lung Cancer Detection and Translational Research Program at the BC Cancer Agency.

Dr. Calum MacAulay holds a BSc in Engineering Physics (Dalhousie University, 1982), MSc (Physics, Dalhousie, 1985), and PhD (Physics, University of British Columbia, 1989). He is currently Head of the Department of Integrative Oncology, British Columbia Cancer Agency. He is also an Associate Member of the Department of Physics and Astronomy and an Associate Professor in the Department of Pathology at UBC.