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Machine Learning-Based Electronic Nose for Universal Mapping of Blood Odors and Diagnosis of Cancer

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Electronic nose (E-Nose) technology is gaining prominence as a tool for cancer diagnostics due to its ability to detect volatile organic compounds in bodily fluids. The aim of this investigation was to standardize a procedure for using a machine learning-based E-Nose to accurately diagnose five different cancers. This prospective diagnostic/prognostic study included 1001 newly diagnosed male and female participants with blood, brain, breast, liver, and lung cancer, as well as healthy controls. Blood samples were collected from all participants for complete blood counts, specific tumour markers testing, and E-Nose measurements. Sensor response patterns at the plateau region were used for training, testing, and machine learning cross-validation. The E-Nose had 100% accuracy, with no false-positives or false-negatives. With an average AUC of 1.0, the support vector machine had 100% sensitivity and specificity, correctly classifying every blood sample from different cancers and healthy controls. The E-Nose had high diagnostic accuracy, sensitivity, and specificity for the detection of cancer in blood samples.

* 1. Introduction

Cancer is characterized by the proliferation of aberrant cells that develop uncontrollably, infiltrate neighbouring tissues, and metastasize to distant organs, leading to death (Scheepers et al., 2022). In 2020, GLOBOCAN reported a total of 19,292,789 newly diagnosed cancer cases and 9,958,133 associated deaths, with an age-standardized rate (ASR) of 190/100,000 for all cancers worldwide (Sung et al., 2021). In 2014, the ASR in Egypt was 166.6/100,000, with liver, breast, and bladder cancers being the most common types (WHO, 2024; WCRFI, 2024). Cancer is predicted to double to 29-37 million new cases by 2040, with a significant incidence in underdeveloped and developing countries (Sung et al., 2021). Of the 15 million deaths at age 30-69 years in 2018, 4.5 million died of cancer, and 70% of these deaths also occurred in these countries (Ibrahim et al., 2014). In 80% of countries, premature cancer mortality trends hinder progress towards achieving the sustainable development goals (SDG) target of 3.4 million by 2030 (Shah et al., 2019). To determine the type and extent of cancer, a comprehensive physical examination is performed together with laboratory testing and imaging procedures such as endoscopy, mammography, US, CT, MRI, and PET scans (Merkow et al., 2017).

The analysis of volatolomic biomarkers in body fluids using the Electronic Nose (E-Nose) technology has revolutionized the diagnosis of blood, breast, head and neck, lung, ovarian, gynaecologic, colorectal, and other malignancies (Mohamed et al., 2014; 2017; 2019; Farraia et al., 2019; Scheepers et al., 2022), as well as tumour cell lines in vitro (Gendron et al., 2007). This method is founded on the premise that pathophysiological processes alter the body’s metabolism, which is directly expressed as a unique change in the compendium of low molecular weight volatile organic compounds (VOCs) (Shirasu & Touhara, 2011). By combining E-Nose sensor responses and binary outcomes with machine learning (ML) algorithms, high levels of accuracy in disease classification and diagnosis could be achieved (Wojnowski & Kalinowska, 2022; Kokabi et al., 2023). Standardized validation studies to assess the E-Nose's accuracy in cancer detection were, however, emphasized by a growing number of oncologists (Malone et al., 2022; Scheepers et al., 2022).

The aim of the current investigation was to develop a global map of blood odours that can assist the oncologist in cancer screening and early diagnosis by using a ML-based E-Nose.

* 1. Methods
     1. Study Design

A total of 1001 male and female cancer patients from the Medical Research Institute Hospital and Alexandria University Main Hospital were recruited in this prospective diagnostic/prognostic study. Newly diagnosed cancer patients were enrolled consecutively before any medical intervention from January 2019 to June 2023. The initial diagnosis began with taking a comprehensive history and thorough medical examinations. Blood samples were collected from the upper limbs of all participants using duplicate sterile vacutainer tubes on EDTA for routine lab investigations and E-Nose measurements. Cancers of the blood (n = 188), brain (n = 72), breast (n = 213), liver (n = 93), and lung (n = 158) were the study's main categories, while healthy controls (n = 277) were those with no evident signs of illness. The exclusion criteria were youngsters, steroid treatment, endocrinopathy, and the presence or suspected presence of infections or autoimmune diseases. The last step in diagnosis involved testing for specific tumor markers, bronchoscopy and thoracoscopy investigations, and imaging radiograms (e.g., X-rays, US, CT, MRI, and PET), yielding a homogenous cohort of only 550 participants. All participants had signed written informed consents and gave blood samples. The Ethics Committee of the Medical Research Institute, Alexandria University, reviewed and approved the study protocol.

* + 1. Electronic Nose Measurements

A single researcher blindly processed the blood tube samples without knowing the subjects' clinical status or reference standard tumour marker values. An E-Nose comprising a set of 10 chemically nonspecific metal oxide semiconductors sensors (PEN3, Airsense Analytics GmbH, Schwerin, Germany) was connected to each sealed vacutainer tube through a 3 mm Teflon tube ending with a size-20G long lure-lock needle. To allow ambient air into the tube, a second, shorter needle was inserted through the seal. Filtered, dry room air was used for delivering the VOCs in the headspace above blood samples to the E-Nose sensor array at a 400 ml/min flow rate. Each time a sample was connected, solenoid valves alternated between room air and headspace VOCs, thereby automatically recording the single changes in sensor electric resistance (R) and relative conductance (G/Go) continuously for a duration of 60 s in an independent file. Prior to the subsequent sample measurement, sensors were flushed with filtered dry room air for 60 s and then zeroed out for 10 s to restore signals to their initial levels (G/Go = 1). All measurements were repeated twice, and ML algorithms were used to extract and analyse 10-sensor stable response patterns in the plateau region at 50 s (Figure 1, right panels).

* + 1. Machine Learning (ML)

ML employs unsupervised and supervised automatic algorithms to learn from data, improve performance, and make decisions and predictions (Wojnowski & Kalinowska, 2022; Kokabi et al., 2023). It detects patterns in datasets to create predictive models, where the accuracy of predicted outputs is directly proportional to the amount of data used for their training (Salama et al., 2021; Meshref et al., 2023). Principal component analysis (PCA) clusters and associates uncategorized datasets based on similarities, patterns, and differences, whereas support vector machine (SVM) uses categorized data for accurate medical diagnosis and prognosis (BasuMallick, 2024).

PCA is a non-parametric ML algorithm used for exploratory medical data analysis and predictive modelling for clustering and classification (Elhaik, 2022). It reduces data dimensionality by transforming potentially correlated E-Nose sensor response time series into principal components (PCs), maximizing variance and data variability, and identifying variable correlations (Mohamed et al., 2014; 2017; 2019). The built-in PCA algorithm (WinMuster, Version 1.6.2.2, Airsense Analytics GmbH, Schwerin, Germany) was applied to transform the E-Nose time series from 10 dimensions to orthogonal x-y coordinates. It is the least-squares transform for the E-Nose time series, with PC #1 having the highest x-coordinate variance and PC #2 the second most y-coordinate variance. PCA displays similarity patterns in clusters, analysing and extracting essential details from the quantitatively dependent 10-dimensional times series variables. It helps identify and classify all investigated group blood samples, including blood, brain, breast, liver, and lung cancer groups, compared to healthy controls.

Vector-based SVM is a supervised ML technique for outlier detection, regression, and data classification (Akinnuwesi et al., 2023). It creates a hyperplane, the best decision boundary in the E-Nose 10-dimensional space, based on support vectors, to determine the optimal training parameter combination for model predictions (Kokabi et al., 2023). The LibLinear-built SVM algorithm uses a one-versus-all multiclass technique, providing maximal penalty and loss function flexibility, and effectively performs with limited and large data (Sarker, 2021). SVM was implemented using Spider 4.14, provided in Anaconda Navigator 1.9.12 and based on Python platform version 3.8.3, running on a core-i7 PC under Windows 11.

* + 1. Input Dataset

The input dataset was comprised of NOS-formatted standard measurement files of E-Nose 10-sensor responses (60 s time series) from blood samples of participants with a confirmed diagnosis of chronic lymphocytic leukaemia (CLL), glioblastoma multiforme (GBM), invasive ductal carcinoma (IDC), hepatocellular carcinoma (HCC), adenocarcinoma (AC), and healthy controls (HC). The cancer input vector for blood samples was a 550  1100 matrix, describing 1100 attributes of 550 blood samples. In the training phase, 80% of the dataset was used, while the remaining 20% was used in the testing phase.

* + 1. Output Vectors

There were six study groups represented by the output vector: blood (CLL), brain (GBM), breast (IDC), liver (HCC), lung (AC) cancer, and HC. The input and output vectors were randomly divided into two sets, and the output of the linear SVM was calculated for varying values of the constant C. The best results were obtained at a C value of 200 and a number of folds equal to 5 for cross-validation.

* + 1. Statistical Analysis

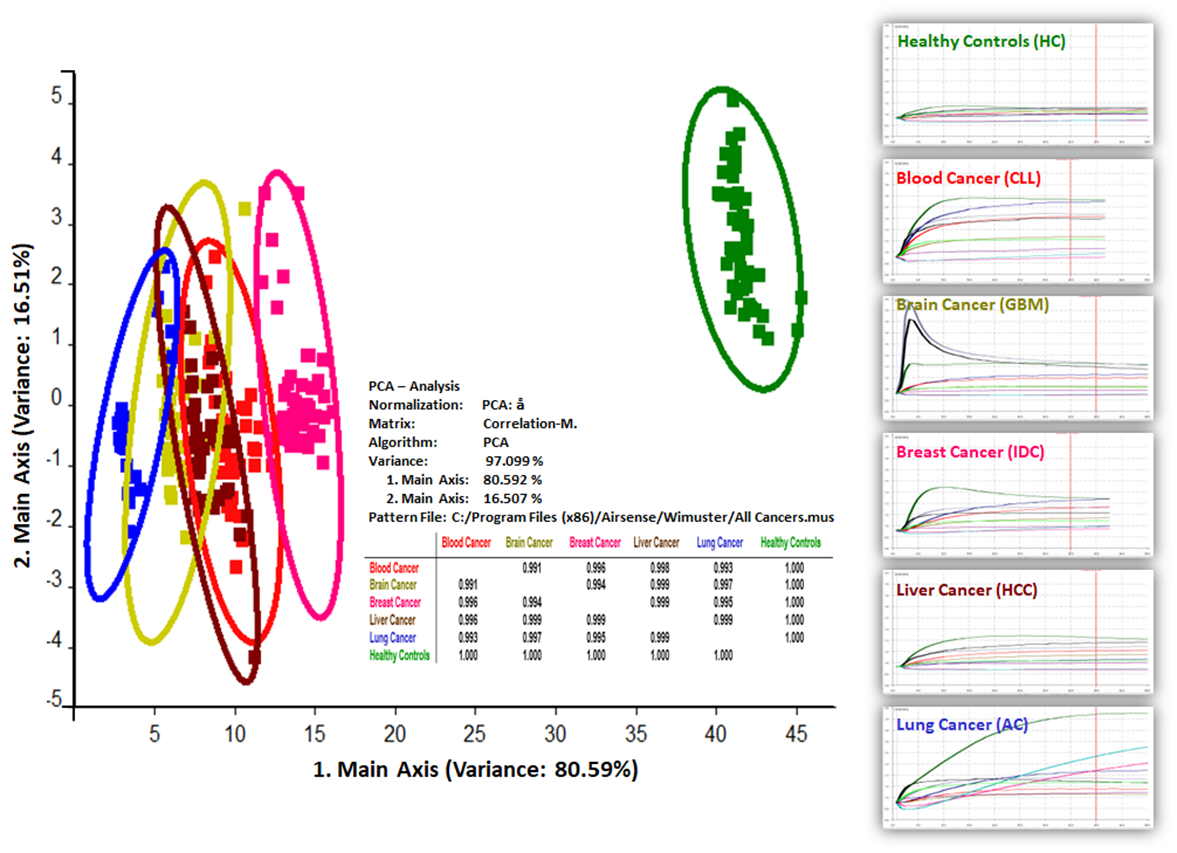
Preciseness, accuracy, sensitivity, specificity, F1-score, and mean absolute error (MAE) were among the performance indicators computed in the study. Graphical representations of cross-validation scores and error rates, as well as the area under the curve (AUC) of the receiver operating characteristic (ROC) analysis for all study groups were also provided.

* 1. Results and Discussion

Based specific tumour markers for cancer diagnosis, the study was carried out on 550 participants with an age range of 49 to 70 years, finally categorized into CLL (n = 100), GBM (n = 50), IDC (n = 150), HCC (n = 50), AC (n = 50), and HC (n = 150). The mean age of cancer patients was 55.53 ± 10.71 years, 171 (42.75%) being males, which included 116 (67.83%) active smokers, while 229 (57.25%) were females, with only 16 (6.99%) active smokers. The HC mean age was 58.22 ± 7.53 years; 78 (52%) were males, of which 51 (34%) were active mild smokers or with a history of smoking. The average age of study participants falls within the middle-aged range, with a significant gender disparity (females were more than 50%) due to the higher number of IDC patients. IDC patients, who were all class 2 obese females (BMI > 35 kg/m2), were significantly heavier than CLL and HCC patients, who were overweight (BMI > 25 kg/m2), while GBM and AC patients were within the normal weight range (BMI < 25 kg/m2).

Figure 1 right panels show the typical sensor responses, which were characteristic fingerprints to the VOCs emanated from blood samples of various cancers (CLL, GBM, IDC, HCC, and AC) and HC. The multidimensional PCA cluster plots are shown in Figure 1 left panel, where the correlation matrix showed that the first and second main PCs had a variance of 80.59% and 16.51%, respectively. There were no false-positive or false-negative results, with a PCA total variance of 97.10%. E-Noses were reported to have a 90% sensitivity and 87% specificity in diagnosing cancer using exhaled breath, based on a pooled analysis of 52 studies involving 3677 cancer patients (Scheepers et al., 2022). Earlier studies also confirmed the PCA algorithm's high sensitivity and specificity in accurately diagnosing major leukaemia types (i.e., ALL, AML, CLL, and CML), breast cancer, and lung cancer in various biological fluids, including blood (Mohamed et al., 2014; 2017; 2019; Liu et al., 2023).

The SVM training, testing, and cross-validation accuracies were 100, 100, and 97.60%, respectively, with a total accuracy of 99.20% (Table 1). The SVM model predictions were exceptionally close to the real values, with minimal deviation from the true data labels (i.e., cancer categories and HC), as by a mean absolute error of zero. With a scoring time of only 0.02 s, the SVM model was ideal for real-time applications. Moreover, the output vectors for all categories of blood samples were perfectly accurate with respect to sensitivity, specificity, recall, and F1-Score. The best cross-validation was achieved, as shown graphically in Figure 2A, which displays the accuracy score throughout the entire blood sample training set. Figure 2B shows that the error rate of the model converged to zero by the end of training, thus the SVM model successfully learned E-Nose patterns, minimizing its errors over time. Error rate measurements showed a zero MAE, thus the SVM model outputs were accurate in predicting true values that coincided with the actual cancer and HC categories (Table 1). The SVM model predictions had a flawless score of 100% for true positives and 0% for false negatives in the confusion matrix, with a sensitivity and specificity of 100% (Figure 2C). An AUC of 1.00 is the best possible performance on an ROC curve, thus, the SVM model accurately classified every single blood sample of various cancers and HC (Figure 2D).



*Figure 1: Typical sensor responses (right panels) and principal component analysis (PCA) (left clusters) for blood samples.*

Table 1: Support vector machine (SVM) training, validation, and testing output results.

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|  | Output Result |
| Training Accuracy (%) | 100 |
| Testing Accuracy (%) | 100 |
| Validation Accuracy (%) | 97.60 |
| Total Accuracy (%) | 99.20 |
| Fit Time (s) | 10.19 |
| Score Time (s) | 0.02 |
| Mean Absolute Error (MAE) | 0.00 |
| Precision (%) | 100 |
| Sensitivity (%) | 100 |
| Specificity (%) | 100 |
| Recall (%) | 100 |
| F1-Score (%) | 100 |

Adding to the outstanding results of the SVM model—high accuracy, zero error rate, and perfect confusion matrix scores—further evaluation of PCA discrimination capacity by the SVM algorithm revealed a perfect AUC (i.e., 1.00). This AUC score suggests the SVM algorithm holds tremendous potential for accurate blood-based cancer diagnosis. These results agree with our recent findings employing deep learning-based computer-aided systems to detect COVID-19 patients in chest X-ray images (Salama et al., 2021) and abdominal lymphadenopathy patients in CT scans (Meshref et al., 2023). Based on the high accuracy, sensitivity, and specificity achieved in this study, ML-based E-Noses could be a reliable alternative or complimentary tool for early cancer detection and personalized medicine (Ferraia et al., 2019; Scheepers et al., 2022).

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*Figure 2: Support vector machine (SVM) learning performance of the training and cross-validation score curves (A), error rate curve (B), receiver characteristic curve (ROC) (C), and the classification confusion matrix (D).*

* 1. Conclusions

The E-Nose has been used to identify specific VOCs in human blood samples, which allows for detecting stereochemical odours of underivatized blood. Using PCA and SVM algorithms, the E-Nose has accurately classified blood samples from tumour markers-proven patients with CLL, GBM, IDC, HCC, and AC, as well as HC, with no false-positive or false-negative results. Thus, we believe a global map of E-Nose cancer odours can assist the oncologist in cancer diagnostic decisions and prognosis.

Nomenclature

AC – Adenocarcinoma

ASR – Age-standardized rate

AUC – Area under the curve

BMI – Body mass index

CLL – Chronic lymphocytic leukemia

E-Nose – Electronic nose

GBM – Glioblastoma multiforme

HC – Healthy controls

HCC – Hepatocellular carcinoma

IDC – Invasive ductal carcinoma

MAE – Mean absolute error

ML – Machine learning

PCA – Principal component analysis

ROC – Receiver operating characteristic

SVM – Support vector machine

VOCs – Volatile organic compounds

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