

Sensor Applications

Electronic Nose-Based Assessment of Cardiovascular Disease Severity Using Blood Analysis

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Abstract—An electronic nose-based approach for cardiovascular disease severity assessment is presented, leveraging blood samples instead of conventional breath analysis to improve standardization within clinical workflows. The proposed method extends current e-nose applications by enabling 3-class discrimination among control subjects and two levels of disease severity, allowing finer clinical stratification. Sensor responses are enhanced through the integration of optimized custom sensors and analyzed using an ensemble machine learning model. A realistic evaluation of performance is ensured by adopting a subject-independent validation strategy based on patient-level group-wise cross-validation, which prevents information leakage from repeated measurements of the same subject. Under these conditions, the system achieved an accuracy of 76% ($\pm 15\%$). These results highlight the potential of combining advanced sensing technologies with rigorous validation protocols to develop reliable and clinically relevant e-nose systems for biomedical applications.

Index Terms—electronic nose, sensor systems and applications, chemical sensors, CVD, ensemble

I. INTRODUCTION

Cardiovascular disease (CVD) remains one of the leading cause of mortality globally, necessitating the development of rapid, non-invasive diagnostic tools for early pathological detection. Volatile organic compounds (VOCs), produced by metabolic shifts and oxidative stress, serve as biological "fingerprints" that reflect a patient's physiological state [1], [2]. Key substances, identified as biomarkers for CVD in exhaled breath, are reported in [3]. They include isoprene, which is directly linked to cholesterol synthesis, and various hydrocarbons, aldehydes, and ketones. Research has also highlighted the significance of acetone, n-pentane, ethanol, and sulfur-containing compounds like hydrogen sulfide in differentiating healthy individuals from those with conditions such as myocardial infarction, heart failure, and cardiac ischemia. Furthermore, environmental exposure to aromatic compounds, specifically benzene, toluene, ethylbenzene, and xylene (BTEX), has been strongly associated with increased cardiovascular risk and adverse outcomes. Gas chromatography-mass spectrometry (GC-MS) is the gold standard for VOC identification, reaching high accuracy but its clinical utility is hindered by high costs, long processing times, and a lack of portability [4], [5].

Current state-of-the-art research in CVD screening highlights a transition toward artificial olfactory systems, or electronic noses (e-noses), which utilize gas sensors arrays and machine learning (ML) to identify complex VOC patterns. Compared to traditional analytical methods, e-noses offer significant pros, including real-time results, reagent-free operation, and bedside portability [6],

[7]. In [8], an e-nose with 19 gas sensors based on metal-oxide semiconductor (MOS) technology was used to classify 275 breath samples from 60 subjects, including 29 patients with HFrEF (heart failure with reduced ejection fraction) and 31 healthy controls. The study achieved a classification accuracy of 85.21% with support vector machine (SVM) model. A similar sensing technology was used in [9], where 362 breath samples were analyzed from 81 subjects using a 19-sensor MOS e-nose and statistical feature extraction. By applying SVM and Neural Network classifiers, a 97.2% accuracy was obtained in recognizing myocardial infarction (MI) against other groups and an 81.5% accuracy for distinguishing stable coronary artery disease (SCAD) from healthy controls. In [10], a commercial e-nose featuring seven quartz microbalance (QMB) sensors were used to evaluate 309 samples from 309 subjects. Using Partial Least Squares Discriminant Analysis (PLS-DA), this study classify patients suffering from congestive heart failure (CHF) from healthy controls with 81% accuracy.

In this paper, the e-nose-based method is used to assess the severity levels in CVD patients. The analysis is performed on minimally-invasive blood samples instead of the more conventional breath samples, since blood collection highly standardized in clinical settings. Moreover, in many clinical workflows, blood sampling is already available for CVD patients [11]. This work extends the conventional e-nose-based CVD classification, reported in literature, by proposing a 3-class discrimination: controls and two levels of disease severity, providing finer clinical stratification. It also introduces a more robust evaluation method using group-wise cross-validation (CV), which prevents information leakage from repeated measurements of the same subject. This yields a more realistic classification performance.

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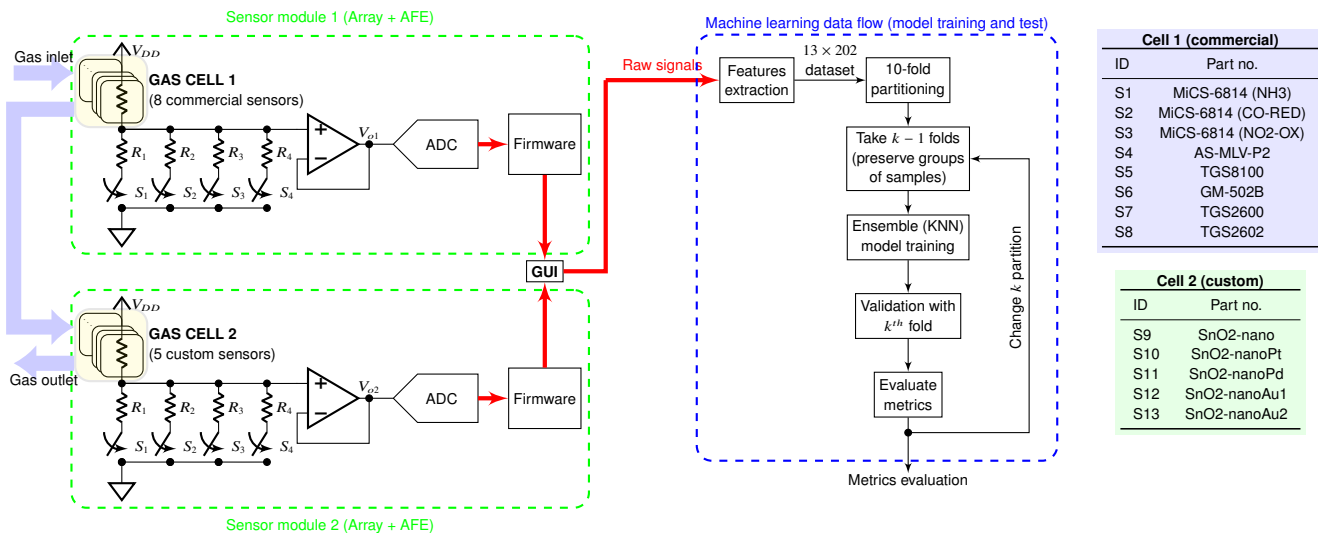


Fig. 1. Architecture diagram of the adopted electronic nose.

II. MATERIALS AND METHODS

A. Samples Collection and Processing

A pilot study involving patient recruitment and blood sample collection was carried out at "Città di Lecce" Hospital-GVM Care & Research under the supervision of a cardiac surgeon. Sample collection and processing were conducted in accordance with the principles of the Declaration of Helsinki and with all applicable national and institutional guidelines. The study protocol was reviewed and approved by the local Ethics Committee (approval number n. 685 of 16/09/2024). Written informed consent was obtained from all participants prior to sample collection. The enrolled sample population was divided into three groups, each consisting of 20 subjects, namely two case groups (CS-1 and CS-2) at different cardiovascular severity levels and one control group (CN). No formal sample size calculation was performed and the cohort size was determined by the availability of subjects during the recruitment period. Accordingly, the results should be considered preliminary and require validation in larger independent cohorts. The CS-1 are CVD patients undergoing elective cardiac surgery (coronary artery bypass grafting - CABG) or percutaneous coronary intervention (PCI, formerly known as angioplasty with stenting) for severe coronary stenosis (case group CS-1). The CS-2 are CVD patients who do not require cardiac surgery or PCI, do not have severe stenosis, and are eligible for treatment with appropriate drug therapy (case group CS-2). The CN are control subjects are orthopaedic patients without atherosclerotic lesions. Morning fasting blood samples were collected via venipuncture into sodium citrate tubes and gently shaken. Aliquots (2 mL) of whole blood were transferred into headspace vials (7 mL) capped with an assembled screw cap with hole with PTFE septum and immediately frozen and stored at -20°C till analysis by SPYROX e-nose. The frozen samples are thawed at room temperature and subsequently the vials are immersed in dry bath keeping at room temperature (25°C) and connected to e-nose fluidic for Volatilome stripping into sensor cell by dynamic headspace mode. Although the cohort size is limited, this work adopts a subject-independent validation strategy and multiple measurements per subject to improve robustness of the classification results.

B. SPYROX Electronic Nose Architecture

The SPYROX e-nose, whose architecture is depicted in Fig. 1 and detailed in [12], [13], is adopted in this work. It includes 8 commercial gas sensors in addition to 5 custom-designed gas sensors, all realized with MOS sensing technology. The used gas sensors, both commercial and custom, are reported in Fig. 1 and are mounted on 2 separated modules, each including its dedicated gas chamber. These are connected in series, as depicted in Fig. 1, thus achieving a 13-sensor array system. The experimental results will prove that the addition of the second cell enriches the diversity of the acquired response, ultimately leading to improved classification performance. From a system-level perspective, the e-nose consists of two main subsystems: a pneumatic unit and an electronic control and acquisition unit. The pneumatic system regulates, through a miniaturized piezoelectric pump, the gas flow from the headspace of a sealed vial to the sensing chambers. The electronic system, instead, coordinates the overall operation, including sensor heating, timing control, data acquisition, and communication with an embedded PC. The entire setup is enclosed in a suitable plexiglass case for laboratory environments. The hardware implementation includes a mainboard which is connected to the sensor modules.

Regarding the analog front-end (AFE), given the wide resistive dynamic range (DR) of MOX sensors it is designed to accomplish the readout of such high DR by keeping high sensitivity. To address this challenge, a multi-range voltage divider architecture is adopted. More specifically, the proposed AFE employs predefined voltage thresholds to determine when to switch between adjacent ranges while maintaining near-optimal sensitivity throughout. As a result, the e-nose can provide accurate sensor measurements, which are fundamental for subsequent data processing and ML-based classification.

C. Feature Extraction and Data Analysis

E-noses produce high-dimensional, multivariate signals with strong inter-sensor correlations, temporal drift, and variability across sessions or devices. These characteristics challenge conventional classifiers (e.g., LDA, SVM), which often struggle to generalize, especially

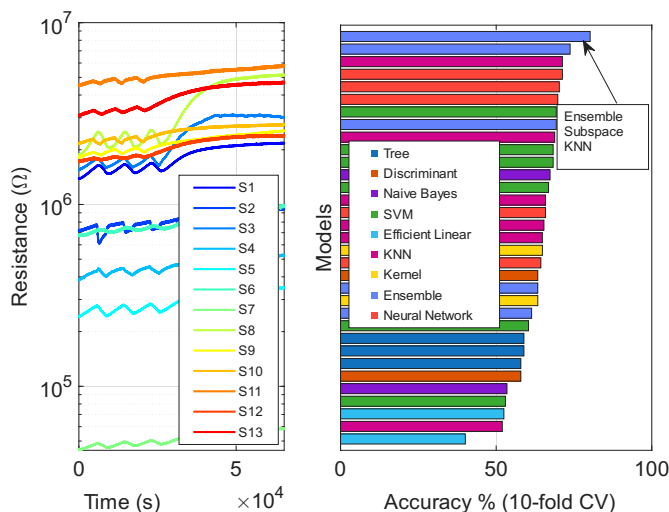


Fig. 2. (left) Example of raw resistance signals acquired from the sensors as they are exposed to a CS-1 blood sample. (right) Comparison chart with mean accuracy obtained by different ML models with standard 10-fold CV.

under limited labeled data and the curse of dimensionality, leading to overfitting [14]. Ensemble methods address these issues by combining multiple learners to improve robustness [15], [16]. More specifically, random subspace techniques train classifiers on different feature subsets, enhancing diversity and reducing the impact of noisy or redundant sensors [17], [18]. This is well-suited for e-nose data, where sensor subsets may capture complementary chemical information. The data flow, involving the model training and test, is depicted in Fig. 1. The validation strategy, involving the trained model is also critical. Standard CV with random partitioning can yield overly optimistic results when samples are correlated due to information leakage [13]. Group-wise CV mitigates this by assigning all samples from the same group to a single fold, ensuring testing on truly unseen data and more realistic performance estimates.

III. EXPERIMENTAL RESULTS

A. Measurements

The measurements are obtained by alternating between gas exposure (20 min) and recovery (40 min). Sensor resistance decreased during exposure and returned toward baseline during recovery, when clean air was flushed through the series-connected gas cells. A 40 min pre-conditioning ensured steady-state operation. Resistance signals were acquired from both modules and sent to an embedded PC (GUI block in Fig. 1) for storage and analysis. Fig. 2 (left) shows an example of raw resistance signals under CS-1 exposure. Referring to Fig. 1, the raw responses were preprocessed for feature extraction, yielding a dataset of size 13 (sensors) $\times$ 202 (observations). For each sensor, a single feature was extracted, corresponding to the normalized negative peak response with respect to the preceding baseline resistance in clean air ($\Delta R/R_0$), i.e., the maximum normalized resistance variation recorded during exposure to the gas sample. Since each sample underwent 3-5 exposure-recovery cycles, multiple observations were extracted per subject, increasing the dataset. Group labels were retained for the subsequent group-wise validation. It is important to note that MOX sensors are cross-sensitive and do not

selectively detect individual VOCs. The e-nose approach instead relies on collective sensor response patterns that form a chemical fingerprint, with classification performed through multivariate pattern recognition rather than compound identification. Ambient temperature and humidity are known to affect MOX sensor responses by modifying the adsorption/desorption equilibrium at the sensing surface and consequently the baseline resistance and sensitivity [19]. In this work, these effects were mitigated by controlled operating conditions and by the closed pneumatic architecture of the SPYROX e-nose, while the influence of high humidity on biological samples was previously evaluated in [12].

B. Results and Discussion

The performance of the proposed electronic nose system was evaluated for classification of the CVD patient categories. A preliminary comparison of several ML models was conducted to identify the most suitable approach for the available dataset. Based on mean accuracy using standard 10-fold CV with random partitioning, the best-performing model was the ensemble subspace KNN classifier, achieving 82%. The comparison of the models is shown in Fig. 2 (right) and all the metrics in these conditions are reported in the red column of Table 1. After selecting the model, training and validation were repeated using 10-fold group-wise CV. The resulting metrics, from classification, are reported in the green column of Table 1. As expected, the resulting mean accuracy drops to 76% ($\pm 15\%$), providing a more realistic estimate of generalization to unseen subjects. The relatively high standard deviation reflects inter-subject variability in volatilomic profiles, which is expected in biomedical data and supports the need for subject-independent validation. In contrast, standard 10-fold CV overestimates performance due to information leakage between samples from the same individual. The model achieved a balanced accuracy of 69% ($\pm 19\%$), indicating moderate consistency across the three classes, though some class-dependent difficulty remains. This is supported by macro recall (69% $\pm 19\%$) and macro F1-score (67% $\pm 19\%$), showing uneven sensitivity and precision across categories. The weighted F1-score reached 76% ($\pm 14\%$), consistent with the overall accuracy. A full set of metrics is reported in Table 1, along with a comparison with state-of-the-art.

The contribution of the custom-made gas sensors was also assessed. As shown by comparing the yellow column (metrics from 8 commercial sensors only) with the green column in Table 1, the mean accuracy increases from 67% to 76% under identical conditions. This improvement is consistent across metrics, confirming that gains are not limited to a single indicator. The enhanced performance suggests that the custom sensors provide complementary and discriminative information, likely capturing volatile patterns not fully detected by the commercial sensor array in cell 1. Despite the reduction in mean accuracy under group-wise validation, the system maintains stable and meaningful performance, demonstrating reliable discrimination across subjects. Kruskal-Wallis tests with false discovery rate (FDR) correction, whose results are reported in Table 2, revealed that several of the most informative sensors, identified by the classifier (namely sensors 4, 5, 9, 10, 11, and 13), exhibited statistically significant differences among the three clinical groups (FDR-adjusted $p < 0.05$).

IV. CONCLUSIONS

An e-nose-based approach for CVD severity was presented, leveraging blood samples instead of conventional breath analysis, thus

TABLE 1. Complete performance comparison.

	This work			[8]	[9]	[10]
Application	CVD vs. Controls			HFrEF vs. Contr.	SCAD vs. Contr. ²	CHF vs. Contr. ²
Biosample	Blood			Breath	Breath	Breath
# Classes	3	3	3	2	2	2
# Sensors	13	13	8	19	19	-
Sample Size	60			60	48 ²	206 ²
ML Model	Ensemble KNN			SVM	SVM	PLS-DA
Validation	Group CV	Rand. CV	Group CV	Train/ test rand.	Train/ test rand.	Rep. k-fold CV
Accur. (mean)	76	82	67	85	81	81 ³
Accur. (std)	15	7	11	5	5	-
Balanced Acc. (mean)	69	82	56	-	-	-
Balanced Acc. (std)	19	7	12	-	-	-
F1 (mean)	67 ¹	82 ¹	56 ¹	85	-	-
F1 (std)	19 ¹	7 ¹	10 ¹	6	-	-
Weighted F1 (mean)	76	82	70	-	-	-
Weighted F1 (std)	14	7	12	-	-	-
Precision (mean)	67 ¹	84 ¹	60 ¹	85	-	-
Precision (std)	18 ¹	7 ¹	9 ¹	6	-	-
Recall (mean)	69 ¹	82 ¹	56 ¹	86	83	80
Recall (std)	19 ¹	7 ¹	12 ¹	8	7	-

¹ The values are reported as macro-averaged values across classes.

² Only "diseases vs. controls" are considered for comparison.

³ Specified with 95% confidence interval (69%–89%).

TABLE 2. Significant sensor features.

Sensor	4	5	9	10	11	13
p (KW)	0.0060	4.2e-05	0.0025	8.5e-05	0.0002	0.0052
p (FDR)	0.0131	0.0006	0.0082	0.0006	0.0009	0.0131

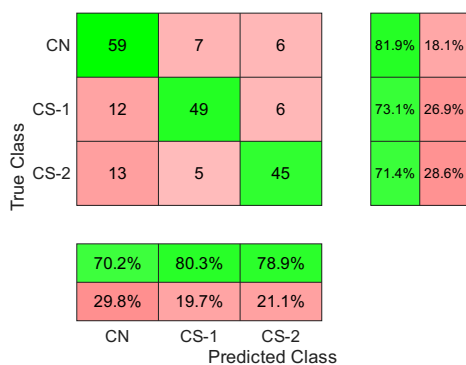


Fig. 3. Confusion chart from training and group-based CV.

improving standardization within clinical workflows. The proposed method extends existing e-nose applications by enabling 3-class discrimination among controls and two levels of disease severity, allowing for finer clinical stratification. A subject-independent validation, based on patient-level group-wise cross-validation, was implemented which prevents information leakage and provides a more realistic estimate of model generalization. Under these conditions, the system achieved an accuracy of 76% ($\pm 15\%$). The results prove the efficacy of combining optimized gas sensing technologies with robust validation strategies in e-noses for biomedical applications.

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