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Advanced methods for teaching electronic-nose technologies to diagnosticians and clinical laboratory technicians

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Abstract

Electronic-detection technologies and instruments increasingly are being utilized in the biomedical field to perform a wide variety of clinical operations and laboratory analyses to facilitate the delivery of health care to patients. The introduction of improved electronic instruments for diagnosing diseases and for administering treatments has required new training of laboratory technicians in order that they may perform routine clinical operations, point-of-care testing, and laboratory analyses using these new diagnostic tools. Continuous education and competency of clinical laboratory technicians in the proper use of these new healthcare tools, such as electronic-nose (e-nose) devices, is required to obtain accurate and timely information needed for making patient management decisions and for developing better and more efficient treatments for patients than are possible with conventional methods. E-nose devices are ideal instruments for the rapid detection and diagnosis of disease via detection of specific volatile organic compounds (VOCs) that are effective bioindicators of disease found within human breath, fluid and tissue samples sent to clinical laboratories for analysis. The proper training of technicians in the effective use of e-nose instruments for healthcare applications requires thorough understanding of the theoretical workings of e-nose devices and practical knowledge of specialized methodologies. This paper provides a summary of some advanced e-nose methodologies and techniques necessary for training clinical laboratory technicians in the proper use and operation of e-nose devices.

Keywords: Analytical instrument operation, Clinical technicians, E-nose methods, Teaching research methods, Science education.

1. Introduction

Many types of electronic-detection technologies have been developed for numerous applications in the biomedical field. Some of these technologies include biosensors, Biological Micro-Electro-Mechanical Systems (BioMEMS), Nano-Electro-Mechanical Systems (NEMS), Molecular Imprinted Polymer (MIP) microsensors, Electroconductive hydrogels (ECH), porous polymers and resins, and Electronic Aroma Detection (EAD) devices such as electronic-noses [37]. Electronic-nose (e-nose) technologies have been developed and used for medical

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diagnostic applications since the mid-1980s when it was discovered that disease and disease-causing organisms could be detected in vitro and in the human body by sensing aberrant compounds produced by diseased tissue that are not present in normal healthy tissues [35]. These aberrant volatile organic compounds (VOCs), often referred to as bioindicator compounds, are organic chemicals consisting of primary and secondary metabolites produced by pathogenic (disease-causing) microorganism themselves or as a result of aberrant metabolic pathways induced in host tissues as a result of pathogenesis. Since the early discoveries of e-nose biomedical applications, it has become clear that there are many other potential uses of these diagnostic gas-sensing devices in healthcare and medicine [36, 37]. Indeed e-nose devices subsequently have been found to be ideal devices for various diagnostic applications within the biomedical field.

Didactic methods and procedures for teaching electronic-nose protocols and operational procedures to clinical laboratory technicians have been published previously based on teaching methods applicable for different phases of e-nose training [38]. These methods have addressed means for applying existing teaching techniques used for training hospital residents, medical students, as well as nurse preceptors or proctors and clinical diagnosticians to be applied specifically for training laboratory technicians in the theory and effective operation of e-nose instruments for clinical diagnoses [11-13, 16, 20, 23, 27]. They include methods for improving the teaching of basic educational requirements for laboratory technicians [6, 22, 28, 30, 39], clinical theory and practice via interactive instructor-to-student feedback, one- and five-minute preceptor techniques [3, 15, 24-26], and ambulatory-medicine teaching methods [8, 17, 18]. The current paper provides some additional advanced details of how these teaching methods can be applied specifically to laboratory methods used in each of the various steps involved in e-nose analytical procedures used in diagnostic clinical (chemical) laboratories. E-nose laboratory methods and analytical procedures are described here with specific recommendations of key factors that improve the performance and effectiveness of instrument operations when applied at each step in analytical processes. Incorporation of these key factors within the training program consequently should improve the quality of training received by laboratory staff and ultimately result in more effective and higher quality results obtained from e-nose analyses.

2. Electronic-nose methods development

The process of developing methods for electronic-nose analyses, whether for clinical point-of-care testing (POCT) or laboratory analyses of samples for diagnostic determinations, involves a series of steps that generally follow the same pattern of activities regardless of the type of aroma (gas) samples to be analyzed. A generalized flow chart of activities, showing the most common steps involved in e-nose methods development and analyses, are presented in Figure 1. The process generally begins with the input of air into the instrument which is passed through a series of filters to remove various types of gaseous and particulate contaminants that may affect or interfere with the analysis. This step may be modified slightly if the input into the instrument is accomplished with the use of an auto-injector device. Most of the moisture in the intake air must be removed because the sensor arrays of most e-nose devices are quite sensitive to the presence of moisture in the sample air. Gaseous water can adhere to and overload individual sensors, precluding the detection of VOCs in the sample. Input air must be allowed to receive and accumulate VOCs from the sample within the sampling bottle during an equilibration period when sample headspace volatiles (VOCs) are allowed to build prior to release into the sensor array. Individual sensors in the array respond to changes in electrical resistance as a result of the adsorption of analyte VOC compounds to the surface of

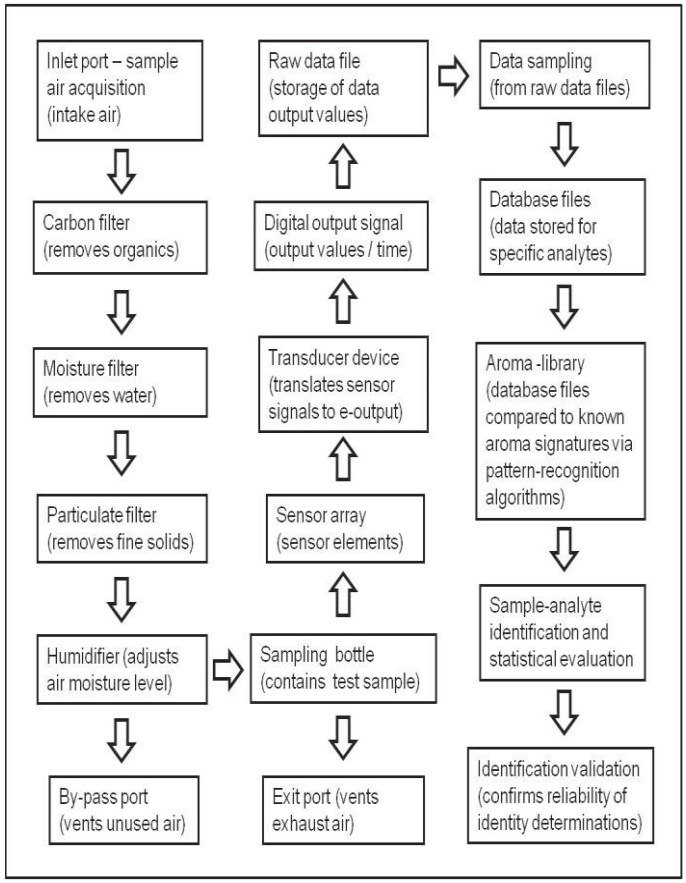

Figure 1. Electronic-nose sample introduction and sample-analysis flowchart

the sensors. A transducer device then translates the electronic signal from each sensor into a digital (or numerical value) that is collectively recorded as the output from the sensor array. Subsequent steps involve the conversion of raw data into database files that are analyzed for validations, statistical evaluations and sample identifications.

2.1 Aroma analyte-sampling method types

Sampling methods for data acquisition from analyte-gas mixtures within electronic-nose devices have a large impact on the uniformity of signal output from an e-nose sensor array. Static sampling, involving the sampling of headspace volatiles from a static air mass within the sampling chamber, generally provides more uniform and stable data outputs than other sampling methods such as dynamic stripping and equilibration sampling [34]. The main advantage of static sampling over other methods is that static sampling avoids the dilution of headspace volatiles which increase sensor stability and sensitivity due to avoidance of perturbations and mixing of sampling air within the sampling chamber. Avoidance of continuous mixing and dilution of sampled air prevents wide variability in sample-analyte concentrations that come in contact with the e-nose sensor array. Instrument architecture and plumbing can be modified so that sample air is vented during sample introduction to avoid these dilution effects. Samples may be introduced from a closed sampling chamber without reference air introduction to maintain uniform sample concentrations during data acquisition. Elimination of headspace dilution effects has also been resolved by

using auto-injectors for e-nose sample introduction and small sampling-chamber volumes for building headspace volatiles prior to introduction into the sensor array.

The sensor array in an electronic-nose is composed of incrementally different sensors that are chosen to respond to a wide range of different chemicals or chemical classes in order to discriminate diverse mixtures of possible analytes. Each sensor in the array produces an output that is collectively assembled to form a distinct pattern of responses (digital fingerprint) which allows the classification and identification of the analyte sample. Thus, the output from the sensor array is integrated to yield a unique signal for a simple or complex mixture of volatile organic compounds (VOCs) present in the headspace of the analyte sample.

The specific number, types and combinations of sensors utilized within e-nose sensor arrays provide opportunities for customization of analytical methods for a wide diversity of analyte sample types and applications. Application-specific sensor arrays are smaller, less expensive, and provide more effective analyses due to the narrower range of possible analytes to be identified. The availability of a wide diversity of e-nose gas-sensor types for designing and customizing sensor arrays for specific biomedical applications allows the production of small, mobile devices for virtually any diagnostic application whether it be the detection of bioindicators of disease, specific pathogen types, aberrant metabolites, or the monitoring of blood glucose and hormone levels. For example, the selection of sensor-array components to detect microbial pathogens may depend upon the particular type of microbe being detected and the type and range of volatile metabolites produced by specific groups of microbes. Pathogenic bacteria tend to produce a greater diversity of more oxidized metabolites (aldehydes, and carboxylic acids), while pathogenic fungi tend to produce more reduced compounds (alcohols, ketones, and esters). Such information is useful for selecting sensors most sensitive to specific classes of organic compounds that are produced by specific groups of microbes. Sensor array flexibility can be further improved by selecting which sensors will be used in the analysis. In laboratory-grade instruments, specific sensors can be turned off when they do not provide significant usefulness in the discrimination. In this way, it is possible to refine the sensor array to limit it to the fewest number of sensors that will provide effective discrimination for each microbial class. However, the specific sensor combination used must be consistent with the sensors used in building reference libraries. Reducing the number of sensors used in an analysis is useful in the development of cheaper portable units for specific applications. Smaller sensor arrays allow for miniaturization of hardware and electronics necessary in portable e-noses.

Consistency and repeatability of data outputs and results between individual e-nose instruments (of the same type and model) also has been a problem in the past due to differences in sensor coating thickness, requiring calibration of sensor arrays and correction of data between individual instruments. This problem was resolved by improved sensor manufacturing (surface-coating) methods to control sensor-coating thickness to a high tolerance.

2.2 Factors for establishing e-nose run procedures and parameters

The development of experimental e-nose run procedures, parameters and methods to define laboratory protocols for specific types of e-nose analyses depends on the type and chemical nature of samples submitted for laboratory analysis and the specific type of diagnostic determinations that are required from the analysis. Such factors as the required sensitivity or detection limits of the test, quantification requirements, and sample-discrimination parameters are important factors to consider during empirical methods development. Analytical methods must provide the precise specific information required for diagnostic determinations or else the method is of little value for clinical decisions and patient treatments and management.

Factors affecting instrument performance and analysis are important considerations when developing run parameters and procedures. The sensor array of most e-nose instruments is strongly affected by the presence of moisture in sampled air. Thus, sample air relative humidity has a large impact on the performance of sensor arrays because they are so sensitive to moisture and easily overloaded by excess moisture resulting in the inability to detect the presence of target analytes. Problems of excessive moisture in sampled air can be controlled with a moisture

filter or dehumidifying unit that adjusts input air relative humidity (RH) to a low level (generally less than 5% RH).

Maintaining low reference air RH assures positive sensor responses in most cases. Effective control of reference air RH using a humidity-control device requires that sample hydration is properly maintained. Some samples that became too dry during cryostorage result in negative (below baseline) responses for all sensors. In such cases, negative sensor responses can be corrected by rehydrating the sample and air-drying to remove free moisture immediately prior to building headspace volatiles during equilibration. Sensor response intensities are affected by sample mass and preparation, equilibration time and temperature, and reference air quality. Sample mass and equilibration times affect the concentration of headspace volatiles. Standardizing sample preparation and equilibration methods helps to control the sample size releasing volatiles for headspace accumulation. Reference air carbon and fine-particulate pre-filters provide assurances of air quality introduced into the sampling chamber. Instrument precision is very high when these controls are strictly maintained.

2.3 Neural net training with known sample analytes

A typical electronic-nose instrument generally consists of a multisensor array, an information processing system such as an artificial neural network (ANN), software with digital pattern-recognition algorithms (PRAs), and reference libraries to discriminate samples by their unique aroma signatures [34]. The ANN is configured via a learning process using software with PRAs that look for differences between patterns of aroma classes (specific aroma types) present in an aroma reference library. This process is allowed to continue through a process called neural net training until a previously specified level of discrimination (determined by preset parameters) is met. The results from these aroma comparisons are subsequently validated and collectively assembled into the aroma reference library to which unknown samples may be compared for classification and identification. The comparison of aroma signatures of unknown samples vs. known aroma signatures in the library is based on the distribution of odor attributes or elements that the unknown sample analyte pattern has in common with aroma patterns present in the databases of the reference library.

A number of different instrument parameters must be set before running neural net training algorithms. These parameters determine the discrimination specificity and limits to be used in making determinations of the relatedness of an unknown sample analyte compared to known aroma patterns present in the reference library. The neural net training parameters, depending on the available choices in individual e-nose instrument operational software, include such options as training threshold, recognition threshold, number of elements allowed in error, learning rate, momentum, error goal (e.g., P#0.05), hidden nodes, maximum iterations (epochs) of the data, and use of normalized vs. non-normalized (actual sensor intensity) input data. These parameters may be modified for specific applications or for improvement of sample-recognition accuracy. A typical training requires 2-35 minutes, depending on the size of the database applied, using an IBM-compatible personal computer with a minimum of 64 mb of random access memory (RAM) and 350 MHz run speed. Neural net trainings are validated by examining training results that compare individual database files for compatibility with its defined aroma class, and usually are displayed using aroma class distributions (percentages) among all aroma classes included in each reference library.

2.4 Aroma reference library construction

Separate aroma reference libraries are usually constructed for each specific diagnostic medical application. For example, aroma reference libraries used for diagnosing diseases caused by specific categories of microbes (viruses, bacteria, and fungi) should be separated and used independently for diagnostic applications. This policy provides more effective diagnoses and reduces the probability of false negative and undetermined test results. All database files may be linked to specific aroma classes for each sample type. Thus, a separate neural net training session should be conducted to create a unique aroma reference library applicable for each microbe category analyzed.

Pattern-recognition algorithms in the analysis software compare signature patterns stored in the reference library to those of unknown samples to look for similarities and differences between these aroma patterns. The differences are often expressed digitally (as numerical values) that are compared in matrix format. The algorithms assign distributions of similar elements found in principal aroma components of the sample that are in common with known patterns in the reference library and then makes a determination of identity based on that distribution.

2.5 Tests and validation of recognition file applicability

Neural net trainings are validated by examining training results that compare individual database files for compatibility with its defined aroma class. The results are displayed using similarity matches of aroma class distributions (percentages) among all aroma classes included in each reference library. Databases that do not conform to specific aroma classes may be omitted from the reference library or the aroma recognition files prior to running unknown analyte samples.

3. Sample collection and preparation methods

The collection of analyte samples prior to clinical laboratory analysis, for the purposes of determining the identification or characterization of sample unknowns, is a very important step for obtaining accurate and effective information needed for patient diagnoses. The number of samples needed for adequate determinations depends on several factors including the effectiveness of obtaining representative samples of the physiological or pathological condition being evaluated, the severity of the condition or ailment under evaluation, the quantity of samples needed for a particular determination or analysis (which may be determined by the required accuracy and detection-limits of the method), and the degree of confirmation (statistical-significance level) needed for the analysis. These are all important considerations necessary to increase confidence in the results.

All of the samples to be collected for diagnosis should be obtained using identical methods and procedures to avoid any variable effects on the quality or characteristics of the sample. In addition, all samples should be taken from the same type, sources, and location of targeted tissues of a patient. Extracted tissue samples or cores should be placed in sealed, aseptic sample containers for immediate transport to the clinical laboratory. Samples that must be transported to the laboratory over large distances should be prefrozen and transported within sample containers covered and surrounded by dry ice within a sealed cooler for overnight transport. If the sample cannot be prepared for analysis and run immediately via e-nose analysis, it should be frozen at -20 C for long-term storage and thawed out immediately prior to sample analysis. This will prevent any addition of unwanted volatiles generated from sample aging or microbial degradation prior to analysis. Tissue samples for cores that became desiccated due to sublimation during cryostorage should be rehydrated immediately prior to analysis, but any free moisture should be removed.

A particular example is the experimental Aromascan A32S e-nose instrument. This experimental model, no longer commercially available, like most other conductive polymer analysis (CPA) e-nose instruments was sensitive to sample size (total amount of organic volatiles or VOCs present) and differences in relative humidity (RH) between the sample and reference gases. Control of sample gas RH to within a specific range above reference air RH was needed to yield the best analytical results [34]. High detector sensitivity to moisture and certain polar compounds, particularly carboxylic acids caused problems in methods development for different types of samples. Dry samples had to be rehydrated in order to facilitate volatilization (when building headspace) to avoid negative signal outputs from the sensor array. Specificity in detection was controlled by the number of iterations used (training duration), confidence level, and other parameters selected during neural net training. Thus, it was possible to detect differences in strains of microbial species if high specificity was used, but this could result in indeterminations if reference library specificity was set too high. Some limitations of CPA included the inability to identify individual chemical species within complex mixtures of metabolic analytes from microbes, to make reliable quantitative determinations (only semi-quantitative), and the long time requirement (up to 30 min) for building head space volatiles prior to analyses. Signal intensity generally was proportional to the quantity of volatiles present, but

not predictably quantifiable. Sample preparation variability and time requirements for headspace building have been largely eliminated by the use of autosamplers.

It is very important that reference libraries are constructed using strains and sample types that originate from the same geographical area or organic source material (such as human tissue or fluid samples) from which unknown samples are to be collected. Sample variability in different geographical areas can have considerable effects on resulting aroma patterns. Thus, attempts to identify samples of a particular type at a location geographically distant from the area where a known reference sample was collected (used in creating the reference library) can result in ambiguous or even incorrect determinations.

4. E-nose pre-run methods and instrument parameters

4.1 Instrument settings

Instrument settings and parameters are largely determined from empirical testing results (for each analyte sample type) to determine the best conditions and settings that provide the most effective results in terms of analyte identifications and discriminations. Laboratory-grade e-nose instruments generally have many more possible instrument settings than portable units. Consequently, methods development and utilization for clinical testing should be instrument-specific as to type and model of e-nose being used for clinical or laboratory analysis. Instrument-specific procedural laboratory manuals are very good reference sources to provide laboratory technicians with information on individual e-nose instrument specifications, control settings, and analytical procedures for use with different types of unknown sample analytes [9]. Practice in operating instrument controls and setting can be effectively practiced using virtual educational laboratories that realistically simulate instrument operations interactively, allowing greater familiarity with operational procedures, controls and methods without the high expense of occupying live online instruments [2, 10, 14]. Similarly, remote-access laboratories provide even more realistic student-training opportunities by allowing remote control of live-training instruments which reduce start-up times and accelerate the learning curve prior to the final live-instrument teaching demonstrations and student certifications that come at the end of the instrument-training process [5, 33].

Required pre-run methods and instrument parameters that must be set prior to sample analyses include such settings as instrument block or sensor temperature (sensor array), air temperature, sample equilibration temperature and time (for building headspace volatiles), sample air relative humidity and flow rate, sample chamber volume, data sampling parameters, data storage path, run cycle schedule, and recognition library to be used. All of these instrument settings and run parameters are determined from empirical tests using test runs with the sample type to be analyzed. Thus, instrument settings are sample-specific because of the large number of sample variables that can affect sensor output such as the nature of the VOCs (chemicals) present in the sample, sample consistency (liquid, solid, powder), moisture content, presence of compounds that may overload (poison) the sensor array, and many other possible physicochemical characteristics of the sample type. A large diversity of different sample types may be received in clinical laboratories for diagnostic analyses including solid excised tissues, body fluid samples (urine, blood, spinal, and organ fluids), and gaseous samples such as exhalation or alveolar air collected from the lung or breath.

4.2 Sampling cycles

Instrument sampling cycles consist of timed intervals for different types of activities during one complete data-acquisition cycle. Data from the sensor array is only one step in the data-acquisition cycle. A typical e-nose run cycle consists of a schedule containing a reference air intake phase, sampling of headspace aroma signatures via the sensor array, a wash with a polar solvent to purge VOCs that have attached to the sensor surfaces, followed by another reference air segment to purge the previous sample volatiles and wash solvents from the sample air stream through the instrument and out the exit port. A reference air purge is then followed by an equilibration period

between runs to allow the next sample headspace volatiles to accumulate in the sampling bottle before the next sampling cycle.

4.3 Sampling parameters

Data slices for further processing and data analysis are generally taken from a timed sampling interval (usually in seconds) near the end of the sampling segment of each run before the sampling-valve is closed. A data slice from the raw data file is used to create a representative aroma class database file. A minimum number (usually at least 10) database files for each aroma class are created from separate replications of each sample type. Aroma signature patterns of individual aroma classes may be averaged to obtain means ± SEM (standard errors of the mean) of raw relative resistance sensor values for statistical comparisons of aroma patterns for each aroma class. Real time determinations of unknown samples utilize recognition files with normalized sensor intensity responses and pattern recognition algorithms and matrices.

5. Post-run procedures

5.1 Data manipulations

Raw data files generated from digital outputs from the sensor array must be converted into database files, through sampling of data slices from the raw data, before statistical analyses are run with database files. Real-time determinations of sample identities can be done using raw data from the sensor array which are compared against the appropriate reference library that contains known database files, representative of the sample being analyzed. However, validations of sample consistency within an aroma class (present in each reference library) requires that databases be created so that the distribution of aroma elements for each aroma class can be determined for individual samples being analyzed and included in each recognition file created with constituent databases included in each aroma library. This process assures that all aroma classes placed in the reference library consist of databases that are representative of each aroma class to a high level of confidence, measured by percentage matches of individual databases to component aroma classes in the reference library. The distribution of percent matches for each sample type, based on aroma classes, indicates the relatedness of sample aroma elements to those of the various aroma classes present among the samples types being compared.

5.2 Statistical analyses

Analysis of data for discrimination of aroma classes and identification can be done with a number of different statistical methods depending on the nature and type of aroma data collected. Some of the more common types of e-nose statistical analysis methods used for aroma data are summarized in Table 1. Principal component analysis (PCA) is the most commonly used statistical comparison for discrimination of aroma classes among unknown samples. PCA methods determine the presence of aroma elements in sample unknowns that are in common with samples from the same aroma class but different from samples from a different aroma class. By this method, aroma elements are expressed in either 2 or 3 dimensions usually plotted using x- and y-axes for 2-dimensional analysis and x-, y-, and z-axes for 3-dimensional analyses. Data points are plotted using plotting units such as eigen values to quantify differences in the distances between principal components of different sample types. Good data clustering suggests good precision and low variability between replications of the same sample type. Thus, PCA aroma maps may be constructed for visual comparisons of relatedness of samples types from different aroma classes.

Common mapping parameters for 2-dimensional or 3-dimensional PCA include number of data passes (iterations) through the data set, minimum errors allowed, scaling factors, and use of normalized or non-normalized input data values. Various types of statistical significance values are calculated to show the significance of PCA determinations and discriminations between sample aroma classes. The types of statistical analyses available for use in association with PCA are usually determined and limited by the specific software programs available for data analysis with individual e-nose instruments. These software programs generally are the same software programs that

control the operation of the instrument and data outputs from the sensor array. Thus, the data analysis capabilities of individual instruments are often limited by the software (and associated capabilities) that comes with the instrument.

Table 1. Data-processing method categories and types for electronic-nose analyses

Method categories	Sub-categories	Method types	Applications	References
Instrument testing	Calibration	Multivariate calibration (MVC)	Inorganic gas detection	[7]
Pattern recognition	Algorithm	K-nearest-neighbor algorithm (KNNA)	Organic refuse detection	[31]
Statistical analysis	Correlation	Canonical correlation analysis (CCA)	Organic hydrocarbon detection	[29]
	Discrimination	Principal component analysis (PCA)	Chemical emissions detection	[1]
		Discriminant factorial analysis (DFA)	Waste-treatment chemical detection	[19]
	Probability	Artificial neural network probability analysis (ANN-PRA)	Toxic industrial chemicals detection	[21]
	Regression	Linear regression analysis (LRA)	Environmental and microbial toxins detection	[4]

The effective teaching of laboratory technicians and diagnosticians in the operational procedures, involved in e-nose clinical laboratory analyses, requires awareness and knowledge of detailed processes required for methods development and operational processes that are specific to these specialized gas-sensing devices. This information is complimentary to various didactic methods described previously for the effective teaching of these specialized methods and processes that are unique to the operation of e-nose instruments, utilized for certain types of laboratory analyses requiring gas-sensing capabilities and aroma-detection methods for diagnostic determinations [38].

6. Clinical evaluations and diagnoses from e-nose analyses

6.1. E-nose applications in primary diagnoses

Electronic-nose devices of various types and operational technologies are used in hospitals and clinical settings to obtain diagnostic information of a patient's physiological state or health condition in real-time, eliminating the need for time-consuming chemical tests that unnecessarily delay application of treatments. Even though the majority of test results obtained from e-nose instruments in the clinical laboratory, either before or after clinical examinations, are used for disease diagnosis or to confirm prior diagnoses using other methods, many other applications of e-nose instruments are employed in healthcare and biomedicine outside of the clinical laboratory [36, 37].

6.2. E-nose applications for confirmation of diagnoses

Electronic nose instruments also may be used as a quick backup test for the confirmation of a previously-determined clinical diagnosis or evaluation to provide confidence that the recommendations for patient care or treatment are appropriate. By this backup confirmational test, the e-nose is used as a redundancy quality assurance (QA) and quality-control (QC) device to assure that mistakes are not made with regard to appropriateness of treatments for individual patients. This application can include not only type of treatments to be applied, but also the quality of treatments applied such as drug type, formulations, and methods of drug delivery. A final real-time confirmation of patient status and diagnosis using fast and reliable electronic devices is a very useful and necessary step to meet higher public expectations of medical standards and practices. More stringent procedures not only avoid treatment mistakes, but also maintain favorable public relations and good reputations of healthcare institutions,

minimizing cases of malpractice which greatly contribute to higher healthcare costs [36]. The addition of electronic noses to help confirm patient status and diagnosis should contribute greatly to the development of more stringent criteria and practices for confirmation of diagnostic determinations prior to application of patient treatments.

7. Conclusions

Electronic-nose devices offer many advantages over conventional diagnostic clinical methods in providing patient laboratory results much faster and often more accurately, allowing earlier detections of diseases and evaluations of patient conditions before symptoms appear. Early treatment of diseases due to early diagnostic detection greatly accelerates the rate of patient recovery and reduces complications due to adverse secondary factors. These analytical capabilities and characteristics of e-nose instruments are compelling reasons for developing e-nose systems for clinical medicine. Continuous monitoring of the physiological states of patients is essential to determine the current condition of patients and whether treatment and recovery is progressing favorably. As an example, the continuous monitoring of serum glucose levels in diabetic patients provides a means of generating alerts when glucose concentration exceeds the normal high and low threshold ranges [32]. Monitoring exhaled VOC biomarkers of endogenous metabolic processes using electronic noses is an ideal means of detecting altered metabolic pathways resulting from diseases such as diabetes [37]. The capability of e-noses to be used as secondary backup sensors for confirming primary diagnoses (made using other methods or procedures) is an effective QA/QC safety procedure to assure that mistakes in treatments do not occur and that patients receive appropriate care and the correct and precise treatments prescribed by physicians.

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