Electronic nose: clinical diagnosis based on soft computing methodologies.

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Electronic Nose: Clinical Diagnosis based on Soft Computing Methodologies

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Abstract—**Recently, the use of smell in clinical diagnosis has been rediscovered due to major advances in odour sensing technology and artificial intelligence. It was well known in the past that a number of infectious or metabolic diseases could liberate specific odours characteristic of the disease stage and among others, urine volatile compounds have been identified as possible diagnostic markers. A newly developed electronic nose based on chemoresistive sensors has been employed to identify *in vitro* 13 bacterial clinical isolates, collected from patients diagnosed with urinary tract infections, gastrointestinal and respiratory infections, and *in vivo* urine samples from patients with suspected uncomplicated UTI who were scheduled for microbiological analysis in a UK Health Laboratory environment. An intelligent model consisting of an odour generation mechanism, rapid volatile delivery and recovery system, and a classifier system based on a neural networks, genetic algorithms, and multivariate techniques such as principal components analysis and discriminant function analysis-cross validation. The experimental results confirm the validity of the presented methods.**

Index Terms—**Neural networks, Genetic algorithms, Electronic noses, Microbial analysis.**

I. Introduction

There is increasing worldwide awareness that bionics and artificial intelligence (AI) will play an important role in many aspects of human activity. Medicine will be no exception, new socio-economical factors and the needs of an evolving global community are demanding the development and application of new intelligent diagnostic and therapeutic near-patient or home-based devices to control disease more effectively [1]. Advanced information technology and satellite communications combined with new intelligent sensors could result in the ability to monitor and control the worldwide spread of diseases like tuberculosis (TB), AIDS, cancer, metabolic diseases and gastric disorders such as *Helicobacter pylori* (HP) infection [2]. Since the early report of an artificial electronic odour detection system by Persaud & Dodd [3], a substantial amount of research has been targeted on the development of novel integrated gas-sensing systems. The potential applications for the Electronic Nose technology are very extensive. Those industries that are using or could use this technology include Food & Drink, Chemical, Petrochemical, Packaging, Pharmaceutical, Flavours & Fragrance, Environmental, Health and Security [4]. Over the past few years there have been an increasing number of attempts to apply artificial olfactory diagnostics in clinical practice [5]. The diagnosis of disease states is a primary pre-requisite of successful medical treatment and as such is a high priority in any area of clinical science. Microbial infections and related causes of illness seem to be one of the more common problems encountered in the world today and are widely reported by the press, especially when so-called "*killer bugs*" or "*antibiotic-resistant*" organisms are mentioned. In many cases, infection with micro-organisms produces a change in the smell of a person, which can be especially noticeable on the breath, in the urine or the stools. Such changes have been commonly used as an aid to diagnosis of disease and in some countries, smelling the patient or the body fluids of the patient was, and still is, an important tool in diagnosis. In 1986, *National Geographic* published an article on "*The intimate sense of smell*" in which the odour of different diseases was described and in which clinicians state that odour is important in diagnosis, especially in the emergency room.

However a critical step before introducing such "smart" devices into the clinic would be the *in vitro* static or dynamic headspace analysis of microbial volatile compounds, extracted from clinical isolates of UTI, HP and respiratory infections. A metabolite may be described as volatile if it is a gas or has a high vapour pressure under the environmental conditions in which it is liberated from a cell. Organic volatile compounds (VOCs) can affect all forms of life, from the pheromones of insects, the odours of plants, to putrefaction. Whether chemo-messengers intraspecies or interspecies (allelochemics), they form complex dynamic systems of odour mixtures which can affect species behaviour and adaptation. The following table presents some microbial volatiles and their biochemical precursors.

Detecting low numbers of bacterial species in clinical samples usually involves time consuming growth in selective media and subsequent isolation and identification by appropriate diagnostic procedures. Complex volatile mixtures are released during bacterial interaction with the

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host tissue or media, and chromatographic techniques have been used in the past to characterise those species on their gas profiles [6]. Recently some novel biomedical, gas-sensing applications have been reported, such as the diagnosis of leg-ulcer streptococcal [7] and respiratory infections [8], detection of diabetes [9]. Gibson *et al.* [10] reported the characterisation of bacterial classes and growth phase prediction by applying sensor arrays combined with neural networks and other pattern recognition methods.

TABLE I
GENERATION OF MICROBIAL VOLATILES DUE TO METABOLIC REACTION WITH SPECIFIC BIOCHEMICAL PRECURSORS

Bacterial species	Medium	Volatile Compound
E. coli, Klebsiella sp.	Arabinose, lactose	Ethanol
Proteus sp., Klebsiella sp, Staph. Aureus, Pseudomonas sp.	Trypticase soy broth	Isobutanol, isopentyl acetate ketones
Proteus sp	L-methionine	Dimethyl sulphide, methyl mercaptan
Proteus sp, Enterococcus sp. Klebsiella sp	Acatyleholine	Trimethylamine, ethyl acetate
Proteus sp, C. septicum	Broth (complex)	Isobutylamine, isopentylamine, ethylamine
Proteus sp	Phenylalanine , valine leucine	Benzaldehyde, isobutyraldehyde isovelaraldehyde
P. aeruginosa	Broth (complex)	Butanol, methyl ketones, 2-heptanone

Recently, a rapid detection of H*elicobacter pylori* and gastroesophageal clinical isolates employing a wide range of metal oxide and conducting polymer sensors combined with neural networks (NNs) and multivariate techniques as been reported [11].

The objectives of this study are to:

- Introduce the application of a newly devcloped intelligent gas-sensing device in a UK Public Health Laboratory environment;
- Analyse 45 specimens of human urine by the application of an intelligent diagnostic model based on novel generation, detection, and rapid recognition of urinary volatile patterns within 5 hrs of receipt of specimens in the laboratory.
- Discriminate *in vitro*, between 13 bacterial clinical isolates all collected from patients diagnosed with Urinary Tract infections (UTI), gastrointestinal and respiratory infections
- Combine classical NN techniques with advanced AI-based methodologies (GA) to generate a powerful hybrid classification tool; demonstrate the power of a GA, by which a sophisticated NN can be trained for improved generalisation and classification performance;
- Adopt a soft fusion of the outputs of multiple classifiers dedicated to specific feature parameters.

II. EXPERIMENTAL

A. Volatile sensing system

A gas sensor array (Bloodhound Sensors) employed 14 electroconductive polymer, semi-micro, chemoresistors produced by electropolymerisation of the corresponding monomers directly onto the sensor surface. Production of sensors primarily involved doped polypyrroles, polythiophenes and polyanilines with different substitute groups in the polymer structure as illustrated in Fig. 1. The sensor array was also mounted in solenoid valves, which provided the headspace sample with carbon-activated filtered clean airflow of 4ml sec^{-1}. Specific selection and polymer tailoring, doping materials and precise manufacturing process can make each of the 14 sensors consistently responsive to a variety of volatile mixtures.

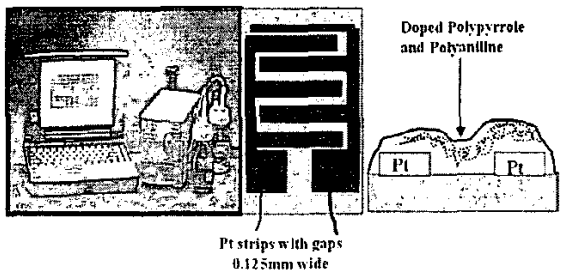

Fig. 1: The Bloodhound gas-sensing unit

The sensor electrodes used were manufactured photolithogra-phically and consisted of a gold interdigitated structure on aluminum substrate with a titanium adhesion layer. Electropolymerisation was carried out by electrode immersion in aqueous or acetonitrile solutions of the monomer and cycling between –0.1V and +0.8V or +1.7V for thiophenes. Teflon upgraded flow cells prevented volatile adsorption onto the housing surfaces. The sensory unit employs a control sample system that generates two calibration points:

- A sensor baseline, which is generated by continuous flow of activated carbon filtered air passing over sensor surfaces and
- A control-sample unit that contains 100ml of sterile water, able to perform a flush-cycle and define a standard reference point.

A specific sampling profile consisted of 5s of absorption time and 16s of desorption time was applied and controlled by specially designed data capture software.

B. In vitro classification of bacterial clinical isolates

The following bacterial species, as illustrated in Table II, were isolated from patients suffering from Septicaemia, Respiratory, wound and Urinary Tract infections (UTI). After primary culture and biochemical profiling and characterisation they were assigned a Gloucestershire Royal Hospital culture collection number.

1) Bacterial volatile generation

The above clinical isolates were recovered on Blood agar plates No.2 (Oxoid), containing 5% sterile horse-blood (Oxoid) for 16hrs following primary isolation, and successful growth the biochemical profiles of all species were identified using conventional microbiological analysis performed at Gloucestershire Public Health laboratory (UK). Each one of the bacterial species was inoculated (10^6 CFU) on blood agar No 2 (Oxoid) containing 5% horse-

blood (Oxoid), urea (1mg ml^{-1}), lactose (2mg ml^{-1}), L-methionine, L-valine and L-leucine (0.5mg ml^{-1}, Sigma) adjusted at pH 7.3.

TABLE II
GENERAL AND BIOCHEMICAL CHARACTERISTICS OF 13 CLINICAL ISOLATES

Species	Hosp. No (GRH PHLS)	Source	Diagnosis/ condition	Biochemical characteristics
Escherichia coli	72999	Urine	UTI	ß-Galactosidase$^+$, Lysine$^+$, Methyl-red $^+$, Ferm.: Lactose$^+$, mannitol$^+$, Xylose $^+$, Indole$^+$
Citrobacter spp.	94513	Blood	Septicaemia	ß-Galactosidase$^+$, Lysine$^-$, Methyl-red$^+$, Ferm.: Lactose$^+$, mannitol$^+$, Xylose $^+$.
Enterobacter cloacae	93986	Faeces	Nosocomial UTI	Extended-spectrum- ß-lactamase, Arginine $^+$, Lysine$^-$, Inositol and Glycerol acid $^-$.
Enterococcus faecalis	72971	Urine	UTI	Acid from: Mannitol $^+$, Lactose$^+$, Sucrose $^+$, Sorbitol$^+$, Hydrolysis of Arginine $^+$, Pyruvate$^+$
Enterococcus spp.	93981	Urine/ faeces	Cystitis	Pyruvate $^+$, melibiose$^+$.
Klebsiella oxytoca	94022	Urine	UTI	Malonate fermentation $^+$, Glucose gas$^+$ Indole $^+$, Urease$^+$, KCN growth$^+$.
Klebsiella pneumoniae	167913	Sputum	Pneumonia	Glucose gas $^+$, Indole$^-$, Urease$^+$, KCN growth $^+$
Lactobacillus spp.	71855	Gastric Juice	Gastric cancer	Catalase $^-$, H_2S gas$^-$.
Proteus spp.	94488	Urine	Bladder Infection	Urease $^+$, H_2S gas$^+$, ß-Galactosidase$^-$, Lactose$^-$.
Proteus mirabilis	94402	Urine	UTI	Urease $^+$, Ornithine decarboxylase$^+$, Lipase $^+$.
Staphylococcus aureus	94707	Wound	Skin lesion	Catalase $^+$, Coagulase$^+$,
Pseudomonas aeruginosa	73021	Sputum	Chest infection	Oxidase $^+$, Gelatinase$^+$, NH_3 from Arginine $^+$.
Streptococcus pyogenes	94777	Throat swab	Sore throat	ß-Haemolysis$^+$, Group A, Ferm.: Lactose $^+$

$^+$ Positive, $^-$ Negative, ^{Ferm} Fermentation, ^{GRH} Gloucestershire Royal Hospital, ^{PHLS} Public Health Laboratory Service, ^{UTI} Urinary Tract Infection.

All bacterial cultures were incubated at 37°C aerobically for approximately 12hrs except *Lactobacillus spp.* that was cultured micro-aerobically at 45°C and pH 6.0. A number of controls containing only sterile cultures were also incubated for the same period of time in order to study the difference between actual bacterial volatile patterns and "noisy" background produced by humidity, sensor aging and natural enzymatic digestion of cultural substrates.

2) Volatile delivery system

Following 12hrs of incubation at 37°C, each of the growing cultures-measured at the stationary phase-were placed into 2l polypropylene Mylar bags and inflated with carbon-activated filtered clean air (Hepavent, Whatman).

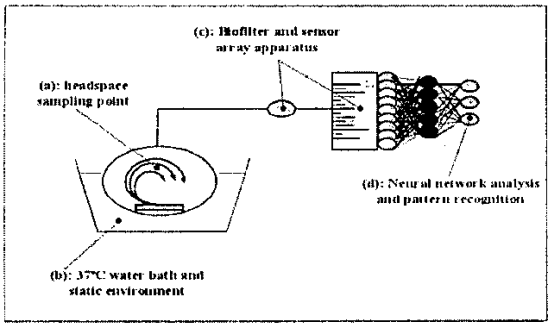

Fig. 2: Schematic representation of experimental apparatus

Each bag was transferred into a 37°C water bath and left to equilibrate for 5min before being connected with the sensory unit through a 15cm long Teflon tubing, a hydrophobic PTFE filter (Hepavent, Whatman), to ensure a sterile less humid environment over the sensor surfaces. The sampling point was adjusted to a set height above the static headspace as illustrated in Fig. 2. A flow rate of 200ml min^{-1} was set automatically by data control software. Additionally environmental conditions at the sampling point, inside the water bath were continuously monitored in order to establish a standardised sampling protocol.

3) Bacterial pattern recognition

Fig. 3 displays a real time sensory response analysed by 5 extracted sensor features that describe sensor-volatile physicochemical interaction and pattern extraction: (a) Divergence: maximum step response, (b) Absorption: maximum rate of change of resistance), (c) Desorption: maximum negative rate of change of resistance, (d) Area under the curve and (e) Ratio Absorption/Desorption. In order to improve the bacterial classification process fourteen conducting polymers and the above 5 features generated a set of 70 sensor parameters. All sensors responses were pre-processed by using a suitable normalisation algorithm [12].

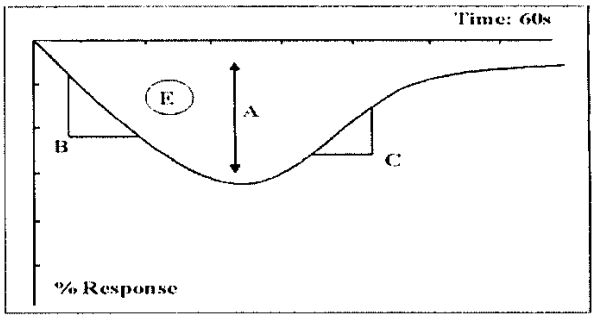

Fig. 3: Parameters measured for each sensor response

C. In vivo classification of Urinary tract infections

UTI is a significant cause of morbidity with 3 million UTI cases each in the USA alone [13]. Thirty-one percent of nosocomial infections in medical intensive care units are attributable to UTI, and it is estimated that 20% percent of females, aged of 20 and 65 years suffer at least one episode per year. There are also links to other complicated or chronic urological disorders such as pyelonephritis, urethritis, and prostatitis[14]. Approximately 80% of uncomplicated UTI are caused by *E.coli* and 20% by enteric pathogens such as *Enterococci*, *Klebsiellae*, *Proteus sp.*, coagulase (-) Staphylococci and fungal opportunistic pathogens such as *Candida albicans* [15]. Current diagnostic techniques require 24-48 hrs to identify pathogenic species in urine midstream specimens (≥ 10^5c ml^{-1}) and apply antibiotic sensitivity tests. Despite the introduction of molecular tests, microscopy and culture remain the gold standard in every day clinical practice.

1) Urine samples and volatile generating kits (VGK)

Forty-five 5ml urine samples (following eukaryotic cell filtering extraction) were collected from randomly selected patients admitted in Gloucestershire PHLS and inoculated into specially made centrifuge bottles (50ml, Sterilin) each containing 95% BHI broth (Oxoid), 5% serum bovine (Oxoid), 0.70mg ml^{-1} of a series of amino acids (L-Leucine,

L-Alanine, L-Serine, L-Valine, L-Asparagine, L-Glutamine, L-Methionine, Sigma), 1mg ml^{-1} Urea (Sigma), 0.75mg ml^{-1} Lactose (Sigma), 0.1mg ml^{-1} Casein (Oxoid), 0.3mg ml^{-1} Acetylcholine (Sigma) to a final volume of 20ml per VGK and incubated aerobically for 5 hrs at 37°C.

2) Flow injection analysis (FIA) of urinary volatiles

After 5 hrs of incubation to coincide with the logarithmic phase of growth, 45 VGK were placed in a 37°C water bath and directly connected with a specifically designed air-filtered sparging (bubbling) system. This consisted of Teflon tubing (Tygon), a hydrophobic biofilter (0.45μm PTFE, Whatman-Hepavent) and an activated carbon filter (Whatman) to provide clean air-flow above the urine headspace. A flow rate of 200ml min^{-1} was set automatically and environmental conditions at the sampling point were continuously monitored. The actual urine sampling time and baseline recovery per specimen was 3 min.

3) Intelligent UTI pattern recognition system

Thirty cases of UTI were identified from 45 randomly selected samples by standard microscopy and culture: 13 patients were infected with E.coli (e), 9 with Proteus sp. (p) and 8 with coagulase (-) Staphylococcus sp., (st). Two genetic training algorithms processed urine data through a parallel evolutionary succession process towards competent NN solutions. The first GA analysed patient data that had been randomly divided into a "training" group of 31 urinary samples (e: 9, p: 6, st: 5 and n: 11) and a group of 14 "unknowns" (e: 4, p: 3, st: 3 and n: 4, 31% of patient collected data).

III. Odour Recognition and Data Analysis

A. In vitro analysis

Two hundred and forty-eight bacterial patterns of 14 classes and 70 normalised sensor parameters constructed a matrix of 17,360 sensor data-items that was analysed by an intelligent system consisting of Radial Basis Function Networks (RBF). Overall, the sensor data matrix was randomly divided into a training group containing 200 bacterial patterns and a testing one of 48 random "unknown" samples.

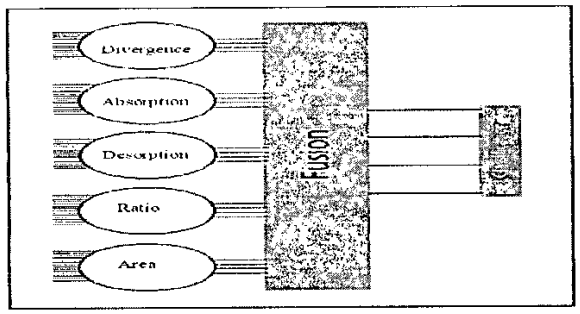

Fig. 4: Multiple Classifier Architecture

Recently, the concept of combining multiple networks has been actively exploited for developing highly reliable neural network systems. One of the key issues of this approach is how to combine the results of the various networks to give the best estimate of the optimal result. A straightforward approach is to decompose the problem into manageable ones for several different sub-networks and combine them via a gating network. The proposed architecture is a neural network system containing five parallel modules, one for each of the bacterial properties as shown in Fig. 4. Each network module makes a classification from a single property and their results are combined, using an averaging approach, to make an overall classification. All modules contain fourteen input nodes and four output nodes. The fourteen input nodes correspond to the fourteen sensor parameters.

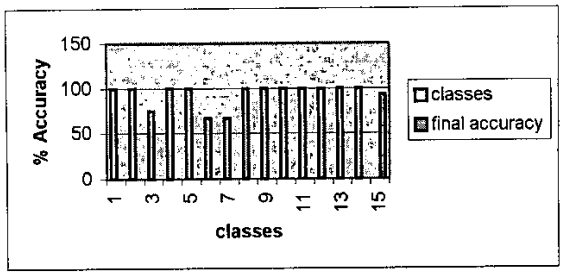

Fig. 5: Fusion analysis results

The four output nodes are sufficient for binary representation of the fourteen classes (13 bacterial classes and the control group). Four binary digits can represent sixteen integers, so each class is assigned one of fourteen binary patterns. Two patterns remained unused. The soft combination of neural classifiers resulted in 93.75% accuracy over the testing dataset, demonstrating in this way the efficiency of this scheme in terms of accuracy and processing-time. The relevant results are illustrated in Fig. 5.

B. In vivo *analysis*

An evolutionary process of 5 generations (3 NNs/ generation) was carried out employing 1 crossover and a mutation rate of 0.5. Additionally the second GA performed a much broader evolutionary optimisation analysis of 100 generations. It also attempted to analyse the same amount of patient data but with a higher ratio of "unknown" proportion (42% of collected patient data) including 26 training samples (e: 8, p: 4, st: 4, n: 10) and 19 "unknown" UTI (e:5, p:5, st:4, n:5). A population of 600 NNs was evolved using an immigration mode, 2 crossovers and a mutation rate of 0.7 towards the "fittest" NN solution.

Both "genetically" selected sensor parameters were also used to perform PCA and DFA-cv. PCA accomplished non-parametrically a significant dimension reduction by minimising minor UTI data variations so that information could be depicted on a few two-dimensional principal component score plots. Two parallel evolutionary algorithms selected 2 NN solutions. The first was a 3-layer (28-12-4) back-propagation NN that used an adaptive learning rate, a momentum of 0.42, an input pattern noise of 0.03 and achieved a 98% prediction rate. Thirteen out of 14 "unknown" UTI samples were identified correctly with

a prediction output confidence ranging from 0.75 to 1.01. The intelligent system failed to characterise only one urine sample previously diagnosed with *E.coli* infection.

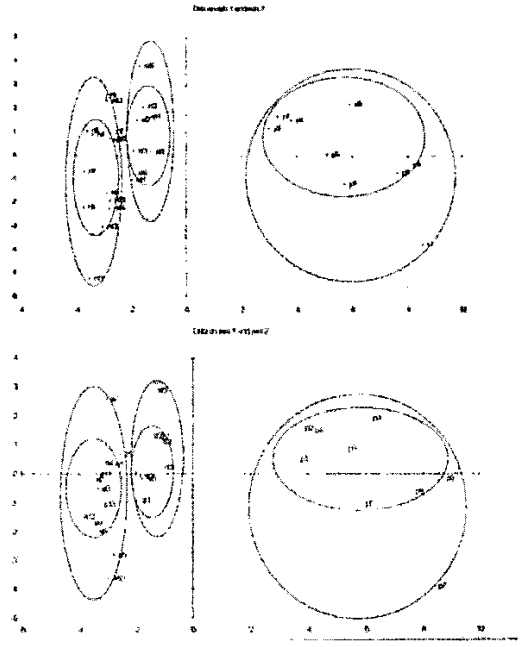

Fig. 6: Extraction of "genetically" selected sensor parameters and two-dimensional representations of PCA clustering between: a. normal urine (n), Proteus sp. (p) and Staphylococcus sp. (st) and b: E.coli (e), Proteus sp. (p) and Staphylococcus sp. (st). (Inner and outer circles divide most closely linearly discriminated patterns from the most drifted ones, respectively).

However, this single pattern confusion was limited to the case of distinguishing between *E.coli* infection and normal urine. Both their prediction confidence outputs were very close-0.37 for *E.coli* and 0.43 for normal urine- but below a 0.5 test tolerance limit.

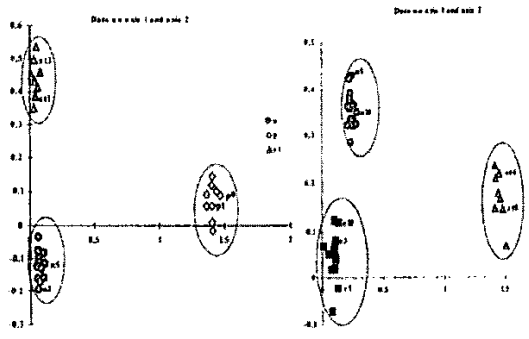

Fig. 7: DFA and 3-group separation between: a. normal urine (n), Proteus sp. (p) and Staphylococcus sp. (st) and b. normal urine, E.coli (e) and Staphylococcus sp.

Twenty-eight "genetically" selected parameters performed PCA and DFA, which displayed two graphical cluster separations between *Proteus sp.*, *Staphylococcus sp.* UTI and normal samples. Cross-validation reclassified correctly 6 "unknown" patient samples (Figs 6a & 7a). Furthermore by extracting all "genetically" selected sensor parameters that had been previously used as input neurones it was possible to reveal hidden non-linear patterns characteristic of each UTI group. Furthermore the second 3-layer NN (22-15-4) achieved a 95% prediction rate and recognised 18 out 19 "unknown" UTI cases. Only one normal patient sample had been mistaken for E.coli infection.

A two-dimensional discrimination plot between 3 of the tested UTI groups (e, st, p) was produced by PCA. DFA also separated patient samples infected with E.coli, Staphylococcus sp. and normal urine samples. Cross validation recognised 7 "unknown" UTI cases (Figs 6b & 7b).

IV. Conclusions

In recent years, antibiotic resistance and the evolutionary emergence of "super bugs" are considered some of the most significant causes of nosocomial infections and have increasingly severe biological, health and economic impact. Conventional diagnostic microbiology requires 24-48hrs to identify each pathogenic species and perform antibiotic sensitivity tests by employing the expertise of skilled personnel, adding significantly to total health care cost. There is need for innovative inexpensive tests to be developed for early diagnosis of infectious diseases and control of antibiotic resistance. The recent use of GC-MS or MS methods accompanied by NN and multivariate analysis although are considered very sensitive, they need highly skilled personnel and are characterised by increasing capital cost. Intelligent gas sensor technology has been applied in several research areas, including biomedicine. Many research groups around the world are actively developing new improved gas sensors with broad sensitivities to certain classes of volatile organic compounds. As these sensors become commercially viable, the EN might well achieve higher levels of acceptance in medical applications.

The present system resulted in the delivery of bacterial odours in the form of repetitive 'sniffs', and achieved higher control by keeping the sampling point, the headspace and liquid volumes constant. Additionally there was continuous monitoring of environmental conditions at the sampling point. There are several advantages in the application of NN models as opposed to other statistical techniques. Their ability to generalise is particularly useful since rough data is often noisy due to some sensor drift. Selecting and constructing the right learning data (input) is crucial in pattern recognition methods. Each class must be composed of representative and reproducible samples. The quantity of these samples does not increase the discrimination confidence instead it is the "quality" of representation carried in each input sample that determines pattern recognition performance. The applied GA-NN technique achieved a high prediction rate and enabled the parallel use of multivariate techniques too, showing a degree of correlation among genetically selected input parameters. The present work proposes a novel application of GA-NN in combination with multivariate techniques in bacterial class discrimination. However, the use of multiple NN fusion is a challenging and more promising approach. The adopted parallel architecture reduces the

dimensionality of the network search space thus increasing both computational efficiency and the probability that optimal network parameters will be found within the search space. Future work will investigate the integration of GAs to the multiple classifier scheme employed however with a more accurate fusion decision criterion, such as the fuzzy integral.

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