

A Software Engineering Framework for Biomedical Diagnostic Systems

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ABSTRACT

Development of intelligent systems to support biomedical applications differs for traditional approaches to systems development. A large number of features needs to be extracted from data and processing of these is not satisfactory by conventional approaches and individuals. Development of such systems greatly changes the amount and nature of information available to physicians, and also the work involved in treating patients. Intelligent systems are learning-based and that makes them easier to adapt when diseases evolve or viruses mutate. This paper presents the use of an electronic nose and a neural network for classification of bacteria. It demonstrates how physicians can utilise it, in order to target their limited resources to specific patients. It also discusses how this work can be generalized in other similar domains and the lessons to be learnt.

Categories and Subject Descriptors

D.2.2 [Software Engineering]: Design Tools and Techniques F.1.1 [Theory of Computation]: Models of Computation, Self-modifying machines

General Terms

Algorithms, Measurement, Experimentation.

Keywords

Biomedical diagnostic systems, neural networks

1. INTRODUCTION

There is increasing worldwide awareness that bionics, data mining and machine learning 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 diseases 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]. In the medical domain, therapies are normally planned on an individual basis. However, it is important to know the characteristics of a group of patients who have the same or similar symptoms. These characteristics can be used to classify symptoms in different categories, each one with similar characteristics, and classify patients. The overall aim of the work described in this paper is used to facilitate the management of treatment of patients through the application and extension of intelligent systems techniques. This is achieved by providing a set of techniques and tools to facilitate classification activities. The use of neural networks for classification is not new in the medical domain. However, development of biomedical applications differs from development of traditional applications. For example, as part of the requirements engineering activity, requirements engineers start from informal and fuzzy requirements expressed by individual users and try to end up with a set of formal, fully understood requirements that represent an integrated view of all the stakeholders involved [7]. However, physicians are not fully aware of what computing technology can offer and therefore it is very difficult to formalise and fully understand their requirements. Their main aim is towards software solutions that will save time and effort and will produce more accurate results than time consuming and inaccurate manual methods. Biomedical applications typically involve classification issues that require the extraction of a large number of features from data, their analysis and the identification of a set of patterns that can be identified as being of interest to physicians. UK Government White Papers [8], [9] describe integrated care as the basis for improving clinical efficiency and effectiveness. This improvement is to be supported by more clinically focused use of information technology and outcome oriented performance assessment. This paper presents a framework for biomedical diagnostic systems and generalises on the findings that are applicable to similar domains.

2. BACKGROUND

Bacterial detection requires analytical methods that can satisfy a series of criteria such as, short detection time ($t \leq 3h$), sensitivity (detection of bacterial concentrations during infection $> 10^5$ cells/ml), specificity (species accurate identification) and low cost. Methods should be rapid and sensitive since the presence of highly virulent bacteria in the human body can cause life threatening complications and immediate antibiotic therapy is usually needed, especially in the case of nosocomial infections. Extremely selective techniques are also required because there are cases in which even low numbers of pathogens mixed with high numbers of normal flora in complex biological samples are responsible for the onset of the

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infection. Conventional identification usually involves morphological evaluation of the micro-organism as well as tests on the species-specific metabolic activity under a variety of conditions. Standard microbiological techniques allow the detection of single bacteria. Amplification of the signal is required through growth of single cell into a colony. However, this process is very time consuming and expensive for hospitals and patients. Enumerating coliform pathogens takes up to 72h, since colony growth to the stationary phase takes between 16-24h. No single test provides a definitive identification of an unknown pathogen. Experts did start to appreciate the mimic of the sense of odour by developing the so-called electronic nose (*e*-nose). The first model of an artificial electronic odour detection system was described during the early 1980s and attempted to mimic some basic functional characteristics of the human olfactory system [3]. The development of instruments that detect and digitally characterise smells by electronic means has been well reported in both the scientific and the topical literature [4]. These instruments, which use arrays of chemically sensitive sensors, have been colloquially dubbed as *e*-noses. They produce a digital response to a complex odour or smell that may then be used to identify or describe that odour by some sort of definitive measure. They are not, in the accurate sense of the term, analytical instruments, but are more comparative in their use and deployment. The past few years have seen some attempts to apply artificial olfactory diagnostics in clinical practice [5]. Diagnosis of disease states is a primary pre-requisite of successful medical treatment and is a high priority in any area of clinical science. Microbial infections and related causes of illness are one of the more common problems encountered in the world today. Infection with micro-organisms may produce 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. 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. Organic volatile compounds can affect all forms of life, from the pheromones of insects, the odours of plants, to putrefaction. Whether chemo-messengers intraspecies or interspecies (allelochemicals) [6], they form complex dynamic systems of odour mixtures which can affect species behaviour and adaptation. Table 1 presents some microbial volatiles and their biochemical precursors. The introduction of intelligent *e*-noses based on gas-sensing devices, shows potential to rediscover the diagnostic power of odours in clinical practice. Due to the low repeatability of the data patterns extracted from these sensors and the fuzzy nature of odour patterns, the use of advanced soft computing intelligence techniques could become a successful tool for diagnosis.

The objectives of this study are to:

- Introduce the application of a newly developed intelligent gas-sensing device
- Discriminate *in vitro*, between 13 bacterial clinical isolates all collected from patients diagnosed with Urinary Tract infections (UTI), gastrointestinal and respiratory infections and reveal hidden bacterial complex patterns by using a learning NN-genetic algorithm (GA) model;

Volatile compound	Medium	Bacterial species
Ethanol	Arabinose, lactose	<i>E. coli</i> , <i>Klebsiella</i> sp.
Isobutanol, isopentyl acetate ketones, 1-undecene	Tryplicase soy broth	<i>Proteus</i> sp., <i>Klebsiella</i> sp., <i>Staph. aureus</i> , <i>Pseudomonas</i> sp.
Dimethyl sulphide, methyl mercaptan	L-methionine	<i>Proteus</i> sp.
Trimethylamine, ethyl acetate	Acetylcholine	<i>Proteus</i> sp., <i>Enterococcus</i> sp., <i>Klebsiella</i> sp.
Isobutylamine, isopentylamine, ethylamine	Broth (complex)	<i>Proteus</i> sp., <i>C. septicum</i>
Benzaldehyde, isobutylaldehyde isovelaraldehyde	Phenylalanine, valine leucine	<i>Proteus</i> sp.
Butanol, methyl ketones, 2-heptanone, 2-aminooctophenone	Broth (complex)	<i>P. aeruginosa</i>

Table 1: Generation of bacterial odours due to metabolic reaction with specific biochemical precursors

- Combine classical NN techniques with advanced AI-based methodologies (GA) to generate a powerful hybrid classification tool;
- Develop a multiple classifier of non-linear pattern recognition problems involving large and noisy data and explore the benefits of a soft fusion method; a hybrid concept of NN methodologies has been adopted;
- Adopt a soft fusion of the outputs of multiple classifiers dedicated to specific feature parameters. One key issue of the approach is focusing to combine the results of the various networks to give the best estimate of the optimal result. In this paper a multiple neural network architecture combined by an evidence fusion technique based on averaging are utilised.

3. EXPERIMENTAL METHOD

Following 12h of incubation at 37oC, 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). Each bag was transferred into a 37oC 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. 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.

4. ODOUR RECOGNITION AND DATA ANALYSIS

A sensory response was 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 sensor responses were pre-processed by using a suitable normalisation algorithm, and then analysed using soft computing techniques.

4.1 Genetically trained neural network (GANN)

In this study, the task of finding NN and database parameters for odour pattern classification has been assigned to a Genetic Algorithms (GA). Two hundred 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 a hybrid intelligent system consisted of a Genetic training engine, a Multilayer Perceptron (MLP) with back-propagation (BP) learning scheme and multivariate methods. The sensor data matrix was randomly divided into a training group containing 177 bacterial patterns and a testing of 71 random “unknown” samples.

4.2 Multiple Neural Network Fusion

Recently, the concept of combining multiple networks has been actively exploited for developing highly reliable NN 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 presumption is that each classifier/sub-network is “an expert” in some local area of the feature space. Sub-networks are local in the sense that the weights in one “expert” are decoupled from the weights in other sub-networks. While a usual scheme chooses one best network from amongst the set of candidate networks based on a winner-takes-all strategy, the current approach runs all multiple networks with an appropriate collective decision strategy. In this study, five sub-networks were developed. Each of them was associated with the five parameters extracted from the sensor response curve. The proposed architecture is a NN system containing five parallel modules, one for each of the bacterial properties/features as shown in Fig. 1. 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. These four output nodes are sufficient for binary representation of the fourteen classes (13 bacterial classes and the control group).

5. IMPACT OF THE APPROACH

In this work the treatment of patients is viewed according to Fig. 2. Classification has divided the symptoms into different classes and physicians can determine the treatment per class. The treatment algorithms (as part of the ‘DO’ stage in the figure) are designed after reference to the available evidence base. This is the standard treatment that physicians would recommend to an individual patient based on individual symptoms. The advantage of the use of classification is that grouping the symptoms and, therefore, the patients, physicians can develop rules of treatment for each group/class. This will save them time and they can spend more time with individual patients that do not seem to respond to the treatment suggested for the class they belong to. Subsequent audits and continuous classification will provide ongoing evidence (the ‘ACT’ stage) for further development of the classification. Changes in classes can also quickly determine evolution of a disease. The developed system will not radically change over time, but it evolves and changes classification (and suggested patient treatment) as more evidence is gathered. The role of physicians in the whole process

changes dramatically. Before introducing the electronic nose and neural network classification they would have to collect a patient’s sample, send it to gas chromatographers (GC) or mass spectrometers (MS) for analysis. Results of the analysis would have to be passed to statisticians who would determine the existence (or not) of bacteria in the samples. The physician would receive this information and after evaluating it would suggest possible treatment. GC and MS equipment are very expensive and therefore are located in central medical or biochemical units in every country. Physicians in remote places would have to send the samples to these units and wait for a number of days to receive the results. Using the proposed approach every medical centre can have electronic nose equipment (which is a much cheaper alternative to GCs and MSs) and the accompanying learning-based intelligent system and perform the whole process themselves in a few hours. The intelligent system produces classification results proven to be superior to the linear statistical methodologies that statisticians/analysts employ [10].

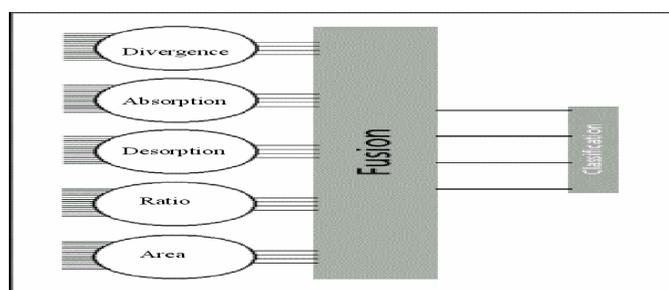


Fig. 1: Multiple Classifier Architecture

The learning approach utilised in this paper is suited in other biomedical areas. For example, in medical endoscopy and colonoscopy microcapsules are beginning to be used. These are swallowed by patients and record images of relevant gastrointestinal organs. The microcapsules will record a large number of video images as they travel within a patient’s body. It is impossible for physicians to study all these hours of video images in order to identify any potential problems. Classification with NNs can be utilised in order to identify potential problems and alert the physicians as to the exact organ that exhibits a problem. Even in other areas, such as bioinformatics, a typical problem is learning and classifying different types of proteins into their mechanistic classes. Again this will be based on a large number of extracted features, such as amino acid composition, length of protein sequence, surface area/molecular weight, hydrophobicity, isoelectric point, amino acid preferences (amino acid interactions in adjacent positions, side chain interactions that are enforced by the helical conformation), secondary structure prediction data (prediction of helical elements).

The application of the electronic nose and adaptive/learning techniques, although successful, has demonstrated that a large number of samples is required and this is very difficult in medical domains. At the same time, this type of application can only be accomplished with supervised learning techniques. This means that an expert needs to initially evaluate the patterns to be trained in order to establish in which category each pattern belongs.

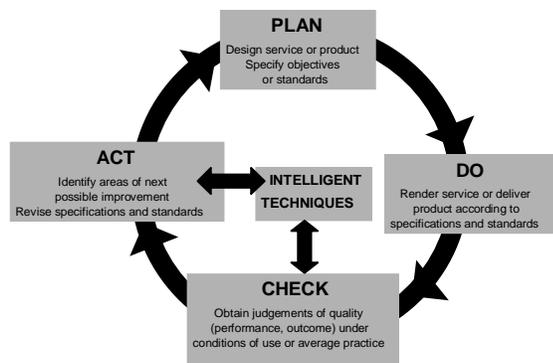


Fig. 2: Treatment of Bacteria Patients

The application of the electronic nose and adaptive/learning techniques, although successful, has demonstrated that a large number of samples is required and this is very difficult in medical domains. At the same time, this type of application can only be accomplished with supervised learning techniques. This means that an expert needs to initially evaluate the patterns to be trained in order to establish in which category each pattern belongs. This type of adaptive systems is suited for guiding experts. They highlight patterns that need special attention. In the case of biomedical applications, the adaptive/learning system can highlight problematic patterns for physician to pay special attention to. The final decision in all cases that are critical (at least in biomedical problems) has to remain with the experts.

6. CONCLUSIONS

The present system resulted in the delivery of bacterial odours in the form of repetitive ‘sniffs’, and achieved high control by keeping the sampling point, the headspace and liquid volumes constant. There was continuous monitoring of environmental conditions at the sampling point. There are several advantages in the application of NNs 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 GANN 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 GANN in combination with multivariate techniques in bacterial class discrimination.

However, use of multiple NN fusion is a challenging and promising approach. The adopted parallel architecture reduces the dimensionality of the network search space and increases computational efficiency and the probability that optimal network parameters will be found within the search space. Binary class representation greatly reduces the number of connections to the

output layer of the neural network, in turn reducing the size of the search space under this architecture. It is hypothesised that the latter also serves to disambiguate classification when modular results are combined, as the combination of four output nodes will be less ambiguous than the combination of fourteen nodes. Another advantage of a modular architecture is the ability to combine network modules based on their classification accuracy when used with different bacterial properties. All networks use the same output scheme, so may be mixed and matched at will. It is assumed that particular properties will be more conducive to classification by some architecture than others. Results showed that under the utilised architecture, weaknesses of individual modules could be compensated by strengths of other modules.

The above approaches can be utilised in other biomedical and bioinformatics areas identified in the previous section.

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