Enterprise in Nanotechnology

Case Study Blue (B).

A Vapour Sensor Array

(Electronic Nose)

Contents

1. Introduction - February 2002

Professor Tibor Zakacs (pronounced *zak'ash*), 56, is a theoretical physicist in the Department of Physics and Astronomy at the University of West Yorkshire (UWY) whose main area of interest is transport in condensed media. After obtaining a degree in physics, he stayed on at Imperial College in London to do a PhD in the quantum electrodynamics of the Kondo effect. After 10 years with Marconi in Germany he returned to university life at UWY. His present research thrusts are directed towards predicting the electrical properties of semiconducting polymers and conducting polymer composite materials eg polymers incorporating nanotubes of metallic nanoparticles in the manufacturing process.

Zakacs has been collaborating with Dr Roberta Bodall over the last 5 years on the design of sensing devices built around arrays of thin-films of conducting polymers. Dr Bodall, 35, took a degree and doctorate in physics at the University of Durham and is also a theoretician specialising in the optical and electronic properties of nanolayered semiconductor structures. She is principal researcher in a project working on quantum cascade lasers funded by the US department of defence.

Three years ago, Zakacs and Bodall, applied for a patent for a sensing device built around the conductivity properties of thin layers of conducting polymers.

Cornel Baudran, a PhD student of Zakacs, from the University of Lannion in France, has managed to fabricate crude precursor devices which demonstrate proof-of-concept.

It was always clear to Zakacs that the success of a vapour sensing array, or *electronic nose*, would depend equally as much on the signal processing aspect of the nose as on the design and construction of the artificial nostrils themselves. Advanced data analysis skills were required which was why very early into the project Zakacs advertised a fellowship in signal processing. The successful appointee was Dr Clark Duquesne who turned out to be perfect for the job with advanced knowledge of not only modern data analysis but also software engineering and microelectronics. A 35 year-old American, Duquesne was the archetypal propeller head whose speech patterns seemed to reflect his preoccupation with mathematical algorithms and software objects. Instead of saying something like, "I had to do the thing about five times before I succeeded", Duquesne's version would be, "I had to go round the loop for *i* equals nought to 4 before I got a return true". Another odd thing about Duquesne was that nobody could ever recall ever having seen him eat anything else apart from Cadbury's Minstrels which he took along with never-ending mugs of strong black coffee. Duquesne had taken a degree and PhD in maths and computing at Berkeley and was working his way round the world solving people's data analysis problems.

2. The Technology

2.1 Intellectual Property

Zakacs and Bodall have two important patents.

Patent 1. Conducting Organic Polymers (COPs)

There is disclosed a conductimetric gas sensor comprising one or more conducting organic polymers; and gas sensitive interrogation means for interrogating a conductimetric property of said one or more polymers; characterised in that at least one of the conducting organic polymers is a substituted polythiophene having a substituent moiety at the 3 position.

A gas sensor can be produced by depositing a layer of a COP between 2 electrodes. The presence of a gas is detected by a change in the direct current resistance of the sensor, typically a few ohms in around 50 ohms, when a gas is adsorbed onto the sensor.

Normally more than one sensor is used with each sensor having a slightly different chemical composition and consequently a different response to each gas analyte. A kind of "smellprint" is therefore produced by the vector formed by the resistance changes in each sensor.

Modern chemometric data analysis techniques such as principal components analysis (PCA) are used to reduce the data to relate the smellprints to chemical identity and to relative concentrations in gas mixtures.

One of the innovations in the first patent was to deposit the sensing COP layer on top of an underlying nanolayer which is laid across the electrical contacts. In this way greater reproducibility in sensor behaviour is obtained. Another innovation was to find certain COPs, renowned for their insolubility, which were more soluble than most others and hence easier to use to create thin films.

The classical advantages of COP sensors are good reproducibility, wide selectivity, ppb sensitivity, reversible sensor response, low power requirements and operation at ambient temperatures.

Patent 2. Method for Detecting Conditions

There is disclosed a method for detecting the occurrence of a condition in a respiring subject comprising the steps of: obtaining an aqueous condensate from respiratory gases exhaled by the subject; detecting certain species present in the aqueous condensate; and correlating the presence of said species with the occurrence of the condition.

Many electronic noses fare badly in analysing directly exhaled breath samples directly due to the high concentration of water vapour which tends to mask the details in the signal. The innovation here was to obtain a condensate of the breath, and sense the headspace vapour above the condensate. Conditions such as pneumonia can be detected.

Also part of the same patent was the use of the sensor to analyse headspace volume of body fluids. For example, urinary tract infection (UTI) could be detected from a urine sample. It is the metabolites of the micro-organisms causing the UTI that are actually detected.

Zakacs, Bodall and Duquesne also have a patent on a data analysis technique. Note here that, at the moment, one cannot patent normal computer programmes (these are subject to copyright). However, one *can* patent a novel design of a neural network designed for pattern recognition, for example.

Patent 3. Neural Net for Analysis of Sensor Array Data

The patent description begins:

"*This invention relates to neural networks, particularly with regard to pattern recognition.*

Multilayer artificial neural networks are commonly used for supervised training problems where input patterns are required to be placed into user defined classes. Such networks consist of sets of processing elements known as neurons or nodes that are arranged into two or more layers . . .

. . . one problem is the need to classify odours into global classes, e.g. floral, fishy, fruity, musky, etc., and then to subdivide each of these global classes into local classes, e.g. jasmine, rose, etc. as a local class of the global floral class."

The patent then goes on to describe the innovative neural network which allows a superior classification process.

3. University of West Yorkshire Enterprise Structure

Establishment of an enterprise and spin-out culture at the University of West Yorkshire is not well-advanced. UWY does not have a lot of experience in creating spin outs and was not successful in obtaining any funds from the government's University Challenge scheme for seed corn purposes. However, there is a newly established not-for-profit company, UWY Innovations Ltd. (UWYI), which is staffed by personnel whose job it is to identify university products and services which are potential candidates for commercialisation and to provide help to the academics involved in the fields of intellectual property rights (IPR), business plans, marketing and finance.

As stated in the university's policy on intellectual property, all rights to innovations made in the course of research by university employees belong to the university (unless under special circumstances where other agreements have been made).

Also, the university will not relinquish the IPR in favour of a spin-out company but will grant exclusive licensing rights. The governing body of the university must give permission for the incorporation of every spin-out company and this will only occur if an IPR agreement has been agreed with the prospective management of the new company. The university, of course, has every wish that the company will succeed and, accordingly, the licensing tariffs are normally set at much more favourable levels than would normally be the case with business-to-business licensing agreements.

UWYI has a team of advisers assigned to particular subject areas. The UWYI adviser whose remit includes nanotechnology is Victoria Gunton, 42, who has a degree and PhD in pharmaceutical chemistry. After university, Gunton spent 5 years as an R&D scientist with a major pharmaceutical company before joining with four friends from university to start up Paisley Pharmaceuticals Ltd which synthesised speciality chemicals to order. With Gunton as Managing Director, this company traded with reasonable success for 8 years before being bought over yielding modest sums for the four founding members and the other shareholders.

In the past 6 months, Gunton has had several meetings with Zakacs and his fellow scientists at which she explained the university's policy on spin-out companies. At the first of these meetings, a spin-out company team was formed which was comprised of the five academics involved. Roberta Bodell agreed to be team leader.

4. Commercialisation

About 500 million urine tests are carried out in the US every year, possibly around 40-50 million in the UK. It costs around £2 to perform a test for a urinary tract infection and the results normally take a day to return. An electronic nose could have the results in seconds.

Cyrano Science's *Cyrano 320* sensor device is having success in many areas, but they haven't yet turned any sharp focus to medical markets despite owning some intellectual property in the field. This was chosen as the particular segment of the market on which to concentrate. Due to the enormity of the American market, one eye had to be on satisfying the American Food and Drugs Administration (FDA) on the reliability of the analysis.

And so a company was formed whose aims initially were to serve the medical diagnosis market.

Zakacs, Bodall, Baudran, Duquesne and Gunton all became directors. Zakacs gave £20K of family money to the project, Bodall contributed £10K and Gunton invested £20K. These sums were eventually to be converted into company shares.

5. Phase 1

The head of the analytical section of the West Yorkshire Hospital was immediately on side when apprised of the potential benefits of the UTI array sensor. He gave permission for some trial tests to be conducted using Baudran's crude prototypes. The tests were a great success. Even with this early stage instrument there were clear positive and negative results. A development programme had to be put into place. The hospital would donate the use of a corner of a lab where the refined device could be tested.

With the first device, there were 12 sensors whose readings were taken by manual switching of the output to an ammeter. The first prototype would take the signal automatically from the sensor array and use off-the-shelf microprocessor and memory chips to control the machine and store smellprints. Up to 100 smells could be stored on the flash memory chip chosen.

The circuit board, microprocessor and memory chip cost around £50.

A machine had to be bought to flash the data onto the memory chip at a cost of £900 plus a computer to control it.

A small pump is required to purge the headspace and direct the vapour over the sensor array (£50)

The unit would display results on an onboard liquid crystal display (LCD) - £100.

The gold leaf and other chemicals for each sensor array cost £30.

The prototype device would be created by rapid prototyping.

Baudran agreed to sign up with the company for a year to develop the device and work with the rapid prototypists given a reasonable salary and a share option. A microbiology graduate would also be required to handle the sampling and develop the methodology.

Duquesne was willing to sign a 1-year contract to work on data analysis as a company employee as long as his terms and conditions were indistinguishable from those of the university and if he had the same access to computing facilities. And he wanted daily supplies of Cadbury's Minstrels as a company perk.

6. The World of Electronic Noses

6.1 Sources of Market Information

Most of the market information in this report has been taken from the following sources:

1. Gassensors web site at www.ipc.uni-tuebingen.de/weimar/nose/gassensors
2. NOSE at nose.uia.ac.be

6.2 Market Size

The global market for instrumental analysis is commonly estimated to be around $18bn.

6.3 Devices on the Market

Table 6.1 lists the companies with commercial e-nose activities with a brief description of their products.

Company	Country of Origin	
Agilent Technology (formerly Hewlett-Packard)	Germany	Uses quadrupole technology to make mass sensor - rugged, stable, reliable. Can ignore dominant components and analyse differentiating factors.
Airsense	Germany	online mass spectrometry
Alpha MOS	France	Instrument combines multiple sensor technology: either Metal-oxide semiconductor (MOS), conducting polymer sensors (CPS) or quartz crystal microbalance (QCM). Technology designed for complex odours & most volatile compounds
Applied Sensor	Sweden	MOSSFET gas sensors for quality control, process control, environmental analysis and medical diagnosis.
Bloodhound Sensors	United Kingdom	See below
Cyrano Sciences	USA	See below
Element	Israel	Established 1992 in cooperation with Science Institute at the University of Iceland. MOS technology. Specialise in putrid fish.
Environics Industry Oy	Finland	Proprietary IMCELL technology, flow through air analysis; electrochemical detection of positive and negative ions
Electronic Sensor Technology	USA	Only US government approved electronic neb. SAW detector validated for environmental monitoring of air, water and soil. Specialises in drugs of abuse, TNT, nitroglycerin, volatile organics in drinking water.
HKR Sensorsysteme	Germany	Founded 1993 by researchers from Technical University of Munich. Highly rated in food and cosmetic fields for ppm concentrations. Portable solution requires laptop data analysis for quartz array acoustic wave sensors
Illumina Inc	USA	Bead array technology for large scale analysis of genetic variation.
Lennartz Electronic	Germany	30 yrs experience in MOS sensors.

		Combines 8 commercially available MO sensors with 8 quartz microbalances for a device which is widely applicable.
Marconi Applied Technologies	UK	Heavy duty player with lot of IPR in MOS, quartz crystals and conducting polymer sensors.
Microsensor Systems	USA	Pioneered SAW sensors. Produce versatile handheld device.
OligoSense	Belgium	Spin off from Imec in Leuven and the University of Antwerp. Oligomeric versions of COPs. Research sensor technology - no commercial device.
Daimler Chrysler Aerospace RST Rostock	Germany	Quartz, SAW, MOS - specialise in space (outer) services.
SMart Nose	Switzerland	Mass spec based.

6.4 Some Details on the Competition

6.4.1 Cyrano Sciences (www.cyranosciences.com) "We digitize smell!"

The most successful electronic nose company is Cyrano Sciences whose hand held device, the *Cyranose 320*, came to market in the first quarter of 2000 and which now retails at around **£6k**.

Cyrano Sciences is a spin-out company from Caltech from which the proprietary technology is licensed with worldwide exclusivity.

Cyrano Sciences has received over $23m in venture capital and private investment.

It has rights to intellectual property on its Polymer Composite Sensor (PCS) technology developed by a number of academics at Caltech. The company itself has 11 granted patents and over 50 patent applications in the fields of PCS, instruments, chips, algorithms, medical diagnostics and digital communications over the internet.

Cyranose Specs

The push of a button on the Cyranose 320 activates a pneumatic pump which takes a sniff of atmosphere through a wand into the testing module then expels it through an exhaust outlet.

Background smell is sampled through a separate inlet so that it can be factored out of the sample.

The sensor is comprised of a ceramic chip containing an array of 32 sensor elements each constructed from a different polymer composite, a conductive plastic which expands in the presence of a specific chemical vapour. Expansion increases the electrical resistance of the polymer and this is the physical property used by the sensor.

The Cyranose 320 is controlled by a 32-bit Hitachi SH4 microprocessor which runs proprietary software which analyses the output from the 32 sensors.

Flash RAM holds a library of several hundred reference smells which are matched to the sensor output.

An analogue output emitting voltage signals corresponding to the sensor output. There are also RS232 and SUB digital output ports.

weight	0.91 kg
sensors	32 bit polymer composite array
battery	NiMH, 4 AA pack or 4AA Alkaline
battery life	3 hours
dimensions	10×22×5 cm
universal power adapter	110-240 V AC external power adaptor
display	320×200 graphic LED backlight
response time	10 s
keypad	scroll up/down, select, cancel, run
communications	RS232 57.6 bps
sampling pump	50-180 cc/min
algorithms	KNN, Kmeans, PCA, CDA
operating temperature	0-40°C
Data Storage	
number of methods	5 on instrument
number of classes per method	6
number of training exposures per class	10
number of saved identifications	up to 100 on Cyranose

Artificial Neural Networks (ANN)

The Cyranose 320 uses ANN technology to train the device to recognise a wide range of smells important in the packaging and food & beverage industries. Some examples given on their web site are:

- quality control of plastic pellet manufacture
- petrol quality control
- basil leaf quality control
- identification of common organic solvents in tankers
- identification of Malabar or Vietnamese pepper
- identification of aircraft fuels

- quality control in cheese flavouring
- identification of lemon and lime raw materials

Another revenue stream for the company is licensing this ANN software which can also be used, for example, in distributed systems to monitor and process data on the Internet.

Mid-term Goals

Crane Sciences aims to shrink the Crannies onto a “nose-chip” cheap enough to be used in smoke detectors and other household or factory-based devices.

6.4.2 Bloodhound Ltd

A spin-out from the University of Leeds formed over 10 years ago. Current products are based on CPS. Recent research has led to gas sensing devices based on discotic liquid crystals (DLC) which are most suited for non-polar analytes.

The BH114 is based on an array of 14 sensors with specialised in-house electronic address and data acquisition systems.

The user-interface is Windows based.

Pulse spectroscopy is a feature unique to Bloodhound - electronic address methods amplify the sensitivity many times allowing the production of a ‘spectroscopic trace’.

6.4.3 Metal Oxide Sensors (MOS)

Made from materials such as tin oxide and chromium titanium oxide, these sensors operate in Wheatstone bridge mode. These have the drawback that they require high temperatures (350-500°C) to work. At this temperature redox reactions occur characteristic of the analyte.

6.4.4 Bulk Acoustic Wave Sensors (BAW) and Surface Acoustic Wave Sensors (SAW)

These sensors are comprised of a quartz crystal coated with a chemically-sensitive film. When deposition occurs the resonant frequency of the crystal changes. The wave studied can either be through the bulk on or the surface. One drawback here is that since these are basically detecting mass changes, one has to design films which are selective to your analyte. This might be difficult for complex mixtures such as UTI sample headspace metabolites.