# The impact of micro and nano sensors in biomedical measurement

Peter Rolfe

Oxford BioHorizons Ltd., Maidstone, Kent, UK
Harbin Institute of Technology, Harbin, China
Advanced Research Inst Science and Engineering, Waseda University, Tokyo, Japan
Tel.: + 44 1442 870785 E-mail: PeterRolfe@aol.com

**Abstract**

This paper reviews the ways in which micro and nano sensors have evolved within biology and medicine. The target measurands include an ever-increasing number of simple and complex molecules, physical quantities, and electrical and magnetic phenomena. Micro sensors based on electrochemical, acoustic, piezoelectric and optical principles are contributing to clinical care of patients who may benefit from the continuous monitoring of critical variables in intensive care or from the ability to perform convenient self-monitoring during normal daily life. Sensors constructed on the nano-scale are now emerging, especially for complex bio-molecules such as DNA. These are strengthening basic research, for example in the study of genetic factors in disease and for discovery of new drugs. Scanning probe technology and nano optics, including surface enhanced Raman spectroscopy, play important roles in these developments. Sensor science and technology has gained significant benefits through inspiration arising from biological sensory systems. This includes the sense of olfaction, which has led to the artificial nose, and the sense of vision that has been emulated in several versions of the artificial retina. The impact of micro and nano sensors on fundamental understanding in biomedicine and on clinical diagnosis and care are highlighted.

**Keywords:** Biomedical measurement, micro/nano sensor, MEMS/NEMS, lab-on-a-chip, cell and tissue engineering, biomimetic sensors, nano optics

## 1. Introduction

Measurement science and technology continue to play vital roles in biomedical research and in routine healthcare. Over recent decades there has been a steady evolution of sensors for biomedical measurement aimed at clinical care in hospitals, fundamental biomedical research in the laboratory, or even self-care in the home [1]. The measurands of interest are diverse, ranging from pressure, force, flow and displacement to electrical field/charge, magnetic flux, and molecular species, such as gases, ions, proteins, bacteria, viruses, and DNA.

The basic study of biological systems has included the detailed investigation of biological sensory mechanisms responsible for the senses of sight, hearing, taste, smell and touch [2]. There have been significant benefits to research in sensor science and technology from the inspiration that derives from these natural sensory systems [3], leading to a variety of activities in so-called biomimicry and biomimetics [4].

Sensor configurations must vary widely to meet the requirements of the measurement site, be it in a blood or tissue sample, or within living cells, tissues or organs. Thus the physical size of the sensor is important in all cases, either in order to reduce the sample volume needed or to minimise the influence that the mere presence of the sensor has on the biological environment in which it is situated. This is where advances in fabrication methods and technologies, such as MEMS and NEMS, play crucial roles and where recent developments have moved the state-of-the-art in terms of sensing phenomena firmly from the micro domain into the nano world. Despite this, complete sensor devices still require appropriate packaging and in many cases this significantly increases the overall dimensions.

## 2. Critical care monitoring with micro-sensors

The most obvious medical impact of microsensors currently is in the clinical care of critically ill patients who may be under intensive care, coronary care or major surgery [5, 6]. Such care involves the continuous monitoring of important physiological variables. The aims are, firstly, to enable changes in the patient's condition to be detected rapidly and, secondly, to assess the effects of therapies so that they can be speedily optimised. Continuous real-time monitoring of key variables can be achieved by attaching sensors to the patient, either on the surface of the body (non-invasive) or directly inside the body (invasive). Figure 1 shows a microsensor attached to a flexible polymer catheter and this can be inserted into an artery or a vein where it can sense one or more measurands.

The range of measurands for which microsensors have been developed is extensive and includes physical and chemical variables. Monitoring blood pressure is vital in critical care and micro pressure sensors based on semiconductor strain gauges are used routinely. Such pressure measurement in these patients can be performed by inserting a flexible polymer catheter into an artery in the wrist. The catheter is filled with saline and then an external pressure sensor can be attached to the catheter. Alternatively, a micro pressure sensor can be inserted directly into the artery, as shown in Fig. 1. In this case the sensing element is a semiconductor strain gauge but interferometric fibre optic sensors based on a Fabry-Perot cavity are also possible [7]. Measurement of pressure inside the head (intra-cranial) or chest (intra-pleural) may be required and these sensors are also suitable for this purpose. For assessing breathing in some patients it is useful to measure respired gas flow and volume and micro anemometers, for example based on thermal dilution, are used routinely for this.

The topic within the clinical microsensors field of most intense research effort has been that of chemical or molecular sensors [8]. Devices have been developed for: blood gases ($O_2$, $CO_2$), ions ($H^+$, $K^+$, $Na^+$, $Ca^{++}$, $Cl^-$), molecules linked to metabolic processes (glucose, lactate, urea, creatinine), drugs, hormones and micro-organisms involved in infection. These sensors can be fabricated with micro-wires (Au, Ag and Pt), of 1 to 20 μm diameter, in amperometric and potentiometric electrochemical devices, encapsulated within a flexible polymer catheter. Alternatively, chemically sensitive FETs can be used, typically for ions (e.g. pH) or, when enzymes are employed, for more complex molecules such as glucose or drugs. Optical sensing is a very important approach for clinical monitoring and glass or polymer optical fibres are widely used as the basis of microsensor construction. These fibres are combined with chromophores or fluorophores to allow a wide range of species to be sensed, including

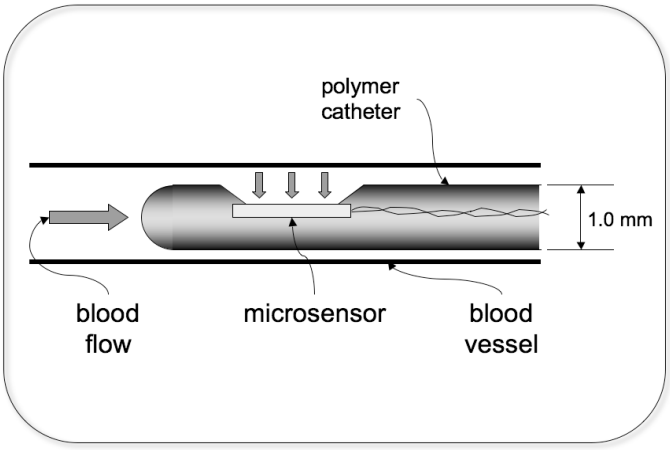




Fig. 2. This shows a microsensor attached to a polymer catheter for direct insertion into an artery or vein. This invasive devices allows continuous real-time monitoring of physical or chemical variables.

gases and ions [9].

The medical impact of microsensor monitoring is being seen in the surveillance of the fetus before and during birth, the intensive care of very small premature babies and the critical care of children and adults.

## 3. Sensor assemblies and arrays

In addition to the importance of microsensors for continuous real-time clinical monitoring there is a growing activity in the development of multiple sensors, both micro and nano, for multi-analyte processing of biological samples, such as blood, urine, tissues and cells, or breath. One important area of work aims to create the so-called 'lab-on-a-chip' [10], in many forms, whereby analyses previously carried out with large-scale laboratory instruments may be performed with simple hand-held instruments. Once samples are removed from a patient, or from a laboratory preparation, a sample chamber is then used for the analysis and this can be a microfluidic or nanofluidic assembly incorporating sensing features. The rapid growth in the development of MEMS and, more recently, NEMS techniques has facilitated the creation of compact analytical platforms with large-scale sensing capabilities.

Analysis of blood samples can be achieved very near to the patient by means of a sensor-chip having an appropriate sample input (see Fig 2 (a)). Once infused or aspirated into the device the sample fluid enters a channel that is configured so as to bring it into contact with a number of sensors, either sequentially or simultaneously. The simplest device can use thick film sensors, for example for measurement of blood gases ($PO_2$, $PCO_2$) and pH. Semiconductor sensors (ISFET, ChemFET, ImmunoFET) are now widely used in this type of device, offering a wide range of possible analytes including gases, ions, proteins, drugs, and hormones. Optical sensors based on semiconductor chips can also be included, offering the enormous power of spectrophotometric analysis. Surface plasmon resonance (SPR) is a further powerful optical technique that has been utilised in sensors for example for receptor or antigen-antibody based sensors.

The application area where there has been the most significant impact of sensor arrays is that of genetic research, which has aimed to establish gene-related predisposition to disease [11]. The DNA microarray (Fig. 2 (b), or gene chip, consists of an array of specific segments of single-stranded DNA attached to, typically, a glass slide and when the matching complementary segment of DNA combines with this – hybridisation - a fluorophore emits radiation. The pattern of fluorescent microdots is then analysed as an image. Microarrays are now being used to study the relationships between genes and the behaviour of cells, for example to discover methods for the early detection of cancers, heart and cerebro-vascular disease, and in tissue engineering.

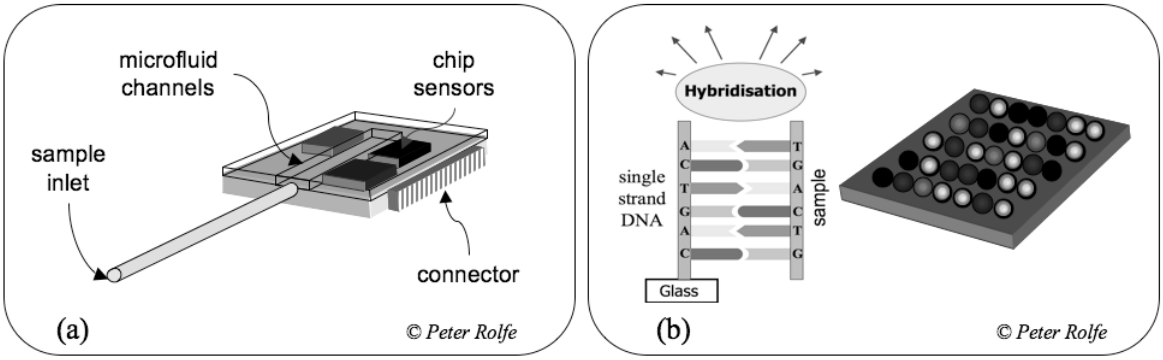


Fig. 2. (a) This shows a sensor assembly with microfluidics and individual sensor chips, suitable for near-patient blood analysis. (b) A DNA microarray is shown. When particular sequences are recognised this produces fluorescent spots and image analysis is then used to derive the results.

Copying nature - *biomimetics* – provides a rich source of inspiration in sensor array development [3, 4]. Biological cells forming the basis of sensory systems for vision, hearing, olfaction (the electronic nose), touch and taste have been emulated in solid-state devices, producing biomimetic chips. These sensor arrays often combine processing in the form of neural networks to achieve very high selectivity and they are beginning to have an impact on the new approach to organ repair and replacement within the field of cellular engineering [3].

## 4. Nanosensing, cells and tissues

Nano sensors are many and various and are already having an impact on cell and tissue research. These sensors are based among other things on optical, electric, magnetic, and acoustic principles [12]. Nanoparticles, nanoshells, nanowires, carbon nanotubes and quantum dots, can be used to create the sensors. Gold nanoparticles (GN) can sense their dielectric environment and this phenomenon can be harnessed in sensor design. The GNs can be functionalised with a molecular recognition element and thereby act as biosensors. Nanoshells, comprising of a spherical dielectric (e.g. silica) core surrounded by a gold or silver coating of a few nm thick, can be interrogated by an appropriate wavelength, from UV to IR, and a plasmon resonance occurs that significantly increases light intensity; surface enhanced Raman spectroscopy (SERS). Nanowire sensors can utilise the measurement of conductivity change that takes place when a macromolecule binds to the nanowire surface.

Semiconductor quantum dots (QDs) can be used effectively to act as fluorescent labels, with $\lambda_e$ dependant on QD size, in cells and tissues, for example to localise or track mesenchymal stem cells when transplanted into tissue or when co-cultured with other cell types [13]. QDs are also now used in an increasing range of sensors [14], for example based on fluorescence resonance energy transfer (FRET) for DNA analysis [15]. Carbon nanotubes (CNs) are offering exciting possibilities for sensor fabrication, due to their unusual electrical and physical properties. A glucose biosensor has been reported in which an array of CNs have been attached to a platinum substrate, glucose oxidase has been immobilised to the CNs, and direct electron transfer from enzyme to Pt electrode has been achieved [16].

## 5. Discussion and conclusion

Micro and nano sensors, assemblies and arrays are being developed and used widely to assist in the continuing advance of biological knowledge and the improved diagnosis and treatment of disease. It is appropriate to link these two types of sensor because in reality micro and nano structures must often be combined in order to fabricate usable devices. This is clearly the case with the sensors that are inserted into arteries and veins for the intensive care monitoring of patients. This may therefore raise the question about the need for smaller and smaller sensing elements, such as QDs that may be around 10 nm in size. In the case of intensive care monitoring sensors the actual problems relate not to the size of the sensing element but to the undesirable interactions (e.g. protein adsorption) that take place between blood and implanted devices, possibly leading to blood clotting and sensor malfunction.

Micro-arrays already have an enormous impact on genetic research and cellular research in general. However, the evolution of nano-arrays is likely to allow more rapid analysis of very large numbers of compounds and this will be especially important in the fields of proteomics, detection of disease markers in clinical samples, and in drug discovery.

Nanoparticles (shells, spheres, rods, wires, tubes, dots) are already finding their way into biological systems including cells and tissues, and also the lungs and gastro-intestinal tract. There is a recognition of the potential risks that such particles may have and every application must be examined thoroughly to evaluate such risks. For example, CdS quantum dots can liberate toxic cadmium if exposed to appropriate levels of UV.

The micro-nano world offers exciting new prospects to achieve sensing of complex molecules that could open the door to the early detection of serious illness though personal health screening.

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