NEMSIC

Hybrid Nano-Electro-Mechanical / Integrated Circuit Systems for Sensing and Power Management Applications

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[1] R = Report, P = Prototype, D = Demonstrator, O = Other

[2] PU = Public, PP = Restricted to other programme participants (including the Commission Services, RE = Restricted to a group specified by the consortium (including the Commission Services), CO = Confidential, only for the members of the consortium (including the Commission Services)

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Executive summary

Within the NEMSIC deliverable D.6.6.1, "Preliminary market analysis and business model", as defined by the DoW from 15/12/2010 v6.9, we are dealing with two interrelated business research directions, as defined in the title of the report. Firstly, we are doing a market research in the field of the gas and "bio" sensing domains for identifying the commercial products and their associated technologies and applications. Secondly, we are trying to develop business models for the future NEMSIC-based gas and bio sensors, in agreement with the major potential applications identified in the report D1.1, of this project, as well as megatrends of our future society with cleaner air requirements and an increased number of older people.

In the field of gas sensing, the market research has revealed a limited number of well established technologies, where the electrochemical and NDIR optical principles are the most extensively used for today's industrial needs, overall the electrochemical technology the most representative for oxygen and toxic gas detection, today. On a horizon of about 10 years, it is expected that low cost semiconductor optical technologies replace the electrochemical technologies and thus respond to most customer needs.

In the field of biosensing, the market research has revealed a limited number of well established technologies, where the surface plasmon resonance (SPR) microarray technology is a serious contender and competes head-to-head with electrochemical detection in both research and application domains. SPR technology provides a non-invasive, label free system for studying biomolecular interactions, thus responding to most customer needs.

The commercial market research documents have revealed the fact that resonant gas and biosensing NEMSIC-based technology is not yet anticipated as an emerging technology for the next ten years, and this fact is revealing once more the basic research character of our NEMSIC project for chemical sensing.

Our report is confirming the results provided by the MNT Gas Sensor Roadmap from 2006 prepared by the MNT Gas Sensor Forum, predicting a more aggressive penetration of the semiconductor optical technology in the commercial gas sensing products of the near future. The data and analysis that we presented in this document are more recent and they include key evolutions observed in the last 5 years, following the MNT report.

By looking at the megatrends in the evolution of our society, and their cascaded impact on the gas and bio-sensing, we are envisioning that the NEMSIC resonant technology with high potential on low cost/size/power consumption coming from integrated circuit technologies like SOI-CMOSFET, and with high sensitivities capabilities coming from high sensitivities of accreted mass resonant detection of NEMS technologies can play the role of future emerging technologies (FET) in the general chemical domain. Thus, applications related to environment monitoring by wireless sensor networks distributed on large ground surface areas or remote health monitoring could be implemented with the help of NEMSIC technologies. It is our belief, that NEMSIC-based integrated gas sensing technologies could play a future role in the 'Guardian Angels" EU-FET flagship

Starting from these considerations we have proposed possible canvas business models for both gas and bio-sensing detection, where companies like Honeywell, with a strong market position on the gas sensing domain can bring the NEMSIC based technologies to the commercial level.

Introduction

The EU-FP-7 program is driving excellence in the European research by defining strategic and ambitious science and technology challenges for the next 10-15 years in order to support EU's medium and long term industrial competitiveness. To perform this strategic vision, the FP-7 is strongly oriented towards future sustainability demands of society as envisioned today from the megatrends like population ageing, rapid decrease of fossil energy resources, exploitation of new renewable energy sources, energy efficiency, climate change, movement of population to sustainable/eco cities, nanotechnology development, and life style and environment preservation. Within the EU-FP-7 programs, the industrial and academic partners are working together to address the challenges and to calibrate the pathway toward implementation of the research results in the next generation of market products.

Our collaborative NEMSIC project is responding to some of the above Information and Communication Technology (ICT) challenges, in terms of pushing the technology and functionality limits of smart micro and nano-systems for gas and bio sensing in the "More than Moore" era, for an increased sensitivity, lower power consumption, high level of integration of the SOI-CMOSFET technology platform for the ultimate realization of future low cost wireless gas sensors able to solve the critical to quality (CTQ) requirements of next generation wireless sensor networks distributed on large areas of the ground for environment monitoring in both industrial processes and residential areas.

In this report we shall briefly describe the market analysis of existing gas and bio-sensing technologies, and then we shall introduce the reader into the megatrends of our society, which will let us know, which are the major megatrends to which our project may offer an answer. Thus, we have created a very good foundation and motivation for the presentation of the market trends in the field of the gas and bio-sensing, trying to identify the emerging technologies in this field.

Our report has confirmed the results provided by the MNT Roadmap from 2006, updating this report with the results and predictions from the last five years. In addition, the present report is creating a first bridge between the megatrends of our society and the gas and bio-sensing technology evolution responding to them, as visionary described in the "Guardian Angels Future Emerging technology (GAs-FET), EU flagship initiative.

In the last part of the report, we shall present possible "Canvas" business models for gas and bio sensors which may be created, on a long term, starting from the resonant NEMS principles.

1. Preliminary Market Research and Analysis in the field of Gas Sensing and Biosensing

Our NEMSIC project is targetting future needs of the gas and bio-sensing market, such as high sensitivies, low electric power/size/cost, high selectivity and real-time communication of the data to user or central server. The complexity of a technology able to respond to all these unmet market requirements, and the time needed to identify the hidden risks will be better elucidated if we realize the gap between present products, technologies and their peformances on one side, and the emerging technologies in the gas-and bio detection and how they all address the future requirements, on the other side. Definitely, NEMSIC based gas and biosensors belong to the future, emerging technologies, and this will become more evident after this comparison of the present and future technologies.

In order to understand what is the present situation at the commercial level in the domain of gas and biosensing technologies we have made a preliminary market research and analyzed what are the well established technologies, products and applications based on CO_2, NO_2, SO_2, VOC (volatile organic compounds) detection, as well as biomolecule detection.

In the field of the gas detection market, Honeywell is a major player, owning the most important gas sensor factories from EU and USA, where City Technology and Honeywell Analytics take together a big share of the gas sensors and detectors global market in both fixed and portable applications, for industrial safety, emmisions, medical and automotive domains.

In the field of biosensing market, glucose Biosensors represents the largest segment cornering a lion's share of the global biosensors market, as stated by the new market research report on Biosensors in Medical Diagnostics. Diabetes management has become an attractive industry by itself, presenting huge opportunities for growth of enhanced diabetes management products, glucose detection devices, and glucose biosensors. Key factors driving growth for glucose biosensors include user-friendly designs, growing diabetic population, and point-of-care applications. Biosensor technology is capable of increasing patient compliance by minimizing careless attitude towards regular monitoring of glucose levels, owing to ease of use and higher accuracy. Roche Diagnostics (Formerly Boehringer Mannheim), LifeScan (Johnson and Johnson), Abbott, Bayer, Medtronic, Becton Dickinson, Home Diagnostics, and Dexcom are few of the major players in the glucose biosensors market. Other biosensors (including biosensors used for testing cholesterol urea, blood gas, and other parameters) are also forecast to register fastest growth of more than 19% over the analysis period.

The United States represents the largest market for medical biosensors globally. Europe trails the US. However, Registering the fastest CAGR of more than 14% through 2015, Asia-Pacific holds the highest growth potential for biosensors. Growing health-related concerns, and an increase in affordability levels with regards to healthcare, are the major factors driving the market for biosensors in Asia-Pacific.

Major companies developing biosensor-based devices profiled in the report include Abbott Point Of Care Inc., Neosensors Limited, Siemens Healthcare Diagnostics Inc., Animas Corp., LifeScan Inc., Medtronic Diabetes, Roche Diagnostics Ltd. Leading developers of biosensor technology analyzed include AgaMatrix Inc., Cranfield Health, LifeSensors Inc., M-Biotech, and Nova Biomedical Corp.

The research report titled "Biosensors in Medical Diagnostics: A Global Strategic Business Report" announced by Global Industry Analysts Inc., provides a comprehensive review of the Biosensors market in Medical Diagnostics, current market trends, key growth drivers, new product innovations/launches, recent industry activity, and profiles of major/niche global market participants. The report provides annual sales estimates and projections for the global biosensors market for the years 2007 through 2015 for the regions, including US, Canada, Japan, Europe, Asia-Pacific and Rest of World. Key product segments analyzed include Medical Biosensors (Glucose Biosensors and Other Medical Biosensors), Environmental Biosensors, and Other Biosensors. More details about this comprehensive market research report can be found at the link http://www.strategyr.com/Biosensors_in_Medical_Diagnostics_Market_Report.asp.

1.1 Commercial Gas Sensing Technologies on the market, today

Commercial gas sensing technologies have been developed and gradually refined in the last decades. The most important ones are the electrochemical, catalytical, infrared, photoionization (PID) and the metal oxide semiconductor (called also solid-state) gas sensing technologies.

The electrochemical technology is used for oxygen and toxic gas detection in both fixed and portable applications. Their basic operation is using the general principle of redox reactions at the interface beween conducting electrodes and liquid electrolytes, where the reduction reaction which is taking place at the cathode is consuming the electrons generated at the electrochemical reactions from the anode/electrolyte interface. By measuring the electron current flowing in the external circuit, between anode (counter electrode) and cathode one can get a proportional indication of the gas to be monitored. Electrochemical sensors represent the workhorse of today's gas sensing technologies and they are used for the detection of a large family of toxic gasses (e.g. CO_2, NO_2, SO_2, NH_3, etc.), as well as for oxygen detection in industrial safety and medical applications. Such simple electrochemical sensors are intrinsically low-power, have low cost and have acceptable reliability/cost ratio.

The catalytic technology is used for the detection of the flammable gases like methane, pentane, as well as hydrogen. The catalytic sensors are also called pellistors (from pellet and resistor) and they consist of a heated platinum coiled resistor containing in the middle the of coil a ceramic bead which is catalyzing the combustion reaction of the gas to be detected. The pellistor is electrically heated to about 500^oC by biasing its platinum resistor with 1 V at about 150 mA. Its initial temperature is further increased when a flammable gas is burning on the bead. The combustion reaction is taking place at such a 'reduced" temperature thanks to the catalytic activity of the ceramic bead which is also containing noble metals within its composition. This temperature increase is measured by the increase of the platinum resistance, which is having a temperature coefficient of about 3900 ppm/^oC. Due to their operation principle, the catalytic sensors are not gas selective and thus they cannot discriminate between different flammable gases which are reaching the sensing surface. On the other hand this is a big advantage, as otherwise, it is very difficult to detect all the flammable gases and hydrogen with the same sensor. From this point of view the catalytic (pellistor) sensors cannot be replaced by the emerging optical gas sensing technology. One of the biggest challenges with this type of flammable gas sensor is the relatively high electric power consumption of the pellistor, which is the most power hungry device of today's portable gas sensing instruments.

The infrared gas sensing technology is based on the gas property to absorb light in the IR wavelength domain. They can be used for the detection of the flammable gases, as well as the toxic gases. Basically, the IR light is absorbed at frequencies that match the energy difference between two vibrational quantum mechanical states of the gas molecules. For example, the CO2 gas is absorbing light in the wavelength band of 4.2-4 µm, while the propane and hexane are absorbing the IR light in the wavelength band of 3.3-3.5 µm. For these sensors one measures the light arrived at the detector and this is divided by the light emitted by the source. Their ratio is proportional to the gas concentration absorbed by the gas to be detected. The main components of an IR gas sensor are: (i) the IR source (e.g. an incandescent lamp), (ii) the detector (e.g. thermopiles, pyroelectric detector), (iii) two bandpass interference filters for allowing the light with the desired wavelength to pass through it, where one filter is located in front of the sensing detector and it is allowing the IR absorption bandwidth of the gas to go through it, while the other (reference) filter is located in the reference loop in front of reference detector and this filter is transparent to all expected gases from the ambient to be sampled. By processing the signal from the sensing and reference loop one can minimize the drift of baseline signal coming from the common mode signals, like light source ageing, (4i) a gas cell which is allowing the gas to be detected to enter there for evaluation and finally (5i) the electronic block for signal processing and sensor data display. To further enhance the quality of the IR gas sensing, a temperature and pressure sensor should be further included in the whole system, and the compensation of the temperature and pressure effects, will be digitally performed in the microprocessor. Because of the required gas-light interaction over a certain pathlength (which increases with decreasing detection limits), this technology cannot be scaled down significantly in size and therefore less suitable for portable applications.

The photoionization detection (PID) technology is used for the detection of most volatile organic compounds (VOC's) which have ionization energy lower than 10.6 eV. The PID sensors are very sensitive but, at the same time they are very non-selective, as they cannot discriminate between the gases with ionization energy lower than 10.6 eV. Their basic operation consists of ionization of the VOC's which diffuse in the sensor chamber. The ionization is induced by means of an UV emitting lamp. As a result of ionization process, the electrons are removed from the VOC molecule and these electrons are captured by the positive biased electrode of a high voltage grid. These electrons, removed from the ionized VOC molecules, generate an electronic current which is proportional to the VOC concentration.

The metal oxide semiconductor (solid state) technology is mainly used for the detection of CO gas in detectors used in domestic applications, as well as for the $CO/NO_x/H_2S$ detection in ventilation control systems of automobiles. The sensor consists of a heated resistor made of metal oxide semiconductor. The metal oxide is increasing its resistance when an oxidizing gas is reacting with the oxygen ad-atoms from the sensor surface, while the same sensor is reducing its resistance when a reducing gas (e.g. CO, H2) is reacting with the oxygen-ad-atoms from the sensor surface. The heater is biased in such a manner so that the metal oxide is reaching the operating temperature at which the maximum sensitivity to the gas to be detected in obtained. The biggest challenge of these sensors is their lack of selectivity and for this reason the critical to life applications are not using such sensors.

1.2 Biosensing Technologies on the Today's Market

About 200 companies worldwide were working in the area of biosensors and bioelectronics at the turn of the century (Weetall, 1999). Some of these companies are still involved in biosensor fabrication/marketing whereas others just provide the pertinent materials and instruments for biosensor fabrication. Most of these companies are working on existing biosensor technologies (Weetall, 1999) and only a few of them are developing new technologies. While the commercial market for blood glucose monitoring continues being the major driving force (over 85%), the commercialization of a handheld biosensor for infectious disease detection can be projected within the next decade. Medical applications overshadow the other application sectors and could be attributed to the increasing rate of obesity and the alarming rise in the rate of diabetes in the industrialized countries. The SPR technology will gain significant attention and with miniaturization and cost reduction, SPR microarray will be a serious contender and competes head-to-head with electrochemical detection in both research and application. The present biosensing principles and assessment have been already extensively described in D1.1. § 2.2.

The classification of a biosensor becomes more intriguing and debatable due to significant advances in microfrabrication and nanotechnology. In the 1960s and 1970s, a biosensor was just a probe, somewhat similar to pH, ion selective or oxygen electrodes equipped with a simple readout device. As the sensing tip has been shrinking to micron and nanosize, other analytical instruments have also become smaller and smaller or even portable and are equipped with more robust and powerful data acquisition and processing. For instance, the room sized mass spectrometers of 1950 can be reduced to a few cubic centimeters. Miniaturized mass spectrometry, chromatography or electrophoresis chips have become feasible and might serve as a viable sensor component. In view of this, the definition of biosensor technology should be revisited to accommodate biosensors as a part of automated instruments. A typical example is the use of an AFM tip to form an AFM-based biosensor (Kaur et al., 2004). Because of the comparatively large number of small and big companies that have engaged in some sort of commercialization, this report will not be able to cover all commercial activities in this field. Except for SPR technology, piezoelectric and other optical detection is not included due to its low market volume and or visibility.

Yellowsprings instruments (YSI). In 1975, YSI (http://www.ysilifesciences.com) commercialized the first analyzer to measure glucose in whole blood. YSI followed this in 1982 with a whole-blood lactate analyzer. Since then, these products have become a standard for clinical diagnostic work at many sites in hospitals. The technology developed by Clark and Lyons over 45 years (Clark and Lyons, 1962) ago still provides fast, accurate glucose and lactate results in whole blood, plasma, serum, and cerebrospinal fluid. Up to 90 g/L glucose and 30 mmol/L lactate can be measured without the need for sample dilution and the results can be obtained in minutes. The analyzer's hematocrit correction option provides accurate glucose results expressed as plasma even when running whole blood. The analyzer requires only a small sample (25 µL), making it practical in neonate applications.

Nova biomedical. Nova's StatStrip™ Glucose Monitor (http://www.novabiomedical.com) has received clearance from the U.S. Food and Drug Administration for use in neonatal testing. Severe hematocrit abnormalities are routinely found in neonates and interfere with glucose measurement. StatStrip is the only glucose monitor with 6s analysis time that measures hematocrit on the strip, automatically correcting glucose values for abnormal hematocrit values. StatStrip measures and corrects electroactive interferences from acetaminophen, uric acid, ascorbic acid, maltose, galactose, xylose, and lactose. StatStrip also eliminates oxygen interference to provide accurate glucose results regardless of the sample's oxygen level. The company also provides a hand-held device for the measurement of blood lactate (muscle performance indicator) using a very small drop of blood (0.7 µL) with an analysis time of 13 s. Nova also commercializes a biosensor that measures creatinine with an analysis time of 30 s and a wide range of BioProfile Analyzers for bioprocessing for monitoring glucose, glutamate, glutamine, glycerol, lactate, and acetate in addition to pH, pO_2, pCO_2, ammonium, and phosphate.

Abbott laboratories. Abbott Laboratories (http://www.abbottdiagnostics.com) acquired MediSense in 1996 for $867 million for the blood electrochemical glucose meter. Abbott then acquired

TheraSense (blood glucose monitoring) and i-STAT for $392 million in early 2004, the latter being a company that commercialized a portable, hand-held analyzer for urea and blood gas analysis. In 2001, the company launched the Precision Xtra, the first personal blood glucose monitor with ketone testing capability. On Jan.18, 2007, Abbott sold its core laboratory diagnostics business included in the Abbott Diagnostics Division and Abbott Point of Care (formerly known as i-STAT) to GE for $8.13 billion. However, Abbott's Molecular Diagnostics and Diabetes Care (glucose monitoring) businesses are not part of the transaction and will remain part of Abbott.

Bayer AG (diagnostics division). The company offers a variety of Glucometer® instruments for blood glucose testing and an in vitro diagnostic immunoassay system for hepatitis A virus. The company has received several granted patents, notably US Patent 6,531,040 that describes an electrochemical sensor for detecting analyte concentration in blood (http://www. bayerdiag.com). The Glucometer Elite® Diabetes Care System is a blood glucose monitoring system based on an electrode sensor technology. Capillary action at the end of the test strip draws a small amount of blood into the detection chamber and the result is displayed in 30 s.

Roche diagnostics AG. Roche Diagnostics (http://www.roche-diagnostics.com) biosensors permit near-painless, continuous measurement of blood glucose level. It markets the Accu-Chek family of products/services for blood glucose monitoring. Its US Patent Number 6,541,216 describes an invention that allows the measurement of blood ketone levels. The Accu-Chek Plus Glucose Meter is preloaded with a drum of 17 diabetes test strips, i.e., no individual strip handling with the test result appearing in 5 s.

Affymetrix. The Affymetrix (http://www.affymetrix.com/index.affx) GeneChip microarray is a workhorse in research institutes as well as pharmaceutical, biotechnology, agrochemical, and diagnostic settings. Gene- Chip microarrays consist of small DNA fragments or probes which are chemically synthesized at specific locations on a coated quartz surface. The precise location where each probe is synthesized is known as a feature, and millions of features are contained on each array. Nucleic acids extracted and labeled from samples are then hybridized to the array, and the amount of label can be monitored at each feature, resulting in a wide range of possible applications on a whole-genome scale, including gene- and exon-level expression analysis, novel transcript discovery, genotyping, and re-sequencing. Over 13,000 scientific publications have used this GeneChip technology. The company also has an impressive number of US patents issued and pending (230 and 420, http://www.affymetrix.com).

Biacore international AB (GE health care). SPR biosensors are optical sensors exploiting special electromagneticwaves, surface plasmon-polaritons, to probe interactions between an analyte in solution and its corresponding recognition element immobilized on the SPR sensor surface. Based on SPR, Biacore's technology provides a non-invasive, label free system for studying biomolecular interactions. The company focuses on drug discovery and development (http://www.BIAcore. com) although it also provides a range of products for determination of food quality and safety. The first system was commercialized in 1989 followed by the second generation model (BiaCore 3000) with high performance in 2003, a system that has been well received in proteomic and clinical research (http://www.biacore.com/ lifesciences/index.html). GE Health purchased Biacore, the largest SPR instrumentation, with 2005 sales of 76.8 million (http://www. allbusiness.com/instrument-business-outlook/1186240-1.html). Biacore is a multi-application research tool, offering a range of data output from yes–no binding data and concentration analysis to detailed affinity, specificity and kinetic data. This model also offers increased integration with mass spectrometry. There are over 2800 references citing Biacore across therapeutic areas including cancer, neuroscience, immunology and infectious disease. It is of interest to note that in most Biacore applications, the ligands are tethered to a carboxylated dextran matrix that coats the chip surface. The carboxyl groups are capable of concentrating proteins at the surface and speeding up the immobilization process. Without this pre-concentration effect, ligand immobilizations can only be realized at concentrations above N1 mg/ml to drive the chemistry. In addition to its high cost (high-end instruments, $250,000–$500,000), BiaCore requires high-quality reagents with high activity, high non-specific binding, high stability, and/or high solubility. SPR array platforms also present a new level of technical challenges, including how to immobilize ligands and/or process large data sets efficiently. Presently, SPR biosensors can monitor up to 100 biological evaluations/ day. The SPR array chip technology is expected to process 100,000 biological evaluations/day. Despite its versatility, the SPR system becomes less applicable for detecting biomolecules which have a molecular weight of less than 5000 Da. However, a surface-competition assay format was developed that allowed indirect detection of smallmolecule binding (Zhu et al., 2000). Other improvement in SPR instrumentation has enabled detection of small molecules, such as drugs (>138 Da) binding to human serum albumin (Frostell-Karlsson et al., 2000) and small oligosaccharides (b1000 Da) binding to an antibody (Hsieh et al., 2004). The long-term stability of the surface layer is questionable when in direct contact with blood and the signal is very sensitive to non-specific binding for real-time measurement in blood (Meadows, 1996). *Applied biosystems and HTS biosystems.* Applied Biosystems (http://www.appliedbiosystems.com) and HTS Biosystems (http://www.htsbiosystems.com) jointly develop the 8500 Affinity Chip Analyzer. The technology is based on grating-coupled SPR and employs a single large flow cell so that 400 ligands can be spotted and analyzed at one time. This system is particularly well suited to examine antibody–antigen interactions and it can detect analytes with molecular masses down to 5000 Da (Applied Biosystems Application Notes about antibody characterization at http://www. appliedbiosystems.com/). For antibody, peptide, and DNA, the preparation of pertinent chips is relatively straightforward because these ligands retain their native structure throughout the preparation process involving drying and reconstitution steps. Patterning methods for more labile enzymes and receptors are still a formidable task and require more elaborate procedures. Nevertheless, the 8500 Affinity Chip Analyzer is expected to open up new possibilities for biosensor analysis. quick and easy BetaStar® test for dairy antibiotics in milk. The BetaStar® US test (AOAC-RI No. 030802) is an extremely simple dipstick test that detects dairy antibiotics in the beta-lactam group, requiring only minimal training and equipment to produce consistently accurate results.

Panbio diagnostics. Technical platforms of this Australian company include the enzyme linked immunosorbent assay, indirect fluorescent antibody test and rapid lateral flowdevices (http://www.panbio.com.au). Panbio activities focus on West Nile virus, Japanese encephalitis, leptospirosis and malaria. The company has two major technology platforms: homogeneous immunoassays and oligo rapid immunochromatography.

Applied biophysics. This company has commercialized an impedance microarray system for probing cells and cell behavior including cell adhesion and proliferation, cytotoxicity, tumor invasion, wound healing, etc. (http://www.biophysics.com). The core technology is the measurement of the change in impedance of a small electrode (250 μm in diameter) microfabricated on the bottom of tissue culture wells and immersed in a culture medium. The attached and spread cells act as insulating particles because of their plasma membrane to interfere with the free space immediately above the electrode for current flow, resulting in a drastic change in the measured impedance. Cell densities ranging from a heavy confluent layer to very sparse layers can be measured with this approach. The technique is sensitive enough for detecting even a single cell. The *Spreeta (Texas instruments) and other SPR biosensors.* This company commercializes compact, low-cost and commercially available SPR-based sensors (http://www.sensatatechnologies. com/files/spreeta-tspr2kxy-product-bulletin.pdf). The units consist of a near-infrared diverging LED light source, a polarizer, a gold sensing layer, a reflecting mirror and a photodiode-array detector. The polarized light is emitted toward the gold sensing surface and reflected at different angles. At certain angles of light incidence, resonance of the gold surface plasmons occurs and the intensity of the reflected light drops dramatically. The light is reflected on a mirror and projected onto the photodiode array where the light intensity is measured. The position of the light intensity minimum is extremely sensitive to changes in refractive index (RI) of the fluid in the sensing area. Therefore, RI changes near the sensing area can be measured by monitoring the light intensity minimum shift over time. However, the Spreeta technology might not be as sensitive as the standard ELISA procedure (Spangler et al., 2001). SensiQ with a dual channel is a state of-the-art data analysis tool to provide kinetic, affinity and concentration data researchers can use with a high degree of confidence. In 2008, the manufacturer of SensiQ (ICx Nomadics Bioinstrumentaion Group, Oklahoma City, OK) just launched SensiQ Pioneer, a fully automated SPR platform while maintaining the cost affordability (http://www.discoversensiq.com). XanTec Bioanalytics GmbH of Germany is another company that commercializes SPR biosensors (http:// www.xantec.com). Notice that the coatings of its sensor chip are claimed to be robust and prevent exposure of hydrophobic nanodomains or pinhole defects which can cause non-specific interactions. 5. Trends and future possibilities. The increasing demands and interests in developing implantable glucose sensors for treating diabetes has led to notable progress in this area, and various electrochemical sensors have been developed forintravascular and subcutaneous applications. However, implantations are plagued by biofouling, tissue destruction and infection around the implanted sensors and the response signals must be interpreted in terms of blood or plasma concentrations for clinical utility, rather than tissue fluid levels (Li et al., 2007). In view of technical feasibilities and challenges, there is greater success in developing hand-held biosensors than implantable devices.

There is also great interest in parallel, high-throughput assays for clinical, environmental, and pharmaceutical applications. This requirement has paved the way for the development of integrated miniaturized devices to reduce the development and production costs, particularly for the applications that require cost-exorbitant biological materials. In this context, the development of disposable biosensors has received a great deal of interest for the detection of biological agents/toxins (Spichiger-Keller, 1998)). One of the key steps in the construction of such miniaturized electrochemical sensors is to select a pertinent method for probe immobilization. For example, the use of an electropolymerized conducting polymer as matrix to immobilize the biorecognition probe is of particular interest. The electrosynthesis of conducting polymers allows for precise control of probe immobilization on surfaces regardless of their size and geometry (Dong et al., 2006). Since the polymerization occurs on the electrode surface, the probes are essentially entrapped in proximity to the electrode. This feature is of particular importance toward the development of sensing microelectrodes and microelectrode arrays to shorten the response time and alleviate interference from the bulk solution. Furthermore, the amount of immobilized probes can be easily controlled either by changing their concentration or by adjusting the thickness of the polymer matrix through the electrode potential, electropolymerization time, or both. Of particular interest is the use of an electropolymerized pyrrolepropylic acid film with high porosity and hydrophilicity to covalently attach protein probes, leading to significantly improved detection sensitivity compared with conventional entrapment methods (Dong et al., 2006). Besides conventional electrode materials such as platinum, gold, silver, glassy carbon, etc., novel electrodes fabricated from diamond doped with boron to extend the overpotential has emerged, particularly for monitoring arsenic in drinkable water (Hrapovic et al., 2007). Nanomaterials such as carbon nanotubes together with nanoparticles (gold, platinum, copper, etc.) have been reported to significantly enhance detection sensitivity and facilitate biomolecule immobilization. Such combined materials also promote electrontransfer reactions between the active sites of the enzyme and the detecting electrode. Notice also that selective and sensitive electrochemical detection of glucose in neutral solution becomes feasible using platinum–lead alloy nanoparticle/carbon nanotube nanocomposites. The recent bloom of nanofabrication technology and biofunctionalization methods for carbon nanotubes (CNTs) has stimulated significant research interest to develop CNT-based biosensors for monitoring biorecognition events and biocatalytic processes (Luong et al., 2007). CNT-based biosensors could be developed to sense only a few or even a single molecule of a chemical or biological agent. Aligned CNT “forests” can act as molecular wires to allow efficient electron transfer between the detecting electrode and the redox centers of enzymes to fabricate reagentless biosensors. Electrochemical sensing methods for DNA can greatly benefit from the use of CNT-based platforms since guanine, one of the four bases, can be detected with significantly enhanced sensitivity. CNTs fluoresce, or emit light after absorbing light, in the near near-infrared region and retain their ability to fluoresce over time. This feature will allow CNT based sensors to transmit information from inside the body. The combination of micro/nanofabrication and chemical functionalization, particularly nanoelectrode assembly interfaced with biomolecules, is expected to pave the way to fabricate improved biosensors for proteins, chemicals, and pathogens. However, several technical challenges need to be overcome to tightly integrate CNT-based platforms with sampling, fluidic handling, separation, and other detection principles. The majority of biosensors reported in the literature require various cleaning/washing steps, separately from the detection process. Furthermore, many detection schemes require the addition of extra reagents including co-enzymes, redox species, etc. To generate a detectable product. The optical sensor deserves a revisit here because of the recent development of fluorescent nanocrystals (quantum dots) and significant progress in photonics. Quantum dots are brighter than molecular dyes, resistant to photobleaching, and amenable to multiplexed detection by controlling the size of the fluorescent nanocrystals to tune the fluorescence wavelength (Bruchez et al., 1998). Nanoparticles can be used to provide nanoprobes for imaging and sensing for early detection of diseases. Nanophotonics deals with manipulation of optical excitation and dynamics on a nanoscale, opening opportunities for many optical and optoelectronic technologies including biosensing. Nanoplasmonics is an area of nanophotonics that deals with optically generated interfacial electromagnetic excitations in metallic nanostructures. Nanomagnetics deals with control, manipulation and utilization of magnetic interactions on nanoscale. Such promising and emerging technology might also provide solutions to the obstacles that impede successful commercialization of biosensors. Gold nanoparticles containing DNA “barcodes” may provide that next generation technology (Stoeva et al., 2006). Biocodes consist of nucleic acid sequences of 30 to 33 bases. Part of each biobarcode recognizes a specific target DNA sequence, while the remainder of each biobarcode is common among all barcodes and is necessary for detection and readout functions in the assay. Each biobarcode is linked to a 30-nanometer-diameter gold nanoparticle. The researchers also constructed magnetic microparticles containing a short piece of DNA that binds to a separate unique region of the target DNA. Optical biosensors could become a powerful tool in the imminent future for the real-time and remote detection of emerging infectious diseases (Monk and Walt, 2004). As high-end instruments, the SPR array equipped with auto-samplers and powerful data acquisition continues to play an important role in the most profitable pharmaceutical and biotechnology companies to speed up the drug discovery and development process. Current technical achievements in SPR microarray will lead to compete against application of immunoassays, a workhorse widely used for determination of numerous important substances. The biosensing platform must function well in a real-world sample environment where selectivity, sensitivity, detection limits, and ruggedness are the four prerequisites. Complex clinical and environmental samples often impede accuracy, sensitivity and the lifetime of the sensor due to cross cross-reactivity, inhibition of the detection method, and non-specific adsorption of unwanted species in the sample. The use of CNTs in biosensing looks very promising as reflected by some significant patents in this area and other research and development endeavors. However, nanostructure-based biosensors could be relatively expensive, with high development and manufacturing costs for the immediate future. It is still uncertain if the increased capability of nanosensors is sufficient to open up large markets, and quickly engendering a rapid decrease in costs. The biosensor has a tremendous potential for the detection of microbial contamination in foodstuffs and the microarray technology can simultaneously and easily detect up to 12 different pathogens. Common bacteria found in meat are Salmonella, E. coli 0157:H7, generic E. coli, L. monocytogenes, Campylobacter jejuni and Yersenia enterocolitica (primarily in red meat). All of these pathogens are associated with stomach illness in human beings. Besides the protection of consumers, food producers can make decisions more quickly about applying treatments such as antiseptics treatment, cooking operations to kill the pathogens and modification of their sanitation plans. The biosensor industry is dominated by a few large multinational companies with enormous sources of finance for technology acquisition and validation. The market entry for a new venture is very difficult unless a niche product can be developed and the company must have vast financial resources for technology development, demonstration, validation, and marketing. An example for a potential niche product is the development of an autonomous system, disposable, low-cost and requiring no external equipment, reagents, or power sources. In this context, of interest is a simple method for patterning paper to create well-defined, millimeter-sized channels, comprising hydrophilic paper enclosed by hydrophobic polymer for the analysis of both glucose and protein urine samples (Martinez et al., 2007). Although it only detects glucose at high concentrations (~2.5 mM), chemistry can be improved and adapted for other important clinical and environmental samples. Another niche market is the rapid and sensitive detection of biological agents that harm people, livestock, or plants. The key issue is trace detection in a short time (b1 min) since small amounts of pathogens can cause illness and releases can be diluted rapidly in the environment. For example, in the food industry or clinical samples, a detection limit of 1 pathogen/g or 1 pathogen/ml is desired. Even with thousands of analytes per pathogen, the required detection limit is 1.7 aM (1.7×10^{-18} M), still a real challenge in analytical chemistry. The U.S. Food Safety Inspection Service has established a zero-tolerance threshold for the most fearful strain E. coli O157:H7 contamination in raw meat products (Jay, 2000). The infectious dosage of E. coli O157: H7 is ten cells whereas the Environmental Protection Agency standard in water is 40 cells/L (Dubovi, 1990). Therefore, the biosensor system must include sample collection and sample preparation, biodetection (often using multiple biosensors), data integration and analysis, and finally reporting of the results. Consequently, the system tends to be costly and complicated. Novel approaches are under development to miniaturize such integrated system to minimize consumables, analysis time and improve reliability. The development of microscale separation devices, particularly micromachined capillary electrophoresis chips coupled with amperometric detection, has received significant attention in recent years (Fischer et al., 2006). Integration of a miniaturized biosensor with a separation scheme will continue to be a subject of intensive investigation. Toxicologic information of drugs, pollutants, toxins, nanomaterials such as quantum dots and nanoparticles should be established to protect human health and environmental integrity. A recent report indicates that long straight carbon nanotubes may be as dangerous as asbestos fibers (Poland et al., 2008). They might cause cancer in cells lining the lung, a pilot study with mice. Nanotubes under twenty micrometers, and long nanotubes which are tangled up into balls, do not cause asbestos-like problems. Although much more work will be required to provide definitive proof, however, considering the terrible effects of asbestos that emerged in the 1960s, researchers are urging caution, particularly for the use of CNTs and other nanomaterials in biosensing, bioimaging, and drug delivery. This is of utmost importance because carbon nanotubes have been advocated for a wide range of products under the assumption that they are no more hazardous than graphite. While annual global spending on nanotechnology research is about 9 billion dollars, only 39 millions are invested in the analysis of the safety of nanomaterials in human and the environment. In this context, cell-based impedance spectroscopy has emerged as one of the potential candidates (Xiao and Luong, 2003) and this system has been adapted for providing cytotoxicity information of quantum dots and other nanomaterials (Male et al., in press). This application could be a niche market for cell-based assays because of their broad applicability for the detection of both known and unknown chemical agents and bioagents. Lastly, attention should be paid to a newclass of affinity proteins, so-called affibodies (Nord et al., 1995; Nygren, 1997). Despite their smaller size and simpler overall structure, these proteins have binding features similar to antibody variable domains in that selective binding with high affinity can be obtained towards various target molecules (Hansson et al.,1999). Such features make them interesting alternatives to antibody fragments for use as recognition units in larger fusion proteins for therapeutic, diagnostic and biosensing applications, a virtually unexplored field. It will remain to be seen whether biosensor technology with novel biorecognition elements can make any breakthrough towards the development of rapid and reliable detection for mad cow disease, a problem which has been waiting for a right solution.

2. Market trends

Today's business strategies and models for all visionary companies are related to major (mega) trends of the entire society and its needs, taking into account the rapid pace of technological changes. These megatrends are more and more considered as Early Warning Systems of future societal needs, and those companies which identify their specific manifestation forms and are adjusting fast to them are the winners for the associated products. The followers will be also welcome in such a huge global market, but they will not take the lion's share.

2.1 Market megatrends related to gas and bio-sensing

A rapid analysis of the megatrends is telling us that the health and environmental awareness, nanotechnology development, sustainable urbanization, globalization/individualization and global prosperity increase are excellent drivers of the strong orientation of the society towards new, clean technologies and bio-technologies which will minimize the environment pollution and minimize greenhouse gas production, and will bring new bio-solutions for creating genetically modified plants and animals, and thus reducing the world hunger.

In this context, we shall try to identify the emerging technologies in the field of environment monitoring and detection of bio-molecules and try to position the NEMSIC technologies in the roadmap of the gas and bio-sensing of the future, as identified by the above megatrends.

2.2. Market trends in the gas sensing field

As described above, today's gas sensor market contains mature technologies which are used in industrial safety, emission, medical and automotive industries and they are also expanding to residential home applications. However, there is still a strong request of the vertical industries embedding gas sensors in detectors and analyzers for more reliable sensors, with less false alarms and higher functional robustness in extreme ambient conditions of temperatures, pressures and humidity.

The extensive use of gas sensors in portable instruments also requires a drastic reduction in electric power consumption of the sensors, so that the autonomy of these battery-powered gas detection instruments increases and lack of operation in critical operations is avoided to assure an increased life safety in dangerous environment. This is already a strong need for the case of commercial portable instruments which are containing gas sensors for O_2, CH_4, H_2S and CO detection, and where the present CH_4 detection is using power hungry sensors.

In the internet and wireless communications era, the gas sensor and associated gas detecting instruments should be able to inform in real time the owner, or even to automatically trigger an actuator for taking automatic actions against dangerous situations with gas concentrations above the threshold limit values.

The industrial growth in developed countries and the accelerated economic development of the developing countries have exhausted the fossil energy resources and for a sustainable evolution of our global society, energy efficiency should be increased, in parallel with new energy sources creation. The extensive use of gas sensors in the feed-back loop of the burning processes for the optimization of natural gas combustion and other fossil energy sources is foreseen. In the same context of increased energy efficiency, as already presented in the D1.1 report, there is a strong need of low cost CO_2 sensors, for demand-control ventilation in HVAC (heating, ventilation and air conditioning) where the amount of air supply in building interiors is determined based on the existing indoor CO_2 concentration, and whose maximum limit for a healthy air is well known and thus automatically preserved, at a minimum electric energy consumption.

The number of gas sensing applications is increasing due to the society's high sensitivity for having a clean ambient air, which is directly related to population health. However, relative to integrated circuits, the cost of gas sensors is not low enough so that they can be used on a very large scale, or in environment monitoring applications extended over a large surface area, and where many millions of such sensors ("e-dust") are to be used to wirelessly control the quality of ambient air. The agglomerated cities, where more than 50% of global population is already living, will require a strict monitoring of gases like NO_x, SO_x, and CO_2. National regulations for NO_x and SO_x annual average concentrations will pose higher and higher restrictions, as is already happening in the US, where their maximum limits are in the range of 50 and 25 ppb respectively.

In the same idea of health and environmental awareness megatrend, the lack of tolerance towards the concentration of volatile organic compounds (VOC) is already well known and workplace regulations for keeping these organic vapours below their TLV are very strict.

Finally, it is important to mention that EU-ROHS directive (Restrictions of Hazardous Substance) is very strict to even the materials that are used inprocess technologies for the realization of different products, including integrated circuits and gas sensors. Thus, it is well known that materials like lead cadmium and mercury are no longer allowed in the fabrication technologies of different products including gas sensors. Here, it is good to mention that lead for example will not be allowed to be used in electrochemical gas sensors for oxygen detection, after 2018. In light of minimizing pollution, also the use of batteries in the abovementioned e-dust needs to be considered carefully as collection and recycling of distributed systems in not trivial and may require novel solutions such as energy harvesting.

2.3. Market trends in the field of bio-sensing

As described above, today's biosensor market contains mature technologies which are used in medicine, agriculture, food safety, homeland security, environmental and industrial monitoring. However, the commercialization of biosensor technology has significantly lagged behind the research output as reflected by a plethora of publications and patenting activities. The rationale behind the slow and limited technology transfer could be attributed to cost considerations and some key technical barriers. Analytical chemistry has changed considerably, driven by automation, miniaturization, and system integration with high throughput for multiple tasks. Such requirements pose a great challenge in biosensor technology which is often designed to detect one single or a few target analytes. Successful biosensors must be versatile to support interchangeable biorecognition elements, and in addition miniaturization must be feasible to allow automation for parallel sensing with ease of operation at a competitive cost. A significant upfront investment in research and development is a prerequisite in the commercialization of biosensors. The progress in such endeavours is incremental with limited success, thus, the market entry for a new venture is very difficult unless a niche product can be developed with a considerable market volume.

The world biosensor market was $7.3 (US) billion in 2003 and was expected to reach over $10 million by 2007 (Fuji-Keizai USA, Inc., 2004) with the medical/health area being the largest sector (Alocilja and Radke, 2003). Similarly, another independent market report indicates that the global market for biosensors and other bioelectronics will grow from 6.1 billion in 2004 to 8.2 billion in 2009 (http://www.bizlib. com/products/ZBU80661.html). Biosensors, particularly glucose sensors, accounted for nearly all of the market in 2003. The total worldwide medical biosensor sales was $7 billion (US) in 2004 and projected to be $8.3 billion (US) by the end of 2007 (Hall, 1990; Fuji-Keizai USA, Inc., 2004) with over 50% and 22% of the biosensor sales in North America and Europe alone. As expected, the glucose biosensor was the most widely commercialized of all biosensors (Newmann et al., 2002; Alocilja and Radke, 2003) considering the number of diabetic patients was 150 million in 2004. Although the number of diabetic cases could double to 300 million by 2025 (Newmann et al., 2004), the market of glucose biosensors is somewhat stagnant. The worldwide market for in vitro diagnostics was estimated to be about $17 billion in 2003 (Weetall,1999) with molecular diagnostics as a fast growing area. Although the molecular diagnostics market was about $1.3 billion in 2003, it might reach $7 billion by 2010 (http://www. geneohm.com). The pharmaceutical research industry has a real need for biosensors to accelerate the progress of drug discovery and screening (Legge, 2004). The pharmaceutical industry with total worldwide biosensor sales in 2004 of about $577 million (US) was expected to grow to $1.5 billion (US) by the end of 2007 with over 50% sales in the North America biosensor market. Public safety and concern, new legislation and recent food contamination in several countries have fostered a major research effort in the environmental and food/agricultural industry. There is an urgent need to ensure that food production and quality meet regulations (Fuji-Keizai USA, Inc., 2004). About 5000 people die each year from Salmonella and/or E. coli induced food poisoning in the USA (Fuji-Keizai USA, Inc., 2004). The global cost of the SARS outbreak was estimated to be 10–100 billion dollars while an outbreak of foot and mouth disease in the UK (2001) was about 5.8 billion dollars in reduced livestock production earnings. Consequently, the environmental and food industries are potentially emerging markets. The worldwide food production industry is worth about $578 US billion and the demand for biosensors to detect pathogens and pollutants in foodstuffs is expected to grow in the near future (Alocilja and Radke, 2003). The total market potential for detection of pathogens in the USA is about $563 million/year with an annual growth rate of 4.5% (Alocilja and Radke, 2003) compared to $150 million/year for the USA food industry sector. Considerable amount of work has focused on the development of biosensors to rapidly detect biowarfare agents.

However, besides the USA and a very few countries, the biosensor market in the biosecurity/military industries in the near future is uncertain. A key issue for homeland security is absolute reliability as 'false negatives' are unacceptable. Too many 'false positives' cause stress and inefficiency, and quickly cause people to ignore warnings. Advances in areas such as toxicity, bioavailability, and multi-pollutant-screening, will widen the potential market and allow biosensors to be more competitive with conventional lab-based procedures.

3. Emerging Technologies for gas and bio-sensing

As described above, the market trends are oriented towards a highly increased number of gas and bio-sensors, of low cost/power/size and high technical performances which will address the requirements of present and future applications aiming for a better industrial process control, a cleaner environment air as well advanced detection of biomolecules for multiple biotechnology applications envisioned by the society megatrends. To meet the above challenges in the field of gas and bio sensing, a major change should occur in the field of innovation and fabrication technologies for next generations of gas and biosensors, which should allow the transition from present technologies, where the gas and biosensors are mainly built by means of low productivity methods (like one by one fabrication) to future technologies where IC like batch fabrication takes over, and where the gas and bio-sensors are made by batch processing, with many thousands of sensor chips per wafer. Our NEMSIC technologies are very well aligned with this trend of batch fabrication, as they are IC-NEMS technology. In the next sections, we shall try to make a preliminary assessment of the existing and emerging technologies in the field of gas and biosensing for multiple applications.

3.1. Emerging technologies for gas sensing

Within this preliminary report we briefly introduce a few emerging technologies specific to gas sensing.

The most important emerging technology for gas sensing which is envisioned to replace the electrochemical technologies and catalytic, pellistor type technologies is the advanced optical technology based on semiconductor technology. The present (commercial) optical technology for detecting a certain gas is based on assembling separate light sources (e.g. an incandescent lamp) and detectors (thermopiles, pyroelectric) working on the absorption "wavelength" (actually an absorption band) of the gas to be detected and then assuring the right optical path between source and detector as well as a gas specific filter in front of the detector. As one can understand from this description, this is a labour intensive fabrication process, and also still an expensive approach, not to mention large size and power consumption of the sensor. This is especially true with respect to electrochemical technology, which in many cases is consuming no power at the sensor level (galvanic type electrochemical sensors). The emerging optical technologies of interest for gas sensing are evolving in two major directions.

The first emerging optical sensing direction is a direct method and it consists of detection of the gas by measuring its light absorption at its specific wavelength, in the NIR (near infrared) or MIR (middle infrared) infrared region, by using semiconductor devices like diode laser and LED's for light sources and their corresponding semiconducting photodiodes as light detectors. The results and products reported by the UK-based company “Gas Sensing Solutions” for CO_2 detection is supporting very well this emerging optical direction.

The second emerging optical sensing direction is an indirect method and it consists of detection of the thermo-mechanical effects of the light absorbed by the gas to be detected. In this method, the optically excited gas (i.e., the gas to be detected) is heated and it is transferring the heat to the surrounding molecules creating thus a pressure wave, which is measured by a specific pressure sensing device. As light source one can use either classical sources or a laser. The detector can be also done by different technologies. This is the so called photoacoustic principle and it has been developed under different technologies from the point of view of the light source, detector and gas chamber. Presently, there is an EU-FP-7 project called “MINIGAS”, which is developing a photoacoustic technology for CO_2 gas detection.

These emerging optical technologies for gas sensing are envisioned to generate large volumes of commercial gas sensors in a time horizon of about 10 years, considering the technology roadblocks that still need to be removed in order to obtain robust gas sensors with high yield, low cost and low power consumption, as needed by the vertical industry of gas detectors and analyzers and their customer applications.

In addition to these emerging major optical technologies, there are other new coming optical technologies based on single chip MEMS-based IR CO_2 sensors where the light source is tuned to CO_2 detection. For this, emitted light confinement at the CO_2 absorption wavelength, a photonic-crystal-enhanced technology is used, while the heater is in the same time a detector of the bolometer type. (The company called “FLIR” is having niche commercial applications of this CO_2 sensor).

On the same direction of the on-chip gas sensing technologies, we can briefly mention here those based on nanomaterials (nanodots, nanowires) and nanoelectronics technology platforms. It is already known that the use of nanostructured metal oxide seminconductor layers used for mimicking the old “solid state gas sensors (like SnO_2 gas sensors) are operating at much higher sensitivities and reduced temperature, and these performances are going to be further exploited in future gas sensing technologies.

In the same emerging direction of on-chip gas sensors and future gas sensing arrays we need to include our innovative NEMSIC based gas sensors, which can become a large gas sensing platform, allowing detection of different types of gases by changing the functionalization on the resonant sensing layer.

3.2. Emerging Technologies for bio-sensing

The fast and progressive growth of the biotechnology and pharmaceutical fields forces the development of new and powerful sensing techniques for process optimization and detection of biomolecules at very low concentrations. During the last years, the simplest MEMS structures, i.e. microcantilevers, have become an emerging and promising technology for biosensing applications, due to their small size, fast response, high sensitivity and their compatible integration into ‘‘lab-on-a-chip’’ devices. The application range is huge due to the high variety of active layers in contact with the microcantilever that can be used, with very different responses under external stimuli, such as conformational changes, selective swelling, thermal expansion, or changes in the intermolecular forces. The active layer response produces either a change in the cantilever bending or/and in its resonance frequency. The detection of different parameters, such as forces, mass, or stiffness, provides different and complementary information that cannot be obtained with other established label-free biosensors. The cantilever-based biosensor is still a young technique in constant development. New devices and detection strategies are continuously emerging looking for better understandings, higher sensitivities and simpler system operation. This technique has already demonstrated very extreme limits of detection. A comparative with other established non-labeled biosensors, showing the limit of detection (LOD) for different compounds models is summarized in D1.1. In most of the cases the lower LOD reported is with a cantilever-based biosensor, especially when high mass biological agents are used and the dynamic mode is applied. The table reported in Fig. 2.2.7. reflects quite well the potential of the mechanical biosensors in the pharmaceutical and medical diagnosis fields. But there are still some questions that must be addressed to finally develop a highly sensitive and reliable integrated platform able to work with real clinical samples. As in any biosensor, the receptor layer must be specifically assembled for each compound to be detected, and the optimal packaging or optimal pH and ionic strength is different for each case. Covalent immobilization protocols together with blocking agents are usually chosen looking for the final biorecetor layer stability, surface regeneration and avoiding non-specific bindings. Working with cantilevers, the optimization of the receptor layer can be a hard task due to the complex relation between the cantilever response (bending or frequency change) and the forces/mass density acting during the recognition process. Functionalization protocols that had been completely established along the years may need to be modified when working with microcantilevers in terms to enhance the cantilever signal. The surface cleanness and morphology play a very important role in the final detected signal and reproducibility, and must be strictly controlled. Moreover, the use of array of microcantilevers is essential, not only for having a reference cantilever to subtract the effect of non-specific bindings or external effects, but to perform the detection of multianalytes in a single sample. For that reason, further research in the functionalization of arrays of microcantilevers is needed, simplifying the described applied techniques, reducing the time consumption, increasing the reproducibility and providing new routes for multi-analyte detection. As well, the limitations of the detection systems must be minimized, reducing the noise, thermal fluctuations of the base signal, simplifying the optical alignment and increasing the integration and packaging of the final system. This includes the miniaturization and integration of microfluidics and the detection readout subsystem. For that purpose, the optical waveguide microcantilevers, or the piezoelectric and piezoresistive ones are promising candidates, because of its high integration and not required alignment. The progress observed during these last few years, when using the static mode and especially with the dynamic mode, must continue. A complete understanding of the surface stress origin is essential to optimize the bending method, reduce the limit of detection and obtain more information about the biological agent under study. In dynamic applications, where the trend is to reduce the cantilever size to increase its sensitivity, the efforts must be addressed towards the noise reduction during the analyte detection, the improvement of the actuation methods and the system resolution for working with viscous samples and the identification of frequency shifts due to mass or stiffness changes. It is clear that micro and nanocantilever-based biosensors have become a competitive technology in the biosensors field, but is still far away from other analytical techniques routinely used in clinical diagnosis laboratories. To that end, the future work should be addressed towards the achievement of a reliable integrated system, able to work with real clinical samples and easy to use for not specialized personnel.

4. Business Model for envisioned NEMSIC's-based sensors

4.1. A brief introduction to the business model concept

In any business development, the business model is an essential step related to the entire business strategy and its practical implementation. In the early stage of a new business development, understanding the market context, the market (mega)trends, and following with the "modelling and simulation" of the new business are the key factors for the success of the new venture. At this stage, the business model is showing the entrepreneurial vision of the organization for creating new products or services, delivering those goods, and capturing added value in the economic and social plan. In the following stages of the business development, the business model can be corrected and further refined based on the market validation of the business concepts, and the manner in which the entire business supply chain is able to address customer needs. Very briefly speaking, the business model defines the value proposition and the entire value chain for the creation of a product or service to be offered to the customer, as well as the manner by which the seller is enticing the customer to pay for the value, and finally, the ability of the organization to convert the payments from the customer into a profit for the organization. In the last six decades there have been many innovations at the level of business model and their practical implementation, starting from the McDonald's business model and reaching the "Dell Computer" business model, just to mention some of the most representative. They are very briefly described in the section called "Business Model" from "Wikipedia". Among the most known business models, we name here the so called "razor and blade" or "bait and hook", which is still used today.

The "bait and hook" business model consists of two products of the same business, where the first one is "baiting" (i.e. "tempting") the customer and the second one is "hooking" the customer, giving him the "dependence" on the first one and thus, on that business in general. Similarly, the "razor and blade" business model expresses the interdependence of the two products in meeting the customer needs. A very good example of the "bait and hook" model comes from the "Adobe" software developer, where, the "Adobe reader" program (the bait) can be download for free, while the "Adobe writer" program (the hook) should be paid, where the cost of "Adobe writer" will compensate the free-of-charge reader program. A similar example is the case of cell phone business where the cell phone itself is almost free (low cost- "bait" product), while the value of the cell phone is rewarded by the cost of the "air time" of the wireless link service (hook service product), which is paying for the cost of that phone.

One of the latest trends in the field of innovative business models, which may impact the gas sensor business is replacing the traditional manner of selling a product to the customer, by selling a "solution" to the customer, and this means that the ownership of the product may not be the major focus for the customer, but instead of it, the function of it, and where the seller is directly in charge of both product and its maintenance and safe operation at the costumer site. This new business model may be correlated with very rapid "moral depreciation" of the technology involved in the realization of new generations of products, or with more sophisticated maintenance technologies, where the customer may not be interested to be part of it.

The building blocks of any business model are generally well accepted by business community and they are described by the so called "Business Model Canvas" of Osterwalder et al (A. Osterwalder, Yves Pigneur, Alan Smith, and 470 practitioners from 45 countries, self-published, 2010), which consists of the following sections : Key partners, Key Activities, Value Propositions, Customer

Relationship, Customer Segments, Key Resources, Channels, Cost Structure and Revenues. Below we shall preliminary show a possible business model for the NEMSIC based gas and bio sensor commercialization. As the same business model can be used for the commercialization of both gas and bio-sensors developed within NEMSIC project, we shall describe below, as an example the business model for the NEMSIC based gas sensors, where Honeywell can act as a commercial company, knowing his strong leadership postion on the gas sensor market. The business model scenario described below is in agreement with the Consortium Agreement (CA) between NEMSIC partners and they represent only a possible approach from the point of view of the scientists, not involving their organization beyond the agreed CA of the NEMSIC-EU-FP-7 project, and not limiting other possible future collaboration approaches. In the field of NEMSIC based gas sensing, we are treating here the business model based on resonant gas sensors which have been considered to be the core of the project. If other sensing principles developed in this project, like (static) nanowire or fluctuation spectroscopy based gas detection, the business model will include Southampton University for nanowire principle, while in the case of fluctuation spectroscopy Honeywell would hold the IP priority for this principle.

4.2. A possible "Canvas business model" for future NEMSIC-based resonant gas sensor commercialization

4.2.1. Key Partners

In the R&D stage for the NEMSIC- based prototype development:

The key partners are : LETI, IMEC, EPFL, HON.

LETI would use its technology research and development facility for developing the prototype of the future NEMSIC-based gas sensor. IMEC (Be and NL) would use their research labs for the research and development of the functionalization technology, prototype reliability research as well as the design and readout electronics, i.e. the integrated circuits for interrogating our future resonant gas (nano)sensor. EPFL would work at the level of device concept, modelling and simulation stage, in strong connection with all the other partners. Honeywell would contribute with its surface functionalization concepts for gas sensing, which have been already theoretically developed during the NEMSIC project, as well as with possible packaging concepts, already theoretically developed during the research phase of the EU-FP-7 project.

In the possible following stage called New Product Introduction (NPI) stage of the NEMSIC-based gas sensors:

The key partners are LETI, IMEC, EPFL, HON and a SOI-CMOS silicon foundry not indentified, yet.

Here, we assume that LETI, IMEC, EPFL and HON may have successfully passed the concept research phase and thus proved the functionality of the prototype, and may have performed the risk analysis of the technology platform and its associated products (in terms of Pareto risk ranking based on Failure Modes and Effect Analysis (FMEA)) and decided to go collectively into NPI phase, where a silicon SOI-CMOS foundry may be directly involved in the technology transfer and preparation for mass production.

If this NPI phase has been successfully passed, then, the academic organizations (LETI, IMEC and EPFL could involve their technology transfer offices (TTO) for agreeing to develop a joint venture.

To continue with the business model for NEMSIC based resonant gas sensor commercialization, here, we make the hypothesis that LETI, IMEC and EPFL have agreed to give a licence to Honeywell for their technology, as industrial partner.

Honeywell (HON) could use of its marketing channels for understanding the customer needs and their conversion to functional technical requirements [as defined by Design for Six Sigma (DFSS) methodology, in the sub-field called Quality Function Deployment (QFD1), which is relating the customer needs to the product performance) of the next generation gas sensors. The NEMSIC-based gas sensing technology platform could generate a next generation of gas sensors for the detection of the environment toxic gases, like, CO_2, SO_2, NO_2, Volatile Organic Compounds (VOC), as well as other toxic gases like H_2S.

The key suppliers for the future NEMSIC-based gas sensors could be the result of the market research performed by Honeywell marketing experts, and more specific by the company called “Honeywell Life Safety”. Possible applications for CO_2 could be in the field of energy efficiency for the HVAC (Heating Ventilation and Air Conditioning) by monitoring the CO_2-based indoor air quality (IAQ) and actuating the ventilators for fresh air only when the CO_2 concentration is above a certain threshold (of about 900 ppm in the room), the so called Demand Control Ventilation (DCV). For DCVD application, Honeywell is already having its own customers. This application was described in the report D1.1, with more details. Other possible applications could be in the field of environment air monitoring with respect to SO_2, NO_2, or VOC concentrations, as shown in the deliverable report D1.1 of the NEMSIC project. The effective suppliers would require a rigorous market investigation as mentioned above.

4.2.2. Key Activities

Assuming that all the above hypotheses are valid, and the mass production of the NEMSIC based gas sensor takes place, key activities will consists in the production planning based on the vertical integrators demands, i.e., those companies which are developing gas detectors and gas analysers. The entire supply chain, from raw material procurement in the silicon foundry up to distribution to the customers integrating the NEMSIC sensors to their gas detection instruments will be dimensioned starting from the market requirements and novel applications, which may emerge down the road, as legislation becomes more restrictive about air environment quality. The advantage of NEMSIC based gas sensor could be the existing large technology platform which could be used for the realization of a large family of gas sensors, where the differentiation between different types of sensors would be obtained by different functionalization technology, the rest of IC processes remaining the same. So, CO_2, NO_2, SO_2, H_2S, VOC detection could be enabled on the IC-SOI-CMOSFET technology platform to which only specific processes at the functionalization level, are added. Stronger restrictions related NO_2, SO_2, and VOC concentrations are coming. Here, we need to mention that in the US there are already strong restrictions about the concentration of NO_2 and SO_2 in the ambient, and this may trigger new applications in the future for detecting these gases as detection systems move from fixed to mobile and personal Therefore, the key activities may involve mass fabrication, distribution through the Honeywell channels to Vertical Integrators, and marketing work for identifying customer needs and potential new customers and killer applications, involving high volumes of NEMSIC based gas sensors.

4.2.3. Customer Value Proposition

In the case of NEMSIC-based gas sensors, we think that the value proposition is: Low cost, low size, low energy consumption of the NEMSIC-based gas sensors at an increased sensitivity, selectivity and reliability with respect to prior-art technologies.

From this point of view, sensors with such capabilities may open the avenue towards gas sensing based personal applications, as well as the development of the large ground area distributed wireless sensor networks for the surveillance of the air quality on large surfaces, and in the sustainable/eco cities of the future.

4.2.4. Customer segment

The NEMSIC based gas sensor business model is envisioning a diversified gas sensing platform as described above, with high flexibility in tailoring the type of gas to be detected by means of the functionalization process, while the SOI-CMOS FET technology platform is not changed as function of the type of sensor produced. The most important customers will be those needing a high volume of gas sensors, as the NEMSIC based gas sensor technology is by definition a high volume batch type of technology, where many millions of sensor may be required. The requirement for a high volume of sensor fabrication from the market is actually the key of the success for this IC-based gas sensor, and this may be correlated with killer applications as discussed above. Simply speaking, a mass market is a key aspect for the success of this business model, where a silicon IC foundry is involved in gas sensor fabrication.

4.2.5. Key resources

The success of this business is shared by the entire value chain of the fabrication and commercialization of the NEMSIC based gas sensors, including here the customer satisfaction and its high volume applications, as a key goal of this endeavour. As an emerging technology, the NEMSIC based gas sensors fabrication is based on a strong IP portfolio in all stages of the sensor fabrication and packaging, where novel in-plane vibrating MOSFET transistors for the resonant sensing should have a reasonable quality factor for being able to vibrate in air at low excitation voltage, and also maintain electrical stability of the sensing MOSFET transistor exposed to ambient. These challenging requirements at the gas sensor level will require innovation on the research and development side and probably a longer period of time before the resonant gas sensor is reaching the commercialization stage. From this point of view, the R&D resources solving the above challenges will play a crucial role for the materialization of the project and preparing the avenue towards business development around our NEMSIC project. Solving the above technical challenges, will give enough support for the more detailed evaluation of the distribution channel, customer relationship or revenue streams which should be considered in detail in relation to these key resources. If Honeywell would be involved at a commercial level, the above concerns would be solved within the already existing business strategy of the company, being already world leader on the market with the gas sensors of today's technologies.

4.2.6. Channels

The channels for the distribution of the NEMSIC based gas sensors will depend on the result of the market research, as it is done by Honeywell for its gas sensors. It is worth to mention that in the case of NEMSIC based gas sensors, which are replacing the existing gas sensor in the existing applications, the distribution channels will be the same we are using today. For novel applications, the marketing department of Honeywell Life Safety could be involved for solving all the specific channels integration, cost-effective distribution strategy.

4.2.7. Cost structure

The cost structure of such IC technology based NEMSIC gas (nano)sensors will be determined by the dedicated departments of Honeywell, and this structure will be strongly correlated with the volume of the sensor manufacturing. The success of such a gas sensing business will be assured only for high volume fabrication, specific to IC technology, as a strong foundation for low cost sensors, as defined in the value proposition.

4.2.8. Revenue streams

It is our belief that Honeywell's customers are willing to pay in the future for the low cost/energy consumption/low size and high performance gas sensor, were the robust, false alarm-free operation to happen. In addition, we think that our customers are going to pay for the use of gas sensors in novel emerging applications, which will make our planet safer and a better place to live. Today, they pay for the best in class sensors we have, according to our well established electrochemical, catalytic and optical technologies, which Honeywell is offering to them in order to satisfy today's market requirements (safety, emission, medicine and automotive industries) and environment air-related legal restrictions. It is possible that in the future our customer want to pay for *a solution* we offer to them, not the asset cost. In this specific case, the advantage of having a company like Honeywell which is a market leader in gas sensing, and has strong business market strategies make much easier the penetration of the future gas sensor in the market.

5. Gas and biological sensor market investigations in other initiatives and future relation with Guardian Angels FET Flagship

5.1 Key recent evolutions in gas sensing compared to other market studies

Prior to this study some other groups and consortia reported on market analysis and trends concerning especially gas sensing, which is a more established field than bio-sensing with key world players and some mature technologies.

A comprehensive analysis concerning the important role of gas sensors and associate market trends has been provided in 2006 by the MNT Gas Sensor Roadmap prepared by the MNT Gas Sensor Forum. The data and analysis that we presented in this document are more recent and include key evolutions observed in the last 5 years, following the MNT report. However, it is important to note that their figure depicted below concerning the following market segments has been proven to be valid:

i. **Fire and domestic gas detection**: as a mature market, with growth in domestic CO.
ii. **Automotive**: with rapid growth in cabin air quality monitoring and with large potential growth in emissions control.
iii. **Industrial safety**: as a mature market with rapid expansion in developing economies.
iv. **Process control and emissions monitoring**: with strong growth driven by legislation and efficiency criteria.
v. **Breath and drugs**: as market with enlarging growth in medical diagnostics, but requiring intensive research.
vi. **Environmental monitoring**: with extremely large potential growth, but technically very challenging because little legislation is in place.
vii. **Security and military**: with event-driven growth, especially in US.

We believe that the approach of NEMSIC is very relevant for domains (i), (ii), (v) and (vi). We would also like to cite that the MNT report has pointed out among the most promising future technologies: 'integrated MEMS using combinatorial sensing arrays with widespread applicability'.

The figure below (Fig. 1) suggests the main global trends and market potentials predicted by UK analysts: the technology maturity is depicted on the vertical axis, from 'R&D' to 'no change' while the horizontal axis shows the potential annual market predicted in 2006. While some of their observed trends have been confirmed, our analysis suggests that the applications of gas sensors and markets in the medical, process/environment and automotive fields have been somehow underestimated.

These fields can benefit much more than expected from NEM sensor emerging technologies; our project and business models point out to new fields of applications and markets centered on **gas sensing based personal applications** and **large ground area distributed wireless sensor networks for the surveillance of the air quality on large surfaces**.

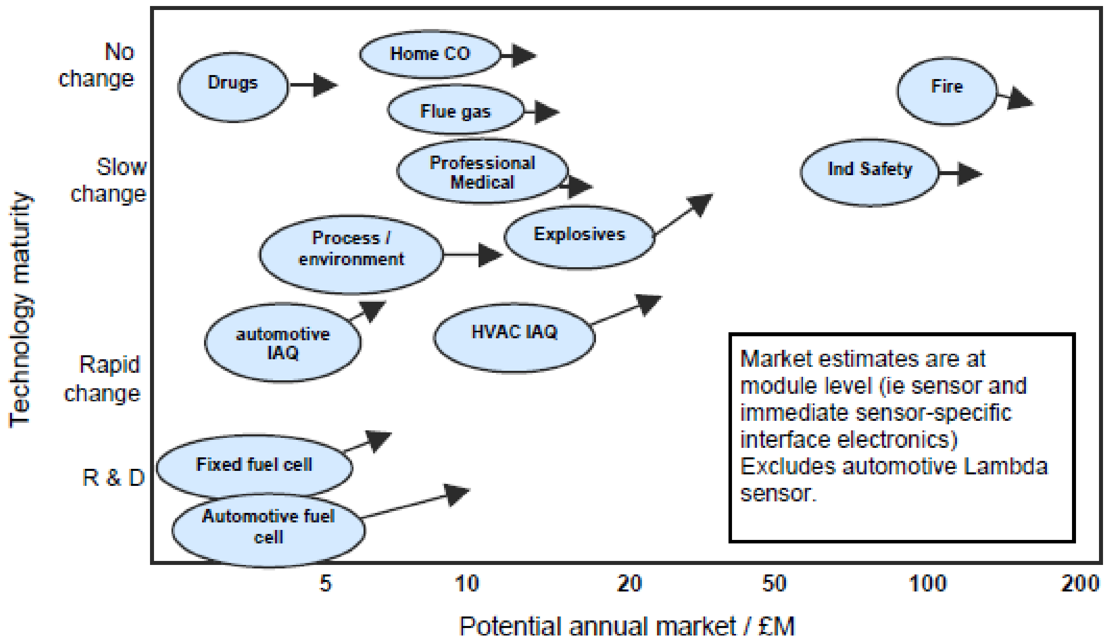

Fig. 1 Maturity of different gas detection markets versus market size. Arrows show anticipated future development (after MNT gas sensor roadmap 2006). Our analysis shows that the evolution markets in Profession Medical, Process/environment and automotive are much quicker and require more innovation and emerging technologies.

5.2 Link with Guardian Angels Physical and Environmental Demonstrators

The Guardian Angels (GAs) for a Smarter Life FET Flagship project proposed a novel approach for future zero-power intelligent autonomous systems-of-systems featuring sensing, computation and communication beyond human aptitudes. The role of Guardian Angels as smart personal companions will be to actively assist humans from their infancy to old ages in complex life situations and environments. These advanced systems are based on most advanced sensor technology and integrated nanosensors are considered among the most interesting technology candidates for the first two generations of Physical and Environmental GAs.

The *Physical Guardian Angels* will be quasi-invisible zero-power body area networks or implantable devices, monitoring vital health signals and taking appropriate actions to preserve the human health. They will acquire a complete view of the person health state by performing real-time ultra-low-power multi-parametric combination of non-intrusive bio-signal sensors (ECG, accelerometers, gyroscopes, pulse oximetry, etc.) and make health warnings.

The *Environmental Guardian Angels* extend their ability from the body to monitoring of the dynamic environment and feature zero-power bi-directional interfaces, full battery-less operation, disruptive scavengers (bio-chemical, thermo-electric, synthetic photosynthesis) personalized data communication and first real thinking algorithms permitting decisional processes. They will be real personal assistants of elderly people and of our children to preserve their integrity. The sophisticated angels will guard people from all dangers that the environment can pose, including pollution and catastrophic events.

This FET Flagship is a unique post-NEMSIC R&D opportunity to exploit the best achieved results in integrated sensors and their electronic interfaces in order to contribute to integrated sensing functions in complex systems. The low dimensionality, low power consumption and natural integration on silicon platforms of NEMSIC sensors make them credible candidates for such future smart systems-of-systems. The remaining challenges are in terms of reliability, robustness, advanced models for accurate design and packaging. These are requirements of major importance for a direct impact of the take-up of NEMSIC devices in industrial products.

6. Conclusions

Within this D6.6.1.report, firstly, we have done a market research in the field of the gas and "bio" sensing domains for identifying the commercial products and their associated technologies and applications. Secondly, we have tried to develop business models for the future NEMSIC-based gas and bio sensors, in agreement with the major potential applications identified in the report D1.1, of this project, as well as megatrends of our future society with cleaner air requirements and an increased number of older people.

In the field of gas sensing, the market research has revealed a limited number of well established technologies, where the electrochemical and NDIR optical principles are the most extensively used for today's industrial needs, overall the electrochemical technology being the most representative for oxygen and toxic gas detection, today. **On a horizon of about 10 years, it is expected that the low cost semiconductor optical technologies replace the electrochemical technologies and thus to respond to most of the customer needs.**

In the field of biosensing, the market research has revealed an even lower number of well established technologies, where the SPR microarray technology is a serious contender and competes head-to-head with electrochemical detection in both research and application domains. SPR technology provides a non-invasive, label free system for studying biomolecular interactions, thus responding to most customer needs. Nevertheless, the fast and progressive growth of the biotechnology and pharmaceutical fields forces the development of new and powerful sensing techniques for process optimization and detection of biomolecules at very low concentrations. In this respect, the simplest **NEMS/MEMS structures, i.e. micro- and nano-cantilevers have the potential to became an emerging and promising technology for biosensing applications**, due to their small size, fast response, high sensitivity and their compatible integration into ''lab-on-a-chip'' devices. In order to enable this, the future work should be addressed towards the achievement of a reliable integrated system, able to work with real clinical samples and easy to use.

The commercial market research documents have revealed the fact that resonant gas and biosensing NEMSIC-based technology is not yet anticipated as an emerging technology for the next ten years, and this fact is revealing once more the basic research character of our NEMSIC project for chemical sensing.

By looking at the megatrend in the evolution of our society, and their cascaded impact on the gas and bio-sensing, we have envisioned that the NEMSIC-based resonant technology, which has high potential on low cost/size/power consumption coming from integrated circuit technologies like SOI-CMOSFET, and which envision high sensitivities capabilities coming from high sensitivities of accreted mass resonant detection of **NEMS technologies can play a major role in future emerging technologies of chemical sensing**. Thus, applications related to environment monitoring by wireless sensor networks distributed on large ground surface areas or remote health monitoring could be implemented with the help of NEMSIC technologies. These domains of research and applications are well covered by the recent FET Flagship initiative Guardian Angels for a Smarter Life and we expect that some of the most promising results of NEMSIC will be integrated and continued in this ambitious project.

Starting from these considerations we have proposed possible canvas business models for both gas and bio-sensing detection, where companies like Honeywell, with a strong market position on the gas sensing domain can bring the NEMSIC based technologies to the commercial level.

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