MASTER THESIS - JAN KOWALCZYK

TRACING EMERGING IRREVERSIBILITIES AND DEVELOPMENT PATHWAYS IN THE FIELD OF NANOSENSOR TECHNOLOGIES

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Abstract

Nanosensor technologies constitute a new emerging field of science and technology with tremendous innovation potential. However, as the technology is still in its infancy many uncertainties and unknowns exist. Nonetheless, due to high expectations and promises, the technology gained a lot of attention from governments, companies and universities as they see potential to benefit from the development and commercialization of such technologies. With their ongoing activities and interaction those actors shape the dynamics and characteristics of the field. Understanding these dynamics is important for actors attempting to benefit from the development. A key concept in this study - which contribute to the understanding of emerging technology dynamics - are emerging irreversibilities. Emerging irreversibilities are "patterns that enable certain actions and interactions (make it easier) and constrain others (make it more difficult to do something else)" (Van Merkerk & Robinson, 2006) and thus influence the development paths a technology follows.

The aim of this thesis is to study and analyze the processes and mechanisms that influence the development of emerging technologies and explore how irreversibilities shape the development of nanosensor technologies. This research effort presents a new methodology to map the development of new emerging fields and irreversibilities. For the three communities (science, industry and government), a database of papers, patents and projects was constructed. Within this database statements were selected pertaining to nanosensor development. We focused on general nanosensor development, as well as on developments in relation to the application areas *food, environmental analysis* and *medicine*. Based on these statements a reconstruction of the developments in the field was made. Two dominant development paths were identified: path A related to electrochemical sensors and path B related to optical nanosensors. Furthermore, the developments in relation to the application areas are described. Based on these narratives the emerging irreversibilities were derived and analyzed. Our findings from this study can contribute to the development of nanosensor technologies as those wishing to coordinate the development can now look to the future in a more informed way. Importantly, we have developed new methods for tracing emerging irreversibilities, which can be seen as an addition to existing mapping tools of emerging technologies.

Keywords: *Nanotechnology; Nanosensors; New & Emerging S&T; Development Pathways; Emerging Irreversibilities; Visions & Expectations; Statement Analysis.*

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Contents

1. Introduction

Throughout history, and especially after the industrial revolution, new fields of science & technology (S&T) have been emerging and with their forthcoming applications radically changing society and social order. These technologies have great impact on our daily life as they make it easier to fulfill, or even change, human needs. New technologies have the potential to help solving societal issues like sustainability, climate change, health, aging, food and energy security. Especially early stage technologies, like nanotechnology, are expected to have great potential for the future to solve such issues (Wood et al., 2003; Selin, 2007; Siegrist, Stampfli, Kastenholz, & Keller, 2008; NanoNextNL, 2012). Furthermore, technological change, and the innovation potential associated to it, is seen as an important driver of economic growth (Dosi, 1982; Nelson & Winter, 1977a; Lundvall, 1988). And in today's 'knowledge economy' developments in new science and technology fields are seen by governments as essential in maintaining the countries' competitive position in the world (Mehta, 2002).

Today, nanotechnology is the fastest growing area of science and technology and is said to be the technology of the 21st century. A multitude of new journals, research themes, expectations and visions, institutions and various other actors are entering the world of nanotechnology (Van Lente et al., 2012). Worldwide investments in nanotechnology research have been exploding in the last decade, reaching billions of dollars annually (Robinson, Ruivenkamp, & Rip, 2007; RNCOS, 2006; Roco, 2003).

But what exactly is nanotechnology? The term nanotechnology manifested itself in the world after the famous speech "There's Plenty of Room at the Bottom" (R. Feynman, 1961) wherein Feynman envisioned a powerful nanotechnology, where it is possible to manipulate and build matter at the scale of atoms. Nanotechnology is sometimes difficult to grasp because it is not a technology in itself. It's rather an umbrella term for science and technologies which are working at a length scale of 1 to 100 nanometers. Due to this, small scale materials can have unique characteristics different to materials at larger scale (Drexler, 2004). Hence new materials, products, with new and better functionalities can be developed. In general nanotechnology is seen as an enabling technology that will enable many applications in different industrial sectors (Robinson, 2010). So nanotechnology is broad and cuts through multiple sectors and research fields. Various technological fields are emerging beneath the term nanotechnology and in many cases new expectations and promises, new networks, agendas and actor arrangements are formed which define the characteristics of the new S&T field (Robinson, 2010).

This thesis will focus on a particular field within nanotechnologies, namely that of nanosensor technologies. A nanosensor is a sensor device with at least one of its sensing dimension smaller than 100nm. (Agrawal & Prajapati, 2012a). In the past decade nanosensors got increasingly more attention by researchers, governments and industry actors as sensors are expected to create value in many different sectors. It is expected that in the coming decennia there will be an increase in the use of data collections in order to facilitate knowledge founded decisions in areas like food processing, industrial production, logistics, healthcare, environmental protection and many more. Sensors are essential elements in the data collection process as they detect and measure physical information of a phenomenon and convert it into a processable signal (NanonextNL, 2012a). Hence sensors are of great importance for society as they facilitate innovations in many industries. There have been several advances in the development of nanosensors for different applications. Along with the different applications there are also different types of nanosensors (e.g. optical, electrical, and mechanical) and different ways to manufacture them. (Agrawal & Prajapati, 2012b; Riu, Maroto, & Rius, 2006a). Many expectations about promising applications ranging from environmental monitoring of fresh water resources, food packaging and logistics, real-time health monitoring, early detection of diseases to low power, and autonomous sensor system with communication means exist. This implies that it is an interesting and dynamic field to study as the technology is in an early state, it has a highly multidisciplinary R&D and a wide range of applications (Porter and Youtie, 2009).

1.1 Problem area

While emerging technologies have enormous innovation potential they are accompanied by many uncertainties caused by unknowns. The technologies are often situated in the realm of science and no market applications are yet available (Robinson, 2010). It is therefore unknown who the relevant actors are, what the new markets will be, what the risks of the technology are or even what the new technology actually is and what kind of development path the technology will follow. Nonetheless, because of high expectations and promises attributed to the new technology, they gain a lot of attention by governments, firms, universities and society as they see potential to benefit from the development and commercialization of these technologies. The expected impact that nanotechnology can have on society creates a need to assess the future of nanotechnology with a focus on the co-evolution of nanoscience, nanotechnology and society (Renn & Roco, 2006). The embedding of new technologies within society is an important aspect of successful technology development. Historical examples of new technologies like GMO and nuclear energy show that the embedment of a technology in society is not to be taken for granted. Those who coordinate and develop strategies for nanotechnology development should consider not only the technological developments but also the governance landscape and application areas it can affect and how these co-evolve (Robinson, 2009; Van Merkerk, 2007). Furthermore, as we live in an age of high investment projects, decision makers want to identify promising directions and options for technological emergence as early as possible in order to choose the 'right' path (Robinson, 2010).

One of the central dilemma’s related to managing emergent technologies is the Collingridge dilemma (Collingridge, 1980) which explains why it is so hard to manage emerging technologies. In the early phases of technological development, the situation is rather fluid and open: multiple technical options are abound and it is easy to steer and change development paths, but the future impact is hard to predict. Once the technology becomes further developed it becomes more visible, but also more difficult to manage or change the direction of the development as the technology has become more entrenched. Thus, in the early stages there is an information problem, and in the later phase a power problem. Actors dealing with emerging technologies are subjected to the high uncertainties which are related to unknown outcomes of applications and investments. However the development of new technologies is not a complete uncertain and random process. Emerging technologies consist mostly of expectations and visions and the further development of the technologies is dependent and influenced by the expectations and visions of relevant actors (Van Merkerk & Van Lente, 2005). Actors act upon expectations and by their actions and interaction, they shape the dynamics of the emerging field. A better understanding of these dynamics is needed to benefit from the development of the technology. Insights on the dynamic of emerging technologies can be gained from science, technology and innovation studies. In particular, theories and concepts originated from evolutionary economics and the sociology of technology and expectations can shed some light on this topic.

As stated above, early stage technologies are in an open or fluid phase where a lot of development paths are still possible. In other words, variation in this stage is high. When the technology develops further, selection of promising options will occur. The process of variation and selection (and retention) is one of the basic mechanism underlying technological developments (Nelson & Winter, 1977b). Furthermore it is necessary to understand that technology development is a process where society and technology influence each other and co-evolve (Bijker *et al.*, 1987). This implies that both need to be considered while studying the emergence of a technology. This is also the case for nanotechnologies, even though the technology exists mostly in laboratories, socio-technical connections are being created. Expectations and visions play a key role in the forging of those socio-technical connections (Brown *et al.*, 2005; Van Merkerk and Van Lente, 2005).

Another seminal theory related to this subject is the theory of path creation and path dependency (David and Arthur, Garud & Karnoe, 2001). These theories imply that technological development depends upon activities and structures of the present and the past, but also that one can mindfully deviate from these structures and create new technological paths. In the early stages of technological development all kind of unorganized or organized activities take place and start to form patterns, these patterns are the starting point for technological paths and are the basis for understanding the emerging phase of a technology. Expectations and visions are a key element in understanding these patterns (Borup and Conrad, 2004; van Lente, 1993; van Lente & Rip, 1998; Brown & Michael, 2003: van Merkerk & Robinson, 2006: Borup et al., 2006).

Expectations and promises help to reduce risk, gain visibility, are necessary to acquire resources, align actors, increase legitimacy and inform strategies (Borup, Brown, Konrad, & Lente, 2006). Furthermore, expectations are said to have a performative force, i.e., they contain a script which is used to attract the interest of various actors in the innovation network. The interest of actors can be transformed in agendas. Agendas are lists of priorities which are to be executed and thus require action. Hence the promises are linked to requirements. This process is labeled in the sociology of expectations as the promise-requirement cycle. Furthermore, actions which result from the agenda setting processes create new networks between relevant actors, and thus shape the structure of an emerging field. *Expectations*, *agendas* and *networks* are the building blocks of the patterns and technological paths within a S&T field. These emerging structures and patterns are the first indicators of new technological development pathways. This indicates that technological paths to the future do not occur at random but are based on events in the present. This is phrased accordingly by Robinson (2009) *'Paths to the future do not fall out of the sky, they are based on the dynamics of the present: there are endogenous futures embedded in the present which can give indications and insights into the transition from present into future' (p.1227).* However, in the early stage of emerging technologies path are not always visible, but still emerging.

What is visible are first orderings or patterns which influence the actions of relevant actors. A key concept to understand the patterns are irreversibilities, or emerging irreversibilities. '*Emerging irreversibilities are patterns that enable certain actions and interactions (make it easier) and constrain others (make it more difficult to do something else)'* p. 413 (Merkerk & Robinson, 2006). Irreversibilities emerge as the result of ongoing interactions of researchers, institutes, policy makers and firms. They decrease the fluidity and openness of possible actions and thus enable and constrain more specific actions. Emerging irreversibilities thus are the starting point of technological paths where alliances, inventions, and agreements lead to inertia such that reversals are unlikely (Merkerk & van Lente, 2005).

1.2 Research question

The goal of the research is to study and analyze the processes and mechanisms which influence the development of emerging technologies. To better understand the socio-technological dynamic which lead to path emergence, and explore how irreversibilities set in as a result of the ongoing interactions of researchers, institutes, policy makers and firms. Nanosensors constitute a promising field of R&D, and arguably emerging irreversibilities will occur in scientific research, firm activities and governmental funded projects. These irreversibilities are the first indicators of path emergence and give insights on implications related to the development of nanosensor technologies. These irreversibilities are interdependent but not necessarily the same. In this thesis the field of nanosensor is analyzed and the developments paths reconstructed. From the development paths the irreversibilities could be derived. Emerging irreversibilities and developments paths are analyzed for the general development of nanosensors as well as for three application domains. These application domains are: *Medicine*, *Environmental Analysis* and *Food Applications*. They were selected based on preliminary desk research on possible applications, where these applications reoccurred most often as most promising. Hence the main research question follows:

RQ: *How have emerging irreversibilities shaped the field of nanosensor technologies in the period 2002-2012 in the scientific research communities, governmental funding programs and firm activities, how do they relate and which implication does this have for the further development of nanosensor technologies?*

1.3 Relevance

This study is a valuable contribution to society, to the scientific literature on emerging (nano) technologies and to mapping methods used in technology assessment practices. This study generates new insight on the emerging field of nanosensor technologies, possible future application and emerging paths are identified. This can benefit those coordinating the development of the technology, as early indicators of possible futures make it easier to intervene at an early stage.

The relevance of socio-technological mapping has been mentioned in literature by many authors (Guston & Circle, 1980; Rohracher, 2001; Smits, van Merkerk, Guston, & Sarewitz, 2008): The goal of socio-technological mapping is to unravel the dynamics of emerging technological fields. However, from an innovation perspective there is a lot of understanding to be gained on emerging technologies, especially about emerging irreversibilities as indicators of the dynamics of emerging fields (Merkerk, 2007; Callon, 1995). Up to date little work has been performed on the path formation processes of early stage technologies (Rip & Kulve, 2008). Van Lente and Merkerk (2005) studied emerging irreversibilities by using the 'three level framework' as a tool to structure statements about expectations, agendas and networks, which are the building blocks of emerging irreversibilities, at three different levels. However, this framework was used to study a specific technology, and in this Thesis a broader field of R&D is under investigation and the three level framework was only used to structure the data for further analysis. Next to this framework this study used statement analysis, to a certain extent, as proposed by Robinson (2007). Thus we combined parts of different tools for the analysis of emerging fields.

Next to these tools this study introduced a new method for analyzing and reconstructing emerging development paths, which is explained in the method section. Hence this study contributes to the developments of methods for mapping and understanding the development of emerging technologies. A better understanding of emerging irreversibilities can allow actors to learn about the history and current development of nanosensor technologies and makes it possible to look at the future in a more informed way.

1.4 Outline

Section 2 presents the theoretical framework, which forms the theoretical foundation of this research. All the theoretical concepts which have been mentioned above and how they are linked together and relate to emerging technologies will be explained in more detail. Section 3 presents the research methodology. The research design, method of data collection and all the steps conducted in this research are explained. Section 4 provides a description on nanosensor technologies so that the reader can get an understanding on what the field of nanosensors entails. The results in section 5 deal with the representation of the found data, the interpretation of the data, a subject tree is constructed and the evolution of the subjects over time is presented. In section 6 the development paths in the field of nanosensors are reconstructed. In section 7 it is discussed how nanosensor technologies can impact the application domains. Now the field of nanosensors is reconstructed and the emerging irreversibilities can be identified. Section 8 deals with the analysis of the emerging irreversibilities. The irreversibilities are presented and their relations are discussed. Finally, section 9 presents the conclusion and discussion. Here the research results are summarized and an answer to the main research question is provided. Furthermore the practical and theoretical implications are presented as well as some reflections on the research methodology.

2. Theory

This chapter provides the theoretical fundament for studying and understanding emerging technological fields, like nanosensor technologies. This study draws mostly on literature from evolutionary economics (Dosi, 1982; Nelson & Winter, 1977; Deuten et al, 1997; Belt & Rip, 1987); and sociology of expectations (Merkerk & Robinson, 2006; van Lente, 1993) (Borup et al., 2006). From these strands of literature, the most relevant concepts are derived and specified for emerging technologies. First some general insights about the innovation process in relation to new technological field will be presented; these insights will be complemented by path dependency and creation theories as those theories play a central role in understanding emerging irreversibilities. Expectations are said to play a key role in the development of new technologies and have effect on the paths the technologies follow. Hence this section will also elaborate on the nature and role of expectations and how they affect the innovation process. The section ends with a conceptual model.

2.1 Evolutionary Economics

Recent thinking in innovation studies emphasize that technological development and innovation processes are complex, non-linear, multi actor and multi-level processes ((Nelson & Winter, 1977b; Smits, van Merkerk, Guston, & Sarewitz, 2008; Lundvall, 1988). Different actors within a technological field e.g. firms, NGO's, governments and research institutes influence the innovation process by their actions and interactions. Furthermore, these actors operate at different levels of aggregations i.e. scientist work in research groups, governments make policies for whole societies. Thus the innovation process can be seen as the outcome of the many interactions and feedbacks between those actors. Especially in the emerging phase of technologies the innovation process is an uncertain and unpredictable endeavor.

Insights from evolutionary economic can shed some light on this innovation process (Dosi, 1982; Nelson & Winter, 1977; Deuten et al, 1997; Belt & Rip, 1987). As mentioned in the introduction, technological development can be understood as process of variation and selection, and moves form an open or fluid phase toward a more stable one where retention of the selected options takes place. In contrast to neo-classical models of innovations technology is seen as endogenous to the economic growth process (Nelson & Winter, 1977b). This means that actual interactions between technology and actors are more important for understanding the process of innovation rather that price and output signals. This focus on interaction of actors emphasizes that technological development is something which is socially constructed. Technology and society mutually influence each other (Bijker *et al.,* 1987), and insights in this socio-technical interplay provide additional understanding of the technology development. Therefore a broad view is necessary to capture the dynamics within emerging technological fields. The technological field can be seen as socio-technical worlds, where networks are formed by actors which are connected through shared expectations, visions, cultures, artifacts, shared beliefs and agendas (Garud & Rappa 1994). Furthermore, the theories state that the process of variation and selection is not blind or complete random but is guided by paradigms which hold certain search heuristics (Dosi *et al.*, 1988). As a result of the process of variation and selections technological development pathways are formed. Due to the actions of the actors certain patterns start to emerge which results in linkages, alignments and networks between actors (Rip and Schot, 2002). These patterns are of interest for the stabilization process of technologies as innovations are built upon these patterns. The emerging patterns have a constraining and enabling effect on the development of a field and thus steer the field in a certain direction. Understanding these patterns increases the understanding of the dynamics of emerging technologies. The mechanisms which form the dynamics of these technologies are mainly articulated in the form of visions and expectations (Rip and Schot, 2002; Van Lente, 1993). But before we will elaborate on visions and expectations a deeper understanding of path dependency/creation theories is necessary.

2.2 Path Dependency, Path Creation & Emerging Irreversibilities

The previous section shows that during the process of variation and selection patterns occur and that the process is not blind or completely random. The patterns are found in how actors interact, position themselves in networks, take decisions etc. (Merkerk, 2007). These patterns are the starting point for new technological paths and are the basis for understanding the emerging phase of a technology.

Theories of path dependency and path creation provide insight in how these patterns influence the development of technological fields. The main point made by these theories is that innovations or new technologies do not fall out of the sky, but are based on activities and structure in the present and the past (David, 1985; Arthur, 1989; Garud & Karnoe, 2001). The theories introduce the concept of paths to illustrate that technologies develop in certain directions. At the early stages of an emerging technological field there are multiple paths to the future possible, technological options abound and the future seems open ended. However, over time, due to the ongoing activities certain options become more promising than others and gain more attention. Investments are made and slowly entrenchment sets in. It becomes more difficult to support other options and the paths to the future become more visible and hardened. In emerging technologies it is more difficult to find such paths as they are still emerging. But what can be found are the first orderings or patterns which lead to path emergence (Van Merkerk & Robinson, 2006a).

To understand how these patterns influence the development the concept of emerging irreversibilities is needed. Emerging irreversibilities are situations or patterns in a developing field of technological R&D which enable and constrain certain actions and interactions. For example, when a new journal is published on a certain topic it will stimulate researchers to focus their activities on that topic, as they have a platform to publish. So it enables researchers to do research on that specific topic and makes it more difficult to peruse other topics. Hence, emerging irreversibilities create a direction for the actions and interactions of actors and structure the field in a new way. The stronger the irreversibility the more fixed and stable the emerging path becomes, as some options gain support and strength while others become less visible and probable (Van Merkerk & Robinson, 2006b). Emerging irreversibilities are the first indicators of entrenchment that takes place in the dynamics of emerging technologies. Examples of emerging irreversibilities are*: a growing attention toward a certain research topic, increased investments, guiding effects of collective roadmaps, recognitions of specific promising applications, shared standards and goals, accepted artefacts, inclusion of new actors in the field* (Merkerk & Robinson, 2006; Merkerk, 2007). This illustrates that entrenchment can already set in far before the technology is commercially available. When the first choices and investment have been made, the structure of an emerging field starts to form. Understanding how irreversibilities occur can provide insights in the dynamics of emerging technologies and can be of use for better governance of current development of a specific field.
So, the emergence and stabilization of paths is the result of complex, heterogeneous, multilevel activities which shape the socio-technical world. The roles and activities of relevant actors within these fields are of interest in studying the dynamic of emerging technologies. The actors involved in the expectations, agenda's and networks are located in scientific research communities, governmental programs and the private sector (Van Merkerk & Robinson, 2006b). Those are the places where irreversibities can occur.

In the early stage of technology development their activities are mainly based on expectations and visions (Brown *et al.*, 2005). Looking at prospective structures (visions and expectations) is necessary to gain understanding about dynamics of the present (Van Lente and Rip, 1998). Hence the next section will address the most relevant concepts from expectation literature in relation to emerging technologies.

2.3 Sociology of Expectations

Emerging technologies and new fields of science and technology are highly future oriented businesses and therefore they do not substantively exist: they mainly exist in the form of expectations, visions and imaginings which shape the potential of the technology. Therefore, expectations and visions are an important unit of analysis when dealing with the innovation process of emerging technologies. As stated in the introduction, expectations play an important role in the emergence of technological field as they attract resources, create legitimacy and guide activities (Van Lente & Rip 1998)(Borup et al., 2006)(Brown & Michael, 2003)(Geels, 2007).

Expectation are defined by Borup et al. (2006) as *"real time representations of future technological situations and capabilities"* p. 286. They are used as a guiding structure in emerging fields as they guide activities and influence agenda setting. By providing legitimacy they help to attract actors and financing (Van Lente, Spitters, & Peine, 2013). Merkerk and Robinson (2006) investigated how expectations influence the emergence of path dependencies. They see the stabilization and de-stabilization of expectations as part of the path development processes. For example when more expectations become shared they start to form visible development pathway for the new technology.

The above indicates that expectations have the power to influence the development, they are said to have a performative force. I.e. when expectations are shared by more and more actors, then the promises linked to those expectations are becoming translated into requirements, and requirements lead to action (Van Lente & Bakker, 2010). The results of the actions are part of the dynamics in the emerging technological field.

Now, let's focus on the characteristics of expectations. Expectations can be voiced by different types of actors, at different levels and the content can differ significantly in character. In the STS literature three types of expectations have been identified: 1) *Specific expectations*, about a certain part of technology, system or process to be developed, 2) *Generalized expectations,* containing a description about the functions which the technology will fulfill in the future*,* 3*) Socio-technical visions,* which contain a scenario about how a technology in general will affect society, and thus includes economic, political and societal aspects (Konrad, 2006; Ruef & Markard, 2010). This distinction is sometimes referred to as project specific-, general-, and framing expectations. Also van Lente (1993) distinguishes between different levels of expectations. They can be at the micro-level (research groups and individual firms), at meso-level (technological field) and at macro-level (technology in society). All the above implies that the development of emerging technologies is embedded in the interplay of expectations at different levels. Expectations are needed for the coordination of different actors and groups and they also mediate between the different levels of organization. Furthermore expectations change over time as they respond to new conditions, findings and problems (Borup et al., 2006). Hence expectations and changes in expectations manifest themselves at the three levels, and the relations between the changes are indications of emerging irreversibilities (Callon, 1991).

2.4 A Conceptual Model

The relevant concepts derived from theory above are presented in a conceptual model, see Figure 1. The model can be seen as the basis for the methodology. We are studying an emerging technology, as it is in the middle of the model. Furthermore the framework exists of two elements, emerging irreversibilities and development pathways. Due to the action and interaction of different actors (within industry, government and academia) development paths are created and emerging irreversibilities occur. What this model emphasizes is that when emerging irreversibilities occurs the direction and visibility of a development pathway increases, and the fluidity of the field decreases. The concepts of the model are filled in empirically in this research, which implies that the development paths and emerging irreversibilities are reconstructed for the field of nanosensor technologies.

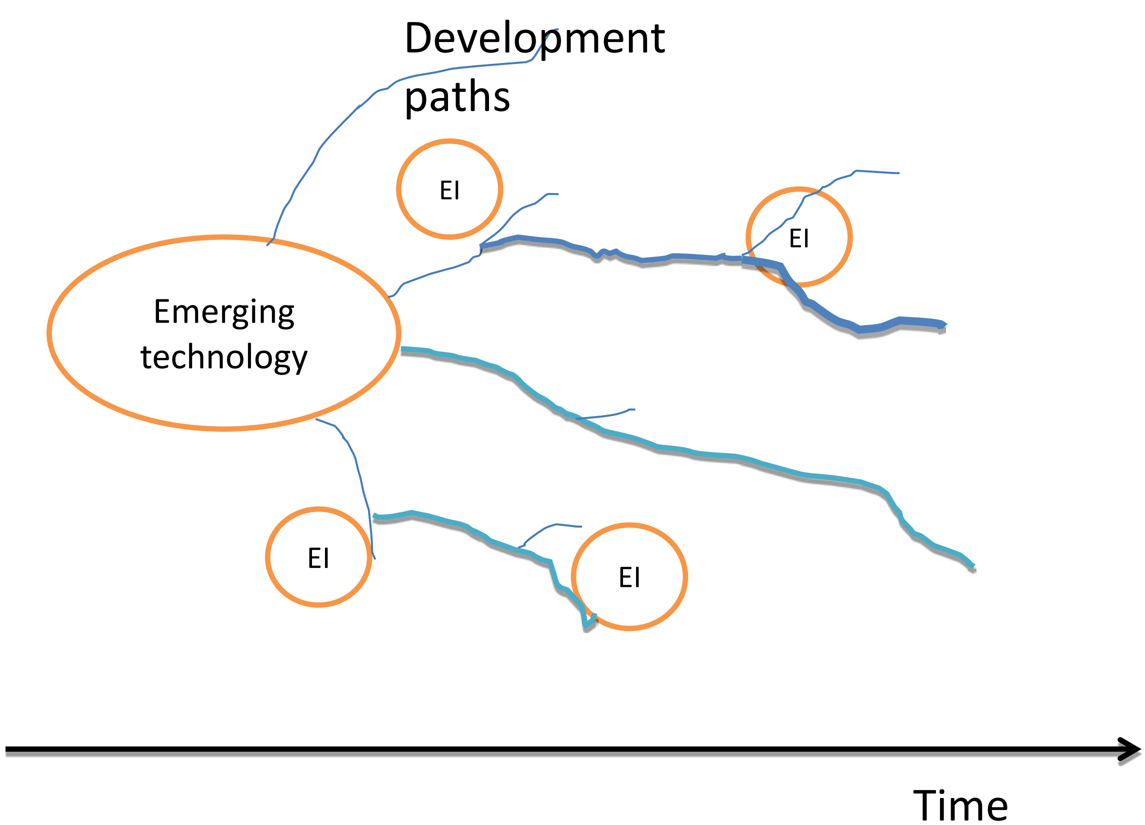


FIGURE 1: CONCEPTUAL MODEL, DEVELOPMENT PATHS BECOME MORE VISIBLE AFTER EMERGING IRREVERSIBILITIES ("EI") OCCUR AND THE FLUIDITY OF THE FIELD DECREASES.

3. Methods

The aim of this research is to explore emerging irreversibilities in the field of nanosensor technologies, with the eventual aim to better understanding the shaping processes of technological paths, and to get a notion of future implications related to the development of nanosensor applications. Nanosensor technologies are still in a very early stage of development and thus the technology mainly consists of evolving expectations, agendas and promises. Such expectations can only be studied in a retrospective study. Hence, the research design of this study is a historical case study on emerging irreversibilities in the field of nanosensor technologies. This historical case study provides an overview of the visions, agendas and expectations circulating amongst relevant actors in the field of nanosensor technologies

The actors involved in the development of nanosensor technologies are divided into three categories: scientific research communities, the funding of research projects by governments and industry actors. This is done because the emerging irreversibilities can manifest themselves in scientific research communities, governmental programs and in the industry sector. Thus these three communities will serve as three lines of inquiry in which we trace the evolution of statements in order to reconstruct the development paths and find emerging irreversibilities.

The method of data analysis is primarily qualitative. Most of the data used in this research was gathered from literature sources consisting of descriptive statements dealing with interpretation and visions of the relevant actors. The content and modality of the statements was analyzed and is thus qualitative in nature.

Nanosensor technologies are used as the case for this study. Nanosensor can be classified as emerging technologies as they are still in the early phase of development and not yet embedded in society. The technology is mainly situated in the scientific realm and not many successful products are on the market. Furthermore the technology cuts through multiple sectors, with multiple future applications and development lines. This makes the field interesting for this study as it is filled with different visions and expectations. However, it is not feasible to analyze all application areas of nanosensor technologies. This research investigates, next to the general development of nanosensors, three promising and important application areas; 1) Nano medicine, where nanosensors can be used for real time health monitoring and for the early detection of diseases(Agrawal & Prajapati, 2012b). 2) Environmental monitoring, where nanosensors can be used to detect harmful substances and 3) Food packaging were nanosensors can monitor the quality of the food and can contribute the better logistics in the food system(Sozer & Kokini, 2009).

Step 1 in this research effort was to create a database of documents which contain statements pertaining to the development of nanosensor. Such statements exist of agendas, expectation, research result, proof of concepts and visions. The statements are the elements which we used in this research to reconstruct the development of the field.

The database related to the scientific research community was created out of articles and review articles form scientific journals on nanotechnology. In order to find those articles Scopus and Web of Science were used as search engines. The search queries "Nanosensor" and "Nanosensor AND Application area (Medicine, Food, Environment)" were used as input. This generated around 1200 articles for nanosensor and 50-70 articles for each application area. From the 1200 articles, for each year (starting in 2002) the 10 most cited papers were selected for our database, and for the application area's all were selected.

The database related to industry developments consists of patents. From each year the patents with the highest forward citation ranking were selected. Forward citations are often used as an indicator for the patents value or significance, and thus can be used to investigate the state of art of the technology. The program AcclaimIP (patent analysis software) was used to find the patents. The search query was "nanosensor" and the patents were sought in the USPT0, WIPO, USAPP, EPO databases which cover almost all the world wide patents. For each year around 20 patents were selected, resulting in a database of 227 patents related to nanosensor inventions.

The database related to governmental projects was derived from the CORDIS database. This database consist of all the EU funded projects which fall under the European framework programs. Within the CORDIS database the search queries "nanosensor", "nano AND Sensor", "nano AND Sensor AND Application Area" were used to find the relevant projects. In total 160 projects were found relating to nanosensor technologies.

Overall the database consists of 296 articles from technological papers, 160 projects descriptions from the CORDIS database, and 227 most cited patents from the USPT, WIPO, USAPP, EP databases. The database can be found in Appendix C.

Step 2 was to manually read and scan the papers, patents and projects description and select statements related to nanosensors. The statements are used as the input to understand the developments of the field as they contain details on expectation, agendas, important actors, research results etc. Robinson et al, (2007) developed a taxonomy to classify statements in to accordance to their strength. The taxonomy consist of six modalities or categories to classify a statement. These categories are: (1) Science Fiction (it may happen accepted as fantasy), (2) Visionary Statements (it may happen but accepted as a reality based fantasy), (3) Guiding Vision (it may happen and we include that in our repertoire of possible directions), (4) Expectations (it will happen), (5) Agendas (We are going to make it happen) and (6) Proof (it is proven and/or demonstrated). The classification is adapted from Robinson (2007) who developed the classification based on the sociology of expectations and Vision Assessment. Appendix A provides an overview of the modalities (with examples) adopted from Robinson (2007) ranging from proof of concept to science fiction statements. The spread of concentration of statements can help the researcher to get a clear view of the different types of statements circulating within a community. Thus while selecting the statements, they were also classified by this taxonomy. Next to the modality of the statements the 'level' of expectations was also included in the database. The levels are; project specific, technological field or society. The three levels relate to the three level framework as proposed by van Lente and Merkerk (2005) which can be used to map the emergence of a technological field at multiple levels, see table 1. This framework makes a distinction between three levels where variation and selection occurs: 1) Locally, within research groups and firms; 2) more generic, at the level of a technological field; 3) In society at large, where governments, NGO's and other actors articulate the social, political and economic aspects of the technology. In this research this framework was only used to structure the statements in a consistent manner.

Table 1: Analytical framework to determine the level of expectations. (Adapted from van Lente et al, 2013)

Label	Description	Example of discourse fragment
Project-specific expectations (research group)	Future characteristics of a technology specific to a product project or firm. Micro level.	That service, called AT&T World Net Voice, will start in three cities, still to be announced, and expand to 16 by the end of the year. AT&T will charge 7.5 to 9 cents (27-1-98, NYT)

Generalized expectations (technological field)	Expectations referring to generalized features of a technology, expressed in impersonal statements. Expectations address the level of the technological field.	One of the more spectacular applications of superconducting magnets might be their use in high-speed trains floating in air. (4-1-87, NYT)
Frames (society)	Rather overarching expectations which place the technology in the context of generic societal problems or promises (societal debates).	It [gene therapy] is also a source of concern and even fear among some intelligent people who know what evil can lurk in the human mind. (1-9-93, NYT)

After conducting step 1 and 2 a database containing 4000 statements was created. This was done with the help of the qualitative analysis software Nvivo 10 which made the coding process manageable. (The Nvivo file with all the statements can be acquired on request). This database contains a wealth of information on nanosensor technologies. Now the question is how to interpret all these statements in order to reconstruct the development of the field and find the emerging irreversibilities.

Step 3 provides an answer to those questions. In order to interpret all these statement a subject tree was constructed. This was done by making a cognitive mind map of the field, with the intention to categorize the statements in a comprehensive, consistent and logical manner. By cognitive mind map we mean a division of subject or categories to which the statements can refer. This division is based on an underlying logic which exists in the field of nanosensors. The division is not based on just the counting of subjects in statements, but rather on subject which makes sense according to actors in the field. It represents the structure which reoccurs in almost all the studied papers. Briefly stated these subjects are: sensor category; recognition-, transducer element; sensing target. The explanation and justification on how the tree is constructed is discussed more extensively in section 5.2. Thus the mind map serves as a framework to consistently follow the statements which represent the developments in the field. As a result a subject tree was reconstructed. The tree is a static representation of the topics within the field together with the amount of statements related to that topic.

Step 4 involved mapping the subject from the subject tree over time. By doing this we actually reconstructed the developments within the field. Thus from the insight gained from the subject tree and its evolution over time we could identify the development paths within the field of nanosensors.

Step 5 involved the qualitative reconstruction of the development paths. Thus by systematically describing the event, agendas, expectations, results etc. we reconstructed the development paths of the field. They main focus in this reconstruction is on agendas, expectations and networks as those are the building blocks of development paths. Within the reconstruction we tried to support our findings with a variety of quotes.

Step 6: Tracing emerging irreversibilities. Within these paths the emerging irreversibilities are already enclosed. The irreversibilities are situations where selection of different options occurred and the possibilities of further development became more defined towards a certain direction. The irreversibilities were found by looking at indicators of emerging irreversibilities. A compilation of indicators based on the work of Merkerk (2007) and Robinson (2010) which are already partial described in theory are presented below in table 2. Based on the indicators possible topics which could be irreversibilities were investigated. These topics were incorporated as an actual irreversibility as it somehow reduced the options of the relevant actors and made it easier to do research in a new better defined direction. For each type of emerging irreversibility it was assessed which indicators applied to that specific irreversibility. Next to the reconstruction of the development paths we described the development in the application areas, where we looked how nanosensor technologies could impact and fulfill the needs of those areas.

Table 2: Indicators of emerging irreversibilities

Indicators of emerging irreversibilities
1) Recognition of breakthroughs
2) Emergence of new topics and research disciplines in the field
3) Societal needs (Link between societal needs and technological opportunities)
4) Technological needs
5) Standards and platforms
6) Emergence of new journals
7) Recognized device in patent database
8) Topics funded by the government
9) Recognitions of specific promising applications
10) Inclusion of new actors within the field

Step 7 involved the reviewing and analyzing of the results. The found emerging irreversibilities are discusses, and compared between the application domains and communities(Academia, Government and Industry). In this way information on the dynamics of emerging irreversibilities is gained(how they relate en to which actors) and we can assess the strength of the irreversibilities. i.e if an irreversibility applies to more actors and multiple levels it is stronger as it has more influence on the development paths. *'It can be argued that the strength an irreversibility is larger when a larger diversity of actors is influenced (multi-actor dynamics) and/or the influence spreads through different levels. (multi-level dynamics*)' (Van Merkerk, 2007). In this study this would for example mean a growing interest towards a certain topic in the scientific communities, funding of the topic in governmental projects and the presence in patents as a sign if industry involvement.

3.1 Reliability and validity

In order to ensure the quality and trustworthiness of this research effort, the following criteria have been taken in account: credibility, transferability, dependability and conformability (Lincoln, 1995).
Credibility (or its equivalent internal validity) refers to whether there is a match between what the researcher is measuring and what he/she is intended to measure based on the theoretical concepts. To ensure credibility, data from multiple sources was used. Data triangulation is a key concept for increasing credibility, where a phenomenon is studied by multiple sources of evidence and by using different perspectives (Yin, 2003). In this thesis for three aspects of nanosensor developments multiple sources are used to reconstruct the development. Furthermore, as this thesis is explorative of nature,

the goal is to increase the understanding of the development of nanosensor technologies, rather than testing causal relationships.

Transferability (or its equivalent external validity) deals with the question whether the findings apply to other contexts (Lincoln, 1995). As this study focuses on nanosensor the results only apply to the field of nanosensor technologies. However the results do contribute to the more general topic of emerging irreversibilities. It provides insights which contribute to a better theoretical understanding on irreversibilities, how they occur, how they interrelate and how they can be studied in practice in further research. Thus, the findings ad to theory which can be applied in other contexts and to methods for studying emerging fields.

Dependability (or reliability), deals with the ability to reproduce this research (Yin, 2009). This is done by precise documentation of all the steps conducted during this research. A list of all the used data is present and all the statements together with the assigned modalities are accessible. An 'auditing approach' is used which holds that researchers make a complete record of all phases of the research process in an accessible manner (Lincoln, 1995).

Conformability (or objectivity) deals with the notion that qualitative research is always subjected to the researcher interpretations of data, as the researcher has to interpret the data of others. In this research case the interpretive part relates especially to the selection of statements, assigning modalities to the statements and to interpret and code the statements. The classification of modalities made by Robinson served as guidance to assign the modalities in a consistent manner. A way to increase objectivity is to let other researchers assign modalities to the statements and label the data. Unfortunately, that is not possible in this thesis.

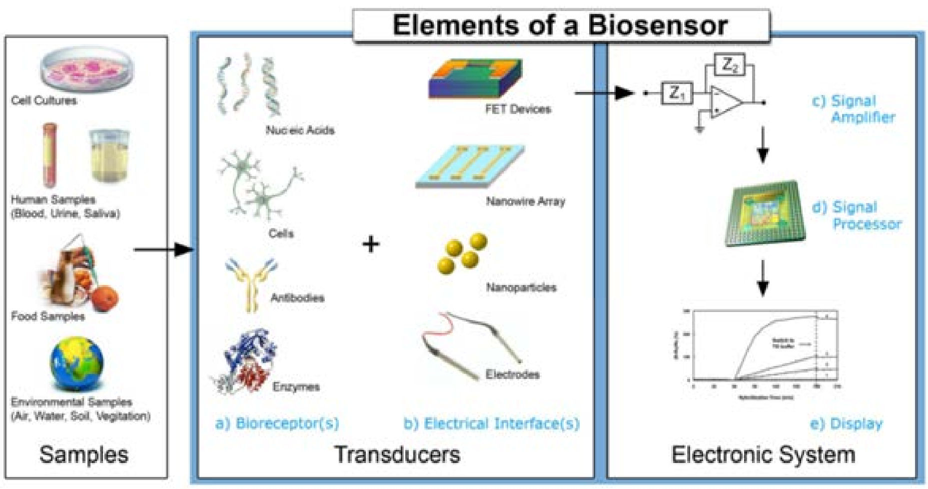
4. Nanosensor Technologies

This chapter is intended as an introduction to the complex field of nanosensor technologies. The state of art of nanosensor technologies will be briefly described. The use of nanostructures and the associated new characteristics of the nano-materials will be explained. The most common functionalities of these new structures in relation to sensor will be presented. Furthermore, the working mechanism and different type of nanosensor will also be addressed in this section.

Nanosensor technologies are a promissory field of R&D which has grown rapidly in the last decade. The number of publications, patents and scientific breakthroughs is rising, governments invest in projects related to nanosensor technologies and first applications are reaching the market. The R&D of nanosensors is especially gaining interest in the application areas: healthcare, environmental monitoring, and Agrifoods. Of these application area's the health care sector is receiving the most attention by industry actors (D. Wei, Bailey, Andrew, & Ryhänen, 2009) (Robinson, Huang, Guo, & Porter, 2013).

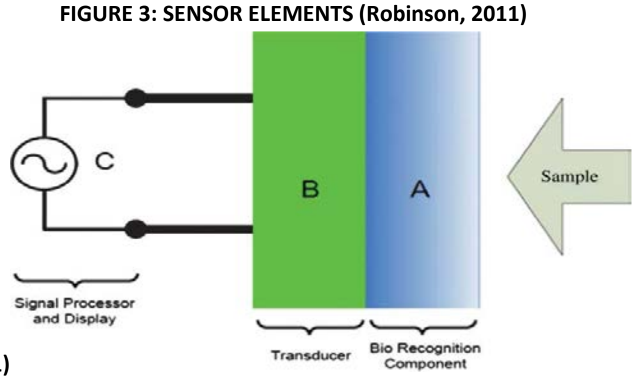
Let's start with what nanosensors are. Nanosensors are sensor devices with at least one of their sensing dimension smaller than 100nm. The purpose of nanosensors is to monitor physical, chemical or biological phenomena. This involves the detection of e.g. bio-chemicals in living cells, measuring small concentration of gases or toxins in the environment, or detecting early disease biomarkers in humans (Lim & Ramakrishna, 2006). These are just of few examples of what nanosensors can do. Such precise measurements on such a small scale are possible because at nanoscale materials exhibit different characteristics and have different properties then in bulk. One of the most logical or intuitive effect is the change in surface/volume ratio. When particles get smaller, there surface area get relatively larger, which has an influence on the chemistry and physics of the surface phenomena (Riu, Maroto, & Rius, 2006b). These new properties of nanomaterials can have significant impact on the functioning of sensors: The sensitivity of sensors can be increased, the detection limits lowered, small samples analyzed and direct detection without labeling is possible (Riu et al., 2006b). Fig. 2 provides an overview of the main elements present in a nano- or biosensor system.

FIGURE 2: SENSOR ELEMENTS (Grieshaber et al, 2008)



Basically, a sensor consists of two main elements: a recognition element and a transducer element. Furthermore the transducer is linked to a readout system which transforms or amplifies the measured signal into understandable information for the user. So the general sensing mechanism is as follows: A sample is detected by the recognition element elements of the sensor, this causes some physical changes in: e.g. electric current, associated wavelength of the material, excitation of electrons, magnetic fields etc. These changes are converted by the transducer element into a measurable signal. The signal can be amplified and converted into usable information for the user (D. Wei, Bailey, Andrew, & Ryhänen, 2009). Fig. 3 provides a clear schematic overview of the sensor elements.

FIGURE 3: SENSOR ELEMENTS (Robinson, 2011)



1)

4.1 The role of nanotechnology in sensor development

Recent developments and progress in the field of nanoscience and technology play a great role in the development of sensor technologies. The most important reason why nanotechnology can play an important role in sensor technologies is due the fact that it deals with phenomena at the same length scale in which people in the sensor industry are interested. It is quite intuitive that if you want to measure something small, it is better to use something small. Due to nanotechnological developments new materials have been discovered and become available. Nanomaterials have approximately the same size as proteins, enzymes, antibodies, DNA which makes them suitable candidates for sensing applications (Uusitalo & Hempel, 2012). Nanomaterials have new and other functionalities than at bulk, (e.g. different surface/are to volume ration, quantum confinement effects, biocompatibility, different electronic properties, optical effects etc.) which can be used to enhance the performance of the recognition are transducer element of a sensor system (Sadik, Aluoch, & Zhou, 2009). These new properties and functionalities allow for the development of new devices and applications.

Now let's focus on some of these nanostructures and their related properties. The following nanostructures are frequently used in the development of nanosensors: nanowires, nanofilms, quantum dots, nanocrystals, nanorods, nanobelts, carbon nanotubes (CNT's), embedded nanostructures and self-assembled nanomaterials (Riu et al., 2006). This list is not exhaustive as more nanoparticles exists and new are being developed and investigated as it is still an emerging field. The exploration of the new nanostructures with new functionalities is one of the key drivers of nano-technological developments. A typical classification of nanostructures is in dimensions; Nanoparticles and nanorods have a 0-D nanostructure. Nanowires, nanobelts and CNT have a 1-D nanostructure. Nanofilms, mambranes or 2-D assemblies have a 2-D structures and nanowires stracks or others assemblies have a 3-D structures. The dimension relate to the directions in wich electrons can travel. So on a nanowire the electrons can travel in one direction, where at a nanoparticle (for example a quantum dot) an electron is trapped (Huang, Peng, Guo, & Alan, 2009).

The development and possibility to make such nanostructures materials has opened new opportunities for analytical and sensing application. The nanostructured materials can be applied in the recognition element of sensors, in the transducer of senors, or in both. One expample of the function of these nanostructures in biorecognition application is called 'target labeling" which uses 1-D and 0-D nanomaterials, (usually semiconductor nanoparticles). In this method the nanoparticels are fixed to the molecules or analytes which are to be sensed. Once the analyte is fixed to the nanostructures, the physicial properties of the particles change(changes in color, fibration, voltage etc.) and the concentration and precense of the analyte can be measured (Robinson et al 2013). For exmaple quantum dots (QD) glow when UV light is shined on them, and different QD have different colors, which makes them suited for detection of different analytes. *'A quantum dot is a location that can contain a single electrical charge, i.e. a single electron. The presence or absence of an electron changes the properties of a quantum dot in some useful way and they can therefore be used for several purposes such as to information storage or useful transducers in sensors.'* (Riu et al., 2006b).

Thus nanotechnology has the potential to improve sensor performance. In literature the following element or parameters are suggested which can and need to be improved in the field of sensor technologies:

- *Sensitivity*; relates to the amount of changes in physical parameters which are needed to create a detectable change in output. So the higher the sensitivity of a sensor the better it can measure small changes at small scale.
- *Selectivity*; relates to the ability of sensors to bind to a specific analyte of interest, and not to other substances in the sample. By increasing the selectivity of sensor devices it becomes possible to make sensors which only react to the desired analyte.
- *Signal to Noise Ratio* relates to the selectivity of the sensor. The higher the ratio the more selective the sensor is.
- *Detection Limits*, this relates to the sensitivity of the sensor. The higher the sensitivity the smaller the amount of analyte which can be detected.
- *Recovery times and Stability*: Once a sensor has measured a specific concentration of a substance the sensor can be saturated or fouled, and thus is unable to detect new substances. The time related to the cleaning or resetting of the sensors is called recovery time.
- *Scalability*: if sensors are to be mass produced it is necessary that the sensor elements, nanomaterials can be fabricated and produces in large quantities.
- *Real time detection*: an important topic in sensor technologies is to get the information in real time without sensing the data to a laboratory or other place for further analysis. The promise of real time sensors offers great opportunities in multiple sectors and is a big driver of the field.
- *Multiplexing*: The ability to detect multiple different analytes on one sensing platform in a single measurement
- *Reduce complexity of sensing process*; thus reducing steps in the sensing process which can become obsolete due the advantages of nanomaterials (e.g. label free sensing methods). (NNI, 2009; Dhand, Das, Datta, & Malhotra, 2011; Erickson, Mandal, Yang, & Cordovez, 2008; Ruedas-Rama, Walters, Orte, & Hall, 2012; Sannomiya & Vörös, 2011; Uusitalo & Hempel, 2012; Wang, 2009; Zhang & Zhang, 2012)

Thus, different nanostructures can lead to different functionalities or sensing priciples which can enhance sensor performace, some examples of the functionalities are; catalytic functions, quantum effects, luminescent effects, magneto resistive effects, high binding capacity, superparamagnetic effect, piezoelectric effect, enhanced electron transfer, enhanced heat transfer etc. In the further parts of this thesis the dominant structures and functionalities will be explained in more detail. The main messege here is that the properties of the nanoparticles improve the performance of materials which can be used in sensing methods (Katz et al, 2004). There exists a variety of nanoscale materials and functionalities of these materials which makes the field of nanosensor highly diverse with potential applications in a variety of sectors (Robinson et al, 2013)

4.2 Categorization of nanosensors

Based on the nanostructures, briefly mentioned above, a lot of different types nanosensors can be made. In order to get a grip on this field the following classifications of sensors can be made. The sensors can be classified based on their transducing mechanism: i.e. (electrical, optical, mechanical etc.) or based on the recognition principle (what are the sensors measuring i.e. DNA, proteins, enzymes etc. or based on their applications (environmental, food, medical diagnosis) (Riu et al., 2006). However the most common and probably most suitable way to organize the different types of sensors is based on their transducing mechanism as almost all papers follow that division. Hence the categories are: Optical-, Electrochemical-, Mechanical and/or vibrational-, Magnetic- and Piezoelectric nanosensors.

4.2.1 Optical nanosensor

An optical nanosensor can be defined as a device with dimensions smaller than 1 mm that is capable of continuous monitoring of a chemical or biological parameter by optically transforming the information into an analytically useful signal (Borisov & Klimant, 2008).
The first optical nanosensors were based on the compound fluorescein located within a nanoparticle, and is used for pH measuring (Sasaki et al, 1996). Such sensing molecules exist of a substrate binding unit and photoactive element, when the substrate binds to a specific analyte a fluorophore absorbs light of a specific wavelength. This is followed by an emission of quantum amounts of light with energy levels corresponding to the energy difference between the ground and excited state (Silva et al, 1997). Based on this difference the measurement of a specific compound can be determined. The changes in photo-vibrational properties are the basis of this sensing concept (Lim & Ramakrishna, 2006). Optical nanosensors are said to be able to analyze in vivo process in the cell, without destroying or modifying the cell activities. (Which was often the case, when using dyes instead of nanoparticles.) So, the minimal invasiveness of optical nanosensor is a significant advantage. Hence, optical nanosensors are especially suited for intracellular measurements (Aylott, 2003).

Most of the optical sensors are based on phenomena related to Plasmonics, fluorescence effects and surface Plasmon resonance techniques. Plasmonics refers to the study of enhanced electromagnetic properties of metallic nanostructures. This principle works as follows: An incident electromagnetic fields caused by e.g. a beam of light irradiates on the surface of a metallic nanostructure, this has an effect on the conducting electrons of the metal as they are displaced into frequency oscillations equal to those of the incident light. The oscillating electrons are called Surface Plasmons and due to their oscillations they produce a new electric field. The origin of the oscillations are called Localized surface Plasmons. '*LSPs can be excited when light is incident on metallic nanoparticles whose size is much smaller than the wavelength of the incident light. At a suitable wavelength, resonant dipolar and multipolar modes can be excited in the nanoparticles, which lead to a significant enhancement in absorbed and scattered light and enhancement of electromagnetic fields inside and near the particles. Hence, the LSPs can be detected as resonance peaks in the absorption or scattering spectra of the metallic nanoparticles. This condition yields intense localized fields which can interact with molecules in contact with or near the metal surface*.'(Vo-Dinh, Wang, & Scaffidi, 2010)

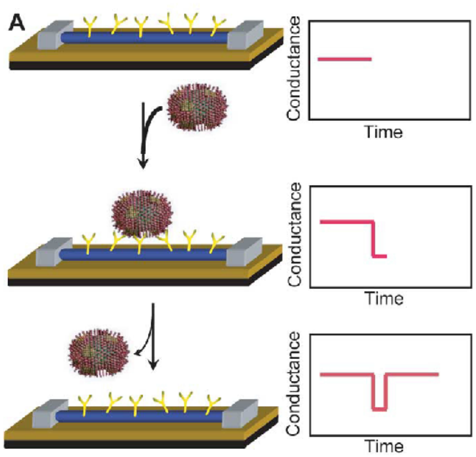
The extremely intense and highly confined electromagnetic fields induced by the LSPR provide a very sensitive probe to detect small changes in the dielectric environment around the nanostructures, which is particularly attractive for sensing applications (Sepúlveda, Angelomé, Lechuga, & Liz-Marzán, 2009).
Another promising spectroscopic method is Raman spectroscopy. This technique involves the probing of a sample with a beam of light which causes a reflection of absorbed light which is a signature of the species in the sample. A common example of this methods is called Surface enhanced Raman Spectroscopy (SERS) which is based on the light scattering phenomena. The developments in the field of optical nanosensors will be described in section 6.2.

4.2.2 Electrochemical nanosensors

Electrochemical sensors are often based on 1 dimensional nanostructures, such as nanowires and nanotubes. Due to the semiconducting properties of these 1D nanostructures they are very promising materials for transduction elements for electronic signals. Electrochemical sensors measure the change in current (amperometry and voltammetry), voltage (potentiometry), impedance or conductance resulting from a chemical reaction that either transfers or separates electric charge with reasonable selectivity and sensitivity. They are thus classified as amperometric/voltammetric, potentiometric, impedance and conductometric sensors based upon their analytical principles of operation (D. Wei, Bailey, Andrew, & Ryh, 2009).

Electromechanical sensors are especially applied in biosensor research and applications. The sensors are usually designed as follows: the biorecognition element (e.g., antibodies, DNA, receptors) detects an analyte of interest which causes a change in current or potential. This is transduced by a solid electrode surface (e.g., Pt, Au, Ag, graphite or carbon-based conductors). Based on difference in the current the concentration of analyte can be determined (Sadik et al., 2009). Within the biosensor developments the Amperometric methods of transduction is the most common. Amperometric biosensors operate by applying a constant potential and monitoring the current associated with the reduction or oxidation of an electro active species involved in the recognition process (Sadik et al., 2009).

FIGURE 4: SCHEMATIC NANOWIRE FET (LIEBER, 2005)



The dominant working principle behind most electrochemical sensing are Field Effect transistors (FET). A FET is a transistor which change in resistance during an binding event of the analyte of interest to the receptor. Because of the changes in resistance the conductivity of the FET changes. Changes in conductivity can be measured an amplified for analytical purposes. FETs are already widely applied in the field of microelectronics. Now, due to the miniaturization processes and new advance in nanoscience it becomes possible to make such FETs at nanoscale using CNT or nanowires as conducting material (Dekker et al, 1998) Fig. 4 gives a schematic representation of a single virus binding to the surface of a nanowire functionalized with an antibody specific to that virus.

Another emerging tool for sensing phenomena at the nanoscale is nanopore detection. This method is also based on electrochemical technique and the principle is as follows: a nanometer size hole is made, usually referred to as pore. The pore can be made synthetically but can also be found in nature in the form channel proteins that are inserted in lipid membranes. When a voltage is applied across the nanopore, an ionic current flows through the nanopore. Now the charged substrate (antibody, DNA, RNA, molecule etc.) is electrophoretically translocated through the pore which causes changes in the ionic current. The changes in current/voltage can now be measured by electrical (patch-clamp) measurement techniques. The changes in voltage represent a signature of the substrate which was trans-located through the pore (Nakane, Wiggin, & Marziali, 2004). The nanopore sensors are now especially popular for DNA sequencing applications. Since 2012, natural nanopore sensors are commercially available on the market for DNA sequencing (Hayden, 2012). Synthetic nanopores, which are much more stable and allow for easier integration with electronics compared to their biological counterparts, appear to be a very promising alternative. For example, nanopores can now be fabricated in atomically thin graphene which brings fast (15 minutes) and relatively cheap (less than 1000$) DNA sequencing within reach for many people (Bayley, 2010). More on the development of electrochemical sensor will be presented in the description of the development paths.

4.2.3 Magnetic nanosensor

The magnetic transduction mechanisms are quite related the field of plasmonics and electromagnetic transducers described earlier. The field of nanotechnology which measures magnetic fields is called magneto electronics or spintronics. The idea behind these methods is that magnetic fields around

certain particles can be measured as a result of interfering magnetic field of sensor devices. The electric field is then transuded to an electric signature based on resistance change of the device.
Magnetic nanoparticles can provide magnetic field signatures that can be detected by those magneto-resistive nanosensors. These nanoparticles can be coated with bio-receptors which will bind with an analyte of interest (i.e DNA, Bacteria, biomarker ect). Thus the magnetic nanoparticles can act as highly selective biolabels for species of interest (NNI, 2009).

4.2.4 Mechanical nanosensor

Nanomechanical sensors are about measuring small vibrations or displacements or oscillations of mechanical structures in response to physical stimuli i.e. changes in pressure, flow rate, viscosity, density, temperature etc. A common design in mechanical sensors is the use of cantilever platforms which are sensitive to small mechanical changes. By monitoring changes in resonance frequency of the sensing element a specific analyte can be determined (Lim & Ramakrishna, 2006). *'This elementary phenomenon has been the basis of a new class of bio-nanomechanical devices as sensing components of integrated microsystems that can perform rapid, sensitive, and selective detection of biological and biochemical entities.'* (Gupta et al., 2006)

4.2.5 Piezoelectric nanosensor

Only recently, another type of nanosensor received a great deal of attention. This nanosensor is based on piezoelectric phenomena. Basically piezoelectricity holds that changes in pressure(mechanical) can cause electrical current. Thus the pressure of substances exerted on the receptor can be measured as an electric current starts to flow. Such sensor are closely related to FET and are called PE-FET (piezoelectric FETs). The principle is basically the same, only now the nanobelts are coated with a self-contracting/expanding polymer which causes stress on the nanobelts and induces electricity. *'Piezoelectricity is an important phenomenon that characterizes the electromechanically coupled response of a material, and it has been widely used in science and technology. At nanoscale, most of the studies had been carried out for exploring the semiconducting properties of quantum dots, NWs as well as nanotubes, but the nano-scale piezoelectric property remained an unexplored field until 2004*. (Z. L. Wang, 2009b). The piezoelectric phenomena also provide another interesting opportunity of the field of nanosensors: The possibility to harvest mechanical energy from the environment and converting it into electric energy to power an autonomous sensor system is a widely shared vision circulating in the field of nanosensor (Lao, Kuang, Wang, Park, & Deng, 2007).

4.3 Biosensors

Biosensors or nanobiosensors represent a large part of the nanosensor development. Biosensors are sensors or analytical devices that make use of a biochemical receptor to provide information on a specific analyte. The receptor is usually in direct contact with the transducer so no other processing steps are needed. Hence the biosensors are expected to be capable of continuously monitoring concentrations of specific analytes. (Martín-Palma, Manso, & Torres-Costa, 2009) Similarly to the classification above, biosensor can be classified based on (bio) receptors and transduction element. The most common bio receptors are whole cells, enzymes, DNA and antibodies. The biosensors can use different transducing elements, however in literature most of the biosensors are based on electrochemical transducers. (Martín-Palma et al., 2009). Biosensors can be applied to a large variety of samples including body fluids, food samples, cell cultures and be used to analyze environmental samples.
This chapter has given an indication of which different nanosensor technologies there are. But as the technology is still in the development phase, this overview is not finite as new possibilities, nanostructures, fabrication methods are still emerging.

5. Results

5.1 Representation of the data

This section provides a sample of the collected statements. The goal is to show the type of statements encountered in the database together with the amount of statements per modality and community. By showing the data here the reader can better understand the conducted research process and see how we derived the final results from these findings. In the table 3, 4, 5 some statement examples are presented with the amount of statements in the left column. Furthermore, the distribution of statement modalities overtime are visualized in figure 2, 3 and 4. This data gives a first overview of what type of statement circulate in the field of nanosensor technologies (within the documents from our database). The main finding is that the majority of the statement could be classified as agenda statements, followed by expectations and proof statements. The categories science-fiction and visionary linkages ware almost absent in the studied material. This is an indication that it is quite clear what the technology is and little speculation on science fiction possibilities are voiced. Furthermore the data is quite technical in nature and intended for specialized readers, one can suspect that popular science magazine or newspapers report would report more on visionary statements.

The statements from all the databases are used to reconstruct the development of the field and developments in relation to the application areas. However not all statements are equally suited to do so. The statements from the patent database are quite technical in nature and do not really relate to the application areas. Hence the patent database could only be used for the general reconstruction of nanosensor technologies and the development paths. The governmental statements in contrast are less technical in nature and usually relate more to general societal needs (e.g. Cancer research), or the need for more fundamental knowledge on certain topics. Hence this database is used as complementary the information for the application domains as well as the description of the development paths. The scientific database contained most of the statements which we used for the reconstruction of the development paths, as well as the description of the application areas. The description of the application domains is thus mainly based on statements within scientific articles and is complemented by statements from the governmental and patent database if the statements were related to the application domain.

When looking at the time element (figures 5, 6, and 7) we see almost no variation in the statement distribution, except for the agenda statement. There we can clearly see an increase over the years in the scientific community which is an indication that more researcher are working on nanosensors.
Another remarkable finding is that very little proof statements are found in the scientific and patent database. One might expect that scientific papers per definition should presents proof. An explanation for this is that during the coding/selection process we were interested in more general statements relating to nanosensors, and less in very specific statements related to a specific samples. In general the selected scientific statements mostly entail agendas on what researchers are working on and expectation related to nanosensors.

For the patent database most statements deal with a device which still is to be developed. Also here the most prevailing statements are of the type agenda. Little expectations are voices in patents and also little proof statements are found. This might be unexpected as a first thought would be that patents should contain proof. However, the examples below show that most statements deal with an invention which might contain a certain technology and is still to be created, and thus is a goal or agenda. Based on such statements a patent can be granted, and no proof is required.

In the governmental database also the agenda statements are most often found, as the project description contain statements on the goal/aim of a project. Furthermore it can be seen that the in relation to patents, and articles more expectations are voiced. This is plausible as the projects need to contain expectations as they have to attract funding which needs to be justified.

Table 3 : Scientific Publications

Statement modalities	Statements examples
Proof **149**	''these examples demonstrate highly sensitive and selective multiplexed electrical detection of protein cancer markers and telomerase using arrays of silicon nanowire field-effect devices.'' ''As first discovered in the early 60s, semiconducting oxides are able to sense gases upon changes of their conductance'' ''This work provides concrete experimental evidence on the effect of SWNT−DNA binding on DNA functionality''
Agenda **1613**	''Given the gas sensing mechanism of semiconducting oxides, the use of nano-sized powders is proposed to improve the performance of gas sensors in order to allow their use in atmospheric pollutant monitoring.'' ''Atmospheric pollutant monitoring is one of the most important applications that need the development of reliable and cheap solid-state gas sensors'' A DNA biosensor with chronopotentiometric detection and an immunosensor with fluorescence detection were applied to the determination of PCBs in river water with a detection limit of 0.2mgL–1 ''the preparation process of nanomaterials including CNTs and nano/micro particles should be further developed in order to improve their sensitivity towards OPs. As examples, the prepared semiconductor nanoparticles with high and stable flouresence properties will dramatically benefit the detection of OPs at low concen tration.'' ''There are questions about the interactions of nanoparticles with the food matrix and within the human body. These questions need to be addressed by future research''
Expectation **557**	''The use of nano-sized semiconducting oxide powders has been found to be very promising for the fabrication of thick- film gas sensors able to detect polluting gases during environmental monitoring field tests'' ''After many years of development, biosensors have begun to move out of the laboratory and into commercial applications. Combining advances in biotechnology, nanotechnology and information processing, these novel devices promise to open the door to many exciting new environmental monitoring solutions.'' ''Due to their unique characteristics and flexibility, biosensors and related techniques show great promise for environmental monitoring applications.'' ''Smart nanoscale materials may reduce these limitations and represent a new way to generate and measure motion in devices and structures. Among the various nanoscale materials, carbon nanotubes (CNTs) exhibit extraordinary mechanical properties.''
Guiding Vision **111**	''From the environmental point of view, this type of biosensor could be used to identify pathogens in water by functionalising the NPs with oligonucleotides that are comple- mentary to the DNA sequences of the pathogens'' ''LSPR sensors could, in theory, be reduced to chips as small as 100nm using single NP spectroscopy tech- niques. LSPR biosensors also satisfy other major prerequisites for biological studies: they are robust and durable, they are effec- tive under physiological conditions and they react minimally to non-specific binding'' ''Biomonitoring studies that can routinely measure chemical and biological molecular markers of exposure and the development of dosimetry models that can factor in these markers offers the potential to better understand the risk factors associated with adverse health.''
Visionary Linkage	''The combination of nanotechnology, biology, and photonics opens the possibility of detecting and manipulating atoms and molecules using nanodevices, which have the potential for a wide variety of

9	medical uses at the cellular level.'' ''The future of nanotechnology is likely to focus on the areas of integrating individual nanodevices into a nanosystem that acts like living specie with sensing, communicating, controlling and responding. A nanosystem requires a nano-power source to make the entire package extremely small and high performance''.
Science fictions **1**	recent publication in Nature projects a picture of computing in 2020: "Computers could go from being back-office number-crunchers to field operatives. Twenty-four hours a day, year-in, year-out, they could measure every conceivable variable of… a human body, at whatever scale might be appropriate… These new computers would take the form of networks of sensors with data-processing and transmission facilities built in"

FIGURE 5: SCIENCE, DISTRIBUTION STATEMENT MODALITIES OEVR TIME

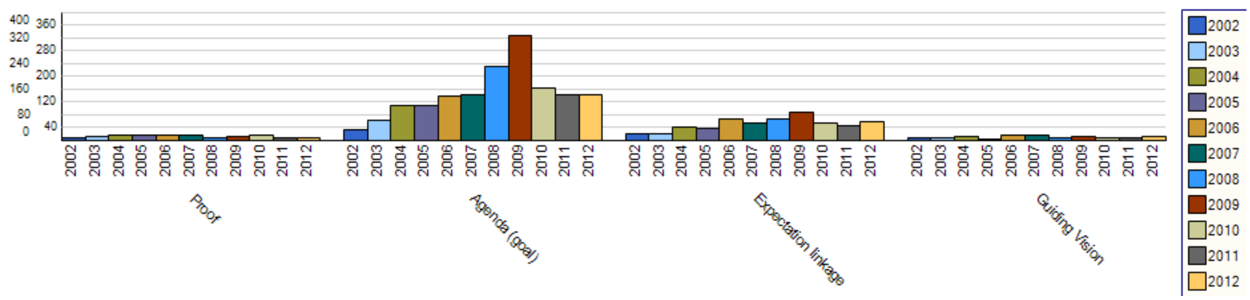


Table 4: Governmental funding

Statement modalities	Statements examples
Proof **13**	''During the REFLAB project at GEM, they reinforced their ability to take a product throughout feasibility studies, product development to scale up manufacturing level. At the end of the project, they were able to manufacture the glucose biosensor in controlled conditions at a level of 1 000 biosensors per day.'' ''In addition to the above technique we have further proof of nanoparticle self- assembly process. When the substrate is pre-patterned in a way to form peaks and valleys the nanoparticles are assembled in a line configuration on the peaks. This way we were able to self-assemble nanowires with a width of 30 nm formed from nanoparticles without the need of any demanding lithographic process.''
Agenda **286**	''The project will aim at developing a set of metal nanosensors to image in vivo the dynamics of manganese and zinc localization and their regulation in Arabidopsis thaliana. An integrated approach in plants, combining the use of mutants impaired in metal transport and metal imaging, will enable us to further understand biological processes underlying the control of metal homeostasis in plants.'' ''BIOMONAR develops multiplexed nano-array biosensors for environmental targets, i.e. pollutants and pathogens.'' The aim of the proposed research is to dissect the mode of action of the mechanism coordinating cell wall integrity maintenance with primary metabolism in Arabidopsis thaliana.
Expectation **142**	''QDs heterostructures are expected to extend the emitted wavelength and to strongly improve the performances of semiconductor LDs (reduced threshold, high operating temperature) as demonstrated with the GaAs and InP technologies.'' ''The development of new generation composites using CNTs as filler material within the matrix is expected to result in the enhancement of the damping properties of the material, the increased fracture toughness and the improvement of its fatigue life. This is expected to occur due to the multiplicity of energy dispersive mechanisms within the material.'' ''The project is significant in view of its potential applications in the field of fast and non-invasive

	medical diagnostics.'' ''The project will apply a multidisciplinary system-wide approach relying on converging technologies (bioinformatics, nanotechnology, modelling) to obtain knowledge for meat safety that will be translated into simple devices and practical indicators of quality and safety.''
Guiding Vision 30	This project will enable the researcher to acquire new expertise in the design of nanosensors for living cells. These robotic fish will be equipped with chemical sensors to find pollutants in the water and modems to create an ad hoc network for communication within the swarm. This will allow the shoal of robot fish to build up a broad map of the pollutants moving through the port in real time whilst adapting naturally to changes in environmental conditions in the port. The project will be of benefit to the EU meat industry, providing useful tools and fundamental knowledge of the spoilage and hazard. It will also impact on the research and informatics communities.
Visionary Linkage 1	The ability to miniaturise devices has completely changed our society and modern technology is constantly pushing towards smaller and lighter devices with enhanced and more diverse functionalities. Future technologies will increasingly rely on materials t hat respond to their environment in a manner that suggests a degree of "intelligence" and nanoscience may offer many of the tools and opportunities that are required in order to a build a foundation for the next scientific revolution.
Science fictions 0	-

FIGURE 6: GOVERNMENT: DISTRIBUTION STATEMENT MODALITIES OVER TIME

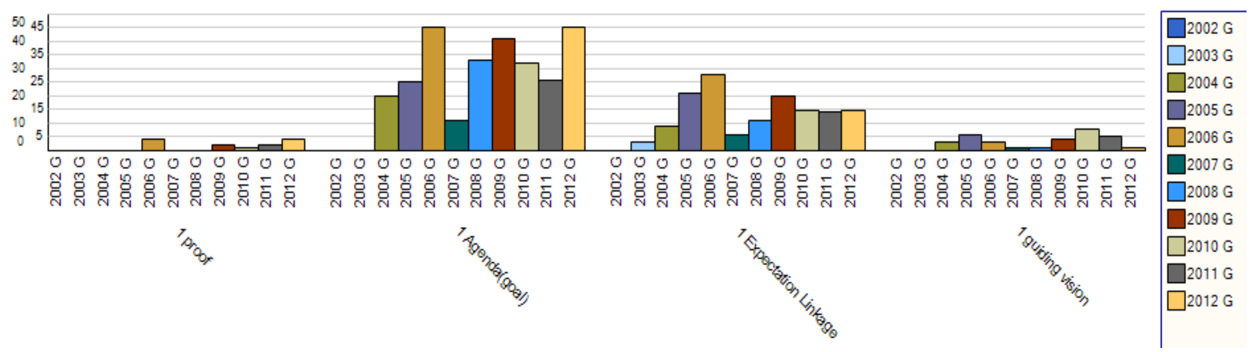
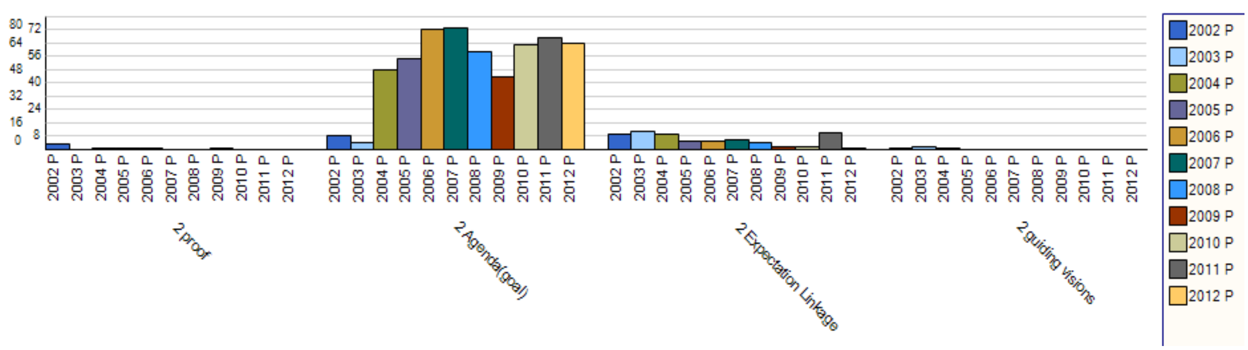


Table 4: Patents

Statement modalities	Statements examples
Proof 10	''Importantly, the fiberless sensors of the present invention are non-toxic and permit the simultaneous monitoring of several cellular processes. In one embodiment, the present invention contemplates the use of such fiberless sensors to monitor a single cell exposed to a variety of noxious or trophic stimuli.'' ''We have shown that NWs can be assembled into parallel arrays with control of the average separation, and by combining fluidic alignment with surface patterning techniques that it is also possible to control periodicity. In addition, we have demonstrated the possibility of layer-by-layer assembly of crossed and more complex structures by varying the flow direction in sequential steps'' ''In addition, proof-of-principle demonstrations of nanotube functionalization for sensing or binding specific molecules in the gas and liquid phases have been successfully made.''
Agenda 573	''The invention relates generally to the sensing of biological agents and, more specifically, to using nano-electronic circuits as transducers to convert and to amplify signals produced by the biological agents and methods for making such nano-electronic circuits.'' ''In another aspect of the present invention, an array of sensors may be implanted. Each sensor in an array may perform a different task. In a related aspect of the present invention, the implanted

	sensor may be powered by a fuel cell that utilizes chemicals that are abundant in a body. These chemicals may include glucose, cholesterol, ATP, and oxygen.'' ''The growth of nanowires such as single and multiple wall carbon nanotubes and semiconductor nanowires has been demonstrated experimentally. Nanowire growth may be initiated using catalysts deposited on the surface of a substrate. Improved techniques for patterning such catalysts are needed.''
Expectation 42	''One dimensional nanostructures, such as nanowires (NWs) and nanotubes (NTs), are ideally suited for efficient transport of charge carriers and excitons, and thus are expected to be critical building blocks for nanoscale electronics and optoelectonics. Studies of electrical transport in carbon NTs have led to the creation of field effect transistors (FETs), single electron transistors, rectifying junctions and chemical sensors.'' ''The nanoparticles PI and P2 are potent enhancers of the spin-spin and spin-lattice relaxation processes. Interestingly, the spin-spin relaxation was furthermore significantly enhanced by oligonucleotide hybridization, rendering the particles as potential magnetic nanosensors.''
Guiding Vision 4	''We believe that flow assembly represents a general strategy for organization of NW and NT building blocks into structures needed for wiring, interconnects and functional devices, and thus could enable a bottom-up manufacturing paradigm for future nanotechnologies.''
Visionary Linkage 1	''In one aspect of the present invention, by using the nanosensors, new possible senses may be created among humans. Humans would be conscious of any disease state at the onset.'' ''For example, a small cluster of cancer cells would be recognized immediately, and that would cause a conscious unpleasant feeling that would be only slightly unpleasant early on, but will grow stronger if the cancer is allowed to grow. This would allow the detection of cancer years earlier than is currently possible.''
Science fictions	-

FIGURE 7: PATENTS, DISTRIBUTION STATEMENT MODALITIES OVER TIME



5.2 Interpretation of the data

Based on the first analysis of the statements and the technology description we tried to interpret the data in such a way which allows for the identification and reconstruction of development pathways within the field of nanosensor technologies which we could follow through time. This was done by making a cognitive mind map of the field, with the intention to categorize the statements in a comprehensive, consistent and logical manner. By cognitive mind map we refer to an underlying logic which is present in the field of nanosensor researchers. The mind map consists of subjects or categories which are important in the field of nanosensors and to which a statement can refer to. Most of the nanosensor papers deals in some way with these categories. Thus the mind map serves as a framework to consistently follow the statements which represent the developments in the field.

Sensor Category

First of all a distinction is made between the type of nanosensor. Almost all the studied papers categorize the sensor based on their working principles, thus in order to follow the developments of the different sensors it makes sense to make such a division as well. Within the field of nanosensors, nanotechnologies based on nano-photonics and nano-electronics have significantly the biggest impact on nanosensor development. Hence electrochemical and optical sensors probably will be most discussed, but also other categories are possible, e.g. magnetic, mechanical and piezoelectric.

Recognition-, Transducer element

Another way to look at the field of nanosensor, and the development pathways, is to focus on how the nanomaterial enhance the sensor performance, and in which part of the sensor they are used. As mentioned before sensor consists of recognition and a transducer element. The nanomaterial can contribute to the recognition-, transducer element, or both. Thus while analyzing the statements we can categorize them based on the part of the sensor were the nanomaterial is used. Robinson described the function which nanomaterial can have in the recognition element as follows: *'The functions of nanomaterials used in recognition can be divided into two classes. The first class is referred to as "target labeling" using "0D" (zero-dimensional) or "1D" (one-dimensional) nanostructured materials (e.g., semiconductor nanoparticles). For this nanobiosensing system, nanostructures are fixed to the biomolecules (or species) that are to be sensed. The second class of nanomaterial functions used in recognition is mainly in the form of replacing the traditional molecular recognition layers. This takes the form of 2D or 3D structures (or constructs) upon which a biomolecule will interact (think of a liquid flowing across a plate, or through a sieve — the nanobiosensing elements will be fixed to the plate or sieve and detect the biomolecules in the liquid)'' (Robinson et al, 2011).* In general when nanomaterial is used in the recognition element of a sensor it is used rather passively, which means that it uses the surface properties, such as surface to volume ratio, surface affinity, and selectivity to biomolecules and cells (Huang et al, 2009).

Nanomaterial used in the transducer element are used in a more active way, which means that the unique properties of nanoscale dimensions (e.g. quantum effects, semiconducting properties, piezoelectric effect etc.) are more emphasized in sensor design. The general tendency in literature on nanosensors is that nanomaterials can have the biggest impact in the transducer element of a sensor device. The transducer can be seen as the heart of the sensor which is the material which converts a recognition event into a measurable signal (NNI, 2009). The working principle of the transducer is also usually similar to the category the sensor is assigned to.

Sensing Target

Yet another way to look at development paths is to focus on what the sensors are actually sensing. Huang et al, have made the following division based on sensing target: 1) cell-based sensing, 2) sensing macromolecules, such as proteins and DNA, 3) sensing small chemical molecules such as Fe, O_2, etc.

The 1st of these focuses on sensing the behaviors of whole cells without knowing detailed information about the sub-cellular matrix, organelles and metabolic pathways. The 2nd path senses by probing bimolecular interactions, either on the cell membranes or inside the cell bodies themselves. The 3rd path emphasizes the presence and concentration level of biologically relevant chemical substances. All three innovation pathways may use nanomaterials either passively or actively.

In sum, we first categorize the statement to the category of working principles, hence we look where the nanotechnology is applied (transducer/receptor) and then we look what the sensing target of the sensor is (cellular/macro molecules/small molecules). Next to this we can specify the sensing targets to really understand what analytes are measured. By doing this a subject tree was constructed and the most dominant development paths can now be followed. Thus the three consist of the categorization made above. The first branches or division consist of the different sensor categories. Within these categories it is assed if the statement refers to the recognition or transducer element, or in many cases both! The next step in the diagram is to specify what the sensor is measuring. Here we take the receptor and transducer together, as they are both needed to sense an analyte, and make a division of what the analyte of interest is in the statements. (See subject tree Fig 8 to get a understanding of the above description.) The analytes which reoccurred more often have a bigger size in the subject tree.

Some complication while categorizing the statements:

- Not all statements could be fit into these categories as some are more general and address different aspects of the field. However they can be used for the qualitative description of the development paths.
- Also, not all statements fit into all the categories, for example: a statement can address a category and sensing target without addressing how the nanomaterials are used in the sensor. In such cases the statements was labeled only in *category* and *sensing target*.
- A statements can fit in more categories at the same time, in those cases it was coded in multiple categories.
- During the statement analysis we found that almost no statement referred to cell-based sensing, hence this category was deleted from the subject three.

Appendix B provides some examples of the coding process.

The first step now is to make a subject tree. The subject tree is a static representation of what is going on in the field. The next step involves the analysis of the topic of the subject tree through time. The topic of the subject tree can be followed through time as percentage of statements or as actual numbers of statements. This gives insight in the development of a category in relation to the other categories, application domains and development in industry, academia and governments.

Based on the insight from the subject tree we identified two development pathways which were followed from 2002-2012. A contextually rich text of nanomaterial-enhanced sensors is presented which includes the description of R&D activities, most interesting findings of research groups, governmental projects, and patent applications in relation to the specific development path. The application domains which can be affected by the nanosensors are also addressed. We tried to see how the needs of an application area can be met by the development within the nanotechnology. In general we will looked for trends, research directions, challenges, drivers, obstacles and indications of possible emerging irreversibilities as presented in the theory/methodology section. Based on the description of the development paths and the emerging irreversibilities are traced.

5.3 Subject tree

FIGURE 8: SUBJECT THREE GENERAL DEVELOPMENT NANOSENSORS

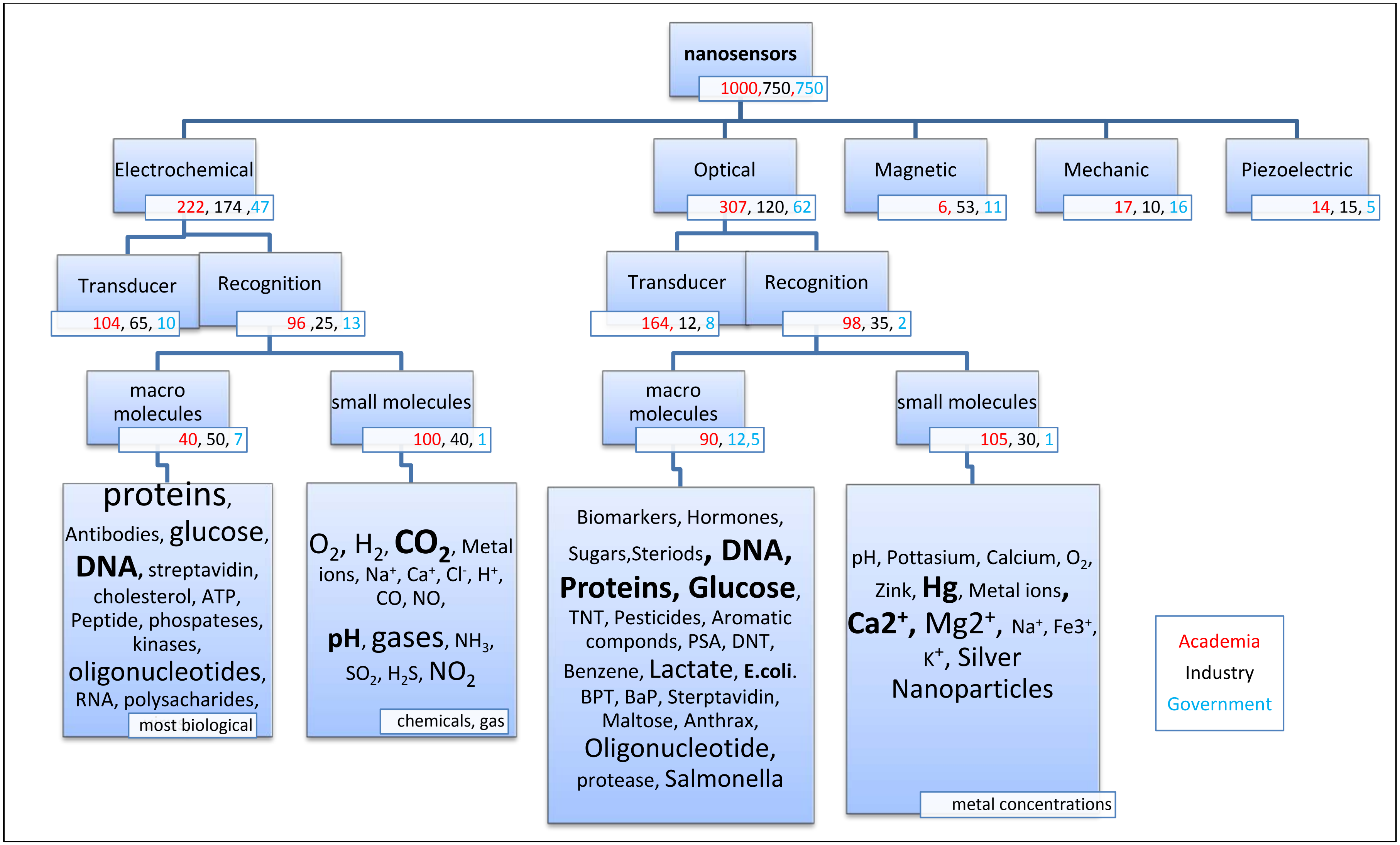


Figure 8 present the created subject tree as described in the previous section. From the subject tree the following findings are derived: For one it is evident that indeed two sensor categories dominate the field. These are the optical and electrochemical sensors. Furthermore the statements relate more often to the transducer element than the recognition element, which implies that research on the transducer element receives more attention than the recognition element of the sensor. However the differences are not that big.

Another interesting finding is that in the scientific literature more statements relate to the optical sensors where at the industry level the electrochemical working principles are more addresses. Also the magnetic sensors are reoccurring more often in the patent database than in the scientific paper or governmental project.
When considering the analytes of interest it can be stated that the electrochemical sensors are better suited for gas detection than the optical techniques, where the optical techniques are better suited for the detection of small concentrations of heavy metals, ions and silver NP. In relation to the macro molecules there is almost no difference between the optical or electrochemical sensors. Both categories have been reported in relation the same type of analytes. However the category of analytes for the optical sensors seems a bit broader.

From the subject tree it is clearly visible that within the studied data most statements come from scientific papers, as they fit better into the categories of the subject three. The statement of the governmental project description where usually not so specific and therefore harder to analyze. In relation the application domain it was even harder to assign the categories to the statements as here the statements not always referred to the working principles, but address more societal issues or articulated needs from the application domain. Hence that information is used for the qualitative description of the application domains. Nonetheless, we reconstructed with the available statements a subject tree for the application areas as well. See figures 9, 10, and 11.

FIGURE 9: SUBJECT TREE FOOD

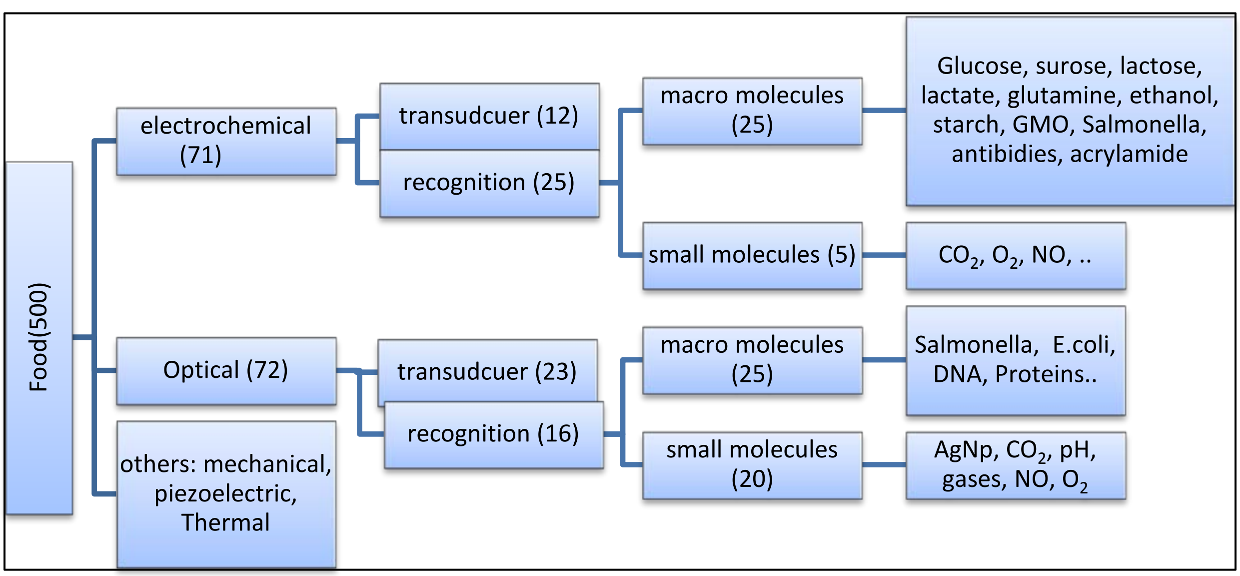


FIGURE 10: SUBJECT TREE ENVIRONMENTAL ANALYSIS

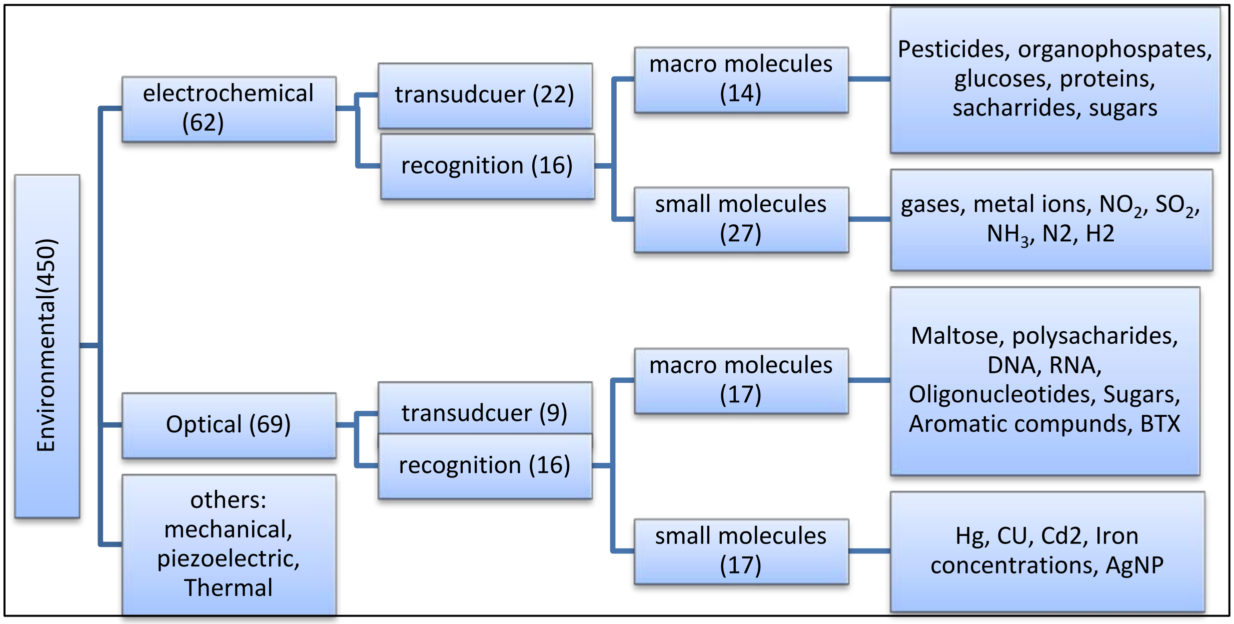
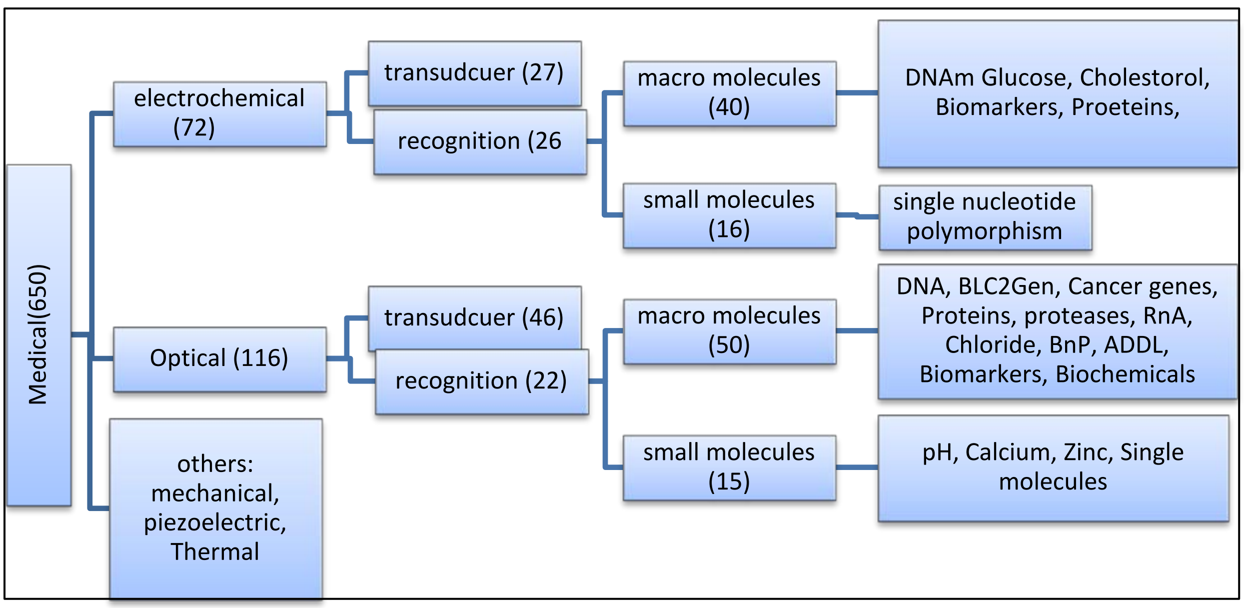


FIGURE 11: SUBJECT TREE MEDICAL APPLICATIONS



The following findings are derived from the subject trees related to the application areas: For one, it seems that the optical sensors are more represented in the medical application, and that macro molecules are primarily the analytes of interest. For the food and environmental application such a distinction cannot be made. Both small molecules and macro molecules, related to pathogens and bacteria, are the analytes of interest.

5.4 Evolution of Subjects over time

Now, the statements which have been classified in subject three are followed and mapped through time. The graphs represent the development of the amount of statements over the years and could give indication of development within the field of nanosensors.

FIGURE 12: ACADEMIA

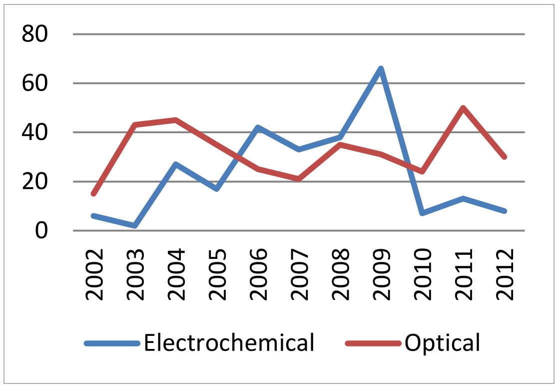


FIGURE 13: INDUSTRY

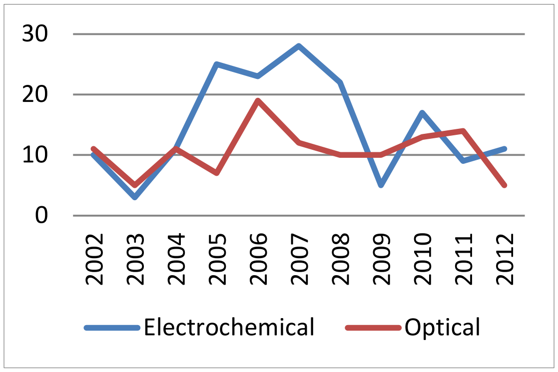


FIGURE 14: GOVERNMENT

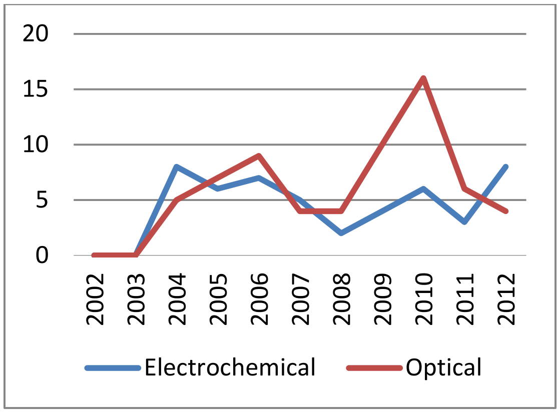


FIGURE 15: SUM GOVERNEMNT, INDUSTRY, ACADEMIA

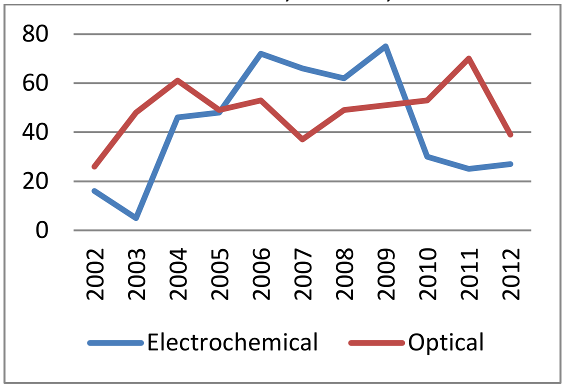


FIGURE 16: DEVELOPMENTS AS % OF THE FIELD

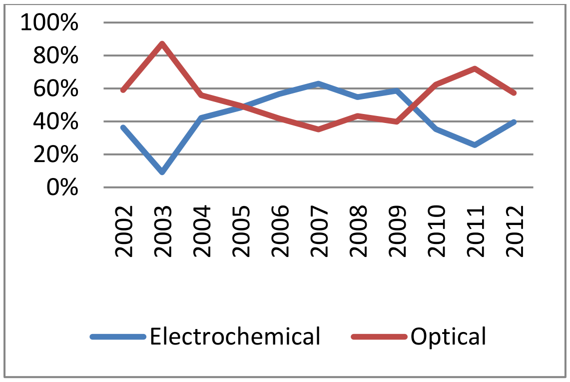


FIGURE 17: EVOLUTION TRANSDUCER, RECOGNITION ELEMENT

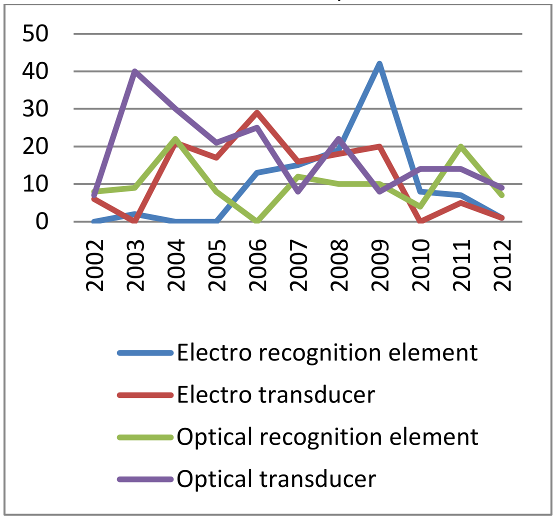


FIGURE 18: INDUSTRY

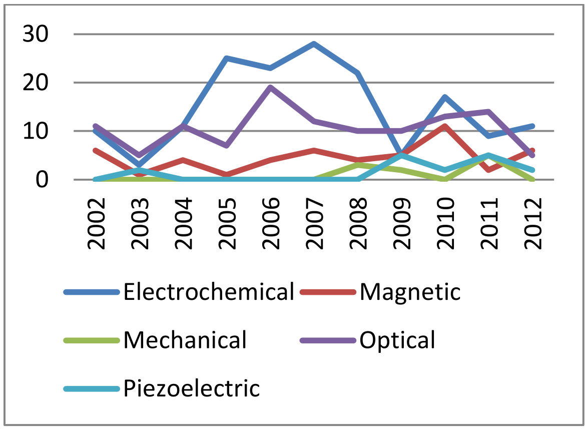


FIGURE 19: FOOD

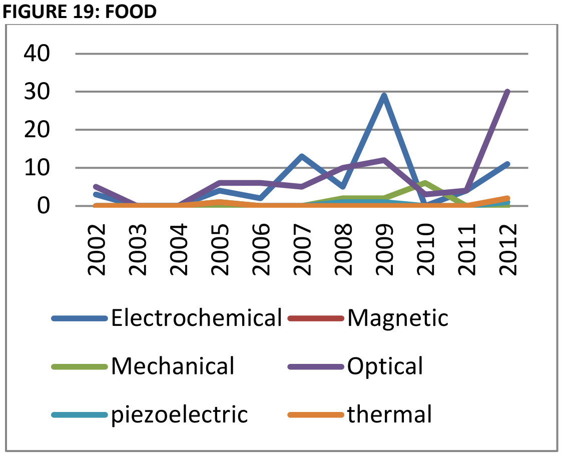


FIGURE 20: ENVIRONMENTAL ANALYSIS

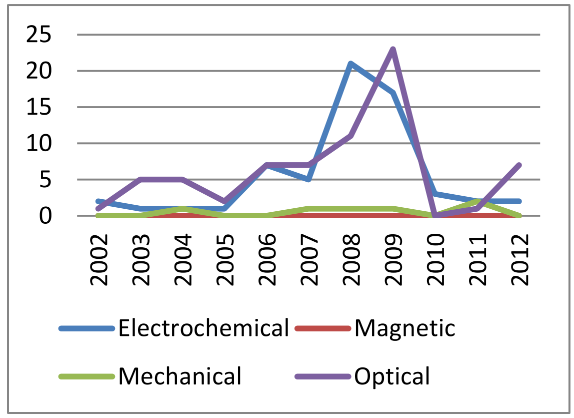
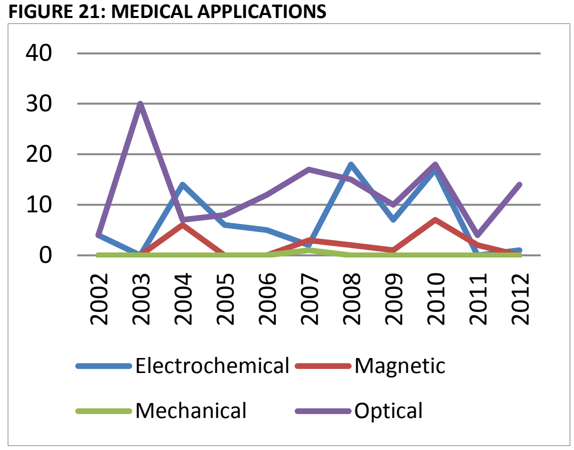


FIGURE 21: MEDICAL APPLICATIONS



The first finding is that there is no significant change in the percentage of optical and electrochemical statements over the years, which implies there is no dominant category or movement towards one. In the scientific literature the amount of statement for optical sensors seems to be more stable, while a rise in electrochemical is seen in the period 2005-2010. However this is only marginal.
A more significant finding is that the electrochemical sensors are much more mentioned in the patent database, which is an indication that firms are more investing in the development of electrochemical sensors. For the governmental perspective nothing can be said as the amount of statements is too small to see some development over time.

Probably the most interesting findings can be made about the evolution of statements in the application areas. As we can see in the graphs the amount of statement for medical applications is quite high form the beginning and stays on that level, while the amount of statement related to the food en environmental applications starts to rise in 2007/2008. This is an indication that those application areas also start to take off, while sensors for the medical application area already were heavily investigated. This is completely in line with some review articles on the development of sensors for the application areas (e.g. Sozer & Kokini, 2009).

Furthermore in all application areas the optical and electrochemical sensors seem to dominate the field. Which implies that all the developments form sensor technologies can be applied in the three fields. This is also an indication that the field is still open, in the fluid phase and that many technological options are still available.

When looking at the evolution of transducer/recognition elements again no significant pattern can be distinguished. Maybe a small indication can be seen that the recognition element of electrochemical sensor is gaining more attention through the years. This could be relates to the functionalization of sensing material which indeed is one of the main research goals in nanosensor research.
Overall the development over time does not show very strong patterns. One reason for this is might be that the amount of statements analyzed is too limited. Nonetheless, some findings could be derived. But maybe more importantly it is an important exercise in the study practices for the development of emerging technological fields. The qualitative reconstruction of the development paths will shed more light on the development patterns and emerging irreversibilities.

6. Reconstruction Development Paths

Based on the statements analysis the development paths can be reconstructed. Two development paths were identified as most important; Path A relates to electrochemical sensors, and path B relates to optical sensors. The most interesting findings of research groups, governmental projects and findings from the patent database which contribute to the development of nanosensor technologies are presented. The description focuses on the elements expectations, agendas and networks as those are the building blocks of development paths. The most profound expectations and how they influence the development are discussed. The agenda and research results which mark important activities and development in the field are presented. The network section deals with the emerging network. However the network section will only present the most important actors, their relations are not fully discussed as this research effort did not entail a network analysis. Instead the focus lies more on expectation, agenda's, and actual research findings with a technological focus. Hence the network section is only a tip of the iceberg of the emerging network structure. Nonetheless it gives an indication of the most important actors and their geographical location. Furthermore, the development is roughly described in chronological order and a division is made between progress in academia, industry and governmental projects. Overall the description of the paths deal with emergence of new topics, new nanomaterial, the use of nanomaterials in sensor research and design, the emergence of new prototypes, new technological needs, emergence of new firms, topics funded by the government etc. which are all possible irreversibilities as they influence and shape the development of the field.

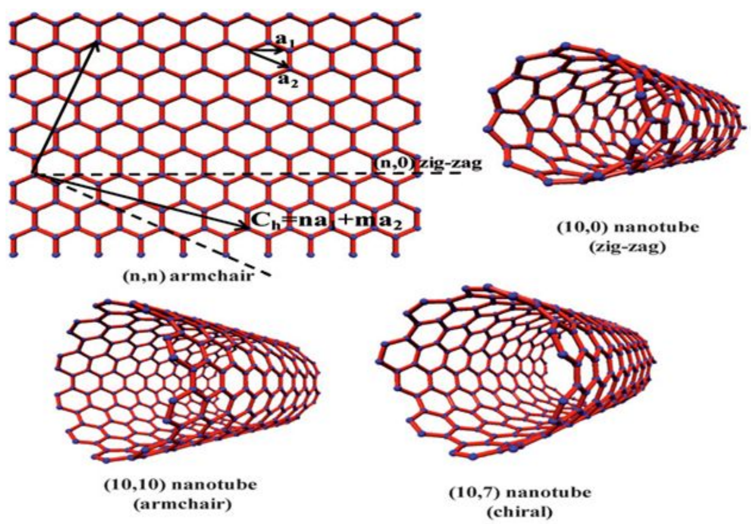
6.1 Path A : Electrochemical Nanosensors

6.1.1 EXPECTATIONS

Research

The expectation on electrochemical nanosensor voiced by researchers are widely present the studied articles. The expectations usually relate to new nanomaterials, their potential use in sensor devices, technological needs, and the potential impact they can have on society. One of the most prevailing nanomaterial in the field of nanotechnology and also nanosensor technologies is a CNT. The material is discovered in 1991 by Sumio Iijima and has received tremendous amount of attention since then. A CNT is allotrope of the material carbon and has a cylindrical one-dimensional nanostructures. The material is a made out of rolled op sheet of hexagonal structured carbon atoms, also called graphene. The CNTs have very interesting properties i.e. electrical conductivity or semi conductivity, and high thermal conductivity depending on the chirality of the nanotube. Fig 22 provides a schematic representation of the different nanotubes. Furthermore CNTs have a hollow structure able to store other molecules inside (Fujii et al., 2005). Depending on the way a carbon sheet is rolled up, the nanotube has different electrical properties (behaving as a metal or a semiconductor).

FIGURE 21: SCHEMATIC REPRESENTATION OF A CNT (RAO ET AL, 2009)



In literature often a distinction is made between single walled CNTs (SWNT) and Multi-walled nanotubes (MWNT). A SWNT is made out of 1 sheet of rolled up graphene and MWCT out of two or more rolled up sheets. Also Carbon Nanofibers (CNF) are described in literature. They are a low cost alternative to MWNT and often used in biosensor development. Due to the interesting electronic and semi-conductive properties together with their large surface areas they are considered to be ideal building blocks for chemical and gas sensors (J. Li, Lu, Ye, Delzeit, & Meyyappan, 2005). Thus expectations on the potential use of CNT in nanosensor devices are really high and have grown rapidly since the discovery of the promising properties of the nanomaterial.

One of the most cited research groups working with CNT in relation to sensor devices is the Charles Lieber group at Harvard University. The group has produced nanosensors based on Field effect transistors. The FETs reported by the lieber group use semiconducting nanowires and are of much smaller scale than in the transistors in the microelectronic industry. *'The underlying concept for detection using these nanowires is based on the classical electrical behavior of FETs, which exhibit a conductivity change in response to variations in the field or potential at their surface*' (D. Wei, Bailey, Andrew, & Ryh, 2009). Such FETs can be used to detect single viruses, single molecules, gases, biomolecules, antibodies etc. depending on the functionalization of the nanowires or nanotubes. Thus expectations are raised on the fact that the CNT can be used in sensor devices, more specifically FET based sensors, and that they are capable of detected a variety of substances. One practical limitation of the FET sensors for the use of in vivo is that the detection sensitivity is dependent upon the ionic strength of the solution. Hence, often prior distilling steps are needed for the analysis of e.g. blood samples.

Nanowires are, just like nanotubes, nanomaterials with a 1D nanostructure and many expectation on their use in sensor device are voiced. E.g. *The nanowires have great potential to be applied in chemical and biological detection devices* (Yu et al., 2005). The FET described above can also be made of nanowires. '*The fundamental sensing mechanism of metal oxide based gas sensors relies on a change in electrical conductivity due to the interaction process between the surface complexes and the gas molecules to be detected'* (Z. L. Wang, 2004a). This explains why nanowires are promising, as they fit into FET, which is one of the most dominant working principles/sensor design in the field of electrochemical sensors. The most studies class of nanowires or nanobelts are the metal oxides. FETs based on ZnO and SnO_2 nanowires are reported by many authors (Xudong Wang, Summers, & Wang, 2004). One of the leading universities related to the development of metal oxide nanowires is the Georgia Institute of Technology. That university is also the place where many expectations on nanosensor development are voices. For example 'Zhang et al, (2003) claimed '*that it would be possible to manufacture a large array of individualized nanowires (either by manipulating their material composition or the way in which each nanowire is functionalized) to create a parallel sensing device that is able to detect many different species and mimic complex functions such as olfaction*' and '*since ZnO nanowires can be massively synthesized by thermal evaporation, the authors claimed that this could open the door to the mass production of sensing devices'* (Riu et al., 2006b). Semi conducting oxide nanowires were discovered in Wang's Laboratory at the Georgia tech university. Since their discovery they attracted an enormous amount of attention. *'The discovery of nanobelts is being attributed to the same category as the discovery of nanotubes and it will stimulate a vast interest in investigating nanobelt-based materials and applications'*.(Z. L. Wang, 2004b). Among the metal oxide nanobelts , ZnO is the most studied and applied in different electronic transistors and chemical sensors(Lao et al., 2007). The following statements also emphasize the importance of ZnO Nanowires:' *From a recent report on the map of physics by Physics World, research in ZnO NWs is as important as quantum computing, dark matters, string theory, semiconductor thin films, photonic crystals and carbon nanotubes'* (Z. L. Wang, 2009b).

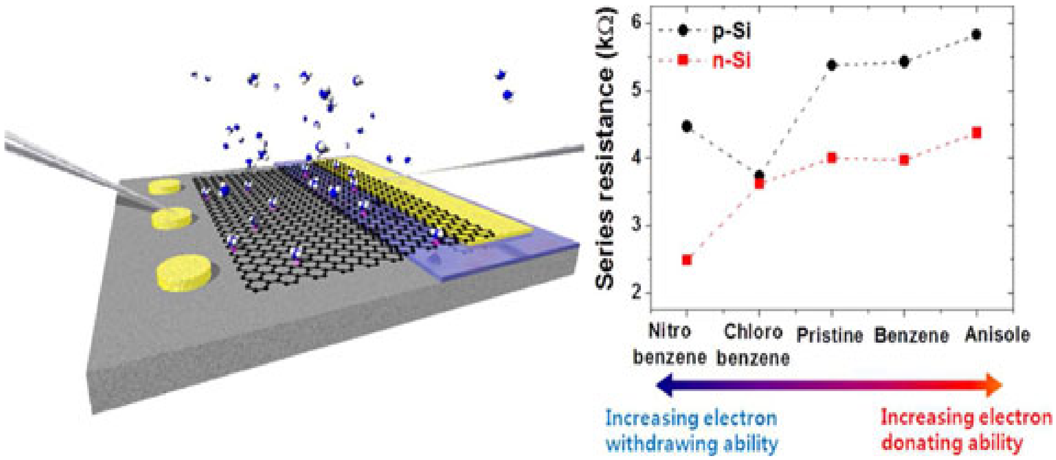
In literature, CNT and Nanowires have been reported is successful sensors for a variety of analytes. For example, the Lieber Group reported on the detection of single virus particles by using nanowire FETs. Also expectation for Multiplexing applications are being made: *'Studies of nanowire devices modified with antibodies specific for either influenza or adenovirus show that multiple viruses can be selectively detected in parallel. The possibility of large-scale integration of these nanowire devices suggests potential for simultaneous detection of a large number of distinct viral threats at the single virus level* '(Patolsky and Lieber, 2005). The majority of nanoFET sensors are immunosensors based on antibody–antigen binding. The NWs can be modified with virus specific antibodies only selective to desired virusses. Due to developments towards multiplexing it is expected that such sensor devices will get information for diagnostics of complex diseases like cancer.

In the studied literature also many expectations on electrochemical sensors relate to biosensors. Biosensors are in turn often classified according to the bioreceptor elements involved in the recognition process. The receptor is usually covalently attached to the transducer. The immobilization of the receptor molecule on the sensor surface is one of the key points determining the sensors performance. The biological recognition elements are usually antibodies, DNA, enzymes and apatemers. Most of the electrochemical bases biosensors are immunosensors. Immunosensors are sensors based on antibody–antigen interactions. Next to the immunosensors also DNA sensors are popular. Here the DNA is used as a probe which interacts with other molecules, e.g. RNA. A similar category are the Aptamers, which are synthetic oligonucleotides that can recognize and bind to virtually any kind of target, including ions, whole cells, drugs, toxins, low-molecular-weight ligands, peptides, and proteins (Guo & Dong, 2009). Thus there is a sort of trend to use biological elements as the receptor element of the sensor. This implies that more research is expected on biological nanomaterials and how they can be connected to the transducer element of the sensor.

Related to this are conducting polymers. Conducting polymers are another interesting group of materials which can be used in nanosensor developments. Often nanotubes and nanowires can be coated with polymers in order to increase their selectivity. Among the polymers, Polyaniline (PANI) and polypyrrole are the most studied. The polymers can be used as matrices which stabilize the immobilization between recognition element and transducer element, and the can act as transducer elements themselves (Dhand et al., 2011). PANI provides opportunities for '*binding biomolecules, tuning their bio-catalytic properties, rapid electron transfer and direct communication to produce a range of analytical signals and new analytical applications'* (Dhand et al., 2011). Hence as expectations on PANI are high it suggests that more researchers will work with that material.

The most recently discovered nanomaterial in nanoscience and with high potential for applications in nano-electrochemical sensors in graphene. Grapene is also an allotrope of Carbon. Graphene is 2D sheet of hexagonal structured carbon atoms in 1 layered sheet. It is only since 2004 that the 1 layered sheets of graphene became available. This was a remarkable discovery, as the 2D allotrope of Carbon is not present in nature. In 2004 Andre Geim and Knistantin Novosolev at the University of Manchester discovered the material Graphene. The 2D nanostructure has very interesting properties; large surface–to–volume ratio, high conductivity and electron mobility at room temperature, low energy dynamics of electrons with atomic thickness, robust mechanical and flexibility. In 2010 the two researchers were awarded with the Noble Prize for their work on graphene. Ever since the discovery and the Noble price the publications on graphene exploded. Since 2004 more than 4300 papers on graphene have appeared (Gan & Hu, 2011). In 2007 it was reported that graphene sensors could detect single molecules of toxic gases. The gas molecules can attach to the chicken wire structure of graphene and change the conductivity of the material. Fig. 23 provide a representation of a graphene based sensor. When a molecule links to the graphene sheet the conductivity/resistance is changed.

FIGURE 23: GRAPHENE SENSOR ON SILICON SUBSTRATE (©ACS)



The graphene based sensors are able to detect gaseous and liquid substances. And it is said that graphene based sensors could provide new sensing platforms for a variety of application in several application areas. Graphene can be used in sensors for DNA, proteins, neurotransmitters, phytohormones, pollutants, metal ions, gases, hydrogen peroxide, and in medical, enzymatic and immunosensors (Gan & Hu, 2011). In our database only few reports of graphene based nanosensor have been found, nonetheless it looks like this is a pioneering discovery which will lead to new sensing platforms and increased research attention. An indication to conform this is by looking at non-scientific publication on nanotechnology websites, where reports and expectations on the use of graphene in nanosensors are prevailing in last years.

Another promising area of electrochemical sensor development are sensor for DNA detection. DNA can be used both as sensing target, but also as the recognition element in sensor design. Electrochemical detection methods based on nanowire and nanotube field effect transistor have been reported for the detection of DNA. However more knowledge on the SWNT-DNA interaction is needed. The ability to measure and analyze DNA sequences and interaction of DNA with the environment could greatly benefit healthcare and diagnostic applications (Tang et al., 2006). The sensors developed by Tang et al, are said to be suited for the integration with Lab on a chip devices. The Lab on a chip is a platform technology for all kind of analytical steps preformed at macro/nano scale on a small chip instead of a laboratory. Lab on chips are usually integrated with microfluidic channels and sensor technologies. Thus expectation are raised within the field of nanosensor that the sensor could be integrated with Lab on chip devices. Such developments would allow for the integration of several analytical functionalities on single chips. However, difficulties still exist in the positioning of nanowires or nanotubes on a defined area on the chip. The difficulty of positioning the nanowires and nanotubes is said to be the reason for the slow diffusion of LOC applications. One of the major technological bottlenecks for LOC applications are the fabrication methods. Thus a lot of research now is directed towards directed-assembly and printing technologies of NWs/CNTs for LOC applications (M. Lee et al., 2009).

Industry

Expectations within the patent database are less pronounced, as most of the statements in patents deal with agenda on what materials or technologies the devices/inventions will consist of. The main materials described in the patents database are nanowires and nanotubes. It is expected that nanowires and nanotubes are the critical building blocks for nanoscale electronics. Such expectations have led to the creation of FET and single electron transistors. Were the FET based sensors are mentioned most often as expected prototype/design of nanosensors. An example of such expectations made in patents is a follows: *'We believe that our successful doping of SiNWs to create n-type and p-type materials will open up exciting opportunities in nanoscale science and technology. Doped SiNWs will be candidates for investigating fundamental issues of transport in 1D nanostructures. The structures studies in this paper are also field effect transistors (FETs), and it will be possible using self-assembly techniques to integrate many SiNW FETs into structures perhaps for nanoelectronics applications' (2002, Lieber.)* Another example of expectations voiced in a patent of the California institute of technology related to CNT*: 'Carbon nanotubes hold great promise in many areas of science and technology, due to their unique physical properties and molecular-scale dimensions. A significant technological advance for these materials has been their incorporation as specific molecular transducers in nanosensors, molecular electronics and as molecular manipulation tools. This potential is based on the remarkable molecular recognition capabilities of carbon nanotubes through covalent chemical bonding, surface charge transfer or electrostatic changes when a specific molecule binds to a tube'.*

Other expectations relate to the actual use of the applications. For example Virtanan Jorma described a part of the invention as follows: *In another aspect of the present invention, the nanosensors may be implanted into the skin or some other organ. They may also be injected into circulation. The sensors may be very small, about the size of a cell, and actually placed inside a cell, if necessary. They may be made of materials, which are stable for years or alternatively dissolve in a body. Because of very small power consumption, a small battery may power the sensors. Information may be retrieved either using radio or microwaves. Alternatively, an external light may access an implanted sensor.*

This implies that firms are already thinking about possible integration of the new devices with new systems and functions which could address societal needs. Such expectation almost always related to medical needs. More specifically the devices related to the monitoring of glucose concentration for diabetes patients. A lot of the expectation deal with devices which can be integrated in the body and measure the glucose concentrations in a continuous manner. An example of such a statement:

'Integrated physiological devices can be constructed to carry out a function depending upon a condition sensed by a sensor of the invention. For example, a nanowire sensor of the invention can sense glucose level and, based upon the determined glucose level can cause the release of insulin into a subject through an appropriate controller mechanism' (2006, President and Fellows of Harvard College Harvard)

These were just of few examples but they clearly illustrate that the expectation in the patent database address the materials CNT and nanowires, the FET based sensor devices and sometimes medical applications.

Governments

This section should present the expectation made in the description of governmental projects related to electrochemical sensors. However, most of the expectations voiced in such project descriptions are too general, addressing societal needs, and do not directly relate to the electrochemical development path. Such statements are discussed in more detail in the application domains. The statements dealing with developments related to this development path are discussed in the agenda section below, as almost all of them consist of the aims of the projects and thus fit better in the agenda section.

6.1.2 AGENDA

Research

This section describes what researchers are working on and what results they make. SWNT have been demonstrated to be effective and highly sensitive materials for the use of nanosensors. The characteristics of the CNT may enable high sensitivity towards charged analytes. However, their selectivity to different gases is not optimal. This shortcoming could be remedied by the functionalization of the CNT. Hence a lot of the described research relates to the functionalization of the materials. There are two main approaches for the functionalization of the nanotubes. One is based on covalent binding of molecules and the other on non-covalent binding. Thus an important topic which is on the agenda of nanosensor researchers is the functionalization of nanomaterials.

Gas sensing, and the use of CNT for gas sensors, is another main topics related to electrochemical sensor developments. The main principle of gas sensors is that molecules attach or bind the nanostructure and change the resistance or conductivity of the material (Rocha, Rossi, Fazzio, & Da Silva, 2008). Kong et al. were the first to present that CNTs could be used in chemical gas sensors. They showed that by exposing a SWNT to the electron withdrawing of e.g. NO_2 or donating of e.g. NH_3 the electrical resistance of the SWNTs dramatically increased or decreased. Today the CNTs-FETs are widely used to detect gases (Riu et al., 2006b).

Related to the development of gas sensors are the development made by Zhang et al,(2002) who developed a NO nanosensor. The sensor technology is based on the etching of a carbon fiber electrode modified with multiple membranes. '*The sensor demonstrated superior sensitivity, selectivity, and stability for NO detection. The use of this nanosensor is very promising in applications for the in situ, in vivo and real-time detection of NO at the single cell and micro-capillary levels*.' (X. Zhang et al., 2002). Zhang, one of the most cited authors in nanosensor research, demonstrated in 2006 a method for the fabrication of functionalized SWNT gas sensors. The nanotubes where functionalized with the molecule Polyaniline (PANI) which is a conducting polymer. PANI is highly selective toward NH_3 (ammonia gas), this invention is an important step towards ammonia sensing applications (T. Zhang, Nix, Yoo, Deshusses, & Myung, 2006). Kang et al,(2006) demonstrated de functionalization of CNT with of Pd nanoparticles which are highly selective for hydrogen gas sensing (Kang et al., 2006). Also Mubeen at al, reported on the use of Pd nanoparticles in hydrogen sensor applications (Mubeen, Zhang, Yoo, Deshusses, & Myung, 2007). The use of material polyethyleneimine (PEI) and Nafion membranes as noncovalent coating of SWNT was demonstrated as highly selective for the detection of NO_2. Another NP often described in senor application is Gold. Functionalization of SWNT with GoldNP has shown to be effective for the measurements of H_2S gas at room temperature (Yan Zhang & Zhang, 2012).

The above results indicate that the functionalization of SWNT in combination with the electrochemical properties of the materials provides a new method for making nanosensors with better sensitivity, selectivity and lower detection limits. Due to the direct conversion of chemical information into an electric signal the devices need very low power, which in turn could lead to miniaturized sensor devices. One of the most promising advantages of this methods is the ability to make sensor arrays which different sensing materials and this enable the possibility to sense different analytes and gases with one sensor array. This concept is often referred to as multiplexing (T. Zhang et al., 2006).

Related to the detection of gases is the detection of volatile organic compounds(VOC), which basically are also gasses made of organic chemicals. VOC are materials with very low boiling points which causes molecules to evaporate and enter the surrounding air. The detection of VOCs is an important aim in sensor technology and in the recent years many research groups have been working on sensors related to VOC (Elosúa et al., 2006).

Overall we can state that nanotubes show great promise for nanosensor applications, however several hurdles must be overcome: The growth of longer nanotubes, controlling the chirality (which determines the properties to a large extend (Dekker, 1999)) during the production process and the bonding of polymers or other recognition element on the nanotube). These are the main topics now addresses by the researchers. Advances made on this topics are encouraging. E.g the controlled growth of SWNT is recently reported by using chemical vapor deposition (CVD) processes (Kang et al., 2006).

The emergence of the nanobased FET sensors started in the 21st century after pioneering work of Kong et al, and Cui et al, on nanotube sensors. After their works many nanosensors using nanowire/nanotube FETs were developed (M. Lee et al., 2009). Also the work of Park er al, (2001) on a real time detection nanosensor based on a nanowire is seen as pioneering work. That research group used silicon nanowires in solid state FET (Haguet et al., 2004).

As mentioned before ZnO is the most promising material within the class of metal oxides. To produce ZnO nanostructure Tin can be used as an excellent catalyst. Researchers have successfully grown aligned nanowires on a polycrystalline alumina substrate using tin as a catalyst. Just as with CNT, nanobelts have a high sensitivity, but rather a low selectivity. Hence surface functionalization is an important topic in nanosensor research. In short we can state that ZnO nanowires are well suited for the development of gas sensors and VOC. Researchers have already reported ZnO based sensors for the detection of vapors such as methanol, ethanol, isopropanol, benzene and other amines (Jiménez-Cadena, Riu, & Rius, 2007). There are many researchers and laboratories working on the use of metal oxides as sensing material, especially on gas sensing application. It would not be feasible to describe all those research practices here, but what we can say is that the main topics the in those researches are; material growth processes, integrating of the material into devices and on the surface modification of functional materials with conducting polymers or other nanoparticles (T. Wei, Yeh, Lu, & Wang, 2009).

Another sensing method based on the electrochemical technique is nanopore based sensing. The basic principle of nanopore sensing is straight forward. The substrate (i.e. antibody, DNA) is translocated through a nanosized hole which causes changes in the ionic current on the hole. The changes in current represent the signature of the substrate translocated through the pore (Nakane et al., 2004). In 2002 Kasianowicz presented a first demonstration of this principles by using membranes as single molecular sensors. This *proof of concept* was demonstrated for single molecule oligonucleotide detection. An advantage of this method compared to optical techniques is stated as follows: '*A major advantage of nanopore sensing, compared to most biochemical assays which use colorimetric, fluorescent, or chemiluminescent effets, is that it only requires measurement of the ionic current through the pore, and thus requires no optics or fluorescent labels*' (Nakane et al., 2004).

The proof op principle of nanopore sensing was demonstrated for several other analytes (e.g., ruthenium tris-(2,20-bi-pyridiyl)2+, methyl viologen2+ and quinine), overall macro molecules. This results look promising, however a disadvantage is that it is difficult to discriminate among different analytes in complex mixtures. Thus the technology is well suited for specific analysis of prepared analytes in laboratory settings. It is especially used for DNA sequencing studies (Gyurcsányi, 2008). Nanopore sensing is often associated with nanofluidics as the analytes usually are in an aqueous solution when passing through a nanopore. Furthermore, the nanopore tips can also be functionalized by immobilizing an antibody on the tip of a nanopore which is selective specific protein or virus etc (Gyurcsányi, 2008). Another strength of nanopore sensing is that it offers the possibility of label free detection methods. The developments of nanopore sensing are phrased by Vlassiouk et al, (2009) as follows: *'Sensing with chemically modified nanopores is an emerging field that in many respects is still in its infancy. The main strength of nanopore sensing is that it implies the possibility of label-free, single-molecule detection by taking advantage of the built-in amplification mechanism. While solid-state nanopores cannot be produced with atomic resolution at present, as their biological counterparts can, their superior robustness and flexibility in terms of size, shape, functionality provides the prerequisites for analysis of real samples'* (Vlassiouk et al, 2009). One of the main challenges in nanopore sensing remains the selectivity towards analytes. As a solution researchers are working on functionalizing the walls of nanopores with recognition elements for specific analytes e.g. the use of biotin to detect avidin or streptavidin (Vlassiouk et al, 2009). The nanopore sensing is a promising technique, however many technical issues must be resolved to develop such sensors for in vivo applications. A future vision of this technology is to assemble such nanopore sensors on membranes of living cells in order to analyse the moleucles present in the cytoplasma.(Nakane et al., 2004) *'Sensing with chemically-modified nanopores is an emerging field that is expected to have major impact on bioanalysis and fundamental understanding of nanoscale chemical interactions down to the single-molecule level'*(Gyurcsányi, 2008).

Industry

One of the most reoccurring research group in the patent database is the Charles Lieber group from Harvard university. As already mentioned in the previous part, this groups conducts research on nanowires, nanotubes and FETs. In 2002 they patented on assembly process of parallel arrays by flow assembly. They believe that '*flow assembly represents a general strategy for organization of NW and NT* *building blocks into structures needed for wiring, interconnects and functional devices, and thus could enable a bottom-up manufacturing paradigm for future nanotechnologies' (…)*

The group has several patents on nanoscale sensor devises. Most aspect of that invention relate to nanowire devices for the determining of analytes suspected to be present in a sample. The invention also relates to methods of immobilization of entities to the nanowires. The entities can be DNA, and bind to analytes like proteins, enzymes etc. '*As an example, an enzyme such as telomerase may be allowed to bind to DNA immobilized relative to a nanoscale wire. The telomerase may extend the length of the DNA, for instance, by reaction with free deoxynucleotide triphosphates in solution; additionally, various properties of the nucleic acid may be determined, for example, using electric field interactions between the nucleic acid and the nanoscale wire'*. A patent description usually provides many examples like the one mentioned above. However it is not feasible to describe them all here. What is notable is that they demonstrate high sensitivity and selectivity of the sensor devices. The sensor devices are said to be suited for label free, real rime, multiplexed detection of cancer markers. CVD is described as the production processes for the production of the nanotubes

Nanomix. Inc is one of the companies holding a lot of patents in the database. It is a company founded in 2002 by researchers from Berkeley University. They are specialized in carbon nanotube biosensor technology and are making products for the point of care diagnostic markets. Also most of the patents relate to CNT as they try to use CNT as a platform technology for sensing applications. They are patenting on functionalization of nanoparticles and the integration of system devices. They presented in their inventions nanosensor capable of detecting analytes specifc to pathogens by using electronic nano-circuits. Those analytes include DNA sequences, RNA sequences, or proteins, or any molecule whose presence is diagnostic of a particular human pathogenic organism. The bacteria species which they can detect are bacteria, protozoa, fungi, viruses and prions. The nano-circuits described in the patents consist of various nanomaterials which are sensitive the changes in electronic current. The sensor device are also described as components of larger systems which include sample handling, transmission of data to remote sites, alarm capabilities, and computer control of operations.

Nanomix also holds patent for nanotube FETS for the detection of CO_2. The nanowire FET works on the same principles described in the scientific research progress chapter above. The patent also elaborates on recognition elements made of polymer coatings to increase sensitivity toward CO molecules. The possibility of multiplexing and using an array of sensor sensitive to different molecules is also discusses. However most of the nanomix patents relate to the measurements of biological species like polynucleotides, proteins, polysaccharides and the like.

Another company holding several patent on nanosensors is Nanosys,Inc. Nanosys is based in the Silicon Valley and is one of the world leading nanotechnology companies in the field of electronic nanostructures. In total the company has 670 patents related to nanotechnology, however not all apply to nanosensors. The company has patented on sensors for intracellular measurement as well as for cellular events. The sensors usually compromise nanowires and nanowire arrays and are called nano-chem-FETs. In 2007 the patents describe nanowires compromising functional groups in order to increase selectivity of the sensors. This implies that the company is actively involved in research on the functionlization of nanomaterials. In 2011 the company patented on methods for detecting analytes in

microfluidic systems. Such method also involved nanowires based ChemFETs. Also in 2011 they patented on Medical device application of nanostructure surfaces. The use of nanostructured surfaces in sensor design has as a goal to prevent the sensor from fouling with other materials. Furthermore the patent described several other nanosensor application in medicine: glucose sensors, cardio sensors, neurosensors/emitter and aptamers. These are all topics addressed by firms in the field of nanosensor technologies for medical applications.
An important prerequisite for the emergence of this new generation of electronic devices is the ability to grow nanowires that have consistent characteristics. *'Current approaches to grow nanowires do not facilitate mass production, do not yield consistent nanowire performance characteristics and can be improved to generate better device performance based on nanowires. What are needed are systems and methods for growing nanowires that facilitate mass production, yield consistent nanowire performance characteristics and generate improved device performance'.(Nanosys, 2004)* This statement indicates that also companies are involved in research on suitable production methods for nanomaterials.

An emerging topic within the nanosensor database is the use of sensor network and sensors in combination with RFID technology. In 2006 the company GenTag incorporated nanowires in RFID sensors. They described a wireless chip diagnostic sensor system. Symbol Technologies, Inc also holds patents on RFID based sensor networks. However the RFID technologies do not necessarily relate directly to electrochemical sensors, as also mechanical or piezoelectric sensors could be integrated in RFID networks.

Next to the reports on the use of CNT also many reports of ZnO nanostrucres in sensor application have been found. For example the State University of New Jersey patented an inventions which provides a multifunctional biological and biochemical sensor technology based on ZnO nanostructures. The ZnO nanotips are used as molecule binding sited for DNA and protein molecules and are applied in FET type sensors. Also ZnO based gas sensors for H2 detection are reported by the University of Central Florida.

Next to the widely reported FET sensors also some patent related to nanopore sensing were found in the database. For example Samsung electronics co., LTD described in 2012 the nanopore sensing principle for detection of single molecules. However it looks like nanopore sensing is not yet widely investigated by industry companies in relation to the FETs.

Governments
This section presents the agendas and aims of the governmental projects related to electrochemical nanosensors. Most of the projects have the aim to increase fundamental knowledge on a specific topic or to bring research group together. The project rarely relate to specific sensor devices or electrochemical nanosensors. Many projects are related to CNT research and intend to gain understanding about the properties, production methods, surface functionalities etc. For example the CANAPE projects brings researcher together from leading laboratories and companies within Europe to produce nanotubes on a bulk scale of ultimately tons per year. The method for the production is chemical vapor deposition (CVD). This projects also contains a toxicological study of CNTs particularly with respect to possible health hazards.

More projects related to CNT are: NOESIS were the aim is to get a better understanding of CNT. The project ARCHITECHTUBE investigated the production processes of CNT with a focus on the CVD method. The Projects SMART NANOTUBE works on the functionalization of the CNT. The Projects OXCNT studied the material properties if CNT filled with gaseous substances. Their aim is '*to prepare new filled SWNTs and then study their structures, physical properties and explore their potential applications. From the fundamental point of view this program should cast light on the relationship between atomic structure and physical properties of solids'. The SANES projects aims for functionalization stratgies of CNT. Other projects related to the growth of nanowires are* DESYGN-IT and CARBONCHIP. This brief overview indicates that CNT are a hot topic in nanosensor research, related to this development path.

The NANOSENS project (2008, Spain) is a projects on nanoparticles and their application in the development of electrochemical molecular beacon biosensors. Molecular beacons are probes made out of single stranded oligonucleotides characterized by a peculiar stem-loop structure. Basically this project focuses on the immobilization of receptor elements on the transducer surface. The proposed approach of the NANOSENS projects was successfully applied in the functionalization of conductive surfaces in the development of electrochemical genosensor (DNA sensors). The proposed approach is very interesting allowing the patterning, at nano level, of conductive surface in a very rapid, versatile and cost effective way. Possible application of the developed approach could be in the microelectronics industry or in the preparation of nanosensors for diagnostic purposes.

The FUNSENS (2008, UK) project aims for developing expertise on nanostructured materials, and applications thereof. Specifically the project focuses on SWNT and electrochemical sensors based on CNT. A key part of the project is to develop functionalization strategies of the nanomaterial.

The SANES project (integrated selfadjusting nano-electronic sensors) started in 2006 aims for the development of CNT based gas sensors. The most important goal of SANES was to develop a sensor with multiplexing capabilities. The prototype developed in this project was able to: measuring temperature (using the built-in Pt sensor), qualitatively differentiating between 16 different gases (4 gases for each sensor) provided that a suitable calibration is available, quantitatively measuring gas concentrations in the 0.1 ppm - 2000 ppm range. The project resulted in a complete gas sensing prototype unit with very high selectivity.

The GNRSENSE Project started in 2010. GNRSENSE stands for Graphene nanoribbon based chemical sensors. Graphene nanoribbens have only been discovered recently and due to their electronic, magnetic and mechanical properties they are expected to be suited for the development of nanosensors. The projects especially aims at a better understanding of the surface chemistry of the graphene nanoribbons. The purpose of this research is to develop chemical based sensors using graphene.

The OFET projects(2012) aims for the development of electrochemical biosensors for point of care applications. The objective is to make electronic, label-free biosensors. Today Europe has a strong position in this research area. *'The objective of this project is to strengthen the research in this new and fast developing strategic research field by teaching and training the next generation of scientists on OFET biosensors developments both in the academia and the private sectors'*. The goal is to develop sensors with fully integrated biological recognition elements, such as antibodies or other receptors to increase the selectivity of the sensors. Next to the medical application, also sensing application in the food and environmental monitoring can benefit from the OFET devices

Overall we can see that the projects description are not very specific, they aim for a better understanding of phenomena at nanoscale and do not yet pertain to specific nanosensor devices or prototypes. However we can see that CNT is the by far most researched materials and the technological issues like label free sensing, multiplexing and the functionalization of nanomaterials are present in the governmental projects.

6.1.3 NETWORKS

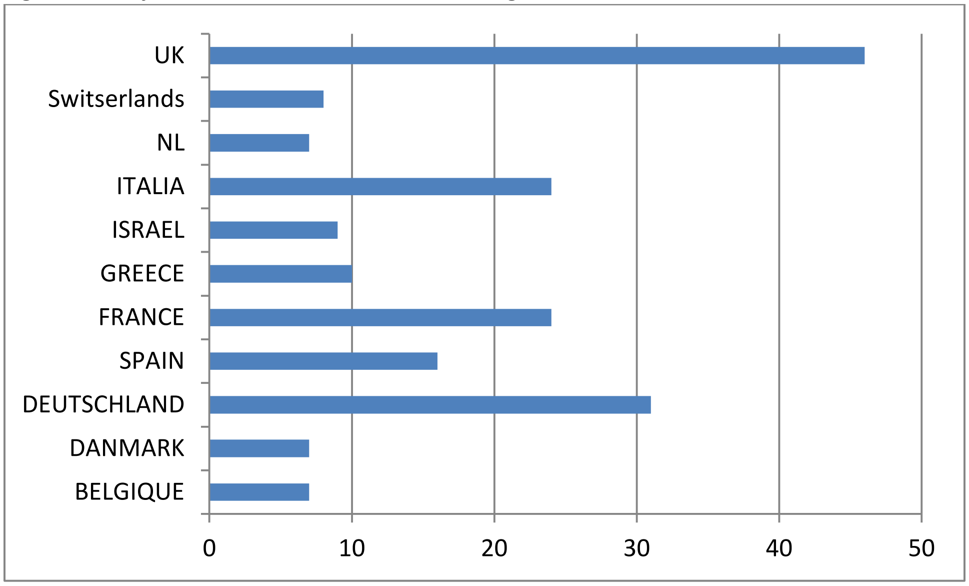
This section will briefly address the biggest actors, with the highest influence on the field of nanosensor technologies. The most cited research groups are presented together with the 10 biggest patent holders in our database.

The most important research group in respect to the development of electrochemical nanosensors is the Charles Lieber group located at the Harvard University. They have by far the most cited publications and thus are a big influence on the development of the field. The group works on CNT and nanowire based sensors, and has greatly contributed to the development of CNT based FET sensors.
The Zhang research group located at the Nanging University reoccurred also many time in our database. Their research focuses on CNT and grapheme and their application in nano- and biosensing.
One of the leading universities related to the development of metal oxide nanowires is the Georgia Institute of Technology Industry were the group of Wang is located.

The following actors hold the most patents in our database: University of Harvard; NanoSys. Inc; NanoMix. Inc; California institute of technology; Nantero, Inc. ; University of Florida; Honeywell International, Inc. ; IBM; MEDtronic. Inc; Life technologies corporations. Most of these actors hold 2-5 patent in our database, were the University of Harvard, Nanaosys. Inc and Nanamix.Inc are the biggest actors holding each around 10 patents. Which is really high taken the limited size of our database. What is notable is that almost all the patent holders are located in the U.S. and that 2 nanotechnology based companies have the most patents. Nanomix. Inc is one of the companies holding a lot of patents in the database. It is a company founded in 2002 by researchers from Berkley university. They are specialized in carbon nanotube biosensor technology and are making products for the point of care diagnostic markets. Another company holding several patent on nanosensor is Nanosys, Inc. Nanosys is based in the Silicon Valley and is one of the world leading nanotechnology companies in the field of electronic nanostructures. As mentioned earlier In total the company has 670 patents related to nanotechnology, however not all apply to nanosensors. The company has patented on sensors for intracellular measurement as well as for cellular events.

We also made a quick analysis of the countries involved in the nanosensor project in the EU framework programs. See figure 24 for the result. All the projects have been incorporated in these statistics, not necessarily related to electrochemical sensors. It can give some indications which EU countries are most involved in nanosensor research.

Figure 24: Projects related to nanosensor technologies in Cordis database.



6.1.4 Summary

From the above findings it can be said that electrochemical techniques plays a major role in the development towards simple, more sensitive and selective sensing techniques. Related to patterns within the field we can see a growth in research and publications on certain topics, after a pioneering discovery. Such discoveries are usually the emergence of a new nanomaterial with novel properties, or the first demonstration of a sensing technique. Such development can be seen for metal-oxide-based semiconducting nanowires, nanotubes and graphene sheets. From the above we can see that several techniques and materials are 'competing' to be applied in sensor applications. This is especially visible for nanowires, metal oxides and CNT as they are all 1D nanostructures. Authors related to development of those materials all raise promising expectations towards their material. For example statements like this '*Generally, the sensitivity of the gas sensors on basis of nanotubes is better than that based on nanowires if both have the chemical composition, because the hollow-structured nanotubes can enrich gases*.' (Liu, 2008) are examples of competing materials. We can see that CNT and Metal oxides are the most applied nanomaterials, where ZnO is the most studied metal Oxide. Furthermore materials like Au, Pd and biological molecules (DNA, Aptamers, antibodies) are often mentions as possible functionalization material of the 1D transducer materials. The electrochemical sensors can also be divides in to classes: gas sensors, particularly suited for the detections of small molecules in the air (breath analyzers, gas leakages, VOC etc.) and Liquid sensors which are particularly suited for the detection of large molecules, often biological components like DNA, viruses, bacteria, proteins etc.

For both sensor platforms (liquid and gas) we can see a development towards smaller, more sensitive and selective sensors. The selectivity is gained to the inherent small scale of nanomaterials, the selectivity is gained by functionalizing nanomaterial towards the analytes of interest. Furthermore the integration of multiple sensors into one array, capable of distinguishing between different analytes (multiplexing) is a shared goal among the nanosensor researchers. Also we see a trend towards the development of label free sensors, as almost all papers state that as a goal and advantage of the sensor under investigation. As this field is still emerging and many technical options exist we identified two potential technology platforms within this path: the FETs and Nanopore sensing. The development of NanoFETs was largely driven by the miniaturization trend in the microelectronics industry. Also nanopore sensing can benefit from that development as it is often stated that nanopore sensors could be integrated on Lab on chips. Together with the development of micro- and nano fluidics this offers opportunities for a new sensing platform.

Another trend in electrochemical sensor development is the integration of sensors with wireless network technologies. The ultimate goal is to make autonomous, low power sensor devices which can communicate with other sensors. This is especially important for environmental applications where measurement need to be done in remote areas (Z. L. Wang, 2010). But also for medical purposes it can be useful. For example nanosensors/capsules can remotely be activated with the intention to deliver drugs to a specific place in the body. The section on medical application will elaborate more on the possibility of targeted drug release.

In respect to the patent database we see that a large part of the patents can be attributes to universities and research institutes, another part to specialized firms in nanotechnology and several patents to large multinationals, like IBM, HP, Samsung. This also supports that claim that most nanosensor firms are strongly relate to universities made by Bogue et al, (2008). What is most striking is that almost all inventions relate to nanowires, often CNT or ZnO nanowires and that those materials are applied in FET based sensor devices. This is an indication that this is the dominant sensor platform for electrochemical sensors. A shared need in the sensor development is the production method of preparing nanotube with consistent characteristics, i.e. same chirality of the tubes.
Another finding is that most of the patents assigned to US based firm or institutes. One should almost expect some bias towards the US in our database. However the patent search was conducted for the databases of USPT, WIPO, USAPP, EP. From this it must be concluded that the US is the leading country in nanosensor development.

6.2 Path B: Optical Nanosensors

6.2.1 Expectations

Research

The expectations on optical nanosensors voiced by researchers usually relate to new nano-materials, their use in optical sensor devices, specific prototypes or models working on a specific working mechanism or to the technological needs of the nanosensor. This section is a reconstruction of the most important findings which contribute to the development of optical nanosensor technologies.

We start this section with some expectation on nanomaterials which are said to be very promising as building blocks for optical nanosensors. As CNT are the dominant materials in the electrochemical sensor development, Quantum Dots (QD) are the most used and studied materials in optical sensor development. A quantum dot is a cluster of a few hundred atoms which typically ranges from 1 to 20 nm, and is often referred to as a nanocrystals. Ever since their emergence they have drawn considerable attention in many research fields. The reason for this is that they possess unique optical properties such as high brightness and narrow emission band as well as other advantages over traditional organic fluorophores (Yi Zhang & Wang, 2012). This is stated accordingly by Martin-Palma et al, (2009): '*The unique fluorescent and overall optical properties of semiconductor quantum dots make them very interesting fluorophores for both in vivo and in vitro biological investigations. Semiconductor nanocrystals are highly light absorbing and luminescent nanoparticles whose absorbance onset and emission maximum shift to higher energy with decreasing particle size due to quantum size effects*'. This implies that QD are well suited for the use for bio-sensing applications. Another statement describing the current status of QD technology is voiced in the same review article accordingly: *The current status of quantum dot technology is expected to evolve in a rapid fashion on many different aspects. The use of novel systems could lead to improved properties including narrower fluorescence emission and longer lifetimes, as well as suppression of blinking and quantum yield enhancement. Also, sensitivity to electric or magnetic fields may play an important role in future biosensor systems* (Martín-Palma et al., 2009)**.** These statements emphasize the potential of QD use in nanosensor design and thus influence the development of the field in favor of QD.

Another group of particles which received a lot of attention in sensor design are metallic NP as they have excellent surface enhanced Raman scattering properties (the SERS principle is discussed to certain extend in the technological background section, and will not be discussed in more detail as it is too technical for this thesis). The most common material from the metal NP in sensor design is a Gold NP. An example of the use of Gold NP and quantum dots is demonstrated by Li, et al, (2011) who developed a nanosensor based on QD and Gold Nanoparticles. When these two particles are in close proximity it enables a nanometal surface energy transfer, which in turn quenches the fluorescence emission of the QDs. Based on this phenomenon the sensor is able to detect Hg2+ detection in water. '*The developed sensor is expected to be used for on-site detection of mercury in a real aquatic environment'* (M. Li, Wang, Shi, Hornak, & Wu, 2011) This demonstrates that the materials can actually be used in successful sensor devices.

Overall the materials in which optical nanosensor researchers are interested in are fluorescent nanoparticles which include QD, metal NP, silica NP and polymer NP. The advantages of these materials are described by Durgadas et al,(2011) as follows: *The fluorescent nanoparticles show unique chemical and optical properties, such as brighter fluorescence, higher photostability and higher biocompatibility, compared to classical fluorescent organic dyes. Moreover, the nanoparticles can also act as multivalent scaffolds for the realization of supramolecular assemblies, since their high surface to volume ratio allow distinct spatial domains to be functionalized, which can provide a versatile synthetic platform for the implementation of different sensing schemes. Their excellent proper ties make them one of the most useful tools that chemistry has supplied to biomedical research, enabling the intracellular monitoring of many different species for medical and biological purposes'*(Durgadas, Sharma, & Sreenivasan, 2011). Such as statement contains a lot of positive expectation in relation to the material and their potential use in biomedical research.

An issue which received a great deal of attention is the toxicity of QD which touches upon the development of the encapsulation of organic fluorophores in a particle matrix. When the QD are embedded in a matrix, usually a polymer matrix, they are isolated from the other parts of the cell. The entrapment enhances the stability and biocompatibility of the fluorophores. This is stated accordingly: *'In recent years, the design and fabrication of organic/inorganic nanocomposites with different combinations have attracted sig nificant attentions from both academic and industrial interests. In particular, much effort has been focused on incorporating noble metal nanoparticles (NPs) into conducting polymers, such as polypyrrole and polyaniline*' (Xuan et al., 2009).

A more recent material which emerged in 2005 in the nanosensor research domain is a carbon dot (CD). '*Carbon dots show similar photo-physical performance and photochemical stability to that of the well-known and already commercialized quantum dots (QDs). Moreover, they show non-blinking fluorescence emission, and they are readily soluble in water with the major advantage of comprising non-toxic elements with a non-toxic response, according to current available in vivo toxicity test .'* (Esteves da Silva & Gonçalves, 2011) The non-toxicity of the CD makes them promising candidates for bio imaging sensors for in vivo diagnostics, where QD usually contain toxic elements like cadmium. '*Although few applications of CDs as nanosensors for chemical analysis have been reported, the results show that they are a very versatile material that can be easily functionalized and immobilized in solid supports acquiring and maintaining the designed reactivity useful for chemical or biochemical analysis'*. Thus, when considering the properties of Carbon dots it is expected that more researchers will work in the future on CD.

We have discussed some of the most promising materials, now we will focus more on the promising sensor devices and prototypes. This will include optical fibre sensors, SERS sensors, LSPR sensors and PEBBLE sensors.

One of the most cited research group on optical nanosensors is the Vo-Dinh group. The Vo-Dinh group is located at the Duke University in California and is doing research at the frontiers of nanobiotechnology. They are especially involved in the development of nanobiosensors. In 2000 the group reported nanosensors with bioreceptors such as antibodies and used them to detect targets inside single cells. Furthermore, The group is working on the development of fiber optic chemical sensors. They expect that these fiber optical sensors can be used for *in vivo* measurements in living cells(Vo-Dinh, 2002). Some of the advantage of the optical fiber sensor, in comparison to widely used fluorescence dye based methods, are already discussed in the nanomaterial part but basically the come down to two main points*:* 1) *protection of the sensing component from interfering species within the intracellular environment and 2) protection of the intracellular environment from any toxic effects of the sensing component* (Aylott, 2003). Thus because they are so small they can enter the cell, and the polymer matrix protects the sensor and cell from toxicity issues. Expectations on the possibilities of the optical fiber sensors are impressive. It is expected that sensor can be developed for multi-analyte detection and for the analysis of protein–protein interactions and similar analyses of other proteins involved in cellular biochemical pathways. This could all be done In vivo (Vo-Dinh & Kasili, 2005).

Optical nanosensor are expected to be used for intracellular measurements *of* pH, oxygen, reactive oxygen species and radicals. But before the sensor can do any measurements they need to be inserted in the cell. Different methods for the delivery of the sensors are still under investigations. Delivery methods like pico injection, gene gun, liposomal delivery, and sequestration are widely used, however no dominant methods is chosen (Borisov & Klimant, 2008). Which emphasizes the fluidity and open state of the field were different technological options exists.

Overall it can be stated that optical nanosensor are very attractive for medical applications in vivo. However as regulation in relation to possible toxic effects of nanomaterials in medical applications are strict, it is unlikely that sensor will be used on humans in the near future. Nonetheless the potential is high, especially for animal experiments (Borisov & Klimant, 2008).

Next to the optical fiber sensor probably the most studied sensor technique is the SERS sensor. The sensor has been of great interest for the investigation of biological molecules and structures. E.g. Kneipp et al stated: '*The ability of very sensitive detection of Raman spectra from highly confined volumes makes SERS a very promising tool for studies in living cells*'. (Kneipp, Kneipp, Wittig, & Kneipp, 2010) Thus while studying the developments in the field, SERS devices will probably play an important role. *The SERS nanosensors usually consist of metal NPs, which act as SERS substrates. In order to enhance the stability and efficiency of the nanoprobes, the metal NPs are usually functionalized by coating the NPs with biomolecules (such as DNA and bovineserumalbumin), polymers, or inorganic layers*.(Xiufang Wang et al., 2011) This emphasizes the importance of the immobilization of nanoparticles with other biological molecules. The immobilization process is expected to be a key challenge in nanosensor development.

LSPR based sensor are another class of optical sensors which emerged in the field of optical nanosensors. LSPR sensors operate by sensing a change in local refractive index, this changes are caused by incoming light. The mechanism is described to some extent in the technological background section. The materials in the LSPR sensors are noble metal NP as they have promising surface characteristics. Especially arrays of triangular silver NPs are often applied in sensor design (Haes, Zou, Schatz, & Van Duyne, 2004). It is expected that the LSPR sensors can be applied in the future for medical diagnostics, biomedical research, and environmental science (Riboh, Haes, McFarland, Ranjit Yonzon, & Van Duyne, 2003). The LSPR sensors are expected to be able to detect many biological molecules such as glucose, DNA, E. coli, anthrax, and other proteins. An important advantage of the LSPR sensor is that it is robust and durable (2005).

Industry

Expectations within the patent database are less pronounced, as most of the statements in patents deal with agendas usually related to the question which materials or technologies the devices/inventions will consist of. Nonetheless some expectations have been found on PEBBLE sensors, SERS and LSPR sensors. It is expected that firms will develop fiber-optic tips which can be used in multi-functional sensors (simultaneously measuring 2 or more analytes) and/or multiplexed fiber tips. Such sensors are expected to be used in the analysis of cellular analytes. The university of California patented on SERS apparatus/systems which are expected to '*determine the presence and concentration of one or more target molecules, and/or changing physical and/or chemical conditions of an analyte such as, for* *example, biological agents, industrial chemicals, toxins, poisons, glucose and pH monitoring, single cell nanosensors, etc. Such a system and method can be implemented in applications that include medicine, health care, biotechnology, environmental monitoring and national security'*. Thus nanosensors are emerging as attractive devices to be employed in a great number of application fields such as microbiology, medicine, environment, automotive, particle physics and defense. Also expectations are voiced on label free optical biosensors as they allow one to study bimolecular complexes without using a fluorescence label or a radiolabel. These are just a few examples, but overall we can state from our analysis that expectation on optical nanosensors are less present in the patent database compared to the electrochemical nanosensors.

Governments

This section should presents the expectation made in the description of governmental projects related to optical sensors. However most of the expectations voiced in such project descriptions are to general, addressing societal needs, and do not directly relate to the optical development path. Such statements are discussed in more detail in the application domains. The statements dealing with developments related to this development path are discussed in the agenda section below, as almost all of them consist of the aims of the projects and thus fit better in the agenda section.

6.2.2 AGENDA

Research

The work of some research groups which contributed to the development of sensor technologies is now discussed. One of the prominent research groups working with QD is The Zhang research groups at Nanjing University, China. They have demonstrated that QDs can undergo FRET (fluorescence resonance energy transfer) phenomena and can be used to analyze interaction between proteins. In 2005 Wang et al, made an important step in the development of nanosensors for medical applications. He demonstrated a nanosensor based on oligonucleotide ligation assays which was able to detect a point mutation, typical of some ovarian tumors in clinical samples. This implies that the QDs have the potential to detect cancers in an early phase (C.-Y. Zhang, Yeh, Kuroki, & Wang, 2005).

Another direction in QD research is towards multiplex target analysis. Researchers are working on target-specific probes which could be integrated into one assay capable of detecting several analytes in one measurement. For example*: 'Goldman et al.(2004) used QDs functionalized with antibodies to perform multiplexed fluoro immunoassays for simultaneously detecting four toxins. This type of sensor could be used for environmental purposes for simultaneously identifying pathogens (like cholera toxin or ricin) in water. The FRET principle was also used to build a maltose biosensor'* (riu et al, 2006) Another example is presented by Xia et al, (2008) who developed a protease sensing system capable of detecting MMP- 2, MMP-7, and uPA which are indicators of tumor cells. This is a demonstration of a multiplex protease assay(Xia et al., 2008). The following statement summarize some of the QD developments and how they influence the field' *New molecular sensing strategies based on QDs have been developed in pursuit of high sensitivity, high throughput, and multiplexing capabilities. For traditional biological applications, QDs have already begun to replace traditional organic fluorophores to serve as simple fluorescent reporters in immunoassays, microarrays, fluorescent imaging applications, and other assay* *platforms. In addition, smarter, more advanced QD probes such as quantum dot fluorescence resonance energy transfer (QD-FRET) sensors, quenching sensors, and barcoding systems are paving the way for highly-sensitive genetic and epigenetic detection of diseases, multiplexed identification of infectious pathogens, and tracking of intracellular drug and gene deliver'* (Sadik et al., 2009). In 2008 a new family of fluorescent nanosensor for the detection of Zn2+ is reported. These nanosensors are based on azamacrocycle derivatization of CdSe/ZnS core/shell quantum dot nanoparticles. These sensors are the first models using QD particles in a receptor-fluorophore system (Maria Jose Ruedas-Rama & Hall, 2008). Many other researchers are working with quantum dots, and produce interesting results which all influence the developments in the field of nanosensor. However it is not the intention to summarize all those research effort in this thesis.

The Vo-Dinh group has developed a new type of nanoprobes using SERS detection. The essence of this technique is that the Raman scattering is enhanced when molecules are absorbed. The information in the resulting signal contains information on the molecular structure which in turn can be used for the determination of the substrate. In past few years it has been demonstrated that single-molecule detection with SERS is possible. Vo-Dinh demonstrated the feasibility of SERS imaging of cell surface receptors using SERS nanoprobes. With this technique they can make images containing spatial and spectral information of chemical substances in cellular environment. Vo-Dinh states that an significant advantage of these nanosensors is the minimal invasiveness, so cells can be analyzed without affecting their functioning. '*Future applications of optical nanoprobes could include multianalyte detection and analysis of protein-protein interactions and similar analyses of other proteins involved in cellular biochemical pathways'* says Vo-Dinh. SERS nanosensors already have been reported capable of detecting HIV, DNA and cancer genes. (Vo-dinh, 2004) *'The advantages of SERS, such as low detection limit, real-time response, both qualitative and quantitative analysis capabilities, a high degree of specificity, and simultaneous multi-component detection, make it applicable in identification and characterization of pharmaceuticals, bacteria, and other molecular species'*

Another important goal for nanosensor researchers is to develop immobilization strategies of the recognitions elements of the sensor on the transducer element. In relation to optical nanosensors the group of Mark and Cosnier have booked some important results on this topic. They have developed; 'an innovative and versatile strategy for immobilization of biorecognition elements on an ITO-coated optical fibre. This biosensor combines electro deposition of the receptor proteins and optical detection through the optical fibre. For example the avidin-biotin affinity interaction has been exploited for construction of an immunosensor'. (Martín-Palma et al., 2009). Another possible breakthrough has been reported by Graham et al, 2008: '*This is the first time that coded nanoparticles have been used to produce a reproducible and clearly defined nano-assembly where the enhancement of Raman scattering from a specifically immobilized tag has switched from an effective "off" to "on" state following the action of a biological recognition event. This is a significant result, opening up many opportunities for the combination of chemical understanding of the surface phenomenon, enhanced spectroscopy and also the biological recognition procedure'* (Graham, Thompson, Smith, & Faulds, 2008)

McFarland and Van Duyne research group is the most cited research group in relation to the development of LSPR sensors based on Ag nanoparticles. (Haes, Zou, et al., 2004). The LSPR wavelength shift response of Ag is used to develop a new class of nano scale optical biosensors. The signal of resonance-shift-based LSPR biosensors relies on the refractive index change upon molecular adsorption on the surface, which is similar to the SERS technology. The Real-time molecular sensing with a single particle using LSPR was first shown in 2003 by the McFarland and Van Duyne research group.(Sannomiya & Vörös, 2011). In 2010 the van Duyne group reported on the LSPR based sensors for gas sensing application. They were the first to develop high-resolution localized surface plasmon resonance (HR-LSPR) sensors to detect He, Ar, and N_2. These research results create new application possibilities for LSPR based sensors (Bingham, Anker, Kreno, & Duyne, 2010).

Next to the LSPR and SERS based sensors, The PEBBLE sensors have been reported by multiple researchers. PEBBLEs are Probes Encapsulated By Biologically Localized Embedding and are usually used for intracellular measurements. In 1998 the PEBBLE concept was introduced by Kopelman and co-workers. Since then the field has developed grown rapidly as an extension of optical fibre based sensors. The PEBBEL show great potential for application to cellular measurement. Sumner et al reported that Pebble sensors can be used for measuring magnesium concentrations within cells. '*An advantage of the Pebble sensor is that the matrix provides dual protection: protection of the dye from cellular components as well as protection of the cell from potentially toxic sensing dyes* (Sumner, Aylott, Monson, & Kopelman, 2002). Park et al, presented a first description of a magnesium nanosensor with great selectivity over interfering ions such as calcium, potassium, and sodium.(Park, Brasuel, Behrend, Philbert, & Kopelman, 2003). The sensors have the characteristics to obtain reliable measurements of intracellular magnesium levels. The main classes of PEBBLE nanosensors are based on matrices of cross-linked polyacrylamide, cross-linked poly(decylmethacrylate) and sol-gel silica. These matrices have been used to fabricate sensors for H^+, Ca^{2+}, K^+, Na^+, Mg^{2+}, Zn^{2+}, Cu^{2+} and Cl^- (Riu et al., 2006b). The PEBBLE platforms can be adapted for various types of analytes and are commonly used with either 'direct measurement' or 'ion-correlation' sensing schemes. Overall we can state the PEBBLE sensors are effective intracellular sensors, combining the physical non-invasiveness of free molecular dyes with the chemical non-invasiveness of pulled fiber optical sensors (Buck et al., 2004).

Industry

It is interesting to note that the majority of the patents are not attributed to large firms bur rather to research institutes and universities. This is a bit in contrast with the electrochemical sensor paths where more companies are present in the database. Now we will present some of the most reoccurring patents on optical sensors.

The Regents of the University of Michigan hold patents on fibreless optical nanosensors for intracellular measurements. Example: '*The invention relates generally to optical fiberless sensors, method of fiberless sensor fabrication and uses of such sensors in cells. The sensors of the present invention are: (1) small enough to enter a single mammalian cell relatively non-invasively, (2) fast and sensitive enough to catch even minor alterations in the movement of essential ions and (3) mechanically stable enough to withstand the manipulation of the sensor to specific locations within the cell*. AND '*the fiberless sensors* *of the present invention are non-toxic and permit the simultaneous monitoring of several cellular processes. In one embodiment, the present invention contemplates the use of such fiberless sensors to monitor a single cell exposed to a variety of noxious or trophic stimuli.'* Basically the invention relates to the identification of cellular responses which lead to diseases.

The most often reoccurring device in the patent database is a devise using SERS technology. The company NanoBioDynamics.INC is patenting on devices using SERS for the detection of substances like bacteria, viruses which can be monitored in real time without the use of labels. The Northwestern University also patented on biosensors using SERS for the detection of intracellular analytes. Their invention usually relates to the in vivo detection of analytes such as glucose. Also the Regents of the University of California patented on devices using the SERS technique. The sensors can be used for pH, ion concentration, temperature, measurements as well as for proteins, DNA, RNA. A few examples:
'The present invention is directed to a surface-enhanced Raman spectroscopy (SERS) apparatus that utilizes designed nanosensors and detection means to determine the presence and concentration of one or more target molecules, and/or changing physical and/or chemical conditions of an analyte.'

'*The present invention provides a desired surface-enhanced Raman spectroscopy (SERS) apparatus/system and method to determine the presence and concentration of one or more target molecules, and/or changing physical and/or chemical conditions of an analyte such as, for example, biological agents, industrial chemicals, toxins, poisons, glucose and pH monitoring, single cell nanosensors, etc. Such a system and method can be implemented in applications that include medicine, health care, biotechnology, environmental monitoring and national security.*'

The University of Georgia Research Foundation. Inc holds patents on Fiber optical SERS systems, portable SERS devices and methods for using these systems for the detections of analytes. A part of the patent: *Briefly described, a representative embodiment of a fiber optic SERS sensor system of the present disclosure, among others, includes: a Raman system and a SERS probe, wherein the Raman system includes a Raman probe interfaced with the SERS probe and an optical fiber system for transmitting a light to the Raman probe from a light source and transmitting a signal light from the Raman probe to a Raman detection system'.* The patents are usually full of such incomprehensive descriptions, however what we can derive from this data is that the University is working on devices which work on the SERS phenomena which implies that this technique is seen as promising. Some other statements illustrate the presence of SERS based sensors in the database:
'The present invention discloses a surface enhanced Raman scattering analysis system and methods for detection of target molecules in a test sample using the analysis system and a sensor for the same. The system has a SERS sensor containing an optical substrate and an array of often functionalized high aspect ratio nanowires disposed on the optical substrate.'

'A method for detection of molecular species or biological agents in a test sample is also provided that uses the analysis system of the present invention having a SERS sensor formed in accordance with one aspect of the invention. The method includes contacting the nanowires on the sensor with a sample to be

analyzed, illuminating an optical substrate, and collecting optical data from the system following the illumination'

'A need exists for an improved Surface-Enhanced Raman Spectroscopy (SERS) method and apparatus/system to determine the presence and concentration of one or more target molecules, and/or changing physical and/or chemical conditions of an analyte. The present invention is directed to such a need'
'Since the initial discovery of (SERS), understanding how the local electromagnetic environment enhances the substrate-adsorbate complex's spectral response has been of central importance. It has become increasingly evident that plasmon resonances of the metallic substrate provide intense, local optical-frequency fields responsible for SERS'

Next to the universities also companies, usually related to the medical sector, hold patents on optical sensors. For example the company *Advanced Cardiovascular Systems.Inc*, holds patents sensor devices capable of detecting NO concentration. The device can be useful for in vivo analysis of vascular health. Another company, *Precisense A-S*, hold patents on optical sensors with the intention to develop optical sensor for the continuous monitoring of glucose concentrations in the blood The invention claimed: *A sensor for in vivo measurement of an analyte, comprising a plurality of particles having a size such that when implanted in a body of a mammal at an implantation site the particles can be ingested by macrophages and transported away from the implantation site, wherein each particle of the sensor contains the components of an assay having a readout which is an optical signal detectable transdermally by external optical means, and wherein the particles are each contained within a biodegradable material preventing ingestion by the macrophages'.*

Another University holding several patents within our database is the University of Illinois. They have patents on fluorescence based biosensors. The sensors are capable of selectively and specifically detecting the presence of an ion in the presence of other ions. The invention claimed: *A biosensor, capable of detecting the presence of a metal ion in a sample in the presence of other ions, comprising: (a) a nucleic acid enzyme, and (b) a substrate for the nucleic acid enzyme, wherein the enzyme comprises a first quencher and is dependent on the metal ion as a cofactor to produce a product from the substrate; and the substrate comprises a second quencher and at least one fluorophore.*

Many other universities/research institutes and small companies reoccurred in the database, however it is not feasible to describe them al here. The universities which reoccurred most often are described and the overall tendency found is that they all work on optical nano sensors, they recognize the importance of nano sensor devices, the application (if discussed) relate to medical devices, but above all they almost always relate to measurements in intracellular compartments. The most important finding is that almost all the patents mention the SERS technique in relation to the sensor devices.

Governments
This section presents the agendas and aims of the governmental projects related to optical nanosensors. Most of the projects have the aim to increase fundamental knowledge on a specific topic.

A few projects relate to the development of QDots. An Exmpale is the projects QUANTUMDOTIMPRINT. The goal of this project is to make the QD water soluble and target them towards specific biomolecules either by surface functionalization or polymeric shell implementation. '*The main objective of the project is the preparation of quantum dots having biocompatible MIP shell capable of selectively recognizing antibiotics'* The DOMINO projects also deals with QD research as it could impacts important societal issues like photonic sensors for environment monitoring, photonic diagnosis devices for health care, laser assisted surgery, free-space optical communication systems. *DOMINO sais to open the route to further long-term research on semiconductor nanostructures and nano-photonic devices.*

A project related to optical sensor devises is PHOTOSENS. The projects aims for a better understanding of photonic and plasmonic dispersion and field localization effects in periodic nanostructures, such as Photonic Crystals, and their applicability to sensing purposes. The project demonstrated a multi-parameter large-area sensor platform for environmental and pharmaceutical sensing.

The objective of the SMARTFIBRE projects is to develop a smart miniaturized system which integrates optical fiber sensor technology, nano-photonic chip technology and low power wireless technology. ''*Due to the innovative approach of integrating micro-technologies, SMARTFIBER will demonstrate a smart system so small (order mm's) that it can be embedded as a whole in the fibber reinforced polymer. As such, the system takes away the main technical roadblock for the industrial uptake of optical fibber sensors as structural health monitoring technology in composite structures: embedding of both fibber sensor and fibber interrogator omits the fragile external fibber coupling to an external interrogator'.*

Another multidisciplinary project is PROSPER. The project covers the emerging fields of photonics, bio-chemistry and endoscopy, and aims for a contribution to the development of a new class of biochemical optical sensors that would significantly improve the healthcare of the future.

PROSPER will address this objective through the demonstration of biosensors based on a functionalized polymer optical fibre (POF) in which specially-designed refractive-index gratings have been written. Immobilised biomolecular receptors on the grafted fibre surface will allow label-free recognition through the monitoring of wavelength shifts in the grating spectral response. The ultimate target of PROSPER is to demonstrate the feasibility of diagnostics outside the laboratory settings. This means a prototype consisting of a packaged polymer biosensor will be developed and tested in a real world setting.
We can conclude that only a limited amount of projects relates to optical nanosensor devices. And that the EU funding related to optical nanosensors is thus rather limited.

6.2.3 NETWORKS

This section will briefly address the biggest actors, with the highest influence on the field of nanosensor technologies. The most cited research groups are presented together with the 10 biggest patent holders in our database.

One of the most cited research group on optical nanosensors is the Vo-Dinh group. The Vo-dinh group is located at the Duke University in California and is doing research at the frontiers of nanobiotechnology. They are especially involved in the development of nanobiosensors based on the SERS technique. Another group with many publications on SERS based sensors is the Haes research group from the IOWA university. Another big actor is the highly cited research group of McFarland and Van Duyne located at the Northwestern university. The group is involved in the development of LSPR nanosensors and van Dyne is the inventor of the LSPR technique.
The following 10 actors hold the most patents in our database. The numbers of patents vary around 2-6 patents per applicant. In order of importance: University of Michigan; University of Illinos; University of California; University of Michigan; University of Georgia; NanoBioDynamics, Inc; engeneOS. Inc ; Cellomics.IN; Advanced Cardiovascular systems. IN; Hewlett Packard. The most remarkable finding is that most of the patents are assigned to universities and not firms and that almost all the assignees are located in the US.

6.2.4 Summary

From the above we can see that optical nano-sensor play an important role in the development of the field. Firms are patenting on optical sensors, new actors emerge, expectations are raised and promising research results are booked. It seems that optical nanosensor could provide the tools to investigate important biological processes at the cellular level in vivo. An important advantage of the nanosensor is that they can be inserted in cell without destroying or interfering with the cellular functions. This is possible due to the polymer matrix in which the QD are usually embedded in. '*For traditional biological applications, QDs have already begun to replace traditional organic fluorophores to serve as simple fluorescent reporters in immunoassays, microarrays, fluorescent imaging applications, and other assay platforms*' (Yi Zhang & Wang, 2012).

The nanomaterials which are expected to have a significant impact in optical nanosensor development are usually QDots and metal nanoparticles, often used in combination. Three prototypes of optical sensors are discussed, The PEBBLE-, LSPR-. and SERS sensors. All of them seem to been promising for intracellular sensing applications. However most attention is received by the SERS sensors, primary by industry actors. It looks like the SERS based sensor is selected as the most promising application of optical sensor technologies. However, a big obstacle for the commercialization of the SERS based nanosensor is the lack of mass fabrication processes for nanophotonic crystals (NNI, 2009).
When looking at what the researchers are working on we see many shared technical goals: increase sensitivity, selectivity, functionalization of the NP, label free detection methods, and especially multiplexing is seen a highly desirable goal by many authors. Interesting to note is that most of the optical nanosensor development seems to be aimed for application in the medical sectors. It is thus expected that the optical nanosensor development will have a big impact in medicine in the future. More on this in the medical applications section.
Overall we can say that research on optical nanosensors looks interesting, and expectations are high. However research is only in an early stage and many of the concept and ideas are not yet used in practice (Borisov and Klimant, 2008).

7. Application domains

The food industry, environmental analysis and medical applications are the domains where nanosensors are said to have a potential significant impact. This chapter will describe nanosensor development in relation to those three areas. First, some general needs from the domains and how sensor technologies can contribute to those needs will be addressed. This section primarily is based on findings from the scientific articles, as the patent database generally did not relate to application areas, but rather to specific working mechanism. Some governmental projects related to the application areas are discussed. Furthermore, we will discussed the developments from the development paths and how they can affect this application area.

7.1 Food

7.1.1 Intro

One of the major drivers of nanosensor research is the ability of nanosensor to detect pathogens and microorganisms, which are responsible for food borne illnesses and contribute to many infectious diseases. New molecular techniques for food pathogen detection are being developed which can improve sensors, selectivity, reusability and simplicity (Arora, Chand, & Malhotra, 2006). Different food borne pathogens are known for causing food borne diseases. The following pathogens are responsible for most of the food borne outbreaks: Campylobacter, Salmonella, Listeria monocytogenes, and Escherichia coli. From these pathogens Salmonella causes 31% of food related deaths, followed by Listeria (28%), Campylobacter (5%), and E. coli (3%) (Valdés, Valdés González, García Calzón, & Díaz-García, 2009). This implies that nanosensors which are able to detect such pathogens will be highly desirable.

More in general there is need to guarantee food safety and quality which also holds that the quality of food should be monitored along the entire food chain which includes growth, production, storage, transportation and consumption. These are all aspects where nanosensors could play a significant role. Next to the food borne pathogens, society is increasingly concerned about the use of genetically modified organisms (GMO) in food products. This raises a need to develop detection and control strategies to detect possible GMOs with the intention to ensure the quality of food, both domestic and international.

In nanosensor research, biosensors have received a lot of attention as potential candidates to address those needs mentioned above. Biosensor have been developed which are able to detect concentrations of sucrose, lactate, alcohol, glutamate, and ascorbic acid, which are found in the majority of food items. Furthermore they can detect the presence of microorganisms, pesticide residues and antibiotics in food samples (Valdés et al., 2009).

Food packaging

One of the main applications of sensor technologies in the food sector is in food packaging. The use of nanosensor, which can detect chemical, pathogens and toxins, can provide the consumers information in real time about the status of the food freshness. This would be an improvements over the often inaccurate expiration dates on packages today *(Azeredo, 2009).* An on-pack sensor strip is often mentioned as a practical application. Such strips should contain optical sensor membranes sensitive to O_2, CO_2 and other gases. The benefit of such an approach is that the quality of the food can be assessed in a non-destructive manner. Today most of the quality assessments techniques are destructive, which means that the food cannot be consumed after analysis. The use of nanosensor technologies could contribute to new nondestructive quality assessment techniques.

Related to the sensor strip is the concept of ‘‘electronic tongue” which tries to simulate the working principles of a biological tongue. Such a device consists of an array of nanosensors which are highly sensitive to different gases which are released by spoiling microorganisms. As a result a color change of the sensor strip provides information on the quality of the food. Such a device is now being developed by Kraft Foods together with researchers from the Rutgers University (Azeredo, 2009). Kraft, one of the biggest companies in the food industry, has created a consortium in the USA called 'Nanotek' to collaborate with academia and research labs in order to develop nanoscale sensors. *'Development of foods capable of changing their color, flavor, or nutritional properties according to a person’s dietary needs, allergies, or taste preferences is on the research agenda of Nestle and Kraft'* (Azeredo, 2009).

There are many analytes which need to be measured in order to assure the quality of food. These analytes can be grouped in toxins, pesticides, pathogens and parasites (Farahi et al. 2012). Besides these elements also gases (O_2, NO, NO_2, CO_2) are important in food packaging. E.g. oxygen allows microorganisms to grow and therefore vacuum packaging is needed. However, probably the most discussed analyte in the studied literature are organophosphorous pesticides(OP) which are used in agriculture. Such compounds are highly toxic and can cause neurological diseases. Thus the monitoring of these compounds is necessary to assure human health protection and environmental control. There is a considerable interest in developing highly sensitive, selective, rapid and reliable analytical methods for OP detection. (Lu et al., 2008)

Nine projects in the EU framework programs are present which contribute to the development of nanosensors in food applications. The projects are listed in Appendix C. The overall aim of those projects is to monitor food quality along the food chain, to detect pathogens and some projects focus on sugar concentrations in food. The importance of monitoring systems is emphasized which requires sophisticated ICT tools and data analysis algorithms. The type of sensors discussed in those projects are usually biosensors, however little information on the working mechanisms of those sensors is disclosed.

7.1.2 Optical

This section will address some of the optical nanosensor developments which can be applied in to food sector.

In 2005 an optically based biosensor was used to screen poultry liver and eggs for the presence of the drug nicarbazin, a feed additive used to prevent outbreaks of coccidiosis in boiler chickens. Mohammed et al,(2003) have also demonstrated the use of this technique to detect the presence of allergens, in particular peanuts, during food production (Terry, White, & Tigwell, 2005). Lee, Sheridan, and Mills (2005) developed an UV-activated colorimetric oxygen indicator, which uses nanoparticles of itania (TiO_2) to photosensitize the reduction of methylene blue by triethanolamine in a polymer encapsulation medium, using UVA light. '[*Upon UV irradiation, the sensor bleaches and remains color less, until it is exposed by oxygen, when its original blue color is restored. The rate of color recovery is proportional to the level of oxygen exposure. This technique could be used to develop oxygen indicator packaging systems for a variety of oxygen-sensitive foods'*. (Azeredo, 2009). Liu et al. (2008) applied the localized SPR (LSPR) of gold nanoparticles covalently coupled with AChE to create a biosensor for detecting OP. The principle of such LSPR fiber-optic biosensors is described in the optical development path. The research of Liu demonstrated that the AChE-modified LSPR biosensor can be used for label-free detection of paraoxon with an excellent sensitivity.

Another recent study demonstrates the feasibility of optical nanosensors for the detection of bacteria. Majdinasab and Aminlari, (2013) have shown that oligonucleotide-capped gold nanoparticles (GNP) probes can be developed into a microbial detection sensor. The sensor is colorimetric and is based on aggregation of DNA-modified GNPs probes. The sensor is very specific and efficient for the detection of pathogenic bacteria. *'This technology appears suitable for the rapid and low-cost detection of pathogenic bacteria, since we have demonstrated the nanoparticle technology can detect specific sequences in un-amplified genomic DNA of bacteria. Future work will focus on further increasing sensitivity of this method, detection of other pathogenic bacteria and application of GNP probes in other assay except the colorimetric approach'* (Majdinasab & Aminlari, 2013).

In general nanosensors that use fluorescent dye particles attached to bacteria antibodies receive a lot of attention. This is a form of labeling, which often increases the complexity of a sensing device, but in this case can be quite fruitful. When a bacterium is present in the food-sample the dye particles will become visible as a result of the interaction of the antibody with bacteria. This method allows for real time detection of bacteria without the need of sending samples to laboratories. Sensors using this technique have been developed to detect Staphylococcus enterotoxin B, E. coli, Salmonella, and Listeria monocytogenes.

Many optical sensors in this field use an antibody as the recognition element and are called immunosensors. Immunosensors are based on exploiting the specific interaction of antibodies with antigens. usually, immunoassays use a label (e.g., enzyme, fluorescent marker, antigen) to detect the immunological reaction (Rana et al. 2010). *'Optical immunosensors include optical fiber or surface plasmon resonance (SPR)-based sensing systems that measure luminescence, fluorescence, reflectance and absorbance, etc. Specific antibodies immobilized onto different fiber probes have been reported for the simultaneous detection of Salmonella, E. coli'* (Arora et al., 2006). Usually the antigens (antibodies are being immobilized a metal surfaces of the nanoparticles. The immobilization is one of the key challenges in nanosensor development. Also magnetic nanoparticles are often described as sensor material. Where the NP are functionalized with antigens and use IR spectroscopy for fingerprint recognition.

We can see that a large fraction of sensor described for food applications are biosensor. Biosensors make use of biological recognition elements, such as antibodies and enzymes. Such biological elements have limitations: they are not always available, they are unstable in organic solvents, high temperature, or extreme pH values. In order to overcome these limitation researchers have tried to synthetically make recognition element. A new development in the field of biosensors is to synthetically make the recognition element and thus mimic nature. This is can be done by the use of molecularly imprinted polymers (Bongaers et al., 2010).

Besides the detection of different bacteria, viruses and pathogens optical nanosensors can be used to detect silver nanoparticles (AgNp) in food or in the environment. Silver-nanoparticles are already widely applied in nanotechnology applications. They are said to be effective as antimicrobial agents and have been implemented in various consumer products including washing machines, refrigerators, clothing, medical devices, and food packaging. Next to the benefits of AgNp they also raise concerns about possible negative effects on living organism and systems. Thus to ensure human health the monitoring of AgNp is needed. Rebe at al, (2012) have developed a human metallothionein (MT) based surface plasmon resonance (SPR) sensor for rapid detection of nanosilver. Their findings show for the first time that AgNPs can be directly detected in their intact form using hMT1A protein in combination with SPR-based sensor. '*The potential application possibilities of this sensor were demonstrated by successfully detecting AgNPs in fresh vegetables and river water extracts*' (Rebe Raz, Leontaridou, Bremer, Peters, & Weigel, 2012).

The possibility of detecting nanoparticles touches upon the safety issues related to the use of nanopoarticles in food applications. As with many applications of nanoparticles many uncertainties about possible toxic effect of nanoparticles exist for humans and the environment. In literature much has been written about the potential for nanosensors to detect hazards and mitigate risk, however very little is known about the effects of deploying nanosensors in the environment and food packages (Gruère, 2011). Hence studies relevant to exposure risk assessment are required for nanoparticle use in food applications.

7.1.3 Electrochemical

This section will address some of the electrochemical nanosensor developments which can be applied in the food sector.

An emerging topic within nanosensor research is the 'electronic nose'. This is a sensor array that can detect and discriminate several volatile compounds based on their electronic responses to the different gas sensors in the array. These sensors are usually gas sensors based on metal oxides. Based on the measurement of the sensor array a signal pattern can be collected and analyzed. In relation to food application this method has relevance for de mycotoxin field as such microorganism and fungal produce gases. Similar to the nose, researchers are also working on an electronic tongue, which also consist of array of sensors. *'The electronic tongue appeared to be capable of distinguishing among different sorts of beverages: natural and artificial mineral waters, individual and commercial brands of coffee, and commercial and experimental samples of soft drinks containing different sweeteners'*.(Viswanathan, Radecka, & Radecki, 2009)

Marques et al, (2009) presented a novel material for electrochemical biosensing. The material is based on conducting gold nanocomposites. The material is suited for improved immobilization of receptor molecules and has good transuding properties. It is expected that the material can be used for the constructions of electrochemical biosensors such as immunosensors, genosensors, and enzymosensors (Marques et al., 2009). Another promising material for the application of electrochemical sensors is graphene. Labroo and Cui demonstrates in 2012 for the first time a graphene-based bio-nanosensor to detect lactate. The researchers anticipate that their results *'could open exciting opportunities for fundamental studies of flexible graphene bioelectronics by using other bioreceptors, as well as a variety of wearable, implantable, real-time, or on-site applications in fields ranging from clinical analysis to defense'* (Labroo & Cui, 2013)

Within the category of electrochemical biosensors a distinction can be made between the potentiometric biosensors and amperometric biosensors. Where the use of amperometric sensors is more popular. Such sensors have been applied in food analysis for the detection of concentrations of sucrose in soft drinks, measuring isocitrate concentrations in fruit juices, and determining urea levels in milk. Amperometric biosensors are especially suited for the detection of consumed oxygen or generated hydrogen peroxide. Both of those elements are electrochemically active as the oxygen can be electrochemically reduced, and hydrogen peroxide can be oxidized (Terry et al., 2005).
There are already some commercially available instruments based on electrochemical biosensors on the market. An example of this is the YSI 2700 SELECT Biochemistry Analyzer, produced by YSI Inc., which is capable of measuring food components like glucose, sucrose, lactose, lactate, lactose, glutamate, choline, glutamine ethanol, hydrogen peroxide, and starch.

In an comprehensive review article on electrochemical sensors Viswanathan(2009) stated that: *'Electrochemical biosensors have been reported for analyzing food and beverages, for detection of GMO content in food , for measuring the freshness of food, etc. Still, there are many avenues to be opened in these fields for the application of electrochemical sensors. At present, there are many proposed and already commercialized devices based on the biosensor principle, including those for pathogens and toxins, some even based on a multichannel configurations*' (Viswanathan et al., 2009). This indicated that electrochemical sensors indeed hold promise and that commercial application already start to emerge. However we have to keep in mind that the field is still in its infancy and most research results are based on experiments in laboratories where different conditions exists compared to the real world.

7.1.4 Challenges

It looks like the development of nanosensors for food applications is taking off. However as the field is still in its infancy still many challenges exist.

- One of the biggest challenges in nanosensor applications for the food industry are real world conditions. Today most of the nanosensor research results are made in labs with controlled conditions. In the food industry the sensors should be capable of working under extreme temperatures, pressures and others changing parameters. In the real world sensors have to deal with the presence of multiple microorganisms and other substances which could interfere with the sensors measurements.

- Another challenge relates to the stability of sensors and analytes when interacting with other species. It is said that changes in fingerprint signature do occur when the analytes interacts with different unknown species, which makes detection and determination harder (Arora et al., 2006).

- Yet another challenge, also related to environmental analysis, is the sampling issue. One can imagine that the scale of the sensors is extremely small compared to the product it is measuring. This implies that the sensor only measures a small part of the food or environment. This is still a big challenge and future research will have to address this problem. Swarms of autonomous wireless sensors networks are often mentioned as possible solutions to this problem.

- As in almost all sensors literature a challenge lies in making the sensors more selective, sensitive, robust, and cheaper. Also multiplexing, which makes multi analyte detection possible, is high on the agenda of many nanosensor researchers. In order to increase selectivity a lot of fundamental research needs to be done on the functionalization of nanomaterials (Sadik et al., 2009).

- Also the immobilization of antigens on the transducer material or close to it is seen as one of the main technical challenges for future research.

- Besides all the technical challenges the availability and fabrication of nanomaterial is key to the successful development of commercially viable biosensors. This is not necessary a challenge for the food application domain as new methods of material production are being developed in others fields were advancement in nanotechnology and science are being made. For example advance in the microelectronics industry can be adapted for sensor fabrication.

-Another challenge is public awareness and legitimacy to use nanomaterials in food applications. As with any new technology, there is a significant challenge to create awareness and gain acceptance of the use of nanotechnology in the food industry. Today almost no regulatory standards exists in relation to the use of nanometarials in the food industry (Sozer & Kokini, 2009).

In short, the developments of nanosensor research and applications in the agriculture and food sector starts to emerge, however the fields is still in its infancy compared to the field of medical applications. (Sozer & Kokini, 2009) *'The analytical aspect of the nanotechnology applied food industry is just starting to emerge'* (Valdés et al., 2009). Application of nanosensors in food safety is very promising and could benefit worldwide human health. We can see a continuous progress where sensitivity and selectivity of the sensors is increasing, however this only accounts for developments in laboratories. Today almost no field testing results are reported. The challenges described above are the topics where nanosensor researchers will probably be working on in the future. In the future it can be expected to see more multiplexed hybrid systems with different combinations of transducer platforms and recognition elements. It is expected that different sensing platforms (optical, electrochemical, and mechanical) will be integrated into one sensing device (Farahi et al. 2012). However the biggest challenges still remain the difficult real world conditions and the sampling issues.

7.2 Environmental Analysis

7.2.1 Intro

A major driver for nanosensor development for environmental application are the worldwide concerns about environmental issues. Due to the negative effect of climate change and ever increasing pollution of the planet a need is created to monitor the environment, which brings a requirement to monitor a wide range of analytes in soil, water and air. Different environmental applications are needed which range from the monitoring of groundwater resources, drinking water analysis, analysis of soils at hazardous waste sites, detection of toxic industrial chemicals, gas leaks, detection of material degradation, and detection of a variety of gases and vapors e.g. methanol, ethanol, 2-propanol, acetone and toluene and greenhouse gasses (Sharpe, 2003). More specifically there is a great interest in the development of small solid state gas sensors that are capable of detecting biomarkers for bacterial pathogens. Nanosensor could be used for the detection of different types of analytes. The following analytes are of most interest and most studied in the literature on nanosensor development in relation to environmental monitoring. The analytes include pesticides, polychlorinated biphenyls, and heavy metals. In the bacteria category the most studied are: Salmonella, thypihmurium, enteritidis, Escherichia coli , Listeria monocytogenes, Staphylococcus aureus , and Cryptosporidium parvum.

Today environmental monitoring usually involves sampling in the field and sending the samples to specialized laboratories where trained personnel can determine the chemical composition and possible toxic effect. This is an expensive, time consuming and inefficient process, hence a need for faster, sensitive and selective, cheap systems is gaining interest (Andreescu & Sadik, 2004).

Now, recent advances in the field of nanosensors, electronics and wireless communication have led to the emergence of sensor networks, which is a hot topic in the development of nanosensors for environmental application. A sensor network is swarm of sensors located at different locations where the sensor connected by a wireless network. This technology enables the possibility to perform sensing tasks in the field without the presence of an operator. Such sensors can measure environmental condition like pressure, temperature, pollutants etc. at places difficult to reach. A big challenge is to make the sensors self-powered which would make them autonomous units. Thus, wireless sensor networks are important in the field of environmental monitoring as they can provide a vast amount of information in real-time at distant locations. The envisioned sensor networks would exist of *'tens of thousands of intelligent sensor nodes providing local measurements as well as overall patterns of change'* (Rodriguez-Mozaz, Alda, Marco, & Barceló, 2005). Such sensors could for example collect data on soil moisture and temperature, which are important variables in controlling the water en heat exchange between the soil and atmosphere which in turn play a role in the development of weather patterns. Thus such data could contribute to a better prediction of weather patterns(Jackson, Mansfield, Saafi, Colman, & Romine, 2008).

As developments in nano science and technology continue to develop, more and more nanoparticle are incorporated in product and exposed to the environment. Unfortunately very little is known about the possible risks and toxic effects of the NP on the environment and on human health. However, it is known that almost all materials can be toxic at high concentration rates. Therefore a need exists to develop detection methods to measure nanoparticle levels in the environment. *'Currently, a very limited suite of devices is available to monitor the release of nanomaterials across the diverse environments where nanomaterials are developed, manufactured, used, and recycled' (NNI, 2009).* To sum up, information on the environmental status is highly needed and nanosensor offer great promise to meet those needs (Rickerby & Morrison, 2007).

Ten projects in the EU framework programs are present which contribute to the development of nanosensors in food applications. The projects are listed in Appendix C. The overall aim of those projects is to develop sensor devices for pathogen detection. The SENSOMETAL projects aims for the detection of small metal concentrations in plants. Other projects use optical sensors for the monitoring of plant metabolism processes. A few projects, like DINAMICS and NANOBE, aim for the development of lab on chip devices where sensors are integrated with micro fluidic technologies. Such chips would enable real time monitoring of processes at distant locations, as sensors would become portable. The BIOMONAR projects aims for the development of multiplexed biosensor arrays capable of detection different types of pathogens. An important topic which is also addressed in the project descriptions is the need for low power, autonomous sensor networks which are capable of communication with the others sensors. Such swarms of sensors are needed for the monitoring of large areas at distant location. A funny projects related to this is the SHOAL projects which has the goal to: '*develop robot fish which will function independently and as part of a larger group to analyze and monitor pollution in a port. These robotic fish will be equipped with chemical sensors to find pollutants in the water and modems to create an ad hoc network for communication within the swarm. This will allow the shoal of robot fish to build up a broad map of the pollutants moving through the port in real time whilst adapting naturally to changes in environmental conditions in the port'*

7.2.2 Optical

This section will address some of the optical nanosensor developments which can be applied in to environmental analysis applications.

In 2003 a research group at the Colorado state university developed a fibre-optic biosensor capable of measuring multiple organic compounds in the groundwater. The device used a detection elements on the tip of the optical fiber. When an analyte is present it leads to pH changes on the tip which in turn can be measured as changes in fluorescence (Sharpe, 2003)

Cao et al. (2002) developed a biosensors which could identify pathogens in water by functionalizing gold nanoparticles with oligonucleotides which are selective to the DNA sequences of pathogens. They used SERS and Raman-active dyes to tag the DNA and RNA targets. The tags in turn could be detected by the Raman scattering of the dye molecules(Riu et al., 2006b). In 2007 Chen et al, also used gold nanoparticle based fluorescent sensor to detect concentration of Hg (II) in aqueous solutions. (Chen et al., 2007)
In 2010 QD-based biosensors where reported as possible stable and sensitive biosensor platforms for the detections of enzymatic activity. The optical biosensor was based on CdSe/ZnS QDs conjugated to AChE and enclosed in an silica matrix. The pores in the silica matrix allow for the transportation of the

analyte to the enzyme and at the same time protect the enzyme form the outer environment. (Buiculescu, Hatzimarinaki, & Chaniotakis, 2010)

The use of QD as semiconducting parts in sensors designs is heavily investigated in the last few years. The QD are especially suited for the detection of heavy metals in aqueous solutions. In contrast to organic molecular dyes the QD have a high pH stability and are resistant to chemical degradation. However in literature only a limited examples of the chemical sensing based on QDs is reported (Koneswaran & Narayanaswamy, 2009). Also sensors based on SPR phenomena are acknowledged monitoring tools for heavy metals. Such sensors use biological recognition elements (e.g. *metal binding proteins)* attached to the sensor surface which allows for the detection of biologically activice compounds(Rebe at al, 2012).

The optical nanosensors are also described as a possible option to monitor silver nanoparticles in the environments. Rebe at al, 2012 described a sensor using *hMT1A protein in combination with SPR-based sensor for the detection of AgNP.* This invention is a first step towards automated screening methods of silver nanoparticles in the environment *(*Rebe Raz, Leontaridou, Bremer, Peters, & Weigel, 2012).

Furthermore, the LSPR biosensors which are also extensively investigated, could be used for environmental purposes to detect viruses, bacteria or other microorganisms in water. Such sensor also use functionalized NPs with antibodies that are sensitive to the microbial toxins (Riu et al., 2006b).

7.2.3 Electrochemical

This section will address some of the electrochemical nanosensor developments which can be applied in to environmental analysis applications.

Traverse et al reported in 2001 on sensors for measuring CO concentration based on TiO_2- thick-film sensors. Since then the TiO_2-based sensors are considered for application in innovative atmospheric pollutant monitoring (Traversa et al., 2001). This example demonstrates that the semiconducting properties of metal oxides are useful for gas sensing application. Next to metal oxides, CNT are the main topic of scientific endeavors: *'One of the most studied materials in relation to electrochemical sensors for environmental monitoring are CNTs. Due to their electronics properties CNT change their conductance capacity upon exposure to different gases like O_2,NO_2, and NH_3. Besides CNT other nanowires and metal oxides are well suited for monitoring gases. For example, the use SnO_2 nanoparticles to monitor air quality is widely reported'* (Goldoni, Larciprete, Petaccia, & Lizzit, 2003).

In 2008 Penza et al demonstrated that the selectivity of CNT could be increased towards specific gases by functionalizing the surface of the tubes with metallic clusters of nanomaterials The CNT can also be coated with polyethylene imine (PEI) to increase selectivity towards NO_2, and with nafion to increase sensitivity towards NH_3. These are examples of how CNT can be functionalized to detect different gases. Further reports have been found on CNT for the detection of He, N_2, H2,O_2 and NH_3. All the examples use the changes in electrical conductivity upon the exposure of gases as the measurement technique. (Penza et al., 2008). The procedure for functionalizing CNT is to absorb a polymer on the surface of a CNT, this is non-covalent bonding as the conductivity of the CNT should not be affected. Different polymers that interact with specific analytes can be developed. The functionalization of the CNT is a hot topic in relation to gas sensing applications. Next to polymers, also enzymes, DNA, and proteins have been widely used for monitoring environmentally important substrates. Another material used gas sensing devices is ZnO nanowire based sensors. 'ZnO is one of the most promising and useful materials for gas sensors, especially for H2 sensing' (Lupan et al., 2010). The following quote summarizes the importance of nanomaterials for electrochemical sensing applications: *'As can be seen, most recent advances in electrochemical biosensors have been based on nanotechnology. The huge interest in nanomaterials is driven by their many desirable properties. In particular, the ability to tailor the size and the structure, and hence the properties, of nanomaterials offers excellent prospects for designing novel sensing systems and enhancing the performance of bioanalytical assay'*. (Farré, Kantiani, Pérez, & Barceló, 2009).

7.2.4 Challenges

Form the description above we see that sensor could have a significant impact on environmental monitoring application. However, as high expectations are present only little or no working applications are yet in place. Furthermore it seems like there is no specific application recognized as most promising, this in contrast to the food packaging application. What is interesting from our analysis is that the optical sensors seem to be particularly suited for the analysis of small metal concentration in plants or the environment and are also better suited for studying processes at the cellular and intracellular level of plants. The electrochemical sensors in turn are better suited for the detection of gases. The technical challenges in relation to optical and electrochemical sensors are already discussed on the development paths. Challenges related to this specific application area are:

- The development of self-powered sensors or very low power operating sensors. As it is necessary to deploy the sensors at distant location it is not feasible to change their batteries on a regular basis. Hence researchers are working on low power sensors. Expectations are high for piezoelectric sensor which could harvest the mechanical/vibrational energy form the environments and convert it into electrical energy which should be enough to power a sensor of nano scale (Z. L. Wang, 2009b).

- The next challenge is to make wireless sensors network so that the autonomous sensor can communicate with each other. This challenge is also closely related to the powering issue as wireless technologies need more power to send radio waves containing information.

- This touches upon the sampling issues which occur due the fact that nano sensor are inherently small and thus measures only a fraction of the environment. In order to overcome this swarms of sensor could be developed which are capable of communicating with each other.

- Next to these issues the researchers face technological challenges related to increased sensitivity, selectivity, multiplexing, immobilization of receptor elements on the transducer element.

7.3 Medical Applications

7.3.1 Intro

Vo-Dinh, a lead researcher on optical nanosensors, stated that: 'Nanosensors could provide the tools to investigate important biological processes at the cellular level in vivo. Not only can antibodies be developed against specific epitopes, but also an array of antibodies can be established, so as to investigate the overall structural architecture of a given protein. Finally, the most significant advantage of the nanosensors for cell monitoring is the minimal invasiveness of the technique'(Vo-Dinh, 2002). These new advantages could significantly impact the healthcare industry. A current trend in clinical medicine is the development toward Lab on Chip(LOC) systems which allow for analytical measurements on single chips, without the need of expensive lab equipment. The development of the LOCs is seen as an important driver of nanosensor development. Also within the biotechnological and biomedical industries a need exists for cellular-level and massive- throughput analytical systems with sensing capabilities. The LOC devices are said to be able to fulfill the needs of the emerging point of care market. Such LOC devices are expected to be used as single blood test to diagnose for a lot of diseases. An interesting point relating to the development of such chips is the integration with micro fluidic technologies. The LOC seems to be an platform technology where developments from the sensor technologies and microfluidics come together (W. G. Lee, Kim, Chung, Demirci, & Khademhosseini, 2010).

Another big promise of nanosensors is the application for early disease diagnostics. Sensor are so small they can detect diseases, or indicators of diseases(biomarkers) in a very early stadium, before more general symptoms become visible. This is especially relevant for the detection of cancer cells. Also other diseases could be detected in an early stage, for example the level of NO in cells could be used diagnostically for the determination Dementia, Parkinson's and Huntington's diseases. Next to diseases inside humans, nanosensor could be used for improved pathogen detection like SARS, mad-cow disease and the avian flu.

Sensors can also play an important role in drug delivery systems were they are used to sense a particular cell, e.g. cancer cell, which allows for very precise detection of tumors. Such a sensor could contain a medicine, which then is released at received signal. Such development would greatly benefit healthcare as such sensor allow for precise and controlled targeting of diseased cells. (Staples, Daniel, Cima, & Langer, 2006)

The development for diagnostics application looks promising. The most envisioned applications are biomarker discovery, cancer diagnosis, and detection of infectious microorganisms. Some expectations: *'Within the next decade, measurement devices based on nanotechnology, which can make thousands of measurements very rapidly and very inexpensively, will become available. Future trends in diagnostics will continue in miniaturization of biochip technology to the nanoscale range. The most common clinical diagnostic application will be blood protein analysis. Blood in systemic circulation reflects the state of health or disease of most organs. Therefore, detection of blood molecular fingerprints will provide a sensitive assessment of health and disease'*. And '*In the near future, the use of nanodiagnostics could* *reduce waiting time for test results. For example, patients with sexually transmitted diseases could provide urine samples when they first arrive at the outpatient clinic or physician practice; the results could then be ready by the time they see the physician. Patients could then be given the prescription immediately, reducing the length of time that the patient has to wait for results, thus decreasing patient anxiety, improving compliance, and making the whole process less costly'*(Jain, 2007).

The improvements in sensing and diagnostic devices opens up the possibility for personalized medicine where people can monitor their own health parameters without the help of trained professionals. This development is often associated with the point of care (POC) technologies. Today the POC devices are limited to pregnancy testing and glucose monitoring. however 'this technology has the potential to change the practice of medicine by providing society with a new medical infrastructure: one that allows individuals to literally take health care into their own hands' (Gaster, Hall, & Wang, 2011). Another tremendous potential of nanosensor development is to diagnose infectious diseases in developing countries. The lab on chip devices could be used as disposable, inexpensive, portable, and easy-to-use detection devices for of infectious diseases.

Today 80-90 % of the biosensor market consist of glucose sensing devices for diabetes patients. Most of these sensors consist of electrochemical biosensors containing enzyme electrodes. However, as Development continue it is expected that more sensor applications will reach the healthcare marker. Cancer diagnostics is one of the most heavily funded research areas related to nanosensor development. In this field breath analyzers have been developed which can detect VOC in the breath of patients which can be used as indicators for cancers states of lung, breast, colorectal, and prostate cancers. 'The analysis of volatile organic compounds (VOCs) that are linked to cancer is a new frontier in medical diagnostics because it is non-invasive and potentially inexpensive. The principle behind this approach is based on cell biology. In particular tumor growth is accompanied by gene and/or protein changes that may lead to peroxidation of the cell membrane species and, hence, to the emission of VOCs' (Peng et al., 2010). After cancer research the most widely studied disease which could be diagnosed by nanosensor is Alzheimer disease. 'The search for viable biomarkers for AD and how to detect these, non-invasively, is a shared goal among many researchers' (Vestergaard, Kerman, & Tamiya, 2006)

Within the EU framework program 50 projects were found related to nanosensor development for medical applications, see appendix C. This is significantly higher than for the other application areas. What is most notable is that the majority of the projects was dedicated to cancer research. The goal of most of those projects is to develop methods for the early diagnostics of cancerous cells. Usually the projects aim for the detection of specific proteins or biomarkers which are responsible for diseases. Sensors are developed for in vivo applications and in vitro. For example breath analyzers are being developed which can indicate of somebody has lung cancer. Many other projects relate to the point of care developments and have a goal to integrate sensor devices on chips. While scanning the project we identified several technological topics on which the researchers are working on: Non-invasiveness of the nanosensors, label free detection methods, the functionalization of nanomaterials (especially CNT) and on multiplexing.

7.3.2 Optical

This section will address some of the optical nanosensor developments which can be applied in to medical sector.

The development within the field of optical nanosensors has the potential to address many challenges in relation to the Alzheimer disease (AD). A shared goal among many researchers is to identify biomarkers associated with AD. 'The most widely used optical sensor in the study of AD biomarkers is localized surface plasmon resonance (LSPR)' (Vestergaard et al., 2006).

'The development of an accurate diagnostic test for Alzheimer's disease is crucial and will help millions to obtain timely and appropriate treatment for their symptoms. With further improvements in both selectivity and sensitivity, the LSPR biosensor has the potential to become an accurate and economical alternative to traditional clinical assays'.(Haes, Hall, Chang, Klein, & Van Duyne, 2004)

The LSPR sensors have been used for the detection of disease biomarkers, and especially for the detection of amyloid beta diffusible ligands (ADDLs) which are associated with AD disease. Heas et al, one of the founder of the LSPR sensor technology, suggested tree applications of the LSPR sensor in AD: '1) Studying the oligomerization of the Aβ in ultra low concentrations, similar to concentrations of in vivo conditions, 2) Screening patients for AD, and 3) Studying the interactions between the pharmaceutics and their target molecules in drug discovery'.

In relation to cancer diagnostics the QD can play a significant role. QD based sensor are developed which are sensitive to cancerous cell, such devices can be inserted into the body and upon interaction with the cancer cell they change their fluorescence characteristics. Hence the cancer location can be identified more precisely (Johnson, Zhukovsky, Cass, & Nagy, 2008). QD can also play an important role in the detection of HIV. The use of a single QD-based nanosensor for multiplex detection of HIV at single-molecule level in a homogeneous format has been reported in 2010 by Zhang et al.

'This single-QD-based nanosensor takes advantage of a simple 'mix and detection' assay with extremely low sample consumption, high sensitivity, and short analysis time and has the potential to be applied for rapid point- of-care testing, gene expression studies, high-throughput screening, and clinical diagnostics' (C. Zhang & Hu, 2010).

The optical sensors can also play a role in the development for in vivo monitoring of glucose concentration of diabetes patients. A vision exists of *'a 'smart tattoo' composed of glucose-responsive, fluorescence-based nanosensors implanted into the skin but interrogated from out- side the body, thus making monitoring non-invasive'*. However, as there is a lack of information and research on nanomaterial toxicity, it is important to consider the potential health and safety issues of such a smart tattoo. In general, there exists a major need to for continued research into any potential health hazards of possible harmful effect of nanomaterials (Zhi, Saxl, & Birch, 2008).

In literature the most profound nanosensor for intracellular measurements is the SERS based immunosensor the SERS-based immuno-nanosensors have been developed that are capable of specifically detecting trace amounts of proteins/antigens in complex environments such as in vivo cells.(H. Li, Sun, & Cullum, 2006)

7.3.3 Electrochemical

Electrochemical based glucose sensors have the biggest impact in the healthcare sector until today. Ever since the initial concept of Clark and Lyons to use glucose enzyme electrodes (1962) an enormous effort has been directed toward the development of reliable devices for diabetes control. Now, since the emergence of CNT, new option for the development of better devices have become available. '*The CNT can be coupled to enzymes and act as an electrical connector between their redox center and the electrode surface such enzyme reconstitution on the end of CNT represents an extremely efficient approach for 'plugging' an electrode into glucose oxidase'.* This opens up the possibility to make better more selective and sensitive and smaller glucose sensors. Such smaller sensors could inserted in the body an continuously monitor the glucose concentrations.

A trend within clinical medicine is to move towards point of care devices. Electrochemical sensors can play a crucial role in that development. The development of electrochemical DNA microarrays for example can greatly contribute to such point of care devices. In recent years enormous progression is made no this topic, however a big challenge remains to multiplex the electro-chemical biosensors into useful sensor arrays. '*Typically, arrays of 30–100 sensors are needed for diagnostic purposes. For example, breast cancer screening requires the testing of 20–30 cancer susceptibility genes plus positive and negative control*'(Sadik et al., 2009).

The FET based sensor can also play a dominant role in the medical sector. They are expected to play an imported role in the development of label free biosensors, as well as multiplexing sensor platforms which could identify several clinically-important biomolecules (Kerman, Saito, Tamiya, Yamamura, & Takamura, 2008).

Another contribution to the medical field can be expected from nanopore based sensing. Nanopore based sensing is particularly suited for the analysis of DNA and thus can provide researchers with valuable information on for example genetic diseases. E.g. The detection of mismatched base pairs in DNA plays a crucial role in the diagnosis of genetic-related diseases and conditions, especially for early stage treatment. Such measurements could be performed in the future based on nanopore sensing.

Researchers are also working on the integration of such sensors with fluidic processes on sensor chips which will allow for portable devices capable of rapid, multiplexed DNA detection which is essential for point of care(POC) clinical diagnostics. *'Although EC biosensors have been widely developed for laboratory-based detection within the past several years, there are very few successful POC devices for clinical diagnostics that are currently commercialized, except for glucose meters.'* Sensitivity, specificity, repeatability and reliability are still challenges in nanopore sensing devices. The ability to produce repeatable and highly reliable measurements is one of the most important challenges facing electrochemical DNA sensors, especially for clinical diagnostics and commercial usage. '*If these challenges are overcome the electrochemical DNA sensors will become will become more prominent clinical diagnostic tools for detecting a broad spectrum of genetic-related diseases and conditions'*(F. Wei, Lillehoj, & Ho, 2010).

7.3.4 Challenges

This application area is very interesting as it is already further developed then the other application domains and the potential impact which nanosensors can have on the wellbeing of humans is enormous. Nonetheless still many challenges exists and almost no nanosensor products are applied in the real world. This is partly due technical limitations and party due to strict safety regulations. The following challenges are identified during this research effort and can be seen as agenda for nanosensor researchers in relation the medical applications.

- First of all, a great challenge lies in biomarker discovery. Biomarkers are substances which are indicators of certain diseases. Today only very little knowledge exists on such biomarkers. Thus in order to identify certain diseases in an early stage it is important to know in what kind of biomarker you are interested in. With the rise of new nanosensor tools this area of research is expected to book significant progress.

- Another challenge is to make the nanosensor in such a manner that they can be inserted into living cell without destroying the cellular structure. Many authors say that it is possible. However it is very essential that this can be done in a reliable robust manner. Not only in a laboratory setting but also in real applications. This touches upon the toxicity issues related to many nanomaterials. More researchers are needed to assess the toxicity effect and how these can be minimized or prevented.

- For the successful development of Lab on chip devices for point of care medicine challenges exist relating to the integration of sensor with micro fluidic devices.

-The usability of sensor devices still needs to be developed. Biomedical sensors should be easy to wear and to use.

- Also ethical issues should be addresses. The nanosensor could provide a wealth on sensitive information, (e.g. based on DNA analysis) on the patient health status. Question can be asked if this is desirable and who is allowed to view such information. This touches upon privacy and security issues. This point implies that the technological development of the sensor devices is not enough for a successful implementation of the technology in society.

8. Analysis Emerging Irreversibilities

8.1 Tracing Emerging Irreversibilities

Now, we have reconstructed the developments in the field in a historical narrative, the most important elements are known and the needs and opportunities for potential application areas are described. We will try to find the emerging irreversibilities within the reconstruction of the paths. This is done based on the indicators of emerging irreversibilities described in the theory and method sections. We have found 9 types of emerging irreversibilities, derived from the reconstructions. They are presented in table 6. The next part of this chapter discusses the irreversibilities in more detail and elaborates on how the indicators apply to the irreversibilities and how the irreversibilities enable/constrain actions of actors in the field. Sometimes it looks like the indicators are similar to the irreversibilities in the table, (e.g. indicator: *technological needs* and Irreversibility: *Technological needs of sensor devices*). However, the irreversibilities in the table are categories and are further specified in the description.

Table 6: Emerging irreversibilities

Emerging Irreversibilities \ Indicators	Breakthroughs	New topics	Societal needs	Technological needs	Standards platforms	new journals	Device in patent database	Funding by governments	Promising applications	New actors
1) The use of new nanomaterials in nanosensor research	X	X						X		X
2) The use of nanomaterial in a specific sensor designs /platforms	X	X		X	X		X	X		X
3) The emergence of prototypes		X		X	X		X	X		X
4) Emerging needs from application area's		X	X	X			X	X		
5) Recognition of promising applications within the domains		X					X		X	X
6) integration with existing technologies, systems , fabrication and manufacturing				X	X		X	X		
7) Technological needs of sensor devices		X	X	X	X		X	X		
8) The emergence of firms in the field of nanosensor							X			X
9)The funding of specific topics by governments			X					X		

1) The use of new nanomaterials in nanosensor research

The first irreversibility relates to the discovery and recognition of new nanomaterials, their novel properties and the recognition of their potential to be applied in sensor devices. Such discoveries are associated with a rise in promising expectation related to that specific material. This triggers other research group to start working with those materials as the materials are recognized as suitable and promising. Hence the path or possibilities of actors involved in nanosensor research becomes more specific as it is better understood which materials could be useful in the enhancement of sensor performance. We will try to support this claim with the following examples:

The first material with a huge impact on nanosensor R&D is CNT, invented in 1991. After this invention the research on the material has exploded and many sensing techniques and prototypes have been developed using the nanotubes as transducer material. Thus actors involved with nanosensor, especially electrochemical nanosensors, are undoubtedly affected by the presence of such a promising material. E.g. it is easier for them to work on CNT as research funds can be acquired more easily. In support if this claim remember the popularity of CNT in the scientific domain and especially in the governmental funded projects. A statement which support this claim is related to the positive characteristic of CNT in relation to other materials: '*One-dimensional nanosensors such as carbon nanotubes (CNT), semiconductor nanowires, and graphene nanoribbons can remedy many of the drawbacks of traditional semiconductor-based gas sensors. Within this class of materials, CNTs have a set of unique and outstanding properties that make them ideal candidates for nanosensors. Recently, it has been experimentally observed that nanotubes can present significant resistance changes upon exposure to a variety of gases* ' (Rocha et al., 2008)

Next to the nanotubes, nanowires based on metal oxides have entered to realm of nanosensor technologies. The metal oxides have promising semiconducting properties, large surface to volume ratio, redox properties of the oxide group and are sensitivity towards gases. In 2001 it was first demonstrated that ZnO nanowires could be used for gas sensing applications, Ever since then, the number of papers published on ZnO nanostructures increased rapidly. Remember the quotes from the Wang research group, at the Georgia tech university, in support of this claim: '*Research in one-dimensional nanostructures of ZnO was first inspired by the discovery of oxide NB by my group and the demonstration of UV lasers in aligned NW arrays in 2001. Ever since then, the number of papers published in ZnO nanostructures increases exponentially'* and also '*carbon nanotubes, silicon NWs and ZnO NWs/NBs are probably the most important 1D nanomaterials in today's research. From a recent report on the map of physics by Physics World, research in ZnO NWs is as important as quantum computing, dark matters, string theory, semiconductor thin films, photonic crystals and carbon nanotubes'* (Z. L. Wang, 2009a)

The emergence of QD is another irreversibility related to the optical path of nanosensor development. Due to its unique fluorescent properties it influenced the field of intracellular sensing. The QD sensor offers many advantages over use of fluorescent organic dyes, which was the classical method used before. Also the use of noble metals in combination with QD can be seen an irreversibility. Ever since the recognition that such a combination triggers FRET based phenomena (in the presence of a target analyte) it as recognized as an option for sensor devices. A quote in support of the claim that QD are replacing other materials for sensing applications: *'For traditional biological applications, QDs have already begun to replace traditional organic fluorophores to serve as simple fluorescent reporters in immunoassays, microarrays, fluorescent imaging applications, and other assay platforms'* (Yi Zhang & Wang, 2012).

The most recent discovered nanomaterial is graphene. The material was discovered in 2004 and awarded for the Noble price in 2010. Just as with CNT the material has many desirable properties which can be applied in nanosensor devices. Promising expectation on possible application of the material in devices have triggered a wave of new publications and research development on the new material.

All of the mentioned emerging materials are in literature coined as breakthroughs, or at least very important discoveries, as can be seen from the examples above. They triggered the emergence of new topics in the field of nanosensors. Moreover, research on the materials is funded by governments, especially research on CNT, but also graphene, nanowires, QD and gold nanoparticles are mentioned. Furthermore new actors (firms, researchers, producers, manufacturers of the materials) are entering the field (remember the actors mention in the network sections of the development paths) and by their presence and actions they shape the development of the field. Thus we can confirm that the emergence of the above mentioned materials are irreversibilities as several indicators apply to this irreversibility.

2) The use of nanomaterial in a specific sensor designs /platforms

A step further than just the recognition of promising new properties of nanomaterials, is the demonstration that the materials actually can be used in sensor devices. Such results show other scientific communities and also industry actors that it actually is possible to make sensor devices based on such materials. A very important event in respect to this topic is the demonstration that CNT can be used as semiconductors in FETs. This was demonstrated by the Cees Dekker group in Delft in 1998. After that discovery a rise in nanoFET research in sensor technologies has seen a steep rise in publications.
A similar dynamics could be identified after the demonstration that ZnO nanowires can be used for gas sensing applications by Kong et al, (2001). Since then many papers reported on the development of sensor platform based on a specific nanomaterial. E.g. CNT based FET sensing platform or ZnO based sensing platforms. Also nanotechnology based companies hold patents on sensing platforms based on a specific nanomaterial. E.g. Nantero.Inc Holds patents on horizontally and vertically orientated CNT based sensing platforms. The nanomaterials of the platform can then be functionalized in order to establish sensitivity towards desired analytes. The development and research of such platform is an emerging irreversibility as it a first step towards a kind of dominant design in the field of nanosensor technologies.

An irreversibility related to nanomaterials in optical sensor development is related to toxicity issues of nanomaterials, as many metal NP or quantum dots are toxic. Such materials should be embedded within a polymer matrix before inserted into a cell. This need has paved the way towards the development of non-invasive PEBBLE sensors. And thus made the development path more clear and diverted away from the old pad were invasive dyes were used for cellular analysis. A quote in support of this development show the advantages in relation to the widely used fluorescence dye based methods: *'An advantage of* *the Pebble sensor is that the matrix provides dual protection: protection of the dye from cellular components as well as protection of the cell from potentially toxic sensing dyes*' (Sumner, Aylott, Monson, & Kopelman, 2002).

De demonstration of nanomaterial use in a successful sensor device can be seen as a breakthrough development in the field of sensing technologies. The above mentioned examples of QD, CNT, ZNO support this claim. Together with the emergence of new devices based on these materials new technological needs and possible sensor platforms start to emerge. E.g. Nanomix. Inc and Nanosys. Inc patented on CNT based sensor platforms. This all implies that the demonstration of nanomaterial use in a successful sensor device is an emerging irreversibility as it clearly shaped the dynamics of the field.

3) The emergence of prototypes

In the development of nanosensor technologies the emergence of new prototypes are important milestones and can be seen as irreversibilities. A working prototype is a demonstration that a working principle is applied in an actual design and that the sensor was able to perform the desired task. This irreversibility is even stronger than the previous in showing other scientific communities and also industry actors that it actually is possible to make sensor devices based on such materials and working principles. Also after reports on the prototype an increase in literature on that type of sensor was signaled. Which is an indication that the recognition of the prototype made the development activities more defined for other actors in the field. The following prototypes emerged in the field:

-The nanobased FET sensors emerged at the beginning of the 21st century after pioneering work of Kong et al, (2001). Since then many other research groups, firms and institutes focus their attention on the FETbased sensors. Today the FET based sensors are the most widely applied design in nanosensor development.

- In 1998 the PEBBLE (Probes Encapsulated By Biologically Localised Embedding) concept was introduced by Kopelman and co-workers. They used optical nanosensors in order to make intracellular measurements. This invention made it possible to insert small nanosensors into cells without destroying or affecting the cell processes.

-The LSPR based sensors was first developed by the McFarland and Van Duyne research group. In 2003 the reported that Real-time molecular sensing with a single particle was possible with a LSPR sensor.

-the SERS based sensor is the most prevailing sensor technique in the field of optical nanosensors. Tuan Vo-Dihn is the main researcher who greatly contributed to the development of the SERS technology for sensor design.

All these prototypes shaped the development of the field. They can be seen as breakthrough achievements and received considerable attention in the scientific field. As a result the prototypes became established topic within the field of nanosensors technologies.

4) Emerging needs from application areas

As needs become more visible and better articulated they can influence the development towards their direction. Hence the needs circulating in the application domains can be used as guidelines for researchers and industry actors for the decision they make regarding R&D activities. The examples below support this claim by linking the needs from the application areas to the nanotechnology based solution in relation to sensors, and showing how this affects sensor developments.

In the environmental analysis domain many needs are voiced for sensor capable of measuring the concentration of toxic gases, CFK's, bacteria, pathogens, gas leakages, metal concentrations and nanoparticles in the environment. Many of these needs are driven by concerns about climate change and safety issues. In order to fulfill those needs the nanosensor have to be capable of performing specific technological tasks. Thus what we see here is that the needs drive the development towards specific technological capabilities of the sensors. In the case for environmental monitoring this implies wireless sensor network, as sensor need to communicate with each other as they are often situated in remote areas. This touches upon the need to integrate the sensor with RFID technologies. Furthermore such sensor should be almost powerless as it is not feasible to change batteries at distant locations. Also swarms of sensors are needed in order to overcome the sampling issues which emerged to the fact that nanosensor only measure a small part of an entire environment. Such needs steer actors in the field of nanosensors to collaborate with experts in wireless network technologies, to work on self-powering devices etc. The need for self-powering devices is a stimulus to develop piezoelectric sensors which can transfer mechanical energy into electricity. An example of this development: *'The first application of nanopiezotronics is the piezoelectric nanogenerator based on ZnO NWs, which demonstrates a unique approach of converting nano- scale mechanical energy into electric energy and harvesting energy from the environment for self-powered nanosystems'* (Lao et al., 2007). Furthermore the need to monitor the ever growing amount of nanoparticles in the environment stimulates research to develop sensing devices capable of detecting the nanoparticles (Remember the optical sensors development for the measurement of silver NP as an example). The above illustrates how the articulation of needs from the application domain can influence the R&D on sensor technologies.

In the food domain the same pattern can be found. Many needs for food monitoring applications are similar to the environmental monitoring needs. The sampling issue is also relevant for food quality assessment applications, the monitoring of feedstock and growth processes. In the food industry a need is present to detects specific analytes e.g. pesticides, microorganism, bacteria etc. Such needs steer the R&D of sensor technologies to invent sensors and analytes which are specific towards the desired bacteria or pesticide. E.g. the detection of organophosphorus pesticides is a highly desired need. This can be seen as en irreversibility as it stimulates researchers to work on OP detection methods. This is also found in sensor literature as many researchers report in OP detection.

For medical applications the following needs and trends are identified which influence the development of the field: First of all there exist a growing trend towards personalized, point of care medicine. This is not a static event, like the discovery of a material, but rather a process. Nonetheless it can be seen as an emerging irreversibility as it influences the activities of involved actors. This is illustrated with the following example: The need for small point of care devices capable of detection and diagnosing diseases have driven sensor development towards smaller, more accurate, sensitive and selective devices. As such sensor should be capable of detecting disease biomarker, research on biomarkers classification is needed. Today very little is known in which biomarkers are responsible for which diseases. Thus the needs for the healthcare industry steers research activities toward biomarker detection methods and towards the integration with small portable devices. Furthermore the noninvasive, non-toxic and label free sensing applications are also highly desirable needs. This stimulated the development toward the development of PEBBLE sensors, which consist of small capsules that can penetrate to cell membranes, they are embedded in a polymer matrix to prevent toxic effects, and eliminate the need for labeling as they directly can measure the desired substance. Thus the needs for non-toxic, label-free, non-invasive sensors together with the trend towards personalized medicine and point of care devices are irreversibilities. Overall the articulated needs in the application areas are on a higher level(society/technological field) in comparison to the research result related to nanomaterials. But as shown above they do influence to development of sensor technologies towards a more specific direction.

5) Recognition of promising applications within the domains

Next to the needs articulated in the application domains also promising applications have been identified. The identification, and recognition by a variety of actors, is also an emerging irreversibility as it gives guidelines for the development of the technology. The recognition of such promising applications can almost be seen as roadmaps for the development. As multiple actors recognize something as a possible future it can help them identify the challenges which are needed to be overcome, or to align actors to stimulate the development toward the desired direction. An import effect which such a recognition of promising options by a majority of the actors has is that the uncertainty about many unknowns is reduced. Hence, as uncertainty is reduced it is easier for actors to decide their actions. The following examples illustrate this.

In the environmental monitoring domain such recognized applications consist of swarms of nanosensors, were the nanosensors are autonomous, self-powered, and integrated with a wireless network. This implies that researchers from these different disciplines, (wireless technology, electronics etc) should work together to realize this application. A statement which illustrates this: *'Wireless sensor networks and biosensors are both subjects of intense current research. Employed together they permit uninterrupted physiological monitoring across broad geography in daily routine as well as emergency medical situations'* (Rodriguez-Mozaz et al., 2005). Furthermore gas sensor for gas leakages and Lab on a chip devices are articulated as promising applications. These are still bread applications, nonetheless they can be a guidance for the actions of actors involved in nanosensor development.

In the food sector applications for food packaging are voiced as most promising, and are already being developed by large food companies. (E.g. remember CRAFT described earlier). Especially the development of sensor strip is seen as a realistic application of nanosensor technologies. Such sensors are attached to the packaging of food and are sensitive the various gases, VOC, and other indicators of undesirable substances. Next to the sensor strip the concept of electric nose and tongue is a reoccurring element in the discussion on sensor for food applications. Such electronic nose and tongue should mimic the actual nose and tongue. This implies that they can differentiate between different types of analytes. Thus multiplexed sensor arrays are seen as promising application in the food sector.

In the Medical application area, the promising application are: glucose nanosensors, drug delivery system, Early disease detection by analyzing droplet of blood, salvia or urine, lab on chip devices and breath analyzers. All those applications are seen as very promising by a variety of actors and thus make it easier for researchers and industry actors to invest money and effort on those options as the uncertainty is reduced by those promising expectations and recognition of a variety of experts in the field.

6) Integration with existing technologies, systems, fabrication and manufacturing issues

Developments in the field of nanosensors have been fruitful: a lot of promising materials have been discovered, and their potential use in sensor device has been demonstrated and a lot of prototypes have been reported (in laboratory setting). The next step in the development of nanosensor devices is the integration of sensor with sensor systems and other technologies, the mass production and fabrication of materials and the integration of the materials into sensors. Also here variation and selection of different options occurs and thus emerging irreversibilities will occur related to those topics.

One trend related to the integration with other technologies is the combination of nanosensor with microfluidic technologies, usually on chips. This trend is an irreversibility as is stimulates actors form both disciplines to cooperate and to look for solution and applications based on sensing technologies in combination with microfluidic devices. The development of Lab on chip devices, described earlier, is an example of this claim.

Another irreversibility is the integration or compatibility with CMOS (Complementary metal–oxide–semiconductor) technology. Sensor which are compatible with CMOS technology, which is the standard in the microelectronic industry, can be much easier implement in existing systems and practical applications. In support of this claim we can say that many patents mention compatibility with CMOS technology. Also several EU projects, e.g. NANORF and MINAml work on compatibility of nanomaterials, especially CNT with CMOS technology. The following quote shows how nanosensor co-develops and is supported by compatible technologies: *'The emergence of high-density sensing and imaging arrays based on imaging fibres has been supported by the development of CCD and CMOS array detectors, high capacity digital storage media, and high speed computers for data processing' (Deiss et al, 2009).*

Yet another irreversibility is related to the growth methods of nanomaterials. An important need for successful development and commercialization of nanosensors is to effectively grow nanowires and other nanostructures that have consistent characteristics. In literature several techniques are describes: E.g. *Thermal evaporation, sol-gel deposition, electro-deposition, dip-pen lithography.* However the most promising and widely applied is the Chemical Vapor Deposition (CVD). The CVD technique can be seen as en irreversibility as it solves many of the articulated needs related to the production of nanowires. And as more actors use CVD is start to become a standard method applied in the field for the growth of nanomaterials. The following quote support the progress towards CVD. *'The hurdles that must be overcome to allow nanotubes to be used for the aforementioned applications include growing longer nanotubes, controlling the chirality, and properly dispersing and bonding nanotubes to polymers. These are the main roadblocks that are being attacked to bring the great properties of nanotubes to macro-scale applications. Recent advances in growing nanotubes are encouraging. Growing mm long arrays of SWNT using the simple CVD process is reported'* (Kang et al., 2006).

7) Technological needs of nanosensor devices

Throughout all the studied material a lot of technological needs, shared by many researchers, of the nanosensor devices have been identified:

- *Functionalization of the transducer material*: Most of the new nanomaterial have a very high sensitivity towards small analytes, however they often lack selectivity towards the desired analytes. A common need for the nanosensor development is to functionalize the nanomaterials with elements which only respond or react to the desires analyte. It is obvious that this challenge needs to be overcome for the technology to be developed further (as otherwise the sensors would just randomly sense targets).

- *Immobilization of recognition element with transducer elements.* One of the key challenges in nanosensor development is to locate the recognition element of the sensor on, or nearby, the transducer element. This should be done in a robust, reliable an repeatable manner.

-*Multiplexing*. Once it is possible, due to functionalized material, to detect the desired analyte it will become desirable to detect multiple analytes in one sensor device. This is already an highly desirable goal for many nanosensor researchers. The need for multiplexing is quite obvious *(i.e. the greater the number of disease markers which can be probed, the more information that can be obtained* (Erickson, Mandal, Yang, & Cordovez, 2008))

- *Label free detection methods*. Label free detectoion methods elminate many steps in the sensing process which greatly reduced the complexity of the sensing process. Nano technology based sensor provide the opportunites for direct sensing, hence many reserachers work on the development on label free sensor techniques.

- *Reversibility of the sensors.* After a receptor interacts with the molecules it is desirable to somehow reset the sensor so that it can be reused. A significant challenge is to design such sensors which can self-clean themselves and thus be reused for new measurement. Nanotechnology might contribute to this goal for example by the discovery of self-correcting materials *(NNI, 2009).*

All the above technological needs represent the topics researchers are working on and thus steer the development towards that direction as they determine the working heuristics in the field of nanosensor researchers.

8) The emergence of firms in the field of nanosensors

Another irreversibility is the presence of new players in the field. They are working on prototype developments and actually have product on the market. Hence, they are creating more and better defined socio-technological connections as they have contacts, collaborations, invested money and an infrastructure which makes it easier for the developments to move in one direction on not in the other. The most prevailing companies in the patent database are Nanomix, Nanosys and Nantero. These are all companies specialized in nano technological development. Next to those companies also large companies have recognized the potential of nanosensor technologies and have patented on nanosensor technologies. These companies include multinationals like IBM, Samsung, HP. Once those large companies start to integrate nanosensor devices into their products this could greatly impact the development of nanosensor as those large companies have the power to enforce new standards which greatly determines the paths a technology follows.

9) The funding of specific topics by governments

When looking at the funding of governmental projects also irreversibilities can be derived. As the topics which are funded the most have to be promising or important in some way, (otherwise the government would not fund the project). And it is easier for researchers to work on such topics as they can acquire funding more easily. Based on the analysis of the funded projects we can state that research on the material CNT and nanosensor in relation to cancer research receive the most funding. This is an emerging irreversibility as it guides researchers to work on those topics. This also demonstrates how societal needs (Cancer research) drive the development of nanosensors.
Another fining which shows that the field is yet in an early phase is that many projects aim for more fundamental understanding of nanomaterials and surface chemistry and are not very specific in relation to nanosensor devices.

8.2 Relation and strength of the Emerging Irreversibilities

This section discusses how the emerging irreversibilities are manifested in the three communities and the application areas. Naturally this information is incorporated in the reconstruction of the field, however this section tries to highlight the relation between the irreversibilities in the different communities. These irreversibilities can for example reinforce each other or be inconsistent e.g. if the government is funding different topic then the firms and researchers expect to be most promising, it could be an indication of inefficient policy and question could be asked if the government should change its funding policy. When comparing the irreversibilities within the three communities and application domains insight can be gained on the emerging technology dynamics, as it becomes a bit clearer were selection of promising options occur and how the irreversibilities shape the development of the field. Other dynamics have also become visible, for example we see that new research result trigger attention of other actors and give rise to new opportunities and applications, which in turn leads to more research groups/firms working on the development of the technology. At the same time concerns are raised at societal level on toxicity, privacy, safety issues etc. Furthermore the strength of the irreversibilities can be determined. We argue that if the same irreversibility can be found in more communities it is stronger as it influences more actors in the field. In this study this would for example mean a growing interest towards a certain topic in the scientific communities, funding of the topic in governmental projects and the presence in patents as a sign of industry involvement. Table 7 provides an overview of the irreversibilities with the division of communities, so the location and relation of the irreversibilities can quickly be identified.

Table 7: Emerging irreversibilities within the three communities

Emerging irreversibilities	Academia	Industry	Governments
1)Materials	CNT, ZnO, Nanowires, Graphene, GoldNP, QD	Mostly CNT	Mostly CNT, few reports and graphene, nanowires and QD
2)Materials in devices	Variety of materials studied	Mostly CNT	Mostly CNT
3)Prototypes	FETs, Nanopore sensing, Optical fiber, LSPR, SERS, PEBBLE, PE-Fet etc.	CNT FETs Nanowire FETSs SERS nanosensors	FETS and SERS based sensors
4) Needs application areas	Needs in all areas voiced (discussed in previous section)	Practically only medical needs discussed, (but overall needs related to application areas are absent)	Needs from Medical applications dominate. Primarily cancer research. Few needs for food en environment mentioned
5)Recognition promising options	electronic nose, tongue, sensor strip. swarms of autonomous wireless sensor networks, etc. (variety of options discussed)	-glucose sensors -point of care devices -integration RFID (few options discussed)	No specific options are discussed.
6) Integration with other technologies	Microfluidics, RFID, WSN, CMOS, fabrication and production: CVD	CMOS technology CVD RFID	Microfluidics CVD RFID and WSN(wireless sensor networks)
7) Technological needs specific to new sensor deigns	-Multiplexing -functionalization -label free -Immobilization -reversibility	-Multiplexing -functionalization -Immobilization	-Multiplexing -functionalization -label free -Immobilization
8) Emergence of firms in the field of nanosensor technologies	(many university spin-offs)	-Nanomix, Nanosys. (new nanotech firms) -IBM, HP, Samsung (large existing firms)	-
9) Funding of specific topics by governments	-	-	CNT, Cancer research, fundamental knowledge on nanomaterials.

Now, we argue that when irreversibilities occur in more communities they will have a bigger influence on the development of the field, as that affect more actors. From the above we can derive that the emergence of the material CNT is the strongest irreversibility. In addition the FET prototype based on CNT seems to be the strongest irreversibility in respect to the emerged prototypes. In respect to the needs we can say that the needs voiced in the medical sectors are present in all three communities, were the needs for environmental and food applications are less profound. Especially needs in relation to early detection methods for cancers are prevailing and can be seen as the strongest irreversibility. In relation to the recognition of promising application no strongest irreversibility can be defined as almost all the expectation are voiced in the academic community. When looking at the integration with other technologies we see similar development in all three communities. This implies that this irreversibility is quite strong. The same hold for the technological needs of the nanosensors. Especially multiplexing, immobilizations and functionalization are irreversibilities which apply to all tree communities. The emergence of firms and topic funded by government cannot be compared between the tree communities as the irreversibilities inherently relate only to one community. What is interesting to say is that the topic funded by the governments are les diverse then the topic and expectation voiced in the scientific community.

The overall tendency or dynamics found is that in academia the diversity of expectation, promising option, materials and prototypes is much higher than in the governmental and industry database. This could be an indication of selection process dynamics. That firms are selecting and patenting only on the most promising options which they think have the potential to become real products. The results also show that the indicators *devises in patent database* and *topic funded by government* almost always applied for the recognition and determination if something is an irreversibility. This might be an indication that the involvement of governments and industry is a prerequisite to become a strong irreversibility. We will discuss this more extensively in the conclusion and discussion. From all the technological options it seems that selection occurred towards the CNT FETS and SERS sensor devices.

9. Conclusion & Discussion

In this thesis we proposed a new route to analyze the emergence of new technologies. More precisely, we developed a method to trace emerging irreversibilities and reconstruct development paths which are formed already in the early phases of technological development. Such an approach can help actors to deal with the many uncertainties present during the emerging processes of technologies. The concept of emerging irreversibilities helped us to identify first signs of new structures that enable and constrain action of the actors which define the developments in the future. To refresh our memory, the main question to be addressed in this thesis was:

How have emerging irreversibilities shaped the field of nanosensor technologies in the period 2002-2012 in the scientific research communities, governmental funding programs and firm activities, how do they relate and which implication does this have for the further development of nanosensor technologies?

In order to answer this question the following step were conducted: first of all we tried to include all relevant actors (scientists, policy makers and firms) which can influence the development of the technology. These three communities served as the starting point of this research effort. A database was reconstructed containing statements, voiced by the relevant actors. The statements were found in the most cited literature of the past decade (see methods section for complete explanation of database). The statements contain information on a variety of topic ranging from agendas, expectations, visions to proof of concepts. The statements were classified based on the division proposed by Robinson (2007). Such a division provides us with the information on the different types of statements circulating within a community. The next step involved the interpretation of the data in such a way that a reconstruction of the field of nanosensor became feasible. In order to do so we created a mind map, containing the relevant subject within the field of nanosensor to which most of the statements could relate. This mind map is based on an underlying logic present in the heuristic of nanosensor researchers. Hence we mapped all the statements in relation to the categories in the subject tree en traced the development over time. In this way we could systematically work through the statement database and reconstruct the field. Two dominant paths were identified: optical and electrochemical nanosensor development. The developments are qualitatively described with a focus on agendas, expectations and networks, as those are the building blocks of development paths. Furthermore the development of nanosensor technologies in relation to the application domains is also analyzed and discussed. Based on the reconstruction of the field in three communities and application domains the irreversibilities could be traced, and the answer to the RQ can be provided. In order to answer the RQ we should present the list of irreversibilities and explain how they shaped to development paths. Hence explain how they relate and which implication this all could have for the development of nanosensor technologies. As this information already has been presented in the previous chapter we will try to be as concise as possible here.

Now, there is a promising field of nanosensor technologies. This field started to emerge at the beginning of the 21stcentury. Due to development in nanoscience and technology new material became available and with their new properties they were expected to enhance sensor performance. The emergence of the new materials is seen as the first emerging irreversibility, as it raised a lot of attention of other researcher which started to work with the new material. The most promising material is CNT for the electrochemical sensors and QD for the optical sensors. The next irreversibility which shaped the dynamics of the field is the demonstration that the new nanomaterials actually could be used in the sensor design. Such results show other scientific communities and also industry actors that it actually is possible to make sensor devices based on such materials. Related to the previous irreversibility is the emergence of new prototypes. A working prototype is a demonstration that a working principle is applied in an actual design and that the sensor was able to perform the desired task. This is an indication that the recognition of the prototype made the development activities more defined for other actors in the field. In the electrochemical sensor pathway the CNT FET and the ZnO FET based sensors are the most prevailing prototypes and thus the strongest irreversibilities. In relation to the optical sensors the PEBBLE, LSPR and SERS based prototypes emerged, where the SERS became the most widely adapted technique for sensor design. While the fundamental knowledge on sensor design increased, expectations in relation to applications started to be voiced. While studying the development in relation the applications several needs from those application domains were identified. The recognition of shared needs are also an emerging irreversibility as they can influence the research field in a way that actors work on topic related the recognized needs. A step further is the recognition of promising options within those application domains. This is an irreversibility as it guides researchers, and other actors, towards the development of that device. Such a recognition reduces uncertainty and stimulates actors to work on that topic, as it already is accepted as promising. Examples are the recognition of sensor strips in food packaging, glucose sensors and other point of care devices.

Now, it seems like the field of nanosensor is on a sound footing, many promising options have been identified, expectation on applications are raised and many successful research result are reported. The next step in the development of nanosensor devices is the integration of sensor with sensor systems and other technologies, the mass production and fabrication of materials and the integration of the materials into sensors. Hence, emerging irreversibilities occur related to those topics. We see a development towards the integration with microfluidics, RFID and wireless sensor technology and talks about integration with CMOS technology. Related to fabrication method the CVD methods seems to becoming the dominant technology for the production of nanomaterial. However the CVD is only suited for the creation of CNT, graphene and nanowires and not QDs and the like. For the creation of QD still no mass production technology is reported. This is an indication that more rigidities start to form in the electrochemical path. The electrochemical paths seems to be less fluid then the optical paths and thus is further in its development compared to the optical sensors. This is also reflected in the patent database where the majority of reported devices relate to CNT FETs. This touches upon the indicator related to devices reported in the patent database. We can see that the CNT FETs are most reported in the database. In relation to the optical sensor the SERS based devices are most represented. This implies that the CNT FETs and SERS sensor are now the two most applied prototypes within the development of nanosensor technologies.

Another irreversibility relates to the technological needs of the nanosensors. These technological needs in relation to the sensors are: Multiplexing, label-free detection, functionalization of nanomaterials, reversibility, and the immobilization nanomaterial on a defined area. The needs can be seen as emerging irreversibilities as they emerged as the result of the development of nanomaterials in sensor design. They represent the topics researchers are working on and thus steer the development towards that direction. They determine the working heuristic of nanosensor researchers.

The last irreversibility relates to the influence of governmental funding on the development of nanosensors. We argue that the topics which are most funded by the governments are irreversibilities, as it becomes easier for actors to work on such topic. These topics are mostly related to CNT research and the early diagnostics of cancers.

Now, the above tells the story of nanosensor development with a focus on how the irreversibilities emerged and shaped the development of the field. Because we investigated three communities also information is gained on how they relate and influence each other. It is argued that when an irreversibility is present at multiple levels and affects multiple communities it is stronger as it has an influence on a bigger variety of actors. The relation of the irreversibilities can be found in the previous chapter. Another interesting finding form this research is that the diversity of topics, technologies, expectations etc. is much higher in the scientific community in relation to the governmental and industry database. This is an illustration of the variation and selection process. Where academia produce a wide variety of promising option, from these option firms and policy makers select only the most promising, and thus reduce the technological variety as the field continues to grow. While doing so they influence the development in a specific direction as it become easier for other actors to work on that topics. In the case of nanosensor technologies we can say that the CNT FET based technology and the SERS based optical sensors are stepping to the foreground as the future technology in sensor design.

Based on our research practical implication for further development can be suggested. We identified the potential application areas and how sensor development can affect them. The main challenges for further development are presented and we informed the reader on the dynamics present in the field of nanosensor technologies. We identified the development paths present and by extrapolating them we could predict future development in the field of nanosensors. However that might be something for further research. A valuable contribution of this thesis is that it increases the understanding of the field of nanosensor technologies. Actors involved in the development of nanosensor research can have a better understanding of the history and the dynamics present in the field. Hence researchers, firms or policy makers can use this information for their agenda setting processes. Furthermore, form the reconstruction of the field the most relevant actors and what they are working on are identified. Such information can be used to align actors and increase cooperation on similar or different topics. Overall many interesting findings on nanosensor development are touched upon in this research. Which can inform actors within the field of nanosensor and allow them to look at the future in a more informed way.

This research has also theoretical implications which relate to the impact of this research on theories related to emerging technologies. The most valuable contribution of this research is that it presents a new method for mapping emerging irreversibilities in new fields of S&T. The methods builds on existing tools or methods, i.e. the three level framework (Van Lente & Merkerk, 2005) as well as on the statement analysis method of Robinson(2007) for studying emerging irreversibilities. The new part of this method is the use of a subject tree with the intention to systematically reconstruct the development of the field. This, in combination with the three communities (Industry, Science, Government) make it an unique tool to trace the irreversibilities and to analyze their relation between the communities. By doing this, the tool (or method) allows for the assessment of the strength of the irreversibilities, as it can be determined to which actors and on what level the irreversibilities occurs. The larger the variety of actors it influences the stronger the irreversibility is. In this research this is empirically demonstrated, and the CNT irreversibility is a good example of a this.

Another contribution can be made to the rather limited literature on indicators of emerging irreversibilities. In this thesis we made a compilation of indicators, based on earlier work of Van Lente(2005), Van Merkerk(2007) and Robinson(2006), and used the indicators as guidance for the identification of emerging irreversibilities. Now we can reflect on the use of those indicators, and say which were the most valuable, if new indicators emerged or if some were not used at all.

When looking at table 6, it can be concluded that the emergence of new journals did not help us in this research to find emerging irreversibilities. This is surprising as in the paper of van Merkerk and van Lente the emergence of new journals is used as an example of an emerging irreversibility. The reason for difference can be found in two explanations. 1) The field is in such an early stage that no journals on nanosensor have yet emerged. However, we did encounter some special issues on nanosensor in more general nanotechnology journals. 2) With this method of statement analysis we are more focused on statements containing agendas and expectation and not so much if new journals emerge. Thus the only way we could find out if new journals emerged is if actors mention the new journals in their statement. The point here is that the emergence of new journals is on a higher level, which could be identified with a different perspective. Hence we argue that even though we did not use it, it still could be an important indicator.

Now which indicators did help us the most to find the irreversibilities? The answer to this question is that one indicator was usually not enough to determine if something is an irreversibility. A combination of indicators was needed to convince us that something is an irreversibility. We can illustrate this with the following: A statement dealing with a breakthrough discovery is reported (e.g. the demonstration of a CNT FET device), which is a first indication to focus on that topic. Hence we looked if that topic indeed is popular and present in the studied material and if its popularity grows over time. Thus the emergence of a topic with the combination of increased research attention over time was for us the most important indicator. Within these identified topics or potential irreversibilities indicators like statements on standards and compatibility with other technologies did confirm and strengthen our understanding and belief that it indeed is an irreversibility. A step further is to check if the topics emerged in the patent en governmental projects database. As it is picked up by industry and governmental actors it implies that selection occurred in relation to that topic and that more actors are involved in the development of the technology in relation to that specific irreversibility. This is also in line with the findings of the comparison of the emerging irreversibilities, where the strongest irreversibilities are manifested in all three communities. Thus this research support the finding that in order to assess if something is a significant irreversibility it should be present in governmental and industry domains.

The indicator technological needs stand more on itself and was only seen as an irreversibility as the majority of the field had the same technological needs. However it is stronger to link the technological needs indicator with the emergence of a new topic indicator. A new technological need can emerge as the result of new opportunities created by development in nanoscience. E.g. Multiplexing, functionalization nanomaterial etc., which are topics, challenges and needs which emerged as the result of new opportunities made possible by the use of nanomaterial. When those needs become shared by more researchers they influence the working heuristics of the researches and thus guide the development of the field.

The indicator promising applications is used in this thesis only in combination with the application domain and is linked to the needs from the application domains. Also here just the recognition is not enough to become an irreversibility. It is important that a large variety of actors is involved in this recognition and that it is in line with the needs form the application domain.

Overall what we can say, and what can be seen as a contribution to theory, is that the indicators should be used in couples, as described above, to demonstrate that something actually is an irreversibility. Furthermore with many of the indicators (i.e. societal needs, technological needs, devices in database, funding, promising application)it is important that the majority of the field is involved, thus that the phenomenon is shared and thus indeed popular. Maybe the most important finding is that the topic should be picked up by the industry and governments and thus should be present in the patent and project database. Thus we should look for combinations of indicators and check for the involvement of industry and governmental actors.

To sum up, the combination of indicators are: breakthroughs on a topic, which is followed by the emergence of that topic in the database and grows in presence, and popularity, over time. Hence, if new technological needs and expectations on standards related to that topic start to emerge it implies that it really becomes an important irreversibility. The presence of that topic in the industry and governmental community is a confirmation that something indeed is a strong irreversibility. Societal needs and recognition of new elements also guide the development but on a rather higher level.

Another contribution to theory is that this thesis empirically showed that a selection of technological options occurs between the different communities. It is demonstrated that technological variety in the scientific domain is high and that industry actors and governments make a selection out of these options.

The methodology used in this paper was only used for nanosensor technologies, however the methodology can be applied to other emerging field of S&T as well. For every field of S&T actors form the three communities are involved and arguable irreversibilities will occur in those three areas. Hence the data and statements can be gathered in a similar manner. The only difference is that the categories of the subject tree have to be different, as those categories are specific to the underlying logics within the studied field. Thus for every new field of S&T a different division of categories is needed.

Some practical implications and limitations in relation to the research methodology and findings are present and should be mention here.

In relation to the constructed database it is remarkable that almost all the patents relate to U.S. based actors, as in the scientific literature also many Asian countries are mentioned. But also many researchers from the U.S. universities are present which confirms the fact that the U.S. is the leader on nanosensor development, based on our database. Nonetheless question can be asked why Asian actors are absent in the patent database. Probably because we did not use databases from Asian patent offices like the SIPO or JPO. Furthermore the governmental projects in turn only relate to the EU. This is done because the EU has an interesting database containing projects. For further research it would be interesting to analyze projects in the US and Asia as well. Regardless of these limitations, our database is quite large and provided us with lots of valuable material.

Probably the biggest limitation of this research approach relates to selecting and coding of the statement. The selection of statements and the process of assigning modalities to the statements is dependent on the interpretation of the researcher and thus may not be reproducible. Within all the data we tried to select only the most relevant statements dealing with nanosensors and preferably future orientated. Most of these statements were voiced in the introduction, conclusions and abstract of the papers, or in relation to patents in the summary and background of the invention. It is plausible that different researchers would select other statements.

A remarkable finding is that very little proof and almost no science fiction statements were found. We can argue that no science fiction statements were found as it is quite clear and well defined what a nanosensor is. Also the nature of the sources is quite technical and intended for an audience in the field of nanosensors. The reason why little proof statement are found is that we were interested in statements dealing with nanosensors and the proof statement in the papers relate more to specific analytes or proteins in a specific experimental set up.

Another difficulty encounter in the analysis process of the statement is the limited technological knowledge of the researcher. And as the studied material is highly technical in nature we could not always be sure if everything is interpreted 100% right. As stated before the field of nanosensor is highly unarticulated with many type of sensors, materials and working principles. This in combination with the technological character of the data made it a complex endeavor to analyze the developments in the field. In sum there is a lot of interpretation and uncertainty involved in such analysis. Nonetheless, in the end we got a grip of the most important developments, so we could reconstruct the development and find the most important irreversibilities.

Even though we gathered 4000 statements it was in some cases too little to see actual patterns through time. This is especially the case for governmental projects. An idea for further research could be to use scientometric data, and try to map the development automatically with the help of software. Off course the nature of the research would be different, as you would lose the qualitative information. An idea could be to first study some review articles or have some interview with experts in the field with the intention to identify the important subjects, and hence trace those subjects within larger databases using some automated tools.

Besides these limitations we were able to make a subject tree, map the statement through time and use this information for the reconstruction of the field. Finding the irreversibilities in the field is also not a straightforward process, as irreversibilities are inherently abstract phenomena. Nonetheless the indicators contributed to the identification and we think the most important irreversibilities are found. Importantly, we presented a new method for mapping new fields of science and technology and tracing irreversibilities. Finally, many valuable insights on the development of nanosensor technologies are presented.

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11. Appendices

11.1 Appendix A: Statement Modalities

Statement modalities (adopted form Robinson, 2010)
Science Fictions indicate long-term fictional ideas, which are accepted as fantasy without demands of feasibility. An example of a Science Fiction linkage could be: "*The dark side of nanotechnology is "grey goo" - the nightmare possibility that "nano-robots" could be programmed to gobble up their surroundings and turn everything on Earth into more nanorobots*" (Park, 2003).
Visionary Linkages indicate long-term technological possibilities, which are accepted as reality-based fantasies, which *could* claim feasibility. An example of a Visionary Linkage could be: "*The behaviour of devices at these scales could eventually mean fundamental changes in the way we build things, forcing us to abandon old ideas*" (Cho, 2001).
Guiding Visions denote more technical and plannable technological futures (Grin & Grunwald, 2000) such as their *paperless office*. An example from the world of molecular machines would be *"Powering nanoscale machinery by nanosized motors that move by in situ conversion of stored chemical energy is one of the most interesting challenges facing nanotechnology."* (Kline et al. 2005 p744). The difference between Guiding Visions and Visionary Linkages is that Guiding Visions imply action, although no actor is positioned to undertake it (a more general statement).
An **expectation linkage**, of a constituent of the future molecular machine world. An example of an expectation linkage could be: "*We expect that the successful formation of fully functional surface-mounted rotors will enable investigation of the concerted action of a large ensemble of unidirectional molecular motors, and that this system might be a first step towards the construction of more elaborate and functional nanosized mechanical devices." (*Van Delden et al 2005. p1340).
A shared **agenda (goal**) of what future action should or will be taken. An example of an agenda statement could be: "*This paper is the first step towards our goal of creating artificial complex systems composed of large numbers of components that move autonomously and that self assemble."(*Ismagilov, R. F. et al. 2002 p654).
Proof: Technological developments that have been demonstrated and are accepted as fact or reality. An example of a proof-linkage could be: "*Nature already provides us with a wide range of biological nanomotors*" (Hess, et al., 2004, p2111)

11.2 Appendix B: Coding Examples

Here some coding examples are presented to illustrate how the subject tree was constructed. The examples in relation to the statement modalities are already enclosed in the text in section 5.1.

***Statement**: The large surface area and other interesting electronic properties of SWNTs make them ideal for de- veloping chemical sensors. The charge transfer between the nanotubes devices and gas molecules such as NO2 and NH3 leads to a reproducible conductivity change which forms the basis for the sensor operation.*

Coding: Electrochemical/ transducer / measures small molecules/ NO2 and NH3

Explanation: it's a electrochemical sensors, transducer element is discussed, measured gas concentrations which are small molecules

***Statement:** Fiber-optic nanobiosensors consisting of antibodies, as biorecognition molecules, coupled to an optical trans- ducer element, have been developed and used to detect biochemical targets, benzopyrene tetrol (BPT), and benzo[a]pyrene (BaP), inside single cells [10–14].*

Coding: Optical/ transducer And receptor/ measures macro molecules/ (BPT BaP)

Explanation: it's a optical sensors, transducer and receptor element discussed, measured *benzopyrene tetrol* which is a macro molecule.

Statement: We present a first demonstration of a transmembrane single molecule sensor (Kasianowicz, 2002) with impl cations to a broad range of engineered transmembrane molecule detectors. By employing electronic molecule detection within a nanopore, we achieve a high signal/noise ratio and specific detection of oligonucleotides with single base resolution.

coding: Electrochemical/ transducer / measures macro molecules/ oligonucleotides

explanation: it's a electrochemical sensors, transducer element discussed, measured oligonucleotides which is a macro molecule

Statement: LSPR-based sensors have been used in biosensing. For instance, streptavidin was quantitatively detected with a subpicomolar limit of detection using triangular silver NPs with biotinylated self assembled monolayers . The arrays of triangular silver NPs were fabricated using Nanosphere Lithography

coding: Optical/ transducer And receptor/ measures macro molecules/ streptavidin

explanation: it's a optical sensors, transducer and receptor element discussed, measured streptavidin which is a macro molecule

11.3 Appendix C: Database

DATABASE SCIENTIFIC ARTICELS

General Nanosensor Development

Ahn, J.-H., Kim, J.-H., Reuel, N. F., Barone, P. W., Boghossian, A. a, Zhang, J., Yoon, H., et al. (2011). Label-free, single protein detection on a near-infrared fluorescent single-walled carbon nanotube/protein microarray fabricated by cell-free synthesis. *Nano letters*, *11*(7), 2743–52.

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DATABASE: GOVERNMENTAL PROJECTS

Governmental projects

Project Acronym	**Reference code**	**Starting Date**	**End Date**
General Projects			
SPECCNT	10384	2004	2005
NANOS4	1528	2004	2007
NANOCHEMSENS	505895	2004	2007
CANAPE	500096	2004	2008
INTAS	6839	2004	2005
S-SCIL	508283	2005	2007
DOMINO	17383	2005	2008
NOVOPOLY	13619	2005	2008
NOESIS	516150	2005	2009
FINAQS	12986	2005	2009
ARCHITECHTUBE	9625	2005	2005
SMARTNANOTUBES	42036	2006	2007
NANORF	28158	2006	2008
OXCNT	24542	2006	2008
NASIMA	980015	2006	
NANOPRIM	33310	2006	2009
CARDEQ	212852	2006	2009
SANES	17310	2006	2009
VSNS	31917	2006	2009

GOLEM	33211	2006	2010
NANOBIOTACT	33287	2006	2010
NANOPHENSIM	201227	2007	2011
NANOSENS	220928	2008	2010
QDCN	220074	2008	2010
EXCELL	214706	2008	2011
ASMENA	214666	2008	2011
SMART	210078	2008	2013
SURFUNCELL	214653	2008	2012
PLANT CELL WALL	237636	2009	2011
FUNSENS	236885	2009	2011
GRAPHENETHIOPHENE	221742	2009	2011
NANOBIOSENS	230802	2009	2011
BOND	228685	2009	2012
NANOBE	227243	2009	2012
QUANTUMDOTIMPRINT	247825	2009	2012
TECHNOTUBES	228579	2009	2012
DELPHINS	240382	2009	2014
NANO-DYN-SYN	232942	2009	2014
MEM-S	244967	2010	2012
GNRSENSE	249225	2010	2013
LASEM	268293	2010	2103
SMARTFIBER	257733	2010	2013
SINAPS	257856	2010	2013
SIMS	257372	2010	2013
NANOPHENSIM	201227		
CNTCONTACT	275345	2011	2013
SSNANO	275336	2011	2013
PROSPER	280161	2011	2016
SQUTEC	267991	2011	2016
DECIMA	302991	2012	2014
NANOSOURCE	218111		
SURFPRO	307760	2013	2017
GANANO	505641	2004	2006
BIODIAGNOSTICS	17002	2005	2008
BIOGNOSIS	16467	2005	2008
ELISHA	505485	2004	2007
GENSENSOR-NANOPARTS	505808	2004	2007
FINAQS	12986	2005	2009
MIND	515757	2005	2010
PE-NANOSTRUCTURES	24997	2006	2008
BENATURAL	33256	2006	2009
INTELTEX	26626	2006	2010
REGMINA	205533	2008	2012
NMU-LIPIDS	203428	2008	2013
DESYGN-IT	505626		
CARBONCHIP	16475	2006	2009
ILISENSE	236628	2009	2011
MOCNA	221515	2009	2011
NANOMAT	229507	2009	2012
PICNQO	252944	2010	2011
NANOBITS	257244	2010	2013

INTIF	226639	2008	2013
PHOTOSENS	263382	2011	2014
MULTIBIOPHOT	259432	2011	2015
RE-ACT	293891	2011	2015
NANOMOL	277784	2011	2016
INSITUNANO	279342	2011	2016
MICREAGENTS	318671	2012	2015
SANTS	33254		
NATURALE-POC		2013	2014
MORPHOSIS	308261	2013	2017
MOEBIUS	910686	2013	2014

ENVIRONMENT

DINAMICS	26804	2007	2011
SENSOMETAL	221482	2009	2012
CELLTOX	256367	2010	2014
BIOMONAR	244405	2010	2014
CELL WALL METABOLISM	301307	2012	2014
MINAMI	34690	2006	2009
WARMER	34472	2006	2009
SHOAL	231646	2009	2012
MOEBIUS	910686	2013	2014
RE-ACT	293891	2011	2015

Food

WIPS	**508379**	2004	2007
REFLAB	31588	2006	2009
NANODETECT	211906	2008	2012
SYMBIOSIS-EU	211638	2008	2012
INSIDEFOOD	226783	2009	2013
BIOCOP	6988		
PROMETHEUS	265558	2011	2014
PATHOGENCOMBAT	7081	2005	2010
UNIQUE-CHECK	230667	2009	2013

Medical Applications

RBCE-GENODIAGNOSENS	221198	2008	2010
MEDIXHALE	327441	2013	2015
GANANO		2004	2006
BIODIAGNOSTICS	17002	2005	2008
BIOGNOSIS	16467	2005	2008
SAFER	4977	2005	2008
MASCOT	27652	2006	2008
BIO-MEDNANO	17350	2006	
NEMOSLAB	27804	2006	2008
SABIO	26554	2006	2008
NACARDIO	37672	2006	2009
CARBIO	35616	2006	2010
P.CEZANNE	8500000	2006	2010
CANCERBIOMECHANICS	42069	2007	2008
EXT-HOSSAM HAICK	42348	2007	2008
NANO-MUBIOP	211383	2008	2011
NANOMA	224594	2008	2011

NANODNASEQUENCING	214840	2008	2011
CD-Medics	216031	2008	2012
NANOTEST	201335	2008	2012
CP-SMARTSURFACES	224880	2008	2012
NASPE	222023	2009	2010
3D-NANOBIODEVICE	229255	2009	2012
NANOANTENNA	241818	2009	2013
NANOTHERAPY	232959	2009	2014
FOSAS	255865	2010	2010
NANOREACTOR	254866	2010	2012
P3SENS	248304	2010	2012
MICROCARE	247641	2010	2014
BIONANOTOOLS	246688	2010	2014
DIAG-CANCER	256639	2010	2015
NANOTOX	293678	2011	2015
QUIDPROQUO	269051	2011	2016
NANO-MUBIOP	211383		
LCAOS	258868	2011	2015
NANOCOURIERS	273133	2012	2014
PEPTIDE NANOSENSORS	294901	2012	2015
NANOP	279818	2012	2016
MEDIXHALE	327441	2013	2016
MEDI-LASE	251531	2010	2014
NADINE	246513	2010	2015
SENSE-OF-CARE			
OFER	316845	2012	2016
SYNINTER	307104	2013	2017
HEALTHY AIMS	1837	2003	2008
NACARDIO	37672	2006	2009
NASPE	222023	2009	2010
SIMBA	261162	2010	2015
SMARTCANCERSENS	318053	2013	2016
ABLADE	324370	2013	2017

DATABASE: PATENTS

Document No. AND LINK PATENT	**Title**	**Publish/Grant Date**
US6143558	Optical fiberless sensors for analyzing cellular analytes	2000-11-07
US6287765	Methods for detecting and identifying single molecules	2001-09-11
US6303290	Encapsulation of biomaterials in porous glass-like matrices prepared via an aqueous colloidal sol-gel process	2001-10-16
US6385363	Photo-induced micro-mechanical optical switch	2002-05-07
US20020056816	Surface plasmon enhanced illumination system	2002-05-16
WO/2002/048701	NANOSENSORS	2002-06-20
US20020130311	Doped elongated semiconductors, growing such semiconductors, devices including such semiconductors and fabricating such devices	2002-09-19
US20020173083	Methodology for electrically induced selective breakdown of nanotubes	2002-11-21
WO/2002/098364	MAGNETIC-NANOPARTICLE CONJUGATES AND METHODS OF USE	2002-12-12
WO/2003/005450	NANOSCALE WIRES AND RELATED DEVICES	2003-01-16

US6548313	Amorphous carbon insulation and carbon nanotube wires	2003-04-15
US6574130	Hybrid circuit having nanotube electromechanical memory	2003-06-03
WO/2003/054931	METHOD AND APPARATUS FOR NANO−SENSING	2003-07-03
US20030134433	Electronic sensing of chemical and biological agents using functionalized nanostructures	2003-07-17
US20030158474	Method and apparatus for nanomagnetic manipulation and sensing	2003-08-21
EP1342075	NANOSENSORS	2003-09-10
US6636652	Optical sensors for the detection of nitric oxide	2003-10-21
US6643165	Electromechanical memory having cell selection circuitry constructed with nanotube technology	2003-11-04
US20040136866	Planar nanowire based sensor elements, devices, systems and methods for using and making same	2004-07-15
US20040005582	Biospecific desorption microflow systems and methods for studying biospecific interactions and their modulators	2004-01-08
US20040180380	Proteome epitope tags and methods of use thereof in protein modification analysis	2004-09-16
US6818907	Surface plasmon enhanced illumination system	2004-11-16
US20040038307	Unique recognition sequences and methods of use thereof in protein analysis	2004-02-26
US20040213307	Nanoscale coherent optical components	2004-10-28
US6706402	Nanotube films and articles	2004-03-16
US6835591	Methods of nanotube films and articles	2004-12-28
US20040078219	Healthcare networks with biosensors	2004-04-22
US6737286	Apparatus and method for fabricating arrays of atomic-scale contacts and gaps between electrodes and applications thereof	2004-05-18
US20040180379	Surface-enhanced raman nanobiosensor	2004-09-16
US6762331	Synthesis of organic nanotubes and synthesis of ultrathin nanowires using same as templates	2004-07-13
US6762025	Single-molecule selection methods and compositions therefrom	2004-07-13
US6831017	Catalyst patterning for nanowire devices	2004-12-14
US6784028	Methods of making electromechanical three-trace junction devices	2004-08-31
US6706566	Methodology for electrically induced selective breakdown of nanotubes	2004-03-16
US20040004485	Carbon nanotube array based sensor	2004-01-08
US6828786	Method and apparatus for nanomagnetic manipulation and sensing	2004-12-07
US6781166	Nanoscopic wire-based devices and arrays	2004-08-24
WO/2004/027822	ORIENTED NANOSTRUCTURES AND METHODS OF PREPARING	2004-04-01
WO/2004/099068	NANOFIBER SURFACES FOR USE IN ENHANCED SURFACE AREA APPLICATIONS	2004-11-18
WO/2004/003535	PLANAR NANOWIRE BASED SENSOR ELEMENTS, DEVICES, SYSTEMS AND METHODS FOR USING AND MAKING SAME	2004-01-08
WO/2004/034025	NANO-CHEM-FET BASED BIOSENSORS	2004-04-22
US20050065741	Sensor platform using a non-horizontally oriented nanotube element	2005-03-24
US20050064508	Peptide mediated synthesis of metallic and magnetic materials	2005-03-24
US6894359	Sensitivity control for nanotube sensors	2005-05-17
US6919592	Electromechanical memory array using nanotube ribbons and method for making same	2005-07-19
US6946851	Carbon nanotube array based sensor	2005-09-20
US20050089890	Multimolecular devices and drug delivery systems	2005-04-28

US20050101841	Healthcare networks with biosensors	2005-05-12
US6882767	Nanowire optoelectric switching device and method	2005-04-19
US6889216	Physical neural network design incorporating nanotechnology	2005-05-03
US20050049472	Implantable biosensor devices for monitoring cardiac marker molecules	2005-03-03
US20050053525	Sensor platform using a horizontally oriented nanotube element	2005-03-10
US20050129573	Carbon dioxide nanoelectronic sensor	2005-06-16
US20050191427	Selective functionalization of carbon nanotube tips allowing fabrication of new classes of nanoscale sensing and manipulation tools	2005-09-01
US6875578	System for cell-based screening	2005-04-05
US20050265914	Carbon nanotube-based glucose sensor	2005-12-01
US6905655	Modification of selectivity for sensing for nanostructure device arrays	2005-06-14
US6905667	Polymer and method for using the polymer for noncovalently functionalizing nanotubes	2005-06-14
US20050043894	Integrated biosensor and simulation system for diagnosis and therapy	2005-02-24
US6914279	Multifunctional biosensor based on ZnO nanostructures	2005-07-05
US6967074	Methods of detecting immobilized biomolecules	2005-11-22
US6942921	Nanotube films and articles	2005-09-13
US20050101026	Photoluminescent polymetalloles as chemical sensors	2005-05-12
US20050208304	Coatings for carbon nanotubes	2005-09-22
US6855202	Shaped nanocrystal particles and methods for making the same	2005-02-15
WO/2005/031299	SENSOR PLATFORM USING A NON-HORIZONTALLY ORIENTED NANOTUBE ELEMENT	2005-04-07
US20060263255	Nanoelectronic sensor system and hydrogen-sensitive functionalization	2006-11-23
US20060125033	Sensor platform using a non-horizontally oriented nanotube element	2006-06-15
US7083104	Applications of nano-enabled large area macroelectronic substrates incorporating nanowires and nanowire composites	2006-08-01
US7005264	Method and apparatus for nucleic acid sequencing and identification	2006-02-28
US7064372	Large-area nanoenabled macroelectronic substrates and uses therefor	2006-06-20
US20060038990	Nanowire optical sensor system and methods for making and using same	2006-02-23
US20060290496	Diagnostic radio frequency identification sensors and applications thereof	2006-12-28
US7051945	Applications of nano-enabled large area macroelectronic substrates incorporating nanowires and nanowire composites	2006-05-30
US7056758	Electromechanical memory array using nanotube ribbons and method for making same	2006-06-06
US20060159916	Nanofiber surfaces for use in enhanced surface area applications	2006-07-20
US7025734	Guidewire with chemical sensing capabilities	2006-04-11
US7144840	TiO2 material and the coating methods thereof	2006-12-05
US7148803	Radio frequency identification (RFID) based sensor networks	2006-12-12
US7074294	Structures, systems and methods for joining articles and materials and uses therefor	2006-07-11
US20060269927	Nanoscale sensors	2006-11-30
US7141416	Multi-purpose optical analysis optical bio-disc for conducting assays and various reporting agents for use therewith	2006-11-28
US20060054936	Nanosensors	2006-03-16
US20060055392	Remotely communicating, battery-powered nanostructure sensor devices	2006-03-16

US7056409	Structures, systems and methods for joining articles and materials and uses therefor	2006-06-06
EP1067378	APPARATUS FOR AUTOMATICALLY MEASURING MINUTE MEMBRANE POTENTIAL	2006-05-03
US20070215960	Methods for Fabrication of Positional and Compositionally Controlled Nanostructures on Substrate	2007-09-20
US20070048181	Carbon dioxide nanosensor, and respiratory CO2 monitors	2007-03-01
US20070116602	NMR device for detection of analytes	2007-05-24
US7235295	Polymeric nanofibers for tissue engineering and drug delivery	2007-06-26
US7176505	Electromechanical three-trace junction devices	2007-02-13
US7228159	Optical sensor containing particles for in situ measurement of analytes	2007-06-05
US20070116627	Carbon nanotube compositions and devices and methods of making thereof	2007-05-24
US7233041	Large-area nanoenabled macroelectronic substrates and uses therefor	2007-06-19
US20070138010	Embedded nanotube array sensor and method of making a nanotube polymer composite	2007-06-21
US7312095	Modification of selectivity for sensing for nanostructure sensing device arrays	2007-12-25
US20070026645	Doped elongated semiconductors, growing such semiconductors, devices including such semiconductors, and fabricating such devices	2007-02-01
US20070158766	Nanosensors	2007-07-12
US7192708	Nucleic acid enzyme biosensors for ions	2007-03-20
US20070132043	Nano-electronic sensors for chemical and biological analytes, including capacitance and bio-membrane devices	2007-06-14
US20070078484	Gentle touch surgical instrument and method of using same	2007-04-05
US7301199	Nanoscale wires and related devices	2007-11-27
US20070208243	Nanoelectronic glucose sensors	2007-09-06
US7194912	Carbon nanotube-based sensor and method for continually sensing changes in a structure	2007-03-27
US20070045756	Nanoelectronic sensor with integral suspended micro-heater	2007-03-01
US7186381	Hydrogen gas sensor	2007-03-06
US7303875	Nano-chem-FET based biosensors	2007-12-04
US7172953	Methods of forming nanoscopic wire-based devices and arrays	2007-02-06
US7163659	Free-standing nanowire sensor and method for detecting an analyte in a fluid	2007-01-16
WO/2007/044034	NANOSCALE WIRE-BASED DATA STORAGE	2007-04-19
US20080204742	Method and System for Optimizing Surface Enhanced Raman Scattering	2008-08-28
US7385266	Sensor platform using a non-horizontally oriented nanotube element	2008-06-10
US20080073505	Nanostructured thin films and their uses	2008-03-27
US7344961	Methods for nanowire growth	2008-03-18
US7335395	Methods of using pre-formed nanotubes to make carbon nanotube films, layers, fabrics, ribbons, elements and articles	2008-02-26
US7394118	Chemical sensor using semiconducting metal oxide nanowires	2008-07-01
US7357018	Method for performing a measurement inside a specimen using an insertable nanoscale FET probe	2008-04-15
US20080125335	Oilfield Apparatus Comprising Swellable Elastomers Having Nanosensors Therein And Methods Of Using Same In Oilfield Application	2008-05-29
US7410904	Sensor produced using imprint lithography	2008-08-12
US20080129457	Identification Method and System and Device Suitable for Said Method and	2008-06-05

	System	
US7335528	Methods of nanotube films and articles	2008-02-26
US20080093226	Ammonia nanosensors, and environmental control system	2008-04-24
US7318907	Surface plasmon enhanced illumination system	2008-01-15
US7335908	Nanostructures and methods for manufacturing the same	2008-02-26
US20080099667	METHODS AND APPARATUS FOR SENSING A PHYSICAL SUBSTANCE	2008-05-01
US20080021339	Anesthesia monitor, capacitance nanosensors and dynamic sensor sampling method	2008-01-24
US7332283	Fluorescence based biosensor	2008-02-19
US7318908	Integrated nanotube sensor	2008-01-15
US20080251723	Electromagnetic and Thermal Sensors Using Carbon Nanotubes and Methods of Making Same	2008-10-16
US7339184	Systems and methods for harvesting and integrating nanowires	2008-03-04
EP1342075	DEVICE CONTANING NANOSENSORS FOR DETECTING AN ANALYTE AND ITS METHOD OF MANUFACTURE	2008-09-10
WO/2008/027078	NANOBIOELECTRONICS	2008-03-06
WO/2008/127314	HIGH-SENSITIVITY NANOSCALE WIRE SENSORS	2008-10-23
WO/2008/039165	CARBON DIOXIDE NANOSENSOR, AND RESPIRATORY CO2 MONITORS	2008-04-03
WO/2008/057578	NMR SYSTEMS FOR IN VIVO DETECTION OF ANALYTES	2008-05-15
US7553371	Porous substrates, articles, systems and compositions comprising nanofibers and methods of their use and production	2009-06-30
US7566478	Methods of making carbon nanotube films, layers, fabrics, ribbons, elements and articles	2009-07-28
US7560366	Nanowire horizontal growth and substrate removal	2009-07-14
US7560136	Methods of using thin metal layers to make carbon nanotube films, layers, fabrics, ribbons, elements and articles	2009-07-14
US7569941	Methods of fabricating nanostructures and nanowires and devices fabricated therefrom	2009-08-04
US7619290	Nanosensors	2009-11-17
US20090281412	System, devices, and methods for detecting occlusions in a biological subject	2009-11-12
US7631697	Oilfield apparatus comprising swellable elastomers having nanosensors therein and methods of using same in oilfield application	2009-12-15
US7564245	NMR device for detection of analytes	2009-07-21
US7622367	Methods and devices for fabricating and assembling printable semiconductor elements	2009-11-24
US7541012	Catalytic material and method of production thereof	2009-06-02
US7557367	Stretchable semiconductor elements and stretchable electrical circuits	2009-07-07
US7569850	Lipid bilayers on nano-templates	2009-08-04
US7538400	Sensor platform using a non-horizontally oriented nanotube element	2009-05-26
US7612185	Nucleic acid biosensors	2009-11-03
US7485419	Biosensors based on directed assembly of particles	2009-02-03
US7521257	Chemical sensor with oscillating cantilevered probe and mechanical stop	2009-04-21
US20090179523	SELF-ACTIVATED NANOSCALE PIEZOELECTRIC MOTION SENSOR	2009-07-16
US20090302235	FLUORESCENT NON-METALLIC PARTICLES ENCAPSULATED IN A METALLIC COATING	2009-12-10
US7522040	Remotely communicating, battery-powered nanostructure sensor devices	2009-04-21

US7534560	Simple catalytic DNA biosensors for ions based on color changes	2009-05-19
US20090227988	Injectable controlled release fluid delivery system	2009-09-10
US20100249692	Systems, devices, and methods including infection-Fighting and monitoring shunts	2010-09-30
US7692218	Method for creating a functional interface between a nanoparticle, nanotube or nanowire, and a biological molecule or system	2010-04-06
US20100085067	ANESTHESIA MONITOR, CAPACITANCE NANOSENSORS AND DYNAMIC SENSOR SAMPLING METHOD	2010-04-08
US7745813	Nanostructures and methods for manufacturing the same	2010-06-29
US20100056892	NANOELECTRONIC MEASUREMENT SYSTEM FOR PHYSIOLOGIC GASES AND IMPROVED NANOSENSOR FOR CARBON DIOXIDE	2010-03-04
US7807265	Partially passivated quantum dots, process for making, and sensors therefrom	2010-10-05
US7694346	Cantilevered probe detector with piezoelectric element	2010-04-06
US7781228	Magnetic resonance system and method to detect and confirm analytes	2010-08-24
US20100084276	Devices and Methods for Target Molecule Characterization	2010-04-08
US7687146	Simple tool for positional diamond mechanosynthesis, and its method of manufacture	2010-03-30
US7712529	Sand control screen assembly and method for use of same	2010-05-11
US7666708	Doped elongated semiconductors, growing such semiconductors, devices including such semiconductors, and fabricating such devices	2010-02-23
US20100025660	SEMICONDUCTOR DEVICES, METHODS OF MANUFACTURE THEREOF AND ARTICLES COMPRISING THE SAME	2010-02-04
US7713779	Photoactive nanocomposite and method for the production thereof	2010-05-11
US7682943	Nanostructures and methods for manufacturing the same	2010-03-23
US7799699	Printable semiconductor structures and related methods of making and	2010-09-21
US7733479	Charged carbon nanotubes for use as sensors	2010-06-08
US7656525	Fiber optic SERS sensor systems and SERS probes	2010-02-02
US20100184062	Method for Identifying and Quantifying Organic and Biochemical Substances	2010-07-22
US20100072994	NMR SYSTEMS FOR IN VIVO DETECTION OF ANALYTES	2010-03-25
US7712527	Use of micro-electro-mechanical systems (MEMS) in well treatments	2010-05-11
US20100035163	Fabrication of nanostructured devices	2010-02-11
US20100102986	SYSTEM AND METHOD TO REMOTELY INTERACT WITH NANO DEVICES IN AN OIL WELL AND/OR WATER RESERVOIR USING ELECTROMAGNETIC TRANSMISSION	2010-04-29
US7704462	Method and apparatus for producing aligned carbon nanotube thermal interface structure	2010-04-27
US20100120174	WATER RELAXATION-BASED SENSORS	2010-05-13
US7972875	Optical systems fabricated by printing-based assembly	2011-07-05
US7972616	Medical device applications of nanostructured surfaces	2011-07-05
US7943491	Pattern transfer printing by kinetic control of adhesion to an elastomeric	2011-05-17
US8066004	System and method for providing a breathing gas	2011-11-29
US20110020788	NMR DEVICE FOR DETECTION OF ANALYTES	2011-01-27
US7992561	Carbon dioxide-sensing airway products and technique for using the same	2011-08-09
US8039847	Printable semiconductor structures and related methods of making and assembling	2011-10-18
US7939218	Nanowire structures comprising carbon	2011-05-10

US20110174874	Transaction Card With Improved Security Features	2011-07-21
US7915151	Doped elongated semiconductors, growing such semiconductors, devices including such semiconductors and fabricating such devices	2011-03-29
US7928343	Microcantilever heater-thermometer with integrated temperature-compensated strain sensor	2011-04-19
US20110163636	MATRIX-ASSISTED ENERGY CONVERSION IN NANOSTRUCTURED PIEZOELECTRIC ARRAYS	2011-07-07
US7960260	Formation of nanowhiskers on a substrate of dissimilar material	2011-06-14
US20110003279	Monitoring devices and processes based on transformation, destruction and conversion of nanostructures	2011-01-06
US20110160643	Systems, devices, and methods including catheters having acoustically actuatable waveguide components for delivering a sterilizing stimulus to a region proximate a surface of the catheter	2011-06-30
US7910064	Nanowire-based sensor configurations	2011-03-22
US7922976	High sensitivity sensor device and manufacturing thereof	2011-04-12
US7906320	Fluorescence based biosensor	2011-03-15
US7892734	Aptamer based colorimetric sensor systems	2011-02-22
US7902353	Nucleic acid enzyme biosensors for ions	2011-03-08
US7948015	Methods and apparatus for measuring analytes using large scale FET arrays	2011-05-24
US20110251469	WIRELESS NANOTECHNOLOGY BASED SYSTEM FOR DIAGNOSIS OF NEUROLOGICAL AND PHYSIOLOGICAL DISORDERS	2011-10-13
US7951422	Methods for oriented growth of nanowires on patterned substrates	2011-05-31
US7982296	Methods and devices for fabricating and assembling printable semiconductor elements	2011-07-19
WO/2011/003197	IN SITU POLYMERIZATION OF CONDUCTING POLY(3,4-ETHYLENEDIOXYTHIOPHENE)	2011-01-13
US8302602	Breathing assistance system with multiple pressure sensors	2012-11-06
US20120157824	MRI AND OPTICAL ASSAYS FOR PROTEASES	2012-06-21
US8181648	Systems and methods for managing pressure in a breathing assistance system	2012-05-22
USD655809	Valve body with integral flow meter for an exhalation module	2012-03-13
US8247849	Two-transistor pixel array	2012-08-21
US8256233	Systems, devices, and methods for making or administering frozen particles	2012-09-04
US8263336	Methods and apparatus for measuring analytes	2012-09-11
US8162050	Use of micro-electro-mechanical systems (MEMS) in well treatments	2012-04-24
US8264014	Methods and apparatus for measuring analytes using large scale FET arrays	2012-09-11
US20120100546	NMR SYSTEMS AND METHODS FOR THE RAPID DETECTION OF ANALYTES	2012-04-26
USD653749	Exhalation module filter body	2012-02-07
US8217433	One-transistor pixel array	2012-07-10
US20120107839	NMR DEVICE FOR DETECTION OF ANALYTES	2012-05-03
US8198621	Stretchable form of single crystal silicon for high performance electronics	2012-06-12
US8113062	Tilt sensor for use with proximal flow sensing device	2012-02-14
US8097926	Systems, methods, and devices having stretchable integrated circuitry for sensing and delivering therapy	2012-01-17
US8102176	NMR device for detection of analytes	2012-01-24
US8115635	RF tag on test strips, test strip vials and boxes	2012-02-14