Characterizing a Technology Development at the Stage of Early Emerging Applications: Nanomaterial-enhanced Biosensors

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ABSTRACT
In this paper we devise Future-oriented Technology Analyses tools to investigate a technology at an interesting development stage – namely, one of early emerging applications. At this stage, technologies show great potential with little commercialization in place. Future development pathways are highly uncertain and heavily dependent on contextual interactions. We apply R&D profiling, R&D to Applications cross-charting, and Technology Delivery System modelling to help understand the phenomena that bear upon development prospects. We develop our approach through a two-tier case study: general treatment of nanomaterial-enhanced biosensors, followed by more specialized treatment of one subset that applies nanoparticles. Results convey the importance of considering technological and social context factors in conjunction with each other to understand likely innovation pathways.

Keywords:
Emerging application; Nanomaterial-enhanced biosensor; Future-oriented Technology Analyses (FTA); Technology Delivery System (TDS); Nanotechnology; Nanoparticle

1. Introduction

"Analysis of emerging technologies" has been of interest for many years. Recently those engaged in Future-oriented Technology Analyses ("FTA" – see http://forera.jrc.ec.europa.eu/fta_2008/intro.html) are beginning to distinguish different science and technology development situations. Clearly, technology forecasting for long-established developments, with dominant platforms (e.g., silicon-based information technologies) and incrementally changing applications are more amenable to trend analyses and growth modeling

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than are newly advancing scientific research areas with no applications yet. FTA recently has begun to differentiate various "New and Emerging Science & Technologies" (**"NEST"**) that warrant differentiated analytical strategies. In this paper we focus on the interesting situation of 1) new scientifically based enhancements of 2) an emerging technology, with 3) some emerging applications. This poses an intriguing methodological challenge to decide what data and methods can yield effective FTA. Our topic – nano-enhanced biosensors – is also of inherent interest for its highly multidisciplinary R&D and wide range of potentially important "emerging applications."

Given the complex and dynamic societal context (development environment), it is very hard to anticipate the developmental paths that such emerging technologies will follow. How to study, forecast, and manage such technologies has bearing on scientists, business managers, policy makers, and the investment community. Emerging technologies can be divided into two types according to the status of their applications: 1) emerging technologies with no applications at present, and 2) emerging technologies with some applications in the market. In this paper, we focus on the latter, in the case of nano-enhanced biosensors. We attempt to figure out the "system picture" of the technological development with emerging applications, including R&D patterns, institutional involvements, major actors, and key markets.

Our present work is aided by two NSF projects that address nanotechnology, with interests in developmental paths and potential implications thereof.[2] Nowadays, nanotechnology is playing an increasingly important role in the development of sensors. Biosensors represent an especially exciting opportunity for high-impact applications benefiting from "nano" attributes. Reviewing

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recent studies, we find a steep increase in the literature on nanobiosensors (Huang et al., 2009). A wide variety of nanomaterials with unique properties have found broad application in biosensors. Although we are in the early days of the emerging technology of using nanomaterials to modify biosensors (Kerman et al. 2008), many papers anticipate dramatic prospects for nanomaterial-enhanced biosensors.

Given the promising future for applications of nanobiosensors, we key on what it will take to "deliver" these applications effectively. We take multiple perspectives to model this complex "Technology Delivery System" ("**TDS**") proposed by Wenk and Kuehn (1977). A national policy interest is to understand global roles, so we compare and track engagement of the leading countries. Shifting to a private sector technology management perspective, we strive to identify the actors and their roles. To anticipate the development pathways for nanobiosensors, it is essential to identify interactions among players and explore potential supports and barriers in the environment. This information could tremendously aid policy makers foster development. The aim of this paper is to begin to build a contextually rich picture of nanomaterial-enhanced biosensors, including profiling R&D patterns, identifying network interactions, developing research-application linkages, and exploring potential application development pathways. To do so, we adapt several FTA and technology management methods, along with suitable visualization tools.

We organize the paper in five sections. Section 2, next, presents the conceptual framework that guides this research and the approach employed in this paper. Section 3 begins with a nanomaterial-enhanced biosensor technology background, followed by documenting the development status and interactions inside and among important actors. Because the commercialization of true nanobiosensors is largely being driven by US companies, this section focuses on the US TDS. A case study of nanoparticle-enhanced biosensors using the methodology and tools explored in Section 2 is then developed in Section 4. Last, a discussion of insights gained from our research into this technology at the stage of emerging applications to inform FTA will constitute Section 5.

2. Conceptual Framework and Approach

Our topic has two notable characteristics: an early stage of applications and highly multidisciplinary R&D. We explore how concepts and findings cross-pollinate and transfer among science, technology, and commercialization in nanobiotechnology (Grodal and Thoma, forthcoming). Further structuring and interpreting the roles and linkages within this emerging socio-technological system -- and highlighting prominent actors, institutions, and knowledge networks -- can help forecast further technological developments (Miyazaki and Islam 2007).

For technologies that are already contributing to some applications, we can compile information on the influential policies, knowledge transfer networks, and market ties. On the other hand, for technologies with few applications yet enabled, we rely upon our colleagues in specific technology fields to perform actor analyses. Given the uncertainty of technologies with just emerging applications, we invest special effort to understand the dynamics that could change the linkages along the "stream" from R&D toward innovation. For example, we are particularly interested in shifts in infrastructure.

Facing such special conditions, we should adapt conventional methods to facilitate our study. Here, we explore five components to help characterize technologies with just emerging applications:

PR) Profile R&D Activity

Ex) Expert Check

CC) Cross-chart from R&D to Applications

TDS) Technology Delivery System Depict;

MPM) Multi-path Mapping

We choose to label these five components to help keep them in mind, while avoiding the tendency to consider them as a linear progression of steps. Figure 1 shows the basic methodological framework we explore for research on technologies with emerging applications.

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Figure 1 about here

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2.1. PR) Profile R&D Activity

While nano-enhanced biosensors are at an emergence stage for applications, there are extensive R&D activities. Bibliometric analysis is a tool for extracting information from large databases seeking patterns for apparently unstructured behaviour. Such analyses can provide technology life-cycle indicators and facilitate forecasting (Daim et al. 2005; 2006; Martino 2003; Porter and Cunningham 2005; Watts 2001).

2.2. EX) Expert Check

For most "NEST" topics, determining what should be included, or not, is not obvious to the Future-oriented Technology Analyst. That person is not apt to be a specialist in the particular NEST. Hence, engaging technical experts is vital.

We suggest doing so at the search stage. Knowledgeable technical professionals can helpfully suggest search terms and, most importantly, review the results (especially key terms and leading players) of initial searches to correct course.

In this biosensor analysis, expert guidance was critical to complete the Cross-charting. Technical and business savvy is extremely helpful in formulating a TDS and in depicting and gauging development pathways (MPM) as well. Finally, we seek to engage various experts to review our interpretations of likely innovation pathways.

We first identify local technical experts, based on bibliometrics and collegial contacts. E-mail questions provide an initial step to enlist cooperation. One-on-one meetings proved very valuable to orient ourselves and the experts, and to decide how best to proceed. If time and resources were to allow, an interactive workshop with a spectrum of relevant experts would be attractive (Robinson and Propp 2008).

2.3. CC) Cross-chart R&D to Applications

In order to span the gap between R&D and future potential applications, it is important to understand the linkages for particular technologies with their emergent applications. The "R&D to Applications Cross-charts" is our key tool to explore the characteristics of R&D, downstream uses, and the relationships among them. We will investigate the linkages among Technologies – Functions – Applications.

2.4. TDS) Technology Delivery System Depict

Technology and society are interrelated, and both are changing rapidly. Changes in technology feed upon themselves, producing a stock of concepts that may be refined, developed, and used as the basis for further change. The development and dissemination of technology creates forces that can cause change in every aspect of society. On the other hand, changes in society produce conditions that influence technological change. We must understand these interrelationships to forecast and manage technology effectively (Porter et al., 1991, 22). For technologies that have already have emerging applications, dynamic environments should be considered as well. Our TDS focuses on socio-technical forces and factors in the immediate contextual environment for nano-enhanced biosensors. It portrays the institutional linkages involved in developing a particular technological innovation. Here, TDS is used to show a "system" picture of the research status, market applications, and future prospects of nano-enhanced biosensors. We are especially interested in uncovering factors that will drive innovation in particular ways, including any barriers that could hinder particular developments. We also seek key leverage points at which the innovation pathways can be strongly influenced.

2.5. MPM) Multi-path Mapping

There are some tools (such as roadmapping) that can be used to serve both short and long term alignment of science and technology (S&T) developments and new product development. Forecast of the likely future development of S&T are generated. However, for technologies with emerging applications, these conventional tools don't seem as well-suited because the likely products are not articulated yet. A promising approach is to build mapping tools based on underlying patterns and indicators of the dynamics of emergence (Robinson and Propp 2008). A plausible variety of paths provide a broader set of strategic choices. These can articulate alternative futures structured in terms of prospective innovation chains and potential commercialization paradigms.

In this paper, we address the first four components in our analytical framework. We intend to pursue Multi-path Mapping in later research. In addition to the multi-level analysis methods mentioned above, we apply special visualizations to help show our findings.

3. Cross-chart and Technology Delivery System for Nanomaterial-enhanced biosensors

3.1. Introduction of biosensor and nanomaterial

A biosensor is a device that combines a biological recognition element with a physical or chemical transducer to detect a biological analyte or to assess the conditions of a biological component under normal and disease states.

In general, a biosensor consists of three components:

A. The biological recognition element that can be a natural biological material (e.g. tissues, cells, and various biomolecules), a biologically derived material, or a biomimic material
B. The transducer or the detector that transforms the signal resulting from the interaction of the target biological analyte with the biological recognition element into a measureable signal
C. Associated electronics or signal processors that are primarily responsible for the display of the results in a user-friendly way.

The schematics of a biosensor are shown in Figure 2.

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Figure 2 about here

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Nanomaterials have morphological features smaller than one hundred nanometers in at least one dimension. With recent advances in nanotechnology, a wide variety of nanomaterials with special and novel properties are fabricated. Nanomaterials applied in biosensors may be divided into the following four categories:

0D: Zero-dimensional structures, including nanoparticles, nanorods, etc.
1D: One-dimensional structures, including nanowires, nanotubes, nanobelts, etc.

2D: Two-dimensional structures, including thin films, membranes, 2D assemblies of nanoparticles or nanowires, etc.

3D: Three-dimensional structures, including assembled nanowire/nanotube stacks, or nanoparticle beds, nanosprings, etc.

3.2. CC) R&D to Applications Cross-chart

How can nanomaterials be effectively used in biosensors? A general "cross-chart" from fundamental nanotechnology to market applications (Figure 3) reveals vital links among nanomaterials, biosensors, and applications. The classification of biosensors in Figure 3 keys on the transduction principles, including mass, thermal, electrochemical, conductometric, and optical sensors. Figure 3 also explores the underlying functions of how nanomaterials can enhance biosensors, which can help future innovation path mapping.

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Figure 3 about here

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Nanomaterials can contribute in either the bio recognition element or the transducer, or both, of a biosensor. The functions of nanomaterials used in bio recognition elements can be divided into two classes. The first class is referred to as "target labelling" using 0D or 1D nanomaterials. Examples include using semiconductor nanoparticles, i.e., quantum dots, as fluorescence labels (Gao et al. 2004) and using paramagnetic nanoparticles as magnetic contract agents (Weissleder et al. 1990). The second class of nanomaterial functions used in bio recognition elements is mainly in the form of replacing the traditional molecular recognition layers using various nanomaterials. This replacement takes advantage of not only the catalytic function of nanomaterials (Daniel and Astruc 2004), but also the high surface areas with a large number of binding sites for molecular interactions (Verpoorte 2004).

Because of the size effect and enhanced properties, using nanomaterials to replace the traditional transduction elements in a transducer usually improves the performance of the transducer. In addition, new transduction mechanisms such as ballistic field-effect transistor can be created from the enhanced electron transport in single-walled carbon nanotubes (Javey et al. 2003). Until today, the nanomaterials used in transducers have mainly been 1D or 2D structures.

At present, our searches of leading R&D databases finds that the most heavily researched nanomaterials include:

- Quantum Dots and Gold (Au) nanoparticles and in 0D nanomaterials;
- Carbon nanotubes, and silicon (Si) nanowires in 1D nanomaterials;
- Au thin films in 2D nanomaterials;
- 3D Carbon Nanotube stacks

Compared with traditional biosensors, nanobiosensors show remarkable advantages in accuracy, detection limits, sensitivity, selectivity, temporal response, and reproducibility. We will investigate the detailed linkages between nano-enabled properties and their advantages in biosensors in a case study in the next section. We will focus on exploring the relevant linkages that guide our understanding of emerging applications and help forecast applications. We identify four key application areas -- healthcare, environment, food/agriculture, and homeland security/defense. Detailed research on applications is explored next concerning the nanobiosensors TDS.

3.3. TDS) Technology Delivery System

Spending on nanotechnology research is broadly similar in the USA, the European Union, and Asia, but commercialization of true nanobiosensors is largely being driven by US companies

(Bogue 2008). In order to capture more detailed information and characteristics of nanomaterial-enhanced biosensor technology, we focus on the contextual environment in the USA. In Figure 4, a limited sociotechnical system composed of institutions directly or indirectly involved in developing nanomaterial-enhanced biosensor technology is displayed. At the societal level, we categorize four key players: governments, R&D groups, manufacturers, and users.

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Figure 4 about here

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- *Governments*

Governments address the social, political, and economic aspects of the new technology field. At present, their most important role is funding R&D. A great number of R&D grants are provided for nanobiosensors. Development efforts focus mostly on the existing biosensors to improve their performance in sensitivity, selectivity, accuracy, and reliability. We note two levels of funds: Federal agencies provide the major share of support -- including the National Science Foundation (NSF); Environmental Protection Agency (EPA); Department of Energy (DOE); and National Institutes of Health (NIH) (Roco 2003). State agencies also contribute to R&D support with relatively smaller shares.

For example, Nanomix Inc., a university spin-off nanosensors company, has received $34.5 million in three rounds of financing to develop a novel diagnostic electronic nose, including sustaining funds from NSF to for $1.1 million and other grants from the Environmental Protection Agency and the Department of Energy (Bogue 2008). An example of state support is that Cornell University has received a $255,000 grant from the New York State Office of

Science, Technology and Academic Research (NYSTAR) to develop implantable medical sensors (Mechanical Engineering-CIME 2006).

Some government agencies attempt to stimulate potential applications via, not only funds, but also instructions and statements of needs. Emerging applications, to date, center in the medical and public health sectors. Meanwhile, the proven abilities of nanobiosensors to detect biological agents show great prospects in potential applications such as fighting against terrorism and bio-defense. For example, the US Department of Homeland Security's Advanced Research Project Agency (HSARPA) has presented ambitious needs for next-generation systems for detecting potential biological and chemical attacks. HSARPA has organized some companies, research institutes, and universities to help to achieve these aims (Bogue 2005).

In addition to the funding role, governments also play important regulatory roles for emerging applications. Since nanobiosensor applications relate strongly to the markets of medical, food, and health interests, relevant regulatory agencies are involved in the guidance of the product development These agencies include CDC (Center for Disease Control and Prevention), FDA (Food and Drug Administration), and USDA(U.S. Department of Agriculture). For example, the benefits of nanobiosensors that may revolutionize cancer diagnosis and therapy cannot be fully realized without safety and clinical efficacy testing, and compliance with regulations. In particular, the elaborate requirements for FDA approval prior to the entry of drugs and medical devices into the marketplace pose a critical consideration for would-be innovations.

- *R&D Groups*

R&D Groups are the most significant contributor during the early developmental periods of most technologies. Nanomaterial-enhanced biosensors -- representing the integration of material sciences, molecular engineering, chemistry, biotechnology, and electrical engineering – present a highly multidisciplinary research picture. This necessarily involves diverse research groups in various universities and institutes. Research advances in biotechnology, nanotechnology, and information processing provide exciting contributions to biosensor technology. Various nanomaterials are fabricated by new nanotechnology with unique physical, chemical, mechanical, electric, magnetic, and optical properties. These properties can be applied to biosensors to enhance the sensitivity and specificity of detection. Further investigations about the multidisciplinary characteristics of nanobiosensors will be presented in our case study in section 4.

In addition to the academic and non-profit/governmental research effort, some of the major biosensor companies are engaged in R&D programs. For example, Roche Diagnostics, the leading glucose biosensor manufacturer, is collaborating with the German Ludwig-Maximilians University on novel principles to detect molecular binding events based on coated gold nanoparticles and a technique termed "nanoparticle plasmon resonance" (Bogue 2004).

- *Manufacturers*

In the early stage of commercialization, start-up companies are playing important roles in nanobiosensor development. In the USA, many companies have obtained R&D funds from government agencies to produce biomedical devices and environmental monitor instruments. Many have raised significant venture finance as well (Bogue 2008). Furthermore, several of the world's large, high-technology companies are also pursuing nanobiosensor developments. For example, Motorola is actively involved with nanotechnology and nanobiosensor research. One of the important characteristics of these manufacturers is their strong links to universities. Unlike start-up & small companies, most of which are University spin-offs or are exploiting university research, large manufacturing companies are involved with nanotechnology within their research centers or through collaborations with universities. For example, a team of researchers from Arizona State University and Motorola Labs, the applied research arm of Motorola Inc., is developing a family of chemical sensors and biosensors based on single-walled CNTs, functionalized with various peptides (Bogue 2008).

Nanomaterial suppliers also contribute to the development. The process of enhancing existing product types with nanotechnology will inevitably gain momentum as a result of the ever-growing number of companies offering nanomaterials. Biosensor manufacturers lacking the resources to develop nanomaterials in-house can now purchase them from suppliers, such as the aptly named Nanomaterials Inc., along with literally dozens of others in the USA.

- *Users*

Biosensors have been developed for more than half century, but only in the last decade have commercial applications based on the new technologies become significantly available (Smith 2005). Till today, few biosensors based on nanomaterials are at work in commercial applications. Meanwhile, the emerging application markets for nanobiosensor technologies are shaping up in three dominant segments: healthcare, environment, and agriculture & food, with the healthcare markets overshadowing the others. At present, the applications of nanobiosensors in healthcare mainly include two parts: clinical diagnosis and medical treatment. Glucose biosensors, which can be considered as the most successful biosensors used in clinical diagnosis so far, account for about 85% of the entire biosensor market (Wang 2008). This is also the "killer application" in the nanobiosensor field. Most of these sensors were developed for the determination of glucose in blood. Only a very small portion of the medical biosensor market now represents determination of other compounds, such as urea, lactate, and cholesterol. In the future, on the one hand, nanobiosensors are projected to be more broadly applied and play important roles in emerging markets, such as cancer markers. They will also be involved in other potential markets as well – e.g., in the field of homeland security and defense, helping detect bioweapons and explosives.

Based on the foregoing TDS discussion, we summarize the future commercialization potential of nanobiosensors from the viewpoints of these four key players in Table 1.

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From Table 1, we find several stimulating factors: a heavily funded research base, strong financial support from government agencies, and the seemingly ready supply of venture finance, combined with a US business environment that fosters high risk technological innovation. Wide involvement of highly multidisciplinary research groups, strong research cooperation between R&D groups and manufacturers, and the ever-growing number of companies offering nanomaterials lead to a considerable amount of fascinating research. Those active researches can fuel innovative strategies for nanobiosensors with improved mechanical, electrochemical, electrical, optical, and magnetic functions. Furthermore, the presence of potential users also contributes to the rapidity and diversification of the development of nanobiosensor commercialization.

Like any emerging field, nanobiosensors also face many challenges. High standards for entering the market present big barriers. The higher regulatory barriers and funding requirements for medical applications are notable. Getting a medical sensor to the marketplace can take 5 years and cost $40 million (Smith 2005). A poorly capitalized sensor developer could go out of business before achieving commercialization. Because of this fact, we postulate that more resources for nanobiosensor companies may shift from the biochemical markets to environmental or other industrial markets. In addition, we notice that commercialization of most chemical sensor and biosensor technologies continues to lag behind research by several years. A major reason has always been the cost consideration and this includes the difficult integration of biosensors into easy-to-use systems.

Problems with nanomaterials also pose great challenges. As we have already seen from Figure 3, nanomaterials for biosensors should be fabricated according to the target structures and functions of the biological molecules. Therefore, general purpose nanomaterials are not apt to be most useful. Moreover, many nanomaterials, especially metals, are toxic, which sets up a barrier for the healthcare market, regardless of their novel properties. For example, gold nanoparticles are the most researched 0D nanomaterials; however, their application in clinical diagnostics is not extensive because of their toxicity. Large-scale production of needed nanomaterials remains an important barrier for nanobiosensors. As a result, the cost of producing nanobiosensors is still very high at present. An important aim of the healthcare market is to use disposable biosensors. Achieving high performance with low cost presents a critical challenge.

The next section explores one subset of this nanobiosensor technology in more depth.

4. Case Study: Nanoparticle-enhanced Biosensors Technology

So far, "0D" nanoparticles have been the most important nanomaterials researched and applied in biosensors (Luo et al. 2006; Zhang, Guo, and Cui 2009). The use of nanoparticles in the design of biosensors has been reviewed intensively. Because of their domination, we probe into Nanoparticle-enhanced Biosensors ("**NPEBs**") as our case study.

We are pursuing the approach of Figure 1 in further detail. Expert engagement is incorporated throughout, so no separate section is needed. The TDS presented in Figure 4 should generally hold here as well. Within the scope of this study, we do not explicitly pursue Multi-Path

Mapping. So this case analysis keys on R&D Profiling and Cross-charting to relate nanotechnologies to particular functional gains, and then to applications of possible importance.

4.1 PR) R&D Profile

In order to find out the development status of nanoparticle-based biosensors, a trend line based on the cumulative number of publications is shown in Figure 5. The datasets used in this bibliometric study come from global nanotechnology publications for the time period 2001 through 2008(part year) extracted from different databases: Science Citation Index (**"SCI"**), INSPEC, EI Compendex, and Factiva. The SCI dataset of publications here is developed using the definition of nanotechnology and the data-cleaning methods described by Porter et al. (2008). Our basic nano search locates abstract records containing "nano*" or any of 7 modular term sets. Within the resulting dataset (of some 500,000 publication abstracts), we then search for those specifically discussing "biosensors," and "nanoparticles." We search on specific biosensor categories (such as glucose, electrochemical and optical), and variants of nanoparticles (such as Ag, Au, Pt, Cds, MnO_2, and SiO_2). Using this approach, 1400 publication records were drawn from SCI. At the same time, we also set up two other datasets drawn from the INSPEC & EI Compendex databases combined, with 1715 records, and from Factiva, with 489 records.

The overall trend of publication counts keeps increasing, which shows that nanoparticles have played a more and more important role in the research and application of biosensors in recent years.

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Examining these three growth curves, we find that 2004 is the key time point for both the SCI and INSPEC & Compendex data series, because the basic research (SCI) and the more applied research (INSPEC/Compendex) on nanoparticle-based biosensors accelerated into a steeper rate of growth at that time. In comparison, the publication counts of Factiva, reflecting broader business and general public attention, started to increase more steeply in 2007. This suggests that the popular business application of nanoparticles in biosensors lags basic and applied research by about three years. The investigation of the nanomaterial-enhanced biosensors TDS also indicates that commercialization is rather limited in comparison with the level of research activity.

R&D policy considerations also interest us in national level comparisons. As an emergent field, there has been much interest by the leading countries in research on nanoparticle-based biosensors. Our research (2009) showed that the US and China are the top two countries, both in publications and citations. In addition, Israel, Italy, and Japan are also leading countries in nanoparticle-biosensor research, with fewer publications but high citations representing high impact.

As mentioned in the TDS analysis in section 3, the R&D groups in nanomaterial biosensors are highly multidisciplinary. Here, we look into one leading country in the nanoparticle biosensor field--the USA to investigate its R&D activities emerging application.

Table 2 lists the top 15 research organizations in the USA for its research publications in NPEBs from our SCI dataset. Apparently, universities have the most shares in the research with Northwestern University overshadowing the others. In addition, the table also reveals the research focus of each organization (based on prevalent key terms) and the latest status of their research (% of publications since 2006).

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Table 2 about here

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For this emerging application, monitoring the research initiatives from these leading countries and top organizations provide important competitive technical intelligence.

Visualizations of the research fields can help us gain perspective on the activity. We have been developing a "science overlay mapping" approach to locate particular research sets on a base science map (Leydesdorff and Rafols, forthcoming; Rafols and Meyer, forthcoming). This approach uses the Subject Categories that Web of Science assigns to journals. So, for a set of publications indexed by Web of Science (in this case, by SCI, which is part of Web of Science), we locate that research by the journals in which it appears. Figure 6 does that for subsets of the "nanoparticles and biosensors" research papers, which are based on the SCI dataset for 2006 through part-year 2008 in order to focus on the emergent characters of the three recent years in the USA. The base map reflects the 175 Subject Categories shown by the background intersecting arcs. The Subject Categories are then grouped into "macro-disciplines" using a form of factor analysis (Principal Components Analysis) based on the degree of co-citation of the Subject Categories in a large sample of articles indexed by Web of Science (Porter and Rafols, forthcoming). These macro-disciplines become the labels in the figure. The "nanoparticles in biosensors" research concentrations appear as nodes on this map. Figure 6 illustrates that nanoparticles in biosensors research in the USA involve a very extensive range of research fields. It is concentrated in the Materials Science and Chemistry macro-disciplines, also involving a number of Biomedical Sciences. In comparison, Chinese research in NPEBs, is heavily Chemistry oriented; American articles are considerably more apt to entail Physics sub-areas (Huang, Guo, and Porter 2009).

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4.2 CC) R&D to Application Cross-chart

In the higher level cross-chart (Figure 3), we have summarized relationships among different kinds of nanomaterials, functions, and applications. Here, we probe at a deeper level to find out what kind of *nanoparticle* properties can contribute to specific biosensor advantages. This will contribute to further innovation path mapping.

By reviewing recent studies, we find that many kinds of nanoparticles have been widely used in biosensors. A major attraction of all nanoparticles in a biosensor context is the potentially high sensitivities that arise from the large number of sites available for molecular interactions due to the high surface to volume ratio (Kim et al. 2004). Another common advantage in nanoparticle-based biosensors is the improved accuracy and stability in using nanoparticles as the solid support or carrier of biological components, such as proteins and DNA. This result benefits from the small physical size of nanoparticles, which minimizes the conformational and activity change of the biological components (Lynch et al. 2007).

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Figure 7 shows detailed ties from the most frequently researched nanoparticles to their unique properties, and to corresponding advantages in biosensor applications. Here, we divide nanoparticles into four families -- polymer nanoparticles, metal nanoparticles, oxide nanoparticles, and semiconductor nanoparticles. All these nanoparticles can be used in biosensors, as long as the particle surface is modified with specific functional group coatings. Since different families of nanoparticles, and sometimes nanoparticles of the same family, can play different roles in biosensor systems, we attempt to summarize the most representative properties taken on by different nanoparticles either in a group or individually. Figure 7 reveals the extremely promising prospects of nanoparticles in designing improved and new biosensors by using their unique chemical and physical properties. For example, biosensors with enhanced sensitivity and selectivity have been developed by making use of the exceptional catalytic effect of Pt and Au nanoparticles (Luo et al., 2006). Furthermore, biosensors capable of simultaneous detection of multiple cancer markers were enabled by the high quantum yield and enhanced photostability of semiconductor nanoparticles such as CdS and CdSe quantum dots (Medintz et al., 2005). We mention that polystyrene nanoparticles offer promising biocompatibility -- i.e., non-toxicity without further surface modification. Therefore, we expect the polymer family of nanoparticles to play an important role in future NPEBs market.

An important trend in NPEB development is using composite nanoparticles with combined properties of polymer, semiconductor, metal, and oxide nanoparticles for multifunctional and more advanced applications. Composite nanoparticles are mainly in the form of core-shell structure. Heavily researched ones include silver-polystyrene particles (Wu et al., 2003), and magnetite-dextran particles (Pankhurst et al., 2003), etc.

4.3 TDS) Technology Delivery System

Despite sharing similar characteristics with the general nanomaterial-enhanced biosensors such as multidisciplinary R&D and strong collaboration between manufacturers and R&D groups, the TDS of NPEBs entails some special considerations. As discussed before, nanoparticles are mainly employed in the bio recognition component part of a biosensor. In most cases, they are suspended in a solvent and act as a mobile biorecognition component without tight attachment to the transducer of the biosensor (see Figure 2). That is, nanoparticle-based biosensors are not standalone devices in general (Peng et al. 2009). As a result, the development of NPEBs is usually separated into two different segments: one focuses on nanoparticle development; the other, on nanoparticle-based biosensor development. Therefore, the manufacturers of NPEBs are required to build even stronger cooperation among R&D groups and nanoparticle suppliers than that of other nanomaterial-enhanced biosensors that are standalone devices or instruments. Future commercialization of NPEBs calls for compatible standards among different market segments as the market develops. Government regulations can play important roles in this aspect.

Another consideration that is particular to the NPEBs is the potential health risks associated with the manufacture and use of such products. These possibilities may arise because free nanoparticles are easily generated and can become aerosols during the manufacturing and handling of NPEBs. Of special concern would be those individuals who are in regular and sustained exposure to free nanoparticles. The exposure to nanoparticles having charactertistics not previously encountered may challenge normal defense mechanisms, such as inflammatory systems (Tsuji et al., 2005). Environmental impact of these free nanoparticles is also problematic. Therefore, extensive studies by NPEB R&D groups on detoxification of nanoparticles and effective measures from regulatory agencies on NPEB manufacturers are needed to foster the potential for effective commercialization.

5. Discussion and Future Prospective

The TDS framework allows us to understand the characteristics of a technology at the "emerging applications stage." We profile the research status and development trends for nano-enhanced biosensors in leading countries and organizations. From Figure 6, we see a strongly multidisciplinary research profile. The "Cross-charting" (Figure 3) relates particular nano materials, to their respective functional gains, linking those to biosensor types and, thence, to possible applications. A second cross-chart (Figure 7) "zooms in" on the potential value-added from four types of nanoparticles, a subset of nanomaterials. The nanomaterials-biosensors TDS identifies a number of enterprise attributes and vital players contributing to potential commercial innovations. Essential in composing these system characterizations are discussions with several colleagues in nano/biotechnology fields. We believe this approach has value in understanding emerging science & technology topics beyond this particular case.

We intend to extend this socio-technical system modelling for nano-enhanced biosensors to explore likely innovation pathways (Merkerk, 2006). For instance, a "technology push" would investigate how electrochemical nanobiosensors utilizing single carbon nanotube (Pumera et al., 2007) might develop into practical applications. Will such technical capabilities advance via a general platform or toward specific, targeted applications? Conversely, a "needs pull" for early disease detection could prompt exploration of how various nanobiosensors could fulfil this need. For example, will nanowire-based biosensor be poised for low concentration detection of target cancer markers? (Berger 2006). As our formulation of the TDS and prospective innovation pathways advances, we would bring to bear further FTA methods to help inform our understanding of the maturation processes of the target science and technology, and likely commercial applications.

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FIGURES

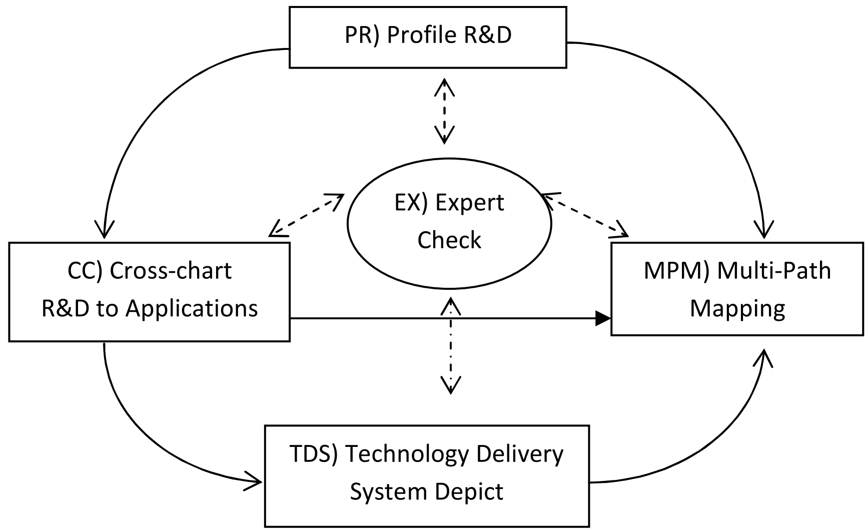

Figure 1 Research Framework

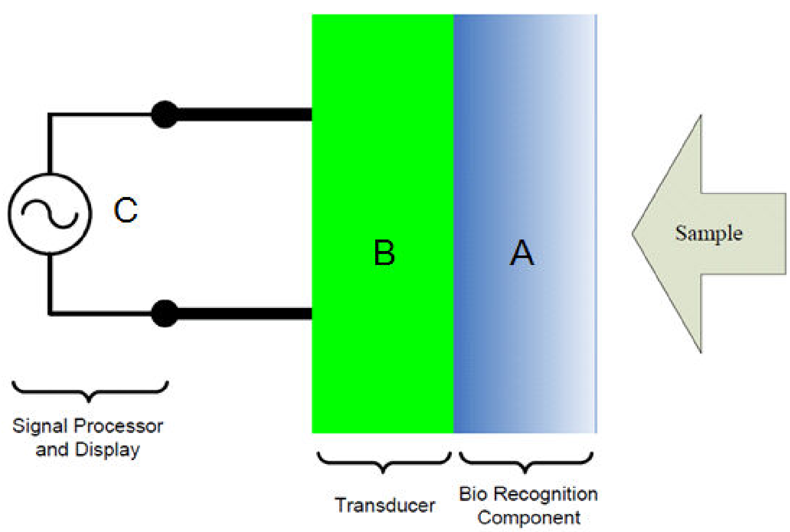

Figure 2 Schematics of a Biosensor

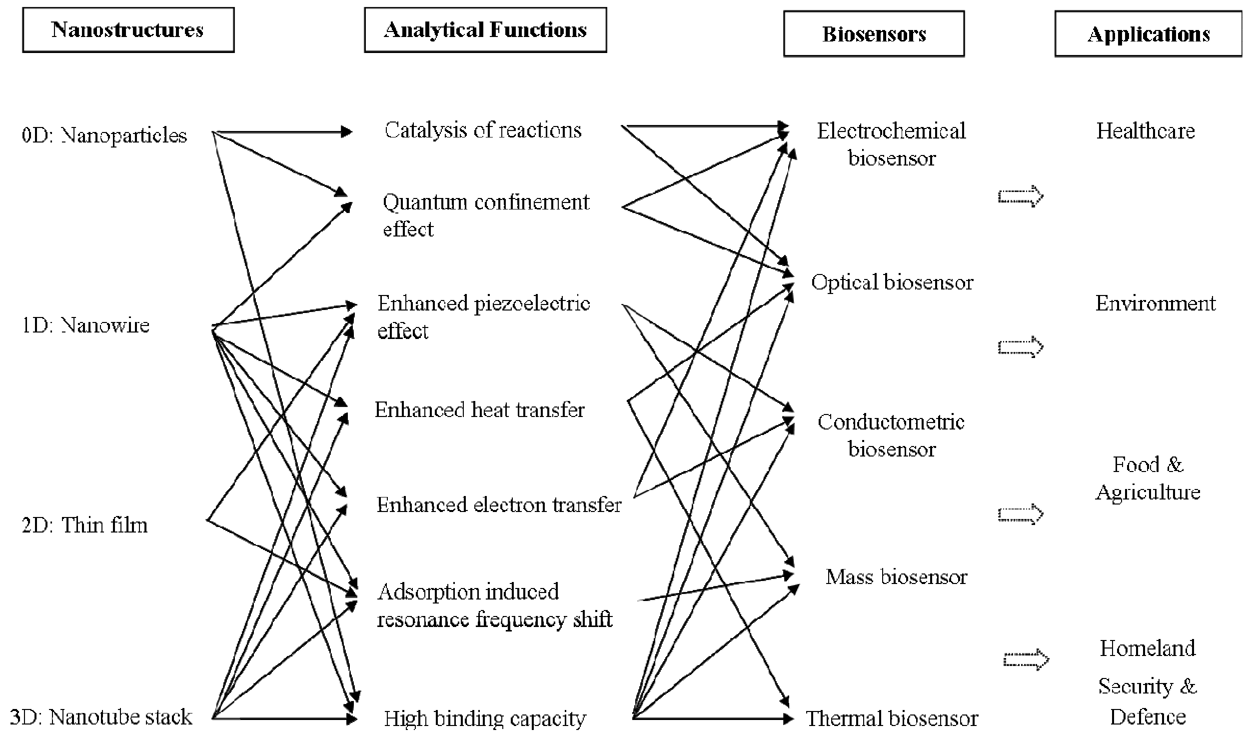

Figure 3. General Nano-biosensor Technology – Application Cross-chart

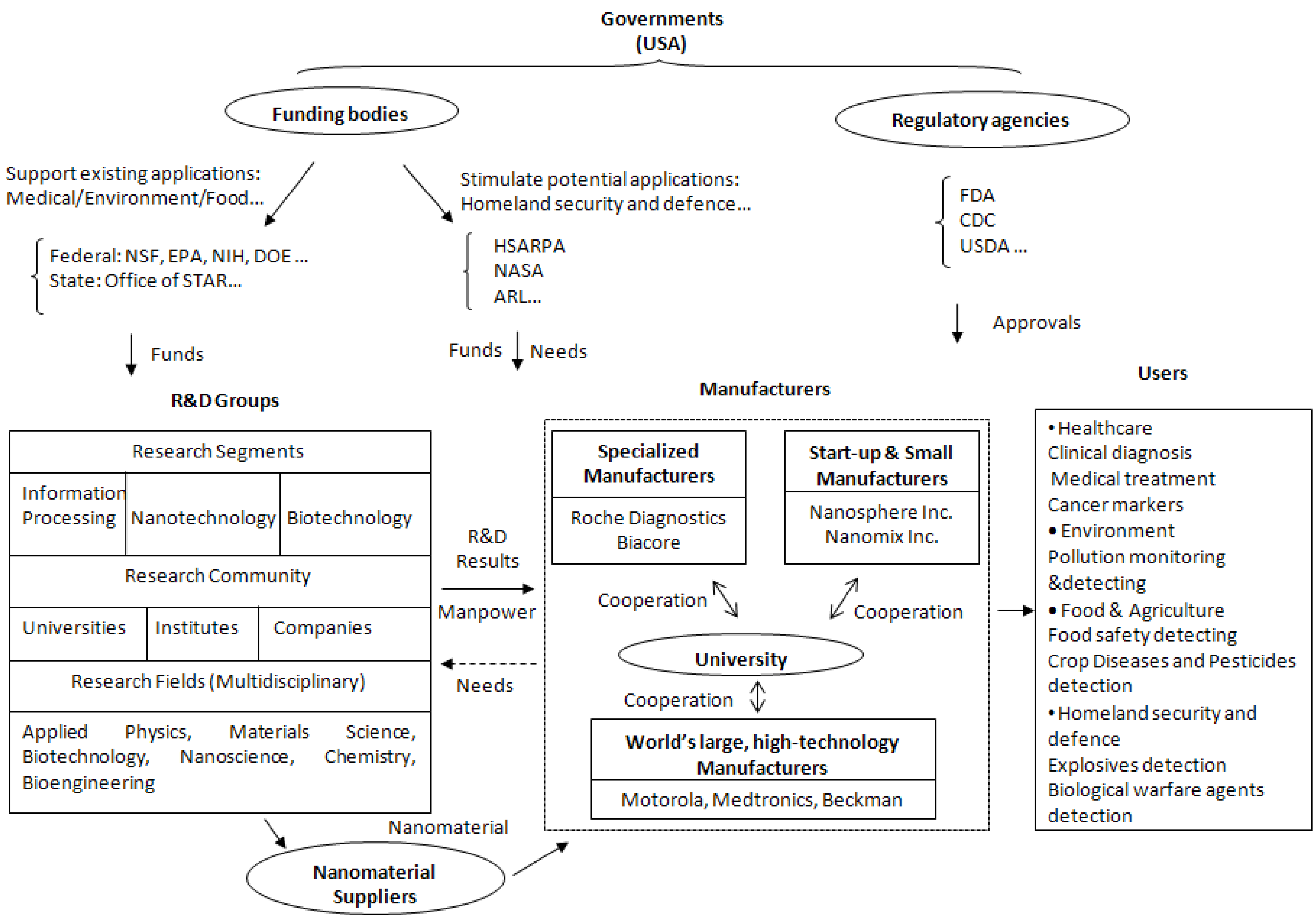

Figure 4 Technology Delivery System Schematic

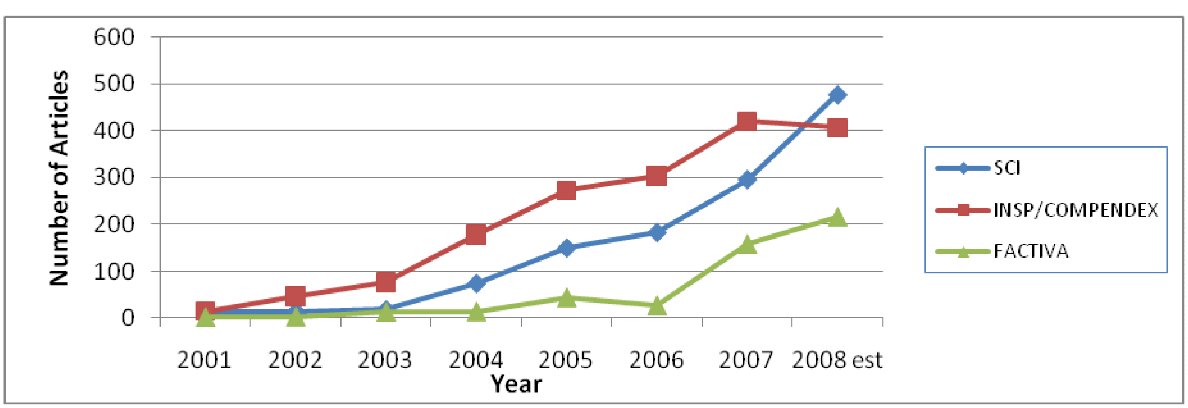

Figure 5 Cumulative Publications of Nanoparticle Applications in Biosensor by Database

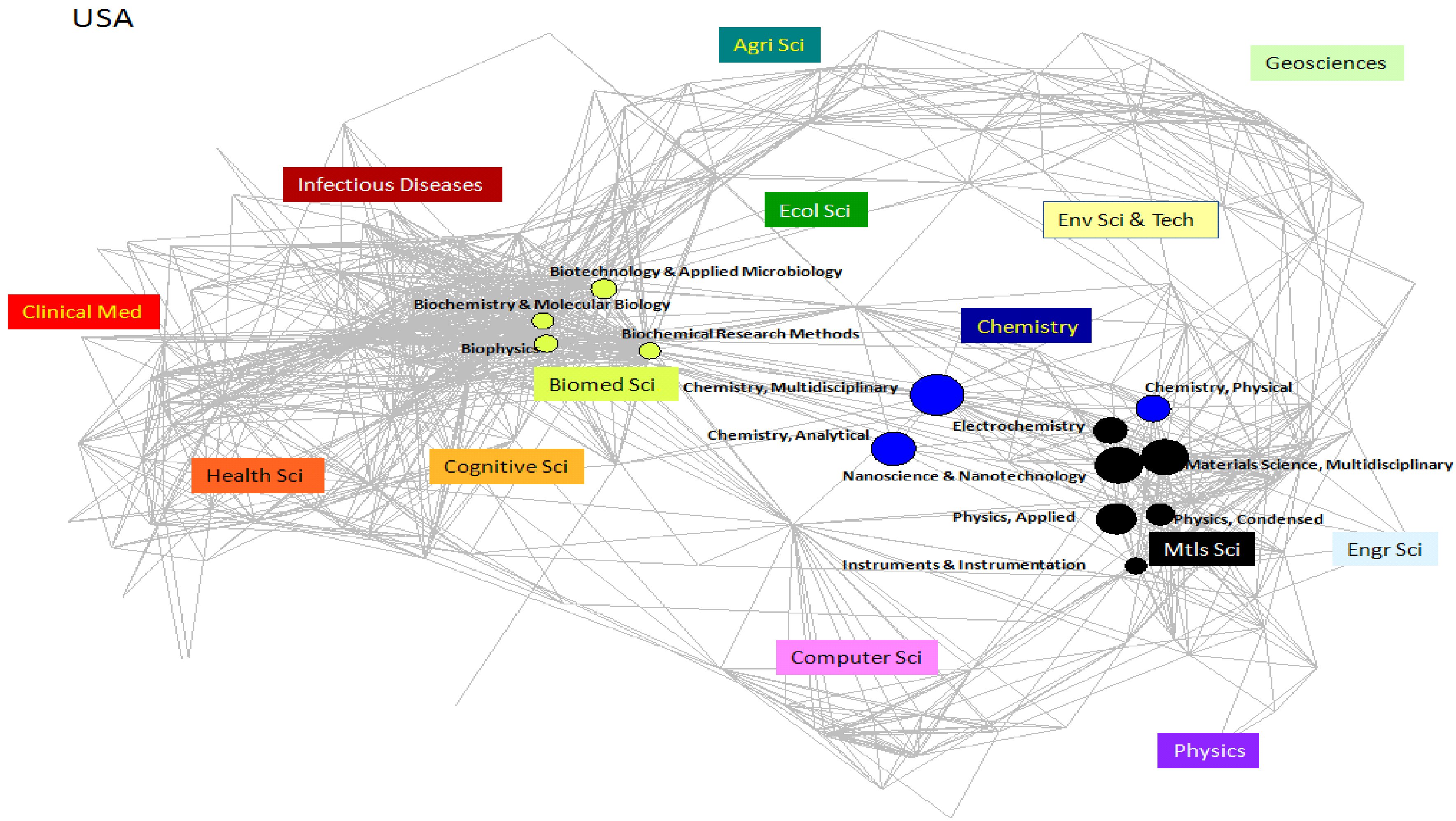

Figure 6 Locating US "Nanoparticles in Biosensors" Research over a Base Map of Science

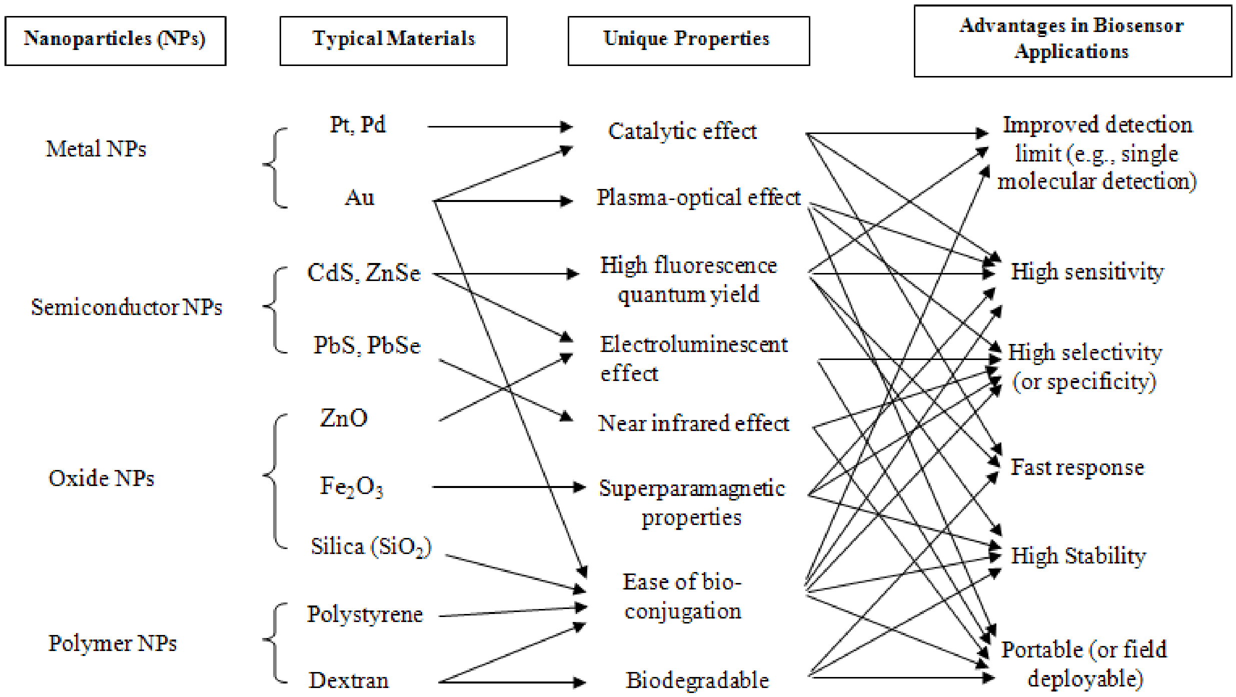

Figure 7 Technology – Application Cross-chart for NPEBs

TABLES:

Table 1 Key Players' Roles in the Development of Nanomaterial-enhanced Biosensors

	Supports	Barriers
Governments	• Strong financial support	• High regulatory barriers
R&D groups	• Steep increase in literatures • Multidisciplinary cooperation • Strong cooperation with manufacturers	• Far away from commercialization • Lack of good integration of biosensor into easy-to-use systems
Manufacturers	• Promising market prospects • Strong cooperation with universities • Ever-growing number of companies offering nanomaterials	• Separate market segments • High standards of door-step to markets • High cost with needed performance • Scaling up manufacture of nanomaterials
Users	• Plenty of needs • Plenty of potential users	• Needs beyond present ability • Safety • Use friendly

Table 2 Profiling the Top 15 R&D Organizations in USA

Affiliation	**Key Terms**	**# Records**
	Top 3 Items	% since 2006
Northwestern Univ	Nanoscale optical biosensor [29] Nanosphere lithography [28] Nobel-matal nanoparticles [15]	39% of 41
Univ Illinois	Gold nanoparticle [10] Biosensor [8] Polynucleotides [6]	56% of 16
Arizona State Univ	Biosensor [9] Nanoparticle [7] Label [4]	62% of 13
Pacific NW Natl Lab	Biosensor [6] Supercritical fluid [4] Clay nanoparticles [3]	64% of 11
Georgia Inst Techno	Biosensor [5] Gold nanoparticle [4] Nanoscale optical biosensor [3]	71% of 7
Univ Texas	Biosensor [4] Nanoparticle [2] Quantum dot [2]	50% of 6
Duke Univ	Silver nanoparticle [2] Nanoscale optical biosensor [2] Nanosphere lithography [2]	50% of 6
Clarkson Univ	Gold nanoparticle [3] Biosensor [3] Glucose oxidase [2]	100% of 6
Stanford Univ	Biosensor [5] Spin-valve sensors [3] Magnetic nanoparticle [3]	67% of 6
Argonne Natl Lab	Nanoscale optical biosensor [3] Silver nanoparticle [2] Magnetic nanoparticle [2]	60% of 5
Brown Univ	Magnetic nanoparticle [3] Metallized peptide [2] Redox enzyme [2]	80% of 5
New Mexico State Univ	Biosensor [5] DNA hybridization [4] Label [2]	0% of 5
Purdue Univ	Biosensor [4]	80% of 5
Penn State Univ	Nanoparticle [2] Enhanced fluorescence [2] Biosensor [2]	80% of 5
Univ Rochester	Biosensor [4] Nanoparticle [3] Molecular beacon [3]	20% of 5