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

lu huang
ying guo
zhengchun peng
alan l porter
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LU HUANG* 1, YING GUO*, ZHENGCHUN PENG ** & ALAN L. PORTER***

*School of Management and Economics, Beijing Institute of Technology, Beijing, China
** Institute for Bioengineering and Bioscience, Georgia Institute of Technology, Atlanta, USA
School of Mechanical Engineering, Georgia Institute of Technology, Atlanta, USA
***Technology Policy and Assessment Center, Georgia Institute of Technology, Atlanta, USA and Search Technology, Inc.

ABSTRACT
We devise Future-oriented Technology Analyses tools to investigate a technology at an interesting development stage of early emerging applications. At this stage, technologies show great potential with little established commercialization. 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 of those. Results convey the importance of considering technological and social context factors together 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) with incrementally changing applications are more amenable to trend analyses and growth modeling

1 Corresponding Author: Lu Huang. Email: lhuang127@gmail.com.
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 (“nanobiosensors” for short) – is also of inherent interest for its highly multidisciplinary R&D (Porter and Youtie 2009) 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 nanobiosensors. We attempt to figure out the “system” 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 [see Acknowledgements]. 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 recent studies, we find a steep increase in the literature on
nanobiosensors (Huang, Guo, and Porter 2009), with a variety of nanomaterials being used. Observers foresee bright prospects for nanobiosensors (Kerman et al. 2008).

Given the promising prospects for 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”) (Wenk and Kuehn 1977). A policy interest is to understand global roles, so we compare and track much interests by a number of countries. Shifting to a private sector technology management perspective, we strive to identify key actors and their roles. To anticipate the development pathways for nanobiosensors, it is essential to explore potential supports and barriers in the environment. This information could aid policymakers foster development. We aim to build a contextually rich picture of nanobiosensors, 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 visualization tools.

Section 2, next, presents our conceptual framework. Section 3 describes nanomaterial-enhanced biosensor technology, then documents its development status and interactions among important actors. Because the commercialization of true nanobiosensors is largely being driven by US companies (Bogue 2008), this section focuses on the US TDS. Section 4 offers a case study of nanoparticle-enhanced biosensors. Lastly, Section 5 discusses insights gained from our research.

2. Conceptual Framework and Approach

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

For technologies with well-developed applications, one can compile information on the influential policies, knowledge transfer networks, and market ties. On the other hand, for technologies lacking significant applications, one relies upon expert opinion to identify those. Given the uncertainty of technologies with barely emerging applications, we invest special effort to understand the infrastructure and dynamics along the “stream” from R&D toward innovation.

Facing such special conditions, we 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**

Nanobiosensors show 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. 2006; Porter and Cunningham 2005).

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.

Expert guidance proved critical throughout this study. We read overview papers, did initial database searches, and identified local researchers, based on bibliometrics and collegial contacts. E-mail was used to enlist cooperation. One-on-one meetings with researchers and professors on campus proved valuable to orient ourselves, and the experts, and to decide how best to proceed. Initial interactions (~four months) helped us understand nanobiosensor types and how nanomaterials might enhance functionality. This occasioned refined database searching for particular nanomaterials [e.g., nanoparticles, carbon nanotubes (“CNTs”), nanowires].

In our second round, we asked our technical colleagues to review our analytical methods and explored who might want to co-author with us. Zhengchun Peng accepted and immediately helped formulate the TDS and complete the cross-charting.

The third expert round entailed a campus workshop (~10 participants including ~5 with particular knowledge in nanomaterials, biomolecular engineering, and biosensing). This focused on mapping likely innovation pathways, following Robinson and Propp (2008). We then called upon our experts again to review our interpretations from the workshop. In the future, we should
engage persons knowledgeable in broader innovation aspects, including production, regulation, marketing, and use.

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 of 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) Depicting the Technology Delivery System

Technology and society are interrelated, and both are changing rapidly. The development and dissemination of technology affects society. On the other hand, societal forces influence technological change. We must understand these interrelationships to forecast and manage technology effectively (Porter et al. 1991, 22).


In our paper, the concept of “technology delivery system” ("TDS") recognizes the inherent uncertainties of “innovation pathways.” The TDS approach is akin to the system representations noted, but especially suitable for “emerging” technologies by distinguishing: 1) the enterprise to develop the innovation and take it to market, and 2) the key contextual factors affecting the
success of that innovation process (Guo et al. under review). Ezra (1975) offered a TDS to help explain why solar energy innovation in residential housing applications was not notably successful. Our TDS considers enterprise elements needed to effect innovation, and it points out influential factors in the immediate nanobiosensor environment. We seek key leverage points at which the innovation pathways can be strongly influenced.

2.5. MPM) Multi-path Mapping

Some tools (such as roadmapping) can be used to serve both short and long term alignment of science and technology (“S&T”) developments and new product development. However, for technologies with “emerging” applications, conventional tools don’t seem well-suited because the likely products are not articulated yet. Mapping “innovation pathways” based on underlying patterns and indicators of the dynamics of emergence (Robinson and Propp 2008) seems promising. Alternative futures structured in terms of prospective innovation chains and potential commercialization paradigms can inform strategic choices.

In this paper, we mainly address the first four components of our analytical framework. We are pursuing innovation pathway mapping, but need to analyze alternatives, with our experts, to assess their prospects.

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

3.1. Introduction of biosensor and nanomaterial

A biosensor 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 (Figure 2):
A. The biological recognition element can be a natural biological material (e.g. tissues, cells, or various biomolecules), a biologically derived material, or a biomimetic material.

B. The transducer 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 are primarily responsible for the display of the results in a user-friendly way.

Nanomaterials have morphological features smaller than one hundred nanometers in at least one dimension. A wide variety of nanomaterials with special and novel properties can be fabricated. Nanomaterials applied in biosensors may be divided into four categories:

0D: Zero-dimensional structures, including nanoparticles
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.

Figure 3 about here

Nanomaterials can contribute in either the biorecognition element or the transducer, or both. The functions of nanomaterials used in biorecognition elements can be divided into two classes. The first is “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 contact agents (Weissleder et al. 1990). The second class used in biorecognition elements mainly supplant traditional molecular recognition layers. This replacement takes advantage of not only the catalytic function of nanomaterials (Daniel and Astruc 2004), but also the high surface areas with large number of binding sites for molecular interactions (Verpoorte 2004).

Because of size effects and enhanced properties, using nanomaterials to replace traditional transduction elements usually improves transducer performance. In addition, new transduction mechanisms, such as ballistic field-effect transistors, 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.

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;
- Gold thin films in 2D nanomaterials;
• 3D Carbon Nanotube stacks

Nanobiosensors show remarkable advantages in accuracy, detection limits, sensitivity, selectivity, temporal response, and reproducibility. We investigate linkages between nano-enabled properties and resultant value added in a case study in the next section. We explore the relevant linkages to help forecast applications. We identify four key application areas -- healthcare, environment, food/agriculture, and homeland security/defense. We next consider institutional factors via 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. Figure 4 displays a limited sociotechnical system composed of institutions directly or indirectly involved in developing nanobiosensor technology. We consider 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. At present, their most important role is funding nanobiosensor R&D. A great number of R&D grants are being provided. 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); Department of Defense (DOD); Department of Homeland Security (DHS); Environmental Protection Agency (EPA); Department of Energy (DOE); and National Institutes of Health (NIH) (Roco 2003).

Big funders now are DOD and DHS, which implies emphasis on early applications in detection for security. Notably, those don’t confront Food & Drug Administration (FDA) regulations. These agencies may provide a market as well -- i.e., government purchasing can provide an essential early market. State agencies also contribute to R&D support with relatively smaller shares, but with important emphasis upon commercialization.

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 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 for anti-terrorism and bio-defense. For example, the DHS 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 achieve these aims (Bogue 2005).

In addition to funding, governments regulate 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 the Centers for Disease Control and Prevention (CDC), FDA, and U.S. Department of Agriculture (USDA). For example, nanobiosensors may revolutionize cancer diagnosis and therapy, but those can’t be realized without safety and clinical efficacy testing, and compliance with regulations. In particular, the elaborate FDA approval process prior to marketing of drugs and medical devices pose a critical consideration for would-be innovators.

- **R&D Groups**

R&D Groups are the most significant contributor during the early developmental periods of most emerging technologies. Nanobiosensors -- 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 with unique physical, chemical, mechanical, electric, magnetic, and optical properties. These properties can enhance the sensitivity and specificity of detection. Further investigations about the multidisciplinary characteristics of nanobiosensors will be presented in Section 4.

In addition to academic and non-profit/governmental research efforts, some 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**

Start-up companies are playing important roles in nanobiosensor development. In the USA, many companies have obtained R&D funds from government agencies to devise biomedical devices and environmental monitor instruments. Many have raised significant venture capital (Bogue 2008). Furthermore, several of the world’s large, high-technology companies are pursuing nanobiosensor developments (e.g., Motorola). 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, is developing a family of sensors based on single-walled CNTs, functionalized with various peptides (Bogue 2008).

Nanomaterial suppliers also contribute to 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. There are more suppliers for CNTs than for nanoparticles. Some research uses novel nanomaterials that are not generally available.
**Users**

Biosensors have been developed for more than a half-century, but only in the last decade have commercial applications based on **nano properties** become significantly available (Smith 2005). Until today, few nanobiosensors are at work in commercial applications. The emerging markets for nanobiosensors are shaping up in three dominant segments: healthcare, environment, and agriculture & food, with healthcare overshadowing the others. Healthcare applications split into two parts: clinical diagnosis and medical treatment. Glucose biosensors -- the most successful diagnostics so far -- account for ~85% of the entire biosensor market (Wang 2008). This is the “killer ap” for nanobiosensors. Only a very small portion of the diagnostics market now represents determination of other compounds, such as urea, lactate, and cholesterol. In the future, 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 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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Table 1 about here

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Table 1 shows several stimulants, including a heavily funded research base and the seemingly ready supply of venture capital. These combine with a US business environment that fosters high risk technological innovation. Wide involvement of highly multidisciplinary research groups, **cooperation between academics/non-profits and manufacturers**, and the growing number of companies offering nanomaterials facilitate innovation. These **forces point** toward nanobiosensors with improved mechanical, electrochemical, electrical, optical, and magnetic
functions. The presence of willing governmental purchasers (DOD/DHS) and medical consumers supports rapid nanobiosensor innovation.

Like any emerging field, nanobiosensors also face challenges. High standards for entering the market present big barriers. 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, we postulate that more resources for nanobiosensor companies may shift from the biomedical markets to environmental or other industrial markets. In addition, we note that commercialization of most chemical and biosensor technologies continues to lag research by several years. Besides cost, integration of biosensors into easy-to-use systems is difficult.

Problems with nanomaterials also pose challenges. As per Figure 3, nanomaterials for biosensors should be fabricated according to the target structures and functions of the biological molecules. Therefore, general purpose nanomaterials may be unsuitable. 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 remains quite high, which impedes the healthcare market aim of disposable biosensors.

3.4. MPM) Multi-path Mapping

Based on these analyses and inputs from our workshop, we offer two main innovation approaches. Here we refer to the two approaches as MPM-1 and MPM-2.
MPM-1 is based on the roles of nanomaterials in biosensors. Two different innovation pathways identified are:

Path 1: Enhancing biorecognition/bioconjugation using nanomaterials in biosensors. In general, this path uses nanomaterials passively. That is, use focuses on surface properties such as surface to volume ratio, surface affinity, and selectivity to biomolecules and cells.

Path 2: Enhancing signal transduction or creating new transduction mechanisms using nanomaterials in biosensors. In general, this pathway seeks to actively use nanomaterials. The use of nanomaterials here focuses on their unique functions, such as quantum effects, piezoelectric effect, etc.

MPM-2 is based on differences in the sensing target. Here, we identify three different innovation pathways taking advantage of nanomaterial enhancements:

Path 1: cell-based sensing

Path 2: sensing macromolecules, such as proteins and DNA

Path 3: sensing small chemical molecules such as Fe, O2, etc.

The 1st of these focuses on sensing the behaviors of whole cells without knowing detailed information about the sub-cellular substance. The 2nd path senses by probing the information of biomolecular interactions either on the cell membranes or inside the cell bodies. The 3rd path emphasizes the presence and concentration level of biologically relevant chemical substances.

All these three innovation pathways may use nanomaterials either passively or actively.

We are still working on the MPM now. Such innovation mapping should address specific key nanomaterials or nanotechnologies, and the particular obstacles, along every path.

The next section explores one subset of this nanobiosensor technology further.
4. Case Study: Nanoparticle-enhanced Biosensor Technology

So far, “0D” nanoparticles have been the most important nanomaterials researched and applied in biosensors (Luo et al. 2006). 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 presented. The TDS presented in Figure 4 should generally hold here as well. Within the scope of this paper, we do not explicitly pursue Multi-Path Mapping. So this case analysis keys on R&D Profiling and Cross-charting to relate nanoparticles to particular functional gains, and then to NPEB applications of possible importance.

4.1 PR) R&D Profile

Figure 5 presents the NPEB trend based on annual research publications. The datasets used in this bibliometric study come from global nanotechnology publications for the time period, 2001 through 2008(part year), extracted from: Science Citation Index (“SCI”), INSPEC, EI Compendex, and Factiva. The SCI set derives from 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, MnO₂, and SiO₂). 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 play an important role in the research and application of biosensors in recent years.

Examining these three growth curves, we find that the basic (SCI) and the more applied (engineering oriented) NPEB research (INSPEC/Compendex) accelerated into a steeper rate of growth ~2004. In comparison, the publication counts of Factiva, reflecting broader business and general public attention, start 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 still rather limited in comparison with the level of research activity.

R&D policy considerations also prompt national level comparisons. As an emergent field, there has been much interest by the leading countries in NPEB research. Our research (Huang, Guo, and Porter 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, suggesting high impact.

As mentioned 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 and emerging applications.

Table 2 lists the top five research organizations in the USA for NPEB research publications (SCI). Universities dominate (of the top 15 two are national labs; the rest, universities); Northwestern University overshadows the others. The table also reveals the research focus of
each organization (based on prevalent key terms) and how much of their research is very recent (% of publications since 2006).

Table 2 about here

For this NEST, monitoring the research initiatives of the leading countries and top organizations provides important competitive technical intelligence. Tracking the emphases of the research leaders can help spot research frontiers.

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 (Rafols and Meyer 2009). 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, based on the SCI dataset for 2006 through part-year 2008 in order to focus on 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 NPEB research concentrations appear as nodes on this map. Figure 6 illustrates that this involves an 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 NPEBs 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 -- polymers, metals, oxide, and semiconductors. 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 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 platinum and gold 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 polymers to play an important role in future NPEBs.

An important trend in NPEB development is using composite nanoparticles to combine properties of polymers, semiconductors, metals, and oxides for multifunctional and more advanced applications. Composite nanoparticles are mainly in the form of core-shell structures. Heavily researched ones include silver-polystyrene particles (Wu et al. 2003) and magnetite-dextran particles (Pankhurst et al. 2003).

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 nanobiosensors that entail 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 particular to the NPEBs is the potential health risk 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 characteristics not previously encountered may challenge normal defense mechanisms, such as inflammatory systems (Tsuji et al., 2006). 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.

For the NPEB case, we focus on the first four steps (Figure 1). We plan to build from these analyses to generate overall nanobiosensor innovation pathways.
5. Discussion and Future Prospects

The TDS framework helps understand the characteristics of a technology at the "emerging applications stage." We profile the research status and development trends for nanobiosensors 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 nanobiosensors to improve already-explored likely innovation pathways. For instance, a "technology push" would investigate how electrochemical nanobiosensors utilizing single carbon nanotubes (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 fulfill this need. For example, will nanowire-based biosensors be poised for low concentration detection of target cancer markers (Berger 2006)? What are the obstacles and opportunities along each pathway based on our TDS analysis? We plan to assess the feasibility of those innovation pathways by comparing potentials and formal plans (Merkerk and Robinson 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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VantagePoint text mining software facilitated the data analyses and visualizations [www.theVantagePoint.com]; Pajek software [http://vlado.fmf.unilj.si/pub/networks/pajek/] is key in generating Figure 6.

References


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

<table>
<thead>
<tr>
<th></th>
<th>Supports</th>
<th>Barriers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Governments</td>
<td>• Strong financial support</td>
<td>• High regulatory barriers</td>
</tr>
<tr>
<td></td>
<td>• Steep increase in literatures</td>
<td>• Far away from commercialization</td>
</tr>
<tr>
<td></td>
<td>• Multidisciplinary cooperation</td>
<td>• Lack of good integration of biosensor into easy-to-use systems</td>
</tr>
<tr>
<td></td>
<td>• Strong cooperation with manufacturers</td>
<td></td>
</tr>
<tr>
<td>R&amp;D groups</td>
<td>• Promising market prospects</td>
<td>• Separate market segments</td>
</tr>
<tr>
<td></td>
<td>• Strong cooperation with universities</td>
<td>• High standards of door-step to markets</td>
</tr>
<tr>
<td></td>
<td>• Ever-growing number of companies offering nanomaterials</td>
<td>• High cost with needed performance</td>
</tr>
<tr>
<td>Manufacturers</td>
<td></td>
<td>• Scaling up manufacture of nanomaterials</td>
</tr>
<tr>
<td>Users</td>
<td>• Plenty of needs</td>
<td>• Needs beyond present ability</td>
</tr>
<tr>
<td></td>
<td>• Plenty of potential users</td>
<td>• Safety</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Use friendly</td>
</tr>
</tbody>
</table>
Table 2 Profiling the Top 5 R&D Organizations in USA

<table>
<thead>
<tr>
<th>Affiliation</th>
<th>Key Terms</th>
<th># Records</th>
</tr>
</thead>
<tbody>
<tr>
<td>Northwestern Univ</td>
<td>Nanoscale optical biosensor [29]</td>
<td>39% of 41</td>
</tr>
<tr>
<td></td>
<td>Nanosphere lithography [28]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nobel-metal nanoparticles [15]</td>
<td></td>
</tr>
<tr>
<td>Univ Illinois</td>
<td>Gold nanoparticle [10]</td>
<td>56% of 16</td>
</tr>
<tr>
<td></td>
<td>Biosensor [8]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Polynucleotides [6]</td>
<td></td>
</tr>
<tr>
<td>Arizona State Univ</td>
<td>Biosensor [9]</td>
<td>62% of 13</td>
</tr>
<tr>
<td></td>
<td>Nanoparticle [7]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Label [4]</td>
<td></td>
</tr>
<tr>
<td>Pacific NW Natl Lab</td>
<td>Biosensor [6]</td>
<td>64% of 11</td>
</tr>
<tr>
<td></td>
<td>Supercritical fluid [4]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clay nanoparticles [3]</td>
<td></td>
</tr>
<tr>
<td>Georgia Inst Techno</td>
<td>Biosensor [5]</td>
<td>71% of 7</td>
</tr>
<tr>
<td></td>
<td>Gold nanoparticle [4]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nanoscale optical biosensor [3]</td>
<td></td>
</tr>
</tbody>
</table>