Critical Reviews in Biotechnology, 2010; 30(2): 79–98

informa
healthcare

REVIEW ARTICLE

Innovation in biotechnology: moving from academic research to product development—the case of biosensors

Christina G. Siontorou, and Fragiskos A. Batzias

Department of Industrial Management and Technology, University of Piraeus, Karaoli & Dimitriou 80, Piraeus, Greece

Abstract

The fast pace of technological change in the biotechnology industry and the market demands require continuous innovation, which, owing to the science base of the sector, derives from academic research through a transformation process that converts science-oriented knowledge to marketable products. There appear to be some inherent difficulties in transforming directly the knowledge output of academic research to industrial use. The purpose of this article is to examine certain transition mechanisms from monodisciplinary academic isolation (curiosity-driven and internal-worth innovation) to university-industry alliances (market-driven and public-worth innovation) through inter-organizational multidisciplinary collaboration and contextualize the analysis with the case of biosensors. While the majority of literature on the subject studies the channels of knowledge transfer as determinants of alliance success (transferor/transferee interactions), either from the university side (science base) or the industry side (market base), this article focuses on the transferable (technology base) and how it can be strategically modeled and managed by the industry to promote innovation. Based on the valuable lessons learnt from the biosensor paradigm, the authors argue that strategic industry choices deal primarily with the best stage/point to intersect and seize the university output, implanting the required element of marketability that will transform an idea to a viable application. The authors present a methodological approach for accelerating the knowledge transfer from the university to industry aiming at the effective transition of science to products through a business model reconfiguration.

Keywords: *Biosensors; decision-making; knowledge acquisition; knowledge management; technology transfer*

Introduction

Biotechnology is a dynamic and diverse industry at the forefront of research and public interest for more than three decades. The distinctive features of this industry are: the strong relationship between innovation and competitiveness (Khilji, Mroczkowski, and Bernstein, 2006; Todt et al., 2007), the collaborative basis of research (Marot et al., 2005; Stuart, Ozdemir, and Ding, 2007; Breznitz, O'Shea, and Allen, 2008), and the importance of small firms (Mangematin et al., 2003; Costa, Fontes, and Heitor, 2004). Biotechnology highlights the importance of firms' capabilities, that is, the ability to mobilize and exploit new knowledge and to reach out and exploit collaboration among the diverse players in the field and across stages of product development, scientific disciplines, and industry frontiers. The sector is characterized by small specialized and dedicated firms, most of which are academic spin-offs that have entered the industry with the explicit aim of exploiting the new technologies of life sciences for different industrial purposes. These firms are having a remarkable and radical impact on pharmaceuticals, medical diagnostics, chemicals, and agriculture. As the biotechnology industry has become more geographically diverse (Thompson and Vonortas, 2005), companies have pursued more cross-border collaborations, whereas global competition in the sector has also increased as investors search for the best deals and most promising technologies, regardless of location.

Universities, research institutes, government agencies, nonprofit organizations, leading hospitals, start-up firms, and large corporations have played key roles in either conducting and/or funding research. Increasingly, complex research questions and widely dispersed expertise and resources have called for multidisciplinary and multi-institutional approaches as the needed skills and capabilities frequently are not housed in one organization. Evidently, collaboration between teams and between institutions has become necessary, and a complex web has proliferated in this field

Address for Correspondence: Christina G. Siontorou, Department of Industrial Management and Technology, University of Piraeus, Karaoli & Dimitriou 80, 18534 Piraeus, Greece. E-mail: csiontor@unipi.gr

(Accepted 20 August 2009)

ISSN 0738-8551 print/ISSN 1549-7801 online © 2010 Informa UK Ltd
DOI: 10.3109/07388550903427298

at multiple levels (multidisciplinary, multi-institutional, and multisectorial) during the recent decades (Powell, Koput, and Smith-Doerr, 1996; Levin, 2004). The science, the technology, the organizational routines, and the institutional and inter-institutional practices are co-evolving (Khilji, Mroczkowski, and Bernstein, 2006; Breznitz, O'Shea, and Allen, 2008). However, variation among organizations in their ability to access external knowledge—and in their skills, funding, and status—have stimulated the emergence of different profiles of partnerships (Marot et al., 2005; Stuart, Ozdemir, and Ding, 2007).

Collaboration has been undoubtedly the success factor in biopharmaceuticals and agrochemicals. Much of the existing literature in strategic alliances locates biotechnology firms upstream of large multinational pharmaceutical corporations: a biotechnology firm conducts research and development and transfers the output(s) to a pharmaceutical or life science company which then undertakes additional development and the marketing of any resulting product (Pisano, 1989; George, Zahra, and Wood, 2002; Reuer, Zollo, and Singh, 2002). Many biotechnology companies, especially small-medium enterprises (SMEs), maintain close links with universities, play the role of the intermediary in the transfer of knowledge from academia to industry (George, Zahra, and Wood, 2002; Khilji, Mroczkowski, and Bernstein, 2006; Stuart, Ozdemir, and Ding, 2007; Breznitz, O'Shea, and Allen, 2008). Although, direct migration of intellectual property from universities to large pharmaceutical corporations is not uncommon (e.g., see Faulkner and De Rond, 2000), the biotechnology companies usually identify and license science created in universities, and then further develop and ultimately transfer this intellectual property to larger firms that possess the resources to commercialize this technology (Stuart, Ozdemir, and Ding, 2007).

Other academic offsprings, however, as biosensors, have not been that successful in finding a place in the life sciences value chain. Despite the huge load of academic research, still persisting and blooming, only a handful of biosensors for environmental and industrial applications have left academia and became a commercial reality (Kissinger, 2005). Glucose meters exempted, biomedical devices, especially for *in vivo* applications, have been massively patented by large corporations as nascent technology opportunity but have never been launched. Some stalled due to the lengthy approval procedure but most have been neglected due to development issues. In fact, the *in vivo* performance of biosensors is so poor, that many companies have abandoned implantable devices all together and are focusing on *ex vivo* systems (Wisniewski, Moussy, and Reichert, 2000). Apparently, the transformation of university-derived knowledge to viable technology has not been effective, although the sector does neither lack collaborative networks of any kind or market opportunities for biosensor technology. In fact, this field has seen many consortia initiated in the public sector and/or developed primarily by scientists in academia (e.g., see Contractor and Lorange, 1988).

Due to the inherent difficulties in transforming directly knowledge output of academic research to industrial know-how, there is not an indiscrete formal mechanism for attaining this transformation. The purpose of this article is to examine certain transition mechanisms from monodisciplinary academic isolations (curiosity-driven and internal-worth innovation) to university-industry alliances (market-driven and public-worth innovation) through inter-organizational, multidisciplinary collaboration, and contextualize the analysis with the case of biosensors. While the majority of literature on the subject studies the channels of knowledge transfer as determinants of alliance success (transferor/transferee interactions), either from the university side (science base) or the industry side (market base), this article focuses on the transferable (technology base) and how it can be strategically modeled and managed by the industry to promote innovation. The work presented draws from the huge scientific and technical literature on the subject, as well as from patent searching and personal communication with both university researchers and industrial managers.

Based on the valuable lessons learnt from the biosensor paradigm, the authors argue that strategic industry choices deal primarily with the best stage/point to intersect and seize the university output, implanting the required element of marketability that will transform an idea to a viable application. Even when a technological breakthrough can be matched with a market opportunity and a promising prototype is produced by academia, consumer needs, production constraints, market conditions and regulatory issues call for further development and adjustment in order to present a product that the market will accept (Paladino, 2007). The authors present a methodological approach for accelerating this knowledge transfer from the university to industry aiming at the effective transition of science to products through a business model reconfiguration.

Why is this research important?

Biosensor research has suffered from a crisis of expectations that has gone on too long. Following the literature on the subject since the 1970s, the discussion of the enormous market benefits of this revolutionary technology is repeated over and over again in every relevant paper published, coming; however, from the scientists conducting the research and not from the market analysts. There, a paradox has been developed: the scientific bodies, sometimes supported by international and governmental agencies, set biosensors as priority (Rodriguez-Mozaz, Lopez de Alda, and Barceló, 2006), while industry is reluctant to apprehend the research output (Salter and Martin, 2001).

Seen from the science-base, biosensor technology is one of the very few scientific fields that resulted in enormous scientific advantages over the last 50 years, and it is probably the first field that engaged in multi-disciplinary collaborations in order to take advantage of a broad range of expertise. Notwithstanding the appealing scientific networks developed, evident from the numerous biosensor institutions

and societies, it seems that the biosensor work is performed because it can be done and not because it is needed; many of the technologies resulting have been funded by government grants to academic institutions where success is measured by publications rather than product development for the clinic or bedside, that is, there is only a subtle (if any) university-industry link, unable to provide academic research with an actual market perspective. Although the glucose meters are a fine example of commercial success, gaining rapid market penetration due to (a) serving a market need and (b) addressing a large market (Wang, 2001), this degree of success is unlikely to translate to other devices that are posted as alternatives to conventional instrumentation and address smaller markets.

In academic research, the economics of the device itself is less important than the ultimate use of the data to create added (scientific) value for knowledge improvement (Breznitz, O'Shea, and Allen, 2008). A significant fraction of biosensor technologies have been developed for biodefense, especially in United States, where cost is not a major issue, and also for (bio)medical purposes (diagnostics or artificial organs), where cost is not a limiting factor and there are quite wide margins as R&D forms the major part of the total cost and added value. Thus, many biosensors are more complex and expensive than current clinical or research detection technologies. In industrial research on the other hand, the cost/benefit analysis defines the priorities. Biosensors are extraordinarily expensive when the cost of developing them greatly exceeds the annual size of the market for the analyte to be served. The conventional techniques, that is, chromatography, mass spectrometry, and immunoassay methods, are much faster to develop for a wide variety of analytes (Guiochon and Beaver, 2004) and, most importantly, are widely known and accepted by the market. It is true that many biosensors have limited technical capabilities, especially in terms of sensitivity; despite the claims for near-to-natural chemoreception, some biosensors are less sensitive than current detection technologies, mainly because the marriage of molecular biology to electronics is not always that successful (Batzias and Siontorou, 2005). It is also true that multianalyte, multisample, or multichannel arrays, developed and/or promised in various forms and formats, cannot exceed the 96- or 384-well plates used for existing ELISA assays. Besides, biosensors are not, by definition, versatile. Small start-up companies and academic spin-offs have been mostly based on the vision of a scientist and his/her determination to translate an idea (i.e., a given biosensor system that had showed considerable potential at bench scale) into a product (Kissinger, 2005). In-house R&D thereafter aimed at modifying the product in order to make it more functional for its intended use or more appealing to the market (Mangematin et al., 2003). While the main product remains the same, as defined by the biological material used (enzymes or DNA or antibodies, etc.) and the transducer (amperometric or piezoelectric or optical, etc.), any modifications (have to) stay within the limitations of this technology. Rarely, these companies have differentiated their product line by adopting a different biosensor technology (Alocilja and Radke, 2003), and that made their effort to handle competition and keep their market share a struggle. That produces another obstacle that limits the spread of this technology: the lack of standards. While for most biomedical technologies there are standards for disposable reagents, there are no standards for biosensor technologies. For example, all ELISA plate readers are designed to read standard size plates and utilize compatible or similar chemistry or detection modes. In contrast, no two biosensors utilize similar assay format or detector. This prevents the development of economy of scale for reagents and disposables, which also leads to losing other benefits of standardization.

Undoubtedly, the biosensor art is rich with exciting new ideas deserving support. The main advantage, and also main drawback, of the biosensor products is their strong science-based character, which obliges industry to capitalize basic research directly, in contrast to (i) engineering-based products that require scale-up before development, or (ii) patent-based (e.g., pharmaceuticals) and secrecy-based (e.g., food/beverages and cosmetics) products that require extensive in-house R&D, which creates/maintains/enriches a corresponding proprietary tradition. Delving into the emergence and evolution of the biosensor field, it becomes evident that when industry got involved, guiding academic research by setting the priorities and the scopes, competitive products have reached the market; when scientists imparted a market perspective to their research, marketable products have been developed within universities; when, visionaries accepted the simple truth that this nascent technology is not an all-purpose panacea but has its limitations, market orientation became more realistic and addressed feasible applications. Moreover, the authors argue that the industry can benefit from the academic output, without having to materialize an entire experimental biosensor system. Biosensors, although not versatile, are not monolithic: a biosensor system consists of independent subsystems that interrelate and collaborate to produce an integral function (Batzias and Siontorou, 2005). A lot of research work has been conducted in improving or even devising these subsystems (hybrid and synthetic materials, mediators, transducer technology, miniaturization formats, micromechanical systems, etc.) that, by means of a suitable methodological framework that considers the needs of industry, as that proposed by the authors herein, can be adapted to industrial R&D in order to impart a product with the required (or desired) degree of innovativeness.

The conceptual shifting from isolated research to collaborative schemes

Biosensors are analytical devices that use a biological-derived/mimicking recognition element (enzyme, antibody, nucleic acids, microorganism, etc.) in intimate contact with a physicochemical transducer (solid-state integrated circuit, metal electrode, optical fiber, etc.) to perceive a target analyte directly without the need for complex specimen processing (Thévenot et al., 1999). In more than half a century of research in biosensors, advancements followed closely the progress

of dedicated individual research groups (IRGs) within academia, which maintained their established research profile and relied on the technical literature for problem-solving or corroboration of results. These "spontaneous" monodisciplinary processes (Figure 1) have led to substantial innovation through the traditional slow schemes of knowledge sharing and dissemination (publishing and personal contacts); having, however, an internal scientific value without any market prospects.

Biosensor research combines and depends on three fields: surface chemistry, transducer technology, and material science (Figure 1). Not surprisingly, research soon assumed an informal multi-disciplinary character, where the IRGs were willing to adopt the advancements of other fields and integrate them into their own research. Biosensors benefited largely by (a) advances in biological surface science regarding the attachment of the biomaterial on the transducer (Toko, 2000), (b) transducer development in integration and miniaturization (Mirsky, 2004), and (c) advances in material science (Kumar, 2007). That has gradually led to formal interdisciplinary university alliances (IDUA), in order to speed up the flow of information. Evidently, research assumed a more coordinated character, where all groups involved were concurrently working within the same scope, some even supported financially by international bodies (e.g., the European Union Concerted Actions, NATO Science Partnerships, etc.). The output seemed more fitted for commercialization, but still more fields needed to be involved for yielding a biosensor product or method: engineers, (bio)informatics specialists, computer scientists, and managers, establishing multi-disciplinary university collaborations (MDUCs). This transition from spontaneous R&D to coordinated research ultimately resulted in defining the key elements that should characterize a marketable biosensor: a process, a multidisciplinary team, an integrated design model, a facility, and a software infrastructure.

For the needs of the present study, the spontaneous R&D is defined as a "push-on" tendency/attempt/procedure characterizing the scientific research performed within an academic environment, pushed by the internal or external (the notorious "publish or perish" clause that dominates these areas) necessity to produce what is considered as their intellectual product. The coordinated R&D is defined as a "pull-out" tendency/attempt/procedure, owing to the processing-to-commercialization organized exploitation of the intellectual product derived from IRGs. The transition phase is defined as the appearance of knowledge concentrators which select relevant works of IRGs in order to transform it to a more exploitable form, according to a preliminary plan that seems to be promising for marketing. This scheme is commonly seen in the biotechnology sector, with the transition phase varying widely; for example, it took 40 years for camptothecin chemotherapy agent to reach the market (from discovery to clinic), driven by the persistence of two researchers on the merits of the active moiety (Oberlies and Kroll, 2004), whereas the transformation of meritorious and successful diagnostic technologies (PCR, DNA sequencing, ELISA, etc.) was generally spontaneous and rapid, driven by scientific need and market forces.

Spontaneous R&D in biosensors—the role of academia

Emerging from Clark's enzyme electrode in 1962, these devices are considered as an offspring of chemical sensors (Figure 1). Following closely, transducer technology at the beginning, their growth was nothing like anticipated, hindered substantially by problems encountered in stabilizing the biological elements on the transducer surface in a way which would not diminish their functionality or their shelf-life (Scheller et al., 1985). It was not until early-1990s that chemical sensor groups, specialized on developing transducers, have benefitted by biotechnology groups, specialized in developing semi-synthetic or fully synthetic biomaterials functioning on these transducers. The first inter-disciplinary university alliances (IDUAs) started to appear solely on the basis of personal relations. Research papers have dramatically increased, prompting more universities and institutes to get involved, establishing more IRGs and subsequently more IDUAs.

Remarkably, joined research papers did not appear until late-90s, where the IDUAs assumed a formal character and started to collaborate within a project, clearly emphasizing on the exploitation of bio-sensing. Still, market reports insist on linking biosensors' future with that of sensors and actuators, maintaining and preserving the original IRG-model. That would be the case of the artificial nose and ear, which, based on the microelectromechanical systems (MEMS), have been erroneously expected to trail the sensors' success. Despite the novelty of these biosensors, forecasting the market scale with any confidence is not feasible (Newman et al., 2004).

The mid-1990s have seen the introduction of small portable, biosensor-based systems that can run various critical analytes on real samples. The prospects of miniaturization and portability have been imposed by the biorecognition concept itself; actually, the biological active area in all biosensors measures a few angstroms. That, prompted the developments in micro-machining and silicon-integrated circuit technology (Newman et al., 2004), finally giving miniaturized electrodes and microliter-processing channels and chambers.

Biosensor development had, though, another major input: model membranes. The research field adopted two parallel directions: one led to thin film technology (Yimit et al., 2005), which enabled transducer integration and miniaturization, while the other led to membrane biosensors (Lindner, Gyurcsányi, and Buck, 2002). A lot of effort, scientific work and faith have been trusted to membrane systems by long-established and dedicated IRGs (e.g., Thompson/Krull group at Toronto University, Tien group at Michigan State University, Turner group at Cranfield University, Nikolelis group at Athens University, Karube group at Tokyo University, Guilbault group in Ireland, Wang group at Arizona State University, Gauglitz group at Tümbingen University) that gave strong IDUAs. However, none of the bench-developed devices has ever reached pilot implementation. This research path gave significant breakthroughs, as discrimination of structurally

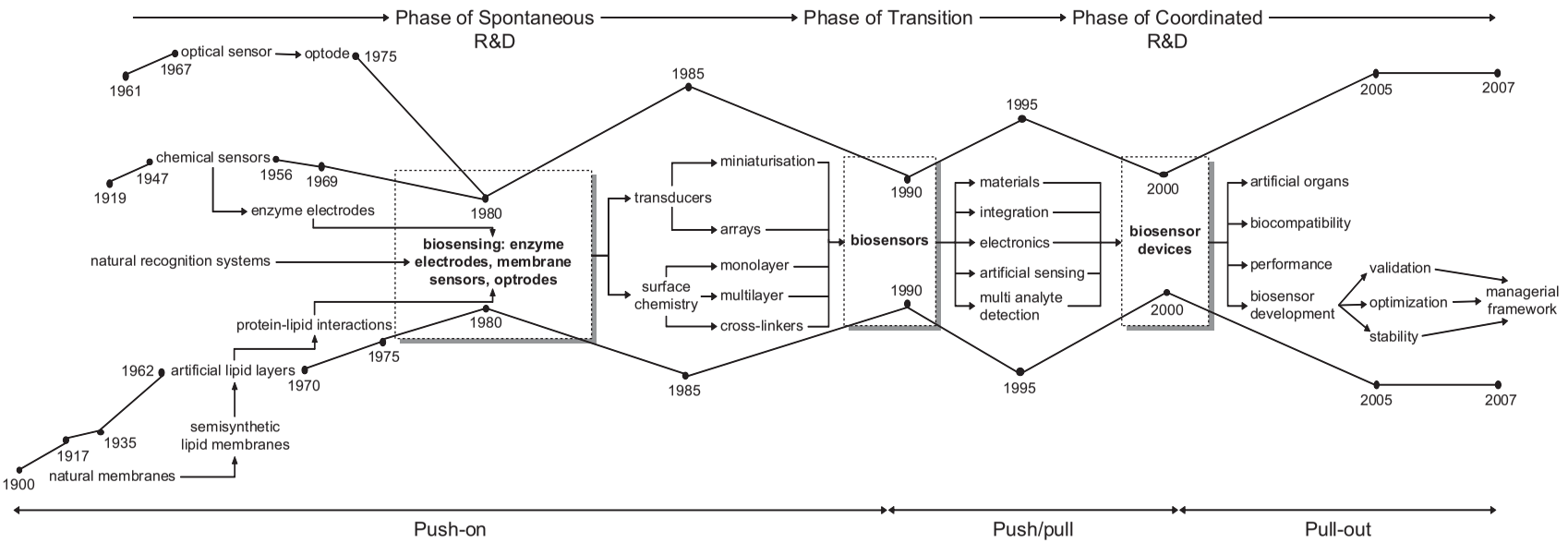

Figure 1. Synoptic presentation of the biosensor research evolution depicting the three phases of transition from spontaneous to coordinated academic activities, as indicated by the scientific literature from 1960 to 2007. The biosensor concept derived from the basic idea to mimic natural sensing through the integration of biological systems with transducers. Drawing elements from these two basic fields at the beginning, the IRGs involved produced hybrid systems and introduced terms as enzyme electrodes (amperometric sensors coupled with enzymes) or optrodes (optical sensors coupled with enzymes). The field, starting to take shape and part in the traditional web of university research through a push-on mechanism, gradually built structure and status, resulting in the formal establishment of the biosensor field, around 1990. At this period, a transition has been clearly taken place, establishing IDUAs and guiding the supporting lateral fields to perform work for and due to biosensors. This transition led gradually to a fully structured sector with a pull-out character, incorporating the supporting fields through MDUCs.

similar compounds with bilayer lipid membrane biosensors (Nikolelis and Siontorou, 1996; Siontorou, Nikolelis, and Krull, 2000), as well as the pioneering work on metal supported self-assembled membranes (Tien and Ottova-Leitmannova, 2003). However, the inherent instability of such films hindered any market prospect despite the various attempts to produce rugged lipid layers (Nikolelis et al., 2005).

The main blessing of biosensor technology lies in its non-solid character. In theory, any biorecognition system can be coupled with any transducer and assembled with any supporting sub-system (e.g., signal amplification, signal transmission), producing numerous combinations that shape into different devices. In all published papers, the distinction of these biosensor parts is clear and, ultimately, research studies their inter-relations, aiming at their effective and efficient inter-connection. Not surprisingly, the field has witnessed novel integrations, such as electrochemistry coupled with fiber optics, enzymatic immunosensors and lab-on-chip devices (Alocilja and Radke, 2003; Kumar, 2007; Rodriguez-Mozaz, Lopez de Alda, and Barceló, 2006; Toko, 2000; Wang, 2001).

The late 1990s have brought another promising path in biosensing, that of shifting from the electrode-concept to hard equipment (e.g., the Surface Plasmon Resonance, SPR). SPR sensing has been demonstrated to be an exceedingly powerful and quantitative probe of the interactions of a variety of bioelements with various analytes. It provides a means not only for identifying these interactions and quantifying their equilibrium constants, kinetic constants and underlying energetics, but also for employing them in very sensitive, label-free biochemical assays (Rich and Myszka, 2001).

The IRGs have managed to structure the new field of research through the creation of persisting IDUAs, releasing numerous new concepts, ideas, and bench technologies in the scientific community, gaining the interest of various fields and even guiding academic research toward the realization of a nascent technology. But still the "push-on" biosensor research explores the theory and tries to achieve its initially-seen potential: (a) low-cost, simple devices with sensitivity and selectivity comparable to nature's ability to detect low-concentration analytes in small specimens; (b) technology-friendly devices that require little user training; (c) real-time in-field monitoring; (d) sophisticated testing.

Emerging need for collaborative networks—the role of industry

The first biosensor system to come to market was for glucose in 1975, the Yellow Springs Glucose Analyzer, but it was not until 1988 that more glucose biosensor instruments were launched. Large corporations have been involved (MediSense, Abbot, Therasense), and the sector has seen a lot of mergers and acquisitions, such as that of Abbott Pharmaceutical purchasing MediSense Inc. in 1996 and TheraSense in 2004. Since then, more than 20 biosensors have been designed for the clinical diagnostics market and sold worldwide but only a few address other analytes, as the Nitrate biosensor (NECI®), coming from small specialized companies, such as the Agamatrix Inc. (USA) and the 77 Elektronika Kft. (Bulgaria). However, commercialization was not the result of a direct university-industry collaboration (D'Orazio, 2003), but either of industrial in-house R&D (the classical concept of industry taking advantage of a marketable idea) or academic spin-off (the classical concept of a scientist seeing market prospects in an experimental set-up). Probably the first clear case of biosensor technology transfer from university to industry is the Biacore® product line, employing SPR biosensing. Biacore began operating in 1984, when expertise from Pharmacia, Linköping Institute of Technology and the Swedish National Defence Research Institute, were brought together with Biacore's predecessor, Pharmacia Biosensor AB (Fallberg and Brynö, 1998). Approximately 65 million US$ have been invested in the development of Biacore and the technology on which it is based. An initial research phase which essentially included development of the fundamental affinity-based biosensor technology comprising surface chemistry, flow systems, and optical detection methods was completed in 1989. The result was a biosensor-based analytical instrument for studying molecular interactions, launched in 1990. Further products followed, all based on SPR technology. The business evolved into an independent commercial enterprise, which posted its first profit in 1994. Another example of direct know-how transfer from academics to industry is the establishment of Agamatrix in 2001 from the collaboration between S. Vu, an expert in machine-learning algorithms, and S. Iyengar who has just finished his PhD in biosensors at Cambridge University. Some university researchers turned to the consultancy industry to offer their insight and experience. For, example, Remedios Ltd, a UK environmental consultancy company spun-out of the University of Aberdeen in 1999.

Academicians, especially in the EU, continue to avoid cooperation with industry, mainly due to secrecy agreements and relevant limitations on publishing (Breznitz, O'Shea, and Allen, 2008), persisting on maintaining the IDUA-model. Numerous patents have been filed by universities (Fernandez and Chow, 2005), on each and every aspect of biosensor technologies (transducers, chemistry, microfluidics, biological systems, etc.), which, unfortunately, instead of promoting the research interest and inviting other players in the field, are blocking the flow of information, thereby limiting and complicating the development, adaptation, and the spread of biosensors. In effect, several problems appear that could not be dealt with internally: (a) knowledge gaps that could not be filled by IRGs or IDUAs, either due to limited resources or expertise required in another discipline, (b) inability to collaborate with other disciplines, either due to lack of motivation or lack of common vocabulary, (c) limited financial support to carry out research, (d) inability to raise investments for prototype development, (e) lack of proper management for inter-laboratory collaborations, and (f) inability to reach industry, which, glucose sensor exempted, was willing to consider more a developed product than a novel concept. The biomedical community is conservative and is unlikely to adopt new technologies unless there is a clear and significant

advantage; in addition, practical limitations do exist due to medical norms, bioethics and established interests.

These needs led to the establishment of a few multidisciplinary university collaborations (MDUCs) in Europe, prompted by opportunity, Europe's strategy (and financial support) to bring industry closer to university research, and the introduction of a more holistic and integrated approach to biosensor development in academia. For example, the RIANA (RIver ANAlyser) project (Tschmelak et al., 2006), supported by the EU, has been conceptualized, designed, developed, and implemented by the Sensors' Group of the Tubingen University, a group with a long history in sensors and actuators (Figure 2). Prototype construction and in field implementation gained largely from the involvement of Siemens AG. The involvement of industry introduced a knowledge-demand re-engineering concept. As field testing revealed the need for multi-analyte detection as well as some drawbacks in data acquisition and elaboration, a new project has been designed on the basis of university-industry collaboration, leading to the fully operational, field tested and validated, remote-controlled multianalyte detection system (AWACCS) for water quality (Tschmelak et al., 2005). AWACCS materialization, within only four years after its conceptualization, proves that progress is significantly speeded-up when team members, under a suitable financial umbrella, coordinate problem-solving efforts to improve product innovation and marketability.

The formation of MDUCs in the United States, supported by government grants and private sponsorships was more rapid and successful in transferring research to the market. For example, the alcohol wristwatch has been developed through collaboration between the University of Southern California and the Brown University Medical School, based on the simulation of alcohol metabolism (Dumett et al., 2008), that will produced by Giner Inc., USA.

Framing the innovative product development—a strategic approach

Apparently, biosensor advancements have been marked by two major approaches: the knowledge supply side (KSS) approach and the knowledge demand side (KDS) approach (Figure 3). The former, driven by the availability of knowledge, supported innovations during the 1990s, while the latter, derived from market needs, has just started to evolve, esp. in USA and Japan. Patent applications on biosensors date back to early 1970s, most, not surprisingly, on glucose meters. The Ames Reflectance Meter, patent issued in 1971, providing a read-out of the unpatented article strips introduced in 1965 by the same company. The development of the article strips had been based on published articles on glucose enzyme electrodes. The biomedical aspect of the biosensors remains in the forefront of industry goals, where more companies are trying to enter the market. Bio-Nano Sensium Technologies, specializing in nanobiotechnology for biomedical devices, has exclusive access to Toumaz Technology's patent portfolio. The increasing number of patents over the last five years reflects the company's rapid progress in its scientific discovery process toward offering advanced wireless biosensors.

A considerable increase of research funding for biosensors has been seen in 2004, along with new lines of funding for technology demonstrators and industrial investment in prototype systems. This can certainly boost the KSS approach, provided that universities will be encouraged to support the area and presupposing liberation of university staff time for R&D, longer term funding for individuals who can demonstrate the quality of their work and its relevance to user requirements, as well as improved support for graduates.

The KDS approach, on the other hand, has proved to provide a strict market-orientation as well as resources necessary for successful commercialization. Most companies, however, realizing the huge cost of research, have decided to collaborate with academics, largely on a short-term basis, although permanent collaborations do exist. In 1996, Bioacore acquired control of EBI Sensors Inc. (Fallberg and Brynö, 1998); this acquisition gave Biacore access to fiber optic sensor technology developed by the University of Washington (USA), of which EBI is the exclusive worldwide licensee. Another kind of permanent collaboration is found within the U.S. Center of Polymer Interfaces and Macromolecular Assemblies (CPIMA), which supports a consortium of industry and academics for focused research (Figure 4).

Notwithstanding, there are still ineffective links between the research base and the end-user. Mechanisms to foster more effective technology transfer and better communication of technological opportunities and user requirements should be established, in order for biosensors to grasp the opportunities ahead. The global market competition has been started to take shape: major breakthroughs come from countries with strong infrastructures for microsystems technology (MST), esp. in the interface between biotechnology and nanotechnology. For example, Germany has growing strengths and capabilities in both fields. Groups from United States and Japan are also starting to focus major research efforts on these interfaces. Competition is also emerging from Taiwan, Korea, Singapore, and China, rendering this a hotly contested field.

Improving the product development process—a tactical approach

Based on the short analysis provided above, some important conclusions can be drawn: (a) the biosensor concept hoards plenty innovations and pioneering ideas with great potential for realizing a nascent technology output; (b) as effectively multi-disciplinary, this field necessitates the collaboration of different expertise in order to produce a field-working prototype; (c) university researchers should implant marketability aspects in their work; (d) industry should become more involved in order to move these devices from the university to market.

Considering the importance of novelty in the market and the effort of companies to increase their products' innovativeness (Salomo, Weise, and Gemünden, 2007), the biosensor field is unquestionable a suitable KSS pool. Industry

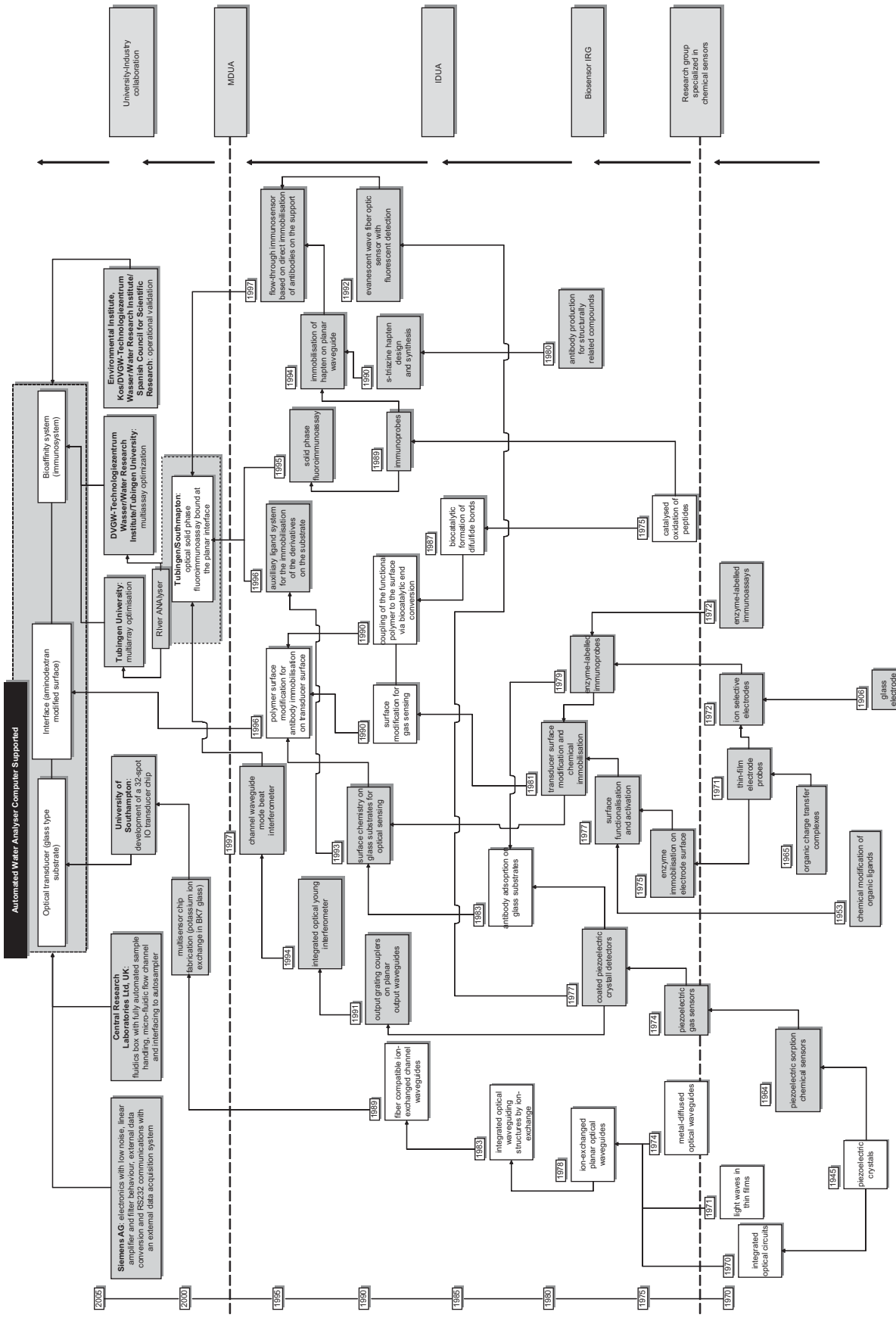

Figure 2. The research path to the development of the AWACCS system has many direct (shaded boxes) and indirect (white boxes) contributions. Started from a group in Tubingen University specialized in chemical sensors, soon gave rise to a dedicated biosensor IRG. The implementation of the RIver ANAlyzer (the RIANA project), the predecessor of AWACCS necessitated the establishment of IDUAs (the main being that with the University of Southampton). The transition from the RIANA system to the AWACCS called for MDUCs and finally realized with the involvement of industry.

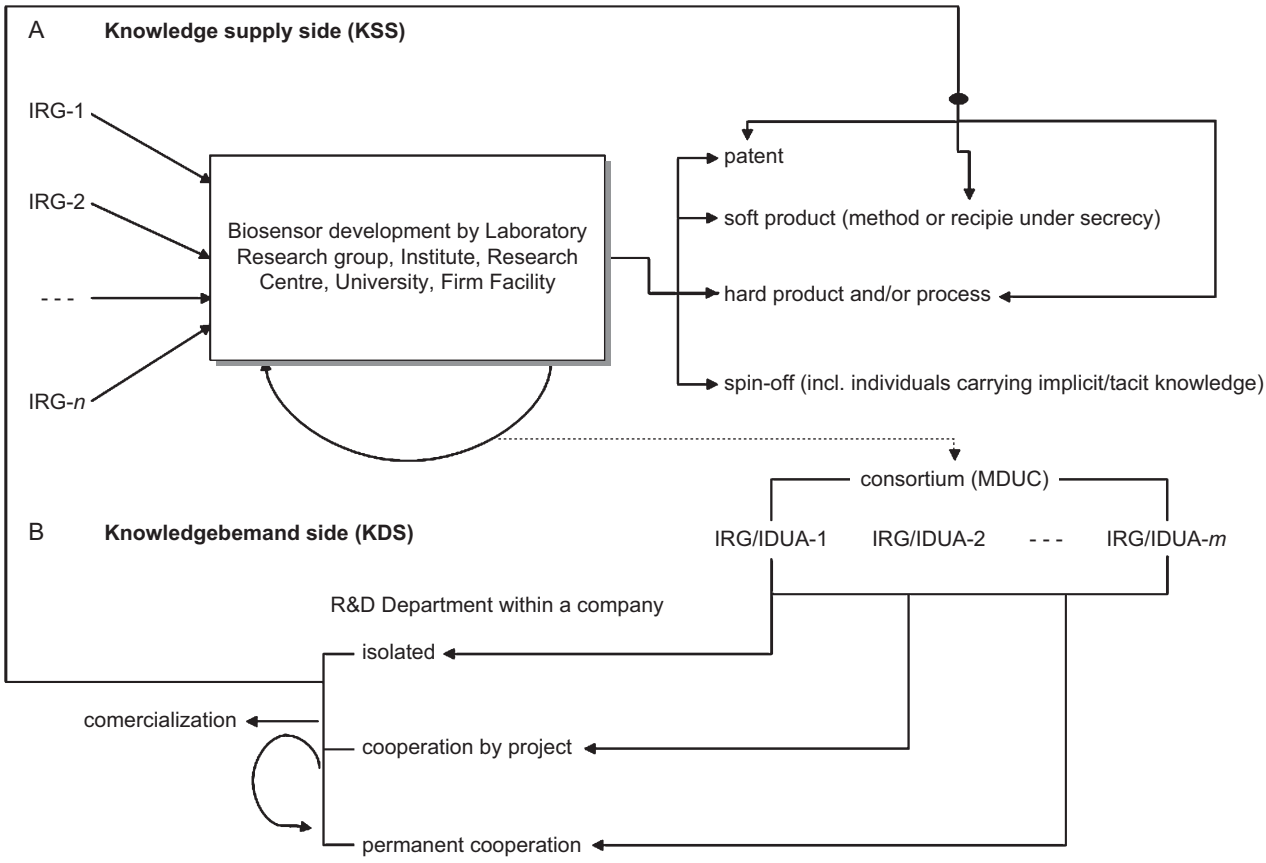

Figure 3. The explicit knowledge flow cycle used as a plan for analyzing the biosensor sector; implicit/tacit knowledge within a spin-off depends on the knowledge of the group it spun-off from and cannot enter directly the flow cycle.

involvement, however, should receive a different form than that commonly seen. This technology is strongly bound to basic science, thus the main responsibility lies within the basic science producers, that is, the academicians. Industry should guide and focus university research by posing the questions that need to be answered and the problems that need to be solved, that is, by setting the goals and formalizing/strengthening the KDS. That, on one hand, would certainly limit the degrees of freedom of the university research but, on the other, would put biosensors into industrial context.

When such a project is decided upon, the determination of the project parts is of major importance and depends upon the company's knowledge, resources and needs. When knowledge is the limiting factor, the project can be divided into biosensor parts, giving rise to alliances with universities/institutions. When the company lacks resources, the division is based on expertise, giving rise to agreements with small specialized companies. Inter- and intra-technical/scientific knowledge and competency may be disseminated in a variety of ways: patent disclosure, publications, technical meetings, conversations between employees of the same or competing companies, partnership within the same consortium that carries out a big project, hiring of employees from rival companies and reverse engineering of products (Costa, Fontes, and Heitor, 2004; Khilji, Mroczkowski, and Bernstein, 2006; Powell, Koput, and Smith-Doerr, 1996; Stuart, Ozdemir, and Ding, 2007).

Depending on the company's needs, technological development, that is, design initialization, *D,* may start from advancing basic research on an early-stage biosensor (deep knowledge level), or from re-engineering/re-designing later stage products (surface knowledge level). Moving toward the surface level, a choice exists between bench-scale (R&D), pilot (prototypes) and marketed versions. The deeper the design initialization goes, the higher the investment required and the uncertainty of the outcome, but the more prominent becomes the differentiation of the product for gaining a satisfactory market share, since the number of degrees of freedom (for scientific research) increases as a function of depth.

The determination of the optimal depth of design initialization, D_{opt}, is of critical importance for reaching the desired result as regards the product, which is *a priori* known not as a physical entity but as set of characteristics/properties. Given the final product desired specifications, the D_{opt}-value can be determined at the minimum total cost $C = C_1+C_2$ (Figure 5A, upper diagram), where C_1 is the partial cost for reaching the surface level and C_2 the cost expected to be paid for exclusively meeting the pre-set specifications, since the higher the D-value, the higher the flexibility (or the number of degrees of freedom) and consequently, the lower the corresponding partial cost. As research experience/data accumulates, C_1 moves downwards to the lower cost curve C_1, also becoming more flat, since the difference from the previous cost-curve is an increasing function of D due to disproportional

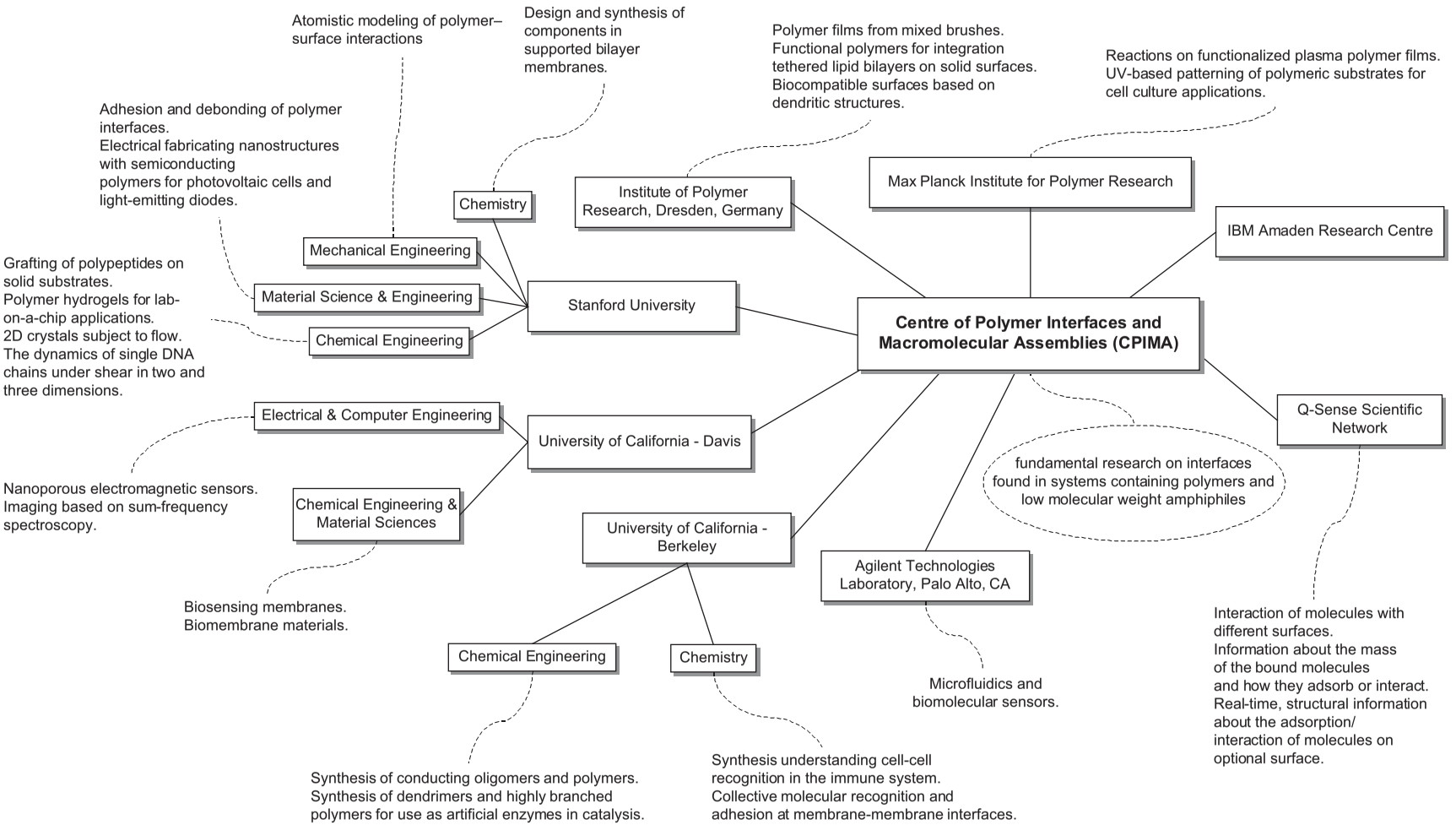

Figure 4. CPIMA is an NSF sponsored partnership, dedicated to fundamental research on interfaces found in systems containing polymers and low molecular weight amphiphiles.

saving of research resources at higher depth-levels where implicit/tacit knowledge acquired by scientists/engineers is dominant. Consequently, D_{opt} determined as the abscissa at (C_1+C_2)min, shifts to D'_{opt}, determined as the abscissa at (C_1+C_2)min, that is, the trend is toward design initialization at more deep levels or closer to basic research regions. In terms of the corresponding marginal costs, $MC_1 = dC_1/dD$ and $MC_2 = |dC_2/dD|$, the minimal value of (C_1+C_2) occurs at $d(C_1+C_2)/dD = 0$ or $dC_1/dD + dC_2/dD = 0$ or $MC_1 = MC_2$, that is, D_{opt} is the abscissa of the intersection point of the respective marginal cost curves; similarly, D'_{opt} is the abscissa of the new intersection point when $MC_1 = MC_2$ (Figure 5A, lower diagram).

The experience/data accumulation described above leading to D_{opt}-value increase, that is, to knowledge deepening, is more expressed in large multinational corporations and industrialized countries, which already have a comparative advantage relative to companies/countries at a lower technology level (Siu and Bao, 2008). This effect sets up a positive feedback mechanism, leading to further D_{opt}-value increase: the more experience/information is accumulated, the more knowledge deepening and specialization is likely to be achieved, usually expressed in issuing more patents and generally proprietary rights, implying an upwards shift of C_2-curve, which becomes also steeper, since the difference $(C_2 - C_2)$ is a decreasing function of D due to disproportional burdening at lower depth-levels where the number of degrees of freedom is low (Figure 5B). The implied increase of D_{opt} to D'_{opt} contributes to further creation of new knowledge, which causes downward shifting C_1-curve as described in Figure 5A, and so on *ad infinitum*. Consequently, at least according to this feedback mechanism, the comparative advantage of the knowledge creator increases continually. Evidently, the law of diminishing returns, equally valid in technology and economics, will set in (after a certain point) as an opposite force, which will slow down the cost decrease.

A methodological framework for facilitating the knowledge transfer from university to industry

Although the above introductory analysis is quite rational, even if a company's decision-making process is based solely on cost minimizations, it should be complemented by incorporating certain other variables/parameters as criteria to obtain a more reliable and multi-faceted D_{opt}-value. The development of a framework for such incorporation and the performance of multicriteria analysis (MCA) linked with case-based reasoning (CBR) are presented herein, where the latter method yields the alternatives for the former. This tool effectively assists the decision-makers in selecting the suitable depth level of product design initialization (four levels have been considered herein: basic/background research, development/scale-up, pilot versions, marketed biosensor versions) in order to assure the successful development of the final product according to predetermined specifications. The use of CBR in MCA potentially leads to reality-closer and more efficient retrieval of alternatives that better represent the university output and is most suitable for utilizing the company's capabilities and enforcing its potential. The formalism adopted is quite flexible to allow for handling a wide range of different cases within this complex and dynamic science-based sector.

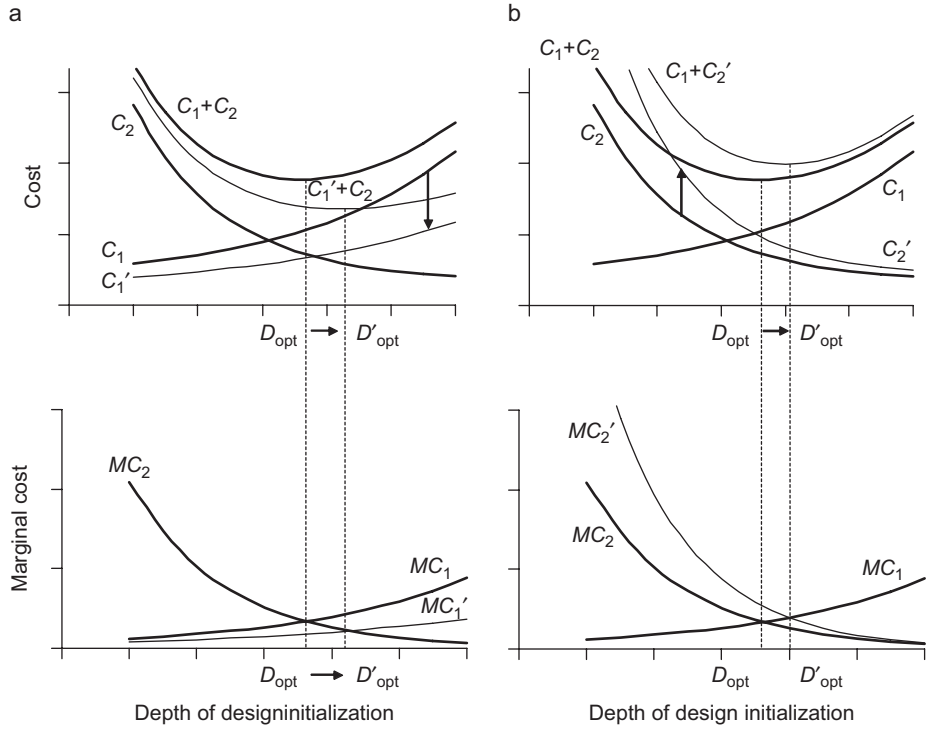

Figure 5. Determination of optimal depth of design initialization (D_{opt}) with only one criterion (cost) forming the objective function, indicating also the impact of (A) experience/data accumulation and (B) specialization increase as expressed by number of patents and extent of proprietary rights.

The integrated CBR/MCA procedural framework

The methodological framework designed and developed by the authors under the form of an algorithmic procedure for selecting D_{opt}, includes 21 activity and 9 decision nodes (designated by numbers and letters, respectively), as presented in Figure 6, connected to a Knowledge Base (KB), designed to serve the needs of the present work (stage 9), and an Intelligent Agent (IA) for retrieving information from external databases (stage 10) (Batzias and Marcoulaki, 2002). The CBR system designed/developed herein comprises a case library, a case retrieval module, a case revision module, and a case retention module. The case library stores biosensor products and research devices, classified according to their stage (level) of development (stage 2), that is, basic/background research, bench scale, R&D at various regulatory phases, prototype or marketed versions, etc. Each case entered is decomposed into functional parts (stage 6); the degree and extent of decomposition depends on the judgment of the expert and the specific needs of the decision-making process for analytical details, depth of knowledge and amount/granularity of information. For example, a biosensor can be decomposed into three parts, namely (i) the target analyte, (ii) the biological/biomimetic element that interacts with the target analyte, and (iii) the physicochemical transducer that detects the interaction and converts it to an electronic signal (Batzias and Siontorou, 2005); however, a more detailed structural and operational decomposition may be required involving the mechanism of signal generation, the biological/biomimetic element/transducer interface, the signal amplification process, the sample pretreatment unit, etc. Upon recombination (stage 8), the parts are re-assembled and their inter- and intra-relations are registered. Re-assembly follows a loose pattern, so that either the whole product or its parts are readily available for retrieval/matching.

The input case ("master probe") is formulated on the basis of the designer's desired specifications for the end-product (stage 3). Clearly, the matching criteria (stage 5) differ from level to level, moving from device operational/ergonomic characteristics at the surface level (marketed versions) to analytical specifications at the basic research level. This entails the adaptation of the probe to fit each level, by loosening/tightening and/or removing/inserting specifications/requirements; in all cases, each level probe should be able to be developed consistently to the initially set desired end-product. Actually, at n levels, the number of probes is $1+(n-1)$, where 1 is the master probe and the $(n-1)$ are the derivatives. The case retrieval module (stage 13) extracts a whole case from the case library that resembles most closely the probe for each level and adapts it to suit the designer's specifications for this level. If no matching on whole cases is successful (decision node A), modular adaptation (engaging the loop of decision nodes B to E and the relevant activity stages) is used to construct a simulated case from case parts, taken either form the same or from different levels. Once the selected case is evaluated and retained (stage 14), it is integrated into the case library as a new database entry. The CBR engine provides one representative case from each level (stage 16), each designating a possible research stage to intersect and seize for further in-house development; the set of representatives thus yielded formulates the comparable alternatives to be evaluated by fuzzy MCA.

Fuzzy MCA (stages 17–20) is used to compare the performance of each level representative with respect to predetermined multiple attributes or criteria, defined by the decision-maker (stage 17), and yields the D_{opt} in the form of best level to adapt and advance, accommodating and building the desired end-product upon the features of this level's representative. The objective function of the multi-criteria problem under consideration is $\mathrm{Max}\{f_1(a),\ldots, f_K(a)|a \in \mathrm{A}\}$ where A is the set of T alternatives and f_k, k=1,...,K, are the K criteria used for evaluation of each alternative. The computational procedure consists of two main steps: (i) the formulation of the preference matrix ($K \times T$), where each element x_{kt} is the evaluation of alternative A_t according to criterion f_k (ii) the ranking of the alternatives, as a result of applying to the rules of the selected MCA method. PROMETHEE (Brans, Vincke, and Mareschal, 1986) has been used as an outranking method in its fuzzy version to account for uncertainty (Batzias and Batzias, 2004), allowing for incomparability (aRb) and weak preference (aQb) between the alternatives a, b, in addition to the strict preference (aPb) and indifference (aIb) on which the "classical" methods are based. The notion of a generalized criterion is used to construct an outranking relation by defining the preference index $\Pi(a,b) = \Sigma w_i P_i(a,b)/ \Sigma w_i$ as the weighted average of the preference functions P_i, that quantifies the preference of the decision maker of alternative a over b, taking into consideration all the criteria. In terms of topology, the preference index values can be represented as a valued outranking graph, the nodes of which are the alternatives. By summing the column elements in each row of the outranking relation matrix, the flow leaving each node is obtained, which shows its outranking character, while by summing the row elements in each column, the entering flow is obtained for each alternative, which shows its outranked character. By considering the leaving and entering flows, as well as the fact that the higher the leaving flow and the lower the entering flow the better the alternative, the partial preorder (PROMETHEE I) is obtained. Although the partial preorder carries more realistic information, sometimes the total preorder (PROMETHEE II) is requested to avoid any incomparability; this preorder is induced by the net flows, that is the difference between the leaving and the entering flows. The generalized criterion used is a piecewise linear preference function $P = H(d) \in [0, 1]$, where d is the difference of the evaluation of two alternatives a, b. The parameters of $H(d)$ are an indifference threshold q, the greatest value of d below which there is indifference, and a preference threshold p, the lowest value of d above which there is strict preference—the interval between q and p can be considered as the weak preference region.

To conclude a partial or complete preorder from the resulting fuzzy sets, the Tseng and Klein method (Tseng and Klein, 1989) was used, which makes pairwise comparison of the alternatives by calculating the (crisp) dominating areas in

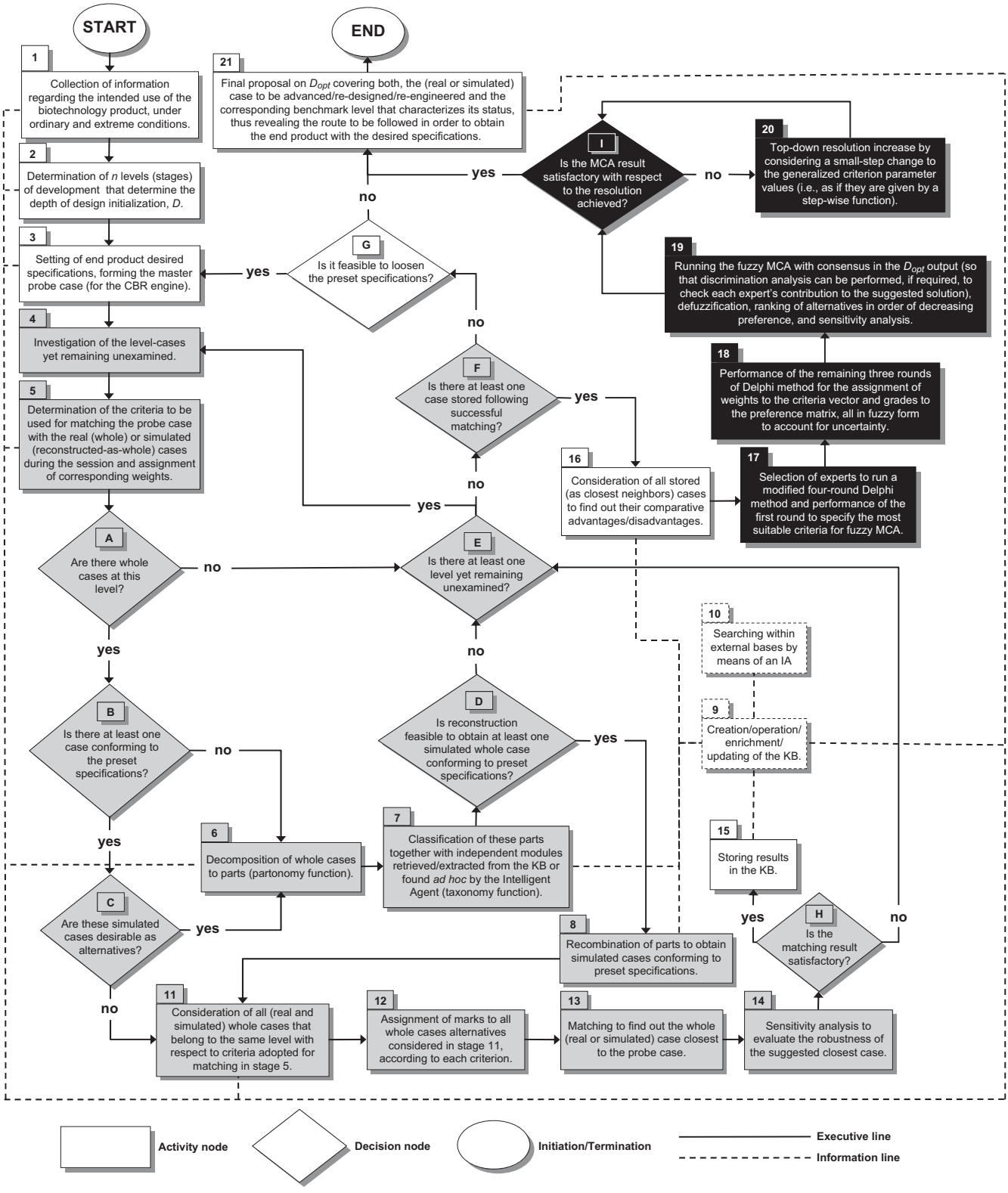

Figure 6. Overview of the computer-aided tool designed/developed herein for determining the optimal depth-of-design initialization, D_{opt}, in biotechnology projects relying on fuzzy multi-criteria analysis linked with case base reasoning. Selection is performed from a pool of candidates at various levels (stages) of development (stage 2). Moving from the surface level (marketed versions) toward the deepest level (background/basic research) flexibility in development and product differentiation is increased, along with risk and uncertainty. Cases are collected and stored according to their level of development. The user formulates a master probe (stage 4), incorporating the desired characteristics and attributes of the final product; the matching criteria (stage 5) are then adopted to each level, producing the derivative probes. The CBR engine (shaded area) yields one case from each level that fits better to the level derivative probe. Fuzzy MCA (dark area) is used to compare the performance of each level representative in respect to pre-determined criteria and yields the D_{opt} in the form of best level to adapt and advance, accommodating and building the desired end-product upon the features of this level's representative.

each pair consisted of triangular fuzzy sets (partial preorder); subsequently, the summation of the elements of each row (alternative) of the domination matrix gives a measure of the strength of each alternative that leads to the total preorder.

Case study

The framework presented has been implemented in the case of a biomedical device for self-monitoring blood glucose (SMBG meter). Although, the state of the art is remarkable, a lot of pending issues provide ample space for improvement though university involvement: (a) minimizing interference from oxidizable substances in the sample matrix (Schuvailo et al., 2006), (b) increasing accuracy under low (under 35%) or high (over 55%) hematocrit levels (Rao et al., 2005), (c) increasing accuracy under hyperbaric conditions (Vote et al., 2001), (d) minimizing sample volume for allowing neonatal screening (Hawdon, Platt, and Aynsley-Green, 1993), (e) alternate site testing (Newman and Turner, 2005), and (f) enhancing user friendliness, for example, by allowing sample volume corrections (Newman and Turner, 2005).

The levels characterizing *D* (stage 2) are four: marketed versions (MV), prototype versions (PV), development/scale-up (DS), and biochemical or basic or background research (BR). DS (including all devices tested at bench scale) and BR levels concern mostly university output as regards (i) methods for reducing interference through the use of barrier membranes to exclude interfering species from reaching the reaction zone or employing enzyme complexes to decrease oxidation potential of the analyte, and (ii) methods for increasing signal-to-noise ratio through mediator incorporation. The PV level, containing all devices that are at some point through the clinical trial phase, represents university-industry collaboration research. The first level, taken almost entirely from industrial in-house R&D, involves (a) methods for developing minimally invasive sample delivery and (b) methods for increasing reliability by implementing software solutions.

The master probe case used in this study (stage 3) has been constructed by taking into account the current market needs, described above as (a)-(f), incorporating a set of operational requirements (linear range, precision, accuracy, interference, performance stability, and sample volume), ergonomic specifications (meter size, display readout, button design, casing, ease of use/convenience, ease of cleaning/maintenance, testing time, alternate site testing) and cost specifications. As depth increases, the derivative "probes" are supported by matching criteria modified accordingly to fit the specific nature of each stage. For example, the term *precision* at the first level is defined as "*not more than 5%, considered as variability of system and user within the mentioned limits at glucose concentration of 30–400 mg/dL 100% of the time*" (U.S. Food & Drug Administration, 1997), whereas at the DS level it is considered more as the analytical validation precision, that is, "*not more that 5% in intra-precision and not more than 10% in inter-precision*" (Ramsay, 1998); in the BR level, *precision* is set as "*coefficient of variation of less than 6% (at 90% confidence interval)*" (U.S. Food & Drug Administration, 1997), which is the analytical barrier.

The BR level of glucose meters does not contain a complete device but deals with innovations or improvements of the device analytic parts. Activating stage 8 and combining the parts dealing with (a) the matrix suitable for direct electron transfer (DET) (Razumiene et al., 2006), (b) the optimum electrode surface that fits DET (Lee et al., 2006), and (c) the novel method for construction of this electrode, a simulated case has been presently constructed (Lim et al., 2005) involving the use of a purroloquinoline quinone (PQQ)-dependent glucose dehydrogenase on carbon nanotubes for direct electron transfer.

For each level a matching is performed to find out the closest to the probe case (stages 11–13). An example referring to the selection of the best representative from the MV level is shown in the Appendix. Following the selection of the best representative at each level (horizontal selection), the alternatives/candidates enter the fuzzy multi-criteria process (vertical selection) in order to determine the D_{opt}. The criteria used in FMCA (stage 17) are: f_1, probability to succeed in developing the final product; f_2, total cost for developing the final product; f_3, expected competitiveness in the market; f_4, perspectives for further development; f_5, maturity of technology; f_6, reliability of the device. The comparable alternatives provided by the CBR engine are A1: the FreeStyle meter of Therasense, which utilizes glucose dehydrogenase as an enzyme, reducing satisfactorily interferences and osmium-based mediators for signal-to-noise ratio increase (MV level); A2: a device employing glucose oxidase and ferricinum-based mediator, with concurrent hematocrit measurement and correction of the glucose measurement through built-in software (Rao et al., 2005) (PV level); A3: a screen printed amperometric biosensor fabricated with water-based carbon ink (DS level); A4: a PQQ-dependent glucose dehydrogenase on carbon nanotubes for direct electron transfer (the simulated BR case).

Scoring (stage 18) has been performed by five biosensor experts employed in the biotechnology industry, using a range of 2–8, the highest value being assigned to the better alternative. While the DS device has more probabilities to succeed (criterion f_1), the BR case has more perspectives for further development (criterion f_4) and the higher expected competitiveness in the market (criterion f_3). The grades given to criterion f_5 (maturity of the technology) are, as expected, inversely proportional to the design depth, that is, the deeper the design level the lower the maturity. Overall, however, the f_3- and f_5-gradings are not high, due to the limitations of the available technology as per the target analyte and the intended use of the device: glucose can be accurately measured in situ photometrically or electrochemically, both options being already studied in depth and detail, allowing for advancements in the sample delivery systems rather than in basic biochemistry. Furthermore, the inconvenience of frequent pricking to the patient has currently turned research toward noninvasive techniques and implantable devices.

On the other hand, the grades given to the criterion f_2 (total cost for developing the final product) do not appear to follow the trend shown in Figure 5, that is, cost increases as

D increases. This appears to hold true only for the BR case, where clearly the cost to meet the desired specifications and convert the untested and nonvalidated research set-up to authorized and ready-to-market product is high, whereas similar grades have been assigned to the other levels. In fact, the dependency of optimal depth on cost is not a monotonic function, in that the conflict variables are the resultant of many underlying parameters, principally referring to the state of the art. Both devices, the A2 and the A3, are extensively tested and validated based on a technology well-established in other fields (Rao et al., 2005) and their adoption/adaptation to the designer's specifications and their conversion to the desired end product are not expected to differ significantly.

The results (stage 19) are shown in Figure 7 at (a) low preferability resolution with medium parameter q, p values (q = 1.5, p=3.0), and (b) high preferability resolution, with low parameter q, p values (q = 0.5, p=1.0). At both levels, the Total Ranking of Alternatives (TRA) is A3>A1>A2>A4, where the symbol ">" stands for "better than." This is a significant indication that the solution suggesting the alternative A3, that is, the screen printed amperometric biosensor from the DS level, is robust, without any indication of incomparability between the "best" product and the suggested as "second-best" FreeStyle meter at the MV level. Robustness is confirmed by monoparametric sensitivity analysis over the wide range ± 50% round the central defuzzified value of each criterion (SAC)—the difference S3 – S1 is always positive, being lower only for quite decreased f_3-, f_4-values. It is worthwhile noting that, with respect to development, the criteria f_4 and f_5 behave as conflict parameters because the devices that utilize mature technologies usually imply lesser perspectives for further development.

Discussion and concluding remarks

Biosensor products relate to an interdisciplinary development approach, fed directly from science-based and academic laboratories, that realizes experimental set-ups to marketable devices. This article has investigated the movement from spontaneous to coordinated schemes in product innovation through a transition phase of knowledge structuring in an exploitable form. This transition, being crucial to future market success of science-based products, should proceed through a knowledge platform as that described in Figure 3, a model that links closely industry and university, derived from the experience gained and the lessons learnt out of the successful and the not so successful published cases and produced devices.

The fast pace of technological change and the market demands for novel and better products requires continuous innovation and fast market introduction. The key issues emerging from the present work refer to early information transfer from university to industry for achieving the product innovation. This implies primarily a market-targeted research strategy in the universities, focusing on industrial needs and not on conventional technology substitution, thus preventing misjustifications of potential and cost-effectiveness. Such an approach could minimize the gap between industry (and market) and university output, providing that this output is suitably handled and managed by industry during its incorporation into in-house R&D.

Biosensors addressed a broad-range of applications, in both diagnostics and biomedicine, on the premises of theoretical capabilities and potential of untested in the field experimental set-ups. It is not advisable to aim *a priori* at replacing conventional and standard detection schemes, since neither the capabilities nor the practicality or the broadness of chromatography or ELISA can be technically and economically be superseded by molecular recognition at the current state-of-the-art. As a matter of fact, when a specific and narrow niche market need has been matched to a viable biosensor model, industry has prompted its transition to a successful product through proper standardization at an acceptable cost, as for example, the Biacore® or NECI® product lines. As regards support by means of subsidy and other financial mechanisms, it should be encouraging research efforts directed rather to add marketability at the technology and needs at hand, than to develop novel and "exotic" technologies. The neglect of this prioritization often results in granting fewer resources for developing current clinical applications, a market that undeniably gives biosensors a strong competitive advantage. On the other hand, the exotic technologies that continue to reach the academic forum should not be overlooked as they bear significant value in revealing and drawing paths for innovative product design and breakthrough solutions. Such discriminating aspects have been also seen in enzyme technology, especially in environmental biotechnology, where the genetically modified microorganisms may have not proliferated as expected but generated an enormous beneficial scientific output in the understanding of microbial population dynamics (Lynch, 1998). Evidently, there is a trade-off concerning the allocation of financial resources between (i) projects aiming at the prompt short-term market development and (ii) projects targeted on knowledge evolution and the drawing of paths that may lead, in the long-run, to innovative achievements. This trade-off, which is a matter of research policy at macro-scale, is rather complicated since projects of category: (i) contribute with new information/knowledge to projects of category (ii) by following a parallel road to the push–pull mechanism presented herein, while the inverse influence is limited.

The methodological framework proposed herein, especially designed for science-based industrial products, is suitable to serve this transition, aiming at the acceleration of knowledge transfer and a successful product delivery. Depending on the size of the company and the available resources, the criteria for MCA are set and weighted so that the D_{opt} suggested by this scheme helps adopting basic science for developing/delivering a product tailor-made to fulfill both the market needs and the company's perspectives. For example, the selection of D_{opt} for the blood glucose meter presented as case example could turn either toward the background or the marketed development stage, depending whether the company is large or small. Whereas, innovation is ascertained in the former

case, taking full advantage of an experimental set-up and prompting the establishment of university-industry (direct or indirect through specialized companies and knowledge mediators) alliance, product differentiation is sought for in the latter case by means of reverse engineering on the basis of university research.

It is worthwhile noting that the changing market environment and the progress in science/technology that is seen in

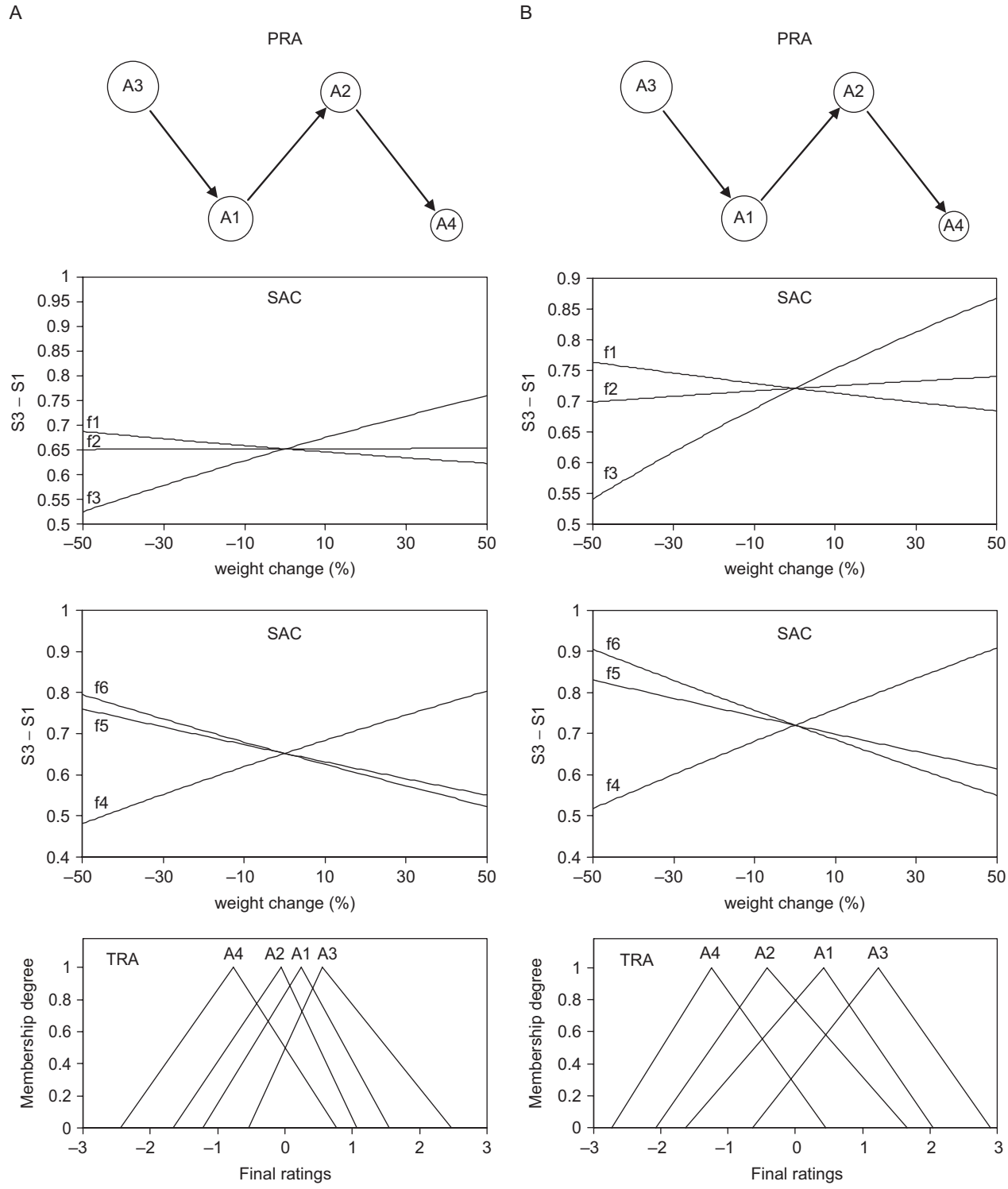

Figure 7. Partial ranking of alternatives, PRA (shown as a set of circles with areas proportional to the crisp number, S_i, which indicate the corresponding relative value of the alternative A_i in the ranking vector), sensitivity analysis of each criterion, SAC, and total ranking of alternatives, TRA (shown as a set of triadic fuzzy numbers in the usual forms of triangles to reveal the common parts which constitute a measure of overlapping along the relative scale of pre-order, that is, the horizontal axis, especially for lower membership function values), at (A) low preferability resolution with medium q, p values and (B) high preferability resolution with low q, p values. The arrow "→" means "better than."

academia (especially in medical diagnostics, pharmacology, occupational hygiene and safety) usually imposes stricter product specifications, either prescribed by legislation or/and required by the public/market (George, Zahra, and Wood, 2002), which implies an upward shifting of C_1-curve to its new position C_1 (Figure 8A). It also becomes steeper, since (C_1 -C) is an increasing function of D due to disproportional burdening at higher depth-levels, where expertise under the form of implicit/tacit knowledge required/expected to be acquired by scientists/engineers is dominant - implying higher cost. The resultant decrease of D_{opt} partially counterbalances the increase described in Figure 5, at least temporarily, since in the medium/long run the expertise incorporated in the product or/and in its production process contributes to experience/data accumulation and knowledge deepening/specialization (Khilji, Mroczkowski, and Bernstein, 2006; Powell, Koput, and Smith-Doerr, 1996), which both increase the D_{opt}-value. Consequently, the comparative advantage of the knowledge creator/supplier increases in the long run with respect to this issue, too (Powell, Koput, and Smith-Doerr, 1996). On the other hand, there is a shifting of C_2-curve to a new position C_2 (Figure 8B) in less developed countries, as a result of pressure put by the public on the multinational corporations and the industrialized countries to loosen proprietary rights, especially in the sectors of food and pharmaceuticals (Siu and Bao, 2008). In this case, the new lower-cost curve is more flat in relation with the old one, since saving of resources is higher at lower D-levels where there is limited need for product/process research and development and the possibility/probability of loosening proprietary rights is higher. The implied short- and long-term decrease of D_{opt} contributes to widening the gap between industrialized and less developed countries (Siu and Bao, 2008) or/and between large knowledge-based multinational corporations and SMEs functioning mainly at local/periphery level (Levin, 2004; Mangematin et al., 2003), at least with respect to the issues examined so far. Nevertheless, the development of a KB such as that designed/implemented for CBR/MCA can shorten this gap, provided it is properly functioning within an SME or a sectoral technical center supporting SMEs, as we have previously reported (Batzias and Batzias, 2004).

This kind of technology transfer can be facilitated either by adopting/adapting information/knowhow coming from the already established KB (stage 9) assessed by a web-based system intelligent agent (stage 10) or by developing an *ad hoc* KB at local level. In the latter case, a modification of the Nonaka's SECI (Socialization, Externalization, Combination, Internalization) model (Nonaka, Umemoto, and Senoo, 1996) can be applied to obtain explicit/transferable knowledge from tacit/implicit knowledge, by means of personnel and associates that have relevant experience. The modification involves the addition of a multiple exogenous latent (i.e., only periodically active) transition mechanism to conduct the procedure, which otherwise lacks orientation/progressiveness in knowledge acquisition; a multiplicity of n^{th} order means that there are n-1 levels further to the basic one, where the model has been initially activated and run m_1 times before going to the second level, where it runs m_2 times, and so on, somehow simulating a FOR-NEXT loop in conjunction with an IF-THEN-ELSE statement, where the repeated part (i.e., the loop) of the algorithmic procedure is the Nonaka's simple model and the IF-part of the conditional statement includes the satisfaction of certain criteria set *a priori* as a frame of

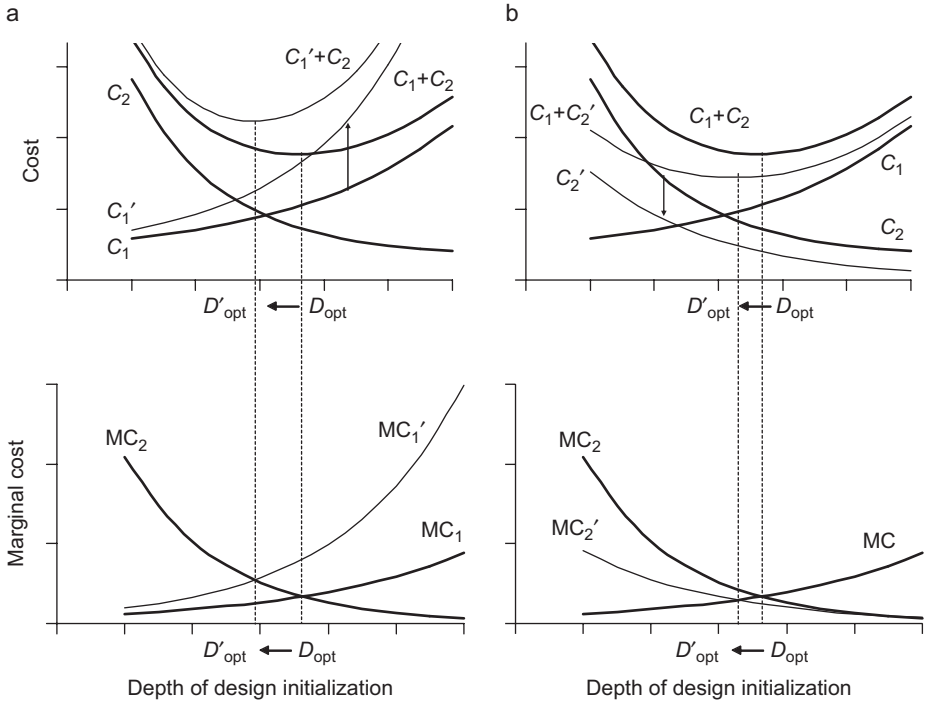

Figure 8. Determination of optimal depth of design (D_{opt}) initialization with only one criterion (cost) forming the objective function, indicating also the short-term impact of (A) imposing stricter specifications on the product/process under design/development and (B) loosening industrial proprietary rights.

linguistic control variables in fuzzy form; therefore, m_i (i=1, 2, …, n) is not known *a priori*, although a maximum value can be assigned as a constraint. Evidently, the number N of times the Nonaka's model will totally run is given by $N=m_1+m_2+\cdots+m_n$, calculated on an *a posteriori* basis.

A typical run of the SECI model in the case of probe determination used herein for implementation includes the following: (i) tacit/implicit knowledge sharing by experts, by means of a controlled vocabulary, keeping personal experience within a subjective mode of expression (Socialization, i.e., implicit to implicit conversion), realized in the determination of the biomedical device to be developed (stage 1) and the development stages to be implemented (stage 2), where strategic decisions on long-term objectives have to be made; (ii) interpretation of tacit/implicit into objective forms within a relevant ontology by using mainly analogues and metaphors as cognitive vehicles (Externalization, i.e., implicit to explicit conversion), expressed in the device decomposition into functional parts (stage 6) and the recombination module (stage 8); (iii) transition to explicit knowledge of higher order to obtain desired structures according to norms set *a priori* (Combination, explicit to explicit conversion), playing an important role in formulating the probe case (stage 3) and setting the criteria for CBR and fuzzy MCA (stages 5 and 18, respectively); (iv) subjective understanding of implications coming from the structures building their realization/utilization, possibly including personal simulation/experimentation (Internalization, i.e., explicit to implicit conversion), materialized in assessing/evaluating the results (stages 14, 16, 19). Although this is a cyclic scheme of continual creation of knowledge, the resultant probe, in a form suitable for testing, comes from executing the states of Combination while the results of testing are subjectively evaluated and incorporated within each expert's personal KB during the successive stages of Internalization, where the IF-THEN-ELSE statement is also activated to indicate continuation/repetition or termination of the knowledge acquisition procedure at the level under consideration. Since we have designed four levels/depths of development stages (i.e., MV, PV, DS, and BR), n=4, while most likely $m_i<m_{i+1}$ (i=1,2,3), because the number of degrees of freedom increases as D increases, an issue that has been already taken into account for locating D_{opt} in Figure 8A and 8B.

In conclusion, the need for continuous innovation as a basis for achieving a sustaining competitiveness is often acknowledged as an industry reality. Similarly, the need of implanting an applied character to university research is prompted by the potential private and public sponsors. The difficulties presented in adopting a university-derived set-up and engineer it to a device, lead many organizations to rely on external innovation paths, as the university-industry technology transfer channel. Yet the effective transfer of knowledge cannot be taken for granted, unless it occurs under the provisions of industry and as a function of the attributes inherent to the nature of the transferable.

Acknowledgements

They also express sincere thanks to the reviewer and to Dr Inge Russell for constructive comments and kind guidance, respectively.

Declaration of interest

The authors thankfully acknowledge the financial support of the Research Centre of the University of Piraeus.

References

Alocilja EC, Radke SM. 2003. Market analysis of biosensors for food safety. Biosens Bioelectron 18: 841–846.

Batzias AF, Batzias FA. 2004. Fuzzy multi-criteria choice of instrumental methods for measuring physical quantities—application in the case of dielectric aluminium anodic oxide films. Proc IEEE Instrument Meas Technol 3: 2217–2222.

Batzias FA, Marcoulaki EC. 2002. Restructuring the keywords interface to enhance CAPE knowledge via an intelligent agent. Comp Aided Chem Eng 10: 829–834.

Batzias FA, Siontorou CG. 2005. Investigating the causes of biosensor SNR decrease by means of fault tree analysis. IEEE Trans Instrum Meas 54: 1395–1406.

Brans JP, Vincke Ph, Mareschal B. 1986. How to select and how to rank projects: The PROMETHEE method. Europ J Oper Res 24: 228–238.

Breznitz SM, O'Shea RP, Allen TJ. 2008. University commercialization strategies in the development of regional bioclusters. J Prod Innov Manag 25: 129–142.

Contractor FM, Sharma P, Dash N, Lupetin AR, Schapiro RL. 1987. Extension of hepatic metastatic tumor along a biliary drainage catheter tract: case report. Cardiovasc Intervent Radiol 10: 303–304.

Costa C, Fontes M, Heitor MV. 2004. A methodological approach to the marketing process in the biotechnology-based companies. Indust Market Manag 33: 403–418.

D'Orazio P. 2003. Biosensors in clinical chemistry. Clin Chim Acta 334: 41–69.

Dumett M, Rosen G, Sabat J, Shaman A, Tempelman L, Wang C, Swift R. 2008. Deconvolving an Estimate of Breath Measured Blood Alcohol Concentration from Biosensor Collected Transdermal Ethanol Data. Appl Math Comput 196: 724–743.

Fallberg P-O, Brynö A. 1998. They just keep on working… Biacore J 5: 17–18.

Faulkner DO, De Rond M. 2000. Cooperative Strategy: Economic, Business and Organizational Issues. Oxford, UK: Oxford University Press.

Fernandez D, Chow M. 2005. Intellectual property strategy in bioinformatics and biochips. Biosens Bioelectron 21: 197–200.

George G, Zahra SA, Wood Jr., DR. 2002. the effects of business-university alliances on innovative output and financial performance: a study of publicly traded biotechnology companies. J Business Vent 17: 577–609.

Guiochon GA, Beaver LA. 2004. Progress and future of instrumental analytical chemistry applied to the environment. Analyt Chim Acta 524: 1–14.

Hawdon JM, Platt MP, Aynsley-Green A. 1993. Neonatal hypoglycaemia—blood glucose monitoring and baby feeding. Midwifery 9: 3–6.

Khilji SE, Mroczkowski T, Bernstein B. 2006. From invention to innovation: toward developing an integrated innovation model for biotech firms. J Prod Innov Manag 23: 528–540.

Kissinger PT. 2005. Biosensors-a perspective. Biosens Bioelectron 20: 2512–2516.

Kumar CSSR. 2007. Nanomaterials for Biosensors. Germany: Wiley-VCH.

Lee CH, Wang SC, Yuan CJ, Wen MF, Chang KS. 2007. Comparison of amperometric biosensors fabricated by palladium sputtering, palladium electrodeposition and Nafion/carbon nanotube casting on screen-printed carbon electrodes. Biosens Bioelectron 22: 877–884.

Levin M. 2004. Cross-boundary learning systems. Syst Pract Action Res 17: 151–159.

Lim SH, Wei J, Lin J, Li Q, Kuayou J. 2005. A glucose biosensor based on electrodeposition of palladium nanoparticles and glucose oxidase onto Nafion-solubilized carbon nanotube electrode. Biosens Bioelectron 20: 2341–2346.

Lindner E, Gyurcsányi RE, Buck RP 2002. Membranes in electroanalytical chemistry: membrane-based chemical and biosensors. In Hubbard AT (ed.), Encyclopedia of Surface & Colloid Science. NY: Marcel Dekker.

Lynch JM. 1998. Terrestrial biotechnology. Curr Opin Biotechnol 9: 247–251.

Mangematin V, Lemarié S, Boissin J-P, Catherine D, Corolleur F, Coronini C, Trommetter M. 2003. Development of SMEs and heterogeneity of trajectories: the case of biotechnology in France. Res Policy 32: 621–638.

Marot M, Selsky JW, Hart W, Reddy P. 2005. Research teams in an Australian biotechnology field: how intellectual property influences collaboration. In: Advances in Interdisciplinary Studies of Work Teams (pp. 1–31), Vol. 11. Elsevier Ltd. Editors: M.M. Beyerlein, S.T. Beyerlein, F. A. Kennedy. Publishing Place: UK

Mirsky VM. 2004. Ultrathin Electrochemical Chemo- and Biosensors: Technology and Performance. Springer Series on Chemical Sensors and Biosensors, Vol. 2. Berlin: Springer.

Newman JD, Turner AP. 2005. Home blood glucose biosensors: a commercial perspective. Biosens Bioelectron 20: 2435–2453.

Newman JD, Tigwell LJ, Turner APF, Warner PJ. 2004. Biosensors—A Clearer View. UK: Cranfield University.

Nikolelis DP, Siontorou CG. 1996. Flow injection monitoring and analysis of mixtures of simazine, atrazine, and propazine using filter-supported bilayer lipid membranes. Electroanalysis 8: 907–912.

Nikolelis DP, Simantiraki MG, Siontorou CG, Toth K. 2005. Flow injection analysis of carbofuran in foods using air stable lipid film based acetylcholinesterase biosensor. Analyt Chim Acta 537: 169–177.

Nonaka I, Umemoto K, Senoo D. 1996. From information processing to knowledge creation: a paradigm shift in business management. Technol Soc 18: 203–218.

Oberlies NH, Kroll DJ. 2004. Camptothecin and taxol: historic achievements in natural products research. J Nat Prod 67: 129–135.

Paladino A. 2007. Investigating the drivers of innovation and new product success: a comparison of strategic orientations. J Prod Innov Manag 24: 534–553.

Pisano GP. 1989. Using equity participation to support exchange evidence from the biotechnology industry. J Law Econ Org 5:109–126.

Powell W, Koput K, Smith-Doerr L. 1996. Inter-organizational collaboration and the locus of innovation: networks of learning in biotechnology. Admin Sci Quart 41: 116–145.

Ramsay G. 1998. Commercial biosensors: applications to clinical, bioprocess, and environmental samples. In: Chemical Analysis: A Series of Monographs on Analytical Chemistry and Its Applications. New York: Wiley-Interscience.

Rao LV, Jakubiak F, Sidwell JS, Winkelman JW, Snyder ML. 2005. Accuracy evaluation of a new glucometer with automated hematocrit measurement and correction. Clin Chim Acta 356: 178–183.

Razumiene J, Vilkanauskyte A, Gureviciene V, Barkauskas J, Meskys R, Laurinavicius V. 2006. Direct electron transfer between PQQ dependent glucose dehydrogenases and carbon electrodes: an approach for electrochemical biosensors. Electrochim Acta 51: 5150–5156.

Reuer JJ, Zollo M, Singh H. 2002. Post-formation dynamics in strategic alliances. Strat Manag J 23: 135–151.

Rich RL, Myszka DG. 2001. Survey of the year 2000 commercial optical biosensor literature. J Mol Recognit 14: 273–294.

Rodriguez-Mozaz S, Lopez de Alda MJ, Barceló D. 2006. Biosensors as useful tools for environmental analysis and monitoring. Anal Bioanal Chem 386: 1025–1041.

Salomo S, Weise J, Gemünden G. 2007. NPD planning activities and innovation performance: the mediating role of process management and the moderating effect of product innovativeness. J Prod Innov Manag 24: 285–302.

Salter AJ, Martin BR. 2001. The economic benefits of publicly funded basic research: a critical review. Res Policy 30: 509–532.

Scheller FW, Schubert F, Renneberg R, Müller H-G, Jänchen M, Weise H. 1985. Biosensors: trends and commercialization. Biosensors 1: 135–160.

Schuvailo OM, Soldatkin OO, Lefebvre A, Cespuglio R, Soldatkin AP. 2006. Highly selective microbiosensors for *in vivo* measurement of glucose, lactate and glutamate. Anal Chim Acta *573*–574: 110–116.

Siontorou CG, Nikolelis DP, Krull UJ. 2000. Flow injection monitoring and analysis of mixtures of hydrazine compounds using filter-supported bilayer lipid membranes with incorporated DNA. Anal Chem 72: 180–186.

Siu W-S, Bao Q. 2008. Network strategies of small Chinese high-technology firms: a qualitative study. J Prod Innov Manag 25: 79–102.

Stuart TE, Ozdemir SZ, Ding WW. 2007. Vertical alliance networks: the case of university-biotechnology-pharmaceutical alliance chains. Res Policy 36: 477–498.

Thévenot DR, Toth K, Durst RA, Wilson GS. 1999. Electrochemical biosensors: recommended definition and classification. Pure Appl Chemi 71: 2333–2348.

Thompson E, Vonortas NS. 2005. Biotechnology evolution and regulation of pharmaceuticals. In:Carruth R (ed.), Global Governance of the Pharmaceuticals Industries: Transatlantic and Trilateral Regulatory Harmonization and Multilateral Policy Cooperation for Drug Safety. The George Washington University, Ch. 9.

Tien H-T, Ottova-Leitmannova A. 2003. Planar Lipid Bilayers (BLMs) and Their Applications. Amsterdam: Elsevier.

Todt O, Gutiérrez-Gracia A, Fernández de Lucio I, Castro-Martínez E. 2007. The regional dimension of innovation and the globalization of science: the case of biotechnology in a peripheral region of the European Union. R&D Manag 37: 65–74.

Toko K. 2000. Biomimetic Sensor Technology. UK: Cambridge University Press.

Tschmelak J, Kumpf M, Käppel N, Proll G, Gauglitz G. 2006. Total internal reflectance fluorescence (TIRF) biosensor for environmental monitoring of testosterone with commercially available immunochemistry: antibody characterization, assay development and real sample measurements. Talanta 69: 343–350.

Tschmelak J, Proll G, Riedt J, Kaiser J, Kraemmer P, Bárzaga L, Wilkinson JS, Hua P, Hole JP, Nudd R, Jackson M, Abuknesha R, Barceló D, Rodriguez-Mozaz S, de Alda MJ, Sacher F, Stien J, Slobodník J, Oswald P, Kozmenko H, Korenková E, Tóthová L, Krascsenits Z, Gauglitz G. 2005. Automated water analyser computer supported system (AWACSS) Part I: Project objectives, basic technology, immunoassay development, software design and networking. Biosens Bioelectron 20: 1499–1508.

Tseng TY, Klein CM. 1989. New algorithm for the ranking procedure in fuzzy decision making", IEEE Trans Syst Man Cybernet 19: 1289–1296.

U.S. Food Drug Administration 1997. Review criteria assessment of portable blood glucose monitoring in vitro diagnostic devices using glucose oxidase, dehydrogenase or hexokinase methodology, draft document.

Vote DA, Doar O, Moon RE, Toffaletti JG. 2001. Blood glucose meter performance under hyperbaric oxygen conditions. Clin Chim Acta 305: 81–87.

Wang J. 2001. Glucose biosensors: 40 years of advances and challenges. Electroanalysis 13: 983–988.

Wisniewski N, Moussy F, Reichert WM. 2000. Characterization of implantable biosensor membrane biofouling. Fresenius J Anal Chem 366: 611–621.

Yimit A, Rossberg AG, Amemiya T, Itoh K. 2005. Thin film composite optical waveguides for sensor applications: a review. Talanta 65: 1102–1109.

Appendix

The query (probe specifications) and the similarity assessment, estimated by means of a distance function dlist(x, y) = abs($x-y$), which is then normalized to get a value in the range [0, 1], of the retrieved cases at the level of marketed versions. The best representative SMBG meter for this level, with 86.4% similarity to the probe, is the FreeStyle, Therasense meters, utilizing glucose dehydrogenase and an Os-based mediator.

				Similarity function										
Query attribute	Specifications weights	Probe		#1	#2	#3	#4	#5	#6	#7	#8	#9	#10	#11
Linear Range	10–600 mg/dL	0.78	1	0.78	0.78	0.468	0.624	0.702	0.78	0.741	0.663	0.663	0.663	0.468
Precision	Low range: <10%	0.8	8	0.711	0.711	0.64	0.178	0.756	0.8	0.8	0.756	0.756	0.8	0.8
	Med. range: <10%	0.8	8	0.711	0.711	0.622	0.756	0.8	0.8	0.8	0.756	0.756	0.782	0.782
	High range: <10%	0.8	8	0.596	0.596	0.569	0.711	0.764	0.764	0.764	0.693	0.693	0.693	0.693
Accuracy	≤ 10%	0.95	8	0.844	0.844	0.855	0.528	0.95	0.422	0.422	0.549	0.549	0.633	0.633
Sample volume	≤ 0.5 mL	0.9	0.5	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9
Hematocrit stability	Over hematocrit variations below 35% and above 55%	0.68	1	0.272	0.272	0.34	0.34	0.612	0.612	0.612	0.272	0.272	0.408	0.408
Cholesterol stability	Up to 600 mg/dL	0.72	600	0.617	0.669	0.463	0.617	0.694	0.694	0.694	0.72	0.72	0.694	0.694
Trigly-cerides stability	Up to 3000 mg/dL	0.7	3000	0.431	0.431	0.027	0	0.7	0.7	0.162	0	0	0.7	0.7
Ease of calibration	Easily and accurately calibrated by nonexperts	0.62	10	0.62	0.62	0.62	−0.069	0.344	0.62	0.138	0.344	0.344	0.138	0.138
Test time	≤ 15 sec	0.83	10	0.322	0.322	0.491	0.491	0.745	0.491	0.491	0.745	0.745	0.661	0.661
Alternate size testing	Yes	0.91	1	0	0	0.91	0	0.91	0	0	0	0.91	0	0.91
Ease of use	Simple use by nonexperts and impaired users	0.65	10	0.433	0.433	0.578	0.289	0.289	0.361	0.289	0.614	0.614	0.217	0.542
Operational use	≥ 2 years	0.32	5	0.16	0.16	0.16	0.24	0.32	0.32	0.32	0.16	0.16	0.24	0.24
Cost	≤ 60 Euro	0.48	50	0.455	0.362	0.455	0.463	0.429	0.429	0.455	0.429	0.429	0.429	0.059
Total		**11.48**		**7.852**	**7.811**	**8.098**	**6.608**	**9.916**	**8.695**	**7.588**	**7.601**	**8.511**	**8.499**	**9.168**
Similarity				**0.684**	**0.68**	**0.705**	**0.576**	**0.864**	**0.757**	**0.661**	**0.662**	**0.741**	**0.74**	**0.799**

Description of cases: #1: Glucometer II/Glucostix (Ames Division, Miles Laboratories, Mulgrave, Vic., Australia); #2: Reflolux II/Haemoglukotest 20-800R (Boehringer Mannheim GmbH, Mannheim, Germany); #3: ExacTechTM, Medisense, Mainz, Germany; #4: Ascensia Elite (former Glucometer Elite) (Bayer Corporation, Tarrytown, NY, USA); #5: FreeStyle (Therasense/Abbott Diabetes Care, Alameda, CA, USA); #6: Ascensia Elite (former Glucometer Elite) (Bayer Corporation, Tarrytown, NY, USA); #7: Accu-Chek (Roche Group, Basel, Switzerland); #8: PCx (Abbot/Medisense, Bedford, MA, USA); #9: SuperStep Flexx (LifeScan Inc., BC, Canada); #10: One Touch (LifeScan Inc., Johnson & Johnson, Milpitas, CA, USA); #11: Glucotrend (Boehringer Mannheim/Roche, Mannheim, Germany).