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13.1 INTRODUCTION

The applications of biosensor and bioelectronic devices may be placed in five categories (Talukder, 2002): agriculture, food analysis, high-throughput screening, medical analysis, and nanobiotechnology. Each of these categories may be further subdivided into different applications, for example, Talukder (2002) indicates that in the category of agriculture one has sensor applications for the detection of herbicide(s) in soil, detection of heavy metals in soil, detection of genetic modifications of foodstuffs, etc. The author provides a thorough in-depth analysis of the market for biosensors, though the report is 3–4 years old.

Zarkoff (2002) indicates that the average annual growth rate (AAGR) for the biosensor market is around 7.5%. Some sectors such as nanobiotechnology have a higher growth rate (8.2%), whereas others such as food monitoring and biosensors used in agriculture have a lower growth rate of 7.2%. This author further indicates that the growth rate for high-throughput screening for the detection of drug targets is 7.5%. However, since presently this sector dominates the biosensor market (77%), Zarkoff (2002) indicates that it is this 7.5% which is also the AAGR of the biosensor market for all biosensor applications. This author further indicates that the market for (a) high-throughput screening and (b) medical analysis for the year 2004 was estimated to be $1.255 billion and $181.4 million, respectively.

Table 13.1 shows the estimated market value for high-throughput screening for the years 2004–2009 (Zarkoff, 2002).

The 8.5% AAGR was presented in Table 13.1 in case there are some reasons, such as (a) strategic new inventions that could significantly impact the biosensor market come into play or (b) a substantial increase in demand for these types of HTS systems to enhance drug discovery.

Zarkoff (2002) emphasizes that medical analysis biosensors is the second largest market, with glucose monitoring for the effective management of diabetes being a major driving force. A gradual increase in obesity of individuals along with increasing stress levels in our daily lives would lead to an increase in the incidence of diabetes, which is already rumored to be reaching epidemic proportions. Thus, apparently, the demand for glucose monitoring systems is not expected to slow down or decrease in the near future. Zarkoff (2002) estimates the medical market for biosensors for the year 2004
Table 13.1

Projected estimated market (in billion dollars) for high-throughput screening systems for drug discovery at an average annual growth rate (AAGR) of 7.5% (adapted from Zarkoff, 2002), and 8.5%, respectively

| Year       | Estimated market for high-throughput screening systems at 7.5% AAGR $ (in billion) | Estimated market for high-throughput screening systems at 8.5% AAGR $ (in billion) |
|------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| Base year, 2004 | 1.255                                                                            | 1.255                                                                            |
| 2005       | 1.349                                                                            | 1.362                                                                            |
| 2006       | 1.450                                                                            | 1.477                                                                            |
| 2007       | 1.559                                                                            | 1.603                                                                            |
| 2008       | 1.676                                                                            | 1.739                                                                            |
| 2009       | 1.802                                                                            | 1.887                                                                            |

at $200 million. Assuming a conservative 90% of this $200 million for glucose monitoring devices yields $180 million as the estimated market for glucose monitoring systems.

A Freedonia report (2002) on the market for biosensors till the year 2006 estimates that the market will grow at 8.6% annual rate. This report is a couple of years old. Further predictions are provided till the year 2011. A later report by Freedonia (2004) indicates that the demand for chemical sensors will grow at a rate of 8.5% through 2008. This is primarily driven by: (a) falling prices for novel sensors and high-performance sensors and (b) microfabricated innovations. The growth of optical sensors will be the fastest. According to this report, the present chemical sensor market stands at $2.8 billion. Forecasts till the year 2008 and 2013 are provided.

Research and Markets (2004) estimates the biosensor market to grow to $10.8 billion by the year 2007 with an annualized growth rate of 10.4%. The report emphasizes that the medical application market continues to overshadow other application areas. It also points out that the rising rate of obesity in the world is leading to increase in rates of diabetics especially in the industrial world. The Research and Markets report (2004) also mentions other areas of biosensor application that include rapid assay biosensors for drug discovery, detection of biological and chemical agents for the war on terrorism, food monitoring, and environmental applications. As expected, there are differences in the AAGR for the biosensor market estimated by different authors or reports.

Rajan (2002) expects the biosensor market to grow at an annual rate of 6.6% to $1.81 billion by the year 2006. This author emphasizes that advances in photolithographic techniques as well as in microfluidics will go a long way in helping remove some of the hurdles that prevented growth in the biosensor industry. Rajan (2002) further emphasizes the particular use of biosensors to monitor food and crops (especially those that are genetically altered) in Europe. The monitoring of foodstuffs includes spoilage and the detection of toxins.

MedMarket Diligence (2003) has recently indicated the applications and market opportunities for nanotechnology and microelectromechanical systems (MEMS) for current medical applications. The report presents a detailed market and technological assessment for medical applications, with special emphasis on clinical diagnostics.
A very recent London South Bank University report by Chaplin (2004) indicates that the estimated world analytical market is 12 billion British pounds. The author estimates the biosensor market to be 0.1% of this analytical market yielding 12 million British pounds. Using an exchange rate of British £1 = $1.9433 (http://finance.yahoo.com/currency?u) (November 03, 2004; 6:30 pm) yields $2.32 million. Chaplin (2004) emphasizes that this market possesses a significant potential for expansion. Lab_Bell, Inc. (2004), a company that makes fast, inexpensive, and sensitive multi-purpose biosensors for the detection of toxic molecules estimates that the biosensor market for the year 2005 is as follows: agrifood is $237 million, environment applications $237 million, and industrial biotechnology $158 million. The small company (nine employees) presently has plans for a $2 million expansion. One of its products makes quantitative the concentration of herbicides, and evaluates the toxicity of effluents in under 10 min.

Lin and Wang (2005) have very recently presented a theoretical approach to biosensor commercialization strategy. These authors also estimate the biosensor market to grow to $10.8 billion by the year 2007. They expect the biosensor market to mushroom in the coming years. They emphasize that the biosensor market presents both opportunities as well as hurdles that need to be overcome. They also emphasize the importance of predicting the biosensor market, and the need to identify and convert promising biosensor technologies for commercial applications. Furthermore, these authors present alternate commercialization strategies for each specific biosensor application, and outline strategies to help predict the best one.

Glucose monitoring systems come under the fast growing sector of point-of-care (POC) diagnostic testing. Other POC tests include pregnancy testing, hepatitis testing, drugs of abuse screening testing, infectious disease testing, HIV, coagulation testing, and fertility testing (Trimark Publications, 2004). These authors indicate that diagnostic testing is an estimated $21 billion market. Both physicians and patients recognize the better management of health care provided by POC testing, and the demand for these types of products is bound to increase. Trimark Publications (2004) further emphasizes that newer technology platforms and better fabrication techniques would lead to more efficient POC devices. These POC devices range from single-use disposable units for individual home use to moderate-sized instrumented diagnostic systems for clinical and hospital use.

In a more recent report, Fuji-Kerzai (2004) indicates that the worldwide market for biosensors in 2003 was $7.3 billion. In contrast to Zarkoff's (2002) 7.5% AAGR for the biosensor market, Fuji-Kerzai (2004) indicates a growth rate of 10.8%. This represents almost a 44% increase in growth rate between that predicted by Zarkoff (2002) and Fuji-Kerzai (2004). This underscores the ‘unreliability’ in the projection figures for the growth rate, worldwide market, etc. Using the Fuji-Kerzai (2004) numbers with a $7.3 billion worldwide market for the year 2003, and an annual growth rate of 10.4% leads to a worldwide market for biosensors, in billion dollars of 8.059, 8.897, 9.823, 10.84, 11.97, and 13.21, for the years 2004, 2005, 2006, 2007, 2008, and 2009, respectively. This author also indicates the important activities of the different major companies throughout their report that are driving the biosensor market. Using the rule of 72, the biosensor market will double in 6.92 years, if the predicted 10.4% growth rate is maintained. A growth rate of 12% would double the biosensor market in 6 years.

The order of importance of the different sectors in the biosensor market is also slightly different according to Fuji-Kerzai (2004) when compared with the Zarkoff (2002)
analysis. Fuji-Kerzai (2004) emphasizes that due to the increasing obesity levels, especially in the industrial world, and the rapid rise in the number of diabetics and the necessity of monitoring glucose levels, the medical area is still the major driving force for the development of biosensors. This is followed by the need for (a) rapid assay biosensors for high-throughput systems to hasten the speed for drug discovery (as required by the pharmaceutical industry), (b) rapid detection biosensors for chemical and biological warfare agents, and finally (c) biosensors to detect food pathogens (food safety) and environmental contaminants. A biosensors and bioelectronics report by Talukder (2002) of the Business Communications Company also indicates the need for biosensors in fermentation and forensic technologies. This report also provides a perspective of public perception and public policy on the regulation of biosensor technologies as they apply to the medical and food industries.

A University of Delaware graduate class, ELEG 667 entitled ‘Biosensors and BioMEMS (2004)’, indicates that there are at least 50 different types of biosensor systems worldwide. This report was downloaded in the year 2004, and seems like quite an old report. However, in the year 2005, the report estimated the clinical diagnostics market to be around $8.5 million (with, as expected, 90% comprising the home glucose market). As expected, different individuals have come up with different numbers for the anticipated market for biosensors in different areas.

Kissinger (2004) indicates that the electrochemical sensors market is at $100 million per year and $1 billion for all sensors. He indicates that the second most common analyte measured after glucose (which is the first) is lactate. However, lactate is a distant second to glucose, and its market is about two orders of magnitude (about 100 times) lower than that of glucose. The author emphasizes that in spite of the large number of publications in this area, the commercial applications of biosensors face severe challenges. The author classifies biosensors in to three types:

(a) **Single use.** Ninety-nine per cent of the commercial market, easy to use, not very precise or accurate, and the cost versus data rate is very high. For example, the electronics cost approximately, $50, electrochemical cell and components ($0.50)

(b) **Intermittent use.** Moderate complexity in use, excellent performance, but high up front cost (approximately $1000–10,000 per instrument cost), good precision and accuracy, moderate cost versus data rate.

(c) **Continuous use.** Very easy to use, poor performance and accuracy, good precision, very low cost versus data rate.

Finally, Kissinger (2004) indicates that practical issues with regard to biosensor manufacture include inventory time at manufacture (about 2 months), shipping (2–10 days), and finally inventory at point of use (2–3 months). This aspect is often ignored.

The emphasis on the detection of harmful biological and chemical agents for protecting civilians and civilian infrastructure is underscored by the US government’s Department of Homeland Security (DHS) budget of $36.5 billion for the year 2004 (Farrell, 2004). It is expected to increase by about 10.1% to $40.2 billion for the year 2005. Biosensors are expected to play a major role here. It is of interest to note that, though the DHS does not do any research itself, it does fund other government agencies such as FBI, CIA, EPA, etc.
Miller (2004) recently indicates that an after-effect of the September 11 attacks in the United States followed by the anthrax incidents have prompted the US Congress to approve plans and spend $500 million for new biosafety space (NIAID, 2003). This biocontainment space is required to develop anti-bioweapon vaccines and drug treatments. The National Institute of Allergy and Infectious Diseases (NIAID, one of the National Institutes of Health in Bethesda, MD) also provided $7–21 million each to build nine new biosafety level-3 (BSL-3) laboratories around the country. This emphasizes the seriousness of the situation and the perceived need for these new laboratories. Furthermore, Kostel (2004) also indicates that there are presently no rapid diagnostic methods to detect Category A bioweapons such as anthrax, botulism, plague, smallpox, tularemia, and viral hemorrhagic fevers. Vaccines and post-exposure therapy are available to various degrees (yes, no, and limited). Kostel (2004) further adds that the number of biosafety level 4 (BSL-4) laboratories will also increase. These are laboratories which may handle lethal biologicals spread through the air, and for which there is no known cure.

Farrell (2004) further emphasizes the need for rapid deployment, and also that biological agents are more difficult to detect than chemical agents. For the rapid detection of harmful biologicals, Baeumner in Farrell (2004) emphasizes the importance of improving the speed of biosensors. Microfluidics does that, but places a limitation on sample size. Baeumner is trying to increase the sample size. The detection is based on the movement of the reaction products along a test strip by capillary action.

The anthrax scare at a few locations in the United States has also prompted the development of on-site, quick detection tests of anthrax spores. Bohannon (2002) describes a rapid, on-site test that is capable of detecting anthrax spores within minutes. This compares with the pregnancy-like test that requires neither specialized training nor any instrumentation. This, if successfully brought to the market, is a good application of point-of-use detection technology.

Niedbala (2002) indicated a novel technology for the rapid, sensitive, on-site multiplex detection of warfare agents. This author used up-converting phosphor receptors. This is a new technology wherein materials up-convert infrared to ultra violet. The up-converting phosphor technology (UPTm) was demonstrated to detect biological agents such as tularensis, plague, and cholera.

Finally, Richard Mathies of the University of California in Farrell (2004) emphasizes that the information and knowledge gained in developing biosensors for biological agent detection can be applied for the diagnosis of disease (dual-action). By pinpointing the bacterium that causes a disease, the medical personnel can minimize the usage of broad-based antibiotics. Though the etiology of diseases such as systemic lupus erythomatosus (SLE) is not clear, the indiscriminate use of broad-based antibiotics is presumed to be a contributing factor in this complex autoimmune disease.

Diabetes is an autoimmune disease, and is attributed to be the pioneer (disease) for the development of biosensor technology. Individuals affected by diabetes, and who require glucose monitoring, constitute quite a large pool of people. Thus, there are so many major players (companies) in this area of glucose detection diagnostics. It is reasonable to anticipate that biosensing devices are available or will soon become available to facilitate in the early detection of other autoimmune diseases such as rheumatoid arthritis (RA), different forms of Cancer, SLE, etc. At least, this was the general sense gathered by this
author whilst attending the International Conference on Immunology held in Stockholm, Sweden, in the summer of 2002, and Montreal, Canada in the summer of 2004. The Singapore Institute of Bioengineering and Nanotechnology (2003) has developed a very sensitive DNA/RNA biosensor for early cancer detection. It uses the principle of hybridization wherein a capture probe is immobilized on the biosensor surface. A DNA/RNA sample hybridizes on the probe surface. The report indicates that the electrical signal generated correlates directly with the extent of hybridization (amount of diseased DNA/RNA).

The autoimmune diseases are slow, insidious, and intractable. Timewise, the earlier one is able to detect these diseases, the earlier one can put the individual on a medical protocol, and help in the management of these diseases. Some of these diseases, like SLE, are difficult to diagnose, since more than one criteria (such as the presence of anti-DNA and creatinine above certain (normal) levels) have to be satisfied before the individual is said to be affected by this disease. It is reasonable to anticipate that in the future, in spite of the low market demand for the detection of autoimmune diseases, biosensors to help detect early markers for these diseases will become a reality, if they have already not done so. For the diagnosis of SLE, the application of microarrays would be a reasonable route to follow. This would permit the simultaneous quantitative detection of the different analytes required and if they are above or below a certain threshold level or range as indicated above for the correct diagnosis of SLE.

Crow and Wohlgemuth (2003) recently indicate that physical insights into the pathogenic mechanisms of disease (for example, SLE) have been attained from the analysis of microarray data of gene expression. Some patterns of gene expression are confirmatory in nature with previous gene expression patterns using other methods, such as increased expression of immune cell surface activation molecules. However, the microarray analysis by Crow and Wohlgemuth (2003) indicates the increased pattern of interferon-induced gene expression in the blood of SLE patients. This study according to these authors underscores the interferon pathway in the hierarchy of gene expression pathways that are involved in systemic autoimmune reactions in general, and SLE, in particular.

In general, it is perhaps safe to say that the immune system is not well understood. The etiology of these autoimmune diseases is definitely not very clear, to say the least, and often there is almost a trial-and-error procedure when prescribing medicines and dosage. There were posters at the International Conference in Montreal held in the summer of 2004, wherein the treatment of refractory arthritis was prescribed, and in some cases, the unfortunate side effects was, for example, tuberculosis. At the International Immunology Conference held in Stockholm in the summer of 2002, one of the invited speakers mentioned that if arthritis has been diagnosed in an individual, it should be ‘attacked vigorously’. There should be no procrastination. All of this emphasizes the early detection of these autoimmune diseases, an area where biosensors can be of considerable assistance. The whole scenario is further exacerbated by the (recent) scrutiny and removal of drugs such as Vioxx, Celebrex, and Naproxen (Alleve) (for the treatment of arthritis), and drugs of a similar nature.

The market for the treatment of autoimmune diseases, besides diabetes and perhaps arthritis, is rather small, and thus it is not unusual for pharmaceutical companies not to venture into these detection devices on a ‘large scale.’ Having said this, it is worthwhile
noting that some companies have invested and have marketed detection devices for these and other types of autoimmune diseases. In lieu of this, it is imperative that biosensors be used to help detect autoimmune disease at an early stage. More companies need to invest in these areas. Healthy competition would be of considerable assistance in the development of drugs, in general, to treat or at least manage autoimmune diseases. This would greatly impact in bringing the price down for these types of drugs, and make them more available to the general public.

Cancer and other autoimmune diseases go through different stages. It is common knowledge that if a cancer is detected at an early stage, the prognosis is much better than if the cancer is detected at a later ('blast') phase. Roughly, one may characterize the three stages of cancer as: initial (time period typically in years), intermediate (time period typically in months), and blast (time period typically in weeks). Of course, the detection of the different forms of cancer is more and more difficult during the initial stages. This is perhaps true at least for some of the diseases such as arthritis. As expected, the detection of arthritis at an early stage (perhaps by a biosensing method) would greatly facilitate the management of this debilitating disease. Novel methods are required to facilitate the early detection of arthritis and other debilitating autoimmune diseases.

DuBois and Shaw (2004) advocate the use of IR spectroscopy in clinical and diagnostic applications. These authors emphasize that IR spectroscopy provides a ‘molecular fingerprint’ of a sample. This is the basis of biomedical applications, for example, diseases lead not only to physical symptoms, but also to changes in the chemical composition of the organs, tissues, and fluids. DuBois and Shaw (2004) further emphasize that these changes are the basis of chemical tests and medical imaging techniques.

Eysel et al. (1997) initially attempted to extract diagnostic information from biofluid IR spectral patterns for the detection and diagnosis of arthritis. Arthritis, like most autoimmune diseases like SLE and cancer, is difficult to diagnose, and particularly to determine the stage the debilitating disease is in. These authors indicate that the onset of arthritis affects the synovial fluid in a systematic way. Each stage of the arthritis or arthritis variant has a unique molecular imprint. As compared to a normal joint, DuBois and Shaw (2004) indicate that the arthritic joint contains an increased volume of less viscous synovial fluid. The synovial fluid contains hyaluronic acid. This polysaccharide provides the lubricating properties and the high-viscosity properties to the synovial fluid.

DuBois and Shaw (2004) indicate that subtle changes in spectral patterns reflect the different forms of arthritis such as osteoarthritis, rheumatoid arthritis, and spondyloarthropathy. These authors indicate the need for fail-safe algorithms that provide an indication of the form of arthritis and the state that it is in based on the spectroscopic signatures of individual fluid specimens. Finally, these authors state that an establishment of links between spectroscopy and diseases will go a long way in the management of these diseases and in lowering health costs.

In a following article in the same journal Mukhopadhay (2004) indicates the increasing application potential for Fourier transform infra red (FTIR) spectrometers. The author quotes Robert Yorkelson of the University of Montana who states, “It is the closest thing we have to an ‘everything’ detector.” Mukhopadhay (2004) emphasizes the emergence of a niche market for portable spectrophotometers after the September 11, 2001 attack. Finally, Mukhopadhay provides cost for portable FTIR spectrometers, which range from a low of $27,000 to a high of $76,000. The weight in kilograms is from a low of 7 to 145
(definitely not portable, as in back-pack form; portable if carried in a car or van). Different sampling accessories are available. Thus, Mukhopadhyay (2004) indicates the flexibility of these instruments to detect a wide variety of samples.

Camilleri (2004), CEO of Cambridge (UK)-based Rapid Biosensor Systems Ltd, indicates the development of a prototype biosensor (breath analyzer) to test for tuberculosis (TB). The disease apparently kills 2 million persons each year. A low-cost biosensor that detects TB at an early stage would be of considerable assistance. Camilleri (2004) indicates that the noninvasive biosensor is portable and also durable. Results are obtained within 5 min as compared to present-day blood tests that take 10 days or more. Besides, the biosensor can be used by nonmedics. This should find use in developing countries, for example, India. The biosensor system is based on the collection of a cough sample, followed by the detection of the pathogen. An immunoassay system is used along with fluorometry. The quick isolation of TB-infected patients should help considerably in the prevention of the spread of this re-emergent disease. The particular advantages of this biosensor are the high speed, low cost, and small size. Camilleri (2004) emphasizes that the intention is to develop a low-cost generic biosensor that would rapidly screen for other infectious diseases too. At present, the biosensor is also capable of detecting *Escherichia coli*.

A report from Drexel University (2004) emphasizes that the major market for biosensors may be found when an immediate assay is required (for example during a medical operation, or in a medical clinic where the physician(s) need some quick answers). Mareno (2004) indicates the development of a biosensor within 18 months to detect organisms such as *Legionella pneumophila*. This organism causes Legionnaire’s disease, which can cause devastating effects on human health. Researchers at RMIT University in Australia are developing a device that would provide rapid identification of pathogens on-site. This would be a significant improvement in laboratory testing of samples that takes days.

Evans (2004) indicates that recently fluorescent polymer has been used to flag bacterial infections caused by *E. coli*. This technique is also being used for the detection of cholera, gingivitis, and hospital based infections. The principle used for detection is that bacteria bind to cell surface carbohydrates. These carbohydrates may be attached to fluorescent polymers. Evans (2004) indicates that the particular advantage of this method is the rapidity of detection. This technique can detect a few bacteria in 10–15 min, whereas other techniques take days to make a similar detection.

Biosensors can also be effectively used in Process monitoring (Biowise, 2000). These authors emphasize that the use of biosensors permit business decisions to be made at an early stage due to the knowledge gained by utilizing the biosensor(s) appropriately. Information about important variables in a process may be obtained on-site, thus saving the time and transportation costs required to transport a sample to and from a testing laboratory. These quick results facilitate quick changes if need be. Table 13.2 shows some costs provided by Biowise (2000). These numbers are a few years old, and have been updated (doubled) to reflect current prices. Also, the original numbers were in British pounds, and they have been converted to US dollars with an exchange rate of British £1 = $1.9433 (http://finance.yahoo.com/currency?u) (November 03, 2004; 6:30 pm).

Biowise (2000) emphasizes that the monitoring of ‘harmful’ chemicals is required due to legislative purposes. For example, hygiene testing is required to safeguard the health of customers and employees. Furthermore, the use of biosensors vis-a-vis laboratory analysis
13.1 Introduction

Table 13.2

| Analyte of interest               | Cost per test ($) | Instrumentation cost ($) |
|-----------------------------------|-------------------|--------------------------|
| Toxicity monitoring               | 16–20             | 20,000–200,000 (depending on application) |
| Biological oxygen demand (BOD)    | ~2–5              | 100,000                  |
| Hygiene monitoring (microbial contamination) | 2–4              | 80,000–120,000 (luminometer) |

"Numbers are rounded to the nearest integer.

of compounds such as phenols, dioxins, benzene, algae, and pesticides, etc. would lead to a considerable decrease in cost, even though the initial investment may be high for instrumentation purposes used along with biosensors. The turn-around time is also considerably decreased and, if this is a critical factor, then this is almost priceless, as an example in the early and rapid detection of biological or chemical warfare agents.

Ruzgas et al. (2000) attempted to develop a biosensor array to permit the fast monitoring of pollution levels in wastewater and pollution incidents. This was a 36-month long project and was funded at 1.115 million Euros. This is equivalent to $1.476 million (exchange rate: 1 Euro = $1.324). Enzyme-, DNA-, and cell-modified electrodes were used. These electrodes were capable of generating a fast multi-variate response on the interaction of phenols, lignins, heavy metals, and surfactants with the biomolecules. The authors emphasize that their method permits a quick estimate of the wastewater toxicity and composition. Ruzgas et al. (2000) further emphasize that an alarm is generated when there is a deviation from a normal or given (set) pattern. One of the biosensor formats that the project intended to generate was screen- and ink-jet printed biosensor arrays.

GenomeCanada (2004) has recently indicated that Virtek in Canada has been awarded a $1.2 million (Canadian) matching grant to develop its fiber optic nucleic acid (FONA) biosensor technology for testing recreational and subsequently drinking water for pathogens. The biosensor is based on a proprietary fluorescence-based fiber optic biosensor and a laser-based detection system. The project is to be able to detect organisms such as *E. Coli*, *Giardia*, and *Cryptosporidium*. Virtek uses a DNA-based platform technology to provide genetic tests for (a) food and drinking water and (b) infectious diseases in humans and animals. The platform facilitates a rapid and an accurate analysis of the pathogens in water.

Virtek will collaborate with GAP EnviroMicrobial Service (Waterloo, Canada) for additional financial support, and with research scientists at the University of Toronto, Canada. The company is continuously looking for additional support to help offset the development cost of the biosensor. They indicate that their biosensor permits an accurate analysis that is economic, selective, and easy to use.

Finally, a disease which has come into prominence in recent years is mad cow disease (bovine spongiform encephalopathy, BSE). Biosensors could perhaps be developed and effectively used to detect this infectious disease in animals. An animal with this disease
if ingested leads to a rare human brain-wasting disease such as variant Creutzfeldt–Jakob disease (vCJD). There is debate on how many cows need to be tested. For example, Normile (2004) recently indicates that more than 20,000 cows are tested annually in US. This number is much larger in Japan and the European Union (1.2 million and 10.4 million, respectively). Some of these numbers (for testing) correlate with when the disease was first detected in the country or region and how many reported known cases have been accounted for. For example, Normile (2004) indicates that the first known case of BSE in US was reported on December 23, 2003. Japan has had nine cases of BSE reported since 2001, whereas the European Union has had 186,000 reported cases since 1986.

Markus-Moser (CEO of BSE test maker Prionics AG in Switzerland) in Normile (2004) indicates that the appropriate level of testing is, and as it should be, a cost-benefit question. This is exacerbated by the fact that the real risk factor is not clearly understood or defined. However, in the US, the beef industry is a $50 billion industry, and thus the governmental agencies such as the Food & Drug Administration (FDA) do take this threat very seriously.

Normile (2004) further indicates that there are three companies whose detection kit (ELISA) costs range from a low value of $7 to a high value of $25. However, the cost per test is much higher, and is estimated to be as high as $60. This is another large market for the possible use of biosensors, especially since the estimated number of cows that need to be tested annually ranges from a low of 1 million to as high as 20 million over a period of 30 months. This author further indicates that the National World Organization for Animal Health’s number for testing is recommended to be 0.01% of the national herd over a period of 30 months. The United Kingdom is more careful with its large number of detected BSE cases. Cows over the age of 30 months are forbidden to enter the food chain. Depending on each countries’ regulations the number of cows that need to be tested may differ, and will increase if (a) there is an outbreak(s) and (b) if there is an increase in the perception of the ‘risk factor’ (which still needs to be carefully determined) involved.

Hueston (Director of the Center of Animal Health and Food Safety at the University of Minnesota) in Normile (2004) correctly provides a sort of balance, and underscores the motive of some testing advocates especially those that have a financial interest in companies that make BSE detection devices. The heart of the problem lies in assessing the appropriate level of risk, which will (a) eventually determine the number of cows that need to be tested annually and (b) thereby define more carefully the market for BSE testing devices such as ELISA and for biosensors.

Biacore (2004) with its SPR biosensor has expanded into the food analysis area. Samples may be analyzed in minutes, which reduces the response time when compared with the traditional methods of testing. Their biosensor can detect vitamins (in health and nutrition food), and veterinary drug residues such as antibiotics and β-agonists in dairy products. Furthermore, their SPR biosensor can detect hazardous natural toxins in food and feed. The Biacore® catalog (2004) provides information on a wide variety of models available. These as mentioned earlier in the book are expensive biosensors. Some of the models available are Biacore C, J, Q, and X. Also in the market are Biacore S51, 2000, and 3000. The different models of the Biacore biosensors may also be used during the different steps involved in drug discovery (Biacore Drug Discovery, 2004). According to the information available, the different models may be used at different steps in drug
discovery and development. For example, Biacore® 3000 may be used during target ID and validation, Biacore S51 for secondary screening, etc.

The Agricultural Research Service of the United States Department of Agriculture in its Annual Report (2002) has outlined briefly the problems associated with detecting pathogenic bacteria in food. These include:

*Speed.* This is essential since processing and distribution systems operate quickly.

*High sensitivity.* An infectious dose may be as small as one organism.

*Selectivity.* Only a few bacteria of the total that are present in food are pathogenic. They represent a small fraction of the total benign bacteria present.

The above authors mention the limitations of the traditional microbiological protocols. Thus, the need for the development of rapid detection, inexpensive, easy-to-use biosensors for use by food producers, processors, retailers, and regulatory agencies.

The ARS, USDA Annual Report (2002) emphasizes that over 5 million cases of food borne bacterial diseases occur in the United States every year. This report is 2–3 years old. This number may have increased. The economic impact of these illnesses are significant with regard to (a) time lost at work, (b) medical bills, and (c) costs associated with recall and destruction of contaminated products.

In a recent news item on television (Channel CNBC News; USA, December 28, 2004; 9:30 am) the CEO of Neuogen, Inc. mentioned that the US is considered to be the 'bread basket' for the world. However, this year the food imports were more than the food exports. Thus, the need for the inspection of food that comes into this country. Detection devices, etc are required for bacteria, etc that come along with the food being imported.

Researchers at Georgia Institute of Technology (Georgia Tech, 2004) in Atlanta, GA have spent over 7 years to develop a biosensor that detects pathogen in poultry and other food stuffs. Their biosensor can detect $10^4$ to $10^7$ cells/ml in less than 30 min. One may compare this to 72 h required by laboratory screening techniques. The biosensor is based on an antigen (pathogen)–antibody reaction. The biosensor surface has a 'capture' antibody, and a 'reporter' antibody. The primary advantage of this biosensor is that no amplification of the cell counts is required, which is the major cause of the time delay. Furthermore, the biosensor is able to detect the pathogen in the presence of other contaminants. Another distinct advantage is the major reduction in the cost for the biosensor which ranges from $1000 to $5000 as compared to the common immunoassay laboratory equipment that may cost in the range of $12000–$20000 per instrument. The researchers emphasize that, however, the field trials are necessary to demonstrate the effectiveness of their biosensor.

The researchers also have plans to extend the application of their biosensor for the detection of other pathogens that include *E. Coli* 0157:H7, generic *E. Coli*, *Listeria monocytogenes*, *Campylobacter jejuni*, and *Yersinia enterocolitica*. All these pathogens, the authors indicate, cause stomach illnesses. *Campylobacter* affects more than 2 million persons every year. However, these authors indicate that the disease is usually mild, and rarely life threatening. This biosensor is more sensitive than ELISA (Enzyme-Linked Immunosorbent Assay), less expensive than polymerase chain reaction (PCR) techniques, and has a rugged design that permits on-line usage (Poultry Tech, 2003).

Knecht et al. (2003) at the Technische Universitat in Munchen, Germany, report on the development of an immunoassay biosensor to detect antibodies in milk rapidly.
They emphasize the importance of detecting these antibodies since they may increase the danger of bacterial resistance and harm intestinal flora. They are also responsible for allergen reactions. As far as cheese and yoghurt making are concerned antibodies in the milk may also inhibit the fermentation reaction. These authors emphasize that their immunoassay microarray technique leads to a reduction in time for antibody detection when compared with ELISA. Furthermore, their biosensor exhibits a robust design and the system components are of moderate costs.

Applied Nanotech Inc. (2003) has developed a versatile biosensor using carbon nanotubes (CNTs). This company indicates that they have immobilized enzymes into CNTs. Electropolymerization along with conducting polymers were used. They emphasize that their newly developed biosensor is low cost, easy to manufacture, and also versatile. It may be used to detect (a) impurities in air and water, (b) glucose levels in the blood, and (c) chemical and biological warfare agents. Furthermore, this company claims that their biosensor is three times more sensitive than other competing biosensors for the detection of hydrogen peroxide.

Berney (2001) indicates the proposed development of a DNA biosensor to identify genetically modified (GM) crops from nonGM crops. This has become essential according to this author due to EU regulations (EU 258/97 and 1139/980). Validated analytical methods are required that rapidly identify the DNA of genetically modified plant material. Berney (2001) anticipates that the effective monitoring of the plant material would lead to an increase in consumer confidence, followed by a subsequent increase in sales. This is a proposed 3-year project with a cost of $1,889,440 Euros. With an exchange rate of 1 Euro = US $1.324, this works out to US $2.515 million. The project is located at the National University of Ireland at Cork, and has four other partners: Murozone Ltd in UK, Ecole Polytechnique Federale de Lausanne in Switzerland, Sy-Lab Gerate in Austria and the National University of Ireland at Cork.

13.2 BOTTLENECKS. DEVELOPMENT COST, AND FUTURE NEEDS FOR BIOSENSOR DEVELOPMENT

The major resistance apparent for the development of biosensors is the lack of mass markets barring a few exceptional cases such as glucose monitoring for diabetes. With a view to a commercial profit, this places a serious hindrance on investment in biosensor technologies. Walsh (2003) indicates that the development cost of a biosensor may exceed $20 million. It is reasonable to assume that the development cost of a biosensor lies between $20 and 30 million, and the time panel involved is between 7 and 10 years. This significant amount of investment and the losses incurred in the initial (recent) years before a profit occurs are bound to hinder smaller-sized companies from entering the market. Some of the drawbacks pointed out by Walsh (2003) include the reliability to produce a competitive product, and the commercial development of technology required to produce a large number of devices. In all fairness, however, this trend is changing gradually now with the increasing investment by US Governmental agencies such as the National Science Foundation (NSF), Department of Defense (DOD), Department of Energy (DOE), Defense Advanced Research Projects Agency (DARPA), etc. However, this section focuses primarily on the bottlenecks and the development cost of a biosensor.
At the outset, it is perhaps appropriate to indicate the importance of linking marketing intelligence to product development as suggested by Khandelwal (2004). This author indicates that the cost of research is a very small fraction compared to the total expense in bringing a product to the market. Though this author’s comments are made with regard to the chemical industry, for all practical purposes they could also be applicable to the development of biosensors.

Walsh (2003) further indicates that some of the drawbacks in biosensor technology include: total integration of the biosensor system, producing inexpensive biosensors in quantity, producing noninvasive biosensors that are self-calibrating, biocompatible biosensors that may be used under in vivo circumstances, and reproducible placement of receptors on a biosensor surface.

Medical Technologies (1994) has listed some of the drawbacks or obstacles in biosensor technology that need to be overcome. Most of them are related to the sensing (biomaterial) of the biosensor. They include sterilization (which will inherently destroy, at least, part of the biomaterial), contamination (limits biosensor to a single use), immobilization of the receptor to the biosensor surface (not well understood, especially its impact on analyte–receptor binding and dissociation kinetics; a focus of this book), and uniformity of receptor preparation. Other factors mentioned include selectivity, detection limit, and reproducibility. New nanofabrication devices to produce these miniaturized biosensors are urgently required. Also, emphasis needs to be placed on improving existing transduction technologies and the application of newer transduction technologies. A single use or a disposable biosensor would exhibit considerable potential to enhance the market share. This is especially true since very little is known about the regeneration of biosensors.

Obducat (2004) indicates that biosensor technologies due to cost issues are relying on semiconductor processes that are one or two generations old. This limits their sensitivities and tends to make the detection slower. Besides, the sensor area is limited since patterns cannot be made smaller than 5–50 μm in line widths. This company indicates that its Obducat Micronano process can make structures that are 100 nm and less. The process uses electron beam lithography. The company emphasizes that these smaller structures permit the manufacture of sensors at a low cost that respond faster and also exhibit a high degree of sensitivity.

van Hoof et al. (2004) recently indicate that microsystems technology is used presently to make tiny sensors. The principle is similar to that used for integrated circuit production. These authors emphasize the advantages of monolithic integration as compared to side-by-side integration. Figure 13.1 shows the side-by-side and the monolithic integration. These authors indicate that monolithic integration saves volume, electric power, and possibly cost. However, this does come at a price in that different materials and processing

![Figure 13.1](image-url)  
*Figure 13.1* Structural organization of two different types of microsensors (van Hoof et al., 2004): (a) side-by-side, (b) monolithic integration.
techniques need to be combined on the same substrate. van Hoof et al. (2004) emphasize the two basic tenets of sensor technology: a good sensor material and a viable process technology.

These authors further emphasize that for future smart sensors for personal health, comfort, and safety monitoring (such as glucose monitoring for diabetics), the sensors need to possess power autonomy, be miniaturized as much as possible, and also be disposable. The advantage of being disposable as suggested by van Hoof et al. (2004) is that they need not be as durable as present-day sensors.

Biotrace International Plc (2002) (http://www.biotrace.com/content.php?hID + 1&nID + 21nID = 36), a British company in Bridgend, United Kingdom, specializes in its bioluminescence rapid biological detection system. It has collaborated with Smiths Group’s Graseby (another British company that specializes in Detection and Protection Systems) wherein the Biotrace system is fully integrated into the Graseby detection and identification system for defense and civilian customers. The Biotrace-patented Adenosine triphosphate (ATP) luminescence system/Smiths Group Detection and Protection System is a novel two-step method for the detection of harmful biological agents.

The system is able to detect harmful biological agents in less than 2 min. The first step involves the ‘nonspecific’ detection of potentially harmful agents (Biotrace). This is followed by a ‘trigger’-specific identifier system (Smiths Group) that pinpoints the particular agent. Graseby emphasizes that its technology is rugged and is able to identify harmful biological agents. Besides, its technology may be integrated into weapons of mass destruction (WMD) detection systems.

Another harmful biological agent detection system is the TIGER biosensor technology being developed by ISIS Pharmaceuticals. TIGER is an acronym for Triangulation Identification Genetic Evaluation of Risks. The company indicates that its Ibis Therapeutics has received $65 million from different governmental agencies to develop this technology. Ibis Therapeutics further indicates that the development of the TIGER technology has been supported by the following governmental agencies for specific purposes:

| Governmental agency                                      | Purpose                     |
|----------------------------------------------------------|-----------------------------|
| Defense Advanced Research Projects Agency                | Bioweapons defense          |
| Centers for Disease Control and Prevention (CDC)         | Epidemiological surveillance |
| Federal Bureau of Investigation (FBI)                    | Microbial agent database    |
| National Institute of Allergy and Infectious Diseases (NIAID) | Biological products screening |

Ibis emphasizes that the TIGER biosensor is capable of simultaneously identifying infectious agents. This includes previously unknown and newly emerging organisms. Furthermore, using its expertise Isis Pharmaceuticals is also developing novel biosensors to identify small molecule antibacterial and antiviral drugs that bind to RNA.

Other companies have also announced partnerships or collaborations to facilitate the detection of harmful biological agents. Innovative Biosensors Inc. (2004) located in
Gaithersburg, MD have indicated a licensing agreement with MIT (Cambridge, USA) to use the CANARY™ technology for use not only in detecting harmful biological agents but also in food testing and in human and clinical diagnostics. The above-mentioned company indicates that the CANARY biosensor researched initially at MIT permits the binding of the antigen to the engineered antibody on a cell surface. This produces light emission which is not only easily detectable in a quick fashion, but also permits high levels of sensitivity and specificity.

Similarly, QTL Biosystems, LLC (2004) located in Santa Fe, NM is collaborating with United First Responders, LLC of Fayette County, PA to manufacture a hand-held biosensor to detect harmful biological agents such as anthrax and ricin. The two companies indicate that about 6 months are required to manufacture the prototype and high-quality units. QTL's expertise lies in integrating chemistry, molecular and cell biology, and in instrumentation. United First Responders provides products and training services with regard to chemical and biological threat detection.

Cross and Freeman (2004) indicate the development of a biosensor based on feeding alternate orthogonal polarization states of light to a chip using a fast liquid crystallization switch. The authors indicate that their method overcomes the restrictions on using one polarization of light at a time for measurement. These authors also indicate that cheap (low cost) biosensor systems are required with a long service between scheduled maintenance. Their method provides extreme surface sensitivity and low chip cost. The authors further indicate that it took 6 years of R&D (research and development) investment to bring their product to the market. No numbers were provided as to the total expense required to bring the biosensor to the market. Their technique is called Dual Polarization Interferometry (DPI) and is capable of subatomic resolution measurement in 'real time.' Changes in thickness of molecular layers of interest may be detected by DPI. These authors emphasize that developments in software should provide upgrades for the biosensor as well as increase the user base. The authors emphasize that market penetration is significantly dependent on the ease of use. Finally, the authors indicate that based on the development of their biosensor they have launched Fairfield Photonics, Ltd. This would facilitate developing more products based on their technology.

NVE Corporation (2004) in Minnesota, USA is developing a biosensor to detect biological warfare agents, real-time DNA testers, and laboratory-on-a-chip diagnostic systems. It will use its working BioMagnetic Interfacing Concepts (BioMagnetICs) biosensors. These materials are a few atoms thick. The company estimates the commercial market for spintronics at about $100 billion per year. The company has been awarded a $1.2 million to develop this concept from the DARPA of the Defense Services office (DSO). The company indicates that the long-term goals are to provide a low-cost hand-held device that is as easy to use as a digital thermometer. Furthermore, accurate results will be provided in minutes rather than in hours.

An area of interest where biosensor may be used as an 'electronic nose' is in demining operations, in other words, to detect land mines. Berg (2003) indicates a 2-year project funded at 4,028,408 Euros (equal to $5,333,612, exchange rate 1 Euro = $1.324) by the European Community (EC). It is multi-organization project that includes the Swedish Rescue Service Agency (SRSA), Biosensor Applications, Sweden, and the Norwegian Peoples Aid (NPA). The goal of the project is to find the smallest quantity of explosives in mines and to reduce the area where mines are located. Furthermore, the project aims
to build a prototype ‘electronic nose’ to verify that a certain area has been cleared of mines. The intention is to be able to detect TNT, RDX, and PETN. One of the goals of the project is to decrease the size of the sensing system so that it may go to areas inaccessible by vehicles. Finally, another goal of the project is to test the system in a simulated mine field, and in a real mine field.

O’Neil (2004) describes an effective biosensor using an air-sampling method to detect drugs and explosives at airports. This author indicates the development of a biosensor for amphetamine and for the detection of cocaine and cannabis. A biosensor for TNT has also been developed, and biosensors for the detection of RDX and PETN are under development. Their biosensor is capable of detecting the harmful analyte in under 3 min. The intention is to reduce the response time to under 30 s.

O’Neil (2004) emphasizes that present-day screening methods are costly, inefficient, and often unreliable. Furthermore, there is considerable inconvenience in (a) the long lines at airport check-in prior to entering the gate area for departure and (b) in the ‘pat down’ procedures (often sensed as overtly intrusive by passengers and the subsequent changes of procedures after considerable passenger complaints). Their company biosensor is an extremely sensitive piezo-electric quartz microbalance system. This author emphasizes that their biosensor is very accurate, is able to sample over a large volume (their system is able to concentrate the sample), and can detect analytes at low concentrations. Their receptor is an antibody, which is very specific for the analytes. Finally, O’Neil (2004) indicates that their biosensor fills the present-day critical need for making the airport screening process more reliable, efficient, and less intrusive. Their biosensor should prove to be cost effective as it may help speed up the flow of passengers, and also help minimize the costs of delay and lost business.

Another area of interest is biofabrication. DARPA, Defense Science Office (http://www.darpa.mil/dso/future/biofab.htm) has initiated a program to examine the possibility for utilizing biological processes to manufacture materials for defense. These processes may perhaps provide opto-electronic materials and photonic devices that may prove useful in biosensor development.

DuPont (2004) has introduced a line of screen-printable thick film conductive materials. These can be used for biosensors in medical monitoring, diagnostics, food and beverage testing, and environmental monitoring. Each material is specifically designed for each application. The company indicates that its materials may be used as both active and passive materials for biosensors. Furthermore, their printable materials may be used cost-effectively in high-volume manufacturing processes for biosensors. The company states that it has been able to make these advanced materials for biosensor applications due to its strengths in materials science, chemistry, and fine particle technology. For example, their platinized carbon may be used as working electrodes in amperometric sensors for analyte detection.

As far as materials are concerned van Hoof et al. (2004) indicate that due to its large processing power per unit area, silicon will presumably remain the material of choice, generally used for smart sensors. The large processing power per unit area permits a decrease in area and a lower cost for the sensor. Finally, these authors indicate that future cheap materials for sensors may probably be polymers, metals, textile materials, or even paper (Ender et al., 2004).
Biowise (2000) too has also mentioned the disadvantages of the receptor molecule used in biosensors. It has classified receptors into: enzymes, antibodies, and microorganisms. Other types of receptors for biosensors are also available. However, at present, we only analyze enzymes, antibodies, and microorganisms. These three types of receptors have advantages also, but here we concentrate only on the bottlenecks/disadvantages. As far as enzymes are concerned these receptors have limited shelf life, they are susceptible to inhibition by other (than the analyte) substances present in the sample, and ambient conditions. The shelf life of these types of biosensors may be increased by improving the way by which the enzyme(s) (or other receptors) are deposited on the biosensor surface (Biowise, 2000). Adverse pH and temperature conditions may quickly inactivate the enzyme making it useless as a receptor. Though significant advances are being made in antibody technology, this is still classified as an emerging technology, and target analytes may thus be limited (Biowise, 2000). Furthermore, antibodies are very specific and cannot detect unknown substances. The speed of response also needs to be improved when using antibodies in an ELISA format. The response time may generally decrease from hours (ELISA format) to minutes when they are used in a biosensor format. When microorganisms are used as receptors in a biosensor format, the results are often variable (Biowise, 2000), and the response time is larger than when other types of receptors are used on biosensor surfaces. Biowise (2000) further indicates that the response time needs to be decreased to the order of 15–60 min when microorganisms are used as receptors on biosensor surfaces for them to become competitive.

Raghupathy (2002) briefly mentions two requirements or performance parameters for effective biosensor operations. These are sensitivity and a fast response. The detection of analyte concentrations at nanomolar or lower is considered as highly sensitive, and the fast response has a time frame of milliseconds.

TFS Sensor Technology (2004a,b) indicates five reasons that are hindering evanescent biosensors from entering the market. These include: nonspecific binding, biological fluorescence, inadequate sensitivity, reproducibility of measurement, and fabrication. This company has attempted to overcome or mitigate these limitations. They have a patented process that treats the optic fiber used for biosensors. The process minimizes nonspecific binding. The company indicates that previously proteins in biological fluids of interest such as blood, serum, and urine have prevented fiber optic biosensors from operating successfully. Furthermore, the natural fluorescence of biological substances present in serum, urine or in environmental samples has prevented fiber optic biosensors to be used in sensitive measurements. Three-fold sensors (TFS) has managed to use sensors wherein the fluorescence characteristics are clearly different from the biological fluorescence exhibited by the compounds that are not of interest. In other words, this type of interference is minimized, and more sensitive measurements may be performed.

TFS Sensor Technology (2004a) further indicates that the signal losses from optical fibers characteristically decrease the sensitivity of fiber optic biosensors. TFS’ biosensor design minimizes these losses, besides improving the collection efficiency for the fluorescence from the biosensor surface. The company emphasizes that their biosensor design permits the detection of analytes at the subpicogram level. A reason that hinders reproducible results is the variations on the fiber optic surface. This points to differing degrees of heterogeneity (different fractal dimensions, $D_f$) (Sadana, 2003). The present author is not surprised with this statement, since in this whole chapter we have indicated
that, in general, the binding and the dissociation coefficient(s) are very sensitive to the
degree of heterogeneity that exists on the biosensor surface. TFS, however, uses a unique
self-calibrating method that minimizes the ill effects of these variations on the fiber optic
surface on the reproducibility. Finally, tapered optical fibers result in yielding a better
sensitivity. However, previous fabrication techniques were not suitable to manufacture
these types of fibers. The TFS design process does overcome this limitation to a large
degree.

Ambri located in Chatswood, New South Wales, Australia (Ambri Annual Report,
2004) has developed the Ion Channel Switch (ICM™) Technology and its successor,
SensiDx™ biosensor. This is aimed at POC assays that may be used not only in the
Hospital Critical Care market but also in medical clinics, doctors’ offices, retail
pharmacies, and at home.

This company emphasizes that its main operational focus is to move both of the systems
towards market readiness. It uses a novel, commercially viable technology (CVT)
milestone to get its biosensor market ready. It uses the following key targets for CVT
evaluation:

*Tests.* Commercial levels of sensitivity demonstrated
*Aalyzer.* Connect Australian hospitals to match demand
*Regulatory.* Use good manufacturing principles (GMP) to develop manufacturing
*Research.* Use next generation membrane chemistry for sensitivity and stability
*Validation.* External evaluation of developments

For example, under the criteria for tests its biosensor system demonstrated the detection
of hCG (for pregnancy) in blood of about 15 mIU/ml and below range with improved
reproducible results. Their system is also able to detect troponin (a clinical marker for
heart attacks). Under the analyzer criteria the company was able to connect their
Sensidex™ system successfully with the Australian Hospital system. Other criteria were
also similarly attained or satisfied.

This systematic (step-wise) procedure would facilitate the fast track development of
their patented ICS™ Technology with a new silicon chip platform. Their miniature
biosensor for POC testing combines the following attributes which include high volume
fabrication at low cost and a tiny disposable biosensor to do several tests simultaneously,
and it is a simple hand-held device.

Ambri emphasizes that due to efficient restructuring and financial discipline
procedures, it has decreased its operating expenses by 42.1%, from $9.5 million to $5.5
million (Australian dollar) for the months July 2002–December 2002 and July 2003–
December 2003, respectively. Note that one Australian dollar is equal to 0.7586 US dollar
(exchange rate December 14, 2004). Their financial report indicates that they have $16
million in reserve and expect to get their next-generation biosensor to the market in about
a year’s time. Furthermore, it has reallocated $8 million to fast track their next-generation
biosensor. This provides one with the perspective of time and financial resources required
to get a competitive, cutting-edge biosensor to the market. Finally, this aggressive
forward-looking company, which has done some successful fund-raising ($22.5 million),
has set-up a POC advisory group, is minimizing investment risk, and attempting to
enhance licensing opportunities for its technology, besides attempting to improve its bottom line via different avenues.

DuBois (2003) in a recent article emphasizes the importance of accelerating speed to market a medical product. He indicates that, and we quote, “the ability to shorten the developmental cycle is critical to financial reward.” He emphasizes the "Thinking-out-of-the-box approach." Though unconventional, these types of approaches have a high reward along with a high risk factor. This author further indicates that a fundamental principle is to set a time frame, and then get the resources together to complete the project. If the resources are not available internally, then one should outsource. This way the company can remain focused without the need for (a) building staff and minimizing (b) overhead and (c) capital expenses. The author emphasizes that the outsourcing industry is estimated to be around $8 billion, and is growing at a rate of 25%. Furthermore, this author emphasizes that in outsourcing communication and trust are the key. Any individual who has done some form of consulting can attest to this.

In chronological order, DuBois (2003) indicates the following steps that are involved in taking the product concept to the market. Though this has been proposed for IVD (in vitro device) medical devices, the procedure is presumably generic, and with suitable modifications may be applied to other concept-to-market ready products. These steps are: concept, preliminary engineering, model creation (efficacy of concept), development engineering (specifications, materials requirements), prototype, final engineering, and pilot release.

DuBois (2003) emphasizes that communication is the key during all the steps. Flaws may thus be corrected, before they become major problems. The author suggests that a quality control group can assist in this during different stages of development.

DuBois (2003) indicates that the market for Diabetes Mellitus (DM) is estimated to be $4.6 billion, with more than 17 million Americans being affected. Out of these the author estimates that 1 million have type 1 DM, and 11 million have type 2 DM. Six million Americans are still undiagnosed. Approximately, one in every four Americans is estimated to have DM.

Newman et al. (2004) indicate that according to the World Health Organization (WHO) the number of diabetics will double worldwide from 150 to 300 million by the year 2025. This represents doubling of the number of diabetics in about 20–22 years. Using the rule of 72, this represents approximately a 3.27–3.6% increase. For all practical purposes, this is a 3% increase, since the rule of 72 does not strictly apply here. Clearly, there is a critical need for a less painful and more efficient glucose testing biosensor.

The measurement of glucose, as indicated elsewhere in this chapter is painful and time-consuming (DuBois, 2003). An accurate monitoring device is required to prevent the onset of other 'cluster' diseases, such as heart attack, blindness, stroke, etc. The poor management of DM increases the probability of these 'cluster' diseases. The author emphasizes the need for (a) a less painful device, (b) testing speed, and (c) accuracy and precision. As a practical fast-track example, DuBois (2003) indicates that Nova Medical and Becton Dickinson (BD) collaborated on a glucose biosensor for Diabetes Mellitus, and in 18 months BD was able to leverage Nova Biomedicals diagnostic to take it from the 'concept' stage to the market. The market for DM is large and expanding. In these 18 months, the hand-held device was designed and developed, the equipment was custom
Sontra Medical Corporation (2004) indicates the co-development of the Symphony Diabetes Management System with Bayer Diagnostics. The company emphasizes the unfilled need for a noninvasive product to measure glucose levels. This, according to the company, is a $5 billion home product market. Their management system consists of a hand-held SonoPrep® device. This device is able to permeate the skin, and the biosensor transmits the glucose levels wirelessly to a glucose meter.

The company estimates the worldwide sales of the market at $5 billion in the year 2004, and the market is estimated to increase to $8 billion by the year 2007. A noninvasive biosensor would significantly improve the compliance rate of measuring glucose levels (which are often painful), and minimize the occurrence of coronary and vascular diseases such as kidney failure, adult blindness, nontraumatic amputation, and nerve damage (Sontra Medical Corporation, 2004). Finally, the company indicates that Phase 1 clinical trials on patients with diabetes was completed in 2003. Sontra Medical Corporation (2004) emphasizes that the patients did not complain of either pain or irritation. However, the product still requires regulatory clearance and is still not commercially available.

Another study by Synthetic Blood International (SBI) (2004) located in Kettering, Ohio, USA indicates that diabetes affects men and women equally, though it affects the elderly more frequently. This company estimates that the direct cost of diabetes is around $50 billion in the US. This is estimated to be around 6% of the total direct personal healthcare expense in the US which is about $830 billion. These authors emphasize that the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) (one of the National Institutes of Health located in Bethesda, Maryland, USA) recommends a very tight control of glucose levels to prevent the onset of complications that arise with diabetes.

There is a critical need as indicated elsewhere in this chapter for a less painful method of measuring glucose levels in the blood to increase the compliance rate. Estimates of the people afflicted with diabetes differ. SBI (2004) estimates that 16 million individuals in the US suffer from diabetes, and about 600,000–700,000 new cases of diabetes are diagnosed every year.

SYPD has developed an implantable glucose biosensor that eliminates the use of finger sticks to monitor glucose levels in the blood. The company indicates that this implantable form of the biosensor is also more accurate than the current portable measuring devices. The biosensor is about the size of a cardiac pacemaker. The company further states that the implant life of the biosensor is expected to be over a year. Finally, the company indicates the worldwide market for their implantable biosensor to be over $1 billion.

Madou (2002) indicates that the high cost of disposable biosensors hinders the introduction of disposable biosensors in the POC market. This author is examining nonsilicon materials (biomaterials) for use in the manufacture of chemical and biosensors. This author indicates that the use of a polyimide material for biosensors has the potential of decreasing the biosensor cost by an order of magnitude than planar electrochemical sensors. Madou (2002) emphasizes that their polyimide biosensor is estimated to cost $0.3–1 (this cost is comparable to glucose-measuring strips) rather than the $3–10 cost for small biosensor arrays. The author emphasizes the additional advantage due to miniaturization, in that the biosensor size will be reduced approximately by 50% when
compared with the present-day biosensors due to improved architectural design facilitated by placing the modular structure of the biosensor one on top of the other, rather than side by side. See Figure 13.1.

May (2004) in a recent article, ‘building a better biosensor’, indicates that even though quite a few biosensors have been prototyped, they may not make it into the field. Biosensors are required that would detect agents at very low levels, in real time, and over long periods (preferably unattended). The trick is to take the laboratory know-how and effectively translate it for use in real-life applications. Portable, inexpensive, and rapidly deployable biosensors are required which can be used on-site. This author emphasizes that problems and challenges remain in translating biosensor detection technologies from the laboratory to the market. Ideally, one would require a universal biosensor that would be able to detect all harmful biological agents.

In a program solicitation for proposals, the NSF (National Science Foundation, NSF 03-512; Sensors and Sensor Networks, 2003) has attempted to address some of the perceived obstacles facing biosensor development. Some of these include:

(a) robustness under anticipated manufacturing schemes
(b) quantification of limits of detection, calibration, and interferences
(c) verification of accuracy
(d) miniaturization
(e) manufacture
(f) human-in-the-loop and closed loop adaptive feedback

The document emphasizes the need for inclusion in sensor development of anticipated progress in adjacent technologies such as wireless communications, nanofabrication, biosystems, and ubiquitous computing.

In a later program solicitation for proposals the NSF (National Science Foundation, NSF 04-522: Sensors and Sensor Networks (Sensors), 2004) indicates that emerging technologies are anticipated to decrease the size, weight, and increase the accuracy of biosensors. Emphasis is placed on integrating large number of sensors into systems that would increase not only the performance but also the lifetime. Furthermore, life cycle costs would also be decreased. The document emphasizes the need to develop functionalized receptors and materials. These would result in next-generation devices, for example, materials of varying porosities that would permit the detection of a single toxic compound in complex mixtures.

In a more recent program solicitation announcement for proposals the NSF (National Science Foundation, NSF 05–526: Sensors and Sensor Networks (Sensors), 2005) is looking for proposals that would ‘seek to advance fundamental knowledge in the area of sensor development.’ The proposal emphasizes that newer and emerging technologies have the potential to decrease the size, weight, and costs of sensors and sensor arrays. It is estimated that these changes would be of an order of magnitude. Furthermore, spatial and temporal resolution will increase along with an increase in accuracy. The NSF is seeking proposals that also lead to sensor integration into engineered systems.

An example of sensor integration is provided by Godso (2002). This author indicates that there is no industry standard for sensor integration. Their company, RPI, provides a sensor integration platform that permits rapid integration and interoperability of different
sensors and sensor networks. The SensorView™ system has the capability of integrating and managing a wide range of disparate and distributed sensors. Furthermore, command, control, and monitoring of the distributed sensors by the SensorView™ platform have been demonstrated.

Other interesting concepts mentioned in the NSF document (NSF 03-512) include liquid surfaces with molecular recognition properties and the requirement of new methods for sensor fabrication, manufacture, and encapsulation. The above document further adds that though false alarms do not have a direct economic impact on the development of a biosensor, they do significantly impact economic and other aspects indirectly, such as time wasted, nuisance factor, etc. Thus, the need to detect and identify false alarms from the sensor data itself.

Santana (2002) indicates the development of the Automated Bioaerosol Collection and Detection (ABCD) system. This system continuously monitors biological agents in carrier facilities. The system automatically conducts tests at intervals of 5 min for near real-time bioaerosol detection.

Carriveau (2002) mentions the application of combining several sensor technologies to produce the next generation of chemical vapor detectors that reduces the false alarm rates during the detection of live chemical warfare agents and difficult interferents. These authors emphasize that their advanced system minimizes both false positive and false negative alarm rates without compromising on overall sensitivity.

Finally, intense competition may be expected from nonbiosensor devices wherein significant improvements and progress have been made to provide a quick and accurate result with a minimum of cost. Companies may perhaps develop a simple strategy where they have a strong base, for example, in glucose monitoring. The profit made in this area may then be successfully re-invested in areas such as autoimmune diseases, for example, rheumatoid arthritis as done perhaps by Abbott Laboratories. Other more complex strategies may be devised by companies in helping to diversify in biosensor development. This will eventually show up in a positive sense in the bottom line.

13.3 SUCCESSFUL AND MODEL COMPANIES FOR BIOSENSOR RESEARCH AND DEVELOPMENT

In this section we will present, as examples, three companies and try to give an idea of their growth. Their market niche will be emphasized which includes their in-house growth, along with growth due to the acquisition of other smaller companies which fit in with their vision of projected growth, and where the biosensor market is heading. At the outset, it needs to be emphasized that in this section the author’s view is presented, which may or may not be coincident with the companies’ vision. This author is trying to present the material as best as can be assimilated from the information that is available in the open literature and from the internet sources.

The three companies that we will present are Biacore, Abbott, and Biosensor Applications AB. Mead (2001) indicates that Biacore International was founded in 1984. It is the leading provider of the surface plasmon resonance (SPR) biosensor. This instrument is continuously being upgraded by the company, and is very frequently used
to analyze biomolecular reactions occurring on surfaces and interfaces. The advantage of the SPR biosensor is that it provides high-quality real-time data of these biomolecular interactions. The software that comes along with it does provide values of the binding and dissociation rate coefficients as well as affinity values. The SPR is an expensive piece of equipment and it generally costs around $300,000–400,000 depending on the model that one purchases. Unfortunately, and this may be the sole opinion of this author, the software program that comes along with the SPR biosensor does not take into account either the diffusional aspects or the degree of heterogeneity that exists on the SPR chip surface whilst analyzing the kinetics of biomolecular reactions. Other biosensor users are also gradually resorting to other types of biosensors to help analyze the kinetics of these biomolecular interactions. However, this point has been discussed quite a bit in the previous chapters of this book and will not be further discussed here. Over here, our main intention is to present an idea of the growth of Biacore from its inception in 1984.

Mead (2001) indicates that Biacore has a niche which is to provide an analytical tool (albeit expensive) to help analyze biomolecular interactions in real-time. Pharmaceutical companies can use this SPR biosensor to help in drug discovery. This is a very popular biosensor and is used frequently in both the industrial and academic environments. This biosensor, as indicated earlier in this book, is finding increasing usage albeit its presumed ‘shortcomings.’

Biacore’s President Ulf Jonsson indicates that the SPR technology was used to start the company in 1984 with an initial investment of $50 million. It took the company 10 years to break even. According to Mead (2001), the company had a revenue of $40.9 million in 2000. Assuming a very reasonable 10% growth rate per year, the revenues for the years 2001–2005 may be initially estimated to be 44.99, 49.49, 54.44, 59.88, 65.87 in million dollars, respectively. Actual numbers are presented in the next paragraph, and the sales growth is more than 10%. The Internet revealed figures for the years after 1999. The company is listed on the Stockholm Exchange as well as on Nasdaq (BCOR).

The annual sales figures for Biacore International AB (Neuchatel, Switzerland) are available. They are presented in Table 13.3a. Numbers for the years 1999, 2000, 2001, and 2002 were available from Hoovers online (http://www.hoovers.com/biacore/). At the outset, please note that the numbers from the Hoover (internet source) and that given in Mead’s (2001) article differ by $5.7 million. The Mead number for the year 2000 is $40.9 million, and the number in the Hoover Internet source for the same year is $46.6 million. This, once again, underscores the ‘unreliability’ in these economic numbers. Nevertheless, we will try to make the best of the situation with whatever is available in either the open literature or Internet sources. We have modeled the data available, and our equation that estimates the projected annual sales till the year 2008 is also presented. Please note that the equation used to provide these projections was based on the sales figures available for 4 years only. Needless to say, market competition and other factors, including geopolitical events may change these numbers for the estimated annual sales for future years. One may note the sharp change in the annual sales figures from the years 2001 and 2002. This represents a net positive change of 36.4%. This may or may not be just a one-time event. Numbers for the years 2003 and 2004 were unavailable at the present time in the open literature.
The data presented in columns 1 and 2 of Table 13.3a were modeled to yield the following equation which is shown in Figure 13.2(a):

$$\text{Annual sales} \, \text{(in million dollars)} = (38.036 \pm 4.597)(\text{year})^{0.3722 \pm 0.1095}$$  \hspace{1cm} (13.1a)

Only four data points were available. The fit is quite good. The availability of more data points would lead to a more reliable fit. Please note that in Figure 13.2(a) year 1 corresponds to 1999, year 2 to 2000, year 3 to 2001, etc. Projections are made from 10 years starting from 1999 to 2008. As indicated above, these are just projections of sales, and geopolitical events and other factors may and will influence the above-mentioned numbers. Nevertheless, the above equation should prove useful to biosensorists, and presumably also to Biacore who are in a much better position to refine the (projected) numbers, since they are the ones who have access to the present-day numbers.

![Figure 13.2](image-url)  
**Figure 13.2** (a) Annual sales figures (in million dollars) for Biacore for the years 1999–2008 (Mead, 2001). Year 1 is 1999, and so on. (b) Annual net income (in million dollars) for Biacore for the years 1999–2008 (Mead, 2001). Year 1 is 1999 and so on.
The annual sales in million dollars is only mildly sensitive to the year (basis year 1999 equal to year 1), as noted by the less than one-half order (equal to 0.3722) of dependence on year. The company would, of course, like to increase the order of dependence on the year, which in other words means a sharper rise in annual sales. Any effort made by Biacore to improve its 'bottom line' would apparently lead to an increase in this order of dependence. Smart, appropriate, and timely acquisitions that significantly impact the bottom line (albeit in the future) could perhaps be one way of doing this. The share price would also be a good indicator of this.

Biaore is making attempts to team-up with key players. For example: *Development and commercialization of the Biacore SPR array technology*. A deal has been signed between Biacore and the Biological Information Research Center (BIRC) of the National (Japan) Institute of Advanced Industrial Science and Technology (AIST). This Japanese Institution specializes in proteonomics. This synergism is aimed at enhancing interactive proteonomics. Science Letter (November 11, 2004; 6:46 pm) (http://www.hoovers.com/free/co/news/detail.xhtml?COID=52773&ArticleID=NR200411) indicates that this synergism would permit the faster generation of detailed proteonomic information by permitting the parallel analysis of biomolecules of interest against panels of proteins. Furthermore, the SPR technologies is ideally suited for drug discovery and high-throughput screening. For example, Mead indicates that the Biacore 3000 may be used upstream in the drug discovery process to help locate appropriate targets. The Biacore S51 may be used in the downstream drug discovery process to help better characterize potential pharmaceutical products.

The next table shows Biacore's annual income in million dollars. Projections of net annual income till the year 2008 are also provided as above for the annual sales figures.

The data presented in columns 1 and 2 of Table 13.3b were modeled to yield the following equation which is shown in Figure 13.2(b):

\[
\text{Annual net income, \$ million} = (5.590 \pm 2.047)(\text{year})^{0.1720 \pm 0.2996} \quad (13.1b)
\]

| Year | Annual sales, \$ (in million; reported\(^a\)) | Annual income, \$ (in million; estimated by eq. 13.1b) |
|------|---------------------------------------------|---------------------------------------------------|
| 1999 | 6.0                                         | 5.59                                             |
| 2000 | 6.3                                         | 6.30                                             |
| 2001 | 4.8                                         | 6.753                                            |
| 2002 | 9.3                                         | 7.095                                            |
| 2003 |                                             | 7.373                                            |
| 2004 |                                             | 7.608                                            |
| 2005 |                                             | 7.812                                            |
| 2006 |                                             | 7.994                                            |
| 2007 |                                             | 8.158                                            |
| 2008 |                                             | 8.3(7)                                           |

\(^a\)Biacore International AB (2004).
Only four data points were available. There is quite a bit of scatter in the data which is reflected in the error of the coefficient that depicts the order (equal to 0.1720 ± 0.2996). There was a decrease in annual net income in the year 2001, and this is reflected in the error and in the figure. The availability of more data points would lead to a more reliable fit. Please note that in Figure 13.1(b) also year 1 corresponds to 1999, year 2 corresponds to 2000, year 3 corresponds to 2001, etc. Projections are made from 10 years starting from 1999 to 2008. As indicated above, these are just projections of annual net income sales, and geopolitical events and other factors may and will influence the above mentioned numbers. In this case, company decisions with regard to personnel and other items would also significantly impact net income figures. This author, as expected, is not privy to this type of confidential company information. Nevertheless, the above equation should prove useful to biosensorists, and presumably also to Biacore who are in a much better position to refine the (projected) numbers, since they are the ones, as mentioned previously, who have access to the present-day numbers.

Abbott Laboratories (Abbott Laboratories Fact Book, 2004) is a health care company that specialized in diagnostics and medical devices amongst other items. In the year 2003, it had a sales income of $19.7 billion. Its two main divisions are the Pharmaceutical Products group with a sales of $11.4 billion, and the Medical Products group with a sales of $8.3 billion. The Medical Products group comprises of (a) US Hospital Products, (b) US Nutritionals, and (c) Worldwide Diagnostics. It is the growth of this Worldwide Diagnostics group that we are interested in here. The sales of the Worldwide Diagnostics group is estimated to be 14.5% of the total sales income of $19.7 billion (Abbott Laboratories Fact Book, 2004; column 26 and 27) for the year 2003.

Table 13.4 shows the estimated Worldwide Diagnostics group from the years 1998 to 2003. In Table 13.4 both the total sales and the sales of the Worldwide Diagnostic group only are presented. The same 14.5% fraction is also used for the years 1998–2002. These numbers are very difficult to obtain, since the author is presumably not a shareholder in Abbott Laboratories. Thus, the same fraction is used, as an approximation, for the previous years.

Table 13.4
Abbott Laboratories Worldwide Diagnostic group sales

| Year | Annual total sales, $ (in million; reported*) | Annual sales for Worldwide Diagnostic group, $ (in million; estimateda) | Annual sales for Worldwide Diagnostic group, $ (in million; estimated from eq. 13.2) |
|------|-----------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| 1998 | 12512.7                                       | 1814                                            | 1687.51                                         |
| 1999 | 13177.6                                       | 1910.7                                          | 2006.24                                         |
| 2000 | 13745.9                                       | 1993.15                                         | 2219.91                                         |
| 2001 | 16285.2                                       | 2361.35                                         | 2385.17                                         |
| 2002 | 17684.7                                       | 2564.28                                         | 2521.79                                         |
| 2003 | 19680.6                                       | 2853.69                                         | 2639.20                                         |

*aAbbott Laboratories Fact Book (2004).*
Abbott Laboratories has a wide variety of diagnostic products (Abbott Laboratories Fact Book, 2004). Some of them are Free Style (blood glucose monitoring), Abbott Prism (screen donated blood for multiple viral assays), the Architech series (t2000, i2000SR, etc.) for cancer, thyroid, fertility, Determine (HIV, hepatitis, and syphilis), PathVision HER-2, DNA probe Kit (HER-2/neu gene in breast cancer patients), and Cell-Dyn 4000 (automated hematology analyzers).

Table 13.4 and Figure 13.3 show the increase in the Abbott Laboratories Worldwide Diagnostic group sales for the years 1998–2003.

The data presented in columns 1 and 3 of Table 13.4 were modeled to yield the following equation which is shown in Figure 13.3:

\[
\text{Worldwide Diagnostic Group Sales, $ million} = (1687.51 \pm 140.83)(\text{year}^{0.2497 \pm 0.0541})
\]  

(13.2)

Only five data points are available. The fit is quite good considering the assumptions that have been made. Please note that in Figure 13.2, year 1 corresponds to 1999, year 2 to 2000, year 3 to 2001, and so on. These are just the estimates of the annual sales figures for the years 1998–2003 for the Abbott Laboratories Worldwide Diagnostic group. Once again, actual numbers are very difficult to get, and thus a ‘real’ comparison is not possible.

The above equation may be used to help provide initial projections of sales for the years 2004–2009. Needless to say, and as indicated above, market competition and other factors, including geopolitical events, may change these numbers for the estimated annual sales for the Worldwide Diagnostic group for future years.

Abbott is very aggressive, as it should be, in acquiring smaller companies and in collaborating with companies that fit its vision of growth in diagnostic products. Appropriate acquisitions would continually benefit its bottom line, and be reflected presumably in the order of dependence on year as shown in eq. 13.2. The present order of dependence is 0.2497. This is 45.17% higher than the order of dependence exhibited in eq. 13.1b for Biacore (equal to 0.1720) that manufactures only the SPR biosensor. Note that in the year 2000, the annual sales figures for Abbott Worldwide Diagnostics were about
Table 13.5

Influence of change in order on sales ratio for Abbott Laboratories Worldwide Diagnostic group

| Year | Sales ratio |
|------|-------------|
| 1 (2004) | 1 |
| 2 (2005) | 1.017 |
| 3 | 1.027 |
| 4 | 1.035 |
| 5 | 1.041 |
| 6 | 1.0456 |
| 7 | 1.0496 |

Abbott Laboratories Fact Book (2004).

300 times (316.4) more than that of Biacore. This factor (level of scale) may be responsible for the other higher order of dependence exhibited in Abbott’s equation (13.2) when compared with that of Biacore’s equation (13.1b). Surely, other factors are also responsible.

It is of interest to see how much the order of dependence on year affects the annual sales. For the sake of comparison let us compare the annual sales given by the following two expressions. The first one is eq. 13.2 with an order of dependence equal to 0.2497 (Abbott’s figures), and the second one assumes a 10% increase in the order of dependence to 0.2746. The numbers are provided in Table 13.5. The first column is the year, with year 1 representing the year 2004, year 2 representing 2005, etc. Please remember these are projected annual sales for the coming years. The second column is the ratio of the numbers obtained using the orders 0.2746 and 0.2497, respectively. In both the cases, the number 1687.51 from eq. 13.2 was used.

This represents a 5% (4.96% actually) change in annual sales in 7 years with a 10% change in the order of dependence. The 5% change is not much, but the base on which it is based is very large (equal to $19786.6 million). A 5% change represents $984 million. This would be over and above the regular growth in sales estimated by eq. 13.2.

As indicated earlier, Abbott Laboratories is acquiring small, more-focused companies at an aggressive pace, that may help increase the previously mentioned influence of the order of dependence on its Worldwide Diagnostic sales by more than 10%. An Abbott Strategic Alliances and Acquisitions document (http://www.abbottdiagnostics.com/Abbott_Us/Alliances.cfm) indicates some of the following alliances and acquisitions. These acquisitions are presented in Table 13.6.

We now present the growth of a small company (less than 24 employees) which up until now has not turned a profit, but is expected to turn a profit in the next few years. Biosensor Applications AB in Sundbyberg, Sweden was sold to private investors by Bofors in 1998 (Annual Report, January 1 to December 31, 2003; http://www.biosensor.se/eng-ekinfo-nyhetsbrev_q1-2003.asp). Up until the year 2003, it had accumulated a loss of 170,947,236 Swedish Kroner. One Swedish Kroner equals 0.150 US dollar (www.exchangerate.com), December 6, 2004; 11:00 am, Central Standard Time). This is equivalent to US $25.6 million. However, the losses incurred by the company shows
Successful and Model Companies for Biosensor Research and Development

Table 13.6
Abbott Laboratories Strategic Alliances and Acquisitions

| Company               | Diagnostic test                                                                 |
|-----------------------|----------------------------------------------------------------------------------|
| Artus GmbH            | Detect a form of coronavirus suspected of causing severe acute respiratory syndrome (SARS) |
| Celera Diagnostics    | In vitro molecular diagnostic products for disease detection                      |
| i-STAT Corporation    | Point-of-care (POC) testing                                                      |
| Therasense Inc.       | Glucose monitoring systems to reduce the pain for testing for glucose              |
| Promega Corporation   | Nucleic acid product testing to automate testing for infectious diseases           |

http://www.abbottdiagnostics.com/Abbott_Us/Alliances.cfm

a decreasing trend, and very shortly the company is expected to show a profit. The losses incurred in the years 2002 and 2003 were 34,245,000 and 27,618,00 Swedish Kroner, respectively (Annual Report, January 1 to December 31, 2003; http://www.biosensor.se/eng-ekinfo-nyhetsbrev_q1-2003.asp). This is equivalent to $5.136 and 4.14 million, respectively. Its losses are decreasing by about $1 million per year. The company is making smart alliances worldwide (North and South America, Europe, the Middle East, India, and Asia). It has also sold its first biosensor system to Japan and has carried out successful tests of its drug detection systems with the Canadian and American Customs authorities. In the year 2003, the company introduced its BIOSENS-D to worldwide markets. Once again, it may be noted that presumably around the year 2008 (10 years after it became independent from Bofors in 1998), Biosensor Applications AB, Sweden will start turning a profit. Though only one example of a small biosensor company is given, these numbers do appear to be typical with regard to investment and time of what it takes to make a biosensor company profitable.

Some examples of the investment and time involved in setting up a biosensor company were given above. Perhaps, it is instructive to provide some real life numbers if one wants to set up a stand-alone biosensor industry. The numbers presented here are different from the ones if one were to just expand or diversify into biosensors. In the second case, biosensors are not the only product that one manufactures and attempts to sell in the market. For much better, and a more detailed, analysis on the commercial applications of biosensors one may refer to Biosensors: A Clearer View by Newman et al. This is an expensive book that has recently come out in 2004, but is presumably well worth its price since it is written and compiled with the leading authority in biosensors.

Different types of biosensors may be made. Initially, one should leverage as much as one can based on one’s expertise. For example, if one has experience with fiber-optic biosensors (for example, worked for a company before, or did a thesis, preferably doctoral), then one can use some, if not all of this knowledge that one already possesses. Money has to be raised to start and run the industry, even before one starts selling one’s
product. That too takes money, and needs to be considered as an ‘expense.’ One may offer an Initial Public Offering (IPO), for example. One may also make appropriate collaborations or strategic partnerships. These aspects are not considered in the numbers given below, since they are very variable, do contribute quite a large fraction of the total costs, and behoove one to explore different avenues to raise the capital required to run the industry, in this case biosensors.

The numbers presented below are for a small biosensor industry that employs 15–20 individuals. Assume that it takes 10–12 years to get the biosensor to the market. We are starting from scratch. This time may be minimized considerably if one were to acquire the technology from some other source, say for example, from university sources, or a ‘specialized boutique’ that has shown that the biosensor runs efficiently in the laboratory, and is looking for commercial partners to bring the biosensor to the market. There are quite a few people like these who are looking for investors. Also, it is not unusual to see investors or investment firms at scientific meetings. This author has attended biotechnological and biomedical meetings. These people were there at these meetings. They may also be present at other types of meetings.

| Number of scientists, administrators, employees | 15–20 |
| Number of years required to develop the biosensor | 10–12 |
| Number of man years required | 150–240 |
| Cost of man-year (scientist, administrator, employee) | $50,000–70,000 |
| Total personnel cost | $7.5–16.8 million |
| Overhead (includes cost of financing project, equipment, supplies) at 200% of personnel cost | $15–33.6 million |
| | $22.5–50.4 million |

This is an expensive project and ranges from approximately $22 to around 50 million. The numbers are very general, and one can use better numbers that are more specific to one’s project. For example, if one is able to use one’s resources more efficiently, by selecting and employing more focused and experienced individuals on the project, then one may save both considerable time and money to successfully launch the biosensor in a ‘highly competitive’ market. Needless to say, a ‘niche market’ would be excellent, but on the other hand its volume in all probability will be very small. Considerable time and money may also be saved by collaborating with like-minded companies, or mutually complementary industries, or build, as indicated earlier, strategic partnerships. However, one needs to carefully balance the risk-gain inherently associated with each choice. Continued improvements in the process, no matter how small, should be the mantra since large sums of money or investment are involved.

The above example indicates the general level of investment required to start-up a biosensor company. It is perhaps useful to do one’s ‘homework’ or research the issue
intensively, from different aspects, preferably by yourself, before one starts to invest time, money, and effort into a cost-intensive long-term project. Most people would consider a ‘business model’ prepared by consultants or experts in this field. Here we will attempt to provide just the basic overall perspectives and guidelines. The details may be filled out later, by interested individual(s), and depending on the type of biosensor project one is looking to establish. We will also attempt to provide a real-life example that perhaps fills the three criteria outlined below. This is just an example; more detailed criteria will surely be required:

**Criteria A.** Identify a market, preferably a large one, even if it is highly competitive. The glucose monitoring market for diabetes quickly comes to mind. Another market, though presumably small, but does exhibit the potential to grow is the market for the diagnosis and monitoring of autoimmune diseases, such as cancer, SLE, and arthritis. Serious consequences are involved if the ailment is not monitored and treated properly.

**Criteria B.** Identify a need in the competitive market that is not yet filled, or the need is filled, but there is considerable room for improvement, for example, the pain and inconvenience for the monitoring of glucose. Another example could be the inconvenience of monitoring different analytes such as auto-antibodies, creatinine, etc for SLE, to help predict a ‘flare’ for the diseases so that it may be better managed. Recognize that one generally resorts to drugs such as steroids to better manage diseases such as SLE. Steroids have very significant side effects.

Most of these drugs have serious side effects, as noted by the intense scrutiny on drugs such as Vioxx (removed from the market by Merck) and on Celebrex (still on the market: Pfizer; December 21, 2004). It may perhaps be useful to have a detection system that helps measure these side effects.

**Criteria C.** Attempt to fill the need with advanced technology and newer approaches. Also, possess plans for future expansion.

Pelikan Technologies in South San Francisco, California (2004) is attempting to introduce a hand-held biosensor that would specifically assist in the monitoring of glucose in the management of diabetes.

**Criteria A.** This is a highly competitive market. This company estimates that there are 18.3 million diabetics in the United States alone. Each year 1.3 million diabetics are added to this number. Most reports, along with the American Diabetic Association (ADA), indicate that this autoimmune disease is reaching epidemic proportions. There are quite a few big name companies that have diagnostic devices and POC monitoring devices for determining glucose levels in blood. If the disease is not treated properly or glucose levels are not monitored carefully, then heart disease, blindness, kidney damage, and other medical conditions may result.

**Criteria B and C.** Measuring of blood glucose levels is extremely painful and inconvenient. This often leads to negligence in glucose monitoring which is undesirable. Better, less invasive and painful measurement techniques would promote the compliance of measuring glucose levels. Pelikan’s innovative and novel technology is aimed to address this issue of inconvenience and pain, and help provide an efficient blood glucose monitoring sensor. Pelikan technology is aimed at transforming the multi-step, painful, and ‘difficult to use’ present-day glucose monitoring systems to a one-step, simple to use and automated, and much less painful...
procedure which is also reliable. Furthermore, the company hopes to use their technology platform for the monitoring of analytes in blood for the detection of other ailments. This aspect cannot be over-emphasized, that is making the POC test painless. Even at a higher cost, it is safe to presume that if the test is painless, most individuals would purchase the POC test, and this would lead to a significantly higher compliance rate.

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