

## Point-of-care biosensor system

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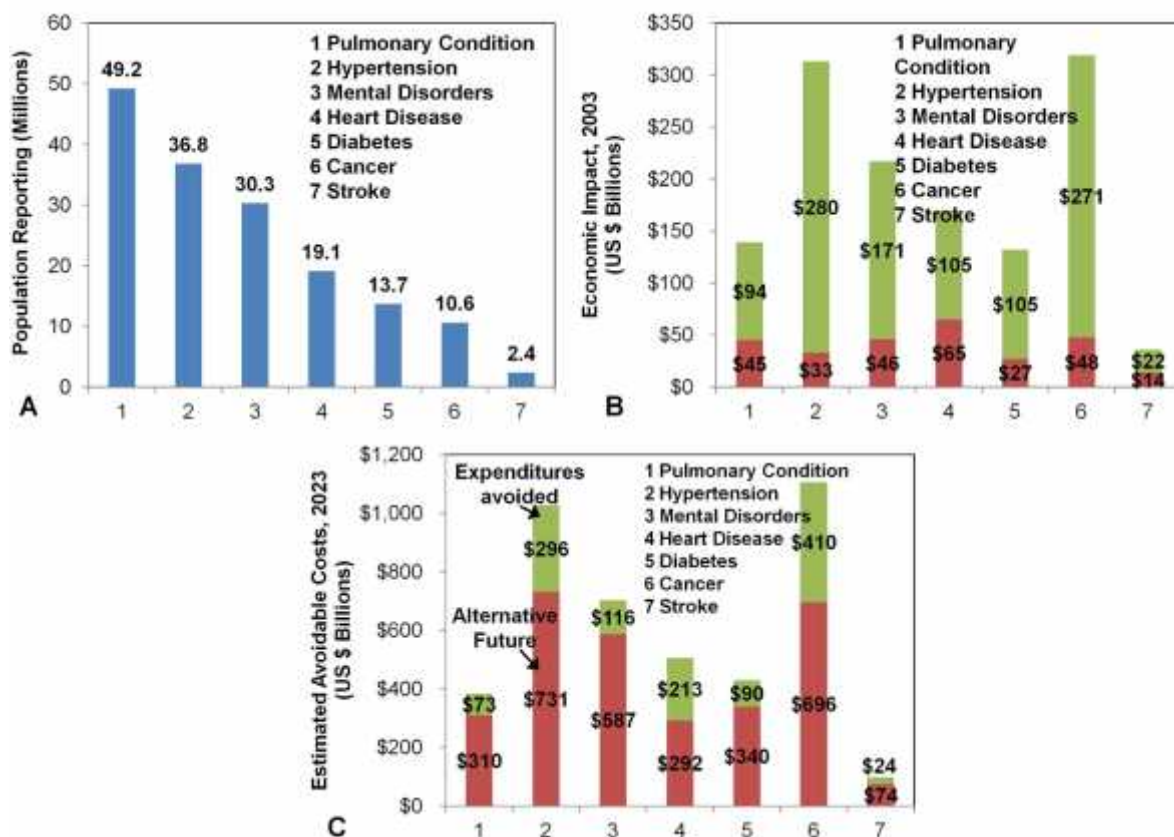
## 1. ABSTRACT

Point-of-care biosensor systems can potentially improve patient care through real-time and remote health monitoring. Over the past few decades, research has been conducted in the field of biosensors to detect patterns of biomarkers and provide information on their concentration in biological samples for robust diagnosis. In future point-of-care applications, requirements such as rapid label-free detection, miniaturized sensor size, and portability will limit the types of biosensors that can be used. This paper reviews label-free detection techniques using Biological MicroElectroMechanical Systems as a potential candidate for point-of-care biosensing applications. Furthermore, detailed surveys have been carried out on wireless networking schemes applicable for a point-of-care environment and on prognostic techniques that will enable decision-support services. This paper concludes by providing a list of challenges that must be resolved before realizing biosensor systems for next-generation point-of-care applications.

## 2. INTRODUCTION

A study conducted by the Milken Institute reported that the total number of individuals in the U.S. affected by chronic diseases in 2003 was around 162 million. The treatment expenditures and loss in productivity projected for 2023 are as high as 790 billion dollars and 3.363 trillion dollars, respectively. It was also estimated that costs totaling 1.33 trillion dollars could be avoided if improvements were made in the prevention and treatment of diseases (1). Figures 1A and 1B present details on the number of people affected by the seven most common chronic diseases in the U.S. and the associated costs in 2003, respectively. Figure 1C presents the estimated costs incurred due to the chronic diseases.

Genomics and proteomics research has elucidated many new biomarkers that have the potential to improve healthcare (2–3). The availability of multiple biomarkers is



**Figure 1.** (A) Number of people reported as having common chronic diseases in U.S. in 2003; (B) economic impact of chronic diseases in U.S. in 2003; and (C) projected annual avoidable costs for the year 2023.

believed to be critical in the diagnosis of complex diseases (4). Detection of biomarkers associated with different stages of disease pathogenesis could further facilitate early detection of diseases and their infection rate (5). Widespread use of these biomarkers will depend upon the development of point-of-care (POC) biosensor devices that will allow real-time, rapid, label-free, and multiplexed detection with high selectivity and sensitivity.

In spite of the rapid explosion of genomics and proteomics research, very few of these biomarkers have transitioned into clinical settings. This is due to the lack of rapid diagnostic techniques that can successfully detect these biomarkers. For example, tuberculosis (TB), a widespread public health problem (20), has proven to be curable (21). However, WHO estimates for 2009 suggest a global detection rate of 63 percent, with only 50 percent of TB cases in Africa being detected (22). Delayed diagnosis has serious consequences, because one untreated pulmonary case can increase the chances of an epidemic (23–24). To obviate such problems, a diagnostic tool is needed that does not require laboratory facilities or demand specialist training. It has been estimated that a single diagnostic test offering 100 percent accuracy could save 625,000 lives per year if widely implemented, and a test with only 85 percent sensitivity and 97 percent specificity might save 392,000 lives, or 22.4 percent of the current

annual worldwide deaths (25). These numbers signify that there is a pressing need to develop new POC diagnostic tools to reduce the number of fatalities and the costs incurred due to growing health concerns.

As health care costs are increasing and with an ageing world population (26), there is an increasing need to remotely monitor the health condition of patients. This includes situations where patients are not confined to hospitals. To address this issue, a variety of POC system prototypes have been produced. Such systems provide real-time feedback information about the health condition of patients, either to the patients themselves or to a medical database accessible to health care providers. Thus, POC systems constitute a new approach to address the issue of managing and monitoring the health of patients suffering from chronic diseases, elderly people, and postoperative rehabilitation patients by performing tasks that are traditionally performed using laboratory testing (27–28). In this paper, information is presented on new technologies in the form of POC biosensors and their integration with appropriate technology to provide clinically relevant information, thereby assisting physicians and clinicians in disease diagnosis. The major technology platform that will be the focus of this discussion is biosensors and their integration into POC systems for the analysis of clinically significant biomarkers.

POC systems for health monitoring may comprise different types of biosensors that are wearable or implantable and capable of measuring physiological parameters such as heart rate, oxygen saturation, changes in plasma protein profile, and patterns of multiple biomarkers and their concentration. The sensed information is then communicated through a wired or wireless link to a central data acquisition node, such as a personal digital assistant (PDA), which can in turn transmit the sensed signals to a medical center (29). These systems would not only reduce response time but would also make testing available in environments where laboratory testing is not feasible (6). These systems not only have applications to medical diagnostics and biological warfare agent detection (7), but the sensor configuration can be modified to suit other applications, such as food quality assurance (8), environmental monitoring (9), and industrial process control (10–11). Other possible applications are also emerging, such as the identification of animal and plant pathogens, field tissue and gene analysis, and diagnostic testing such as for malarial strains and water purity analysis (6).

Furthermore, early diagnosis of critical health changes could enable the prevention of fatal events (30). Such early diagnosis requires continuous monitoring. Current physiological sensing systems are unsuitable for unobtrusive, recurrent, long-term, low-cost health monitoring. The next generation of POC biosensor systems could enable better early detection of critical changes in a patient's health condition. Hence, POC biosensor systems are expected to act not only as data collection systems, but they must also learn the health baselines of individual patients and discover problems autonomously by detecting alarming health trends using advanced information processing algorithms. Also, next-generation POC systems should satisfy certain medical criteria while operating under several ergonomic constraints and significant hardware resource limitations. Designing such systems is a very challenging task, since a lot of highly constraining and often conflicting requirements have to be considered. Specifically, the design needs to take into account size and weight factors; also, its presence should not hinder a patient's actions. Furthermore, radiation concerns and other issues need to be accounted for. Also, the security and privacy of the collected clinical data must be guaranteed, while system power consumption must be minimal in order to increase the operational life of the system (29–32).

In this paper we identify the important elements of an integrated POC system that will satisfy the requirements of future health care services. We also discuss in detail the state of the art in each of these elements and the issues related to their implementation in a complete POC system. The aim of this review is not to criticize but rather to serve as a reference for researchers and developers to provide direction for future research requirements. Section 3 presents the important elements that have to be integrated in a POC system. In Section 4 biosensors as the main tool for diagnostics are discussed and their classification based on sensing method, transduction

mechanism, and the type of receptor is presented. Section 5 reviews the requirements of wireless biosensors to enable remote health monitoring which is followed by network-level architecture for a POC system to route information from the POC system to clinicians. Section 6 introduces the concept of prognostics in health care using the information from POC systems. Research issues for implementing a POC wireless system are discussed in Section 7, and conclusions are presented in Section 8.

### 3. ELEMENTS OF FUTURE POC SYSTEMS

POC systems are viewed as integrated systems that can process clinical samples for a number of different types of biomarkers in a variety of settings, such as clinical laboratories, doctors' offices, and more. Basically, POC systems make state-of-the-art technology platforms accessible to a large population pool. From a diagnostic or prognostic perspective, POC systems must provide the clinician with the ability to have access to a wealth of molecular information for providing profiles of a variety of biomarkers using novel biosensing technology that in the past have been accessible only at major healthcare centers. The development of new biosensing technologies will provide opportunities for better screening of at-risk patients, tighter surveillance of disease recurrence, and better monitoring of treatment. In addition, POC technologies are by their very nature low-cost in their implementation, making large-scale screening for disease prevention more attractive to health care insurers (4).

The small size and simple construction of Biological MicroElectroMechanical Systems (BioMEMS) used for the detection of biological and chemical agents are ideally suited for POC lab-on-a-chip systems that are capable of detecting multiple biomarkers in the environment and on humans as well as performing sampling and analysis for critical data evaluation (33). For this reason, BioMEMS has been receiving widespread attention in the biosensor research community in recent years. Applications dealing with diagnosis, sensing, and detection are the areas targeted most by BioMEMS engineers. The design, fabrication, and process steps for BioMEMS for diagnostics are different depending on the application and the materials used. BioMEMS have been used to handle biological samples for the detection of microorganisms, cells, proteins, viruses, and DNA (34). Moreover, the areas of low-cost POC testing, battlefield diagnostics, and homeland security require inexpensive, low-power, reliable devices (35).

Current challenges in developing BioMEMS for diagnosis, sensing, and detection are 1) characterization and development of biosensors with low detection limits (as low as a few femtomolars in concentration or pg/mL), high sensitivity, and specificity (36); 2) methods to identify and mitigate noise effects that are both intrinsic and extrinsic; 3) accurate identification of analytes; 4) use of materials that are biocompatible and have mechanical properties that enable improved sensitivity with low electrical losses; and 5) creating low-noise readout methods. Procedures for separation and manipulation of

pathogens have also been one of the major problems in developing such sensors (33) (37). Also, since biosensors for POC applications are sometimes used as either implanted sensors or wearable sensors, it is important to ensure that the sensor materials are biocompatible so as to ensure that there are no harmful effects on patients; also, sensor materials should not degrade rapidly over time (38–39). Biocompatibility in turn can cause sensor node failure (39) due to biofouling, hermiticity of encapsulation, electrode passivation, and limited lifetime of the immobilized enzymes (40–41).

Recently, there has been an increase in interest to integrate POC biosensors with microfluidics, which has permitted the miniaturization of conventional techniques to enable high-throughput and low-cost measurements through lab-on-a-chip systems (12). Lab-on-a-chip systems take advantage of several intrinsic characteristics of microfluidics, including laminar flow, low consumption of costly reagents, minimal handling of hazardous materials, short reaction time required for analysis, multiple sample detection in parallel, portability, and versatility in design (13). Systems for biomolecular assays (14–15) and bio-separations (16–17), including the separation of circulating tumor cells or plasma from whole blood, have been reported in the past (18–19).

In order to realize remote monitoring and provide real-time feedback information, biosensors with wireless link capability are desirable. Transmission of sensed data in the overall context of a POC biosensor system needs to be performed for communicating the collected clinical information to the healthcare provider or to a remote medical station. Typically, a biosensor network is deployed to aid data transfer from the POC to the medical database. A biosensor network is defined as a collection of sensor nodes that comprises a variety of biosensors, memory, data processing capabilities, and communication block (42). A combination of wireless MEMS and biosensors meets the demands of future medical wireless biosensor systems. For reliable data transfer, a POC wireless biosensor network uses a two-tiered network architecture (43–44). The lower tier involves the distribution of biosensors in the POC, and the higher tier includes data routing to a central server. In a biosensor network, each biosensor senses its environment and sends the raw data collected to a base station (45). Direct transmission by a biosensor to the base station is not a very efficient way of routing data. Hence, a network topology is employed to efficiently transfer the data. The most common network topologies used to route data are 1) the cluster-based approach and 2) the tree-based approach.

A cluster is basically a group of co-located sensor nodes that have formed a group to minimize their communication energy costs. A typical cluster is characterized by a leader node called the cluster head. The cluster head is the sensor that is responsible for collecting data from its cluster members, aggregating it, and forwarding it to the base-station. Therefore, in this topology the cluster heads are the nodes that perform the long distance communication to the base station and, hence, consume more energy than the cluster member that

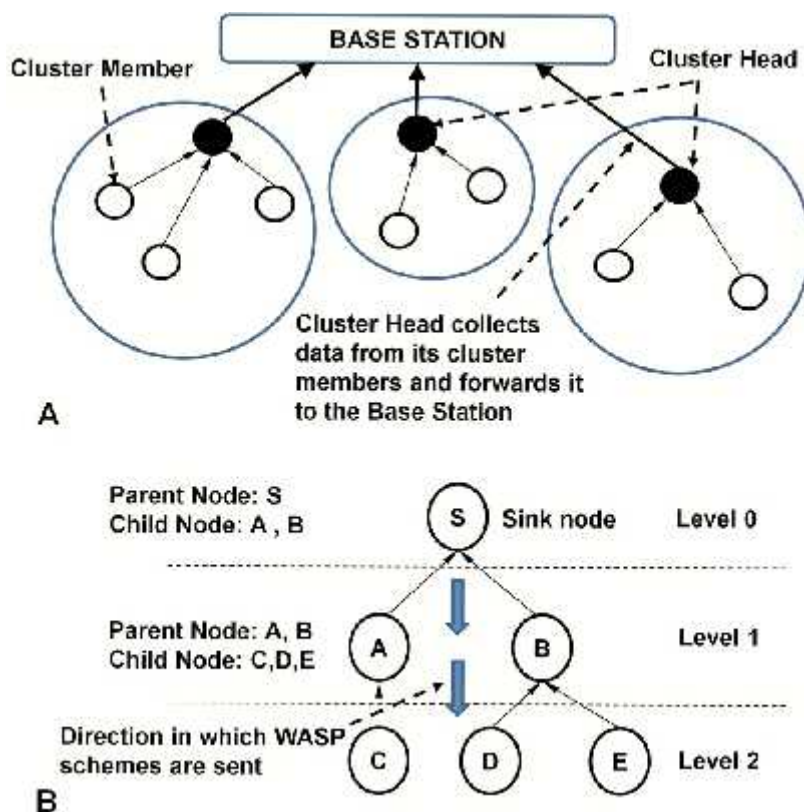
performs only short-distance communication. In order to prevent the cluster head node from dying due to a lack of energy, the cluster node is periodically rotated. In the long run, therefore, the energy consumption due to communication is averaged out or spread out over the entire network (45).

Another network topology that is commonly preferred is the tree-based approach. Here the nodes form a tree-based structure for routing information. The final data collection node is called the sink node. A set of nodes transmit data to the sink node and form the first level of the tree. These nodes in turn receive information from another set of nodes forming the second level of tree structure. In this level, the former set of nodes act as parent nodes to the latter. In the next level, the child nodes in the second level in turn act like parent nodes and receive information from another set of nodes. This hierarchy continues till all the nodes form a part of the network. Wireless autonomous spanning tree protocol (WASP) is a medium access protocol that is used in a tree-based approach. Here, each node will tell its children in which slot they can send their data by using a special message: a WASP scheme. This WASP scheme is unique for every node and constructed by the node itself. A node uses the schemes to control the traffic of its children and simultaneously to request more resources from its parents for these children. This minimizes the coordination overhead because each scheme is used by the parent and the children of the sending node. Everything the node has to know to generate this scheme can be obtained by listening to the WASP-schemes coming from its parent node (i.e., one level up in the tree) and from its children (i.e., one level down in the tree). Consequently, the division of the time slots is done in a distributed manner (46). Figures 2A and 2B shows a typical cluster and tree topology respectively.

In addition to the above described requirements, an important and possibly required feature in a POC system is the ability to provide embedded decision support, i.e., to extract higher level information from raw bio-signals obtained from the biosensors. In a scenario where numerous POC biosensor systems are deployed to continuously monitor several patients, a large quantity of multidimensional data would be accumulated for each patient. It would be tedious for professionals to examine the entire data set in order to detect anomalies in health trends. Hence, the other requirement is to perform early identification (prognosis) and thus prevention (health management) of diseases and health episodes. This requires advanced inference logic and embedded signal processing capabilities to identify anomalies in the health condition of the patient. In related work (47–48), researchers have embedded machine learning algorithms in mobile phones to detect heart arrhythmias in the monitored EKG signals. Using a network of biosensors, additional physiological information can be obtained and can be fused using machine learning techniques to make an estimation of the patient's health state (49).

## 4. MEMS FOR BIOSENSING

Biosensors are devices used to selectively detect the presence of specific biomolecules or compounds in a



**Figure 2.** Commonly used wireless network topologies: (A) Cluster topology and (B) tree topology.

given environment by carrying out physical or chemical transduction. Biosensors produce an electrical equivalent of the change reflected in the biologically sensitive element acting as the sensor head (50–51). BioMEMS are defined as biosensor devices that are constructed using techniques based on micro/nano-scale fabrication. BioMEMS are used for identifying, immobilizing, growing, purifying, processing or manipulating, analyzing, and identifying biological and chemical analytes (37) (52–53). The increased surge in BioMEMS for biosensing applications is primarily due to the fact that microfabrication technology has resulted in miniaturization of sensing devices. This has led to increased sensitivity resulting from sensors reduced in size to the scale of the analyte, leading to better performance, increased reliability of extracted data, and reduction in detection time. Also, effective reagent volumes are reduced, making the system cost-effective. Furthermore, miniaturization allows for portability, which is one of the main requirements for POC applications (50) (54). For example, Feltis *et al.* (6) constructed a fully self-contained, hand-held biosensor based on the Surface Plasmon Resonance (SPR) technique, with the size of the complete sensor unit being 15 x 8 cm. They were able to measure changes as small as  $3.3 \times 10^{-6}$  refractive index units and were able to detect the biological toxin ricin at 200 ng/mL in 10 min.

The range of potential applications of BioMEMS technology is broad. BioMEMS is the largest and most studied area is diagnostics for POC testing applications.

Some of the recent research works in the field of POC diagnostics using BioMEMS include the following: Hwang *et al.* (55), who proposed and experimentally proved a novel detection method for detecting bacterial cells in blood; Abbas *et al.* (56), who developed a millimeter wave BioMEMS for the detection of nitric oxide synthase (NOS) for ex-vivo applications; and Tremeler and Sarikaya (57), who combined genetic tools with synthetic nanoscale constructs to create a research methodology called Molecular Biomimetics.

#### 4.1. Biosensors for POC technologies

A biosensor is traditionally defined as a bioanalytical device incorporating a biological material or a biomimic (e.g., antibodies or nucleic acids) that is intimately associated with or integrated within a physicochemical transducer or transducing microsystem. The transducer may be optical, electrochemical, thermometric, piezoelectric, or magnetic (4) (58). The purpose of the transducer is to aid in producing an electronic signal that is proportional to a single analyte or a related group of analytes. The essential elements of a biosensor (Figure 3) are (1) the bio-recognition element (bio-receptor), (2) the transducing element, (3) the excitation element, and (4) the readout modality. However, some biosensors might not contain any excitation element.

One of the critical functionality requirements of biosensors is bio-recognition element selectivity for a specific target analyte and the ability to maintain this

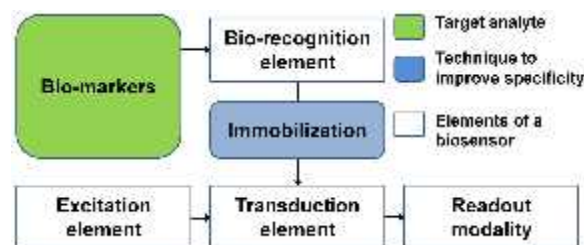
**Table 1.** Biosensor classification based on transduction mechanism

Transduction Mechanism	Method
Mechanical	Stress sensing Mass sensing
Optical	Fluorescence Chemiluminescence Bioluminescence Surface Plasmon Scattering Evanescent Waves Interferometry
Electrical	Conductometric Capacitive
Piezoelectric	Quartz Crystal Microbalance (QCM) Surface Acoustic Wave (SAW)
Electrochemical	Potentiometric Amperometric Ion Sensitive FET <sup>1</sup> (ISFET) Chemical FET (ChemFET)
Thermal	Calorimetric

<sup>1</sup>Field Effect Transistor

**Table 2.** Types of biosensors based on receptors

Receptor	Type
Enzyme	Bioaffinity/Biocatalysis
Antibody/Antigen	Bioaffinity (Immunosensor)
Nucleic Acids/DNA	Biocatalysis
Biomimetic Materials	Bioaffinity
Cellular Structures/Cells	Biocatalysis
Ionophore	Bioaffinity



**Figure 3.** Schematic representation of a biosensor containing the biorecognition element, transducer, and physical output that is related to the concentration of the analyte of interest.

selectivity in the presence of interfering species or compounds (59). Selectivity depends on the ability of the bio-receptor to bind to the analyte. Highly selective biological recognition systems have been developed using bio-receptors that are developed from biological origins (such as antibodies and ligands) or that have been patterned after biological systems (synthetic-based recognition elements such as aptamers, peptides, surface-imprinted polymers, or molecularly imprinted polymers) (57). Another functionality requirement of a biosensor is sensitivity. Sensitivity depends on multiple factors, including the geometry of the sensing surface (60), sensor material properties (61), resolution of the measurement system, and the surface chemistry used in immobilizing the bio-recognition element on the sensing surface (62). The two commonly used forms of surface chemistry are (1) silane chemistry and (2) thiol chemistry. Silane chemistry is preferred *in situations* where the sensing surface material is silica, silicon, or plastic. Thiol chemistry is utilized when the sensing surface is potentially made of metals (mostly

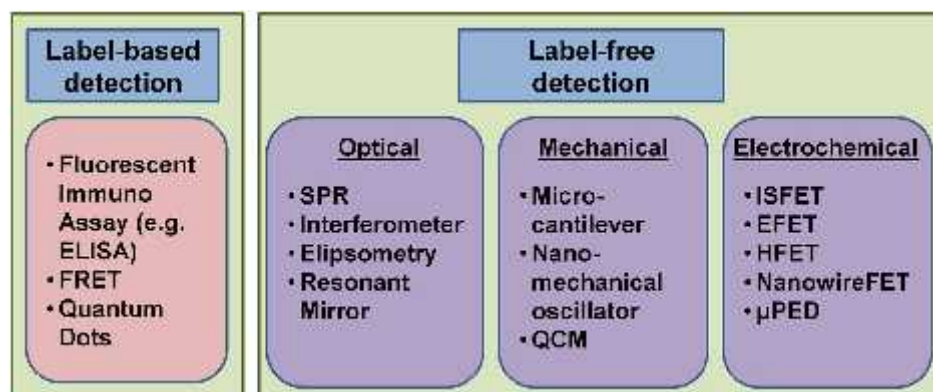
gold). In 2006, Bailey *et al.* (63) introduced the DNA-encoded antibody library (DEAL) technique. Both for pathological examination or for fundamental biology studies, different classes of biomolecules are measured typically in heterogeneous samples, thus introducing unavoidable sources of noise that are hard to quantify. The DEAL technique was proposed for spatially multiplexed detection of single-strand DNAs (ssDNAs) and proteins on the same diagnostic platform. DEAL is based on the coupling of ssDNA oligomers onto antibodies that are then combined with the biological sample of interest. Spotted DNA arrays are then utilized to spatially stratify the biomolecules. Bailey *et al.* demonstrated the DEAL technique for (1) the detection of multiple proteins, (2) the co-detection of ssDNAs, proteins, and cells, and (3) the sorting of cell lines and primary immune cells.

Widespread use of biosensors in POC applications will ultimately depend upon the development of biosensing techniques that allow rapid, label-free detection of multiple biomarkers with high selectivity and sensitivity. There are two major strategies for the detection of biomarkers: label-based and label-free detection. Existing bio-detection systems mainly rely on fluorescence transduction methods (also called labeled detection, since a fluorescent dye/tag is used to identify the biomarker concentration by either labeling the bounded biomarkers or the unbounded bio-recognition sites) to detect the binding of biomarkers to a biorecognition element due to its high sensitivity and selectivity, and sufficient temporal and spatial resolution (65). In other words, label-based techniques require the labeling of query molecules with labels such as fluorescent dyes, radioisotopes, or epitope tags (66). This includes the enzyme-linked immunoabsorbent assay (ELISA), a common clinical approach for protein marker detection that has a detection limit as low as a few femtomolars in concentration, and the Frequency Resonant Energy Transfer (FRET) transduction method. However, these labeling strategies often alter the surface characteristics and natural activities of the query molecules. Moreover, labeling procedures are laborious and lengthy and they limit the number and types of query molecules that can be studied. This makes labeling impractical for use in POC applications (64) (67). In contrast to label-based techniques, label-free detection methods depend on the measurement of an inherent property of the query itself, such as mass or dielectric property, and it also avoids interference due to tagging molecules, thereby aiding in the rapid determination of reaction kinetics of biomolecular interactions in real time (68–70). This is the reason that label-free detection holds potential for rapid diagnosis in a POC setting.

#### 4.2. Biosensor classification

Apart from classification based on sensing strategy, i.e., label-based or label-free sensing (see Figure 4), biosensors are also classified based on the type of transduction mechanism employed (Table 1) and the type of bio-receptor used (Table 2). The ability to recognize the “target” or biomarker in a mixed population is viewed as a critical step in any diagnostic assay. The biomarker can be present intracellularly or extracellularly. Whatever the





**Figure 4.** Classification of biosensors based on sensing method.

sampling matrix might be, the biomarker must be recognized and collected from a heterogeneous population. In addition, the marker can be as complex as a whole cell or as simple as a single molecule (such as a prostate-specific antigen (PSA)) (4). Hence, the specificity of the biosensor is determined by the receptor or the recognition element, and this directly affects the sensitivity of the biosensor. Biosensors can be classified into two types based on the bio-receptor used. The bio-receptors can be classified as (1) the bioaffinity type and (2) the biocatalytic type receptors (71). In bioaffinity-based reception, the receptor does not affect or change the target material, while in a biocatalytic receptor; the receptor catalyzes a biochemical reaction. Most enzymes correspond to biocatalytic receptor types. In some cases where enzymes are not available to detect certain biomolecules, antibodies are used for highly selective reception.

The most commonly used bio-receptors are 1) antibodies, 2) enzymes, 3) nucleic acids, and 4) synthetic bio-recognition elements. Antibodies are biological molecules that exhibit very specific binding capabilities for specific structures. An antibody is a complex molecule made up of hundreds of individual amino acids arranged in a highly ordered sequence. Biosensors that depend on antigen-antibody binding are called immunosensors. One of the most widely used immuno assays is the enzyme-linked immunoabsorbent assay (ELISA) technique (73).

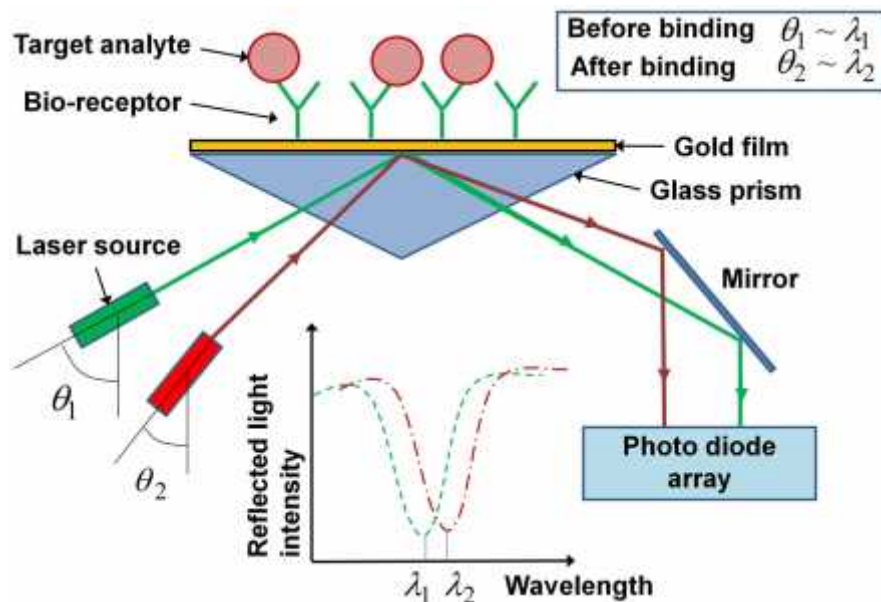
Enzymes are often chosen as bio-receptors based on their specific binding capabilities as well as their catalytic activities. In biocatalytic recognition mechanisms, the detection is amplified by a reaction catalyzed by macromolecules called biocatalysts. The catalytic activity provided by enzymes allows for much lower limits of detection than would be obtained with common binding techniques. Presnova *et al.* (72) demonstrated electrochemical biosensors based on horseradish peroxidase where the peroxidase is the enzyme that catalyzes the oxidation of a variety of organic molecules in the presence of hydrogen peroxide.

Another biorecognition mechanism that has been receiving a lot of interest in the last decade involves the hybridization of deoxyribonucleic acid (DNA) or

ribonucleic acid (RNA). Here, if the sequence of bases composing a certain part of the DNA is known, then the complementary sequence (which is called the probe) can be synthesized. By unwinding the double-stranded DNA into single strands and adding the probe, and then annealing the strands, the probe will hybridize to its complementary sequence on the target DNA. Ueberfeld *et al.* (74) designed a reversible fluorescent DNA probe that can be used to determine the concentration of single-stranded DNA in solution by using a ratiometric fluorescence measurement.

Recently, synthetic ligands have been studied for a variety of targets, such as aptamers and ligands. The advantage of using synthetic bio-receptors over other bio-recognition elements is that they are robust structures that can be placed in different environments without losing their specificity, can be made by using wet chemistry techniques, and can be easily structurally modified to support the addition of other sensing elements. Yao *et al.* (75) developed the “one-bead one-compound” (OBOC) combinatorial library method (where each resin bead displays a unique peptide) and whole cell binding assay to synthesize and identify D-amino acid-containing cancer cells.

As stated earlier, label-free detection techniques hold the potential for inexpensive, noninvasive, and informative clinical diagnoses, particularly in point-of-care settings. Recently, there has been increasing interest among industry and the scientific community in using BioMEMS sensors for carrying out label-free detection. The miniaturized size of MEMS sensors aids in reducing measurement time, increasing sensitivity, and minimizing invasiveness. A couple of research efforts to realize label-free detection using RF MEMS have been reported recently. Kim *et al.* (76) demonstrated a detection method based on RF electric signals and MEMS to detect glucose oxidase (GOx). Dalmay *et al.* (77) developed a detection method using microwave frequencies to study cell electrical parameters. Arvind *et al.* (78) demonstrated two parallel modes of sensing using a single RF MEMS shunt capacitor to detect *Staphylococcus aureus* using mouse monoclonal IgG3 proteins. Surface stress change and RF signal losses due to specific biomolecular binding are two parallel sensing modes that have been realized.



**Figure 5.** Detection principle of an SPR device. Biomolecular interactions at the sensing surface layer are monitored through a shift in the resonance wavelength.

#### 4.3. Label-free detection techniques using BioMEMS sensors

Many label-free techniques (Figure 4) have been successfully demonstrated in the past using micron-size biosensors. However, these techniques also have issues regarding sensitivity and specificity. Further, expensive fabrication techniques, morphological anomalies, and insufficient knowledge of biosensors often restrict their use. Here we present the most commonly employed label-free detection techniques, namely, 1) surface plasmon resonance (SPR), 2) microcantilevers, 3) quartz crystal microbalance (QCM), and 4) biological field effect transistors (BioFETs). All these sensors are constructed using techniques based on micro-/nano-scale fabrication and thus can be considered as BioMEMS sensors.

##### 4.3.1. Surface plasmon resonance (SPR)

SPR is a surface-sensitive spectroscopic method that measures changes in the refractive index of a bio-sensing material at the interface between metal surfaces, usually a thin gold film (50–100 nm) coated on a glass slide, and a dielectric medium (70). Owing to high loss in the metal, the associated charge density wave, also called the surface plasma wave (SPW), propagates with high attenuation in the visible and near-infrared spectral regions. Changes in the refractive index of the sensing surface may be determined by optically interrogating the SPR. During interrogation, optical radiation is used to excite the SPW, which results in the resonant transfer of energy into the SPW. SPR manifests itself by resonant absorption of the energy of the optical wave (79). In order to detect biomarkers, the gold surface in SPR is immobilized with the bio-recognition element. Unlabeled query molecules (target) are added, and any changes in the angle of reflection of light caused by the binding of these molecules

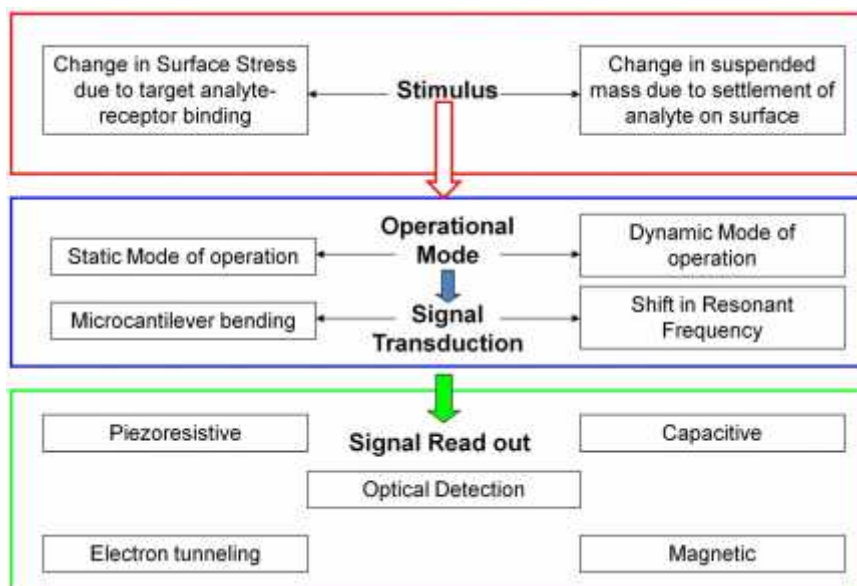
to the immobilized bio-receptors are measured to characterize biomolecular interactions in real time. The angle at which the minimum intensity (corresponding to the maximum resonant energy transfer) of the reflected light is obtained is known as the “SPR angle” (see Figure 5), which is directly related to the amount of biomolecules bound to the gold surface. The advantages of SPR include real-time (85), multiplexed, qualitative, as well as quantitative detection. Also, SPR is sensitive to conformational changes on the gold surface. However, SPR is limited to the use of gold or silver surfaces alone.

SPR has been employed in a wide variety of bio-assays, such as the analysis of association or dissociation kinetics of biomolecules (80), drug discovery (81), rapid detection of cancer biomarkers (82), and antigen–antibody interactions in protein microarrays (83). Yu *et al.* (84) exploited the highly sensitive nature of SPR to detect very low concentrations (0.1 ng/mL) of domoic acid analyte having very low molecular weight (310 g/mol). Recently, Feltis *et al.* (6) constructed a fully self-contained, handheld SPR device that is capable of duplicating many laboratory-based tests with a sensitivity range similar to many commercial ELISA-based immuno-assays.

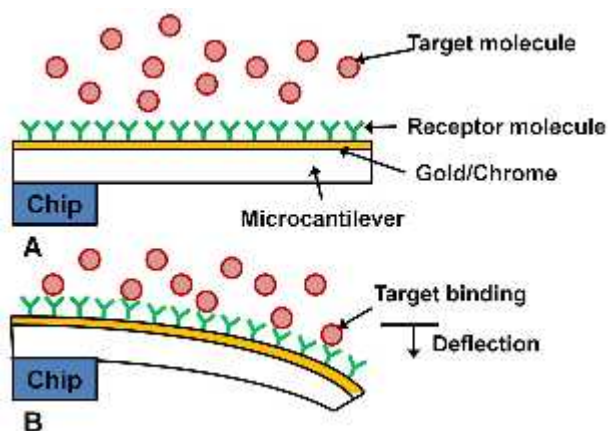
##### 4.3.2. BioMEMS microcantilever

Electro-mechanical detection of biochemical entities and reactions has been demonstrated at the nano and micro-scale using microcantilever structures (60). Past studies reported that when specific biomolecular interactions occur on one surface of a microcantilever beam, the cantilever bends (86–89) (see Figure 7). The recent discovery (2001) of the origin of nanomechanical motion generated by DNA hybridization and protein–ligand binding (88) provided some insight into the specificity of the technique. In addition, its use for DNA–DNA





**Figure 6.** Operation modes and transduction mechanism used in BioMEMS microcantilever.



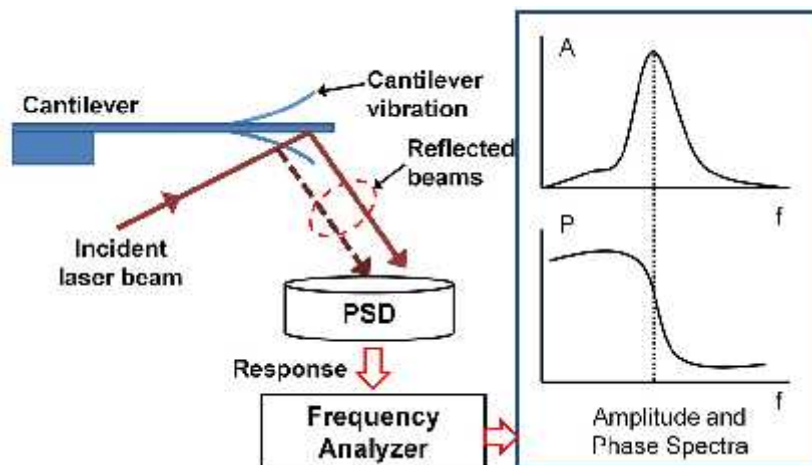
**Figure 7.** Cantilever beam response: (A) initial state and (B) sensing state.

hybridization detection, including accurate positive/negative detection of one-base pair mismatches, has also been reported (88–89). Besides being label-free, this technology readily lends itself to the formation of microarrays using well-known microfabrication techniques (90), thereby offering the promising prospect of high throughput protein analysis. However, it remains unclear whether the cantilever sensing technique has sufficient sensitivity and specificity to detect disease-related proteins at clinically relevant conditions and concentrations. Gu et al. (91) in 2001, demonstrated the feasibility of using microcantilevers for detecting disease-related proteins by detecting PSA as an example of both protein–protein binding in general and tumor marker detection in particular.

In microcantilever biosensors there are two modes of sensing used for detection: stress sensing and mass sensing. Stress sensing is carried out by coating one side of the cantilever beam with a bio-receptor that

adsorbs target biomolecules. The adsorption results in the expansion or compression of the bio-receptor layer, which then induces surface stress on the cantilever beam, and thus the cantilever bends due to stress. In the latter type of sensing, the cantilever is actuated to vibrate in its resonant frequency. The binding of the biomolecule with a bio-receptor changes the frequency of vibration. The shift in resonant frequency is analyzed to detect the concentration of the biomolecule (92).

Surface stress–based micro-cantilevers have been proposed and utilized because of their ease of operation, higher sensitivity, and the ease to study surface stress during adsorption through optical detection (as in atomic force microscopy (AFM)) and piezoresistive detection (92–94). The microcantilever having precise deflection measurement techniques allows for the detection of surface stresses as small as  $10\text{E-}4\text{ N/m}$  (95).



**Figure 8.** Schematic of optical detection system for measuring microcantilever deflection.

DNA hybridizations were the first biological sensing methods demonstrated using microcantilever-type sensors. McKendry *et al.* (96) used an eight-cantilever array to detect unlabeled DNA hybridizations at nanomolar concentrations within minutes. Zhang *et al.* (97) used microcantilevers in rapid and label-free detection of biomarker transcripts in human RNA in the picomolar range. Protein-based cantilever structures started evolving after the discovery of appropriate enzymes and antibodies. The late evolution of protein-based cantilevers is due to the fact that the sensitivity of microcantilevers for protein detection is much less compared to the detection of DNA. Biomolecule detection and analysis using proteins have also been reported by Wu *et al.* (91). Arntz *et al.* (98) used a biosensor similar to the McKendry array (96) for real-time detection of cardiac biomarker proteins: myoglobin and kinase, whose level indicates heart disease. Further, Arntz *et al.* (98) were the first to report that the sensitivity of protein detection by a cantilever array technique is several orders of magnitude less than that reported in DNA hybridization.

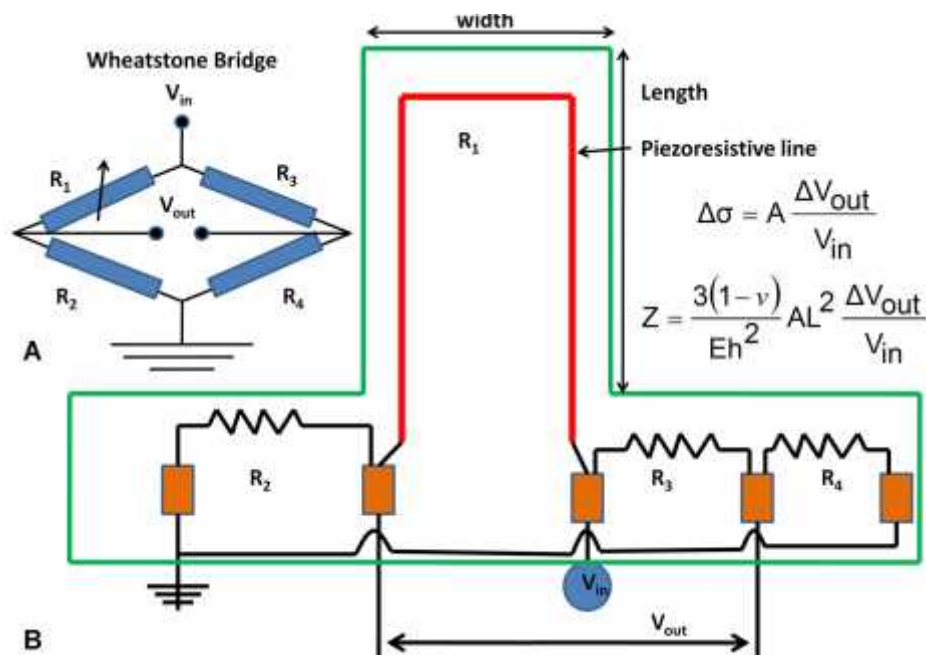
The general concept of a BioMEMS cantilever device is that it detects changes in surface stress due to adsorption-induced force and resonant frequency variation due to mass loading (99). Fritz *et al.* (86) reported that the bending motion is caused by changes in the surface stress of a cantilever beam, but the origin of the surface-stress change was first elucidated by Wu *et al.* (88), who also reported that deflection may be upward or downward depending on the type of molecules involved. Wu *et al.* (88) also suggested that cantilever deflection is created because of the interplay between changes in configurational entropy and intermolecular energy induced by specific biomolecular reactions between biomolecules such as antibodies and analytes. Figure 6 lists the operation modes, signal transductions, and read-out mechanisms with respect to microcantilever-based biosensors. The most commonly used molecular detection methods for measuring the bending of a microcantilever (Figure 7) are the optical deflection method or piezoresistive techniques. In the

optical deflection method a low-intensity laser is reflected off of the cantilever and is focused onto a position-sensitive detector (PSD) (Figure 8). Low intensity laser beams are used so that the biomolecules coated on the surface of the cantilever are not affected (88) (99).

The major advantage of the optical detection method is that it is capable of detecting deflections on the order of  $10^{-10}$  m (100). This detection scheme demands high precision and alignment, which makes the optical diagnosing system expensive. Also, the aqueous environment causes thermal management issues, leading to erroneous readings. Due to these disadvantages, a piezoresistive method of detection is preferred for portable sensors. In a piezoresistive microcantilever system (Figure 9), a loop of piezoresistive material, such as polysilicon, is embedded onto the cantilever surface. When the cantilever bends, it causes the bending of piezo material, which results in a change in its resistance (i.e., deflection implies that the piezoresistive material undergoes a stress that causes a strain, which leads to a change in resistance). This change in resistance can be determined by using a Wheatstone circuit. Though less sensitive than optical detection methods, piezoresistive methods can detect deflections on the order of nanometers. The readout system can be integrated on the chip (which is not the case with optical detection) and is thus more appropriate for wireless sensing.

#### 4.3.3. Quartz crystal microbalance (QCM)

Quartz crystal microbalance (QCM) based biosensors are a viable alternative to microcantilevers due to their sensitive mass detection capabilities and their ability to monitor in real time. The general operating principle of a QCM biosensor is a decrease in the crystal's resonant frequency following the binding of the target biomolecules. When a rigid mass binds to the oscillating crystal surface, the shift in the resonance frequency is proportional to the mass bound. This was first proved by Sauerbrey (101) in 1959. Henceforth, QCM has been used to quantify the number of target cells in a sample. Targets



**Figure 9.** Schematic of a piezoresistive BioMEMS microcantilever.

detected by QCM include Chlamydia (102), Salmonella (103), Bacillus (104), Pseudomonas (105), and Escherichia coli (106). Recently, Poitras *et al.* (107) developed a biosensor using QCM with dissipation monitoring (QCM-D) and validated it by detecting Escherichia coli (E. coli) O157:H7. The advantage of using QCM-D over traditional QCM is that it gives insight into the viscoelastic properties of the adsorbed mass. The biosensor response in QCM-D is the initial slope of the dissipation shift as a function of elapsed time (Dslope). The Dslope provides the important advantage of rapid online bacteria detection.

#### 4.3.4. Electrochemical biosensors

Recently, an impressive number of inventive designs for biosensors based on electrochemical sensing have appeared. These biosensors are also considered to be chemically modified electrodes (CMEs), since electronic conducting, semiconducting, and ionic conducting materials are coated with biochemical films (108–109). These types of sensors combine the bio-receptors with electrochemical transducers to produce a biosensor that provides a simple, accurate, and inexpensive platform for patient diagnosis.

There are different types of electrochemical biosensors that have been commonly reported on in the past: 1) amperometric, 2) potentiometric, 3) field-effect transistor (FET), and 4) conductometric biosensors (110). Amperometry is based on the measurement of the current resulting from the electrochemical oxidation or reduction of an electroactive species. It is usually performed by maintaining a constant potential at a working electrode (usually gold or carbon) or on an array of electrodes with respect to a reference electrode. The resulting current is directly correlated to the bulk concentration of the electroactive species (111–112). Similarly, potentiometric

measurements involve the determination of the potential differences between an indicator and reference electrode when there is no significant current flowing between them. The most common potentiometric devices are pH electrodes or gas selective (CO<sub>2</sub> and NH<sub>3</sub>) electrodes (110). The potential differences between these indicator and reference electrodes are proportional to the logarithm of the ion activity or gas fugacity (or concentration), as described by the Nernst-Donnan equation (113–114). Also, many enzyme reactions, such as that of urease, and other biological membrane receptors may be monitored by ion conductometric or impedimetric devices using interdigitated microelectrodes (115). Drummond *et al.* (116) carried out an in-depth survey of the approaches to electrochemical detection of selected DNA sequences, such as direct electrochemistry of DNA, electrochemistry at polymer-modified electrodes, electrochemistry of DNA-specific redox reporters, electrochemical amplification with nano-particles, and electrochemical devices based on DNA-modified charge transport chemistry.

Another important class of electrochemical devices is the biologically active field effect transistors (BioFETs). These are biosensor types that use a semiconductor transducer. The basic idea of BioFETs stems from ion-selective field-effect transistors (ISFETs). In ISFETs, the gate of a MOSFET (metal-oxide-semiconductor field-effect transistor) is replaced by an ion-selective layer, an aqueous solution, and a reference electrode (118–120). Such devices measure the concentrations of certain ion species in the liquid and therefore act as pH sensors. More recently, biosensors such as EnFETs (enzyme FETs), ImmunoFETs, and DNAFETs have been devised upon the ISFET concept by replacing the ion-selective layer of ISFETs with layers of immobilized enzymes, antibodies, or DNA strands (121–

123). Gupta *et al.* (124) used a different kind of FET called the heterojunction (HFET) for in-vivo electrochemical detection of physiological salt concentration. They reported the detection of streptavidin and clinically relevant levels of biotinylated monokine induced by interferon gamma (MIG) at physiological salt concentrations with AlGaN HFETs. High charge sensitivity and electrical stability in buffers makes HFETs an attractive platform for in-vivo detection.

### 4.4. Lab-on-a-chip for point-of-care testing

Lab-on-a-chip is a system or device that can be used to perform a combination of analyses on a single miniaturized device for biological and clinical assays (125). These systems are designed to either detect a single or a class of biomolecules, or they have system-level analytical capabilities for a broad range of biomolecules, known as a micro total analysis system (micro-TAS) (126). These devices offer advantages such as integrating sample handling and preparation, mixing, separation, lysing of cells, and detection (37). These devices are also capable of purifying, isolating, and characterizing samples, and such a platform integrates sample treatment modules together with separation and detection modules, all brought together using the functionality of MEMS techniques (127). Currently, the focus on bioparticle manipulation methods to separate and identify biomolecules is based on electrostatic techniques such as electrophoresis, electroosmosis, electrofusion, electrowetting, and dielectrophoresis (DEP) (125). Most of the bioparticle separation is done using DEP techniques. Pohl *et al.* (128) introduced the term DEP; they described the translational motion of neutral matter caused by the polarization effects in non-uniform electric fields.

Recently, there has been an increase in interest regarding the use of microfluidic paper-based electrochemical devices, also called micro-PEDs, for quantifying the concentration of various analytes in aqueous solutions, including biological fluids such as urine, serum, and blood (117). The surge in interest is due to the advantages of micro-PEDs: (1) they are light-weight, portable, single-use, and disposable; (2) they are flexible and foldable; (3) they have excellent reproducibility with high sensitivity and accuracy; (4) they do not require professional medical personnel or complicated instruments; and (5) they allow for the integration of high-density detection systems into small devices (129–132).

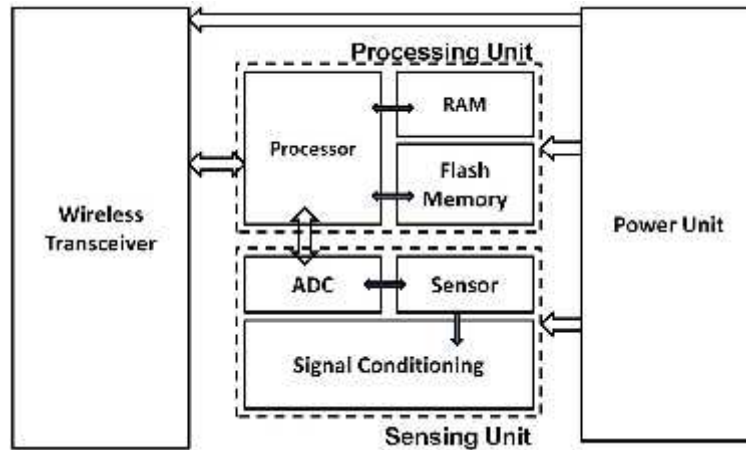
Also, there have been research efforts in the past to realize rapid multiplexed detections using lab-on-a-chip devices. Fan *et al.* (133) reported an integrated microfluidic system to address the issue of multiplexed detection of protein in microliter quantities of blood using fluorescent labels. Fan *et al.* developed the integrated blood barcode chip (IBBC) to address the need for microchips that integrate on-chip plasma separations from microliter quantities of whole blood with rapid in-situ measurements of multiple plasma proteins. The immunoassay region of the chip is a microscopic barcode, integrated into a microfluidics channel and customized for the detection of many proteins and/or for the quantification of a single or few proteins over a broad concentration range. Zheng *et al.* (134) reported label-free, real-time multiplexed detection of

protein cancer markers with high selectivity and femtomolar sensitivity using antibody-functionalized silicon-nanowire field-effect sensors.

## 5. WIRELESS BIOSENSORS

Wireless networks allow secure and instant access to patient reports and medical and administration records. This helps in reducing errors, making decisions more quickly, and increasing quality of care (135). Wireless technology is credited with improving the flow of information unfettered by the constraints of location or time. Secure wireless healthcare enables healthcare organizations to confidently access medical applications and services, such as electronic health records, decision support, e-prescribing, and e-research (136). Also, secure wireless healthcare offers the wireless foundation to deploy mobile care applications and location-aware services. This allows easy access to information for POC services regardless of the location. Access to patient information by healthcare professionals at the POC is critical for improving patient safety and medical care (137).

Biosensors with wireless link capabilities are desirable because wireless sensing systems can monitor health conditions in real time and can also enable new health care services, such as real-time drug delivery. Although bio-assays for various pathogenic bacteria, proteins, and DNA based on BioMEMS systems have been reported, their potential holds only if they can be reused for further sensing by dissociating the detected pathogens from the corresponding antibodies. Traditionally, biosensors in labs are reused by dissociating biomarkers such as detected proteins using strong chemical formulations. This method handicaps the use of both wearable and implantable sensors. Chen *et al.* (138) demonstrated a wireless BioMEMS sensor for the detection of C-reactive proteins (CRP). This CRP BioMEMS sensor deals with the problem of reusability through electrically controlled protein-antibody binding. The advantage of the sensor system was dissociation, which was realized by applying a low-frequency 0.2 Hz 1V AC electric field to the sensor. Previously, Brod *et al.* (139) were the first to report and demonstrate electrical control on antigen-antibody binding for the modulation of molecular recognition next to an electrode in a pH biosensor. They demonstrated that the binding of an antibody to an antigen can be controlled electrically in a reversible manner. The antigen-antibody binding was monitored using electrochemical surface plasmon resonance (SPR). Application of a bias that is -0.5 V or more negative with respect to an Ag/AgCl reference electrode caused the antigens to detach from the antibodies. When the negative bias was removed, the antigens and antibodies had their binding ability restored. Similar efforts to control molecular interactions using electrical means have been reported. This includes modulation of an enzyme immobilized on a membrane (140), redox reactions (141–143), dissociation of molecules by reducing covalent bonds (144), and electrophoretic and electrostatic control over DNA hybridization (145–146). However, in some applications the antibody can potentially be desorbed from the sensing surface. In such applications, the DEAL



**Figure 10.** Functional block diagram of wireless sensor module.

approach circumvents the denaturation of antibodies. This is because DNA patterns are robust to dehydration and can survive at elevated temperatures (80–100 degrees Celsius) (133).

### 5.1. Wireless biosensor architecture

A sensor provides the interface between the physical world and electronic systems, and a sensor node incorporates the sensor along with the signal conditioning unit, processing unit, and communication module. It is the function of the sensor nodes to acquire the sensed data and transmit them to the personal server or data acquisition hardware. With advancements in MEMS technology, micro-size inexpensive sensor nodes are becoming more realizable (147). A wide range of commercially available components-off-the-shelf (COTS) sensors have been deployed to monitor vital signals, the behavior of humans, and the surrounding environment. These include accelerometers and gyroscopes, electrocardiography (EKG), electromyography (EMG), electroencephalography (EEG) electrodes, pulse oximetry, respiration, carbon dioxide (CO<sub>2</sub>), blood pressure, blood sugar, humidity, and temperature sensors (148).

Figure 10 shows the functional blocks of a wireless sensor module. The major four blocks of a sensor module are the 1) power supply, 2) radio system, 3) processing unit, and 4) sensing module. The processing unit is composed of volatile and nonvolatile memory and a microcontroller. The sensor module in turn consists of a filter, analog to digital converter (ADC), and a sensor head. The type of sensor being used depends on the application (149). The sensor senses the physiological data and is preconditioned (by amplification and filtering) to levels suitable for digitization. The digitized data is transmitted to the data acquisition device. A processor is programmed to control and coordinate the activities of the sensor node for internal data acquisition and establishing communication with the personal server. The processor also controls the switching of the individual components of the sensor node between sleep and wakeup modes to save battery power when not in use.

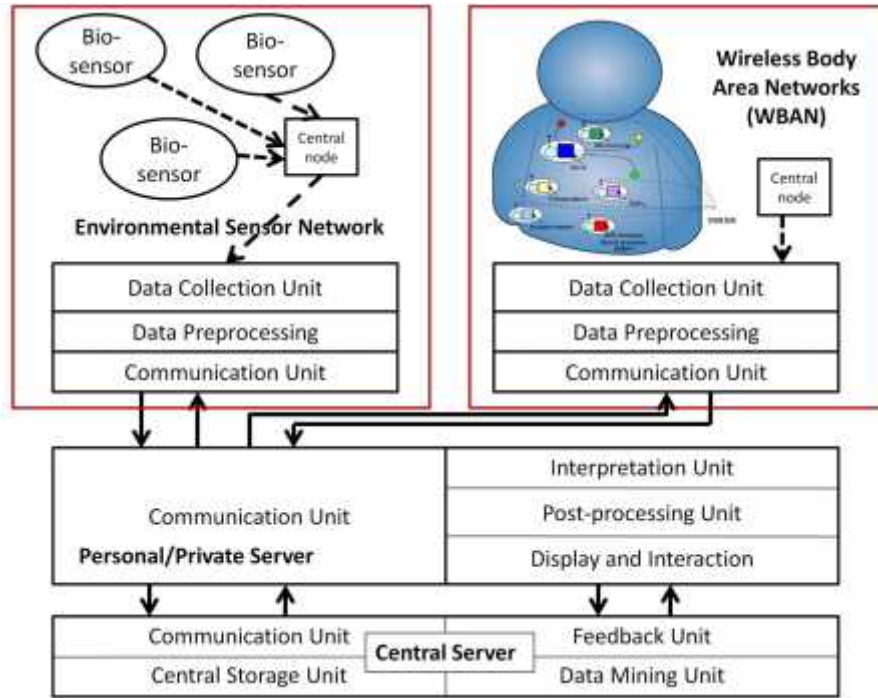
Power consumption is constrained in wireless sensor nodes for medical applications. Lowering the power consumption can prolong the lifetime of sensors. However, this adds an additional challenge to the digital signal processor (DSP) for supporting radio-frequency (RF) transmissions between severely power-limited nodes. Self-powered wireless sensors are preferred in applications where sensors are implanted, because, once implemented, it is difficult to access the sensor to recharge the battery.

Because of advances in MEMS along with improvements in nano-engineering techniques, the fabrication and manufacturing of micro-size sensors has become feasible (150). This has increased the potential for producing smaller implantable and wearable sensors and has also changed the traditional way of measuring human physiological parameters. Recently, MEMS electrodes for EKG acquisition have been developed by the fabrication of micro-size needles or electrodes on silicon polymers (147). Brown *et al.* (151) developed a fluorescent hydrogel-alginate microspherical optical glucose sensor, which serves as an example for miniaturized nano-engineered sensors. Najafi *et al.* (152) carried out a study on the use of battery-less MEMS implants for cardiovascular applications. This is a physiological sensor that includes an array of micro-needles for use in an implanted blood pressure sensor. A more detailed review of BioMEMS for implanted biosensors has been provided by Grayson *et al.* (153).

### 5.2. POC wireless system model and architecture

Prognostics in health care refer to methods of survival analysis and estimation of the rate of health deterioration. In order to carry out prognostics, physiological parameters and health deterioration parameters must be monitored. To understand and evaluate the prognostics of human health, biosensor networks must be deployed both in the environment and on patients. Works related to wireless sensor networks for environmental sensing, event detection, and specific target sensing have been studied in the past. Buratti *et al.* (154) reviewed wireless sensor technologies, their applications,





**Figure 11.** Two-level network architecture for point-of-care wireless systems.

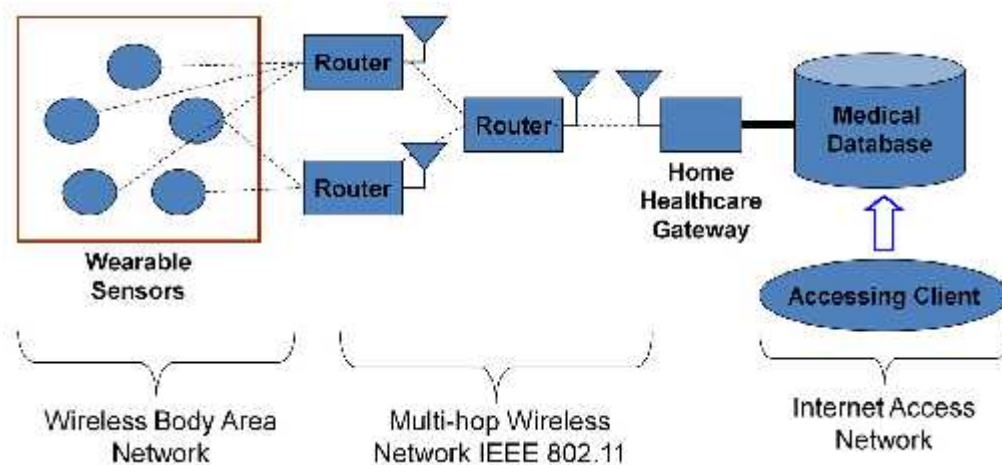
standards, features in design, and evolution. Mahfuz and Ahmed (155) studied the suitability of wireless sensor networks (WSN) from the available communication system standards (ZigBee and Bluetooth) and CMOS-level architecture for environmental monitoring, protection, and control. Cao *et al.* (147) presented a comparison of IEEE 802 wireless standards for communication with an emphasis on the physical layer of the ISO/OSI layered architecture model.

In the context of POC systems, transmission of measured data needs to be performed 1) for communicating the data from the biosensors to the central node and 2) for sending the aggregated data from the central node to a remote medical database or the healthcare provider (29). In the first scenario, the user's mobility and comfortableness are hindered by the use of wires. Hence, in this case, the sensor nodes can form a body area network (BAN) for transmitting the data to a central node, which can be a personal digital assistant (PDA) or a custom-designed microcontroller-based device. Wireless BAN (WBAN) is a radio-frequency-based networking technology that interconnects small nodes around the human body, each of which has sensing capabilities (156–157). A WBAN network is slightly different from a wireless personal area network (WPAN) in the sense that WPAN interconnect devices are centered on an individual person's workspace and are intended to provide coverage distances of 10 m. Also, WBANs differ from general WSN, which imposes new technical challenges (157). First, there are two types of nodes existing in WBANs: 1) sensors that are placed on the body or implanted inside the human body, and 2) router nodes whose main function is to relay data to the medical

database (141–159). This is different from WSNs, wherein all nodes act both as sensor and relay nodes (160). Second, the number of nodes deployed in a WBAN is comparatively less than in WSNs, as nodes are either placed on or inside the body. This places a limitation on the reliability of data due to the reduction in redundant information provided by multiple nodes sensing the same physiological parameter (156). Third, WBANs exhibit relatively stable data rates compared to WSNs (which perform event-based monitoring) due to the need for periodic physiological monitoring, which demands continuous operation and thus requires power management. Finally, WBANs are used for critical parameter monitoring; latency must be largely avoided. In WSNs the nodes can be stationary or mobile, and node mobility does not occur in a group. WBAN nodes are associated with the wearer's mobility, and thus mobility occurs in a group (160–161).

A WBAN is a health monitoring network of sensor nodes that is implanted or worn by a person called the host (162). The biosensor network consists of a group of biosensors, an external device called the control node that is placed on or close to the human body, and an external base station to relay data to the global network (Figure 11) (167). The sensor nodes in the WBAN are heterogeneous, possessing the ability to measure multiple stimuli from the host's body (163–164), and each consists of a processor, memory, transceiver, sensors/actuators, and a power unit (167). These nodes are assumed to be built to survive extreme conditions, such as variation in temperature and humidity (165), and are powered using batteries or energy harvesting mechanisms that harvest energy from body movements, vibration, body heat

## Point-of-care biosensor system



**Figure 12.** CareNet network model.

production, and bio-fuels (166). These biosensors perform the tasks of sensing physiological information, processing it, transmitting it to the control node, receiving external signals, and triggering actions such as drug delivery. The control node acts as both the data aggregation and routing point. The control node also sends the data collected periodically to an external base station, where it is stored for further processing. The control node and the base station have significantly higher transmission and processing capabilities than the biosensors (167).

The Vanderbilt Advanced NETWORK Systems Lab in conjunction with the University of California, Berkeley and Cornell University developed an integrated wireless sensor network for remote health care called the CareNet (Figure 12). It was developed with the goal of reliably and securely collecting physiological data and transmitting the data to a medical database where healthcare providers can access patient health information (168–169). Laerhoven and Gellersen (163) suggested that a large number of low quality sensors can perform the task of monitoring as effectively as a few high quality sensors. Such a network will have multiple sensors measuring the same stimuli, providing redundancy and increasing fault tolerance, while at the same time being less intrusive and more favorable for regular wearing due to their light weight and small form factor (162). In line with such a claim, networks up to 192 and 255 nodes have been proposed by Choi *et al.* (170).

Research projects such as CodeBlue, MobiHealth, and iSIM have also led to the concrete establishment of a WBAN system (171–173). IEEE 1073 has been focusing on standardizing a layered architecture solution for wireless communication in wireless body area networks (WBANs) (141) (174). The entire system architecture (presented by Jovanov *et al.* (175)) involves a two-tiered wireless heterogeneous networking infrastructure. Lo and Yang (175) developed a WBAN hardware platform based on this architecture using COTS (components off-the-shelf).

WBAN sensor devices are lightweight, wearable and mobile, which also means that they have low computation and communication power and a small amount of memory. A tele-healthcare system would employ a network comprising individual health monitoring systems that connects to the healthcare providers (centered on a medical server) through the Internet (177–178). The medical server resides at the top of this hierarchy and is optimized to provide service for a large number of users and encompasses a complex network that also connects medical personnel and healthcare professionals. This network is a multi-hop IEEE 802.11-based wireless network or mobile phone network (e.g., GPRS, 3G) (179). The lower tier consists of a number of sensor nodes that are strategically placed on an individual's body. The sensor nodes sample vital signals and transfer the relevant data to a personal server (PS; technically the control node), which is generally a PDA for mobile patients or a home-based PC for elderly patients for in-home monitoring (180–181) through a wireless link. The PS and the sensor nodes collectively form a network that is generally called a personal network (182) and that has a computerless architecture to access sensor data. The personal server interfaces with the WBAN nodes through a network coordinator that implements ZigBee (IEEE 802.15.4) or Bluetooth connectivity (182). Practically, this interconnectivity can be realized using radio waves, lasers, sound waves, light waves, or infrared radiation. Radio connectivity (IEEE 802.15.4) is preferred because for shorter range the connectivity can be established with lesser power and smaller antenna size than other schemes (183). The personal server sets up and controls the WBAN and provides a graphical or audio interface to the user and transfers information about the individual's health status to the health care provider. Table 3 compares commonly used short distance communication schemes.

Yang *et al.* (183) fabricated and demonstrated a wearable RFID-enabled sensor node for continuous biomedical monitoring and discussed the dielectric characterization of fabric substrates, inkjet-printing of

**Table 3.** Comparison of short distance communication schemes

	<b>ZigBee (IEEE 802.15.4)</b>	<b>Bluetooth (Open Standard)</b>	<b>WLAN<sup>1</sup> (IEEE 802.11)</b>
<b>Frequency Band</b>	2.4 GHz	2.4 GHz	2.4 GHz
<b>Bandwidth</b>	5 MHz	1 MHz	20 MHz
<b>Data rate</b>	250 kbps <sup>2</sup> (2.4 GHz)	1 Mbps <sup>3</sup>	>11Mbps
<b>Multiple Access Scheme</b>	CSMA/CA <sup>4</sup>	FHSS <sup>5</sup>	OFDMA <sup>6</sup> ,CSMA/CA
<b>Transmitter Power</b>	0 dBm	4 - 10 dBm	24 dBm
<b>Range</b>	10m	10m	100m

<sup>1</sup>Wireless Local Area Network, <sup>2</sup>kilo bits per second, <sup>3</sup>mega bits per second, <sup>4</sup>Carrier Sense Multiple Access/Collision Avoidance

<sup>5</sup>Frequency Hop Spread Spectrum, <sup>6</sup>Orthogonal Frequency Division Multiple Access

conductive nano-particle silver ink, design of RFID antennas, and integration of sensor active and passive devices for a wireless biomedical application. A simple and cost-effective health care system was developed and named UbiMon (184). NASA, in collaboration with Stanford University, developed a wearable physiological monitoring system for astronauts for continual monitoring of physiological parameters during space missions (185). The MIT Media Lab developed MITHril, a wearable computing platform compatible with both custom-made and COTS sensors that interfaces humans and computers (186–187). Harvard University further extended and demonstrated the formation of ad-hoc networks in their project CodeBlue (188–189) to facilitate automatic vital signal collection and real-time analysis of human health when placed on patients in hospitals or disaster environments.

WBANs target diverse applications, including healthcare, real-time monitoring of athletes, workplace safety, consumer electronics (short range wireless technologies for human-computer interaction (HCI)) (190–191), secure authentication and safeguarding of uniformed personnel, and health monitoring of astronauts during space missions. Also, handicapped people can be assisted using intra-body communications (IBCs), as proposed by Riaz and Shimamoto in (190). WBANs are categorized based on factors such as the type of sensor for a particular application, radio system requirements (e.g., data rate), network topologies, and type of application (156).

WBANs extend conventional bedside monitoring to ambulatory monitoring, providing a POC to patients, the elderly (192), and others for both hospital and home-based scenarios (168). The objective of POC wireless systems is to provide monitoring, diagnostic, autonomous diagnostic, alarm, and emergency services along with management of electronic medical records (EMRs) of patients (193). The CodeBlue project at Harvard University was developed to provide a solution for pre-hospital and in-hospital emergency care, stroke patient rehabilitation, and disaster response. Some of the sensors developed for CodeBlue include a wireless two-lead EKG (194), accelerometer, gyroscope, and an electromyographic (EMG) sensor for monitoring patients with strokes. It uses the ZigBee protocol to communicate among the nodes. It also uses a mesh topology without any centralized server or database for storage and control of information. Due to multi-hop transmission the system experiences packet loss, and thus the bandwidth per receiver is limited to 40 kbps (163) (184) (195).

The Advanced Health and Disaster Aid Network (AID-N) developed at Johns Hopkins University has an architecture similar to that of CodeBlue (196). It provides monitoring service for mass casualties during a disaster by using electronic tags similar to RFID tags. The system uses a global positioning system (GPS) for outdoor localization and a Mote Track system for indoor tracking. Wi-Fi and cellular networks are employed to facilitate communication between personal servers and the central server.

The wearable health monitoring system (WHMS) developed at the University of Alabama aims at providing a telemedicine system for ambulatory health status monitoring. WHMS has a star-topology network. A personal server is implemented on a PDA or a PC, which co-ordinates data collection from sensor nodes using a TDMA scheme (195). The MITHril project (186–187) includes an EKG, skin temperature, and galvanic skin response sensor that is wearable and used for sensing and context-aware interaction (197). Further extensions were made to a multi-user wireless distributed wearable computing platform that utilizes Wi-Fi connectivity to relay data from a personal server (implemented on a PDA) to a central server (184).

Similar to WHMS, another research project involves the efforts of eight European countries and fifteen other partners to create an ambient intelligent microsystems platform for mobile services and applications (known as MIMOSA). It employs a mobile phone as a user-carried interface device. To enable local connectivity between the sensor nodes, WiBree (Bluetooth low-energy technology) and RFID tags were used. To provide an application programming interface for local connectivity and to facilitate sensor readings, NanoIP and simple sensor interface (SSI) protocols have been integrated into MIMOSA (198).

Human gesture recognition has been proven to be very useful for the handicapped. Schwiebert *et al.* (199) came up with a smart sensor with a novel approach to provide a complete system for restoring vision to visually-impaired persons from the signals generated by an external camera to an array of sensors that electrically stimulate the retina via a wireless interface. The Wireless Sensor Node for Motion Capture System with Accelerometers (WiMoCA) (200) is concerned with the design and implementation of a distributed gesture recognition system. The network system uses a star topology, and data connectivity is realized using a time division multiple access (TDMA) approach. Sensing modules are made of

**Table 4.** List of frequency bands for WBAN<sup>1</sup>

Description		Frequency Band
Implant	MICS <sup>2</sup>	402–405 MHz
On-body	-	13.5 MHz
On-body	-	5–50 MHz (HBC <sup>3</sup> )
On-body	WMTS <sup>4</sup>	600 MHz
On-body	ISM <sup>5</sup>	900 MHz
On-body	ISM (ZigBee)	2.4 GHz
On-body	UWB <sup>6</sup>	3.1–10.6 GHz

<sup>1</sup>Wireless Body Area Network, <sup>2</sup>Medical Implant Communications Service, <sup>3</sup>Human Body Communication, <sup>4</sup>Wireless Medical Telemetry Service, <sup>5</sup>Industrial, Scientific, and Medical, <sup>6</sup>Ultra-wideband

tri-axial accelerometers operating at 868 MHz with a peak data rate of 100 kbps (201).

Lo and Yang (200) (202) studied the need for gesture recognition and came up with a way to identify hand movement. Other related work with respect to wireless medical systems can be found in (203–210). A more detailed discussion on WBAN applications in cardiovascular disease, cancer detection, asthma, and telemedicine systems can be found in (141).

In the context of WBAN, the IEEE 802.15.6 Task Group (TG) 6 is developing a communication standard for low-power wireless sensor nodes operating in and around a patient's body. As pointed out by Pantelopoulous and Bourbakis (29), the standard under development should support scalable data rates ranging from 1 kbps to hundreds of Mbps over a distance of 2–5m with a network size of 100 nodes and guarantee very low latency and power consumption (around 0.1–1 mW) (157).

### 5.3. WBAN infrastructure

Table 4 provides a reference to the most important frequency bands for POC wireless communication (157). In order to design and develop a reliable system suitable for WBAN, knowledge of radio propagation channels is needed (211). WMTS is the licensed WBAN for medical telemetry systems, but it has a restricted bandwidth (around 14 MHz). The other bands, such as ISM (2.4 GHz), include bands to protect adjacent channel interference. The MICS band operating in the range of 402–405 Hz is dedicated for implanted sensor communication. Ultra-wideband (UWB) operates at a higher frequency allocated between 3.1 to 10.6 GHz and will be looked upon more in future research. Currently, most of the WBAN services are confined to the 2.36–2.4 GHz band so as to leverage COTS integration and avoid interference from neighboring wireless channels.

## 6. PROGNOSTICS IN POC APPLICATIONS

Reliability is a prime factor of concern for industrial and medical devices, since the functional degradation of products during operation in the field can be catastrophic (212). During World War II, the reliability of military equipment became a serious matter of concern (213). Since then there has been an increase in interest on the part of industry to study the durability or lifetime of devices by monitoring the ongoing health of products and

systems in order to predict failures and provide warnings in advance of catastrophic failure (214). Vichare and Pecht (215) have defined prognostics as a method of prediction or estimation of the future state of health based on current and historical health conditions. Further, this lifetime prediction study was extended and applied to study the survival time of cancer patients. The term “remaining useful life” (RUL) used by industrial reliability engineers is called “survival analysis” by cancer researchers (213). Recently, survival analysis refers to a method of analyzing data in disciplines such as medicine, epidemiology, environmental health, marketing, and astronomy. Analogous to system-level failure prediction, prognosis in health care involves techniques that combine sensing, recording, and interpreting environmental, operational, and performance parameters to carry out survival analysis for public health.

Health monitoring is one of the main application areas for pervasive computing (216). The evolution of biosensors for POC diagnostics and prognostics has been motivated by the advancement in information and communication technologies, microfluidics, and microelectronics. Future POC diagnostic systems are expected to support artificial intelligence algorithms through the use of decision support processes, in order to provide accurate and efficient diagnostic results in real time (213). Decision support processing is a critical component of a POC system since they can assist novice practitioners and nurses in their diagnostic and clinical judgment (217). POC wireless systems require the integration of current lab-on-a-chip technologies with decision support services operated by standalone devices.

In the context of POC systems, prognostics is performed for two different purposes. First, prognostics is used to estimate the RUL of a POC system at each time instant so as to avoid system failure and reduce system downtime. This can be accomplished through the use of traditional techniques of prognostics and health management (PHM) by interpreting the parameters indicative of (1) performance degradation, i.e., deviation of operating parameters from their expected values; (2) physical degradation of critical subcomponents; or (3) changes in operation environment (214). The second type of health monitoring at POC refers to the diagnosis of diseases and estimation of survival time. Survival time no longer means the time to death (213). It refers to the time period from a starting point to the occurrence of a certain event.

In POC systems, prognosis of human health conditions is a theoretical model, as in the traditional PHM approach. This theoretical model is built on the assumption that the health symptoms that are used to identify the presence of health risks are embedded in physiological signals from the patient. Hence, the objective of these theoretical models is to represent the collected physiological information in an efficient manner, identify patterns from the extracted information that correspond to pathological symptoms, and finally use this information to detect the health condition. Systems that provide this type of functionality are called clinical decision support systems

(DSS). Some efforts in the past pertaining to DSS can be found in (218–221).

### 6.1. Prognostic approaches for devices and systems

In this section, the different types of prognostic approaches as applied to devices and systems are discussed. Since POC systems have just started receiving attention in the clinical arena, no reports on previous work relating to prognostics and POC systems are available in the public domain. However, with the increasing demand for availability of medical systems, the need for prognostics will also soon be realized.

#### 6.1.1. Prognostic approaches

Early studies in prognostics focused on component-level reliability evaluation based on an understanding of component degradation and their loading conditions (222–223). Based on these approaches, Pecht *et al.* (224) proposed methods to use life cycle models to improve the design and manufacturing capability of electronic components. These studies led to the new theory of predicting failures based on physics-of-failure (PoF) models (225–226). Methods to select parameters and modeling approaches for failure prediction have also been investigated (227–227). In order to address situations where PoF methods are not suitable, data-driven approaches were developed that use statistical techniques to predict component failures based on their performance information (229). These approaches rely on the assumption that the statistical characteristics of performance data are relatively unchanged unless there is a fault or malfunction of the system or component. Thus the main objective in data-driven approaches involves precisely detecting anomalies in performance data. Commonly used data-driven approaches include the sequential probability ratio test (SPRT) (230), support vector machines (SVMs) (231), Bayesian SVM (232), and Mahalanobis distance (233–238). Cheng and Pecht (239) also investigated the use of a multivariate state estimation technique as an input for the prediction of RUL.

#### 6.1.2. Fusion prognostics

Data-driven approaches fail to distinguish between failure mechanisms when the physical understanding of component failure is not incorporated. Recognition of this fact has led to the development of a fusion model that integrates a physical understanding of failure with data-driven techniques, thereby exploiting the benefits of both PoF and data-driven methods (240–241). Recent publications from the Center for Advanced Life Cycle Engineering (CALCE) at the University of Maryland have focused mainly on identifying a pre-cursor parameter related to the physics of component failure and employing machine learning techniques to forecast anomalies in the performance trend. Gu *et al.* (242) developed a method to assess failures in electronic components under vibrational loading. Kwon *et al.* (243) presented a prognostic technique to detect interconnect failure precursors using RF impedance monitoring and the sequential probability ratio test (SPRT) under thermo-mechanical loading conditions. Patil *et al.* (244) focused on identifying precursor parameters for enabling prognostics of insulated gate bipolar transistors.

### 6.1.3. System prognostics

In relation to system-level prognostics, Pecht (245) presented a road map for how prognostic approaches at the component level should be carried out to predict and avoid system failures. Sun *et al.* (246) analyzed the benefits of applying prognostics to systems. However, due to the presence of multiple critical components in a system, there are multiple failure modes and mechanisms that need to be tracked to predict system failure. Wang *et al.* (247) developed a model to address this situation where each component and failure mode is modeled individually and then pooled together to form the system inspection model.

### 6.2. Prognosis of health condition

Prognostics in health care refers to the method incorporated in tracking the progression of health symptoms from which an estimate can be obtained about the patient's health condition. According to Pantelopoulou and Bourbakis (49), "Prognostics uses a theoretical model to follow the progression of health symptoms so as to be able to derive, at any given time, an estimation of the user's health condition in order to detect health risks by identifying dangerous health trends."

In POC systems, these models utilize the information extracted using biosensors as input for estimating future health conditions. However, such signals are fuzzy in nature. Hence, Pantelopoulou and Bourbakis (49) proposed a prognostics methodology based on fuzzy language for estimating the health conditions of patients whereby the current state of the corresponding fuzzy finite-state machine (FSM) signifies the current estimated health state. Also a stochastic petri net model (SPN) has been employed for the interaction scheme between the user and the biosensor system. This approach classifies the bio-signals used in the identification of health symptoms into three categories to define the states of the FSM. The bio-signals that are used as input are classified as 1) value-specific signals, whose instantaneous values carry the diagnostic content; 2) morphology-specific signals, which contain diagnostic information in the structure of the signal; and 3) patient voice recording, which is used as feedback.

The most important component of the POC diagnostic/prognostic system concerns the modeling of knowledge based on patient's clinical data and real-time monitored data. This component serves two purposes: 1) to extract new and useful knowledge and 2) to provide prediction methods for diagnosis as well as detection of susceptibility for a particular disease (248). In order to extract new and potentially useful knowledge, cluster analysis (249) and association rule mining (250) are applied. Classification techniques (250) are applied to create predictive models for the diagnosis and detection of disease.

### 6.3. Survival analysis

Traditionally, prognostics in the medical arena have been performed using survival analysis techniques. Various types of statistical approaches have been used for analyzing survival data. As stated earlier, the primary variable in survival analysis is the survival time, which is



modeled as a non-negative random variable (252). Standard statistical methods are not suitable for analyzing survival time because 1) the survival time may be longer than the study time (one type of censoring of survival data) and 2) the distribution of survival times is more skewed than symmetrical (213). According to McGarty (252), in order to adopt a statistical technique for analyzing survival data, the evaluation of some natural process is embedded in the statistical model with the assumption that the model is a useful approximation of the real process (252). The major applications of survival analysis in public health include estimation of the distribution of the survival time, testing hypotheses of equal survival distributions, and identification of prognostic factors (213).

Survival time can be defined by three survival functions (254): 1) the survivorship function; 2) the probability density function, which is also known as unconditional failure rate; and 3) the hazard function, which is also known as instantaneous failure rate, age-specific failure rate, or conditional mortality rate. The hazard function is a measure of the proneness to failure as a function of the age of the individual (215) (255).

The objective in carrying out survival analysis is to estimate the survival function and cumulative hazard function, which helps in predicting the survival time. Various parametric and non-parametric approaches have been proposed in the past for estimation of the survival and hazard function (254).

Let  $T$  denote survival time, a non-negative random variable. As stated earlier,  $T$  is the time period from the starting point of the study to the occurrence of a certain event. The event may be death or hospitalization (213). Mathematically, let  $T_0$  be a time-to-event variable (256), and let  $C$  be the fixed right censoring time (252), which may occur when a patient leaves during the study or survives past the end of the study period. Then the survival variable  $T$  and the censoring indicator  $\delta$  are defined as follows:

$$T = \min \{T_0, C\} \quad (1)$$

$$\delta = \begin{cases} 1 & \text{if } T_0 > C \\ 0 & \text{if } T_0 \leq C \end{cases} \quad (2)$$

The survivorship or survival function is denoted by  $S(t)$ , which is defined as

$$S(t) = \Pr(T > t) = 1 - F(t) \quad (3)$$

where  $F(t)$  is the probability distribution function of  $T$ . The associated probability density function is defined as

$$f(t) = \lim_{\Delta t \rightarrow 0} \frac{\Pr(t < T < t + \Delta t)}{\Delta t} \quad (4)$$

On the other hand, the hazard function  $h(t)$  is defined as

$$h(t) = \lim_{\Delta t \rightarrow 0} \frac{\Pr(t < T < t + \Delta t | T > t)}{\Delta t} \quad (5)$$

The three functions  $S(t)$ ,  $f(t)$  and  $h(t)$  are mathematically equivalent, and even if only one of them is known, the other two functions can be derived. According to the proportional hazard (PH) model the hazard function is proportional to the baseline hazard function, i.e.,

$$h(t) = h_0(t) \exp(\beta \cdot X) \quad (6)$$

where  $h_0(t)$  denotes the baseline hazard function,  $\beta$  represents the distribution parameter, and  $X$  denotes an observed predictor of  $T$  (252). The baseline hazard function is estimated using parametric or non-parametric models (257). Thus, once a baseline hazard function is estimated, the proportional hazard, survival function, and the probability density function of survival time can be predicted.

In certain cases the effects of left truncation and right censoring data are required. A joint survival analysis approach is required to tackle such problems. Shemayakin and Youn (258) presented a brief overview of using Copula models for joint survival analysis. Copula models are popular for modeling dependencies between random variables, and thus their application includes the failure of paired organs or body functions or physiological parameters in health science and predicting human mortality.

## 7. EXISTING CHALLENGES IN POC SYSTEMS

In this section we discuss the challenges facing WBAN that need to be addressed before WBAN technologies are widely deployed for POC solutions.

### 7.1. Biocompatibility and sensor packaging

Since WBAN sensors are deployed on the body or even implanted inside, size and physical compatibility with human tissues are critical. Sensors must be made from biocompatible materials so that the sensor material does not negatively affect patients or degrade over time (259). Common materials for biomedical devices include synthetic or biological polymers, metals, and ceramics. Aluminium nitride is inert with respect to the body and thus makes it a feasible choice for biomedical sensors (260). Biocompatibility itself can cause failures due to biofouling, hermeticity of encapsulation, electrode passivation, and the limited lifetime of the immobilized enzymes (261–263). One method of confronting the failure due to bio-fouling is to use micro-sensor arrays. This helps in improving reliability, as it is very unlikely that all the sensors will fail at the same time (263). Apart from biocompatibility, the material chosen for biosensors at the POC must also have certain electrical and mechanical properties to reduce electrical losses and improve sensitivity.

### 7.2. Wireless operation

Lowering the power consumption of the radio link can greatly reduce the size and prolong the lifetime of a sensor. Otis *et al.* proposed a 400 microwatt receiver and 1.6 milliwatt transmit transceiver for wireless sensor networks (264). Yoo *et al.* (265) proposed an approach that uses the human body as the medium of data transmission

for low energy on-body data transmission. As mentioned earlier, UWB has proven to be the dominant emerging technology for wearable sensors (266). UWB can theoretically produce a data rate up to 1Gbps.

Antenna design is one of the determining factors for a reliable and energy-efficient wireless communication link. The antenna has to be optimized in order to maximize the throughput of the radio. Alomainy *et al.* (267) proposed a planar compact antenna structure for miniaturized on-body sensors. Higgins suggested different types of antenna design for implantable sensors (268–269). Ullah *et al.* (270) discusses the design of an implantable antenna for operation in the MICS band. In the same paper, the physical layer and medium access control (MAC) layer performance of body sensor networks are discussed. Zhen *et al.* (271) analyzed the performance of clear channel assessment (CCA) by in-body and on-body nodes and demonstrated that on-body sensor nodes cannot see the activity of in-body nodes when they are 3m away from the surface of the body.

Apart from low-power wireless transceivers, communication protocol is also an essential component for the development of energy efficient wireless sensors (263). Dave *et al.* (272) studied the energy efficiency and quality of service (QoS) performance of IEEE 802.15.4 and IEEE 802.11e. Timmons and Scalon (273) analyzed the performance of IEEE 802.15.4 for use in biomedical sensors in BANs. They showed that when properly configured with low data rate asymmetric traffic, the sensors can operate for at least 10 years without battery replacement. Li and Tan (274) proposed a novel time division multiple access (TDMA) protocol for an on-body sensor network that exploits bio-signal features to perform TDMA synchronization and improve energy efficiency. Other protocols, such as wide area system secure (WASP) and CICADA, have also been proposed (275–277). A number of low power communication protocols have been proposed for wireless sensor networks, such as low-energy adaptive clustering hierarchy (LEACH) (278), power aware multi-access with signaling (PAMAS) (279), sensor-MAC (or) S-MAC (280), and Berkeley-MAC (or) B-MAC (281). Very recently, Marinkovic *et al.* (282) presented an energy-efficient medium access control protocol suitable for communication in a wireless body area network for remote monitoring of physiological signals using a low duty cycle TDMA strategy. De Silva *et al.* (283) investigated the impact of inter-user interference and its behavior with respect to the number of networks and the rates at which these networks communicate. They observed that inter-user interference can cause up to 35 percent loss in packet delivery ration.

Though energy-efficient MAC protocols have been devised, there is still a need for accurate models that take into account factors such as reliability, latency, mutual interference, energy consumption, and mobility effect. Howard (284) studied the energy efficiency of error-correcting coding in low-power links that connect the implant and the external device. However, there is a need for more in-depth evaluation of all other scenarios.

### 7.3. Security

Privacy requires effective and efficient authentication techniques in WBANs. It was suggested that the ideal way to provide user authentication is to use complex but distinguishable human body characteristics. Cherukuri *et al.* (167) used the same method and proposed an approach wherein biometrics derived from the body are used for securing the keying material. A similar approach was presented by Venkatasubramanian *et al.* (285) with two schemes that rely on the novel technique of using physiological values from the wearer's body for securing a cluster topology formation. Venkatasubramanian *et al.* (286) presented a novel key agreement scheme that allows two sensors in a WBAN to agree to a common key generated using electrocardiogram (EKG) signals for providing security for real EKG data. Still, a mechanism needs to be devised to differentiate between different levels of security to identify and distinguish life-threatening events from other events with various security priorities.

### 7.4. Power restrictions

Sensors for WBAN applications have power restrictions. This is mainly due to their small size and the absence of wires. Integrated power supplies such as a batteries, will drain out of power. Hence, there is a need to switch to passive power sources such as solar power, vibration, motion, air flow, temperature difference, and infrared radiation. Raghunathan *et al.* (287) discuss the key issues and tradeoffs that arise in the design of solar energy harvesting in wireless embedded systems and present a design, implementation, and performance evaluation of Helimote sensors. Mitcheson *et al.* (288) developed a vibration-based generator designed for wearable/implantable devices that is capable of delivering up to 2 micro-Joules/cycle. Similarly, Reilly *et al.* (289) proposed a system to harvest vibration energy from a piezoelectric thin film. IMEC developed a 3 x 3 x 1.5 cm<sup>3</sup> thermal micro-power generator that is capable of converting thermal energy to 4 microwatt power at 5 degrees Celsius temperature difference on the thermopile. Although techniques for generating power from passive sources have been proposed, the power generated is insufficient for continuous operation. Thus, to deal with this issue, there is a need for an external wireless power source to generate and wirelessly transfer power to the sensors. Recently, MIT researchers have reported transferring energy through a wireless medium to power electronic devices over a short range using evanescent waves (290). Huang *et al.* (291) demonstrated a technique to harvest power from solar energy.

### 7.5. Standards and rules

Efforts have been made to develop standards for WBAN for POC (292). However, pervasive health monitoring and treatments employing WBAN require standardized rules for operation in ambulatory environments and the provision of POC services without limitations on the wearer's location or mobility while also taking into account individual privacy. Also, sensor fabrication, minimum biocompatible property requirements, power consumption, and minimum

detectable levels of particular biomarkers must be standardized.

## 8. DISCUSSION

The growing number of fatalities resulting from chronic diseases has led to increased efforts to develop POC systems for remote health monitoring and patient care. To understand the improvements necessary for such systems, the fundamental elements of future POC systems must be examined in detail. This paper addresses this issue by identifying the elements that need to be integrated so as to satisfy the increasing demands of the medical community. Also, this paper has covered the state of the art in research and development of these elements in order to serve as a reference for researchers and industry members. The objective of this paper was not to criticize existing technology but to serve as a reference and provide direction for further research and development.

Today, both labeled and label-free biosensors are being developed to enable the detection of biomarkers such as nucleic acids, proteins, and antigens in biological samples such as body fluids, blood plasma, saliva, and urine. The label-based detection techniques that are currently used in laboratory settings have certain advantages and limitations. These methods are capable of detecting biomarkers with concentrations as small as 10 fg/mL. A major limitation of this approach that hinders its use in POC applications is the use of query molecules with fluorescent labels that require longer response time and optical measurement systems that are not suitable for portable applications. Thus the current focus in POC research is on label-free techniques that depend upon the measurement of the query molecule properties. In this paper, the four most commonly used label-free detection biosensors (SPR, microcantilevers, QCM, and electrochemical) have been reviewed. Recently, new forms of label-free detection biosensors, such as Young's Interferometer (293–294), nanoparticles (295–300), genetically engineered cells (301–303), and carbon nanotubes (304–307), have also been reported.

Another area of research in POC applications is in networks for transferring information obtained from biosensors to health care providers (personal physicians, hospitals, and health insurance providers). It has been common practice to use a two-tiered network architecture for data transfer. The first tier consists of a biosensor network that connects the biosensors to a central node that acts as a data acquisition unit. The second tier includes the path from the central node to a medical database. Currently, a wireless network is used for the first tier and traditional Internet and mobile phone networks are exploited in the second tier. Challenges for the first tier include the type of network protocol used, the type of network security incorporated, the power radiated by the antenna, the type of network topology employed, and the power consumed for data transfer at each biosensor node. As for the second tier, the only major concern has been latency. In traditional Internet and mobile networks, increased traffic causes a

delay in information delivery. This latency could lead to fatal events during medical emergencies.

Although several technological issues regarding POC biosensor systems still need to be resolved, it is expected that continuous monitoring of physiological signals will enable proactive patient health management via prognostics. Hence, researchers in the POC technology development field have started placing equal importance on transferring these biosensor systems into clinical decision support systems (DSSs). These systems provide additional functionality that interprets the sensed information, thereby helping clinicians in decision making. To enable decision support services, knowledge needs to be embedded into the prognostics model regarding the occurrence and degree of several different health symptoms related to a variety of health disorders. However, the frequency of occurrence of a specific symptom and its severity level are fuzzy in nature. Hence, it is appropriate to develop prognostic methodologies based on a fuzzy language for the prediction of the future health conditions of patients.

## 9. ACKNOWLEDGEMENTS

The authors would like to thank the more than 100 companies and organizations that support research activities at the Center for Advanced Life Cycle Engineering at the University of Maryland annually. The authors would also like to thank Prof. Rama Chellappa, Dr. Rajender Gattu, and Prof. Luisa Wu for their valuable inputs in this paper.

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**Abbreviations:** POCT: Point-of-Care Testing, POC: Point-of-Care, BioMEMS: Biological Micro-Electro Mechanical

Systems, ESN: Environmental Sensor Network, WBAN: Wireless Body Area Network, SPR: Surface Plasmon Resonance, QCM: Quartz Crystal Microbalance, AFM: Atomic Force Microscopy, CMOS: Complementary Metal Oxide Semiconductor, FET: Field Effect Transistor, PSD: Position Sensitive Device, DEP: Dielectrophoresis, CRP: C-Reactive Proteins, COTS: Components off the Shelf, ECG: Electrocardiogram, WPAN: Wireless Personal Area Network, RUL: Remaining Useful Life, WSN: Wireless Sensor Network, RFID: Radio Frequency Identification, TDMA: Time Division Multiple Access, UWB: Ultra-Wideband,  $\mu$ TAS: Micro Total Analysis System, HM: Health Management (or Health Monitoring), BIT: Built-In test, MAC: Medium Access Control

**Key Words:** Biological MicroElectroMechanical Systems (BioMEMS), Biosensors, Health management (HM), Point-of-care (POC), Survival analysis, Wireless body area network (WBAN), Review

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