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The Applications of BioMEMS in Diagnosis, Cell Biology, and Therapy: A Review

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Abstract Bio-microelectromechanical systems (BioMEMS) have myriad applications that range from surgical tools to gene-sequencing chips. A full review of all its applications is beyond the scope of the present paper. This study is a comprehensive overview of applications of BioMEMS in the diagnosis of diseases, scientific research based on cell biology, and therapy or treatment of medical conditions. This is a review, from a biologist's perspective, of the current foci of research in these areas. The design and working principles applied are described, and progress made thus far is traced. Some of the design concepts that are likely to play an important role in future applications are also identified. Additionally, the major challenges to be overcome in order for BioMEMS technology to meet its full potential have been described.

Keywords BioMEMS · Microdevices · Diagnosis · Cell-Sorting · Therapy · Applications

1 Introduction

Microelectromechanical systems (MEMS) are micrometer-scale devices that integrate electrical and mechanical functions. These devices are created using microfabrication (electrical components) and micro-manufacturing (mechanical components) technology. Such microdevices were first and most extensively used in the automotive industry and are now finding myriad of other applications. MEMS technology has seen many advances and exhaustive research and development in the twenty first century. In this paper, the focus is on BioMEMS, a class of MEMS which incorporate biological entities and principles or those MEMS devices that have a biological application.

These devices require less sample volumes for analysis. The fabrication technology enables design of compact and portable diagnostic kits. Higher sensitivity and shorter analysis times have been reported in comparison with traditional laboratory methods. MEMS devices are compatible in size with cells and organelles, enabling their detailed study. And perhaps, most importantly, once the technology is perfected, BioMEMS are economically mass produced, and the production is highly reproducible. These inherent advantages have driven the interest in research in this area.

An introduction to BioMEMS would be incomplete without at least a brief discussion of the main design principles involved, the role of nanotechnology in its development, and the fabrication techniques unique to these devices. We cover these areas in the following sections.

1.1 BioMEMS Design Principles

Most BioMEMS devices involve extremely small volumes of fluid and thus the application of microfluidics technology which involves the manipulation and control of very small volumes of fluid in very small channels. Fluids can be moved through these microchannels using various mechanical or electrical principles (use of pressure, electric potential). Microfluidics and microfabrication technology enable massive parallelization of diagnoses, thus facilitating the lab-on-chip approach. Microfluidic devices also contain sensors of micron-scale for analyte detection from minimal sample volumes and with reduced analysis times. Chemicals are

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patterned on MEMS using methods such as micro-contact printing and photolithography [1].

Interactions between biological molecules can be detected and converted to a signal reading using various detection principles such as fluorescence, impedance, magneto-resistivity, microcantilever technology, quartz crystalline microbalances, etc. [2, 3]. MOSFET-embedded microcantilevers have been reported to detect as low as 5-nm deflections as result of antibody reactions [4]. Microcantilever deflection detected by the interruption of an optical beam is another commonly applied strategy to obtain readable signal owing to their higher sensitivity when compared to piezo-sensitive approaches, in spite of the higher production costs [5, 6]. Some diagnostic chips incorporate multiple microcantilevers which can each detect specific biomolecules. The stress on each microcantilever can be detected separately and converted to a signal. Acoustic transducers are also being incorporated in BioMEMS due to their high sensitivity (they can detect the addition of a single nucleotide base) and their small size and mass. Acoustic transducers have been used in MEMS for pathogen sensing in biological fluids such as saliva and urine. Acoustic beams can also be used to detach/lyse cells with great precision [7].

1.2 The Impact of Nanotechnology

Nanotechnology has made it possible to develop sensors and probes comparable in size to bacterial cells or even biomolecules such as antigens and viruses [8]. Nanowells, nanotubes, and nanowires have been used for sensing pathogens, to capture and focus cells [9], and to develop immunosensors with higher sensitivity. Nanostructures such as nanowires have an added advantage due to their similar size and dimensions in comparison to biomolecules such as DNA [10]. This size compatibility allows nanowires to detect DNA in concentrations of the femtomolar range (10^{-15} mol/L) [11]. Nanowires are also more ideal than microcantilevers for the label-free detection of DNA sequences and mutations by hybridization [12]. Bio-conjugated nanoparticles on the other hand have provided an advantage in terms of easier control and detection of the sample. For example, quantum dots exhibit various advantages when used for fluorescent labeling and QD-antibody conjugates are now preferentially used for pathogen detection [13]. Nanoparticles such as magnetic beads (easily manipulated using a magnetic field) [14, 15] and gold nanoparticles (to amplify electric signal) [16] are also used extensively to trap and concentrate cells and for signal amplification.

1.3 BioMEMS Fabrication

Micromachining technologies such as deep reactive ion etching [17], LIGA [18, 19], laser pulse [20], and various others can be used to etch out microchannels with precise direction and size. Microchannels are fabricated using materials such as glass or plastic which can be easily functionalized [2]. Due to the advantages of nanowires and other nanostructures for biological applications, a number of nanoelectromechanical systems (NEMS)-based platforms are being developed and NEMS fabrication techniques are being fine tuned for the design of sensors [21, 22].

In MEMS systems, silicon is preferred as the fabrication material as it is easy to work with and technology for micromachining of this material has been in place for decades. In BioMEMS, the biocompatibility of the material is an important aspect to be considered during fabrication. SU-8, a negative epoxy-based photo-resist is widely used in the fabrication of microcantilever-based biosensors due to its biocompatibility, strength, and functionalization with DNA without using thiol–Au chemistry [23, 24]. Even though silicon has its advantages, polymers are found to be advantageous in fabrication in terms of reduced time, complexity, and cost of prototyping [25, 26]. Biological samples contain proteins which tend to adhere to surfaces and can clog channels and foul the surfaces of sensors, thereby reducing their durability. Therefore, choosing material for fabrication requires careful consideration. Poly(methyl methacrylate) [26] and poly(dimethylsiloxane) (PDMS) [27] are two commonly used polymers in microfluidic devices.

A special consideration during fabrication of BioMEMS is the thermo-sensitive nature of most biological entities. During packaging of the chip, the temperature must be maintained as low as possible because biological molecules are often thermo-labile. Novel methods such as lamination using SU-8 are being developed to enable low-temperature packaging [28].

2 Applications of BioMEMS Technology

At first, efforts were focused on designing BioMEMS to carry out single functions like immunoassays and gel electrophoretic separations. In 1994, it was established that it is possible to achieve single-stranded (polyacrylamide) or double-stranded (hydroxyethyl cellulose) DNA separations on photolithographically defined glass microchips [29]. This was much faster than any established laboratory method; further research lead to the design of BioMEMS to carry out other individual functions like PCR, cell capture, and DNA sequencing. Almost from the infancy of BioMEMS technology, a great deal of focus has been on the design of "lab-on-a-chip" which integrates a number of laboratory techniques or functions on to a single chip (millimeters or centimeters in size). BioMEMS have diverse applications, and in the following section, applications that fall into the aforementioned categories are discussed and described.

Our comprehensive survey of published literature regarding BioMEMS helped us identify three key areas of application that is of interest to a biologist. The use of BioMEMS for the *diagnosis of pathogen-related and genetic diseases*, in the *research of cellular and intra-cellular functions and characteristics*, and for the *therapy and monitoring of medical conditions*. We present a description of research in these areas in the following section.

2.1 Diagnostic Applications

There is a clear need for point-of-care testing and diagnosis of many pathogen-related and other diseases, because early detection and treatment is a key factor in successfully fighting a disease. This is especially applicable to under-developed and developing regions where access to traditional medical testing is scarce and expensive. Epidemics are also more prominent in such regions because of poor standards of hygiene and living. Laboratory methods of detecting pathogens such as cell culture and plating are accurate but require days to provide results, so they cannot be used for on-site detection. Some publications describing the various applications of BioMEMS in diagnosis and pathogen detection are listed in Table 1.

For diagnostic purposes, the use of proteins can be challenging due to various factors such as their chemical complexity, instability, a tendency for non-specific interactions and the problems associated with specific fluorescence tagging of proteins. Nucleic acids, on the other hand, are simpler molecules, more stable, and easier to detect using intercalating dyes [29]. Detection and identification of pathogens based on nucleic acids requires cell lysis, extraction, and purification of nucleic acids, often amplification using PCR, detection and conversion to output reading [2]. Efforts have been made to integrate sample preparation, amplification, and detection steps on a single chip [47, 48]. Several portable analytical systems based on nucleic acid detection are available commercially, produced by companies such as Gen-probe, Idaho Technology, and IQuum, Cepheid [2].

Based on the sensors used and the analyte or parameter being detected or measured for diagnosis, we have further classified diagnostic applications into the following categories.

2.1.1 Pathogen Detection

Microchips have been designed as early as 1999 for detection of viruses such as herpes simplex virus and hepatitis C virus using simple separation and hybridization techniques in reduced analytical times [49, 50]. The earliest methods

Table 1 Examples of applications of BioMEMS in diagnosis

Diagnostic parameter	Diagnostic principle	Reference
Pathogens		
Hepatitis B virus (HBV)	Piezoresistive microcantilever	[30]
Dengue virus	Silicon nanowire (SiNW)-based sensor for hybridization	[11]
HIV	Sandwich assay using antibody coated microbeads	[31]
Methicillin-resistant *Staphylococcus aureus*	Microfluidic system with fluorescence based detection	[32]
Bacteria (general)	PEG hydrogel, with bacteria-specific antibody	[33]
Genetic conditions		
Alzheimer's disease	Microarrays using quantum dots and nanocrystals	[34]
Genetic diseases (general)	PCR, microarray, fluorescence	[35]
Biochemicals/biomolecules		
Hemoglobin-A1c	Potentiometric immunosensor	[36]
Glucose (implantable)	Competitive binding of glucose to concanavalin A	[37]
Glucose (ex vivo)	Capacitance based, immobilized 11-MUA (11-mercaptoundecanoic acid) and GOD (glucose oxidase)	[38]
Transcutaneous oxygen	Amperometry	[39]
Cholesterol	Au nanowires immobilized with cholesterol oxidase and cholesterol esterase	[40]
Cancer biomarkers	Interferometric sensor	[41]
Biomarkers (general)	Surface plasmon resonance, paper-based electrochemical sensing	[42, 43]
Imaging/physical parameters		
GI tract disorders	CMOS, LED, imaging	[44]
GI cancers	Spectroscopy	[45]
Heart rate and core body temperature	Phonocardiographic and piezoelectric sensors	[46]

involved the separation of DNA on polyacrylamide and hydroxyethyl cellulose gels followed by laser-induced fluorescence detection on a microchip platform. This principle was also applied to detect B and T cell lymphoproliferative disorders [51] because this condition results in an intense band of mono-clonally derived lymphocyte cell DNA and can be easily detected. Sensor chips have been developed for detection of pathogens from human biological fluid samples. One such study reports detection of bacterial pathogens (4×10^{-4} CFU/ml) in urine samples using sandwich hybridization assay in 45 min [52]. Lower detection limits (as low as 1.6×10^{-2} cells/ml) have been reported using an array of microelectrodes in interdigitated array configuration [53, 54].

For detection of viral load, HIV in particular, the simplest microfluidics-based chip incorporates microbeads coated with an antibody that binds virus with higher capturing efficiency due to the high surface/volume ratio. This complex then interacts with the quantum dot-conjugated second antibody and virus is quantified by measuring fluorescence intensity. A detection limit of 22 ng/ml was achieved, compared to 360 ng/ml in conventional ELISA, which also takes 4–6 times as much time for analysis [31]. Other applications of microfluidics and nanotechnology have also been achieved such as an interferometer-based sensor for detection and quantification, chips for virus imaging and counting, and of course, PCR-based detection on microchips [55].

2.1.2 Genetic Diagnosis

Single nucleotide polymorphisms and mutations involved in various diseases such as fragile X syndrome, Huntington's disease, homocysteinemia, hypercholestremia, muscular dystrophy, etc. can also be detected on multi-channel microplates and microchips with accurate results [29]. Single-stranded conformational polymorphism (SSCP), allele-specific PCR, and heteroduplex analysis (HAD) are techniques which have been successfully implemented in microchips for the detection of mutations involving single bases [56–58]. HAD and SSCP mainly detect differences in electrophoretic mobility between wild type and mutated DNA. Genetic disorders can also be detected using labeled probes for healthy wild type and mutant forms of DNA (which characterizes the disease). This approach has been applied to develop microdevices for the detection of diseases such as thalassemia. β-thalassemia is a disease caused by more than 200 different sets of mutations in the β-globin gene. The more prominent mutations encountered in a population varies with region and genetic backgrounds. A flexible microchip platform, which can be modified for use in different geographical areas, has been designed [59] for the diagnosis of thalassemia.

2.1.3 Biochemicals and Biomolecules

A multitude of biosensors have been developed to detect and quantify various components such as glucose, alcohol, cholesterol, uric acid, lactate, pH, blood gas, hemoglobin, and biomarkers of disease like lamin (for liver fibrosis) in blood and other samples [1], that can indicate a disease or physiological condition. The integration of a number of these devices onto a single chip would be the next obvious step.

2.1.4 Imaging and Physical Parameters

Electrical impedance of a tissue or cell depends on its morphology, permeability, and organization so electrical impedance tomography can be used for non-invasive characterization of tissue, to differentiate between healthy and cancerous tissue (skin cancer screening) and to monitor growth and differentiation of artificial tissue [60]. Ingestible microdevices have also been developed to study the gastro-intestinal tract for diagnoses using wireless endoscopy and to acquire data such as pH, temperature, conductivity, and dissolved oxygen using multiple sensors on the chip. Such a chip can not only find application in the study of the human body and diagnosis of diseases but can also be used in the industry to inspect pipes, ducts, tubes, and other areas where access is a problem [61].

2.2 Applications in the Study of Cell Biology

It is important to understand cellular functions and characteristics for applications in pharmacology, medicine, diagnostics, and drug delivery. Some examples of the use of BioMEMS for the study of cells are listed in Table 2.

Dielectrophoretic forces applied using strip electrodes patterned on the surfaces of a microchannel can be used to deviate (sort) or trap (isolate) cells. This principle is largely applied to concentrate, focus, sort, and handle cells in lab-on-chip devices [60]. Label-free counting and characterization of living cells passing through a detection point in a microchannel using impedance measurements provides information about cell size, membrane capacitance, and cytoplasm conductivity as a function of frequency. Above a certain frequency, the cell membrane is not a barrier to current and under such conditions, information about intra-cellular structures can be obtained. This information can be used to discriminate between different cell types [60]. Optical methods such as fluorescence sorting using microfabricated fluorescence-activated cell sorting and others such as magnetic cell sorting have also been developed [71, 72]. Label-free cell sorting and separation has been achieved on a microdevice employing various filtration mechanisms, biomimetic principles, optics, and physical parameters and a detailed comparison of these methods can be obtained in a

Table 2 Examples of applications of BioMEMS in cell biology

FUNCTION	PRINCIPLE	REFERENCE
Sorting		
Concentration and purification of HIV type 1 virions	Antibody- conjugated supermagnetic nanoparticles, magnetic separation	[62]
Counting CD4+ T cells in HIV infected patients	Antibody based capture and CCD imaging	[63]
Concentration of bacteria from liquid samples	Enhanced evaporation using porous PTFE membrane	[64]
Characterization		
Selective capture and manipulation of quorum-sensing bacteria	Nanofactories with multiple modules to study the QS response	[65]
Cancer cell properties	Flow cytometry, Nano Intravital device (NANIVID)	[66, 67]
Cell culture		
Enhanced cell function	Microfluidic coculture platform	[68]
Intercellular electromechanical transduction	Microdevice for electrical stimulation and response measurement	[69]
Anti-cancer drug evaluation	Microwell array	[70]

review by Gossett et al. [73]. Cell counting by measuring the change in total ionic concentration of solution after cell lysis is another approach that has been applied to detect as low as 20 cells/μl.

Another application of cell capture that has gained interest recently, is the capture and detection of fragile circulatory tumor cells (CTCs) for early diagnosis of cancer metastasis [74, 75]. These cells are rarely found in blood and highly prone to rupture when captured. The use of a microfabricated parylene membrane filter enabled high capture efficiency, viability, moderate enrichment, and high throughput. Considering the fact that the occurrence of CTCs in blood is rare and transient, the likelihood of using such a chip for diagnosis is open to debate. However, it could be a useful tool in the study of CTCs.

Single cells can be analyzed on microchips using lab-chip patch clamps for electrophysiological studies, mass spectroscopy chips, microfluidic chambers to study neural activity, microdevices to study cell response to shear stress, and to study cell volume responses, etc. [76]. Changes in cell volume can be indicative of response to various extracellular factors and this characteristic can be measured by an impedance-based sensor to study the effect of various drugs and chemicals on cell physiology. A microfluidic platform enables rapid changing of solutions and can be used to mimic a variety of culture conditions and microenvironment to study the response of cells to spatial and temporal signals and conditions [76]. Cell response can be observed under various simulated stress conditions such as temperature, pressure, and shear-using MEMS. The behavior of cells under an applied chemical gradient has also been studied [77].

A MEMS device with array technology employing hollow SiO2 microneedles has been developed for cell manipulation and analysis. A piezoelectric thin film was actuated with this device for regulation of cell functions. There are also developments in imaging of single cell activities wherein a new probe called "bioprobe," using hollow SiO2 needles, was incorporated in the AFM for high resolution. This can also be used in extraction and delivery of biomolecules into the cell [78]. Cell migration has also been studied using PDMS microchannels [79].

Neural circuits are being studied by measuring and recording the activity of neurons and response to stimuli using multi-electrode arrays to simultaneously probe many neurons in culture conditions. As the behavior of these cells is different under such conditions than in situ, implantable probes are being developed and optimized [80].

Identification and online monitoring of bacterial pathogens and yeast cells has been achieved by a number of research groups [81–84]. One study reports the identification of two different bacterial pathogens based on impedance measurements and use of antibodies for cell binding in a microfluidic chamber, the sensitivity of which can be altered by changing the size of the chamber [81].

DNA sequencing can also be achieved on microfabricated devices. Early reads were limited to around 150 bases due to short channel lengths. Efforts have been made to increase the read lengths and reads of up to 800 bases have been achieved but at a significantly longer analysis time. Approaches in this area are being constantly refined for better resolution, shorter analytical times, and higher throughput [29]. A BioMEMS 786 sequencer has been developed which can process up to 7 million bases per day and is about seven times faster than other high-throughput sequencers [85]. BioMEMS devices have been used to lyse cells; extract DNA, mRNA, or protein; and analyze this material in order to characterize the cells. Microfluidic platforms are also being developed for applications such as RNA-interference screening, with several advantages in comparison to traditional microarray printing [86].

Cell culture on a lab-on-a-chip platform has been attempted many times but is hardly a routine application because cell

culture takes a long time, sometimes days, and BioMEMS are all about faster analysis times [87]. Cell culture is, however, also used to study proliferation of specific cell types and interaction between heterotypic cells. Microfluidic channel-based systems have been developed for cell culture where cells grow on glass and PDMS. Such cell cultures have also been used to study the growth and development of tissues and embryos. In real physiological systems, different kinds of cells interact with each other and these interactions can be studied by cell patterning on MEMS to achieve co-cultivation of heterotypic cells. Different chemicals that adhere to different cell types have been patterned on the MEMS to attain this effect [88]. The Levkin Research Group at the University of Heidelberg [89, 90] along with many others across the globe, is making significant advances in developing methods and surfaces for micropatterning.

2.3 Applications in Therapy and Treatment

Researchers are developing microdevices like cochlear implants, cardiac defibrillators, deep-brain stimulators (for Parkinson's disease and other movement disorders) and retinal implants because micro-manufacturing techniques are more reproducible than conventional methods, in addition to the size advantage. There is also on-going research to develop an array of micro- and nano-filters to carry out kidney function [91]. Biocompatible intravascular/intracranial/intracardiac pressure sensor implants have been fabricated to monitor blood pressure in patients with heart conditions and aneurysms [85]. A company called CardioMEMS Inc. has developed such pressure sensors which also incorporate wireless technology and are activated by radio-frequency waves. These devices enable non-invasive monitoring of blood pressure and stent grafts. MEMS sensors can also be incorporated into implants such as pacemakers to optimize their performance [92]. The strength and size of MEMS also makes it suitable for isolating implanted cells to prevent immunorejection [93].

The integration of a biosensor and drug-delivery system into a single device (responsive drug delivery system) would be ideal for the management of a number of illnesses. An example of such a device that has been developed is a glucose sensor with an integrated reservoir and dispenser for insulin, employing glucose oxidase immobilized on a hydrogel as the detecting unit and polymer/gold microvalves for dispensing insulin [94]. The challenges associated with such a design include the limited size of the drug reservoir and the durability of the biosensor. Implantable sensors for physiological parameters such as glucose and blood pressure [95], which can also behave in a responsive manner, are being developed to enable the monitoring of disease and improve the patients' quality of life. In an implantable system, parameters like blood pressure, pulse rate, SpO_2, respiration, electrocardiogram, electromyogram, body temperature, or urinary disturbance is measured by a sensing device. The sensing component, for example, can be a pressure sensor, phototransistor, or temperature sensor. This information can be transmitted using wireless communication systems like Bluetooth, ZigBee, and Ultra-Wide Band, and the data is stored using a personal digital assistant or a processor board to be studied further in a hospital [96].

The fouling, durability, and compatibility issues with ex vivo biosensors are obviously elevated in in vivo applications. In addition, encapsulation (which can isolate the sensor from analyte) of such sensors by human tissue, or their degradation are some concerns being addressed currently with research on biocompatible packaging material [97]. Silicon and glass are the materials used for the fabrication of devices for in vitro detection and analysis but even biocompatible materials can induce a degree of reaction in the body. Certain polymers such as parylene are seen to be more biocompatible but the process for their microfabrication is the bottleneck in the development of such devices. Polymers are, however, being used in in vitro diagnostic devices because of the ease of structuring and optical transparency which simplifies the use of optical detection methods.

A number of companies and research organizations are working on MEMS-based systems and micropumps for drug delivery because of their high reproducibility which reduces batch-to-batch variation during production, an important factor in drug delivery. Some of these devices work based on the degradation of membranes and other biodegradable parts of the implant, which results in the release of the drug from a reservoir. Other devices can be actively controlled, and release the drug based on electrochemical/electrical signals or micropumps [98]. Devices available commercially include inhalers with MEMS-based dispenser nozzles, silicon and polymer microneedles, insulin micropumps, and injection pumps. Challenges include increasing durability and controlling the amount of drug dispensed from degradation-based reservoirs in addition to biocompatibility and the long-time period involved in the development of such therapeutic solutions because of clinical trial stages and approval from the FDA.

Neural prostheses are also being developed in miniaturized forms to counter the effects of various neurological disorders while causing minimal damage to surrounding tissue (due to the size of the device) [99]. The first neural probes developed for stimulation and recording were stiff, brittle microwire and silicon-based arrays that did not have the long-term stability and reliability for use as implants. Implantable electrodes are used to study brain function but if fabricated using non-flexible materials like silicon, they may lose functionality over a period of time due to glial scarring. Flexible microelectrode arrays fabricated using polyimides and other materials are being developed to overcome these problems [60].

Technology that enables micron-scale fabrication has also been leveraged in designing microneedles and surgical tools. Microneedles (made of silicon, glass, or metal) increase the permeability of skin and thus multiply the efficiency of transport of therapeutic molecules while, at the same time, being painless. Micro surgical tools such as nano-knives incorporating sensors, and piezoelectric actuation have also been designed to facilitate minimally invasive and extremely precise surgery [99].

3 Challenges and Future Prospects

There are a number of key issues that are being addressed in the field of BioMEMS research and design. Some of these are described in the following section and future possibilities are discussed.

3.1 Sample Volumes and Detection Limits

Small volumes unfortunately also mean less detectable signal and this is especially true when developing diagnostic kits that detect biomarkers or cells (like CTCs) which have a short survival time in the bloodstream, and may not be present in a random microliter volume of blood. Detection limits of analyte present in low quantities can be improved by concentrating the sample. This is achieved using various techniques such as the use of microfilters, ultrasound-standing waves for focusing cells onto sensor surface, capillary electrophoresis, dielectrophoresis, etc. [2]. The hybridization signal generated by probe–target interaction can also be further amplified using various strategies such as use of enzyme labels, nanoparticles, redox probes, intercalators, etc.

3.2 Detection Principles

Detection of pathogens is mainly carried out using immunosensors and PCR but these methods do not report on factors such as virulence of cells, so other approaches are being considered. RNA is quickly degraded after cell lysis, so detection of RNA can provide more information about the virulence of cells when compared to DNA-PCR detection. RNA purification, amplification using nucleic-acid sequence-based amplification and fluorescence detection on a microdevice in a short time (30 min) has been reported [100]. The identification of highly selective biomarkers is also essential to make cell-based diagnosis and sorting on microdevices more acceptable for commercial use.

Aptamers are short, single-stranded oligonucleotides that exhibit a high-binding affinity and specificity for particular target molecules or cells due to their specific and complex three-dimensional structure. Because of this property and the fact that they are easily and cost-effectively synthesized and manufactured, have made the use of aptamers in diagnostics an attractive new strategy. The selection and application of aptamers has been easily adapted to microfluidic platforms. SELEX (for the selection of aptamers) has been made with less labor and time-intensive on a microfluidic platform using various approaches such as capillary electrophoresis, sol–gel entrapment, magnetic bead-based selection, etc. [101]. Aptasensors are used in the detection of biomarkers like thrombin and IgE, cancer detection, and detection of infectious microorganisms like HIV virus and viral and bacterial proteins. Aptamers have the added advantage that they are more thermally stable than antibodies and are easily labeled with fluorescence tags. In optical aptasensors, aptamers are labeled with fluorescence or luminophore [102]. Label-free detection systems are also available like surface plasmon resonance, diffraction grating, evanescent field-coupled waveguide mode, optical resonance, or Brewster angle straddle interferometry [103].

3.3 Biocompatibility and Biofouling

Clogging of microchannels due to non-specific binding is a problem often encountered and significantly reduces the re-usability of a BioMEMS device. Contamination of the sample between steps is also a matter of concern. The mixing of fluids is an important area of study with various approaches such as the use of Y- and T-junction channels, micropumps, and microvalves being analyzed and optimized [87]. Fouling, encapsulation, and degradation of implantable or even non-implanted analytical microdevices by biological fluids and tissue have been a matter of concern. Protein-resistant material such as oligo ethylene glycol (OEG) is now used to prepare nonfouling surfaces in microchips. Based on this, a highly selective oligonucleotide-incorporated nonfouling electrode surface was developed by self assembly of OEG-terminated thiols and thiolated-DNA probes together and applied to electrochemical DNA sensors. Such an electrode surface exhibited decreased non-specific interactions [104]. When fabricating implantable devices, aspects like power consumption, communication range, data transfer rates, environment, size, and cost also need to be addressed [105]. The limits of biocompatibility can be illustrated by an intraocular glucose sensor implant that was tested with and without biocompatible coating [106]. The one with coating performed for 6 months compared to 3 months in the other case. While this is progress, there is yet a long way to go to develop truly long-term implantable solutions. A patient's medical data is of highly sensitive nature, so security and privacy of transmitted data also needs to be taken into consideration.

3.4 Integrated Diagnostic Chips

Complete integration is another desirable design consideration that is being explored extensively. Biological analysis usually involves a number of pre-treatment steps such as centrifugation, lysis, removal of contaminants, and DNA extraction. A lab-on-a-chip also usually requires a computer to read and convert the results of an analysis into a conventional format. In point-of-care diagnostics involving nucleic acid extraction, a major challenge is sample preparation, due to the complexity of the process and the variation in samples being analyzed [107]. Efforts are being made to integrate every possible pre-treatment step using membrane filtration and mini-centrifuges, and some headway is being made with designs such as the lab-on-a-CD [108]. A wholly integrated chip which incorporates all pre-treatment steps and also has its own digital display for the results would make BioMEMS technology more commercially viable. Regulations in most countries mandate zero tolerance for some pathogens such as *Escherichia coli* O157:H7, *Salmonella* and *Listeria monocytogenes* in food and water. On-site, cheap, reliable, rapid, and sensitive pathogen detection methods with a low-detection limit are thus the need of the hour [2]. Automation and remote monitoring are other desirable features of detection kits for pathogen sensing in food and water.

3.5 Cell and Tissue Studies

Mimicking extracellular matrix components of nano and micro-scale on a MEMS platform due to the size compatibility is an idea that has been widely discussed. There are, however, studies reporting that that cell orientation and elongation may vary with difference in the aspect ratio of microchannels [109, 110] and these aspects, in addition to many others, need to be studied and verified for precise surface patterning. Biocompatibility, specific adhesion, effect of topography on cells, and durability of fabrication material are some of these aspects.

4 Conclusion

The importance of MEMS for biological applications is growing rapidly, with numerous opportunities in diverse applications. The key to its use lies in exploiting features that are unique to MEMS (such as analyte sensitivity, electrical responsiveness, temporal control, and feature sizes similar to cells and organelles).

This review has elucidated the immense potential for BioMEMS in the development of point-of-care and other diagnostics, the major contributions that can be made in research at the cell and molecular biology levels, and in the monitoring and management of lifestyle diseases.

The scale of interest and the rate of progress in research on this topic assure us that the challenges we have identified in this area will be overcome sooner rather than later, in order to recognize the full potential of BioMEMS.

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