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Koushik Guha
Gorachand Dutta
Arindam Biswas
K. Srinivasa Rao *Editors*

MEMS and Microfluidics in Healthcare

Devices and Applications Perspectives

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Preface

The significance of medical MEMS is increasing exponentially from past two decades. There exist numerous MEMS diagnostic devices for detection of blood pressure, glucose, TB, Hepatitis, etc. This is possible due to the multi-disciplinary fields fusing together to make a potent solution for the existing problems. MEMS has proven to be capable of paving bridge between medicine and engineering field, which helps in developing medical instruments. The controllability of sample volume, response time, and size of these devices is satisfactory. The research on the biomaterials to realize such medical devices has a huge scope in future. Furthermore, the book is aimed to study different microfluidic devices. The microfluidics technology has vast number of medical applications ranging from μTAS, drug delivery, DNA sequencing, cancer and COVID-19 detection, and organ on chip. Presently, organ-on-chip technology is prevailing in the scientific community, it can be expected that within a decade there will be marketed microphysiological devices. Microfluidics is capable of regenerating any organ functional physiology and pathophysiology which can be useful in disease diagnosis and organ replacement as well. The present book focuses on the past developments and future research directions in MEMS and microfluidic medical device field, the research available currently on these instruments is intriguing. Though there were plenty of marketed devices, MEMS technology has not yet been explored to its potential. This book primarily focuses on the reader's enlightenment on MEMS medical devices by introducing all the diagnostic devices and treatment tools at one place. The book covers in-depth technical works and general introductions to the devices such that the book can reach technical and general audience as well. In addition, the fabrication techniques of bio-MEMS and bio-microfluidic devices will also be elaborated, which makes the book a complete guide from device development to fabrication stages.

Therefore, in this text, all the above mentioned are covered through chapters spanning from 1 to 12. The first chapter "N/MEMS Biosensors: An Introduction" covering Introduction to N/MEMS Biosensors and the second chapter "Lab-On-A-Chip Technology in Health Care" explains Lab-on-a-Chip Technology in Health Care. The third chapter "A Review on Recent Trends in the Segregation of Red Blood Cells Using Microfluidic Devices" presents recent trends in the segregation of red blood cells using microfluidic devices. The fourth chapter "A Road Map to Paper-Based Microfluidics Towards Affordable Disease Detection" deals with paper-based microfluidics and its journey toward affordable disease diagnosis and the fifth chapter "Critical Review and Exploration on Micro-pumps for Microfluidic Delivery" presents a critical review and exploration on micro-pumps for microfluidic delivery. The sixth chapter "Fabrication Techniques and Materials for Bio-MEMS" introduces fabrication techniques and materials for bio-MEMS. The seventh chapter "In-silico Analysis of Expandable Radiofrequency Electrode for Ablation of Hepatic Tumors" proposes an in-silico analysis of expandable radiofrequency electrode for ablation of hepatic tumors and the eighth chapter "Lab-On-Chip Electrochemical Biosensor for Rheumatoid Arthritis" describes a work on lab-on-chip electrochemical biosensor for rheumatoid arthritis. The ninth chapter "Transdermal Injection with Microneedle Devices in Healthcare Sector: Materials, Challenging Fabrication Methodologies, and its Limitations" indulges with transdermal injection with microneedle devices in healthcare sector: materials, challenging fabrication methodologies, and its limitations. The work on an economical and efficient method for the fabrication of spiral micromixer is presented in the tenth chapter "An Economical and Efficient Method for the Fabrication of Spiral Micromixer". The eleventh chapter "Damping Estimation and Analysis for High Performance Inertial MEMS for Early Detection of Neurological Disorders During Pregnancy" is all about damping estimation and analysis for high-performance inertial MEMS for early detection of neurological disorders during pregnancy. Finally, the last chapter "Affinity Biosensing: Modeling of Adsorption Kinetics and Fluctuation Dynamics" presents the concept of affinity biosensing: modeling of adsorption kinetics and fluctuation dynamics.

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Kharagpur, India — Gorachand Dutta
Asansol, India — Arindam Biswas
Guntur, India — K. Srinivasa Rao

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Koushik Guha is awarded Distinguished Faculty Award 2021 by NIT Silchar for his outstanding performance in teaching and research. Recently, he has been awarded IETE R S Khandpur award 2022 for his achievements and outstanding contribution at national and international level in the field of 'Medical Instrumentation' covering education, research, design, development, and production. Dr. Guha is also awarded Institute of Smart Structures and Systems Young Scientist award (ISSS, IISc Bangalore) 2021 for his contribution in MEMS/NEMS sensors and actuators. He is Optimistic Researcher and Associate Professor in the Department of Electronics and Communication Engineering, National Institute of Technology Silchar, India. He is now Associate Dean of Academic Affairs and Former Assoc. Dean of Students Welfare in NIT Silchar. Dr. Guha is awarded five international patents and one national patent. He has been nominated Fellow of Institution of Electronics and Telecommunication Engineers (IETE) and Institute of Scholars (InSc) Government of India. He has been Active and Regular Reviewer of (SCI/SCIE journals) and various IEEE hosted/sponsored conferences.

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Arindam Biswas received M.Tech. degree in Radio Physics and Electronics from University of Calcutta, India, in 2010 and Ph.D. from NIT Durgapur in 2013. He has worked as Postdoctoral Researcher at Pusan National University, South Korea. Dr. Biswas has received DST-JSPS Invitation Fellow at RIE, Japan, DST-ASEAN Invitation Fellow at Duy Tan University, Vietnam and Taylors University, Malaysia,

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N/MEMS Biosensors: An Introduction

Vinayak Pachkawade

Abstract In the twenty-first century, biosensors have gathered much wider attention than ever before, irrespective of the technology that promises to bring them forward. With the recent COVID-19 outbreak, the concern and efforts to restore global health and well-being are rising at an unprecedented rate. A requirement to develop precise, fast, point-of-care, reliable, easily disposable/reproducible and low-cost diagnostic tools has ascended. Biosensors form a primary element of hand-held medical kits, tools, products, and/or instruments. They have a very wide range of applications such as nearby environmental checks, detecting the onset of a disease, food quality, drug discovery, medicine dose control, and many more. This chapter explains how Nano/Micro-Electro-Mechanical Systems (N/MEMS) can be enabling technology toward a sustainable, scalable, ultra-miniaturized, easy-to-use, energy-efficient, and integrated bio/chemical sensing system. This study provides a deeper insight into the fundamentals, recent advances, and potential end applications of N/MEMS sensors and integrated systems to detect and measure the concentration of biological and/or chemical analytes. Transduction principle/s, materials, efficient designs, including readout technique, and sensor performance are explained. This is followed by a discussion on how N/MEMS biosensors continue to evolve. The challenges and possible opportunities are also discussed.

Keywords Biosensors · N/MEMS · Health and well-being · BioMEMS · Applications

1 Introduction

Biosensors are playing a crucial role in today's biomedical science and technology [1]. Biosensors allow the sensitive and precise detection of a range of biological or chemical contaminants [1–5]. It is a device that measures biological or chemical reactions and generates an output signal in proportion to the concentration of a target

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analyte in the reaction. Typical elements of a biosensor are shown in Fig. 1. It consists of the following elements: (1) a small inlet/channel (μfluidic) to collect/navigate the sample/solution to the sensing system. A sample may be in the form of a solid, liquid, gas, or combination thereof. A sample in solid form may contain dust, dirt, soot, or smoke particles. Samples in the gaseous form include air with a mixture of oxygen, nitrogen, carbon dioxide, or other hazardous gas elements. A liquid sample may include bodily fluids, for example, nasal swabs, saliva, blood, semen, sweat, urine, etc. Analyte/s in the samples are a target substance to be detected. For example, particulate matter (PM) is an analyte whose concentration in the surrounding air is to be measured. Triglyceride is an analyte whose concentration in the blood is to be measured. In clinical applications, analytes of interest are glucose, vitamins, hemoglobin, molecules, proteins, amino acids, urea, bodily gases, toxins, specific biomarkers (to detect chronic disease), living cells, and pathogens (viruses and bacteria). (2) Next element is called bioreceptors (see Fig. 1). Bioreceptors are a group of molecules that are deposited/immobilized (as a thin film/layer) onto the surface of a transducer. Bioreceptors interact with the sample/solution to precisely recognize the target analyte/antigen. Such interaction between the bioreceptor molecules and target analyte is termed biorecognition. The output of a biorecognition event may result in a change in mass, light, color, temperature, pH level, etc. (3) A sensor converts this form of energy into a measurable signal in either optical or electrical form (conductance/impedance, charge/current, potential/voltage, frequency/phase, etc.). Here, we use the words transducer and sensor interchangeably. (4) A sustaining electronics in the biodevice/module can process the sensor output by further amplification, filtering, analog-to-digital (A/D) conversion, and microprocessor/memory storage. Eventually, the module shows the reading on the computer or an embedded display in real time. A wireless data transmission may also be added to the unit.

Figure 2 shows the information on the potential areas of applications of biosensors. Biosensors are widely being deployed for environmental check (to detect hazardous gas elements), to detect the onset of the existing/future disease, monitoring the quality of food and beverages at places where these are stored, on farms to inspect soil quality, in medicine dose control, and many other.

2 Characteristics of a Biosensor

In the biosensing development platform, the following parameters are of the most importance. Researchers are continuously finding ways to improve the following features (see Fig. 3).

Sensitivity/Resolution: It is defined as the smallest possible change in the physical/biological/chemical properties of a transducer that can be resolved after the biomass/target analyte/s are adsorbed/absorbed by the sensor surface (i.e., after the reaction occurs). Sensitivity (also expressed in %) can be given as the ratio of change in the sensor output per unit change in the input. It is also called the detection limit.

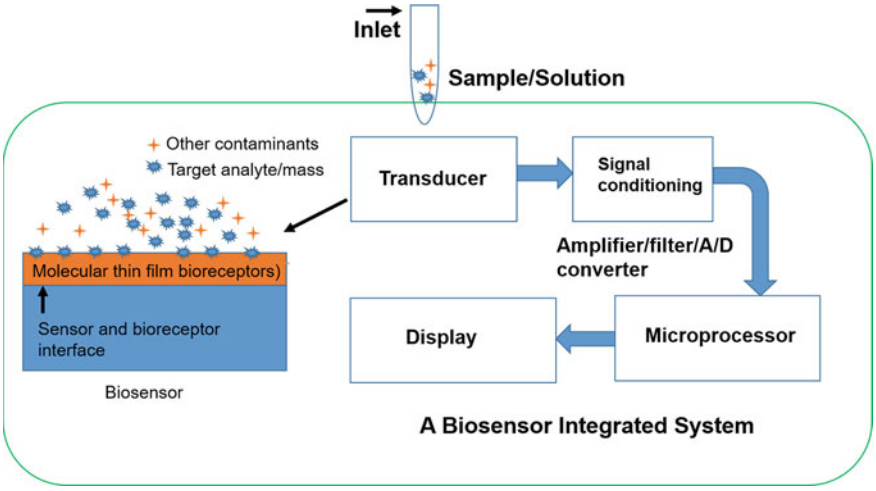

Fig. 1 A typical bio/chemical sensing platform. Bioreceptors enable the selective detection of a target analyte in the sample. A transducer's job is to convert the biorecognition process into measurable output. Such measurable output is then correlated to the detection and concentration of a target analyte

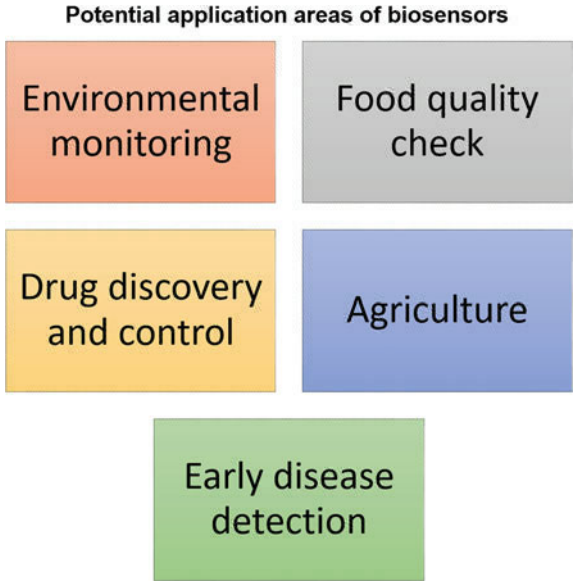

Fig. 2 A diagram showing potential application areas where biosensors are used. There are many other areas where biosensors are primarily used

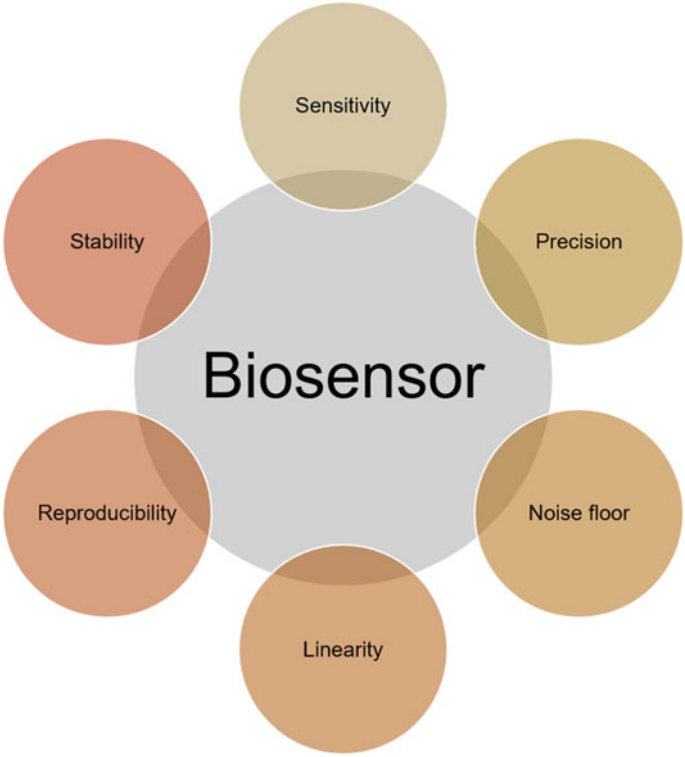

Fig. 3 Performance parameters in biosensor development

A mass sensor, for example, can show resolution up to fg/ml to record the concentration of analyte traces in a liquid sample. Measuring a lowest possible concentration of a specific analyte/s (for example, antigen) can be associated with an underlying medical condition for which doctors can prescribe a test.

Precision: Precision is an important feature of a biosensor. Precision/selectivity/specificity indicates the ability of a bioreceptor thin film molecule to detect/recognize a specific analyte within a mixture of other contaminants in a sample under test (see Fig. 1). An example of precision is the contact of an antigen with the antibody. Typically, antibodies act as bioreceptors and are immobilized on the surface of the transducer. A solution/sample that contains the antigen is exposed to the transducer, where antibodies should interact specifically with the antigens. To develop a biosensor, precision is the key characteristic.

Stability: The stability of a sensor is the characteristic to avoid responding to changes in the environmental conditions (i.e., temperature, humidity, vibrations, pressure, etc.), thereby preventing a false output. To address this issue, a provision is made in the embedded electronics to compensate for environmental drifts in the sensor output. Such common-mode signals can be canceled using a differential sensor readout.

Reproducibility: Reproducibility is the capability of the biosensor module to produce the same output when the experiment/test is repeated. It implies that the sensor provides an average value close to the correct value when a sample is measured several times. Reproducible sensor output indicates the high consistency and robustness of a biosensor.

Noise floor: This parameter provides the baseline above which a sensor output can reliably be detected/measured. Noise in the sensing system stems from i) the intrinsic noise in the sensing element and ii) electronics. Therefore, a sensor is designed to reduce the overall noise. Lower the noise floor, better the sensor signal-to-noise ratio (S/N), or say sensitivity/resolution.

Linearity and Dynamic range: A sensor can show linear changes in the output per unit change in the input. The output of a sensor should produce a linear response to different concentrations being measured. This characteristic is also often represented by the % nonlinearity in the sensor output. Linear dynamic range (expressed in dB) is the ratio of the maximum to the minimum sensor output.

3 N/MEMS Biosensor (BioMEMS)

N/MEMS features scalability, ultra-high sensitivity, energy efficiency, and compatibility to easily integrate with microelectronics[6–8]. N/MEMS offers outstanding precision in the detection and measurement of ultra-small elements. This advantage comes with the miniaturization N/MEMS offers. For example, a nominal mass of N/MEMS can scale down to nanograms or even smaller. It is therefore possible to detect and measure things at 10^{-15}, 10^{-18}, or even lower scale. Miniaturization also means a small footprint, weight, energy, and Internet of sensors (IoS), all at reduced system-level cost. With N/MEMS, it is possible to precisely detect the target analyte and measure its concentration. This is achieved through precisely recording even the minutest shift in the sensor output [4, 9, 10]. Transduction principles such as piezo-electricity, piezo-resistivity, electro-static, electro-magnetic, electro-thermal, optical, etc. are popularly used in the development of the N/MEMS-enabled bio/chemical sensors.

3.1 Mass Accumulation

N/MEMS devices are operated by the principle of gravimetric sensing [7, 11]. Mass accumulation is characterized by the adsorption/absorption (biorecognition) of the mass of a particle or target element in a biological/chemical sample. N/MEMS transducer is a mechanical cantilever/tuning-fork/plate/disk/bar/membrane. This transducer is set in a static or a dynamic mode (vibrate at a particular frequency called a natural resonant frequency). Figure 4 shows a schematic illustration of an N/MEMS

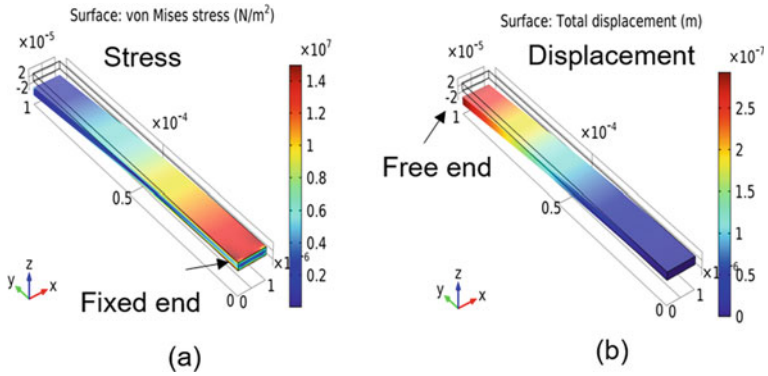

Fig. 4 A static N/MEMS transducer that can be used to sense and quantify target bio/chemical contaminants in a sample. Part **a** shows a stress profile of a structure that can be used to use piezo-resistive transduction. Part **b** shows a displacement profile of a structure that can be used to use capacitive transduction

transducer that can be used as a primary element in a typical N/MEMS biosensing platform. As seen in Fig. 4, a transducer (cantilever in this case) in a static form is used for sensing purposes. A transducer surface is functionalized to attract specific molecules. The functionalization takes place by depositing/loading nanoparticles (for example, gold nanoparticles) onto the surface of a cantilever. After this, target molecules are attached to the nanoparticles. Such mass accumulation leads to the gradient in (i) the surface stress (σ) (see Fig. 4a), (ii) surface strain, and (iii) a position/displacement of a cantilever (see Fig. 4b). In other words, the transducer is actuated by the component of the force exerted by the bio/chemical reaction that occurs at the surface of a transducer.

For the sensing part, a set of resistors (forming a Wheatstone bridge electronic circuit) is embedded at the other end of a cantilever, where it is fixed/anchored (see Fig. 4). At this end, the stress is maximum. Another viable method of sensing is to monitor a change in the parallel plate capacitance at the free end of a cantilever. At this end, displacement is maximum. A bottom electrode placed beneath the free end of the cantilever can be used to detect the capacitive gradient when the cantilever moves.

3.2 Materials

Usually, silicon/polysilicon is used to construct such a transducer. In recent years, piezoelectric materials (for example, aluminum nitride (AlN) and quartz) have become a popular choice in realizing several potential applications in BioMEMS [4]. However, materials such as silicon, piezo, etc. are suited only for non-invasive applications, a procedure that does not require inserting an instrument through the skin

or into a body. Such materials can be a part of N/MEMS-enabled biosensors. These sensors can then be used for monitoring environmental parameters, lab-on-chip, laboratory tests, wearable gadgets, etc. Given the biocompatibility issue, materials such as Polydimethylsiloxane (PDMS) and other polymers are also widely used for biosensing [12]. Another application of PDMS is that a transducer can be embedded into the μ channels made by PDMS for lab-on-chip fluid testing applications.

3.3 N/MEMS Resonators for Ultra-Precise Bio/Chemical Sensing

N/MEMS resonators are one of the most promising candidates to develop a wide range of applications in medical diagnostic and instrumentation [1, 4, 8, 13–16]. N/MEMS resonators offer extremely high-quality factors (Q) and high frequency. These two parameters result in exceptionally high parametric sensitivity. Additionally, the N/MEMS resonant sensing platform provides good output stability. Due to their highly precise output, N/MEMS resonators are extremely useful to sense environmental, physical, biological, and chemical quantities. They can detect multiple analytes in parallel, and offer immunity toward a false output. Being a primary component in many commercial applications, N/MEMS resonators are today a popular choice to develop low-cost, miniaturized, reliable, reproducible, and precise sensing solutions. Possible areas of applications are point-of-care/remote monitoring of target parameters in the environment, agriculture, medicine, health, and well-being, thus democratizing sensing across the globe. N/MEMS resonators operate on the principle of gravimetric sensing. The N/MEMS mass sensor is reported to detect particle concentration as low as attogram (ag) or even zeptogram (zg). Figure 5 shows a representative example of a N/MEMS resonator that can be used to detect and quantify the concentration of a target contaminant in a biological/chemical sample. Upon adsorption/absorption of a target trace/particle, a shift in the resonant frequency of a transducer can be accurately recorded (in real time). These shifts can be correlated to the concentration of the contaminant/s. The essential assumption is that adsorption/absorption of a mass, Δm is much smaller than the nominal mass, M of the resonant transducer ($\Delta m << M$).

3.4 Multiple Analyte Detection Using N/MEMS

Figure 6 shows a platform parallel processing using N/MEMS sensors. As seen, $C_1 - C_n$ are the cantilevers arranged as an array. These sensors are attached to a common base. Each of the cantilevers is coated/immobilized/functionalized with a *specific* bioreceptor thin film to attract the target molecules/particles. Such a sensing platform is highly useful for the fast testing of multiple parameters in bio/chemical

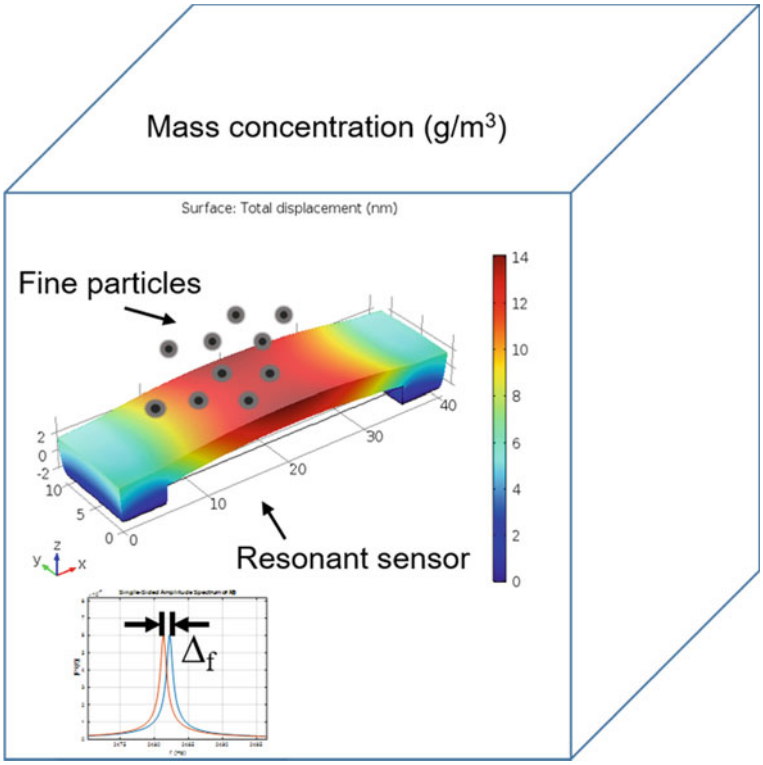

Fig. 5 A representative example schematic of a resonant mass sensor for particle detection and concentration measurement of a target analyte. Δf indicates the shift in the resonant frequency, i.e., transducer output

samples. Due to simultaneous testing and processing, the overall cost is low. Such a platform is compact and efficient. However, a specific coating of n number of sensing units in an array is required. Such a requirement may be a trade-off with the advantages in terms of cost and time.

4 Summary, Outlook, and Conclusion

This chapter introduced the basics of biosensors and how N/MEMS sensors can be used in several bio/chemical applications. The chapter started by providing an overview of a typical N/MEMS-enabled bio/chemical sensing platform. The N/MEMS sensors can be used to detect and precisely quantify several biological and chemical contaminants. This scientific area requires expertise, experience, and collaborations across the multi-domains (mechanics, optics, biology, chemistry, physics, and microelectronics). A static mode N/MEMS can be used to monitor

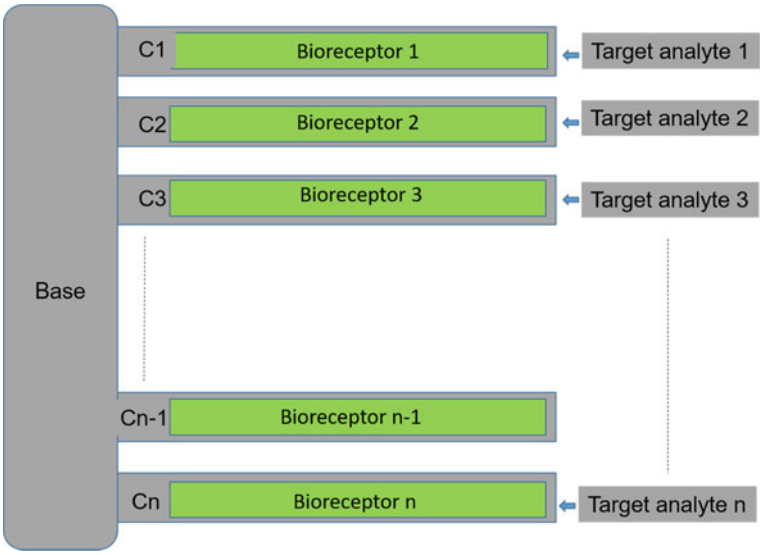

Fig. 6 An array of N/MEMS sensors to specifically detect and measure the concentration of a target analyte in a sample. A parallel test and processing of multiple analytes in the sample are useful in terms of cost and time

the surface stress, strain, or displacement when the mass of a target particle/analyte is attached to the sensor. An electro/optical sensing mechanism or a combination thereof can then be used to read and correlate the sensor output to the presence and concentration of the target element/s in a sample. A dynamic (resonant) mode N/NEMS is also used as a high-sensitivity transducer in biological and chemical applications. Here, a transducer element is set to vibrate at the designed frequency. When the mass of a target particle/analyte is adsorbed/absorbed on the chemically functionalized surface of a transducer, a change in the effective mass of the resonant transducer results in a change in the frequency.

N/MEMS-enabled hand-held biosensor modules can be employed for many applications. These applications are health care, surgery, drug discovery/dose control, recognition of pollutants, detection of micro-organisms responsible for causing a disease, and markers to indicate disease in bodily liquids/fluids (blood, urine, saliva, semen, sweat, etc.). Typical applications of BioMEMS also include sensors measuring intravascular blood pressure, therapeutics applications (e.g., drug delivery actuators, disease monitors), pacemakers, and defibrillators. Biosensors can be implantable or wearable. These are also part of sensing systems for real-time monitoring of several body parameters such as pulse rate, blood pressure, oxygen, and neurological activities.

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Lab-On-A-Chip Technology in Health Care

Neha Mishra

Abstract In the current era when early disease diagnosis is a need of the hour for the proper cure, LOC devices are the most reliable and promising solution. Lab-on-a-chip (LoC) devices are used for point-of-care diagnostics as they are compact, cost-effective, integrable, and multiple diagnostics can be performed on a single chip. For this reason, there are different diagnostic techniques used for LOC devices such as optical detection, PCR, qPCR, paper-based assays, and lab-on-a-chip using microfluidic platforms. The main focus of the aforesaid technique is the simplification of device design with multiplexed processes and the availability of automation to make LOC devices user-friendly. In this chapter, different techniques and processes are discussed which are used in diagnostic and healthcare applications.

Keywords Microfabrication · Biosensor · Microfludic channel · Optical detection

1 Introduction

A microfluidic platform consists of a group of precisely defined, fabricated microfluidic operating components. Miniaturization, automating, and parallelizing chemical processes [1, 2] are made possible by lab-on-a-chip (LOC) technologies. Because they employ less chemical reagent in modularly constructed, miniaturized devices, LOC devices have a lower cost advantage. The ability to operate quickly in a small space is another significant benefit of LOC devices; this is made possible by the parallelization of response chambers. The throughput and automation of analytical systems are also increased by LOC technology. To regulate fluidics at the micro- and nanoscales, LOC devices can be created (Fig. 1), and depending on the scale difference, these devices are sometimes referred to as microfluidics and nano-fluidics. Micro-channels or nano-channels in LOC technology offer control of fluids in minuscule quantities to enable biological processes in incredibly small volumes.

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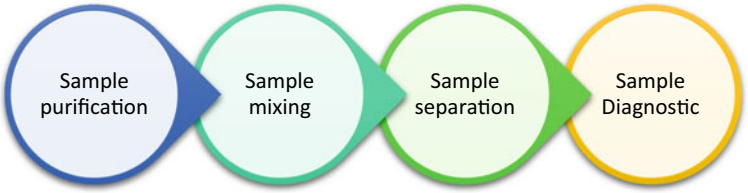

Fig. 1 Basic component of lab-on-a-chip technology

Utilizing the photolithography process, integrated circuits and microchannels can have fluid control components and routes created. For LOC to become a comprehensive system, it also needs the integration of micro-pumps, valves, micro-electrodes, electrical fields, and micro-electronics [3].

Smaller and faster electronic devices are produced as a result of advances in integrated circuit technology and wafer fabrication facilities. Silicon or glass and polymers are the foundation of microfluidic manufacturing. Despite having well-controlled mechanical and chemical qualities, silicon and glass require more expensive manufacturing processes. One mould can be used as a master for fabricating multiple devices in the case of polymers, however, using soft lithography or hot embossing. This makes it possible to produce disposable goods in large quantities. In contrast, polymers' mechanical and chemical properties have reliability issues, which necessitate surface modification for reliable device functionality [4]. In many cases, PoC diagnostics involve lateral flow assays. These assays include moving a liquid sample that contains the target analyte through various zones of polymeric strips that have immobilized capture probes that can interact with the analyte as shown in Fig. 2 [5, 6]. Commercially available pregnancy tests for the detection of human chorionic gonadotropin hormone present in bio-analyte (urine) are widely used for lateral flow assays. These tests use a sandwich-based immunoassay to detect the target protein, which is realized by a colour shift that can be seen with the unaided eye [5–8]. The key benefits of lateral flow tests include their affordability, convenience of use, simplicity, and extended shelf life. However, multiplexing and flow rate control are difficult with lateral flow assays since they call for a lot of chemicals and relatively significant volumes of material [5–8]. By offering fine flow control through various microfluidic channel geometry, microfluidic technology has been used to overcome these restrictions [8, 9]. Figure 2 illustrates the basic schematic diagram of the lateral flow assay, which explains how the process works. A small amount (generally in microliters) of the analyte is placed into the sample pad and then the analyte will go slowly to the probe pad through capillary action. The target analyte is beholden by tagged detection probes. It will take to the detection membrane, and then be captured on a line where capture probes are immobilized [5]. For proof-of-concept diagnostics of several analytes, capillary-driven microfluidic chips have been employed [6, 10–13]. For instance, a triage system is commercially available, which consists of a disposable protein chip and a portable analyzing device, that attempts to identify a wide range of medical disorders [14, 15] (Table 1).