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Point-of-Care (POC) Devices by Means of Advanced MEMS

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Abstract

Microelectromechanical systems (MEMS) have become an invaluable technology to advance the development of point-of-care (POC) devices for diagnostics and sample analyses. MEMS can transform sophisticated methods into compact and cost-effective microdevices that offer numerous advantages at many levels. Such devices include microchannels, microsensors, etc., that have been applied to various miniaturized POC products. Here we discuss some of the recent advances made in the use of MEMS devices for POC applications.

Introduction

Microelectromechanical systems (MEMS) technology provides devices that are fabricated using micromachining techniques. Development in MEMS technology in the recent decades has greatly influenced our daily life. As MEMS presents several physical advantages (e.g. miniaturized dimensions, cost/material efficiency and minimal weight) and functional advantages (e.g. low-power consumption, higher sensitivity and better resolution) a wide range of applications in numerous fields have taken off throughout these years. The development of integrated circuit (IC)-compatible surface micromachining technology resulted in some of the first examples of fabricated microactuators. Further developments in the fabrication processes [1,2] opened door to numerous applications, such as the construction of micromotors and micromirrors [3]. Although sensors used in the automotive industry and printer heads were the principal markets for MEMS technology for years, more recently, the advancement in Smartphones opened up the market for MEMS gyroscopes and accelerometers with improved stability due to developments in temperature compensation and packaging technologies [4-6]. In parallel, applications in optics and information

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technologies showed remarkable progress [7,8]. Similarly, with its compact working dimensions and integration with microfluidics, MEMS show a huge potential for biotechnology applications. Although the issue of biocompatibility often requires further investigation when using MEMS devices for *in vivo* applications [9], most of the current attempts are based on *in vitro* applications. Despite many attempts to integrate MEMS in POC devices only a handful has become commercially available, while many promising approaches and ideas are still under development. This field is developing rapidly and it is near impossible to provide a comprehensive overview of available MEMS POC devices partly due to the nature of the subject that combines numerous technologies and manufacturing methods. Moreover, the highly dynamic field of biomedical MEMS (BioMEMS) is characterized by continuous introduction of new ideas and devices with their frequent replacement by significantly improved or even entirely new competitors. In these regards, our attempt to summarize current state of MEMS based POC devices should not be viewed as a comprehensive guide but merely provides directions for further exploration of the role of MEMS POC in biomedical sciences.

MEMS utilize various technologies to develop and fabricate micro and even nano-scale devices and complex systems combining diverse chemical and physical properties. Perhaps MEMS represents one of the most interdisciplinary areas in engineering and science that combines and uses principles from a wide range of technical areas including mechanical engineering, materials science, chemistry, optics, fluid dynamics, and many others. BioMEMS specializing specifically in the fabrication of devices for sensing and detection finds its main applications in biomedical sciences. More specifically many attempts to apply MEMS for the development of POC devices have been made based on the high demand for precision, effectiveness, portability, and efficiency. This article will provide a short overview of recently developed MEMS POC devices and future trends in BioMEMS.

Some of the key features desired in POC diagnostics are speed, accuracy, and portability. MEMS devices provide an ideal platform for building such POC tests in many different forms. It has been established that MEMS devices are capable of separating, mixing, transferring, isolating, and capturing biological materials. The main target analytes in a POC device are cells, proteins, nucleic acids, and small molecules, which are collected and analyzed quickly. POC devices are not only time-efficient, but can be performed in the presence of or near the patient. The samples are not transported to laboratories to be tested, so the results can be obtained in a timely fashion and directly used for the diagnosis beside the patient. As a result, the workload of the skilled technicians can be decreased and more complex diagnostic protocols are completed more promptly. Similarly, using the POC devices the results are immediately obtained by the doctors, nurses or even the patients themselves, without going through costly and time-consuming laboratory and bureaucratically structured hospital. POC devices are also ideal for use in countries and geographical regions where there are no easy access to laboratories and hospitals. As a result, various types of POC devices have been developed for different purposes. Some of the most widely used POC devices, such as blood glucose measurements and pregnancy tests, indicate that in-home testing by the patient is in high demand.

Many POC devices employ microfluidics. Paper-based microfluidics devices are gathering a lot of attention lately because of their simple handling, easy storage, disposability, and low cost [10-12]. Simple microfluidic channel based devices with immunoassay based detection methods are also quite common. Micromachining technology plays an important role in such kinds of microchannel based devices. More complex devices use integrated mechanical or electrical elements, including advanced MEMS. Some sensors, heaters, actuators, cantilevers, rotors, valves, resonators and similar MEMS components can be integrated depending on the ultimate purpose. With increasing device complexity the required equipment increases as well. However, the devices will provide more detailed results. While a paper-based microfluidic device can mainly focus on the presence of analytes or molecules in a solution, microchannel based devices can perform more complex bioassays, and MEMS devices can even perform mechanical and/or electrical characterization of the existing analytes or molecules with high precision.

Much of the work in recent years has been focused on applying established capabilities of MEMS to specific purposes. By miniaturizing POC devices by utilizing lab-on-chip (LOC) designs, cost of monitoring and caring for patients is greatly reduced. The challenge is to compete with the standards of currently used instruments and equipment to generate data with accuracy, sensitivity, speed, and little to no discomfort to the user. By optimizing features for specific applications, various POC assays/tests have been developed. Further, appropriate markers (antibodies, small molecules, etc.) that would work within the required range with enough sensitivity must be chosen in order to take advantage of the capabilities of MEMS devices.

Requirements and Categories of MEMS based POC devices

Devices for POC are designed for near instant medical testing in the immediate vicinity of the patient. In this respect they must comply with a number of technical requirements ensuring reliable target (metabolite, protein or DNA) identification and quantification in the environment that is remote from medical or laboratory facilities. Therefore, POC devices must be portable for easy transportation, reliable to ensure correct diagnosis and feature short simple protocols for fast and accurate analysis.

Generally POC devices may be categorized based on the detected analyte or clinical marker. Clinical disease or physiological markers may be divided into several main categories that includes imaging markers: cell based markers (blood cell counts etc.), metabolite markers (small molecule glucose, aminoacid or cholesterol), protein markers (used everywhere from neurodegenerative diseases to infectious diseases) and nucleic acid markers.

Although we do not extend the topic to MEMS based POC imaging, we would like to report that remarkable developments in this area have been achieved in the recent years. Piezoelectric or capacitive micromachined ultrasonic transducers [13-16] showing high resolution ($<100\text{ }\mu\text{m}$ [16]) with low-cost and low-voltage characteristics enable new applications in healthcare, biometrics and personal health monitoring. Similarly, optical coherence tomography (OCT) using fast and low-power consumption MEMS micromirrors or micromotors provides ideal performance for endoscopic [17-22] or ophthalmic retinal

imaging [23,24]. CMOS sensors can also be counted in this group when they are used for lenseless imaging [25]. We can extend this list by adding MEMS ring resonators for AFM imaging [26].

Capturing and characterization of single and/or specific cells

The ability to procure single cells for further molecular characterization is an essential task for modern biomedical sciences. Captured single cells may be used for subculturing or clonal expansion, as well as biophysical and molecular characterization of intracellular contents. Several approaches have recently been developed for the isolation of specific cells from heterogeneous mixtures. With this advancement in single cell isolation and analysis, POC designs have made use of MEMS technology in order to capture single cells for characterization and analysis. Some of the common approaches that have been in use are described below.

Microwell array based technology is an attractive approach for high-throughput single cell capture and analysis. Numerous micro-fabricated devices have recently been reported for single cell capture and analysis, such as cell isolation using antibody as affinity capture agents from blood [27-32]. Most of these devices use various seeding protocols that involve deposition of a large numbers of cells onto a chip surface. One of the remaining challenges is an excessive cell loss and relatively low seeding efficiency [30] that mainly depends on the seeding flow, chip surface affinity and well geometry. Desirable features of microwell array based approach are its ability to sustain cell viability for prolonged periods of time with media and supplement changes as needed. Antibodies are widely used as affinity capture agents for cells found in blood such as T cells [33], B lymphoblasts [34], B cells [32] and circulating tumor cells (CTC) [35].

Routine detection of CTCs using POC devices has a huge potential for disease assessment. Periodic detection of the number of CTCs in the patient's blood and the mechanical and biological characterization of those CTCs would be a great tool to monitor cancer progression. POC devices that count CTCs have to filter an extremely small number of target cells first. Microfabricated structures or electrodes are used for most common label-free techniques developed in the recent years for filtration [36-38], hydrodynamic chromatography [39-41] and dielectrophoresis [42,43]. To achieve CTC characterization in POC devices, advanced MEMS integration is crucial. An example of mechanical characterization of filtered CTCs uses atomic force microscopy (AFM) [44]. Although it is difficult to envision a device using AFM as a POC device, an appropriate advanced MEMS design might make this approach applicable to POC tests. Micro heater integrated microfluidic devices (capable of on-chip polymerase chain reaction) can be used for the biological characterization of the CTCs after filtering with magnetic separation [45]. Moreover, electrical characterization of the cells is also possible using impedance measurements [46].

One of the limitations for MEMS actuators, resonators and cantilevers when used for biomedical applications is the reduced Q factor due to liquid immersion. This dramatically affects the sensitivity of the actuation. A clever design to alleviate such problems is

integrating the microfluidic channel inside a cantilever [47]. As a result of this design, fabricated microcantilever structures can be electrostatically actuated without compromising the Q factor because the solutions to be tested can flow inside the channel buried in the cantilever structure. Thus high sensitivity can be achieved to detect the mass changes in the channels inside the cantilever. Using this technique, the number of cells in a solution can be determined [47]. By using a more complex system with dual suspended microchannel resonators, single cell characterization (mass, volume and density) can be performed [48].

Nucleic acid detection

Particular DNA sequence or presence of a specific RNA transcript is an important clinical marker. An essential group of DNA/RNA detection methods used in the fields of diagnostics, food safety, environmental monitoring and biodefense are comprised of various DNA amplification strategies. They permit rapid pathogen identification and feature high sensitivity and specificity. Perhaps the most commonly used amplification technique is Polymerase Chain Reaction (PCR) permitting million fold amplification of a target DNA template. PCR is a robust, inexpensive and extremely sensitive approach for the detection of even a single copy of target DNA template. However, because PCR based amplification usually requires fairly expensive and bulky equipment, appropriate laboratory settings, and labeling reagents, the search for more cost- and time-efficient, easy-to-use, sensitive, accurate, and portable methods of DNA detection continues.

Recently, MEMS-based technologies demonstrated a great potential for POC DNA diagnostics [49]. Microfluidic technologies (MTs) based on interconnected micron-dimension channels have been developing rapidly as powerful methods that can overcome the challenges imposed by the conventional detection platforms and enable POC detection of pathogens by LOC devices [50-54]. MTs, often seen as a part of MEMS, allow the integration of various assays into a single chip, enable automatic detection, reduce reagent consumption and reaction times, increase reliability and throughput, lower costs and don't require highly skilled personnel [50,51,55]. However, many of them are still relatively bulky, time- and energy-consuming and costly due to the use of peripheral instruments, such as fluorescent detector or PCR machine [52-54,56].

PCR based microfluidics devices have been developed, but the complex design and integration, energy consumption, and high rate of contamination have restricted their wide spread application [57,58]. To overcome the limitations of PCR, isothermal DNA amplification methods have been utilized in the microchip format [49]. Most of them have reduced reaction time, provide real linear amplification, and do not require expensive instruments. Perhaps, rolling circle amplification (RCA) that can generate more than a billion-fold amplification within 1 hour [59,60] is one of the most attractive candidate for integration in POC microfluidics devices [61]. In RCA a single-stranded DNA circle is replicated by ϕ 29 DNA polymerase to generate long tandem repeat products. It allows rapid and simple detection of a single molecule, is easily quantified, and requires minimal equipment and personnel training [49,62]).

Traditionally amplified DNA is often detected optically with the use of a fluorescent label. Fluorescence-based optical DNA detection methods require expensive chemicals and equipment, and suffer from artifacts caused by bleaching of the fluorophores. Other methods, such as scanning probe microscopy, also require expensive and bulky instruments, not suitable for POC devices. As alternative to amplification strategies, electrochemical detection of nucleic acids was found to be a convenient principle allowing incorporation of these technologies, which includes a variety of new fabrication techniques and materials [63-67]. Electrochemical DNA detection may be realized through changes in several DNA properties including current, impedance, conformational changes etc. Nanomaterials find a wide area of applications for their use in the DNA detection devices as an essential material for capture probes, electrode coating and fabrication [68]. New materials allow for better capturing properties increasing sensitivity and a detection time.

Electrochemical DNA detection is well integrated into LOC systems and easily realized in an extremely fast and cheaply [69,70]. The geometrical resolution is also not restricted, which is often the case with optical methods [69-75]. As a final point, MEMS based RNA/DNA detection envisions development of a universal POC compatible DNA analysis system capable of a sample preparation, DNA/RNA isolation and detection with minimal costs, time and operator involvement.

Protein and small molecule detection

Proteins can serve as key disease markers that may be present in blood or other bodily fluids [76]. Various proteins have long been captured by immunoassay and use of antibodies within MEMS devices [76]. The cantilever with integrated microfluidics elements can be used for protein detection as well. Although cells were detected with a spike in the resonance frequency while passing the channel [48], proteins can be detected by attaching on the channel surface and thus as a decrease in the resonance frequency due to the increased mass [47]. One other option is to use the cantilever structure at the air-liquid interface. This approach might decrease the sensitivity, but can still be used for protein detection [77].

Small molecules consist of electrolytes, gases, and other molecules that can be immunologically or electrochemically detected. It is common to use POC devices to monitor such analytes as glucose, pH, hemoglobin, hormones, etc. Although commercialized POC tests, such as for pregnancy, consist of flow immunochromatographic assays, some clinical assays are based on electrochemical detection. Paper-based microfluidics has been coupled with electrochemical detection for glucose, lactate and uric acid [78,79]. Although amperometric biosensors are more common, conductometric biosensor array was recently developed to simultaneously detect several carbohydrates [80].

Viscosity measurement of complex fluids

POC microfluidic devices were constructed for the measurements of blood viscosity and flow rate [81,82], essential parameters for monitoring variations in physiological and pathological conditions due to cardiovascular diseases or inflammation. Flow-switching principle was used to measure viscosity in complex fluids [81]. Briefly, two or more of the

parallel channels merging in a “junction” channel may be used in a microfluidics format to identify the difference in the viscosity between fluids (e.g. test and experiment) by detecting the reverse flow-rate change due to the phase differences between the fluids. Such method of hydrodynamic balancing can comparatively measure viscosities without specific labeling or calibration procedure. Based on the same principle, the three-step sequential microflow controls permit label free and sensorless monitoring of the blood viscosity and flow rate [82]. Earlier, POC central venous catheter was developed to provide measurements of blood viscosity via electrical impedance technique *in vivo* [83].

Conclusions

Integration of MEMS in a POC device enables miniaturized mechanical and electrical components to replace laboratory equipment and instruments for the analysis of various biological analytes. Microfabrication offers device miniaturization leading to a reduction of the sample and reagent volumes that increase overall efficiency and requirements for POC devices [84]. MEMS technologies coupled with microfluidics permit development of lab-on-a-chip (LOC) devices [71,85-87]. , triggering development of commercial POCs [84,88]. MEMS technology offers the advantages of a LOC format that includes small reagents volume, compact size, high-throughput analysis, low power consumption and importantly integration of various devices and functionalities. However, many of the POC devices and principles have been designed and introduced decades ago. Although certain improvements have been implemented many of them are not fundamental and do not change the approach in general. Various new devices based on microfluidics principles may be very efficient but do not qualify as a substantially new technology. This by all means does not imply that recently introduced devices are not efficient or don't offer significant improvements in cost reduction, further miniaturization or processing speed. Often devices proposing new detection or manufacturing principle have long transition from research bench to a patient bedside due to insufficient funding at the early developmental stages and intricate regulations for medical device approval [84,89]. Therefore, we tried to give a brief overview of both improved POC devices with established principle of action (e.g. microfluidics, immunoassay based microchips) and devices offering somewhat new approach for the detection of disease relevant analytes.

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Highlights

This review discusses some of the recent advances in the development of POC devices using MEMS technologies. More specifically the following aspects were reviewed:

1. Desired features of MEMS based POC devices;
2. MEMS based POC devices for capturing and characterization of single cells;
3. Detection of nucleic acids with MEMS based POC devices;
4. Measurement of proteins, small molecules and viscosity.