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Lab-on-Chip Technology: A Review on Design Trends and Future Scope in Biomedical Applications

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Abstract

Lab-on-Chip (LoC) integrates various analyses such as biochemical operations, chemical synthesis, DNA sequencing onto a single chip which otherwise would have been performed in laboratory taking sufficient amount of time. Due to the miniaturization of these biochemical operations, better diagnostic speed, cost efficiency, ergonomy, sensitivity and so on can be achieved. This paper gives the detailed description of Lab-on-Chip technology including its system components. Ongoing worldwide research projects based on LoC technology have been investigated and various constraints that need to be fulfilled for designing a LoC system are presented. The biomedical applications of LoC in different fields like in diagnostics, cellomics, in environmental studies to control the effect of pathogens, to check the food quality such as for the detection of various antibiotic families in raw milk have also been discussed. Finally, the current open research issues of this technology along with the possible future research scope in the biomedical area have been presented.

Keywords: *Biomedical Systems, Biosensor, MEMS, Microfluidics, Lab-on-Chip*

1. Introduction

Lab-on-Chip technology implies those techniques that perform various laboratory operations on a miniaturized scale such as chemical synthesis and analysis on a single chip leading to a handheld and portable device. In other words, LoC is a device which is capable of scaling the single or multiple laboratory functions down to chip-format. The size of this chip ranges from millimeters to a few square centimeters. [1]

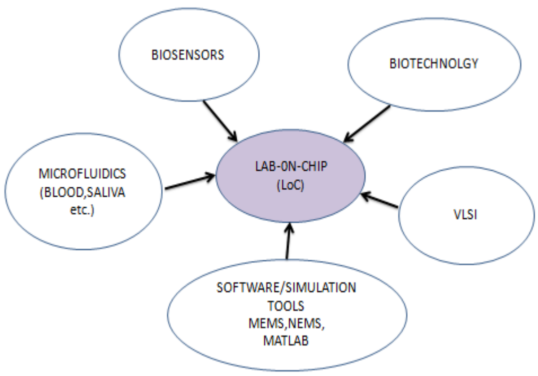

Figure 1. Interdisciplinary Field of LoC

LoC is basically the integration of fluidics, electronics, optics and biosensors [2]. The main motive of LoC is the need for the state-of-art pathological analysis

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on-the-go. LoCs prove to be useful for finding the methods for the early stage diagnosis of deadly and chronic diseases. Due to the advent of advanced technologies such as MEMS, NEMS, the integration of large number of interdisciplinary modules on a single chip [3] is possible as shown in figure 1.

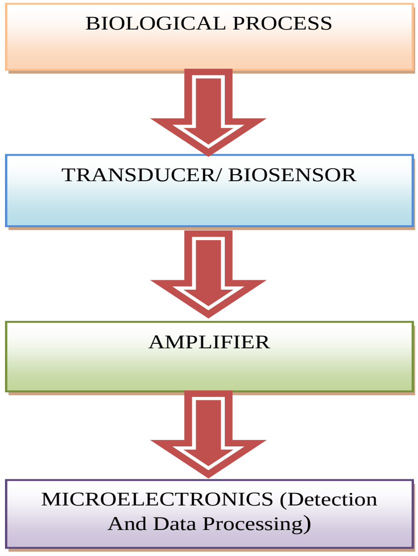

Figure 2. Schematic Representation of Lab-on-Chip Process

Figure 2 represents the various steps involved in Lab-on-Chip processing. The LoC processing initiates by collecting the physiological sample and then from this sample, the extraction of particular analyte/biomarker is done. Depending upon the biomedical application, the transducer will act on the analyte electrically, electromechanically optically or mechanically. The next step involves counting, sorting and amplification of the transducer output is performed according to the application. Finally, the amplified sample is processed using microelectronics techniques. Current trend shows the growth of research in this area. In many universities across the world, many groups are formed that are dedicating their research in this area. For example, BIOS in University of Twente, Mina Med in Germany, and Nanobe in Finland [3] are some of the groups. Their main motive is to understand naonofluidics and nanosensing, to connect micro/nano eng. with biomedical and life science fields, to develop new micro and nano technologies for LOC, and to demonstrate new LOC applications.

2. Design Constraints and Advantages of Lab-on-Chip Technology

A LoC is a device which is capable of scaling the single or multiple laboratory functions down to chip-format [4]. The size of this chip ranges from millimetres to few square centimetres. Extremely small fluid volumes of less than pico litres can be handled by LoC. High throughput screening and automation also becomes possible by the introduction of LoC technology. LoC devices are often indicated by "μTAS" (Micro Total Analysis Systems) and are a subset of MEMS (Micro-electro-mechanical systems) devices. LoC technology is closely related to the microfluidics which is primarily the combination of physics, the study and manipulation of small quantities of fluids. The major difference between LoC and μTAS is that μTAS generally indicates the integration of the total sequence of lab processes in order to perform chemical analysis whereas LoC is dedicated to the integration of one or several of the lab processes onto a single chip. The applications of LoC in the medical field such as to diagnose HIV infections and in the field of plant sciences have been explored.

The paper [5] presents the on-going research activities in LoC technology and recent advancements in the handling of various biological processes medical applications. The progress and success of available technological tools leads to the fabrication of Micro-Electro-Mechanical-System (MEMS) that integrate micromechanical and microelectronic structures in one system leading to interdisciplinary applications. MEMS and microelectronics differ in technological approaches inspite of the fact the MEMS have grown from microelectronics. The MEMS approach known as microflidics helps in the handling of small fluid volumes even less than picolitres. The scaling of one or several of the lab processes onto a single chip-format is known as LoC which has the capability of handling micro and nano particles by combining several laboratory functions on one chip. To perform chemical analysis, MEMS is used. Photolithography which is directly derived from microelectronic fabrication is the the basis for most LoC fabrication processes and is discussed in this paper.

A review [6] on various promising system integration techniques for microfluidics has been presented along with their merits, challenges and applications. The emerging microfluidic strategies in order to perform the effective integration of multiple microfluidic components leading to fully automated lab-on-a-chip systems are: (i) Multilayer Soft Lithography; (ii) Capillary Driven and Paper-based Microfluidics; (iii) EWOD Driven Droplet Microfluidics; (iv) Multiphase Microfluidics; (v) Centrifugal Microfluidics; (vi) Electrokinetics, and (vii) Hybrid Microfluidics. Due to on-going research in this area, fully automated microfactories can now be thought of that will have the capability of performing various biochemical analyses at a much low cost for a wide spectrum of biomedical and biological engineering applications. The obstacle in the designing of LoC or microfluidic devices for biomedical applications is that most of these applications need sensitive detection modules like thermal cyclers for PCR reactions, mass spectrometers for sample analyses, microscopes for cells, fluorescence visualization and bacteria.

The two major challenges that come in the way for the rapid development of microfluidic Lab-on-Chip systems have been addressed in [7]. The first challenge is to investigate the technologies and new polymer materials for chip preparation and the second challenge is to choose the best label-free method for the detection of analytes in microchannels. For the demonstration purposes, a general Lab-on-Chip concept i.e. CE (capillary electrophoresis) in chip format is used. The CE chips are then fabricated and characterized using different polymers such as cycloolefine copolymer, PMMA etc. and the polyether ether ketone (PEEK) come out to be the best polymer having the outstanding performance. Capacitively coupled contactless conductivity measurement (CCD), an electrical detection method is used for analyte detection. Thus, a completely miniaturized and low-cost CE chip is developed known as “MinCE” and different applications are demonstrated such as in medical area, for the quantitative determination and measurement of lithium (an antidepressant) in blood serum suitable for point of care diagnostics. Other applications that are demonstrated include proteinogenic amino acids detection for bio analytics and in beverages, saccharides determination for in situ food analysis. Finally, CCD application is extended for the highly sensitive detection of biologically relevant macromolecules particularly DNA. One of the limitations of this chip system is that in order to get high performance and accurate results, it is essential to individually optimize the different process parameters.

Different stages involved in the construction and development of a lab on-a-chip (LOC) system has been discussed in [8]. For miniaturizing the conventional and current laboratory devices and apparatus, this state-of-art technology use different polymer materials. First, the independent unit components of this microfluidic system are introduced and then for realizing a Lab-on-Chip system, the functional integration of each component into one monolithic system is demonstrated. Specifically, a microscale PCR unit, a microscale injection component and a technique for assembling the device under mild environment conditions are demonstrated. Fabrication of all the unit components is done by the use of a PDMS elastomer and pressure is used for the actuation of a sample flow. By this technique, it is possible to replace the expensive and bulky peripheral components such as heaters and pumps. This also solves the issues of contamination and degradation of sample and extends the application of LoC at the molecular level in case of urodynamic studies.

In [9], recently developed nanosensors are presented. These nanosensors are required to improve the efficiency of LoC systems in biological and chemical applications and they have the capability of measuring the biomolecular binding directly. The two sensors presented in this paper are Si-NW (Silicon Nanowire) sensors based on field effect and the platform of second sensor is based on metal nanostructured surfaces. Almost all electrical sensors as Si-NW biosensor have advantages since they have the capability of direct integration with the conventional circuits necessary for miniaturized and compact sensing systems. Si-NW sensors can be demonstrated as pH sensors having Nernstian sensitivity and it becomes possible to have the real-time measurements of DNA hybridization. Nanostructured metal surface based sensor platform defines nanogaps precisely suitable for Raman spectroscopy and SERS (surface-enhanced Raman scattering) application.

3. Design Constraints and Advantages of Lab-on-Chip Technology

An overview of the various possibilities that microfluidics can offer for biomedical applications has been provided in [10]. The integration of multifunction on a single chip such as actuators, sensors, wireless communication and signal processing; and the implementation of microfluidic to microelectronics has led to the possibility of a novel, innovative and complex LoC. The applications of CMOS and microfluidic co-integration are presented in this paper. This paper also explains the actual trend needed to achieve higher frequencies such as millimeter and microwave ranges. Then the numerous applications are targeted for better life monitoring and to permit personalized medicine with therapeutic and early diagnostic applications. From this, we can conclude that the convergence of microfluidic and CMOS platforms will successfully lead to the portable, handheld, low-cost point-of-care devices. The limitation is that it becomes necessary to face the high challenges and even surpass them like heterogeneous integration and the challenge of fluid handling at the packaging and system level also and not only at the circuit level for reaction, sensing and manipulations.

In [11], the requirements for the development of a disposable and smart plastic biochip used in clinical diagnostics applications and for Point-of-Care Testing (POCT) are presented. This paper gives a comprehensive overview of the development of smart passive LoC system, incorporating microfluidic system with on-chip power source embedded on it and the integration of biosensor array. The advantages of this fully integrated system include the control of volume precisely with the help of manipulations of microfluids and all this is done with the low cost on-chip components. The applications demonstrated with this chip include the biochemical detection of various parameters such as the measurement of lactate level and glucose in human blood and gas concentration like partial oxygen measurement in blood. Finally, a handheld analyzer is developed used for the multi parameter measurement and detection applications required for POCT systems.

The capability of Lab-on-Chip technology in the field of life science is investigated in [12]. Microfluidic or Lab-on-Chip technology enables the several sequential experimental steps to be integrated into one single automated process and thus leads to downscaling. With the help of this technology, many enormous tasks such as deciphering of human genome, automated analysis of biomolecules and development of novel targeted therapeutics now become possible in a much faster manner. Conventional techniques such as capillary electrophoresis or gel electrophoresis used commonly for the analysis of RNA, DNA, proteins and for the quantization of nucleic acids are very laborious and time consuming. LoC technology offers several advantages to overcome the limitations of conventional techniques such as ease-of-use, rapid analysis, minimal sample requirement, reduced waste generation and minimized exposure to hazardous materials.

In [13], many diseases such as TB, HIV, and malaria are identified that need immediate attention and require new health technologies for their prevention, on-time diagnosis and therapeutics. One such promising solution can now be thought of because of the recent advances in the LoC technology. On-going research in this technology leads to the rapid emergence of such devices that can prove to be very useful for improving the health of people especially in developing countries. Special design criteria for these LoC devices to be deployed in developing countries are also discussed. The main focus of this review is to explore the role of LoC devices in the field of diagnostics. The other applications of LoC technology identified and discussed are efficient and automated drug delivery, environmental sensing and monitoring.

4. Application of Lab-on-Chip Technology

The increased demand of LoC devices in many areas is due to the various technological advantages of LoC technology such as portability, automated sample handling, re-configurability etc. Immunoassay LoC for bacteria detection, Real time PCR detection chips, DNA chip, Gene Chip, Cellular Analysis chip, Flow Cytometer LoC (for HIV) etc. are some of the applications of LoC technology in the biomedical field. [14]

The review [15] presents the characteristic of microfluidic LoC to be used for meeting the requirements and improving the efficiency of Point-of-Care diagnostic systems. Since the required functional modules and working principles generally depend on target analytes, so the applications of POCT systems are categorized according to the type of analyte such as cells, proteins, metabolites and nucleic acids. POCT systems have the ability to detect specific biomarkers from these analytes. These different biomarkers require different assays, diagnostic principles and operating systems. Thus in each category, configuration of modules, detection methods and advantages and disadvantages of Lab-on-Chip based POCT diagnostic systems are reviewed.

The development of disposable and fully-integrated Lab-on-Chip devices for microfluidic and clinical applications especially in biological fluids for the point of care testing and monitoring of simultaneous parameters has been studied in [16]. This chip is fabricated by the integration of biosensors, optical filters and electronic circuits on a single chip. A Lab-on-Chip device is proposed that uses acoustic streaming technique for promoting the pumping and mixing of microfluids inside microchannels so as to improve the microfluidic device performance. To generate this acoustic streaming, a transducer is used which is based on a piezoelectric material like β-PVDF (polyvinylidene fluoride prepared in its β-phase). This polymer is processed to be functionally graded for being able to maintain the heating and to control the movement of fluids in conjunction with the input signal that is applies to the transducer. To facilitate the portability of LoC with less mixing time and to obtain high precision and reliability, it is proposed to use the white light source and spectrophotometry as the detection technique which can be made possible by the co-integration of highly selective optical interference filters on CMOS.

The impact of LoC devices on biofunctionalization, synthesis, clinical translation and in-vitro and in-vivo evaluation of inorganic nanomaterials for biomedical applications is discussed in [17]. The LoC methods results in consumption of less energy and fast synthesis of quantum dots and inorganic nanomaterials such as metals, nanocomposites, and metal oxides etc. In this article, the comparison is made between tubular continuous and chip-based flow systems. This also shows the requirement of LoC devices for faster completion of clinical translations by carrying out superior in vitro studies. Because of the recent advances in the field of computational simulations, now it becomes possible to synthesize the inorganic nanomaterials-based nanomedicine in a single construct using LOC technology useful for theranostic applications.

The recent advances in the Lab-on-Chip technology and design strategies that lead to the development of universal sample-to-result microfluidic devices useful for efficient pathogen detection with high specificity and sensitivity has been presented in [18]. The main focus is given on the development of accessory-free and totally integrated self-contained microchips that will have many advantages such as point-of-care diagnosis, handling of small volumes of sample, rapid detection time, miniaturization and portability. This will help in reducing the mortality rate and in controlling the propagation of life-threatening diseases such as tuberculosis (TB), HIV and so on.

The work in [19] presents the need for the development of LoC devices required for the multiplexed detection of various antibiotic families in raw milk. It is reported that four antibiotic families are excessively used in dairy diet leading to stronger bacterial resistance. This will pose a serious problem and threatens the efficient antibacterial treatment in humans. Precisely, the antibiotic families of sulfonamides, tetracyclines, βlactams, and fluoroquinolones are of interest. An automated, easy to use, fast and cost-effective multiplexed sensing system was developed for detecting these antibiotic families.

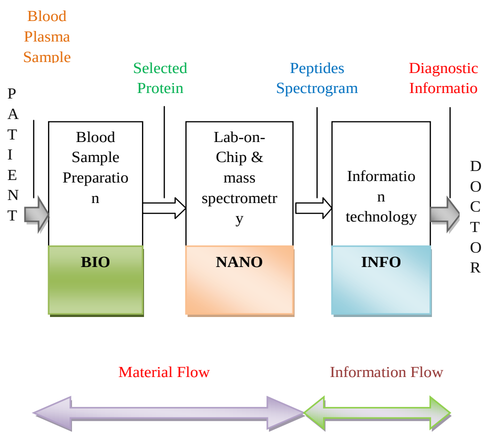

Figure 3. The LOCCANDIA Diagnostic Analysis Chain [20]

The proteomics profiling techniques integrated with the information management methodologies and analysis platform is described in [20]. The main objective of this is the identification of clinically relevant analytes and biomarkers for the detection of pancreatic cancer in the early phases. Since pancreas are LoCated deep in the abdomen, the ultrasonic and physical detection of pancreatic cancer becomes complex and cumbersome task and almost about 95% of all such cases are diagnosed in last stages; for e.g. in stage III or IV resulting in high mortality rate. In this, the LOCCANDIA project is discussed, shown in figure 3. This project is primarily concerned for the diagnosis of pancreatic cancer in early stage. This can be done by validating the plasma protein which is integrated with aprofiling application with the help of a Lab-on-Chip development i.e. a novel nanotechnology based platform a full proteomics analysis chain. The success of this project is based on the seamless combination of bio, nano and data processing and information management methodologies.

Authors in [21] describe the emergence of LoC devices for the biomarker-based identification and early detection of oral cancer. Head and neck cancers constitute almost 40% of the oral cavity cancers. Other types of oral cavity cancers include squamous cell carcinomas of the lips, tongue, gums, buccal mucosa, hard and soft palate and floor of the mouth. OSCC (Oral squamous cell carcinoma) is a deadly cancer and results in high mortality, morbidity and disfigurement. Conventional diagnostic and screening methods for OSCC are not cost-efficient and are not highly accurate and require sophisticated equipments, modern laboratory and lengthy and elaborate processing by skilled personnel. The motive to overcome these issues leads to the need of a miniaturized, accurate, automated, integrated and inexpensive lab –on- chip. In order to screen the patients for OSCC, this microfluidic LoC will accept saliva as input sample, which is then processed by minimally trained personnel and thus provide the results on time. Within the chip, the identification of oral cancer and precancer(dysplastic) cells will be possible by means of membrane-associated cell proteins which are singularly expressed on dysplastic and cancer cells' membranes and have unique gene transcription profiles.

The paper [22] addresses the need for microfluidics-based LoCs that can be used as complementary tools in controlling the effects of pathogenic agents so as to prevent the damage of environment. These LoC systems are easy to operate, fast, sensitive, sufficiently reliable and portable and thus offer several advantages as compared to conventional methods that are expensive, tedious and time consuming. The major application of LoC systems in pathogen detection includes DNA-based methods based on electrochemical techniques. The systems' fluid mechanics is discussed at the nanoscale level. The main limitation is that the use of mechanical pumps needed for fluid transmission requires attention and degrades the performance.

The potential of LoCs in the medical area is illustrated in [23]. Three examples have been presented to illustrate the potential of LoC in the medical field. First, in the case of maniac patients for monitoring lithium in their blood, a prefilled, disposable chip which is based on capillary electrophoresis is discussed. Lithium in an oral manner is often used to treat the patients suffering from bipolar disorder. So, a glass chip based on capillary electrophoresis and vacuum-prefilled with buffer solution is fabricated and now commercialized by the company Medimate. This same chip also has the potential to determine magnesium and calcium in cow blood in order to detect milk fever. It is seen that sodium in urine can also be measured by this chip platform which is highly useful for kidney patients. In the second example, in order to determine male fertility, a simple chip used to count the sperm cells in semen is presented. Lastly, advanced in-vitro models used for drug development are presented. As an example of organ on chip, blood-brain barrier on chip is realized that is used to establish a versatile platform for the screening of drug and possesses the potential to greatly replace and reduce animal testing.

The requirement for a simple, fast and on-time diagnosis and elimination of global concern diseases such as malaria led to the emergence of Lab-on-Chip PCR diagnostic method. In this study [24], the LoC technology is described that has the potential to overcome the challenges of expensive, complex and conventional molecular diagnostics especially in developing countries. This technology has the capability to control the life-threatening disease malaria in the following ways; as a diagnostic measure for acute malaria, can be used for surveillance in elimination settings and as a tool in clinical evaluations of new vaccines and drugs. This work presents a novel molecular technology that has the potential to make a remarkable contribution in the surveillance and diagnosis of various infectious diseases such as sexually transmitted infections (STI) and for detecting various infection causing pathogens and genetic markers.

One of the most common and chronic diseases of today is Tuberculosis, causing high mortality rate due to the inefficient diagnosis and improper treatment. MDR-TB (Multidrug-resistant tuberculosis) is one of the stages of TB that require on time diagnosis and expensive treatment for a long period of time. The WHO (World Health

Organization) has also endorsed the specific molecular diagnostic techniques so as to improve the fast diagnosis of MDR-TB [25]. The effectiveness of current methods is restricted by limited versatility, inappropriate interpretation of silent mutations and the geographical distribution and genotypic diversity of Mycobacterium tuberculosis complex (MTBC). To overcome all these challenges, STMicroelectronics (Geneva, Switzerland) has developed a Lab-on-Chip device known as VerePLEX Biosystem [26]. This molecular LoC based system has the potential to diagnose the MDR-TB considering time constraint and to rapidly detect the common Nontuberculous Mycobacteria (NTM) so as to reduce the mortality and morbidity rate. The user friendly interface; speedy and versatile performance of this system makes it suitable for routine laboratory use.

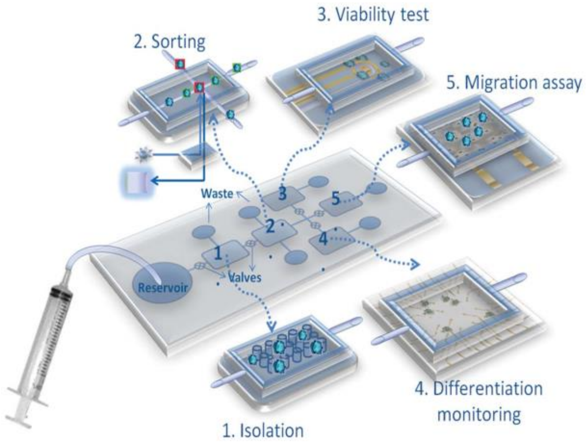

Figure 4. Example of a modular lab on a chip for stem cell studies

A modular Lab-on-Chip for the study of stem cells is presented in [27] and shown in figure 4. The development of such a device requires the integration of several sensing modules and microfluidic components on a chip needed to perform cell detection, isolation and counting, differentiation studies and migration of assays or viability. In this article, various advantages of cell chips have been discussed that cover almost all possible requirements of a cell biology laboratory resulting in a fully integrated cell study system. The role of microfluidics in this system is to create chemical gradients, for isolating specific cell types and for integrating three-dimensional scaffolds. Inefficient recovery of cells is one of the major limitations of micruifluidic approach especially in the case of rare cells that are at very low concentrations [28]. So for capturing the cells in the microfluidic channels, it has been proposed to coat the alginate based hydrogels with specific antibodies. In general, we can conclude that in comparison to the traditional cell culture techniques cellomics have enable the biologists to manage the complex environments in an automated and easy way with measurement reproducibility and increased throughput.

5. Future Scope

It is widely discussed that Microfluidic LoCs have great potential to revolutionize the biomedical field and possess the capability to give a boost to healthcare sector. But still this LoC technology would seem to be a dream especially in developing countries. In the low-resource areas such as developing countries, efforts are still required to improve the business model under which LoC devices are produced and to make people aware about their efficient use.

Many infectious diseases are there such as malaria, HIV and AIDS, measles, TB, lower respiratory conditions and so on that require timely diagnosis and treatment so as to reduce the mortality rate [29].

Now-a-days, Swine Flu, Zika Virus and Ebola Virus are killing thousands of people and causing the risk of epidemic. For all these diseases, LoCs diagnostics are desperately needed because of their ability to provide diagnosis in real time so as to improve the disease-management landscape. Moreover, this technology can proven to be useful for finding a novel way to treat central nervous system disorders such as Parkinson's disease and spinal cord injury with the help of extracting sufficient cerebrospinal fluid needed to perform conventional assays [30]. The potential of this technology can further be explored for autoimmune joint diseases like rheumatoid arthritis.

6. Conclusion

Based on the survey, it is seen that LoC devices have wide range of applications. Research in this technology mainly focuses on chemical synthesis, DNA analysis and human diagnostics. They can be used in different areas such as in diagnostics, bioanalysis, and biosensing, for environmental monitoring including testing of water and food quality, for testing of different drugs, in pharmaceutics and so on. They have the advantage of low power consumption, portability, modularity, reconfigurability etc. They automate the laboratory processes like sample transport, dispensing and mixing and have the capability of reducing the time of laboratory tests to a great extent. Due to their various capabilities, it becomes now possible to detect the chronic and life threatening diseases like cancer, TB etc. in the early stages leading to the reduction in mortality rate. LoCs devices are suitable for point-of-care diagnosis as they provide the fast and on-time diagnosis results. Till today, Lab-on-Chip for monitoring the lithium level in maniac patients is successfully tested. For many other applications, platforms for designing LoCs have been proposed.

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