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LAB-ON-CHIP: PRINCIPLE, DESIGN, TECHNOLOGY AND DIAGNOSTIC TARGETS

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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 have also been discussed. The current open research issues of this technology along with the possible future research scope in the biomedical area have been presented.

Keywords: Lab-on-Chip, Design, Technology, Applications, Diagnostic targets.

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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]**.

In the recent decades technologies evolving from the translation of microsystems and microelectronics manufacturing techniques have led to the creation of a variety of novel devices with the ability to encapsulate a variety of laboratory processes into a singular miniaturized platform, the so called, lab-on-a-chip. The field of lab-on-a-chip, and its related microsystems counterpart technologies (microfluidics, MEMS/NEMS, μTAS etc) have now developed into truly multidisciplinary fields, requiring equal contributions from fields ranging across biology, chemistry, software development, physics and material science, in addition to the traditional skills of microfabrication and engineering used in their original inception and development **[2]**. LoC is basically the integration of fluidics, electronics, optics and biosensors. 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**. The concept of LOC is based on microfluidics. Microfluidics is the technology of manipulating and controlling fluids and particles at micron and submicron dimensions and the technology associated with the development of methods and devices to undertake such operations **[4]**. Using building blocks to form microfluidic platforms enables the implementation of assay miniaturization. Such platforms, characterized by fluidic channels and chambers, will enable the miniaturization, integration, automation and parallelization, as in performing multiple tests at the same time, of (bio) chemical processes. Microfluidic-based LOC devices are particularly useful for applications in drug discovery, life sciences, ecology and clinical (in vitro) diagnostics **[5]**.

The largest LOC market segment, which is clinical diagnostics, can be divided between point-of-care (POC) testing (i.e., a diagnostic test performed near the patients without needing a clinical laboratory) and central laboratory-based testing (i.e., diagnostic laboratory in a hospital). Clinical diagnostics ranges from relatively simple immune chromatographic

strips, similar to pregnancy tests, to highly complex systems requiring external machinery and expert training for their handling. Clinical diagnostic applications also include detecting nucleotides and peptides that are considered early indicators of disease.

In many ways, the features of LOC devices fulfill the requirements for a POC diagnostic device: low consumption of reagents and sample, miniaturization of device and fast turn-around time for analysis. It is a versatile technology that enables the miniaturization of complex fluid handling and integrated detection.

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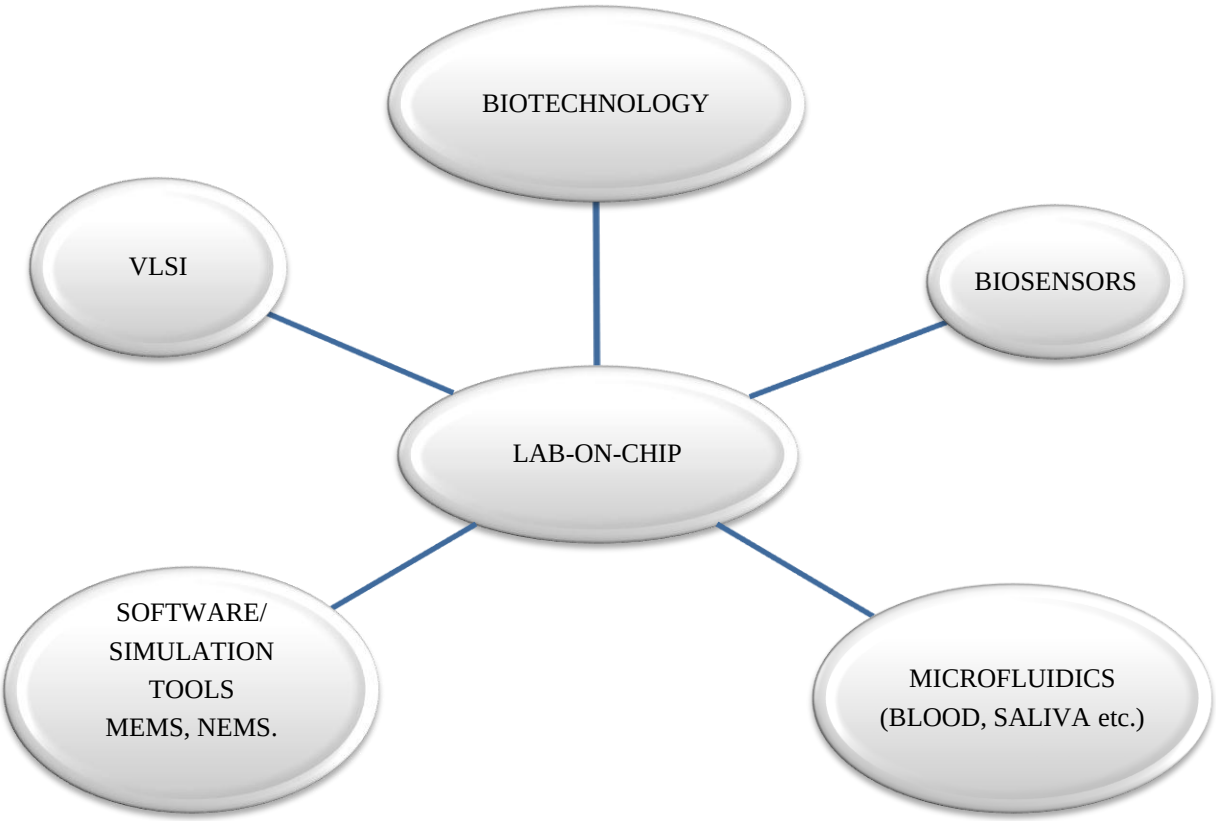

Figure 1: Interdisciplinary field of lab-on-chip.

ADVANTAGES

LOCs may provide advantages, which are specific to their application. Typical advantages are:

- low fluid volumes consumption (less waste, lower reagents costs and less required sample volumes for diagnostics)
- faster analysis and response times due to short diffusion distances, fast heating, high surface to volume ratios, small heat capacities.
- better process control because of a faster response of the system (e.g. thermal control for exothermic chemical reactions)
- compactness of the systems due to integration of much functionality and small volumes.
- massive parallelization due to compactness, which allows high-throughput analysis
- lower fabrication costs, allowing cost-effective disposable chips, fabricated in mass production.
- part quality may be verified automatically.
- safer platform for chemical, radioactive or biological studies because of integration of functionality, smaller fluid volumes and stored energies.

DISADVANTAGES

The most prominent disadvantages of Labs-on-chip are:

- The micro-manufacturing process required to make them is complex and labor intensive,

requiring both expensive equipment and specialized personnel.

- Most LOCs are novel proof of concept application that are not yet fully developed for widespread use **[6]**.
- In the microliter scale that LOCs deal with, surface dependent effects like capillary forces, surface roughness or chemical interactions are more dominant. This can sometimes make replicating lab processes in LOCs quite challenging and more complex than in conventional lab equipment.
- Detection principles may not always scale down in a positive way, leading to low signal-to-noise ratios.

APPLICATIONS OF LAB-ON-A-CHIP

Lab-on-a-chip (LOC) technology has seen spectacular growth over the years. The potential uses for LOC in medicine and health applications are unlimited. Areas such as personalized medicine, early diagnostics, and drug patenting have immensely benefitted from LOC technology. Advantages such as reduced costs, low sample volumes, and ease of use allow LOC technology to be used extensively in point-of-care diagnostics in less-developed countries. Some health applications of LOC technology are highlighted below:

Diagnosis of Infectious Diseases

One of the major applications of LOC devices is the rapid and early diagnosis of infectious diseases, especially in the developing world. This technology can be widely used in epidemiological studies conducted in developing areas due to the ease with which it can be adapted to the conditions prevailing in such countries.

Research and development is underway to adapt LOC technology to the detection of microorganisms that cause several diseases such as malaria, tuberculosis, diarrhea, pertussis, and dengue **[6]**. The disposable enterics card (DEC) is an LOC-based application that helps detect enteric infections caused by organisms such as *Escherichia coli*, *Shigella dysenteriae*, Salmonella, and Shiga Toxin-producing *Escherichia coli*. These organisms can be detected from a small amount of fecal sample on a microchip.

Handheld Diagnostics

Handheld diagnostic devices using LOC can rapidly analyze blood samples of patients and precisely detect various strains of HIV, thus allowing tailored treatment plans which are more effective and also helping to minimize drug wastage and drug resistance **[7, 8]**.

LOC-based devices are a boon to fighting diseases in the developing world as they allow mass diagnostic operations which do not require special expertise. The technology also requires only finger-prick blood samples doing away with conventional test tubes that store blood samples whilst reducing costs by requiring lower reagent volumes.

Detection of Analytes

LOC technology has been successfully used in the detection of analytes such as electrolytes in blood samples e.g. the iSTAT from Abbott Diagnostics rapidly analyzes very low volumes of blood. It contains arrays of electrodes deposited on silicon cartridges to form a biosensor. When a few drops of sample blood enter the cartridge via capillary action they are chemically treated before analysis. Following this, a handheld electromechanical device measures the concentration of electrolytes or other analytes in the blood sample.

Diagnostic Chips for Bipolar Disorder, Cancer, and Male Fertility

LOC devices have been successfully used for monitoring blood lithium levels of patients suffering from bipolar disorder and urinary sodium levels in patients with kidney dysfunction. Traditional manual methods of determining sperm count have been replaced by microfluidic chips that determine sperm concentration using electrical impedance measurements **[9]**.

These LOC-based chips allow rapid and accurate counting of sperm cells and indicate fertile and sub-fertile concentrations, thus allowing easy determination of male fertility. Early diagnosis of intestinal cancer is now possible due to a disposable LOC-inspired nanopill that detects intestinal tumors at a very early stage and passes the information to an external receiver. The low-cost device uses nanowires that can detect cancer biomarkers such as hypermethylated DNA at very low concentrations.

LOC and Smart Phones

Researchers have developed a smart phone attachment that can detect multiple infectious diseases in a few minutes from a drop of blood. Detection zones in a tiny cartridge present in the phone detect antibodies in blood that enters the cartridge thus discerning a disease.

This device was field tested by the researchers in some community clinics in Rwanda and it was used to screen 96 patients for HIV and syphilis. The results were 96% as accurate as those received from standard lab tests in detecting various infections **[10, 11]**.

The new device is cheap and uses much less power for detection and result display, making it a great tool for easy diagnostics via mobile clinics on the field. A large-scale trial is being planned for the device to establish its efficacy in the detection of infectious diseases in the developing world.

DEVICE SUBSTRATE MATERIALS

The main issues in the manufacturing techniques for microfluidic devices usually lie in the area of forming microfluidic channels, which are micro/ nanostructures. Various materials are used for the manufacture of microfluidic channels.

Silicon

Historically, microfluidic channels were patterned directly into silicon **[12]**. In general, the advantages of using silicon as a structural material include its good mechanical properties, excellent chemical resistance, well characterized processing techniques and the capability of integrating control/sensing circuitry.

Glass

Glass substrate is also used due to its excellent optical transparency and ease of electro-osmotic flow. One of the most successful examples of using glass as a substrate material in LOC applications is the capillary electrophoresis chip, which is manufactured using glass etching and fusion bonding techniques. The optical transparency is required for most LOC devices that use optical detection **[13]**.

Polymers

Nowadays, polymers or plastics have become popular materials due to their low cost, ease of manufacture, and favorable biochemical reliability and compatibility. Polymers are promising materials in LOC applications because they can be used for mass production using casting, hot embossing, injection molding and soft lithography techniques. This mass-production capability allows the commercialization of disposable LOCs. The workhorse material has been polydimethylsiloxane **[14]**.

Polydimethylsiloxane is an inexpensive, clear elastomeric polymer with rubbery mechanical properties at room temperature. Polydimethylsiloxane is mixed in small batches, poured onto moulds with micro-scale features and cured at moderate temperatures for minutes to hours. Cast microfluidics can be cut into shapes easily. Open poly-dimethylsiloxane channels are closed by adhering the channel-bearing component to a glass slide or a second, flat piece of polydimethylsiloxane. Inlets and outlets can be formed easily by using punch tools. Another way of using polydimethylsiloxane for creating channels and molds is by soft lithography. The soft lithography method is used to transfer a thin, molecular pattern onto a surface **[15,16]**. This can be done by micro stamping, stencil patterning, and microfluidic patterning. Furthermore, 3D structures can be created using multilayer lithography, whereby layers of material are sequentially added and patterned to build microfluidic systems containing valves and pumps entirely out of polymeric material

Other thermoplastics and new polymeric materials, including derivatives of polyacrylate, polystyrene, polyethylene and cyclo olefin (co) polymers, can be utilized for microfluidic-based LOC devices **[17]**.

Paper

Recently, the manufacturing of paper-based LOCs has been introduced, allowing an even cheaper and more simplified method for manufacturing LOC devices **[18]**. Paper-based LOC devices, commonly referred to as microfluidic paper-based analytical devices (μPADs), often have the ability to analyse a single liquid sample for multiple analytes.

They are more functional than traditional dipstick type paper tests. This functionality is achieved by creating pathways or channels for flow within paper sheets, allowing the formation of distinct regions that can be functionalized with chemical indicators.

MICROFLUIDIC UNIT OPERATIONS

Similar to the platforms in the application-specific integrated circuit industry in microelectronics, which provide elements and processes to make electronic circuitries, a dedicated microfluidic platform comprises a set of microfluidic elements. These elements have to be able to perform thebasic fluidic unit operations required within a given application area **[19]**.

Pumping and Valving

Microfluidic analytical systems require micropumps and microvalves enabling precise control of sample, buffer, and reagent flow and delivery. Microvalves are sometimes regarded as a part of micropumps. Micropumps and microvalves are necessary for many next-generation LOC devices that integrate features such as sample separation, complex assays that include incubation, mixing, or separation steps and more quantitative outputs. Several mechanisms have been suggested for transporting the fluids in microfluidic systems and they can be categorised in displacement and dynamic pumping. Displacement pumps exert pressure forces on the fluid through one or more moving boundaries. Micropumps can be based on reciprocating or rotary actuations or may have piezoelectric, peristaltic, (thermo) pneumatic, electrostatic and electromagnetic moving units to displace fluids **[20]**.

Electrical and mechanical micropumps are largely employed in microfluidic manipulation. Electric micropumps utilize electrokinetics, piezoelectrics, or magnetohydrodynamics, while mechanical micropumps utilize hydrodynamic pressure, thermal expansion, osmotic pressure, or other transducer or induced forces. Electrocapillary, an important electrokinetic pumping mechanism, boosted the development of lab-on-chip devices. This achievement caused the realization of miniaturized analytical instruments, namely on-chip

chromatographic systems. Other pumping mechanisms employ thermal gradients, or magnetophoresis.

Mixing

Sample dilution, resuspension of dried reagents, and reaction of multiple reagents in LOC devices often require rapid and efficient mixing. However, mixing in microfluidic platforms is difficult because flow is laminar and mixing is dominated by diffusion unless special measures are taken. Efficient micro-mixing can be achieved through a number of active and passive mixing mechanisms **[21]**. In active mixing, external driving forces such as acoustic waves, magnetic beads coupled with moving permanent magnets, or actuated air bubbles enhance the mixing of samples. In passive mixing, liquids are driven through microstructures designed to increase the contact area between different streams and to speed up diffusive or induce chaotic mixing.

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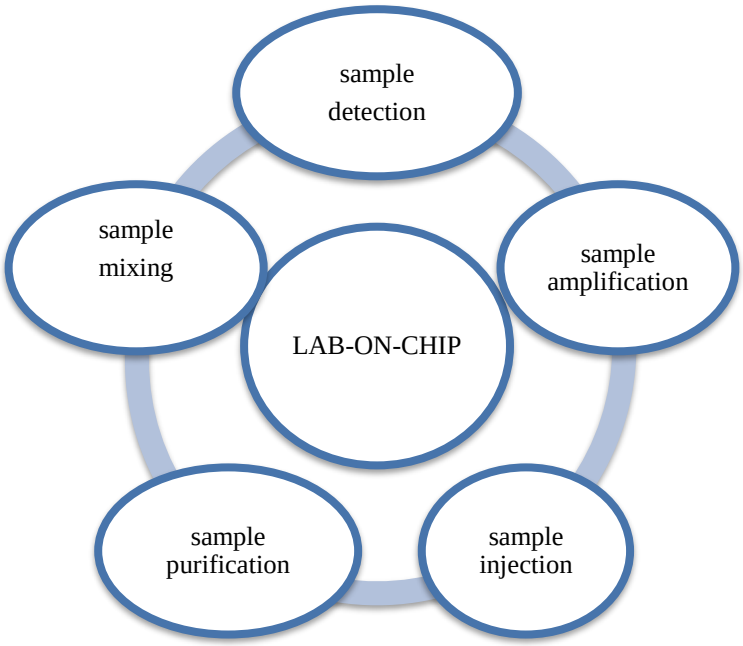

Figure 2: Basic microfluidic unit operations.

Separation

The beginning of modern microfluidic and LOC devices is closely linked to separations of (bio) chemical substances, in particular using electrophoresis. Separation is important for LOC devices because it increases the target purity by removing interfering agents prior to detection. Separation methods include capillary electrophoresis, di-electrophoresis, isoelectric focusing, liquid (electro) chromatography, size-based filtration, magnetic fields, acoustic waves, optical tweezers, and various combinations of flow, diffusion, and sedimentation based phenomena **[6]**.

Reagent Storage

For practical LOC devices, it is necessary to store reagents for extended periods on or in the device. Reagent, e.g. enzymes or antibodies, can be stored in a wet or dry state. The latter is often preferred in those cases where drying does not cause total and unrecoverable loss of activity, because reagents that are successfully dried typically exhibit improved stability relative to those stored wet **[22]**. On-chip storage of dry reagents is well-developed. Lateral flow assay strips are dry and include reagents, typically at least one type of antibody and often two, and other reagents as well. Glucose sensors include dried glucose oxidase and electron-transfer catalysts.

There is not, however, a single best process for freeze-drying, lyophilizing, or otherwise depositing and drying reagents in a form from which they are readily reconstituted. The addition of sugars, e.g. trehalose, is a widely utilized method to improve reagent stability and retention of activity **[22]**.

Large fluid volumes require off-chip storage, but small volumes can be stored within the device with appropriate sealing and release methods. Blister pack technology, well-developed by the pharmaceutical industry, has been reported as a component of LOC systems. Caution must be exercised when implementing liquid storage using polymer films,

many of which have significant permeability to water vapour. Polydimethylsiloxane is among the worst in this regard. Some fluorocarbons and cyclic olefin (co)polymers are better, and most polymers can be rendered impermeable by vacuum deposition of a thin film of metal such as aluminium.

Sample Preparation

Sample preparation, a necessary analytical step, is important in achieving adequate sensitivity and specificity in any detection platform. This is especially important in the case of complex matrices, such as blood, saliva, and interstitial fluid. Sample preparation encompasses sample concentration, diffusion, filtration, purification and fractionation of analytes from analytically noisy background matrices. Although large numbers of LOC devices accommodate unprocessed blood samples, the range of assays that can be performed is limited by the lack of well-developed on-chip sample preparation methodologies **[23]**.

Microfluidic Platforms

A microfluidic platform provides a set of fluidic unit operations which are designed for easy combination within a well-defined manufacturing technology.

Lateral Flow Tests

In lateral flow tests, also known as test strips, the liquids are driven by capillary forces. Liquid movement is controlled by the wettability and feature size of the porous or microstructured substrate. All required chemicals are pre-stored within the strip. Typically, the readout of a test is done optically and is often implemented as colour change of the detection area that can be seen by the naked eye. A common example of this type of test is the pregnancy test strip.

Linear-actuated Devices

Linear-actuated devices control liquid movement by mechanical displacement of liquid, e.g. by a plunger. Liquid control is mostly limited to a one-dimensional liquid flow in a linear fashion without branches or alternative fluid pathways. Typically, liquid calibrants and reaction buffers are pre-stored in pouches. One example of the linear-actuated device is the i-STAT® analyzer (Abbott Point of Care Inc, USA). With this portable hand-held analyser, several blood parameters, such as electrolytes and coagulation, can be measured using different disposable cartridges. The blood sample is introduced into the cartridge and placed inside the analyser. First, calibrant solution is released to provide a baseline and thereafter the sample is pushed into the measuring chamber, which displaces the calibrant solution. Blood parameters are then determined and results are displayed by the analyser **[6]**.

Pressure-driven Laminar Flow

A pressure-driven laminar flow platform is characterized by liquid transport mechanisms based on pressure gradients, usually leading to hydrodynamically stable laminar flow profiles in microchannels. There is a broad range of different implementations in terms of using external or internal pressure sources such as syringes, pumps or micropumps, gas expansion principles, pneumatic displacement of membranes, etc. The samples and reagents are processed by injecting them into chip inlets either batch-wise or in a continuous mode.

Microfluidic Large-scale Integration

Microfluidic large-scale integration describes a microfluidic channel circuitry with chip integrated microvalves based on flexible membranes between a liquid guiding layer and a pneumatic control-channel layer. The microvalves are closed or open corresponding to the pneumatic pressure applied to the control channels. Just by combining several microvalves, more complex units such as micropumps, mixers, multiplexers, etc., can be built up with hundreds of units on a single chip.

Segmented Flow Microfluidics

Segmented flow microfluidics describes the principle of using small liquid plugs and/or droplets immersed in a second immiscible continuous phase (gas or liquid) as stable micro-confinements within closed microfluidic channels. Those micro-confinements are in the picolitre to microlitre volume range. They can be transported by pressure gradients and can be merged, split, sorted and processed without any dispersion in microfluidic channels **[24]**.

Centrifugal Microfluidics

All processes in centrifugal microfluidics are controlled by rotating a microstructured substrate. This provides several relevant forces for liquid transport; centrifugal force, capillary force, Coriolis force and Euler force.

Assays are implemented as a sequence of liquid operations arranged from radially inward positions to radially outward positions. Spinning CD-like fluidic disks transport samples and reagents by the interplay of the abovementioned forces. Fluids can be pumped towards the rim of the disk at a wide range of flow rates through control of the spin speed, channel dimensions and surface energy, and various geometric details, with temporary capillary 'stop valves' opened to fluid passage simply by increasing rotational velocity **[25]**. Microfluidic unit operations include metering, switching, aliquoting, etc., and can be used for processes such as DNA extraction or plasma separation. When Newton's laws of motion are transformed to a uniformly rotating frame of reference, the Coriolis (Fc) and centrifugal forces (Fω) appear. Both forces are proportional to the mass

of the object. The Coriolis force is proportional to the rotation rate and the centrifugal force is proportional to its square. The Coriolis force acts in a direction perpendicular to the rotation axis and to the velocity of the body in the rotating frame and is proportional to the object's speed in the rotating frame. The centrifugal force acts outwards in the radial direction and is proportional to the distance of the body from the axis of the rotating frame. These additional forces are termed inertial forces. They allow the application of Newton's laws to a rotating system. For a non-uniformly rotating reference frame, when there is variation in rotation speed, the Euler force (Fe) appears.

Electrokinetics

In electrokinetics platforms microfluidic unit operations are controlled by electric fields acting on electric charges, or electric field gradients acting on electric dipoles. Several electrokinetic effects such as electro-osmosis, electrophoresis, dielectrophoresis and polarization superimpose each other and can be used in the same LOC, dependent on buffers and/or sample. For instance, for the transport of a liquid bulk electro-osmosis can be used, while other effects can be used to separate different molecules or particles from the bulk liquid. An example of this platform is the microfluidic electrophoresis chip used for DNA/RNA analysis on the Bioanalyser developed **[26]**.

Electrowetting

Electrowetting platforms use droplets immersed in a second immiscible continuous phase (gas or liquid) as stable micro-confinements. The droplets reside on a hydrophobic surface that contains a one or two-dimensional array of individually addressable electrodes. The voltage between a droplet and the electrode underneath the droplet defines its wetting behavior. By changing voltages between neighboring electrodes, droplets can be generated, transported, split, merged and processed.

Surface Acoustic Waves

The surface acoustic-waves platform uses droplets residing on a hydrophobic surface in a gaseous environment (air). The microfluidic unit operations are mainly controlled by acoustic shock waves travelling on the surface of the solid support. These shock waves are generated by surrounding sonotrodes, defining the droplet manipulation area.

MICRO-CONSTRUCTION TECHNIQUES

Traditional Lithographic Techniques

Micro-device construction techniques began as a zeta offshoot of the computer chip processing industry, in which hard substrates, most commonly silicon, are used as the primary construction material. The basic paradigm of standard lithographic techniques involves the use of electromagnetic radiation, typically ultraviolet (UV) light, to transfer a pattern to a surface, such as silicon, covered with photoresist **[12]**. The ‘‘mask’’ that contains the pattern can be as simple as an overhead with the desired design printed on it or more elaborate, such as a chrome mask. The pattern is transferred to the photoresist- covered surface by shining electromagnetic radiation through the mask onto the surface. Typically ultraviolet (UV) light is used, although electromagnetic waves with narrower wavelengths, such as X-rays, have been used to achieve a finer resolution. The photoresist is then developed such that the areas exposed to the electromagnetic radiation behave in an opposite manner to unexposed areas; one set of areas polymerizes and remains on the surface while the other set is washed away. Now that the mask has been transferred to the surface, any one or a number of surface modification techniques, or a sequence of techniques, can be deployed. Chemical etchants, in which exposed surfaces are ‘‘eaten away’’ while protected surfaces remain, are one example of surface modification techniques. Glass and silicon are the two most typical substrates used for fabricating **[13]**.

Photolithographic development of microelectrodes and microchannels on a wafer substrate:

(a) metallization of the substrate by sputtering a metal film of Au, Pt, or ITO;

(b) spin coating of photosensitive resist film onto the metal film;

(c) exposure of the photosensitive film via a photomask that results in the transfer of the desired electrode patterns onto the photosensitive film;

(d) after photo-development, chemical etching removes the bare metallized areas, which results in the formation of the electrodes;

(e) spin coating of an SU8 photoresist layer;

(f) exposure of the SU8 photoresist film via photomasks and development;

(g) chemical etching and removal of the unwanted SU8 resist. The revealed half microchannel has sidewalls made of the SU8 material.

Soft Lithography

Soft lithography is an alternative fabrication technique, based on direct printing or molding of polymers. In soft lithography, instead of stiff photomasks, elastomers are used as stamps, molds, or masks, in order to replicate patterns (**Figure. 6**). In soft lithography the silicone elastomer PDMS (polydimethylsiloxane) is widely preferred because of its easiness to cast, its biocompatibility, hydrophobicity, and sealing properties **[27]**. Soft lithography is recommended only for rapid prototyping in research. Because of the soft materials used in soft lithography, distortions of stamps and molds are problems that prevent soft lithography from becoming a viable manufacturing technique.

For example, the widespread PDMS swells when it comes in contact with oleic solvents.

Sequential steps of the soft fabrication process, which can produce features of a few hundreds of microns:

(a) a hard master substrate made of metal, glass or plastic, casts on a mold material which can be polymer, thermoplastic, PDMS or PMMA;

(b) upon heating and pressurization the mold deforms to the shape of the master;

(c) lifting off the master reveals the microchannels

Diagnostic Targets

Proteins

Current LOC devices utilize immunoassay technology, including antigen-antibody binding. These assays target disease-specific protein markers, such as glycated haemoglobin (HbA1c) for diabetes, C-reactive protein (CRP) for inflammation indicating cardiovascular disease, D-dimer for thrombosis, and troponin I or T for cardiac damage, prostate-specific antigen for prostate cancer, bacterial and viral infection-related markers such as human immunodeficiency virus (HIV), influenza, chlamydia, and hepatitis **[6]**.

The best-known protein-detection device, the pregnancy test kit, measures the pregnancy hormone human chorionic gonadotropin. The test's key component is the lateral flow strip. Currently, Bio-Alternative Medical Devices Ltd (UK) is developing a next-generation pregnancy test utilizing a technology for reading and quantifying traditional chromatography-based lateral flow immunoassay tests. The design incorporates novel sensors, diagnostics, display, and power management capabilities.

Metabolites and Small Molecules

Metabolites are products of chemical processes that generate energy, nutrients or wastes. Because of the similarities in their physiological transport and detection approaches for LOC assays, they are grouped together with blood ions (Na+, K+, Cl-, etc.) and small-molecule organic substances, including non-protein hormones, e.g. epinephrine and cortisol. Levels of these molecules are often diagnostic indicators of disease. The current panel of metabolites most often targeted by POC diagnostic are glucose, cholesterol, triglycerides, creatinine, lactate, ammonia, and urea **[6]**.

The best-known metabolite, glucose, enables the diagnosis and management of diabetes mellitus. Glucose biosensors account for approximately 85% of the entire biosensor market **[28]**. Diabetic complications are controllable with tight regulation of glucose levels. Most diabetic patients now regulate their condition at home using hand-held blood glucose meters that analyse a small capillary blood sample.

A prominent and one of the early LOC devices for blood analysis is the i-STAT® system (Abbott Point of Care Inc, USA). This hand-held system carries out different analyses (depending on which cartridge is loaded) ranging from ions, carbohydrates (glucose and lactate), blood gases (pO_2 and pCO_2) to peptides (brain natriuretic peptide), proteins (thrombin) and other blood indicators such as haematocrit.

Analytes are detected at clinically relevant levels in 65 µl whole blood samples within two minutes **[29]**. The cartridge contains a fluidic system for sample distribution to different thin-film electrodes measuring analytes via conductivity or ion-selective electrode potentiometry, depending on the analyte type.

Nucleic Acids

Nucleic acid diagnostics, often referred to as molecular diagnostics, measure DNA or various types of RNA in order to assay particular genomic or genetic details of a patient or to assay nucleic acid sequences unique to invading pathogens. Polymerase chain reaction (PCR) and numerous other methods of selectively copying ('amplifying') preselected nucleic acid sequences are often part of such assays. These tests are one of the most challenging assays to develop due to additional steps required for sample pre-treatment (e.g. cell sorting, isolation, lysis and nucleic acid extraction), signal amplification, and target contamination and instability **[30]**.

Pathogens

Bacteria, viruses and parasites are important analytical targets, particularly those that cause infectious diseases **[31]**. Rapid identification of the causative pathogen of an infection can reduce treatment costs, reduce suffering, help systems against spreading of disease, and save lives. Because species and strain identification is required, pathogens are often diagnosed using nucleic acid identification. In some cases, immunoassays are utilized for the diagnosis via the specific antibodies that are present in an infected host.

Cells

The identification and enumeration of specific (human) cells in blood and other samples is a rapidly expanding field in POC diagnostics. In addition to basic blood cell counting, it has been widely recognized that POC cell assay-based devices could implement diagnostic and prognostic testing for infectiousdiseases, cancers, inflammatory responses and haematological parameters **[30]**.

DETECTION PRINCIPLES

The detection principles for sensors on microfluidic-based LOC devices are classified into several types, including optical, electrochemical, magnetic and mass sensitive methods. The trend in the development of detectors has been to pursue two key

qualities: sensitivity and selectivity, aiming to minimize the numbers of false negatives and false positives.

Optical Detection

Conventional optical detection methods, including absorbance, fluorescence and chemiluminiscence, have all been applied in LOC devices. Miniaturizing devices that use optical detection is generally difficult because of the expensive hardware it requires. Furthermore, due to the shorter optical paths through the sample, sensitivity is reduced and increased noise from non-specific adsorption to the walls of the chamber can be caused by a lower surface-to-volume ratio **[32]**. To address these issues, many integrated optical systems are being explored in which new techniques are integrated onto the microfluidic device to reduce costs and increase sensitivity.

Electrochemical Detection

Electrochemical detection methods can be divided into three types of measurements, namely amperometric, potentiometric, and impedimetric measurements. The most commonly used biosensors are amperometric ones. Typically, they generate current in proportion to the concentration of the detected analyte, used for instance in glucose assays.

Potentiometric detection examines the difference in potential between two reference electrodes separated by a selective permeable membrane. Impedimetric biosensors operate by measuring the change in impedance caused by changes in resistance at the sensor [**33**]. Depending on the target analyte, all three detection methods can be used by the modern version of the i-STAT® system **[30]**.

Magnetic Detection

Magnetic particles can be used to concentrate and localize analytes. Moreover, they can be used as labelling technology for detection without the requirements of fluorescent dyes. Stimulated by advances in memory devices, magnetic particle detection technology has evolved rapidly, the most promising and sensitive methods now using the giant magnetoresistance (GMR) effect, with detectors based on so-called spin valves or magnetic tunnel junction methods **[6]**.

Philips Research (the Netherlands) reported the development of a compact biosensor platform to detect biomolecules with superparamagnetic particles labels using GMR sensors. The silicon detection chip is packaged in a disposable cartridge that integrates electrical connections for readout and fluidic subsystem. Recently, sensitive detection of amplified DNA on this system was reported using a miniaturized detection platform suitable for POC application **[34]**.

Mass Sensitive Detection

Mass sensitive detection entails the recognition of molecules based on their mass. The detector gives a response that is proportional to the mass of the molecules or materials. Mechanical transducers for POC applications oscillate or resonate. These include micro- and nanocantilevers **[35]** as well as various acoustic wave devices such as the quartz-crystal microbalance and a range of the surface acoustic wave family **[36]**. Operating characteristics such as frequency and signal attenuationfor piezoelectric devices are affected by the mass and mechanical properties of molecules and materials linked to their oscillating surfaces.

LOC TECHNOLOGIES

Chemical Analysis

Chemical analysis of samples is mostly done using chromatographic separation techniques, such as high performance liquid chromatography with ultraviolet detection or mass spectrometry detection, or gas chromatography with mass spectrometry detection. As stated in the introduction, one of the first LOC applications to be developed was the µTAS. Using this system, chemicals were separated for analysis with capillary electrophoresis **[13]**. The sample is electro-osmotically transported and metered inside the chip, then separated via capillary electrophoresis and analysed by fluorescence detection. Zhang *et al.* (2007) described a method for the detection of morphine and codeine in human urine using electrochemical detection as well. A polydimethylsiloxane microchip with electrochemical detection was developed for rapid separation and detection of trace amounts of these two compounds. It was found that morphine and codeine were well separated within 140 s. Compared with the conventional methods, the presented method had several advantages such as lower instrument cost, less reagent consumption and shorter analysis time **[37]**.

More recently, chemical analysis technology for LOC purposes is being implemented for the detection of, among many others, blood gasses, electrolyte analyses and lactate determination **[38]**.

Immunoassay-based Technologies

Immunoassay-based technologies are mostly used for detection of specific protein biomarkers for disease or infection. These immunoassays comprise the binding of a specific antibody to a unique site on a target biomarker (antigen). The generation of a signal resulting from antigen capture is predominantly realized by some type of label on a secondary reaction antibody. There are many different types of antibody labels and selection is dependent on the specific detection methodology. These include fluorescent labels, enzymes for catalysis of colour

changing/redox reactions, paramagnetic particles (inductance/magnetic field based measurement) and metallic colloids as surface enhanced Raman spectroscopy probes **[33]**. Commercial antibody-based POC devices have most commonly used traditional lateral flow technology. One basic example, as previously mentioned, is the pregnancy test to detect the hormone human chorionic gonadotropin. A simple colour reaction shows if the protein is present in the urine sample. Immunofiltration is another application of an antibody-based detection method. The sample is filtrated through porous membranes containing immobilized antibodies that can detect the analyte of interest. This principle is applied in the NyoCard and Afineon systems from Axis-Shield to identify CRP and HbA1c, among other things.

Currently, steps are being taken to increase the sensitivity of immune-based assays. An approach has been developed that combines the single molecule sensitivity of enzyme-linked immunosorbent assay (ELISA) with microscopic bead encoding techniques to provide highly sensitive, multiplexed detection of proteins **[39]**.

DNA/RNA-based Technologies

Miniaturized nucleic acid amplification systems are essential for the development of genetic marker-based POC diagnostics **[40]**.

PCR is a process for amplifying short regions of interest in DNA using an enzyme-based method. With the use of repeated cycling steps of denaturation, annealing and elongation for DNA replication, millions of copies can be created. Improvements in thermal cycling speed, instrument size, and reaction volume are necessary for POC applications. The bulky instrumentation and large reaction volume required in conventional benchtop thermal cyclers lead to large thermal mass, which reduces the temperature transition speed and reaction efficiency. These shortcomings can be addressed through miniaturization in a so-called microPCR system. This refers to a microfluidic chip with microlitre or nanolitre volume size chambers for the execution of single or multiple PCRs. These systems can be classified in two major principles, the static chamber PCR and flow-through PCR. In static chamber PCR, the temperature of the chamber containing the sample and PCR reagent is cycled and, in flow-through PCR, the reagent travels through different chambers with various temperatures **[41]**.

Before the PCR steps can take place most of the time, nucleic acids need to be extracted and purified from the sample. Many current methods for lysing cells that are used can be divided into four groups. (1) Mechanical lysis employs cellular contact forces to crush or burst the cells. One method for mechanical lysis is to force the cell through a filter with openings too small for a whole cell to pass through, thus shearing the cell membrane. Walls may even include sharp 'microknives', causing cell rupture and release of cell content. Another basic method is simply to burst the cells by deforming the cell to the point that the membrane bursts. One such method uses a polydimethylsiloxane membrane to crush cells and break their membranes. (2) Thermal lysis uses high temperatures to disrupt the cell membrane. (3) Chemical lysis uses a chemical buffer, such as sodium dodecyl sulphate, or enzymes to break down the cell membrane. (4) Electrical lysis induces cell membrane porosity with a low-strength electric field or complete lysis of the cells with a stronger field **[23]**. After lysis the nucleic acids can be extracted using differentextraction techniques, which can be categorized as different methods; silica-based surface affinity, electrostatic interaction, nanoporous membrane filtration, and functionalized microparticles **[23,42]**. Integrated microsystems that simultaneously implement cell sorting, cell lysis and DNA purification steps have been developed and used **[43]**.

However, with new methods, DNA detection can take place with the raw samples. Recently, Manage *et al*. (2013) described the use of an in-gel PCR cassette with multi-target and multi-sample detection. The cassette contains capillary reaction units and is configured in a format for testing simultaneously up to 16 patients for two or more targets. It accommodates different sample types on the same cassette, has integrated positive and negative controls, and allows flexibility for multiple geometries. PCR reagents in the cassette are desiccated to allow storage at room temperature with rehydration by raw sample at the time of testing. The sample is introduced to the cassette via a transfer pipette simply by capillary force. DNA amplification is done in a portable instrument for PCR thermal cycling with fluorescence detection of amplified products. This platform allows multiparameter clinical testing with a pre-assembled cassette that requires only the introduction of a raw sample **[44]**.

Nucleic-acid-based LOC technologies can be used for identification of pathogens [**26**], but may also be of use in personalized medicine.

Flow Cytometry

Flow cytometry has become a very powerful tool for cell-based assays. It is routinely used in diagnostics to quantify (counting), isolate and examine cells (e.g. different subtypes of lymphocytes) according to their size, granularity and expression of specific surface antigens **[45]**. There are three key components of a typical flow cytometer, the first being a fluidic mechanism that causes all of the cells in a suspension

to line-up in a single file as they flow down a channel. The second key component is a set of detectors (such as lasers of different wavelengths) that can probe individual particles, along with the fluid stream, flowing past the detector and obtain information (such as whether a given cell has taken a particular fluorescent dye) that indicates one or more specific properties of the cell. This information, along with the known velocity of the cell travelling down the channel, can then be taken advantage of by the third key component of the flow cytometer to steer target cells to specific downstream collection chambers. Although conventional state-of-the-art flow cytometers can measure and subsequently sort particles based on a combination of as many as ten parameters and/or achieve throughputs as high as ~10,000 cells per second, they do suffer from serious drawbacks. Besides requiring expert operators, they also require large volumes of sheath fluid (~1 l of sheath fluid per 1 ml of sample) and high performance pumping systems to operate, thereby making them non-portable and expensive for routine diagnostic procedures in the clinical setting. In addition, modern fluorescence-activated cell sorters are usually expensive.

To overcome these limitations, much effort has been put into the development of microfluidic flow cytometry. Miniature versions of flow cytometers can replace conventional glass capillary-based systems with microfluidic chips that employ integrated optics and hydrodynamic or electrokinetic-based flow-switching systems for collecting cells of interest. Examples of commercial benchtop flow cytometers are the Agilent 2100 Bioanalyzer® (Agilent Technologies Inc, USA) and the Cyflow® Space (Partec GmbH, Germany). Portable flow cytometers are the CyFlow® miniPOC (PartecGmbh, Germany) and the Alere Pima CD4 Analyser (AlereInc, USA).

FUTURE SCOPE

New lab-on-chip devices must emerge that demonstrate a positive impact on clinical diagnostics. The trend is to improve sterility, multiple analysis and parallel processing with increased efficiency and speed. Future lab-on-chip devices will consume ultralow power, will be smaller and lighter with more emphasis on the user comfort. Improvements in portability should emphasize easy sample introduction and fluidic connectivity. Communication technologies like wireless networking, information management and advanced user interface, visualization and navigation technologies through adapted screens will be embedded. Standardization will condition device reliability, interoperability, biocompatibility, electromagnetic compatibility, interconnectivity, readouts, weight and size. The functionality of future lab-on-chip devices is foreseen to improve clinical tests and will be shifted from general-purpose laboratory instruments to strictly personalized devices. To date the lab-on-chip devices are determined by applications in bioanalysis. Additionally to mixing, measuring, sorting or separation, microfluidic lab-on-chips are foreseen to facilitate on-chip supramolecular chemistry, biomedical implants, biomimetics, and hybrid systems incorporated with blood vessels. Future applications will certainly include nanobiotechnologies. Envisions consider nanoscaled channels, where surface effects, rather than volume, dominate liquid behaviour. Chemical synthesis of macromolecules will be actualized molecule-by-molecule, ensuing fully controllable and accurate synthesis of bioproducts, independent of the constraints of statistics and diffusions parameters that rule present chemistry in vessels. Experts claim that the complexity of lab-on-chip devices is increasing at rates comparable to Moore's law. Most of the present lab-on-chip devices operate with external computing units. The future trend is to develop fully standalone lab-onchip devices with embedded computing and calibrating capabilities. Further development of microfluidic biocomputers will take place that will use biological macromolecules, such as nucleic acids or proteins, to perform computations including storing, retrieving, and biological data processing through application of biochemical principles. DNA computation employs massive parallelism inherent in the small scale of molecules to speed up decisions. The hybridization 130 of nucleic acids can be either exploited to encode strands of nucleotides to clone nucleic acids, or to self-assembly oligonucleotides. Emphasis is given to improving methods for hybridization by surpassing various physicochemical constraints and use DNA to compute in environments where it is uniquely capable of operating, such as smart drug delivery to individual cells. Further variations in biocomputing use proteins instead of nucleic acids, or DNA hairpin formation, self-assemblies and cellular computation, in which cells are considered computational elements. Networking individual lab-on-chip devices is foreseen to boost lab-on-chip functionalities, as information can be exchanged between individual devices via computer servers in hospitals. Experts speak about interconnecting lab-on-chips to the patients' databases for online updating their medical records and to perform classification of the diseases. Networking biochips can benefit telemedicine, where lab-on-chip testers will be capable of transferring test results to doctors entirely remotely. The upcoming generations of lab-on-chip devices will be cabled or wirelessly interconnected in network-centric data links, being synchronized as terminal testers for the

same or different patients, located at a distance. In rural and urban areas lab-on-chip technology can contribute to ubiquitous monitoring the diseases, pathogens, or toxic substances in the environment. For example, miniaturized biochemical marine sensors, submerged in seawaters, can sample contaminants in the oceans. The functionality of such environmental biochips is based on various principles including monitoring oxygen levels, cell analysis of phytoplankton, observation of methane, nitrate and phosphates in seawaters. Moreover, autonomous integrated biochips may be distributed in public areas, in buildings, airports, subways, parks, stadiums, schools, and stores, to collect biochemical information and detect the onset of major infectious pathogens or record signs of pollutions, either on air, sea or land. The impact of lab-on-chip devices in everyday life is expected to be analogous and as revolutionary as integrated circuits and microelectronics. Lab on-chip devices will irrevocably influence medicine, chemistry, biology, biotechnology and bioelectronics.

Table 1: Companies and LOC devices.

Company	Country	Name of device/chip/system	M/D	Application
AbaxisInc	USA	Piccolo® Xpress	M	blood analysis
Abbott Diabetes Care Inc	USA	FreeStyle Lite®	M	blood glucose
Abbott Point of Care Inc	USA	i-STAT®	M	cardiac markers, blood gases, electrolyte analyses, lactate, coagulation, haematology
Abbott Point of Care Inc	USA	i-STAT® 1 Wireless	M	cardiac markers, blood gases, electrolyte analyses, lactate, coagulation, haematology
AlereInc	USA	Alere Triage® MeterPro	M	BNP, CK-MB, D-dimer, myoglobin, NGAL, troponin I, PLGF
AlereInc	USA	Alere™ INRatio® / INRatio® 2	M	Anticoagulation
Arkray Global Business Inc	Japan	GLUCOCARD 01	M	blood glucose
Axis-Shield plc	UK	Afineon	M	CRP, HbA1c, ACR, lipid
Atonomics A/S	Denmark	Atolyzer	D	cardiovascular disease, prostate cancer
Axis-Shield plc	UK	NyoCard	M	CRP, HbA1c, D-dimer, U-albumine
Bayer Diabetes Care	Switzerland	CONTOUR® XT	M	blood glucose
Bayer Diabetes Care	Switzerland	CONTOUR® NEXT USB	M	blood glucose
Bayer Diabetes Care	Switzerland	CONTOUR® USB	M	blood glucose
BD Biosciences	USA	BD FACSCount™ System	M	HIV diagnostics / CD4 count
BD Biosciences	USA	BD FACSCalibur™ System	M	HIV diagnostics / CD4 count (research
Bio-Rad Laboratories Inc	USA	in2it™ A1C	M	boronate affinity chromatography
Biosurfit SA	Portugal	spinit®	D	blood tests, CRP test
Burnet Institute	Australia	Semi-quantitative CD4 Test	D	HIV diagnostics / CD4 count
Cardinal Health	USA	Cardiac STATus™ Test	M	hand-held cardiac marker bedside test
Cepheid	USA	GeneXpert System®	M	pathogen / biomarker detection
Clearbridge BioLoc Pvt Ltd	Singapore	AssayQuest™	D	ELISA
Daktari Diagnostics	USA	Daktari™ CD4 Counter	D	HIV diagnostics / CD4 count
DiagnoSwiss SA	Switzerland	immuDrop™	M	generic system for the detection of biomarkers
DiagnoSwiss SA	Switzerland	immuSpeed™	M	generic system for the detection of biomarkers
DNA Electronics	UK	Genalysis®	D	single nucleotide polymorphisms; microchip-based technology
EKF Diagnostics Holdings plc	UK	Lactate Scout+	M	Lactate
EpocalInc (Alere)	Canada	epoc™	M	blood chemistry
F. Hofmann-La Roche Ltd	Switzerland	Accu-Chek® Aviva	M	blood glucose
F. Hofmann-La Roche Ltd	Switzerland	Accu-Chek® Aviva Nano	M	blood glucose

F. Hofmann-La Roche Ltd	Switzerland	Accu-Chek® Performa	M	blood glucose
F. Hofmann-La Roche Ltd	Switzerland	Accu-Chek® Performa Nano	M	blood glucose
F. Hofmann-La Roche Ltd	Switzerland	Accu-Chek Active®	M	blood glucose
F. Hofmann-La Roche Ltd	Switzerland	Accu-Chek® Compact Plus	M	blood glucose
F. Hofmann-La Roche Ltd	Switzerland	Accu-Chek® Mobile	M	blood glucose
F. Hofmann-La Roche Ltd	Switzerland	Accu-Chek® Inform	M	blood glucose (hospital setting)
F. Hofmann-La Roche Ltd	Switzerland	Accutrend® Plus	M	blood glucose, cholesterol, triglycerides,
F. Hofmann-La Roche Ltd	Switzerland	CoaguChek® XS	M	PT/INR value (home)
F. Hofmann-La Roche Ltd	Switzerland	CoaguChek® XS Plus	M	PT/INR value (physician's practice)
F. Hofmann-La Roche Ltd	Switzerland	CoaguChek® XS Pro	M	PT/INR value (high throughput anticoagulation centre& hospital setting)
F. Hofmann-La Roche Ltd	Switzerland	cobas b 123 POC	M	blood gases
Focus Diagnostics Inc	USA	3M™ Integrated Cycler	M	pathogen detection (real-time PCR)
GenefluidicsInc	USA	Asklepios	D	proteins, nucleic acids and small molecules (research use)
Gyros AB	Sweden	GyrolabxP&Bioaffy® CDs	M	protein quantification
Helena Laboratories	USA	Cascade POC Analyzer	M	haemostasis assays
HologicInc	USA	TLiIQ® System	M	fetal fibronectin test
Innovative Biosensors Inc	USA	BioFlash-Dx™	M	pathogen detection
IQuumInc	USA	Liat™ Analyser	D	HIV diagnostics / CD4 count
Kernel Int'l Corp	Taiwan	MultiCheck™ ET-222	M	blood glucose, Hb
Kernel Int'l Corp	Taiwan	MultiCheck™ ET-202	M	blood glucose, Hb
Kernel Int'l Corp	Taiwan	MultiCheck™ ET-102	M	Cholesterol
Kernel Int'l Corp	Taiwan	MultiCheck™ ET-101	M	blood glucose
LifeScanInc	USA	OneTouch® Ultra®2	M	blood glucose
LifeScanInc	USA	OneTouch® UltraMini®	M	blood glucose
LifeScanInc	USA	OneTouch® UltraSmart®	M	blood glucose
LifeScanInc	USA	OneTouch® Verio™IQ	M	blood glucose
LifeScanInc	USA	OneTouch® Verio™Pro	M	blood glucose
Macherey-Nagel GmbH & Co KG	Germany	URYXXON® Relax	M	Urine analysis
Macherey-Nagel GmbH & Co KG	Germany	URYXXON® 500	M	Urine analysis
MBio Diagnostics	USA	MBio™ Diagnostics CD4 System	D	HIV diagnostics / CD4 count
MBio Diagnostics	USA	MBio™ Array System	D	multiple immunoassays; infectious, diseases applications
Magna Diagnostics GmbH	Germany	MAZER™	D	technology based on magnetic nanoparticles
Medimate BV	Netherlands	MedimateMultireader®	M	bipolar disorder, chronic kidney disease,
Menarini Diagnostics	Italy	Glucocard Memory 2	M	blood glucose
Menarini Diagnostics	Italy	Glucocard Memory PC	M	blood glucose
Menarini Diagnostics	Italy	GlucoMen® Lx	M	blood glucose & ketone
Menarini Diagnostics	Italy	GlucoMen® Lx Plus	M	blood glucose
Menarini Diagnostics	Italy	GlucoMen® Gm	M	blood glucose
Menarini Diagnostics	Italy	GlucocardXmeter	M	blood glucose
Menarini Diagnostics	Italy	StatStrip™	M	blood glucose (hospital setting)

Menarini Diagnostics	Italy	Aution MICRO	M	urine analysis
Micronics Inc	USA	ABORhCard®	M	blood type identification
Micronics Inc	USA	PanNAT™	M	single and/or multiplexed nucleic acid amplification assay
MycroLab Diagnostics Pty Ltd	Australia	Micro®Card	D	complete assay process on-card
NanomixInc	USA	Sensation™ technology	D	troponin I
NanomixInc	USA	Nanomix Asthma Management System	D	asthma; carbon nanotube electronic detection platform
Nipro Diagnostics Inc	USA	TRUEresult®	M	blood glucose
Opko Health Inc	USA	4Kscore™	M	kallikrein biomarkers
Partec GmbH	Germany	CyFlow® miniPOC	M	HIV diagnostics / CD4 count
Partec GmbH	Germany	CyFlow® Space	M	HIV diagnostics / CD4 count (benchtop analyser)
Philips Healthcare	Netherlands	Minicare	D	cardiac damage
Response Biomedical Corporation	Canada	RAMP	M	cardiac biomarkers (troponin I, NT-proBNP)
Siemens AG	Germany	DCA Vantage™ Analyzer	M	HbA1c
Siemens AG	Germany	Stratus CS Acute Care	M	cardiac biomarkers
Siemens AG	Germany	CLINITEK Status®+ Analyzer	M	urine analysis
Siemens AG	Germany	RAPIDPoint340/350	M	blood gases, electrolytes
SpinChip Diagnostics AS	Norway	-	D	blood analyses; proteins, cells, DNA/RNA, nutrients, drugs
STmicroelectronics	Switzerland	In-Check™ platform	M	PCR micro-reactor
TearLab Corporation	USA	TearLab™ Osmolarity System	M	dry eye disease, ocular allergy
Taidoc Technology Corporation	Taiwan	TD-4116	M	blood glucose
Taidoc Technology Corporation	Taiwan	TD-4257A	M	blood glucose
TREND Pharma GmbH	Germany	TESTAmed® GlucoCheck Plus	M	blood glucose
TREND Pharma GmbH	Germany	TESTAmed® GlucoCheck Advance	M	blood glucose
Vital Diagnostics	Australia	Eon™ One	M	serum, plasma, whole blood (HbA1c), urine

CONCLUSIONS

The most appropriate materials, fabrication techniques and assembling methods for manufacturing lab-on-chip devices were reviewed in this article. Lab-on-chip devices must be made of materials that are biocompatible, chemically inert, reliable and reusable for lifetime. Presently, gold or platinum are most suitable for structuring conductive elements. Fluoropolymers and silanes are the most suitable for hydrophobizing fluid-solid interfaces. Oxidegrown films or plasma-deposited films, particularly the thermally or anodically grown SiO2 and Ta2O5, are the most efficient for insulating the conductive elements of the lab-on-chip devices.

Highly reliable lab-on-chip devices are still a long way ahead. The complexity and technological problems to be solved are enormous. Major obstacle is the technological limitation of the present micofabrication materials. Until new revolutionary materials are introduced, any tremendous development in comparison to the present state should not be expected. To date development of lab-on-chip devices is analogous to the state of the electronics before the discovery of semiconductors. However, once new synthetic materials become available, especially new nanomaterials, an enormous boost, analogous to this of microelectronics in the semiconductors era, is anticipated. It means that lab-on-chip designers are awaiting innovations from material science and chemistry to solve reliability, biocompatibility and integration problems. Furthermore, lab-on-chip technology acquires improvements in the device production methods, and is forecasted to acquire specific technologies from physical sciences and other disciplines of engineering, as well as from biology.

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