Lab-on-a-Chip Devices and Opportunities for Latin America and the Caribbean

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***Abstract*– Lab on a chip devices are an alternative for accessible, cost-effective and early detection medical tests. MEMS technologies provide possibilities for reduction of reagent volume, sample size and fast in-situ diagnosis. This review summarizes the main working principles and applications of Lab on a Chip devices and their potential for strengthening research at higher education facilities and improving the health systems in Latin America and the Caribbean.**

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I. Introduction

Scaling of physical phenomena leads to devices with lower power consumption, higher efficiency, lower weight and cost. The miniaturization capabilities offered by microfabrication techniques enable reduction of reagent and sample volumes for medical and biochemical diagnosis. Lab on chip devices have arisen as a response to the necessity of low cost, time effective, automated laboratory tests by integrating one or more functions in one miniaturized device, such as sample transport, precise extraction of small sample volumes (down to pL), reagent mixing, heating, evaluation, analysis, synthesis and quantification for medical, biotechnological, chemical, biological, aeronautics and environmental monitoring applications. This review summarizes the main working principles and components of Lab on Chip devices and presents their applications, challenges and market

The idea of a technology for a device unifying data acquisition and measurement together with sensing and analysis and a response to analysis results was brought into practice for the first time in 1979 at Stanford University with the development of a gas chromatograph fabricated on a 2-inch silicon die [1]. This is considered the first Lab on chip device. By the late 80s and early 90s, Lab on chip technology experienced a fast development especially in Europe, with the development of total analysis microsystems (μTAS) [2]. These systems were originally designed for improving chemical separation techniques, particularly capillar electrophoresis [3] and were later applied in experiments with biological material, DNA and RNA, proteins, cells and bacteria, taking benefit of PDMS technology and motivated by the potential market for biomedical tests..

In 1999, Agilent Technologies and Caliper Technologies Corporation jointly introduced the first commercial Lab-on-a-chip device, intended for protein analysis [4]. In 2012, the Lab on a chip and microarrays market was $2.73 billion, and the forecasted market size for 2018 is $14.49 billion [5], whereas other forecast announces the lab on chip market size to grow a factor of 4 from the 2013 value, reaching $5.7 billion by 2018[6].

II. Working principles of lab-on-a-chip devices

Lab-on-a-chip technology may include sensors and actuators; pumps, valves and microsensors play a key role in these systems. In the following sections, an overview of their working principles is presented.

A. Micromixers

One of the main important tasks of Lab-on-a-chip systems for short-time chemical reactions is mixing. The reduced dimensions of Lab on a chip devices lead to Reynolds numbers minor than 1, that is, laminar flow regime. As a consequence, mixing is slow and caused by diffusion. To solve this issue, several mixing mechanisms have been developed, applying energy to the flux or a microarray mixer, zig-zag, serpentine or T-shape mixers. Mixing efficiency will depend on the ratio of micromixer´s number of teeth per unit length to channel diameter and turn angle.

B. Micropumps

Micropumps are responsible for fluid transport along the device´s microchannels. They can be in direct or indirect contact to the fluid. Its actuation mechanism can be mechanical or non-mechanical. Mechanical micropumps are based on a mobile part, usually implemented by means of a diaphragm that transmits pressure to the fluid in a container chamber. The actuating principle of the diaphragm can be piezoelectric, pneumatic, electrostatic and electromagnetic. On the other hand, non-mechanical pumps can also be implemented, with the main advantage of eliminating mobile parts. Micropump fabrication is mainly based on photolithography, anisotropic etching and ionic bonding. PDMS and glass are common materials. Ionic bonding is used for silicon-glass systems, whereas PDMS-silicon systems are

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bonded by means of UV radiation. In both cases is necessary to control pressure to ensure correct, permanent sealing. Other common materials are glass and Parylene. Table I summarizes and compares the main working principles and characteristics of micropumps. As can be observed in Table I, there are several physical effects which can be implemented on PDMS, glass and PMMA substrates; among these surface tension, electrostatic and thermal micropumps have the advantages of low cost and ease of fabrication.

C. Microvalves

Microvalves regulate flux into the channels by restriction of fluid paths. This is achieved by changing its direction, mixing or decreasing flux. According to the presence or absence of external actuation, valves can be classified in active or passive, respectively. Active valves require an actuator causing a force on a mobile valve part, allowing or blocking fluid flow. Passive valves rely on a flux opposing element or a reduction of channel diameter and thus are easy to fabricate. Table II presents a summary of the working principles of MEMS microvalves and their comparison.

Considering active valves, the fabrication complexity and materials reported narrow the implementation options. Ease of fabrication and low cost materials can be obtained applying mainly by electrostatic effects or memory shape alloys.

D. Microsensors

Microsensors can be classified as electrochemical, optical, piezoelectric and mechanical. Lab-on-a-chip microsensors usually require consideration of temperature, pressure and compatibility with chemical and biological samples to avoid interferences in the measurement or sensor degradation. Common electrode materials for biosensors are platinum, gold, silver, stainless steel and PEDOT-covered gold [53, 54] due to their low conductivity, good mechanical characteristics, chemical inertness and large operating voltage range. Lab-on-a-chip can benefit from PEDOT-covered gold, which offers the advantage of lower impedance in the low frequency range.

For the immobilization of biological elements, materials forming links between biocatalytic species or proteins are required, such as glutaraldehydes and hexamethyl diisocyanate or non-conductive polymers such as polyacrylamides and polyphenol [53], which use physical adsorption with biomolecules. For biocompatible membranes for process such as osmosis, materials such as PVC, polyethylene, polymethacrylate and polyrethane are frequently used, not only due to their physical and chemical properties, but also because they avoid interaction between membrane and analyte. The main working principles for these sensors are summarized in Table III.

Colorimetry is widely used for sensing in microfluidic devices. Another appealing technique is electrochemical sensing, which can also greatly benefit from when combined with nanotechnology for improving adsorption and specificity. This would be the same situation of mechanical sensors, which can be implemented using PDMS, but the required dimensions may prevent its fabrication at low cost research facilities.

III. Research Potential of Lab-on-a-chip Devices in Latin America and the Caribbean

The simplicity and system integration provided by Lab-on-a-chip technology for implementation of multiple tasks such as sample preparation, separation, amplification and detection, has largely extended their use in biomedical applications, which is currently are the largest market of Lab-on-a-chip devices. Examples of their uses are immunoassays with plasma generation for electrochemical detection, infectious disease diagnostics based on platforms that integrate sample preparation, PCR, integrated valves for DNA-based diagnosis, quantification, biochemical analysis for evaluation and quality control of DNA, RNA, proteins and cells. Very precise results can be obtained within 30-40 minutes. One of the widespread techniques for amplification of DNA and biological molecules is PCR in agar, together with fluorescence or similar visualization methods. Lab-on-a-chip, however, can achieve even better resolution, since the miniaturization of electrodes lead to high sensitivity.

Methods for hybridization and detection of chemical compounds have also been developed. Microheaters, temperature microsensors and fluorescent detection can be integrated; extraction and manipulation of genomic DNA fragments is also possible.

Another important use of Lab-on-a-chip devices for chemical synthesis is concentration measurements and kinetic behavior of reactions. Determination of reaction mechanisms and duration is of importance for the pharmaceutical industry.

Lab-on-a-chip devices present several advantages such as: 1) low sample volume, leading to an effective use of the sample and lower reagent costs, 2) portability and in situ fast analysis, required for continuous and personalized monitoring of the patient or analyte, 3) higher selectivity and yield for chemical synthesis, 4) automated operation and scalability by test parallelization, 4) availability of low cost materials and reduced fabrication costs for mass production and prototyping, 5) materials suitable for disposable systems for medical analysis, 6) high reactivity and improved optical detection in chemical analysis. In the medical field, Lab-on-a-chip devices contain microneedles for non-invasive collection or dispensing of small amounts of liquid without causing discomfort to the patient, precisely controlling the amount of analyte or collected sample and the penetration in the skin.

Lab-on-a-chip technology is an excellent choice for implementing point-of-care devices, offering portable medical analysis without the need of costly and sophisticated equipment, fast obtention of results without involving an extensive knowledge of the diagnosis principle involved. Several studies have proven the effectiveness of Lab-on-a-chip

devices as portable diagnosis tools in detection of infected microorganisms, biological analytes and blood analysis. Lab-on-a-chip systems can also be used for controlled, personalized drug delivery according patient´s response to a treatment, extent of disease and current conditions. Moreover, these devices can complement medical diagnosis by environmental monitoring, for example, in the detection of pathogen agents in water and food for human consumption.

According to the Panamerican Health Organization, 30% of the population of Latin America and the Caribbean has no access to health services; this lack of health coverage can be attributed to poverty and geographical barriers [80]. Moreover, the World Health Organization has identified 17 neglected tropical diseases affecting the lower income population Latin America and the Caribbean (LAC), whose financial condition is associated with difficulties to access clean water and adequate sanitary conditions [81]. According to the Interamerican Development Bank, 200 million latin americans are at risk of being affected by these diseases [82].

In addition to that, LAC region is strongly affected by ischemic heart disease, stroke, lower respiratory infections, diabetes, chronic obstructive pulmonary disease and diarrheal diseases [83].

In order to improve health coverage, LAC countries have implemented several strategies, leading to successful results. However, there is still room for improvement in terms of coverage improvement and quality of health care, even in cases of high coverage. For example, Costa Rica implemented a universal primary attention model that started in the 70´s and evolved to the so-called EBAIS (Equipos Básicos de Atención Integral en Salud) points of care, covering 94% of the population by 2010, including attention to immigrants [84]. Furthermore, when patients are unable to visit health care facilities, ambulatory health care is provided. Despite this effort to bring health services everywhere, and especially to rural areas, waiting lists are an important problem to solve. One of the factors affecting health care is the fact that almost all laboratory diagnostic tests are carried out at the main laboratories of the health system. To solve this particular issue, Lab-on-a-chip devices can contribute to increasing the diagnostic capabilities of both point of care and ambulatory care. In this way, only the tests required for more detailed analysis or complex cases would be carried out at the main laboratories. Besides the clear advantage of portability and low cost of Lab on a chip devices, fast diagnosis can help reducing the higher costs derived from disease evolvement due to late patient attention.

Considering the specific needs of the LAC region, the availability of low cost and easy to implement fabrication techniques, on Lab on-a-chip devices can be a fertile field for collaborative research, innovation and entrepreneurship at the local level. Regionally developed technology would find also opportunities for expansion in Asia and Africa, as LAC populations present affections common to those of other third-world countries. Detection of risk factors using Lab-on-a-chip provides another application niche for LAC researchers, largely involving water quality assessment including testing the presence of bacteria, virus or chemical contaminants.

The most important tests required include blood, urine, and mucous samples. Analysis and detection of electrolytes, glucose, hemoglobin, cholesterol, coagulation, cardiac markers, drug and pathogen screening and infectious disease diagnostics for HIV/AIDS, tuberculosis, malaria, dengue, and similar diseases; antigens, proteins, pH, lactate, iron, lead, among other analysis can be implemented at low cost with Lab-on-Chip systems.

Lab-on-a-chip technology not only benefits from a broad spectrum of physical effects that can be used for sensing, but also of simple fabrication techniques which do not necessarily involve costly research facilities. Although some universities in LAC have important investment in laboratory facilities and equipment, most of them are not able to implement and maintain a clean room and advanced microfabrication equipment. Fortunately, microfluidics presents very important advantages with respect to other MEMS: they may not require deep submicron or nanometric structures to implement practical applications, there are biomedical and environmental applications available which can be solved with microfluidics and thus are attractive for funding, and low cost substrates and techniques are available, which opens interesting research possibilities for researchers with limited resources and provides an attractive alternative for creating laboratory experiments for engineering and science higher education, as well as participation of undergraduate and graduate students in research. Low-cost materials such as glass, paper, recycled CDs, PDMS and PCB substrates are suitable for affordable academic research and for massive manufacturing of the final product. Laser patterning, plastic molding, hot embossing, screen printing, PCB technology, 3D and inkjet printing are examples of available fabrication techniques which can be easily implemented or are already available at research facilities in LAC; combined with wet chemistry for functionalization, the resulting structures are enabled for detection and analysis. Considering the materials, fabrication methods and sensing principles reported in literature, we identify four approaches to overcome financial and technical difficulties of conventional, silicon-based microfabrication for Lab-on-a-chip research in Latin America:

-Fabric/thread-based sensing
-3D printed-microfluidics
-Paper-based microfluidics
-PDMS-based microfluidics

In literature there are very encouraging examples of the capabilities of low-cost Lab-on-a-chip devices. In [85], 3D printing has been used to create a microfluidic device for single-step detection of dengue from saliva samples. In this device, substances and particulates are removed which

interfere with sensing, thus making possible to detect dengue using a small sample volume.

The group of Martínez [86] presented the first approach for paper-based microfluidics in a pioneering paper describing the fabrication procedure and demonstrations of this technique for detection and quantitative analysis of glucose and protein in artificial urine, in addition to patterned paper as an alternative to the traditional plastic well plates. The possibility of 3D paper-based microfluidics has also been described by this group. Recently, the capabilities of paper-based microfluidics have been enhanced by the addition of valve actuators [87]. The actuators´ effectiveness has been proved as part of a microfluidic device for malaria detection.

In [88], an automated colorimetric ELISA assay for detection of human chorionic gonadotropin was implemented using a nitrocellulose membrane. Channels and barriers were created through inkjet printing. The device requires no power source and performs the complete analysis with 100µL sample in only one step. Paper coated with silicone was treated in [89] to create assay well patterns demonstrated in chemoluminescent blood detection. Silicone was selectively removed with help of a CO Laser. The exposed surface was coated with silica microparticles to improve hydrophilic flow in patterned channels. Silicone is thus proposed as an alternative to wax, SU-8 and PDMS coatings.

The effectiveness of paper and flexible materials to implement different lab-on-a-chip analysis was demonstrated in [90], where three tests were implemented: detection of HIV, lymphocyte, Escherichia Coli and Staphylococcus Aureus. For HIV detection, channels were patterned on a flexible polyester film and silver electrodes were deposited for sensing by means of electrical impedance spectroscopy. Functionalized polyester was used to count lymphocyte count by fluorescence. A cellulose substrate with gold conjugated nanoparticles was tested for detect and quantify E. Coli and S. Aureus by colorimetry. Also, a DNA amperometric detection lab on a chip device fabricated on a commercially available PCB process was demonstrated in [91].

Lab-on-a-chip devices based on plastic foils for numerous examples of commercial and academic devices for applications ranging from PCR-based DNA analysis, immunoassays and cell culture [92]. Major efforts on developing devices based on this technology were carried out in the Lab-on-a-Foil project funded by the European Union, which successfully matured this technology demonstrating detection of colorectal cancer from blood samples, phytoplankton analysis for environmental applications, campylobacter and salmonella detection in food and a skin patch for drug detection [93].

An alternative material for colorimetric assays is cotton thread [94], as demonstrated with microfluidics for the detection of proteins, nitrite, ketone, glucose and alkaline phosphatase [95]. A very attractive advantage of this method is that it does not require any microfabrication technique or pumping at all, since the thread itself acts as a hydrophilic microchannel, providing transport of fluid to the detection region. The thread is sewn on a plastic substrate or encapsulated between plastic matrices or adhesive tapes. After assembling the devices, they are treated with wet chemistry for a specific assay. The fabrication procedure is so simple that, with little training, workers with little formal education can carry it out. In this way, this technology could fulfill double purpose: to benefit the poorest regions with job and access to health.

IV. CONCLUSIONS

Lab-on-a-chip devices can become a very valuable tool for improving health coverage and quality of life in LAC, and presents very good conditions to strengthen research and innovation in LAC as well as networking of researchers by solving common issues in the region and complementing their research expertise in physics, chemistry, medicine, biology, among others. A wide range of sensing effects is available to implement Lab-on-a-chip devices. Low cost substrates and microfabrication techniques are key enabling features for this technology in Latin America and the Caribbean. This also provides the opportunity of involving real-life applications in higher education teaching by laboratory experiments for science and engineering students. Lab-on-a-chip technology could potentially contribute to the economic growth of the region by creating jobs for both trained (research and development) and untrained (massive manufacture) population. Besides biomedical applications, environmental, veterinary and food control devices can be researched and implemented.

The numerous advantages of Lab-on-a-chip devices can be fully exploited when their fabrication, commercialization and application consider cost and end-consumer´s needs and living conditions from the early design stages through the final product. Lack of trained personnel and energy sources, logistics of transportation and storage, tolerance to different temperatures and environments, can be listed among these constraints.

TABLE I
MEMS MICROPUMPS

Physical effect	Actuation mechanism	Materials	Advantages	Disadvantages
Surface tension [7, 8]	Gravity pressure due to Laplace Law	Traditional micropipette materials, PMMA	Low cost Easy to fabricate	Requires laminar homogeneous flows Low flow velocities (20 mm/s) Affected by asymmetries and roughness in channels
Piezoelectric [9, 10]	Deflection of piezo membrane attached to diaphragm	PDMS, sol-gel $Pb(Zr,Ti)O_3$ (PZT)	Operating frequency can achieve hundreds of Hz High force Medium flow rates (160 µL/min)	May require large operating voltages
Pneumatic [11, 12]	Gas filled chamber transmits pressure to fluid containing chamber	PDMS	Medium flow rates (449 µL/min) Operating frequency in the tens of Hz	Complex geometries High power consumption Long response times
Electrostatic [13, 14]	Repulsion or attraction among substrate and diaphragm electrodes	Metal, Polyimide, Glass	Easy to fabricate, CMOS compatible Can be implemented with biocompatible materials Low power consumption. Fast response time. Low frequency response (Hz)	Very high actuation voltage (>100V) High power consumption Medium flow rates (100's µL min). Limited operating range due to pull-in.
Electromagnetic [15, 16]	Lorenz force in elastic membrane caused by integrated permanent magnet and inductor	PPMA, NdFeB, PDMS	High flow rates (mL/ min) Operating frequency in the tens of Hz Low actuation voltage Relatively large displacement	High power consumption
Electrokinetic [17, 18]	Electroosmosis External electric field induces charge, opposite charges in the fluid cause movement	Si, ESCO, platinum and titanium.	Large flow rate (hundreds of µm s) Low cost Easy to fabricate Flow direction controlled by applied external field Very high operating frequency (10-100kHz)	Requires electrically conductive solutions
Optofluidic [19, 20]	Light beam on dielectric creates electric field gradient attracting particles	PDMS, photocurable hydrogels, thermoset plastics, elastomers, PFPE	In situ flux controlled by intensity and direction of electric field	High actuation voltage Very low flow rates (10^{-2} µL/min)
Thermal [21, 22]	Fluid partial evaporation causes flux by gas displacement, pressure and bubble coalescense	Silicon, Aluminum, PMMA, polyimide, silicon nitride (Si3N4)	Easy to fabricate. Membrane can be made of some different materials. Flow direction controlled by temperature. Low actuation voltage	Low reliability. High power consumption. Slow response time. Thermal fatigue due to thermal cycle
Electric surface tension [23, 24, 25, 26]	Upon imposing an electric polarization, ions in an electrolyte are set in motion by a potential gradient.	PDMS	Parameters and variables can be strongly controlled Low power consumption	Very low flow rates (10^{-2} µL/min) Low frequency range (25 Hz) May require high voltages (>100V)
Diffusion [27]	Liquid in a fluid microchannel moves due to diffusion of a gas through a membrane in response to pressure differentials	Silicon, PDMS, polyimides, polyamides, polycrylates and polysiloxanes	Parameters and variables can be strongly controlled	Complex fabrication Very low flow rates (10^{-1} µL/min)
Ferrofluids [28, 29]	Magnetic actuation of ferrofluids with dynamic magnetic fields	PMMA, NdFeB	Easy to control Medium flow rate (tens of µL/min)	Complex fabrication
Electroosmotic [30, 31]	Parallel arrays of hundreds of narrow, deep trenches	Silicon	Medium flow rate (hundreds of µL/min)	Complex fabrication Very large actuation voltages

	designed to enhance the transfer of momentum into the fluid phase			
Peristaltic [32, 33]	Radially symmetrical contraction and relaxation that propagates in a wave down a tube, in an anterograde direction.	PDMS, PMMA	High flow rate (up to ml/min)	Requires mechanical/electrical actuation
Centrifugal force [34, 35]	Liquid released by centrifugal force produced by an actuator	PMMA, NdFeB, LTCC-technology	Very high flow rate (thousands of ml/min) Operating frequency in the 100Hz range	Requires mechanical/electrical actuation
Piezoelectric [36, 37, 38]	Inlet choking phenomenon	Silicon, PMMA, PDMS	Easy to control Operating frequency in the 100Hz range High flow rate (1000´s of μL/min) Easy to optimize mechanically High switching speed Low power consumption	Complex fabrication Medium flow rates improved by adding secondary pumps Small displacement range High actuation voltage

TABLE II
MEMS MICROVALVES

Physical effect	Actuation mechanism	Materials	Operating frequency	Advantages	Disadvantages
Thermopneumatic [39, 40, 41, 42]	Heated fluid expansion causes force on the valve actuator Phase change liquid	SU-8 PDMS on glass or silicon, isopropanol, methanol, 3M FC3284, 3M HFE 7000	Limited by thermal time constants of fluid <10Hz	No external power source required Wide range of fluids for actuation	High power consumption Low flow rates High actuation voltage
Piezoelectric [43, 44]	Membrane deflection or piezostack in response to applied potential Piezoelectric stack	Lead zirconate titanate (PZT)	up to tens of kHz	High flow rates possible with hidraulic amplification High operating frequencies possible	Small stroke High actuation voltages
Electrostatic [45, 46]	Electrostatic forces between membrane and fixed electrode	PDMS	from Hz to MHz	Easy to manufacture Capable of fast response Pressure up to kPa	High power consumption Low flow rates High actuation voltage
Memory shape alloys [47, 48]	Reversible phase transformation in response to temperature	NiTi	< 100 Hz	Simple, compact geometries High stroke Able to handle high pressure High flow rates Low operating voltages	High power consumption Slow response
Electrowetting [49, 50]	Contact angle of droplet on surface changes according to applied voltage Ferrofluid conducted by electrowetting on dielectric (EWOD) Polymer changes phase by temperature, polymer droplet conducted by EWOD	Ta_2O_5 Parylene C Nb_2O_5 Glass substrates Su-8, PVDF, Cyanoethyl pullulan, CEP, Teflon, Cytonix	10kHz	No moving parts required	High actuation voltage Fast response

Electromagnetic [51,52]	Force between current conducting wires and a magnetic field created by permanent magnets or external inductors.	$Ni_{50}Fe_{50}$, Fe	0.1Hz-100Hz	Medium operating voltage Large displacement Linear control Fast open response	Low flow rates

TABLE III
MEMS MICROSENSORS

Physical effect	Actuation mechanism	Materials	Sensed variable	Advantages	Disadvantages
Schottky diode [55]	Selective absortion on the surface of the gate layer, changing Schottky energy barrier	Silicon, palladium alloy	Gas components and concentration	Selective sensing High speed response	Very specific fabrication materials
Electrochemical [56, 57, 58, 59, 60, 61, 62]	Conductivity or capacitance measurement, potentiometry, voltammetry and amperometry, ion-selective detection, redox potential.	Silicon, polyimide, platinum, $BMIPF_6$, polymers.	Glucose, lactose, oxygen, specific subtrates, gases, etc	Large range of sensors for the same parameter	Usually difficult to characterize
ISFET/MOSFET [63, 64, 65, 66, 67, 68]	Ion selective effect	CMOS silicon	Light intensity	Compatible with CMOS technology	Complex fabrication
Optical [69, 70, 71, 72, 73]	Luminescence at wavelength defined according to variable and concentration.	Glass, Teflon substrates Optical fiber, semiconductor light sources	Fluorescence intensity, gradients of light intensity, spectral composition, chemical substances	Non-invasive to the sample under test. In case of biological studies it requires genetically modified cell lines or fluorescent markers that alter the cells	Complex material systems required to implement the sensors Labels or fluorescent markers may be required
Thermoelectric [74, 75]	Peltier-Seebeck and Thomson effects	Bi, Sb on Kapton substrate	Ethanol, temperature, detection of exotermic reactions Heat flux	Capable of high sensitivity	Very low signal level (nV-μV)
Piezoelectric [76,77]	Mass detection by induced piezovoltage or change in resonant frequency	ZnO YX-$LiNbO_3$	DNA hybridation Protein interaction Antigen, gas, ion, toxics and explosives	Fast response Implemented as cantilever or surface acoustic wave device	Piezoelectric materials are usually complex compounds
Mechanical [78, 79]	Chemical agent mass or flow causes deformation of deflective parts detected by photodiodes or laser interferometry	SU-8, SiN, PDMS	DNA fragmentation, biomolecule detection Flow detection	Linear mass-deformation relation	Sensitivity decreases exponentially as flow increases

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