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Integration of Biosensors and Associated Electronics on Lab-on-Chip Devices

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Introduction

Lab-on-chip technology focuses on the development of microdevices, called microfluidic lab-on-chips (Fig. 1). These devices are capable of performing various laboratory functions and assessments by handling tiny amounts (10^{-9}-10^{-18} litres) of biochemical samples and process them quickly [1]. The samples may consist of metabolites, proteins, nucleic acids, viruses, or cell suspensions.

The measuring apparatuses of microfluidic lab-on-chip devices consist of miniaturized biosensors of various types, including optical sensors, impedimetric and electrochemical ones. Critical is the biocompatibility of the interfaces between the sensing elements and the liquid samples. The controlling and processing electronics usually consist of mixed signal circuitries, memories, and processing units, usually DSP processor or FPGA, which is capable of analyzing signals. Measurement information can be shown on external computer monitor, or on an integrated on-chip display. Individual lab-on-chip devices can be networked together and perform as network of synchronized microsensors.

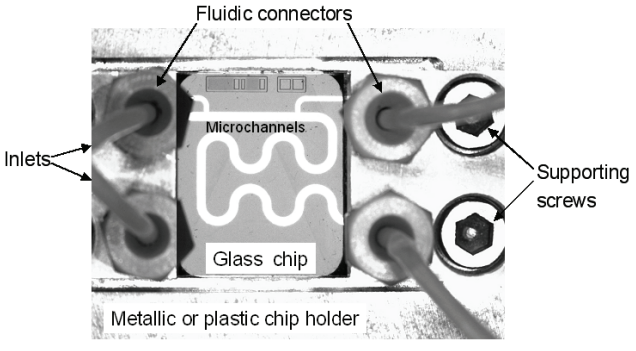

Fig. 1. A microfluidic lab-on-chip device fitted into its holding case. The fluidic chip is made of glass and includes a network of microchannels where tiny fluidic volumes can be transported and processed. The dimentions of this glass chip are 1.5 x 2.5 cm and the diameter of the microchannel 0.5 mm. Optical or electronic sensors can be adapted externally or directly intergated onto the glass chip

Advantages and applications of lab-on-chip devices

The establishment of lab-on-chip technology, the last two decades, arose from the necessity of incorporating chemical analytical apparatuses into submillimeter capillaries (microchannels). The ultimate goal for lab-on-chip technology is to achieve comparable sensitivity, resolution and functionality as this of benchtop laboratorial instruments. Miniaturization is a fundamental concept in lab-on-chip technology, as handling reduced volumes it rapidly speeds up analyses. The feasibility of integrating electronics, the possibility of automating bio-analyses and biosyntheses and of adjusting procedures online, as well as increasing the sample throughput, made lab-on-chip technology very attractive to scientists and engineers and a large network of research groups and manufacturing enterprises has been established worldwide.

Today the concepts of lab-on-chip technology are fully established and motivate researchers and engineers in a competition of developing uncountable types of microfluidic lab-on-chip devices of diverse functionalities. Experts claim that the complexity of lab-on-chip devices increases at rates comparable to Moore's law. Notable technical advantages that characterize lab-on-chip devices are compactness, portability, modularity, reconfigurability, embedded computing, automated sample handling, reduced electronic noise, reduced power consumption, and straightforward integration of microfuidic components and electronics by means of photolithography.

In addition to the use of minimal amounts of samples, analytes, and reagents, the lab-on-chip devices are fully enclosed and this reduces contamination of the carried samples. Furthermore, lab-on-chip devices are capable of supporting a wide range of laboratorial functions including sampling, routing, transport, dispensing and mixing, mostly with reduced moving or spinning components, therefore increases their usability and lifespan. Due to their small size and the tiny fluidic volumes that they handle, the lab-on-chip devices offer: (a) precise microfluidic transportation via the use of electrokinetics or micropumping, (b) efficient separation of biochemical

species, (c) precise measurements, (d) efficient control of the concentration of the reactants, and (e) fast and reliable synthesis of monodisperse bioproducts.

The lab-on-chip devices are affordable and simple to maintain. The microfluidic channels can be easily cleaned and sterilized with chemical solutions of sodium hydroxide, nitric acid, decanol, ethanol, bleach, or ethylene oxide [2]. Alternative to chemical cleaners, ultraviolet radiation, autoclaving, or heat, can sterilize microfluidic devices too. Capillary plasma can dissolve organic remains inside microchannels.

Key manufacturing advantages that make lab-on-chip devices affordable are: achievable mass production, reasonable replacement cost, short manufacturing time, simplified quality tests, and broad range of supporting computer aided design and simulation software tools. Most of the advantages of the fluidic lab-on-chip devices are analogous to those of the integrated electronic chips.

Design concepts, materials and fabrication methods

Major steps in the manufacturing process of lab-on-chip devices are: computer aided design, modeling, prototyping, optimization and fabrication. For commercial devices, reliability and quality tests are essential in the production process (Fig. 2).

The lab-on-chip devices can be designed with computer aided design software dedicated for micro-electromechanical devices, or with any ordinary computer aided design software that supports multilayer drawing and vector graphics. The performance of lab-on-chip devices can be modeled by means of finite element simulation. Chip makers must simulate heterogeneous and multiple components and should deal with complex fluidic flows. It is convenient to consider circuit analogies when modeling microfluidic chips: the reservoirs are comparable to electrical capacitors as they are storage components; the microchannels are equivalent to wires as they carry flows; the microvalves are analogous to electronic switches as they offer selectivity; and the micropumps are analogous to voltage or current sources as they move the flows.

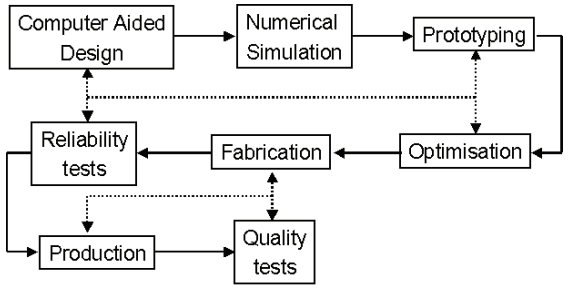

Fig. 2. Design and manufacturing flow for producing lab-on-chip devices

Lab-on-chip devices should be designed modular in order to allow expansion to varied functions. The goal is reconfiguration for varieties of applications. The embedded software and the functionality of microprocessors are reconfigurable. On the hardware, dynamic reconfiguration can be obtained on the segmented flow of microreactors as their substances can be mixed or altered.

The electromagnetic compatibility of a lab-on-chip device should be carefully considered because measurement and control signals may interfere. To eliminate electromagnetic interferences, timeslot sharing of the signals is an option. The electronic circuits should comply with the electromagnetic compatibility standards of radio frequency electronics. Any circuit on a lab-on-chip device should be designed in a way that minimizes the electrical connections. This is particularly important in impedimetric lab-on-chip devices that operate at radio and microwave frequencies where the electrical lengths influence the measurement of the impedance.

The lab-on-chip devices should be designed to easily maintained. A microfluidic device should allow easy channel washing and sample filling. The chip holders and the other connecting components should be easily handled, assembled and easily used by the operators. Many lab-on-chip devices might be requested to fulfill specific customized tasks, but still the chipmaker should design the device in a manner that provides the user the fundamentals for handy maintenance, calibration and operation.

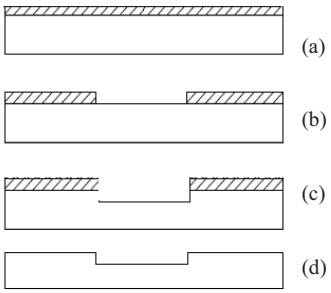

Fig. 3. Microfabrication process: (a) exposition of a photosensitive-coated substrate to ultraviolet light to replicate features; (b) development of the photoresist by desolving the exposed areas, (c) chemical etching, (d) revelation of the desired feature (in this case a microchannel) after total removal of the protective photoresist film

The modern lab-on-chip devices are mostly made of a combination of: (a) crystalline materials such as glass and silicon, (b) polymers like acrylic, polyester, polycarbonate, photoresists, thermoplastics, and (c) molds like the elastomer polydimethylsiloxane. The microfabrication procedure for producing lab-on-chips on solid crystalline substrates is analogous to this of integrated microelectronic chips. The fabrication process requires photolithography that replicates features onto a photosensitive-coated substrate by means of successive photomasks which are exposed to ultraviolet illumination. Then chemical etchers reveal the structures (Fig. 3). Exposition of many successive photomasks produces multilayered structures. Photolithography has continuous improvements in the ability of resolving ever-smaller features, but also in producing high-aspect-ratio features. Each implementation of photolithography has its own specific requirements, but there is common succession that involves the followings: metallisation, exposition, etching, and dishing [3]. Alternative to etching is lift-off, where the metal is sputtered on top of an inversely patterned photoresist and fills the gaps. Lifting-off the photoresist film reveals the metal patterns. Final step is chip-assembly via cross-

linkage of two opposing structures, by means of heat (case of thermoplastics) or anodic bonds (case of metallised surfaces). Polymer adhesive is a sealing option which allows to reopen the chips upon heating.

Soft lithography is a lesser, to photolithography, resolution method that is based on direct stamping of molds on glass wafers [4, 5]. The molds can be elastomers, such as polydimethylsiloxanes, which easily casts and seals upon application of uniform pressure (Fig. 4). Soft lithography is useful only for rapid prototyping, in the optimization procedure of microfluidic devices, since cannot guarantee high reliability of the produced devices.

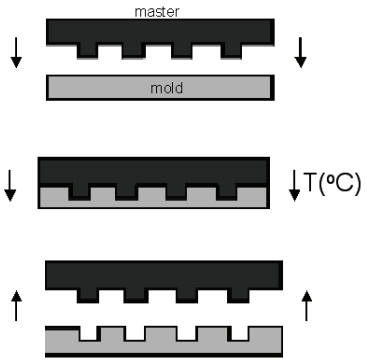

Fig. 4. Soft fabrication is capable of producing features of only few hundreds of microns. A hard master (dark) made of metal, glass, or plastic, casts on a mold material (grey) which may be a polymer or thermoplastic. After heat and pressurisation the mold deforms to the shape of the master, and lifting-off the master, reveals the microchannels

Alternative of etching channels on silicon or glass is possible to mill them directly on softer polymer substrates. Polymer substrates, such as polycarbonates, have varied interfacial and structural characteristics. Polymers have reduced to glass transparency, but better thermal conductance. Microfluidic channels can be developed from polymers by means of plastic molding or micromachining [6, 7]. Particularly fluoropolymers, such as polytetrafluoroethylene, are handy materials for structuring microfluidic channels, since they are soft against milling tools, and also they are hydrophobic that highly eases a liquid to flow within. For rapid prototyping casting of polydimethylsiloxane by means of silicon or metallic masters can produce microfluidic channels [8]. Under uniform mechanical pressure, polydimethylsiloxane can seal various smooth substrates, such as glass, silicon, silicon nitride, polyethylene, glassy carbon, polystyrene, fluorocarbons and metals. Polydimethylsiloxane offers much higher hydrophobicity than other materials, unfortunately swells against organic solvents like oils, but remains unaffected against water, nitromethane, ethylene glycol, acetonitrile, perfluorotributylamine, perfluorodecalin and propylene carbonate.

For producing microelectrodes, conductive elements and electrical contacts, appropriate metals are the biocompatible and chemically inert gold, platinum, and titanium. Films of gold, platinum and titanium, or of the transparent Indium Tin Oxide (ITO), can be sputtered or deposited by evaporation on wafer substrates. The electrodes can be produced by means of photolithography at resolutions of few micrometers. Alternatively, it is possible to produce microelectrodes by milling thinly metallised substrates, at resolution of some hundreds of micrometers. In lab-on-chip devices the electrodes are often coated in order to prevent electrolysis with the contacting fluids. For electric insulation, films like silicon dioxide, silicon nitride, or tantalum pentoxide, are very effectual due to their dielectric and crystalline robustness. But in the case of ultra low voltage devices, such as electrochemical or bioimpedimetric ones, the electrodes can be bare. Other usage of metal films entails microheating elements.

Hydrophobization of the interior of the microfluidic channels repulses aqueous fluids and enhances their flow to remain laminar. Different hydrophobization methods exist, ranging from spontaneous covalent bonding of hydrophobic self-assembles, such as octadecyltricloro-silanes (a process called silanization) to chemical and plasma deposition of fluoropolymers [3, 9, 10]. Alternative to channel hydrophobization is to introduce hydrophobic fluorosurfactants directly into the fluid, with comparable results as with hydrophobic coatings [11].

For controlling microfluidic flows, micro-actuators can be integrated in lab-on-chip devices. Actuators can be made of elastomers such as electroactive polymers or membranes. The electroactive polymers are an important class of materials for microvalve fabrication, or micropump fabrication, as they can be precisely controlled electrically.

Biosensors, signaling, measuring methods, electronics

Lab-on-chip devices may incorporate biosensors with biochemical recognition microstructures such as receptors (that are made of enzymes, nucleotides, antibodies), absorbers, cross-linkers, electrochemical, electromechanical, or thermal elements that measure responses of the measurand fluids. Depending on the type of the sensing element, a biosensor can be capable of detecting thermal agitations, elastic deformations, or electrical or optical deviations, as response to the sample's electrochemical potential, conductivity, optical refraction, spatial displacements, or temperature gradients. The output of an analog signal is proportional to the magnitude of the measured quantity. The response signals should be accurate, precise, reproducible and linear over the useful analytical range. The response signals should also be filtered from electronic noises.

Essential for a biosensor is to operate effectively, accurately, precisely, reliably, swiftly, to minimize its effect on the measured samples, to respond fast, and to consume minimal power since sensors are highly energy consuming active components in lab-on-chip devices. The specifications of biosensors are determined by their operational range, frequency response, linearity, resolution, sensitivity, selectivity, hysteresis and output noise.

The output signal of a biosensor is usually weak and superimposed with electronic noise. This signal is filtered and amplified afterwards. It is usually digitized via a circuitry of amplifiers, signal conditioning and mixed signal electronics. Subsequently the digital signal is processed in a microprocessor. The microprocessor might

generate a feedback response via an actuator and influence the measurand fluid. The information of a measurement is then post-processed and displayed on an external computer screen (Fig. 5).

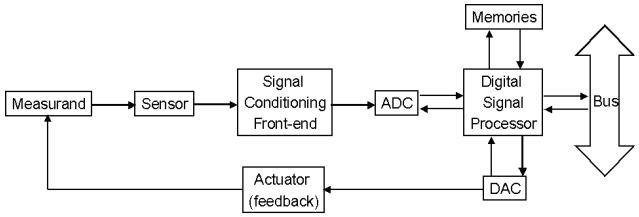

Fig. 5. Essential electronic measurement circuit. It builds on the microfluidic chip or on separate circuit board connected to the chip. The measuring circuit incorporates a sensor, an analog front-end that conditions the measuring signals, mixed signal circuits (ADC), and a digital signal processor that analyses the signals. Depending on the measuring methodology, the sensor can be electrical, optical, or pressure detector. The analyzed data can be further sent via a bus to external computer for post-processing and visualization on external screen. Based on the information data, the processor is possible to adjust the sample's condition via the use of a controllable actuator (mechanical, electrical, optical tweezers)

An optical biosensor is capable of measuring optical spectra and intensities. The illumination is usually a laser source with the light transmitted through planar optical guides through a path of miniaturized optical filters, or transmitter through peripheral optical fibres. Optical apparatuses on lab-on-chip devices exploit optical principles like absorbance [12, 13], infrared and Raman spectroscopy [14], scattering [15], refractive index [16], surface plasmon resonance [17], plasma emission and fluorescence [18]. In order to visualize cells or macromolecules in solutions, it is required to label these substances with chemiluminescence, fluorescence, or radioactive markers. Although labelling a substance provides accurate detection, visualization and clarity, it has disadvantages since requires markers that impact the biochemical solutions, and also requires chemical processing with specific chemical protocols.

Since all biochemical reactions are associated with heat conduction, temperature changes due to reactions can be detected on-chip by thermal elements. Thermistors with sensitivities down to a millionth of Celsius are appropriate. Most thermal biosensors employ enzymes as biological recognition elements. Enzymatic reactions may produce heats up to tens of kJ/mol, which is measurable, however antibody-antigen reactions are not thermally measurable.

Piezoelectric sensors employ ceramic films (e.g. barium titanate, lead titanate, lead zirconate titanate) that undergo, upon application of electric potential, elastic deformation with accuracy of micrometers. An alternating voltage induces standing waves in the crystal of the ceramic at a characteristic frequency. This frequency is highly dependent on the elasticity of the ceramic film, such that if the film is coated with biological receptors, the binding of macromolecule to the receptors will produce a change in the resonance frequency, which induces electric signal. The piezoelectric films may be directly connected to electronic circuits without any special interface, but usually signal-conditioning circuitry is required to filter the noise and to average the response signal.

Enzymatic sensors can measure oxygen levels and pH relying on ionic and electron diffusion due to catalytic reactions on electrodes coated with enzymes, where the catalytic reaction produces response electronic signals. Enzymatic sensors focus in glucose for blood test. Bacteria or other cells within solutions utilize physiological signal responses where the generated electrical signals are proportionally to oxygen concentrations produced by the cell metabolism.

Electrochemical activity within electrolytic solutions relies on ionic flow. The electrochemical biosensors work either as ammeters where they measure currents proportional to the ionic concentration with values ranging between pA-μA, or measure as voltmeters. They can assess ionic conductivity, or monitor the metabolism of a cell culture through the measurement of ionic concentrations. An electrochemical biosensor employs three bare ring electrodes that circulate the microchannel: a reference electrode, a working electrode (cathode or anode), and a counter electrode. The reference electrode establishes a reference potential against which variable potentials can be measured. The working electrode measures either current or voltage that is produced on its surface by electrolytic reactions. The measured potential is then subtracted from that of the reference electrode. An interfacing circuit amplifies the measuring current and converts it to an output voltage (Fig. 6). Electrochemical biosensors may also employ four ring electrodes, which highly minimize the capacitance of electrode polarization. Contactless conductivity detection works with insulated electrodes. It measures changes of the ohmic resistance of the solution.

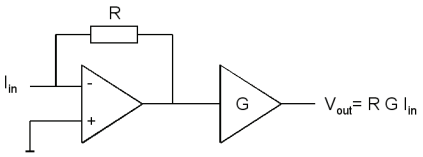

Fig. 6. Analog front-end circuitry of a transimpedance amplifier for electrochemical measurements. The transimpedance amplifier converts the measured current to voltage for analog-to-digital conversion

Characterization of cell suspensions by means of impedimetric lab-on-chip devices is of growing importance because it provides high-speed and label-free cell concentration analysis, sizing and population study. Single frequency sine wave excitation is the simplest method and most widely used therefore. But the characterisation of substances only at one frequency is not enough informative. Therefore, excitations at more frequencies have been introduced. For covering a wide frequency band with a continuous excitation spectrum, pseudo-random excitations are introduced, for example maximum length series of rectangular pulses [19, 20], or chirp signals, both sine wave and rectangular wave based ones [21]. Impedance sensors offer direct usable electric signals and a multitude of different utilizable information carried by spectral signals. The modern digital signal processing offers fast and precise measurements and does not require

peripherals once the electronic modules with the signal processor are embedded in the microfluidic chips.

The analog amplification blocks in an impedance spectroscopy front-end might consist of, depending on the particularity of the signal conditioning, either differential transimpedance amplifiers (current-to-voltage converter), or differential difference amplifiers, or operational transconductance amplifiers (voltage-to-current converter). The first one, the differential transimpedance amplifier, is mostly used (Fig. 7).

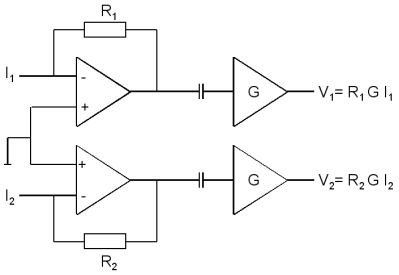

Fig. 7. Example of transimpedance circuitry for differential impedance measurements

Biocompatibility and defects

Biocompatibility concerns the device safe to meet specific standards in order to avoid material decomposition, oxidation, and to prevent biochemical samples from toxicity, sentitization, irritation, metalosis (spread of toxic metal traces), precipitation, erythrocyte clotting or other irregularities [22]. The biocompatibility of a device concerns only those of its components that contact the biochemical substances.

There are numbers of possible defects, which should be considered in the design of lab-on-chip devices. Since most microfluidic channels are made hydrophobic, most enzymes, proteins and cells adsorb to hydrophobic areas, an effect called biofouling. Biofouling disorders the device because hydrophilises the microchannels, which affects the flow. Biofouling overlays the biosensoric elements and consequently degrades the accuracy of the measurements. Silicon, silicon nitride, silicon dioxide, gold, platinum, titanium, and photoresists, are all biocompatible with reduced biofouling and cytoxicity [23]. To prevent adhesion of cells in microfluidic channels, surfactants like poloxamer copolymers can be added inside the fluids [24].

Future trends and conclusions

The expectation in lab-on-chip technology is to manufacture fully standalone microfluidic devices with embedded biosensing, computer and calibration possibility. The trend is to enhance multiple analysis and parallel sample processing with increased efficiency and speed. Future lab-on-chip devices are foreseen to demonstrate ultralow power consumption, advanced user interface through navigation displays, wireless networking, computerized information management, improved fluidic connectivity and become smaller and lighter. Standardization must define rules about quality, reliability, interoperability, biocompatibility, electromagnetic compatibility, interconnectivity, weight and size [25].

Future lab-on-chip technology is foreseen to enhance clinical tests and demonstrate a positive impact on pharmaceutics, therapeutics and personalized diagnostics. To date the lab-on-chip devices are determined by applications in bio-analysis. Further to diagnostics, future lab-on-chips are foreseen to further facilitate chemical synthesis, supramolecular chemistry, molecular motors and nanorobots, biomedical implants, biomimetics, and hybrid systems incorporated with blood vessels [26]. Future applications will incorporate nanobiotechnologies. Envisions consider nanoscaled channels where surface effects, rather than volume, dominate liquid sample behaviour. This will result to the accurate synthesis of bioproducts, independent from the constraints of statistics and diffusions parameters that rule present chemistry performed in laboratory vessels. Research in nanofluidics enhances single cell and single molecule analysis, which tests the fundamentals of cell biology and biochemistry [27]. It is foreseen development of fluidic biocomputers that will use nucleic acids, proteins, or peptides, to perform computations including storing, retrieving, and biological data processing through application of biochemical principles [28].

The impact of microfluidic lab-on-chip devices in everyday life is expected analogous and as revolutionary as of this of the integrated microelectronic circuits. Lab-on-chip devices highly influence medicine, chemistry, biology, biotechnology and bioelectronics.

Acknowledgements

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Lab-on-chip devices comprise a class of bioelectronic miniaturized devices that incorporate microfluidic and biosensing apparatuses on a single chip. They are dedicated for analyzing and processing biochemical liquid samples, which may consist of enzymes, proteins, nucleotides, or even cells and viruses. Furthermore, lab-on-chips may enhance synthesis of biochemical products. The importance of lab-on-chip devices lies on their potentiality of advancing the development of environmental monitoring sensors and also point-of-care analyzers in medicine. This article presents the usual microfabrication methods for manufacturing lab-on-chip devices, with emphasis on the integration of the biosensor, the biocompatibility of the sensing element of the biosensor, and the essential electronics. Three major types of biosensors are analyzed: optical, impedimetric and electrochemical ones. Ill. 7, bibl. 28 (in English; abstracts in English and Lithuanian).

A. T. Giannitsis, T. Parve, M. Min. Biojutiklių ir specializuotos elektronikos integracija „laboratorijos mikroschemose“ įrenginiuose // Elektronika ir elektrotechnika. – Kaunas: Technologija, 2011. – Nr. 4(110). – P. 61–66.

„Laboratorijos mikroschemose“ įrenginiai priskiriami prie miniatiūrinių prietaisų. Biojutikliai ir skysčio analizės prietaisai gali tilpti viename luste. Dėl to, jie gali būti naudojami fermentų, baltymų, ląstelių ir net virusų analizei. Tokie prietaisai yra puikūs analizatoriai ir gali būti plačiai taikomi medicinoje. Pateikiami bendrieji „laboratorijos mikroschemose“ gamybos metodai, ypač daug reikšmės teikiant biojutikliams ir jų suderinamumui. Išanalizuoti trys pagrindiniai jutiklių tipai. Il. 7, bibl. 28 (anglų kalba; santraukos anglų ir lietuvių k.).