Development and characterisation of silicon microfluidic components and systems

PhD theses

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Deep-brain microprobes

By aging of the society, brain-related clinical cases like paralysis, epilepsy or Parkinson diseases are remarkably increasing acting as critical issues to be solved for today medicine. Medical attendance and rehabilitation of such diseases is very challenging for both patients and their relatives. The aim of modern neurophysiology is to improve their quality of life. Processing of signals generated by brain neurons is of great importance in neurophysiology, since a large amount of information can be gained about the dynamics of neural system and the relationship between brain and motor function activity. As a result of efforts in this field, a wide range of structural material like silicon has been used to fabricate probes, which is applicable to register the activity of brain cells in non-human experiments extending our knowledge about the above issues.

Researchers have used pharmacologic intervention (e.g. systematic injection) anti-inflammatory agents can be transported into the tissue around the microprobes, and noticed that the response of neighboring cells and neural tissues changed. Drug delivery in acute experiments can be easily implemented, however, during chronic implantation, the local injection of drugs is more critical. The advantages of the latter are that smaller amount of biological sample is necessary, cells can be directly excited, while peripheral metabolism and the reactive response of neural tissue is excluded increasing the long-term stability of the device.

My goal in the field of neural microdevices was to design and realize multi-functional microprobes integrating a parallel system of electric sensing or excitation and local drug delivery functions into a single substrate. Since the characterization of the mechanical and fluidic properties of microprobes fabricated by the proposed technology are especially important for future application, a number of ex vivo and in vivo experiments have been carried out to evaluate microprobe performance.

Diagnostics of vascular diseases in the microscale

Currently, cardiovascular diseases are among the leading reasons of casualties worldwide. Almost every third fatal occasion originates from such illnesses. Fast diagnostics are essential to anticipate the deterioration of several diseases. Therefore, the research and development of microanalytical systems (Lab-on-a-chip, μTAS – mikro-Total-Analysis-System) are increasingly heading toward the downscaling and cost-effective fabrication of today’s medical microdevices. Such systems are able to complete complex analytical tasks that demanded the presence of serious hardware before. In the microscale not only the adaptation of analytical principles means great challenge, but the transport and preparation of biological samples are still relevant issues. Since hydrodynamic phenomena are often different than in the macroscopic world, the solution of sample manipulation (extraction, dilution, separation, transport to the active region) is a great challenge for microengineers of micro- and nanofluidic systems.

The aim of the vast majority of clinical tests is the detection of the presence and quantity of several proteins, ions, crystalloids or diluted gas in blood plasma. Since the cell components of blood are not desired during measurements, the first step is remove these particles from the blood plasma. If the measurements is to be embedded in a microsystem, the integration of separation is important.

The presence of proteins can be efficiently identified by solid-state nanopore membranes as sensing elements. Nanopore sensing is an extremely sensitive analytical method due to the nanoscale pore geometry (shape and surfaces), which makes the interactions between pore
surface and molecule of analytes to contribute to the control of ion or molecule transport. The detection principle is based on the selective interaction of pores and the analysed component which reduces the permeability of nanopores for the measured marker ion or molecules, and therefore produces a flux change equivalent to the analytical signal. Sensitivity is outstanding, since extremely small immobilized component causes apparent modulation in ion or molecule flux.

My work in the field of diagnostics of cardiovascular diseases focuses on the design and realisation of a silicon based microfluidic system, which contains the functions of sample preparation as well as the sensing element. To prepare whole blood, plasma separation and dilution has to be optimized in the microscale and the integration of a detection unit highly sensitive to blood proteins has to be implemented in a single microsystem. This way a rapid diagnosis can be set up in the case of diseases demanding fast intervention (e.g. stroke) in situ.

**Goals**

**Goal 1**

My aim in the field of neural electrodes was to realise and characterise microprobes involving the functions of drug delivery and electrophysiological measurements in a single substrate. The fabrication of sealed and leak-free microchannels in silicon is eventually expected to result in planar substrate surface after processing to facilitate the integration of appropriately dense net of electrodes on the microprobe. Since the integrated microchannels have a significant effect on both mechanical and hydrodynamic properties of device, a comprehensive characterisation is necessary. In later case in vivo experiments usually gives more valuable information.

**Goal 2**

My aim in the field of biomedical diagnostics was to design and realise a microfluidic system, which contains sample preparation functions and sensing elements, and additionaly makes a preliminary detection of vascular diseases available on the premises. To analyse the collected blood samples, a reliable and integrable microfluidic separator unit is necessary, which performs the separation of blood cells and plasma, as well as the transportation of sample analytes towards the sensing transducer (e.g. solid-state nanopore membrane).

**Methods**

Sample preparation of microsystems in this dissertation is based on conventional process steps of Si semiconductor technology (thin film deposition, photolithography, etching). Technology related researches are supported by microscopic investigations (optical, SEM & AFM) and by technology simulations performed by SILVACO ELITE code. Characterization of the realized microsystems is performed by self-designed measurement setup (both mechanical and microfluidic measurements). Results were analyzed by methods of descriptive statistics and COMSOL Multiphysics simulation code. In vivo tests of microelectrodes was conducted in the operating room of MTA TTK KPI.
New scientific results

Thesis Group I: I developed and characterised deep-brain silicon microprobes (up to 7cm) containing both microfluidic and electrical functions.

I.1. I developed a process sequence based on MEMS process flow, that is feasible for the integration of drug delivery and electrical functions in a single neural silicon microprobe.

a) I developed the technology of buried microfluidic channels in single-crystalline silicon by using of deep reactive ion etching and selective aluminum deposition, which finally resulted in planar surface facilitating subsequent photolithography for further integration of IC or MEMS components [K1, L1, Sz1].

b) I determined how the fabrication parameters affect the shape of the realized microchannels. I found that anisotropy during SF6 etching increases as trench depth (up to 110µm) is increasing. My experiments proved that increasing trench width (between 2-6µm) and/or decreasing aspect ratio (between 12-3) causes increase in etch rate of SF6 etching (between 6-25 µm/etch cycle) [L2].

c) I proved that the proposed buried microfluidic channels can be integrated into single multi-electrodes [K2].

I.2. I performed the mechanical and hydrodynamic characterisation of the realised microprobes.

a) I experimentally characterised the response of non-hollow and hollow silicon microprobes having several geometric properties (cross-section, length) to axial loading and determined the relationship between probe geometry and fracture forces. I found that fracture force of DRIE etched silicon microprobes is increasing by larger cross-section (with width and thickness in the range of 200-400µm), and the integrated microchannels may cause deteriorate force values by 80%. I also found that displacement of microchannel axis inside the probeshaft (inclined angle of tip edges is 30°) enhances the robustness of hollow microprobes.

b) I tested the mechanical robustness of non-hollow microprobes by in vivo insertion into rat brain. I determined the relationship between insertion speed and penetration force and dimpling in the case of several microprobe cross-section. I found that increasing the insertion speed in the regime of 1-10.2mm/min causes remarkable increase in penetration force (between 30-160mN). I also determined that dimpling (between 1-1.7mm) increases monotone by increasing interfacial area of the probes.

c) I experimentally characterised the hydrodynamic behaviour of buried microchannels integrated into hollow microprobe shafts between pressure range 0-250kPa. I determined that in the investigated pressure regime leak-free injection can be performed. I also determined that pressure-flow characteristics through the proposed microchannels is linear in the analyzed cross-section range (200-405µm²). I proved by in vivo injection that hollow microprobes are feasible to be used for neural drug delivery in the µL/min range [K2].

Thesis Group II: I realised and optimized a glass-silicon based microfluidic separator. Integrating the proposed separation principle into a biochemical sensor, I developed an autonomous lab-on-a-chip system including nanopore membrane as transducer element.

II.1. I realised and carried out the performance characterisation and optimization of a micromachined particle separation system based on Zweifach-Fung principle.
a) I designed and realised silicon-glass heterostructures to analyse the effect of geometric properties on the performance of passive particle separator utilizing Zweifach-Fung principle. I found that increasing main (of width between 15-37µm) and daughter (of width between 10-25µm) channel cross-section improves separation efficiency by even 20%, but deteriorate purity efficiency by even 10% in case of fixed hydrodynamic resistance ratios (2-10) between bifurcation branches and fixed channel depth (10µm). I determined that increasing the angle of bifurcation decrease purity by 7% in average [K3, L3].

b) Besides performance analysis, I performed experiments and modeling which proved that lateral migration is an inherently dominant effect of Zweifach-Fung separation. Based on my results, I proposed a concept of cascade bifurcation system which can be applicable for further enhancement of separation purity by structural focusing of particles and placing daughter microchannels out of the critical velocity streamlines [K3, L3].

II.2. I established a Lab-on-a-chip concept which includes a sub-system for whole blood manipulation and solid-state nanopore membrane as transducer.

a) I designed and developed the fabrication technology of a silicon-glass heterogenous microfluidic system, which includes sample transport and preparation (dilution/separation) and integrated read-out facilitating biochemical detection based on solid-state nanopore transducers [K4, K5].

b) I proved the applicability of the system by measuring the electrical performance by impedance spectroscopy. I found that serial and parallel impedance of microfluidic environment including sample preparation and transport functions is comparably smaller than that of the nanopore impedance. Therefore, the sensing principle can be applied even as part of the proposed integrated microfluidic platform. [K4, K5].

Utilization of scientific results

Results detailed in Thesis Group I contributed to the fabrication of neural microprobes in the MEMS Laboratory of TTK-MFA, which has been successfully used in neurophysiological measurements in the Institute of Cognitive Neuroscience and Psychology and in the Institute for Logistics and Production Engineering of Bay Zoltán Applied Research Nonprofit Ltd.

Results detailed in Thesis Group II contributed to the improvements of international consortial grants like P3SENS (Polymer Photonic multiparametric biochemical SENSor for Point-of-care diagnostics) and CAJAL4EU (ENIAC project on Nanoelectronics-based biosensor technology platforms) projects.
List of publications

Publications related to my PhD theses:

Journal papers:


Conference papers:


Patent

[Sz1] Fekete Z., Pongrácz A., Szendrey Á., Fürjes P., Battistig G.: CMOS technológiába integrálható eljárás egykristályos Si alapú, eltemetett mikrofluidikai csatornahálózattal rendelkező eszköz előállítására, a szubsztrát felület planaritásának megőrzése mellett, P1100170
Other publications

Journal papers:


Conference papers:


Publication in Hungarian:
