Sensors and Actuators B 215 (2015) 300–315

Contents lists available at ScienceDirect

Sensors and Actuators B: Chemical

journal homepage: www.elsevier.com/locate/snb

# Recent advances in silicon-based neural microelectrodes and microsystems: a review

Zoltan Fekete[a,b,*]

[a] Department of Microsystems Engineering (IMTEK), University of Freiburg, Georges-Koehler-Allee 103, 79110 Freiburg, Germany
[b] Research Group for Implantable Microsystems (neuroMEMS), Centre for Energy Research, Hungarian Academy of Sciences, Konkoly-Thege út 29-33, H-1121 Budapest, Hungary

ARTICLE INFO

*Article history:*
Received 13 January 2015
Received in revised form 19 March 2015
Accepted 26 March 2015
Available online 6 April 2015

*Keywords:*
Silicon microelectrodes
Neural probes
Neural implants
neuroprosthetics
brain–machine interfaces

ABSTRACT

Developments in neurotechnology are recently driven by newly national and international brain research initiatives worldwide. The challenging goal of understanding how the human brain works requires a vast amount of information gained by neural sensors. Microelectrodes implanted in the central nervous system are extensively used to record electric activity inside the brain tissue. More recently, deep-brain stimulation in Parkinson disease proved the feasibility of such electrodes in human medical treatments as well. To add novel sensor or even actuator functions to these microelectrodes, limitations of recent fabrication technologies have to be considered. To date, silicon microtechnology offered the highest potential to meet the demands of neural applications regarding multiple functions integrated on a single implantable microsystem. Besides reproducibility and low variability of silicon-based microelectrodes, combination of various functionalities like standard electrophysiology, integrated signal processing, local drug delivery, neurochemical detection and optogenetic stimulation is also possible using these microsystems. This ability makes silicon microelectrodes good candidates to provide high-resolution recording and stimulation in the electric, fluidic, chemical or optical domain in more complex neurophysiological experiments in the future.

The aim of this review is to give an overview on various aspects of silicon-based implantable neural microelectrodes and microsystems developed in the last decade. Microfabrication approaches of 2-D and 3-D arrays are summarized. Features of the latest active microelectrodes including CMOS signal processing circuitry are compared. Integration methods of convection enhanced drug delivery functions for local administration of pharmacons are demonstrated. Performance of recent silicon-based chemical sensors for the detection of neurotransmitters is also studied. An analysis on the latest developments in silicon-based optrodes for optogenetic and thermogenetic stimulation is also included in this paper. Microelectrode-tissue interaction is described through the evaluation of recent experimental studies on in vitro and in vivo biocompatibility.

## Contents

1. Introduction ..... 301
2. Microfabrication approaches ..... 302
   2.1. Micromachining of electrode arrays ..... 302
   2.2. Assembly techniques for 3-D configurations of Michigan probes ..... 303
3. Microelectrode functions ..... 304
   3.1. Electrical circuits for interfacing neurons ..... 304
   3.2. Drug delivery ..... 306

---

* Correspondence to: Research Group for Implantable Microsystems (neuroMEMS), Centre for Energy Research, Hungarian Academy of Sciences, Konkoly-Thege út 29-33, H-1121 Budapest, Hungary. Tel.: +36 306123218.
*E-mail address:* fekete@mfa.kfki.hu

http://dx.doi.org/10.1016/j.snb.2015.03.055
0925-4005/

3.3. Optical stimulation and imaging ........ 307
3.4. Neurochemical monitoring ........ 308
4. Biocompatibility ........ 309
4.1. Macroscopic approach ........ 309
4.2. Micro- and nanoscale approaches ........ 310
4.3. In vivo chronic performance ........ 311
5. Conclusion ........ 312
Acknowledgments ........ 312
References ........ 312
Biography ........ 315

## 1. Introduction

The rapid development of Information and Communication Technologies (ICT) has triggered the launch of several promising national (BRAIN Initiative, US; MINDS, Japan; BrainLinks-BrainTools, Germany), international (Human Brain Project, European Union) and industry-driven (Blue Brain Project, IBM) research initiatives aiming the mapping and modeling of the human brain or brain diseases. These targeted research projects rely on the recent advances in medical informatics and novel neurotechnological approaches. The role of neurotechnology is to engineer physical, chemical or biological systems to interact neural cells in a controlled manner. Currently, a lot of invasive and non-invasive technique is used to record or influence neural activity. The most popular invasive technique is based on the application of electrophysiological multielectrode arrays (MEA) or simply microelectrodes penetrating into the brain tissue providing information from deep-brain structures.

The first use of microelectrodes in neural investigations dates back to the 1950s. Initially, metal wire electrodes were extensively used to monitor the extracellular electrical activity in neurophysiology experiments [1]. The rapid development in microelectronics technology gave rise to the introduction of silicon based microelectrodes. In the 1970s, Wise et al. [2] reported the first silicon-based microprobe to interface neural tissues, which was fabricated by the aid of micromachining techniques of integrated circuit (IC) industry. Since this pioneering work, silicon-based microfabrication techniques are among the dominant tools in manufacturing of neural microelectrode arrays with microscale precision [3]. The introduction of silicon MEMS (micro-electro-mechanical systems) technology, including various surface and bulk micromachining techniques, significantly standardized the fabrication of microprobes. The use of photolithography processes provided well-defined size and spacing of recording sites, while various geometry and configuration of electrode shafts became available [4]. Besides high accuracy, the repeatability and low unit costs featured the proposed batch fabrication schemes. The inherent ability of silicon micromachining is to facilitate the direct integration of signal processing circuitry on the backend of so-called active silicon microelectrodes [5–7]. The current trends in the size and density of recording sites and leads induce demands on integrated preamplifiers and multiplexers to handle the recorded data at a reasonable spatiotemporal resolution and signal-to-noise ratio. Besides the support of electrophysiological recording, very large scale integration of microelectronic components [7] can be an enabling technique in the system integration of telemetry functions [8] or optical imaging sensors [9], which have been rarely considered, as well.

Passive electrodes do not contain read-out electronics, but offer the combination of traditional electrophysiology with various functions in the optical or chemical domain.

In recent years, the method of optogenetics enabled the stimulation of genetically modified living neural cells by light [10]. Delivering light of specific wavelength in a spatially controlled fashion in the central nervous system combined with simultaneous recording is now available due to microelectrode technology [11,12]. By the reduction of the characteristic size of such microsystems, high-resolution control of even single cells would be possible. Promising demonstrations in this fields have been presented [13,14], but also poorly exploited in combination with implantable neural sensors. The advances in micro- and nanofabrication techniques e.g. e-beam lithography [15] or two-photon lithography [16] open up new possibilities to address the realization of optical stimulation and imaging subcomponents on penetrating silicon microsensors to overcome physical limitations of currently available optical imaging techniques.

The role of neurochemical signals in the brain is also getting more important since the evolution of several brain disorders is attributed to their disturbed balance. Silicon-based sensors have been successfully presented to make correlation between electrical and neurochemical activity by using the same device [17,18]. The development of closed-loop systems [19] to measure and control neurodegenerative diseases may benefit from the progress of this specific field. The integration of local drug delivery function in such microsystems is also desired, if the blood brain barrier has to be circumvented, and administration of therapeutic drugs in a spatiotemporal fashion is necessary. Silicon neural microelectrodes have also proved their potential in this respect in experiments on living animals [20,21].

In terms of biocompatibility, silicon-based probes have shown promising results; especially their chronic in vivo performance is quite remarkable [22–25]. In spite of studies, some fundamental issues including the circumstances of implantation methods [26], physical [27] and chemical properties [28] of the implant surface have to clarified in order to boost signal quality and long-term reliability.

The progress in microfabrication approaches now allows to take advantage of the silicon substrate as functional component as well [29,30], while the combination of functional silicon and polymer parts in neural sensors [31,32] initiates novel hybrid concepts on how to reduce the mechanical mismatch between the implant and the brain tissue, and therefore diminishing the immune response. Further improvements in 3D arrays have also shown the potential of the silicon-based approach in high-density or high resolution recording and stimulation [33] [134]; however, the possibility to combine other functions with electric recording in a 3D fashion is not yet fully exploited and characterized.

All the above results show the versatility of silicon microelectrode technology in the integration of various microcomponents for specific neural applications. If we take the recent breakthroughs in related engineering fields into account, it can be concluded that there is still a lot of room to increase the integration level of these microelectrode systems. Combination of state-of-the-art technology with that of silicon microtechnology may open up new possibilities to increase the resolution of recording and stimulation techniques.