DE GRUYTER Current Directions in Biomedical Engineering 2017; 3(2): 675–678

Shubratha Koralagundi Gopalakrishnaiah, Kevin Joseph and Ulrich G. Hofmann*

Microfluidic drive for flexible brain implants

Abstract: Flexible polyimide probes, used for neuronal signal acquisition, are thought to reduce signal deteriorating gliosis, improving the quality of recordings in brain machine interfacing applications. These probes suffer from the disadvantage that they cannot penetrate brain tissue on their own, owing to their limited stiffness and low buckling forces. A microfluidic device as an external micro-drive which aids in the insertion of flexible polyimide neural probes in 0.6% Agarose gel is presented here.

Keywords: Flexible probes, Microfluidics, Buckling, Dimpling, Implantation.

https://doi.org/10.1515/cdbme-2017-0142

1 Introduction

The quality of acquired signals in brain-machine interfaces require reliable, stable and functional coupling between neural tissue and implanted electrodes. Neuronal multisite electrodes are used in brain-machine interfaces to record the activity in brain, which when used in long term investigations, quickly succumb to the immune response of the brain to a foreign body [1–3]. The cellular response is thought to isolate and encapsulate the implanted electrodes by displacing adjacent neurons [4]. The size of electrode and the stiffness of substrate material contribute to the tissue trauma resulting from insertion [5]. Batch fabricated rigid Silicon probes have a Young's modulus of 190 GPa, while the brain's Young's modulus is orders of magnitude smaller (~25kPa) [6]. Due to this mismatch in mechanical properties of brain and implanted probe, mechanical disruption of the neuropil occurs. To tackle this, thin film-like flexible polyimide probes were designed, intended to mechanically comply with the adjacent brain tissue in at least one dimension [7–9]. This is expected to reduce micro-movement between the tissue and electrode and, minimize glial sheath build up around the electrode [10–12]. Unfortunately, the structural features of these probes pose challenges during insertion into the brain [13,14]. Probes with increased thickness and width can easily withstand higher forces during insertion, but this in turn is expected to cause a stronger tissue response [5]. The use of insertion aids for flexible probes increases tissue damage, limiting the advantages of flexible electrodes [15]. We propose in the following the use of a microfluidic device to provide the necessary forces for pial penetration of flexible probes by means of fluid forces. The goal is to achieve implantation without the use of implantation aids.

1.1 Buckling and dimpling phenomena

Microprobe implantation in rat brain is influenced by a phenomenon dubbed "dimpling" and is most prominently visible in large craniotomies. It describes deformation of brain upon localized [probe tip] load. Upon further progression of the probe, the strain in the pial membrane reaches a peak, the pia ruptures locally and the probe penetrates the surface, resulting in a spring-back of the compressed brain, and a drop in strain [16]. Both deformation and spring-back are expected to cause tissue damage and thus should be minimized [5]. The force required for the initial penetration of the pia has been reported to be in the range of a few mN (~5mN) [17]. Another factor influencing tissue damage during implantation is the speed at which the probe is inserted. It has been established in various studies that faster insertion results in lower vascular damage and easier penetration of the pia mater [5,18,19].

***Corresponding author: Ulrich G. Hofmann:** Section of Neuroelectronic Systems, Faculty of Medicine, University of Freiburg, Germany, e-mail: ulrich.hofmann@coregen.uni-freiburg.de
Shubratha Koralagundi Gopalakrishnaiah, Kevin Joseph: Section of Neuroelectronic Systems, Faculty of Medicine, University of Freiburg, Germany, e-mail: shubratha.kg@gmail.com, kevin.joseph@uniklinik-freiburg.de

Open Access. © 2017 Shubratha Koralagundi Gopalakrishnaiah et al., published by De Gruyter. BY-NC-ND This work is licensed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 License.

In order to achieve successful insertion of any neuronal probe, the probe must be sufficiently mechanically robust to withstand the penetration force. In other words, penetration force must not exceed the critical buckling force the neuronal probe can withstand [13]. Although there are several modes of beam buckling, we consider only the first mode, as it gives us a lower bound for acceptable load. Our multisite probes are modeled as a column clamped at one end and pinned at the other (fixed-pinned buckling case) [20]. The theoretical load a probe can carry without buckling is given by Euler's equation:

$$F_{cr} = \frac{K\pi^2 EI}{L^2}$$

where F_{cr} is the buckling force, K is the effective column length factor (K=2.045 for fixed-pinned case), E is the elastic modulus of the probe, L is the unsupported beam length, and, I is the area moment of inertia of the probe, which varies as cube of thickness of the probe ($I = wt^3/12$), as shown in Figure 1.

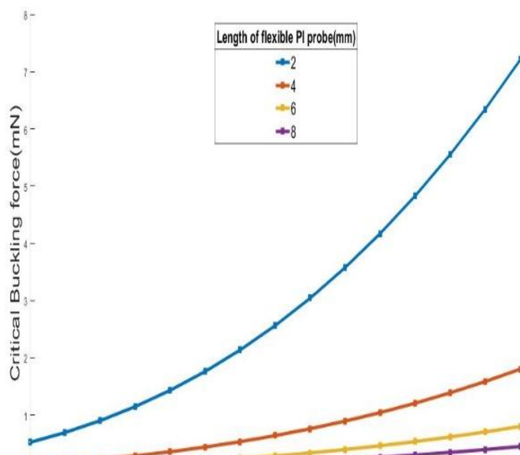

Figure 1: Graph showing variation of critical buckling load with various thickness and length of flexible polyimide probe.

2 Materials and methods

2.1 Fabrication

Y-shaped microfluidic channels were fabricated using Polydimethysiloxane (PDMS, Sylgard 184, Dow Corning) mixed in the ratio of 10:1 of elastomer and curing agent and cast on a mold to have an effective inner diameter of 1.5 mm. This mixture was cured at 100°C for 45 minutes and 1.5 mm

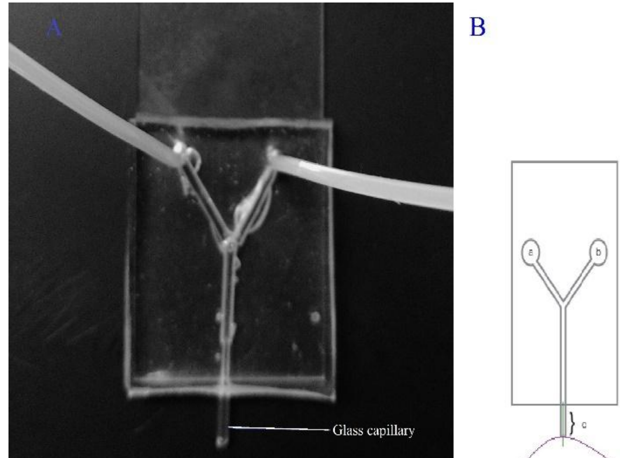

Figure 2: (A) Microfluidic device with a glass capillary mounted at the outlet. (B) Sketch of microfluidic device mounted on a micromanipulator on top of "brain model" from agarose.

inlet holes were punched through the PDMS using a Biopsy punch (pfm medical, Germany). PDMS substrate with channels embossed on one face was bonded to a clean microscopic glass slide using a plasma deposition device (Corona SB, BlackholeLab, Paris) to produce a sealed fluidic system. A glass capillary (O. D=1.5mm, Sutter Instruments, USA) was then mounted at the outlet port and a flexible probe without connector pad was placed in it, as shown in Figure 2.

Table 1: Dimensions of the Microfluidic channels

	Length [mm]	Width [mm]
Main channel	15	1.5
Side channels	10	1.5
Glass Capillary	8	1.5

2.2 Experimental setup

The whole microfluidic device was mounted on a micromanipulator and placed above a slab of clear 0.6% Agarose gel. Pressurized air-water injection was used to drive the flexible probe rapidly into the agarose slab. PTFE tubing (O. D=1.5mm) was used as a conduit for water (inlet a), and compressed air (inlet b), as shown in Figure 2B. The pressurized air originated from a clinical use supply and its output was manually controlled and monitored.

Figure 3: Air Pressure profile applied during flexible probe implantation.

2.3 Insertion procedure

The microfluidic device was advanced close to the target, which, in this case, is 0.6% agarose gel, the Young's modulus of which is similar to brain tissue. This similarity most likely does not extend to brains' viscous properties [21]. The glass capillary was positioned just above the surface of the agar gel. A pressure pulse (~0.4 bar) was applied to produce an initial insertion of the probe in agar, thus overcoming the penetration forces exerted on it. The pressure profile applied at the inlet of device is as shown in Figure 3. Water (<0.5 ml) was then injected to produce a focused flow of water most suited for insertion of probe. The micromanipulator was simultaneously retracted away from the surface during this jet injection. The use of air aids in the initial penetration of the flexible probe into agarose, and eliminates the need for large liquid volumes necessary for focused stream generation [22].

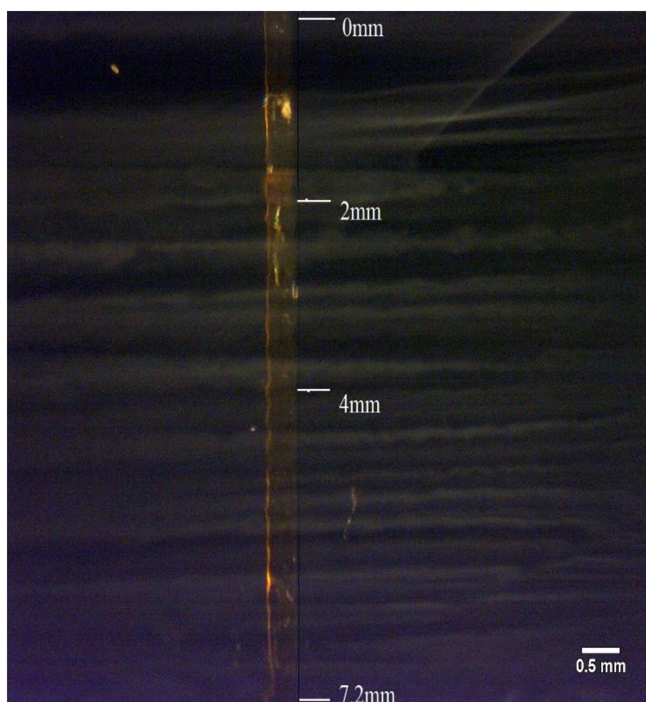

Figure 4: Flexible probe 400 μm wide and 10 μm thick implanted in agarose, imaged using a custom built white light selective plane microscope [21].

3 Results

The advantage of this method is the successful implantation of very flexible, film-like polyimide probes into agarose slabs, modelling brain regions; without any external aids or stiffeners. The implantation was tested into 0.6% agarose gel and we could implant our flexible probes up to a depth of 7.2mm as shown in Figure 4.

4 Discussion

Flexible microprobes are receiving increasing interest with respect to their beneficial long term characteristics as compared to rigid wires. However, the implantation of flexible probes itself is a matter of concern, as removable implantation aids [15,23] increase the surgical footprint, thus potentially nullifying the flexible probes' advantages.

Fluidics supported insertion of carbon nanotube fibers was reported recently (personal communication Jacob T. Robinson), but to our knowledge no attempt was made up till now to implant film like polyimide probes in brain-like materials that way.

The presented approach of implantation by fluidic force actuation aims to ameliorate the stab wound artefact by avoiding use of external aids. We were able to achieve an insertion of up to 7.2mm in 0.6% agarose, with just air and water pressures inside fluidic channels yielding only minimal injection of fluid. The results show that insertions achieved were not without problems as the probes occasionally buckled once they were inside the agar gel. Further investigations with respect to microfluidic drive geometry and fluid pressures have to be made in order to overcome this bending of the flexible polyimide probe inside the agar gel and obtain precise positioning of the probe. Also, implantation of the flexible probe along with its connector pad by using another inlet port has to be carried out. Further investigations to ascertain the effect of probe insertion, and air-water pressures on brain tissue by means of in vivo imaging and histology studies must be conducted. This could pave the way for improved signal recording and glial scar free neural interfaces in brain machine interfacing applications.

Acknowledgment

We would like to acknowledge Jacob T Robinson who have previously reported on fluidic insertion of carbon nanotubes, upon which this work was inspired.

Author's Statement

Research funding: The authors acknowledge partial funding by the Cluster of Excellence BrainLinks-BrainTools (DFG EXC 1086). Conflict of interest: Authors state no conflict of interest. Informed consent: Informed consent is not applicable. Ethical approval: The conducted research is not related to either human or animals use

References

[1] Nolta NF, Christensen MB, Crane PD, Skousen JL, Tresco PA. BBB leakage, astrogliosis, and tissue loss correlate with silicon microelectrode array recording performance. Biomaterials. 2015 Mar 30;53:753–762.

[2] Marin C, Fernández E. Biocompatibility of intracortical microelectrodes: current status and future prospects. Front Neuroengineering. 2010 May 28;3:8.

[3] Williams JC, Rennaker RL, Kipke DR. Stability of chronic multichannel neural recordings: Implications for a long-term neural interface. Neurocomputing. 1999 Jun;26-27:1069–1076.

[4] Polikov VS, Tresco PA, Reichert WM. Response of brain tissue to chronically implanted neural electrodes. J Neurosci Methods. 2005 Oct 15;148(1):1–18.

[5] Welkenhuysen M, Andrei A, Ameye L, Eberle W, Nuttin B. Effect of insertion speed on tissue response and insertion mechanics of a chronically implanted silicon-based neural probe. IEEE Trans Biomed Eng. 2011 Nov;58(11):3250–3259.

[6] Felix S, Shah K, George D, Tolosa V, Tooker A, Sheth H, et al. Removable silicon insertion stiffeners for neural probes using polyethylene glycol as a biodissolvable adhesive. Conf Proc IEEE Eng Med Biol Soc. 2012;2012:871–874.

[7] Stieglitz T, Gross M. Flexible BIOMEMS with Electrode Arrangements on Front and Back Side as Key Component in Neural Prostheses and Biohybrid Systems. In: Obermeier E, editor. Transducers '01 eurosensors XV. Berlin, Heidelberg: Springer Berlin Heidelberg; 2001. p. 358–361.

[8] Löffler S, Xie Y, Detemple P, Moser A, Hofmann UG. An implantation technique for polyimide based flexible array probes facilitating neuronavigation and chronic implantation. Biomedical Engineering / Biomedizinische Technik. 2012 Jan 6;57(SI-1 Track-S).

[9] Boehler C, Kleber C, Martini N, Xie Y, Dryg I, Stieglitz T, et al. Actively controlled release of Dexamethasone from neural microelectrodes in a chronic in vivo study. Biomaterials. 2017 Jun;129:176–187.

[10] Lo M, Wang S, Singh S, Damodaran VB, Kaplan HM, Kohn J, et al. Coating flexible probes with an ultra fast degrading polymer to aid in tissue insertion. Biomed Microdevices. 2015 Apr;17(2):34.

[11] Sharp AA, Ortega AM, Restrepo D, Curran-Everett D, Gall K. In vivo penetration mechanics and mechanical properties of mouse brain tissue at micrometer scales. IEEE Trans Biomed Eng. 2009 Jan;56(1):45–53.

[12] Subbaroyan J, Martin DC, Kipke DR. A finite-element model of the mechanical effects of implantable microelectrodes in the cerebral cortex. J Neural Eng. 2005 Dec;2(4):103–113.

[13] Weltman A, Yoo J, Meng E. Flexible, penetrating brain probes enabled by advances in polymer microfabrication. Micromachines. 2016 Oct 4;7(10):180.

[14] Luan L, Wei X, Zhao Z, Siegel JJ, Potnis O, Tuppen CA, et al. Ultraflexible nanoelectronic probes form reliable, glial scar-free neural integration. Science advances. 2017 Feb 15;3(2):e1601966.

[15] Richter A, Xie Y, Schumacher A, Löffler S, Kirch RD, Al-Hasani J, et al. A simple implantation method for flexible, multisite microelectrodes into rat brains. Front Neuroengineering. 2013 Jul 24;6:6.

[16] Olamat, A. E., Nkemasong N., Pohl B. M., Hofmann U. G. [2010]. Physical and FEM simulation of microprobe insertion into rat brain. European COMSOL Conference 2010. Paris.

[17] Jensen W, Yoshida K, Hofmann UG. In vivo implant mechanics of single-shaft microelectrodes in peripheral nervous tissue. 2007 3rd International IEEE/EMBS Conference on Neural Engineering. IEEE; 2007. p. 1–4.

[18] Bjornsson CS, Oh SJ, Al-Kofahi YA, Lim YJ, Smith KL, Turner JN, et al. Effects of insertion conditions on tissue strain and vascular damage during neuroprosthetic device insertion. J Neural Eng. 2006 Sep;3(3):196–207.

[19] Li L, Zhou J, Li Y, Chen F, Wang Y. Insertion force of micro-probe into brain phantom. 2016;(Ifmeita):310–316.

[20] Singh S, Lo M-C, Damodaran VB, Kaplan HM, Kohn J, Zahn JD, et al. Modeling the Insertion Mechanics of Flexible Neural Probes Coated with Sacrificial Polymers for Optimizing Probe Design. Sensors Basel Sensors. 2016 Mar 4;16(3).

[21] Yassine, M. F., K. Joseph and U. G. Hofmann [2017]. Setup of a white light selective plane microscope to investigate microprobe insertion in a brain model. to appear EMBEC and NBC 2017. Tampere, IFMBE.

[22] Trebbin M, Krüger K, DePonte D, Roth SV, Chapman HN, Förster S. Microfluidic liquid jet system with compatibility for atmospheric and high-vacuum conditions. Lab Chip. 2014 May 21;14(10):1733–1745.

23]. Kozai TDY, Kipke DR. Insertion shuttle with carboxyl terminated self-assembled monolayer coatings for implanting flexible polymer neural probes in the brain. J Neurosci Methods. 2009 Nov 15;184(2):199–205.