Journal of Neuroscience Methods 180 (2009) 290–295

Contents lists available at ScienceDirect

Journal of Neuroscience Methods

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

A minimally invasive displacement sensor for measuring brain micromotion in 3D with nanometer scale resolution

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ARTICLE INFO

Article history:
Received 1 December 2008
Received in revised form 7 April 2009
Accepted 9 April 2009

Keywords:
Brain micromotion
Active stabilization
Electrophysiology
Imaging
Displacement sensor
Optoelectronic devices

ABSTRACT

Electrophysiological recordings from a single or population of neurons are currently the standard method for investigating neural mechanisms with high spatio-temporal resolution. It is often difficult or even impossible to obtain stable recordings because of brain movements generated by the cardiac and respiratory functions and/or motor activity. An alternative approach to extensive surgical procedures aimed to reduce these movements would be to develop a control system capable of compensating the relative movement between the recording site and the electrode. As a first step towards such a system, an accurate method capable of measuring brain micromotion, preferably in 3D, in a non-invasive manner is required. A wide variety of technical solutions exist for displacement measurement. However, increased sensitivity in the measurement is often accompanied by strict limitations to sensor handling, implementation and external environment. In addition, majority of the current methods are limited to measurement along only one axis. We present a novel, minimally invasive, 3D displacement sensor with displacement resolution exceeding 70 nm along each axis. The sensor is based on optoelectronic detection of movements of a spring-like element with three degrees of freedom. It is remarkably compact with needle-like probe and can be packaged to withstand considerable mishandling, which allow easy implementation to existing measurement systems. We quantify the sensor performance and demonstrate its capabilities with an *in vivo* measurement of blowfly brain micromotion in a preparation commonly used for electrophysiology.

1. Introduction

In an ideal experiment one would be able to monitor neural activity of unconstrained animals while they behave in the natural environment. Although this is not feasible with current technologies, it is possible to perform electrophysiological recordings from the brain while approximating natural conditions in the laboratory. However, even with an immobilized animal, the brain is going through significant micromotion often-making *in vivo* electrophysiology challenging. The main movement sources consist of periodic physiological processes such as cardiac and/or respiratory pulsations as well as movements generated by the muscles close to the recording site. In minimally restrained preparations, such as head fixed vertebrates or tethered insects, there often exist additional movement artifacts due to voluntary behavior or spontaneous motor activity. Additional brain motion may be induced by the vibrations in the measurement system or those caused by the experimenter.

Careful characterization of the micromotion has been performed in few animal models. In cat, the brain motion was shown to consist of two main components: the arterial component with amplitude of 110–266 μm and the respiratory component giving rise to large 300–950 μm plateau-like displacements (Britt and Rossi, 1982). In the anesthetized rat, surface micromotion was measured to be 2–25 μm as induced by the respiratory pressure changes and 1–3 μm attributable to the vascular pulsations. Additional long-term drifts on the order of 80 μm were observed and found to be correlated with the level of anesthesia (Muthuswamy et al., 2003). In another study 30–40 μm brain movements were observed in a head fixed rat running on a track ball, effectively preventing stable intracellular recordings from cortical neurons (Fee, 2000). In their preparation the loss of the recording typically occurred with 5–10 μm movements.

Methods of stabilizing the brain vary from preparation to preparation. Typically they involve extensive surgical procedures aimed to eliminate movement sources (e.g. Britt and Rossi, 1982) and/or attaching recording instruments securely to stable structures close to the recording site, such as the cranium (e.g. Helmchen et al., 2001; Lee et al., 2006). In an elegant study the brain motion of the zebra finch and the rat were determined and actively compensated

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doi:10.1016/j.jneumeth.2009.04.004

during *in vivo* intracellular recordings either by prediction based on physiological signals or by motion measured directly from the cranial surface (Fee, 2000). However, the direct method used in the study to measure displacement was limited to 1D and, therefore, it is best suited for situations where movement is mainly along the electrode axis and/or the electrode is very compliant tolerating the motion perpendicular to its axis.

Common commercial methods to measure displacement are typically based on capacitive, inductive, reluctive or potentiometric sensing (Norton, 1998). For higher performance, scanning probe microscopy, especially the atomic force microscopy (AFM), provides a tool to image surfaces with a very high resolution (Sarid, 1994). However, measurements are limited to small displacements in only one dimension. Another common method for high accuracy displacement sensing, especially in research settings, is laser interferometry (Fee, 2000; Malacara and Thompson, 2001). Similarly to the AFM, it is limited to only one dimension and it has special requirements for the implementation, making it impractical for many applications. In general, sensors capable of multidimensional displacement sensing are not common, but they can be found, e.g. in coordinate measuring machines (Miguel et al., 1998; Oiwa and Nishitani, 2004).

Despite the plethora of commercially available sensors, we did not find one suitable for our application given their size, resolution or implementation constraints. In this study, we present a novel 3D displacement sensor and demonstrate its suitability for *in vivo* measurements of the brain micromotion.

2. Materials and methods

2.1. Electronics

Photo-interrupters are optical transceivers typically consisting of a GaAs LED as an infrared emitter and Si phototransistor as a detector. Transmitted optical power is measured as a light current through the detector and it is directly proportional to the light blocked (or passed) by an obstacle placed between the emitter and detector. Sensing range depends on the detector slit width, which is usually 150, 300 or 500 μm. We used a photo-interrupter (Rohm Rpi-124F) with emission wavelength of 950 nm, detector slit width of 150 μm and the gap between emitter and detector of 1 mm.

Low noise electronics was developed to monitor photo-interrupter light current (Fig. 1). Voltage reference (Linear Technology Co., LT1461) is used to make a stable 5 V operating voltage for the whole circuit. Operational amplifier (op-amp; Analog Devices Inc., AD8629) and a transistor form constant current source for the transmitter LED. The current is controlled with the reference voltage in non-inverting input of the op-amp and with the resistance in the transistor emitter. Detected light current is measured

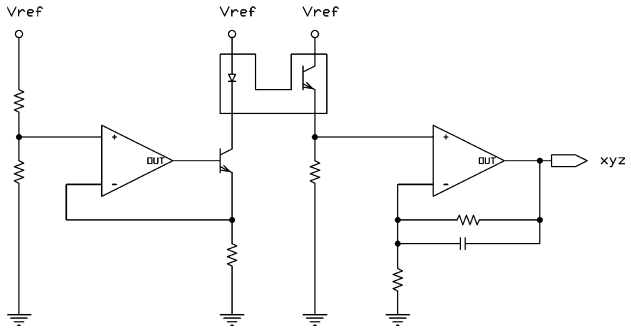

Fig. 1. Schematics of the electrical circuit used for the measurements. Operating principle and component types are explained in Section 2.

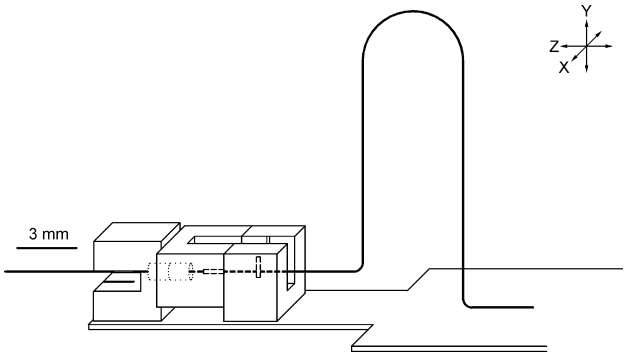

Fig. 2. Illustration of the 3D displacement/force sensor showing the tungsten wire and arrangement of the photo-interrupters placed on alumina platform. Aluminum foil flags (dashed rectangles) were glued on the wire between the emitter/detector pairs drawn as rectangular slots in each photo-interrupter. Axes definitions as used throughout the study.

as a voltage across the resistor and amplified to 0–5 V using the second channel of the op-amp. The op-amp is a dual chopper-stabilized (auto-zero) rail-to-rail input/output op-amp, which reduces offset voltage and drift afflicting accurate dc-measurements (offset voltage of 1 μV and drift of 0.002 μV/°C). Chopping action also eliminates $1/f$ noise, which is a major noise source in electronic dc-measurements (Northrop, 2005).

2.2. Sensor calibration

Displacement–force calibration of the 1D prototype was done using distance encoded positioner (SmarAct GmbH, SL2040 XYZ), load cell (Kyowa Electronic Instruments Co., LTS-50GA), multimeter (Hewlett Packard Co., 3457A) and digital voltmeter (Precision Mastech Enterprises Co., MY-64). Displacement calibration of the 3D prototype (Fig. 2) was carried out with the prototype fixed rigidly to a positioner from the tip of the spring-like element (Piezosystem Jena GmbH, Tritor 100 SG). Measured data was low-pass filtered (1 kHz 3 dB corner frequency) and collected with a data acquisition board (Meilhaus Electronic GmbH, ME-4600).

2.3. Mechanical model

A mechanical model of the spring-like element was developed using finite element method (FEM), which is a numerical modeling technique developed to solve differential equations by splitting a continuous domain into a set if discrete elements (Strang and Fix, 1973). It is generally used to model and simulate complex physical systems, e.g. in mechanical engineering and structural analysis. We used ANSYS software to generate the mechanical model by importing a 3D CAD-model of the prototype using a rectangular mesh with 32,000 nodes (ANSYS, Ansys Inc., USA). ANSYS Workbench was used for the simulations.

2.4. Brain micromotion measurements

A blowfly (*Calliphora vicina*) was fixed ventral side up to a piece of glass using beeswax. Legs were removed and the head tilted forward and fixed in place to provide access to the posterior side of the head. Head capsule was opened, brain surface exposed and bathed in saline. No further surgical operations were conducted to enable measuring brain motion in a minimally invasive preparation. The preparation was transferred to a vibration-isolated table located in an EM-shielded room. Mechanical micromanipulator (Sutter Instrument Co., MP-85) was used to place tip of the tungsten wire in touch with the brain (Fig. 3). Data was recorded with a computer controlled data acquisition system with a sampling fre-