Nanoelectrode Arrays for measuring Sympathetic Nervous Activity

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Nanoelectrode Arrays for measuring Sympathetic Nervous Activity

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Abstract—This paper reports on the use of arrays of nanoelectrodes to measure activity of the Sympathetic Nervous System. Measurements of the Sympathetic Nervous Activity (SNA) have not been easy; primarily because of poor signal-to-noise ratio (SNR). We report improved SNR of SNA measurements achieved by the use of novel Planar Nanoelectrode Arrays (PNA). Nano scale features on the electrodes provide increased contact area with the host nerve reducing the limiting (Johnson) noise. These electrodes are fabricated using standard CMOS compatible fabrication techniques on a high resistivity silicon substrate and used to measure SNA in test animals. For comparison, traditional wire electrodes were used simultaneously to measure the same signal. The PNAs consistently exhibit significant improvement in the SNR of the measured SNA (35.71 dB vs. 25.08 dB for the wire electrode). Moreover, the PNAs are capable of recording events lost in the noise floor of the wire electrodes.

I. INTRODUCTION

The Sympathetic Nervous system exerts part control over many involuntary functions of the body in order to maintain homeostasis. Although continually active, it has the property of adjusting in response to stressful situations like trauma, fear, hypotension and hypoglycemia. SNA is akin to communication signals and takes the form of a series of pulses or a spike train. Salient features of such a spike train are the signal amplitude, the SNR and the frequency of the spikes. The main motivation behind this work is to test the hypothesis that the use of recording electrodes incorporating nano scale features can allow the continuous monitoring of SNA with improved signal-to-noise ratio SNR, ultimately improving our understanding of “sympathetic tone”. If a biophysical relationship is found between sympathetic activity and life-threatening cardiovascular diseases, it is conceivable that by monitoring autonomic signals in high risk patients, earlier diagnosis by medical personnel would be possible. Treatment could then be started earlier, thereby increasing the possibility of preventing the ensuing morbid or fatal events. For this purpose, it is imperative to be able to measure SNA with high sensitivity. Traditionally SNA measurements have not been easy because of poor SNR. Mathematically, SNR is given as:

\[ \text{SNR} = 20 \log \left( \frac{V_{signal}}{V_{noise}} \right) \text{ dB} \]  

Here \( V_{signal} \) is the amplitude of the signal in volts while \( V_{noise} \) is the average noise value of the signal, also in volts.

There are different sources of noise in electrical measurements but Thermal or Nyquist-Johnson noise is the limiting noise. In this work we present an attempt to reduce the Johnson noise limit by incorporating nano-scale features on the surface of a planar electrode – hence the name PNA. Fig.1 shows an image of a section of the electrode surface made with a confocal imaging system. Electrodes are fabricated with metal nanoprobes with a pitch of ~ 1.5 \( \mu \)m. The probe height is controllable and can be fabricated to pierce the host nerve up to different depths. The examples shown in this work are ~ 2 \( \mu \)m tall. The increased electrode area and hence reduced electrode resistance improves the SNR
After fabrication, dicing, wirebonding and packaging, the PNAs were compared against traditional wire electrodes in the measurement of SNA using a digital data recorder.

II. PLANAR NANOELECTRODE ARRAYS

A. Noise in Electrical Measurements

Various types of noise in electrical measurements include Shot noise, flicker (1/f) noise, and thermal (Nyquist-Johnson noise)\[1\]. Thermal noise generated by the random thermal motion of charge carriers in an electric conductor is the limiting noise present in the system. In order to improve the sensitivity of the system, the Johnson noise will have to be reduced. The Johnson noise expressed as a voltage is given by:

\[ V_J = 4k_BRT\Delta f^{1/2} \] \( \text{(V Hz}^{-1/2} \text{)} \) \( \text{(2)} \)

where \( V_J \) is the Johnson noise voltage (V), \( k_B \) is the Boltzman constant \( 1.38 \times 10^{-23} \text{ (m}^2\text{kg}^{-1}\text{s}^{-2}\text{K}^{-1}) \), \( R \) is the circuit (including electrode) resistance (\( \Omega \)), \( T \) is the temperature (K), and \( \Delta f \) is the frequency bandwidth over which the measurements are made (Hz.). For applications where temperature and/or bandwidth reduction are not options, the circuit resistance remains the only parameter that can be used to reduce the Johnson noise. Provided the electrode resistance is the dominant resistance in the circuit, increasing the surface area of the electrode reduces the Johnson noise of the circuit.

B. Fabrication of Nanoelectrode Arrays

The nanoelectrode arrays were fabricated using standard CMOS compatible fabrication techniques. High resistivity double side polished silicon wafers with resistivity > 10,000 \( \Omega \text{cm} \) were used. Each device consisted of two electrodes. Since SNA measurements were made in a differential mode, high resistance was necessary to provide maximum isolation between the adjacent electrodes on a single chip. Thermal oxidation was used to grow ~ 500nm of silicon oxide on the silicon (Fig. 2(a)). This oxide is necessary to provide preferential oxidation downstream in the processing to fashion the sharp nanoprobes. Following e-beam lithography using a Vistec VB-6\textsuperscript{TM} to generate the pattern to form the micropillars, a dry etch process in a Panasonic E620\textsuperscript{TM} etcher was used to create an array of micro pillars. The micropillars were composed of ~2\( \mu \text{m} \) tall Si, with 500nm of SiO\textsubscript{2} (Fig. 2(b)). A thermal oxidation process was employed to fashion conical tips in the Si micropillars(Fig. 2(c)). This was a crucial step during the fabrication process but is well documented in literature\[2\],\[3\]. The extent of oxidation determines the height of the nanoprobe as well as the sharpness of the nanotip. The Oxide is etched away using standard buffered oxide etch (BOE) solution to yield sharp Si pillars that serve as a mold for silicon nitride (SiN) cones (Fig. 2(d)). A Low Pressure Chemical Vapor Deposition (LPCVD) process is used to deposit ~ 1000Å silicon nitride on the silicon wafer covering the nanoprobe array (Fig. 2(e)). The SiN cones are then made hollow by removing the Si using a wet potassium hydroxide (KOH) etch process from the backside of the wafer. Back side lithography was employed to create openings in the SiO\textsubscript{2} from the backside using a Karl Suss MA6 aligner (Fig. 2(f)). The hollow SiN molds were filled with gold by

Figure 2. PNA fabrication process flow: (a) Growth of SiO\textsubscript{2}, (b) formation of micro-pillars, (c) thermal oxidation to form nanotips, (d) wet etch of SiO\textsubscript{2}, (e) deposition of LPCVD SiN, (f) wet Si etch from backside, (g) backside Au evaporation, (h) removal of SiN above the nanotips and wet etch of the backside Au to isolate electrodes and form bond pads, (i) Wirebonding to the backside Au pads and insulation of the device backside using Araldite 2011.
evaporating approximately 1µm of gold using an e-beam evaporator (Fig. 2(g)). The blanket gold layer on the back was fashioned into gold contact pads using optical lithography and a wet etch process with Transene TFA gold etchant (Fig. 2(h)). This also isolates the two electrodes and associated bond pads on the back side of the wafer. The devices were diced using a dicing saw before the individual devices were cleaned and stripped of protective photoresist using solvents. Up to this point, the metal nanoprobes were covered with SiN film that had served as a mold for tip formation earlier on. The SiN film was removed using an SF₆ based dry etch process, thus exposing the nanoprobe array (Fig. 2(h)). The individual devices were then bonded to wires using epoxy conductive adhesive EPO-TEK EE129-4 (Electronic Microscopy Sciences, Hatfield, PA). After the electrical contacts were made, insulating elastomer Araldite 2011 (Huntsman, Los Angeles, CA) was used for electrical isolation of the devices on the backside (Fig. 2(i)).

Figure 3. SEM image of an array of Au nanoprobes. The nanoprobes are ~ 2µm tall and have a tip dia. of ~250nm. Also shown is a less magnified SEM image of the extent of the array in an electrode (inset)

III. MEASUREMENTS

Sympathetic Nervous Activity was measured on an animal model (dog). To compare the performance of the PNA to a conventional wire electrode, simultaneous measurements were made using both types of electrodes. To enable differential mode measurements, both the devices consisted of two electrodes each. The electrodes were placed on an exposed stellate ganglion of the test animal (Fig. 6). The signal from the electrodes was fed to a DAM 50™ differential amplifier made by World Precision Instrument for pre-amplification before being input to an Axon Instruments Low Noise Data Acquisition System Digidata 1440A™.

Figure 4. After fabrication and dicing, each device is wirebonded before being covered with insulating elastomer (Araldite 2011) on the backside. The devices are 2.5mm x 4.0mm and have two electrodes to facilitate differential mode SNA measurements. The device shown above has over 120,000 nanoprobes

Figure 5. PNA (a) and conventional metal wire electrode (b) placed on exposed left stellate ganglion of a test animal for simultaneous SNA measurements

Figure 6. Sample SNA over a 1s interval showing EKG signals (top) as well as voltages measured using a conventional wire electrode (middle) and a PNA(bottom). Within the red outline are examples of events recorded by the PNA but not by the wire electrode.
A sampling rate of 10kHz was used during measurements. While the metal wires pierced the nerve, the PNA sat atop the ganglion and was secured with sutures to adjacent tissue (Fig. 5). Alpha-chloralose was used as the anesthetic. Nerve activity was stimulated by injecting Apamin to the left stellate ganglion. A sample neurograph over a 1s time interval is shown in Fig. 6. The horizontal axis shows time in seconds while the vertical axis is voltage in Volts. The electrocardiograph (EKG) signal as well as the SNA measured with the wire electrode and PNA is shown. It can be seen that the signal pulses are much more prominent when measured with the PNA. The maximum recorded signal voltages were 91.55±8.2μV and 30.51±6.8μV for the PNA and metal wire respectively. The mean noise voltages were measured to be 1.5±3.9μV and 1.7±5.6μV for the PNA and wire electrode respectively. The fact that the noise voltages are not much different for the two types of devices can be attributed to the noise signals not being at the limiting values. This can be addressed by designing a quieter measurement set up. Using (2), the SNR is 35.71dB for the PNA and 25.08dB for the metal wire. This is an improvement of over 10dB in the SNR of the SNA by using the PNA instead of conventional metal wire electrodes. Moreover, as can be seen in Fig. 6, the PNA is able to detect relatively weaker signals that are lost in the noise floor when using conventional metal wire electrodes. These signals could potentially provide useful information.

IV. CONCLUSIONS

Planar nanoelectrode arrays have been fabricated on high resistivity silicon wafers using standard CMOS compatible fabrication techniques. The devices were tested on animal models and have consistently exhibited improved SNR over conventional metal hook electrodes. The SNR of the measured SNA improves from 25.08dB in case of metal wire electrodes to 35.71dB in case of the PNAs. Moreover, lower amplitude pulses are distinctly measurable only when using the PNA.

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