Development of Implantable Wireless Biomicrosystem for Measuring Electrode-Tissue Impedance

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Abstract

The increase of impedance between electrode and tissue is the most relevant factor to cause the power loss in the implantable electrical stimulation application. This study aims to develop an implantable wireless biomicrosystem for impedance measurement between microelectrode and tissue through inductive link. A transcutaneous wireless transmission scheme was adopted in this study from which the power and command were transmitted into implantable module by using high efficient power transmitter and amplitude-shift keying (ASK) modulation technique. A sinusoidal wave approach with peak detector was applied for estimating impedance. The measured impedance were sampled and converted into digital signal which can be transmitted outwards through the same radio frequency (RF) link by using the load shift keying (LSK) modulation method. The developed wireless impedance measurement module was first validated during in-vitro test in which the increase in impedance was mainly due to the gradual adhesion of protein of blood plasma to microelectrode surface. The impedance measurements of our designed module were comparable to those obtained from the commercial LCR meter. For in-vivo monitoring the electrode-tissue impedance, the microelectrode was implanted between the skin and muscle of Wistar rat's dorsum. Those results indicated that total impedance decreased or maintained at the first three days and gradually increased around the fourth day after implantation.

Keywords: Biomicrosystem, Bi-directional Wireless Transmission, Impedance measurement, Neural prostheses

Introduction

In recent years, various biomicrosystems with specific sensors or actuators utilizing wireless powering and communication technology have been designed as biomedical devices for clinical applications or fundamental studies [1,2]. Among these applications, neural prostheses (NP) are devices that utilize electrical stimulation to generating artificial action potentials similar to natural ones to activate the damaged or disabled nervous system for restoring motor and sensation functions. In neural prostheses applications, implantable microstimulators and stimulation electrodes have offered new possibilities for the treatment of many organ failures [1,2,3]. Especially, implantable electrodes are placed around the peripheral nerve which can selectively stimulate the damaged nervous system for function restoration or to sense the neural activities for feedback purposes [4]. Among these implantable electrodes, nerve cuff electrode is one of the most suitable for nerve-based activation of the human nervous system because it is the least invasive and easiest to install [5].

For the implantable nerve cuff-type microelectrode, there are two interfaces, namely, the interface between epineurium connected tissue and the inner surface of the cuff microelectrode and that between periprosthetic tissue and the outer part of the cuff microelectrode. It is desirable that the repairing periprosthetic tissue may glue on the outer surface of the cuff microelectrode to support the execution of nerve stimulation and proximal muscle movement. Unlike the contact with central nervous system, the surface of inner cuff microelectrode is preferably nonadhered to protein and cells of the peripheral nerve to deliver the stimulation current to the nerve axons or to receive the action potential signal from axons [6].

The performance of electrical stimulation using the functional microelectrode is influenced by many factors. The most influential factor may come from the increase of electrode impedance at the interface between the nearby epineurial connective tissue and the inner surface of the cuff

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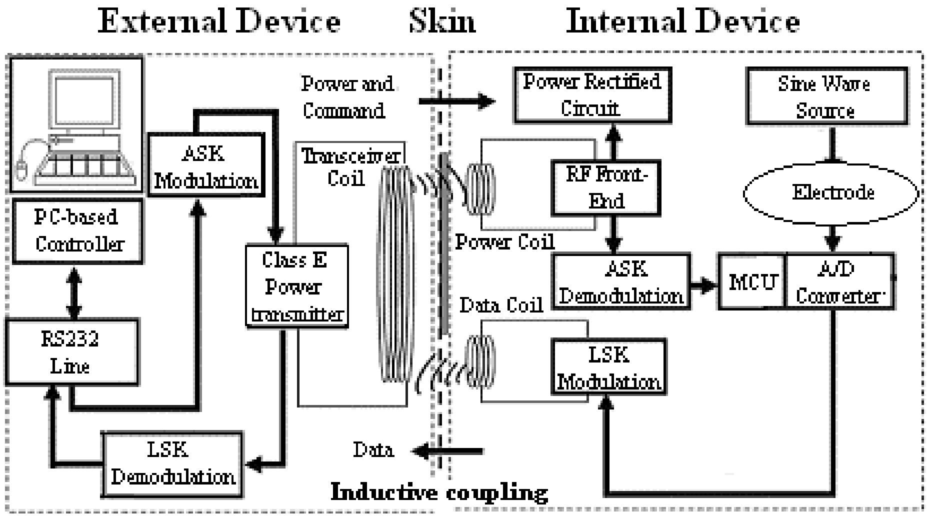


Figure 1. Overall system block diagrams of the bi-directional implanted device.

microelectrode. As the nerve microelectrode becomes sheathed, its electrode impedance increases, which may result in a deficiency in nerve stimulation or signal recording. The loss of electrical power owing to the increase of electrode impedance is the most relevant. The power loss factor should be as low as possible and also stable when encompassed the peripheral nerve or surrounded muscular tissue [6]. Thus, it is essential to design an implantable wireless module to continuously monitor the impedance between cuff electrode and tissue.

The aim of this study was to design an implantable impedance measurement module with bi-directional wireless transmission for in-vivo measurement of the impedance of nerve cuff electrodes. The wireless transmission system was based on an external transceiver unit which provides power and transmits data to the implantable device through a bi-directional inductive link. The wireless biomicrosystem was first validated by in-vitro impedance measurement resulting from the adhesion of blood plasma to cuff electrode surface. For in-vivo test, the cuff electrodes were coated with a layer of silicon gel which was implanted between the skin and muscle of Wistar rat's dorsum for in-vivo evaluation. The electrode-tissue impedance measurements recorded by our implantable biomicrosystem were compared with those detected by an LCR analyzer.

Material and Methods

A. Overall structure of wireless implantable biomicrosystem

The wireless transmission of power and commands of the implanted biomicrosystem was via a transcutaneously inductive link. In our design, the inductive link consists of two sets of resonant circuits which are realized by one transceiver coil at the external module and two internal coils for power and data transmission, respectively. When facing each other, the external coil and the internal power coil form a transformer which allows energy to transfer from the external transmitter to the internal implant [7]. The transmitted commands can be acquired after filtering out the digital signals modulated in the magnetic coupling power waveform. For outward transmission, the acquired digital data can be serially modulated on the reflection of transceiver coil via changing the properties in the internal data coil for transmitting out the digital data, alternately to the power transmission [7].

The overall structure of implanted biomicrosystem which can be divided into two major parts: the internal implantable module and the external control module, as depicted in Figure 1. The external unit consists of PC-based control panel written in VB program, data acquisition program programmed in LabVIEW, amplitude-shift keying (ASK) modulation module, class-E power transmitter, load shift keying (LSK) demodulation module and transceiver coil. The internal unit consists of power rectified circuit, ASK demodulation module, PIC microcontroller, impedance measurement circuit and LSK modulation module. In the implanted device, there is neither auxiliary battery nor percutaneous lead wires or cable connecting to external device.

The external unit transmits the power and command into the implant via RF telemetry. The commands are externally generated, binary coded, and transmitted by gating the RF waveform on and off [8][9]. Several researchers have successfully demonstrated the use of ASK modulation and high-efficiency class-E power amplifiers for inward transmission of power and commands simultaneously. The class-E amplifier scheme and ASK modulation techniques, proposed by [10][11], are adopted in the study. In ASK modulation, the amplitude of a carrier oscillation is switched between two amplitude states in the carrier according to the digital signal. The overall power and command recovery circuitry, which includes a receiving LC resonant tank, a power regulator with rectifier and voltage stabilizer, and two-staged ASK demodulator. When the class-E power amplifier transmits the power and embedded commands via the electromagnetic coupling, the LC parallel resonant tank is tuned such that its resonant frequency corresponds to the 2 MHz

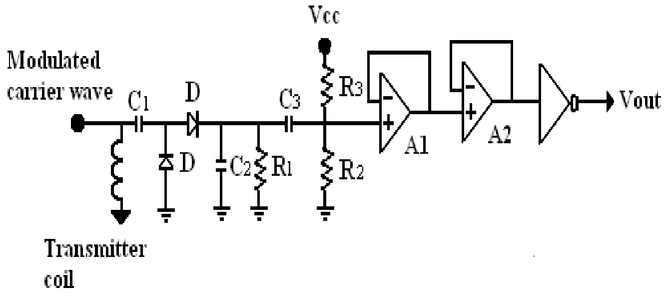


Figure 2. The external wireless transmission reader.

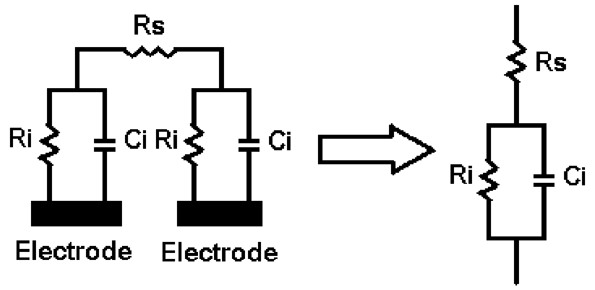


Figure 3. The electrical impedance model of a cuff electrode with serial resistance (Rs) and parallel resistance (Ri) and capacitance (Ci) originating from electrode- tissue interface.

carrier frequency of the external transmitter. The power supply of the implant is stabilized to ±6V and +3V by means of zener diodes and a negative voltage converter (LM2664). To recover the digital commands, the ASK demodulator recovers the original command data from the modulated RF wave. This is a two-staged process and is composed of an envelope detector and voltage divider after the same LC resonant tank of power recovery. The envelope detector, which consists of a low-pass filter and a high-pass filter, extracts the high-low signal variation of the 2 MHz carrier wave with a dc offset. After the implantable device receives the command signal, the implant decodes the command signals which include data acquisition setup for impedance measurement.

For outward transmission of measured data, current approach uses a two-coil strategy to protect the weak biological signal from the effects of the strong RF electromagnetic fields generated by the inductive coupling. The impedance reflection technique, utilizing a LSK modulation method, is generally adopted in implantable biomicrosystem application [9]. Our modified LSK scheme employs the characteristics of load impedance of the internal circuitry which is reflected to the transceiver coil to transmit the sensing data. Consequently, high-low voltages are induced in the primary resonant loop of the class-E transceiver. The function of the external LSK demodulation circuit is to extract the high-low fluctuating signal generated by the LSK modulation. The reader (i.e. the LSK demodulator), as shown in Figure 2, consists of a peak detector, an envelope detector, an adjusting circuit for the dc offset and voltage inverter. The

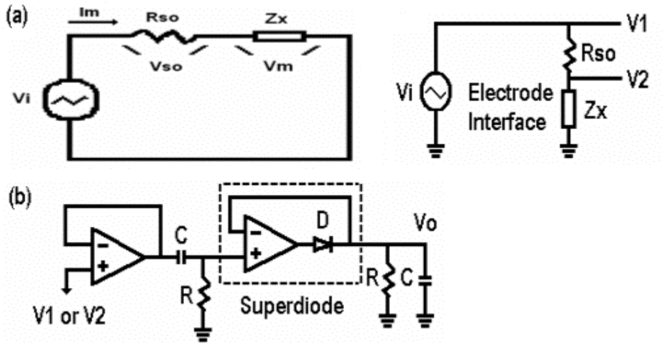


Figure 4. (a) The simplified model of sinusoidal approach for impedance measurement with a sinusoidal generator and a peak detector circuit, (b).

peak detector serves only to detect the modulated signal. The envelope detector, which consists of a low-pass filter and a high-pass filter, extracts the high-low signal variation of the 2 MHz carrier wave with a dc offset. Finally, the demodulated signal is then passed through the voltage inverter for level adjustment and transmitted to the PC via an RS-232 interface. The LabVIEW program collected and display the reconstructed data online. The recorded physiological signal could be post-processing in MATLAB.

B. The implantable wireless module for impedance measurement

To measure the impedance between cuff electrode and tissue, a parallel circuit mode, as illustrated in. Figure 3, was selected. To model the interface between cuff electrode and tissue, the resistance of saline solution in in-intro study and body fluid in in-vivo study, depicted as Rs in the parallel circuit mode, is assumed to be infinitesimal. Therefore, the effect of the parallel resistance (Ri) and parallel capacitance (Ci) have relatively more significant than that of serial resistance (Rs).

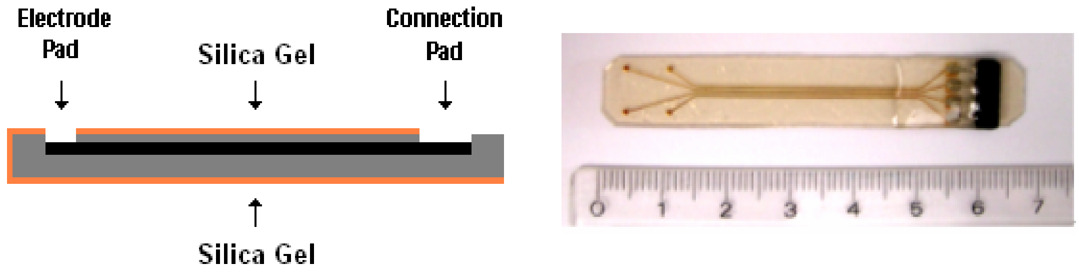
Common approach utilizes sine wave as source from which the impedance can be estimated from the simplified model of impedance measurement by using Ohm's law. [12]. Figure 4(a) depicts the simplified model of sinusoidal approach with source V_i for impedance measurement. Under this structure, the value of Rso is chosen as 220 KΩ. The impedance of electrode was calculated as follows:

$$\left|I_m\right| = \frac{\left|V_{so}\right|}{R_{so}} \tag{2.1}$$

$$\left|Z_x\right| = \frac{\left|V_m\right|}{\left|I_m\right|} \tag{2.2}$$

where, $\left|V_{os}\right|$ is the voltage on source resister R_{so}, $\left|V_m\right|$ and $\left|I_m\right|$ are output signal voltage and current with electrode impedance $\left|Z_x\right|$.

From the electrode-tissue impedance model, one of the common approaches is to apply the sinusoidal waveform as source and measure the amplitude difference and phase



(a) (b)

Figure 5. (a). The model of microelectrode after package. (b) the packaged microelectrode which was coated with a layer of silica gel (MED-1137, UnSil) for in-vivo test.

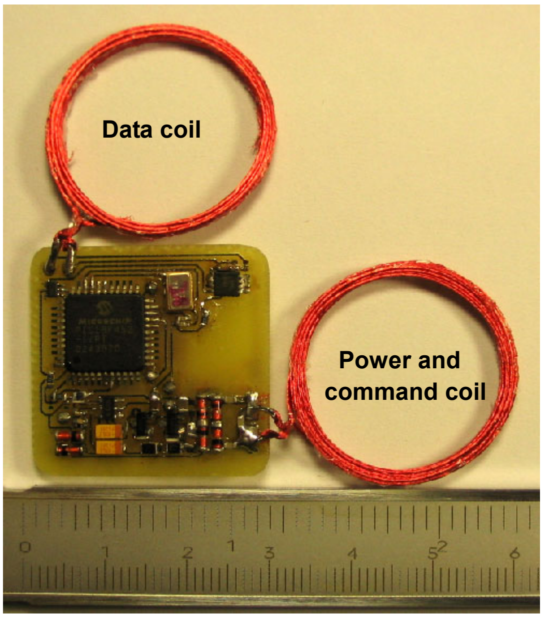


Figure 6. The implantable impedance measurement system.

between the input sinusoidal source from which the impedance and capacitance of the impedance model can be estimated. However, to measure the phase shift between source and measured output requires a very fast sampling rate. In this study, a simplified approach which estimates impedance from the known sinusoidal source and a peak detector.

Since the power consumption is a key factor in the implanted module, a low power consumption of Wien bridge oscillator is used to generate the sine wave source. The selection of "suitable" frequencies was mainly based on criteria that the spectrum of nerve signal is within range of 0.5~3.0 kHz, and the stimulation of the peripheral nerve being applied in the range of 10 Hz~2.0 kHz. Therefore, the impedance measured frequency of 1.2 kHz was chosen in this study. The sine wave output was limited below 5Vpp. Herein, a peak detection scheme, as shown in Figure 4(b), is used to estimate the total impedance. The peak of sine wave of V1 and V2 are all rectified to DC value. Therefore, the total impedance between cuff electrode and tissue can be calculated as:

$$\text{Total impedance (Zx)} = \frac{V_2 \times R_{SO}}{V_1 - V_2} = \frac{220V_2}{V_1 - V_2} \tag{2.3}$$

Where, the value of Rso is chosen at 220 KΩ. In the peak detector circuitry, the superdiode is used as a half-wave rectifier that could reduce the forward bias of the diode.

C. Experimental setup

<u>*In vitro validation of impedance measurement*</u>

The cell adhesion or protein absorption phenomena are inevitable on the surfaces of the microelectrode which result in an increase in the tissue-electrode impedance along the implantation time. The adhesion of the protein of blood plasma to the cuff electrode surface was used for *in-vitro* validation test of impedance measurement. Blood plasma was obtained from three male New Zealand white rabbits by centrifuged at 1200 rpm for 15 min and diluted to 1:3 with saline solution (i.e. 0.9% NaCl in D.I. water, pH value ≈7.0). The diluted blood plasma was heated to 37°C and incubated with Au/PI film of the cuff microelectrode at 100% humidity. For protein sediment test, the impedance value of microelectrode was measured 24 hours intervals for 14 days by using our wireless impedance measurement module as well as a standard commercially available LCR analyzer (Agilent 4294A precision LCR analyzer).

<u>*In-vivo measurement of electrode-tissue impedance*</u>

For in-vivo experiments, four male Wistar rats were used for implantation. Before implanting, the cuff electrode was coated with a layer of silica gel (MED-1137, UnSil). Figure 5(a) shows the model of microelectrode after package. Figure 5(b) show the packaged microelectrode which was coated with a layer of silica gel (MED-1137, UnSil) for *in-vivo* test. The length of microelectrode is 6 cm. The electrode pad is used to contact with tissue and the connection pad is used to connect with wireless impedance measurement device. The electrode was implanted between the skin and muscle of rat's dorsum for 10 days. For the *in-vivo* test, total impedance was measured from the contacting pads of electrodes extruded outside the rat's skin by an LCR analyzer and implanted impedance measurement device at 24-hour intervals. The amplitude of testing signal for LCR analyzer was 10 mVrms (AC). Data analyses were processed using MATLAB V6.5 software offline.

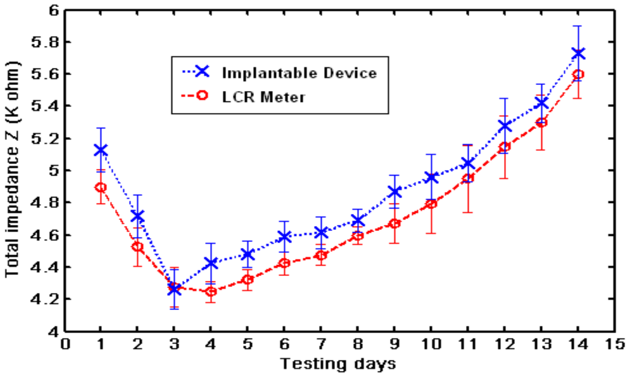


Figure 7. The total impedance (Z) versus the testing days of in vitro tests

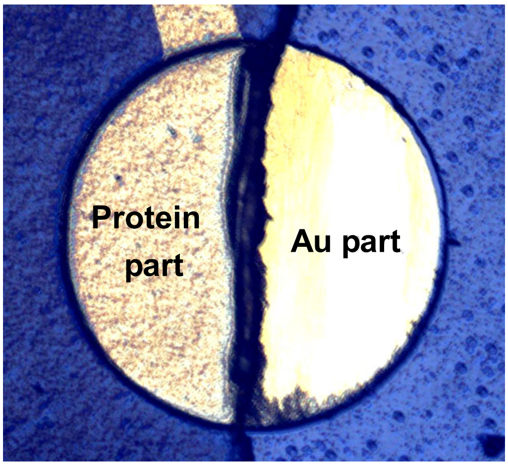


Figure 8. The microelectrode with and without residual protein upon the tested surface

Results

A. Specifications of implantable wireless module

In this study, the external device consists of external transceiver, RF transmission coil and external demodulator. The implantable device equips with two coupling coils, one for inward power and command transmission and another for outward data transmission. The RF transmitter coils are made of Litz wire (strands 48 AWG) formed in multi-twisted thin lines by twisting 8 bundles in a line and 175 strands in a bundle which gives a high inductance value. The implantable device is fabricated with surface mount device (SMD) components and mounted on a double-layer printed circuit board (PCB), as shown in Figure 6.

This prototype of implantable impedance measurement device is built on a double layered rectangular PCB in 3 * 3 cm^2, where overall power consumption of implanted device was measured around 70 mW. The maximum operating distance between the transceiver coil and receiver coil is about 3.5 cm for coupling enough power for implant operation. The diameter of data coil and power coil are 2.5cm. For the implantable impedance measurement device, we chose the microcontroller PIC18F452 (Microchip Company) with six channels of 10-bits A/D converter. The maximum digital data transmission rate can reach as high as 115 kbps.

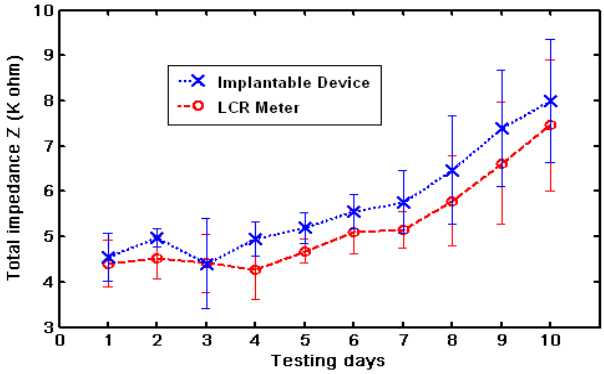


Figure 9. The total impedance (Z) versus the testing days of in vivo tests

B. Measurement of electrode-tissue impedance

In-vitro validation of impedance measurement

In the in vitro experiment, the total impedance for Au/PI samples treatment versus testing days is plotted in Figure 7. The total impedance decreased gradually and then increased after the fourth day. The total impedance increased with a rate of 0.135 KΩ/day. The measured results are comparable to those of LCR meter. Their correlation coefficient is 0.99.

At the end of the incubation period, samples were taken out, shortly washed with D.I. water and one of protein accumulative part are scraped, then the samples were dried overnight in a desiccator. Subsequently, a microscope (Olympus BX51) was employed to observe the fractional coverage of residual protein upon the tested surface, which indicated its affinity to the primarily deposited protein. Figure 8 shows the microelectrode with and without residual protein upon the tested surface. As a consequence, protein deposition on a chronically implanted surface tended to obtain an analogous protein-thickening deposition and surface morphology at their steady states.

In-vivo measurement of electrode-tissue impedance

In our in-vivo experimental measurement, the packaged microelectrode was implanted between the skin and muscle of Wistar rat's dorsum for 10 days. Figure 9 exhibits the total impedance (Z) measurements versus testing days for 10 days. At the initial stage, the total impedance maintained at similar level. After the fourth day, the total impedance increased at a rate of 0.533 KΩ/day. The measured results are comparable to those of LCR meter. Their correlation coefficient is 0.984.

Discussion and Conclusion

In this study, we have implemented the wireless implantable device for impedance measuring by using discrete electronic components. The wireless implantable biomicrosystem uses two coils configuration. One coil is for transferring power and command which receives the power and commands for implantable impedance measurement operation. Another is data coil which is used to transmit the data to external device. The two-coil scheme provides better protection of the weak signals against the strong RF electromagnetic fields. For the impedance measurement device, it can be used for in-vitro validation and for in-vivo measurement of the impedance between cuff microelectrode and tissue. In the impedance measurement device, we utilized sinusoidal signal of 1.2 kHz as source and applied peak detector for best estimation of impedance which has better accuracy. However, the maximal sampling rate of the implantable device was 4 kHz which is not accurate enough to acquire the phase shift in the measured waveform. Our adaptation of peak detector approach for measuring the total impedance avoid the high sampling rate problem and achieve a acceptable impedance measurement scheme.

In this study, the multi-polar cuff electrodes were used for in vitro and in vivo impedance measurement tests for 14 days and 10 days. From in vitro experiment, we observed that the total impedance decreased for the first three days and then gradually increased up to 14 days. The decrease of total impedance at the initial stages could be related to the conductivity of ions in saline solution, soon after contacting with the microelectrode surface. The increase of microelectrode impedance was mainly correlated with the protein pile-up on the microelectrode surface. The initial decrease in impedance presumably depends on the ionic strength of a complex, including an electrical double layer, formed in the vicinity of the electrified microelectrode. This particular instance exhibits an analogous reaction as the illustration of the *primary salt effect*, one of the mechanisms by which ionic strength affects reaction kinetics. The nature of the effect is easy to understand through well-known *Debye-Hückel* theory, which stands to reason that the interaction is sensitive to the net force between the reacting ions. In present case, the electrified microelectrode surface was regarded as a group of reacting ions [6]. As a consequence, the ionic strength of the complex determined the extent of the ionic atmosphere around the charged surface, which in turn dictated the average force field in the vicinity of Au/PI surface [6].

Both in vitro and in vivo tests, total impedance measured by our approach is comparable with those measured by an LCR analyzer. It is believed that nerve cuff electrodes are the most suitable nerve-based electrodes for electrical activation of the human nervous system because they are the least invasive and easiest to install [13]. When the cuff electrode was implanted into the tissue, the protein of the blood plasma or the cells maybe accumulated on the microelectrode surface. That will change the impedance between cuff electrode and tissue. The performance of electrical stimulation or sensing using the functional microelectrode would be influenced by the increase in impedance which may result in a deficiency in nerve stimulation or signal recording. The loss of electrical power should be as low as possible when the microelectrode is implanted into tissue. Therefore, the impedance measurement technique can be used before nerve stimulation or signal recording to ensure good contact between electrode and nerve tissue. If the measured impedance value is known in stable condition, it would ensure both the nerve stimulation and signal recording are viable. In addition, the microelectrode combined with other components as an invasively implantable device should follow the criteria for implantable materials, which are not physically or chemically harmful to the peripheral nerves during long-term implantation.

Our ongoing project is to minimize the whole system by utilizing the micro SMD components or chip-in-package technique. Further studies will require biocompatible packaging which is essential for long-term observation of time-course changes in smaller animals like rats. In addition, our current simplified approach measures the peak voltage and considers the total impedance, including resistance and capacitance at the measured frequency. By using a simple phase detector, current device can acquire the phase shift of sine wave in impedance measurement to analyze both resistance and capacitance components between cuff electrode and tissue for observing the factors which result in the increase of total impedance during implantation.

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