DEVELOPMENT OF AN IMPLANTABLE WIRELESS BIOMICROSYSTEM WITH IMPEDANCE SPECTROSCOPY MEASUREMENT AND NERVE STIMULATION FUNCTIONS

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ABSTRACT

In neural prosthetic applications, cuff electrodes have been utilized for providing peripheral nerve electrical stimulation and signal sensation. It is imperative to monitor the impedance of implantable cuff electrodes for effective sensing and stimulating schemes. This study aimed to implement an implantable wireless biomicrosystem for providing constant stimulation currents as well as for measuring cuff electrode impedance via a magnetic-inductive link. For continuous in vivo impedance monitoring, a transcutaneous magnetic coupling technique was adopted for transmitting power and commands into the internal module of the biomicrosystem and transmitting outwards the impedance measurement. For impedance measurement, the two-terminal and four-terminal methods were adopted for measuring the electrode-tissue interfacing impedance and tissue impedance. To avoid the high sampling rate required, a gain-phase detector was utilized for direct output of the magnitude and phase shift of a sinusoidal current input for impedance measurement. The same voltage-controlled current source can be converted for the nerve stimulation function with a mono-phasic pulse input. The adjustable stimulation parameters, including the stimulation intensity and frequency, can be controlled via the external module. Validation tests of impedance measurement and microstimulation function were first performed in an impedance model of resistor in parallel with capacitor and later by immersing the entire implantable wireless biomicrosystem with cuff electrode in saline solution. The measured impedance differences were less than 10 % in comparison with those measured by precision LCR meter. After the test of the *in vitro* saline solution, the implantable biomicrosystem is now ready for *in vivo* animal experiments.

Key words: Impedance measurement, Cuff electrode, Implantable device, Wireless transmission

I. INTRODUCTION

For its easy fabrication, flexibility, and non-penetrating harmlessness, cuff electrodes have been adopted for the peripheral nerve stimulation and neural signal sensation in many neural prosthetic studies [1, 2, 3]. In general, the cuff electrodes of varied forms can be easily wrapped around a nerve for restoring the nerve functions by activating or modulating the damaged nervous system [4]. In addition, the implanted cuff electrodes have been applied as sensing devices for detecting feedback source to the nervous system during the restoration of neuromuscular disorders [5]. However, the performance of electrical stimulation or neural sensation using the implanted cuff electrode has been influenced by several factors. Among them, the increase of electrode imped-

ance at the interface between the nearby connective tissue could be the most influential factor. As the nerve cuff electrode becomes sheathed, an increase in electrode impedance may result in deficiency in nerve stimulation or signal recording [6]. Thus, impedance measurement of the implanted cuff electrode would be essential to obtain information about the interface between the implanted electrode and the surrounding nervous tissue.

In general, there are two types of impedance measurement techniques including two-terminal and four-terminal methods. In the two-terminal measurement method, the potential difference is measured between the two sensing electrodes. Since the current flows through the interfacing electrode and tissue, the measured value includes the impedance of both interfacing electrode and tissue. In the four-terminal method, the current is injected into the two outermost electrodes whereas the voltage difference between two inner electrodes is recoded. Due to the high-input impedance, there is very little current flow into the amplifiers. Thus, the voltage difference measured in two inner electrodes can accurately represent the measured tissue impedance with a negligible interfacing impedance of electrodes [7, 8].

For *in vivo* studies, an implantable wireless biomicrosystem is desirable for long-term nerve stimulation and impedance monitoring purposes. With the wireless transmission scheme, the problem of wire passing through skin and causing wound infection can be resolved. For long-term and *in vivo* animal experiment, several factors should be taken into consideration in the design of implantable wireless biomicrosystem for both stimulation and impedance sensing purposes [9, 10]. First, it must be small in size and can be hermetically encapsulated with a biocompatible package for *in vivo* implantation. Second, the utilization of a battery should also be avoided for long-term implantation. Thus, an implantable biomicrosystem that can be powered from an external transmitter coil using the transcutaneous magnetic coupling technique is desired. In addition, the implanted device should wirelessly deliver the commands inwards and transmit the measured data outwards. Furthermore, the implanted device with both impedance spectroscopy measurement and stimulation functions should be carefully designed to avoid the problems of interfering with each other or consuming too much power. This kind of integrated wireless biomicrosystem with cuff electrode for both impedance sensing and nerve stimulation functions has been less investigated.

The aim of this study was to implement an implantable wireless biomicrosystem that can deliver stimulation as well as provide electrode-tissue impedance measurements. The implantable device relied on the external module that transmitted both power and commands into the internal module via the transcutaneous coupling technique. For knowing the stimulation efficiency beforehand, the implanted biomicrosystem could also measure the electrode-tissue interfacing impedance for transmitting outwards. The measurements of

frequency-swept impedance measurement were first compared with those measured by LCR analyzer (Agilent 4294A precision LCR analyzer). Then, the developed implantable wireless biomicrosystem encapsulated in glass package was immersed in a saline solution for system validation.

II. MATERIAL AND METHOD

A. The design and fabrication of cuff electrodes

The nerve cuff electrode was fabricated in a clean room on 4-inch polished single crystal Si (100) wafer by using Micro-Electro-Mechanical-System (MEMS) technique. Fig. 1 depicts the structure of the cuff electrode which is used for nerve stimulating with impedance measurement option. Two masks were employed during the fabrication process. One was used for patterning the Au electrode and the other one was used for opening the insulating polyimide layer. In the fabrication process, the Au of 200 nm thickness was coated by electron beam evaporation and sandwiched in 15 μm thick biocompatible polyimide as the substrate in the lower layer and a 10 μm thick layer as an insulating surface in the upper layer, as shown in Fig. 1(a). Fig. 1(b) shows the layout of the cuff electrode in which the inter-electrode distances of four microelectrodes are 3 mm, 10mm, and 3mm, respectively. The contact area of each electrode pad is 8*2 mm^2. After lifting off the electrode from the Si wafer, a metal stick was used to spiral the electrode for curing with a heating apparatus. After winding longitudinally, the diameter of the cuff electrode is about 2 mm with a length of 18 mm. The thin film cuff electrode was connected to the implantable wireless module with Teflon insulated platinum-iridium wires (A-M System, Inc.).

B. Overall structure of wireless implantable biomicrosystem

The whole implantable biomicrosystem, depicted in Fig. 2, comprises an external control unit and an internal module for delivering stimulation and impedance sensing. The external module includes PC-based host, Class-E transmitter, amplitude shifted-key (ASK) modulator, load shifted-key (LSK) demodulator [11] and a trans-
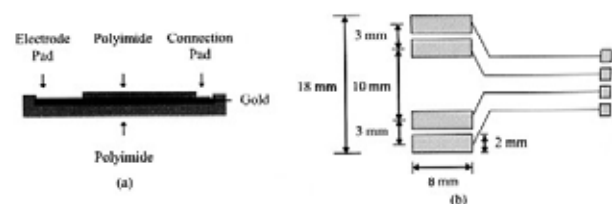

Fig. 1. (a) The structure of cuff electrode fabricated by MEMS technique. The upper and lower layers are polyimide, and middle layer is Au pattern. (b) The specifications and layout of cuff electrode.
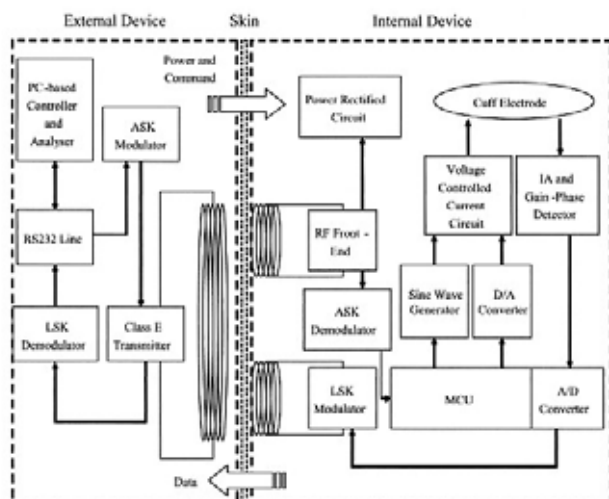
Fig. 2. Overall system block diagrams of the implantable biomicrosystem for impedance sensing and nerve stimulation functions.

ceiver coil. The implantable module contains radio-frequency (RF) front-end, power recovery circuitry, a micro control unit, and a voltage-controlled current circuit for the microstimulator as well as a gain-phase detector for detecting the neural interfacing impedance of the cuff electrode.

In the internal module, there was neither auxiliary battery nor percutaneous lead wires connecting to an external device. The power and data were transmitted via a 2 MHz RF inductive coupling link. The transcutaneous inductive coupling link generally consisted of two resonant circuits which were realized by one transceiver coil at the external module and two round-shaped coils for power and data transmission respectively. When facing each other, the inductive coupling transmitted the power and command from the external module to the internal module through the skin [12]. After the internal module received the power and command, the internal components were commanded to perform for either impedance measurement or nerve stimulation schemes. For impedance measurement, the measured impedance values were converted to digital data via the analog digital converter (ADC) which is embedded in the micro control unit. Finally, the digital data can be serially modulated by the LSK modulator and transmit the data outwards. By using the coupling coil, the serially modulated data was demodulated as the serial binary data which were transmitted to the PC and displayed on a GUI designed using LabVIEW. The nerve stimulation scheme with adjustable intensity and frequency parameters can be controlled via the external control unit. The detailed circuit diagrams for the transcutaneous inward coupling of power and command as well as outward transmission of sensed data can be referred to [13].

C. The implantable wireless module for impedance measurement and nerve stimulation

In general, there are two approaches to measure the impedance of cuff electrode depending on the driving sources, either pulse or sinusoidal current. Pulse current approach delivers a short pulse-width current to the cuff electrode and then measures the resulting voltage to calculate the electrode impedance using Ohm's law. Due to the capacitance effect of double-layered electrode-tissue interface, the measured voltage would be in charge and discharge form which requires adequate sampling points to accurately derive the amplitude change and phase shift from the resulting voltage. Another disadvantage of the pulse current approach is that the microelectrodes are susceptible for accumulating electric charge on electrode-tissue interface from mono-phasic pulse current. Those accumulated charges could affect the voltage base line and the resulting voltage of the pulse current which might further deteriorate the accuracy in the impedance estimation in pulse current mode. However, sinusoidal excitation current with a balanced charge would not cause ion accumulation on an electrode surface and can avoid the oxidation of electrodes. For a sinusoidal current approach, it is feasible to estimate the impedance from the magnitude change and phase shift between the injected current and the recorded voltage. Thus, the sinusoidal current approach is adopted in this study.

The detailed block diagram of the impedance measurement and microstimulation device is shown in Fig. 3. The sine wave generator (AD9833) produces the exciting current with peak-to-peak value of 30 μA via the voltage-controlled current source. The frequency range of a sinusoidal wave depends on the recording signal and stimulation pulse-width. The range of impedance spectroscopy between 500 Hz and 10 kHz was chosen in this study because the frequency range of the measured nerve signal is between 500 Hz to 3 kHz and the stimulation pulse is also in the similar range [6]. The exciting sinusoidal current was injected into the two outermost cuff electrodes from which the voltage differences and phase shift between two outermost and inner electrodes were measured. From the impedance measurement principle, the impedance measured by the outermost electrodes is related to the electrode interfacing plus nerve tissue impedance whereas the inner electrodes measured the nerve tissue impedance only.

However, direct sampling of the resulting sinusoidal signal of the proposed range, 500 – 10 kHz, might require a higher sampling rate that exceeds the limited data transmission rate of the current transcutaneous coupling, less than 10 kHz in general. Alternatively, a gain-phase detector which can directly output the magnitude's ratio and phase shift was adopted in this study. The potential differences measured across inner electrodes and outermost ones, denoted as V1 and V2, as well as the voltage across a reference resistor, V3, were delivered into the gain-phase detector (AD8302). The measured DC outputs including the magnitude's ratio and phase difference were sampled by a 10-bit resolution A/D at a relatively low sampling rate. The sampled data were transmitted outwards for deriving the measured resistance

and capacitance.

The full circuit of the gain-phase detector is depicted in Fig. 4. In order to operate at a low frequency, the Co=30μF was chosen for the high pass corner frequency of $f_{HP}(kHz) = \dfrac{2}{C_o(uF)} = 0.067kHz$. However, the outputs of the gain-phase detector, the magnitude's ratio and phase difference, were not stable when operating at a low frequency range. An additional capacitor of $C_f = 10\mu F$ was used for stabilizing the output value. Finally, the magnitude's ratio and phase difference can be calculated as follows [14]:

$$|Z_x| = R_{so} \times 10^{\frac{Vmag - 900mV}{600mV}} \qquad (1)$$

$$\theta = -\left(\frac{900mV - Vphs}{10mV/degrees} + 90° \right) \qquad (2)$$

where $R_{so} = 100\,\Omega$, Vmag and Vphs are the output values of the magnitude's ratio and phase difference in the gain-phase detector.

In addition to impedance measurement, the same device can be directly used for nerve stimulation after using several switches to control the scheme. The circuit of the voltage-controlled current source is depicted in Fig. 5. Under the nerve stimulation, the SW1 is closed which results in an equivalent resistance of R1 in parallel to R2. Therefore, the stimulation current can be expressed as:

$$I_{stimulation} = \frac{R_3 \times V_i}{(R_1 // R_2) \times [(R_1 // R_2) + R_3]} \qquad (3)$$

where Vi is the source voltage of the pulse wave generated by the digital to analog converter (AD5312) via SW2. Another switch, SW3, is used to ground the electrode which can avoid the oxidation of the cuff electrode and ion accumulation on the electrode interface. When the current source is low, the SW3 is closed for grounding the V_x that causes no current flow through the tissue. On the other hand, the SW3 is opened for delivering the stimulating current flowing through the tissue to achieve the nerve stimulation. The voltage-controlled current source generates constant current at the pulse width of 200 μs with an amplitude of 0~2mA and frequency range of 0.5~10Hz for nerve stimulation.

D. Experimental setup for system validation

The double-layer interface between the cuff electrode and tissue has been commonly modeled as a parallel resistor-capacitor network in series with a negligible value of the resistor [15]. Thus, the simplified R//C model has been chosen for calibrating the two-terminal impedance measurement. The resistance of 300 Ω and 5 kΩ and capacitance of 22 nF and 100 nF which were determined from the lower and upper bound of the fabricated cuff electrode were chosen. In the calibration experiments, the impedance was measured by swept-frequency from 500 Hz to 10 kHz with an exciting sinusoidal current of 30 μA. The measured magnitude and phase shift of the impedance can be compared with LCR analyzer.

To verify the impedance measurement, the developed implantable device was immersed in a saline solution to measure the magnitude change and phase shift of the cuff electrode using the two-terminal impedance measurement technique. The immersion of the entire module in saline solution also can validate the wireless transmission function and the hermetic package of the
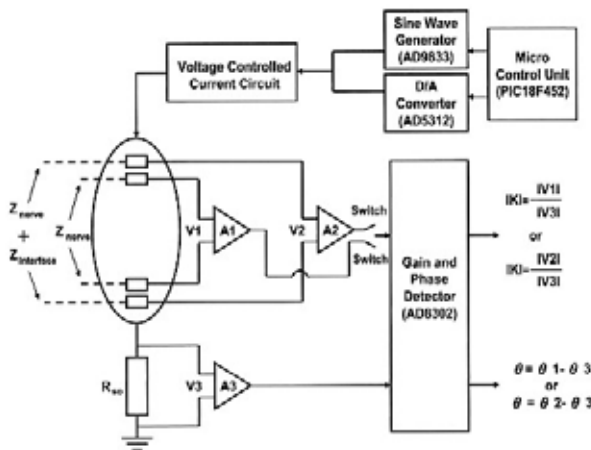

Fig. 3   The configuration of nerve stimulation and impedance measurement using two-terminal and four-terminal schemes.
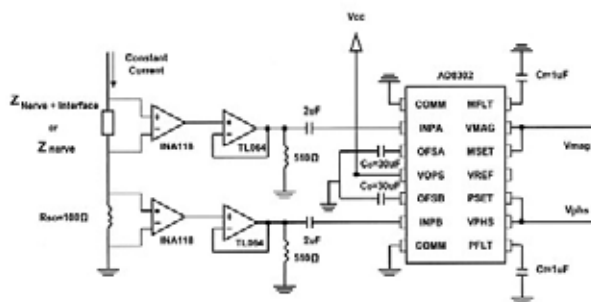

Fig. 4   The full circuit of gain-phase detector for extracting the magnitude's ratio and phase shift of measured impedance.
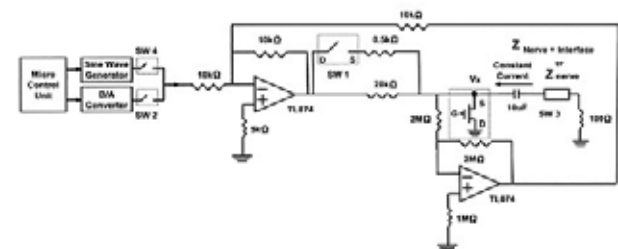

Fig. 5   The voltage-controlled current circuit is used for nerve stimulation and impedance measurement.

module. The external coil was placed outside the beaker for power transmission and data acquisition for impedance measurement, as shown in Fig. 6. Varied concentrations of saline solution were used to simulate different tissue impedance which was measured by the four-terminal impedance measurement method. The saline solutions of 0.9% and those diluted with 1:1, 1:10 and 1:20 of distilled water were tested for swept-frequency between 500 Hz and 10 kHz. The data received wirelessly in the external module was sent to a computer to calculate the magnitude and phase shift of the measured impedance. Due to the parallel resistor-capacitor network was adopted in the study, the resistance and capacitance of saline solution which is supposedly independent of electrode-interfacing impedance could be calculated.

For *in vitro* stimulation experiment, command was sent from the external control unit to generate the desired constant pulse current being delivered into the cuff electrode immersed in the saline solution. The output voltage was then measured from the saline solution to verify the feasibility of microstimulation via the cuff electrode.

III. RESULTS

A. Implantable wireless biomicrosystem

In this study, the magnetic-coupling link uses a circular transmitter coil with an inner diameter of 9 cm and an outer diameter of 12 cm for power and data transmission at a RF carrier frequency of 2 MHz. This external coil was powered with a class-E amplifier for transmitting the power and command inwards to the internal module. The RF transmitter coils were 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 of 12 turns which yielded a high inductance value of 21 μH. The implantable wireless module equipped with two coupling coils of 2.5 cm in diameter using the same stranded Litz wires at an inductance of 7 μH. For better

stability, one of the coils was used for receiving power and command, and another was employed for transmitting measured impedance data. This implantable device was built on four-layered circular PCBs with a diameter of 1.7 cm and a height of 1.3 cm. The wireless module is encapsulated in the glass container which is 2.0 cm in diameter and 1.6 cm in height, then glued and coated with PDMS for biocompatibility, as shown in Fig. 7. The cuff electrode was connected to the implantable biomicrosystem by using the Teflon insulated platinum-iridium wires of suitable length depending on the desired *in vivo* experiment. The total implantable biomicrosystem dissipates around 130 mW of power. In order to receive enough power for implantable biomicrosystem operation, the transmitter and receiver coils have to be face-to-face within 1.5 cm which is sufficient for *in vivo* implantation experiments with coupling coils placed close to the skin of animal. The detailed specifications of the implantable biomicrosystem module are listed in Table 1.

B. System validation for impedance measurement and stimulation function

For system validation, the two-terminal impedance measurement was first verified from the simplified R//C model. Fig. 8 shows the magnitude and phase shift of the tested impedance models, combination of four selected pairs of R and C, which were scanned from 500 Hz to 10 kHz. The impedance measurements of the implantable biomicrosystem were compared with those of LCR analyzer. We can find both measurements were quite consistent except the phase shift at lower scanning frequencies, e.g. 500 and 1 kHz.

Fig. 9 shows the magnitude and phase shift of the cuff electrode immersed in 0.9% saline solution measured by the two-terminal impedance measurement. A decreased trend of magnitude and an increased trend in phase shift were found along the increase of swept-frequency. The differences in magnitude change and phase
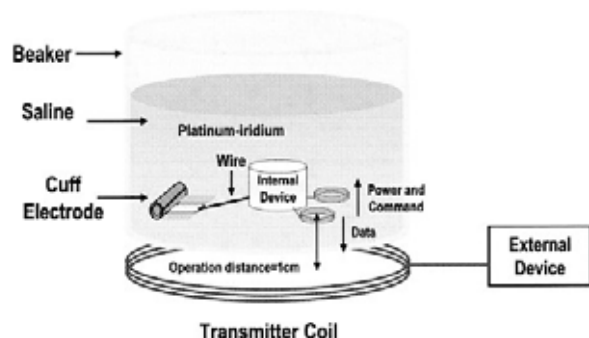

Fig. 6   Experimental setup for validating the implantable biomicrosystem by immersing the entire unit in saline solution for verifying the impedance measurement and nerve stimulation functions.

Fig. 7   The implantable wireless biomicrosystem is encapsulated in a glass package with wire connection to cuff electrode.

shift between our system and LCR analyzer was less than 10%. The derived resistance and capacitance representing the electrode-tissue interfacing impedance spectroscopy of the saline solution are shown in Fig. 10. We can observe that the decrease in resistance and in capacitance along with the increase of scanning frequency. Similarly, the major disparities occurred at a low scanning frequency of 500 Hz.

For the calibration of four-terminal impedance measurement, the implantable device with cuff electrode

Table 1 The specifications of the implantable biomicrosystem with impedance measurement and current stimulation functions.

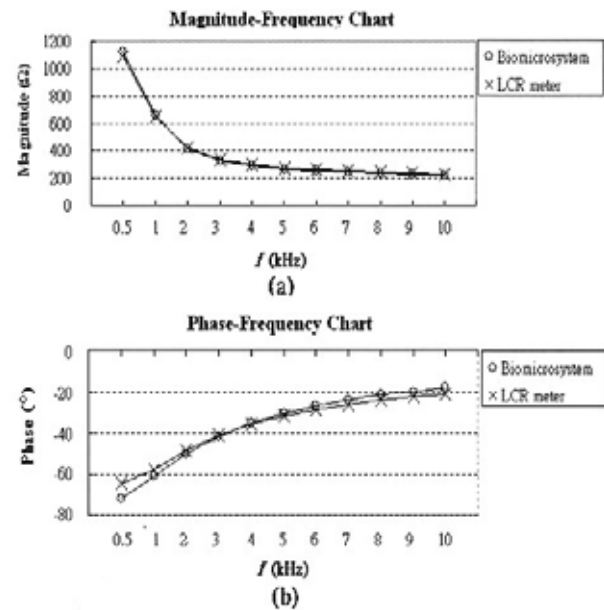| Power amplifier	Class E amplifier
Carrier frequency	2 MHz
Transmitter coil	Litz wire, 90 mm diameter, 12 turns, 21 H
Power and command coil	Litz wire, 25 mm diameter, 12 turns, 7 H
Data coil	Litz wire, 25 mm diameter, 12 turns, 7 H
Inward modulation	ASK
Outward modulation	LSK
Transmission distance	1.5 cm (max.)
Size of packaged implanted biomicrosystem	2.0 cm in diameter and 1.6 cm in height
Diameter of internal coil	2.5 cm
Stimulation pulse frequency	0.5 Hz~20 Hz
Stimulation pulse width	200 μs
Stimulation pulse amplitude	0 mA~2 mA, with 200 steps
Impedance measurement frequency	0.5 kHz~10 kHz
Impedance measurement current	30 μA

Fig. 9 Comparisons of (a) magnitude and (b) phase shift between implantable biomicrosystem and LCR analyzer when the cuff-electrode is immersed in the saline solution.
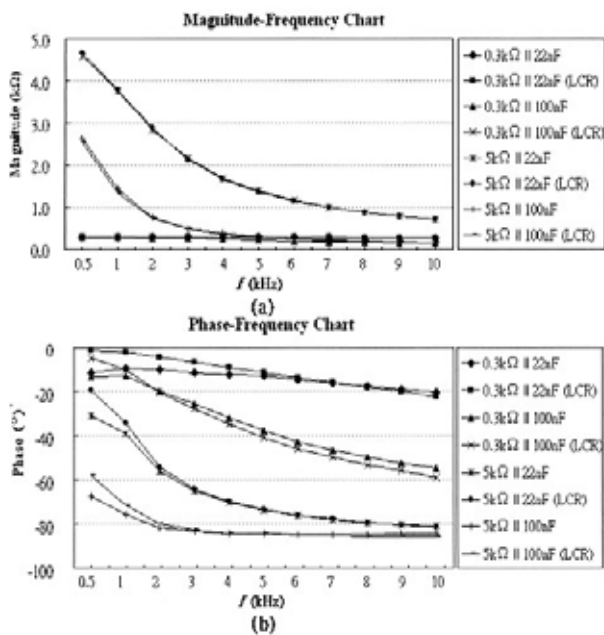

Fig. 8 Comparisons of (a) magnitude and (b) phase shift of varied combination of parallel resistor-capacitor models measured by the implantable biomicrosystem and LCR analyzer.
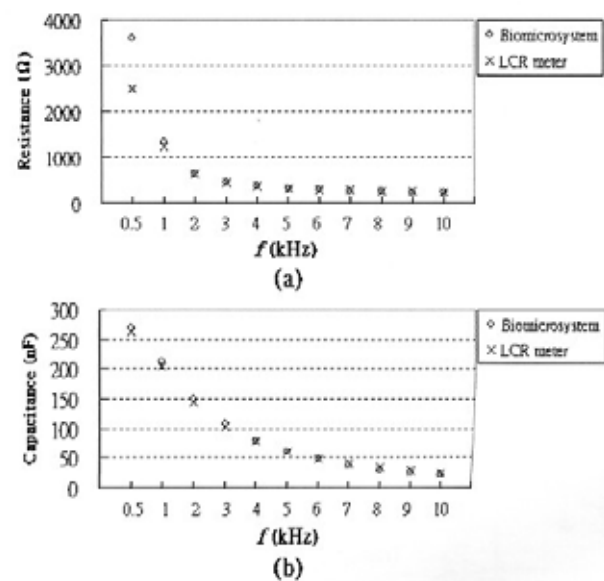

Fig. 10 The resistance and capacitance of cuff electrode derived from measurements of magnitude and phase shift of implantable biomicrosystem and LCR analyzer.

was immersed in the saline solutions of different concentrations, 0.9% and those diluted with 1:1, 1:10 and 1:20 distilled water. Varied concentrations of saline solutions represent different tissue loads for testing the four-terminal impedance spectroscopy measurement. Fig. 11 shows the relationship between the magnitude and phase changes measured in different saline solutions across the swept-frequency. We can observe that the increased impedance magnitude in more diluted saline solution with lower conductivity which is independent of scanned frequency. However, the impedance phase component decreased as the saline concentration dropped.

In the validation experiment for nerve stimulation, a constant-current pulse of 1 mA with 200 µs pulse width and 1 Hz stimulation frequency was delivered into the cuff electrode. Fig. 12 shows the stimulation waveform which was recorded with a probe closely placed between the two terminals of the cuff electrode in the saline solution. Correct pulse width of stimulation waveforms can be observed with zero voltage baseline which was held by using the grounding switch, SW3. However, the oblique stimulation waveform might be originated from the capacitance effect of double-layer electrode-tissue interface.

IV. DISCUSSION AND CONCLUSION

It is essential to monitor the impedance of an implanted electrode for the sake of effective sensing and
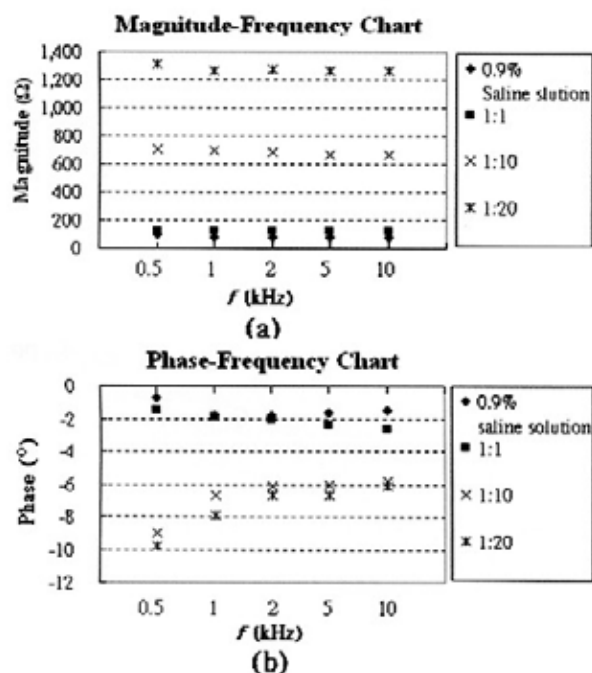

Fig. 11 The measurements of magnitude and phase shift measured under different concentrations of saline solutions for testing the four-terminal impedance measurement.

stimulating schemes. In this study, we have implemented the implantable wireless biomicrosystem for impedance measurement and nerve stimulation using discrete electronic components. The whole size of the implantable biomicrosystem after packaging is 2.0 cm in diameter and 1.6 cm in height which is quite suitable for implantation in animals like the New Zealand rabbit. With the maximum effective transmission distance of about 1.5 cm, this is useful for over-skin transcutaneous coupling studies in most of the biomedical applications. The implantable biomicrosystem was first validated by employing the parallel resistor-capacitor models. After that, the impedance measurement and microstimulation functions were verified by using the cuff electrode immersed in the saline solution. The major feature of current implantable device is that the voltage-controlled current circuit not only can generate nerve stimulation pulse but also can be used for impedance measurement.

The effective transmission distance is an important parameter for wireless transmission technique which is determined by several factors including the configuration of coupling coils, modulation schemes, and power consumption of internal module. The latter is extremely important because the entire power consumption was magnetic coupling from an external coil over air medium to the internal coil. As a result, the high power consumption of the internal module may reduce the effective transmission distance. With more and more components included in the internal module, such as the integrated impedance sensing and nerve stimulation functions in our case, it is essential to manage the requirement for lowering power consumption. Except choosing low-power components, a better power management is another alternative. In the study, the power management was considered under the condition that the impedance measurement and stimulation scheme was not operated simultaneously. Thus, we always can use the same voltage-controlled current circuit for impedance measurement and nerve stimulation which were operated by different source inputs. This approach not only reduces the
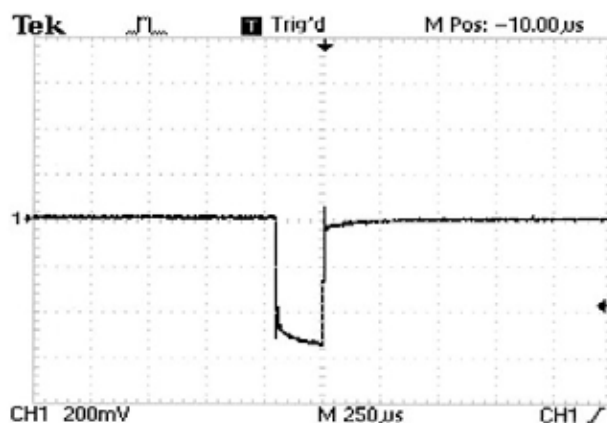

Fig. 12 The stimulation waveform recorded between the two terminals of cuff electrode immersed in the saline solution.

power consumption but also minimizes the size of the implantable biomicrosystem. Thus, the operation of impedance measurement or microstimulation can be determined by the command transmitted from the external device via inductive link. Alternatively, the utilization of a miniature rechargeable battery may be the solution in the future version of our implantable biomicrosystem. Since safe, miniature, and efficient rechargeable batteries have been developed, the magnetic coupling could become a power recharging scheme under which the limitation for immediate power transmission can be alleviated. With the combination of power management and rechargeable battery, it is expected the effective operation distance could be increased to 2~3 cm without significant increase in the size of the implanted module.

Although the four-terminal method has been commonly used to measure bioimpedance spectroscopy [14], it is also essential to check the electrode-tissue impedance using the two-terminal method before the nerve stimulation to comfirm the contact between the cuff electrode and nerve. If the electrode interfacing impedance value is too high, it might be due to the accumulation of protein of blood plasma or cells on the electrode surface or the cuff broken electrode. However, if the value is too low, there could be a short circuit in the broken cuff electrodes. Our developed impedance measurement scheme can provide both two-point and four-point impedance measurement schemes which would be an important feature for future animal implantation experiments. Our ongoing project is to observe the time-course changes in impedance of implanted polyimide-based cuff electrodes encircling the sciatic nerve of a rabbit. The changes in impedance of the cuff electrode with varied surface modification schemes of self-assembled monolayer (SAMs) in the *in vivo* animal studies [6] will become feasible using our currently developed implantable module. In addition, experiments are designed to measure the torque output of stimulating the sciatic nerve of a rabbit to observe interplay between electrode-tissue impedance and stimulation efficiency in a time-course scheme that has not been possible before [16].

In addition, bioimpedance spectroscopy measurement has been developed as an essential technique for characterizing human tissue without destructive biopsy. By comparing the normal condition with the tissue of pathological changes, impedance measurement can be applied for diagnosis purposes. The currently developed implantable biomicrosystem with impedance measurement can be extended to other applications. For example, research has investigated the conditions of tumor and myocardial ischemia [17] or the possibilities of early diagnosis of cancer [18] via bioimpedance spectroscopy measurement. Our implantable biomicrosystem for impedance monitoring should provide several important advantages such as placement close to the organ located deep inside the body that has been difficult for direct measurement of impedance. Long-term and time-course monitoring of the impedance changes of these diseased organs or tissues might broaden our knowledge about the occurrence of diseased tissue in a longitudinal time frame.

In conclusion, we have implemented the implantable biomicrosystem for providing nerve stimulation and measuring cuff electrode interfacing impedance via inductive coupling technique. The impedance of the cuff electrode interface and nerve can be measured by employing the two-terminal and four-terminal methods respectively. For the stimulation function, the mono-phasic pulse current was designed for nerve stimulation. Those schemes of impedance measurement and stimulation function can be flexibly controlled by the external module. After the hermetic testing in the *in vitro* saline solution, the implantable biomicrosystem is ready for *in vivo* animal experiment. The designed module is suitable for evaluating the effectiveness of surface-modified electrodes for various *in vivo* experiments. Furthermore, current implantable wireless biomicrosystem can be extended for various applications of bioimpedance spectroscopy for monitoring and diagnosis purposes in addition to the neural stimulation and sensing in neural prosthetic applications.

ACKNOWLEDGMENTS

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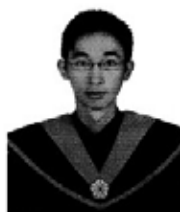
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