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In vivo Performance Evaluation of Implantable Wireless Neural Signal Transmission System for Brain Machine Interface

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ABSTRACT

A brain-machine interface (BMI) has recently been introduced to research a reliable control of machine from the brain information processing through single neural spikes in motor brain areas for paralyzed individuals. Small, wireless, and implantable BMI system should be developed to decode movement information for classifications of neural activities in the brain. In this paper, we have developed a totally implantable wireless neural signal transmission system (TiWiNets) combined with advanced digital signal processing capable of implementing a high performance BMI system. It consisted of a preamplifier with only 2 operational amplifiers (op-amps) for each channel, wireless bluetooth module (BM), a Labview-based monitor program, and 16 bit-RISC microcontroller. Digital finite impulse response (FIR) band-pass filter based on windowed sinc method was designed to transmit neural signals corresponding to the frequency range of 400 Hz to 1.5 kHz via wireless BM, measuring over −48 dB attenuated in the other frequencies. Less than ±2% error by inputting a sine wave at pass-band frequencies for FIR algorithm test was obtained between simulated and measured FIR results. Because of the powerful digital FIR design, the total dimension could be dramatically reduced to 23×27×4 mm including wireless BM except for battery. The power isolation was built to avoid the effect of radio-frequency interference on the system as well as to protect brain cells from system damage due to excessive power dissipation or external electric leakage. *In vivo* performance was evaluated in terms of long-term stability and FIR algorithm for 4 months after implantation. Four TiWiNets were implanted into experimental animals' brains, and single neural signals were recorded and analyzed in real time successfully except for one due to silicon-coated problem. They could control remote target machine by classify neural spike trains based on decoding technology. Thus, we concluded that our study could fulfill in vivo needs to study various single neuron-movement relationships in diverse fields of BMI.

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INTRODUCTION

An integrated BMI has widely been studied in an interdisciplinary research field that focuses on analyzing brain information from single neural activities instead of electroencephalogram (EEG) signals for more precision control. As a result, various microelectrode array BMI systems implanted into the human cerebral cortex have recently been developed in an attempt to make a sophisticated control of movement for paralyzed individuals by decoding neural activities. Including multichannel preamplifier, digital signal processing, wireless telemetry, wireless energy transmission, and classification methods of neural spikes, the whole system of the neural recording has also been attempted to be designed for chronic researches with biocompatibility. The implementation of a wireless interface requires transmission protocol of all neural signals, amplification with signal processing, and no bit error. A fully implantable neural microsystem should be combined with such robust wireless interface to establish the complex processes such as movement control for paralyzed patients, including diagnostic and therapeutic applications. Recently, there are many advances in BMI system capable of realizing these functions (Hewett et al., 1997; Snyder et al., 1997; Snyder et al., 1998; Chapin et al., 1999; Chapin, 2000; Wessberg et al., 2000; Wolpaw et al., 2002; Popovic, 2003; Chapin, 2004). Most of these papers used EEG or ECoG signals to record BMI signals. Their advantages as non-invasive BMI are convenient, safe, and easy-to-operate, but it lacks the spatial resolution and the desired bandwidth which is necessary to analyze time-varying motor signals to accurately control machines in real time (Moxon et al., 2001; Nicolelis, 2001; Carmena et al., 2003). In recent years, BMI research has been active in developing a totally implantable wireless BMI system for chronic neural recordings and many approaches have been made to develop various microelectrode arrays for minimally invasive BMI's applications as miniature, wireless and safe; real time control of a robot arm using simultaneously recorded neurons in the motor cortex (Chapin et al., 1999), implantable microelectronic devices (Strydis et al., 2006; Strydis et al., 2008), and the low power wireless system (Obeid et al., 2004). However, there are still such some problems as low signal-to-noise ratio (SNR), original signal losses due to low input impedance of a preamplifier, and large dimension due to hardware-dependent filter design. Therefore, in this paper, we developed a fully implantable, miniature, wireless, and microelectrode array BMI system being capable of implementing high SNR. The minimization of power consumption is a critical issue in the design of battery powered applications like the TiWiNets. Power isolation configuration could protect brain cells from damage due to excessive power dissipation or external electric leakage. Digital finite impulse response (FIR) windowed sinc filter was implemented in the microcontroller. Due to the design of the powerful digital FIR filter, the TiWiNets' real size newly developed could be reduced dramatically to dimension of 23×27×4 mm including BM except battery. *In vivo* performance was evaluated by transmitting neural spikes acquired in the TiWiNets implanted in intracranial brain areas sequentially in terms of long-term stability and FIR algorithm. Here, development of a whole system was presented with the way of designing high input impedance of the preamplifier and high performance FIR filtering. Also, Labview-based monitor program was developed in the receiver module on PC to find neural spike classification methods for a reliable control of machine.

MATERIALS AND METHODS

System discription

The TiWiNets record wirelessly neural signals from specific motor brain areas to control a user interface of any remote machine for communication purposes, or artificial limb as actuator. Fig. 1 shows

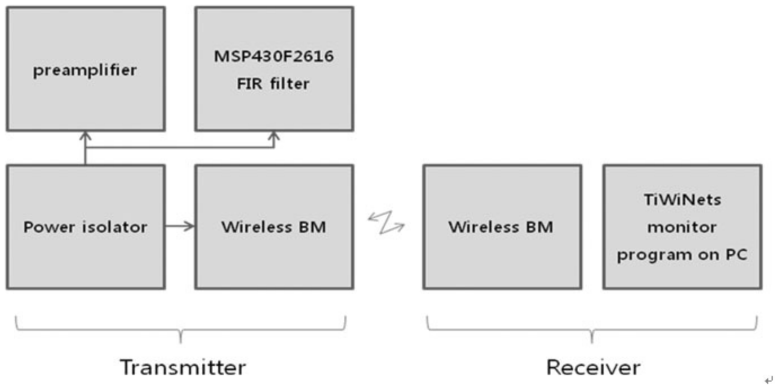

Fig. 1. Functional block diagram of the TiWiNets.

functional block diagram including wireless interface in both transmitter and receiver modules. The transmitter module consists of a preamplifier, microcontroller (MSP430F2616, TI CO. Ltd., TX, USA), wirelessly communication Bluetooth module (BM, FB155BC, Firmtech Co. Ltd., Seoul, Korea), and power isolation. Digital FIR filtering was implemented in the microcontroller to improve long-term stability as well as to reduce system dimension. Of the TiWiNets, the transmitter module implanted into animals' intracranial area was capable of sending neural spikes to remote receiver in real time via the wireless BM with a baud rate of 230 kbps. The preamplifier with only 2 op-amp (operational ampilifier; LMV324M, National Semiconductor Corp. California, USA) for single channel was designed to amplify the neural signals in high input impedance of the head-stage by modifying standard amplifier configuration, passing the frequency range of 156 Hz to 15.6 kHz in 1st order passive band-pass filter. In the microcontroller, digital FIR band-pass filter (0.3 Hz to 1.5 kHz) with Hanning window was performed based on Windowed sinc method. The overall voltage gain was 150×510. The receiver module consists of the user-friendly TiWiNets monitor program on PC including wireless BM. It enabled the TiWiNets to control any remote machines wirelessly by decoding various actions from analyzing neural signals on monitor program in real-time. To avoid the effect of the radio-frequency interference on neural signals, the power isolator (AduM5201, Analogue devices, USA) was introduced, providing 3.6 V for BM and constant 3.3 V for preamplifier and microcontroller respectively.

High Zin preamplifier design

High input impedance (Zin) head-stage is required for use in a bioinstrumentation to minimize the loss of signal source. High Zin means that the preamplifier can be applied to any type of microelectrode array with high resistance without signal distortion because the resistance of microelectrode array usually ranges from ~100 Ω to ~MΩ depending on its length and substance. Thus, the standard amplifier's configuration has one major drawback in developing BMI system. The main drawback is its input impedance in the head-stage of the preamplifier. Bias current via R3 should be enough large to operate properly op-amp by connecting small resistance of R3. Because the input resistance seen into the noninverting amplifier circuit as a whole is the value of R3, this may not be sufficiently high in BMI system. Signal source resistance of 2 kΩ in the microelectrode array with 20 cm in length we used was measured. Thus, the standard amplifier configuration must be modified. Fig. 2 was designed to obtain high Zin in the head-stage of capacitor-coupled noninverting amplifier from single power supply. Its closed-loop voltage gain (Av) and Zin are given by equation 1 and 2, respectively. Input impedance in the modified noninverting amplifier is theoretically calculated by product of R3 and open-loop gain (Ao), because capacitor, C2 can be considered as short-circuit when ac signal is inputted to op-amp. However, in practice, calculated Zin is a little different from measured Zin due to stray capacitance virtually connected between two input terminals. Capacitive reactance of Xc3 was used to be the same with RL (load resistance) so

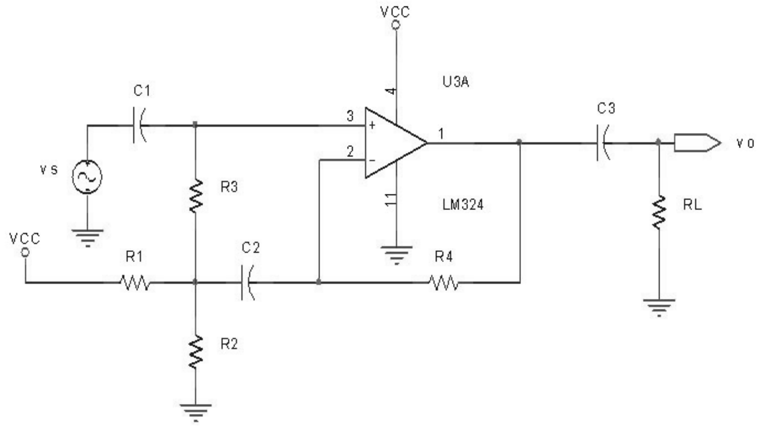

Fig. 2. High input impedance (Zin) capacitor-coupled noninverting amplifier with single power supply.

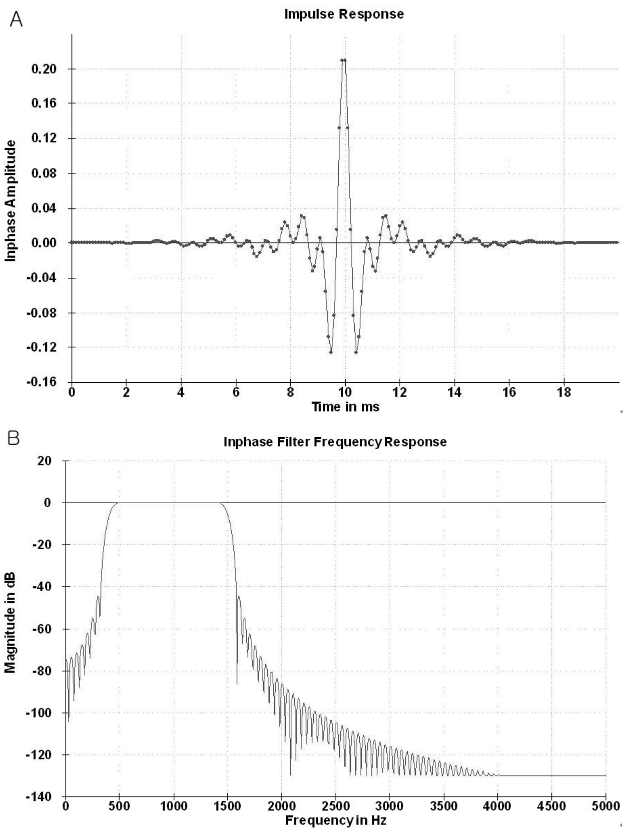

Fig. 3. Digital FIR band-pass filter design (0.4 Hz to 1.5 kHz): (A) impulse response, and (B) frequency response.

that the amplitude of output signal could be approximately −3 dB in all pass-band frequencies.

$$Av = \frac{R4 + R1 \parallel R2}{R1 \parallel R2} \text{ ------ Equation 1}$$

$$Zin = (1 + Ao\beta)R3 \text{ ------ Equation 2}$$

High performance FIR implementation

In digital FIR filter design, we found that an initial impulse response (Fig. 3A) was derived by taking the Inverse Discrete Fourier Transform of the desired frequency response. Then, the impulse response was refined by applying Hanning window to it. It is an iteration algorithm that accepts filter specifications in terms of pass-band and stop-band frequencies, pass-band ripple, and stop-band attenuation. Digital filtering in the TiWiNets presented an optimal minimum phase FIR filter algorithm that supported arbitrary magnitude response specifications, high coefficient accuracy, and real and complex filters. To practically program the FIR filter algorithm in the MSP430 microcontroller, it considered three things: 1) put the input sampled signal in analog-to-digital convertor into the delay line, 2) multiply each sampled signal in the delay line by the corresponding coefficient and accumulate the result, and 3) shift the delay line by one sample to make room for the next input sample. FIR algorithms were developed in assemble-language to reduce processing time with circular buffer mechanism. To skip needless calculation, we applied three things to FIR algorithms: 1) zero-valued coefficients were not included to calculate taps, and 2) because impulse response has characteristics of symmetry, the sampled signals which will be multiplied by the same coefficient value were pre-added, prior to doing the multiplication. A circular buffer by duplicating the logic of a circular buffer in assembly software was implemented in the way of the multiply-accumulate operation. Taken altogether, we de-

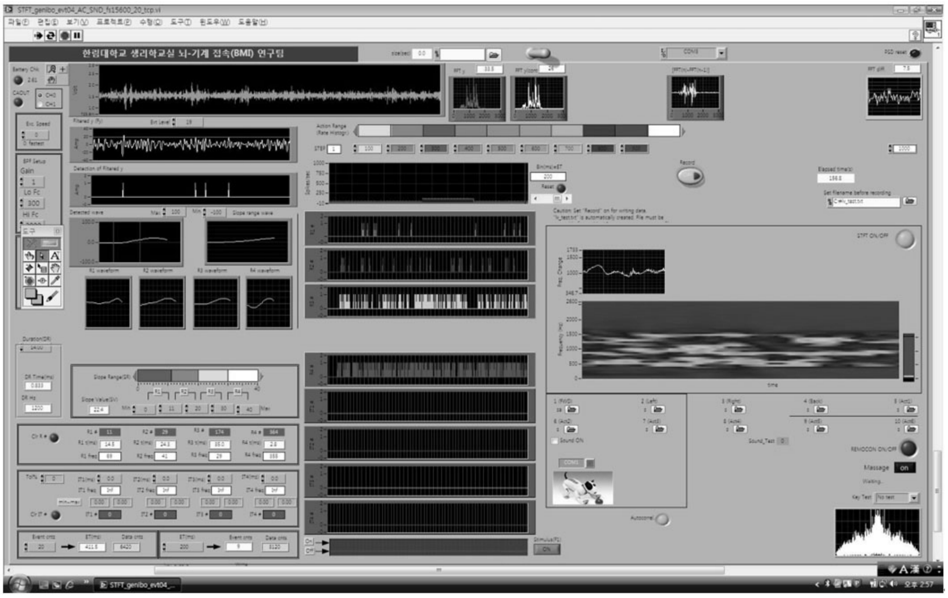

Fig. 4. The Labview based TiWiNets monitor program including time- and frequency-domain analyses.

signed a real band-pass filter with pass-band frequencies of 0.4 Hz to 1.5 kHz representing cutoff frequencies, and over −48 dB attenuation measured for other frequencies. FIR algorithm performance was tested by inputting a sine wave at one or more frequencies and seeing if the output sine has the expected amplitude without any signal distortion representing almost pass-band ripple of 0 dB. Fig. 3B shows digital FIR band-pass filter frequency response (0.4 Hz to 1.5 kHz) with 200-tap coefficients at sampling frequency of 10 kHz.

TiWiNets monitor program

Neural spike train classification (STC) methods for BMI system in the receiver were introduced on the TiWiNets monitor program. The objective is to generate machine control commands out of time series of neural spike trains using various STC methods, or predict cortical responses to whisker stimulation in rats. It was reported that single neural activities reflect ongoing brain information from motor brain areas. The monitor developed based on Labview application software (Fig. 4) displays real-time neural spikes in graphical and numerical forms, acquired on PC via wireless BM in the transmitter of the TiWiNets. Time series curves were provided, and compared with the time series curve of the reference threshold capable of predicting activities of neurons. Among STC methods, non-stationary time series was analyzed in the time-frequency plane to evaluate the BMI performance through representation of time-frequency patterns of the signal's train. Time-domain rate histogram was introduced and applied for obtaining neural activity classifiers by using the threshold detection algorithm during the specified period of time. Also, different patterns of time series were classified using auto-correlation algorithm to discriminate the similarity between a given time series and a lagged version of itself over successive time intervals. The result of autocorrelation can be useful for determining whether different neural activities representing different brain information in the same motor brain area occurred during the specified period of time. Using spike detection algorithm with auto-reference, we could find the strength of neural activities around the specific brain area, discrimination in the spike train, and spike timing information. The slope of increase of amplitude in the single spike was calculated to classify neural signals in 4 steps according to the steepness. In this paper, tests for machine control strategy were performed based on rate histogram scenario consisting of 10 steps according to the threshold detection rate. It was shown that the rate histogram could be useful as control variables by allowing volitional control of robot or any remote devices in real-time.

Animal preparation for an in vivo performance evaluation

We performed a series of experiments on 6 male Spraque-Dawley rats weighing 230 to 280 g, 2 male/1 female Yorkshire terrier dogs weighing 2.0 to 3.0 kg, and 1 male Dachshund dog weighing 5.0 kg, in accordance with the guidelines and practices established for the Hallym University Animal Care and Use Committee. The environment of breeding room was maintained at condition that temperature was 22±2°C and relative humidity was 55±10%. Artificial lighting maintained 12 hrs per day. Animals were housed 1 per cage with food and water was available ad libitum. Animals were anesthetized with Zoletil 50 (i.m., Virbac, France, 10 mg/kg) and xylazine (Bayer Korea, Korea, 5 mg/kg). A relatively large craniotomy (2∼3 mm diameter) was made bilaterally over the prefrontal cortex (PFC) of dog and somatosensory area of rat. The PFC region (1.5 cm anterior to bregma, 0.5∼1.0 cm lateral from midline, 0.5∼1.5 cm ventral to the dorsal surface of the dog brain surface) of the left and right PFC was identified according to brain sample and slice, and two channel tungsten-wire recording electrodes (tungsten microwire, A-M systems, USA, 40 μm diameter, teflon-coated) were positioned with the tips of electrodes perpendicular to the cortex. Then it was lowered targeting the layer III∼IV of PFC with precise electrode mover (Narishige, Japan). The somatosensory of rat is 2 mm posterior from bregma, 6 mm lateral from midline, according to rat brain map (Paxinos and Watson, 1999).

Experimental protocol

After 2 weeks for recovery, the operating conditions of TiWiNets in the set of experiments were compared to those prior to *in vivo* experiments. For tests of the normal operation of the TiWiNets, monitor program was loaded on PC using a user interface to confirm whether arbitrary wireless communication data were transmitted successfully. In addition, there are some useful tests for real-time wireless transmission capabilities as a reference indicator to assess the system's ability to function properly at different distance without any problems. We applied the TiWiNets to decode the neural spikes which were identified and isolated into single units on a TiWiNets software displayed on a mobile computer. The rate histogram was based on time domain analysis from the single cell detection algorithms in real time. Firing rates of a neuron were divided up to 9 levels and 10 command windows. These windows were used to allocate appropriate output functions, which had various meanings for people interacting with dogs. We switched these functions for control various home electronic appliances such as light, MP3, TV, and they used to play many different kinds of pre-recorded human verbal expressions.

RESULTS

Fig. 5 shows the real TiWiNets newly developed for a wireless neural recording system. Two modules are combined with microcontroller plus preamplifier and wireless communication system capable of acquiring neural signals at the sampling rate of 10 kHz, and transmitting them at a baud rate of 230 kbps in range of up to 20 m. Total power consumption of the TiWiNets has been measured to be approximately 93 mA with wireless BM on. Its dimension was 23×27×4 mm. High input impedance preamplifier was designed in the head-stage to provide minimum signal loss. The voltage gain, 0.9998 of the preamplifier input stage was calculated based on the lumped model of RC circuit. Due to the

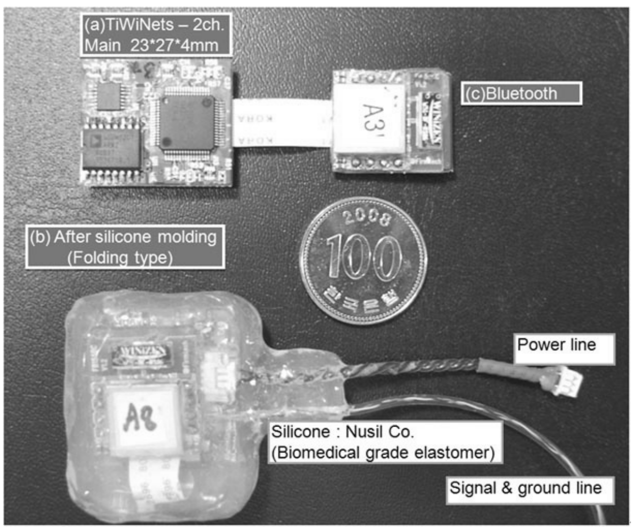

Fig. 5. The real TiWiNet system: (a) the transmitter module of TiWiNet system with dimension of 23×27×4 mm without battery, and (b) silicone-coated TiWiNets for implantation into dog's body.

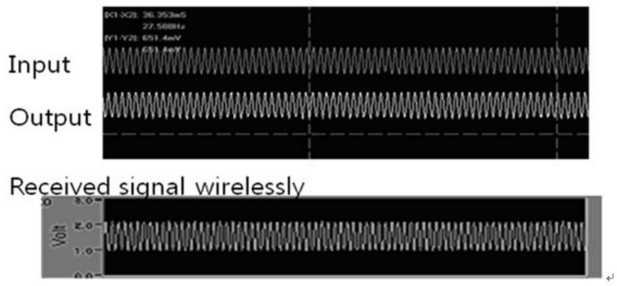

Fig. 6. The measured results of sinusoidal signal with input frequency of 1.4 kHz in the FIR performance test. The first signal (sampled input signal), the second one (FIR-filtered output), and the third one (received signal wirelessly in the TiWiNets monitor program on PC).

stray capacitance between both op-amp input terminals, the leakage impedance occurred, and as a result, the calculated high Zin decreased by approximately 15%. The voltage noise of the preamplifier was measured as 10.5 nV/$\sqrt{\mathrm{Hz}}$ using spectrum analyzer. Its power consumed approximately 1 mA at 3.3 V power supply. Two channels were built of an AC coupling circuit at the preamplifier op-amp input with only 2 op-amps for each channel. Digital FIR band-pass filter was programmed in the MSP430 microcontroller with the bandwidth from 0.4 Hz to 1.5 kHz at 200-tap coefficients. Sampled input signals and FIR coefficients were 16-bit in data length, but FIR-filtered output data were 32-bit to reduce the error caused by conversions using hardware multiplier of the microcontroller. The simulated results showed that the accuracy of the final FIR result was less than 0.01%. Fig. 6 shows that there was no significant difference between the simulated and measured errors for 1.4 kHz pass-band frequency in FIR performance test because our oscilloscope performance was limited in measuring output signals attenuated over −48 dB with respect to 1 volt. Wireless data transmission capability was tested in real-time for over 1 hour per day during 4 months. FIR-filtered output signal in three TiWiNets implants was wirelessly transmitted to the monitor program in the receiver module on PC via BM successfully. However, one of four TiWiNets implants was damaged due to silicone-coated problems. The transmitter was limited by its transmission power and range due to implantation. In the implanted environment, transmission capability was decreased by approximately 30% in terms of transmission range. Fig. 6, also, shows that the amount of information that has been wirelessly transmitted during a predetermined time period in the distance of 10 m. Digital FIR-filter implementation improved SNR comparing to that by using only the preamplifier band-pass filter. Neural signals transmitted wirelessly were displayed and analyzed in the monitor program on PC in real-time to decode various actions for remote machine. And then decoded information was sent to remote target machine by sending messages bit by bit from PC by serial mode communication. Fig. 7 shows the whole process of the TiWiNets operation in vivo test. In the wireless TiWiNets, no transient errors causing bit errors were found in the distance of 20 m.

DISCUSSION

A totally implantable wireless BMI system was developed in department of physiology of Hallym University, Korea. The wireless transmission system enabled the TiWiNets to allow many degrees of freedom for use in various BMI applications. Digital FIR band-pass filter in the microcontroller was completely executed with the sampling frequency of 10 kHz and 200-tap filter coefficients. The firmware program in the microcontroller was combined with C-language and assembly to reduce processing time. All advanced signal analysis was divided into the time-and frequency-domain in a Labview-based monitor program on PC. The time-domain analysis includes autocorrelation, slope calculation, and threshold detection algorithm, while the frequency-domain analysis includes short time Fourier Transform, time-frequency spectrum, and inverse discrete Fourier Transform. In *in vivo* experiment evaluation, four TiWiNets were implanted into the dog's brain, and one of them was damaged due to corrosion caused by a weak silicone-package. Wireless systems introduce some new risks and the probability of failure is often higher than in wired systems. When all the risks or threats are considered, safety requirements determined, adequate measures should be applied to minimize risks in future. Because the message correctness is the key to the safety, validation methods in total design of the TiWiNets are needed. Increase of communication rates may be

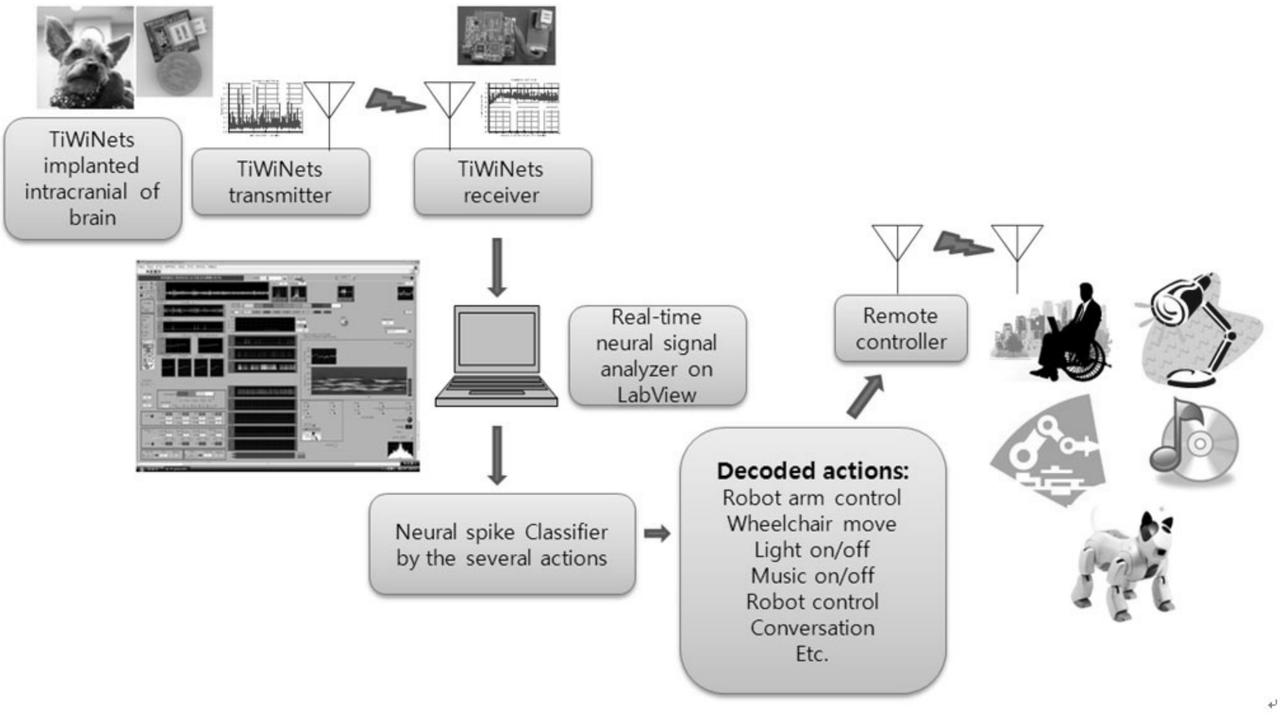

Fig. 7. The whole process of the TiWiNets operation *in vivo* test.

required to improve the system bandwidth for a specific BMI application. For machine control, we used one-way communication to single machine, but in future we will introduce one-way communication to several machines, two-way communication between two specified nodes, or wireless network with a master node. In ongoing studies, we are developing a wireless energy transmission system and much smaller TiWiNets. We hope our study will be possible to build a wireless neural recording system to enjoy ubiquitous BMI world regardless of environment conditions for paralyzed individuals.

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