MS. THESIS

Development of Complex Modulatory Microwave Brain Stimulation System

복잡한 변조가 가능한 뇌 자극 시스템 개발

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Abstract

In this thesis, a modulated brain stimulation signal generator with microwave carrier was developed and fabricated. Using the fabricated system, the continuous theta burst stimulation protocol signal was applied to mouse hippocampus. Micro-drive wires were used to measure firing rate of brain cell. Stimulation effect was verified by measuring the difference of firing rate before and after stimulation.

Brain cell affects each other by neuro-network. To limit the stimulation depth, 6.5 GHz was chosen as a carrier frequency of stimulation signal which has short skin depth in biological tissue. Stimulation protocol frequency is few Hertz (Hz), and 6.5 GHz carrier frequency is in the pulses. Continuous wave in microwave frequency was modulated. To realize the functionality, a modulator coupled voltage controlled oscillator, buffer with variable load, 2-stage differential power amplifier, amplitude detector with DC shifting and transformer were used.

Voltage controlled oscillator was used to generate 6.5 GHz microwave carrier. For modulation, the conventional method is to use switches which is connected to signal path. In this thesis, modulator switches are connected to gate of current source n-type metal-oxide-semiconductor (MOS) field-effect transistor (FET). Three switches are connected in parallel to support theta burst stimulation signal using only pulse generator. Modulation is done by turning voltage controlled oscillator on and off. Cross-coupled structure with p-type MOS load is applied to the voltage controlled oscillator. The buffer is used to minimize load variation of oscillator due to power amplifier when voltage swings rail-to-rail. Also, variable load is added using n-type MOSFET on-resistance. Total output power can be controlled by changing the control voltage of the variable load. Since 20 dBm output power is needed for stimulation, the

power amplifier is needed to satisfy the power condition. The 2-stage power amplifier is used for both gain and maximum output power satisfaction. 0.5 mm sized FET is used for driver stage and 2 mm sized FET for the main stage. In 6.5 GHz, parasitic components cannot be neglected. The differential structure was applied for minimizing parasitic effect such as source degeneration due to inductance. Cascade structure and C_{gs} reduction technique are used to overcome breakdown voltage. Further studies can be done by varying waveform of the stimulation signal. For DC shifted waveform, amplitude detector and DC shifting are applied to the system. Amplitude detector uses cascode structure to hold large voltage swing. Diode connected MOS rectifier, and low pass filter are used to make DC which is same as the amplitude of output swing. The transformer was applied to make differential output signal to single-ended for single-ended structure stimulator.

The fabricated system was verified by mouse experiment. Continuous theta burst stimulation signal was applied to mouse hippocampus. Micro-drive wires are used to measure the firing rate of hippocampus cells. Stimulation effect was verified by place map difference of before and after stimulation.

Keywords: Brain stimulation system, modulator coupled voltage controlled oscillator, microwave, modulation signal

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Chapter 1 Introduction

Today, various brain stimulation methods are used for therapeutic purposes. Drug treatment for brain disorders have limitation. Brain stimulation is getting attention for alternative method. Unlike drug, brain stimulation has advantage of having no resistance as the treatment is repeated. Also, direct effect of brain stimulation maximizes plasticity after brain damage.

There are invasive method and non-invasive method in the brain stimulation. For invasive method, deep brain stimulation is mostly used. Deep brain stimulation needs a thin probe to be implanted in the brain by surgery [1]. Since the probe is implanted, stimulation signal generator should be also implanted in the body. Due to its size, it is normally implanted at the chest. Stimulation signal generator and probe is connected by wire which is placed under the skin. Deep brain stimulation can effectively stimulate specific deep region in the brain. However, brain surgery can cause infection and patient has inconvenience due to periodic battery replacement surgery of stimulation signal generator [2]. There are many methods for non-invasive brain stimulation. Electroconvulsive therapy is known for its effectiveness in medication-resistant depression [3]. To perform electroconvulsive therapy, the patient should be anesthetized and be given a muscle relaxant. Normally, 800 mA current is applied for 1 to 6 seconds. For safety, patient's electrocardiogram, blood pressure and other biometrics should be monitored in real time. Electroconvulsive therapy can cause many side effects such as short term amnesia due to high current. Another method is transcranial direct current stimulation [4]. This method uses two sponge electrodes with 20 to 35 cm^2 area, attached on the scalp. Its area can be adjusted to control the stimulation area. Brain region near anode is depolarized and cathode is hyperpolarized. 2 mA direct current is applied for transcranial direct current stimulation. It has advantage of cheap price and easy implementation. However, direct current path between the electrodes is unclear which makes hard to specify stimulated region. Transcranial magnetic simulation uses time-varying magnetic field to stimulate brain region under the coil. The signal source makes pulse current and is applied to coil. Few Hz pulse generates low frequency magnetic field. There are many studies to focus stimulation area for transcranial magnetic stimulation. Figure-8 coil, coil arrays have better for localizing field [5],[6]. However it is still not enough to reveal the brain circuit by specifying brain region.

Microwave frequency stimulation can be a method having enough localization of field. Due to its short skin depth in bio tissue, microwave stimulates only small region of brain. Also, using commercial signal generator and modulator, pilot study has shown effective brain modulation using modulated microwave signal. In this study, brain stimulation signal generator has been developed integrating into one chip. Voltage controlled oscillator with modulator coupled to current source has been proposed for high isolation between on and off operation. Multiple switches are used to supported complex stimulation protocol for better stimulation effect compared to single pulse modulation. Power detector with voltage shifter was added to make voltage swing from zero. Fabricated system was used to measure change of single cell unit data before, during and after brain stimulation to mouse.

Chapter 2 Brain Stimulation System

2.1 Introduction

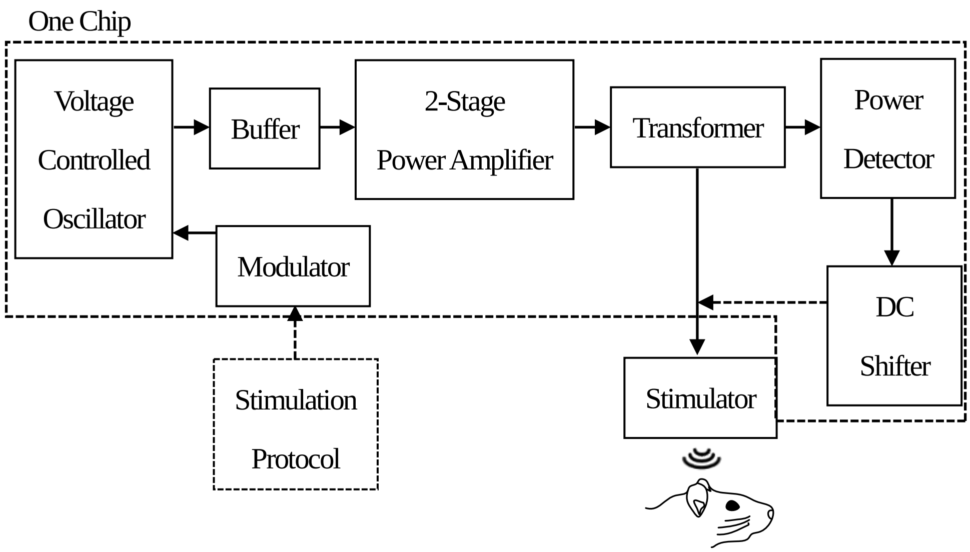


Figure 2.1 Brain stimulation system block diagram

In this study 6.5 GHz was chosen as a carrier frequency of stimulation signal. 6.5 GHz carrier with envelope of complex protocol such as theta burst stimulation should be generated for brain stimulation. Also for patient customized stimulation, carrier frequency and output power level should be varied. Developed system should support these functionality. Figure 2.1 is a block diagram of developed system. System was fabricated using 0.28μm silicon-on-insulator CMOS process. Voltage controlled oscillator was designed to cover 6.5 GHz since the experiment would be done using 6.5 GHz carrier. Modulator was coupled to voltage controlled oscillator. It modulates voltage controlled oscillator by turning on and off. Modulator is realized using NMOS transistor switch. When the gate voltage is below threshold, switch is off which makes oscillator on and above threshold, switch is on and oscillator gets off. By controlling the switching frequency, wanted modulation pulse with microwave carrier is generated.

Buffer is added between voltage controlled oscillator and power amplifier. It suppresses the load variation of oscillator caused by power amplifier operation. Oscillation frequency is determined by load of oscillator. Buffer stabilizes oscillation frequency during stimulation. Also variable load using NMOS transistor was applied to control the output power of the system.

Since the output power of the oscillator is not enough for the brain stimulation power amplifier is placed after oscillator. 2-stage power amplifier increases the power from oscillator to make appropriate stimulation. For high gain and power, power amplifier is composed of driver stage and main stage. Power amplifier was also fabricated using silicon-on-insulator CMOS process. Cascode structure was used to overcome low breakdown voltage of process. Differential structure was used to reduce parasitic component effect in microwave frequency.

The brain stimulation was done using single-ended signal type. So, transformer was applied after power amplifier. Transformer converts differential signal from power amplifier to single-ended signal. 1 to 2 ratio with lateral coupling was used. For size efficiency, it was fabricated with silicon-on-insulator CMOS process.

Power detector and DC shifter were used to change the DC voltage level at output. The output voltage of transformer swings from $-V_{amp}$ to $+V_{amp}$. To make swing from zero, DC voltage of amplitude should be applied without affecting AC characteristic. Power detector was used to detect amplitude of output transformer. Cascode amplifier and diode connected MOS transistor was used to detect the amplitude.

Stimulator used in this study is conventional planar type which has lowest reflection coefficient at 6.5 GHz. For DC shift operation, stimulator was varied to have capacitive characteristic at low frequency.

2.2 Modulator Coupled Voltage Controlled Oscillator

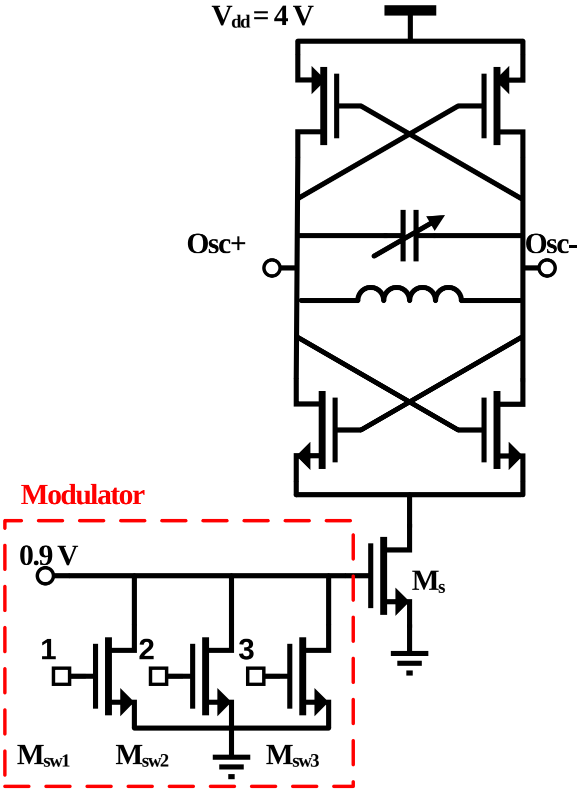


Figure 2.2 Schematic of modulator coupled voltage controlled oscillator

The brain stimulation is done by modulating continuous wave signal. There are two ways to get continuous wave signal. One is using commercial signal generator to get continuous wave signal. However, commercial generator size is large and consumes large power. So, it is preferred to generate microwave signal in the system. Voltage controlled oscillator was used as

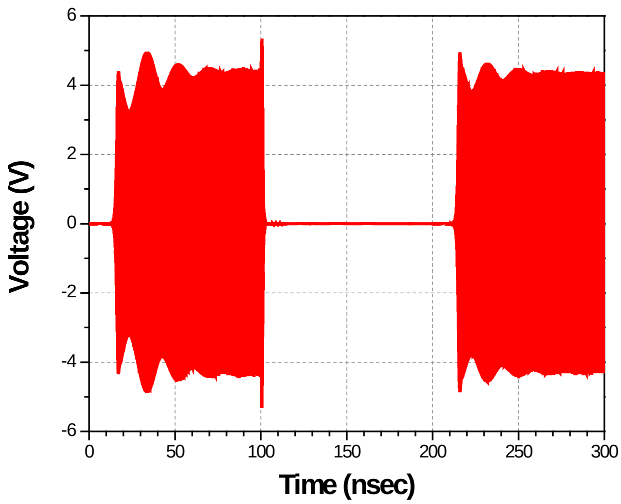


Figure 2.3 Simulated 1 MHz modulation transient result

a component of the system. Figure 2.2 is a schematic of the modulator coupled voltage controlled oscillator. Cross-coupled structure with PMOS transistor load and current source (M_s) to bias were used to realize oscillator. The voltage controlled oscillator uses varactor to adjust the center frequency. The modulator is realized using NMOS transistor switch and connected to the gate of current transistor. Figure 2.3 is simulated 1 MHz modulation result using Agilent advanced design system 2014 simulator when modulation pulse was applied to switches (M_{sw1}, M_{sw2}. M_{sw3}). 1 MHz pulse modulation with 6.5 GHz microwave frequency carrier in transient result is shown. 1 MHz pulse was used in simulation to verify the upper limitation of modulation in the circuit. Normally, modulation frequency of brain stimulation protocol used in the experiment does not exceed 1 kHz. Modulation in the oscillator is done by turning voltage controlled oscillator on and off. In the simulation result above, total set up time which is addition of start-up time and fluctuation time is nearly 50 ns. Compared to 100 Hz stimulation protocol, oscillation set up time is negligible. Figure 2.4 is simulated of modulator coupled voltage

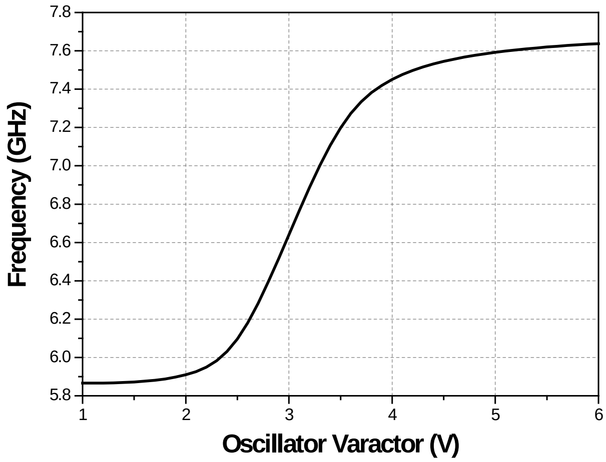


Figure 2.4 Simulated voltage controlled oscillator frequency tuning range

controlled oscillator frequency tuning ranges using Agilent advanced design system 2014 simulator. Measured result shows frequency range from 5.87 GHz to 7.64 GHz.

There are some studies that theta burst stimulation protocol is effective for brain stimulation [7],[8]. Theta burst stimulation protocol can be made in two ways. Continuous wave signal can be modulated to theta burst stimulation signal using one switch. Using data generator, theta burst stimulation protocol pulse can be generated and given to the gate of the NMOS transistor. The other method is using multiple switches with single pulse modulation each. Summation of multiple single pulses can generate complex theta burst stimulation signal. For example, continuous theta burst stimulation protocol can be realized by switches by applying 5 Hz, 10 Hz and 50 Hz pulses on each switch. To support various theta burst stimulation protocol 3 switches are needed. The later method is preferable due to expensive and large size data generator. Single pulse generator is more cheap and adequate for size effcient system. In the past studies, the switch was connected to signal path between buffer and power amplifier. Series switch degrades

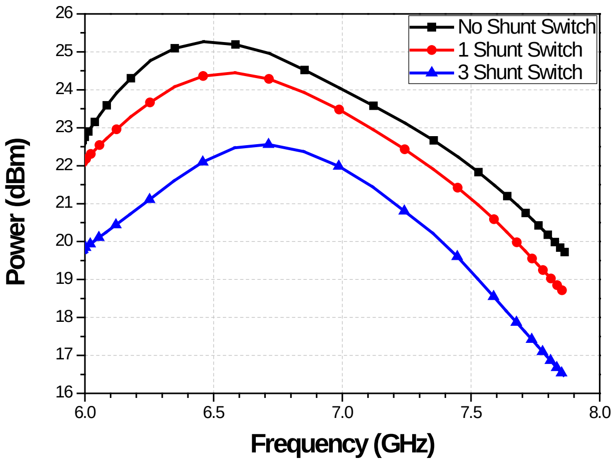


Figure 2.5 Multiple shunt switch effect on output power degradation due to parasitic effect in microwave frequency in simulation

output power due to on-resistance of NMS transistor and resistance increases as number of switches are added. Shunt switch at signal path can avoid on-resistance proble. However, when multiple shunt switches are connected to the signal path, the parsitic capacitance effect becomes larger in microwave frequency. Figure 2.5 shows the parasitic capacitance, C_{ds} and C_{gd} effect is not negigible at microwave frequency in simulation. It was done by adding no shunt switch from three shunt switches at signal path after voltage controlled oscillator. If multiple switches are used to support complex theta burst stimulation protocol, system output power is degraded due to large parasitic capacitance at signal path. Also this method does not give enough switching isolation between on and off. When switch is on, most of signal is grounded but, some signal enters the power amplifier and delivered to stimulator as shown in Figure 2.6. This leads power leakage when the system should not deliver power to stimulator. Since the NMOS transistor switch is fabricated by silicon-on-insulator CMOS process, the breakdown should considered when switching the large power. If amplitude exceeds 4 V, other topology is needed

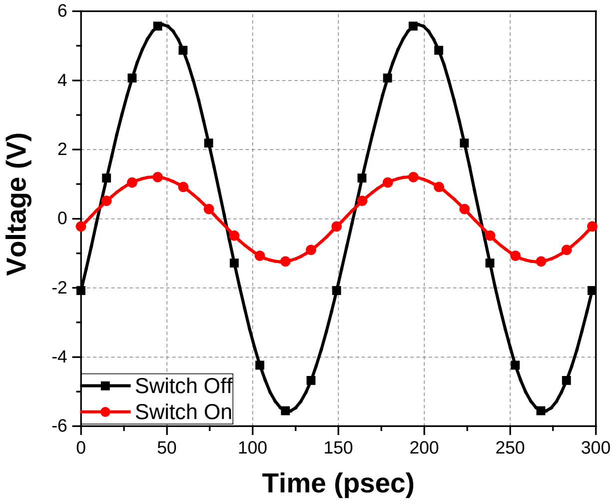


Figure 2.6 Low isolation when shunt switch topology used

to overcome the breakdown voltage problem. In the proposed structure, modulator consists of 3 switches are connected to the gate of the current source used in volatge controlled oscillator. Theta burst stimulation protocol can be generated by using only pulse generator without problems dicussed above.

2.3 Buffer

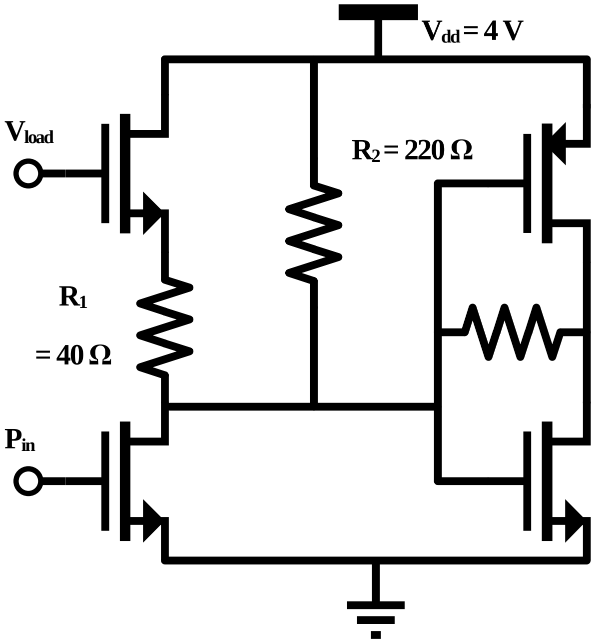


Figure 2.7 Schematic of the buffer with variable load

The buffer is placed between modulator coupled voltage controlled oscillator and power amplifier for isolation. The oscillation frequency is determined by inductance and capacitance at the load of the oscillator. Input impedance of power amplifier are sensitive to input power level. If the input impedance is changed, its change directly affects the oscillation frequency. Buffer is used to reduce the effect of load variation at oscillator. Common-source amplifier with variable load resistance and inverter with resistive feedback structure were used for the buffer as shown in Figure 2.7. Using variable load, output power of the system can be changed which is needed for patient-specific stimulation. For transcranial magnetic stimulation, intensity is

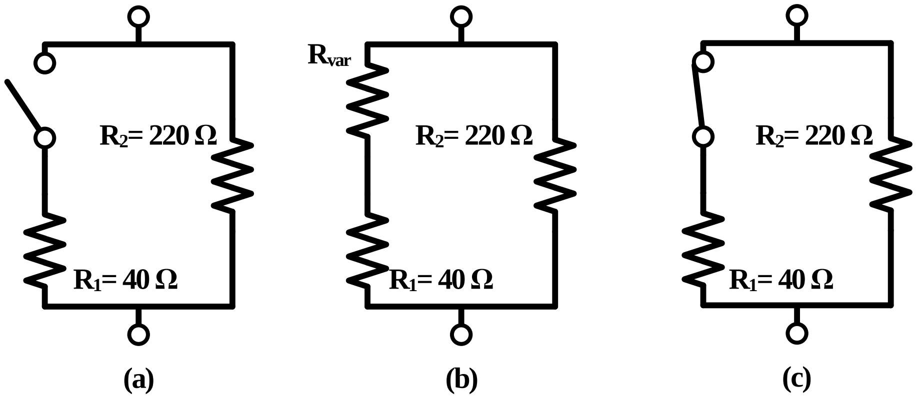


Figure 2.8 Variable load operation when NMOS transistor is at (a) off (b)triode (c)saturation

adjusted for each patient when treatment is done [9]. Variable load resistance is realized using on-resistance of the NMOS transistor. Load of buffer varies from $R_1 \| R_2$ to R_2 by controlling voltage of V_{load}. Figure 2.8 shows the operation of variable load at buffer to control the output

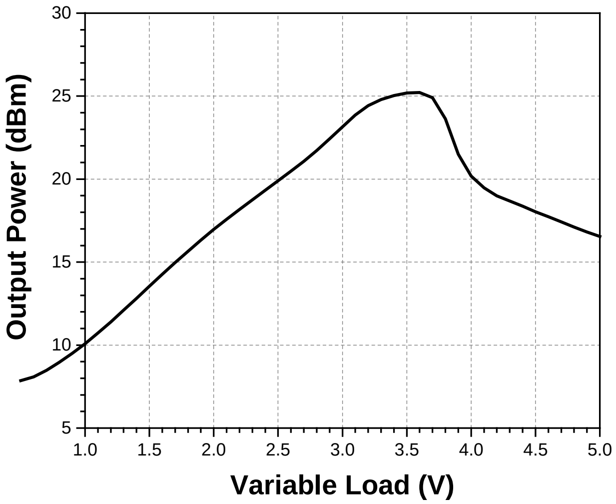


Figure 2.9 Simulated and measured output power tuning range

power of the brain stimulation system. When gate voltage of NMOS transistor is low, it works as opened switch. The load becomes R_2 which is 220 Ω due to opened switch connected in series to R_1 (Figure 2.8 (a)). As the voltage of the NMOS transistor gate increases, it becomes triode region where transistor works as variable resistance. Load becomes $(R_{var}+R_1)\|R_2$ and this state is used for adjust the intensity of brain stimulation in this study (Figure 2.8 (b)). The load impedance value is between $R_1\|R_2$ and R_2. If gate voltage becomes larger near V_{dd} which is 4 V, NMOS transistor falls into saturation region where it works as a short circuit due to low on-resistance. In this case, load resistance becomes $R_1\|R_2$ which is 33.8 Ω (Figure 2.8 (c)). Inverter with resistive feedback for stability was used in the buffer. Simulated output power tuning range is plotted in Figure 2.9. Simulated output power varies from 7.9 dBm to 25 dBm when tuning the voltage of the variable load transistor from 1 V to 3.5 V.

2.4 2-stage Differential Power Amplifier

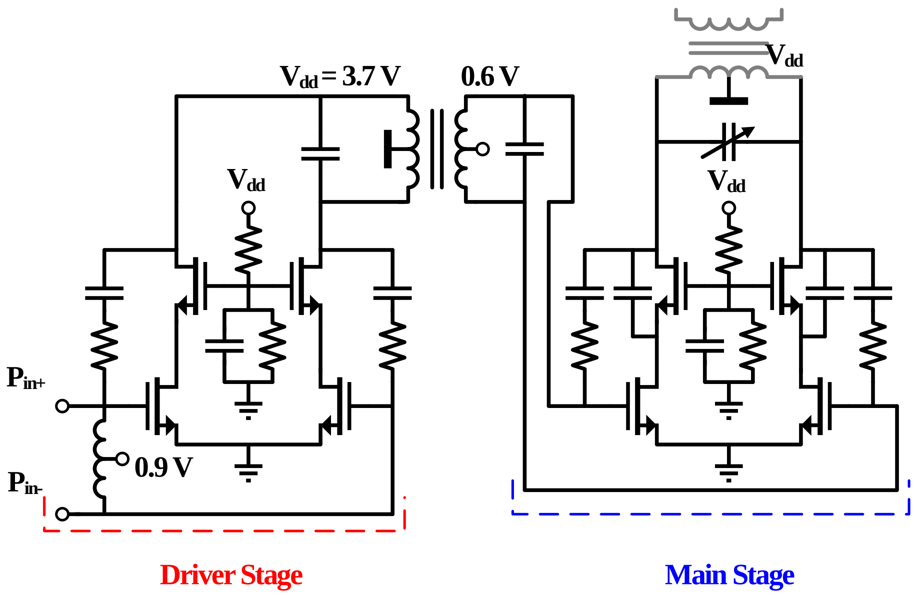


Figure 2.10 Schematic of designed 2-stage differential power amplifier

Brain stimulation changes neural activity by electromagnetic field, not heat. Over 30 dBm power is used for heating treatment in previous studies [10]. The maximum output power of the system is determined as 20 dBm in this study. Figure 2.10 is schematic of designed power amplifier. 20 dB power gain is needed to satisfy the determined power due to 0 dBm output at buffer. 2-stage PA was chosen to make over 20 dB gain condition. Cascode structure was applied to hold 3.7 V drain voltage. In the cascode structure, voltage swing between common-source transistor and common-gate transistor should be carefully considered in the circuit design. High voltage swing in the cascode node can occur and this may exceed the breakdown voltage of the transistor. So, C_{gs} reduction technique is used to overcome breakdown voltage of the transistor [11]. By adding shunt capacitor at the gate of common-gate transistor, voltage swing at the gate node is non-zero due to voltage dividing. Voltage swing is delivered to gate node by ratio of parasitic C_{gs} and added shunt capacitor. So, V_{gs} becomes small which makes common-gate transistor having more tolerance for high swing voltage. Also, differential structure was used to avoid parasitic effects such as bonding inductance effect. Compared to single-ended structure, differential structure has virtual ground in the center. The virtual ground disables the parasitic effect in microwave frequency. Since whole system except stimulator was integrated into one chip, varactor was used to adjust the load matching. The output of main stage at power amplifier is directly connected to integrated transformer. If transformer is connected in off-chip, fine tuning can be done by adjusting the value of chip capacitor. However, due to integration varactor is used for fine tuning. Also, varactor matching topology gives flexibility of matching when using other microwave frequencies such as 6 GHz or 7 GHz. 0.5 mm sized transistor is used for driver stage and 2 mm size transistor for main stage for sufficient gain and maximum output power. Simulated result shows 25 dBm as maximum power and 19 % efficiency.

2.5 Transformer

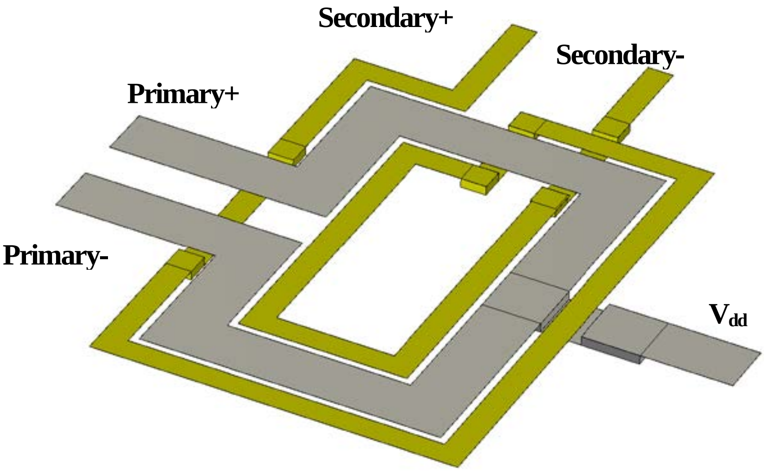


Figure 2.11 Structure of the integrated transformer

The brain stimulation is done by applying stimulation signal using stimulator. In this study, stimulator input is single-ended type. Since, power amplifier generates differential signal, transformer is needed to convert to single-ended signal. The transformer can be realized in two ways. One is using multi-layer printed circuit board technology. The advantage of printed-circuit board technology based transformer is high efficiency. Compared to integrated circuit metal thickness, multi-layer printed circuit board metal thickness is thicker. Thick metal has small loss which makes high efficient transformer. In the previous work, 7-layer printed-circuit board transformer had about 90 % efficiency. The other method is integrating transformer with other circuits. It has advantage of small size compared to printed-circuit board technology. 7-layer printed-circuit board transformer had a size of 3 mm × 5 mm while the integrated transformer size is 0.18 mm × 0.18 mm. Figure 2.11 is structure of the integrated transformer. The top metal is thickest of metal line used in the process. So, the top metal was used in transformer for low loss. In the transformer topology, vertical coupling is usually more efficient than lateral coupling when transforming signal. For integrated transformer, vertical coupling uses lower metal which is thin and high loss. Although transforming efficiency is high, high metal loss makes overall efficiency degradation. Also, lower metal cannot hold large current due to its thin thickness. Lateral coupling structure was chosen for higher efficiency. Primary metal width is 32 μm which is twice as large as secondary coil. It is due to hold large direct current and alternating current. Drain voltage is given to power amplifier from center tap of primary coil. At the cross over region, secondary coil uses two lower metal lines for current density problem. Secondary coil width is smaller than primary because it only needs to hold alternating current density. 1 to 2 ratio was used for matching which converts impedance by 1 to 4 ratio. It is easier to match from 12.5 Ω to R_{opt} which is optimum load of power amplifier to produce maximum power (nearly 6 Ω) than from 50 Ω to R_{opt}. The integrated transformer showed 76 % efficiency in the simulation.

2.6 Power Detector and DC Shifter

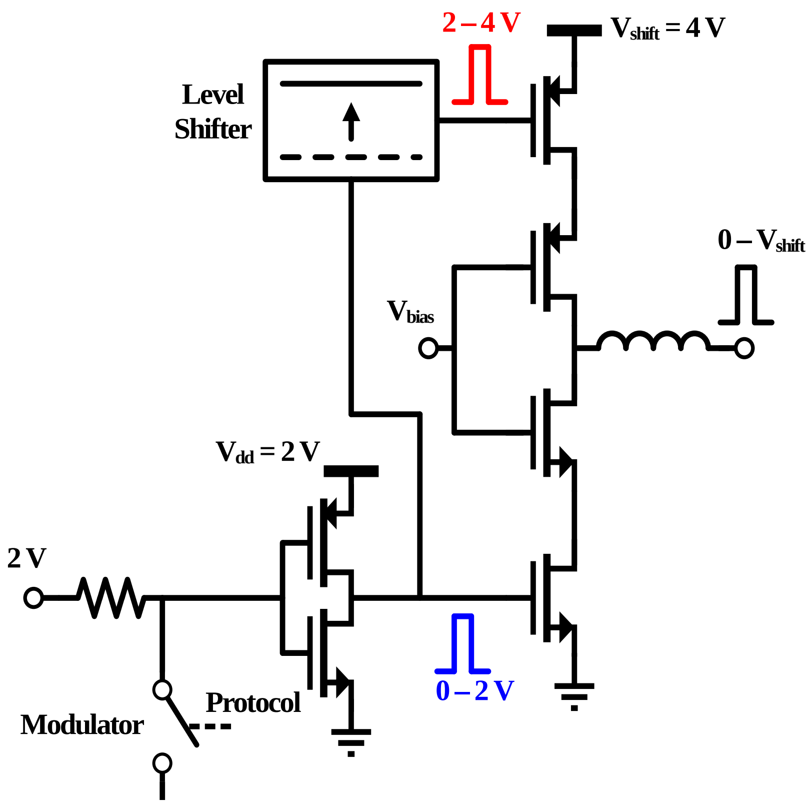


Figure 2.12 Schematic of DC shifting circuit. 4 V DC shifting was done as an example.

Theta burst stimulation protocol needs to swing from zero voltage. In the system, transformer converts differential signal to single-ended signal which alternates between negative and positive amplitude. To shift the output voltage alternating from zero voltage, exact amplitude of output swing should be detected and same DC voltage as amplitude should be

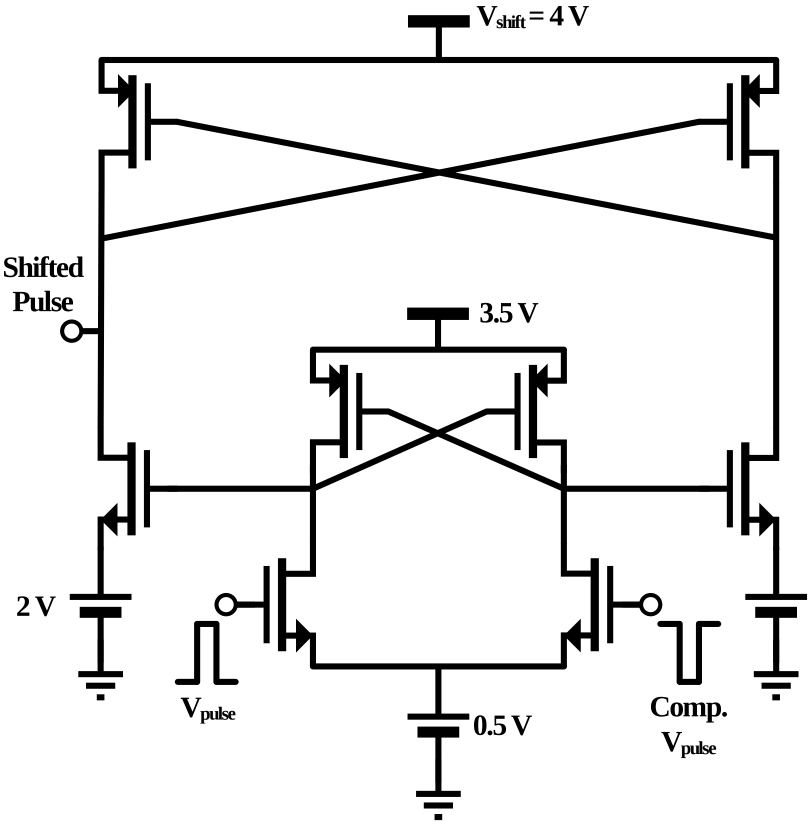


Figure 2.13 Schematic of 2-stage level shifter. 4 V shifting is used as an example.

given to the output without affecting output power. There are two ways to realize this operation. First is making table of voltage amplitude for every power level. Shifting DC voltage value is given to DC shifter which is shown in Figure 2.12. In Figure 2.12, 4 V DC shifting is done as an example. The DC shifting should be done only when output power exists. Since level shifter always generates DC voltage, additional modulator is needed to synchronize output power protocol and DC shifting protocol. Cascode inverter structure is used to support over 4 V DC shifting. Level shifter is applied to assure all node voltage is below breakdown. Figure 2.13 is schematic of 2-stage level shifter. 2-stage was used to make all voltages between nodes are

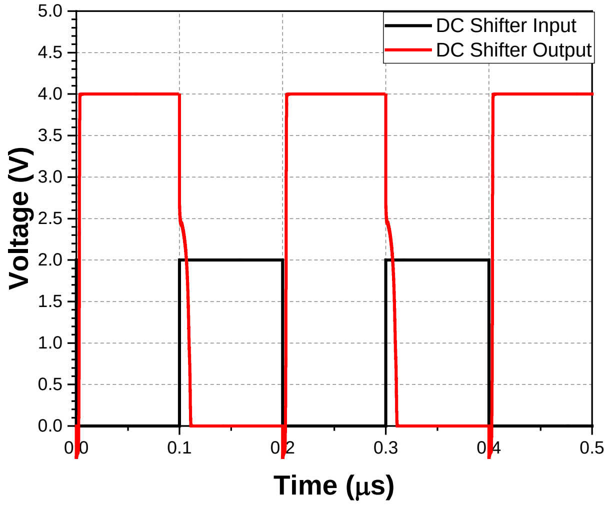


Figure 2.14 Simulated 0 – 4 V shifting result

under breakdown. For 4 V shifting, level shifter gets two inputs which are complementary pulse from 0 V to 2 V. Cross-coupled PMOS loads are used for each stage for low power operation. Other bias voltages used in the circuits should be changed when the value of DC shifting is varied. The simulated DC shifting is plotted in Figure 2.14. It swings 0 V to 4 V without violating any breakdown voltages in each node. The shifting DC is given using large inductor to minimize output power degradation in microwave frequency.

2.7 Fabricated System

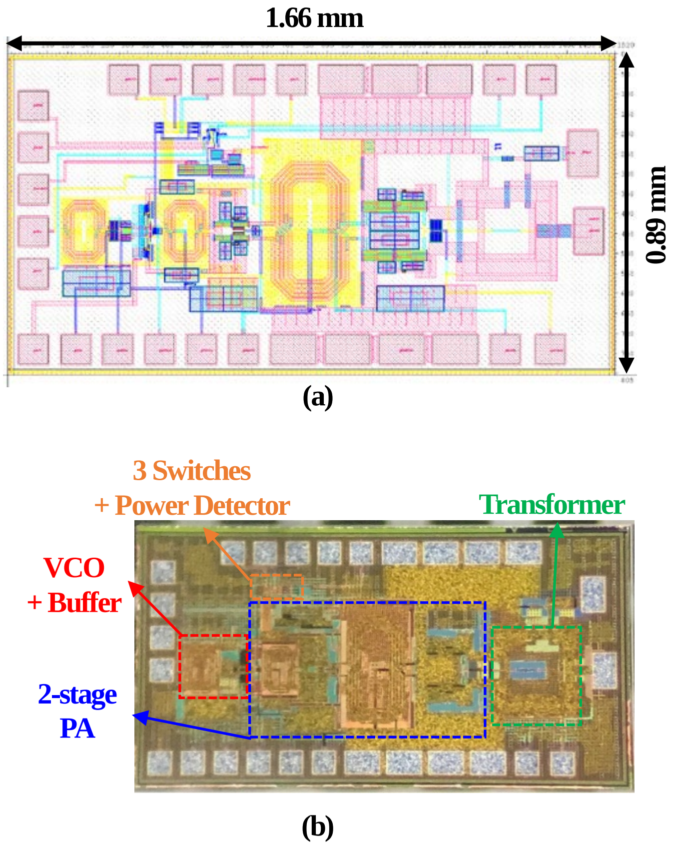


Figure 2.155 (a) Layout and (b) photograph of fabricated stimulation signal generator chip

The brain stimulation signal generation circuit was fabricated using 0.28-µm silicon-on-insulator CMOS process. Figure 2.15 is layout and photograph of fabricated system chip. The

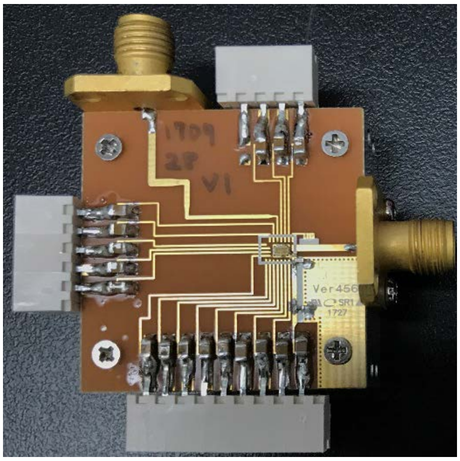


Figure 2.166 Photograph of fabricated system

size of chip is 1.66 mm × 0.89 mm. The chip is mounted on 30 mm × 30 mm jig as shown in Figure 2.16. Figure 2.17 is measured result of frequency tuning range for fabricated system.

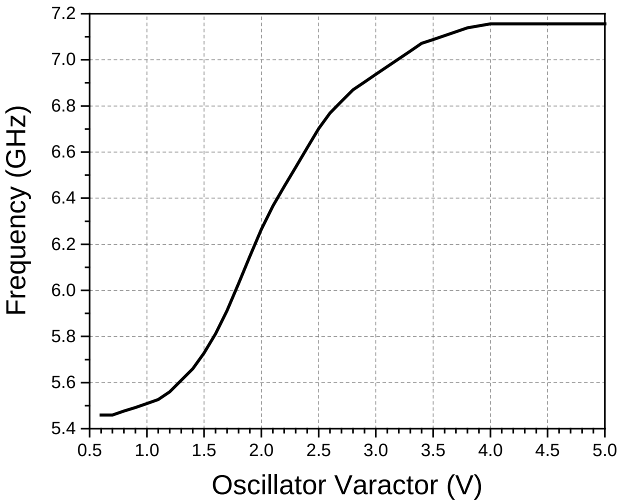


Figure 2.17 Measured frequency tuning range of fabricated system

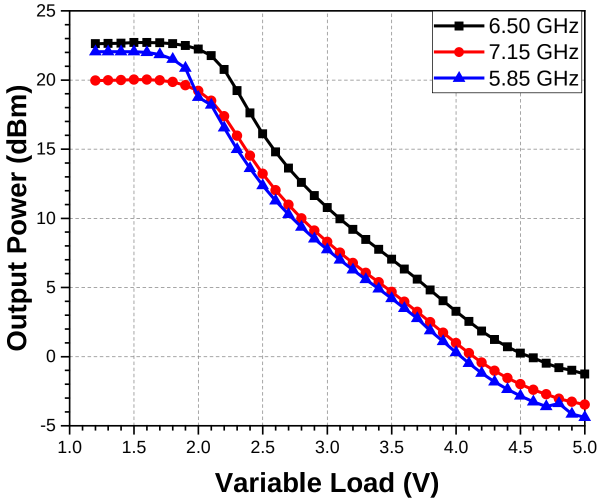


Figure 2.17 Output power tuning range by controlling variable load voltage for 6.5 GHz and $\pm$10 % frequencies.

Frequency can be varied from 5.46 GHz to 7.16 GHz by controlling varactor at voltage-controlled oscillator from 0.5 V to 5 V. The measured result of power tuning range by varying variable load transistor gate voltage is plotted in Figure 2.18. At 6.5 GHz, output power varies from -1.26 dBm to 22.71 dBm. Also, power tuning range at 7.15 GHz and 5.85 GHz were measured which is frequency varied 10 % from 6.5 GHz. It showed same power range from 2 V to 4 V variable load voltage. Overall power is lower for other frequencies due to 6.5 GHz optimized circuit. Figure 2.19 is transient result of DC shifted modulation with 6.5 GHz carrier. Theta burst stimulation signal can be generated with voltage swing from 0 V. Total efficiency of fabricated system is 11.5 %.

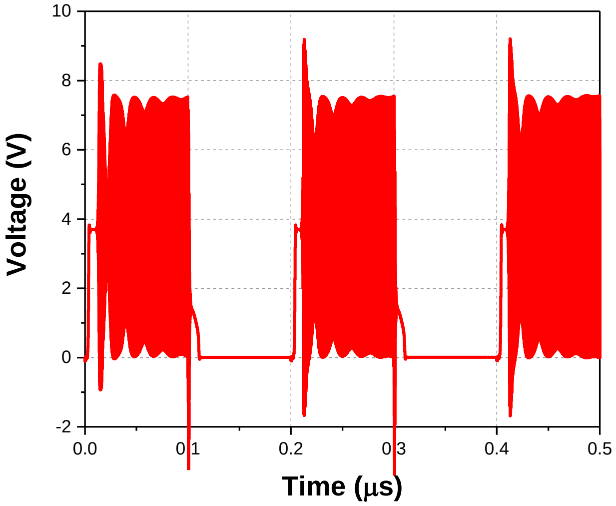


Figure 2.18 DC shifted modulation with 6.5 GHz carrier transient result in simulation

Chapter 3 Mouse Experiment

3.1 Environment

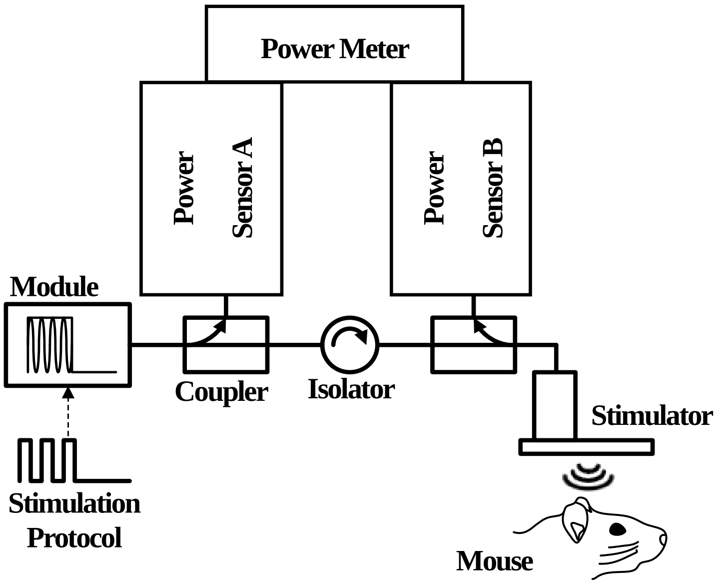
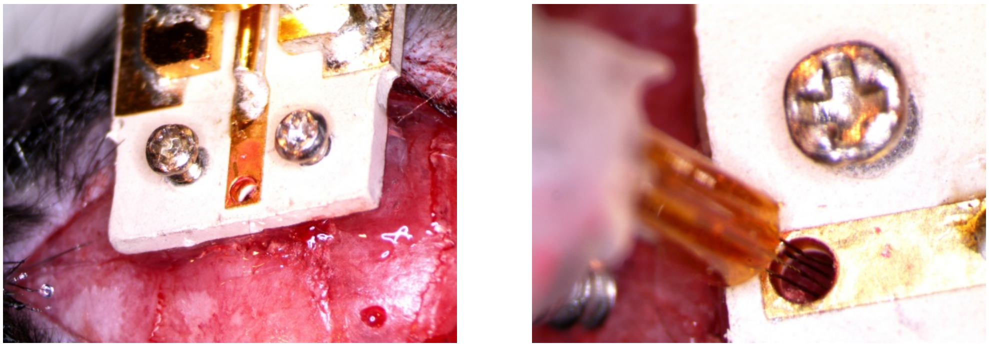


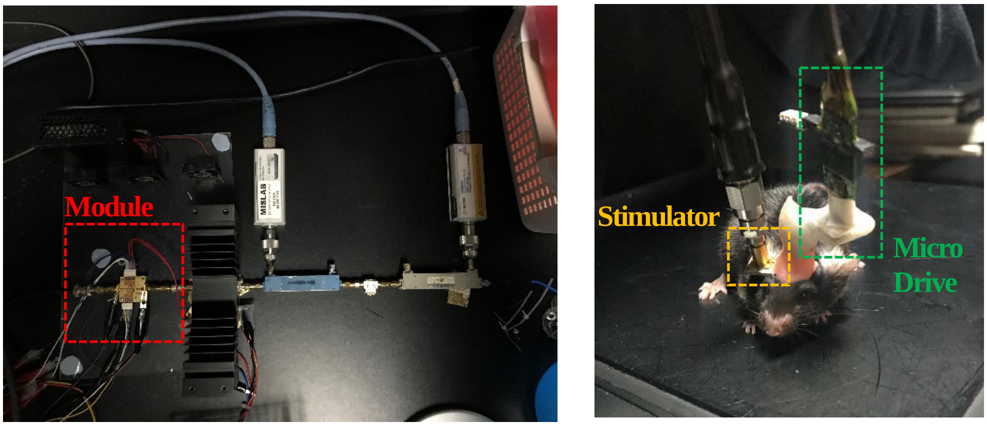
Figure 3.1 Block diagram of stimulation experiment environment

The brain stimulation system was validated by measuring motor cortex single unit cell data. Figure 3.1 is a block diagram of experiment setting. Two commercial power sensors (Agilent N8481A), power meter (Agilent E4417A), isolator (Ditom DMI6018) was set as Figure 3.1 to measure delivered power of the stimulator. The stimulator was implanted on each mouse using screw and dental cement (Figure 3.2 (a)). To measure single unit cell data, the motor drill was



(a) (b)

Figure 3.3 (a) Implanted stimulator using screws and (b) inserted micro drive through via hole to brain



(a) (b)

Figure 3.2 Photograph of experiment (a) module, coupler, isolator, power sensor and (b) stimulator implanted mouse

used to make hole with 1.2 mm diameter on the skull as shown in Figure 3.2 (b). Measuring wire was inserted to the brain through via hole of the stimulator. Surgery removing skull of the mouse was done only to measure firing rate of the brain cell. Microwave modulated brain stimulation itself does not need surgery to remove skull. Brain stimulation signal was generated

Figure 3.4 Circular case to measure firing rate for place map

by module using stimulation protocol. Figure 3.3 show photographs of experiment setup. Module, couple, isolator and power sensors can be seen in Figure 3.3 (a). Stimulator and micro-drive for measuring firing rate are implanted on mouse head as shown in Figure 3.3 (b) [12]. Hippocampus was chosen to be stimulated in this study due to theta burst stimulation. Theta burst stimulation was originated from hippocampus electroencephalogram signal. Hippocampus is related to function of short and long term memory in the brain. Also place map was drew to verify stimulation effect. Figure 3.4 shows the experimental setting of place map. In this study, we expect modulated brain stimulation signal using microwave carrier can neuromodulate the hippocampus.

3.2 Experiment Results

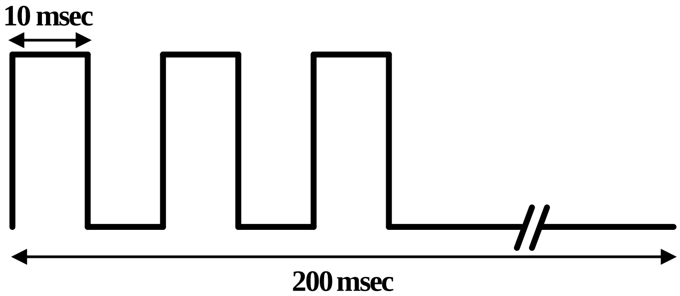


Figure 3.5 Continuous theta burst stimulation protocol

Figure 3.5 shows the specification of protocol used in the experiment. Continuous theta burst stimulation was used for the protocol. Continuous theta burst stimulation protocol consists of three single pulses with 10 msec width and no output for rest of time. Total period is 200 msec and this shape is repeated for 20 minutes in the experiment. Total 18,000 pulses were applied to mouse hippocampus. In each pulse, 6.5 GHz microwave works as carrier.

Output power of system is 40 mW for continuous wave. Average reflection for the stimulation was 4 mW which makes 36 mW delivered to stimulator. To find the stimulation effect on firing rate, 20 minutes pre-measure was done as baseline. The firing rate of baseline was used as reference value. The firing rate was measured during stimulation and after stimulation for 20 minutes each. Also, place map was made using circular chamber and camera. Ability to represent location was measured by constructing place maps of hippocampal pyramidal cells in behaving mice. Place cell has properties to show location dependent firing patterns. Figure 3.6 and Figure 3.7 shows place map of pre-stimulation and after stimulation. During stimulation, place map cannot be made due to rigid microwave cable which limits the

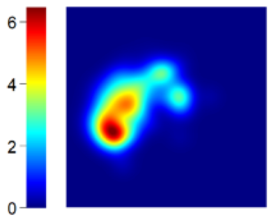
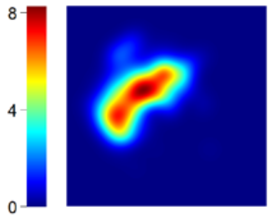
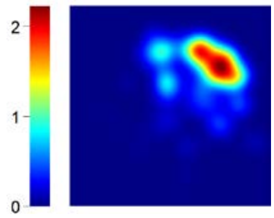
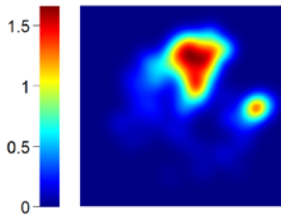
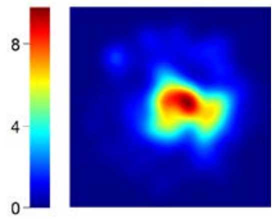
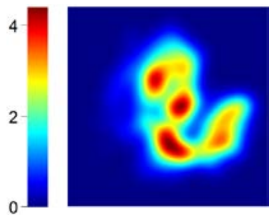
Cell	Baseline	After Stimulation
1		
2		
3		
4		

Figure 3.6 Place map of baseline and after stimulation. 4 cells of mouse 1 are measured using micro-drive

movement of mouse. Place map of baseline indicates that brain cell is activated due to its position. For each cells, recognizing the position is different. After 20 minutes of continuous theta burst stimulation, place map had changed. The stimulated cells still have ability to remember the position. It shows position-specific firing spikes. However, compared to place map of baseline, the position where the spikes frequently occur, has changed. This result shows

Cell	Baseline	After Stimulation
1		
2		
3		
4		
5		

6

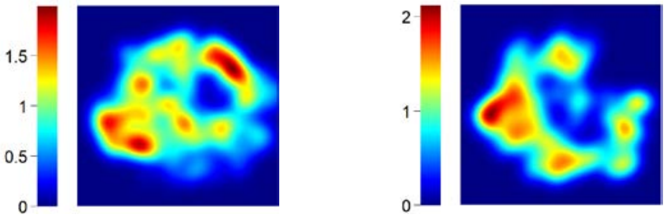
7 

Figure 3.7 Place map of baseline and after stimulation. 7 cells of mouse 2are measured using micro-drive

Table 3-1 Cross-correlation of before and after stimulation

cell	Cross-correlation
Mouse1 - 1	0.007875
Mouse1 - 2	0.204838
Mouse1 - 3	0.109253
Mouse1 - 4	0.242555
Mouse2 - 1	0.049437
Mouse2 - 2	0.081823
Mouse2 - 3	0.024552
Mouse2 - 4	0.022717
Mouse2 - 5	0.004032
Mouse2 - 6	0.017149
Mouse2 - 7	0.008458

modulated brain stimulation with 6.5 GHz frequency using theta burst stimulation protocol had an effect on brain place cell activity which recall function was affected. Cross-correlation of place cell was calculated to compare before and after stimulation effect. Table 3-1 shows cross-correlation value of each cells which place map was drawn. Average of cross-correlation value is 0.07. It shows that stimulation on hippocampus had an effect of location representation function.

Chapter 4 Conclusion

In this study, brain stimulation was verified using mouse experiment. Non-invasive method of stimulation method was used due to no surgical operation and easy implementation. Modulated brain stimulation signal generator using microwave carrier was fabricated with monolithic microwave integrated circuit. All components which are modulator coupled voltage controlled oscillator, buffer, 2-stage cascode power amplifier, amplitude detector, DC voltage shifter and transformer are integrated into one chip except for the stimulator. The system miniaturization was done using 0.28-µm silicon-on-insulator CMOS process. The modulated brain stimulation signal generator system with microwave carrier frequency has ability to control carrier frequency, support complex protocol and stimulus power optimization for patient-specific stimulation. The maximum output power of the system is 22.71 dBm with 11.5 % efficiency.

The verification of system was done by mouse experiment. 6.5 GHz was chosen as a carrier frequency of stimulation signal for its short skin depth in biological tissue. Continuous theta burst stimulation protocol was used for its higher effect on hippocampus compared to single pulse modulation. The target brain region is hippocampus Three 10 msec pulses were repeated in the period of 200 msec for 20 minutes. The brain cell activity, firing rate was measured using micro-drive. Wires are inserted to brain and measured. This measurement is precise because it directly measures firing rate compared to indirect methods.

Hippocampus place cell activity has been modulated after stimulation. Place cell still had an ability to represent the location. However, representing location was varied after 20 minutes continuous theta burst stimulation. Average cross-correlation value of measured cell was 0.07

which means location representation before and after stimulation had changed clearly. This shows stimulation can modulate cell activity on mouse behavior. Further research can be done by studying more on pulse shape, carrier frequency and other brain stimulus region.

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Abstract (In Korean)

본 논문에서는 마이그로파를 반송파로서 사용하는 변조된 뇌 자극 신호 발생기를 개발 및 제작하였다. 제작된 시스템을 사용하여 연속적인 theta burst 자극 프로토콜 신호를 쥐의 해마에 인가하였다. 마이크로 드라이브의 전선을 사용하여 뇌 세포의 발화율을 측정하였다. 자극 전 후의 발화율 비교를 통하여 자극 효과를 검증하였다.

뇌 세포들은 뇌 신경망을 통해 서로에게 영향을 준다. 이러한 영향을 제한하기 위하여, 생체조직에서 짧은 투과 깊이를 갖는 6.5 GHz가 반송파 주파수로서 채택되었다. 자극 프로토콜은 수 헤르츠 단위의 주파수이며 6.5 GHz 반송파가 펄스에 맞춰 발생된다. 이러한 기능을 구현하기 위해, 변조기가 결합된 전압 제어 발진기, 가변 부하를 갖는 버퍼, 2단 차동 전력 증폭기, DC 시프팅이 가능한 진폭 검출기, 그리고 트랜스포머가 사용되었다.

전압 제어 발진기는 6.5 GHz의 반송파를 생성하기 위해 사용되었다. 변조를 위한 일반적인 방법은 신호 경로에 스위치를 연결하는 것이다. 본 논문에서는 변조기로서 동작하는 스위치가 전류 소스로서 동작하는 n-형 금속 산화물 반도체 전계 효과 트랜지스터의 게이트에 연결된다. 3개의 스위치가 병렬로 연결되며, 펄스 생성기만으로 theta burst 자극 프로토콜 신호를 발생시킬 수 있다. 전압 제어 발진기를 켜거나 끄는 방식으로 변조가 진행된다. P-형 부하를 갖는 교차 결합 구조가 전압 제어 발진기에 사용되었다. 전압이 크게 발생하게 되면 부하 임피던스가 변할 수 있는데, 이를 막기 위해 버퍼가 사용되었다. 또한 n-형 금속 산화물 반도체 전계 효과 트랜지스터의 온 저항을 사용하여 가변 부하로서 동작할 수 있도록 하였다. 가변 부하에 걸리는 전압을 제어함으로서 시스템의 총 출

력 전력을 조절할 수 있다. 자극을 위해서는 20 dBm 이상의 출력 전력이 필요한데, 이러한 이득 및 최대 출력 전력을 조건을 만족시키기 위해 2 단 전력 증폭기가 사용되었다. 드라이버 스테이지는 0.5 mm의 폭을 갖는 트랜지스터가, 메인 스테이지에서는 2 mm의 폭을 갖는 트랜지스터가 사용된다. 또한 6.5 GHz의 고주파에서는 회로에 존재하는 기생 성분을 무시 할 수 없다. 차동 구조는 인덕턴스에 의한 소스 악화와 같은 기생 성분 효과를 최소화 하기 위해 적용되었다. 캐스코드 구조와 C_{gs} 감소 기술은 트랜지스터가 버틸 수 있는 최대 한계 전압을 극복하기 위해 사용되었다. 자극 신호의 파형 변화를 이루어내어 더 많은 연구를 진행 시킬 수 있다. DC 시프팅이 가능한 진폭 검출기가 이를 위해 시스템에 추가되었다. 진폭 검출기는 한계 전압을 극복하기 위해 캐스코드 구조를 사용한다. 다이오드 연결이 된 트랜지스터 정류기와 저역 통과 필터는 출력 스윙의 진폭과 동일한 DC 전압 값을 만드는데 사용된다. 차동 출력 신호를 단일 종단 구조인 자극기에 전달하기 위해 트랜스포머가 사용되었다.

쥐 실험을 통해 제작된 시스템이 검증되었다. 연속적인 theta burst 자극 신호를 쥐의 해마에 인가하였다. 마이크로 드라이브 전선은 해마 세포의 발화율을 측정하는데 사용하였다. 자극 효과는 자극 전후의 장소 맵 차이를 통해 검증하였다.