Design and investigation of novel neural stimulation by magnetic resonance coupling

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2017

Pradhan, R. (2017). Design and investigation of novel neural stimulation by magnetic resonance coupling. Doctoral thesis, Nanyang Technological University, Singapore.

<http://hdl.handle.net/10356/72088>

<https://doi.org/10.32657/10356/72088>

**NANYANG
TECHNOLOGICAL
UNIVERSITY**

**DESIGN AND INVESTIGATION OF NOVEL NEURAL
STIMULATION BY MAGNETIC RESONANCE
COUPLING**

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SCHOOL OF ELECTRICAL AND ELECTRONIC ENGINEERING

2017

**DESIGN AND INVESTIGATION OF NOVEL NEURAL
STIMULATION BY MAGNETIC RESONANCE COUPLING**

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A thesis submitted to the Nanyang Technological University in partial
fulfilment of the requirement for the degree of
Doctor of Philosophy

2017

Acknowledgement

I would like to express my heartfelt gratitude to my supervisor, Associate Professor Dr Zheng Yuanjin, for his constant support, immense patience, valuable feedback and suggestions. He has helped me with significant inputs towards my research, professional growth and career planning, throughout the entire duration of my graduate studies. I am greatly indebted to him for his enthusiasm and faith in me during the difficult times. Without his broad vision, deep insight and strong encouragement, this work would not have been possible.

I would like to express my sincere appreciation to all students and staff in VIRTUS, VALENS and Neuroscience lab at LKC Medicine for their help, and constant effort in providing a friendly research environment. I would also like to thank my co-supervisors and lab mates, Dr Ch'ng Toh Hean, Dr Yeung Sai Ho, Dr Feng Chen and Mr Rahul Kishore for their help during the project.

I would like to acknowledge the school of Electrical and Electronics Engineering, Nanyang Technological University, Singapore, for the financial support of my Research Scholarship.

I would like to thank everyone who offered help during my research work and for being there with me throughout this journey: NTU (Heavy Chele Group), NUS (Mutual Admiration Society) and Block 932-Bhailog. Special gratitude to my friends, Dr Subhrajit Roy, Dr Soumyabrata Dev and Mr Zishan Ali, who started their doctoral journey along with me and have been a constant source of encouragement. A special word of mention to my dearest friends, Ms Abhispa Sahu and Mr Randeep Kumar Sahani, who have always kept me motivated in the most difficult circumstances throughout my life. I am highly indebted to all the above set of people in my life, without whom I may not be the person I am today.

I am eternally grateful to my parents Mr Susanta Kumar Pradhan and Mrs Rita Pradhan and my sister Ms Saloni Pradhan, for their support and belief in me throughout this entire duration. None of this would have been ever possible without their understanding, blessings and faith in me. They have been a constant source of encouragement and a pillar of support all my life.

I would like to dedicate this thesis to all these wonderful people in my life who have always wished the best for me.

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Abstract

Stimulation methods for treatment of neural disorders have evolved tremendously over the years ranging from invasive methods i.e. Deep Brain Stimulation (DBS) to non-invasive methods i.e. Transcutaneous Electric Nerve Stimulation (TENS) and Transcranial Magnetic Stimulation (TMS). This study hence first reviews existing literature for pain mechanism and how electrical stimulation is useful for treatment of pain. The existing commercial treatment options are analyzed to determine the technical drawbacks which could be overcome, to develop a more effective system for therapy.

The proposed system comprises of a pair of coils, where current is induced in the secondary coil wirelessly and electric field is induced in the region between the coils due to magnetic resonance coupling. Addition of resonant structures and ferrite cores to this system has been studied, which enhanced the induced electric field (1.22 times due to addition of ferrite cores at 450 kHz source frequency). This study has been further extended for design and construction of a pair of figure-of-eight coils, coupled by magnetic resonance coupling (MRC), to generate (150 V/m per Ampere) electric field at the focal points for electromagnetic therapy related applications. For practical applications, which require adjustment of the focal point, a tri-mode coupled coil is proposed, where the focal adjustment of the E field can be optimized by tuning the current ratio across coils, which signify different modes of operation. A comparative study was also performed between the proposed magnetic resonant coupling (MRC) stimulation, magnetic stimulation (MS) and transcutaneous electrical nerve stimulation (TENS), in terms of the operating mechanism, ex-vivo tissue voltage measurement and electromagnetic simulation analysis. MRC RF stimulator was found to have several advantages compared to others to induce current in the biological medium for stimulation applications. These coils were then used for gene delivery in 3T3 cells, where they were able to achieve highly efficient transfection rates.

Design and construction of MRC Figure of 8 coils, optimization of parameters depending on the application, and comparative advantages of the proposed technique over existing technologies has been the major contributions for this thesis. Besides, some of the future works and preliminary results in terms of new biomedical applications (drug delivery, gene delivery), improving the efficacy of the proposed system (magneto-acoustic stimulation) and future experiments (Von frey experiments for threshold determination of pain in mice) has also been highlighted.

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Abbreviations

TENS	Transcutaneous Electric Nerve Stimulation
TMS	Transcranial Magnetic Stimulation
DRG	Dorsal Root Ganglion
SG	Substantia Gelatinosa
NT	Neurotransmitter
SLIGRL	ligand Ser-Leu-Ile-Gly-Arg-Leu
GRP	Gastrin releasing peptide
BNP	B-type natriuretic peptide
NPRA	Natriuretic polypeptide receptor subtype A
GRPR	Gastrin releasing peptide receptor
fMRI	Functional Magnetic Resonance Imaging
MRC	Magnetic resonance coupling
US	Ultrasound
E	Electric field intensity (V/m)
B	Magnitude flux density (T)
J	Current density (A/m ²)
f_0	Self-resonance frequency (Hz)
f_m	Lowest resonance frequency (Hz)
f_e	Highest resonance frequency (Hz)
f_1	First operation frequency (Hz)
f_2	Second operation frequency (Hz)
f_3	Third operation frequency (Hz)
μ_0	Permeability of the free space (H/m)
σ	Electrical conductivity (S/m)
N	Number of turn of the coil
I	Magnitude of current flowing through the coil (A)
I_1	Magnitude of current flowing through coil 1 (A)
I_2	Magnitude of current flowing through coil 2 (A)

$d\mathbf{l}'$	Differential coil element
$\mathbf{r}'$	Position vector of the differential element $d\mathbf{l}'$
$\mathbf{r}$	Position vector of the observation point
x, y, z	Cartesian coordinates
D	Distance between coils 1 and 2 (m)
L_m	Mutual inductance (H)
L	Self-inductance (H)
C	Capacitor cascaded in series to the coil for resonance
R	Coil resistance plus the resistance of the small resistor cascaded in series to the coil (Ω)
L_1, L_2	Inductor values in the multi-impedance matching network (H)
C_1, C_2, C_3	Capacitor values in the multi-impedance matching network (F)
R_S	Source resistance (Ω)
V_S	Source voltage (V)
G_{I1}	Transconductance between coil currents I_1 and source voltage V_S (A/V)
G_{I2}	Transconductance between coil currents I_2 and source voltage V_S (A/V)
G_{E1}	Electric field gain between the electric field E_1 induced at the observation point (contributed by the coil current I_1) and the product of the coil current I_1 and frequency ($\text{V}/\text{AmHz}^{-1}$)
G_{E2}	Electric field gain between the electric field E_2 induced at the observation point (contributed by the coil current I_2) and the product of the coil current I_2 and frequency ($\text{V}/\text{AmHz}^{-1}$)
θ	Phase difference between the current across the two coils 1 and 2 ($^\circ$)
d	Distance between the two terminals of the voltage measurement (m)
P_σ	Ohmic power density (W)

Chapter-1:

Introduction

1.1 Background and Motivation

Stimulation is the result of an action of various agents on muscles, nerves or a sensory end organ by which activity is aroused. Stimulation as a treatment option for the treatment of various neurological disorders has evolved over the years ranging from invasive stimulation (electrical stimulation, optical stimulation), slightly invasive and noninvasive stimulation methods (magnetic stimulation techniques such as TENS, TMS). It has been successfully used for treatment of disorders such as pain, muscle spasm, skin wounds, bone fractures, depression, insomnia, muscle atrophy, tinnitus and others [1]- [7]. Based on the existing literature, stimulating nerves with varying intensity of current might induce different chemical responses or activate neurotransmitters leading to treatment of various disorders. This is due to the specific action of the neurotransmitters. The stimulation depends on three parameters, 1) the orientation of the coil with respect to the head or body as the case maybe, 2) the current waveform through the coil, and 3) the type of coil.

Brain stimulation therapy has garnered more interest due to inability of certain mental disorders to respond to conventional treatment methods. Since Baker introduced the use of magnetic fields to stimulate the human motor cortex and the peripheral nerves, which can produce effects like muscle twitches; there has been tremendous interest in this effect from the medical field. Since the time varying magnetic field induces an electric current, this electric current can be used to activate the neurons or stimulate muscles, without using any electrodes. The induced electric field changes the electric potential of the nerve fiber, generating an action potential for transmission of information or any action. Using a time varying magnetic field to stimulate the tissues is non-invasive, convenient, safe and effective as

compared to electric stimulations [8] – [16]. However, the design of full scale magnetic stimulation systems consists of many challenges- such as using a low current, deep penetration effect, low cost, portability and enhancing user friendliness.

Different types of magnetic stimulation systems have been developed, which are presently being used for treatment of a wide range of disorders. In this thesis, we concentrate on studying these existing magnetic stimulation systems which have been used for treatment of neural disorders, and developing a unique hardware system prototype, which is effective, low cost, low power and can be replicated for usage across a wide audience. The focus is on developing a system which can induce a large amount of current which can be customized depending on the magnitude of magnetic field required to be induced for the particular application. The developed system must provide a clear advancement on the existing state of art technologies, and a comparative study has been performed in this regard with respect to a particular application by both simulation and experimental methods.

1.2 Thesis Contribution

The major contributions of this thesis are listed below.

- **Enhancement of electric field in a non-invasive magnetic stimulation system:** The theory behind magnetic stimulation systems has been studied in a lot of detail. Addition of resonant structure and ferrite cores to a system of coils have been proposed to increase the electric field needed for stimulation. Enhancement of electric field due to usage of the proposed system has been quantified using both simulations and experimental results. A non-invasive biomedical resonance stimulation system has been proposed, highlighting the clear advantages of the system to enhance the electric field induced in biological tissue.
- **Magnetic Resonance coupling coils for Biomedical Applications:** Design and construction of Figure of 8 coils coupled by Magnetic Resonance Coupling to generate electric field at focal points for biomedical applications has been proposed. These designed coils have been found to use low power, and achieve stronger focus than existing coil systems. This has been verified using both simulations and experiments. Different modes of operations for these coils have been

designed, where the electric field induced and the focal point can be optimized and tuned, depending on the requirements of the user for a particular biomedical application.

- **Optimization and comparison among various coil designs/ existing stimulation systems for biomedical applications:** Comparative studies are performed with regards to simulation and ex-vivo experiments, where the proposed coil stimulation set-up is compared to available commercial stimulation systems, highlighting the advantages of the proposed system in comparison to state of the art technologies. The proposed system was found to increase efficiency of transfection for 3T3 cells compared to conventional approaches. Use of low frequency ultrasound to improve the efficiency of this existing stimulation set-up can be considered as future scope for this work, besides considering the proposed set-up as a platform technology for various biomedical applications.

1.3 Thesis Organization Structure

The thesis is organized into 9 different chapters.

Chapter 1 provides the background and motivation for the work. This is followed by the primary contributions of the thesis and the organization of the thesis.

Chapter 2 provides a brief overview of pain mechanism and how electrical stimulation is useful for treatment of pain. Existing magnetic stimulation techniques are reviewed which have been used for treatment of pain. Applications such as itch, depression and insomnia have also been introduced, where electrical stimulation is already in use for treatment and may be future potential applications for the proposed system.

Chapter 3 introduces the concept of magnetic resonance coupling. Different kinds of primary and secondary coil structures are discussed with their construction, which have been used to enhance the electric field induced for stimulation.

Chapter 4 introduces a pair of coils coupled by magnetic resonance coupling, which effectively induced a current at the biological medium for potential biomedical applications. Ferrite cores were added to the set-up which showed larger induced current due to eddy current generation, as compared to the coils without core, verified in both theory and simulations.

Chapter 5 proposes the design and construction of a specific kind of coils- Figure of 8 coils coupled by magnetic resonance coupling for biomedical applications. Detailed construction of these coils is discussed, and optimization of parameters is performed to obtain the desired electric field for a required biomedical applications. Ex-vivo experiments and measurements are performed to validate the proposed set of coils.

Chapter 6 introduces the design of a tri-mode coupled coil which enables three modes of operation for inducing electromagnetic field, where the focal adjustment of the E field can be optimized. The interacting between frequency of operation, coupling between the coils and the current ratios induced are analyzed during the various modes of operation. The concept is proven using simulation, measurement and ex-vivo experimental results. Practical considerations for usage of these coils for biomedical applications are also discussed.

Chapter 7 performs a comparative study among different stimulation techniques such as proposed magnetic resonance coupling, magnetic stimulation and transcutaneous electric nerve stimulation. The comparison is performed with regards to electric field induced (in both simulations and ex-vivo experiments) and focal point for stimulation with regards to various biomedical applications.

Chapter 8 performs a comparative study among various magnetic stimulation techniques for gene delivery application with in-vitro experimentation results is discussed. The comparative advantages of the proposed stimulation system in the earlier chapter is quantified and discussed, as compared to already existing stimulation systems.

Chapter 9 concludes the whole thesis. Future works with regards to drug delivery in cancer cells using magnetic and acoustic stimulation, enhancing the stimulation performance by using low pulsed ultrasound to perform neural stimulation, and the proposition for a magneto-acoustic stimulation set-up to perform animal experiments with a closed loop feedback system for neuro-therapy, to develop a system similar to acupuncture is discussed.

Chapter-2:

Literature on Neural Disorders and Existing Stimulation Techniques

Abnormalities in the brain, spinal cord or nerves can result in a range of symptoms leading to a neurological disorder. Nerves tend to lie deep under the skin but can still become exposed to damage. Individual neurons, and the neural networks and nerves into which they form, are susceptible to electrochemical and structural disruption. A report stated that neurological disorders and their sequelae (direct consequences) affect as many as one billion people worldwide, with expenses ranging upto \$600 billion alone for pain [17]. This chapter focuses on treatment of pain using electrical stimulation, and explains potential mechanisms in which pain perception is reduced due to electrical stimulation. Neural disorders with similar biological mechanisms such as itch, depression and insomnia where electrical stimulation has been shown to be useful for treatment have been also briefly introduced. A brief introduction to existing stimulation techniques for treatment of pain has also been provided to form a better understanding.

2.1 Pain

Pain could be termed as an unpleasant sensory and emotional experience which could be related with tissue damage, or described in terms of such damage. The exact mechanism of pain and its dual role as an important physiological entity, a disease has intrigued scientists and philosophers for years. Its history can be traced long back when Charles Darwin described pain as a ‘homeostatic emotion’ essential for the survival of species. Descartes in the 17th century then proposed that pain is caused due to activation of a straight line channel from the skin to the brain. In the 19th century, pain was explained on the basis of stimulation of any kind of nerve fibers and those signals are transmitted to the spinal cord (pattern theory) or on the basis of specific nociceptors at the site of pain (specificity theory). In 1965, Melzack and Well proposed the “gate theory” of pain which stated that nerve impulses flow from peripheral nerves to CNS and a gate controls the flow of nerve impulses, “closed state” reducing the pain sensation. They further modified it to state that pain experience is not a simple relationship between tissue damage and pain [18]. Pain is normally perceived at the thalamus and then transferred to higher centres of brain for perception and interpretation. Generally, two types of fibers, large A-delta fibers (fast pain) and C fibers (slow or chronic pain) are used for transmission of pain impulses. Various mechanisms have been proposed to inhibit the transmission of pain impulse which provides pain relief.

Fig 2.1 Various stages of pain mechanism [Figure:
https://www.painedu.org/tools/pathophysiology_pain.asp]

Electrically stimulating the periaqueductal grey (PAG) can release *enkephalin* inter-neuron which can block the gate to A-delta and C neurons at Substantia Gelatinosa (SG) resulting in pain relief. Stimulation of Dorsal Root Ganglion (DRG) can lead to activation of large fibers and SG cells which can lead to pain relief due to decreased T-cells activity. Electrical stimulation can also lead to inducing responses from opoid receptors which inhibit neurotransmitter release from primary afferent terminals in spinal cord and activate descending inhibitory controls in midbrain resulting in less perceived pain. Opioid drugs inhibit neurotransmitter release by coupling via G proteins directly to Na^+ and Ca^{2+} ion channels which can contribute to pain relief. Also, stimulation of certain neurotransmitters can lead to analgesic effects from certain neurotransmitters thereby, controlling the neural activity of pain impulse resulting in pain relief [18]-[19].

Fig 2.2 Pathways showing the effect of various type of fibers for pain transmission [Figure: <http://www.d.umn.edu/~jfitzake/Lectures/DMED/Somatosensation/Somatosensation/GateTheory.html>]

Fig 2.3 The opening and closing of gates in gate theory of pain [Figure: <http://medical-dictionary.thefreedictionary.com/gate-control+theory>]

2.2 Itch, Depression and Insomnia:

Itch, or pruritus, could be better described as an unpleasant sensation which evokes a desire to scratch. Although it may be acute, chronic itch originates from many different etiologies and is a burdensome condition with serious unmet clinical need. Primary afferent sensory neurons (nociceptive fibers) are responsible for detecting a variety of sensory stimuli which includes touch, temperature, chronic pain and itch. The axons of these neurons collect information from the skin and transmit them to their respective cell bodies in Dorsal Root ganglion, and the information is passed onto the thalamus. There is a considerable overlap in the pathways of signaling molecules which transmit itch and pain. The incidence of itch is widespread across all the global countries with incidence ranging from 10-15%. Itch is known to lead to various skin disorders, raising the cost of treatment significantly [20] – [21].

Clinical depression, also known as melancholia can often occur due to a variety of reasons which could be dejection, sadness, despondency, anger, fear, delusions and obsessions. It is the most predominant mental health problem worldwide among the working group population. Depression can act for both long and short durations, depending on the factors responsible for it. This duration can be significantly reduced with the help of medical treatment being administered to the patient. Few of the prevalent approaches which have been used widely for treatment of depression are Vagus Nerve Stimulation (VNS), Deep Brain Stimulation (DBS) and repetitive Transcranial Magnetic Stimulation (rTMS). During the period of depression, increased activity is found in the brain region called Broadmann Area 25 (which could be stimulated). Approximately 17.5 million people suffer from depression in US with estimated medical costs being \$30.4 billion per year. In Europe, more than 32 million people were affected with costs being 92 billion euros in 2010.

Insomnia termed as the lack of sleep or sleep disorder which affects a person's driving ability, performance, cognitive skill, psychomotor coordination, mood, memory, concentration and enjoyment of family and social life. Insomnia usually results due to insufficient accumulation of melatonin which disturbs the sleep-wake cycle (circadian system). Some of the likely mechanism for insomnia treatment:

- a. Stimulation the areas of brain which secrete dopamine and catecholamine, returning the experimentally imbalanced neurotransmitter homeostasis back to its original homeostatic condition.
- b. Maximally producing neurotransmitter (NT) (firing of NTs across synaptic space) achieving homeostatic balance due to inhibitory effect of neuron.

Approximately 30-35% of the general population occasionally experience insomnia and 10-12% have chronic insomnia. Both insomnia and depression are very significant problems affecting a major portion of the society, with major medical implications if not treated. However, there is still a lack of proper scientific understanding of these disorders [22] – [24].

Most of the neural disorders mentioned above presently rely on conventional treatment options such as medicines, drugs, physiotherapy, meditation etc. Pain and Itch have medicines and physiotherapy as treatment options, but they provide temporary relief and are not always effective. For depression and Insomnia, medicines, drugs are used, which can have lot of side effects (includes being over dependent on drugs). There is no golden approach to therapy on these neural disorders based on a proper scientific understanding which is widely prevalent.

2.3 Stimulation Techniques for Treatment of Neural Disorders:

Stimulation as an approach for treatment of such neural disorders has been explored since a very long time. This thesis however, focuses on stimulation by use of electric fields. Treatment modalities, which cater to the pharmacological side (including drugs, pain killers etc.) have not been included in the discussion. There have been invasive (Deep brain stimulation, transcranial direct current stimulation, Cranial Electric Stimulation) and noninvasive techniques such as transcutaneous electrical nerve stimulation (TENS), Transcranial magnetic nerve stimulation (TMS) techniques discovered for treatment of these neural disorders, but none of them have been used universally on a large scale. Invasive methods usually involve high costs of treatment, have lot of side effects and are found to be inconvenient.

TENS is convenient, uses low current, non-invasive (electrodes placed on the skin with gel) and has been found to be effective only at surface level due to lack of deep penetration. TMS normally produces a high magnetic field to induce a current which is used for stimulation. It has deep penetration but lacks localization effect i.e. fMRI needed to localize which results to high operating costs.

Fig 2. 4 Example of TENS stimulator being used on a patient [Figure: <http://greenvalleydme.com/images/tens.jpg>]

Fig 2. 5 Mechanism of working of a TMS stimulator [Figure: <http://ijarece.org/wp-content/uploads/2014/01/IJARECE-VOL-3-ISSUE-1-83-88.pdf>]

Fig 2.6 Example of TMS stimulator being used on patient [Figure:
http://images.flatworldknowledge.com/stangor/stangor-fig13_010.jpg]

In a nutshell, the various prevalent stimulation categories for the treatment of important neurological disorders like pain are summarized below:

The existing options for the treatment of back pain include:

- **Surgical:** Neuroplasty with Racz catheter, laser discectomy, spinal cord stimulation (SCS) and open back surgery: highly complicated, lot of risks involved, last option for treatment.
- **Minimally invasive:** Lumbar Epidural Steroid Injection (LESI) provides relief upto three months: severe complications involved and efficacy varies in the long run [25]-[29].
- **TENS** (Transcutaneous electric nerve stimulator): Have a only **surface effect** (electrodes placed at skin), no deep penetration (1~2 cm), poor localization effect [1]-[3].
- **TMS** (Transcranial magnetic stimulator): **Safety and portability issues**, uses a large current (which can be harmful), bulky set-up with a precise localization component (not convenient), only used in hospitals (skilled supervision required), high cost of treatment, lots of complications (death if current is delivered at wrong location, as it has deep penetration) [4]-[5].

- **Invasive PRF** (Pulsed Radiofrequency): Stimulation of Dorsal Root Ganglion (DRG) has shown promising results. The existing PRF stimulators are invasive, precise localization required, use needles to inject an electrode for stimulation (large current) which can be harmful [6], [30]-[31].

2.4 Summary

None of these methods are very popular with patients and used in home care settings due to the reasons stated above. Moreover, there is a lack of understanding of the exact mechanisms of the diseases presently, and most of the current existing techniques are based on the limited understanding of the disease state. Currently, there is no noninvasive convenient safe stimulator for pain relief (cervical and lumbar radicular pain) with deep penetration (>10 cm) and effective therapeutic effects. So, there is a need for a portable, safe and convenient stimulation device which can achieve deep penetration for providing strong pain relief. We propose a daily used noninvasive PRF stimulator which can stimulate deep neural nerves using a small current without the need of a separate localization equipment, thereby being safe, portable, low cost, easy to use and provides a strong pain relief effect, similar as surgical and implant technique. A comparison of the proposed system with the existing stimulation systems is shown in the Table 2.1.

Table 2. 1 Comparison of the proposed device with existing systems

	Current Type	Treatment time	Power Consumed	Cost (in SGD)	Size	Penetration Depth	Localization	Existing companies
TENS	Mono Phasic (100 mA)	Upto 16 hrs per day	Low (9 V battery)	200-500	Portable	Surface level: 1-2 cms	No localization	LG, Amtrex
TMS	Biphasic (5-10 kA)	Repetitive usage (20-30 hrs)	Very High (2-3 kW)	50000	Bulky: Used in hospitals	Upto 2-6 cms: outer cortex	Use of fMRI for localization	Magstim, Neurostar

Problems:

1. Power Consumption
2. Device costs
3. Portability
4. Penetration Depth
5. Convenience for Usage
6. Localization/ Efficacy

Research Statement: Can we design a safe, portable, low cost and easy to operate stimulation device with high efficacy for home care settings?

Chapter-3:

A Noninvasive Magnetic Stimulator Utilizing Secondary Ferrite Cores and Resonant Structures for Field Enhancement

In this chapter, secondary ferrite cores and resonant structures have been used for field enhancement. The tissue was placed between a double square source coil and a secondary ferrite core. Resonant coils were added which aided in modulating the electric field in the tissue. The field distribution in the tissue was measured using electromagnetic simulations and ex-vivo measurements with tissue. Calculations involve the use of finite element analysis (Ansoft HFSS) to represent the electrical properties of the physical structure. The setup was compared to a conventional design in which the secondary ferrite cores were absent. It was found that the induced electric field could be increased by 122%, when ferrite cores were placed below the tissue at 450 kHz source frequency. The induced electric field was found to be localized in the tissue, verified using ex-vivo experiments.

3.1 Introduction

The development of ferrite cores which could be used for power applications at kHz frequencies have helped in the manufacture of magnetic stimulators working at these frequencies. Ferrite cores have been utilized to increase the electric field in the nerve. Magnetic stimulators provide a spatial rate of change of electric field in the tissue by producing a magnetic field created by a varying current flowing through the primary coil. The major advantages of this type of stimulation include minimal discomfort to patients and its noncontact, noninvasive nature. Clinical applications predominantly use the Figure of Eight (FOE) coils. Other topologies like the double square coils, Cadwell coils, and the quad square coils also exist. Literature estimates that larger activation per unit current is produced when quad and square coils are used [8]. For low frequency magnetic stimulation, air cores have been used.

Power consumption for these magnetic stimulators, which consists of Transcranial Magnetic Stimulation (TMS) and repetitive Transcranial Magnetic Stimulation (rTMS) modalities are very high. The study of pulsed electromagnetic fields in human tissues required the scaling down of the stimulation systems. One such work involves the use of ferrite cores in quad coils at frequencies between 200 kHz - 1 MHz to achieve stimulation [9]. The stimulation depends on three parameters, 1) the orientation of the coil with respect to the head or body as the case may be, 2) the current waveform through the coil and 3) the type of coil.

Since Baker introduced the use of magnetic fields to stimulate the human motor cortex and the peripheral nerves, which can produce effects like muscle twitches; there has been tremendous interest in the medical field. Design of full scale magnetic stimulation systems consists of many challenges. During the discharge phase, a magnetic stimulator typically produces an output power of 5 MW. In the case of TMS/rTMS, this would imply that a capacitor needs to convert the charge stored into a magnetic energy in 100 μ s [10]. When higher frequencies are chosen, this results in stringent requirements for capacitor selection and eventually becomes a bottle-neck. Extensive work on the use of rTMS and TMS for curing various diseases like visceral pain, chronic neuropathic pain and fibromyalgia has been presented in literature. These modalities involve passing high intensity current pulses through a coil of wire, thereby inducing a magnetic field as high as 2-4 T [11]. Fast changing currents can be produced by two approaches, namely, using the SCR (silicon controlled rectifier) based charging and discharging

circuit, controlled by a PWM input, using similar circuits as IGBTs [12]-[13].

Increasing the field localization for stimulation has been yet another field of research. 3D finite element simulation has been used to determine the field localization and the electric field at the point of stimulation. Stimulation is carried out by using a FOE coil, with a conductive plate having a window placed under it. The field localization was improved due to the addition of the conductive plate, but the electric field in the tissue decreased 2 fold for the same FOE coil dimensions [14].

This chapter proposes a setup which utilizes the use of ferrite cores and resonant structures to enhance the induced electric field, and compares it to a conventional design. This chapter is organized as follows: In Section 3.2, the background theory for the construction of the non-invasive magnetic stimulator and use of resonant structures will be introduced. In Section 3.3, the simulation set-up, parameters estimation and the set-up for the ex-vivo experiments will be presented. In Section 3.4, the results from the simulation set-up and experimental set-up will be discussed. Finally, the conclusion will be given in Section 3.5.

3.2 Background Theory

3.2.1 Frequency selection for stimulation

Recently there have been studies which estimate the effects of magnetic fields and time varying currents from kHz to MHz frequencies. It has also been found that the membrane voltage increased with increase in frequency of the applied magnetic field [32]. The increase in membrane voltage is considered enough evidence to perform frequency selection for magnetic stimulation. It should be noted that at lower frequencies, the induced electric field in the tissue is smaller. The membrane voltage alone does not help in determining the suitable value for stimulation. It is shown in literature that the nerve acts as a low pass filter and internally amplifies low frequency signals compared to high frequency signals. This has been demonstrated in Fig 3.1 (a), where nerve acts as an idealized low pass RC circuit filter. This is because the nerve consists of capacitors and resistors which help in functioning as a low pass filter with a large DC gain. At higher frequencies capacitors tend to act as short circuits lowering the DC gain. The initial estimate of the electric field's amplification factor is given by the following equation:

$$G_E(\omega) = \frac{E_m(\omega)}{E_e} = \frac{3R_c}{2d} \frac{1}{1+j\omega\tau_m} \quad (3.1)$$

where

$$\tau_m = \frac{R_c C_m}{\frac{2\lambda_i \lambda_e}{\lambda_i + \lambda_e} + \frac{R_c}{d} \lambda_m} \quad (3.2)$$

Where, R_c is the cell radius (μm), C_m is the specific capacitance of the membrane ($\mu\text{F}/\text{cm}^2$), d is the membrane thickness which is equal to 3×10^{-9} (m), λ_i is the conductivity of the cytoplasm ($\text{mS} \cdot \text{m}^{-1}$), λ_m is the conductivity of the membrane ($\text{mS} \cdot \text{m}^{-1}$), λ_e is the conductivity of the extracellular ($\text{mS} \cdot \text{m}^{-1}$). E_m is the electric field inside the membrane (V/m). However, this model does not consider the second order effects. $\epsilon_i, \epsilon_m, \epsilon_e$ are the permittivity of the cytoplasm, the membrane and the extracellular medium respectively and measured in F/m. ϵ_e was taken as 77.8 F/m and ϵ_m was taken as 3.95 F/m. A more precise version of the amplification factor is given below.

$$G_E(\omega) = \frac{3\lambda_e^* [3R_c^3 \lambda_i^* + (3dR_c^2 - d^2 R_c)(\lambda_m^* - \lambda_i^*)]}{K - 2(R_c - d)^3 (\lambda_e^* - \lambda_m^*)(\lambda_i^* - \lambda_m^*)} \quad (3.3)$$

Where,

$$K = 2R_c^3 (\lambda_m^* - 2\lambda_e^*) \left(\lambda_m^* - \frac{1}{2} \lambda_e^* \right). \quad (3.4)$$

where, $\lambda^* = \lambda + j\omega\epsilon$. Here, second order effects are also considered. The nerve amplification function generates a zero at 100 MHz, the effects felt by the zero were not considered in the first order solution. The above calculation is not exact because it considers the nerve as a cylinder [15], [33]-[34].

Exact formulation is tedious because the exact geometry of the nerve is to be incorporated and solved by numerical methods and hence is not considered in this work. By substituting the extracellular medium, the amplification factor was plotted to get an approximate estimate of the frequency range to be chosen. Four extracellular mediums, namely blood, fat, bone and muscle were chosen for the estimation for which the conductivities are obtained from literature [34]-[35]. The logarithmic magnitude of the amplification factor and the log magnitude of the frequency were plotted to obtain Fig. 3.1. It was seen that the decrease in the amplification factor was predominant for frequencies greater

than 1 MHz. In the case of fat tissue, the amplification factor had significant reduction even before 1 MHz; hence frequencies in the order of hundreds of kHz were chosen for analysis.

Fig 3.1 (a) Nerve as a low pass filter circuit (b) Amplification factor as a function of frequency

3.2.2 Primary Electric field due to the coils

Excitation to action potential threshold in the sub threshold regime can be determined by a passive linear model. The cable equation for excitation of a linear nerve model by an electric field can be expressed as:

$$\lambda_m^2 \frac{\partial \vec{E}_x(x, t)}{\partial x} = \tau \frac{\partial V_m(x, t)}{\partial t} - \lambda_m^2 \frac{\partial^2 V_m(x, t)}{\partial x^2} + V_m(x, t). \quad (3.5)$$

where the length and time constants are defined as

$$\lambda_m = \sqrt{\frac{r_m}{r_i}} \text{ and } \tau_m = c_m r_m. \quad (3.6)$$

Where, x is the distance along the axis of the nerve fibre when the nerve fibre is aligned along the x axis. E_x is the electric field along x axis. V_m is the trans-membrane voltage which is the voltage difference between the intracellular and extracellular fluid. r_m and r_i is the membrane resistance times unit length and the intracellular resistance respectively. c_m is the membrane capacitance per unit length. $\partial E_x / \partial x$ is the activation function.

The primary electric field generated due to the magnetic field created by a rate of change of current through the coil is given by the following equation:

$$\vec{dE^p} = \frac{-\mu_0 N \left(\frac{di}{dt} \right) d\vec{l}}{4\pi R}. \quad (3.7)$$

where, dE^p is the primary electric field, μ_0 is the permeability of free space, $\frac{di}{dt}$ is the rate of change of electric current, $d\vec{l}$ is an element of the coil, N is the number of turns and R is the distance between the coil element and the point where the electric field is calculated.

For generating the required electric field in the nerve, various types of coils have been used for magnetic stimulation in literature. This is because magnetic stimulation provides the following advantages: 1) no contact to skin and non-invasive, 2) Ability to move and control the point of stimulation with ease. Though other coil structures have also been used, larger activating function per unit area has been achieved when square and quad coils are used. Electric field induced in the tissue can be calculated from the equation

$$\vec{E}_{Source}(\vec{r}) = -\frac{\partial I_1}{\partial t} \frac{\mu_0}{4\pi} \int_S \frac{d\vec{l}'_{Source}}{|\vec{r} - \vec{r}'|} - \nabla \phi_1. \quad (3.8)$$

where, $\vec{E}_{Source}$ is the electric field produced in the tissue due to a current carrying source coil, I_1 is the current across the primary coil, $d\vec{l}'$ is an infinitesimal coil section and $\vec{r}'$ is the vector from each section to the point $\vec{r}$. ϕ_1 is the electric potential due to surface charge accumulation. For our calculations here, a double square coil is used. Adopting the methods proposed [8], we obtain the following relations for activation function.

$$\frac{\partial E_x}{\partial x} = -\frac{\mu_{eq}}{4\pi} \left\{ N \left(\frac{dI_1}{dt} \right) (-A + B + C - D - E + F) \right\} - \nabla \phi_1 \quad (3.9)$$

where

$$\begin{aligned}
A &= \frac{2}{\sqrt{x^2 + y^2 + (h-p)^2}} \\
B &= \frac{1}{\sqrt{(s-x)^2 + y^2 + (h-p)^2}} \\
C &= \frac{1}{\sqrt{(s+x)^2 + y^2 + (h-p)^2}} \\
D &= \frac{1}{\sqrt{(s-x)^2 + (s-y)^2 + (h-p)^2}} \\
E &= \frac{1}{\sqrt{(s+x)^2 + (s+y)^2 + (h-p)^2}} \\
F &= \frac{2}{\sqrt{x^2 + (s-y)^2 + (h-p)^2}} \quad (3.10)
\end{aligned}$$

where, x and y are the co-ordinates in the plane of the coil. s is the length of a side of the square coil. h is the total distance between the source and the receiver coil. p is the point at which the electric field is measured. N denotes the number of turns in the primary coil.

3.2.3 Use of Resonant Structures for field enhancement

Now, it is to be estimated if a secondary structure is able to help the increase of the electric field at the nerve. We know from Maxwell's equations that

$$\oint E \cdot dl = -\frac{\partial}{\partial t} \int_s B \cdot ds. \quad (3.11)$$

Where, E is the electric field and B is the magnetic field. Ferrites can be used as flux concentrators, thereby increasing the flux in the path between the primary and the secondary ferrite. This leads to the increase in electric field induced at the tissue.

Soft ferrites are hard, brittle and chemically inert. These materials are black or dark-grey. Compounds of either Manganese/Zinc or of Nickel/Zinc are primarily used. Magnetic properties are exhibited if below the Curie temperature. They possess high resistivity and high permeability. Composition of the

oxides can be adjusted to tune the permeability during manufacturing process. Addition of resonating structures help in modifying the electric field. Rate of change of current in the primary coil can cause currents to flow in the secondary coil. This provides a change in the field distribution, thereby modifying the electric field to a small extent.

Wireless power transfer experiments were first carried out by Nikola Tesla. Recent interest in wireless power transfer is due to the work reported which used the method of resonant coupling for mid-range wireless power transfer. This was based on the understanding that a physical system can be reduced to a set of differential equations by using coupled mode theory [36].

$$\dot{a}_S = -i(\omega_S - i\Gamma_S)a_S - ika_D + Fe^{-i\omega t} \quad (3.12)$$

$$\dot{a}_D = -i(\omega_D - i\Gamma_D)a_D - ika_S \quad (3.13)$$

where, ω_S and ω_D are the resonant frequencies of the isolated objects and Γ_S and Γ_D are the intrinsic decay rates due to absorption and radiated losses. k is the coupling co-efficient. F is the driving term and a is a variable defined so that the energy contained in the object is $|a_{S,D}(t)|^2$. When such a resonating structure is placed, it will generate an electric field which is given by:

$$\vec{E}_{receiver}(\vec{r}) = -\frac{\partial I_2}{\partial t} \frac{\mu_0}{4\pi} \int_S \frac{d\vec{l}_{receiver}}{|\vec{r}-\vec{r}'|} - \nabla\phi_2 \quad (3.14)$$

Assuming that a current flows in the secondary structure due to resonance, the electric field created by it on the nerve is given by:

$$\frac{\partial E_x}{\partial x} = -\frac{\mu_{eq}}{4\pi} \left[M \left(\frac{dI_2}{dt} \right) \left(\frac{1}{\sqrt{(x_0 - x)^2 + (y_0 - y)^2 + p^2}} \right) \right] \quad (3.15)$$

This field has a vectorial additive effect to the electric field produced due to the primary coil, thereby modulating the electric field in the nerve. Here, x_0 and y_0 refer to points on the receiver coil. M is used to refers to the number of turns in the receiver coil. μ_{eq} is the effective permittivity [9].

3.3 Materials and Methods

3.3.1 Simulation set-up

The Ansoft Simulation setup, shown below in Fig 3.2 consisted of a primary coil (double square coil) for focusing the electric field to the tissue. The primary coil had ferrite cores for concentrating the flux. The secondary structure was varied as ferrite cores, ferrite cores and resonating/non-resonating coil, double square coils and vacuum. A fat tissue was placed in between the primary coil and the secondary structure. The structure (comprising of primary and secondary structures with a fat tissue placed between them) was enclosed in an air box. Finite Element-Boundary Integral (FE-BI) method was used to solve the structure. The simulation setup used in Ansoft HFSS [37] is shown in Fig. 3.2.

Fig 3.2 Top view of the simulation setup, b) Bottom view of the simulation setup, c) Side view of the simulation setup. Ferrites, fat tissue, copper are shown in light blue, brown and grey respectively

FE-BI method available in HFSS was used. The wavelength was in the range of around 1 km. Air box size was chosen as 11.1x11.1x11.1 m³. The values of ϵ_r , μ_r and σ of the fat tissue were 31.565, 1 and 0.024906 S/m respectively. The values of ϵ_r , μ_r and σ for the ferrite were 12, 1000 and 0.01 Siemens/m respectively and the values of ϵ_r , μ_r and σ of copper were taken as 1, 0.999991 and 5.8x10⁷ Siemens/m. The fat tissue, the air box, the secondary coil, the ferrite cores, the input capacitor, the secondary ferrite core, secondary capacitor and the primary coil had 1912, 45996, 3577, 935, 6708, 912, 117 and 4066

tetrahedron mesh elements respectively at 550 kHz. An input power of 500 W was provided to the source coil. The fat tissue had a thickness of 0.25 cm. Fields 0.2 cm below the tissue were analyzed.

3.3.2 Parameter estimation based on circuit calculations

The parameters were chosen based on theoretical circuit model calculations and used as parameters for software based electromagnetic computation. The calculations of the parameter values are shown below.

1) Receiver coil resistance (R_r): Because of skin effect, the current density on the surface of the wire is higher than that at the center of the wire. This is taken into consideration while calculating the resistance of the wire. The resistance is given as follows:

$$R_r = \frac{2\pi a M}{\sigma 2\pi r \delta} \quad (3.16)$$

Where, a is the radius of the coil, M is the number of turns, r is the cross sectional area of the wire (0.071 cm), σ is the conductivity of the wire. The material chosen for the wire is copper and so $\sigma=5.8 \cdot 10^7$. δ is the skin depth [38].

$$\delta = \frac{1}{\sqrt{\pi f \mu_0 \sigma}} \quad (3.17)$$

where, μ_0 is the permeability of free space ($\mu_0=4\pi \cdot 10^{-7}$). Solving for δ and substituting in (3.16), we obtain the resistance values at 450 kHz, 500 kHz and 550 kHz for the wires of radius 2 cm and 3 cm.

2) Coil resistance R_L : The measurement is done by taking R_L as 50 Ω . R_r is negligible compared to R_L .

3) Source coil resistance R_s : The source coil is a double-square coil with each side, $s=5$ cm. Number of turns, $N=1$. *Number of coils* is 2, because the coil is a double-square coil. D is the width of the wire.

$$R_s = \text{Number of coils} \cdot \frac{4sN}{\sigma 4D\delta} \quad (3.18)$$

which gives $R_s=1.75 \text{ m}\Omega$ at 450 kHz, $1.845 \text{ m}\Omega$ at 500 kHz and $1.935 \text{ m}\Omega$ at 550 kHz. It should be noted that the calculations in this section do not take into consideration the effects caused due to the ferrites. Calculations of resistances for the copper coils are carried out.

3.3.3 Ex-vivo experimental set-up

Besides, validation of the simulations, experiments for determining the electric field induced due to the stimulation set-up has also been carried out using a pork tissue with the dimensions of 2 cm x 2.5 cm x 2 cm. Here, the voltage across the tissue was measured using electrodes, both with and without the presence of ferrite cores. The primary coil is used as double square coils, whereas for the secondary structures, resonant structures have been used. The secondary ferrite was chosen as a cylinder.

Fig 3.3 Ex-vivo experimental set-up to measure voltage across electrodes for the simulated set-up

3.4 Results and Discussion

Fig. 3.4 shows the results for the maximum electric field observed in the tissue when the radius of the ferrite core is varied. In Fig. 3.4, for calculation it should be noted that the secondary structure is only a ferrite core. It was observed that when the radius of the ferrite core was chosen as 3 cm, the maximum induced electric field in the tissue was obtained.

Fig 3.4 Simulation results for variation of maximum electric field with respect to frequency for different ferrite radius

Fig 3.5 Comparison studies (simulation results) with different dimension of coils and resonant structures
(a) Left handed coils of radius 2 cm with ferrite, double square coils and vacuum placed under the tissue. (b) Right handed coils of radius 2 cm with ferrite, double square coils and vacuum placed under the tissue. (c) Left handed

coils of radius 3 cm with ferrite and vacuum placed under tissue (d) Right handed coils of radius 3 cm with ferrite and vacuum placed under the tissue.

Power transfer with coils placed was found to be the maximum, when the radius of the coil was chosen to be 3 cm and hence calculations were adopted for coils and ferrite structures having radius of 3 cm. It is to be noted that the coils were wound around the ferrite core. Two terminologies are adopted in the calculation of these values. The coils which are wound in the anticlockwise direction when viewed from the source coil are called right handed coils and the coils which are wound in the clockwise direction when viewed from the source coil are called left handed coils.

The primary coil was kept constant as a double square coil. The secondary coils and cores were varied and the results for the same are indicated in Fig. 3.4 and Fig. 3.5. It is to be noted that in Fig. 3.5(a) and Fig. 3.5(b), double square coils are used as secondary coils. For obtaining each point in Fig. 3.4 and Fig. 3.5, calculations were carried out separately in HFSS. Resonant coils were those coils which satisfied the values for the equation $f_0 = \frac{1}{2\pi\sqrt{LC}}$, where f_0 is the resonant frequency and L and C are the inductance and capacitance of the secondary coils with or without the ferrites. The non-resonant coils were simulated by replacing the capacitor with a short when simulation was performed.

From simulation results in Fig 3.5(c) and Fig 3.5 (d) where ferrite cores were used, it was shown that the electric field increased by 121.71% at 450 kHz, 112.8% at 500 kHz and 109.8% at 550 kHz. Placing ferrite cores under the tissue hence, led to considerable difference in the electric field distribution. Modulation of electric field thus produced was also possible by adding resonating/ non-resonating coils in the presence or absence of these ferrite cores. Inferences obtained are stated as follows 1) power consumption can be reduced for generating the same electric field by using secondary ferrite cores, 2) Scaling of devices is possible since the power can be reduced, 3) Modulation of electric field is performed by the use of coils, 4) The theory explained earlier is validated.

Fig 3.6 Equivalent circuit diagram of the entire system

Fig 3.7 Induced electric field at a frequency of 450 KHz (Left) vacuum is placed below the tissue (Right) a ferrite core of radius 2 cm is placed under the tissue

Fig. 3.6 shows the equivalent circuit diagram of the system. Calculations of these individual values can be obtained by following the procedure described earlier in equations 3.17 - 3.19. Simulation results obtained from the electromagnetic analysis is presented in Fig. 3.7. for visualization of the electric fields, when vacuum and ferrite core of radius 2 cm is placed under the tissue at a frequency of 450 KHz. Fig. 3.8 and Fig. 3.9 depict the measurement results using these coils which have been performed according to the set-up shown in Fig. 3.3. The measurements for the proposed set-up have been performed in both scenarios; by using just electrodes and pork tissue placed between the electrodes. The use of ferrite core structures for both the above mentioned set-up, has been found to increase the induced electric field across the electrodes by 122% as opposed to no use of ferrite cores measurement results. The results therefore, were both verified in experiment and theory.

Fig 3.8 Measured voltage at 450 kHz across normal electrodes (Left) without ferrite cores (Right) with ferrite cores

Fig 3.9 Measured voltage at 450 kHz across pork tissue (Left) without ferrite cores (Right) with ferrite cores

3.5 Summary

In summary, mathematical modeling and analysis are carried out in the first section which aids in estimation of frequency and selection of primary coil and secondary structures. This work estimated that the electric field improved by 122% at 450 kHz when ferrite cores were placed below the tissue. It was found out that modification of the electric field is possible through the addition of secondary resonant and non-resonant coils in the absence and presence of ferrite cores. This device set-up can aid in stimulation and also can be used for carrying out experiments on the analysis of high frequency magnetic fields in the human body at reduced power consumption. The simulation has been carried out in an environment which can mimic the real scenario. Measurements are performed by using coils connected to instrumentation amplifiers are performed with normal electrodes and tissue placed in

between, for both ferrite cores and no ferrite cores. The measurement results are found to be similar to that of simulation results.

Ferrite cores operating at these frequencies which are used for high power applications are available in the market. In this case, “material 79” obtained from Ferrite Corporation can be used as the core. Power amplifier topologies are available in market which can provide the input power required for stimulation (AP400B by Advanced Test Equipment Corporation). The stimulator can be used for various neural stimulation applications which require modulation of electric fields in the brain, such as pain, depression, insomnia, epilepsy etc, presently being addressed using implant solutions placed within the brain . Studying of small structures like retina and the effects of magnetic fields on them can also be accomplished because of the scalability of the stimulator.

Chapter-4

A Noninvasive Magnetic Resonance Biomedical System

This paper proposes a pair of coils coupled by magnetic resonance coupling, which effectively induced a current at the biological medium for potential biomedical applications. Calculations and field estimation was done using finite element modeling software. Ferrite cores were added to the set-up which showed larger induced current density in the tissue (more than 2 times) due to eddy current generation, as compared to the coils without core. Further, experiments were conducted with an animal tissue placed between two resonating coils, which showed similar results with an induced current of 0.07 mA using 1NI coil. Also, 1.6 times larger current was induced in the tissue when ferrite cores were used as compared to air core.

4.1 Introduction

Radio Frequency (RF) electromagnetic field is useful for inducing electric current at the target biological medium in many biomedical applications such as pulsed electromagnetic field therapies [39], RF ablation [40], transcranial magnetic stimulation (TMS) [16], and thermoacoustic imaging [41].

When an electric field $\mathbf{E}$ is induced at an object with conductivity σ , it induces a current where the current density $\mathbf{J}$ is given by:

$$\mathbf{J} = \sigma \mathbf{E}. \quad (4.1)$$

Although a similar design was presented in [42], none of the experimental results was presented. In the coupled coils, a current is driven from an active source to the primary coil, which is then wirelessly transferred to the secondary coil. The electromagnetic field generated by the coils induced a current in the tissue at resonant frequency. Addition of ferrite cores into the set-up further enhances the induced current for potential biomedical applications.

This chapter is organized as follows: In Section 4.2, the proposed design of the set of coils and determination of the electric field induced by them will be discussed. In Section 4.3, the circuit model of the proposed coil configuration will be presented, and the current induced in the tissue due to the proposed set-up and addition of ferrite cores will be simulated. In Section 4.4, the ex-vivo measurement results will be discussed. Finally, the conclusion will be given in Section 4.5.

4.2 Electric Field generated by coils

Consider a circular coil of N turns with radius r and negligible thickness, the electric field intensity $\mathbf{E}$ can be computed from its magnetic potential under quasi-static condition [43], which results as

$$\mathbf{E}(\mathbf{r}) = \frac{\mu_0 \omega N I}{4\pi} \oint_C \frac{d\mathbf{l}'}{|\mathbf{r} - \mathbf{r}'|}, \quad (4.2)$$

where μ_0 is the permeability, N is the number of turn of the coil, I is the magnitude of current flowing through the coil, $d\mathbf{l}'$ is the differential coil element, $\mathbf{r}$ and $\mathbf{r}'$ are the position vectors of the observation

point and that of the differential element $d\mathbf{l}'$. Since the factor of N is already in the equation, there is no need to integrate the path for each turn. Since the assumption of negligible thickness could introduce error, a more accurate E-field strength will be obtained from electromagnetic simulation.

Since the pair of MRC coils consists of two magnetic coils, the overall E-field induced can be computed by the superposition of the field contributed by the primary and the secondary coils.

4.3 Coil Configuration and Simulation Analysis

This section provides simulation results for the proposed concept. All the simulations were performed in CST Microwave Studio Suite 2012 and LTspice. The tissue model was constructed in the software by using conductivity values of different layers of tissues obtained from [44].

4.3.1 Current In The Tissue Due To MRC

Fig. 4.1 describes the basic structure of our proposed concept. A current is passed in the primary coil, leading to induced current the tissue for stimulation. The circuit implementation for the proposed structure is shown in Fig. 4.2. LC tank is used for experiments. Port 1 is connected to a current source. Port 2 is connected to a capacitor. Probes are adjusted to monitor current in the circuit.

Fig 4. 1 Experimental set-up for tissue between two helical coils

Fig 4. 2 Circuit model implementation for the proposed model

Fig. 4.3 shows the frequency sweep results of the P1 and P2 curves, where current is plotted against frequency. Two peak values of resonant frequency are found in accordance with the MRC theory, however, we use the first peak value for resonance at 704 kHz. Frequency and transient analysis in LTspice using circuit model as shown in Fig. 4.4 This demonstrates that when two coils magnetically resonate at the same frequency, the resonated pole separates into two. At the smaller pole, the current in the two coils will be in the same phase. As a result, the magnetic field between them will be enhanced. At the resonant frequency, the magnetic field H is generally a closed loop with the coil and is nearly perpendicular to the tissue. The induced current in the tissue was approximately 0.05 mA with 1NI coil (where N and I are the turns, current in the coil).

4.3.2 Effect Of Addition Of Ferrite Cores

The addition of ferrite core into the coils set-up was found to increase the concentration of magnetic field density. Fig. 4.5 clearly shows the difference of induced current density in the tissue, with and without the presence of ferrite cores. This increase in current density is due to generation of more eddy currents at resonant frequency, resulting from the high electrical conductivity of ferrite core. Fig. 4.6 shows that the resonant frequency peaks shifts due to addition of ferrite cores as compared to no cores due to the large inductance value of the cores.

Fig 4. 3 Frequency sweeping results in a tissue showing the peaks due to resonance at two different frequencies

Fig 4. 4 Frequency and transient analysis of the MRC coils

Fig 4. 5 Current distribution pattern in the tissue (a) at resonant frequency (b) due to ferrites

Fig 4. 6 Frequency sweep results comparison between ferrite and no ferrite core

4.4 Measurement Results

The simulation results are verified by the measurement results obtained during in vitro experiments. Firstly, the concept of MRC is verified using the two coils. A muscle tissue from pig is then used to measure the current produced within the tissue during MRC. It was found that when the tissue is placed between the two coils, an electric field is induced across the tissue. Enhancement of current in the tissue due to addition of ferrite cores in the set-up is also studied.

Fig. 4.7 describes the experimental set-up of the system. Both the primary and secondary coils used in the set-up have 6 turns and a radius of 2.5 cm. The pig muscle (pork) tissue with a dimension of 4cm×2cm×1cm is placed between the coils. The primary coil is driven by a power amplifier, which is a push-pull amplifier with a P-type and an N-type power MOSFETs. The induced signal in tissue is pulsed to avoid thermal heat accumulation. The push-pull amplifier can follow the burst gate signal without much attenuation of amplitude. The current in the primary coil can be tuned by changing the control voltage of the power amplifier. Resonance is observed at about 1130 kHz with air core and 930 kHz with ferrite core when placed 2 cm apart.

Fig 4. 7 The system and circuit diagram of the proposed set-up

Fig. 4.8 shows that when the current amplitude in the primary coil (I_p) and secondary coil (I_s) are 0.05A and 0.25A, the current induced in the tissue (I_t) is about 0.13mA (i.e. approx. 0.07mA by using 1NI coil; similar to the simulation result of 0.05 mA). The small gap comes due to the different conditions used during the simulation and experiment setups, such as frequency. Fig. 4.9 shows that with the introduction of ferrite core structures in the coils, the induced current in the tissue increases to about 0.21 mA (1.6 times than without core). The experimental results are similar to the simulation results obtained. The gap between simulation and test results is because ferrite cores used in the test are loosely inserted in the coil due to its non-uniform shape, and low characteristic frequency of the ferrite core.

Fig 4. 8 Measured current in the air core coils and tissue

Fig 4. 9 Measured current in the ferrite core coils and tissue

4.5 Summary

In this chapter, the simulation and measurement result for the Magnetic Resonance Coupling (MRC) coil is presented. The coil is used for inducing current in the biological medium for potential biomedical application. At the resonant frequency, current was induced in the tissue and its magnitude was estimated to be approximately 0.05 mA in the simulation result. Ferrite core is also used to increase the field strength and hence the current induced in the tissue. More comprehensive tissue models and various modifications of coil designs would be included in the future studies. The set-up is covered by our US patent application and is currently being developed further for animal trials.

Chapter 5:

Focused Magnetic Resonance Coupling Coils for Electromagnetic Therapy Applications

This chapter presents design and construction of a pair of figure-of-eight coils, coupled by magnetic resonance coupling (MRC), which could generate (150 V/m per Ampere, i.e. approx. 1.5 times current density in tissue, compared to TENS, explained in Section 5.5) electric field at the focal points for electromagnetic therapy related applications. The E field generated at the targeted site would be significantly enhanced under the same amount of current flowing through the MRC figure-of-eight coils compared to normal coils, due to the superposition of E field contributed by the coils. Further, the MRC figure-of-eight coil is designed and the results are verified in theory, simulation and experiments. In the ex-vivo tissue measurement, 35% current and 82% ohmic power improvement were observed. Since it can enhance the current and ohmic power, the MRC figure-of-eight coils are promising solutions for electromagnetic therapy applications. The potential applications of the coils include non-invasive RF stimulation, thermoacoustic imaging, electromagnetic field therapies, and radio frequency ablation etc.

5.1 Introduction

Coils are widely used for generating electric and magnetic field to induce electric current at the focus in many electromagnetic therapy related applications such as thermoacoustic imaging , [41], [45] – [46], magnetic stimulation [3], [47] – [48], pulsed electromagnetic field therapies [39], [49] – [50], and radio frequency (RF) ablation [40] , [51]- [52]. An electric field $\mathbf{E}$ induced in an object with conductivity σ , generates a current where the current density $\mathbf{J}$ is given by:

$$\mathbf{J} = \sigma \mathbf{E} \quad (5.1)$$

Under the conduction of current, its ohmic power density P_o is given by

$$P_o = \frac{|\mathbf{J}|^2}{\sigma} = \sigma |\mathbf{E}|^2 \quad (5.2)$$

Both parameters are important for the electromagnetic therapy related applications. For instance, the induced current would be useful in stimulation, while Ohmic power density is usually useful for heating as in RF ablation and thermoacoustic applications. Several factors need to be considered during coil design to induce current at the target. Firstly, the electric field must be focused at the target while minimizing the $\mathbf{E}$ field at other areas. Note that the focus of the electric field is not just a point, but rather a line perpendicular to the orientation of the coil. Secondly, the ratio or gain of the induced $\mathbf{E}$ field at the focus divided by the current conducting the coils should be maximized, for the sake of using a smaller current to prevent heating up the coil. Thirdly, a very large coil should not be used which is too bulky and affects the actual implementation of the applications. The second and the third criteria involve a tradeoff because the larger the coil radius, the larger is the gain. This tradeoff is derived from the electromagnetic formulas in the next section considering a quasi-static frequency in the condition that the wavelength (which is 666.7 m at 450 kHz) is much longer than the distance between the desired observation point and the coil.

This chapter is aimed at proposing a new figure-of-eight [47] coil configuration which improves the coil design with respect to the above mentioned design criteria. The new coil configuration applies the

concept of magnetic resonance coupling (MRC) [53] – [55], which is composed of one active driven primary coil and a passive secondary coil coupled with each other, involving transfer of energy, when they are in resonance. Although there are two coils, only one source is required because the secondary coil is driven by the magnetic field radiated from the primary coil. Under MRC, the primary coil and the secondary coil would conduct the same or similar magnitude of current at the resonant frequency. Hence, both coils induce electromagnetic field and hence electromotive force at the target, thereby doubling the current density induced at the target. The proposed configuration drives two coils with a single-port drive through MRC without the need of using two independent source. It results that the equipment cost which include a signal generator and a power amplifier as well as the space can be saved. On the other hand, the figure-of-eight coil [47] configuration, which is popular in the literature to focus the magnetic field, could also double the current density induced at the tissue. This chapter will present the combination of figure-of-eight coil [47] and MRC [53] – [55], thereby further increasing the current density and ohmic power density induced at the tissue.

This chapter is organized as follows: In Section 5.2, the design theory of the MRC figure-of-eight coils will be introduced. In Section 5.3, the simulation results of electromagnetic field distribution of the coils will be presented. In Section 5.4, the design, fabrication and measurement of the MRC coil will be discussed. In Section 5.5, the biomedical ex-vivo experiments to demonstrate the current and heat induced at the pig muscle tissue (pork) using the focused MRC figure-of-eight coil will be performed. Finally, the conclusion will be given in Section 5.6.

5.2 Design Theory: Figure-of-Eight Coil

In this section, the theories for the design of MRC figure-of-eight coil are introduced. These include the configurations of different coil designs, electromagnetic field distribution, self-inductance, mutual inductance, MRC and its equivalent circuit models.

5.2.1 Configurations of the Coil Designs

In this chapter, three types of coils are considered. Firstly, it is the circular coil as depicted in Fig. 5.1(a). The coil consists of N turns of radius r along the same x - y coordinates and a current of

magnitude I flows through the coil. Secondly, it is the figure-of-eight coil as depicted in Fig. 5.1(b), which is composed of two coil elements with radius r , where both of them consist of N turns but the current I flowing through the two coils are in opposite directions to each other (clockwise and anticlockwise). This opposition is designed to enforce superposition of $\mathbf{E}$ field of the two coil elements at the focus point. Thirdly, it is the MRC figure-of-eight coil proposed in this chapter as depicted in Fig. 5.2. It is composed of two figure-of-eight oriented in the xy -plane separated by the distance D along the z axis. The primary coil couples and transfers energy to the secondary coil, and both of them would conduct the same or similar magnitude of current at the resonant frequency under MRC. The actual 3D model of the coil is shown in Fig. 5.3.

Fig 5. 1 Configuration of a magnetic coil: (a) circular coil, (b) figure-of-eight coil

Fig 5. 2 Configuration of the MRC figure-of-eight coil

Fig 5. 3 A 3D modelling illustration of the MRC figure-of-eight coil

5.2.2 Electromagnetic Field Distribution

Consider a circular coil of N turns with negligible thickness as given in Fig. 5.1(a), the magnetic flux density $\mathbf{B}$ can be computed using the Bio-Savart Law [43] by integrating along the whole current path C of the coil:

$$\mathbf{B}(\mathbf{r}) = \frac{\mu_0 N I}{4\pi} \oint_C \frac{d\mathbf{l}' \times (\mathbf{r} - \mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|^3}, \quad (5.3)$$

where μ_0 is the permeability, N is the number of turns of the coil, I is the magnitude of current flowing through the coil, $d\mathbf{l}'$ is the differential coil element, $\mathbf{r}$ and $\mathbf{r}'$ are the position vectors of the observation point and that of the differential element $d\mathbf{l}'$. Since the factor of N is already presented in the equation, it negates the need to integrate the path for each turn. Although the assumptions such as negligible thickness and quasi-static conditions [43] could introduce errors, the actual value of the $\mathbf{E}$ field strength can be further obtained from a more accurate electromagnetic simulation.

Meanwhile, the vector magnetic potential $\mathbf{A}$ [43] is related to $\mathbf{B}$ by

$$\mathbf{B} = \nabla \times \mathbf{A}, \quad (5.4)$$

where $\mathbf{B}$ is the magnetic flux density. Then, $\mathbf{A}$ can be computed by

$$\mathbf{A}(\mathbf{r}) = \frac{\mu_0 NI}{4\pi} \oint_C \frac{d\mathbf{l}'}{|\mathbf{r} - \mathbf{r}'|}. \quad (5.5)$$

The electric field $\mathbf{E}$ generated by the magnetic coils is then calculated as the derivate of the vector magnetic potential $\mathbf{A}$, which results as

$$\mathbf{E}(\mathbf{r}) = \frac{\mu_0 \omega NI}{4\pi} \oint_C \frac{d\mathbf{l}'}{|\mathbf{r} - \mathbf{r}'|}, \quad (5.6)$$

where ω is the angular frequency of the current. From Eq. (5.6), we know that the higher frequency, the larger is the $\mathbf{E}$ field.

Moreover, since the assumption is quasi-static, the distance of the coil to the observation point $|\mathbf{r} - \mathbf{r}'|$ should be negligible compared to the wavelength used here. For instance, the wavelength of a 450 kHz radio wave in free space is 666.7 meter, which is much longer than the distance involved in imaging, stimulation, and therapy application, usually less than a few meters.

Furthermore, the computation of $\mathbf{E}$ and $\mathbf{B}$ field of the figure-of-eight coil, as depicted in Fig. 5.1(b), could be performed based on the superposition of the $\mathbf{E}$ and $\mathbf{B}$ field contribution of the two coil elements, but the opposition of current directions between the two coils should be taken in account. Similarly, the $\mathbf{E}$ and $\mathbf{B}$ field of the MRC figure-of-eight coils, as depicted in Fig. 5.2, can be computed

by the superposition of the field contributed by the primary and the secondary coils. Hence, the total $\mathbf{E}$ field will be enhanced at the focus.

5.2.3 Self-Inductance

The self-inductance is calculated as the magnetic flux linkage per unit current in the coil itself. For a regular circular coil design as depicted in Fig. 5.1 (a), the self-inductance L can be calculated as [56]:

$$L = N^2 r \mu_0 \left[\ln \left(\frac{8r}{a} \right) - 2 \right] \quad (5.7)$$

where r is the radius of the coil and a is the radius of the wire. Then, the self-inductance of a figure-of-eight coil, which can be considered as two coils located adjacent to each other as depicted in Fig. 5.1(b), can be approximated as the double of the value calculated using Eq. (5.7), neglecting the mutual coupling between the two coil elements.

5.2.4 Mutual Inductance

Consider two coils separated by distance d coupled to each other, the mutual inductance can be calculated by Neumann Formula:

$$L_m = \frac{\mu_0}{4\pi} \oint_{C_1} \oint_{C_2} \frac{\mathbf{dl}_1 \cdot \mathbf{dl}_2}{R}, \quad (5.8)$$

$\mathbf{dl}_1$ and $\mathbf{dl}_2$ are the differential coil elements of the two coils coupling to each other, respectively, and R is the distance between the differential elements.

5.2.5 MRC and the Equivalent Circuit Models

The MRC coil consists of one active driving primary coil and a passive secondary coil coupled with each other, involving transfer of energy at their resonant frequency. Capacitors C should be cascaded to both coils, for resonance to occur. Coil resistance R and the input source characterized by impedance R_s

and voltage V_s are also included, resulting in the circuit diagram as shown in Fig. 5.4. Before considering the mutual coupling between the coils, the self-resonance angular frequency ω_0 of the RLC resonator is:

$$\omega_0 = \frac{1}{\sqrt{LC}} \quad (5.9)$$

Then, the coupling between the two coils is characterized by its coupling coefficient, which can be calculated by the ratio between the mutual inductance and self-inductance [53]:

$$k = \frac{L_m}{L} \quad (5.10)$$

With the consideration of the mutual coupling, the equivalent T-type coupling circuit is given in Fig. 5.5, which makes it convenient for circuit design and analysis [53]. The resonant frequency of MRC coils occurs at two frequencies ω_e and ω_m (where $\omega_e > \omega_m$) adjacent to the self-resonance angular frequency ω_0 , where the distance between the two resonant frequencies can be computed using the coupling coefficient k :

$$k = \frac{\omega_e^2 - \omega_m^2}{\omega_e^2 + \omega_m^2} \quad (5.11)$$

From Eq. (5.8), when the distance D between the coils increases, the mutual inductance between the two coils decreases, and hence the coupling coefficient k . Moreover, the distance D will affect the coupling efficiency in delivering the power to the secondary coil. Longer the distance, smaller is the efficiency as demonstrated in [53].

Fig 5. 4 The equivalent circuit of the two coils in magnetic coupling

5.2.6 Input Impedance and Q-factor

With the circuit model of Fig. 5.5, the input impedance Z and hence the Q -factor of the MRC figure-of-eight coil, together with the RLC resonators formed by the figure-of-eight coil and circular coil cascaded with capacitors can be analyzed. (The parameters of the MRC coil will be shown in Section 5.4.) The magnitudes of the input impedance $|Z|$ of the resonators are shown in Fig. 5.6, where all of them are designed to have the same resonant frequency. Then, the Q factor of the resonators can be calculated by using the formula:

$$Q = \frac{f_0}{2\Delta f}, \quad (5.12)$$

where f_0 is the resonance frequency, and Δf is bandwidth of the resonator. In MRC, both the primary and the secondary coils resonate at the same frequency. The Q factors of the resonators from MRC coil, figure-of-eight coil, and circular coil are calculated as 75.1, 65.8 and 62.6, respectively. Although both the figure-of-eight coil and circular coil results a high Q factor as the primary characteristics of RLC resonators, it also showed that the MRC resonator has the highest Q factor in the comparison.

Fig 5. 5 The equivalent T-type coupling model of the MRC coil

Fig 5. 6 Input impedance of the resonators with different coil configuration

5.3 Electromagnetic Field Simulation

In this section, the theoretical results of $\mathbf{B}$ and $\mathbf{E}$ field are calculated using Eqs. (5.3) and (5.4), respectively. The calculation is based on the coil radius $r = 4.5$ cm, $s = 5.0$ cm, number of turn $N = 20$, and the assumption that the currents across the both coils are in phase. The separation distance between the two coils is $D = 9.0$ cm (a representative separation in most of applications). The three coil types introduced in Section 5.2, i.e. circular coil, figure-of-eight coil and MRC figure-of-eight coils, are compared. The comparison are based on the same amount of current, i.e. one ampere (1 A), flowing through them so that the heating effect for each coil element would be similar.

The $\mathbf{E}$ field distribution of the compared coils along the x , y , z axis centered at the focus position in the penetration depth $D/2$, which is equivalent to the central point of the MRC figure-of-eight coil, is shown in Figs. 5.7 – 5.9, respectively. In the figures, the origin of the xyz coordinates is selected as the central point of the MRC figure-of-eight coil for a clearer comparison. It can be clearly seen that the MRC

figure-of-eight coil focuses the E-field as well as doubling the magnitude at the focus along the x - and y -axis. Along the z -axis, the electric field attenuates when the observation point is moving away from the coils. Meanwhile, in the MRC coil, since both coils contain the same amount of current, the magnitude of $\mathbf{E}$ decreases when the observation point is moving away from either coils, and reaches the minimum point at the center. In terms of spatial resolution, a half power factor or an $\mathbf{E}$ field magnitude ratio of 0.707 is used. From Figs. 5.7 – 5.9, the spatial resolution at the three axis centered at $(x, y, z) = (0, 0, 0)$ is given by (i) x -axis: -2.9 cm to +2.9 cm, (ii) y -axis: -4.2 cm to +4.2 cm, and (iii) z -axis: -2.4 cm to +2.4 cm.

The comparison of $\mathbf{B}$ field distribution of the coils along the x -axis is shown in Fig. 5.10. Different from the $\mathbf{E}$ field, the magnitude of the $\mathbf{B}$ field at the focus point is minimal. However, the $\mathbf{B}$ field does not have any contribution in Eqs. (5.1) and (5.2) for magnitude of electric current or Ohmic power density. Also for this reason, the $\mathbf{B}$ field distribution of the coils along the y - and z - directions is not included here.

Moreover, the 2D electric and magnetic field distribution surrounding the coils might be of significant interest, e.g. for the analysis of electromagnetic compatibility issues. In this case, it would be more effective to generate the results using the electromagnetic software (e.g. CST). To obtain a contour color map which compares the magnitudes at different locations, the field magnitude is normalized to the maximum value and compared in decibel (dB).

The $\mathbf{E}$ field distribution of the coil in the planes $x = 0$, $y = 0$, and $z = 0$ are shown in Figs. 5.11 – 5.13, respectively. From the figures, it can be observed that the field distribution is strongest near the coil, and remains strong between the two coils, but decays out fast out behind the coils. The $\mathbf{E}$ field is strongest in the line $y = 0$ (Fig. 5.10), similar to the result in Fig. 5.7. From Fig. 5.12 and 5.13, the $\mathbf{E}$ field is strongest at the line $x = 0$, similar to the result in Fig. 5.6.

The $\mathbf{B}$ field distribution of the coil is also important because the varying $\mathbf{B}$ field is the source of electromagnetic induction which generates $\mathbf{E}$ field across the biological medium. The mathematical relationship is given by:

$$\nabla \times \mathbf{E} = -\frac{\partial \mathbf{B}}{\partial t}, \quad (5.13)$$

The $\mathbf{B}$ field distribution of the coil in the plane $y = 0$ is shown in Fig. 5.14. From the figure, there is a null (in blue color) at the location $x = 0, z = 0$, which matches exactly with the null at the center of Fig. 5.9. At resonance, magnetic field coupled from the primary coil to the secondary coil, which induces current at the secondary coil and results similar field distribution around the two coils.

Since the stimulation is taking part in biological medium, the electrical property of the medium is suggested to be considered to find out if the magnetic flux $\mathbf{B}$ can penetrate it to the simulation area for electromagnetic induction. Two more cases are considered: (i) a small piece muscle tissue of the size $1.0 \text{ cm} \times 2.5 \text{ cm} \times 3.5 \text{ cm}$, (ii) a large piece of muscle tissue of the size $2.0 \text{ cm} \times 15 \text{ cm} \times 25 \text{ cm}$ is sandwiched by two layers of bone tissue of the same size. The muscle tissue is modelled with the conductivity of $\sigma = 0.8 \text{ S/m}$ and dielectric constant of $\epsilon_r = 56.8$, whereas the bone tissue is modelled with $\sigma = 0.1 \text{ S/m}$ and $\epsilon_r = 100$ (the tissue data in [46], [47], [57], [58] is taken into account). The $\mathbf{B}$ field distribution of the cases (i) and (ii) are shown in Figs. 5.15 and 5.16, respectively. It is clearly shown that the biological medium does not block the magnetic flux which is essential for electromagnetic induction.

Fig 5. 7 The E field distribution of different coils along the x-axis

Fig 5. 8 The E field distribution of different coils along the y-axis

Fig 5. 9 The E field distribution of different coils along the z-axis

Fig 5. 10 The B field distribution of different coils along the x-axis

Fig 5. 11 The contour color map of E field distribution of the MRC Figure-of-Eight coil in the yz-plane ($x = 0$)

Fig 5. 12 The contour color map of E field distribution of the MRC Figure-of-Eight coil in the xz-plane ($y = 0$)

Fig 5. 13 The contour color map of E field distribution of the MRC Figure-of-Eight coil in the xy-plane ($z = 0$)

Fig 5. 14 The contour color map of B field distribution of the MRC Figure-of-Eight coil in the xz-plane ($y = 0$)

Fig 5. 15 The contour color map of B field distribution of the MRC Figure-of-Eight coil in the xz-plane ($y = 0$) with a muscle tissue of the size $1.0 \text{ cm} \times 2.5 \text{ cm} \times 3.5 \text{ cm}$

Fig 5. 16 The contour color map of B field distribution of the MRC Figure-of-Eight coil in the xz-plane ($y = 0$) with a muscle tissue sandwiched by two layers of bone tissue. The size of each layer is $2 \text{ cm} \times 15 \text{ cm} \times 25 \text{ cm}$

5.4 Design, Fabrication and Measurement

In this section, the coils will be designed based on the theory presented in Section 5.2. In this work, the coils are designed at 450 kHz, which is in the mid frequency range of the pulsed electromagnetic energy therapy [49, Table 3]. However, the application frequency can be modified by using different values of capacitors to adjust the resonating frequency. In our design, the primary goal is to drive an **E** field intensity of 150 V/m which is used in magnetic stimulation [59]- [60]. The basic steps in designing of coils are mentioned as follows:

- i) Determination of distance between the coil based on the application
- ii) Determination of electric field to be induced at the stimulation site
- iii) Determination of coil parameters such as radius and number of turns
- iv) Fabrication of coils based on the parameters from (i) – (iii)
- v) Measurement of resonant frequency of the coils
- vi) Determination of parameters for the impedance matching network
- vii) Measurement of current across the coils, and voltage induced in the biological medium
- viii) Optimization of input parameters in the driving circuit to obtain the desired induced voltage

5.4.1 Design Implementation

The design parameters of the coils are given in Table 5.1. The separation distance of the coils D is kept at 9 cm, which is sufficiently wide for most of the therapy applications [60]. The diameter of the coil is designed to be same as D , which provides enough mutual coupling for the MRC operation. The penetration depth of the **E** field would then be defined as $D/2$ to consider the depth of an object being put between the coils. Also, the number of turn in the coil N is 20, which is selected such that it is sufficiently enough to drive 150 V/m using less than 10 A calculated from Eq. (5.6).

After the fabrication of the figure-of-eight coil, it is measured by network analyzer to obtain its actual inductance, which is $L = 106 \mu\text{H}$. Meanwhile, another fabricated circular coil of the same number of

turns and radius is measured $L_c = 50.6 \mu\text{H}$. Hence, if there is no mutual coupling, it is expected that the figure-of-eight coil has the inductance of $2L_c = 101.2 \mu\text{H}$. It is suggested the difference is caused by the mutual inductance between the loops of the figure-of-eight coil, which can be calculated by $L_l = L - 2L_c = 4.8 \mu\text{H}$. Using the Neumann Formula equation (5.8) to calculate instead would result $L_l = 6.79 \mu\text{H}$, which are quite close to the measured one. Furthermore, the mutual coupling between the two figure-of-eight coils for MRC is measured to be $L_m = 2.18 \mu\text{H}$ by the measurement result of the coupling coefficient k (will be shown later in the section).

A capacitor is then cascaded with the coil which is calculated from Eq. (5.9). A small resistor with high power rating (0.11Ω) is also cascaded to the coil such that the current across the coil can be measured with the voltage across the resistor.

After the MRC coil is built up with the capacitors cascaded as depicted in Fig. 5.5, the input impedance is measured with a network analyzer to determine the frequency response under different separation distances D , the result being given in Table 5.2. The lowest resonant frequency ω_m and its input impedance were observed and recorded. The higher resonant frequencies which results in the opposition of current direction or minimal current in the primary coil are ignored. When D decreases, the increase of coupling coefficient results in the decrease of the lower resonant frequency ω_m , which is well matched with the theory in Section 5.2. Meanwhile, when the secondary coil does not exist in the measurement, there exists only one resonance point which is the self-resonant frequency defined in Eq. (5.7), $f_0 = 456.84 \text{ kHz}$.

Next, the circuit is matched to $R_S = 50 \Omega$ so that it can be driven using a commercial pulse amplifier (TOMCO RF pulse amplifier BT00250-Gamma) and a signal generator (Tektronix AFG 3252). LC network is used for impedance matching as depicted in Fig. 5.17. The values L_X and C_B can be calculated by [59]:

$$L_X = \frac{\sqrt{R_L (R_S - R_L)}}{\omega_m} \quad (5.14)$$

$$C_B = \frac{\sqrt{(R_S - R_L) / R_L}}{\omega_m R_S} \quad (5.15)$$

From the calculation and the availability of the components, the finalized values are $L_X = 4.5 \mu\text{H}$ and $C_B = 26 \text{ nF}$. After cascading the matching network, the completed experimental prototype is shown in Fig. 5.18.

5.4.2 Measurement and Testing

The completed prototype is then measured using a network analyzer. From the measured lower and the higher resonant frequencies (ω_m and ω_e), the coupling coefficient k for different separation distances can be estimated using Eq. (5.11), as shown in Fig. 5.19. The simulated and the measured scattering parameter S_{11} of the prototype at the nominal separation distance $D = 9 \text{ cm}$ and the case without the secondary coil is shown in Fig. 5.20. The 10 dB return loss bandwidth at $D = 9 \text{ cm}$ and the one without the secondary coil are 454.0 kHz – 457.0 kHz and 456.5 kHz – 460.1 kHz, respectively.

Further, the MRC coil is driven using a 50 Ω pulse power amplifier. Since the ratio of the current flowing through the two coils varies with the frequency, the frequency where the two currents become similar is recorded, which is 455.5 kHz. At this frequency, the MRC coil is driven with a pulse amplifier with a pulse of 1 ms duration and an output voltage of 245 V_{peak} , where the currents of both coils are recorded. The simulation using LT spice® [62] and the measurement results are shown in Fig. 5.21 and Fig. 5.22, respectively, which are similar. A lower frequency of 451.5 kHz is reached in the simulation because the components used in implementation are not exactly as the theoretical calculated values.

It can be noticed that both coils have a short transient response to settle down completely. Then, in the steady state, the current in the primary coil is similar to that of the secondary coil, which is in between 8 to 9 A peak current in the measurement result. Comparing to the requirement of 8.32 A peak current to drive 150 V/m as stated in Table 5.1, the basic MRC coil design requirement is fulfilled. Meanwhile, a higher voltage can be used to drive the coil when a higher **E** field magnitude is required.

Table 5. 1 MRC Coils Design Parameters in a modular approach (top to bottom)

Specification / Parameters	Values
Separation Distance D of the two Coils	9.0 cm
Radius of Coil r	4.5 cm
Number of Turns N	20
Distance between the Coil Centers s	5.0 cm
Penetration Depth $D/2$	4.5 cm
E-field Magnitude for each Ampere Coil Current*	18.03 V/m
Current needed to induce an E-field of 150V/m*	8.32 A
Measured Self Inductance L	106 μ H
Calculated Mutual Inductance L_m	4.31 μ H
Capacitor Needed $C = 1/(\omega^2 L)$	1.175 nF
Measured Resistance of Coil R_C	2.29 Ω

*Values are calculated at the Penetration Depth

Table 5. 2 Measured resonant frequencies against separation distance

Separation Distance D (cm)	Lowest Resonant Frequency ω_m (kHz)	Input Resistance R_L (Ohm)
7	452.039	3.53
7.5	453.241	3.43
8	453.241	3.21
8.5	454.44	3.35
9	455.64	3.11
Infinite	456.84	2.29

Fig 5. 17 The complete MRC circuit with impedance matching

Fig 5. 18 The fabricated prototype of the complete MRC circuit

Fig 5. 19 The coupling coefficient k for different separation distance D evaluated from the measurement result

Fig 5. 20 The simulated and the measured scattering parameter S_{11} of the complete MRC circuit

Fig 5. 21 Simulated current of the primary and the secondary coils at 451.5 kHz

Fig 5. 22 Measured current of the primary and the secondary coils at 454.5 kHz

5.5 Biomedical Ex-Vivo Experiments

In this section, the MRC figure-of-eight coil is verified for a current induction in a biological medium. In the experiment, a piece of pig muscle tissue (pork) with the size of $1.0 \text{ cm} \times 2.5 \text{ cm} \times 3.5 \text{ cm}$ is placed in between the MRC coils to induce electromotive force on it as illustrated in Fig. 5.23. Voltage V is then measured across the tissue using an oscilloscope. With the conductivity of pork approximated as $\sigma = 0.8 \text{ S/m}$ (the conductivity data of pork and muscle tissue as given in [57, Table 3] and [46] is taken into reference). The current across the tissue can then be calculated by

$$I = \frac{V\sigma A}{l}, \quad (5.16)$$

where $l = 3.5$ cm is the length and $A = 2.5$ cm² is the cross-sectional area of the tissue. The magnitude of the current density $|\mathbf{J}|$ across the tissue can be determined by

$$|\mathbf{J}| = \frac{I}{A} \quad (5.17)$$

Using the frequency of 455.5 kHz same as used in the previous section, the input voltage is adjusted such that the voltage across the 0.11 Ω resistor in series with both the primary and the secondary coils are approximately 0.6 V, resulting as 5.45 A. When the separation distance of the MRC coil is $D = 9$ cm, the voltage across the pork is shown in Fig. 5.24. The voltage when the secondary coil is removed from the setup is also recorded after slightly adjusting the frequency (to 548.2 kHz) and input voltage such that the primary coil current keeps unchanged at approximately 5.45 A. The voltage induced ratio across the tissue in the case of MRC coil and figure-of-eight coil are 0.3796 V_{peak} and 0.2812 V_{peak} , respectively, giving the voltage or current ratio of 1.35 (i.e. 35 % improvement) and ohmic power ratio of 1.82 (i.e. 82 % improvement). The voltage induced by the traditional circular coil (Fig. 5.1a) instead with the same number of turns and radius is also included in the figure, giving 0.1926 V_{peak} only. Since the electric field and magnetic field is proportional to the current conducting the coil as given from equations (5.3) and (5.6), the above comparisons are based on the same conduction current across the coils. Acc. to Eqs. (5.12) and (5.13), the current I flowing through the tissue is 2.2 mA, where the magnitude of the current density $|\mathbf{J}|$ is 8.68 A/m². It is known that the transcutaneous electric nerve stimulation (TENS) uses a current density of 4 mA/in² (i.e. 6.2 A/m²) at the stimulation site for pain relief applications [63, Fig. 2]. The current set-up achieves magnitude of the same order (8.68 A/m²), being completely non-invasive. The induced voltage ratio is less than the ideal ratio, because there is a phase difference between currents in the primary and the secondary coils, which is recorded to be 65° when $D = 9$ cm.

Fig 5. 23 Ex-vivo experiment setup using pig tissue (pork cut)

Fig 5. 24 Measured voltage across the pig tissue (pork cut) when $D = 9$ cm

5.6 Summary

In this chapter, the MRC figure-of-eight coil was designed and presented targeted for electromagnetic therapy related applications. From the theoretical results as well as the experiment results, the advantages of the proposed MRC figure-of-eight coil are that it can generate a larger electric field and hence current across the tissue compared with the circular coil and figure-of-eight coil when with same conduction current. The summary of the comparison is given in Table 5.3. It suggested that the proposed design is more powerful or effective compared to the circular coil and figure-of-eight coil. The improvement of the current and ohmic power density are 35 % and 82 %, respectively, compared to the case of using one figure-of-eight coil only under the same magnitude of current passing through them. In the experimental result, the current density induced in the pig muscle tissue is 8.68 A/m^2 , which is of the same order being TENS for pain relief. In future work, the structure of the whole MRC system will be improved such that the phase difference between the currents conducting the primary coil and the secondary coil becomes minimal, thereby further improving the current density and ohmic power

density. Another future work should customize the MRC coils for real applications in non-invasive RF stimulation, thermoacoustic imaging, electromagnetic field therapies, and/or radiofrequency ablation. Moreover, the tuning of **E** field distribution from the coil setup can be also considered in the future.

Table 5. 3 Comparison among the coil designs

	Maximum E at the penetration depth for each ampere conducting the coil	Maximum B at the penetration depth for each ampere conducting the coil	Measured voltage across the tissue	Calculated current denisty across the tissue based on measurment
Circular Coil	4.51 V/m	0.99×10^{-4} A/m	0.1926 V	4.40 A/m^2
Figure-of-Eight Coil	9.02 V/m	1.04×10^{-4} A/m	0.2812 V	6.43 A/m^2
Proposed MRC Figure-of-Eight Coil	18.04 V/m	2.05×10^{-4} A/m	0.3796 V	8.68 A/m^2

Chapter-6:

A Tri-Mode Coupled Coil with Tunable Focal Point Adjustment for Bio-Medical Applications

This chapter proposes the design of a tri-mode coupled coil which enables three modes of operation for inducing electromagnetic field, where the focal adjustment of the E field can be optimized. The setup consists of two identical figure-of-eight coils, namely coil 1 and coil 2, coupled to each other by magnetic resonance coupling. Coil 1 is driven by active source, where coil 2 is driven by the magnetic field coupled from coil 1. The frequency of operation would affect the coupling between the coils and hence the current ratios induced. In the first and the second modes, the current dominates at the first coil and the second coil, respectively. In the third mode, both coils conduct similar amount of currents. The concept is proven by measuring the current ratios of the coils and the voltage induced in biological tissues. The current ratios in the first and the second modes are measured as maximum 13.0 and minimal 0.258 at frequencies 487.7 kHz and 453.2 kHz, respectively, while the current ratio measured in the third mode is 1.03. The tri-mode coil could potentially be applied for biological applications such as pulsed electromagnetic energy treatment and thermoacoustic imaging.

6.1 Introduction

In biomedical engineering, magnetic coils [9] are often used to induce electromagnetic field and hence electromotive force to conduct current in the biological mediums. It replaces the traditional approach which applies electrodes on the skin directly to conduct current [64] which is usually due to lack of deep penetration and localization. This is because more current is expected to flow near the surface of the skin instead, where the path is shorter resulting in lesser resistance. Using magnetic coils to induce current is also better compared to some other approaches which involve implantation of electrodes/ coils under the skin [65] – [67], in the sense of being non-invasive. The applications of magnetic coils include magnetic stimulation [16], [47] – [48], pulsed electromagnetic field therapies [39], [49] – [50], thermoacoustic imaging [41], [45] – [46], and radio frequency (RF) ablation [40], [51] – [52]. The current density $\mathbf{J}$ is proportional to the electric field $\mathbf{E}$ induced in the biological medium, where the proportional constant is the conductivity [43]:

$$\mathbf{J} = \sigma \mathbf{E} \quad (6.1)$$

Hence, in this chapter the magnitude of the $\mathbf{E}$ field generated by the coils will be the main consideration. On the other hand, the geometrical distribution of the $\mathbf{E}$ field is also a main concern. Programmable subwavelength coil arrays to generate focused electric field and magnetic field patterns (with the help of switches) for biomedical applications have been described earlier in literature [68] - [70]. Considering the case of magnetic stimulation, a sufficient large current should be induced at the target only, while the current induced in the other areas should be minimized. Therefore, it will be beneficial to design a coil where the distribution of the $\mathbf{E}$ field can be adjusted so as to optimize the current induced at different locations.

To summarize, since the $\mathbf{E}$ field governs the magnitude of current induced in the biological medium as given in equation (6.1), the magnitude of $\mathbf{E}$ field that can be generated by the coils and its distribution would be the primary interest or performance indicator of the coil design. The magnetic flux density $\mathbf{B}$ would be the secondary interest, due to its relationship to the $\mathbf{E}$ field by Faraday's law:

$$\nabla \times \mathbf{E} = -\frac{\partial \mathbf{B}}{\partial t}, \quad (6.2)$$

This indicates that the varying $\mathbf{B}$ field would induce $\mathbf{E}$ field which is commonly known as electromagnetic induction. However, using $\mathbf{E}$ field for analysis would be much simpler as being a more direct indicator as stated in equation (6.1).

In this chapter, a coil setup which can adjust the electric field distribution by changing the operation modes is designed. The block diagram of the setup is given in Fig. 6.1. It consists of two identical figure-of-eight coils, namely coil 1 and coil 2, coupled to each other by magnetic resonance coupling [54] – [55], [71]. The detailed structure and operation principle of the system will be explained in the remaining sections. The proposed coil circuit setup supports three operation modes. The difference between the three modes is characterized by the ratio between the magnitude of currents conducting coils 1 and 2, which results in different $\mathbf{E}$ field distributions among the modes. The combination of the three modes could be applied to optimize the $\mathbf{E}$ field distribution based on the location of the excitation target for the sake of minimizing the $\mathbf{E}$ field out of the target.

The setup will be referred as tri-mode coupled coil in this chapter, which is applied to optimize the electromagnetic field distribution for focal tuning. Furthermore, based on the tri-mode coil configuration, a formula based methodology is developed for tunable focal point adjustment within the two coils by selecting the operation mode and the input voltage. Although the coupled coils using the magnetic resonance coupling (MRC) [54] – [55], [71] – [73] has been proposed, those designs are not for changing the distribution of $\mathbf{E}$ field that can adjust the stimulation location. Meanwhile, the distribution of the $\mathbf{E}$ field is designed to be adjusted according to the location to be excited.

Although it is also possible by moving an actively driven external coil to change the $\mathbf{E}$ field instead of changing the operation mode, it is supposed that the mechanical movement by motors has a slower response time than the change of operation mode which can be electrically controlled. Moreover, the proposed device is steady during operation, while the device would be moving during operation if it depends on the mechanical approach. Last but not least, the proposed method applies one active source

only to coil 1, which does not require another active source to drive coil 2. It could simplify the system and hence operating at a lower cost.

The chapter is organized as follows: In Section 6.2, the theory and the design of the tri-mode coupled coil will be introduced. In Section 6.3, the electric field distribution of the tri-mode operation will be simulated. In Section 6.4, the procedures of tuning focus with the coils will be introduced. In Section 6.5, the coil measurement result will be presented. In Section 6.6, an ex-vivo tissue experiment will be performed to verify the tri-mode concept for the electromagnetic induction. In Section 6.7, the discussion on several practical issues will be included for further clarification of the design. Finally, the conclusion will be given in Section 6.8.

Fig 6. 1 Block diagram of the tri-mode couple coil setup

6.2 Tri-Mode Coupled Coil Design

In this section, the theories of the tri-mode coupled coil design with the multi-impedance matching network will be introduced.

6.2.1 System and Coil Configuration

The block diagram of the setup is given in Fig. 6.1. It consists of two identical figure-of-eight coils separated by $D = 9$ cm (as shown in most representative application for a penetration depth of 4.5 cms), namely coil 1 and coil 2, coupled to each other by magnetic resonance coupling [54] – [55], [71]. Coil 1 is driven by signal generator, which is cascaded to the power amplifier and the multi-impedance matching network. Coil 2 is driven by the magnetic field coupled from coil 1 only (without any other source). 3D model of the coupled coils (Coil 1 and Coil 2) is illustrated in Fig. 6.2, where each of them

has 20 turns and a coil diameter of 9 cm. The distance between the two coil centers in each of the figure-of-eight coil is 5 cm. The figure also shows the current direction respective to a time instant while the polarity alternates sinusoidally. The proposed coil circuit setup supports three operation modes at three adjacent frequencies which have different input impedance. Therefore, the multi-impedance matching network in Fig. 6.1 is used to match the coil so that the coil can be used for the three operation modes.

Fig 6. 2 A pair of magnetic coupled figure-of-eight coils

6.2.2 Circuit Configuration

Firstly, the pair of figure-of-eight coils with self-inductance L (as illustrated in Fig. 6.1) is cascaded with capacitor C as depicted in Fig. 6.3. A small resistor (0.11Ω) is cascaded in series with the resonator so that the current flowing through the coil can be measured by detecting the voltage across the resistor. The cascaded reactive components are selected such that the resonant frequencies at the both coils are the same for magnetic resonance coupling. For demonstration purposes, the resonant frequency is chosen as 450 kHz which is at the mid-range of the pulsed electromagnetic energy therapy [49, Table 3]. Meanwhile, the resonating frequency and thus the application frequency are adjustable by changing the values of the capacitors which resonate with the coils. The self- and mutual- inductances of the coil are measured to be $L = 106 \mu\text{H}$ and $L_m = 2.51 \mu\text{H}$, while the capacitor cascaded is $C = 1.14 \text{ nF}$. Hence, the input impedance of the circuit is given in Fig. 6.4. It can be noticed that there are three resonance frequencies where the reactance equals zero. The first one is the self-resonance frequency, given by [71]

$$f_0 = \frac{1}{2\pi\sqrt{LC}} \quad (6.3)$$

which results as $f_0 = 457.7$ kHz.

The additional second and the third resonance frequencies (lowest resonance frequency f_m and highest resonance frequency f_e) are resulted from the mutual inductance L_m between the two coils, given by:

$$f_m = \frac{1}{2\pi\sqrt{(L + L_m)C}}, \quad (6.4)$$

$$f_c = \frac{1}{2\pi\sqrt{(L - L_m)C}}, \quad (6.5)$$

which are calculated as $f_m = 452.6$ kHz and $f_e = 462.9$ kHz.

Fig 6. 3 The circuit configuration of the coil circuit

Fig 6. 4 Input impedance of the coil circuit

6.2.3 Tri-Mode Operations

The coil will be applied for three adjacent operating frequencies with different current ratio, which are used for three operation modes. In the first mode, the current is dominated at coil 1 while minimized at coil 2, so that the $\mathbf{E}$ field near coil 1 is large. This mode 1 is used to minimize the electromagnetic field distribution near coil 2 where is not near the focal point located near coil 1. In the second mode, the current is dominated at coil 2 while minimized at coil 1, which is counter-mode to the first mode. This mode 2 is used to minimize the electromagnetic field distribution near coil 1 where is not near the focal point located near coil 2. In the third mode, the magnitudes of the currents conducting at the two coils are the same, both $\mathbf{E}$ field near the two coils is large, and also superposed and enlarged the $\mathbf{E}$ field at the center between the two coils. As using only one coil would require very large current to generate adequate $\mathbf{E}$ field magnitude at the center which is far away from the coils, the mode 3 is used to prevent overloading the current at the either coil and the $\mathbf{E}$ field magnitude near it by utilizing both coils to superpose a large $\mathbf{E}$ field at the center.

For the operation principle, define I_1 and I_2 as the currents conducting coil 1 and coil 2, respectively. Then, the current ratio between coil 1 and coil 2, I_1/I_2 is given in Fig. 6.5.

At the first mode operation frequency f_1 , $I_1 > I_2$, the current is dominated at coil 1 whereas minimized at coil 2. The current ratio is selected to be large while not too far away (at around 5 % of f_0) from the resonance frequencies so that the three operation frequencies will be similar. Therefore, $f_1 = 480$ kHz is selected.

At the second mode operation frequency f_2 , $I_2 > I_1$, the current is dominated at coil 2 whereas minimized at coil 1. Therefore, the minimum point on the curve is chosen, which is the self-resonance frequency $f_2 = f_0 = 457.7$ kHz.

Although the first and the second operations are similar, they are not redundant because they are corresponding to the target at different location. Although this can also be achieved by switching the positions of the coils (with the active source connected to coil 1), the response time of the mechanical switching approach would be more significant as compared to the proposed electrical switching approach. Moreover, it would become a moving device instead of the proposed steady device.

At the third mode operation frequency f_3 , $I_1 = I_2$, the magnitudes of the currents conducting at coil 1 and coil 2 are the same. Therefore, the current ratio of 1 is selected, which is either f_m or f_e . However, $f_3 = f_m = 452.6$ kHz is selected instead of f_e , because the phase difference between the currents conducting at the two coils is much larger in f_e , leading to the cancellation of the **E** field between the coils.

To summarize the choice of the frequency points for tri-mode operation, f_2 and f_3 are chosen based on equations (6.3) and (6.4), while f_1 is chosen based on the domination of current at coil 1 and the frequency being not too far away from f_0 (at around 5 % of f_0).

Fig 6. 5 The current ratio between the coils

6.2.4 Multi-Impedance Matching Network

According to Fig. 6.4, the input impedance under different operating frequencies is different. In order to maximize the current conducting in the coils when they are driven by a $50\ \Omega$ pulse power amplifier, the input impedance of the three operation frequencies should be matched to $50\ \Omega$ with reactive components. Consider the three operation frequencies at 452.6 kHz, 457.7 kHz, and 480 kHz, their input impedances are $4.8\ \Omega$, $24.1\ \Omega$, and $2.6 + j\ 27\ \Omega$, respectively. A multi-impedance matching network should be designed to match the three operation frequencies to $50\ \Omega$ effectively.

The multi-impedance matching network is shown in Fig. 6.6, which is integrated with the coil circuit. It is composed of a multi-section LC ladder network [74]. The values of the components are optimized by the gradient-based optimizer in Advanced Design System ® (ADS) [75] to match the operating frequencies to $50\ \Omega$. The target of the matching is to make the scattering parameter S_{11} to be smaller than -6 dB so that the reflected power is less than 25%, which is a practice or standard of impedance matching applied in mobile communication [54]. The optimization results $L_1 = 11\ \mu\text{H}$, $L_2 = 4.95\ \mu\text{H}$, $C_1 = 33\ \text{nF}$, $C_2 = 56\ \text{nF}$, and $C_3 = 56\ \text{nF}$. From Fig. 6.5, it is shown that the current ratio between the coils does not vary with the cascaded matching network, so the impedance matching does not affect the tri-mode operation.

The matching network is implemented using lumped capacitors and inductors with soldering as shown in Fig. 6.7. It should be noticed that at lower frequency, the capacitors and inductors are difficult to be implemented using transmission line network since the wavelength is very large (666.7 m at 450 kHz), instead using lumped component is the best approach. The simulated and the measured scattering parameter S_{11} are shown in Fig. 6.8. The discrepancy between the simulation result and the measurement result could be caused by the difference between the theoretical values and the actual implemented values of the lumped capacitors and inductors, and also the extra inductance due to the lead wires and soldering. To demonstrate the sensitivity of the circuit value, L_1 is changed to $10.4\ \mu\text{H}$ in the simulation and the result is included in Fig. 6.8. As L_1 decreased, the lower band is spread to a wider band, while the higher band is shifted to a higher frequency. However, despite the discrepancy between the simulation and the actual circuit values, the measured S_{11} of the three operation modes ($I_1 > I_2$, $I_2 > I_1$, $I_1 = I_2$) has a return loss of smaller than -6 dB. The measurement result of the current ratio of the operation modes will be shown in Section 6.5.

Fig 6. 6 The coil circuit integrated with the multi-impedance matching network

Fig 6. 7 Fabricated lumped components multi-impedance matching network

Fig 6. 8 The simulated and the measured return loss of the multi-impedance matched network

6.3 Electric Field Distribution of Coil

In this section, the electric field distribution of the coil under the three operation modes will be demonstrated.

6.3.1 Mathematical Formula

Firstly, consider a circular coil of N turns with negligible thickness, the electric field $\mathbf{E}$ generated by it can be computed by integrating along the whole current path C of the coil [71]:

$$\mathbf{E}(\mathbf{r}) = \frac{\mu_0 \omega N I}{4\pi} \oint_C \frac{d\mathbf{l}'}{|\mathbf{r} - \mathbf{r}'|}, \quad (6.6)$$

where μ_0 is the permeability, N is the number of turn of the coil, I is the magnitude of current flowing through the coil, $d\mathbf{l}'$ is the differential coil element, $\mathbf{r}$ and $\mathbf{r}'$ are the position vectors of the observation point and that of the differential element $d\mathbf{l}'$. Since the factor of N is already in the equation, there is no need to integrate the path for each turn. Meanwhile, there are two coils (coils 1 and 2) as depicted in Fig. 6.2, the total $\mathbf{E}$ field at any observation point will be the superposition of the $\mathbf{E}$ field contributed by the two coils.

6.3.2 Electric Field Distribution of the Tri-Mode Coil

As the theme of this chapter, the electric field distribution of the coil in different operation mode is different. This is achieved by the different current ratio in the operation modes.

(i) First operation mode: $I_1 > I_2$

Consider the first operation mode where $I_1 > I_2$. From Fig. 6.5, $I_1/I_2 = 3.85$ at $f_1 = 480$ kHz, the calculated electric field distribution for every 1 A conducting coil 1 is shown in Fig. 6.9, where the phase difference between the two coils (which is not adjustable) is also taken into account. With the direction of the coordinate axis defined in Fig. 6.2, the origin of the xyz coordinates is selected as the central point of the tri-mode coil setup, i.e. the central point in between coils 1 and 2. In the figure, coils 1 and 2 are located at $z = -4.5$ cm and 4.5 cm, respectively. It can be noticed that the $\mathbf{E}$ field is much stronger near coil 1. Furthermore, the 2D $\mathbf{E}$ and $\mathbf{B}$ field distribution on a contour color map obtained by

electromagnetic simulation (using CST Studio Suite ® [77]) at the plane yz -plane ($x = 0$) are shown in Fig. 6.10 and Fig. 6.11, respectively. It is observed that both the $\mathbf{E}$ and $\mathbf{B}$ field are much stronger near coil 1 than that of coil 2. Although there is some field leakage outside the coils, those regions are not within our interest of biomedical applications and hence can be ignored.

(ii) Second operation mode: $I_2 > I_1$

Consider the second operation mode where $I_2 > I_1$. From Fig. 6.4, $I_1/I_2 = 0.333$ at $f_2 = 457.6$ kHz, the calculated electric field distribution for every 1 A conducting coil 2 is also shown in Fig. 6.9. It can be noticed that the $\mathbf{E}$ field is much stronger near coil 2. Also, the 2D $\mathbf{E}$ and $\mathbf{B}$ field distribution on a contour color map obtained by electromagnetic simulation at the plane yz -plane ($x = 0$) are shown in Fig. 6.12 and Fig. 6.13, respectively. It is observed that both the $\mathbf{E}$ and $\mathbf{B}$ field are much stronger near coil 2 than that of coil 1.

(iii) Third operation mode: $I_1 = I_2$

Consider the third operation mode where $I_1 = I_2$. From Fig. 6.4, $I_1 = I_2$ at $f_3 = 452.6$ kHz, the calculated electric field distribution for every 1 A conducting both coils is shown in Fig. 6.9. It can be noticed that the $\mathbf{E}$ field is strong at the both side of the coils and also superposed and enlarged the $\mathbf{E}$ field at the center. When comparing the three modes for $\mathbf{E}$ field distribution near the center, it is obvious that using the mode 3 is the most effective when the target is near the center. Also, the 2D $\mathbf{E}$ and $\mathbf{B}$ field distribution on a contour color map obtained by electromagnetic simulation at the plane yz -plane ($x = 0$) are shown in Fig. 6.14 and Fig. 6.15, respectively. It is observed that both the $\mathbf{E}$ and $\mathbf{B}$ field are strong in between the both coils and at the center.

Fig 6. 9 The simulated E field distribution for the three operation modes

Fig 6. 10 The contour color map of E field distribution of the tri-mode coupled coil in the yz-plane ($x = 0$) in the first operation mode at $f_1 = 480$ kHz

Fig 6. 11 The contour color map of B field distribution of the tri-mode coupled coil in the yz-plane ($x = 0$) in the first operation mode at $f_1 = 480$ kHz

Fig 6. 12 The contour color map of E field distribution of the tri-mode coupled coil in the yz-plane ($x = 0$) in the second operation mode at $f_2 = 457.6$ kHz

Fig 6. 13 The contour color map of B field distribution of the tri-mode coupled coil in the yz-plane ($x = 0$) in the second operation mode at $f_2 = 457.6$ kHz

Fig 6. 14 The contour color map of E field distribution of the tri-mode coupled coil in the yz-plane ($x = 0$) in the third operation mode at $f_3 = 452.6$ kHz

Fig 6. 15 The contour color map of B field distribution of the tri-mode coupled coil in the yz-plane ($x = 0$) in the third operation mode at $f_3 = 452.6$ kHz

6.4 Focus Tuning Procedures

In this section, the focus tuning procedures when using the coils will be discussed.

6.4.1 Operation Mode Selection

As depicted in the previous sections, when the excitation location is near coil 1, the operation mode 1 is preferred which would weight low the current conducting at coil 2. It is because coil 2 is not effective to induce **E** field at the excitation point, but it would increase the **E** field near coil 2.

In contrast, when the excitation location is near coil 2, the operation mode 2 is preferred which would weight low the current conducting at coil 1. This would minimize the **E** field near coil 1 which is not near the excitation point.

When the excitation location is near the center, operation mode 3 is preferred which would conduct current equally at both coils because the **E** field generated by both coil is effective to increase the **E** field level at the excitation point. Since the **E** field attenuates with distance from the source, using only one coil would need a much larger current to generate adequate **E** field magnitude at the center, compared with the locations near the coils. Hence, the mode 3 which utilizes both the current at both coils would be effective to prevent overloading of current at the either coil and the **E** field magnitude near it, by superposing the **E** field from both coils at the center. Therefore, depending on the *z*-coordinates of the excitation location, the operation modes are selected as follows:

(i) Mode 1: $\frac{-D}{2} < z < \frac{D}{6}$

(ii) Mode 2: $\frac{D}{6} < z < \frac{D}{2}$

(iii) Mode 3: $\frac{-D}{2} \leq z \leq \frac{D}{6}$

6.4.2 Voltage Level Determination

In the determination of the voltage levels at the sources, the ratio between the source voltage and the current conducting at the coils, as well as the ratio between the electric field and the current conducting at the coils, should be calculated.

Firstly, from circuit theory, the current conducting at the coil is proportional to the source voltage. The transconductance between the coil currents (I_1 and I_2) and the source voltage V_s are given by:

$$G_{I1} = \frac{I_1}{V_s} \quad (6.7)$$

$$G_{I2} = \frac{I_2}{V_s} \quad (6.8)$$

Secondly, from electromagnetic theory [43], the electric field induced at the observation point is proportional to the coil current as well as the frequency. The electric field gain between the electric field induced at the observation point and the product of the coil current and frequency is given by:

$$G_{E1} = \frac{E_1}{I_1 f}, \quad (6.9)$$

$$G_{E2} = \frac{E_2}{I_2 f}, \quad (6.10)$$

where E_1 and E_2 are the magnitudes of the electric field intensity induced at the observation point contributed by coil 1 current I_1 and coil 2 current I_2 , respectively. Then, from the above equations, the electric field induced at the observation point can be related to the source voltage by:

$$E_1 = G_{E1} G_{J1} f V_s, \quad (6.11)$$

$$E_2 = G_{E2} G_{J2} f V_s. \quad (6.12)$$

The overall voltage induced by the two coils is then the superposition of the **E** field is given by:

$$E = |G_{E1} G_{J1} + G_{E2} G_{J2} e^{j\theta}| f V_s \quad (6.13)$$

where θ is the phase difference between the currents I_1 and I_2 , respectively. Therefore, the voltage of the source V_s can be calculated from the required **E** field at the observation point:

$$V_s = \frac{E}{|G_{E1}G_{J1} + G_{E2}G_{J2}e^{j\theta}|fV_s} \quad (6.14)$$

Fig 6. 16 The flowchart of selecting the operation mode and the source input voltage

6.4.3 Overall Flowchart

The procedure to determine which mode to be chosen as well as the source voltage is given in Fig. 6.16. Before the start of the excitation of the coil, the gains G_{J1} , G_{J2} , G_{E1} and G_{E2} , and the phase difference θ should be calculated from the circuit analysis and electromagnetic analysis. The gains G_{E1} and G_{E2} are dependent on the excitation locations where the corresponding values at different locations can be calculated and stored in a database. After the calculation, the user can determine the excitation location and the **E** field magnitude according to the application. For example, in magnetic stimulation, the magnitude of the **E** field is selected as 150 V/m in the literature [59] - [60]. Then, the operation mode is calculated by the excitation location, and the source input voltage is calculated by the required **E** field

magnitude. After all, the coil circuit can be excited to generate a required **E** field level at the excitation location while minimizing the **E** field level out of the target.

6.4.4 Verification of Formulas

In this subsection, the focus tuning formulas would be applied at different excitation locations for verifications. Three typical excitation locations would be demonstrated, which are $z = -2$ cm, $z = 0$ cm, and $z = 3$ cm, where each of them corresponds to each of the three operation modes, respectively. The **E** field magnitude for excitation is set as 150 V/m, as previous applied for magnetic stimulation in the literature [59] - [60]. For the procedure of operation, the flowchart as given in Fig. 6.16 can be referred.

(i) Excitation at $z = -2$ cm with 150 V/m

When the excitation location is at $z = -2$ cm, operation mode 1 would be applied. From the circuit analysis in Fig. 6.6, G_{I1} equals $I_1/V_S = 0.038$ A/V and G_{I2} equals $I_2/V_S = 0.010$ A/V with the phase difference $\theta = 175.3^\circ$, at operation mode 1 using $f_1 = 480$ kHz. From Eqs. (6.9) and (6.10), $G_{E1} = 3.941 \times 10^{-5}$ (V/AmHz⁻¹) and $G_{E2} = 1.124 \times 10^{-5}$ (V/AmHz⁻¹). According to Eqt. (6.14), the calculated source voltage $V_S = 225.5$ V, so that the coil currents are driven as $I_1 = 8.57$ A and $I_2 = 2.26$ A. The calculated electric field distribution is shown in Fig. 6.17, which verified that the **E** field intensity at $z = -2$ cm is 150 V/m.

(ii) Excitation at $z = 3$ cm with 150 V/m

When the excitation located is at $z = 3$ cm, operation mode 2 would be applied. From the circuit analysis in Fig. 6.6, G_{I1} equals $I_1/V_S = 0.014$ A/V and G_{I2} equals $I_2/V_S = 0.041$ A/V with the phase difference $\theta = 88.1^\circ$, at operation mode 2 using $f_2 = 457.6$ kHz. From Eqs. (6.9) and (6.10), $G_{E1} = 8.647 \times 10^{-6}$ (V/AmHz⁻¹) and $G_{E2} = 5.898 \times 10^{-5}$ (V/AmHz⁻¹). According to Eqt. (6.14), the calculated source voltage $V_S = 135.1$ V, so that the coil currents are driven as $I_1 = 1.89$ A and $I_2 = 5.54$ A. The calculated electric field distribution is also shown in Fig. 6.17, which verified that the **E** field intensity at $z = 3$ cm is 150 V/m.

(iii) Excitation at $z = 0$ cm with 150 V/m

When the excitation located is at $z = 0$ cm, operation mode 3 would be applied. From the circuit analysis in Fig. 6.6, G_{I1} equals $I_1/V_S = 0.029$ A/V and G_{I2} equals $I_2/V_S = 0.028$ A/V with the phase difference $\theta = 19.5^\circ$, at operation mode 3 using $f_3 = 452.6$ kHz. From Eqs. (6.9) and (6.10), $G_{E1} = G_{E2} = 2.004 \times 10^{-5}$ (V/AmHz⁻¹). According to Eqt. (6.14), the calculated source voltage $V_S = 294.4$ V, so that the coil currents are driven as $I_1 = 8.54$ A and $I_2 = 8.24$ A. V_S , I_1 and I_2 are the largest within the three cases because the distance from the nearest coil is farther. The calculated electric field distribution is also shown in Fig. 6.17, which verified that the **E** field intensity at $z = 0$ cm is 150 V/m.

In general, based on the operation mode selection and the desired **E** field level of 150 V/m, the calculated source voltage for different excitation locations using equation (6.14) are given in Fig. 5.18. This verified that the excitation location can be adjusted to various locations between the two coils by selecting the operation mode and the source voltage V_S . The figure indicates that the farther the distance from the coils, the larger the source voltage required for generation of similar **E** field magnitude at the excitation location. This is due to the fact that **E** field attenuates with distance from the coils, and therefore a larger source voltage would be required to conduct larger currents to the coils and hence generate an adequately large magnitude of **E** field at a farther excitation location. For example, the excitation location of $z = -2$ cm requires $V_S = 207.0$ V, while the excitation location of $z = -2.2$ cm requires $V_S = 225.5$ V, when both are calculated for 150 V/m.

Fig 6. 17 The simulated E field distribution for the three excitation positions to achieve an intensity of 150 V/m

Fig 6. 18 The calculated source voltage V_s for different excitation location in the three operation modes to achieve an intensity of 150V/m

6.5 Coil Measurement

In this section, the fabricated tri-mode coupled coil as shown in Fig. 6.19 is measured to verify the calculation results. In the measurement, the tri-mode coupled coil is driven using a 50 Ω pulse amplifier with signal generator. The currents flowing through the coils are measured by detecting the voltage across the small resistor in series with the coil (as mentioned in Section 6.2). Since there exists differences between the theoretical values and the actual implemented circuit component values, the actual frequencies of the three operation modes are little bit shifted from the simulated operation frequencies.

6.5.1 First Operation Mode: $I_1 > I_2$

Consider the first operation mode where $I_1 > I_2$. From Fig. 6.8, the measured S_{11} is of local minimum at 487.7 kHz. Since this frequency point is away from the resonance frequency to give $I_1 > I_2$ with impedance matching done to minimize the return loss, it is selected as the first operation mode as $f_1 = 487.7$ kHz.

At this frequency, the MRC coil is driven with a pulse of 1 ms duration so that the voltage is controlled to give coil 1 current of around 5 A, where the currents of both coils are recorded in Fig. 6.20. It should be noticed that current has a short transient response of around 0.2 ms before it reaches the steady state.

At the steady state, the measured current ratio of $I_1/I_2 = 13.0$. According to this measured ratio, the calculated electric field distribution for every 1 A conducting at coil 1 according to Eq. (6.6) is shown in

Fig. 6.21. Again, coil 1 and coil 2 are located at $z = -4.5$ cm and 4.5 cm, respectively. It can be noticed that the **E** field is much stronger near coil 1.

6.5.2 Second Operation Mode: $I_2 > I_1$

Consider the second operation mode where $I_2 > I_1$. From the measurement, the frequency which results a minimum ratio of I_1/I_2 is measured and used as the second operation mode, which is $f_2 = 453.2$ kHz.

At this frequency, the MRC coil is driven with a pulse of 1 ms duration so that the voltage is controlled to give coil 2 current of around 5 A, where the currents of both coils are recorded in Fig. 6.22. Again, it should be noticed that current has a short transient response of around 0.2 ms before it reaches the steady state.

At the steady state, the measured current ratio of $I_1/I_2 = 0.258$. According to this measured ratio, the calculated electric field distribution for every 1 A conducting coil-1 according to Eq. (6.6) is also shown in Fig. 6.21. It can be noticed that the **E** field is much stronger near coil 2.

6.5.3 Third Operation Mode: $I_1 = I_2$

Consider the third operation mode where $I_1 = I_2$. From the measurement, the frequency which result $I_1 = I_2$ below f_2 is measured and used as the third operation mode, which is $f_3 = 451.1$ kHz.

At this frequency, the MRC coil is driven with a pulse of 1 ms duration so that the voltage is controlled to give the current across both coils of around 5 A, where the currents of both coils are recorded in Fig. 6.23. Again, it should be noticed that current has a short transient response of around 0.2 ms before it reaches the steady state.

At the steady state, the measured current ratio of $I_1/I_2 = 1.03$. According to this measured ratio, the calculated electric field distribution for every 1 A conducting at coil 1 according to Eq. (6.6) is also shown in Fig. 6.21. Again, it can be noticed that the **E** field is strong at the both side of the coils and also superposed and enlarged the **E** field at the center.

Fig 6. 19 The fabricated coupled coil for measurement

Fig 6. 20 The measured current ratio is given for the operation mode 1 at $f_1 = 487.7$ kHz

Fig 6. 21 The calculated E field distribution according to the measured current ratio

Fig 6. 22 The measured current ratio is given for the operation mode 2 at $f_2 = 453.2$ kHz

Fig 6. 23 The measured current ratio is given for the operation mode 3 at $f_3 = 451.1$ kHz

6.6 Ex-Vivo Tissue Measurement

In this section, ex-vivo tissue experiment [71] will be done to verify the tri-mode concept on field distribution. In the experiment, the tri-mode coupled coil is driven using a $50\ \Omega$ pulse amplifier with signal generator on the three operation modes. Then, a piece of pig muscle tissue of the size $1.0\text{ cm} \times 2.0\text{ cm} \times 3.5\text{ cm}$ is placed in between the coils to induce voltage and current on it through electromagnetic induction, as illustrated in Fig. 6.24. Electrodes are used to measure the induced voltage across it. For each of the operation mode, the induced voltage at three positions (i) near coil 1: $z = -2$ cm, (ii) at the center: $z = 0$ cm, (iii) near coil 2: $z = 2$ cm, are compared by relocating the position of the tissue. This can verify the tri-mode concept on the field distribution.

First of all, the signal generator voltage is fixed at $0.5 V_{\text{peak}}$ with the frequency 451.1 kHz, then the source voltage from the pulsed amplifier becomes $V_s = 451.5 V_{\text{peak}}$, which induced voltage across the tissue under mode 3 (451.1 kHz) where both coils 1 and 2 are delivering magnetic field with the same current. The induced voltages at the three positions $z = -2, 0$, and 2 cm are shown in Figs. 6.25 – 6.27, respectively. From the figures, although the voltage is contributed by the magnetic field radiated from the two coils, the transient response when the tissue is placed at different locations are similar and the steady state is as short as around 0.1 ms in all the three cases.

Next, the voltage measurement of the tissue is repeated at the mode 1 (487.7 kHz) and mode 2 (453.2 kHz) to find the relative magnitude of the voltage induced at the positions $z = -2, 0$, and 2 cm. The magnitude of the voltage measured is then normalized to the maximum and compared in Table 6.1. The data shown in the table completely verified the concept of the tri-mode coil: In the mode 1, the voltage induced near coil 1 would be strongest while being weak near coil 2. In mode 2, the voltage induced near coil 2 would be strongest while being weak near coil 1. In mode 3, the fact that the voltage induced is strongest near the coils can also be found in the experiment result, where the voltage induced would be decreased with the increase of the distance from the coils. However, the electromagnetic induction is contributed by both coils and hence decay fewer along the distance among the three modes, thereby resulting a larger induced voltage at the center. Despite of the successful experiment results, it should be pointed out that an assumption of the experiment is the constant resistivity of the tissue within the operation.

Fig 6. 24 Illustration of the ex-vivo experiment

Fig 6. 25 The induced voltage at the tissue at $z = -2$ cm (tissue placed near coil 1)

Fig 6. 26 The induced voltage at the tissue at $z = 2$ cm (tissue placed near coil 2)

Fig 6. 27 The induced voltage at the tissue at $z = 0$ cm (tissue placed at centre)

Table 6. 1 The normalized measured voltage at different locations and different operating modes

	$z = -2$ cm (The tissue is placed near the coil 1)	$z = 0$ cm (The tissue is placed at the center)	$z = 2$ cm (The tissue is placed near the coil 2)
Mode 1 (Current is strong at coil 1)	1.000	0.524	0.286
Mode 2 (Current is strong at coil 2)	0.376	0.464	1.000
Mode 3 (Current is strong at both coil)	0.816	0.755	1.000

6.7 Discussion on Practical Issues

In this section, several practical issues of the tri-mode coil design will be discussed for further clarification of the design.

6.7.1 Comparing different coil configuration

In this subsection, the use of a pair figure-of-eight coils are compared to a pair of circular coils and square coils. The calculated **E** field distribution of the compared coils along the x - and y -axis at $z = 0$ cm for every 1 A conducting at both coils 1 and 2 is shown in Figs. 6.28 and 6.29. This is the situation in mode 3, where both coils are conducting the same current. The origin of the coordinates is selected as the central point of the coupled coils. For ease of analysis in the comparison, the phase difference between coils 1 and 2 is assume to be zero of that the **E** field contributed from the two coils are added up totally. For a fair comparison, the coils are compared in the same number of turns. The diameters of the figure-of-eight coils and the circular coil, as well as the diagonal of the square coil are all 9 cm. From the comparison, it is obvious that the main benefit of using a pair of figure-of-eight coil is the finer focusing of **E** field along the x - and the y - axis at $x = y = 0$ cm.

6.7.2 The symmetry of the E field in the mode 3

From the literature [78] - [79], some secondary effects on the generated magnetic field are found and consequently the generated electric field which is due to manufacturing mismatches or assembly misalignments in the circular coils.

It can be concluded easily by inspection that there might be the same effects or even more another experimental imperfection effects in a pair of 8-shape coils, too. Therefore, by considering the given simple prototype system (refer to Fig. 6.19), it might be difficult to achieve symmetrical experimental E fields distributions as given in Fig. 6.21 (Operation Mode 3).

For the above concerns, it is necessary to observe how large the error is introduced to affect the symmetry of **E** field. This can be observed by the experiment in Section 6.6, where the voltage induced at the tissue is measured at different location along the z-axis. There is a relation between the voltage V and the **E** field induced [80]

$$V = d|\mathbf{E}| \quad (6.15)$$

where d is the distance between the two terminals of the voltage measurement, and the assumption is constant $|\mathbf{E}|$ magnitude between the two terminals. Therefore, according to this equation, the tissue measurement in Section 6.6 can be used as an **E** field probe to estimate the field induced at the tissue. Another trial of the tissue measurement is done in operation mode 3 with more locations involved from $z = -3$ cm to $z = 3$ cm, while the result is presented in Fig. 6.30. Practically, it can be observed that the voltages measured at the two sides are quite symmetric (with maximum imperfection 12.5 % at $z = 2$ cm), although they are not perfectly equal to each other.

6.7.3 Effect of the medium in between the coils

It should be noticed that equation (6.6) is used to calculate the **E** field distribution. However, this **E** field formulation is valid only in free (homogeneous) space. If there is a conductive body between the coils, the **E** field distribution will significantly change from that given by equation (6.6) due to different medium is involved. For example, although the pork tissue used in the previous section is a poor conductor ($\sigma = 0.8$ S/m [43]), it still have large effect on the **E** field induced. This can be observed by the following time harmonic equation derived from the ampere law [43], [81]:

$$\mathbf{E} = \frac{1}{\sigma + j\omega\epsilon} \nabla \times \mathbf{H} \quad (6.16)$$

It is clear that the $\mathbf{E}$ field induced by electromagnetic induction must be much smaller in the tissue, where the change of magnitude in different medium is reflected by the denominator term.

However, the accurate information of biological medium might not be included during the design of the coils, because the biological medium to be placed in between the models varies case by case. For instance, considering different patients have different body size, using a fixed model of biological medium would be impractical.

Instead, the free space condition could be used as a reference in the design process. This is because a 450 kHz magnetic flux should be able to penetrate the tissue which is a poor conductor with high dielectric constant (some previous simulation from the author group in a MRC coil design could be found at [71] and [80]). The penetration of magnetic flux is similar to that of the traditional magnetic stimulation [9], [16], [47]–[48] which operates at lower frequencies. Then, from equation (6.16), the penetrated magnetic flux should be able to induce $\mathbf{E}$ field at the tissue. If a larger magnitude of $\mathbf{H}$ is involved in equation (6.6) (e.g. due to a larger magnitude of current passing through the coils), the larger should be the magnitude of the induced $\mathbf{E}$ no matter the medium is tissue or air. This should explain why free space is used as a design reference in this chapter. For a comparison with the literature [48], the shape of $\mathbf{E}$ field distribution as observed in Fig. 6.28 for a figure-of-eight coil simulation under free space is similar to that of the slinky-2 coil (i.e. figure-of-eight coil) from the experimental measurement under saline solution in [48, Fig. 3].

For further verification, the simulated $\mathbf{E}$ field distribution of mode 3 with a piece of muscle tissue ($\sigma = 0.8 \text{ S/m}$, $\epsilon_r = 56.8$ [22]) of the size $24 \text{ cm} \times 12 \text{ cm} \times 4 \text{ cm}$ is shown in Fig. 5.31. It is verified that the $\mathbf{E}$ field is much smaller in the tissue than in the air, while there is still a focusing pattern inside the tissue. The simulated field distribution is a good agreement with that calculated in Figs. 6.9 and 6.28.

6.7.4 Recapping the objective of the tri-mode operation

From literature study, it might not be possible to use any combination of coils placed outside the conductor to focus the $\mathbf{E}$ field in depth in spherical geometry [81]. The largest $\mathbf{E}$ field always occurs at

the boundary of such a conductor. Moreover, from Figs. 6.21 and 6.30, it is clear that the magnitude of **E** field attenuates with the increase of distance between the coils and the observation point. This does not imply that the design is not valid. Actually, the objective of the tri-mode design is not to create a local maximum of **E** field along the *z*-axis as indicated in Figs. 6.21 and 6.30.

Instead, the objective of the tri-mode coil design is to generate three different operations modes so as to make a better electromagnetic field distribution in different operation scenario. To recap the statements in Section 6.2.3: Mode 1 is used to minimize the electromagnetic field distribution near coil 2 where is not near the focal point located near coil 1; Mode 2 is used to minimize the electromagnetic field distribution near coil 1 where is not near the focal point located near coil 2. Mode 3 is used to prevent overloading the current at the either coil and the **E** field magnitude nearby by utilizing both coils to superpose a large **E** field at the center.

6.7.5 Bio-medical Applications

Physically, the coil design provides two functions: (i) inducing current at biological medium by electromagnetic induction, which can be observed by the equations (6.1) and (6.2); (ii) heating the biological medium from the electric power produced by the induced current, where the ohmic power density P_σ under the conduction of current is given by

$$P_\sigma = \frac{|\mathbf{J}|^2}{\sigma} = \sigma |\mathbf{E}|^2 \quad (6.17)$$

The current induced and hence the heating generated at the biological medium could be used for biological applications. For instance, the pulsed electromagnetic energy treatment [48] considers the delivery of pulsed RF energy to a tissue for therapeutic effects. The coils in this chapter are designed at 450 kHz that is in the mid frequency range of the pulsed electromagnetic energy treatment [49, Table 3]. Furthermore, the thermoacoustic imaging [41] applies heating for thermal expansion of tissue which leads to the generation of an acoustic wave for imaging purposes. Since the above depends on current induced in the tissue by electromagnetic induction, the current distribution at a piece of muscle tissue is simulated (at mode 3) and shown in Fig. 6.32. Since air is not conductive, there is no current induced at

the air region although there is $\mathbf{E}$ field. Instead, current is induced along the piece of tissue. The current induced in the tissue would cause the generation of heat due to equation (6.17), which could potentially be applied for pulsed electromagnetic energy treatment [49] and thermoacoustic imaging [41] applications.

Fig 6. 28 E field distribution of different coils along the x-axis

Fig 6. 29 E field distribution of different coils along the y-axis

Fig 6. 30 The normalized measured voltage at different locations at mode 3

Fig 6. 31 E field distribution of mode 3 in the xz-plane ($y = 0$) with a muscle tissue of the size $24 \text{ cm} \times 12 \text{ cm} \times 4 \text{ cm}$

Fig 6. 32 Current distribution of mode 3 in the xz-plane ($y = 0$) with a muscle tissue of the size $24 \text{ cm} \times 12 \text{ cm} \times 4 \text{ cm}$

6.8 Summary

In this chapter, a tri-mode coil has been designed which operates in three operation modes. The $\mathbf{E}$ field distribution can be configured by changing the current ratio in coil 1 and coil 2. A focus tuning procedure has been formulated which determines the operation mode and the source voltage to be applied according to the excitation location and the $\mathbf{E}$ field intensity at the target. The formulas have been verified through an example which could generate 150 V/m at the target location $z = -2 \text{ cm}$, 0 cm , and 3 cm . The proposed method can be applied for different constraints in different applications. The

concept of the tri-mode in electromagnetic induction is also verified in the ex-vivo tissue experiment in Section 6.6.

The limitation of the setup would be the fact that only three modes are useful for different field distribution with the current setup of two coils. Therefore, in future work, more coils or a coil array can be applied instead of using just coils 1 and 2. With more coils involved, the ratio between the current across the coils and thus the **E** field distribution might have more combinations, which could further optimize the induction of current in the biological medium as well as achieving multiple excitation targets as demonstrated in Fig 6.33. Moreover, the actual implementation of the biological applications such as pulsed electromagnetic energy treatment [49] and thermoacoustic imaging [41] are also suggested to be the future work.

Fig 6. 33 Customization of proposed coil depending on focal point for stimulation

Chapter 7:

Comparing the Magnetic Resonant Coupling Radiofrequency Stimulation to the Traditional Approaches: Ex-vivo Tissue Voltage Measurement and Electromagnetic Simulation Analysis

Recently, the design concept of magnetic resonant coupling has been adapted to electromagnetic therapy applications such as non-invasive radiofrequency (RF) stimulation. This technique can significantly increase the electric field radiated from the magnetic coil at the stimulation target, and hence enhancing the current flowing through the nerve, thus enabling stimulation. In this chapter, the developed magnetic resonant coupling (MRC) stimulation, magnetic stimulation (MS) and transcutaneous electrical nerve stimulation (TENS) are compared. The differences between the MRC RF stimulation and other techniques are presented in terms of the operating mechanism, ex-vivo tissue voltage measurement and electromagnetic simulation analysis. The ex-vivo tissue voltage measurement experiment is performed on the compared devices based on measuring the voltage induced by electromagnetic induction at the tissue. The focusing effect, $\mathbf{E}$ field and voltage induced across the tissue, and the attenuation due to the increase of separation between the coil and the target are analyzed. The electromagnetic stimulation will also be performed to obtain the electric field and magnetic field distribution around the biological medium. The electric field intensity is proportional to the induced current and the magnetic field is corresponding to the electromagnetic induction across the biological medium. The comparison between the MRC RF stimulator and the MS and TENS devices revealed that

the MRC RF stimulator has several advantages over the others for the applications of inducing current in the biological medium for stimulation purposes.

7.1 Introduction

The application of magnetic resonant coupling (MRC) [54] has been very popular in wireless power transfer due to its high efficiency. Meanwhile, the coil design using MRC has recently been proposed for electromagnetic therapy applications [71] such as non-invasive radiofrequency (RF) stimulation. The setup consists of two coils, namely primary coil and secondary coil, coupled to each other. Both coils are cascaded with resonating networks, which are designed so that both coils are resonating at same frequency. Although there are two coils, only one active source is used to drive the primary coil. The secondary coil does not need another active source, and it is driven by the magnetic field coupled from the primary coil. At resonance, the primary and the secondary coil are conducting the same current. Both current conducting the primary coil and the secondary coil would superpose the magnetic field contributed by them around the biological medium such as tissue placed in between the two coils. This technique is beneficial to generate a higher magnitude of electric field $\mathbf{E}$ at the stimulation target compared to the case when a single coil is used. The higher the magnitude of the $\mathbf{E}$ field, the higher the current passing through the biological medium, leading to a more effective neural stimulation and hence, MRC is a very promising technique for neural stimulation using MRC. However, from existing related studies, there is lack of a comparative study of MRC and traditional electric or magnetic based neural stimulation techniques which are magnetic stimulation (MS) [16], [82]–[88] and transcutaneous electrical nerve stimulation (TENS) [89]–[91]. In these existing techniques, MS applies a magnetic coil, which is conducting a high magnitude of current with a low frequency of 1 – 10 kHz, to induce electric field in the biological medium which stimulates the nerve at the target. Meanwhile, TENS attach two electrodes at the two parts of human body, where current is conducted between the electrodes and passes through the human tissue that serves the stimulation effect.

In this chapter, the RF stimulation technique using MRC is compared to MS and TENS. The comparisons are based on the operating mechanisms, ex-vivo tissue voltage measurement and electromagnetic simulation analysis. The comparisons in the chapter will show that the MRC RF

simulator has advantages over MS and TENS. Firstly, from the electromagnetic theory point of view, the electric field intensity generated by electromagnetic induction from magnetic coil is proportional to the operating frequency. It follows that MS, which is operating at a much lower frequency, needs a much higher current conducting the coil to induce the same magnitude of current density at the biological medium compared to the MRC RF stimulation. Secondly, from the ex-vivo tissue voltage measurement, although both the MRC RF stimulator and MS stimulator induced voltage inside the tissue, the attenuation due to a longer distance from the coils become less in the MRC RF stimulator compared to the MS. Thirdly, from the electromagnetic simulation, the MRC RF stimulator achieved good focusing effect which focuses the electric field at the center. Furthermore, TENS has poor deep penetration and localization effect compared to MRC RF. Therefore, the MRC RF stimulator is a better device compared to the traditional MS and TENS in terms of inducing current in the biological medium for stimulation purposes. The above mentioned comparisons are presented in detail within the following sections.

7.2 Mechanism of operation

This section will introduce the mechanism of operation of MRC RF Stimulation, MS, and TENS.

7.2.1 Magnetic Resonant coupling (MRC) Radiofrequency (RF) stimulation

The MRC RF stimulation applies a pair of coils, coupled by magnetic resonant coupling, to induce strong RF electromagnetic field and hence current on human nerve for stimulation purpose. In the literature, RF wave has been applied widely in pulsed electromagnetic field therapies [39], [49]–[50]. The system diagram of the MRC RF stimulation is shown in Fig. 7.1. The signal generator generates the signal for stimulation which is amplified by a pulse power amplifier. Two resonant networks resonate with the primary and the secondary figure-of-eight coils respectively, so that they resonate at the same RF frequency for the condition of MRC. A matching network is then used for impedance matching to the MRC resonator. Under MRC, the primary coil conducts the same magnitude of current as the secondary coil. Both currents then induce RF electric field to the stimulation area, thereby inducing magnetic field in the biological medium placed in between the coils according to the Biot-Savart law

[43]. The magnetic flux density $\mathbf{B}$ generated by a circular coil of N turns with negligible thickness can be computed by integrating along the whole current path C of the coil [71]:

$$\mathbf{B}(\mathbf{r}) = \frac{\mu_0 N I}{4\pi} \oint_C \frac{d\mathbf{l}' \times (\mathbf{r} - \mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|^3} \quad (7.1)$$

where μ_0 is the permeability, N is the number of turn of the coil, I is the magnitude of current flowing through the coil, $d\mathbf{l}'$ is the differential coil element, $\mathbf{r}$ and $\mathbf{r}'$ are the position vectors of the observation point and that of the differential element $d\mathbf{l}'$ respectively. Since the current I is changing in the pulse waveform, the magnetic flux density $\mathbf{B}$ also changes with time. Then, the change of magnetic field would induce electric field in the biological medium of stimulation, governed by the Faraday's law [43]:

$$\nabla \times \mathbf{E} = -\frac{\partial \mathbf{B}}{\partial t} \quad (7.2)$$

With the electric field induced, the current density $\mathbf{J}$ in the biological medium during stimulation is given by:

$$\mathbf{J} = \sigma \mathbf{E} \quad (7.3)$$

where σ is the conductivity. The current flowing through the nerve results in stimulation effect.

When a human body part is placed in between the primary and the secondary coils, current would be induced at the nerve which initiates the stimulation process. A burst of RF pulse signal is then presented as a waveform from the stimulation process. The pulse operation with a low duty cycle ($\leq 1\%$) ensures the power dissipation in the biological medium is low which ensures RF safety is taken into consideration.

The waveform of the MRC RF stimulator is given as:

$$f(t) = A \sin 2\pi f_c t, \text{ mod}(t, T_r) < T_d \quad f(t) = 0, \text{ otherwise} \quad (7.4)$$

where t is the time, T_d is the duration of the RF pulse, T_r is the repetition period of the RF pulse, and f_c is the frequency of the RF pulse. For the actual implementation of the MRC RF stimulator, $f(t)$ is applied as a voltage signal, which is generated by a signal generator and amplified by a power amplifier. A is the voltage magnitude from the signal generator of the MRC RF stimulator, which can be amplified through a power amplifier. The MRC stimulator voltage waveform $f(t)$ is proportional to the magnitude of current conducting the coil I and hence proportional to the magnitude flux density $\mathbf{B}$ in the differential equation (7.2). The proportional relation between the magnitude of current conducting the coil and the magnitude flux can be observed in equation (7.1). The larger the magnitude of the voltage $f(t)$, the larger the current I , and hence the larger the magnetic flux density $\mathbf{B}$.

Then, $\text{mod}(t, T_r)$ is modulus after t is divided by T_r . The duty cycle D is given by [92]:

$$D = \frac{T_r}{T_d} \quad (7.5)$$

Using a small duty cycle, it can decrease the average power dissipated to the tissue by multiplying the peak power to the duty cycle. The peak power P_P and the average power P_A are related by the duty cycle D [92] as:

$$P_A = P_P \times D \quad (7.6)$$

For instance, assuming a large peak power P_P of 100 W is applied with the duty cycle D of 1%, the average power would become 1 W. The advantage of applying RF stimulation instead of low frequency is that the electric field increases with the increase in the conducting current of the coil. To demonstrate this effect, the electric field $\mathbf{E}$ generated by a circular coil of N turns with negligible thickness can be computed by integrating along the whole current path C of the coil [71]:

$$\mathbf{E}(\mathbf{r}) = \frac{\mu_0 f_c N I}{2} \oint_C \frac{d\mathbf{l}'}{|\mathbf{r} - \mathbf{r}'|} \quad (7.7)$$

where f_c is the RF frequency. It can be easily concluded that the higher the frequency, the higher the magnitude of the $\mathbf{E}$ field; hence a larger current is thus induced in the biological medium as given in equation (7.3) due to its proportional relationship with current density. Previous analysis in existing literature [93] shows that the stimulation threshold also increases with the frequency, so that the rate of increase of the threshold would be different to the rate of increase of the $\mathbf{E}$ field intensity. For instance, when the stimulus frequency increases (in a continuous sine wave), the rate of the increase in reaction thresholds of dairy cows is slower than the rate of increase in stimulus frequency [93]. In any case, the operating frequency of the MRC RF system is adjustable by changing the capacitance value of the capacitor in cascade with the coil because

$$f_0 = \frac{1}{2\pi\sqrt{LC}} \quad (7.8)$$

Fig 7.1 MRC RF stimulation system architecture

7.2.2 Magnetic Stimulation (MS)

MS conducts a high current pulse to a magnetic coil and induces electric field in the biological medium which stimulates the nerve at the target. Two types of pulses are common in MS, which are monophasic pulse and biphasic pulse. Unlike the MRC (where RF waveform is applied for stimulation), MS uses a

monophasic or biphasic pulse for stimulation. Frequency used in MS is 1-10 kHz, so the pulse duration is about hundreds of microseconds [88].

The biphasic pulse [16] is considered in this chapter since it is more effective and the MS system architecture is depicted in Fig. 7.2. It usually consist of a magnetic stimulation driver which charges up and discharge a capacitor³ to generate a pulse. The pulse passes through a magnetic coil and generates magnetic field across the target biological tissue medium according to Biot-Savart law (Equation 7.1). The magnetic field then induces electromotive force on the biological tissue and thus inducing current based on Faraday's law.

A sinusoidal biphasic pulse can be represented by:

$$\begin{aligned} f(t) &= A \sin 2\pi f_c t, \text{ mod}(t, T_r) < 1/f_c \\ f(t) &= 0, \text{ otherwise} \end{aligned} \quad (7.9)$$

where t is the time, T_r is the repetition period of the biphasic pulse, and f_c is the frequency of the biphasic pulse. The biphasic waveform can be generated by charging up a capacitor, followed by discharging it so that the current stored in the capacitor flow to the magnetic coil to generate a large magnetic field for electromagnetic induction at target. biological medium.

Fig 7.2 Magnetic stimulation system architecture

7.2.3 Transcutaneous Electrical Nerve Stimulation (TENS)

TENS applies two electrodes at two parts of human body which conducts a current between them [89]. The current passes through the human tissue which serves the stimulation effects and in comparison to the MRC and RF stimulation, TENS lacks localization effect and deep penetration because the skin is not a good conductor and has resistance which affects the current reaching the nerve when the voltage is applied at the surface of the skin. The TENS system architecture is depicted in Fig. 7.3. The current I from the TENS device into the surface of the skin can be computed by the Ohm's law [94]:

$$I = \frac{V_s}{R_e} \quad (7.10)$$

where V_s represents the voltage generated by the TENS device and R_e is the equivalent total resistance between the positive and the negative electrodes. Meanwhile, there are different layers of the skin and the current flows in multipath from one electrode to another. The current across the stimulation area of interest would be less than the total current I and more current is expected to flow near the surface of the skin instead of deep penetration because the path is shorter which results in less resistance.

Fig 7.3 Transcutaneous electrical nerve stimulation system architecture

7.3 Ex-vivo Voltage Measurement on Tissue

In this section, ex-vivo tissue experiments of voltage measurement are done by measuring the voltage across a box of pig muscle tissue (i.e. pork cut) and the size of the tissue is selected based on the spatial resolution of the focal region, which is dependent mainly on the radius of the magnetic coil.

7.3.1 Focal region of the magnetic coil and the size of the tissue

The magnetic coil used for MRC RF stimulation has 20 turns with a radius of 9 mm [54]. The large radius and the large number of turns were chosen because these two parameters are both proportional to the magnitude of $\mathbf{E}$ field induced at the focal region for each ampere of current conducting the coil due to equation (7.7), and hence capable of generating a larger current across the biological medium due to equation (7.3). To visualize the focal region, the $\mathbf{E}$ field distribution along the three Cartesian axes is computed as shown in Table 7.1, where the $\mathbf{E}$ field distribution along the axes are plotted in Fig. 7.4. The field magnitude is computed by equation (7.7), while also taking the phase difference between the two coils (i.e. 65°) into consideration. In equation (7.7), the integral can be computed by integrating every differential element of the coil, where each differential element is divided by the absolute distance between the differential element and the observation point. Since the MRC RF stimulator consists of the primary coil and the secondary coil, the $\mathbf{E}$ field contributed by both coils should be computed and added together. The focal region is defined by half power change from the central point of the MRC coupled coil ($x = y = z = 0$ cm), which is given by (i) x -axis: -2.9 cm to 2.9 cm, y -axis: -4.3 cm to 4.3 cm, z -axis: -2.2 cm to 2.2 cm. Therefore, the dimensions of the tissue used in ex-vivo experiment should be smaller than the focal region. The size of the tissue is chosen as 2.5 cm (x -axis) $\times$ 3.5 cm (y -axis) $\times$ 1.0 cm (z -axis), whereas the voltage is excited by different stimulators including MRC RF, MS, and TENS. The box of tissue for ex-vivo measurement is depicted in Fig. 7.5. The piece of tissue is stored in a plastic box, where aluminum electrodes of dimensions approximately 1.0 cm $\times$ 2.5 cm are attached to the two sides of the piece of tissue. The voltage of the piece of tissue would then be measured through the edges of the aluminum electrodes using an oscilloscope with wire connections.

Table 7.1 The calculated $\mathbf{E}$ field distribution per ampere conducting the coils at different location along the 3 axes

	Electric Field Intensity $ \mathbf{E} $ (V/m)
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Location along the axis (cm)	<i>x</i> -axis	<i>y</i> -axis	<i>z</i> -axis
-15	3.19	1.39	2.14
-14	3.74	1.65	2.65
-13	4.32	1.97	3.31
-12	4.87	2.37	4.21
-11	5.24	2.88	5.43
-10	5.20	3.51	7.12
-9	4.51	4.31	9.53
-8	3.06	5.30	13.06
-7	0.93	6.51	18.48
-6	1.70	7.94	27.45
-5	4.62	9.55	43.99
-4	7.63	11.23	44.29
-3	10.50	12.80	28.44
-2	12.95	14.10	20.42
-1	14.63	14.94	16.45
0	15.23	15.23	15.23
1	14.63	14.94	16.45
2	12.95	14.10	20.42
3	10.50	12.80	28.44
4	7.63	11.23	44.29
5	4.62	9.55	43.99
6	1.70	7.94	27.45
7	0.93	6.51	18.48
8	3.06	5.30	13.06
9	4.51	4.31	9.53
10	5.20	3.51	7.12

11	5.24	2.88	5.43
12	4.87	2.37	4.21
13	4.32	1.97	3.31
14	3.74	1.65	2.65
15	3.19	1.39	2.14

Fig 7.4 The calculated E field distribution per ampere conducting the coils at different location along the three Cartesian axes

Fig 7.5 A piece of tissue of dimensions 2.5 cm × 3.5 cm × 1.0 cm for ex-vivo voltage measurement with MRC RF stimulation, MS and TENS

7.3.2 Magnetic Resonant coupling (MRC) Radiofrequency (RF) stimulation

The ex-vivo voltage measurement setup using MRC RF is given in Fig. 7.6. The piece of tissue is placed in between two figure-of-eight coils. One coil is driven by a pulse power amplifier and a signal generator as previously depicted in Fig. 7.1, while another coil is driven by MRC. The radius of the coils is 4.5 cm with 20 windings at each side of each figure-of-eight coil while the distance between the two coils is 9 cm. Since the piece of tissue is placed at the center between the two coils, the distance between the piece of tissue and either coil is 4.5 cm.

Due to Biot-Savart law and Faraday law as given in equations (7.1) and (7.2), electric field and current would be induced across the piece of tissue. Thus, voltage is induced across the two edges of the piece of tissue that can be measured. In the experiment, a 450.5 kHz RF signal is used to drive the MRC coil and hence, the overall MRC RF stimulation system induces a transient response where the induced voltage start from the zero value to the steady state value. RF voltage pulse duration of 1 ms, which is measured from the tissue placed at the middle between the two coils is given in Fig. 7.7 and the voltage magnitude becomes steady at around 0.15 ms. Since the measured magnitude of voltage is scalable with the source signal magnitude as well as the distance between the tissue and the coils, the absolute magnitude of the waveform is not the primary interest but rather the shape and transient response of the waveform.

The transient response at startup of the measured magnitude of voltage is also shown in Fig. 7.8 (a). To show the effect of the attenuation due to the distance between the coil and stimulation point, the voltage measured at steady state when the tissue is placed at different location in the z-axis is shown in Fig. 7.8 (b). It should be noticed that the transient response would be some different when the tissue is placed at different locations because the transient response of the current conducting the two coils is also different [71]. However, the transient response should not be the main concern as Fig. 7.7 shows that the main

portion of measured waveform is in steady state. Meanwhile, the transient response of the current I can be taken into account in the calculation of the field in equations (7.1) and (7.7). However, it should be noticed that the transient response is not the main concern when the waveform duration is significantly long compared to the transient response duration.

Since the primary and the secondary coils are placed at -4.5 cm and 4.5 cm, respectively, the measured voltage is stronger when the tissue is placed near the either coil. From the figure, it can be seen the trend of attenuation of electric field intensity along z -axis that was given in Fig. 7.4 is very similar to that of the voltage induced, which is due to the proportional relationship between the $\mathbf{E}$ field and the voltage:

$$V = d|\mathbf{E}| \quad (7.11)$$

where d is the distance between the two terminals of the voltage measurement, and the assumption is constant $|\mathbf{E}|$ magnitude between the two terminals. The conductivity of the tissue has certain effect on the magnitude of $\mathbf{E}$ field, which can be observed from the following time harmonic equation derived from the ampere law [43]:

$$\mathbf{E} = \frac{1}{\sigma + j\omega\epsilon} \nabla \times \mathbf{H} \quad (7.12)$$

where ω is the angular frequency and ϵ is the permittivity. From equation (7.12), it is expected that the magnitude of $\mathbf{E}$ field is much smaller in tissue (e.g. muscle tissue assuming $\sigma = 0.8$ S/m) compared to air ($\sigma \approx 0$ S/m) at 450 kHz. From the equation, the magnitude of the induced $\mathbf{E}$ field becomes different in different medium, where the change of magnitude is reflected in denominator term of equation (7.12)

Fig 7.6 Ex-vivo voltage measurement on pig muscle tissue with the MRC RF stimulator

Fig 7.7 Overall response of the measured voltage waveform at the tissue of the MRC RF stimulation

Fig 7.8 Measured voltage response of the RF MRC stimulation across the piece of tissue (a) The transient response of the measured voltage when the tissue is placed at the center (b) The measured voltage at steady state at different location along the z-axis

7.3.3 Magnetic Stimulation (MS)

The ex-vivo voltage measurement setup using a commercial magnetic stimulator (Model: MagVenture MagPro Compact®) is given in Fig.7. 9. The magnetic stimulator generates a $280 \mu\text{s}$ biphasic pulse across the figure-of-eight coil (Model: MagVenture MC-B35). The surface of the coil is attached tightly

to the piece of tissue. According to the specification of the figure-of-eight coil model, it has an inner radius of 24 mm and an outer radius of 47 mm, winding height of 9 mm, and number of winding given by $2 \times (3 \times 4)$.

Similar to MRC RF stimulation, MS generate magnetic field from current conducting coil across the stimulation region according to Biot-Savart law, and the changing magnetic field induces electric field in the piece of tissue and hence current due to electromagnetic induction (Faraday's law). The voltage is then induced at the edge of the piece of tissue and measured as shown in Fig. 7.10. In the measurement, the tissue is placed 2.5 cm away from the coil. Again, magnitude of voltage induced is scalable by changing the input source level and the distance between the coil and the piece of tissue, and hence the waveform is the primary interest. The biphasic pulse contains both the positive and negative voltage in the total timespan of approximately $280 \mu s$. When tissue is located at different distances from the coil, corresponding maximum voltages of pulses measured across the tissue are shown in Fig. 7.11.

Fig 7.9 Ex-vivo voltage measurement on pig muscle tissue with the magnetic stimulator

Fig 7.10 Measured voltage across the piece of tissue excited by the magnetic stimulator

Fig 7.11 Measured voltage across the tissue when it is placed at different locations away from the coil

7.3.4 Transcutaneous Electrical Nerve Stimulation (TENS)

The ex-vivo voltage measurement setup using a commercial transcutaneous electrical nerve stimulator (Model: Genial ® JOZ-B62) is given in Fig. 7.12. The stimulator generates a biphasic voltage pulse train across two electrodes which is attached at the edges of the piece of tissue, thereby conducting

pulse current to the piece of tissue. The voltage across the piece of tissue is then measured as shown in Fig. 7.13. The TENS device generates a biphasic pulse train in a total duration of 15.6 ms and becomes idle for another 17 ms before the start of the next pulse train. Again, the induced voltage could be adjusted by changing the voltage applied to the electrodes.

Fig 7.12 Ex-vivo voltage measurement on pig muscle tissue with the TENS device

Fig 7.13 Measured voltage across the piece of tissue excited by the TENS device

7.4 Electromagnetic Simulation of Electric and Magnetic Field Distribution

In the previous section, we have shown how the stimulation waveform could be obtained from the MRC stimulator, commercial MS and TENS devices. However, computing the electric field and current distributions of the tissue is quite difficult; therefore, we shall make use of electromagnetic stimulation with the aid of CST Studio Suite ®²². In the simulation, a rectangular piece of tissue would be assumed, so that the result would be comparable to the previous section concerning measurement. Although the frequency response of the tissue often changes with frequency [95] the fixed tissue parameters [46] of $\sigma = 0.8 \text{ S/m}$ and $\epsilon_r = 56.8$ will be used in the following analysis. The electric field distribution is directly related to the current distribution in the tissue due to the proportional relation in equation (7.3).

7.4.1 Magnetic Resonant coupling (MRC) Radiofrequency (RF) stimulation

MRC figure-of-eight coils as well as a piece of tissue of are modelled in the electromagnetic simulation as shown in the left subfigure of Fig. 7.14. In the model, current of the frequency 450 kHz flows through the coils and generates magnetic field which induce current in the tissue. The distribution of the electric field $\mathbf{E}$ in the tissue when the size are $2.5 \text{ cm} \times 3.5 \text{ cm} \times 1.0 \text{ cm}$ and $20 \text{ cm} \times 10 \text{ cm} \times 5 \text{ cm}$ are shown in Figs. 7.15(a) and 7.16(a), respectively. In the figures, brighter the color, larger is the magnitude of the electric field. It can be seen that the electric field intensity, which is proportional to current density, is strongest at the center for both tissue sizes. Hence, it is shown that the figure-of-eight MRC coil for RF stimulation focus its stimulation effect at the center of the tissue. Therefore, the electromagnetic simulation result gives similar characteristic to the calculated result in Fig. 7.4, where the focusing location is also at the center. Then, the distribution of magnetic flux density $\mathbf{B}$ as demonstrated in Fig. 7.17(a) shows that the magnetic field penetrates the tissue and is essential for electromagnetic induction to generate current in the tissue. Unlike the electric field where the strongest magnitude occurs at the center, the magnetic field is weaker at the center than the locations around it. However, the magnitude of $\mathbf{B}$ at the center does not contribute to the current density at the same location as indicated in equation (7.3), where magnitude of $\mathbf{E}$ is the point of emphasis.

7.4.2 Magnetic Stimulation (MS)

A figure-of-eight coil and a piece of tissue are modelled in the electromagnetic simulation as shown in the middle subfigure of Fig. 7.14. Current of frequency 10 kHz flows from the electrical source to the coil which induces magnetic field. The magnetic field radiated from the coil induces current in the tissue due to electromagnetic induction. The distribution of the electric field $\mathbf{E}$ in the tissue when the size are $2.5\text{ cm} \times 3.5\text{ cm} \times 1.0\text{ cm}$ and $20\text{ cm} \times 10\text{ cm} \times 5\text{ cm}$ are shown in Figs. 7.15(b) and 7.16(b), respectively. The electric field and therefore current is induced in the tissue in both tissue sizes, but the distribution appears to be different from the MRC RF stimulator. Meanwhile, just as in the case of the MRC RF simulator, the magnitude of the $\mathbf{E}$ field is stronger at the center than of the locations around it, which is due to the focusing effect achieved by the figure-of-eight coil. Then, the distribution of magnetic flux density $\mathbf{B}$ is shown in Fig. 7.17(b), which also demonstrates that the magnetic field can penetrate the tissue which is essential for electromagnetic induction. Again, the magnitude of $\mathbf{B}$ at the center does not contribute to the current density at the same location, but the magnitude of $\mathbf{E}$ is proportional to the current density as indicated in equation (7.3).

7.4.3 Transcutaneous Electrical Nerve Stimulation (TENS)

The connecting wires from the TENS source and a piece of tissue are modelled in the electromagnetic simulation as shown in the right subfigure of Fig. 7.14. In the model, voltage applied to the electrodes and the current flows directly from the TENS sources into the tissue. As shown in the literature research in Ref. 8 (Table 7.2), transcutaneous neural stimulation with the frequency ranging from 14 Hz to 360 Hz leads to excellent pain relief, the frequency applied in this work is in the mid-range 100 Hz. The distribution of the electric field $\mathbf{E}$ in the tissue when the size are $2.5\text{ cm} \times 3.5\text{ cm} \times 1.0\text{ cm}$ and $20\text{ cm} \times 10\text{ cm} \times 5\text{ cm}$ are shown in Figs. 7.15(c) and 7.16(c), respectively. It can be seen that the electric field intensity, which is proportional to current density, is strongest near the electrodes and the central shortest current path for both tissue sizes and the electric field intensity attenuates far from them. It is because more current would flow through the shortest path between the two electrodes which results in less resistance compared with other longer paths. This implies that the TENS lacks deep penetration and localization effect. The distribution of magnetic flux density $\mathbf{B}$ is shown in Fig. 7.17(c) and although the

source of magnetic field is not the coil, the magnetic field is generated by the current conducting the connecting wires, electrodes, and tissue due to the Maxwell-Ampere law [43]:

$$\nabla \times \mathbf{H} = \mathbf{J} + \frac{\partial \mathbf{D}}{\partial t} \quad (7.13)$$

Fig 7.14 Ex-vivo electromagnetic simulation models

Fig 7.15 E field distribution of the Ex-vivo electromagnetic simulation models for the tissue size of 2.5 cm × 3.5 cm × 1.0 cm (a) MRC RF (b) MS (c) TENS

(a) MRC RF

(b) MS

(c) TENS

Fig 7.16 E field distribution of the Ex-vivo electromagnetic simulation models for the tissue size of 20 cm $\times$ 10 cm $\times$ 5 cm (a) MRC RF (b) MS (c) TENS

(a) MRC RF

(b) MS

(c) TENS

Fig 7.17 B field distribution of the Ex-vivo electromagnetic simulation models for the tissue size of 20 cm $\times$ 10 cm $\times$ 5 cm .

7.5 Summary

The MRC RF stimulation is compared to the traditional MS and TENS in terms of the mechanism of operation, ex-vivo tissue experiments, and electromagnetic simulation. Since the electric field intensity generated by electromagnetic induction from magnetic coil is proportional to the operating frequency according to equation (7.7), the electric field generated from the low frequency MS (1 – 10 kHz) should be lower (at least 45 times lower) than that generated by the MRC RF stimulator (450 kHz) based on the same current. Since electric field is proportional to the current density generated at the biological medium, it follows that the MS needs a much higher current (at least 45 times higher) to induce the same magnitude of current density compared to the MRC RF stimulation.

From the ex-vivo tissue experiments, both the MRC RF stimulator and MS stimulator induced similar amount of voltage in the tissue. However, the attenuation due to a longer distance from the coils becomes less pronounced from the MRC RF stimulator when compared to the MS. In the literature of coil design consideration [105], the ratio of the stimulation intensity observed at two different depths represents the attenuation in depth. Hence, the attenuation due to a longer distance from the coils in the MRC RF stimulator as well as that of the MS can be observed by the following figure-of-metric M :

$$M = \frac{V_{focus}}{V_{1.0cm}} \quad (7.14)$$

where $V_{1.0cm}$ and V_{focus} are the voltage when the tissue is placed at 1.0 cm away from coil and at the focus respectively. The focus is defined by the center between the two MRC coils. The comparison of the figure-of-metric is based on the two facts: firstly, the longer the distance from the coil, the larger the attenuation of E field and hence, lower voltage is detected. Secondly, different coils have a different attenuation rate based on the distance which is reflected by the value of M . The values of M of the MRC RF stimulator and the MS, captured from Figs. 7.8 and 7.13, are 0.5514 and 0.1693 respectively. This shows that the MRC RF stimulator attenuation is lower compared to that of the MS. This is contributed by the fact that the MRC RF stimulator is operated by the magnetic field produced from the two coils rather than only one coil in the case of MS. Both coils would contribute to electric field and superposition at center, thereby reducing the spatial attenuation from the coils.

From the electromagnetic stimulation, all the approaches induced electric field in the tissue which is proportional to the current density due to equation (7.3). The MRC RF stimulator achieved good focusing effect which focuses the electric field at the center as observed from Figs. 7.15 and 7.16. It results that the current density is larger at the center compared to that of the locations around it. Therefore, relating to the real RF stimulation application, it facilitates the stimulation taking place at the target instead of stimulating various locations at the same time in human body. Also, the distribution of magnetic flux density $\mathbf{B}$ as shown in Fig. 7.17 demonstrates that the magnetic field penetrates the tissue which facilitates electromagnetic induction to generate current through the tissue.

Meanwhile, for the case of TENS device, the electric field intensity is strongest near the electrodes and the central shortest current path, but attenuates greatly at the locations far from them. This shows that the TENS lacks deep penetration and localization effects compared to the MRC RF stimulator. The differences between MRC RF stimulation and MS in the simulation results of the electric field and magnetic field distribution are due to the coil configuration (MRC figure-of-eight coils versus a single figure-of-eight coil) as well as the difference in the frequency of operation (450 kHz versus 10 kHz). Meanwhile, the electric field distribution of the TENS is totally different from MRC RF stimulation and MS because the current is conducted directly through electrodes of the TENS devices and the electric field is determined by the current conducted as indicated in equation (7.3).

Finally, it is worthy of note that there are three advantages for the MRC RF stimulator. Firstly, MRC RF stimulator requires a lower current conducting the coils to induce the same magnitude of current density compared to the MS. Secondly, MRC RF stimulator attenuation is lower with respect to the distance compared to the MS. Thirdly, the MRC RF stimulator has better focusing performance compared to the TENS devices. This has been summarize briefly in Table 7.2

Table 7. 2 Comparison of Proposed MRC with TENS and TMS

	Current Type	Treatment time	Power Consumed	Cost (in SGD)	Size	Penetration Depth	Localization	Existing companies
TENS	Mono Phasic (100 mA)	Upto 16 hrs per day	Low (9 V battery)	200-500	Portable	Surface level: 1-2 cms	No localization	LG, Amtrex
TMS	Biphasic (5-10 kA)	Repetitive usage (20-30 hrs)	Very High (2-3 kW)	50000	Bulky: Used in hospitals	Upto 2-6 cms: outer cortex	Use of fMRI for localization	Magstim, Neurostar
Proposed MRC	Pulsed RF (100-1000 mA)	Usage for 20-30 mins	Battery supplied	200-1000	Portable	Upto 10 cms	Tuning of focal point and Sensing	None
<div> <div>↓</div> <div>Lesser heat induced due to signal pattern (over 100 times)</div> </div> <div> <div>↓</div> <div>Large E field (150 V/m) induced: Reduced treatment time</div> </div> <div> <div>↓</div> <div>Reduced power consumption due to MRC (20-100 times)</div> </div> <div> <div>↓</div> <div>Miniaturized portable home care set-up (15 times less cost)</div> </div> <div> <div>↓</div> <div>Large B field for deep penetration (similar or more than TMS)</div> </div> <div> <div>↓</div> <div>Tri-mode MRC coil</div> </div>								

Chapter 8:

Comparative Study of Gene Delivery using Magnetic Stimulation Techniques

Magnetofection involves the use of an external magnetic field to increase the transfection in difficult to transfect cell lines like 3T3 cells. This chapter proposes the use of an external magnetic field (from both coils) and static magnets to perform a comparative study on the efficiency of transfection obtained. This short study is performed by varying parameters such as type of magnetic field applied (static/ TMS/ MRC coils), type of waveform used (monophasic, biphasic, pulsed RF) for stimulation, duration of application of magnetic field (0 mins, 15 mins, 45 mins) and observation period post stimulation (24 hrs, 48 hrs). The results obtained are then analysed to compare the different modalities and whether their combination can be utilized to enhance the transfection rates.

8.1 Introduction

Delivery of DNA material inside 3T3 cells has been known to be an inefficient process. Different kinds of methods such as electroporation and magnetofection have been considered in this regard. Electroporation involves the application of an electric field to a cell suspension, which causes the cell membrane to be permeable for external materials to enter inside the cell. Use of electric field to create a charge difference between the DNA material (negatively charged) and the cell (positively charged) was explored, so that the DNA can enter inside the cell, leading to green fluorescence [96] - [98]. Various parameters with the maximum possible intensity from Transcranial Magnetic Stimulation and Magnetic stimulation using coils were applied to the cells, however no green fluorescence was observed due to binding of DNA with Calcium Phosphate precipitate (indicating no transfection was achieved). It is in this regard that magnetofection as a concept was explored. Magnetofection involves the application of a magnetic field, in combination with DNA attached to magnetic nanoparticles, which pull the complexes inside the cells, for binding of DNA leading to fluorescence (indicating cell transfection), as shown in Fig 8.1.

The aim of these experiments is to test the following hypothesis:

- (a) Increased duration of treatment by magnetic field will lead to higher transfection.
- (b) Comparison of transfection efficiency with similar time duration of treatment for both static magnetic field and magnetic field from coils.
- (c) Stimulate only one of the cover slips inside the well of a 6 well plate. Compare the transfection efficiency of both the cover slips which involves treatment as per stated above in (b).
- (d) Increased number of transfected cells due to cells being transfected for 48 hrs (cover slips) compared to 24 hrs (cover slips)

8.2 Materials and Methods

5.0 µg DNA and 5.0 µl of PolyMAG for NIH-3T3 cells was used. These magnetic nanoparticles (Polymag) were obtained from Chemicell GMBH [99] – [103]. Cells were seeded for each of the

wells in a 6 well dish 1 day prior to Magnetofection. Magnetofection was performed by application of the static magnetic plate and by application of magnetic field from coils for 15/45 mins. The cells were observed for red fluorescence due to use of mCherry under the microscope for analysing varying degree of transfection. The cells were fixed with Hoerchst dye for quantifying the number of cells to be compared against the number of transfected cells to determine the efficacy of transfection. The set-up is shown in Fig 8.2. The parameters used have been mentioned in Table 8.1

For the stimulation due to coils, the following parameters were used provided by the function generator:

Amplitude: 10 Vp-p

Frequency of coil: 5.1 MHz

Number of cycles (Burst): 100

Frequency of gating signal: 1 KHz

Duty Cycle: 20%

TMS : 1 pulse every 5s

Fig 8. 1 Magnetofection mechanism for cell transfection [116]

Coils were exactly placed below one of the cover slips, which is fixed at 24 hrs. The other cover slip in the well was fixed at 48 hrs. Cells were fixed and cell counting was done using macros using MATLAB 2015 ® after images were taken from a confocal fluorescence microscope to quantify the results. 5 images were taken for each of the conditions (cover slips) after fixing the cells. The number of red (transfected cells) and blue (number of cells) are quantified to determine the approximate ratio of transfection and validate the hypothesis.

Fig 8. 2 Magnetic stimulation using coils for pulsed and continuous waveform

Table 8. 1 Parameters used for stimulation in each of the wells

Well	Parameters
1	Magnetofection Plate (0 mins)
2	Magnetofection Plate (15 mins)
3	Magnetofection Plate (45 mins)
4	Pulsed waveform Stimulation from coil (15 mins)
5	Continuous waveform Stimulation from coil (15 mins)
6	Stimulation from TMS- biphasic waveform (15 mins)

8.3 Results

Images are taken using a confocal microscope for each of the conditions in the 6 wells where the cover slips are stimulated. Wells are marked as 1-6 where each well was applied with the condition stated below in Fig 8.3 and Fig 8.4. The total number of red and blue cells in the images are analysed for each of the images and in total, to determine the transfection efficiency for each of wells, as shown in Fig 8.5. Table 8.2 lists out the quantified results obtained for the experiments performed.

Fig 8. 3 Transfection observed in each of the wells in a 6 well dish 24 hrs post stimulation

Fig 8. 4 Transfection observed in each of the wells in a 6 well dish 48 hrs post stimulation

Fig 8. 5 Transfection efficiency for 3T3 cells due to various parameters 24 hrs and 48 hrs post stimulation

Table 8. 2 Number of transfected cells and observed transfection efficiency for each of the wells

Well	Parameters	Time	No of cells (Red/ Blue)	Efficiency (%)	No of cells (Red/ Blue)	Efficiency (%)
			24 hrs		48 hrs	
1	Magnetofection Plate	(0 mins)	4/ 257	1	4/ 194	2
2	Magnetofection Plate	(15 mins)	29/ 233	13	16/ 150	11
3	Magnetofection Plate	(45 mins)	34/ 225	15	47/ 308	15
4	Pulsed waveform Stimulation from coil	(15 mins)	12/ 220	5	1/ 21	4
5	Continuous waveform Stimulation from coil	(15 mins)	34/ 222	15	2/ 24	8
6	Stimulation from TMS- biphasic waveform (15 mins)	(15 mins)	24/ 365	7	8/ 167	4

8.4 Discussion and Analysis

Different factors such as time of stimulation, type of stimulation and their effect on transfection levels have been quantified and further analysed using graphical representation as shown below from Fig 8.6- Fig 8.11.

The following has been observed and analysed with respect to the proposed hypothesis for the experiments

(a) Increased duration of treatment by magnetic field will lead to higher transfection.

- 45 mins treatment from magnetofection plate (static magnetic field) resulted in greater efficiency (number of transfected cells)

(b) Comparison of transfection efficiency with similar time duration of treatment for both static magnetic field and magnetic field from coils.

- Continuous waveform from coil stimulation yields similar efficiency as magnetofection plate (static magnet) for 15 mins duration.

(c) Stimulate only one of the cover slips inside the well of a 6 well plate. Compare the transfection efficiency of both the cover slips.

- The stimulation was focused on only one of the wells. The cells in this cover slip showed greater number of transfected cells compared to the other cover slip.

- This can be analysed by the decreasing efficiency of transfection post 48 hrs (contrary to similar efficiency for static field, where both cover slips were exposed to the same static field).

(d) Increased number of transfected cells due to cells being transfected for 48 hrs (cover slips) compared to 24 hrs (cover slips)

- Increase in the number of transfected cells for static (45 mins treatment). But, the ratio of blue dyed nuclei: transfected cells will approximately be the same.

Fig 8. 6 Cell count for the condition: Static magnetic field for 0 min

Fig 8. 7 Cell count for the condition: Static magnetic field for 15 min

Fig 8. 8 Cell count for the condition: Static magnetic field for 45 min

Fig 8. 9 Cell count for the condition: Pulsed Waveform stimulation for 15 min

Fig 8. 10 Cell count for the condition: Continuous waveform stimulation for 15 min

Fig 8. 11 Cell count for the condition: TMS biphasic waveform stimulation for 15 min

The present studies could be extended along these directions, stated as follows:

- 1) This set-up could be further extended to observe the transfection efficiency for longer time duration using both coils and the magnetofection plate independently.
- 2) A set up which includes combination of magnetofection plate and coil stimulation, where both are placed on either side of the 6 well plate, focused at the cover slip may be considered to further increase the transfection efficiency for the 3T3 cells.
- 3) The optimized parameters obtained from the above experiments may then be used to extend these studies to achieve gene delivery in neurons.
- 4) The use of magnetic resonance coupling Figure of 8 coils maybe considered for this set-up, instead of just one coil presently used. This will enhance the magnetic field generated at the cover slips, greatly enhancing the transfection efficiency

8.5 Summary

A comparative study among the different magnetic stimulation techniques has been performed with respect to their efficacy for gene delivery. It has been found that the magnetic stimulation from coils has been found to be very effective, almost comparable to that of static magnetic field with regards to rate of transfection efficiency. Also, longer the time for which electric field is applied, higher will be the rate of efficiency of transfection. Preliminary results have been presented with potential for using MRC Figure of 8 coils for the proposed gene delivery set-up to enhance the efficiency further.

Chapter 9:

Conclusion and Future Work

In the present study, firstly, magnetic stimulation for biomedical applications was studied in detail. Different kinds of stimulation structures to enhance the electric field induced for stimulation are discussed. Ferrite cores and secondary structures such as resonant coils are proposed, which are shown to increase the electric field induced at the point of stimulation. Magnetic resonance coupling between these primary and secondary structures is proposed, with specific consideration to design and construction of Figure of 8 coils. This concept is verified in both simulations and ex-vivo experiments. The design of these coils is optimized further to tune the focal point and electric field to be induced depending on the application to be considered. Lastly, the proposed set of coils are compared with existing stimulation techniques such as Magnetic Stimulation and Transcutaneous Electric nerve stimulation for their advantages, with regards to the focal point, electric field induced and their efficacy of usage for biomedical applications such as drug delivery. .

This chapter discusses some of the future works in terms of applications, improving the efficacy of the proposed system and future experiments which could be conducted.

9.1 Drug Delivery with Gold Nanorods using magnetic and acoustic stimulation

Gold nanorods have been shown to be good carrier agents for delivering drugs at the required site in case of cancer cells [104]. The objective of the study is to increase the uptake of gold nanorods bind with SiRNA into these cancer cells due to usage of Ultrasound Stimulation. It has already been established that the proposed set-up enhances the uptake of nanorods into the cells [105]. These nanorods when combined with SiRNA molecules and magnetic nanoparticles, will further help in achieving targeted drug delivery, enhancing the rate of drugs delivery for these cancer cells, thereby achieving higher efficacy for drug delivery in case of cancer cells.

Fig 9. 1 Set-up to observe the uptake of gold nanorods using Ultrasound Stimulation [105]

These set of experiments would ideally be carried out in 2 phases. The steps for the same are presented in brief.

Phase-1:

- 1) The set-up will be constructed according to the figure shown in Fig 9.1. Ultrasonic intensity in the tube will be measured.
- 2) The zeta potential of the AuNRs will be measured. The AuNRs will be then linked with siRNA and their zeta potential will be measured again to confirm that the AuNRs has been linked with siRNA.
- 3) The AuNRs + siRNA will then be added into cancer cells. Imaging and viability assay, migration assay and flow cytometry will be performed.

4) The AuNRs + siRNA will be added into cancer cells. The cells will then be treated with focused Ultrasound and the cell assays will be repeated.

Phase-2:

- 1) Customized nanorods + MNPs will be bought.
- 2) These are then loaded with SiRNA molecules
- 3) A combination of magnetic field + Ultrasound will be used to perform stimulation and the results will be compared after performing the assays as listed in Phase-1.

9.2 Pulsed Ultrasound for stimulation of somatosensory circuits:

Ultrasound as a means for stimulating the tissue has been existent since a very long time. Based on the frequency of US being used, the US waves can either have a therapeutic effect or a diagnostic effect on the human body. Low frequency pulsed US has been found to differentially modulate activity of A-delta and C fibers which are involved in pain/itch transmission. The motor circuit response has been observed in amice using an EMG which involves involve movement of different muscles and activation of different brain parts during pain/ no pain. This study could potentially help in identifying the sites localizing the effect of stimulation for maximum stimulation response. Some of the parameters which could be used for reference are mentioned in the Table 9.1.

Table 9. 1 Stimulation parameters for pulsed ultrasound [106] - [108]

Stimulus parameters	Permissible values
Pulse Repetition Frequency	1.2 to 3.0 KHz
Spatial Peak temporal avg. intensity (Ispta)	21-163 mW/cm2
Total Stimulus duration	26-333 ms
Peak rare factional pressure	0.070-0.097 Mpa
Pulse intensity Integrals	0.017-0.095 mJ/cm2
Spatial Peak Pulse Average Intensities (Isppa)	0.075-0.299 /cm2

Some of the reasons which could make pulsed US at a low frequency useful for treatment of neural disorders are as follows:

- a. Pulsed US waveforms are known to elicit action potentials and synaptic transmission in hippocampal slices. This action potential can be useful for reducing the action potential during transmission of neural disorders.
- b. Brain derived neurotropic factor – one of the neuromodulators for hippocampal plasticity is regulated by neuronal activity due to US. This neuronal activity can be further suppressed.
- c. Targeted stimulation of specific protein channels and receptors is possible using US waveforms. This targeted stimulation of the ion channels may decrease the value of ion current/ action potential leading up to the thalamus.
- d. US has been known to generate mechanical pulses in lipid bilayers and these mechanical waves are shown to influence channel activity as shown in Fig 9.2. These increase the intake of ions at these channels thereby decreasing the intensity of action potential which carries the signal. All ion channels are mechanically sensitive to some degree. Classic voltage gated ion channels such as Na⁺, K⁺ exhibit gating properties which are mechano-sensitive [106] – [108].

Fig 9. 2 Mechanically sensitive gating properties of US [106]

Ultrasound as a treatment modality has also been shown to be very effective compared to traditional treatment options for stimulation such as Transcutaneous Electric Nerve Stimulation, Transcranial Magnetic Stimulation, Deep Brain stimulation and others. Some of the reasons for the same, why Ultrasound (US) is considered as a promising technology for treatment of neural disorders has been stated below. However, more studies need to be done to establish the exact reasons and mechanisms for the same.

1. Spatial variations of ultrasonically induced fields are much more rapid than fields associated with TMS, since in US, fields change in magnitude of US wavelength (less than a millimetre). Magnitude of electric field gradients in US, are comparable to that of TMS. Since gradient of the field rather than its strength is responsible for neural stimulation, US would be more effective compared to TMS.
2. Transmission of US pulse at any repetition frequency and modulation of continuous ultrasonic wave is possible, which is not the case in case of TMS. A series of rapid pulses with short repetition period compared to depolarization time constant is more effective than a pure sinusoid stimulus. Pulsed US in this case maybe be more effective.
3. The shape of the US waveform can be modulated by using a non-symmetric transducer or transmitting the pulse through a dispersive medium (acts as a filter), or by using multi-layered transducers.

These effects can be further explored by combining these non-linear effects of US to the proposed magnetic stimulator system [106] – [108]. Proper study of these effects and integration of ultrasound stimulation into the proposed magnetic stimulation system will enhance neuromodulation.

9.3 Magneto-Acoustic Resonance Stimulation System:

The proposed neural stimulator will employ the use of magnetic resonance coupling (MRC) and ultrasound, where their interactions will produce magneto-acousto-electric current for neural stimulation. The system architecture is shown in Fig. 9.3. In the proposed setup, the two microcoil arrays (combination of various MRC coils) will generate strong electromagnetic field which will induce a current to be used for stimulation. In the set-up even though there are two microcoil arrays, only one signal source is used. This is because the secondary microcoil array will be driven by the magnetic field radiated from the primary microcoil array. Under the proposed MRC, the primary microcoil array and the secondary microcoil array would conduct the same or similar magnitude of current at the resonance frequency. Hence, both microcoil arrays will induce electromagnetic field and hence electromotive force at the target, thereby doubling the current density (i.e. improvement of 100%) induced at the target.

Moreover, the magnetic field produced by the microcoil arrays would interact with the ultrasound radiation force radiated from the ultrasound transducer, producing a Lorentz-force generated current, namely magneto-acousto-electric current, to enhance the stimulation effect. Besides, Low frequency US has been known to be used for modulation of neural activity. Ultrasound due to its mechanical wave nature, would lead to cavitation effect which could be used to permeate the cell membranes, with drugs loaded onto these microbubbles for drug delivery applications into the diseased cells. This would also present a unique non-invasive approach, which might lead to opening and closing of membranes, for drug delivery in combination with the magnetic stimulation, where magnetic nanoparticles loaded with drugs could further enhance the stimulation effect. Moreover, in presence of a static magnetic field, the ultrasound transducer can be used to detect magneto-acoustic signals emanating from the biological medium to study the efficacy or rate of drug delivery, and also to monitor the effect of neural stimulation on these cells [21], [35], [49], [57], [106], [109]- [112], . This would provide a precise feedback system to study the therapeutic effect of the proposed stimulation system.

These advantages provided by the magnetic stimulation and ultrasound stimulation would be inherited by the proposed hybrid neural stimulation device which will be a unique closed loop stimulation system. The effect of stimulation will be monitored using thermo-acoustic, magneto-acoustic sensing/ imaging of the stimulation effect. This feedback will then be utilized to optimize the parameters for stimulation.

Fig 9. 3 Schematic diagram of the whole set-up with frog's leg placed between the coils for stimulation

Animal experiments with Sprague Dawley rats (Von-Frey test) could be performed to measure the effect of pain relief due to stimulation from the proposed magneto-acoustic stimulation device with a Pulsed RF signal. The protocol for the same has been mentioned in Fig 9.4. The system would then be extended to other animal models for itch relief, insomnia and depression for testing before human trials are performed. The conceived device can act as alternative therapy for Acupuncture with better efficacy, resulting from better understanding of disease. The evolution of the device with wireless acupuncture set-up is our end achievable as shown in Fig 8.5.

Fig 9. 4 Application of Pulsed Radiofrequency Currents to Rat Dorsal Root Ganglia Modulates Injury-Induced Tactile Allodynia [113]

Fig 9. 5 Overall picture of the conceived neural therapy device

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