

Neurovascular Coupling and Cerebrovascular Reactivity Analysis through Near-Infrared Spectroscopy

A Thesis submitted in partial fulfilment of
the requirements for the degree of
Doctor of Philosophy

by

Yashika Arora

Enrollment No. D15051

Under the supervision of

Dr. Shubhajit Roy Chowdhury



to the

**SCHOOL OF COMPUTING AND ELECTRICAL ENGINEERING
INDIAN INSTITUTE OF TECHNOLOGY MANDI**

March, 2021

DECLARATION BY THE RESEARCH SCHOLAR

I hereby declare that the entire work embodied in this Thesis is the result of investigations carried out by me in the School of Computing and Electrical Engineering, Indian Institute of Technology Mandi, under the supervision of Dr. Shubhajit Roy Chowdhury and that it has not been submitted elsewhere for any degree or diploma. In keeping with the general practice, due acknowledgements have been made wherever the work described is based on finding of other investigators.

Place:

Signature:

Date:

Name:

DECLARATION BY THE RESEARCH ADVISOR

I hereby certify that the entire work in this Thesis has been carried out by Yashika Arora under my supervision in the School of Computing & Electrical Engineering, Indian Institute of Technology Mandi, and that no part of it has been submitted elsewhere for any Degree or Diploma.

Signature:

Name of the Guide:

Date:

ACKNOWLEDGEMENTS

I am thankful to all the wonderful people from near and far for supporting me in doing my thesis. This thesis is also the result of my journey at IIT Mandi: the place and community which has evolved me and gave many opportunities to grow. It has been a journey filled with memorable experiences and great encounters with fabulous people.

First and foremost, I would like to acknowledge my supervisor Dr. Shubhajit Roy Chowdhury for his valuable guidance, support and inspirations throughout the journey. I would like to thank my doctoral committee members: Dr. Arnav Bhavsar, Dr. Tushar Jain, Dr. Rajanish Giri and Dr. Samar Agnihotri who provided sound suggestions and encouragement during the entire course.

I want to thank Dr. Anirban Dutta for his support and insightful suggestions and mentoring me during Overseas Visiting Doctoral Fellowship funded by Science and Engineering Research Board (SERB), a statutory body of the Department of Science and Technology, Government of India. I would like to thank Prof. Dr. Ulrich G. Hofmann and Ms. Rand K. Almajidy, University Medical Center Freiburg, Germany for their significant suggestions on near-infrared spectroscopic design during Personnel Exchange Program visit under DST-DAAD project. I would like to thank Dr. Swathi Ramasahayam for helping me in preliminary experiments related to skin optics. I would like to acknowledge Dr. Makii Muthalib, Mehak Sood, Utkarsh Jindal and Dr. Pierre Besson for performing the human study and Prof. Stephane Perrey for providing the near infrared spectroscopic data.

I would also like to convey my thanks to all the members of Biomedical Systems Lab, Multimedia, Analytics, Networks and Systems Group, for their encouragement and support. I am especially appreciative to Bodhayan Nandi, Gaurav Sharma, Prateek Kumar Sonker and Soham Mukherjee for their valuable inputs. I am thankful to my lab members: Kshitij Shakya, Dalchand Ahirwar, Sweta Ghosh, Bidisha Biswas, Vaibhav Bedi, Vikram, Ashish Tiwari and Raktim Bhattacharya. I would like to acknowledge Akash K Rao, Sharey Deep Gularia and my seniors: Krishan Sharma, Krati Gupta and Indu for their helpful inputs.

I am grateful to my friends at the campus, at home and around the world for making the journey pleasant and supporting in special ways. Special thanks to Amrutha for being with me on various levels. I am grateful to my friends and batch mates: Bindu Sharan, Dhairya Singh Arya, Mohammad Faizan Ahmad, Paromita Dutta, Ragini Sinha, Sujata, Kushal Preeti, Sahil Walia, Arshdeep Singh Boparai, Ashish Kumar, Prabhjot Kaur, Vyoma Singh, Manju Bisht, Harsha Mathur, Ankita Mathur, Sunita, Manu Shree, Shruti Kaushik, Dauood Saleem, Mona Subramaniam, Vijender Kumar Sharma, and Avinash Kumar. I want to thank Roopa Ravichandar, Carmon Koenigsknecht, and Rishabh Sharma at University at Buffalo. To my little sister – Varnika Miglani, thank you for cheering me in all of my quests and motivating me to chase my dreams.

Lastly and more eminently, I thank my parents and my brothers. Their guidance and regular support have helped me a lot.

ABSTRACT

Near-infrared spectroscopy (NIRS) is a portable non-invasive tool to analyze the organic composition of a sample by the application of near-infrared light. For instance, in a routine medical check-up, a small clip: pulse oximeter is placed on the index finger which employ NIRS technique to determine the oxygen in the blood. In brain imaging, NIRS detect the local hemodynamic response with reasonable spatial resolution, better temporal resolution and comfort compared to other brain imaging modalities like magnetic resonance imaging (MRI) and electroencephalogram (EEG). It is an optical imaging technique that is sensitive to light and skin optics parameters. The usage of optode (light emitter-detector pair) for detecting the NIRS signals to estimate the cerebral oxygenation levels is hindered considerably by surface roughness profile of skin, which necessitates the optodes to be positioned at certain angle with respect to the skin surface and not perpendicularly on the skin surface. In the present study, first an attempt has been made to optimize the placement of NIRS optodes in reflection photoplethysmographic sensor system by analyzing the roughness of surfaces of skin layers. Its implications on cerebral cortex imaging down the line have been presented to obtain accuracy in cerebral hemodynamic response.

The second part of the work focuses on cortical excitability through various electrode configurations of anodal transcranial direct current stimulation (tDCS). tDCS method involves application of weak direct current using non-invasive electrodes placed on the scalp. tDCS have shown to modulate both cortical neural activity and hemodynamics and is used in various neuro-rehabilitation strategies. However, the underlying mechanism of tDCS is not completely known and there is a huge inter-individual variedness in the responses to tDCS. This study evaluates the effect of various anodal tDCS designs with regard to electric field and voltage distribution using subject's specific anatomy in a computational framework. The study evaluates the effect of conventional and high definition transcranial direct current stimulation (HD-tDCS) by utilizing synthetic magnetic resonance image volumes for normal and lesioned brain.

The study next focuses on the application of NIRS to analyze the correlation between cerebrovascular reactivity (CVR) and neurovascular coupling (NVC). Cerebrovascular reactivity represents the responsiveness of cerebral blood vessels to vasoactive stimuli.

And, neurovascular coupling is a phenomenon through which neuronal activity elicits a local change in cerebral blood flow (CBF). This leads to the notion of neurovascular unit (NVU) consisting of the vascular smooth muscle, perivascular space, synaptic space and, astrocyte glial cell. Several neural disorders are associated with impaired NVC. The study postulates a correlation between neurovascular coupling and cerebrovascular reactivity under the effect of tDCS based on experimental NIRS data. The study presents a computational model to evaluate vessel volume response under anodal transcranial direct current stimulation considering a basic system of neurovascular unit. The proposed model based on neurovascular dynamics tracked vascular response elicited through neuronal activity via various signaling pathways during anodal tDCS. It was found that the stimulation can perturb the vessel response via both neuronal and non-neuronal pathways. The proposed model specifies the signaling pathways in a compartment model of neurovascular unit with respect to evoked hemodynamic responses in a computational framework which is otherwise extremely difficult to examine in wet lab environment. The computational modeling of neurovascular coupling and cerebrovascular reactivity measured through NIRS will possibly enable the understanding of underlying dynamics of non-invasive current stimulation.

PREFACE

Material presented in Chapters of this thesis have been either published or intended for publication in international, peer-reviewed journals and international conference proceedings.

Chapter 1:

S. Roy Chowdhury, G. Sharma, **Y. Arora**, "Cerebral oxygenation studies through near infrared spectroscopy: A review", *Advanced Materials Letters*, Vol. 11(3), 20031482 (1-10), 2020.

Chapter 3:

Y. Arora, S. Ramasahayam, S. Roy Chowdhury, "An Optimal Reflection Photoplethysmographic Sensor System based on Skin Optics", *IEEE Sensors Journal*, Vol. 18, No. 17, pp. 7233-7241, 2018.

G. Sharma*, **Y. Arora***, S. Roy Chowdhury "Studies on Rat Brain Phantoms for the Development of Near-Infrared Spectroscopy (NIRS) System", In Proceedings of the 11th International Joint Conference on Biomedical Engineering Systems and Technologies (BIOSTEC 2018) - Volume 1: BIODEVICES, pages 157-163.**Equal Contribution*

Chapter 4:

Y. Arora and S. R. Chowdhury, "Cortical Excitability through Anodal Transcranial Direct Current Stimulation: a Computational Approach," *Journal of Medical Systems*, vol. 44, no. 2, pp. 1-13, 2020.

Y. Arora, S. Roy Chowdhury, "Assessing the role of electrodes for high-definition transcranial direct current stimulation configurations on cortical excitability in a computational framework", 13th International Conference on Complex Medical Engineering (CME 2019), Dortmund, Germany, September 23-25, 2019.

Chapter 5:

Y. Arora, A. Dutta, S. Roy Chowdhury, "Pathways of hemodynamic response during anodal transcranial direct current stimulation: a computational approach" 5th International Conference on Neurorehabilitation (ICNR 2020), Vigo, Spain, October 13-15, 2020.

Chapter 6:

Submitted to PLOS Computational Biology, Preprint Available:

Y. Arora, P. Walia, M. Hayashibe, M. Muthalib, S. R. Chowdhury, S. Perrey, and A. Dutta,
"Grey-box linear modeling to analyze functional near-infrared spectroscopy-based
cerebrovascular reactivity to anodal high-definition tDCS in healthy humans," 2020.

TABLE OF CONTENTS

Declaration by the Research Scholar	i
Declaration by the Research Advisor.....	ii
Acknowledgements	iii
Abstract.....	v
Preface.....	vii
Table of Contents	ix
List of Figures.....	xiii
List of Tables	xx
List of Symbols, Abbreviations and Nomenclature	xxii
Chapter 1: Introduction	1
1.1 Background.....	2
1.1.1 Anatomical Perspective	2
1.1.2 Near-Infrared Spectroscopic Imaging.....	6
1.1.3 Transcranial Direct Current Stimulation	10
1.2 Motivation	14
1.3 Scope of the Thesis.....	14
1.4 Contribution of the Thesis	15
1.5 Thesis Outline.....	16
Chapter 2: Overview of Neurovascular Coupling and Cerebrovascular Reactivity. 19	
2.1 Neurovascular Coupling and Cerebral Blood Flow: Measurements in Functional Neuroimaging.....	19
2.2 Cellular Models of Neurovascular Coupling.....	22
2.3 Neurovascular System Dynamics.....	26

2.4 Brain Imaging modalities and its integration with tDCS	32
2.5 Cerebrovascular Effects of Transcranial Direct Current Stimulation	34
2.5.1 Cerebrovascular Reactivity due to Transcranial Direct Current Stimulation	34
2.5.2 NIRS-tDCS Coupled Studies.....	35
2.6 Summary.....	37
Chapter 3: Studies on Skin Optimized Near-Infrared Spectroscopy and its Implications on Cerebral Cortex Imaging.....	39
3.1 Introduction	39
3.2 Background: Skin Optics.....	40
3.2.1 Absorption Coefficients of Skin Layers	41
3.2.2 Scattering Coefficient of Skin Layers.....	42
3.2.3 Depth of Penetration of Light into Skin Layers.....	43
3.3 Surface Scattering Theory	43
3.3.1 Scattering by Rough Surfaces.....	44
3.3.2 Theoretical Analysis	45
3.4 Experimental Analysis.....	49
3.4.1 Reflectance by Skin Layers	50
3.4.2 Root Mean Square (RMS) Surface Roughness	51
3.4.3 Position of Optode Pair.....	51
3.5 Near-infrared Light Propagation in Head.....	54
3.6 Rat Brain Phantoms Studies	56
3.6.1 Phantom Preparation.....	57
3.6.2 Near Infrared Spectroscopy System Set-up.....	58
3.6.3 Experimental Protocol	59
3.6.4 Results.....	60

3.7 Skin Optimized NIRS for Evaluating Cerebral Response.....	64
3.8 Conclusion.....	65
Chapter 4: Computational Studies on Cortical Excitability through Anodal Transcranial Direct Current Stimulation.....	67
4.1 Introduction	67
4.2 Methods	68
4.2.1 MRI Models.....	69
4.2.2 Synthetic Data Processing	69
4.2.3 tDCS Montages.....	69
4.3 Results	73
4.3.1 Computation Synthetic MRI volumes (Normal versus Lesion brain regions) ..	73
4.3.2 m x n HD-tDCS with Different Types of Electrodes	76
4.3.3 Outer Ring HD-tDCS Configuration.....	80
4.4 Conclusion.....	83
Chapter 5: Neurovascular Coupling and Cerebrovascular Reactivity through NIRS Imaging: Grey-box Model.....	85
5.1 Introduction	85
5.2 Materials and Methods	87
5.2.1 NIRS Imaging during tDCS: Experimental Protocol	87
5.2.2 Grey-box Model Dynamics and Assumptions.....	92
5.2.3 Physiologically Detailed Neurovascular Compartmental Dynamics	93
5.2.4 Investigation of the Four Pathways: Vessel Response during Anodal tDCS ..	104
5.2.5 Physiologically Detailed Model Response	106
5.3 Results	107
5.4 Conclusion.....	109

Chapter 6: Systems Analysis of Cerebrovascular Reactivity to Anodal Transcranial Direct Current Stimulation in Healthy Humans.....	111
6.1 Introduction	111
6.2 Materials and Methods	112
6.2.1 Participants and the Experimental Protocol.....	112
6.2.2 Model Architecture	113
6.2.3 Model Analysis	114
6.3 Results	115
6.3.1 Hemodynamic Response from Experimental NIRS-tDCS Data	115
6.3.2 Physiologically Detailed Model Linearization for Grey-box Analysis of Experimental Data	117
6.3.3 Grey-box Model Analysis using Experimental Data.....	119
6.4 Conclusion.....	124
Chapter 7: Conclusion and Future Scope.....	127
7.1 Summary of the Present Work	127
7.2 Conclusion.....	129
7.3 Limitations and Future Work	131
Appendix A: Model Parameters	133
Appendix B: Systems Analysis: Linearization & Identification (Chapter 6).....	137
References	147