Translational Modeling of Non-Invasive Electrical Stimulation

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Translational Modeling of Non-Invasive Electrical Stimulation

Dennis Q. Truong*

Department of Biomedical Engineering, City College of New York, New York, NY, USA 10031

A dissertation submitted to the Graduate Faculty in Engineering in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

City College of New York

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Email address: dtruong@ccny.cuny.edu
This manuscript has been read and accepted for the Graduate Faculty in Engineering in satisfaction of the dissertation requirement for the degree of Doctor of Philosophy

______________________________________  __________
Marom Bikson, Chair of Examining Committee  Date

______________________________________  __________
Ardie D. Walser, Associate Dean for Academic Affairs  Date

EXAMING COMMITTEE

Prof. Marom Bikson, Dept. of Biomedical Engineering, City College of the City University of New York

Prof. Lucas C. Parra, Dept. of Biomedical Engineering, City College of the City University of New York

Prof. Jacek Dmochowski, Dept. of Biomedical Engineering, City College of the City University of New York

Prof. John H. Martin, Dept. of Physiology, Pharmacology, and Neuroscience, City College of the City University of New York

Dr. Zhi-De Deng, Experimental Therapeutics & Pathophysiology Branch, National Institutes of Mental Health, NIH

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Abstract

Seminal work in the early 2000’s demonstrated the effect of low amplitude non-invasive electrical stimulation in people using neurophysiological measures (motor evoked potentials, MEPs). Clinical applications of transcranial Direct Current Stimulation (tDCS) have since proliferated, though the mechanisms are not fully understood. Efforts to refine the technique to improve results are on-going as are mechanistic studies both in vivo and in vitro. Volume conduction models are being applied to these areas of research, especially in the design and analysis of clinical montages. However, additional research on the parameterization of models remains.

In this dissertation, Finite Element Method (FEM) models of current flow were developed for clinical applications. The first image-derived models of obese subjects were developed to assess the relative impact of fat delineation from skin. Body mass index and more broadly inter-individual differences were considered. The effect of incorporating the meninges was predicted from CAD-based (Computer Aided Design) models before being translated into image-derived head models as an “emulated” CSF conductivity. These predictions were tested in a recently validated database of head models. Multi-scale models of transcutaneous vagus nerve stimulation (tVNS) were developed by coupling image-derived volume conduction models with physiological compartment modeling. The impact of local tissue inhomogeneities on fiber activation were considered.
Acknowledgements

This dissertation is the culmination of a multitude of years and personal efforts. Many of the studies and publications I worked on – and am proud of – are not featured in this context. Likewise, many of the people that have contributed are not listed. To you, I am humbled. I am grateful. Thank you.

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1. Background and Significance

Transcranial Direct Current Stimulation (tDCS) is a non-invasive low intensity (< 4 mA) brain stimulation technique re-discovery in the early 2000’s. DC stimulation over the motor cortex at 1 mA was found to alter cortical excitability as verified by motor evoked potentials (MEPs) (Nitsche & Paulus, 2000). Since this initial neurophysiological discovery, many clinical applications have been explored including depression, pain, schizophrenia, motor and speech rehabilitation following stroke, addiction, and more (Baker, Rorden, & Fridriksson, 2010; Brunelin et al., 2012; Brunoni, Valiengo, et al., 2013; A. DaSilva et al., 2010; D. J. Edwards et al., 2009; Fregni et al., 2008). TDCS and transcranial Electrical Stimulation (tES) in general have several desirable qualities like affordability and limited risk, the most commonly reported adverse events being skin irritation. (Marom Bikson et al., 2016; Nitsche et al., 2008). Effect sizes however remain small and varied (Horvath, Carter, & Forte, 2014) warranting additional research to refine the technique. A multitude of factors could be affecting clinical results, such as stimulation intensity, polarity, and focality (Batsikadze, Moliadze, Paulus, Kuo, & Nitsche, 2013; Nitsche et al., 2008; Nitsche & Paulus, 2000). Research has suggested brain state, lesion morphology, stimulation timing, adjunct pharmacology, and BDNF polymorphism may also influence outcomes (Antal et al., 2010; Brunoni, Ferrucci, et al., 2013; Fritsch et al., 2010; Hamilton, Chrysikou, & Coslett, 2011; Thirugnanasambandam et al., 2011). Finite Element Method (FEM) models of tDCS can and have been applied to address some of the issues related to stimulation parameters. New stimulation montages optimized for focality or intensity have been developed through modeling (Datta et al., 2009a; Dmochowski, Datta, Bikson, Su, & Parra, 2011; Ruffini, Fox, Ripolles, Miranda, & Pascual-Leone, 2014). Aspects of device design such as electrode size and gel conductivity have been investigated (Kronberg & Bikson, 2012; Saturnino, Antunes, & Thielscher, 2015). However,
many of the remaining physiological issues warrant in vivo or in vitro research. FEM models may not directly address these issues, but models can be used to translate and scale these physiological findings to clinical application and vice versa.

Conventionally, stimulation techniques can be grouped into two categories: protocols that *induce* activity of neurons (supra-threshold), and protocols that exert *modulatory* effects on ongoing neuronal activity and excitability (sub-threshold). The first group includes high-intensity short-pulse transcranial electrical stimulation (tES), transcranial magnetic stimulation (TMS), electroconvulsive therapy (ECT), and paired associative stimulation (PAS). The second group, includes forms of low-intensity sustained tES including transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), transcranial pulsed current stimulation (tPCS), and transcranial random noise stimulation (tRNS). The electric field intensities produced in the brain by supra-threshold techniques are two orders of magnitude above sub-threshold techniques (Boggio et al., 2006; Datta, Dmochowski, Guleyupoglu, Bikson, & Fregni, 2013; Lindenberg, Zhu, & Schlaug, 2012; Peterchev et al., 2012; Salvador, Mekonnen, Ruffini, & Miranda, 2010; Suh, Kim, Lee, & Kim, 2009b; Suh, Lee, Cho, Kim, & Kim, 2010; Dennis Q. Truong, Magerowski, Blackburn, Bikson, & Alonso-Alonso, 2013; Turkeltaub et al., 2011) which allows for action potentials to be triggered (Radman, Ramos, Brumberg, & Bikson, 2009).

Theories have been developed on possible mechanisms of action involving subthreshold changes to cortical and subcortical excitability (A. F. DaSilva et al., 2012a; Nitsche et al., 2008).

### 1.1 Prior non-invasive brain stimulation models

With the increasingly recognized value of computational forward models in informing tDCS montage design and interpretation of results, there has been advances in modeling tools and
proliferation of technical publications (M. Bikson et al., 2008; Marom Bikson, Datta, Rahman, & Scaturro, 2010a; A. F. DaSilva et al., 2012a; Datta, Baker, Bikson, & Fridriksson, 2011a; Datta et al., 2009a; Faria, Leal, & Miranda, 2009; Halko MA, 2011; Mendonca et al., 2011; Miranda, Lomarev, & Hallett, 2006; Oostendorp et al., 2008; Parazzini, Fiocchi, Rossi, Paglialonga, & Ravazzani, 2011; Sadleir, Vannorsdall, Schretlen, & Gordon, 2010; Salvador, Mekonnen, Ruffini, & Miranda, 2010; Suh, Kim, Lee, & Kim, 2009; Turkeltaub et al., 2012; Wagner et al., 2007a). At this stage, the limitations of computational current flow modeling in informing clinical protocols seems to rest largely with how these models can be used, rather than any specific technical challenge. Nevertheless, careful consideration of the development of modeling techniques can provide insight on how models can be leveraged.

The work done in Miranda et al. 2006 was among the earliest numerical modeling efforts that specifically examined tDCS montages and intensities in the context of a “spherical head”. Later, the focality of cortical electrical fields was compared across small electrode configurations proposed to achieve targeted modulation (Datta, Elwassif, Battaglia, & Bikson, 2008a)(Datta, Elwassif, Battaglia, & Bikson, 2008). Wagner et al. (2007) was the first CAD (Computer Aided Design) rendered head model that analyzed current density distributions for various montages, including healthy versus cortical stroke conditions. The more recent modeling efforts have been mostly MRI derived. Oostendorp et al. (2008) was the first to consider anisotropy in the skull and the white matter. Datta et al. (2009) built the first high-resolution head model with gyri/sulci specificity. Suh et al. (2009) concluded that skull anisotropy causes a large shunting effect and may shift the stimulated areas. Sadleir at al. (2010) compared modeling predictions of frontal tDCS montages to clinical outcomes. Datta et al. (2010) studied the effect of tDCS montages on TBI and skull defects. Parazzini et al. (2011) was the first to analyze current flow patterns across
sub-cortical structures. Dmochowski et al. (2011)\textsuperscript{20} showed how a multi-electrode stimulation can be optimized for focality and intensity at the target. Recent efforts have focused to build patient-specific models and compare modeling predictions to experimental outcomes. In considering new electrode montages, especially in potentially vulnerable populations (e.g. skull damage, children), forward models are the main tool used to relate the externally controllable dose parameters (e.g. electrode number, position, size, shape, current) with resulting brain current flow.

Computational modeling has long suggested that induced cortical electric fields are low (Datta et al., 2009a; Miranda et al., 2006; Wagner et al., 2007a). Recent validation studies have confirmed low cortical electric fields (~0.4 V/m per mA of stimulation). (Huang, Liu, et al., 2017a; Opitz et al., 2017). However, it is important to recognize that supra-threshold techniques are expected to ultimately effect behavior by modulating endogenous networks while sub-threshold techniques can influence firing in active systems (Reato, Rahman, Bikson, & Parra, 2010b).

1.2 Prior modeling of cranial nerves

Clinically applied montages for tDCS have been modeled with a focus on cortical modulation. However, electric field is known to spread through superficial tissue and extracephalic tDCS montages have been predicted to induce electric field at the brainstem and cervical spine (Marom Bikson et al., 2010a; Grecco et al., 2015). There is evidence of neuromodulation through extracephalic regions of interest including cranial nerves (Groves & Brown, 2005; Rush et al., 2000). Adapting models of common tDCS montages to assess extracephalic stimulation could contribute to or negate alternative mechanistic theories related to tDCS. Skin shunting, the rerouting of current through a more conductive preferential pathway, has been an expected part of transcranial stimulation (Miranda et al., 2006; Opitz, Paulus, Will, Antunes, & Thielser, 2015a; D.Q. Truong, Magerowski, Pascual-Leone, Alonso-Alonso, & Bikson, 2012). However, little
consideration has been made of the cranial nerves that innervate the face and neck in these transcranial stimulation techniques. Cranial nerve stimulation presents an alternative for the neuromodulatory action of some tDCS protocols. Cranial nerves themselves have been investigated as targets for stimulation (Groves & Brown, 2005; Pop, Murray, Markovic, & DeGiorgio, 2011). The vagus nerve in particular has been investigated as a region of interest in similar neuropsychiatric applications (Brunoni, Valiengo, et al., 2013; George, Rush, Sackeim, & Marangell, 2003; Rush et al., 2000). Nerve stimulation has been studied and simulated with volume conductor models like in tDCS (Arle, Carlson, & Mei, 2016; Helmers et al., 2012; Lee, Hershey, Bradley, & Yearwood, 2011; Wesselin, Holsheimer, & Boom, 1999; Zhu, Li, Wei, & Sui, 2017), however, these models typically feature simplified idealized local anatomical targets (many modalities are invasive) using CAD models instead of image-derive anatomy. Nerve stimulation models, having a suprathreshold mechanism, make extensive use of physiological modeling to predict activation thresholds of targets and contraindication targets (Arle et al., 2016; Helmers et al., 2012; McIntyre, Richardson, & Grill, 2002; Zhu et al., 2017). Combining the modeling techniques from these fields would allow for cranial nerves to be investigated as another non-invasive stimulation modality. Cranial nerve stimulation, which has been modeled invasively (Arle et al., 2016; Helmers et al., 2012), could be assessed non-invasively using detailed image-derived models.

The electrical stimulation of nerves has been studied many context; motor fibers, auditory nerve, vagus nerve, and trigeminal to name a few. Early animal studies experimentally measured nervous tissue properties in rabbits, rats, and toad (Chiu, Ritchie, Rogart, & Stagg, 1979; Frankenhaeuser & Huxley, 1964; Schwarz & Eikhof, 1987). Seminal work by Hodgkin and Huxley created the first model of membrane electrical kinetics based on a squid axon (Hodgkin & Huxley, 1952).
Mcneal then combined physiological nerve fiber models with volume conductor models to simulate the response to an externally applied electric field (McNeal, 1976). Subsequent modeling has extended the application of these membrane models to clinical use. Computer models of functional electrical stimulation in motor fibers (Rattay & Aberham, 1993; Veltink, Veen, Struijk, Holsheimer, & Boom, 1989) auditory nerve stimulation using cochlear implants (Frijns & Kate, 1994), sensory nerve fiber stimulation (Struijk, Holsheimer, Heide, & Boom, 1992) in spinal cord stimulation have been developed.

1.3 non-invasive Vagus Nerve Stimulation (nVNS)

While other cranial nerve stimulation modalities have been studied and modeled, only vagus nerve stimulation (VNS) has been modeled with combined volume conductor and nerve activation models (Arle et al., 2016; Helmers et al., 2012). The methodology, however, draws from decades of work on excitable tissues in general. Strength-Duration curves first described by Weiss (1901) and Lapicque (1907) (Geddes, 2004) are still used to assess and validate pulsed stimulation models. SCS and TENS have a history of using volume conductor and nerve activation models, though the targets and constraints vary between anatomical systems (Lee et al., 2011; Struijk, Struijk, Holsheimer, & Boom, 1993; Wesselink et al., 1999; Zhu et al., 2017).

Vagus nerve stimulation (VNS) has been approved for treatment resistant epilepsy since 1997 (Schachter & Saper, 1998). It has been targeted for many other indications such as depression, anxiety, obesity (George et al., 2003; Groves & Brown, 2005; Rush et al., 2000). While the mechanism is unclear, theories have been developed based on the anatomical and functional projections of the nerve. The vagus nerve is known to be a mixed nerve carrying both afferent and efferent information with fibers divided in an 80% to 20% ratio (Foley & DuBois, 1937). The efferents innervate the heart as part of the parasympathetic system, the right vagus nerve projecting
into the sinoatrial node and the left vagus nerve projecting into the atroventricular node (Randall & Ardell, 1985). The afferents project to the nucleus tractus solitarius (NTS). The NTS in particular is believed to primary target for therapeutic applications with its subsequent projections to the locus coeruleus and the dorsal raphe nuclei, regions associated with norepinephrine and serotonin release (Dorr & Debonnel, 2006; Fornai, Ruffoli, Giorgi, & Paparelli, 2011; Krahl, Clark, Smith, & Browning, 1998; Nemeroff et al., 2006).

Though the vagus nerve is long with many branches -- it extends through the head, neck, and torso -- the cervical branch is commonly the target of invasive stimulation. Recent studies have investigated noninvasive transcutaneous stimulation of the cervical vagus nerve as well as the auricular branch, but neither have been studied in as much depth as invasive VNS. Few multiscale models of VNS exist. The two studies that have been published (Arle et al., 2016; Helmers et al., 2012) model invasive VNS cuff electrode with the goal of predicting specific fiber activation given an electrode shape and stimulation intensity.

1.4 Vagus Nerve Anatomy and Physiology

Anatomically the vagus nerve, like other nerves, is not a homogenous structure. Histological slices of the vagus nerve reveal a sheath of connective tissue, the epineurium, encapsulating multiple fiber bundles called fascicles. In the space between the epineurium and fascicles is another layer of laminar connective tissue, the perineurium, which also carries blood vessels (Arle et al., 2016). The nerve fibers grouped within fascicles can be further classified by size and function. These classifications are A, B, and C fibers. A fibers being the largest (5-20 mm), B fibers being small (<3 mm), and C fibers being the smallest (0.4-2 mm) (Erlanger & Gasser, 1930). Threshold sensitivity and likewise recruitment order from VNS was found to follow the same pattern (0.02 - 0.2 mA, 0.04-0.6 mA, >2.0 mA respectively) (Bailey & Bremer, 1938; Groves & Brown, 2005).
A and B fibers are myelinated, while C fibers are not. Conduction velocities of vagal fibers have been estimated for A, B, C fibers to be 30-90 m/s, 10-20 m/s, and 0.3-6 ms respectively (Bailey & Bremer, 1938; Chase, Sterman, & Clemente, 1966; Groves & Brown, 2005; Woodbury & Woodbury, 1990). The majority of fibers in the vagus nerve are C-fibers, in cats this is estimated to be 65-80% (Woodbury & Woodbury, 1990). The vagus nerve has a mix of afferent and efferent fibers, 80% are afferents and 20% are efferents (Foley & DuBois, 1937). Generally A-alpha are afferent fibers responsible for proprioception, A-beta and A-gamma are afferents involving stretch receptors, A-delta are nociceptive afferents. In vagus nerve, A and B fibers convey mechano-sensitive cardio-pulmonary information. B fibers are involved in vasomotor and visceromotor function. C fibers are involved in vasomotor and visceromotor information as well as slow pain, temperature, and touch. C fibers are in Cardio-pulmonary chemoreflexes. (Groves & Brown, 2005)

Studies investigating stimulation frequency found that frequencies of 50 Hz and greater caused damage to the vagus nerve (50-100 Hz, 2.5 mA, biphasic pulse pairs, 100 microseconds/phase) (Agnew & McCreery, 1990; McCreery, Agnew, Yuen, & Bullara, 1990; Woodbury & Woodbury, 1990; Zabara, 1992). Typical clinical frequencies for epilepsy are between 20 and 30 Hz (Groves & Brown, 2005).

1.5 Model Interpretation

When interpreting simulation predictions, it is important to recognize that the intensity of current flow in any specific brain region does not translate in any simple (linear) manner to the degree of brain activation or modulation, even when considering current direction. Moreover, neurophysiological studies indicate changes in “excitability” may not be monotonic with stimulation (Lindenberg, et al., 2012). For example increasing stimulation amplitude or duration
can invert the direction of modulation, as can the level of neuronal background activity (M.A. Nitsche & Paulus, 2001). However, to a first approximation, it seems reasonable to predict that regions with more current flow are more likely to be affected by stimulation while regions with little or no current flow will be spared the direct effects of stimulation. As a first step to understanding the mechanism of action of tDCS, a relationship between model predicted regional current flow and changes in functional activation was demonstrated (Halko et al., 2011). The “quasi-uniform” assumption considers that if the electric field (or current density) is uniform on the scale of a region/neuron of interest, then “excitability” may be modulated with local electric field intensity (M. Bikson et al., 2004) (see discussion in Datta et al., 200812 and Miranda et al., 200725).

Clinical models of suprathreshold stimulation incorporate two scales of modeling: a physiological nerve model and a volume conductor model. Most tES models have relied on volume conductor simulations alone, though other suprathreshold stimulation modalities like deep brain stimulation (DBS) and spinal cord stimulation (SCS) have incorporated both model types (Butson & McIntyre, 2005). Physiological modeling of nerve or neuron excitability serves to answers several questions. Early animal models allowed researchers to assess the role of certain membrane channels and their relative concentrations (Chiu et al., 1979; Struijk et al., 1993). Clinically applied models allowed researchers to assess possible mechanisms for clinical protocols. For example, models and experiments of vagus nerve stimulation (VNS) and transcutaneous electrical nerve stimulation (TENS) have been used to predict the specific fiber type activated during standard stimulation protocols (Arle et al., 2016; Helmers et al., 2012; Zhu et al., 2017). In DBS, electrode design and it's affect on the spatial focality of excitatory stimulation (region of influence) has been modeled (Butson & McIntyre, 2005). Subthreshold stimulation as with tDCS can be modeled and has been
in a poster by (Aberra, Grill, & Peterchev, 2017). Interpreting the results of subthreshold stimulation is, however, subtle. A precise activation threshold is not known; rather, the subthreshold membrane polarization of neurons of varying cell types can be predicted (Aberra et al., 2017). While the spatial distribution of membrane polarization may largely reflect cellular orientation relative to the applied electric field (Radman, Ramos, Brumberg, & Bikson, 2009), the amount of polarization would be expected to vary in time dependent stimulation modalities (i.e. tACS or tPCS) (Geddes, 2004). Subthreshold membrane potentials could be use in comparisons between these modalities.

1.6 Overview

When do details matter in image-derived models of non-invasive stimulation? This thesis explores the assumptions made in model parameterization and assesses when these assumptions are adequate for clinical applications. Specifically, the parameterization of fat is considered in obese subjects. Modeling of the CSF while taking into account the presence of meninges is considered. The effect of soft tissue inhomogeneity on nerve fiber activation is assessed in a combined volume conduction – nerve activation model.

Chapter 2 describes our effort to translate tDCS to obese subjects. The role of subcutaneous fat, which was previously ignored, is assessed to determine if obesity specific dose requirements are necessary. More broadly, we seek to answer if fat representation within skin is a necessary component of individualized image-derived head models.

Chapter 3 proposes a pragmatic approach for simulating the effect of the meninges on cortical electric fields during tES. While the resolution required to model meningeal layers is technically
prohibitive in image-derived models, we propose emulating the effect of the meninges through an adjustment of CSF conductivity. Spherical models are used to inform more detailed image-derived models. The proposed method is tested in a validated dataset.

Chapter 4 expands upon conventional image-derived head models to incorporate physiological models of nerve activation. The first image-derived head model of nVNS is developed. The effect of soft-tissue (i.e. skin, fat, muscle) representation on predicted fiber activation is assessed.
Chapter 2: Computational modeling of transcranial direct current stimulation (tDCS) in obesity: impact of head fat and dose guidelines

This chapter is adapted from: (Dennis Q. Truong, Magerowski, Blackburn, Bikson, & Alonso-Alonso, 2013a) & (D.Q. Truong et al., 2012)

2.1 Introduction

Obesity is a major public health concern worldwide. In the United States alone, 78 million adults and approximately 12.5 million children and adolescents were obese between 2009-2010 (Ogden, Carroll, Kit, & Flegal, 2012). Research indicates that these numbers will continue to rise. The largest increase will be in severe obesity, with its accompanying surge in comorbid conditions and related healthcare costs (Finkelstein et al., 2012; Wang, McPherson, Marsh, Gortmaker, & Brown, 2011). The medical, social, and economic consequences of obesity have focused global attention on the condition and spawned numerous public health initiatives. Still, therapeutic options remain limited. New treatment strategies are required to halt the rise in obesity and limit future economic and societal costs.

A growing body of evidence, mostly from human neuroimaging studies, suggests that dysregulation in brain regions that process cognitive and reward aspects of food may be a key component of obesity (Alonso-Alonso & Pascual-Leone, 2007; Appelhans, 2009; Carnell, Gibson, Benson, Ochner, & Geliebter, 2012; Dagher, 2012; Volkow, Wang, Tomasi, & Baler, 2012; Zheng, Lenard, Shin, & Berthoud, 2009)). Thus, modulating brain activity with neurotechnologies may open new therapeutic avenues. Compared to other neuromodulatory techniques, transcranial direct current stimulation (tDCS) offers significant advantages due to its relative safety, noninvasiveness, low-cost, and portability (M.A. Nitsche et al., 2008).
By delivering a weak direct current to the scalp via two electrodes—anode and cathode—
tDCS can modulate the transmembrane potential of neurons, modify excitability, and induce
plasticity changes. Over time, these can translate into clinical effects in diverse patient populations
(Brunoni et al., 2012; M.A. Nitsche, et al., 2008; M. A. Nitsche & Paulus, 2011). Preliminary data
support a potential role for tDCS in the modulation of appetite and eating behavior in humans.
Three small trials report acute changes in food craving, desire to eat, attentional bias to food, and
actual food intake following one session of tDCS targeting the dorsolateral prefrontal cortex
(DLPFC) (Fregni et al., 2008; Goldman et al., 2011; Montenegro et al., 2012).

To optimize stimulation parameters in obese subjects requires knowing the potential
influence of head fat on current density distribution. It is well-established that head anatomy and
variations in tissue layers, including fat (Shahid, Weng, & Ahfock, 2011; D. Q. Truong,
Magerowski, Pascual-Leone, Alonso-Alonso, & Bikson, 2012), critically affect how current
density is distributed in the brain (M. Bikson, Rahman, & Datta, 2012; M. Bikson, Rahman, Datta,
Fregni, & Merabet, 2012; Sadleir, et al., 2010; T. Wagner et al., 2007). Across anatomically typical
adults, variation in peak cortical current density can vary >two-fold (Datta, Truong, Minhas, Parra,
& Bikson, 2012).

Therefore, the presence of a thickened layer of fat around the head in obese individuals
could influence brain current flow and resulting neuromodulation during tDCS administration.
Investigating if and how to alter tDCS dose to accommodate variations in BMI is timely. Interest
in the use of this technology in obese subjects is growing, for both the modulation of craving-
related processes, and more broadly, for neuropsychiatric treatment of patients who often have
obesity as a comorbidity. The purpose of this study was to systematically examine the role of head
fat on the distribution of current during tDCS using MRI-derived high-resolution computational
models to evaluate whether current dosing standards for tDCS are adequate for the obese population.

2.2 Methods

2.2.1 Subjects

To determine the effect of head fat on current density distribution during tDCS, we created models from MRI images of five human subjects categorized according to BMI, from normal (18.5–24.9 kg/m$^2$) to super obese (>50 kg/m$^2$). Subjects were a 35-year-old female with a BMI of 53.5 kg/m$^2$ (S1), a 47-year-old female with a BMI of 43.4 kg/m$^2$ (S2), a 22-year-old female with a BMI of 38.3 kg/m$^2$ (S3), and a 25-year-old female with a BMI of 20.9 kg/m$^2$ (S5). We also included a 36-year-old male subject with a BMI of 25.1 kg/m$^2$ (S#) who participated in prior tDCS computational modeling studies (M. Bikson, Datta, Rahman, & Scaturro, 2010; Datta, et al., 2012).

2.2.2 MRI data collection and segmentation

We performed high-resolution T1-weighted magnetization prepared rapid gradient echo (MPRAGE) MRI scans at the Center for Biomedical Imaging, Boston University School of Medicine, using a 3-T Philips Achieva scanner (Philips Medical Systems, Best, The Netherlands) equipped with a Synergy-L Sensitivity Encoding (SENSE) head coil. Acquisition parameters were: TE = 3.2 ms; TR = 6.92 ms; flip angle = 8°; FOV = 256 mm; resolution = 256 x 256; slice thickness = 1.2 mm; no gap; and voxel size of 1 x 1 x 1.2 mm.

The scans were segmented into 7 tissues: air, skin, fat, skull, cerebral spinal fluid (CSF), gray matter, and white matter.
Automated segmentation algorithms from Statistical Parametric Mapping (SPM8, Wellcome Trust Centre for Neuroimaging, London, UK) were used in conjunction with updated tissue probability maps (Rorden, Bonilha, Fridriksson, Bender, & Karnath, 2012) to generate an initial segmentation of air, skin, skull, CSF, gray matter, and white matter. Additional post-processing algorithms smoothed artifacts and corrected for discontinuities (Y. Huang et al., 2012). We added fat segmentation through a threshold flood fill of skin, and manually corrected lingering errors in continuity and detail in all tissues with ScanIP 4.2 (Simpleware Ltd, Exeter, UK).

Two models (S# and S5) were artificially “fattened” by dilating the segmentation of fat. Fat was merged with the outer surface of skin, and then dilated isometrically up to 10 mm. A duplicate of this merged fat and skin segmentation mask was then dilated an additional 3 mm to form a new skin surface. No tissues other than skin and fat were altered in these models.

We measured the thicknesses of skin, fat, bone, and CSF for each model from the segmentation data. Measurements were performed over both motor strips (5 times each) and averaged.

2.2.3 Modeling of tDCS

Stimulation electrodes, sponge pads, and gels were modeled in SolidWorks (Dassault Systèmes Corp., Waltham, MA) and imported into ScanIP for meshing. Three montages were modeled: 5x7 cm pads with anode over the motor strip (C3) and cathode over the contralateral supra-orbital (M1-SO); 5x7 cm pads with anode over the inferior frontal gyrus (F8) and cathode over the contralateral supra-orbital (IFG-SO); and a high-definition (HD) electrode ring configuration (5 cm radius)
providing anodal stimulation over the motor strip (4x1 over C3). An adaptive tetrahedral meshing algorithm was used in ScanIP to generate meshes between $6 \times 10^6$ to $14 \times 10^6$ quadratic elements.

Finite element method (FEM) models were created in COMSOL multiphysics 3.5a (COMSOL, Inc., Burlington, MA) using the aforementioned meshes. Models were created using electrostatic volume conductor physics with material conductivities defined as follows: (in S/m): air, $1 \times 10^{-15}$; skin, 0.465; fat, 0.025; skull, 0.01; CSF, 1.65; gray matter, 0.276; white matter, 0.126; electrode, $5.99 \times 10^7$; saline-soaked sponge, 1.4; and conductive gel, 0.3. We applied boundary conditions to simulate direct current stimulation. The surfaces of the cathodes were grounded ($V=0$), while the surfaces of the anodes had a current density of $1 \text{A/m}^2$. All other exterior surfaces were electrically insulated.

2.3 Results

2.3.4 Optimized segmentation, including fat delineation

Fig. 1 shows the segmentation of all head tissue layers for each of the five subjects. We were able to delineate the fat layer with great detail in all cases. In all the tissue layers, including fat, we observed a high degree of interindividual variability in head anatomy.

2.3.5 Current distribution in three tDCS montages

We tested two standard (5x7 cm pads) tDCS montages and a HD-tDCS montage with the ring (4x1) electrode configuration. Following 1 mA current injection, we predicted substantial interindividual variability in current peak values and distribution, including focality (Fig. 2). HD-tDCS resulted in more focal and robust distribution of electric currents. From lowest to highest
peak amplitude, the individuals ranked S3, S2, S#, S1, and S5. This ranking was the same in each of the montages.

We observed differences in both intensity and individual variation between montages; 4x1 HD-tDCS was the least intense ($\mu = 0.190$ V/m) with the most variation ($\sigma = 0.094$ V/m), while M1-SO and IFG-SO were comparable ($\mu = 0.317$ and 0.330 V/m; $\sigma = 0.041$ and 0.039 V/m). This finding was corroborated by previous studies that reported an inverse relationship between focality and intensity; in effect a tradeoff between HD electrode ring configurations and large sponge pads (Datta et al., 2009a; Dmochowski et al., 2011).

Across all three montages, the subject head with the intermediate BMI in the sample (S3; BMI: 38.3 kg/m$^2$) corresponded to the lowest overall intensity. The highest peak was in S5, which corresponded to the individual with the lowest BMI (20.9 kg/m$^2$).

2.3.6 Role of head fat and other tissue thickness in current distribution

Table 1 shows individual data for specific tissue thicknesses as well as total thickness weighed by conductivity. We observed a positive trend between BMI and head fat thickness (Spearman’s rho=0.8; $p=0.107$), but did not see any simple linear association between current intensity and subject BMI, or thickness measurements of skin, fat, skull, and CSF. The rank of tissue thicknesses compared to peak electric field (Spearman’s rho=-1; $p=0.044$) only when summed and weighed by corresponding conductivities. Peak values were dominated by the most conductive layers (Skin and CSF). The decrease in peak electric field with increasing Skin and CSF conductance may be related to shunting through those layers.

2.3.7 Effect of intrasubject fat layer dilation
In the absence of an evident relationship between BMI and brain current flow across subjects (where other tissues were also different), we evaluated the influence of increasing fat thickness within an individual (with all other factors being equal). In the fat dilated head models, we observed a drop in peak electric field in an extreme, but not physiologically typical, scenario (fat thickness >10-15 mm) (Fig. 3). Increasing the layer of fat at a physiologically observed range (a few millimeters) did not have a significant effect.

*Skin current density across subjects and montages* As a proxy for skin tolerability, we analyzed the current density of the skin at the electrode contact, specifically the boundary between sponge and skin or electrode gel and skin (Fig. 4). Overall, the highest difference in current density magnitude was observed between the 4x1 HD-tDCS montage versus the M1-SO and IFG-SO montages. Variations in current density magnitude were minimal between subjects. The spatial distribution of current density resembled that of previous studies resulting in hot spots along the edges of the contact boundary (Kronberg & Bikson, 2012).

**2.4 Discussion**

2.4.1 *Variations in brain current flow with increasing BMI*

In this study, we examined the effect of BMI and head fat on current density distribution. We used computational models to systematically address this problem in three common tDCS montages that were simulated in five human subjects with different BMIs. We found that current density variability between subjects does not appear to have a direct and/or simple link to BMI. For example, we observed that peak amplitudes in an extreme case of obesity (BMI >50 kg/m²) were comparable to those found in non-obese cases. Further, simulated dilation of the fat layer revealed a within-subject significant effect only at supraphysiological values of fat thickness.
When combined with previous modeling studies, our results suggest that head fat contributes to current density distribution in conjunction with other anatomical differences. Ultimately, the variation among individuals is likely the result of a multitude of factors, not just BMI. According to our data, differences in head fat thickness contribute an extra 10% variability in peak cortical current density in addition to the previously reported >2-fold variability that exists across normal (non-obese) individuals (Datta, et al., 2012).

2.4.2 Effect of fat on tDCS current distribution

Our findings show that BMI does not, in itself, significantly predict brain current flow intensity, nor do physiological increases in individual BMI. Yet these findings do not diminish the validity of studies indicating that fat influences current flow and that the omission of fat in computational models (e.g., representation as skin) reduces precision (Shahid, et al., 2011).

In the first case, the hypothetical removal of fat will influence current flow. In the second case, failure to implement fat in computational models may change predicted brain current by up to 60% (D. Q. Truong, et al., 2012). Our results reinforce the utility of individual, MRI-derived computational models, and their value in guiding and supporting the development of new clinical applications of tDCS.

2.4.3 Clinical and safety considerations

Our modeling data suggest that compared to variations seen in healthy lean subjects (Datta, et al., 2012), head fat influences current density distribution, but its relative contribution is small when other sources of variability related to head anatomy are added. Therefore, no special considerations
regarding tDCS dose and safety may be needed for use in clinical trials involving overweight or obese individuals.

These results are in line with recent reports of an acute decrease in self-reported measures of food craving following one session of tDCS over the dorsolateral prefrontal cortex in overweight/obese subjects (BMI 25.2 to 43.5 kg/m²; Montenegro et al. 2012; BMI>30 kg/m² in 31.6% of the sample; Goldman et al. 2011). Neither of these investigations mentioned adverse effects related to tDCS administration using standard electrode sponges at 2 mA intensity for 20 minutes. According to current guidelines, the parameters used in these studies were within the recommended safety range associated with behavioral and clinical effects in different experimental and clinical contexts (Brunoni, et al., 2012; M.A. Nitsche, et al., 2008; M. A. Nitsche & Paulus, 2011). The combination of modeling and experimental evidence suggests that the current guidelines are both safe and sufficient for neuromodulation of brain activity across the normal-to-obese BMI spectrum.

tDCS dose is not adjusted across subjects in the latest clinical guidelines, and it is assumed that a significant safety margin between current protocols and the potential for injury exists (M. Bikson, Datta, & Elwassif, 2009; Liebetanz et al., 2009). The marginal effects of high and low body fat on brain current flow seen in this study also indicate that current safety guidelines are sufficient. Nonetheless, as with any new investigation, caution should be used when applying this technique in clinical applications in the field of obesity and eating disorders. These models, which predict only current flow, do not consider potential differences in neurophysiological changes and/or sensitivity for the same brain electric field.

Previous studies have reported behavioral effects using similar montages as the ones we modeled at low intensities (1 mA) (M.A. Nitsche, et al., 2008; M. A. Nitsche & Paulus, 2011). All
evidence available to date on tDCS in food craving comes from studies that have used an intensity of 2 mA. Therefore, it is uncertain whether 1 mA could still induce neuromodulatory effects that translate into behavioral outcomes. These predictions should be confirmed with empirical data.

A final consideration can be made regarding the implications of our findings for current density at the level of the skin. Like Truong et al. (D. Q. Truong, et al., 2012), we did not find any evidence of significant differences in current density on the skin associated with a thicker layer of head fat. Rather, current density was most sensitive to the choice of electrode; the highest intensity being generated by HD electrodes, which have been shown to be tolerable to 2mA of stimulation under specific configurations (Minhas, Datta, & Bikson, 2011). Any additional skin-related risks or adverse effects (e.g., burning and other scalp sensations) in the obese population are not observed in this model. However, current density hotspots at the skin/electrode contact can be particularly sensitive to idiosyncratic details of the electrode and potentially the skin surface (Kronberg & Bikson, 2012). As the prevalence of skin conditions tends to be higher in obese than in normal-BMI individuals (Scheinfeld, 2004) (Scheinfeld, 2004), we recommend careful interviewing of subjects and skin inspection as suggested in current tDCS guidelines (M.A. Nitsche, et al., 2008; M. A. Nitsche & Paulus, 2011).

2.4.4 Limitations of the present study

The largest peak amplitudes in all montages were found in the lowest BMI (BMI 20.9 kg/m²), which also corresponded to the smallest head size. This observation suggests that current distribution may alter significantly in individuals with lower-than-normal BMI. We did not sample the underweight BMI spectrum (<18.5 kg/m²). However, future studies are needed to address and
clarify this potential issue and its clinical implications for the future use of tDCS in low BMI individuals, including those with anorexia nervosa or cachexia (Hecht, 2010).

This study makes predictions based on computational models with precision limited by the accuracy of segmentation (Figure 1) and tissue conductivity assignments. Other permutations and refinements, such as the addition of further tissue masks and anisotropy, only have value in informing clinical guidelines if 1) extra precision is added rationally rather than for complexity; and 2) relative changes in current flow across models have a significant effect on clinical dosing decisions (M. Bikson & Datta, 2012; M. Bikson, Rahman, & Datta, 2012).

2.5 Conclusion

In sum, evidence indicates that current guidelines for the administration of tDCS in the general population can be extended to those who have obesity. High-resolution computational models that include head fat provide individualized prediction of tDCS current density, and can accurately guide and support tDCS protocols in emerging clinical applications.
Fig. 1. Segmentation of five subjects with varying BMI (S1, S2, S3, S5, S#), seven tissue compartment models (skin, fat, skull, cerebral spinal fluid (CSF), gray matter, white matter, and air). High-Resolution MRI scans were segmented using a combination of automated and manual techniques. Specific anatomical considerations, such as continuity of CSF, were verified or corrected. Images are shown on the same scale.
Table 1. Quantifying Individual Differences. BMI and thickness of tissues surrounding the brain were measured at EEG 10-20 positions C3 and C4. Total thickness and total thickness weighted by conductivity are also listed. Images are shown on the same scale.

<table>
<thead>
<tr>
<th></th>
<th>53.5</th>
<th>43.4</th>
<th>38.3</th>
<th>20.9</th>
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<td><strong>BMI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Skin (mm)</strong></td>
<td>3.79</td>
<td>5.38</td>
<td>5.23</td>
<td>3.10</td>
<td>5.79</td>
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<tr>
<td><strong>Fat (mm)</strong></td>
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<td>5.18</td>
<td>2.30</td>
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<td>2.43</td>
</tr>
<tr>
<td><strong>Bone (mm)</strong></td>
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<td>4.90</td>
<td>5.68</td>
<td>4.79</td>
<td>4.75</td>
</tr>
<tr>
<td><strong>CSF (mm)</strong></td>
<td>2.71</td>
<td>2.45</td>
<td>2.71</td>
<td>2.26</td>
<td>2.30</td>
</tr>
<tr>
<td><strong>Total (mm)</strong></td>
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<td>17.91</td>
<td>15.92</td>
<td>11.97</td>
<td>15.26</td>
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<td>6.39</td>
<td>6.72</td>
<td>7.02</td>
<td>5.26</td>
<td>6.60</td>
</tr>
</tbody>
</table>
Fig. 2. Resulting peak electric field magnitude simulated in three montages (M1-SO, 4x1 HD-tDCS over M1, IFG-SO) across subjects. Variations in intensity occur across individuals, but these individual variations are consistent in ranking across montages (S3<S2<#<S1<S5).
**Fig. 3.** Influence of fat thickness in isolation. Fat was dilated isometrically with 3 mm of skin cover; other tissues were unchanged. A moderate increase in the thickness of fat caused little change in peak electric field. There was a slight increase (5.7%) in S# and a slight decrease (8.9%) in S5. Increasing the thickness of fat beyond that physiologically observed led to noticeable decreases in intensity in both S# (15.6%) and S5 (25.7%). Varying the thickness of tissues surrounding the brain not only changes the overall conductance, but also the orientation of the electrodes with respect to the brain.
Chapter 3: Enhanced tES and tDCS computational models by meninges emulation

3.1 Introduction

There is extensive literature on the usefulness of computational models of current flow in the study and optimization of transcranial Direct Current Stimulation (tDCS) and more generally transcranial Electrical Stimulation (tES) (Dannhauer, Brooks, Tucker, & MacLeod, 2012; A. F. DaSilva et al., 2012b; Dmochowski et al., 2013). For example, models suggest that current flow during tDCS is between rather than only under electrodes, and that High-Definition tDCS can be used to focalize stimulation (Datta, Elwassif, Battaglia, & Bikson, 2008b). Models also predict that anatomical differences may explain inter-individual variability (Datta, Truong, Minhas, Parra, & Bikson, 2012; Dennis Q. Truong, Magerowski, Blackburn, Bikson, & Alonso-Alonso, 2013b). Acknowledging repeated and consistent experimental validation of model accuracy (Antal et al., 2014; Datta, Zhou, Su, Parra, & Bikson, 2013; D. Edwards et al., 2013; Huang, Liu, et al., 2017b; Jog et al., 2016; Opitz et al., 2016), there remains value in ongoing efforts to enhance model precision—especially as models support rational target engagement and personalized stimulation in expanding clinical trials (Marom Bikson et al., 2018).

A key advance in the creation of accurate and useful models was the development of gyri-precise models based on high-resolution MRI and the use of a priori information to correct models beyond image resolution (Datta et al., 2009b)—notably ensuring continuity of the cerebrospinal fluid (CSF), which can be less than the MRI slice thickness. Subsequent studies have demonstrated the key role of CSF in shaping the delivery of current to the brain during transcranial electrical stimulation (Datta, Baker, Bikson, & Fridriksson, 2011b; Miranda, Mekonnen, Salvador, & Ruffini, 2013a; Opitz, Paulus, Will, Antunes, & Thielscher, 2015b; Teichmann et al., 2016) as it presents a significantly higher conductivity than other tissue.
While CSF is represented as a homogenous mask spanning from the skull to the brain (the skull-brain interface), the anatomy in fact includes meningeal layers comprised of the dura mater, arachnoid mater, and pia mater. Meninges are relatively resistive and occupy a significant portion of the skull-brain interface — roughly 15 to 50% (Bashkatov et al., 2003; Fournier, Combès, Roberts, Braga, & Prima, 2011; Kuchiwaki, Inao, Ishii, Ogura, & Gu, 1997; Saboori & Sadegh, 2015) of the skull-brain interface distance; this alters the effective conductivity skull-brain interface compared to a pure CSF mask (Wendel, Narra, Hannula, Kauppinen, & Malmivuo, 2008). Moreover, even the CSF compartment itself includes arachnoid trabeculae (Saboori & Sadegh, 2015), increasing tortuosity and so in situ resistivity.

While the anatomy in unequivocal, including meninges in tDCS / tES models is computationally restrictive. Computational models that are both high-resolution (e.g. 0.1 mm voxel) and large (e.g. span the entire head) can require intractably detailed meshes for numerical FEM solutions. To include the meninges within the volume conventionally modeled as homogenous CSF, upsampling to at least a resolution of ~0.05 mm (corresponding to half the thinnest layer thickness) would be required. Typical image-derived head models are created at 1 mm, some as low as 0.5 mm (Dannhauer et al., 2012; Huang, Parra, & Haufe, 2016; Miranda et al., 2013a; Dennis Q. Truong et al., 2013b), but just a two-fold increase in isotropic resolution corresponds to an eight-fold increase in number of voxels ($2^3$) and so of memory for each image volume (MRI and Masks) used to create the model.

As an alternative, we propose to continue modeling the skull-brain interface as a homogenous mask while assigning it a lower conductivity that provides a reasonable approximation specifically regarding underlying current flow in the brain. Such an approach not only maintains computational burden, but it allows seamless integration with all image-segmentation and modeling pipelines already developed for tES / tDCS (Dannhauer et al., 2012; Dmochowski, Bikson, & Parra, 2012; Huang, Datta, Bikson, & Parra, 2017; Huang et al., 2013; Jung, Kim, & Im, 2013; A. Thielscher, Antunes, & Saturnino, 2015;
Dennis Q. Truong et al., 2014). To verify the practical impact of such an approach, and generally assess the role of the meningeal layers (pia, arachnoid, and dura), in tES / tDCS we first applied concentric sphere models. A 9-shell model (white matter, grey matter, pia, CSF, arachnoid, dura, skull, fat, skin) was developed and compared to a conventional 6-shell model (white matter, grey matter, CSF, skull, fat, skin) with the conductivity of the CSF compartment adjusted (“emulated”) to match cortical electric field in the 9-shell model. The emulated CSF was then simulated in a MRI-derived head models, including from a dataset of human subjects with intracranial recordings during tES. This allowed us to experimentally validate the accuracy of emulated CSF/meninges vs conventional CSF models.

3.2 Methods

3.2.1 Spherical Head Models with Meningeal Layers

CAD-derived (Computer Aided Design) spherical head models were developed to isolate the effect of meningeal layers. Geometries were defined in a Finite Element Method (FEM) package (COMSOL 5.1), material properties and boundary conditions were applied, and cortical electric field was solved as in the image-derived head models (see “image-derived models” for more detail on FEM settings). Nine concentric spheres of 76.49, 72.76, 71.76, 64.03, 62.92, 62.72, 61.63, 61.53, 58.93 mm radii were modeled to represents the scalp, fat, skull, dura matter, arachnoid mater, CSF, pia mater, gray matter, and white matter. This corresponded to layer thicknesses of 3.73, 1, 7.73, 1.11, 0.2, 1.09, 0.1, 2.6 mm respectively with white matter as the core [Fig. 1]. Layer thicknesses for white matter, grey matter, CSF, skull, fat, and skin were based on previously published spherical head model dimensions for an adult head (Datta et al., 2008b). Meningeal layer (dura, arachnoid, pia) thicknesses were estimated from literature (Bashkatov et al., 2003; Fournier
et al., 2011; Kuchiwaki et al., 1997; Saboori & Sadegh, 2015) noting references are varied due to the heterogenous geometry of the layers themselves. Thickness of the skull-brain interface layers (Meninges and CSF) were estimated under constraints: (1) Thickness rank (largest to smallest) was CSF (sub-arachnoid space), dura, arachnoid, and pia, (2) total thickness of the skull-brain interface layers was maintained at the CSF thickness of previously published models, and (3) meningeal layers were modeled to the highest range of their respective possible thickness, as a worst case scenario. Unless otherwise stated, “conventional” conductivities of tissue layers were: (in units of S/m) scalp 0.465; fat 0.025; skull 0.010; dura mater 0.100; arachnoid mater 0.125; CSF 1.650; pia mater 0.150; white matter 0.126 and gray matter 0.276 (Datta et al., 2011b; C. Gabriel, Gabriel, & Corthout, 1996). Electrode and conductive gel or sponge was modeled as $5.8 \times 10^7$ or 1.4 S/m respectively. Tissue conductivity of meningeal layers were similarly approximated from literature, and was modeled under the following constraints: (1) Conductivities of meninges were between that of scalp and skull, and (2) an assumed conductivity rank of lowest to highest from pia mater to dura mater was maintained.

Spherical head models were modeled across four tissue conductivity conditions, four electrode montages, and five skull-brain interface compositions. This produced a 4x4x5 table of conditions (Table 1). The four tissue conductivity conditions tested were to assess the relative impact of meningeal parameterization: (1) Conventional conductivities of skull, dura, arachnoid, CSF, and pia were modeled; (2) meningeal conductivities were doubled, (3) skull conductivity was increased to an extreme literature value (from 0.01 to 0.08 S/m) (Hoekema et al., 2003), and (4) both meningeal and skull conductivities were doubled. Within each of the previous tissue conductivity conditions, four montages were tested (anode-cathode 180°, anode-cathode 90°, anode-cathode 45°; and concentric 4x1 ring with 45° radius, Fig.1.C) representing a span of
potential electrode placements. Skull-brain interface composition was then assessed in five conditions (Fig.1.C): (1) All layers were modeled as CSF per convention; (2) a layer of dura mater was introduced and the remainder was modeled as CSF, (3) dura and arachnoid mater were included and the remainder was modeled as CSF, (4) all layers (dura, arachnoid, CSF and pia) were modeled, or (5) all layers were modeled as a single tissue but with a conductivity fitted to emulate the results of modeling all meningeal layers and CSF. The fifth composition was the basis for CSF emulation against the fourth full-detail composition.

Model results were assessed using four metrics for brain electric field (EF): (1) minimum EF magnitude was calculated, (2) maximum EF magnitude was calculated on the cortical (grey matter) surface, (3) maximum EF magnitude was calculated within the brain (grey and white matter cross-section), and (4) EF spread on the cortical surface was quantified as the percent surface area above half the maximum surface EF, or Area Half Max (AHM). These metrics were used to determine an effective emulated CSF conductivity to be applied to the entire skull-brain interface that could reproduce the effect of detailed meningeal layers for each tissue conductivity condition and each electrode montage (Table 1). The median emulated CSF conductivity was selected.

3.2.2 Image-derived Exemplary Head Models

The effect of the meninges as incorporated in the emulated CSF conductivity was assessed in three health subject models with two common montages each. Cortical electric field was predicted in three exemplary neural typical heads of varying sizes (small, medium, large) using gyri precise image-derived data from previous studies (Marom Bikson, Datta, Rahman, & Scaturro, 2010b; Datta et al., 2012; Huang et al., 2016; Dennis Q. Truong et al., 2013b). Results compared the effects of using emulated versus conventional CSF conductivity. The head models were selected to be exemplary of high accuracy segmentation: (1) S#, a large head size, has been a reference
head model used in previous tDCS modeling (Datta et al., 2009b, 2012, Dennis Q. Truong et al., 2014, 2013b); (2) ICBM-NY head, medium size, was created more recently (2016) (Huang et al., 2016) to be a reference tES model base on averaged anatomy from 152 subjects (MNI / ICBM 152) (Fonov, Evans, McKinstry, Almli, & Collins, 2009); (3) S5, a small head, used in tDCS models on inter-individual variability (Knotkova et al., n.d.; Seibt, Brunoni, Huang, & Bikson, 2015; Dennis Q. Truong et al., 2013b). High resolution MRIs (1 mm³ isotropic) were segmented as white matter, grey matter, CSF, skull, fat, and skin. As in previous tES modeling studies dura, arachnoid, and pia matter were not individually segmented. Stimulation electrodes, sponge pads, and gels were modeled in SolidWorks (Dassault Systèmes Corp., Waltham, MA) and imported into ScanIP for meshing. Two common montages were modeled: the M1-SO montage with an anode over the motor cortex (M1) and cathode over contralateral supra-orbital (SO) was modeled with 5x5 cm electrode and sponges, and the 4x1 montage with a center anode over M1 and surrounding electrodes 5 cm from center was modeled with small (1 cm radius) high-definition (HD) electrodes in a concentric ring configuration. In each case the position of M1 was chosen based on the 10-20 system for scalp electrodes (Jasper, 1958). An adaptive tetrahedral meshing algorithm was used in ScanIP to generate meshes between 6 × 10⁶ and 14 × 10⁶ quadratic elements.

Finite element method (FEM) models were created in COMSOL multiphysics 5.1 (COMSOL, Inc., Burlington, MA) using the aforementioned meshes. Models were created using electrostatic volume conductor physics with material conductivities defined as follows: (in S/m): air, 1 × 10⁻¹⁵; skin, 0.465; fat, 0.025; skull, 0.01; CSF, 1.65 (conventional conductivity) or 0.85 (emulated conductivity); gray matter, 0.276; white matter, 0.126; electrode, 5.8 × 10⁷; saline-soaked sponge or gel, 1.4. (Datta et al., 2011b; C. Gabriel et al., 1996). Boundary conditions were applied to the
model surfaces. Cathode surfaces were grounded (V=0) and anode surfaces summed to 1mA inward current). All other exterior surfaces were electrically insulated n · J = 0 A/m² and the Laplace equation (∇ ∗ (σ∇V) = 0) was solved. The resulting cortical electric field was interpreted as a correlate for neuromodulation (Marom Bikson et al., 2004).

3.2.3 Validation in Subjects with Intracranial Recordings

The effect of the emulated CSF conductivity (versus conventional CSF conductivity) was further assessed using intracranial recordings under TES from 10 subjects published in Huang, Liu, et al., 2017 (Huang, Liu, et al., 2017b). Previously meshed head models (13) for these subjects were re-solved in an FEM package with both the emulated CSF conductivity (0.85 S/m) and the conventional conductivity (1.65 S/m). Models were parameterized as those in section 2.2 Image-derived Exemplary Head Models, but without the inclusion of fat. Electrodes were modeled as they were experimentally, 2 x 2 cm on the forehead (Fpz) and occiput (Oz). One subject had three additional electrode montages with recordings (Fpz-shifted-left and Oz, Fpz and Oz-shifted-right, both Fpz-shifted-left and Oz-shifted-right). Other details specific to the experimental setup included the presence of craniotomies over the temporal lobe and effectively insulated (10⁻¹⁴ S/m) electrode strips. Additional details on the experimental setup can found in Huang, Liu, et al., 2017 (Huang, Liu, et al., 2017b). Pearson correlation coefficients of the electric field were calculated between the model and the intracranial recordings for both CSF conductivity conditions. Paired t-test were calculated between conditions.

3.3 Results

3.3.1 Optimization of Emulated CSF in Concentric Spheres Modeling
In concentric sphere models, electric fields generally increased as more of the meningeal layers (from homogenous CSF, to CSF with dura, to CSF with dura and arachnoid, CSF with dura and arachnoid and pia) were added; absolute electric fields increased across the surface and depth of the brain, while relative focality increased (AHM decreased). To understand the sensitivity of these changes to model parameters several montages (2 electrodes at 180, 90, 45, and 5 electrodes in a 4x1 montage) and tissue property assumptions were evaluated (Table 1). Doubling the conductivities of the meningeal layers (Table 1.2) did not produce notable changes in measures of brain electric fields intensity or focally compared to conventional meninges conductivities (Table 1.1). Increasing skull conductivity from 0.01 to 0.08 S/m produced an increase in brain electric field amplitude and relative focality, with addition of meninges either with conventional (Table 1.3) or doubled conductivity (Table 1.4) further enhancing amplitude and relative focality.

For all the conditions noted above, cortical electrical fields were also predicted with a homogeneous CSF compartment (no explicit meninges) with emulated conductivity. A range of CSF layer conductivities in the 6-layered model (0.5 to 1.65 S/m) were simulated, and for each case compared to the corresponding 9-layered model. For absolute electric fields and relative focality, a 6-layered model CSF-compartment conductivity of ~0.85 S/m was found to provide a reasonable approximation of the 9-layered model across electrode montages and other tissue property assumptions. This was robust across conditions; an outcome that was not trivial and supporting the general use of 0.85 S/m as an emulated CSF-compartment approximation.

3.3.2 Emulated CSF in Image-derived Models

Starting with three exemplary MRI-derived models (large, medium, and small) and two montages (M1-SO and 4x1), cortical electric fields were predicted for conventional (1.65 S/m) and emulated (0.85 S/m) CSF-compartment conductivity. An incremental but notable increase in cortical electric
field (ranging from 16-60%) was predicted across all subjects and montages when applying the emulated CSF-layer value in lieu of the conventional value (Fig. 2). There was no gross change in current flow patterns through the brain, such that the M1-SO montage produced diffused and clusters peaks between electrodes while the 4x1 Montage restricted current to inside the electrode rings. Nor was there a change in the ranking of subjects by peak brain electric field for each montage (i.e. the small and large heads had the highest and lowest electric field, respectively, for any given CSF conductivity and montage). Thus, these changes, while notable quantitively, do not necessarily challenge qualitative conclusions from past modeling efforts using conventional CSF conductivity.

Finally, brain current flow was predicted in MRI-derived models of 10 subjects with epilepsy, where intra-cranial voltages were previously recorded during tES [10]. The accuracy of predicted voltage gradients using conventional (1.65 S/m) and emulated (0.85 S/m) CSF-compartment conductivity were compared. Correlation between model and experimental data significantly improved when using emulated CSF conductivity (Fig. 3).

3.4 Discussion

On the one hand, more sophisticated modeling techniques - notably the introduction and now standardized gyri-precise modeling workflow (Datta et al., 2009b) - can advance understanding and practices of tES / tDCS. On the other hand, addition of modeling complexity that does not translate to human trials or clinical practice, may be only of “academic” value (Marom Bikson & Datta, 2012; Shahid, Bikson, Salman, Wen, & Ahfock, 2014). Modeling the skull-brain interface as pure CSF, which is highly conductive, is conspicuous since a substantial fraction of the space is occupied by meninges, which is relatively resistive. The explicit modeling of meningeal layers would dramatically increase computational burden (e.g. 0.05 mm voxel length), and so the cost of
added complexity would need to be justified. However, our approach was to reproduce the relevant outcomes of the presence of meninges simply with an emulated-CSF value. This produced an incremental but validated increase in model accuracy. There is no added computational complexity cost and no impact on segmentation and modeling pipelines (Dannhauer et al., 2012; Huang, Datta, et al., 2017; Jung et al., 2013; Miranda, Mekonnen, Salvador, & Ruffini, 2013b; Parazzini et al., 2011; Sadleir et al., 2010; Windhoff, Opitz, & Thielcher, 2013). We argue that given emulated-CSF increases model accuracy (Fig. 3) with no added implementation cost, it can become the new standard in tDCS / tES modeling. We propose this correction would be equally useful for any models of transcranial brain stimulation that depends on electrical conductivity (Deng, Lisanby, & Peterchev, 2014, 2011; Axel Thielcher, Opitz, & Windhoff, 2011).

There is a general consensus on tissue properties used in tES / tDCS current flow models, (Marom Bikson & Datta, 2012; Dannhauer et al., 2012; Datta et al., 2009b; Jung et al., 2013; Laakso, Tanaka, Koyama, De Santis, & Hirata, n.d.; Miranda et al., 2013b; Opitz et al., 2015b; Parazzini et al., 2011; Sadleir et al., 2010; Wagner et al., 2007b); with deviations (Datta et al., 2009b; Jung et al., 2013; Laakso et al., n.d.; Parazzini et al., 2011) based on variation in assigned tissue conductivity (Akhtari et al., 2002; Baumann, Wozny, Kelly, & Meno, 1997; C. Gabriel et al., 1996; S. Gabriel, Lau, & Gabriel, 1996; Geddes & Baker, 1967; Hoekema et al., 2003). CSF conductivity is not controversial — when isolated. However, this does not address in situ conductivity of the sub-arachnoid space nor correct for volume that should not be occupied by CSF (Felgenhauer, 1974; Merrill, Goldman, Sedman, & Ebert, 1981; Saunders, Habgood, & Dziegielewska, 1999).

The approach we develop here is akin to partial volume mixing formulas used to estimate the effective conductivity of heterogeneous mixtures. Partial volume formulas using MRI intensity to scale CSF conductivity is another possible technique (Laakso et al., n.d.), but qualitative features
of typical T1 and T2 scans makes this approach less robust (image intensities are relative). Nor would such an approach allow levering of the extensively developed tools for tES modeling including automatic image segmentation for subject specific modeling. Rather, CSF-emulation can be immediately integrated into all modeling pipelines and software.

Given the present assumptions of modeling a continuous ~ 1 mm skull-brain interface (as CSF), the ease of implementation, and improved accuracy based on intra-cranial validation, we suggest the skull-brain interface be modeled at a conductivity of 0.85 S/m versus a more conductive pure CSF conductivity (1.65 S/m). There is no cost in regarded to complexity, no need to modify existing modeling tools, and therefore no evident rationale to not emulate CSF moving forward in models of tES techniques including tDCS.
Figure 1: Workflow used to emulate the effect of individual meningeal layers on image-derived head models using spherical models. Detailed image-derived (voxel-based) head models (A1). Whereas image-derived models represent the skull-brain interface as pure CSF (A2), in fact the space includes the meninges (A3). Meninges are intractable to explicitly simulate in a full image-derived head model. Models were simplified to (B1) a vector-based spherical head model where either pure CSF (B2) or presence of meninges (B3) can be modeled. The inclusion of individual meningeal layers within the conventional CSF volume was tested in four montages (C1) to derive an emulated CSF conductivity (C3) to mimic fully detailed (C2) cortical electric field results. The effect of conventional CSF
and emulated CSF conductivities were then compared in imaged-derived head models. While the skull-brain interface remains one compartment ($D_1$, $D_2$), assigning it an emulated conductivity is intended to approximate how the presence meninges would alter brain current flow (brain electric fields $D_3$, $D_4$).

Table 1: Comparison of electric fields produced in the brain using spherical models of varied precision (meninges layers represented) conductivity (skull and meninges) and montages (bipolar at 45, 90, and 180 and 4x1). Minimum and maximum cortical (surface) electric fields, maximum electric field throughout the brain, and percent Area Half Max (AHM). The resulting emulated CSF conductivities ((1) 0.8 S/m, (2) 0.849 S/m, (3) 0.905 S/m, (4) 0.89 S/m) were used...
to arrive at the median emulated CSF conductivity (0.85 S/m) used in the image-derived head models.

Figure 2: Computational models in standard MRI-derived head models comparing brain electric fields using conventional and emulated CSF conductivity. Segmentation masks showing the anatomical view of the layers of three individuals varying in age, gender, and head size. Two montages were modeled for each subject (M1-SO and 4x1). Cortical electric field was
predicted using conventional CSF conductivity or emulated CSF conductivity. A more resistive emulated CSF layer raises the predicted electric field across all subjects and montages.

**Figure 3**: Across 13 trials in 10 subjects, correlations between model-predicted electric field using either conventional or emulated CSF values with in vivo recorded values. Models using emulated CSF conductivity were better correlated to experimental measures compared to models using conventional CSF conductivity (p=0.008, t(12)=3.17). Each line represents a trial (montage and subject combination) and each marker represents a subject. One subject (diamond marker) was assessed under four different montages.
Chapter 4: High-resolution Multi-Scale Computational Model for Non-invasive Cervical Vagus Nerve Stimulation

This chapter is adapted from (Mourdoukoutas, Truong, Adair, Simon, & Bikson, 2018).

4.1 Introduction

Neuromodulation using vagus nerve stimulation (VNS) is a promising treatment for a range of central and peripheral disorders. The vagus nerve is the primary parasympathetic branch of the autonomic nervous system regulating multiple organ systems including breathing, heart rate, peristalsis and gastric emptying. It also plays an important role in the regulation of the body’s inflammatory responses, through an anti-inflammatory pathway mediated by acetylcholine (Bonaz, Picq, Sinniger, Mayol, & Clarençon, 2013; Tracey, 2007). VNS is a potential strategy for treating inflammatory conditions like rheumatoid arthritis and Crohn’s disease (Bonaz, et al., 2013; Tracey, 2007; Zhou et al., 2014), increasing brain training and rehabilitation (S. A. Hays, 2016; Seth A Hays, Rennaker, & Kilgard, 2013; Porter et al., 2012; Van Leusden, Sellaro, & Colzato, 2015), and direct or adjunctive therapy for the treatment of epilepsy (Cukiert, 2015; Panebianco, Rigby, Weston, & Marson, 2015), depression (Grimm & Bajbouj, 2010; Rong et al., 2016), stroke (Ay, Lu, Ay, & Gregory Sorensen, 2009; Ay, Nasser, Simon, & Ay, 2016; Dawson et al., 2016), tinnitus (De Ridder, Vanneste, Engineer, & Kilgard, 2014; Lehtimaki et al., 2013), headache (Gaul et al., 2016; Yuan & Silberstein, 2015), traumatic brain injury (Neren et al., 2016; Pruitt et al., 2016; Smith et al., 2005), post-traumatic stress disorder (PTSD) (George et al., 2008; Pena et al., 2014), and Alzheimer’s disease (C. A. Merrill et al., 2006; Sjögren et al., 2002).

Invasive VNS, with an implanted pulse generator and electrodes coiled around the cervical branch of the vagus, is FDA approved for the treatment of medically refractory epilepsy and major depressive disorder (MDD) (Patil, Chand, & Andrews, 2001; Tronnier, 2015). For the treatment
of epilepsy, VNS has been shown to reduce both seizure frequency and severity (Cukiert, 2015; Panebianco, et al., 2015). In patients with MDD symptom severity is reduced, (Grimm & Bajbouj, 2010; Rong, et al., 2016), though long term follow-up is still ongoing (Albert et al., 2015).

Non-invasive stimulation of the vagus nerve has been developed, using transcutaneous stimulation to target the auricular branch of the vagus nerve at the concha of the outer ear (Aihua et al., 2014; Kraus et al., 2013; Lehtimaki, et al., 2013; Rong, et al., 2016; Van Leusden, et al., 2015) or the cervical branch of the vagus at the neck (Ay, et al., 2016; Gaul, et al., 2016; Stephen D Silberstein et al., 2016; S. D. Silberstein et al., 2016). These devices do not require surgical implantation of a stimulator (Aalbers, Rijkers, Klinkenberg, Majoie, & Cornips, 2015) and therefore have the potential to dramatically increase accessibility to VNS. Cervical nVNS (gammaCore, electroCore LLC) has now been FDA approved for the acute treatment of pain associated with episodic cluster headache (S. D. Silberstein, et al., 2016).

Despite the significant advances in the science and technology of nVNS, questions remain about optimal treatment paradigms, including signal amplitude and dosing regimen. Computational current flow and neuron activation models underpin brain stimulation design. Prior modeling efforts have focused on invasive VNS or peripheral nerve stimulation in general, but have not included the macroscopic and mesoscopic details that may be relevant to nVNS(Jeffrey E. Arle, Carlson, & Mei, 2016; J. E. Arle, Carlson, Mei, & Shils, 2014; Goodall, Kosterman, Holsheimer, & Struijk, 1995; Helmers et al., 2012b). Invasive VNS protocols typically have electrode cuffs positioned directly on the nerve itself, whereas nVNS electrodes are in contact with skin. These prior studies examined the influence of intermediary tissue (scar tissue) relevant to invasive stimulation, but much more tissues exist between nVNS electrodes and the nerve. In this
study, a multi-scale computational approach was taken to predict the cellular targets of cervical nVNS - an essential step toward elucidating and optimizing both treatment and mechanisms. Indeed, our results using an exemplary dose show the importance of previously unrecognized precision in modeling methods (including local tissue) in prediction fidelity.

4.2 Methods

High resolution T1 and T2 MRI-scans (1 mm³ voxels) extending between the C7 vertebra and the vertex were segmented into eleven tissue masks using automated algorithms and manual segmentation techniques as previously described (Tracey, 2007). The MRI-derived model is the first to accurately reproduce details of macroscopic (e.g. skin, muscle) and mesoscopic (vertebra, CSF, anatomical details, nerve sheath) tissues (Figure 1). T1-weighted scans were collected using a GRE sequence with a TR of 1900 ms, TE of 2.2 ms. T2-weighted scans were collected using a SPACE sequence with a TR of 3200 ms and TE of 402 ms. Automated segmentation algorithms were used to create an initial six tissue (skin, skull, cerebral spinal fluid (CSF), grey matter, white matter, air/sinus) model (Ashburner & Friston, 2005; Y. Huang et al., 2013). Post processing filters were used to smooth, close holes and discontinuities, and remove floating voxel artifacts in skull, CSF, and grey matter (Y. Huang, et al., 2013). Additional tissues and anatomical detail was manually segmented in ScanIP (Simpleware, Synopsys) to include fat, muscle, intervertebral disk, and ligaments. Three levels of anatomical detail were prepared, which consisted of uniform soft tissue (skin, fat, ligament and intervertebral disk merged) and a single mask vagus nerve, full anatomical detail with the vagus nerve encapsulated in a connective tissue sheath, and full anatomical detail with a single mask vagus nerve (no tissue sheath) (Fig 1).

An adaptive tetrahedral mesh was generated using voxel-based meshing algorithms contained in ScanIP (Simpleware, Synopsys). Multiple mesh densities were refined to within a 1% error in
voltage and current density at the vagus nerve resulting in a model size of approximately 30M tetrahedral elements for the full anatomy model. Finite element method (FEM) models were generated using the aforementioned meshes in COMSOL Multiphysics to simulate current flow generated through the neck during stimulation. We modeled an nVNS bipolar electrode montage with two, 2 cm radius electrodes separated (center to center) by 4 cm, positioned over the cervical vagus nerve. The Laplace equation for electrostatics ($\nabla \cdot (\sigma \nabla V) = 0$) was applied and solved as the field equation given: insulated ($J \cdot n = 0$) external boundaries, a normal current density equivalent to 30 mA ($J \cdot n \times \text{Area}_{\text{anode}} = 30 \text{ mA}$) on the anode, and a ground ($V = 0$) condition on the cathode. Results were linearly scaled to assess different stimulation intensities corresponding to typical currents used clinically.

The voltage profile along the vagus nerve solved for in FEM simulations was sampled into 1000 transverse slices at a $\Delta x$ of 0.14 mm along the nerve. We considered three related “driving functions” for local nerve stimulation that are fiber independent, and a fourth biophysical fiber specific neuron model. The driving functions where 1) electric field magnitude (Marom Bikson et al., 2015; Deng, Lisanby, & Peterchev, 2013; Wagner, Zahn, Grodzinsky, & Pascual-Leone, 2004), which is reasonable predictor of polarization under the quasi-uniform assumption (M. Bikson, Dmochowski, & Rahman, 2013) – especially with complex neuronal morphology; 2) electric field magnitude along the vagus nerve, which more directly approximates polarization at terminals, branch, and membrane property changes (Arlotti, Rahman, Minhas, & Bikson, 2012; McIntyre & Grill, 1999; Rubinstein, 1993); 3) derivative of electric field along the nerve, which is called the “activating function” and determines local transmembrane current drive (D. R. Merrill, Bikson, & Jefferys, 2005; Warman, Grill, & Durand, 1992a). All these driving function have been previously considered (Ranck, 1975; Tranchina & Nicholson, 1986) and it is beyond
the scope of this paper to judge superiority, but each driving function is derived from the prior one, and contrasting them facilitates understand the role of tissue segmentation detail across this chain – which is an innovation of our work-flow

For the neuron model, the average voltage of each slice was projected into micro-scale models in NEURON (Hines & Carnevale, 1997) to predict nerve activation. Previous studies analyzing compound action potentials in vagus nerves have categorized fibers into three groups: A- (Aα-, Aβ-, and Aδ-), B-, and C-fibers (Gasser & Grundfest, 1939; Hursh, 1939). Voltages were applied as extracellular potentials on a long axon (145 mm) with diameters corresponding to A, B, and C fibers (22, 10, 1 µm). Active and passive parameters were assigned using values from literature (Bahl, Stemmler, Herz, & Roth, 2012; Migliore, 1996). We developed an approach whereby we modeled rheobase thresholds, namely the response to a long duration pulse. This allowed us, as a first approximation, to remove considerations of neuron dynamics and stimulation train parameters such a number, pulse shape, frequency and duty-cycle which while important (Abejon et al., 2015; Rattay, Paredes, & Leao, 2012; Rattay & Wenger, 2010; Sahin & Tie, 2007) would incur a large set of addition fiber specific parameterizations (Helmers, et al., 2012b; Mollet et al., 2013; Pelot, Behrend, & Grill, 2017; Rattay, 1998; Samoudi et al., 2017; Werginz, Fried, & Rattay, 2014)-whereas our focus was to address the role of tissue modeling. The assumption also supports future efforts to optimize stimulation approaches leveraging linearity (see Discussion). Indeed, the wave parameters of the only currently FDA approved nVNS device, gammaCore, are close to rheobase (Reilly, 2012)

Cervical, vagus nerve depth from the gammaCore electrodes was measured by ultrasonography. The average distances from the electrode surfaces to the vagus nerves were 1.27 +/- .20 and 1.24
+/- .26 cm for the right and left sides, respectively so an average of 1.25 cm was used for the modeling. (Lerman et al., 2016)

4.3 Results

For non-invasive vagus nerve stimulation (nVNS), current applied through electrodes on the neck must penetrate ~1.25 cm through varied soft tissue (e.g. muscle) from the skin surface. The overall current path may be influenced by details of head shape (e.g. neck circumference) and deeper tissues (e.g. vertebra). As a first step to model nVNS, we adapted and enhanced a high-resolution model of the head and neck, and simulated current flow using an exemplary macro-electrode montage (Figure 1). Given the complexity of the anatomy (M. Bikson & Datta, 2012), we considered several levels of detail and tissue properties to understand sensitivity to model parameters. The role of macroscale detail was considered by comparing a realistic inhomogeneous model (with each tissue assigned a specific resistivity) with a homogenous model (where all tissues were assigned the same resistivity), and by altering – on both models – the resistivity of the bulk soft tissue (Figure 2). The role of mesoscale detail was considered by adding an insulating tissue sheath around the vagus nerve (Figure 2), as well as by evaluating the role of local tissue changes around the nerve (Figure 3). Finally, micro-scale stimulation of specific nerve activation was modeled across these conditions supporting predictions of sensitivity and selectivity.

Stimulation with macro surface electrodes produced current flow throughout the neck that rapidly decreased with distance from the surface >1.5 cm (Figure 1). At the depth of the vagus nerve (~1.2 cm) the local current density maximum was between the two electrodes. Electric field (E-field) can be quantified by considering intensity along the vagus nerve under various model assumptions (Figure 2). In the homogenous model (Figure 2A) the E-field magnitude (Figure 2A, top) roughly
reflected distance from the stimulation electrodes, and E-field directed along the nerve even more so (Figure A, middle). The derivative of the E-field along the nerve (Figure 2A, bottom) was then a bi-modal profile, with a peak limited by the gradual rate of spatial change of the E-field. Changing tissue resistivity produced an expected linear scaling of all these driving terms.

In contrast to the homogenous case, for the inhomogeneous models, both without (Figure 2B) and with (Figure 2C) a sheath, predicting driving functions were not smooth. While there was a general trend to decrease with distance from the electrode (at large distances from the electrodes there is no significant generated current flow), meso-scale tissue changes resulted in local maxima. The role of local tissue (resistivity) changes in this profile is supported by their co-localization with changes in tissue type (Figure 3) and by the dulling of the fluctuations by the inclusion of a sheath (Figure 2C), which essentially dampens the influence of other local tissues. For the most direct measure of polarization along long axons, using the activating function (Figure 2B, 2C bottom row), the resulting maximum and minimum are also determined by this tissue inhomogeneity – namely when the nerve passes through tissues of varies resistivity there is an associated change in activating function. In the inhomogeneous models, increasing bulk tissue resistivity generally increases driving functions, but with region specific scaling factors, and the location of activating function peaks remains unchanged. To our knowledge this is the first demonstration that meso-scale tissue properties, namely the extension of the vagus nerve through high and low resistivity surrounding tissues, is the governing factor in determining driving functions in nVNS. Moreover, despite the presence of sheaths around major nerves, this is the first modeling of effects of current flow around a nerve. Overall, these results strongly support the importance of state-of-the-art detail in segmentation.
Finally, we considered resulting activation of axon sub-types in the vagus nerve, with separate analysis for the three scales of model detail. The ranking order of sensitivity of A-fibers, followed by B-fibers, and then C-fibers did not change across all modeled conditions (Table 1), consistent with long-standing theory on fiber size and recurrent order (Rattay, 1998; Rattay & Aberham, 1993; Yoshida & Horch, 1993). However, the absolute thresholds (applied nVNS current) varied across models, as expected given changes in the activating function (Figure 2C, bottom). At stimulation intensities comparable to clinical nVNS protocols, the current flow patterns and nerve neurophysiology resulted in preferential activation of A-fibers and large B- fibers. This is consistent with clinical and animal studies showing nVNS effects mediated by vagus firing of predominantly A- and large B- fibers but not the smaller, myelinated B or non-myelinated C fibers responsible for producing bradycardia and bronchoconstriction. (Engel, Blake, & Liebler, 2015; Krahl, Senanayake, & Handforth, 2001)

4.4 Discussion

We developed a state-of-the art computational model to support the interpretation and design of cervical nVNS protocols. We emphasize the difference between a model with “complexity” but without accuracy (i.e. detail for its own sake, incorrectly segmented tissue compartments) and accurate models that prioritize accurate segmentation of the most relevant tissues (M. Bikson & Datta, 2012). The latter requires careful a priori knowledge about structure-function that may exceed resolution of the anatomical (MRI) scans but none-the-less profoundly influences current flow patterns, including tissue continuity. Our model workflow advances nerve stimulation modeling at the macro- (cm) and meso- (mm) scales (Figure 1). At the meso-scale, unlike
geometric models generated using CAD (Jeffrey E. Arle, et al., 2016; Capogrosso et al., 2013; Helmers et al., 2012a), our model captures idiosyncratic differences in anatomy that influence current clustering (Figure 2). At the same time, our findings emphasize that highly “detailed” models that do not validate segmentation accuracy (Howell & McIntyre, 2016; Parazzini et al., 2014) are subject to spurious results. Our simulations indicate that the inhomogeneous properties of tissue immediately surrounding nerves strongly influence membrane polarization by stimulation. Passage of axons along tissues with varied conductivities (e.g. soft tissue to bone) leads to a sudden change in electric field (activating function) that, in turn, increases axon membrane polarization (Figure 3B). However, the presence of encapsulating tissue, such as a fat sheath, can effectively dull these electric field transients, reducing axon membrane polarization (Figure 3C). In contrast to the role of local tissue properties, macro-scale tissue properties (tissue between the electrodes and the nerve) influence the total current delivered near the target, which scales the electric field along the axon (Figure 2, colored lines) untimely influencing polarization magnitude.

Our approach to modeling nerve activation was heuristic but supported by more sophisticated biophysical studies. The maximal polarization achieved at any given intensity, for arbitrarily long pulses, was predicted by the response to a DC (static) field. Moreover, this step function-based threshold should approximate polarization achievable by optimized pulse trains – based on consideration of single cell dynamics as a low-pass filter. This step is methodologically important and novel as it linearizes an otherwise complex optimization problem. This method ignores non-linear contributions of complex membrane dynamics (e.g. resonance) (Stacey & Durand, 2000) or synaptic (Rahman et al., 2013) and network effects (Reato, Rahman, Bikson, & Parra, 2010a), but is especially reasonable for axons of passage (axons that do not terminate or initiate near the
electrodes) (McIntyre & Grill, 2000) as the case for cervical vagus nerve stimulation. Using step-function based thresholds would not capture relative differences in strength-duration (e.g. chronaxie) between fiber types such as A and C. (Reilly & Diamant, 2011)

As linearity is preserved, this approach lends itself to efforts to automatically optimize stimulation approaches (M. Bikson & Datta, 2012). For any given axon morphology and biophysics, electrode montage, and tissue properties, the stimulation current threshold to activate an action potential can be calculated. In turn, this means that (given the same electrode montage and modeling assumptions) for any given applied current, which axons can be activated (assuming optimized waveform) can be predicted. This in turn allows understanding axon recruitment and selectivity for any given stimulation approach (independent of waveform), and supports tractable optimization efforts using a look-up-table matching stimulation dose with axon threshold. Importantly, accurate modeling of tissue properties (see above) can categorically influence activation prediction (Table 1). Our modeling advancements for macro/mesa-scale current flow (based on tissue representation) and micro-scale nerve activation (DC-Rheobase look-up-table) generalize to a wide range of brain stimulation models spanning spinal cord stimulation (Capogrosso, et al., 2013; Laakso et al., 2014; Parazzini, et al., 2014), cortex/deep brain stimulation (Butson, Cooper, Henderson, & McIntyre, 2007; Iacono, Makris, Mainardi, Angelone, & Bonmassar, 2013; McIntyre, Grill, Sherman, & Thakor, 2004), and peripheral/cranial nerve stimulation (Krasteva, Papazov, & Daskalov, 2003; Parrini, Delbeke, Romero, Legat, & Veraart, 1999; Warman, Grill, & Durand, 1992b).
In trying to encompass the scale needed for non-invasive stimulation, some limitations did arise. Previous VNS models (Jeffrey E. Arle, et al., 2016; J. E. Arle, et al., 2014; Helmers, et al., 2012b; McIntyre, Richardson, & Grill, 2002; Zhu, Li, Wei, & Sui, 2017) have considered finer physiological detail including distribution of fibers in fassicles, varying fiber dynamics, blockage threshold, and the presence of local polarity peaks (virtual anode and cathodes). These studies can be leveraged in future work to develop more physiologically detailed models. Future models of nVNS can explore the effects of interindividual anatomical differences, varied electrode designs and locations (Jacek P Dmochowski, Abhishek Datta, Marom Bikson, Yuzhuo Su, & Lucas C Parra, 2011), and experimental validation of current flow and target engagement (Hammond, Uthman, Reid, & Wilder, 1992) (Nonis, D'Ostilio, Schoenen, & Magis, 2017) (Jog et al., 2016) (Yu Huang et al., 2017).

Notwithstanding these potential refinements, the methods developed in this study provide a foundation for modeling non-invasive vagus nerve stimulation from macroscale image-derived data, including the ability to predict nerve sensitivity and selectivity. This workflow is exemplified for the case of non-invasive electrical stimulation of the cervical vagus nerve. We predicted, using a specific electrode montage, that at a typical clinical applied current of ~ 10 mA, electric fields produced along the right vagus nerve are sufficient to activate A-fibers and larger B-fibers but not C-fibers (based simply on fiber diameter). These models support emerging clinical evidence of efficacy and tolerability (Aihua, et al., 2014; Gaul, et al., 2016; Stephen D Silberstein, et al., 2016; S. D. Silberstein, et al., 2016) that properly designed non-invasive vagus nerve stimulation is a targeted neuromodulation tool, and can be an alternative to an implanted stimulator, without the associated morbidities.
Figure 1: High-resolution model of nVNS current flow. (A) MRI derived model including bone, brain, muscle and other soft tissue masks, and vagus nerve (green). (B) Stimulation of nVNS with electrode placement showing flux lines map gross current flow patterns through neck, with false color of local current density (>10 A/m$^2$ max). Gross current flow patterns are determined by electrode position and anatomy. (C) Inset showing expansion of current flow around vagus nerve (1.44 A/m$^2$ max) using the given electrode montage. (D) Arrow plots of gross current density pattern and current density on vagus nerve in false colors. The current density (proportional to electric field) along the nerve supports the prediction of activation, depending on fiber type. All models are under the quasi-static assumption with the anode in red and cathode in blue for illustration of instant direction.
Figure 2: Role of tissue properties around nerve in predicting driving forces for activation. Three drivers of neuronal polarization: Electric field magnitude (top row), electric field component aligned with the nerve (middle row), and spatial derivative of electric field (activating function) in the direction of the nerve (bottom row). Three conditions of tissue detail are modeled: (A, first column) simplified homogenous soft tissue (muscle, fat, ligament, intervertebral disk merged); (B, second column) full inhomogeneous soft tissue anatomy without a fat sheath surrounding the vagus nerve; (C, third column) full inhomogeneous soft tissue anatomy with a fat sheath surrounding the vagus nerve. In each case, soft tissue conductivity was doubled (red), unaffected (blue) and halved (green). Whereas in a simplified homogeneous soft tissue case (A) drivers of activation are smooth, with full inhomogeneous soft tissue anatomy (B, C) local maximum are observed (0.217 m, 0.250...
m and 0.269 m) corresponding to changing tissue around the nerve (see Figure 4). The addition of a sheath generally dulls the influence of these transitions.
Figure 3: Illustration of local tissue inhomogeneity around nerve leading to transients in drivers of activation. (A) 0.180 m (B) 0.217 m (C) 0.250 m (D) 0.263 m (E) 0.269 m. Five anatomical cross sections showing cases in which either fat and soft tissue (A, B, C, E) or just fat (D) borders the vagus nerve. Slices (B, C, D, E) are relatively close to the stimulating electrodes while slice (A) is relatively far.
Table 1: Nerve fiber threshold and activation selectivity under varied tissue models. For each stimulation current, a check indicates action potential generation (current above rheobase threshold) while a cross indicates no action potential generation (current below rheobase threshold). (A) Condition of full soft tissue compartment. (B) Condition of full anatomy without a fat sheath surrounding the vagus nerve. (C) Condition of full anatomy with a fat sheath surrounding the vagus nerve. In general, the lowest thresholds were predicted for the condition of full anatomy without sheath (B) corresponding to the most significant driving functions (Figure 2). For a similar reason, addition of a sheath in the full model (C) slightly increases thresholds. In all cases, thresholds decreased for larger nerves. Macro- and meso-scale anatomical details thus influence predictions on fiber type activation threshold and so selectivity.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Rheobase: 1 mA</th>
<th>10 mA</th>
<th>30 mA</th>
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<tbody>
<tr>
<td>A (22 μm)</td>
<td>X</td>
<td>✓</td>
<td>✓</td>
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Conclusion & Discussion

Clinically applied models of non-invasive stimulation aim to relate stimulation dose to a predictor of neuromodulation. This can be used to prospectively inform electrode position and stimulator intensity, or assessments can be made regarding stimulation focality and efficacy after the fact. Changes in model parameters are worthwhile if they can influence these results. In the case of modeling fat in obese subjects, no correlation was found between BMI or fat thickness and cortical electric fields. Even when accounting for individual variability by modulating fat within a subject, physiologically extreme dilations (12 to 16 mm) in subcutaneous fat resulted in non-monotonic changes that were relatively small (< 30%) in comparison to inter-subject and montage variability.

In the case of CSF and meninges emulation, however, subtle changes in CSF conductivity were found to improve model predictions in a validated dataset. While these changes in predicted cortical electric field were again relatively small (<30%), the cost of implementation is minimal. Using a combined CSF-meninges conductivity is a simple actionable update that can be applied to existing model pipelines. Individualized conductivities or additional segmentation masks have the potential to improve accuracy as well, but the increased complexity of those methods would limit immediate application.

While fat had a relatively small effect on cortical electric fields in tDCS, in nVNS skin/soft tissue parameterization matters. The addition of fat and muscle as well as connective tissue affected predicted fiber type activation. Anatomically, the vagus nerve is directly surrounded by this soft tissue mask whereas the brain has skull and CSF. The segmentation and parameterization of this tissue domain had a direct impact on modeling results. NVNS being understood to have a
suprathreshold mechanism also had a distinct predictable non-linearity in contrast with tDCS where cortical electric fields and efficacy are interpreted in relative terms.

In the future, the ideal validation experiment would be to use direct intra-cranial recordings in a range of obese subjects. Direct recordings of people before and after weight gain or weight loss would be ideal to control for inter-individual variability, but the practical circumstances to allow this could be prohibitive. Direct intracranial recordings of transcranial stimulation have only been published twice in recent years (Huang, Liu, et al., 2017a; Opitz et al., 2017). These experiments were made possible through epileptic patients awaiting surgery. If this dataset is expanded to include subjects with a range of BMI's, models incorporating subcutaneous fat could be used to predict recorded fields.

Animal models of non-invasive stimulation may be more practical in this regard. Models could simulate experiments using invasive recording electrodes. Some preliminary work in non-invasive stimulation models in animals has been completed (Song, Truong, Bikson, & Martin, 2015). Experiments using implanted electrodes could be used to directly measure induced fields. For suprathreshold modalities (i.e. nVNS), compound action potentials (CAP) can be recorded. The shape of the CAP can be used to calculate conduction velocities and estimate fiber type composition (Bailey & Bremer, 1938; Chase et al., 1966; Woodbury & Woodbury, 1990).
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