INTRAORAL NEUROMODULATION TO TREAT SWALLOWING DISORDER AND OBSTRUCTIVE SLEEP APNEA, BASED ON ELECTRICAL CHARACTERIZATION OF THE TONGUE AND SOFT PALATE

A Thesis

by

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ABSTRACT

Intraoral functions are results of complex sensorimotor loop operations, and therefore vulnerable to the small functional or neural defects. To secure the vital intraoral functions, it is important to find a way to favorably intervene the intraoral sensorimotor loop operations. The tongue and the soft palate are heavily associated with several sensorimotor loops for intraoral functions, with their dense neural innervations and occupancy of intraoral space. Electrical neuromodulation onto the tongue and the soft palate have a great potential to solve the problems in intraoral functions, such as swallowing, breathing, and talking. However, both the tongue and the soft palate have not been characterized well yet for electrical neuromodulation. In this study, we characterized electrical impedance between electrodes across the tongue and the soft palate, measured stimulation thresholds for perception, and identified type of perception evoked by the stimulation. For impedance characterization, we selected R-R-C model, which is typically used for skin impedance characterization. We found the equivalent series resistance, parallel resistance, and parallel capacitance values for R-R-C model, as 1.837 kΩ, 5.741 kΩ, and 30.148 nF, respectively. We also found that the perception thresholds for the tongue tip, lateral-inferior side of the tongue, and the soft palate as 0.16, 0.34, and 1.47 mA, respectively. As the amplitude of stimulation increases, subjects felt more natural pressure-like sensation than electrical tingling, in all three locations. Subjects could not distinguish the temporal difference of perception between 25 and 100 Hz well. The discomfort at the highest amplitude of stimulation was described as stabbing on the soft palate and stiffness on the tongue. Based on the electrical characterization of the tongue and the soft palate, we found out the effect of electrical neuromodulation, onto the tongue and the soft palate, on the pharyngeal phase of swallowing and obstructive sleep apnea, which is one of the most important intraoral sensorimotor loop operations.

ACKNOWLEDGMENTS

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Contributors

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All other work conducted for the thesis was completed by the student independently.

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NOMENCLATURE

OSA	Obstructive Sleep Apnea
CDC	Center for Disease Control and Prevention
TTOS	Thermal Tactile Oral Stimulation
NMES	Neuromuscular Electrical Stimulation
MEMS	Micro-Electro-Mechanical System
R_S	Series Resistance
R_P	Parallel Resistance
C_P	Parallel Capacitance
PT	Perception Threshold
DT	Discomfort Threshold
MT	Middle Threshold
AT	Activation Threshold
TT	Tongue Tip
TS	Lateral-Inferior Side of the Tongue
SP	Soft Palate

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1. INTRODUCTION AND PROBLEM STATEMENT

The intraoral space is the first and sometimes also the last gateway for the interaction between the body and the outside for several vital functions such as mastication, swallowing, breathing, and talking. Because they are outcomes of the series of well-orchestrated voluntary and involuntary sensorimotor loops, they are vulnerable to the small functional or neural defects caused by physical or pathological nervous system damage, neurodegenerative diseases, or even aging. For example, stroke, spinal cord injury, head and neck cancer, and Parkinson's disease often cause problems in swallowing, with issues in pharyngeal muscle coordination for involuntary phase of swallowing [1]. Alzheimer's disease, Parkinson's disease, and pneumonitis increase suffocation rate, especially in elderly, because of the decreased functionality of mastication and swallowing [2]. Emotional trauma and even anxiety, as well as stroke and traumatic brain injury, often result in speech problems like stuttering, following problems in subtle tongue motor control [3]. Combination of obesity and aging often deteriorates obstructive sleep apnea (OSA), by narrowing down the airway for breathing and/or decreasing the agility of the posterior part of the oral tongue [4].

The tongue and the soft palate play an important role in intraoral operations. The tongue and the soft palate are heavily associated with several intraoral sensorimotor loops, which take part in vital intraoral operations (e.g., mastication, swallowing, breathing, and talking), as shown in Fig. 1. They are intriguing intraoral organs occupying most of the intraoral space, and composed of complex neuromuscular structure. The tongue occupies ~87 % of the volume of the oral cavity for human [5], and is composed of unique muscular structure like heart muscles, therefore it experiences minimal fatigue after demanding tasks such as talking and mixing the food during eating. The agile movement of the tongue is also critical for the mastication, swallowing, breathing,

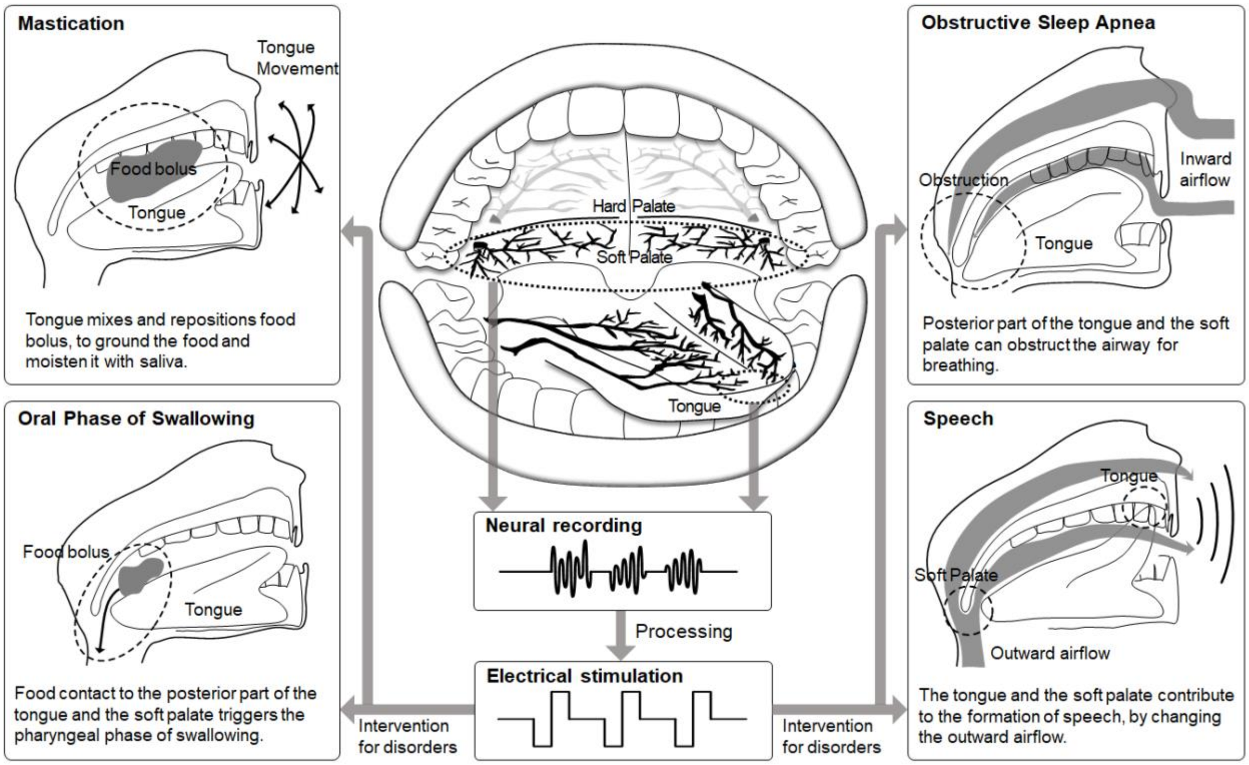


Figure 1.1. The four representative intraoral sensorimotor loop operations, where the tongue and the soft palate play an important role. Block diagram of closed-loop neural recording and stimulation and dense innervation of cranial nerves in the tongue and the soft palate are also shown, which can be used to intervene the intraoral sensorimotor loops.

and talking. The soft palate covers the posterior area of the intraoral space, and interacts with food, saliva, air, and the tongue. The soft palate is also changing its shape dynamically during swallowing, breathing, and talking [1, 6, 7].

A neurological disorder of the feeding mechanism in swallowing, referred to as dysphagia, means a food bolus and liquid bolus lead to causing problems while they reach from the mouth to the stomach through pharynx and esophagus. Dysphagia prevails among adults of 4.0 % annually and the average number of days affected is 139 days per year [8]. Occasionally, dysphagia induces life-threatening health conditions such as achalasia, dehydration, aspiration pneumonia, chronic lung disease, and choking [9]. A majority of patient groups, who suffer from neurodegenerative disease such as Parkinson's disease, post-stroke and Alzheimer's disease, are susceptible to dysphagia. In addition, elderly people who have sarcopenia are likely to have sarcopenic dysphagia. According to the Center for Disease Control and Prevention (CDC), Parkinson's disease is the second most common neurodegenerative disease after Alzheimer's disease and stroke is the fifth leading cause of deaths in the United States. Moreover, Parkinson's disease and Amyotrophic Lateral Sclerosis results in 90% of patients to suffer from mild to extreme dysphagia [10]. In this regard, dysphagia needs to be managed effectively to prevent the patients from unexpected health threats by providing rehabilitation.

Currently, swallowing exercises, dietary changes, surgery and neuro-muscular stimulation are utilized to treat pharyngeal dysphagia [11]. Neuromuscular stimulation has huge potential because it opens the possibility of providing direct intervention to the nerves and muscles responsible for swallowing. One approach, which stimulates the intraoral sensory receptors, is referred to as thermal-tactile oral stimulation (TTOS) [12]. A cold laryngeal mirror or an iced lemon glycerin swab is used to stimulate areas around the oropharynx, such as the faucial arches, the soft palate, and the back of the tongue.

Another approach, which stimulates the pharyngeal muscles, is referred to as neuromuscular electrical stimulation (NMES) [13]. Surface electrodes are attached to the neck region and under the chin to stimulate the underlying muscles used for swallowing. Most of the NMES devices, currently available in the market, target a wide area of the mouth or neck for simulation because of the complexity of the muscular structure in the neck region. This broad targeting requires large electrodes for stimulation, thereby reducing the spatial resolution of the stimulation. Additionally, most of these devices don't track the swallowing activity of a patient and therefore don't target the simulation with the swallowing phase. This leads to low temporal resolution of the device. The density of muscles in the neck region also increases the power required for stimulation leading to sharp pain being experienced by patients.

Multiple branches of cranial nerves (V, VII, IX, X, XII) are innervated onto the tongue for the intraoral sensorimotor operations [14]. For example, posterior and lateral-inferior side of the tongue is innervated by glossopharyngeal and hypoglossal nerves, which contribute to triggering of the pharyngeal phase of swallowing, control saliva secretion, and control extrinsic muscles of the tongue [15, 16]. While the hard palate is mainly composed of bony structure with minimal innervation of nerves, the soft palate is innervated by cranial nerves, such as lesser palatine nerve and tonsillar branch of glossopharyngeal nerve, which also contribute to triggering of the pharyngeal phase of swallowing [17-19]. The sphenopalatine ganglion, located a few mm above the soft palate, is known as delivering neural signal contributing to migraine [20]. The importance of the tongue and the soft palate for intraoral sensorimotor operations, known till now, may be a tip of iceberg considering the complex innervation of cranial nerves, and the investigation is still on-going [17, 21].

It is important to design effective intervention to modulate the intraoral sensorimotor loop operation. Therefore, intervening the sensorimotor loop operations, via the tongue and the soft palate, would play an important role in addressing the problems of swallowing. There are largely two major challenges to effectively intervene the intraoral sensorimotor loop operation of swallowing via the tongue and the soft palate: 1) Implementation: whole system should be integrated well into the small intraoral device without interfering with the natural intraoral functions and 2) Interfacing: intervention of the intraoral sensorimotor loop operation of swallowing should be done via a specific intraoral interface that is effective on modulating the sensorimotor loop operation.

Wearable and implantable implementation to intervene intraoral sensorimotor loop is feasible. With advancement of integrated circuit (IC) fabrication and design techniques, micro-electro-mechanical systems (MEMS) technology, and wireless power transfer between small magnetic coils and high-efficiency rectification techniques, size of the electrical system and the battery became small enough to be integrated inside the mouth [22-24]. Indeed, the intraoral recording and stimulation systems could be implemented as a form of dental retainer or braces to monitor tongue movement or masticatory force of the teeth and to stimulate tongue muscles [25-28]. Intraoral systems with similar functions could be also implemented as implantable devices and integrated into the tongue or the soft palate [29, 30].

To intervene sensorimotor loop via the tongue and the soft palate, electrical stimulation is a promising candidate. Electrical stimulation showed its efficacy on sensorimotor loop intervention in several body operations, such as gait modulation and excitation of peristalsis [31-33]. The upper-limb prosthesis with bi-directional neural interface showed that electrical nerve stimulation could evoke natural tactile feedback and enabled fine prosthetic finger control [34]. Electrical stimulation has also shown its efficacy by being applied to the tongue and the soft palate, on modulating the intraoral sensorimotor loop operation [21, 35, 36], and further investigation is currently on-going. Also, electrical stimulation does not need bulky mechanical structure as the current pulse is all it needs, which enables miniaturization of the system to minimize the user discomfort.

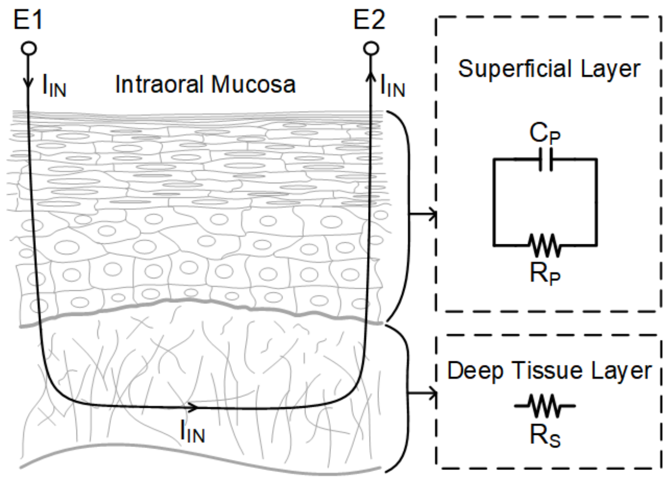
Characterization of the electrical impedance across the tongue and the soft palate is critical, for effective neuromodulation. To design the right circuitry for neural stimulation and to promote the effectiveness of the neuromodulation, characterization of the electrical impedance across the tongue and the soft palate is critical. Indeed, it is an urgent issue considering the importance of vital intraoral functions and to meet the increasing needs of intraoral neuromodulation system [21, 27, 37]. Till now, characterization of the electrical impedance across the tongue and the soft palate have been reported with limited information. Although the impedance of the tongue, buccal mucosa, labial mucosa, and hard palate was reported, the measured frequency ranges are over kHz range that is outside of the frequency of neuromodulation [38, 39]. Note that, the effective frequency range for neuromodulation is around 10-200 Hz, based on the experiments in human and also the firing rate of action potential [40-42]. Study on the soft palate for the neuromodulation is even further limited than that of the tongue. Not only the electrical characterization of the soft palate has not been studied yet, but also the anatomy on soft palatal nerves is still in question and active research is currently on-going [17].

Characterization of the perception is important to study the effect of electrical stimulation. Several cranial nerves innervated onto the tongue and the soft palate play an important role in delivering sensory information (e.g., glossopharyngeal and lesser palatine nerves) [17, 43]. Also, the thresholds for activating sensory feedback is usually much lower than those for activating the muscle, which makes the sensory augmenting feature of the electrical stimulation more practical in neuromodulation [44]. Characterization of the perception is a useful way to investigate the sensory augmentation aspect of the electrical stimulation, especially in human study [45]. The cranial nerves innervating onto the tongue and the soft palate are hardly accessible without highly invasive surgery [46, 47]. Also, even though the nerves become accessible by surgery, it would be challenging to decode the recorded compound action potential considering the complex interweaved anatomy of the cranial nerves.

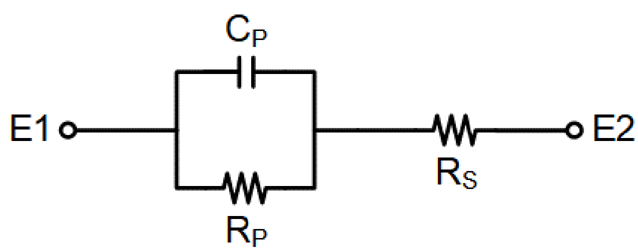
In this study, we firstly characterized the electrical interface on the tongue and the soft palate in three ways: 1) Measurement of electrical stimulation thresholds for perception and discomfort, respectively, to find the right amplitude and frequency for sensory augmentation, and 2) Identification of the perception evoked by stimulation with selected amplitude and frequency, using the Likert-scale questionnaires, 3) Characterization of electrical impedance between electrodes mounted on the tongue and the soft palate, 4) Neuromodulation based on the characterization. Based on the electrical characterization of the tongue and soft palate, we tested the efficacy of electrical neuromodulation to change the amplitude and timing of the pharyngeal phase of swallowing, to open upper airway caused by obstruction of soft palate and the tongue, and to test the potential of electrical neuromodulation to treat dysphagia and OSA.

2. IMPEDANCE MODELING AND SYSTEM IMPLEMENTATION

2.1. Modeling Impedance between Electrodes across the Tongue and the Soft Palate



(a)



(b)

Figure 2.1. a) Physiological model of oral mucosa, with the conversion process into simplified equivalent impedance circuit model and (b) Equivalent impedance circuit model. E1 and E2 represent bipolar stainless-steel electrodes attached onto the tongue and the soft palate. The black line in (a) shows current path through stratum corneum, superficial tissue layer, and deep tissue layer between E1 and E2.

As the skin and the oral mucosa have similar tissue structure to each other, we adopted the R-R-C model, as in Fig. 2.1 [48-50]. The superficial layer of the oral mucosa is similar to the epidermis of the skin, as in Fig. 2.1a, although the contact impedance would be a bit smaller with a watery surface. The underlying connective tissue structure is also similar to the dermis of the skin, although the composition is a bit different [51]. Based on the R-R-C model, we characterized the electrical interface between the electrodes across the tongue and the soft palate. The total impedance between electrodes can be expressed as eq. (1) and the voltage formed between electrodes by current input can be expressed as eqs. (2) and (3) in s-domain and time domain, respectively.

$$Z(s) = R_S + \frac{R_P}{1+s \cdot R_P \cdot C_P} \tag{1}$$

$$V(s) = I(s) \cdot (R_S + \frac{R_P}{1+s \cdot R_P \cdot C_P}) \tag{2}$$

$$v(t) = i(t) \cdot R_S + i(t) \cdot R_P \cdot \left(1 - e^{-t/R_P \cdot C_P}\right) + d \tag{3}$$

2.2. Selection of the Locations for Electrical Characterization

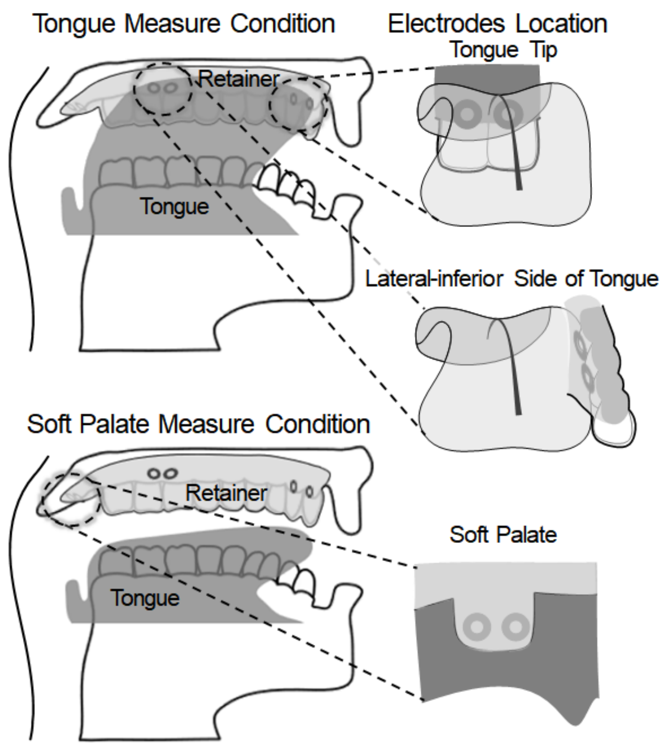
We first selected the tongue tip, as the location has high spatial resolution to be used for sensory substitution [52, 53]. The tongue tip can be used to detect the beginning of involuntary swallowing phase [54]. The taste buds for sweetness are also located on the tongue tip, which opens the potential for virtual sweet to treat diabetes [55]. We also selected the lateral-inferior side of the tongue, innervated by glossopharyngeal and hypoglossal nerves, which play an important role in tongue movement during mastication, saliva secretion, and involuntary swallowing [16, 19, 56]. Finally, we selected the medioanterior side of the soft palate, in between the mid-palatal line and the 2nd molar, where the lesser palatine nerve and the tonsillar branch of glossopharyngeal nerve are located. Note that stimulation on tonsillar branch of glossopharyngeal nerve was effective on eliciting reflex swallowing [57] and stimulation on sphenopalatine ganglion, where lesser palatine nerve is branched out, was effective on relieving migraine [58].

2.3. Preparation of Dental Stone and Dental Retainer for Each Subject

Dental impression was fabricated for each subject in the lab, using disposable dental impression trays and alginate powder. Dental stone was then fabricated for each subject in the lab, using dental stone powder, as an engraving on the dental impression. The upper dental retainer was then fabricated as Essix-type dental retainer in the lab, by pressing 1-mm thermoforming dental sheet onto the dental stone using the vacuum forming machine.

2.4. Preparation and Integration of Electrodes onto the Dental Retainer

For electrical analysis of the tongue and the soft palate, the electrodes are essential to electrically interact with the intraoral space. We selected stainless-steel bipolar electrodes, which are bio-compatible and small enough to be used on both the tongue and the soft palate. Multi-threaded bio-compatible stainless- steel wires were welded onto the stainless-steel electrodes. For the electrodes to stay onto the surface of the tongue and the soft palate, we integrated the electrodes onto the upper dental retainer customized for each subject. As in Fig. 2.2, three pairs of electrodes were adhered to the retainer, on the designated locations of the tongue and the soft palate. The 1st pair is located at the posterior side of the central incisor, for the tongue tip to contact easily [54]. The 2nd pair is located superior to the 2nd premolar and the 1st molar, for the lateral-inferior side of the tongue to contact easily. The 3rd pair is located on the medioanterior side of the soft palate, in between the mid-palatal line and the 2nd molar. Note that the 3rd pair is located on the top of the retainer to access the soft palate, while the other two pairs are located on the bottom of the retainer to contact to the tongue.



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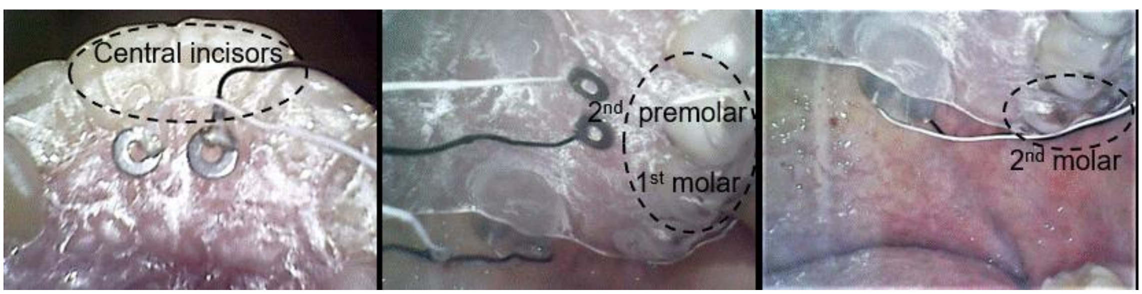


(b)

Figure 2.2. (a) Graphical description of the intraoral electrodes embedded onto the retainer and tongue postures to measure the characteristics of electrical interface onto the soft palate, the tongue tip, and the lateral-inferior side of the tongue; (b) Actual implementation of intraoral electrodes mounted onto the Essix-type palatal retainer, for each of three intraoral locations.

2.5. System Implementation for Electrical Characterization and Neuromodulation

We adopted the step-response method for characterizing electrical impedance, instead of impedance spectroscopy using different frequencies of sine waves, for the following two reasons. First, step-response method is known to provide accurate parameter estimation if the model is based on resistor and capacitor [59, 60]. Secondly, electrical stimulation usually employs square wave instead of sine wave, and therefore characterization using square wave would better model the impedance for stimulation. To evaluate the thresholds for stimulation and perception evoked by the stimulation, bi-phasic control signals were produced, in a similar way as the step current was produced. For characterizing the perception threshold and type of perception, constant-current stimulation was selected over constant-voltage stimulation, to avoid potential tissue damage with high current. To minimize the charge imbalance, bi-phasic current stimulus was selected [61].

ATmega328 microcontroller, along with a unipolar to bipolar output converter, generated a step or bi-phasic control signal, for characterizing impedance, and perception, and neuromodulation, respectively. The analog-to-digital converter embedded in the ATmega328 read the voltage output in response to the step current, for characterizing impedance. The Howland current pump generated a bi-phasic current stimulus according to the bi-phasic control signal, for characterizing perception. The electronics was connected to the stainless-steel bipolar electrodes via bio-compatible stainless-steel wires through the side of the mouth in between the lips. The electrical system was also connected to the computer via USB interface, for the operator to trigger the current stimulus and to save the voltage output. For neuromodulation for dysphagia, we additionally used 3-axis accelerometer ADXL337 that generate voltage output for each x,y, and z direction.

3. EXPERIMENTAL DESIGN

3.1. Human Subject Recruitment

The experiment was performed in accordance with relevant guidelines/regulations, according to the procedure described in the protocol approved by the Institutional Review Board of Texas A&M University (IRB2017-0781F). The informed consent was collected from all subjects. Six healthy human subjects participated in the study. Subjects consisted of four males and two females. All subjects were over the age of 18, and the average age of subject group was 29.5 years. During the whole test period, subjects were asked to wear their customized Essix-type palatal retainers, integrated with three pairs of electrodes on the tongue and the soft palate.

3.2. Selection of Frequencies for Stimulation Test

We selected two frequencies for stimulation: 25 and 100 Hz. 25 Hz was selected to represent the low-frequency stimulation, which is similar to the firing rate of cutaneous afferent volley [62]. It has also been reported that 20-30 Hz stimulation was successful in neuromodulation of the bladder or bowel having similar mucosal structure [63, 64]. 100 Hz has been selected as this frequency has been used as a rule of thumb for transcutaneous electrical stimulation to evoke electrotactile feedback [65, 66]. The studies with fingertip further justify the use of both frequencies, as the perception for electrotactile feedback is different between stimulation with frequencies below 40 Hz and the stimulation with frequencies over 70 Hz [67].

3.3. Experiment 1: Thresholds for Perception and Thresholds for Discomfort

Experiment 1 was designed to determine the amplitude of current for electrical stimulation to evoke perception. We set two kinds of thresholds: 1) the minimum current level where subjects reported any sensation (i.e., perception threshold; PT), and 2) the maximum current level where subjects reported any discomfort by the stimulation (i.e., discomfort threshold; DT). We identified

PT and DT for each subject, for three different intraoral locations, at two different stimulation frequencies: 25 and 100 Hz.

3.4. Experiment 2: Identification of the Perception

In experiment 2, we identified the perception associated with selected frequency and amplitude, with the Likert-scale questionnaires. We selected amplitudes as PT+(DT-PT)×0.1, PT+(DT-PT)×0.5, and PT+(DT-PT)×0.9, for each frequency. We intentionally placed 10% margins for both minimum and maximum amplitudes to address the adaptation and temporal variation of the biological system.

After each set of stimulation was applied, subjects were asked to complete survey questionnaires, to evaluate their perception regarding “tingling vs. pressing” and “pulsing vs. buzzing”. The first criteria (tingling vs. pressing) provides an idea of how natural the electrotactile feedback is, and the second criteria provides an information of the temporal sensory resolution in each area. We also asked subjects’ perception regarding “stabbing vs. stiffness”, when they reported discomfort at the maximum amplitude.

3.5. Experiment 3: Electrical Impedance Characterization

In experiment 3, we characterized the impedances between electrodes mounted on the tongue tip, lateral-inferior side of the tongue, and the soft palate, respectively. A step function of the current input was applied to each area and the voltage output was recorded in real time. For the tongue-tip, subjects were asked to move the tongue tip forward and softly push the electrodes located on the retainer at the posterior side of central incisors. For the lateral-inferior side of the tongue, subjects were asked to lift up and softly contact the tongue to the position of electrodes. For the soft-palatal area, the electrodes were located between the upper side of the retainer and the soft palate, and subjects were asked to locate their tongue at the resting position (i.e., bottom side of the mouth) to avoid any interference.

Two subjects (1 male, 1 female) finished total 5 times of the impedance test per each site, for the data integrity. For the impedance test, we applied PT and middle threshold (MT) which is (PT+DT)/2 current input as a single step function for 1 milli-second to figure out the parameters by curve fitting [68]. The amplitude of the current was set as PT to be minimum sensory threshold value for the subjects [69]. The time for the current input was set as 1 milli-second, to characterize electrical impedance with the same pulse width we used for stimulation.

3.6. Experiment 4: Neuromodulation Based on the Characterization

In experiment 4, we electrically stimulated on the soft palate for dysphagia and on the tongue for OSA in order to validate the effect of neuromodulation based on the characterization from the experiment 1, 2, and 3. We selected 100 Hz, and applied bi-phasic current stimuli to the soft palate for dysphagia, and to the tongue for OSA with the current amplitude between PT and DT. We monitored the superior-inferior (x-axis) and anterior-posterior (z-axis) direction movement timing of laryngeal excursion during 10 times swallowing a sip of water for dysphagia, and monitored the moment of upper airway opening change with sound change of exhalation airflow after inhalation during 3 times electrical stimulation on the medial-inferior side of the tongue (i.e., activation threshold; AT) for OSA.

4. EXPERIMENTAL RESULT

4.1. Experiment 1: Thresholds for Minimal Perception and Any Potential Discomfort

The perception and discomfort thresholds (i.e., PT and DT) are summarized in Fig. 4.1. PT was measured as 0.19/0.39/1.76 (TT/TS/SP) and 0.14/0.29/1.17 mA, for 25 and 100 Hz of stimulation frequency, respectively. DT was measured as 1.33/4.03/10.97 and 0.92/2.88/7.28 mA, for 25 and 100 Hz of stimulation frequency, respectively. Among three intraoral locations, the tongue tip showed lowest threshold for the current stimulus to evoke electrotactile perception. For all three locations, both PT and DT did not change by the stimulation frequency, although there was a weak tendency of increase at lower frequency.

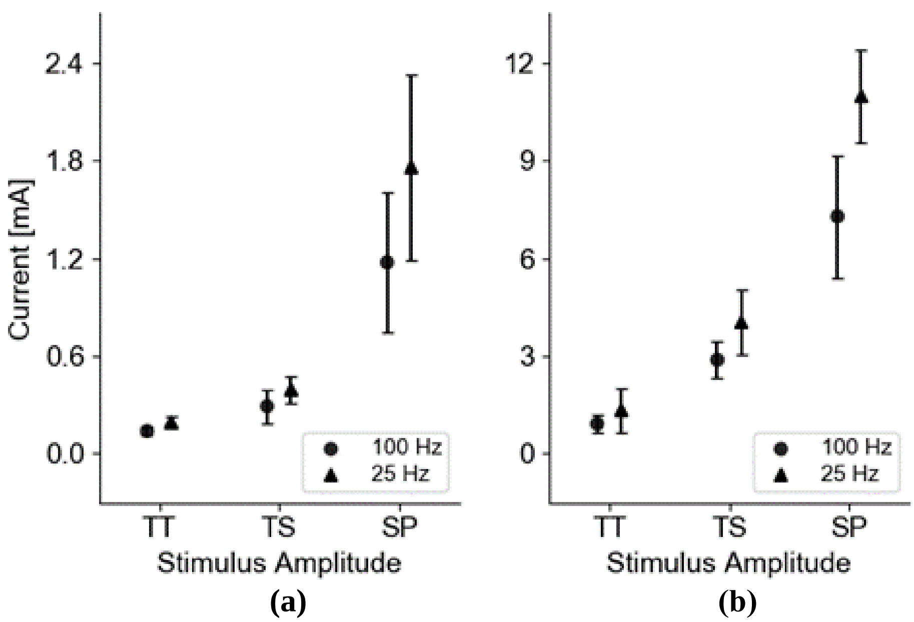


Figure 4.1. Measurement results of (a) perception threshold (PT) and (b) discomfort threshold (DT), for three intraoral locations (TT, TS, and SP) (Error bar indicates standard error).

4.2. Experiment 2: Evaluation of the Perception

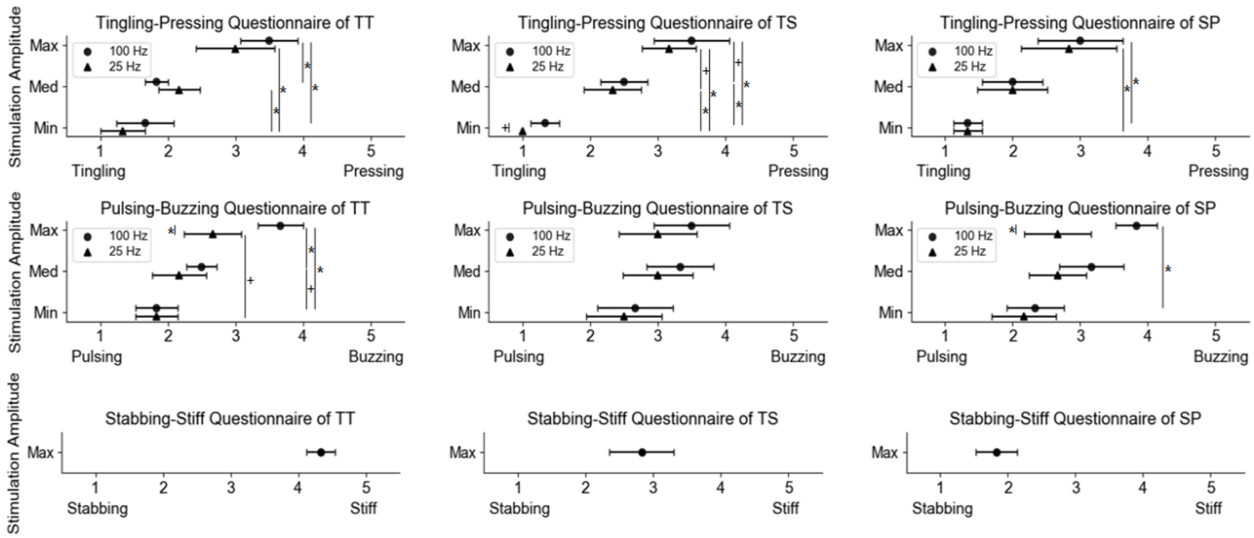


Figure 4.2. Identification of the perception by Likert-scale questionnaire, according to the stimulation amplitude and frequency, for the tongue tip (TT), and the lateral-inferior side of the tongue (TS), and the soft palate (SP) respectively. To test the difference between two values, two-tailed Welch's t-test was used with 95 % confidence level (*) and 90% confidence level (†).

The characterization of subjects' perception for each combination of frequency and amplitude is described in Fig. 4.2. Overall, as the stimulation amplitude was increased, subjects felt more pressing than tingling. The tendency could be observed in all three locations, and was most obvious at the lateral-inferior side of the tongue. Also, as either stimulation amplitude or stimulation frequency was increased, subjects tend to feel more buzzing than pulsing, except at the lateral-inferior side of the tongue.

Regarding the perception at the maximum stimulation amplitude where subjects felt discomfort, subjects felt more stabbing sensation at the soft palate, while they felt more stiff sensation at the tongue tip. Regarding the lateral-inferior side of the tongue, subjects found it as neither stabbing nor stiffness. These sensations evoked at the maximum stimulation amplitude did not depend on the frequency (i.e., same answer for each frequency).

4.3. Experiment 3: Electrical Impedance Characterization

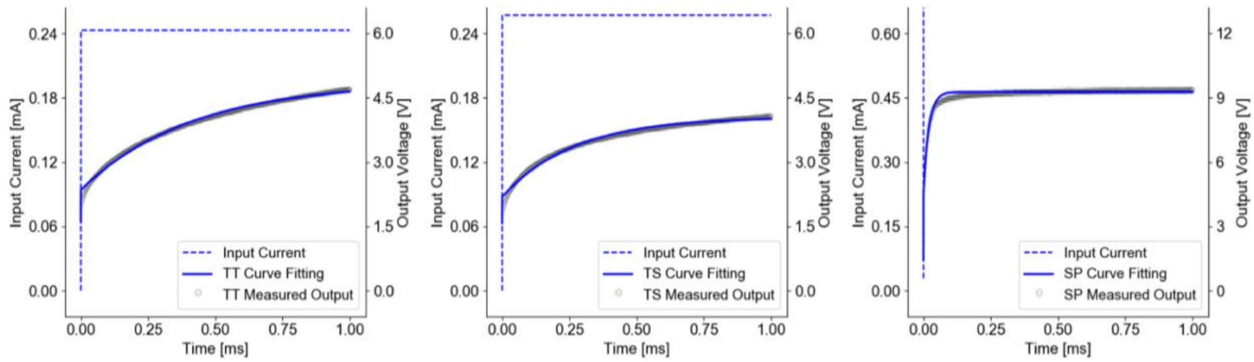


Figure 4.3. Exemplary measurement results (grey dots) and curve fitting (blue line), with one subject, are shown. Blue dashed line indicates the current input. TT, TS and SP represent tongue tip, lateral-inferior side of the tongue side, and soft palate, respectively.

In order to extract each parameter (R_S, R_P and C_P) from the R-R-C impedance model in Fig. 2.1, a curve fitting method was used with the eq. (3). The fitted curves showed good agreement with the measurement data at each location, as in Fig. 4.3. In regression analysis, which tested the match between the measurement data and the R-R-C model, we could get R-square values of 0.9891/0.9889, 0.9851/0.9700, and 0.9629/0.9188 at (PT / MT), for the tongue tip (TT), the lateral-inferior side of the tongue (TS), and the soft palate (SP), respectively, on average for the subjects. At three intraoral locations in the trials of the subjects, the R_S was measured as 2.974/1.959/1.514 kΩ (TT/TS/SP) at PT and 2.488/1.115/0.972 kΩ at MT on average, the R_P was measured as 9.358/4.984/6.821 kΩ at PT and 6.360/2.323/4.601 kΩ at MT on average, and the C_P was measured as 41.423/45.017/10.914 nF at PT and 53.361/24.942/5.232 nF at MT on average. Among the three locations, both R_S and R_P were largest at the tongue tip. In case of C_P, the lateral inferior side of the tongue showed the largest value at PT among the three areas and the tongue tip showed the largest value at MT. The soft palate showed the smallest R_S and C_P value among the three areas. Further detail of the result is shown in Fig. 4.4. Table. We summarize the comparison with the other works on skin. We could not include comparison with the other works on oral mucosa, as this work is the first impedance modeling approach of the oral mucosa.

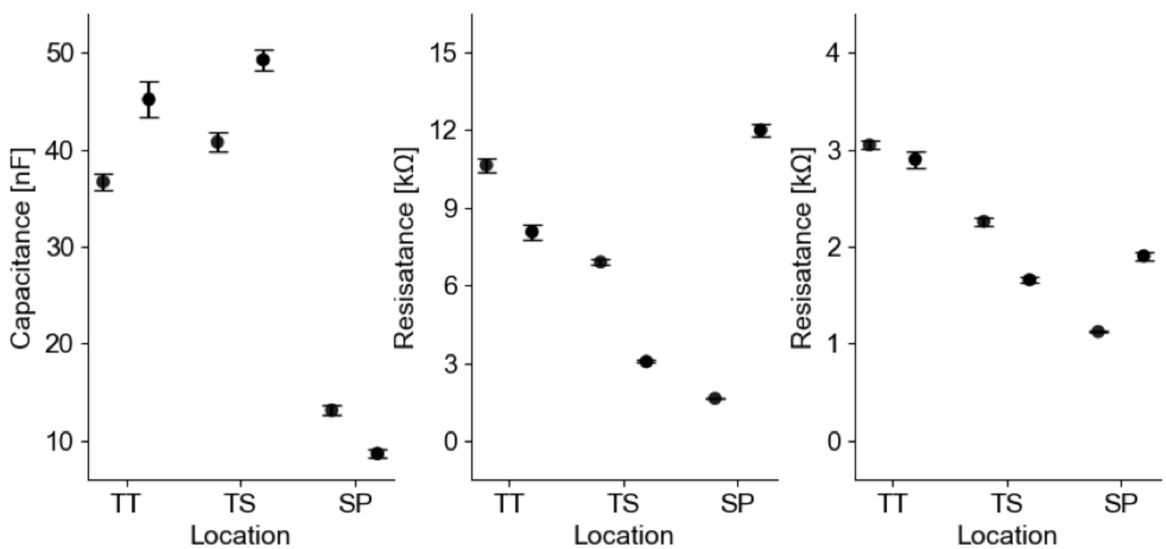


Figure 4.4. Extracted parameter values for the equivalent circuit model on three intraoral locations (TT, TS, and SP), obtained from the curve fitting with measurement results: (a) C_P, (b) R_P, and (c) R_S.

4.4. Experiment 4: Neuromodulation Based on the Characterization

In Fig 4.5, the timing information associated with pharyngeal phase of swallowing was described. The neuromodulation outcome for dysphagia is shown Table 1. The onset timing value was measured by the difference between the tongue tip touch time to the tongue tip electrode pair and maximum peak-value time of the accelerometer x-axis and z-axis outputs on the neck. For the start of pharyngeal phase of swallowing, we used the fact that the tongue tip touches the posterior side of the central incisors. [70]

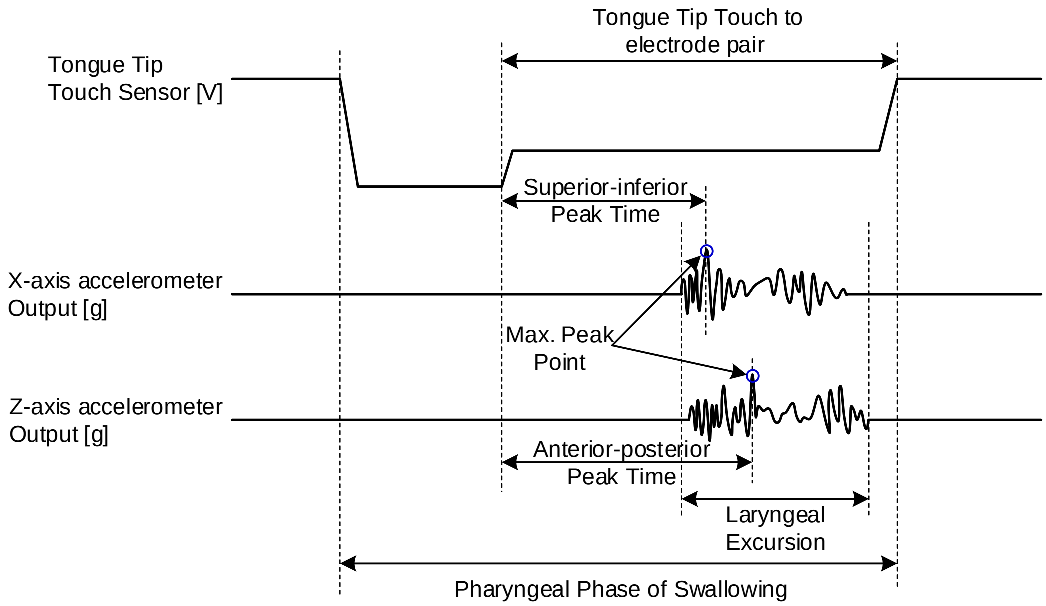
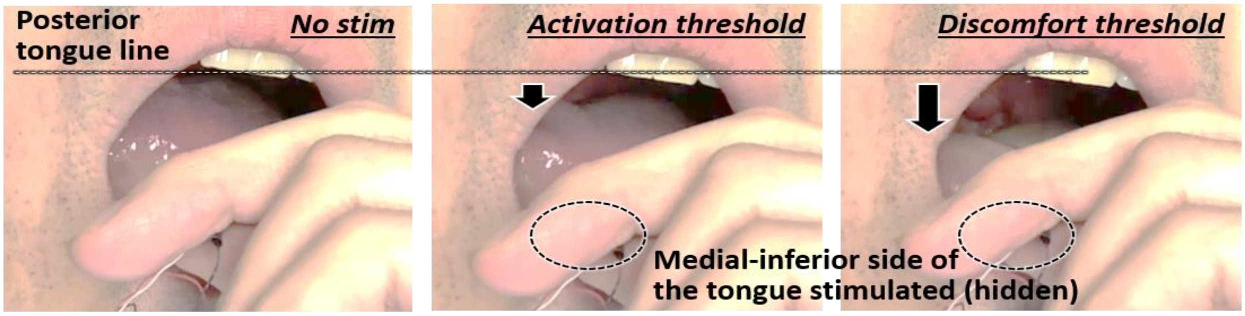


Figure 4.5. Timing information of pharyngeal phase of swallowing

Movement Direction		Without Electrical Stimulation [ms]	With Electrical Stimulation [ms]
Anterior-posterior	Average	264.231	146.957
	Std.	68.596	88.459
Superior-inferior	Average	201.645	124.783
	Std.	51.924	65.259

Table 4.1. Onset timing value of laryngeal excursion with and without electrical stim ulation during pharyngeal phase of swallowing.

In Fig. 4.6, the opening change steps of intentionally blocked upper airway by the tongue was illustrated. Upper airway opening moments were compared with the tongue movement from posterior baseline and exhalation sound change from stridor to smooth in terms of stimulation condition. Without any current stimulation on the medial-inferior side of the tongue, the upper airway was still blocked during exhalation which sound is stridor. However, at AT, stimulation



(a) (b) (c)

Figure 4.6. Upper airway opening change steps (a) No stimulation, (b) stimulation with activation threshold (AT), and (c) discomfort threshold (DT) with the posterior tongue line by increasing input current.

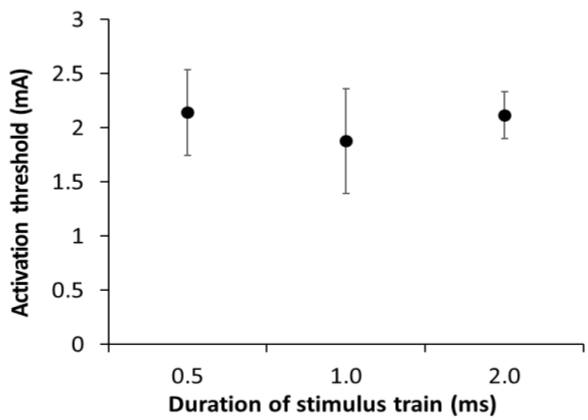


Figure 4.7. Measurement result of activation threshold (AT) in term of stimulation pulse width for obstructive sleep apnea (OSA).

current based on Fig. 4.7, the tongue started to move a bit forward and down, and stridor exhalation sound started to become smoother. At DT, the upper airway was more opened than at AT.

5. DISCUSSION

Non-invasive intraoral stimulation across the tongue and the soft palate can evoke electrotactile feedback, which could be modulated by both amplitude and frequency of stimulation. Based on the questionnaire results (Fig. 4.2), We concluded that the electrical stimulation can evoke an electrotactile feedback on the tongue tip, the lateral-inferior side of the tongue, and the soft palate. Both the naturalness (i.e., tingling vs. pressing) and the temporal identification (i.e., pulsing vs. buzzing) could be adjusted by the stimulation amplitude and frequency. Stimulation of higher amplitude evoked more natural pressure-like than artificial tingling-like sensation, for all three locations, and vice versa. Higher amplitude and higher frequency of stimulation provided more buzzing than pulsing sensation, and vice versa.

Temporal resolution of the intraoral locations to electrotactile feedback is lower than that of the fingertip, and especially lower at the lateral-inferior side of the tongue. In our prior work with the fingertip tactile augmentation, via transcutaneous electrical stimulation, subjects reported that lower frequency provides clear pulsing and higher frequency provides clear buzzing [60]. However, at intraoral locations, we could not see clear difference between frequencies. At least, with the maximum stimulation amplitude, subjects reported more pulsing at 25 Hz and more buzzing at 100 Hz, both at the tongue tip and the soft palate. However, they reported no difference between pulsing and buzzing at the lateral-inferior side of the tongue. This result suggests that lateral-inferior side of the tongue is less sensitive to the temporal changes of the electrotactile feedback than other two intraoral locations. We expect that it is perhaps because the tongue tip and the soft palate interact more with the food than the lateral-inferior side of the tongue.

Stabbing and stiff sensations between the tongue locations and the soft palate. The type of uncomfortable sensation with the high amplitude of stimulation is different according to the locations of stimulation. Subjects reported stabbing sensation on the tongue, but stiff sensation on the soft palate. We expect that it is because of the difference in muscle composition. As the tongue consists of actively-contractile muscles, the stimulation at high amplitude perhaps contracted the muscle at the tongue with uncomfortable strength. However, as the soft palate consists of minimally-contractile muscles [71], the stimulation at high amplitude perhaps activated the pain fibers rather than contracting the muscles. This difference may also explain the higher amplitude thresholds on the soft palate than the tongue locations.

R-R-C model fits well to represent the impedance between electrodes across the tongue and the soft palate. The curve fitting (Fig. 4.3) and the regression analysis showed that the voltage output with the step current input can be well explained by the R-R-C impedance model. This R-R-C model can be useful to design electrical interface across the tongue and the soft palate, mainly in designing neural recording and stimulation system. We expect that the values would not change much by the selection of the electrodes, because the contact impedance of the oral mucosal surface would be minimally variable with the watery environment.

Based on the measurement result, capacitance of the intraoral R-R-C model is within almost similar range, usually reported in 10-100 nF range. The parallel R-C will work almost as a R at frequencies less than 200 Hz, as the impedance of 30 nF capacitance will have magnitude of ~53 kΩ at 100 Hz. In other words, the oral mucosal tissue layer is more likely two series resistance ($R_S + R_P$) in electrical domain, at frequencies used for the neuromodulation. Considering that the R_S is less than R_P for both the tongue and soft palate, the resistance of superficial layer of the tongue and soft palate (R_S) is the dominant parameter at the neuromodulation frequency between 10 and 200 Hz.

Constant-current stimulation would be better than constant-voltage stimulation in the intraoral space due to low contact impedance of the mucosal surface. It is a common sense that the intraoral surface will provide a low impedance path in between electrodes because of the watery mucosal surface and smooth intraoral organ. The R-R-C values obtained in this study suggest that impedance between intraoral electrodes, spaced less than 1 cm, will be a bit less than 10 kΩ, which is impedance at 100 Hz to the wet skin [72]. Note that, the parallel resistance R_P, the series resistance Rs, which is less than 10 kΩ for all subjects, will keep the total impedance as being less than 10 kΩ. Therefore, the current might no be well controlled at constant-voltage stimulation. For example, current will not be limited under 1 mA if the stimulation voltage is less than 5 V. It also agrees with the fact that licking 9-V battery by tongue evokes pain sensation or damaging the tongue tissue instead of evoking tingling.

Constant-current stimulation is necessary for neuromodulation in intraoral sensorimotor loops, to have consistent effect across subjects. Fig. 4.4 shows that values of resistance and capacitance are highly variable across subjects. That is, the consistency of the stimulation cannot be guaranteed by the constant-voltage stimulation. Note that the action potential is generated by the inward/outward movement of charges through the membrane, and amount of charge exchange is determined by the amount of current multiplied by the duration of the current pulse [73]. Of course, each person will have difference threshold and different amount of current will be needed for consistent effect across people. However, varying impedance across subjects suggest that constant-current stimulation is necessary for effective and consistent intraoral neuromodulation.

6. CONCLUSION

In this paper, we characterized the electrical interface on the tongue and the soft palate in three ways: 1) stimulation thresholds evoking perception and discomfort for each of three intraoral locations, 2) subjects' perception at different amplitudes and frequencies of stimulation, and 3) impedance between electrodes across the tongue and the soft palate. Based on the electrical characterization, for neuromodulation, we intervened the sensorimotor loops associated with dysphagia and OSA with electrical stimulation. We found that the R-R-C model can well represent the electrical impedance across the three intraoral locations on the tongue and the soft palate. We also found that constant-current stimulation with 0.1 to 2 mA current amplitude, at both 25 and 100 Hz, could evoke electrotactile feedback on the tongue and the soft palate. The perception was mostly tingling at the lower stimulation amplitude but became pressure-like sensation at the higher stimulation amplitude. The equivalent characterization of the tongue and the soft palate was an important step forward to find the way of applying electrical stimulation across the tongue and the soft palate, to intervene the intraoral sensorimotor loops associated with dysphagia and OSA properly and effectively.

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