# A SUBJECT-SPECIFIC BIOMECHANICAL MODELING APPROACH TO UNDERSTANDING SEX DIFFERENCES IN NECK STRENGTH

A Dissertation

by

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## ABSTRACT

Neck pain and injury are highly prevalent conditions that constitute a growing global healthcare burden. Females are at greater risk of neck injury from impact, are more likely to have persistent neck pain, and have poorer treatment outcomes than males. Neck muscular strength differs significantly between the sexes and is believed to be an important modifiable factor in injury prevention strategies and pain treatment protocols. Given the increased prevalence of mechanical neck pain and the lack of effective treatment, there is a need for investigation into the factors underlying neck strength. This information would help tailor preventative and therapeutic interventions to the individual, with sex-specificity as a much needed first step in personalization. This dissertation investigates the morphological, biomechanical, and neuromuscular factors of neck strength through the development and analysis of subject-specific neck biomechanical models. These three strength factors correspond to the three studies of the dissertation: (1) *Sex and Posture Dependence of Neck Muscle Size-Strength Relationships*, (2) *Subject-Specific Neck Modeling Unveils Sex Differences in Muscle Moment Arm and Cervical Spine Load During Maximal Contractions*, and (3) *Subject-Specific Maximum Muscle Tension: An Index to Capture Neuromuscular Differences in Neck Strength*. This three-part, stepwise approach integrates subjects' medical imaging with biomechanical measurements taken during maximal neck exertions to achieve a novel degree of subject-specificity in neck biomechanical modeling, one that affords the unique opportunity to investigate individual differences in neck strength factors. The discovered sex differences in neck structure and function provide insight into how potential pathomechanisms of neck pain and injury as well as potential targets for preventative or therapeutic intervention may differ between the sexes.

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## CONTRIBUTORS AND FUNDING SOURCES

### Contributors

This work was supervised by a dissertation committee consisting of Professors Xudong Zhang [advisor], John C. Criscione and Roozbeh Jafari of the Department of Biomedical Engineering, and Carolyn Cannon of the Department of Microbial Pathogenesis and Immunity.

The experiment by which all data were collected was performed by Dr. Zhang and his lab at the University of Pittsburgh Medical Center. All modeling and analysis work conducted for the dissertation was completed by the student independently.

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# NOMENCLATURE

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| ACSA | Anatomical Cross-sectional Area |
| CT | Computed Tomography |
| DSX | Dynamic Stereo Radiography |
| EMG | Electromyography |
| FE | Flexion-Extension |
| LCS | Local Coordinate System |
| LOA | Line of Action |
| MRI | Magnetic Resonance Imaging |
| MV | Muscle Volume |
| MVC | Maximum Voluntary Contraction |
| PCSA | Physiological Cross-sectional Area |
| RCSA | Reconstruction-based Cross-sectional Area |

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# 1. INTRODUCTION

## 1.1. Background and clinical motivation

Neck pain is growing in prevalence, health care expenditure, and years lived with disability and is disproportionately affecting females.[1-8] Global prevalence of neck pain is estimated to be 4.9% but is considerably higher in North American men and women, 5.3% and 7.6%, respectively[8]; global prevalence of neck pain lasting at least three months has also increased by approximately 21% over the past 10 years.[3] In addition to being more likely to suffer from neck pain, women are at greater risk of neck injury from impact, are more likely to have persistent neck pain, and have poorer outcomes from neck pain treatment.[7,9-11] The majority of neck pain cases lack a clear, correctable pathology like cervical radiculopathy or myelopathy and thus fall under the label of "nonspecific" or "mechanical" neck pain.[12-14] Mechanical neck pain treatment, for both sexes, lacks high quality, evidence-based recommendations and thus further compounds the growth of the already high prevalence rates.[14-16] Because neck injury and pain are complex phenomena with numerous possible etiologies and proposed pathomechanisms,[13,14,17-19] tailoring preventative or therapeutic interventions to the individual may yield more successful outcomes than one-size-fits-all methods, with sex-specificity as a much needed first step in personalization.[2,6,7]

While the causes of mechanical neck pain are unclear, both acute, traumatic events and subacute to chronic onsets are common clinical presentations, with neck strength being intimately tied to their development and treatment.[14] Regarding traumatic events, head and cervical spine injury risk secondary to unsafe head accelerations in impact scenarios are a growing concern, and these events may also lead to the development of chronic neck pain.[20-24] In an effort to identify modifiable protective factors for neck injury risk, neck muscle size and strength have been the focus of recent investigations in sports medicine.[25-29] While research in this area has been consistent in establishing an inverse relationship between neck strength and head acceleration under laboratory settings,[30-33] translation of these findings into head injury or neck pain incidence prediction has shown mixed results.[29,34,35] Regarding subacute to chronic presentations, both lower neck muscle size as well as decreased isometric neck strength have been associated with chronic mechanical neck pain patients, but it is unclear how the two are related mechanistically.[36-39] Lastly, from a treatment perspective, neck strength has been shown to increase during successful therapy, and active neck strengthening has been one of the few common components among therapeutic protocols that have shown some success at ameliorating pain in randomized control trials; this has led to its adoption into recommended clinical practice, but the reason for this effect remains unknown.[14-16,40-42] Given the aforementioned sex differences in neck pain and injury epidemiology, that nonspecific neck pain may arise from a blend of mechanical and neurological etiologies,[18,19,43,44] and the role of neck strength in pain prevention and treatment, there is a need to investigate neck strength and determine the extent to which sex differences in neck structure and function give rise to sex differences in the etiology and treatment of neck pain and injury.

**1.2. Experimental approach**

Biomechanical modeling is a powerful tool that integrates anatomy (musculoskeletal geometry), kinematics, and kinetics to offer estimates for otherwise unmeasurable information.[45-52] While simple modeling involves regression or basic spring-damper systems, more elaborate computer or mathematical biomechanical models have been developed to estimate internal loading using inverse dynamics calculations and predict injury risk in situations not replicable in a lab setting.[53-55] Rather than using biomechanical modeling to identify which *scenarios or tasks* may cause neck injury or pain, using a subject-specific approach allows researchers to identify which *patients or populations* may develop pain or injury from a given task or scenario as well as how to tailor treatment to a specific individual rather than comparing therapeutic interventions on a population level. Previous attempts to address the injury prediction objective include those motivated by athletic safety concerns, but there is a need for subject-specific investigation in the occupational health, automotive safety, and neck pain treatment fields, and especially a comparison between males and females.[25-27,29,30,32,33,56,57] Subject-derived bone and muscle geometry, including anatomically correct, curved muscle path representation is needed to generate accurate and fully personalized models. Given that such models are necessary to investigate individual differences in neck strength and biomechanics and that current computer-based modeling systems do not allow for such individualization, the research presented in this dissertation develops a unique stand-alone modeling method incorporating subject-specific *in vivo* imaging and biomechanical data.

By investigating the inter-relationships between neck musculoskeletal anatomy, biomechanics, and neck strength with an unprecedented level of subject-specificity, the presented work attempts to determine the extent to which biomechanical and non-biomechanical factors contribute to neck strength and the sex differences therein. This contribution is expected to advance the science base, understanding, and computational modeling of neck biomechanics in the context of strength capacity and injury prevention.

### 1.3. Overview of dissertation

This contribution comprises a systematic three-part modeling endeavor that takes advantage of a recently established experimental database of integrated neck biomechanical measurements. This database includes measures of neck strength, muscle morphometry from MRI, vertebral geometry and kinematics from CT and dynamic stereo-radiography (DSX), muscle activation and fatigue from surface electromyography (EMG), and head-neck kinematics from a motion capture system. The three parts represent three distinct steps in identifying how differences in strength, anatomy, and biomechanics interact on a subject-specific level and may contribute to sex differences. The first study compares neck strengths, muscle sizes, and muscle size-strength relationships to find and characterize sex differences. The second study develops and validates biomechanical models by integrating subject-specific MRI, CT, DSX, EMG, and strength data. The third study uses these models to explore sex differences in non-biomechanical strength factors and determines the effect of contraction coordination on neuromuscular strength factor effectiveness. These three studies correspond to three specific aims:

**AIM 1: To statistically correlate neck muscle size with neck strength and identify sex differences therein.** Participant strength is measured in three different postures. Muscles are segmented from neck MRIs, and muscle size is characterized using three metrics: anatomical cross-sectional area, muscle volume, and an MRI-based estimate of physiological cross-sectional area. Inter-posture strength correlations and muscle size-strength correlations are analyzed using linear regression and sex differences are identified.

**AIM 2: To develop and validate subject-specific neck biomechanical models that predict the muscle tension during maximum force exertion and use the models to explore sex differences in biomechanical factors.** Vertebral kinematics from DSX co-registered with MRI-segmented muscle morphometry are used to define unique muscle moment arms in each posture. Subject-specific muscle size, moment arms, and exertion force are integrated to develop biomechanical models. The models are validated by comparing predicted muscle activation (as normalized muscle stress) required to maintain static equilibrium at the C6-C7 joint to normalized EMG amplitude. Model analysis of maximal exertion reveals sex differences in spinal loading.

**AIM 3: To identify a metric with which to investigate sex differences in non-biomechanical strength factors and determine the effect of co-contraction on maximum muscle stress using biomechanical models**. By using the developed biomechanical models to study maximal neck exertions, a biomarker involving maximal muscle stress, $\alpha$, is calculated for each individual. Distributions of $\alpha$ are compared across the sexes. EMG-based measures of agonist-antagonist muscle co-contraction are compared to individual $\alpha$ values and analyzed to identify sex differences and to quantify the role of contraction strategy in sex differences in the neuromuscular factors of strength.

# 2. SEX AND POSTURE DEPENDENCE OF NECK MUSCLE SIZE-STRENGTH RELATIONSHIPS

## 2.1. Introduction[*]

Neck pain is growing in prevalence, health care expenditure, and years lived with disability.[2-5,8] The global prevalence of neck pain is estimated to be 4.9% and is considerably higher in women (5.8% prevalence) than men (3.9% prevalence).[8,58] Among a multitude of factors that may play a role in the causation and control of neck pain and injury, neck strength and muscle size have more demonstrable effects and are readily measurable. Studies have used dynamic impact simulations, static strength tests, and muscle measurements to explore relationships that can inform protective or interventional strategies.[25-29] Evidence from laboratory research in this area has been consistently suggesting an inverse relationship between neck strength and head acceleration.[30-33] Neck muscle size and strength have also been found to decrease in patients with chronic neck pain and increase during successful therapy.[36-39,41,42] However, translation of these findings into neck pain or injury incidence prediction has shown mixed results.[29,34,35] This gap highlights the need for a clearer understanding of the role of neck muscle and strength in injury biomechanics.[59-65]

Studies investigating the role of specific musculature in strength build on the accepted linear relationship between muscle size and joint force production capacity.[66,67] Such relationships have been constructed to compare young versus old or trained versus untrained.[68-73] Anatomical

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cross-sectional area (ACSA) measured by ultrasonography, the fastest and most accessible method of quantifying muscle size, has been utilized in prior strength analyses.[29] Muscle volume (MV), measured from MRI, has been shown to be a better determinant of arm strength than ACSA, though this has yet to be evaluated for the neck muscles.[69,74,75] Prior investigations of size-strength relationships lumped a single regression model without separating males and females in spite of the bimodal distributions of both strength and size.[74] Such an approach inflates the correlation strength and does not allow for sex-specific analyses and insights, while sex differences have been reported not only in neck pain incidence but also in neck impact injury risk, persistency, and treatment outcome.[2,6,7,9-11]

Motivated by the belief that prolonged deviated neck posture is a risk factor for neck pain and the fact that prior injury prediction studies had only evaluated neck strength in a neutral posture, recent investigations have studied neck strength in different directions and non-neutral positions.[76-80] However, none have studied in depth how different muscles in the neck affect strength in different postures or examined neck flexion strength in an extended head-neck position, a posture commonplace in sports and in occupational environments when overhead work is performed.[81] Variability in strength across postures may be more complicated than changed muscle length. As Vasavada et al. (1998) showed in a computer modeling study, the sternocleidomastoid (SCM), commonly regarded as the primary muscle generating neck flexion, exhibits extension moment arms at the skull-C2 and C2-T1 "joints" (as defined by Software for Interactive Musculoskeletal Modeling-SIMM) when in an extended head-neck posture. This provokes the question of whether the agonist-vs-antagonist role of the SCM as well as other muscles may be posture-dependent.

Therefore, the purpose of this study was to elucidate neck muscle size-strength relationships by examining three questions. First, are strength differences between the sexes reducible to muscle size differences? Second, how does a change in posture affect strength prediction from muscle size? Third, how do ACSA and MV compare with a solely MRI-based estimate of physiological cross-sectional area (PCSA) as alternative predictors of neck strength?

## 2.2. Methods

### *2.2.1. Participants*

Forty healthy adults (20 males, 20 females), aged 21 – 45, free from neck pain or any prior neck injury, were recruited to participate in the study. The study protocol, approved by the Institutional Review Board, was explained in detail to the participants who then provided written consent. Ten participants' data were excluded from the study due to poor MRI or strength measurement quality, leaving 13 males and 17 females for analysis; in particular, nine participants'

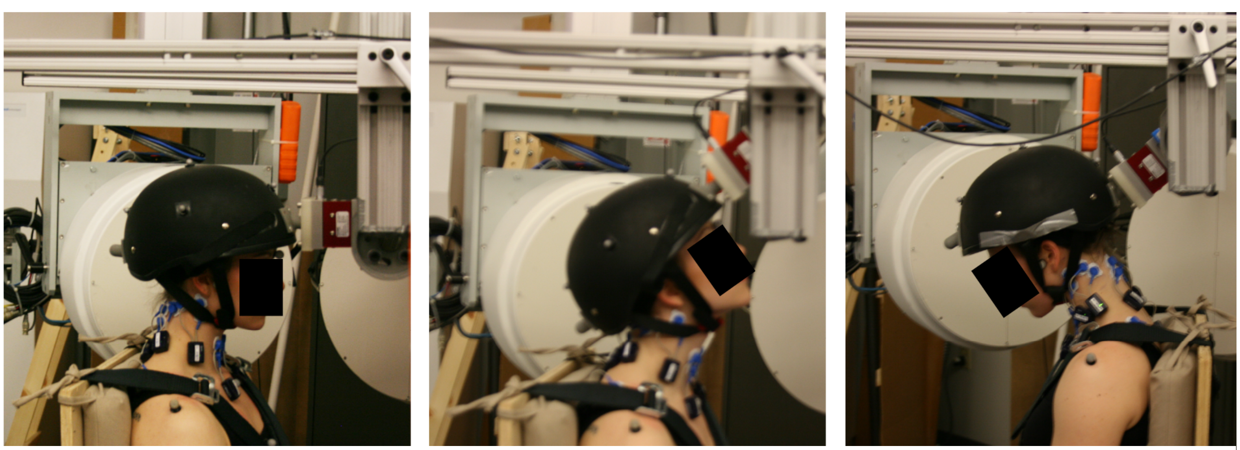


**Figure 2-1.** The adjustable frame and seat were custom-designed to accommodate participants with a broad range of anthropometry. The experimental apparatus allowed six ways of translational adjustment (3 directions for load cell positioning, vertical frame adjustment, and both vertical and anteroposterior movement of the seat) and two degrees of rotational freedom (about the mediolateral axis for the load cell to permit flexion/extension changes and about the vertical axis for the swivel-chair to permit both anterior and posterior exertions). Neck strength was tested in three conditions: (A) anterior exertion in neutral posture; (B) anterior exertion in 40° extended posture; (C) posterior exertion in 40° flexed posture. The flexion-extension angle was measured by the Frankfort plane (as defined by motion capture markers placed on tragion and infraorbital landmarks) relative to the horizontal plane.

MRI scans were subject to excessive motion artifact and image blur such that muscle boundaries were indiscernible.

### *2.2.2. Strength measurement*

A custom-designed testing frame housed a seat and a tri-axial load cell (FUTEK Advanced Sensor Technology, Inc., Irvine, CA) and was made adjustable to accommodate neck exertions in a variety of postures by individuals with a wide range of anthropometry (Fig. 2-1). More detailed descriptions of this testing apparatus are available in prior publications.[82,83] Participants were secured to the seat with a four-strap harness and were fit with an appropriately sized (out of three sizes) Daytona half-shell helmet (Ennis Kirk, Inc., Rush City, MN) with interior padding and a chin strap. 3D printed plastic hemispheric protrusions were mounted to the front and back of the helmet and were designed to mate with a spherical concavity attached to the load cell to prevent slipping and permit quick disengagement. After an initial warmup, participants performed neck exertions in three conditions: (A) flexion in a neutral posture, (B) flexion in 40° of head-neck extension, (C) and extension in 40° of flexion. The 40° angle, measured as the angle between the Frankfort plane and the horizontal, was chosen so that the postural deviation would be substantial enough to evoke a salient effect yet achievable by all participants with varied neck ranges of motion. In each condition, participants performed four exertions with maximal voluntary intensity, two for a minimum of 5 seconds and two sustained-till-exhaustion. The sustained trials were included in strength analysis to account for the difficulty and novelty of neck exertions by affording participants a longer time window for maximal force production.[84] Ample rest of at least twice the duration of the prior trial was given between exertions. Resultant force data from the load cell were smoothed with a 50ms moving average window. Strength for a given trial was determined by identifying the 0.5 second interval during which the greatest force was produced and taking the average force across the interval.[74] Participant strength in a given posture was determined as the highest strength value out of all four trials in that posture.

*2.2.3. Muscle morphometry measurement*

All participants underwent MR imaging at the University of Pittsburgh Medical Center (UPMC) Magnetic Resonance Research Center (MRRC). Axial images of participants' entire necks in a supine posture were captured with a 3T clinical scanner (proton density-weighted, turbo-spin echo sequence; TE=9.0ms; slice thickness=3.0mm; no gap). Neck muscle bellies were manually outlined in each MRI slice by one analyst using Mimics 20.0 (Materialise Inc., Ann Arbor, MI) (Fig. 2-2). In addition to the original 30 scans, MRIs of four randomly chosen participants (two male and two female) were segmented again, no sooner than two months after the original segmentation process, to evaluate segmentation reliability. Fourteen total muscle pairs were segmented as 10 paired muscular groups. The sternocleidomastoid, anterior scalene, infrahyoid, longus capitis and colli, and levator scapula muscles were segmented from C1 to their origins, and all remaining muscles were segmented from C1 to C7. To adapt ultrasonographic ACSA measurement to MRI, ACSA was determined as the largest cross-sectional area of a muscle in any single MRI slice.[26,29] MV was calculated by multiplying the sum of a muscle's segmented area from all slices by slice thickness.[85-89] The calculation of physiological cross-sectional area (PCSA) requires a muscle's optimal fiber length and pennation angle, neither readily accessible with MRI. A novel method was introduced for PCSA estimation without involving generic (i.e., not subject-specific) data. This method calculated muscle length (ML) as the length of a 3D cubic polynomial curve-fitted to the centroids of the segmented MRI slices. A reconstruction-based cross-sectional area (RCSA) was then obtained by dividing MV by ML.

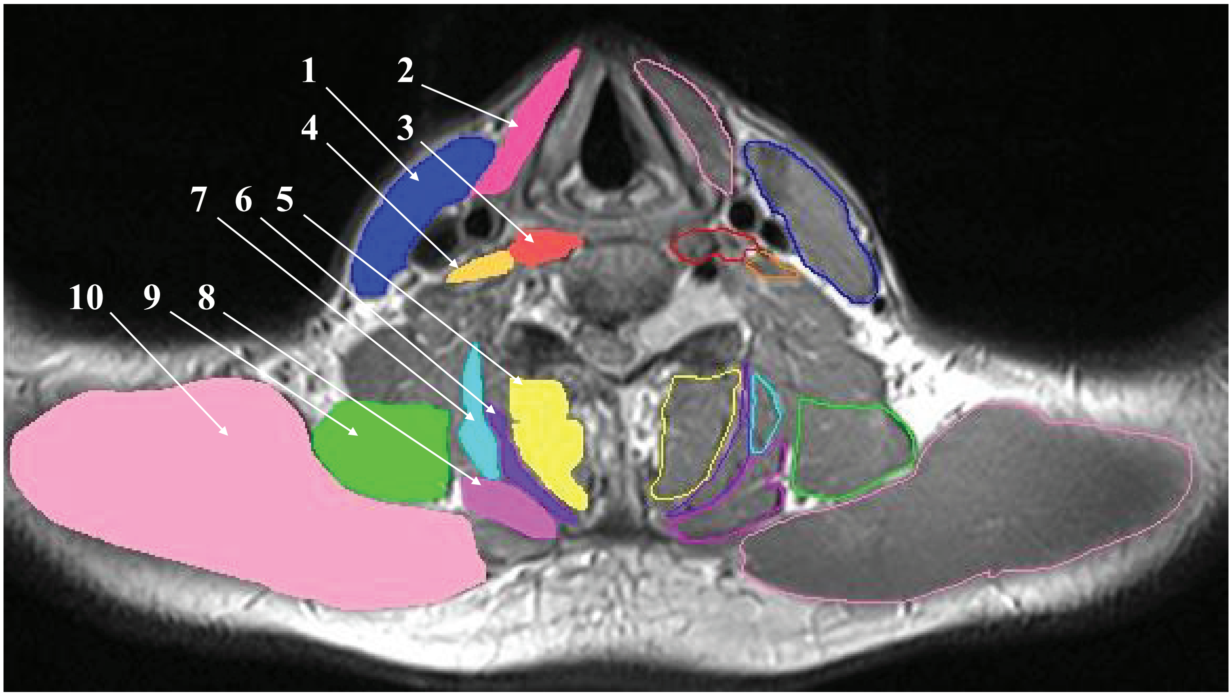



**Figure 2-2.** Segmented muscle bodies in a cross-sectional MRI at the C6 level: 1. sternocleidomastoid (SCM); 2. infrahyoid muscles (IH); 3. longus colli and longus capitis (Longus); 4. anterior scalene (AS); 5. semispinalis cervicis and multifidus (Deep); 6. semispinalis capitis (SSC); 7. longissimus cervicis and longissimus capitis (Longiss); 8. splenius capitis and splenius cervicis (SPL); 9. levator scapula (LS); and 10. trapezius (Trap).

*2.2.4. Statistical analysis*

Descriptive statistics of anthropometric measures were obtained for male and female participants separately and were compared using Student's t-tests to test for significant differences in age, height, weight, and BMI. Muscle measurement reliability was determined by calculating percent difference in muscle size between original and duplicate muscle segmentations on a muscle-by-muscle basis and then taking the average percent difference; this was repeated for each morphometric measure. Strength measurement reliability was assessed by calculating intra-class correlation coefficients for each condition [90]. Student's t-tests were used to compare male to female muscle size across the three metrics and to compare male to female strengths in each of the three conditions. The difference of means, $\delta$, and the 95% confidence interval of $\delta$ was reported for each anthropometric and strength comparison. Linear regression was used to correlate strength in condition A to strengths in the other two conditions for each sex. Correlation was also used to identify linear relationships between muscle or muscle group size ($cm^2$ for ACSA, $cm^3$ for MV, and $cm^2$ for RCSA) to neck exertion strength (N). Student's t-tests were used to compare male to female regression model coefficients. The relative distance of a size-strength model intercept to 0, as determined by percent confidence interval, was used to evaluate model validity.[91,92] Pearson's product-moment correlation coefficient ($r$) was used to report the strength of linear relationships between strength measures and of muscle size-strength relationships. The coefficient of determination ($R^2$) was used to quantify the amount of variance in strength explained by the variance in muscle size.

## 2.3. Results

### *2.3.1. Anthropometry and muscle morphometry*

A comparison of anthropometric measures between male and female participants found height to be the only significantly ($\alpha = 0.05$) different feature between the two (Table 2-1). Test-retest reliability for muscle size from segmentation was 4.7%, 5.1%, and 6.5% for MV, RCSA, and ACSA respectively. All muscles were significantly larger in males than in females, except for the AS; these findings were similar across muscle metrics (Table 2-2).

**Table 2-1.** Statistical summary and comparison of age, anthropometry, and BMI between the male and female participants.

| | Male (n =13) | Female (n =17) | *p*-Value | Difference ($\delta$) | 95% CI of $\delta$ |
|---|---|---|---|---|---|
| Age | 30.5 (±1.7) | 30.8 (±1.7) | 0.900 | -0.30 | [-5.19, 4.58] |
| Height (cm) | 174.7 (±2.4) | 168.2 (±1.9) | **0.045*** | 6.46 | [0.15, 12.77] |
| Weight (kg) | 72.3 (±3.5) | 65.7 (±2.5) | 0.131 | 6.51 | [-2.05, 15.07] |
| BMI | 23.5 (±0.7) | 23.2 (±0.6) | 0.690 | 0.38 | [-1.55, 2.31] |

**Table 2-2.** Comparison of segmented muscle size between the male and female participants.

| Muscle Name | Muscle ACSA ($cm^2$) | | | Muscle RCSA ($cm^2$) | | | Muscle Volume ($cm^3$) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Male (n=13) | Female (n=17) | *p*-Value | Male (n=13) | Female (n=17) | *p*-Value | Male (n=13) | Female (n=17) | *p*-Value |
| SCM | 9.88 (±0.59) | 7.06 (±0.35) | <0.001* | 5.57 (±0.30) | 4.13 (±0.17) | <0.001* | 107.9 (±6.4) | 72.7 (±3.5) | <0.001* |
| IH | 5.08 (±0.16) | 3.38 (±0.14) | <0.001* | 3.14 (±0.12) | 2.22 (±0.10) | <0.001* | 34.5 (±2.0) | 22.2 (±0.8) | <0.001* |
| Longus | 4.05 (±0.15) | 3.13 (±0.12) | <0.001* | 2.33 (±0.07) | 1.78 (±0.07) | <0.001* | 34.9 (±1.4) | 25.5 (±1.2) | <0.001* |
| AS | 3.49 (±0.20) | 3.35 (±0.22) | 0.646 | 1.82 (±0.11) | 1.77 (±0.12) | 0.778 | 12.4 (±0.9) | 12.7 (±1.0) | 0.853 |
| Deep | 8.05 (±0.33) | 6.27 (±0.18) | <0.001* | 5.42 (±0.17) | 4.19 (±0.13) | <0.001* | 37.3 (±2.3) | 28.4 (±1.3) | 0.001* |
| SSC | 9.86 (±0.33) | 6.74 (±0.23) | <0.001* | 5.53 (±0.23) | 3.69 (±0.13) | <0.001* | 60.6 (±3.2) | 38.2 (±1.5) | <0.001* |
| Longiss | 2.43 (±0.15) | 1.59 (±0.06) | <0.001* | 1.15 (±0.05) | 0.87 (±0.03) | <0.001* | 13.1 (±0.7) | 9.5 (±0.5) | <0.001* |
| SPL | 6.95 (±0.36) | 5.04 (±0.21) | <0.001* | 5.00 (±0.26) | 3.66 (±0.14) | <0.001* | 55.5 (±3.2) | 39.1 (±1.6) | <0.001* |
| LS | 12.69 (±0.74) | 9.71 (±0.90) | 0.020* | 4.46 (±0.16) | 3.18 (±0.18) | <0.001* | 68.8 (±3.1) | 50.1 (±2.7) | <0.001* |
| Trap | 50.07 (±6.78) | 26.46 (±4.84) | 0.007* | 6.51 (±0.69) | 3.97 (±0.60) | 0.010* | 88.1 (±11.5) | 46.5 (±8.9) | 0.007* |

### *2.3.2. Strength*

On average, female strength was 68.0%, 58.7%, and 70.1% of male strength in conditions A, B, and C, respectively (Table 2-3). Participants produced significantly more force in condition C than in A and significantly more force in A than in B. For females, strength in condition A was strongly correlated to strengths in non-neutral postures, but no such correlation was found for males (Table 2-4). Intra-class correlation coefficients for strength measurement reliability were 0.86, 0.73, and 0.72 for conditions A, B, and C, respectively.

**Table 2-3.** Statistical summary and comparison of strength (in Newtons) in each condition between males and females

| Condition | Male | Female | *p*-Value | Difference ($\delta$) | 95% CI of $\delta$ |
|---|---|---|---|---|---|
| A | 113.8 (±8.3) | 77.4 (±6.7) | 0.002* | 36.4 | [14.8, 57.9] |
| B | 74.3 (±6.7) | 43.6 (±4.2) | <0.001* | 30.7 | [15.3, 46.1] |
| C | 159.2 (±9.9) | 111.6 (±6.2) | <0.001* | 47.6 | [24.6, 70.5] |

**Table 2-4.** Comparison of correlations of strength in conditions A to strengths in non-neutral conditions. Pearson's *rho* (and *p*-values) are reported for males and females.

| Condition | Male | Female |
|---|---|---|
| B | 0.43 (0.147) | 0.77 (<0.001*) |
| C | 0.42 (0.148) | 0.71 (0.001*) |

*2.3.3. Neck muscle size-strength relationships*

The neck muscle size-strength relationships as characterized by the linear regression models are sex and posture dependent (Fig. 2-3 & Fig. 2-4). All relationships reported below were found to be significant with 0 falling within the relatively narrower 80% confidence intervals of regression model intercepts unless otherwise stated. In condition A, the sex-specific models showed significant correlations between total superficial flexor size (AS+SCM+IH) and strength (Fig. 2-3). There was no significant difference in regression slope between males and females, while the regression models for females had consistently lower $R^2$. At the individual muscle level, only the SCM was significantly correlated with strength. For males, this significance was consistent across all morphometric measures, which was not the case for females. The $R^2$ values for female SCM models were markedly lower than those of males. A significant relationship

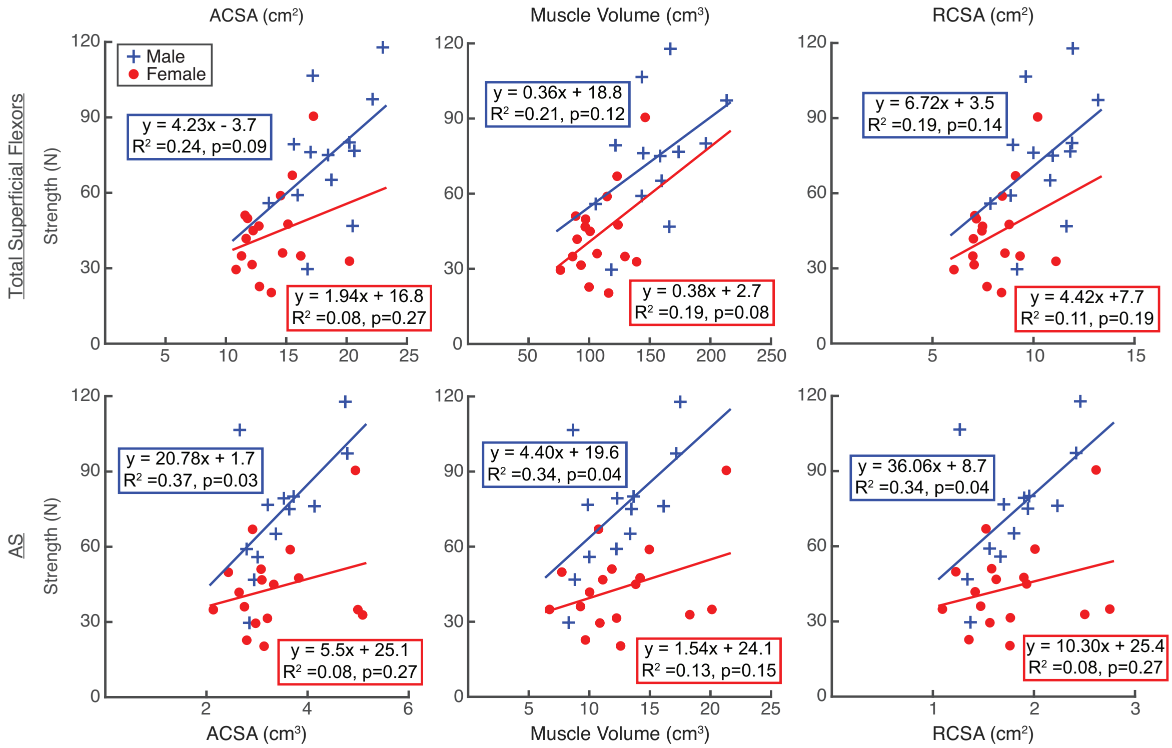



**Figure 2-3.** Sex-specific neck muscle size-strength relationships in condition A identified by linear regression for the total superficial flexor (AS+SCM+IH) and SCM alone, comparing three morphometric measures (ACSA, MV, and RCSA).

between IH volume and strength was found in females. In condition B, a significant relationship was found between AS size and exertion strength for males but not for females (Fig. 2-4). In condition C, no significant correlations were found for males; several significant correlations were identified for females but with 0 falling outside the 80% confidence interval for model intercepts.

## 2.4. Discussion

The growing concerns of neck pain and head injury have motivated biomechanical investigation of measures or modifiable factors pertinent to the causation and prevention of these injuries. Neck muscle strength and size have been identified as potential measures, but their interplay and relationships remain poorly understood, especially with regard to sex differences. This study examined muscle size-strength relationships across varied postures in order to identify

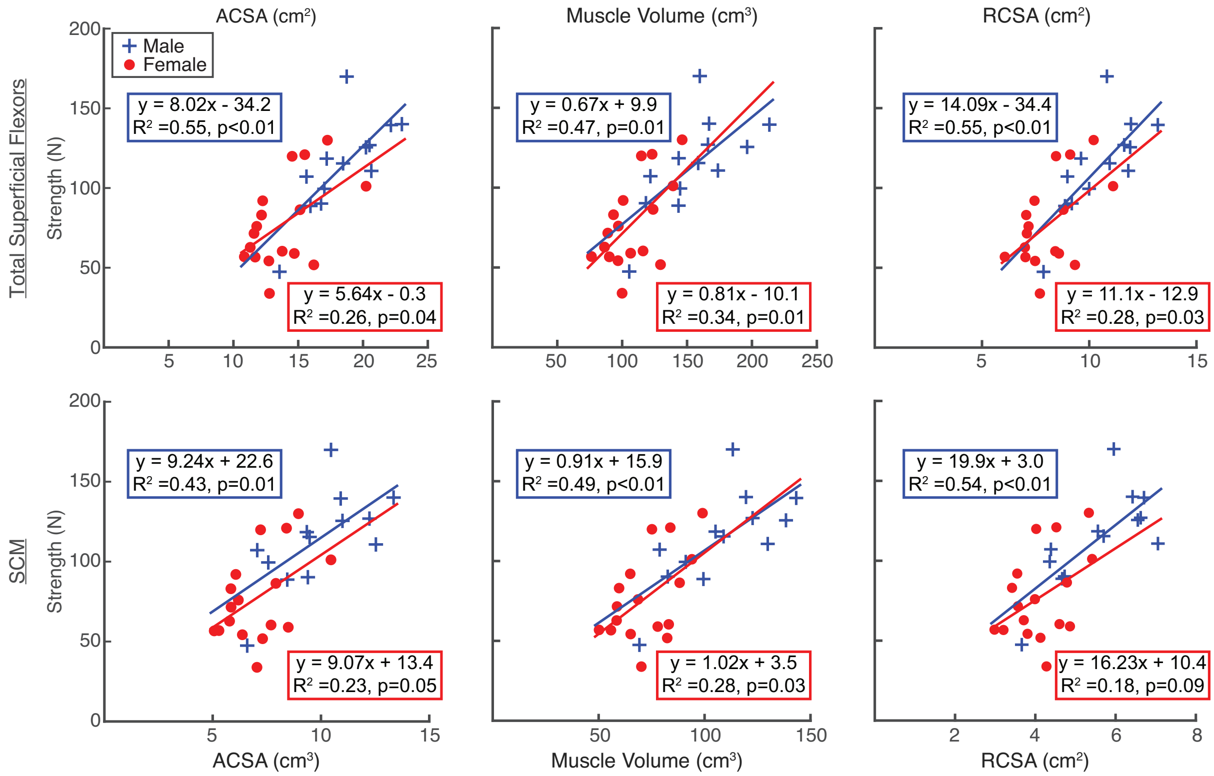



**Figure 2-4.** Sex-specific neck muscle size-strength relationships in condition B identified by linear regression for the total superficial flexor (AS+SCM+IH) and AS alone, comparing three morphometric measures (ACSA, MV, and RCSA).

potential sex differences, determine the roles of muscles or muscle groups in specific neck exertions, and compare three muscle size metrics.

The reliability of this study, in terms of strength measurement, MRI segmentation, and the size-strength relationships themselves, compares favorably with previous studies. As measured by ICCs, reliability of strength measurement ranged from good to excellent across the experimental conditions.[77,93] The present study showed an intra-observer variability of less than 5% for muscle volume measurement. No prior studies have reported reliability measures of manual muscle segmentation in the neck, but MRI segmentation variability of rotator cuff muscle volume was reported to be less than 4%.[85,94] As a whole, segmentation for muscle volume has been shown to have errors generally under 5%, calculated by water displacement.[85,95,96] The reliability of the muscle size-strength relationships from linear regression can be interpreted from the y-intercepts of the models. A positive intercept for the linear relationship would imply force generation without muscle, signifying the potential for misleading results; more specifically, intercepts significantly deviating from 0 may indicate submaximal muscle activation or poor measurement of strength or muscle size.[91,92] Hence, regression models correlating muscle size to strength are deemed unreliable when intercepts fail to meet this criterion. All significant relationships reported in this study exhibited intercepts not significantly different from 0, falling within the narrower 80% confidence intervals.

Sex differences in strength appear to result primarily from differences in muscle size, but differences in the predictability of this relationship point to more complex underlying reasons. In the subject population, the only significant anthropometric sex difference was height; nonetheless, males were significantly stronger than females, with ratios similar to those found in previous studies.[77,97] Models found no significant sex difference in model slopes, except for the AS in an extended posture. This supports the hypothesis that the difference in neck strength, at least in the neutral posture, can be attributed to muscle size. In other words, there is no sex-specific effect granting male muscle more strength. However, while there was no clear difference between slopes of the relationships, a greater percentage of strength variability was left unexplained by muscle size in females, as all male muscle size-strength relationships yielded higher $R^2$ values. One explanation could be the greater variation of muscle morphometry, specifically muscle moment arms, in females compared to males. However, this does not explain why females exhibited significant inter-posture strength correlations while males did not. For females, strength in condition C was a strong predictor of strength in condition A in spite of the fact that the exertions are in opposite directions involving antagonistic muscles. Thus, there appears to be some set of qualities, apart from muscle size or morphometry, endowing greater strength to some females but not others. Though fiber type composition of neck muscle may vary between subjects, it has been shown to have little effect on muscle specific tension.[98] A larger difference in activation of agonists and antagonists between strong and weak females could explain this phenomenon.[99] An investigation of this hypotheses would require integrating subject-specific muscle morphometry and electromyographic (EMG) data with the muscle size and strength measurement techniques used in this study. Given the observed sex differences and disparities in prevalence and treatment outcomes, future research into neck strengthening intervention is warranted and should analyze males and females separately.

Though weak in females, muscle size-strength relationships were strong in males and provided evidence for the contribution of specific muscles to the neck exertions studied. The $r$ of 0.74 for total superficial flexor RCSA to neutral flexion force is comparable to muscle size-strength relationships in other joints including the shoulder, elbow, and wrist.[69,74,75,91,98] The SCM is widely regarded as the primary flexor of the neck and has been the focal muscle for sport-related perturbation studies.[29,100,101] Our results show that SCM size variation accounts for 44% of neutral flexion strength variation in males, and the $r$ of 0.73 is similar to the relationships reported for elbow flexors and extensors.[69,75] Because the SCM has been shown to generate an extension moment about C7, we hypothesized that the other anterior neck muscles (Longus, IH, or AS) would show stronger relationships with strength in condition B.[102] Longus size has been linked to chronic neck pain; however, its short moment arm prevents large joint torque generation.[36] The IH contribution to flexion has been shown *in silico* using musculoskeletal modeling software, OpenSim.[103] The IH muscles contribute to head-neck flexion by indirectly creating downward force on the mandible. The lack of direct force to the mandible, through a chin strap akin to a football helmet, may explain why a significant IH size-strength relationship was largely not observed in our study (except MV-strength correlation in females). Therefore, it was not surprising to find that the AS had the strongest relationship with neck flexion strength in condition B. Given that this exertion is commonplace in sports where an anterior torso lean and an upright head are common, quantification of AS size in neck strengthening studies for injury risk may be beneficial. The development of strength intervention strategies should consider a full range of positions to account for weak inter-position strength correlation and differing muscle involvement. Further research to identify neck extensor size-strength relationships is warranted.

No significant difference was observed among the three muscle morphometric measures for depicting size-strength relationships. For other muscles and joints, MV and ACSA have been compared with mixed results.[69,75] In the present study, RSCA-based relationships had intercepts closer to 0 and MV models were slightly stronger. For the purpose of neck strength correlation analysis, there appears to be no obvious disadvantage to use ACSA in terms of accuracy and sensitivity. For more clinically oriented studies where efficiency, cost-effectiveness, and portability may take priority, ultrasonographic measurement of ACSA would be recommended for data acquisition.

Several limitations of this study are noted to inform future investigations. Nine participants' data were excluded due to image blur caused by excessive motion artifact in MRI scans. Muscle segmentation was performed manually slice-by-slice, a time-consuming process that limited the number of replicates used for reliability analysis. Static strength was measured in the present study given the equipment constraint and interest in statically held deviated postures. Dynamic strength data may be more pertinent to acute head or neck injury prevention applications.

In conclusion, the findings from the current study of neck muscle size-strength relationship highlight the importance of sex differences and testing a full range of motion for clearer understanding of the relationship and development of strength-based injury prevention strategies.

# 3. ADVANCED SUBJECT-SPECIFIC NECK MUSCULOSKELETAL MODELING UNVEILS SEX DIFFERENCES IN MUSCLE MOMENT ARM AND CERVICAL SPINAL LOAD

## 3.1. Introduction

Neck pain and injury are growing concerns that disproportionately affect females.[1-10,20-24,104,105] Neck strength is believed to be an important modifiable factor in injury prevention strategies and pain treatment protocols; however, mechanical neck pain treatment cannot be characterized as successful, and women have significantly poorer outcomes than men.[11,14,15,17-19,26,30-33,36,40,42-44] Personalization, by way of targeting specific preventative or therapeutic strengthening interventions according to an individual's unique neck anatomy and physiology may hold the key to discovering successful protocols. An improved understanding of neck biomechanics, with a particular focus on muscular strength, can shed new light on evaluating the efficacy of personalized interventions and those addressing the sex disparities in neck pain prevalence and treatment outcomes.

Biomechanical modeling is an investigative approach that allows researchers to simulate the human musculoskeletal system in exertions and movements to study the otherwise unmeasurable biomechanics of internal structures.[45-52] In addition to advancing the state of knowledge about structure and function as well as their relationships, biomechanical modeling has been a valuable tool in identifying injury risk factors and elucidating causal pathways. Originally designed for whole body musculoskeletal biomechanics analysis, software tools like OpenSim and AnyBody have become the standard platforms for model comparison and development, streamlining inverse dynamics calculations and subsequent muscle activation approximation.[103,106,107] The latest neck biomechanical model built in OpenSim, the HYOID model (Fig. 3-1), uses musculoskeletal anatomy based off a 50th percentile male subject.[103] In the OpenSim platform and therefore the model, bones are modeled as rigid bodies, muscles as one-dimensional Hill-type contractile elements, and joints as frictionless connections with ranges of motion and degrees of freedom defined anatomically.[106,107] Although an improvement over prior neck musculoskeletal models, the HYOID model has two noted pitfalls: limited level for subject-specificity and poor recreation of maximal strength capability.

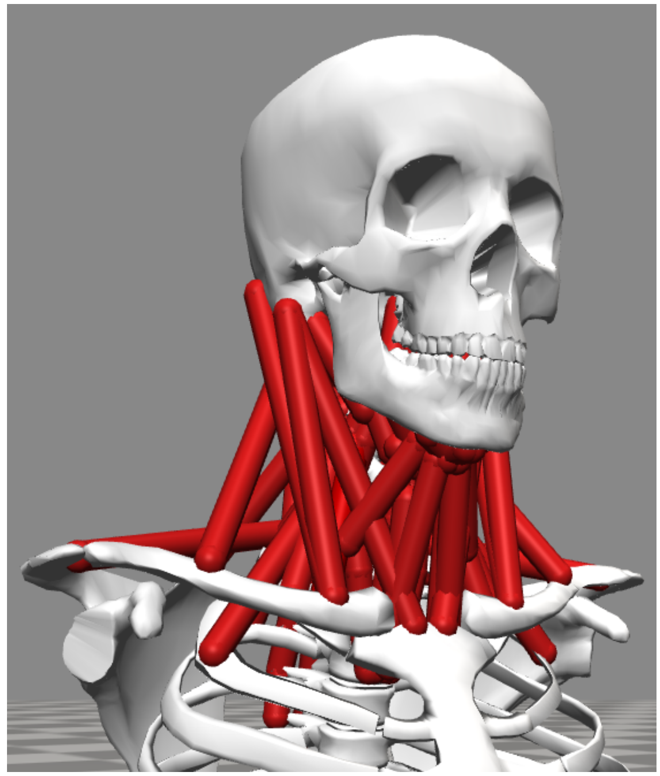


**Figure 3-1.** The HYOID model as seen in the OpenSim visualizer. Note the 1D representations of muscles.

These two pitfalls preclude investigation of individual variation during maximal exertion and thus constitute a gap between biomechanical modeling and potential translational research into personalized applications. The HYOID model has limited subject-specificity capability because it is built using generic anatomical data and muscle force generating properties and only allows for scaling based on anthropometry.[108] As an example, the morphology of the clavicle is generic, as are the landmarks that denote muscle-bone attachment sites; thus, one-dimensional representations of muscle paths are not specific to the given subject, simply scaled to best fit the participant's anthropometry. Attempts to correct force generating properties, by scaling physiologic cross-sectional area (PCSA) values with subject-specific muscle volumes (MVs), have been marginally effective in the shoulder and unsuccessful in neck modeling.[109,110] Additionally, all OpenSim models use a singular constant for maximum muscle stress across all muscles and all individuals.[106,111,112] While some progress toward personalization has been made by way of creating a female-specific model, the model was constructed using generic female anatomy without accounting for individual anatomical differences beyond anthropometry.[86,113] With regard to maximum force production capacity, neck models often require reserve actuators or scaling factors to replicate force values measured from human strength testing. The HYOID model must multiply extensor strength by a factor of 1.4 and flexor strength by a factor of 2.7 to match experimentally obtained force outputs.[103] While this is seen as an improvement given that the best prior model's flexion strength was 1/15$^{th}$ of experimental values, it is evident that the HYOID model cannot accurately recreate muscle tensions in maximal exertions. Thus, the current HYOID model, as well as the OpenSim modeling platform, in general is not well suited for investigating sex or individual differences in neck structure, function, and strength.

A critical first step toward personalization of prevention as well as treatment strategies is the development of accurate, subject-specific neck biomechanical models that can discern possible subtle structural variation accounting for manifested functional differences. Comparisons of this variety that would advance therapeutic interventions include chronic pain patients versus healthy controls, pre- and post-treatment or preventative therapy, and those with and without neck pain risk factors (the most important being male-female comparisons given the differences in epidemiology and treatment outcomes). Therefore, the objectives of this study are to develop highly subject-specific biomechanical models for static neck exertions and demonstrate their utility by using the models to elucidate sex differences in neck force production and potential injury risk.

## 3.2. Methods

### *3.2.1. Data acquisition*

The data used for developing the neck biomechanical models and in the subsequent model-based analysis were acquired from an experiment[82,83,114] in which participants underwent two medical imaging sessions and a biomechanical testing session. High resolution computed tomography (CT) and magnetic resonance imaging (MRI) scans of participants' neck regions were obtained to provide detailed bone and soft tissue morphological information, respectively. In the biomechanical testing session, participants performed static maximum voluntary contractions

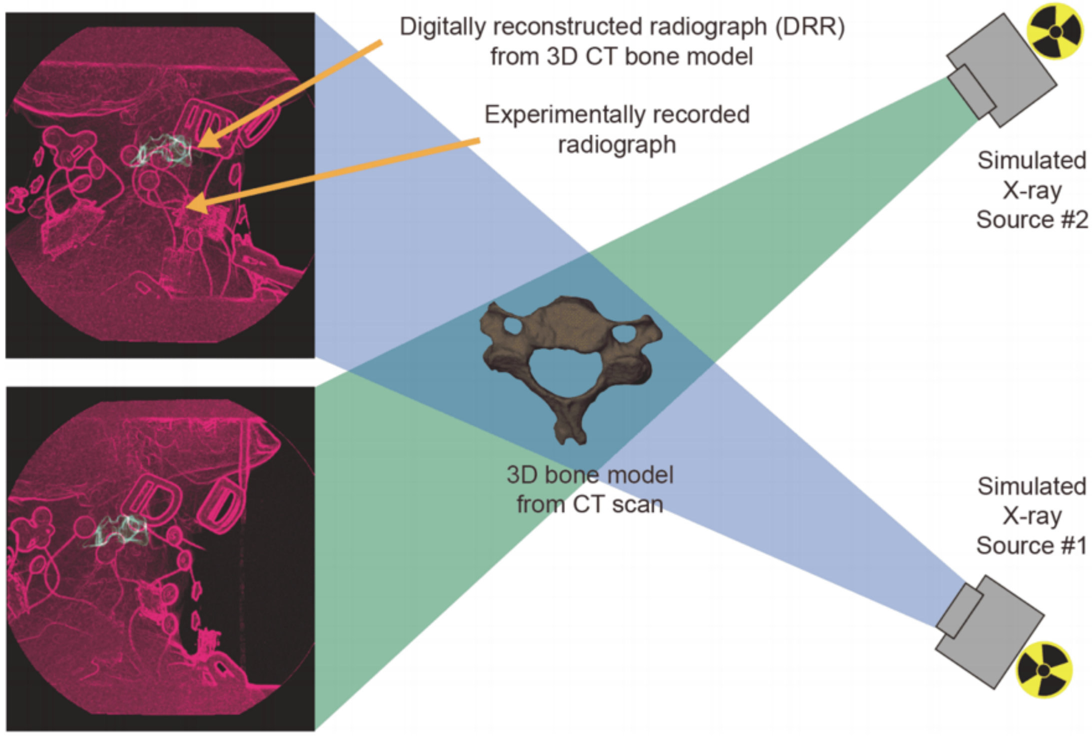



**Figure 3-2.** A conceptual depiction of the model-based-tracking procedure on C1. A ray-tracing algorithm created digitally reconstructed radiographs using 3D bone models from CT. Bone position and orientation could be manipulated until the DRRs matched the bone image in both DSX radiographs. This process was repeated for each bone for every frame.

(MVCs) in the following neck exertion direction and posture conditions: (A) flexion in a neutral posture, (B) flexion in 40° of head-neck extension, and (C) extension in 40° of flexion. These exertions were performed against a multi-axial load cell via a custom-made helmet worn by the participants while they were seated with their torsos restrained. In addition to the static tasks, participants performed free flexion-extension, lateral bending, and axial rotation movements. While these exertions and motions were completed, a dynamic stereo radiography (DSX) system (Fig. 3-2), a motion capture (MoCap) system, and a surface electromyography (EMG) system measured cervical vertebrae positions and motions, gross kinematics, and muscle activity, respectively. For the MoCap system, three surface markers were placed on the helmet (Front, Top, Right), five on the face (forehead, left and right infraorbitals, left and right tragion notches), and four on the rest of the body (C7, sternum, left and right shoulders). A total of eight EMG electrodes were placed on the skin overlying the infrahyoids, sternocleidomastoid, splenius capitis, and upper trapezius muscles bilaterally.

From the original database consisting of 40 healthy adults, twenty-three (11 males and 12 females, aged 21 – 45) were selected for this study based on criteria that included adequate MRI quality for muscle border distinction, sufficient DSX image quality of all 7 vertebrae, acceptable number of MoCap markers for head and load cell position tracking, and proper task execution with force measurement. The study protocol, approved by the Institutional Review Board, was explained in detail to the participants who provided written consent.

*3.2.2. Model development*

The development of subject-specific models integrated CT, MRI, DSX, motion capture, load cell, and EMG data and proceeded in four distinct steps: (1) CT-MRI co-registration, (2) posture-dependent muscle geometry specification, (3) optimization-based muscle redundancy solution, and (4) EMG-based model validation.

*3.2.2.1. CT-MRI co-registration*

Three-dimensional (3D) point cloud representations of involved neck muscles, reconstructed from MRI segmentation,[114] were co-registered with 3D bone models of cervical vertebrae reconstructed from CT segmentation. This was required to define muscle paths in relation to vertebral position and orientation or, grossly, one's neck posture.[115] Vertebral bone models segmented from MRI suffered from substantial volume including structural details critical for anchoring muscle paths. This necessitated the use of CT-segmented vertebrae and, thus, co-registration of MRI- to CT-segmented vertebrae. The challenge associated with co-registration of a complex, high-degree-of-freedom structure like the spine is that the poses adopted during the two imaging modalities are never identical. Unfortunately, the CT segmented cervical column, as a whole, cannot be placed into the MRI reconstruction due to differences of participants' neck postures between the two imaging modalities. A "pose-matching" co-registration procedure was implemented. It utilized CT-based bone models in a series of poses recorded during the flexion-extension range of motion task by DSX and identified the pose that best matched that adopted during MR imaging. This matching minimized curvature difference, quantified as the Fréchet distance between two 3D polynomials fit to the centers of the vertebral foramina in CT- and MRI-segmented models. For each frame of the FE trial, a 3D polynomial was fit to the centroids of the circles that were fit to each bone's vertebral foramen. A similar polynomial was fit to the MRI-segmented vertebrae's vertebral foramina. By identifying the frame in the FE trial that best matched the cervical spine curvature observed from the MRI, we were able to position CT-segmented vertebrae into the MRI-derived muscle geometries (Fig. 3-3 and Fig. 3-4).

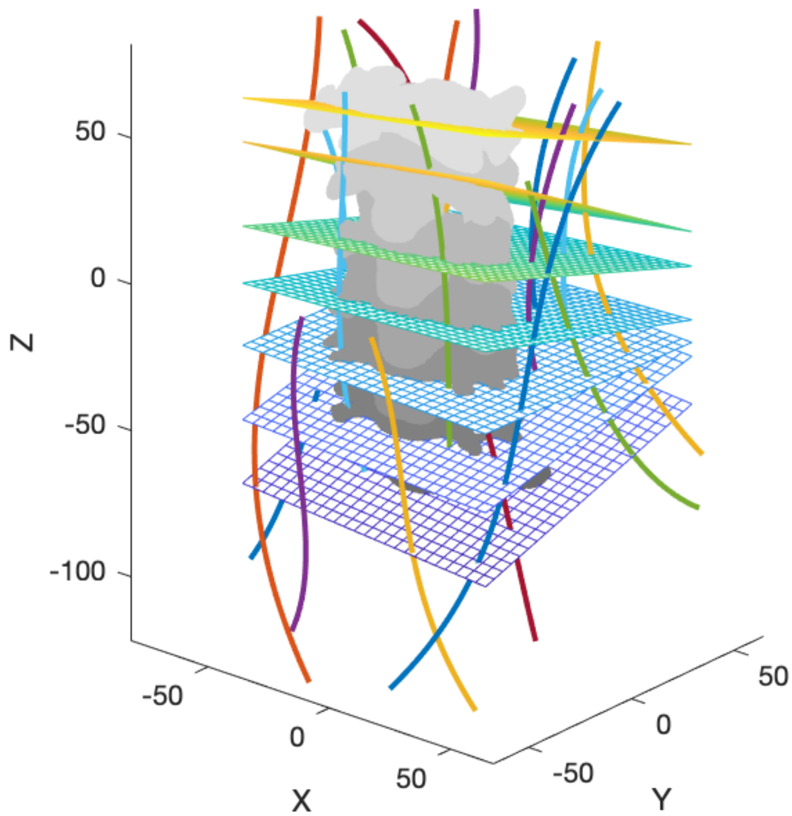



**Figure 3-3.** Muscle path polynomials with co-registered CT vertebrae.

*3.2.2.2. Posture-dependent muscle geometry specification*

After co-registration, individual muscle paths were defined in reference to vertebral positions and orientations. Local coordinate systems (LCSs) were defined for each vertebra using PCA (wherein X was positive anteriorly, Y was positive left laterally, and Z was positive superiorly). MRI-based muscle path identification utilized a segmentation and reconstruction-based technique wherein a 3D polynomial was fit to the centroids of 3mm slices of each muscle point-cloud reconstruction, identical to the polynomial used in ML calculation by Reddy.[114] The intersection point of a muscle's polynomial and a specific vertebra's "transverse" (XY) plane was saved as a "via-point" for that vertebra (in the vertebral LCS) such that muscles whose paths travel the length of the cervical spine had seven via-points (Fig. 3-5). Doing so for all muscles for a given vertebra results in a cross-sectional "snapshot" of muscle positions at a given vertebral level. Thus,

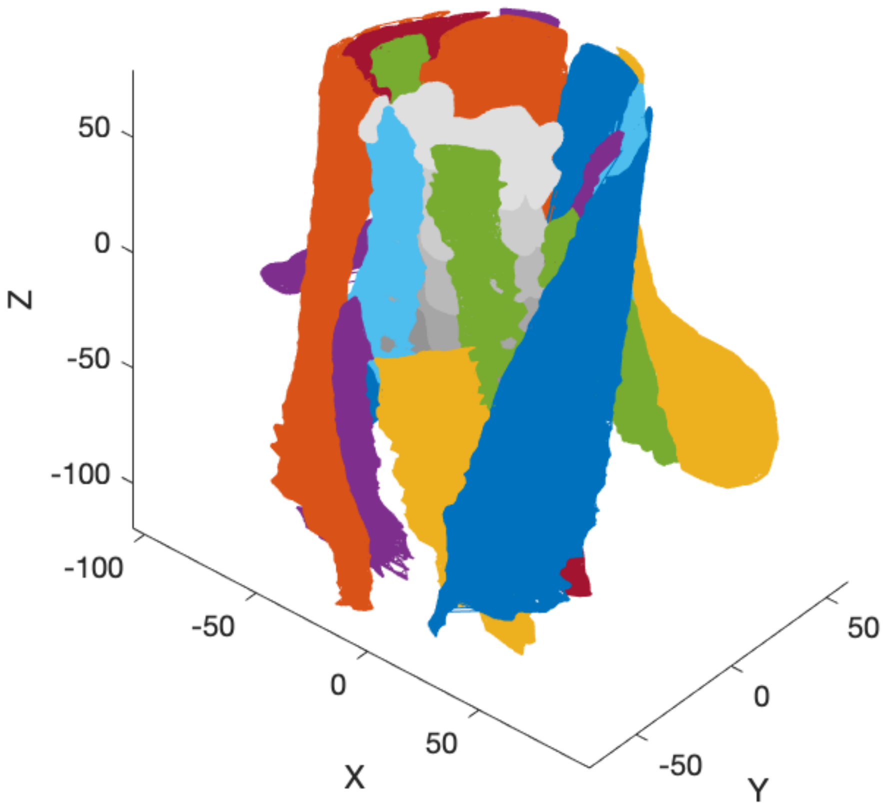



**Figure 3-4.** CT-segmented vertebrae co-registered with MRI muscle point clouds.

DSX-derived vertebral orientations provided simulated muscle path data where actual data could not be captured. This strategy is an adaptation of the moving muscle points (MMP) approach using vertebral kinematics in lieu of MRI imaging of the neck in multiple postures.[116] This quasi-via-points muscle representation is also a departure from the 1D approach of OpenSim and allows for more precise moment arm calculation approaches.[117,118]

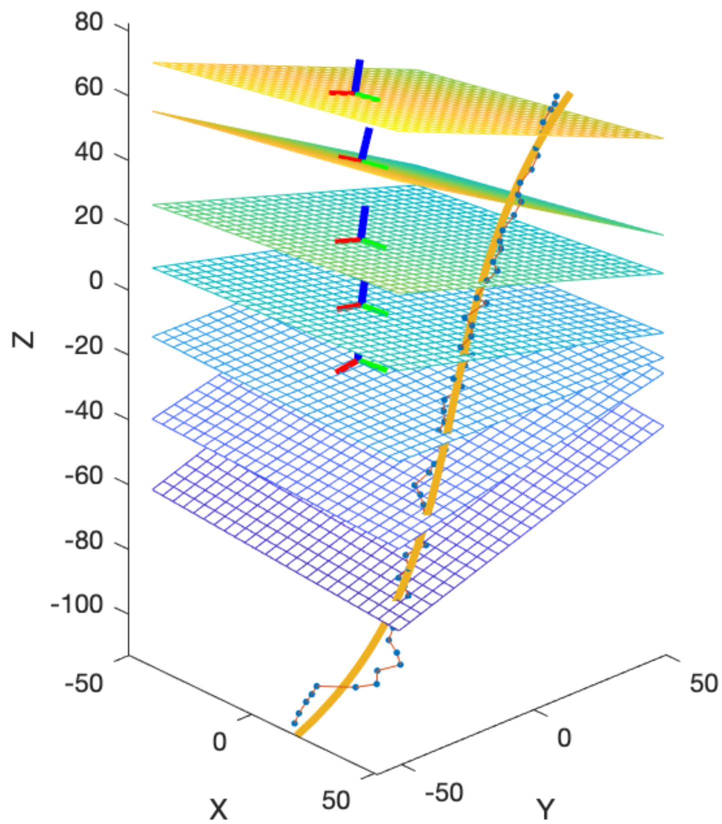



**Figure 3-5.** The 3D polynomial line (gold) is fit to the slice centroids (blue dots connected by red lines). The transverse planes of the seven cervical vertebrae are shown along with their LCSs. The intersections of the polynomial and the planes are saved as "via-points" in each LCS.

Upon defining via-points in vertebral LCSs, DSX-derived vertebral kinematics were used to reconstruct muscle paths, defined using polynomial curves, in various exertion postures (Fig. 3-6). A polynomial was fitted to the via points to redefine the new muscle path in the actual, adopted posture. Among multiple methods available for muscle moment arm calculation,[101,119,120] the geometric method was chosen for its simplicity and because it allows for moment arm calculation about a spinal joint of choice.[121] The tangent line to the polynomial curve at a given spinal level was characterized as the muscle's line of action (LOA) at that spinal level. In the present study, moments were resolved about the centroid of the C6 vertebra; however, the models were constructed in a manner that allows for alternative choices of vertebral level as the reference origin.

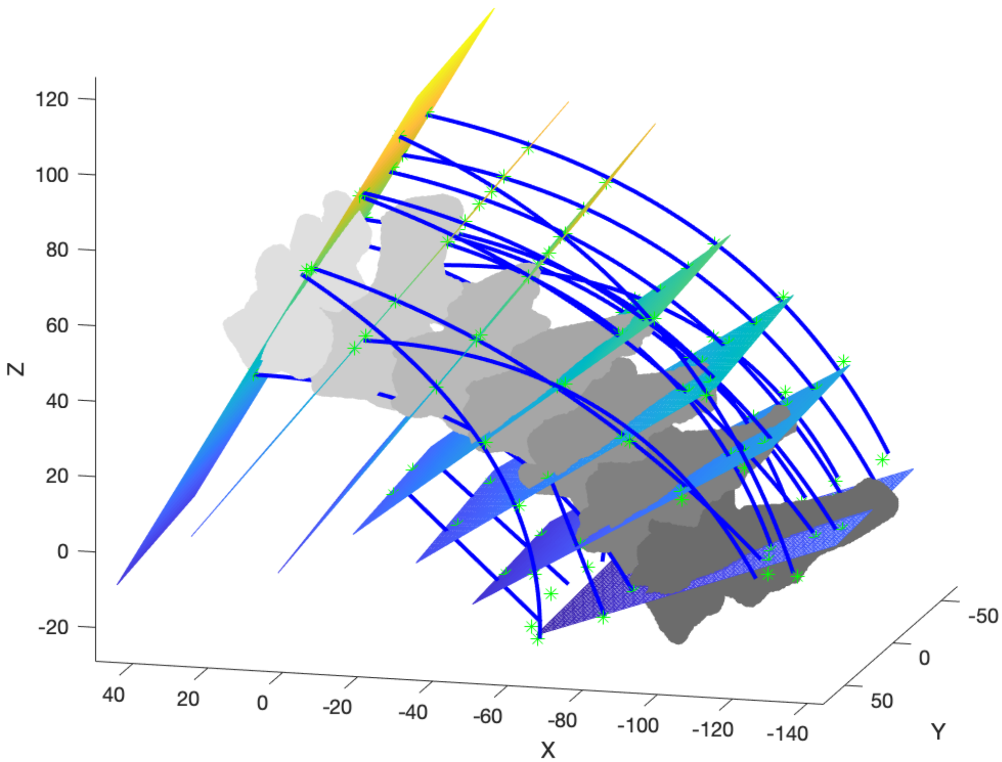
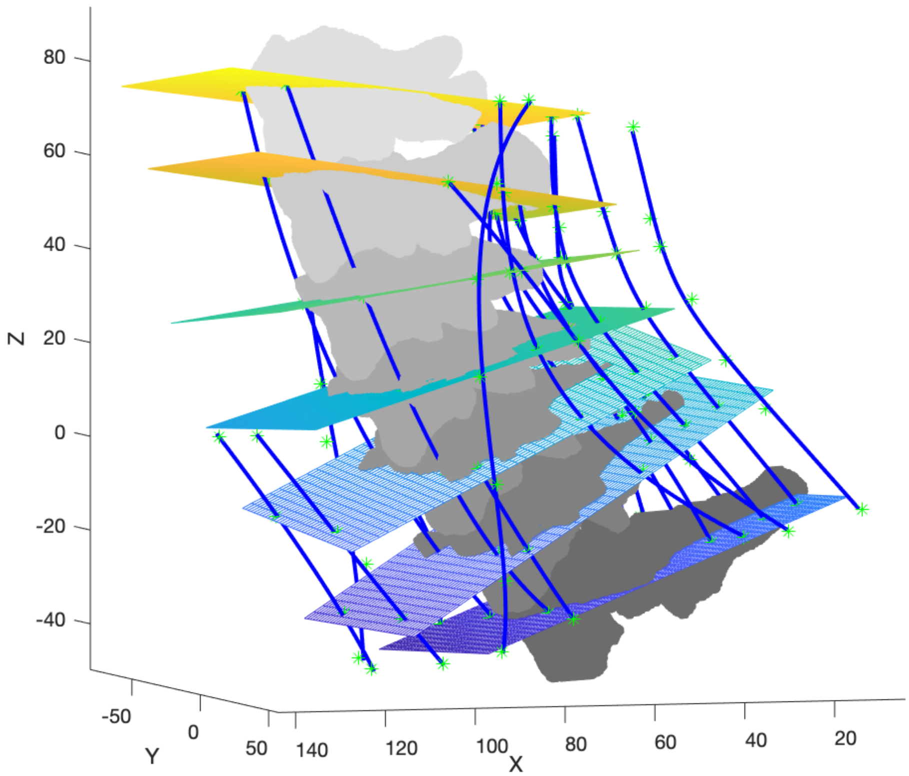



**Figure 3-6.** Reconstructed muscle paths fit to via-points as determined by vertebral kinematics in configurations C (above), B (next page top), and A (next page bottom). Note how the polynomials used to estimate muscle paths adjust to the newly adopted posture by matching the movement of the via points (as defined by vertebral kinematics).



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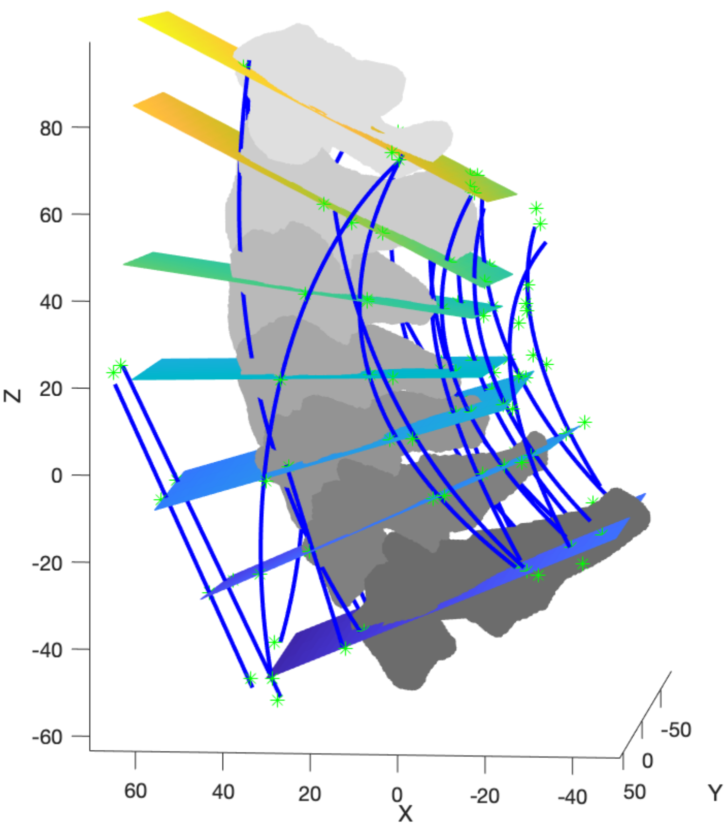

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*3.2.2.3. Muscle force and cervical spine disc force determination*

The external forces applied to the models included gravitational force due to head mass and exertion reactive force. Head mass was estimated using skull circumference and literature data.[122,123] The center of mass of the head was defined as the midpoint of the left and right tragion notches (LTra and RTra)[123] where markers were placed and captured by the MoCap system. The load cell force vector acted on the head-neck system at the midpoint of the forehead and front of helmet markers for conditions A and B. For condition C, the load cell point of contact was calculated as the forehead marker reflected about the coronal plane. The direction of this force vector was the intersection of the midsagittal plane and the Frankfort plane (as defined by the LTra, RTra, right infraorbital, and left infraorbital markers).

Once the external forces and their lines of action were determined and muscle geometry characterized, a system of equations for static equilibrium was generated. Thus, the equations for equilibrium took the following form:

$$\vec{M}(t) = \vec{r}^E \times \vec{F}^E + \vec{r}^H \times \vec{F}^H + \sum_{i=1}^{m} \vec{r}_i^M \times \vec{F}_i^M + \sum_{i=1}^{s} \vec{r}_i^S \times \vec{F}_i^S \tag{3-1}$$

$$\vec{F}(t) = \vec{F}^E + \vec{F}^H + \sum_{i=1}^{m} \vec{F}_i^M + \sum_{i=1}^{s} \vec{F}_i^S \tag{3-2}$$

where equations (3-1) and (3-2) respectively describe moment and force equilibria in the coordinate system defined with respect to the C6 vertebra. The terms *m* and *s* represent the number of muscles and spinal forces involved. $\vec{F}^E$, $\vec{F}^H$, $\vec{F}^M$, and $\vec{F}^S$ represent exertion force, head weight, muscle forces, and spinal forces, respectively. $\vec{r}^E$, $\vec{r}^H$, $\vec{r}^M$, and $\vec{r}^S$ represent the moment arms of the aforementioned forces. Note that spinal compression and shear forces, generated by the loading of passive tissues (e.g., ligaments, cartilage, intervertebral discs), were modeled as grouped vectors passing through the point at which rotational equilibrium was calculated, C6 in this case;[124] thus, their moment arms are null, and the right-most term of (Eqn. 1) was reduced to 0. Given that the tasks were flexion and extension exertions, only moment about the mediolateral axis was considered in solving for muscle tensions.

Upon defining the system of equations for static equilibrium, the tensions of the individual muscles were solved using an optimization algorithm. While different choices for equations restricting the solution space and objective functions exist,[125-128] this study utilized the objective function, *U*, which minimizes the sum muscle stresses cubed (Eqn. 3-3).[107,126] This objective function is widely accepted and used for muscle force prediction under volitional conditions and was adopted in modeling platforms such as OpenSim.[106,111]

$$(3\text{-}3)\quad U = \sum_{i=1}^{n} \frac{F_i}{RCSA_i}^{p}$$

A lower bound of 0 restricted muscle stress to only tension, and a nominal (not reached) upper limit of $175 N/cm^2$ was also placed. Once muscle tensions were resolved to meet the moment equilibrium with respect to the center of C6, balancing forces identified shear and compressive forces on the spine at that joint.[129] In this manner, muscle stresses and spinal forces were calculated for each frame of a given trial. As each participant performed two MVC tasks in each configuration, this process was performed for all trials. While there were no subjects for whom EMG data from both trials in a given configuration were subject to measurement error, skin-hair artifact, or incomplete data capture, 11 trials (out of 138 total possible trials) were omitted from analysis. Effects of these errors or artifacts included amplitude spikes and extreme activation values far beyond the average recorded signal from the electrode and highly erratic signals (not corresponding to the characteristic curves observed).

*3.2.2.4. EMG-based model validation*

The model was validated by comparing predicted muscle stress to the corresponding EMG amplitude, both normalized.[84,130-132] EMG amplitudes were quantified as RMS over a 50 ms interval and filtered using a 10-500Hz Butterworth bandpass filter and notch filters 60Hz intervals to remove noise and power line interference. EMG amplitude data were then normalized to maximum recorded amplitude for that muscle and then averaged across left and right. Muscle stress for a given timepoint was normalized by the muscle's peak stress at the timepoint of maximal force thus yielding a pseudo-% activation metric, better comparable to EMG for validation. This method avoids the "residual activator" or "scaling" problem prior neck musculoskeletal models (e.g., the HYOID neck model in OpenSim) have faced as this method's maximum allowable muscle stress is not constrained to a single value but can vary from individual to individual. Therefore, a subject-specific optimization approach was used to generate normalized muscle stress curves for each muscle in each trial. Normalized stresses for the SCM, Hyoid, SPL, and Trap muscles were also averaged across left and right sides. Normalized activation and stress profiles for the four muscles were resampled to generate 100 data points for each trial to facilitate comparison across varied exertion durations.

*3.2.3. Model-based analysis and hypothesis testing*

Model accuracy was reported as root mean square error (RMSE), wherein RMSE was calculated for each muscle comparing %-activation (EMG amplitude compared to muscle stress) for each trial. RMSEs were then averaged for each sex for each muscle. A prerequisite for model-based analysis is that model accuracy is consistent across subjects. Individual RMSEs were inspected to confirm that no bias was apparent. Spinal compression forces were calculated as peak compression over a 0.5s interval and were normalized to exertion force over the same interval. Student's t-tests with an $\alpha$ level of 0.05 were used to identify significant male-female differences in muscle moment arms and spinal compression forces.

## 3.3. Results

### *3.3.1. Model validation and accuracy*

The subject-specific models recreated muscle tension profiles (Fig. 3-7) that closely resembled EMG-measured muscle activity (Fig. 3-7), including the ramp-up, sustained hold, and relaxation phases, for agonist muscles (SCM and Hyoid in flexion exertions; SPL and Trap in extension exertions). The models predicted antagonist muscle (SPL and Trap in flexion exertions, SCM and Hyoid in extension exertions) inactivity, and only modest co-contractions were indicated by EMG (Fig. 3-7). Correlations ($R^2$) between model-predicted muscle tension and EMG-measured muscle activation for the agonist muscles were high (table 3-1). RMSEs ranged from 15.1% to 25.7% (Fig. 3-8).

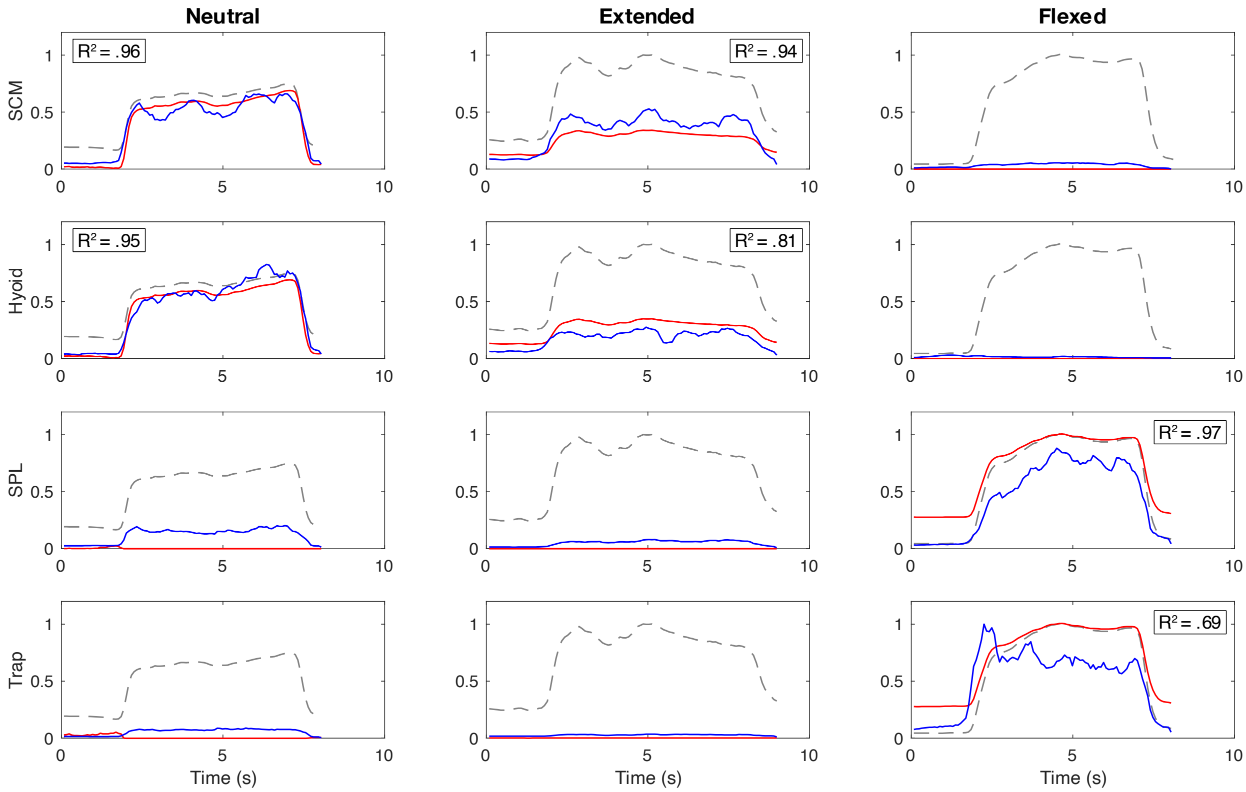


**Figure 3-7.** Sample of exertion force, muscle stress, and EMG amplitude curves from one representative subject. Each column corresponds to each posture or condition (A, B, C), and each row corresponds to each muscle. Exertion force measured by the load cell is shown in black on the top row only to provide a sense of how force was being generated by the participant over the duration of the trial. Normalized muscle stresses are shown in red, and normalized EMG amplitudes are shown in blue for each muscle. Note that while force was normalized to strength in that posture, muscle stresses and activations were normalized to a single maximum across postures (allowing for cross-posture comparison).

### *3.3.2. Sex differences*

Males, in general, have greater neck muscle moment arms, defined with respect to the center of the C6 vertebra near the base of the neck (Fig. 3-9 and Table 3-1). Among 10 neck muscles, significant sex differences were found in one flexor (Hyoids) and five extensor muscles (Deep, Longiss, SPL, SSCa, and LS). These significant differences were consistent in moment arms across the postures, which did vary but only by 6% at most. No significant sex difference in the variability of muscle moment arms was observed. Metrics of participant anthropometry, height and weight, did not show a clear correlation to moment arm for either males or females.

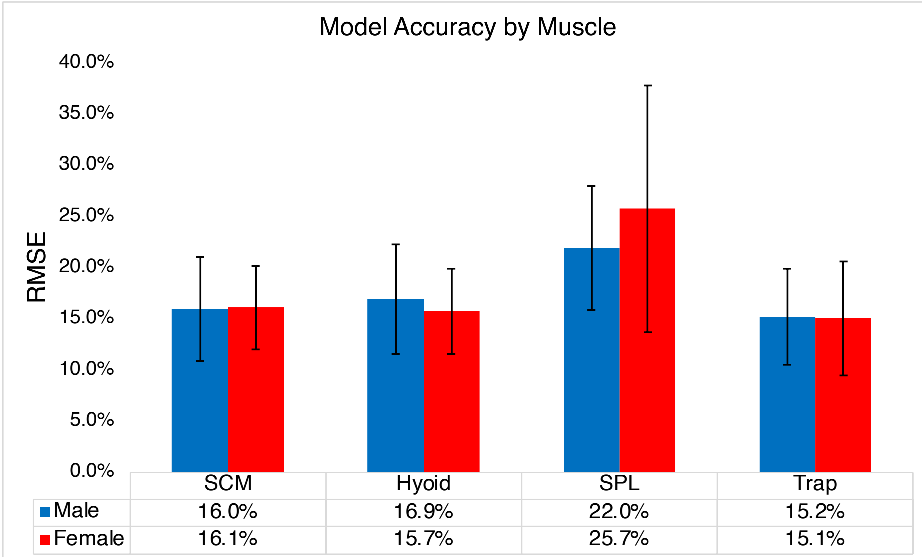


**Figure 3-8.** Average RMSEs for each sex for each muscle averaged across conditions are shown. Error bars depict standard deviation. Model accuracy does not differ significantly between males and females for any muscle.

**Table 3-1.** Flexion-extension muscle moment arm means (and standard deviations) in mm at C6.

| Muscle Group: | SCM | Hyoids | Longus | AntSca | Deep |
|---|---|---|---|---|---|
| MALE | 22.3 (4.8) | **43.3 (2.9) *** | 17.6 (2.1) | 15.1 (2.8) | **-19.1 (2.5) *** |
| FEMALE | 23.4 (3.8) | **39.7 (2.1) *** | 17.7 (1.0) | 14.2 (2.0) | **-16.8 (2.1) *** |
| **Muscle Group:** | **Longiss** | **SPL** | **SSCa** | **Trap** | **LS** |
| MALE | **-13.0 (2.5) *** | **-33.2 (3.6) *** | **-24.4 (3.3) *** | -22.0 (6.9) | **-16.5 (3.3) *** |
| FEMALE | **-8.1 (3.0) *** | **-26.6 (3.8) *** | **-20.8 (2.3) *** | -20.0 (5.1) | **-11.8 (5.4) *** |

Spinal compression forces at C6, predicted by the subject-specific models, were normalized by the corresponding exertion forces and compared between sexes across three postures (Fig. 3-10). In the neutral posture, spinal compression per unit of exertion force was moderately higher in males; in the flexed posture, spinal compression was substantially higher in females; in the extended posture, there was no statistically significant difference. Across all three postures, however, variability of spinal compression was much greater in females than males, and the disparity was most pronounced in the extended posture.

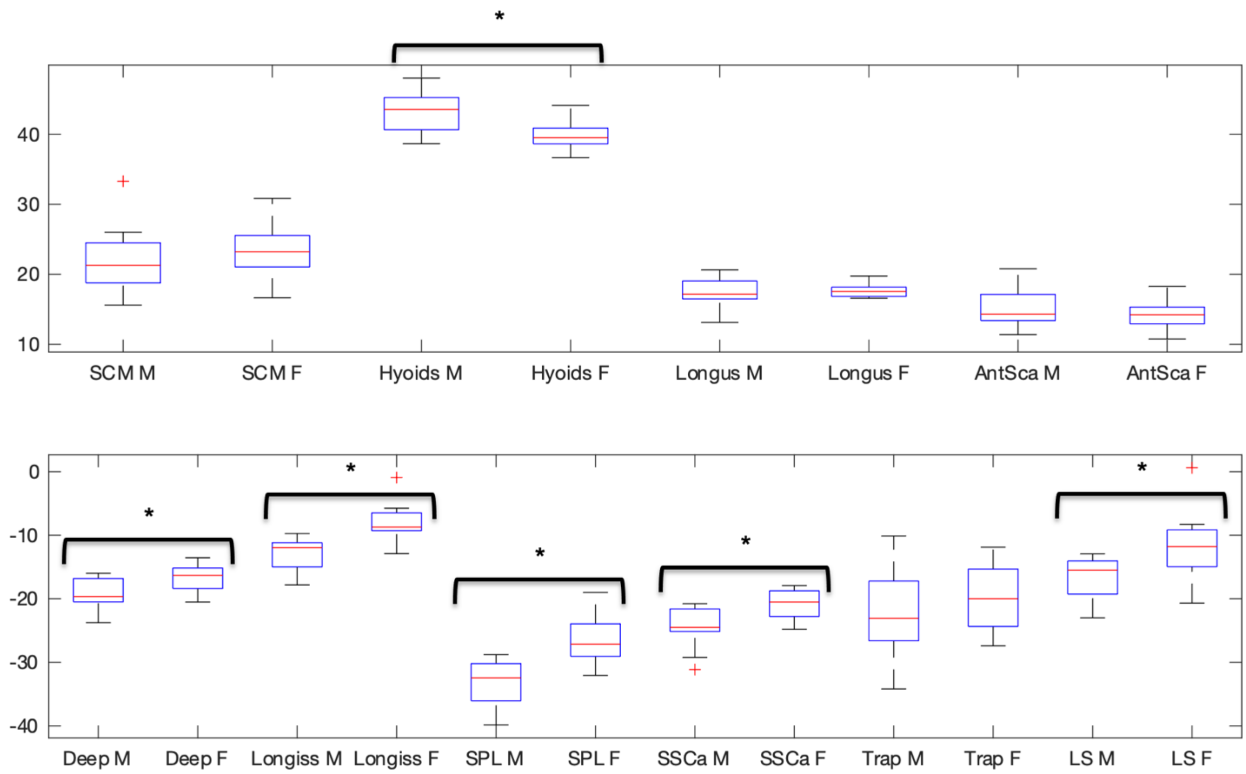


**Figure 3-10.** Distributions of flexion-extension muscle moment arms (in mm) at C6 are depicted in boxplot form for each sex. Moment arms are about an axis that is positive left-laterally (i.e., positive moment arms indicate a flexion moment and negative indicate extension). In addition to the aforementioned four muscle pairs, the longus capitis + colli (Longus), anterior scalene (AntSca), semispinalis cervicis + multifidus (Deep), longissimus capitis and cervicis (Longiss), semispinalis capitis (SSCa), and levator scapula (LS) are shown.

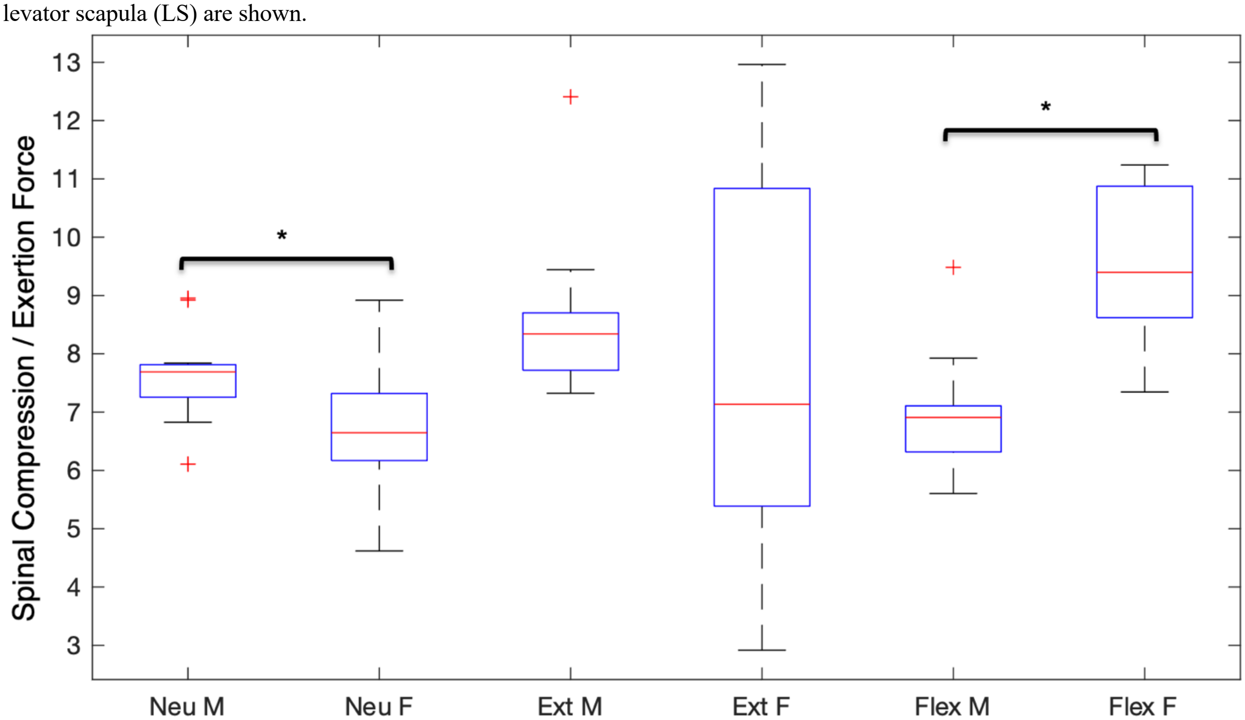


**Figure 3-9.** Distributions of spinal compression normalized to exertion force are shown for males and females in each posture. Significant differences were noted in the neutral and flexed postures.

### 3.4. Discussion

The present study was driven by an overarching goal to elucidate the biomechanical underpinning of sex differences in neck pain incidence and neck strength as a modifiable factor believed to play a role in injury prevention and treatment. An *in silico* approach was adopted wherein we constructed subject-specific biomechanical models incorporating individual, unique musculoskeletal anatomies and used the models to digitally explore the hypothesized sex differences in neck structure and function and their pertinence to neck injury incidence.

More accurate anatomical representation of a model does not necessarily translate into more accurate biomechanical prediction by the model. Biomechanical model accuracy can be evaluated through a variety of qualitative and quantitative means, and the choice of RMSE reflects our intention of reporting a rigorous accuracy metric that can be improved upon in future studies. Prior neck modeling studies reported accuracy by comparing models' moment generating capacity to *in vivo* human experimentation;[102,103,133,134] however, utilization of these models requires "scaling factors" or reserve actuators to address inaccuracy. Additionally, this concept of model "accuracy" does not align with the general concept of validation in the larger field of biomechanical modeling, where EMG to model estimated muscle activity is more common.[132,135,136] Qualitative comparison of EMG activation and model-estimated muscle activation is often used and has been deemed appropriate for validation.[131,132,137-144] Semi-quantitative methods have also been used, quantifying correlation between the two curves, though this is best done when comparing peak or maximal values to each other, not over the length of a trial (note that these studies and those above are primarily lower extremity and gait-focused work).[145-149] Only one prior modeling study quantified error; Trinler et. al. reported mean absolute error (MAE) between %muscle activity from EMG and as predicted by static optimization and computed muscle control algorithms (both in the OpenSim platform).[149] Trinler reported MAEs ranging from 13 – 69% for some experimental conditions and used a 30% MAE cutoff as a criterion to judge which algorithms were "accurate". In this study, RMSE, a relatively higher error metric than MAE due to an increased penalty for large deviations, was reported and averaged 17.9% for all muscles in all trials. Thus, relative to existing neck and other biomechanical models, the presented approach generated models with at least satisfactory accuracy.

The neck muscle moment arm data presented in this study provides the biomechanical modeling community with a better understanding of how neck muscle anatomy can vary across sexes and within select populations. Sex differences in neck muscle size have been identified by our group and presented previously.[114] While muscle moment arm calculation methods have been well-studied, actual neck muscle moment arm analysis has explored various postures but has been limited to small sample sizes, precluding sex-based comparison.[119,120,150] Vasavada et. al. quantified muscle moment arms using a single model with generic anatomy in a precursor platform to OpenSim, thus using straight muscle paths.[102] Ackland et. al. studied five cadaveric head-neck complexes to understand muscle moment arm using the tendon excursion method, a method that provides a numerical value for a muscles moment arm for the entire act of "neck flexion" or other movements.[101] Lastly, Suderman carried out numerous studies utilizing MRI data from two participants' necks in various postures to analyze moment arms using various methods, emphasizing the importance of curved muscle path in neck muscle moment arm calculation.[116-118] The presented moment arm analysis of 11 males and 12 females provides a richer dataset for the purpose of understanding how these values vary across populations. Our results show a general trend that males have greater moment arms than females, and this difference was significantly true for the hyoids and 5 extensor muscle groups. The authors recognize two relatively simplistic sources for this difference. Males have larger neck muscles, which may cause more superficial muscles to be displaced farther from the center, thus increasing moment arm.[86,114] Males also have larger cervical vertebrae, which could cause the same effect.[151] Apart from these two anatomical sources, greater intermuscular fat or thicker and more abundant connective tissue may also play a role in causing the observed phenomenon. Vasavada and Suderman's approach of using serial MRI and ours of using dynamic radiography along with a single MR scan both represent the state of the art in musculoskeletal geometry data acquisition. The two approaches can complement each other: the kinematics interpolated using the sequential MR scans can be improved using the "gold standard" skeletal motion data from dynamic radiography, whereas muscle deformation or path change extrapolated from skeletal motion can be verified and enhanced using addition MR imaging. Future endeavors combining both approaches could consummate the representation of moving and deforming neck muscles and further improve model accuracy.

Findings from advanced subject-specific modeling shed some new light on sex differences in neck biomechanics and injury propensity. Neck compression and posture have been studied as potential factors in the development of pain or injury.[152] While a causative link has not been established, the potential that remains coupled with the epidemiological sex differences in neck pain motivated the biomechanical investigation into spinal loading. Spinal compression was calculated as axial force at C6, in the C6 LCS, for the 0.5s interval of greatest force, and compression forces were generally comparable to those observed in Choi's modeling study and well below axial failure loads.[124,153,154] We devised the cervical spine disc compressive loading per unit exertion force metric as a surrogate measure of biomechanical stress to discern how individuals—males or females—differ in the transmission of external forces into internal stress. Significantly shorter moment arms for almost the entire extensor muscle group in females is the primary factor causing substantially higher spine loading per unit exertion force experienced by females in extension with a flexed neck—the “dropped head” position most constantly assumed in work or leisure activities. This uncovers a viable link connecting the biomechanical sex differences with the reported epidemiological sex difference in neck pain. Further, the greater variability of spinal compression in females may also be indicative of increased propensity for neck injury. Even in flexion exertions with a neutral or extended position where the mean spinal compression force was slightly lower in females, the dispersion for females was so much wider that a significant portion of the females would endure more than the most stressed males when meeting the same force requirement (i.e., performing the same physical task). It is noteworthy that there does not appear to be any sex difference in the variability of muscle moment arms, suggesting the sex disparity in spine loading variability arises from sources other than anatomical or morphological variability.

The limitations of the presented work ultimately come down to two main issues: data acquisition and the optimization approach to estimating muscle tension. Unfortunately, several participants’ data were excluded due to poor MRI, motion capture, EMG, and strength measurement data quality. However, the MRI and EMG protocols had limitations that have clear and simple solutions. MRI slice thickness was 3mm, too thick to capture vertebral detail needed to accurately coregister ct-segmented vertebrae on a per-vertebra basis, thereby forcing the use of the DSX-based coregistration method. Lowering the slice thickness to 1mm could easily rectify this issue and would avoid any discrepancies between cervical position during the matched frame from the dynamic FE trial and that adopted during MR imaging, discrepancies that would ultimately affect moment arm calculations. Also, utilizing alternative sequences to proton density may facilitate faster muscle segmentation. Regarding EMG, while fine wire electrodes would reduce crosstalk and greatly enhance the detail of muscle activity information acquired, this method is understandably too invasive for most protocols. However, a muscle-specific MVC trial to normalize EMGs would allow researchers to better understand load sharing between muscles. Regarding optimization in biomechanical modeling, this study utilized an objective function that minimized the sum of muscle stresses cubed, a function that is very similar to that of OpenSim but different in one crucial way: it does not assume a universal maximum for muscle stress, specific tension. While OpenSim sets specific tension to 35N/cm$^2$ based on single fiber animal muscle testing,[112] we allowed this quantity to vary across individuals and muscles, a choice that reflects the original motivation of personalization. Research on human specific tension has shown wide ranges, without a clear answer, thus demonstrating the plausibility of variation of this value across individuals and muscles.[155-159] Further research on maximal muscle stress in biomechanical modeling of the neck is warranted. Additionally, regarding optimization, the choice of objective function precludes antagonist muscle activation, an obstacle common to many biomechanical models. While EMG-assisted optimization may better recreate physiological function and more accurately reflect internal loading, that approach was not used in this study as it would conflict with the quantification of model accuracy. In summary, future work should utilize smaller MRI slice thickness, individual muscle EMG MVC protocols, and should investigate maximal muscle stress or specific tension and its role in biomechanical modeling.

In conclusion, this study developed subject-specific neck musculoskeletal models incorporating accurate individual anatomy of 11 males and 12 females in maximum voluntary exertions and used the models to investigate sex differences in neck biomechanics. The study unveiled that females have significantly shorter neck extensor muscle moment arms and thus endure higher cervical spine disc compressive loading when making the same extension exertion with a flexed neck. This biomechanical cause and effect, combined with greater variability of spine loading, exposes the female population to an increased risk of neck injury.

# 4. SUBJECT-SPECIFIC MAXIMUM MUSCLE TENSION: AN INDEX TO CAPTURE NEUROMUSCULAR DIFFERENCES IN NECK STRENGTH

## 4.1. Introduction

Women are disproportionately affected by neck pain, experience neck injuries from impacts at higher rates, and have poorer injury treatment outcomes than males, as neck pain and injuries continue to be a growing global health burden.[1-11,14,20-24,104,105] Neck strength, which also differs significantly between the sexes, may play an albeit not fully understood role in protection against neck injury and is deemed an essential component of successful treatment.[15,17,26,30-33,36,40,42] For this reason, neck strength and the factors underlying it have been studied in an effort to better understand, prevent, or treat neck pain and injury.[25-27,29-31,35]

To gain an understanding of strength and its factors, researchers have studied strength changes and identified associated adaptations, generally classifying them into two categories: morphological and neurological.[160,161] The primary component of the former is muscle size change, arguably the most studied factor in strength.[66] Other morphological changes pertain to intramuscular changes, (e.g., muscle fiber and myofibril growth, selective fiber type changes, and muscle architecture changes), that may also affect muscle size.[160] Neurological adaptations range from muscular level changes (increased motoneuron firing frequency or improved motor unit recruitment) to brain level changes (improved corticospinal excitability or improved muscle activation coordination, including agonist-antagonist co-contraction).[162-165] These neurological adaptations help explain the phenomenon of individuals with smaller muscles and muscle moment arms being able to generate more torque than individuals with greater ones. Empirical research on neck strength has examined some of these adaptations, albeit only in isolation. Biomechanical modeling allows for the studying of multiple factors mechanistically and analyze their relationships; however, to date, individual differences in neurological adaptation have been minimally represented in modeling.

Biomechanical modeling has been the primary tool used to quantify otherwise unmeasurable kinetics and kinematics and simulate injurious scenarios; biomechanical models have been employed to study healthy and pathological neck mechanics, including strength.[52,102,103,124,166] Unfortunately, biomechanical models generally lack the ability to account for or investigate into the aforementioned strength adaptations. Until recently, neck biomechanical modeling allowed only for minimal subject-specificity, wherein models could only be scaled to match gross anthropometry of a given subject.[52,103,134] Therefore, simulations of maximal force outputs only accounted for the overall size of a subject, not their unique muscle morphometry (viz., muscle size and moment arm). The effect of all other neuromuscular adaptations is translated into the mechanical property of maximum muscle stress, termed "specific tension", that is allowed by the biomechanical model. OpenSim, the primary biomechanical modeling platform, assumes a single value for maximum muscle stress, for all muscles, for all individuals, thus making it impossible to account for inter-individual variation in or intra-individual adaptation of the factors that would affect this value.[106,111,167] The assumed value of maximum muscle stress, $35 N/cm^2$, is a result of a recommendation to adhere to measurements from experiments on single muscle fibers from murine animal models, despite the fact that maximum muscle stress is known to differ between and change within individuals.[112,155,157,158,168] Optimization-based modeling approaches often only account for agonist muscle activation, meaning that muscle coordination as agonist-antagonist co-contraction also impacts modeled muscle stress. Fortunately, the recent development of personalized neck biomechanical modeling affords the opportunity to address these shortcomings and investigate the effects of neuromuscular strength adaptations.

The new personalized biomechanical models, built upon advanced medical imaging and subject-specific musculoskeletal geometry, may enable investigation into the individual variation of biomechanical as well as neuromuscular factors of muscular strength (Chapter 3). For biomechanical factors, neck muscle size and muscle moment arms have been shown to differ significantly between the sexes.[114] However, what remains unknown is whether some neuromuscular factors differ in how they contribute to strength between the sexes. To answer this question, an index for the effectiveness of neuromuscular strength factors must be identified to allow for quantitative comparisons. This index should reflect individual variation in strength while accounting for variation in the known biomechanical factors of strength. Once identified, the index can be compared to various measurements of neuromuscular strength factor effectiveness (e.g., EMG) to elucidate the relative contribution of the studied factor. Additionally, comparisons across populations may uncover differences in the degree to which specific neuromuscular factors contribute to strength.

Thus, the objective of this study is to experiment with the recently developed in neck biomechanical models in identifying an index for neuromuscular physiology that correlates well with strength. This new index is sought for testing the hypothesis that contraction coordination, by way of agonist-antagonist co-contraction, is correlated to the index and differs between the sexes.

## 4.2. Methods

### *4.2.1. Experimental protocol and database*

Twenty-three thoroughly subject-specific neck biomechanical models (11 male, 12 female) were used for experimentation in this study. The personalized models, shown to accurately estimate muscle activations, were created by integrating anatomical and biomechanical (motion capture, dynamic stereo radiography, and load cell) data (Chapter 3). These data were originally collected from participants who underwent a medical imaging protocol (CT and MRI scans of cervical region for bony and soft tissue anatomy, respectively) followed by experimental testing of neck exertion, which has been described previously.[82,83,114] Participants performed maximal voluntary contractions, exerting a force from their head to a load cell in three configurations: A) flexion (anterior force production) in a neutral posture, B) flexion in a 40° extended posture, and C) extension (posterior force production) in a 40° flexed posture. During the trials, surface electromyography (EMG) electrodes placed on skin overlying the sternocleidomastoid (SCM), infrahyoids (Hyoid), splenius capitis (SPL) and trapezius (Trap) muscle groups bilaterally, captured muscle electrical activity. A given muscle's EMG signal as RMS amplitude was normalized to the peak (50ms) amplitude recorded by that electrode across all trials.

### *4.2.2. Muscle tension index identification*

The desired index would be able to quantitatively capture the effect of neuromuscular factors on strength—specifically isometric maximum force production. This single metric would be able to explain the phenomenon wherein individuals with less advantageous biomechanics (muscle size and moment arm) exhibit greater strength. Thus, this index would quantify the amount of force an individual can generate in their musculature while accounting for muscle size, namely

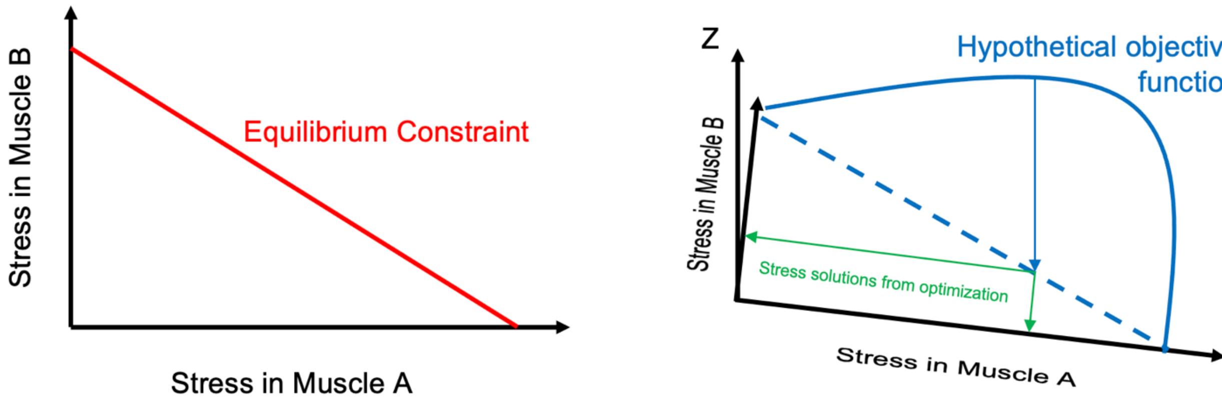


**Figure 4-1.** A hypothetical biomechanical solution space is shown, with stress in muscle A as the X axis and stress in muscle B as the Y axis. On the left, the solution space is restricted to the red line by the equilibrium constraint. On the right, a third dimension is added, with the criterion of the hypothetical objective function on the Z axis. This hypothetical objective function maximizes the criterion to identify a single solution within the solution space (that which is defined by the equilibrium constant). This solution corresponds to a specific assignment of muscle stresses to muscles A and B.

cross-sectional area. The developed models estimate muscle loads by generating muscle tension in response to external forces on the head (strength force) to maintain a static equilibrium, with respect to flexion-extension moment. There are, however, an infinite number of solutions of load allocation that would satisfy the equilibrium constraints (termed the muscle indeterminacy problem). One way to approach the muscle indeterminacy problem is with the use of optimization, where an objective function is hypothesized to represent an underlying muscle activation strategy. A simplified, two agonist muscle case is illustrated in Figure 4-1. With the moment arms and muscle cross-sectional areas accounted for by the model, all solutions for muscle load allocation must fall on the line determined by the equilibrium constraint (red). A hypothetical objective function generates a surface in a third dimension which becomes a single curve when the equilibrium constraint is applied. By optimizing a criterion in the third dimension, a solution can be identified, allocating load to each muscle (Fig 4-1). Though the objective function used in the developed models was shown to accurately identify muscle load when compared to EMG, it nonetheless presupposes a universal muscle coordination choice for all participants, thus assuming one component of the set of neuromuscular strength factors while also estimating different stresses for each muscle.

The desired index is a single quantity for an individual that encompasses all neuromuscular strength factors, including muscle coordination. Previous empirical studies investigating neuromuscular factors of strength grouped all agonists together, assuming a uniformly maximal activation,[155,169,170] an assumption that is also made when determining biomechanical model strength capacities.[102,103,134] Thus, a similar assumption was made in this modeling study: for a given trial, all agonist muscles are maximally activated and thus have the same tensile stress. This singular value of muscle stress quantifies the effectiveness of neuromuscular strength factors and facilitates comparisons between individuals and populations.

To identify an index of muscle tensile stress for a given modeled system (exertion), an additional constraint was imposed on the solution space. An upper limit of muscle stress, applied to all muscles, was raised until a solution point was identified (Fig 4-2). This solution satisfied the equilibrium constraint with each agonist muscle having the same stress. This singular value of muscle stress, the lowest ceiling for muscle stress for which a solution remains, is termed "α" following Crowninshield's convention and quantifies the effectiveness neuromuscular strength adaptations.[126]

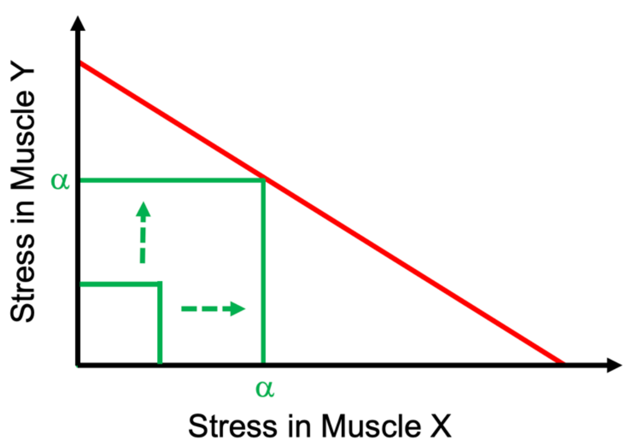

**Figure 4-2.** As in Fig 1, the solution space is defined as the line determined by the equilibrium constraint. However, rather than utilizing a criterion and objective function in an added dimension, an upper limit on muscle stress is raised (in green), uniformly with respect to all muscles within the system, until a single solution is identified. This solution sets a single stress for all muscles, and this value is termed "α".

Using a hypothetical example to aid in verification, if given a subject ($S_1$) who can produce a certain force for a given configuration, let $\alpha_1$ be the solution for $S_1$'s trial. If one assumes that another subject ($S_2$) has identical biomechanics (same moment arms for all forces and muscles), is able to generate the same force, but has smaller muscles than $S_1$, let $\alpha_2$ be the solution for $S_2$'s trial. Within this hypothetical example, it is necessarily true that $\alpha_2 > \alpha_1$, thus capturing the phenomenon of an individual with smaller muscles being able to generate equivalent strength due to increased effectiveness of neuromuscular strength factors.

### *4.2.3. Hypothesis testing and statistical analysis*

For each subject in each configuration, an $\alpha$ was calculated using peak force (averaged over 0.5s) exerted during a MVC trial. As a validation step, $\alpha$ was then correlated to strength independently for each configuration and each sex. Distributions of $\alpha$ were calculated for each posture and sex, and Student's t-tests were used to determine statistically significant sex differences. To understand the relationship between agonist-antagonist co-contraction and $\alpha$, EMG-derived muscle activation data was averaged across the 0.5s window of maximal force production for each sex in each configuration. For the configurations in which $\alpha$ was significantly correlated to strength for both sexes, a measure of agonist-antagonist co-contraction was calculated and then correlated to $\alpha$ for each sex.

## 4.3. Results

### *4.3.1. Maximum muscle stress and strength*

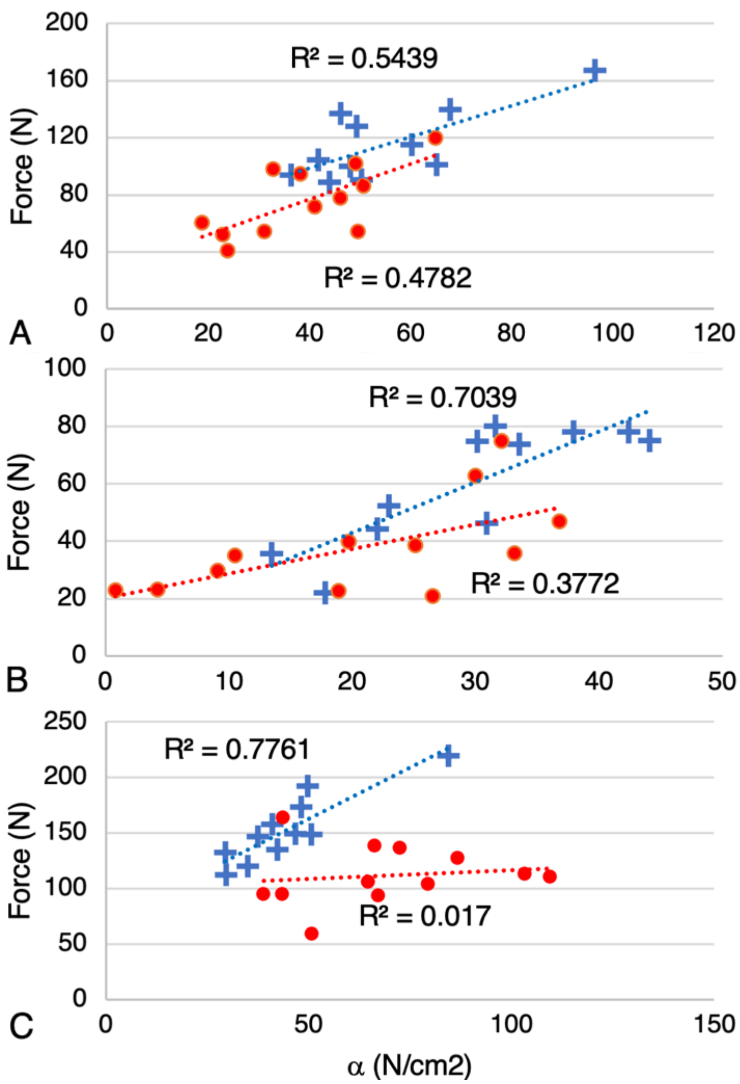


**Figure 4-3.** α to strength correlations are shown for males (blue) and females (red) in each configuration (A, B, C). All correlations depicted are significant ($\alpha = 0.05$) except for females in configuration C.

Upon calculating α for each subject in each configuration, α was correlated to strength for each sex (Fig. 4-3). α was significantly correlated to strength (with an average $R^2$ of 0.483) for all sexes and postures except females in configuration C, neck extension in a 40° flexed posture. $R^2$ values quantify the amount of strength variation that can be explained by variation in α, and thus the extent to which neuromuscular factors play a role in strength. The significance of the relationships and the strength of the correlations serves as evidence for the validity of the metric. Males generally showed higher correlations than females.

After performing correlation as a form of validation, distributions of a were calculated and tested for sex differences (Fig. 4-4 and Table 4-1). Significant sex differences were found in configurations A and C (neutral flexion and flexed extension).

*4.3.2. Muscle contraction coordination and maximum muscle stress*

**Table 4-1.** Mean values of the boxplot in Fig. 4-4 are shown here. Males had significantly higher $\alpha$ values in the neutral posture (configuration A) and significantly lower values in the flexed.

| Alpha (N/cm²) | A | B | C | Average |
|---|---|---|---|---|
| Male | 55.05 | 29.71 | 44.95 | 43.24 |
| Female | 39.12 | 20.58 | 68.89 | 42.86 |

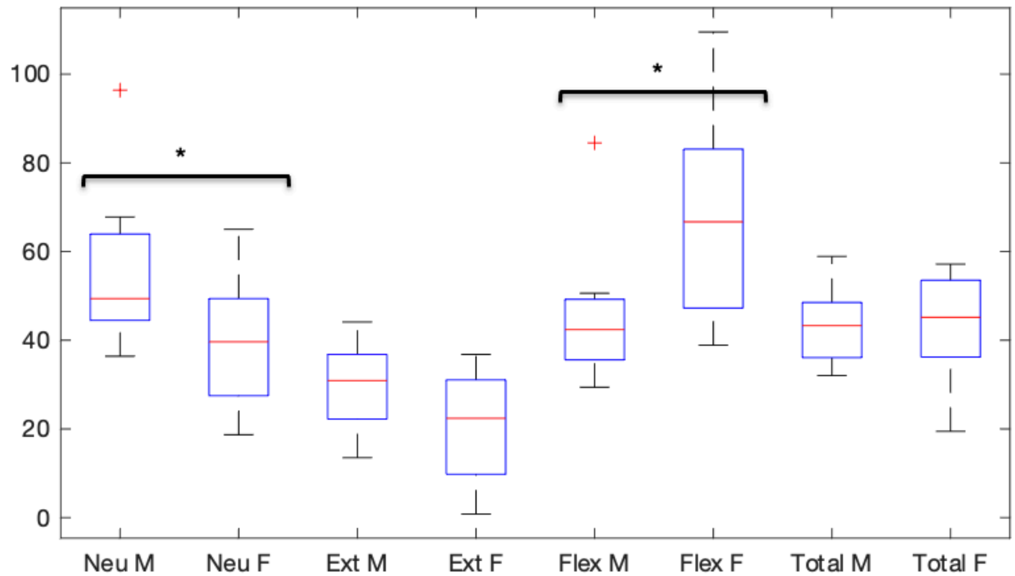


**Figure 4-4.** Distributions of $\alpha$ (in N/cm$^2$) are shown for each sex in each configuration and an average across all configurations.

After quantifying the relationship of $\alpha$ to strength and identifying sex differences in the distributions of $\alpha$, the last question remaining was "how does muscle contraction coordination, a known component of neuromuscular strength adaptation, relate to the discovered metric?" The simplest method of quantifying muscle contraction coordination would be obtaining a measure that describes relative agonist-antagonist co-contraction. The first step in doing so was quantifying the relative activations of the measured muscles in each configuration during the time window of maximal strength (Fig. 4-5).

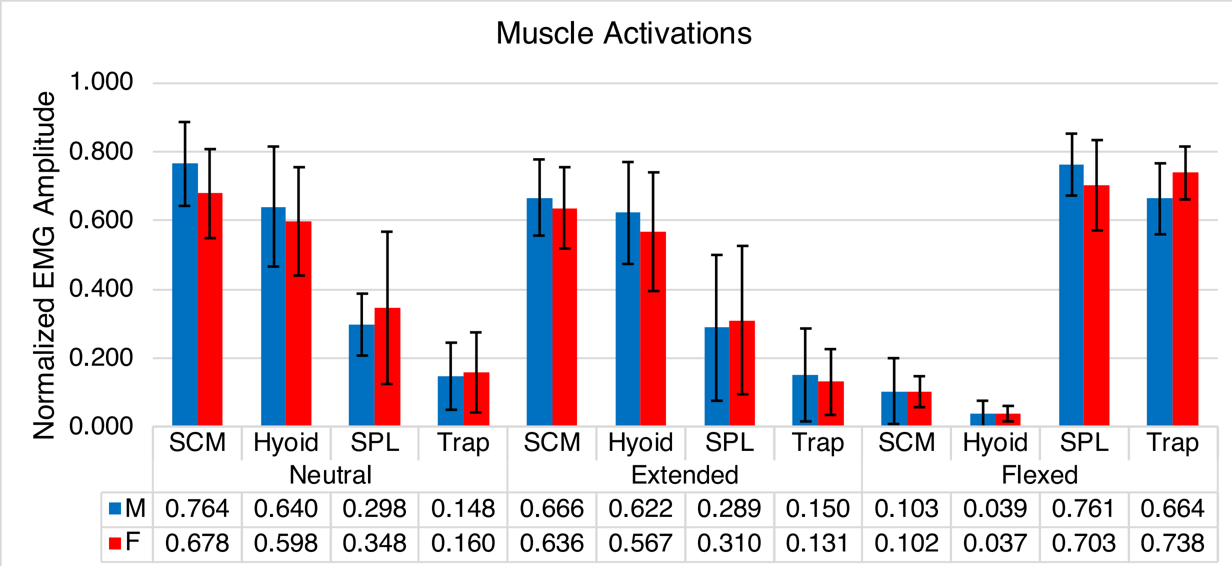


**Figure 4-5.** Average EMG amplitudes in the 0.5s window of maximal force exertion for a given configuration are shown for the four measured muscles (averaged across bilateral pairs), for males (blue) and females (red). Neck flexors (SCM and Hyoid) are agonists in configurations A and B, and neck extensors (SPL and Trap) are agonists in configuration C.

In the neck flexion tasks, the splenius capitis (SPL) appeared to show the highest activation of the antagonists, and the sternocleidomastoid (SCM) appeared to show the highest activation of the agonists. Because the neck flexors showed only low antagonist activation in configuration C, and because the validation step yielded only significant correlation between a and strength for males, exertions in the flexed posture were excluded from agonist-antagonist co-contraction analysis. Because the SCM and SPL muscles showed higher activation for the agonist and antagonist groups, respectively, they were chosen for the calculation of a co-contraction measure. Thus, an agonist-antagonist ratio was calculated as SCM activation divided by SPL activation for each subject in both configurations (A and B). This measure was then correlated to $\alpha$ for each sex to determine the relationship between co-contraction and neuromuscular strength factor effectiveness (Table 4-2). While no significant relationships were identified for males, females

| Pearson r (*p*) | Neutral | Extended |
|---|---|---|
| Male | 0.12 (0.733) | 0.12 (0.721) |
| Female | **-0.71 (0.010)** | **-0.68 (0.015)** |

**Table 4-2.** Pearson correlation coefficients and *p*-values are shown for correlations between agonist-antagonist co-contraction and $\alpha$ in configurations A and B for each sex.

showed a strong negative correlation between agonist-antagonist ratio and $\alpha$. For females, higher antagonist activation was correlated with more effective neuromuscular strength physiology or adaptation.

**4.4. Discussion**

The objective of this study was to utilize a recent development in subject-specific neck biomechanical modeling to investigate a potential metric for the effectiveness of neuromuscular factors in neck strength. This metric, $\alpha$, was found and then validated through correlation to strength, thereby demonstrating the amount of strength variation attributable to non-biomechanical factors. Lastly, contraction coordination was shown to play a significant role in neuromuscular strength factor effectiveness for females, but in a surprising way.

Individual variation in the neuromuscular physiology that contributes to strength accounts for a large portion of variation in neck strength. The significant and strong correlations between $\alpha$ and strength evidence this claim. The use of maximum muscle stress as a measure for neuromuscular strength adaptation is not a novel concept, as muscle stress has been studied as a counterpart to muscle hypertrophy when subjected to strength training protocols or atrophy as a consequence of aging.[155,169,170] Nonetheless, the use of a personalized neck biomechanical model that allows for variation in maximum muscle stress is a deviation from the norm, one that opens the door to future research into the non-biomechanical causes for variable force generating capacities. The finding that variation in $\alpha$ explains a large portion of strength variation does not mean, however, that biomechanical strength factors account for the remaining portion of strength variation because the two are not necessarily orthogonal variables. It is more likely the case that the causative stimulus for increased muscle size, as an example, also led to downstream effects on neuromuscular strength adaptation.[160,161] Nevertheless, it is apparent that strength adaptation occurs at many different levels, only some of which are accounted for with traditional biomechanical models that presuppose a universal value for maximum muscle stress.

While no significant sex difference in effectiveness of neuromuscular strength factors was observed when $\alpha$ values were averaged across postures, analysis of each posture independently found that males had significantly higher $\alpha$s in configuration A and lower in configuration C. First, the overall average values for $\alpha$ (43.24 N/cm$^2$ for males and 42.86 for females) differ only slightly from the 35 N/cm$^2$ assumption of maximum muscle stress in OpenSim models.[106,111,167] However, these values varied across postures and also between the sexes. Males showed greater neuromuscular strength adaptation in the neutral posture. Unfortunately, it may not be appropriate to arrive at the conclusion that females showed more effective neuromuscular strength adaptation in the flexed posture. This is due to the validation step discussed above, in which female $\alpha$ to strength correlation in configuration C was not significant. The potential source for the lack of correlation during validation as well as the relatively higher variation in $\alpha$ for females in the flexed posture is unclear. Task unfamiliarity or novelty would lead to lower $\alpha$ values as participants would be unable to optimize muscle contraction coordination, as can be seen in configuration B. However, female $\alpha$s in the flexed posture were markedly higher than the rest, and the task is an exertion common to the workplace, where computer or office work may demand a slight head down posture. It is important to note that changes in muscle lengths were assumed to be negligible by the biomechanical modeling approach. Thus, it is plausible that this assumption led to artificially lower $\alpha$ values in the non-neutral postures, depending on muscles' optimal fiber lengths. Nonetheless, what is evident from the presented distributions of $\alpha$ is that variation in model maximum muscle stress exists and that the proposed method using the newly developed biomechanical models are capable of using this metric to detect differences in neuromuscular strength adaptation for the neck.

One component of neuromuscular strength adaptation, agonist-antagonist muscle co-contraction, was shown to significantly and negatively correlate to $\alpha$ in neck flexion tasks for females only. The negative correlation between an agonist/antagonist muscle activation ratio and neuromuscular strength factor effectiveness is *prima facie* counterintuitive. Because tension in antagonist muscle would actively counteract the generation of the desired moment, increased agonist activation and decreased antagonist activation is considered a strength adaptation and has evidence to that end.[99,160] However, relatively increased antagonist activation was found in females with stronger neuromuscular physiology. This may be due in part to the higher complexity of the neck joint relative to other, simpler studied joints like the knee and elbow. Maintaining cervical lordosis may be a more important component of anterior force generation for women than for men. Another explanation for the sex difference may be due to muscle crosstalk. First, the choice to calculate an agonist/antagonist ratio using SCM/SPL was to show the potential utility in a simple 2-electrode system for neck muscle co-contraction measurement. However, the SPL electrode may have picked up activity of the deep spinal extensors, the muscles responsible for maintaining lordosis, and this effect may have been greater in females due to their having generally narrower necks. Further work is needed to better characterize the role of antagonist muscle activity in neck exertions as it appears to play an important role in neuromuscular strength adaptation.

In addition to the aforementioned limitations pertaining to the use of the biomechanical models, two other limitations may have introduced sources of error that may be improved upon in future studies. First, normalization of EMG amplitude was performed using maximal exertions for neck flexion and extension not with movements that would specifically target the measured muscle groups. A more detailed normalization approach may provide more accurate muscle activation data. Second, strength was measured from MVC trials, with participants performing two such exertions in each posture. Unfortunately, due to EMG electrode malfunction or interference, it was sometimes the case that only one MVC trial was available for analysis. Neck exertions, as a whole, are novel tasks with which most participants are unfamiliar given the rarity of such exertions in daily life. Additional repetitions are needed to accurately assess strength in unconventional or novel tasks, where unfamiliarity may lead to artificially low strength values.[84] These correctable sources of error should be addressed in future neck strength research.

In conclusion, there is a need in biomechanical modeling to acknowledge and attempt to address individual differences in the effects of neuromuscular physiology on muscle forces and strength. This study has demonstrated a potential solution by identifying a new metric for this phenomenon through the modeling of maximal neck exertions. Sex differences were found in the importance of antagonist muscle activation during neck flexion, a finding that warrants further investigation as it pertains to neck strengthening interventions for head-neck injury prevention and neck pain treatment.

# 5. CONCLUSIONS

The goal of this dissertation was to address the need to investigate neck strength in a manner that examines the extent to which sex differences in neck structure and function may give rise to sex differences in the etiology and treatment of neck pain and injury. This work split the factors of strength into three: muscle size, muscle moment arm, and neuromuscular physiology. By establishing statistical and biomechanical models, sex differences were found in each of these factors. The functional effects of these sex differences were then identified as potential causative factors of neck pain and injury as well potential targets for neck strengthening as preventative or therapeutic intervention.

## 5.1. Contributions

The first contribution of this work was in the quantification of male and female neck muscle sizes and their relationships to neck strength because muscle size is often considered the most easily modifiable factor in neck strength. Manual neck muscle segmentation from MRI was performed on a novel scale of thirty participants (13 male, 17 female), providing the scientific community with valuable muscle morphometry data. This rich dataset afforded the opportunity to separately analyze the role of muscle size in neck strength for each sex. Significant muscle size-strength correlations evidenced the claim that muscle size plays a considerable role in neck strength, but male size-strength relationships were markedly stronger than females. This implies that factors other than muscle size determine a larger portion of neck strength for females than males.

The next strength factor studied was muscle moment arm, the other biomechanical variable in neck strength. To analyze neck muscle moment arms, identify sex differences therein, and investigate the potential biomechanical effects of those sex differences on neck function, a truly subject-specific biomechanical modeling protocol was developed. The latest neck biomechanical model lacked the capability for subject-specificity beyond anthropometry-based scaling and were unable to accurately simulate muscle loads in maximal exertions. New biomechanical models were constructed from medical imaging, incorporating the given subject's unique musculoskeletal morphometry. Validation of the models showed that model estimates of muscle activation accurately reflected EMG measures. Analysis on the models found that specific muscle moment arms of males were greater than females. The effect of these biomechanical differences was studied by way of quantifying neck compression forces relative to exertion strength. When normalized to force acting on the head during maximal exertion, females exhibited significantly higher neck compression in the flexed posture and markedly higher variance overall. Given the plausibility of a causative role of vertebral disc compression in neck pain and injury, the discrepancies in pain prevalence and injury incidence between may be explained by this finding.

After identifying sex differences in the biomechanical factors of neck strength and their potential effects on neck function, the remaining strength factors, grouped together under the umbrella of "neuromuscular physiology" remained. To evaluate the effectiveness of neuromuscular strength factors, an experimental approach was taken to the newly developed biomechanical models. An individual's ability to generate tension in their musculature was quantified by a new metric found through the modeling of maximal exertions. To investigate this metric of neuromuscular physiology further, by identifying the size of the role of muscle contraction coordination in this group of strength factors, the newly defined metric was correlated to a measure of agonist-antagonist co-contraction. While no significant relationships were identified for males, the agonist/antagonist activation ratio was negatively correlated to neuromuscular strength factor effectiveness for women, highlighting the importance of antagonist activation.

When taken together, the identification of sex differences in three different components underlying neck strength reveals a trend that is consistent with biological sex differences at a cellular level. Of the modifiable biomechanical strength factors, muscle size played a larger role in males than for females. When analyzing neuromuscular strength factors, cortical- or cerebellar-level effects appeared to play a larger role for females than males, implying that lower, muscular-level changes were more likely greater factors for males. These findings point to a trend that changes or differences at the muscle level better determine strength for males while differences or adaptations at the neural level are more important for females. Males exhibit higher quantities of androgen hormone receptors in the myonuclei of neck muscles; this sex difference is not observed at the extremities.[171] Given the effect of androgen hormones on muscle tissue and the sex differences in androgen hormone concentrations,[172-174] it is plausible that the observed trend in the discoveries of this dissertation is an effect of this fundamental biological sex difference. This work helps to bridge the gap between cellular and biological differences to clinical and epidemiological findings.

In addition to the mentioned dataset, methodological, and scientific contributions made, this work also offers a philosophical point, one that highlights the potential benefits of adopting a new perspective on biomechanical research. While much of prior biomedical research has focused on uncovering standard biochemical pathways and generalized effects of treatments on large sample populations, the field is beginning to recognize the advantages of subject-specificity. Given the context of growing interest in the concept of personalized medicine, this work sought to identify the effects of analyzing biomechanics not from a 50$^{th}$ percentile or generic perspective but from a starting point of subject-specificity. Human biomechanics, especially in the occupational health and injury safety space, has largely focused on safety and injury thresholds, utilizing models to simulate potentially harmful scenarios. While such work has been instrumental in developing necessary safety thresholds for military, manual labor, and other applications for general populations, the field largely lacks modalities by which to analyze specific subject groups and individual persons. Together, the three studies presented in this dissertation offer answers to how and why the utilization of a personalized approach to biomechanical analysis is a frontier that warrants exploration.

### 5.2. Future Work

Future neck pain research building from the work presented can follow two general trajectories: (1) mechanistic investigation of pain and injury using a modeling approach or (2) translational, clinical research into potential preventative or therapeutic neck strengthening intervention. Regarding the former, the established personalized neck biomechanical modeling procedure has been shown to be accurate and useful in identifying differences between populations. Application of these models to different subject populations may identify further biomechanical differences. Additionally, the application of these models to submaximal neck exertions may provide necessary muscle activation data to better analyze the structural effects of fatigue during sustained-till-exhaustion neck contractions. Regarding the second trajectory, while muscle size measurement to quantify hypertrophic changes to strengthening intervention has been performed, future work could quantify neuromuscular changes, specifically muscle contraction coordination, during strengthening interventions in women. A longitudinal study involving the comparison of individuals' personalized models pre- and post-strengthening intervention would shed more light on the identified sex differences in strength adaptation and their effect on neck function.

This dissertation serves not only as a diving board for deeper research into neck pain and injury biomechanics but also as an example of how personalized modeling may be applied to other joints, movement, or, more broadly, fields of biomedical research. Because each model developed in this work was constructed from subject-specific imaging, one can view each model as a “digital twin,” an *in silico* copy that captures geometric or physiologic details missed by generic methods. These representations can be analyzed themselves (cross-sectionally or for outcome measures after an intervention or treatment) or be the subjects of *in silico* simulation experimentation. There are four primary avenues in which applying this style of personalized, imaging-based investigation to the field of biomechanics could provide clinical benefit: 1) high-incidence or high-impact injury prevention or risk reduction in high-risk populations, 2) injury rehabilitation and physical therapy, 3) non-specific or mechanical pain reduction or prevention, 4) task performance enhancement. Regarding the first, serial imaging of individuals at high risk for overuse injuries (e.g., supraspinatus tendinopathy in swimmers, or ulnar collateral ligament injury in baseball pitchers) could allow researchers to investigate why certain individuals develop injuries while others do not as well as facilitate translational research directed at preventing the discovered pathological mechanisms. Regarding the second, the choice between operative and nonoperative treatment can depend on the extent to which physical therapy has success. Tailoring physical therapy to an individual’s specific anatomy (acquired through imaging and modeling) may facilitate the standardization of therapeutic interventions and lead to a shift in the balance between nonoperative vs operative management of specific injuries. Targeting different muscle groups or inducing stress-related hypertrophic changes in specific supportive tissues may allow for improved outcomes over an evidence-based but one-size-fits-all approach. The third avenue follows the lines of reasoning outlined previously when discussing future neck pain work but applied to other nonspecific or mechanical pain conditions for which a clearly defined injury pathomechanism or etiology remains undiscovered. Examples of this type of pain could include low back pain, adhesive capsulitis, and degenerative arthritic conditions. Lastly, the fourth area of application pertains to individuals for whom the primary goal is the completion of a specific task. The performance of elite athletes, for example Olympic weightlifters whose sole goal is to maximize the amount of weight lifted, or military personnel, whose goals may pertain to maintaining cerebral bloodflow during aerial maneuvers or preventing muscle atrophy during long-duration space travel, could be enhanced through the personalization of intervention to the specific individual given their unique anatomy and biomechanics. While anthropometry may offer some degree of subject-specificity in the four mentioned applications and will likely remain the most popular option for much of biomechanical modeling investigation given cost and ease of access, there is a need for further investigation pairing medical imaging and biomechanics for the purpose of personalization. Marrying radiology to biomechanics unlocks the door to a new and exciting frontier, one I look forward to exploring.

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